

Adjuvant Exemestane with Ovarian Suppression in Premenopausal Breast Cancer

Olivia Pagani, M.D., Meredith M. Regan, Sc.D., Barbara A. Walley, M.D., Gini F. Fleming, M.D., Marco Colleoni, M.D., István Láng, M.D., Henry L. Gomez, M.D., Carlo Tondini, M.D., Harold J. Burstein, M.D., Edith A. Perez, M.D., Eva Ciruelos, M.D., Vered Stearns, M.D., Hervé R. Bonnefoi, M.D., Silvana Martino, D.O., Charles E. Geyer, Jr., M.D., Graziella Pinotti, M.D., Fabio Puglisi, M.D., Diana Crivellari, M.D., Thomas Ruhstaller, M.D., Eric P. Winer, M.D., Manuela Rabaglio-Poretti, M.D., Rudolf Maibach, Ph.D., Barbara Ruepp, Pharm.D., Anita Giobbie-Hurder, M.S., Karen N. Price, B.S., Jürg Bernhard, Ph.D., Weixiu Luo, M.S., Karin Ribí, Ph.D., Giuseppe Viale, M.D., Alan S. Coates, M.D., Richard D. Gelber, Ph.D., Aron Goldhirsch, M.D., and Prudence A. Francis, M.D.,
for the TEXT and SOFT Investigators and the International Breast Cancer Study Group*

ABSTRACT

BACKGROUND

Adjuvant therapy with an aromatase inhibitor improves outcomes, as compared with tamoxifen, in postmenopausal women with hormone-receptor-positive breast cancer.

METHODS

In two phase 3 trials, we randomly assigned premenopausal women with hormone-receptor-positive early breast cancer to the aromatase inhibitor exemestane plus ovarian suppression or tamoxifen plus ovarian suppression for a period of 5 years. Suppression of ovarian estrogen production was achieved with the use of the gonadotropin-releasing-hormone agonist triptorelin, oophorectomy, or ovarian irradiation. The primary analysis combined data from 4690 patients in the two trials.

RESULTS

After a median follow-up of 68 months, disease-free survival at 5 years was 91.1% in the exemestane-ovarian suppression group and 87.3% in the tamoxifen-ovarian suppression group (hazard ratio for disease recurrence, second invasive cancer, or death, 0.72; 95% confidence interval [CI], 0.60 to 0.85; $P < 0.001$). The rate of freedom from breast cancer at 5 years was 92.8% in the exemestane-ovarian suppression group, as compared with 88.8% in the tamoxifen-ovarian suppression group (hazard ratio for recurrence, 0.66; 95% CI, 0.55 to 0.80; $P < 0.001$). With 194 deaths (4.1% of the patients), overall survival did not differ significantly between the two groups (hazard ratio for death in the exemestane-ovarian suppression group, 1.14; 95% CI, 0.86 to 1.51; $P = 0.37$). Selected adverse events of grade 3 or 4 were reported for 30.6% of the patients in the exemestane-ovarian suppression group and 29.4% of those in the tamoxifen-ovarian suppression group, with profiles similar to those for postmenopausal women.

CONCLUSIONS

In premenopausal women with hormone-receptor-positive early breast cancer, adjuvant treatment with exemestane plus ovarian suppression, as compared with tamoxifen plus ovarian suppression, significantly reduced recurrence. (Funded by Pfizer and others; TEXT and SOFT ClinicalTrials.gov numbers, NCT00066703 and NCT00066690, respectively.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Pagani at the Institute of Oncology of Southern Switzerland, Ospedale San Giovanni, 6500 Bellinzona, Switzerland, or at ibcsgcc@ibcsg.org.

*The investigators in the Tamoxifen and Exemestane Trial (TEXT) and Suppression of Ovarian Function Trial (SOFT) and the leadership and staff of the International Breast Cancer Study Group are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on June 1, 2014, and updated on June 12, 2014, at NEJM.org.

N Engl J Med 2014;371:107-18.

DOI: 10.1056/NEJMoa1404037

Copyright © 2014 Massachusetts Medical Society.

THE MOST EFFECTIVE ADJUVANT ENDOCRINE therapy for premenopausal women with hormone-receptor (estrogen, progesterone, or both)-positive breast cancer is uncertain. Tamoxifen for at least 5 years is a standard of care.¹⁻³ Adjuvant suppression of ovarian function (hereafter, ovarian suppression) may be recommended in addition. For postmenopausal women, adjuvant therapy with an aromatase inhibitor, as compared with tamoxifen, improves outcomes.²⁻⁹

In 2003, the International Breast Cancer Study Group (IBCSG) initiated two randomized, phase 3 trials, the Tamoxifen and Exemestane Trial (TEXT) and the Suppression of Ovarian Function Trial (SOFT), involving premenopausal women with hormone-receptor-positive early breast cancer, through collaboration with the Breast International Group (BIG) and the North American Breast Cancer Group. The trials were designed to determine whether adjuvant therapy with the aromatase inhibitor exemestane improved disease-free survival, as compared with tamoxifen, among premenopausal women treated plus ovarian suppression and to determine the value of ovarian suppression in women who were suitable candidates for treatment with adjuvant tamoxifen. Here we report the results of the planned¹⁰ primary combined analysis of data from TEXT and SOFT comparing adjuvant exemestane plus ovarian suppression with adjuvant tamoxifen plus ovarian suppression after a median follow-up of 68 months.

METHODS

PATIENTS

Eligibility in each trial required documented premenopausal status. Inclusion criteria were histologically proven operable breast cancer confined to the breast and ipsilateral axilla, with the exception of internal-mammary-node involvement detected by means of sentinel-node biopsy, and tumor that expressed estrogen or progesterone receptors in at least 10% of the cells, as assessed with the use of immunohistochemical testing. Patients with synchronous bilateral hormone-receptor-positive breast cancer were eligible. Patients had undergone either a total mastectomy with subsequent optional radiotherapy or breast-conserving surgery with subsequent radiotherapy. Either axillary dissection or a negative sentinel-node biopsy was required. Macrometastasis in a sentinel node required axillary dissection or irradiation.

All the patients in TEXT and the patients in SOFT who did not receive chemotherapy underwent randomization within 12 weeks after definitive surgery; patients in SOFT who received adjuvant or neoadjuvant chemotherapy underwent randomization within 8 months after completing chemotherapy, once a premenopausal level of estradiol was confirmed. Consistent with this design, patients in SOFT, but not those in TEXT, were allowed to receive adjuvant oral endocrine therapy before randomization.

STUDY DESIGNS

TEXT was designed to evaluate 5 years of therapy consisting of exemestane plus the gonadotropin-releasing-hormone (GnRH) agonist triptorelin versus tamoxifen plus triptorelin in women who received ovarian-suppression therapy from the start of adjuvant therapy. Eligible women were randomly assigned in a 1:1 ratio to receive oral exemestane (Aromasin, Pfizer), at a dose of 25 mg daily, plus triptorelin (Decapeptyl Depot [triptorelin acetate], Ipsen; or Trelstar Depot [triptorelin pamoate], Debio), at a dose of 3.75 mg administered by means of intramuscular injection every 28 days, or oral tamoxifen at a dose of 20 mg daily plus triptorelin. Bilateral oophorectomy or ovarian irradiation was allowed after at least 6 months of triptorelin.

Chemotherapy was optional in TEXT, and if administered, was started concomitantly with triptorelin; oral endocrine therapy was started after the completion of chemotherapy. If chemotherapy was not administered, oral endocrine therapy was started 6 to 8 weeks after the initiation of triptorelin, to allow for a decline in ovarian estrogen production. Randomization to open-label treatment was performed by means of the IBCSG Internet-based system, with the use of permuted blocks, and was stratified according to the intended use of adjuvant chemotherapy (yes vs. no) and lymph-node status (negative vs. positive).

SOFT was designed to evaluate 5 years of exemestane plus ovarian suppression versus tamoxifen plus ovarian suppression versus tamoxifen alone in women who remained premenopausal after the completion of adjuvant or neoadjuvant chemotherapy or in women for whom adjuvant tamoxifen alone was suitable treatment. Eligible women were randomly assigned in a 1:1:1 ratio to exemestane plus ovarian suppression (trip-

torelin, bilateral oophorectomy, or ovarian irradiation), tamoxifen plus ovarian suppression, or tamoxifen alone. Randomization was stratified according to prior use of adjuvant or neoadjuvant chemotherapy (yes vs. no), lymph-node status (negative vs. positive), and intended initial method of ovarian suppression, if the woman was assigned to a group that included ovarian-suppression therapy.

In TEXT and SOFT, protocol-assigned endocrine therapy continued for 5 years from the date of randomization, and the protocols (available with the full text of this article at NEJM.org) did not address the issue of extended adjuvant endocrine therapy beyond 5 years, except the requirement to record any therapy. Bisphosphonates were not permitted unless indicated for reduced bone density (T score, -1.5 or lower) or required for participation in a randomized trial of adjuvant bisphosphonate therapy. Adjuvant trastuzumab was allowed. Patient assessments, recording of adverse events, and quality-of-life self-assessments followed a regular schedule (see the Supplementary Appendix, available at NEJM.org).

The primary end point was disease-free survival, defined as the time from randomization to the first appearance of one of the following: invasive recurrence of breast cancer (local, regional, or distant), invasive contralateral breast cancer, second (nonbreast) invasive cancer, or death without breast-cancer recurrence or second invasive cancer. Secondary end points included the following: time interval without breast cancer, defined as the time from randomization to the recurrence of invasive breast cancer (local, regional, or distant) or invasive contralateral breast cancer; time interval before a recurrence of breast cancer at a distant site, defined as the time from randomization to the recurrence of breast cancer at a distant site; and overall survival, defined as the time from randomization to death from any cause. For patients who did not have an end-point event, the times were censored at the date of the last follow-up visit (or for the analysis of overall survival, the date at which the patient was last known to be alive).

STUDY OVERSIGHT

TEXT (IBCSG trial number 25-02) and SOFT (IBCSG trial number 24-02) were coordinated by the IBCSG, which was responsible for the study designs, randomization, collection and manage-

ment of data, medical review, data analysis, and reporting. The ethics committee at each participating center approved the study protocols, and all the patients provided written informed consent. The IBCSG data and safety monitoring committee reviewed safety data semiannually.

Pfizer and Ipsen, the respective manufacturers of exemestane and triptorelin, donated the study drugs; neither manufacturer imposed restrictions with respect to the trial data. The manuscript was written solely by the authors, who vouch for the data and analyses reported and for the fidelity of the study to the protocol. The steering committee (which included employees of Pfizer and Ipsen) reviewed the manuscript and were responsible for the decision to submit it for publication.

STATISTICAL ANALYSIS

The original statistical analysis plans for TEXT and SOFT were to compare disease-free survival between treatment groups within each trial separately, with a planned secondary combined analysis of exemestane plus ovarian suppression versus tamoxifen plus ovarian suppression. However, the patients enrolled in the studies had lower-risk characteristics than had been anticipated in the design assumptions, and the rate of disease-free survival was better than expected. To ensure timely answers to the trial questions, protocol amendments to the analysis plans were adopted in 2011, designating the combined analysis of data from TEXT and SOFT as the primary analysis of exemestane plus ovarian suppression versus tamoxifen plus ovarian suppression. The comparison of tamoxifen plus ovarian suppression versus tamoxifen alone in SOFT, to determine the value of adding ovarian suppression to tamoxifen, has not been analyzed and is not part of the present report.

We calculated that, with an estimated 436 events of disease recurrence, second invasive cancer, or death by the third quarter of 2013, the study would have at least 84% power to detect a hazard ratio of 0.75 with exemestane plus ovarian suppression versus tamoxifen plus ovarian suppression in the primary combined analysis, at a two-sided alpha level of 0.05. The original statistical designs and sample-size assumptions and the amended plans have been described previously.¹⁰ The steering committee proposed, and the data and safety monitoring committee endorsed, the amended analysis plans without

knowledge of the data according to treatment assignment. No interim analyses were performed.

Analyses were performed according to the intention-to-treat principle. Kaplan–Meier estimates of time-to-event end points were calculated. Cox proportional-hazards regression analyses and the log-rank test, stratified according to trial, receipt or no receipt of chemotherapy, and lymph-node status, were used to estimate hazard ratios, 95% confidence intervals, and P values comparing the two groups. The heterogeneity of the treatment effect according to subgroup was investigated by means of tests of treatment-by-covariate interaction. Quality-of-life data over the 5-year treatment period were analyzed as the change from baseline in quality-of-life indicators, with the use of mixed-effects regression modeling. The visit cut-off date was August 31, 2013, and the database-lock date for analysis was February 1, 2014.

RESULTS

STUDY POPULATION

From November 2003 through April 2011, we randomly assigned 2359 premenopausal women to exemestane plus ovarian suppression and 2358 to tamoxifen plus ovarian suppression. Two thirds of the women were enrolled at BIG centers and one third at North American centers. After exclusions, 4690 women were included in the intention-to-treat population (Fig. 1). The median age of the patients at randomization was 43 years (Table 1). A total of 42.6% of the patients did not receive chemotherapy, and 57.4% received chemotherapy either after randomization in TEXT (34.3% of all patients) or before randomization in SOFT (23.2%). Among patients in SOFT who had received chemotherapy previously, 41.7% had received tamoxifen for an average of 4 months before randomization while waiting for premenopausal status to be established or reestablished. Node-positive disease was present in 42.2% of the patients overall, and in 20.7% and 8.3% of the patients in TEXT and SOFT, respectively, who did not receive chemotherapy.

EFFICACY

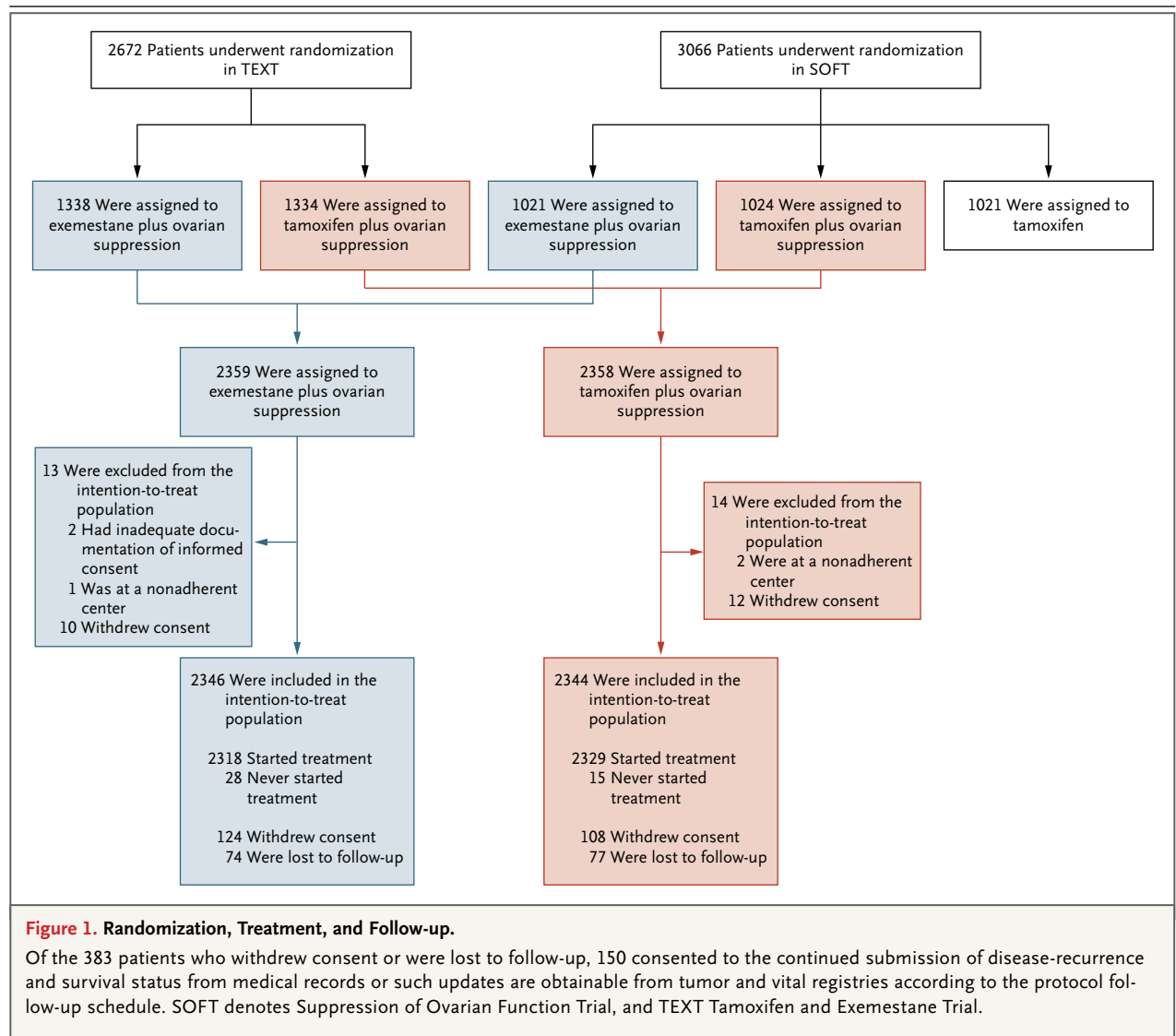
After a median follow-up of 68 months, 514 patients (11.0%) had disease recurrence or second invasive cancer or died. The rate of disease-free survival at 5 years was 91.1% (95% confidence

interval [CI], 89.7 to 92.3) among patients assigned to receive exemestane plus ovarian suppression, as compared with 87.3% (95% CI, 85.7 to 88.7) among those assigned to tamoxifen plus ovarian suppression (hazard ratio for recurrence, second invasive cancer, or death, 0.72; 95% CI, 0.60 to 0.85; $P<0.001$) (Fig. 2A). A total of 60.1% of first events involved distant sites, and 13.6% were second, nonbreast, invasive cancers (Table S3 in the Supplementary Appendix). Prospectively planned subgroup analyses did not reveal any striking heterogeneity of treatment effects (Fig. S1 in the Supplementary Appendix), including in subgroups defined according to trial and status with respect to chemotherapy (Fig. 3).

At 5 years, 92.8% (95% CI, 91.6 to 93.9) of the patients assigned to receive exemestane plus ovarian suppression were free from breast cancer, as compared with 88.8% (95% CI, 87.3 to 90.1) of those assigned to receive tamoxifen plus ovarian suppression (hazard ratio for recurrence, 0.66; 95% CI, 0.55 to 0.80; $P<0.001$) (Fig. 2B). Among patients who did not receive chemotherapy and were assigned to receive exemestane plus ovarian suppression, 97.6% of the patients in TEXT and 97.5% of those in SOFT remained free from breast cancer at 5 years (Fig. S2 in the Supplementary Appendix).

The recurrence of breast cancer at a distant site was reported in 325 patients (6.9%), and at 5 years the rate of freedom from distant recurrence was 93.8% (95% CI, 92.7 to 94.8) among patients assigned to receive exemestane plus ovarian suppression, as compared with 92.0% (95% CI, 90.7 to 93.1) among those assigned to receive tamoxifen plus ovarian suppression (hazard ratio for recurrence, 0.78; 95% CI, 0.62 to 0.97; $P=0.02$) (Fig. 2C). Among patients who received chemotherapy, the rate of freedom from distant recurrence at 5 years was 2.6 percentage points higher among those who were assigned to exemestane plus ovarian suppression than among those who were assigned to tamoxifen plus ovarian suppression in TEXT and 3.4 percentage points higher in SOFT (Fig. S3 in the Supplementary Appendix).

Death was reported in 194 patients (4.1%); 7 patients died without breast-cancer recurrence or second invasive cancer. Overall survival at 5 years was 95.9% (95% CI, 94.9 to 96.7) among patients assigned to exemestane plus ovarian sup-



pression and 96.9% (95% CI, 96.0 to 97.6) among those assigned to tamoxifen plus ovarian suppression; the difference was not significant (Fig. 2D).

ADVERSE EVENTS

At the median follow-up of 68 months, 30.2% of the patients were still receiving some or all protocol-assigned treatments, 56.1% had completed treatment, and 13.7% had stopped all protocol-assigned treatments early (16.1% of the patients in the exemestane-ovarian suppression group and 11.2% of those in the tamoxifen-ovarian suppression group) (Table S4 in the Supplementary Appendix). Targeted adverse events of grade 3 or

4 were reported in 30.6% of the patients assigned to receive exemestane plus ovarian suppression and in 29.4% of those assigned to receive tamoxifen plus ovarian suppression. The events of grade 3 or 4 that were reported most frequently were hot flushes, musculoskeletal symptoms, and hypertension (Table 2). Depression was reported in 50.2% of patients, with grade 3 or 4 depression in 4.1% of the patients.

Osteoporosis (T score, less than -2.5) was reported in 13.2% of the patients assigned to exemestane plus ovarian suppression and in 6.4% of those assigned to tamoxifen plus ovarian suppression. Fractures, musculoskeletal symptoms,

Table 1. Characteristics of Patients in TEXT and SOFT, Overall and According to Trial and Chemotherapy Stratum.*

Characteristic	No-Chemotherapy Cohorts		Chemotherapy Cohorts†		Overall (N=4690)
	TEXT (N=1053)	SOFT (N=943)	TEXT (N=1607)	SOFT (N=1087)	
Age at randomization — no. (%)					
<35 yr	41 (3.9)	14 (1.5)	191 (11.9)	224 (20.6)	470 (10.0)
35–39 yr	123 (11.7)	68 (7.2)	289 (18.0)	312 (28.7)	792 (16.9)
40–49 yr	768 (72.9)	690 (73.2)	1048 (65.2)	515 (47.4)	3021 (64.4)
≥50 yr	121 (11.5)	171 (18.1)	79 (4.9)	36 (3.3)	407 (8.7)
Lymph-node status — no. (%)					
Negative	835 (79.3)	865 (91.7)	542 (33.7)	470 (43.2)	2712 (57.8)
Positive	218 (20.7)	78 (8.3)	1065 (66.3)	617 (56.8)	1978 (42.2)
Tumor size — no. (%)‡					
≤2 cm	847 (80.4)	800 (84.8)	738 (45.9)	537 (49.4)	2922 (62.3)
>2 cm	203 (19.3)	139 (14.7)	844 (52.5)	508 (46.7)	1694 (36.1)
HER2 positive — no. (%)	54 (5.1)	30 (3.2)	272 (16.9)	211 (19.4)	567 (12.1)
Interval from surgery to randomization — mo					
Median	1.5	1.8	1.2	8.0	1.6
Interquartile range	1.1–1.9	1.3–2.4	0.9–1.6	5.7–10.1	1.1–2.7
Endocrine therapy before randomization — no. (%)§	—	44 (4.7)	—	453 (41.7)	—

* A more complete summary of characteristics is provided in Table S1 in the Supplementary Appendix. Characteristics were well balanced according to treatment assignment (Table S2 in the Supplementary Appendix). The statistical analysis plan did not specify hypothesis testing regarding comparisons between these groups. HER2 denotes human epidermal growth factor receptor 2, SOFT Suppression of Ovarian Function Trial, and TEXT Tamoxifen and Exemestane Trial.

† Among patients who received chemotherapy, patients in TEXT received chemotherapy during the trial, and those in SOFT had received chemotherapy before enrollment.

‡ Data were missing for 3 patients in TEXT who did not receive chemotherapy, for 4 in SOFT who did not receive chemotherapy, for 25 in TEXT who received chemotherapy, and for 42 in SOFT who had received chemotherapy previously.

§ Oral endocrine therapy before randomization was allowed in SOFT while premenopausal status was established or re-established; it was not allowed in TEXT.

vaginal dryness, decreased libido, and dyspareunia were reported more frequently in patients assigned to exemestane plus ovarian suppression, whereas thromboembolic events, hot flushes, sweating, and urinary incontinence were reported more frequently in patients assigned to tamoxifen plus ovarian suppression. Gynecologic cancer occurred in seven patients assigned to exemestane plus ovarian suppression and in nine assigned to tamoxifen plus ovarian suppression, including endometrial cancers in two and five patients, respectively.

QUALITY OF LIFE

Changes from baseline in global indicators of mood, physical well-being, and coping effort

were similar in the two treatment groups during the treatment period. Patients assigned to exemestane plus ovarian suppression reported significantly more detrimental effects of bone or joint pain and vaginal dryness and a greater loss of sexual interest, whereas patients assigned to tamoxifen plus ovarian suppression were significantly more affected by hot flushes and vaginal discharge.¹²

DISCUSSION

The combined analysis of data from TEXT and SOFT shows that among premenopausal women with hormone-receptor-positive breast cancer, adjuvant endocrine therapy with exemestane plus

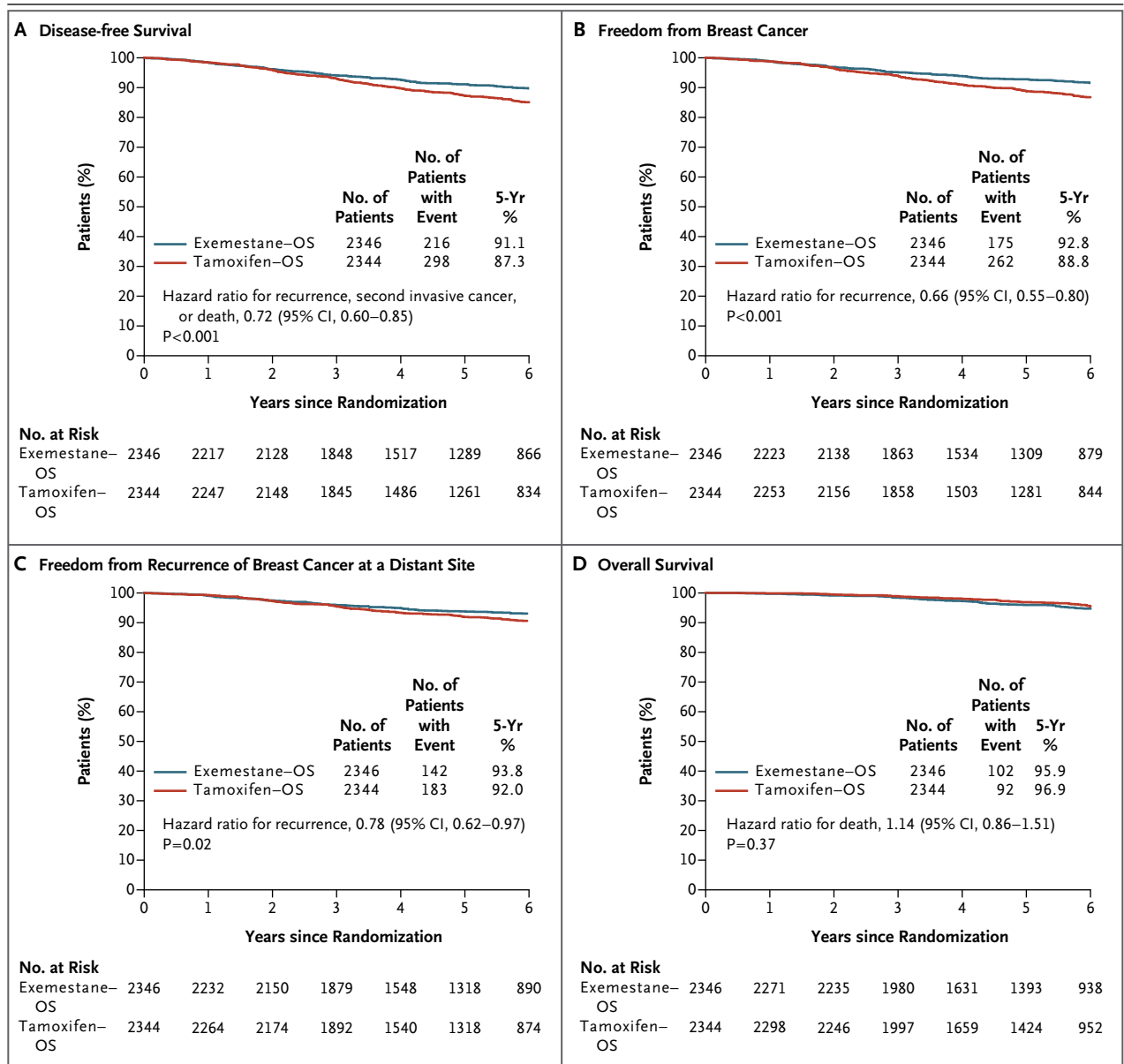


Figure 2. Kaplan–Meier Estimates of Disease-free Survival, Freedom from Recurrence of Breast Cancer, Freedom from Recurrence of Breast Cancer at a Distant Site, and Overall Survival after a Median Follow-up of 68 Months, According to Treatment Assignment.

The hazard ratio in Panel A is for disease recurrence, second invasive cancer, or death without breast-cancer recurrence or second invasive cancer. The 5-year values are based on Kaplan–Meier estimates of the time to an event. OS denotes ovarian suppression.

ovarian suppression, as compared with tamoxifen plus ovarian suppression, significantly improved disease-free survival and lengthened the time without breast cancer, and the time without distant recurrence. The observed relative reduction of 28% in the risk of disease recurrence, second invasive cancer, or death and the relative reduction of 34% in the risk of breast-cancer re-

currence among premenopausal women compare favorably with the results of randomized trials of adjuvant aromatase inhibitors versus tamoxifen in postmenopausal women. With a similar median follow-up period, the BIG 1-98 and Arimidex, Tamoxifen, Alone or in Combination (ATAC) trials showed 19% and 26% reductions, respectively, in the risk of breast-cancer recurrence^{5,7,13}

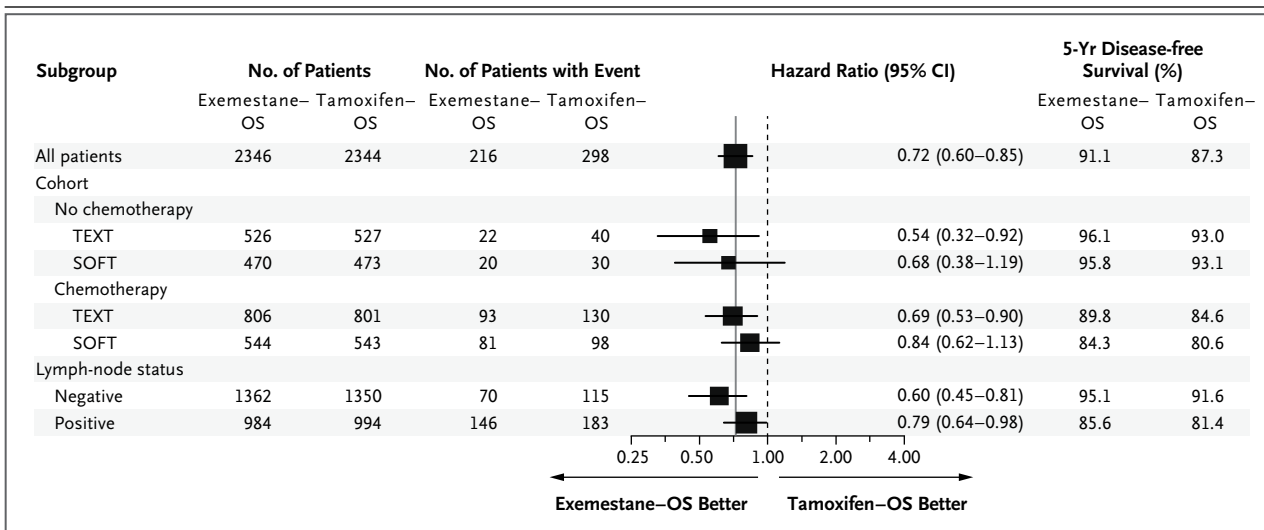


Figure 3. Results of the Cox Proportional-Hazards Model for the Comparison of Disease-free Survival, According to Treatment Group, among All Patients and According to Patient Cohort.

The solid vertical line at 0.72 indicates the overall hazard-ratio estimate. The x axis is scaled according to the natural logarithm of the hazard ratio. The size of the squares is inversely proportional to the standard error of the hazard ratio. Among patients who received chemotherapy, the patients in TEXT began receiving chemotherapy concurrently with adjuvant ovarian suppression with triptorelin, whereas those in SOFT had completed all chemotherapy before enrollment.

with aromatase inhibitors, as compared with tamoxifen.

In the current analysis, the absolute improvement of 4.0 percentage points in the proportion of patients without breast cancer at 5 years with exemestane plus ovarian suppression, as compared with tamoxifen plus ovarian suppression, reflects reductions in local, regional, and contralateral events and in distant events. Although local, regional, and contralateral breast events are potentially curable, they require treatment and affect patient well-being. The majority (60%) of the first events of disease recurrence, second invasive cancer, or death involved the recurrence of breast cancer at a distant site. Patients selected to receive chemotherapy had, on average, higher-risk clinicopathologic features (associated with a greater risk of recurrence) than did those who did not receive chemotherapy. Among patients who received chemotherapy, exemestane plus ovarian suppression, as compared with tamoxifen plus ovarian suppression, increased the proportion of patients without breast cancer at 5 years by 5.5 percentage points in TEXT and by 3.9 percentage points in SOFT and the proportion of patients without distant recurrence at 5 years by 2.6 percentage points in TEXT and by 3.4 per-

centage points in SOFT (Fig. S3 in the Supplementary Appendix).

Although there was no significant difference in overall survival according to randomized treatment, conclusions are premature at 68 months of follow-up in this patient population. Trials evaluating 5 years of therapy with an adjuvant aromatase inhibitor versus tamoxifen therapy in postmenopausal women have shown no significant survival advantage after a median follow-up of 5 years, with absolute improvements in the proportion of patients without breast cancer of 3.4 percentage points and 2.8 percentage points in BIG 1-98 and ATAC, respectively, with the adjuvant aromatase inhibitor, as compared with tamoxifen.^{5,7,13}

In the Austrian Breast and Colorectal Cancer Study Group-12 (ABCSG-12) trial,¹⁴ a total of 1803 premenopausal women with hormone-receptor-positive breast cancer (5.8% of whom had received neoadjuvant chemotherapy) were randomly assigned to receive 3 years of adjuvant therapy with anastrozole plus ovarian suppression (goserelin) or tamoxifen plus ovarian suppression, with or without the bisphosphonate zoledronic acid administered every 6 months. After a median follow-up of 62 months, 186 patients had local

Table 2. Targeted Adverse Events Reported during Follow-up, According to Treatment Assignment.*

Adverse Event	Exemestane plus Ovarian Suppression (N = 2318)				Tamoxifen plus Ovarian Suppression (N = 2325)			
	Any Event	Grade 3 or 4 Event	no. of patients with event	% (95% CI)	Any Event	Grade 3 or 4 Event	no. of patients with event	% (95% CI)
Allergic reaction or hypersensitivity	115	5.0 (4.1–5.9)	11	0.5 (0.2–0.8)	107	4.6 (3.8–5.5)	9	0.4 (0.2–0.7)
Injection-site reaction	168	7.2 (6.2–8.4)	1	<0.1 (0.0–0.2)	187	8.0 (7.0–9.2)	1	<0.1 (0.0–0.2)
Hot flushes	2125	91.7 (90.5–92.8)	232	10.0 (8.8–11.3)	2169	93.3 (92.2–94.3)	279	12.0 (10.7–13.4)
Depression	1165	50.3 (48.2–52.3)	87	3.8 (3.0–4.6)	1164	50.1 (48.0–52.1)	102	4.4 (3.6–5.3)
Sweating	1264	54.5 (52.5–56.6)	—	—	1371	59.0 (56.9–61.0)	—	—
Insomnia	1348	58.2 (56.1–60.2)	89	3.8 (3.1–4.7)	1361	58.5 (56.5–60.5)	100	4.3 (3.5–5.2)
Fatigue	1420	61.3 (59.2–63.2)	73	3.1 (2.5–3.9)	1463	62.9 (60.9–64.9)	67	2.9 (2.2–3.6)
Hypertension	527	22.7 (21.0–24.5)	151	6.5 (5.5–7.6)	509	21.9 (20.2–23.6)	169	7.3 (6.2–8.4)
Cardiac ischemia or infarction	16	0.7 (0.4–1.1)	7	0.3 (0.1–0.6)	7	0.3 (0.1–0.6)	3	0.1 (0.0–0.4)
Thrombosis or embolism	24	1.0 (0.7–1.5)	19	0.8 (0.5–1.3)	50	2.2 (1.6–2.8)	45	1.9 (1.4–2.6)
Nausea	721	31.1 (29.2–33.0)	17	0.7 (0.4–1.2)	671	28.9 (27.0–30.7)	13	0.6 (0.3–1.0)
Musculoskeletal symptoms	2057	88.7 (87.4–90.0)	254	11.0 (9.7–12.3)	1766	76.0 (74.2–77.7)	122	5.2 (4.4–6.2)
Osteoporosis	894	38.6 (36.6–40.6)	10	0.4 (0.2–0.8)	586	25.2 (23.5–27.0)	6	0.3 (0.1–0.6)
Fractures	158	6.8 (5.8–7.9)	29	1.3 (0.8–1.8)	120	5.2 (4.3–6.1)	18	0.8 (0.5–1.2)
Vaginal dryness	1214	52.4 (50.3–54.4)	—	—	1101	47.4 (45.3–49.4)	—	—
Decreased libido	1042	45.0 (42.9–47.0)	—	—	950	40.9 (38.9–42.9)	—	—
Dyspareunia	707	30.5 (28.6–32.4)	53	2.3 (1.7–3.0)	601	25.8 (24.1–27.7)	32	1.4 (0.9–1.9)
Urinary incontinence	304	13.1 (11.8–14.6)	6	0.3 (0.1–0.6)	414	17.8 (16.3–19.4)	7	0.3 (0.1–0.6)
CNS cerebrovascular ischemia	5	0.2 (0.1–0.5)	4	0.2 (0.0–0.4)	11	0.5 (0.2–0.8)	8	0.3 (0.1–0.7)
CNS hemorrhage	15	0.6 (0.4–1.1)	1	<0.1 (0.0–0.2)	21	0.9 (0.6–1.4)	2	0.1 (0.0–0.3)
Glucose intolerance†	54	2.3 (1.8–3.0)	11	0.5 (0.2–0.8)	54	2.3 (1.7–3.0)	15	0.6 (0.4–1.1)
Hyperglycemia†	61	2.6 (2.0–3.4)	13	0.6 (0.3–1.0)	80	3.4 (2.7–4.3)	15	0.6 (0.4–1.1)
Any targeted adverse event	2279	98.3 (97.7–98.8)	710	30.6 (28.8–32.6)	2285	98.3 (97.7–98.8)	683	29.4 (27.5–31.3)

* The information here includes data from the 4643 patients in the safety population who received a protocol-assigned treatment. Targeted adverse events and other adverse events of grade 3 or higher were categorized according to the *Common Terminology Criteria for Adverse Events*, version 3.0.¹¹ Dashes indicate that grade 3 or 4 was not a possible grading for that adverse event. No patient had a targeted adverse event of grade 5. CNS denotes central nervous system.

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

or regional recurrence, cancer in the contralateral breast, distant metastasis, or second primary carcinoma or died from any cause, with no significant difference in the rate of disease-free survival between patients who received anastrozole plus ovarian suppression and those who received tamoxifen plus ovarian suppression (hazard ratio for disease progression or death, 1.08; 95% CI, 0.81 to 1.44).

The difference between the results of the ABCSG-12 trial and the results of the TEXT and SOFT trials may relate to greater statistical power in the combined analysis of TEXT and SOFT (with three times the number of events of disease recurrence, second invasive cancer, or death in TEXT and SOFT as in the ABCSG-12 trial), to different treatment durations, or to both. The 3-year duration of aromatase inhibitor therapy in the ABCSG-12 trial may have been insufficient, as compared with 3 years of tamoxifen, which is known to exert a carryover effect after the cessation of treatment.¹⁵ A difference in the efficacy of the aromatase inhibitors is unlikely, given the absence of a difference observed in postmenopausal women in the MA.27 trial.¹⁶ The ABCSG-12 trial showed a lower rate of overall survival with anastrozole plus ovarian suppression than with tamoxifen plus ovarian suppression (hazard ratio for death, 1.75; 95% CI, 1.08 to 2.83), with a total of 73 deaths, whereas no significant difference was detected with 194 deaths in the TEXT–SOFT analysis. The ABCSG-12 trial showed a significant improvement in disease-free survival among women randomly assigned to receive the bisphosphonate zoledronic acid, as compared with those who did not receive zoledronic acid. TEXT and SOFT did not permit the routine use of bisphosphonates, and only a minority of women reported bisphosphonate use during adjuvant therapy.

In TEXT and SOFT, women had the option of receiving adjuvant chemotherapy after discussion with their physician. Chemotherapy was not administered to 1996 women (43%), and 21% of the patients in TEXT who did not receive chemotherapy had node-positive disease. Nevertheless, the rate of freedom from breast cancer at 5 years was more than 97% among women who did not receive chemotherapy and were assigned to exemestane plus ovarian suppression (Fig. S2 in the Supplementary Appendix). The majority of patients were enrolled at BIG centers, where multigene

assays to assess risk of recurrence were not standard during the enrollment years. Predominantly on the basis of conventional clinicopathologic features, physicians identified a group of premenopausal women with truly endocrine-responsive breast cancer who had very good outcomes without adjuvant chemotherapy. These results indicate that at least a proportion of premenopausal women who receive a diagnosis of hormone-receptor-positive breast cancer may have an excellent prognosis with highly effective adjuvant endocrine therapy alone.

For women who receive chemotherapy, the timing of the initiation of ovarian suppression is worthy of consideration. TEXT and SOFT differed with respect to the approach to the initiation of ovarian suppression in women who received chemotherapy. Patients in TEXT began receiving adjuvant ovarian suppression with triptorelin concurrently with chemotherapy, an average of 1.2 months after surgery; patients assigned to exemestane plus ovarian suppression had a rate of freedom from breast-cancer recurrence at 5 years of 91.5% (Fig. S3 in the Supplementary Appendix), despite the fact that 66% of the women in TEXT who received chemotherapy had node-positive disease. The early initiation of ovarian suppression to target the estrogen-receptor pathway concurrently with chemotherapy deserves further investigation.

The SOFT cohort of patients who received chemotherapy completed all chemotherapy before enrollment and initiated protocol-assigned ovarian suppression and oral endocrine therapy an average of 8 months after surgery, with 4 months of adjuvant tamoxifen therapy during the intervening period. This cohort included younger patients on average — owing to the requirement to retain premenopausal status — than did the TEXT cohort that received chemotherapy. The cohort also had a greater proportion of patients with lymph-node-negative disease; this could be related in part to physicians' reluctance, at least in some countries, to include high-risk patients in a trial considering tamoxifen alone after chemotherapy. The longer time from diagnosis to study entry may account for the higher proportion of breast-cancer recurrences in this cohort, as compared with the TEXT cohort that received chemotherapy (Fig. S3 in the Supplementary Appendix).

The adverse-event profiles of exemestane plus

ovarian suppression and tamoxifen plus ovarian suppression were similar to those seen in postmenopausal women, and the percentages of adverse events of grade 3 or 4 were similar in the two treatment groups. Between-group differences were observed with respect to specific symptoms, but the overall quality-of-life assessment did not favor either treatment. The early cessation of all protocol-assigned treatment was more frequent among patients who received exemestane plus ovarian suppression than among those who received tamoxifen plus ovarian suppression (16% vs. 11%).

In premenopausal women, an additional benefit of ovarian suppression in women who receive 5 years of adjuvant tamoxifen, with or without chemotherapy, is uncertain. A meta-analysis of trials that included patients randomly assigned to receive 2 years of a GnRH agonist plus tamoxifen versus 2 years of tamoxifen alone showed that adding ovarian suppression was associated with an estimated 14.5% reduction in recurrence (95% CI, -32.7 to 8.6) without chemotherapy and an estimated 15.9%

reduction in recurrence (95% CI, -42.4 to 22.6) after chemotherapy.¹⁷

We conclude that for premenopausal women with hormone-receptor-positive breast cancer, adjuvant treatment with ovarian suppression plus the aromatase inhibitor exemestane, as compared with ovarian suppression plus tamoxifen, provides a new treatment option that reduces the risk of recurrence. Premenopausal women who receive ovarian suppression may now benefit from an aromatase inhibitor, a class of drugs that until now has been recommended only for postmenopausal women.

Supported by Pfizer, Ipsen, the International Breast Cancer Study Group, and the National Cancer Institute.

Dr. Fleming reports receiving a study drug for investigation in a clinical trial from Corcept Therapeutics; Dr. Colleoni, receiving fees for serving on advisory boards from Boehringer Ingelheim, Taiho Pharmaceutical, AbbVie, and AstraZeneca and consulting and lecture fees from Novartis; Dr. Stearns, receiving grant support from Pfizer and Novartis; Dr. Ruhstaller, receiving travel support and fees for serving on an advisory board from Novartis; and Dr. Viale, receiving fees for serving on advisory boards from Novartis, Roche, and Eli Lilly. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

The authors' affiliations are as follows: the Institute of Oncology of Southern Switzerland, Lugano Viganello (O.P.), Breast Center, Kantonsspital St. Gallen, St. Gallen (T.R.), University Hospital Inselspital, Bern (M.R.-P., J.B.), and International Breast Cancer Study Group (IBCSG) Coordinating Center, Bern (M.R.-P., R.M., B.R., J.B., K.R.) — all in Switzerland; IBCSG Statistical Center, Dana-Farber Cancer Institute, Harvard Medical School (M.M.R.), Susan F. Smith Center for Women's Cancers, Dana-Farber Cancer Institute, Harvard Medical School (H.J.B., E.P.W.), IBCSG Statistical Center, Dana-Farber Cancer Institute (A.G.-H., W.L.), IBCSG Statistical Center, Frontier Science and Technology Research Foundation (K.N.P.), and IBCSG Statistical Center, Dana-Farber Cancer Institute, Harvard Medical School, Harvard School of Public Health, Frontier Science and Technology Research Foundation (R.D.G.) — all in Boston; Tom Baker Cancer Centre, Calgary, AB, Canada (B.A.W.); the University of Chicago Medical Center, Chicago (G.F.F.); the Division of Medical Senology, European Institute of Oncology (M.C.), IBCSG Central Pathology Center, European Institute of Oncology, University of Milan (G.V.), and European Institute of Oncology (A.G.), Milan, Medical Oncology, Ospedale Papa Giovanni XXIII, Bergamo (C.T.), Medical Oncology, Ospedale di Circolo and Fondazione Macchi, Varese (G.P.), the Department of Oncology, University Hospital of Udine, University of Udine, Udine (F.P.), and Medical Oncology, Centro di Riferimento Oncologico, Aviano (D.C.) — all in Italy; National Institute of Oncology, Budapest, Hungary (I.L.); Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru (H.L.G.); Mayo Clinic, Jacksonville, FL (E.A.P.); Hospital Universitario 12 de Octubre, Madrid (E.C.); Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore (V.S.); Institut Bergonié Comprehensive Cancer Center, Université de Bordeaux, INSERM Unité 916, Bordeaux, France (H.R.B.); the Angeles Clinic and Research Institute, Santa Monica, CA (S.M.); Massey Cancer Center, Virginia Commonwealth University School of Medicine, Richmond (C.E.G.); and the University of Sydney, Sydney (A.S.C.), and Peter MacCallum Cancer Center, St. Vincent's Hospital, University of Melbourne, Melbourne, VIC (P.A.F.) — all in Australia.

REFERENCES

1. Carlson RW, Allred DC, Anderson BO, et al. Breast cancer: clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2009;7:122-92.
2. Burstein HJ, Prestrud AA, Seidenfeld J, et al. American Society of Clinical Oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. *J Clin Oncol* 2010;28:3784-96.
3. Goldhirsch A, Winer EP, Coates AS, et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. *Ann Oncol* 2013;24:2206-23.
4. Winer EP, Hudis C, Burstein HJ, et al. American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: status report 2004. *J Clin Oncol* 2005;23:619-29.
5. Colleoni M, Giobbie-Hurder A, Regan MM, et al. Analyses adjusting for selective crossover show improved overall survival with adjuvant letrozole compared with tamoxifen in the BIG 1-98 study. *J Clin Oncol* 2011;29:1117-24.
6. The BIG 1-98 Collaborative Group. Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer. *N Engl J Med* 2009;361:766-76.
7. Howell A, Crusick J, Baum M, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 2005;365:60-2.

8. Coombes RC, Kilburn LS, Snowdon CF, et al. Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. *Lancet* 2007;369:559-70.
9. van de Velde CJ, Rea D, Seynaeve C, et al. Adjuvant tamoxifen and exemestane in early breast cancer (TEAM): a randomised phase 3 trial. *Lancet* 2011;377:321-31.
10. Regan MM, Pagan O, Fleming GF, et al. Adjuvant treatment of premenopausal women with endocrine-responsive early breast cancer: design of the TEXT and SOFT trials. *Breast* 2013;22:1094-100.
11. Common Terminology Criteria for Adverse Events Version 3.0. (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae_v3.pdf).
12. Bernhard J, Luo W, Ribi K, et al. Patient-reported endocrine symptoms, sexual functioning, and quality of life (QoL) in the IBCSG TEXT and SOFT trials: adjuvant treatment with exemestane (E) plus ovarian function suppression (OFS) versus tamoxifen (T) plus OFS in premenopausal women with hormone receptor-positive (HR+) early breast cancer (BC). *J Clin Oncol* 2014;32:557. abstract.
13. Regan MM, Neven P, Giobbie-Hurder A, et al. Assessment of letrozole and tamoxifen alone and in sequence for postmenopausal women with steroid hormone receptor-positive breast cancer: the BIG 1-98 randomised clinical trial at 8.1 years median follow-up. *Lancet Oncol* 2011;12:1101-8.
14. Gnant M, Mlineritsch B, Stoeger H, et al. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial. *Lancet Oncol* 2011;12:631-41.
15. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet* 2011;378:771-84.
16. Goss PE, Ingle JN, Pritchard KI, et al. Exemestane versus anastrozole in postmenopausal women with early breast cancer: NCIC CTG MA.27—a randomized controlled phase III trial. *J Clin Oncol* 2013;31:1398-404.
17. LHRH-agonists in Early Breast Cancer Overview Group. Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. *Lancet* 2007;369:1711-23.

Copyright © 2014 Massachusetts Medical Society.