

ORIGINAL ARTICLE

Tailoring Adjuvant Endocrine Therapy for Premenopausal Breast Cancer

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ABSTRACT

BACKGROUND

In the Suppression of Ovarian Function Trial (SOFT) and the Tamoxifen and Exemestane Trial (TEXT), the 5-year rates of recurrence of breast cancer were significantly lower among premenopausal women who received the aromatase inhibitor exemestane plus ovarian suppression than among those who received tamoxifen plus ovarian suppression. The addition of ovarian suppression to tamoxifen did not result in significantly lower recurrence rates than those with tamoxifen alone. Here, we report the updated results from the two trials.

METHODS

Premenopausal women were randomly assigned to receive 5 years of tamoxifen, tamoxifen plus ovarian suppression, or exemestane plus ovarian suppression in SOFT and to receive tamoxifen plus ovarian suppression or exemestane plus ovarian suppression in TEXT. Randomization was stratified according to the receipt of chemotherapy.

RESULTS

In SOFT, the 8-year disease-free survival rate was 78.9% with tamoxifen alone, 83.2% with tamoxifen plus ovarian suppression, and 85.9% with exemestane plus ovarian suppression ($P=0.009$ for tamoxifen alone vs. tamoxifen plus ovarian suppression). The 8-year rate of overall survival was 91.5% with tamoxifen alone, 93.3% with tamoxifen plus ovarian suppression, and 92.1% with exemestane plus ovarian suppression ($P=0.01$ for tamoxifen alone vs. tamoxifen plus ovarian suppression); among the women who remained premenopausal after chemotherapy, the rates were 85.1%, 89.4%, and 87.2%, respectively. Among the women with cancers that were negative for HER2 who received chemotherapy, the 8-year rate of distant recurrence with exemestane plus ovarian suppression was lower than the rate with tamoxifen plus ovarian suppression (by 7.0 percentage points in SOFT and by 5.0 percentage points in TEXT). Grade 3 or higher adverse events were reported in 24.6% of the tamoxifen-alone group, 31.0% of the tamoxifen–ovarian suppression group, and 32.3% of the exemestane–ovarian suppression group.

CONCLUSIONS

Among premenopausal women with breast cancer, the addition of ovarian suppression to tamoxifen resulted in significantly higher 8-year rates of both disease-free and overall survival than tamoxifen alone. The use of exemestane plus ovarian suppression resulted in even higher rates of freedom from recurrence. The frequency of adverse events was higher in the two groups that received ovarian suppression than in the tamoxifen-alone group. (Funded by Pfizer and others; SOFT and TEXT ClinicalTrials.gov numbers, NCT00066690 and NCT00066703, respectively.)

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*A list of the investigators in the SOFT and TEXT trials and in the International Breast Cancer Study Group is provided in the Supplementary Appendix, available at NEJM.org.

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ADJUVANT TREATMENT WITH TAMOXIFEN for 5 years reduces the recurrence of premenopausal estrogen-receptor-positive breast cancer, with increasing benefits for overall survival during 5 to 15 years of follow-up.¹ Extending the duration of tamoxifen treatment to 10 years further improves outcomes.² The effect of adding ovarian suppression has been less certain.³ Among women with estrogen-receptor-positive tumors, those who are under the age of 35 years (who usually retain ovarian estrogen production despite chemotherapy) have a higher risk of recurrence than those who are 35 years of age or older.^{4,5}

In 2003, the International Breast Cancer Study Group initiated two randomized trials, the Suppression of Ovarian Function Trial (SOFT) and the Tamoxifen and Exemestane Trial (TEXT), involving premenopausal women with hormone-receptor-positive early breast cancer. SOFT was designed to determine the value of adding ovarian suppression to tamoxifen and to determine the role of the aromatase inhibitor exemestane plus ovarian suppression. TEXT was designed to determine the value of exemestane as compared with tamoxifen in women treated with ovarian suppression.

After a median follow-up of 5.6 years, the primary results of SOFT did not show a significantly higher rate of disease-free survival with the addition of ovarian suppression to tamoxifen than with tamoxifen alone, although the addition of ovarian suppression reduced recurrence rates among women at increased risk for recurrence who received adjuvant chemotherapy.⁶ Results of the combined analysis of SOFT and TEXT after a median follow-up of 5.7 years showed that exemestane plus ovarian suppression resulted in significantly higher rates of disease-free survival than the rates with tamoxifen plus ovarian suppression.⁷ Here, we report results of a prespecified updated analysis of SOFT and the combined analysis of data from SOFT and TEXT⁸ after a median follow-up of 8 and 9 years, respectively. We also report on the subgroup of women with cancers that were negative for human epidermal growth factor receptor 2 (HER2), who made up the majority of patients enrolled in the two trials.

two trials included women with documented premenopausal status and operable breast cancer that expressed estrogen or progesterone receptors in at least 10% of cells. The use of chemotherapy was optional. All the patients who were enrolled in TEXT underwent randomization within 12 weeks after definitive surgery, and if chemotherapy was received, it was initiated concurrently with ovarian suppression after randomization. The patients in SOFT who did not receive chemotherapy also underwent randomization within 12 weeks after definitive surgery. The patients in SOFT who received chemotherapy had received it previously, remained premenopausal, and underwent randomization within 8 months after completing chemotherapy, once a premenopausal estradiol level had been confirmed by a local laboratory.

TRIAL DESIGNS

Women who were enrolled in SOFT were randomly assigned in a 1:1:1 ratio to receive tamoxifen at a dose of 20 mg daily, tamoxifen plus ovarian suppression, or exemestane at a dose of 25 mg daily plus ovarian suppression. Treatment was to be administered for 5 years from randomization. Ovarian suppression was achieved by a choice of triptorelin at a dose of 3.75 mg by intramuscular injection every 28 days, bilateral oophorectomy, or ovarian irradiation.⁶ Patients receiving triptorelin could subsequently undergo oophorectomy or irradiation. Randomization was stratified according to receipt of previous chemotherapy, lymph-node status, and intended initial ovarian suppression method, if assigned.

Women who were enrolled in TEXT were randomly assigned in a 1:1 ratio to receive exemestane plus triptorelin or tamoxifen plus triptorelin for 5 years after randomization. Bilateral oophorectomy or ovarian irradiation was allowed after at least 6 months of receipt of triptorelin. Randomization was stratified according to the intended use of adjuvant chemotherapy and lymph-node status. The assessment of patients and recording of adverse events followed a regular schedule. (Details regarding the assessments are provided in the trial protocol and in the Supplementary Appendix, both available with the full text of this article at NEJM.org.)

METHODS

PATIENTS

The trial designs and eligibility criteria in SOFT and TEXT have been described previously.⁶⁻⁸ The

PRIMARY AND SECONDARY END POINTS

In the two trials, the primary end point in the time-to-event analysis was disease-free survival, which was defined as survival free of the first oc-

currence of one of the following: invasive recurrence of breast cancer (local, regional, or distant), invasive contralateral breast cancer, a second (non-breast) invasive cancer, or death without recurrence or a second cancer. Key secondary end points were the interval without breast cancer (defined as the time from randomization to the recurrence of local, regional, or distant invasive breast cancer or invasive contralateral breast cancer), the interval from randomization to the recurrence of breast cancer at a distant site, and overall survival, which was defined as the time from randomization until death from any cause.

ADVERSE EVENTS

We systematically queried for 22 targeted adverse events and collected other adverse events of grade 3 or higher using the Common Terminology Criteria for Adverse Events, version 3.0.⁹ The assessment of patients and systematic recording of the 22 targeted adverse events followed a regular schedule.

TRIAL OVERSIGHT

SOFT and TEXT were coordinated by the International Breast Cancer Study Group, which was responsible for the trial designs, data collection, management, and analysis. The ethics committee at each participating center approved the trial protocol, and all the patients provided written informed consent. Pfizer and Ipsen, the respective manufacturers of exemestane and triptorelin, donated the drugs used in the trials; neither company had any role in the conduct of the trials or in the analyses of the data. The tamoxifen that was used in the trials was provided by prescription. The manuscript was written solely by the authors, who vouch for the data and analyses reported and fidelity of the trials to the protocols. The steering committee (which included employees of Pfizer and Ipsen) reviewed the manuscript and made the decision to submit it for publication.

STATISTICAL ANALYSIS

The original and amended statistical analysis plans for SOFT and TEXT have been described previously.⁸ The test for the superiority of tamoxifen plus ovarian suppression over tamoxifen alone was the primary analysis in SOFT (calculated with a two-sided alpha level of 0.05), and the comparison between exemestane plus ovarian suppression and tamoxifen alone was a secondary objective (calculated as an estimate and 95% confidence interval, without a statistical test).⁶ An analysis of the

combined data from SOFT and TEXT was performed to compare exemestane plus ovarian suppression with tamoxifen plus ovarian suppression with a two-sided alpha level of 0.05.⁷

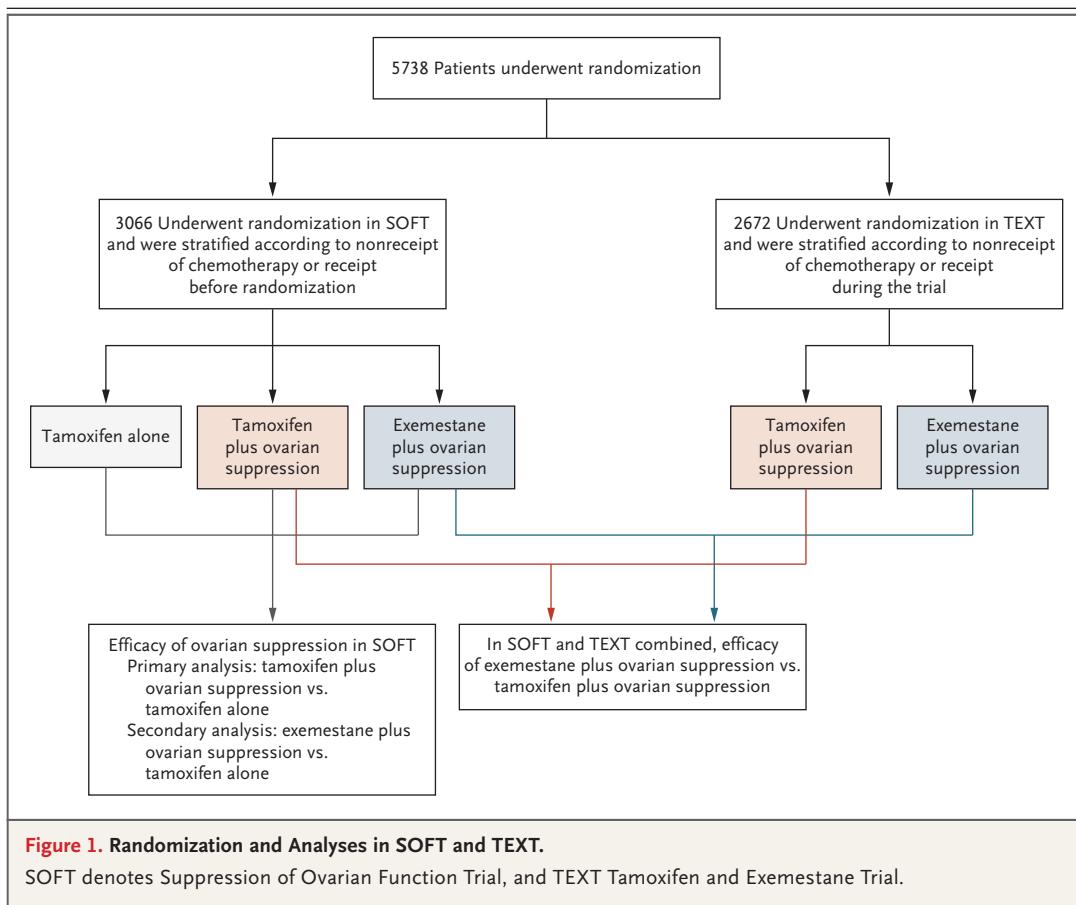
Analyses were performed according to the intention-to-treat principle, with the calculation of Kaplan-Meier estimates of time-to-event end points. In SOFT, we used stratified log-rank tests to compare tamoxifen plus ovarian suppression with tamoxifen alone, with stratification according to receipt or nonreceipt of previous chemotherapy and lymph-node status. In the combined analysis of data from SOFT and TEXT, we compared exemestane plus ovarian suppression with tamoxifen plus ovarian suppression, with stratification according to trial, receipt or nonreceipt of chemotherapy, and lymph-node status. We used stratified Cox proportional-hazards regression to estimate hazard ratios and 95% confidence intervals. The heterogeneity of the treatment effect according to subgroup was investigated by means of tests of treatment-covariate interaction; P values for these tests were not adjusted for multiple comparisons. Analyses that focused on the HER2-negative population include estimates and 95% confidence intervals, which were not adjusted for multiple comparisons, so inferences should be viewed as preliminary.

RESULTS

PATIENTS

From December 2003 through January 2011, we randomly assigned 1021 premenopausal women to receive tamoxifen alone, 1024 to receive tamoxifen plus ovarian suppression, and 1021 to receive exemestane plus ovarian suppression in SOFT. After exclusions, 3047 women were included in the intention-to-treat population for the two pairwise comparisons of tamoxifen alone versus tamoxifen plus ovarian suppression and exemestane plus ovarian suppression (Fig. 1, and Fig. S1 in the Supplementary Appendix). A total of 1628 patients (53.4%) had received chemotherapy before randomization (Table 1). The median age of the patients who had received chemotherapy was 40 years, as compared with a median age of 46 years among those who had not received chemotherapy. Node-positive disease was present in 34.5% of the patients. The majority of the patients (84.9%) had HER2-negative tumors.

From November 2003 through April 2011, we randomly assigned 1338 premenopausal women



to receive exemestane plus ovarian suppression and 1334 to receive tamoxifen plus ovarian suppression in TEXT. After exclusions, 2660 women were included in the intention-to-treat population. A total of 1607 patients (60.4%) received chemotherapy after randomization (Table 1). After exclusions, 4690 women were included in the combined SOFT and TEXT intention-to-treat population for the comparison between exemestane plus ovarian suppression and tamoxifen plus ovarian suppression (Fig. 1, and Fig. S5 in the Supplementary Appendix). HER2-negative disease was present in 86.0% of the patients in the combined population.

For the updated analyses, 87.5% of all the patients in SOFT and TEXT had clinical follow-up data, and 4.4% had national registry-based follow-up only. The numbers of patients who withdrew consent or were lost to follow-up were similar across the treatment groups (Figs. S1 and S5 in the Supplementary Appendix).

EFFICACY OF OVARIAN SUPPRESSION IN SOFT

After a median follow-up of 8 years, the 8-year rate of disease-free survival was 83.2% among patients assigned to receive tamoxifen plus ovarian suppression and 78.9% among those assigned to receive tamoxifen alone (hazard ratio for recurrence, a second invasive cancer, or death, 0.76; 95% confidence interval [CI], 0.62 to 0.93; $P=0.009$), for a difference of 4.2 percentage points (Fig. 2A, and Table S1 in the Supplementary Appendix). Among the patients who were assigned to receive exemestane plus ovarian suppression, the rate of disease-free survival was 85.9%, a difference of 7.0 percentage points over tamoxifen alone (hazard ratio, 0.65; 95% CI, 0.53 to 0.81) (Fig. 2A). Of 518 first events, 279 (53.9%) involved distant sites, 51 (9.8%) were invasive contralateral breast cancers, 105 (20.3%) involved locoregional sites, and the remaining 83 events (16.0%) involved second (non-breast) cancers or deaths from other causes (Table S2 in the Supplementary Appendix). No evidence

Table 1. Characteristics of the Patients in SOFT and TEXT at Baseline, According to Chemotherapy Status.*

Characteristic	SOFT		TEXT	
	No Chemotherapy (N=1419)	Chemotherapy (N=1628)†	No Chemotherapy (N=1053)	Chemotherapy (N=1607)†
Median age — yr	46	40	45	43
Age group — no. (%)				
<35 yr	21 (1.5)	329 (20.2)	41 (3.9)	191 (11.9)
35–39 yr	110 (7.8)	473 (29.1)	123 (11.7)	289 (18.0)
40–49 yr	1045 (73.6)	772 (47.4)	768 (72.9)	1047 (65.2)
≥50 yr	243 (17.1)	54 (3.3)	121 (11.5)	80 (5.0)
Lymph-node status — no. (%)				
Negative	1294 (91.2)	701 (43.1)	835 (79.3)	542 (33.7)
Positive	125 (8.8)	927 (56.9)	218 (20.7)	1065 (66.3)
Tumor size — no. (%)				
≤2 cm	1213 (85.5)	800 (49.1)	846 (80.3)	738 (45.9)
>2 cm	199 (14.0)	764 (46.9)	204 (19.3)	846 (52.6)
Unknown	7 (0.5)	64 (3.9)	3 (0.3)	23 (1.4)
HER2 status — no. (%)‡				
Negative	1329 (93.7)	1257 (77.2)	991 (94.1)	1317 (82.0)
Positive	53 (3.7)	313 (19.2)	53 (5.0)	276 (17.2)
Unknown or not assessed	37 (2.6)	58 (3.6)	9 (0.9)	14 (0.9)
Median interval from surgery to randomization (IQR) — mo	1.8 (1.2–2.4)	8.0 (5.7–10.3)	1.5 (1.1–1.9)	1.2 (0.9–1.6)

* Percentages may not total 100 because of rounding. HER2 denotes human epidermal growth factor receptor 2, IQR interquartile range, SOFT Suppression of Ovarian Function Trial, and TEXT Tamoxifen and Exemestane Trial.

† Among patients who received chemotherapy, patients in SOFT had received chemotherapy before randomization and those in TEXT received chemotherapy during the trial concurrently with ovarian suppression.

‡ Among the patients with HER2-positive disease, HER2-directed therapy was administered to 220 of 366 patients (60.1%) in SOFT (including 3 patients who did not receive chemotherapy and 217 patients who had received chemotherapy previously) and to 156 of 329 patients (47.4%) in TEXT (including 9 patients who did not receive chemotherapy and 147 patients who received chemotherapy).

of heterogeneity of relative treatment effect according to previous receipt or nonreceipt of chemotherapy was noted (Fig. 2B and 2C). Recurrences were more frequent in the patients who had received chemotherapy, with an 8-year rate of disease-free survival in this cohort of 71.4% among patients assigned to receive tamoxifen alone, 76.7% among those assigned to receive tamoxifen plus ovarian suppression, and 80.4% among those assigned to receive exemestane plus ovarian suppression, differences as compared with tamoxifen alone of 5.3 and 9.0 percentage points, respectively (Fig. 2C).

In subgroup analyses, the only notable heterogeneity of treatment effect was according to HER2 status (Fig. S2A in the Supplementary Appendix).

The results suggested a greater benefit from the addition of ovarian suppression to tamoxifen, as compared with tamoxifen alone, among women with HER2-positive disease (hazard ratio for recurrence, a second invasive cancer, or death, 0.41; 95% CI, 0.22 to 0.75) than among those with HER2-negative disease (hazard ratio, 0.83; 95% CI, 0.67 to 1.04; $P=0.04$ for interaction) (Fig. 3). The estimates of relative treatment effect with exemestane plus ovarian suppression as compared with tamoxifen alone were similar for HER2-positive and HER2-negative disease ($P=0.44$ for interaction) (Fig. 3, and Fig. S2B in the Supplementary Appendix). Among the patients who received chemotherapy for HER2-negative tumors, the rate of disease-free survival at 8 years was 71.9%

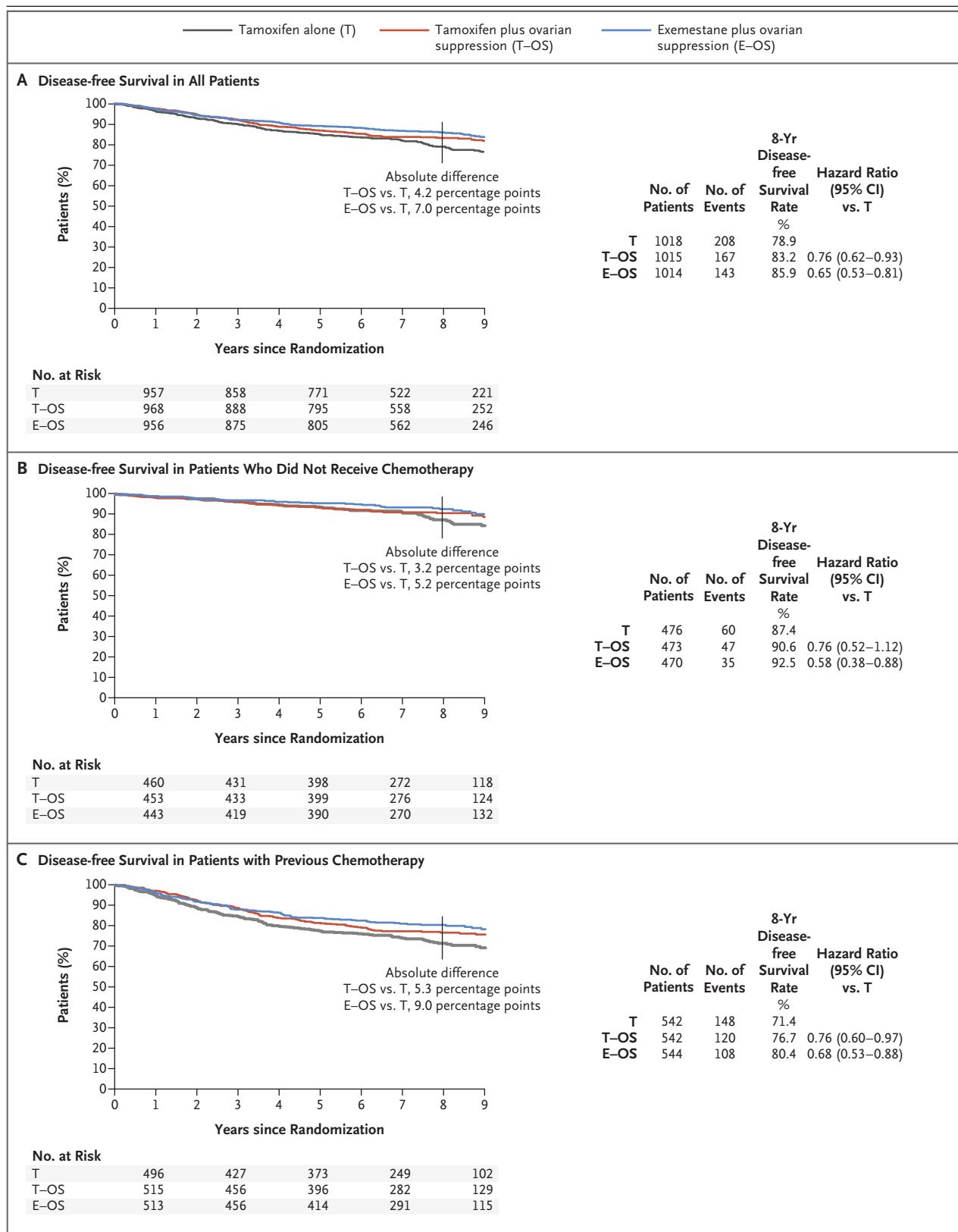


Figure 2 (facing page). Kaplan–Meier Estimates of Disease-free Survival after a Median Follow-up of 8 Years in SOFT.

Shown are Kaplan–Meier estimates of the rates of disease-free survival in SOFT according to treatment assignment — tamoxifen alone (T), tamoxifen plus ovarian suppression (T–OS), or exemestane plus ovarian suppression (E–OS) — among all the patients in the trial (Panel A) and according to chemotherapy status (Panels B and C). In Panel A, tamoxifen plus ovarian suppression resulted in a 24% lower relative risk of recurrence, a second invasive cancer, or death than tamoxifen alone ($P = 0.009$). In each panel, the 8-year data are highlighted by a black vertical line. The hazard ratios are for disease recurrence, a second invasive cancer, or death.

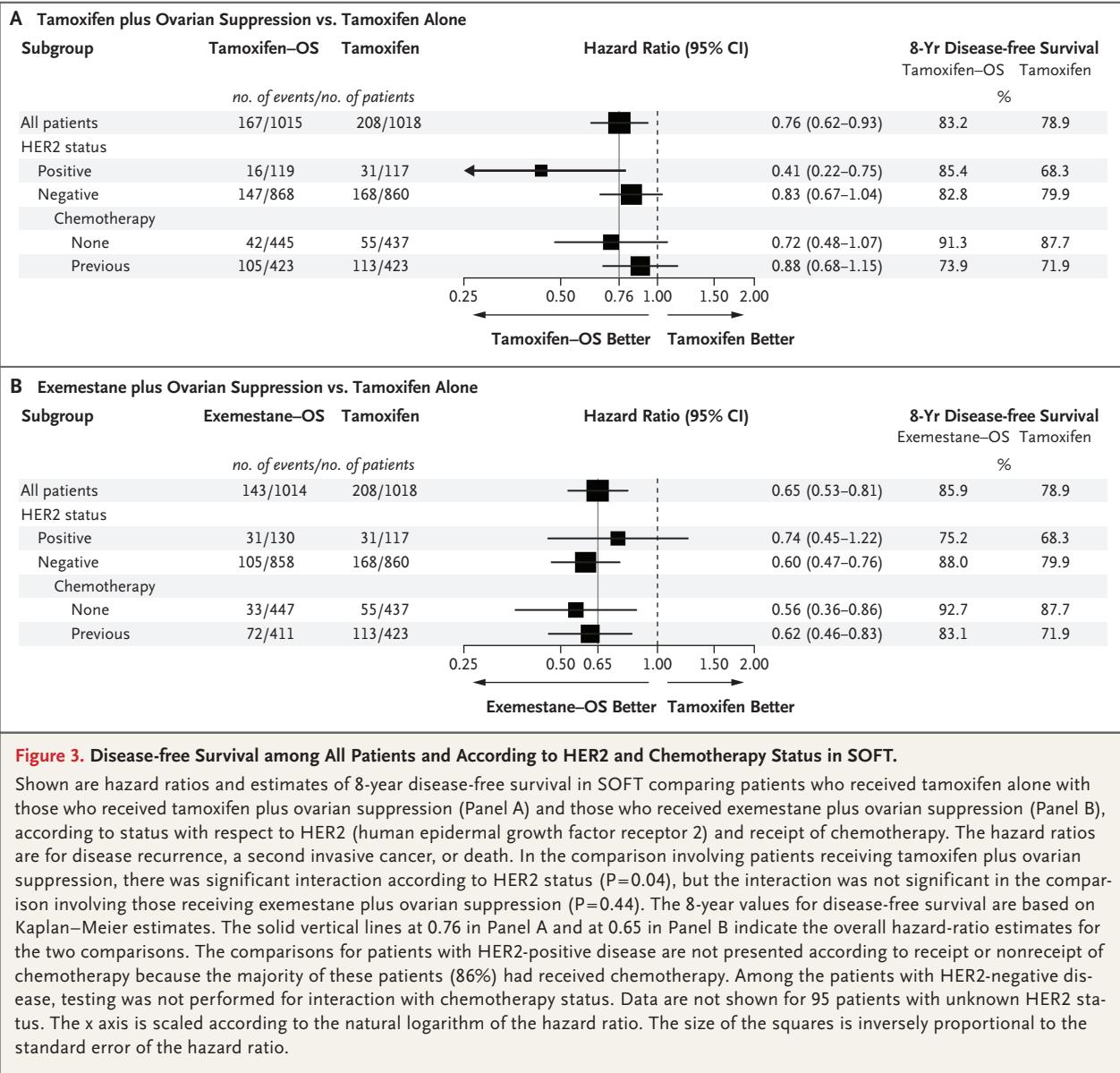
among the patients assigned to receive tamoxifen alone, 73.9% among those assigned to receive tamoxifen plus ovarian suppression, and 83.1% among those assigned to receive exemestane plus ovarian suppression, differences of 2.0 and 11.2 percentage points, respectively, as compared with tamoxifen alone.

Recurrence of breast cancer at a distant site was reported in 306 of 3047 patients (10.0%) in SOFT. The addition of ovarian suppression to tamoxifen did not result in a significantly lower rate of distant recurrence than that with tamoxifen alone (hazard ratio for recurrence, 0.86; 95% CI, 0.66 to 1.13; $P=0.28$). The rate of distant recurrence was lower among patients assigned to receive exemestane plus ovarian suppression than among those assigned to receive tamoxifen alone (hazard ratio, 0.73; 95% CI, 0.55 to 0.96) (Fig. 4A). Most distant recurrences occurred in patients who had received chemotherapy (Fig. 4C). The 8-year rate of freedom from distant recurrence in this cohort was 80.0% among patients assigned to receive tamoxifen alone, 82.1% among those assigned to receive tamoxifen plus ovarian suppression, and 84.5% among those assigned to receive exemestane plus ovarian suppression. Among patients who received chemotherapy for HER2-negative tumors, the 8-year rate of freedom from distant recurrence was 80.8% among patients assigned to receive tamoxifen alone, 79.8% among those assigned to receive tamoxifen plus ovarian suppression, and 86.8% among those assigned to receive exemestane plus ovarian suppression.

Death was reported in 225 patients (7.4%), and 9 deaths occurred without a preceding cancer-

associated event (Tables S2C and S3 in the Supplementary Appendix). The rate of overall survival in SOFT at 8 years was significantly higher with tamoxifen plus ovarian suppression (93.3%; 95% CI, 91.4 to 94.8) than with tamoxifen alone (91.5%; 95% CI, 89.4 to 93.2) (hazard ratio for death, 0.67; 95% CI, 0.48 to 0.92; $P=0.01$) (Fig. 4B). The rate of overall survival among patients assigned to receive exemestane plus ovarian suppression was 92.1% (95% CI, 90.0 to 93.7) (hazard ratio for death vs. tamoxifen, 0.85; 95% CI, 0.62 to 1.15). Most deaths occurred in patients who had received chemotherapy. The rate of overall survival at 8 years in the chemotherapy cohort was 89.4% among patients assigned to receive tamoxifen plus ovarian suppression and 85.1% among those assigned to receive tamoxifen alone (hazard ratio for death, 0.59; 95% CI, 0.42 to 0.84). In this cohort, the rate of overall survival among those assigned to receive exemestane plus ovarian suppression was 87.2% (hazard ratio for death vs. tamoxifen, 0.79; 95% CI, 0.57 to 1.09) (Fig. 4D). Among the patients who had received previous chemotherapy for HER2-negative tumors, the 8-year overall survival rate was 85.2% among patients assigned to receive tamoxifen alone, 87.7% among those assigned to receive tamoxifen plus ovarian suppression (hazard ratio for death vs. tamoxifen, 0.70; 95% CI, 0.48 to 1.02), and 88.7% among those assigned to receive exemestane plus ovarian suppression (hazard ratio for death vs. tamoxifen, 0.71; 95% CI, 0.49 to 1.05).

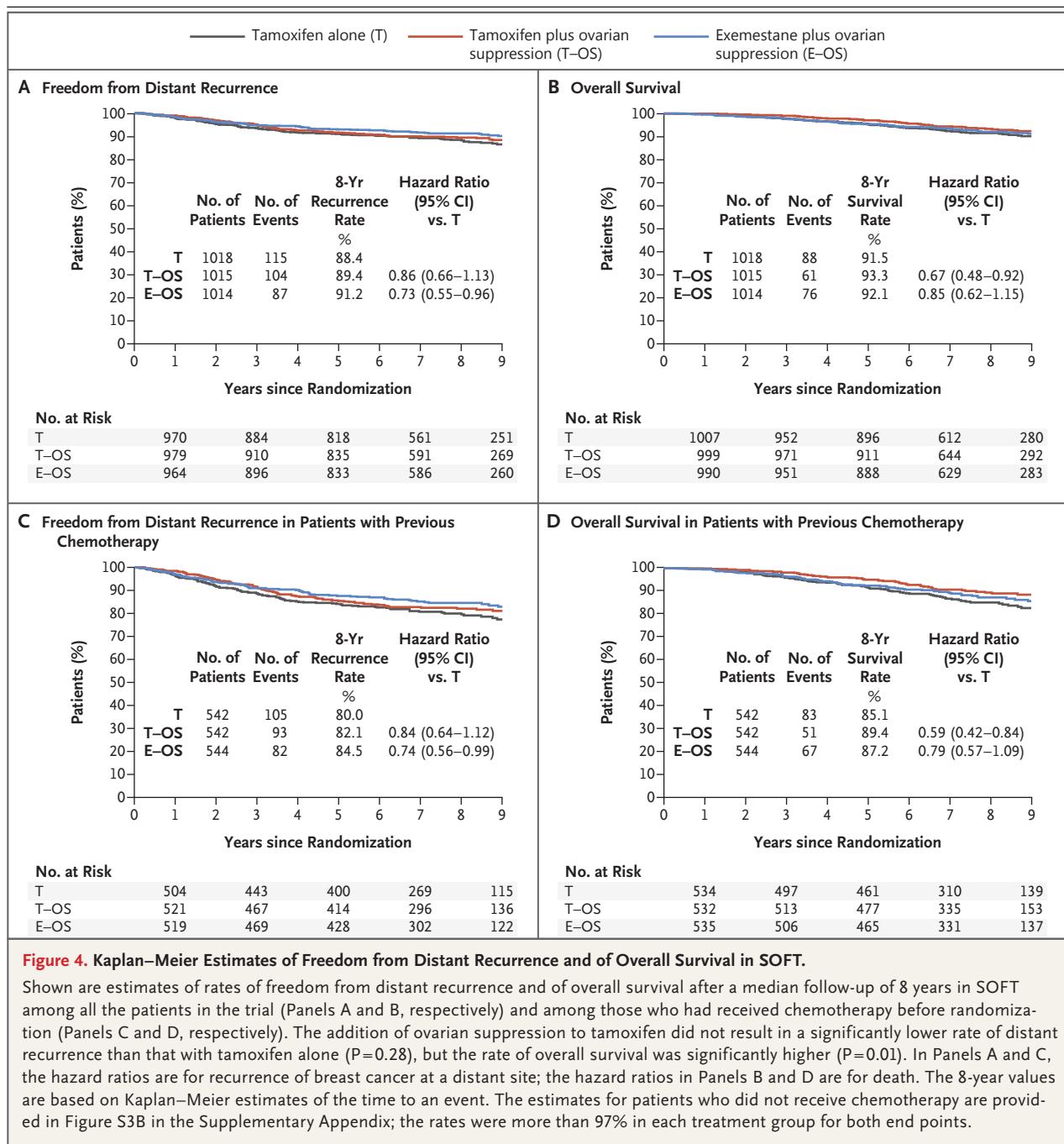
Among patients in SOFT who did not receive chemotherapy, 23.2% of the first disease-free survival events were contralateral breast cancers (Table S2 in the Supplementary Appendix). The 8-year rate of freedom from breast cancer in this cohort was 91.4% (95% CI, 87.8 to 94.0) among patients assigned to receive tamoxifen alone, 93.6% (95% CI, 90.9 to 95.6) among those assigned to receive tamoxifen plus ovarian suppression, and 95.4% (95% CI, 92.8 to 97.1) among those assigned to receive exemestane plus ovarian suppression (Fig. S3A in the Supplementary Appendix). There were 26 distant recurrences; 12 of 24 deaths in this cohort (50%) occurred in the absence of distant recurrence, with more than 97% of the patients free of distant recurrence and alive in each treatment group at 8 years (Table S3 and Fig. S3B in the Supplementary Appendix).



EFFICACY OF EXEMESTANE OR TAMOXIFEN WITH OVARIAN SUPPRESSION

After a median follow-up of 9 years of the 4690 patients in the combined population enrolled in TEXT and SOFT whose protocol-assigned therapy included ovarian suppression (Fig. 1, and Fig. S5 in the Supplementary Appendix), 720 patients (15.4%) had disease recurrence, had a second invasive cancer, or had died. The 8-year disease-free survival rate was 86.8% among patients assigned to receive exemestane plus ovarian suppression and 82.8% among those assigned to

receive tamoxifen plus ovarian suppression, a difference of 4.0 percentage points (hazard ratio for recurrence, a second invasive cancer, or death, 0.77; 95% CI, 0.67 to 0.90; $P<0.001$) (Fig. 5A, and Table S5 in the Supplementary Appendix). In subgroup analyses, the only heterogeneity of treatment effect was according to HER2 status (Fig. S6 in the Supplementary Appendix). Among the patients with HER2-negative tumors, the 8-year disease-free survival rate was 88.1% among patients assigned to receive exemestane plus ovarian suppression and 82.7% among those assigned to re-



ceive tamoxifen plus ovarian suppression, a difference of 5.4 percentage points (hazard ratio, 0.70; 95% CI, 0.60 to 0.83) (Fig. 6).

The recurrence of breast cancer at a distant site was reported in 433 patients (9.2%). The 8-year rate of freedom from distant recurrence was 91.8% among patients assigned to receive exemestane

plus ovarian suppression and 89.7% among those assigned to receive tamoxifen plus ovarian suppression, a difference of 2.1 percentage points (hazard ratio for recurrence, 0.80; 95% CI, 0.66 to 0.96; $P=0.02$) (Fig. 5B). Among patients with HER2-negative tumors, the 8-year rate of freedom from distant recurrence was 93.0% among

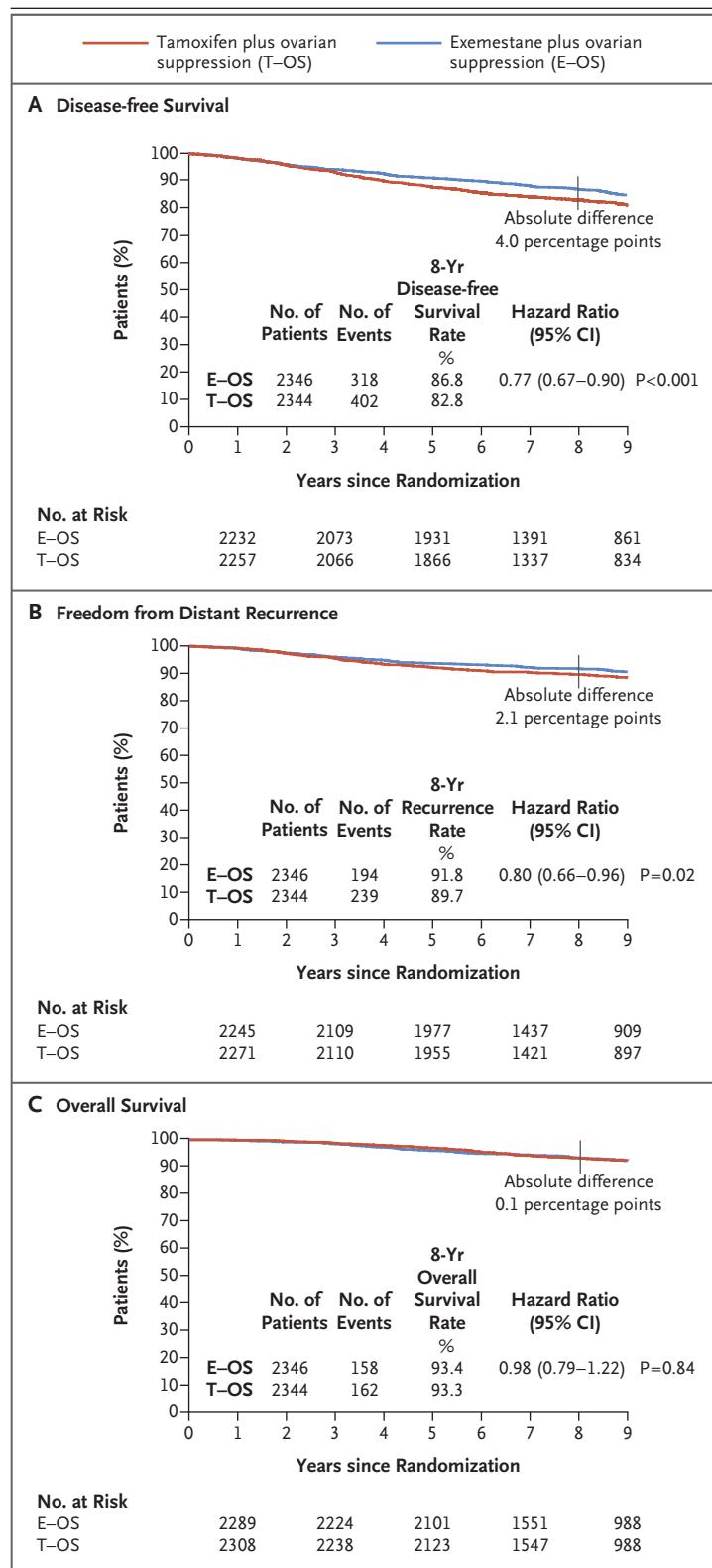


Figure 5. Kaplan-Meier Estimates of Disease-free Survival, Freedom from Distant Recurrence, and Overall Survival in the Combined SOFT and TEXT Population.

Shown are estimates of disease-free survival (Panel A), freedom from distant recurrence (Panel B), and overall survival (Panel C) among patients who received tamoxifen plus ovarian suppression (T-OS) and those who received exemestane plus ovarian suppression (E-OS) after a median follow-up of 9 years in the combined population. In each panel, the 8-year data are highlighted by a black vertical line. The hazard ratio in Panel A is for disease recurrence, a second invasive cancer, or death. In Panels B and C, the hazard ratios are for distant recurrence of breast cancer and for death, respectively. The 8-year values are based on Kaplan-Meier estimates of the time to an event.

patients assigned to receive exemestane plus ovarian suppression and 89.6% among those assigned to receive tamoxifen plus ovarian suppression, a difference of 3.5 percentage points (hazard ratio for recurrence, 0.69; 95% CI, 0.56 to 0.85) (Fig. 6). The majority of distant recurrences (87.8%) occurred among patients who had received chemotherapy (Fig. S7B in the Supplementary Appendix). In the combined population, more than 96% of the patients who did not receive chemotherapy were free from distant recurrence at 8 years in each treatment group (Fig. S7C in the Supplementary Appendix). In the HER2-negative chemotherapy cohorts, the 8-year rate of freedom from distant recurrence was higher among those assigned to receive exemestane plus ovarian suppression than among those assigned to receive tamoxifen plus ovarian suppression (by 7.0 percentage points in SOFT and 5.0 percentage points in TEXT) (Fig. 6).

In the combined analysis, 320 patients (6.8%) had died after a median follow-up of 9 years. The rate of overall survival at 8 years was 93.4% among patients assigned to receive exemestane plus ovarian suppression and 93.3% among those assigned to receive tamoxifen plus ovarian suppression (hazard ratio for death, 0.98; 95% CI, 0.79 to 1.22; P = 0.84) (Fig. 5C); among those with HER2-negative tumors, the corresponding rates were 94.1% and 93.4% (hazard ratio for death, 0.86; 95% CI, 0.68 to 1.10) (Fig. 6). Death without a preceding cancer-associated event was reported in 4 patients assigned to receive exemestane

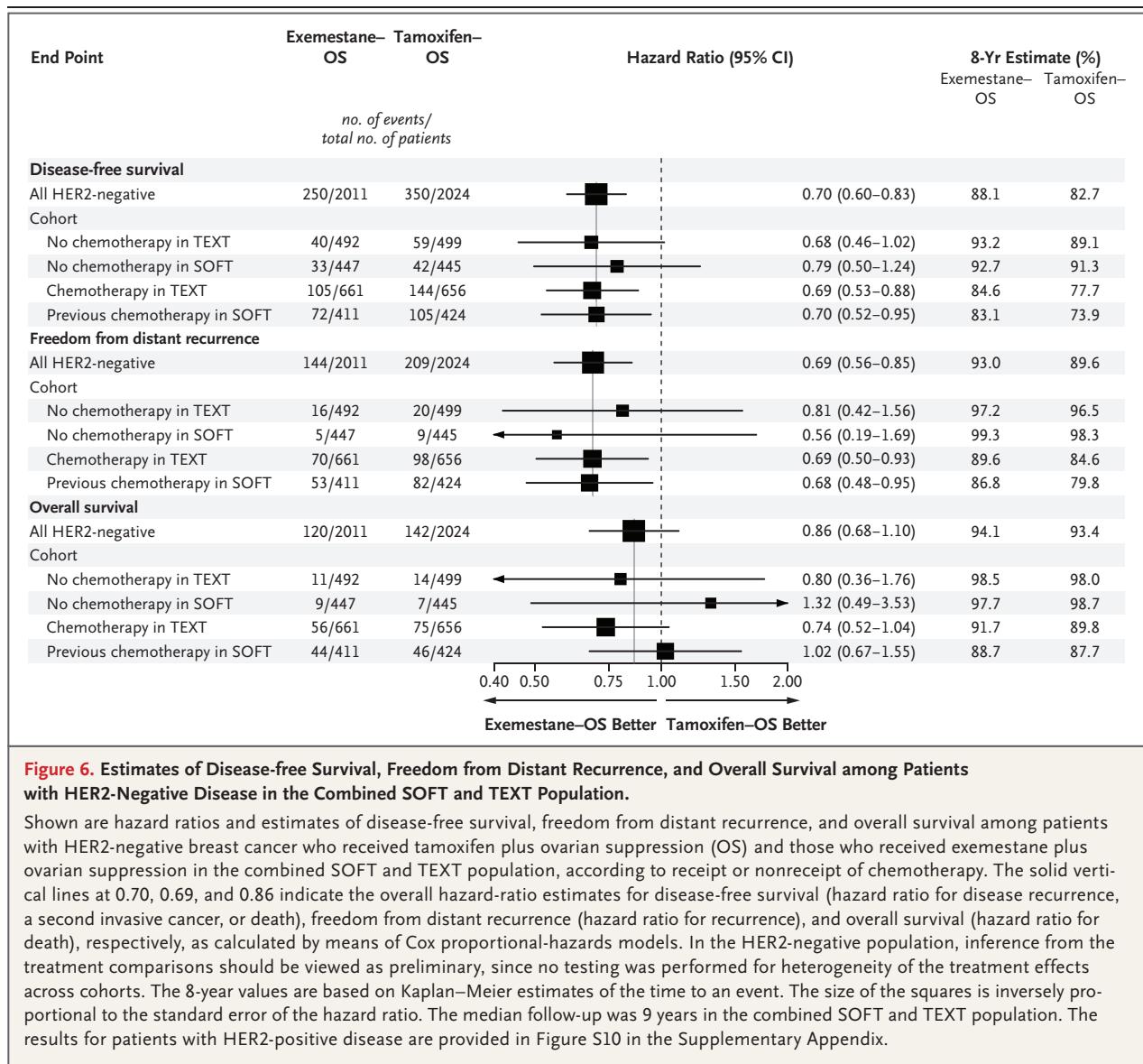


Figure 6. Estimates of Disease-free Survival, Freedom from Distant Recurrence, and Overall Survival among Patients with HER2-Negative Disease in the Combined SOFT and TEXT Population.

Shown are hazard ratios and estimates of disease-free survival, freedom from distant recurrence, and overall survival among patients with HER2-negative breast cancer who received tamoxifen plus ovarian suppression (OS) and those who received exemestane plus ovarian suppression in the combined SOFT and TEXT population, according to receipt or nonreceipt of chemotherapy. The solid vertical lines at 0.70, 0.69, and 0.86 indicate the overall hazard-ratio estimates for disease-free survival (hazard ratio for disease recurrence, a second invasive cancer, or death), freedom from distant recurrence (hazard ratio for recurrence), and overall survival (hazard ratio for death), respectively, as calculated by means of Cox proportional-hazards models. In the HER2-negative population, inference from the treatment comparisons should be viewed as preliminary, since no testing was performed for heterogeneity of the treatment effects across cohorts. The 8-year values are based on Kaplan–Meier estimates of the time to an event. The size of the squares is inversely proportional to the standard error of the hazard ratio. The median follow-up was 9 years in the combined SOFT and TEXT population. The results for patients with HER2-positive disease are provided in Figure S10 in the Supplementary Appendix.

plus ovarian suppression and in 8 patients assigned to receive tamoxifen plus ovarian suppression (Table S6 in the Supplementary Appendix).

TREATMENT AND ADVERSE EVENTS

Early discontinuation of assigned oral endocrine therapy, with or without alternative therapy, occurred in 22.5% of the tamoxifen group in SOFT, 19.3% of the combined tamoxifen–ovarian suppression group, and 23.7% of the combined exemestane–ovarian suppression group (Tables S4 and S8 in the Supplementary Appendix). The rate

of early cessation of ovarian suppression by triptorelin without substitution of ovarian ablation was 19.0% in the combined population and was similar between the groups (Table S8 in the Supplementary Appendix).

Targeted adverse events of grade 3 or higher were reported in 24.6% of the tamoxifen group in SOFT, 31.0% of the combined tamoxifen–ovarian suppression group, and 32.3% of the combined exemestane–ovarian suppression group (Table 2). Thrombosis or embolism of any grade was reported in 2.2% of the patients in the tamoxifen–

Table 2. Targeted Adverse Events during Treatment.*

Adverse Event	Tamoxifen (N=1005)		Tamoxifen plus Ovarian Suppression (N=2326)		Exemestane plus Ovarian Suppression (N=2317)	
	Any Event	Grade 3 or 4 Event	Any Event	Grade 3 or 4 Event	Any Event	Grade 3 or 4 Event
		number of patients (percent)				
Any targeted adverse event	962 (95.7)	247 (24.6)	2295 (98.7)	721 (31.0)	2288 (98.7)	748 (32.3)
Allergic reaction or hypersensitivity	35 (3.5)	2 (0.2)	110 (4.7)	9 (0.4)	122 (5.3)	12 (0.5)
Injection-site reaction	4 (0.4)	0	189 (8.1)	1 (<0.1)	174 (7.5)	1 (<0.1)
Hot flushes	808 (80.4)	78 (7.8)	2175 (93.5)	284 (12.2)	2141 (92.4)	234 (10.1)
Depression	476 (47.4)	41 (4.1)	1195 (51.4)	108 (4.6)	1197 (51.7)	95 (4.1)
Sweating	492 (49.0)	NA	1391 (59.8)	NA	1286 (55.5)	NA
Insomnia	470 (46.8)	30 (3.0)	1383 (59.5)	105 (4.5)	1375 (59.3)	89 (3.8)
Fatigue	612 (60.9)	34 (3.4)	1496 (64.3)	70 (3.0)	1450 (62.6)	75 (3.2)
Hypertension	181 (18.0)	57 (5.7)	550 (23.6)	188 (8.1)	564 (24.3)	168 (7.3)
Cardiac ischemia or infarction†	5 (0.5)	4 (0.4)	10 (0.4)	6 (0.3)	17 (0.7)	7 (0.3)
Thrombosis or embolism	22 (2.2)	17 (1.7)	53 (2.3)	47 (2.0)	27 (1.2)	20 (0.9)
Nausea	241 (24.0)	0	692 (29.8)	14 (0.6)	747 (32.2)	17 (0.7)
Musculoskeletal symptom	703 (70.0)	67 (6.7)	1809 (77.8)	132 (5.7)	2082 (89.9)	263 (11.4)
Osteoporosis	138 (13.7)	1 (0.1)	648 (27.9)	7 (0.3)	977 (42.2)	10 (0.4)
Fracture	53 (5.3)	8 (0.8)	140 (6.0)	23 (1.0)	179 (7.7)	37 (1.6)
Vaginal dryness	426 (42.4)	NA	1144 (49.2)	NA	1245 (53.7)	NA
Decreased libido	434 (43.2)	NA	981 (42.2)	NA	1056 (45.6)	NA
Dyspareunia	242 (24.1)	16 (1.6)	636 (27.3)	35 (1.5)	733 (31.6)	56 (2.4)
Urinary incontinence	166 (16.5)	6 (0.6)	433 (18.6)	9 (0.4)	317 (13.7)	9 (0.4)
CNS cerebrovascular ischemia	6 (0.6)	4 (0.4)	10 (0.4)	7 (0.3)	6 (0.3)	5 (0.2)
CNS hemorrhage	15 (1.5)	0	26 (1.1)	2 (0.1)	19 (0.8)	1 (<0.1)
Glucose intolerance‡	18 (1.8)	4 (0.4)	68 (2.9)	23 (1.0)	63 (2.7)	15 (0.6)
Hyperglycemia‡	20 (2.0)	1 (0.1)	92 (4.0)	20 (0.9)	71 (3.1)	14 (0.6)

* Data are for patients in the safety populations in SOFT and TEXT who initiated a protocol-assigned treatment, including 1005 patients who were randomly assigned to receive tamoxifen in SOFT and 4643 patients who were randomly assigned to receive tamoxifen plus ovarian suppression (2326 patients) or exemestane plus ovarian suppression (2317 patients) in SOFT or TEXT. Data are missing for 4 patients (1 in the tamoxifen group and 3 in the tamoxifen–ovarian suppression group) who initiated treatment but withdrew consent within 1 month after randomization and for whom no adverse-event data were submitted. The 22 targeted adverse events and other adverse events of grade 3 or higher were categorized according to the Common Terminology Criteria for Adverse Events, version 3.0.⁹ The 95% confidence intervals for the percentages are provided in Table S9 in the Supplementary Appendix. CNS denotes central nervous system, and NA not applicable.

† One patient in the tamoxifen group in SOFT had grade 5 cardiac ischemia or infarction; no other grade 5 targeted adverse events were reported.

‡ Glucose intolerance (diabetes) and hyperglycemia were added as targeted adverse events in 2011 and therefore may be underreported.

only group, in 2.3% of those in the tamoxifen–ovarian suppression group, and in 1.2% of those in the exemestane–ovarian suppression group. Musculoskeletal symptoms of grade 3 or 4 occurred in 6.7% of the patients in the tamoxifen group, in 5.7% of those in the combined tamoxifen–ovarian suppression group, and in 11.4% of those in the combined exemestane–ovarian sup-

pression group. Osteoporosis (defined as a T score of less than –2.5, which corresponds to a grade 2, 3, or 4 adverse event) was reported in 3.9% of the patients in the tamoxifen group, in 7.2% of those in the combined tamoxifen–ovarian suppression group, and in 14.8% of those in the combined exemestane–ovarian suppression group. Vaginal dryness and dyspareunia were most frequent in

the exemestane–ovarian suppression group. Hypertension and glucose problems were more frequent in the two ovarian-suppression groups than in the tamoxifen-only group.

DISCUSSION

In the previously reported results of SOFT, we found that the addition of ovarian suppression to adjuvant tamoxifen did not result in a significantly better rate of disease-free survival than tamoxifen alone after a median follow-up of 5.6 years.⁶ However, our updated analysis after a median follow-up of 8 years showed significantly higher rates of disease-free and overall survival with the addition of ovarian suppression to tamoxifen than with tamoxifen alone. Tamoxifen plus ovarian suppression resulted in a 24% lower relative risk of recurrence, a second invasive cancer, or death than tamoxifen alone ($P=0.009$), which translated into an absolute difference of 4.2 percentage points in the rate of disease-free survival at 8 years. Exemestane plus ovarian suppression resulted in an even higher rate of disease-free survival, with a difference of 7.0 percentage points as compared with tamoxifen alone.

Our updated combined analysis of data from SOFT and TEXT showed that after a median follow-up of 9 years, treatment with exemestane plus ovarian suppression resulted in sustained and consistently higher rates of disease-free survival and freedom from distant recurrence than the rates with tamoxifen plus ovarian suppression. Among premenopausal women receiving ovarian suppression, the observed difference of 2.1 percentage points in freedom from distant recurrence at 8 years favoring an aromatase inhibitor over tamoxifen was similar to that observed in postmenopausal women treated with 5 years of aromatase inhibitors as compared with tamoxifen.¹⁰

Given the side effects of ovarian suppression, the overall results of SOFT do not imply that this treatment should be prescribed for all premenopausal women with hormone-receptor-positive early breast cancer. Although the relative treatment effects were similar regardless of receipt or nonreceipt of chemotherapy, the absolute benefits were larger in the cohort of patients who remained premenopausal after previous chemotherapy. These patients had higher-risk clinicopathological features, including a younger age (median, 40 years), which contributed to a higher

risk of recurrence. In this cohort, the rate of disease-free survival observed with tamoxifen plus ovarian suppression was 5.3 percentage points higher than that with tamoxifen alone, and the rate was 9.0 percentage points higher with exemestane plus ovarian suppression. Improvements in overall survival are now evident at 8 years in SOFT among the women who had received chemotherapy and were assigned to receive ovarian suppression with either tamoxifen or exemestane, as compared with those assigned to receive tamoxifen alone.

Among the women receiving ovarian suppression, the benefits of exemestane over tamoxifen were also more clinically meaningful in those at increased risk for recurrence, with increased rates of disease-free survival among women who had received chemotherapy. Among the patients who received exemestane plus ovarian suppression in the chemotherapy cohorts, the rate of disease-free survival was higher by 3.7 percentage points in SOFT and by 6.0 percentage points in TEXT than the rate with tamoxifen plus ovarian suppression; the rates of freedom from distant recurrence were higher by 2.5 percentage points and 3.6 percentage points, respectively. In the combined analysis of data from SOFT and TEXT involving all the women who had received ovarian suppression, no significant difference in 8-year overall survival emerged according to whether they were assigned to receive exemestane or tamoxifen. Given the long natural history of breast cancer with hormone-receptor positivity, conclusions regarding overall survival remain premature.

The majority of patients in the two trials had HER2-negative tumors, and for these women, the largest absolute difference in SOFT was seen with exemestane plus ovarian suppression, as compared with tamoxifen alone. In the SOFT HER2-negative chemotherapy cohort, absolute differences of 11.2 percentage points in disease-free survival and of 6.0 percentage points in freedom from distant recurrence favoring exemestane plus ovarian suppression were observed at 8 years. In the combined analysis of the HER2-negative population, the 8-year rates of freedom from distant recurrence were higher among patients assigned to receive exemestane plus ovarian suppression than among those assigned to receive tamoxifen plus ovarian suppression (by 7.0 percentage points in SOFT and by 5.0 percentage points in TEXT). Distant recurrence in a premenopausal woman

has a great effect on her quality of life and on both personal and family fulfillment and is associated with a substantial economic burden.¹¹ A more consistent benefit for aromatase inhibitors than for tamoxifen was also seen in patients with HER2-negative cancers in a meta-analysis of three randomized trials involving postmenopausal women that was conducted by the Translational Aromatase Inhibitor Overview Group, in which heterogeneous treatment effects were observed in patients with HER2-positive cancers.¹²

Since randomization in SOFT began in 2003, not all the patients with HER2-positive cancers received HER2-targeted therapy (60.1%). Heterogeneity in the treatment effect was evident according to HER2 status. In particular, as compared with women who had HER2-negative cancers, those with HER2-positive cancers in the SOFT chemotherapy cohort had greater benefit with tamoxifen plus ovarian suppression than tamoxifen alone and less benefit with exemestane plus ovarian suppression (Fig. 3, and Figs. S9 and 10 in the Supplementary Appendix).

Among the patients who did not receive chemotherapy, distant recurrence was reported in 26 patients (1.8%) in SOFT and 37 patients (3.5%) in TEXT after a median follow-up of 8 years and 9 years, respectively. This cohort in SOFT had low-risk clinicopathological features and had a higher rate of freedom from breast cancer with exemestane–ovarian suppression than with tamoxifen alone (by 4.0 percentage points) (Fig. S3A in the Supplementary Appendix). However, since intensification of adjuvant endocrine therapy was predominantly associated with lower risks of local, regional, and contralateral breast cancer events, tamoxifen alone remains an appropriate adjuvant therapy for these women. In TEXT, all the patients who had undergone randomization were assigned to receive ovarian suppression, and 20.7% of the TEXT cohort who did not receive chemotherapy had lymph-node–positive disease. The combined comparison of ovarian suppression plus either an aromatase inhibitor or tamoxifen in SOFT and TEXT differs from the results of the Austrian Breast and Colorectal Cancer Study Group Trial 12¹³ in many ways; such differences may have partially resulted from the high percentage of patients in the Austrian trial (>85%) who did not receive chemotherapy (Table S10 in the Supplementary Appendix).

Women who receive the diagnosis of hormone-

receptor–positive breast cancer before the age of 35 years are at particular risk for recurrence.^{4,5,14,15} On the basis of the primary findings in SOFT,⁶ guidelines were revised to include recommendations for the use of ovarian suppression in this age group.^{16–18} The 8-year results in this age group in SOFT showed that the rate of freedom from distant recurrence was 82.4% with exemestane plus ovarian suppression, 77.5% with tamoxifen plus ovarian suppression, and 73.8% with tamoxifen alone (differences of 8.6 percentage points and 3.7 percentage points, respectively) (Fig. S4 in the Supplementary Appendix).

Potential benefits from ovarian suppression and aromatase inhibitors must be weighed against increased rates of acute^{19,20} and late toxic effects. Population studies involving women undergoing premenopausal bilateral oophorectomy without estrogen replacement have shown increased rates of subsequent side effects, including depression, hyperlipidemia, cardiovascular disease, diabetes, osteoporosis, and death from any cause.^{21–23} Such side effects may be treated with various strategies (e.g., the use of bisphosphonates to preserve bone density, which may also reduce cancer recurrence¹³). The toxicity profiles of exemestane plus ovarian suppression as compared with tamoxifen plus ovarian suppression remain similar to those seen in postmenopausal women. A greater proportion of women who were assigned to receive exemestane plus ovarian suppression had early discontinuation of oral endocrine therapy than those assigned to receive tamoxifen plus ovarian suppression (23.7% vs. 19.3%). In individual patients, clinicians are tasked with weighing side effects and the effect on quality of life^{19,20} associated with intensifying endocrine therapy against the risks of nonadherence and recurrence and the expected absolute improvement²⁴ in disease outcome.

Longer follow-up is planned for SOFT and TEXT, since data regarding survival and late adverse events are immature. In randomized trials of adjuvant endocrine therapy, maximal separation of Kaplan–Meier curves for overall survival has typically occurred more than 10 years after randomization.^{1,2,25} In a recent study, distant recurrences continued to occur in the follow-up period from 5 to 20 years after diagnosis.²⁶ After a median follow-up of 8 years or 9 years, the effects of ovarian suppression and aromatase inhibitors may not yet be fully appreciated.

We conclude that adding ovarian suppression to tamoxifen resulted in significantly higher rates of disease-free survival among premenopausal women than the use of tamoxifen alone. Further improvement was seen with exemestane plus ovarian suppression. For patients who have HER2-negative cancers and are at increased risk for recurrence, the absolute benefits of exemestane plus ovarian suppression in reducing recurrence (particularly distant recurrence) make this combination worthy of use in clinical practice. In women who were deemed to be at sufficient risk for recurrence to receive adjuvant chemotherapy and who retained premenopausal estradiol status after chemotherapy, ovarian suppression resulted in clinically meaningful improvements in disease-free survival. Such patients who received ovarian suppression plus either tamoxifen or exemestane had higher rates of overall survival at

8 years than those who received tamoxifen alone.

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APPENDIX

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