Daily oral ibandronate with adjuvant endocrine therapy in postmenopausal women with estrogen receptor–positive breast cancer (BOOG 2006-04) randomized phase III TEAM-IIB trial

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Daily Oral Ibandronate With Adjuvant Endocrine Therapy in Postmenopausal Women With Estrogen Receptor–Positive Breast Cancer (BOOG 2006-04): Randomized Phase III TEAM-IIB Trial

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abstract

PURPOSE For postmenopausal patients with breast cancer, previous subgroup analyses have shown a modest benefit from adjuvant bisphosphonate treatment. However, the efficacy of oral nitrogen-containing bisphosphonates such as ibandronate is unclear in this setting. TEAM-IIB investigates adjuvant ibandronate in postmenopausal women with estrogen receptor–positive (ER+) breast cancer.

METHODS TEAM-IIB is a randomized, open-label, multicenter phase III study. Postmenopausal women with stage I-III ER+ breast cancer and an indication for adjuvant endocrine therapy (ET) were randomly assigned 1:1 to 5 years of ET with or without oral ibandronate 50 mg once daily for 3 years. Major ineligibility criteria were bilateral breast cancer, active gastroesophageal problems, and health conditions that might interfere with study treatment. Primary end point was disease-free survival (DFS), analyzed in the intention-to-treat population.

RESULTS Between February 1, 2007, and May 27, 2014, 1,116 patients were enrolled, 565 to ET with ibandronate (ibandronate arm) and 551 to ET alone (control arm). Median follow-up was 8.5 years. DFS was not significantly different between the ibandronate and control arms (HR, 0.97; 95% CI, 0.76 to 1.24; log-rank $P = .811$). Three years after random assignment, DFS was 94% in the ibandronate arm and 91% in the control arm. Five years after random assignment, this was 89% and 86%, respectively. In the ibandronate arm, 97/565 (17%) of patients stopped ibandronate early because of adverse events. Significantly more patients experienced GI issues, mainly dyspepsia, in the ibandronate arm than in the control arm (89 [16%] and 54 [10%], respectively; $P < .003$). Eleven patients in the ibandronate arm developed osteonecrosis of the jaw.

CONCLUSION In postmenopausal women with ER+ breast cancer, adjuvant ibandronate 50 mg once daily does not improve DFS and should not be recommended as part of standard treatment regimens.

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ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Metastatic spread of breast cancer is still the leading cause of cancer-related mortality in women.[1] Because hormone receptor–positive breast cancer cells prefer an osseous microenvironment, about 70% of breast cancer metastases are bone recurrences.[2,3] Nitrogen-containing bisphosphonates such as ibandronate affect bone metabolism by inhibiting key enzymes of the intracellular mevalonate pathway.[4] This decreases osteoclast-mediated bone resorption and osteoclast survival, causing an increase in bone density and a decreased release of cytokines and growth factors.[5] Preclinical studies suggest a direct antitumor effect by inhibition of tumor proliferation, induction of apoptosis, and enhanced immunosurveillance.[6] However, the exact anticancer mechanism of bisphosphonates is still unclear.

Several trials have investigated the effect of (neo)adjuvant bisphosphonates on cancer recurrence.[7-9] In 2015, a meta-analysis of 26 trials comparing patients treated with and without adjuvant bisphosphonates showed a reduction in breast cancer recurrence and mortality in the subgroup of women who were postmenopausal at the onset of treatment, but not in the

CONTEXT

Key Objective

Most distant breast cancer recurrences are bone relapses. Nitrogen-containing bisphosphonates such as ibandronate alter bone metabolism and can theoretically reduce the risk of bone recurrences. Previous subgroup analyses have suggested that postmenopausal patients can benefit from bisphosphonate treatment combined with endocrine therapy. The randomized TEAM-IIB trial investigates adjuvant oral ibandronate for postmenopausal patients with hormone receptor–positive breast cancer.

Knowledge Generated

Although the ibandronate arm seemed to have better disease-free survival and less bone recurrences at 3 years after random assignment, with longer follow-up, both arms have similar disease-free survival and recurrence rates. Around 17% of patients in the ibandronate arm stopped treatment early because of adverse events.

Relevance

It is still an unresolved question which is the optimal class, dose, schedule, and treatment duration of bisphosphonates, and which postmenopausal patients should be selected for bisphosphonate treatment. TEAM-IIB study results suggest that 3-year daily ibandronate should not be the recommended strategy.

premenopausal subgroup.[10] Thus far, the use of nitrogen-containing bisphosphonates has not been studied in exclusively postmenopausal patients.

The randomized TEAM-IIB trial investigates the addition of daily oral ibandronate to adjuvant endocrine therapy (ET) in postmenopausal women with estrogen receptor–positive (ER+) breast cancer. The registered dose of ibandronate to reduce skeletal events in the metastatic setting was used (50 mg once daily). This paper describes the results of the TEAM-IIB trial, including safety and toxicity.

METHODS

TEAM-IIB is a randomized, open-label multicenter clinical phase III trial, conducted in 37 hospitals in the Netherlands. The study protocol (Protocol, online only) was approved by the Medical Ethics Committee of the Netherlands Cancer Institute.

Participants

Eligible patients were postmenopausal and diagnosed with invasive stage I-III ER+ breast cancer, defined as estrogen receptor $\geq$ 10% (estrogen receptor–positive) and/or progesterone receptor $\geq$ 10% (progesterone receptor–positive). Patients had completed locoregional treatment and (neo)adjuvant chemotherapy following national guidelines, and had an indication for adjuvant ET. Postmenopausal status was defined as age $\geq$ 50 years and amenorrhea for $>$ 1 year at diagnosis, or bilateral surgical oophorectomy and no use of hormone replacement therapy. In case of doubt, postmenopausal status was confirmed biochemically.

Exclusion criteria were bilateral breast cancer, prior invasive breast cancer in the past 15 years, a history of bone disease with potential interference of bone metabolism, active dental or gastroesophageal problems, a creatinine clearance of $<$ 30 mL/min, and other conditions that might interfere with the study treatment or determination of causality of adverse events (AEs).

Random Assignment

All patients provided written informed consent for inclusion in the study. Patients were enrolled by local investigators and were centrally randomly assigned. Details on stratification are described in Appendix 1 (online only).

Procedures

Included patients were randomly assigned to either ET (control arm) or ET combined with ibandronate (ibandronate arm). For ET, the study protocol followed the guidelines of the National Breast cancer Organization of the Netherlands,[11] meaning all patients with human epidermal growth factor receptor 2–negative (HER2–) disease were to be prescribed tamoxifen (TAM) 20 mg once daily for 2-3 years, followed by exemestane 25 mg once daily for 2-3 years, for a total of at least 5 years. Patients with HER2+ breast cancer, or patients who received neoadjuvant exemestane in the TEAM-IIA trial, were treated with exemestane monotherapy for 5 years.[12] Extended use of ET was given according to the Dutch national guidelines. In the ibandronate arm, patients additionally received oral ibandronate 50 mg once daily for 3 years.

All patients were followed until at least 10 years after random assignment. Patients diagnosed with osteonecrosis of the jaw (ONJ) during follow-up had to stop ibandronate immediately. Patients with a history of osteoporosis, defined by a T-score of $<$ –2.5 by dual-energy X-ray absorptiometry (DEXA) scan, were allowed to participate, and if randomly assigned to the control arm, they were allowed to continue their own bisphosphonate for 3 years or switch to ibandronate 150 mg once a month combined with calcium and vitamin D. A sensitivity

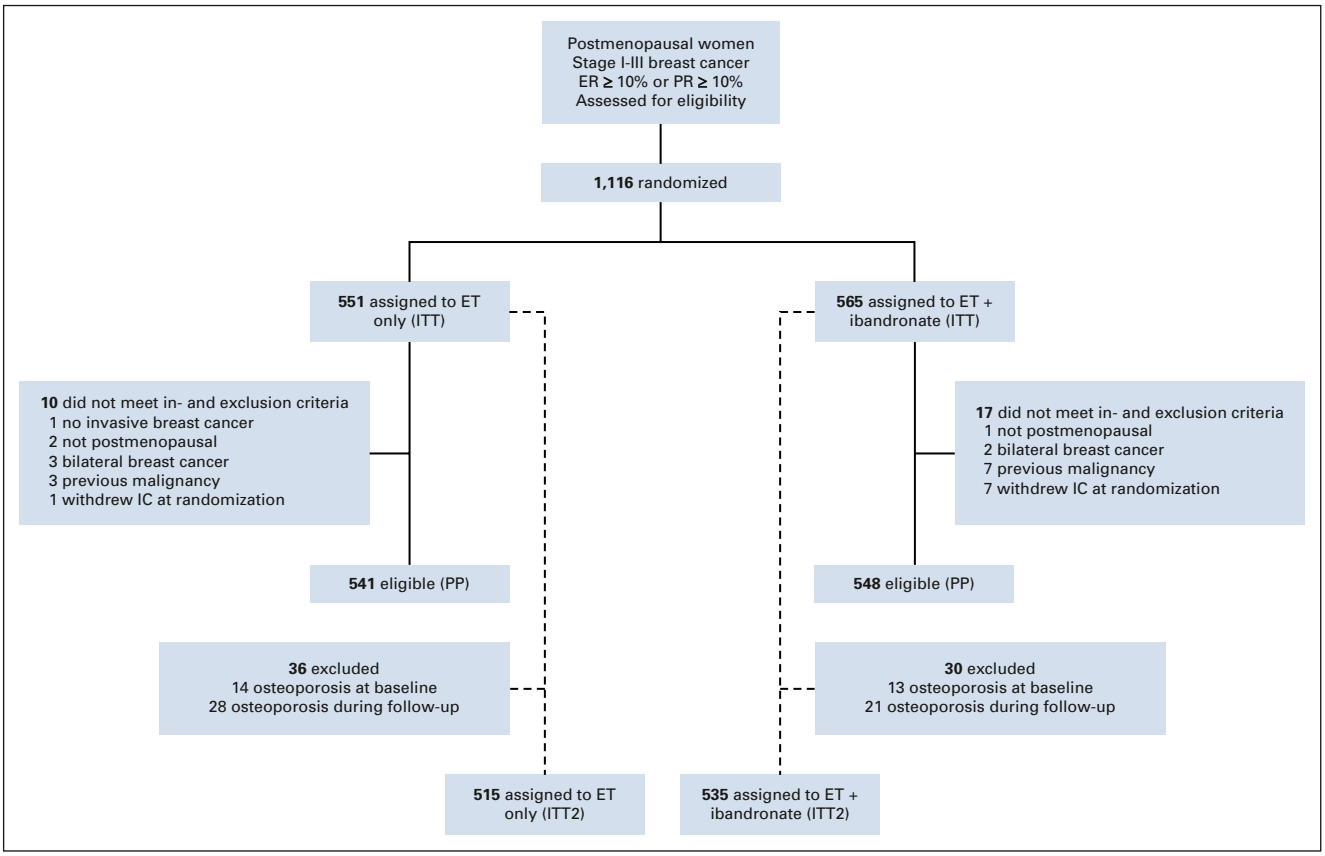

FIG 1. CONSORT diagram. ER, estrogen receptor; ET, endocrine therapy; IC, informed consent; ITT, intention-to-treat; PP, per-protocol; PR, progesterone receptor.

analysis was predefined in the study protocol to assess any diluting effect.

DEXA scans were recommended for all patients starting with exemestane treatment at baseline and 3 years after starting treatment. Detailed information about follow-up intervals and assessments at each visit is described in the study protocol (Protocol).

An independent data monitoring committee regularly reviewed the progress and safety of the trial. The independent data monitoring committee also reviewed the interim analysis, which was performed after enrollment of 100 patients. This is described in Appendix 1.

Outcomes

The primary end point was 3-year disease-free survival (DFS), which included any breast cancer recurrence, second primary breast cancer, ductal carcinoma in situ, or death of any cause as event. DFS was calculated between random assignment and the occurrence of an event or end of follow-up, whichever came first.[13]

Secondary end points were 5-year DFS, overall survival (OS), and recurrence-free interval (RFi), defined as the interval between random assignment and any breast cancer recurrence, excluding contralateral breast cancer and ductal carcinoma in situ. Other end points were cumulative incidence rates of locoregional recurrence, distant recurrence, bone metastases, and visceral metastases. Appendix 1 provides detailed information on all outcome measures.

AEs were assessed during the first 3 years after random assignment, using the Common Terminology Criteria for Adverse Events version 3.0 for collection and version 4.03 for analysis.

Statistical Analysis

Initially, a 91% and 94% 3-year DFS was assumed for the control and ibandronate arms, respectively. To achieve a power of 90% and an alpha of 5% for a two-sided log-rank test, 2,058 patients needed to be included. The trial protocol was amended in June 2009 because accrual was slower than expected. The power was decreased from 90% to 80%, the inclusion period was extended from 4 to 6 years, and on the basis of data from the TEAM trial,[14] the assumed DFS was increased to 92% and 95% for the control and ibandronate arms, respectively. This resulted in an adjusted sample size of 1,116 patients.

Primary and secondary end points were analyzed in the intention-to-treat (ITT) population, defined as all randomly assigned patients (ITT). A predefined sensitivity analysis

TABLE 1. Baseline Characteristics of the Intention-to-Treat Population

Characteristic	All	Ibandronate	Control
Total, No.	1,116	565 (50.6)	551 (49.4)
Age, years			
< 50	27 (2.4)	16 (2.8)	11 (2.0)
50-59	424 (38.0)	210 (37.2)	214 (38.8)
60-69	470 (42.1)	244 (43.2)	226 (41.0)
≥ 70	195 (17.5)	95 (16.8)	100 (18.1)
Median (IQR)	62 (56-67)	62 (57-67)	62 (56-67)
BMI, kg/m^2			
Median (IQR)	26.5 (23.7-30.1)	26.4 (23.5-30.1)	26.7 (24.1-30.4)
Pathologic tumor size[a]			
Tis	1 (0.1)	1 (0.2)	0 (0.0)
T1	634 (56.8)	325 (57.5)	309 (56.1)
T2	414 (37.1)	210 (37.2)	204 (37.0)
T3	43 (3.9)	16 (2.8)	27 (4.9)
T4	21 (1.9)	11 (1.9)	10 (1.8)
Unknown	3 (0.3)	2 (0.4)	1 (0.2)
Nodal status			
N0/N0(i+)	558 (50.0)	287 (50.8)	271 (49.2)
N1	428 (38.4)	213 (37.7)	215 (39.0)
N2	88 (7.9)	43 (7.6)	45 (8.2)
N3	38 (3.4)	19 (3.4)	19 (3.4)
Unknown	4 (0.3)	3 (0.5)	1 (0.2)
Histologic grade			
1	157 (14.1)	66 (11.7)	91 (16.5)
2	631 (56.5)	330 (58.4)	301 (54.6)
3	290 (26.0)	148 (26.2)	142 (25.8)
Unknown	38 (3.4)	21 (3.7)	17 (3.1)
Histologic subtype			
Ductal	861 (77.2)	441 (78.1)	420 (76.2)
Lobular	156 (14.0)	73 (12.9)	83 (15.1)
Other	96 (8.6)	49 (8.7)	47 (8.6)
Unknown	3 (0.2)	2 (0.4)	1 (0.2)
HER2 status			
Negative	1,010 (90.5)	510 (90.3)	500 (90.7)
Positive	106 (9.5)	55 (9.7)	51 (9.3)
Hormone receptor status			
ER+/PR+	823 (73.7)	417 (73.8)	406 (73.7)
ER+/PR–	287 (25.7)	147 (26.0)	140 (25.4)
ER–/PR+	6 (0.5)	1 (0.2)	5 (0.9)
Chemotherapy			
Anthracycline	179 (16.0)	95 (16.8)	84 (15.2)
Anthracycline plus taxane	422 (37.8)	213 (37.7)	209 (37.9)
Other	22 (2.0)	10 (1.8)	12 (2.2)
None	493 (44.2)	247 (43.7)	246 (44.6)

(continued on following page)

TABLE 1. Baseline Characteristics of the Intention-to-Treat Population (continued)

Characteristic	All	Ibandronate	Control
Anti-HER2 medication[b]			
Yes, No./n (%)	75/106 (70.8)	42/55 (76.4)	33/51 (64.7)
No, No./n (%)	31/106 (29.2)	13/55 (23.6)	18/51 (35.3)
ET			
AI only	189 (16.9)	91 (16.1)	98 (17.8)
TAM → AI	839 (75.2)	426 (75.4)	413 (75.0)
TAM only	65 (5.8)	36 (6.4)	29 (5.3)
Other	21 (1.9)	10 (1.8)	11 (2.0)
Unknown	2 (0.2)	2 (0.4)	0 (0.0)
Median duration, years (IQR)	5.01 (4.78-5.27)	5.01 (4.89-5.42)	5.00 (4.58-5.22)
Bisphosphonates at baseline			
Yes	11 (1.0)	2 (0.4)	9 (1.6)
No	1,103 (98.8)	561 (99.3)	542 (98.4)
Unknown	2 (0.2)	2 (0.4)	0 (0.0)

NOTE. Data are No. (%) unless otherwise indicated. Because of rounding, percentages may not total to 100%.

Abbreviations: AI, aromatase inhibitor; BMI, body mass index; ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; IQR, interquartile range; PR, progesterone receptor; TAM, tamoxifen; Tis, tumor in situ.

[a]117 patients received neoadjuvant systemic treatment, and clinical size was reported for these patients.

[b]Out of number of patients who had HER2 expression.

was performed on the ITT population excluding patients with osteoporosis diagnosed by routine DEXA scans (ITT2). A predefined per-protocol (PP) analysis was performed on the ITT population excluding patients with major exclusion criteria violations (Fig 1).

DFS and OS were estimated using Kaplan-Meier survival analyses, and treatment arms were compared using log-rank tests. RFi and other cumulative incidence rates were estimated using competing risk survival analyses.[15] HRs and corresponding 95% CIs were estimated from Cox regression models. As predefined in the study protocol, Cox regression models were used to explore the influence of stratification and prognostic factors on DFS. Each factor was evaluated for inclusion in the multivariable model, and only factors significant at the 10% level were considered.

The proportional hazards assumption was assessed using the Schoenfeld residuals approach.[16] Since the proportional hazards assumption for randomized treatment was indeed violated for DFS, additional analyses were performed to address this issue. An interaction between treatment and time (using a categorical covariate distinguishing between the first time period, from random assignment to 3 years, and the second time period, starting at 3 years after random assignment until the end of follow-up) was added, which is an established method to estimate time-dependent treatment effects.[17] In univariate analyses, this is equivalent to separately estimating the HR over the second period by a landmark analysis, which included all patients that were event-free for DFS at 3 years after random assignment. Similar analyses were performed for the secondary end points.

Following the study protocol, chi-square tests were used to analyze differences in AEs between treatment groups in case the type of AE or the event frequency was judged to be clinically relevant.

Unplanned exploratory univariable subgroup analyses to test for heterogeneity of treatment effect were performed for DFS and RFi using prognostically relevant variables.

P values smaller than .05 were considered statistically significant. Data lock for the current analyses was set at March 19, 2021. Analyses were performed using SPSS version 26.0. and *R* version 3.5.2.

This study is registered with the Netherlands Trial Register, NL774.

RESULTS

Between February 1, 2007, and May 27, 2014 a total of 1,116 postmenopausal women were recruited and randomly assigned, of whom 551 to standard ET (the control arm) and 565 to daily oral ibandronate for 3 years combined with standard ET (the ibandronate arm; Fig 1). For the large majority of patients, standard ET equates 5 years. Some patients received extended ET, following Dutch national treatment guidelines.

Baseline characteristics are summarized in Table 1. The median age was 62 years (interquartile range, 56-67 years). 106/1,116 (10%) patients had HER2+ breast cancer, and

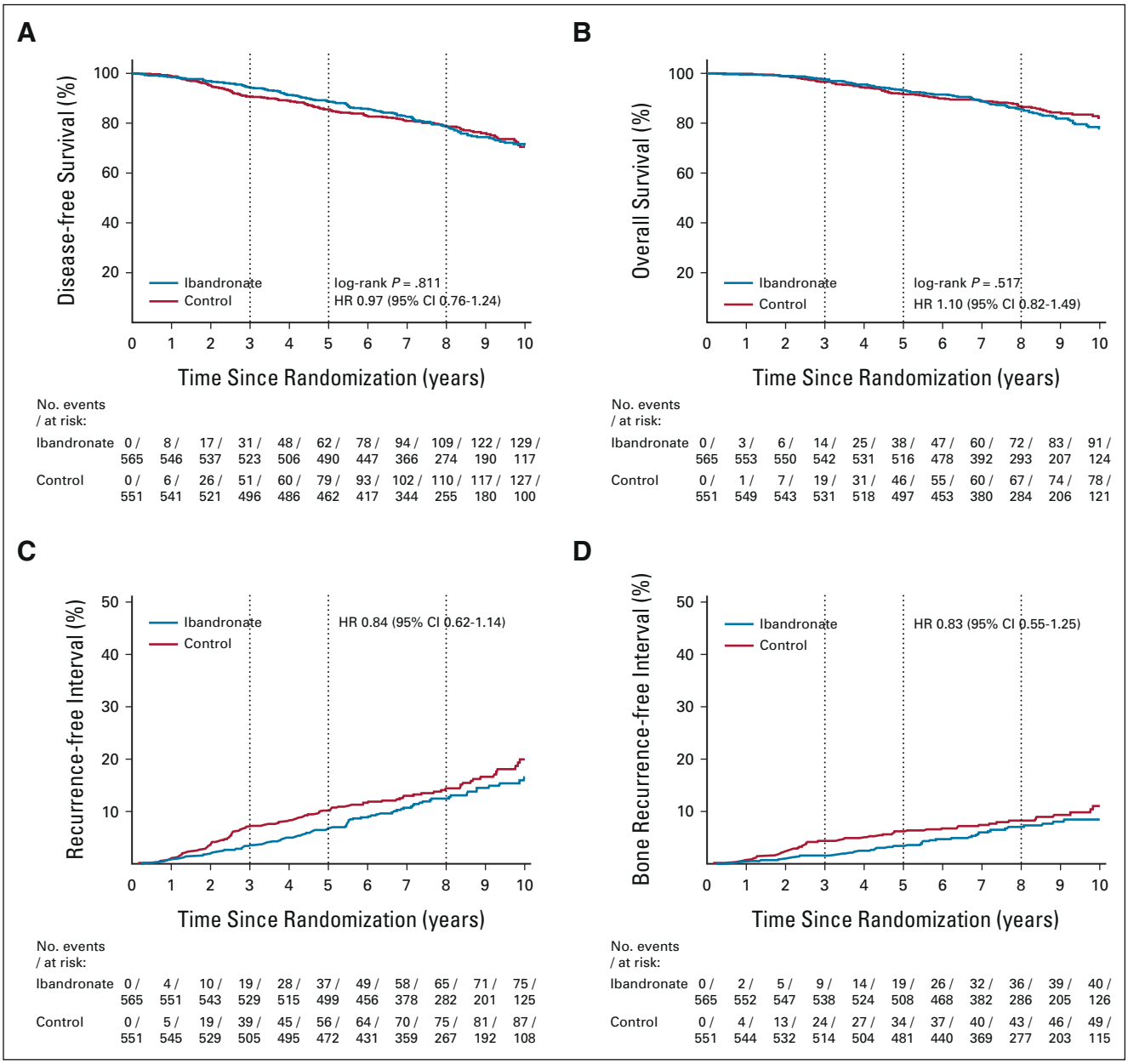

FIG 2. Kaplan-Meier estimates of (A) DFS and (B) OS, and (C) cumulative incidence estimates of any recurrence and (D) bone recurrences in the intention-to-treat population. DFS, disease-free survival; HR, hazard ratio; OS, overall survival; RFi, recurrence-free interval.

623/1,116 (56%) patients received chemotherapy. In 452/1,116 (41%) patients, the treating physician opted for an ET regimen that differed from the study protocol, such as 5 years of TAM monotherapy or a different aromatase inhibitor (AI) than exemestane. Median follow-up at data lock was 8.5 years (interquartile range, 7.1-10.0 years) after random assignment.

There was no significant difference in DFS between the ibandronate and control arms (HR, 0.97; 95% CI, 0.76 to 1.24; log-rank $P = .811$; Fig 2A). Three years after random assignment, there were 31 events in the ibandronate arm, resulting in a DFS of 94% (95% CI, 92 to 96), and 51 events in the control arm (DFS 91% [88 to 93]). At 5 years after random assignment, there were 62 events in the ibandronate arm (DFS 89% [86 to 91]) and 79 events in the control arm (DFS 86% [83 to 88]), and 8 years after random assignment, 109 in the ibandronate arm (DFS 79% [75 to 82]) and 110 in the control arm (DFS 79% [75 to 82]; Table 2).

The Schoenfeld residuals approach showed a violated proportional hazards assumption ($P = .024$; Appendix Fig A1, online only). Therefore, a potential interaction between time and treatment effect was examined. When truncated at 3 years after random assignment, DFS was numerically

TABLE 2. Primary and Secondary End Points on the Basis of Kaplan-Meier Survival Estimates (DFS and OS) and on Cumulative Incidence Estimates (Recurrences) in the Intention-to-Treat Population

	Ibandronate (n = 565)		Control (n = 551)	
Outcome Measure	**No. of Events/No. at Risk**	**Point Estimate (95% CI)**	**No. of Events/No. at Risk**	**Point Estimate (95% CI)**
DFS, years				
3	31/523	94% (92 to 96)	51/496	91% (88 to 93)
5	62/490	89% (86 to 91)	79/462	86% (83 to 88)
8	109/274	79% (75 to 82)	110/255	79% (75 to 82)
OS, years				
3	14/542	98% (96 to 99)	19/531	97% (95 to 98)
5	38/516	93% (91 to 95)	46/497	92% (89 to 94)
8	72/293	86% (83 to 89)	67/284	87% (84 to 90)
Any recurrence, years				
3	19/529	3% (2 to 5)	39/504	7% (5 to 10)
5	37/499	7% (5 to 9)	56/472	10% (8 to 13)
8	65/282	12% (10 to 16)	75/267	14% (12 to 18)
Locoregional recurrence, years				
3	7/537	1% (1 to 3)	11/523	2% (1 to 4)
5	13/506	2% (1 to 4)	18/485	3% (2 to 5)
8	21/289	4% (3 to 6)	24/273	5% (3 to 7)
Distant recurrence, years				
3	14/533	3% (2 to 4)	33/510	6% (4 to 8)
5	30/504	5% (4 to 8)	46/479	8% (6 to 11)
8	55/282	11% (8 to 14)	60/277	12% (9 to 15)
Bone recurrence, years				
3	9/537	2% (1 to 3)	24/513	4% (3 to 6)
5	19/508	3% (2 to 5)	34/481	6% (4 to 9)
8	36/286	7% (5 to 10)	43/277	8% (6 to 11)
Bone recurrence as first event, years				
3	7/537	1% (1 to 3)	15/513	3% (2 to 5)
5	13/508	2% (1 to 4)	23/481	4% (3 to 6)
8	25/286	5% (3 to 7)	29/277	6% (4 to 8)
Visceral recurrence, years				
3	10/537	2% (1 to 3)	24/517	4% (3 to 6)
5	25/509	4% (3 to 7)	32/488	6% (4 to 8)
8	42/284	8% (6 to 11)	42/281	8% (6 to 11)

Abbreviations: DFS, disease-free survival; OS, overall survival.

higher in the ibandronate arm than in the control arm (HR, 0.59; 95% CI, 0.38 to 0.92). In a landmark analysis starting at 3 years after random assignment, DFS was lower in the ibandronate arm than in the control arm (HR, 1.22; 95% CI, 0.91 to 1.63; Appendix Table A1, online only, Appendix Fig A2, online only).

OS in the ibandronate arm was similar to the control arm, with 14 and 19 deaths at 3 years, 38 and 46 at 5 years, and 72 and 67 deaths at 8 years after random assignment, respectively (HR, 1.10; 95% CI, 0.82 to 1.49; log-rank $P = .517$; Fig 2B). There were no deaths reported to be related to ibandronate. Causes of death were similar between the treatment arms as well (Appendix Table A2, online only).

The cumulative incidence of breast cancer recurrences was similar in the ibandronate arm and the control arm, with 19 and 39 events at 3 years after random assignment, 37 and 56 at 5 years, and 65 and 75 events at 8 years after random assignment, respectively (Table 2, Fig 2C).

The risk of bone recurrences was not significantly reduced by using ibandronate (HR, 0.83; 95% CI, 0.55 to 1.25; Fig 2D). The cumulative incidence of bone recurrences at 8 years after random assignment was 7% (95% CI, 5 to 10, 36 events) and 8% (6 to 11, 43 events) in the ibandronate arm and control arm, respectively (Table 2).

Of all patients who started treatment with ibandronate (n = 543), 163 (30%) patients stopped early. The main reason to stop early was AEs (n = 97/163 [60%]). Of these, 53/97 (55%) patients stopped within the first 6 months of study treatment (Appendix Fig A3A, online only). Of all patients who stopped ibandronate because of AEs, 31/97 (32%) stopped because of GI issues. Adherence to ET was similar in both treatment arms (Appendix Fig A3B).

AEs (all grades) that occurred in ≥ 5% of the patients are summarized in Table 3. In total, 933/1,116 (84%) patients reported at least one AE, 473/565 (84%) in the ibandronate arm and 460/551 (84%) in the control arm. Of all AEs reported, the ibandronate arm reported a higher number of GI events, mainly dyspepsia, compared with the control arm (89 and 54 events, respectively; Appendix Table A3, online only). The number of patients who developed osteonecrosis was also significantly higher in the ibandronate arm compared with the control arm (12 and 1 events, respectively; $P = .002$). In the ibandronate arm, 11 of 12 events (92%) were classified as ONJ. Of the 12 patients in the ibandronate arm who developed osteonecrosis, nine cases occurred while the patient was on an AI, whereas three of the ONJ events occurred while the patient was on TAM treatment. Osteoporosis and osteopenia occurred less frequently in the ibandronate arm compared with the control arm (36 and 62 events, respectively; Table 3). Bone fractures occurred in 22 (3.9%) patients in the ibandronate arm and 26 (4.7%) patients in the control arm.

TABLE 3. Incidence of Adverse Events, All Grades and Occurring in ≥ 5% of Patients, Between Random Assignment and 3.25 Years

Adverse Event	All, No. (%)	Ibandronate, No. (%)	Control, No. (%)	*P*
Total	1,116	565 (50.6)	551 (49.4)	
Hot flashes	381 (34.1)	184 (32.6)	197 (35.8)	.262
Arthralgia	269 (24.1)	145 (25.7)	124 (22.5)	.217
Fatigue	196 (17.6)	93 (16.5)	103 (18.7)	.327
Depression	105 (9.4)	45 (8.0)	60 (10.9)	.094
Pain in extremity	102 (9.1)	54 (9.6)	48 (8.7)	.624
Osteoporosis or osteopenia	98 (8.8)	36 (6.4)	62 (11.3)	**.004**
Nausea	88 (7.9)	48 (8.5)	40 (7.3)	.444
Decreased range of joint motion	87 (7.8)	42 (7.4)	45 (8.2)	.648
Lymphedema	83 (7.4)	35 (6.2)	48 (8.7)	.109
Back pain	74 (6.6)	33 (5.8)	41 (7.4)	.283
Peripheral sensory neuropathy	71 (6.4)	35 (6.2)	36 (6.5)	.817
Dizziness	63 (5.6)	30 (5.3)	33 (6.0)	.623
Alopecia	52 (4.7)	23 (4.1)	29 (5.3)	.345
Myalgia	50 (4.5)	29 (5.1)	21 (3.8)	.286
Maculopapular rash	50 (4.5)	19 (3.4)	31 (5.6)	.068
Dyspepsia	48 (4.3)	37 (6.5)	11 (2.0)	**< .001**

NOTE. *P* values are derived from Pearson's chi-squared tests. Bold values represent statistical significance.

A predefined sensitivity analysis (ITT2) was performed to assess any diluting effect of including patients with osteoporosis. DEXA scans were performed in 431/565 patients in the ibandronate arm and in 434/551 patients in the control arm. Thirty-six patients in the control arm and 30 patients in the ibandronate arm had a history of or were diagnosed with osteoporosis during the study, and they were excluded from the ITT2 analyses (Fig 1). The ITT2 analysis showed similar results to those obtained with the ITT analyses (data not shown).

A predefined PP population was also analyzed. In total, 10 and 17 patients in the control and ibandronate arms, respectively, did not meet all inclusion and exclusion criteria, and were excluded from the PP population (Fig 1). This analysis also showed results consistent with the ITT analyses (data not shown).

Unplanned univariable analyses of prognostically relevant subgroups are shown in Figure 3. For DFS, heterogeneity of treatment effect was observed for histologic tumor grade (*P* value for interaction .049; Fig 3A). For RFi, no heterogeneity of treatment effect was observed (Fig 3B).

DISCUSSION

TEAM-IIB, the largest randomized controlled trial in specifically postmenopausal women with ER+ breast cancer, evaluates the benefit of adding an oral nitrogen-containing bisphosphonate, ibandronate, to adjuvant ET, and found no difference in overall DFS between the ibandronate arm and the control arm. A significant difference was observed in the first 3 years after diagnosis, which disappeared with longer follow-up. An interaction between time and treatment effect was observed, although a landmark analysis of DFS starting at 3 years after random assignment until end of follow-up showed no significant difference in DFS between the treatment arms.

Evaluation of secondary outcomes also showed only a short-term benefit of ibandronate. During the first 5 years after random assignment, patients in the ibandronate arm had few recurrences overall, and also less recurrences in bone, specifically. This is in line with results from preclinical research and the EBCTCG meta-analysis.[10] Despite the favorable short-term effects of ibandronate on disease-free survival and (bone) recurrence rate, ibandronate was not beneficial with longer follow-up. After 8 years of follow-up, the (bone) recurrence rate was similar between the

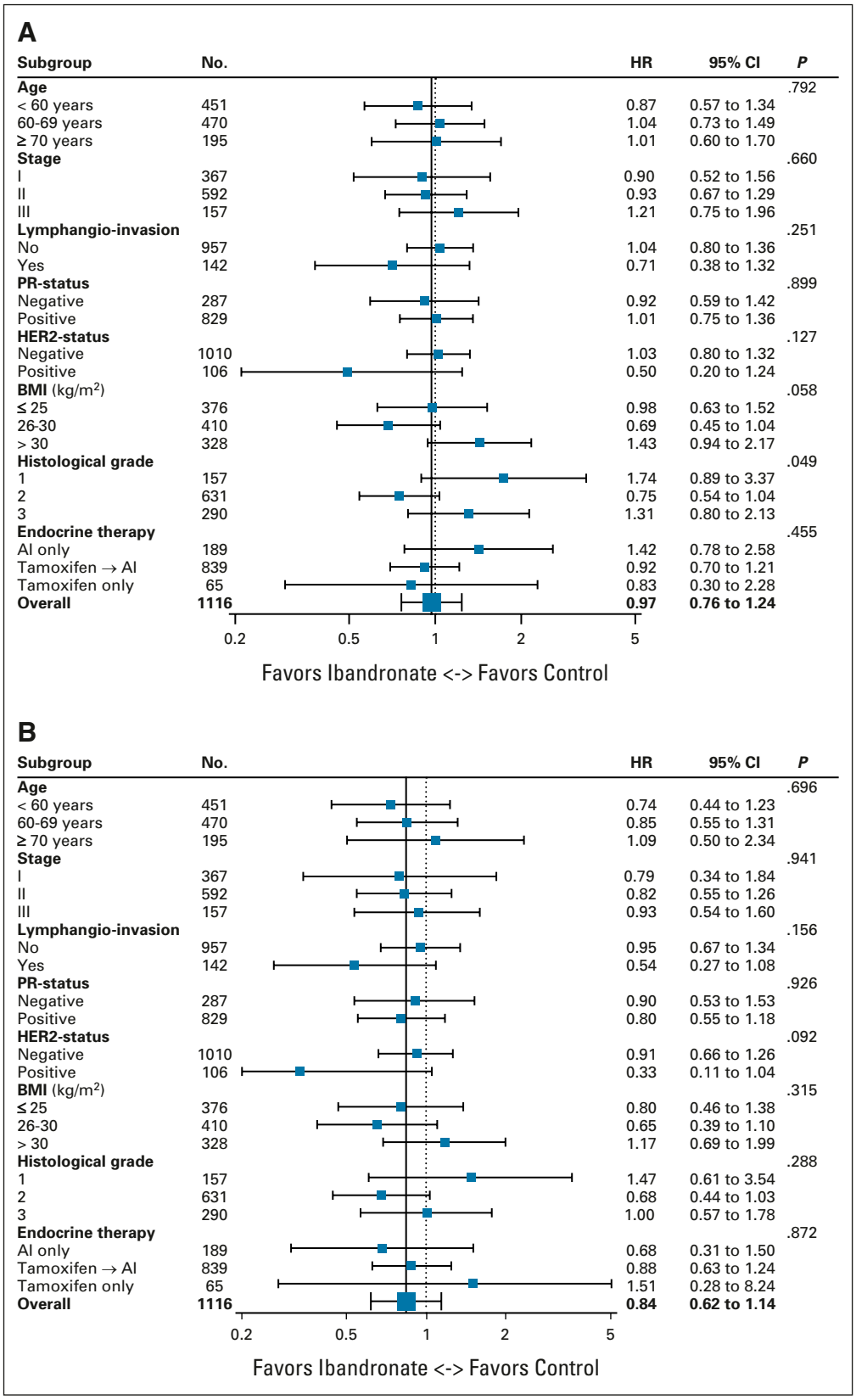

FIG 3. Univariable subgroup analyses of (A) disease-free survival and (B) recurrence-free interval at 8 years after random assignment in the intention-to-treat population. AI, aromatase inhibitor; BMI, body mass index; ET, endocrine therapy; HER2, HR, hazard ratio; PR, progesterone receptor; TAM, tamoxifen.

ibandronate arm and the control arm. These results were also consistent with the EBCTCG meta-analysis, and it was especially notable that the point estimates for bone recurrence presented here were almost identical to those of the EBCTCG meta-analysis, namely 7.8% and 8.8% for the ibandronate arm and control arm, respectively, versus 7.8% and 9.0% in the meta-analysis. All landmark analyses starting at 3 years after random assignment showed no statistically significant differences between treatment arms.

The short-term results were not statistically significant in the multivariable analyses either. This suggests that the observed differences could be due to chance. Second, a potential explanation could be the delaying effect bisphosphonates have on recurrences instead of a preventive effect. Nitrogen-containing bisphosphonates greatly reduce osteoclast activity and can inhibit bone resorption by up to 2 years after discontinuing treatment.[18] Metastatic breast cancer cells that are present in osseous tissue are less likely to grow into detectable metastases while bone turnover is still suppressed, and stay dormant. However, when osteoclasts regain regular activity, the osseous microenvironment changes in favor of the metastatic cells, and opportunity arises for metastases to grow.[19]

Finally, since most patients in TEAM-IIB switched from TAM to AI after 2-3 years, the type of ET in combination with bisphosphonates might matter. However, the relation between the type of ET including switch and recurrences should be interpreted with caution, as these analyses may be influenced by immortal time bias.

Another limitation of this study is the use of HR as a measure of treatment effect. Considering that the proportional hazards assumption is not met for the primary end point, the HR might be a potentially inaccurate measure of treatment effect. The landmark analyses starting at 3 years after random assignment were performed to adjust for this potential imprecision, which showed no significant differences between treatment arms either.

Other trials investigating nitrogen-containing bisphosphonates did not observe a discordance between short-term and long-term effects of bisphosphonates.[7,20] The GAIN trial, which also studied adjuvant ibandronate 50 mg once daily for 2 years, did not observe any benefit of ibandronate for DFS or OS.[21] Studies such as the GAIN, AZURE, and NSABP-B34 trials showed that the benefit of bisphosphonates seems largely restricted to women with low estrogen levels at the time of treatment, although the mechanism behind this remains unclear.[7,9,21] Estrogens may interfere with the antitumor effect of bisphosphonates, or the altered bone structure in the absence of estrogens may be relevant. The results from the TEAM-IIB trial demonstrate that in the long-term, ibandronate is not beneficial for postmenopausal patients.

Moreover, ibandronate treatment carries considerable side effects. Bisphosphonates are associated with flu-like symptoms, musculoskeletal pain, and hypocalcemia. Incidence of serious AEs, such as ONJ and nephrotoxicity, is low. Most trials report an incidence of $< 1\%$ for both toxicities. Notably, in TEAM-IIB, the incidence of ONJ was 1.9%, mostly in women using an AI, which raises the question whether the combination with AIs in postmenopausal women may increase this risk. TAM increases bone mineral density in postmenopausal women by acting as an estrogen agonist in osseous tissue, whereas AIs cause osteoporosis through disrupting the bone remodeling cycle by increasing osteoclast-mediated bone resorption.[22,23] Bisphosphonates decrease bone remodeling, but also decrease angiogenesis and cause poor wound healing. Therefore, the concurrent administration of AIs and high-dose ibandronate may increase the risk of developing osteonecrosis compared with the combination of ibandronate and TAM.[24,25]

Although patient satisfaction with oral formulations is generally high and oral bisphosphonates are usually well accepted, 18% of TEAM-IIB patients stopped their ibandronate treatment early because of AEs, and approximately a third of those had GI complaints.

It is still an unresolved question which is the optimal class, dose, schedule, and duration of bisphosphonates, and which postmenopausal patients should be selected for bisphosphonate treatment. The results presented here suggest that daily ibandronate for 3 years should not be the recommended strategy. The planned update of the EBCTCG meta-analysis might also provide more insights to answer these questions.

In conclusion, the data presented here are an important contribution to the field and the results from TEAM-IIB do not support using daily ibandronate as adjuvant treatment in unselected postmenopausal women with ER+ stage I-III breast cancer.

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DISCLAIMER

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

EQUAL CONTRIBUTION

S.B.V. and I.N. are joint first authors. C.J.H.v.d.V. and S.C.L. are joint last authors.

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DATA SHARING STATEMENT

Currently, no mechanism is in place to allow sharing of individual deidentified patient data. Requests sent to the corresponding author will be considered on a case-by-case basis.

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Daily Oral Ibandronate With Adjuvant Endocrine Therapy in Postmenopausal Women With Estrogen Receptor–Positive Breast Cancer (BOOG 2006-04): Randomized Phase III TEAM-IIB Trial

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APPENDIX 1

Random Assignment and Stratification

Patients were randomly assigned by a computer in a 1:1 ratio. Stratification was performed according to Pocock's minimization strategy by center, age (< 50 *v* 50-59 *v* 60-69 *v* ≥ 70 years), human epidermal growth factor receptor 2 status (positive [+] *v* negative [–]), hormone receptor status (estrogen receptor [ER]+progesterone receptor [PR]+ *v* ER+PR– *v* ER–PR+), tumor grade (1 *v* 2 *v* 3 *v* Gx), tumor size (T1 *v* T2 *v* T3 *v* T4a-c), nodal status (pN0 *v* pN0/i+ *v* pN1 [mi] *v* pN1 *v* pN2 *v* pN3 *v* pNx), neoadjuvant endocrine therapy (none *v* 3 months *v* 6 months), time between surgery and random assignment (< 3 months *v* 3-6 months *v* > 6 months), and (neo)adjuvant chemotherapy (yes *v* no).[26] There was no masking in this open-label trial.

Interim Analysis

The interim analysis was performed with all data available on March 31, 2014. The included number of patients at that moment was 1,083, 549 in the ibandronate arm and 534 in the control arm. Median follow-up was 1.98 years (interquartile range, 0.69-3.77 years). Five occurrences of renal toxicity (grade 2 or higher) and two occurrences of osteonecrosis of the jaw were registered. In total, there were 76 disease-free survival (DFS) events, and 39 deaths were recorded. The results of the interim analysis and the report by the independent data monitoring committee did not warrant any amendments to the study protocol, and the trial was continued.

Description of Primary, Secondary, and Other End Points

For DFS, the occurrence of a local, regional, or distant relapse, contralateral breast cancer, second primary breast cancer, and death of any cause was counted as an event. Patients were censored if they experienced no events at the end of follow-up.

An overall survival event was defined as death of any cause. Patients were censored if they were alive at the end of follow-up. Causes of death were registered by the participating centers.

For recurrence-free interval, also cumulative incidence of any recurrence, the occurrence of a local, regional, or distant relapse was considered an event. Death without recurrence was considered a competing event. If patients were recurrence-free and alive at the end of follow-up, they were censored.

For the cumulative incidence of locoregional recurrence, the occurrence of a local or regional relapse was considered an event. Death without locoregional recurrence was considered a competing event. If patients were locoregional recurrence-free and alive at the end of follow-up, they were censored.

For distant recurrence, the occurrence of a distant relapse was considered an event. Death without distant recurrence was considered a competing event. If patients were distant recurrence-free and alive at the end of follow-up, they were censored.

For bone recurrence, the occurrence of a relapse in bone was considered an event. Death without a bone recurrence was considered a competing event. If patients were bone recurrence-free and alive at the end of follow-up, they were censored. For bone recurrence as first event, the occurrence of any relapses other than in bone was considered a competing event as well.

For visceral recurrence, a relapse in the thoracic, retroperitoneal, or abdominal cavity was considered an event. Death without a visceral recurrence was considered a competing event. If patients were visceral recurrence-free and alive at the end of follow-up, they were censored.

All end points are measured from the date of random assignment until date of (competing) event or date of last follow-up moment.

For measuring adherence, start and stop dates were collected and registered for ibandronate as well as endocrine therapy. Stopping ibandronate early was defined as stopping 3 months or longer before the planned stop date, thereby having a total ibandronate treatment duration of 2.75 years or less.

Justification of Choice of Time Point

The consideration to choose 3 years as the time point for the primary end point as well as the cutoff for the landmark analysis was both a clinical and statistical one. On the basis of research available at the design stage of the TEAM-IIB trial, the decision was made to treat the intervention arm with ibandronate for 3 years.[27] Therefore, the primary end point was also decided to be 3-year DFS. The landmark analysis was not predefined in the study protocol. Because of the treatment duration and the primary end point, which were predefined in the study protocol, the decision was made to start the landmark analysis at 3 years as well, to stay consistent.

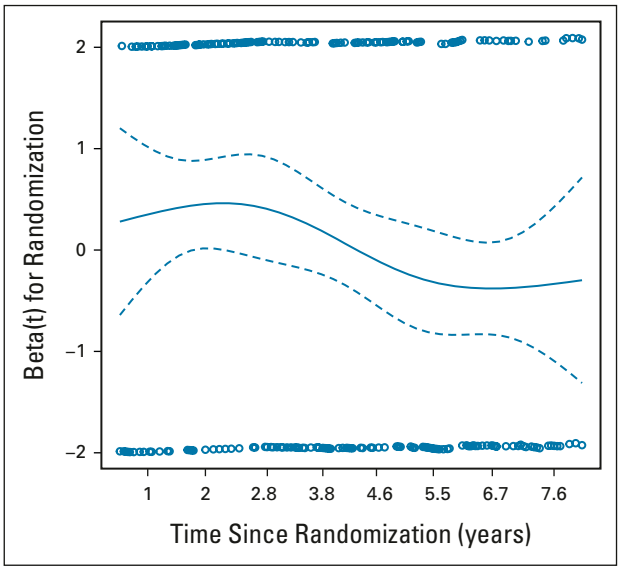

FIG A1. Schoenfeld residuals–based test following Therneau and Grambsch[17] for disease-free survival in the intention-to-treat population.

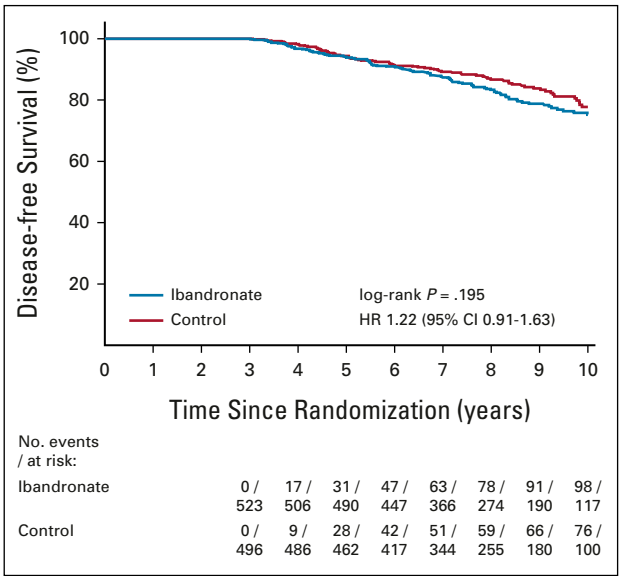

FIG A2. Landmark analysis starting at 3 years after random assignment of DFS in the intention-to-treat population. DFS, disease-free survival; HR, hazard ratio.

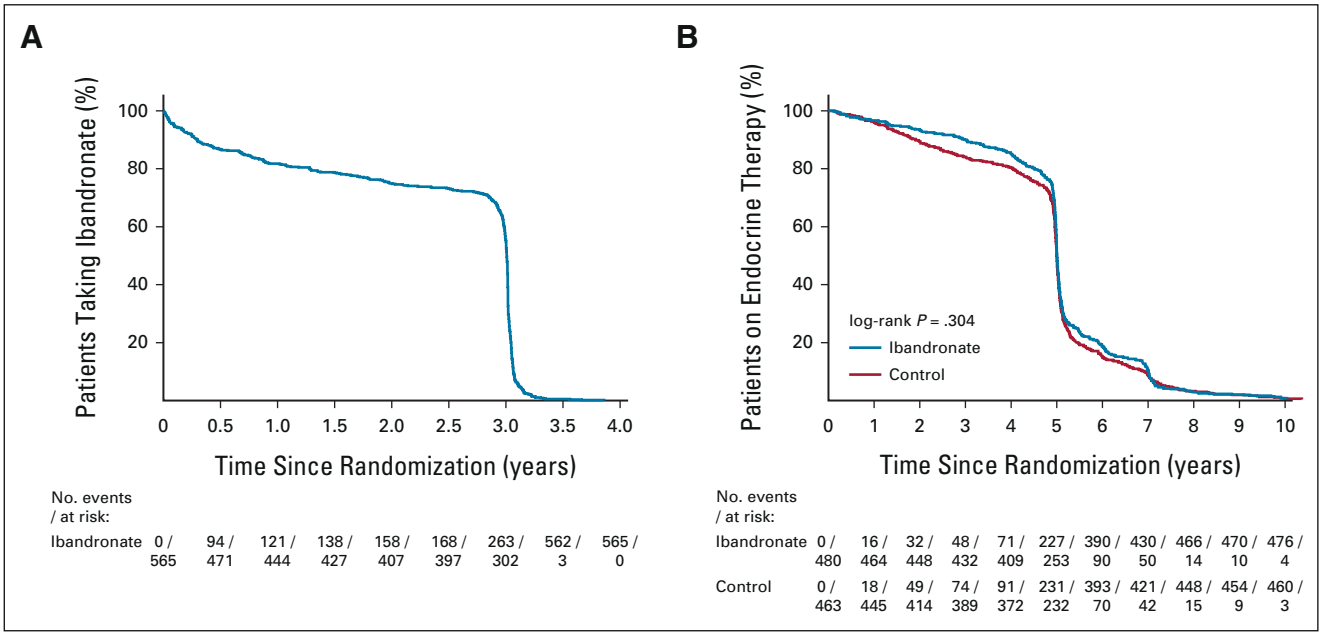

FIG A3. (A) Patients taking ibandronate and (B) patients on adjuvant ET. ET, endocrine therapy.

TABLE A1. Primary and Secondary End Points Truncated at 3 Years After Random Assignment and as Landmark Analyses Starting at 3 Years After Random Assignment in the Intention-to-Treat Population

Outcome Measure	HR[a]	95% CI	HR[b]	95% CI
DFS				
Random assignment—3 years	0.590	0.378 to 0.922	0.982	0.627 to 1.539
3 years—end of FU	1.216	0.905 to 1.633	1.199	0.882 to 1.630
Overall	0.971	0.762 to 1.238	0.999	0.777 to 1.283
OS				
Random assignment—3 years	0.726	0.364 to 1.447	1.000	0.498 to 2.008
3 years—end of FU	1.219	0.873 to 1.701	1.154	0.821 to 1.623
Overall	1.104	0.819 to 1.488	1.000	0.738 to 1.354
Any recurrence				
Random assignment—3 years	0.474	0.274 to 0.820	1.000	0.596 to 1.679
3 years—end of FU	1.122	0.767 to 1.641	1.130	0.758 to 1.686
Overall	0.837	0.616 to 1.136	0.925	0.668 to 1.280
Locoregional recurrence				
Random assignment—3 years	0.625	0.242 to 1.611	0.635	0.243 to 1.663
3 years—end of FU	1.006	0.537 to 1.885	1.066	0.541 to 2.101
Overall	0.868	0.516 to 1.459	0.876	0.508 to 1.511
Distant recurrence				
Random assignment—3 years	0.414	0.221 to 0.773	0.648	0.354 to 1.184
3 years—end of FU	1.250	0.814 to 1.919	1.275	0.815 to 1.995
Overall	0.857	0.609 to 1.206	1.000	0.707 to 1.415
Bone recurrence				
Random assignment—3 years	0.365	0.170 to 0.785	0.344	0.157 to 0.751
3 years—end of FU	1.265	0.752 to 2.127	1.228	0.710 to 2.123
Overall	0.826	0.547 to 1.248	0.956	0.622 to 1.469
Bone recurrence as first event				
Random assignment—3 years	0.454	0.185 to 1.114	0.440	0.175 to 1.104
3 years—end of FU	1.292	0.690 to 2.418	1.311	0.674 to 2.552
Overall	0.901	0.548 to 1.483	0.990	0.546 to 1.797
Visceral recurrence				
Random assignment—3 years	0.407	0.195 to 0.851	0.363	0.169 to 0.780
3 years—end of FU	1.395	0.838 to 2.324	1.380	0.818 to 2.329
Overall	0.912	0.610 to 1.364	0.875	0.579 to 1.322

NOTE. The control arm is used as reference, and HRs represent the ibandronate arm.

Abbreviations: DFS, disease-free survival; FU, follow-up; HR, hazard ratio; OS, overall survival.

[a]Univariable Cox regression model.

[b]Multivariable Cox regression model. Included variables are age, hormone receptor status, time between surgery and random assignment, body mass index, radiotherapy, tumor size, nodal status, and type of surgery.

TABLE A2. Number of Events in the Intention-to-Treat Population

Event	All, No.	Ibandronate, No.	Control, No.
Total	1,116	565	551
Breast cancer			
All breast cancer events	194	92	102
Recurrences	165	77	88
Local	35	16	19
Regional	29	12	17
Distant	132	62	70
Visceral	96	46	50
Bone	93	42	51
Bone as first event	62	30	32
New primary breast tumor	38	19	19
Carcinoma in situ	10	6	4
Invasive	28	13	15
Other primary cancers	89	48	41
Second primary without breast cancer	83	46	36
Angiosarcoma of the breast	2	1	1
Mortality	173	87	81
Breast cancer–related	100	43	53
Second primary malignancy	32	17	15
Cardiac	13	8	5
Pulmonary	7	5	2
Other	12	8	4
Unknown	9	6	2
DFS events	261	128	129

Abbreviation: DFS, disease-free-survival.

TABLE A3. All Adverse Events by System Organ Class and Common Terminology Criteria for Adverse Event Grade (version 4.03)

	All		Ibandronate		Control	
System Organ Class	**Grades 1-2**	**Grades 3-5**	**Grades 1-2**	**Grades 3-5**	**Grades 1-2**	**Grades 3-5**
Cardiac disorders	6 (0.5)	6 (0.5)	1 (0.2)	4 (0.7)	5 (0.9)	2 (0.4)
Endocrine disorders	4 (0.4)	0 (0.0)	3 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Eye disorders	4 (0.4)	6 (0.5)	1 (0.2)	3 (0.5)	3 (0.5)	3 (0.5)
GI disorders	131 (11.7)	12 (1.1)	85 (15.0)	4 (0.7)	46 (8.3)	8 (1.5)
General disorders and site conditions	35 (3.1)	5 (0.4)	14 (2.5)	2 (0.4)	21 (3.8)	3 (0.5)
Hepatobiliary disorders	0 (0.0)	4 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)	3 (0.5)
Infections and infestations	28 (2.5)	21 (1.9)	13 (2.3)	11 (1.9)	15 (2.7)	10 (1.8)
Injury and procedural complications	9 (0.8)	11 (1.0)	4 (0.7)	6 (1.1)	5 (0.9)	5 (0.9)
Investigations	9 (0.8)	2 (0.2)	6 (1.1)	1 (0.2)	3 (0.5)	1 (0.2)
Metabolism and nutrition disorders	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Musculoskeletal and connective tissue	304 (27.2)	16 (1.4)	143 (25.3)	10 (1.8)	161 (29.2)	6 (1.1)
Neoplasms[a]	9 (0.8)	5 (0.4)	6 (1.1)	2 (0.4)	3 (0.5)	3 (0.5)
Nervous system disorders	39 (3.5)	15 (1.3)	24 (4.2)	9 (1.6)	15 (2.7)	6 (1.1)
Psychiatric disorders	18 (1.6)	7 (0.6)	11 (1.9)	4 (0.7)	7 (1.3)	3 (0.5)
Renal and urinary disorders	7 (0.6)	4 (0.4)	4 (0.7)	3 (0.5)	3 (0.5)	1 (0.2)
Reproductive system and breast disorders	16 (1.4)	7 (0.6)	7 (1.2)	6 (1.1)	9 (1.6)	1 (0.2)
Respiratory and thoracic disorders	7 (0.6)	2 (0.2)	2 (0.4)	1 (0.2)	5 (0.9)	1 (0.2)
Skin and subcutaneous tissue disorders	35 (3.1)	4 (0.4)	17 (3.0)	2 (0.4)	18 (3.3)	2 (0.4)
Vascular disorders	115 (10.3)	28 (2.5)	50 (8.8)	13 (2.3)	65 (11.8)	15 (2.7)
All	778 (69.7)	155 (13.9)	391 (69.2)	82 (14.5)	387 (70.2)	73 (13.2)

NOTE: Data are represented as No. (%).

[a]Excluding basal cell carcinoma.