# Adjuvant Endocrine Therapy Trials in Premenopausal Patients

**The International Breast Cancer Overview has demonstrated that adjuvant ovarian ablation significantly reduces mortality in premenopausal women, and tamoxifen reduces mortality in both pre- and postmenopausal women with ER-positive tumors. Current clinical trials are addressing a number of important issues related to these two key interventions, including the impact of combining these therapies with chemotherapy. New trials are also combining aromatase inhibitors and ovarian suppression in premenopausal women, particularly in light of the recent ATAC trial data demonstrating an advantage to anastrozole in postmenopausal women.**

### PHASE III RANDOMIZED COMPARISON OF ADJUVANT THERAPIES IN PREMENOPAUSAL WOMEN WITH RESECTED NODE-POSITIVE HORMONE RECEPTOR-POSITIVE ADENOCARCINOMA OF THE BREAST

Closed Protocol

Protocol IDs: INT-0101, CLB-9192, EST-5188, SWOG-8851

Projected Accrual: 1,503 eligible patients

| Eligibility | Premenopausal, node-positive, hormone receptor-positive patients within 12 weeks of surgery, who received no prior endocrine or chemotherapy |
|---|---|
| ARM 1 | Surgery ➜ CAF |
| ARM 2 | Surgery ➜ CAF ➜ Z x 5 years |
| ARM 3 | Surgery ➜ CAF ➜ ZT x 5 years |

CAF=cyclophosphamide, doxorubicin, fluorouracil; Z=goserelin; T=tamoxifen

*SOURCE:* NCI Physician Data Query, February 2003.

### PHASE III RANDOMIZED STUDY OF ADJUVANT TAMOXIFEN, OVARIAN SUPPRESSION AND/OR CHEMOTHERAPY IN WOMEN WITH STAGE I, II AND IIIA BREAST CANCER — Closed Protocol

Protocol IDs: CRC-TU-BR3010, EU-94029, SCTN-BR9401/BR9402, UKCCCR-ABC, YRCO-ABC

Projected Accrual: Approximately 6,000 women (4,000 premenopausal, 2,000 postmenopausal)

| Eligibility | Stage I, II or IIIA breast cancer |
|---|---|
| ARM 1 | Tamoxifen |
| ARM 2 | Tamoxifen + [CMF x 6 or AC x 4] |
| ARM 3 | Tamoxifen + ovarian suppression |
| ARM 4 | Tamoxifen + ovarian suppression + [CMF x 6 or AC x 4] |

Postmenopausal women are randomized to arms 1 or 2.

Randomization for pre- and perimenopausal women is based on the clinician's judgment of appropriate adjuvant therapy (chemotherapy and/or ovarian suppression). Patients may be randomized as follows: among all four groups; for chemotherapy alone; for ovarian suppression alone; for ovarian suppression with nonrandomized assignment to chemotherapy; for chemotherapy with nonrandomized assignment to ovarian suppression.

*SOURCE:* NCI Physician Data Query, February 2003.

### KEY QUESTIONS IN THE MANAGEMENT OF PREMENOPAUSAL PATIENTS WITH ER/PR-POSITIVE TUMORS

- Importance of amenorrhea as a determinant of therapy
- Optimal duration of ovarian ablation if an LHRH analogue is used
- Value of ovarian ablation after chemotherapy, particularly for women who remain premenopausal after adjuvant chemotherapy
- Utility of combined hormone therapy such as ovarian ablation with tamoxifen, or aromatase inhibitors
- Long-term side effects of ovarian suppression

### INT-0101 TRIAL RESULTS: 7.4 YEARS FOLLOW-UP

| | DFS | Survival | DFS <40 yrs old |
|---|---|---|---|
| CAF | 58% | 77% | 49% |
| CAFZ | 64% | 78% | 59% |
| CAFZT | 73% | 80% | 59% |

*DERIVED FROM:* NE Davidson, Presentation, San Antonio Breast Cancer Symposium, 2001.

### PLANNED OR ONGOING TRIALS OF ADJUVANT ENDOCRINE THERAPY IN PREMENOPAUSAL PATIENTS

| Study | Entry | Intervention | Target Accrual | Status |
|---|---|---|---|---|
| ABCSG AU12 | Stage I, II | Tamoxifen + goserelin ± Zoledronate<br>Anastrozole + goserelin ± Zoledronate | 1,250 | 600 patients ongoing |
| IBCSG TEXT | T1-T3, pN0-N2 | Ovarian suppression + Exemestane<br>Ovarian suppression + Tamoxifen | 2,025 | Planned |
| IBCSG SOFT | T1-T3, pN0-N2 | Tamoxifen<br>Ovarian suppression + Tamoxifen<br>Ovarian suppression + Exemestane | 2,700 | Planned |

*DERIVED FROM:* ASCO Technology Assessments: Aromatase inhibitors as adjuvant therapy for women with hormone receptor positive breast cancer.

### *INTERGROUP 0101 STUDY OF ADJUVANT OVARIAN ABLATION*

In the best of all worlds, we would have had a fourth arm of CAF followed by tamoxifen. At the time, however, we weren't sure that we could accrue to that trial in a timely fashion and have something to talk about. The disease-free survival was better for the group receiving CAFZT compared to CAFZ. There was a borderline improvement with CAFZ compared to CAF.

An unplanned, retrospective subset analysis demonstrated that younger women — arbitrarily defined as under age 40 — seemed to do better with goserelin. Perhaps that's not surprising, because those women are the least likely to be made postmenopausal by chemotherapy. There's also a suggestion that women with premenopausal estrogen levels after chemotherapy were destined to derive benefit from goserelin. The big clinical question now is what to do with the young woman who is premenopausal at the end of chemotherapy.

*—Nancy E Davidson, MD*

### *ADJUVANT OVARIAN ABLATION IN A NONPROTOCOL SETTING*

In the ECOG study, patients received CAF, which everyone would consider state-of-the-art chemotherapy. In that trial, there was additional benefit from adding ovarian ablation to CAF — certainly among women under age 40. That study really changed my thinking.

If a woman with an ER-positive cancer receives adjuvant chemotherapy and does not stop menstruating, I routinely add an LHRH agonist with tamoxifen.

*—I Craig Henderson, MD*

### *LHRH AGONISTS PLUS TAMOXIFEN*

Combination endocrine therapy is a conceptual change for us. We eliminated that approach a couple of decades ago, perhaps because of small, inadequately powered trials that were clearly unable to detect the type of differences we can identify today with larger studies. With better research tools now available, we are returning to the concept of complete estrogen blockade — a strategy that started several decades ago with hypophysectomy and adrenalectomy.

*—Gabriel Hortobagyi, MD*

### *COMBINING LHRH AGONISTS AND AROMATASE INHIBITORS IN PREMENOPAUSAL WOMEN*

I'm very enthusiastic about the research strategy of looking at LHRH agonists with aromatase inhibitors. Extrapolating from the early data in postmenopausal breast cancer, which suggested that anastrozole may have superior efficacy compared to tamoxifen, this seems like a rational strategy to transfer to premenopausal women as well. The two issues are whether or not it is actually going to be efficacious, and what is the cost in terms of side effects. I wouldn't utilize this strategy outside the context of a clinical trial.

The adjuvant ovarian suppression trial that I am most enthusiastic about is SOFT — Suppression of Ovarian Function Trial. Premenopausal, ER-positive women who may or may not have received chemotherapy will be randomized to tamoxifen for five years, ovarian suppression/ablation plus tamoxifen, or ovarian suppression/ablation plus an aromatase inhibitor. This very interesting trial will help us address several issues. Does ovarian ablation or suppression add to tamoxifen? And if this is an important strategy, is it better to use tamoxifen or an aromatase inhibitor in those suppressed women?

*—Nancy E Davidson, MD*

### SELECT PUBLICATIONS


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