Optimal Long-Term Endocrine Therapy

The optimal adjuvant hormonal therapy strategy for postmenopausal women is controversial. The ITA, IES, ABCSG-8 and ARNO 95 trials demonstrated significant advantages for women switching to an aromatase inhibitor (AI) after two to three years of tamoxifen, and a meta-analysis of these trials evaluating switching to the AI anastrozole presented in San Antonio demonstrated a survival advantage to the switch. Other presentations at San Antonio highlighted the distinction between switching and sequencing analyses. Ultimately, this question will be answered by the BIG FEMTA trial which randomly assigned patients to letrozole or tamoxifen initially and after two to three years. Additional data from trial MA17, which randomly assigned postmenopausal women who had completed 4.5 to six years of adjuvant tamoxifen to five years of placebo or letrozole, was also presented in San Antonio and demonstrated a significant benefit in the patients who were rerandomized from the placebo arm of MA17 to letrozole after unblinding and a benefit to increasing durations of letrozole following adjuvant tamoxifen up to 48 months.

SWITCHING OR SEQUENCING* 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)

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

EXTENDED ADJUVANT HORMONAL THERAPY 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)

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

META-ANALYSIS OF TRIALS EVALUATING SWITCHING TO ANASTROZOLE: ARNO 95, ABCSG-8 AND ITA (N = 4,006)

	Hazard ratio [95% CI]	p-value
DFS (ITT population)	0.59 [0.48-0.74]	<0.0001
OS (ITT population)	0.71 [0.52-0.98]	0.038

DFS = disease-free survival; ITT = intention to treat; OS = overall survival

Hazard ratios are for anastrozole/tamoxifen.
Hazard ratio <1.0 favors anastrozole.

"As was observed in the individual trials, this meta-analysis demonstrates that patients switched to anastrozole experience significantly fewer recurrences than those patients remaining on tamoxifen. These advantages translate into a benefit in the long-term endpoint of overall survival. Consistency of effect was seen between the three trials. …Switching to anastrozole results in a benefit in overall survival. These data confirm that postmenopausal women currently receiving adjuvant tamoxifen should be switched to anastrozole."

SOURCE: Jonat W et al. Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 18.

MA17 POST-UNBLINDING: PATIENTS SWITCHING FROM PLACEBO TO LETROZOLE (N = 1,655) VERSUS CONTINUING PLACEBO (N = 613)

	Adjusted hazard ratio [95% CI]	p-value
DFS	0.31 [0.18-0.55]	<0.0001
DDFS	0.28 [0.13-0.62]	0.002
OS	0.53 [0.28-1.00]	0.05
CBC	0.23 [0.07-0.77]	0.017

DFS = disease-free survival; DDFS = distant disease-free survival
OS = overall survival; CBC = contralateral breast cancer

Hazard ratios are for those switching to letrozole/placebo. Hazard ratio <1.0 favors switching from placebo to letrozole.

Note: Patients who completed five years of letrozole on MA17 are eligible for rerandomization on NCIC-CAN-MA17R comparing letrozole x five years versus placebo x five years.

SOURCES: Goss PE et al. Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 16; National Cancer Institute of Canada Clinical Trials Group, September 2005.

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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. **Updated analysis of NCIC CTG MA17 post unblinding.** Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 16.

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Jakesz R et al. **The benefits of sequencing adjuvant tamoxifen and anastrozole in postmenopausal women with hormone-responsive early breast cancer: 5 year-analysis of ABCSG Trial 8.** Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 13.

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.

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.

Jonat W et al. **Switching from adjuvant tamoxifen to anastrozole in postmenopausal women with hormone-responsive early breast cancer: A meta-analysis of the ARNO 95 trial, ABCSG Trial 8, and the ITA trial.** Presentation. San Antonio Breast Cancer Symposium 2005;Abstract 18.

SWITCHING TO 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 (AI). We have excellent data for both exemestane and anastrozole. 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.

— 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)

There is a lot of interesting statistical work that has come out of Dana-Farber looking at modeling of outcomes from natural history studies and meta-analyses. The model attempted to see if a sequencing strategy might be better than five years of an aromatase inhibitor. And their publication suggests that it would be, which is a fascinating hypothesis. My feeling is that we should find out, and the BIG 1-98 study is designed to answer that question.

Until 1-98 shows a difference in outcome for patients who receive five years of letrozole versus a sequence of tamoxifen and letrozole, I think that the standard of care for a newly diagnosed patient is to give them five years of an aromatase inhibitor.

— Kevin R Fox, MD (Interview, September 2005)

I have been impressed by the results of MA17. This is an indication that hormone receptor-positive patients are extremely difficult to cure and are at risk of relapse five, 10, 12 years after diagnosis.

On the other hand, we clearly have an increasing number of active endocrine agents. I think the optimal therapy in the future is going to be a smart sequence of agents covering at least 10 years. And I think it's because of this that I don't like the idea of giving an AI up front to everybody.

Maybe you can give an AI for 10 years, but nobody knows that. And there are patients who are going to develop resistance to the drug. So in view of that, I tend to look at the profile of the tumor and if I'm dealing with a highly endocrine-responsive tumor, with low proliferation genes, I think there is a very low risk of relapse for this patient if you put her on tamoxifen for two years.

— Martine J Piccart-Gebhart, MD, PhD.
Breast Cancer Update *2006 (2)*

It is important to study the duration of aromatase inhibitor therapy. The NSABP will take patients who 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)*