

**REGIONAL DRUG AND THERAPEUTICS CENTRE  
(NEWCASTLE)**

**AROMATASE INHIBITORS IN THE TREATMENT  
OF EARLY BREAST CANCER**

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## ABOUT THIS REPORT

This is one of a series of evaluations prepared by the Regional Drug and Therapeutics Centre (Newcastle). The aim is to give objective information and guidance to commissioners of health services, prescribers and others both on clinical aspects of the subject and on arrangements for prescribing. The reports are prepared by a multidisciplinary team within the Centre and reviewed by health authority personnel and appropriate external specialists. However, responsibility for the content and conclusions rest solely with the Regional Drug and Therapeutics Centre. We welcome comments on reports and suggestions for future topics. The following reports are available:

<b>Subject</b>	<b>Date issued</b>
Palonosetron for the prevention of nausea and vomiting associated with cancer chemotherapy	March 2007
Alemtuzumab in the management of chronic lymphocytic leukaemia	March 2007
Omalizumab in the management of severe, persistent, allergic asthma	June 2006
Bortezomib second-line in the management of multiple myeloma	March 2006
Adjuvant docetaxel or paclitaxel in the management of early stage breast cancer	March 2006
Erlotinib in the management of non-small cell lung cancer	March 2006
Ibritumomab in the management of B-cell follicular non-Hodgkin's lymphoma	March 2006
Rituximab in combination with CVP chemotherapy for the management of follicular non-Hodgkin's lymphoma.	March 2006
Pemetrexed in the management of malignant pleural mesothelioma	February 2006
Pegvisomant in the management of acromegaly	January 2006
Ibandronic acid in the management of hypercalcaemia of malignancy, bone pain and the prevention of skeletal events associated with skeletal metastases	August 2005
Teriparatide in the management of osteoporosis	July 2004
Adefovir dipivoxil for the treatment of chronic hepatitis B infection <b>(N)</b>	May 2004
An update on newer agents for the treatment of pulmonary hypertension	February 2004
Drotrecogin alfa (activated) in the management of severe sepsis <b>(N)</b>	December 2002
Agalsidase alfa and beta in the management of Fabry disease	July 2002
Carbamyl glutamate in the management of N-acetylglutamate synthetase deficiency	July 2002
Erythropoietin in the management of cancer related anaemia	July 2002
Interferon alfa in the management of malignant melanoma	November 2001
Imatinib (Glivec®, STI-571), in the management of chronic myeloid leukaemia <b>(N)</b>	November 2001
Atypical antipsychotics in the management of dementia	June 2001
Iloprost and epoprostenol in the management of pulmonary hypertension	February 2001
Verteporfin for age related macular degeneration	November 2000
Temozolomide for high grade gliomas <b>(N)</b>	May 2000
New drugs for rheumatoid arthritis <b>(N)</b>	May 2000
Ribavirin and interferon alfa for chronic hepatitis C <b>(N)</b>	March 2000
Low molecular weight heparins in venous thrombo-embolic disease	November 1999

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***Aromatase inhibitors in the treatment of early breast cancer***

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Low molecular weight heparins in unstable coronary artery disease	November 1999
Octreotide	July 1999
Drug treatment of obesity <b>(N)</b>	July 1999
Interferon alfa in Hepatitis C <b>(N)</b>	May 1999
Interferon beta in MS <b>(N)</b>	May 1999 (update)
Topotecan for ovarian cancer <b>(N)</b>	December 1998 (update)
Somatotrophin for GHD in adults	December 1998 (update)
Paclitaxel in ovarian cancer <b>(N)</b>	December 1998 (update)
Interferon alfa for haematological malignancy	July 1998
Irinotecan for colorectal cancer <b>(N)</b>	July 1998
Antiretroviral therapy	July 1998
Topotecan for ovarian cancer <b>(N)</b>	July 1998
Dornase alfa for cystic fibrosis	July 1998 (update)
New drugs for Alzheimer's disease <b>(N)</b>	February 1998
Atypical antipsychotics in the management of schizophrenia <b>(N)</b>	February 1998
Somatropin for GHD in adults <b>(N)</b>	January 1998
Taxanes in breast cancer <b>(N)</b>	July 1997
Alglucerase for Gaucher's disease	July 1997 (update)

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Agents which have been reviewed by the National Institute for Health and Clinical Excellence (NICE) are indicated by the presence of a **(N)** after the report name. Please refer to the NICE website to access the guidance for these agents/conditions.

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***Aromatase inhibitors in the treatment of early breast cancer***

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## **SUMMARY**

- **Breast cancer is the most common malignancy in females and accounts for about 32% of all cancer cases in women. In England in 2003 there were 36,500 new cases of breast cancer in women, representing an age-standardised incidence rate of 144 per 100,000 of the female population. The five year-survival rate is approximately 80%.**
- **The aromatase inhibitors (AI) letrozole, anastrozole and exemestane are licensed for the treatment of early stage breast cancer (EBC) in various settings. Letrozole and anastrozole are both licensed for the adjuvant treatment of postmenopausal women with hormone receptor-positive invasive EBC (primary therapy), and the treatment of EBC in postmenopausal women who have received prior adjuvant tamoxifen therapy (sequential therapy). Exemestane is licensed for the treatment of EBC only after prior adjuvant tamoxifen therapy.**
- **The efficacy of letrozole, anastrozole and exemestane in the adjuvant setting has been proven in a number of large RCTs. All trials showed statistically significant improvements in disease-free survival with absolute risk reductions of between 2.5% and 8.8% for the use of AIs compared with tamoxifen either as primary or sequential therapy and 4.6% when compared to placebo alone as extended therapy. However, only one trial has demonstrated a modest, but statistically significant improvement in overall survival.**
- **All three AIs have similar toxicity profiles. Compared with tamoxifen they are associated with a significantly reduced incidence of endometrial cancer, venous thromboembolism, hot flushes, and vaginal discharge. Conversely, they are associated with an increased risk of osteoporosis, bone fractures, and musculoskeletal pain. The clinical relevance of the small increased risk of cardiovascular events and hypercholesterolaemia with AIs compared to tamoxifen is difficult to assess and warrants further investigation.**
- **NICE guidance states that anastrozole, exemestane and letrozole, within their licensed indications, are recommended options for the adjuvant treatment of early oestrogen-receptor-positive invasive breast cancer in postmenopausal women.**
- **The choice of treatment strategy should be made after discussion between the responsible clinician and the patient about the risks and benefits of the options available and should include whether the patient has received tamoxifen as part of their treatment so far, the side-effect profiles of the individual drugs and, in particular, the assessed risk of recurrence.**
- **In those patients with a contraindication to AIs, those with osteoporosis or at high risk of developing osteoporosis and for those patients who decline or are intolerant of AIs, tamoxifen 20mg daily for five years can be considered as an effective alternative to AIs for the treatment of EBC.**

- Adjuvant aromatase inhibitor treatment should only be prescribed and the response supervised by an oncologist experienced in the use of anti-cancer therapies.
- As per product license, one years treatment costs £1,084 for letrozole, £1,080 for exemestane, and £894 for anastrozole. The cost of one years treatment with tamoxifen is £34.
- If patients were to receive an AI instead of tamoxifen as primary therapy the incremental cost would be £86,079 for letrozole, and £70,472 for anastrozole per 100,000 of the female population for the first year (not including calcium and vitamin D supplementation, or the requirement for DEXA scanning and bisphosphonates in some patients). The incremental cost for switching to an AI after two-to-three years of tamoxifen would be £85,779 for exemestane, and £70,472 for anastrozole. Extending adjuvant therapy with letrozole after completion of five years tamoxifen would cost £88,892 per year.
- All three treatment strategies: primary adjuvant therapy, sequential therapy (unplanned switch) and extended adjuvant therapy are considered cost-effective by NICE.
- The cost per QALY for anastrozole and letrozole, compared with tamoxifen in the primary adjuvant setting are estimated to be £21,600 and £ 22,800, respectively, based on an analysis over 35 years. The cost per QALY for anastrozole and exemestane, compared with tamoxifen in the unplanned switching setting are estimated to be £13,800 and £15,900, respectively. In the extended adjuvant setting the cost per QALY for letrozole compared to with placebo is estimated to be £9,200.
- Trials are on-going to determine the correct sequencing and optimal duration of adjuvant endocrine therapy and the most appropriate agent for use in each of the different adjuvant settings. Direct head-to-head comparisons of AIs in the adjuvant setting and studies investigating the use of prophylactic bisphosphonates are currently underway. Future studies may help to identify those subgroups of patients for whom AIs may be particularly appropriate as primary therapy.

## **BACKGROUND**

In England breast cancer is the most common malignancy in females and accounts for about 32% of all cancer cases in women.<sup>1</sup> In 2003 there were 36,509 new cases of female breast cancer registered in England, representing an age-standardised incidence rate of 144 per 100,000 of the female population.<sup>1</sup> Mortality from breast cancer in the UK has fallen dramatically since the introduction of the national breast screening program in 1988 for women aged between 50 and 70.<sup>2</sup> In the period 1989 to 2005 age-standardised death rates for female breast cancer have fallen by 33%.<sup>3</sup> Around 10,300 women died from breast cancer in England in 2005, a crude rate of 40.2 deaths per 100,000 women.<sup>3</sup> Earlier detection and improved treatment have meant that survival rates have risen. Five year-survival rate among the 132,300 women diagnosed with breast cancer during 1998-2001 was 80 per cent.<sup>4</sup>

Breast cancer risk is strongly associated with age with more than 80% of cases occurring in postmenopausal women (assuming the average age of menopause is 51 years of age).<sup>1,5</sup> There are in general 2 peaks of incidence, in the 5<sup>th</sup> and in the 8<sup>th</sup> decade of life. These two peaks reflect lifetime exposure to endogenous sex steroid hormones and reproductive history. The first and largest peak is primarily influenced by ovarian hormones and reproductive history such as early menarche, late first pregnancy, low-number of live-born children (parity) and late menopause. The second peak is influenced by extra-ovarian sources of oestrogen as well as by use of hormone replacement therapy (HRT).<sup>6-8</sup> Obesity, alcohol consumption and genetic predisposition also play an important role.

When breast cancer is diagnosed the extent of the disease should be assessed and the tumour staged. There are two commonly used systems of staging breast cancer which describe the size and spread of the disease. The American Joint Committee on Cancer (AJCC)<sup>9</sup> TNM system classifies breast cancers according to the size of the primary **T**umour, the extent of lymph **N**ode involvement, and the absence or presence of **M**etastases. In the UK the overall stage grouping system devised by the International Union Against Cancer (UICC)<sup>10</sup> is more commonly used and this system incorporates the more global TNM classification.<sup>8</sup> In this system cancer that remains localised in the ducts and non-invasive, is known as ductal carcinoma *in situ* (DCIS; stage 0). Stages I and II describe early breast cancer (EBC) which is invasive at the time of diagnosis, and stages III and IV denote locally advanced disease and metastatic breast cancer respectively (appendix I).

Treatment of breast cancer is primarily determined by the extent of the disease. Approximately 80% of breast cancers are diagnosed at an early stage.<sup>11</sup> In early breast cancer (stage I, IIa and IIb) all detected disease is confined to the breast or in the case of node-positive disease, the breast and locoregional lymphnodes, and all disease can be removed surgically.<sup>12</sup> Surgery is considered appropriate treatment for around 89% of patients with EBC,<sup>13</sup> and several surgical options with various levels of breast tissue conservation are available. The choice of surgical procedure is dependent upon the size of the tumour relative to the breast, the desired cosmetic outcome and on the patients willingness to undergo further adjuvant treatment.<sup>14</sup>

Despite successful surgical removal of all macroscopic disease, undetected micrometastatic deposits of disease may remain locally, or at distant sites and if left untreated could eventually develop into a life-threatening recurrence.<sup>12,15</sup> In approximately 50% of women with confirmed breast cancer the disease will reoccur

within 5 years of initial therapy.<sup>16</sup> Following surgery, adjuvant treatment such as radiotherapy, chemotherapy, hormonal therapy or a combination of these is usually offered to patients in order to eradicate any remnants of disease, reduce recurrence and improve long term survival.<sup>15,16</sup> Selection of an appropriate adjuvant treatment is determined by disease characteristics (stage, risk of recurrence and hormone receptor status of the tumour) and on patient characteristics (age, menopausal status and patients wishes). Chemotherapy and radiotherapy are associated with many unpleasant side-effects and are not appropriate for all patients. Because oestrogen plays a pivotal role in the promotion and development of breast cancer,<sup>7,17</sup> oestrogen receptor (ER) status is one of the most important factors in predicting outcome and in selecting therapy. Around 80-89% of postmenopausal women with breast cancer are expected to have tumours that are hormone receptor-positive (although the percentage varies with age).<sup>11,18</sup> Since endocrine therapy based on the blockade of oestrogen synthesis is very effective and reasonably non-toxic, it should therefore be considered for all patients who have a tumour that expresses oestrogen or progesterone receptors.<sup>19</sup>

### **TAMOXIFEN**

Tamoxifen is a selective oestrogen receptor modulator (SERM) and has been the standard hormonal therapy for postmenopausal women with receptor-positive breast cancer for the last 30 years because of its proven efficacy and reasonable safety profile.<sup>12,14,20</sup> The Oxford Overview Analysis of randomized trials using adjuvant tamoxifen, showed that in 18,000 women with ER+ tumours five years of tamoxifen reduced the absolute risk of recurrence by 14.9% (23.3% vs. 38.2%,  $p < 0.0001$ ), and mortality by 5.9% (22.1% vs. 28.0%,  $p < 0.0001$ ).<sup>12,20</sup> These benefits appeared largely independent of menopausal status, age, or whether or not chemotherapy was previously administered. Although five years of tamoxifen therapy results in a greater risk reduction than shorter periods of therapy, extending adjuvant tamoxifen therapy for more than five years has not been shown to further improve survival.<sup>21</sup>

Long-term tamoxifen treatment is associated with several side-effects, due mainly to its oestrogenic activity on selected tissues. Although tamoxifen is a competitive ER antagonist in breast tissue, it is a partial agonist of the ER in bone, the endometrium and other tissues.<sup>22</sup> Whilst the agonist effects of tamoxifen can be beneficial in that they may help prevent bone demineralization in postmenopausal women, they are also detrimental in that they are associated with increased risks of endometrial cancer, uterine cancer, and thromboembolism.<sup>22</sup> The relative risk of developing endometrial cancer has been shown to be between two to four times higher in women taking tamoxifen than in an age matched population.<sup>23</sup> These side-effects and the fact that many women with EBC develop resistance to tamoxifen and subsequently experience substantial rates of both new primary tumours and relapses at all sites has led to a search for alternative more effective endocrine therapies with fewer long-term complications. By virtue of their peripheral mode of action aromatase inhibitors (AIs) offer an attractive new treatment modality for receptor-positive breast cancer.

## **AROMATASE INHIBITORS**

Aromatase inhibitors (AIs) are a class of drugs that suppress oestrogen production through inhibition or inactivation of the final step in their synthesis, the conversion of androgens to oestrogens.<sup>24</sup> In the premenopausal woman, the ovaries are the primary source of serum oestrogen, and only a small proportion comes from peripheral tissues. After menopause ovarian production declines and oestrogens are synthesized mainly through the aromatisation of adrenal and ovarian androgens in non-glandular tissues, in particular subcutaneous adipose tissue.<sup>25-27</sup> Aromatase (oestrogen synthetase) is the enzyme that catalyses the final rate-limiting step in the synthesis of oestrogens and is expressed in peripheral tissues, including, skin, muscle, and adipose and breast tissue.<sup>24,27</sup> In addition, two thirds of breast cancer tumours express the aromatase enzyme and synthesize significant amounts of oestrogen locally within the tumour.<sup>27</sup>

AIs are described as first-, second-, and third-generation inhibitors according to their chronological order of clinical development and are further characterised as type I or type II inhibitors according to their mode of action.<sup>27</sup> The type I inhibitors are steroidal analogues of androstenedione and bind irreversibly to the androgen-binding site of the aromatase enzyme. The type II inhibitors are non-steroidal and bind reversibly to the P450 site of aromatase.<sup>24-27</sup> The third-generation inhibitors, developed in the early 1990's, include the non-steroidal inhibitors letrozole and anastrozole and the steroidal inactivator exemestane.<sup>24,27</sup> In contrast to earlier AIs, which also affected adrenal corticosteroidal metabolism, resulting in marked toxicities, the third-generation inhibitors appear to demonstrate almost complete specificity at clinical doses, offering significant safety advantages over their non-selective predecessors.<sup>28,29</sup> With daily oral administration all three of these agents have been shown to cause near-complete inhibition of aromatase activity in postmenopausal women within two-to-four days of commencing therapy.<sup>25,30</sup>

The third-generation AIs have been shown to be superior to tamoxifen in terms of time to progression in patients with known hormone receptor status and have become established as first-line hormonal therapies for advanced breast cancer.<sup>27,30-32</sup> In addition these agents demonstrated comparable survival rates with tamoxifen with an acceptable safety profile. More recently, substantial clinical evidence has emerged supporting the use of AIs as adjuvant therapy for hormone-sensitive EBC. To date AIs have been evaluated as treatment for EBC in more than 27,000 postmenopausal women. Two main approaches have been taken in these studies. The first is to compare the AIs head-to-head with tamoxifen, and the second is to sequence the AIs after two-to-five years of tamoxifen. The purpose of this report is to review the efficacy, safety and place in treatment of aromatase inhibitors in postmenopausal women with EBC.

## **LETROZOLE**

Letrozole (Femara<sup>®</sup>) is a reversible non-steroidal once-a-day oral aromatase inhibitor currently indicated in the UK for:<sup>33</sup>

- Adjuvant treatment of postmenopausal women with hormone receptor-positive invasive early breast cancer.

- Treatment of early invasive breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy.
- First-line treatment in postmenopausal women with advanced breast cancer
- Advanced breast cancer in postmenopausal women in whom tamoxifen or other anti-oestrogen therapy has failed.
- Pre-operative therapy in postmenopausal women with localised hormone-receptor positive breast cancer, to allow subsequent breast-conserving surgery in women not originally considered candidates for breast-conserving surgery.

### **ANASTROZOLE**

Anastrozole (Arimidex<sup>®</sup>) is a reversible non-steroidal once-a-day oral aromatase inhibitor currently indicated in the UK for: <sup>34</sup>

- Adjuvant treatment of postmenopausal women with hormone receptor-positive early invasive breast cancer.
- Adjuvant treatment of early breast cancer in hormone receptor positive postmenopausal women who have received 2 to 3 years of adjuvant tamoxifen.

### **EXEMESTANE**

Exemestane (Aromasin<sup>®</sup>) is an irreversible steroidal once-a-day oral aromatase inhibitor currently indicated in the UK for: <sup>35</sup>

- Adjuvant treatment of postmenopausal women with oestrogen receptor-positive invasive early breast cancer, following two to three years of initial adjuvant tamoxifen therapy.
- Treatment of advanced breast cancer in women with natural or induced postmenopausal status whose disease has progressed following anti-oestrogen therapy.

## **EFFICACY**

### **AROMATASE INHIBITORS AS PRIMARY ADJUVANT THERAPY**

Two randomised, adjuvant trials have assessed the efficacy of third-generation aromatase inhibitors in comparison with tamoxifen as primary therapy for early breast cancer.

### **LETROZOLE AS PRIMARY ADJUVANT THERAPY**

The Breast International Group (BIG-1-98) study was designed to compare the safety and efficacy of adjuvant letrozole (2.5mg/day) versus tamoxifen (20mg/day) in postmenopausal women with hormone receptor-positive EBC, post surgery.<sup>30,36</sup> This

study is an ongoing randomised, double-blind, multi-centre trial in 8,028 women. It is currently the only clinical trial to incorporate both a head-to-head comparison of letrozole with tamoxifen and a sequencing of both agents, during the first 5 years following breast cancer surgery. Participants were randomly assigned to one of 4 treatment arms; 5 years of tamoxifen, 5 years of letrozole, 2 years of tamoxifen followed by 3 years of letrozole, or 2 years of letrozole followed by 3 years of tamoxifen. This primary analysis compared only the two groups assigned to receive letrozole initially with the two groups assigned to receive tamoxifen initially. The primary endpoint was disease-free survival (DFS), defined as any breast cancer recurrence, invasive contralateral breast cancer; a second primary cancer; or death without a recurrence. Specified secondary endpoints included overall survival (OS), systemic DFS and safety.

The primary analysis was performed after 779 DFS events had been observed; 351 in the letrozole group and 428 in the tamoxifen group. At a median follow-up of 25.8 months, DFS was significantly greater in the letrozole group than in the tamoxifen group (HR, 0.81; 95% CI 0.70-0.93;  $p=0.003$ ). This corresponds to an absolute benefit of 1.9% (91.2% vs. 89.3%, NNT=53) in DFS in favour of letrozole. Compared with tamoxifen, letrozole significantly reduced the risk of distant recurrence (HR, 0.73; 95% CI 0.60-0.88;  $p=0.001$ ). The five-year estimates of DFS were 84.0% in the letrozole group and 81.4% in the tamoxifen group, corresponding to an absolute benefit of 2.6% (NNT=39). Overall fewer women died in the letrozole group (166 patients, 4.1%) than in the tamoxifen group (192 patients, 4.8%), but OS did not differ significantly between the two treatment groups (HR 0.86; 95% CI 0.70-1.06;  $p=0.16$ ).

### **ANASTROZOLE AS PRIMARY ADJUVANT THERAPY**

The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial is the largest study of AIs in breast cancer to date, and provides the longest follow-up. This was a randomised, double blind, multi-centre trial designed to compare tamoxifen with anastrozole as a single agent and tamoxifen with a combination of the two drugs.<sup>23,37,38</sup> A total of 9,366 post menopausal women who had completed prior surgery and/or chemotherapy for invasive breast cancer were randomised to one of three treatment arms: anastrozole 1 mg daily ( $n=3125$ ), tamoxifen 20 mg daily ( $n=3116$ ), or the combination daily ( $n=3125$ ) for five years. Initial analyses at 33 and 47 months showed that anastrozole significantly prolonged DFS, time-to-recurrence (TTR) and reduced the incidence of contralateral breast cancer (CLBC) compared to tamoxifen.<sup>23,37</sup> Combination treatment did not improve outcome compared to tamoxifen monotherapy and this arm was closed after these analyses. At the final analysis, after a median follow-up of 68 months anastrozole significantly improved DFS (HR 0.87; 95% CI 0.78-0.97;  $p=0.01$ ), TTR (HR 0.79; 95% CI 0.70-0.90;  $p=0.0005$ ) and incidence of CLBC (HR 0.58; 95% CI 0.38-0.88;  $p=0.01$ ) compared to tamoxifen.<sup>38</sup> This corresponds to an absolute benefit of 2.5% in DFS at 68 months in favour of anastrozole (81.6% vs. 79.1%, NNT=40). Hormone-receptor-positive disease yielded the greatest benefit in terms of DFS and TTR. Overall survival did not differ significantly between the two groups (HR 0.97; 95% CI 0.85-1.12;  $p=0.7$ ).<sup>38</sup>

## **AROMATASE INHIBITORS AS SEQUENTIAL THERAPY**

Several trials have evaluated the efficacy of switching to an aromatase inhibitor following two-to-three years of tamoxifen treatment.<sup>39-43</sup>

### **ANASTROZOLE AS SEQUENTIAL THERAPY**

In the combined analysis of the Austrian Breast Cancer Study Group and Arimidex Novadex 95 (ABCSG-8 and ARNO-95) trials, 3,224 postmenopausal patients, all with receptor-positive disease, who had received two years of adjuvant tamoxifen (20 or 30 mg daily) after primary surgery were randomised to either continue on tamoxifen (n=1,606) therapy for a total of five years or switch to 1mg anastrozole (n=1,618) for the remaining three years.<sup>39</sup> Both trials were prospective, multi-centre, randomised, open-label studies with broadly similar inclusion criteria and outcome measures. The primary endpoint was event-free survival (EFS), defined as time to relapse at any site or incidence of CLBC. At median follow-up of 28 months there was an HR of 0.60 (95% CI 0.44-0.81, p=0.0009) in favour of anastrozole at three years post switch for the occurrence of an event. This corresponds to an absolute benefit of 3.1% in terms of the estimated EFS at three years (95.8% vs. 92.7%, NNT=33). Significantly fewer metastases arose in the anastrozole-treated patients compared to those receiving only tamoxifen (HR 0.61; 95% CI 0.42-0.87; p=0.0067), corresponding to an absolute decrease of 2% in the risk of metastases for women switching to anastrozole (5% vs. 3%, NNT=50). OS at three years post switch was not significantly different between the two treatment groups (97% vs. 96%, p=0.16).

The Italian Tamoxifen Anastrozole Trial (ITA) was a prospective, randomised, multicentre trial also designed to assess the efficacy of switching postmenopausal women who were already taking tamoxifen to anastrozole.<sup>40</sup> A total of 448 patients who had received two to three years of adjuvant tamoxifen were randomly assigned to either receive anastrozole 1mg daily (n=223) or to continue receiving tamoxifen therapy (n=225), for a combined total duration of five years endocrine treatment. The primary endpoint was DFS, defined as time to locoregional or distant recurrence, but excluding CLBC. Preliminary results after a median follow-up of 36 months showed a significant improvement in DFS in the anastrozole group compared with tamoxifen (HR of 0.35; 95% CI 0.18-0.68, p=0.001). This corresponds to an absolute benefit of 8.8% in DFS in favour of anastrozole (94.6% vs. 85.8%, NNT=12). These results were recently confirmed by an updated analysis.<sup>41</sup> At a median follow-up 64 months (range 12-93) DFS was significantly longer in the anastrozole group compared to tamoxifen (HR of 0.56; 95% CI 0.35-0.89, p=0.01), corresponding to an absolute benefit of 7.8% (87.4% vs. 79.6%, NNT=13). No significant difference in OS between the two groups was observed in either analysis.

### **EXEMESTANE AS SEQUENTIAL THERAPY**

To date only one trial has been published evaluating the impact of exemestane as adjuvant therapy in early breast cancer.<sup>42,43</sup> The Intergroup Exemestane Study (IES) was designed to investigate whether exemestane could prolong DFS in

postmenopausal women who remained free of recurrence after receiving two to three years of adjuvant tamoxifen therapy.<sup>42</sup> A total of 4,742 women were randomised to receive tamoxifen 20mg daily for a total of five years (n=2380) or exemestane 25mg daily for two to three years sequentially after two to three years of tamoxifen (n=2362). The results of this study were released early on the basis of a planned interim analysis. At median follow-up 30.6 months, DFS was significantly greater in the exemestane group than in the tamoxifen group (HR 0.68 [95%CI, 0.56-0.82], p<0.001). This corresponds to an absolute benefit in terms of the estimated DFS at 3 years of 4.7% (91.5% vs. 86.8%, NNT=22). Exemestane significantly reduced the incidence of CLBC (HR 0.44; 95% CI 0.20-0.98; p=0.04) compared to tamoxifen. Overall survival at this time point did not differ significantly between the two groups (HR 0.88; 95% CI 0.67-1.16; p=0.37). In an updated analysis at a median follow-up of 55.7 months,<sup>43</sup> DFS was significantly greater in the exemestane group than in the tamoxifen group, HR 0.76 (95%CI, 0.66 - 0.88, p=0.0001). This corresponds to an absolute benefit of 3.3% (NNT=31) in terms of DFS at the end of treatment (i.e. 2.5 years after randomisation), and 3.4% (NNT=30) benefit five years after randomisation. There was a modest improvement in OS in favour of exemestane when 122 patients with oestrogen-receptor-negative disease were excluded from the analysis (HR 0.83; 95% CI 0.69-1.00; p=0.05). This corresponds to an absolute benefit in terms of OS of 1.7% (90.9% vs. 89.2%, NNT=59).

### **AROMATASE INHIBITORS AS EXTENDED ADJUVANT THERAPY**

The efficacy of extended aromatase inhibitor therapy following five years of tamoxifen treatment has been assessed in one trial.<sup>44,45</sup>

### **LETROZOLE AS EXTENDED ADJUVANT THERAPY**

The MA-17 study was designed to test the effectiveness of five years of adjuvant letrozole therapy in postmenopausal women with EBC who have completed approximately five years (range 4.5-6) of adjuvant tamoxifen therapy.<sup>44,45</sup> This international, phase III, randomised, double-blind, placebo controlled trial involved 5,187 women who were randomly assigned to receive letrozole 2.5mg daily (n=2,593) or placebo (n=2,594) orally for five years. The primary endpoint was DFS, defined as time from randomisation to the recurrence of the primary disease (in the breast, chest wall, or nodal or metastatic site) or the development of a new primary breast cancer in the contralateral breast. This definition did not include women who had died without either recurrence of breast cancer or new diagnosis of CLBC, as these patients were censored. Specified secondary endpoints included OS, Quality of life (QoL) and long-term safety.

At the first interim analysis (median follow-up of 2.4 years) there was a significant improvement in the estimated 4 year DFS in the letrozole group compared with placebo (HR, 0.57; 95% CI 0.43-0.75; p=0.00008).<sup>44</sup> This corresponds to an absolute benefit of 6.0% in the terms of DFS at 4 years in favour of letrozole (92.8% vs. 86.8%, NNT=17). Fewer local regional or distant recurrences were observed in the letrozole group compared to placebo (2.4% and 4.1%, respectively), as well as CLBC (0.5% and 1%, respectively). There was no significant difference in the four-year estimated overall survival between the two groups (96.0% vs.94.0%, p=0.25).

After this analysis the trial was terminated and the results communicated to the participants. Efficacy data from an updated analysis after a median follow-up of 30 months were consistent with the initial findings.<sup>45</sup> The study continued to report a benefit in terms of DFS (94.4% vs.89.8%,  $p<0.001$ ) corresponding to an absolute benefit of 4.6% in favour of letrozole (NNT=22). However, OS was the same for both arms (95.4% vs.95.0%,  $p=0.3$ ). In an unplanned subgroup analysis a significant improvement in OS compared with placebo was observed in both lymph node-positive patients (HR 0.61; 95% CI 0.38-0.98,  $p=0.04$ ) and in patients who had taken tamoxifen for more than five years (HR 0.56; 95% CI 0.33-0.97,  $p=0.04$ ).

## **ADVERSE EFFECTS**

### **AROMATASE INHIBITORS AS PRIMARY ADJUVANT THERAPY**

#### **LETROZOLE AS PRIMARY ADJUVANT THERAPY**

In the Big 1-98 study more patients in the letrozole group than in the tamoxifen group reported at least one protocol specified adverse event of any grade (73% vs. 64%, respectively).<sup>30,36</sup> However the rate of serious adverse events was similar in the two groups (1.7% for both). Fractures were significantly more frequent in the letrozole group than the tamoxifen group (5.7% vs. 4.0%, respectively,  $p=0.001$ ) with a significantly shorter time to first fracture reported within four weeks after the end of treatment ( $p<0.001$ ). Hypercholesterolaemia was more frequent in the letrozole group (43.6% vs. 19.2%, respectively). Tamoxifen decreased serum total cholesterol levels from baseline at 6, 12 and 24 months, whereas letrozole treatment resulted in no relevant changes over time (-12.0, -13.5 and -14.1% vs. 0, 0 and -1.8%, respectively). The overall incidence of adverse cardiac events was similar in the two groups (3.7% vs. 4.1%, respectively). However, there was a significantly increased risk of grade 3, 4 or 5 cardiac events in women taking letrozole (2.1% vs. 1.1%,  $p=0.001$ ).

Compared with tamoxifen, letrozole was associated with significantly fewer thromboembolic events (1.5% vs. 3.5%,  $p<0.001$ , numbers needed to harm (NNH) = 50). This means that treating 50 women with letrozole for just over two years would be expected to result in one thromboembolic event. Letrozole was also associated with a significantly lower rate of vaginal bleeding (3.3% vs. 6.6%,  $p<0.001$ , NNH=30), fewer endometrial biopsies (2.3% vs. 9.1%,  $p<0.001$ , NNH=15), and fewer invasive endometrial cancers (0.1% vs. 0.3%, NNH=500), although the latter was not statistically significant ( $p=0.18$ ).

#### **ANASTROZOLE AS PRIMARY ADJUVANT THERAPY**

In the ATAC study treatment with anastrozole was associated with significant reductions in the incidence of endometrial cancer (0.2% vs. 0.8%), venous thromboembolic events (2.8% vs. 4.5%), ischaemic cerebrovascular events (2.0% vs. 2.8%), vaginal bleeding (5.4% vs. 10.2%), hot flushes (35.7% vs. 40.9%), and vaginal discharge (3.5% vs. 13.2%) compared with tamoxifen.<sup>23,37,38</sup> The incidence

of fractures (7.7% vs. 11%) and arthralgia (29.4% vs. 35.6%) was less common in the tamoxifen group.

## **AROMATASE INHIBITORS AS SEQUENTIAL ADJUVANT THERAPY**

### **ANASTROZOLE AS SEQUENTIAL THERAPY**

In the combined analysis of ABCSG-8 and ARNO-95 studies there were significantly fewer thromboses (0.2% vs. 0.7%) and significantly more fractures (2% vs. 1%) in patients treated with anastrozole than in those treated with tamoxifen.<sup>39</sup> The incidence of endometrial cancer was numerically higher in those who continued on tamoxifen compared to those who switched to anastrozole (7 vs. 1), though this difference was not significant ( $p=0.069$ ).

In the ITA study, after a median follow-up of 36 months overall significantly more adverse events were reported in the anastrozole group compared with the tamoxifen group (43.9% vs. 36.0%,  $p=0.04$ )<sup>40</sup> However, significantly more serious events occurred in the tamoxifen group (22.0% vs. 13.9%,  $p=0.04$ ). More patients in the tamoxifen group had a second primary non-breast cancer (3.5% vs. 1.8%), specifically cancer of the endometrium (2.2% vs. 0.5%). In a recently updated analysis at 64 months follow-up,<sup>41</sup> overall more patients in the anastrozole group experienced at least one adverse event (93.7% vs. 67.1%,  $p=0.000$ ). However, the numbers of patients experiencing serious adverse events were comparable (17.8% vs. 16.6%,  $p=0.7$ ), except for those developing serious gynaecological problems (including endometrial cancer) who were significantly more numerous in the tamoxifen group (5.3% vs. 0.9%,  $p=0.006$ ).

### **EXEMESTANE AS SEQUENTIAL THERAPY**

Provisional safety data from the IES study showed that exemestane was associated with a higher incidence of arthralgia (5.4% vs. 3.6%) and diarrhoea (4.3% vs. 2.3%) than tamoxifen, but gynaecological symptoms, vaginal bleeding (5.5% vs. 4.0%), and muscle cramps (4.4% vs. 2.8%) were more common with tamoxifen.<sup>42</sup> More patients in the tamoxifen group had a second primary non-breast cancer that occurred before a distant relapse (2.2% vs. 1.1%), specifically cancer of the endometrium and lung (0.5% vs. 0.2% for both, respectively). However, these individual differences were not statistically significant. There was a non-significant increase in the incidence of osteoporosis and reported fractures in the exemestane group as compared with the tamoxifen group.

## **AROMATASE INHIBITORS AS IEXTENDED ADJUVANT THERAPY**

### **LETROZOLE AS EXTENDED ADJUVANT THERAPY**

At the first interim analysis of the MA-17 study there were no significant differences between letrozole and placebo in the incidence of osteoporosis ( $p=0.07$ ) or fracture rates ( $p=0.24$ ).<sup>44</sup> In the updated analysis, letrozole was associated with significantly

higher incidence of hot flushes (58% vs. 54%), anorexia (6% vs. 4%), arthralgia (25% vs. 21%), myalgia (15% vs. 12%) and alopecia (5% vs. 3%), but significantly lower incidence of vaginal bleeding (6% vs. 8%) compared with placebo.<sup>45</sup> Newly diagnosed osteoporosis was higher in the letrozole group compared with placebo (8.1% vs. 6.0%), although the incidence of bone fractures was similar for both groups (5.3% vs. 4.6%).

### **SUMMARY OF ADVERSE EFFECTS OF AROMATASE INHIBITORS**

Letrozole, anastrozole and exemestane have similar toxicity profiles. Compared with tamoxifen they are associated with a significantly reduced incidence of endometrial cancer, venous thromboembolism, hot flushes, and vaginal discharge. Conversely, AIs are associated with an increased risk of osteoporosis, bone fractures, and musculoskeletal pain. The clinical relevance of the small increased risk of cardiovascular events and hypercholesterolaemia with AIs compared to tamoxifen is difficult to assess and warrants further investigation.

## **DOSAGE, ADMINISTRATION AND COST**

### **LETROZOLE**

Letrozole is available as 2.5mg tablets, supplied in 28 and 145 tablet packs.<sup>33</sup> The recommended dose of letrozole is one 2.5mg tablet administered once a day, without regard to meals. Treatment with letrozole should continue until tumour progression is evident. No dose adjustment is required for elderly patients. Patients treated with letrozole do not require glucocorticoid or mineralocorticoid replacement therapy.

### **ANASTROZOLE**

Anastrozole is available as 1mg tablets, supplied in 20, 28, 30, 84, 98, 100 and 300 tablet packs.<sup>34</sup> The recommended dose of Anastrozole is one 1mg tablet administered once a day, without regard to meals. The recommended duration of treatment is five years. No dose adjustment is required for elderly patients. Patients treated with anastrozole do not require glucocorticoid or mineralocorticoid replacement therapy.

### **EXEMESTANE**

Exemestane is available as 25mg tablets, supplied in 30 and 90 tablet packs.<sup>35</sup> The recommended dose of letrozole is one 25mg tablet administered once a day, preferably after a meal. In patients with EBC, treatment with exemestane should continue until completion of five years of combined sequential adjuvant hormonal therapy (exemestane followed by tamoxifen), or earlier if tumour relapse occurs. No dose adjustment is required for elderly patients. Patients treated with exemestane do not require glucocorticoid or mineralocorticoid replacement therapy.

## **OSTEOPOROSIS PROPHYLAXIS**

Because AIs are potent oestrogen lowering agent, reductions in bone mineral density can be anticipated. The impact of AIs on long-term fracture risk remains undetermined. During adjuvant treatment with AIs, those patients at high risk of osteoporosis (> 65, early menopause, known osteopenia, low dietary calcium, smoker, alcohol excess, weight < 57kg) should have their bone mineral density (BMD) formally assessed by bone densitometry e.g. DEXA scanning at the commencement of treatment.<sup>33-35</sup> Although adequate data to show the effects of therapy in the treatment of the bone mineral density loss caused by AI are not yet available, treatment for osteoporosis should be initiated as appropriate and patients treated with an AI should be carefully monitored.<sup>46</sup> All patients should be commenced on daily oral calcium (500mg) and vitamin D supplementation (400 I.U.) and given lifestyle advice when aromatase inhibitors are started.

- If T score greater than -1 then 2 yearly BMD measurements are recommended
- Women with osteopenia (T score between -1 and -2.5) should have BMD monitored annually.
- Women with osteoporosis (T score worse than -2.5) should have BMD monitored annually and an approved bisphosphonate should be commenced.

## **COST**

Treatment	Dose	Cost per year*
Letrozole	2.5 mg daily	£1,084.05
Exemestane	25 mg daily	£1,080.40
Anastrozole	1 mg daily	£893.72
Tamoxifen	20 mg daily	£34.31 (generic)

- Prices from Monthly Index of Medical Specialities, March 2007<sup>47</sup>

Aromatase inhibitors have significant cost implications across primary and secondary care, although this would be expected to be focused in primary care. AIs represent a new treatment modality for hormone receptor positive EBC and therefore a new cost pressure. Patient interest and pressure to receive therapy is already in evidence. In England in 2003 there were 36,500 new cases of breast cancer in women, representing an incidence rate of 144 per 100,000 of the female population. AIs will only be prescribed for postmenopausal women, and this group accounts for around 80% of breast cancer cases (assuming the average age of menopause is 51 years of age).<sup>5</sup> This would equate to around 115 new cases per 100,000 population per year. Of these up to 89% are expected to have hormone receptor-positive tumours.<sup>11</sup> Assuming that up to 80% of these are likely to present with early stage disease,<sup>11</sup> this translates to around 82 patients each year per 100,000 of the female population

who would be eligible for treatment with an AI. If all new patients were to receive letrozole instead of tamoxifen as primary therapy the incremental cost would be £86,079 per 100,000 population for the first year. As letrozole was only associated with significant improvement in OS compared to placebo in patients with node-positive disease at diagnosis there is potential for targeting this group of patients in the first instance to manage the financial impact. If all new patients were to receive anastrozole instead of tamoxifen as primary therapy, the incremental cost would be £70,472 per 100,000 for the first year. The incremental cost for switching to an AI after two-to-three years of tamoxifen would be £85,779 for exemestane, and £70,472 for anastrozole. Extending adjuvant therapy with letrozole after completion of five years tamoxifen treatment would cost £88,892 per 100,000 population per year. As AI therapy is likely to improve outcomes drug costs would increase on a yearly basis as the number of patients being treated accumulates. These figures do not take into account calcium and vitamin D supplementation, or the requirement for DEXA scanning and bisphosphonates in some patients.

### **COST-EFFECTIVENESS**

All three treatment strategies: primary adjuvant therapy, sequential therapy (unplanned switch) and extended adjuvant therapy are considered cost-effective by NICE.<sup>13,48</sup> The cost per quality adjusted life year (QALY) gained for anastrozole and letrozole, compared with tamoxifen in the primary adjuvant setting are estimated to be £21,600 and £22,800, respectively, based on an analysis over 35 years.<sup>13</sup> The cost per QALY for anastrozole and exemestane, compared with tamoxifen in the unplanned switching setting are estimated to be £13,800 and £15,900, respectively.<sup>13</sup> In the extended adjuvant setting the cost per QALY for letrozole compared to with placebo is estimated to be £9,200.<sup>13</sup>

These 'basecase' results are considered conservative in that they assume that the benefits of aromatase inhibitors over tamoxifen or placebo seen during the treatment period are gradually lost during the following 10 years.<sup>13</sup> An alternative 'benefits maintained' scenario, in which the annual rate of recurrence is assumed to be the same in both arms following the treatment period, shows that the incremental cost effectiveness ratios are typically at least 50% lower under this assumption. This reduces the cost-effectiveness of around £10,000, £5,000 and £3,000 in the primary adjuvant, unplanned switching and extended adjuvant settings, respectively. The limited evidence available regarding benefits after the treatment period suggests that the 'benefits maintained' scenario may be more realistic.<sup>13</sup>

A costing template has been developed to support the NICE guidance on hormonal therapies for the adjuvant treatment of early oestrogen-receptor-positive breast cancer. By varying the assumptions and feeding in data that reflect local circumstances, this template can be used to estimate the local cost implications.

[TA112 Breast cancer \(early\) - hormonal treatments: costing template and report](#)

## **PLACE IN TREATMENT**

### **PREMENOPAUSAL WOMEN**

Tamoxifen remains the recommended adjuvant endocrine therapy for premenopausal women. Because of the risk of ovarian cysts, aromatase inhibitors and inactivators should not be used in premenopausal women without concomitant ovarian blockade with gonadotrophin releasing hormone analogues.<sup>27</sup> There is currently limited data on the efficacy of combining AIs with ovarian suppression (OS), although this will be addressed in the SOFT (suppression of ovarian function)<sup>49</sup> and TEXT (tamoxifen and exemestane)<sup>50</sup> trials. Therefore the use of AIs in combination with ovarian suppression should only be considered in those patients whom the use of tamoxifen is clearly contraindicated.

### **POSTMENOPAUSAL WOMEN**

The Oxford overview analysis showed that in women with ER+ tumours five years of tamoxifen significantly reduced the risk of recurrence and overall mortality.<sup>12</sup> Therefore, tamoxifen treatment for five years should be considered the standard therapy for women with DCIS (stage 0) treated with breast-conserving therapy or mastectomy, especially those with ER+ DCIS. The benefit of tamoxifen for ER-DCIS is uncertain and there is no evidence to support the use of AIs in this setting.

Until recently, tamoxifen was the only antioestrogen agent approved in the UK for the adjuvant treatment of EBC (stage I to IIb). Results of recent large adjuvant trials investigating the efficacy of adjuvant AIs in EBC has led to the approval of letrozole,<sup>33</sup> anastrozole<sup>34</sup> and exemestane<sup>35</sup> in this setting. Because study design, baseline characteristics and DFS definitions often differ, direct comparisons of DFS cannot be made across trials. However, the data are consistent in demonstrating that the use of a third-generation AI in postmenopausal women with EBC significantly reduces the risk of recurrence, including CBLC and distant metastases, compared to tamoxifen. All trials showed statistically significant improvements in DFS with absolute risk reductions of between 2.5% and 8.8% for the use of AIs compared with tamoxifen either as primary or sequential therapy and 4.6% when compared to placebo alone as extended therapy. However, only one trial has demonstrated a modest, but statistically significant improvement in OS.<sup>43</sup>

Despite the available data using AIs as adjuvant treatment, many questions remain regarding the optimal treatment strategy for newly diagnosed EBC patients. Whether an AI should be offered initially (replacing tamoxifen), or at some time after completion of two to five years of tamoxifen, has not been clearly established. Based on the current evidence it can only be concluded that there are potential benefits from using an AI at some stage in the adjuvant treatment of postmenopausal women with hormone receptor-positive breast cancer. The recent ASCO technology assessment<sup>31</sup> and the National Comprehensive Cancer Network (NCCN) guidelines<sup>51</sup> recommend that adjuvant therapy for EBC includes an AI either as primary therapy or after tamoxifen in order to reduce the risk of recurrence.

NICE guidance states that the AIs anastrozole, exemestane and letrozole, within their licensed indications, are recommended options for the adjuvant treatment of early oestrogen-receptor-positive invasive breast cancer in postmenopausal women.

The choice of treatment strategy (that is, primary adjuvant treatment with an aromatase inhibitor, switching from tamoxifen to an aromatase inhibitor or use of an aromatase inhibitor after completion of 5 years of tamoxifen treatment) should be made after discussion between the responsible clinician and the patient about the risks and benefits of the options available. Consideration of the strategy to be adopted should include whether the patient has received tamoxifen as part of their treatment so far, the side-effect profiles of the individual drugs and, in particular, the assessed risk of recurrence.<sup>48</sup> However, the licence for sequential anastrozole was not considered in the Final Appraisal Document (FAD), as this license was granted after the deadline for submissions to NICE for consideration had passed. Therefore, for the majority of postmenopausal women with newly diagnosed EBC (stage I to IIb) an AI may be considered as part of their adjuvant management, either as primary therapy for five years, especially in those with known risk factors for thromboembolic events, or sequentially with two to three years of tamoxifen followed by two to three years of an AI to a combined total of five years adjuvant therapy. The significant improvements in DFS observed with primary adjuvant AI therapy suggest that it may not be appropriate to wait two-to-five years to start AI therapy. However, the data should not be interpreted as a recommendation for the routine use of AIs in all patients with postmenopausal receptor-positive EBC; rather they suggest that AIs represent a suitable alternative to tamoxifen for a selective group of patients based on their medical history and risk of relapse. The rationale for considering the use of AIs in each of these temporal settings is outlined below.

Primary adjuvant therapy with letrozole or anastrozole was tested in two large scale trials against tamoxifen and found to significantly increase DFS in postmenopausal women with endocrine responsive disease.<sup>23,30,36-38</sup> In the BIG 1-98 study, primary adjuvant letrozole therapy significantly reduced the risk of recurrent disease compared with tamoxifen.<sup>30,36</sup> In particular, letrozole appeared to reduce the rate of distant metastases compared to tamoxifen, a clinically relevant finding since women who develop distant metastasis have a significantly higher risk of dying from their disease. In terms of the absolute data available at the median follow-up period of 25.8 months, the absolute difference of 1.9% in the rate of DFS events would equate to a an NNT of 53. This means that for every 53 women treated with letrozole instead of the “gold standard” tamoxifen one additional woman would be alive and free from disease recurrence at just over two years. Although this trial failed to show a significant benefit in terms of overall survival, letrozole treatment demonstrated an estimated difference of 2.6% in the rate of DFS at five years (extrapolated data, (NNT=39)) which is similar to that reported in the ATAC study.<sup>23,37,38</sup> The major criticism of the BIG 1-98 study is the relatively short follow-up period of 25.8 months, given the natural history of the disease. Longer follow-up is necessary to ascertain whether letrozole will continue to reduce the risk of relapse for several years after cessation of treatment, as has already been shown for tamoxifen.

The ATAC trial is the only study of AIs in the adjuvant setting to provide full five year efficacy data. This study compared five years of anastrozole with tamoxifen, or a combination of the two agents.<sup>23,37,38</sup> At a median follow-up 68 months anastrozole treatment was associated with an absolute benefit in terms of DFS of 2.5% (NNT=40). However, no significant improvement in OS was observed. Combination treatment was not shown be superior to tamoxifen alone and this arm was closed early. Although this study confirms the efficacy and tolerability of anastrozole as primary adjuvant treatment for EBC, a direct comparison with letrozole in this setting

cannot be made. Based on the data from the BIG 1-98 and ATAC studies both letrozole (2.5 mg daily) and anastrozole (1mg daily) can be considered as an effective and safe alternative regimen to tamoxifen for the primary adjuvant therapy of EBC. Letrozole (2.5 mg daily) and anastrozole (1mg daily) are currently licensed in the UK for this indication.

An alternative sequential approach of tamoxifen for two to three years followed by a switch to an AI for a combined total of five years adjuvant therapy has been evaluated in three randomised trials.<sup>39-43</sup> In both the ITA study and the combined analysis of the ABCSG-8 and ARNO-95 studies anastrozole treatment was associated with a significant improvement in terms of DFS events compared to tamoxifen alone (absolute benefit 7.8% (NNT=13), and 3.1% (NNT=32), respectively).<sup>39-41</sup> However, no statistically significant difference in OS was observed in either study. The largest trial investigating the efficacy of sequential AI therapy was the IES study which examined the efficacy of a switch to exemestane after two to three years of tamoxifen therapy.<sup>42,43</sup> At a median follow-up of 55.7 months, exemestane treatment was associated with an absolute benefit in DFS of 3.3% at the end of treatment (i.e. 2.5 years after randomisation, NNT=31), and a 3.4% benefit in DFS five years after randomisation (NNT=30).<sup>43</sup> To date this is the only study of an AI to show a treatment effect which persists after treatment discontinuation, similar to that observed after five years of tamoxifen. Furthermore, when patients with oestrogen-receptor-negative were excluded this study showed a modest but statistically significant improvement in OS in favour of exemestane (absolute benefit 1.7%, NNT=59). Based on this evidence, for postmenopausal women who have already received between two and five years of tamoxifen, a switch to an AI for the remainder of the five year treatment duration should be considered. Exemestane 25 mg and anastrozole 1mg daily are currently licensed in the UK for this indication. Consideration should be given to remaining on tamoxifen if there is an established risk of osteoporosis.

The efficacy of letrozole in extended adjuvant therapy after completion of tamoxifen treatment for five years was examined in the MA-17 trial.<sup>44,45</sup> This study compared five years of adjuvant letrozole therapy with placebo after completion of about five years of tamoxifen. After a median follow-up of 2.4 years, letrozole treatment was associated with an estimated benefit in four-year DFS of 6.0% compared with placebo (NNT=45).<sup>44</sup> In an updated analysis after a median follow-up of 30 months the study continued to report a benefit in terms of DFS (absolute benefit 4.6%, NNT=22).<sup>45</sup> Although there was no overall improvement in OS, results of a subgroup analysis revealed that letrozole was associated with significant improvement in OS compared to placebo in patients with node-positive disease at diagnosis, but not in those with node-negative disease. While precise interpretation of this study is limited due to its early termination, the data suggests that for high-risk node-positive postmenopausal women that have already received five years of tamoxifen, a switch to an AI for a minimum of 2.5 years may be considered. Letrozole is currently the only AI licensed in the UK for this indication. In those patients who have had tamoxifen therapy discontinued over three months earlier there is no direct evidence of benefit and the use of letrozole in this situation should be based on the individual patient risk profile. For low-risk node-negative postmenopausal women there is currently no evidence to support the use of more than five years of total endocrine treatment. In all instances more than five years of AI therapy is currently not recommended. There is no evidence to support the use of tamoxifen after an AI in the adjuvant setting.

In those patients with a contraindication to AIs, those with osteoporosis or at high risk of developing osteoporosis and for those patients who decline or are intolerant of AIs, tamoxifen 20mg daily for five years can be considered as an effective alternative to AIs for the treatment of EBC.

The use of AIs in the adjuvant setting has been shown to be generally well-tolerated with a relatively low rate of severe toxicity. It is clear that unlike tamoxifen, AIs are not associated with an increased risk of thromboembolism or endometrial cancer. However, with AI therapy there are major concerns regarding the apparent increased rate of bone disorders and fractures as a result of profound oestrogen deprivation.<sup>27</sup> Although the clinical implications of the bone disorders associated with AIs treatment are undetermined; it is possible, given the concerns regarding the long-term effects of oestrogen deprivation that the safety profile may change with the accumulation of data, especially as the most serious sequelae of osteoporosis, such as hip fractures, may only occur after many years of follow-up. Ongoing monitoring of these issues will be crucial in optimising treatment in this setting. Furthermore, in the BIG 1-98 study there was a significant increase in the incidence of serious cardiovascular events among women given letrozole compared to those receiving tamoxifen.<sup>30,36</sup> This potential for AIs to increase cardiovascular events was also suggested in both the ATAC and IES studies.<sup>42,44,45</sup> Whether this finding simply reflects a cardioprotective effect of tamoxifen is unclear. Nonetheless, the potential for AIs to cause serious cardiovascular events is a major cause for concern and warrants close and careful evaluation, since cardiovascular disease is a common cause of death among breast cancer patients, particularly among those with low-risk disease. Therefore, a full adverse event profile at five years and beyond is essential to enable a complete comparison of the risks and benefits of adjuvant therapy with AIs to be made.

Currently there are no data from adjuvant studies comparing the different AIs on a head-to-head basis. Thus there is a clear lack of information regarding any potential differences in efficacy as well as side effects between the agents. Efficacy and safety data derived from one agent cannot be extrapolated to other AIs. Therefore, treatment decisions should be based on available trial data for each agent and the use of AIs in any of these temporal settings should reflect the licensed indication wherever possible. Further data from large, well-controlled studies is needed to determine the correct sequencing of adjuvant endocrine therapy and the most appropriate agent for use in the different adjuvant settings.

## **ARRANGEMENTS FOR PRESCRIBING**

Adjuvant AI treatment should only be prescribed and the response supervised by an oncologist experienced in the use of anti-cancer therapies.

## **FUTURE DEVELOPMENTS**

There is an absolute requirement to establish those predictive factors which are able to identify patients who are most likely to benefit from AIs. Emerging evidence suggests that tumour progesterone receptor status and HER-2 status might indicate a better response to an aromatase inhibitor than to tamoxifen in the adjuvant

setting.<sup>52,53</sup> Future studies will help to identify those subgroups of patients for whom AIs may be particularly appropriate for primary therapy.

Because of the relatively short duration of follow-up in most adjuvant trials it is not possible to draw definite conclusions regarding the long-term safety of AI treatment in the adjuvant setting. It is possible given the concerns regarding the long-term effects of oestrogen deprivation on bone resorption that the toxicity profile may change with the accumulation of data. Therefore, careful monitoring of bone mineral density and consideration of proactive treatment will become important adjuncts to AI use. There are currently several trials underway that address the use of prophylactic bisphosphonates in patients undergoing adjuvant AI therapy. The large randomised Z-FAST, ZO-FAST and E-ZO-FAST studies will determine whether upfront or delayed zoledronic acid (ZA) therapy can decrease BMD losses in patients undergoing treatment with letrozole.<sup>54</sup>

Despite the proven efficacy of AIs in the treatment of EBC the optimal treatment strategy has yet to be fully defined. Data from large, well-controlled studies is needed to determine the correct sequencing and optimal duration of adjuvant endocrine therapy and the most appropriate agent for use in each of the different adjuvant settings. Results of the sequential treatment arm of the BIG-1-98 trial (letrozole vs. tamoxifen) are expected in February 2008.<sup>55</sup> Direct head-to-head comparisons of AIs in the adjuvant setting are underway; the FACE trial (Letrozole vs. Anastrozole)<sup>56</sup> and the US Intergroup MA27 trial (exemestane v. anastrozole).<sup>57</sup>

The National Institute for Clinical Excellence (NICE) is currently developing clinical guidelines on the diagnosis and treatment of early breast cancer and is expected to publish final guidance in January 2009 (Wave 9).<sup>58</sup>

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## APPENDICES

### **Appendix I. Abridged version of the TNM classification for breast cancer from the AJCC cancer staging manual, 6TH edition.**

#### **TNM staging system for breast cancer**

##### **Tumour size: (T)**

<b>TX</b>	Primary tumour cannot be assessed
<b>TO</b>	No evidence of primary tumour
<b>Tis</b>	carcinoma <i>in situ</i>
<b>T1</b>	Tumour ≤ 2 cm in greatest dimension
<b>T2</b>	> 2 cm but ≤ 5 cm
<b>T3</b>	> 5 cm
<b>T4</b>	Tumour of any size with direct extension to chest wall or skin

##### **Lymph nodes: (N)**

<b>NX</b>	Regional lymph nodes cannot be assessed
<b>NO</b>	No regional lymph node metastasis
<b>N1</b>	Metastasis in movable ipsilateral axillary lymph node(s)
<b>N2</b>	Metastasis in ipsilateral axillary lymph nodes fixed or matted
<b>N3</b>	Metastasis in ipsilateral infraclavicular lymph node(s)

##### **Distant metastasis (M)**

<b>MX</b>	Distant metastasis cannot be assessed
<b>MO</b>	No distant metastasis
<b>M1</b>	Distant metastasis

#### **Breast cancer clinical stage grouping**

##### **Early breast cancer**

**Stage 0:** Ductal carcinoma in situ (DCIS) is cancer that has not spread past the ducts or lobules of the breast (the natural boundaries). It is also called non-invasive cancer.

**Stage I:** The tumour is small and has not spread to the lymph nodes.

**Stage IIa:** Any one of these conditions:

- The tumour is smaller than 2 cm, and has spread to 1-3 axillary lymph nodes under the arm.
- The tumour is between 2 cm and 5 cm, but has not spread to the axillary lymph nodes.
- There is no evidence of a tumour in the breast, but there is cancer in the axillary lymph nodes.

**Stage IIb:** Any one of these conditions:

- The tumour is between 2 cm and 5 cm, and has spread to 1-3 axillary lymph nodes.
- The tumour is larger than 5 cm, but has not spread to the axillary lymph nodes.

#### **Advanced breast cancer**

**Stage IIIa:** Any of these conditions:

- The tumour is smaller than 5 cm, and has spread to 4-9 axillary lymph nodes.
- The tumour is larger than 5 cm, and has spread to 1-9 axillary lymph nodes or internal mammary nodes.

**Stage IIIb:**

The tumour has spread to the chest wall or caused swelling or ulceration of the breast or is diagnosed as inflammatory breast cancer. It may or may not have spread to the lymph nodes under the arm, but has not spread to other parts of the body.

**Stage IIIc:**

Tumour of any size that has not spread to distant parts of the body, but has spread to the lymph nodes above the collarbone, under the collarbone, or both the nodes inside the breast and under the arm.

**Stage IV:**

The tumour can be any size and has spread to distant sites in the body, usually the bones, lungs, liver, or chest wall.

#### **Correlation of clinical and TNM staging system**

<b>UICC STAGE</b>	<b>TNM CLASSIFICATION</b>
Stage 0	0 Tis
Stage I	T1, N0, M0
Stage IIa	T0-1, N1, M0 or T2, N0, M0
Stage IIb	T2, N1, M0 or T3, N0, M0
Stage IIIa	T3, N1, M0 or T0-3, N2, M0
Stage IIIb	T4, any N, M0
Stage IIIc	any T, N3, M0
Stage IV	any T, any N, M1

**Appendix IV. Eastern Cooperative Oncology Group performance status**

<b>Grade</b>	<b>ECOG</b>
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Adapted from Toxicity and Response Criteria of the Eastern Cooperative Oncology Group <sup>59</sup>

**Appendix V. summary of trials**

**Key:** DB - double-blind; DFS – disease free survival; ECOG - Eastern Cooperative Oncology Group performance status (see appendix IV); EFS – event free survival; FSH – follicle stimulating hormone; HR – hazard ratio; HRT – hormone-replacement therapy; ITT - intention-to-treat; LH – luteinising hormone; MC - multi-centre; NNH - numbers needed to harm; NNT – numbers needed to treat; OL – open label; OS – overall survival; Pbo – placebo; Pts – patients; R – Randomised; RCT - Randomised controlled trial; SERM – selective oestrogen-receptor modulator.

**Letrozole as primary adjuvant therapy**

Reference	Design	Intervention	Patient numbers	Inclusion Criteria	Exclusion Criteria	Primary outcome	Results	Adverse effects
BIG 1-98 <sup>30</sup> <sup>36</sup>	RCT, DB, MC	Tamoxifen 2.5mg/day or letrozole 2.5mg/day  (Arm A) Tamoxifen 5 years.  (Arm B) Letrozole 5 years.  (Arm C) Tamoxifen for 2 years followed by letrozole for 3 years.  (Arm D) Letrozole for 2 years followed by tamoxifen for 3 years.	R = 8,028  (18 patients withdrew consent and did not start treatment).  ITT = 8,010  (letrozole n = 4,003 & tamoxifen n = 4,007)	Postmenopausal women with breast cancer positive for either oestrogen receptors (ER+) or progesterone receptors (PgR+), or both.  Primary surgery with resulting clear margins and adequate haematologic, renal, and hepatic function were required.	Evidence of metastatic disease; previous or concurrent cancer other than adequately treated non-invasive breast cervical or skin cancer within 5 years before randomisation.	Disease-free survival (DFS).  (Defined as the time from randomisation to recurrence of invasive breast cancer, invasive contralateral breast cancer, second non- breast malignancy, or death without recurrence).	*At median follow-up 25.8 months, DFS was significantly greater in the letrozole group than in the tamoxifen group, HR 0.81 (95%CI, 0.70 - 0.93, p=0.003). This corresponds to an absolute benefit in terms of DFS of 1.9% (91.2% vs. 89.3%, NNT 53).  Estimated 5-year DFS for patients receiving letrozole was 84.0% compared to 81.4% for tamoxifen, absolute benefit 2.6% (NNT=39).  There was no significant difference in OS between groups.  * Letrozole data was obtained from arm B and the first 2 years of arm D, and compared to tamoxifen data from arm A, and the first 2 years of arm C. All events occurring within 30 days of therapy switch in arms C and D were included in the analysis.	587 pts on letrozole and 643 pts on tamoxifen reported at least one serious adverse event. Pts on letrozole had significantly more bone fractures (5.7% vs. 4.0%, p=0.001) , and hyper- cholesterolaemia (43.6% vs. 19.2%).  Overall incidence of cardiac events was similar in the two groups (3.7% vs. 4.1%). However, letrozole significantly increased the risk of grade 3, 4 or 5 cardiac events in (2.1% vs. 1.1%, p=0.001).  Letrozole was associated with significantly fewer thromboembolic events (1.5% vs. 3.5%, p<0.001

**Anastrozole as primary adjuvant therapy**

Reference	Design	Intervention	Patient numbers	Inclusion Criteria	Exclusion Criteria	Primary outcome	Results	Adverse effects
ATAC 23,37,38	RCT, DB, MC	Anastrozole 1mg/day or tamoxifen 20mg/day  (Arm A) Anastrozole 5 years.  (Arm B) Tamoxifen 5 years.  (Arm C)* Anastrozole and Tamoxifen for 5 years.	R = 9,366  ITT = 9,283  (Anastrozole n = 3,092, tamoxifen n= 3,094, and combination = 3,097)  n	Postmenopausal women with histologically proven operable invasive breast cancer.  Patients with negative or unknown hormone- receptor status were included as at that time assessment of status was not routinely available in some countries	Evidence or history of metastatic disease (excluding squamous or basal- cell carcinoma of the skin or carcinoma in-situ of the cervix); chemotherapy > 8 weeks after surgery or completed >8 weeks prior to randomisation; prior hormonal therapy except if tamoxifen was started before surgery and received for < 29 days.	Disease-free survival (DFS).  (Defined as time to earliest occurrence of local or distant recurrence, new primary breast cancer, or death from any cause).	At median follow-up 68 months, DFS was significantly greater in the anastrozole group than in the tamoxifen group, HR 0.87 (95%CI, 0.78 -0.97, p=0.01). This corresponds to an absolute benefit in terms of DFS of 2.5% (81.6% vs. 79.1%, NNT = 40).  There was no significant difference in OS between groups.  * The combination arm was closed early because of low efficacy.	Withdrawals due to adverse events were significantly lower with anastrozole than tamoxifen (11.1% vs. 14.3%, p=0.0002).  Anastrozole was also associated with significant reductions in the incidence of endometrial cancer (0.2% vs. 0.8% p=0.02), thromboembolic events (2.8% vs. 4.5%, P=0.0004), ischaemic cerebrovascular events (2.0% vs. 2.8%, P=0.03), vaginal bleeding (5.4% vs. 10.2%, P<0.0001), vaginal discharge (3.5% vs. 13.2%, P<0.0001) and hot flushes (35.7% vs. 40.9%, P<0.0001).  Tamoxifen was associated with significantly fewer fractures (7.7% vs. 11.0%, P<0.0001), and less athralgia (29.4% vs. 35.6%, P<0.0001), than anastrozole.

**Anastrozole as sequential therapy**

Reference	Design	Intervention	Patient numbers	Inclusion Criteria	Exclusion Criteria	Primary outcome	Results	Adverse effects
GABG <sup>39</sup> (combined analysis of ABCSG-8 & ARNO-95)	RCT, OL, MC	Anastrozole 1mg/day or tamoxifen 20 or 30mg/day  (Arm A) Tamoxifen 2 years then anastrozole 3 years.  (Arm B) Tamoxifen 5 years.	R = 3,224 ABCSG-8 n=2,262, ARNO-95 n=962  ITT = 3,224 (Anastrozole n = 1,618 and tamoxifen n=1,606)	Postmenopausal women ≤80 years of age (ABCSG) or ≤75 years (ARNO) with histologically verified, locally treated or minimally invasive breast cancer without previous chemotherapy, hormone therapy or radiotherapy, tumour infiltration up to ten (ABCSG) or nine (ARNO) lymph nodes, and absence of organ metastases. All patients had endocrine-responsive tumours.	Indeterminate menopausal status; presence of secondary malignant disease; tumour infiltration of skin or breast muscles and presence of other concomitant serious medical problems- e.g. those involving bone marrow function, CNS, cardiac insufficiency or uncontrolled local or systemic infection.	Event-free survival (EFS).  (Defined as time to relapse at any site or incidence of contralateral breast cancer).	At median follow-up 28 months, EFS was significantly greater in the anastrozole group than in the tamoxifen group, HR 0.60 (95% CI, 0.44 -0.81, p=0.0009). This corresponds to an absolute benefit in terms of the estimated EFS at 3 years of 3.1% (95.8% vs. 92.7%, NNT = 33).  Significantly fewer metastases arose in the anastrozole-treated patients compared to those receiving only tamoxifen (HR 0.61; 95% CI 0.42-0.87; p=0.0067), corresponding to an absolute decrease of 2% in the risk of metastases for women switching to anastrozole (5% vs. 3%, NNT=50).  There was no significant difference in OS between groups.	Anastrozole was associated with significant more fractures (2.1% vs. 1.0%, p=0.015) and significantly fewer thromboses (0.2% vs. 0.8%, p=0.034) compared with tamoxifen.  In the ABCSG trial anastrozole was associated with significantly more reports of nausea (2.2% vs. 0.9%, p=0.016). However, the overall incidence of specified adverse events was similar for both groups.  No adverse events were prespecified in the ARNO protocol.

**Anastrozole as sequential therapy**

Reference	Design	Intervention	Patient numbers	Inclusion Criteria	Exclusion Criteria	Primary outcome	Results	Adverse effects
ITA <sup>40,41</sup>	RCT, MC	<p>Anastrozole 1mg/day or tamoxifen 20mg/day</p> <p>(Arm A) Tamoxifen for 2 to 3 years then anastrozole for a total duration of treatment of 5 years.</p> <p>(Arm B) Tamoxifen 5 years.</p>	<p>R= 448</p> <p>ITT = 448 (Anastrozole n = 223 and tamoxifen n= 225)</p>	Postmenopausal women with histologically verified primary breast cancer; positive hormone-receptor (oestrogen) status; positive axillary nodes, and no evidence of metastatic disease.	Evidence or history of metastatic disease (excluding adequately treated carcinoma of the skin or carcinoma in-situ of the cervix), and any condition that may jeopardise compliance to treatment.	<p>Disease-free survival (DFS).</p> <p>(Defined as the time from randomisation to disease recurrence, including both locoregional and distant recurrences (except contralateral breast cancer)).</p>	<p>At median follow-up 36 months, DFS was significantly greater in the anastrozole group than in the tamoxifen group, HR 0.35 (95%CI, 0.18 - 0.68, p=0.001). This corresponds to an absolute benefit in terms of DFS of 8.8% (94.6% vs. 85.8%, NNT=12).</p> <p>In an updated analysis at median follow-up 64 months, DFS was significantly greater in the anastrozole group than in the tamoxifen group, HR 0.56 (95%CI, 0.35 - 0.89, p=0.01). This corresponds to an absolute benefit in terms of DFS of 7.8% (87.4% vs. 79.6%, NNT=13).</p> <p>There was no significant difference in OS between groups in either analysis.</p>	<p>Overall there were more adverse events in the anastrozole group (43.9% vs. 36.0%, p=0.04). However, significantly more serious events occurred in the tamoxifen group (22.0% vs.13.9%, p=0.04). There were significantly more gynaecological changes, including endometrial cancer in the tamoxifen group (11.3% vs. 1.0%, p=0.0002).</p> <p>Updated analysis = overall adverse events 93.7% vs. 67.1%, p=0.000 for anastrozole vs. tamoxifen; serious adverse events were comparable 17.8% vs.16.6%, p=0.7, respectively &amp; serious gynaecological problems including endometrial cancer were significantly more numerous in the tamoxifen group (5.3% vs. 0.9%, p=0.006).</p>

**Exemestane as sequential therapy**

Reference	Design	Intervention	Patient numbers	Inclusion Criteria	Exclusion Criteria	Primary outcome	Results	Adverse effects
IES <sup>42,43</sup>	RCT, DB, MC	<p>Exemestane 25mg/day or tamoxifen 20mg/day</p> <p>(Arm A) Tamoxifen for 2 to 3 years then exemestane for a total duration of treatment of 5 years.</p> <p>(Arm B) Tamoxifen 5 years.</p>	<p>R= 4,742</p> <p>ITT = 4,742 (Exemestane n = 2,362 and tamoxifen n= 2,380)</p>	<p>Postmenopausal women with histologically confirmed, completely resected unilateral invasive breast cancer that was positive for oestrogen receptors and had received tamoxifen for at least 2 years but not more than 3 years and one month. Adequate haematologic, renal and liver function at time of randomisation.</p>	<p>Presence of tumour with known negative oestrogen-receptor status; evidence of local relapse or a distant metastasis since diagnosis; clinically significant skeletal, cardiac, or endocrine disorder; use of HRT within 4 weeks or randomisation; clinical evidence of severe osteoporosis or history of previous cancer other than squamous or basal-cell carcinoma of the skin or carcinoma in-situ of the cervix; taking concomitant anticoagulants, or SERM other than tamoxifen.</p>	<p>Disease-free survival (DFS).  (Defined as time from randomisation to recurrence of breast cancer at any site, diagnosis of a second primary breast cancer, or death from any cause).</p>	<p>At median follow-up 30.6 months, DFS was significantly greater in the exemestane group than in the tamoxifen group. HR 0.68 (95%CI, 0.56 - 0.82, p&lt;0.001), absolute benefit 4.7% (91.5% vs. 86.8%, NNT=22).</p> <p>In an updated analysis (median follow-up 55.7 months), DFS was significantly greater in the exemestane group than in the tamoxifen group, HR 0.76 (95%CI, 0.66 - 0.88, p=0.0001), corresponding to an absolute benefit of 3.3% (NNT=31) in terms of DFS at 2.5 years after randomisation, and a 3.4% (NNT=30) benefit five years after randomisation. Exemestane was associated with a modest improvement in OS when ER- patients were excluded (HR 0.83; 95% CI 0.69-1.00; p=0.05), absolute benefit 1.7% (90.9% vs. 89.2%, NNT=59).</p>	<p>Exemestane was associated with a significantly lower incidence of thromboembolic disease (1.0% vs. 1.9%, p=0.003) and gynaecological symptoms (5.8% vs. 9.0%, p&lt;0.001) than tamoxifen.</p> <p>Updated analysis = exemestane was associated with a significantly lower incidence of thromboembolic disease (1.9% vs. 3.1%, p=0.01) and serious gynaecological symptoms (7.0% vs. 10.6%, p&lt;0.0001) than tamoxifen. The number of endometrial cancers did not differ significantly between groups.</p>

**Letrozole as extended adjuvant therapy**

Reference	Design	Intervention	Patient numbers	Inclusion Criteria	Exclusion Criteria	Primary outcome	Results	Adverse effects
MA-17 <sup>44,45</sup>	RCT, DB, Pbo	Letrozole 2.5 mg or placebo orally daily for 5 years.	R = 5187 (letrozole n = 2593 & placebo n = 2594)  17 patients (10 in the letrozole arm and 7 in the placebo arm) were excluded from the analysis because of non-compliance with "good Clinical Practice" Guidelines (n = 5,170).	Women were eligible if ≥ 50 years of age at start of adjuvant tamoxifen therapy, if they were younger than 50 years at start of tamoxifen therapy and were either postmenopausal or had undergone bilateral oophorectomy or were premenopausal but became amenorrhic during chemotherapy or treatment with tamoxifen, or if they had postmenopausal levels of LH or FSH.  Previous adjuvant tamoxifen therapy lasting 4.5 to 6 years with discontinuation of therapy <3 months prior to enrolment.  Histologically confirmed primary breast cancer. A tumour that was oestrogen and/or progesterone receptor positive.  ECOG performance status of 0, 1 or 2 and life expectancy of more than 5 years.	Presence of another type of cancer other than skin cancer or carcinoma in situ of the cervix.  Concurrent use of study drugs.  Concomitant systemic HRT or concomitant treatment with a selective oestrogen-receptor modulator.	Disease-free survival (DFS).  (Defined as the time from randomisation to the earliest recurrence of the primary disease (in the breast, chest wall, or nodal or metastatic sites) or the development of a new primary breast cancer in the contralateral breast).	*At first interim analysis (median follow-up 2.4 years) there was a significant improvement in the estimated 4 year DFS in favour of the letrozole group compared with placebo (HR, 0.57; 95% CI 0.43-0.75; p=0.0008). This corresponds to an absolute benefit of 6.0% in the terms of DFS at 4 years (92.8% vs. 86.8%, NNT=17).  *The study was terminated after this interim analysis and letrozole offered to all participants randomised to placebo  In an updated analysis (median follow-up of 30 months) the study continued to report a benefit in terms of DFS (94.4% vs.89.8%, p<0.001) corresponding to an absolute benefit of 4.6% in favour of letrozole (NNT=22).  There was no significant difference in OS between groups in either analysis.	Low-grade hot flushes, arthritis, arthralgia, and myalgia were more frequent in the letrozole group. Vaginal bleeding was more common in the placebo group.  New diagnoses of osteoporosis and cardiovascular events were higher in the letrozole group compared to placebo, but these were not statistically significant (p=0.07 and p=0.40, respectively). The rates of fracture were similar between the two groups.  4.5% of the letrozole and 3.6% of the placebo group discontinued treatment because of adverse effects (p=0.11).