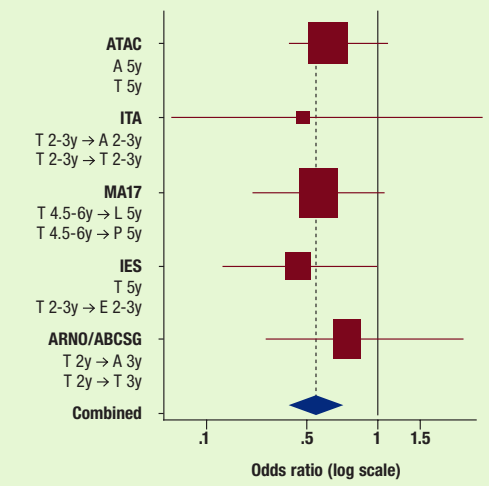
Breast Cancer Prevention

In the NSABP-P-1 and IBIS-1 trials, chemoprevention with tamoxifen was found to reduce the incidence of breast cancer in women at higher risk. The ATAC adjuvant trial demonstrated a further reduction in the incidence of contralateral breast cancer with anastrozole compared to tamoxifen. The aromatase inhibitors are being evaluated in ongoing chemoprevention trials in postmenopausal women. In addition to the reduced rate of second cancers, the more favorable safety and tolerability of these agents is the basis for evaluation in the high-risk setting. NSABP-P-2 (the STAR trial) compares tamoxifen to raloxifene, and it is likely that the agent with the better risk-benefit ratio will be compared in a new trial to an aromatase inhibitor.

CONTRALATERAL BREAST CANCER IN TRIALS OF ADJUVANT AROMATASE INHIBITORS



A = anastrozole; T = tamoxifen; L = letrozole; P = placebo; E = exemestane

BIG 1-98	Letrozole x 5y	Tamoxifen x 5y	*p*-value
Contralateral breast cancer (invasive)	0.4%	0.7%	0.125

SOURCES: Adapted with permission from the American Society of Clinical Oncology. Cuzick J. Aromatase inhibitors for breast cancer prevention. *J Clin Oncol* 2005;23(8):1636-43; Thürlimann B, for the BIG 1-98 Collaborative. Presentation. St Gallens 2005.

KEY ADVERSE EVENTS IN ADJUVANT TRIALS OF AROMATASE INHIBITORS VERSUS TAMOXIFEN

	ATAC[1]		BIG 1-98[2]	
	A	T	L	T
Hot flashes	35.7%	40.9%	33.5%	38.0%
Endometrial cancer	0.2%	0.8%	0.2%	0.5%
Hysterectomy	1.3%	5.1%	—	—
Ischemic cerebrovascular events	2.0%	2.8%	1.0%	1.0%
Venous thromboembolic events	2.8%	4.5%	1.5%	3.5%
Joint symptoms/arthralgias	35.6%	29.4%	20.3%	12.3%
Fractures	11.0%	7.7%	5.7%	4.0%

A = anastrozole; T = tamoxifen; L = letrozole

SOURCES: [1] Howell A et al. *Lancet* 2005;365(9453):60-2; [2] Thürlimann B et al. Presentation. ASCO 2005.

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

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

P = placebo; T = 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.

ONGOING OR RECENTLY CLOSED CHEMOPREVENTION AND DCIS TRIALS

Protocol ID	Eligibility	Target accrual	Schema
CAN-NCIC-MAP3, PFIZER-EXEAPO-0028-150	High-risk, postmenopausal, age 35 and over	4,560	Exemestane vs placebo
NCI-04-C-0044	High-risk, postmenopausal	45	Exemestane
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
CAN-NCIC-MAP.1, NCT00238316	High-risk, postmenopausal, mammographic density occupying ≥25% of the breast	120	Letrozole vs placebo
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, PFIZER-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
CRUK-IBIS-II-DCIS, BIG-5-02, EU-20226	Postmenopausal, age 40 to 70, ER/PR-positive (>5% positive cells), DCIS	4,000	Anastrozole vs tamoxifen
NSABP-B-35, CTSU	Postmenopausal, ER/PR-positive or borderline, DCIS	3,000	Anastrozole vs tamoxifen

SOURCE: NCI Physician Data Query, December 2005.

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.

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.

Cuzick J. **Aromatase inhibitors for breast cancer prevention.** *J Clin Oncol* 2005;23(8):1636-43.

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.

Thürlimann B, for the BIG 1-98 Collaborative. **Letrozole as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer. First results of IBCSG 18-98/BIG 1-98.** Presentation. Primary Therapy of Early Breast Cancer 9th International Conference 2005.

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 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.* Breast Cancer Update *2003 (2)

RATIONALE FOR CLINICAL TRIALS OF AROMATASE INHIBITORS IN THE PREVENTATIVE SETTING

Data from the adjuvant trials provide a compelling rationale for exploring the use of AIs in the prevention setting. Their efficiency is greater than that of tamoxifen, especially for new contralateral tumors, suggesting that 70% to 80% of ER-positive breast cancers can be prevented with these drugs…

The AIs also are better tolerated than tamoxifen, without the gynecologic and thrombotic complications, but do lead to bone mineral loss and increased fracture rates in the absence of additional bone-sparing therapy. An important question will be the effectiveness of bisphosphonates in arresting and/or reversing bone loss associated with the almost complete depletion of estrogen associated with AIs.

— Jack Cuzick, PhD.* J Clin Oncol *2005;23(8):1636-43.

ONGOING TRIALS EVALUATING AROMATASE INHIBITORS FOR BREAST CANCER PREVENTION

…A number of AI prevention trials are being designed for implementation in high-risk women. Most developed is the IBIS-II trial, which draws on the contralateral benefit demonstrated in ATAC. Consisting of two arms designed around different high-risk populations, this dual study will test anastrozole for its ability to reduce breast cancer risk. In one arm, 4,000 women with ductal carcinoma-in-situ will be randomly assigned to anastrozole versus tamoxifen for 5 years. The other, prevention, arm will randomly assign 6,000 high-risk women to anastrozole versus placebo for 5 years. The IBIS-II prevention arm will focus on invasive and noninvasive breast cancer as a primary end point, and osteoporosis and fractures as key secondary end points. The National Cancer Institute of Canada is incorporating exemestane into its Mammary Prevention 3 trial.

— Barbara K Dunn, MD et al.* J Clin Oncol *2005;23:357-67.

SIDE-EFFECT PROFILE OF AROMATASE INHIBITORS COMPARED TO TAMOXIFEN

The safety profile in the ATAC update still favors anastrozole. The incidence of endometrial cancer is 0.2 percent with anastrozole and 0.8 percent with tamoxifen. The new data revealed a 5.1 percent rate of hysterectomy with tamoxifen and only slightly over one percent with anastrozole. Also, with anastrozole we seldom see gynecological side effects, such as bleeding or discharge, and we see no increased risk of strokes or pulmonary embolism.

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