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 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.\textsuperscript{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.\textsuperscript{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 planned\textsuperscript{10} 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 irra-
diation), 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 meth-
oid of ovarian suppression, if the woman was
assigned to a group that included ovarian-sup-
pression therapy.

In TEXT and SOFT, protocol-assigned endo-
crine 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 endo-
crine therapy beyond 5 years, except the require-
ment 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 Supplemen-
tary Appendix, available at NEJM.org).

The primary end point was disease-free sur-
vival, defined as the time from randomization to
the first appearance of one of the following: inva-
sive recurrence of breast cancer (local, regional,
or distant), invasive contralateral breast cancer,
second (nonbreast) invasive cancer, or death with-
out breast-cancer recurrence or second invasive
cancer. Secondary end points included the follow-
ing: interval of time without breast cancer, de-
fined as the time from randomization to the
recurrence of invasive breast cancer (local, re-
gional, or distant) or invasive contralateral breast
cancer; interval of time 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 sur-
vival, 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 partici-
pating center approved the study protocols, and
all the patients provided written informed con-
sent. The IBCSG data and safety monitoring com-
mittee 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 com-
mittee (which included employees of Pfizer and
Ipsen) reviewed the manuscript and were respon-
sible 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 sepa-
ately, with a planned secondary combined analy-
sis 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 analy-
sis of exemestane plus ovarian suppression ver-
sus tamoxifen plus ovarian suppression. The
comparison of tamoxifen plus ovarian suppress-
sion versus tamoxifen alone in SOFT, to deter-
mine 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 ovar-
ian 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 (23.2%). Among patients in TEXT 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, 0.78; 95% CI, 0.62 to 0.97; P = 0.02) (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 the recurrence of breast cancer at a distant site 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 the recurrence of breast cancer at a distant site 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 suppression 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. 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.

Figure 1. Randomization, Treatment, and Follow-up.
Of the 383 patients who withdrew consent or were lost to follow-up, 150 consented to the continued submission of disease-recurrence and survival status from medical records or such updates are obtainable from tumor and vital registries according to the protocol follow-up schedule. SOFT denotes Suppression of Ovarian Function Trial, and TEXT Tamoxifen and Exemestane Trial.
as 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 ovarian suppression, as compared with tamoxifen plus ovarian suppression, significantly improved disease-free survival and lengthened the

<table>
<thead>
<tr>
<th>Table 1. Characteristics of Patients in TEXT and SOFT, Overall and According to Trial and Chemotherapy Stratum.*</th>
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<tbody>
<tr>
<td><strong>Characteristic</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Age at randomization — no. (%)</td>
</tr>
<tr>
<td>&lt;35 yr</td>
</tr>
<tr>
<td>35–39 yr</td>
</tr>
<tr>
<td>40–49 yr</td>
</tr>
<tr>
<td>≥50 yr</td>
</tr>
<tr>
<td>Lymph-node status — no. (%)</td>
</tr>
<tr>
<td>Negative</td>
</tr>
<tr>
<td>Positive</td>
</tr>
<tr>
<td>Tumor size — no. (%)‡</td>
</tr>
<tr>
<td>≤2 cm</td>
</tr>
<tr>
<td>&gt;2 cm</td>
</tr>
<tr>
<td>HER2 positive — no. (%)</td>
</tr>
<tr>
<td>Interval from surgery to randomization — mo</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Interquartile range</td>
</tr>
<tr>
<td>Endocrine therapy before randomization — no. (%)§</td>
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<td>—</td>
</tr>
</tbody>
</table>
interval of time without breast cancer, and the interval of time without recurrence of breast cancer at a distant site. 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 recurrence 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 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 the recurrence of breast cancer at a distant site at 5 years by 2.6 percentage points in TEXT and by 3.4 percentage 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.\textsuperscript{5,7,13}

In the Austrian Breast and Colorectal Cancer Study Group–12 (ABCSG-12) trial,\textsuperscript{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 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 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.\textsuperscript{5,7,13}

\begin{table}[!h]
\centering
\begin{tabular}{|l|c|c|c|c|c|}
\hline
\textbf{Subgroup} & \textbf{No. of Patients} & \textbf{No. of Patients with Event} & \textbf{Hazard Ratio (95\% CI)} & \textbf{5-Yr Disease-free Survival (\%)} \\
\hline
\textbf{All patients} & 2346 & 2344 & 216 & 298 & 0.72 (0.60–0.85) & 91.1 & 87.3 \\
\hline
\textbf{No chemotherapy} & & & & & \\
\textbf{TEXT} & 526 & 527 & 22 & 40 & 0.54 (0.32–0.92) & 96.1 & 93.0 \\
\textbf{SOFT} & 470 & 473 & 20 & 30 & 0.68 (0.38–1.19) & 95.8 & 93.1 \\
\hline
\textbf{Chemotherapy} & & & & & \\
\textbf{TEXT} & 806 & 801 & 93 & 130 & 0.69 (0.53–0.90) & 89.8 & 84.6 \\
\textbf{SOFT} & 544 & 543 & 81 & 98 & 0.84 (0.62–1.13) & 84.3 & 80.6 \\
\hline
\textbf{Lymph-node status} & & & & & \\
\textbf{Negative} & 1362 & 1350 & 70 & 115 & 0.60 (0.45–0.81) & 95.1 & 91.6 \\
\textbf{Positive} & 984 & 994 & 146 & 183 & 0.79 (0.64–0.98) & 85.6 & 81.4 \\
\hline
\end{tabular}
\caption{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.}
\end{table}

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 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.

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 the recurrence of breast cancer at a distant site at 5 years by 2.6 percentage points in TEXT and by 3.4 percentage 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.\textsuperscript{5,7,13}
Adjuvant Exemestane in Premenopausal Breast Cancer

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

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Exemestane plus Ovarian Suppression (N = 2318)</th>
<th>Tamoxifen plus Ovarian Suppression (N = 2325)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Event</td>
<td>Grade 3 or 4 Event</td>
</tr>
<tr>
<td></td>
<td>no. of patients with event</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td></td>
<td>no. of patients with event</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td></td>
<td>no. of patients with event</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>Allergic reaction or hypersensitivity</td>
<td>115</td>
<td>5.0 (4.1–5.9)</td>
</tr>
<tr>
<td>Injection-site reaction</td>
<td>168</td>
<td>7.2 (6.2–8.4)</td>
</tr>
<tr>
<td>Hot flushes</td>
<td>2125</td>
<td>91.7 (90.5–92.8)</td>
</tr>
<tr>
<td>Depression</td>
<td>1165</td>
<td>50.3 (48.2–52.3)</td>
</tr>
<tr>
<td>Sweating</td>
<td>1264</td>
<td>54.5 (52.5–56.6)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1348</td>
<td>58.2 (56.1–60.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1420</td>
<td>61.3 (59.2–63.2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>527</td>
<td>22.7 (21.0–24.5)</td>
</tr>
<tr>
<td>Cardiac ischemia or infarction</td>
<td>16</td>
<td>0.7 (0.4–1.1)</td>
</tr>
<tr>
<td>Thrombosis or embolism</td>
<td>24</td>
<td>1.0 (0.7–1.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>721</td>
<td>31.1 (29.2–33.0)</td>
</tr>
<tr>
<td>Musculoskeletal symptoms</td>
<td>2057</td>
<td>88.7 (87.4–90.0)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>894</td>
<td>38.6 (36.6–40.6)</td>
</tr>
<tr>
<td>Fractures</td>
<td>158</td>
<td>6.8 (5.8–7.9)</td>
</tr>
<tr>
<td>Vaginal dryness</td>
<td>1214</td>
<td>52.4 (50.3–54.4)</td>
</tr>
<tr>
<td>Decreased libido</td>
<td>1042</td>
<td>45.0 (42.9–47.0)</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>707</td>
<td>30.5 (28.6–32.4)</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>304</td>
<td>13.1 (11.8–14.6)</td>
</tr>
<tr>
<td>CNS cerebrovascular ischemia</td>
<td>5</td>
<td>0.2 (0.1–0.5)</td>
</tr>
<tr>
<td>CNS hemorrhage</td>
<td>15</td>
<td>0.6 (0.4–1.1)</td>
</tr>
<tr>
<td>Glucose intolerance†</td>
<td>54</td>
<td>2.3 (1.8–3.0)</td>
</tr>
<tr>
<td>Hyperglycemia†</td>
<td>61</td>
<td>2.6 (2.0–3.4)</td>
</tr>
<tr>
<td>Any targeted adverse event</td>
<td>2279</td>
<td>98.3 (97.7–98.8)</td>
</tr>
</tbody>
</table>

* 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. 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.
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.¹⁰ 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 therapy targeting the estrogen-receptor pathway by means of ovarian suppression given 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.

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APPENDIX

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