



Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer

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The standard adjuvant endocrine treatment for postmenopausal women with hormone-receptor-positive localised breast cancer is 5 years of tamoxifen, but recurrences and side-effects restrict its usefulness. The aromatase inhibitor anastrozole was compared with tamoxifen for 5 years in 9366 postmenopausal women with localised breast cancer. After a median follow-up of 68 months, anastrozole significantly prolonged disease-free survival (575 events with anastrozole vs 651 with tamoxifen, hazard ratio 0.87, 95% CI 0.78-0.97, $p=0.01$) and time-to-recurrence (402 vs 498, 0.79, 0.70-0.90, $p=0.0005$), and significantly reduced distant metastases (324 vs 375, 0.86, 0.74-0.99, $p=0.04$) and contralateral breast cancers (35 vs 59, 42% reduction, 12-62, $p=0.01$). Almost all patients have completed their scheduled treatment, and fewer withdrawals occurred with anastrozole than with tamoxifen. Anastrozole was also associated with fewer side-effects than tamoxifen, especially gynaecological problems and vascular events, but arthralgia and fractures were increased. Anastrozole should be the preferred initial treatment for postmenopausal women with localised hormone-receptor-positive breast cancer.

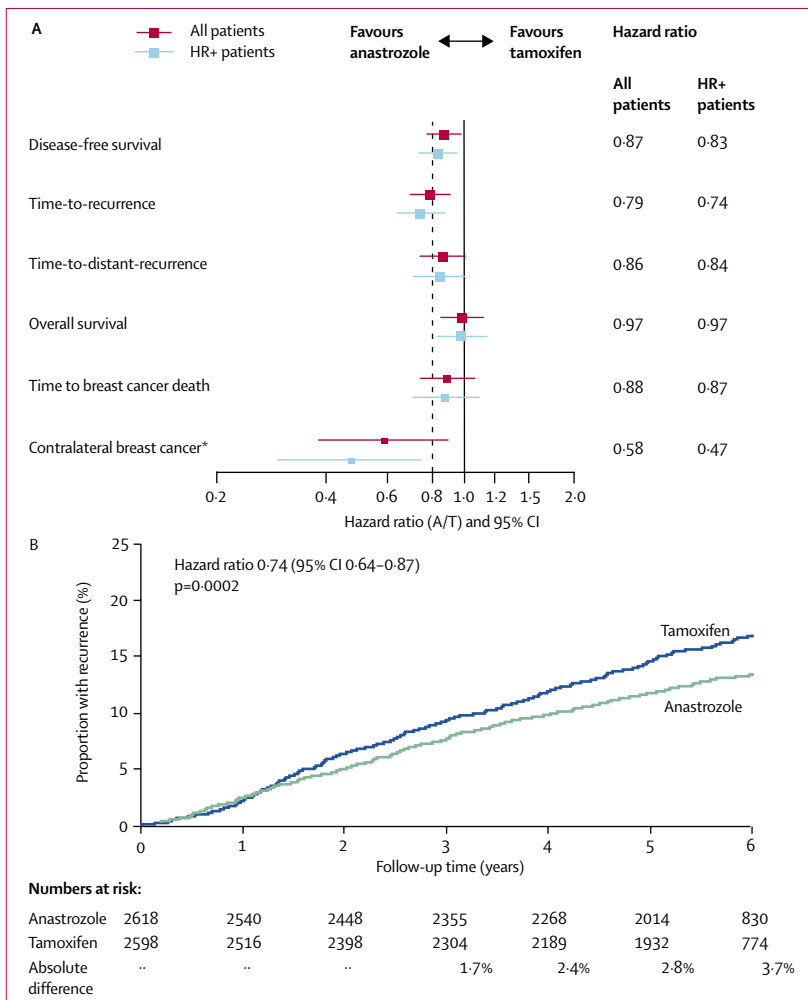


Figure: (A) Efficacy endpoints for all patients and hormone-receptor-positive patients and (B) time-to-recurrence in hormone-receptor-positive patients
A=anastrozole. T=tamoxifen. HR+=hormone-receptor-positive. *Odds ratio calculated instead of hazard ratio.

The standard adjuvant endocrine treatment for postmenopausal women with hormone-receptor-positive localised breast cancer is 5 years of tamoxifen. Nevertheless, recurrences and side-effects limit its usefulness.¹ The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, a double-blind randomised trial, compared 5 years of the aromatase inhibitor anastrozole alone with tamoxifen alone, or the combination, as adjuvant therapy in 9366 postmenopausal women with localised breast cancer.^{2,3} Primary objectives were to discover whether anastrozole is at least as effective as tamoxifen in postmenopausal women with localised breast cancer, and/or offers benefits in safety or tolerability over tamoxifen in this group of patients. Initial analyses of the ATAC trial at 33 and 47 months of median follow-up showed that anastrozole significantly prolonged disease-free survival and time-to-recurrence, and reduced the incidence of contralateral breast cancer, compared with tamoxifen.^{2,3} After these analyses, the combination treatment arm was closed because of low efficacy. Details of the trial design, methods, primary objectives, and endpoints have been reported previously.²

Here we compare the efficacy and tolerability of anastrozole with that of tamoxifen after a median follow-up of 68 months. This time extends beyond the planned 5-year treatment period and only 8% of patients remain on trial treatment.

Treatment with anastrozole led to significant improvements compared with tamoxifen for disease-free survival (575 vs 651 events, hazard ratio 0.87, 95% CI 0.78-0.97, $p=0.01$) and time-to-recurrence (402 vs 498, 0.79, 0.70-0.90, $p=0.0005$). A greater advantage was seen in disease-free survival (0.83, 0.73-0.94, $p=0.005$) and in time-to-recurrence (0.74, 0.64-0.87, $p=0.0002$) in hormone-receptor-positive patients (figure 1A). This 26% risk reduction over tamoxifen for time-to-

recurrence is in addition to the 47% risk reduction previously shown for 5 years of tamoxifen versus placebo in adjuvant studies.⁴ No significant differences were noted in effect according to subgroup at the 1% level, and the hazard rate was lower for anastrozole in all subgroups except for patients who were hormone-receptor-negative or whose hormone-receptor status was unknown.

Absolute differences in recurrence rates increased over time, even beyond 5 years of scheduled treatment, suggesting that there is a carryover effect for anastrozole similar to that observed for tamoxifen,⁴ at least in the short-term (figure 1B). The benefits of anastrozole were seen at all times after the first year of follow-up. In particular, the high hazard rate seen in years 1–3 for tamoxifen was substantially suppressed by anastrozole. We noted a significant overall benefit in time-to-distant-recurrence for anastrozole (324 vs 375 events, hazard ratio 0.86, 95% CI 0.74–0.99, $p=0.04$), with a similar trend in the subset of hormone-receptor-positive patients (0.84, 0.70–1.00, $p=0.06$).

The incidence of contralateral breast cancer was substantially reduced by anastrozole compared with tamoxifen (all patients 35 vs 59, 42% reduction, 95% CI 12–62, $p=0.01$; hormone-receptor-positive patients 53%, 25–71, $p=0.001$). Since tamoxifen shows a 50% reduction in the occurrence of these tumours in hormone-receptor-positive patients compared with placebo,⁴ the findings from the ATAC study suggest that anastrozole treatment might prevent 70–80% of hormone-receptor-positive tumours in women at high risk of breast cancer.

831 women died; 500 (60%) after recurrence of breast cancer and 331 (40%) without recurrence and due to other causes. Overall survival was similar for anastrozole and tamoxifen (hazard ratio 0.97, 95% CI 0.85–1.12, $p=0.7$); a 12% reduction in deaths from breast cancer in the anastrozole group was not significant (0.88, 0.74–1.05; $p=0.2$). However, since the trial population had a relatively good prognosis (5695 [61%] of patients were lymph-node-negative and 5959 [64%] had tumours 2 cm or smaller in diameter), it is too early to expect a difference in survival. For example, it took at least 7 years to show a significant survival advantage for tamoxifen versus placebo in previous adjuvant studies.⁵ The significant reductions in recurrence and distant recurrence associated with anastrozole strongly suggest that a reduction in deaths from breast cancer will eventually be seen.

Since almost all patients have completed their scheduled 5 years of therapy, the safety and tolerability data during treatment can be deemed final. Withdrawals due to adverse events were significantly less common with anastrozole (344, 11.1%) than with tamoxifen (442, 14.3%; $p=0.0002$). Drug-related serious adverse events were also significantly less common with anastrozole (146, 4.7%) than with tamoxifen (271, 9.0%; $p<0.0001$).

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

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

Table: Prespecified adverse events on treatment or within 14 days of discontinuation

Treatment with anastrozole was associated with significant reductions in the incidence of endometrial cancer, thromboembolic events, ischaemic cerebrovascular events, vaginal bleeding, hot flushes, and vaginal discharge, compared with tamoxifen (table). Tamoxifen was associated with fewer fractures and less arthralgia than was anastrozole. Fracture rates per 1000 woman-years were 22.6 for anastrozole and 15.6 for tamoxifen (hazard ratio 1.44, 95% CI 1.21–1.68, $p<0.0001$). The incidence of hip fracture was low and similar for anastrozole and tamoxifen (table). Findings of several studies show that bisphosphonates are effective in maintaining bone density¹ in women with breast cancer. The risk ratios for all the prespecified adverse events in the present report were similar to those noted in previous analyses,^{2,3} suggesting that the safety profile of anastrozole remains unchanged during the 5-year treatment period. No new safety concerns emerged.

This analysis of the ATAC trial confirms the efficacy and tolerability benefits of anastrozole as initial adjuvant treatment for postmenopausal women with localised breast cancer. The results are only applicable to anastrozole, since it is unknown how differences between the aromatase inhibitors affect their clinical usefulness. Results from studies evaluating anastrozole or exemestane after 2–3 years of adjuvant tamoxifen, compared with continuing tamoxifen, suggest that it is reasonable to switch patients currently on tamoxifen

to an aromatase inhibitor.¹ The present data suggest that it is not appropriate to wait 5 years to start an aromatase inhibitor. **Furthermore, the higher rates of recurrence (especially in years 1–3), and the increased numbers of adverse events and treatment withdrawals associated with tamoxifen, lend support to the approach of offering the most effective and well tolerated therapy at the earliest opportunity. 5 years of anastrozole should now be considered as the preferred initial adjuvant endocrine treatment for postmenopausal women with hormone-receptor-positive localised breast cancer.**

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ATAC Trialists' Group

Full list of trialists and principal and main co-investigators in the ATAC Trial available at <http://image.the.lancet.com/extras/04let1120webappendix.pdf>

Contributors

A Howell is the current principal investigator and chairs the writing and steering committees. M Baum was the original principal investigator and played an active role in protocol design and trial governance. A Buzdar participated in the trial management and data interpretation. J Cuzick was responsible for the statistical analysis, and participated in trial design and data interpretation. M Dowsett participated in the trial design and conduct, and in data interpretation. J F Forbes coordinated entry of patients from the Australia New Zealand Breast Cancer Trials Group to the trial. G Hochtin-Boes participated in the coordination of the trial. J Houghton participated in design issues, the overall operational management of the trial, and the preparation of trial results for analysis. G Y Locker participated in the management of the trial. J S Tobias contributed to the design of the study. All contributors participated in writing the paper.

Conflict of interest statement

A Howell has received honoraria and appeared on speakers' bureaux for AstraZeneca. M Baum has received travel grants, honoraria for lectures, and occasional consultancy fees for AstraZeneca. A Buzdar has received research grants, travel awards, and honoraria from AstraZeneca. J Cuzick is statistical consultant to, and has received research funds from, AstraZeneca. M Dowsett has received paid consultancy from AstraZeneca and is in receipt of grants from AstraZeneca for work done in his laboratory. J F Forbes has received honoraria from AstraZeneca, Novartis, and Lilly for attendance at advisory board meetings. He is responsible for the undertaking of clinical trials by the Australia New Zealand Breast Cancer Trials Group, which have been supported by education/research grants from various pharmaceutical companies. G Hochtin-Boes is an employee of AstraZeneca. J Houghton holds a contract with AstraZeneca for operational management and to support some of the monitoring of the trial. She has also received travel awards and honoraria from AstraZeneca. G Y Locker has received research grants and appeared on speakers' bureaux for AstraZeneca. J S Tobias has received occasional honoraria and travel expenses from AstraZeneca. All have seen and approved the final version of the manuscript.

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