Sequential Adjuvant Hormonal Therapy Following Tamoxifen

Since the first International Breast Cancer Overview presented at the 1985 NIH Consensus Conference, tamoxifen was considered the mainstay of adjuvant hormonal therapy for women with early breast cancer; however, the selection of optimal adjuvant hormonal therapy for postmenopausal women is currently controversial. Recent trials — NCIC-MA17, ITA, EU-20149, ABCSG-8 and ARNO 95 — have evaluated the role of aromatase inhibitors as follow-up therapy to adjuvant tamoxifen. NCIC-MA17 randomly assigned postmenopausal women who had completed 4.5 to 6 years of adjuvant tamoxifen to five years of placebo or adjuvant letrozole. ITA and EU-20149 randomly assigned postmenopausal women who had completed two to three years of adjuvant tamoxifen to continue tamoxifen versus switching to an aromatase inhibitor. These trials of sequential adjuvant hormonal therapy demonstrated significant therapeutic advantages to switching to an aromatase inhibitor.

PHASE III TRIAL OF EXEMESTANE VERSUS TAMOXIFEN FOLLOWING TWO TO THREE YEARS OF ADJUVANT TAMOXIFEN

Protocol IDs: CRC-TU-TEAM, EU-20149, IES (Intergroup Exemestane Study)
Accrual: 4,724 (Closed)

Eligibility	Postmenopausal women who have received two to three years of adjuvant tamoxifen
ARM 1	Tamoxifen x 2-3y
ARM 2	Exemestane x 2-3y

RESULTS OF UPDATED SURVIVAL ANALYSIS*

Variable	Hazard ratio (exemestane vs tamoxifen)	95% confidence interval	*p*-value
Disease-free survival	0.73	0.62-0.86	0.0001
Breast cancer-free survival	0.70	0.58-0.83	0.00005
Time to contralateral breast cancer	0.50	0.26-0.97	0.04
Overall survival	0.83	0.67-1.02	0.08

* Updated analysis with 615 disease-free survival events and 339 deaths at a median follow-up of 37.4 months

SOURCES: Coombes C. Presentation. San Antonio Breast Cancer Symposium, 2004.

NCI Physician Data Query, January 2005.

RANDOMIZED PHASE III STUDY OF LETROZOLE VERSUS PLACEBO IN POSTMENOPAUSAL WOMEN WITH PRIMARY BREAST CANCER WHO HAVE COMPLETED AT LEAST FIVE YEARS OF ADJUVANT TAMOXIFEN

Protocol ID: CAN-NCIC-MA17
Accrual: 5,187 (Closed)

Eligibility	Postmenopausal patients with ER/PR-positive breast cancer previously treated with adjuvant tamoxifen for 4.5 to 6 years
ARM 1	Letrozole x 5y
ARM 2	Placebo x 5y

DISEASE-FREE SURVIVAL AND RECURRENCES OR A NEW CONTRALATERAL PRIMARY TUMOR (MEDIAN FOLLOW-UP 2.4 YEARS)

Variable	Letrozole (n=2,575)	Placebo (n=2,582)	*p*-value
Estimated 4-year DFS*	93%	87%	<0.001
Recurrences or a new contralateral primary tumor	75 (2.9%)	132 (5.1%)	<0.00008

* Disease-free survival

SOURCES: NCI Physician Data Query, January 2005.

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.

ANASTROZOLE VERSUS TAMOXIFEN AFTER TWO YEARS OF ADJUVANT TAMOXIFEN

Protocol IDs: ABCSG-8, ARNO 95 (Combined)
Accrual: 3,224 (Closed)

Eligibility	Postmenopausal women with hormone-sensitive breast cancer previously treated with adjuvant tamoxifen for two years
ARM 1	Tamoxifen x 3y
ARM 2	Anastrozole x 3y

COMBINED RESULTS FROM 3,224 WOMEN ENROLLED IN THE ABCSG TRIAL 8 AND THE ARNO 95 TRIAL*

Variable	Hazard ratio (anastrozole vs tamoxifen)	95% confidence interval	*p*-value
Event-free survival†	0.60	0.44-0.81	0.0009
Distant recurrence-free survival	0.61	0.42-0.87	0.0067
Overall survival	0.76	0.52-1.12	0.16

* Analysis with 177 events, 104 deaths at median follow-up of 28 months

† Includes locoregional disease, contralateral breast cancer and distant recurrences

SOURCE: Jakesz R. Presentation. San Antonio Breast Cancer Symposium, 2004.

ITA TRIAL: ANASTROZOLE VERSUS TAMOXIFEN IN WOMEN ALREADY RECEIVING ADJUVANT TAMOXIFEN (MEDIAN FOLLOW-UP TWO YEARS)

Protocol ID: ITA (Italian Tamoxifen Arimidex®)
Accrual: 448 (Closed)

Eligibility	Postmenopausal patients with ER/PR-positive primary breast cancer previously treated with adjuvant tamoxifen for two to three years
ARM 1	Anastrozole x 2-3y
ARM 2	Tamoxifen x 2-3y

Treatment	Event-free survival		Progression-free survival	
	Hazard ratio	*p*-value	Hazard ratio	*p*-value
Tamoxifen n=225	1.0	—	1.0	—
Anastrozole n=223	0.36 (95% CI, 0.21-0.63)	0.0004	0.35 (95% CI, 0.18-0.69)	0.002

"These findings confirm the role of A in the treatment of early breast cancer. Furthermore, the findings show that switching patients on adjuvant T to treatment with adjuvant A appears to decrease their risk of relapse and death. A was found to be more effective and induce less serious adverse effects than T in women already on treatment with this antiestrogen."

SOURCE: Boccardo F. Presentation. San Antonio Breast Cancer Symposium, 2003;Abstract 3.

SELECT PUBLICATIONS

Boccardo F et al. **Anastrozole appears to be superior to tamoxifen in women already receiving adjuvant tamoxifen treatment.** *Breast Cancer Res Treat* 2003;Abstract 3.

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; Intergroup Exemestane Study. **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.

Coombes RC et al. **The Intergroup Exemestane Study: A randomized trial in postmenopausal patients with early breast cancer who remain disease-free after two to three years of tamoxifen — Updated survival analysis.** *Breast Cancer Res Treat* 2004;Abstract 3.

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.

Jakesz R et al. **Benefits of switching postmenopausal women with hormone-sensitive early breast cancer to anastrozole after 2 years adjuvant tamoxifen: Combined results from 3,123 women enrolled in the ABCSG Trial 8 and the ARNO 95 Trial.** *Breast Cancer Res Treat* 2004;Abstract 2.

SWITCHING PATIENTS FROM ADJUVANT TAMOXIFEN TO AROMATASE INHIBITORS

I now feel confident that women who have been on tamoxifen for two or three years should switch to an aromatase inhibitor. We now have excellent data for both exemestane and anastrozole from three trials. Boccardo's small ITA trial was the first to report, then the large IES study and the joint Austrian-German study that was presented in San Antonio. Overwhelming evidence indicates that a switch is beneficial.

In patients on tamoxifen for one or four years, I think I would still switch. You can wait forever for refinements. No one is ever going to do a trial of a switch at one year or a switch at four years. We just have to stretch the available evidence and be sensible about it, and I think it would be reasonable to switch.

In women who have already received five years of tamoxifen, the MA17 trial is a well-conducted trial. It shows proof of principle that you can influence the natural history of breast cancer after five years of tamoxifen. I've gone on record that I'm bitterly disappointed that they closed the trial and then switched the placebo group to letrozole, because they are now treating the placebo group with experimental therapy — five years on tamoxifen, an average of two and a half years on placebo, and then letrozole. That is an unproven treatment and I don't think we'll ever really learn the long-term benefit and toxicity.

I think we're going way beyond the data. What worries me is that I don't think we can correct this situation. We'll always be left with an area of uncertainty; however, to their eternal credit, the MA17 and NCIC groups have redeemed themselves by being prepared to do a second randomization for duration, which would be at five years of the aromatase inhibitors.

— Michael Baum, MD, ChM

Our group presented the combined analysis of the Austrian and German trials, which compared switching to anastrozole after two years of tamoxifen versus continuing tamoxifen for five years in the adjuvant setting in postmenopausal patients with receptor-positive disease. This is a very clean study with 100 percent hormone receptor positivity.

The results showed a 40 percent reduction in risk of relapse for those who switched to anastrozole, meeting our stopping boundaries for the trial. In terms of side effects and toxicity, we have observed what all the aromatase inhibitor trials have shown — a benefit of aromatase inhibitors in terms of gynecological side effects but more fractures compared to the tamoxifen group.

Although the IES study is more mature, the effects are very comparable in magnitude, however, we have to be cautious making indirect comparisons between trials. Personally, I was hoping that exemestane would be better in terms of bone because of its steroidal nature, but this does not appear to be the case. A significant increase in osteoporosis and an overall low rate of fractures still occur; therefore, the preclinical potential benefit of the steroidal aromatase inhibitor does not materialize in the clinic. For a clinical situation, I think it's fair to say these trials are very comparable.

In terms of selection of an aromatase inhibitor in a postmenopausal woman, I follow the data and use anastrozole up front anastrozole or exemestane after two to three years and letrozole after five years. This is what I believe a clinical trialist has to do. I believe that what has changed since the last San Antonio Breast Cancer Symposium is that we should now consider it mandatory to discuss these options with patients.

— Michael Gnant, MD

For postmenopausal patients who are on tamoxifen for any length of time, our practice today is to switch to an aromatase inhibitor. At one time we would leave patients on tamoxifen if they were already on tamoxifen, because no evidence indicated that crossing over was beneficial. But the result of all three of the crossover trials that came out this past year indicate no justification to continue tamoxifen.

— Gabriel N Hortobagyi, MD