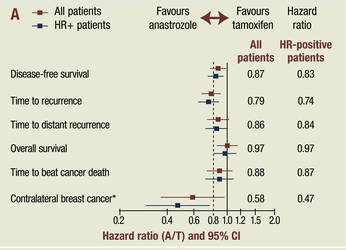
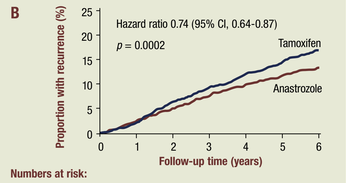
Arimidex, Tamoxifen Alone or in Combination (ATAC) Trial

The ATAC trial reported initial results in December 2001, demonstrating an advantage in disease-free survival (DFS) with the third-generation aromatase inhibitor anastrozole compared to tamoxifen. An advantage was also seen in safety and tolerability with regard to thrombotic events and endometrial cancer, although fractures and arthralgias were more common in women treated with anastrozole. At the 2003 San Antonio Breast Cancer Symposium, further data were presented demonstrating an even greater advantage to anastrozole compared to tamoxifen in women with ER-positive, PR-negative tumors. At the recent 2004 San Antonio meeting, data were presented from the third analysis at 68 months. An advantage to anastrozole in disease-free survival continued to be present with about one in four relapses on tamoxifen avoided with anastrozole.

ATAC TRIAL 68-MONTH ANALYSIS: EFFICACY ENDPOINTS AND TIMES TO RECURRENCE





Numbers at risk:

Anastrozole	2,618	2,540	2,448	2,355	2,268	2,014	830
Tamoxifen	2,598	2,516	2,398	2,304	2,189	1,932	774
Absolute difference	—	—	—	1.7%	2.4%	2.8%	3.7%

Figure: (A) Efficacy endpoints for all patients and HR-positive patients and (B) time-to-recurrence in HR-positive patients

A = anastrozole; T = tamoxifen; HR = hormone receptor
* Odds ratio calculated instead of hazard ratio

SOURCE: With permission from ATAC Trialists' Group. **Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer.** *Lancet* 2005;365:60-2.

RECURRENCE RATES IN THE ATAC TRIAL ACCORDING TO ESTROGEN AND PROGESTERONE RECEPTOR STATUS

Receptor status	N	Hazard ratio for anastrozole versus tamoxifen (95% CI)*	Anastrozole (%)	Tamoxifen (%)
ER+ PR+†	5,704	0.82 (0.65-1.03)	7	8
ER+ PR-†	1,370	0.48 (0.33-0.71)	9	17
ER- PR+	220	0.79 (0.40-1.5)	22	26
ER- PR-	699	1.04 (0.73-1.47)	27	27

* Hazard ratios less than one indicate values in favor of anastrozole.
† From 68-month analysis: HR in ER/PR-positive (0.84), ER-positive/PR-negative (0.43)

SOURCES: Dowsett M, on behalf of the ATAC Trialists' Group. **Analysis of times to recurrence in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial according to estrogen receptor and progesterone receptor status.** *Breast Cancer Res Treat* 2003;82(Suppl 1):7;Abstract 4.

† Howell A. Presentation. San Antonio Breast Cancer Symposium, 2004.

ATAC TRIAL 68-MONTH ANALYSIS: ADVERSE EVENTS*

	Anastrozole (%)	Tamoxifen (%)	Odds ratio (anastrozole vs tamoxifen)	*p*-value
Drug-related AE	60.9	68.4	—	<0.0001
Drug-related SAE	4.7	9.0	—	<0.0001
AE leading to withdrawal	11.1	14.3	—	0.0002
Hot flashes	35.7	40.9	0.80	<0.0001
Vaginal bleeding	5.4	10.2	0.50	<0.0001
Vaginal discharge	3.5	13.2	0.24	<0.0001
Endometrial cancer	0.2	0.8	0.29	0.02
Ischemic cerebrovascular events	2.0	2.8	0.70	0.03
Venous thromboembolic events	2.8	4.5	0.61	0.0004
Joint symptoms/ arthralgia	35.6	29.4	1.32	<0.0001
Fractures†	11.0	7.7	1.49	<0.0001
Hysterectomy	1.3	5.1	—	<0.0001

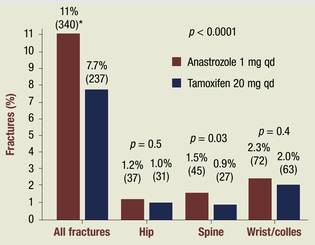
AE = adverse events; SAE = serious adverse events

* Adverse events on treatment or within 14 days of discontinuation
† Fractures occurring before recurrence (includes patients no longer on treatment)

SOURCES: ATAC Trialists' Group. **Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer.** *Lancet* 2005;365:60-2.

Howell A. Presentation. San Antonio Breast Cancer Symposium, 2004.

ATAC TRIAL: BONE FRACTURE ADVERSE EVENTS AT THE UPDATED ANALYSIS



* Numbers in parenthesis refer to numbers of patients with a fracture

SOURCE: ATAC Trialists' Group. **Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer.** *Lancet* 2005;365:60-2.

SELECT PUBLICATIONS

ATAC Trialists' Group. **Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer.** *Lancet* 2005;365:60-2.

Baum M et al; The ATAC (Arimidex, Tamoxifen Alone or in Combination) Trialists' Group. **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(9):1802-10.

Baum M et al; ATAC Trialists' Group. **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(9324):2131-9.

Dowsett M, on behalf of the ATAC Trialists' Group. **Analysis of time to recurrence in the ATAC (Anastrozole, Tamoxifen, Alone or in Combination) trial according to estrogen receptor and progesterone receptor status.** *Breast Cancer Res Treat* 2003;82(Suppl 1):7;Abstract 4.

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Locker GY et al. **The time course of bone fractures observed in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial.** *Proc* ASCO 2003;Abstract 98.

Locker GY et al; ATAC Trialists' Group. **Cost-utility analysis of anastrozole versus tamoxifen as primary adjuvant therapy in postmenopausal women with early breast cancer from a US healthcare system perspective: The 5-year completed treatment analysis of the ATAC ('Arimidex', Tamoxifen Alone or in Combination) trial.** *Breast Cancer Res Treat* 2004;88(Suppl 1):7;Abstract 2085.

CONCLUSIONS FROM THE ATAC TRIALISTS' GROUP

"The present data suggest that it is not appropriate to wait five 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. Five years of anastrozole should now be considered as the preferred initial adjuvant endocrine treatment for postmenopausal women with hormone-receptor-positive localised breast cancer."

— ATAC Trialists' Group. Lancet *2005;365:60-2.*

68-MONTH FOLLOW-UP OF THE ATAC TRIAL

The ATAC trial has reached a very important point in its evolution with a median follow-up of 68 months. Almost all of the patients are now off therapy, and we have one year of follow-up after the therapy was completed.

I believe this is probably the most important of the three analyses, and this latest analysis allows me, as a practicing clinician, to change my mind and change practice. I speak not only as a practicing clinician but also as the past principal investigator of the trial. A *Lancet* article was published in parallel with the 2004 San Antonio presentation and, as a group, we have stuck our necks out and now would say that anastrozole is the preferred initial treatment for postmenopausal women with hormone receptor-positive disease.

The simplest interpretation of the results is that anastrozole prevents one in four of the relapses we see in patients on tamoxifen. That translates into highly significant improvements in disease-free survival, recurrence-free survival and distant disease-free survival.

We are familiar with Kaplan-Meier curves, which are useful for the statistical analysis but don't truly reflect what's going on as the hazard ratios do. A high and narrow peak for relapse occurs at two years, which then comes down again. Then a second, much flatter peak for relapse occurs at about five years.

In the hazard rate analysis plot from the ATAC trial, we're seeing two peaks with tamoxifen. The first peak is lowered with tamoxifen, but a peak still occurs. In the anastrozole arm, the initial peak is lost and the second peak is flatter. I believe this is the most profoundly important observation in this trial — not only to help make therapeutic decisions, but also to give a fascinating biological insight.

The strongest argument for starting adjuvant endocrine therapy with an aromatase inhibitor is that anastrozole almost ablates that first peak. If you wait two to three years, as some of the trials are reporting, the effects are wonderful, but meanwhile you've lost those patients who will relapse and ultimately die in those first two years.

— Michael Baum, MD, ChM

ADJUVANT AROMATASE INHIBITORS AS INITIAL THERAPY IN POSTMENOPAUSAL WOMEN

Since the third-generation aromatase inhibitors are better than tamoxifen, my postmenopausal patients with ER-positive disease who have not yet started adjuvant hormonal therapy will initially receive an adjuvant aromatase inhibitor — preferably anastrozole. We started using adjuvant anastrozole instead of tamoxifen after the first presentation of the ATAC trial results.

Even if tamoxifen and anastrozole had been therapeutically equivalent, anastrozole would still be preferable because it was better tolerated. For us, the issue of osteopenia was always secondary. We already had experience with the bisphosphonates and monitoring patients for osteoporosis because chemotherapy and ovarian ablation produce premature menopause and accelerated bone resorption. We felt quite comfortable in switching our front-line adjuvant therapy to anastrozole.

— Gabriel N Hortobagyi, MD