Sequencing Tamoxifen and Aromatase Inhibitors in Postmenopausal Patients

28TH ANNUAL San Antonio Breast Cancer Symposium 5

The optimal adjuvant hormonal therapy strategy for postmenopausal women is controversial. A number of trials have evaluated the role of aromatase inhibitors following tamoxifen. MA17 randomly assigned postmenopausal women who had completed 4.5 to six years of adjuvant tamoxifen to five years of placebo or letrozole. In ITA, IES, ABCSG-8 and ARNO 95, postmenopausal women who had completed two to three years of adjuvant tamoxifen were randomly assigned to continue tamoxifen or switch to an aromatase inhibitor. These trials of sequential adjuvant hormonal therapy have demonstrated significant advantages for women switching to an aromatase inhibitor. In an extension of MA17 and in a proposed trial through the NSABP, women who complete five years of hormonal therapy will be randomly reassigned to another five years of letrozole or placebo.

EVALUATING THE STRATEGY OF SWITCHING FROM ADJUVANT TAMOXIFEN TO AN AROMATASE INHIBITOR

Study	N	Randomization	Study endpoints	Hazard ratio
ABCSG-8/ ARNO 95	3,224	TAM (T) x 2y → anastrozole (A) x 3y TAM x 2y → TAM x 3y	EFS DRFS OS	A/T = 0.60 (p = 0.0009) A/T = 0.61 (p = 0.0067) A/T = 0.76 (p = 0.16)
IBCSG-18-98/ EU-99022/ IBCSG-1-98	8,010	TAM x 5y Letrozole (L) x 5y TAM x 2y → letrozole x 3y Letrozole x 2y → TAM x 3y	DFS* OS*	L/T = 0.81 (p = 0.003) L/T = 0.86 (p = 0.16) NR NR
IES/ICCG-960 EXE031-C1396- BIG9702	4,742	TAM x 5y TAM x 2-3y → exemestane (E) x 2-3y	DFS BCFS OS Time to contralateral breast cancer	E/T = 0.68 (p < 0.001) E/T = 0.63 (p < 0.001) E/T = 0.88 (p = 0.37) E/T = 0.44 (p = 0.04)
Italian (ITA)	426	TAM x 2-3y → anastrozole x 2-3y TAM x 2-3y → TAM x 2-3y	Relapse Death	A/T = 0.36 (p = 0.006) A/T = 0.18 (p = 0.07)
GROCTA 4B	380	TAM x 3y → aminoglutethimide (AG) x 2y TAM x 3y → TAM x 2y	EFS	AG/T = 1 (p = 0.6)

TAM = tamoxifen; EFS = event-free survival; DRFS = distant relapse-free survival; OS = overall survival; DFS = disease-free survival; NR = not yet reported
BCFS = breast cancer-free survival

* Endpoint for monotherapy; analysis of sequential endocrine treatment not yet completed; HR <1.0 favors aromatase inhibitors

EXTENDED ADJUVANT HORMONAL THERAPY WITH AROMATASE INHIBITORS AFTER FIVE YEARS OF TAMOXIFEN

Study	N	Randomization	Study endpoints	Hazard ratio
CAN-NCIC-MA17/SWOG-NCIC-MA17/ IBCSG-BIG97-01/CALGB-49805	5,187	TAM x 4.5-6y → letrozole x 5y TAM x 4.5-6y → placebo x 5y	Relapse Death	L/P = 0.57 (p = 0.00008) L/P = 0.76 (p = 0.25)
ABCSG-6a	856	GROCTA 4B → anastrozole x 3y GROCTA 4B → no treatment x 3y	EFS	Anastrozole/ no treatment = 0.64 (p = 0.047)

TAM = tamoxifen; EFS = event-free survival

SOURCES: Boccardo F et al. *Proc SABCS* 2003;Abstract 3; Boccardo F et al. *J Clin Oncol* 2001;19(22):4209-15; Boccardo F et al. *J Clin Oncol* 2005;23(22):5138-47; Jakesz R et al. Presentation. San Antonio Breast Cancer Symposium 2004;Abstract 2; Thürlimann BJ et al. BIG 1-98. Presentation. ASCO 2005;Abstract 511; Jakesz R et al. *Proc ASCO* 2005;Abstract 527; NCI Physician Data Query, September 2005; Goss PE et al. *N Engl J Med* 2003;349(19):1793-802; Coombes RC et al. *N Engl J Med* 2004;350(11):1081-92. NSABP website, www.nsabp.pitt.edu; www.ibcsg.org.

PHASE III RANDOMIZED STUDY OF ADJUVANT EXEMESTANE VERSUS ADJUVANT TAMOXIFEN FOLLOWED BY EXEMESTANE

Protocol IDs: CRC-TU-TEAM, EU-20149, NCT00032136
Target Accrual: 5,700 (Open)

Eligibility	**Stage I-IIIA breast cancer; postmenopausal; age 50 or over with natural amenorrhea for at least one year, chemotherapy-induced amenorrhea for at least two years, radiation-induced amenorrhea; under age 50 with FSH assay confirming postmenopausal status; ER- and/or PR-positive; any age with bilateral oophorectomy or amenorrhea for at least five years**
ARM 1	**Exemestane x 5y**
ARM 2	**Tamoxifen x 2-3y → exemestane x 2-3y***

* In a proposed amendment based on the IES results, Arm 2 will be changed from tamoxifen x five years.

Trial lead organization:

Cancer Research UK Clinical Trials Unit — Birmingham
Daniel Rea, MD, Protocol Chair, Ph: 44-121-507-5241

SOURCES: NCI Physician Data Query, September 2005; Henderson IC. *Am J Oncol* 2005;4(5 Suppl 9):40-3.

PROPOSED NSABP TRIAL OF DURATION OF AROMATASE INHIBITORS

Protocol ID: NSABP (Pending)
Projected Accrual: 3,840 (Planned to open early 2006)

Eligibility	**Stage I-IIIA breast cancer; postmenopausal, ER- and/or PR-positive, five years of hormonal therapy consisting of either five years of an aromatase inhibitor or up to three years of tamoxifen followed by an aromatase inhibitor (for a total of five years)**
ARM 1	**Placebo x 5y**
ARM 2	**Letrozole x 5y**

RERANDOMIZATION OF NCIC-CAN-MA17

Protocol ID: NCIC-CAN-MA17R
Target Accrual: 1,800 (Open)

Women completing approximately five years of letrozole on MA17 who are free of recurrence and completed letrozole no more than six months previously will be eligible for rerandomization on NCIC-CAN-MA17R comparing letrozole x five years versus placebo x five years.

SOURCES: NSABP Protocol Summary, September 2005; National Cancer Institute of Canada Clinical Trials Group, September 2005; Henderson IC. *Am J Oncol* 2005;4(5 Suppl 9):40-3.

SELECT PUBLICATIONS

Boccardo F et al. **Anastrozole appears to be superior to tamoxifen in women already receiving adjuvant tamoxifen treatment.** *Proc SABCS* 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.

Boccardo F et al. **Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: Preliminary results of the Italian Tamoxifen Anastrozole trial.** *J Clin Oncol* 2005;23(22):5138-47.

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.

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, on behalf of the ABCSG. **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.** Presentation. San Antonio Breast Cancer Symposium 2004;Abstract 2.

Jakesz R, on behalf of the ABCSG. **Extended adjuvant treatment with anastrozole: Results from the Austrian Breast and Colorectal Cancer Study Group Trial 6a (ABCSG-6a).** *Proc ASCO* 2005;Abstract 527.

SEQUENCING AROMATASE INHIBITORS AFTER ADJUVANT TAMOXIFEN

I am now absolutely confident that women who have been on tamoxifen for two or three years should switch to an aromatase inhibitor. We have excellent data for both exemestane and anastrozole from three trials. Boccardo's small ITA trial with anastrozole was the first to report, followed by the large IES study with exemestane and the joint Austrian-German study of anastrozole presented in San Antonio. Overwhelming evidence indicates that a switch to an aromatase inhibitor is beneficial. I recommend the switch regardless of whether the patient has been on tamoxifen for one year or four years. You can wait forever for refinements, but 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. The MA17 trial is a well-conducted trial in women who have already received five years of tamoxifen. It shows proof of the principle that you can influence the natural history of breast cancer after five years of tamoxifen.

— *Michael Baum, MD, ChM.* Breast Cancer Update *2005 (2)*

The aromatase inhibitors add benefit immediately after surgery, after two to three years of tamoxifen or as extended adjuvant therapy. In breast cancer, the highest risk of recurrence is typically within the first two to three years after surgery. In women who participated in the ATAC trial, you can see a difference in the disease-free survival curves well before the two and a half year mark. Not only do you lose patients to an early breast cancer recurrence in the first two to three years, but you also lose some women to adverse events on the tamoxifen arm. The IES study and MA17 do not really take those facts into consideration because those patients have already dropped out prior to randomization. I typically offer anastrozole to the majority of postmenopausal patients with receptor-positive tumors after surgery and chemotherapy. When patients come in after two to three years of tamoxifen, I discuss switching them to an aromatase inhibitor. At the end of five years of tamoxifen, I discuss letrozole.

— *Maura N Dickler, MD.* Breast Cancer Update *2005 (2)*

I use exemestane after two to three years of tamoxifen based on the IES data. However, if you compare the IES exemestane data to the data from the combined ARNO 95/ABCSG-8 trials, in which the patients were switched to anastrozole, the agents appear to be similar in terms of efficacy. The hazard ratio for disease-free survival was 0.73 in the IES study and 0.60 in the ARNO study, so I believe these two agents are equivalent in this situation. We now have data to support the use of either anastrozole or exemestane after two or three years of tamoxifen. After five years of tamoxifen, we only have the MA17 trial data, so I use letrozole in this setting.

— *Anthony Howell, MD.* Breast Cancer Update *2005 (4)*

In the combined trials of ABCSG-8 and ARNO 95, more than 3,200 postmenopausal patients, all with receptor-positive disease, were exposed to two years of adjuvant tamoxifen after surgery. We then randomly assigned them to tamoxifen or anastrozole for three years. It was clean, informative data. In the IES trial, exemestane resulted in a risk reduction of approximately 35 percent, whereas in the combined trials, the risk of an event was reduced by 40 percent with anastrozole. Most of the difference in the event rate with anastrozole was due to a huge reduction in distant metastases.

— *Raimund V Jakesz, MD.* Breast Cancer Update *2005 (3)*

It is important to study the duration of aromatase inhibitor therapy. The NSABP will take patients that complete five years of an aromatase inhibitor or took tamoxifen for two to three years and then switched to an aromatase inhibitor and randomly assign them to either continue an aromatase inhibitor — letrozole — versus placebo for five years. We will essentially do what we did in the NSABP-B-14 extension trial but with aromatase inhibitors.

— *Eleftherios P Mamounas, MD, MPH.* Breast Cancer Update *2005 (9)*