

Tailored Treatment Investigations for Premenopausal Women with Endocrine Responsive (ER+ and/or PgR+) Breast Cancer: The SOFT, TEXT, and PERCHE Trials

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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 (Goldhirsch 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 24-02) is for women who remain premenopausal after surgery alone (randomization within 12 weeks) or after completion of adjuvant and/or neoadjuvant CT (randomization between 2 weeks and 6 months after the final CT dose). Premenopausal status is determined by estradiol (E₂) level. Patients who receive Tam or an aromatase inhibitor during the 6-month post-CT period are eligible. Randomized treatments are: Tam (20 mg daily for 5 years); Tam plus OFS (either triptorelin [GnRH analog] 3.75 mg by injection every 28 days for 5 years or surgical oophorectomy or ovarian irradiation); and 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 within 5 years for SOFT, 1845 patients within 4.5 years for TEXT, and 1750 patients within 7 years for PERCHE. Pharmacia/Pfizer is the pharmaceutical partner.

Background

(Goldhirsch et al. *J Natl Cancer Inst Monographs*. 2001;30:44-51)

- Breast cancer in women < 35 years old has a less favorable 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 hormonal 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

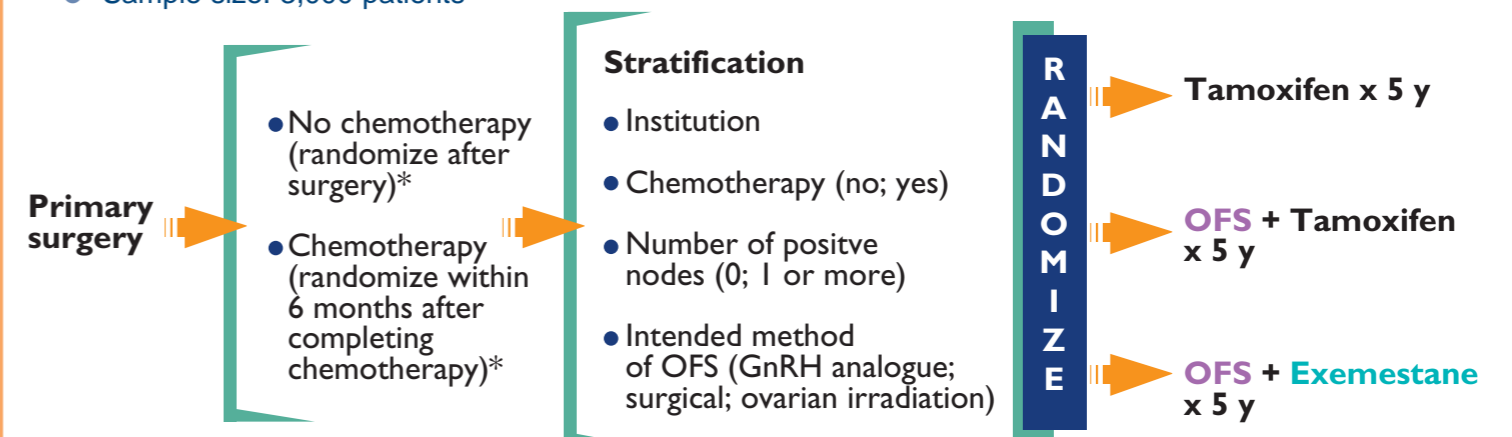
The favorable safety profile of exemestane is probably related to the steroidal nature of the drug and its 17-hydro metabolite. (Goss P. *San Antonio* 2002. Abstract 415.)

Tailored Treatment Investigations

- Population:** Premenopausal women (status determined by estradiol level) with endocrine-responsive (ER ≥ 10% and/or PgR ≥ 10%) early breast cancer
- 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)
- Participation:** North American Breast Intergroup and Breast International Group (BIG)
- Coordinating Group:** International Breast Cancer Study Group (IBCSG)
- 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

SOFT Trial

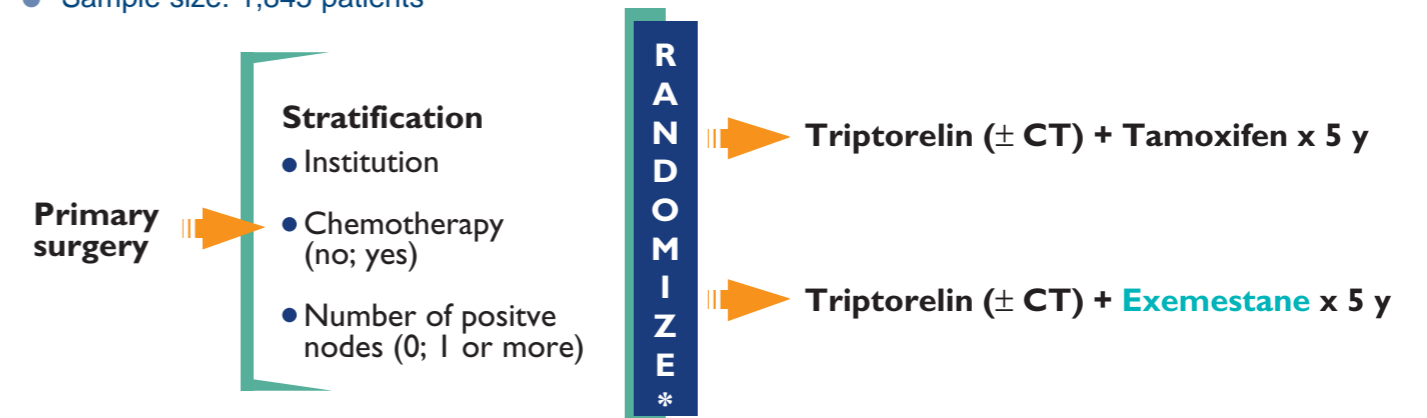
- For women who remain premenopausal after surgery alone (randomization within 12 weeks) or after completion of neoadjuvant and/or adjuvant chemotherapy (randomization between 2 weeks and 6 months after the final chemotherapy)
- Patients receiving tamoxifen or an anti-aromatase agent during the 6-month post-chemotherapy period are eligible
- Sample size: 3,000 patients



* Patients may have received tamoxifen or anti-aromatase agent prior to randomization. OFS = ovarian function suppression with GnRH analog (triptorelin 3.75 mg IM q 28 d x 5 y) or surgical oophorectomy or ovarian irradiation. Tamoxifen 20 mg po qd; exemestane 25 mg po qd.

TEXT Trial

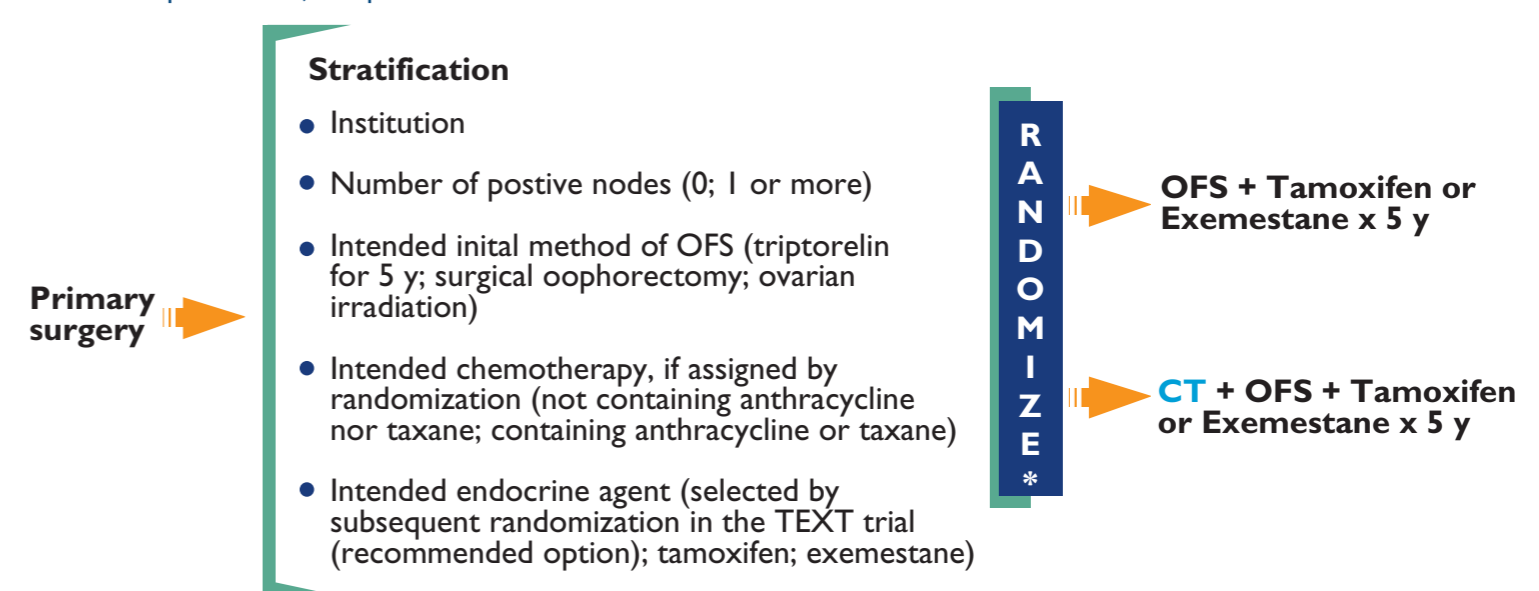
- For women who receive OFS from the start of adjuvant therapy (randomization within 12 weeks of surgery and prior to any adjuvant therapy)
- Chemotherapy, if given, must be started with the GnRH analog and followed by the tamoxifen or exemestane
- Use of chemotherapy is by investigator choice or by randomization in the PERCHE trial.
- Sample size: 1,845 patients



* Randomization prior to receiving any adjuvant systemic therapy. CT = chemotherapy by investigator choice or by randomization in the PERCHE trial. Triptorelin 3.75 mg IM q 28 d; tamoxifen 20 mg po qd; exemestane 25 mg po qd.

PERCHE Trial

- For women who receive OFS from the start of adjuvant therapy (randomization within 12 weeks of surgery and prior to any adjuvant therapy)
- For women for whom the role of adding chemotherapy to "complete estrogen blockade" is uncertain.
- In patients randomized to chemotherapy, chemotherapy must be started with the GnRH analog and followed by the tamoxifen or exemestane
- Sample size: 1,750 patients



*Randomization prior to receiving any adjuvant chemotherapy. CT = recommended chemotherapy: ≥ 2 months if an anthracycline is included or ≥ 4 months if no anthracycline is given; OFS = ovarian function suppression with GnRH analog (triptorelin 3.75 mg IM q 28 d x 5 y or surgical oophorectomy or ovarian irradiation). Exemestane 25 mg po qd; tamoxifen 20 mg po qd.

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