Original article

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

Meredith M. Regan a, b, *, Olivia Paganic, d, Gini F. Fleming e, Barbara A. Walley f, Karen N. Price a, g, Manuela Rabaglio h, i, Rudolf Maibach h, Barbara Ruepp i, Alan S. Coates c, j, Aron Goldhirsch c, k, Marco Colleoni c, k, Richard D. Gelber a, b, g, l, Prudence A. Francis c, m, n, on behalf of the International Breast Cancer Study Group (IBCSG) and the SOFT and TEXT Investigators 1

a International Breast Cancer Study Group Statistical Center, Dana-Farber Cancer Institute, Boston, MA, USA
b Harvard Medical School, Boston, MA, USA
c International Breast Cancer Study Group, Bern, Switzerland

d Institute of Oncology of Southern Switzerland (IOSI), Ospedale Italiano, Viganello, Lugano, Switzerland and Swiss Group for Clinical Cancer Research (SAKK), Bern, Switzerland

e Alliance for Clinical Trials in Oncology and University of Chicago Hospitals, Chicago, IL, USA
f National Cancer Institute of Canada Clinical Trial Group and Tom Baker Cancer Centre, Calgary, Alberta, Canada
g Frontier Science and Technology Research Foundation, Boston, MA, USA
h International Breast Cancer Study Group Coordinating Center, Bern, Switzerland

* Corresponding author. Harvard Medical School, Boston, MA, USA. Tel.: +1 617 632 2471; fax: +1 617 632 5444.
E-mail addresses: mregan@jimmy.harvard.edu (M.M. Regan), olivia.pagani@ibcsg.org (O. Pagani), gfleming@medicine.bsd.uchicago.edu (G.F. Fleming), barbara.walley@albertahealthservices.ca (B.A. Walley), price@jimmy.harvard.edu (K.M. Price), manuela.rabaglio@ibcsg.org (M. Rabaglio), rudolf.maibach@ibcsg.org (R. Maibach), barbara.ruepp@ibcsg.org (B. Ruepp), alan.coates@ibcsg.org (A.S. Coates), aron.goldhirsch@ibcsg.org (A. Goldhirsch), marco.colleoni@ieo.it (M. Colleoni), gelber@jimmy.harvard.edu (R.D. Gelber), prue.francis@petermac.org (P.A. Francis).

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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, assessing the unique comparison of tamoxifen + OFS versus tamoxifen alone (n = 2045). The first reports are anticipated in mid- and late-2014.
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 [12]. 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 worldwide 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 (Fig. 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 (Fig. 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 [Debiopharm]) 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 (Fig. 1). TEXT focuses the AI question on premenopausal patients for whom OFS is indicated from the start of adjuvant therapy. Eligibility required

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

Trial Registration

TEXT: Clinicaltrials.gov NCT00066703
SOFT: Clinicaltrials.gov NCT00066690

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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-analog; trastuzumab was allowed). Oral endocrine therapy was to start after adjuvant chemotherapy was completed, or approximately 6–8 weeks after initiation of GnRH-analog, whichever was later. All patients started OFS with GnRH-analog for at least 6 months, after which patients could opt to undergo bilateral oophorectomy or bilateral ovarian irradiation at any time.

SOFT

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

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., BRCA1/2 gene carriers) were not eligible. Patients could have received adjuvant oral endocrine therapy (but not GnRH-analogs) 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

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)

Stratify:

- Chemo planned
- Nodal Status

Tamoxifen + OFS (Triptorelin)

Exemestane + OFS (Triptorelin)

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)

Stratify:

- Prior chemo
- Intended OFS
- Nodal Status

Tamoxifen

Tamoxifen + OFS

Exemestane + OFS

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.

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.
according to prior (neo)adjuvant chemotherapy, lymph node status and intended method of OFS. For patients randomized to receive OFS, the use of GnRH-analog, bilateral oophorectomy or bilateral ovarian irradiation was by patient preference and patients who began with GnRH-analog 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-analog, 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-analog 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 (Fig. 2(A)). 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- analogs in which the 5-year breast cancer recurrence was around 18% among patients treated with GnRH-analog 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 (Fig. 2(B)). 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 DFS, 91% of patients planned GnRH-analog as the initial method of DFS.

**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 unacceptable 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 + DFS versus tamoxifen + DFS would implement the originally-planned combined analysis of TEXT and SOFT (Fig. 3(A)). The power of such a combined comparison (two-sided \( \alpha = 0.05 \) level) would be at least 95%, 84% and 63% to detect a 30%, 25% and 20% reduction in hazard, respectively, with exemestane + DFS.

2. DFS question: the primary analysis from SOFT would focus on the unique comparison of tamoxifen + DFS versus tamoxifen alone, tested at the two-sided \( \alpha = 0.05 \) level (Fig. 3(B)). 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 + DFS.

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 planned 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 DFS 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—via 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-analog (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-negative 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-analogs as adjuvant therapy \[5\] estimated 5-year breast cancer recurrence around 18% among predominantly node-positive patients treated with GnRH-analog plus tamoxifen, with or without chemotherapy. More recently, the ABCSG–12 trial (enrolled 1999–2006) in a premenopausal endocrine-responsive patient population with node-negative disease in 30% and no adjuvant 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-negative 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 \[13,14,16–21\], 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/NCCCTG-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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Conflict of interest statement

None of the authors have any conflicts to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jbreast.2013.08.009.

References


SUPPLEMENTARY MATERIAL

Appendix 1 Design features common to TEXT and SOFT

As a planned suite of trials, a majority of trial design features were common to the trials, and are summarized below.

Eligibility

The trials enrolled premenopausal women with histologically-proven, resected, hormone receptor-positive (defined as \( \text{ER} \geq 10\% \) and/or progesterone receptor (PgR) \( \geq 10\% \) by immunohistochemistry at local institutions) early invasive breast cancer. Premenopausal status was defined by estradiol levels in the premenopausal range according to institutional parameters (the exception to biochemical confirmation was patients who had been menstruating regularly and had not used any form of hormonal contraception or any other hormonal treatments during the 6 months prior to randomization). The tumor was to be confined to the breast and axillary lymph nodes without detected metastases elsewhere, with the exception of tumor in internal mammary chain nodes by sentinel node procedure. Patients must have had proper surgery for primary breast cancer with no known clinical residual loco-regional disease, including documentation of negative margins of resection after breast-conserving surgery; radiotherapy was optional after mastectomy and was required after breast-conserving surgery. Either axillary lymph node dissection or a negative axillary sentinel node biopsy (pN0(sn) or pN1mi) was required; those patients with positive sentinel nodes must have had either an axillary dissection or radiation of axillary nodes. Radiation therapy was according to accepted guidelines and local standards. Patients with synchronous bilateral invasive disease (diagnosed histologically within 2 months) were eligible, provided the bilateral disease met all eligibility criteria.

Submission of pathology material for confirmation of hormone receptors by the IBCSG Central Pathology Office was mandatory (consent to use for future research was optional).

The exclusion criteria included: previous bilateral oophorectomy or ovarian irradiation; pregnant or lactating at the time of randomization or desiring pregnancy within 5 years; use of tamoxifen or other selective estrogen receptor modulator or hormone replacement therapy within one year prior to breast cancer diagnosis; previous or concurrent invasive malignancy cancer (other than adequately treated basal-cell or squamous-cell carcinoma of the skin, \textit{in situ} non-breast carcinoma without invasion, contra- or ipsilateral \textit{in situ} breast carcinoma, or selected non-breast invasive malignancies diagnosed at least 5 years prior to randomization without recurrence [stage I papillary thyroid cancer, stage Ia cervical carcinoma, stage Ia or Ib endometrioid endometrial cancer, borderline or stage I ovarian cancer]); non-malignant systemic disease that would prevent prolonged follow-up.
**Endocrine Treatment**

In each trial, the oral endocrine therapy was either tamoxifen (20 mg orally daily, by prescription) or the steroidal aromatase inhibitor exemestane ([Aromasin®; Pfizer] 25 mg orally daily, by study supply) until 5 years from the date of randomization. Ovarian function suppression (OFS) was by gonadotropin-releasing hormone (GnRH) analogue triptorelin (supplied by the study either as Decapeptyl® Depot [Ipsen] or Trelstar® Depot [Debio]; 3.75 mg by intramuscular injection) every 28±3 days until 5 years from date of randomization, or bilateral surgical oophorectomy or bilateral ovarian irradiation (with biochemical confirmation of cessation of ovarian function after 2 months).

**Concomitant treatments**

Additional hormonal and concurrent investigational treatments were not allowed, though prior investigational agents were allowed. Bisphosphonates were not allowed except in the case that osteoporosis developed, or if the patient participated in a trial testing bisphosphonates in the adjuvant breast cancer setting. Trastuzumab was allowed when indicated.

**Study procedures**

Study visits were every 3 months during year one, every 6 months during the next 5 years, and yearly follow-up thereafter. Study visits required physical exam and collection of adverse events and concomitant medications, with laboratory tests and imaging as medically indicated. Targeted adverse events (Allergic Reaction/Hypersensitivity, Injection Site Reaction, Hot Flashes/Flushes, Mood Alteration-Depression, Sweating, Insomnia, Fatigue, Hypertension, Cardiac Ischemia/Infarction, Thrombosis/Embolism, Nausea, Musculoskeletal Symptoms, Osteoporosis, Fractures, Vaginal Dryness, Libido Decrease, Dyspareunia, Urinary Incontinence, central nervous system (CNS) Cerebrovascular Ischemia, CNS Hemorrhage) and other grade 3 or higher adverse events of endocrine therapies were collected using Common Terminology Criteria for Adverse Events (CTCAE) v3.0. Participation in quality-of-life studies was required and spanned every 6 or 12 months between randomization and 6 years after randomization.

**Randomization**

Randomization was performed using a web-based system, either by a cooperative group randomization center or directly from the participating center, with the use of permuted blocks and was stratified according to factors specific to the trial, with institutional balancing.

**Endpoints**

The primary endpoint was invasive disease-free survival (DFS), defined as the time from randomization to the first suspicion of the following events: invasive recurrence at local, regional, or distant sites; a new invasive cancer in the contralateral breast; any
secondary (non-breast) malignancy; or a death without prior cancer event. Secondary endpoints included overall survival, breast cancer-free interval, and distant recurrence-free interval\(^1\).

REFERENCES

Appendix 2 Derivation of 5-year DFS estimates for sample size considerations

A baseline 5-year DFS was estimated under the assumption that TEXT and SOFT would enroll predominantly younger premenopausal women, most receiving chemotherapy prior to enrollment (SOFT) or concurrent with GnRH analogue (TEXT), and about 60% having lymph node-positive disease. SOFT in particular aimed to focus the OFS question on the subset of women who would be most likely to benefit, i.e., women with endocrine-responsive disease plus premenopausal status either after completion of (neo)adjuvant chemotherapy or following surgery alone. These women were anticipated to be on average younger than the median age for premenopausal breast cancer and most likely under 40 years of age.

Though SOFT entered patients who did not receive chemotherapy, IBCSG did not anticipate enrolling many such patients. From IBCSG Trial VIII (enrolled 1990-1999), 15.6% of patients maintained menses following 6 cycles CMF chemotherapy, ranging from 78% of patients aged ≤35 years to 10% of patients aged 41 to 45 years. Patients who remain premenopausal following chemotherapy are likely to have an outcome similar to that observed for patients ≤35 years, as the majority of patients in this age group maintain menses. A review of data from IBCSG, NSABP, ECOG and SWOG indicated that women ≤35 years with ER-positive, lymph node-positive disease who were treated with chemotherapy alone had about a 40% 5-year DFS, and assuming a 40% reduction in risk of relapse by adding tamoxifen, estimated 5-year DFS of 58%. This estimate agrees with the 59% 5-year DFS based on 109 women in CALGB 9344, ≤35 years with ER positive, lymph node-positive disease who received chemotherapy plus tamoxifen [personal communication]. Premenopausal women with ER-positive, lymph node-negative disease in IBCSG Trial V had a 70% 5-year DFS without tamoxifen. Adding tamoxifen should improve this to 81%. Assuming that about 60% of patients enrolled in this trial would have lymph node-positive disease, 67% 5-year DFS was estimated for the tamoxifen-alone control group in SOFT (with or without prior chemotherapy).

We hypothesized a 25% additional risk reduction associated with GnRH analogue, resulting in an estimated 74.1% 5-year DFS for tamoxifen+OFS. A further 25% risk reduction for exemestane+OFS, to 79.8% 5-year DFS, was assumed.

REFERENCES


Appendix 3 Participating Centers and Groups

Trial IBCSG 25-02 / BIG 3-02 / TEXT and IBCSG 24-02 / BIG 2-02 / SOFT


IBCSG Scientific Committee: A. Goldhirsch, A.S. Coates, Marco Colleoni (Co-Chairs)


IBCSG Coordinating Center, Bern, Switzerland: A. Hiltbrunner (Director), R. Kammler, R. Maibach, M. Rabaglio, B. Ruepp, P. Sicher, S. Roux

IBCSG Statistical Center, Dana-Farber Cancer Institute, Boston, MA, USA: R.D. Gelber (Director), M.M. Regan (Group Statistician), J. Aldridge, M. Bonetti, A. Giobbie-Hurder, K. Gray, H. Huang, K.N. Price, L. Zickl


IBCSG Central Pathology Office, European Institute of Oncology, Division of Pathology, Milan, Italy: G. Viale, D. Lepanto, O. Pala

IBCSG Quality of Life Office: J. Bernhard, K. Ribi

National Cancer Institute: J. Abrams, J. Zujewki

NCI Clinical Trials Support Unit (CTSU)/Westat: M. Hering, M. Greene, A. Nelson, M. Balois Ouellette, S. Riordan

ALMAC: W. Mahon, E. Whitney, J. Bryant

CTSU Regulatory Office: R. Catalano, D. Marinucci, B. Niewood, R. Lambersky

Alliance (CALGB) Pathology Coordinating Office, Ohio State University, Columbus, OH, USA: W. Frankel, S. Jewell

Dana-Farber Cancer Institute, Boston, MA, USA (IND): E. Winer, J. Savoie, J. Doherty

Pfizer Study Support: B. Campanelli, J.A. Graham, B. Klingele, A. Nieto

Ipsen Study Support: E. Chetaille, J. Amauri Soares, C. Descot, S. Hemont-Dacosta

TEXT TRIAL

BREAST INTERNATIONAL GROUP (BIG)

International Breast Cancer Study Group (IBCSG)
Australia and New Zealand Breast Cancer Trials Group (ANZBCTG)
Australia
Coffs Harbour Base Hospital, Coffs Harbour, New South Wales
Liverpool Hospital, Liverpool, New South Wales
Macarthur Cancer Therapy Centre, Campbelltown, New South Wales
Calvary Mater Newcastle, Waratah, New South Wales
Riverina Cancer Care Centre, Wagga Wagga, New South Wales
Tamworth Rural Referral Hospital, Tamworth, New South Wales
Tweed Hospital, Tweed Heads, New South Wales
Lismore Base Hospital, Lismore, New South Wales
Royal Brisbane and Women’s Hospital, Herston, Queensland
Flinders Medical Centre, Bedford Park, South Australia
Launceston General Hospital, Launceston, Tasmania
Royal Hobart Hospital, Hobart, Tasmania
Austin Health, Heidelberg, Victoria
Box Hill Hospital, Box Hill, Victoria
Victorian Breast and Oncology Care, East Melbourne, Victoria
Maroondah Hospital, Ringwood East, Victoria
Peter MacCallum Cancer Centre, East Melbourne, Victoria
St. Vincent’s Hospital Melbourne, Fitzroy, Victoria
Royal Perth Hospital, Perth, Western Australia

Belgium
Institute Jules Bordet, Brussels
Centre Hospitalier Peltzer-La Tourelle, Verviers
Centre Hospitalier Regional de la Citadelle, Liège
Centre Hospitalier Universitarie Sart Tilman, Liège
U.Z. Gasthuisberg, Leuven
Centre Hospitalier Regional de Huy, Huy

Egypt
National Cancer Institute, Cairo University, Cairo
Cairo Oncology Centre, Cairo

Hungary
National Institute of Oncology, Budapest

India
Tata Memorial Hospital, Mumbai

Italy
Dipartimento di Oncologia, Azienda Ospedaliero-Università di Udine, Udine, Italy
Centro di Riferimento Oncologico, Aviano
Fondazione Salvatore Maugeri, Pavia
Istituto Europeo di Oncologia, Milano
Ospedale degli Infermi, Rimini
Ospedale di Circolo e Fondazione Macchi, Varese
Ospedali Riuniti di Bergamo, Bergamo
Sandro Pitigliani Medical Oncology Unit, Hospital of Prato, Prato
Spedali Civili, Brescia
Unita Operativa de Medicina Oncologica, Ospedale Ramazzini, Carpi
Azienda Sanitaria di Bolzano, Balzano
Istituto Clinico Humanitas, Rozzano

Peru
Instituto de Enfermedades Neoplásicas, Lima

Slovenia
Institute of Oncology, Ljubljana

South Africa
Sandton Oncology Centre, Johannesburg

Sweden
Sahlgrenska University Hospital, Gothenburg
Linkoping University Hospital, Linkoping

Switzerland
Swiss Association for Clinical Cancer Research (SAKK)
Centre Hospitalier Universitaire Vaudois, Lausanne
Inselklinik Bern
Oncocare Engeried, Bern
Institute of Oncology of Southern Switzerland (Ospedale San Giovanni, Bellinzona; Ospedale Regionale di Lugano, (Civico & Italiano), Lugano; Ospedale Regionale Beata Vergine, Mendrisio; Ospedale Regionale La Carità, Locarno; Istituto Cantonale di Patologia, Locarno)
Kantonsspital St. Gallen, St. Gallen
Rätisches Kantonos-/Regionalspital, Chur
Kantonsspital Basel, Basel
Onkologiezentrum Thun-Berner Oberland, Thun
Zürich Frauenklinik, Zürich

German Breast Group (GBG)
Caritas-Krankenhaus St. Josef, Regensburg
Mammazentrum, Klinikum Deggendorf, Deggendorf
St. Vincentius Kliniken Karlsruhe, Karlsruhe
Klinikum Rosenheim, Rosenheim
Dr. Horst Schmidt Kliniken, Wiesbaden
Klinikum Mittelbaden, Baden-Baden
Universitäts-Frauenklinik Leubeck, Leubeck

National Cancer Research Institute (NCRI) United Kingdom
South Tyneside District Hospital, South Shields
Peterborough District Hospital, Peterborough
South Manchester University Hospital, Manchester

NORTH AMERICA BREAST CANCER GROUPS

American College of Surgeons Oncology Group (ACOSOG, now part of the Alliance for Clinical Trials in Oncology)
Cancer and Leukemia Group B (CALGB ACOSOG, now part of the Alliance for Clinical Trials in Oncology)
Clinical Trials Support Unit (CTSU)
Eastern Cooperative Oncology Group (ECOG, now part of ECOG/ACRIN)
National Institution of Canada Clinical Trials Group (NCIC CTG)
National Surgical Adjuvant Breast and Bowel Project (NSABP)
North Central Cancer Treatment Group (NCCTG ACOSOG, now part of the Alliance for Clinical Trials in Oncology)
Radiation Therapy Oncology Group (RTOG)
Southwest Oncology Group (SWOG)

NORTH AMERICAN PARTICIPATING CENTERS
Canada
Cross Cancer Institute, Edmonton, Alberta
Tom Baker Cancer Center, Calgary, Alberta
Dr. Leon Richard Oncology Centre, Moncton, New Brunswick
Windsor Regional Cancer Center, Windsor, Ontario
Trillium Health Center, Mississauga, Ontario
London Regional Cancer Center, London, Ontario
Hamilton Regional Cancer Center, Hamilton, Ontario
Trillium Health Centre - W Toronto, Toronto, Ontario
Hôpital Du Sacre-Coeur de Montreal, Montreal, Quebec
Hôpital Charles LeMoyne, Greenfield Park, Quebec
Allan Blair Cancer Center, Regina, Saskatchewan
Saskatoon Cancer Center, Saskatoon, Saskatchewan

United States of America
University of Arkansas, Little Rock, AR
Presbyterian Hospital, Whittier, CA
University of California at San Diego, San Diego, CA
Desert Regional Medical Center, Palm Springs, CA
University of California Medical Center At Irvine, Orange, CA
San Francisco General, San Francisco, CA
University of California at San Francisco, San Francisco, CA
Mercy General Hospital, Carmichael, CA
Saint Joseph Medical Center, Burbank, CA
Sutter Community Hospital, Sacramento, CA
University of California San Diego Cancer Center, San Diego, CA
University of Colorado, Denver, CO
The Shaw Regional Cancer Center, Aurora, CO
University of Connecticut, Farmington, CT
Walter Reed Army Medical Center, Washington, DC
Sibley Memorial Hospital, Washington, DC
University of Miami Sylvester Cancer Center, Miami, FL
Mayo Clinic Jacksonville, Jacksonville, FL
Comprehensive Cancer Care Specialist At Boca Raton, Boca Raton, FL
Northeast Georgia Medical Center, Gainesville, GA
Siouxland Hematology - Oncology Associates, Sioux City, IA
Saint Luke's Mountain States Tumor Institute, Boise, ID
Kootenai Cancer Center, Coeur D'Alene, ID
Evanston Northwestern Healthcare, Evanston, IL
John H. Stroger, Jr., Hospital of Cook County, Chicago, IL
Resurrection Medical Center, Chicago, IL
University of Chicago, Chicago, IL
Decatur Memorial Hospital, Decatur, IL
Oncology-Hematology Associates of Central Illinois, Peoria, IL
Carle Center CCOP, Urbana, IL
Saint Joseph's Medical Center, South Bend, IN
Memorial Hospital of South Bend, South Bend, IN
Michiana Hematology Oncology P.C., South Bend, IN
Fort Wayne Medical Oncology/Hematology Incorporated, Fort Wayne, IN
Northern Indiana Consortium, South Bend, IN
Northern Indiana Cancer Research Co, South Bend, IN
Mount Carmel Regional Cancer Center, Pittsburg, KS
Stormont-Vail Regional Health Center, Topeka, KS
Cancer Center of Kansas - Wichita, Wichita, KS
Via Christi Regional Medical Center, Wichita, KS
Cancer Center of Kansas - Pratt, Pratt, KS
Cancer Center of Kansas-Medical Arts Tower, Wichita, KS
Addison Gilbert, Gloucester, MA
Tufts Medical Center, Boston, MA
Massachusetts General Hospital, Boston, MA
Dana-Farber Cancer Center, Boston, MA
Beth Israel Deaconess Medical Center, Boston, MA
Faulkner Hospital, Boston, MA
North Shore Cancer Center, Salem, MA
Emerson Hospital, Boston, MA
Suburban Hospital, Bethesda, MD
University of Maryland Cancer Center, Baltimore, MD
Mercy Medical Center, Baltimore, MD
Frederick Memorial Hospital, Frederick, MD
Central Maine Medical Center, Lewiston, ME
William Beaumont Hospital, Royal Oak, MI
Saint Mary's Hospital, Ann Arbor, MI
United Hospital, St. Paul, MN
Abbott-Northwestern Hospital, St. Louis Park, MN
Mercy Hospital, Coon Rapids, MN
Mayo Clinic, Rochester, MN
Saint John's Hospital - Heathcare, Minneapolis, MN
Metro-Minnesota CCOP, Minneapolis, MN
Ridgeview Medical Center, Waconia, MN
Saint Louis University Hospital, St Louis, MO
Washington School of Medicine, St Louis, MO
Saint John's Regional Health Center, Springfield, MO
Kansas City CCOP, Kansas City, MO
Billings Clinic, Billings, MT
Montana Cancer Consortium CCOP, Billings, MT
Moses H. Cone Memorial, Greensboro, NC
Presbyterian Hospital, Charlotte, NC
Mission Hospitals Inc, Asheville, NC
Forsyth Memorial Hospital, Winston-Salem, NC
Margaret R. Pardee Memorial Hospital, Hendersonville, NC
Hope, A Women’s Cancer Center, Asheville, NC
Medcenter One Health Systems, Bismarck, ND
Dakota Clinic, Fargo, ND
University of Nebraska Medical Center, Omaha, NE
Portsmouth Regional Hospital, Portsmouth, NH
South Jersey Healthcare, Vineland, NJ
Hackensack University Medical CCOP, Hackensack, NJ
Virtua West Jersey Hospitals, Marlton, NJ
New York University Medical Center, New York, NY
Albert Einstein College/Medicine, Bronx, NY
Montefiore Medical Center, Bronx, NY
Roswell Park Cancer Institute, Buffalo, NY
Aultman Hospital, Canton, OH
Geisinger Wyoming Valley, Danville, PA
Geisinger Medical Group, Danville, PA
North East Medical Oncology Associates, Hazleton, PA
Greenville CCOP, Greenville, SC
Sioux Valley Clinic - Oncology, Sioux Falls, SD
Erlanger Medical Center, Chattanooga, TN
Doctor’s Hospital of Laredo, Laredo, TX
University of Vermont, Burlington, VT
Mountainview Medical, Berlin, VT
Swedish Hospital Medical Center, Seattle, WA
University of Washington Medical Center, East Seattle, WA
Madigan Army Medical Center, Tacoma, WA
Group Health Cooperative of Puget Sound, Seattle, WA
Aspirus Wausau Hospital Center, Wausau, WI
Oncology Alliance-Glendale, Glendale, WI
Columbia Saint Mary's Hospital, Milwaukee, WI
West Virginia University, Morgantown, WV
SOFT TRIAL
BREAST INTERNATIONAL GROUP (BIG)

International Breast Cancer Study Group (IBCSG)

Australia and New Zealand Breast Cancer Trials Group (ANZBCTG)

**Australia**

Canberra Hospital, Garran, Australian Capital Territory
Border Medical Oncology, Wodonga, New South Wales
Calvary Mater Newcastle, Waratah, New South Wales
Coffs Harbour Health Campus, Coffs Harbour, New South Wales
Liverpool Hospital, Liverpool, New South Wales
Macarthur Cancer Therapy Centre, Campbelltown, New South Wales
Manning Rural Referral Hospital, Taree, New South Wales
Concord Repatriation General Hospital, Concord, New South Wales
Tweed Hospital, Tweed Heads, New South Wales
Riverina Cancer Care Centre, Wagga Wagga, New South Wales
Royal North Shore Hospital, St. Leonards, New South Wales
Royal Prince Alfred Hospital, Camperdown, New South Wales
St. George Hospital, Kogarah, New South Wales
St. Vincent's Hospital, Darlinghurst, New South Wales
The Mater Hospital, North Sydney, New South Wales
Nambour Hospital, Nambour, Queensland
Princess Alexandra Hospital, Woolloongabba, Queensland
St. Andrews Toowoomba Hospital, Toowoomba, Queensland
Royal Brisbane and Women's Hospital, Herston, Queensland
Royal Adelaide Hospital, Adelaide, South Australia
St. John of God Hospital, Bunbury, South Australia
Launceston General Hospital, Launceston, Tasmania
North West Regional Hospital, Burnie, Tasmania
Royal Hobart Hospital, Hobart, Tasmania
Austin Health, Heidelberg, Victoria
Ballarat Oncology and Haematology Services, Wendouree, Victoria
Alfred Hospital, Melbourne, Victoria
Box Hill Hospital, Box Hill, Victoria
Maroondah Hospital, Ringwood East, Victoria
Monash Medical Centre, East Bentleigh, Victoria
Peter MacCallum Cancer Center, East Melbourne, Victoria
St. Vincents Hospital, Fitzroy, Victoria
Victorian Breast and Oncology Care, Melbourne, Victoria
Mount Hospital, Perth, Western Australia
Sir Charles Gairdner Hospital, Nedlands, Western Australia
St. John of God Hospital, Subiaco, Western Australia

**New Zealand**

Auckland City Hospital, Auckland
Christchurch Hospital, Christchurch
Palmerston North Hospital, Palmerston North
Waikato Hospital, Hamilton
Brazil
Hospital de Clinicas de Porto Alegre, Porto Alegre

Chile
Grupo Oncológico Corporativo Chileno de Investigación (GOCCHI)
Instituto Nacional del Cancer, Santiago
Hospital San Juan de Dios, Santiago
Hospital San Borja Arriaran, Santiago
Hospital Clinico de la Universidad de Chile, Santiago
Hospital dr.sotero Del Rio, Santiago
Hospital Militar, Santiago
Centro De Patologia Mamaria, Santiago
Hospital Dr. Juan Noe Crevani, Arica
Hospital Base de Valdivia, Valdivia
Instituto De Radiomedicina, Vitacura

Hungary
National Institute of Oncology, Budapest

India
Tata Memorial Hospital, Mumbai

Italy
Centro di Riferimento Oncologico, Aviano
Azienda Sanitaria di Bolzano, Balzano
Ospedali Riuniti di Bergamo, Bergamo
Ospedale degli Infermi, Biella
Unita Operativa de Medicina Oncologica, Ospedale Ramazzini, Carpi
Oncologia Medica Fano Italy, Fano
Ospedale Civile di Lecco, Lecco
Istituto Europeo di Oncologia, Milano
Mirandola Hospital, Mirandola, Italy
Fondazione Salvatore Maugeri, Pavia
Sandro Pitigliani Medical Oncology Unit, Hospital of Prato, Prato
Ospedale degli Infermi, Rimini
Ospedale di Circolo e Fondazione Macchi, Varese
Dipartimento di Oncologia, Azienda Ospedaliero-Universitaria di Udine, Udine, Italy

Peru
Instituto de Enfermedades Neoplásicas, Lima

South Africa
Sandton Oncology Centre, Johannesburg

Sweden
Sahlgrenska University Hospital, Gothenburg
Linkoping University Hospital, Linkoping
Central Hospital Karlstad, Karlstad
Karolinska University Hospital, Stockholm
Lund University Hospital, Lund
Switzerland
Swiss Association for Clinical Cancer Research (SAKK)
Centre Hospitalier Universitaire Vaudois, Lausanne
Inselspital, Berne
Kantonsspital St. Gallen, St. Gallen
Rätisches Kantonos-/Regionalspital, Chur
Kantonsspital Basel, Basel
Onkologiezentrum Thun-Berner Oberland, Thun
Oncocare Engeried, Bern
Zürich Frauenklinik, Zürich
Brust-Zentrum Zurich, Zurich
Dr. Mannhart, Cham
Kantonsspital Aarau (AG), Aarau
Kantonsspital Baden, Baden
Tumor- und Brustzentrum Zetup St. Gallen, St. Gallen

Solid Tumor Intensification Group (SOLTI) Spain
Hospital Clinic i Provincial de Barcelona, Barcelona
Hospital Universitari Vall D' Hebron, Barcelona
Hospital Universitario 12 de Octubre, Madrid
Centro Oncologico Md Anderson, Madrid
Hospital Son Llatzer, Palma de Mallorca
Clinica Univ. De Navarra, Pamplona
Instituto Valenciano de Oncologia, Valencia
Hospital Son Dureta (Palma de Mallorca), Palma de Mallorca
Hospital Santiago De Compostela, Santiago de Compostela
H.U. Arnau de Vilanova, Lleida
Hospital Universitario Lozano Blesa, Zaragoza
Hospital Universitario Virgen Macarena, Sevilla
Hospital Clinico Universitario de Valencia, Valencia
Hospital Ramon Y Cajal, Madrid
Hospital Sant Joan de Reus, Reus
Hospital Reina Sofia De Cordoba, Cordoba
Hospital Dr Negrin, Las Palmas de Gran Canari
Hospital Sant Pau i Santa Tecla, Tecla

CENTRAL AND EAST EUROPEAN ONCOLOGY GROUP (CEEOG)
Medical University of Gdansk, Gdansk, Poland
Institute of Oncology & Radiology of Serbia, Belgrade, Serbia

EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER (EORTC)
ZNA Middelheim, Antwerpen, Belgium
Cliniques Universitaires St-Luc UCL, Brussels, Belgium
Centre Hospitalier Etterbeek Ixelles, Brussels, Belgium
U.Z. Leuven, Leuven, Belgium
C.H.U. Sart-Tilman, Liege, Belgium
Hopital De Jolimont, Haine St. Paul, Belgium
Clinique Sainte Elisabeth, Namur, Belgium
Algemeen Ziekenhuis Sint-Augustinus, Wilrijk, Belgium
Centre Henri Becquerel, Rouen, France
Institut Claudius Regaud, Toulouse, France
Institut Jean Godinot, Reims, France
Centre Leon Berard, Lyon, France
Institut Bergonie, Bordeaux, France
Centre Georges Francois-Leclerc, Dijon, France
Centre Rene Huguenin, Saint-Cloud, France
Institut Curie, Paris, France
Centre Eugene Marquis, Rennes, France
C.H.R.U. de Limoges, Limoges, France
Clinique Mutualiste de l'Estuaire, Saint-Nazaire, France
Clinique De L'alliance, Tours, France
Institut Gustave Roussy, Villejuif, France
Rambam Medical Center, Haifa, Israel
Assaf Harofeh Medical Center, Zerifin, Israel
The Netherlands Cancer Institute, Amsterdam, Netherlands
Onze Lieve Vrouwe Gasthuis, Amsterdam, Netherlands
Leids Universitair Medisch Centrum, Leiden, Netherlands
Centro de Lisboa, Lisboa, Portugal
Marmara University Hospital, Istanbul, Turkey

German Breast Group (GBG)

DRK Kliniken Berlin Köpenick, Berlin
Praxis Dr. Tessen, Goslar
Martin-Luther- Universität Halle-Wittenberg, Halle an der Saale
Universitätsfrauenklinik Erlangen, Erlangen
Universitäts Frauenklinik Mannheim, Mannheim
Klinikum Mittelbaden/Stadtklinik Baden-Baden, Baden-Baden
Universitäts-Frauenklinik, Freiburg i. Br.
Dr. Horst Schmidt Kliniken, Wiesbaden
Kreisklinik Ebersberg, Ebersberg
St. Vincentius Krankenhaus, Karlsruhe
Klinikum Landshut GmbH, Landshut
Universitäts Frauenklinik, Frankfurt/Main
Caritas-Krankenhaus St. Josef, Regensburg
Klinik für Frauenheilkunde und Geburtshilfe der Universität Regensburg, Regensburg

All Ireland Cooperative Clinical Research Group (ICORG)

Beaumont Hospital, Dublin
Mater Misericordiae Hospital, Dublin
Mater Private Hospital, Dublin
South Infirmary Victoria Hosp, Cork
Univ College Hospital Galway, Galway

National Cancer Research Institute (NCRI), United Kingdom
Southend Hospital NHS Trust, Westcliff-on-Sea, Essex, United Kingdom
South Tyneside District Hospital, South Shields, Tyne & Wear, UK
Weston Park Hospital, Sheffield, South Yorkshire, England
Mount Vernon Hospital, Northwood, Middlesex, UK
Luton & Dunstable Hospital, Luton, England
Clatterbridge Centre for Oncology, Wirral, UK
Ipswich Hospital, Ipswich, UK
Great Western Hospital, Swindon, UK
New Cross Hospital, Wolverhampton, UK
Whiston Hospital, Prescot, UK
Aberdeen Royal Infirmary, Aberdeen, UK
Royal Marsden Hospital - Fulham, London, England
Royal Marsden Hospital - Sutton, Surrey, England
York Hospital, York
St. James Univ Hospital, Leeds
North Manchester General Hospital, Manchester
Harrogate District Hospital, Harrogate
Stepping Hill Hospital, Stockport
Russells Hall Hospital, Dudley

NORTH AMERICA BREAST CANCER GROUPS

American College of Surgeons Oncology Group (ACOSOG, now part of the Alliance for Clinical Trials in Oncology)
Cancer and Leukemia Group B (CALGB, now part of the Alliance for Clinical Trials in Oncology)
Clinical Trials Support Unit (CTSU)
Eastern Cooperative Oncology Group (ECOG, now part of ECOG/ACRIN)
National Institution of Canada Clinical Trials Group (NCIC CTG)
National Surgical Adjuvant Breast and Bowel Project (NSABP)
North Central Cancer Treatment Group (NCCTG, now part of the Alliance for Clinical Trials in Oncology)
Radiation Therapy Oncology Group (RTOG)
Southwest Oncology Group (SWOG)

NORTH AMERICAN PARTICIPATING CENTERS

Canada
Doctor H. Bliss Murphy Cancer Center, St. John's, Newfoundland
BCCA-Vancouver Cancer Center, Vancouver, British Columbia
University of Montreal Hospital Group, Montreal, Quebec
Hopital Du Sacre-Coeur de Montreal, Montreal, Quebec
Hôpital Charles LeMoyne, Greenfield Park, Quebec
Kingston Regional Cancer Center, Kingston, Ontario
Ottawa Health Research Institute, Ottawa, Ontario
Thunder Bay Regional Health Science Centre, Thunder Bay, Ontario
Regional Cancer Program of The Hopital Regional de Sudbury Region, Sudbury, Ontario
Hamilton Regional Cancer Center, Hamilton, Ontario
Odette Cancer Centre, Toronto, Ontario
London Regional Cancer Center, London, Ontario
Cancercare Manitoba, Winnipeg, Manitoba
Allan Blair Cancer Center, Regina, Saskatchewan
Cross Cancer Institute, Edmonton, Alberta
Tom Baker Cancer Center, Calgary, Alberta
Cancer Center - Southern Interior, Kelowna, British Columbia
Penticton Regional Hospital, Penticton, British Columbia
BCCA-Fraser Valley Cancer Center, Surrey, British Columbia

United States of America
Providence Alaska Medical Center, Anchorage, AK
University of Alabama, Birmingham, AL
University of California at Los Angeles (UCLA), Los Angeles, CA
University of Southern California, Los Angeles, CA
Scripps Clinic - La Jolla, La Jolla, CA
University of California At San Diego, San Diego, CA
Eisenhower Medical Center, Rancho Mirage, CA
Kaiser Permanente South San Francisco, Vallejo, CA
University of California at San Francisco, San Francisco, CA
John Muir Medical Center, Concord, CA
Kaiser Permanente - Fremont, Fremont, CA
Kaiser Permanente-Vallejo, Vallejo, CA
Kaiser Permanente-Walnut Creek, Vallejo, CA
Bay Area Tumor Institution CCOP, Oakland, CA
Kaiser Permanente-Oakland, Vallejo, CA
Alta Bates Hospital, Berkeley, CA
Kaiser - Santa Clara, Santa Clara, CA
Kaiser Permanente Santa Teresa (San Jose), Vallejo, CA
Memorial Medical Center, Modesto, CA
Mercy General Hospital, Carmichael, CA
Kaiser Permanente-Sacramento, Vallejo, CA
Kaiser Permanente, San Francisco, San Francisco, CA
Santa Rosa CCOP, Sana Rosa, CA
Mercy Regional Cancer Center, Redding, CA
Kaiser Permanente, Roseville, Roseville, CA
Kaiser Permanente, Redwood City, Redwood City, CA
Stanford University Medical Center, Stanford, CA
Kaiser Permanente-Richmond, Richmond, CA
San Joaquin CCOP, San Joaquin, CA
Kaiser Permanente CCOP, San Diego, CA
Palo Alto Medical Foundation-Camino Division, Mountain View, CA
Glendale Memorial Hospital and Health Center, Glendale, CA
Contra Costa Regional Medical Center, Martinez, CA
Tom K Lee Inc, Oakland, CA
North Colorado Medical Center, Denver, CO
Penrose-Saint Francis Healthcare, Colorado Springs, CO
Memorial Hospital Colorado Springs, Colorado Springs, CO
North Suburban Medical Center, Thornton, CO
Front Range Cancer Specialists, Fort Collins, CO
Longmont United Hospital, Longmont, CO
Sky Ridge Medical Center, Lone Tree, CO
The Shaw Regional Cancer Center, Aurora, CO
Hartford Hospital, Hartford, CT
Greenwich Hospital, Greenwich, CT
Norwalk Hospital, Norwalk, CT
Stamford Hospital, Stamford, CT
Eastern Connecticut Hematology and Oncology Associates, Norwich, CT
Northwest Connecticut Oncology - Hematology Associates, Torrington, CT
Walter Reed Army Medical Center, Washington, DC
Georgetown University Hospital, Washington, DC
Washington Hospital Center, Washington, DC
Sibley Memorial Hospital, Washington, DC
Christiana Healthcare Services - Christian Hospital, Newark, DE
Bayhealth Medical Center, Dover, DE
Memorial Cancer Institute, Hollywood, FL
University of Miami Sylvester Cancer Center, Miami, FL
Mount Sinai Medical Center CCOP, Miami Beach, FL
Holy Cross Hospital, Fort Lauderdale, FL
Sarasota Memorial Hospital, Sarasota, FL
Dekalb Medical Center, Atlanta, GA
Emory University, Atlanta, GA
Memorial Health University Medical Center, Savannah, GA
Northside Hospital, Atlanta, GA
Atlanta Regional CCOP, Atlanta, GA
Wellstar Kennestone Hospital, Atlanta, GA
John B. Amos Community Cancer Center, Columbus, GA
Augusta Oncology Associates, Inc., Augusta, GA
St. Joseph's/Candler Health System, Savannah, GA
University of Hawaii, Honolulu, HI
McFarland Clinic, Ames, IA
Mercy Medical Center - North Iowa, Mason City, IA
Medical Associates Clinic, Professional Corporation, Dubuque, IA
Finley Hospital, Dubuque, IA
Iowa Blood and Cancer Care, PLC, Cedar Rapids, IA
Medical Oncology and Hematology Associates, Des Moines, IA
Loyola University Medical Center, Maywood, IL
Rush University Medical Center, Chicago, IL
University of Chicago, Chicago, IL
Weiss Memorial Hospital, Chicago, IL
St. Anthony Medical Center, Rockford, IL
Decatur Memorial Hospital, Decatur, IL
Memorial Medical Center, Springfield, IL
Edward Hospital, Naperville, IL
Ingalls Memorial Hospital, Harvey, IL
Carle Cancer Center CCOP, Urbana, IL
Community Regional Cancer Care North, Indianapolis, IN
Indiana University Medical Center, Indianapolis, IN
Saint Vincent Hospital, Indianapolis, IN
Fort Wayne Medical Oncology/Hematology Incorporated, Fort Wayne, IN
Northern Indiana Consortium, South Bend, IN
Horizon Oncology Center, Lafayette, IN
Cancer Center of Kansas - Wichita, Wichita, KS
Via Christi Regional Medical Center, Wichita, KS
Louisiana State University, Shreveport, LA
Lahey Clinic Medical Center, Burlington, MA
Tufts Medical Center, Boston, MA
Massachusetts General Hospital, Boston, MA
Dana-Farber Cancer Center, Boston, MA
Beth Israel Deaconess Medical Center, Boston, MA
Faulkner Hospital, Boston, MA
North Shore Cancer Center, Salem, MA
Suburban Hospital, Bethesda, MD
Johns Hopkins University, Baltimore, MD
Anne Arundel Medical Center, Annapolis, MD
Kaiser Permanente - Largo Medical Center, Largo, MD
Kaiser Permanente - Shady Grove Medical Center, Rockville, MD
Eastern Maine Medical Center, Brewer, ME
Mercy Hospital, Portland, ME
William Beaumont Hospital, Royal Oak, MI
Saint Joseph Mercy Hospital, Ann Arbor, MI
University of Michigan Medical Center, Ann Arbor, MI
Wayne State University, Detroit, MI
Grand Rapids Clinical Oncology Program, Grand Rapids, MI
Marquette General Hospital, Marquette, MI
Mid-Michigan Medical Center, Midland, MI
Hematology Oncology Associates of Ohio and Michigan, Lambertson, MI
Regions Hospital, Minneapolis, MN
United Hospital, St. Paul, MN
Duluth Clinic, Duluth, MN
Mayo Clinic, Rochester, MN
Saint John's Hospital - HealthEast, Minneapolis, MN
Virginia Piper Cancer Institute, Minneapolis, MN
Metro-Minnesota CCOP, Minneapolis, MN
North Memorial Medical Health Center, Robbinsdale, MN
Saint Francis Regional Medical Center, Shakopee, MN
Hutchinson Health Care, Hutchinson, MN
Washington School of Medicine, St Louis, MO
Saint John's Regional Health Center, Springfield, MO
Missouri Baptist Medical Center, Saint Louis, MO
Kansas City CCOP, Kansas City, MO
Montana Cancer Consortium CCOP, Billings, MT
Alamance Health Services, Burlington, NC
University of North Carolina, Chapel Hill, NC
Duke University Medical Center, Durham, NC
Mission Hospitals Inc, Asheville, NC
Wayne Memorial Hospital, Goldsboro, NC
Forsyth Memorial Hospital, Winston-Salem, NC
FirstHealth of the Carolinas, Moore Regional Hospital, Pinehurst, NC
Northeast Medical Center, Concord, NC
Hope, A Women's Cancer Center, Asheville, NC
Altru Hospital, Grand Forks, ND
Methodist Cancer Center, Omaha, NE
Elliot Hospital, Manchester, NH
Frisbie Hospital, Lebanon, NH
Cheshire Medical Center, Dartmouth, NH
Dartmouth Hitchcock Medical Center, Lebanon, NH
New Hampshire Oncology Hematology, Concord, NH
Saint Barnabas Medical Center, Livingston, NJ
Cooper Hospital University Medical Center, Newark, DE
Cancer Institute of New Jersey, New Brunswick, NJ
Monmouth Medical Center, Long Branch, NJ
Cancer Institute of New Jersey At Hamilton, Trenton, NJ
Virtua West Jersey Hospitals, Marlton, NJ
Hematology Oncology Associates, Albuquerque, NM
University of Nevada At Reno Washoe Medical Center, Reno, NV
Saint Vincent's Hospital and Medical Center of New York, New York, NY
Memorial Sloan Kettering Cancer Ctr, New York, NY
Weill Medical College of Cornell University, New York, NY
Staten Island University Hospital, Staten Island, NY
Albert Einstein College/Medicine, Bronx, NY
Montefiore Medical Center, Bronx, NY
North Shore University Hospital, Manhasset, NY
Long Island Jewish Medical Center, New Hyde Park, NY
Brookdale Hospital Medical Center, Brooklyn, NY
Roswell Park Cancer Institute, Buffalo, NY
Rochester General Hospital, Rochester, NY
Doctors Hospital, Columbus, OH
Ohio State University Hospital, Columbus, OH
Columbus CCOP, Columbus, OH
Cleveland Clinic Foundation, Cleveland, OH
Case Western Reserve University, Cleveland, OH
MetroHealth Medical Center, Cleveland, OH
Fairview Hospital, Cleveland, OH
Forum Health, Youngstown, OH
University of Cincinnati Medical Center, Cincinnati, OH
Good Samaritan Hospital - Dayton, Dayton, OH
Aultman Hospital, Canton, OH
Samaritan North Health Center, Dayton, OH
St. Charles Hospital, Toledo, OH
Lima Memorial Hospital, Toledo, OH
Grady Memorial Hospital, Delaware, OH
Cleveland Clinic Wooster Specialty Center, Wooster, OH
University of Oklahoma Health Science Center, Oklahoma City, OK
Saint Charles Medical Center, Bend, OR
Kaiser Permanente, Portland, OR
Columbia River Oncology Program, Portland, OR
Allegheny Cancer Center Network, Pittsburgh, PA
University of Pittsburgh, Pittsburgh, PA
Mount Nittany Medical Center, Hershey, PA
Penn State Milton S. Hershey Medical Center, Hershey, PA
York Hospital, York, PA
Lancaster General Hospital, Lancaster, PA
Geisinger Medical Center, Danville, PA
Guthrie Medical Center, Sayre, PA
Grand View Hospital, Sellersville, PA
Abramson Cancer Center of The University of Pennsylvania, Philadelphia, PA
Fox Chase Cancer Center, Philadelphia, PA
Chester County Hospital, West Chester, PA
St. Mary Regional Cancer Center, Langhorne, PA
Abington Memorial Hospital, Abington, PA
Scranton Hematology Oncology, Scranton, PA
Rhode Island Hospital, Providence, RI
Women's and Infants Hospital, Providence, RI
Spartanburg CCOP, Spartanburg, SC
Spartanburg Regional Medical Center, Spartanburg, SC
Sioux Valley Clinic - Oncology, Sioux Falls, SD
Erlanger Medical Center, Chattanooga, TN
Meharry Medical College, Nashville, TN
Thompson Cancer Survival Center, Knoxville, TN
Jones Clinic, Germantown, TN
Medical City Dallas Hospital, Dallas, TX
Presbyterian Hospital of Dallas, Dallas, TX
Scott and White CCOP, Temple, TX
M.D. Anderson Cancer Center, Houston, TX
Baylor College of Medicine, Houston, TX
Doctor's Hospital of Laredo, Laredo, TX
Virginia Commonwealth University, Richmond, VA
University of Vermont, Burlington, VT
Green Mountain Oncology Group CCOP, Bennington, VT
Swedish Hospital Medical Center, Seattle, WA
University of Washington Medical Center, East Seattle, WA
Southwest Washington Medical Center, Vancouver, WA
Northwest CCOP, Tacoma, WA
University of Wisconsin, Madison, WI
Saint Vincent Hospital, Green Bay, WI
Aspirus Wausau Hospital Center, Wausau, WI
Gundersen Clinic, Limited, LaCrosse, WI
Midelfort Clinic, Eau Claire, WI
Dean Clinic, Madison, WI
Aurora Baycare Medical Center, Green Bay, WI
Green Bay Oncology LTD at Saint Mary's Hospital, Green Bay, WI
Marshall University Medical Center, Huntington, WV
Edwards Comprehensive Cancer Center, Huntington, WV