Title: Adjuvant treatment of premenopausal women with endocrine-responsive early breast cancer: Design of the TEXT and SOFT trials

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Trial Registration:

TEXT: Clinicaltrials.gov NCT00066703

SOFT: Clinicaltrials.gov NCT00066690

ABSTRACT

Objectives: In 2003 the International Breast Cancer Study Group (IBCSG) initiated the TEXT and SOFT randomized phase III trials to answer two questions concerning adjuvant treatment for premenopausal women with endocrine-responsive early breast cancer: 1-What is the role of aromatase inhibitors (AI) for women treated with ovarian function suppression (OFS)? 2-What is the role of OFS for women who remain premenopausal and are treated with tamoxifen?

Methods: TEXT randomized patients to receive exemestane or tamoxifen with OFS. SOFT randomized patients to receive exemestane with OFS, tamoxifen with OFS, or tamoxifen alone. Treatment was for 5 years from randomization.

Results: TEXT and SOFT successfully met their enrollment goals in 2011. The 5738 enrolled women had lower-risk disease and lower observed disease-free survival (DFS) event rates than anticipated. Consequently, 7 and 13 additional years of follow-up for TEXT and SOFT, respectively, were required to reach the targeted DFS events (median follow-up about 10.5 and 15 years). To provide timely answers, protocol amendments in 2011 specified analyses based on chronological time and median follow-up . To assess the AI question, exemestane+OFS versus tamoxifen+OFS, a combined analysis of TEXT and SOFT became the primary analysis (n=4717). The OFS question became the primary analysis from SOFT, the unique comparison of tamoxifen+OFS versus tamoxifen alone (n=2045). The first reports are anticipated in mid- and late-2014.

Conclusions: We present the original designs of TEXT and SOFT and adaptations to ensure timely answers to two questions concerning optimal adjuvant endocrine treatment for premenopausal women with endocrine-responsive breast cancer.

Keywords: premenopausal; endocrine-responsive; early breast cancer; adjuvant therapy; trial design

INTRODUCTION

In 2003 the International Breast Cancer Study Group (IBCSG) initiated a suite of three complementary tailored treatment investigations, the SOFT, TEXT and PERCHE trials, designed to answer questions concerning adjuvant treatment for premenopausal women with endocrine-responsive early breast cancer, what is the role of: 1) ovarian function suppression (OFS) for women who remain premenopausal and are treated with tamoxifen? 2) aromatase inhibitors for women treated with OFS? 3) chemotherapy for women treated with OFS plus oral endocrine therapy?

Adjuvant treatment for premenopausal women with endocrine-responsive (i.e., estrogen receptor (ER) and/or progesterone receptor (PgR)-positive) disease is often a matter of physician and patient choice, because of limited data on optimal approaches to treat individuals within this population. Tamoxifen, chemotherapy and ovarian ablation are individually effective adjuvant treatments for women under 50 years with ER-positive breast cancer[1,2]. Current recommendations include treatment with tamoxifen for at least 5 years. Five years of tamoxifen reduces the odds of recurrence by 40% when added to adjuvant chemotherapy[3,4]. Gonadotropin-releasing hormone (GnRH)-agonists show similar efficacy to chemotherapy in the absence of tamoxifen, but additional benefit from OFS for women who receive 5 years of tamoxifen with or without adjuvant chemotherapy is uncertain[5]. Aromatase inhibitors (AIs) are superior to tamoxifen for postmenopausal women with endocrine-responsive breast cancer, but in the high-estrogen environment of young women they would not be effective if women retain, or regain by hypothalamic and pituitary stimulation, ovarian function under AI therapy[6]. Treatment with OFS provides an opportunity to test whether AIs can also improve outcomes for premenopausal women.

The conduct of these randomized phase III trials required world-wide participation through collaboration of the Breast International Group (BIG) and the North American Breast Cancer Groups. Over 7.5-years from 2003 to 2011, 5742 premenopausal women were enrolled at over 500 centers in 27 countries on 6 continents in:

TEXT (Tamoxifen and Exemestane Trial): to determine the role of AIs for women who receive OFS from the start of adjuvant therapy **(Figure 1)**;

SOFT (Suppression of Ovarian Function Trial): to determine the role of OFS and the role of AIs for women who remain premenopausal after completion of (neo)adjuvant chemotherapy, or for whom tamoxifen alone following surgery is a reasonable treatment option **(Figure 1)**;

PERCHE (Premenopausal Endocrine-Responsive Chemotherapy): to determine the value of adding chemotherapy to combined endocrine therapy with OFS plus oral endocrine therapy.

Although SOFT and TEXT successfully enrolled the targeted number of patients, the trials have faced challenges. PERCHE closed prematurely in 2006 with only 29 patients enrolled[7]. Completion of TEXT and SOFT enrollment was anticipated within 5 years and first reporting about 7 years after the trials' initiation. However the characteristics of the enrolled patients differ from those anticipated in the protocols, and overall patient outcomes are better than expected, necessitating an adaptation of the trials' analysis plans. We present the original designs of TEXT and SOFT and the adaptations to overcome these challenges and ensure timely answers to questions concerning adjuvant treatment for premenopausal women with endocrine-responsive early breast cancer.

TRIAL DESIGNS

Design features common to TEXT and SOFT

As a planned suite of trials, a majority of trial design features were common to both trials. Details of eligibility, concomitant treatments, study procedures and randomization that were common to TEXT and SOFT are provided in **Appendix 1**.

Briefly, the trials enrolled premenopausal women with histologically-proven, resected, hormone receptor-positive (defined as ER≥10% and/or PgR≥10%) early invasive breast cancer. Premenopausal status was defined by estradiol levels in the premenopausal range according to institutional parameters. The tumor was to be confined to the breast and axillary lymph nodes without detected metastases elsewhere. Patients must have had proper local-regional treatment for primary breast cancer with no known residual loco-regional disease. Study visits were every 3 months during year one, every 6 months during the next 5 years, and yearly thereafter.

The oral endocrine therapy was either tamoxifen or the steroidal AI exemestane (Aromasin® [Pfizer]). OFS was by GnRH-analogue triptorelin (Decapeptyl® Depot [Ipsen] or Trelstar® Depot [Debio]) administered 4-weekly for 5 years, bilateral surgical oophorectomy, or bilateral ovarian irradiation (with biochemical confirmation of cessation of ovarian function after 2 months).

The primary endpoint was invasive disease-free survival (DFS), defined as the time from randomization to the first onset of the following events: invasive recurrence at local, regional, or distant sites; new invasive cancer in the contralateral breast; secondary (non-breast) malignancy; or death without prior cancer event.

The IBCSG coordinates the trials and is responsible for the study designs, data collection and management, medical review, data analysis and reporting. A Steering Committee oversees the trials and a Data and Safety Monitoring Committee (DSMC) reviews the trials semi-annually. Ethics committees and required health authorities of

each participating center approved the study protocol(s) and all patients gave written informed consent.

Trial-specific design features

TEXT

The TEXT randomized, two-arm, phase III trial was designed to investigate the efficacy of the AI exemestane with OFS, achieved by use of GnRH-analogue, compared with tamoxifen+OFS (**Figure 1**). TEXT focuses the AI question on premenopausal patients for whom OFS is indicated from the start of adjuvant therapy. Eligibility required enrollment within 12 weeks of definitive surgery and excluded patients who had already received any (neo)adjuvant chemotherapy or endocrine therapy.

Patients were randomized, with 1:1 allocation, to receive either exemestane or tamoxifen with OFS for 5 years from date of randomization. Randomization was stratified according to lymph node status and planned use of adjuvant chemotherapy (chemotherapy use and regimen was by investigator choice and was to start at the same time as GnRH-analogue; trastuzumab was allowed). Oral endocrine therapy was to start after adjuvant chemotherapy was completed, or approximately 6 to 8 weeks after initiation of GnRH-analogue, whichever was later. All patients started OFS with GnRH-analogue for at least 6 months, after which patients could opt to undergo bilateral oophorectomy or ovarian irradiation at any time.

SOFT

The SOFT randomized, three-arm, phase III trial was designed to investigate the role of OFS and the role of the AI exemestane (**Figure 1**), with three primary comparisons: tamoxifen+OFS versus tamoxifen alone; exemestane+OFS versus tamoxifen alone; and exemestane+OFS versus tamoxifen+OFS. SOFT focuses the OFS question on women who would be most likely to benefit, i.e., endocrine-responsive breast cancer with premenopausal status either after completion of (neo)adjuvant chemotherapy or following surgery alone.

Eligibility required enrollment either: (a) within 8 months of the final dose of chemotherapy once premenopausal status was confirmed by estradiol levels (e.g., patients with temporary chemotherapy-induced amenorrhea who regained premenopausal status within 8 months were eligible); or (b) within 12 weeks of definitive surgery if no adjuvant chemotherapy was planned. Because of the tamoxifen-alone arm, patients who would be likely to have bilateral oophorectomy within 5 years (e.g., *BRCA*1/2 gene carriers) were not eligible. Patients could have received adjuvant oral endocrine therapy (but not GnRH-analogues) for up to 8 months prior to randomization. The 8-month criterion was an early protocol amendment (increased from 6 months) to overcome logistical challenges of enrolling a patient who presented after regaining premenopausal status at a 6-months post-chemotherapy standard-of-care visit.

Patients were randomized, with 1:1:1 allocation, to receive tamoxifen alone, tamoxifen+OFS or exemestane+OFS for 5 years from the date of randomization. Randomization was stratified according to prior (neo)adjuvant chemotherapy, lymph node status and intended method of OFS. For patients randomized to receive OFS, the use of GnRH-analogue, bilateral oophorectomy or bilateral ovarian irradiation was by patient preference and patients who began with GnRH-analogue could opt to undergo surgery or irradiation at any time.

Original statistical design assumptions and sample size considerations

Each trial's statistical design assumed uniform accrual, exponential distribution of DFS, and two-sided logrank tests with trial-wise 0.05-level α-error. Each analysis would implement stratified logrank tests and Cox proportional hazard regression, and Kaplan-Meier estimates of the DFS distribution. Four interim and the final analysis were planned using O'Brien-Fleming boundaries.

TEXT

TEXT planned enrollment was 1845 patients. The design projected that 4.5 years of uniform accrual, plus 2.4 years of additional follow-up, would be sufficient to observe the target of 396 DFS events, which would provide 80% power to detect 25% reduction in hazard with exemestane+OFS versus tamoxifen+OFS (hazard ratio (HR)=0.75; 79.8% versus 74.1% 5-year DFS, respectively).

SOFT

SOFT planned enrollment was 3000 patients for the 3 arms. The design projected that 5 years of uniform accrual, plus 1.9 years of additional follow-up would be sufficient to observe the target of 783 DFS events (522 per pairwise comparison) to have 80% power to detect a 25% reduction in hazard relative to control 5-year DFS of 67% (HR=0.75; 74.1% versus 67.0% 5-year DFS; 2-sided α=0.0167). If tamoxifen+OFS would result in a 25% reduction in hazard to 74.1% 5-year DFS, then power was 68% to detect a further 25% reduction with exemestane+OFS to 79.8% 5-year DFS.

Derivation of 5-year DFS estimates

Because all women in TEXT would receive GnRH-analogue, they were expected to be younger premenopausal women, most of whom would also receive chemotherapy. For SOFT, predominantly very young women who remained premenopausal after adjuvant chemotherapy were expected to be enrolled. IBCSG estimated 51% 5-year DFS with chemotherapy alone, based on trials suggesting 40% and 70% 5-year DFS with chemotherapy alone for node-positive and node-negative disease, respectively, in women under 35-years with ER-positive tumors[8,9], and assuming about 60% of enrolled patients would have node-positive disease. A 40% reduction in risk of relapse by adding tamoxifen[3] was assumed, resulting in an estimated 5-year DFS of 67% among patients

treated with tamoxifen in the SOFT control arm. A 25% reduction in hazard by adding OFS to tamoxifen (74.1% 5-year DFS) and a further 25% reduction in the hazard with exemestane+OFS (79.8% 5-year DFS) were hypothesized. Additional details are provided in **Appendix 2**.

Planned combined analysis of TEXT and SOFT

From the outset, the protocols planned to combine the data of TEXT with the two arms of SOFT comparing exemestane+OFS versus tamoxifen+OFS. Differences in the two trials with respect to selection and treatment for women who received chemotherapy (i.e., TEXT enrolled patients following surgery and used concurrent GnRH-analogue and chemotherapy, while SOFT enrolled patients who remained premenopausal following chemotherapy and initiated OFS after completion of chemotherapy) were taken into account in the combined analysis plan. The statistical power of such a combined comparison (two-sided α=0.05) would be at least 88%, 98% and 99% to detect a 20%, 25%, and 30% reduction in hazard, respectively, with exemestane+OFS versus tamoxifen+OFS under the protocol assumptions regarding accrual duration and additional follow-up.

TRIAL PROGRESS

Patient enrollment and characteristics

TEXT

Between November 2003 and April 2011, TEXT enrolled 2672 patients **(Figure 2A)**. The median age was 43 years (interquartile range (IQR) 40-46) and 48% of patients had lymph node-positive disease. At randomization, 60% of patients had adjuvant chemotherapy planned **(Table 1)**.

By November 2007, 2039 of the planned 1845 patients had enrolled, and enrollment was suspended. Because of the faster-than-expected enrollment rate and lower-risk characteristics of enrolled patients than anticipated, Amendment 2 (July 2008) re-opened enrollment with an increased target sample size of 2639 patients. A revised estimate of 80% 5-year DFS in the tamoxifen+OFS control group (with corresponding 25% reduction in hazard to 84.6% 5-year DFS for exemestane+OFS) was hypothesized based on the 2007 overview meta-analysis of GnRH-analogues in which the 5-year breast cancer recurrence was around 18% among patients treated with GnRH-analogue plus tamoxifen[5]. With the observed enrollment pattern and revised hazards, the increased sample size was projected to reach the target of 396 DFS events within 0.5 years of the original design, or 7.4 years since first enrollment.

SOFT

Between December 2003 and January 2011, SOFT enrolled 3066 patients **(Figure 2B)**. The median age was 43 years (IQR, 38-47) and 35% of patients had node-positive disease **(Table 1)**. 53% of patients were randomized after prior (neo)adjuvant chemotherapy and their median time from surgery was 8 months (IQR, 6-10); the remaining 47% of patients were randomized after surgery at a median time from surgery of 2 months (IQR, 1.2-2.4). If randomized to OFS, 91% of patients planned GnRH-analogue as the initial method of OFS.

Adaptations in the statistical design and analysis plans

As of October 2010, the overall DFS event rates—blinded to treatment assignment—were substantially lower than originally anticipated: approximately 1.7% and 2% per year versus the protocol-specified 6% and 8% per year in TEXT and SOFT, respectively. IBCSG projected an additional 7 and 13 years of follow-up to observe the targeted 396 and 783 DFS events in TEXT and SOFT, respectively (at median follow-up of 10.5 and 15 years). Increasing the sample size could hasten reaching the required events, but finances constrained this possibility.

The Steering Committee considered this delay to be unacceptably long (reporting 14 and 20 years after first enrollment versus 6.9 years originally-anticipated). The Committee decided to change the timing of analysis from “event-driven” to “time-driven” with a planned data cut-off during the third quarter of 2013, when the median follow-up should be at least 6 and 5 years in TEXT and SOFT, respectively. It was recognized that an analysis with fewer events than targeted would substantially reduce statistical power for the original protocol-planned primary objectives (approximately 60% in TEXT and 35% in SOFT to detect 25% reductions in hazards, assuming the October 2010 event rates continued). Therefore amendments of the TEXT and SOFT protocols (July 2011) revised the analysis plans for the first reporting of the trial objectives:

1. AI question: the primary analysis comparing exemestane+OFS versus tamoxifen+OFS would implement the originally-planned combined analysis of TEXT and SOFT **(Figure 3A)**. The power of such a combined comparison (two-sided α=0.05 level) would be at least 95%, 84% and 63% to detect a 30%, 25% and 20% reduction in hazard, respectively, with exemestane+OFS.
2. OFS question: the primary analysis from SOFT would focus on the unique comparison of tamoxifen+OFS versus tamoxifen alone, tested at the two-sided α=0.05 level **(Figure 3B)**. IBCSG estimated power to be at least 80%, 69%, 52% and 34% to detect 33.5%, 30%, 25% and 20% reductions in hazard, respectively, with tamoxifen+OFS.

These power calculations assumed a data cut-off in the third quarter of 2013 and persistence of the October 2010 DFS event rates, which project 250 DFS events in

TEXT and 280 DFS events in SOFT (about 93 per group under the null hypothesis) at the time of data cut-off. The revised analysis plans removed planned interim efficacy analyses.

The Steering Committee's decision was endorsed by the DSMC. These committees did not receive, nor did the IBCSG Statistical Center have knowledge of, outcome data according to treatment group prior to this decision. The first report of the combined analysis of the AI question is anticipated in mid-2014. The report of the OFS question from SOFT is anticipated in late 2014 after about 6 additional months of follow-up and a median follow-up of at least 5 years is reached.

Patient follow-up will continue and updates of efficacy results are planned approximately every two years after the first report.

DISCUSSION

Clinical trial protocols for adjuvant treatment of breast cancer are developed years, sometimes decades, before the analysis and reporting of the trial results, and therefore the designs may need to be adapted over time. Although some trial adaptations are prospectively anticipated (e.g. group-sequential designs with interim efficacy/futility analyses), the need for mid-trial changes—to eligibility criteria, trial procedures, or statistical design—via protocol amendment is common. Despite our intentions to write the perfect trial protocol, reality may not match the assumptions and the best course of action is to change the plan. The European Medicines Agency (EMEA) guidelines anticipate trial adaptations[10-11]. With all adaptations, the ability of the trial to meet its primary objective must be maintained, and in particular for statistical changes, appropriate control of type I error and maintaining a high probability of answering the question (power) must be considered, while balancing the timeliness of reporting trial results that may have a clinical impact[10-12].

The analysis of an adjuvant breast cancer trial with a time-to-event primary endpoint such as DFS is dictated by the number of accumulated events. In the design phase we balance feasibility considerations concerning total sample size and duration of patient enrollment and follow-up to achieve the required number of events, which itself depends on the assumed event hazards and type I and II errors. An adaptation may be recommended based on an unblinded assessment of the treatment effect (i.e. by a DSMC at a planned interim analysis), a blinded assessment of the event rate as lower than expected, or an assessment of another feature such as compliance with treatment assignment.

Driving many trial adaptations is a lower-than-anticipated event rate[13-14]. Estimation of the event hazard is challenging, and the impact of over-estimating the hazard may not always be adequately considered during the design. Assumptions to estimate the

hazard rely on the results of past clinical trials, and are based on treatments, standards of care, and tumor assessment tools from ten to twenty years prior. Better outcomes may be observed because of earlier detection leading to earlier diagnosis and longer time to recurrence, improved loco-regional treatments, staging and measurement of hormone receptors, and increased use of targeted treatments such as trastuzumab for HER2-positive disease. Such changes may in particular reduce the early events observed in past trials in premenopausal endocrine-responsive disease. When the TEXT and SOFT trials were developed in 2002, there were limited mature outcome data from trials of premenopausal women with endocrine-responsive breast cancer treated with adjuvant tamoxifen. Tamoxifen had been tested predominantly in postmenopausal women, although the 1998 EBCTCG Overview provided evidence of its benefit for women under 50 years of age[3]. Therefore, assumptions for estimating 5-year DFS for SOFT and TEXT planning were based on trial data of premenopausal women who received no tamoxifen, to which the EBCTCG estimate of tamoxifen benefit was applied.

The effectiveness of tamoxifen in premenopausal women with endocrine-responsive early breast cancer has since been demonstrated. IBCSG Trial 13-93 (enrolled 1993-1999) reported in 2006 a 41% reduction in hazard from adding tamoxifen after chemotherapy (75% versus 62% 5-year DFS)[15]. A year earlier, E5188/INT0101 (enrolled 1989-1994) reported a 26% reduction at 9 years from adding tamoxifen to chemotherapy plus GnRH-analogue (68% versus 60% 9-year DFS)[16]. Notably, the 5-year DFS reported in these trials suggests that the assumed estimates for tamoxifen alone or tamoxifen+OFS after chemotherapy in patients with node-positive disease used in planning TEXT and SOFT were too pessimistic, and thus DFS events would accumulate more slowly than anticipated. The 2007 overview meta-analysis of GnRH analogues as adjuvant therapy[5] estimated 5-year breast cancer recurrence around 18% among predominantly node-positive patients treated with GnRH-analogue plus tamoxifen, with or without chemotherapy. More recently, the ABCSG-12 trial (enrolled 1999-2006) in a premenopausal endocrine-responsive patient population with node-positive disease in 30% and neoadjuvant chemotherapy in 5%, reported 88% DFS at median follow-up of about 5 years in patients treated with OFS plus oral endocrine therapy[17], which was much higher than 70% 5-year DFS originally-anticipated for their OFS plus tamoxifen control group[13].

A well-estimated event rate also requires accurate anticipation of the enrolled population, and in TEXT and SOFT the characteristics of enrolled patients were more favorable than anticipated. IBCSG expected younger patients—younger than the median age for premenopausal breast cancer and mostly under age 40—60% of whom would have node-positive disease and the vast majority treated with chemotherapy. By contrast, the median age in both trials is 43 years, in SOFT 35% had node-positive disease and only 53% received prior chemotherapy, and in TEXT 48% had node-

positive disease and 60% were planned for chemotherapy. Thus the unanticipated enrollment of lower-risk, older premenopausal patients would also lead to lower-than-expected event rates.

Many adjuvant breast cancer trials have adapted the trial design, sample size or analysis plan mid-course[13,14,16,18-21]. TEXT as well as E5188/INT0101[16] and ABCSG-12[13], also in premenopausal populations, increased sample size. But sample size increases are constrained by the feasibility of continuing enrollment and costs, whereas increasing duration of follow-up affects the timeliness of reporting results. Another option is to reconsider the clinically-meaningful effect size or type I and II errors. An increase of the effect size was also part of the ABCSG-12 adaptation, from HR=1.6 to HR=1.8[13]. The type I error has been adapted in TEXT and SOFT by removing planned interim efficacy analyses. APHINITY[22] recently addressed unanticipated patterns of enrollment composition and pace by limiting enrollment in Amendment B to patients with node-positive disease and increasing the sample size. Other prospectively planned combined analyses of two adjuvant therapy trials, leading to timely dissemination of results with good statistical power, include the ABCSG-8/ARNO trials[18] and NSABP-B39/NCCTG-N9831 trials[19]. The original designs of TEXT and SOFT made assumptions about the characteristics of enrolled patients and their outcomes that were overly pessimistic. Consequently the event rate was over-estimated and the duration of follow-up time to reach the targeted number of events for final analysis was under-estimated. The revised analysis plan will enable the initial results to be disseminated in 2014, whereas waiting for the originally-planned number of events would result in a delay of several years. This timeline will provide the oncology community with the long-anticipated results of these trials, and answer two important questions for the adjuvant treatment of premenopausal women with endocrine-responsive breast cancer.

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CONFLICTS OF INTEREST

None of the authors have any conflicts to declare.

REFERENCES

1. Early Breast Cancer Trialists Collaborative Group: Effects of adjuvant tamoxifen and of cytotoxic therapy on mortality in early breast cancer: an overview of 61 randomized trials among 28,896 women. N Engl J Med 1988;319:1681-1692.

2. Early Breast Cancer Trialists Collaborative Group: Systemic treatment of early breast cancer by hormonal, cytotoxic or immune therapy: 133 randomized trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Lancet 1992;339:1-15 and 71-85.

3. Early Breast Cancer Trialists Collaborative Group: Tamoxifen for early breast cancer: an overview of the randomised trials. Lancet 1998;351:1451-1467.

4. Fisher B, Dignam J, Wolmark N et al: Tamoxifen and chemotherapy for lymph node negative, estrogen receptor-positive breast cancer. J Natl Cancer Inst 1997;89:1673-1682.

5. LHRH-agonists in Early Breast Cancer Overview Group: Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. Lancet 2007;369:1711-1723.

6. Smith IE, Dowsett M, Yap Y-S, Walsh G, Lonning PE, Santen RJ, Hayes D. Adjuvant aromatase inhibitors for early breast cancer after chemotherapy-induced amenorrhoea: caution and suggested guidelines. J Clin Oncol 2006;24:2444-7.

7. Regan MM, Pagani O, Walley B, Torrisi R, Perez EA, Francis P, Fleming GF, Price KN, Thürlimann B, Maibach R, Castiglione-Gertsch M, Coates AS, Goldhirsch A, Gelber RD for the SOFT/TEXT/PERCHE Steering Committee and the International Breast Cancer Study Group. Premenopausal endocrine-responsive early breast cancer: Who receives chemotherapy? Ann Oncol 2008;19:1231-41

8. Goldhirsch A, Gelber RD, Yothers G, Gray RJ, Green S, Bryant J, Gelber S, Castiglione-Gertsch M, Coates AS: Adjuvant therapy for very young women with breast cancer: need for tailored treatments. JNCI Monographs 2001;30:44-51.

9. Goldhirsch A, Castiglione M, Gelber RD for the International Breast Cancer Study Group. A single perioperative adjuvant chemotherapy course for node-negative breast cancer: five-year results of Trial V. J Natl Cancer Inst Monographs 1992; 11: 89-96.

10. European Medicines Agency. CHMP/ICH/363/96; September 1998: ICH Topic E9. Statistical Principles for Clinical Trials. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000366.jsp&mid=WC0b01ac0580032ec4 (Accessed 23 February 2013).

11. European Medicines Agency. CHMP/EWP/2459/02; 18 Oct 2007: Reflection paper on methodological issues in confirmatory clinical trials planned with an adaptive design. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000366.jsp&mid=WC0b01ac0580032ec4 (Accessed 23 February 2013).

12. Chuang-Stein C, Anderson K, Gallo P, Collins S. Sample size reestimation: A review and recommendations. Drug Info J 2006;40:475-84.

13. Gnant M, Mlineritsch B, Schippinger W, Luschin-Ebengreuth G, Pöstlberger S, Menzel C, Jakesz R, Seifert M, Hubalek M, Bjelic-Radisic V, Samonigg H, Tausch C, Eidtmann H, Steger G, Kwasny W, Dubsky P, Fridrik M, Fitzal F, Stierer M, Rücklinger E, Greil R; ABCSG-12 Trial Investigators, Marth C. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. N Engl J Med 2009;360:679-91. (with Supplementary Material accessed 23 February 2013: http://www.nejm.org/doi/suppl/10.1056/NEJMoa0806285/suppl_file/nejm_gnant_679sa1.pdf)

14. Coleman RE, Marshall H, Cameron D, Dodwell D, Burkinshaw R, Keane M, Gil M, Houston SJ, Grieve RJ, Barrett-Lee PJ, Ritchie D, Pugh J, Gaunt C, Rea U, Peterson J, Davies C, Hiley V, Gregory W, Bell R; AZURE Investigators. Breast-cancer adjuvant therapy with zoledronic acid. N Engl J Med 2011;365:1396-405.

15. International Breast Cancer Study Group. Tamoxifen after adjuvant chemotherapy for premenopausal women with lymph node-positive breast cancer: IBCSG Trial 13-93. J Clin Oncol 2006;24:1332-1341.

16. Davidson NE, O'Neill AM, Vukov AM, Osborne CK, Martino S, White DR, Abeloff MD. Chemoendocrine therapy for premenopausal women with axillary lymph node-positive, steroid hormone receptor-positive breast cancer: results from INT 0101 (E5188). J Clin Oncol 2005;23:5973-82.

17. Gnant M, Mlineritsch B, Stoeger H, Luschin-Ebengreuth G, Heck D, Menzel C, Jakesz R, Seifert M, Hubalek M, Pristauz G, Bauernhofer T, Eidtmann H, Eiermann W, Steger G, Kwasny W, Dubsky P, Hochreiner G, Forsthuber EP, Fesl C, Greil R; Austrian Breast and Colorectal Cancer Study Group. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial. Lancet Oncol 2011;12:631-41.

18. Jakesz R, Jonat W, Gnant M, Mittlboeck M, Greil R, Tausch C, Hilfrich J, Kwasny W, Menzel C, Samonigg H, Seifert M, Gademann G, Kaufmann M, Wolfgang J; ABCSG and the GABG. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. Lancet 2005;366(9484):455-62.

19. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson NE, Tan-Chiu E, Martino S, Paik S, Kaufman PA, Swain SM, Pisansky TM, Fehrenbacher L, Kutteh LA, Vogel VG, Visscher DW, Yothers G, Jenkins RB, Brown AM, Dakhil SR, Mamounas EP, Lingle WL, Klein PM, Ingle JN, Wolmark N. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005; 353:1673-84.

20. Zujewski JA, Kamin L. Trial assessing individualized options for treatment for breast cancer: the TAILORx trial. Future Oncol 2008;4:603-610.

21. Hormone Therapy With or Without Combination Chemotherapy in Treating Women Who Have Undergone Surgery for Node-Negative Breast Cancer (The TAILORx Trial)**.** ClinicalTrials.gov NCT00310180 (accessed 23 February 2013).

22. A Randomized Multicenter, Double-blind, Placebo-controlled Comparison of Chemotherapy Plus Trastuzumab Plus Placebo Versus Chemotherapy Plus Trastuzumab Plus Pertuzumab as Adjuvant Therapy in Patients With Operable HER2-positive Primary Breast Cancer. ClinicalTrials.gov NCT01358877 (accessed 13 August 2013).

Table 1. Treatment assignment and stratification factors for patients randomized in TEXT and SOFT.

	TEXT	SOFT
Number of patients randomized	*2672*	*3066*
Treatment Assignment		
Tamoxifen 5 years	--	1021 (33%)
Tamoxifen plus OFS 5 years	1334 (50%)	1024 (33%)
Exemestane plus OFS 5 years	1338 (50%)	1021 (33%)
Stratification Factors		
Chemotherapy use		
Prior (neo)adjuvant chemotherapy	--	1636 (53%)
Adjuvant chemotherapy planned	1592 (60%)	
Lymph node positive (including pN1mi)	1278 (48%)	1078 (35%)
Intended method of OFS at randomization*		
GnRH-analogue (triptorelin)	2672 (100%)	2783 (91%)
Surgical oophorectomy	--	239 (8%)
Ovarian irradiation	--	44 (1%)

* In SOFT, intended method *if* randomized to receive OFS

Abbreviations: TEXT=Tamoxifen and Exemestane Trial; SOFT=Suppression of Ovarian Function Trial; OFS=ovarian function suppression; GnRH=gonadotropin-releasing hormone.

FIGURE CAPTIONS

Fig. 1 Designs for the TEXT (IBCSG 25-02/BIG 3-02) and SOFT (IBCSG 24-02/BIG 2-02) international, randomized phase III clinical trials

Abbreviations: TEXT=Tamoxifen and Exemestane Trial; SOFT=Suppression of Ovarian Function Trial; Chemo=chemotherapy; OFS=ovarian function suppression; i.m.=intramuscular; p.o.=by mouth

Fig. 2 Enrollment in the TEXT and SOFT trials. (A) TEXT: Between November 2003 and April 2011, TEXT enrolled 2672 patients; enrollment was suspended 1 December 2007 and re-opened by protocol amendment released in July 2008, with enrollment restarted in December 2008. (B) SOFT: Between December 2003 and January 2011, SOFT enrolled 3066 patients; as of January 2010 enrollment was limited to sites participating in substudies.

Abbreviations: TEXT=Tamoxifen and Exemestane Trial; SOFT=Suppression of Ovarian Function Trial.

Fig. 3 The two planned primary efficacy analyses to answer questions concerning adjuvant treatment for premenopausal women with endocrine-responsive early breast cancer: (A) What is the role of aromatase inhibitors? Comparison of exemestane+OFS versus tamoxifen+OFS by combining the common treatment arms of the TEXT and SOFT trials (N=4717 randomized). (B) What is the role of OFS for women who remain premenopausal? Comparison of tamoxifen+OFS versus tamoxifen alone in SOFT (N=2045 randomized)

Abbreviations: TEXT=Tamoxifen and Exemestane Trial; SOFT=Suppression of Ovarian Function Trial; Chemo=chemotherapy; OFS=ovarian function suppression

SUPPLEMENTARY MATERIAL

1-Design features common to TEXT and SOFT
2-Derivation of 5-year DFS estimates for sample size considerations
3-Participating Centers and Groups

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SUPPLEMENTARY MATERIAL

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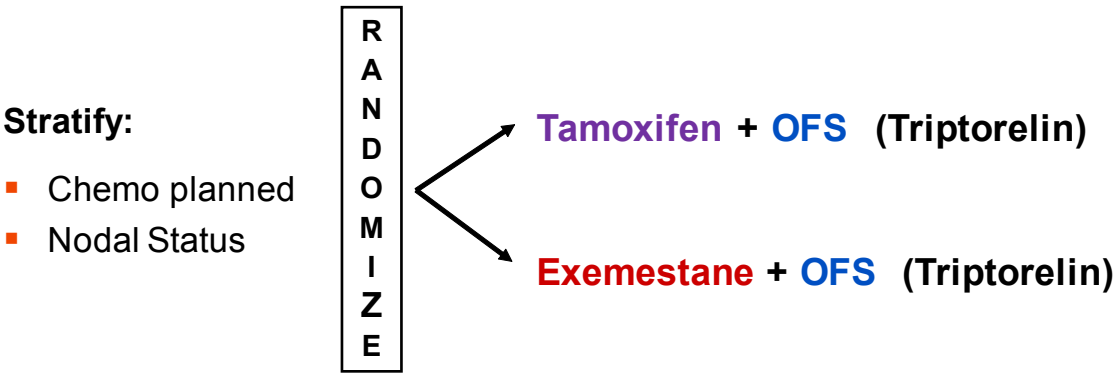
TEXT

Population: Premenopausal women with endocrine-responsive early breast cancer who should receive OFS from the start of adjuvant therapy.

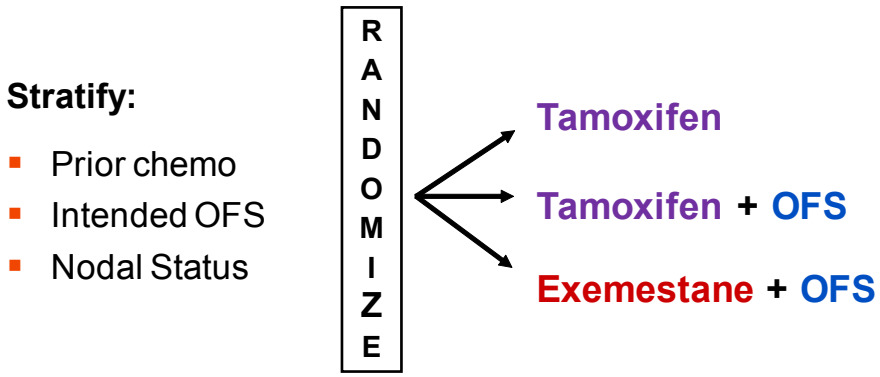
Enrollment November 2003 through April 2011
Final accrual: 2672 (revised target: 2639)



SOFT

Population: Premenopausal women with endocrine-responsive early breast cancer who remain premenopausal after chemotherapy or after surgery alone.

Enrollment December 2003 through January 2011
Final accrual: 3066 (target: 3000)



All treatment arms were 5-year durations from randomization.
Tamoxifen 20 mg/day p.o.; **Exemestane** 25 mg/day p.o.
OFS:
TEXT, all patients started OFS with triptorelin (3.75 mg i.m. every 28±3 days) for at least 6 months, after which patients could opt to undergo bilateral oophorectomy or bilateral ovarian irradiation at any time.
SOFT, from the time of randomization, the use of triptorelin, bilateral oophorectomy or bilateral ovarian irradiation was by patient preference, and patients who began with triptorelin could opt to undergo bilateral oophorectomy or bilateral ovarian irradiation at any time.

A

TEXT		SOFT	
		Tamoxifen	(N=1021)
Tamoxifen + OFS	(N=1334)	Tamoxifen + OFS	(N=1024)
Exemestane + OFS	(N=1338)	Exemestane + OFS	(N=1021)

B

TEXT		SOFT	
		Tamoxifen	(N=1021)
Tamoxifen + OFS	(N=1334)	Tamoxifen + OFS	(N=1024)
Exemestane + OFS	(N=1338)	Exemestane + OFS	(N=1021)