Chemoprevention and Management of DCIS

Tamoxifen reduced the incidence of breast cancer 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 cancer — 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. *Lancet* 2002;360(9336):817-24.

REDUCTION IN INCIDENCE OF CONTRALATERAL BREAST CANCER WITH ANASTROZOLE VERSUS TAMOXIFEN: 68-MONTH UPDATE FROM THE ATAC TRIAL

	Reduction	95% CI	*p*-value
All patients	42%	12-62	0.01
Hormone receptor-positive patients	53%	25-71	0.001

CI = confidence interval

SOURCE: ATAC Trialists' Group. **Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer.** *Lancet* 2005;365(9453):60-2.

ACTIVE CLINICAL TRIALS COMPARING TAMOXIFEN TO ANASTROZOLE IN WOMEN WITH DCIS

Protocol ID	Eligibility	Randomization	Target accrual
CRUK-IBIS-II-DCIS, BIG-5-02, EU-20226	Postmenopausal, ages 40 to 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, December 2004.

INCIDENCE OF INVASIVE BREAST CANCER FOLLOWING RALOXIFENE THERAPY IN WOMEN WITH OSTEOPOROSIS: EIGHT YEARS OF MORE PLUS CORE TRIAL DATA

	Raloxifene	Placebo	Hazard ratio	*p*-value
Cumulative incidence	1.4 per 1,000 women-years	4.2 per 1,000 women-years	0.34 (95% CI, 0.22-0.50)	< 0.001

SOURCE: Martino S. Presentation. San Antonio Breast Cancer Symposium, 2004;Abstract 22.

OTHER ONGOING OR RECENTLY CLOSED CHEMOPREVENTION TRIALS

Protocol ID	Eligibility	Target accrual	Schema
CAN-NCIC-MAP3, PFIZER-EXEAP0-0028-150	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
UTSMC-0799-302	High-risk, pre- or postmenopausal, age 35 and over	130	Tamoxifen 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
NU-NCI-00B2	Initiating tamoxifen for risk reduction or sole systemic therapy for breast cancer, premenopausal, age 20 to 45	100	Tamoxifen
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
BCM-H-9315	Known carrier or at risk for BRCA1 or BRCA2 mutation, pre- or postmenopausal, age 18 and over	100	Bexarotene vs placebo
NSABP-P-2 (STAR)	High-risk, postmenopausal, age 35 and over	19,000	Tamoxifen vs raloxifene

SOURCE: NCI Physician Data Query, December 2004.

SELECT PUBLICATIONS

ATAC Trialists' Group. **Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer.** *Lancet* 2005;365(9453):60-2.

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.** *Lancet* 2002;360(9336):817-24.

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.

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

Martino S et al. **Effect of raloxifene on the incidence of invasive breast cancer in postmenopausal women stratified by baseline serum estradiol level: Results of the continuing outcomes relevant to Evista (CORE) trial.** *Proc SABCS* 2004;Abstract 22.

ATAC TRIAL DATA ON SECOND BREAST CANCERS

"The incidence of contralateral breast cancer was substantially reduced by anastrozole compared with tamoxifen. ... Since tamoxifen shows a 50% reduction in the occurrence of these tumours in hormone-receptor-positive patients compared with placebo, the findings from the ATAC study suggest that anastrozole treatment might prevent 70 to 80% of hormone-receptor-positive tumours in women at high risk of breast cancer."

— ATAC Trialists' Group. Lancet *2005;365(9453):60-2.*

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 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, MD, 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 well tolerated.

Aromatase inhibitors have a significant effect in invasive cancer, and it's highly likely they will also impact DCIS. Craig Allred has shown that DCIS is even more likely to be ER-positive than invasive cancer. If that's true, we have even more reason to be optimistic about the studies of aromatase inhibitors in DCIS.

— Patrick I Borgen, MD

NSABP-B-35 was designed shortly before the ATAC study was publicized, so data from ATAC and MA17 were not available to us. It was initiated because of the growing body of evidence that aromatase inhibitors appear to be effective in settings in which tamoxifen is efficacious. Indeed, two large studies in advanced disease showed drugs like anastrozole were either equivalent to or even slightly better than tamoxifen. The dramatic reduction in second or contralateral breast cancer in women who received anastrozole versus tamoxifen seen in the ATAC trial is exciting and emphasizes the importance of our trial.

— Richard G Margolese, MD

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 percent 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