



Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial



Jack Cuzick, Ivana Sestak, Michael Baum, Aman Buzdar, Anthony Howell, Mitch Dowsett, John F Forbes, on behalf of the ATAC/LATTE investigators

Summary

Background The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial was designed to compare the efficacy and safety of anastrozole (1 mg) with tamoxifen (20 mg), both given orally every day for 5 years, as adjuvant treatment for postmenopausal women with early-stage breast cancer. In this analysis, we assess the long-term outcomes after a median follow-up of 120 months.

Methods We used a proportional hazards model to assess the primary endpoint of disease-free survival, and the secondary endpoints of time to recurrence, time to distant recurrence, incidence of new contralateral breast cancer, overall survival, and death with or without recurrence in all randomised patients (anastrozole $n=3125$, tamoxifen $n=3116$) and hormone-receptor-positive patients (anastrozole $n=2618$, tamoxifen $n=2598$). After treatment completion, we continued to collect data on fractures and serious adverse events in a masked fashion (safety population: anastrozole $n=3092$, tamoxifen $n=3094$). This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN18233230.

Findings Patients were followed up for a median of 120 months (range 0–145); there were 24 522 woman-years of follow-up in the anastrozole group and 23 950 woman-years in the tamoxifen group. In the full study population, there were significant improvements in the anastrozole group compared with the tamoxifen group for disease-free survival (hazard ratio [HR] 0.91, 95% CI 0.83–0.99; $p=0.04$), time to recurrence (0.84, 0.75–0.93; $p=0.001$), and time to distant recurrence (0.87, 0.77–0.99; $p=0.03$). For hormone-receptor-positive patients, the results were also significantly in favour of the anastrozole group for disease-free survival (HR 0.86, 95% CI 0.78–0.95; $p=0.003$), time to recurrence (0.79, 0.70–0.89; $p=0.0002$), and time to distant recurrence (0.85, 0.73–0.98; $p=0.02$). In hormone-receptor-positive patients, absolute differences in time to recurrence between anastrozole and tamoxifen increased over time (2.7% at 5 years and 4.3% at 10 years) and recurrence rates remained significantly lower on anastrozole than tamoxifen after treatment completion (HR 0.81, 95% CI 0.67–0.98; $p=0.03$), although the carryover benefit was smaller after 8 years. There was weak evidence of fewer deaths after recurrence with anastrozole compared with tamoxifen treatment in the hormone-receptor-positive subgroup (HR 0.87, 95% CI 0.74–1.02; $p=0.09$), but there was little difference in overall mortality (0.95, 95% CI 0.84–1.06; $p=0.4$). Fractures were more frequent during active treatment in patients receiving anastrozole than those receiving tamoxifen (451 vs 351; OR 1.33, 95% CI 1.15–1.55; $p<0.0001$), but were similar in the post-treatment follow-up period (110 vs 112; OR 0.98, 95% CI 0.74–1.30; $p=0.9$). Treatment-related serious adverse events were less common in the anastrozole group than the tamoxifen group (223 anastrozole vs 369 tamoxifen; OR 0.57, 95% CI 0.48–0.69; $p<0.0001$), but were similar after treatment completion (66 vs 78; OR 0.84, 95% CI 0.60–1.19; $p=0.3$). No differences in non-breast cancer causes of death were apparent and the incidence of other cancers was similar between groups (425 vs 431) and continue to be higher with anastrozole for colorectal (66 vs 44) and lung cancer (51 vs 34), and lower for endometrial cancer (six vs 24), melanoma (eight vs 19), and ovarian cancer (17 vs 28). No new safety concerns were reported.

Interpretation These data confirm the long-term superior efficacy and safety of anastrozole over tamoxifen as initial adjuvant therapy for postmenopausal women with hormone-sensitive early breast cancer.

Funding AstraZeneca.

Introduction

Previous reports from the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial^{1–3} have shown significantly prolonged disease-free survival, lower rates of recurrence and distant recurrence, and significantly reduced contralateral breast cancer in patients treated with anastrozole compared with tamoxifen. Additionally,

anastrozole was associated with significantly fewer serious adverse events than tamoxifen, including fewer patients with endometrial cancer, but increased numbers of fractures and reports of arthralgia during treatment.⁴ Dowsett and colleagues⁵ have summarised the role of aromatase inhibitors, such as anastrozole, in the adjuvant treatment of early breast cancer.

Published Online
November 17, 2010
DOI:10.1016/S1470-2045(10)70257-6

For the list of ATAC/LATTE investigators, see *Lancet Oncol* 2008; 9: 45

Cancer Research UK, Centre for Epidemiology, Mathematics, and Statistics, Wolfson Institute of Preventive Medicine, Queen Mary School of Medicine and Dentistry, University of London, London, UK (Prof J Cuzick PhD, I Sestak PhD); Cancer Research UK and UCL Cancer Trials Centre, University College London, London, UK (Prof M Baum MD); MD Anderson Cancer Centre, University of Texas, Department of Breast Medical Oncology, Houston, TX, USA (Prof A Buzdar MD); Christie Hospital NHS Trust, University of Manchester, Cancer Research UK Department of Medical Oncology, Manchester, UK (Prof A Howell MD); Department of Academic Biochemistry, Royal Marsden Hospital, London, UK (Prof M Dowsett PhD); and School of Medical Practice and Population Health, University of Newcastle, Newcastle, NSW, Australia (Prof J F Forbes MD)

Correspondence to: Prof Jack Cuzick, Cancer Research UK Centre for Epidemiology, Mathematics, and Statistics, Wolfson Institute of Preventive Medicine, Queen Mary School of Medicine and Dentistry, University of London, Charterhouse Square, London EC1M 6BQ, UK
j.cuzick@qmul.ac.uk

A 10-year median follow-up of the ATAC trial was completed to satisfy a US Food and Drug Administration requirement for updated efficacy and safety information. This analysis provided about 13 months of additional follow-up data beyond the previously published 100-month follow-up report,³ but only assessed disease-free survival, time to recurrence, overall survival, and safety for all patients. Here, we extend this analysis to include also time to distant recurrence and incidence of contralateral breast cancer, and report the updated data from the ATAC trial at 120 months follow-up.

Methods

Patients and procedures

The ATAC trial has been described in detail previously.⁶ Briefly, eligible patients were postmenopausal women with histologically proven operable invasive breast cancer.

Patients were randomly assigned (1:1:1) to receive active anastrozole plus tamoxifen placebo, active tamoxifen plus anastrozole placebo, or active anastrozole plus active tamoxifen. Anastrozole was given as 1 mg and tamoxifen as 20 mg daily oral tablets for 5 years. The combination treatment group was discontinued after the initial analysis because it showed no efficacy or tolerability benefits over tamoxifen alone. Here, we report updated results for the tamoxifen and anastrozole monotherapy groups.

The protocol was approved by the appropriate local regulatory and ethics authorities for each participating centre. The trial was done in accordance with the Declaration of Helsinki (1996 revision) and under the principles of good clinical practice.

The primary endpoint was disease-free survival, defined as time from randomisation to the earliest occurrence of local or distant recurrence, new primary breast cancer, or

For the ATAC protocol see <http://www.astrazenecaclinicaltrials.com/drug-products/arimidex?itemId=9022922>

	0-2 years (number of events)			0-5 years (number of events)			>5 years (number of events)			All follow-up (number of events)			
	A*	T†	HR (95% CI)	A*	T†	HR (95% CI)	A*	T†	HR (95% CI)	A*	T†	HR (95% CI)	p value
Disease-free survival													
All randomised patients	203	242	0.83 (0.69-1.00)	496	568	0.86 (0.76-0.97)	457	454	0.97 (0.85-1.11)	953	1022	0.91 (0.83-0.99)	0.04
Hormone-receptor-positive patients	127	169	0.74 (0.59-0.93)	358	422	0.83 (0.72-0.95)	377	402	0.89 (0.77-1.02)	735	824	0.86 (0.78-0.95)	0.003
Time to recurrence													
All randomised patients	158	198	0.79 (0.64-0.98)	358	438	0.81 (0.70-0.93)	256	278	0.89 (0.75-1.05)	614	716	0.84 (0.75-0.93)	0.001
Hormone-receptor-positive patients	92	134	0.68 (0.52-0.88)	247	314	0.77 (0.65-0.91)	209	244	0.81 (0.67-0.98)	456	558	0.79 (0.70-0.89)	0.0002
Time to distant recurrence													
All randomised patients	130	141	0.92 (0.72-1.17)	289	335	0.86 (0.73-1.00)	192	209	0.90 (0.74-1.10)	481	544	0.87 (0.77-0.99)	0.03
Hormone-receptor-positive patients	74	93	0.79 (0.58-1.07)	199	229	0.86 (0.71-1.04)	153	179	0.83 (0.67-1.03)	352	408	0.85 (0.73-0.98)	0.02
Contralateral breast cancer													
All randomised patients	5	21	0.24 (0.09-0.63)	32	48	0.66 (0.42-1.03)	41	57	0.69 (0.46-1.04)	73	105	0.68 (0.50-0.91)	0.01
Hormone-receptor-positive patients	4	18	0.22 (0.07-0.65)	24	43	0.54 (0.33-0.90)	38	53	0.68 (0.45-1.03)	62	96	0.62 (0.45-0.85)	0.003
Death—all causes													
All randomised patients	117	102	0.97 (0.74-1.27)	340	359	0.92 (0.79-1.06)	394	388	1.01 (0.88-1.16)	734	747	0.97 (0.88-1.08)	0.6
Hormone-receptor-positive patients	66	62	1.00 (0.70-1.42)	233	255	0.87 (0.73-1.04)	330	331	0.99 (0.85-1.15)	563	586	0.95 (0.84-1.06)	0.4
Death after recurrence													
All randomised patients	72	58	1.05 (0.74-1.49)	202	229	0.85 (0.71-1.03)	193	212	0.91 (0.75-1.10)	395	441	0.89 (0.77-1.02)	0.09
Hormone-receptor-positive patients	31	27	1.04 (0.61-1.76)	122	147	0.78 (0.61-1.01)	162	173	0.93 (0.75-1.15)	284	320	0.87 (0.74-1.02)	0.09
Death without recurrence													
All randomised patients	45	44	0.87 (0.57-1.33)	138	130	1.03 (0.81-1.30)	201	176	1.14 (0.93-1.39)	339	306	1.10 (0.94-1.29)	0.2
Hormone-receptor-positive patients	35	35	0.97 (0.60-1.56)	111	108	1.00 (0.77-1.31)	168	158	1.04 (0.85-1.31)	279	266	1.04 (0.88-1.22)	0.09

A=anastrozole. T=tamoxifen. HR=hazard ratio. *All randomised patients n=3125; hormone-receptor-positive patients n=2618. †All randomised patients n=3116; hormone-receptor-positive patients n=2598.

Table 1: Efficacy endpoints for all patients and hormone-receptor-positive patients in different follow-up periods

death from any cause. Secondary endpoints were time to recurrence, which included new contralateral tumours, but not deaths from non-breast-cancer causes before recurrence; time to distant recurrence, defined as the time between randomisation and the first report of distant recurrence, censoring at deaths without recurrence; contralateral breast cancer; death after recurrence; and overall survival.

Statistical analysis

Hazard ratios (HR) and 95% CIs were based on partial likelihood estimates for Cox's proportional hazards model without adjustment for covariates.⁷ All time-to-event curves were truncated after 10 years of follow-up, but HRs include all events until database cutoff (March 31, 2009). Hazard rate curves were smoothed with an Epanechnikov kernel with optimum bandwidth chosen by cross-validation.⁸ All analyses were done using Stata (version 10.1). A *p* value of less than or equal to 0.05 was deemed significant.

The full study population (3125 patients in the anastrozole group and 3116 in the tamoxifen group) and the predefined hormone-receptor-positive subpopulation (2618 patients in the anastrozole group and 2598 in the tamoxifen group) were included in efficacy analyses. Women with known hormone-receptor-positive tumour status (defined as oestrogen-receptor-positive or progesterone-receptor-positive, or both, according to local laboratory standards) were predefined as a clinically important subgroup for all efficacy endpoint analyses; this subgroup is now considered the clinically relevant group for hormone treatment.⁹

Safety analyses were based on treatment first received in all randomised patients (anastrozole *n*=3092; tamoxifen *n*=3094). Only serious adverse events and fracture rates (allowing for multiple episodes at least 1 year apart so that women with an early fracture were still included in later follow-up analyses) were recorded after treatment completion and updated results are reported here. A full analysis of all adverse events has been reported previously.⁴

The ATAC trial is registered as an International Standard Randomised Controlled Trial, number ISRCTN18233230.

Role of the funding source

The study was developed by the new studies working party of the Cancer Research UK Breast Cancer Trial Group before a sponsor was identified. The management of the trial was subsequently coordinated and supervised by the steering committee and the international coordinating committee, with funding and organisational support from the trial sponsor, AstraZeneca. The sponsor was represented in the minority on both committees. The independent statistician (JC) had full access to the data and was responsible for providing regular information to the independent data monitoring committee. The sponsor had access to all data except for

the randomisation codes until unmasking. All authors were responsible for the data interpretation, writing of the report, and final approval of the manuscript for

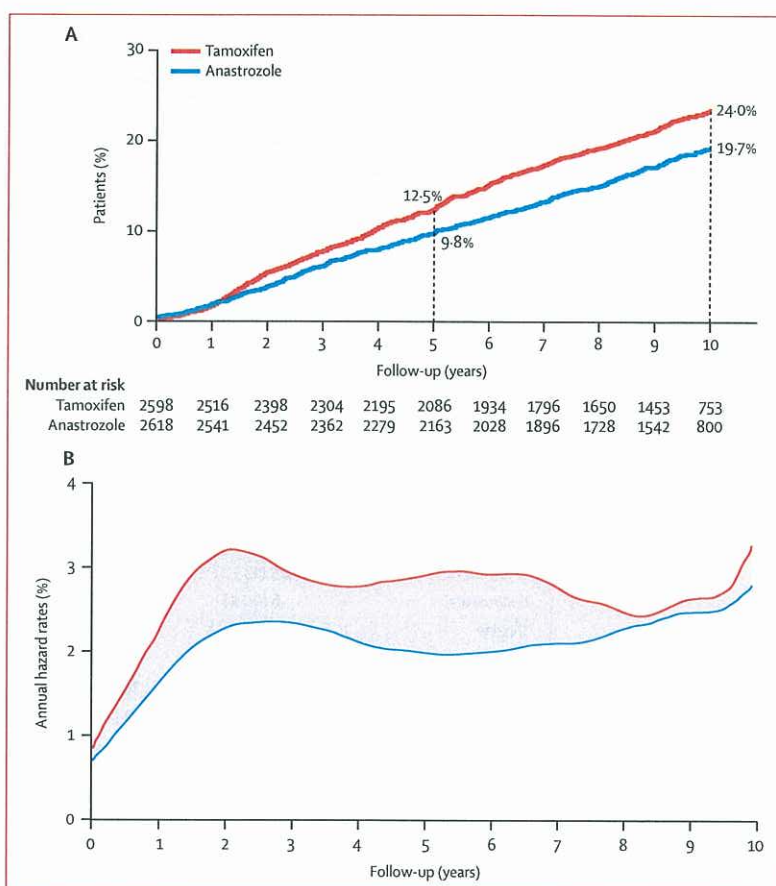


Figure 1: Curves for time to recurrence in hormone-receptor-positive patients

(A) Kaplan-Meier prevalence curves and (B) smoothed hazard rate curves.⁸ Numbers at risk differ in some cases from those provided in the 100-month analysis³ because of additional follow-up data.

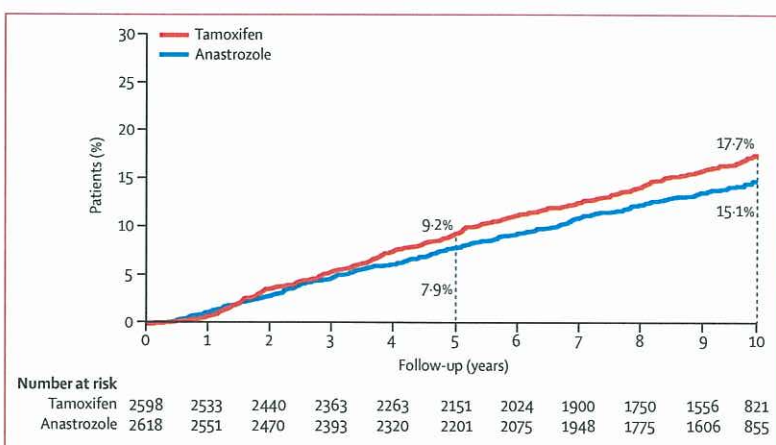


Figure 2: Kaplan-Meier curve for time to distant recurrence in hormone-receptor-positive patients

Numbers at risk differ in some cases from those provided in the 100-month analysis³ because of additional follow-up data.

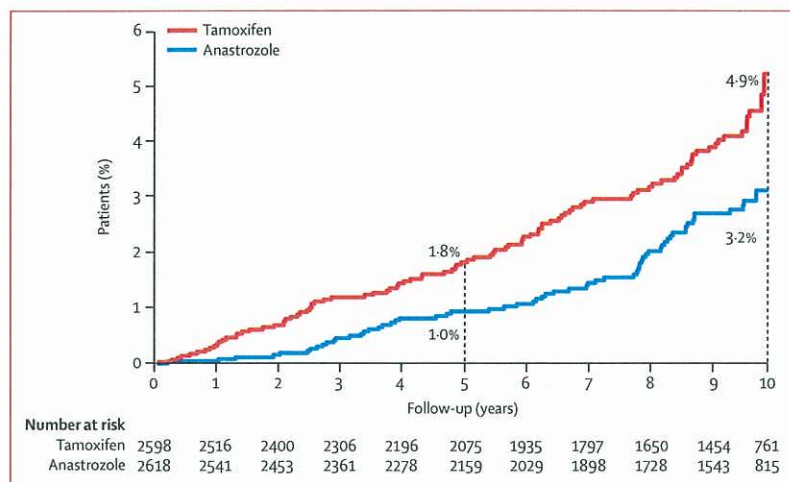


Figure 3: Kaplan-Meier curves for contralateral breast cancer in hormone-receptor-positive patients. Numbers at risk differ in some cases from those provided in the 100-month analysis³ because of additional follow-up data.

	Anastrozole (n=3092)	Tamoxifen (n=3094)
All cancers	425 (13.7%)	431 (13.9%)
Endometrial	6 (0.2%)	24 (0.8%)
Ovarian	17 (0.5%)	28 (0.9%)
Melanoma	8 (0.3%)	19 (0.6%)
Lung	51 (1.6%)	34 (1.1%)
All gastrointestinal*	104 (3.4%)	72 (2.3%)
Colorectal	66 (2.1%)	44 (1.4%)
Gastric	12 (0.4%)	8 (0.3%)
Bladder	7 (0.2%)	9 (0.3%)
Head and neck	12 (0.4%)	5 (0.2%)
Leukaemia	10 (0.3%)	13 (0.4%)
Non-Hodgkin lymphoma	11 (0.4%)	12 (0.4%)
Skin (non-melanoma)	102 (3.3%)	107 (3.5%)
Other	117 (3.8%)	123 (4.0%)

* Colorectal, gastric, gallbladder, anus, duodenum, liver, oesophagus, pancreas.

Table 2: Non-breast cancers in the safety population

See Online for webappendix

submission. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Median follow-up for this analysis was 120 months (range 0–145). This follow-up included a total of 48 473 woman-years of follow-up (24 522 woman-years for anastrozole and 23 950 woman-years for tamoxifen). Baseline characteristics have been described previously;⁶ the median age at this analysis was 72 years (IQR 65–91).

Table 1 summarises the results for all efficacy endpoints for all randomised patients and the hormone-receptor-positive subgroup. Overall, hazard ratios were similar to those in the previous report.³ Treatment with anastrozole

led to improved disease-free survival, lower time to recurrence, and lower time to distant recurrence rates compared with treatment with tamoxifen. An absolute reduction of recurrence of 2.7% at 5 years and 4.3% at 10 years was reported for anastrozole compared with tamoxifen in the hormone-receptor-positive patients (figure 1). In the hazard rate curves, rates for recurrence for this subgroup also remained lower on anastrozole compared with tamoxifen throughout the study, although there appeared to be less difference after 8 years. Distant recurrence rates also remained lower on anastrozole compared with tamoxifen in the hormone-receptor-positive subgroup throughout follow-up, with an absolute difference of 2.6% at 10 years (figure 2). Additionally, the incidence of contralateral breast cancer was lower in those treated with anastrozole than those on tamoxifen both in the full study population and in the hormone-receptor-positive subgroup (table 1; figure 3), persisting with longer follow-up.

The greatest relative reduction in time to recurrence, contralateral breast cancer, and disease-free survival associated with anastrozole compared with tamoxifen was seen in the first 2 years of active treatment (table 1), but these differences between treatment groups were sustained throughout the entire follow-up period, including after treatment completion. Reductions in distant recurrence rates were similar between groups throughout follow-up. In a post-hoc analysis, we also examined endpoints in hormone-receptor-negative and hormone-receptor-unknown patients, but no effect was seen for any endpoint, except for weak evidence of an increase in deaths without recurrence in the hormone-receptor-unknown population ($p=0.03$; webappendix); however, this finding is difficult to interpret because of multiple comparisons.

In the safety population, there was no significant difference in non-breast cancers between groups (odds ratio [OR] 0.98, 95% CI 0.85–1.14; $p=0.8$; table 2). However, there were fewer endometrial cancers (OR 0.25, 95% CI 0.08–0.63) and melanomas (0.42, 0.16–1.00) in the anastrozole group than the tamoxifen group, but only the difference in endometrial cancer remained significant after Bonferroni correction ($p=0.001$). There was weak evidence of more lung (OR 1.51, 95% CI 0.96–2.41) and colorectal cancers (1.51, 1.01–2.27) in the anastrozole group than in the tamoxifen group.

Significantly more fractures were reported during treatment in the anastrozole group than the tamoxifen group (451 vs 351; OR 1.33, 95% CI 1.15–1.55; $p<0.0001$). However, after treatment completion, the incidence of fractures was similar between the two groups (110 anastrozole vs 112 tamoxifen; OR 0.98, 95% CI 0.74–1.30; $p=0.9$; 10-year rate 2.0% vs 1.5%; figure 4). For the entire study period, the incidence of hip fractures was similar between treatment groups (48 anastrozole vs 46 tamoxifen; OR 1.04, 95% CI 0.68–1.61; $p=0.8$), whereas spinal fractures were more often reported in the

anastrozole group (68 anastrozole vs 46 tamoxifen; OR 1.49, 95% CI 0.01–2.22).

Overall, treatment-related serious adverse events were less common in the anastrozole group than the tamoxifen group (223 anastrozole vs 369 tamoxifen; OR 0.57, 95% CI 0.48–0.69; $p < 0.0001$), but rates were similar after treatment completion (66 anastrozole vs 78 tamoxifen; OR 0.84, 95% CI 0.60–1.19; $p = 0.3$). In the full study population, 1481 deaths were reported (table 3). There was weak evidence of lower death rates for recurrence in the anastrozole group than the tamoxifen group ($p = 0.09$; table 1), but there was little difference in overall mortality in both the full study population and the hormone-receptor-positive subgroups. Similar mortality rates were seen in the safety population, both overall (725 vs 745, OR 0.97, 95% CI 0.86–1.09), after recurrence (389 vs 439, OR 0.87, 95% CI 0.75–1.02), and without recurrence (336 vs 306, OR 1.11, 95% CI 0.94–1.31). No differences in non-breast cancer causes of death were apparent (table 3).

Discussion

This 10-year analysis of the ATAC trial confirms the previously reported efficacy and tolerability benefits of anastrozole as initial adjuvant therapy for postmenopausal women with early hormone-receptor-positive breast cancer (panel; table 4). Tamoxifen has shown a carryover benefit for recurrence in the first 5 years after treatment, but not after that.⁹ This so-called carryover effect for recurrence was larger for anastrozole than for tamoxifen in the present study and remained significant for the entire 10-year follow-up period. However, the additional benefit beyond that achieved with tamoxifen might be waning after about 8 years, and further follow-up is needed to see how long this effect will be maintained with anastrozole. Greater reductions in time to recurrence, rates of contralateral breast cancer, and disease-free survival were seen in the first 2 years of follow-up compared with later follow-up periods. No information on oestrogen-receptor, progesterone-receptor, or human epidermal growth-factor status of the contralateral tumours is available at present, but this information is being sought as part of the long-term follow-up of ATAC, now known as LATTE (Long-term Anastrozole versus Tamoxifen Treatment Effects).

Deaths after recurrence were not significantly lower with anastrozole than with tamoxifen over the 10 years of follow-up. In view of the significant reduction in distant recurrence, deaths after recurrence might become significantly lower with anastrozole than tamoxifen in the future, but further follow-up is needed for this endpoint. Deaths without recurrence were not significantly higher with anastrozole than with tamoxifen, but no differences for any specific non-breast cancer causes of death were noted and overall mortality did not differ significantly between the two groups. Overall, there was no difference in the occurrence of

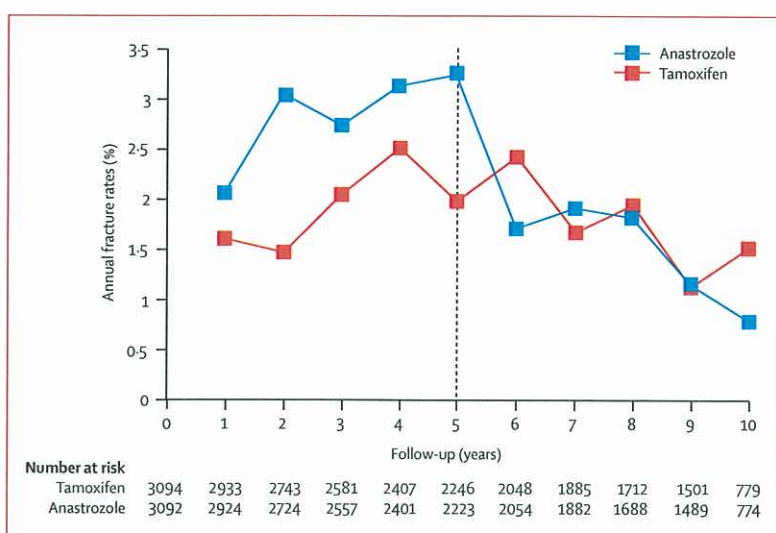


Figure 4: Fracture rates in the full study population

Numbers at risk differ in some cases from those provided in the 100-month analysis³ because of additional follow-up data.

	Anastrozole (n=3125)	Tamoxifen (n=3116)
Total deaths	734 (23.5%)	747 (24.0%)
Deaths after recurrence	395 (12.6%)	441 (14.2%)
Deaths without recurrence	339 (10.8%)	306 (9.8%)
Cardiovascular	91 (2.9%)	95 (3.0%)
Cerebrovascular	33 (1.1%)	36 (1.2%)
Other cancer	108 (3.5%)	82 (2.6%)
Other	107 (3.4%)	93 (3.0%)

Table 3: Deaths in the full study population

non-breast cancers, although there were some differences for particular cancers. However, a causal relation for these differences is difficult to assess because of multiple comparisons. Of the 11 non-breast cancers that we compared, only the higher rate of endometrial cancer with tamoxifen compared with anastrozole remained significant after a Bonferroni correction and, in view of multiple previous reports,⁹ this difference is certain to be real. The higher occurrence of colorectal cancer in anastrozole-treated women than those on tamoxifen is also possibly causal in view of the known reduction in colorectal cancer when patients are treated with oestrogen, as in hormone replacement therapy.²³ However, this higher occurrence of colorectal cancer was not significant after correction for multiple comparisons and was not seen with letrozole, another aromatase inhibitor,²¹ thus, doubt still remains as to whether this effect is causal. Information on stage, histology, and other tumour characteristics was not uniformly collected for non-breast cancers.

Over 90% of all patients without recurrence remained masked to treatment and none were on trial treatment at

	Number randomised	Median follow-up (months)	Disease-free survival hazard ratio (95% CI)
ATAC³			
Tamoxifen for 5 years	3116	120	..
Anastrozole for 5 years	3125	..	0.86 (0.78–0.95)*
Anastrozole and tamoxifen for 5 years	3125	33	NA
BIG 1-98¹⁹			
Tamoxifen for 5 years	2459	76	..
Letrozole for 5 years	2463	..	0.88 (0.78–0.99)
Letrozole for 5 years	1546	71	..
Tamoxifen for 2 years followed by letrozole for 3 years	1548	..	1.05 (0.84–1.32)
Letrozole for 2 years followed by tamoxifen for 3 years	1540	..	0.96 (0.76–1.21)
TEAM¹⁴			
Tamoxifen for 2–3 years followed by exemestane for 2–3 years	4868	33	..
Exemestane for 5 years	4898	..	0.89 (0.77–1.03)
IES¹⁵			
Tamoxifen for 5 years	2372	56	..
Tamoxifen for 2–3 years followed by exemestane for 2–3 years	2352	..	0.76 (0.66–0.88)
ABCSG8/ARNO¹⁶			
Tamoxifen for 5 years	1606	28	..
Tamoxifen for 2 years followed by anastrozole for 3 years	1618	..	0.60 (0.44–0.81)†
ITA¹⁷			
Tamoxifen for 5 years	225	64	..
Tamoxifen for 2 years followed by anastrozole for 3 years	223	..	0.57 (0.38–0.85)†
MA.17¹⁸			
Tamoxifen for 5 years	2594	30	..
Tamoxifen for 5 years followed by letrozole for 5 years	2593	..	0.58 (0.45–0.76)
NSABP-B33¹⁹			
Tamoxifen for 5 years	779	30	..
Tamoxifen for 5 years followed by exemestane for 5 years	786	..	0.68 (p=0.07)‡
ABCSG6²⁰			
Tamoxifen for 5 years	469	62	..
Tamoxifen for 5 years followed by anastrozole for 3 years	387	..	0.64 (0.41–0.99)†

NA=not applicable. *Hormone-receptor-positive patients only. †Breast cancer recurrence only, not disease-free survival. ‡95% CI was not provided in the paper.

Table 4: Trials of third-generation aromatase inhibitors as adjuvant treatment for early breast cancer

the time of this analysis. For these reasons, we do not think that many patients without recurrence received anastrozole or any other adjuvant treatment after the initial 5-year treatment period, although this was not recorded. Severe adverse events were similar between treatment groups after treatment and no new safety concerns were reported. In particular, the increased fracture rate with anastrozole during treatment did not continue after treatment, suggesting that this is a short-term effect that could be managed with dual-energy x-ray absorptiometry

Panel: Research in context

Systematic review

We searched Medline for articles published in any language between January, 2000, and August, 2010, with the search term "aromatase inhibitor". We also checked the reference lists of publications of known trials. No additional trials were identified that had not been identified in previous overviews^{5,10} or by direct contact with authors. Two trials had compared anastrozole to tamoxifen in advanced breast cancer^{11,12} and the results suggested a better efficacy and safety profile in the adjuvant setting with anastrozole compared with tamoxifen, which is why we undertook the ATAC trial. There have been several trials on adjuvant treatment of breast cancer with aromatase inhibitors, either as initial treatment or after tamoxifen.^{3,13–20} A meta-analysis on aromatase inhibitors versus tamoxifen for breast cancer treatment,⁵ an update of a trial of letrozole,²¹ and a trial using exemestane in 9766 postmenopausal women,²² have been reported. Altogether, there have been ten trials assessing aromatase inhibitors in the adjuvant setting (table 4).

Interpretation

ATAC was the first trial to show that an aromatase inhibitor is more effective and has fewer serious side-effects than tamoxifen in the adjuvant setting. This has now been confirmed in several other trials using a range of aromatase inhibitors.^{3,21} The present analysis extends these results for anastrozole to a longer follow-up time and provides important long-term evidence supporting the previous findings.

These trials have led to changes in all major guidelines for breast cancer treatment to now recommend the use of an aromatase inhibitor in the adjuvant treatment of early oestrogen-receptor-positive breast cancer. The present study suggests that, at least for anastrozole, the benefits of anastrozole are maintained or extended with long-term follow-up and provides more support for the use of anastrozole as the initial adjuvant treatment in this setting. Present trials are aimed at identifying the optimum duration of aromatase inhibitor treatment by comparing 5 versus 10 years of treatment with an aromatase inhibitor.

scans and bisphosphonates when needed. In the ATAC trial,^{1–3} bisphosphonate use was low during the active treatment period (10% of patients on anastrozole and 7% of those on tamoxifen). However, clinical guidelines²⁴ now recommend use of bisphosphonates for women with low bone-mineral density who are receiving treatment with an aromatase inhibitor. We are in the process of developing predictive models for deaths from other causes and severe adverse events; although this is a complex analysis, age and comorbidities at entry seem to be key factors.

Contributors

JC, MD, and MB designed the trial. AB, MB, JFF, and AH collected data. JC (independent statistician) and IS analysed data and drafted the report. All authors took part in data interpretation, writing the report, and approved the final version.

Conflicts of interest

JC has received grants, honoraria, travel grants, and payment for lectures from AstraZeneca. IS has received travel support from AstraZeneca. AB has received a grant and travel support from AstraZeneca. AH has received travel support from AstraZeneca, consultancy fees from Genentech and Pfizer, payment for lectures from AstraZeneca, and money from Pfizer and Roche for DMC meetings. MD has received travel support from AstraZeneca, board membership fees, grants, and payments for lectures from AstraZeneca and Novartis, and has a patent registered with Novartis. JFF has received honoraria and travel support from AstraZeneca. MB has no conflicts of interest.

Acknowledgments

The study was funded by AstraZeneca.

References

- Baum M, Buzdar A, Cuzick J, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses. *Cancer* 2003; 98: 1802–10.
- Howell A, Cuzick J, Baum M, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 2005; 365: 60–62.
- Forbes JF, Cuzick J, Buzdar A, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. *Lancet Oncol* 2008; 9: 45–53.
- Buzdar A, Howell A, Cuzick J, et al. Comprehensive side-effect profile of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: long-term safety analysis of the ATAC trial. *Lancet Oncol* 2006; 7: 633–43.
- Dowsett M, Cuzick J, Ingle J, et al. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. *J Clin Oncol* 2010; 28: 509–18.
- Baum M, Buzdar AU, Cuzick J, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet* 2002; 359: 2131–39.
- Cox DR. Regression models and life tables. *J R Stat Soc* 1972; 34: 187–220.
- Jones MC, Wand MP. Kernel smoothing. Boca Raton, FL: CRC Press, 1994.
- Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; 365: 1687–717.
- Cuzick J, Sasieni P, Howell A. Should aromatase inhibitors be used as initial adjuvant treatment or sequenced after tamoxifen? *Br J Cancer* 2006; 94: 460–66.
- Bonnerterre J, Thürlimann B, Robertson JF, et al. Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. *J Clin Oncol* 2000; 18: 3748–57.
- Nabholtz JM, Buzdar A, Pollak M, et al. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. Arimidex Study Group. *J Clin Oncol* 2000; 18: 3758–67.
- Joerger M, Thürlimann B. Update of the BIG 1-98 Trial: where do we stand? *Breast* 2009; 18 (suppl 3): S78–82.
- Jones SE, Seynaeve C, Hasenburger A, et al. Results of the first planned analysis of the TEAM (tamoxifen exemestane adjuvant multinational) prospective randomized phase III trial in hormone sensitive postmenopausal early breast cancer. 31st Annual San Antonio Breast Cancer Symposium; Dec 10–14, 2008; San Antonio, TX, USA. Abstract 15.
- Coombes RC, Kilburn LS, Snowdon CF, et al. Survival and safety of exemestane versus tamoxifen after 2–3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. *Lancet* 2007; 369: 559–70.
- Jakesz R, Jonat W, Gnani M, et al. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. *Lancet* 2005; 366: 455–62.
- Boccardo F, Rubagotti A, Guglielmini P, et al. Switching to anastrozole versus continued tamoxifen treatment of early breast cancer. Updated results of the Italian tamoxifen anastrozole (ITA) trial. *Ann Oncol* 2006; 17 (suppl 7): vii10–14.
- Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med* 2003; 349: 1793–802.
- Mamounas EP, Jeong JH, Wickerham DL, et al. Benefit from exemestane as extended adjuvant therapy after 5 years of adjuvant tamoxifen: intention-to-treat analysis of the National Surgical Adjuvant Breast And Bowel Project B-33 trial. *J Clin Oncol* 2008; 26: 1965–71.
- Jakesz R, Samonigg H, Greil R, et al, on behalf of the ABCSG. Extended adjuvant treatment with anastrozole: results from the Austrian Breast and Colorectal Cancer Study Group Trial 6a (ABCSG-6a). *J Clin Oncol* 2005 23 (suppl 16): 527 (abstr).
- Mouridsen H, Giobbè-Hurder A, Goldhirsch A, et al. Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer. *N Engl J Med* 2009; 361: 766–76.
- Rea D, Hasenburger A, Seynaeve C, et al. Five years of exemestane as initial therapy compared to 5 years of tamoxifen followed by exemestane: the TEAM trial, a prospective, randomized, phase III trial in postmenopausal women with hormone-sensitive early breast cancer. *Cancer Res* 2009; 69 (24 suppl): abstr 11.
- Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004; 291: 1701–12.
- Reid DM, Doughty J, Eastell R, et al. Guidance for the management of breast cancer treatment-induced bone loss: a consensus position statement from a UK Expert Group. *Cancer Treat Rev* 2008; 34 (suppl 1): S3–18.

