

ORIGINAL ARTICLE

Endocrine Therapy plus Zoledronic Acid in Premenopausal Breast Cancer

Michael Gnant, M.D., Brigitte Mlineritsch, M.D., Walter Schippinger, M.D., Gero Luschin-Ebengreuth, M.D., Sabine Pöstlberger, M.D., Christian Menzel, M.D., Raimund Jakesz, M.D., Michael Seifert, M.D., Michael Hubalek, M.D., Vesna Bjelic-Radicic, M.D., Hellmut Samonigg, M.D., Christoph Tausch, M.D., Holger Eidtmann, M.D., Günther Steger, M.D., Werner Kwasny, M.D., Peter Dubsy, M.D., Michael Fridrik, M.D., Florian Fitzal, M.D., Michael Stierer, M.D., Ernst Rücklinger, Ph.D., and Richard Greil, M.D., for the ABCSG-12 Trial Investigators*

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.)

From the Medical University of Vienna (M.G., R.J., M. Seifert, G.S., P.D., F.F.), Hanusch Hospital (M. Stierer), and the Austrian Breast and Colorectal Cancer Study Group (E.R.) — all in Vienna; Paracelsus Medical University Salzburg, Salzburg (B.M., C.M., R.G.); Medical University of Graz, Graz (W.S., G.L.-E., V.B.-R., H.S.); Hospital of the Sisters of Mercy (S.P., C.T.) and General Hospital Linz (M.F.) — both in Linz; Medical University of Innsbruck, Innsbruck (M.H.); and Wiener Neustadt Hospital, Wiener Neustadt (W.K.) — all in Austria; and the University of Schleswig-Holstein, Kiel, Germany (H.E.). Address reprint requests to Dr. Gnant at the Medical University of Vienna, Währinger Gürtel 18-20, A-1090 Vienna, Austria, or at michael.gnant@meduniwien.ac.at.

*The investigators participating in the Austrian Breast and Colorectal Cancer Study Group trial 12 (ABCSG-12) are listed in the Appendix.

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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 γ/δ 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-posi-

tive 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 γ T1a [γ represents the size of the residual tumor after chemotherapy or surgery, rather than the initial size of the tumor]), T4d, and γ T4 tumors; a history of other neoplasms; preoperative radiotherapy; pregnancy, lactation, or both; and contraindications for study medications. The Reiner score²³ 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

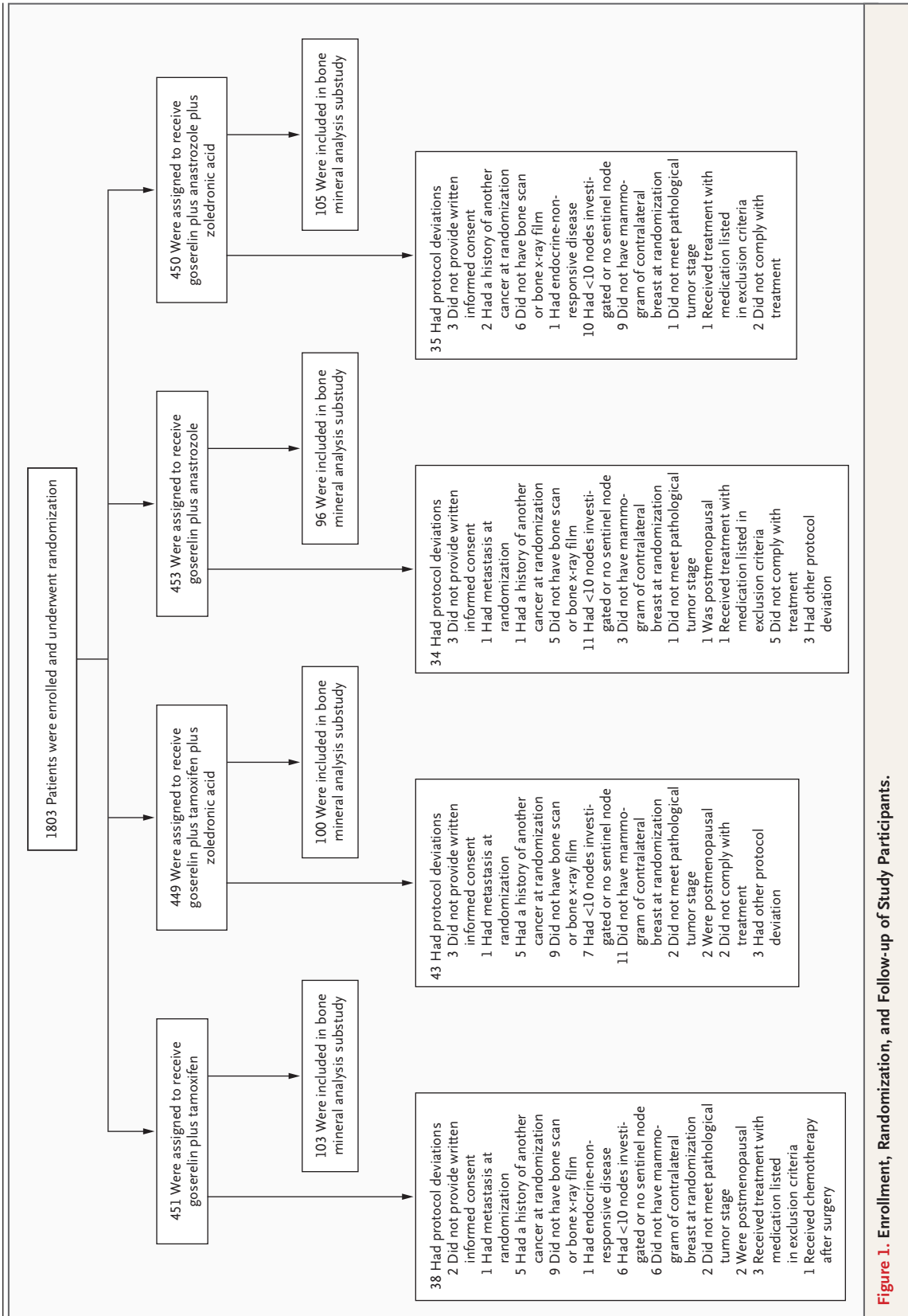


Figure 1. Enrollment, Randomization, and Follow-up of Study Participants.

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. of events	
			No Zoledronic Acid (N=904)	Zoledronic Acid (N=899)
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

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

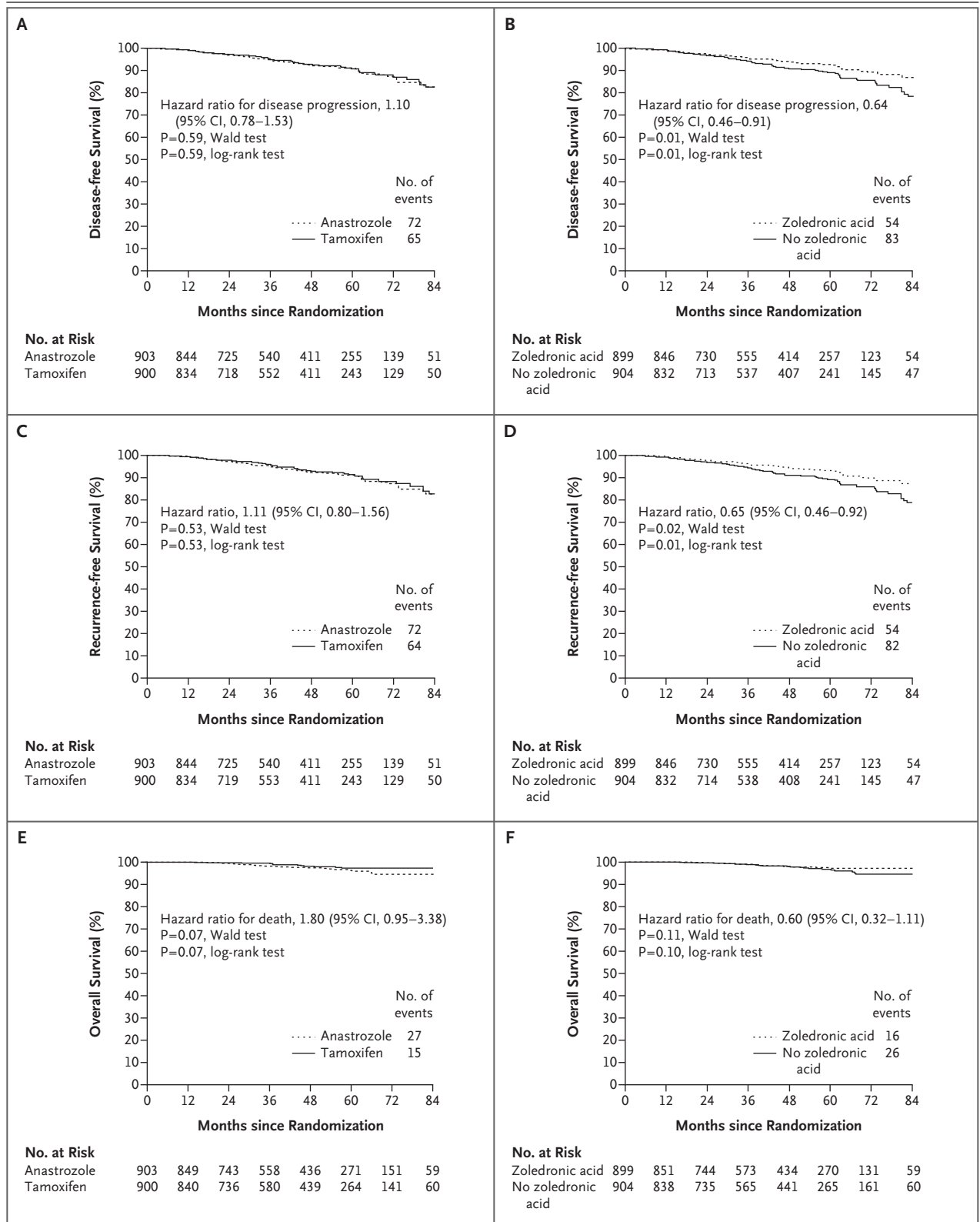
The primary end point of disease-free survival (Panels A and B) and the secondary end points of recurrence-free survival (Panels C and D) and overall survival (Panels E and F) are shown for women with breast cancer who received adjuvant endocrine therapy without zoledronic acid (Panels A, C, and E) and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

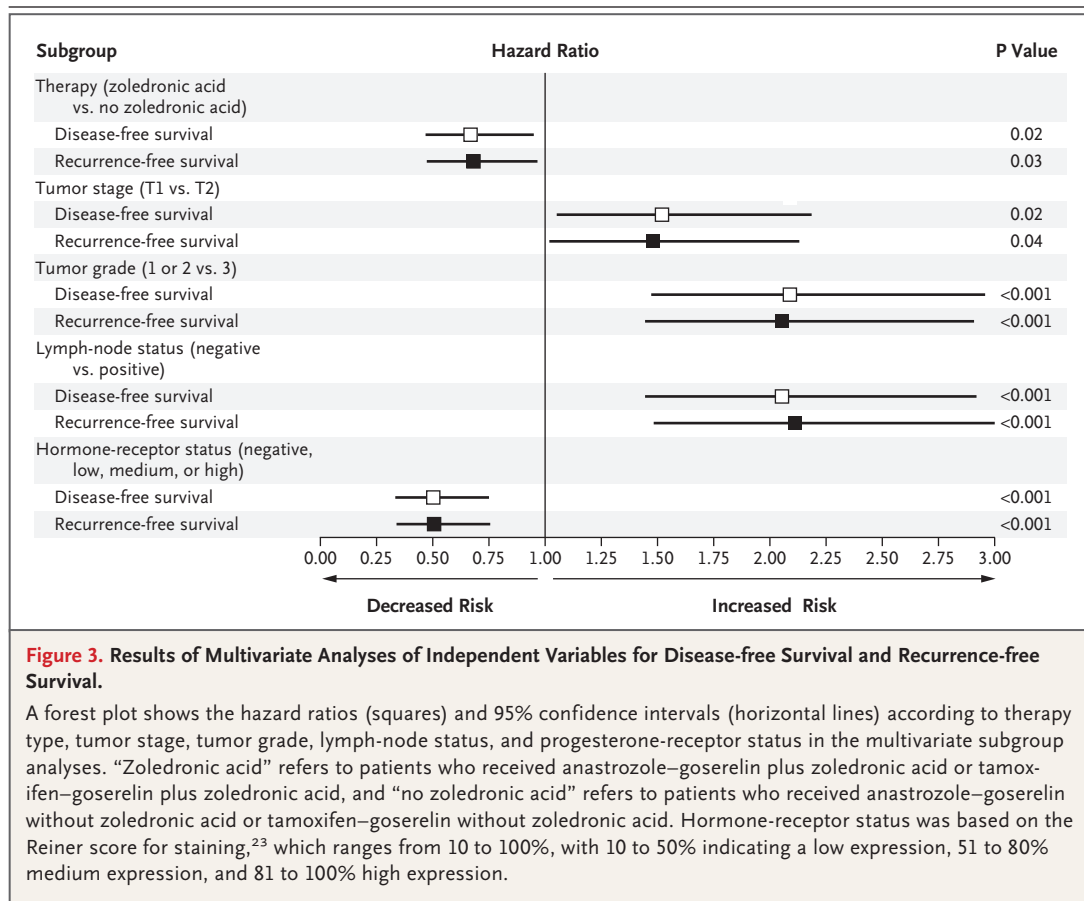
zoledronic acid represents a 36% reduction in the risk of disease progression, as compared with patients who received endocrine therapy alone ($P=0.01$). Results of the full Cox multivariate regression are provided in Table 3 in the Supplementary Appendix. The addition of zoledronic acid also improved 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).

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





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*
	<i>number of patients (percent)</i>				
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 μ mol 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

The ABCSG-12 writing committee consisted of Drs. Gnant, Jakesz, Greil, C. Marth, Seifert, Dubsy, and Tausch. In addition to the authors, the members of the ABCSG-12 were as follows: **Austria:** Vienna University, Vienna: S. Taucher, T. Bachleitner-Hofmann, S. Schoppmann, M. Rudas, U. Pluschnig, D. Hussian, U. Sevela, R. Bartsch, G. Locker, C. Wenzel, C. Dadak, R. Obwegeser, E. Kubista, E. Asseryanis, R. Möslinger-Gehmayr, E. Hanzal, C. Sam; **Salzburg Hospital, Salzburg:** P. Mayer, M. Moik, C. Rass, R. Reitsamer, G. Russ; **Graz University and Graz Hospital, Graz:** T. Bauernhofer, A.-K. Kasperek, P. Wagner, U. Langsenlehner, P. Krippel, M. Balic, E. Andritsch, R. Schaberl-Moser, B. Lilleg, W. Weitzer, G. Hofmann, H.-J. Mischinger, F. Ploner, M. Smola, H. Stöger; **Wiener Neustadt Hospital, Wiener Neustadt:** D. Depisch, A. Lenauer, K. Haider, T. Payrits; **Linz Hospital, Linz:** R. Greul, G. Hochreiner, G. Wahl; **Sankt Veit Hospital, Sankt Veit:** J. Tschmelitsch, A. Reichenauer; **Friesach Hospital, Friesach:** V. Wette; **Hanusch Hospital, Vienna:** U. Selim, S. Artner, H. Matzinger, A. Galid, J. Baumann, M. Medl; **Sisters of Mercy Hospital, Vienna:** U. Schmidbauer, M. Wunderlich; **Oberpullendorf Hospital, Oberpullendorf:** F. Hofbauer, M. Lang; **Güssing Hospital, Güssing:** W. Horvath, I. Luisser, G. Fandl; **Oberwart Hospital, Oberwart:** M. Prager; **Wiener Neustadt Hospital, Wiener Neustadt:** Zentrum Ost Hospital, Vienna: P. Kier, K. Renner; **Lainz Hospital, Vienna:** M. Pichler, M. Weigert, F. Sevela, P. Sevela, U. Denison, C. Peters-Engl, N. Veneziano; **Leoben Hospital, Leoben:** R. Kocher, F. Stangl; **Graz University, Graz:** R. Winter; **Zams Hospital, Zams:** P. Sandbichler, W. Schennach, M. Mühlthaler; **Lienz Hospital, Lienz:** P. Anderl, B. Mitterdorfer, U. Draxler, B. Volgger; **Sisters of Mercy Hospital, Linz:** R. Helfgott, C. Schmidhammer, D. Heck, F. Kugler, M. Aufschnaiter, G. Michlmayr, R. Schildberger; **Feldkirch Hospital, Feldkirch:** A. Haid, R. Köberle-Wührer; **Wolfsberg Hospital, Wolfsberg:** W. Döller, E. Melbinger; **Schwarzach Hospital, Schwarzach:** J. Berger, R. Lenzhofer, W. Zeilmann, B. Medek, S. Schäfer; **Bregenz Hospital, Bregenz:** H. Stephan, F.X. Schmid; **Wilhelminenspital, Vienna:** H. Ludwig, P. Sagaster; **Mistelbach Hospital, Mistelbach:** G. Reiner, D. Semmler; **Waldviertel Hospital, Waidhofen/Thaya:** A. Kretschmer; **Thermenklinikum Baden:** H. Trapl, R. Tichatschek;

Hospital Mostviertel, Scheibbs: P. Magg; Klosterneuburg Hospital, Klosterneuburg: C. Bosse; Melk Hospital, Melk: G. Weissinger, B. Labuda; Neunkirchen Hospital, Neunkirchen: B. Hartmann, A. Bernhaus; Hospital Donauklinikum, Tulln: P. Lechner, B. Zeh; Vöcklabruck Hospital, Vöcklabruck: B. Beer, W. Simma, B. Pichler-Gebhard, L. Schiller, K. Wilthoner, F. Haslbauer; Clinical Center Wels-Grieskirchen, Wels-Grieskirchen: J. Thaler, V. Trommet, S. Pillichshammer, C. Baldinger, P. Oppitz, T. Kühn, L. Wimmer, R. Koplmüller; Linz Hospital, Linz: C. Tausch; Ried Hospital, Ried: S.A. Wenzl-Eybl; Schärding Hospital, Schärding: H. Haberfellner; Hospital Elisabethinen, Linz: R. Függer, W. Havlicek; Kirchdorf Hospital, Kirchdorf: C. Hinterbuchinger, W. Aschauer, G. Grenzfürter; Klagenfurt Hospital, Klagenfurt: J. Omann, A. Urbana, K. Holzmillner; Feldbach Hospital, Feldbach: H. Hofmann, C. Radl; Dornbirn Hospital, Dornbirn: W. Neunteufel, C. Poysl, K. Bischofberger; Medical University Innsbruck, Innsbruck: C. Marth, M. Widschwendner, A. Bergant, A. Zeimet, H. Müller, B. Volgger, A. Ramoni; Kufstein Hospital, Kufstein: B. Spechtenhauser, C. Felgel-Farnholz, S. Alick; Hospital Hall in Tirol, Innsbruck: K. Matthä, A. Bachmann; Fürstenfeld Hospital, Fürstenfeld: E. Hartner, H.L. Seewann; Villach Hospital, Villach: J. Keckstein, F. Tuttlies, D. Pacher; Villach Hospital and Private Hospital, Villach: K. Unterrieder. **Germany:** University Hospital Kiel, Kiel: W. Jonat; Frauenklinikum vom Roten Kreuz, Munich: W. Eiermann, J. Seitz, M. Sanchez, C. Hanusch, R. Lorch, U. Jessat, M. Stehle; University Hospital Munich, Munich: L. Sommer, M. Franz; Elisabeth Hospital Kassel, Kassel: B. Conrad, G. Hopf, A. Balwanz, E. Stütz; Vivantes Klinikum am Urban, Berlin: K.P. Hellriegel, S. Shim; Hospital Gifhorn, Gifhorn: T. Dewitz; Hospital St. Marien Amberg, Amberg: S. Vietoris, M. Beha; Hospital for Tumor Biology, Freiburg: N. Marschner; Internal-Hematological Center Oldenburg, Oldenburg: B. Otremba, D. Reschke.

REFERENCES

- Forbes JF, Cuzick J, Budzar A, Howell A, Tobias J, Baum M. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. *Lancet Oncol* 2008;9:45-53.
- Jakesz R, Greil R, Gnant M, et al. Extended adjuvant therapy with anastrozole among postmenopausal breast cancer patients: results from the randomized Austrian Breast and Colorectal Cancer Study Group Trial 6a. *J Natl Cancer Inst* 2007;99:1845-53. [Erratum, *J Natl Cancer Inst* 2008;100:226.]
- Jakesz R, Jonat W, Gnant M, et al. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. *Lancet* 2005;366:455-62.
- Jonat W, Gnant M, Boccardo F, et al. Effectiveness of switching from adjuvant tamoxifen to anastrozole in postmenopausal women with hormone-sensitive early-stage breast cancer: a meta-analysis. *Lancet Oncol* 2006;7:991-6. [Erratum, *Lancet Oncol* 2007;8:6.]
- Thurlimann B, Keshaviah A, Coates AS, et al. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *N Engl J Med* 2005;353:2747-57.
- 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.
- Li CI, Daling JR, Malone KE. Incidence of invasive breast cancer by hormone receptor status from 1992 to 1998. *J Clin Oncol* 2003;21:28-34.
- Early Breast Cancer Trialists' Collaborative Group. Ovarian ablation in early breast cancer: overview of the randomised trials. *Lancet* 1996;348:1189-96.
- Davidson NE, O'Neill AM, Vukov AM, et al. Chemoendocrine therapy for premenopausal women with axillary lymph node-positive, steroid hormone receptor-positive breast cancer: results from INT 0101 (E5188). *J Clin Oncol* 2005;23:5973-82.
- Jakesz R, Hausmaninger H, Kubista E, et al. Randomized adjuvant trial of tamoxifen and goserelin versus cyclophosphamide, methotrexate, and fluorouracil: evidence for the superiority of treatment with endocrine blockade in premenopausal patients with hormone-responsive breast cancer — Austrian Breast and Colorectal Cancer Study Group Trial 5. *J Clin Oncol* 2002;20:4621-7.
- Cuzick J, Ambroisine L, Davidson N, et al. 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.
- Goldhirsch A, Wood WC, Gelber RD, Coates AS, Thurlimann B, Senn HJ. Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007. *Ann Oncol* 2007;18:1133-44. [Erratum, *Ann Oncol* 2007;18:1917.]
- Forward DP, Cheung KL, Jackson L, Robertson JF. Clinical and endocrine data for goserelin plus anastrozole as second-line endocrine therapy for premenopausal advanced breast cancer. *Br J Cancer* 2004;90:590-4.
- Bundred NJ, Campbell ID, Davidson N, et al. Effective inhibition of aromatase inhibitor-associated bone loss by zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: ZO-FAST Study results. *Cancer* 2008;112:1001-10.
- Brufsky A, Harker WG, Beck JT, et al. Zoledronic acid inhibits adjuvant letrozole-induced bone loss in postmenopausal women with early breast cancer. *J Clin Oncol* 2007;25:829-36.
- Gnant M, Mlineritsch B, Luschin-Ebengreuth G, et al. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density substudy. *Lancet Oncol* 2008;9:840-9.
- Gnant M, Mlineritsch B, Luschin-Ebengreuth G, et al. Zoledronic acid prevents cancer treatment-induced bone loss in premenopausal women receiving adjuvant endocrine therapy for hormone-responsive breast cancer: a report from the Austrian Breast and Colorectal Cancer Study Group. *J Clin Oncol* 2007;25:820-8.
- Avilés A, Nambo MJ, Neri N, Castañeda C, Cleto S, Huerta-Guzmán J. Antitumor effect of zoledronic acid in previously untreated patients with multiple myeloma. *Med Oncol* 2007;24:227-30.
- Daubiné F, Le Gall C, Gasser J, Green J, Clézardin P. Antitumor effects of clinical dosing regimens of bisphosphonates in experimental breast cancer bone metastasis. *J Natl Cancer Inst* 2007;99:322-30.
- Lin A, Park J, Melisko M, et al. Zoledronic acid as adjuvant therapy for women with early stage breast cancer and disseminated tumor cells in bone marrow. Presented at the 6th European Breast Cancer Conference (EBCC-6), Berlin, April 15-19, 2008 (poster).
- Mystakidou K, Katsouda E, Parpa E, Kelekis A, Galanos A, Vlahos L. Randomized, open label, prospective study on the effect of zoledronic acid on the prevention of bone metastases in patients with recurrent solid tumors that did not present with bone metastases at baseline. *Med Oncol* 2005;22:195-201.
- Santini D, Vincenzi B, Galluzzo S, et al. Repeated intermittent low-dose therapy with zoledronic acid induces an early, sustained, and long-lasting decrease of peripheral vascular endothelial growth factor levels in cancer patients. *Clin Cancer Res* 2007;13:4482-6.
- Reiner A, Neumeister B, Spona J, Reiner G, Schemper M, Jakesz R. Immunocytochemical localization of estrogen and progesterone receptor and prognosis in human primary breast cancer. *Cancer Res* 1990;50:7057-61.
- Rosen LS, Gordon D, Kaminski M, et al. Zoledronic acid versus pamidronate in

- the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. *Cancer J* 2001;7:377-87.
25. Draxler W, Mittlböck M. Basic principles in the planning of clinical trials in surgical oncology. *Eur Surg J* 2006;38:27-32.
 26. Cox DR. Regression models and life-tables. *J R Stat Soc [B]* 1972;34:187-220.
 27. Akaike H. A new look at the statistical model identification. *IEEE Trans Automat Control* 1974;19:716-23.
 28. Howell A, Cuzick 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.
 29. Wolff AC, Davidson NE. Still waiting after 110 years: the optimal use of ovarian ablation as adjuvant therapy for breast cancer. *J Clin Oncol* 2006;24:4949-51.
 30. Bria E, Nistico C, Cuppone F, et al. Benefit of taxanes as adjuvant chemotherapy for early breast cancer: pooled analysis of 15,500 patients. *Cancer* 2006;106:2337-44.
 31. Jagdev SP, Coleman RE, Shipman CM, Rostami-H A, Croucher PI. The bisphosphonate, zoledronic acid, induces apoptosis of breast cancer cells: evidence for synergy with paclitaxel. *Br J Cancer* 2001;84:1126-34.
 32. Senaratne SG, Pirianov G, Mansi JL, Arnett TR, Colston KW. Bisphosphonates induce apoptosis in human breast cancer cell lines. *Br J Cancer* 2000;82:1459-68.
 33. Winter MC, Holen I, Coleman RE. Exploring the anti-tumour activity of bisphosphonates in early breast cancer. *Cancer Treat Rev* 2008;34:453-75.
 34. Croucher PI, De Raeve H, Perry MJ, et al. Zoledronic acid treatment of 5T2MM-bearing mice inhibits the development of myeloma bone disease: evidence for decreased osteolysis, tumor burden and angiogenesis, and increased survival. *J Bone Miner Res* 2003;18:482-92.
 35. Hiraga T, Williams PJ, Ueda A, Tamura D, Yoneda T. Zoledronic acid inhibits visceral metastases in the 4T1/luc mouse breast cancer model. *Clin Cancer Res* 2004;10:4559-67.
 36. Rack BK, Jueckstock J, Genss EM, et al. Effect of zoledronate on persisting isolated tumor cells in the bone marrow of patients without recurrence of early breast cancer. Presented at the 30th Annual San Antonio Breast Cancer Symposium (SABCS), San Antonio, December 13–16, 2007 (poster).
 37. Dieli F, Vermijlen D, Fulfaro F, et al. Targeting human gammadelta T cells with zoledronate and interleukin-2 for immunotherapy of hormone-refractory prostate cancer. *Cancer Res* 2007;67:7450-7.
 38. Kunzmann V, Bauer E, Feurle J, Weissinger F, Tony HP, Wilhelm M. Stimulation of gammadelta T cells by aminobisphosphonates and induction of anti-plasma cell activity in multiple myeloma. *Blood* 2000;96:384-92.
 39. Brufsky A, Bundred N, Coleman R, et al. Integrated analysis of zoledronic acid for prevention of aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole. *Oncologist* 2008;13:503-14.
 40. Zaghoul MS, Boutrus R, El-Hosieny H, A-Kader Y, El-Attar I, Nazmy M. A controlled prospective randomized placebo-controlled trial of zoledronic acid in bony metastatic bladder cancer patients. *J Clin Oncol* 2008;26:Suppl:257s. abstract.
 41. Hirsh V, Major PP, Lipton A, et al. Zoledronic acid and survival in patients with metastatic bone disease from lung cancer and elevated markers of osteoclast activity. *J Thorac Oncol* 2008;3:228-36.
 42. Lipton A, Cook R, Saad F, et al. Normalization of bone markers is associated with improved survival in patients with bone metastases from solid tumors and elevated bone resorption receiving zoledronic acid. *Cancer* 2008;113:193-201.
 43. Aft R, Watson M, Ylagan L, et al. Effect of zoledronic acid on bone marrow micrometastases in women undergoing neoadjuvant chemotherapy for breast cancer. *J Clin Oncol* 2008;26:Suppl:46s. abstract.
 44. Diel IJ, Solomayer EF, Costa SD, et al. Reduction in new metastases in breast cancer with adjuvant clodronate treatment. *N Engl J Med* 1998;339:357-63.
 45. Ha TC, Li H. Meta-analysis of clodronate and breast cancer survival. *Br J Cancer* 2007;96:1796-801.
 46. Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med* 2003;349:1793-802.
 47. Diel IJ, Fogelman I, Al-Nawas B, et al. Pathophysiology, risk factors and management of bisphosphonate-associated osteonecrosis of the jaw: is there a diverse relationship of amino- and non-aminobisphosphonates? *Crit Rev Oncol Hematol* 2007;64:198-207.
 48. Khosla S, Burr D, Cauley J, et al. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 2007;22:1479-91.
 49. Weitzman R, Sauter N, Eriksen EF, et al. Critical review: updated recommendations for the prevention, diagnosis, and treatment of osteonecrosis of the jaw in cancer patients — May 2006. *Crit Rev Oncol Hematol* 2007;62:148-52.

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CORRECTION

Endocrine Therapy plus Zoledronic Acid in Premenopausal Breast Cancer

To the Editor: Gnant et al. (Feb. 12 issue)¹ report on the Austrian Breast and Colorectal Cancer Study Group trial 12 (ABCSG-12) (ClinicalTrials.gov number, NCT00295646), which looked at the use of goserelin plus either tamoxifen or anastrozole with or without zoledronic acid in premenopausal women with breast cancer. The authors conclude that the addition of zoledronic acid improved disease-free survival and that treatment with tamoxifen and treatment with anastrozole were associated with similar rates of disease-free survival. However, a separate analysis of the group of patients who received anastrozole without zoledronic acid would be of interest.

Frederik Wenz, M.D.

University Medical Center Mannheim
68167 Mannheim, Germany
frederik.wenz@medma.uni-heidelberg.de

References

1. Gnant M, Mlineritsch B, Schippinger W, et al. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *N Engl J Med* 2009;360:679-691.

To the Editor: Gnant et al. report a 4-year rate of 90.8% for disease-free survival in the group of premenopausal women with breast cancer who received endocrine therapy alone and a rate of 94.0% in the group that received endocrine therapy plus zoledronic acid. Data from this trial that were presented at the American Society of Clinical Oncology meeting in 2008 showed that the effect of zoledronic acid was driven almost exclusively by the findings in the cohort of patients who received anastrozole, whereas little effect was discernible for the patients who received tamoxifen. With only 137 events contributing to these analyses, the test for interaction comparing the effectiveness of zoledronic acid between the anastrozole group and the tamoxifen group is expected to be nonsignificant. What was the effect of zoledronic acid on the anastrozole and tamoxifen groups?

Richard D. Gelber, Ph.D.
Dana-Farber Cancer Institute
Boston, MA 02115

Stefan Aebi, M.D.
Bern University Hospital
CH-3010 Bern, Switzerland

To the Editor: Gnant et al. describe the results of the combination of tamoxifen plus goserelin; however, this combined therapy is not a standard option for the typical premenopausal patient with breast cancer enrolled in this study. In most centers, outside the context

of a clinical trial, such patients would be offered 5 years of tamoxifen plus or minus chemotherapy,¹ with the possible addition of ovarian ablation for women under the age of 35 years who did not have chemotherapy-induced amenorrhea.^{2,3} The combination of ovarian suppression and tamoxifen is being prospectively addressed in the Suppression of Ovarian Function Trial (SOFT) (ClinicalTrials.gov number, NCT00066690). In addition, the duration of the tamoxifen exposure (3 years) cannot be considered a standard, level I, evidence-based form of adjuvant hormonal therapy.

Artur Katz, M.D.
Aknar Calabrich, M.D.
Hospital Sirio Libanes
01308-050 São Paulo, Brazil
artkatz@uol.com.br

Everardo D. Saad, M.D.
Dendrix Research
04534-000 São Paulo, Brazil

References

1. Goldhirsch A, Wood WC, Gelber RD, Coates AS, Thürlimann B, Senn HJ. Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007. *Ann Oncol* 2007;18:1133-1144. [Erratum, *Ann Oncol* 2007;18:1917.]
2. Rabaglio M, Aebi S, Castiglione-Gertsch M. Controversies of adjuvant endocrine treatment for breast cancer and recommendations of the 2007 St Gallen Conference. *Lancet Oncol* 2007;8:940-949.
3. Goldhirsch A, Gelber RD, Yothers G. Adjuvant therapy for very young women with breast cancer: need for tailored treatments. In: The National Institutes of Health Consensus Development Conference: adjuvant therapy for breast cancer. *Journal of the National Cancer Institute Monographs*. No. 30. Bethesda, MD: National Cancer Institute, December 2001:44-51.

To the Editor: Gnant et al. did not compare disease-free survival between the group of patients who received goserelin plus tamoxifen plus zoledronic acid and the group that received goserelin plus anastrozole plus zoledronic acid. An uneven distribution of HER-2/neu overexpression among the groups might have influenced the outcomes of this study. Predictive markers such as HER-2/neu overexpression should be included in the analysis.

Lin Nan Li, Ph.D.
Peng Wen Dong, M.D.
Xijing Hospital
Xi'an 710032, China
linanlin@fmmu.edu.cn

To the Editor: In Table 2 of the article by Gnant et al., there is a trend favoring tamoxifen with respect to distant recurrence and death. In the

two groups of patients who received endocrine therapy, there were 15 deaths in the tamoxifen group, as compared with 27 in the anastrozole group (hazard ratio, 1.80; 95% confidence interval, 0.95 to 3.38). The P value of 0.70 for overall survival (as presented in Fig. 2E of the article) is not understandable; we would expect a P value of 0.07 on the basis of the 95% confidence interval and event numbers.

Toralf Reimer, M.D.

Bernd Gerber, M.D., Ph.D.

University of Rostock

18059 Rostock, Germany

toralf.reimer@med.uni-rostock.de

To the Editor: Gnant et al. report that six doses of zoledronic acid prolonged disease-free survival in premenopausal patients with breast cancer who were undergoing adjuvant endocrine therapy. Bisphosphonates are commonly prescribed in association with vitamin D supplementation. However, there is no mention as to whether vitamin D was prescribed to patients in this trial.

Vitamin D decreases the cellular proliferation of cancer cells,¹ so that vitamin D supplementation represents a potential confounder in the interpretation of the study results. In addition, hypovitaminosis D is relatively common in premenopausal women,² and this condition may be worsened by estrogen deprivation.³ Vitamin D deficiency in early breast cancer has been found to be associated with an increased risk of distant recurrence and death.⁴

On these grounds, it would be interesting to know whether any of the patients who were treated with zoledronic acid received vitamin D supplementation, whether these patients had a different outcome, and whether there was an interaction in terms of outcome between zoledronic acid and anastrozole.

Alfredo Berruti, M.D.

Consuelo Buttigliero, M.D.

Luigi Dogliotti, M.D.

University of Turin

10043 Orbassano, Italy

alfredo.berruti@gmail.com

References

- Holick MF. Vitamin D: its role in cancer prevention and treatment. *Prog Biophys Mol Biol* 2006;92:49-59.
- Nesby-O'Dell S, Scanlon KS, Cogswell ME, et al. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: third National Health and Nutrition Examination Survey, 1988-1994. *Am J Clin Nutr* 2002;76:187-192.
- Dick IM, Prince RL, Kelly JJ, Ho KK. Oestrogen effects on calcitriol levels in post-menopausal women: a comparison of oral versus

transdermal administration. *Clin Endocrinol (Oxf)* 1995;43:219-224.

- Goodwin PJ, Ennis M, Pritchard KI, Koo J, Hood N. Frequency of vitamin D (Vit D) deficiency at breast cancer (BC) diagnosis and association with risk of distant recurrence and death in a prospective cohort study of T1-3, N0-1, M0 BC. *J Clin Oncol* 2008;26:Suppl:9s-9s.

To the Editor: The pharmacokinetic properties of zoledronic acid do not support the hypothesis of Gnant et al. that this drug has antitumor effects in tissue other than bone. After intravenous administration, bisphosphonates spread in calcified and noncalcified tissues, but their levels decline quickly in noncalcified tissues, and the decline is proportionate to the decrease in the plasma concentration.^{1,2} In animal models, repeated injections of zoledronic acid (every 4 days) were required to reduce the number of metastatic foci outside bone, in which zoledronic acid did not induce apoptosis.³

Bone marrow-derived mesenchymal stem cells are recruited to the stroma of developing tumors. Karnoub et al.⁴ demonstrated that mesenchymal stem cells greatly increase the metastatic potential of breast-cancer cells by secreting chemokines and growth factors that sustain breast-cancer migration, invasion, and metastases. In this regard, we have recently shown that zoledronic acid affects the ability of mesenchymal stem cells to secrete angiogenic factors that promote breast-cancer metastasis.⁵ We propose that the antitumor activity of zoledronic acid in patients with breast cancer is related to its action on mesenchymal stem cells within the bone marrow microenvironment.

Antonella De Luca, Ph.D.

Nicola Normanno, M.D.

Istituto Nazionale Tumori Fondazione Pascale

80131 Naples, Italy

nicnorm@yahoo.com

References

- Chen T, Berenson J, Vescio R, et al. Pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with bone metastases. *J Clin Pharmacol* 2002;42:1228-1236.
- Lin JH. Bisphosphonates: a review of their pharmacokinetic properties. *Bone* 1996;18:75-85.
- Hiraga T, Williams PJ, Ueda A, Tamura D, Yoneda T. Zoledronic acid inhibits visceral metastases in the 4T1/luc mouse breast cancer model. *Clin Cancer Res* 2004;10:4559-4567.
- Karnoub AE, Dash AB, Vo AP, et al. Mesenchymal stem cells within tumour stroma promote breast cancer metastasis. *Nature* 2007;449:557-563.

5. De Luca A, Gallo M, Maiello M, et al. Zoledronic acid affects the expression of VEGF in breast cancer cells and in bone marrow stromal cells through direct and indirect mechanisms. Presented at the 99th Annual Meeting of the American Association for Cancer Research, San Diego, CA, April 12–16, 2008.

The author replies: In response to Wenz, Gelber and Aebi, Katz et al., Li and Dong, and Reimer and Gerber: according to St. Gallen and National Comprehensive Cancer Network guidelines, goserelin plus tamoxifen is an accepted treatment for premenopausal patients with endocrine-responsive breast cancer, and luteinizing hormone-releasing hormone agonists alone are associated with a strong trend toward reduced rates of recurrence and death.¹ In the ABCSG-12 study, the selection of 3 years of endocrine therapy was based on the findings of the ABCSG-5 trial (ClinicalTrials.gov number, NCT00309478) (which examined 3 years of goserelin, then 5 years of tamoxifen).² However, 5 years of continuous endocrine therapy may not be necessary in this low-risk population, since it would be difficult to improve the 98.2% 4-year overall survival achieved in the group receiving zoledronic acid in the ABCSG-12 trial. We agree that long-term follow-up of SOFT and Triptorelin with Exemestane on Tamoxifen (TEXT) (NCT00066703) may provide more definitive guidance on the use of aromatase inhibitors in premenopausal patients with breast cancer.

The ABCSG-12 study was designed and powered to show whether the addition of zoledronic acid to endocrine therapy improved outcomes, as compared with endocrine therapy alone. A specific interaction test did not reveal any difference in the treatment effect between the group receiving anastrozole plus zoledronic acid and the group receiving tamoxifen plus zoledronic acid. Therefore, at this time, it is not possible to conclude that the effect of zoledronic acid was driven primarily by the findings in one cohort. Longer follow-up of the zoledronic acid effect may help to determine whether meaningful differences exist.

Reimer and Gerber are correct in pointing out that there was a non-significant trend favoring tamoxifen over anastrozole for survival, and both P values in Figure 2E should be 0.07 rather than 0.70. (The article has been corrected at NEJM.org.)

In response to Li and Dong: we did not prospectively determine the HER-2/neu status of patients in our study. However, since patients underwent randomization, the proportion of HER-2/neu-positive patients is likely to have been balanced among the study groups and is unlikely to have confounded the trial outcomes.

In response to Berruti et al.: vitamin D levels and vitamin D supplementation were not part of our protocol and therefore were not prospectively recorded. However, we agree that this could be an important factor and should be elucidated in future trials of adjuvant bisphosphonates.

We agree with De Luca and Normanno that the antitumor effects of zoledronic acid may be mediated by preventing the secretion of an-

giogenic factors by mesenchymal stem cells in bone marrow. This is entirely consistent with the idea that zoledronic acid makes the bone-and-marrow microenvironment less favorable "soil" for tumor-cell growth. One hypothesis is that bone may provide a sanctuary for dormant micrometastases that may later seed distant metastases. Preliminary clinical data suggest that the antitumor activity of zoledronic acid may include the inhibition of angiogenesis, immunostimulatory effects through the activation of gamma delta T cells,³ and a reduction in the number of disseminated tumor cells in bone marrow.⁴ In addition, recent results from the neoadjuvant subgroup analysis of the Adjuvant Zoledronic Acid to Reduce Recurrence (AZURE) (NCT00072020) trial indicate that zoledronic acid has direct antitumor activity.⁵ Therefore, stimulation of a wide array of antitumor effects by zoledronic acid may inhibit disease progression in areas other than bone in patients with breast cancer.

Michael Gnant, M.D.
 Medical University of Vienna
 A-1090 Vienna, Austria
 michael.gnant@meduniwien.ac.at

for the ABCSG-12 Trial Investigators

References

1. Cuzick J, Ambrosine L, Davidson N, et al. 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;369:1711-1723.
2. Jakesz R, Hausmaninger H, Kubista E, et al. Randomized adjuvant trial of tamoxifen and goserelin versus cyclophosphamide, methotrexate, and fluorouracil: evidence for the superiority of treatment with endocrine blockade in premenopausal patients with hormone-responsive breast cancer – Austrian Breast and Colorectal Cancer Study Group Trial 5. *J Clin Oncol* 2002;20:4621-4627.
3. Santini D, Martini F, Fratto ME, et al. In vivo effects of zoledronic acid on peripheral gammadelta T lymphocytes in early breast cancer patients. *Cancer Immunol Immunother* 2009;58:31-38.
4. Lin AY, Park JW, Scott J, et al. Zoledronic acid as adjuvant therapy for women with early stage breast cancer and disseminated tumor cells in bone marrow. *J Clin Oncol* 2008;26:Suppl:20s-20s.
5. Winter MC, Thorpe HC, Burkinshaw R, Beevers SJ, Coleman RE. The addition of zoledronic acid to neoadjuvant chemotherapy may influence pathological response — exploratory evidence for direct anti-tumor activity in breast cancer. Presented at the 31st Annual San Antonio Breast Cancer Symposium (SABCS), San Antonio, TX, December 11–13, 2008. poster.