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ORIGINAL REPORT

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

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See accompanying editorial on page 3920

ABSTRACT

Purpose
The effects of ovarian function suppression (OFS) on survival and patient-reported outcomes were evaluated in a phase III trial in which premenopausal women were randomly assigned to tamoxifen with or without OFS.

Patients and Methods
Premenopausal women with axillary node-negative, hormone receptor–positive breast cancer tumors measuring ≤ 3 cm were randomly assigned to tamoxifen alone versus tamoxifen plus OFS; adjuvant chemotherapy was not permitted. Primary end points were disease-free survival (DFS) and overall survival (OS). Secondary end points included toxicity and patient-reported outcomes. Patient-reported outcome data included health-related quality of life, menopausal symptoms, and sexual function. These were evaluated at baseline, 6 months, 12 months, and then annually for up to 5 years after registration.

Results
In all, 345 premenopausal women were enrolled: 171 on tamoxifen alone and 174 on tamoxifen plus OFS. With a median follow-up of 9.9 years, there was no significant difference between arms for DFS (5-year rate: 87.9% v 89.7%; log-rank $P = .62$) or OS (5-year rate: 95.2% v 97.6%; log-rank $P = .67$). Grade 3 or higher toxicity was more common in the tamoxifen plus OFS arm (22.4% v 12.3%; $P = .004$). Patients treated with tamoxifen plus OFS had more menopausal symptoms, lower sexual activity, and inferior health-related quality of life at 3-year follow-up ($P < .01$ for all). Differences diminished with further follow-up.

Conclusion
When added to tamoxifen, OFS results in more menopausal symptoms and sexual dysfunction, which contributes to inferior self-reported health-related quality of life. Because of early closure, this study is underpowered for drawing conclusions about the impact on survival when adding OFS to tamoxifen.

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INTRODUCTION

Ovarian function was related to breast cancer in 1882, when Nunn[1] reported cancer regression 6 months after menopause. The first known therapeutic oophorectomy occurred in 1895 on a woman with recurrent breast cancer.[2,3] Pharmacologic advances involving luteinizing hormone-releasing hormone (LHRH) agonists and improved surgical technique permitted the study of ovarian function suppression (OFS) in the adjuvant setting. Several trials demonstrate benefits from ovarian suppression or surgical oophorectomy equaling or exceeding benefits from cytotoxic chemotherapies in patients with hormone receptor–positive breast cancer.[4-9] A meta-analysis[10] by the Early Breast Cancer Trialists' Group suggests that OFS reduces breast cancer recurrence and mortality in the absence of

other therapies. However, a second meta-analysis[8] suggests that LHRH agonists alone do not improve recurrence or mortality, although adding them to other therapies reduces both recurrence and death following recurrence. Some consider OFS to be standard of care.[11]

Questions about OFS persist, and its role remains uncertain. It is not the recommended standard of care in North America, where tamoxifen alone is considered standard adjuvant endocrine therapy for premenopausal women.[12] In the absence of definitive survival benefits, patient-reported outcomes (PROs) such as health-related quality of life (HRQoL) should be considered when use of OFS is considered. Understanding the additional toxicity from OFS beyond that of tamoxifen is complicated. Some published studies assess OFS versus cytotoxic chemotherapy.[5,6,13-15] Other studies assess the impact of OFS in settings in which women are essentially past cytotoxic chemotherapy (which induces ovarian failure in premenopausal women).[7,16-18] Only a few studies contain a tamoxifen alone arm.[19,20] Furthermore, most published trials of OFS have not reported PROs such as HRQoL, hot flashes, and sexual dysfunction. The SOFT (Suppression of Ovarian Function Trial) study will address the value that OFS adds to standard adjuvant endocrine therapy in premenopausal women. SOFT randomly assigned women to tamoxifen alone versus tamoxifen plus OFS or aromatase inhibitor plus OFS. That phase III trial has completed accrual, but definitive results have not been reported for the tamoxifen versus tamoxifen plus OFS arms.[21] SOFT included a significant proportion of women (54%) receiving adjuvant chemotherapy.[21]

The Eastern Cooperative Oncology Group (ECOG) undertook a phase III trial comparing tamoxifen versus tamoxifen plus OFS in premenopausal women with node-negative, hormone receptor–positive primary invasive breast cancers who did not receive adjuvant chemotherapy (Phase III Comparison of Tamoxifen v Tamoxifen With Ovarian Ablation in Premenopausal Women With Axillary Node–Negative Receptor-Positive Breast Cancer ≤ 3 cm; E-3193, INT-0142). Primary objectives included comparing the overall survival (OS) and disease-free survival (DFS) between the two arms. Secondary objectives included toxicity and PROs such as comparison of menopausal symptoms, sexual function, and HRQoL between treatment arms. The trial was terminated before reaching the enrollment goal because of slow accrual; however, it completed the necessary accrual to meet the PRO objectives. We report the study results here.

PATIENTS AND METHODS

Patient Population

Eligible patients were premenopausal women with node-negative, estrogen receptor (ER) –positive and/or progesterone receptor (PgR) –positive primary invasive breast cancers. Primary tumors had to be ≤ 3 cm in greatest diameter. Randomization was required within 84 days of definitive breast surgery (mastectomy or breast conservation). Premenopausal status was defined as a menstrual period within the past 6 months without prior oophorectomy, or in the case of prior hysterectomy, as age 55 years or younger with one or both ovaries remaining and an estradiol level in the normal premenopausal range. Patients could not have received prior systemic therapy for breast cancer, aside from ≤ 12 weeks of tamoxifen. Patients were ineligible if they had any evidence of locally advanced or metastatic disease at diagnosis. The institutional review boards at each registering institution approved the protocol. All patients provided written informed consent.

Treatment

In this open-label, randomized phase III trial, patients were randomly assigned 1:1 to tamoxifen alone or tamoxifen plus OFS by using permuted blocks within strata with dynamic balancing across main institutions and their affiliated networks. Stratification factors included hormone receptor status, tumor size, and type of OFS. The treatment schedule for the tamoxifen alone arm was tamoxifen 20 mg orally per day for 5 years; the schedule for the tamoxifen plus OFS arm was tamoxifen 20 mg orally per day for 5 years combined with OFS. OFS was per patient or physician choice and could consist of LHRH analog (goserelin 3.6 mg depot every 4 weeks for 5 years beginning within 4 weeks of random assignment; leuprolide acetate 3.75 mg every 4 weeks for 5 years beginning within 4 weeks of random assignment), surgical ablation (done within 12 weeks of random assignment), or radiation ovarian ablation (20 Gy in 10 fractions within 12 weeks of random assignment[22]). No dose reductions were permitted. Other adjuvant systemic therapies including chemotherapy were not permitted.

End Points and Assessments

The primary end points were disease-free survival (DFS) and overall survival (OS). Secondary end points included toxicity and difference in Functional Assessment of Cancer Therapy-Breast (FACT-B) scores at 6 and 12 months. Additional PROs were prespecified as exploratory end points. DFS was defined as time from random assignment to the earliest of disease recurrence, new primary breast cancer, or death as a result of any cause, censoring patients without recurrence or death at the date of last disease assessment known to be disease free. OS was defined as time from random assignment to death as a result of any cause, with living patients censored at last evaluation date. Disease recurrence and survival were assessed every 6 months for the first 5 years and yearly thereafter. Adverse events were assessed on the same schedule by using National Cancer Institute Common Toxicity Criteria, version 1.[23]

Participants were surveyed to evaluate menopausal symptoms, sexual function, and HRQoL. Assessment of menopausal symptoms was conducted with questions from the Postmenopausal Estrogen/Progestin Intervention checklist,[24] which consisted of 15 questions devoted to various symptoms. Assessment of sexual function was conducted by using the Sexual Activity Questionnaire,[25] which consisted of five questions about sexual activity. Assessment of HRQoL was measured by using FACT-B (Version 3), which consisted of 27 general questions pertaining to patients with all cancers plus nine additional questions specific to patients with breast cancer.[26] Assessments of PROs were performed at baseline, at 6 and 12 months, and yearly thereafter for up to 5 years following registration.

Statistical Analysis

The target enrollment was 1,600 eligible patients, with 90% power to detect 33% reduction in the hazard of recurrence from adding OFS to tamoxifen (5-year DFS rate of 83.0% v 88.3%) by using a log-rank test with a one-sided type I error rate of 0.025. This design also gives 81% power to detect a 33% reduction in the hazard of death (5-year OS of 90.0% for tamoxifen alone v 93.2% for tamoxifen plus OFS) by using a log-rank test with a one-sided type I error rate of 0.025. For PROs, 110 patients per arm give 90% power to detect a difference of five points in the FACT-B total score at 6 and 12 months by using a two-sample t test with an overall type I error rate of 0.05 (Bonferroni adjustment was made for these comparisons), assuming the common standard deviation of 10.5. The target sample size for PRO end points was 367 patients, assuming a 40% loss in PROs by 12 months, for an effective sample size of 220.

All analyses were conducted in all eligible patients following the intent-to-treat principle. Associations between categorical or binary variables were examined by using the χ^2 and Fisher's exact tests.[27] The distribution of OS and DFS was estimated by using the Kaplan-Meier method[28] and compared between treatment arms by the log-rank test. Cox proportional hazards model[29] was used to estimate the treatment effect after adjusting for baseline covariates. A two-sample t test was used to compare PRO scores or score changes between treatment arms. Analysis of variance test was used to compare PRO scores based on type of OFS. Multivariable linear mixed effect models with unstructured covariance matrices were constructed to estimate the time profile for PRO end points and

to assess the treatment difference over time, assuming that any missing data were missing at random. A sensitivity analysis was conducted by using the lognormal survival model for analyzing longitudinal data that incorporates the nonignorable censoring mechanism.[30] A bootstrap method[31] was applied to estimate the SEs of the regression coefficients in the lognormal survival models. All P values were for two-sided tests; $P < .05$ was considered statistically significant except for FACT-B comparisons at 6 and 12 months ($P < .025$ was used based on Bonferroni adjustment). No adjustment was made for multiple comparisons for other end points. SAS 9.0 (SAS Institute, Cary, NC) and STATA 11.2 (STATA, College Station, TX) were used for analyses.

RESULTS

Patient Demographics and Disease Characteristics

A total of 345 participants were enrolled between September 1994 and November 1997, 171 on tamoxifen alone and 174 on tamoxifen plus OFS. The final analysis, including all clinical outcomes and PRO end points, was conducted in March 2003 with median follow-up time of 5.86 years. However, participants were observed for recurrence and survival until June 2007 (median follow-up, 9.9 years; range, 0.2 to 12.3 years). DFS and OS analyses were updated in July 2011 and are presented here.

The CONSORT diagram is provided in Figure 1. Of 345 registered participants, eight (four receiving tamoxifen and four receiving tamoxifen plus OFS) were ineligible; one patient (tamoxifen plus OFS) withdrew after random assignment and thus never started the assigned treatments. By the intent-to-treat principle, the total number of analyzable participants is the 337 eligible patients. The two arms were well balanced with respect to known patient characteristics (Table 1). At study entry, the median age was 45 years (range, 26 to 55 years). Most participants were white (91%) with tumors ≤ 2 cm
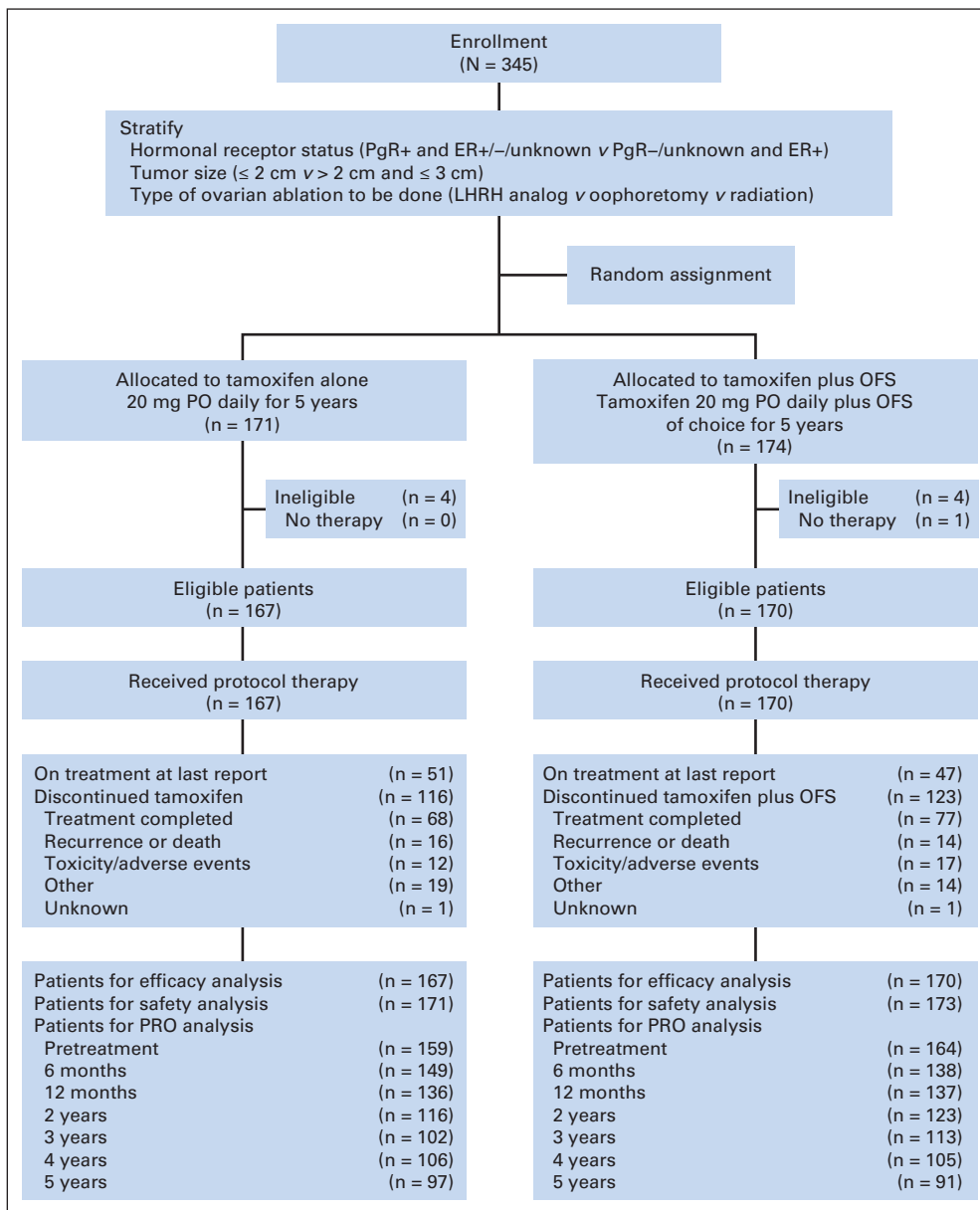
Fig 1. CONSORT diagram for Tamoxifen and Ovarian Ablation in Treating Patients With Node-Negative, Receptor-Positive Breast Cancer (E-3193) trial. ER, estrogen receptor; LHRH, luteinizing hormone-releasing hormone; OFS, ovarian function suppression; PgR, progesterone receptor; PO, orally; PRO, patient-reported outcome.

Table 1. Patient Demographic and Disease Characteristics (n = 337 analyzable participants)

Characteristic	Tamoxifen Alone (n = 167)		Tamoxifen + OFS (n = 170)	
	No.	%	No.	%
Age, years				
Median	46		44	
Range	26-55		30-54	
26-40	22	13.2	36	21.2
41-50	117	70.1	111	65.3
51-55	28	16.8	23	13.5
Race/ethnicity				
White	154	92.2	154	90.6
Black	7	4.2	9	5.3
Other	5	3.6	7	4.1
Unknown	1		0	
Hormone receptors				
ER positive, PgR positive	147	88	149	87.7
ER positive, PgR negative	13	7.8	14	8.2
ER positive, PgR unknown	1	0.6	2	1.2
ER negative, PgR positive	4	2.4	4	2.4
ER unknown, PgR positive	2	1.2	1	0.6
Tumor size, cm				
≤ 1.0	22	13.2	15	8.8
1.1-2.0	117	70.1	126	74.1
> 2.0	28	16.8	29	17.1
Type of OFS				
LHRH	—	—	61	36
Oophorectomy	—	—	72	42
Radiation	—	—	22	13
Refused OFS	—	—	15	9
Surgical procedure				
Breast conservation	97	58.1	112	65.9
Mastectomy	70	41.9	58	34.1

Abbreviations: ER, estrogen receptor; LHRH, luteinizing hormone-releasing hormone; OFS, ovarian function suppression; PgR, progesterone receptor.

(83%), which were both estrogen receptor–positive and progesterone receptor–positive (88%). Participants randomly assigned to tamoxifen plus OFS generally chose to undergo surgical ablation of ovarian function via oophorectomy (42%), followed by medical suppression with an LHRH agonist (36%).

Treatment

As of March 2003, 116 participants (69%) receiving tamoxifen and 123 (72%) receiving tamoxifen plus OFS reported discontinuing treatment; the reasons cited for treatment discontinuation were similar between the arms. The most common reason cited was treatment completion (68 [41%] receiving tamoxifen and 77 [45%] receiving tamoxifen plus OFS; P = .441). Twenty-nine patients (8.6%; 12 receiving tamoxifen, 17 receiving tamoxifen plus OFS) discontinued treatment because of adverse events and 30 patients (8.9%; 16 receiving tamoxifen, 14 receiving tamoxifen plus OFS) discontinued as a result of recurrence or death. In addition to patients who discontinued treatment, 15 patients (9.0%) receiving tamoxifen plus OFS refused OFS and four (2.4%) receiving tamoxifen also received OFS.

DFS and OS

As of June 2007 (when follow-up for survival and recurrence stopped), 45 DFS events (tamoxifen, 24; tamoxifen plus OFS, 21) and

24 deaths had been observed among 337 eligible participants (Fig 2). The 5-year OS rate for tamoxifen was 95.2% (95% CI, 90.5% to 97.6%) compared with a rate of 97.6% (95% CI, 93.6% to 99.1%) for tamoxifen plus OFS (log-rank P = .67; Fig 2A). The adjusted hazard ratio (HR) was 1.19 (95% CI, 0.52 to 2.70) for tamoxifen versus tamoxifen plus OFS. The 5-year DFS rate for tamoxifen was 87.9% (95% CI, 81.9% to 92.0%) compared with the rate of 89.7% (95% CI, 83.9% to 93.5%) for tamoxifen plus OFS (log-rank P = .62; Fig 2B). The adjusted HR was 1.17 (95% CI, 0.64 to 2.12) for tamoxifen versus tamoxifen plus OFS.

Appendix Tables A1 and A2 (online only) display the results for the prespecified subgroup analysis based on OFS type and race. The estimated HRs for DFS and OS were not statistically significant, based on OFS type (Appendix Table A1). Among white women, the HR was 1.18 (95% CI, 0.63 to 2.21; P = .60) for DFS for tamoxifen versus tamoxifen plus OFS, and among nonwhite women, the HR was 1.02 (95% CI, 0.13 to 7.96; P = .98; Appendix Table A2).

Toxicity

The most common grade 3 or higher toxicities were hot flashes, weight gain, neuropsychiatric adverse effects, such as anxiety or depression, and neurologic adverse effects, such as somnolence and confusion (Table 2). The proportion of grade 3 or greater toxicity was higher for tamoxifen plus OFS compared with tamoxifen (22.4% *v* 12.3%; P = .004). No lethal adverse events were reported in the study.

PROs

Overall, compliance with PRO assessments was high and was similar between the two arms in all follow-up visits in the study (Fig 1). More than 93% of the patients submitted the PRO forms at baseline in both arms. At months 6 and 12, the retention rate was 83% and 79%, respectively, in the overall sample; thus, the prespecified effective sample size of 220 patients at 12 months was achieved. Combining all time points, a total of 1,889 surveys (68.2%) were completed. Among missing surveys, 433 (15.6%) were missing because of institutional error, 153 (5.5%) because of patient refusal, and 46 (1.7%) because of patient expiration.

Table 3 and Figure 3 display the mean scores for PRO end points by treatment arm at each visit time in analyzable patients per protocol. Patients receiving tamoxifen plus OFS reported worse HRQoL as measured by the mean scores on both the FACT-General (FACT-G) and FACT-B cancer subscales compared with those receiving tamoxifen alone at all time points (Figs 3A and 3B). These differences became more pronounced over time and reached statistical and clinical significance for FACT-G at year 3 (difference, 6.39). This difference decreased over time. Women receiving tamoxifen plus OFS had more menopausal symptoms at all time points compared with women receiving tamoxifen alone, with statistically significant differences at 1, 2, and 3 years of follow-up (Fig 3C, Table 3). Sexual activity was lower among women receiving tamoxifen plus OFS compared with women receiving tamoxifen alone at all follow-up time points after month 6 (Fig 3D, Table 3), and differences were statistically significant. Appendix Table A3 (online only) displays PRO score changes between follow-up and baseline visits by arm. The tamoxifen plus OFS arm persistently had more differences from baseline starting at 6 months in menopausal and sexual activity compared with the tamoxifen alone arm.
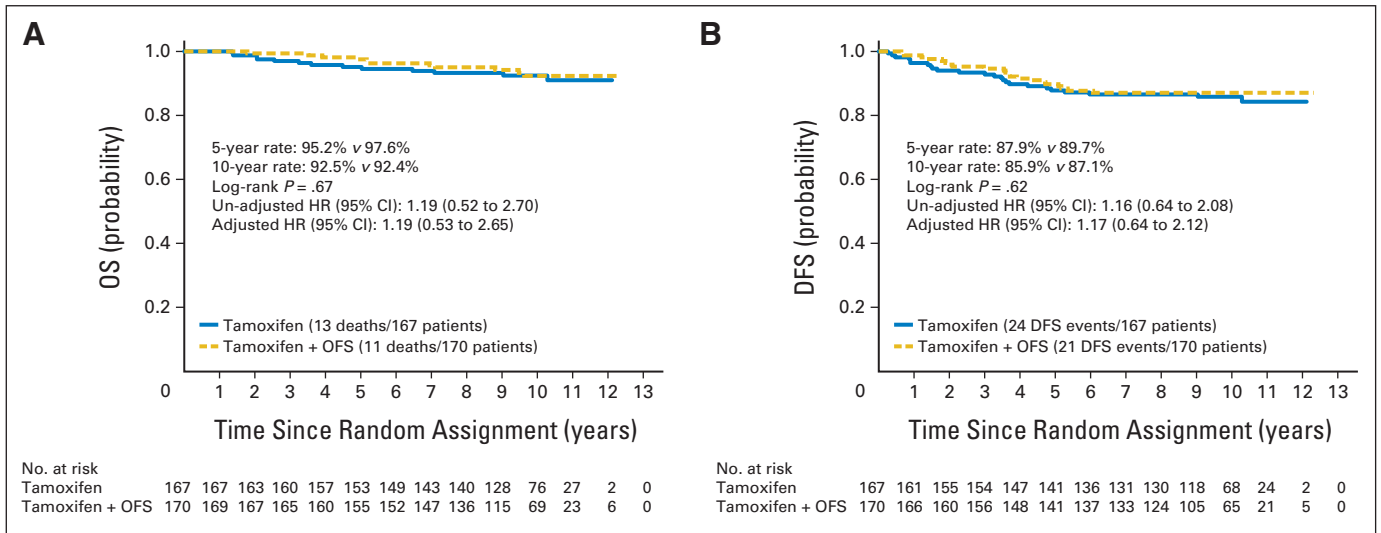
Fig 2. Comparison of (A) overall survival (OS) and (B) disease-free survival (DFS) by treatment in analyzable patients. HR, hazard ratio; OFS, ovarian function suppression.

Linear mixed effect models analysis showed similar results after adjusting for age, race, hormone receptor status, tumor size, and surgical procedure (Appendix Table A4, online only). The lognormal survival model analysis was conducted as a sensitivity analysis, and the results showed no significant changes compared with the previous results after considering the possible informative censoring as a result of death (data not shown).

PROs were examined by OFS type among patients on the tamoxifen plus OFS arm in the report. Patients with surgically induced menopause had slightly lower scores over all PRO end points at year 3, although this was statistically significant only for the FACT-B subscale and Sexual Activity Questionnaire (Appendix Table A5, online only). Given the small numbers as well as small overall differences in scores, results should be interpreted with caution.

DISCUSSION

E-3193 is a randomized phase III trial comparing tamoxifen alone with tamoxifen plus OFS for premenopausal women with early-stage breast cancer. The trial closed to accrual before meeting the enrollment goal for survival end points. DFS and OS were excellent overall; because of this and the early termination of accrual, the DFS and OS comparisons are underpowered. However, valuable data about toxicity, menopausal symptom burden, sexual function, and HRQoL were obtained. Accrual met the protocol's prespecified target goal for the PRO end points. PRO results suggest that adding ovarian suppression to tamoxifen leads to increased toxicity, more menopausal symptom burden, and lowered sexual function, all ultimately translating into lower HRQoL. The difference in HRQoL scores between the two arms is statistically significant and clinical meaningful by year 3.[32] However, the negative impact of OFS diminished over time, likely because increasing numbers of women receiving tamoxifen alone reached menopause (median age at study entry was 45 years). Outcomes for the tamoxifen alone arm in particular trended upward and were significantly better at year 3 than at baseline, consistent with other studies of HRQoL in women receiving endocrine therapy.[33]

Limited data are available comparing OFS in addition to or in place of standard adjuvant endocrine therapy for premenopausal breast cancer

Table 2. Grade 3 or Higher Toxicities by Treatment Arm							
	Tamoxifen Alone (n = 171) Grade				Tamoxifen + OFS (n = 174) Grade		
	3		4		3		4	
Toxicity Type	No.	%	No.	%	No.	%	No.	%
Hot flashes	8	4.7	—		28	16.1	—	
Neuropsychiatric*	2	1.2	2	1.2	4	2.3	—	
Neuroclinical†	1	0.6	—		4	2.3	—	
Allergy	—		—		1	0.6	—	
Weight gain	4	2.3	—		6	3.4	—	
Vaginal dryness	—		—		1	0.6	—	
Changes in libido	—		—		1	0.6	—	
Anemia	—		—		—		1	0.6
Clotting disorders	—		—		1	0.6	—	
Itching	1	0.6	—		—		—	
Night sweats	—		—		1	0.6	—	
Dizziness	1	0.6	—		—		—	
Liver	—		—		1	0.6	—	
Edema	—		—		1	0.6	—	
Hypoglycemia	—		—		1	0.6	—	
Pain	—		—		1	0.6	—	
Insomnia	2	1.2	—		—		—	
Endometriosis	1	0.6	—		—		—	
Amenorrhea	1	0.6	—		—		—	
Hypertension	—		—		1	0.6	—	
Highest grade	16	11.1	2	1.2	38	21.8	1	0.6

Abbreviation: OFS, ovarian function suppression.
*Included anxiety and depression.
†Included somnolence; confusion; hallucinations; coordination issues such as tremors, nystagmus, ataxaia, and dysdiadokinesis; and headache.

Table 3. Comparison of PRO End Points Between Tamoxifen Alone and Tamoxifen Plus OFS in Analyzable Participants

End Points	Tamoxifen Alone			Tamoxifen + OFS			Difference in Mean	P (t test)
	No.	Mean	SD	No.	Mean	SD		
FACT-B*								
Baseline	103†	113.30	16.87	102	110.26	19.48	3.04	.23
Month 6	134	112.28	19.72	128	112.35	18.12	−0.07	.98
Year 1	130	114.47	17.74	132	110.96	18.52	3.51	.12
Year 2	109	114.02	19.70	113	109.39	19.35	4.63	.08
Year 3	99	118.18	15.92	104	110.46	20.49	7.72	.003
Year 4	98	114.65	17.52	96	113.14	19.24	1.52	.57
Year 5	93	117.04	17.51	84	116.24	15.49	0.80	.75
FACT-G‡								
Baseline	158	86.24	13.18	164	85.79	13.91	0.45	.76
Month 6	149	86.98	14.61	137	86.26	14.57	0.72	.68
Year 1	136	88.52	13.24	137	86.18	14.61	2.34	.17
Year 2	116	89.19	14.93	123	85.50	15.06	3.69	.06
Year 3	102	92.47	12.15	113	86.54	16.08	5.39	.003
Year 4	106	90.10	13.37	104	88.57	14.85	1.54	.43
Year 5	97	91.30	12.87	91	89.88	12.62	1.42	.45
Breast subscale§								
Baseline	104†	25.98	5.12	102	25.13	5.68	0.85	.26
Month 6	134	25.68	6.10	129	25.56	5.47	0.12	.88
Year 1	130	25.88	5.82	132	24.72	5.60	1.16	.10
Year 2	109	25.22	6.03	113	23.75	5.85	1.47	.07
Year 3	99	25.87	5.07	104	24.38	5.89	1.49	.06
Year 4	98	25.18	5.57	97	24.84	5.75	0.34	.67
Year 5	94	25.85	6.21	85	25.78	5.62	0.07	.94
Menopausal symptoms‖								
Baseline	148	47.61	7.99	157	48.71	7.99	−1.10	.23
Month 6	139	42.13	9.16	128	40.21	8.59	1.92	.08
Year 1	131	42.85	9.04	136	39.40	8.71	3.45	.002
Year 2	114	42.59	9.13	118	38.74	8.06	3.85	.001
Year 3	97	43.37	8.41	113	39.78	8.59	3.59	.003
Year 4	105	41.98	8.98	103	40.86	8.11	1.12	.35
Year 5	97	43.22	9.46	90	41.83	8.08	1.39	.28
Sexual function¶								
Baseline	128	15.83	3.40	145	15.97	3.77	−0.14	.75
Month 6	118	14.45	4.58	115	13.08	4.38	1.37	.020
Year 1	110	14.00	4.59	123	12.50	4.79	1.50	.016
Year 2	98	13.83	5.25	106	11.87	4.68	1.96	.005
Year 3	81	13.84	4.77	103	11.20	4.73	2.64	< .001
Year 4	85	13.26	4.76	85	11.38	4.73	1.87	.011
Year 5	80	13.18	4.85	78	11.45	4.49	1.73	.022

Abbreviation: FACT-B, Functional Assessment of Cancer Therapy-Breast; FACT-G, FACT-General; OFS, ovarian function suppression; PRO, patient-reported outcome; SD, standard deviation.
*Out of possible score 144, higher score indicates better HRQL.
†On the original version of the baseline survey, the last page containing the breast subscale was missing. Thus, the FACT-B and breast subscales are unavailable for some patients. This was corrected in early 1995.
‡Out of possible score of 108, higher scores indicate better HRQL.
§Out of possible score of 36, higher scores indicate fewer breast cancer-specific symptoms.
‖Out of possible score of 60, higher scores indicate fewer complaints or difficulty.
¶Out of possible score of 20, higher scores indicate better sexual activity.

(ie, tamoxifen). PRO data are similarly lacking. As shown in Table 4,[34-40] studies have mainly examined OFS compared with or combined with cytotoxic chemotherapy. Trials examining tamoxifen alone versus tamoxifen plus OFS have used short durations of OFS (2 years). Our results suggest that durations of less than 3 years fail to capture the adverse effect peak and the HRQoL nadir from OFS.[34,35] Because inclusion criteria varied widely from trial to trial, it is difficult to quantify the impact of chemotherapy-induced ovarian failure in women randomly assigned to tamoxifen alone after adjuvant chemotherapy. Women receiving tamoxifen who had chemotherapy-induced ovarian failure would have symptoms mimicking tamoxifen plus OFS.

SOFT will provide valuable insights into the survival benefit from OFS as well as its impact on PROs such as hot flashes and loss of sexual interest. Particular strengths of E-3193 (when viewed in light of SOFT) include the maturity of our data. Furthermore, our patients were not exposed to chemotherapy; thus, the added symptom burden seen is solely
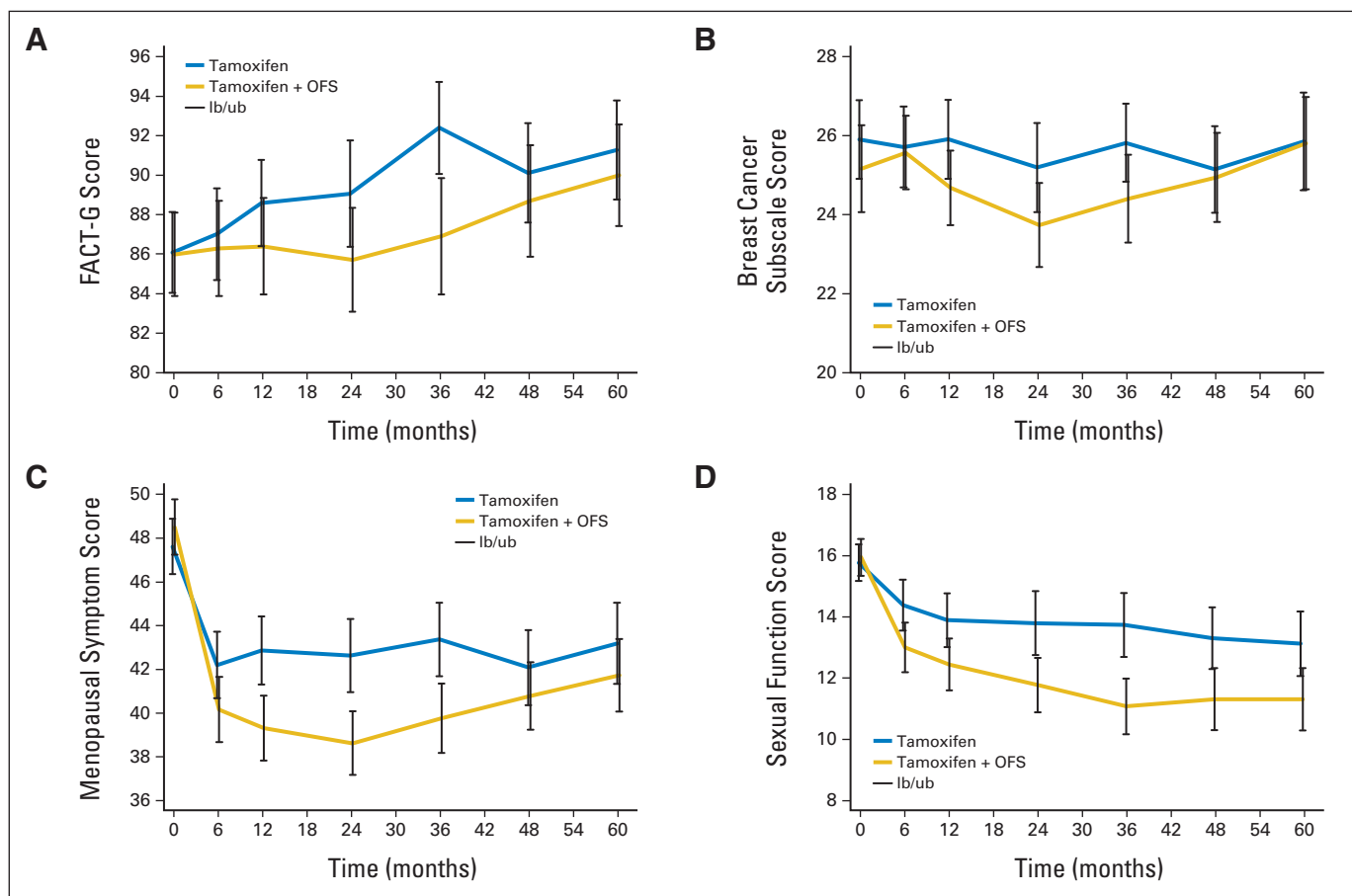
Fig 3. Patient-reported outcome scores for (A) Functional Assessment of Cancer Therapy-General (FACT-G), (B) breast cancer subscale, (C) menopause symptom, and (D) sexual function assessments and 95% CIs over time by treatment arm in analyzable patients. Vertical lines represent 95% CIs. lb/ub, lower border/upper border; OFS, ovarian function suppression.

a result of OFS. This is a unique feature of our data that will not be recapitulated by SOFT (although SOFT eligibility requirements carefully define the required residual menstrual function.)

One limitation of our study was the early termination of the trial because of poor accrual (although this applies only to the efficacy end points because the sample size needed for the PRO end points was achieved). In addition, participants were not blinded to assigned treatment arm, which could have influenced their perception of adverse effects. However, practical considerations make it unlikely that patients and treating physicians could have been blinded to continued menstrual function. Another limitation is the absence of data on other outcomes potentially impacted by OFS such as bone health, vaginal atrophy, or cognitive function. Finally, as is typical for PRO end points, multiple comparison adjustment was made only for the primary PRO end points, although multiple measures were administered at multiple time points in the study.

In conclusion, this study provides unique insight into the detrimental impact of OFS beyond that seen with tamoxifen alone. The impact of OFS on PROs is not complicated by the prior use of chemotherapy and its effects on ovarian function, unlike in many other studies. Questions generated by this research include exploring shorter durations of OFS, which might result in less symptom burden for patients. Given these data and in the absence of definitive data for improvement in DFS or OS with OFS, the Cancer Care Ontario guidelines endorsed by American Society of Clinical Oncology are appropriately cautious about adding OFS to tamoxifen.[12] These data provide valuable information for oncologists and patients who are debating whether to add OFS to tamoxifen.

AUTHOR CONTRIBUTIONS

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Manuscript writing: All authors
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Table 4. Sample Published Studies in Premenopausal Breast Cancer Containing an OFS Arm

Trial Name	Trial Acronym or Study Group	Reference	Population	Menopausal Status	Stage	Receptor and Node Status	Chemotherapy Permitted	Treatment Arms	Outcomes Measured
				Key Inclusion Criteria					
Tamoxifen Versus Anastrozole, Alone or in Combination With Zoledronic Acid	ABCSG-12	Gnant et al[11,36]	1,803	Pre	I-II	Hormone receptor positive, < 10 positive nodes	Yes	Tamoxifen + goserelin for 3 years v aromatase inhibitor + goserelin for 3 years (also randomized to zoledronic acid or not)	DFS, OS, toxicity
	ZEBRA	Jonat et al[37]	1,640	Pre or peri	II	Node positive, age ≤ 50 years	Yes	CMF v goserelin for 2 years	DFS, OS, toxicity, QOL[34]
Phase III Randomized Comparison of Adjuvant Therapies in Premenopausal Women with Resected Node-Positive Hormone Receptor–Positive Adenocarcinoma of the Breast: CAF (CTX/DOX/5-FU) v CAF Followed by ZDX v CAF Followed by ZDX/TMX	E5188/INT 0101	Davidson et al[7]		Pre		Node positive, hormone receptor positive	Yes	After CAF, randomized to no treatment v goserelin for 5 years v goserelin + tamoxifen for 5 years	TTR, DFS, OS, toxicity
Scottish Cancer Trials Breast Group		Thomson et al[38]	332	Pre		Node positive	Yes	CMF v ablation (surgical or radiation)	Recurrence, survival
	ABCSG-5	Jakesz et al[5]	1,034 assessable	Pre	I-II		Yes	CMF v tamoxifen for 5 years + goserelin for 3 years	RFS, OS, toxicity
Adjuvant Chemotherapy, Goserelin, or Their Sequential Combination for Pre/Perimenopausal Patients with Node-negative Breast Cancer	IBCSG Trial VIII	International Breast Cancer Study Group et al[6]	1,111	Pre or peri	III	Randomized, hormone receptor positive, node negative, T1	Yes	CMF v CMF + goserelin for 18 months v goserelin for 2 years v no treatment (no treatment arm was discontinued with only 42 patients enrolled)	DFS, OS, toxicity
	GABG IV-A	von Minckwitz et al[13]	771	Pre		Node negative, hormone receptor positive	Yes	CMF v goserelin for 2 years	EFS, OS, toxicity
	GABG IV-B	Kaufmann et al[16]	776	Pre		Initially only hormone receptor negative, but amended to include hormone receptor positive, node positive	Yes	Hormone receptor–negative patients treated with chemotherapy, randomized to goserelin for 2 years v no further treatment	EFS, OS, toxicity
Zoladex in Premenopausal Patients	ZIPP	Hackshaw et al[17]	2,076	Pre	I-II	Age < 50 years	Yes	Randomized after primary therapy to no treatment v goserelin for 2 years v tamoxifen for 2 years v goserelin for 2 years + tamoxifen	EFS, OS, QOL[35]
Takeda Adjuvant Breast Cancer Study with Leuprorelin Acetate	TABLE	Schmid et al[14,15]	589 assessable	Pre or peri assessable	II-IIIa	Assessable, node positive, estrogen receptor positive	Yes	CMF v leuprorelin acetate for 2 years	RFS, OS
	ABC OAS Trial	Adjuvant Breast Cancer Trials Collaborative Group[20]	2,144	Pre or peri		T1-3aN0-1	Yes	Tamoxifen for 5 years v tamoxifen + OFS for 5 years	RFS, OS

(continued on following page)

Table 4. Sample Published Studies in Premenopausal Breast Cancer Containing an OFS Arm (continued)

Trial Name	Trial Acronym or Study Group	Reference	Population	Menopausal Status	Stage	Receptor and Node Status	Chemotherapy Permitted	Treatment Arms	Outcomes Measured
	Fédération Nationale des Centres de Lutte contre le Cancer	Arriagada[18]	926	Pre		Node positive or grade 2 to 3	Yes	Chemotherapy v chemotherapy + OFS (irradiation or surgical ablation or triptorelin for 3 years)	DFS, OS
Trial 02	Italian Breast Cancer Adjuvant Study Group	Boccardo[19]	244	Pre or peri		Estrogen receptor positive	Yes	CMF v OFS (irradiation or surgical ablation v goserelin for 2 years) + tamoxifen for 5 years	DFS, OS, toxicity
	GOCSI	De Placido et al[39]	466	Pre		Node positive	Yes	Goserelin + tamoxifen for 2 years v observation	DFS, toxicity
	DBCG	Ejlertsen et al[40]	762	Pre		High risk (node positive or > 5 cm primary)	Yes	Pelvic irradiation v CMF	DFS, OS
Tamoxifen and Ovarian Ablation in Treating Patients With Node-Negative, Receptor-Positive Breast Cancer	E-3193, INT-0142		345	Pre		Hormone receptor positive, node negative	No	Tamoxifen for 5 years v tamoxifen + OFS for 5 years	DFS, OS, PROs, toxicity

NOTE. If chemotherapy was used, the type was not specified by the protocol.
Abbreviations: ABCSG, Austrian Breast and Colorectal Cancer Study Group; CAF, cyclophosphamide + doxorubicin + fluorouracil; CMF, cyclophosphamide + methotrexate + fluorouracil; CTX, chemotherapy; DBCG, Danish Breast Cancer Cooperative Group; DOX, doxorubicin; DFS, disease-free survival; EFS, event-free survival; FU, fluorouracil; GABG, German Adjuvant Breast Cancer Study Group; GOCSI, Gruppo Oncologico Centro-Sud-Isole; OAB, Ovarian Ablation or Suppression; OS, overall survival; OFS, ovarian function suppression; peri, perimenopausal; pre, premenopausal; PRO, patient-reported outcome; QOL, quality of life; RFS, recurrence-free or relapse-free survival; TMX, tamoxifen; TTR, time to recurrence; ZDX, Zoladex; ZEBRA, Zoladex Early Breast Cancer Research Association.

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GLOSSARY TERMS

estrogen receptor (ER): ligand-activated nuclear proteins, belonging to the class of nuclear receptors, present in many breast cancer cells that are important in the progression of hormone-dependent cancers. After binding, the receptor-ligand complex activates gene transcription. There are two types of estrogen receptors (ERα and ERβ). ERα is one of the most important proteins controlling breast cancer function.

ERβ is present in much lower levels in breast cancer, and its function is uncertain. Estrogen receptor status guides therapeutic decisions in breast cancer.

health-related quality of life (HRQoL): a broad multidimensional concept that usually includes self-reported measures of physical and mental health.

Cancer Survivorship Guide for Patients and Their Families
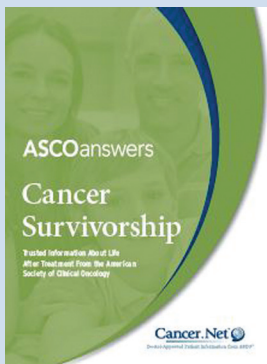
This comprehensive workbook contains trusted information about coping with psychological, physical, sexual, reproductive, financial, and work-related challenges, and allows survivors to list the signs, symptoms, and late effects they should talk with their doctor about right away. New features added to this resource include a **blank cancer treatment summary** and **survivorship care plan form** that patients and providers can fill out together. This booklet can be ordered in bundles of 50 from the ASCO University Bookstore at **www.cancer.net/estore** with a 20% discount for ASCO members and free shipping.

ASCO
American Society of Clinical Oncology

Acknowledgment

Appendix

Table A1. HRs and 95% CIs by Type of OFS Among Eligible Patients				
Outcome and Treatment	No. of Patients	HR	95% CI	*P*
DFS, unadjusted				
Tamoxifen *v* tamoxifen + LHRH analog	228	1.44	0.59 to 3.53	.421
Tamoxifen *v* tamoxifen + oophorectomy	239	0.93	0.46 to 1.91	.850
Tamoxifen *v* tamoxifen + radiation	189	1.06	0.32-3.54	.918
DFS, adjusted				
Tamoxifen *v* tamoxifen + LHRH analog	228	1.47	0.59 to 3.65	.408
Tamoxifen *v* tamoxifen + oophorectomy	239	0.98	0.47 to 2.03	.955
Tamoxifen *v* tamoxifen + radiation	189	0.93	0.27 to 3.22	.905
OS, unadjusted				
Tamoxifen *v* tamoxifen + LHRH analog	228	1.14	0.37 to 3.49	.822
Tamoxifen *v* tamoxifen + oophorectomy	239	1.40	0.46 to 4.28	.559
Tamoxifen *v* tamoxifen + radiation	189	0.57	0.16 to 2.01	.385
OS, adjusted				
Tamoxifen *v* tamoxifen + LHRH analog	228	1.19	0.38 to 3.78	.763
Tamoxifen *v* tamoxifen + oophorectomy	239	1.38	0.44 to 4.32	.576
Tamoxifen *v* tamoxifen + radiation	189	0.48	0.12 to 1.82	.277

NOTE. Tamoxifen + ovarian function suppression (OFS) is the reference group for all comparisons. A hazard ratio (HR) > 1 indicates improved outcome for tamoxifen + OFS (ie, higher risk for tamoxifen). Variables included in the adjusted models were age (≤ 40, 41-50, ≥ 51 years), tumor size (< 1, 1-2, > 2 cm), hormone receptor (progesterone receptor (PgR) positive or PgR negative/PgR unknown), and most extensive surgery (breast-sparing procedure or mastectomy). Race and menopausal status were not included because of lack of variability in the data (315 patients were white; 336 patients were premenopausal).
Abbreviations: DFS, disease-free survival; LHRH, luteinizing hormone-releasing hormone; OS, overall survival.

Table A2. Estimated HR for Treatment Within Race Among Eligible Patients				
Outcome	Race	No. of Patients	HR	95% CI	*P*
DFS	White	308	1.18	0.63 to 2.21	.599
	Other	29	1.02	0.13 to 7.96	.984
OS	White	308	0.98	0.42 to 2.32	.969
	Other*		—		

NOTE. Tamoxifen + ovarian function suppression is the reference group for all comparisons. A hazard ratio (HR) > 1 indicates improved outcome for tamoxifen + ovarian function suppression (ie, higher risk for tamoxifen alone arm). Adjusted for age (≤ 40, 41-50, ≥ 51 years), tumor size (< 1, 1-2, > 2 cm), hormone receptor (progesterone receptor (PgR) positive or PgR negative/PgR unknown), and most extensive surgery (breast-sparing procedure or mastectomy).
Abbreviations: DFS, disease-free survival; OS, overall survival.
*Not computable (zero deaths in this group).

	Tamoxifen Alone			Tamoxifen + OFS			
PRO/Baseline Time Point	No. of Participants	Mean	SD	No. of Participants	Mean	SD	P (t test)
FACT-B							
Month 6	94	−0.09	14.82	84	−0.02	14.40	.97
Year 1	88	0.43	14.56	86	−1.27	15.36	.45
Year 2	70	0.82	15.03	72	0.64	14.02	.94
Year 3	69	4.06	14.72	68	0.00	18.38	.16
Year 4	66	1.90	15.71	66	0.05	17.61	.53
Year 5	64	1.88	16.05	52	5.30	15.36	.25
FACT-G							
Month 6	144	1.20	11.74	137	−0.12	11.87	.35
Year 1	132	1.96	12.00	135	−1.04	11.40	.038
Year 2	114	2.56	12.71	123	0.73	12.62	.27
Year 3	101	5.51	11.69	111	1.15	14.19	.016
Year 4	103	3.49	13.69	103	1.13	13.06	.21
Year 5	95	3.94	13.35	89	2.44	13.05	.44
Breast subscale							
Month 6	95	−0.45	4.87	85	−0.25	5.19	.80
Year 1	89	−0.36	5.27	86	−0.79	5.94	.61
Year 2	70	−0.75	4.54	72	−1.24	5.58	.57
Year 3	69	−0.14	5.01	68	−0.88	6.69	.47
Year 4	66	−0.80	4.70	66	−0.99	5.86	.83
Year 5	66	−0.97	5.95	53	1.47	6.36	.033
Menopausal symptoms							
Month 6	126	−5.24	8.19	123	−8.90	9.05	.001
Year 1	119	−4.80	8.20	129	−9.72	9.03	< .001
Year 2	105	−5.60	8.70	115	−9.57	9.69	.002
Year 3	89	−4.13	9.47	107	−9.23	9.40	< .001
Year 4	95	−5.71	9.32	99	−9.00	9.46	.016
Year 5	90	−4.46	9.56	84	−7.71	10.20	.031
Sexual function							
Month 6	99	−1.67	3.81	105	−2.99	4.03	.017
Year 1	99	−1.92	3.95	113	−3.29	4.29	.017
Year 2	87	−2.23	4.62	99	−4.47	5.07	.002
Year 3	73	−2.22	4.33	95	−4.73	4.91	.001
Year 4	73	−3.04	4.72	79	−4.78	5.55	.041
Year 5	72	−3.06	4.90	69	−4.86	5.09	.034

Table A3. PRO Score Changes Compared With Baseline by Treatment Arm

Abbreviation: FACT-B, Functional Assessment of Cancer Therapy-Breast; FACT-G, FACT-General; PRO, patient-reported outcome; SD, standard deviation.

Table A4. Multivariable Linear Mixed Effect Model Analysis for PRO End Points

End Point	Variable	Coefficient	95% CI	P
FACT-G	Treatment (tamoxifen + OFS v tamoxifen alone)	−0.54	−3.61 to 2.54	.733
	Time points (v baseline)			
	Month 6	0.99	−0.63 to 2.62	.232
	Year 1	2.05	0.32 to 3.78	.020
	Year 2	2.61	0.70 to 4.53	.008
	Year 3	5.05	2.92 to 7.18	< .001
	Year 4	3.13	0.84 to 5.43	.007
	Year 5	3.38	0.83 to 5.93	.009
	Treatment-by-time interaction			
	Tamoxifen + OFS at month 6	−1.33	−3.65 to 0.99	.262
	Tamoxifen + OFS at year 1	−2.97	−5.42 to −0.53	.017
	Tamoxifen + OFS at year 2	−2.49	−5.17 to 0.19	.069
	Tamoxifen + OFS at year 3	−5.06	−8.03 to −2.09	.001
	Tamoxifen + OFS at year 4	−2.73	−5.97 to 0.51	.098
	Tamoxifen + OFS at year 5	−3.48	−7.10 to 0.14	.059
Breast subscale	Treatment (tamoxifen + OFS v tamoxifen alone)	−0.95	−2.30 to 0.41	.171
	Time points (v baseline)			
	Month 6	−0.39	−1.25 to 0.48	.381
	Year 1	−0.39	−1.28 to 0.50	.389
	Year 2	−0.78	−1.74 to 0.18	.113
	Year 3	−0.57	−1.59 to 0.45	.276
	Year 4	−1.14	−2.21 to −0.06	.038
	Year 5	−0.60	−1.73 to 0.54	.306
	Treatment-by-time interaction			
	Tamoxifen + OFS at month 6	0.35	−0.89 to 1.59	.579
	Tamoxifen + OFS at year 1	−0.54	−1.81 to 0.72	.400
	Tamoxifen + OFS at year 2	−0.41	−1.77 to 0.95	.556
	Tamoxifen + OFS at year 3	−0.40	−1.84 to 1.04	.590
	Tamoxifen + OFS at year 4	−0.25	−1.78 to 1.27	.743
	Tamoxifen + OFS at year 5	−0.54	−2.18 to 1.10	.518
Menopausal symptom	Treatment (tamoxifen + OFS v tamoxifen alone)	1.04	−0.83 to 2.90	.275
	Time points (v baseline)			
	Month 6	−5.22	−6.50 to −3.94	< .001
	Year 1	−5.00	−6.34 to −3.66	< .001
	Year 2	−5.35	−6.80 to −3.89	< .001
	Year 3	−4.40	−6.01 to −2.78	< .001
	Year 4	−5.52	−7.22 to −3.83	< .001
	Year 5	−4.61	−6.48 to −2.75	< .001
	Treatment-by-time interaction			
	Tamoxifen + OFS at month 6	−3.58	−5.40 to −1.76	< .001
	Tamoxifen + OFS at year 1	−4.80	−6.67 to −2.93	< .001
	Tamoxifen + OFS at year 2	−4.35	−6.39 to −2.32	< .001
	Tamoxifen + OFS at year 3	−4.66	−6.89 to −2.44	< .001
	Tamoxifen + OFS at year 4	−3.50	−5.89 to −1.11	.004
	Tamoxifen + OFS at year 5	−3.91	−6.56 to −1.27	.004
Sexual function	Treatment (tamoxifen + OFS v tamoxifen alone)	−0.16	−1.12 to 0.79	.739
	Time points (v baseline)			
	Month 6	−1.44	−2.16 to −0.72	< .001
	Year 1	−1.88	−2.63 to −1.13	< .001
	Year 2	−2.17	−2.99 to −1.36	< .001
	Year 3	−2.32	−3.23 to −1.41	< .001
	Year 4	−2.75	−3.71 to −1.78	< .001
	Year 5	−3.22	−4.28 to −2.16	< .001
	Treatment-by-time interaction			
	Tamoxifen + OFS at month 6	−1.45	−2.45 to −0.44	.005
	Tamoxifen + OFS at year 1	−1.52	−2.56 to −0.49	.004
	Tamoxifen + OFS at year 2	−2.01	−3.14 to −0.88	< .001
	Tamoxifen + OFS at year 3	−2.24	−3.48 to −1.00	< .001
	Tamoxifen + OFS at year 4	−1.99	−3.35 to −0.64	.004
	Tamoxifen + OFS at Year 5	−2.12	−3.61 to −0.63	.005

NOTE. Adjusted covariates included age, race, hormone receptor status, tumor size, and surgical procedure. The estimated coefficients for these adjusted covariates and the estimated random effects parameters are not shown in the table. The coefficient for variable "treatment: tamoxifen + OFS v tamoxifen alone" showed the treatment difference in the PRO end point at baseline. The coefficient for variable "Time points (v baseline)" showed the difference in PRO end point between a follow-up time point and the baseline visit on tamoxifen. The sum of the coefficients for "Time point" and "Treatment-by-time interaction" showed the difference in PRO end points between a follow-up time point and the baseline visit on tamoxifen + OFS. The sum of the coefficients for "Treatment" and "Treatment-by-time interaction" showed the difference in PRO end points between treatment arms at a follow-up time point.

Abbreviations: FACT-G, Functional Assessment of Cancer Therapy-General; OFS, ovarian function suppression; PRO, patient-reported outcome.

Table A5. PRO Scores by OFS Type in Patients in the Tamoxifen + OFS Arm

PRO/Time Point	LHRH Agonist		Oophorectomy		Radiation		P (ANOVA test)
	Mean	SD	Mean	SD	Mean	SD	
FACT-B							
Baseline	109.30	20.95	112.90	17.74	108.20	15.15	.60
Month 6	113.10	18.94	111.50	18.28	113.90	17.02	.85
Year 1	111.70	20.16	110.90	18.43	112.20	15.89	.95
Year 2	107.10	20.41	112.30	17.85	111.80	13.83	.38
Year 3	116.60	18.83	107.60	16.14	116.60	18.67	.040
Year 4	115.10	22.15	111.30	17.80	114.60	19.29	.68
Year 5	117.50	15.15	116.00	14.35	116.50	18.34	.92
FACT-G							
Baseline	86.65	14.82	86.61	12.63	83.23	11.93	.55
Month 6	87.10	14.15	85.89	14.35	86.15	16.96	.91
Year 1	86.60	16.12	86.31	14.05	87.06	13.09	.98
Year 2	83.87	15.09	87.44	14.22	88.13	11.61	.39
Year 3	91.05	14.71	84.82	13.03	89.13	15.19	.10
Year 4	89.39	16.35	87.62	14.22	89.31	15.21	.84
Year 5	91.90	12.37	88.58	12.15	90.43	14.55	.54
Breast subscale							
Baseline	25.89	5.81	25.20	5.43	24.44	6.13	.71
Month 6	25.94	6.11	25.30	5.44	25.22	3.89	.81
Year 1	24.91	5.31	24.55	6.01	25.17	5.61	.90
Year 2	23.24	6.16	24.43	5.97	23.46	4.29	.60
Year 3	25.45	5.21	23.49	5.79	27.36	4.18	.040
Year 4	25.56	6.57	24.29	5.48	25.33	5.10	.60
Year 5	25.90	5.27	26.09	5.65	25.54	5.90	.95
PEPI							
Baseline	48.28	7.74	49.28	8.03	49.66	7.35	.70
Month 6	42.37	8.40	38.97	8.17	38.48	9.65	.09
Year 1	41.17	7.75	37.86	8.90	40.41	7.48	.10
Year 2	39.50	8.95	38.34	6.51	36.57	6.84	.44
Year 3	42.25	7.04	38.25	8.53	39.88	9.02	.07
Year 4	41.43	8.40	40.05	7.88	40.29	7.43	.74
Year 5	42.08	8.22	41.17	7.76	42.92	6.05	.74
SAQ							
Baseline	16.49	3.23	15.90	3.74	15.74	4.25	.61
Month 6	14.42	4.35	12.19	3.88	13.53	4.68	.041
Year 1	14.12	3.87	11.45	4.78	13.27	4.91	.012
Year 2	13.13	5.07	11.16	4.33	10.90	2.82	.09
Year 3	13.11	3.95	10.14	4.82	10.85	5.24	.014
Year 4	12.27	4.18	10.85	5.04	10.69	4.44	.43
Year 5	12.56	3.97	10.68	4.88	11.11	3.33	.25

Abbreviation: ANOVA, analysis of variance; FACT-B, Functional Assessment of Cancer Therapy-Breast; FACT-G, FACT-General; LHRH, luteinizing hormone-releasing hormone; OFS, ovarian function suppression; PEPI, Postmenopausal Estrogen/Progestin Intervention (checklist); PRO, patient-reported outcome; SAQ, Sexual Activity Questionnaire; SD, standard deviation.