Adjuvant Endocrine Therapy Trials in Postmenopausal Patients

Tamoxifen has been the predominant form of adjuvant endocrine therapy utilized in clinical practice since the first International Breast Cancer Overview was presented at the 1985 NIH Consensus Conference. Successive overviews and a number of individual trials have demonstrated that greater benefit was observed with increasing duration of therapy up to five years. The ATAC adjuvant 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. No advantage was seen with the combination of anastrozole and tamoxifen. An update to this data set was reported in San Antonio in December demonstrating continued divergence of the DFS curves favoring anastrozole. Several adjuvant endocrine therapy trials are currently examining the related issues of duration of tamoxifen treatment, sequencing tamoxifen with aromatase inhibitors and the use of the other third-generation aromatase inhibitors.

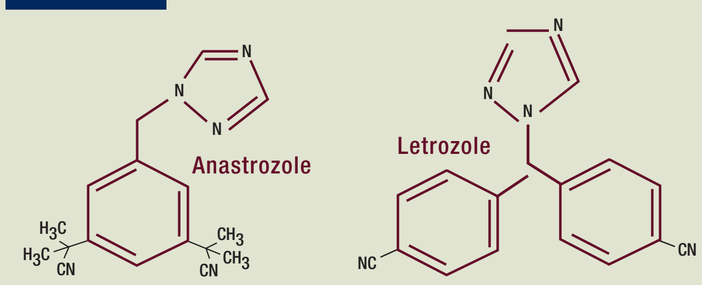
ONGOING PHASE III RANDOMIZED ADJUVANT TRIALS COMPARING AROMATASE INHIBITORS TO TAMOXIFEN

Protocol ID	Eligibility	Randomization Arms
CRC-TU-TEAM/ EU-20149	Any N; primary tumor > 3cm or grade III & > 1 cm, MO	ARM 1: Tamoxifen x 5 years ARM 2: Exemestane x 5 years
IBCSG-1-98/ EU-99022	pT1, pT2, pT3; pN0, pN1, pN2; MO	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

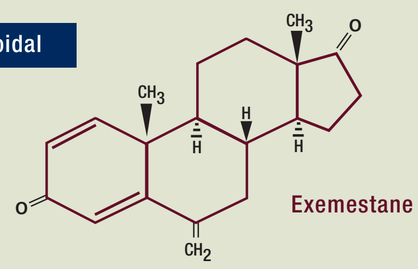
SOURCE: NCI Physician Data Query, February 2003.

3RD GENERATION AROMATASE INHIBITORS

Non-steroidal



Steroidal



ONGOING PHASE III RANDOMIZED TRIALS EVALUATING THE OPTIMAL DURATION OF ADJUVANT TAMOXIFEN

Protocol ID	Eligibility	Randomization Arms
CRC-TU-ATTOM/ EU-98042	≥ 2 years of adjuvant tamoxifen	ARM 1: Stop tamoxifen ARM 2: Continue tamoxifen for at least 5 extra years
ATLAS/ EU-96064	5 years adjuvant tamoxifen	ARM 1: Stop tamoxifen ARM 2: Continue tamoxifen for at least 5 extra years

SOURCE: NCI Physician Data Query, February 2003.

ONGOING PHASE III RANDOMIZED TRIALS EVALUATING THE CONTINUATION OF ADJUVANT HORMONAL THERAPY WITH AN AROMATASE INHIBITOR

Protocol ID	Eligibility	Randomization Arms
NSABP B-33	Stage I, II or IIIA; 57-66 months adjuvant tamoxifen	ARM 1: Exemestane x 2 years ARM 2: Placebo x 2 years
SWOG-JMA17/ BIG 97-01/ CLB-49805	4.5-6 years adjuvant tamoxifen	ARM 1: Letrozole x 5 years ARM 2: Placebo x 5 years

SOURCE: NCI Physician Data Query, February 2003.

ATAC TRIAL DATA UPDATE: 47-MONTH FOLLOW-UP

After 47 months, the disease-free survival data from the ATAC trial look very good. The curves continued to diverge, and there is no sign that they are coming together. It's like a primary election with 80 percent of the precincts reporting, and a pretty solid lead for a candidate. It's very likely that in five years, the anastrozole arm will be superior in terms of relapse-free survival. Given its current lead, it's virtually impossible that it won't be.

Tamoxifen only reduces mortality by about 30%, so there's a lot of room for improvement. At this time, no mortality data on anastrozole has been presented — it's simply too early to tell. It is possible that because of the kind of relapses anastrozole prevents that there won't be as great an effect on survival as disease-free survival. However, if it has a large effect on either, it would still be considered beneficial.

— Peter Ravdin, MD, PhD

POTENTIAL DIFFERENCES BETWEEN AROMATASE INHIBITORS (A.I.s) IN THE ADJUVANT SETTING

I do not know if this is a class effect of aromatase inhibitors. I can only speak for anastrozole in the ATAC trial. There are subtle differences in the pharmacology and pharmacokinetics of the two nonsteroidal aromatase inhibitors (anastrozole and letrozole), and even more with the steroidal aromatase inhibitor exemestane. These differences could lead to different results. Although I suspect that they will have similar efficacy, I don't think we can assume they will have the same adverse events.

—Michael Baum, ChM, FRCS

A very important question that needs to be addressed is the interchangeability in the adjuvant setting of the available aromatase inhibitors — anastrozole, letrozole and exemestane. Right now, there is only data with anastrozole. The other two agents are available for use by physicians, but there is no safety and efficacy data for them in the adjuvant setting. I have reservations about saying that this is a class effect, and switching to another aromatase inhibitor for which we do not have any adjuvant data.

—Aman Buzdar, MD

The degree of aromatase inhibition is slightly different between the agents. There have been claims that letrozole reduces estrogen levels fractionally more than the other aromatase inhibitors. While this difference may or may not translate into an efficacy benefit, there are two sides to every sword — it also may translate into a worse side-effect profile. My personal view is that the differences we will see between the aromatase inhibitors in the adjuvant setting will most likely be in terms of their side-effect profiles rather than efficacy.

—John F Robertson, MD, FRCP

SEQUENCING A.I.s AFTER TAMOXIFEN

For women already receiving tamoxifen, I would leave them on tamoxifen. It is a very safe and effective drug with decades of proven experience. For women finishing their course of tamoxifen, I encourage physicians to think about enrolling women in those trials studying the effects of sequencing treatments, such as tamoxifen followed by an aromatase inhibitor.

—Harold Burstein, MD, PhD

SELECT PUBLICATIONS

The 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):2131-2139.

Baum M. **A vision for the future?** *Br J Cancer* 2001;85(Suppl 2):15-18.

Boeddinghaus IM, Dowsett M. **Comparative clinical pharmacology and pharmacokinetic interactions of aromatase inhibitors.** *J Steroid Biochem Mol Biol* 2001;79(1-5):85-91.

Brodie A. **Aromatase inhibitors in breast cancer.** *Trends Endocr Metab* 2002;13(2):61-65.

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

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.

Fisher B et al. **Five versus more than five years of tamoxifen for lymph node-negative breast cancer: Updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial.** *J Natl Cancer Inst* 2001;93(9):684-690.

Wellington K, Faulds DM. **Anastrozole in early breast cancer.** *Drugs* 2002;62(17):2485-2492.

Copyright © 2003 NL Communications, Inc. All rights reserved. Poster information is for educational purposes only and not to be used in patient care. Please see full prescribing information and protocols.