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Position Paper

The role of aromatase inhibitors as adjuvant therapy for early breast cancer in postmenopausal women

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Abstract

For endocrine therapy of hormone-sensitive advanced breast cancer in postmenopausal women, the third-generation aromatase inhibitors, letrozole, anastrozole, and exemestane, are effective both as alternatives to tamoxifen in first-line treatment and following first-line tamoxifen failure. These three agents are currently being evaluated as adjuvant therapy of early breast cancer, again relative to the standard, tamoxifen. Three treatment strategies are under investigation: replacement of tamoxifen as adjuvant therapy for 5 years (early adjuvant therapy); sequencing of tamoxifen before or after an aromatase inhibitor during the first 5 years (early sequential adjuvant therapy); or following 5 years of tamoxifen (extended adjuvant therapy). Results of the first early adjuvant trial (Arimidex®, Tamoxifen Alone or in Combination [ATAC]) demonstrated that anastrozole was significantly more effective than tamoxifen in reducing the risk of disease recurrence. Two trials sequencing 2–3 years of an aromatase inhibitor after 2–3 years of tamoxifen have also reported results. A large trial (International Collaborative Cancer Group [ICCG] trial 96) found switching to exemestane to be significantly superior to continuing on tamoxifen in disease-free survival, and in a small study (Italian Tamoxifen Arimidex [ITA] trial), similarly sequencing anastrozole after tamoxifen significantly reduced the hazard of recurrence compared with remaining on tamoxifen. Extended adjuvant therapy with 5 years of letrozole versus placebo following 5 years of tamoxifen was evaluated in the MA.17 trial. Compared with placebo, letrozole resulted in a significant improvement in disease-free survival that was irrespective of whether patients had lymph node-positive or -negative tumours. Results of these four trials emphasise the important role of aromatase inhibitors in the adjuvant setting, yet the optimal approach still needs to be defined. A number of trials further evaluating the three adjuvant treatment strategies are ongoing.

Keywords: Aromatase inhibitor; Letrozole; Anastrozole; Exemestane; Early breast cancer; Adjuvant endocrine therapy

1. Introduction

Oestrogen is the predominant breast cancer cell mitogen, and inhibition of oestrogen receptor (ER) activation is an important prevention and treatment strategy [1–3]. For women with early breast cancer that is ER-positive (ER+), standard adjuvant treatment is with the antioestrogen tamoxifen for 5 years, which reduces risk of recurrence by 47% and risk of death by 26% over the next 10 years [4,5].

While aromatase inhibitors also prevent ER-mediated breast cancer cell stimulation, they do so through suppression of oestrogen biosynthesis rather than by blocking the ER. Highly selective and potent third-generation aromatase inhibitors include the non-steroidal agents letrozole (Femara®) and anastrozole (Arimidex®), and the steroid exemestane (Aromasin®) [6]. While all three agents effectively reduce total-body oestrogen synthesis after menopause (when ovarian production of oestrogen has virtually ceased) [7], letrozole is the most potent

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agent, achieving the greatest degree of oestrogen reduction in experimental and clinical studies [6,8]. All 3 aromatase inhibitors are active in second-line treatment of metastatic breast cancer [9–13], a setting in which they have been readily adopted due to proven superiority over former standards, the progestin megestrol acetate or the first-generation aromatase inhibitor, aminoglutethimide. These agents have also shown either superiority or equivalence vs. tamoxifen in the first-line setting [14–19].

In randomised phase III second-line comparisons of aromatase inhibitors, letrozole was superior to aminoglutethimide in the overall response rate (ORR), median duration of response, time to progression (TTP), time to treatment failure, and overall survival (OS) [10] and superior to anastrazole in ORR [13]. The promising results for the aromatase inhibitors in second-line advanced breast cancer led to investigation of these agents in earlier stages of breast cancer.

In the first-line locally advanced or metastatic breast cancer setting, letrozole has proven superior efficacy in TTP, ORR and clinical benefit rate (CBR) compared with tamoxifen in randomised phase III trials [15,16], whereas anastrozole is at least equivalent to tamoxifen in all of these end-points [14].

Both drugs demonstrated an equivalent median survival compared with tamoxifen, but letrozole was statistically superior to tamoxifen in early survival [14–16]. Randomised phase II data demonstrated activity of exemestane in the first-line setting [17], and recently presented data from the extended phase III trial demonstrated exemestane to be significantly superior to tamoxifen in ORR, and in progression-free survival (PFS) [18,19].

2. Evaluation of aromatase inhibitors as adjuvant therapy: rationale and general strategies

The body of positive evidence for this new class of agents in advanced breast cancer supported the evaluation of aromatase inhibitors as adjuvant therapy in postmenopausal women with early breast cancer [20–22]. However, the rationale for such an extensive trial programme also lies in the limitations of the current standard, tamoxifen.

Need to improve upon the toxicity profile caused by oestrogenic effects on some organ systems: Long-term tamoxifen treatment is also associated with a progressively increasing risk of endometrial cancer and thromboembolic events, which contributed to the unfavourable outcome of extended adjuvant tamoxifen therapy in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 [5].

Acquired resistance, agonist vs. antagonist activity: Preclinical studies have shown that development of resistance is associated with loss of typical antagonist activity in favour of a weak agonist effect [23].

Continuing risk of recurrence following tamoxifen: Despite the positive impact of adjuvant tamoxifen on survival, there is a substantial incidence of breast cancer recurrences during the next 7 years following treatment [24].

Limited duration of effectiveness: Results of NSABP trial B-14 revealed that extending tamoxifen treatment beyond the commonly recommended 5 years does not provide further survival benefits and may even partially reverse the earlier benefit: When patients were re-randomised after 5 years of tamoxifen to either continue tamoxifen for an additional 5 years or to receive placebo, those patients remaining on tamoxifen had significantly shorter disease-free survival (DFS) [24].

Three main strategies are currently being investigated to improve upon standard treatment with 5 years of tamoxifen by integrating aromatase inhibitors into early breast cancer therapy [22,25–27]: replacing tamoxifen with an aromatase inhibitor for the first 5 years post-surgery (*early adjuvant therapy*); sequencing tamoxifen and aromatase inhibitor during the first 5 years post-surgery (*early sequential adjuvant therapy*); and using an aromatase inhibitor after 5 years of tamoxifen post-surgery (*extended adjuvant therapy*). The design of the aromatase inhibitor adjuvant trials reflecting these different approaches will be reviewed in the following pages. Available results will be summarised, and the clinical implications for patients with early breast cancer will be discussed.

3. Aromatase inhibitors as early adjuvant therapy

3.1. ATAC (Arimidex, tamoxifen alone or in combination)

3.1.1. Trial design

This large ($N = 9366$) randomised phase III trial was the first to report results of a direct comparison of an early adjuvant aromatase inhibitor vs. tamoxifen for 5 years, and the only study to evaluate the combination of an antioestrogen and an aromatase inhibitor for 5 years (Fig. 1) [28,29]. Surgery for invasive operable early breast cancer in postmenopausal women was followed by randomisation to three arms: anastrozole 1 mg/day ($n = 3125$), tamoxifen 20 mg/day ($n = 3116$), and the combination of both agents ($n = 3125$). The primary trial end-point was DFS, and secondary end-points were incidence of contralateral breast primary cancers, time to distant recurrence, and survival. Subprotocols were included to address potential detrimental effects of anastrozole or tamoxifen on quality of life (QOL), bone mineral density (BMD), and endometrium. Demographics were well balanced (Table 1) [28].

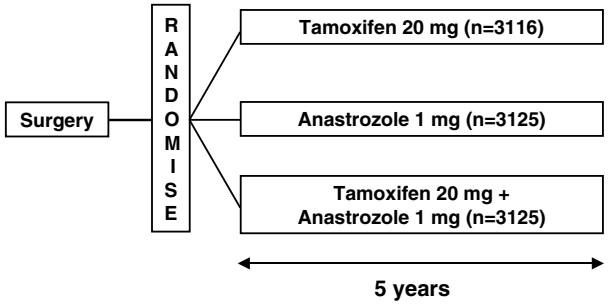


Fig. 1. ATAC trial schema.

Table 1
ATAC trial: patient characteristics in the single-agent arms [28]

Characteristic	Anastrozole (n = 3125)	Tamoxifen (n = 3116)
Mean age (years)	64	64
Receptor status (%)		
Positive	84	83
Negative	8	9
Unknown	8	8
Nodal status (%)		
Positive	35	34
Negative	60	62
Unknown	5	5
Prior adjuvant chemotherapy (%)	22	21
Prior adjuvant radiotherapy (%)	63	63

ATAC, Arimidex, tamoxifen alone or in combination.

3.1.2. Results

Efficacy data at 47 months' median follow-up [29] are available for this trial and remain fairly consistent with those obtained at the initial analysis after 33 months' median follow-up [28]. For all end-points, no significant differences were observed between the tamoxifen-alone and the combination arms. The reasons for this disappointing finding have not been fully defined, but a likely explanation would be the heightened sensitivity to the oestrogenic activity of tamoxifen in the presence of pronounced oestrogen suppression. Only the data on anastrozole vs tamoxifen will be reviewed.

At 47 months' median follow-up, a total of 885 first events (local or distant recurrence, contralateral breast cancer, or death without recurrence) were recorded in the 2 single-agent arms. Efficacy results for the overall (intent-to-treat) patient population are summarised in Table 2. Hazard ratios (HRs) significantly favoured anastrozole over tamoxifen, for DFS and time to recurrence [29,30]. The 14% relative risk reduction corresponds to an absolute risk reduction of 2.4% (86.9% vs. 84.5%, respectively; $P = 0.030$). Further follow-up at 60 months, representing the full duration of trial therapy, is still pending, as is the final OS analysis.

Table 2
ATAC trial: efficacy at 47 months' median follow-up [29,30]

Efficacy parameter*	Hazard or odds ratio†	95% Confidence interval	P Value
Disease-free survival	0.86	0.76–0.99	0.030
Incidence of new contralateral primary breast tumours‡	0.62	0.38–1.02	0.062
Time to recurrence	0.83	0.71–0.96	0.015

* Overall intent-to-treat patient population.
‡ Odds ratio.
† A ratio of <1 favours anastrozole over tamoxifen.

In subgroup analysis in the ATAC trial, some inconsistencies in efficacy were observed. In the 33-month analysis [28], the advantage of anastrozole over tamoxifen was demonstrated to be non-significant in a number of subgroups, which may have been due to the relatively small number of events so far. Most impressive was the lack of benefit in patients with receptor-negative tumours and in patients with prior chemotherapy. In the updated analysis [29], there was no benefit for two subgroups of patients, those with four or more affected nodes and those with prior chemotherapy (HR 0.98, confidence limit [CL] = 0.76–1.28; and HR 0.95, CL 0.72–1.25, respectively).

Exploratory analysis of HRs for time to recurrence according to ER and progesterone receptor (PgR) status found that receptor status was a predictor. A marked improvement with anastrozole vs. tamoxifen occurred in patients who had ER+/PgR-tumours compared with patients with PgR+ tumours (Table 3) [31]. Those results were not affected by nodal status, tumour size or grade, or prior adjuvant chemotherapy.

The overall incidence of contralateral breast cancers was significantly reduced with anastrozole (HR 0.42, $P = 0.007$) at 33 months' follow-up, but this reduction was only borderline significant at 47 months' follow-up (HR 0.62, $P = 0.06$). When looking at contralateral invasive breast cancer only, the difference in favour of anastrozole remained significant at both analyses (HR

Table 3
ATAC trial: exploratory analysis of time to recurrence by ER and PgR status [31]

Hormone receptor status	Hazard ratio*
ER+/PgR+	0.82
ER+/PgR−	0.48
ER−/PgR+	0.79
ER−/PgR−	1.04

ER, oestrogen receptor; PgR, progesterone receptor.
* A ratio of <1 favours anastrozole over tamoxifen.

0.30, $P = 0.001$; and HR 0.57, $P = 0.044$, respectively) [28,29].

The safety profile of anastrozole in the ATAC trial remains consistent with longer follow-up [28,29]. As could be expected from an agent inducing oestrogen suppression, anastrozole led to significantly fewer endometrial cancers, occurrences of vaginal bleeding and discharge, cerebrovascular events, and venous thromboembolic events. Tamoxifen was significantly superior with respect to the incidence of musculoskeletal disorders and fractures (Table 4) [28–30]. Two-year results indicate a progressive loss of BMD in the anastrozole arm compared with the tamoxifen arm (for lumbar spine, anastrozole: −2.6% at year 1, and −4.0% at year 2; tamoxifen: +1.2% at year 1, and +1.9% at year 2) [32].

Table 4
ATAC trial: incidence of predefined adverse events at first analysis [28]

Adverse event	Incidence (%)		*P* Value
	Anastrozole ($n = 3092$)	Tamoxifen ($n = 3094$)	
Hot flushes	34.3	39.7	<0.0001
Musculoskeletal disorders	27.8	21.3	<0.0001
Vaginal discharge	2.8	11.4	<0.0001
Vaginal bleeding	4.5	8.2	<0.0001
Endometrial cancer	0.1	0.5	0.02
Fractures	5.9	3.7	<0.0001
Ischaemic cardiovascular disease	2.5	1.9	0.14
Ischaemic cerebrovascular event	1.0	2.1	0.0006
Any venous thromboembolism	2.1	3.5	0.0006
Deep venous thrombosis ± pulmonary embolism	1.0	1.7	0.02

3.2. BIG 1-98 (monotherapy arms)

3.2.1. Trial design

BIG 1-98 is currently evaluating letrozole (2.5 mg/day) vs. tamoxifen (20 mg/day) as adjuvant therapy in postmenopausal women with ER+ and/or PgR+ primary breast cancer (Fig. 2) [27,33]. This large randomised, double-blind, double-dummy, multicentre phase III trial is being conducted by the International Breast Cancer Study Group/Breast International Group and is also known as the BIG FEMTA trial.

Following complete tumour excision, trial participants were randomised to receive either letrozole ($n = 2446$) or tamoxifen ($n = 2446$) for 5 years. As in ATAC, the primary end-point is DFS, and secondary end-points include locoregional and distant DFS, OS, and safety [33]. Patients were allowed to receive radio- and chemotherapy and were stratified by adjuvant chemotherapy (prior vs. concurrent vs. none), type of surgery (modified radical mastectomy vs. less extensive surgery), and participating study centre. Planned companion substudies are evaluating treatment effects on lipid metabolism and bone metabolism.

In addition to the monotherapy arms discussed in this section, the BIG 1-98 trial is also assessing early sequential adjuvant therapy with letrozole and tamoxifen, in 2 crossover arms.

Patient accrual was completed in April 2003 and initial results on the monotherapy arms are expected in early 2005.

3.3. TEAM

3.3.1. Trial design

The Tamoxifen Exemestane Adjuvant Multicentre trial (TEAM, also known as TEAM EXE) is currently being conducted by the Cancer Research Campaign Trials Unit in the United Kingdom and has completed

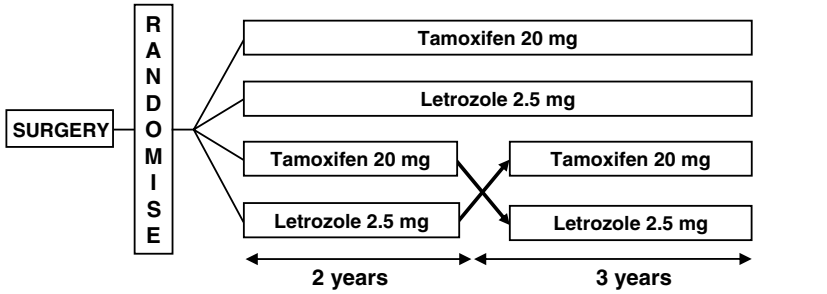


Fig. 2. BIG 1-98 trial schema.

recruitment of approximately 4400 postmenopausal patients with early breast cancer [27,34]. Started in 2001, this open-label, multicentre phase III trial randomizes patients who had ER+ and/or PgR+ tumours to either exemestane 25 mg/day or tamoxifen 20 mg/day, as adjuvant monotherapy for 5 years (Fig. 3). Adjuvant chemotherapy is permitted, and patients are stratified according to hormone receptor status (ER+ vs. ER−/PgR+ vs. ER+/PgR-unknown), prior chemotherapy (none vs. taxane-based vs. anthracycline-based vs. other), and nodal status (negative vs. 1–3 positive vs. 4 or more positive) prior to randomisation. The primary objective of this trial is to determine if 5 years of exemestane improves DFS compared with tamoxifen. Secondary end-points are OS, safety profiles, and the incidence of new primary breast cancers [34].

Five substudies will separately evaluate endometrial changes, lipids, QOL, tolerability, and bone. Those substudies will be combined in a meta-analysis of overall drug efficacy (Fig. 3) [25,26].

Because of recent results of the ICCG 96 trial (see below) showing that switching from tamoxifen to exemestane after 2–3 years improves DFS compared with remaining on tamoxifen, the TEAM trial is being amended to effect such a switch.

3.3.2. Preliminary results

Preliminary results of a small lipid substudy were recently reported [35]. Exemestane, like tamoxifen, stabilised total cholesterol and high-density lipoprotein. Unlike tamoxifen, exemestane slightly increased low-density lipoprotein and significantly decreased triglycerides. These results were similar to effects of anastrozole in postmenopausal women with early breast cancer and remain to be confirmed within larger patient populations [36].

4. Aromatase inhibitors as early sequential adjuvant therapy

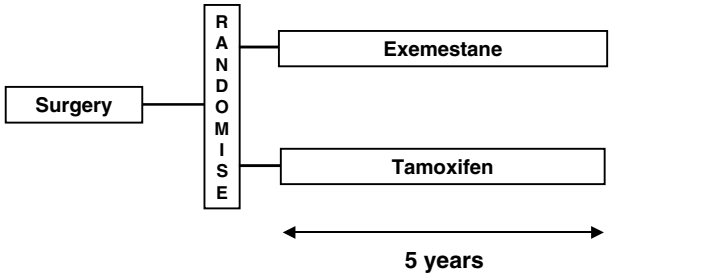
4.1. ICCG 96 (IES)

4.1.1. Trial design

This double-blind, randomised adjuvant exemestane sequencing trial is being conducted by the International Collaborative Cancer Group (ICCG 96, or Intergroup Exemestane Study [IES]). The objective was to compare standard 5 years of tamoxifen with the sequential use of tamoxifen and exemestane for a total treatment duration of 5 years. Patients enrolled were postmenopausal women with ER+ early breast cancer, who were disease-free following 2–3 years of tamoxifen (20 or 30 mg/day) ($N = 4742$). Patients were randomised to another 2–3 years of tamoxifen (20 or 30 mg, according to the initial dose) or 2–3 years of exemestane (25 mg/day) (Fig. 4). The primary end-point was DFS, defined as the time from randomisation to recurrence of breast cancer at any site, or occurrence of new contralateral breast cancer. Secondary end-points included OS, incidence of contralateral breast cancer, and long-term tolerability. Companion studies are examining bone metabolism, QOL, and endometrial changes. Main patient characteristics were well balanced between the two groups (Table 5) [37].

4.1.2. Results

At the second prospectively planned analysis of the ICCG 96 trial (449 events, 30.6 months' median follow-up after randomisation), exemestane decreased the risk of recurrence by 32% ($P = 0.00005$) [37]. Estimated 3-year DFS was significantly higher with exemestane than with tamoxifen (91.5% vs. 86.8%, respectively) (Fig. 5) [37]. Very similar HRs were reported for the subgroups with node-negative or -positive tumours



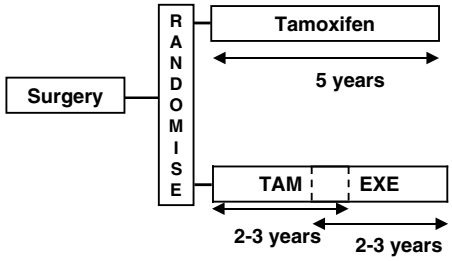
Milestones

Activated	May 2001
Planned accrual	4400

Companion Studies

- Endometrial changes
- Quality of life
- Lipids
- Bone
- Tolerability

Fig. 3. TEAM trial schema.



Milestones	
Activated	March 1999
Planned accrual	4100
Actual accrual	4742

Companion Studies

- Bone metabolism (BMD)
- Quality of life
- Endometrial changes

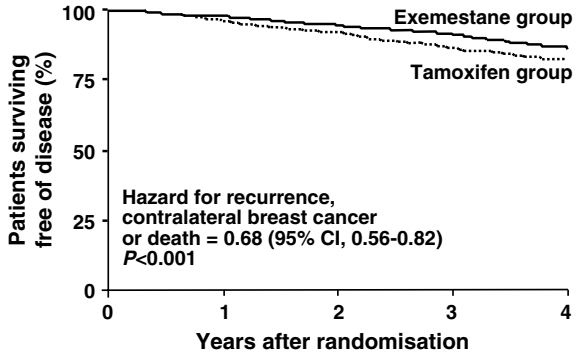
Fig. 4. ICCG 96 trial schema. TAM, tamoxifen; EXE, exemestane.

and in the subgroups with or without prior chemotherapy. Additional analyses demonstrated significant superiority of exemestane in risk of distant disease (HR 0.66, $P = 0.0004$) and in the risk of contralateral breast cancer (HR 0.44, $P = 0.04$). At this stage, there is no difference in OS (HR 0.88, $P = 0.37$). More second primary non-breast cancers are reported in the tamoxifen group (53 vs. 27), of which only a minority was ascribed to endometrial cancer (11 vs. 5) [37].

Table 5
ICCG 96 trial: patient characteristics [37]

Characteristic	Exemestane ($n = 2362$)	Tamoxifen ($n = 2380$)
Mean age (years)	64	64
Receptor status (%)		
ER-positive	81	81
ER-negative	1	1
ER-unknown	17	17
Nodal status (%)		
Positive	44	44
Negative	51	51
Unknown	5	5
Prior adjuvant chemotherapy (%)	32	32

Overall, exemestane was well tolerated in comparison with tamoxifen (Table 6) [37]. Although preclinical data had indicated a bone-protective activity for exemestane [38], there was an increase in the incidence of osteoporosis observed in patients who switched to exemestane (7.4% vs. 5.7% in the tamoxifen-only arm; $P = 0.05$). Together with results of a placebo-controlled safety trial [39], the results of ICCG 96 indicate that exemestane is associated with a decrease in BMD. In addition, there were toxicities in the exemestane arm (diarrhoea, visual disturbances, and increased vascular events) that are not associated with non-steroidal aromatase inhibitors in the adjuvant setting [37].



No. of Events/No. at Risk					
Exemestane	0/2362	52/2168	60/1696	44/757	20/201
Tamoxifen	0/2380	78/2173	90/1682	76/730	18/185

Fig. 5. ICCG 96 trial: Kaplan–Meier curves for DFS, comparing exemestane with tamoxifen. Coombes RC, Hall E, Gibson LJ, *et al.* A randomised trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *N Engl J Med* 2004;350:1081–1092 [37]. ©2004 Massachusetts Medical Society. Adapted in 2004 with permission of Massachusetts Medical Society.

Table 6
ICCG trial: incidence of main adverse events [37]

Type of Event*	Incidence (%)		*P* Value
	Exemestane ($n = 2362$)	Tamoxifen ($n = 2380$)	
Hot flashes	42.0	39.6	0.28
Pain or aches	33.2	29.4	0.17
Osteoporosis	7.4	5.7	0.05
Gynaecological symptoms	5.8	9.0	<0.001
Arthralgia	5.4	3.6	0.01
Diarrhoea	4.3	2.3	<0.001
Thromboembolic disease	1.0	1.9	0.003
Visual disturbances	7.4	5.7	0.04

* Any grade.

4.2. ITA trial

4.2.1. Trial design

This is a small open-label randomised trial of tamoxifen for 5 years, vs. 2–3 years of tamoxifen followed by anastrozole (1 mg/day) for 5 years total treatment duration ($N = 448$) [40,41]. Patients were postmenopausal, ER+ and node-positive, and approximately 45% had prior adjuvant chemotherapy. This trial had important limitations. Time on tamoxifen prior to switching to anastrozole was highly variable (median 28 months; range, 20–40 months), in contradiction to the inclusion criteria of not more than 3 years of prior tamoxifen. The trial was also very small, which resulted in small numbers of events, and was open-label.

4.2.2. Results

At 36 months' median follow-up, total events (locoregional or distant recurrences, or new contralateral breast primary cancers) were reported to be fewer in the sequential arm than in the tamoxifen-only arm [41]. The hazard of recurrence was significantly reduced in the sequential arm compared with the tamoxifen arm (0.36; $P = 0.006$). Compared with the tamoxifen arm, sequential anastrozole treatment was associated with more gastrointestinal symptoms and a higher incidence of hypercholesterolaemia, but fewer gynaecological symptoms [40].

4.3. BIG 1-98 (sequential arms)

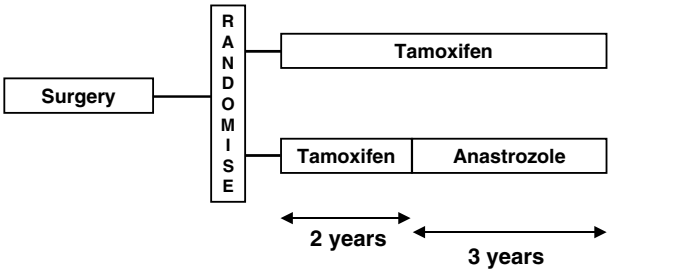
4.3.1. Trial design

This ongoing, randomised, double-blind, controlled phase III trial has 2 sequence arms, one with letrozole for 2 years followed by tamoxifen for 3 years ($n = 1530$), and the other with tamoxifen for 2 years followed by letrozole for 3 years ($n = 1530$) (Fig. 2) [33]. Results are not yet available.

4.4. ARNO

4.4.1. Trial design

ARNO (Arimidex-Nolvadex) is a phase III trial with adjuvant sequencing of anastrozole after tamoxifen for a total of 5 years vs. tamoxifen alone for 5 years, being conducted by the Austrian Breast Cancer Study Group in collaboration with the German Adjuvant Breast Cancer Group. It is a two-arm multicentre study begun in 1996, with a target accrual of 3500 patients who are postmenopausal and had hormone-sensitive breast cancer (Fig. 6). Patients are randomised to either tamoxifen (20 or 30 mg/day) for 5 years, or to 2 years of tamoxifen followed by 3 years of anastrozole [25]. Trial end-points are relapse-free survival, OS, and tolerability (with optional QOL assessment). In design, ARNO is similar to two arms of the BIG 1-98 trial (tamoxifen monotherapy arm, and tamoxifen-then-letrozole arm). The trial was opened in 1996; results are available in late 2004.



Milestones	
Activated	October 1996
Planned accrual	2500
Accrual to date	1700

Companion Studies

- Quality of life (optional)

Fig. 6. ARNO trial schema.

5. Aromatase inhibitors as extended adjuvant therapy

5.1. MA.17

5.1.1. Trial design

This large, double-blind, placebo-controlled phase III trial is being conducted by the National Cancer Institute of Canada Clinical Trials Group. The objective of the MA.17 trial was to determine whether using letrozole as extended adjuvant therapy following standard tamoxifen will further improve patient outcome. Enrolled patients ($N = 5187$) were postmenopausal women who had early breast cancer that was ER+ and/or PgR+ (except for 2% who were receptor-unknown) and who were disease-free following 5 years (range, 4.5 to 6 years) of tamoxifen (20 mg/day) and had discontinued that treatment <3 months prior to enrollment. Patients were stratified according to receptor status (positive vs unknown), nodal status (positive vs. negative vs. unknown), and prior adjuvant chemotherapy (yes vs. no), and were randomised to receive either letrozole (2.5 mg/day) or placebo for 5 years, as extended adjuvant therapy (Fig. 7) [42]. The primary end-point was DFS, defined as the time from randomisation to recurrence of the primary disease, either locally or as distant metastasis, or to development of a new primary cancer in the contralateral breast. Secondary end-points were OS, rate of contralateral breast cancer, long-term safety and tolerability, and QOL. Two companion studies were designed to prospectively evaluate end-organ effects of prolonged treatment with letrozole on bone metabolism ($n = 226$) and lipid metabolism ($n = 347$) [22]. Main patient characteristics were well balanced between the 2 treatment groups (Table 7) [42].

5.1.2. Results

At the first prospectively planned interim analysis of the MA.17 trial (207 events, 2.4 years' median follow-up), letrozole decreased the risk of breast cancer recurrence (local or metastatic recurrences or new contralateral breast cancers) by 43% vs. placebo ($P = 0.00008$). There was a progressive improvement in DFS with letrozole vs. placebo during 4 years of continued treatment, with an estimated 4-year DFS that was significantly higher in the letrozole arm (93% vs. 87%, respectively; $P < 0.001$) (Fig. 8) [42]. Subanalysis revealed that letrozole reduced the risk of recurrence significantly irrespective of nodal status, by 40% ($P = 0.003$) in node-positive patients and by 53% ($P = 0.005$) in node-negative patients. The number of breast cancer-associated deaths is small (9 for letrozole vs. 17 for placebo at 4 years), and the improved OS had not reached statistical significance (96% vs. 93.6%, respectively; HR 0.76, $P = 0.25$) [42].

The benefit of letrozole in reducing the risk of recurrence at the first interim analysis far exceeded the expected difference and the prospectively determined stopping boundary of this trial, prompting the unblinding of the trial by the Independent Data Safety and Monitoring Committee [42].

Letrozole was generally well tolerated, with similar rates of discontinuation in both treatment arms (letrozole 4.5% vs. placebo 3.6%; $P = 0.11$). Most adverse events were mild (grades 1 or 2), with letrozole being significantly superior with respect to vaginal bleeding, while placebo was associated with significantly lower incidences of hot flashes and muscle and bone pain

Table 7
MA.17 trial: patient characteristics [42]

Characteristic	Letrozole ($n = 2575$)	Placebo ($n = 2582$)
Postmenopausal (inferred) (%)	>99	>99
Receptor status (%)		
Positive	98	98
Unknown	2	2
Nodal status (%)		
Positive	46	46
Negative	50	50
Unknown	4	4
Prior adjuvant chemotherapy (%)	46	46
Prior adjuvant radiation therapy (%)	60	59

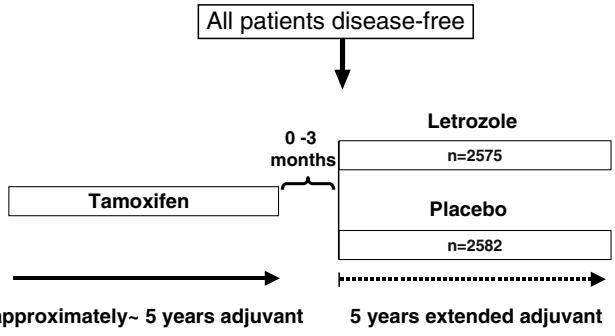


Fig. 7. MA.17 trial schema [42].

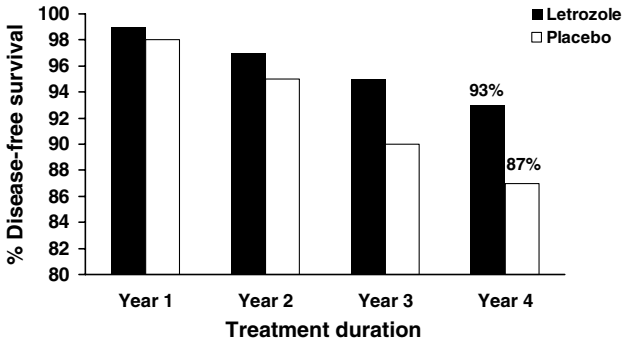


Fig. 8. MA.17 trial: progressive changes in DFS with each year of continued treatment with letrozole vs. placebo [42].

(Table 8) [42]. Patients on letrozole, compared with those on placebo, reported slightly more cases of patient-reported new-onset osteoporosis (5.8% vs. 4.5%, respectively) and clinical fractures (3.6% vs. 2.6%, respectively), but these differences were not significant. There was also no significant difference between the letrozole and placebo groups in the rate of early discontinuation of treatment [42].

QOL data revealed small to moderate differences in outcomes of global physical and mental health measurements that favoured placebo over letrozole in some domains, but these differences were of questionable clinical relevance. Overall, letrozole did not show a substantial adverse effect on QOL relative to placebo [43].

Updated efficacy and safety results have recently been reported and largely confirmed those of the initial interim analysis. However, at a median follow-up of 2.5 years, node-positive patients on letrozole showed a significant OS benefit compared with those on placebo [44]. In this high-risk population, characterised by an incrementally larger overall number of events than in the node-negative population, mortality was significantly reduced with letrozole compared with placebo, by 39% ($P = 0.04$). Furthermore, there was a 39% reduction in risk of the generally most fatal recurrences—distant metastases—an effect seen in both node-positive and node-negative patients [44].

Table 8
MA.17 trial: incidence of adverse events (all grades*) and treatment discontinuation [42]

Adverse Event	Incidence (%)		*P* Value
	Letrozole ($n = 2154$)	Placebo ($n = 2145$)	
Hot flashes	47.2	40.5	<0.001
Arthritis	5.6	3.5	<0.001
Arthralgia	21.3	16.6	<0.001
Myalgia	11.8	9.5	0.02
Osteoporosis	5.8	4.5	0.07
Vaginal bleeding	4.3	6.0	0.01
Hypercholesterolaemia	11.9	11.5	0.67
Cardiovascular events	4.1	3.6	0.40
Toxicity-related discontinuation of treatment	4.5	3.6	0.11
Clinical fractures	3.6	2.9	0.24

* Adverse events were primarily grade 1 or 2.

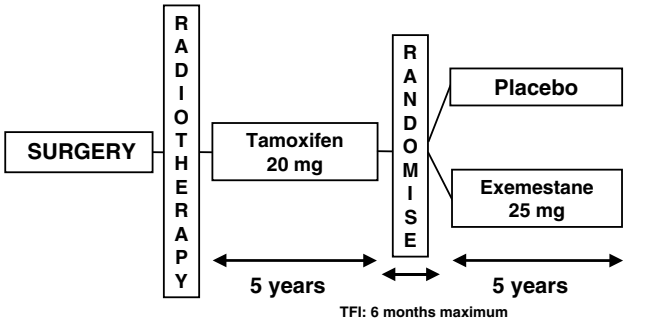
5.2. NSABP B-33

5.2.1. Trial design

The design of this phase III trial is outlined in Fig. 9. Patients were disease-free postmenopausal women with early stage ER+ and/or PgR+ breast cancer who had completed approximately 5 years of tamoxifen therapy (57–66 months). Within 6 months of completing that therapy, patients are randomised to either exemestane (25 mg/day) or placebo, for an additional 5 years. Projected total patient accrual was 3000 [45]. Based on the MA.17 trial results, the placebo arm of NSABP B-33 was closed in October 2003 [46]. No trial results have been reported.

6. Discussion

With the demonstration of the superiority or equivalence of third-generation aromatase inhibitors compared with tamoxifen in first-line treatment of metastatic breast cancer, large adjuvant breast cancer trials are currently evaluating all three of these agents for long-term efficacy and safety relative to the current standard of tamoxifen for 5 years. Use of the aromatase inhibitors in the adjuvant setting include evaluation of relatively short-term (DFS) and long term (OS) efficacy, and safety in terms of toxicity, QOL, and organ effects caused by the endocrine properties of the treatment in



Milestones	
Activated	May 1, 2001
Planned accrual	3000

Companion Studies
- Lipid metabolism
- Bone metabolism
- Quality of life

Fig. 9. NSABP B-33 trial design. TFI, tamoxifen-free interval.

dramatically suppressing oestrogen synthesis in postmenopausal women.

In the adjuvant trials reported so far, the aromatase inhibitors have been tested in three different settings: The early adjuvant setting (ATAC), the early sequential adjuvant setting (ICCG 96, ITA) and the extended adjuvant setting (MA.17). In all cases, early efficacy and safety data indicate their superiority over the current standard of 5 years treatment with tamoxifen alone. However, when making the prospective decision between the different treatment strategies represented in these trials. The existing data should be weighed carefully.

There are differences between the third-generation aromatase inhibitors in their mode of action and in their potency [47], and, so far, no comparative data from randomised adjuvant trials are available to relate those differences to clinical activity. Therefore, data with either of the drugs in one of the adjuvant settings cannot be translated to the other drugs, and only indirect comparisons are scientifically warranted.

In the early adjuvant setting, the ATAC trial results have demonstrated the efficacy of anastrozole as adjuvant therapy. At 47 months' median follow-up, anastrozole reduced the relative risk of recurrence by 14% compared with tamoxifen, corresponding to an absolute risk reduction of 2.4%. On the basis of this small absolute – yet statistically significant – advantage, the United States Food and Drug Administration recently approved anastrozole for adjuvant therapy in postmenopausal women. Most other health authorities have limited the use of this agent to patients not eligible for tamoxifen, due to contraindications or side-effects. These data are considered insufficiently mature and the risk reduction too small for a general recommendation of anastrozole as an alternative treatment option to tamoxifen in the adjuvant setting, either by the American Society of Clinical Oncology or the St. Gallen Consensus Panel [48,49].

The long-term superiority of anastrozole over tamoxifen remains uncertain. OS data are not yet available, and a long-lasting (carryover) benefit of tamoxifen [4] must be taken into consideration [49]. The optimum duration of anastrozole therapy also remains to be ascertained [26].

Additional important information about the upfront adjuvant use of aromatase inhibitors will be available from other large trials comparing 5 years of one of those agents with 5 years of tamoxifen. The TEAM trial uses exemestane and BIG 1-98 uses letrozole. The results of the latter trial are expected to be presented early in 2005.

The early sequential approach was evaluated in the ICCG 96 trial [37]. At 30.6 months' median follow-up, there was a relative reduction in the risk of recurrence of 32%, corresponding to an estimated 4.7% absolute reduction at 3 years, with switching to exemestane compared with remaining on tamoxifen. As in other adjuvant trials, OS and long-term safety remain to be determined. The relevance of the early sequential ITA trial is limited by violations of the inclusion criteria, the small trial size and numbers of events, and the open-label design. Nevertheless, the efficacy results are consistent with those in the ICCG 96 trial.

The early sequential trials both used 5 years of tamoxifen treatment as the reference group. Indirect comparison of these trials suggests that sequencing tamoxifen with an aromatase inhibitor (ICCG 96) may be superior to non-sequenced therapy with an aromatase inhibitor alone (ATAC), based on relative risk reductions of 32% and 14%, respectively. Whether this may be ascribed to the different approaches or efficacies with each aromatase inhibitor or to a selection of hormone-responsive patients during the tamoxifen therapy remains to be elucidated. Other remaining questions include the optimal sequence of tamoxifen and aromatase inhibitor and the optimal duration of treatment with the sequences. The BIG 1-98 trial, which includes two monotherapy arms of letrozole vs tamoxifen, and two sequential arms of tamoxifen and letrozole with sequencing in each direction, will provide answers to some of these questions.

Using the extended approach, MA.17 is the only trial to have reported data. Treatment with letrozole was associated with a 43% relative reduction in risk of recurrence, corresponding to an estimated 6% absolute risk reduction at 4 years [42]. The significant benefit with letrozole was observed irrespective of nodal status. Indeed, in the updated analysis, letrozole significantly improved survival in the node-positive subgroup [50].

The impressive DFS improvement seen with extended adjuvant letrozole in MA.17 is particularly notable, given that the optimum benefits of tamoxifen would have occurred in that population prior to beginning letrozole treatment, and there may also have been a carryover tamoxifen effect [42,44].

One key question relates to the optimal duration of treatment with an aromatase inhibitor. The MA.17 trial was recently amended to continue extended letrozole beyond 5 years. Future trials should also address the question of treatment duration with both the early monotherapy and early sequential approaches.

7. Conclusions

With the current standard of 5 years adjuvant treatment with tamoxifen offered to patients with receptor-positive disease, thousands of women's' lives have been saved.

Evidence of the superior efficacy of aromatase inhibitors in early end-points grows increasingly strong. We are eagerly awaiting data of long-term efficacy and

safety in the ongoing trials, and many questions concerning the most effective future usage of tamoxifen and aromatase inhibitors in the adjuvant setting are still being addressed. These questions relate primarily to the optimal single agent or sequence, duration of treatment, and selection of individual patients.

However, according to the currently available data, 5 years treatment with tamoxifen alone may no longer be considered an acceptable standard for postmenopausal patients with receptor-positive early breast cancer.

Already, some treatment centres have replaced the current standard of tamoxifen with anastrozole in the early adjuvant setting. However, the majority of patients, who are still offered early tamoxifen, and the estimated 500 000 world-wide who currently receive tamoxifen, should be considered candidates for treatment with an aromatase inhibitor, either switching to exemestane following approximately 2 to 3 years treatment with tamoxifen or starting letrozole following the completion of 5 years treatment with tamoxifen.

Conflict of interest statement

Henning T. Mouridsen, MD, PhD, Professor of Oncology, Rigshospitalet, Copenhagen, Denmark, has disclosed that he has served as a consultant for, and received honoraria from, Novartis, and AstraZeneca.

Nicholas J. Robert, MD, Chair, Breast Cancer Committee, Fairfax-Northern Virginia Hematology-Oncology, Fairfax, Virginia, has disclosed that he has served as a consultant for, and received honoraria from, Novartis and AstraZeneca.

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