Chemoprevention and Management of DCIS

Tamoxifen reduced the incidence of breast cancer in women at high risk in the NSABP-P-1 and IBIS-I trials. NSABP-P-2 (the STAR trial) compares another SERM (raloxifene) to tamoxifen in that setting. Data from the ATAC trial — demonstrating an advantage to anastrozole over tamoxifen in reduction of contralateral cancers — hint toward the future use of aromatase inhibitors in a chemoprevention setting, such as the recently launched IBIS-II trial comparing anastrozole to a placebo. The widespread utilization of screening mammography has led to a dramatic increase in the number of women diagnosed with DCIS. NSABP trials B-17 and B-24 demonstrated a stepwise improvement in local and contralateral tumor control with the use of breast radiotherapy and tamoxifen in women who underwent a lumpectomy. NSABP-B-35 and IBIS-II will compare anastrozole to tamoxifen in postmenopausal patients with DCIS.

NSABP-P-1 AND IBIS-I STUDIES: BREAST CANCER EVENTS

Trial	No. of patients		Total invasive and noninvasive cancers		
	Placebo	Tam	Placebo	Tam	OR (95% CI)
NSABP-P-1	6,707	6,681	244	124	0.51 (0.39-0.66)
IBIS-I	3,574	3,578	101	69	0.68 (0.50-0.92)

Tam = tamoxifen; OR = odds ratio; CI = confidence interval

SOURCES: Chlebowski RT et al. *J Clin Oncol* 2002;20(15):3328-43. IBIS Investigators. *The Lancet* 2002;360(9336):817-24.

CONTRALATERAL BREAST CANCER IN THE ATAC TRIAL

	Anastrozole (n=3,125)	Tamoxifen (n=3,116)
CL (invasive)	20	35
CL (DCIS)	5	5

CL = contralateral breast cancer

"Reductions in contralateral breast cancer rates remained in favor of anastrozole (OR=0.62 [0.38–1.02], p=0.062), with statistical significance achieved in the hormone-receptor positive sub-group (OR=0.56 [0.32–0.98], p=0.042)."

SOURCE: The ATAC Trialists' Group. *Cancer* 2003;98(9):1802-10.

ACTIVE CLINICAL TRIALS COMPARING TAMOXIFEN TO ANASTROZOLE IN POSTMENOPAUSAL WOMEN WITH DCIS

Protocol ID	Eligibility	Randomization	Target accrual
CRUK-IBIS-II-DCIS, BIG-5-02, EU-20226	Postmenopausal, ages 40-70 ER/PR-positive, (>5% positive cells)	Anastrozole versus tamoxifen	4,000
NSABP-B-35, CTSU, ACOSOG-NSABP-B-35, NCCTG-NSABP-B-35, SWOG-NSABP-B-35	Postmenopausal, ER/PR-positive or borderline	Anastrozole versus tamoxifen	3,000

SOURCE: NCI Physician Data Query, September 2004.

INCIDENCE OF INVASIVE BREAST CANCER FOLLOWING RALOXIFENE THERAPY IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS: MORE AND CORE TRIAL DATA

Trial	Incidence of invasive breast cancer		
	Raloxifene	Placebo	Hazard ratio
Four years of raloxifene therapy versus placebo*	1.3 per 1,000 women-years	4.7 per 1,000 women-years	0.28 (95% CI = 0.17-0.46) n=61 $p < 0.001$
Eight years of raloxifene therapy versus placebo†	1.4 per 1,000 women-years	4.2 per 1,000 women-years	0.34 (95% CI = 0.22-0.50) n=7705 $p < 0.001$

*MORE trial: Patients were randomly assigned to raloxifene 60 mg/day vs raloxifene 120 mg/day vs placebo x 4 years. Breast cancer incidence was a secondary outcome of the MORE trial.

†MORE trial followed by CORE trial in which patients were randomly assigned to raloxifene 60 mg/day vs placebo x 4 years. Breast cancer incidence was a primary endpoint of the CORE trial.

SOURCE: Martino S. Presentation. ASCO, 2004;Abstract 1000.

ONGOING OR RECENTLY CLOSED CHEMOPREVENTION TRIALS

Protocol ID	Eligibility	Target accrual	Schema
CAN-NCIC-MAP3, PFIZER-EXEAPO-0028-150	High-risk, postmenopausal, age 35 and over	5,100	Exemestane vs exemestane + celecoxib vs placebo
NCI-04-C-0044	High-risk, postmenopausal	72	Exemestane + celecoxib vs exemestane
SWOG-S0300	High-risk, premenopausal, age 18 and over	100	Celecoxib vs placebo
DFCI-00024, UCLA-0210012-02	High-risk based on estradiol level >9 pg/mL, postmenopausal, age 35 and over	110	Letrozole vs placebo
KUMC-HSC-8919-02	High-risk for ER-negative, premenopausal, age 18 to 55	110	Celecoxib
CHNMC-IRB-02164	High-risk, premenopausal, age 21 to 48	10	Deslorelin + estradiol + testosterone
CRUK-IBIS-IIB, EU-20227	High-risk, ER/PR-positive (>5% positive cells) in patients with prior DCIS, postmenopausal, age 40 to 70	6,000	Anastrozole vs placebo
CAN-NCIC-MAP2, PHARMACIA-971-ONC-0028-088	Radiologic density occupying ≥25% of the breast, postmenopausal	120	Exemestane vs placebo
NCRI-IBIS-RAZOR, EU-20053, UKCCCR-IBIS-RAZOR	High genetic risk, premenopausal, age 30 to 45	150	Goserelin + raloxifene vs surveillance

SOURCE: NCI Physician Data Query, September 2004.

SELECT PUBLICATIONS

Chlebowski RT et al; American Society of Clinical Oncology Breast Cancer Technology Assessment Working Group. **American Society of Clinical Oncology technology assessment of pharmacologic interventions for breast cancer risk reduction including tamoxifen, raloxifene, and aromatase inhibition.** *J Clin Oncol* 2002;20(15):3328-43.

Cuzick J. **Aromatase inhibitors in prevention—data from the ATAC (arimidex, tamoxifen alone or in combination) trial and the design of IBIS-II (the second International Breast Cancer Intervention Study).** *Recent Results Cancer Res* 2003;163:96-103.

Cuzick J et al; IBIS investigators. **First results from the International Breast Cancer Intervention Study (IBIS-I): A randomised prevention trial.** *The Lancet* 2002;360(9336):817-24.

Fisher B et al. **Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial.** *The Lancet* 1999;353(9169):1993-2000.

Fisher B et al. **Tamoxifen for prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study.** *J Natl Cancer Inst* 1998;90(18):1371-88.

Martino S et al. **Incidence of invasive breast cancer following 8 years of raloxifene therapy in postmenopausal women with osteoporosis: Results from the Continuing Outcomes Relevant to Evista (CORE) trial.** *Proc ASCO* 2004;Abstract 1000.

ATAC TRIAL DATA ON SECOND BREAST CANCERS

Some might argue that the reduction of contralateral breast cancer in ATAC looks less promising with the updated data than with the original data — it has gone from about a 60 percent to about a 50 percent relative reduction in contralateral breast cancer in the receptor-positive group. We had the same experience early on with tamoxifen. This suggests that these agents don't prevent cancer, but rather delay the appearance of cancer. Perhaps anastrozole delays the appearance of breast cancer for longer than tamoxifen. I am very confident that anastrozole will reduce the risk of new receptor-positive breast cancers — the adjuvant setting will predict the preventive setting. The issue to me is the trade-off and harm-to-benefit ratio.

— Michael Baum, ChM

CLINICAL TRIALS OF AROMATASE INHIBITORS IN DCIS

NSABP-B-35 and IBIS-II are important trials, both comparing anastrozole and tamoxifen in postmenopausal patients with DCIS. In our experience with large numbers of patients, aromatase inhibitors are better tolerated than tamoxifen. Despite the results of the randomized trials, patients complain of weight gain on tamoxifen. Other problems include hot flashes, menopausal symptoms and possibly a low level of clinical depression. Patients also worry about endometrial cancer and blood clots. With aromatase inhibitors, some arthralgias are reported, but these agents are very well tolerated.

Aromatase inhibitors have already proven to have a significant effect in invasive cancer, and it's highly likely they will impact DCIS as well. We know that the majority of DCIS lesions are likely to be ER-positive. Craig Allred has shown that age-per-age, tumor-for-tumor, DCIS is even more likely to be ER-positive than invasive cancer. If that's true, then we have even more reason to be optimistic about the studies of aromatase inhibitors in DCIS.

— Patrick I Borgen, MD

The NSABP study comparing tamoxifen and anastrozole for patients with DCIS is essentially a trial aimed at preventing invasive breast cancer. Aromatase inhibitors have emerged as good agents for the treatment of metastatic breast cancer, both second- and first-line, and the pivotal results from the ATAC trial demonstrated adjuvant anastrozole was more effective than tamoxifen in reducing recurrence rates and contralateral breast cancers. If patients with DCIS fail, it's usually in the ipsilateral or contralateral breast rather than in the regional nodes or distant sites. Aromatase inhibitors are well tolerated in general. In the ATAC trial, the safety profile of anastrozole was impressive. Patients had fewer thromboembolic events, endometrial cancers and menopausal symptoms than with tamoxifen, but with aromatase inhibitors we need to monitor bone density and fractures.

— Eleftherios P Mamounas, MD, MPH

ESTROGEN RECEPTOR STATUS AND TAMOXIFEN EFFICACY

NSABP-B-24 compared adjuvant tamoxifen to placebo in patients with DCIS. After four or five years of follow-up, the tamoxifen arm showed a 30 percent benefit, but we didn't understand the relationship of this response rate to the tumor's hormone receptor status. When the trial was initiated, assessing hormone receptors wasn't required, but tumors were banked to conduct biological studies. In a central lab, we later measured the estrogen and progesterone receptors by immunohistochemistry on approximately 600 paraffin blocks distributed between the two arms of the study. The data convincingly demonstrated that the benefit from tamoxifen was entirely restricted to the ER-positive cohort; the ER-negative cohort showed no evidence of benefit. Approximately 25% of DCIS cases are truly ER-negative and we can conclude from our data that tamoxifen does not reduce the recurrence rate in patients with ER-negative DCIS.

— D Craig Allred, MD