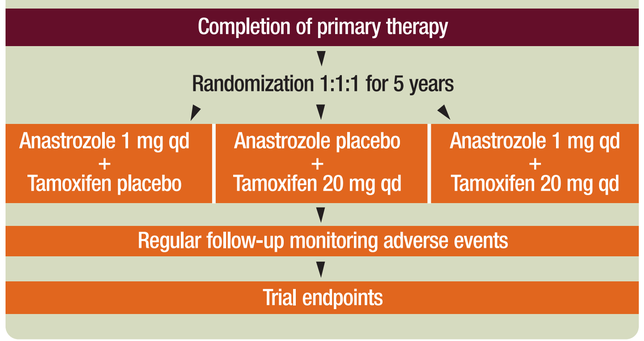
Anastrozole, Tamoxifen, Alone or in Combination (ATAC)

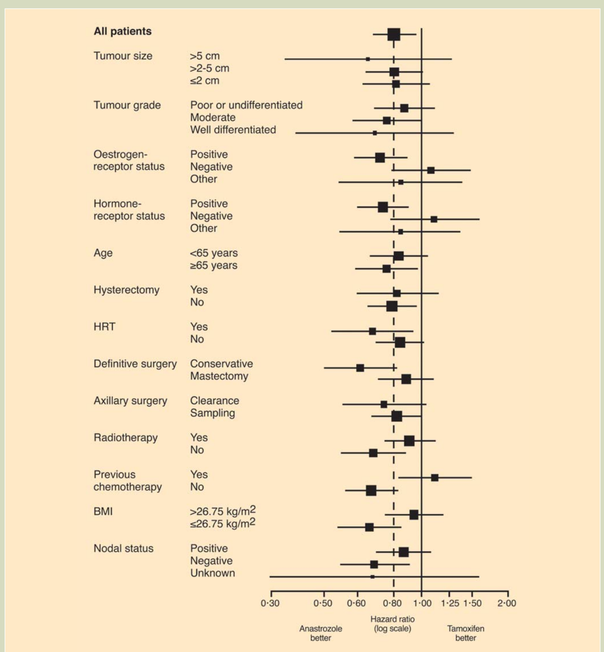
On December 10, 2001, the initial results of the ATAC trial were presented at the San Antonio Breast Cancer Symposium and subsequently published in *The Lancet* on June 22, 2002. The study randomized more than 9,000 women to either tamoxifen, anastrozole or the combination. The US Food and Drug Administration granted a six-month priority review status, and on September 5, 2002, anastrozole was approved as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer.

These groundbreaking data are being updated at this meeting with 47 months of follow-up and continue to demonstrate that in postmenopausal women with primary invasive breast cancer, the third-generation aromatase inhibitor, anastrozole, conferred an advantage over tamoxifen in terms of disease-free survival and rates of contralateral breast cancers. No advantage has been observed when combining anastrozole with tamoxifen. The 2002 ASCO Technology Assessment supported the use of anastrozole in specific situations when tamoxifen is problematic, but the overall conclusion — which will be evaluated on an ongoing basis as new data emerge — was that tamoxifen continues to be the "standard of care."

ATAC TRIAL DESIGN — POSTMENOPAUSAL WOMEN WITH INVASIVE BREAST CANCER



SUBGROUP ANALYSIS OF TIME TO RECURRENCE FOR TAMOXIFEN COMPARED TO ANASTROZOLE



Data are hazard ratios and 95% CIs. HRT=hormone replacement therapy. BMI=body-mass index

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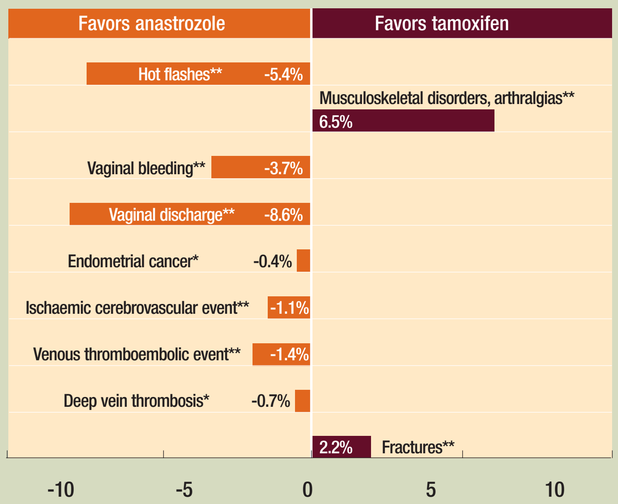
TRIAL RESULTS (MEDIAN FOLLOW-UP OF 33 MONTHS)

	Anastrozole (n=3125)	Tamoxifen (n=3116)	Combination (n=3125)
Local recurrence	67	83	81
Distant recurrence	158	182	204
Contralateral breast cancer*	14	33	28
Invasive	9	30	23
DCIS	5	3	5
Deaths before recurrence	78	81	70
Total event rates	317 (10.1%)	379 (12.2%)	383 (12.3%)
ER/PR-positive patients 3-year DFS estimate**	91.2%	89.3%	88.9%

Anastrozole compared to tamoxifen
***Odds ratio 0.42 (0.22-0.79), p=0.007**
****Hazard ratio 0.78 (0.65 – 0.91), p=0.005**

DERIVED FROM: *Lancet* 2002;359:2131-2139.

SIGNIFICANT DIFFERENCES IN PRE-DEFINED ADVERSE EVENTS



Difference between anastrozole and tamoxifen adverse events (%)
*** p< 0.5, ** p< 0.01**

DERIVED FROM: *Lancet* 2002;359:2131-39.

CLINICAL IMPLICATIONS

There is a spectrum of responses to this data. Very cautious clinicians opt to use tamoxifen until we have long-term data. The ATAC trial results do, however, reassure these individuals that patients who are not good candidates for tamoxifen (i.e. history of thromboembolic disease or cerebrovascular accidents) can be given anastrozole. Many physicians already do this, but the data give us more confidence to possibly lower the threshold to use anastrozole. Other physicians believe that the efficacy data from the ATAC trial is sufficient to use adjuvant anastrozole at the present time.

—John F Robertson, MD, FRCS

At this time, the use of adjuvant anastrozole is analogous to the switch made in the late 1980s of offering chemotherapy to high-risk, node-negative patients when an advantage was demonstrated in disease-free survival. As the data were unfolding, some argued that it was necessary to see a survival advantage, but I believe that would have deprived patients of a successful intervention.

—Nicholas Robert, MD

SAFETY PROFILE

One of the most exciting parts of the ATAC trial is the safety profile of anastrozole. There was a highly significant reduction in the incidence of hot flashes, vaginal discharge and vaginal bleeding. This reduction in vaginal bleeding is significant, because fewer women will be referred to gynecologists to exclude endometrial cancer. Perhaps even more important is the significant reduction of life-threatening events such as strokes, cerebrovascular accidents and thromboembolic events. Apart from bone mineral density — which I think we can handle if we anticipate it — the safety profile strongly favors anastrozole over tamoxifen. I'm convinced that adjuvant bisphosphonates reduce the risk of bone metastases during therapy. We need to determine if there is synergism between aromatase inhibitors and bisphosphonates.

—Michael Baum, ChM, FRCS

COMMENTS FROM THE ASCO TECHNOLOGY ASSESSMENT

"The panel is of the unanimous opinion that the results of the ATAC trial should be considered preliminary and that a 5-year course of tamoxifen remains the standard adjuvant hormonal treatment for women with hormone receptor-positive breast cancer…

…The panel considers it reasonable to initiate adjuvant hormonal therapy with an aromatase inhibitor in postmenopausal women who are thought to have a relative or absolute contraindication to adjuvant tamoxifen…

…While recognizing the paucity of direct data, the panel considers it reasonable to use adjuvant hormonal treatment with an aromatase inhibitor in postmenopausal women with hormone receptor–positive cancers who had been taking tamoxifen or raloxifene at diagnosis and who are, therefore, considered clinically resistant to these antiestrogen agents…

"…The only evidence in the adjuvant setting involves anastrozole. Furthermore, the panel notes that closely related agents with similar mechanisms of action may have different toxicity profiles. For this reason, the panel considers anastrozole the preferred agent if an aromatase inhibitor is used in the adjuvant setting."

— Winer EP et al. J Clin Oncol 2002;20:3317-3327.

SELECT PUBLICATIONS

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):2131-2139.

Buzdar A, Howell A. **Advances in aromatase inhibition: Clinical efficacy and tolerability in the treatment of breast cancer.** *Clin Cancer Res* 2001;7:2620-2635.

Buzdar AU. **Anastrozole (Arimidex) — an aromatase inhibitor for the adjuvant setting?** *Br J Cancer* 2001;85(2 suppl):6-10.

Goss PE, Strasser K. **Aromatase inhibitors in the treatment and prevention of breast cancer**. *J Clin Oncol* 2001;19:881-894.

Howell A et al. **Where do selective estrogen receptor modulators (SERMs) and aromatase inhibitors (A.I.s) now fit into breast cancer treatment algorithms?** *J Steroid Biochem Mol Biol* 2001;79:227-237.

Johnson PE, Buzdar A. **Are differences in the available aromatase inhibitors and inactivators significant?** *Clin Cancer Res* 2001;7(12 suppl):4360s-4368s.

Ragaz J. **Adjuvant trials of aromatase inhibitors: Determining the future landscape of adjuvant endocrine therapy.** *J Steroid Biochem Mol Biol* 2001;79:133-141.

Winer EP et al. **American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for women with hormone receptor-positive breast cancer: Status report 2002.** *J Clin Oncol* 2002;20(15):3317-3327.