Adjuvant Tamoxifen Plus Ovarian Function Suppression Versus Tamoxifen Alone in Premenopausal Women With Early Breast Cancer: Patient-Reported Outcomes in the Suppression of Ovarian Function Trial

Karin Ribi, Weixiu Luo, Jürg Bernhard, Prudence A. Francis, Harold J. Burstein, Eva Ciruelos, Meritxell Bellet, Lorenzo Pavesi, Ana Lluch, Marilena Visini, Vani Parmar, Carlo Tondini, Pierre Kerbrat, Antonia Perelló, Patrick Neven, Roberto Torres, Davide Lombardi, Fabio Puglisi, Per Karlsson, Thomas Ruhstaller, Marco Colleoni, Alan S. Coates, Aron Goldhirsch, Karen N. Price, Richard D. Gelber, Meredith M. Regan, and Gini F. Fleming

See accompanying article on page 1573

Author affiliations appear at the end of this article.

Published online ahead of print at www.jco.org on March 28, 2016.

Written on behalf of the Suppression of Ovarian Function Trial (SOFT) investigators and the International Breast Cancer Study Group (IBCSG); investigators and affiliations are listed in the Appendix (online only). SOFT received financial support for trial conduct from Pfizer, the IBCSG, and the US National Cancer Institute (NCI). Pfizer and Ipsen provided drug supply. The coordinating group of IBCSG was supported by Frontier Science and Technology Research Foundation, the Swiss Group for Clinical Cancer Research, NCI (Grant No. CA75362 to M.M.R.), Cancer Research Switzerland/Oncosuisse, and the Foundation for Clinical Cancer Research of Eastern Switzerland. Grant support for cooperative groups was as follows: Australia and New Zealand Breast Cancer Trials Group (National Health and Medical Research Council Grants No. 351161, 510788, and 1105058); Southwest Oncology Group (NIH Grant No. CA32102); Alliance (NIH Grant No. U10-CA180821); Eastern Cooperative Oncology Group–American College of Radiology Imaging Network (NIH Grants No. CA21115 and CA16116); National Surgical Adjuvant Breast and Bowel Project/NCIC Oncology (NIH Grants No. U10-CA-12027, U10-CA-69651, U10-CA-37377, and U10-CA-69974); and National Cancer Institute of Canada (NIH Grant No. CA077202 and Canadian Cancer Society Research Institute Grants No. 015469 and 021039).

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Clinical trial information: NCT00066690

Corresponding author: Karin Ribi, PhD, International Breast Cancer Study Group Coordinating Center, Effingerstrasse 40, 3008 Bern, Switzerland; e-mail: karin.ribi@ibcsg.org.

© 2016 by American Society of Clinical Oncology

0732-183X/16/3414w-1601w/\$20.00

DOI: 10.1200/JCO.2015.64.8675

ABSTRACT

Purpose

The Suppression of Ovarian Function trial showed improved disease control for tamoxifen plus ovarian function suppression (OFS) compared with tamoxifen alone for the cohort of premenopausal patients who received prior chemotherapy. We present the patient-reported outcomes.

Patients and Methods

The quality-of-life (QoL) analysis includes 1,722 of 2,045 premenopausal patients with hormone receptor–positive breast cancer randomly assigned to receive adjuvant treatment with 5 years of tamoxifen plus OFS or tamoxifen alone. Chemotherapy use before enrollment was optional. Patients completed a QoL form consisting of global and symptom indicators at baseline, every 6 months for 24 months, and annually during years 3 to 6. Differences in the change of QoL from baseline between the two treatments were tested at 6, 24, and 60 months with mixed models for repeated measures with and without chemotherapy and overall.

Results

Patients on tamoxifen plus OFS were more affected than patients on tamoxifen alone by hot flushes at 6 and 24 months, by loss of sexual interest and sleep disturbance at 6 months, and by vaginal dryness up to 60 months. Without prior chemotherapy, patients on tamoxifen alone reported more vaginal discharge over the 5 years than patients on tamoxifen plus OFS. Symptom-specific treatment differences at 6 months were less pronounced in patients with prior chemotherapy. Changes in global QoL indicators from baseline were small and similar between treatments over the whole treatment period.

Conclusion

Overall, OFS added to tamoxifen resulted in worse endocrine symptoms and sexual functioning during the first 2 years of treatment, with variable magnitudes of treatment differences. Short-term differences in symptom-specific QoL, treatment burden, and coping effort between treatment groups were less pronounced for patients with prior chemotherapy, the cohort that benefited most from OFS in terms of disease control.

J Clin Oncol 34:1601-1610. © 2016 by American Society of Clinical Oncology

INTRODUCTION

Clinical results from the recently published Tamoxifen and Exemestane Trial (TEXT) and Suppression of Ovarian Function Trial (SOFT) provide new treatment options for premenopausal women with endocrine-responsive early breast cancer.^{1,2} In SOFT, adding ovarian function

suppression (OFS) to tamoxifen did not significantly improve disease-free survival versus tamoxifen alone in the overall population.² However, the addition of OFS improved disease outcomes in women at sufficient risk for recurrence to warrant adjuvant chemotherapy and who remained premenopausal thereafter.

When determining the most appropriate adjuvant endocrine therapy with the individual

patient, adverse effect profiles are a concern, and patient-reported outcomes provide valuable complementary information.^{3,4} With respect to exemestane versus tamoxifen in patients who received OFS, there were no differential effects on global quality of life (QoL), yet there were distinct effects on the burden of endocrine symptoms.⁵

The effect of OFS on patient-reported outcomes in patients who received adjuvant tamoxifen was investigated in the Zoladex in Premenopausal Patients (ZIPP)^{6,7} and the Eastern Cooperative Oncology Group E-3193⁸ trials. Results indicate a greater detrimental effect on menopausal symptoms and sexual activity during treatment with OFS compared with tamoxifen alone.⁶⁻⁸ In E-3193, overall QoL was worse when OFS was added to tamoxifen compared with tamoxifen alone at 3 years, with subsequent lessening of differences.⁸

For many women, chemotherapy is likely to be part of their adjuvant therapy. The effect of chemotherapy on the perception of endocrine symptoms is poorly understood. In the ZIPP trial, the type of endocrine therapy had different effects on patient-reported symptoms only in patients who did not receive chemotherapy.⁶

In parallel to the efficacy analysis of SOFT,² we investigated patients' experiences of individual symptoms and QoL when adding OFS to tamoxifen, also considering the influence of prior chemotherapy use. If adjuvant treatment includes OFS, current recommendations favor an aromatase inhibitor over tamoxifen.⁹ Therefore, we also present QoL results for exemestane plus OFS compared with tamoxifen alone.

PATIENTS AND METHODS

Study Design and Participants

SOFT was designed to evaluate adjuvant endocrine therapy in women who remained premenopausal after completion of (neo)adjuvant chemotherapy and in premenopausal women for whom adjuvant tamoxifen alone was considered suitable treatment (for details, see Data Supplement). SOFT eligibility criteria have been described elsewhere.^{2,10} Patients who did not receive chemotherapy were randomly assigned within 12 weeks of definitive surgery. Patients who received chemotherapy were randomly assigned within 8 months after completing chemotherapy, once a premenopausal estradiol level was confirmed. The ethics committee of each participating center approved the study protocol, and all patients gave written informed consent.

Treatment

Eligible women were randomly assigned 1:1:1 to receive oral tamoxifen (20 mg once per day), tamoxifen plus OFS, or oral exemestane (25 mg once per day) plus OFS for 5 years from the date of random assignment. OFS was achieved using triptorelin at a dose of 3.75 mg by intramuscular injection every 28 days, bilateral oophorectomy, or bilateral ovarian irradiation. Random assignment was stratified by chemotherapy use (yes/no), lymph node status (positive/negative), and intended initial method of OFS, if assigned. Patients may have received oral endocrine therapy before random assignment. Protocol-assigned endocrine therapy was to cease 5 years from random assignment.

QoL Assessment

Patients completed the International Breast Cancer Study Group QoL Core Form¹¹ and a trial-specific module at baseline, every 6 months for 2 years, then annually for years 3 through 6. The forms were to be

completed at the clinic, before diagnostic procedures (exception: baseline) and before treatment was given and regardless of disease status. Eligibility exceptions were cognitive or physical impairment that interfered with the QoL assessment and inability to read any of the languages available on the core form. The core form includes global indicators for physical well-being,¹² mood,¹³ coping effort,¹⁴ subjective health estimation,¹⁵ and five indicators specific to symptoms and adverse effects.¹⁶ The module consisted of 12 endocrine symptom indicators, one global indicator for treatment burden,¹⁷ and a question regarding sexual activity during the past 6 months (yes/no). The selection of endocrine symptoms was based on the findings of two breast cancer prevention trials^{18,19} and a symptom checklist²⁰⁻²² (see Data Supplement). All indicators were in linear analog self-assessment format¹⁶ and transformed to range from 0 to 100, with higher numbers reflecting a better condition. For all indicators, a clinically significant change was conservatively defined as at least ± 8 points.²³

Prospectively Defined Hypotheses

Primary. Primary hypotheses were as follows: (1) Patients receiving tamoxifen plus OFS will report more hot flushes compared with those receiving tamoxifen alone. (2) Patients receiving tamoxifen plus OFS will report a higher loss of sexual interest compared with those receiving tamoxifen alone. (3) There will be a differential effect on specific menopausal symptoms (ie, more vaginal discharge in patients receiving tamoxifen only, and more vaginal dryness, sleep disturbance, and bothersome weight gain in patients receiving tamoxifen plus OFS).

Secondary. Secondary hypotheses were as follows: (1) There will be no difference in global QoL indicators (mood, physical well-being, or coping effort) in patients receiving tamoxifen plus OFS compared with those receiving tamoxifen alone, but patients receiving tamoxifen plus OFS will report higher treatment burden than those receiving tamoxifen alone. (2) Patients who report worse menopausal symptoms during the first 6 months on endocrine therapy will also report delayed adaptation in global domains (coping effort, mood, and physical well-being).

Statistical Analysis

From the intent-to-treat (ITT) efficacy analysis population, patients were excluded from the QoL analysis for the following reasons: a QoL eligibility exemption; participating centers with poor overall QoL submission compliance ($< 60\%$ of QoL assessments; Data Supplement); or no QoL data submitted (Fig 1).

For each QoL indicator, changes from baseline to each time point were calculated (time point minus baseline scores) and summarized in figures descriptively as means with 95% CIs. Mixed-effects linear modeling for repeated measures analyzed the effects of treatment on changes from baseline in QoL indicators. Models included chemotherapy cohort, treatment assignment (tamoxifen *v* tamoxifen plus OFS), time point (seven time points, categorical), and the two- and three-way interactions, without regard for statistical significance of the interaction parameters. Models were adjusted for the following baseline covariates: age, race/ethnicity, body mass index, menstruation status, family history of breast or ovarian cancer, nodal status, tumor size, tumor grade, and human epidermal growth factor receptor 2 status. An unstructured covariance was used. For hypothesis testing, within each cohort and overall, model contrasts estimated mean differences between treatment groups, 95% CIs, and Wald *P* values for testing the treatment differences versus zero at short (month 6), intermediate (month 24), and long term (month 60).

For secondary hypothesis 2, the model added a covariate of more versus less severe menopausal symptoms during the first 6 months of therapy, which was created by categorizing the change in hot flushes at the median. The mean difference between the two severity groups in QoL change from baseline to 6, 12, 18, and 24 months was estimated and tested.

Hypothesis tests were two-sided, consistent with the protocol. The reported *P* values were not adjusted for testing of multiple QoL indicators over time to look for consistency of the signal among comparable QoL indicators. As supplementary analyses of the effect of exemestane plus OFS

Fig 1. CONSORT flowchart to identify the intent-to-treat (ITT) quality-of-life population (N = 3,066). OFS, ovarian function suppression; QoL, quality of life; SOFT, Suppression of Ovarian Function Trial.

on symptom burden and QoL relative to tamoxifen alone, changes in all indicators from baseline over time were summarized descriptively without formal comparison.

RESULTS

Patient and Disease Characteristics

Of the 3,066 premenopausal women enrolled onto SOFT between December 2003 and January 2011, 2,045 were randomly assigned to tamoxifen or to tamoxifen plus OFS, with 2,033 patients in the ITT efficacy population. After exclusions, 1,722 patients remained in the ITT QoL population for the primary analysis comparing tamoxifen plus OFS versus tamoxifen alone (Fig 1). Median follow-up was 5.6 years (interquartile range, 4.4 to 6.8 years); 63 patients (3.7%) died within 60 months.

The median age at random assignment was 43 years. Node-positive disease was present in 36% of patients, and 55% of patients received prior chemotherapy. Overall, 27% of patients also received prior oral endocrine therapy for an average duration of 16 weeks (interquartile range, 8 to 22 weeks). Among patients who received prior chemotherapy, 45% received endocrine therapy before random assignment. Patient and disease characteristics at random assignment were balanced across treatment groups. Patients in the chemotherapy cohort had higher risk disease characteristics (greater proportions had node-positive disease, human epidermal

growth factor receptor 2–positive disease, and tumor size > 2 cm) and were younger (Table 1; Data Supplement). Patient, disease, and treatment characteristics were generally balanced between the ITT QoL population and excluded patients (Data Supplement), although excluded patients had lower rates of physician-reported symptoms at random assignment (data not shown).

The overall QoL form submission rate (QoL ITT population) was 84% between baseline and 60 months but declined over time, with rates of 89% at 6 months, 83% at 24 months, and 74% at 60 months. Submission rates were similar between the randomly assigned treatment groups and chemotherapy cohorts.

Changes in QoL Symptom and Global Indicators Over Time

Vasomotor symptoms showed the greatest early worsening from baseline, as shown for hot flushes by treatment and chemotherapy cohort (Figs 2A and 2B). Thereafter, hot flushes improved continuously in patients receiving tamoxifen plus OFS but without reaching baseline scores, whereas scores worsened slightly in patients receiving tamoxifen. Patients reported a continuous decline in sexual interest over the whole treatment period, with a clinically meaningful decrease observed between months 6 and 60 (range, –8 to –11) in patients on tamoxifen plus OFS, and after 36 months (–9 at month 36 and –9 at month 60) in patients on tamoxifen (Figs 2C and 2D). Changes in gynecologic symptoms were smaller

Table 1. Patient Characteristics Overall and According to Chemotherapy Cohort and Treatment Assignment

Characteristic	No Chemotherapy				Prior Chemotherapy				Overall	
	T (n = 385)		T+OFS (n = 387)		T (n = 476)		T+OFS (n = 474)		(n = 1,722)	
	No.	%	No.	%	No.	%	No.	%	No.	%
Age, years										
< 35	3	0.8	5	1.3	93	19.5	104	21.9	205	11.9
35 to < 40	28	7.3	26	6.7	137	28.8	125	26.4	316	18.4
40 to < 45	113	29.4	116	30.0	156	32.8	151	31.9	536	31.1
45 to < 50	178	46.2	169	43.7	74	15.5	80	16.9	501	29.1
≥ 50	63	16.4	71	18.3	16	3.4	14	3.0	164	9.5
Median	46		46		40		40		43	
IQR	43-48		43-49		36-44		35-44		38-47	
Nodal status										
Negative	348	90.4	352	91.0	206	43.3	202	42.6	1,108	64.3
Positive	37	9.6	35	9.0	270	56.7	272	57.4	614	35.7
Tumor size > 2 cm	46	11.9	64	16.5	221	46.4	220	46.4	551	32.0
HER2 positive	20	5.2	16	4.1	89	18.7	92	19.4	217	12.6
Time from final surgery to random assignment, months										
Median	1.8		1.9		8.2		8.1		3.6	
IQR	1.2-2.4		1.3-2.5		5.8-10.7		6.0-10.1		1.8-8.5	
Endocrine therapy before random assignment*	24	6.2	20	5.2	224	47.1	202	42.6	470	27.3

NOTE. Characteristics were well balanced according to treatment assignment. A more complete summary of characteristics is provided in the Data Supplement. Abbreviations: HER2, human epidermal growth factor receptor 2; IQR, interquartile range; OFS, ovarian function suppression; T, tamoxifen.

*Oral endocrine therapy before random assignment was allowed while premenopausal status was established or re-established. In the no chemotherapy cohort, average duration was 5 weeks (IQR, 3 to 7 weeks) for patients assigned to T and 5 weeks (IQR, 2 to 7 weeks) for patients assigned to T+OFS; in the prior chemotherapy cohort, average duration was 17 weeks (IQR, 10 to 24 weeks) for patients assigned to T and 16 weeks (IQR, 10 to 23 weeks) for patients assigned to T+OFS.

than for vasomotor symptoms and marginally clinically meaningful (Fig 3). Only for vaginal dryness did patients in both arms report a clinically meaningful worsening at 24 and 60 months. Both treatment groups reported a clinically meaningful worsening over time regarding bone and joint pains and being troubled by weight gain. Changes in other symptoms (ie, headaches, being irritable, feeling dizzy, appetite, feeling sick, tiredness) and global QoL indicators for physical well-being, mood, and health perception were small over time and similar in each treatment group (Figs 3 and 4).

Treatment Comparisons

Baseline QoL scores were similar between treatment arms (Table 2). Treatment comparisons are presented in Figs 2 to 4 and Table A1, online only. Treatment differences for changes in hot flashes (primary hypothesis 1) and sweats from baseline were substantial at 6 and 24 months, with women receiving tamoxifen plus OFS significantly more affected than those receiving tamoxifen alone. These differences were not present at 60 months.

The decline in sexual interest was significantly greater in patients receiving tamoxifen plus OFS at 6 months but not at 24 and 60 months (primary hypothesis 2). At baseline, 73% and 75% of the patients receiving tamoxifen plus OFS and tamoxifen alone, respectively, reported being sexually active. These proportions remained quite stable at 6, 24, and 60 months in both groups (tamoxifen plus OFS: 76%, 75%, and 69%, respectively; tamoxifen: 81%, 79%, and 74%, respectively). If sexually active, patients receiving tamoxifen plus OFS experienced significantly greater changes in difficulty becoming aroused than patients receiving tamoxifen alone at 6 and 24 months.

Patients receiving tamoxifen plus OFS experienced a significantly greater exacerbation in vaginal dryness over the whole treatment period (primary hypothesis 3), whereas patients on tamoxifen alone

experienced a significantly greater increase in vaginal discharge and vaginal itching/irritation in the short and intermediate term.

Patients receiving tamoxifen plus OFS experienced significantly more sleep disturbance at 6 months (primary hypothesis 3) than those receiving tamoxifen alone, but not at the later time points. Bone and joint pain was reported significantly more often in patients receiving tamoxifen compared with those receiving tamoxifen plus OFS at 60 months. No significant differences between the treatments groups were observed for all other symptoms.

Patients receiving tamoxifen plus OFS had slightly less improvement in coping effort and were more burdened by treatment at 6 and 24 months than those receiving tamoxifen alone (secondary hypothesis 1).

Changes over time in symptom burden and QoL for patients receiving exemestane plus OFS relative to the other two groups were summarized descriptively without formal comparison (Appendix Fig A1, online only). In patients receiving exemestane plus OFS, hot flashes and sweats worsened to a greater extent than those receiving tamoxifen alone, but to a lesser extent than those receiving tamoxifen plus OFS, at short and intermediate terms. Among the three treatment groups, patients receiving exemestane plus OFS were most affected by sexual dysfunction and vaginal dryness but least affected by vaginal discharge over the whole treatment period. Patients receiving exemestane plus OFS reported a greater worsening in bone and joint pains compared with the other two treatment groups. Changes in global QoL were similar in all three groups, with slightly greater treatment burden for exemestane plus OFS in the short term.

Adaptation

Overall, patients with more severe hot flashes compared with those with less severe hot flashes during the first 6 months had less

improvement in coping scores at this time point ($\Delta = -4$, $P = .0029$) but not thereafter (secondary hypothesis 2). Among patients without prior chemotherapy, patients who had more severe hot flashes at 6 months also experienced a slightly greater decline in physical well-being at this time point compared with the group with less severe hot flashes ($\Delta = -6$, $P = .0045$). No consistent difference in change of mood was observed between the two severity groups (data not shown).

Impact of Chemotherapy

Patients receiving prior chemotherapy were randomly assigned, on average, 8 months from final surgery, which was substantially later than those who did not receive chemotherapy (Table 1). Patients receiving prior chemotherapy reported lower baseline scores for vasomotor, gynecologic, and sexual symptoms; for bone and joint pain; and for being troubled by weight gain compared with the no chemotherapy cohort (Table 2). Thus, changes over time in these symptoms were smaller in this cohort

compared with the cohort without chemotherapy, as shown for hot flashes (Figs 2A and 2B). Baseline scores for the other symptoms and global indicators were similar between the two chemotherapy cohorts (Table 2).

At short term, the magnitude of treatment differences between tamoxifen plus OFS and tamoxifen alone varied among the two chemotherapy cohorts (Fig 5). In the cohort with prior chemotherapy, treatment differences were less pronounced for hot flashes ($\Delta = -26$), sweats ($\Delta = -19$), loss of sexual interest ($\Delta = -6$), difficulties becoming aroused ($\Delta = -4$), and sleep disturbance ($\Delta = -6$) in contrast to the cohort without chemotherapy (hot flashes, $\Delta = -32$; sweats, $\Delta = -27$; loss of sexual interest, $\Delta = -9$; difficulties becoming aroused, $\Delta = -8$; sleep disturbance, $\Delta = -15$). Furthermore, treatment differences were not statistically or clinically significant in the chemotherapy cohort for vaginal discharge ($\Delta = 1$), vaginal itching/irritation ($\Delta = 1$), bone/joint pain ($\Delta = 2$), coping ($\Delta = -2$), and treatment burden ($\Delta = -3$) in contrast to the cohort without prior chemotherapy (vaginal discharge, $\Delta = 7$; vaginal itching/irritation, $\Delta = 6$; bone/joint

Fig 2. (A) Scores for hot flashes (mean with 95% CIs; higher score indicates better condition) from baseline to 60 months according to treatment assignment and chemotherapy cohort. (B) Change in hot flush scores from baseline to 6, 24, and 60 months according to chemotherapy cohort. (C) Scores for loss of sexual interest (mean with 95% CIs; higher score indicates better condition) from baseline to 60 months according to chemotherapy cohort. (D) Change in scores for loss of sexual interest from baseline to 6, 24, and 60 months according to chemotherapy cohort. The vertical line at ± 8 indicates the minimal clinically meaningful change in quality-of-life (QoL) scores. Chemo, chemotherapy; OFS, ovarian function suppression; T, tamoxifen

Fig 2. (Continued).

pain, $\Delta = -6$; coping effort, $\Delta = -7$; treatment burden, $\Delta = -12$; each $P < .01$). Similarly, treatment differences between exemestane plus OFS and tamoxifen alone were less pronounced in the cohort with prior chemotherapy (Appendix Figs A2A and A2B, online only). No such pattern of treatment differences between the chemotherapy cohorts was observed at the intermediate- or long-term time points (Appendix Figs A2A and A2B).

DISCUSSION

In SOFT, patients reported considerable changes in key endocrine symptoms, with patients receiving tamoxifen plus OFS showing more detrimental effects than those receiving tamoxifen alone. Changes in global QoL domains were small with differences between the randomly assigned treatments being marginally clinically meaningful for treatment burden. Coping effort decreased slightly over time in both groups and may reflect patient adaptation.

Overall, these results correspond with our hypotheses and confirm previous findings.⁶⁻⁸ In contrast to the E-3193 trial,⁸ we found that treatment differences for most endocrine symptoms diminished after 2 years and were no longer clinically meaningful at 5 years. At this time point, the average age was 48 years, and more women may have reached menopause. The differing proportions of patients who had OFS achieved by luteinizing hormone-releasing hormone analog (36% in E-3193; 81% in SOFT throughout treatment) and the absence of chemotherapy in E-3193 may explain the more pronounced treatment differences observed in E-3193 compared with SOFT. A subgroup analysis in E-3193 indicated slightly better patient-reported outcomes for these patients compared with those with surgically induced menopause.⁸ Direct comparison between the SOFT and the E-3193 patient-reported outcomes is complicated by the use of a summary score and the lack of consideration of clinically significant treatment differences for menopausal symptoms and sexual activity in E-3193. SOFT showed that the magnitudes of differences between treatments varied for individual symptoms, with vasomotor and sexual symptoms experienced as most burdensome, especially for patients on tamoxifen plus OFS.

Fig 3. Change in quality-of-life (QoL) symptom indicator scores from baseline to 6, 24, and 60 months, according to treatment assignment, overall across chemotherapy cohorts. The vertical line at ± 8 indicates the minimal clinically meaningful change in QoL scores. OFS, ovarian function suppression.

For gynecologic symptoms, changes over time and differences between treatments, even if statistically significant, were marginally clinically meaningful. However, 19% of patients in the total sample stopped tamoxifen, and 21% of patients discontinued triptorelin early.² A substantial minority of patients

are expected to suffer from burdensome symptoms.²⁴ Women's judgment of gains in survival that make endocrine treatment worthwhile varies considerably, and larger benefits are required to make it worthwhile compared with chemotherapy.^{25,26} Our results provide a detailed picture of patients' perception of

Fig 4. Change in quality-of-life (QoL) global indicator scores from baseline to 6, 24, and 60 months, according to treatment assignment, overall across chemotherapy cohorts. The vertical line at ± 8 indicates the minimal clinically meaningful change in QoL scores. OFS, ovarian function suppression.

Table 2. Baseline Quality-of-Life Scores According to Chemotherapy Cohort and Treatment Assignment

Symptom/Global Indicator	No Chemotherapy				Prior Chemotherapy			
	T		T+OFS		T		T+OFS	
	Mean Score	SD	Mean Score	SD	Mean Score	SD	Mean Score	SD
Vasomotor								
Hot flushes	88.7	20.4	91.2	16.9	71.7	29.9	70.7	33.2
Sweats (including night sweats)	84.9	19.9	87.4	19.1	74.4	27.5	73.5	30.0
Sexual symptoms								
Loss of sexual interest	78.5	26.7	78.7	27.0	68.6	30.2	65.4	31.1
Difficulties in becoming aroused	85.3	20.3	83.4	23.0	72.9	27.7	70.3	27.8
Gynecologic symptoms								
Vaginal discharge	88.0	17.5	87.1	17.8	77.7	24.5	79.7	22.4
Vaginal dryness	89.7	18.0	92.0	15.4	80.2	25.9	79.8	25.2
Vaginal itching/irritation	91.1	17.3	92.1	14.8	86.2	21.5	85.5	22.7
Musculoskeletal/neurologic pain								
Bone or joint pain	83.2	23.1	83.3	23.3	76.1	26.6	74.5	28.4
Headaches	82.1	23.5	82.6	22.4	83.0	21.4	82.2	23.2
GI symptoms								
Appetite	80.1	22.2	81.8	21.5	80.5	21.5	80.8	20.5
Feeling sick (nausea/vomiting)	91.5	16.3	93.7	13.3	91.0	17.5	91.1	17.1
Constitutional/psychological symptoms								
Sleep disturbance	71.2	27.1	70.7	27.4	67.2	29.4	67.2	29.0
Tiredness	58.4	29.3	60.2	26.3	58.4	25.9	53.4	26.1
Troubled by weight gain	84.9	24.2	84.0	24.7	70.3	30.9	68.5	32.1
Being irritable	74.2	25.2	75.3	23.1	71.8	24.9	71.5	24.5
Feeling dizzy	89.6	17.4	91.1	15.8	86.6	20.3	86.9	19.3
Global indicators								
Physical well-being	75.0	23.3	77.6	20.8	77.1	22.1	76.8	20.9
Mood	71.6	23.8	72.2	22.5	75.2	21.8	73.8	23.0
Coping effort	66.9	27.0	69.8	24.9	67.7	26.2	69.2	25.7
Treatment burden	77.3	24.9	78.9	22.6	70.4	25.2	71.5	24.4
Health perception	72.9	21.1	72.8	20.9	70.8	21.9	72.3	21.1

NOTE. All indicators range from 0 to 100, with higher scores indicating a better condition.
Abbreviations: OFS, ovarian function suppression; SD, standard deviation; T, tamoxifen.

individual symptoms over time and can facilitate the discussion of specific adverse effects between physicians and patients.

If the combination of OFS with an aromatase inhibitor is recommended⁹ for women at higher risk of recurrence, the benefit of exemestane plus OFS has to be balanced particularly with the detrimental effects of sexual problems, vaginal dryness, and bone and joint pains. On the basis of descriptive results, these symptoms were expressed substantially more often by patients receiving exemestane plus OFS compared with those receiving tamoxifen alone. Sexual problems are a serious concern considering that they persisted over the whole treatment period in all three treatment groups. Survivorship studies show that sexual dysfunction even continues beyond the treatment phase²⁷ and that younger women have higher rates of sexual dysfunction than expected in healthy women.²⁸

We observed a clinically relevant short-term impact of chemotherapy. The cohort with prior chemotherapy had worse baseline scores for responsive symptoms, possibly caused by chemotherapy and reflecting that half of these patients received tamoxifen before enrollment. Contrary to our expectation, chemotherapy did not exacerbate adverse effects. Differences between treatments in short-term symptom changes (eg, hot flushes, sleep disturbance, bone/joint pains), treatment burden, and coping effort were less pronounced or even statistically and clinically insignificant in patients who received prior chemotherapy. This

confirms earlier findings that differential effects of endocrine treatments are seen primarily among patients who have not received chemotherapy.⁶

One limitation of our study is that 7% of participating centers were excluded for the QoL evaluation as a result of poor form submission rates, despite a pragmatic measurement approach based on linear analog self-assessment indicators as used in previous International Breast Cancer Study Group trials. Longitudinal QoL assessment in more than 500 centers worldwide is a challenge. Submission rates decreased over time, but overall, they were balanced between the randomly assigned treatments. Sensitivity analysis confirmed that results were robust to the analysis approach for missing data. Specific clinically relevant domains such as depression and sexual and cognitive functioning could not be addressed in detail but will be investigated in a subset of patients from SOFT and TEXT.

In conclusion, our results confirm the detrimental effect of adding OFS to tamoxifen on endocrine symptom burden. Compared with previous studies, we showed that the cumulative burden of OFS varied for individual symptoms. The effect of OFS on impaired symptom-specific QoL, treatment burden, and coping effort during the first 2 years of treatment was less pronounced for patients who received prior chemotherapy, the cohort that benefited most from OFS in terms of disease control.

Fig 5. Change in quality-of-life (QoL) symptom and global indicator scores from baseline to 6 months according to chemotherapy cohorts (side by side). The vertical line at ± 8 indicates the minimal clinically meaningful change in QoL scores. The baseline scores for each indicator are summarized according to cohort and treatment in Table 2. OFS, ovarian function suppression.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Karin Ribi, Jürg Bernhard, Prudence A. Francis, Harold J. Burstein, Marco Colleoni, Alan S. Coates, Aron Goldhirsch, Richard D. Gelber, Gini F. Fleming
Administrative support: Karen N. Price

Provision of study materials or patients: Prudence A. Francis, Harold J. Burstein, Eva Ciruelos, Meritxell Bellet, Lorenzo Pavesi, Ana Lluch, Marilena Visini, Vani Parmar, Carlo Tondini, Pierre Kerbrat, Antonia Perelló, Patrick Neven, Roberto Torres, Davide Lombardi, Fabio Puglisi, Per Karlsson, Thomas Ruhstaller, Gini F. Fleming
Collection and assembly of data: Prudence A. Francis, Harold J. Burstein, Eva Ciruelos, Meritxell Bellet, Lorenzo Pavesi, Ana Lluch, Marilena Visini, Vani Parmar, Carlo Tondini, Pierre Kerbrat, Antonia Perelló, Patrick Neven, Roberto Torres, Davide Lombardi, Fabio Puglisi, Per Karlsson, Thomas Ruhstaller, Meredith M. Regan, Gini F. Fleming

Data analysis and interpretation: Karin Ribi, Weixiu Luo, Jürg Bernhard, Alan S. Coates, Karen N. Price, Richard D. Gelber, Meredith M. Regan
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

- Pagani O, Regan MM, Walley BA, et al: Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. *N Engl J Med* 371:107-118, 2014
- Francis PA, Regan MM, Fleming GF, et al: Adjuvant ovarian suppression in premenopausal breast cancer. *N Engl J Med* 372:436-446, 2015

- Hershman DL: Perfecting breast-cancer treatment: Incremental gains and musculoskeletal pains. *N Engl J Med* 372:477-478, 2015
- Jankowitz RC, Puhalla S, Davidson NE: Should we embrace or ablate our urge to (ovarian) suppress? *J Clin Oncol* 32:3920-3922, 2014
- Bernhard J, Luo W, Ribi K, et al: Patient-reported outcomes with adjuvant exemestane versus tamoxifen in premenopausal women with early breast cancer undergoing ovarian suppression (TEXT

and SOFT): A combined analysis of two phase 3 randomised trials. *Lancet Oncol* 16:848-858, 2015

- Nystedt M, Berglund G, Bolund C, et al: Side effects of adjuvant endocrine treatment in premenopausal breast cancer patients: A prospective randomized study. *J Clin Oncol* 21:1836-1844, 2003
- Berglund G, Nystedt M, Bolund C, et al: Effect of endocrine treatment on sexuality in premenopausal breast cancer patients: A prospective randomized study. *J Clin Oncol* 19:2788-2796, 2001

8. Tevaarwerk AJ, Wang M, Zhao F, et al: Phase III comparison of tamoxifen versus tamoxifen plus ovarian function suppression in premenopausal women with node-negative, hormone receptor-positive breast cancer (E-3193, INT-0142): A trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 32:3948-3958, 2014
9. Coates AS, Winer EP, Goldhirsch A, et al: Tailoring therapies-improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. *Ann Oncol* 26:1533-1546, 2015
10. Regan MM, Paganini O, Fleming GF, et al: Adjuvant treatment of premenopausal women with endocrine-responsive early breast cancer: Design of the TEXT and SOFT trials. *Breast* 22:1094-1100, 2013
11. Bernhard J, Hürny C, Coates AS, et al: Quality of life assessment in patients receiving adjuvant therapy for breast cancer: The IBCSG approach. *Ann Oncol* 8:825-835, 1997
12. Butow P, Coates A, Dunn S, et al: On the receiving end. IV: Validation of quality of life indicators. *Ann Oncol* 2:597-603, 1991
13. Hürny C, Bernhard J, Coates A, et al: Responsiveness of a single-item indicator versus a multi-item scale: Assessment of emotional well-being in an international adjuvant breast cancer trial. *Med Care* 34:234-248, 1996
14. Hürny C, Bernhard J, Bacchi M, et al: The Perceived Adjustment to Chronic Illness Scale (PACIS): A global indicator of coping for operable breast cancer patients in clinical trials. *Support Care Cancer* 1:200-208, 1993
15. Hürny C, van Wegberg B, Bacchi M, et al: Subjective health estimations (SHE) in patients with advanced breast cancer: An adapted utility concept for clinical trials. *Br J Cancer* 77:985-991, 1998
16. Bernhard J, Sullivan M, Hürny C, et al: Clinical relevance of single item quality of life indicators in cancer clinical trials. *Br J Cancer* 84:1156-1165, 2001
17. Bernhard J, Maibach R, Thürlimann B, et al: Patients' estimation of overall treatment burden: Why not ask the obvious? *J Clin Oncol* 20:65-72, 2002
18. Day R, Ganz PA, Costantino JP, et al: Health-related quality of life and tamoxifen in breast cancer prevention: A report from the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Clin Oncol* 17:2659-2669, 1999
19. Fallowfield L, Fleissig A, Edwards R, et al: Tamoxifen for the prevention of breast cancer: Psychosocial impact on women participating in two randomized controlled trials. *J Clin Oncol* 19:1885-1892, 2001
20. Ganz PA, Day R, Ware JE Jr, et al: Base-line quality-of-life assessment in the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial. *J Natl Cancer Inst* 87:1372-1382, 1995
21. Greendale GA, Reboussin BA, Hogan P, et al: Symptom relief and side effects of postmenopausal hormones: Results from the Postmenopausal Estrogen/Progestin Interventions Trial. *Obstet Gynecol* 92:982-988, 1998
22. Alfano CM, McGregor BA, Kuniyuki A, et al: Psychometric properties of a tool for measuring hormone-related symptoms in breast cancer survivors. *Psychooncology* 15:985-1000, 2006
23. Sloan JA, Dueck A: Issues for statisticians in conducting analyses and translating results for quality of life end points in clinical trials. *J Biopharm Stat* 14:73-96, 2004
24. Maunsell E, Goss PE, Chlebowski RT, et al: Quality of life in MAP.3 (Mammary Prevention 3): A randomized, placebo-controlled trial evaluating exemestane for prevention of breast cancer. *J Clin Oncol* 32:1427-1436, 2014
25. Duric V, Stockler M: Patients' preferences for adjuvant chemotherapy in early breast cancer: A review of what makes it worthwhile. *Lancet Oncol* 2:691-697, 2001
26. Duric VM, Fallowfield LJ, Saunders C, et al: Patients' preferences for adjuvant endocrine therapy in early breast cancer: What makes it worthwhile? *Br J Cancer* 93:1319-1323, 2005
27. Bober SL, Varela VS: Sexuality in adult cancer survivors: Challenges and intervention. *J Clin Oncol* 30:3712-3719, 2012
28. Schover LR: Premature ovarian failure and its consequences: Vasomotor symptoms, sexuality, and fertility. *J Clin Oncol* 26:753-758, 2008

Affiliations

Karin Ribi, Aron Goldhirsch, and Jürg Bernhard, International Breast Cancer Study Group Coordinating Center; Jürg Bernhard, Bern University Hospital, Inselspital, Bern; Thomas Ruhstaller, Breast Center St Gallen, Swiss Group for Clinical Cancer Research, and International Breast Cancer Study Group, St Gallen, Switzerland; Weixiu Luo, Karen N. Price, Richard D. Gelber, and Meredith M. Regan, International Breast Cancer Study Group Statistical Center; Weixiu Luo, Harold J. Burstein, Richard D. Gelber, and Meredith M. Regan, Dana-Farber Cancer Institute; Harold J. Burstein, Alliance for Clinical Trials in Oncology; Karen N. Price and Richard D. Gelber, Frontier Science and Technology Research Foundation; Richard D. Gelber and Meredith M. Regan, Harvard Medical School, Boston, MA; Gini F. Fleming, The University of Chicago Medical Center and Alliance for Clinical Trials in Oncology, Chicago, IL; Prudence A. Francis, International Breast Cancer Study Group, Peter MacCallum Cancer Center, St Vincent's Hospital, University of Melbourne, Melbourne, Victoria; Australia and New Zealand Breast Cancer Trials Group, University of Newcastle, Newcastle; Alan S. Coates, International Breast Cancer Study Group and University of Sydney, Sydney, New South Wales, Australia; Eva Ciruelos, University Hospital 12 de Octubre and SOLTI Group, Madrid; Meritxell Bellet, Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, and SOLTI Group, Universitat Autònoma de Barcelona, Barcelona; Ana Lluch, Hospital Clínico Universitario de Valencia, InCIVA Biomedical Research Institute, University of Valencia and SOLTI Group, Valencia; Antonia Perelló, Hospital Universitari Son Espases and SOLTI Group, Palma de Mallorca, Spain; Lorenzo Pavesi, Salvatore Maugeri Foundation and International Breast Cancer Study Group, Pavia; Marilena Visini, Ospedale Civile di Lecco and International Breast Cancer Study Group, Lecco; Carlo Tondini, Ospedale Papa Giovanni XXIII and International Breast Cancer Study Group, Bergamo; Davide Lombardi, Centro di Riferimento Oncologico and International Breast Cancer Study Group, Aviano; Fabio Puglisi, University Hospital of Udine, University of Udine, and International Breast Cancer Study Group, Udine; Marco Colleoni and Aron Goldhirsch, European Institute of Oncology and International Breast Cancer Study Group, Milan, Italy; Vani Parmar, Breast Services, Tata Memorial Hospital and International Breast Cancer Study Group, Mumbai, India; Pierre Kerbrat, Centre Eugène Marquis, Université de Rennes 1, Rennes, France; Pierre Kerbrat and Patrick Neven, European Organisation for Research and Treatment of Cancer, Brussels; Patrick Neven, UZ Gasthuisberg, Leuven, Belgium; Roberto Torres, Instituto Nacional del Cancer, Chilean Cooperative Group for Oncologic Research Group, and International Breast Cancer Study Group, Santiago, Chile; and Per Karlsson, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Sahlgrenska University Hospital, and International Breast Cancer Study Group, Gothenburg, Sweden.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Adjuvant Tamoxifen Plus Ovarian Function Suppression Versus Tamoxifen Alone in Premenopausal Women With Early Breast Cancer: Patient-Reported Outcomes in the Suppression of Ovarian Function Trial

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

Karin Ribi

No relationship to disclose

Weixiu Luo

No relationship to disclose

Jürg Bernhard

No relationship to disclose

Prudence A. Francis

Travel, Accommodations, Expenses: Roche

Other Relationship: Pfizer

Harold J. Burstein

No relationship to disclose

Eva Ciruelos

No relationship to disclose

Meritxell Bellet

Honoraria: AstraZeneca

Consulting or Advisory Role: AstraZeneca

Lorenzo Pavesi

No relationship to disclose

Ana Lluch

Consulting or Advisory Role: Novartis, Roche, Pfizer

Marilena Visini

No relationship to disclose

Vani Parmar

No relationship to disclose

Carlo Tondini

No relationship to disclose

Pierre Kerbrat

No relationship to disclose

Antonia Perelló

No relationship to disclose

Patrick Neven

No relationship to disclose

Roberto Torres

Research Funding: Roche, GlaxoSmithKline

Travel, Accommodations, Expenses: Sanofi

Davide Lombardi

No relationship to disclose

Fabio Puglisi

No relationship to disclose

Per Karlsson

No relationship to disclose

Thomas Ruhstaller

Consulting or Advisory Role: Roche, AstraZeneca

Marco Colleoni

Honoraria: Novartis

Consulting or Advisory Role: Boehringer Ingelheim, Taiho Pharmaceutical, AbbVie, AstraZeneca, Pierre Fabre, Pfizer

Alan S. Coates

No relationship to disclose

Aron Goldhirsch

No relationship to disclose

Karen N. Price

No relationship to disclose

Richard D. Gelber

Research Funding: AstraZeneca (Inst), GlaxoSmithKline (Inst), Novartis (Inst), Roche (Inst), Celgene (Inst), Merck (Inst), Pfizer (Inst)

Meredith M. Regan

Research Funding: Veridex (Inst), OncoGenex (Inst), Pfizer (Inst), Ipsen (Inst), Novartis (Inst), Merck (Inst), Ferring (Inst), Celgene (Inst), AstraZeneca (Inst)

Gini F. Fleming

Research Funding: Corcept Therapeutics (Inst)

Other Relationship: Aeterna Zentaris

Acknowledgment

We thank the patients, physicians, nurses, and trial coordinators who participated in the SOFT clinical trial. Presented in part at the 37th San Antonio Breast Cancer Symposium, San Antonio, TX, December 9-13, 2014.

Appendix

Suppression of Ovarian Function Trial Investigators and the International Breast Cancer Study Group Participants

Steering Committee: P.A. Francis (Chair, SOFT Co-Chair), G.F. Fleming (Suppression of Ovarian Function Trial [SOFT] Co-Chair), M.M. Regan (Trial Statistician), R. Torrisi, L. Blacher, H. Bonnefoi, E. Ciruelos, A.S. Coates, M. Colleoni, N. Dif, R.D. Gelber, A. Goldhirsch, T. Goulioti, T. Heckman-Scolese, A. Hiltbrunner, R. Kammeler, R. Maibach, O. Ortmann, O. Pagani, E.A. Perez, K.N. Price, M. Rabaglio, B. Ruepp, K. Tryfonidis, K. Scott, H. Shaw, G. Viale, G. von Minckwitz, B.A. Walley, D. Zardavas, L. Cisar (Pfizer), E. Chetaille (Ipsen)

International Breast Cancer Study Group (IBCSG) Scientific Committee: A. Goldhirsch, A.S. Coates, M. Colleoni (Co-Chairs)

IBCSG Foundation Council: R. Stahl (President), S. Aebi, A.S. Coates, M. Colleoni, R.D. Gelber, A. Goldhirsch, M. Green, P. Karlsson, I. Kössler, I. Láng

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

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

IBCSG Data Management Center, Frontier Science and Technology Research Foundation, Amherst, NY: L. Blacher (Director), K. Scott (DM Section Head), M. Blackwell, A. Cesario, A. Dickinson, K. Donahue, M. Greco, P. Gonzalez, T. Heckman-Scolese, R. Hecker, R. Hinkle, M. Kalera, K. Lupejkis, A. Mora de Karausch, V. Palermo, H. Shaw, J. Swick-Jemison

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

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

US National Cancer Institute (NCI): J. Abrams, J.A. Zujewski

US 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 (Cancer and Leukemia Group B) Pathology Coordinating Office, Ohio State University, Columbus, OH: W. Frankel, S. Jewell

Dana-Farber Cancer Institute, Boston, MA (US Food and Drug Administration Investigational New Drug): E.P. Winer, J. Savoie

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

Ipsen Study Support: E. Chetaille, J. Amauri Soares, C. Descot, S. Hemont-Dacosta, F. Bismuth, P. Chevreau, H. Bibas

Participating Centers and Principal Investigators

Centers with accrual of more than one patient included in quality-of-life analysis.

SOFT

Breast International Group

IBCSG

Australia and New Zealand Breast Cancer Trials Group (ANZBCTG), Australia; Prof. John Forbes, Dianne Lindsay, Lauren Boyes.

Austin Health, Heidelberg, Victoria; J. Stewart

Ballarat Oncology and Haematology Services, Wendouree, Victoria; G. Kannourakis

Border Medical Oncology, Wodonga, Victoria; C. Underhill

Calvary Mater Newcastle, Waratah, New South Wales; A. van der Westhuizen

Canberra Hospital, The, Garran, Australian Capital Territory; A. Davis

Coffs Harbor Health Campus, Coffs Harbor, New South Wales; K. Briscoe
 Concord Repatriation General Hospital, Concord, New South Wales; P. Beale
 Launceston General Hospital, Launceston, Tasmania; S. Gauden
 Liverpool Hospital, Liverpool, New South Wales; E. Moylan
 Macarthur Cancer Therapy Centre, Campbelltown, New South Wales; S. Della-Fiorentina
 Manning Rural Referral Hospital, Taree, New South Wales; E. Livshin
 Maroondah Hospital, Ringwood East, Victoria; J. Chirgwin
 Mater Hospital, The, North Sydney, New South Wales; F. Boyle
 Monash Medical Centre, East Bentleigh, Victoria; M. White
 Mount Hospital, Perth, Western Australia; A. Chan
 Nambour Hospital, Nambour, Queensland; G. Hawson
 Peter MacCallum Cancer Center, East Melbourne, Victoria; P.A. Francis
 Riverina Cancer Care Centre, Wagga Wagga, New South Wales; J. Hill
 Royal Adelaide Hospital, Adelaide, South Australia; P.G. Gill
 Royal Brisbane and Women's Hospital, Herston, Queensland; M. Nottage
 Royal Hobart Hospital, Hobart, Tasmania; D. Boadle
 Royal Prince Alfred Hospital, Camperdown, New South Wales; J. Beith
 St Andrews Toowoomba Hospital, Toowoomba, Queensland; P. Vasey
 St John of God Hospital, Bunbury, Western Australia; M. Buck
 St John of God Hospital, Subiaco, Western Australia; S. Ng
 St Vincent's Hospital, Fitzroy, Victoria; R. Snyder
 St Vincent's Hospital, Darlinghurst, New South Wales; R. Epstein
 Tweed Hospital, The, Tweed Heads, New South Wales; E. Abdi
 Victorian Breast and Oncology Care, Melbourne, Victoria; M. Chipman
 ANZBCTG, New Zealand. Auckland City Hospital, Auckland; V.J. Harvey
 Christchurch Hospital, Christchurch; B. Fitzharris
 Waikato Hospital, Hamilton; I. Campbell
Brazil. Hospital de Clinicas de Porto Alegre, Porto Alegre; J. Villanova Biazús
Grupo Oncológico Corporativo Chileno de Investigación (GOCCHI), Chile; A. Corvalan, B. Muller.
 Instituto Nacional del Cancer, Santiago; R. Torres
 Hospital San Juan de Dios, Santiago; S. Torres
 Hospital San Borja Arriaran, Santiago; J. Letzkus
 Hospital Clinico de la Universidad de Chile, Santiago; O. Barajas
 Hospital Dr Sotero Del Rio, Santiago; H. Rojas
 Centro De Patologia Mamaria, Santiago; M.E. Bravo
 Hospital Base de Valdivia, Valdivia; B. Cardemil
 Instituto De Radiomedicina, Vitacura; R. Baeza
India. Tata Memorial Hospital, Mumbai; V. Parmar
Italy. Centro di Riferimento Oncologico, Aviano; D. Crivellari
 Azienda Sanitaria di Bolzano, Bolzano; C. Graiff
 Ospedali Riuniti di Bergamo, Bergamo; C. Tondini
 Ospedale degli Infermi, Biella; M. Clerico
 Unita Operativa de Medicina Oncologica, Ospedale Ramazzini, Carpi; A. Fabrizio
 Oncologia Medica Fano Italy, Fano; R. Mattioli
 Ospedale Civile di Lecco, Lecco; M. Visini
 Fondazione Salvatore Maugeri, Pavia; L. Pavesi
 Ospedale di Circolo e Fondazione Macchi, Varese; G. Pinotti
 Dipartimento di Oncologia, Azienda Ospedaliero-Universitaria di Udine, Udine; F. Puglisi
South Africa. Sandton Oncology Centre, Johannesburg; D. Vorobiof
Sweden. Sahlgrenska University Hospital, Gothenburg; P. Karlsson
 Central Hospital Karlstad, Karlstad; B. Loden

Karolinska University Hospital, Stockholm; J. Bergh
 Lund University Hospital, Lund; P. Malmström
 Skaraborg Hospital Skovde, Skovde; A. Nissborg
 Southern Elfsborg Hospital Boras, Boras; P. Karlsson
Swiss Association for Clinical Cancer Research (SAKK), Switzerland.
 Centre Hospitalier Universitaire Vaudois, Lausanne; K. Zaman
 Inselspital, Berne; M. Rabaglio
 Kantonsspital St Gallen, St Gallen; T. Ruhstaller
 Rätisches Kantonos/Regionalspital, Chur; R. von Moos
 Kantonsspital Basel, Basel; C. Rochlitz
 Onkologiezentrum Thun-Berner Oberland, Thun; D. Rauch
 Oncocare Engeried, Bern; K. Buser
 Zürich Frauenklinik, Zurich; N. Gabriel
 Brust-Zentrum Zurich, Zurich; C. Rageth
 Kantonsspital Aarau (AG), Aarau; A. Schoenenberger
 Tumor Zentrum Hirslanden Klinik, Aarau; R. Popescu
 Kantonsspital Baden, Baden; C. Caspar
 Tumor und Brustzentrum Zetup St Gallen, St Gallen; H.J. Senn

SOLTI, Spain; E. Ciruelos

Hospital Clinic i Provincial de Barcelona, Barcelona; M. Muñoz
 Hospital Universitari Vall D'Hebron, Barcelona; M. Bellet
 Hospital Universitario 12 de Octubre, Madrid; E. Ciruelos
 Centro Oncologico MD Anderson, Madrid; A. González Martín
 Hospital Son Llatzer, Palma de Mallorca; J.G. Catalán
 Clinica Univ. De Navarra, Pamplona; J.M. Aramendia
 Hospital Son Dureta (Palma de Mallorca), Palma de Mallorca; J. Rifa
 Hospital Santiago De Compostela, Santiago de Compostela; R. López
 H.U. Arnau de Vilanova, Lleida; A. Llombart
 Hospital Universitario Virgen Macarena, Sevilla; J.A. Virizuela
 Hospital Clinico Universitario de Valencia, Valencia; A. Lluch
 Hospital Sant Joan de Reus, Reus; M. Melé
 Hospital Reina Sofia De Cordoba, Cordoba; J.R. de la Haba
 Hospital Dr Negrin, Las Palmas de Gran Canari; Negrin; U. Bohn
 Hospital Sant Pau i Santa Tecla, Tecla; C. Pérez Segura

Central and East European Oncology Group; J. Jassem

Poland. Medical University of Gdansk, Gdansk, Poland; J. Jassem
Serbia. Institute of Oncology and Radiology of Serbia, Belgrade, Serbia; Z. Neskovic-Konstantinovic

European Organisation for Research and Treatment of Cancer; N. Dif, J. Bogaerts, K. Tryfonidis

Belgium. ZNA Middelheim, Antwerpen; A. Vandebroek
 Cliniques Universitaires St-Luc UCL, Brussels; M. Berliere
 U.Z. Gasthuisberg, Leuven; P. Neven
 Centre Hospitalier Universitarie Sart Tilman, Liège; G. Jerusalem
 Hopital De Jolimont, Haine St Paul; C. Mitine
 Clinique Sainte Elisabeth, Namur; P. Vuylsteke
 Algemeen Ziekenhuis Sint-Augustinus, Wilrijk; L. Dirix
France. Centre Henri Becquerel, Rouen; C. Moldovan
 Institut Claudius Regaud, Toulouse; B. de Lafontan
 Institut Jean Godinot, Reims; C. Jouannaud
 Centre Leon Berard, Lyon; T. Bachelot
 Centre Georges Francois-Leclerc, Dijon; I. Desmoulins

Centre Rene Huguenin, Saint-Cloud; E. Brain
Institut Curie, Paris; J.Y. Pierga
Centre Eugene Marquis, Rennes; P. Kerbrat
Centre Hospitalier Régional Universitaire de Limoges, Limoges; N. Tubiana-Mathieu
Clinique Mutualiste de l'Estuaire, Saint-Nazaire; V. Delecroix
Clinique De L'alliance, Tours; A. Fignon
Israel. Rambam Medical Center, Haifa; G. Fried
Netherlands. Onze Lieve Vrouwe Gasthuis, Amsterdam; O. Leeksa
Portugal. Centro de Lisboa, Lisboa; A. Moreira
Turkey. Marmara University Hospital, Istanbul; F. Dane

German Breast Group; S. Buchholz, K. ReißMüller, S. Loibl, G. Von Minckwitz

Praxis Dr Tessen, Goslar; H.W. Tessen
Universitätsfrauenklinik Erlangen, Erlangen; M.W. Beckmann
Klinikum Mittelbaden/Stadtklinik Baden-Baden, Baden-Baden; A. Hahn
Dr. Horst Schmidt Kliniken, Wiesbaden; F. Lorenz-Salehi
St. Vincentius Kliniken, Karlsruhe; O. Tomé
Caritas-Krankenhaus St Josef, Regensburg; S. Buchholz
Krankenhaus der Barmherzigen Brüder, Regensburg; H. Stauder

All Ireland Cooperative Oncology Research Group

Beaumont Hospital, Dublin; L. Grogan
Mater Misericordiae Hospital, Dublin; J. McCaffrey
Mater Private Hospital, Dublin; J. McCaffrey
University College Hospital Galway, Galway; M. Keane
South Infirmary-Victoria University Hospital, Cork; S. O'Reilly
Adelaide, Meath and National Children's Hospital, Dublin; J. Walshe

Institute of Cancer Research–Clinical Trials and Statistics Unit on Behalf of the National Cancer Research Institute Breast Clinical Studies Group, United Kingdom; R. Coleman, J. Bliss, A. Gillman, N. Atkins

South Tyneside District Hospital, South Shields, Tyne & Wear; G. Mazdai
Weston Park Hospital, Sheffield, South Yorkshire; R. Coleman
Mount Vernon Hospital, Northwood, Middlesex; A. Makris
Luton & Dunstable Hospital, Luton; A. Makris
Clatterbridge Centre for Oncology, Wirral; S. O'Reilly
Great Western Hospital, Swindon; D. Cole
New Cross Hospital, Wolverhampton; M Churn
Aberdeen Royal Infirmary, Aberdeen; R. Todd
Royal Marsden Hospital–Fulham, London; I.E. Smith
Royal Marsden Hospital–Sutton, Surrey; I.E. Smith
York Hospital, York; J. Joji
St James Univ Hospital, Leeds; T. Perren
Harrogate District Hospital, Harrogate; J. Joji
Stepping Hill Hospital, Stockport; A. Chittalia
Russells Hall Hospital, Dudley; P. Ramachanara

North American Breast Cancer Group

American College of Surgeons Oncology Group (ACOSOG, now part of Alliance for Clinical Trials in Oncology)
Cancer and Leukemia Group B (CALGB, now part of Alliance for Clinical Trials in Oncology)
Eastern Cooperative Oncology Group (now part of ECOG-ACRIN Cancer Research Group); N. Davidson, V. Stearns, R.M. O'Regan, S. Gluck
National Cancer Institute of Canada Clinical Trials Group (NCIC CTG); K.I. Pritchard, T. Whelan, K. Gelmon, M. Webster
National Surgical Adjuvant Breast and Bowel Project (NSABP, now part of NRG Oncology)

North Central Cancer Treatment Group (NCCTG, now part of Alliance for Clinical Trials in Oncology); J.N. Ingle
Radiation Therapy Oncology Group (RTOG, now part of NRG Oncology)
Southwest Oncology Group; G.N. Hortobagyi, S. Martino, J.R. Gralow, A.F. Scott

North American Participating Centers

Canada. Doctor H. Bliss Murphy Cancer Center, St John's, Newfoundland; J.S. McCarthy
BC Cancer Agency (BCCA)-Vancouver Cancer Center, Vancouver, British Columbia; H. Kennecke
Centre Hospitalier de l'Université de Montréal–Hotel Dieu du Montreal, Montreal, Quebec; A. Robidoux
Hôpital Du Sacre-Coeur de Montreal, Montreal, Quebec; J.A. Roy
Hôpital Charles LeMoine, Greenfield Park, Quebec; C. Prady
Cancer Centre of Southeastern Ontario at Kingston General Hospital, Kingston, Ontario; V. Kumar
Ottawa Hospital Research Institute, Ottawa, Ontario; S.F. Dent
Thunder Bay Regional Health Science Centre, Thunder Bay, Ontario; D. Vergidis
Health Sciences North, Sudbury, Ontario; P.G. Lopez
Juravinski Cancer Centre at Hamilton Health Sciences, Hamilton, Ontario; R.G. Tozer
Odette Cancer Centre, Toronto, Ontario; K.I. Pritchard
London Regional Cancer Center, London, Ontario; K.R. Potvin
Cancercare Manitoba, Winnipeg, Manitoba; D. Grenier
Cross Cancer Institute, Edmonton, Alberta; K.S. Tonkin
Tom Baker Cancer Center, Calgary, Alberta; B.A. Walley (Chair), M. Webster (Primary Investigator)
BCCA Cancer Center for the Southern Interior, Kelowna, British Columbia; S. Ellard
BCCA-Fraser Valley Cancer Center, Surrey, British Columbia; G. K. Pansegrau
Allan Blair Cancer Centre, Regina, Saskatchewan; M. Salim
United States of America. Providence Alaska Medical Center, Anchorage, AK; J.E. Anderson
University of California at Los Angeles (UCLA), Los Angeles, CA; P.A. Ganz
University of Southern California, Los Angeles, CA; C.A. Russel
Scripps Clinic–La Jolla, La Jolla, CA; J.F. Kroener
University of California San Diego Moores Cancer Center, San Diego, CA; B.A. Parker
John Muir Medical Center, Concord, CA; J.T. Ganey
Kaiser Permanente–Fremont, Fremont, CA; L. Fehrenbacher
Alta Bates Hospital, Berkeley, CA; D.H. Irwin
Kaiser Permanente Santa Teresa (San Jose), Vallejo, CA; L. Fehrenbacher
Mercy General Hospital, Carmichael, CA; M. Javeed
Kaiser Permanente–San Francisco, Vallejo, CA; L. Fehrenbacher
Santa Rosa Memorial Hospital, Santa Rosa, CA; I.C. Anderson
Stanford University Medical Center, Stanford, CA; I.L. Wapnir
Kaiser Permanente, San Diego, CA; J.A. Polikoff
Glendale Memorial Hospital and Health Center, Glendale, CA; G. Al-Jazayrly
Penrose-Saint Francis Healthcare, Colorado Springs, CO; E.R. Pajon
Front Range Cancer Specialists, Fort Collins, CO; D. Medgyesy
Longmont United Hospital, Longmont, CO; E.R. Pajon
The Shaw Regional Cancer Center, Aurora, CO; A.D. Elias
Greenwich Hospital, Greenwich, CT; B.J. Drucker
Norwalk Hospital, Norwalk, CT; R.C. Frank
Eastern Connecticut Hematology and Oncology Associates, Norwich, CT; K. Jagathambal
Northwest Connecticut Oncology–Hematology Associates, Torrington, CT; D.S. Brandt
Georgetown University Hospital, Washington, DC; C. Isaacs
Washington Hospital Center, Washington, DC; A. Aggarwal
Sibley Memorial Hospital, Washington, DC; F. Barr
Christiana Healthcare Services–Christian Hospital, Newark, DE; D.D. Biggs
Mount Sinai Medical Center Community Clinical Oncology Program (CCOP), Miami Beach, FL; M.A. Schwartz

Holy Cross Hospital, Fort Lauderdale, FL; R.C. Lilenbaum
 Sarasota Memorial Hospital, Sarasota, FL
 Dekalb Medical Center, Atlanta, GA; T.E. Seay
 Emory University, Atlanta, GA; R.M. O'Regan
 Memorial Health University Medical Center, Savannah, GA; H.C. Lebos
 Atlanta Regional CCOP, Atlanta, GA; T.E. Seay
 Augusta Oncology Associates, Augusta, GA; M.R. Keaton
 Mercy Medical Center–North Iowa, Mason City, IA; W.W. Bate
 Medical Associates Clinic, Professional Corporation, Dubuque, IA; C. Holm
 Loyola University Medical Center, Maywood, IL; K.S. Albain
 University of Chicago, Chicago, IL; H.L. Kindler
 St Anthony Medical Center, Rockford, IL; R.E. Nora
 Decatur Memorial Hospital, Decatur, IL; J.L. Wade
 Memorial Medical Center, Springfield, IL; J.L. Wade
 Ingalls Memorial Hospital, Harvey, IL; M.F. Kozloff
 Carle Cancer Center CCOP, Urbana, IL; K.M. Rowland
 Community Regional Cancer Care North, Indianapolis, IN; R. Walling
 Indiana University Medical Center, Indianapolis, IN; K.D. Miller
 Fort Wayne Medical Oncology/Hematology Incorporated, Fort Wayne, IN; S.R. Nattam
 Northern Indiana Consortium, South Bend, IN; R.H. Ansari
 Via Christi Regional Medical Center, Wichita, KS; S.R. Dakhil
 Louisiana State University, Shreveport, LA; G.M. Mills
 Tufts Medical Center, Boston, MA; J.K. Erban
 Massachusetts General Hospital, Boston, MA; H.J. Burstein
 Dana-Farber Cancer Institute, Boston, MA; H.J. Burstein
 Beth Israel Deaconess Medical Center, Boston, MA; H.J. Burstein
 North Shore Cancer Center, Salem, MA; K.J. Krag
 Suburban Hospital, Bethesda, MD; C.B. Hendricks
 Johns Hopkins University, Baltimore, MD; A.C. Wolff
 Anne Arundel Medical Center, Annapolis, MD; S.P. Watkins
 Kaiser Permanente–Shady Grove Medical Center, Rockville, MD; L.C. Hwang
 Eastern Maine Medical Center, Bangor, ME; H.M. Segal
 Mercy Hospital, Portland, ME; R.C. Inhorn
 William Beaumont Hospital, Royal Oak, MI; D. Zakalik
 University of Michigan Medical Center, Ann Arbor, MI; A.F. Schott
 Mid-Michigan Medical Center, Midland, MI; M.R. Hurtubise
 Regions Hospital, Minneapolis, MN; D.J. Schneider
 United Hospital, St Paul, MN; P.J. Flynn
 Duluth Clinic, Duluth, MN; R.J. Dalton
 Mayo Clinic, Rochester, MN; J.N. Ingle
 Saint Francis Regional Medical Center, Shakopee, MN; D.J. Schneider
 Washington University School of Medicine, St Louis, MO; M.J. Naughton
 Saint John's Regional Health Center, Springfield, MO; J.W. Goodwin
 Missouri Baptist Medical Center, Saint Louis, MO; A.P. Lyss
 Montana Cancer Consortium CCOP, Billings, MT; B.T. Marchello
 University of North Carolina, Chapel Hill, NC; T.C. Shea
 Mission Hospitals, Asheville, NC; M.J. Messino
 Forsyth Memorial Hospital, Winston-Salem, NC; J.O. Hopkins
 Northeast Medical Center, Concord, NC; J.G. Wall
 Hope, A Women's Cancer Center, Asheville, NC; D.J. Hertzfel
 Altru Hospital, Grand Forks, ND; T. Dentchev

Elliot Hospital, Manchester, NH; D. Weckstein
 Dartmouth Hitchcock Medical Center, Lebanon, NH; P.A. Kaufman
 Saint Barnabas Medical Center, Livingston, NJ; R.A. Michaelson
 Cooper Hospital University Medical Center, Newark, NJ; D.D. Biggs
 Cancer Institute of New Jersey, New Brunswick, NJ; D.L. Toppmeyer
 Cancer Institute of New Jersey at Hamilton, Trenton, NJ; D.L. Toppmeyer
 University of Nevada at Reno Washoe Medical Center, Reno, NV
 Saint Vincent's Hospital and Medical Center of New York, New York, NY; P. Klein
 Memorial Sloan-Kettering Cancer Center, New York, NY; C.A. Hudis
 Weill Medical College of Cornell University, New York, NY; J. Leonard
 Staten Island University Hospital, Staten Island, NY; M. Odaimi
 Albert Einstein College/Medicine, Bronx, NY; C.M. Pellegrino
 Montefiore Medical Center, Bronx, NY; C.M. Pellegrino
 North Shore University Hospital, Manhasset, NY; D.R. Budman
 Brookdale Hospital Medical Center, Brooklyn, NY; M.R. Kalavar
 Roswell Park Cancer Institute, Buffalo, NY; E.G. Levine
 Ohio State University Hospital, Columbus, OH; C.D. Bloomfield
 Cleveland Clinic Foundation, Cleveland, OH; G.T. Budd
 Case Western Reserve University, Cleveland, OH; P. Silverman
 Fairview Hospital, Cleveland, OH; G.T. Budd
 Aultman Hospital, Canton, OH; J.A. Schmotzer
 Samaritan North Health Center, Dayton, OH; H.M. Gross
 Lima Memorial Hospital, Toledo, OH; P.L. Schaefer
 Cleveland Clinic Wooster Specialty Center, Wooster, OH; G.T. Budd
 Kaiser Permanente, Portland, OR; N.R. Tirumali
 Allegheny Cancer Center Network, Pittsburgh, PA; N. Wolmark
 University of Pittsburgh, Pittsburgh, PA; A.M. Brufsky
 Lancaster General Hospital, Lancaster, PA; R.J. Gottlieb
 Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; S.M. Domchek
 Fox Chase Cancer Center, Philadelphia, PA; L.J. Goldstein
 Chester County Hospital, West Chester, PA; W.E. Luginbuhl
 St Mary Regional Cancer Center, Langhorne, PA; R.E. Reilly
 Abington Memorial Hospital, Abington, PA; W.G. Andrews
 Scranton Hematology Oncology, Scranton, PA; M. Hyzinski
 Rhode Island Hospital, Providence, RI; W.M. Sikov
 Women's and Infants Hospital, Providence, RI; D.S. Dizon
 Sioux Valley Clinic—Oncology, Sioux Falls, SD; M.A. Mazurczak
 Erlanger Medical Center, Chattanooga, TN; L.L. Schlabach
 Jones Clinic, Germantown, TN; B.A. Mullins
 Presbyterian Hospital of Dallas, Dallas, TX; J.F. Strauss
 The University of Texas MD Anderson Cancer Center, Houston, TX; M.C. Green
 Baylor College of Medicine, Houston, TX; R.M. Elledge
 Doctor's Hospital of Laredo, Laredo, TX; G.W. Unzeitig
 University of Vermont, Burlington, VT; S. Burdette-Radoux
 Swedish Hospital Medical Center, Seattle, WA; S.E. Rivkin
 Southwest Washington Medical Center, Vancouver, WA; K.S. Lanier
 University of Wisconsin, Madison, WI; J.A. Stewart
 Saint Vincent Hospital, Green Bay, WI; T.J. Saphner
 Midelfort Clinic, Eau Claire, WI; G.S. Nambudiri
 Green Bay Oncology LTD at Saint Mary's Hospital, Green Bay, WI; T.J. Saphner
 Marshall University Medical Center, Huntington, WV; M.R.B. Tria Tirona

Patient-Reported Outcomes in the SOFT Trial

Fig A1. Change of symptom and global quality-of-life (QoL) indicator scores from baseline to 6, 24, and 60 months, according to treatment assignment, for the three treatment assignments in the Suppression of Ovarian Function Trial, overall across chemotherapy cohorts. The vertical line at ± 8 indicates the minimal clinically meaningful change in QoL scores. E, exemestane; OFS, ovarian function suppression; T, tamoxifen.

Fig A2. (A) Change of symptom and global quality-of-life (QoL) indicator scores from baseline to 6, 24, and 60 months, according to treatment assignment, for the three treatment assignments in the no prior chemotherapy cohort in the Suppression of Ovarian Function Trial (SOFT) trial. (B) Change of symptom and global QoL indicator scores from baseline to 6, 24, and 60 months, according to treatment assignment, for the three treatment assignments in the prior chemotherapy cohort in SOFT trial. The vertical line at ± 8 indicates the minimal clinically meaningful change in QoL scores. E, exemestane; OFS, ovarian function suppression; T, tamoxifen.

B

Fig A2. (Continued).

Table A1. Differences between treatment groups in changes of symptom and global indicators from baseline

Quality of Life/symptom indicator	Estimated Difference between Treatment Groups (T+OFS minus T)											
	6 months				24 months				60 months			
	Mean	95% LCL	95% UCL	P-value	Mean	95% LCL	95% UCL	P-value	Mean	95% LCL	95% UCL	P-value
Symptom indicators												
Hot flushes	-29	-33	-26	<.0001	-15	-19	-11	<.0001	-4	-9	0	.057
Sweats (incl. night sweats)	-23	-26	-19	<.0001	-9	-13	-6	<.0001	-3	-7	1	.12
Vaginal discharge	4	1	7	.0027	3	1	6	.017	1	-2	4	.50
Vaginal dryness	-5	-8	-2	.00055	-6	-9	-3	.00038	-6	-10	-2	.0030
Vaginal itching/irritation	4	1	6	.0053	3	0	6	.044	-1	-4	2	.61
Loss of sexual interest	-8	-11	-4	<.0001	-3	-7	0	.056	-3	-7	1	.16
Difficulties in becoming aroused	-6	-10	-3	.00016	-4	-8	-0	.029	0	-4	5	.88
Bone or joint pain	-2	-5	1	.19	-1	-4	2	.55	5	1	9	.0081
Headaches	-1	-4	1	.26	1	-2	3	.65	-1	-5	2	.42
Appetite	-1	-3	2	.65	-0	-3	2	.92	-1	-4	2	.55
Feeling sick (nausea/vomiting)	-0	-3	2	.74	-0	-3	2	.70	-0	-3	2	.84
Sleep disturbance	-11	-14	-8	<.0001	-2	-5	1	.17	-0	-4	4	.91
Tiredness	1	-2	4	.58	0	-3	3	.89	4	0	8	.028
Troubled by weight gain	-3	-6	0	.066	-4	-7	-0	.033	-0	-4	4	.90
Being irritable	0	-2	3	.86	-1	-4	2	.54	-1	-4	3	.67
Feeling dizzy	-1	-3	2	.56	-0	-2	2	.89	0	-3	3	.97
Global indicators												
Physical well-being	-2	-4	1	.17	-1	-4	1	.40	2	-1	6	.17
Mood	-1	-3	2	.69	-0	-3	3	.90	2	-1	5	.29
Coping effort	-4	-7	-2	.00073	-3	-6	-1	.015	-2	-5	2	.31
Treatment burden	-8	-10	-5	<.0001	-4	-7	-1	.0057	-1	-4	3	.72
Health perception	-2	-5	-0	.024	-1	-3	2	.54	1	-1	4	.32

NOTE. Mean < 0 indicates T+OFS had greater worsening than T alone. Mean differences between treatment groups, 95% CIs and Wald P-values were estimated with mixed-models contrasts for testing the differences versus zero at short- (6 months), intermediate- (24 months) and long-term (60 months). Some zeroes appear as (-0) because of rounding.

Abbreviations: LCL, lower confidence limit; OFS, ovarian function suppression; T, tamoxifen; UCL, upper confidence limit.