Ductal Carcinoma *In Situ* (DCIS): NSABP B-35, IBIS-II Trials

The widespread utilization of screening mammography has led to a dramatic increase in the number of women diagnosed with DCIS. More than 54,000 women will be diagnosed this year in the United States. Clinical research has focused on optimizing control of the index lesion with minimal morbidity and in preventing the occurrence of new primary tumors. 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 treated with lumpectomy, although a new analysis by Allred was presented at the San Antonio Breast Cancer Symposium demonstrating that the advantage to tamoxifen was observed only in women with detectable estrogen receptors. A new NSABP study and another trial in the United Kingdom will evalute anastrozole in postmenopausal patients with DCIS, with the hope that tumor control will be improved with fewer side effects.

NSABP B-35: TAMOXIFEN VERSUS ANASTROZOLE IN POSTMENOPAUSAL PATIENTS WITH DUCTAL CARCINOMA *IN SITU* — Open Protocol

Projected Accrual: 3,000 Patients

Eligibility	**Postmenopausal women with DCIS treated with lumpectomy, ER-/PR-positive or borderline**

Stratification: Age (<60 versus ≥60)

ARM 1	**Tamoxifen 20 mg + placebo qd x 5 yrs + XRT**
ARM 2	**Anastrozole 1 mg + placebo qd x 5 yrs + XRT**

Study Contact: Richard Margolese, Chair
National Surgical Adjuvant Breast and Bowel Project
Tel: 412-330-4600

SOURCE: Richard Margolese, Personal Communication, October 2002.

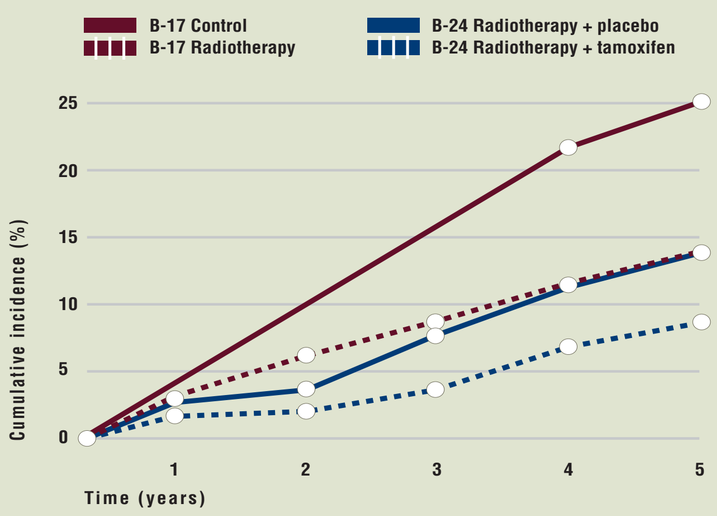
IBIS-II DCIS: INTERNATIONAL, MULTI-CENTRIC STUDY OF TAMOXIFEN VERSUS ANASTROZOLE WITH POSTMENOPAUSAL WOMEN WITH DUCTAL CARCINOMA *IN SITU* (DCIS) — Open Protocol

Projected Accrual: 4,000 patients

Eligibility	**Postmenopausal women, DCIS removed within last six months, ages 40-70**
ARM 1	**Tamoxifen 20 mg qd + placebo**
ARM 2	**Anastrozole 1 mg qd + placebo**

SOURCE: Jack Cuzick, Personal Communication, November 2002.

NSABP DCIS TRIALS: CUMULATIVE INCIDENCE OF INVASIVE AND NONINVASIVE EVENTS IN THE IPSILATERAL AND CONTRALATERAL BREAST



B-17: Radiotherapy reduced the incidence of noninvasive IBT from 13.4% to 8.2% (p = .007), and reduced the incidence of invasive IBT from 13.4% to 3.9% (p < .0001)

B-24: 5 yr breast cancer events: 8.2% tamoxifen vs 13.4% placebo (p=0.0009)

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.

Fisher ER et al. **Pathologic findings from the National Surgical Adjuvant Breast Project (NSABP) eight-year update of Protocol B-17: Intraductal carcinoma.** *Cancer* 1999;86(3):429-438.

PHASE III RANDOMIZED STUDY OF WHOLE BREAST RADIOTHERAPY VERSUS OBSERVATION WITH OR WITHOUT OPTIONAL TAMOXIFEN IN WOMEN WITH GOOD-RISK DUCTAL CARCINOMA *IN SITU* OF THE BREAST — Open Protocol

Protocol IDs: CAN-NCIC-MA26, CLB-49801, CTSU, RTOG-9804, RTOG-DEV 1026

Projected Accrual: 1,790 patients

Eligibility	**DCIS ≤ 2.5cm, no prior chemo or XRT or concurrent hormone treatment (except tamoxifen)**
ARM 1	**Observation with optional tamoxifen qd x 5 years**
ARM 2	**Radiotherapy daily 5 times per week for 3.5 - 5.5 weeks + optional tamoxifen qd x 5 years**

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SOURCE: NCI Physician Data Query, February 2003.

SELECT PUBLICATIONS

The ATAC Trialists' Group. **Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: First results of the ATAC randomised trial.** *Lancet* 2002;359:2131-2139.

Allred DC et al. **Estrogen receptor expression as a predictive marker of the effectiveness of tamoxifen in the treatment of DCIS: Findings from NSABP Protocol B-24.** *Breast Cancer Res Treat* 2002; Abstract 825.

Bordeleau L et al. **A comparison of four treatment strategies for ductal carcinoma in situ using decision analysis.** *Cancer* 2001;92:23-29.

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.

Fisher ER et al. **Pathologic findings from the National Surgical Adjuvant Breast Project (NSABP) eight-year update of Protocol B-17: Intraductal carcinoma.** *Cancer* 1999;86(3):429-438.

Morrow M et al. **Standard for the management of ductal carcinoma *in situ* of the breast (DCIS).** *CA Cancer J Clin* 2002;52(5):256-276.

Skinner KA, Silverstein MJ. **The management of ductal carcinoma in situ of the breast.** *Endocr Relat Cancer* 2001;8:33-45.

Vicini FA, Recht A. **Age at diagnosis and outcome for women with ductal carcinoma-*in-situ* of the breast: A critical review of the literature.** *J Clin Oncol* 2002;20(11):2736-2744.

Wolff AC, Davidson NE. **Use of SERMs for the adjuvant therapy of early-stage breast cancer.** *Ann N Y Acad Sci* 2001;949:80-88.

NSABP TRIAL COMPARING ANASTROZOLE TO TAMOXIFEN IN DCIS

The driving force of current research is to move away from the concept that DCIS is simply a surgical problem — and that if you obtain 10 mm margins, the patient is cured and no adjuvant therapy is needed. And it's not really important to argue about whether there's a set of patients who don't need radiation therapy. Even if we take out the index DCIS, the risk for these women to have another tumor in either breast in the future is at least as high or higher than the risk for women in the NSABP P-1 prevention trial. Chemoprevention in DCIS is an important issue, and we need to find out how to do this best.

As enormously successful as the Prevention Trial was in reducing the incidence of cancer by 50%, everybody understands that there must be a more effective or safer drug than tamoxifen.

That's the driving force for us to do another DCIS trial. The ATAC trial is addressing the use of anastrozole in invasive breast cancer, but we need to ask the same question in noninvasive disease. One can't assume that the results of one trial can be transferred to another situation.

—Richard Margolese, MD

The NSABP B-35 trial will replicate two arms of the ATAC trial in women with DCIS. Since these are very low-risk women, it is important to determine whether the risk-benefit ratio will justify the use of an aromatase inhibitor. The additional 50% reduction in contralateral breast cancer, associated with anastrozole in the ATAC trial, justifies the design of this trial in women with DCIS.

—Eleftherios Mamounas, MD

IMPACT OF ER-DATA FROM NSABP B-24

Craig Allred presented an abstract at San Antonio demonstrating that ER-positive patients in NSABP B-24 respond well to tamoxifen. The question of whether ER-negative patients respond still seems to be open. There was room for the possibility that there still would be a minor effect, although this is probably a function of false negatives in the ER determinations. ER-negative cases done in Craig's lab showed no apparent effect from tamoxifen.

We have incorporated ER-determination into the eligibility requirements for NSABP B-35. DCIS patients will need ER determinations done, and only patients with ER-positive or borderline DCIS can take part in the study. We ask for blocks or core samples at headquarters so that we can do ER determinations in a lab like Craig's as well as other array of studies to try to understand more about this disease.

—Richard Margolese, MD

SELECTION OF DCIS PATIENTS FOR RADIATION THERAPY

DCIS is a heterogeneous group of lesions, and because of that, there's never going to be a single treatment that works for all patients — so there's always going to be controversy about the optimal treatment. In terms of local therapy, you can do excisions of various sizes with or without radiation or you can do a mastectomy. I have a reputation for not wanting to give radiation to DCIS patients, but that's not true. We recommend it to many, but not all, patients. It's relatively expensive and it's a bit inconvenient. Also, if you give radiation therapy for DCIS and the patient develops an invasive recurrence, radiation can't be given again. If you don't give radiation and there is an invasive recurrence, you can excise and irradiate.

— Melvin Silverstein, MD