Abstract
Chemotherapy (CT), tamoxifen (Tam), and ovarian ablation/suppression (OFS) are effective adjuvant therapies for premenopausal women with ER+ breast cancer. The aromatase inhibitor, exemestane (Exe), also warrants study in this population. In a BIG – North American Intergroup collaboration coordinated by IBCSG, 3 complementary trials (tailored treatment investigations) will be conducted to assess adjuvant therapies for premenopausal women with ER+ and/or PgR+, breast cancer (Goldhirsh et al. J Clin Oncol 2002;20:1956-1957). One trial is for women whose doctors ordinarily use Tam alone as endocrine therapy (either after surgery alone or after completion of CT), and 2 trials are for women whose doctors prefer to use OFS from the start of adjuvant therapy. The Suppression of Ovarian Function Trial (SOFT; IBCSG 25-02) is for women who receive OFS from the start of adjuvant therapy (randomization within 12 weeks of surgery). Randomization is to either Tam or Exe. In TEXT, OFS must be achieved by triptorelin for at least the first 6 months on study. CT, if given, should be started with the triptorelin and followed by the Tam or Exe. Use of CT is by investigator/patient choice or by randomized assignment in the PERCHE trial. The Premenopausal Endocrine Responsive Chemotherapy trial (PERCHE; IBCSG 26-02) features randomization either to OFS plus Tam or Exe, or to CT plus OFS plus Tam or Exe. Women for whom the role of adding CT to “complete estrogen blockade” is uncertain, should be offered PERCHE (to determine whether or not CT is used) and then TEXT (to determine choice of Tam or Exe). Activation is anticipated in May 2003. Target accruals are 3,000 patients in 5 years for SOFT, 1,845 patients within 4.5 years for TEXT, and 1,750 patients within 7 years for PERCHE. Pharmacia/Pfizer is the pharmacologic partner.

Background

- Breast cancer in women <35 years old has a better prognosis.
- Adjuvant chemotherapy offers substantial benefit in premenopausal women.
- Treatment results are similar in older and younger premenopausal women with endocrine-unresponsive tumors.
- Very young women with endocrine-responsive breast cancer have a statistically higher risk of relapse compared with older premenopausal women with endocrine-responsive tumors.
- Chemotherapy has less endocrine effects in women <35 compared with older premenopausal women.
- Endocrine therapies appear to be an essential component of an effective adjuvant therapy program.
- It is unknown if the addition of ovarian suppression to tamoxifen with or without chemotherapy improves outcomes in young women.
- The optimal methods of delivering adjuvant therapies to young premenopausal women are unknown, including:
  - The most effective approach to ovarian function suppression.
  - The effects of combined endocrine therapies and the choice of best agent (AI or SERM).
  - The effect of ovarian function suppression in combination with chemotherapy.
  - Appropriate timing, duration, and intensity of chemotherapy and endocrine therapies.
  - Impact of personal, family, professional, and quality of life issues involved in selection of therapy.

Exemestane as the Anti-Aromatase Agent of Choice
Exemestane has a promising clinical profile:
- Irreversible aromatase inactivator
- Lack of induction of aromatase enzyme activity.
- Beneficial effects on lipid profile and bone metabolism.

The favorable safety profile of exemestane is probably related to the steroidal nature of the drug and its 17-hydro metabolites. (Gusa P, San Antonio 2002. Abstract 41.5.)

Tailored Treatment Investigations

- Population: Premenopausal women (status determined by estradiol (E2) level). Patients who receive Tam or OFS plus Tam or Exe (25 mg daily for 5 years) plus OFS. The Tamoxifen and Exemestane Trial (TEXT; IBCSG 25-02) is for women who receive OFS from the start of adjuvant therapy (randomization within 12 weeks of surgery). Randomization is to either Tam or Exe. In TEXT, OFS must be achieved by triptorelin for at least the first 6 months on study. CT, if given, should be started with the triptorelin and followed by the Tam or Exe. Use of CT is by investigator/patient choice or by randomized assignment in the PERCHE trial. The Premenopausal Endocrine Responsive Chemotherapy trial (PERCHE; IBCSG 26-02) features randomization either to OFS plus Tam or Exe, or to CT plus OFS plus Tam or Exe. Women for whom the role of adding CT to “complete estrogen blockade” is uncertain, should be offered PERCHE (to determine whether or not CT is used) and then TEXT (to determine choice of Tam or Exe). Activation is anticipated in May 2003. Target accruals are 3,000 patients in 5 years for SOFT, 1,845 patients within 4.5 years for TEXT, and 1,750 patients within 7 years for PERCHE. Pharmacia/Pfizer is the pharmacologic partner.

- For women whose doctors prefer tamoxifen alone as endocrine therapy, either after surgery alone or after completion of chemotherapy:
  - SOFT: Suppression of Ovarian Function Trial (IBCSG 24-02).

- For women whose doctors prefer to use ovarian function (OFS) suppression from the start of adjuvant therapy. (Women for whom the role of adding chemotherapy to complete estrogen blockade is uncertain, should be offered PERCHE to determine whether or not chemotherapy is used and then TEXT to determine choice of tamoxifen or exemestane.):
  - TEXT: Tamoxifen and Exemestane Trial (IBCSG 25-02).  
  - PERCHE: Premenopausal Endocrine-Responsive Chemotherapy Trial (IBCSG 26-02).

- Pharmaceutical Partner: Pharmacia Corporation.

- Objective: To compare adjuvant therapies (ovarian function suppression, exemestane, tamoxifen, chemotherapy) for premenopausal women with endocrine-responsive breast cancer in terms of disease-free survival, overall survival, and quality of life.

Conclusions
The SOFT, TEXT, and PERCHE trials will investigate in premenopausal women with endocrine-responsive early breast cancer:
- The value of ovarian function suppression.
- The role of anti-aromatase agents combined with ovarian function suppression.
- The need for chemotherapy in addition to endocrine therapy.
- The impact of treatment on quality of life and safety.