Adjuvant Endocrine Therapy Trials in Postmenopausal Patients

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. The first overall survival analysis from the ATAC trial will be presented at this meeting, and other trials evaluating letrozole and exemestane as up-front therapy in postmenopausal patients are maturing and are likely to have initial data available in the near future.

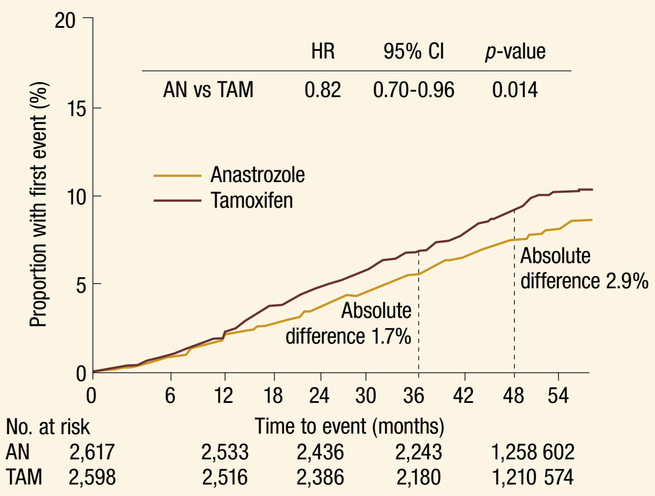
RECURRENCE RATES IN THE ATAC TRIAL ACCORDING TO ESTROGEN AND PROGESTERONE RECEPTOR STATUS

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.

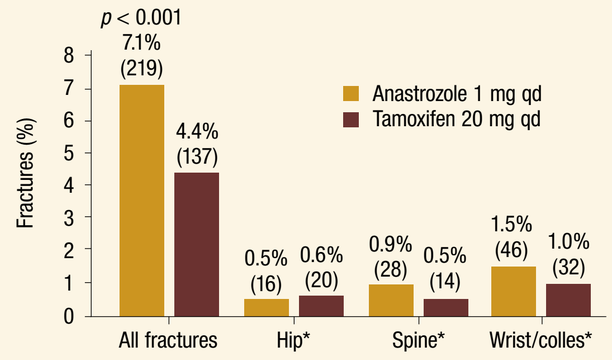
SOURCE: Dowsett M, on Behalf of the ATAC Trialists' Group. **Analysis of time to recurrence in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial according to estrogen receptor and progesterone receptor status.** *Breast Cancer Res Treat* 2003;82(1 Suppl 1):6.

PROBABILITY OF FIRST EVENT IN RECEPTOR-POSITIVE POPULATION IN THE ATAC TRIAL



DERIVED FROM: Buzdar A. Presentation. San Antonio Breast Cancer Symposium, 2002.

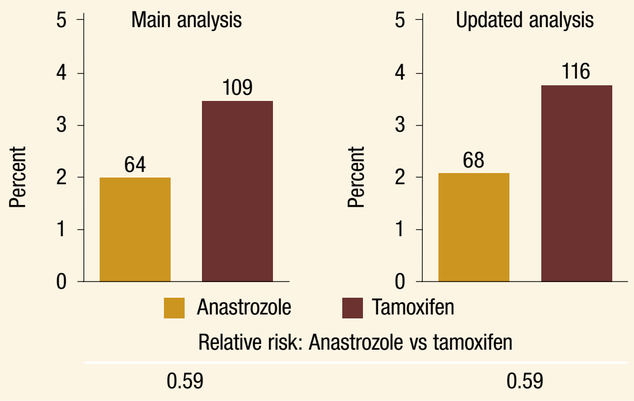
ATAC TRIAL: BONE FRACTURE ADVERSE EVENTS AT THE UPDATED SAFETY ANALYSIS



Numbers in brackets refer to numbers of patients with a fracture
* *p*-value not available (only predefined adverse events were analyzed)

SOURCE: Locker G. Poster. Lynn Sage Breast Cancer Symposium, 2003.

ATAC TRIAL: VENOUS THROMBOEMBOLIC EVENTS



SOURCES: The ATAC Trialists' Group. *Cancer* 2003;98:1802-10.
The Lancet 2002;359:2131-9.

PHASE III STUDY OF EXEMESTANE VERSUS ANASTROZOLE WITH OR WITHOUT CELECOXIB

Protocol IDs: CAN-NCIC-MA27, CALGB-CAN-NCIC-MA27, ECOG-CAN-NCIC-MA27, NCCTG-N0434, SWOG-CAN-NCIC-MA27
Target Accrual: 6,830 (Open)

Eligibility	Postmenopausal, ER/PR-positive Invasive breast cancer
ARM 1	Exemestane x 5 years + celecoxib x 3 years
ARM 2	Exemestane x 5 years + placebo x 3 years
ARM 3	Anastrozole x 5 years + celecoxib x 3 years
ARM 4	Anastrozole x 5 years + placebo x 3 years

Study Contact:
Paul Goss, MD, PhD
NCIC-Clinical Trials Group
Tel: 617-724-3200

SOURCE: NCI Physician Data Query, October 2004.

PHASE III STUDY OF ADJUVANT LETROZOLE VERSUS TAMOXIFEN IN POSTMENOPAUSAL WOMEN WITH OPERABLE, HORMONE RECEPTOR-POSITIVE BREAST CANCER

Protocol IDs: IBCSG-1-98, EU-99022, IBCSG-18-98, NOVARTIS-2026703019, DAN-DBCG-IBCSG-1-98, FRE-FNCLCC-IBCSG-1-98
Accrual: 5,180 (Closed)

Eligibility	Postmenopausal, ER- and/or PR-positive Node-positive or node-negative
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 2004.

SELECT PUBLICATIONS

Allred D et al. **Estrogen receptor expression as a predictive marker of the effectiveness of tamoxifen in the treatment of DCIS: Findings from NSABP Protocol B-24.** *Breast Cancer Res Treat* 2002;Abstract 30.

Baum M 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(9):1802-10.

Boccardo F et al. **Anastrozole appears to be superior to tamoxifen in women already receiving adjuvant tamoxifen treatment.** *Breast Cancer Res Treat* 2003;83(Suppl 1):6.

Boccardo F et al. **Sequential tamoxifen and aminoglutethimide versus tamoxifen alone in the adjuvant treatment of postmenopausal breast cancer patients: Results of an Italian cooperative study.** *J Clin Oncol* 2001;19(22):4209-15.

Coombes RC et al. **A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer.** *N Engl J Med* 2004;350(11):1081-92.

Distler W et al. **Impact of age on the gynecologic adverse event (AE) profile of anastrozole (A) or tamoxifen (T) in the ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial.** *Proc ASCO* 2004;Abstract 770.

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.** *Breast Cancer Res Treat* 2003;82(1 Suppl 1):6.

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;83(Suppl 1):7.

Goss PE 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(19):1793-802.

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.

ATAC ADJUVANT TRIAL: SUBGROUP ANALYSIS OF PATIENTS WITH ER-POSITIVE, PR-NEGATIVE DISEASE

The ATAC trial enrolled 9,366 patients, and the first report demonstrated a significant benefit for the patients with hormone receptor-positive disease who were treated with anastrozole compared to tamoxifen. The hazard ratio for disease-free survival in this group was 0.78. The 47-month analysis had a similar hazard ratio. Because the ATAC trial was designed in 1994 and initiated in 1996, it didn't require the patients to have ER- and/or PR-positive disease for enrollment.

Hence, a very small proportion of patients had ER- and PR-negative disease, and a larger cohort had ER- or PR-unknown disease. We retrospectively analyzed the histological blocks from those patients for their ER and PR status to obtain a more comprehensive view of the influence of the ER and PR status on the outcomes of the trial. We asked whether the PR status had any impact on the relative benefit associated with anastrozole and tamoxifen in patients with ER-positive disease.

In the patients with ER- and PR-positive disease, which consisted of approximately 5,700 patients, anastrozole was more beneficial than tamoxifen, with a hazard ratio of 0.82. In the patients with ER-positive and PR-negative disease, a very substantial difference was noted, with a hazard ratio of 0.48, indicating that patients treated with adjuvant anastrozole had half as many relapses as patients treated with adjuvant tamoxifen. The comparison between patients with ER- and PR-positive disease to patients with ER-positive and PR-negative disease was borderline for statistical significance. Although this was a retrospective subgroup analysis, I hope that other aromatase inhibitor trials will perform the same analyses to substantiate this finding.

— Mitchell Dowsett, PhD

We don't know why the ER-positive, PR-negative phenotype behaves so differently, but Dowsett and Osborne have formulated a hypothesis that involves contrasting the effect of tamoxifen versus anastrozole on the classical nuclear versus nonclassical membrane estrogen receptor pathways. When the nuclear pathway is intact, estrogen activates the estrogen receptor, which induces the synthesis of the progesterone receptor; however, we can hypothesize that pathway is not functioning in ER-positive, PR-negative tumors. If the membrane pathway is activated, it can lead to the activation of growth factor receptors and induce cell growth.

Tamoxifen is an antagonist in the nuclear pathway (hypothetically, the nonfunctioning pathway in the ER-positive, PR-negative subset) and it's an agonist in the membrane pathway, which may result in stimulating growth factors and tumor growth. On the other hand, aromatase inhibitors reduce estrogen levels to nearly zero and are antagonists on both pathways. This may explain the striking additional benefit of anastrozole seen in the ER-positive, PR-negative subset, which is the phenotype for 20 percent of breast cancer patients.

The HER2 assays have not yet been performed in the ATAC trial, but some have speculated that the subset of patients with the ER-positive, PR-negative phenotype may also be HER2-positive. However, we've known for years that only 10 or 15 percent of HER2-positive tumors are ER-positive and, while most of those are PR-negative, I don't believe that small subset could be entirely responsible for these intriguing results.

— D Craig Allred, MD

TIME COURSE OF BONE FRACTURES IN ATAC

"Six-monthly fracture rates… remained fairly constant for both A (anastrozole) (range 0.93 to 1.57) and T (tamoxifen) (0.58 to 1.37), with the greatest difference between A and T seen at 18 and 24 mths. After 24 mths, the 6-monthly fracture rates seen with A reached a plateau. Overall osteoporotic fractures, encompassing sites of hip + spine + wrist, showed similar patterns. Anastrozole leads to an increased fracture incidence compared with T, a drug known to have a positive effect on bone. Importantly, the fracture rate in the A-treated group appeared to have stabilized after reaching a peak at 2 years."

— Locker GY et al. **Proc ASCO** *2003;Abstract 98.*