



**NATIONAL BREAST
CANCER CENTRE**

Incorporating the
Ovarian Cancer Program

AROMATASE INHIBITORS AS ADJUVANT THERAPY FOR POST-MENOPAUSAL WOMEN WITH HORMONE RECEPTOR-POSITIVE EARLY BREAST CANCER:

SUPPORTING EVIDENCE FOR THE NATIONAL BREAST CANCER
CENTRE HORMONAL THERAPIES GUIDELINES WORKING GROUP

MAY 2005

PREPARED BY THE NATIONAL BREAST CANCER CENTRE

FUNDED BY THE AUSTRALIAN GOVERNMENT
DEPARTMENT OF HEALTH AND AGEING

Aromatase inhibitors as adjuvant therapy for post-menopausal women with hormone receptor-positive early breast cancer: Supporting evidence for the National Breast Cancer Centre Hormonal Therapies Guidelines Working Group

was prepared and produced by:

The National Breast Cancer Centre

92 Parramatta Road, Camperdown NSW, Australia

Locked Bag 16, Camperdown NSW 1450

Telephone: +61 2 9036 3030

Fax: +61 2 9036 3077

Website: www.nbcc.org.au

Email: directorate@nbcc.org.au

© National Breast Cancer Centre 2006

ISBN Online: 978-1-74127-053-2

This work is copyright. Apart from any use as permitted under the Copyright Act 1968, no part might be reproduced by any process without prior written permission from the National Breast Cancer Centre. Requests and enquiries concerning reproduction and rights should be addressed to the Communications Manager, National Breast Cancer Centre, Locked Bag 16, Camperdown NSW 1450 Australia.

Recommended citation

National Breast Cancer Centre. *Aromatase inhibitors as adjuvant therapy for post-menopausal women with hormone receptor-positive early breast cancer: Supporting evidence for the National Breast Cancer Centre Hormonal Therapies Guidelines Working Group*. Camperdown, NSW: NBCC, 2006.

Disclaimer

The National Breast Cancer Centre does not accept any liability for any injury, loss or damage incurred by use of or reliance on the information. The National Breast Cancer Centre develops material based on the best available evidence, however it cannot guarantee and assumes no legal liability or responsibility for the currency or completeness of the information.

Copies of this report can be downloaded from the National Breast Cancer Centre website: www.nbcc.org.au

The National Breast Cancer Centre is funded by the Australian Government Department of Health and Ageing.

ACKNOWLEDGEMENTS

The National Breast Cancer Centre gratefully acknowledges the support of all the individuals and groups who contributed to the development of this review.

Funding

Funding for the development of this review was provided by the Australian Government Department of Health and Ageing.

Working Group

This review was developed with input from a multidisciplinary Working Group:

Associate Professor Martin Stockler (Chair)

Dr Fran Boyle

Dr Nicholas Wilcken

Professor Ian Olver

Mr David Oliver

Dr Melissa Bochner

Dr Liz Kenny

Ms Lee Millard

Dr Julie Thompson

Ms Susan Timbs

National Breast Cancer Centre Staff

The following people were involved in the development of this review:

Dr Elmer Villanueva

Ms Rosemary Vagg

Dr Alison Evans

Mr Andy Moore

Dr Karen Luxford

Dr Helen Zorbas

CONTENTS

List of Tables	vi
Aim	1
Methods	2
Selection criteria	2
Results	5
Methodological quality	5
Aromatase inhibitors as initial adjuvant endocrine therapy	6
Aromatase inhibitors as adjuvant endocrine therapy after 2-3 years of tamoxifen	12
Aromatase inhibitors as adjuvant endocrine therapy after 5 years of tamoxifen	16
Trials investigating the sequencing of aromatase inhibitors and tamoxifen as initial adjuvant therapy	20
Trials comparing aromatase inhibitors head-to-head	21
References	26
List of abbreviations	28
Appendix A: Search strategy	29
Appendix B: Study flow	30
Appendix C: Data tables	31

LIST OF TABLES

Table 1. Electronic databases used in the search	2
Table 2. Summary results for overall survival	23
Table 3. Summary results for disease-free survival*†	23
Table 4. Summary results for distant recurrence (a component of disease-free survival)*	24
Table 5. Summary results for ipsilateral breast recurrence (a component of disease-free survival)*	24
Table 6. Summary results for contralateral breast recurrence (a component of disease-free survival)*	24
Table 7. Summary results for local recurrence (a component of disease-free survival)*	25
Table 8. Summary results for serious adverse events*†	25

AIM

The aim of this review was to identify and evaluate evidence from randomised controlled trials on the effectiveness and safety of aromatase inhibitors (AIs) as adjuvant therapy for post-menopausal women with hormone receptor-positive early breast cancer in the following settings:

- as initial adjuvant therapy;
- after 2–3 years of tamoxifen; and
- after 5 years of tamoxifen.

In addition, evidence on the effectiveness and safety of adjuvant AI therapy for post-menopausal women with hormone receptor-positive early breast cancer was evaluated with regard to:

- its use in women for whom tamoxifen is contraindicated;
- sequencing of therapy (ie, AI as initial adjuvant therapy followed by tamoxifen compared with tamoxifen as initial adjuvant therapy followed by AI); and
- head-to-head comparisons of different AIs (ie, one AI compared with another).

METHODS

A sensitive search strategy was developed based on the identification of studies on the treatment of post-menopausal women with hormone receptor-positive early breast cancer (Appendix A). We searched electronic databases to May 2005 (Table 1) and performed limited hand-searching of a subset of journals and conference abstracts. Internet searches were used to supplement the information available on recently completed and ongoing trials.

Table 1. Electronic databases used in the search

Resource	Issue or access date
PubMed	May 2005
Medline (Ovid)	1966–May 2005
PreMedline (Ovid)	May 2005
CINAHL (Ovid)	1982–May 2005
Cochrane Library	Issue 2, 2005

In addition, reference lists of related systematic reviews were checked for additional trials that were not identified through electronic means.

The application of selection criteria followed a two-stage process. Studies were first eliminated on the basis of information contained in titles or abstracts. The full text of studies that were judged to meet selection criteria and those for which a decision could not be made on the basis of information found in the title and abstract were retrieved and examined. Evaluations were performed independently and any discrepancies were resolved by discussion. The studies that passed full text assessment form the basis of this review. Appendix B outlines the study flow.

SELECTION CRITERIA

TYPES OF STUDIES

Only randomised controlled trials were included. Systematic reviews were used to assist in identifying trials. For the examination of cost outcomes, studies employing other study designs were included.

TYPES OF PARTICIPANTS

The population of interest was post-menopausal women with hormone receptor-positive early breast cancer (positive for oestrogen receptors, progesterone receptors, or both).

TYPES OF INTERVENTIONS

The intervention of interest was third-generation AIs (anastrozole, letrozole, exemestane). Eligible comparators (depending on the specific research question) included tamoxifen, placebo or other AIs.

TYPES OF OUTCOME MEASURES

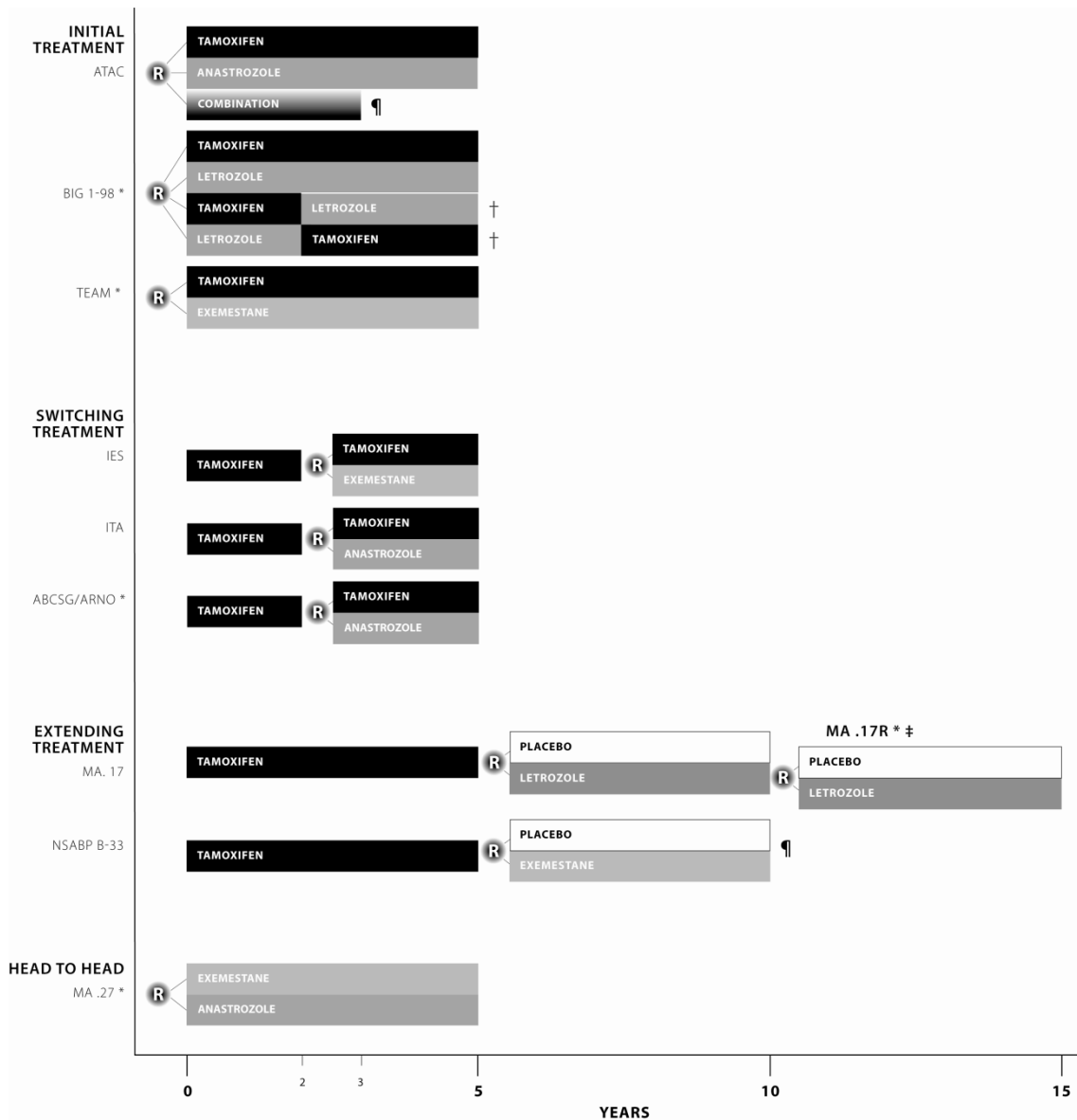
The outcomes of interest, listed in order of decreasing priority, are outlined below.

- Overall survival (OS), defined as the time from randomisation to death from any cause.
- Disease-free survival (DFS), variously defined as the time from randomisation to recurrence or death. Definitions of DFS are provided where available because of variations between the trials. For instance, all trials counted distant recurrences as events, but only some counted new contralateral breast cancers as events.
- Adverse events (AEs), including treatment-related death.
- Health-related quality of life (HRQoL).
- Costs and cost-effectiveness.

The quality of the included studies was assessed using four criteria: blinding, allocation concealment, comparability of subjects at baseline and use of intention-to-treat analysis principles.

All results are presented according to the research question under examination. Comparisons of treatments are presented as hazard ratios (HRs), odds ratios (ORs) or absolute differences. Where possible, 95% confidence intervals (CIs) and p-values are provided. Values calculated by the authors of this review are enclosed in braces (“{ }”). This is a systematic review, but not a meta-analysis. Results are summarised and tabulated, but not pooled together.

Figure 1. Study designs of included trials



* Ongoing trials. † These arms will provide evidence on effects of sequencing. ‡ MA.17R is a continuation of MA.17. ¶ Discontinued.

RESULTS

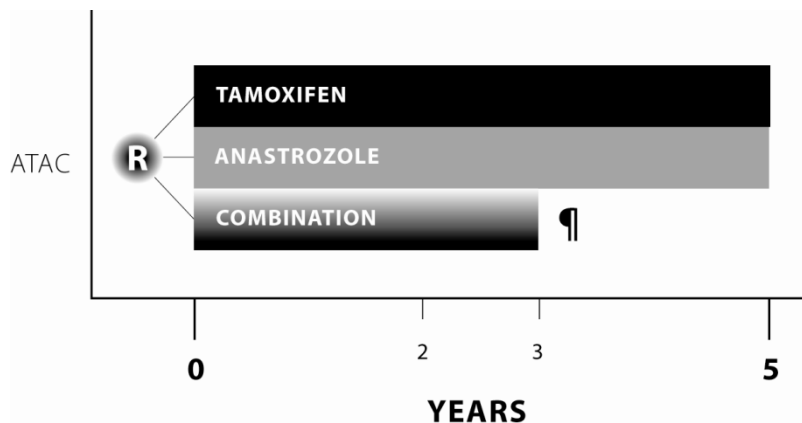
Information on nine trials was available. The major design attributes and interventions are described in Figure 1.

METHODOLOGICAL QUALITY

The methodological quality was high for all three trials whose major outcomes have been reported in the peer-reviewed literature (ATAC, IES, MA.17). Randomisation was centrally performed and coordinated, allocation was concealed, groups were similar at baseline and intention-to-treat analyses were applied. The methodological quality of trials presented at meetings and conference presentations could not be reliably assessed because of the limited information available.

AROMATASE INHIBITORS AS INITIAL ADJUVANT ENDOCRINE THERAPY

ARIMIDEX, TAMOXIFEN ALONE OR IN COMBINATION (ATAC) TRIAL



¶ Discontinued

Trial characteristics

The ATAC Trial¹⁻⁵ enrolled a total of 9366 post-menopausal women who had completed primary surgery and chemotherapy for invasive breast cancer. Women with unknown or negative hormone receptor status were eligible. Women were randomised to one of three treatment arms: 1 mg anastrozole daily (n=3125); 20 mg tamoxifen daily (n=3116); or anastrozole 1 mg plus tamoxifen 20 mg daily (n=3125). The combination arm was abandoned after an early interim analysis suggested that it was inferior to the other two arms.² There have been three reports of the main findings after median follow-up times of 33,¹ 47² and 68 months.⁴ In this section, results for the outcomes of interest from reports with the longest follow-up times are summarised.

Characteristics of the study population at baseline

The treatment groups were similar at baseline. The mean age was 64 years; 84% were known to have hormone receptor-positive disease, 8% were known to have hormone receptor-negative disease, and 8% had unknown hormone receptor status; 60% had no axillary lymph node involvement, a quarter had between one and three nodes involved and about 10% had at least four nodes involved. Tumours measuring 2 cm or less were present in about 63% of patients.

Findings

Overall survival

OS was similar in the tamoxifen and anastrozole arms (831 events in total [no group-specific information available]; HR 0.97; 95% CI 0.85, 1.12; p=0.7).

Disease-free survival

DFS was better on anastrozole than on tamoxifen (575 vs 651 events; HR 0.87; 95% CI 0.78, 0.97; p=0.01). Time to recurrence (defined as the time from randomisation to recurrence of disease) was better on anastrozole (402 vs 498 events; HR 0.79; 95% CI 0.70, 0.90; p=0.0005). Time to distant recurrence was better on anastrozole (324 vs 375 events; HR 0.86; 95% CI 0.74, 0.99; p=0.04). Fewer incident contralateral breast cancers developed on anastrozole (35 vs 59 events; HR 0.58; 95% CI 0.38, 0.88; p=0.01).

Adverse events

Withdrawals due to AEs were less common on anastrozole than tamoxifen (344 vs 442 events; p=0.0002). Treatment-related serious AEs were less common on anastrozole than tamoxifen (146 vs 271 events; p<0.0001).

The AEs that were more common on anastrozole than tamoxifen were: arthralgia (36% vs 29%; p<0.0001) and fractures (11% vs 8%; p<0.0001).

The AEs that were more common on tamoxifen than anastrozole were: hot flushes (36% vs 41% events; p<0.0001); vaginal bleeding (5% vs 10%; p<0.0001); vaginal discharge (4% vs 13%; p<0.0001); venous thromboembolic events (3% vs 4%; p=0.0004); ischaemic cerebrovascular events (2% vs 3%; p=0.03); deep venous thromboembolic events (1.6% vs 2.4%; p=0.02); and endometrial cancer (0.2% vs 0.8%; p=0.02).

The AEs that occurred with similar frequencies on anastrozole and tamoxifen were: mood disturbances (19% vs 18%; p=0.2); fatigue or tiredness (19% vs 18%; p=0.3); nausea and vomiting (13% vs 12%; p=0.7); cataracts (6% vs 7%; p=0.1); and ischaemic cardiovascular disease (4% vs 3%; p=0.1).

Health-related quality of life

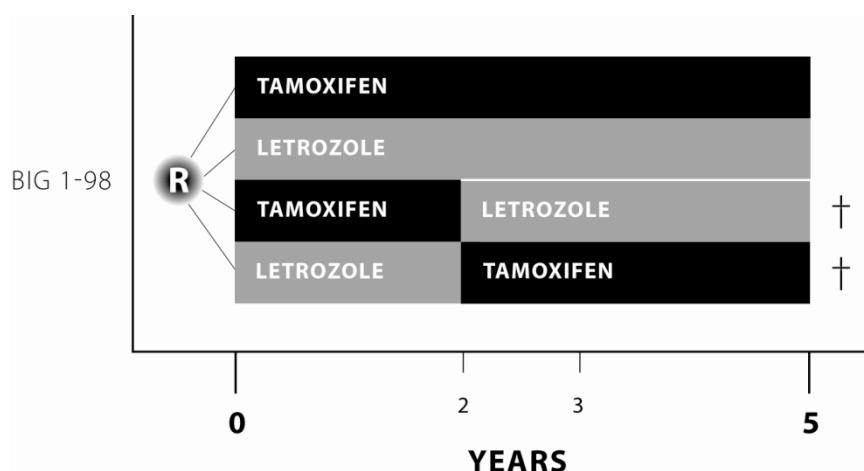
HRQoL was assessed in a subset of all 1105 patients (anastrozole n=335, tamoxifen n=347, combination n=339) using the Functional Assessment of Cancer Therapy-Breast (FACT-B) and an Endocrine Subscale (ES) questionnaire.³ The primary endpoint was the Trial Outcome Index (TOI) of the FACT-B, which is the sum of its physical well-being, functional well-being and breast cancer subscales. Baseline characteristics were well balanced across the treatment groups. There were no significant differences during treatment between the three groups in TOI scores, total ES scores, or other subscales at 3 and 24 months of follow-up. TOI scores improved to a similar extent over 24 months in all three groups. Scores for the physical well-being, functional well-being and breast cancer subscales were also similar in all three groups. Total ES scores in all three groups worsened over the first 3 months, and then stabilised between 3 and 24 months. Women on anastrozole reported significantly more vaginal dryness, painful intercourse and loss of sexual interest, but fewer cold sweats and less vaginal discharge than women on tamoxifen.

Cost-effectiveness

A decisional analysis model based on the ATAC data was presented at the 2004 San Antonio Breast Cancer Symposium.⁵ The model suggests that a cohort of 1000 post-menopausal women with hormone receptor-positive early breast cancer treated with

anastrozole would gain 215 quality-adjusted life years (QALYs) at an additional cost of US\$5.11 million over a 25-year horizon compared with tamoxifen treatment. The incremental cost-effectiveness ratio of anastrozole to tamoxifen was US\$23,740 per QALY gained or US\$29,132 per life-year gained.

ONGOING TRIAL: INTERNATIONAL BREAST CANCER STUDY GROUP (IBCSG) 18-98 / BIG 1-98 TRIAL



† These arms will provide evidence on effects of sequencing.

Trial characteristics

Information about the BIG 1-98 Trial was available from a presentation during the 2005 St Gallen Conference.⁶ The trial is designed to compare letrozole (2.5 mg daily) and tamoxifen (20 mg daily), used either on their own or sequentially. Patients randomised to the first two arms received either letrozole or tamoxifen for the entire 5 years. Those randomised to the last two arms received letrozole or tamoxifen for the first 2 years and then switched to the other drug for 3 years. Data are currently available only for the direct comparison of letrozole versus tamoxifen, which used complete information from the first two arms and the first 2 years of the last two arms (before switching, median follow-up 26 months).

Characteristics of the study population at baseline

BIG 1-98 randomized 8010 post-menopausal women who had completed primary surgery and chemotherapy for invasive breast cancer to letrozole (n=4003) or tamoxifen (n=4007). Only women with hormone receptor-positive tumours were eligible. Baseline characteristics were well balanced between the two arms. The median age of participants was 61 years; 52% were node-negative (41% had at least one node involved); and 65% had tumours measuring 2 cm or less.

Findings

Overall survival

There were fewer deaths on letrozole than on tamoxifen, but the difference was not statistically significant (166 vs 192; HR 0.86; p=0.08).

Disease-free survival

DFS was better on letrozole than tamoxifen (8.8% vs 10.7%; HR 0.81; 95% CI 0.70, 0.93; p=0.003). Local recurrence rates (defined as recurrence in the ipsilateral breast or chest wall) were lower on letrozole than tamoxifen (0.5% vs 0.9%; p=0.047). Contralateral breast cancers were less frequent on letrozole than tamoxifen, but the difference was not

significant (0.4% vs 0.7%; $p=0.13$). Distant recurrences were less frequent on letrozole than tamoxifen (4.4% vs 5.8%; $p=0.006$).

Adverse events

Adverse events more common on letrozole than tamoxifen included: hypercholesterolaemia (44% vs 19%; $\{p<0.001\}$) and bone fractures (6% vs 4%; $\{p<0.001\}$).

Adverse events less common on letrozole than tamoxifen included: hot flushes (34% vs 38%; $\{p<0.001\}$); night sweats (14% vs 16%; $\{p=0.007\}$); endometrial biopsies (2% vs 7%; $\{p<0.001\}$); vaginal bleeding (3% vs 7%; $\{p<0.001\}$); thromboembolic events (1% vs 2%; $\{p<0.001\}$) and invasive endometrial cancer (0.2% vs 0.4%; $\{p=0.08\}$).

No results were available on HRQoL or costs.

ONGOING TRIAL: TAMOXIFEN EXEMESTANE ADJUVANT MULTINATIONAL (TEAM) TRIAL



TEAM⁷ will examine the effectiveness and safety of exemestane versus tamoxifen as adjuvant therapy in post-menopausal women with hormone receptor-positive early breast cancer. The study planned to recruit 4400 patients (recruitment closed in October 2003), randomly allocated to five years of exemestane or tamoxifen treatment. Endpoints include relapse-free survival, OS, incidence of contralateral breast cancer, safety, tolerability and quality of life.

AROMATASE INHIBITORS AS ADJUVANT ENDOCRINE THERAPY AFTER 2–3 YEARS OF TAMOXIFEN

INTERGROUP EXEMESTANE STUDY (IES)



Trial characteristics

IES⁸ enrolled a total of 4742 post-menopausal women with histologically proven, oestrogen receptor-positive (or unknown receptor status), invasive breast cancer who had completed primary surgery and chemotherapy. Patients who had completed at least 2 years, but no more than 3 years and 1 month, of adjuvant tamoxifen therapy were randomised to receive oral exemestane (25 mg daily, n=2362) or tamoxifen (20 mg daily, n=2380) for a total of 5 years of adjuvant therapy. Results are available with a median follow-up time of 31 months.

Characteristics of the study population at baseline

Baseline characteristics for both groups were comparable. Patients had a mean age of 64 years; 81% had oestrogen receptor-positive disease, 55% had progesterone receptor-positive disease; 50% were node-negative, and 30% had one to three involved nodes.

Findings

Overall survival

OS was similar in the two arms. There were fewer deaths on exemestane than tamoxifen, but the difference was not statistically significant (93 {3.9%} vs 106 {4.4%}; HR 0.88; 95% CI 0.67, 1.16; p=0.41).

Disease-free survival

DFS (defined as freedom from recurrence, contralateral breast cancer or intercurrent death) was better on exemestane than tamoxifen (183 {7.7%} vs 266 {11.2%} events; HR 0.68; 95% CI 0.56, 0.82; p<0.001). No hazard ratios or comparative statistics were given for individual components of DFS.

Local recurrence only (21 {0.9%} vs 33 {1.4%}; {p by Fisher's exact test=0.132}), distant recurrence (114 {4.8%} vs 174 {7.3%}; {p by Fisher's exact test<0.001}) and primary cancers in the contralateral breast (9 {0.4%} vs 20 {0.8%}; p=0.04) were less common in women on exemestane.

Adverse events

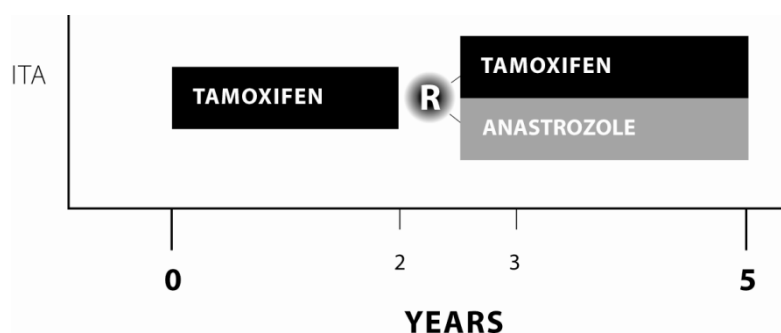
Withdrawals due to AEs were more common on exemestane than tamoxifen (138 vs 121). AEs more common in women on exemestane were: visual disturbances (170 [7.4%] vs 133 [5.7%]; $p=0.04$); osteoporosis (171 [7.4%] vs 133 [5.7%]; $p=0.05$); arthralgia (124 [5.4%] vs 85 [3.6%]; $p=0.01$); and diarrhoea (100 [4.3%] vs 54 [2.3%]; $p<0.001$).

AEs more common in women on tamoxifen were: gynaecologic symptoms (135 [5.8%] vs 211 [9.0%]; $p<0.001$); vaginal bleeding (93 [4.0%] vs 129 [5.5%]; $p=0.05$); cramps (64 [2.8%] vs 102 [4.4%]; $p<0.001$); and thromboembolic disease (24 [1.0%] vs 45 [1.9%]; $p=0.003$).

AEs for which there was no significant difference between exemestane and tamoxifen were: cardiovascular disease other than myocardial infarction (984 [43%] vs 913 [39%]; $p=0.11$); hot flushes (967 [42%] vs 923 [40%]; $p=0.28$); pain or aches (766 [33%] vs 684 [29%]; $p=0.17$); fatigue (545 [24%] vs 547 [24%]; $p=0.82$); insomnia (449 [20%] vs 406 [17%]; $p=0.30$); sweating (429 [19%] vs 418 [18%]; $p=0.95$); headaches (428 [19%] vs 378 [16%]; $p=0.09$); dizziness (288 [13%] vs 279 [12%]; $p=0.81$); nausea (248 [11%] vs 258 [11%]; $p=0.59$); and depression (120 [5%] vs 93 [4%]; $p=0.24$).

No results were available on HRQoL and costs.

ITALIAN TAMOXIFEN ARIMIDEX (ITA) TRIAL



Trial characteristics

Information about the ITA Trial was available from an abstract of the 2005 American Society of Clinical Oncology Annual Meeting.⁹ The ITA Trial enrolled a total of 448 post-menopausal women with oestrogen receptor-positive breast cancer with lymph node involvement who were taking tamoxifen 20 mg daily for at least two years. Patients were then randomised to receive anastrozole 1 mg daily (n=223) or continue tamoxifen (n=225) for a total treatment period of five years. Results are available with a median follow-up time of 52 months.

Characteristics of the study population at baseline

Baseline characteristics were similar in the two treatment groups. All patients had oestrogen receptor-positive tumours with involved lymph nodes.

Findings

Overall survival

There were fewer deaths on anastrozole than on tamoxifen, but the difference was not statistically significant (9 vs 17; HR 0.52; 95% CI 0.23, 1.17; p=0.1).

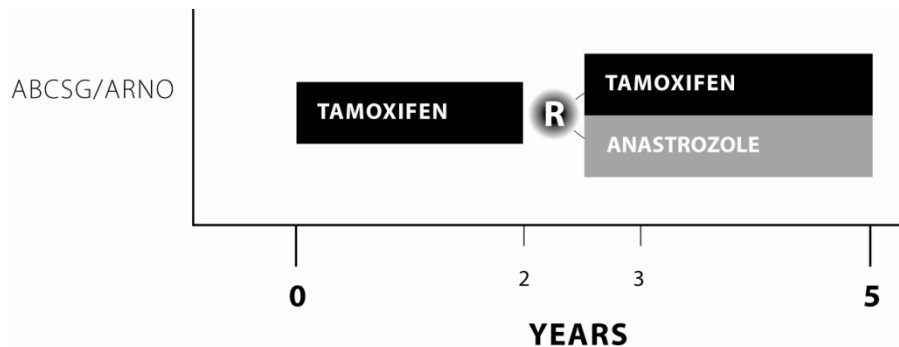
Disease-free survival

Relapse was less common on anastrozole than tamoxifen (HR 0.42; 95% CI 0.26, 0.66; p=0.0001), as were disease progression (HR 0.43; 95% CI 0.25, 0.73; p=0.001) and local progression (HR 0.13; 95% CI 0.03, 0.59; p=0.002). Distant progression was also less common on anastrozole, but not quite statistically significant (HR 0.57; 95% CI 0.32, 1.02; p=0.06).

Adverse events

The percentages of women developing at least one AE were similar in both arms (anastrozole 46% vs tamoxifen 40%; p=0.2). There were seven reported cases of endometrial cancer, six on tamoxifen and one on anastrozole (Relative Risk (RR) 0.17; 95% CI 0.02, 1.38; p=0.12). No results were available for HRQoL and costs.

ONGOING TRIALS: AUSTRIAN BREAST CANCER STUDY GROUP (ABCSG) 8 / ARIMIDEX-NOLVADEX (ARNO) 95 TRIALS



Trial characteristics

ABCSG 8 / ARNO 95 are two trials being conducted to examine the effectiveness and safety of anastrozole after two years of tamoxifen therapy versus continuing tamoxifen therapy for the remaining three years of adjuvant therapy in post-menopausal women with hormone receptor-positive early breast cancer. Preliminary results were reported at the 2004 San Antonio Breast Cancer Symposium.¹⁰ A total of 3123 patients were recruited and randomised to switch to anastrozole (n=1563) or continue tamoxifen (n=1560). Results are available with a median follow-up of 26 months.

Characteristics of the study population at baseline

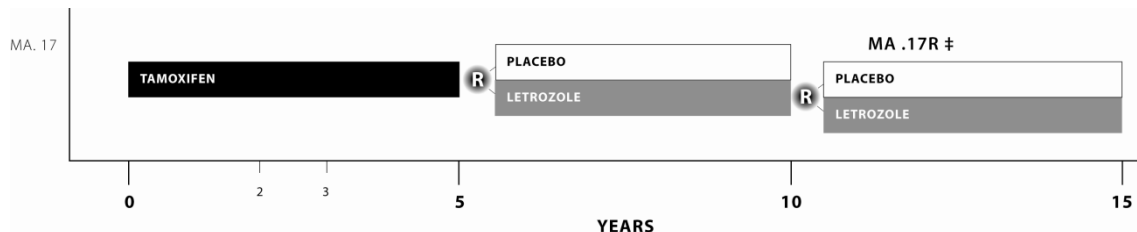
Patients had a mean age of 63 years, all had receptor-positive disease and 27% were node-positive.

Findings

Relapse-free survival (definition unavailable) was less common on anastrozole than continued tamoxifen (HR 0.59; 95% CI 0.42, 0.82; p=0.002). No results were available for AEs, HRQoL and costs.

AROMATASE INHIBITORS AS ADJUVANT ENDOCRINE THERAPY AFTER 5 YEARS OF TAMOXIFEN

MA.17 TRIAL



‡ MA.17R is a continuation of MA.17.

Trial characteristics

The MA.17 Trial^{11–13} enrolled a total of 5187 post-menopausal women with histologically proven, hormone receptor-positive, invasive breast cancer who had completed primary surgery, chemotherapy, and 4.5 to 6 years of adjuvant tamoxifen therapy that had been stopped for less than three months. Patients were randomly assigned to receive 2.5 mg of letrozole daily (n=2593) or placebo (2594) for 5 years. Results are available with a median follow-up of 2.4 years.

Characteristics of the study population at baseline

Baseline characteristics were similar in the two treatment groups. Patients had a median age of 62 years; 98% had hormone receptor-positive disease and half the cancers were node-negative.

Findings

Overall survival

OS at 4 years was similar for both groups (letrozole 96% vs placebo 94%; difference 2.4%; 95% CI -0.9%, 5.6%), and while there were fewer deaths on letrozole than placebo, this difference was not statistically significant (31 vs 42 deaths, p=0.25).

Disease-free survival

DFS at 4 years was better on letrozole than tamoxifen (93% vs 87%; difference 6%; 95% CI 2%, 10%; p<0.001). Comparisons for individual components of DFS were not reported. Events significantly less common on letrozole than placebo were: local ipsilateral breast recurrence only (6 vs 19, {p=0.02}); local ipsilateral chest wall recurrence only (2 vs 7, {p=0.18}); incident cancer in contralateral breast only (14 vs 26, {p=0.08}); and distant recurrence (47 vs 76, {p=0.01}).

Adverse events

Withdrawals due to AEs occurred in similar numbers of women on letrozole and placebo (256 vs 254). AEs more common in women on letrozole were: hot flushes (47% vs 40%; p<0.001); arthralgia (21% vs 17%; p<0.001); myalgia (12% vs 10%; p=0.02); and arthritis (6% vs 4%; p<0.001).

Vaginal bleeding was the only AE less common on letrozole than placebo (4% vs 6%; p=0.01).

AEs that were not statistically significantly different between the two arms (letrozole vs placebo) were: fatigue (30% vs 28%; p=0.26); sweating (22% vs 21%; p=0.28); headache (18% vs 19%; p=0.65); oedema (17% vs 16%; p=0.17); dizziness (12% vs 11%; p=0.54); hypercholesterolaemia (12% vs 12%; p=0.67); constipation (10% vs 10%; p=0.72); osteoporosis (6% vs 4%; p=0.07); cardiovascular events (4.1% vs 3.6%; p=0.40); and clinical fractures (3.6% vs 2.9%; p=0.24).

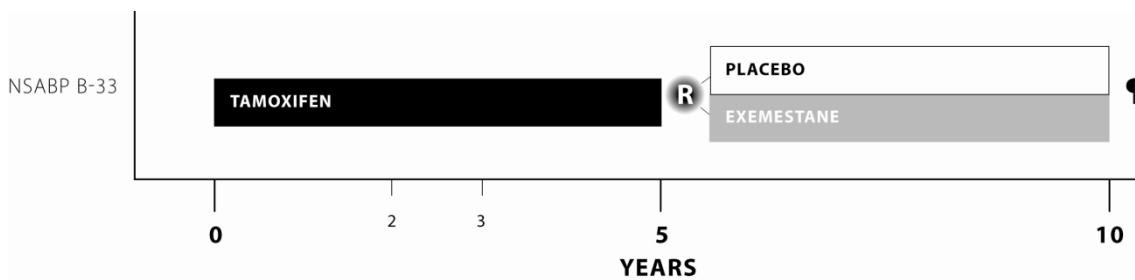
Health-related quality of life

A subset of patients (3582 of 5187) enrolled in the MA.17 Trial participated in the HRQoL substudy.¹³ Quality of life was assessed with a generic measure of health status (SF-36) and a disease-specific questionnaire (Menopause Specific Quality of Life [MENQOL]) at baseline, 6 months from randomisation and annually thereafter. There were no statistically significant differences between groups in mean change scores over the period of the study. Quality of life subdomains showed small to moderate (less than 0.3 standard deviations) impairments in physical functioning, bodily pain, vitality, vasomotor symptoms and sexual function in women on letrozole.

Cost-effectiveness

A decision analysis model based on the MA.17 data was presented at the 2004 San Antonio Breast Cancer Symposium.¹² The model suggests that the incremental cost-effectiveness ratio of letrozole to placebo was US\$17,640 per life year gained.

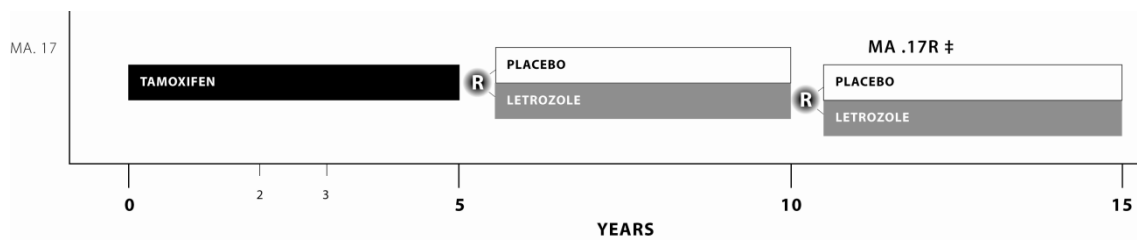
ONGOING TRIAL: NSABP B-33 TRIAL



|| Discontinued

The NSABP B-33 Trial¹⁴ is examining the effectiveness and safety of 5 years of exemestane versus placebo in post-menopausal women with receptor-positive breast cancer who have completed surgery, chemotherapy and 5 years of tamoxifen. The study aimed to randomise 3000 women to exemestane 25 mg or placebo daily for 5 years. Endpoints of interest include DFS, OS, time to treatment failure, height, fractures, bone mineral density and quality of life. Recruitment to this trial was closed in June 2003 following dissemination of the results of MA.17.

ONGOING TRIAL: MA.17R TRIAL

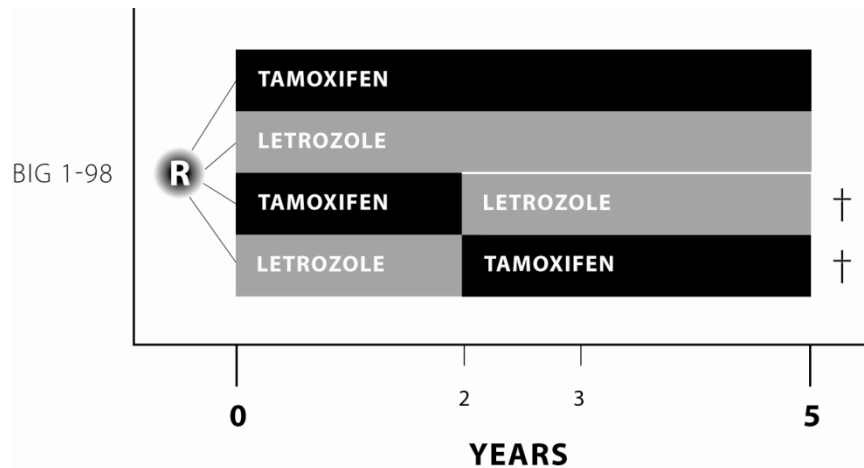


‡ MA.17R is a continuation of MA.17.

Based on information presented at the Primary Therapy of Early Breast Cancer 9th International Conference in St Gallen, Switzerland, MA.17R¹⁵ will examine the effectiveness and safety of 5 years of letrozole versus placebo in 1800 women who have completed 5 years of letrozole in the experimental arm of MA.17.

TRIALS INVESTIGATING THE SEQUENCING OF AROMATASE INHIBITORS AND TAMOXIFEN AS INITIAL ADJUVANT THERAPY

ONGOING TRIAL: IBCSG 18-98 / BIG 1-98 TRIAL

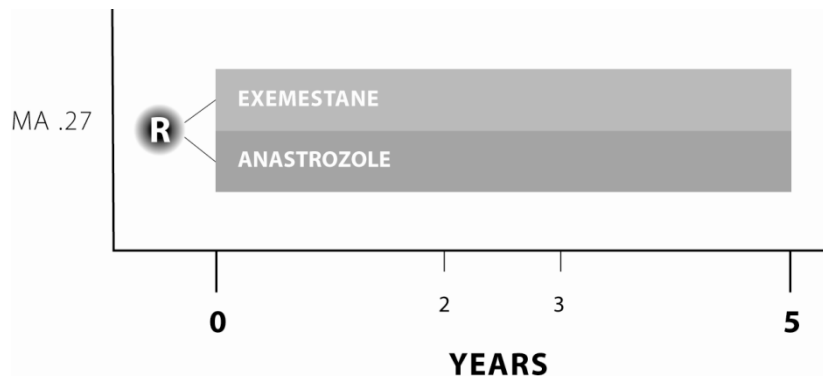


† These arms will provide evidence on effects of sequencing.

Information about the BIG 1-98 Trial was available from a presentation during the Primary Therapy of Early Breast Cancer 9th International Conference in St Gallen, Switzerland.⁶ The trial was designed as a four-arm study comparing letrozole (2.5 mg daily) with tamoxifen (20 mg daily) for 5 years. Patients randomised to the first two arms received either letrozole or tamoxifen for the entire 5 years. Those randomised to the last two arms received letrozole or tamoxifen for the first 2 years and switched drugs for the remaining 3 years. Data are available only for the primary core analysis (median follow-up of 26 months), which used complete information from the first two arms and the first 2 years of the last two arms.

TRIALS COMPARING AROMATASE INHIBITORS HEAD-TO-HEAD

ONGOING TRIAL: MA.27 TRIAL



The MA.27 Trial¹⁶ is examining the effectiveness and safety of exemestane versus anastrozole as adjuvant therapy in post-menopausal women with receptor-positive breast cancer. MA.27 aims to randomise 6830 women to either exemestane or anastrozole daily for 5 years. The trial was originally designed to also test the effect of adding celecoxib, but this component was dropped when information became available about the adverse cardiac effects of celecoxib. The primary endpoint is event-free survival. Secondary outcomes include OS, time to distant recurrence, incidence of contralateral breast cancer, clinical fractures, cardiovascular mortality and morbidity, and toxic effects.

There are no known trials investigating the use of AIs in women for whom tamoxifen therapy is contraindicated.

The major outcomes for the trials discussed here are summarised according to research question and trial in Tables 2 to 8. Data tables specific for each trial are found in Appendix C.

Table 2. Summary results for overall survival

	Trial	Median follow-up	Number of events/N, Intervention	Number of events/N, Control	Hazard ratio, intervention vs control (95% CI)	p-value
Initial treatment	ATAC 2004	68 months	Not stated Anastrozole	Not stated Tamoxifen	0.97 (0.85, 1.12)	0.7
	BIG 1-98 2005 Presentation	26 months	166/4003 Letrozole	192/4007 Tamoxifen	0.86 {0.71, 1.06}	0.08
Switching treatment	IES 2004	31 months	93/2362 Exemestane	106/2380 Tamoxifen	0.88 (0.67, 1.16)	0.37
	ITA 2005 Abstract	52 months	9/223 Anastrozole	17/225 Tamoxifen	0.52 (0.23, 1.17)	0.1
Continued treatment	MA.17 2003	29 months	31/2575 Letrozole	42/2582 Placebo	0.76 (0.48, 1.21)	0.25

Table 3. Summary results for disease-free survival*†

	Trial	Median follow-up	Number of events/N, Intervention	Number of events/N, Control	Hazard ratio, intervention vs control (95% CI)	p-value
Initial treatment	ATAC 2004	68 months	575/3125 Anastrozole	651/3116 Tamoxifen	0.87 (0.78, 0.97)	0.01
	BIG 1-98 2005 Presentation	26 months	8.8% {352}/4003 Letrozole	10.7% {429}/4007 Tamoxifen	0.81 (0.70, 0.93)	0.003
Switching treatment	IES 2004	31 months	183/2362 Exemestane	266/2380 Tamoxifen	0.68 (0.56, 0.82)	<0.001
	ITA 2005 Abstract	52 months			0.42 (0.26, 0.66)	0.0001
	ABCSG 8 / ARNO 95 2004 Abstract	26 months			0.59 (0.42, 0.82)	0.002
Continued treatment	MA.17 2003	29 months	{7.2%} {185}/2575 Letrozole	{13.2%} {341}/2582 Placebo	0.61 (0.47, 0.79)	<0.001

* Figures in braces are values calculated by the authors from information provided in the source publication.

† The definition of disease-free survival may differ across studies. Refer to the text for a complete description of the definition used.

Table 4. Summary results for distant recurrence (a component of disease-free survival)*

	Trial	Median follow-up	Number of events/N, Intervention	Number of events/N, Control	Hazard ratio, intervention vs control (95% CI)	p-value
Initial treatment	ATAC 2004	68 months	324/3125 Anastrozole	375/3116 Tamoxifen	0.86 (0.74, 0.99)	0.04
	BIG 1-98 2005 Presentation	26 months	4.4% {176}/4003 Letrozole	5.8% {232}/4007 Tamoxifen	{0.76 (0.63, 0.92)}	0.006
Switching treatment	IES 2004	31 months	114/2362 Exemestane	174/2380 Tamoxifen	{0.66 (0.52, 0.83)}	{<0.001}
	ITA 2005 Abstract	52 months			0.57 (0.32, 1.02)	0.06
Continued treatment	MA.17 2003	29 months	47/2575 Letrozole	76/2582 Placebo	{0.62 (0.43, 0.89)}	{0.011}

* Figures in braces are values calculated by the authors from information provided in the source publication.

Table 5. Summary results for ipsilateral breast recurrence (a component of disease-free survival)*

	Trial	Median follow-up	Number of events/N, Intervention	Number of events/N, Control	Hazard ratio, intervention vs control (95% CI)	p-value
Continued treatment	MA.17 2003	29 months	6/2575 Letrozole	19/2582 Placebo	{0.32 (0.13, 0.79)}	{0.016}

* Figures in curly braces are values calculated by the authors from information provided in the source publication.

Table 6. Summary results for contralateral breast recurrence (a component of disease-free survival)*

	Trial	Median follow-up	Number of events/N, Intervention	Number of events/N, Control	Hazard ratio, intervention vs control (95% CI)	p-value
Initial treatment	ATAC 2004	68 months	35/3125 Anastrozole	59/3116 Tamoxifen	0.58 (0.38, 0.88)	0.01
Switching treatment	IES 2004	31 months	9/2362 Exemestane	20/2380 Tamoxifen	0.44 (0.20, 0.98)	0.04
Continued treatment	MA.17 2003	29 months	14/2575 Letrozole	26/2582 Placebo	{0.54 (0.28, 1.03)}	{0.082}

* Figures in braces are values calculated by the authors from information provided in the source publication.

Table 7. Summary results for local recurrence (a component of disease-free survival)*

	Trial	Median follow-up	Number of events/N, Intervention	Number of events/N, Control	Hazard ratio, intervention vs control (95% CI)	p-value
Switching treatment	IES 2004	31 months	21/2362 Exemestane	33/2380 Tamoxifen	{0.64 (0.37, 1.10)}	{0.140}
	ITA 2005 Abstract	52 months			0.13 (0.03, 0.59)	0.002

* Figures in braces are values calculated by the authors from information provided in the source publication.

Table 8. Summary results for serious adverse events*†

	Trial	Median follow-up	Number of events/N, Intervention	Number of events/N, Control	Hazard ratio, intervention vs control (95% CI)	p-value
Initial treatment	BIG 1-98 2005 Presentation	26 months	587/3965 Letrozole	643/3984 Tamoxifen	{0.92 (0.83, 1.02)}	{0.106}
Switching treatment	ITA 2003 Abstract	24 months	14/208 Anastrozole	29/218 Tamoxifen	{0.50 (0.28, 0.93)}	{0.037}

* Figures in curly braces are values calculated by the authors from information provided in the source publication.

† The nature of serious adverse events was not qualified.

REFERENCES

1. Baum M, Budzar AU, Cuzick J, *et al.* Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet* 2002;359(9324):2131–9.
2. Baum M, Budzar A, Cuzick J, *et al.* Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses. *Cancer* 2003;98(9):1802–10.
3. Fallowfield L, Cella D, Cuzick J, *et al.* Quality of life of postmenopausal women in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) Adjuvant Breast Cancer Trial. *J Clin Oncol* 2004;22(21):4261–71.
4. Howell A, Cuzick J, Baum M, *et al.* Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 2005;365(9453):60–2.
5. Locker GY. Cost-utility analysis of anastrozole versus tamoxifen as primary adjuvant therapy in post-menopausal women in early breast cancer from a US healthcare system perspective: the 5-year completed treatment analysis of the ATAC('Arimidex', Tamoxifen Alone or in Combination) trial. Paper presented at: San Antonio Breast Cancer Symposium, 2004; San Antonio, TX, USA.
6. Thurlimann B. Letrozole as adjuvant endocrine therapy for post-menopausal women with receptor-positive breast cancer: first results of IBCSG 18-98/BIG 1-98. Paper presented at: Primary Therapy for Early Breast Cancer 9th International Conference, 2005; St Gallen, Switzerland.
7. US National Cancer Institute. Clinical Trials (PDQ). TEAM. Available at: <http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=69260&version=HealthProfessional&protocolsearchid=1501391> . Accessed March 17, 2005.
8. Coombes RC, Hall E, Gibson LJ, *et al.* A randomized trial of exemestane after two to three years of tamoxifen therapy in post-menopausal women with primary breast cancer. *N Engl J Med* 2004;350(11):1081–92.
9. Boccardo F. Switching to anastrozole (ANA) vs continued tamoxifen (TAM) treatment of early breast cancer (EBC). Updated results of the Italian tamoxifen anastrozole (ITA) trial. Paper presented at: 41st Annual Meeting of the American Society of Clinical Oncology (ASCO), 2005; Orlando, Florida, USA.
10. Jakesz R, Kaufmann M, Gnant M, *et al.* Benefits of switching post-menopausal women with hormone-sensitive early breast cancer to anastrozole after 2 years adjuvant tamoxifen: combined results from 3,123 women enrolled in the ABCSG

Trial 8 and the ARNO 95 Trial. Paper presented at: San Antonio Breast Cancer Symposium (SABCS), 2004; San Antonio, Texas, USA.

11. Goss PE, Ingle JN, Martino S, *et al.* A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med* 2003;349(19):1793–802.
12. Karnon J, Johnston SRD, Delea TE, *et al.* Cost-effectiveness of extended adjuvant letrozole after five years of tamoxifen in postmenopausal early breast cancer. *J Clin Oncol* 2004;22(14S):6044.
13. Whelan T, Goss PE, Ingle JN, *et al.* Assessment of quality of life (QOL) in MA.17, a randomized placebo-controlled trial of letrozole in postmenopausal women following five years of tamoxifen. *J Clin Oncol* 2004;22(14S):517.
14. US National Cancer Institute. Clinical Trials (PDQ). NSABP B-33. Available at: <http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=68640&version=HealthProfessional&protocolsearchid=1501459>. Accessed March 17, 2005.
15. National Cancer Institute of Canada. Clinical Trials Group. MA.17R. Available at: http://www.ctg.queensu.ca/public/Clinical_Trials/public_ph_3_trial_summary.html#MA17R . Accessed August 8, 2005.
16. US National Cancer Institute. Clinical Trials (PDQ). MA.27. Available at: <http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=316325&version=HealthProfessional&protocolsearchid=1501386>. Accessed March 17, 2005.

LIST OF ABBREVIATIONS

ABCSG	Austrian Breast Cancer Study Group
AE	Adverse events
AI	Aromatase inhibitor
ARNO	Arimidex – Nolvadex
ATAC	Arimidex, Tamoxifen Alone or in Combination
BIG	Breast International Group
CI	Confidence interval
DFS	Disease-free survival
ES	Endocrine Subscale
FACT-B	Functional Assessment of Cancer Therapy – Breast
HR	Hazard ratio
HRQoL	Health-related quality of life
IBCSG	International Breast Cancer Study Group
IES	Intergroup Exemestane Study
ITA	Italian Tamoxifen Arimidex
MENQOL	Menopause Specific Quality of Life
NSABP	National Surgical Adjuvant Breast and Bowel Project
OR	Odds ratio
OS	Overall survival
QALY	Quality-adjusted life year
RR	Relative risk
TEAM	Tamoxifen Exemestane Adjuvant Multinational
TOI	Trial Outcome Index

APPENDIX A: SEARCH STRATEGY

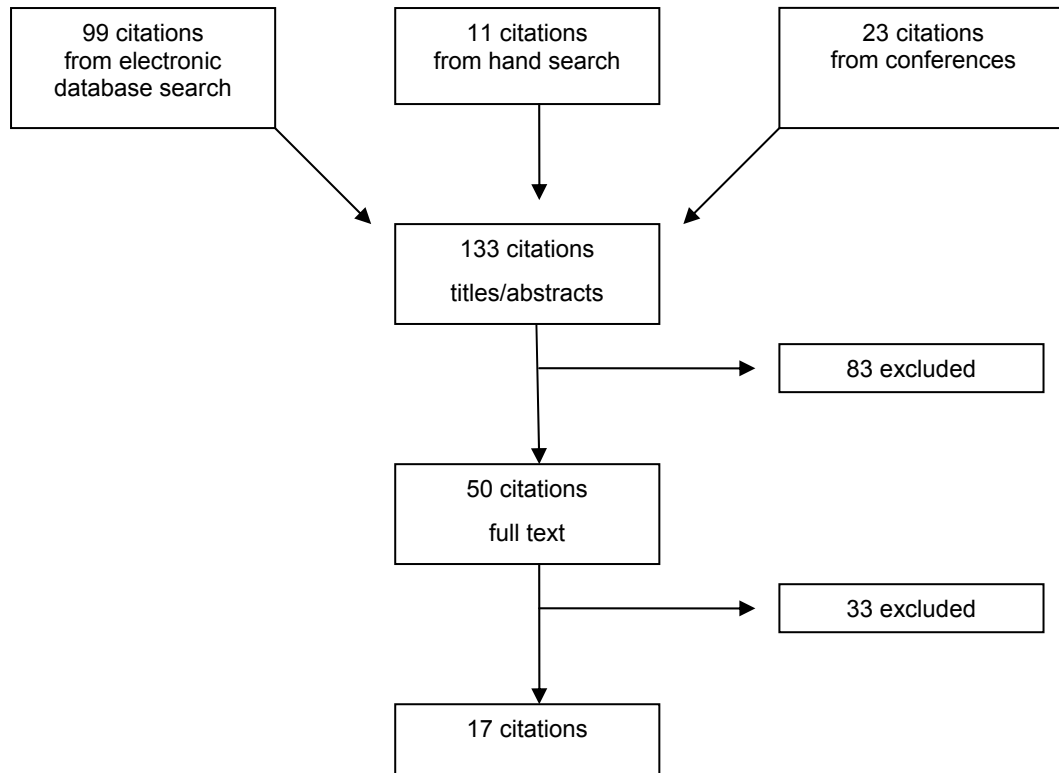
SEARCH 1:

("postmenopause" OR "postmenopausal") AND ("breast neoplasms" or "breast cancer" or "breast neoplasia") AND (treatment OR therapy) AND ("hormone receptor positive" OR "hormone responsive" OR "estrogen receptor positive" OR "ER positive" OR "ER+" OR "HR positive") AND ("early breast cancer" OR EBC OR "early disease" OR "early stage" OR "stage I" OR "stage II")

SEARCH 2:

(postmenopaus*) AND (breast AND (neoplas* OR cancer)) AND (treat* OR therap*) AND ("hormone receptor positive" OR "hormone responsive" OR "estrogen receptor positive" OR "ER positive" OR "ER+" OR "HR positive") AND ((early AND (disease OR stage)) OR EBC OR "stage I" OR "stage II")

APPENDIX B: STUDY FLOW



APPENDIX C: DATA TABLES

AROMATASE INHIBITORS AS INITIAL ADJUVANT ENDOCRINE THERAPY

Table A1. Trial characteristics

Trial	Location of study	Population, Number of subjects	Nature of intervention	Nature of control	Median follow-up
ATAC	International	9366 patients (3125 Anastrozole, 3116 Tamoxifen, 3125 Combination)	Anastrozole 1 mg Anastrozole 1 mg + Tamoxifen 20 mg	Tamoxifen 20 mg	68 months (reports at 33.3 and 47 months available)
ATAC Quality of Life Substudy	International	1021 patients (335 Anastrozole, 347 Tamoxifen, 339 Combination)	Anastrozole 1 mg Anastrozole 1 mg + Tamoxifen 20 mg	Tamoxifen 20 mg	24 months
BIG 1-98 2005 Presentation	International	8010 primary core analysis (4003 Letrozole, 4007 Tamoxifen)	Letrozole	Tamoxifen	25.8 months

Table A2. Summary of outcomes

Trial	Details of study	Outcomes	Size of treatment effect	Precision of estimate of treatment effect (95% CI)	p-value
ATAC 2002	Anastrozole compared with tamoxifen Median follow-up 33 months	Disease free survival	HR 0.83 HR 0.78*	0.71, 0.96 0.65, 0.93*	0.013 0.005*
		Distant recurrence	180 vs 203 events		
		Primary contralateral breast cancer	14 vs 33 events HR 0.42	0.22, 0.79	0.007
		Local recurrence	67 vs 83 events		
ATAC 2003	Anastrozole compared with tamoxifen Median follow-up 47 months	Disease-free survival	HR 0.86 HR 0.82*	0.76, 0.99 0.70, 0.96*	0.03 0.014*
		Time to recurrence	HR 0.83 HR 0.78*	0.71, 0.96 0.65, 0.93*	0.015 0.007*
		Contralateral breast cancer	25 vs 40 events OR 0.62 20 vs 35 events* OR 0.56*	0.38, 1.02 0.32, 0.98*	0.062 0.042*
ATAC 2004	Anastrozole compared with tamoxifen Median follow-up 68 months	Disease-free survival	575 vs 651 events HR 0.87 HR 0.83*	0.78, 0.97 0.73, 0.94*	0.01 0.005*
		Overall survival	HR 0.97	0.87, 1.12	0.7
		Time to recurrence	402 vs 498 events HR 0.79 HR 0.74*	0.70, 0.90 0.64, 0.87*	0.0005 0.0002*
		Distant metastases	324 vs 375 events HR 0.86 HR 0.84*	0.74, 0.99 0.70, 1.00*	0.04 0.06*
		Contralateral breast cancer	35 vs 59 events HR 0.58 HR 0.47*	0.38, 0.88 0.29, 0.75*	0.01 0.001*

* For receptor positive patients.

Table A2. Summary of outcomes (continued)

Trial	Details of Study	Outcomes	Size of treatment effect	Precision of estimate of treatment effect (95% CI)	p-value
BIG 1-98 2005 Presentation	Letrozole compared with tamoxifen Median follow-up 25.8 months	Disease-free survival	8.8% vs 10.7% HR 0.81	0.70, 0.93	0.003
		Overall survival	166 vs 192 events HR 0.86		0.08
		Local recurrence	0.5% vs 0.9%		0.047
		Contralateral breast cancer recurrence	0.4% vs 0.7%		0.125
		Distant recurrence	4.4% vs 5.8 %		0.006

* For receptor positive patients.

Table A3. Adverse events reported in final results of ATAC (from ATAC Trialists' Group, 2005⁴ Reprinted with permission from Elsevier (*The Lancet* 2005;365(9453):60–2))

Adverse event	Number of patients (%)		Odds ratio, anastrozole vs tamoxifen (95% CI)	p-value
	Anastrozole (n=3092)	Tamoxifen (n=3094)		
Hot flushes	1104 (35.7%)	1264 (40.9%)	0.80 (0.73, 0.89)	<0.0001
Nausea and vomiting	393 (12.7%)	384 (12.4%)	1.03 (0.88, 1.19)	0.7
Fatigue/tiredness	575 (18.6%)	544 (17.6%)	1.07 (0.94, 1.22)	0.3
Mood disturbances	597 (19.3%)	554 (17.9%)	1.10 (0.97, 1.25)	0.2
Arthralgia	1100 (35.6%)	911 (29.4%)	1.32 (1.19, 1.47)	<0.0001*
Vaginal bleeding	167 (5.4%)	317 (10.2%)	0.50 (0.41, 0.61)	<0.0001
Vaginal discharge	109 (3.5%)	408 (13.2%)	0.24 (0.19, 0.30)	<0.0001
Endometrial cancer†	5 (0.2%)	17 (0.8%)	0.29 (0.11, 0.80)	0.02
Fractures‡	340 (11.0%)	237 (7.7%)	1.49 (1.25, 1.77)	<0.0001*
Hip	37 (1.2%)	31 (1.0%)	1.20 (0.74, 1.93)	0.5
Spine	45 (1.5%)	27 (0.9%)	1.68 (1.04, 2.71)	0.03*
Wrist/Colles	72 (2.3%)	63 (2.0%)	1.15 (0.81, 1.61)	0.4
All other sites§	220 (7.1%)	142 (4.6%)	1.59 (1.28, 1.98)	<0.0001*
Ischaemic cardiovascular disease	127 (4.1%)	104 (3.4%)	1.23 (0.95, 1.60)	0.1
Ischaemic cerebrovascular events	62 (2.0%)	88 (2.8%)	0.70 (0.50, 0.97)	0.03
Venous thromboembolic events	87 (2.8%)	140 (4.5%)	0.61 (0.47, 0.80)	0.0004
Deep venous thromboembolic events	48 (1.6%)	74 (2.4%)	0.64 (0.45, 0.93)	0.02
Cataracts	182 (5.9%)	213 (6.9%)	0.85 (0.69, 1.04)	0.1

* In favour of tamoxifen. † n=2229 for anastrozole, 2236 for tamoxifen, excluding patients with hysterectomy at baseline, recorded at any time. ‡ Patients with one or more fractures occurring at any time before recurrence (includes patients no longer receiving treatment). § Patients may have had one or more fractures at different sites.

Table A4. Targeted adverse events (any grade) reported in BIG 1-98 presentation, Jan 2005⁶

Adverse event	Number of patients (%)		Odds ratio, letrozole vs tamoxifen (95% CI)	p-value
	Letrozole (N=3965)	Tamoxifen (N=3984)		
CVA/TIA Grade 3–5	(1.2) 46 (1.2)	(1.1) 42 (1.1)		
Thromboembolic events Grade 3–5	(1.0) 30 (0.8)	(2.4) 79 (2.0)		
Other cardiovascular events Grade 3–5	(8.7) 143 (3.6)	(8.3) 101 (2.5)		
Bone fracture	228 (5.8)	162 (4.1)	1.44	0.0006
Vaginal bleeding	(3.3)	(6.6)		
Endometrial biopsies (patients)	74 (1.9)	288 (7.2)		
Invasive endometrial cancer	6 (0.2)	15 (0.4)	0.40	0.078
Nausea	(8.8)	(9.5)		
Vomiting	(2.7)	(2.6)		
Hypercholesterolaemia*	(43.6)	(19.2)		
Hot flushes	(33.6)	(38.1)		
Night sweats	(14.0)	(16.2)		

* Grade 1: 35.1% of patients receiving letrozole, 17.3% of patients receiving tamoxifen.

AROMATASE INHIBITORS AS ADJUVANT ENDOCRINE THERAPY AFTER TWO TO THREE YEARS OF TAMOXIFEN

Table B1. Trial characteristics

Trial	Location of study	Population, Number of subjects	Nature of intervention	Nature of control	Median follow-up
IES 2004	International	Patients already completed 2–3yrs tamoxifen 4742 patients (2362 Exemestane, 2380 Tamoxifen)	Exemestane 25 mg/day	Tamoxifen 20 mg/day	30.6 months
ITA 2003 Abstract	Italy	426 patients (208 Anastrozole, 218 Tamoxifen)	Anastrozole 1 mg/day	Tamoxifen 20 mg/day	24 months
ITA 2005 Abstract	Italy	448 patients (223 Anastrozole, 225 Tamoxifen)	Anastrozole 1 mg/day	Tamoxifen 20 mg/day	52 months
ABCSG/ARNO 2004 Abstract	Germany/Austria	2 trials 3123 total patients (1563 Anastrozole, 1560 Tamoxifen)	Anastrozole	Tamoxifen	26 months

Table B2. Summary of outcomes

Trial	Details of Study	Outcomes	Size of treatment effect	Precision of estimate of treatment effect (95% CI)	p-value
IES 2004	Exemestane compared with tamoxifen	Disease-free survival	183 vs 266 events HR 0.68	0.56, 0.82	0.00005
		Overall survival	93 vs 106 events HR 0.88	0.67, 1.16	0.37
		Breast cancer-free survival	HR 0.63	0.51, 0.77	0.00001
		Survival free of distant disease	HR 0.66	0.52, 0.83	0.0004
		Contralateral breast cancer	HR 0.44	0.20, 0.98	0.04
		Thromboembolic events	1.3% vs 2.4%		0.007
ITA 2003 Abstract	Anastrozole compared with tamoxifen Median follow-up 24 months	Events	10 vs 26 events		
		Relapse	HR 0.36	0.17, 0.75	0.006
		Death	HR 0.18	0.02, 1.57	0.07
		Serious adverse events	14 vs 29 events		
ITA 2005 Abstract	Anastrozole compared with tamoxifen Median follow-up 52 months	Event-free survival	HR 0.42	0.26, 0.66	0.0001
		Death	9 vs 17 events HR 0.52	0.23, 1.17	0.1
		Progression-free survival	HR 0.43	0.25, 0.73	0.001
		Local progression-free survival	HR 0.13	0.03, 0.59	0.002
		Distant progression-free survival	HR 0.57	0.32, 1.02	0.06
ABCSG/ARNO 2004 Abstract	Anastrozole compared with tamoxifen	Recurrence-free survival	HR 0.59	0.42, 0.82	<0.0018

Table B3. Adverse events reported in IES (from Coombes *et al* 2004⁸ ©2004 Massachusetts Medical Society. All rights reserved.)

Adverse event*	Exemestane group					Tamoxifen group					p-value
	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	
	Number (percent)										
Cardiovascular disease other than myocardial infarction					984 (42.6)					913 (39.2)	0.11
Hot flashes	504	363	97	3	967 (42.0)	493	342	84	4	923 (39.6)	0.28
Pain or aches	392	305	61	8	766 (33.2)	383	242	55	4	684 (29.4)	0.17
Fatigue	336	178	31	0	545 (23.6)	352	157	36	2	547 (23.5)	0.82
Insomnia	269	143	37	0	449 (19.5)	234	140	31	1	406 (17.4)	0.30
Sweating	222	153	51	3	429 (18.6)	215	145	57	1	418 (17.9)	0.95
Headaches	272	129	26	1	428 (18.6)	243	116	17	2	378 (16.2)	0.09
Dizziness	206	73	9	0	288 (12.5)	192	74	13	0	279 (12.0)	0.81
Nausea	177	57	14	0	248 (10.8)	189	53	16	0	258 (11.1)	0.59
Visual disturbances	134	32	4	0	170 (7.4)	115	8	10	0	133 (5.7)	0.04
Osteoporosis					171 (7.4)					134 (5.7)	0.05
Gynaecologic symptoms					135 (5.8)					211 (9.0)	<0.001
Arthralgia					124 (5.4)					85 (3.6)	0.01
Depression	68	50	2	0	120 (5.2)	51	37	5	0	93 (4.0)	0.24
Diarrhoea	63	28	8	1	100 (4.3)	37	16	1	0	54 (2.3)	<0.001
Vaginal bleeding	49	33	11	0	93 (4.0)	73	50	5	1	129 (5.5)	0.05
Cramps	45	16	3	0	64 (2.8)	60	37	3	2	102 (4.4)	<0.001
Thromboembolic disease	11	4	8	1	24 (1.0)	11	13	15	6	45 (1.9)	0.003
Including ungraded serious adverse events					30 (1.3)					55 (2.4)	0.007

* Data are given for adverse events whose incidence in the two groups differed by 1% or more, for which the difference between groups was significant at the 1% level, or whose incidence was at least 10% in either group. Grades are according to Common Toxicity Criteria of the National Cancer Institute, version 1.0. Data on cardiovascular disease, gynaecologic symptoms, osteoporosis and arthralgia were available for 2309 patients in the exemestane group and 2332 patients in the tamoxifen group; data on the other adverse events were available for 2305 and 2329 patients, respectively. Pain or aches, arthralgia, depression, diarrhoea and cramps were recorded in an "other" category; data are preliminary and may underestimate the true incidence. For graded adverse events, p-values were determined by trend tests combining grades 3 and 4.

NB At the time of publication the p-values listed in this table were incorrect. The table has been corrected on the Journal's web site at www.nejm.org.

AROMATASE INHIBITORS AS ADJUVANT ENDOCRINE THERAPY AFTER FIVE YEARS OF TAMOXIFEN

Table C1. Trial characteristics

Trial	Location of study	Population, Number of subjects	Nature of intervention	Nature of control	Median follow-up
MA.17 2003	International	Patients already completed 5 yrs tamoxifen 5187 patients (2593 Letrozole, 2594 Placebo)	Letrozole 2.5 mg/day	Placebo	28.8 months
MA.17 2004	International	Patients already completed 5 yrs tamoxifen 5187 patients (2593 Letrozole, 2594 Placebo)	Letrozole 2.5 mg/day	Placebo	Not stated
MA.17 2004 Quality of Life Substudy	As above	Substudy – Quality of Life 3582 patients	As above	As above	36 months

Table C2. Summary of outcomes

Trial	Details of study	Outcomes	Size of treatment effect	Precision of estimate of treatment effect (95% CI)	p-value
MA.17 2003	Letrozole compared with placebo	Disease-free survival	93% vs 87%		
		Overall survival	HR 0.76	0.48, 1.21	0.25
MA.17 2004 Abstract	Letrozole compared with placebo	Disease-free survival	HR 0.57	Not stated	Not stated
MA.17 2004 Substudy Abstract	Letrozole compared with placebo Quality of Life	SF36 physical functioning	6% increase		<0.001
		Bodily pain	5% increase		0.001
		Vitality	5% increase		0.005
		MENQOL vasomotor	8% increase		<0.001
		MENQOL physical	5% increase		0.004
		MENQOL sexual	4% increase		0.02

Table C3. Adverse events reported in MA.17 * (from Goss *et al* 2003¹¹ ©2003 Massachusetts Medical Society. All rights reserved.)

Adverse event	Letrozole group (n=2154)					Placebo group (n=2145)					p-value
	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	
	<i>Number (percent)</i>										
Oedema	305	62	3	0	370 (17.2)	267	65	2	1	335 (15.6)	0.17
Hot flashes	636	380	0	0	1016 (47.2)	552	317	0	0	869 (40.5)	<0.001
Fatigue	520	112	11	0	643 (29.9)	477	125	5	0	607 (28.3)	0.26
Sweating	360	116	0	0	476 (22.1)	323	122	0	0	445 (20.7)	0.28
Constipation	185	35	4	0	224 (10.4)	169	45	2	0	216 (10.1)	0.72
Vaginal bleeding	75	15	2	0	92 (4.3)	92	32	2	2	128 (6.0)	0.01
Arthritis	86	27	6	1	120 (5.6)	57	17	1	0	75 (3.5)	<0.001
Hypercholesterolaemia	237	19	1	0	257 (11.9)	215	28	4	0	247 (11.5)	0.67
Clinical fractures					77 (3.6)					63 (2.9)	0.24
Cardiovascular events					88 (4.1)					77 (3.6)	0.40
Osteoporosis					124 (5.8)					97 (4.5)	0.07
Dizziness	218	36	5	0	259 (12.0)	207	33	5	0	245 (11.4)	0.54
Headache	301	74	14	0	389 (18.1)	306	80	12	1	399 (18.6)	0.65
Arthralgia	274	164	21	0	459 (21.3)	218	123	14	0	355 (16.6)	<0.001
Myalgia	160	81	13	0	254 (11.8)	134	61	9	0	204 (9.5)	0.02

* Data are for adverse events whose incidence in the two groups differed by more than 1% or whose incidence was at least 10% in either group. Grades are according to the Common Toxicity Criteria of the National Cancer Institute, version 2.0. Data on clinical fractures, cardiovascular events and osteoporosis were available for 2166 women in the letrozole group and 2157 women in the placebo group.