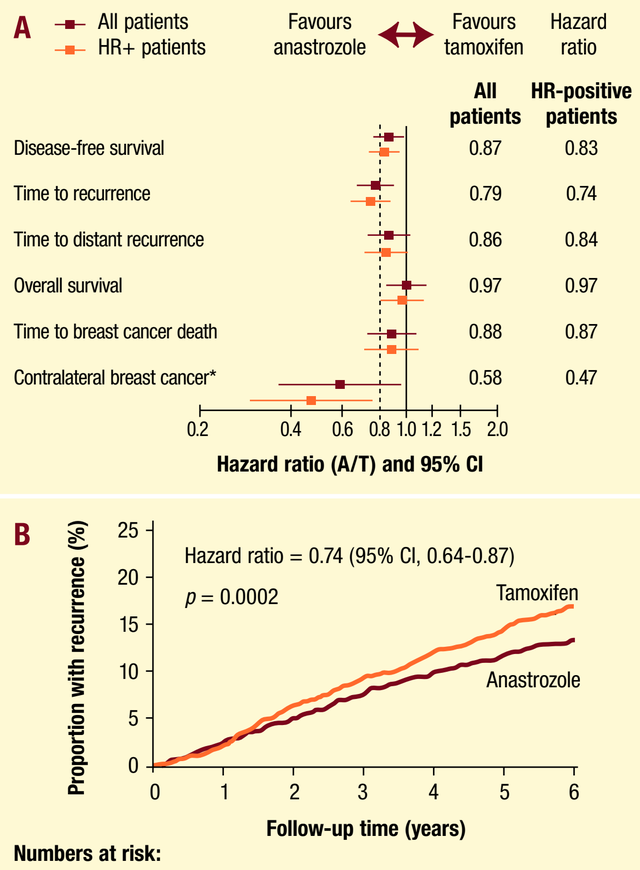
Aromatase Inhibitors as Adjuvant Therapy

28TH ANNUAL
San Antonio Breast Cancer Symposium
4

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 now 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. An ongoing clinical trial will now compare the efficacy of two aromatase inhibitors — anastrozole and exemestane — as adjuvant therapy in women with hormone receptor-positive breast cancer.

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: 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 breast cancer, 60-2, 2005, with permissions 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 (0.40-1.5)
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. *Breast Cancer Res Treat* 2003;82(Suppl 1):7;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, October 2005.

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

	HR (95% CI)	*p*-value
Disease-free survival (DFS)	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)

SOURCE: BIG 1-98 Collaborative Group. www.ibcsg.org.

ADJUVANT EXEMESTANE VERSUS ANASTROZOLE IN POSTMENOPAUSAL WOMEN

Protocol IDs: CAN-NCIC-MA27, NCT00066573, CALGB-CAN-NCIC-MA27, ECOG-CAN-NCIC-MA27, NCCTG-N0434, SWOG-CAN-NCIC-MA27
Target Accrual: 5,800 (Open)

Eligibility	Postmenopausal women with Stage I-III invasive ER- and/or PR-positive breast cancer
ARM 1	Anastrozole x 5 years
ARM 2	Exemestane x 5 years

Trial lead organizations:

NCIC-Clinical Trials Group: *Paul E Goss, MD, PhD, Protocol Chair Ph: 617-724-3118*

North Central Cancer Treatment Group: *James N Ingle, MD, Protocol Chair, Ph: 507-284-8432, Email: ingle.james@mayo.edu*

Cancer and Leukemia Group B: *Matthew J Ellis, MB, PhD, Protocol Chair Ph: 314-362-8903; 800-600-3606*

Eastern Cooperative Oncology Group: *George W Sledge Jr, MD, Protocol Chair, Ph: 317-274-0920; 888-600-4822, Email: gsledge@iupui.edu*

Southwest Oncology Group: *G Thomas Budd, MD, Protocol Chair Ph: 216-444-6480*

SOURCE: NCI Physician Data Query, September 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, 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.

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.

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.

CONTROVERSIES IN SELECTION OF INITIAL TREATMENT

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 localized breast cancer.

— ATAC Trialists' Group. **Lancet** ***2005;365(9453):60-2.***

Several groups have looked at statistical modeling of the optimal long-term sequencing of an AI after tamoxifen vs immediate use of an AI — Jack Cuzick's group in London, the Dana-Farber group with Hal Burstein, and our own group in Houston with our statistician Sue Hilsenbeck. All of these models suggested similar findings, and they could not rule out a moderate benefit from sequencing compared to immediate use if one looks at the long-term results after 10 years in the large subgroup of ER/PR-positive tumors. Although there is a peak in recurrence at 2-3 years, ultimately more patients recur after year 5 than in the first 5 years, and the sequence of tamoxifen followed by an AI could turn out to be a better strategy. While it is true that we can't necessarily go by the results of mathematical models, they do provide some evidence of what the possibilities of these different strategies might be over the long term.

— C Kent Osborne, MD. **Breast Cancer Update** ***2005, Special CME Meeting Edition***

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)***

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, although it was reported differently. 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)***