ORIGINAL ARTICLE

# Endocrine Therapy plus Zoledronic Acid in Premenopausal Breast Cancer

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## ABSTRACT

### BACKGROUND

Ovarian suppression plus tamoxifen is a standard adjuvant treatment in premenopausal women with endocrine-responsive breast cancer. Aromatase inhibitors are superior to tamoxifen in postmenopausal patients, and preclinical data suggest that zoledronic acid has antitumor properties.

### METHODS

We examined the effect of adding zoledronic acid to a combination of either goserelin and tamoxifen or goserelin and anastrozole in premenopausal women with endocrine-responsive early breast cancer. We randomly assigned 1803 patients to receive goserelin (3.6 mg given subcutaneously every 28 days) plus tamoxifen (20 mg per day given orally) or anastrozole (1 mg per day given orally) with or without zoledronic acid (4 mg given intravenously every 6 months) for 3 years. The primary end point was disease-free survival; recurrence-free survival and overall survival were secondary end points.

### RESULTS

After a median follow-up of 47.8 months, 137 events had occurred, with disease-free survival rates of 92.8% in the tamoxifen group, 92.0% in the anastrozole group, 90.8% in the group that received endocrine therapy alone, and 94.0% in the group that received endocrine therapy with zoledronic acid. There was no significant difference in disease-free survival between the anastrozole and tamoxifen groups (hazard ratio for disease progression in the anastrozole group, 1.10; 95% confidence interval [CI], 0.78 to 1.53; P=0.59). The addition of zoledronic acid to endocrine therapy, as compared with endocrine therapy without zoledronic acid, resulted in an absolute reduction of 3.2 percentage points and a relative reduction of 36% in the risk of disease progression (hazard ratio, 0.64; 95% CI, 0.46 to 0.91; P=0.01); the addition of zoledronic acid did not significantly reduce the risk of death (hazard ratio, 0.60; 95% CI, 0.32 to 1.11; P=0.11). Adverse events were consistent with known drug-safety profiles.

### CONCLUSIONS

The addition of zoledronic acid to adjuvant endocrine therapy improves disease-free survival in premenopausal patients with estrogen-responsive early breast cancer. (ClinicalTrials.gov number, NCT00295646.)

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The optimal management of endocrine-responsive early breast cancer in premenopausal women remains controversial. Although aromatase inhibitors have shown benefits beyond those of tamoxifen in postmenopausal women,[1-6] their benefits in premenopausal women, among whom endocrine-responsive disease accounts for 62% of early breast cancers, are unknown.[7] The combination of ovarian suppression with the use of gonadotropin-releasing hormone analogues and tamoxifen is a standard of care for premenopausal women because it is at least as effective as established cytotoxic chemotherapy regimens and is better tolerated than chemotherapy.[8-12]

In a study involving premenopausal women with advanced breast cancer, ovarian suppression combined with an aromatase inhibitor reduced circulating estrogen levels by an additional 76% as compared with ovarian suppression plus tamoxifen.[13] This reduction could increase the efficacy of treatment, and for this reason, aromatase inhibitors are also under investigation as alternatives to tamoxifen in premenopausal women with early breast cancer.[11]

Bisphosphonate therapy reduces the risk of skeletal-related events in patients with bone metastases and can inhibit bone loss. Zoledronic acid prevents bone loss associated with aromatase inhibitors in postmenopausal women[14,15] and premenopausal women[16,17] with early breast cancer. Emerging evidence suggests that zoledronic acid also has antitumor and antimetastatic properties, including the inhibition of angiogenesis, tumor-cell invasion, and adhesion in bone; the induction of apoptosis; antitumor synergy with cytotoxic chemotherapy; and immunomodulatory effects through induction of $\gamma/\delta$ T cells.[18-22] These findings were the background and rationale for the Austrian Breast and Colorectal Cancer Study Group trial 12 (ABCSG-12), which was designed to evaluate the efficacy of 3 years of treatment with ovarian suppression plus anastrozole or tamoxifen with or without zoledronic acid in premenopausal women with early breast cancer.

## METHODS

### PATIENTS

Premenopausal women who had undergone primary surgery for stage I or II estrogen-receptor–positive breast cancer, progesterone-receptor–positive breast cancer, or both, who had fewer than 10 positive lymph nodes, and who were scheduled to receive standard therapy with goserelin were eligible for enrollment. Exclusion criteria were T1a (except yT1a [y represents the size of the residual tumor after chemotherapy or surgery, rather than the initial size of the tumor]), T4d, and yT4 tumors; a history of other neoplasms; preoperative radiotherapy; pregnancy, lactation, or both; and contraindications for study medications. The Reiner score[23] for staining of tumor-cell nuclei was used to define expression levels of the estrogen and progesterone receptors (on a scale of 10 to 100%, with 10 to 50% indicating low expression, 51 to 80% indicating medium expression, and 81 to 100% indicating high expression). Tumors with high expression of estrogen and high expression of progesterone, high expression of estrogen and medium expression of progesterone, high expression of estrogen and low expression of progesterone, medium expression of estrogen and high expression of progesterone, or low expression of estrogen and high expression of progesterone were categorized as highly endocrine-responsive.

Preoperative chemotherapy was allowed, but none of the patients received adjuvant chemotherapy. Postoperative radiotherapy was administered according to institutional guidelines. The full protocol, including all amendments and the plan for statistical analysis, is included in the Supplementary Appendix, available with the full text of this article at NEJM.org.

### STUDY DESIGN

Patients were randomly assigned (in a 1:1:1:1 ratio with the use of a two-by-two factorial design) to receive goserelin (3.6 mg given subcutaneously every 28 days) plus either tamoxifen (20 mg per day given orally) or anastrozole (1 mg per day given orally), with or without zoledronic acid (initially 8 mg given intravenously every 4 weeks). Protocol amendments made on October 27, 2000, after 254 patients had been enrolled, reduced the dose of zoledronic acid to 4 mg every 6 months and increased the infusion time to 15 minutes, modifications that were consistent with the dose and schedule used to prevent aromatase inhibitor–associated bone loss in other studies.[24] Efficacy analyses were conducted as of March 31, 2008.

The primary end point was disease-free survival, which was defined as the time from randomization to the first occurrence of one or more of

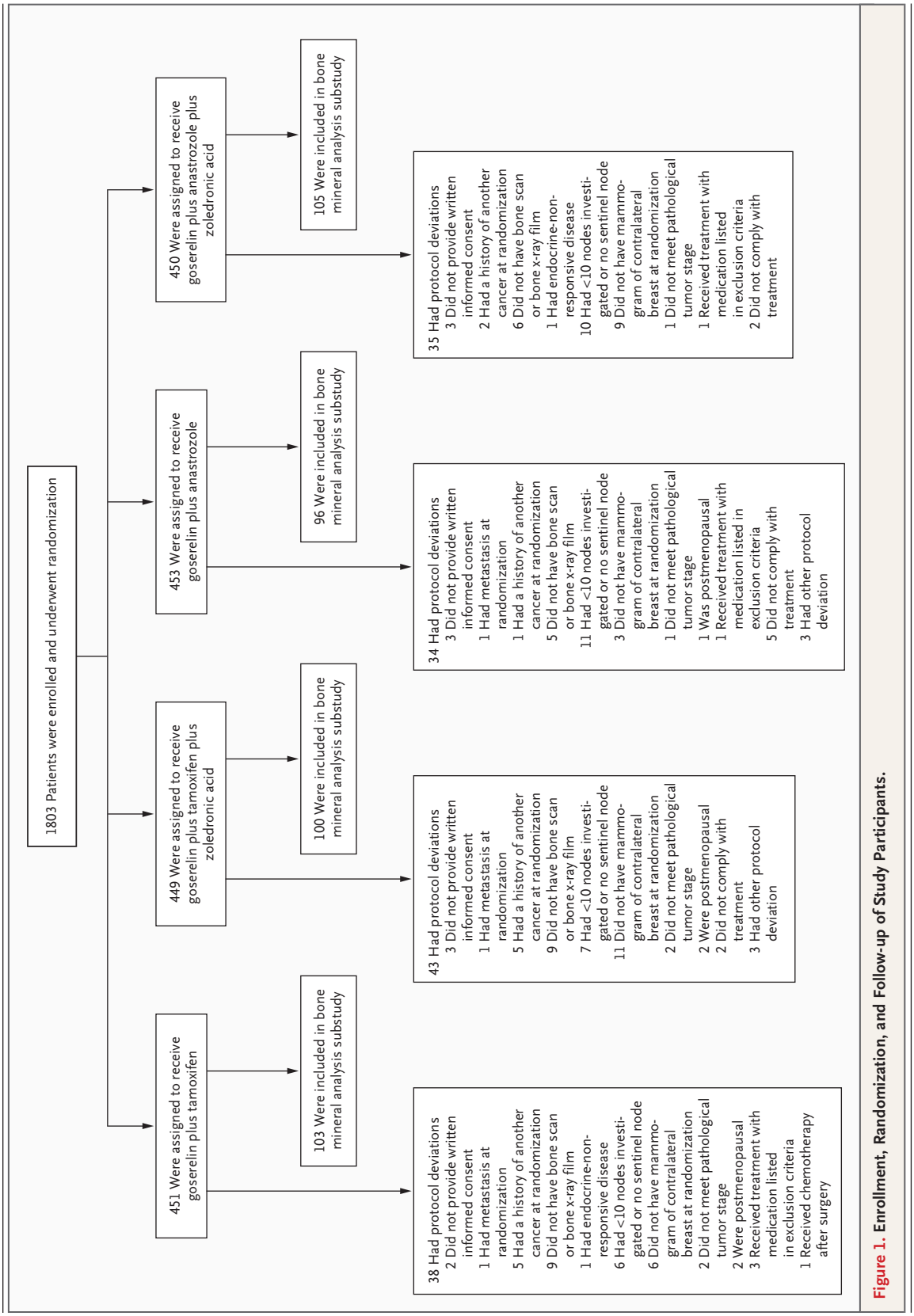



**Figure 1. Enrollment, Randomization, and Follow-up of Study Participants.**

**Table 1. Demographic and Baseline Disease Characteristics of Patients in the Intention-to-Treat Population.***

| Characteristic | Tamoxifen (N=451) | Tamoxifen plus Zoledronic Acid (N=449) | Anastrozole (N=453) | Anastrozole plus Zoledronic Acid (N=450) |
|---|---|---|---|---|
| Age at study entry | | | | |
| Median — yr | 45.5 | 45.3 | 45.0 | 44.5 |
| Range — yr | 27.6–56.5 | 27.5–56.3 | 25.9–56.3 | 28.8–56.4 |
| ≤40 yr — no. (%) | 80 (17.7) | 67 (14.9) | 88 (19.4) | 91 (20.2) |
| >40 yr — no. (%) | 370 (82.0) | 382 (85.1) | 364 (80.4) | 358 (79.6) |
| Cancer stage — no. (%) | | | | |
| T1 | 338 (74.9) | 335 (74.6) | 348 (76.8) | 339 (75.3) |
| ≥T2 | 99 (22.0) | 98 (21.8) | 93 (20.5) | 97 (21.6) |
| Unknown | 13 (2.9) | 16 (3.6) | 11 (2.4) | 13 (2.9) |
| Nodal status — no. (%) | | | | |
| Negative | 301 (66.7) | 295 (65.7) | 303 (66.9) | 302 (67.1) |
| Positive | 136 (30.2) | 138 (30.7) | 139 (30.7) | 135 (30.0) |
| Unknown | 13 (2.9) | 16 (3.6) | 10 (2.2) | 12 (2.7) |
| Histologic grade — no. (%) | | | | |
| 1 or 2 | 344 (76.3) | 344 (76.6) | 344 (75.9) | 339 (75.3) |
| 3 | 93 (20.6) | 89 (19.8) | 97 (21.4) | 98 (21.8) |
| Unknown | 13 (2.9) | 16 (3.6) | 11 (2.4) | 12 (2.7) |
| Estrogen-receptor status — no. (%)† | | | | |
| Negative | 16 (3.5) | 19 (4.2) | 15 (3.3) | 17 (3.8) |
| Low expression | 51 (11.3) | 61 (13.6) | 54 (11.9) | 58 (12.9) |
| Medium expression | 166 (36.8) | 149 (33.2) | 167 (36.9) | 153 (34.0) |
| High expression | 204 (45.2) | 204 (45.4) | 206 (45.5) | 210 (46.7) |
| Unknown‡ | 14 (3.1) | 16 (3.6) | 11 (2.4) | 12 (2.7) |
| Progesterone-receptor status — no. (%)† | | | | |
| Negative | 40 (8.9) | 32 (7.1) | 34 (7.5) | 36 (8.0) |
| Low expression | 52 (11.5) | 64 (14.3) | 58 (12.8) | 59 (13.1) |
| Medium expression | 160 (35.5) | 142 (31.6) | 149 (32.9) | 131 (29.1) |
| High expression | 185 (41.0) | 195 (43.4) | 200 (44.2) | 212 (47.1) |
| Unknown‡ | 14 (3.1) | 16 (3.6) | 12 (2.6) | 12 (2.7) |
| Preoperative chemotherapy — no. (%) | | | | |
| No | 406 (90.0) | 404 (90.0) | 408 (90.1) | 405 (90.0) |
| Yes | 24 (5.3) | 23 (5.1) | 24 (5.3) | 26 (5.8) |
| Unknown | 21 (4.7) | 22 (4.9) | 21 (4.6) | 19 (4.2) |

* All patients received goserelin. Percentages may not total 100 because of rounding.
† Hormone-receptor status was defined by the Reiner score for staining,[23] which is based on a scale of 10 to 100%, with 10 to 50% indicating low expression of the estrogen and progesterone receptors, 51 to 80% indicating medium expression, and 81 to 100% indicating high expression.
‡ Patients in this category were identified as having protocol violations; they were included in the intention-to-treat analysis but excluded from the Cox regression analyses.

the following: a local or regional recurrence, cancer in the contralateral breast, distant metastasis, second primary carcinoma, or death from any cause. If the observation period ended before any disease event occurred, the data were censored. Recurrence-free survival, overall survival, and measures of bone mineral density (reported previously[16,17]) were secondary end points, and survival

**Table 2. Events in the Intention-to-Treat Population.***

| Event | Tamoxifen (N=900) | Anastrozole (N=903) | No Zoledronic Acid (N=904) | Zoledronic Acid (N=899) |
|---|---|---|---|---|
| | | | *no. of events* | |
| All events | 65 | 72 | 83 | 54 |
| Recurrence | | | | |
| Locoregional | 16 | 14 | 20 | 10 |
| Distant | 29 | 41 | 41 | 29 |
| Bone metastases | 18 | 21 | 23 | 16 |
| Contralateral breast cancer | 10 | 6 | 10 | 6 |
| Secondary malignant condition | 9 | 10 | 10 | 9 |
| Death | | | | |
| All | 15 | 27 | 26 | 16 |
| Without previous recurrence | 1 | 1 | 2 | 0 |

* Only the first event per patient is included.

free of bone metastasis was an exploratory end point. The number needed to treat for one patient to receive clinical benefit was calculated as the inverse of the fractional reduction in risk.

The frequency of adverse events and changes in laboratory values were used to assess safety throughout the study. Every 3 months, renal function was evaluated. Serious adverse events were defined as any adverse events that were lethal or life-threatening, resulted in permanent damage, required inpatient hospitalization or extension of inpatient treatment, or placed the patient at risk and necessitated medical or surgical intervention.

The ABCSG-12 protocol was designed by the authors and written by the ABCSG scientific board. ABCSG, an academic nonprofit organization, sponsored the trial and maintained sole responsibility for data management, data monitoring, and all analyses. Data were collected by physicians, study nurses, and other study-center staff and processed in the central ABCSG data center. All authors had access to the primary data and vouch for the accuracy and completeness of the data analyses. The authors wrote the manuscript. Novartis donated zoledronic acid, and AstraZeneca donated goserelin, anastrozole, and tamoxifen, but neither company was involved in data collection or analysis.

### STATISTICAL ANALYSIS

The analysis was based on the intention-to-treat principle (the intention-to-treat population included all patients who underwent randomization),[25] performed according to a predefined plan for statistical analysis, and approved by an independent data-monitoring committee. Covariates (risk factors) in the applied statistical models were analyzed descriptively for continuous variables such as age, and data based on an ordinal scale or categorical data such as T stage were described with the use of frequencies and percentages. Treatments were compared with the use of a Cox proportional-hazards regression model, with only the treatment group as a covariate, and the log-rank test was used for disease-free survival, recurrence-free survival, and overall survival.[26] The proportional-hazards assumption was confirmed for the interaction of time to disease progression with the following therapy variables: anastrozole as compared with tamoxifen and zoledronic acid as compared with no zoledronic acid (Table 1 in the Supplementary Appendix). Kaplan–Meier plots for disease-free survival, recurrence-free survival, and overall survival were used for each comparison. Additional Cox analyses were conducted with consideration of the stratification criteria used for randomization in order to adjust for potential confounding effects. All models were chosen on the basis of goodness-of-fit according to the Akaike information criterion.[27] All results were based on two-sided analyses and quantified with hazard ratios, associated 95% confidence intervals, and P values according to the Wald test.

The study was originally powered with a targeted enrollment of 1250 patients to detect the superiority of disease-free survival with anastro-

zole as compared with tamoxifen. After a recommendation by the international advisory board, the sample was increased to 1800 patients, with 90% power for a hazard ratio of 1.8 with a two-sided alpha error of 0.05, to include approximately 124 events. The two between-group tests of the primary end point were calculated with a two-sided significance level of 2.5%, with the application of the Bonferroni–Holm adjustment for multiple comparisons. Secondary and exploratory end points were analyzed with a two-sided significance level of 5%. In addition, sensitivity analyses of disease-free survival were conducted for subgroups excluding the 98 patients who received any 8-mg dose of zoledronic acid and the 404 patients in the bone mineral density substudy (Table 2 in the Supplementary Appendix). Calculations were performed with the use of SAS statistical software, version 9.1 (SAS Institute).

## RESULTS

### STUDY POPULATION

A total of 1803 patients were enrolled between 1999 and 2006 (Fig. 1). The treatment groups were well matched with regard to demographic and baseline disease characteristics (Table 1). The median age was 45 years; 75% of the patients had T1-stage cancer, and 30% had node-positive cancer. All tumors were estrogen-receptor–positive, progesterone-receptor–positive, or both; 85% of the patients had scores that indicated highly endocrine-responsive early breast cancer; and 5.4% of the patients had received neoadjuvant chemotherapy.

### EFFICACY

At a median follow-up period of 47.8 months, 137 events met the criteria for the primary end point; these events included 42 deaths, 30 locoregional relapses, 70 distant relapses (39 in bone), 16 events in the contralateral breast, and 19 new primary tumors that were not located in the breast (Table 2). Rates of disease-free survival (Fig. 2A), recurrence-free survival (Fig. 2C), and overall survival (Fig. 2E) did not differ significantly between the anastrozole and tamoxifen groups. In contrast, the addition of zoledronic acid significantly improved disease-free survival, as compared with the use of endocrine therapy alone, at a median follow-up of 47.8 months (845 of 899 patients [94.0%] were free of disease vs. 821 of 904 [90.8%], P=0.01) (Fig. 2B). The absolute increase of 3.2 percentage points in disease-free survival among patients who received zoledronic acid represents a 36% reduction in the risk of disease progression, as compared with patients who received endocrine therapy alone (P=0.01). Results of the full Cox multivariate regression are provided in Table 3 in the Supplementary Appendix. The addition of zoledronic acid also improved recurrence-free survival at 47.8 months, as compared with endocrine therapy alone (845 of 899 patients [94.0%] were free of recurrence vs. 822 of 904 [90.9%]; absolute difference, 3.1 percentage points; P=0.01 by the log-rank test), and reduced the risk of recurrence by 35% (P=0.02) (Fig. 2D). In the two groups of patients who received zoledronic acid, there were 16 deaths, as compared with 26 deaths in the groups that received endocrine treatment only (hazard ratio, 0.60; 95% confidence interval [CI], 0.32 to 1.11; P=0.11) (Fig. 2F). Because of the low number of events, the addition of zoledronic acid did not significantly improve survival free of bone metastasis (32% risk reduction; hazard ratio, 0.68; 95% CI, 0.36 to 1.27; P=0.22) (Fig. 1 in the Supplementary Appendix).

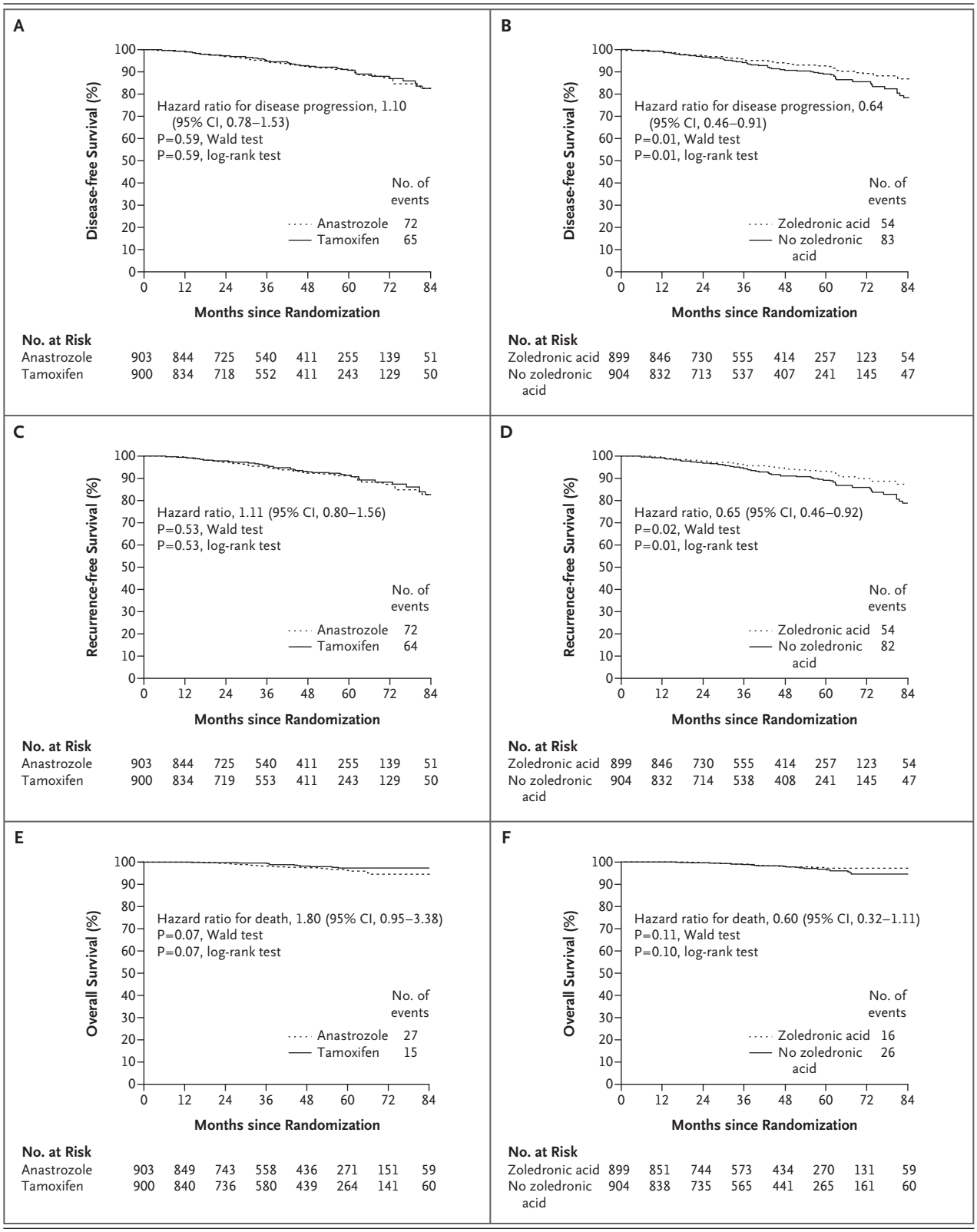
**Figure 2 (facing page). Kaplan–Meier Estimates of Survival.**

The primary end point of disease-free survival (Panels A and B) and the secondary end points of recurrence-free survival (Panels C and D) and overall survival (Panels E and F) are shown for women with breast cancer who received adjuvant endocrine therapy without zoledronic acid (Panels A, C, and E) and those who received adjuvant endocrine therapy with or without zoledronic acid (Panels B, D, and F).

Sensitivity analyses that excluded patients in the bone mineral density substudy revealed hazard ratios for disease progression that were similar to those in the intention-to-treat population for both anastrozole as compared with tamoxifen (hazard ratio, 1.39; 95% CI, 0.92 to 2.10) and zoledronic acid as compared with no zoledronic acid (hazard ratio, 0.70; 95% CI, 0.46 to 1.06). Similarly, the results for patients who received only 4 mg of zoledronic acid and those in the per-protocol population were consistent with the intention-to-treat analyses (Table 2 in the Supplementary Appendix).

As compared with patients who did not receive zoledronic acid, patients who received zoledronic acid had fewer events in all event categories, including locoregional and distant recurrence, bone metastases, and disease in the contralateral breast (Table 2).

A prospectively planned Cox analysis of disease-free survival and recurrence-free survival with



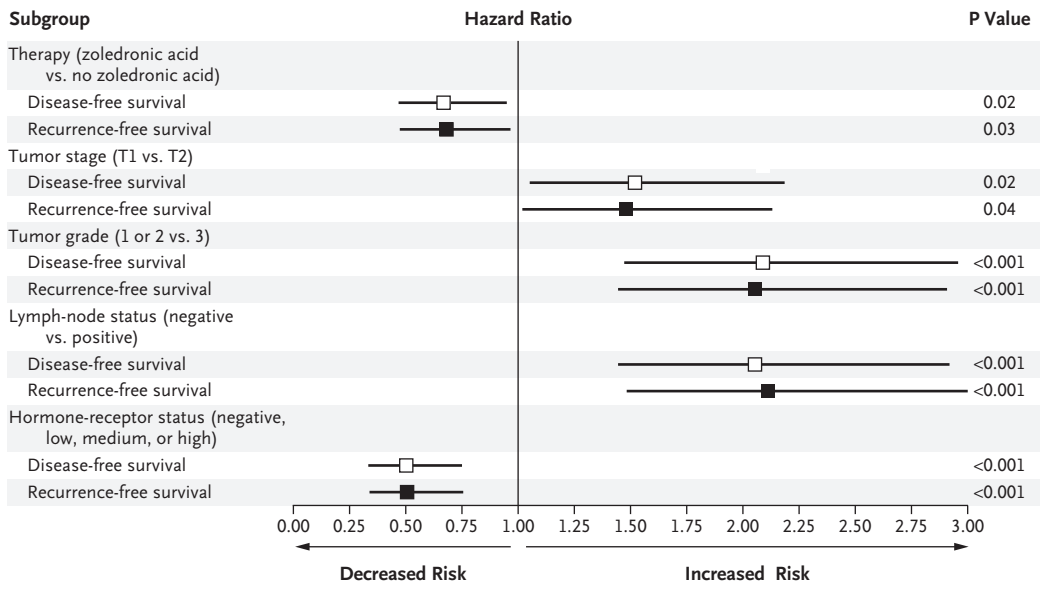



**Figure 3. Results of Multivariate Analyses of Independent Variables for Disease-free Survival and Recurrence-free Survival.**

A forest plot shows the hazard ratios (squares) and 95% confidence intervals (horizontal lines) according to therapy type, tumor stage, tumor grade, lymph-node status, and progesterone-receptor status in the multivariate subgroup analyses. "Zoledronic acid" refers to patients who received anastrozole–goserelin plus zoledronic acid or tamoxifen–goserelin plus zoledronic acid, and "no zoledronic acid" refers to patients who received anastrozole–goserelin without zoledronic acid or tamoxifen–goserelin without zoledronic acid. Hormone-receptor status was based on the Reiner score for staining,[23] which ranges from 10 to 100%, with 10 to 50% indicating a low expression, 51 to 80% medium expression, and 81 to 100% high expression.

the use of stepwise selection of variables identified independent variables that were significantly associated with risks of events (Fig. 3). Patients who received zoledronic acid had a 33% reduction in the risk of disease progression (P=0.02) and a 32% reduction in the risk of recurrence (P=0.03), as compared with patients who received endocrine therapy alone, in the multivariate model (the full multivariate model is shown in Table 3 in the Supplementary Appendix). The number needed to treat with zoledronic acid to prevent disease progression in 1 patient was 31 at a median follow-up of 47.8 months.

### SAFETY

Women who received anastrozole alone, as compared with those who received tamoxifen alone, had higher incidences of arthralgia (25% vs. 12%) and bone pain (28% vs. 21%) (Table 3). Treatment that included zoledronic acid, as compared with treatment that did not include zoledronic acid, was associated with slightly higher incidences of bone pain (35% vs. 25%), arthralgia (24% vs. 18%), and fever (9% vs. 2%) (Table 6 in the Supplementary Appendix). In addition, the bone-related adverse events in the patients who received both zoledronic acid and endocrine therapy appear to have been additive, given the higher incidence of arthralgia and bone pain among patients who received endocrine therapy with zoledronic acid as compared with those who received endocrine therapy without zoledronic acid. Overall, there were no significant differences between groups with regard to the incidence of serious adverse events that occurred in 10% or less of the patients, except that the incidence of uterine polyps was higher among patients who received tamoxifen than among those who received anastrozole (P<0.001) (Table 3, and Table 7 in the Supplementary Appendix).

In this trial, three suspected cases of osteonecrosis of the jaw were reported in patients who received zoledronic acid. In all three patients, the diagnosis was ruled out after a detailed review of dental records. No serious renal events were reported. Among a total of 16,863 measurements of serum creatinine, levels above the upper limit of

**Table 3. Adverse Events and Serious Adverse Events during Treatment.**

| Event | Tamoxifen (N=451) | Tamoxifen plus Zoledronic Acid (N=449) | Anastrozole (N=453) | Anastrozole plus Zoledronic Acid (N=450) | P Value* |
|---|---|---|---|---|---|
| | *number of patients (percent)* | | | | |
| **Adverse events** | | | | | |
| Arthralgia | 52 (11.5) | 65 (14.5) | 112 (24.7) | 150 (33.3) | <0.001 |
| Bone pain | 94 (20.8) | 132 (29.4) | 128 (28.3) | 185 (41.1) | <0.001 |
| Fracture | 1 (0.2) | 1 (0.2) | 1 (0.2) | 0 | 0.91 |
| Fatigue | 70 (15.5) | 82 (18.3) | 93 (20.5) | 98 (21.8) | 0.08 |
| Depression, sleep disturbances | 70 (15.5) | 74 (16.5) | 97 (21.4) | 80 (17.8) | 0.11 |
| Cognitive disorder | 0 | 4 (0.9) | 3 (0.7) | 9 (2.0) | 0.01 |
| Nausea and vomiting | 23 (5.1) | 29 (6.5) | 32 (7.1) | 48 (10.7) | 0.01 |
| Dizziness | 13 (2.9) | 9 (2.0) | 7 (1.5) | 18 (4.0) | 0.11 |
| Headache | 59 (13.1) | 59 (13.1) | 63 (13.9) | 85 (18.9) | 0.05 |
| Peripheral nerve disease | 17 (3.8) | 22 (4.9) | 14 (3.1) | 29 (6.4) | 0.09 |
| Muscle cramp | 9 (2.0) | 8 (1.8) | 2 (0.4) | 4 (0.9) | 0.10 |
| Morning stiffness | 11 (2.4) | 14 (3.1) | 33 (7.3) | 35 (7.8) | <0.001 |
| Hot flushes | 28 (6.2) | 27 (6.0) | 25 (5.5) | 25 (5.6) | 0.96 |
| Fever | 9 (2.0) | 34 (7.6) | 11 (2.4) | 46 (10.2) | <0.001 |
| Hypertonia | 14 (3.1) | 20 (4.5) | 20 (4.4) | 25 (5.6) | 0.35 |
| Tachycardia | 2 (0.4) | 9 (2.0) | 5 (1.1) | 10 (2.2) | 0.07 |
| Thrombosis | 0 | 0 | 0 | 1 (0.2) | 0.50 |
| Leg edema | 9 (2.0) | 10 (2.2) | 2 (0.4) | 2 (0.4) | 0.02 |
| Cutaneous reaction | 19 (4.2) | 5 (1.1) | 18 (4.0) | 15 (3.3) | 0.02 |
| Skin disease | 23 (5.1) | 32 (7.1) | 16 (3.5) | 26 (5.8) | 0.11 |
| Impaired vision | 36 (8.0) | 27 (6.0) | 22 (4.9) | 29 (6.4) | 0.29 |
| Uterine polyp | 5 (1.1) | 0 | 1 (0.2) | 1 (0.2) | 0.07 |
| Periodontal disease† | 5 (1.1) | 3 (0.7) | 0 | 6 (1.3) | 0.05 |
| **Serious adverse events** | | | | | |
| Arthralgia | 0 | 1 (0.2) | 0 | 1 (0.2)‡ | 0.37 |
| Bone pain | 0 | 0 | 0 | 1 (0.2)‡ | 0.50 |
| Fracture | 6 (1.3) | 4 (0.9) | 4 (0.9) | 7 (1.6) | 0.75 |
| Depression, sleep disturbances | 1 (0.2) | 3 (0.7) | 0 | 1 (0.2) | 0.20 |
| Cognitive disorder | 0 | 0 | 0 | 1 (0.2) | 0.50 |
| Dizziness | 1 (0.2) | 0 | 0 | 1 (0.2) | 0.62 |
| Headache | 1 (0.2) | 0 | 0 | 1 (0.2) | 0.62 |
| Peripheral nerve disease | 4 (0.9) | 1 (0.2) | 4 (0.9) | 10 (2.2) | 0.04 |
| Fever | 1 (0.2) | 1 (0.2) | 1 (0.2) | 2 (0.4) | 0.88 |
| Hypertonia | 2 (0.4) | 0 | 1 (0.2) | 3 (0.7) | 0.38 |
| Tachycardia | 1 (0.2) | 0 | 1 (0.2) | 1 (0.2) | 1.00 |
| Thrombosis | 3 (0.7) | 5 (1.1) | 0 | 0 | 0.01 |
| Cutaneous reaction | 3 (0.7) | 5 (1.1) | 1 (0.2) | 3 (0.7) | 0.41 |
| Skin disease | 8 (1.8) | 8 (1.8) | 3 (0.7) | 5 (1.1) | 0.36 |
| Uterine polyp | 40 (8.9) | 51 (11.4) | 7 (1.5) | 5 (1.1) | <0.001 |
| Periodontal disease† | 0 | 1 (0.2) | 0 | 1 (0.2) | 0.37 |

* P values are for a four-group comparison according to Fisher's exact test.
† There were no confirmed cases of osteonecrosis of the jaw.
‡ There was one event in the group of patients who received anastrozole plus zoledronic acid; this event was associated with previous hip replacement.

the normal range were rare, and 99% of the values were 1.1 mg per deciliter (97 μmol per liter) or less. All adverse events and serious adverse events are listed in Tables 4 and 5 in the Supplementary Appendix.

## DISCUSSION

The results of our study showed that in premenopausal women with early breast cancer, treatment with anastrozole and treatment with tamoxifen were associated with similar rates of disease-free survival. The addition of zoledronic acid to adjuvant endocrine therapy increased the rate of disease-free survival, as compared with endocrine therapy alone. At a median follow-up of 47.8 months, 821 of 904 patients who received endocrine therapy alone (90.8%) were free of disease, and 878 of 904 patients (97.1%) were alive; in the cohort of patients who received zoledronic acid, 845 of 899 patients (94.0%) were disease-free and 883 of 899 (98.2%) were alive. The absolute difference in disease-free survival was 3.2 percentage points, favoring the patients who received zoledronic acid as compared with the patients who did not receive zoledronic acid (P=0.01). This difference is similar to the 5-year absolute difference in disease-free survival observed in trials comparing tamoxifen with aromatase inhibitors in postmenopausal women with early breast cancer.[5,28] These outcomes add to the growing body of data showing that subgroups of patients with low-risk or intermediate-risk, endocrine-responsive early breast cancer can be spared the adverse events of cytotoxic therapy after locoregional treatment.[29] In our study, treatment with goserelin was given for 3 years, on the basis of the outcomes in a previous trial (the Austrian Breast and Colorectal Cancer Study Group trial 5).[10]

Although the duration of endocrine therapy in premenopausal patients varies internationally (i.e., from 2 to 5 years), the data from ABCSG-12 indicate that ovarian suppression with endocrine therapy for 3 years can produce excellent outcomes in a population with low-to-intermediate risk. The estimated number needed to treat to prevent disease progression in 1 patient in the intention-to-treat cohort was 31 in the group of patients who received zoledronic acid at a median follow-up of 47.8 months. In contrast, in a meta-analysis of taxane therapy in postmenopausal women with early breast cancer, the numbers needed to treat to prevent disease progression in 1 patient were 28 with the use of paclitaxel (with a median follow-up of 60 to 69 months) and 31 with the use of docetaxel (with a median follow-up of 43 to 60 months).[30] Thus, the addition of zoledronic acid to endocrine therapy is consistent with the number needed to treat for cancer therapies that in the past have caused a shift in treatment standards.

The significant benefit of zoledronic acid with respect to disease-free survival may be explained by several antitumor mechanisms. In preclinical studies, zoledronic acid inhibited tumor-cell adhesion, invasion, and proliferation and induced apoptosis in a variety of human tumor cell lines. It also delayed disease progression in animal models of human cancers and acted synergistically with many chemotherapy agents.[18,20-22,31-36] Early data suggest that zoledronic acid can stimulate antitumor immune reactions[37,38] and exert antiangiogenic effects.[22] Moreover, in the integrated analysis of the Zometa–Femara Adjuvant Synergy Trial, zoledronic acid significantly reduced disease recurrence among postmenopausal women with early breast cancer when it was administered at the dose used in premenopausal women in ABCSG-12.[39] In small pilot studies involving inpatients with advanced disease, zoledronic acid increased survival free of bone metastases among 40 patients with aggressive solid tumors and reduced disease recurrence and prolonged overall survival among 94 patients with multiple myeloma and 40 patients with bladder cancer.[18,21,40] Furthermore, recent subgroup analyses suggest that zoledronic acid may improve overall survival as compared with placebo among patients with high bone-turnover rates because of bone metastases[41,42] and may improve the efficacy of neoadjuvant chemotherapy in reducing tumor size.[33]

In patients who were receiving adjuvant therapy,[14-16] zoledronic acid (at a dose of 4 mg every 6 months) prevented bone loss caused by aromatase inhibitors. Moreover, several studies have shown a reduced incidence of micrometastases in the bone marrow of patients with breast cancer who have received zoledronic acid.[20,36,43] Taken together, previous data and our findings suggest that zoledronic acid may exert antitumor effects both in and outside of bone.

Improved disease-free survival with bisphosphonate treatment has been reported,[44] but a meta-analysis of this trial and subsequent trials involving patients with breast cancer revealed no significant difference in overall survival, survival free of bone metastasis, or survival free of non-

skeletal metastasis with treatment that included clodronate as compared with adjuvant treatment.[45] In our trial, the addition of zoledronic acid did not significantly improve overall survival at the median follow-up. The similar rates of disease-free and recurrence-free survival with anastrozole and tamoxifen in our study were unexpected, given the superiority of aromatase inhibitors over tamoxifen in postmenopausal women.[1-5,46]

Clinical experience with aromatase inhibitors in premenopausal women is limited, and our results indicate that the benefits of aromatase inhibitors seen in postmenopausal women do not apply to premenopausal women, perhaps because of the dominant effect of ovarian suppression on estrogen levels in premenopausal women. Moreover, long-term administration of goserelin can reduce androgen levels, thereby limiting the available substrate for aromatase activity. In general, adverse events in our trial were as expected. Bisphosphonates are known to induce transient fever and bone pain, particularly after the first infusion. Osteonecrosis of the jaw has been uncommon in patients receiving complex treatment regimens for cancer, including bisphosphonates, chemotherapy, and radiotherapy,[47-49] but osteonecrosis did not develop in any of the patients in our trial or in other trials in which zoledronic acid was administered at a dose of 4 mg every 6 months.[39] There were also no signs of renal toxicity, adding to the evidence that this adverse event is rare in the adjuvant setting.[39] Side effects of endocrine treatments were as expected. Overall, there was no unexpected increase in serious adverse events or treatment-related deaths.

In conclusion, in premenopausal women with endocrine-responsive early breast cancer, after a median follow-up of 47.8 months, goserelin plus anastrozole yielded clinical outcomes that were similar to those with goserelin plus tamoxifen, and the addition of zoledronic acid to endocrine therapy significantly improved disease-free survival.

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## APPENDIX

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