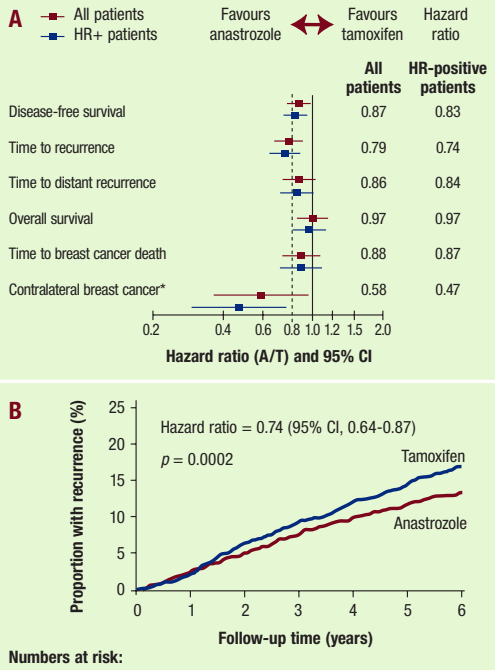
Aromatase Inhibitors as Adjuvant Therapy

In the 68-month follow-up of the ATAC trial, adjuvant anastrozole continued to significantly prolong disease-free survival and time to recurrence and reduce distant metastases and contralateral breast cancers compared to tamoxifen. Data presented at the 2003 and 2004 San Antonio Breast Cancer Symposia demonstrated a greater advantage associated with adjuvant anastrozole in women with ER-positive, PR-negative tumors as compared to ER/PR-positive tumors. BIG FEMTA, a second trial comparing an aromatase inhibitor to tamoxifen, has also demonstrated with less than three years of follow-up a significant improvement in disease-free survival, time to recurrence and time to distant metastases with adjuvant letrozole. A new central review of ER, PR and HER2 status in this trial was reported at San Antonio in December and demonstrated a similar benefit to the aromatase inhibitor regardless of PR status.

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

HR = hormone receptor; A = anastrozole; T = tamoxifen

* Odds ratio calculated instead of hazard ratio

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

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

Receptor status	N	Anastrozole (%)	Tamoxifen (%)	Hazard ratio for anastrozole versus tamoxifen (95% CI)*
ER+/PR+	5,704	7	8	0.82 (0.65-1.03)
ER+/PR-	1,370	9	17	0.48 (0.33-0.71)
ER-/PR+	220	22	26	0.79 (0.40-1.50)
ER-/PR-	699	27	27	1.04 (0.73-1.47)

* Hazard ratios less than one indicate values in favor of anastrozole.

SOURCE: Dowsett M, on behalf of the ATAC Trialists' Group. *Proc SABCS* 2003;Abstract 4.

BIG FEMTA/BIG 1-98: LETROZOLE VERSUS TAMOXIFEN AS ADJUVANT ENDOCRINE THERAPY

Protocol IDs: IBSCG-1-98, EU-99022, IBCSG-18-98, NOVARTIS-2026703019, NCT00004205, DAN-DBCG-IBCSG-1-98, FRE-FNCLCC-IBCSG-1-98
Accrual: 8,028 (Closed)

Eligibility	Postmenopausal women; receptor-positive breast cancer
ARM 1	Tamoxifen x 5 years
ARM 2	Letrozole x 5 years
ARM 3	Tamoxifen x 2 years → letrozole x 3 years
ARM 4	Letrozole x 2 years → tamoxifen x 3 years

SOURCE: NCI Physician Data Query, December 2005.

BIG 1-98: 25.8-MONTH EFFICACY ENDPOINTS OF LETROZOLE VERSUS TAMOXIFEN

	HR (95% CI)	*p*-value
Disease-free survival	0.81 (0.70-0.93)	0.003
ER+/PR+	0.84	—
ER+/PR-	0.83	—
Overall survival	0.86 (0.70-1.06)	0.16
ER+/PR+	1.00	—
ER+/PR-	0.79	—
Time to recurrence	0.72 (0.61-0.86)	0.0002
Time to distant metastases	0.73 (0.60-0.88)	0.0012

HR = hazard ratio for letrozole versus tamoxifen (<1.0 favors letrozole)

SOURCES: BIG 1-98 Collaborative Group. www.ibcsg.org; Thürlimann BJ. Presentation. ASCO 2005.

BIG 1-98 CENTRAL REVIEW PROJECT: DISEASE-FREE SURVIVAL (DFS) IN BIG 1-98 ACCORDING TO HORMONE RECEPTOR AND HER2-RECEPTOR STATUS

DFS	HR	95% CI
All patients (N = 4,399)	0.71	—
According to ER/PR status		
ER+/PR+ (n = 3,330)	0.67	0.51-0.88
ER+/PR- (n = 832)	0.88	0.55-1.41
According to HER2 status		
HER2+ (n = 234)	0.68	0.33-1.41

HR = hazard ratio for letrozole versus tamoxifen (<1.0 favors letrozole)

Presenter's conclusions:

- Benefit of letrozole versus tamoxifen is maintained irrespective of PR status in patients with ER+ tumors
- Tamoxifen resistance for ER+/PR- tumors was not observed
- Resistance to endocrine treatments for ER+/HER2+ tumors requires further evaluation

SOURCE: Viale G et al. Presentation. San Antonio Breast Cancer Symposium 2005.

SELECT PUBLICATIONS

Burstein HJ et al. **Optimizing endocrine therapy in postmenopausal women with early stage breast cancer: A decision analysis for biological subsets of tumors.** *Proc ASCO* 2005;Abstract 529.

Cuzick J, Howell A. **Optimal timing of the use of an aromatase inhibitor in the adjuvant treatment of postmenopausal hormone receptor-positive breast cancer.** *Proc ASCO* 2005;Abstract 658.

Dowsett M, on behalf of the ATAC Trialists' Group. **Analysis of time to recurrence in the ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial according to estrogen receptor and progesterone receptor status.** *Proc SABCS* 2003;Abstract 4.

Howell A et al; 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(9453):60-2.

Howell A, on behalf of the ATAC Trialists' Group. **ATAC ('Arimidex', Tamoxifen, Alone or in Combination) completed treatment analysis: Anastrozole demonstrates superior efficacy and tolerability compared with tamoxifen.** Presentation. San Antonio Breast Cancer Symposium 2004;Abstract 1.

Punglia RS et al. **Optimizing adjuvant endocrine therapy in postmenopausal women with early-stage breast cancer: A decision analysis.** *J Clin Oncol* 2005;23(22):5178-87.

Thürlimann BJ et al. **BIG 1-98: Randomized double-blind phase III study to evaluate letrozole (L) vs tamoxifen (T) as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer.** *Proc ASCO* 2005;Abstract 511.

Viale G et al. **Central review of ER, PgR and Her-2 in Big 1-98 evaluating letrozole vs tamoxifen as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer.** Presentation. San Antonio Breast Cancer Symposium 2005.

68-MONTH FOLLOW-UP OF THE ATAC TRIAL

The simplest interpretation of the ATAC data 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.

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.
Breast Cancer Update *2005 (1)*

CONTROVERSIES IN SELECTION OF INITIAL TREATMENT

I think that when you look at a randomized study like ATAC where, in the first two years, more patients recur on tamoxifen than on the AI, it is pretty hard to suggest that you start tamoxifen and then switch. And, to me, until somebody shows me in a randomized fashion that those patients end up better at the end of five years, I'm approaching virtually all my postmenopausal patients up front about starting with an AI.

— Kathy I Pritchard, MD.
Breast Cancer Update *2006 (2)*

There are two key points made favoring up-front therapy with an aromatase inhibitor. The first is that potentially fatal distant metastases occur in the first 24 months at a slightly higher rate in women on tamoxifen. The second is that tamoxifen-treated women have a higher risk of serious side effects than those receiving an AI. So the argument is made that tamoxifen in those initial two years is inappropriate, and you should give the AI up front.

However, theoretical models have been created — such as Cuzick's and Burstein's — using mathematical gymnastics to determine the optimal strategy over a 10-year period in different patients. Right now, we don't have definitive evidence about which strategy is superior, and that's why the guidelines are split. I don't think that this can be resolved by further debate. It can only be resolved by further data.

— Paul E Goss, MD, PhD.
Breast Cancer Update *2006 (1)*

BIG FEMTA/IBCSG-1-98/BIG 1-98: LETROZOLE VERSUS TAMOXIFEN UP FRONT OR SEQUENTIALLY

The efficacy results in BIG FEMTA were essentially the same as those in the ATAC trial at the 30-month point. The hazard reduction was similar, and the side-effect profile was by and large the same. A few differences were seen. They found a benefit for letrozole only in patients with node-positive disease, which is difficult to understand. It's probably a chance finding, but we need to follow that.

At this stage, they've found no difference in efficacy between the patients with PR-positive and PR-negative disease. We have to acknowledge that the data are different from what's been observed in other trials. The third and most worrying finding is the substantial excess in cardiovascular deaths for letrozole compared to tamoxifen, which hasn't been observed in the trials with anastrozole. Whether this is due to chance or differences in cardiovascular mortality is important to know. Letrozole is a slightly more potent aromatase inhibitor, and it is not clear whether that has an impact.

— Jack Cuzick, PhD.
Breast Cancer Update *2005 (6)*