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

Gibson L, Dawson C, Lawrence D, Bliss J

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2007, Issue 1

http://www.thecochranelibrary.com

WILEY

TABLE OF CONTENTS

HEADER 1
ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
BACKGROUND 2
OBJECTIVES 3
METHODS 3
RESULTS 6
DISCUSSION 11
AUTHORS' CONCLUSIONS 12
ACKNOWLEDGEMENTS 12
REFERENCES 12
CHARACTERISTICS OF STUDIES 17
DATA AND ANALYSES 42

[Intervention Review]

Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women

Lorna Gibson[2], Claire Dawson[1], David Lawrence[3], Judith Bliss[1]

[1]Clinical Trials and Statistics Unit, The Institute of Cancer Research, Sutton, UK. [2]Cancer and Public Health Unit, London School of Hygiene and Tropical Medicine, London, UK. [3]Brent Teaching Primary Care Trust, Middlesex, UK

Contact address: Judith Bliss, Clinical Trials and Statistics Unit, The Institute of Cancer Research, 15 Cotswold Road, Sutton, Surrey, UK. j.bliss@icr.ac.uk.

Editorial group: Cochrane Breast Cancer Group.
Publication status and date: Unchanged, published in Issue 3, 2009.
Review content assessed as up-to-date: 29 September 2005.

Citation: Gibson L, Dawson C, Lawrence D, Bliss J. Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women. *Cochrane Database of Systematic Reviews* 2007, Issue 1. Art. No.: CD003370. DOI: 10.1002/14651858.CD003370.pub2.

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. Aminoglutethimide 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 are classified as either first, second or third generation. Aminoglutethimide (AG) was the first AI and although effective it was poorly tolerated. This was supplanted by 4-hydroxy androstenedione (formestane) which was better tolerated. Third generation AIs fall into two principal categories (a) non-steroidal, reversible triazole derivatives (anastrozole, fadrozole, letrozole, vorozole) and (b) steroidal, irreversible inhibitors (exemestane). The most widely used AIs are currently anastrozole, exemestane and letrozole.

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 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 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 certain minimum percentage of participants (Bezwoda 1998; Buzdar 2001; Dombernowsky 1998; Goss 1999; Mauriac 2003; Mourisden 2001), some used worst toxicity grades (Falkson 1996; Thuerlimann 1996; 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 Carrion 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; Mauriac 2003; Thuerlimann 1997). One additional study (Dombernowsky 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

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 aminogluthetimide, 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 aminoglutethimide 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 Bezwoda 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 randomisation 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 labelled 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 baseline 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 1995). 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 (Bonneterre 2001; Buzdar 1996a; Buzdar 2001; Ingle 1986; Dombernowsky 1998; Thuerlimann 1996) and were calculated for six trials (Bezwoda 1998; Goss 1999; Kaufmann 2000; Milla-Santos 2003; Rose 1986; Russell 1997). In terms of progression-free survival, HRs were reported in the publications of four trials (Bonneterre 2001; Buzdar 2001; Ingle 1986; Mourisden 2001). The remaining six trials (Dombernowsky 1998; Goss 1999; Kaufmann 2000; Mauriac 2003; Russell 1997; Thuerlimann 1997) had sufficient data for calculation of the HRs.

1. Overall survival

Data on survival were available in 12 trials reporting an estimated 2576 events in 4548 women. No data were available for formestane. 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 individual 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 specific 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 anastrozole (Bonneterre 2001; Mauriac 2003) and letrozole (Buzdar 2001; Dombernowsky 1998; Mourisden 2001) were not statistically 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 (aminoglutethimide, 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 (aminoglutethimide, 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 signficantly 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 33.61, 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 signicantly 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-

vestrant had data on rash. AIs were not associated with a statistically significant increased risk of rash and there was statistically significant heterogeneity among the three studies with MA as the comparator (P = 0.04).

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 (Gershanovich 1998). Letrozole was compared with a different AI in all the trials (Gershanovich 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 Gershanovich 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 (Gershanovich 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 (Bonneterre 2001) and letrozole (Mourisden 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-

ter than tamoxifen as first-line therapy. There was considerable heterogeneity (P = 0.006) by type of AI. Exemestane and letrozole were the only AIs that were statistically significantly better than tamoxifen but in both cases the results are only based on one study. The other AIs appear to have little impact on objective response.

Aromatase inhibition as second-line therapy versus any other therapy

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) .

DISCUSSION

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

one, 500 mg* in three, 750 mg in one and 1000 mg in one (* dose doubled after a specific period of treatment). The comparator was tamoxifen in four studies (20 mg in two, 30 mg in one, 40 mg in one), MA 160 mg in one, MPA 1000 mg in one and HC 20 mg in one. Not all endpoints were available in each study: three reported overall survival, two progression-free survival, five clinical benefit and seven objective response.

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.

AUTHORS' CONCLUSIONS

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.

ACKNOWLEDGEMENTS

The authors were funded by Cancer Research UK. Lorna Gibson would like to thank Julian Peto and Isabel dos Santos Silva for their support. The authors would like to thank the Cochrane Breast Cancer Group for their support and are indebted to Olivia Fletcher for critical reading of the manuscript.

REFERENCES

References to studies included in this review

Alonso-Munoz 1988 *{published data only}*
Alonso-Munzo MC, Ojeda-Gonzalez M, Beltran-Fabregat M, Dorca-Ribugent J, Lopez-Lopez L, Borras-Balada J, et al.Randomized trial of tamoxifen versus aminoglutethimide and versus combined tamoxifen and aminoglutethimide in advanced postmenopausal breast cancer. *Oncology* 1988;**45**: 350–3.

Bezwoda 1998 *{published data only}*
* Bezwoda WR, Gudgeon A, Falkson G, Jordaan JP, Goedhals L. Fadrozole versus megestrol acetate: a double-blind randomised trial in advanced breast cancer. *Oncology* 1998;**55**:416–20.

Bonneterre 2001 *{published data only}*
* Bonneterre J, Buzdar A, Nabholtz JA, Robertson JFR, Thuerlimann B, von Euler M, et al.Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma. *Cancer* 2001;**92**(9): 2247–58.
Bonneterre J, Thuerlimann B, Robertson JFR, Krzakowski M, Mauriac L, Koralewski P, et al.Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the tamoxifen or arimidex randomized group efficacy and tolerability study. *Journal of Clinical Oncology* 2000;**18**(22):3748–57.
Nabholtz JM. Advanced breast cancer updates on anastrozole versus tamoxifen. *Journal of Steroid Biochemistry and Molecular Biology* 2003;**86**:321–5.
Nabholtz JM, Bonneterre J, Buzdar A, Robertson JFR, Thuerlimann B. Anastrozole (Arimidex) versus tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: survival analysis and updated safety results. *European Journal of Cancer* 2003;**39**:1684–89.
Nabholtz JM, Buzdar A, Pollak M, Harwin W, Burton G, Mangalik A, et al.Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in

postmenopausal women: results of a North American multicenter randomized trial. *Journal of Clinical Oncology* 2000;**18**(22):3758–67.
Thuerlimann B, Robertson JFR, Nabholtz JM, Buzdar A, Bonneterre J. Efficacy of tamoxifen following anastrozole ('Arimidex') compared with anastrozole following tamoxifen as first-line treatment for advanced breast cancer in postmenopausal women. *European Journal of Cancer* 2003; **39**:2310–17.
Vergote I, Bonneterre J, Thuerlimann B, Robertson J, MKrzakowski M, Mauriac L, et al.Randomised study of anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women. *European Journal of Cancer* 2000;**36**(Suppl:):81–91.

Buzdar 1996a ***{published data only}***

* Budzar A, Jonat W, Howell A, Jones SE, Blomqvist C, Vogel CL, et al.Anastrozole, a potent and selective aromatase inhibitor, versus megestrol acetate in postmenopausal women with advanced breast cancer: results of overview analsyis of two phase III trials. *Journal of Clinical Oncology* 1996;**14**(2000 - 11).
Buzdar AU, Jonat W, Howell A, Jones SE, Blomqvist CP, Vogel CL, et al.Anastrozole versus megestrol acetate in the treatment of postmenopausal women with advanced breast carcinoma. *Cancer* 1998;**83**(6):1142–52.
Buzdar AU, Jonat W, Howell A, Plourde PV. Arimidex: a potent and selective aromatase inhibitor for the treatment of advanced breast cancer. *Journal Steroid Biochemistry Molecular Biology* 1997;**61**(3-6):145–9.
Drummond M, Thompton E, Howell A, Jonat W, Buzdar A, Brown J. Cost-effectiveness implications of increased survival with anastrozole in the treatment of advanced breast cancer. *Journal of Medical Economics* 1999;**2**:33–43.
Jonat W, Howell A, Blomqvist C, Eiermann W, Winblad G, TyrrellC, et al.A randomized trial comparing two doses of the new selective aromatase inhibitor anastrozole (Arimidex) with megestrol acetate in postmenopausal women with advanced breast cancer. *European Journal of Cancer* 1996; **32A**(3):404–12.
Robertson JFR, Howell A, Buzdar A, von Euler M, Lee D. Static disease on anastrozole provides similar benefit as objective response in patients with advanced breast cancer. *Breast Cancer Research and Treatment* 1999;**58**:157–62.

Buzdar 1996b ***{published data only}***

* Buzdar A, Smith R, Vogel C, Bonomi P, Keller AM, Favis G, et al.Fadrazole HCl (CGS-16949A) versus megestrol acetate in postmenopausal patients with metatatic breast carcinoma: results of two randomized, double-blind, controlled multi-institutional trials. *Cancer* 1996;**77**(12): 2503–13.

Buzdar 1996c ***{published data only}***

Buzdar A, Smith R, Vogel C, Bonomi P, Keller AM, Favis G, et al.Fadrazole HCl (CGS-16949A) versus megestrol acetate in postmenopausal patients with metatatic breast carcinoma: results of two randomized, double-blind, controlled multi-institutional trials. *Cancer* 1996;**77**(12):2503–13.

Buzdar 2001 ***{published data only}***

* Buzdar A, Douma J, Davidson N, Elledge R, Morgan M, Smith R, et al.Phase III, multicenter, double-blind, randomized study of letrozole, an aromatase inhibitor, for advanced breast cancer versus megestrol acetate. *Journal of Clinical Oncology* 2001;**19**(14):3357–66.

Canney 1988 ***{published data only}***

* Canney PA, Priestman TJ, Griffiths T, Latief TN, Mould JJ, Spooner D. Randomized trial comparing aminoglutethimide with high-dose medroxyprogesterone acetate in therapy for advanced breast carcinoma. *Journal of the National Cancer Institute* 1988;**80**(14):1147–51.

Dombernowsky 1998 ***{published data only}***

* Dombernowsky P, Smith I, Falkson G, Leonard R, Panasci L, Bellmunt J, et al.Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double-blind randomized trial showing a dose effect and improved efficacy and tolerability compared with megestrol acetate. *Journal of Clinical Oncology* 1998;**16**(2):453–61.

Falkson 1996 ***{published data only}***

* Falkson CI, Falkson HC. A randomised study of CGS 16949A (fadrozole) versus tamoxifen in previously untreated postmenopausal patients with metastatic breast cancer. *Annals of Oncology* 1996;**7**:465–69.

Gershanovich 1998 ***{published data only}***

* Gershanovich M, Chaudri HA, Campos D, Lurie H, Bonaventura A, Jeffrey M, et al.Letrozole, a new oral aromatase inhibitor: randomised trial comparing 2.5mg daily, 0.5 mg daily and aminoglutethimide in postmenopausal women with advanced breast cancer. *Annals of Oncology* 1998;**9**:639–45.
Gershanovitch M. Letrozole, a new aromatase for advanced breast cancer. *Voprosy onkolgii* 45;**4**:361–68.

Goss 1999 ***{published data only}***

* Goss PE, Winer EP, Tannock IF, Schwarz LH. Randomized phase III trial comparing the new potent and selective third generation aromatase inhibitor vorozole with megestrol acetate in postmenopausal advanced breast cancer patients. *Journal of Clinical Oncology* 1999;**17**(1):52–63.

Ingle 1986 ***{published data only}***

* Ingle JN, Green SJ, Ahmann DL, Long HJ, Edmonson JH, Rubbin J, et al.Randomized trial of tamoxifen alone or combined with aminoglutethimide and hydrocortisone in women with metastatic breast cancer. *Journal of Clinical Oncology* 1986;**4**(6):958–64.

Kaufmann 2000 ***{published data only}***

Hillner BE, Radice D. Cost-effectiveness analysis of exemestane compared with megestrol in patients with advanced breast carcinoma. *Cancer* 2001;**91**(3):484–89.
Kaufmann M, Bajetta E, Dirix LY, Fein LE, Jones SE, Cervek J, et al.Exemestane improves survival compared with megestrol acetate in postmenopausal patients with advanced breast cancer who have failed on tamoxifen: results of a

double-blind randomised phase III trial. *European Journal of Cancer* 2000;**36**(Suppl):81–91.
* Kaufmann M, Bajetta E, Dirix LY, Fein LE, Jones SE, Zilembo N, et al.Exemestane is superior to megestrol acetate after tamoxifen failure in postmenopausal women with advanced breast cancer: results of a phase III randomised double-blind trial. *Journal of Clinical Oncology* 2000;**18**(7): 1399–1411.

Kleeberg 1997 ***{published data only}***
* Kleeberg UR, Dowsett M, Carrion RP, Dodwell DJ, Vorobiof DA, Aparicio LA, Robertson JFR. A randomised comparison of oestrogen suppression with anastrozole and formestane in postmenopausal patients with advanced breast cancer. *Oncology* 1997;**54**(Suppl 2):19–22.
Vorobiof DA, Kleeberg UR, Perez-Carrion R, Dodwell DJ, Robertson JFR, Calvo L, et al.A randomized, open, parallel-group trial to compare the endocrine effects of oral anastrozole (Arimidex) with intramuscular formestane in postmenopausal women with advanced breast cancer. *Annals of Oncology* 1999;**10**:1219–25.

Leitzel 1995 ***{published data only}***
* Leitzel K, Teramoto Y, Konrad K, Chinchilli VM, Volas G, Grossberg H, et al.Elevated Serum c-erb B-2 Antigen Levels and decreased response to hormone therapy of breast cancer. *Journal of Clinical Oncology* 1995;**13**(5):1129–35.

Mauriac 2003 ***{published data only}***
Howell A, Robertson JFR, Quaresma Albano J, Ascgermannova A, Mauriac L, Kleeberg UR, et al.Fulvestrant, formerly ICI 182, 780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. *Journal of Clinical Oncology* 2002;**20**(16):3396–403.
* Mauriac L, Pippen JE, Quaresma Albano J, Gertler SZ Osborne CK. Fulvestrant (Faslodex) versus anastrozole for the second-line treatment of advanced breast cancer in subgroups of postmenopausal women with visceral and non-visceral metasteses: combined results from two multicentre trials. *European Journal of Cancer* 2003;**39**(9):1228–33.
Osborne CK, Pippen J, Jones, SE, Parker LM, Ellis M, Come S, et al.Double-blind, randomized trial comparing the efficacy and tolerability of the fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: results of a North American Trial. *Journal of Clinical Oncology* 2002;**20** (16):3386–95.
Robertson JFR, Osborne CK, Howell A, Jones SE, Mauriac L, Ellis M, et al.Fulvestrant versus Anastrozole for the treatment of advanced breast carcinoma in postmenopausal women. *Cancer* 2003;**98**(2):229–38.
Vergote I. Fulvestrant versus anastrozole as second-line treatment of advanced breast cancer in postmenopausal women. European Journal of Cancer 2002; Vol. 38, issue 6:Suppl: 57-8.

Mercer 1993 ***{published data only}***
* Mercer PM, Ebbs SR, Fraser SCA, Coltart RS Bates T. Trial of aminoglutethimide vs hydrocortisone as second-line hormone treatment of advanced breast cancer. *European Journal of Surgical Oncology* 1993;**19**:254–8.

Milla-Santos 2003 ***{published data only}***
Milla-Santos A, Milla L, Portella J, Rallo L, Pons M, Rodes E, et al.Anastrozole versus tamoxifen as first-line therapy in postmenopausal patients with hormone-dependent advanced breast cancer. *American Journal of Clinical Oncology* 2003;**26**(3):317–22.

Mourisden 2001 ***{published data only}***
Mourisdan H, Sun Y, Gershanovich M, Perez-Carrion R, Becquart D, Chaudri-Ross HA, Lang R. Superiority of letrozole to tamoxifen in the first-line treatment of advanced breast cancer: evidence from metastatic subgroups and a test of functional ability. *The Oncologist* 2004;**9**:489–96.
Mourisden H, Gershanovich M, Sun Y, Perez-Carrion R, Boni C, Monnier A, et al.Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. *Journal of Clinical Oncology* 2003;**21**(11):2101–9.
* Mourisden H, Gershanovich M, Sun Y, Perez-Carrion R, Boni C, Monnier A, et al.Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced brreast cancer: results of a phase III study of the international letrozole breast cancer group. *Journal of Clinical Oncology* 2001;**19**(10):2596–606.

Paridaens 2003 ***{published data only}***
Atalay G, Dirix L, Biganzoli L, Beex L, Nooji M, Cameron D, et al.The effect of exemestane on serum lipid profile in postmenopausal women with metastatic breast cancer: a comparison study to EORTC Trial 10951, 'Randomized phase II study in first line hormonal treatment for metastatic breast cancer with exemestane or tamoxifen in postmenopausal patients'. *Annals of Oncology* 2004;**15**(2): 211–7.
* Paridaens R, Dirix L, Lohrisch C, Beex L, Nooji M, Cameron D, et al.Mature results of a randomized phase II multicenter study of exemextane versus tamoxifen as first-line hormone therapy for postmenopausal women with metastatic breast cancer. *Annals of Oncology* 2003;**14**: 1391–8.

Perez Carrion 1994 ***{published data only}***
* Perez Carrion R, Alberola Candel V, Calabresi F, Michel RT, Santos R, Delozier T, et al.Comparison of the selective aromatase inhibitor formestane with tamoxifen as first-line therapy in postmenopausal women with advanced breast cancer. *Annals of Oncology* 1994;**5**:Suppl 7 19-24.

Powles 1984 ***{published data only}***
* Powles TJ, Ashley S, Ford HT, Gazet JC, Nash AG, Neville AM, Coombes RC. Treatment of disseminated breast cancer with tamoxifen, aminoglutethimide, hydrocortisone, and danazol, used in combination or sequentially. *The Lancet* 1984:1369–72.

Rose 1986 ***{published data only}***
Rose C, Kamby C, Mouridsen HT, Andersson M, Bastholt L, Moller KA, et al.Combined endocrine treatment of

elderly postmenopausal patients with metastatic breast cancer. *Breast Cancer Research and Treatment* 2000;**61**(2): 103–10.

* Rose C, Kamby C, Mouridsen HT, Bastholt L, Brincker H, Skovaard-Poulsen H, et al.Combined endocrine treatment of postmenopausal patients with advanced breast cancer. A randomised trial of tamoxifen vs. tamoxifen plus aminoglutethimide and hydrocortisone. *Breast Cancer Research and Treatment* 1986;**7**:Suppl 45-50.

Rose 2003 ***{published data only}***

* Rose C, Vtoraya O, Pluzanska A, Davidson N, Gershanovich M, Thomas R, et al.An open randomised trial of second-line endocrine therapy in advanced breast cancer. *European Journal of Cancer* 2003;**39**(16):2318–27.
Tobias JS, Howell A. An open randomised trial of second-line endocrine therapy in advanced breast cancer: comparison of the Aromatase inhibitors letrozole and anastrozole. *European Journal of Cancer* 2004;**40**(12):1913.

Russell 1997 ***{published data only}***

* Russell C, Green SJ, O'Sullivan J, Hynes HE, Budd T, Congdon JE, et al.Megestrol acetate and aminoglutethimide/hydrocortisone in sequence or in combination as second-line endocrine therapy of estrogen receptor-positive metastatic breast cancer: a southwest oncology group phase III trial. *Journal of Clinical Oncology* 1997;**15**(7):2494–501.

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 Treament* 2001;**64**:77.

Thuerlimann 1996 ***{published data only}***

* Thuerlimann B, Beretta K, Bacchi M, Castiglione-Gertsch M, Goldhirsch A, Jungi WF, et al.First-line fadrozole HCI (CGS 16949A) versus tamoxifen in postmenopausal women with advanced breast cancer. *Annals of Oncology* 1996;**7**: 471–9.

Thuerlimann 1997 ***{published data only}***

Bernhard J, Casiglione-Gertsch M, Hsu Schmitz S-F, Thuerlimann B, Cavalli F, Morant R, et al.Quality of life in postmenopausal patients with breast cancer after failure of tamoxifen: formestane versus megestrol acetate as second-line hormonal treatment. *European Journal of Cancer* 1999; **35**(6):913–20.
Bernhard J, Thuerlimann B, Hsu Schmitz S-F, Castiglione-Gertsch M, Cavalli F, Morant R, et al.Defining clinical benefit in postmenopausal patients with breast cancer under second-line endocrine treatment: does quality of life matter. *Journal of Clinical Oncology* 1999;**17**(6):1672–79.
* Thuerlimann B, Castiglione M, Hsu-Scmitz SF, Cavalli F, Bonnefoi H, Fey MF, et al.Formestane versus megestrol acetate in postmenopausal breast cancer patients after failure of tamoxifen: a phase III prospective randomised cross over trial of second-line hormonal treatment (SAKK 20/90). *European Journal of Cancer* 1997;**33**(7):1017–24.

Tominaga 2003 ***{published data only}***

* Tominaga T, Adachi I, Sasaki Y, Tabei T, Ikeda T, Takatsuka Y, et al.Double-blind randomised trial comparing the non-steroidal aromatase inhibitors letrozole and fadrozole in postmenopausal women with advanced breast cancer. *Annals of Oncology* 2003;**14**:62–70.

References to studies excluded from this review

Abe 2002 ***{published data only}***

* Abe R, Tominaga T, Nomizu T, Nomura Y, Takashima S, Koyama H, et al.CGS20267 (letrozole), a new aromatase inhibitor: late phase II study for postmenopausal women with advanced or recurrent breast cancer (no. 1) - investigation of recommended clinical dose CGS20267 Study Group. *Gan To Kaguku Ryoho* 2002;**29**(5):729–40.

Bajetta 1994 ***{published data only}***

* Bajetta E, Zilembo N, Buzzoni R, Noberasco C, Di Leo A, Bartoli C, et al.Endocrinological and clinical evaluation of two doses of formestane in advanced breast cancer. *British Journal of Cancer* 1994;**70**:145–50.
Ferrari L, Zilembo N, Bajetta, Buzzoni R, Noberasco C, Martinetti A, et al.Effect of two 4-hydroxyandrostenedione doses on serum insulin-like growth factor I levels in advanced breast cancer. *Breast Cancer Research and Treatment* 1994;**30**:127–32.

Bajetta 1997 ***{published data only}***

* Bajetta E, Zilembo N, Noberasco C, Martinetti A, Mariani L, Ferrari L, et al.The minimal effective exemestane dose for endocrine activity in advanced breast cancer. *European Journal of Cancer* 1997;**33**(4):587–91.

Bajetta 1997a ***{published data only}***

* Bajetta E, Ferrari L, Celio L, Mariana L, Miceli R, Di Leo A, et al.The aromatase inhibitor letrozole in advanced breast cancer: effects on serum insulin-like growth factor (IGF)-I and IGF-binding protein-3 levels. *Journal of steroid Biochemistry* 1997;**63**(4-6):261–7.

Bajetta 1999 ***{published data only}***

* Bajetta E, Zilembo N, Dowsett M, Guillevin L, Di Leo A, Celio L, et al.Double-blind, randomised, multicentre endocrine trial comparing two letrozole doses in postmenopausal breast cancer patients. *European Journal of Cancer* 1999;**35**(2):208–13.

Beretta 1990 ***{published data only}***

* Beretta KR, Hoeffken K, Kvinnsland S, Trunet P, Chaudri HA, Bhatnagar AS, et al.CGS 16949A, a new aromatase inhibitor in the treatment of breast cancer- a phase I study. *Annals of Oncology* 1990;**1**(6):421–6.

Bruning 1989 ***{published data only}***

* Bruning PF, Bonfer JMG, Hart AAM, van der Linden E, de Jong-Bakker M, Moolenaar AJ, Nooijen WJ. Low dose aminoglutethimide without hydrocortisone for the treatment of advanced postmenopausal breast cancer. *European Journal of Clinical Oncology* 1989;**25**(2):369–76.

Bruning 1990 ***{published data only}***

* Bruning PF, Bonfrer JMG, Wildiers J, Jassem J, Beex LVAM, Schorangel J, Nooijen WJ. Second-line endocrine

treatment of postmenopausal advanced breast cancer preliminary endocrine results of a 5-arm randomized phase II trial of medium vs low dose aminoglutethimide, with or without hydrocortisone vs hydrocortisone alone (EORTC 10861). *Journal of Steroid Biochemistry* 1990;**37**(6):1013–9.

Dixon 2000 *{published data only}*

* Dixon JM, Renshaw L, Bellamy C, Stuart M, Hoctin-Boes G, Miller WR. The effects of neoadjuvant anastrozole (Arimidex) on tumor volume in postmenopausal women with breast cancer: a randomized, double-blind, single-center study. *Clinical Cancer Research* 2000;**6**(6):2229–35.

Dowsett 1989 *{published data only}*

Dowsett M, Cunningham DC, Stein RC, Evans S, Dehennin L, Hedley A, Coombes RC. Dose-related endocrine effects and pharmokinetics of oral and intramuscular 4-hydroxyandrostenedione in postmenopausal breast cancer patients. *Cancer Research* 1989;**49**:1306–12.

Dowsett 1990 *{published data only}*

* Dowsett M, Stein RC, Mehta A, Coombes RC. Potency and selectivity of the non-steroidal aromatase inhibitor CGS 16949A in postmenopausal breast cancer patients. *Clinical Endocrinology* 1990;**32**:623–34.

Dowsett 1994 *{published data only}*

Bonnefoi HR, Smith IE, Dowsett M, Trunet, Houston SJ, da Luz RJ, et al.Therapeutic effects of the aromatase inhibitor fadrozole hydrochloride in advanced breast cancer. *British Journal of Cancer* 1996;**73**:539–42.

* Dowsett M, Smithers D, Moore J, Trunet PF, Coombes RC, Powles TJ, et al.Endocrine changes with the aromatase inhibitor fadrozole hydrochloride in breast cancer. *European Journal of Cancer* 1994;**30A**(10):1453–8.

Dowsett 1995 *{published data only}*

* Dowsett M, Jones A, Johnston SRD, Jacobs S, Trunet P, Smith IE. In vivo measurement of aromatase inhibition by letrozole (CGS 20267) in postmenopausal patients with breast cancer. *Clinical Cancer Research* 1995;**1**:1511–5.

Geisler 1996 *{published data only}*

* Geisler J, King N, Dowsett M, Ottestad L, Lundgren S, Walton P, et al.Influence of anastrozole (Arimidex), a selective, non-steroidal aromatase inhibitor, on in vivo aromatisation and plasma oestrogen levels in post menopausal women with breast cancer. *British Journal of Cancer* 1996;**74**:1286–91.

Geisler 2002 *{published data only}*

* Geisler J, Haynes B, Anker G, Dowsett M, Loenning PE. Influence of letrozole and anastrozole on totla body aromatization and plasma estrogen levels in postmenopausal breast cancer patients evaluated in a randomised, cross-over study. *Journal of Clinical Oncology* 2002;**20**(3):751–7.

Ingle 1997 *{published data only}*

* Ingle JN, Johnson PA, Suman VJ, Gerstner JB, Mailliard JA, Camoriano JK, et al.A randomized phase II trial of two dosage levels of letrozole as third-line hormonal therapay for women with metastatic breast carcinoma. *Cancer* 1997;**80**: 218–24.

Johnston 1994 *{published data only}*

* Johnston SRD, Smith IE, Doody D, Jacobs S, Robertshaw H, Dowsett M. Clinical and endocrine effects of the oral aromatase inhibitor vorozole in postmenopausal patients with advanced breast cancer. *Cancer Research* 1994;**54**: 5875–81.

Miller 1996b *{published data only}*

* Miller AA, Lipton A, Henderson IC, Navari R, Mulagha MT, Cooper J. Fadrozole hydrochloride in postmenopausal patients with metastatic breast carcinoma. *Cancer* 1996;**78**: 789–93.

Pronzato 1993 *{published data only}*

* Pronzato P, Rubagotti A, Amoroso D, Bertelli G, Queirolo P, Sertoli MR, Rosso M, et al.Second-line hormone therapy for breast cancer. Uselessness of first-line continuation. *American Journal of Clinical Oncology* 1993;**16**(6):522–5.

Raats 1992 *{published data only}*

Falkson G, Raats JI, Falkson H. Fadrozole hydrochloride, a new nontoxic aromatase inhibitor for the treatment of patients with metastatic breast cancer. *Journal of Steroid and Biochemistry and Molecular Biology* 1992;**43**(1-3):161–5.

* Raats JI, Falkson G, Falkson H. A study of fadrozole, a new aromatase inhibitor, in postmenopasual women with advanced metastatic breast cancer. *Journal of Clinical Oncology* 1992;**10**(1):111–6.

Svenstrup 1994 *{published data only}*

* Svenstrup B, Herrstedt J, Bruenner N, Bennet P, Wachmann H, Dombernowsky P. Sex hormone levels in postmenopausal women with advanced metastatic breast cancer treated with CGS 169 49A. *European Journal of Cancer* 1994;**30A**(9):1254–8.

Wang 2003 *{published data only}*

* Wang HQ, Ren CC, Feng WJ, Lin MB, Xiong YQ, Huang P, Zhao WH, Hao XS, Chen SB, Yan Z. Treatment of advanced metastatic breast cancer with exemestane, a multicenter randomized controlled study of 195 cases. *Zhonghua Yi Xue Za Zhi* 2003;**83**(3):188–90.

References to ongoing studies

ECOG E4101 *{published data only}*

ECOG E4101. Ongoing study Starting date of trial not provided. Contact author for more information.

Efect *{published data only}*

Efect

Phase III. Ongoing study Starting date of trial not provided. Contact author for more information.

ICR-CTSU Sofea *{published data only}*

Sofea

Phase III. Ongoing study March 2004.

Paridaens 2003 *{published data only}*

Phase III EORTC-10951. Ongoing study Starting date of trial not provided. Contact author for more information.

Additional references

Beatson 1896

Beatson GT. On the treatment of inoperable cases of carcinoma of the mamma. Suggestions for a new method of treatment with illustrative cases. *Lancet* 1896;**2**:104–7.

Ferlay 2000

Ferlay J, Bray F, Pisani P, Parkin DM. Globocan 2000: Cancer Incidence, Mortality and Prevalence Worldwide. 1. Lyon: IARC Press, 2001.

Hayward 1977

Hayward JL, Carbone PP, Heuson JC, Kumaoka S, Segaloff A, Rubens RD. Assessment of response to therapy in advanced breast cancer: a project of the Programme on Clinical Oncology of the International Union Against Cancer, Geneva, Switzerland. *Cancer* 1977;**39**(3):1289–94.

Howell 1997

Howell A, Dowsett M. Recent advances in endocrine therapy of breast cancer. *British Medical Journal* 1997;**315**: 863–6.

Ibrahim 1995

Ibrahim NK, Buzdar AU. Aromatase inhibitors: current status. *American Journal of Clinical Oncology* 1995;**18**(5): 407–17.

Jonat 1996

Jonat W, Howell A, Blomqvist C, et al.A randomized trial comparing two doses of the new selective aromatase inhibitor anastrazole (Arimidex) with megestrol acetate in postmenopausal women with advanced breast cancer. *European Journal of Cancer* 1996;**32A**:404–412.

Miller 1996a

Miller WR. Aromatase inhibitors. *Endocrine-related Cancer* 1996;**3**:65–79.

Parmar 1995

Parmar MKB, Machin D. *Survival analysis: A Practical Approach*. John Wiley, 1995.

Roseman 1997

Roseman BJ, Buzdar AU, Singletary SE. Use of aromatase inhibitors in postmenopausal women with advanced breast cancer. *Journal of Surgical Oncology* 1997;**66**:215–20.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

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

Bonneterre 2001 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Buzdar 1996a

Methods	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)
Participants	Age range 29 - 97 Advanced breast cancer Progressed on anti-oestrogen for advanced disease or progressed on or during adjuvant TAM WHO perf status < 3
Interventions	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
Outcomes	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
Notes	FU median duration 6m 3 no treatment, 1 wrong treatment, 8 lost to FU Intention to treat analysis

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

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 metastic 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

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Buzdar 1996c

Methods	Protocol 06 Multicentre, 55 sites, N = 303 Oct 1989 - Aug 1992 Double-blind, parallel, controlled equivalence Randomisation method not specified
Participants	Age range 36 - 92 Metastatic breast cancer At least one prior hormonal treatment for metastic 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*)

	Assessable patients: 150 v 148 Patients evaluable for toxicity:152 v 151 Drug code broken 18m after end of enrolment Treatment continued until disease progression
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

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Buzdar 2001

Methods	International, multicentre, 120 sites in US, Canada, Europe, N = 602 Three arm study (only two arms inculded 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 antioestrogen 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

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

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: minumum 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

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

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, 1:1:1allocation 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

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

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*)

	Minimum treatment 8w
Outcomes	Survival, TTF, duration of overall response, toxicity, objective response rates,
Notes	FU 14 to 1122d, median FU 153d Intention to treat analysis 2 ineligible, 1 lost to FU 74 patients evaluable

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Gershanovich 1998

Methods	International, multicentre, 11 countries, 86 sites N = 555 Three arm study (only two arms included in review N = 363) Open-label 1:1:1 Baseline no major differences
Participants	Median age letrozole 2.5mg 66y, letrozole 0.5 mg 64y, AG 65y Advanced or metastatic breast cancer Measurable/evaluable advanced disease WHO perf status < 3
Interventions	letrozole 2.5mg v letrozole 0.5mg v AG 500 mg Numbers in each treatment arm: 185 v 192 v 178 (letrozole 2.5mg arm excluded from review N = 192) Assessable patients: 173 v 162
Outcomes	Response, TTP, TTF, survival, tolerability and safety, overall survival
Notes	FU duration median > 20m 44 not assessable & counted as non-responders in the analysis Median duration of treatment 5m Modified intention to treat population ie enrolled and received study medication

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Kaufmann 2000

Methods	International, multicentre, Oct 1995 - May 1998, 19 countries, 144 centres N = 769 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

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

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

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

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		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

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		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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 Histologicaly 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*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

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

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Perez Carrion 1994

Methods	International, multicentre, May 1988 - December 1990, N = 409 Open study, equivalence trial Baseline characteristics well matched
Participants	Age range 38 - 87 WHO perf status < 3

Perez Carrion 1994 (*Continued*)

Interventions	formestane 250mg im v TAM 30mg Numbers in each treatment arm: 203 v 206 Assessable patients: 173 v 175
Outcomes	Response, survival, TTP, TTF, tolerability
Notes	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

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Powles 1984

Methods	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
Participants	Patients with disseminated breast cancer who had not previously received TAM, AG or danazol No endocrine or chemotherapy within 6w
Interventions	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
Outcomes	Tumour response
Notes	FU duration not reported

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

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*)

Outcomes	Primary - TTP Secondary- objective response, duration of response, rate and duration of overall clinical benefit, overall survival, general safety
Notes	FU duration not reported

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Russell 1997

Methods	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
Participants	Age range 33 - 92 Progressive metastatic disease Measurable or evaluable lesion Patients had received TAM in advanced setting No prior MA or AG
Interventions	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
Outcomes	Response, TTF, survival, toxicity
Notes	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

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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 (*Continued*)

	Analysis on data to Dec 1995, median FU of survivors 3y	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Thuerlimann 1997

Methods	Feb 1991 - Jun 1995, N = 179 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		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Tominaga 2003

Methods	Japan, multicentre, 62 sites, N = 157 Double blind, double dummy, parallel groups Adaptive dynamic balancing method	

Tominaga 2003 (*Continued*)

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

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

KPS - Karnofsky Performance Status
AG - aminoglutethimide
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

w/o - without

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

Study	Reason for exclusion
Abe 2002	dose comparison of same AI (letrozole)
Bajetta 1994	dose comparison of same AI (formestane)
Bajetta 1997	dose comparison of same AI (exemestane)
Bajetta 1997a	dose comparison of same AI (letrozole)
Bajetta 1999	dose comparison of same AI (letrozole)
Beretta 1990	dose comparison of same AI (letrozole)
Bruning 1989	dose comparison of same AI (aminoglutethimide)
Bruning 1990	dose comparison of same AI (aminoglutethimide)
Dixon 2000	dose-comparison of same AI (anastrozole)
Dowsett 1989	dose-comparison of same AI (formestane)
Dowsett 1990	dose-comparison of same AI (fadrozole)
Dowsett 1994	dose-comparison of same AI (fadrozole)
Dowsett 1995	dose-comparison of same AI (letrozole)
Geisler 1996	outcome: aromatase levels and plasma oestrogen levels
Geisler 2002	outcome: aromatase levels and plasma oestrogen levels
Ingle 1997	dose comparison of same AI (letrozole)
Johnston 1994	dose comparison of same AI (vorozole)
Miller 1996b	dose comparison of same AI (fadrozole)
Pronzato 1993	AI (aminoglutethimide) versus same AI plus tamoxifen
Raats 1992	dose comparison of same AI (fadrozole)
Svenstrup 1994	dose comparison of same AI (fadrozole)

(*Continued*)

Wang 2003	Non-English paper.

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

ECOG E4101

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

Efect

Trial name or title	Efect Phase III
Methods	
Participants	Target accrual = 660 HR+ women with advanced disease who have previously received a non-steroidal AI therapy
Interventions	faslodex v exemestane
Outcomes	
Starting date	
Contact information	AstraZeneca
Notes	currently recruiting in North America, Europe, South Africa, South America, Russia and Israel

ICR-CTSU Sofea

Trial name or title	Sofea Phase III
Methods	
Participants	Target accrual = 750 women with metastatic disease who have failed after non-steroidal AI
Interventions	faslodes v 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

Paridaens 2003

Trial name or title	Phase III EORTC-10951
Methods	
Participants	Postmenopausal women with metastatic and progressive disease or locally recurrent and inoperable
Interventions	exemestane v tamoxifen
Outcomes	
Starting date	
Contact information	robert.paridaens@uz.kuleven.ac.be
Notes	phase II to phase III study

HR+ HER positive

DATA AND ANALYSES

Comparison 1. AI versus non-AI

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

5.6 letrozole 2.5 mg	4	1782	Odds Ratio (M-H, Random, 95% CI)	0.77 [0.61, 0.96]
5.7 vorozole 2.5 mg	1	452	Odds Ratio (M-H, Random, 95% CI)	1.25 [0.83, 1.88]
6 Objective response (randomised)	25	8458	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.77, 1.06]
6.1 aminoglutethimide (any dose)	7	1041	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.68, 1.64]
6.2 formestane 250 mg	2	586	Odds Ratio (M-H, Random, 95% CI)	1.13 [0.78, 1.65]
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 fadrozole 2 mg	5	1080	Odds Ratio (M-H, Random, 95% CI)	1.21 [0.87, 1.69]
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]

Comparison 2. AI versus non-AI: Toxicity

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 hot flushes	18		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 AI versus tamoxifen	7	2616	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.88, 1.29]
1.2 AI versus megestrol acetate	9	3379	Odds Ratio (M-H, Fixed, 95% CI)	1.77 [1.42, 2.20]
1.3 AI versus fulvestrant	1	846	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.70, 1.35]
1.4 AI versus medroxyprogesterone acetate	1	218	Odds Ratio (M-H, Fixed, 95% CI)	0.20 [0.06, 0.73]
2 nausea	15		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 AI versus tamoxifen	6	2548	Odds Ratio (M-H, Random, 95% CI)	1.29 [0.78, 2.13]
2.2 AI versus megestrol acetate	8	3208	Odds Ratio (M-H, Random, 95% CI)	1.84 [1.37, 2.47]
2.3 AI versus fulvestrant	1	846	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.71, 1.31]
3 vomiting	8		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 AI versus tamoxifen	2	1239	Odds Ratio (M-H, Fixed, 95% CI)	1.23 [0.79, 1.90]
3.2 AI versus megestrol acetate	5	2319	Odds Ratio (M-H, Fixed, 95% CI)	2.03 [1.42, 2.90]
3.3 AI versus fulvestrant	1	846	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.60, 1.35]
4 diarrhoea	9		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 AI versus tamoxifen	3	2149	Odds Ratio (M-H, Fixed, 95% CI)	1.64 [1.06, 2.55]
4.2 AI versus megestrol acetate	5	1961	Odds Ratio (M-H, Fixed, 95% CI)	1.48 [1.02, 2.13]
4.3 AI versus fulvestrant	1	397	Odds Ratio (M-H, Fixed, 95% CI)	1.41 [0.84, 2.35]
5 rash	12		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 AI versus tamoxifen	4	711	Odds Ratio (M-H, Random, 95% CI)	33.61 [4.71, 239.97]
5.2 AI versus megestrol acetate	6	2496	Odds Ratio (M-H, Random, 95% CI)	1.83 [0.77, 4.39]
5.3 AI versus medroxyprogesterone acetate	1	218	Odds Ratio (M-H, Random, 95% CI)	111.71 [6.75, 1849.91]
5.4 AI versus fulvestrant	1	397	Odds Ratio (M-H, Random, 95% CI)	1.39 [0.77, 2.50]
6 vaginal bleeding	4		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 AI versus tamoxifen	1	1017	Odds Ratio (M-H, Fixed, 95% CI)	0.45 [0.16, 1.32]
6.2 AI versus megestrol acetate	2	915	Odds Ratio (M-H, Fixed, 95% CI)	0.29 [0.13, 0.65]
6.3 AI versus medroxyprogesterone acetate	1	218	Odds Ratio (M-H, Fixed, 95% CI)	0.10 [0.01, 0.77]
7 thromboembolic	6		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 AI versus tamoxifen	2	1228	Odds Ratio (M-H, Fixed, 95% CI)	0.48 [0.27, 0.85]
7.2 AI versus megestrol acetate	3	863	Odds Ratio (M-H, Fixed, 95% CI)	0.54 [0.26, 1.10]
7.3 AI versus fulvestrant	1	846	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.56, 2.31]

8 arthralgia	6		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 AI versus tamoxifen	2	1031	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.81, 1.60]
8.2 AI versus megestrol acetate	4	1439	Odds Ratio (M-H, Fixed, 95% CI)	1.40 [0.98, 2.00]

Comparison 3. Current AIs versus non-AI

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

Comparison 4. Current AIs versus non-AI: Toxicity

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

2.2 AI versus megestrol acetate	4	2036	Odds Ratio (M-H, Fixed, 95% CI)	1.45 [1.09, 1.95]
2.3 AI versus fulvestrant	1	846	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.71, 1.31]
3 vomiting	5		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 AI versus tamoxifen	1	1017	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.67, 1.72]
3.2 AI versus megestrol acetate	3	1636	Odds Ratio (M-H, Fixed, 95% CI)	1.77 [1.11, 2.83]
3.3 AI versus fulvestrant	1	846	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.60, 1.35]
4 diarrhoea	6		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 AI versus tamoxifen	2	1927	Odds Ratio (M-H, Fixed, 95% CI)	1.49 [0.95, 2.35]
4.2 AI versus megestrol acetate	3	1278	Odds Ratio (M-H, Fixed, 95% CI)	2.40 [1.34, 4.29]
4.3 AI versus fulvestrant	1	397	Odds Ratio (M-H, Fixed, 95% CI)	1.41 [0.84, 2.35]
5 rash	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 AI versus megestrol acetate	3	1636	Odds Ratio (M-H, Random, 95% CI)	1.63 [0.47, 5.70]
5.2 AI versus fulvestrant	1	397	Odds Ratio (M-H, Random, 95% CI)	1.39 [0.77, 2.50]
6 vaginal bleeding	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 AI versus tamoxifen	1	1017	Odds Ratio (M-H, Fixed, 95% CI)	0.45 [0.16, 1.32]
6.2 AI versus megestrol acetate	2	915	Odds Ratio (M-H, Fixed, 95% CI)	0.29 [0.13, 0.65]
7 thromboembolic	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 AI versus tamoxifen	1	1017	Odds Ratio (M-H, Fixed, 95% CI)	0.53 [0.30, 0.96]
7.2 AI versus megestrol acetate	1	515	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.30, 1.73]
7.3 AI versus fulvestrant	1	846	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.56, 2.31]
8 arthralgia	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 AI versus tamoxifen	2	1031	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.81, 1.60]
8.2 AI versus megestrol acetate	1	363	Odds Ratio (M-H, Fixed, 95% CI)	1.77 [0.89, 3.51]

Comparison 5. AI versus different AI

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival (reported)	1		HR (Fixed, 95% CI)	Subtotals only
1.1 letrozole	1		HR (Fixed, 95% CI)	0.64 [0.49, 0.84]
2 Progession-free survival (reported or calculated)	1		HR (Fixed, 95% CI)	Subtotals only
2.1 letrozole	1		HR (Fixed, 95% CI)	0.72 [0.57, 0.91]
3 Clinical benefit (assessable)	4		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 letrozole	3	1092	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.56, 0.93]
3.2 anastrozole	2	663	Odds Ratio (M-H, Fixed, 95% CI)	1.29 [0.92, 1.79]
4 Objective response (assessable)	4		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 letrozole	3	1092	Odds Ratio (M-H, Fixed, 95% CI)	0.53 [0.39, 0.73]
4.2 anastrozole	2	663	Odds Ratio (M-H, Fixed, 95% CI)	1.59 [1.07, 2.37]
5 Clinical benefit (randomised)	4		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 letrozole	3	1233	Odds Ratio (M-H, Fixed, 95% CI)	0.74 [0.57, 0.94]
5.2 anastrozole	2	773	Odds Ratio (M-H, Fixed, 95% CI)	1.25 [0.90, 1.72]
6 Objective response (randomised)	4		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 letrozole	3	1233	Odds Ratio (M-H, Fixed, 95% CI)	0.54 [0.40, 0.74]
6.2 anastrozole	2	782	Odds Ratio (M-H, Fixed, 95% CI)	1.50 [1.01, 2.23]

Comparison 6. AI as first-line therapy versus any other therapy (tamoxifen)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival (reported or calculated)	2		HR (Fixed, 95% CI)	0.96 [0.81, 1.13]
1.1 anastrozole as first-line therapy	1		HR (Fixed, 95% CI)	0.97 [0.81, 1.16]
1.2 fadrozole as first-line therapy	1		HR (Fixed, 95% CI)	0.91 [0.63, 1.32]
2 Progression-free survival (reported or calculated)	3		HR (Fixed, 95% CI)	0.78 [0.70, 0.86]
2.1 formestane as first-line therapy	1		HR (Fixed, 95% CI)	0.93 [0.68, 1.28]
2.2 anastrozole as first-line therapy	1		HR (Fixed, 95% CI)	0.82 [0.71, 0.95]
2.3 letrozole as first-line therapy	1		HR (Fixed, 95% CI)	0.70 [0.60, 0.82]
3 Clinical benefit (assessable)	8	3036	Odds Ratio (M-H, Random, 95% CI)	0.70 [0.51, 0.97]
3.1 aminoglutethimide (any dose)	2	263	Odds Ratio (M-H, Random, 95% CI)	0.67 [0.39, 1.13]
3.2 formestane 250 mg	1	348	Odds Ratio (M-H, Random, 95% CI)	1.36 [0.87, 2.13]
3.3 anastrozole 1 mg	2	1259	Odds Ratio (M-H, Random, 95% CI)	0.48 [0.16, 1.44]
3.4 exemestane 25 mg	1	113	Odds Ratio (M-H, Random, 95% CI)	0.47 [0.22, 0.99]
3.5 fadrozole 2 mg	1	209	Odds Ratio (M-H, Random, 95% CI)	1.09 [0.58, 2.06]
3.6 letrozole 2.5 mg	1	844	Odds Ratio (M-H, Random, 95% CI)	0.63 [0.48, 0.82]
4 Objective response (assessable)	10	3287	Odds Ratio (M-H, Random, 95% CI)	0.81 [0.62, 1.06]
4.1 aminoglutethimide (any dose)	3	440	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.50, 1.61]
4.2 formestane 250 mg	1	348	Odds Ratio (M-H, Random, 95% CI)	1.20 [0.77, 1.87]
4.3 anastrozole 1 mg	2	1259	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.65, 1.11]
4.4 exemestane 25 mg	1	113	Odds Ratio (M-H, Random, 95% CI)	0.26 [0.11, 0.62]
4.5 fadrozole 2 mg	2	283	Odds Ratio (M-H, Random, 95% CI)	1.20 [0.69, 2.09]
4.6 letrozole 2.5 mg	1	844	Odds Ratio (M-H, Random, 95% CI)	0.58 [0.42, 0.78]
5 Clinical benefit (randomised)	8	3210	Odds Ratio (M-H, Random, 95% CI)	0.75 [0.55, 1.02]
5.1 aminoglutethimide (any dose)	2	292	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.38, 2.08]
5.2 formestane 250 mg	1	409	Odds Ratio (M-H, Random, 95% CI)	1.25 [0.85, 1.86]
5.3 anastrozole 1 mg	2	1259	Odds Ratio (M-H, Random, 95% CI)	0.48 [0.16, 1.44]
5.4 exemestane 25 mg	1	122	Odds Ratio (M-H, Random, 95% CI)	0.55 [0.27, 1.13]
5.5 fadrozole 2 mg	1	221	Odds Ratio (M-H, Random, 95% CI)	1.23 [0.69, 2.21]
5.6 letrozole 2.5 mg	1	907	Odds Ratio (M-H, Random, 95% CI)	0.65 [0.50, 0.84]
6 Objective response (randomised)	10	3505	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.65, 1.11]
6.1 aminoglutethimide (any dose)	3	507	Odds Ratio (M-H, Random, 95% CI)	1.01 [0.52, 1.96]
6.2 formestane 250 mg	1	409	Odds Ratio (M-H, Random, 95% CI)	1.18 [0.77, 1.80]
6.3 anastrozole 1 mg	2	1259	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.65, 1.11]
6.4 exemestane 25 mg	1	122	Odds Ratio (M-H, Random, 95% CI)	0.30 [0.13, 0.69]
6.5 fadrozole 2 mg	2	301	Odds Ratio (M-H, Random, 95% CI)	1.28 [0.76, 2.15]
6.6 letrozole 2.5 mg	1	907	Odds Ratio (M-H, Random, 95% CI)	0.59 [0.43, 0.79]

Comparison 7. AI as second-line therapy versus any other therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival (reported or calculated)	2		HR (Fixed, 95% CI)	0.80 [0.66, 0.96]
1.1 anastrozole as second-line therapy	1		HR (Fixed, 95% CI)	0.78 [0.61, 1.00]
1.2 letrozole as second-line therapy	1		HR (Fixed, 95% CI)	0.82 [0.63, 1.07]
2 Progression-free survival (reported or calculated)	6		HR (Random, 95% CI)	1.08 [0.89, 1.31]
2.1 aminoglutethimide (any dose)	1		HR (Random, 95% CI)	1.25 [0.91, 1.72]
2.2 formestane 250 mg biweekly	1		HR (Random, 95% CI)	0.93 [0.68, 1.28]
2.3 anastrozole 1 mg	1		HR (Random, 95% CI)	1.34 [1.16, 1.55]
2.4 exemestane 25 mg	1		HR (Random, 95% CI)	0.82 [0.70, 0.97]
2.5 letrozole 2.5 mg	1		HR (Random, 95% CI)	0.98 [0.77, 1.25]
2.6 vorozole 2.5 mg	1		HR (Random, 95% CI)	1.27 [1.04, 1.56]
3 Clinical benefit (assessable)	11	3721	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.87, 1.14]
3.1 aminoglutethimide (any dose)	2	274	Odds Ratio (M-H, Fixed, 95% CI)	1.19 [0.74, 1.92]
3.2 formestane 250 mg biweekly	1	173	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.41, 1.39]
3.3 anastrozole 1mg	2	1367	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.84, 1.29]
3.4 exemestane 25 mg	1	703	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.66, 1.22]
3.5 fadrozole 2 mg	3	773	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.77, 1.41]
3.6 letrozole 2.5 mg	2	431	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.64, 1.42]
4 Objective response (assessable)	13	4170	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.81, 1.14]
4.1 aminoglutethimide (any dose)	3	348	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.66, 1.81]
4.2 formestane 250 mg biweekly	1	173	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.46, 2.25]
4.3 anastrozole 1 mg	2	1367	Odds Ratio (M-H, Fixed, 95% CI)	1.12 [0.84, 1.50]
4.4 exemestane 25 mg	1	703	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.54, 1.23]
4.5 fadrozole 2 mg	3	773	Odds Ratio (M-H, Fixed, 95% CI)	1.17 [0.76, 1.80]
4.6 letrozole 2.5 mg	2	431	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.41, 1.04]
4.7 vorozole 2.5 mg	1	375	Odds Ratio (M-H, Fixed, 95% CI)	0.70 [0.34, 1.42]
5 Clinical benefit (randomised)	11	3846	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.86, 1.12]
5.1 aminoglutethimide (any dose)	2	279	Odds Ratio (M-H, Fixed, 95% CI)	1.16 [0.72, 1.86]
5.2 formestane 250 mg biweekly	1	177	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.40, 1.31]
5.3 anastrozole 1 mg	2	1367	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.84, 1.29]
5.4 exemestane 25 mg	1	769	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.66, 1.19]
5.5 fadrozole 2 mg	3	779	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.77, 1.41]
5.6 letrozole 2.5 mg	2	475	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.65, 1.41]
6 Objective response (randomised)	13	4453	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.80, 1.12]