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Single agent versus combination chemotherapy for metastatic breast cancer (Review)

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[Intervention Review]

Single agent versus combination chemotherapy for metastatic breast cancer

Sue Carrick[1], Sharon Parker[2], Charlene Thornton[3], Davina Ghersi[4], John Simes[5], Nicholas Wilcken[6]

[1]Twins Research Australia, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Australia. [2]Centre for Primary Health Care and Equity, University of NSW, Sydney, Australia. [3]School of Medicine, University of Western Sydney, Penrith, Australia. [4]Research Policy and Translation, National Health and Medical Research Council, Canberra, Australia. [5]NHMRC Clinical Trials Centre, The University of Sydney, Camperdown, Australia. [6]Medical Oncology, Crown Princess Mary Cancer Centre, Westmead, Australia

Contact: Sue Carrick, suecarrick@sevenswifts.com.

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ABSTRACT

Background

Combination chemotherapy regimens are frequently favoured over single agents for the treatment of metastatic breast cancer, in an attempt to achieve superior tumour response rates. It is not known however whether giving more intensive chemotherapy regimens results in better health outcomes, when both survival and toxicity are considered, and whether better response rates and rates of progression free survival actually translate to better overall survival.

Objectives

To compare single agent with combination chemotherapy for the treatment of metastatic breast cancer.

Search methods

We searched the Cochrane Breast Cancer Group Specialised Register November 2008. Handsearching of recent conference proceedings was also undertaken.

Selection criteria

Randomised trials of single agent chemotherapy compared to combination therapy in metastatic breast cancer.

Data collection and analysis

Two authors independently assessed trials for eligibility and quality, and extracted data. Hazard ratios were derived for reported time-to-event outcomes.Response rates were analysed as dichotomous variables. Toxicity and quality of life data were extracted where present.

Main results

Forty three eligible trials (48 comparisons) were identified. These included 9742 women, 55% of whom were receiving first-line treatment for metastatic disease. For overall survival there was a statistically significant difference in favour of the combination regimens with no heterogeneity (HR 0.88, 95% CI 0.83-0.93, p<0.00001). Results were very similar when trials of first-line treatment were analysed, and for analyses where the single agent was also included in the combination regimen. Combination regimens showed a statistically significant advantage for survival over single agent taxane (HR 0.82; 95% CI 0.75-0.89, p<0.00001), but not anthracycline (HR 0.94.86-1.02, p=0.15).

Combination regimens were also associated with significantly better time to progression (HR 0.78, 95% CI 0.74 - 0.82, p<0.00001) and response (RR 1.29, 95% CI 1.14 -1.45, p<0.0001) although heterogeneity was statistically significant in both instances and probably due to clinical diversity of the participants and interventions.

Women receiving combination regimens experienced a statistically significant detrimental effect on white cell count, increased alopecia and nausea and vomiting.

Authors' conclusions

Combination chemotherapy regimens show a statistically significant advantage for survival, tumor response and time to progression in women with metastatic breast cancer but they also produce more toxicity. An unresolved question is whether combination regimens are more effective than single agents given sequentially.

PLAIN LANGUAGE SUMMARY

Single agent versus combination chemotherapy for metastatic breast cancer

Metastatic breast cancer is cancer that has advanced and spread beyond the breast and regional lymph nodes. Although many women will live with advanced disease for many years, treatment is aimed at the alleviation of symptoms rather than cure. The first choice of treatment for advanced disease is dependent on hormone status (whether the tumour is stimulated to grow by oestrogen and progesterone) or whether the tumour overexpresses human epidermal growth factor receptor-2 (HER-2) and can be treated with trastuzumab (herceptin). Most women with advanced disease will however receive chemotherapy (anti-cancer agents) either as their first treatment, because their disease has become resistant to some treatments, or in combination with other types of treatments. Chemotherapy drugs can be given alone (single agent) or two or more drugs can be given together (combination chemotherapy). The aim of this review was to compare whether using a more intensive regimen (more than one drug) was better than the single agent treatment for women with advanced disease. We identified 43 eligible trials (48 comparisons- as some trials tested more than one comparison). These trials included 9742 women, 55% of whom were receiving their first treatment with chemotherapy for metastatic disease. The review found a benefit for the combination chemotherapy for survival (all trials). This was also the case when trials of first-line treatment only were analysed, and whether the single agent was also included in the combination or not. Combination treatments were also associated with significantly better time to progression (time after treatment until the disease progressed) and response (whether the tumour gets smaller as a result of the treatment). Women receiving combination treatment however experienced more adverse effects of treatment including a decrease in their white cell count, increased hair loss and nausea and vomiting. For women making a decision about treatment, it should be noted that this review was not able to address the issue of whether combination regimens are more effective than sequential treatment with different single agents. Some individual trials raised the possibility that giving a multiagent regimen sequentially with immediate cross-over from one agent to the next on progression may result in survival times similar to that seen when all the agents are given together

An important consideration for women with advanced disease is the balance between the benefit of treatment and the harms or adverse effects that these treatments may have. Unfortunately only 11 trials in this review reported information relating to quality of life. In general, survival gains with combination therapy came at the cost of a significant increase in toxicity and impact on other psychological and social factors which are known to contribute to a sense of quality of life for this group of women. There were insufficient data in this review to comment on the overall impact of the two treatment options on net clinical benefit from the women's perspective. Women with advanced disease will therefore need to seek the information to allow them to make decisions about the potential benefits of additional treatments (small survival gains) in progressing metastatic disease and the impact this can have on their quality of life.

BACKGROUND

Description of the condition

Breast cancer is the most common type of cancer in women and the most common cause of cancer-death in that group. In 2000 there were over 1 million new cases and approximately 373,000 deaths from breast cancer world wide; with an age standardised death rate (ASR) of 12.51 (per 100,000). ASRs of 25 or greater were recorded that same year byfor Barbados (25.53), Belgium (26.63), Denmark (29.16), Hungary (25.21), Iceland (36.78), Ireland (25.76), Israel (26.32), Malta (28.39), the Netherlands (27.76), New Zealand (25.94), Switzerland (25.17), Uruguay (26.27) and the UK (26.81) (Ferlay 2002).

With advances over the last few decades, a greater proportion of women are being diagnosed with breast cancer at an earlier stage when curative approaches are still possible. Regardless, 20-85% of patients depending on stage, tumour biology and treatments used will go on to develop distant metastases (disease which has spread to other parts of the body) Cardoso 2002. This may be due to subclinical micrometastases despite adequate primary therapy. An additional 6-10% will present with metastatic disease at primary diagnosis (Colozza 2007). Metastatic disease is treatable but not curable. Average survival is currently between one to two years, although some women may live with the disease for many years with good quality of life (Colozza 2007 Smith 2006).

Description of the intervention

Treatment of metastatic breast cancer (MBC) with chemotherapy has undergone several distinct historical phases. Therapy with single agents was first introduced in the 1960's but these agents provided short tumour response. In the 1970's combination regimens such as CMF(cyclophosphamide, methotrexate and 5-fluoricil) were developed demonstrating further improvements in response (>40%) and time to progression. The incorporation of anthracyclines into newer generation regimens such as AC (doxorubicin and cyclophosphamide) came later in the 1980's (Nabholtz 2002). Taxanes (docetaxel, paclitaxel) emerged in the 1990's as a result of a rapid collection of data from high quality prospective randomised controlled trials involving tens of thousands of patients. Taxanes were quickly recognised as evidence based components of therapy for metastatic breast cancer, initially tested as single agents in two settings, patients with, and without prior anthracycline exposure (Crown 2004).

In terms of predictive factors (patient or tumour characteristics that help to forecast a response to a given treatment), evidence exists in the metastatic setting only for an association between response to endocrine therapy and expression of hormone receptors, and response to trastuzumab related to human epidermal growth factor receptor-2 (HER-2) status (Colozza 2007, Nabholtz 2002). Trials that have attempted to identify prognostic factors for patients who may benefit from combination chemotherapy have been conducted but only oestrogen receptor status, disease free interval and number of visceral sites have been identified as having a positive relationship (Overmoyer 2003). In endocrine sensitive disease, treatment may safely begin with endocrine therapy (Wilcken 2003) but ultimately most women with metastatic breast cancer will receive chemotherapy either because they have hormone receptor negative disease or because their disease has become refractory to endocrine therapy (Hortobagyi 1996). Currently trastuzumab is recommended at the same time as chemotherapy for patients who have not already received chemotherapy for metastatic breast cancer or given alone to patients who have already received chemotherapy for metastatic disease or if chemotherapy is not appropriate (NBCC 2007). Anthracycline combinations are frequently used as first line treatment in hormone-unresponsive MBC and taxanes are extensively used in combination with anthracyclines or when treatment with anthracyclines has failed (Martín 2007)

Generally speaking, most chemotherapeutic agents used in the treatment of cancer show a steep dose-response curve in pre-clinical studies. This has led cancer clinicians and researchers to conclude that increasing the intensity of treatment will result in an increase in the rate and duration of response, and hence to improvements in survival (Hryniuk 1987). Increased dose intensity may also come at the cost of increased toxicity. If palliation is the primary goal of treatment, and anticipated survival is limited, then toxicity and quality of life become important factors when deciding on a treatment regimen.

How the intervention might work

It is commonly thought that combining chemotherapy agents will result in regimens that are more active with improved tumour response and progression rates and hence, better overall survival.

The question of whether to use single agent chemotherapy or combinations when treating women with metastatic breast cancer however remains partially unresolved. Experience over the last thirty years suggests that the use of polychemotherapy produces a higher response rate and increased time to progression (TTP) when compared to a single agent. A systematic review by Fossati (Fossati 1998) included survival analysis of polychemotherapy agents versus single agents in 2,442 patients. This review found a significantly better complete and partial response rate associated with the combination regimens and a survival advantage (HR 0.82, 95% CI, 0.75 to 0.90).

More recently, two large individual trials have also demonstrated survival benefits for combination regimens when compared with very credible single agents, both in the post-anthracycline setting. In the first (O'Shaughnessy 2002), docetaxel plus capecitabine led to better overall survival than docetaxel alone with an improvement of 3 months in median survival and no measurable decline in quality of life. Toxicity was described as manageable, although anecdotal reports suggest this is a relatively toxic regimen and many clinicians do not use it. The second study has been presented but not yet published in the peer-reviewed literature (Albain KS 2004). Women received either paclitaxel alone (3 weekly) or with gemcitabine, and again overall survival was better, with an improvement in median survival of about 3 months. Toxicity is again described as manageable, and this is borne out by anecdotal reports.

In addition, single agent gemcitabine, capecitabine and vinorelbine have been shown to be effective for patients who have progressed during or following anthracycline treatment with response rates of 20-30%, median survival of one year and acceptable safety profiles (O'Shaughnessy 2002, O'Shaughnessy 2005).

Why it is important to do this review

Opinion is currently divided as to whether improvements in response and time to progression (TTP) necessarily correlate with an improvement in survival in this setting, or, whether combination chemotherapy is superior to the sequential use of single agent anthracyclines and taxanes (Cardoso 2002, Nabholtz 2002, O'Shaughnessy 2005).It is also not known which patients will benefit from which regimens. Combination regimens such as anthracycline/ taxane combinations are considered appropriate by some clinicians for patients with rapidly progressing visceral disease (i.e. hepatic metastases, pulmonary lymphangitic spread) followed by sequential single agent treatment (Overmoyer 2003, Seidman 2003) and others find this approach more appropriate in an adjuvant setting (Seidman 2003).

OBJECTIVES

The objective of this review was to compare single-agent chemotherapy with combination chemotherapy regimens in the management of women with metastatic breast cancer. This includes the following:

- Question 1: regimen A (drug A alone) versus drug A plus other (for example methotrexate versus cyclophosphamide, methotrexate and 5-fluorouracil)
- Question 2: regimen A (drug A alone) versus drug C plus other (for example docetaxel versus 5-fluorouracil plus vinorelbine)

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled clinical trials.

Types of participants

Included were women with advanced (metastatic) breast cancer, either newly diagnosed or recurrent. Trials including both women with metastatic disease and women with locoregionally recurrent disease were eligible for inclusion if data were provided separately for each group, or if women with isolated locoregional recurrence comprised less than 20% of the total group. There were no age restrictions.

In the protocol for this review it was proposed that trials containing women receiving first line chemotherapy (no previous chemotherapy for metastatic disease) only be included in this review. This was later changed to include subsequent lines of treatment. Hence, results are presented by treatment line (i.e. 100% first-line and all lines combined). Trials with participants with locoregional disease were not included in the analysis of 100% firstline therapy for metastatic disease.

Types of interventions

Intervention Group: any conventional chemotherapy regimen containing a combination of chemotherapeutic agents.
Comparator: any conventional single-agent chemotherapy regimen.

This includes the following:

- Question 1: regimen A (drug A alone) versus drug A plus other (for example methotrexate versus cyclophosphamide, methotrexate and 5-fluorouracil)
- Question 2: regimen A (drug A alone) versus drug C plus other (for example docetaxel versus 5-fluorouracil plus vinorelbine)

Trials where endocrine therapy was given to both treatment groups were also included as were trials that may, or may not, have specified recommended treatment upon disease progression or initial treatment failure. High dose chemotherapy regimens were excluded.

Patients with advanced disease who progress on the treatment they are randomised to receive, will often have treatment changed at the time of progression. In some instances this may involve crossing over to the other arm of the trial and in other cases may involve receiving other treatment off-study. Trials where patients crossed over to the other treatment arm at the time of progression are, therefore, included in this review and analysed according to the treatment they were first 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) are included only where data are reported for the first treatment.

Types of outcome measures

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). This is also referred to as Progression-free survival (PFS).
3. Response - the proportion of patients with a complete or partial response (Complete response is defined as complete disappearance of all measurable disease for some minimum time period. Partial response is defined as shrinkage of tumour such that shrinkage post-treatment is <50% of shrinkage pre-treatment for some minimum time period in the absence of growth of any lesion or the appearance of new lesions).
4. Quality-of-life measures (trial specific instruments)
5. Toxicity (Grade 3 or more: WHO criteria) - Toxicities of interest were nausea and vomiting, alopecia, and reduction in the level of white cell count (WCC<2000) (Leukopenia, neutropenia)

Time to treatment failure (TTF) was a planned outcome for this review. It 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. Five trials (seven comparisons) reported TTF (ANZBCTG 2001; Falkson G 1990; French Epi (A) 1991; French Epi (B) 1991; Nabholtz JM 1999;Sledge G(A) 2003; Sledge G(B) 2003) however not all trials used definitions in alignment with our pre-specified definition. This outcome was therefore not included in this review. However one trial (Sledge G(A) 2003; Sledge G(B) 2003) labelled a curve as TTF but reported the outcome as TTP. In the absence of a clear definition by the trial report, and taking into account their reporting of the data as TTP, this trial was included in the analysis for TTP.

This review also attempted to investigate treatment-related death, which for the purpose of this review is 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.

Search methods for identification of studies

Electronic searches

(a) Cochrane Breast Cancer Specialised Register

For the first full version of this review (Carrick 2005), the Specialised Register maintained by the Cochrane Breast Cancer Group was searched on 13/08/2004 (details of search strategies used by the group for the identification of studies and the procedure used to code references are outlined in the group's module http://www.mrw.interscience.wiley.com/cochrane/clabout/articles/BREASTCA/frame.html). Studies coded as 'advanced breast cancer' and 'chemotherapy' on the Specialised Register were extracted for consideration. This search was repeated on 12/11/2008 for this update.

Searching other resources

Conference Proceedings

Abstracts and posters from conferences were also included if they provided sufficient information on the results to warrant their inclusion for this review update.

The American Society of Clinical Oncology (ASCO) conference proceedings 2004 and 2007 were searched for any relevant abstracts. Only ASCO conference proceedings from 2004 and 2007 were searched as all other years are already included in the Cochrane Breast Cancer Specialised Register.

References from Published Studies

The reference lists of other related literature reviews, such as those by Fossati 1998 and Stockler 2000 were searched for the original review only.

A copy of the full article for each reference reporting a potentially eligible trial was obtained, where possible. Where this was not possible, attempts were made to contact authors to provide additional information.

Reference lists were not searched for the updated review as they had already been searched for the original review.

Unpublished Literature

Unpublished data were included if there were results available.

Data collection and analysis

Selection of studies

At least two authors (SC, SP or CT) applied the selection criteria (including the quality of randomisation) to each reference identified by the search strategy. A third reviewer resolved any discrepancies regarding eligibility or quality.

Data extraction and management

The primary outcomes were overall survival (OS) and time-to-progression (TTP)/progression-free survival (PFS) for which the hazard ratio (HR) is the most appropriate statistic. When possible, the HR and associated variances were extracted directly from the trial publication(s). If not reported the HR was obtained indirectly using the methods described by Parmar 1998 by using either other available summary statistics or by extracting data from published Kaplan-Meier curves. The hazard ratio (HR) and associated statistics were calculated, where necessary, using an Excel spreadsheet developed by the Meta-analysis Group of the MRC Clinical Trials Unit, London (Tierney 2007). 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 a cycle of treatment, and maximum follow-up was estimated based on the last reported event on the 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) minus 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 a combination regimen versus a regimen where only one chemotherapy agent was used. HRs less than 1.0 favour combination regimens and values greater than 1.0 favour the control group (single drug chemotherapy).

Response rates were analysed as dichotomous variables (complete and/or partial versus stable disease or no response) and a pooled relative risk was derived. Response has been reported based on assessable (not randomised) patients as most of the trials reported the data for this group. Random effects model was used for pooling as there was significant heterogeneity. Toxicity was analysed by extracting the total number of grade III and/or IV events and the number at risk for each trial. These were summed and used to calculate a single relative risk (with 95% confidence intervals). The specific toxicities of interest for this review were effect of chemotherapy on WCC (leukopenia and neutropenia), nausea or vomiting and alopecia.

Quality-of-life data were collated from those trials reporting it. Trials used a variety of instruments (Table 1). As a result, data were not statistically synthesised but summarised and evaluated qualitatively.
This review also attempted to investigate treatment-related deaths which, for the purpose of this review, were defined as deaths due to the toxicity of the drug and not related to disease progression. If an individual trial did not define treatment related death but used the terms "toxic death" or "lethal toxicity" then the information was included in the review.

Where multi-arm trials were included in the meta-analysis and one treatment arm was included in more than one treatment comparison, the number of events and the number of women in that arm were divided by the number of treatment comparisons. This method was used to avoid the multiple use of women in the pooled estimate of treatment effect while retaining information from each arm of the trial.

Assessment of risk of bias in included studies

Risk of bias was assessed using the Cochrane domain based evaluation.

Assessment of heterogeneity

Heterogeneity was assessed by visual inspection of the forest plots and the chi squared test and I squared statistic. A random-effects meta-analysis was used for pooling the outcomes of response and toxicity and a P value of 0.10 was used to determine statistical significance for the chi-squared test for these outcomes.

Subgroup analysis and investigation of heterogeneity

Proposed sub-group analyses (by menopausal status, hormone receptor status and disease stage) were not conducted because the information was not reported or because the data were difficult to extract from the trial reports.

Post hoc protocol amendment

Post-hoc subgroup analyses were conducted for type of regimen. In addition studies incorporating non-standard chemotherapy (high dose chemotherapy) were excluded as these are the subject of a separate review.

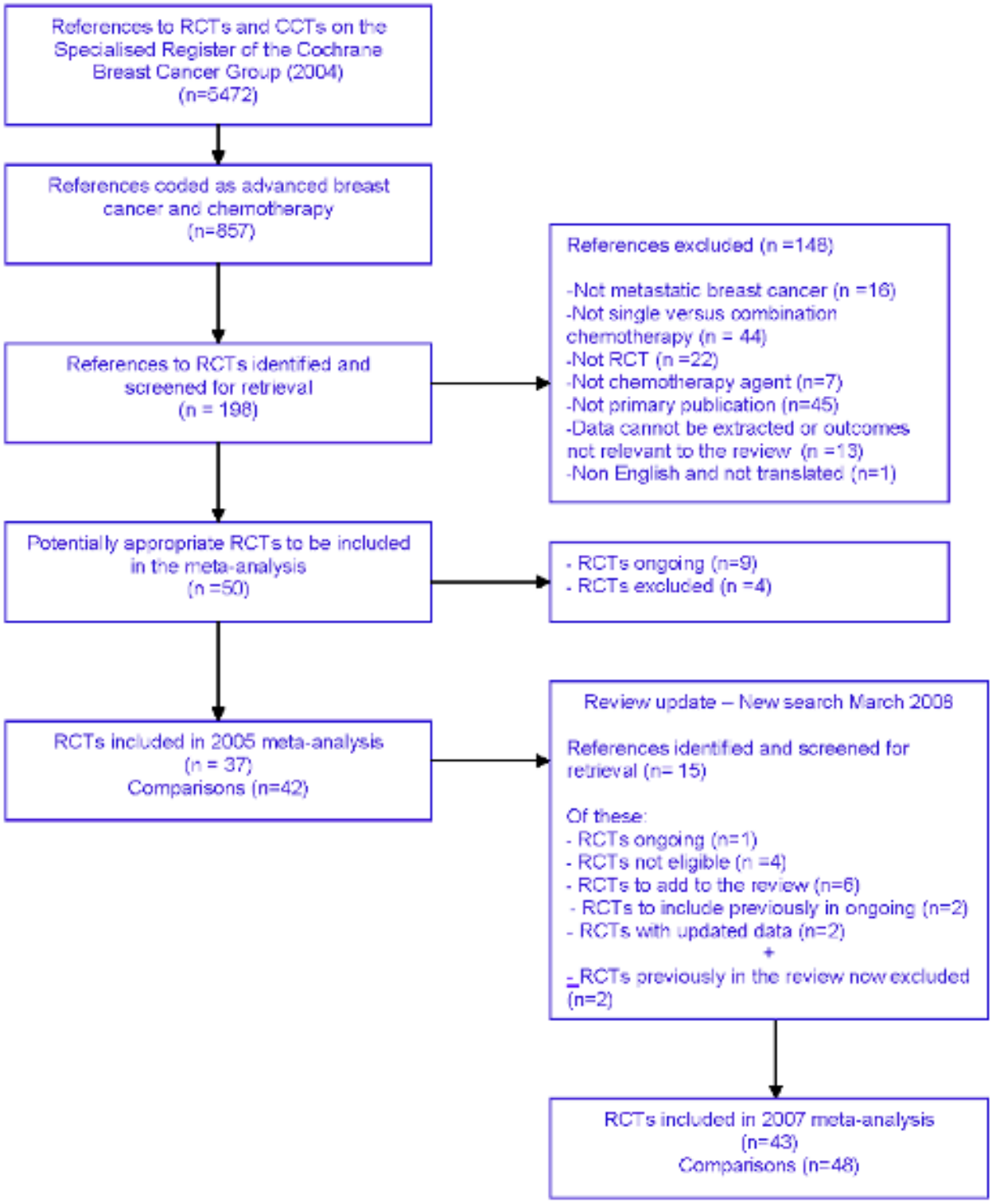
RESULTS

Description of studies

For the first review conducted in 2004, the Specialised Register of the Cochrane Breast Cancer Group contained 5,472 references of which 857 were coded as references to studies of chemotherapy and advanced breast cancer. For this search 198 were identified as potentially relevant to the review but 148 were excluded. Fifty complete papers were obtained leading to the exclusion of a further 13 references. This left a total of 37 references to trials for inclusion in the meta-analysis. Because some of the trials incorporated two comparators, 42 separate comparisons were included in the original review.

For this update, a further 15 references to trials were screened. This resulted in the inclusion of 6 new trials (Albain KS 2004, GEICAM 2007, Norris B 2000; O'Shaughnessy J 2001; Stockler M 2006, Thomas E 2008) and 2 trials which had previously been classified as 'ongoing' (Ejlertsen B 2004; Heidemann E 2004). In addition two RCTs included in the first review Keller AM 2004; Liu T 1986) were excluded on the basis of further assessment during the update. Ultimately 43 trials (yielding 48 comparisons) were included in the review update (Figure 1).

Figure 1. Quorum flow chart



A summary of the trials included in the analyses and the questions that they address can be found in Additional Figures 02 and 03. The five included trials that used two comparators are French Epi 1991; Hoogstraten 1976; Venturino 2000; Sledge 2003 and Takayama 2000. To accommodate the data-entry requirements of Review Manager, the separate comparators for these trials have been referenced as A and B in this review.

Thirty trial comparisons addressing question A were included (Ahmann DL 1974(1); Ahmann DL 1974(2); Albain KS 2004;

Andersson M 1986; Berruti D 2002; Carmo-Pereira 1980; Ejlertsen B 2004; Falkson G 1990; French Epi (A) 1991; French Epi (B) 1991; GEICAM 2007, Gundersen S 1986; Heidemann E 2004; Ingle J 1985; Ingle J 1989; Joensuu H 1998; Mouridsen HT 1977; Nielsen D 2000; Nielson D 1990; Norris B 2000; O'Shaughnessy J 2002; Rubens RD 1975; Sledge G(A) 2003; Sledge G(B) 2003; Steiner R 1983; Takayama T(A) 2000; Takayama T(B) 2000; Tashiro H 1994; Thomas E 2008, Vaughn CB 1988) .

Eighteen eligible trial comparisons addressing question B were identified **(** Ahmann DL 1974(3); ANZBCTG 2001; Bishop J 1999; Bonneterre J 2002; Canellos GP 1976; Eagan RT 1976; Erkisi M 1997; Fraser S 1993; Heidemann E 2002; Hoogstraten B(A)1976; Hoogstraten B(B)1976; Icli F 2005, Nabholtz JM 1999; O'Shaughnessy J 2001; Sjostrom J 1999; Stockler M 2006; Venturino A(A) 2000; Venturino A (B) 2000)**.**

Not all trials identified provided information on all outcomes. Please refer to Figure 2 and Figure 3 for a summary.

Figure 2. Summary of included trials with extractable data Q1

Trial ID	Survival Curve	Median survival	TTP Curve	Median TTP	Overall response	Grade III/IV Toxicity	Treatment related deaths	Sub-group
Q 1.Regimen A versus A + other								
Ahmann DL, 1974(1)	Y	Y	NR	NR	Y	NE	Nil reported	B
Ahmann DL, 1974(2)	Y	Y	NR	NR	NR	NE	Nil reported	B
Albain K 2004	Y	Y	Y	Y	Y	N/vomiting Neutropenia	N=2	D
Andersson M 1986	Y	NR	Y	Y	Y	N/vomiting	N=4	A
Berrutti D 2002	NR	NR	Y	NR	Y	N/vomiting Leukopenia	N=6	A
Carmo-Pereira J 1980	Y	Y	NR	NR	Y	N/vomiting Alopecia Leukopenia	Nil reported	C
Ejlertsen B 2004	Y	Y	Y	N	Y	N/vomiting Leukopenia	N=11	A
Falkson G 1990	Y	Y	NR	Y	Y	NR	Nil reported	B
French Epi Group (A) 1991	Y	NR	Y	NR	Y	NE	Nil reported	A
French Epi Group (B) 1991	Y	NR	Y	NR	Y	NE	Nil reported	A
GEICAM 2007	N	Y	Y	Y	Y	N/Vomiting Alopecia Neutropenia	N=2	No sub-group
Gunderson S 1986	Y	NR	NR	NR	Y	N/vomiting Alopecia	Nil reported	A
Heidemann E 2004	Y	Y	Y	Y	Y	N/Vomiting Leukopenia	Nil reported	A
Ingle J 1985	Y	Y	Y	Y	Y	N/vomiting Leukopenia alopecia	N=3	A
Ingle J 1989	Y	Y	Y	Y	Y	N/vomiting Leukopenia	N=3	A
Joensuu H 1998	Y	Y	Y	Y	Y	N/vomiting Alopecia Leukopenia	Nil reported	A
Mouridsen H 1977	NR	NR	NR	NR	Y	Alopecia Leukopenia	Nil reported	B
Nielson D 2000	Y	Y	Y	Y	Y	NR	N=6	A
Nielson D 1990	Y	Y	Y	Y	Y	NE	N=4	A
Norris B 2000	Y	Y	N	Y	Y	N/vomiting Alopecia Granulo-cytopenia	N=3	A
O'Shaughnessy J 2002	Y	Y	Y	Y	Y	N/vomiting Alopecia Neutropenia	N=5	D
Rubens RD 1975	Y	NR	NR	NR	Y	NR	N=1	B
Sledge G (A) 2003	Y	Y	Y	Y	Y	N/vomiting Leukopenia	N=8	A
Sledge G (B) 2003	Y	Y	Y	Y	Y	Leukopenia Vomiting	N=6	D
Steiner R 1983	NR	Y	NR	NR	Y	N/vomiting Alopecia Leukopenia	N=2	A
Takayama T (A) 2000	Y	NE	Y	NE	Y	N/vomiting WCC	NE	C
Takayama T (B) 2000	Y	NE	Y	NE	Y	N/vomiting WCC	NE	B
Tashiro H 1994	Y	Y	N	NR	Y	N/vomiting Leukopenia Alopecia	Nil reported	C
Thomas E 2008	N	N	Y	Y	Y	N/vomiting Alopecia Leukopenia	N=15	No sub-group
Vaughn CB 1988	Y	Y	Y	Y	Y	N/vomiting Alopecia Leukopenia	N=1	A

NR – Not reported, NE – Not extractable

Figure 3. Summary of included trials with extractable data Q2

Trial ID	Survival Curve	Median survival	TTP Curve	Median TTP	Overall response	Grade III/IV Toxicity	Treatment related deaths	Sub-group
Q 2. Regimen A versus Regimen C								
Altmann DL, 1974(3)	Y	Y	NR	NR	NR	NR	Nil reported	E
ANZBCTG 2001	NR	NR	NR	NR	Y	N/vomiting Leukopenia Alopecia	Nil reported	E
Bishop J 1999	Y	Y	Y	Y	Y	N/vomiting Alopecia Leukopenia	NR	F
Bonneterre J 2002	Y	Y	Y	Y	Y	N/vomiting Neutropenia Alopecia	N=6	F
Canellos JP 1976	Y	Y	NR	NR	Y	Leukopenia	Nil reported	G
Eagan RT 1976	NR	NR	NR	NR	Y	Leukopenia Alopecia	N=1	G
Erksi M 1997	NR	Y	NR	NR	Y	NR	N=1	G
Fraser S 1993	Y	Y	NR	Y	Y	NE	Nil reported	E
Heidemann E 2002	Y	Y	Y	Y	Y	N/vomiting Alopecia	Nil reported	NA
Hoogstraten B (A) 1976	NR	NR	NR	NR	Y	Leukopenia Alopecia	NE	E
Hoogstraten B (B) 1976	NR	NR	NR	NR	Y	Leukopenia Alopecia	NE	E
Icli F 2005	Y	Y	Y	Y	Y	Nausea Leukopenia	N=6	F
Nabholtz JM 1999	Y	Y	Y	Y	Y	NR	N=7	F
O'Shaughnessy J 2001	Y	Y	Y	Y	Y	N/vomiting Alopecia Neutropenia	N=3	G
Sjostrom J 1999	Y	Y	Y	Y	Y	Nausea Alopecia	N=4	F
Stockler M 2006	Y	Y	Y	Y	Y	Neutropenia/N/ Vomiting Alopecia	Nil reported	G
Venturini A (A) 2000	NR	Y	NR	Y	Y	Leukopenia Alopecia	Nil reported	G
Venturino A (B) 2000	NR	Y	NR	Y	Y	Leukopenia Alopecia	Nil reported	G

NR – Not reported, NE – Not extractable

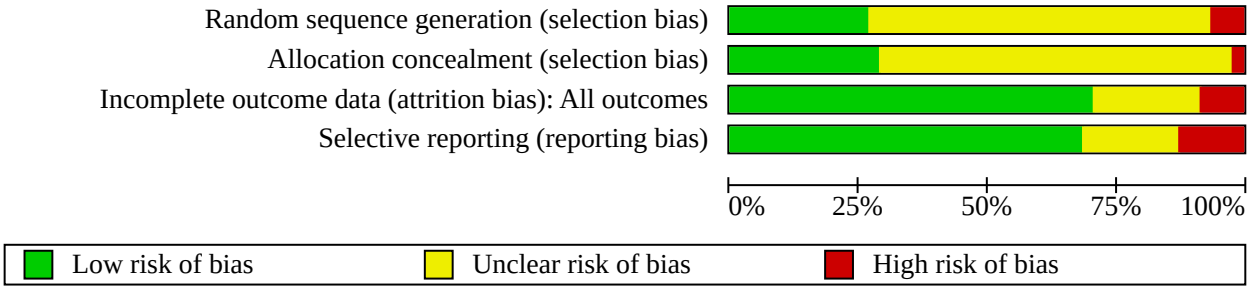
Risk of bias in included studies

Each study was reviewed according to its design and how the study was conducted to assess the potential for bias. Trial quality was assessed using the Cochrane Risk of Bias tables. This assessment was done retrospectively in this update for all 43 trials (48 comparisons). The items assessed were:
- Sequence generation
- Allocation concealment
- Incomplete outcome data
- Selective outcome reporting

Blinding was not assessed. Given the nature of the interventions used in the management of breast cancer it is not possible, nor practical, to expect blinding of the intervention or outcome assessment.

It was not possible to accurately assess the method of randomisation or allocation concealment used in most studies due to a lack of information in the published articles. Please refer to Figure 4

Figure 4. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Effects of interventions

For ratios of treatment effects for time-to-event outcomes HRs less than 1.0 favour combination regimens and values greater than 1.0 favour the control group (single drug chemotherapy).

For ratios of treatment effects for response and toxicity RRs greater than 1.00 favour combination regimens.

When interpreting the plots for each question and subgroup, readers may want to refer to the summary of included trials (Figure 5, Figure 6, Figure 2and Figure 3), particularly given the variety of the combination regimens assessed.

A total of 9742 women were randomised to 43 eligible trials (48 comparisons). Of these, the majority had histologically-confirmed metastatic breast cancer, with 5354 (55%) women receiving first-line chemotherapy. Of the women randomised, data were available for overall survival for 82%, response for 93% and time to progression for 67%.

Figure 5. Summary of regimens Q1

Trial ID	Arm 1 (single)	Arm 2 (combined)	% Firstline for MBC	Accrual*
Ahmann DL 1974 (1)	CCNU	F+ C+ P +/- V[1]	100%	43
Ahmann DL 1974 (2)	I	F+ C+ P +/- V[1]	100%	40
Albain K 2004	PACL	PACL + Gem	100%	529
Andersson 1986	A	A+ MMC	22.5%	89
Berrutti D 2002	E	E+ CDDP	100%	185
Carmo-Pereira J 1980	F	CMFVP	100%	135
Ejlertsen B 2004	E	E + V[3]	100%	387
Fallson G 1990	CTX	CMFVP	100%	111
French Epi Group (A) 1991	E	FEC 50	100%	275
French Epi Group (B) 1991	E	FEC 75	100%	277
Geicam 2007	V[2]	V[3] +Gem	36%	252
Gunderson S 1986	A	V[1]+A+C	100%	128
Heidemann E 2004	M	M+TXT	100%	179
Ingle J 1985	A	A + MTL	100%	158
Ingle J 1989	A	A+ V[1]+ MMC	100%	185
Joensun H 1998	E	E+C+F	100%	303
Mourisden H 1977	C	CMFVP	100%	55
Nielsen D 2000	E	E+ CDDP	100%	155
Nielsen D 1990	E	E+V[2]	48%	143
Norris B 2000	A	A + V[3]	75%	303
O'Shaughnessy J 2002	TXT	TXT + CCB	33%	511
Rubens RD 1975	C	CMFV[2]P	100%	99
Sledge G (A) 2003	A	A+ PACL	71%	367
Sledge G (B) 2003	PACL	A+ PACL	71%	364
Steiner R 1983	A	A + V[1]	100%	119
Takayama T (A) 2000	F	F + C	Unclear	111
Takayama T (B) 2000	C	F + C	Unclear	109
Tashiro H 1994	FT	UFT + placebo	86%	60
Thomas E 2008	IX	IX + CCB	85%	752

Figure 5. (Continued)

Thomas E 2008	IX	IX + CCB	85%	752
Vaughn CB 1988	A	A+ETO	Unclear	122

* Includes numbers accrued and randomised where available or assessable numbers if randomised not provided

Figure 6. Summary of regimens Q2

Trial ID	Arm 1 (single)	Arm 2 (combined)	% Firstline for MBC	Accrual*
Ahmann DL, 1974(3)	A	F+C+P+/-V[1]	100%	48
ANZBCTG 1994	MZA	CMFP	100%	391
Bishop J 1999	PACL	CMFP	100%	209
Bonnetterre J 2002	TXT	F + V[3]	34%	178
Canellos JP 1976	L-PAM	CMF	100%	184
Eagan RT 1976	ETO	V[1]+A	Assumed 2nd line	39
Erksi M 1997	ETO	FAC	48%	60
Fraser S 1993	E	CMF	Unclear	40
Heidemann E 2002	MZA	FEC	100%	260
Hoogstraten B (A) 1976	A	CMFVP (Intermittent)	100%	177
Hoogstraten B (B) 1976	A	CMFVP- (Weekly)	100%	185
Ioli F 2002	PACL	ETO+CDDP	20%	201
Nabholtz JM 1999	TXT	MMC +V[2]	38%	392
O'Shaughnessy J 2001	CCB	CMF	100%	95
Sjostrom J 1999	TXT	M+ F	First and second line	283
Stockler M 2006	CCB	CMF	100%	323
Venturino A 2000	V[3]	LEUC+F	N – all second line	66
Venturino A 2000	V[3]	MZA+LEUC+F	N – all second line	66

Includes numbers accrued and randomised where available or assessable numbers if randomised not provided

Abbreviations

A -Doxorubicin; C-Cyclophosphamide; CCB – Capecitabine; CCNU - lomustine; CDDP – cisplatin; CMFVP– cyclophosphamide, methotrexate, fluorouracil; vincristine ; prednisone: DBD -mitolactol; E-epirubicin; Ecyclof – epirubicin, cyclophosphamide, fluorouracil; ETO – etoposide/VP-16; F – fluorouracil; I - ifosamide; Iphosphamide (cyclophosphamide analogue); Gem – Gemcitabine ; LEUC – leucovorin; *L-PAM - L-phenylalanine mustard/Melphalan; M – methotrexate; MMC – mitomycin; MTL – mitolactol; MZA – mitoxantrone; O-oophorectomy; P-prednisone/prednisolone; PACL-paclitaxel; PLD - Peglyated liposomal doxorubicin; *TXT - docetaxel; FT-5 Flouro – 1 (Tetrahydro-2furyl) – uracil (analogue of 5FU) –Tegafur; *UFT – tegafur, uracil; V[1]- vincristine; V[2]- vinblastine; V[3]- vinorelbine; V[1]- vindesine

Overall survival Sufficient data were available from 36 of the 48 comparisons (reporting an estimated 5156 deaths in 7147 women) to enable a HR for overall survival for a single chemotherapy agent versus combination regimens to be calculated. There was a statistically significant difference in survival, favouring combination regimens, with a HR of 0.88 (95% CI 0.83 to 0.93, p<0.00001). There was no statistically significant heterogeneity across the trials (chi squared = 48.56, 35 df, p=0.06).

The results for overall survival were similar when the analysis was limited to the 21 trials in women receiving first-line chemotherapy involving an estimated 2782 deaths in 3982 women (HR 0.88, 95% CI 0.81 to 0.94, p= 0.0005) however there was statistically significant heterogeneity (chi squared = 39.06, 20 df, p=0.007, I^2=49%).

Question 1 - Regimen A (single) versus Regimen A +other Twenty five of the 28 eligible comparisons provided information on survival for question 1 (reporting an estimated 3647 deaths in 4935 women). There was a statistically significant difference in survival, favouring combination regimens, with a HR of 0.88 (95% CI 0.83 to 0.94, p = 0.0002). There was no significant heterogeneity across the trials (chi squared =27.04, 24 df, p=0.30).

Question 2 - Regimen A (single) versus Regimen C Eleven of the 18 eligible comparisons provided information on overall survival for Question 2. There was no statistically significant difference in survival between the regimens with a HR of 0.86 (95% CI 0.78 to 0.96, P=0.005). There was statistically significant heterogeneity (chi squared =21.42,10 df, p=0.02; I^2=53%).

Single agent taxane versus all combinations Eight comparisons (2646 women)**,** provided information on overall survival where a single agent taxane was compared to a combination regimen containing any chemotherapy agent. There was a statistically significant benefit in favour of the combination regimens with a HR of 0.82 (95% CI 0.75 to 0.89, P<0.00001). There was no evidence of heterogeneity (chi squared = 7.40, 7 df, p=0.39).

Single agent anthracycline versus all combinations Sixteen comparisons (2985 women), provided information on overall survival where a single agent anthracycline was compared to a combination regimen containing any chemotherapy agent. There was no statistically significant benefit between the groups with a HR of 0.94 (95% CI 0.86 to 1.02, P=0.15). There was no evidence of heterogeneity (chi squared = 8.14,15 df, p=0.92).

Time to progression (TTP) Sufficient data were available from 27 comparisons (reporting an estimated 5480 events in 6501 women) to enable a HR for time to progression to be calculated. There was a statistically significant difference in favour of the combination regimens with a HR of 0.78 (95% CI 0.74 to 0.82, p<0.00001). There was statisticially significant heterogeneity for this outcome (chi squared = 71.88, 26 df, p<0.00001; I^2=64%).

Limiting the analysis to the 13 comparisons of first-line chemotherapy,with an estimated 2558 deaths in 3201 women produced similar results. There was a statistically significant benefit in favour of the combination regimens with a HR of 0.87 (95% CI 0.81 to 0.94, p=0.0003). There was significant heterogeneity (chi squared =26.36,12 df, p=0.01; I^2=54%).

Question 1 - Regimen A (single) versus Regimen A +other Eighteen of the 30 comparisons provided information on time to progression for question 1. Data from the 4521 women randomised to these comparisons yielded statistically significant differences in favour of the combination regimens over single-agent treatment with a HR of 0.76 (95% CI 0.71 to 0.80, p<0.00001). There was no evidence of significant heterogeneity (chi squared =20.96, 17 df, p=0.23).

Question 2 - Regimen A (single) versus Regimen C
Nine of the 18 comparisons provided information on time to progression for question 2. Data from the 1980 women randomised to these comparisons showed a statistically significant difference favouring combination regimens over single-agent treatment with a HR of 0.85 (95% CI 0.78 to 0.93, p=0.0003). There was significant heterogeneity (chi squared =46.56, 8 df, p<0.00001; I^2=83%).

Single agent taxane versus all combinations
Seven comparisons (2302 women) provided information on time to progression for single agent taxane compared to a combination regimen containing any chemotherapy agent. There was a statistically significant benefit in favour of the combination regimens with a HR of 0.72 (95% CI 0.67 to 0.79, P<0.00001). There was significant heterogeneity (chi squared = 27.74,6 df, p=0.0001; I^2=78%).

Single agent anthracycline versus all combinations
Thirteen comparisons (2352 women), provided information on time to progression where a single agent anthracycline was compared with a combination regimen containing any chemotherapy agent. There was a statistically significant difference in favour of the combination regimens with a HR of 0.82 (95% CI 0.75 to 0.89, P<0.00001). There was no evidence of heterogeneity (chi squared =13.19, 12 df, p=0.36).

Response
Data from 46 of the 48 comparisons (9044 assessable women) were available to enable a relative risk for overall tumour response to be calculated. It is recognised that there were some differences in the definition of response across (but not within) trials. There was a statistically significant difference in favour of combination regimens with a RR of 1.29 (95% CI 1.14 to 1.45, p<0.0001) for assessable patients. There was significant heterogeneity across trials (chi squared =177.93, 45 df, p<0.00001, I^2 =75%). Similarly, if the analysis was limited to the 4767 assessable women in the 25 first-line comparisons, there was a statistically significant difference in favour of combination regimens with a RR of 1.35 (95% CI 1.16 to 1.56, p<0.0001). There was significant heterogeneity across trials (chi squared = 86.05, df 24, p<0.00001, 1^2 =72%).

Question 1 - Regimen A (single) versus Regimen A +other Twenty nine of 30 comparisons eligible for question 1 provided information on response. Based on the 6102 assessable women, there was a statistically significant difference in favour of combination regimens with a RR of 1.37 (95% CI 1.20 to 1.56, p<0.00001). Significant heterogeneity was seen across the trials (chi squared =99.40, 28 df, p<0.00001, 1^2 = 72%).

Question 2 - Regimen A (single) versus Regimen C
Seventeen of 18 comparisons eligible for question 2 provided information on response. Based on the 2942 assessable women, there was no statistically significant difference between either regimens with the RR being 1.13 (95% CI 0.87 to 1.47, p=0.37). Significant heterogeneity was seen across the trials (chi squared =74.69, 16 df, p<0.00001, 1^2 = 79%).

Single agent taxane versus all combinations
Eight comparisons (2578 women), provided information on response for single agent taxane compared to a combination regimen containing any chemotherapy agent. There was no statistically significant benefit in between regimens with a RR 1.03 (95% CI 0.72 to 1.48, P=0.87). There was evidence of heterogeneity (chi squared = 65.32, 7 df, p<0.00001, I^2 = 89%).

Single agent anthracycline versus all combinations
Twenty comparisons (3798 women), provided information on response where a single agent anthracycline was compared with a combination regimen containing any chemotherapy agent. There was a modest although statistically significant difference in favour of the combination regimens with a RR of 1.19 (95% CI 1.06 to 1.34, P = 0.003). There was evidence of heterogeneity (chi squared = 38.87, 19 df, p=0.005, I^2 = 51%).

Toxicity Of the 48 eligible comparisons, 36 provided some data on grade 3/4 toxicities of interest (WCC, alopecia and nausea and vomiting). Please refer to Figure 2; Figure 3. Of these, 35 comparisons reported on WCC (7810 assessable women), 21 comparisons on alopecia (4818 assessable women) and 30 comparisons on nausea and vomiting (7487 assessable women).

Overall, combination chemotherapy was associated with a statistically significant detrimental effect on WCC with a RR of 1.49 (95% CI 1.24 to 1.79, p<0.0001). There was evidence of heterogeneity (chi squared = 607.34, 34 df, p< 0.00001, I^2 = 94%)

There was no statistically significant difference between the groups for alopecia (RR 1.12, 95% CI 0.81 to 1.54, p=0.48) or for nausea and vomiting (RR 1.29, 95% CI 0.96 to 1.74, p=0.09). There was evidence of heterogeneity (chi squared = 394.44, 20 df, p< 0.00001, I^2 = 95%) and (chi squared = 172.40, 29 df, p< 0.00001, I^2 = 83%) respectively.

There was marked evidence of heterogeneity for overall toxicity and analysis of toxicity data addressing questions 1 and 2.

Question 1 - Regimen A (single) versus Regimen A +other For question 1, 21 comparisons includeding data on WCC (5164 assessable patients), 11 reported on alopecia (2778 assessable patients) and 20 reported on nausea and vomiting (5149 assessable patients). Based on these trials combination chemotherapy was associated with a statistically significant detrimental effect on WCC (RR 1.69, CI 1.30 to 2.20, p=0.0001) and increased alopecia (RR 2.18, 95% CI 1.10 to 4.30, p=0.031). There was no statistically significant difference between single agent and combination chemotherapy for nausea and vomiting (RR 1.16, 95% CI 0.81 to 1.65, p=0.41).

Question 2 - Regimen A (single) versus Regimen C
For question 2, 14 comparisons reported on WCC (2646 assessable patients), 10 comparisons reported on alopecia (2040 assessable patients), and 10 comparisons (2338 assessable patients) reported on nausea and vomiting. There was no statistically significant difference for WCC (OR 1.27, 95% CI 0.93 to 1.74, p=0.13). Combination chemotherapy was associated with significantly more nausea and vomiting toxicity (RR 1.79, 95% CI 0.93 to 3.43, p=0.08). For alopecia however, single-agent chemotherapy was associated with more toxicity (RR 0.63, 95% CI 0.31 to 1.27) but this did not reach significance.

Treatment-related death

Twenty four comparisons reported deaths during their respective trial periods. These were variously defined but were included in this review if the trial reported death due to the toxicity of the drug and not to disease progression, "toxic death", "lethal toxicity" or "treatment related death". Seventeen comparisons reported data for this outcome for question 1 and seven comparisons for question 2.
For trials reporting treatment related or sudden/unexplained death, 57 deaths occurred in the single agent arms and 53 in the combination arms. There was no statistically significant difference between the single agent and the combination regimens overall (RR 1.09, 95% CI 0.72 to 1.66, p = 0.83). There was no evidence of heterogeneity.

Of the trials reporting treatment-related death in their single-agent arms, eleven comparisons (Andersson M 1986; Berruti D 2002; Ejlertsen B 2004; Ingle J 1985; Ingle J 1989; Nielson D 1990; Nielsen D 2000; Norris B 2000; Sledge G(A) 2003; Steiner R 1983; Vaughn CB 1988) involved the use of anthracyclines (29 deaths), and seven (Albain KS 2004; Bonneterre J 2002; Icli F 2005; Nabholtz JM 1999; O'Shaughnessy J 2002; Sjostrom J 1999; Sledge G(B) 2003) involved trials of taxanes (18 deaths).
There was also no difference when single-agent chemotherapy was tested against combination therapy not containing that agent (RR 0.91, 95% CI 0.41 to 2.04, p=0.83), or when the single-agent was also used in the combination regimen (RR 1.14, 95% CI 0.69 to 1.88, p= 0.61).

Quality of life (QoL) A total of 11 trials (yielding 12 comparisons) (Albain KS 2004; ANZBCTG 2001; Bishop J 1999; Fraser S 1993; Heidemann E 2002; Joensuu H 1998; Nabholtz JM 1999; Norris B 2000; O'Shaughnessy J 2002; Sledge G(A) 2003; Sledge G(B) 2003; Sjostrom J 1999) had QoL as a major end point (Table 1).

A variety of QoL instruments were used including: LASA, Spitzer, Nottingham Health Profile (NHP), WHO Analogue and Satisfaction Scales Questionnaire, Brunners Score, Rotterdam Symptom Checklist (RSCL), FACT-B and the EORTC QLQ-C30 Global Health Score. The QoL indicators for patients typically assessed were mood, pain, nausea and vomiting, diarrhoea, hair loss, loss of appetite and social functioning. Two trials (Bishop J 1999: ANZBCTG 2001) also rated clinician assessment of the patients QoL using the Spitzer quality-of-life index.

Five trials reported some statistically significant differences between the treatment arms. Only one trial (Albain KS 2004) reported a statistically significant advantage in global QoL. Participants in this trial recorded a significantly and consistently better global QoL for the single drug arm (paclitaxel). In two trials (Heidemann E 2002: Joensuu H 1998), better QoL was associated with single-agent chemotherapy. Heidemann 2002 reported that patients receiving mitoxantrone reported less hair loss, nausea and vomiting. Patients in the Joensuu 1998 trial treated with epirubicin showed no difference in psychological dimensions of QoL but reported less physical distress and nausea at 6 months and at other assessable points during the trial. Two trials (Nabholtz JM 1999: ANZBCTG 2001) reported results favouring both single and combination regimens. Nabholtz JM (1999) found a significant difference in QoL for patients in the docetaxel arm in terms of nausea and vomiting and loss of appetite but for patients in the mitomycin plus vinblastine arm for role and social functioning. The authors also concluded that as patients with the poorest health did not complete the QoL questionnaires, QoL might be

overestimated in both groups. In ANBCTG (2001) patients in the combination arm (CMFP) reported better QoL for the first three months for pain, mood, and nausea and vomiting but worse QoL for hair loss. Results were similar overall. Although O'Shaughnessy J 2002 found no statistically significant differences, there was a trend towards less deterioration in the global score for the combination arm (docetaxel and capecetibine).

Subgroup analyses

The eligible studies identified involved a variety of different drugs, doses and regimens. Prior to pooling the results of studies, and blind to the results of individual studies, two medical oncologists (JS and NW) who were not involved in assessing eligibility or data extraction, were asked to determine a clinically meaningful way of grouping studies relative to the number and quality of eligible trials. They were provided with details of the drugs, dosages and schedules compared in each trial.

Four sub-groups relating to question 1 were subsequently analysed and three sub-groups relating to question 2.

Question 1. Addition of a drug to a chemotherapy regimen: Twenty eight comparisons compared a single drug with a combination regimen that included the same drug. An analysis was done for the pooled trials and by the following sub-groups.

I.Subgroup A: single anthracycline versus anthracycline plus other
II.Subgroup B: single alkylating agent versus alkylating plus other
III.Subgroup C: single antimetabolite agent versus antimetabolite plus other
IV.Subgroup D: single taxane agent versus taxane plus other

Sub Group A: single anthracycline versus anthracycline plus other

Fifteen trials (16 comparisons) compared a single anthracycline with an anthracycline-containing regimen. Of these, 6 trials (7 comparisons) compared epirubicin with an epirubicin-containing regimen and 7 trials compare doxorubicin with a doxorubicin-containing regimen (Figure 5; Figure 2).

Overall survival

Data from fourteen comparisons reporting an estimated 2043 deaths in 2897 women, contributed to the calculation of a HR for overall survival. There was no evidence of a difference in favour of either regimen with a HR of 0.95 (95% CI 0.87 to 1.04, p= 0.25) and no heterogeneity (chi squared = 4.53, 13 df, p= 0.98).

Time to progression (TTP)

Twelve comparisons reported on TTP. Of these, seven compared epirubicin with a epirubicin containing regimen and four compared doxorubicin with a doxorubicin containing regimen. The pooled data (from 2312 randomised women) showed a statistically significant difference between the regimens in favour of combination regimens with a HR of 0.82 (95% CI 0.0.75 to 0.89, p<0.00001). There was no heterogeneity (chi squared = 11.46, 11 df, P= 0.41).

Response

For the 16 comparisons, there was a statistically significant difference between regimens for response in favour of the combination regimens with an RR of 1.15 (95% CI 1.02 to 1.31, p=0.03). There was evidence of significant heterogeneity (chi squared =31.87, 15 df, p=0.007; I^2=53%).

Sub Group B: Single alkylating agent versus alkylating + other

Six comparisons compared a single alkylating agent with an alkylating-containing regimen.

Overall survival

Five comparisons (reporting an estimated 293 deaths in 375 women) enabled a HR for overall survival to be calculated. There was no evidence of a difference in favour of either regimen with a HR of 0.91 (CI 0.72 to 1.15, p=0.45) and no heterogeneity (chi-squared = 1.31, 4 df, p=0.86).

Time to progression

Only one comparison (Takayama T(B) 2000) reported time to progression (HR of 0.55, CI 0.36 to 0.84, p= 0.006).

Response

Five comparisons reported data on response with a statistically significant difference between regimens in favour of the combination regimens with an OR of 1.99 (95% CI 1.31 to 3.04, p= 0.001). There was evidence of heterogeneity (chi-squared =11.97, 4 df, p= 0.02).

Sub Group C: Single antimetabolite agent versus antimetabolite + other

Three trials compared a single antimetabolite agent with an alkylating containing regimen. All three compared fluorouracil and a fluorouracil-containing regimen (see Figure 02 and 04).

Overall survival

The pooled survival data (reporting an estimated 196 deaths in 279 women) suggested a statistically significant benefit in favour of combination regimens with an HR of 0.62 (CI 0.46 to 0.82, p= 0.0009). There was significant heterogeneity (chi-squared =8.15, 2 df, p= 0.02). A HR of 0.62 represents a 38% reduction in the risk of death for women on the antimetabolite-containing regimen compared with women receiving the antimetabolite.

Time to progression

Only one trial (Takayama T(A) 2000) reported time to progression (HR of 0.84, CI 0.54 to 1.28, p= 0.41).

Response

The three trials reporting response suggest a statistically significant benefit in favour of the combination regimens (RR of 2.95, 95% CI 1.92 to 9.62, P<0.00001) with no heterogeneity (chi squared =2.26, 2 df, p= 0.32, I^2=11%).

Sub Group D: Single taxane agent versus taxane + other

Three comparisons reporting on 1407 randomised women, compared single taxane with a taxane-containing regimen (Albain KS 2004; O'Shaughnessy J 2002;Sledge G(B) 2003).

Overall survival

There was a significant difference in survival between the two arms (HR 0.81, 95% CI 0.72 to 0.91 p=0.0004) and no significant heterogeneity (chi squared = 2.10, 2 df, p=0.35).

Time to progression (TTP)

Two comparisons reported a statistically significant difference in favour of the combination arm for TTP (HR 0.69, 95% CI 0.61 to 0.78, p<0.00001) (Albain KS 2004; O'Shaughnessy J 2002). There was no heterogeneity.

Response

The pooled data for response suggested a statistically significant benefit in favour of the combination regimen (RR of 1.52, 95% CI 1.26 to 1.83, p<0.0001) There was no evidence of heterogeneity (chi-squared =3.13, 2 df, p=0.21)

2. Grouped by question 2: Regimen A versus C + other Eighteen comparisons compared a single drug with a combination regimen that did not include that drug. An analysis was done for the pooled trials and by the following sub-groups.
I.Subgroup E: single anthracycline agent versus non-anthracycline combination regimen
II.Subgroup F: single taxane versus non taxane, non-anthracycline containing combination regimen
III.Subgroup G: single non-taxane, non-anthracycline agent versus other combination regimen

Sub Group E: single anthracycline agent versus non-anthracycline combination regimen
Five comparisons compared a single antimetabolite agent with an alkylating containing regimen (see Figure 03).

Overall survival
The pooled survival data from two comparisons showed a statistically significant benefit in favour of the combination regimen (HR 0.57, CI 0.33 to 0.98, p=0.04). There was no heterogeneity (chi squared =0.33, 1 df, p=0.56).

Time to progression (TTP)
Only one trial (Fraser S 1993) reported time to progression (HR 0.52, CI 0.26 to 1.02, p=0.06)

Response
Pooling data from four comparisons with 714 assessable women suggested a statistically significant benefit in favour of combination regimens (RR 1.42, CI 1.15 to 1.76, p=0.001). There was no significant heterogeneity (chi squared = 2.78, 3 df, p=0.43).

Sub Group F: single taxane versus non taxane, non anthracycline containing combination regimen
Five trials compared a single taxane with non-taxane combination regimens (964 deaths of 1262 women).

Overall survival
The pooled data showed a statistically significant survival benefit for the combination regimens with a HR of 0.83 (95% CI 0.73 to 0.95, p=0.005) and no significant heterogeneity (chi squared =5.20, 4 df, p=0.27).

Time to progression (TTP)
The pooled data for time-to-progression suggested a statistically significant benefit in favour of the combination regimen with an HR of 0.75 (95% CI 0.67 to 0.84, p<0.00001). There was statistically significant heterogeneity (chi squared =26.55, 4 df, p<0.0001; I^2=85%).

Response
There was no difference between the groups for response (RR 0.80, CI 0.48 to 1.33, p=0.001) with marked evidence of heterogeneity (chi squared =32.11, 4 df, p<0.00001; I^2=88%).

Sub Group G: single non-taxane, non-anthracycline agent versus other combination regimen

Overall survival
Survival data were available from three comparisons (Canellos GP 1976; O'Shaughnessy J 2001; Stockler M 2006) and showed no difference between the groups. There was statistically significant heterogeneity (chi squared =10.18, 2 df, p=0.006; I^2=80%).

Time to progression (TTP)
This outcome was reported by two comparisons (O'Shaughnessy J 2001; Stockler M 2006) and showed no difference between the groups. There was no significant heterogeneity.

Response There was no statistically significant advantage for either group in regard to tumour response with RR=1.28, 95% CI 0.79 to 2.08, p=0.31) with evidence of significant heterogeneity (chi squared =17.72, df 6, p=0.007; I^2=66%).

DISCUSSION

It is generally thought that combining chemotherapy agents will result in regimens with superior tumour response and progression and improved overall survival.

The overall survival data analysed for this review, based on 7147 randomised women (5168 deaths), showed a statistically significant benefit for the use of combination chemotherapy regimens compared with single agent regimens (HR 0.88; 95% CI 0.83 to 0.93, p<0.00001). Results were very similar for overall survival for women receiving first-line chemotherapy and for the analysis of first-line treatment where the single agent was also included in the combination regimen. Where the single agent was not included in the combination regimen for first-line treatment there was no significant difference between the groups. However one trial, (Stockler M 2006), showed a survival benefit in favour of the single agent (capecitabine). It is possible that this was due to better tolerability (evident from QoL and toxicity data) than with CMF. Three times as many participants were still taking the single agent after twelve months in this trial.

Combination regimens also prevailed in the analysis of a single agent taxane versus any combination (HR 0.82; 95% CI 0.75 to 0.89, p<0.00001), with no difference being shown between the groups for the analysis of single agent anthracycline. The failure to show a difference in this case may be due to prior exposure to anthracyclines either in the metastatic or adjuvant setting. For both of these comparisons there was no statistically significant heterogeneity.
Combination regimens were also associated with better time to progression and significantly improved response rates. The addition of chemotherapy agents to the same single-agent cytotoxic generally created a more intense regimen and resulted in a greater anti-tumour response, and toxicity related to alopecia and reduced white cell count.

Subgroup analyses by class did not find any advantage for single agents. When added to a regimen, taxane appeared to confer an advantage compared to its use as a single agent. The addition of anthracycline to a regimen appeared to offer a statistically significant benefit for time to progression and response over anthracycline given alone although there was no difference between them for overall survival. The sub-group analyses should however be interpreted with some caution given the smaller number of patients available in each subgroup, and the potential for confounding. For example, this review has not been able to take into consideration that some women will have been pre-treated

(increasingly in an adjuvant setting or for metastatic disease) with a taxane or anthracycline. In addition some regimens in this review used agents which are no longer considered standard treatment and which could be regarded as suboptimal chemotherapy - regimens containing mitomycin, vinblastine, and fluorouracil for example.

Increased toxicity, namely nausea and vomiting, alopecia and reduction in white cell count was consistently associated with combination regimens. This is not unexpected given the range of combinations and levels of activity. This review included trials published from the late 1970s to the present and as such reflect a wide variation in the management of side effects including dose reduction, anti-emetics and growth factor support. Rates of toxic or treatment related death were similar in both groups (57 deaths in the single agent arms and 53 in the combination regimen arms).

Considerable heterogeneity was evident across the various time to progression and response analyses. This is likely to reflect clinical diversity of the participants (menopausal status, hormone receptor status, disease stage and HER2 status) and interventions (the varying efficacy of the comparator regimens, the different agents, dosages and schedules) leading to an intervention effect which was different in different trials. An attempt was made to account for the clinical heterogeneity by grouping the trials according to sub-groups reflecting common treatment practices however many subgroups were then too small for meaningful analysis.
The findings in relation to quality of life offer mixed results and our observations are based on the subjective interpretation of only eleven individual trial reports. In general, survival gains with combination therapy came at the cost of a significant increase in toxicity and impact on other factors such as psychosocial morbidity, which contribute to the quality of life for this group of women. There were insufficient data in this review to comment on the overall impact of the regimens on net clinical benefit from the women's perspective. Clinical trials research increasingly includes routine assessment of quality of life indicators. These trials also need to take into account the information needs of women which support their decision-making about the potential benefits of additional treatments (small survival gains) in progressing metastatic disease and the impact this has on their quality of life.

Although this review shows a benefit for the major outcomes in favour of the combination regimen chemotherapy, there are many factors which are unaccounted for in this review, including hormone receptor status and HER2 status of the participants. This review was also not able to address the issue of whether combination regimens are more effective than single agents given sequentially. Some individual trials raised the possibility that giving a multiagent regimen sequentially with immediate cross-over from one agent to the next on progression may result in survival times similar to that seen when all the agents are given together (e.g. Sledge G(A) 2003, Sledge G(B) 2003). This is a question which equally should be addressed.

In addition this review has not addressed the increasing use of targeted biologics such as trastuzumab and bevacizumab, and the effect that treatment with these agents may have on the way chemotherapy is administered.

AUTHORS' CONCLUSIONS

Implications for practice

Combination-chemotherapy regimens appear to offer a benefit in overall survival, time to progression and response over traditional single chemotherapy agents that include cyclophosphamide, fluorouracil, epirubicin, lomustine and ifosamide. The findings are consistent with the review of Fossati 1998 although they are not necessarily applicable to some of the more modern single agents including, docetaxel, paclitaxel and capecitabine for example.

The main limitation in this review is that very few studies actually reported the rate of cross-over to the additional agent upon progression on mono-therapy. A further systematic review is underway which will compare combination chemotherapy to the same drugs given sequentially.

Implications for research

Additional research is needed to further explore the relationships between response, toxicity, time to progression, survival and quality of life for single and combination regimens particularly in relation to modern cyctotoxic agents and targeted therapies. All trials of chemotherapy regimens must include rigorous quality of life measures to be integrated with all treatment research in order to extract the most meaningful data for patient decision making and care.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Ahmann DL 1974(1)

Study characteristics	
Methods	RCT - consecutive candidates for cytotoxic treatment at the clinic Baseline comparability
Participants	43 women with MBC confirmed histopathologically and suitable for serial measurement 100% MBC 100% Firstline Postmenopausal Randomised and assessable no: 1) n = 22 2) n = 21
Interventions	CCNU (Lomustine) vs F+C+P+/- V1 1) Methyl CCNU 225mg/sq MPO day 1 2) 5 Fluorouracil 8mg daily IV for 5 days + Cyclophosphamide 4mg daily IV for 5 days + Prednisone PO 30 mg 2/52, 20mg 3rd week, 10mg thereafter plus or minus Vincristine 1.4mg/m2 IV day 1 and 5 (11 patients from group 2)
Outcomes	Survival curve - ascertained from associated paper - Kaplan-Meier estimate Median survival 1) 11.7 mths (9.1 -15.5 mths) 2) 18.6 mths (9.3 - 25.1 mths) Response 1) 1/22 2) 12/21 Toxicity data - NE One death (adriamycin arm) - post mortum did not find attributable to treatment.
Notes	F/U - min 1.8mths (rounded up to 2mths (based on 2 cycles) - max 120mths (estimated from curve) First of three trials - with a combined total of 131 patients. Crossover at progression of disease - 11/21 to Vincristine from group 2 All patients included in the analysis for all three trials - all but one patient observed till death (still alive at time of report) Pooled data from all 3 trials also analysed - single versus combination therapy but not used in this review

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

Ahmann DL 1974(1) *(Continued)*

Random sequence generation (selection bias)	High risk	Publication states Patients were consecutive candidates for cytotoxic treatment at the clinic. It is unclear if this means consecutively sampled or consecuetively allocated
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Insufficient information to fully assess

Ahmann DL 1974(2)

Study characteristics	
Methods	Accrual (May 1972- December 1972) RCT - consecutive candidates for cytotoxic treatment at the clinic
Participants	40 women with measurable disease, metastatic, locally inoperable or recurrent breast cancer 100% MBC 100% Firstline Randomised and assessable no: 1) n = 20 2) n = 20
Interventions	I vs F+C+P+/- V1 1) Iphosphamide 4 mg/m2 IV day 1 (analogue of cyclophosphamide) 2) 5 Fluorouracil 8mg daily IV for 5 days + Cyclophosphamide 4mg daily IV for 5 days + Prednisone PO 30 mg 2/52, 20mg 3rd week, 10mg thereafter plus or minus Vincristine 1.4mg/m2 IV day 1 and 5 (9 patients from group 2)
Outcomes	Survival curve - ascertained from associated paper - Kaplan-Meier estimate Median survival 1) 17.6 mths (8.1 - 22.5 mths) 2) 13.3 mths (9.7 - 18.3 mths) Response and toxicity data cannot be extracted
Notes	F/U - min 1.8mths (rounded up to 2 mths (based on 2 cycles) - max 98mths (estimated from curve) Second of three trials - with a combined total of 131 patients. Crossover at progression of disease - 11/21 to Vincristine from group 2 All patients included in the analysis for all three trials - all but one patient observed till death (still alive at time of report) Pooled data from all 3 trials also analysed - single versus combination therapy but not used in this review

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

Ahmann DL 1974(2) *(Continued)*

Random sequence generation (selection bias)	High risk	Publication states Patients were consecutive candidates for cytotoxic treatment at the clinic. It is unclear if this means consecutively sampled or consecuetively allocated
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Insufficient information to fully assess

Ahmann DL 1974(3)

Study characteristics	
Methods	RCT - consecutive candidates for cytotoxic treatment
Participants	48 women with quantifiable metastatic disease 100% MBC 100% Firstline Randomised and assessable no: 1) n = 20 2) n = 28
Interventions	A vs F+C+P+/- V1 1) Doxorubicin 60 mg/m2 IV day 1 repeated every 3-4 weeks 2) 5 Fluorouracil 300mg daily IV for 5 days + Cyclophosphamide 4mg daily IV for 5 days + Prednisone PO 30 mg 2/52, 20mg 3rd week, 10mg thereafter plus or minus Vincristine 1.4mg/m2 IV day 1 and 5 (12 patients received the multiple regimen plus Vincristine)
Outcomes	Survival curve - ascertained from associated paper - Kaplan-Meier estimate Median survival 1) 13.7mths (10.0 - 16.5) 2) 22.1 mths (16.4 -27.3) Response and toxicity data cannot be extracted
Notes	F/U - min 1.8mths (rounded up to 2 mths (based on 2 cycles) - max 102mths (estimated from curve) Third of three trials - with a combined total of 131 patients. Crossover at progression of disease All patients included in the analysis for all three trials - all but one patient observed till death (still alive at time of report) Pooled data from trials also analysed - single versus combination therapy but not used in this review

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

Ahmann DL 1974(3) *(Continued)*

Random sequence generation (selection bias)	High risk	Publication states Patients were consecutive candidates for cytotoxic treatment at the clinic. It is unclear if this means consecutively sampled or consecuetively allocated
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Insufficient information to fully assess

Albain KS 2004

Study characteristics	
Methods	Accrual - (August 1999 - April 2002). RCT - centrally randomised patients, multi-centred international. Phase III. Baseline Comparability
Participants	529 women with unresectable, locally recurrent or metastatic lesions At least 96.9% MBC 100% Firstline Randomised no: 1) n = 262 2) n = 267 Assessable no: 1) n = 259 2) n = 262
Interventions	PACL vs PACL + Gem 1) Paclitaxel 175 mg/m2 (3hr) every 3/52 2) Paclitaxel 175 mg/m2 (3hr) day 1 + Gemcitabine 1250 mg/m2 day 1 then Gemcitabine 1250 mg/m2 day 8
Outcomes	Overall survival and TTP curves - measured from 3 weeks following randomisation till death. Kaplan-Meier curves. Median survival 1) 15.8 mths (14.4, 17.4) 2)18.5 mths (16.5, 21.2) Median TTP 1) 2.9 months 2) 5.2 months OR (CR and PR) 1) 57/259 2) 107/262 Toxicity (3-4)

Albain KS 2004 *(Continued)*

	Nausea and vomiting 1) 2/259 2) 2/262 Neutropenia 1) 11/259 2) 48/262 Toxic death 1) 1/259 2) 1/262
Notes	F/U survival min 1mth - 12mths (based on curve) F/U TTP min 1mth - 37mths (based on curve)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Just states 'randomised'
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Cannot assess as this is a conference abstract
Selective reporting (reporting bias)	Unclear risk	Insufficient information

Andersson M 1986

Study characteristics

Methods	Accrual - (Jan 1981- August 1984) RCT - centrally registered and allocated randomly in a non stratified way Groups comparable in all ways except number of organ sites which was higher in the combination arm
Participants	89 women with histological evidence of breast cancer with measurable and/or evaluable lesions At least 63% MBC (% dominant site - bone and viscera) 22.5% Firstline 77.5% Secondline Randomised no: 1) n = 45 2) n = 44 Assessable no: (following discontinuation of Mitomycin arm) 1) n = 42(median age 59; 46-67) 2) n = 39 (median age 61; 44-70)
Interventions	A vs A+ MMC 1) Doxorubicin 75 mg/m2 IV every 3/52

Andersson M 1986 *(Continued)*

	2) Doxorubicin 45mg/m2 IV every 3/52 + Mitomycin 10 mg/m2 IV every 6/52
Outcomes	Survival and TTP curves - Kaplan-Meier estimates Median TTP 1) 5.2 mths (4.7 - 6.5) 2) 7.7 mths (5.4 - 10.1) Response (CR and PR) 1) 20/42 2) 19/39 Toxicity WHO 3-4 Nausea and vomiting 1) 8/42 2) 20/39 Toxic death - 4 patients in combination arm - thrombopenia (2); cardiomyopathy (2)
Notes	F/U survival min 2mths - max 31mths (estimated from curve) F/U min 2mths - max. 17mths (estimated from curve) 101 patients initially randomised to a arm of single mitomycin but this was discontinued (12 patients) due to severe toxicity. These patients are not included in the analysis Two patients in each group were not evaluable for response due to treatment refusal - these were included in the analysis for TTP, survival and toxicity. There was no loss to follow up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States "centrally registered and allocated randomly in a non stratified way"
Allocation concealment (selection bias)	Low risk	Centrally randomised
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two patients in each group were not evaluable for response due to treatment refusal - these were included in the analysis for TTP, survival and toxicity. There was no loss to follow up
Selective reporting (reporting bias)	Low risk	Protocol not available but but all expected outcomes reported

ANZBCTG 2001

Study characteristics

Methods	Accrual (January 1988 - June 1993) RCT - randomisation method not described Stratification based on performance status, site of metastases and institution Multi-centre - Australian and New Zealand
Participants	391 women with advanced breast cancer 100% MBC

ANZBCTG 2001 *(Continued)*

	100% Firstline Randomised no: 1) n = 197 2) n = 194 Assessable no: 1) n = 192 2) n = 190
Interventions	MZA vs CMFP 1)Mitozantrone 14mg/m2 day 1 2)CMFP cyclophosphamide 100mg/m2 po days 1-4 methotrexate 40mg/m2/ iv days 1 and 8 5 Fluorouracil 600mg/m2 IV days 1 and 8 Prednisone 40mg/m2 po days 1-14 Patients crossed over to the alternative treatment at progression
Outcomes	OS or TTP curves are not included as these were available only for post crossover TTF curve excluded OR (CR +PR) 1)47/197 2)70/194 Toxicity WHO 3-4 Nausea and vomiting 1) 62/192 2) 53/190 Alopecia 1) 83/197 2) 131/194 WCC 1) 56/197 2) 60/194 QOL - Spitzer QL index
Notes	Updated data provided by trialist 2003 - Only data from the first line comparison is included in this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Protocol available - all pre-specified outcomes reported

Berruti D 2002

Study characteristics	
Methods	Accrual (October 1995 - March 2001) RCT - Multicentre Randomisation not described (stratification by investigator site done prior to randomisation) Major clinical characteristics well balanced across the 2 arms
Participants	185 women with measurable or assessable (WHO criteria) and histologically proven MBC 100% MBC 100% Firstline Randomised no: 1) n = 93 (median age = 59; 28-75) 2) n = 92 (median age 57; 33-75)
Interventions	E vs E+CDDP 1) EPI only = 60 mg/m2 slow IV push on days 1 and 2 2) EPI+CDDP = EPI 60 mg/m2 slow IV push on days 1 and 2 + CDDP 30mg/m2 x 1hr IV infusion on days 1 and 2 CDDP and EPI infusions were repeated every 21 days A median of 6 cycles (1-8) was given
Outcomes	Survival - Not reported for arm of interest. PFS curve poor quality. Excluded. OR (CR + PR) 1) 47/93 2) 53/92 Toxicity: WHO 3-4 Nausea and vomiting 1) 17/91 2) 24/90 Leukopenia 1) 2/91 2) 4/90 Toxic death 1) 3 2) 3
Notes	F/U TTP - min 4.5mths - max 64mths (estimated from no of cycles and curve) Patients randomised into 4 arms **** Only EPI and CDDP arms of this study included ITT - stated in text

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

Berruti D 2002 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Bishop J 1999

Study characteristics	
Methods	Accrual (Sept 1993 - 1997) RCT - 17 centres - Aust and NZ - Randomisation done by computer generated randomisation charts - stratified by institution
Participants	209 women with histologically proven metastatic or locally advanced breast cancer 100% MBC 100% Firstline Randomised no: 1) n = 107 (median age 54; range 36-73) - 2 did not receive treatment) 2) n = 102 (median age 54; range 32-80 - 3 did not receive treatment)
Interventions	PACL vs CMFP 1) Paclitaxel 200mg/m2 IV over 3hrs for 8 cycles - 24 weeks 2) CMFP = Cyclophosphamide 100mg/m2 oral on days 1-14 + Methotrexate 40mg/m2 IV on days 1 and 8 + Flurouracil 600mg/m2 IV on days 1 and 8 + Prednisone 40mg/m2 orally on days 1-14 for 6 cycles with EPI as 2nd line therapy
Outcomes	Survival and PFS curves - Kaplan-Meier product limit method. OS and PFS measured from the date of randomisation and the close out date for all survival analysis was Feb 20, 1997 Median survival 1) 17.3mths 2) 13.9 mths Median TTP 1) 5.3mths 2) 6.4 mths OR (CR+PR) 1) 31/107 2) 36/102 Toxicity (3-4) Leukopenia 1) 29/107 2) 66/102 Nausea and vomiting 1) 1/107 2) 8/102 Alopecia 1) 81/107

Bishop J 1999 *(Continued)*

	2) 24/102 Toxic death- NR QOL- instrument linear analog scale- Spitzer for physicians
Notes	F/U survival and PFS- minimum 17mths - max 40mths (stated in text) All major end points done by Intention to treat analysis 30% (1) and 20% (2) still alive at close out - Feb 20 1997 43 and 39 received 2nd line

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation done by computer generated randomisation charts
Allocation concealment (selection bias)	Low risk	Centrally randomised
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Bonneterre J 2002

Study characteristics

Methods	Accrual (June 1995 - July 1997) RCT - Multi centre (22) Phase lll study - randomisation one to one basis, stratified by accruing centre Baseline characteristics well balanced between study groups
Participants	178 women with histologically confirmed MBC and measurable or evaluable disease Previously treated with Anthracycline based chemotherapy 34% first line Randomised No 1) n = 88 2)n = 90 Assessable no: (176) 2 in arm 1 did not receive treatment leaving: 1) n = 86 (median age 54.9; 27.9-79) 2) n = 90 (median age 54.55; 31.6-74.5)
Interventions	TXT vs F+V3 1) Docetaxel (100mg/m-2 every three weeks) 2) 5-fluorouracil (750 mg/m-2 per day continuous infusion)+ vinorelbine 25mg/m-2 over a 30 minute infusion on days 1 and 5 of the 3 week cycle
Outcomes	Survival and TTP curves - Kaplan-Meier - calculated from first treatment infusion Median survival

Bonneterre J 2002 *(Continued)*

	1) 16 mths 2)15 mths Median TTP 1) 6.5 mths 2) 5.1 mths OR (CR+PR) assessed every 3 cycles and fully assessed 28 days after final infusion 1) 37/86 2) 35/90- Toxicity (WHO3/4) Neutropenia 1) 65/86 2) 60/90 Nausea and vomiting 1) 4/86 2) 5/90 Alopecia 1) 38/86 20 7/90 Toxic Deaths 1) 1 (CCF) 2) 5 (3 sepsis/1 liver failure/ 1 liver and renal failure).
Notes	F/U survival and TTP - min 10.4mths - 45mths (stated in text 176 patients treated - Results ITT where possible Median follow up - 30.3 mths (10.4-45.0 mths) reported by the authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Publication states "randomisation one to one basis"
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Canellos GP 1976

Study characteristics

Methods	RCT, multi-centre - Randomisation not described Stratified according to prior hormonal therapy and menopausal status

Canellos GP 1976 *(Continued)*

	Groups well balanced
Participants	184 women with histologically confirmed MBC, previously untreated by cytotoxic chemotherapy 100% MBC 100% Firstline Randomised no: 1) n = 91 2) n = 93
Interventions	L-PAM (melphalan) vs CMF 1) L-phenylalanine mustard 6 mg/m2 (po) for 5 days every 6 wks 2) 5-Flurouracil 600 mg/m2 iv days 1 & 8 + Cyclophosphamide 100 mg/m2 po daily x 14 days + Methotrexate 60 mg/m2 iv days 1 & 8 CMF was a 14 day course of treatment every 28 days.
Outcomes	Survival curve - Kaplan-Meier No TTP curves Median survival 1) 9 mths 2) 12 mths OR (CR+PR) 1) 18/91 2) 49/93 Toxicity Nadir WBC,<2000/mm3 1) 7/91 2) 37/93 Toxic death - NR
Notes	F/U - (min 3mths based on number of cycles - max 18mths estimated from curve) Duration of response statistically significant All patients evaluated (ITT)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Carmo-Pereira 1980

Study characteristics	
Methods	RCT single-centre Portugal Randomisation not described - Stratified according to menopausal state, disease free interval and predominant lesion Baseline comparability
Participants	135 patients with metastatic BC in progression and refractory to endocrine therapy and irradiation - histologically proven metastatic and measurable disease 100% MBC 100% firstline Randomised no: 1) n = 67 (median age 47.5) 2) n = 68 (median age 50)
Interventions	F vs CMFVP 1) 5 FU 500mg/m2 IV days 1-5, then 500mg/m2 weekly 2) Combination of 5 drugs CMFVP protocol (5-FU 300mg/m2 IV, MXT 15m/g2, IV, VCR 0.65mg/m2 IV weekly for 2 weeks) + (CPP 75mg/m p.o daily for 2 weeks alternating with a 2 week rest period and PNS 20mg/m2 po daily with diminishing dose) followed by a maintenance dose used for 3 weeks off treatment
Outcomes	Survival curve - life table method estimated from the commencement of treatment Median survival 1) 5 mths 2) 16 mths OR (CR+PR) 1) 12/67 2) 47/68 Toxicity (WHO 3-4) Nausea and vomiting 1) 67/67 2) 30/68 Alopecia 1) 0/67 2) 59/68 Leukopenia 1) 0/67 20 7/68 Toxic death - NR
Notes	F/U min 6 mths (estimated from treatment cycles) - max 44 mths (estimated from curve) ITT all analyses All of the single drug group had died by the end of the trial

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported

Carmo-Pereira 1980 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Eagan RT 1976

Study characteristics	
Methods	RCT Randomisation not described - stratified by site Groups fairly comparable - Single group was younger and closer to menopause
Participants	39 women previously treated and failed CT Anthracycline and Taxane naive 100% MBC Unclear as to whether pre-treatment was as adjuvant treatment or treatment for MBC Assessable no: 1) n = 19 2) n = 20
Interventions	ETO (VP-16) vs V1+A 1) VP- 16 - slow infusion over 30-45 minutes on days 1,3,5, repeated every 4-5 weeks 2) Vincristine + Adriamycin - 1.5mg V1 IV on days 1 and 2 and A 45mg/m2 IV on day 3 Treatment repeated every 4-5 weeks All drug dosages adjusted to produce adequate but clinically tolerable effects
Outcomes	No survival curves or TTP curves Response (PR only) 1) 2/19 2) 4/20 Toxicity: Leukopenia 1) 16/19 2) 18/20 Alopecia 1) 17/19 2) 19/20 Toxic death 1) 0 2) 1 (CNS Haemorrhage)
Notes	Not ITT - 42 patients entered the trial - 3 patients disqualified post randomisation due to protocol violations. Randomised numbers not provided by group Crossover on treatment failure
Risk of bias	

Eagan RT 1976 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported states 'partially randomised'
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Some missing outcome data but not enough information to fully assess
Selective reporting (reporting bias)	High risk	The study fails to report survival or TTP

Ejlertsen B 2004

Study characteristics	
Methods	Accrual (February 1995 - January 1999) RCT - 15 departments Scandanavia Randomisation performed centrally and stratified by centre Patient and tumour characteristics comparable at baseline
Participants	387 women with histologically proven metastatic breast cancer. Anthracycline and cytotoxic naïve 100% MBC 100% Firstline Randomised no: 1) n = 194 2) n = 193
Interventions	E vs E + V3 1) Epirubicin 90 mg m2 day 1 every 3/52 2) Epirubicin 90 mg/m2 day 1 every 3/52 + Vinorelbine 25 mg/m2 days 1 and 8 every 3/52
Outcomes	Survival and PFS curve - Kaplan-Meier curves. Median survival 1) 8.2 months 2) 10.1 months OR (CR+PR) 1) 81/194 2) 96/193 Toxicity Leukopenia 1) 23/194 2) 97/193 Nausea/vomiting 1) 41/194 2) 12/193

Ejlertsen B 2004 *(Continued)*

	Toxic death 1) 3 (febrile neutropenia, sepsis) 2) 7 (febrile neutropenia, sepsis + 1 (cardiac toxicity)
Notes	F/U survival min 3mth - max 36mths F/U PFS min 1mth - max 36mths ITT Toxicity - 7 patients were never treated but it is not known which group they came from,

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised using a central randomisation centre
Allocation concealment (selection bias)	Low risk	Centrally randomised
Incomplete outcome data (attrition bias) All outcomes	High risk	Intent to treat analysis stated however seven patients were never treated and are not included in the analysis for toxicity.
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Erkisi M 1997

Study characteristics

Methods	Accrual (March 1992- March 1994) RCT - Turkey, multi-centre Randomisation not described
Participants	60 patients with metastatic BC or recurrent BC, histologically proven and measurable disease Anthracycline naive 100% MBC 48% Firstline Randomised no: 1) n = 30 (median age 52; range 26-69) 2) n = 30 (median age 47; range 24-66)
Interventions	ETO vs FAC 1)Etoposide 200 mg/day op for 5 days, every 3 weeks 2)Fluorouracil 500 mg/m2 iv every 3 weeks + Doxorubicin 50 mg/m2 iv every 3 weeks + Cyclophosphamide 500 mg/m2 iv every 3 weeks
Outcomes	No survival curves or TTP curves provided - survival data assessed by life table method and Mantel-Cox test Median survival 1) 16mths 2) 14mths

Erkisi M 1997 *(Continued)*

	OR (CR and PR): 1) 16/30 2) 12/30 Toxicities of interest not reported - Toxic death 1) 0 2) 1 (granulcytopenia and infection)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	All expected outcomes reported

Falkson G 1990

Study characteristics

Methods	Accrual (May 1973 -May 1977) RCT - Multi centre randomisation not described -stratified according to institution Baseline comparability not discussed
Participants	111 women. No prior treatment, <50yrs 100% MBC 100% Firstline Randomised no: 1) n = 54 2) n = 57 Assessable no: 1) n = 51 (3 ineligible) 2) n = 52 (5 ineligible)
Interventions	CTX vs CMFVP 1) Ooph + CTX 300 mg/m2 IV per day x5 weekly till toxicity 2) Ooph + VPCMF VCR 0.25 mg/kg IV weekly x8 + Pred .75mg/kg po daily x 3 weeks + CTX 2mg/kg po daily x 8 weeks + MTX.75mg/kg iv weekly +

Falkson G 1990 *(Continued)*

	5-FU 12 mg/kg IV weekly x 8
Outcomes	Survival curve - Kaplan-Meier - estimated from randomisation or Ooph- not really clear. No TTP curve. TTF curve excluded. Median survival 1) 30 mths 2) 26 mths Median TTP 1) 14mths 2) 12mths CR 1) 17/51 2) 19/52 Toxicity Nausea/vomiting 1) 2/51 2) 6/52 WCC 1) 48/51 2) 22/52
Notes	FU min 46 - max 179 mths (reported in text) Report on three studies - Cancer and Leukaemia Group B (CALGB 7382) is the only single versus combination (with oophorectomy)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Three patients from the single arm and five from the combination arm were deemed ineligible after entering the trial and were not included in the analyses
Selective reporting (reporting bias)	Unclear risk	All expected outcomes reported

Fraser S 1993

Study characteristics

Methods	Accrual (Oct 1988- Dec 1989) RCT - randomisation not described 2 centres UK Groups well balanced except for age - which was not statistically significantly different

Fraser S 1993 *(Continued)*

Participants	40 women with advanced breast cancer including histologically proven locally advanced disease, rapidly progressing primary disease and metastatic disease failing to respond to hormonal measures Randomised no: 1) n = 21 (median age 52; 26-80) 2)n = 19 (median age 63; 39-84)
Interventions	E vs CMF 1) Epirubicin 20mg IV into fast running 0.9% saline every 7 days 2) Cyclophosphamide 100mg/m-2 orally on day 1-14, Methotrexate 35mg/m-2 IV on days 1 and 8 and 5 Fluorouracil 600mg/m-2 IV on days 1 and 8, on a 28 day cycle (CMF)
Outcomes	Survival curve - Kaplan-Meier life table method - survival analysed from start of treatment to last event on the curve. No TTP curve Median survival 1) 55 weeks 2) 57 weeks Median TTP 1) 7 weeks 2) 24 weeks OR (CR + PR) 1) 6/21 2) 11/19 Toxicity not available by group. CMF caused more alopecia, nausea and vomiting and haematological toxicity (above grade 1) There were no fatalities Three QOL measures - LASA, NHP, Qualitator - well described
Notes	F/U min 6mth -max 27mths (based on curves) ITT for response/TTTF Excluded from firstline analysis as contained locally advanced cases

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States 'randomised'
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

French Epi (A) 1991

Study characteristics	
Methods	RCT - Randomisation not described - Stratified on the basis of bone mets/or not Multi centre 13 institutions, France Baseline - More lymph node mets in the FEC50 combination group
Participants	275 women with histologic evidence of breast cancer with recurrent or metastatic disease 100% MBC 100% Firstline Randomised no: 1) n = 140 2) n = 135 Assessable no: 1) n = 132 (median age 53; 26-70). (n) for effectiveness = 121; toxicity = 125 2) n = 129 (median age 53; 30-70) (n) for effectiveness = 121; toxicity = 126
Interventions	E vs FEC 50 1) Epirubicin 75 mg/m2 iv 2) FEC 50 Epirubicin 50 mg/m2 iv day 1 X 21 day cycle + 5-Flurouracil 500 mg/m2 iv + Cyclophosphamide 500 mg/m2 (All treatments repeated every 21 days)
Outcomes	Survival curve - Kaplan-Meier method - ? from randomisation or? from treatment TTF curve provided however as authors report this as TTP, this has been included OR (CR+PR) 1) 37/121 duration of response = 315 days (range 84-1107) 2) 54/121 duration of response = 378 days (range 84-1008) Toxicity Treatment ceased due to cardiac toxicity in 15 patients (7 in the single group;3 in the combination group) Nausea and vomiting and granulopenia reported by percentage of total cycles of chemotherapy Toxic death- NR six cases of cardiac failure - all controlled by symptomatic treatment
Notes	F/U survival min 8mths (based on cycles) - max - 40mths (1200 days reported from curves) F/U TTP min 4mths - max 40mths based on curve

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data well balanced between the groups

French Epi (A) 1991 *(Continued)*

Selective reporting (reporting bias)	Low risk	All expected outcomes reported

French Epi (B) 1991

Study characteristics	
Methods	RCT - Randomisation not described - Stratified on the basis of bone mets/or not Multi centre 13 institutions, France Baseline comparability
Participants	277 women with histologic evidence of breast cancer with recurrent or metastatic disease 100% firstline Randomised no: 1) n = 140 2) n = 137 Assessable no: 1) n = 132 (median age 53; 26-70) (n) for effectiveness = 121; toxicity = 125 2) n = 130 (median age 51; 22-70) (n) for effectiveness = 123; toxicity = 127
Interventions	E vs FEC 75 1) Epirubicin 75 mg/m2 iv vs 2) FEC 75 Epirubicin 75 mg/m2 + Cyclophosphamide 500 mg/m2 iv day 1 x 21 day cycle + 5-Flurouracil 500 mg/m2 iv day (All treatments repeated every 21 days)
Outcomes	Survival and TTP curve - Kaplan-Meier method - ? from randomisation or? from treatment OR (CR+PR) 1) 37/121 duration of response = 315 days (range 84-1107) 2) 55/123 duration of response = 395 days (range 22-1139) Toxicity Treatment ceased due to cardiac toxicity in 15 patients (7 in the single group; 5 in the combination group) Nausea and vomiting and granulopenia reported by percentage of total cycles of chemotherapy Toxic death - NR Six cases of cardiac failure - all controlled by symptomatic treatment
Notes	F/U survival min 8mths (based on cycles) - max - 40mths (1200 days reported from curves) F/U TTP min 4mths - max 40mths based on curve

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

French Epi (B) 1991 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data well balanced between the groups
Selective reporting (reporting bias)	Unclear risk	All expected outcomes reported

GEICAM 2007

Study characteristics	
Methods	Accrual (January 2001 - March 20050 RCT - Randomisation generated by computer generated random code Multi-centre, six countries Stratified by centre, number of treatment lines for MBC Baseline comparibility
Participants	252 women with histologically confirmed locally recurrent and metastatic breast cancer not amenable to curative surgery or radiotherapy At least 75% MBC 36% first line - previously treated with anthracyclines and taxanes Randomised no: 1) n=127 (median age 57; 35-80) 2) n= 125 (median age 58; 28-82) Assessable no: 1) n= 126 - 1 patient previously treated with vinorelbine 2) n=125
Interventions	V3 versus V3 +Gem 1) Vinorelbine 30mg/m2 IV days 1 and 8 2) Vinorelbine 30mg/m2 IV days 1 and 8 +Gemcitabine 1200mg/m2 IV days 1 and 8 Treatment cycle 21 days
Outcomes	PFS curve. No OS curve Median survival 1) 16.4 months (11.6-21) 2) 15.9 months (12.6-19.1) Median PFS 1) 4 months (2.9-5.1) 2) 6 months (4.8-7.1) OR (CR+PR) 1) 33/126 2) 45/125 Toxicity (WHO ¾) Nausea/vomiting 1) 3/125 2) 4/123 Neutropenia 1) 55/125 2) 75/123

GEICAM 2007 *(Continued)*

	Alopecia 1) 21/125 2) 21/123 Toxic death 1) n=1 (acute liver failure) 2) n=1 (septic shock)
Notes	FU 1-25 months (estimated from curve) Trial unblinded Analysis ITT

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centrally randomised at the GEICAM headquarters using computer generated random code
Allocation concealment (selection bias)	Low risk	Central randomisation
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Gundersen S 1986

Study characteristics

Methods	Accrual (June 1982- December 1983) RCT - Allocation by random number generation - no stratification Norway - multi-centre Groups well balanced according to age, disease free interval and time from first metastases to randomisation
Participants	128 women with metastatic BC, histologically proven with evaluable lesions Those previously treated with Adriamycin were excluded - all were hormone resistant- 100% MBC 100% Firstline Randomised no: 1) n = 62 (Mean age 59) 2) n = 66 (Mean age 56)
Interventions	A vs V1+A+C 1) Doxorubicin 20 mg/week to max dose 750 mg/m2 2) Vincristine 2 mg + Adriamycin 50 mg/m2 to max dose 500 mg/m2 + Cyclophosphamide 600 mg/m2 (VAC every 3 weeks)

Gundersen S 1986 *(Continued)*

Outcomes	Overall survival curves calculated by actuarial life table method - survival calculated from start of treatment No TTP curves Mean TTF 1) 33 mths 2) 29mths OR (CR+PR) 1) 19/62 2) 24/66 Toxicity WHO 3 Vomiting 1) 4/62 2) 43/66 Alopecia 1) 5/62 2) 52/66 Toxic death - NR
Notes	F/U min 3mths (based on first assessment of response or review of treatment)- max 24mths (from survival curve ITT -

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation by random number generation
Allocation concealment (selection bias)	Low risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Heidemann E 2002

Study characteristics

Methods	Accrual (1992-1997) RCT - Random number generation - central statistical institute - stratified according to disease free state and metastases Germany, multi-centre Groups well balanced except for receptor status
Participants	260 women with measurable metastatic BC fulfilling high risk criteria previously untreated for MBC Histologically documented ABC stage IV Anthracycline naive

Heidemann E 2002 *(Continued)*

	100% MBC 100% Firstline Randomised no: 1) 127 2) 133 Evaluable for efficacy and QOL 1) 119 2) 119 Evaluable for toxicity 1) 131 2) 125
Interventions	MZA vs FEC 1) Mitoxantrone 12 mg/m2 IV by short infusion x21 days 2) FEC 5-Flurouracil 500 mg/m2 IV + Epirubicin 50 mg/m2 + Cyclophosphamide 500 mg/m2 IV every 3 weeks, max 12 cycles 2nd and 3rd line treatment fixed
Outcomes	Survival and TTP curves - Kaplan-Meier life table method - from commencement of treatment Median survival 1) 14.1 mths 2) 15.8 mths Median TTP 1) 4.4 mths 2) 6.15 OR (CR + PR) 1) 30/119 2) 43/119 Toxicity (WHO 3-4) Nausea /vomiting 1) 9/131 2)37/125 Alopecia 1)6/131 2) 77/125 Toxic death - NR QOL - Brunners score
Notes	F/U survival and TTP min 0.99 - max 73.68mths (Stated in text)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number generation

Heidemann E 2002 *(Continued)*

Allocation concealment (selection bias)	Low risk	Centrally randomised
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quorum of missing patients provided - balanced across both groups unlikely to have a clinically relevant impact
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Heidemann E 2004

Study characteristics	
Methods	Accrual June 1997- December 2001 RCT Phase IV Randomisation by central fax/phone in blocks of variable length. Stratified by institution Germany, multi-centre Demographic and prognostic criteria generally similar in both arms except that more patients had a Disease free interval </= 18months in the single agent arm
Participants	179 women with histologically proven MBC (High risk); at least one measurable lesion, WHO performance status 0-2, adequate hematologic, renal and hepatic function. High 100% MBC 100% Firstline Randomised no: 1) n = 89 2) n = 90 ITT 176 1) n = 87 2) n = 89
Interventions	M vs M+TXT 1) Mitoxantrone 12 mg/m2 IV on day 1 every 3 weeks until complete response (plus 2 cycles) progressive disease or cumulative dose of 160mg/m2 2) Mitoxantrone 12 mg/m2 IV on day 1 every 3 weeks plus docetaxel 80 mg/m2 as a 1 hour infusion on day 1 every 3 weeks for a maximum of 6 cycles
Outcomes	OS and PFS curves- from date of randomisation until progressive disease, death or last contact Median survival 1) 15.6 months 2) 17.2 months Median TTP 1) 4.9 months 2) 8.0 months OR (CR+PR) 1) 20/86 2) 441/87 Toxicity (WHO ¾) Nausea/vomiting

Heidemann E 2004 *(Continued)*

	1) 5/85 2) 5/85 Leukopenia 1) 53/85 2) 76/85 Toxic death - NR
Notes	F/U Median 43.6 months stated Text states 176 patients ITT analyses (1 excluded due to cerebral metastases; 2 insufficient data)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random number generation
Allocation concealment (selection bias)	Low risk	Centrally randomised
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Hoogstraten B(A)1976

Study characteristics

Methods	Accrual (Jan 1972 - Feb 1974) RCT - Initial randomisation into three treatment groups with non compulsory 'crossover' following relapse or failure to respond - method not described North America, multi-centre
Participants	177 women with measurable MBC 100% MBC 100% Firstline Assessable no: 1) n = 79 2) n = 98
Interventions	A vs CMFVP-(Intermittent) 1) Doxorubicin 60 mg/m2 iv every 3 weeks 2) Intermittent - Vincristine 0.625 mg/m2/ iv days 1 and 5 + Methotgrexate 4 mg/m2/ iv dx5 + 5-Flurouracil 180 mg/m2/ iv dx5 + Cyclophosphamide 120 mg/m2 iv dx5 + Prednisone 40 mg/m2/day X 5 then crossover
Outcomes	No OS or TTP curves

Hoogstraten B(A)1976 *(Continued)*

	OR (CR+PR) 1) 31/79 (median duration of response 4 mths) 2) 39/98 (median duration of response 10 mths) Toxicity (WHO 3-4) Leukopenia 1) 24/79 2) 40/98 Alopecia 1) 47/79 2) 5/98 Toxic death not included as numbers cited in text and tables are inconsistent
Notes	Not ITT - Of the reported accrual numbers (n=297) 14 (across all 3 arms of the trial) were not evaluable and not analysed due to protocol violations and lack of adequate data. Randomised numbers not reported by group. Phase I only considered in this review Arm 1 versus Arm 2 -Leukopenia was the dose limiting response

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States 'randomised'
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	14 (across all 3 arms of the trial) were not evaluable and not analysed due to protocol violations and lack of adequate data.
Selective reporting (reporting bias)	High risk	All expected outcomes not reported

Hoogstraten B(B)1976

Study characteristics

Methods	Accrual (Jan 1972 - Feb 1974) RCT - Initial randomisation into three treatment groups with non compulsory 'crossover' following relapse or failure to respond - method not described North America, multi-centre
Participants	185 women with measurable MBC 100% MBC 100% Firstline Assessable no: 1) n = 79 2) n = 106
Interventions	A vs CMFVP- (Weekly) 1) Doxorubicin 60 mg/m2 iv every 3 weeks

Hoogstraten B(B)1976 *(Continued)*

	2) Weekly Vincristine 0.625 mg/m2/week iv + Methotrexate 15 mg/m2/wk iv + 5-Flurouracil 300 mg/m2/wk iv + Cyclophosphamide 60 mg/m2/day po + Prednisone 30 mg/m2/day X 14 20 mg/m2/day X 14 10 mg/m2/day then crossover
Outcomes	No OS or TTP curves OR (CR+PR) 1) 31/79 (median duration of response 4 mths) 2) 63/106 (median duration of response 8 mths) Toxicity 3-4 Leukopenia 1) 24/79 2) 30/106 Alopecia 1) 47/79 2) 13/106 Toxic death not included as numbers cited in text and tables are inconsistent
Notes	Not ITT - Of the reported accrual numbers (n=297) 14 (across all 3 arms of the trial) were not evaluable and not analysed due to protocol violations and lack of adequate data. Randomised numbers not reported by group. Phase I only considered in this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States 'randomised'
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	14 (across all 3 arms of the trial) were not evaluable and not analysed due to protocol violations and lack of adequate data.
Selective reporting (reporting bias)	High risk	All expected outcomes not reported

Icli F 2005

Study characteristics

Methods	Accrual (December 1997 - August 2002 Prospective randomised non blinded multicentre Phase III study Central randomisation - No stratification for prognostic factors or centres Baseline comparability: no significant imbalance noted or reported

Icli F 2005 *(Continued)*

Participants	201 women with histological or cytological confirmation of locally advanced or metastatic adenocarcinoma of the breast. Measurable disease previously treated with anthracyclines 96% MBC 20% Firstline, 60% second line, 20% third line Randomised no: 1) n = 101 (Median age 49; 24-70) 2) n = 100 (Median age 47; 26-69) Assessable no: 1) n = 97 2) n = 96 Assessable for response: 1) n = 91 2) n = 94
Interventions	PACL vs ETO+CDDP 1) Paclitaxel 175 mg/m2, DI q3 weeks 2) Cisplatin 70mg/m2 IV, DI q3 weeks +oral etoposide -1650 mg bid, po, D 1-7q 3 weeks Crossover from single arm = 42; Crossover from combination arm = 30 Crossover was allowed for pts with PD at any stage. Also patients with SD could crossover after two cycles of the allocated treatment
Outcomes	Survival and TTP curves included - Kaplan Meier Median survival 1) 9.5 mths 2) 14 mths Median TTP 1) 3.9 2) 5.5mths OR (CR+PR) 1) 21/94 2) 33/91 Toxicity WHO 3-4 Nausea 1) 15/97 2) 1/96 Neutropenia 1) 18/97 2) 11/96 Toxic death 1) 3 (2 neutropenia + 1 unknown) 2) 2 (neutropenia)
Notes	F/U survival min 4mths - max 48mths (based on median no. of cycles and last event on the OS curve) F/U TTP min 4mths - max 40mths (based on median no. of cycles and last event on the OS curve) Not ITT - Paper states OS calculated on ITT

Risk of bias

Bias	Authors' judgement	Support for judgement

Icli F 2005 *(Continued)*

Random sequence generation (selection bias)	Low risk	Centrally randomised
Allocation concealment (selection bias)	Low risk	Centrally randomised
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced across groups
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Ingle J 1985

Study characteristics	
Methods	Accrual (Sept 1979 - April 1982) RCT - Randomised according to dynamic allocation scheme - Stratification based on ECOG North America, multi-centre Baseline comparability not discussed or reported
Participants	158 women with histologic confirmation of breast cancer and progressive metastatic disease Previous combination chemotherapy but no doxorubicin, anthracycline or mitolactol 100% MBC 100% Firstline Randomised no: 1) n = 79 2) n = 79 Assessable no: 1) n = 74 (median age 59; 37-79) 2) n = 77 (median age 56; 32-76)
Interventions	A vs A + MTL 1) Doxorubicin 60 mg/m2 iv day 1 x monthly 2)Doxorubicin 40 mg/m2 iv day 1 x monthly, max 500mg/m2 + Mitolactol 135 mg/m2 po days 1-10, 180 mg/m2 after max Dox reached.
Outcomes	Survival and TTP curves - Kaplan Meier Median survival 1) 232 days 2) 225 days Median TTP 1) 186 days 2) 178 days OR (CR+PR) 1) 26/74 2) 25/77 Toxicity Leukopenia 1) 62/70

Ingle J 1985 *(Continued)*

	2) 53/67 Nausea and vomiting 1) 11/74 2) 12/77 Alopecia 1) 41/74 2) 26/77 Toxic death 1) 3 2) 0
Notes	F/U survival and TTP min 1.1 mth estimated from cycles) - max 50 mths (based on events on curve) Not ITT

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised according to dynamic allocation scheme
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Not ITT- five from the single arm and 2 from the combination arm were disqualified and not included in the analyses however reasonably balanced across arms
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Ingle J 1989

Study characteristics

Methods	Accrual (Nov 1982- Feb 1987) RCT - Randomised dynamic allocation scheme - ECOG </= 3 Stratified according to score - North America - multi-centre Good balance between groups reported
Participants	185 women with histologically confirmed breast and progressive metastatic disease pre- and postmenopausal 100% MBC Assumed 100% Firstline Randomised no: 1) n = 95 (mean age 58) 2) n = 90 (mean age 57) Assessable no: 1) n = 68 2) n = 63

Ingle J 1989 *(Continued)*

Interventions	A vs A+ V1+ MMC 1) Doxorubicin 60 mr/m2 iv x monthly 2) Doxorubicin 50 mg/m2 iv days 1 & 29 + Vincristine 1mg/m2 iv days 1 & 29 + Mitomycin-C 10 mg/m2 day 1 every other cycle Cycle length 56 days crossover - after failure to D alone, could receive 3) Secondary treatment + Vincristine 1mg weekly for 5 weeks, then 1.2.mg/m2 every 5 weeks + Mitomycin-C 12 mg/m2 every 5 weeks
Outcomes	Survival and TTP curve - Kaplan Meier - from date of randomisation Median survival 1) 8.4 mths 2) 9.2 mths Median TTP 1) 2.7 mths 2) 4.2 mths OR (CR+PR) 1) 24/95 2) 39/90 Toxicity Leukopenia 1) 61/91 2) 75/87 Nausea and vomiting 1) 30/95 2) 31/90 Toxic death 1) 2 2) 1
Notes	F/U survival min 3mths - max 36mths(based on last event on the curve) F/U TTP min 3mths - max 24mths (based on last event on the curve)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised using a dynamic allocation scheme
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Joensuu H 1998

Study characteristics	
Methods	Accrual (July 1991-April 1996) RCT - Centralised randomisation Finnish Cancer registry, Helsinki Stratification according to treatment centre and WHO treatment status Multi-centre - Finland Groups well balanced on all variables
Participants	303 women with histologically verified breast cancer that had given rise to distant metastases 100% firstline Randomised no: 1) n = 153 (median age 56; 33-72) 2) n = 150 (median age 55; 26-72) Assessable for response: 1) n = 140 2) n = 143 Assessible for toxicity: 1) n = 151 2) n = 149
Interventions	E vs E+C+F 1)Epirubicin 20 mg/m2 iv weekly 2)Cyclophosphamide 500 mg/m2 day 1 + Epirubicin 60 mg/m2 iv day 1 of cycle + 5-Fluorouracil 500 mg/m2 iv day 1 next cycle day 22
Outcomes	Survival and TTP curves - Kaplan-Meier product limit method - from commencement of chemotherapy to death or last day of F/u Median survival 1) 16 mths 2) 18 mths Median TTP 1) 8 mths 2) 10mths OR (CR+PR) 1) 67/140 2) 79/143 Toxicity WHO 3-4 Nausea/vomiting 1) 18/151 2) 50/149 Alopecia 1) 18/151 2) 105/149 Leukopenia 1) 16/151 2) 41/149 Toxic death - NR

Joensuu H 1998 *(Continued)*

	QOL Rotterdam symptom checklist (RSCL) 285 patients.
Notes	F/U survival and TTP min 3mths (based on cycles) - max 61mths (last event on the curve) **ITT analysis but survival analysis was repeated after 9 patients were found to be ineligible

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by computer generated random digits
Allocation concealment (selection bias)	Low risk	Centrally randomised
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis but survival analysis was repeated after 9 patients were found to be ineligible with the results remaining essentially similar
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Mouridsen HT 1977

Study characteristics

Methods	RCT - stochastic array of numbers, closed envelope Denmark - multi-centre Baseline comparability not reported or discussed
Participants	55 consecutive women with histologically verified and measurable metastatic disease /post-menopausal <75yrs with no prior chemotherapy 100% MBC 100% firstline Randomised no: 1) n = 27(median age 61; 48-76) 2) n = 28 (median age 62; 44-70) Assessable no: 1) n = 24 2) n = 27
Interventions	C vs CMFVP 1) Cyclophosphamide 3 mg/kg/day 2) Cyclophosphamide 2 mg/kg/day oral + Vincristine 0.025 mg/kg IV, + Methotrexate 0.75 mg/kg IV + 5-Fluorouracil 12mg/kg IV + Prednisone 0.75 mg/kg oral
Outcomes	No survival or TTP curves OR (CR + PR) 1) 6/24 (median duration of response 210 days) 2) 17/27 (median duration of response 400 days)

Mouridsen HT 1977 *(Continued)*

	Toxicity WHO3-4 Leukopenia <1000 only reported in this review 1) 1/24 2) 4/27 Alopecia 1) 8/24 2) 21/27 Toxic deaths - Nil reported
Notes	Poor quality print. Not ITT - 4 patients died of (progressive disease) after randomisation and were not included in analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised using stochastic array of numbers
Allocation concealment (selection bias)	High risk	Closed envelope - can be corrupted
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not ITT - 4 patients died of (progressive disease) after randomisation and were not included in analysis
Selective reporting (reporting bias)	High risk	Some expected outcomes not reported

Nabholtz JM 1999

Study characteristics

Methods	Accrual (July 1994 - February 1997) RCT- Phase III Randomisation centralised - block design by institution - no stratification by characteristics - non blinded, Canadian multicentre Groups well balanced for pre-treatment characteristics
Participants	392 women over the age of 18 with histologically or cytologically proven metastatic progressive adenocarcinoma of the breast and measurable or non measurable but assessable disease 100% MBC 38% Firstline All participants previously treated with anthrycycline CT for advanced disease or disease progression within 12 months of the end of anthrycycline therapy given as adjuvant treatment. Excluded if pretreated with mitomycin, vinca alkaloids or taxoids Randomised no: 1) n = 203 (median age 51; 30-73)) 2) 189 (median age 52;32-78)) Assessable no:

Nabholtz JM 1999 *(Continued)*

	1) n = 200 2) n = 187
Interventions	TXT vs MMC +V2 1) Docetaxel 100 mg/m2 iv every 3 weeks 2) Mitomycin 12 mg/m2 iv every 6 wks + Vinblastine 6 mg/m2 iv every 3 wks Maximum 10 treatment cycles
Outcomes	Survival and TTP curves included - Kaplan-Meier method - TTP from date of randomisation TTF curve excluded Median survival 1) 11.4 mths 2) 8.7 mths Median TTP 1) 19 weeks 2) 11 weeks OR (CR+PR) 1) 59/179 2) 21/171 Toxicity WHO 3-4 Nausea and vomiting 1) 14/200 2) 9/187 Neutropenia 1) 188/200 2) 176/187 Toxic death 1) 4/203 (sepsis, pneumonia, unspecified infection, unexplained respiratory failure) 2) 3/189 (hemolytic uremia, progressive lymphangitic carcinomatosis) QOL - EORTC QLQ-C30
Notes	F/U survival and TTP min 4.5 mths - max 33mths (from curve) ITT - 5 patients who did not receive treatment (3;2) were included in the efficacy analysis, including survival. Analysis of response and TTP was also done on eligible and assessable population

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation centralised using a block design by institution
Allocation concealment (selection bias)	Low risk	Centrally randomised
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data balanced across groups

Nabholtz JM 1999 *(Continued)*

Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Nielsen D 2000

Study characteristics	
Methods	Accrual (July 1987-Nov 1990). Phase III RCT. Consecutive patients were centrally registered and then randomised after stratification by ECOG performance status Denmark Groups comparable on age, performance status, prior adjuvant therapy, menopausal status, sites and number of metastatic sites, disease free interval to first recurrence and lead time from prior adjuvant chemotherapy
Participants	155 women with histologically proven locally advanced or MBC and bidemensionally measurable disease 92% MBC 100% Firstline Randomised no: 1) n = 81 (median age 52; 34-68) 2) n = 74 (median age 55; 27-69) Assessable no: 1) n = 74 2) n = 65
Interventions	E vs E+ CDDP 1) Epirubicin 70 mg/m2 days 1 and 8 every 4 weeks 2) Epirubicin 60mg/m2 days 1and 8 + Cisplatin 100mg/m2 day 1 every 4 weeks
Outcomes	Survival and TTP curves - Kaplan Meier estimate. TTP calculated as time from first drug administration Median survival 1) 15.1 mths (0.1-63.3) 2) 21.5 mths (21.5 (0.1-77.7) Median TTP 1) 8.4 mths (0.1-66.3) 2) 15.3 mths (0.1-77.7) OR (CR+PR) 1) 45/74 2) 43/65 Toxicity WHO 3-4 WCC 1) 59/74 2) 60/65 Toxic death 1) 2 2) 4

Nielsen D 2000 *(Continued)*

Notes	FU survival and TTP min 1mth - max 77.7 mths based on text ITT for response, survival and toxicity - although 10 declared ineligible, 6 refused treatment. No loss to follow up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Centrally randomised but method not described
Allocation concealment (selection bias)	Low risk	Centrally randomised
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Nielson D 1990

Study characteristics

Methods	Accrual (January 1983 - December 1986) RCT- Consecutive patients were centrally registered and after stratification by performance status were randomised? method not fully described Denmark Baseline comparability
Participants	143 women with histologically proven advanced progressive breast cancer with measurable or evaluable disease - prior adjuvant or CT for MBC No prior anthracycline 100% MBC 48% First line Randomised no: 1) n = 76 (median age 56; 28-69) - Oophorectomy in 4 pts 2) n = 67 (median age 55; 33-70) - Oophorectomy in 6 pts Evaluable for response and toxicity: 1) n = 72 2) n = 61
Interventions	E vs E+V4 1) Epirubicin 60 mg/m2 iv days 1&8 every 4 wks 2) Epirubicin 45 mg/m2 + Vindesine 3 mg/m2 iv day 1 & 8 every 4 weeks
Outcomes	Survival and TTP curves - from randomisation - survival and TTP - Kaplan Meier estimates Median survival 1) 12mths 2) 12mths

Nielson D 1990 *(Continued)*

	Median TTP 1) 6mths 2) 6mths OR (CR+PR) 1) 38/72 (median duration of CR - 4 mths) 2) 28/61 (median duration of CR- 16mths Toxicity - NE Toxic death 1) 4 (CCF) 2) 0
Notes	F/U survival min 0 - 80mths (stated in text F/U TTP min 2mths - 36mths (Text and last event on the curve) Appears ITT

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Centrally randomised but method not described
Allocation concealment (selection bias)	Low risk	Centrally randomised
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Norris B 2000

Study characteristics

Methods	Accrual (January 1992 - July 1995) RCT - randomisation performed centrally at the NCIC CTG central office Multi-centre (Canada), Groups comparable at baseline for age, menstrual status and disease type
Participants	303 histologically proven and/or measurable metastatic breast cancer Vinca alkaloid, anthracycline and mitoxantrone naïve 100% MBC 75% First line Randomised no: 1) n = 149 2) n = 151 Assessable for response: 1) n = 144 2) n = 145

Norris B 2000 *(Continued)*

	Assessable for toxicity: 1) n = 149 2) n = 151
Interventions	A vs A + V3 1) Doxorubicin 70 mg/m2 day 1 every 3/52 2) Doxorubicin 70 mg/m2 day 1 + Vinorelbine 25 mg/m2 days 1 and 8 every 3/52 changed to 1) Doxorubicin 60 mg/m2 day 1 every 3/52 2) Doxorubicin 40 mg/m2 day 1 + Vinorelbine 20 mg/m2 on days 1 and 8 every 3/52
Outcomes	Survival curve Kaplan-Meier. No TTP curve Median survival 1) 14.4 mths 2) 13.8 mths Median TTP 1) 6.1 months 2) Median 6.2 months OR (CR+PR) 1) 44/144 2) 55145 Nausea and vomiting 1) 45/149 2) 29/151 Alopecia 1) 36/149 2) 33/151 Granulocytopenia 1) 129/149 2) 132/151 Toxic death 1) 2/149 (cardiomyopathy, febrile neutropenia) 2) 1/151 (febrile neutropenia) Quality of life _EORTC QLQ-30
Notes	F/U min 1mth - max 34mths (based on curve). No loss to F/U **Dosing changed in November 1992 following 16 of the first 65 patients experiencing febrile neutropenia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Centrally randomised but method unclear
Allocation concealment (selection bias)	Low risk	Centrally randomised

Norris B 2000 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

O'Shaughnessy J 2001

Study characteristics	
Methods	Accrual (May 1996 - May 1997) RCT - randomised sequentially in a 1:2 ratio per country 23 international centres Well balanced at baseline
Participants	95 women with histologically proven advanced breast cancer not previously treated with cytotoxic therapy 100% MBC 100% Firstline Randomised no: 1) n = 62 2) n = 33
Interventions	CCB vs CMF 1) Capecitabine 1255 mg/m2 twice daily for two weeks followed by a 1 week rest period 2) Cyclophosphamide 600 mg/m2 + Methotrexate 40 mg/m2 + 5-FU 600 mg/m2 once every 3 weeks Both regimens were conducted for up to 18 weeks
Outcomes	Survival and TTP curves Median survival 1) 9.6 mths 2) 17.2 mths Median TTP 1) 3.0 mths 2) 4.1 mths OR (CR+PR) 1) 18/61 2) 5/32 Toxicity WHO 3-4 Nausea and vomiting 1) 7/61 2) 3/32 Neutropenia 1) 5/61 2) 13/32 Alopecia 1) 0/61

O'Shaughnessy J 2001 *(Continued)*

	2) 1/32 Toxic death 1) 3 2) 0
Notes	F/U survival min 1mth - max 23mths (based on the curve) F/U TTP min 1mth-12mth (based on the curve) ITT used for all reported outcomes although 2 patients were removed following randomisation Initial treatment period was 18 weeks. Patients with progressive disease were withdrawn from the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States 'patients were randomised'
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

O'Shaughnessy J 2002

Study characteristics

Methods	RCT - Phase III Multi-centre (75 centres, 16 countries) Randomisation by country using a block size of four via a computer assisted, touch tone central randomisation service - Previous use of Paclitaxel was the only variable used for stratification Baseline characteristics well balanced between the treatment groups
Participants	511 women >/=18 with histologically or cytologically confirmed breast cancer with unresectable locally advanced and/or metastatic disease - at least one bi-dimensionally measurable lesion. All patients had BC which recurred after anthracycline treatment. Ineligible if they had received docetaxel containing regimens previously (paclitaxel OK) 99% MBC 66% First line Randomised no: 1) 256 (Median age 51 (25-75)) 2) 255 (Median age 52 (26-79)) Assessable for toxicity: 1) 255 2) 251
Interventions	TXT vs TXT +CCB 1) docetaxel 100 mg/m2 every 3 weeks

O'Shaughnessy J 2002 *(Continued)*

	2) capecitabine 1,250 mg/m2 twice daily on days 1-14 + docetaxel 75mg/m2
Outcomes	Survival and TTP curves - Kaplan-Meier Median survival 1) 11.5mths 2) 14.5 mths Median TTP 1) 4.2 mths 2) 6.1 mths Objective Response - best response 1) 77/256 2) 107/255 Toxicity WHO 3-4 Nausea 1) 5/255 2) 15/251 Alopecia 1) 18/255 2) 15/251 Neutropenia 1) 38/255 2) 40/251 Toxic death 1) 1 - neutropenic sepsis 2) 4 - enterocolitis, sepsis, pulmonary oedema, hepatic coma QOL - European organisation for research and treatment of cancer EORTC QLQ- C30 Global Health Score 230 pts group 1; 224 group 2
Notes	F/U survival min 23mths (stated) - max 44mths (last event on curve) F/U TTP min 23mths (stated) - max 44mths (last event on curve) All efficacy data ITT - safety was assessed using pts who received at least one dose of study medication and for whom follow up data was available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by country using a block size of four via a computer assisted, touch tone central randomisation service
Allocation concealment (selection bias)	Low risk	Centrally randomised
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Rubens RD 1975

Study characteristics	
Methods	Accrual (June 1970- December 1974) RCT - no details of methodology provided UK single centre Groups comparable at baseline
Participants	99 women with advanced breast cancer, relapsed or failed on endocrine therapy 100% MBC 100% Firstline Randomised no: 1) n = 49 2) n = 50
Interventions	C vs CMFV2P 1) Cyclophosphamide 200-300 mg iv depending on wt 2) Cyclophosphamide 100 mg/day po for 14 days + 5-Flurouracil 500 mg iv + Methotrexate 25 mg iv + Vinblastine 5 mg iv FMV days 1,8,15 followed by 4 wk rest period, then cycle repeated
Outcomes	Survival curve - life table method - from commencement of chemotherapy No TTP curve Response (objective plus total remission) 1) 29/49 (median duration of response 5.5 mths 2) 32/50 median duration of response 7mths Toxic death 1) 1 (septicemia) 2) 0
Notes	F/U min 6mths (stated) - max 42 mths (last event on curve) ITT including 3 group 2 patients who died between randomisation and commencement of treatment Toxicity data not discernable from text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information provided to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information provided to permit judgement

Sjostrom J 1999

Study characteristics	
Methods	Accrual (December 1994 - October 1997) RCT - Phase III - method of randomisation not described Scandinavia, Estonia and Poland - multi centre Baseline comparability on patient characteristics
Participants	283 women with 100% MBC who had failed previous firstline anthracycline therapy or had failed previous adjuvant anthracycline therapy First and second line Randomised no: 1)143 (Median age 50 (27-69)) 2)140 (Median age 51 (26-59)) Assessable for response: 1) n = 143 2) n = 139 Assessable for toxicity: 1) n = 140 2) n = 139 3 patients in the single agent arm did not receive treatment
Interventions	TXT vs M+ F 1) Docetaxel 100 mg/m2 iv every 3 wks 2) Methotrexate 200 mg/m2 days 1&8 every 3 wks + 5-Fluorouracil 600 mg/m2 iv days 1&8 every 3 wks
Outcomes	Survival and TTP curves (from date of randomisation) Median survival 1) 10.4 mths 2) 11.0 mths Median TTP 1) 6.3 mths 2) 3 mths OR (CR+PR) 1) 61/143 2) 29/139 Toxicity WHO 3-4 (280 evaluable for haematological safety and 269 for haematological toxicity) Nausea 1) 6/140 2) 11/139 Alopecia 1) 74/140 2) 17/139 WCC 1) 108/140 2) 22/139 Toxic death 1) 3 (2 febrile leucopenia and 1 generalised infected erythroderma)

Sjostrom J 1999 *(Continued)*

	2) 1 (febrile leucopenia) QOL EORTC QLQ-C30
Notes	F/U survival and TTP min 4mths - max 36mths (stated in text) ITT on all efficacy analysis Crossover on progression recommended

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Sledge G(A) 2003

Study characteristics

Methods	Accrual (February 1993 - September 1995) RCT - methodology not described North America, multi-centre Well balanced for race, age, ER status, disease free interval, dominant site of disease, number of sites of disease, performance status and prior systemic therapy
Participants	367 women with histologically confirmed breast adenocarcinoma with progressing regional or metastatic disease - May have received adjuvant therapy if it had ceased 6 mths previously or prior to hormonal therapy - 100% MBC 71% Firstline Randomised no: 1) n = 245 (Median age 58; 25-79) 2) n = 244 (Median age 56; 27-78)) Assessable no: 1) n = 224 2) n = 230
Interventions	A vs A+PACL 1) Doxorubicin 60 mg/m2 every 3 wks to 8 cycles or progression 2) Doxorubicin 50 mg/m2 iv + Paclitaxel 150 mg/m2 continuous infusion over 24 hrs Cross over at time of progression

Sledge G(A) 2003 *(Continued)*

Outcomes	OS curves - log rank test. OS measured from date of study entry to death/date of progressive disease TTF curve. Excluded. Median survival 1) 19.1mths 2) 22.4mths Median TTF 1) 6mths 2) 8.2 mths Response (objective) 1) 81/224 2) 108/ 230 Toxicity Mod - Sev (NCI criteria) Leukopenia 1) 111/224 2) 126/230 Vomiting 1) 15/224 2) 10/230 Toxic death 1) 6/224 2) 4/230 QoL - Functional assessment of cancer therapy - breast (fact B) administered at baseline and 16 weeks
Notes	F/U survival and TTP min 6mths (based on maximum of eight cycles of 3 weeks) - max 75mths(last event on curve) Not ITT - 739 patients were initially randomised - 731 total in trial based on group numbers provided in the text. Text states 16 patients excluded and 33 pts excluded from the analysis for reasons of ineligibility Excluded from firstline analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting to permit judgement
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Sledge G(B) 2003

Study characteristics	
Methods	Accrual (February 1993 - September 1995) RCT - methodology not described North America, multi-centre Well balanced for race, age, ER status, disease free interval, dominant site of disease, number of sites of disease, performance status and prior systemic therapy
Participants	364 women with histologically confirmed breast adenocarcinoma with progressing regional or metastatic disease - May have received adjuvant therapy if it had ceased 6 mths previously or prior to hormonal therapy - 100% MBC 71% Firstline Randomised no: 1) n = 242 (Median age 56; 27-76) 2) n = 244 (Median age 56; 27-78)) Assessable no: 1) n = 229 2) n = 230
Interventions	PACL vs A+PACL 1) Paclitaxel 175 mg/m2/24 hrs 2) Doxorubicin 50 mg/m2 iv + Paclitaxel 150 mg/m2 continuous infusion over 24 hrs Cross over at time of progression
Outcomes	OS curve - log rank test - OS measured from date of study entry to death/date of progressive disease TTF curve. Excluded. Median survival 1) 22.5 mths 2) 22.4mths Median TTF 1) 6.3 mths 2) 8.2 mths Response (objective) 1) 78/229 2) 108/ 230 Toxicity Mod - Sev (NCI criteria) Leukopenia 1) 137/229 2) 126/230 Vomiting 1) 6/229 2) 10/230 Lethal toxicity 1) 4/229 2) 4/230 QoL - Functional assessment of cancer therapy - breast (fact B) administered at baseline and 16 weeks

Sledge G(B) 2003 *(Continued)*

Notes	F/U survival and TTP min 6mths (based on maximum of eight cycles of 3 weeks) - max 75mths(last event on curve) Not ITT - 739 patients were initially randomised - 731 total in trial based on group numbers provided in the text. Text states 16 patients excluded and 33 pts excluded from the analysis for reasons of ineligibility Excluded from firstline analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting to permit judgement
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Steiner R 1983

Study characteristics

Methods	Accrual (May 1977 - Jan 1980) RCT - methodology not described Groups at baseline similar in age and diagnosis, post operative disease free interval and time interval between diagnosis and commencement of treatment. Performance status more favourable in combination group
Participants	119 women with MBC with no prior chemotherapy for ABC, no signs of cardiac failure and the presence of progressive disease in evaluable lesions 116 patients had previous endocrine therapy 100% MBC 100% firstline Randomised numbers not provided Assessable no: 1) n = 53 2) n = 54
Interventions	A vs A + V1 1) Doxorubicin 70 mg/m2 IV on day 1 of a 3/52 cycle 2) Doxorubicin 70 mg/m2 IV on day 1 of a 3/52 cycle + Vincristine 1.4 mg/m2 (max 2mg) on days 1 and 8 **Maximum of 8 courses
Outcomes	No survival curves. Survival curves for responders only No TTP curves

Steiner R 1983 *(Continued)*

	Median survival 1) 10mths 2) 14mths OR (CR+PR) 1) 30/53 2) 28/54 Toxicity: Nausea and vomiting 1) 42/53 2) 47/54 Alopecia 1) 44/53 2) 47/54 WCC 1) 3/53 2) 10/54 Toxic death 1) 1/53 (septicaemia) 2) 1/54 (pantocytopenia)
Notes	Not ITT - 119 women were entered into the study but 10 were excluded from the analysis. A further 2 women who died soon after randomisation were included in the survival analysis but not in the response analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Randomisation numbers not provided and insufficient information provided to permit judgement
Selective reporting (reporting bias)	High risk	Provides survival information for responders only

Stockler M 2006

Study characteristics

Methods	Accrual dates not stated RCT, multi-centre, international Randomisation not described in abstract Well balanced at randomisation
Participants	323 women with advanced breast cancer

Stockler M 2006 *(Continued)*

	100% MBC 100% Firstline Randomised no: 1) 214 2) 109
Interventions	CCB (intermittent/continuous) vs CMF 1) Capecitabine 2000 mg/m2 days 1-14, rest day 15-21 OR capecitabine 200 mg/m2 days 1-21 2) Cyclophosphamide (dose not stated) days 1-14 + Methotrexate (dose not stated) days 1 and 8 + 5-FU (dose not stated) days 1 and 8
Outcomes	Survival and PFS curves Median survival 1) 22 mths 2) 18 months Median PFS 1) 6mths 2) 7mths OR (CR+PR) 1) 42/214 2) 18/109 Toxicity WHO 3-4 Neutropenia 1) 3/214 2) 24/109 Nausea and vomiting 1) 12/214 2) 4/109 Alopecia 1) 1/214 2) 2/109 Toxic death - NR
Notes	F/U survival and PFS min 1mth and max 33mths (based on curve) Results calculated from poster presentation only as full paper not yet available CCB arms combined to achieve OS, toxicity and response data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data

Stockler M 2006 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Takayama T(A) 2000

Study characteristics	
Methods	Accrual (March 1990 - September 1997). Japan RCT - Double blind randomised comparative study - can't determine methodology
Participants	111 women with advanced breast cancer 100% MBC ? 100% Firstline Randomised numbers not provided. Assessable no: 1) n = 57 2) n = 54
Interventions	F vs F+C 1) 5 Fluorouracil 300mg/day orally 2) 5 Fluorouracil 300mg/day orally + Cyclophosphamide 150 mg/day
Outcomes	Survival and PFS curve included - can't determine method OR (CR+PR) 1) 8/57 2) 20/54 Toxicity WHO 3-4 Nausea and vomiting 1) 1/57 2) 0/54 WCC 1) 0/57 2) 24/54
Notes	F/U survival min 5mths - max 60mths (based on curve) F/U PFS min 1mth - max 24mths max (based on curve) Not ITT - 181 pts entered the trial but only 166 described **Japanese - some included tables in English - limited information ** some information has been Interpreted by a Japanese speaking person Abstract suggests 100% firstline but unclear in table of patient characteristics so excluded from firstline analysis
Risk of bias	

Takayama T(A) 2000 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not repoted
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Some missing data but insufficient information provided to permit judgement
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Takayama T(B) 2000

Study characteristics	
Methods	Accrual (March 1990 - September 1997). Japan RCT - Double blind randomised comparative study - can't determine methodology
Participants	109 women with advanced breast cancer 100% MBC ? 100% Firstline Randomised numbers not provided Assessable no: 1) n = 55 2) n = 54
Interventions	C vs F+C 1) Cyclophosphamide 150 mg/day 2) 5 Fluorouracil 300mg/day orally + Cyclophosphamide 150 mg/day
Outcomes	Survival and PFS curve included - can't determine method Response 1) 13/55 2) 20/54 Toxicity (3-4) Nausea and vomiting 1) 0/55 2) 0/54) WCC 1) 24/55 2) 24/54 Toxic death - NR
Notes	F/U survival min 5mths - max 60mths (based on curve)

Takayama T(B) 2000 *(Continued)*

	F/U PFS min 1mth - max 24mths max (based on curve) Not ITT - 181 pts entered the trial but only 166 described **Japanese - some included tables in English - limited information ** Some information has been interpreted by a Japanese speaking person Abstract suggests 100% firstline but unclear in table of patient characteristics so excluded from firstline analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Some missing data but insufficient information provided to permit judgement
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Tashiro H 1994

Study characteristics

Methods	Accrual (November 1986 - November 1989). RCT - Randomisation using a table of random sampling numbers was controlled by the head of the hospitals pharmacy department. Double Blind Japan - single centre Groups comparable at baseline
Participants	60 women with progressive advanced or metastatic breast cancer which can be measured or evaluated pre- and postmenopausal 100% MBC 86% Firstline Randomised no: 1) 30 (mean age 56.5) 2) 30 (mean age 55.4) Assessable no: 1) n = 28 2) n = 28
Interventions	FT vs UFT + placebo 1) 5 Fluoro-1-(tetrahydro - 2 furyl)- uracil (an analogue of 5 FU) 800 mg/day (Tegafur) 2) Tegafur 400 mg/day + Uracil 896 mg/day taken as 2 capsules

Tashiro H 1994 *(Continued)*

	+ 2 x placebo single agent capsules orally 2xday
Outcomes	Survival curve - Kaplan-Meier method - calculated from the commencement of chemo No TTP Median survival 1) 34 mths 2) 47mths OR (CR+PR) 1) 6/28 2) 11/28 Toxicity WHO 3-4 Alopecia 1) 0/28 2) 0/28 WCC 1) 0/28 2) 0/28 Nausea and vomiting 1) 0/28 2) 0/28 Toxic death - NR
Notes	F/U survival and TTP min 20mths - max 62mths (stated in text) ITT including 3 group 2 patients who died between randomisation and start of treatment Excluded from firstline analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation using a table of random sampling numbers
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Thomas E 2008

Study characteristics

Methods	Accrual September 2003 - January 2006 Multi centre - 22 countries RCT - randomisation method not described Baseline comparability

Thomas E 2008 *(Continued)*

Participants	752 women with measurable locally advanced or MBC pre-treated with or resistant to anthracyclines and taxanes At least 85% MBC 8% Firstline Randomised no: 1) n= 377 2) n= 375 Assessable no: 1) n= 368 2) n= 369
Interventions	CCB versus CCB +IX 1) Capecitabine 2500mg/m2 oral, 2 divided doses days 1-14 2) Capecitabine 2000mg/m2 oral in two divided doses each day days 1-14 + Ixabepilone 40mg/m2 3 hr IV infusion on day 1 21 day cycle
Outcomes	PFS curve estimated by Kaplan-Meier method and compared using log rank test No OS curve but survival analysis planned once 631 patients have died Median PFS 1) 4.2 months (3.81-4.5) 2) 5.8 months (5.45-6.97) OR (CR+PR) 1) 54/377 2) 130/375 Toxicity (WHO ¾) Nausea/vomiting 1) 13/368 2) 25/369 Leukopenia 1) 21/368 2) 210/369 Alopecia 1) 3/368 2) 27/369 Toxic death 1) n=3 (neutropenia related) 2) n=12 (neutropenia related)
Notes	FU 1-25 months (estimated from curve) ITT for PFS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

Thomas E 2008 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Vaughn CB 1988

Study characteristics	
Methods	RCT - Method not described Stratified as good or poor risk North America - 22 member institutions of the South West Oncology Group Baseline comparability for age, menopausal status, performance status, ER status and site of metastasis
Participants	122 women with histologically proven advanced adenocarcinoma of the breast with a measurable lesion. Prior treatment with CMFVP 100% MBC Unclear if participants were firstline or subsequent line. Randomised no: 1) n = 63 2) n = 58 Assessable no: 1) n = 59 (Median age 55; 23-76) 2) n = 56 (Median age 55; 33-80))
Interventions	A vs A+ETO 1) Doxorubicin 60 mg/m2, day 1 (good risk patients) or 45 mg/m2, day 1 (poor risk patients) 2) Doxorubicin 35 mg/m2, day 1 (good risk) or 30 mg/m2, day 1 (poor risk) + VP-16 75 mg/m2/day x 5 days (good risk) or 50 mg/m2/day x 5 days (poor risk)
Outcomes	Survival and TTP curves - estimated from date of randomisation Median survival 1) 8.5mths 2) 9.8mths Median TTP 1) 4.2mths 2) 5.1mths OR (CR + PR) 1) 14/59 2) 13/56 Toxicity (SWOG criteria) Alopecia 1) 57/59 2) 57/56) Leukopenia 1) 16/59

Vaughn CB 1988 *(Continued)*

	2) 32/56 Nausea and vomiting 1) 10/59 2) 2/56 Toxic death 1) 1 (cardiac toxicity) 2) 0
Notes	F/U survival min 1mth (one cycle) - max 66mths (last event on curve) F/U TTP min 1mth (one cycle) - max 52mths (last event on curve) Not ITT analysis - 7 ineligible patients excluded from the analysis (4 in group 1 and 3 in group 2). Three pts with treatment deviations were excluded from toxicity tables but otherwise included in the arms they were randomised to. Nine and 8 patients respectively who discontinued treatment early were included in the analysis. Excluded from firstline analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data equal across arms
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Venturino A(A) 2000

Study characteristics

Methods	RCT - Phase II - methodology not described Italian - multi centre Groups comparable
Participants	66 women with histopathologically confirmed diagnosis of breast cancer, progressive metastatic disease with assessable lesions and one previous chemotherapy for MBC 100% MBC All second line Randomised no: 1) n = 33 (median age 62.5; 34-74) 2) n = 33 (median age 60; 49-70)
Interventions	V3 vs LEUC+F 1) Vinorelbine 30mg/m2 IV weekly

Venturino A(A) 2000 *(Continued)*

	2) Leucovorin 100mg/m2 IV + 5 Fluorouracil 370 mg/m2 IV
Outcomes	No survival or TTP curves Median survival 1) 9.5mths 2) 9 mths Median TTP 1) 2mths 2) 3mths OR (CR + PR) 1) 8/33 (median 9; 4-17) 2) 10/33 (median 11; 6-52) Toxicity WHO 3-4 Leukopenia 1) 6/33 2) 1/33 Alopecia 1) 0/33 2) 0/33 Toxic death - NR
Notes	ITT - -All patients assessable for response and toxicity

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	No survival or TTP reported

Venturino A (B) 2000

Study characteristics

Methods	RCT - Phase II - methodology not described Italian - multi centre Groups comparable
Participants	66 women with histopathologically confirmed diagnosis of breast cancer, progressive metastatic disease with assessable lesions and one previous chemotherapy for MBC 100% MBC

Venturino A (B) 2000 *(Continued)*

	All second line Randomised no: 1) 33 - median age 62.5 (34-74) 2) 33 median age 60.5 (41-71) Assessable no: 1) 33 2) 32 - 1 lost at randomisation -
Interventions	V3 vs MZA+LEUC+F 1) Vinorelbine 30mg/m2 IV weekly 2) Mitoxantrone 12 mg/m2 IV day 1 + Leucovorin 100mg/m2 IV +5 Fluorouracil 370 mg/m2 IV
Outcomes	No survival or TTP curves Median survival 1) 9.5mths 2) 9 mths Median TTP 1) 2mths 2) 5mths OR (CR + PR) 1) 8/33 (median 9; 4-17) 2) 7/32 (median 10;5-33) Toxicity WHO 3-4 Leukopenia 1) 6/33 2) 1/32 Alopecia 1) 0/33 2) 0/32 Toxic deaths - nil reported
Notes	ITT - -All but one patient from arm 2 assessable for response and toxicity

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	No survival or TTP reported

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

Study	Reason for exclusion
Anonymous 2002	Listed in review (2005) in ongoing studies. Data unavailable and status of trial unknown
Doroshow 1997	Listed in review (2005) in ongoing studies. No longer registered as ongoing on NCI registry and no data available.
Jackisch C 1999	Listed in review (2005) in ongoing studies. Excluded due to allowance of participants to have up to 6 treatment cycles of induction chemotherapy prior to enrolment.
Kaufman PA 1998	Randomised numbers not available. Author did not respond to request for additional data.
Keller AM 2004	Was included in initial review based on data obtained from ASCO 2001 conference proceeding (Abstact number 115). Removed from review following review of full published paper (2004) which further clarified the regimes studied. Of the 151 participants in the control arm 129 were receiving single agent vinorelbine and 22 received mitomycin C plus vinblastine. Data was not provided separately for combination and single agent regimens within the control group.
Legha, 1979	Response data on one arm only available. Also patients found to be intolerant of treatment were excluded from the analysis. Limited toxicity data available.
Liu T 1986	Was included in the initial review but excluded based on a post hoc consideration of the decision not to include high dose chemotherapy regimens.
Mann GB 1985	Not all outcomes for the review available. Study includes small numbers and authors report a number of protocol violations.
Nemoto T. 1978	Randomised numbers not available. Sequential. Toxicity and response data is provided for all sequences and is not extractable for sequence of interest.
Perez E 2001	Listed in review (2005) in ongoing studies. Trial is listed on NCI registry as closed - author was contacted but did not know of this trial. Trial registry informed.

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

Burzynski 1999

Study name	BRI-BR-10 Phase II Randomised Study of Methotrexate with or without Antineoplaston A10 Capsules in Women with Advanced Breast Cancer
Methods	
Participants	30-70 patients with metastatic BC North America single-centre 100% firstline ER -ive Postmenopausal
Interventions	Methotrexate po 5 days on/5 days off vs Methotrexate po 5 days on/5 days off + Antineoplaston A10, 7 times daily until max tolerated dose reached
Outcomes	Response

Burzynski 1999 *(Continued)*

	Toxicity
Starting date	Not known
Contact information	Principal Investigator: Dr Stanislaw Burzynski, Burzynski Research Institute, Houston, Texas, USA Phone: 713-597-0111
Notes	

Butler FO 2004

Study name	A study of Docetaxel monotherapy or DOXIL/CAELYX and Doxetaxel in patients with advanced breast cancer
Methods	
Participants	? patients with advanced breast cancer Female >18 years
Interventions	Doxorubicin injection and docetaxel vs docetaxel alone
Outcomes	Response TTP Toxicity QOL
Starting date	Not known
Contact information	Principal Investigator: Fred Butler, Investigative Clinical Research, LLC, Indianapolis, Indiana, 46254, USA
Notes	Identified in 2006 search for review update

Heidemann E 2001

Study name	Phase III Randomised Study of Mitoxantrone vs CMF - Cyclophosphamide/Methotrexate/ Fluorouracil
Methods	
Participants	296 women 35-80yrs Pre and post menopausal Histologically verified metastases 100% firstline
Interventions	Mitoxantrone vs CMF
Outcomes	Survival

Heidemann E 2001 *(Continued)*

	QOL TTP Performance status Response
Starting date	Not known
Contact information	Hansjochen Wilke
Notes	

Yunus F. 2000

Study name	Phase III Randomised Study of Paclitaxel with or without Gemcitabine in Women with Unresectable, Locally Recurrent, or Metastatic Breast Cancer
Methods	
Participants	? patients Histologically or cytologically proven unresectable locally recurrent, or Metastatic Breast Cancer
Interventions	Paclitaxel vs Paclitaxel with or without Gemcitabine
Outcomes	Not known
Starting date	Not known
Contact information	Furhan Yunus Eli Lilly and Company
Notes	

DATA AND ANALYSES

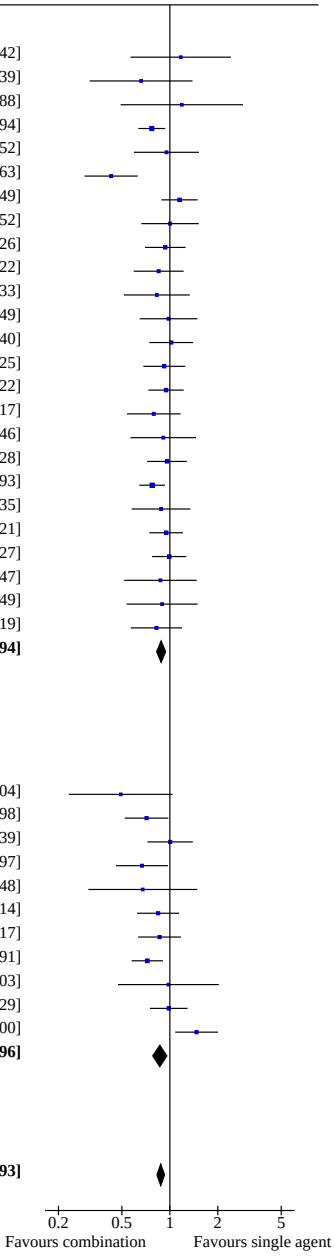
Comparison 1. Overall survival

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Overall survival - randomised patients - all trials	36	7147	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.88 [0.83, 0.93]
1.1.1 Question 1: Regimen A (single) versus Regimen A + other	25	4935	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.88 [0.83, 0.94]
1.1.2 Question 2: Regimen A (single) versus Regimen C (combination)	11	2212	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.86 [0.78, 0.96]
1.2 Overall survival - randomised patients - first line	21	3982	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.88 [0.81, 0.94]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2.1 Question 1: Regimen A (single) versus Regimen A + other	14	2820	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.88 [0.80, 0.96]
1.2.2 Question 2: Regimen A (single) versus Regimen C (combination)	7	1162	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.87 [0.75, 1.01]
1.3 Overall survival - Question 1 - Regimen A versus A + other - randomised patients	25	4935	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.88 [0.83, 0.94]
1.3.1 Sub group A: Single anthracycline agent versus anthracycline + other regimen	14	2897	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.95 [0.87, 1.04]
1.3.2 Sub group B: Single alkylating versus alkylating + other	5	375	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.91 [0.72, 1.15]
1.3.3 Sub group C: Single antimetabolite versus antimetabolite + other	3	279	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.62 [0.46, 0.82]
1.3.4 Sub group D: Single taxane versus taxane + other	3	1384	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.81 [0.72, 0.91]
1.4 Overall survival - Question 2 - Regimen A versus Regimen C - randomised patients	10	1952	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.87 [0.78, 0.97]
1.4.1 Sub group E: Single anthracycline agent versus non-anthracycline combination regimen	2	88	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.57 [0.33, 0.98]
1.4.2 Sub group F: Single taxane versus non-taxane, non-anthracycline containing combination regimen	5	1262	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.83 [0.73, 0.95]
1.4.3 Sub group G: Single non-taxane, non-anthracycline agent versus other combination regimen	3	602	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	1.06 [0.85, 1.33]
1.5 Overall survival - single agent taxane versus all combination	8	2646	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.82 [0.75, 0.89]
1.6 Overall survival - single agent anthracycline versus all combinations	16	2985	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.94 [0.86, 1.02]

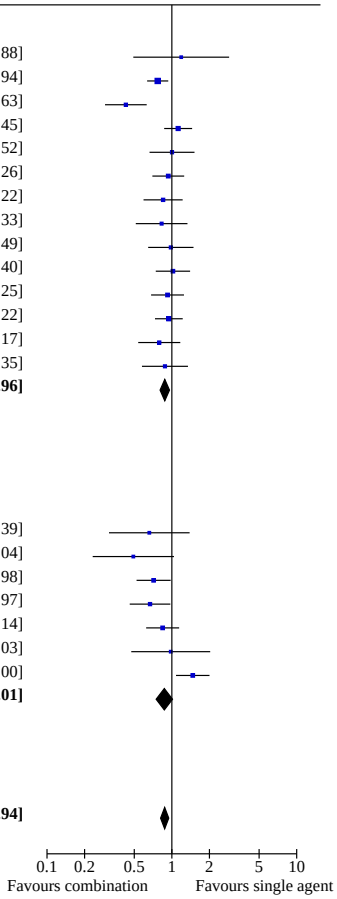
Analysis 1.1. Comparison 1: Overall survival, Outcome 1: Overall survival - randomised patients - all trials

Study or Subgroup	Combination Events	Combination Total	Single agent Events	Single agent Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
1.1.1 Question 1: Regimen A (single) versus Regimen A + other								
Tashiro H 1994	17	30	18	30	1.15	7.3	0.6%	1.17 [0.57 , 2.42]
Ahmann DL 1974(1)	18	21	20	22	-2.89	6.95	0.5%	0.66 [0.31 , 1.39]
Ahmann DL 1974(2)	18	20	16	20	0.85	4.92	0.4%	1.19 [0.49 , 2.88]
Albain KS 2004	214	267	212	262	-26.47	101.37	8.0%	0.77 [0.63 , 0.94]
Andersson M 1986	32	44	34	45	-0.85	17.45	1.4%	0.95 [0.60 , 1.52]
Carmo-Pereira 1980	49	68	62	67	-22.08	26.03	2.0%	0.43 [0.29 , 0.63]
Ejlertsen B 2004	112	193	105	194	7.78	55.74	4.4%	1.15 [0.88 , 1.49]
Falkson G 1990	41	54	43	57	0.07	22.34	1.8%	1.00 [0.66 , 1.52]
French Epi (A) 1991	86	135	47	70	-2.94	44.66	3.5%	0.94 [0.70 , 1.26]
French Epi (B) 1991	84	137	47	70	-4.77	29.53	2.3%	0.85 [0.59 , 1.22]
Gundersen S 1986	37	66	38	62	-3.19	16.91	1.3%	0.83 [0.51 , 1.33]
Heidemann E 2004	48	89	50	87	-0.41	21.99	1.7%	0.98 [0.65 , 1.49]
Ingle J 1985	70	79	70	79	0.77	38.32	3.0%	1.02 [0.74 , 1.40]
Ingle J 1989	74	92	81	95	-3.33	41.79	3.3%	0.92 [0.68 , 1.25]
Joensuu H 1998	115	150	118	153	-3.25	58.76	4.6%	0.95 [0.73 , 1.22]
Nielsen D 2000	68	74	62	81	-5.93	25.53	2.0%	0.79 [0.54 , 1.17]
Nielson D 1990	52	65	63	76	-1.63	17.07	1.3%	0.91 [0.57 , 1.46]
Norris B 2000	90	151	93	149	-1.92	46.73	3.7%	0.96 [0.72 , 1.28]
O'Shaughnessy J 2002	203	255	222	256	-28.65	111.95	8.8%	0.77 [0.64 , 0.93]
Rubens RD 1975	45	50	42	49	-2.71	21.35	1.7%	0.88 [0.58 , 1.35]
Sledge G(A) 2003	86	115	178	229	-3.49	65.17	5.1%	0.95 [0.74 , 1.21]
Sledge G(B) 2003	86	115	174	224	-0.55	62.86	4.9%	0.99 [0.77 , 1.27]
Takayama T(A) 2000	15	27	35	57	-1.9	13.98	1.1%	0.87 [0.52 , 1.47]
Takayama T(B) 2000	15	27	35	55	-1.64	14.59	1.1%	0.89 [0.53 , 1.49]
Vaughn CB 1988	51	59	56	63	-5.43	28.04	2.2%	0.82 [0.57 , 1.19]
Subtotal (95% CI)		**2383**		**2552**			**70.9%**	**0.88 [0.83 , 0.94]**
Total events:	1726		1921					
Heterogeneity: Chi² = 27.04, df = 24 (P = 0.30); I² = 11%								
Test for overall effect: Z = 3.78 (P = 0.0002)								
1.1.2 Question 2: Regimen A (single) versus Regimen C (combination)								
Ahmann DL 1974(3)	24	28	17	20	-4.86	6.84	0.5%	0.49 [0.23 , 1.04]
Bishop J 1999	84	102	79	107	-13.08	38.87	3.1%	0.71 [0.52 , 0.98]
Bonneterre J 2002	69	90	68	88	0.17	35.73	2.8%	1.00 [0.72 , 1.39]
Canellos GP 1976	48	93	60	91	-11.02	27.38	2.2%	0.67 [0.46 , 0.97]
Fraser S 1993	12	19	15	21	-2.44	6.23	0.5%	0.68 [0.31 , 1.48]
Heidemann E 2002	75	127	86	133	-7.05	41.54	3.3%	0.84 [0.62 , 1.14]
Icli F 2005	80	100	87	101	-5.97	40.15	3.2%	0.86 [0.63 , 1.17]
Nabholtz JM 1999	150	189	141	203	-24.33	74.66	5.9%	0.72 [0.58 , 0.91]
O'Shaughnessy J 2001	14	33	26	62	-0.15	7.25	0.6%	0.98 [0.47 , 2.03]
Sjostrom J 1999	105	139	102	143	-0.78	51.71	4.1%	0.99 [0.75 , 1.29]
Stockler M 2006	63	109	104	214	15.55	40.32	3.2%	1.47 [1.08 , 2.00]
Subtotal (95% CI)		**1029**		**1183**			**29.1%**	**0.86 [0.78 , 0.96]**
Total events:	724		785					
Heterogeneity: Chi² = 21.42, df = 10 (P = 0.02); I² = 53%								
Test for overall effect: Z = 2.80 (P = 0.005)								
Total (95% CI)		**3412**		**3735**			**100.0%**	**0.88 [0.83 , 0.93]**
Total events:	2450		2706					
Heterogeneity: Chi² = 48.56, df = 35 (P = 0.06); I² = 28%								
Test for overall effect: Z = 4.69 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.10, df = 1 (P = 0.75), I² = 0%								



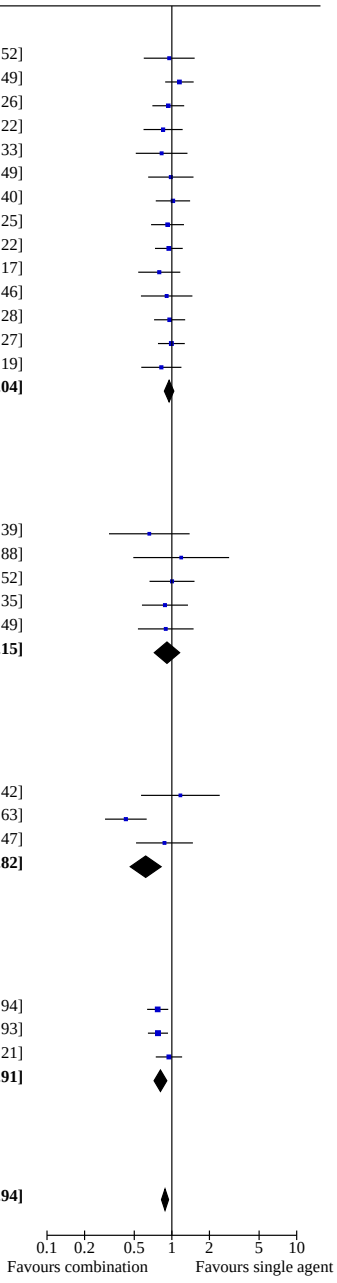
Analysis 1.2. Comparison 1: Overall survival, Outcome 2: Overall survival - randomised patients - first line

Study or Subgroup	Combination Events	Combination Total	Single agent Events	Single agent Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
1.2.1 Question 1: Regimen A (single) versus Regimen A + other								
Ahmann DL 1974(2)	18	20	16	20	0.85	4.92	0.7%	1.19 [0.49 , 2.88]
Albain KS 2004	214	267	212	262	-26.47	101.37	14.9%	0.77 [0.63 , 0.94]
Carmo-Pereira 1980	49	68	62	67	-22.08	26.03	3.8%	0.43 [0.29 , 0.63]
Ejlertsen B 2004	115	193	112	194	6.72	57.85	8.5%	1.12 [0.87 , 1.45]
Falkson G 1990	41	54	43	57	0.07	22.34	3.3%	1.00 [0.66 , 1.52]
French Epi (A) 1991	86	135	47	70	-2.94	44.66	6.6%	0.94 [0.70 , 1.26]
French Epi (B) 1991	84	137	47	70	-4.77	29.53	4.3%	0.85 [0.59 , 1.22]
Gundersen S 1986	37	66	38	62	-3.19	16.91	2.5%	0.83 [0.51 , 1.33]
Heidemann E 2004	48	89	50	87	-0.41	21.99	3.2%	0.98 [0.65 , 1.49]
Ingle J 1985	70	79	70	79	0.77	38.32	5.6%	1.02 [0.74 , 1.40]
Ingle J 1989	74	92	81	95	-3.33	41.79	6.1%	0.92 [0.68 , 1.25]
Joensuu H 1998	115	150	118	153	-3.25	58.76	8.6%	0.95 [0.73 , 1.22]
Nielsen D 2000	68	74	62	81	-5.93	25.53	3.8%	0.79 [0.54 , 1.17]
Rubens RD 1975	45	50	42	49	-2.71	21.35	3.1%	0.88 [0.58 , 1.35]
Subtotal (95% CI)		**1474**		**1346**			**75.1%**	**0.88 [0.80 , 0.96]**
Total events:	1064		1000					
Heterogeneity: Chi² = 21.63, df = 13 (P = 0.06); I² = 40%								
Test for overall effect: Z = 2.95 (P = 0.003)								
1.2.2 Question 2: Regimen A (single) versus Regimen C (combination)								
Ahmann DL 1974(1)	18	21	20	22	-2.89	6.95	1.0%	0.66 [0.31 , 1.39]
Ahmann DL 1974(3)	24	28	17	20	-4.86	6.84	1.0%	0.49 [0.23 , 1.04]
Bishop J 1999	84	102	79	107	-13.08	38.87	5.7%	0.71 [0.52 , 0.98]
Canellos GP 1976	48	93	60	91	-11.02	27.38	4.0%	0.67 [0.46 , 0.97]
Heidemann E 2002	75	127	86	133	-7.05	41.54	6.1%	0.84 [0.62 , 1.14]
O'Shaughnessy J 2001	14	33	26	62	-0.15	7.25	1.1%	0.98 [0.47 , 2.03]
Stockler M 2006	63	109	104	214	15.55	40.32	5.9%	1.47 [1.08 , 2.00]
Subtotal (95% CI)		**513**		**649**			**24.9%**	**0.87 [0.75 , 1.01]**
Total events:	326		392					
Heterogeneity: Chi² = 17.42, df = 6 (P = 0.008); I² = 66%								
Test for overall effect: Z = 1.81 (P = 0.07)								
Total (95% CI)		**1987**		**1995**			**100.0%**	**0.88 [0.81 , 0.94]**
Total events:	1390		1392					
Heterogeneity: Chi² = 39.06, df = 20 (P = 0.007); I² = 49%								
Test for overall effect: Z = 3.46 (P = 0.0005)								
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%								



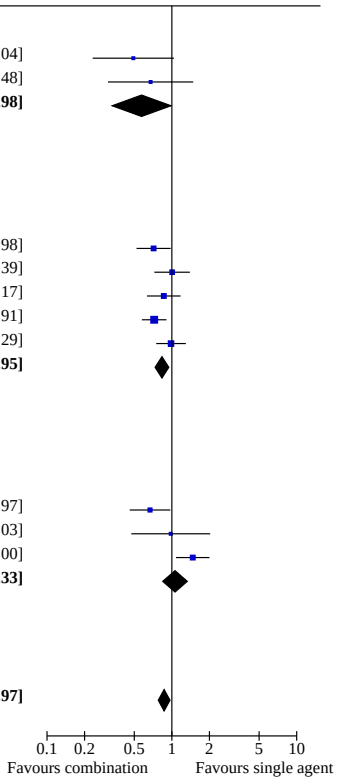
Analysis 1.3. Comparison 1: Overall survival, Outcome 3: Overall survival - Question 1 - Regimen A versus A + other - randomised patients

Study or Subgroup	Combination Events	Combination Total	Single agent Events	Single agent Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
1.3.1 Sub group A: Single anthracycline agent versus anthracycline + other regimen								
Andersson M 1986	32	44	34	45	-0.85	17.45	1.9%	0.95 [0.60 , 1.52]
Ejlertsen B 2004	112	193	105	194	7.78	55.74	6.2%	1.15 [0.88 , 1.49]
French Epi (A) 1991	86	135	47	70	-2.94	44.66	5.0%	0.94 [0.70 , 1.26]
French Epi (B) 1991	84	137	47	70	-4.77	29.53	3.3%	0.85 [0.59 , 1.22]
Gundersen S 1986	37	66	38	62	-3.19	16.91	1.9%	0.83 [0.51 , 1.33]
Heidemann E 2004	48	89	50	87	-0.41	21.99	2.4%	0.98 [0.65 , 1.49]
Ingle J 1985	70	79	70	79	0.77	38.32	4.3%	1.02 [0.74 , 1.40]
Ingle J 1989	74	92	81	95	-3.33	41.79	4.6%	0.92 [0.68 , 1.25]
Joensuu H 1998	115	150	118	153	-3.25	58.76	6.5%	0.95 [0.73 , 1.22]
Nielsen D 2000	68	74	62	81	-5.93	25.53	2.8%	0.79 [0.54 , 1.17]
Nielson D 1990	52	65	63	76	-1.63	17.07	1.9%	0.91 [0.57 , 1.46]
Norris B 2000	90	151	93	149	-1.92	46.75	5.2%	0.96 [0.72 , 1.28]
Sledge G(A) 2003	86	115	174	224	-0.55	62.86	7.0%	0.99 [0.77 , 1.27]
Vaughn CB 1988	51	59	56	63	-5.43	28.04	3.1%	0.82 [0.57 , 1.19]
Subtotal (95% CI)		**1449**		**1448**			**56.1%**	**0.95 [0.87 , 1.04]**
Total events:	1005		1038					
Heterogeneity: Chi² = 4.53, df = 13 (P = 0.98); I² = 0%								
Test for overall effect: Z = 1.14 (P = 0.25)								
1.3.2 Sub group B: Single alkylating versus alkylating + other								
Ahmann DL 1974(1)	18	21	20	22	-2.89	6.95	0.8%	0.66 [0.31 , 1.39]
Ahmann DL 1974(2)	18	20	16	20	0.85	4.92	0.5%	1.19 [0.49 , 2.88]
Falkson G 1990	41	54	43	57	0.07	22.34	2.5%	1.00 [0.66 , 1.52]
Rubens RD 1975	45	50	42	49	-2.71	21.35	2.4%	0.88 [0.58 , 1.35]
Takayama T(B) 2000	15	27	35	55	-1.64	14.59	1.6%	0.89 [0.53 , 1.49]
Subtotal (95% CI)		**172**		**203**			**7.8%**	**0.91 [0.72 , 1.15]**
Total events:	137		156					
Heterogeneity: Chi² = 1.31, df = 4 (P = 0.86); I² = 0%								
Test for overall effect: Z = 0.75 (P = 0.45)								
1.3.3 Sub group C: Single antimetabolite versus antimetabolite + other								
Tashiro H 1994	17	30	18	30	1.15	7.3	0.8%	1.17 [0.57 , 2.42]
Carmo-Pereira 1980	49	68	62	67	-22.08	26.03	2.9%	0.43 [0.29 , 0.63]
Takayama T(A) 2000	15	27	35	57	-1.9	13.98	1.6%	0.87 [0.52 , 1.47]
Subtotal (95% CI)		**125**		**154**			**5.2%**	**0.62 [0.46 , 0.82]**
Total events:	81		115					
Heterogeneity: Chi² = 8.15, df = 2 (P = 0.02); I² = 75%								
Test for overall effect: Z = 3.32 (P = 0.0009)								
1.3.4 Sub group D: Single taxane versus taxane + other								
Albain KS 2004	214	267	212	262	-26.47	101.37	11.2%	0.77 [0.63 , 0.94]
O'Shaughnessy J 2002	203	255	222	256	-28.65	111.95	12.4%	0.77 [0.64 , 0.93]
Sledge G(B) 2003	86	115	178	229	-3.49	65.17	7.2%	0.95 [0.74 , 1.21]
Subtotal (95% CI)		**637**		**747**			**30.9%**	**0.81 [0.72 , 0.91]**
Total events:	503		612					
Heterogeneity: Chi² = 2.10, df = 2 (P = 0.35); I² = 5%								
Test for overall effect: Z = 3.51 (P = 0.0004)								
Total (95% CI)		**2383**		**2552**			**100.0%**	**0.88 [0.83 , 0.94]**
Total events:	1726		1921					
Heterogeneity: Chi² = 27.04, df = 24 (P = 0.30); I² = 11%								
Test for overall effect: Z = 3.78 (P = 0.0002)								
Test for subgroup differences: Chi² = 10.95, df = 3 (P = 0.01), I² = 72.6%								



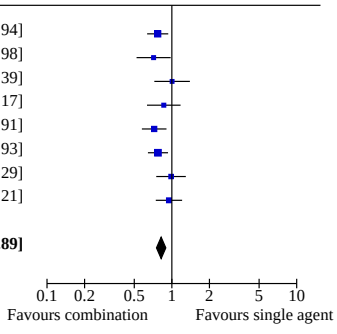
Analysis 1.4. Comparison 1: Overall survival, Outcome 4: Overall survival - Question 2 - Regimen A versus Regimen C - randomised patients

Study or Subgroup	Combination Events	Combination Total	Single agent Events	Single agent Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
1.4.1 Sub group E: Single anthracycline agent versus non-anthracycline combination regimen								
Ahmann DL 1974(3)	24	28	17	20	-4.86	6.84	2.1%	0.49 [0.23 , 1.04]
Fraser S 1993	12	19	15	21	-2.44	6.23	1.9%	0.68 [0.31 , 1.48]
Subtotal (95% CI)		**47**		**41**			**4.0%**	**0.57 [0.33 , 0.98]**
Total events:	36		32					
Heterogeneity: Chi² = 0.33, df = 1 (P = 0.56); I² = 0%								
Test for overall effect: Z = 2.02 (P = 0.04)								
1.4.2 Sub group F: Single taxane versus non-taxane, non-anthracycline containing combination regimen								
Bishop J 1999	84	102	79	107	-13.08	38.87	11.8%	0.71 [0.52 , 0.98]
Bonneterre J 2002	69	90	68	88	0.17	35.73	10.9%	1.00 [0.72 , 1.39]
Icli F 2005	79	100	87	101	-5.97	40.15	12.2%	0.86 [0.63 , 1.17]
Nabholtz JM 1999	150	189	141	203	-24.33	74.66	22.7%	0.72 [0.58 , 0.91]
Sjostrom J 1999	105	139	102	143	-0.78	51.71	15.7%	0.99 [0.75 , 1.29]
Subtotal (95% CI)		**620**		**642**			**73.3%**	**0.83 [0.73 , 0.95]**
Total events:	487		477					
Heterogeneity: Chi² = 5.20, df = 4 (P = 0.27); I² = 23%								
Test for overall effect: Z = 2.83 (P = 0.005)								
1.4.3 Sub group G: Single non-taxane, non-anthracycline agent versus other combination regimen								
Canellos GP 1976	48	93	60	91	-11.02	27.38	8.3%	0.67 [0.46 , 0.97]
O'Shaughnessy J 2001	14	33	26	62	-0.15	7.25	2.2%	0.98 [0.47 , 2.03]
Stockler M 2006	63	109	104	214	15.55	40.32	12.3%	1.47 [1.08 , 2.00]
Subtotal (95% CI)		**235**		**367**			**22.8%**	**1.06 [0.85 , 1.33]**
Total events:	125		190					
Heterogeneity: Chi² = 10.18, df = 2 (P = 0.006); I² = 80%								
Test for overall effect: Z = 0.51 (P = 0.61)								
Total (95% CI)		**902**		**1050**			**100.0%**	**0.87 [0.78 , 0.97]**
Total events:	648		699					
Heterogeneity: Chi² = 21.39, df = 9 (P = 0.01); I² = 58%								
Test for overall effect: Z = 2.59 (P = 0.010)								
Test for subgroup differences: Chi² = 5.67, df = 2 (P = 0.06), I² = 64.7%								



Analysis 1.5. Comparison 1: Overall survival, Outcome 5: Overall survival - single agent taxane versus all combination

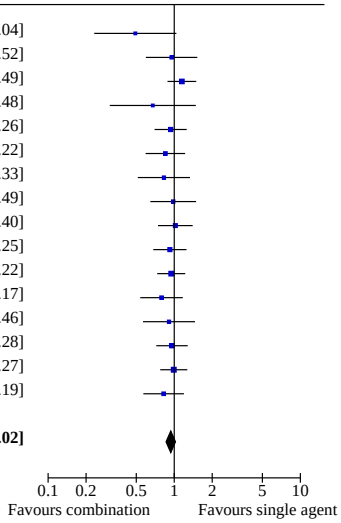
Study or Subgroup	Combination Events	Combination Total	Single agent Events	Single agent Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Albain KS 2004	214	267	212	262	-26.47	101.37	19.5%	0.77 [0.63 , 0.94]
Bishop J 1999	84	102	79	107	-13.08	38.87	7.5%	0.71 [0.52 , 0.98]
Bonneterre J 2002	69	90	68	88	0.17	35.73	6.9%	1.00 [0.72 , 1.39]
Icli F 2005	79	100	87	101	-5.97	40.15	7.7%	0.86 [0.63 , 1.17]
Nabholtz JM 1999	150	189	141	203	-24.33	74.66	14.4%	0.72 [0.58 , 0.91]
O'Shaughnessy J 2002	203	255	222	256	-28.65	111.95	21.5%	0.77 [0.64 , 0.93]
Sjostrom J 1999	105	139	102	143	-0.78	51.71	10.0%	0.99 [0.75 , 1.29]
Sledge G(A) 2003	86	115	178	229	-3.49	65.17	12.5%	0.95 [0.74 , 1.21]
Total (95% CI)		**1257**		**1389**			**100.0%**	**0.82 [0.75 , 0.89]**
Total events:	990		1089					
Heterogeneity: Chi² = 7.40, df = 7 (P = 0.39); I² = 5%								
Test for overall effect: Z = 4.50 (P < 0.00001)								
Test for subgroup differences: Not applicable								



Analysis 1.6. Comparison 1: Overall survival, Outcome 6: Overall survival - single agent anthracycline versus all combinations

Study or Subgroup	Combination Events	Combination Total	Single agent Events	Single agent Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Ahmann DL 1974(3)	24	28	17	20	-4.86	6.84	1.3%	0.49 [0.23 , 1.04]
Andersson M 1986	32	44	34	45	-0.85	17.45	3.4%	0.95 [0.60 , 1.52]
Ejlertsen B 2004	112	193	105	194	7.78	55.74	10.8%	1.15 [0.88 , 1.49]
Fraser S 1993	12	19	15	21	-2.44	6.23	1.2%	0.68 [0.31 , 1.48]
French Epi (A) 1991	86	135	47	70	-2.94	44.66	8.6%	0.94 [0.70 , 1.26]
French Epi (B) 1991	84	137	47	70	-4.77	29.53	5.7%	0.85 [0.59 , 1.22]
Gundersen S 1986	37	66	38	62	-3.19	16.91	3.3%	0.83 [0.51 , 1.33]
Heidemann E 2004	48	89	50	87	-0.41	21.99	4.2%	0.98 [0.65 , 1.49]
Ingle J 1985	70	79	70	79	0.77	38.32	7.4%	1.02 [0.74 , 1.40]
Ingle J 1989	74	92	81	95	-3.33	41.79	8.1%	0.92 [0.68 , 1.25]
Joensuu H 1998	115	150	118	153	-3.25	58.76	11.3%	0.95 [0.73 , 1.22]
Nielsen D 2000	68	74	62	81	-5.93	25.53	4.9%	0.79 [0.54 , 1.17]
Nielson D 1990	52	65	63	76	-1.63	17.07	3.3%	0.91 [0.57 , 1.46]
Norris B 2000	90	151	93	149	-1.92	46.75	9.0%	0.96 [0.72 , 1.28]
Sledge G(A) 2003	86	115	174	224	-0.55	62.86	12.1%	0.99 [0.77 , 1.27]
Vaughn CB 1988	51	59	56	63	-5.43	28.04	5.4%	0.82 [0.57 , 1.19]
Total (95% CI)		**1496**		**1489**			**100.0%**	**0.94 [0.86 , 1.02]**
Total events:	1041		1070					

Heterogeneity: Chi² = 8.14, df = 15 (P = 0.92); I² = 0%
Test for overall effect: Z = 1.45 (P = 0.15)
Test for subgroup differences: Not applicable



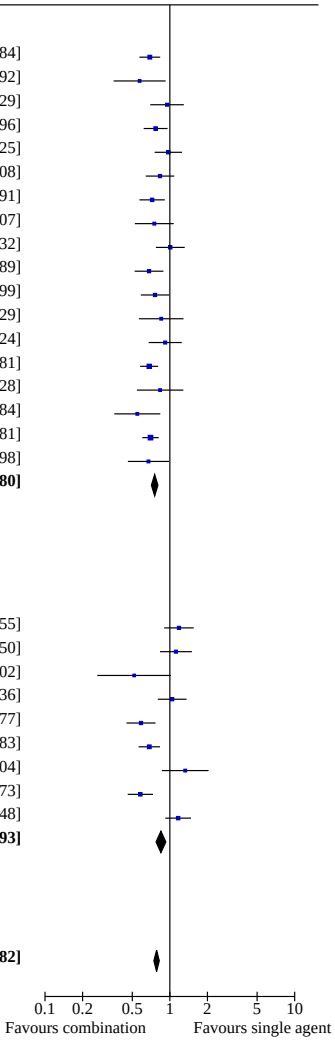
Comparison 2. Time to progression

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Time to progression - randomised patients - all trials	27	6501	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.78 [0.74, 0.82]
2.1.1 Question 1: Regimen A (single) vs Regimen A + other	18	4521	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.76 [0.71, 0.80]
2.1.2 Question 2: Regimen A (single) vs Regimen C (combination)	9	1980	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.85 [0.78, 0.93]
2.2 Time to progression - randomised patients - first line	13	3201	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.87 [0.81, 0.94]
2.2.1 Question 1: Regimen A (single) versus Regimen A + other	9	2314	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.81 [0.74, 0.88]
2.2.2 Question 2: Regimen A (single) versus Regimen C (combination)	4	887	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	1.08 [0.94, 1.25]
2.3 Time to progression - Question 1 - Regimen A versus A + other - randomised patients	16	3518	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.77 [0.72, 0.83]
2.3.1 Sub Group A: Single anthracycline agent versus anthracycline + other regimen	12	2312	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.82 [0.75, 0.89]
2.3.2 Sub group B: Single alkylating agent versus alkylating agent + other	1	82	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.55 [0.36, 0.84]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3.3 Sub group C: Single antimetabolite versus antimetaboloite + other	1	84	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.84 [0.54, 1.28]
2.3.4 Sub group D: Single taxane versus taxane + other	2	1040	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.69 [0.61, 0.78]
2.4 Time to progression - Question 2 - Regimen A versus Regimen C - randomised patients	8	1720	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.78 [0.71, 0.86]
2.4.1 Sub group E - Single anthracycline agent versus non-anthracycline combination regimen	1	40	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.52 [0.26, 1.02]
2.4.2 Sub group F - Single taxane versus non-taxane, non-anthacycline containing combination regimen	5	1262	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.75 [0.67, 0.84]
2.4.3 Sub group G - Single non-taxane, non-anthracycline agent versus other combination regimen	2	418	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.95 [0.77, 1.17]
2.5 Time to progression - single agent taxane versus all combinations	7	2302	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.72 [0.67, 0.79]
2.6 Time to progression - Single agent anthracycline versus all combinations	13	2352	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.82 [0.75, 0.89]

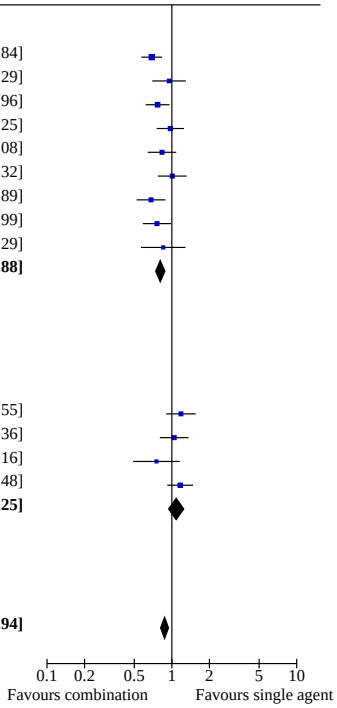
Analysis 2.1. Comparison 2: Time to progression, Outcome 1: Time to progression - randomised patients - all trials

Study or Subgroup	Combination Events	Combination Total	Single agent Events	Single agent Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
2.1.1 Question 1: Regimen A (single) vs Regimen A + other								
Albain KS 2004	180	267	197	262	-38.69	104.65	6.8%	0.69 [0.57 , 0.84]
Andersson M 1986	29	44	35	45	-9.31	16.69	1.1%	0.57 [0.35 , 0.92]
Berruti D 2002	78	92	81	93	-2.06	39.98	2.6%	0.95 [0.70 , 1.29]
Ejlertsen B 2004	141	193	155	194	-20.78	79.13	5.2%	0.77 [0.62 , 0.96]
French Epi (A) 1991	110	135	56	70	-1.68	60.31	3.9%	0.97 [0.76 , 1.25]
French Epi (B) 1991	105	137	56	70	-10.13	55.83	3.6%	0.83 [0.64 , 1.08]
GEICAM 2007	102	125	111	126	-22.88	70.08	4.6%	0.72 [0.57 , 0.91]
Heidemann E 2004	63	89	71	87	-8.58	29.9	1.9%	0.75 [0.52 , 1.07]
Ingle J 1985	75	79	75	79	0.47	54.3	3.5%	1.01 [0.77 , 1.32]
Ingle J 1989	79	90	90	95	-20.92	54.49	3.6%	0.68 [0.52 , 0.89]
Joensuu H 1998	124	150	129	153	-15.38	56.17	3.7%	0.76 [0.59 , 0.99]
Nielsen D 2000	61	74	68	81	-3.62	22.78	1.5%	0.85 [0.57 , 1.29]
Nielson D 1990	59	67	69	76	-3.57	41.35	2.7%	0.92 [0.68 , 1.24]
O'Shaughnessy J 2002	231	255	250	256	-53.4	139.9	9.1%	0.68 [0.58 , 0.81]
Takayama T(A) 2000	19	27	43	57	-3.77	20.98	1.4%	0.84 [0.54 , 1.28]
Takayama T(B) 2000	19	27	47	55	-12.8	21.31	1.4%	0.55 [0.36 , 0.84]
Thomas E 2008	302	375	322	377	-59.92	167.88	10.9%	0.70 [0.60 , 0.81]
Vaughn CB 1988	45	56	59	63	-10.55	26.74	1.7%	0.67 [0.46 , 0.98]
Subtotal (95% CI)		**2282**		**2239**			**69.2%**	**0.76 [0.71 , 0.80]**
Total events:	1822		1914					
Heterogeneity: Chi² = 20.96, df = 17 (P = 0.23); I² = 19%								
Test for overall effect: Z = 9.13 (P < 0.00001)								
2.1.2 Question 2: Regimen A (single) vs Regimen C (combination)								
Bishop J 1999	99	102	102	107	8.72	51.88	3.4%	1.18 [0.90 , 1.55]
Bonneterre J 2002	86	90	83	88	5	44.39	2.9%	1.12 [0.83 , 1.50]
Fraser S 1993	15	19	20	21	-5.48	8.33	0.5%	0.52 [0.26 , 1.02]
Heidemann E 2002	98	127	101	133	2.37	54.84	3.6%	1.04 [0.80 , 1.36]
Icli F 2005	91	100	98	101	-28.56	53.69	3.5%	0.59 [0.45 , 0.77]
Nabholtz JM 1999	174	189	179	203	-37.69	99.42	6.5%	0.68 [0.56 , 0.83]
O'Shaughnessy J 2001	27	33	48	62	5.88	20.72	1.4%	1.33 [0.86 , 2.04]
Sjostrom J 1999	132	139	128	143	-38.38	70.58	4.6%	0.58 [0.46 , 0.73]
Stockler M 2006	93	109	170	214	10.44	68.14	4.4%	1.17 [0.92 , 1.48]
Subtotal (95% CI)		**908**		**1072**			**30.8%**	**0.85 [0.78 , 0.93]**
Total events:	815		929					
Heterogeneity: Chi² = 46.56, df = 8 (P < 0.00001); I² = 83%								
Test for overall effect: Z = 3.58 (P = 0.0003)								
Total (95% CI)		**3190**		**3311**			**100.0%**	**0.78 [0.74 , 0.82]**
Total events:	2637		2843					
Heterogeneity: Chi² = 71.88, df = 26 (P < 0.00001); I² = 64%								
Test for overall effect: Z = 9.58 (P < 0.00001)								
Test for subgroup differences: Chi² = 4.36, df = 1 (P = 0.04), I² = 77.0%								



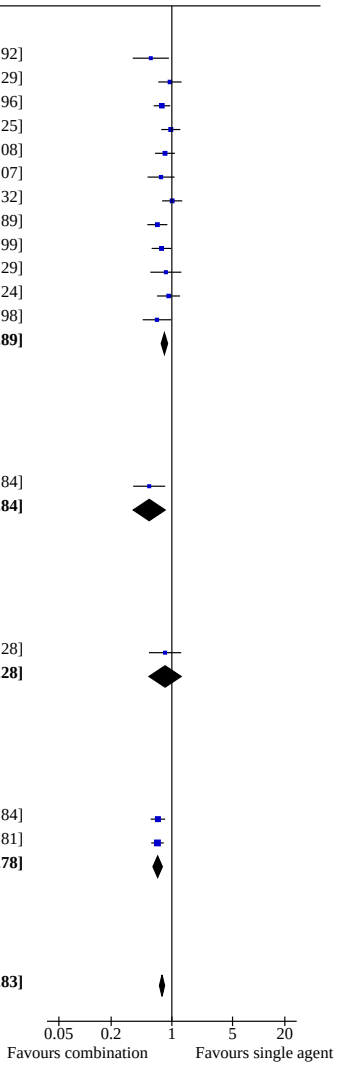
Analysis 2.2. Comparison 2: Time to progression, Outcome 2: Time to progression - randomised patients - first line

Study or Subgroup	Combination Events	Combination Total	Single agent Events	Single agent Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
2.2.1 Question 1: Regimen A (single) versus Regimen A + other								
Albain KS 2004	180	267	197	262	-38.69	104.65	14.5%	0.69 [0.57 , 0.84]
Berruti D 2002	78	92	81	93	-2.06	39.98	5.5%	0.95 [0.70 , 1.29]
Ejlertsen B 2004	141	193	155	194	-20.78	79.13	10.9%	0.77 [0.62 , 0.96]
French Epi (A) 1991	110	135	56	70	-1.68	60.31	8.3%	0.97 [0.76 , 1.25]
French Epi (B) 1991	105	137	56	70	-10.13	55.83	7.7%	0.83 [0.64 , 1.08]
Ingle J 1985	75	79	75	79	0.47	54.3	7.5%	1.01 [0.77 , 1.32]
Ingle J 1989	79	90	90	95	-20.92	54.49	7.5%	0.68 [0.52 , 0.89]
Joensuu H 1998	124	150	129	153	-15.38	56.17	7.8%	0.76 [0.59 , 0.99]
Nielsen D 2000	61	74	68	81	-3.62	22.78	3.1%	0.85 [0.57 , 1.29]
Subtotal (95% CI)		**1217**		**1097**			**73.0%**	**0.81 [0.74 , 0.88]**
Total events:	953		907					
Heterogeneity: Chi² = 10.46, df = 8 (P = 0.23); I² = 24%								
Test for overall effect: Z = 4.91 (P < 0.00001)								
2.2.2 Question 2: Regimen A (single) versus Regimen C (combination)								
Bishop J 1999	99	102	102	107	8.72	51.88	7.2%	1.18 [0.90 , 1.55]
Heidemann E 2002	98	127	101	133	2.37	54.84	7.6%	1.04 [0.80 , 1.36]
O'Shaughnessy J 2001	27	33	48	62	-5.88	20.72	2.9%	0.75 [0.49 , 1.16]
Stockler M 2006	93	109	170	214	10.44	68.14	9.4%	1.17 [0.92 , 1.48]
Subtotal (95% CI)		**371**		**516**			**27.0%**	**1.08 [0.94 , 1.25]**
Total events:	317		421					
Heterogeneity: Chi² = 3.58, df = 3 (P = 0.31); I² = 16%								
Test for overall effect: Z = 1.12 (P = 0.26)								
Total (95% CI)		**1588**		**1613**			**100.0%**	**0.87 [0.81 , 0.94]**
Total events:	1270		1328					
Heterogeneity: Chi² = 26.36, df = 12 (P = 0.010); I² = 54%								
Test for overall effect: Z = 3.61 (P = 0.0003)								
Test for subgroup differences: Chi² = 12.32, df = 1 (P = 0.0004), I² = 91.9%								



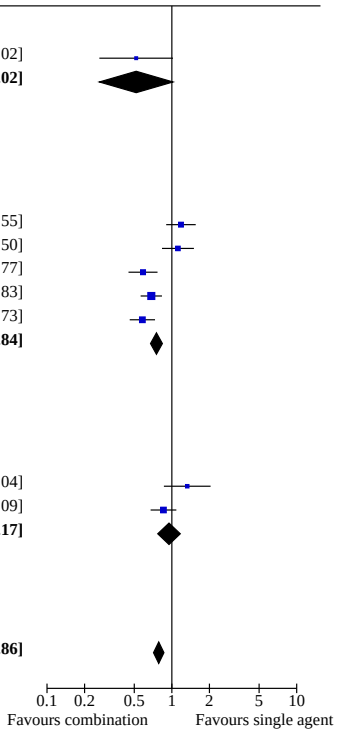
Analysis 2.3. Comparison 2: Time to progression, Outcome 3: Time to progression - Question 1 - Regimen A versus A + other - randomised patients

Study or Subgroup	Combination Events	Combination Total	Single agent Events	Single agent Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
2.3.1 Sub Group A: Single anthracycline agent versus anthracycline + other regimen								
Andersson M 1986	29	44	35	45	-9.31	16.69	2.0%	0.57 [0.35 , 0.92]
Berruti D 2002	78	92	81	93	-2.06	39.98	4.8%	0.95 [0.70 , 1.29]
Ejlertsen B 2004	141	193	155	194	-20.78	79.13	9.6%	0.77 [0.62 , 0.96]
French Epi (A) 1991	110	135	56	70	-1.68	60.31	7.3%	0.97 [0.76 , 1.25]
French Epi (B) 1991	105	137	56	70	-10.13	55.83	6.8%	0.83 [0.64 , 1.08]
Heidemann E 2004	63	89	71	87	-8.58	29.9	3.6%	0.75 [0.52 , 1.07]
Ingle J 1985	75	79	75	79	0.47	54.3	6.6%	1.01 [0.77 , 1.32]
Ingle J 1989	79	90	90	95	-20.92	54.49	6.6%	0.68 [0.52 , 0.89]
Joensuu H 1998	124	150	129	153	-15.38	56.17	6.8%	0.76 [0.59 , 0.99]
Nielsen D 2000	61	74	68	81	-3.62	22.78	2.8%	0.85 [0.57 , 1.29]
Nielson D 1990	59	67	69	76	-3.57	41.35	5.0%	0.92 [0.68 , 1.24]
Vaughn CB 1988	45	56	59	63	-10.55	26.74	3.2%	0.67 [0.46 , 0.98]
Subtotal (95% CI)		**1206**		**1106**			**65.2%**	**0.82 [0.75 , 0.89]**
Total events:	969		944					
Heterogeneity: Chi² = 11.46, df = 11 (P = 0.41); I² = 4%								
Test for overall effect: Z = 4.58 (P < 0.00001)								
2.3.2 Sub group B: Single alkylating agent versus alkylating agent + other								
Takayama T(B) 2000	19	27	47	55	-12.8	21.31	2.6%	0.55 [0.36 , 0.84]
Subtotal (95% CI)		**27**		**55**			**2.6%**	**0.55 [0.36 , 0.84]**
Total events:	19		47					
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.77 (P = 0.006)								
2.3.3 Sub group C: Single antimetabolite versus antimetaboloite + other								
Takayama T(A) 2000	19	27	43	57	-3.77	20.98	2.5%	0.84 [0.54 , 1.28]
Subtotal (95% CI)		**27**		**57**			**2.5%**	**0.84 [0.54 , 1.28]**
Total events:	19		43					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.82 (P = 0.41)								
2.3.4 Sub group D: Single taxane versus taxane + other								
Albain KS 2004	180	267	197	262	-38.69	104.65	12.7%	0.69 [0.57 , 0.84]
O'Shaughnessy J 2002	231	255	250	256	-53.4	139.9	17.0%	0.68 [0.58 , 0.81]
Subtotal (95% CI)		**522**		**518**			**29.7%**	**0.69 [0.61 , 0.78]**
Total events:	411		447					
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.93); I² = 0%								
Test for overall effect: Z = 5.89 (P < 0.00001)								
Total (95% CI)		**1782**		**1736**			**100.0%**	**0.77 [0.72 , 0.83]**
Total events:	1418		1481					
Heterogeneity: Chi² = 19.51, df = 15 (P = 0.19); I² = 23%								
Test for overall effect: Z = 7.48 (P < 0.00001)								
Test for subgroup differences: Chi² = 8.04, df = 3 (P = 0.05), I² = 62.7%								



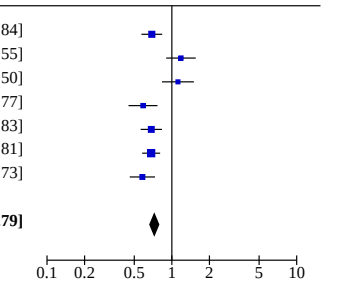
Analysis 2.4. Comparison 2: Time to progression, Outcome 4: Time to progression - Question 2 - Regimen A versus Regimen C - randomised patients

Study or Subgroup	Combination Events	Combination Total	Single agent Events	Single agent Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
2.4.1 Sub group E - Single anthracycline agent versus non-anthracycline combination regimen								
Fraser S 1993	15	19	20	21	-5.48	8.33	2.0%	0.52 [0.26 , 1.02]
Subtotal (95% CI)		**19**		**21**			**2.0%**	**0.52 [0.26 , 1.02]**
Total events:	15		20					
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.90 (P = 0.06)								
2.4.2 Sub group F - Single taxane versus non-taxane, non-anthacycline containing combination regimen								
Bishop J 1999	99	102	102	107	8.72	51.88	12.4%	1.18 [0.90 , 1.55]
Bonneterre J 2002	86	90	83	88	5	44.39	10.6%	1.12 [0.83 , 1.50]
Icli F 2005	90	100	98	101	-28.56	53.69	12.9%	0.59 [0.45 , 0.77]
Nabholtz JM 1999	174	189	179	203	-37.69	99.42	23.8%	0.68 [0.56 , 0.83]
Sjostrom J 1999	132	139	128	143	-38.38	70.58	16.9%	0.58 [0.46 , 0.73]
Subtotal (95% CI)		**620**		**642**			**76.7%**	**0.75 [0.67 , 0.84]**
Total events:	581		590					
Heterogeneity: Chi² = 26.55, df = 4 (P < 0.0001); I² = 85%								
Test for overall effect: Z = 5.08 (P < 0.00001)								
2.4.3 Sub group G - Single non-taxane, non-anthracycline agent versus other combination regimen								
O'Shaughnessy J 2001	27	33	48	62	5.88	20.72	5.0%	1.33 [0.86 , 2.04]
Stockler M 2006	93	109	170	214	-10.54	68.24	16.4%	0.86 [0.68 , 1.09]
Subtotal (95% CI)		**142**		**276**			**21.3%**	**0.95 [0.77 , 1.17]**
Total events:	120		218					
Heterogeneity: Chi² = 3.05, df = 1 (P = 0.08); I² = 67%								
Test for overall effect: Z = 0.49 (P = 0.62)								
Total (95% CI)		**781**		**939**			**100.0%**	**0.78 [0.71 , 0.86]**
Total events:	716		828					
Heterogeneity: Chi² = 34.81, df = 7 (P < 0.0001); I² = 80%								
Test for overall effect: Z = 4.95 (P < 0.00001)								
Test for subgroup differences: Chi² = 5.21, df = 2 (P = 0.07), I² = 61.6%								



Analysis 2.5. Comparison 2: Time to progression, Outcome 5: Time to progression - single agent taxane versus all combinations

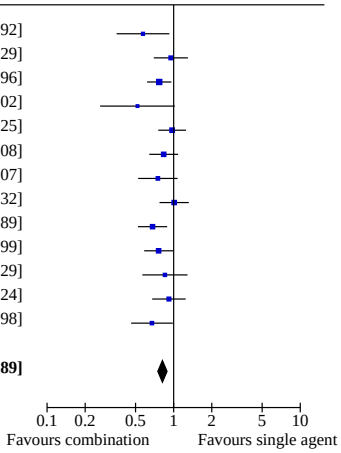
Study or Subgroup	Combination Events	Combination Total	Single agent Events	Single agent Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Albain KS 2004	180	267	197	262	-38.69	104.65	18.5%	0.69 [0.57 , 0.84]
Bishop J 1999	99	102	102	107	8.72	51.88	9.2%	1.18 [0.90 , 1.55]
Bonneterre J 2002	86	90	83	88	5	44.39	7.9%	1.12 [0.83 , 1.50]
Icli F 2005	90	100	98	101	-28.56	53.69	9.5%	0.59 [0.45 , 0.77]
Nabholtz JM 1999	174	189	179	203	-37.69	99.42	17.6%	0.68 [0.56 , 0.83]
O'Shaughnessy J 2002	231	255	250	256	-53.4	139.9	24.8%	0.68 [0.58 , 0.81]
Sjostrom J 1999	132	139	128	143	-38.38	70.58	12.5%	0.58 [0.46 , 0.73]
Total (95% CI)		**1142**		**1160**			**100.0%**	**0.72 [0.67 , 0.79]**
Total events:	992		1037					
Heterogeneity: Chi² = 27.74, df = 6 (P = 0.0001); I² = 78%								
Test for overall effect: Z = 7.70 (P < 0.00001)								
Test for subgroup differences: Not applicable								



Analysis 2.6. Comparison 2: Time to progression, Outcome 6: Time to progression - Single agent anthracycline versus all combinations

Study or Subgroup	Combination Events	Combination Total	Single agent Events	Single agent Total	O-E	Variance	Weight	Peto Odds Ratio Exp[(O-E) / V], Fixed, 95% CI
Andersson M 1986	29	44	35	45	-9.31	16.69	3.1%	0.57 [0.35 , 0.92]
Berruti D 2002	78	92	81	93	-2.06	39.98	7.3%	0.95 [0.70 , 1.29]
Ejlertsen B 2004	141	193	155	194	-20.78	79.13	14.5%	0.77 [0.62 , 0.96]
Fraser S 1993	15	19	20	21	-5.48	8.33	1.5%	0.52 [0.26 , 1.02]
French Epi (A) 1991	110	135	56	70	-1.68	60.31	11.0%	0.97 [0.76 , 1.25]
French Epi (B) 1991	105	137	56	70	-10.13	55.83	10.2%	0.83 [0.64 , 1.08]
Heidemann E 2004	63	89	71	87	-8.58	29.9	5.5%	0.75 [0.52 , 1.07]
Ingle J 1985	75	79	75	79	0.47	54.3	9.9%	1.01 [0.77 , 1.32]
Ingle J 1989	79	90	90	95	-20.92	54.49	10.0%	0.68 [0.52 , 0.89]
Joensuu H 1998	124	150	129	153	-15.38	56.17	10.3%	0.76 [0.59 , 0.99]
Nielsen D 2000	61	74	68	81	-3.62	22.78	4.2%	0.85 [0.57 , 1.29]
Nielson D 1990	59	67	69	76	-3.57	41.35	7.6%	0.92 [0.68 , 1.24]
Vaughn CB 1988	45	56	59	63	-10.55	26.74	4.9%	0.67 [0.46 , 0.98]
Total (95% CI)		**1225**		**1127**			**100.0%**	**0.82 [0.75 , 0.89]**
Total events:	984		964					

Heterogeneity: Chi² = 13.19, df = 12 (P = 0.36); I² = 9%
Test for overall effect: Z = 4.78 (P < 0.00001)
Test for subgroup differences: Not applicable

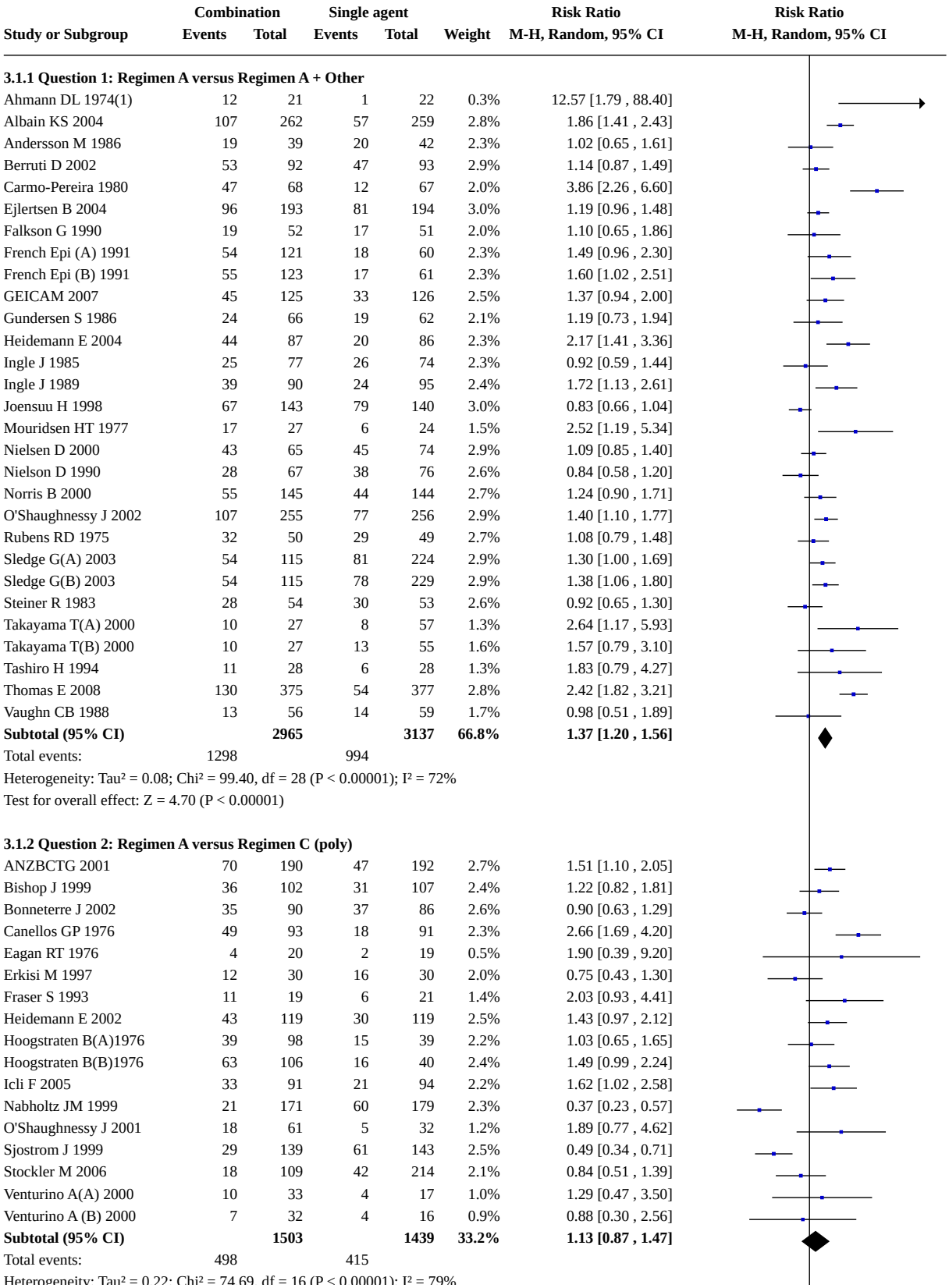


Comparison 3. Overall response

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Overall response - assessable patients-all trials	46	9044	Risk Ratio (M-H, Random, 95% CI)	1.29 [1.14, 1.45]
3.1.1 Question 1: Regimen A versus Regimen A + Other	29	6102	Risk Ratio (M-H, Random, 95% CI)	1.37 [1.20, 1.56]
3.1.2 Question 2: Regimen A versus Regimen C (poly)	17	2942	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.87, 1.47]
3.2 Overall response - assessable patients first line	25	4767	Risk Ratio (M-H, Random, 95% CI)	1.35 [1.16, 1.56]
3.2.1 Question 1: Regimen A versus Regimen A + other	17	3055	Risk Ratio (M-H, Random, 95% CI)	1.38 [1.14, 1.66]
3.2.2 Question 2: Regimen A versus Regimen C (poly)	8	1712	Risk Ratio (M-H, Random, 95% CI)	1.31 [1.01, 1.69]
3.3 Overall response - Question 1 - Regimen A versus A + other - assessable patients	27	5125	Risk Ratio (M-H, Random, 95% CI)	1.32 [1.16, 1.50]
3.3.1 Sub group A: Single anthracycline agent versus anthracycline + other regimen	16	3084	Risk Ratio (M-H, Random, 95% CI)	1.15 [1.02, 1.31]
3.3.2 Sub group B: Single alkylating agent versus alkylanting agent + other	5	390	Risk Ratio (M-H, Random, 95% CI)	1.60 [0.96, 2.67]
3.3.3 Sub group C: Single antimetabolite versus antimetabolite + other	3	275	Risk Ratio (M-H, Random, 95% CI)	2.95 [1.92, 4.52]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3.4 Sub group D: Single taxane versus taxane + other	3	1376	Risk Ratio (M-H, Random, 95% CI)	1.52 [1.26, 1.83]
3.4 Overall response - Question 2 - Regimen A versus Regimen C - assessable patients	16	2713	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.84, 1.48]
3.4.1 Sub group E - Single anthrycycline agent versus non-anthrycycline combination regimen	4	714	Risk Ratio (M-H, Random, 95% CI)	1.42 [1.15, 1.76]
3.4.2 Sub group F - Single taxane versus non-taxane, non-anthrycycline containing combination regimen	5	1202	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.48, 1.33]
3.4.3 Sub group G - Single non-taxane, non-anthrycycline agent versus other combination regimen	7	797	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.79, 2.08]
3.5 Overall response - single agent taxane versus all combinations	8	2578	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.72, 1.48]
3.6 Overall response - single agent anthracycline versus all combinations	20	3798	Risk Ratio (M-H, Random, 95% CI)	1.19 [1.06, 1.34]

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

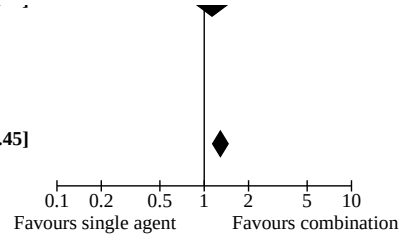


Study or Subgroup	Combination Events	Combination Total	Single agent Events	Single agent Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Question 1: Regimen A versus Regimen A + Other						
Ahmann DL 1974(1)	12	21	1	22	0.3%	12.57 [1.79 , 88.40]
Albain KS 2004	107	262	57	259	2.8%	1.86 [1.41 , 2.43]
Andersson M 1986	19	39	20	42	2.3%	1.02 [0.65 , 1.61]
Berruti D 2002	53	92	47	93	2.9%	1.14 [0.87 , 1.49]
Carmo-Pereira 1980	47	68	12	67	2.0%	3.86 [2.26 , 6.60]
Ejlertsen B 2004	96	193	81	194	3.0%	1.19 [0.96 , 1.48]
Falkson G 1990	19	52	17	51	2.0%	1.10 [0.65 , 1.86]
French Epi (A) 1991	54	121	18	60	2.3%	1.49 [0.96 , 2.30]
French Epi (B) 1991	55	123	17	61	2.3%	1.60 [1.02 , 2.51]
GEICAM 2007	45	125	33	126	2.5%	1.37 [0.94 , 2.00]
Gundersen S 1986	24	66	19	62	2.1%	1.19 [0.73 , 1.94]
Heidemann E 2004	44	87	20	86	2.3%	2.17 [1.41 , 3.36]
Ingle J 1985	25	77	26	74	2.3%	0.92 [0.59 , 1.44]
Ingle J 1989	39	90	24	95	2.4%	1.72 [1.13 , 2.61]
Joensuu H 1998	67	143	79	140	3.0%	0.83 [0.66 , 1.04]
Mouridsen HT 1977	17	27	6	24	1.5%	2.52 [1.19 , 5.34]
Nielsen D 2000	43	65	45	74	2.9%	1.09 [0.85 , 1.40]
Nielson D 1990	28	67	38	76	2.6%	0.84 [0.58 , 1.20]
Norris B 2000	55	145	44	144	2.7%	1.24 [0.90 , 1.71]
O'Shaughnessy J 2002	107	255	77	256	2.9%	1.40 [1.10 , 1.77]
Rubens RD 1975	32	50	29	49	2.7%	1.08 [0.79 , 1.48]
Sledge G(A) 2003	54	115	81	224	2.9%	1.30 [1.00 , 1.69]
Sledge G(B) 2003	54	115	78	229	2.9%	1.38 [1.06 , 1.80]
Steiner R 1983	28	54	30	53	2.6%	0.92 [0.65 , 1.30]
Takayama T(A) 2000	10	27	8	57	1.3%	2.64 [1.17 , 5.93]
Takayama T(B) 2000	10	27	13	55	1.6%	1.57 [0.79 , 3.10]
Tashiro H 1994	11	28	6	28	1.3%	1.83 [0.79 , 4.27]
Thomas E 2008	130	375	54	377	2.8%	2.42 [1.82 , 3.21]
Vaughn CB 1988	13	56	14	59	1.7%	0.98 [0.51 , 1.89]
Subtotal (95% CI)		**2965**		**3137**	**66.8%**	**1.37 [1.20 , 1.56]**
Total events:	1298		994			
Heterogeneity: Tau² = 0.08; Chi² = 99.40, df = 28 (P < 0.00001); I² = 72%						
Test for overall effect: Z = 4.70 (P < 0.00001)						
3.1.2 Question 2: Regimen A versus Regimen C (poly)						
ANZBCTG 2001	70	190	47	192	2.7%	1.51 [1.10 , 2.05]
Bishop J 1999	36	102	31	107	2.4%	1.22 [0.82 , 1.81]
Bonneterre J 2002	35	90	37	86	2.6%	0.90 [0.63 , 1.29]
Canellos GP 1976	49	93	18	91	2.3%	2.66 [1.69 , 4.20]
Eagan RT 1976	4	20	2	19	0.5%	1.90 [0.39 , 9.20]
Erkisi M 1997	12	30	16	30	2.0%	0.75 [0.43 , 1.30]
Fraser S 1993	11	19	6	21	1.4%	2.03 [0.93 , 4.41]
Heidemann E 2002	43	119	30	119	2.5%	1.43 [0.97 , 2.12]
Hoogstraten B(A)1976	39	98	15	39	2.2%	1.03 [0.65 , 1.65]
Hoogstraten B(B)1976	63	106	16	40	2.4%	1.49 [0.99 , 2.24]
Icli F 2005	33	91	21	94	2.2%	1.62 [1.02 , 2.58]
Nabholtz JM 1999	21	171	60	179	2.3%	0.37 [0.23 , 0.57]
O'Shaughnessy J 2001	18	61	5	32	1.2%	1.89 [0.77 , 4.62]
Sjostrom J 1999	29	139	61	143	2.5%	0.49 [0.34 , 0.71]
Stockler M 2006	18	109	42	214	2.1%	0.84 [0.51 , 1.39]
Venturino A(A) 2000	10	33	4	17	1.0%	1.29 [0.47 , 3.50]
Venturino A (B) 2000	7	32	4	16	0.9%	0.88 [0.30 , 2.56]
Subtotal (95% CI)		**1503**		**1439**	**33.2%**	**1.13 [0.87 , 1.47]**
Total events:	498		415			
Heterogeneity: Tau² = 0.22; Chi² = 74.69, df = 16 (P < 0.00001); I² = 79%						

Analysis 3.1. (Continued)

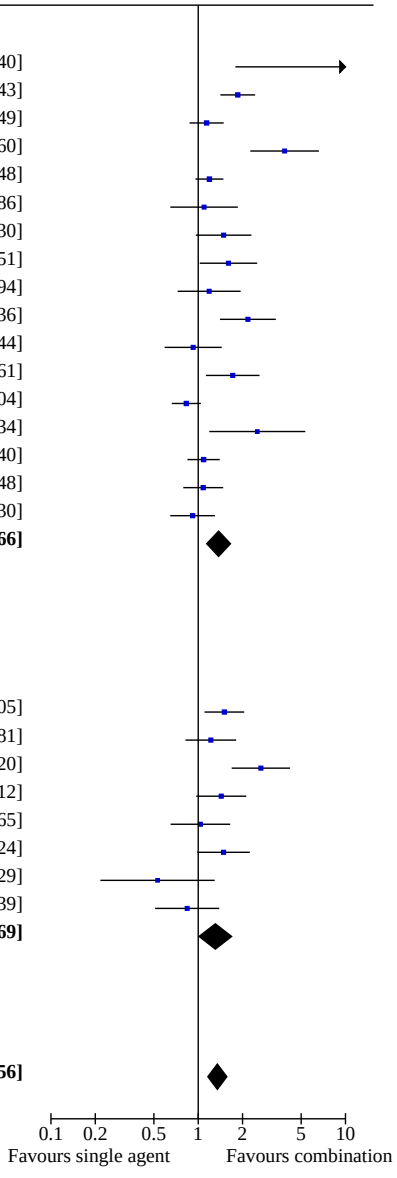
Total events: 498 415
Heterogeneity: Tau² = 0.22; Chi² = 74.69, df = 16 (P < 0.00001); I² = 79%
Test for overall effect: Z = 0.90 (P = 0.37)

Total (95% CI) **4468** **4576** **100.0%** **1.29 [1.14 , 1.45]**
Total events: 1796 1409
Heterogeneity: Tau² = 0.11; Chi² = 177.93, df = 45 (P < 0.00001); I² = 75%
Test for overall effect: Z = 4.10 (P < 0.0001)
Test for subgroup differences: Chi² = 1.64, df = 1 (P = 0.20), I² = 39.1%

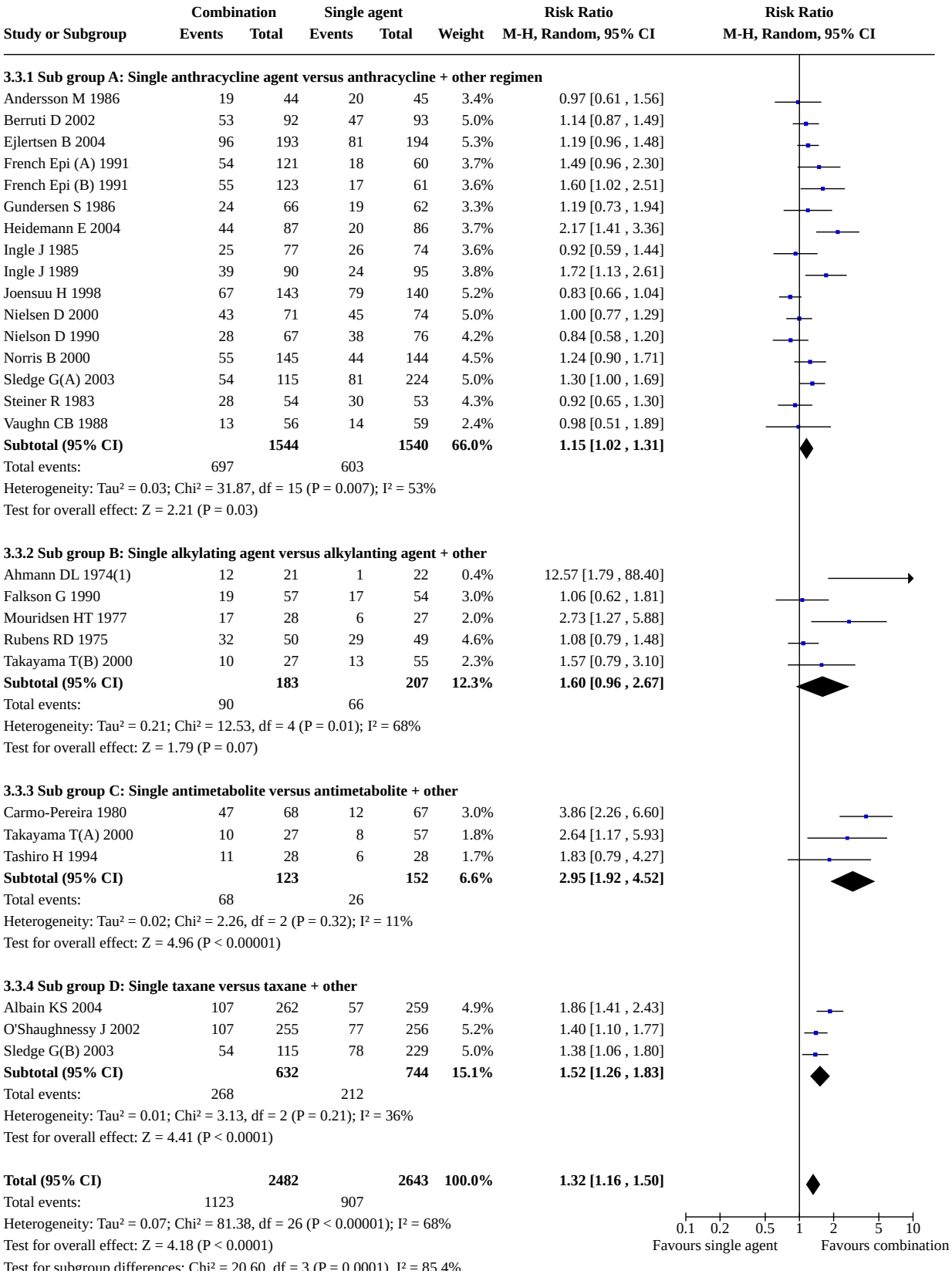


Analysis 3.2. Comparison 3: Overall response, Outcome 2: Overall response - assessable patients first line

Study or Subgroup	Combination Events	Total	Single agent Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 Question 1: Regimen A versus Regimen A + other						
Ahmann DL 1974(1)	12	21	1	22	0.5%	12.57 [1.79 , 88.40]
Albain KS 2004	107	262	57	259	5.1%	1.86 [1.41 , 2.43]
Berruti D 2002	53	92	47	93	5.1%	1.14 [0.87 , 1.49]
Carmo-Pereira 1980	47	68	12	67	3.4%	3.86 [2.26 , 6.60]
Ejlertsen B 2004	96	193	81	194	5.4%	1.19 [0.96 , 1.48]
Falkson G 1990	19	52	17	51	3.5%	1.10 [0.65 , 1.86]
French Epi (A) 1991	54	121	18	60	4.0%	1.49 [0.96 , 2.30]
French Epi (B) 1991	55	123	17	61	3.9%	1.60 [1.02 , 2.51]
Gundersen S 1986	24	66	19	62	3.7%	1.19 [0.73 , 1.94]
Heidemann E 2004	44	87	20	86	4.0%	2.17 [1.41 , 3.36]
Ingle J 1985	25	77	26	74	3.9%	0.92 [0.59 , 1.44]
Ingle J 1989	39	90	24	95	4.1%	1.72 [1.13 , 2.61]
Joensuu H 1998	67	143	79	140	5.4%	0.83 [0.66 , 1.04]
Mouridsen HT 1977	17	27	6	24	2.4%	2.52 [1.19 , 5.34]
Nielsen D 2000	43	65	45	74	5.2%	1.09 [0.85 , 1.40]
Rubens RD 1975	32	50	29	49	4.8%	1.08 [0.79 , 1.48]
Steiner R 1983	28	54	30	53	4.6%	0.92 [0.65 , 1.30]
Subtotal (95% CI)	**1591**		**1464**		**69.2%**	**1.38 [1.14 , 1.66]**
Total events:	762		528			
Heterogeneity: Tau² = 0.10; Chi² = 67.39, df = 16 (P < 0.00001); I² = 76%						
Test for overall effect: Z = 3.37 (P = 0.0008)						
3.2.2 Question 2: Regimen A versus Regimen C (poly)						
ANZBCTG 2001	70	190	47	192	4.8%	1.51 [1.10 , 2.05]
Bishop J 1999	36	102	31	107	4.3%	1.22 [0.82 , 1.81]
Canellos GP 1976	49	93	18	91	3.9%	2.66 [1.69 , 4.20]
Heidemann E 2002	43	119	30	119	4.3%	1.43 [0.97 , 2.12]
Hoogstraten B(A)1976	39	98	15	39	3.8%	1.03 [0.65 , 1.65]
Hoogstraten B(B)1976	63	106	16	40	4.2%	1.49 [0.99 , 2.24]
O'Shaughnessy J 2001	5	32	18	61	1.9%	0.53 [0.22 , 1.29]
Stockler M 2006	18	109	42	214	3.6%	0.84 [0.51 , 1.39]
Subtotal (95% CI)	**849**		**863**		**30.8%**	**1.31 [1.01 , 1.69]**
Total events:	323		217			
Heterogeneity: Tau² = 0.08; Chi² = 18.41, df = 7 (P = 0.01); I² = 62%						
Test for overall effect: Z = 2.06 (P = 0.04)						
Total (95% CI)	**2440**		**2327**		**100.0%**	**1.35 [1.16 , 1.56]**
Total events:	1085		745			
Heterogeneity: Tau² = 0.09; Chi² = 86.05, df = 24 (P < 0.00001); I² = 72%						
Test for overall effect: Z = 3.96 (P < 0.0001)						
Test for subgroup differences: Chi² = 0.10, df = 1 (P = 0.75), I² = 0%						



Analysis 3.3. Comparison 3: Overall response, Outcome 3: Overall response - Question 1 - Regimen A versus A + other - assessable patients



Analysis 3.3. (Continued)

Test for overall effect: Z = 4.18 (P < 0.0001)
Test for subgroup differences: Chi² = 20.60, df = 3 (P = 0.0001), I² = 85.4%

0.1 0.2 0.5 1 2 5 10
Favours single agent Favours combination

Analysis 3.4. Comparison 3: Overall response, Outcome 4: Overall response - Question 2 - Regimen A versus Regimen C - assessable patients

Study or Subgroup	Combination Events	Combination Total	Single agent Events	Single agent Total	Weight	Risk Ratio M-H, Random, 95% CI
3.4.1 Sub group E - Single anthrycycline agent versus non-anthrycycline combination regimen						
ANZBCTG 2001	70	194	47	197	7.9%	1.51 [1.11 , 2.07]
Fraser S 1993	11	19	6	21	5.3%	2.03 [0.93 , 4.41]
Hoogstraten B(A)1976	39	98	15	39	7.1%	1.03 [0.65 , 1.65]
Hoogstraten B(B)1976	63	106	16	40	7.4%	1.49 [0.99 , 2.24]
Subtotal (95% CI)		**417**		**297**	**27.6%**	**1.42 [1.15 , 1.76]**
Total events:	183		84			
Heterogeneity: Tau² = 0.00; Chi² = 2.78, df = 3 (P = 0.43); I² = 0%						
Test for overall effect: Z = 3.28 (P = 0.001)						
3.4.2 Sub group F - Single taxane versus non-taxane, non-anthrycycline containing combination regimen						
Bishop J 1999	36	102	31	107	7.4%	1.22 [0.82 , 1.81]
Bonneterre J 2002	35	90	37	86	7.7%	0.90 [0.63 , 1.29]
Icli F 2005	33	91	21	94	7.1%	1.62 [1.02 , 2.58]
Nabholtz JM 1999	21	171	60	179	7.1%	0.37 [0.23 , 0.57]
Sjostrom J 1999	29	139	61	143	7.6%	0.49 [0.34 , 0.71]
Subtotal (95% CI)		**593**		**609**	**36.9%**	**0.80 [0.48 , 1.33]**
Total events:	154		210			
Heterogeneity: Tau² = 0.30; Chi² = 32.11, df = 4 (P < 0.00001); I² = 88%						
Test for overall effect: Z = 0.88 (P = 0.38)						
3.4.3 Sub group G - Single non-taxane, non-anthrycycline agent versus other combination regimen						
Canellos GP 1976	49	93	18	91	7.1%	2.66 [1.69 , 4.20]
Eagan RT 1976	4	20	2	19	2.4%	1.90 [0.39 , 9.20]
Erkisi M 1997	12	30	16	30	6.6%	0.75 [0.43 , 1.30]
O'Shaughnessy J 2001	18	61	5	32	4.7%	1.89 [0.77 , 4.62]
Stockler M 2006	18	109	42	214	6.8%	0.84 [0.51 , 1.39]
Venturino A(A) 2000	10	33	4	17	4.2%	1.29 [0.47 , 3.50]
Venturino A (B) 2000	7	32	4	16	3.9%	0.88 [0.30 , 2.56]
Subtotal (95% CI)		**378**		**419**	**35.6%**	**1.28 [0.79 , 2.08]**
Total events:	118		91			
Heterogeneity: Tau² = 0.25; Chi² = 17.72, df = 6 (P = 0.007); I² = 66%						
Test for overall effect: Z = 1.02 (P = 0.31)						
Total (95% CI)		**1388**		**1325**	**100.0%**	**1.11 [0.84 , 1.48]**
Total events:	455		385			
Heterogeneity: Tau² = 0.24; Chi² = 72.84, df = 15 (P < 0.00001); I² = 79%						
Test for overall effect: Z = 0.73 (P = 0.46)						
Test for subgroup differences: Chi² = 4.23, df = 2 (P = 0.12), I² = 52.8%						

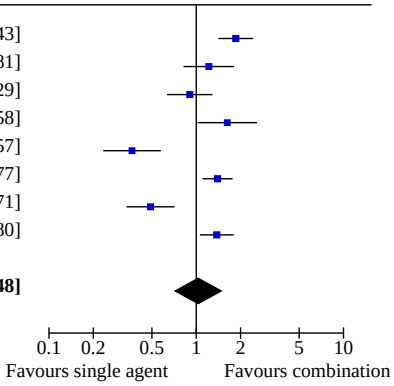
Risk Ratio M-H, Random, 95% CI

0.1 0.2 0.5 1 2 5 10
Favours single agent Favours combination

Analysis 3.5. Comparison 3: Overall response, Outcome 5: Overall response - single agent taxane versus all combinations

Study or Subgroup	Combination Events	Combination Total	Single agent Events	Single agent Total	Weight	Risk Ratio M-H, Random, 95% CI
Albain KS 2004	107	262	57	259	13.2%	1.86 [1.41 , 2.43]
Bishop J 1999	36	102	31	107	12.1%	1.22 [0.82 , 1.81]
Bonneterre J 2002	35	90	37	86	12.5%	0.90 [0.63 , 1.29]
Icli F 2005	33	91	21	94	11.5%	1.62 [1.02 , 2.58]
Nabholtz JM 1999	21	171	60	179	11.6%	0.37 [0.23 , 0.57]
O'Shaughnessy J 2002	107	255	77	256	13.4%	1.40 [1.10 , 1.77]
Sjostrom J 1999	29	139	61	143	12.3%	0.49 [0.34 , 0.71]
Sledge G(B) 2003	54	115	78	229	13.2%	1.38 [1.06 , 1.80]
Total (95% CI)		**1225**		**1353**	**100.0%**	**1.03 [0.72 , 1.48]**
Total events:	422		422			

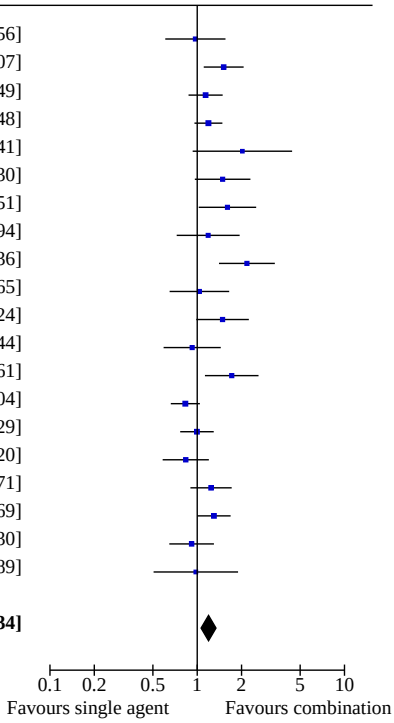
Heterogeneity: Tau² = 0.23; Chi² = 65.32, df = 7 (P < 0.00001); I² = 89%
Test for overall effect: Z = 0.17 (P = 0.87)
Test for subgroup differences: Not applicable



Analysis 3.6. Comparison 3: Overall response, Outcome 6: Overall response - single agent anthracycline versus all combinations

Study or Subgroup	Combination Events	Combination Total	Single agent Events	Single agent Total	Weight	Risk Ratio M-H, Random, 95% CI
Andersson M 1986	19	44	20	45	3.9%	0.97 [0.61 , 1.56]
ANZBCTG 2001	70	194	47	197	6.0%	1.51 [1.11 , 2.07]
Berruti D 2002	53	92	47	93	6.8%	1.14 [0.87 , 1.49]
Ejlertsen B 2004	96	193	81	194	7.7%	1.19 [0.96 , 1.48]
Fraser S 1993	11	19	6	21	1.8%	2.03 [0.93 , 4.41]
French Epi (A) 1991	54	121	18	60	4.3%	1.49 [0.96 , 2.30]
French Epi (B) 1991	55	123	17	61	4.1%	1.60 [1.02 , 2.51]
Gundersen S 1986	24	66	19	62	3.7%	1.19 [0.73 , 1.94]
Heidemann E 2004	44	87	20	86	4.3%	2.17 [1.41 , 3.36]
Hoogstraten B(A)1976	39	98	15	39	3.9%	1.03 [0.65 , 1.65]
Hoogstraten B(B)1976	63	106	16	40	4.6%	1.49 [0.99 , 2.24]
Ingle J 1985	25	77	26	74	4.1%	0.92 [0.59 , 1.44]
Ingle J 1989	39	90	24	95	4.5%	1.72 [1.13 , 2.61]
Joensuu H 1998	67	143	79	140	7.6%	0.83 [0.66 , 1.04]
Nielsen D 2000	43	71	45	74	6.9%	1.00 [0.77 , 1.29]
Nielson D 1990	28	67	38	76	5.2%	0.84 [0.58 , 1.20]
Norris B 2000	55	145	44	144	5.8%	1.24 [0.90 , 1.71]
Sledge G(A) 2003	54	115	81	224	6.9%	1.30 [1.00 , 1.69]
Steiner R 1983	28	54	30	53	5.4%	0.92 [0.65 , 1.30]
Vaughn CB 1988	13	56	14	59	2.4%	0.98 [0.51 , 1.89]
Total (95% CI)		**1961**		**1837**	**100.0%**	**1.19 [1.06 , 1.34]**
Total events:	880		687			

Heterogeneity: Tau² = 0.03; Chi² = 38.87, df = 19 (P = 0.005); I² = 51%
Test for overall effect: Z = 2.99 (P = 0.003)
Test for subgroup differences: Not applicable

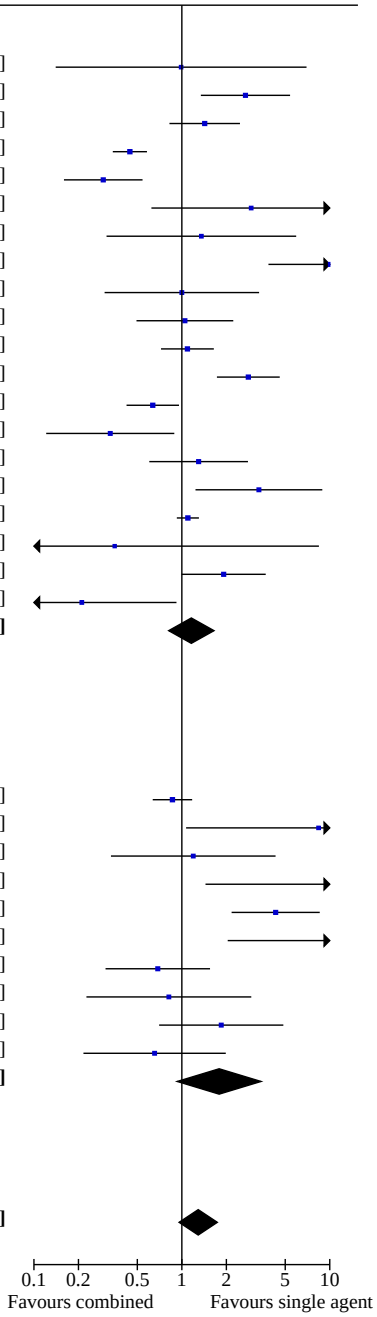


Comparison 4. Toxicity - Nausea and vomiting

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Nausea and vomiting - asssessable patients - all trials	30	7487	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.96, 1.74]
4.1.1 Question 1: Regimen A versus A + other	20	5149	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.81, 1.65]
4.1.2 Question 2: Regimen A versus Regimen C (poly)	10	2338	Risk Ratio (M-H, Random, 95% CI)	1.79 [0.93, 3.43]
4.2 Nausea and vomiting - Question 1 - Regimen A versus A + other - assessable patients	17	4793	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.75, 1.80]
4.2.1 Sub-group A: Single antracycline agent versus anthracycline + other regimen	12	2958	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.74, 2.05]
4.2.2 Sub group B: Single alkylating versus alkylating + other	1	103	Risk Ratio (M-H, Random, 95% CI)	2.94 [0.62, 13.90]
4.2.3 Sub group C: Single antimetabolite versus antimetabolite + other	2	246	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.34, 0.58]
4.2.4 Sub group D: Single taxane versus taxane + other	3	1486	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.63, 2.65]
4.3 Nausea and vomiting - Question 2 - Regimen A versus Regimen C - assessable patients	9	2082	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.79, 2.66]
4.3.1 Sub group E: Single anthracycline agent versus non-anthracycline combination regimen	2	422	Risk Ratio (M-H, Random, 95% CI)	3.44 [0.11, 104.44]
4.3.2 Sub-group F: Single taxane versus non-taxane, non-anthracycline containing combination regimen	5	1244	Risk Ratio (M-H, Random, 95% CI)	2.16 [0.78, 6.00]
4.3.3 Sub-group G: Single non-taxane, non-anthracycline agent versus other combination regimen	2	416	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.31, 1.66]

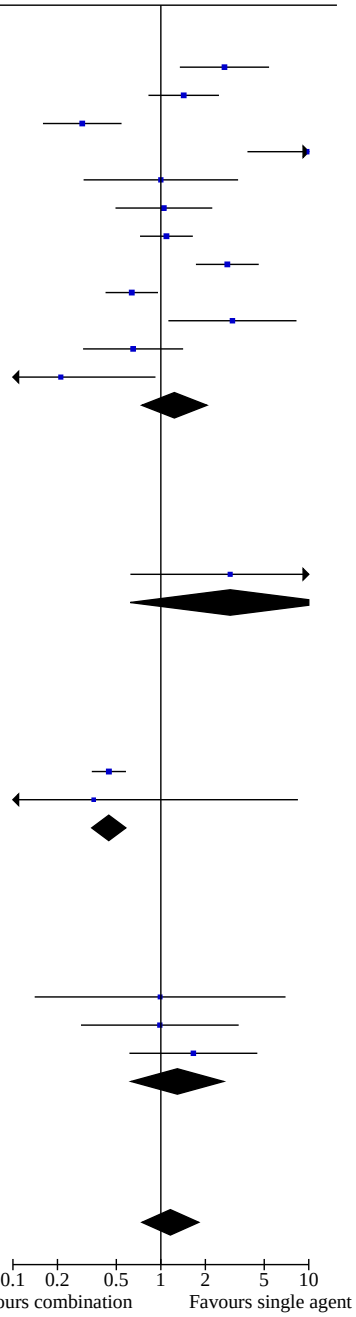
Analysis 4.1. Comparison 4: Toxicity - Nausea and vomiting, Outcome 1: Nausea and vomiting - asssessable patients - all trials

Study or Subgroup	Combination Events	Combination Total	Single agent Events	Single agent Total	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 Question 1: Regimen A versus A + other						
Albain KS 2004	2	262	2	259	1.6%	0.99 [0.14 , 6.97]
Andersson M 1986	20	39	8	42	4.1%	2.69 [1.34 , 5.39]
Berruti D 2002	24	90	17	91	4.5%	1.43 [0.82 , 2.47]
Carmo-Pereira 1980	30	68	67	67	5.1%	0.45 [0.34 , 0.58]
Ejlertsen B 2004	12	193	41	194	4.3%	0.29 [0.16 , 0.54]
Falkson G 1990	6	52	2	51	2.2%	2.94 [0.62 , 13.90]
GEICAM 2007	4	123	3	125	2.3%	1.36 [0.31 , 5.93]
Gundersen S 1986	43	66	4	62	3.4%	10.10 [3.85 , 26.48]
Heidemann E 2004	5	85	5	85	2.8%	1.00 [0.30 , 3.33]
Ingle J 1985	12	77	11	74	3.9%	1.05 [0.49 , 2.23]
Ingle J 1989	31	90	30	95	4.8%	1.09 [0.72 , 1.65]
Joensuu H 1998	50	149	18	151	4.6%	2.82 [1.73 , 4.59]
Norris B 2000	29	151	45	149	4.8%	0.64 [0.42 , 0.96]
O'Shaughnessy J 2002	5	255	15	251	3.3%	0.33 [0.12 , 0.89]
Sledge G(A) 2003	10	115	15	224	3.9%	1.30 [0.60 , 2.80]
Sledge G(B) 2003	10	115	6	229	3.3%	3.32 [1.24 , 8.91]
Steiner R 1983	47	54	42	53	5.2%	1.10 [0.92 , 1.30]
Takayama T(A) 2000	0	54	1	57	0.7%	0.35 [0.01 , 8.45]
Thomas E 2008	25	369	13	368	4.2%	1.92 [1.00 , 3.69]
Vaughn CB 1988	2	56	10	59	2.3%	0.21 [0.05 , 0.92]
Subtotal (95% CI)		**2463**		**2686**	**71.4%**	**1.16 [0.81 , 1.65]**
Total events:	367		355			
Heterogeneity: Tau² = 0.44; Chi² = 129.65, df = 19 (P < 0.00001); I² = 85%						
Test for overall effect: Z = 0.82 (P = 0.41)						
4.1.2 Question 2: Regimen A versus Regimen C (poly)						
ANZBCTG 2001	53	190	62	192	5.0%	0.86 [0.64 , 1.17]
Bishop J 1999	8	102	1	107	1.5%	8.39 [1.07 , 65.92]
Bonneterre J 2002	5	90	4	86	2.7%	1.19 [0.33 , 4.30]
Fraser S 1993	10	19	0	21	0.9%	23.10 [1.45 , 369.26]
Heidemann E 2002	37	125	9	131	4.1%	4.31 [2.17 , 8.56]
Icli F 2005	15	96	1	97	1.6%	15.16 [2.04 , 112.49]
Nabholtz JM 1999	9	187	14	200	3.8%	0.69 [0.30 , 1.55]
O'Shaughnessy J 2001	3	32	7	61	2.7%	0.82 [0.23 , 2.95]
Sjostrom J 1999	11	139	6	140	3.4%	1.85 [0.70 , 4.85]
Stockler M 2006	4	109	12	214	3.0%	0.65 [0.22 , 1.98]
Subtotal (95% CI)		**1089**		**1249**	**28.6%**	**1.79 [0.93 , 3.43]**
Total events:	155		116			
Heterogeneity: Tau² = 0.70; Chi² = 39.04, df = 9 (P < 0.0001); I² = 77%						
Test for overall effect: Z = 1.75 (P = 0.08)						
Total (95% CI)		**3552**		**3935**	**100.0%**	**1.29 [0.96 , 1.74]**
Total events:	522		471			
Heterogeneity: Tau² = 0.44; Chi² = 172.40, df = 29 (P < 0.00001); I² = 83%						
Test for overall effect: Z = 1.68 (P = 0.09)						
Test for subgroup differences: Chi² = 1.31, df = 1 (P = 0.25), I² = 23.8%						

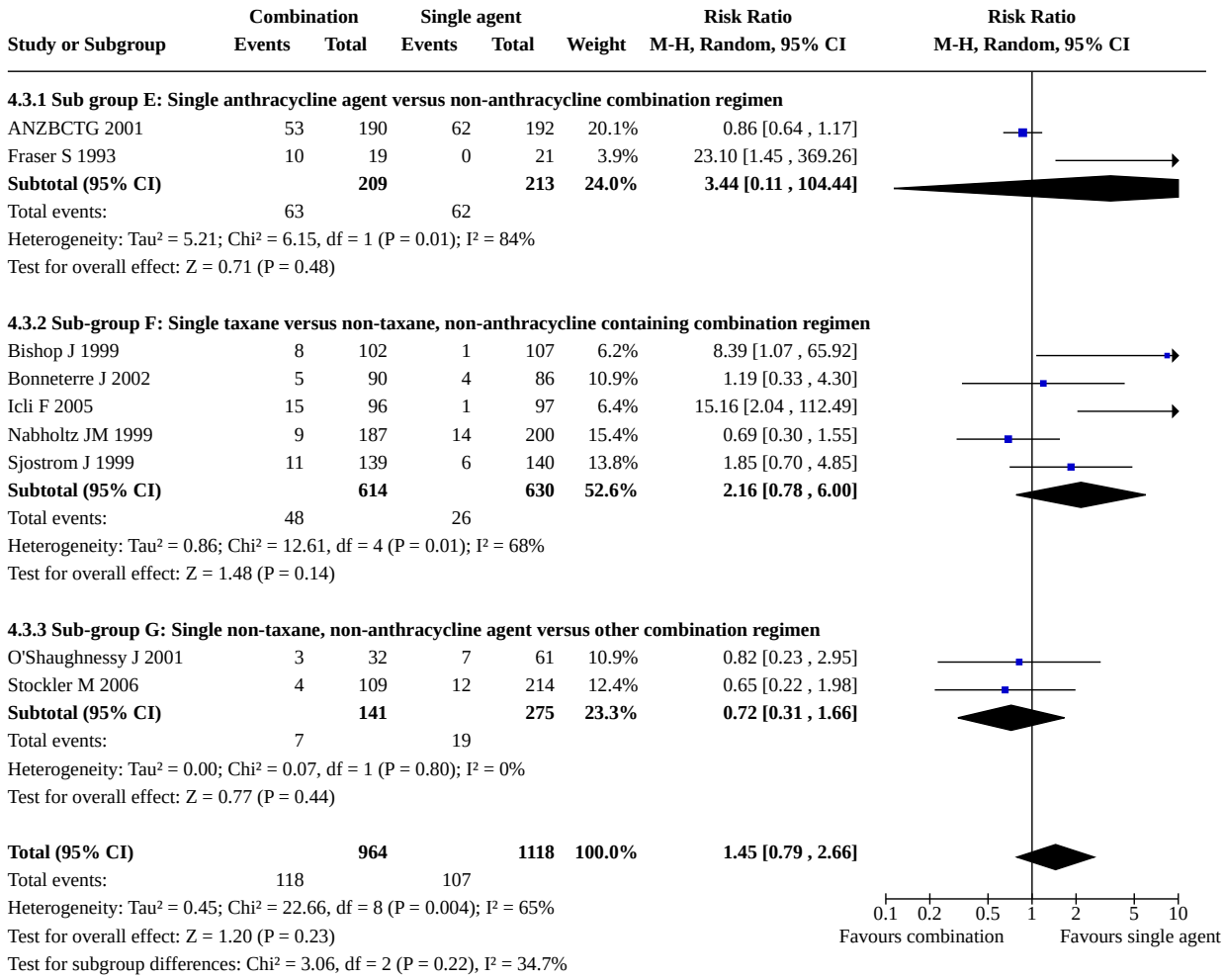


Analysis 4.2. Comparison 4: Toxicity - Nausea and vomiting, Outcome 2: Nausea and vomiting - Question 1 - Regimen A versus A + other - assessable patients

Study or Subgroup	Combination Events	Combination Total	Single agent Events	Single agent Total	Weight	Risk Ratio M-H, Random, 95% CI
4.2.1 Sub-group A: Single antracycline agent versus anthracycline + other regimen						
Andersson M 1986	20	39	8	42	6.4%	2.69 [1.34 , 5.39]
Berruti D 2002	24	90	17	91	6.8%	1.43 [0.82 , 2.47]
Ejlertsen B 2004	12	193	41	194	6.7%	0.29 [0.16 , 0.54]
Gundersen S 1986	43	66	4	62	5.6%	10.10 [3.85 , 26.48]
Heidemann E 2004	5	85	5	85	4.9%	1.00 [0.30 , 3.33]
Ingle J 1985	12	77	11	74	6.2%	1.05 [0.49 , 2.23]
Ingle J 1989	31	90	30	95	7.2%	1.09 [0.72 , 1.65]
Joensuu H 1998	50	149	18	151	7.0%	2.82 [1.73 , 4.59]
Norris B 2000	29	151	45	149	7.2%	0.64 [0.42 , 0.96]
O'Shaughnessy J 2002	15	251	5	255	5.5%	3.05 [1.12 , 8.26]
Sledge G(A) 2003	10	230	15	224	6.2%	0.65 [0.30 , 1.41]
Vaughn CB 1988	2	56	10	59	4.1%	0.21 [0.05 , 0.92]
Subtotal (95% CI)		**1477**		**1481**	**73.7%**	**1.23 [0.74 , 2.05]**
Total events:	253		209			
Heterogeneity: Tau² = 0.64; Chi² = 77.30, df = 11 (P < 0.00001); I² = 86%						
Test for overall effect: Z = 0.82 (P = 0.42)						
4.2.2 Sub group B: Single alkylating versus alkylating + other						
Falkson G 1990	6	52	2	51	3.9%	2.94 [0.62 , 13.90]
Subtotal (95% CI)		**52**		**51**	**3.9%**	**2.94 [0.62 , 13.90]**
Total events:	6		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.36 (P = 0.17)						
4.2.3 Sub group C: Single antimetabolite versus antimetabolite + other						
Carmo-Pereira 1980	30	68	67	67	7.4%	0.45 [0.34 , 0.58]
Takayama T(A) 2000	0	54	1	57	1.5%	0.35 [0.01 , 8.45]
Subtotal (95% CI)		**122**		**124**	**9.0%**	**0.44 [0.34 , 0.58]**
Total events:	30		68			
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%						
Test for overall effect: Z = 6.00 (P < 0.00001)						
4.2.4 Sub group D: Single taxane versus taxane + other						
Albain KS 2004	2	262	2	259	3.1%	0.99 [0.14 , 6.97]
O'Shaughnessy J 2002	5	255	5	251	4.8%	0.98 [0.29 , 3.36]
Sledge G(B) 2003	10	230	6	229	5.5%	1.66 [0.61 , 4.49]
Subtotal (95% CI)		**747**		**739**	**13.4%**	**1.29 [0.63 , 2.65]**
Total events:	17		13			
Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 2 (P = 0.78); I² = 0%						
Test for overall effect: Z = 0.70 (P = 0.48)						
Total (95% CI)		**2398**		**2395**	**100.0%**	**1.16 [0.75 , 1.80]**
Total events:	306		292			
Heterogeneity: Tau² = 0.67; Chi² = 120.84, df = 17 (P < 0.00001); I² = 86%						
Test for overall effect: Z = 0.66 (P = 0.51)						
Test for subgroup differences: Chi² = 21.03, df = 3 (P = 0.0001), I² = 85.7%						



Analysis 4.3. Comparison 4: Toxicity - Nausea and vomiting, Outcome 3: Nausea and vomiting - Question 2 - Regimen A versus Regimen C - assessable patients



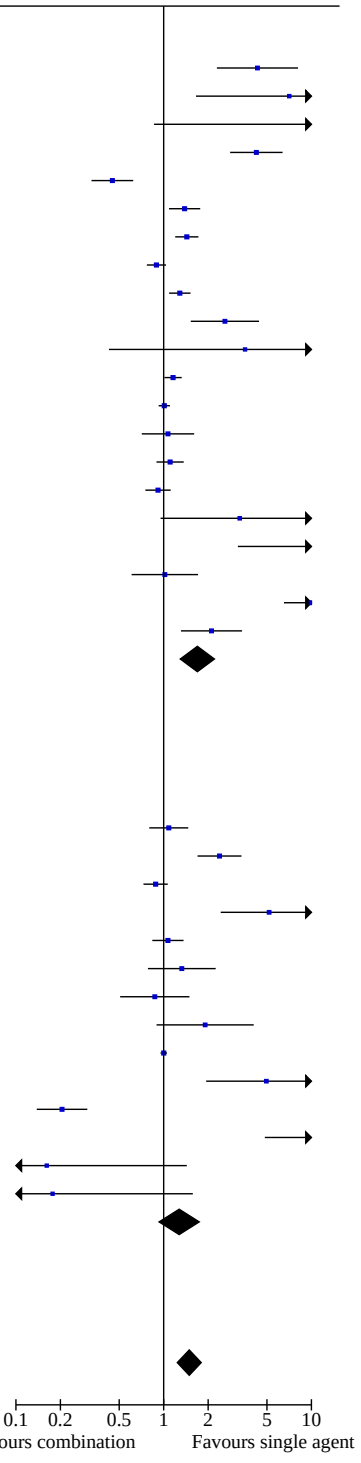
Comparison 5. Toxicity - White cell count

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 WCC - assessable patients - all trials	35	7810	Risk Ratio (M-H, Random, 95% CI)	1.49 [1.24, 1.79]
5.1.1 Question1: Regimen A versus A +other	21	5164	Risk Ratio (M-H, Random, 95% CI)	1.69 [1.30, 2.20]
5.1.2 Question 2: Regimen A versus Regimen C	14	2646	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.93, 1.74]
5.2 WCC - Question 1 - Regimen A versus A + other - assessable patients	19	4463	Risk Ratio (M-H, Random, 95% CI)	1.35 [1.10, 1.65]
5.2.1 Sub group A: Single anthracycline agent versus anthracycline + other regimen	12	2974	Risk Ratio (M-H, Random, 95% CI)	1.48 [1.19, 1.83]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.2.2 Sub group B: Single alkyating agent versus alkylating agent + other	3	263	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.28, 1.10]
5.2.3 Sub group C: Single antimetabolite versus antimetabolite + other	2	246	Risk Ratio (M-H, Random, 95% CI)	28.06 [3.85, 204.44]
5.2.4 Sub group D: Single taxane versus taxane + other	2	980	Risk Ratio (M-H, Random, 95% CI)	1.93 [0.37, 10.03]
5.3 WCC - Question 2 - Regimen A versus Regimen C - assessable patients	13	2367	Risk Ratio (M-H, Random, 95% CI)	1.54 [1.08, 2.18]
5.3.1 Sub group E: Single anthracycline agent versus non-anthracycline combination regimen	3	665	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.85, 1.37]
5.3.2 Sub-group F: Single taxane versus non-taxane, non-anthracycline containing combination regimen	4	965	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.85, 2.11]
5.3.3 Sub-group G: single non-taxane, non-anthracycline agent versus other combination regimen	6	737	Risk Ratio (M-H, Random, 95% CI)	1.70 [0.43, 6.63]

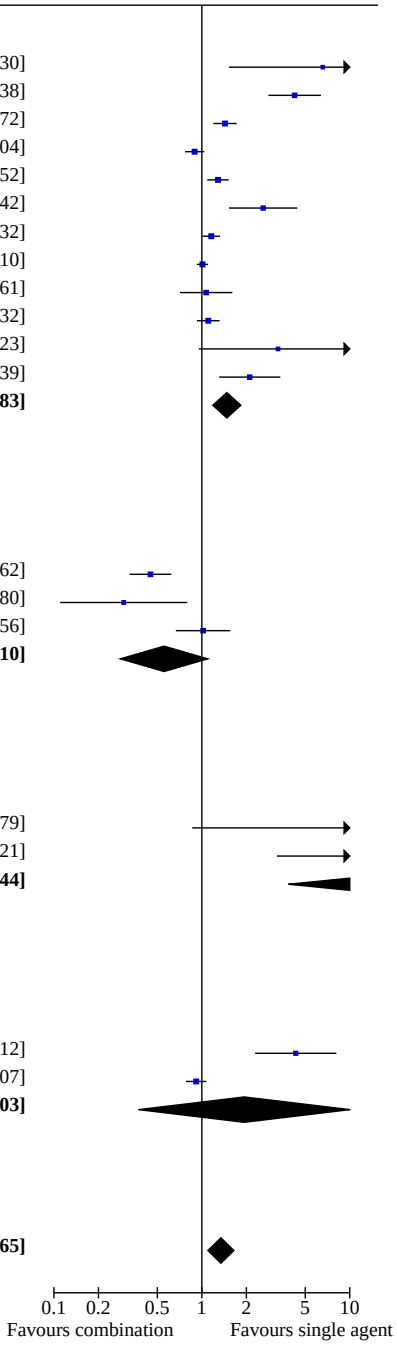
Analysis 5.1. Comparison 5: Toxicity - White cell count, Outcome 1: WCC - assessable patients - all trials

Study or Subgroup	Combination Events	Total	Single agent Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
5.1.1 Question1: Regimen A versus A +other						
Albain KS 2004	48	262	11	259	2.8%	4.31 [2.29 , 8.12]
Berruti D 2002	14	90	2	91	1.2%	7.08 [1.66 , 30.25]
Carmo-Pereira 1980	7	68	0	67	0.4%	14.78 [0.86 , 253.79]
Ejlertsen B 2004	97	193	23	194	3.4%	4.24 [2.82 , 6.38]
Falkson G 1990	22	52	48	51	3.6%	0.45 [0.32 , 0.62]
GEICAM 2007	75	123	55	125	3.8%	1.39 [1.09 , 1.77]
Heidemann E 2004	76	85	53	85	3.9%	1.43 [1.20 , 1.72]
Ingle J 1985	53	67	62	70	4.0%	0.89 [0.77 , 1.04]
Ingle J 1989	75	87	61	91	4.0%	1.29 [1.09 , 1.52]
Joensuu H 1998	41	149	16	151	3.1%	2.60 [1.53 , 4.42]
Mouridsen HT 1977	4	27	1	24	0.6%	3.56 [0.43 , 29.66]
Nielsen D 2000	60	65	59	74	4.0%	1.16 [1.01 , 1.32]
Norris B 2000	132	151	129	149	4.1%	1.01 [0.93 , 1.10]
O'Shaughnessy J 2002	40	251	38	255	3.4%	1.07 [0.71 , 1.61]
Sledge G(A) 2003	63	115	111	224	3.9%	1.11 [0.89 , 1.37]
Sledge G(B) 2003	63	115	137	229	3.9%	0.92 [0.75 , 1.12]
Steiner R 1983	10	54	3	53	1.5%	3.27 [0.95 , 11.23]
Takayama T(A) 2000	12	27	0	57	0.4%	51.79 [3.18 , 843.53]
Takayama T(B) 2000	12	27	24	55	3.1%	1.02 [0.61 , 1.71]
Thomas E 2008	210	369	21	368	3.4%	9.97 [6.52 , 15.25]
Vaughn CB 1988	32	56	16	59	3.2%	2.11 [1.31 , 3.39]
Subtotal (95% CI)		**2433**		**2731**	**61.6%**	**1.69 [1.30 , 2.20]**
Total events:	1146		870			
Heterogeneity: Tau² = 0.29; Chi² = 396.44, df = 20 (P < 0.00001); I² = 95%						
Test for overall effect: Z = 3.87 (P = 0.0001)						
5.1.2 Question 2: Regimen A versus Regimen C						
ANZBCTG 2001	60	190	56	192	3.7%	1.08 [0.80 , 1.47]
Bishop J 1999	66	102	29	107	3.6%	2.39 [1.70 , 3.36]
Bonneterre J 2002	60	90	65	86	3.9%	0.88 [0.73 , 1.07]
Canellos GP 1976	37	93	7	91	2.4%	5.17 [2.43 , 11.00]
Eagan RT 1976	18	20	16	19	3.8%	1.07 [0.84 , 1.36]
Hoogstraten B(A)1976	40	98	12	39	3.1%	1.33 [0.78 , 2.25]
Hoogstraten B(B)1976	30	106	13	40	3.0%	0.87 [0.51 , 1.49]
Icli F 2005	17	96	9	97	2.4%	1.91 [0.90 , 4.07]
Nabholtz JM 1999	176	187	188	200	4.1%	1.00 [0.95 , 1.05]
O'Shaughnessy J 2001	13	32	5	61	2.0%	4.96 [1.94 , 12.67]
Sjostrom J 1999	22	139	108	140	3.5%	0.21 [0.14 , 0.30]
Stockler M 2006	24	109	3	214	1.6%	15.71 [4.84 , 51.01]
Venturino A(A) 2000	1	33	3	16	0.6%	0.16 [0.02 , 1.43]
Venturino A (B) 2000	1	32	3	17	0.6%	0.18 [0.02 , 1.58]
Subtotal (95% CI)		**1327**		**1319**	**38.4%**	**1.27 [0.93 , 1.74]**
Total events:	565		517			
Heterogeneity: Tau² = 0.24; Chi² = 152.85, df = 13 (P < 0.00001); I² = 91%						
Test for overall effect: Z = 1.52 (P = 0.13)						
Total (95% CI)		**3760**		**4050**	**100.0%**	**1.49 [1.24 , 1.79]**
Total events:	1711		1387			
Heterogeneity: Tau² = 0.22; Chi² = 607.34, df = 34 (P < 0.00001); I² = 94%						
Test for overall effect: Z = 4.20 (P < 0.0001)						
Test for subgroup differences: Chi² = 1.83, df = 1 (P = 0.18), I² = 45.5%						



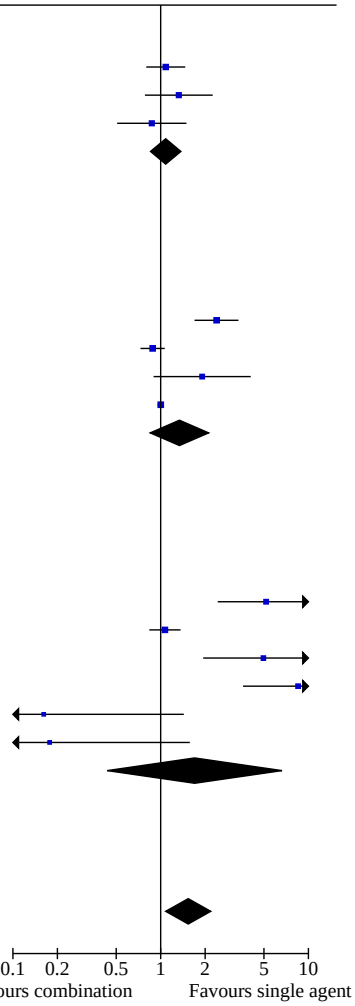
Analysis 5.2. Comparison 5: Toxicity - White cell count, Outcome 2: WCC - Question 1 - Regimen A versus A + other - assessable patients

Study or Subgroup	Combination Events	Combination Total	Single agent Events	Single agent Total	Weight	Risk Ratio M-H, Random, 95% CI
5.2.1 Sub group A: Single anthracycline agent versus anthracycline + other regimen						
Berruti D 2002	13	90	2	91	1.5%	6.57 [1.53 , 28.30]
Ejlertsen B 2004	97	193	23	194	6.0%	4.24 [2.82 , 6.38]
Heidemann E 2004	76	85	53	85	7.5%	1.43 [1.20 , 1.72]
Ingle J 1985	53	67	62	70	7.6%	0.89 [0.77 , 1.04]
Ingle J 1989	75	87	61	91	7.5%	1.29 [1.09 , 1.52]
Joensuu H 1998	41	149	16	151	5.1%	2.60 [1.53 , 4.42]
Nielsen D 2000	60	65	59	74	7.7%	1.16 [1.01 , 1.32]
Norris B 2000	132	151	129	149	7.8%	1.01 [0.93 , 1.10]
O'Shaughnessy J 2002	40	251	38	255	6.0%	1.07 [0.71 , 1.61]
Sledge G(A) 2003	126	230	111	224	7.5%	1.11 [0.93 , 1.32]
Steiner R 1983	10	54	3	53	2.0%	3.27 [0.95 , 11.23]
Vaughn CB 1988	32	56	16	59	5.5%	2.11 [1.31 , 3.39]
Subtotal (95% CI)		**1478**		**1496**	**71.8%**	**1.48 [1.19 , 1.83]**
Total events:	755		573			
Heterogeneity: Tau² = 0.11; Chi² = 126.08, df = 11 (P < 0.00001); I² = 91%						
Test for overall effect: Z = 3.50 (P = 0.0005)						
5.2.2 Sub group B: Single alkyating agent versus alkylating agent + other						
Falkson G 1990	22	52	48	51	6.6%	0.45 [0.32 , 0.62]
Mouridsen HT 1977	4	27	12	24	2.7%	0.30 [0.11 , 0.80]
Takayama T(B) 2000	24	54	24	55	5.9%	1.02 [0.67 , 1.56]
Subtotal (95% CI)		**133**		**130**	**15.2%**	**0.56 [0.28 , 1.10]**
Total events:	50		84			
Heterogeneity: Tau² = 0.27; Chi² = 10.94, df = 2 (P = 0.004); I² = 82%						
Test for overall effect: Z = 1.70 (P = 0.09)						
5.2.3 Sub group C: Single antimetabolite versus antimetabolite + other						
Carmo-Pereira 1980	7	68	0	67	0.5%	14.78 [0.86 , 253.79]
Takayama T(A) 2000	24	54	0	57	0.5%	51.67 [3.22 , 829.21]
Subtotal (95% CI)		**122**		**124**	**1.0%**	**28.06 [3.85 , 204.44]**
Total events:	31		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.41, df = 1 (P = 0.52); I² = 0%						
Test for overall effect: Z = 3.29 (P = 0.001)						
5.2.4 Sub group D: Single taxane versus taxane + other						
Albain KS 2004	48	262	11	259	4.5%	4.31 [2.29 , 8.12]
Sledge G(B) 2003	126	230	137	229	7.6%	0.92 [0.78 , 1.07]
Subtotal (95% CI)		**492**		**488**	**12.0%**	**1.93 [0.37 , 10.03]**
Total events:	174		148			
Heterogeneity: Tau² = 1.36; Chi² = 25.53, df = 1 (P < 0.00001); I² = 96%						
Test for overall effect: Z = 0.79 (P = 0.43)						
Total (95% CI)		**2225**		**2238**	**100.0%**	**1.35 [1.10 , 1.65]**
Total events:	1010		805			
Heterogeneity: Tau² = 0.13; Chi² = 194.46, df = 18 (P < 0.00001); I² = 91%						
Test for overall effect: Z = 2.87 (P = 0.004)						
Test for subgroup differences: Chi² = 16.24, df = 3 (P = 0.001), I² = 81.5%						



Analysis 5.3. Comparison 5: Toxicity - White cell count, Outcome 3: WCC - Question 2 - Regimen A versus Regimen C - assessable patients

Study or Subgroup	Combination Events	Combination Total	Single agent Events	Single agent Total	Weight	Risk Ratio M-H, Random, 95% CI
5.3.1 Sub group E: Single anthracycline agent versus non-anthracycline combination regimen						
ANZBCTG 2001	60	190	56	192	10.0%	1.08 [0.80 , 1.47]
Hoogstraten B(A)1976	40	98	12	39	8.7%	1.33 [0.78 , 2.25]
Hoogstraten B(B)1976	30	106	13	40	8.6%	0.87 [0.51 , 1.49]
Subtotal (95% CI)		**394**		**271**	**27.3%**	**1.08 [0.85 , 1.37]**
Total events:	130		81			
Heterogeneity: Tau² = 0.00; Chi² = 1.20, df = 2 (P = 0.55); I² = 0%						
Test for overall effect: Z = 0.65 (P = 0.52)						
5.3.2 Sub-group F: Single taxane versus non-taxane, non-anthracycline containing combination regimen						
Bishop J 1999	66	102	29	107	9.8%	2.39 [1.70 , 3.36]
Bonneterre J 2002	60	90	65	86	10.5%	0.88 [0.73 , 1.07]
Icli F 2005	17	96	9	97	7.2%	1.91 [0.90 , 4.07]
Nabholtz JM 1999	176	187	188	200	10.8%	1.00 [0.95 , 1.05]
Subtotal (95% CI)		**475**		**490**	**38.3%**	**1.34 [0.85 , 2.11]**
Total events:	319		291			
Heterogeneity: Tau² = 0.18; Chi² = 52.35, df = 3 (P < 0.00001); I² = 94%						
Test for overall effect: Z = 1.26 (P = 0.21)						
5.3.3 Sub-group G: single non-taxane, non-anthracycline agent versus other combination regimen						
Canellos GP 1976	37	93	7	91	7.2%	5.17 [2.43 , 11.00]
Eagan RT 1976	18	20	16	19	10.3%	1.07 [0.84 , 1.36]
O'Shaughnessy J 2001	13	32	5	61	6.1%	4.96 [1.94 , 12.67]
Stockler M 2006	26	109	6	214	6.6%	8.51 [3.61 , 20.05]
Venturino A(A) 2000	1	33	3	16	2.1%	0.16 [0.02 , 1.43]
Venturino A (B) 2000	1	32	3	17	2.1%	0.18 [0.02 , 1.58]
Subtotal (95% CI)		**319**		**418**	**34.4%**	**1.70 [0.43 , 6.63]**
Total events:	96		40			
Heterogeneity: Tau² = 2.47; Chi² = 81.23, df = 5 (P < 0.00001); I² = 94%						
Test for overall effect: Z = 0.76 (P = 0.45)						
Total (95% CI)		**1188**		**1179**	**100.0%**	**1.54 [1.08 , 2.18]**
Total events:	545		412			
Heterogeneity: Tau² = 0.30; Chi² = 171.48, df = 12 (P < 0.00001); I² = 93%						
Test for overall effect: Z = 2.40 (P = 0.02)						
Test for subgroup differences: Chi² = 1.00, df = 2 (P = 0.61), I² = 0%						



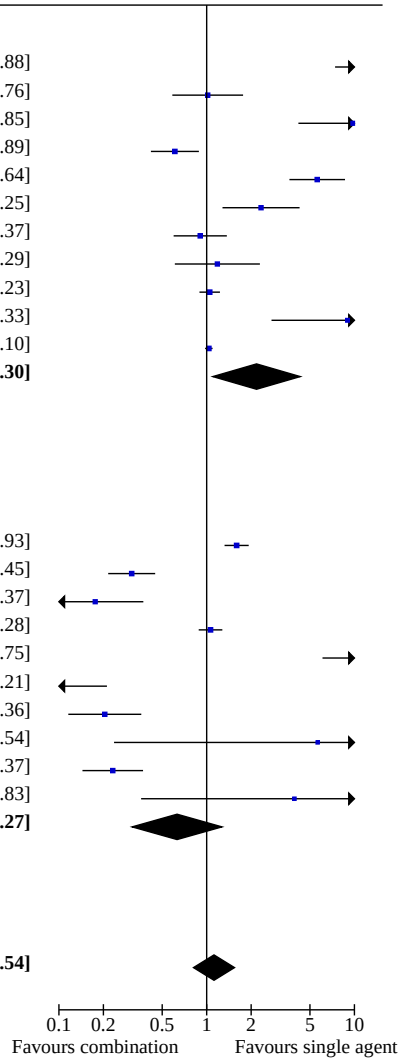
Comparison 6. Toxicity - Alopecia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Alopecia - assessable patients - all trials	21	4818	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.81, 1.54]
6.1.1 Question 1: Regimen A (single) versus A + other	11	2778	Risk Ratio (M-H, Random, 95% CI)	2.18 [1.10, 4.30]
6.1.2 Question 2: Regimen A versus Regimen C	10	2040	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.31, 1.27]
6.2 Alopecia - Question 1 - Regimen A versus A + other - assessable patients	9	2299	Risk Ratio (M-H, Random, 95% CI)	1.86 [0.96, 3.64]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.2.1 Sub group A: Single anthracycline agent versus anthracycline + other regimen	7	1607	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.82, 2.85]
6.2.2 Sub group B: Single alkyating agent versus alkylating agent + other	1	51	Risk Ratio (M-H, Random, 95% CI)	2.33 [1.28, 4.25]
6.2.3 Sub group C: Single antimetabolite versus antimetabolite + other	1	135	Risk Ratio (M-H, Random, 95% CI)	117.28 [7.40, 1858.88]
6.2.4 Sub group D: Single taxane versus taxane + other	1	506	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.61, 2.29]
6.3 Alopecia - Question 2 - Regimen A versus Regimen C -assessable patients	9	1784	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.21, 0.78]
6.3.1 Sub group E: Single anthracycline agent versus non-anthracycline combination regimen	3	665	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.05, 1.40]
6.3.2 Sub-group F: Single taxane versus non-taxane, non-anthracycline containing combination regimen	3	664	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.19, 0.35]
6.3.3 Sub-group G: single non-taxane, non-anthracycline agent versus other combination regimen	3	455	Risk Ratio (M-H, Random, 95% CI)	2.05 [0.38, 11.18]

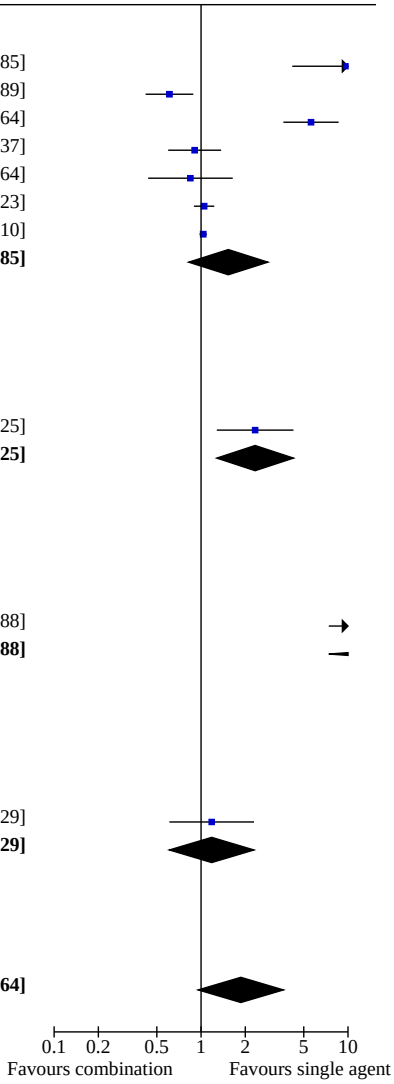
Analysis 6.1. Comparison 6: Toxicity - Alopecia, Outcome 1: Alopecia - assessable patients - all trials

Study or Subgroup	Combination Events	Combination Total	Single agent Events	Single agent Total	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 Question 1: Regimen A (single) versus A + other						
Carmo-Pereira 1980	59	68	0	67	1.1%	117.28 [7.40 , 1858.88]
GEICAM 2007	21	123	21	125	5.4%	1.02 [0.59 , 1.76]
Gundersen S 1986	52	66	5	62	4.4%	9.77 [4.18 , 22.85]
Ingle J 1985	26	77	41	74	5.9%	0.61 [0.42 , 0.89]
Joensuu H 1998	105	149	19	151	5.7%	5.60 [3.63 , 8.64]
Mouridsen HT 1977	21	27	8	24	5.2%	2.33 [1.28 , 4.25]
Norris B 2000	33	151	36	149	5.8%	0.90 [0.60 , 1.37]
O'Shaughnessy J 2002	18	255	15	251	5.0%	1.18 [0.61 , 2.29]
Steiner R 1983	47	54	44	53	6.3%	1.05 [0.89 , 1.23]
Thomas E 2008	27	369	3	368	3.4%	8.98 [2.75 , 29.33]
Vaughn CB 1988	56	56	57	59	6.4%	1.03 [0.98 , 1.10]
Subtotal (95% CI)		**1395**		**1383**	**54.7%**	**2.18 [1.10 , 4.30]**
Total events:	465		249			
Heterogeneity: Tau² = 1.16; Chi² = 541.67, df = 10 (P < 0.00001); I² = 98%						
Test for overall effect: Z = 2.24 (P = 0.03)						
6.1.2 Question 2: Regimen A versus Regimen C						
ANZBCTG 2001	131	190	83	192	6.3%	1.59 [1.32 , 1.93]
Bishop J 1999	24	102	81	107	5.9%	0.31 [0.22 , 0.45]
Bonneterre J 2002	7	90	38	86	4.7%	0.18 [0.08 , 0.37]
Eagan RT 1976	19	20	17	19	6.3%	1.06 [0.88 , 1.28]
Heidemann E 2002	77	125	6	131	4.6%	13.45 [6.08 , 29.75]
Hoogstraten B(A)1976	5	98	23	39	4.3%	0.09 [0.04 , 0.21]
Hoogstraten B(B)1976	13	106	24	40	5.3%	0.20 [0.12 , 0.36]
O'Shaughnessy J 2001	1	32	0	61	0.9%	5.64 [0.24 , 134.54]
Sjostrom J 1999	17	139	74	140	5.6%	0.23 [0.14 , 0.37]
Stockler M 2006	2	109	1	214	1.4%	3.93 [0.36 , 42.83]
Subtotal (95% CI)		**1011**		**1029**	**45.3%**	**0.63 [0.31 , 1.27]**
Total events:	296		347			
Heterogeneity: Tau² = 1.03; Chi² = 226.53, df = 9 (P < 0.00001); I² = 96%						
Test for overall effect: Z = 1.29 (P = 0.20)						
Total (95% CI)		**2406**		**2412**	**100.0%**	**1.12 [0.81 , 1.54]**
Total events:	761		596			
Heterogeneity: Tau² = 0.41; Chi² = 394.44, df = 20 (P < 0.00001); I² = 95%						
Test for overall effect: Z = 0.70 (P = 0.48)						
Test for subgroup differences: Chi² = 6.19, df = 1 (P = 0.01), I² = 83.8%						

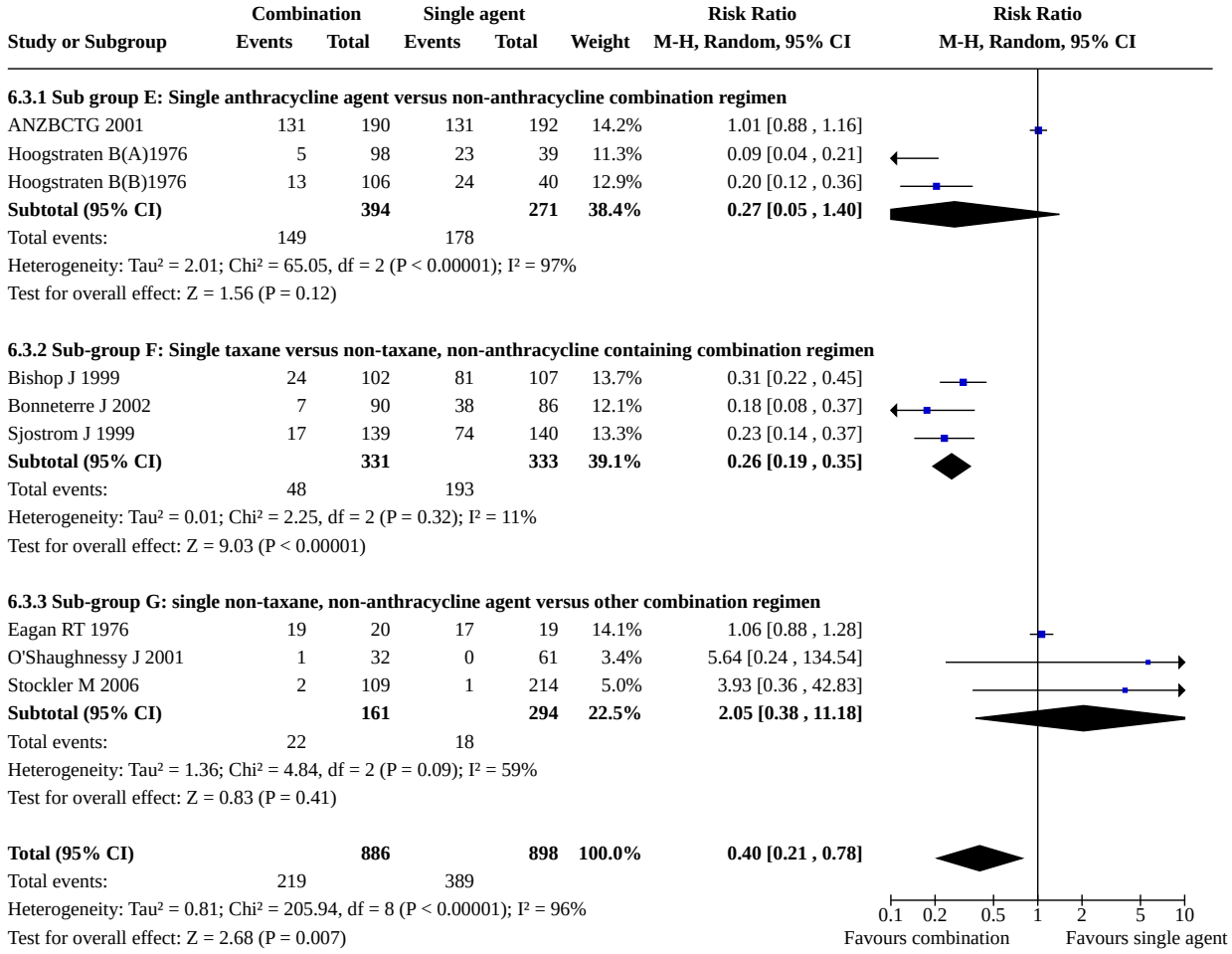


Analysis 6.2. Comparison 6: Toxicity - Alopecia, Outcome 2: Alopecia - Question 1 - Regimen A versus A + other - assessable patients

Study or Subgroup	Combination Events	Combination Total	Single agent Events	Single agent Total	Weight	Risk Ratio M-H, Random, 95% CI
6.2.1 Sub group A: Single anthracycline agent versus anthracycline + other regimen						
Gundersen S 1986	52	66	5	62	9.6%	9.77 [4.18 , 22.85]
Ingle J 1985	26	77	41	74	11.0%	0.61 [0.42 , 0.89]
Joensuu H 1998	105	149	19	151	10.9%	5.60 [3.63 , 8.64]
Norris B 2000	33	151	36	149	10.9%	0.90 [0.60 , 1.37]
O'Shaughnessy J 2002	15	251	18	255	10.3%	0.85 [0.44 , 1.64]
Steiner R 1983	47	54	44	53	11.3%	1.05 [0.89 , 1.23]
Vaughn CB 1988	56	56	57	59	11.4%	1.03 [0.98 , 1.10]
Subtotal (95% CI)		**804**		**803**	**75.4%**	**1.53 [0.82 , 2.85]**
Total events:	334		220			
Heterogeneity: Tau² = 0.64; Chi² = 271.53, df = 6 (P < 0.00001); I² = 98%						
Test for overall effect: Z = 1.35 (P = 0.18)						
6.2.2 Sub group B: Single alkyating agent versus alkylating agent + other						
Mouridsen HT 1977	21	27	8	24	10.4%	2.33 [1.28 , 4.25]
Subtotal (95% CI)		**27**		**24**	**10.4%**	**2.33 [1.28 , 4.25]**
Total events:	21		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.76 (P = 0.006)						
6.2.3 Sub group C: Single antimetabolite versus antimetabolite + other						
Carmo-Pereira 1980	59	68	0	67	3.9%	117.28 [7.40 , 1858.88]
Subtotal (95% CI)		**68**		**67**	**3.9%**	**117.28 [7.40 , 1858.88]**
Total events:	59		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.38 (P = 0.0007)						
6.2.4 Sub group D: Single taxane versus taxane + other						
O'Shaughnessy J 2002	18	255	15	251	10.3%	1.18 [0.61 , 2.29]
Subtotal (95% CI)		**255**		**251**	**10.3%**	**1.18 [0.61 , 2.29]**
Total events:	18		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.49 (P = 0.62)						
Total (95% CI)		**1154**		**1145**	**100.0%**	**1.86 [0.96 , 3.64]**
Total events:	432		243			
Heterogeneity: Tau² = 1.02; Chi² = 462.65, df = 9 (P < 0.00001); I² = 98%						
Test for overall effect: Z = 1.83 (P = 0.07)						
Test for subgroup differences: Chi² = 11.30, df = 3 (P = 0.01), I² = 73.4%						



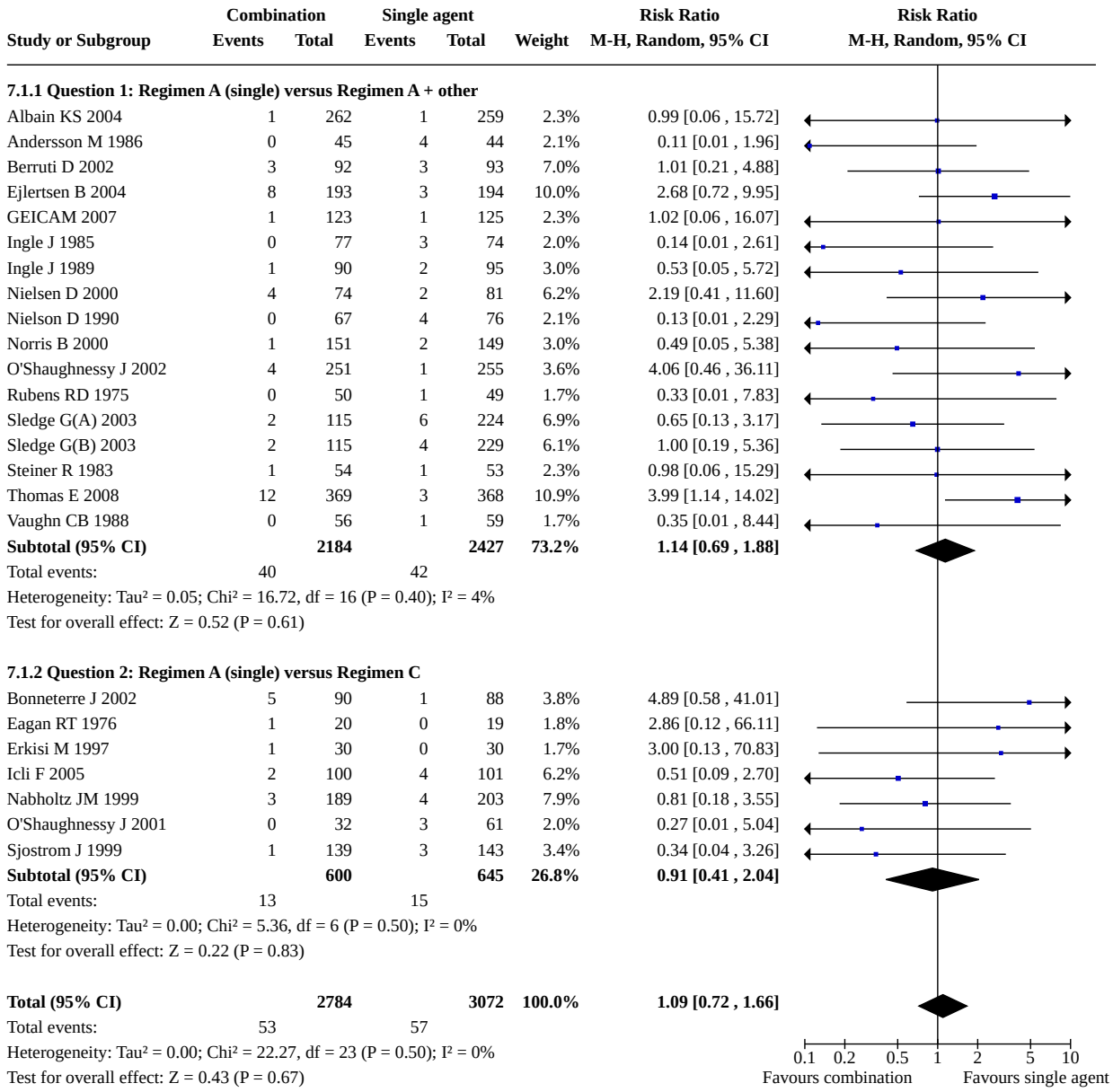
Analysis 6.3. Comparison 6: Toxicity - Alopecia, Outcome 3: Alopecia - Question 2 - Regimen A versus Regimen C -assessable patients



Comparison 7. Treatment related death

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Treatment related death - assessable patients - all trials	24	5856	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.72, 1.66]
7.1.1 Question 1: Regimen A (single) versus Regimen A + other	17	4611	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.69, 1.88]
7.1.2 Question 2: Regimen A (single) versus Regimen C	7	1245	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.41, 2.04]

Analysis 7.1. Comparison 7: Treatment related death, Outcome 1: Treatment related death - assessable patients - all trials



ADDITIONAL TABLES

Table 1. Quality of life

Trial ID	Instruments used	Summary of findings
Albain 2004	Patients completed a Brief Pain Inventory (BPI) and Rotterdam Symptom Checklist (RSCL) prior to each cycle	291 patients completed BPI and 350 completed RSCL. The mean RSCL global QOL score for patients receiving the combined regimen was significantly and consistently better than that reported by the patients in the single drug arm; this was also clinically significant. Mean changes and trends in pain intensity and interference were similar across treatment arms

Table 1. Quality of life *(Continued)*

ANZBCTG 2001	Patients completed 14 linear analogue assessment scales; the clinician used the Spitzer QL-index, at least each 3 months.	Patient rated quality of life was significantly better for CMFP than Mitoxantrone over the first 3 months, in terms of pain, mood and nausea and vomiting, though worse in terms of hair loss and similar overall.
Bishop 1999 (ANZ TITG)	Patients completed linear analog scales (LASA) sand physician completed Spitzer QOL index	QOL measures (physical well-being, mood, nausea and vomiting, appetite, overall quality of life and physician-rated quality of life) were slightly better in the taxane arm. The exception was pain which was slightly better in the non-taxane arm. Differences were not statistically significant.
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 diary 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 theLASA 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.
Heideman 2002	Patients completed the Graduated WHO Analogue and Satisfaction Scales questionnaire at baseline, and day 1 of each cycle. A modified Brunners score (MBS) was applied to assess gain from treatment.	87% (201/238) of randomised patients, treated until progression returned QOL questionnaires. 100% complete data was available to calculate the MBS for 46% patients (110/238). 38% patients (91/238) had single missing values but where evaluable. A significant gain from treatment was reported for the mitoxantrone arm (P=<0.001) explained as a result of significantly less hair loss and nausea/vomiting.
Joensuu 1998	Patients completed the Rotterdam Symptom Checklist (RSCL) which includes 30 QOL items grouped in two subscales that correspond to psychological and physical distress and eight items that describe physical activities	Data on QOL were available for 94% of randomised patients (285/303). No difference between the two arms was found in the psychological dimension of QOL analysis. Patients treated with epirubicin (single agent) showed less physical distress at 6 months after commencing treatment (P=0.002) with scores tending to be lower also for that group at other times chosen for analysis. Similarly patients treated with epirubicin reported less nausea (P <0.01). They also reported less stomach pain, diarrhoea, hair loss and itching although this was not statistically significant. Patients in the combination group were more likely to report the therapy to be difficult at 6 and 9 months from randomisation than those in the single group (P= 0.04 and 0.02 respectively)
Nabholtz 1999 (304 Study Group)	Patients completed EORTC QLQ-C30	72% of questionnaires returned for docetaxel and 68% for MV for baseline and cycle 2, but deteriorated to 59% for docetaxel and 61% for MV by cycle 8. Attrition more evident in MV and did not occur at random. Significantly higher proportion of patients in MV discontinued treatment due to deterioration in condition: authors conclude that patients in the poorest health did

Table 1. Quality of life *(Continued)*

		not complete QOL questionnaires, hence QOL may be overestimated in both groups. Groups similar at baseline for global health, physical functioning and symptoms except for role functioning and diarrhoea (imbalance in favour of docetaxel). Results: No signficant difference in global health status. Significant difference in favour of docetaxel for nausea/vomiting and loss of appetite, and in favour of MV for role and social functioning.
Norris B 2000	EORTC QLQ-C30 Global Health Score at baseline on or before day 1 of the first cycle of chemotherapy and at cycle 3 and cycle 6.	In total 230 patients (3 cycles of treatment) filled out 2-4 questionnaires and 191 patients (6 cycles of treatment) filled out 2-5 questionnaires. There was no significant difference between the arms or the profiles of the mean global QOL scores or any of the 8 additional domains (cognitive, emotional, physical, role, social, fatigue, nausea/vomiting and pain) over the first 6 cycles. QOL scores showed a significant improvement over time in the global, emotional, social, pain, and nausea/vomiting domains for patients receiving 6 cycles.
Sledge 2003 (ECOG E1193)	Patients completed FACT-B	93% (687/738) of randomised patients, and 94% (640/683) of eligible patients completed the baseline survey. 70% (451/683) of eligible patients completed the follow up survey at week 16. The authors concluded that there was no statistically significant difference in overall quality of life score, or in any of the subscales, between any of the treatment groups.
Sjostrom 1999	Patients completed EORTC QLQ-C30	Overall compliance with return of questionnaires for entire study was 82%. Physical deterioration greater in MF hence possible bias in its favour. No statistically significant difference at baseline or by cycle 4 in any functional or symptom scale. No significant difference in median values of mean changes in QOL scores from baseline to cycle 6.
O'Shaughnessy 2002	Patients completed the EORTC QLQ-C30 Global Health Score. A comparison of treatment arms was made at day 127.	No significant difference was found between the treatment arms. There was a trend towards less deterioration of Global Health Score in the combination arm over time. The impact of chemotherapy induced side effects, as measured by the systemic therapy side effects symptom scale, was similar in the two treatment arms.

WHAT'S NEW

Date	Event	Description
6 February 2018	Review declared as stable	This clinical question has been replaced. Instead, it was important to know whether giving a combination of drugs at the same time was more effective than giving the same drugs one at a time (sequential treatment). This question has been covered in a new Cochrane review. See http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008792.pub2/abstract

HISTORY

Protocol first published: Issue 4, 2001
Review first published: Issue 2, 2005

Date	Event	Description
19 February 2009	New search has been performed	Review update Issue 2, 2009

Date	Event	Description
18 February 2009	New citation required but conclusions have not changed	Accumulation of changes
7 May 2008	New search has been performed	Update of review
7 May 2008	Amended	Converted to new review format.
24 January 2008	Amended	republished with updated contact details
23 February 2005	New citation required and conclusions have changed	First publication of the review
28 August 2001	Amended	First publication protocol

CONTRIBUTIONS OF AUTHORS

For the 2008 update of this review CT undertook the search and assessed trials for eligibility with SP and SC. CT, SP and SC extracted data from all new trials and those with additional information. These three authors updated data tables. SP and SC revised the text of the review and updated the results and discussion which was reviewed by NW. SP and SC retrospectively assessed trials for quality using the Cochrane Risk of Bias tool. SP revised and re-formatted all figures.

For the first publication of this review in 2005 SC undertook the review including assessment of trial eligibility, data extraction, analyses and writing of the review. SP conducted the eligibility assessment, extracted and entered data and contributed to the interpretation. JS, NW and DG provided clinical input and commented on the drafts of the first review.

DG designed the review protocol.

DECLARATIONS OF INTEREST

Nil conflict of interest

SOURCES OF SUPPORT

Internal sources

- NHMRC Clinical Trials Centre, Australia

External sources

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

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Post-hoc subgroup analyses were conducted for type of regimen. In addition studies incorporating non-standard chemotherapy (high dose chemotherapy) were excluded as these are the subject of a separate review.

NOTES

This review was updated in August 2008. A new search was conducted March 2008 and the review has undergone significant and accumulated change. A summary of changes is included below:
New trials added:
Albain 2004; Ejlertsen 2004; GEICAM 2007; Heidemann 2004; Norris 2000; O'Shaughnessy 2001; Stockler 2006;Thomas 2007
Additional data added for previously included trials:
Heidemann 2002 - Overall survival and TTP curve data re-done
Updated survival information for O'Shaunnessy 2002 (Norris paper) minimum 27mths follow up
Updated data for Icli 2002 - Now Icli 2005
Trials removed from the 2005 systematic review:
Keller 2004- Was included in initial review based on data obtained from ASCO 2001 conference proceeding (Abstact number 115). This trial was subsequently removed from the updated review following retrieval of the full published paper (2004) which further clarified the

regimens studied. Of the 151 participants in the control arm 129 were receiving single agent vinorelbine and 22 received mitomycin C plus vinblastine. Data was not provided separately for combination and single agent regimens within the control group.
Liu 1986 - Was included in the initial review but excluded at update. This exclusion was based on a post hoc consideration to not include high dose chemotherapy regimens. Clinical discussion confirmed that this review should reflect standard/conventional chemotherapy regimens
Trials previously in ongoing - now excluded from the review (See Characteristics of excluded studies table):
Anonymous 2002; Doroshow 2000; Jackish 1999; Perez 2001
New ongoing trial:
Butler 2004

All data was checked for this update and all sections of the text revised. The background and discussion was re-written. Risk of bias tables were done retrospectively for all 43 trials (48 comparisons)

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents [*administration & dosage]; Antineoplastic Combined Chemotherapy Protocols [*administration & dosage]; Breast Neoplasms [*drug therapy] [mortality]; Disease Progression; Quality of Life; Randomized Controlled Trials as Topic; Treatment Outcome

MeSH check words

Female; Humans