Clinical Trials of Breast Cancer Chemoprevention

The 1998 publication of the initial results of the NSABP P-1 trial brought the issue of chemoprevention in high-risk women to the forefront of attention in both the lay press and the medical literature. While tamoxifen reduced the incidence of breast cancer in high-risk women in both P-1 and the recently reported IBIS-I trial, NSABP P-2 (the STAR trial) is comparing another SERM (raloxifene) to tamoxifen in this setting. An updated 2002 ASCO Technology Assessment endorsed the implementation of additional research in chemoprevention. The recent presentation of the ATAC trial — demonstrating an advantage to anastrozole over tamoxifen in reduction of contralateral cancers — hints toward future trials of the aromatase inhibitors in a chemoprevention setting, such as the recently launched IBIS-II trial comparing anastrozole to a placebo. Ultimately, with a number of available effective agents, issues of toxicity and side effects may become paramount.

RANDOMIZED, PLACEBO-CONTROLLED CLINICAL TRIAL TO DETERMINE THE WORTH OF TAMOXIFEN FOR PREVENTING BREAST CANCER — Closed Protocol

Protocol ID: BCPT-1, NCI-P91-0022, NSABP-P-1
Actual Accrual: 13,388 women

Eligibility	**Pre- and postmenopausal women ≥ 35 years old at high risk for breast cancer**
ARM 1	**Tamoxifen 20 mg qd x 5 years**
ARM 2	**Placebo x 5 years**

Fisher 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):1371-1388.

SOURCE: NCI Physician Data Query, February 2003

STUDY OF TAMOXIFEN AND RALOXIFENE (STAR) FOR THE PREVENTION OF BREAST CANCER — Open Protocol

Protocol ID: NSABP-P-2
Projected Accrual: 22,000 women

Eligibility	**Postmenopausal women at risk (LCIS or ≥ 1.66% five-year probability) for developing breast cancer**
ARM 1	**Tamoxifen + placebo x 5 years**
ARM 2	**Raloxifene + placebo x 5 years**

Quality of life assessed at baseline and six-month intervals to five years, then annually thereafter.

Study Contact:
Norman Wolmark, Chair. Tel: 412-359-3336
National Surgical Adjuvant Breast and Bowel Project

SOURCE: NCI Physician Data Query, February 2003

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

Trial	# Patients Randomized		Total Invasive and Noninvasive Cancer		
	Placebo	Tam	Placebo	Tam	OR 95% CI
P-1	6,707	6,681	244	124	0.51 0.39-0.66
IBIS-1	3,566	3,573	101	69	0.68 0.50-0.92

DERIVED FROM: Chlebowski RT et al. *J Clin Oncol* 2002;20(15): 3328-3343 & IBIS Investigators. *Lancet* 2002;360(9336):817-24.

CONTRALATERAL BREAST CANCERS IN THE ATAC TRIAL

	AN (n=3125)	TAM (n=3116)
CL (invasive)	20	35
CL (DCIS)	5	5

CL=contralateral breast cancer

"Reductions in contralateral breast cancer rates remained in favor of AN (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)."

DERIVED FROM: Buzdar A et al. Breast Cancer Res Treat 2002; Abstract 13.

INTERNATIONAL BREAST CANCER INTERVENTION STUDY-1 — Closed Protocol

Protocol ID: IBIS-1
Actual Accrual: 7,152 women

Eligibility	**Women aged 35-70 at high risk for breast cancer**
ARM 1	**Tamoxifen 20 mg qd x 5 years**
ARM 2	**Placebo x 5 years**

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

INTERNATIONAL BREAST CANCER INTERVENTION STUDY-2 — Open Protocol

Protocol ID: IBIS-2
Projected Accrual: 6,000 women

Eligibility	**Increased breast cancer risk**
ARM 1	**Anastrozole 1 mg qd x 5 years**
ARM 2	**Placebo x 5 years**

SOURCE: Jack Cuzick, PhD, Personal Communication, November 2002.

SELECT PUBLICATIONS

Chlebowski RT et al. **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):3328-3343.

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Goss PE, Strasser K. **Aromatase inhibitors in the treatment and prevention of breast cancer.** *J Clin Oncol* 2001;19(3):881-894.

IBIS Investigators. **First results from the International Breast Cancer Intervention Study (IBIS-I): A randomised prevention trial.** *Lancet* 2002;360(9336):817-824.

O'Reagan RM, Jordan VC. **Tamoxifen to raloxifene and beyond.** *Semin Oncol* 2001;28(3):260-273.

Vogel VG. **Follow-up of the breast cancer prevention trial and the future of breast cancer prevention efforts.** *Clin Cancer Res* 2001;7(12Suppl):4413s-4418s; discussion 4411s-4412s.

Wickerham DL, Tan-Chiu E. **Breast cancer chemoprevention: Current status and future directions.** *Semin Oncol* 2001;28:253-259.

ASCO TECHNOLOGY ASSESSMENT OF PHARMACOLOGIC INTERVENTIONS FOR BREAST CANCER RISK REDUCTION: KEY CONCLUSIONS

"Tamoxifen (at 20 mg/d for 5 years) may be offered for women with a 5-year projected breast cancer risk of ≥ 1.66%. Risk/benefit models suggest that younger women, women without a uterus, and women at higher breast cancer risk, derive the greatest clinical benefit with least side effects. Raloxifene is not recommended to lower breast cancer risk. It should be reserved for its approved indication: to prevent or treat bone loss in postmenopausal women. Aromatase inhibitors or aromatase inactivators are not recommended to lower breast cancer risk. Clinical trial evaluation of potential chemoprevention agents, either alone or in combination, is encouraged."

—Chlebowski RT et al. J Clin Oncol 2002;20(15):3328-3343.

In comparing the 2002 ASCO technology assessment to the 1999 assessment, the big change is that we now have much greater confidence in the reliability of our estimates of tamoxifen's effects. Now, there are more than 2,000 events, and we have greater confidence in the effects of tamoxifen — maybe a 40% risk reduction — and in the side-effect profile. We now talk about recommending tamoxifen for short-term risk reduction of breast cancer — for about five years. We don't have long-term information, and we're much more cognizant of the side effects. It seems younger women and women without a uterus derive the principal benefit, based largely on risk-benefit models that have been developed.

—Rowan Chlebowski, MD

UPDATED CONTRALATERAL BREAST CANCER DATA FROM THE ATAC TRIAL

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 a 60 percent to a 50 percent relative reduction in contralateral breast cancer in the receptor-positive group. We had the same experience early on with tamoxifen. The extremely dramatic difference seen at three years was reduced over the next few years. This suggests that these endocrine agents don't prevent cancer, but rather delay the appearance of cancer. Perhaps anastrozole delays the appearances of breast cancer for longer than tamoxifen.

I am very confident that anastrozole will reduce the risk of receptor-positive breast cancers — the adjuvant setting will predict the preventive setting. The issue to me is the trade-off and harm/benefit equation.

—Michael Baum, ChM, FRCS

ATAC has significant implications for prevention, and the IBIS-2 trial will evaluate anastrozole in this setting and in DCIS. We need to explore this further in the United States with definitive studies in postmenopausal high-risk women. In this subgroup, the toxicity of tamoxifen is substantial.

The main safety concerns with tamoxifen are the agonist effects (i.e., risks of thromboembolic complications and small risk of endometrial cancer). Even women with just vaginal bleeding without endometrial cancer still have to go through a number of tests and procedures before we know that they don't have the problem. There's no question that the safety profile of anastrozole is much better than tamoxifen. Anastrozole is an agent with almost nonexistent side effects — at least in the preliminary analysis of the data — making it a very attractive agent to be evaluated in the prevention setting.

—Aman Buzdar, MD