Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women (Review)

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Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women

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ABSTRACT

Background
Hormonal treatments for advanced or metastatic breast cancer, such as tamoxifen and the progestins megestrol acetate and medroxyprogesterone acetate, have been in use for many years. Aromatase inhibitors (AIs) are a class of compounds that systemically inhibit oestrogen synthesis in the peripheral tissues. Aminogluthimide was the first AI in clinical use (first generation) and had a similar tumour-regressing effect to other endocrine treatments, which showed the potential of this alternative type of therapy. Other AIs have since been developed and the third generation AIs anastrozole, exemestane and letrozole are in current use. Randomised evidence on response rates and side effects of these drugs is still limited.

Objectives
To compare aromatase inhibitors to other endocrine therapy in the treatment of advanced breast cancer in postmenopausal women.

Search strategy
The Cochrane Breast Cancer Group Specialised Register was first searched on 3 December 2004 using the codes for "advanced" and "endocrine therapy". Details of the search strategy applied to create the Register and the procedure used to code references are described in the Cochrane Breast Cancer Group module on The Cochrane Library. The search was updated to 30 September 2005 and additional publications were included. Experts were consulted to determine that no relevant studies had been excluded.

Selection criteria
Randomised trials comparing the effects of any aromatase inhibitor versus other endocrine therapy, no endocrine therapy or a different aromatase inhibitor in the treatment of advanced (metastatic) breast cancer.

Data collection and analysis
Data from published trials were extracted by two independent review authors. A third independent author then carried out a further cross check for accuracy and consistency. Hazard ratios (HR) were derived for analysis of time-to-event outcomes (overall and progression-free). Odds ratios (OR) were derived for objective response and clinical benefit (both analysed as dichotomous variables). Toxicity data were extracted where present and treatments were compared using odds ratios. All but one of the studies included data on one or more of the following outcomes: overall survival, progression-free survival, clinical benefit and objective response.
Main results

Thirty studies were identified, twenty five of which were included in the main analysis of any AI versus any other treatment (9416 women). The pooled estimate showed a significant survival benefit for treatment with an AI over other endocrine therapies (HR 0.89, 95% CI 0.82 to 0.96). A subgroup analysis of the three commonly prescribed AIs (anastrozole, exemestane, letrozole) also showed a similar survival benefit (HR 0.88, 95% CI 0.80 to 0.96). The results for progression-free survival, clinical benefit and objective response were not statistically significant and there was statistically significant heterogeneity across types of AI. There were very limited data to compare one AI with a different AI, but these suggested an advantage for letrozole over anastrozole. All the trials of AIs used exclusively as first-line therapy were against tamoxifen. There was an advantage to treatment with AIs in terms of progression-free survival (HR 0.78, 95% CI 0.70 to 0.86) and clinical benefit (OR 0.70, 95% CI 0.51 to 0.97) but not overall survival or objective response. There was considerable heterogeneity across studies when considering clinical benefit (P = 0.001). Use of an AI as second-line therapy showed a significant benefit in terms of overall survival (HR 0.80, 95% CI 0.66 to 0.96) but not for progression-free survival (HR 1.08, 95% CI 0.89 to 1.31), clinical benefit (OR 1.00, 95% CI 0.87 to 1.14) or objective response (OR 0.96, 95% CI 0.81 to 1.14). This is difficult to interpret due to the extreme heterogeneity across AIs for progression-free survival but not the other endpoints.

AIs have a different toxicity profile to other endocrine therapies. For all AIs combined, they had similar levels of hot flushes (especially when compared to tamoxifen) and arthralgia, increased risks of nausea, diarrhoea and vomiting, but a decreased risk of vaginal bleeding and thromboembolic events compared with other endocrine therapies. A similar pattern of risks and benefits was still seen when analyses were limited to the currently most-prescribed third generation AIs.

Authors’ conclusions

In women with advanced (metastatic) breast cancer, aromatase inhibitors including those in current clinical use show a survival benefit when compared to other endocrine therapy.

Plain Language Summary

Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women

Advanced (or metastatic) breast cancer is cancer that has spread beyond the breast. Endocrine therapy removes the influence of oestrogen on breast cancer cells and can prevent the cells from growing and spreading in early breast cancer if the tumour is hormone sensitive. Following a positive initial response to endocrine treatment, second and third line endocrine therapy is used until the disease becomes hormone resistant. This may extend a woman's life and improve her quality of life. Hormonal treatments for advanced breast cancer include tamoxifen, the progestins megestrol acetate and medroxyprogesterone acetate and aromatase inhibitors (AIs). AIs reduce the body's ability to make oestrogen (synthesis) and have tumour-regressing effects. The AIs in current clinical use include anastrozole, exemestane and letrozole.

The review authors identified 30 controlled studies in which over 10,000 women were randomised to treatment groups. Giving AIs improved survival (hazard ratio 0.9) but overall benefits on progression-free survival, clinical benefit and objective response were unclear. Studies using AIs as first-line and second-line therapy reported benefits of therapy that varied with the different AIs and measures of effectiveness. These agents have some different toxicity. AIs had similar levels of hot flushes and sweating (especially when compared to tamoxifen); increased risks of arthritic pain (arthralgia), rash, diarrhoea, nausea and vomiting; but decreased risk of vaginal bleeding and blood clotting (thromboembolic) events compared with other endocrine therapies.

Background

Breast cancer is the most common cause of cancer and cancer mortality in women worldwide (Ferlay 2000). Metastatic breast cancer occurs when the cancer has spread beyond the breast and regional node areas. Breast cancer can progress to metastatic disease despite a range of adjuvant systemic therapies. Once breast cancer is metastatic, it is no longer curable but it is treatable. The aim
of any further treatment is to improve the individual’s quality and length of life.

Endocrine therapy removes the influence of oestrogen on breast cancer cells, preventing the cancer cells from growing and spreading and has been shown to improve survival in early breast cancer. Early methods of therapy consisted of endocrine organ ablation by surgery (Beatson 1896) but these procedures have largely been superseded by effective hormonal treatments.

Most endocrine therapies either block the binding of oestrogen to its receptor or reduce serum and tumour concentrations of oestrogen. A positive initial response to endocrine treatment is a good indication for use of second and even third-line endocrine therapy until the disease becomes hormone resistant (Roseman 1997). The most important predictor of response to hormone therapy is the oestrogen receptor (ER) status of the original tumour.

Currently, the most widely-used endocrine therapy for treatment of hormone-sensitive metastatic disease is tamoxifen (Howell 1997). Tamoxifen is an oral, non-steroidal competitive ER antagonist. Tamoxifen, however, also has an agonist effect and although patients may relapse and develop acquired resistance to tamoxifen, this does not mean that they will not respond to other endocrine therapy.

Other endocrine therapies used in this setting are fulvestrant, megestrol acetate (MA) and medroxyprogesterone acetate (MPA). Fulvestrant is an ER antagonist that downregulates the ER and reduces progesterone receptor content but, unlike tamoxifen, does not have an agonist effect. It is used as a treatment for tamoxifen-resistant advanced disease. MPA and MA are oral progestogens which have been shown to have significant antitumour activity after failure of other endocrine therapies in postmenopausal patients.

In postmenopausal women, oestrogen is no longer produced in the ovaries but androgens (mainly from the adrenal glands) are converted into oestrogens in peripheral tissue by the enzyme aromatase (Miller 1996a). Aromatase inhibitors (AIs) are a class of compounds that act systemically to inhibit oestrogen synthesis in tissues. AIs are of two types, reversible and irreversible; both types of inhibitors compete with normal substrates for binding on the enzyme. The non-competitive inhibitors (which are steroidal) leave the enzyme permanently inactivated (Ibrahim 1995).

AIs have a different toxicity profile to other endocrine therapies, although some that mimic menopausal symptoms due to depletion of oestrogen are the same, such as hot flushes and sweating. Adverse events particular to AIs include stomach upsets (nausea, vomiting, diarrhoea), rash and arthralgia. AG was poorly tolerated and can cause drowsiness, fever and inhibition of cortisol synthesis. Formestane, although generally well-tolerated as a treatment, resulted in local reaction around the injection site. Tamoxifen which was most widely used before AIs, can cause endometrial changes including vaginal bleeding and increased risk of thromboembolic events. Side effects with progestogens are usually mild but may include hot flushes, night sweats, nausea and indigestion, fluid retention, weight gain and headaches as well as an increased risk of thromboembolism. Fulvestrant can have similar oestrogen deprivation side effects, injection site reactions, vomiting and diarrhoea.

AIs are now being used increasingly in the treatment of early breast cancer which may have an impact on their use in advanced (metastatic) disease.

**OBJECTIVES**

The aim of this systematic review was to compare aromatase inhibitors to other endocrine therapy in the treatment of advanced (metastatic) breast cancer in postmenopausal women.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

Only randomised controlled studies in the following populations were included:

- trials of patients with advanced (metastatic) breast cancer
- trials with results stratified by stage of disease so that it was possible to identify the subgroup of patients with advanced or metastatic breast cancer

**Types of participants**

Postmenopausal women with advanced or metastatic breast cancer either at diagnosis or upon relapse

- excluding those with local recurrence only;
- oestrogen receptor (ER) positive or status unknown;
- with no restrictions on metastatic site or age of the women;
- inclusion not limited to use of an AI as first-line therapy.
### Types of interventions
- Aromatase inhibitors versus any other endocrine treatment
- Aromatase inhibitors versus no endocrine treatment
- Aromatase inhibitors plus other endocrine treatment versus other endocrine treatment alone
- Direct comparison between different aromatase inhibitors

### Types of outcome measures
Outcome measures were defined a priori as follows:

**Primary outcome**

Overall survival (defined as time from date of randomisation to date of death from any cause)

**Secondary outcomes**

1. Progression-free survival (defined as time from date of randomisation to disease progression), also known as time to progression.
2. Clinical response rate. This comprises objective response (those women with either complete or partial shrinkage of the tumour) and clinical benefit (objective response plus stable disease for more than 24 weeks)*
3. Treatment toxicity (particularly AI related)
4. Quality of life (QOL), where available and comparable
5. Dropout rate
6. Time to treatment end (stopped or changed due to toxicity)
* International Union Against Cancer (UICC) guidelines for evaluation of these criteria (Hayward 1977).

**Subgroup analyses**

Performed where data were sufficient
- first-line therapy (where the AI was given as initial therapy for advanced disease);
- second-line therapy (where the advanced disease had already been treated with a different AI or another endocrine therapy);
- ER positive versus ER unknown;
- according to site of distant metastases and differential treatment effect.

### Search methods for identification of studies

The Cochrane Breast Cancer Group Specialised Register was first searched on 3 December 2004 using the codes for “advanced” and “endocrine therapy”. Details of the search strategy applied to create the Register and the procedure used to code references are described in the Cochrane Breast Cancer Group module on The Cochrane Library. The Cochrane Central Register of Controlled Trials (CENTRAL) and relevant conference proceedings were also searched. Reference sections of each published paper were searched for additional studies. The authors subsequently updated the search to 30 September 2005.

### Data collection and analysis

**Assessing trials for eligibility**

**Study selection**

Trials identified through the search strategy were reviewed by two of the authors (CLD, LJG) who independently decided on eligibility; any differences were resolved by discussion and confirmed by a third author (DJL). Any exclusions have been justified and documented in the table Characteristics of excluded studies.

**Quality control and peer review**

Two authors (LJG and CLD) made an independent assessment of the quality of the trial based on the quality of the randomisation. For unpublished trials, information has been obtained from the protocol or other available source; however unpublished trials were not included in the review but are included in the ongoing trials. Where information was missing or additional information was required the authors were contacted but only two replies were received.

**Assessment of the methodological quality**

The quality of all studies deemed eligible was reviewed independently by two review authors (LJG, CLD) and discrepancies were resolved by discussion. The quality of each study was assessed based on reports in the publication on:
- quality of randomisation;
- comparability between the baseline characteristics of the treatment arms;
- inclusion of all randomised participants in the analysis;
- details of dropouts.

Randomisation was assessed by grading the allocation concealment (for example blinded, stratified) as A = adequate, B = unclear, C = inadequate (see Characteristics of included studies). It was not possible to assess the quality of randomisation accurately in all studies due to lack of information in the published articles. Any imbalance between treatment arms, both in numbers and characteristics, was taken into account in the grading.

Intention-to-treat statements: analyses that were stated to be by intention to treat included all randomised patients for the primary endpoint. However, it is common practice to report response variables, that is clinical benefit and objective response, only on ‘assessable’ patients. We have reported these outcomes on both assessable and randomised patients.

Description of the eligibility and exclusion criteria: all studies described in detail the patient characteristics of those patients eligible for the study. The table Characteristics of included studies includes information on the balance of baseline characteristics, details of patients excluded after randomisation, definitions of the outcome measures, duration of follow up and median length of follow up.

**Data extraction**

Data extraction was performed independently by two of the review authors (CLD, LJG) using data extraction forms designed for the purpose. Data extracted included details of treatment arms and patient numbers, baseline patient characteristics, tumour response...
rates, time to progression, median survival and median follow up. Data on toxicity and quality of life were extracted at a later date. The authors were not blinded to the source of the document for article selection or data extraction. A third author (DJL) assessed the data collected to ensure consistency and accuracy. Any differences were resolved by discussion. Data were extracted on quality as described in ‘Assessment of the methodological quality’. Hazard ratios and their associated variances were extracted for all measures available. If a hazard ratio and confidence interval were not reported, these values were calculated (Parmar 1995). Of the report authors (n=8) who were contacted for supplementary information on the primary endpoints, only two replied (and the data were not available).

**Analysis**

The most complete dataset feasible was assembled. Data were, however, only available for the following endpoints: overall survival, progression-free survival, clinical benefit, objective response and toxicity. The Cochrane Review Manager software (RevMan) was used to analyse the data. Statistical heterogeneity between studies was assessed using the chi-squared statistic. Overall and progression-free survival were analysed using time-to-event methods and for this the hazard ratio (HR) is the most appropriate statistic. If a HR and corresponding confidence intervals (CI) were not reported, these values were calculated indirectly using median time to event (progression or survival) and the number of events extracted from the published Kaplan-Meier curves following the method of Parmar 1995. A weighted average of survival duration across studies was then calculated. A fixed effect model was used for the primary analyses (see the Cochrane Handbook for Systematic Reviews of Interventions) unless there was significant heterogeneity, in which case a random effects model was used. Ratios of treatment effects for time-to-event were reported so that HRs less than 1.0 favour the AI regimen. Response rates were obtained from the tables of best response presented for each trial. Response has been analysed based on assessable (not randomised) patients as most of the trials included in this review only reported response in this way. As a sensitivity analysis, we also analysed results by intention to treat (ITT) and there was no difference. Response rates were analysed as dichotomous variables (for example objective response compared complete or partial response versus stable disease or no response). An odds ratio (OR) and its associated 95% CI was calculated for each trial and a pooled OR derived. Ratios of treatment effects on response were reported so that ORs less than 1.0 favour the AI regimen. Not all toxicities (also known as side effects or adverse events) were reported in this review. We selected six predefined toxicities from expert experience, reflecting side effects specific to AIs (nausea, diarrhoea, rash, arthralgia) and other hormonal treatments (hot flushes, vaginal bleeding, thromboembolic events). Each side effect was analysed as a dichotomous variable (yes or no) with the effect of the AI considered separately to that of the comparator. This was deemed the most informative method of presentation as the different comparators have different toxicity profiles whereas AIs have similar toxicity profiles. An OR and its associated 95% CI were calculated for each trial and a pooled OR derived. Ratios of treatment effects for toxicity were reported so that ORs less than 1.0 favour the AI regimen. Not all trials had data on toxicity and for those that did the data were not consistent among trials. Toxicity data were available for only 22 of the trials comparing an AI with a non-AI. Within studies, the reported toxicities varied both in the number and range and type of toxicities reported as well as the criteria used for reporting. Some studies reported predefined or selected toxicities (Bonneterre 2001; Kaufmann 2000; Mauriac 2003), some chose to report toxicities occurring in a certain minimum percentage of participants (Bezwoda 1998; Buzdar 2001; Dombiernowsky 1998; Goss 1999; Mauritac 2003; Thuerlimann 1997) or major toxicity (Canney 1988), one reported toxicity grades 1 to 4 separately (Paridaens 2003), one used common toxicities (Buzdar 1996a) though what this means was not defined, two reported adverse experiences (Buzdar 1996b; Buzdar 1996c) and one reported all toxicities (Rose 1986). Four studies did not state which reporting criteria they used. In addition, one study (Perez Carion 1994) only reported on the toxicities considered to be treatment-related and has not been included. Despite the different reporting criteria the data were pooled so this must be borne in mind when looking at the absolute numbers.

**Quality of Life**

Eight studies quoted quality of life (QOL) as a secondary endpoint (Bezwoda 1998; Buzdar 1996b; Buzdar 1996c; Buzdar 2001; Goss 1999; Kaufmann 2000; Mauritac 2003; Thuerlimann 1997). One additional study (Dombiernowsky 1998) mentioned that a QOL instrument was used at baseline and at each visit whilst on treatment but it was not mentioned as an endpoint nor were any data included. Three of the eight studies (Bezwoda 1998; Buzdar 1996b; Buzdar 1996c) did not report any QOL data. Only one (Thuerlimann 1997) has published two papers on the QOL data in detail. There are several reasons why the limited QOL data are not included in this review: heterogeneous changes among patients, that is different symptoms and side effect profiles; different methods of drug application, that is injection versus tablets; use of four different QOL instruments at several different timepoints; some results given as responders versus non-responders rather than by treatment groups; some QOL measures based on clinician-reported rather than patient-reported symptoms.

**Dropout rates**

The number of actual dropouts was very difficult to quantify as the quantity and quality of reporting varied greatly. Numbers of patients were not given in six studies; numbers were not always
given by treatment arm and only six studies gave full details. Three studies quoted the number of patients withdrawn due to toxicity as “a small number” (Buzdar 1996b; Buzdar 1996c; Kaufmann 2000). Thus the patients that could be confidently identified as lost to follow up, refusals or withdrawals totalled 51.

Time to treatment end

No studies specifically stated time to treatment end. However, all but three of the studies (Leitzel 1995; Powles 1984; Tominaga 2003) reported on at least one of the following: time to progression, time to failure or time to death, or both of the latter.

Results are presented graphically and all figures follow the same format. Each trial is presented as a single line within each category. The point estimate of the treatment effect is represented by a square, the size of which is proportional to the size of the study. The associated 95% CI is included as a horizontal line. The summary in each category is represented by a diamond, the north–south axis is the pooled estimate and the east–west axis is the 95% CI.

A pooled analysis was performed in each group, but the results from each aromatase inhibitor (AI) were considered separately within the same group, where possible. This approach is considered to be more informative due to differences between the AIs (first versus second versus third generation; steroidal versus non-steroidal). Post hoc, it was decided also to present the pooled results for the AIs in current clinical use (by definition the newer, third generation AIs) separately as this is more relevant to the clinical situation today. The AIs included were: aminoglutethimide (first generation), formestane (second generation), anastrozole, exemestane, fadrozole, letrozole and vorozole (third generation). The non-AIs included are megestrol acetate (MA), tamoxifen, fulvestrant, medroxyprogesterone acetate (MPA) and hydrocortisone (HC).

In all cases, tests for heterogeneity have been performed across all studies and in each of the treatment groupings outlined above. Instances of statistically significant heterogeneity will be discussed in the results section.

All analyses were based on the intention-to-treat principle (ITT) as far as possible, comparing all women allocated to one treatment versus all those allocated to the other, irrespective of compliance. Thus the result may slightly underestimate any treatment effects. However, analysis on response used the number of assessable women as the denominator, as this is the accepted method. As a sensitivity analysis, both denominators were used (see figures) and there was no major difference for response when comparing assessable to ITT. For statistical tests a P value of less than 0.05 was considered to denote statistical significance.

The Cochrane Review Manager Software (RevMan4) was used to analyse the data.

RESULTS

Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women (Review)

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Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

The search strategy yielded 152 English-language references, of which 133 were possibly eligible. Twenty five of the 133 references, relating to 22 trials were excluded as they compared the same AI at different doses. However, if a study compared two doses of an AI with a comparator the study was included using the arm with the standard dose of that particular AI versus the comparator. Other references were excluded because they were either non-English language papers, reviews, non-randomised studies or conference proceedings without the addition of published data. The exception to this the conference abstract by Schmid 2001 which is included as it presented several of the endpoints of this review in abstract form and there is no published paper of this study. From these, 50 relevant references were identified relating to 25 randomised trials which fulfilled the eligibility criteria. An additional five references for five studies were identified by the authors from reference lists in papers and reviews.

Thirty trials were included in this review and these trials randomised 11,208 women. There was a great deal of variation across studies. Trials ranged in size from 60 (Kleeberg 1997) to 1021 patients (Bonneterre 2001). Twelve studies randomised patients from multiple countries; of the remaining 18 studies, three were limited to the UK, two each from Spain and South America, and one from Canada, Denmark, Japan, Switzerland, and the US. The country was not reported in the remaining six studies.

Within the 30 trials, 9723 women were randomised in 26 trials comparing AIs with non-AIs, and 1485 women were randomised in four trials of one AI versus a different AI. It should be noted that seven studies included two different doses of an AI compared with a third comparison. The decision was made to include only data from the arm of the study which included the most commonly used dose of the AI. For anastrozole this was 1 mg and for fadrozole 2.5 mg, or 2 mg if 2.5 mg was not used. The number of included randomised women for all 30 studies was 10,054.

Of the 26 trials comparing AIs with non-AIs, seven used the first generation AI aminogluthethimide, two used the second generation AI formestane, and 17 used a third generation AI (anastrozole, four trials; exemestane, two; fadrozole, six; letrozole, four; vorozole, one). In these studies the comparator was tamoxifen in 11 trials, MA in 12, MPA in one, hydrocortisone (HC) in one and fulvestrant in one. The four trials of AIs versus a different AI compared letrozole versus aminogluthethimide and anastrozole, fadrozole, exemestane or anastrozole versus formestane.

In 10 of the 30 studies (randomising 3635 women), any AI was used as first-line treatment versus any other comparator, which was tamoxifen in all of them. In 14 of 30 studies (5349 randomised women) any AI was compared with any comparator as second-line therapy. In the remaining seven trials the AIs were used as both first and second-line treatments within the trials but as the
data were not split by this variable they were not included in these
comparisons.
Data for all endpoints were not available in the published reports.
Thus five principal endpoints with sufficient data were identified: overall survival, progression-free survival, response (either based on
clinical benefit or objective response) and treatment toxicity. These
principal endpoints were not available from all papers. Where
data were unavailable, authors were approached for supplementary
data.
Data were not available in the published reports for all groups
outlined in the review protocol. The most data were available for
the AI versus any non-AI group and therefore results for all five
endpoints were presented as well as a subgroup consisting of data
from the three most commonly prescribed AIs, that is anastrozole,
exemestane and letrozole. In addition, the results of four of the
five endpoints (not toxicity) outlined above are presented in three
separate groups based on: individual AIs versus different AIs, AIs
used as first-line treatment only, AIs used as second-line therapy
only.

**Risk of bias in included studies**

Thirty randomised studies were included in this review. Non-randomised studies were excluded at the selection stage as they did
not fulfil the inclusion criteria. One of the included studies did
not have data on the primary or secondary endpoints so could not
be included in any analysis. It should be noted that trials by the
author of one of the included studies Bezwo 1998, relating to
high dose chemotherapy, have been found to include falsified data.
However, no such findings have been reported for trials included
in this review and there was therefore no reason to exclude this
study. Analysis was performed with and without this study and
there was no difference in the pooled results, although for clinical
benefit the result became just significant.
It was not possible to assess the quality of all studies accurately
due to lack of information, including the quality of the randomi-
sation process, in the published articles. Randomisation was rated
as adequate in 18 studies but there were insufficient details of the
randomisation process in the remaining 12 and so they were la-
belled as unclear. Of these, no randomisation method was given
in six studies and four were reported to have parallel groups. No
studies were deemed to have inadequate randomisation from the
information given in the published papers and none were excluded
for this reason.
Baseline characteristics were not commented upon in 10 studies,
five studies commented on a slight imbalance. One study (Buzdar
1996a) had an imbalance in the treatment arm but this was
believed to be an artefact. All other studies reported balanced base-
line characteristics in all arms.
The AI arm in some of the older studies (Alonso-Munoz 1988;
Canney 1988; Ingle 1986; Powles 1984; Rose 1986; Russell 1997)
did not compare an AI by itself but in combination with another
treatment.

**Summary of numbers of women used in the analysis**

| Women randomised, all arms | 11,208 |
| Women randomised, included arms | 10,054 |
| Women randomised, assessable (for response) | 8842 |

**Effects of interventions**

Over 10,000 women were randomised to the included arms of 30
trials, but time-to-event data was only available for about half
of them. The results of the meta-analysis should be interpreted
bearing this in mind.

**Aromatase inhibitors versus any non-aromatase inhibitor**

Of the 26 trials comparing an AI versus a non-AI one had no
data on response or survival by treatment arm although these were
included as endpoints (Leitzel 1993). Of the remaining 25 trials,
data were available on overall tumour response rates data in all 25,
clinical benefit in 22, progression-free survival in 10 and overall
survival in 12 trials. For overall survival, the reported figures were
available from the publications for six trials (Bonnerette 2001;
Buzdar 1996a; Buzdar 2001; Ingle 1986; Dombernowsky 1998;
Thuerlimann 1996) and were calculated for six trials (Bezwo 1998;
Goss 1999; Kaufmann 2000; Milla-Santos 2003; Rose 1986; Russell 1997).
In terms of progression-free survival, HRs were
depicted across the treatment groups. Data on individual AIs were sparse and no conclusions could be drawn.

1. **Overall survival**

Data on survival were available in 12 trials reporting an estimated
2576 events in 4548 women. No data were available for formes-
tane. The pooled HR of 0.89 (95% CI 0.82 to 0.96) shows a
statistically significant 11% benefit of treatment (P = 0.003) with
an AI, with a consistent effect across all subgroups. Data on indi-
vidual AIs were sparse and no conclusions could be drawn.

2. **Progression-free survival**

Data on progression were available in 10 trials reporting an estimated
3791 events in 5355 women. Progression was not statically
significantly associated with the use of an AI (HR 0.97, 95% CI
0.83 to 1.14). This overall effect is virtually uninterpretable due
to the significant heterogeneity by type of AI and also within spe-
cific AIs. Exemestane was statistically significantly better than the
non-AI whereas vorozole was significantly worse. The exemestane
results are based on a single study. The pooled HRs for both anas-
trozole (Bonnerette 2001; Mauriac 2003) and letrozole (Buzdar
1996a; Dombernowsky 1998; Mourisden 2001) were not statisti-
cally significant with highly significant heterogeneity across the
studies (P<0.00001 and P = 0.01, respectively).
3. Proportion of women with clinical benefit (7594 assessable women)

Data were available for seven AIs (aminogluthethimide, formestane, anastrozole, exemestane, fadrozole, letrozole, vorozole) from 22 trials. Approximately one quarter of the data came from two studies (Bonneterre 2001; Mourisden 2001). The AIs were not shown to be superior to the non-AIs (P = 0.09) and there was statistically significant heterogeneity (P = 0.004) across studies.

4. Proportion of women with objective response (7919 assessable women)

Twenty five trials reported objective response. Data were available for seven AIs (aminogluthethimide, formestane, anastrozole, exemestane, fadrozole, letrozole, vorozole). The pooled OR suggested no statistically significant effect of treatment with an AI (P = 0.09) and again there was statistically significant heterogeneity (P = 0.02). Of the individual AIs, only letrozole was associated with a statistically significant benefit over the non-AI (OR 0.65, 95% CI 0.51 to 0.82) in 1637 women randomised (Buzdar 2001; Dombernowsky 1998; Mourisden 2001; Schmid 2001).

5 Toxicity

Not all trials had data on toxicity and for those that did the data were not consistent among all trials. Toxicity data were available for only 22 of the trials comparing an AI with a non-AI. Within studies, the reported toxicities varied both in the number or range and type of toxicities reported as well as the criteria used for reporting. Some studies reported predefined or selected toxicities (Bonneterre 2001; Kaufmann 2000; Mauriac 2003) some chose to report toxicities occurring in a minimum percentage of participants (Bezwoda 1998; Buzdar 2001; Dombernowsky 1998; Goss 1999; Mauriac 2003; Mourisden 2001), some used worst toxicity grade (Falkson 1996; Thuerlimann 1996; Thuerlimann 1997) or major toxicity (Canney 1988), one reported toxicity grades 1 - 4 separately (Paridaens 2003), one used common toxicities (Buzdar 1996a) though what this means is not defined, two reported adverse experiences (Buzdar 1996b; Buzdar 1996c) and one reported all toxicities (Rose 1986). Four studies did not state which reporting criteria they used. For the study of an AI against fulvestrant (Mauriac 2003), data on toxicity were obtained from different sources. The combined analysis of the two trials 0020 and 0021 reported predefined events and data on hot flushes and thromboembolic events were available. The separate publications of the results of 0020 and 0021 detailed toxicities occurring in 10% or more of the participants. Trial 0020 reported data on both nausea and vomiting so these were combined with these data from 0021. In addition, trial 0021 had data on the frequency of diarrhoea and rash. Four studies did not state which reporting criteria they used. One study (Perez Carrion 1994) only reported on the toxicities considered to be treatment-related and has not been included. Despite these reporting differences, data from all trials were pooled as otherwise there would have been too few data for each comparator and symptom. The analyses have been split according to the comparator due to the different toxicity profiles of each comparator and so the pooled results have not been reported.

Hot flushes

Hot flushes was the specific toxicity that was most widely reported. Data on hot flushes were available from 18 studies with 7059 women. Of these, seven compared an AI with tamoxifen, nine with MA and one each with fulvestrant and MPA. The use of an AI had very similar risk of hot flushes to tamoxifen and fulvestrant. The AI was associated with statistically significantly more reports of hot flushes than with MA (OR 1.77, 95% CI 1.42 to 2.20) but less than with MPA (OR 0.20, 95% CI 0.06 to 0.73) which had data from only one trial.

Nausea

Data on nausea were available from 15 studies with 6602 women. Another two trials reported data on nausea and vomiting combined. Of the 15, six compared an AI with tamoxifen, eight with MA and one with fulvestrant. AIs were associated with a statistically significant increase in risk of nausea compared to MA (OR 1.84, 95% CI 1.37 to 2.47) but there was no statistically significant difference between AIs and tamoxifen (P = 0.32) or fulvestrant (P = 0.81).

Vomiting

Two studies had data on nausea and vomiting combined and so were not included. Data on vomiting were available from two studies comparing AIs with tamoxifen, five versus MA and one versus fulvestrant for a total of 4404 women. The AI was statistically significantly worse when compared to MA (OR 2.03, 95% CI 1.42 to 2.90). The comparisons with tamoxifen and fulvestrant suggested no statistically significant differences.

Diarrhoea

Nine studies with 4507 women had data on diarrhoea toxicity. Of these, three compared an AI with tamoxifen, five with MA and one with fulvestrant. AIs were associated with a statistically significant higher rate of diarrhoea than either tamoxifen (OR 1.64, 95% CI 1.06 to 2.55) or MA (OR 1.48, 95% CI 1.02 to 2.13) but not fulvestrant (P = 0.19).

Rash

Twelve studies with 3822 women had data on rash toxicity. Of these, four compared an AI with tamoxifen, six with MA, and one each with MPA and fulvestrant. AIs were associated with a statistically significant increased risk of rash when compared with tamoxifen (OR 3.61, 95% CI 4.71 to 239.97) and for the one trial versus MPA (OR 111.71, 95% CI 6.75 to 1849.91) but not against MA or fulvestrant. Within the comparison with MA there was statistically significant heterogeneity (P = 0.0005).

Vaginal bleeding

Data on vaginal bleeding were reported in four studies of 2150 women, two compared an AI with MA and one each with tamoxifen and MPA. Compared with MA, there was a statistically significant benefit of 71% to treatment with the AI (OR 0.29, 95% CI 0.13 to 0.65). The one trial versus MPA also found a statistically
significant difference with an OR of 0.10 (95% CI 0.01 to 0.77). There was no statistically significant difference between AIs and tamoxifen (P = 0.15).

*Thromboembolic events*

Thromboembolic event data were available from six studies with 2937 women. Two compared an AI with tamoxifen, three with MA and one with fulvestrant. The AI had a statistically significant advantage over tamoxifen (OR 0.48, 95% CI 0.27 to 0.85) only.

*Arthralgia*

Data on arthralgia were available for 2470 women in two studies versus tamoxifen (N = 1031) and four studies versus MA (N = 1439). There was no statistically significant difference between the AIs and either tamoxifen or MA.

**Subgroup analysis: aromatase inhibitors in current clinical use versus any non-aromatase inhibitor**

Ten of the 25 trials comparing an AI with a non-AI were on the three AIs in current clinical use, namely anastrozole, exemestane and letrozole. The pooled results for these are reported. Data on overall survival and time to progression were available from only six trials but response rates and clinical benefit were available from all 10. In terms of survival, HRs were reported in the publications of four trials (anastrozole (Bonneterre 2001; Buzdar 1996a) and letrozole (Buzdar 2001; Dombernowsky 1998). Another two trials (Kaufmann 2000; Milla-Santos 2003) had sufficient data for calculation of the HRs. For time to progression, the corresponding number of trials were three (Bonneterre 2001; Buzdar 2001; Mourisden 2001) and three (Dombernowsky 1998; Kaufmann 2000; Mauriac 2003), respectively.

1. **Overall survival**

Data on survival were available from six trials (Bonneterre 2001; Buzdar 1996a; Buzdar 2001; Dombernowsky 1998; Kaufmann 2000; Milla-Santos 2003). The AI was statistically significantly superior to the non-AI with a HR of 0.88 (95% CI 0.80 to 0.96), equivalent to a 12% benefit of treatment with an AI. This effect was consistent across all subgroups.

2. **Progression-free survival**

Data on progression were available from six trials (Bonneterre 2001; Buzdar 2001; Dombernowsky 1998; Kaufmann 2000; Mauriac 2003; Mourisden 2001) reporting an estimated 3060 events in 4333 women. Use of an AI was not statistically significantly associated with a change in the hazard of progression (HR 0.92, 95% CI 0.75 - 1.13). The results varied by type of AI with only exemestane (one trial only) being statistically significantly better than the non-AI and there was no evidence of an effect for anastrozole. There was significant heterogeneity both in the pooled result (P<0.00001) and within the anastrozole trials (P<0.00001).

3. **Proportion of women with clinical benefit (5079 assessable women)**

Data were available from 10 trials. The pooled OR suggested a statistically significant advantage to the AI of 22% (OR 0.78, 95% CI 0.63 to 0.96). There was statistically significant heterogeneity among the trials (P = 0.002).

4. **Proportion of women with objective response (5079 assessable women)**

All 10 trials reported objective response. The pooled OR of 0.77 (95% CI 0.62 to 0.96) showed a statistically significant advantage to the AI but there was statistically significant heterogeneity (P = 0.03) across the trial results. There was also significant heterogeneity within the exemestane trials.

5. **Toxicity**

One of the suggested benefits of the third generation AIs is a reduced toxicity profile. Therefore toxicity data were extracted for the three most commonly used AIs at this time, that is anastrozole, exemestane and letrozole. The results were presented by comparator as the comparators have different toxicity profiles whereas the AIs have similar toxicity profiles. The denominators for the comparison of anastrozole with fulvestrant vary depending on whether the combined trial results were available (hot flushes, nausea, vomiting, thromboembolic events) or not (diarrhoea, rash).

*Hot flushes*

Hot flushes was the specific toxicity that was reported most widely. Data on hot flushes were available from eight of the 10 studies, with 4930 women. Three studies compared the AI with tamoxifen, four with MA and one with fulvestrant. The use of an AI had a very similar risk of hot flushes to tamoxifen and fulvestrant but was associated with statistically significant more reports of hot flushes than with MA (OR 1.69, 95% CI 1.24 to 2.30).

*Nausea*

Data on nausea were available from eight of the 10 studies, with 4930 women. Of the eight studies, three compared an AI with tamoxifen, four with MA and one with fulvestrant. The AIs had statistically significantly more reports of nausea than MA (OR 1.45, 95% CI 1.09 to 1.95) but there was no statistically significant difference when the AIs were compared to tamoxifen or fulvestrant.

*Vomiting*

Five studies with 3499 women had data on vomiting alone and only one made the comparison with tamoxifen. There was no statistically significant differences between the AI and either tamoxifen or fulvestrant. Compared with MA, the AIs had a statistically significantly increased risk of vomiting (OR 1.77, 95% CI 1.11 to 2.83).

*Diarrhoea*

Six studies with 3602 women had data on diarrhoea toxicity. Two compared an AI with tamoxifen, three with MA and one with fulvestrant. There was a statistically significant increased risk of diarrhoea with the AIs against MA (OR 2.40, 95% CI 1.34 to 4.29).

*Rash*

Four studies with 2033 women comparing AIs with MA or ful-
Vaginal bleeding
Data on vaginal bleeding were reported in three studies with 1932 women, one compared an AI with tamoxifen and two with MA. There was a statistically significant benefit to treatment with the AIs in comparison with MA (OR 0.29, 95% CI 0.13 to 0.65).

Thromboembolic events
Thromboembolic event data were available for 2378 women in three studies but there was only one study per comparator (tamoxifen, MA or fulvestrant). AIs were associated with a statistically significantly lower incidence of thromboembolic events than tamoxifen (OR 0.53, 95% CI 0.29 to 0.96) but not compared with MA or fulvestrant.

Arthralgia
Data on arthralgia as a specific side effect were only available for 1394 women in three studies, two versus tamoxifen and one versus MA. Against both comparators, the AI was not statistically significantly associated with a difference in the incidence of arthralgia.

Other analyses
Aromatase inhibitors versus any different aromatase inhibitor
A total of 1481 women in four trials were randomised to one AI versus a different AI. Of these, all four had data on response but only one had results on overall survival and progression-free survival (Gershovanich 1998). Letrozole was compared with a different AI in all the trials (Gershovanich 1998, Rose 2003, Tominaga 2003) except that of Kleeberg 1997 which compared anastrozole with formestane. The study by Rose and colleagues (Rose 2003) compared letrozole to anastrozole and in this section has been included in both the letrozole and anastrozole groups.

1. Overall survival
The Gershovanich 1998 study cited above was the only one in this section that had data on overall survival. Letrozole had a statistically significant reduced HR of 0.64 (95% CI 0.49 to 0.84) giving a 36% advantage in survival over aminoglutethimide treatment.

2. Progression-free survival
Only one study had data on progression from 551 women (Gershovanich 1998). In this study, letrozole was associated with a reduced hazard (HR 0.72, 95% CI 0.57 to 0.91) showing a 28% advantage in terms of progression-free survival compared to aminoglutethimide.

3. Proportion of assessable women with clinical benefit (1152 assessable patients)
Data were available from 1152 assessable women. Letrozole was statistically significantly associated with a statistically significant clinical benefit compared with a different AI (OR 0.72, 95% CI 0.56 to 0.93). There was no significant study heterogeneity, P = 0.57.

4. Proportion of assessable women with objective response (1152 assessable patients)
Data were available from 1152 assessable women. The pooled overall result is not presented as Rose 2003 was included in both individual AI comparisons and so would be counted twice. Letrozole was statistically significantly different from any other AI (OR 0.53, 95% CI 0.39 - 0.73). Results of all letrozole studies are consistent (test for heterogeneity P = 0.45). Anastrozole appeared to be significantly inferior to a different AI (OR 1.59, 95% CI 1.07 to 2.37).

Aromatase inhibition as first-line therapy versus any other therapy (tamoxifen)
Ten studies that randomised 3635 women used AIs exclusively as first-line therapy for advanced (metastatic) disease and all comparisons were against tamoxifen. We did not include any studies that were mixed first and second-line. Data from two studies with 1242 women (anastrozole and fadrozole) were available for overall survival and three studies with 2139 women (one study each on formestane, anastrozole, and letrozole) for progression-free survival. All 10 studies reported results for objective response and eight studies for clinical benefit.

1. Overall survival
Data were only available from two studies with 1242 women, one each on anastrozole and fadrozole. There was no statistically significant difference in the effect of treatment with an AI compared to tamoxifen.

2. Progression-free survival
Data were available from three of the 10 studies. The first-line AI regimen was statistically significantly superior to tamoxifen with a decreased hazard of 0.78 (95% CI 0.70 to 0.86). Anastrozole (Bonnetete 2001) and letrozole (Mouridsen 2001) were statistically significantly different from tamoxifen (reduced hazard of 18% and 30%, respectively).

3. Clinical benefit (3036 assessable women)
Data on clinical benefit were available from 3036 assessable women. As results for individual AIs, except for aminoglutethimide and anastrozole, were based on only a single study the pooled result is emphasised. The AIs were significantly better than tamoxifen as first-line therapy (OR 0.70, 95% CI 0.51 to 0.97) but there was significant heterogeneity across the AIs (P = 0.001). The individual results for exemestane and letrozole were statistically significant in the analysis of assessable women but for letrozole only based on the analysis of randomised women.

4. Proportion of assessable women with objective response (3287 assessable women)
Data on objective response were available from 3287 assessable women. Aminoglutethimide was the only AI with more than two studies published. The AIs were not statistically significantly bet-
Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women (Review)  
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DISCUSSION

Women who had previously been treated with endocrine therapy, either a different AI or non-AI, for advanced (metastatic) disease and received the study AI as second-line therapy were included in 14 trials. Aminoglutethimide was used as second-line in three studies, formestane in one, anastrozole in two, exemestane in one, fadrozole in three, letrozole in two and vorozole in one. The majority of the comparisons (10) were against MA. One trial (Rose 2003) which compared anastrozole to letrozole was not included in the analysis. We did not include trials where there was a mixture of first and second-line therapy.

Data on objective response were available from all of the trials, clinical benefit from 11 trials, HRs for progression-free survival from six trials and HRs for overall survival from two trials.

1. Overall survival

Data on overall survival were limited, with data from two trials of different AIs, anastrozole and letrozole. Second line treatment with an AI was statistically significantly associated with a decreased hazard of death (HR 0.80, 95% CI 0.66 to 0.96). This effect was consistent for both AIs (heterogeneity $P = 0.79$).

2. Progression-free survival

AI use was not associated with a statistically significant difference in the risk of progression. There was significant heterogeneity ($P = 0.0002$) across studies with use of either anastrozole or vorozole associated with a significantly increased risk of progression and exemestane associated with a statistically significant decrease.

3. Proportion of assessable women with clinical benefit (3721 assessable women)

There did not appear to be any effect in terms of a statistically significant clinical benefit when an AI was used as second-line therapy. This lack of effect was consistent across AI subgroups (heterogeneity $P = 0.95$).

4. Proportion of assessable women with objective response (4170 assessable women)

Overall there was no statistically significant difference between the use of an AI as second-line therapy and any other therapy. When looking at individual AIs none showed any evidence of a benefit, but this was based on small numbers. There was no statistical heterogeneity ($P = 0.33$).

This review demonstrates that there is a survival benefit of 11% from using AIs for the treatment of advanced (metastatic) breast cancer. This finding is not consistent across all AIs, with the greatest benefit associated with the AIs in current clinical use, namely anastrozole, exemestane and letrozole. However, data on survival were only available for about half of the women and one of the trials (Buzdar 1996a) was not designed or powered to detect significant differences in survival.

The positive effects of AIs in terms of tumour response when given as first or second-line therapy were statistically significant for first-line therapy where the comparator was tamoxifen. There were no data available on other comparators. When comparing the effect of the AI as second-line therapy there was no statistically significant difference when considering tumour response. In terms of progression-free survival, there was a statistically significant decreased hazard of progression for treatment with the AIs as first line-therapy only. The paucity of data makes it difficult to make any firm conclusions in terms of overall survival.

In terms of toxicity, AIs are known to be associated with a higher incidence of nausea, diarrhoea, rash and arthralgia but a lower risk of vaginal bleeding and thromboembolic events. There was a higher incidence of hot flushes with AIs when compared to MA but not when compared to tamoxifen. However, combining data across studies was difficult as both the toxicities reported and the criteria for reporting toxicities, if they were reported at all, varied greatly.

This review has combined data from a wide variety of studies that were carried out over 20 years. Some of the trials did not use an AI as a single agent but in combination with another endocrine therapy. There was heterogeneity both across types of AI and within each AI. The results of studies of three generations of AIs have been combined as well as results from studies of steroidal and non-steroidal therapy. This has been forced to some extent by the lack of data on individual AIs.

Evidence of heterogeneity between trials was identified for tumour response rates and progression-free survival though not overall survival. The reasons for this are unknown but this statistical heterogeneity may be explained by clinical heterogeneity. It may be that outcomes involving subjective endpoints, that is tumour response, may be subject to variation whereas the hard endpoint used in the survival analysis is unequivocal. Other contributory factors may be the difference in dosage of some AIs and significant differences in the proportion of patients who were truly hormone receptor positive.

Within each AI, studies varied in terms of sample size, dose of AI, comparison regimen, outcomes, length of follow up and quality of reporting. For example, the seven studies of aminoglutethimide consisted of between 62 and 313 patients; three of the studies were of first-line therapy, three second-line and one mixed. Doses of aminoglutethimide used were 125 mg in one study, 250 mg* in
The patient's ting. The limited quality of life data which was reported did not in favour of the AI (groups, however some differences were found with some subscales.

There are very limited data on quality of life reported in this setting. The limited quality of life data which was reported did not show any significant differences between the AI and comparator groups, however some differences were found with some subscales in favour of the AI (Goss 1999; Kaufmann 2000). The patient's perspective in advanced disease treatment is an important endpoint and should be included in studies as it would aid interpretation in this mainly palliative setting.

A lack of standardised reporting of clinical endpoints impacted upon the analysis of all AIs, not just aminoglutethimide. Therefore, it was not possible to include all studies in each section, which impacted on the power of certain analyses, especially overall and progression-free survival. In addition, many of the data required to carry out analyses of prospectively identified subgroups, as set out in the review protocol were not available. We could not, therefore, identify specific subgroups of women who may benefit from AI use.

If the description of randomisation is used as a barometer of reporting trial quality, it appears that this has improved over time. For example, in the studies of the first generation AI aminoglutethimide, six of seven randomisations were categorised as unclear whereas only two of the seven third generation AI letrozole trials were considered as such.

A U T H O R S’ C O N C L U S I O N S

Implications for practice

Historically, the treatment for advanced (metastatic) breast cancer has been with hormonal treatments such as tamoxifen or the progestins MA or MPA. This review confirms a survival benefit of treating advanced (metastatic) breast cancer with the third generation aromatase inhibitors (anastrozole, exemestane and letrozole) that are being used clinically today.

Implications for research

This review would benefit from additional publications with greater survival details, that is median survival and number of events, for those studies that did not publish them originally. Further data from exemestane trials are required to evaluate this AI more completely. Efforts should be made to standardise reporting of toxicity, and a quality of life component should also be included.

A C K N O W L E D G E M E N T S

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R E F E R E N C E S

References to studies included in this review

Alonso-Munoz 1988 {published data only}

Bezwoda 1998 {published data only}

Bonneterre 2001 {published data only}


Buzdar 1996b *published data only*  
Buzdar 1996c *published data only*  

Kleeberg 1997 *(published data only)*

Leitzel 1995 *(published data only)*

Mauriac 2003 *(published data only)*

Mercer 1993 *(published data only)*

Milla-Santos 2003 *(published data only)*

Mourisden 2001 *(published data only)*

Paridaens 2003 *(published data only)*

Perez Carrion 1994 *(published data only)*

Powles 1984 *(published data only)*

Rose 1986 *(published data only)*


Schmid 2001 *published data only* * Schmid P, Wischnewsky MB, Possinger K. Self organizing maps and prognosis of advanced breast cancer patients with bone metastases receiving letrozole or MA. *Breast Cancer Research and Treatment* 2001;64:77.


References to studies excluded from this review


Bruning 1990 *published data only* * Bruning PF, Bonfier JMG, Wildiers J, Jassem J, Beex LVAM, Schorangel J, Nooijen WJ. Second-line endocrine...

**Dowsett 1998** [published data only]

**Dowsett 1999** [published data only]

**Dowsett 2000** [published data only]

**Geisler 1999** [published data only]

**Johnston 1999** [published data only]

**Miller 1996b** [published data only]

**Pronzato 1993** [published data only]

**Raats 1992** [published data only]

**Svenstrup 1994** [published data only]

**Wang 2003** [published data only]
Beatson 1896

Ferlay 2000

Hayward 1977

Howell 1997

Ibrahim 1995

Jonat 1996

Miller 1996a

Parmar 1995

Roseman 1997

* Indicates the major publication for the study
## Characteristics of included studies [ordered by study ID]

### Alonso-Munoz 1988

| Methods | Spain, multicentre, N = 105, Dec 1982 - Dec 1985  
Three arm study (only two arms included in review N = 70)  
Randomisation method not given  
Baseline characteristics balanced |
|---|---|
| Participants | Age range 37 - 75  
Proven metastatic breast cancer, measurable disease sites  
No previous endocrine therapy |
| Interventions | AG (500mg for 2w, then 100mg) v TAM 40mg v AG + TAM 40mg  
Numbers in each treatment arm: 35 v 35 v 35  
(AG+TAM arm data excluded from review N = 35)  
Assessable patients (two included arms): 31 v 34  
Patients evaluable for toxicity (two included arms): 33 v 34 |
| Outcomes | Toxicity, TTP, response rate  
Not survival |
| Notes | 11 not evaluable (4 AG, 6 TAM + AG, 1 TAM) due to: 4 died within 6w, 1 discontinued treatment, 5 toxicity, 1 lost to FU  
FU duration not given  
TTP not given by treatment arm |

### Bezwoda 1998

| Methods | South Africa, multicentre, N = 96  
Double-blind, double-dummy  
Balanced block stratification by centre  
Baseline slight imbalance in ER status: 28% v 20% ER+ |
|---|---|
| Participants | Age range 44 - 82  
Measurable or evaluable metastatic breast cancer  
Prior TAM treatment  
No previous treatment with AI  
ECOG perf.status < 3 |
### Bezwoda 1998 (Continued)

| Interventions | fadrozole 2mg v MA 160mg  
|               | Numbers in each treatment arm: 46 v 50  
|               | Assessable patients: 46 v 50  
|               | Patients evaluable for toxicity: 46 v 50  
|               | Treatment until progression or for 1y; median duration 20w |
| Outcomes      | Primary - response rate, TTP, TTF, survival  
|               | Secondary - QOL, performance status, pain assessment |
| Notes         | FU to relapse or death  
|               | Median FU not stated  
|               | Intention to treat analysis  
|               | Subsidiary analysis on a per protocol basis (41 v 43)  
|               | 7 major protocol violations, 2 refusals, 1 early death, 1 lost to FU (numbers not consistent) |

### Bonneterre 2001

| Methods       | International, multicentre study, Feb 1996 - July 1998, combined results of two trials  
|               | 97 sites in US and Canada, N = 353  
|               | 83 sites in Europe, Australia, New Zealand, South Africa, South America, N = 668  
|               | Total randomised = 1021  
|               | Double-blind, double-dummy  
|               | Baseline characteristics well-balanced |
| Participants  | Age range 30 - 92  
|               | Advanced or metastatic breast cancer |
| Interventions | anastrozole 1mg v TAM 20mg  
|               | Numbers in each treatment arm: 171 v 182 (N America) and 340 v 328 (rest of world)  
|               | Assessable patients: 511 v 510  
|               | Patients evaluable for toxicity: 506 v 511  
|               | Treatment continued until disease progression |
| Outcomes      | Primary - objective response, TTP, tolerability  
|               | Secondary - TTF, survival |
| Notes         | FU to progression and death  
|               | Median FU not known  
|               | Number of dropouts not given |

### Risk of bias

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Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women (Review)

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### Allocation concealment?

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### Buzdar 1996a

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<tr>
<td>Methods</td>
<td>International, multicentre. 122 centres: 49 in North America, 73 in Europe, Australia, South Africa, Double-blind anastrozole, open megestrol acetate Randomisation method - blocks of 6 (Europe), blocks of 3 (N America), parallel groups Two trials combined (N = 764): North America (N = 346) and Europe, Australia, South Africa (N = 378) Three arm study (only two arms included in review N = 516) Baseline: apparent imbalance in one treatment group (believed to be artefact)</td>
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<td>Participants</td>
<td>Age range 29 - 97</td>
<td>Advanced breast cancer Progressed on anti-oestrogen for advanced disease or progressed on or during adjuvant TAM WHO perf status &lt; 3</td>
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<td>Interventions</td>
<td>anastrozole 1mg v anastrozole 10mg v MA 160mg Numbers in each treatment arm: 263 v 248 v 253 (anastrozole 10mg arm excluded from review N = 248) Assessable patients (two included arms): 263 v 253 Patients evaluable for toxicity (two included arms): 262 v 253 Treatment continued until disease progression or withdrawal from treatment for other reasons</td>
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<tr>
<td>Outcomes</td>
<td>Primary - TTP, tumour response, tolerability Secondary - TTF, response duration, survival Clinical assessment every 4w until week 24, every 12w until week 48 then every 3m until progression</td>
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<tr>
<td>Notes</td>
<td>FU median duration 6m 3 no treatment, 1 wrong treatment, 8 lost to FU Intention to treat analysis</td>
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*Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women (Review) © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.*
### Buzdar 1996b

#### Methods
- Protocol 03
- Multicentre, 47 sites, N = 380
- Feb 1989 - Dec 1991
- Double-blind, parallel, controlled equivalence
- Randomisation method not specified

#### Participants
- Age range 35 - 92
- Metastatic breast cancer
- At least one prior hormonal treatment for metastatic disease more than 3m previously
- Prior AI use an exclusion
- Performance status < 3

#### Interventions
- Fadrozole 2mg v MA 160mg
- Numbers in each treatment arm: 196 v 184
- Drug code broken 18m after end of enrolment
- Assessable patients: 195 v 184
- Patients evaluable for toxicity: 196 v 184
- Treatment continued until disease progression

#### Outcomes
- Objective response rate, TTP, survival, toxicity, duration of response, survival, QOL

#### Notes
- Published together with protocol 06 (Buzdar 1996c)
- FU until progression
- Intention to treat analysis N = 379
- 1 patient excluded but included in safety and tolerability

#### Risk of bias

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<td>Yes</td>
<td>A - Adequate</td>
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</table>

### Buzdar 1996c

#### Methods
- Protocol 06
- Multicentre, 55 sites, N = 303
- Double-blind, parallel, controlled equivalence
- Randomisation method not specified

#### Participants
- Age range 36 - 92
- Metastatic breast cancer
- At least one prior hormonal treatment for metastatic disease more than 3m previously
- Prior AI use an exclusion
- Performance status < 3

#### Interventions
- Fadrozole 2mg v MA 160mg
- Numbers in each treatment arm: 152 v 151
### Buzdar 1996c (Continued)

<table>
<thead>
<tr>
<th>Assessable patients: 150 v 148</th>
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<tbody>
<tr>
<td>Patients evaluable for toxicity: 152 v 151</td>
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<tr>
<td>Drug code broken 18m after end of enrolment</td>
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<tr>
<td>Treatment continued until disease progression</td>
</tr>
</tbody>
</table>

#### Outcomes

- **Primary** - overall tumour response (TTP, TTF, survival)
- **Other** - earliest diagnosis of PD, tolerability, safety, QOL

#### Notes

- Published together with protocol 03 (Buzdar 1996b)
- FU: 33m for tumour response/safety (median 5.5m)
- 45m for survival (median 18 to 20m)
- Intention to treat analysis N = 298
- Not designed or powered to detect differences in survival

### Risk of bias

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</table>

### Buzdar 2001

#### Methods

- International, multicentre, 120 sites in US, Canada, Europe, N = 602
- Three arm study (only two arms included in review N = 400)
- Double-blind, double dummy, phase III
- Randomisation by country w/o stratification by centre
- Enrolment over 30 months
- Baseline characteristics no imbalance

#### Participants

- Age range not given
- Locally advanced/locoregionally recurrent/metastatic breast cancer
- At least one measurable/assessable lesion
- Relapsed or progressed while on anti-oestrogen or relapsed within 12m of stopping anti-oestrogen
- Chemotherapy for advanced disease allowed
- KPF >=50%

#### Interventions

- Letrozole 2mg v letrozole 10mg v MA 160mg
- Numbers in each treatment arm: 202 v 199 v 201
- Letrozole 2mg arm excluded from review N = 202
- Assessable patients: 182 v 180
- Patients evaluable for toxicity: 199 v 201
- Treatment continued until disease progression or withdrawal for other reason

#### Outcomes

- Primary - tumour response
- Secondary - TTF, TTP, survival, QOL
**Buzdar 2001 (Continued)**

| Notes | FU period 48m after the first visit of the last patient randomised  
Intention to treat analysis  
23 ineligible and excluded from tumour analyses |

**Risk of bias**

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</table>

**Canney 1988**

| Methods | UK, number of centres not given, N = 218  
Randomised without stratification, performed centrally by phone over 24m |
|---------|---------------------------------------------------------------------|
| Participants | Median age 64  
Actively progressive disease  
Received hormonal therapy with tamoxifen  
Received no anticancer therapy within preceding 4w |
| Interventions | AG (250mg for 2w, increased to 500mg if not toxic effect plus 40mg HC) v high dose MPA 1000mg  
Numbers in each treatment arm: 106 v 112  
Patients evaluable for toxicity: 106 v 112 |
| Outcomes | Duration of response, survival, time to response |
| Notes | FU duration: minimum 9m, median 55w for AG, 57w MPA  
7 patients either violated protocol or did not meet entry criteria but included in analyses  
Crossover on failure  
No variation between groups in known prognostic variables. |

**Risk of bias**

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<td>Yes</td>
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</tbody>
</table>
### Dombernowsky 1998

**Methods**
- International, multicentre, Mar 1993 - Sep 1994
- 10 countries, 91 sites, N = 551
- Three arm study (only two arms included in review N=363)
- Double-blind, randomisation stratified by country; computer-generated permuted blocks of size 6 or 3, 1:1:1 allocation
- Baseline characteristics balanced

**Participants**
- Advanced/locoregionally recurrent/metastatic breast cancer
- Measurable/assessable disease
- Failure to respond to previous anti-oestrogen
- WHO perf status < 3

**Interventions**
- Letrozole 0.5mg v letrozole 2.5mg v MA 160mg
- Numbers in each treatment arm: 188 v 174 v 189
- (letrozole 0.5mg arm excluded from review N = 188)
- Assessable patients: 153 v 166
- Patients evaluable for toxicity: 174 v 189

**Outcomes**
- Primary - overall tumour response (TTP, TTF, survival)
- Other - earliest diagnosis of PD, tolerability, safety

**Notes**
- FU: 33m for tumour response/safety (median 5.5m)
- 45m for survival (median 18 to 20m)
- Intention to treat analysis
- Not designed or powered to detect differences in survival as significant

### Risk of bias

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### Falkson 1996

**Methods**
- South Africa, single centre, N = 80
- Sep 1991 - Dec 1994
- Randomisation method not given
- Baseline: difference of 10y in median age of patients in arm 1 v arm 2

**Participants**
- Age range 43 - 90
- Progressive, inoperable, recurrent or metastatic breast cancer
- No prior treatment for advanced disease
- ECOG < 3

**Interventions**
- Fadrozole 2mg v TAM 20mg
- Numbers in each treatment arm: 40 v 40
- Assessable patients: 36 v 38
- Patients evaluable for toxicity: 40 v 40
### Falkson 1996 (Continued)

<table>
<thead>
<tr>
<th>Minimum treatment</th>
<th>8w</th>
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<tbody>
<tr>
<td>Outcomes</td>
<td>Survival, TTF, duration of overall response, toxicity, objective response rates,</td>
</tr>
<tr>
<td>Notes</td>
<td>FU 14 to 1122d, median FU 153d</td>
</tr>
<tr>
<td></td>
<td>Intention to treat analysis</td>
</tr>
<tr>
<td></td>
<td>2 ineligible, 1 lost to FU</td>
</tr>
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<td></td>
<td>74 patients evaluable</td>
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#### Risk of bias

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### Gershanovich 1998

<table>
<thead>
<tr>
<th>Methods</th>
<th>International, multicentre, 11 countries, 86 sites N = 555</th>
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<tbody>
<tr>
<td></td>
<td>Three arm study (only two arms included in review N = 363)</td>
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<tr>
<td></td>
<td>Open-label 1:1:1</td>
</tr>
<tr>
<td></td>
<td>Baseline no major differences</td>
</tr>
<tr>
<td>Participants</td>
<td>Median age letrozole 2.5mg 66y, letrozole 0.5 mg 64y, AG 65y</td>
</tr>
<tr>
<td></td>
<td>Advanced or metastatic breast cancer</td>
</tr>
<tr>
<td></td>
<td>Measurable/evaluable advanced disease</td>
</tr>
<tr>
<td></td>
<td>WHO perf status &lt; 3</td>
</tr>
<tr>
<td>Interventions</td>
<td>letrozole 2.5mg v letrozole 0.5mg v AG 500 mg</td>
</tr>
<tr>
<td></td>
<td>Numbers in each treatment arm: 185 v 192 v 178</td>
</tr>
<tr>
<td></td>
<td>(letrozole 2.5mg arm excluded from review N = 192)</td>
</tr>
<tr>
<td></td>
<td>Assessable patients: 173 v 162</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Response, TTP, TTF, survival, tolerability and safety, overall survival</td>
</tr>
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#### Risk of bias

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</table>
**Goss 1999**

**Methods**
- Nov 1991 - Dec 1995
- Multicentre, 29 sites in Canada and 38 in US, N = 452
- Open-label, stratified by disease status
- Baseline characteristics comparable

**Participants**
- Age range 39 - 90
- Advanced breast cancer, histologically confirmed
- Progressed after tamoxifen treatment

**Interventions**
- vorozole 2.5mg v MA 160mg
- Numbers in each treatment arm: 225 v 227
- Assessable patients: 190 v 185
- Patients evaluable for toxicity: 195 v 198
- 2nd line treatment after tamoxifen

**Outcomes**
- Primary - response rate
- Secondary - TTP, survival, duration of response, safety subjective symptoms, QOL

**Notes**
- Median FU 11.6m (vorozole) 9.9m (MA)
- 1 withdrawn before treatment
- 4 ineligible, 18 Adverse Events, 1 lost to FU, 18 other

**Risk of bias**

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</table>

**Ingle 1986**

**Methods**
- US, number of centres not known, N = 102
- Randomised using Pocock-Simon approach to adaptive randomisation, stratified

**Participants**
- Age range 38 - 83
- Progressive metastatic disease
- Measurable or evaluable lesion
- ECOG perf status < 4
- No prior therapy with either AG or TAM

**Interventions**
- TAM 20mg v TAM (20mg) + AG (500mg for 2 weeks then 1000mg) + HC (100mg daily for 2 weeks then 40mg)
- Numbers in each treatment arm: 49 v 51
- Assessable patients: 49 v 51
- Patients evaluable for toxicity: 48 v 46

**Outcomes**
- Objective response, TTP, survival, toxicity
**Ingle 1986** (Continued)

| Notes | No data on duration of FU  
|       | Target accrual = 160 but terminated early due to excess toxicity on the TAM + AG + HC arm  
|       | 2 patients ineligible |

**Risk of bias**

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</table>

**Kaufmann 2000**

**Methods**

Double-blind, parallel-group, phase III  
Baseline characteristics comparable

**Participants**

Age range 30 - 91  
Advanced breast cancer  
Progressed or relapsed during tamoxifen treatment

**Interventions**

exemestane 25mg v MA 160mg  
Numbers in each treatment arm: 366 v 403  
Assessable patients: 337 v 366  
Patients evaluable for toxicity: 358 v 400

**Outcomes**

Objective response, TTP, TTF, survival, tumour response, duration of tumour control, tumour related signs and symptoms, QOL, tolerability

**Notes**

FU median duration 48.9w  
6 randomised but not treated  
66 not evaluable for tumour response  
Intention to treat analysis

**Risk of bias**

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</tbody>
</table>
Kleeberg 1997

Methods
International, multicentre, 27 Jun - 1 Dec 1995
18 centres, Europe and South Africa, N = 60
open label, parallel group, comparative
Baseline good balance re age, weight, prior tamoxifen treatment

Participants
Age range 40 - 84
Advanced breast cancer
Measurable or evaluable disease

Interventions
anastrozole 1mg oral per day v formestane 250mg im every 2w
Numbers in each treatment arm: 29 v 31
Assessable patients: 29 v 31
Treatment until disease progression

Outcomes
Primary - oestradiol suppression and tolerability
Secondary - response rates, TTP, adverse events, blood oestrone sulphate, patient and doctor perception of treatment

Notes
No details re randomisation exclusions or FU
Not powered to detect clinically significant difference in oestrogen suppression between the two arms

Risk of bias

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</table>

Leitzel 1995

Methods
Location and date of study not given
Multicentre, N = 300
Double-blind, double-dummy, parallel
Randomisation method not given

Participants
Age range 18 - 85
Metastatic breast cancer
ECOG < 3

Interventions
fadrozole 2mg v MA 160mg
Numbers in each treatment arm not given
duration of intervention not given
Second-line treatment

Outcomes
Tumour response, progression, c-erbB-2 Antigen in serum

Notes
FU until death
Results not given by treatment group
Survival was not given by treatment group although it was measured
Leitzel 1995  (Continued)

### Risk of bias

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Mauriac 2003

**Methods**

Data were combined and published from two trials 0020 and 0021 (May 1997 - September 1999)
- **Trial 0020**: multicentre, phase III, open, parallel group
  - Europe, Australia and South Africa, 83 centres, N = 451
- **Trial 0021**: multicentre, phase III, double blind, double dummy, parallel group
  - North America, N = 400
- Combined data from both trials included in review N = 851

**Participants**

- Age range 33 - 89
- Locally advance or metastatic breast cancer
- Progressed during adjuvant endocrine therapy or first-line therapy for advanced disease
- WHO performance status < 3

**Interventions**

- Fulvestrant 250mg/month im v anastrozole 1mg
- **Trial 0020**: Numbers in each treatment arm: 222 v 229
- **Trial 0020**: Numbers in each treatment arm: 206 v 194
- Combined trials (included in review): Numbers in each treatment arm: 423 v 428
- Assessable patients: 423 v 428
- Patients evaluable for toxicity: 423 v 423
- Continued until objective disease progression or other events required withdrawal

**Outcomes**

- TTP, Objective response, tolerability, QOL

**Notes**

- Combined data median FU 15.1m
- Intention to treat analysis
- Additional to protocol noninferiority of fulvestrant with anastrozole was carried out retrospectively

### Risk of bias

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</table>
Mercer 1993

Methods
UK, query single centre, Jan 1987 - Dec 1990, N = 61
No information regarding randomisation
Groups well matched but after exclusions numbers small

Participants
Eligibility ≥50 years
Age range 45 - 86
Advanced breast cancer
Progressive disease on tamoxifen (adjuvant or treatment)

Interventions
Low dose AG 125mg v HC 20mg
Number in each treatment arm: 28 v 33
Assessable patients: 27 v 29

Outcomes
Tumour response, TTF, side-effects and overall survival

Notes
FU details not given
5 patients excluded

Risk of bias

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Milla-Santos 2003

Methods
Spain, single centre, N = 238, May 1997 - Dec 1999
Randomisation following Meinert’s methodology.
Baseline characteristics comparable

Participants
Age range 55 - 77
Histologically confirmed advanced breast cancer, measurable disease sites
No previous endocrine therapy
ECOG<3

Interventions
Anastrozole 1mg v TAM 40mg
Numbers in each treatment arm: 121 v 117
Assessable patients: 121 v 117

Outcomes
Primary - response rates, clinical benefit, TTP in patients achieving a CB, overall survival, toxicity

Notes
FU to 35m
intention to treat analysis
All patients evaluable
Analysis cutoff 1 April 2001

Risk of bias
### Milla-Santos 2003  (Continued)

<table>
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#### Mourisden 2001

**Methods**
- International, multicentre, Nov 1996 - Jan 1999
- 29 countries, 201 sites, N = 939
- Double-blind, double-dummy, parallel group
- Baseline characteristics well-balanced

**Participants**
- Age range 31 - 96
- Locally advanced/locoregionally recurrent/metastatic breast cancer which is measurable/assessable
- Previous chemotherapy allowed for advanced disease
- WHO perf status < 3

**Interventions**
- letrozole 2.5mg v TAM 20mg
- Numbers in each treatment arm: 453 v 454
- Assessable patients: 421 v 423
- Patients evaluable for toxicity: 455 v 455
- Treatment continued until disease progression

**Outcomes**
- Primary - TTP
- Secondary - tumour response rate, TTF, ORR, survival, tolerability, KPS

**Notes**
- FU median 32m
- Intention to treat analysis
- 907 analysed, 32 excluded
- Analysis cutoff March 2000
- Survival not reported
- 729 discontinued treatment of which 391 ‘crossed over’

### Risk of bias

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</tbody>
</table>
### Paridaens 2003

**Methods**

International, multicentre, October 96 - May 99
13 centres in 6 countries, N = 122
Open-label phase II, randomised centrally using minimization by EORTC, stratified by centre, adjuvant TAM, CT for metastatic disease, dominant disease site
The trial was designed as a randomised phase II study not to enable comparison of the efficacy of the two drugs but to establish a 'go, no-go' rule for exemestane activity and safety before a formal randomised phase III trial. Patients randomised into the phase II study will be incorporated into the phase III study

**Participants**

Age range 37 - 87
measurable metastatic or locally recurrent inoperable breast cancer
No prior hormone therapy for metastatic disease
ECOG perf status < 3

**Interventions**

exemestane 25mg v TAM 20mg
Numbers in each treatment arm: 62 v 60
Intention to treat analysis: 61 v 59
Toxicity data: 62 v 59
Assessable patients: 56 v 57
Patients evaluable for toxicity: 62 v 59
Treatment continued until disease progression

**Outcomes**

Response rates
Stop go for phase III
Phase II therefore inadequate power, no statistical comparison of efficacy of endpoints between the two treatments were planned or performed

**Notes**

FU details
2 patients (1 exemestane, 1 TAM) ineligible as not having metastatic breast cancer, 7 additional (5 exemestane, 2 TAM) not evaluable for response, 1 lost to FU
Phase II patients to be included in phase III study
Intention to treat analysis

### Risk of bias

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### Perez Carrion 1994

**Methods**

Open study, equivalence trial
Baseline characteristics well matched

**Participants**

Age range 38 - 87
WHO perf status < 3
**Perez Carrion 1994 (Continued)**

<table>
<thead>
<tr>
<th>Interventions</th>
<th>formestane 250mg im v TAM 30mg Numbers in each treatment arm: 203 v 206 Assessable patients: 173 v 175</th>
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</thead>
<tbody>
<tr>
<td>Outcomes</td>
<td>Response, survival, TTP, TTF, tolerability</td>
</tr>
<tr>
<td>Notes</td>
<td>FU details not reported 61 patients not evaluable, 10 lost to FU, 3 refusals Intention to treat analysis Trial closed early due to changes in clinical practice, ie increasing use of TAM in the adjuvant setting</td>
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### Risk of bias

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**Powles 1984**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Sept 1979 - June 1983 UK, single centre, N = 222 Previously determined allocation list unknown to clinician. Baseline characteristics mean age marginally greater for TAM patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Patients with disseminated breast cancer who had not previously received TAM, AG or danazol No endocrine or chemotherapy within 6w</td>
</tr>
<tr>
<td>Interventions</td>
<td>TAM 20mg v TAM 20mg + AG 750mg + danazol 300mg + HC 40mg Number on each treatment arm: 111 v 111 Assessable patients: 99 v 99 Patients evaluable for toxicity: 111 v 111 Treatment continued until 3m assessment (unless rapid development of tumour in meantime) otherwise stopped when evidence of tumour progression arose either through failure to respond or because of relapse after response or stabilisation of disease</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Tumour response</td>
</tr>
<tr>
<td>Notes</td>
<td>FU duration not reported</td>
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### Risk of bias

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### Rose 1986

**Methods**
- Denmark, multicentre, June 1979 - Sept 1988, 4 centres \( N = 313 \)
- Three arm study (only two arms included in review \( N = 215 \))
- Randomised by centre, non-stratified, stochastic array of numbers, closed envelope system
- Baseline characteristics well balanced

**Participants**
- Age > 65, age range 66 - 84
- First recurrence of metastatic breast cancer
- Progressive disease with measurable and/or evaluable lesions
- Performance status < 4

**Interventions**
- TAM 30mg v TAM 30mg + AG 250mg qid + HC 60mg v TAM 30mg + fluoxymesterone 20mg
- Numbers in each treatment arm: 108 v 107 v 98
  - TAM + fluoxymesterone excluded from review \( N = 98 \)
- Assessable patients: 83 v 94
- Patients evaluable for toxicity: 87 v 97
- Treatment until progression (minimum 12 weeks)

**Outcomes**
- TTF, TTP, survival, toxicity

**Notes**
- FU duration not reported
- 34 ineligible
- 21 not evaluable
- 9 lost to FU
- 258 fully evaluable

### Risk of bias

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<td>Allocation concealment?</td>
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</table>

### Rose 2003

**Methods**
- International phase IIIb/IV, 19 countries, multicentre, 112 sites, \( N = 713 \)
  - Dec 1997 - Nov 1999
- Open, random assignation stratified by centre via predetermined randomisation list
- Baseline characteristics well balanced

**Participants**
- Age range 27 - 92
- Advanced or metastatic breast cancer with measurable and/or evaluable disease
- Histologically/cytologically confirmed
- Previous treatment with anti-oestrogen
- WHO performance status 0-2

**Interventions**
- letrozole 2.5mg v anastrozole 1mg
- Numbers in each treatment arm: 356 v 357
- Assessable patients: 299 v 304
### Rose 2003 (Continued)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcomes</strong></td>
<td>Primary - TTP Secondary- objective response, duration of response, rate and duration of overall clinical benefit, overall survival, general safety</td>
<td></td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>FU duration not reported</td>
<td></td>
</tr>
</tbody>
</table>

#### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

### Russell 1997

<table>
<thead>
<tr>
<th>Methods</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>May 1984 - November 1990, Phase III, N = 288 Three arm study (only two arms included in review N = 155) No stratification Treatment arms reasonably well balanced</td>
<td></td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Age range 33 - 92 Progressive metastatic disease Measurable or evaluable lesion Patients had received TAM in advanced setting No prior MA or AG</td>
<td></td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>MA 160mg v AG (500mg for 2w then 1000mg) + HC (100mg for 2w then 40mg) v MA 160mg + AG (500mg for 2w then 1000mg) + hydrocortisone Numbers in each treatment arm: 75 v 80 v 80 (MA 160mg + AG (500mg for 2w then 1000mg) + hydrocortisone arm data excluded from review N = 80) Assessable patients: 42 v 32 Patients evaluable for toxicity: 88 v 89</td>
<td></td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Response, TTF, survival, toxicity</td>
<td></td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>FU median duration amongst those still alive = 5.2y (213 had died) 53 ineligible (38 re misunderstanding re prior TAM use,7 due to life threatening visceral involvement, 3 with less than 6 months of TAM, 2 ER -, 1 prior hormonal therapy other than TAM, 1 no confirmed disease sites) Patients on MA or AG alone were crossed over after progression</td>
<td></td>
</tr>
</tbody>
</table>

#### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>
Schmid 2001

| Methods | International, multicentre, N = 171  
|         | Three arm study (only two arms included in review N = 112)  
|         | Double-blind |
| Participants | Mean age 64.5  
|         | Advanced breast cancer with bone metastases |
| Interventions | letrozole 2.5mg v letrozole 0.5mg v MA 160mg  
|         | Number in each treatment arm: 52 v 59 v 60  
|         | letrozole 0.5mg arm excluded from review N = 59  
|         | Assessable patients: 48 v 53 |
| Outcomes | Objective response, clinical benefit, TTP, survival |
| Notes | Publication only available as abstract but sufficient data to include |

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

Thuerlimann 1996

| Methods | Switzerland, Phase III multicentre, 7 sites, N = 221  
|         | June 1988 - Dec 1994  
|         | Phone randomisation, stratified, minimisation not double blind  
|         | Baseline: prognostic factors well-balanced apart from metastatic site |
| Participants | Age range 39 - 87  
|         | Measurable/evaluable advanced breast cancer  
|         | Indication for hormone treatment  
|         | ECOG < 2 |
| Interventions | fadrozole 2mg v TAM 20mg  
|         | Numbers in each treatment arm: 111 v 110  
|         | Eligible patients: 105 v 107  
|         | Assessable patients: 103 v 106  
|         | Patients evaluable for toxicity: 104 v 107  
|         | First-line treatment  
|         | Treatment until progression |
| Outcomes | TTF, response rate, toxicity, overall survival, TTP, subjective benefit (not reported), duration of response |
| Notes | FU 7½ y  
|         | Eligible patients: 212  
|         | 9 ineligible(6 fadrozole, 3 TAM)  
|         | 12 withdrawals  
|         | Crossover only after failure so not analysed |
### Thuerlimann 1996

Analysis on data to Dec 1995, median FU of survivors 3y

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
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### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Thuerlimann 1997

Methods  
Stratified  
Baseline characteristics well-balanced (only difference in weight)

Participants  
Age range 43 - 87  
Advanced breast cancer  
Histologically and/or cytologically proven with measurable/evaluable disease  
Failed prior adjuvant and/or palliative tamoxifen treatment ie second-line treatment  
Prior chemotherapy allowed  
ECOG perf status < 3

Interventions  
formestane 250mg im (biweekly) v MA 160mg  
Numbers in each treatment arm: 91 v 86  
Assessable patients: 90 v 83  
Patients evaluable for toxicity: 90 v 81

Outcomes  
TTF, toxicity

Notes  
FU duration not reported  
2 ineligible, 4 dropouts  
173 fully evaluable  
After failure of randomised treatment 75 patients `crossed over`

### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

### Tominaga 2003

Methods  
Japan, multicentre, 62 sites, N = 157  
Double blind, double dummy, parallel groups  
Adaptive dynamic balancing method
| Participants                  | Mean age 59.7 (letrozole) and 61.0 (fadrozole)  
Advanced disease  
Measurable or assessable pathological lesions |
|-------------------------------|------------------------------------------------|
| Interventions                 | letrozole 1mg v fadrozole 2mg  
Numbers in each treatment arm: 79 v 78  
Assessable patients: 77 v 77  
Minimum 8w treatment  
Treatment until disease progressed or patient experienced toxicity resulting in discontinuation |
| Outcomes                      | ORR, safety of letrozole compared to fadrozole |
| Notes                         | FU median 13.3m |

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

KPS - Karnofsky Performance Status  
AG - aminogluthethimide  
AI - aromatase inhibitor  
CB - clinical benefit  
ECOG - Eastern Cooperative Oncology Group  
EORTC - European Organization for the Research and Treatment of Cancer  
ER - oestrogen receptor  
FU - follow up  
im - intramuscular  
mg - milligram  
TAM - tamoxifen  
MA - megestrol acetate  
MPA - medroxy progesterone acetate  
HC - hydrocortisone  
N - number of patients  
ORR - objective response rate  
PD - progressive disease  
perf status - performance status  
qid - four times daily  
QOL - quality of life  
TTF - time to failure  
TTP - time to progression  
d - days  
w - weeks  
m - months  
y - years  
WHO - World Health Organisation
### Characteristics of excluded studies  [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abe 2002</td>
<td>dose comparison of same AI (letrozole)</td>
</tr>
<tr>
<td>Bajetta 1994</td>
<td>dose comparison of same AI (formestane)</td>
</tr>
<tr>
<td>Bajetta 1997</td>
<td>dose comparison of same AI (exemestane)</td>
</tr>
<tr>
<td>Bajetta 1997a</td>
<td>dose comparison of same AI (letrozole)</td>
</tr>
<tr>
<td>Bajetta 1999</td>
<td>dose comparison of same AI (letrozole)</td>
</tr>
<tr>
<td>Beretta 1990</td>
<td>dose comparison of same AI (letrozole)</td>
</tr>
<tr>
<td>Bruning 1989</td>
<td>dose comparison of same AI (aminoglutethimide)</td>
</tr>
<tr>
<td>Bruning 1990</td>
<td>dose comparison of same AI (aminoglutethimide)</td>
</tr>
<tr>
<td>Dixon 2000</td>
<td>dose-comparison of same AI (anastrozole)</td>
</tr>
<tr>
<td>Dowsett 1989</td>
<td>dose-comparison of same AI (formestane)</td>
</tr>
<tr>
<td>Dowsett 1990</td>
<td>dose-comparison of same AI (fadrozole)</td>
</tr>
<tr>
<td>Dowsett 1994</td>
<td>dose-comparison of same AI (fadrozole)</td>
</tr>
<tr>
<td>Dowsett 1995</td>
<td>dose-comparison of same AI (letrozole)</td>
</tr>
<tr>
<td>Geisler 1996</td>
<td>outcome: aromatase levels and plasma oestrogen levels</td>
</tr>
<tr>
<td>Geisler 2002</td>
<td>outcome: aromatase levels and plasma oestrogen levels</td>
</tr>
<tr>
<td>Ingle 1997</td>
<td>dose comparison of same AI (letrozole)</td>
</tr>
<tr>
<td>Johnston 1994</td>
<td>dose comparison of same AI (vorozole)</td>
</tr>
<tr>
<td>Miller 1996b</td>
<td>dose comparison of same AI (fadrozole)</td>
</tr>
<tr>
<td>Pronzato 1993</td>
<td>AI (aminoglutethimide) versus same AI plus tamoxifen</td>
</tr>
<tr>
<td>Raats 1992</td>
<td>dose comparison of same AI (fadrozole)</td>
</tr>
<tr>
<td>Svenstrup 1994</td>
<td>dose comparison of same AI (fadrozole)</td>
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</table>
## Characteristics of ongoing studies [ordered by study ID]

### ECOG E4101

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>ECOG E4101</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>Target accrual = 148 postmenopausal women with HR+ metastatic breast cancer previously treated with up to two chemotherapy regimens and/or one prior endocrine therapy</td>
</tr>
<tr>
<td>Interventions</td>
<td>faslodex + iressa v arimidex + iressa</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Starting date</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Contact information</strong></td>
<td>Dr RW Carlson or AstroZeneca</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>currently recruiting in the USA</td>
</tr>
</tbody>
</table>

### Efect

<table>
<thead>
<tr>
<th>Trial name or title</th>
<th>Efect</th>
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</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Phase III</td>
</tr>
<tr>
<td>Participants</td>
<td>Target accrual = 660 HR+ women with advanced disease who have previously received a non-steroidal AI therapy</td>
</tr>
<tr>
<td>Interventions</td>
<td>faslodex v exemestane</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Starting date</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Contact information</strong></td>
<td>AstraZeneca</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>currently recruiting in North America, Europe, South Africa, South America, Russia and Israel</td>
</tr>
<tr>
<td><strong>ICR-CTSU Sofea</strong></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>
| **Trial name or title** | Sofea  
Phase III |
| **Methods** |  |
| **Participants** | Target accrual = 750 women with metastatic disease who have failed after non-steroidal AI |
| **Interventions** | faslodex vs faslodex + anastrozole vs exemestane |
| **Outcomes** |  |
| **Starting date** | March 2004 |
| **Contact information** | Dr SRD Johnston, Royal Marsden Hospital email: sofea-icrctsu@icr.ac.uk |
| **Notes** | Open to recruitment in UK |

<table>
<thead>
<tr>
<th><strong>Paridaens 2003</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial name or title</strong></td>
<td>Phase III EORTC-10951</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Postmenopausal women with metastatic and progressive disease or locally recurrent and inoperable</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>exemestane vs tamoxifen</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Starting date</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Contact information</strong></td>
<td><a href="mailto:robert.paridaens@uz.kuleven.ac.be">robert.paridaens@uz.kuleven.ac.be</a></td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>phase II to phase III study</td>
</tr>
</tbody>
</table>

HR+ HER positive
### Comparison 1. AI versus non-AI

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Overall survival (reported or calculated)</td>
<td>12</td>
<td></td>
<td>HR (Fixed, 95% CI)</td>
<td>0.89 [0.82, 0.96]</td>
</tr>
<tr>
<td>1.1 aminoglutethimide (any dose)</td>
<td>3</td>
<td></td>
<td>HR (Fixed, 95% CI)</td>
<td>0.88 [0.72, 1.08]</td>
</tr>
<tr>
<td>1.2 anastrozole 1 mg</td>
<td>3</td>
<td></td>
<td>HR (Fixed, 95% CI)</td>
<td>0.90 [0.79, 1.03]</td>
</tr>
<tr>
<td>1.3 exemestane 25 mg</td>
<td>1</td>
<td></td>
<td>HR (Fixed, 95% CI)</td>
<td>0.85 [0.72, 0.99]</td>
</tr>
<tr>
<td>1.4 fadrozole 2 mg</td>
<td>2</td>
<td></td>
<td>HR (Fixed, 95% CI)</td>
<td>1.04 [0.77, 1.40]</td>
</tr>
<tr>
<td>1.5 letrozole 2.5 mg</td>
<td>2</td>
<td></td>
<td>HR (Fixed, 95% CI)</td>
<td>0.88 [0.73, 1.05]</td>
</tr>
<tr>
<td>1.6 vorozole 2.5 mg</td>
<td>1</td>
<td></td>
<td>HR (Fixed, 95% CI)</td>
<td>1.10 [0.49, 2.47]</td>
</tr>
<tr>
<td>2 Progression-free survival (reported or calculated)</td>
<td>10</td>
<td></td>
<td>HR (Random, 95% CI)</td>
<td>0.97 [0.83, 1.14]</td>
</tr>
<tr>
<td>2.1 aminoglutethimide (any dose)</td>
<td>2</td>
<td></td>
<td>HR (Random, 95% CI)</td>
<td>1.07 [0.73, 1.55]</td>
</tr>
<tr>
<td>2.2 formestane 250 mg</td>
<td>1</td>
<td></td>
<td>HR (Random, 95% CI)</td>
<td>0.93 [0.68, 1.28]</td>
</tr>
<tr>
<td>2.3 anastrozole 1 mg</td>
<td>2</td>
<td></td>
<td>HR (Random, 95% CI)</td>
<td>1.05 [0.65, 1.70]</td>
</tr>
<tr>
<td>2.4 exemestane 25 mg</td>
<td>1</td>
<td></td>
<td>HR (Random, 95% CI)</td>
<td>0.82 [0.70, 0.97]</td>
</tr>
<tr>
<td>2.5 letrozole 2.5 mg</td>
<td>3</td>
<td></td>
<td>HR (Random, 95% CI)</td>
<td>0.87 [0.68, 1.11]</td>
</tr>
<tr>
<td>2.6 vorozole 2.5 mg</td>
<td>1</td>
<td></td>
<td>HR (Random, 95% CI)</td>
<td>1.27 [1.04, 1.56]</td>
</tr>
<tr>
<td>3 Clinical benefit (assessable)</td>
<td>22</td>
<td>7594</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.88 [0.76, 1.02]</td>
</tr>
<tr>
<td>3.1 aminoglutethimide (any dose)</td>
<td>5</td>
<td>637</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.89 [0.65, 1.23]</td>
</tr>
<tr>
<td>3.2 formestane 250 mg</td>
<td>2</td>
<td>521</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>1.05 [0.59, 1.86]</td>
</tr>
<tr>
<td>3.3 anastrozole 1 mg</td>
<td>4</td>
<td>2626</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.74 [0.48, 1.12]</td>
</tr>
<tr>
<td>3.4 exemestane 25 mg</td>
<td>2</td>
<td>816</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.71 [0.39, 1.31]</td>
</tr>
<tr>
<td>3.5 fadrozole 2 mg</td>
<td>4</td>
<td>982</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>1.05 [0.80, 1.38]</td>
</tr>
<tr>
<td>3.6 letrozole 2.5 mg</td>
<td>4</td>
<td>1637</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.77 [0.60, 1.00]</td>
</tr>
<tr>
<td>3.7 vorozole 2.5 mg</td>
<td>1</td>
<td>375</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>1.35 [0.88, 2.07]</td>
</tr>
<tr>
<td>4 Objective response (assessable)</td>
<td>25</td>
<td>7919</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.88 [0.75, 1.02]</td>
</tr>
<tr>
<td>4.1 aminoglutethimide (any dose)</td>
<td>7</td>
<td>888</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.92 [0.62, 1.38]</td>
</tr>
<tr>
<td>4.2 formestane 250 mg</td>
<td>2</td>
<td>521</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>1.16 [0.79, 1.70]</td>
</tr>
<tr>
<td>4.3 anastrozole 1 mg</td>
<td>4</td>
<td>2626</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.95 [0.77, 1.17]</td>
</tr>
<tr>
<td>4.4 exemestane 25 mg</td>
<td>2</td>
<td>816</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.49 [0.17, 1.48]</td>
</tr>
<tr>
<td>4.5 fadrozole 2 mg</td>
<td>5</td>
<td>1056</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>1.18 [0.85, 1.65]</td>
</tr>
<tr>
<td>4.6 letrozole 2.5 mg</td>
<td>4</td>
<td>1637</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.65 [0.51, 0.82]</td>
</tr>
<tr>
<td>4.7 vorozole 2.5 mg</td>
<td>1</td>
<td>375</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.70 [0.34, 1.42]</td>
</tr>
<tr>
<td>5 Clinical benefit (randomised)</td>
<td>22</td>
<td>8008</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.89 [0.78, 1.02]</td>
</tr>
<tr>
<td>5.1 aminoglutethimide (any dose)</td>
<td>5</td>
<td>671</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.92 [0.67, 1.25]</td>
</tr>
<tr>
<td>5.2 formestane 250 mg</td>
<td>2</td>
<td>586</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>1.00 [0.58, 1.70]</td>
</tr>
<tr>
<td>5.3 anastrozole 1 mg</td>
<td>4</td>
<td>2626</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.74 [0.48, 1.12]</td>
</tr>
<tr>
<td>5.4 exemestane 25 mg</td>
<td>2</td>
<td>891</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.78 [0.53, 1.17]</td>
</tr>
<tr>
<td>5.5 fadrozole 2 mg</td>
<td>4</td>
<td>1000</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>1.08 [0.82, 1.41]</td>
</tr>
</tbody>
</table>
6.1 aminoglutethimide (any dose)  
25 8458 Odds Ratio (M-H, Random, 95% CI) 0.90 [0.77, 1.06]
6.2 formestane 250 mg  
4 1782 Odds Ratio (M-H, Random, 95% CI) 0.77 [0.61, 0.96]
6.3 anastrozole 1 mg  
4 2626 Odds Ratio (M-H, Random, 95% CI) 0.95 [0.77, 1.17]
6.4 exemestane 25 mg  
2 891 Odds Ratio (M-H, Random, 95% CI) 0.52 [0.20, 1.37]
6.5 tamoxifen 10 mg  
2 891 Odds Ratio (M-H, Random, 95% CI) 0.52 [0.20, 1.37]
6.6 letrozole 2.5 mg  
4 1782 Odds Ratio (M-H, Random, 95% CI) 0.65 [0.52, 0.82]
6.7 vorozole 2.5 mg  
1 452 Odds Ratio (M-H, Random, 95% CI) 0.67 [0.33, 1.37]

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
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<tbody>
<tr>
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<tr>
<td>1.1 AI versus tamoxifen</td>
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<td>2548</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.07 [0.88, 1.29]</td>
</tr>
<tr>
<td>1.2 AI versus megestrol acetate</td>
<td>9</td>
<td>3379</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.77 [1.42, 2.20]</td>
</tr>
<tr>
<td>1.3 AI versus fulvestrant</td>
<td>1</td>
<td>846</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.97 [0.70, 1.35]</td>
</tr>
<tr>
<td>1.4 AI versus medroxyprogesterone acetate</td>
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<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.20 [0.06, 0.73]</td>
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<tr>
<td>2 nausea</td>
<td>15</td>
<td>2548</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
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<tr>
<td>2.1 AI versus tamoxifen</td>
<td>6</td>
<td>2548</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>1.29 [0.78, 2.13]</td>
</tr>
<tr>
<td>2.2 AI versus megestrol acetate</td>
<td>8</td>
<td>3208</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>1.84 [1.37, 2.47]</td>
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<tr>
<td>2.3 AI versus fulvestrant</td>
<td>1</td>
<td>846</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.96 [0.71, 1.31]</td>
</tr>
<tr>
<td>3 vomiting</td>
<td>8</td>
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<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
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<tr>
<td>3.1 AI versus tamoxifen</td>
<td>2</td>
<td>1239</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.23 [0.79, 1.90]</td>
</tr>
<tr>
<td>3.2 AI versus megestrol acetate</td>
<td>5</td>
<td>2319</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>2.03 [1.42, 2.90]</td>
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<td>3.3 AI versus fulvestrant</td>
<td>1</td>
<td>846</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.90 [0.60, 1.35]</td>
</tr>
<tr>
<td>4 diarrhoea</td>
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<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
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<td>4.1 AI versus tamoxifen</td>
<td>3</td>
<td>2149</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.64 [1.06, 2.55]</td>
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<td>4.2 AI versus megestrol acetate</td>
<td>5</td>
<td>1961</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.48 [1.02, 2.13]</td>
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<td>4.3 AI versus fulvestrant</td>
<td>1</td>
<td>397</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.41 [0.84, 2.35]</td>
</tr>
<tr>
<td>5 rash</td>
<td>12</td>
<td>2548</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>Subtotals only</td>
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<td>5.1 AI versus tamoxifen</td>
<td>4</td>
<td>711</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>33.61 [4.71, 239.97]</td>
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<tr>
<td>5.2 AI versus megestrol acetate</td>
<td>6</td>
<td>2496</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>1.83 [0.77, 4.39]</td>
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<tr>
<td>5.3 AI versus medroxyprogesterone acetate</td>
<td>1</td>
<td>397</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>111.71 [6.75, 1849.91]</td>
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<tr>
<td>5.4 AI versus fulvestrant</td>
<td>1</td>
<td>397</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>1.39 [0.77, 2.50]</td>
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<td>6 vaginal bleeding</td>
<td>4</td>
<td>2548</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
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<td>6.1 AI versus tamoxifen</td>
<td>1</td>
<td>1017</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.45 [0.16, 1.32]</td>
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<td>6.2 AI versus megestrol acetate</td>
<td>2</td>
<td>915</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.29 [0.13, 0.65]</td>
</tr>
<tr>
<td>6.3 AI versus medroxyprogesterone acetate</td>
<td>1</td>
<td>218</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.10 [0.01, 0.77]</td>
</tr>
<tr>
<td>7 thromboembolic</td>
<td>6</td>
<td>2548</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>7.1 AI versus tamoxifen</td>
<td>2</td>
<td>1228</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.48 [0.27, 0.85]</td>
</tr>
<tr>
<td>7.2 AI versus megestrol acetate</td>
<td>3</td>
<td>863</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.54 [0.26, 1.10]</td>
</tr>
<tr>
<td>7.3 AI versus fulvestrant</td>
<td>1</td>
<td>846</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.14 [0.56, 2.31]</td>
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</table>
### Comparison 3. Current AIs versus non-AI

<table>
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<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Overall survival (reported or calculated)</td>
<td>6</td>
<td></td>
<td>HR (Fixed, 95% CI)</td>
<td>0.88 [0.80, 0.96]</td>
</tr>
<tr>
<td>1.1 anastrozole 1 mg</td>
<td>3</td>
<td></td>
<td>HR (Fixed, 95% CI)</td>
<td>0.90 [0.79, 1.03]</td>
</tr>
<tr>
<td>1.2 exemestane 25 mg</td>
<td>1</td>
<td></td>
<td>HR (Fixed, 95% CI)</td>
<td>0.85 [0.72, 0.99]</td>
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<tr>
<td>1.3 letrozole 2.5 mg</td>
<td>2</td>
<td></td>
<td>HR (Fixed, 95% CI)</td>
<td>0.88 [0.73, 1.05]</td>
</tr>
<tr>
<td>2 Progression-free survival (reported or calculated)</td>
<td>6</td>
<td></td>
<td>HR (Random, 95% CI)</td>
<td>0.92 [0.75, 1.13]</td>
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<tr>
<td>2.1 anastrozole 1 mg</td>
<td>2</td>
<td></td>
<td>HR (Random, 95% CI)</td>
<td>1.05 [0.65, 1.70]</td>
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<tr>
<td>2.2 exemestane 25 mg</td>
<td>1</td>
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<td>HR (Random, 95% CI)</td>
<td>0.82 [0.70, 0.97]</td>
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<tr>
<td>2.3 letrozole 2.5 mg</td>
<td>3</td>
<td></td>
<td>HR (Random, 95% CI)</td>
<td>0.87 [0.68, 1.11]</td>
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<tr>
<td>3 Clinical benefit (assessable)</td>
<td>10</td>
<td>5079</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.78 [0.63, 0.96]</td>
</tr>
<tr>
<td>3.1 anastrozole 1 mg</td>
<td>4</td>
<td>2626</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.74 [0.48, 1.12]</td>
</tr>
<tr>
<td>3.2 exemestane 25 mg</td>
<td>2</td>
<td>816</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.71 [0.39, 1.31]</td>
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<tr>
<td>3.3 letrozole 2.5 mg</td>
<td>4</td>
<td>1637</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.77 [0.60, 1.00]</td>
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<tr>
<td>4 Objective response (assessable)</td>
<td>10</td>
<td>5079</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.77 [0.62, 0.96]</td>
</tr>
<tr>
<td>4.1 anastrozole 1 mg</td>
<td>4</td>
<td>2626</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.95 [0.77, 1.17]</td>
</tr>
<tr>
<td>4.2 exemestane 25 mg</td>
<td>2</td>
<td>816</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.49 [0.17, 1.48]</td>
</tr>
<tr>
<td>4.3 letrozole 2.5 mg</td>
<td>4</td>
<td>1637</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.65 [0.51, 0.82]</td>
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<td>5 Clinical benefit (randomised)</td>
<td>10</td>
<td>5299</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.79 [0.64, 0.96]</td>
</tr>
<tr>
<td>5.1 anastrozole 1 mg</td>
<td>4</td>
<td>2626</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.74 [0.48, 1.12]</td>
</tr>
<tr>
<td>5.2 exemestane 25 mg</td>
<td>2</td>
<td>891</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.78 [0.53, 1.17]</td>
</tr>
<tr>
<td>5.3 letrozole 2.5 mg</td>
<td>4</td>
<td>1782</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.77 [0.61, 0.96]</td>
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<tr>
<td>6 Objective response (randomised)</td>
<td>10</td>
<td>5299</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.78 [0.64, 0.95]</td>
</tr>
<tr>
<td>6.1 anastrozole 1 mg</td>
<td>4</td>
<td>2626</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.95 [0.77, 1.17]</td>
</tr>
<tr>
<td>6.2 exemestane 25 mg</td>
<td>2</td>
<td>891</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.52 [0.20, 1.37]</td>
</tr>
<tr>
<td>6.3 letrozole 2.5 mg</td>
<td>4</td>
<td>1782</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.65 [0.52, 0.82]</td>
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</tbody>
</table>

### Comparison 4. Current AIs versus non-AI: Toxicity

<table>
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<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
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<tbody>
<tr>
<td>1 hot flushes</td>
<td>8</td>
<td></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>1.1 AI versus tamoxifen</td>
<td>3</td>
<td>2048</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.13 [0.91, 1.39]</td>
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<tr>
<td>1.2 AI versus megestrol acetate</td>
<td>4</td>
<td>2036</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.69 [1.24, 2.30]</td>
</tr>
<tr>
<td>1.3 AI versus fulvestrant</td>
<td>1</td>
<td>846</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.97 [0.70, 1.35]</td>
</tr>
<tr>
<td>2 nausea</td>
<td>8</td>
<td></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>2.1 AI versus tamoxifen</td>
<td>3</td>
<td>2048</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.89 [0.72, 1.11]</td>
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### Comparison 5. AI versus different AI

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<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
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<tr>
<td>Overall survival (reported)</td>
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<td></td>
<td>HR (Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>1.1 letrozole</td>
<td>1</td>
<td></td>
<td>HR (Fixed, 95% CI)</td>
<td>0.64 [0.49, 0.84]</td>
</tr>
<tr>
<td>2 Progression-free survival (reported or calculated)</td>
<td>1</td>
<td></td>
<td>HR (Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>2.1 letrozole</td>
<td>1</td>
<td></td>
<td>HR (Fixed, 95% CI)</td>
<td>0.72 [0.57, 0.91]</td>
</tr>
<tr>
<td>3 Clinical benefit (assessable)</td>
<td>4</td>
<td></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>3.1 letrozole</td>
<td>3</td>
<td>1092</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.72 [0.56, 0.93]</td>
</tr>
<tr>
<td>3.2 anastrozole</td>
<td>2</td>
<td>663</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.29 [0.92, 1.79]</td>
</tr>
<tr>
<td>4 Objective response (assessable)</td>
<td>4</td>
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<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
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<td>4.1 letrozole</td>
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<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.53 [0.39, 0.73]</td>
</tr>
<tr>
<td>4.2 anastrozole</td>
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<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.59 [1.07, 2.37]</td>
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<td>5 Clinical benefit (randomised)</td>
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<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>5.1 letrozole</td>
<td>3</td>
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<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.74 [0.57, 0.94]</td>
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<td>5.2 anastrozole</td>
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<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.25 [0.90, 1.72]</td>
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<tr>
<td>6 Objective response (randomised)</td>
<td>4</td>
<td></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>6.1 letrozole</td>
<td>3</td>
<td>1233</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.54 [0.40, 0.74]</td>
</tr>
<tr>
<td>6.2 anastrozole</td>
<td>2</td>
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<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.50 [1.01, 2.23]</td>
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</table>
### Comparison 6. AI as first-line therapy versus any other therapy (tamoxifen)

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
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<tbody>
<tr>
<td><strong>1 Overall survival</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(reported or calculated)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1.1 anastrozole as first-line therapy</td>
<td>1</td>
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<td>HR (Fixed, 95% CI)</td>
<td>0.97 [0.81, 1.16]</td>
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<tr>
<td>1.2 fadrozole as first-line therapy</td>
<td>1</td>
<td></td>
<td>HR (Fixed, 95% CI)</td>
<td>0.91 [0.63, 1.32]</td>
</tr>
<tr>
<td><strong>2 Progression-free survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(reported or calculated)</td>
<td></td>
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<td></td>
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<tr>
<td>2.1 formestane as first-line therapy</td>
<td>1</td>
<td></td>
<td>HR (Fixed, 95% CI)</td>
<td>0.93 [0.68, 1.28]</td>
</tr>
<tr>
<td>2.2 anastrozole as first-line therapy</td>
<td>1</td>
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<td>HR (Fixed, 95% CI)</td>
<td>0.82 [0.71, 0.95]</td>
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<tr>
<td>2.3 letrozole as first-line therapy</td>
<td>1</td>
<td></td>
<td>HR (Fixed, 95% CI)</td>
<td>0.70 [0.60, 0.82]</td>
</tr>
<tr>
<td><strong>3 Clinical benefit</strong></td>
<td>8</td>
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<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.70 [0.51, 0.97]</td>
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<tr>
<td>(assessable)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>3.1 aminogluthethimide (any dose)</td>
<td>2</td>
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<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.67 [0.39, 1.13]</td>
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<tr>
<td>3.2 formestane 250 mg</td>
<td>1</td>
<td>348</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>1.36 [0.87, 2.13]</td>
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<tr>
<td>3.3 anastrozole 1 mg</td>
<td>2</td>
<td>1259</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.48 [0.16, 1.44]</td>
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<tr>
<td>3.4 exemestane 25 mg</td>
<td>1</td>
<td>113</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.47 [0.22, 0.99]</td>
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<tr>
<td>3.5 fadrozole 2 mg</td>
<td>1</td>
<td>209</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>1.09 [0.58, 2.06]</td>
</tr>
<tr>
<td>3.6 letrozole 2.5 mg</td>
<td>1</td>
<td>844</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.63 [0.48, 0.82]</td>
</tr>
<tr>
<td><strong>4 Objective response</strong></td>
<td>10</td>
<td>3287</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.81 [0.62, 1.06]</td>
</tr>
<tr>
<td>(assessable)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.1 aminogluthethimide (any dose)</td>
<td>3</td>
<td>440</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.90 [0.50, 1.61]</td>
</tr>
<tr>
<td>4.2 formestane 250 mg</td>
<td>1</td>
<td>348</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>1.20 [0.77, 1.87]</td>
</tr>
<tr>
<td>4.3 anastrozole 1 mg</td>
<td>2</td>
<td>1259</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.85 [0.65, 1.11]</td>
</tr>
<tr>
<td>4.4 exemestane 25 mg</td>
<td>1</td>
<td>113</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.26 [0.11, 0.62]</td>
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<tr>
<td>4.5 fadrozole 2 mg</td>
<td>2</td>
<td>283</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>1.20 [0.69, 2.09]</td>
</tr>
<tr>
<td>4.6 letrozole 2.5 mg</td>
<td>1</td>
<td>844</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.58 [0.42, 0.78]</td>
</tr>
<tr>
<td><strong>5 Clinical benefit</strong></td>
<td>8</td>
<td>3210</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.75 [0.55, 1.02]</td>
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<tr>
<td>(randomised)</td>
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<td></td>
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<td>5.1 aminogluthethimide (any dose)</td>
<td>2</td>
<td>292</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.89 [0.38, 2.08]</td>
</tr>
<tr>
<td>5.2 formestane 250 mg</td>
<td>1</td>
<td>409</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>1.25 [0.85, 1.86]</td>
</tr>
<tr>
<td>5.3 anastrozole 1 mg</td>
<td>2</td>
<td>1259</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.48 [0.16, 1.44]</td>
</tr>
<tr>
<td>5.4 exemestane 25 mg</td>
<td>1</td>
<td>122</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.55 [0.27, 1.13]</td>
</tr>
<tr>
<td>5.5 fadrozole 2 mg</td>
<td>1</td>
<td>221</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>1.23 [0.69, 2.21]</td>
</tr>
<tr>
<td>5.6 letrozole 2.5 mg</td>
<td>1</td>
<td>907</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.65 [0.50, 0.84]</td>
</tr>
<tr>
<td><strong>6 Objective response</strong></td>
<td>10</td>
<td>3505</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.85 [0.65, 1.11]</td>
</tr>
<tr>
<td>(randomised)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>6.1 aminogluthethimide (any dose)</td>
<td>3</td>
<td>507</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>1.01 [0.52, 1.96]</td>
</tr>
<tr>
<td>6.2 formestane 250 mg</td>
<td>1</td>
<td>409</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>1.18 [0.77, 1.80]</td>
</tr>
<tr>
<td>6.3 anastrozole 1 mg</td>
<td>2</td>
<td>1259</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.85 [0.65, 1.11]</td>
</tr>
<tr>
<td>6.4 exemestane 25 mg</td>
<td>1</td>
<td>122</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.30 [0.13, 0.69]</td>
</tr>
<tr>
<td>6.5 fadrozole 2 mg</td>
<td>2</td>
<td>301</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>1.28 [0.76, 2.15]</td>
</tr>
<tr>
<td>6.6 letrozole 2.5 mg</td>
<td>1</td>
<td>907</td>
<td>Odds Ratio (M-H, Random, 95% CI)</td>
<td>0.59 [0.43, 0.79]</td>
</tr>
</tbody>
</table>
Comparison 7. AI as second-line therapy versus any other therapy

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Overall survival (reported or calculated)</td>
<td>2</td>
<td></td>
<td>HR (Fixed, 95% CI)</td>
<td>0.80 [0.66, 0.96]</td>
</tr>
<tr>
<td>1.1 anastrozole as second-line therapy</td>
<td>1</td>
<td></td>
<td>HR (Fixed, 95% CI)</td>
<td>0.78 [0.61, 1.00]</td>
</tr>
<tr>
<td>1.2 letrozole as second-line therapy</td>
<td>1</td>
<td></td>
<td>HR (Fixed, 95% CI)</td>
<td>0.82 [0.63, 1.07]</td>
</tr>
<tr>
<td>2 Progression-free survival (reported or calculated)</td>
<td>6</td>
<td></td>
<td>HR (Random, 95% CI)</td>
<td>1.08 [0.89, 1.31]</td>
</tr>
<tr>
<td>2.1 aminoglutethimide (any dose)</td>
<td>1</td>
<td></td>
<td>HR (Random, 95% CI)</td>
<td>1.25 [0.91, 1.72]</td>
</tr>
<tr>
<td>2.2 formestane 250 mg biweekly</td>
<td>1</td>
<td></td>
<td>HR (Random, 95% CI)</td>
<td>0.93 [0.68, 1.28]</td>
</tr>
<tr>
<td>2.3 anastrozole 1 mg</td>
<td>1</td>
<td></td>
<td>HR (Random, 95% CI)</td>
<td>1.34 [1.16, 1.55]</td>
</tr>
<tr>
<td>2.4 exemestane 25 mg</td>
<td>1</td>
<td></td>
<td>HR (Random, 95% CI)</td>
<td>0.82 [0.70, 0.97]</td>
</tr>
<tr>
<td>2.5 letrozole 2.5 mg</td>
<td>1</td>
<td></td>
<td>HR (Random, 95% CI)</td>
<td>0.98 [0.77, 1.25]</td>
</tr>
<tr>
<td>2.6 vorozole 2.5 mg</td>
<td>1</td>
<td></td>
<td>HR (Random, 95% CI)</td>
<td>1.27 [1.04, 1.56]</td>
</tr>
<tr>
<td>3 Clinical benefit (assessable)</td>
<td>11</td>
<td>3721</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.00 [0.87, 1.14]</td>
</tr>
<tr>
<td>3.1 aminoglutethimide (any dose)</td>
<td>2</td>
<td>274</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.19 [0.74, 1.92]</td>
</tr>
<tr>
<td>3.2 formestane 250 mg biweekly</td>
<td>1</td>
<td>173</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.75 [0.41, 1.39]</td>
</tr>
<tr>
<td>3.3 anastrozole 1 mg</td>
<td>2</td>
<td>1367</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.04 [0.84, 1.29]</td>
</tr>
<tr>
<td>3.4 exemestane 25 mg</td>
<td>1</td>
<td>703</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.90 [0.66, 1.22]</td>
</tr>
<tr>
<td>3.5 fadrozole 2 mg</td>
<td>3</td>
<td>773</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.04 [0.77, 1.41]</td>
</tr>
<tr>
<td>3.6 letrozole 2.5 mg</td>
<td>2</td>
<td>431</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.96 [0.64, 1.42]</td>
</tr>
<tr>
<td>4 Objective response (assessable)</td>
<td>13</td>
<td>4170</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.96 [0.81, 1.14]</td>
</tr>
<tr>
<td>4.1 aminoglutethimide (any dose)</td>
<td>3</td>
<td>348</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.09 [0.66, 1.81]</td>
</tr>
<tr>
<td>4.2 formestane 250 mg biweekly</td>
<td>1</td>
<td>173</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.01 [0.46, 2.25]</td>
</tr>
<tr>
<td>4.3 anastrozole 1 mg</td>
<td>2</td>
<td>1367</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.12 [0.84, 1.50]</td>
</tr>
<tr>
<td>4.4 exemestane 25 mg</td>
<td>1</td>
<td>703</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.81 [0.54, 1.23]</td>
</tr>
<tr>
<td>4.5 fadrozole 2 mg</td>
<td>3</td>
<td>773</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.17 [0.76, 1.80]</td>
</tr>
<tr>
<td>4.6 letrozole 2.5 mg</td>
<td>2</td>
<td>431</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.65 [0.41, 1.04]</td>
</tr>
<tr>
<td>4.7 vorozole 2.5 mg</td>
<td>1</td>
<td>375</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.70 [0.34, 1.42]</td>
</tr>
<tr>
<td>5 Clinical benefit (randomised)</td>
<td>11</td>
<td>3846</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.99 [0.86, 1.12]</td>
</tr>
<tr>
<td>5.1 aminoglutethimide (any dose)</td>
<td>2</td>
<td>279</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.16 [0.72, 1.86]</td>
</tr>
<tr>
<td>5.2 formestane 250 mg biweekly</td>
<td>1</td>
<td>177</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.72 [0.40, 1.31]</td>
</tr>
<tr>
<td>5.3 anastrozole 1 mg</td>
<td>2</td>
<td>1367</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.04 [0.84, 1.29]</td>
</tr>
<tr>
<td>5.4 exemestane 25 mg</td>
<td>1</td>
<td>760</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.88 [0.66, 1.19]</td>
</tr>
<tr>
<td>5.5 fadrozole 2 mg</td>
<td>3</td>
<td>779</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.04 [0.77, 1.41]</td>
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<tr>
<td>5.6 letrozole 2.5 mg</td>
<td>2</td>
<td>475</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.96 [0.65, 1.41]</td>
</tr>
<tr>
<td>6 Objective response (randomised)</td>
<td>13</td>
<td>4453</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.95 [0.80, 1.12]</td>
</tr>
</tbody>
</table>