Adjuvant Endocrine Therapy Trials in Premenopausal Patients

Tamoxifen has an established role as adjuvant systemic therapy for premenopausal women with estrogen receptor-positive breast cancer. A number of major current clinical trials are evaluating the role of ovarian ablation/suppression combined with either tamoxifen or an aromatase inhibitor. A related and important issue is the impact of chemotherapy-related ovarian suppression in these patients. While it will be many years before data on disease-free and overall survival are available from these studies, an Austrian study reported by Gnant at the San Antonio Breast Cancer Symposium in 2002 demonstrated that bone loss associated with ovarian suppression combined with either tamoxifen or anastrozole can largely be avoided by the use of the bisphosphonate zoledronate. These data will be updated at this year's meeting.

RANDOMIZED ADJUVANT TRIAL OF TAMOXIFEN AND GOSERELIN VERSUS CYCLOPHOSPHAMIDE, METHOTREXATE AND FLUOROURACIL IN PREMENOPAUSAL PATIENTS

Protocol ID: ABCSG-05
Projected Accrual: 1,034 patients (Closed)

Eligibility	Patients with Stage I or II ER-/PR-positive breast cancer
ARM 1	Surgery (+RT) → goserelin q28d x 3 years + tamoxifen x 5 years
ARM 2	Surgery (+RT) → CMF on days 1, 8 q28d

ABCSG-05 TRIAL RESULTS: 5-YEAR FOLLOW-UP

	Goserelin + tamoxifen (n=511)	CMF (n=523)	*p*-value
Breast cancer-specific deaths	41 (8%)	51 (10%)	0.900
Relapses	88 (17%)	109 (21%)	0.0176
Local recurrences	24 (5%)	42 (8%)	0.0029
Cancer in opposite breast	3 (1%)	12 (3%)	0.0001

SOURCES: Gnant M. Presentation. San Antonio Breast Cancer Symposium, 2002.

Jakesz R et al. **Randomized adjuvant trial of tamoxifen and goserelin versus cyclophosphamide, methotrexate, and fluorouracil: Evidence for the superiority of treatment with endocrine blockade in premenopausal patients with hormone-responsive breast cancer – Austrian Breast and Colorectal Cancer Study Group Trial 5.** *J Clin Oncol* 2002;20(24):4621-27.

PHASE III STUDY COMPARING LHRH AGONIST WITH TAMOXIFEN OR ANASTROZOLE WITH OR WITHOUT ZOLEDRONATE

Protocol ID: ABCSG-AU12
Target Accrual: 1,250 (Open)

Eligibility	Premenopausal Hormone-responsive breast cancer, Stages I/II
ARM 1	Tamoxifen + goserelin
ARM 2	Anastrozole + goserelin
ARM 3	Tamoxifen + goserelin + zoledronate
ARM 4	Anastrozole + goserelin + zoledronate

SOURCE: Gnant M. San Antonio Breast Cancer Symposium, 2002;Abstract 12.

SOFT: SUPPRESSION OF OVARIAN FUNCTION TRIAL

Protocol ID: IBCSG 24-02
Target accrual: 3,000 patients (Open)

Eligibility	Premenopausal Estradiol (E_2) in the premenopausal range either after CT or without CT ER ≥10% and/or PgR ≥10%
ARM 1	Tamoxifen x 5 y
ARM 2	OFS + tamoxifen x 5 y
ARM 3	OFS + exemestane x 5 y

CT = chemotherapy; OFS = ovarian function suppression using triptorelin x 5 years or surgical oophorectomy or ovarian irradiation

SOURCE: www.ibcsg.org

TEXT: TAMOXIFEN AND EXEMESTANE TRIAL

Protocol ID: IBCSG 25-02
Target accrual: 1,845 patients (Open)

Eligibility	ER ≥10% and/or PgR ≥10% Candidates to begin GnRH analogue from the start of adjuvant therapy
ARM 1	GnRH ± CT + tamoxifen x 5 y
ARM 2	GnRH ± CT + exemestane x 5 y

CT = chemotherapy; GnRH = triptorelin x 5 years, but oophorectomy or radiation is allowed after 6 months

SOURCE: www.ibcsg.org

PERCHE: PREMENOPAUSAL ENDOCRINE RESPONSIVE CHEMOTHERAPY TRIAL

Protocol ID: IBCSG 26-02
Target Accrual: 1,750 patients (Open)

Eligibility:	Premenopausal ER ≥10% and/or PgR ≥10% Patients for whom CT is considered to be a randomized option (lower risk)
ARM 1	OFS + TEXT or T or E x 5 y
ARM 2	OFS + TEXT or T or E x 5 y + any CT

CT = chemotherapy; OFS = ovarian function suppression using triptorelin or surgical oophorectomy or radiation; TEXT = randomized trial comparing tamoxifen versus exemestane; T = tamoxifen; E = exemestane

SOURCE: www.ibcsg.org

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Love RR et al. **Her-2/neu overexpression and response to oophorectomy plus tamoxifen adjuvant therapy in estrogen receptor-positive premenopausal women with operable breast cancer.** *J Clin Oncol* 2003;21(3):453-7.

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OVARIAN SUPPRESSION IN THE TREATMENT OF PREMENOPAUSAL WOMEN

The IBCSG is coordinating a series of three nested trials: SOFT, PERCHE and TEXT. These trials address what is probably the most important conceptual question in premenopausal breast cancer right now: Beyond tamoxifen, does planned ovarian suppression benefit patients?

In particular, does it benefit women who receive chemotherapy or who don't receive chemotherapy, and if a woman experiences chemotherapy-related amenorrhea, does she still need ovarian suppression? We probably won't have the data for at least five or 10 years, but these are very important trials in which community oncologists can participate to answer these critical questions.

Currently, I consider ovarian suppression for two groups of patients. The first group consists of patients at high risk — multiple positive nodes, high-risk tumors — and women less than 35 or 40 years of age who may not go into menopause with chemotherapy. The other group includes women who are at the opposite end of the spectrum — very low-risk tumors, smaller tumors, node-negative — for whom the benefits of chemotherapy are very small. In these women, I present ovarian suppression as an option, not necessarily in addition to chemotherapy but perhaps even instead of it.

— Harold J Burstein, MD, PhD

ABCSG-AU12: LHRH AGONIST WITH TAMOXIFEN OR ANASTROZOLE WITH OR WITHOUT ZOLEDRONATE

The ABCSG-12 trial has four arms comparing goserelin/tamoxifen to goserelin/anastrozole with or without zoledronic acid. We included zoledronic acid because it's the most potent bisphosphonate pharmacokinetically, and we were concerned about the risk of osteoporosis with the aromatase inhibitors. Chemotherapy is only permitted as neoadjuvant therapy.

We did not include a tamoxifen-only arm because we tried to build upon our own results with goserelin/tamoxifen, which is now a national standard in Austria. I also believe tamoxifen-only treatment in premenopausal women is debatable because reasonable evidence indicates that you need to include some cytotoxic treatment.

The early results of ABCSG-12 demonstrate that the combination of goserelin/anastrozole, and goserelin/tamoxifen to a lesser degree, leads to significant deterioration in bone mineral density in premenopausal women and that this can be completely counteracted by zoledronic acid. Even though tamoxifen has an agonistic effect on bone, when combined with goserelin it results in a net reduction in bone density. The bone deterioration is more pronounced with anastrozole/goserelin, but the difference is not significant at this time. The main message is that zoledronic acid was able to completely prevent bone loss regardless of which hormone combination the patients received.

— Michael F Gnant, MD

The ABCSG trial 12 demonstrated increased bone density from zoledronate at six months and one year among patients treated with an LHRH agonist plus tamoxifen or anastrozole. We need to follow that study because these were early data from only about 100 patients, and it's a much larger trial than that.

I'm regularly asked, "Should I automatically administer a bisphosphonate when starting an aromatase inhibitor?" I prefer to monitor bone density because some patients won't need a bisphosphonate at all. Most of the patients aren't going to lose significant bone mineral density quickly, so you can do a baseline study, monitor patients and institute bisphosphonates at an appropriate time based on the WHO criteria for osteoporosis and osteopenia.

— Julie R Gralow, MD