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Position Paper

Adjuvant endocrine therapy in postmenopausal women with early breast cancer: Where are we now?

M. Baum *

Clinical Trials Group, Department of Surgery, Charles Bell House, 67–73 Riding House Street, London W1W 7EJ, UK

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Abstract

Tamoxifen has been the standard of care for adjuvant endocrine therapy of early breast cancer. In postmenopausal women, data now suggest that alternative agents (aromatase inhibitors [AIs]) may have improved long-term risk:benefit profiles and thus have the potential to improve outcome. The 'Arimidex', Tamoxifen, alone or in combination (ATAC) trial has shown that anastrozole provides improved disease-free survival (DFS) and time to recurrence, significantly reduced time to distant metastases and superior overall tolerability compared with tamoxifen when used as initial adjuvant therapy. Results have already led to a reconsideration of current recommendations for adjuvant therapy. Other ongoing trials include studies that are evaluating the benefits of sequencing of endocrine agents both within the standard 5-year adjuvant treatment period and as additional therapy in the post-adjuvant period. Three recently reported trials have suggested that switching from tamoxifen to an AI after 2–3 years of treatment leads to better outcomes than 5 years of tamoxifen. Finally, the NCIC MA 17 trial has shown that switching to an AI after 5 years of tamoxifen improves DFS compared with placebo.

These are momentous discoveries that have improved our biological understanding and will inevitably change the management of breast cancer in the near future.

Keywords: Adjuvant; Endocrine; Postmenopausal; Tolerability; Risk:benefit; Switching; Hormone; Early breast cancer

1. Introduction

Endocrine manipulation has been used with great success for the treatment of hormone-sensitive breast cancer, and the dramatic fall in mortality from the disease in both the UK and the USA over the past 15 years has been attributed to its use [1].

The first pioneering report of endocrine manipulation of breast cancer was made by Beatson, who carried out a landmark series of cases of surgical castration for the treatment of advanced breast cancer. Approximately 50 years later, Huggins and his colleagues first described surgical adrenalectomy as second-line endocrine therapy [2]. Over the next 50 years endocrinologists and clinicians made a concerted effort to understand and exploit the mechanisms underlying these treatments for optimal clinical benefit. A 'thread' that runs through this endeavour has been the search for the mechanism of response. Identification of the role of oestrogen receptor (ER) in selecting the most appropriate patients for treatment was a fundamental step in meeting this aim.

Until recently, tamoxifen, a selective oestrogen receptor modulator (SERM), had been the endocrine therapy of choice for hormone-responsive early breast cancer in postmenopausal women, having been used for more than 30 years. Concerns over serious side effects associated with long-term use of tamoxifen, such as increased

* Tel.: +44 20 7679 9679; fax: +44 20 7679 9678.
E-mail address: michael@mbaum.freeserve.co.uk.

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incidence of endometrial cancer [3–7] and thromboembolic events [8,9], coupled with the development of resistance [10], has led to the development of additional agents with improved efficacy and tolerability.

For postmenopausal women, the major source of oestrogen is from peripheral aromatisation of androgens synthesised in the adrenal gland. The rate-limiting step in the pathway is catalysed by the aromatase enzyme and agents have therefore been developed that inhibit this key enzyme [11]. The modern third-generation aromatase inhibitors (AIs), which include the non-steroidal agents anastrozole and letrozole and the steroidal compound exemestane, show increased potency with respect to both aromatase inhibition and subsequent oestrogen suppression compared with earlier AIs, such as aminoglutethimide [12,13]. The third-generation AIs have been shown to be successful in advanced breast cancer [14–21] and both anastrozole and letrozole are now being evaluated in the adjuvant setting in patients with ER-positive tumours [22–25]. Recent clinical data from the 'Arimidex', Tamoxifen, alone or in combination (ATAC) trial indicate that the position of tamoxifen as first-choice adjuvant therapy in postmenopausal women is now being challenged by the AIs and this paper reviews these data and their potential relevance to clinical practice.

2. Current status of adjuvant therapy with tamoxifen

The first trials of adjuvant tamoxifen therapy started in the late 1970s and involved control groups that were given no therapy *versus* tamoxifen for 1 or 2 years [26]. The Nolvadex Adjuvant Trial Organisation (NATO) study, which involved 1100 women, was the first study to show an advantage for disease-free survival (DFS) in patients receiving adjuvant tamoxifen compared with placebo [27]. Most of the patients were postmenopausal and with or without nodal involvement, although node-positive premenopausal women were also included. Less than half of the patients had histologically proven involved nodes. After a median follow-up of 66 months there was a significant reduction in recurrence rate (36%) and mortality (29%) in patients receiving tamoxifen relative to placebo [28].

NATO was followed by other studies investigating adjuvant tamoxifen for 2 or 5 years and the first overview of the results demonstrated that it was associated with reductions in relative risk of relapse (25%) and death (17%) over a 10-year follow-up period, regardless of nodal status [29]. Postmenopausal women with ER-positive tumours received the greatest benefit. This was confirmed in the most recent overview published in 1998 [29], and the as yet unpublished 2000 overview has established that only women with ER-positive breast cancer should receive adjuvant tamoxifen. The overview of 55 trials with adjuvant tamoxifen administered for 1 year, 2 years or 5 years *versus* no treatment in patients with early stage breast cancer [29] showed that tamoxifen treatment produced highly significant benefits in terms of both disease recurrence and mortality (proportional reductions in recurrence were 18%, 25% and 41%; proportional reductions in death rate were 10%, 15% and 22% for 1, 2 and 5 years of tamoxifen treatment, respectively; $P < 0.00001$ for each). Further investigations have been carried out to compare the effect of 2, 5 and >5 years of treatment with tamoxifen [5,30–33]. From these studies, 5 years of tamoxifen treatment appears to be the optimal duration of therapy in terms of patient benefit. The benefit from 5 years of tamoxifen therapy persists through 10 years of follow-up. No additional advantage was obtained from continuing tamoxifen therapy for more than 5 years [5].

Further clarification of optimal treatment duration is being investigated in two ongoing adjuvant trials – the adjuvant Tamoxifen Treatment offers more (aTTom) trial, which is being performed in the UK, and its international counterpart, the Adjuvant Tamoxifen – Longer Against Shorter (ATLAS) trial [34], both of which completed recruitment in March 2005. In the aTTom trial, women who have been taking tamoxifen for at least 2 years (5 years now recommended) are randomised to discontinuation or continuation of treatment for a further 3 years [35,36], while the ATLAS trial is randomizing women who have received tamoxifen for about 5 years to discontinuation or to tamoxifen for a further 5 years [37].

The use of tamoxifen is limited by the partial agonist activity it exerts on the ER, which is associated with its potentially life-threatening side effects, including increased incidence of endometrial cancer and uterine sarcoma [3,5,38,39]. Tamoxifen has been shown to double the risk of endometrial cancer after 1 or 2 years of treatment, and the risk quadruples after 5 years of treatment [6]. The relationship between tamoxifen and endometrial cancer is time-dependent, which is of particular concern in the adjuvant setting where the duration of therapy is relatively long. The risk is also irrespective of dose and does not decrease after cessation of treatment [7].

Studies have also provided evidence that the use of tamoxifen increases the risk of thromboembolic events [5,8,9]. After 5 years of tamoxifen treatment the incidence of thromboembolic events was higher for tamoxifen-treated than placebo-treated patients (1.7% *versus* 0.4%) in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial [5]. Hence, despite its efficacy these serious risks associated with long-term use of tamoxifen limit its risk:benefit profile as an adjuvant therapy.

3. The role of aromatase inhibitors for postmenopausal women

The first-generation AI aminoglutethimide became available approximately 25 years ago [40], but was unable to rival tamoxifen due to its lack of selectivity for the aromatase enzyme and its consequent toxicity. After further development, formestane, a second-generation AI, possessing fewer side effects than aminoglutethimide, became available in 1993 [41]. Modern 'third-generation' AIs are highly specific for aromatase and have been shown to be effective and well tolerated as second-line therapies for postmenopausal women with advanced breast cancer who have progressed on tamoxifen [14,19,21,42]. In addition, anastrozole and letrozole have been show to be more effective compared with tamoxifen in the first-line setting in advanced disease [18,20,43,44], with anastrozole also having significant tolerability benefits [18,20]. AIs do not possess the same partial oestrogenic agonist activity as tamoxifen, therefore fewer serious adverse events associated with their use were expected. As a result, these AIs represent ideal candidates for replacing tamoxifen in the adjuvant setting for postmenopausal women with hormone receptor-positive tumours, although the effects (for example on bone) of the more complete oestrogen suppression provided by these agents also needs to be considered.

4. Aromatase inhibitors as adjuvant therapy in postmenopausal women

There are several ongoing studies involving third-generation AIs in the adjuvant setting (Table 1). Of these studies, the ATAC and Breast International Group (BIG) 1–98 trials are the only studies that directly compare an AI with tamoxifen as adjuvant therapy reported to date. The Italian Tamoxifen Anastrozole (ITA) trial, in which patients who had received 2–3 years of adjuvant tamoxifen were randomised to continue on tamoxifen or switch to anastrozole for the remainder of the 5-year adjuvant treatment period, was the first of the switching trials to be reported [45]. In addition, two other large multinational trials have investigated switching to an AI. The first of these, the BIG Intergroup Exemestane Study (IES) [46], studied the steroidal AI exemestane, and the second, the combined Austrian and German trials (ABCSG 8/ARNO 95) [47], studied anastrozole in the same setting. Finally, data are now available for the MA 17 trial of 'extended adjuvant therapy' in which patients received 5 years' standard adjuvant therapy with tamoxifen and were then randomised to placebo or letrozole for a further 5 years [25].

5. Comparison of AIs *versus* tamoxifen as initial adjuvant therapy in early breast cancer

The ATAC trial was designed to test the hypotheses that anastrozole was non-inferior or superior to tamoxifen and that the combination of anastrozole and tamoxifen was superior to tamoxifen alone as standard adjuvant therapy of postmenopausal women newly diagnosed with early breast cancer (Fig. 1). A total of 9366 patients were recruited from 381 centres in 21 countries.

The initial and updated analyses of the ATAC trial demonstrated that anastrozole significantly prolonged DFS and time to recurrence (TTR), and reduced the incidence of contralateral breast cancer compared with tamoxifen [22,23]. However, the combination treatment arm was closed after the initial analysis as no advantages were seen in efficacy and tolerability over the tamoxifen arm.

Table 1
Ongoing randomised adjuvant AI trials

Trial name	Patient status	Trial description
Anastrozole		
ATAC	Postmenopausal	5 years of anastrozole alone, tamoxifen alone or the combination (duration 47 months only for combination)
ABCSG AU08	Postmenopausal	2 years of tamoxifen then randomised to 3 years of anastrozole or 3 years of tamoxifen
GR0001	Postmenopausal	2 years of tamoxifen then randomised to 3 years of anastrozole or 3 years of tamoxifen
ITA	Postmenopausal	2 years of tamoxifen then randomised to 3 years of anastrozole or 3 years of tamoxifen
ABCSG AU06	Postmenopausal	5 years of tamoxifen *versus* 2 years of tamoxifen plus aminoglutethimide then 3 years of tamoxifen. Both arms followed by 3 years of anastrozole
Ham-AT	Postmenopausal	6 months of anastrozole alone, tamoxifen alone or anastrozole plus tamoxifen
Letrozole		
BIG 1-98	Postmenopausal	Tamoxifen (5 years) *versus* tamoxifen (2 years) followed by letrozole (3 years) *versus* letrozole (5 years) *versus* letrozole (2 years) followed by tamoxifen (3 years)
NCIC MA.17	Postmenopausal	Tamoxifen (5 years) followed by placebo or letrozole (5 years)
Exemestane		
BIG 02-97	Postmenopausal	Tamoxifen (5 years) *versus* tamoxifen (2 years) followed by exemestane (3 years)

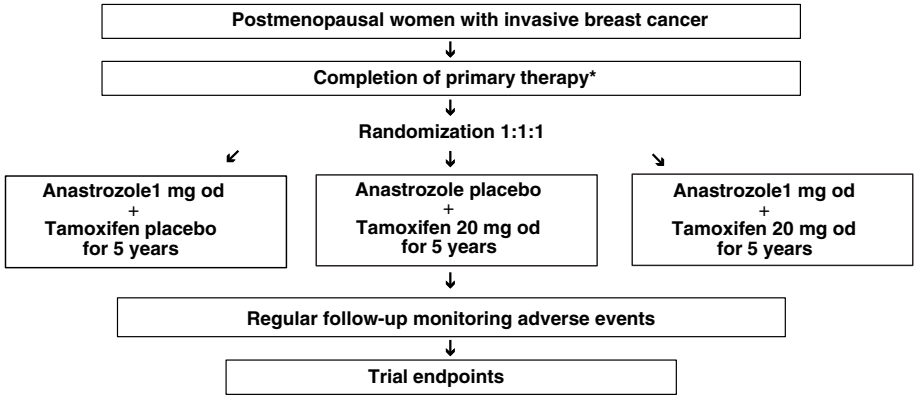

Fig. 1. Design of the ATAC trial. *Surgery ± radiotheraphy ± chemotheraphy (patients may start trial theraphy while still receiving radiotheraphy).

After a median follow-up of 68 months, when only 8% of patients remained on trial treatment, a completed treatment analysis was performed [24]. Anastrozole demonstrated significant improvements in DFS (hazard ratio [HR] 0.87; 95% confidence intervals [CI] 0.78, 0.97; $P = 0.01$) and TTR (HR 0.79; 95% CI 0.70, 0.90; $P = 0.0005$) compared with tamoxifen. In the hormone receptor-positive subgroup (84% of the total population studied) DFS (HR 0.83; 95% CI 0.73, 0.94; $P = 0.005$) and TTR (HR 0.74; 95% CI 0.64, 0.87; $P = 0.0002$) (Fig. 2) were also significantly longer for anastrozole compared with tamoxifen. Notably, in terms of DFS and TTR, the absolute benefit of anastrozole over tamoxifen increased over time, even beyond completion of 5 years' scheduled treatment. Absolute differences in DFS and TTR (Fig. 2) also increased out to 6 years in the hormone receptor-positive subgroup.

There was a significant reduction in contralateral breast cancer in the anastrozole *versus* the tamoxifen group (all patients 42% reduction, 95% CI 12, 62; $P = 0.01$; hormone receptor-positive patients 53% reduction, 95% CI 25, 71; $P = 0.001$) and a significant overall benefit was reported in time to distant recurrence for anastrozole (HR 0.86; 95% CI 0.74, 0.99; $P = 0.04$).

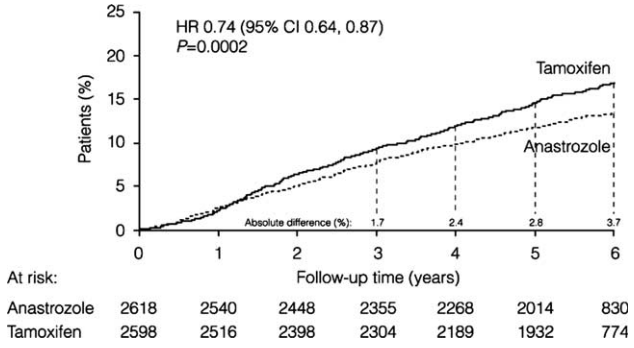

Fig. 2. Time to recurrence in the hormone receptor-positive population at 1, 2, 3, 4, 5 and 6 years of treatment. CI = confidence intervals. Reprinted with permission from Elsevier (*The Lancet*, 2005, **365**, 60–62) [24].

A similar trend was observed in the subset of hormone receptor-positive patients (HR 0.84; 95% CI 0.70, 1.00; $P = 0.06$). Overall survival was similar between treatment groups, demonstrating that anastrozole maintains the established survival benefit seen with tamoxifen (HR 0.97; 95% CI 0.85, 1.12; $P = 0.7$). There was a 12% reduction in breast cancer deaths with anastrozole, although this did not reach statistical significance (HR 0.88; 95% CI 0.74, 1.05; $P = 0.2$).

In terms of tolerability, predefined adverse events occurred with similar relative frequency in the completed treatment analysis compared with previous reports throughout the trial [22,23] but the absolute incidence of adverse events increased with longer follow-up. Treatment with anastrozole was associated with significant reductions in the incidence of endometrial cancer, thromboembolic events, including pulmonary embolism and deep venous thromboembolic events, ischaemic cerebrovascular events, hot flushes, vaginal bleeding and discharge, compared with tamoxifen (Table 2) [24]. Furthermore, with the on-treatment safety data almost complete, the number of cardiovascular deaths in the anastrozole arm and the tamoxifen arm was similar (49 *versus* 46, respectively) [48]. Withdrawals due to adverse events were significantly less common with anastrozole than with tamoxifen (11.1% *versus* 14.3%, respectively; $P = 0.002$) [24]. Likewise, drug-related serious adverse events were also significantly less common with anastrozole (4.7% *versus* 9.0%; $P < 0.0001$) [24].

Although a higher incidence of fractures occured in the anastrozole arm, it appears that after the initial increase in the first 2 years of therapy in the updated analysis (anastrozole *versus* tamoxifen, 7.1% *versus* 4.6%; $P < 0.001$) [23], the relative fracture risk stabilised over time even though the patients remained on treatment [49] (Fig. 3). This pattern continued with no further change in relative fracture risk for the full 68-month treatment period [24]. To date, anastrozole is the only AI with long-term safety and tolerability data from 5 years' adjuvant treatment of postmenopausal women with early breast cancer.

Table 2
Predefined adverse events on treatment or within 14 days of discontinuation

Adverse event	No. patients (%)		Odds ratio[a] (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 (asthenia)	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
Joint symptoms	1100 (35.6)	911 (29.4)	1.32 (1.19, 1.47)	<0.0001[d]
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[b]	5 (0.2)	17 (0.8)	0.29 (0.11, 0.80)	0.02
Fractures[c]	340 (11.0)	237 (7.7)	1.49 (1.25, 1.77)	<0.0001[d]
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[d]
Wrist/colles	72 (2.3)	63 (2.0)	1.15 (0.81, 1.61)	0.4
All other sites[e]	220 (7.1)	142 (4.6)	1.59 (1.28, 1.98)	<0.0001[d]
Ischaemic cardiovascular disease	127 (4.1)	104 (3.4)	1.23 (0.95, 1.60)	0.1
Ichaemic 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

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[a] Anastrozole *versus* tamoxifen.
[b] $N = 2229$ for anastrozole and 2236 for tamoxifen (excluding patients with hysterectomy at baseline), recorded at any time.
[c] Patients with $\geqslant 1$ fractures occurring at any time before recurrence (includes patients no longer receiving treatment).
[d] In favour of tamoxifen.
[e] Patients may have had $\geqslant 1$ fracture at different sites; CI = confidence intervals.

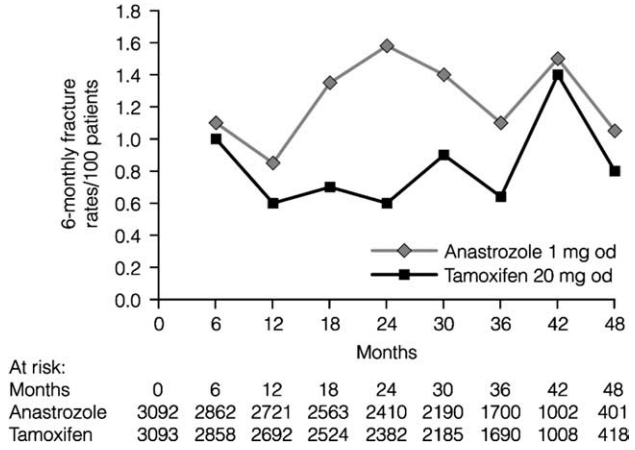

Fig. 3. Fracture rates assessed at 6-monthly intervals in postmenopausal patients with early breast cancer in the anastrozole and tamoxifen groups.

The quality of life (QoL) of postmenopausal women participating in the ATAC trial during the first 2 years of treatment has also been assessed [50]. Two years' treatment with anastrozole, given alone or in combination with tamoxifen, did not appear to have a detrimental impact on QoL compared with use of tamoxifen alone. In fact, compared with baseline, the QoL may improve over time in a pattern which was roughly equivalent across treatment arms. The QoL subprotocol data show that the efficacy benefits demonstrated in patients in the anastrozole group were not at the expense of QoL, but there are differences in type and severity of endocrine symptoms associated with anastrozole or tamoxifen that need to be considered by clinicians and patients when making treatment decisions.

Results from the primary analysis of the BIG 1-98 phase III trial have recently been reported [51]. The BIG 1-98 trial was designed 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. The primary analysis, performed at a median follow-up of 26 months, compared tamoxifen with letrozole, combining patients from monotherapy and sequential arms, as adjuvant therapy in 8028 postmenopausal women with ER-positive early breast cancer. A second analysis, not yet completed, will evaluate the sequential arms.

Letrozole demonstrated a significant improvement compared with tamoxifen in the primary endpoint of DFS (HR 0.81; 95% CI 0.70, 0.93; $P = 0.003$). All other efficacy endpoints also favoured letrozole, including TTR (HR 0.72; 95% CI 0.61, 0.86; $P = 0.0002$) and time to distant recurrence (HR 0.73; 95% CI 0.60, 0.88; $P = 0.0012$).

A total of 587 patients on letrozole, compared with 643 patients on tamoxifen, reported at least one serious adverse event. Letrozole was associated with an increased risk of bone fractures but a decreased risk of venous thromboembolic side effects compared with tamoxifen. Compared with tamoxifen, women treated with letrozole have a greater risk of stroke and cardiac

events. There was an increase in cardiac deaths (26 and 13 for letrozole and tamoxifen, respectively) and in deaths due to cerebrovascular events (7 and 1 for letrozole and tamoxifen, respectively). These events raise concerns at this early stage of assessment and further investigations with longer follow-up are necessary to establish the long-term safety and tolerability of letrozole.

It is important not to extrapolate data from the ATAC trial to other AIs, as there are differences in the pharmacological profiles of AIs, including safety, pharmacokinetics, effects on lipids, bone absorption, steroidogenesis and specificity. Clinical differences between the AIs are now beginning to appear (*e.g.* cardiovascular deaths in ATAC/BIG 1-98) and these may become more apparent following long-term treatment [13,52]. Indeed, the American Society of Clinical Oncology Technology assessment of the ATAC data notes that closely related agents with similar mechanisms of action may have different toxicity profiles [53].

6. Switching adjuvant endocrine treatment

During adjuvant treatment it may be desirable or necessary to switch patients from one treatment to another. Possible rationales for switching adjuvant treatment from tamoxifen are reduced tamoxifen exposure, which is known to be associated with serious side effects when used in the long term, and tamoxifen resistance. In addition, it is possible that switching patients who have already begun on tamoxifen to an AI may provide improved outcomes irrespective of the occurrence of serious side effects or tamoxifen resistance. However, until recently it was unclear if the advantages of anastrozole compared with tamoxifen seen in the ATAC trial might also apply to women already taking adjuvant tamoxifen. The results from the ITA trial first highlighted the potential benefits of switching from adjuvant tamoxifen to adjuvant anastrozole.

Preliminary results of the ITA trial comparing 3 years of treatment with anastrozole or tamoxifen after an initial 2-year treatment with tamoxifen were presented at the San Antonio Breast Cancer Symposium, 2003 [45]. A total of 426 patients who had received 2 years of tamoxifen and were disease-free were assigned to continue on tamoxifen ($N = 218$) or receive anastrozole ($N = 208$). Events in each group are shown in Table 3. After adjusting for age, number of involved nodes, tumour grade and primary treatment, the results were in favour of anastrozole. A decreased risk of relapse (HR 0.36; 95% CI 0.17, 0.75; $P = 0.006$) and of death (HR 0.18; 95% CI 0.02, 1.57; $P = 0.07$), was apparent in those who had switched to anastrozole compared with those who remained on tamoxifen, and switching was associated with fewer serious adverse events (14 *versus* 29) [45]. These data suggest that patients already part way through their adjuvant tamoxifen course can still receive the benefits of anastrozole, in terms of a lower risk of disease recurrence and fewer serious adverse events, by changing therapy to anastrozole after 2–3 years rather than remaining on tamoxifen treatment. Though promising, the ITA is a small trial with a small number of events and without explicit stopping rules.

Table 3
Events in the ITA trial

	Patients switched to anastrozole for 3 years ($N = 208$)	Patients remaining of tamoxifen for 5 years ($N = 218$)
Total	10	26
Disease recurrences	8	19
Second primary tumours	2	5
Deaths in the absence of progression	0	2

Findings from the ITA study, which support switching to an AI, have now been confirmed by two other trials, the BIG IES [46] and the combined ABCSG 8/ARNO 95 trial [47]. The IES is the largest study to date to investigate switching from tamoxifen to an AI compared with completing adjuvant therapy with tamoxifen [46]. The trial has followed 4742 women, who were randomised to switch to exemestane after 2–3 years' tamoxifen, for a median of 30.6 months. Exemestane significantly improved DFS compared with the standard 5 years' tamoxifen (HR 0.68; 95% CI 0.56, 0.82; $P < 0.001$). Cases of contralateral breast cancer were also reduced for women receiving exemestane (HR 0.44; 95% CI 0.20, 0.98; $P = 0.04$). Exemestane increased the risk of osteoporosis, arthralgia, visual disturbances and diarrhoea compared with tamoxifen but was associated with a lower incidence of thromboembolic disease, gynaecological symptoms, vaginal bleeding and cramps.

The prospectively planned combined analysis of the ABCSG 8/ARNO 95 trial included more than 3000 women who, following primary surgery and exposure to 2 years of tamoxifen, received either 3 years of tamoxifen or 3 years of anastrozole [47]. At a median follow-up of 26 months, there were 110 events (local or metastatic recurrence or contralateral breast cancer) among women on tamoxifen and 67 events among women on anastrozole. Three-year event-free survival favoured switching to anastrozole (HR 0.60; 95% CI 0.44, 0.81; $P = 0.0009$). Anastrozle also demonstrated a 39% improvement in distant recurrence-free survival compared with tamoxifen (HR 0.61; 95% CI 0.42, 0.87; $P = 0.0067$). Adverse events are consistent with the previously reported event profile for anastrozole, although tolerability data are only currently available from the ABCSG 8 arm of the trial.

7. Evaluation of the benefits of extended adjuvant therapy

Results of a double-blind, placebo-controlled trial (MA 17; Fig. 4) to evaluate whether postmenopausal women with hormone receptor-positive early breast cancer who have completed 5 years of tamoxifen would benefit from treatment with letrozole for an additional 5 years have recently been published [25].

After a median follow-up of 2.4 years there was a significant difference in DFS ($P < 0.001$), with 75 recurrences (local or metastatic) or new primary contralateral breast cancers in the letrozole group ($N = 2575$) compared with 132 in the placebo group ($N = 2582$). Although the estimated 4-year DFS rates were significantly higher for letrozole (93% and 87% for letrozole and placebo, respectively; $P \leqslant 0.001$), only 20 patients were eligible for analysis at this time point, and therefore the data are not robust [25] (Table 4 and Fig. 5).

Adverse events, such as hot flushes, arthralgia, and myalgia, were more common in the letrozole group than the placebo group ($P < 0.05$), whereas vaginal bleeding was more common in the placebo group ($P = 0.01$). The incidence of cardiovascular events or new fractures were numerically increased in the letrozole group compared with the placebo group, although these differences were not significant ($P = 0.40$ and 0.24, respectively).

Due to the highly significant result *versus* placebo at the preliminary analysis, the trial was terminated early and the results were published, diminishing the clinical usefulness of the data. The very short follow-up of these data prevents the long-term outcomes of these different states from being established and thus the current data may not be meaningful [54]. The recurrence data available are a composite of local, metastatic and new primary cancer, which convey different risk probabilities and are associated with different treatment strategies. There are also some concerns about the consequences of long-term use of letrozole due to its potent oestrogen suppressive effects, and it is thought that the early cessation of the study may mean that long-term adverse events are underestimated [55].

Table 4
Disease-free and overall survival in years 1 through 4 in the MA.17 trial

Variable	Letrozole group (%) ($N = 2575$)	Placebo group (%) ($N = 2582$)	Absolute difference (95% confidence interval)
Disease-free survival			
Yr 1	98.6	97.8	0.8 (0.0, 1.5)
Yr 2	96.7	94.8	1.9 (0.6, 3.3)
Yr 3	95.3	90.2	5.0 (2.7, 7.3)
Yr 4	92.8	86.8	6.0 (2.0, 10.1)
Overall survival			
Yr 1	99.8	99.7	0.1 (−0.2, 0.4)
Yr 2	98.9	98.6	0.3 (−0.5, 1.1)
Yr 3	97.7	96.9	0.8 (−0.8, 2.3)
Yr 4	96.0	93.6	2.4 (−0.9, 5.6)

A final analysis of this study at a median follow-up of 2.5 years was presented at the 40th Annual Meeting of the American Society of Clinical Oncology [56]. Results were similar to the published interim analysis although updated survival data indicated that the group of women treated with letrozole had an 18% reduced risk of death compared with those who received placebo, and women with node-positive disease had a 39% reduced risk of death if treated with letrozole compared with placebo.

8. Discussion

Many elements need to be considered when assessing optimal endocrine treatment regimens for hormone

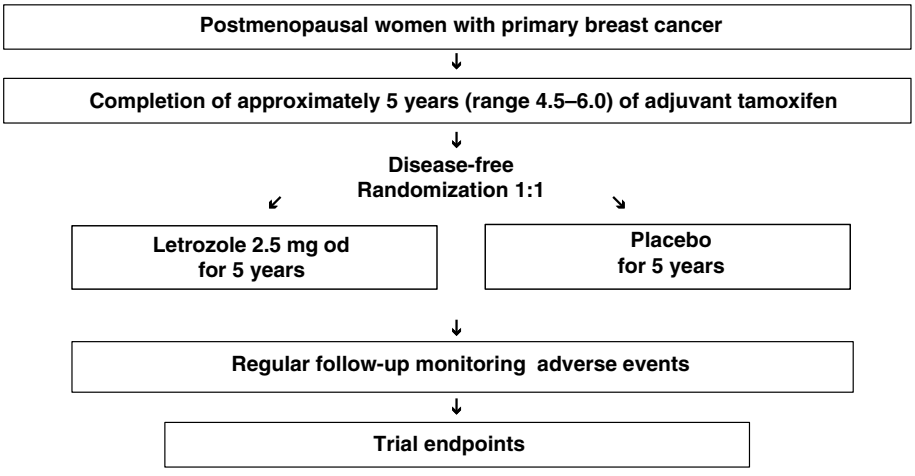

Fig. 4. Design of the MA.17 trial.

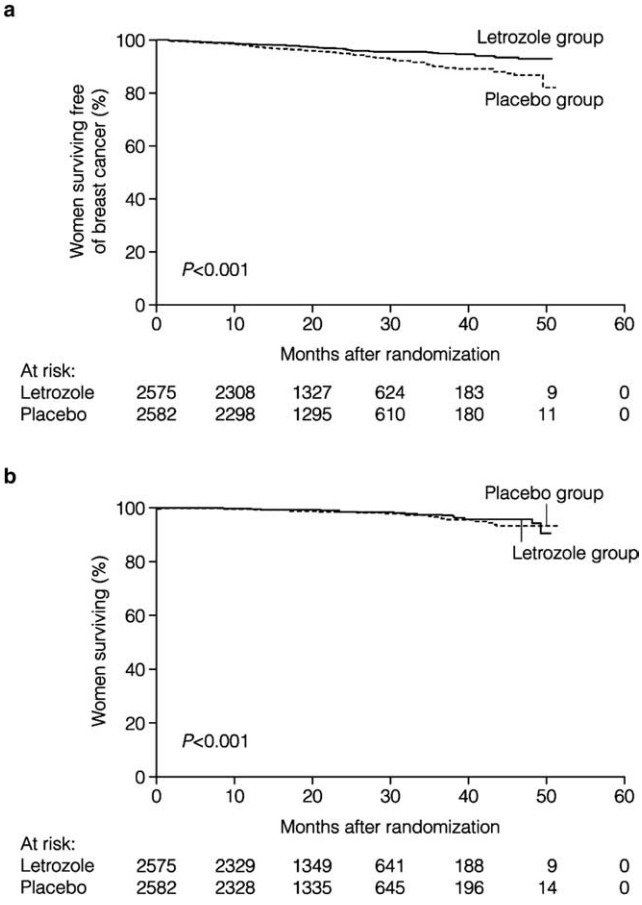

Fig. 5. Kaplan-Meier estimates of (a) disease-free survival and (b) overall survival from the MA 17 trial.

receptor-positive patients, including the efficacy and safety profile of the agents used, and the QoL of the patient. Alongside the emerging data are guidelines which assess the relevance of the research findings and translate these into clinical practice. These provide both prescribing guidance for the physician and clear information for patients. Guidelines state that endocrine treatment, including AIs, should be initiated only for hormone receptor-positive tumours [57]. Furthermore, given the encouraging data from the trials described above, recommendations for the use of tamoxifen, up till now the endocrine therapy of choice in the adjuvant setting, have been revised.

The initial, updated and completed treatment analyses of the ATAC trial represent the results of the largest trial to report to date and provide information on efficacy and tolerability [22–24]. The ATAC completed treatment analysis reinforces the results of the first and updated analyses and demonstrates that anastrozole provides superior efficacy to tamoxifen for DFS, TTR, time to distant recurrence and incidence in contralateral breast cancer. In 2004, the American Society of Clinical Oncology (ASCO) Health Services Research Committee panel reviewed their guidelines on the adjuvant therapy of hormone-sensitive early operable breast cancer. For the first time the ASCO panel recommended that 5 years of tamoxifen alone is no longer the optimal adjuvant treatment and that the preferred treatment should include the use of an AI to reduce the risk of tumour recurrence [53]. The ASCO panel supports the use of evidence-based medicine and recommends giving the AI with the best available data for a particular patient and setting. The robust efficacy and safety data recorded in the ATAC trial, including more than 5 years' follow-up, indicate that anastrozole should be the primary option for initial adjuvant therapy. Only anastrozole has established efficacy and safety data as initial therapy, with over 5 years' long-term follow-up. It must be noted that the ATAC completed treatment analysis (68 months), the BIG 1-98 data and the ABSCG 8/ARNO 95 data, were not included in the ASCO decision. Guidelines from the Eighth International Breast Cancer Study Group meeting (St. Gallen, Switzerland) state that tamoxifen is the preferred option but highlight the use of anastrozole for patients intolerant to tamoxifen or when tamoxifen is contraindicated [58]. The existing St Gallen Consensus Guidelines are now 2 years old and were based only on data from the ATAC trial at 47 months' follow-up. The National Comprehensive Cancer Network (NCCN) Practice Guidelines, 2005 [59], specify which of the AIs to use in each setting and recommends using the drug with the best available data. The NCCN reviewed data from the ATAC, ITA, IES and MA 17 trials. In postmenopausal women with breast cancer the NCCN recommends 5 years of anastrozole as initial adjuvant therapy or, after an initial 2–3 years' tamoxifen, switching to anastrozole for a completed course of 5 years of hormonal therapy. In previously premenopausal patients who have become postmenopausal after an initial 2–3 years' tamoxifen the NCCN recommends switching to anastrozole.

Given that the recent MA 17 extended adjuvant letrozole trial was terminated early [25], the results, although promising, are unlikely to result in future changes to advisory guidelines. Furthermore, while this study is of interest to patients about to complete 5 years of tamoxifen, it does not address the issue of optimal adjuvant therapy. Women with early breast cancer are at their greatest risk of disease recurrence during the first 5 years after initial diagnosis and treatment received during the first 5 years is therefore paramount to successful outcomes. Data obtained from the ATAC trial suggest that anastrozole is more effective than tamoxifen in reducing disease recurrence in postmenopausal women during this 5-year period and therefore it is reasonable to expect that anastrozole may replace tamoxifen as adjuvant therapy of choice in the short to medium term. Furthermore, a recent re-analysis of the ATAC data based on hazard rates

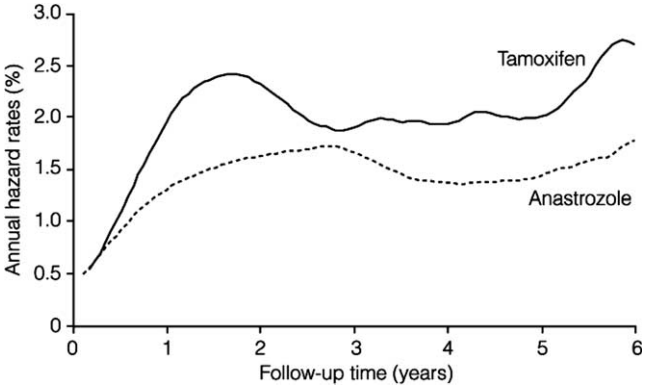

Fig. 6. Smoothed hazard rates for recurrence for anastrozole *versus* tamoxifen in hormone receptor-positive patients. Reprinted with permission from Elsevier (*The Lancet*, 2005, **365**, 1225–1226) [60].

at 6-monthly intervals demonstrates a dramatic flattening of the peak hazard for the anastrozole treated group compared with that seen in the tamoxifen group at 2 years [60] (Fig. 6), strengthening the argument in favour of starting the AI immediately after surgery rather than waiting for 2 years to pass. A biological model that explains these observations was coincidently published a short time before they appeared in press [61].

Despite the continued use of tamoxifen, trials are now being initiated with anastrozole as the control arm [62], clearly demonstrating that anastrozole is increasingly being seen as standard treatment in the adjuvant setting for postmenopausal women with early breast cancer. Indeed, data from the ATAC and BIG 1-98 trials provide substantial evidence that tamoxifen should no longer be viewed as the standard of care for adjuvant therapy of postmenopausal women. The higher rates of recurrence, adverse events and withdrawals from treatment with tamoxifen, and the substantial benefit of anastrozole over the first 3 years, justify the approach of offering the most effective therapy at the earliest opportunity. However, a benefit of long-term AI treatment on overall survival compared with tamoxifen is not expected at this stage as it took at least 7 years to show a significant survival advantage for tamoxifen *versus* placebo in previous adjuvant studies [63].

The optimal sequence in which treatments are given, as well as the optimal duration of therapy, is paramount to achieving maximal patient benefit. Emerging switching data [45–47], which strengthen the balance of superiority of anastrozole over tamoxifen, and further follow-up survival data for anastrozole will undoubtedly influence future changes to regulatory guidelines, as will a number of other ongoing clinical trials. It is essential therefore that patients are notified of the results, and the limitations of existing and emerging data so that they are able to make informed decisions when faced with endocrine treatment choices.

Conflict of interest statement

I have been in receipt of consultancy fees and travel costs from AstraZeneca and Novartis. I was previously the Principal Investigator of the ATAC trial.

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