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ORIGINAL REPORT

Denosumab Compared With Zoledronic Acid for the Treatment of Bone Metastases in Patients With Advanced Breast Cancer: A Randomized, Double-Blind Study

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See accompanying editorial on page 5127

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ABSTRACT

Purpose
This randomized study compared denosumab, a fully human monoclonal antibody against receptor activator of nuclear factor κ B (RANK) ligand, with zoledronic acid in delaying or preventing skeletal-related events (SREs) in patients with breast cancer with bone metastases.

Patients and Methods
Patients were randomly assigned to receive either subcutaneous denosumab 120 mg and intravenous placebo (n = 1,026) or intravenous zoledronic acid 4 mg adjusted for creatinine clearance and subcutaneous placebo (n = 1,020) every 4 weeks. All patients were strongly recommended to take daily calcium and vitamin D supplements. The primary end point was time to first on-study SRE (defined as pathologic fracture, radiation or surgery to bone, or spinal cord compression).

Results
Denosumab was superior to zoledronic acid in delaying time to first on-study SRE (hazard ratio, 0.82; 95% CI, 0.71 to 0.95; $P = .01$ superiority) and time to first and subsequent (multiple) on-study SREs (rate ratio, 0.77; 95% CI, 0.66 to 0.89; $P = .001$). Reduction in bone turnover markers was greater with denosumab. Overall survival, disease progression, and rates of adverse events (AEs) and serious AEs were similar between groups. An excess of renal AEs and acute-phase reactions occurred with zoledronic acid; hypocalcemia occurred more frequently with denosumab. Osteonecrosis of the jaw occurred infrequently (2.0%, denosumab; 1.4%, zoledronic acid; $P = .39$).

Conclusion
Denosumab was superior to zoledronic acid in delaying or preventing SREs in patients with breast cancer metastatic to bone and was generally well tolerated. With the convenience of a subcutaneous injection and no requirement for renal monitoring, denosumab represents a potential treatment option for patients with bone metastases.

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INTRODUCTION

Up to 80% of patients with metastatic breast cancer develop bone metastases that induce increased osteoclast activity resulting in local bone destruction and skeletal complications, including pain, hypercalcemia, and skeletal-related events (SREs).[1] SREs comprise radiation therapy to alleviate pain or prevent fracture, surgery to bone to treat or prevent fractures, and pathologic fracture or spinal cord compression that can result in paresthesias, incontinence, and paralysis.[2-5] SREs occur in up to 64% of patients with metastatic breast cancer when they are not treated with bisphosphonates,[4] and the burden of SREs contributes to a substantial erosion in quality of life for many advanced breast cancer patients.[6-8]

Intravenous bisphosphonates, predominantly zoledronic acid (Zometa, Novartis Pharmaceuticals East Hanover, NJ),[9] are effective at preventing SREs. The American Society of Clinical Oncology recommends initiating treatment with intravenous bisphosphonates in breast cancer patients who have evidence of bone destruction on plain radiographs.[10] However, SREs still occur in a large proportion of patients despite intravenous

bisphosphonate therapy.[11,12] Nephrotoxicity has been shown to be associated with zoledronic acid therapy and increases with extended treatment.[9,13-16] To minimize this risk, zoledronic acid is contraindicated for patients with creatinine clearance levels < 30 mL/min, and in patients with creatinine clearance < 60 mL/min, it is dose-adjusted for baseline renal function. Zoledronic acid is infused over a minimum of 15 minutes, and it is withheld if creatinine rises to further reduce the risk of renal injury, per zoledronic acid prescribing information.[9] Additionally, acute-phase reactions (flu-like symptoms) to intravenous bisphosphonate infusions occur frequently and may further complicate management of patients.[9] Therefore, new treatments that further reduce SREs and/or limit toxicity are needed.

Metastatic tumor cells in bone may secrete cytokines and growth factors that induce osteoblasts to release receptor activator of nuclear factor κ B ligand (RANKL), a key mediator of osteoclast formation, function, and survival.[17] Osteoclasts resorb bone, thereby releasing growth factors that may promote tumor cell proliferation, metastasis, and survival, thus perpetuating a vicious cycle of tumor expansion and bone resorption.[18] Denosumab is a fully human monoclonal antibody that specifically binds human RANKL to inhibit osteoclast activity that results in reduced bone resorption, tumor-induced bone destruction, and SREs. Denosumab may potentially disrupt the vicious cycle.

Studies in postmenopausal women with osteoporosis and in women receiving aromatase inhibitors for early-stage breast cancer showed that denosumab was generally well tolerated as a subcutaneous 60-mg injection every 6 months and resulted in suppression of bone turnover and increased bone mineral density.[19,20] In a large trial of women with postmenopausal osteoporosis, denosumab resulted in significant reductions in the incidence of vertebral, nonvertebral, and hip fractures.[19] Two phase II trials of patients with bone metastases further demonstrated that denosumab, at doses ranging from 30 to 180 mg administered every 4 or every 12 weeks, was similar to intravenous bisphosphonates in suppressing bone turnover markers including urine N-telopeptide (uNTx) and in delaying SREs.[21,22] Results from these studies also supported using the higher dosing regimen of denosumab (120 mg every 4 weeks) that was selected for the current trial. Both the dose and schedule were optimized for maximum and sustained suppression of uNTx, a known predictor of SREs and survival[23] in patients with bone metastases.[21,24,25] In this randomized phase III trial, we compared denosumab with zoledronic acid in delaying or preventing SREs in patients with breast cancer metastatic to bone.

PATIENTS AND METHODS

Patients

Eligible patients were age ≥ 18 years with histologically or cytologically confirmed breast adenocarcinoma, current or prior radiographic (x-ray, computed tomography, or magnetic resonance imaging) evidence of at least one bone metastasis, with adequate organ function (including albumin-adjusted serum calcium ≥ 2.0 mmol/L [≥ 8.0 mg/dL] and ≤ 2.9 mmol/L [≤ 11.5 mg/dL] calculated by central laboratory), and Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2. Patients with creatinine clearance < 30 mL/min (Cockcroft-Gault formula) were excluded because zoledronic acid is contraindicated in this patient population.[9] Other key exclusion criteria included prior intravenous bisphosphonate treatment, current or prior oral bisphosphonates for treatment of bone metastases, nonhealed dental/oral surgery, and prior malignancy within 3 years before random assignment. History of breast cancer (diagnosis, hormone receptor status, human epidermal growth factor receptor 2 [HER2] status, and location of metastatic bone disease) and SREs were also obtained.

Study Design

This international, randomized, double-blind, double-dummy, active-controlled study compared denosumab with zoledronic acid for the treatment of bone metastases in breast cancer patients and involved 322 centers in Europe, North America, South America, Japan, Australia, India, and South Africa. Patients were randomly assigned to receive either a subcutaneous injection of denosumab 120 mg and an intravenous infusion of placebo every 4 weeks or an intravenous infusion (lasting no less than 15 minutes) of zoledronic acid 4 mg and a subcutaneous injection of placebo every 4 weeks. Intravenous products (placebo or zoledronic acid) were dose-adjusted on the basis of baseline creatinine clearance ≤ 60 mL/min and were held for renal function deterioration on-study (until serum creatinine returned to within 10% of baseline values), per zoledronic acid prescribing information. There was no requirement for dose adjustment with denosumab. Randomization was stratified by prior SRE, prior oral bisphosphonate use, current chemotherapy, and geographic region (Japan or Other).

Daily supplementation with calcium (≥ 500 mg) and vitamin D (≥ 400 U) was strongly recommended. All cancer-specific therapies such as chemotherapy and hormonal therapy were allowed, except for oral or intravenous bisphosphonates or unapproved investigational products or devices. Patients who discontinued investigational product but continued with scheduled visits were followed for SREs through the primary analysis data cutoff date (March 2009), and all patients were followed for survival unless they withdrew consent or were lost to follow-up. The study duration from first patient enrollment to the primary analysis was approximately 34 months.

All patients provided written informed consent before any study-specific procedure was performed, except for three patients in the zoledronic acid group who were excluded from analysis because properly documented informed consent was not obtained (Fig 1). The study was approved by the institutional review board or ethics committee for each site.

Assessment of Outcomes

SRE was defined as pathologic fracture (excluding major trauma), radiation therapy to bone, surgery to bone, or spinal cord compression. Hypercalcemia of malignancy was assessed separately. Fractures were assessed by skeletal surveys (x-rays) every 12 weeks or by radiographic assessments (x-ray, computed tomography, or magnetic resonance imaging) during the course of standard care and were identified or confirmed independently by at least two radiologists through blinded central radiology review. Spinal cord compression events were also confirmed by blinded central radiology review. Radiation to bone included use of radioisotopes. Surgery to bone included procedures to set or stabilize a fracture or to prevent an imminent fracture or spinal cord compression. On-study visits occurred at baseline and every 4 weeks thereafter. A data monitoring committee reviewed safety and efficacy data at regular intervals. Bone turnover markers (uNTx corrected for urine creatinine levels [uNTx/Cr] and bone-specific alkaline phosphatase [BSAP]) were measured at baseline and week 13.

End Points

The primary end point was time to first on-study SRE (noninferiority test). Secondary efficacy end points were time to first on-study SRE (superiority test) and time to first and subsequent on-study SREs (multiple event analysis). Subsequent events must have occurred at least 21 days apart from the most recent event to ensure that linked events (eg, surgery to repair a fracture or multiple doses of radiation during a course of treatment) were not counted as separate SREs.

Safety end points included incidence of treatment-emergent adverse events (AEs), changes in laboratory values, and incidence of antidenosumab antibodies. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) v12.0 system. Oral examinations were conducted twice yearly. Osteonecrosis of the jaw (ONJ) events were adjudicated by an independent, blinded ONJ adjudication committee consisting of an external panel of experts.

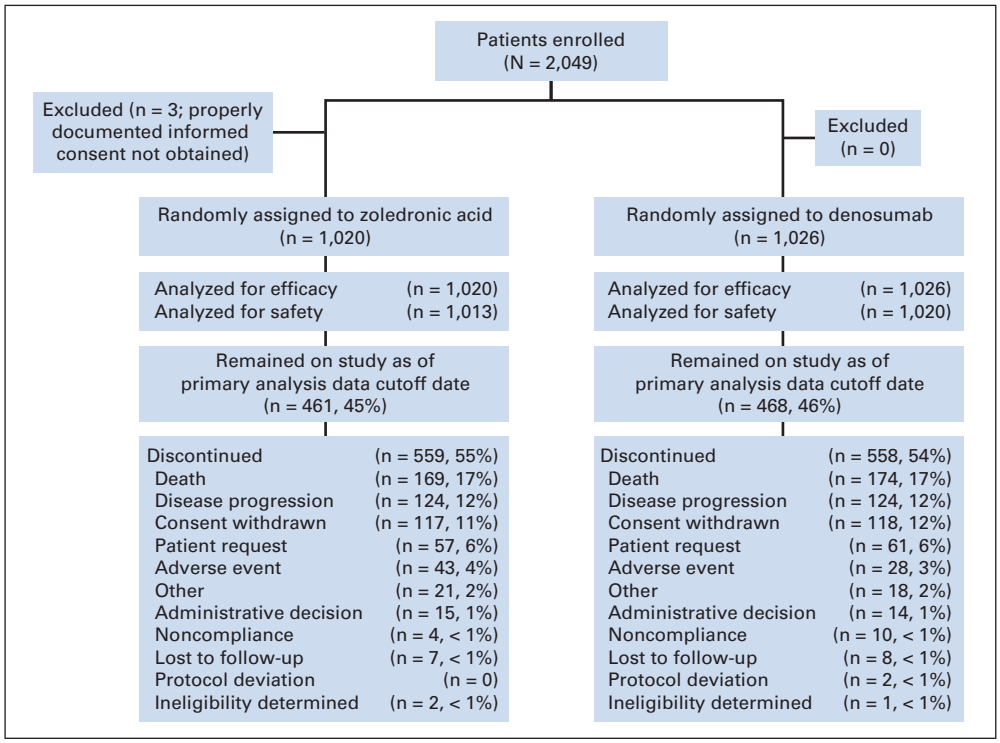

Fig 1. Patient disposition.

Exploratory end points included overall survival, disease progression, skeletal morbidity rate (allowing one event per assessing period [3 weeks]), and percent change from baseline to week 13 in uNTx and BSAP levels.

Statistical Analysis

Enrollment of 1,960 patients (980 per group) was planned. If the true hazard ratio (HR) was 0.9, 745 patients with at least one SRE were estimated to provide 97% power to detect noninferiority of denosumab to zoledronic acid, based on a synthesis approach[26] designed to demonstrate that denosumab preserves greater than 50% of the treatment effect of zoledronic acid. Assuming a true HR of 0.8 for both secondary end points and a correlation coefficient of 0.6 between the two end points, 745 patients with an SRE were also estimated to provide 90% power to detect superiority of denosumab to zoledronic acid for at least one of these end points.

The Appendix (online only) includes a full description of the statistical analysis. In this intention-to-treat analysis, primary and secondary efficacy analyses were conducted hierarchically ($\alpha = .05$). Statistical inferences of treatment effect on secondary efficacy end points were conducted because denosumab was declared noninferior to zoledronic acid. To control overall type I errors for multiple comparisons at a significance level of 0.05, secondary efficacy end points were tested simultaneously (Hochberg procedure). Time to first SRE was analyzed using a Cox model. Time to first and subsequent on-study SREs was analyzed using the Andersen and Gill approach.[27] Exploratory efficacy end points were tested at a significance level of 0.05 without multiplicity adjustments. All statistical testing was two-sided.

Incidence of AEs was summarized for patients who received at least one active dose of investigational product. No formal statistical testing was done for multiple safety comparisons. AEs with nominal P values $< .05$ are described. The proportion of patients with adjudicated positive ONJ was compared in prespecified fashion by treatment group using Fisher's exact test. Antidenosumab antibody assessments were conducted using screening methods described previously.[28]

RESULTS

Patients

Patients were enrolled between April 2006 and December 2007 (1,026 denosumab, 1,020 zoledronic acid; Fig 1). Patient characteristics were generally balanced, including age, menopausal status, and ECOG status (Table 1). Seventy-two percent of patients were hormone receptor–positive, 18% were HER2 positive, more than 50% also had visceral metastases, and 40% were receiving chemotherapy within 6 weeks of random assignment. Median time from initial diagnosis of bone metastasis to random assignment was 2 months. Median time on study was 17 months; 45% of patients continued on-study at the time of the primary analysis. The most common reasons for study discontinuation were death (17%), disease progression (12%), and consent withdrawal (12%).

The proportion of patients who received on-study cancer treatments for their breast cancer was also balanced between treatment groups (96.7%, denosumab; 95.4%, zoledronic acid; Appendix Table A1, online only). A similar proportion of patients received on-study hormonal therapy (68.6% and 67.7%) or chemotherapy (63.5% and 64.9%) in the denosumab and zoledronic acid groups, respectively.

Efficacy

Denosumab significantly delayed time to first on-study SRE by 18% compared with zoledronic acid (HR, 0.82; 95% CI, 0.71 to 0.95; $P < .001$ noninferiority; $P = .01$ superiority; Fig 2A). The treatment effect of denosumab was consistent over time compared with zoledronic acid. Median time to first on-study SRE was 26.4 months

Table 1. Baseline Demographics and Characteristics

Patient Demographic or Characteristic	Zoledronic Acid Q4W (4 mg) (n = 1,020)		Denosumab Q4W (120 mg) (n = 1,026)	
	No.	%	No.	%
Women	1,011	99.1	1,018	99.2
Postmenopausal	831	82.2	839	82.4
Median age, years	56.0		57.0	
Q1	49.0		49.0	
Q3	65.0		65.0	
≥ 65	266	26.1	275	26.8
ECOG status				
0	488	48	504	49
1	444	44	451	44
2	82	8	68	7
Missing or other	6	< 1	3	< 1
More than two metastatic bone lesions*	240	24	242	24
Prior SRE†	373	37	378	37
Prior therapy				
Chemotherapy	825	81	831	81
Recent chemotherapy†‡	408	40	410	40
Hormonal therapy	728	71	755	74
Aromatase inhibitor therapy	504	49	527	51
Oral bisphosphonates†	38	4	42	4
Median time from primary cancer diagnosis to initial diagnosis of bone metastasis, months	35.4		32.8	
Q1	8.6		7.0	
Q3	75.5		78.7	
Median time from initial diagnosis of bone metastasis to random assignment, months	2.0		2.1	
Q1	1.1		1.0	
Q3	4.9		5.1	
Hormone receptor (ER/PR) status				
Positive	726	71	740	72
Unknown	129	13	121	12
HER2 status				
Positive	194	19	183	18
Unknown	350	34	321	31
Presence of visceral metastases	525	51	552	54
Liver	182	18	211	21
Lung	210	21	216	21
Other	369	36	369	36

Abbreviations: Q4W, every 4 weeks; Q1, first quartile; Q3, third quartile; ECOG, Eastern Cooperative Oncology Group; SRE, skeletal-related event; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.
*By central read of skeletal survey.
†Based on randomization stratification.
‡Recent chemotherapy: chemotherapy administration within 6 weeks before random assignment.

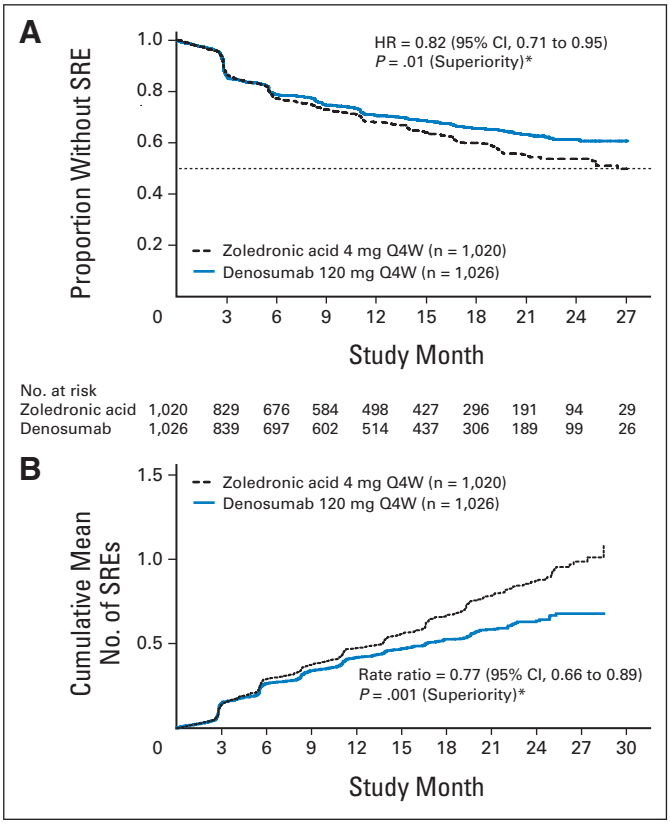

Fig 2. Kaplan-Meier estimates of (A) time to first skeletal-related event (SRE) and (B) time to first and subsequent SREs (multiple event analysis), which is represented as the cumulative mean number of SREs over time. Drugs were administered every 4 weeks. HR, hazard ratio; Q4W, every 4 weeks. (*) Adjusted for multiplicity.

for the zoledronic acid group and has not yet been reached for the denosumab group.

Denosumab reduced the risk of developing multiple SREs (time to first and subsequent SREs) by 23% compared with zoledronic acid (rate ratio, 0.77; 95% CI, 0.66 to 0.89; $P = .001$; Fig 2B). Denosumab reduced the mean skeletal morbidity rate, defined as the ratio of the number of SREs per patient divided by the patient's time at risk, by 22% compared with zoledronic acid (0.45 events *v* 0.58 events per patient per year for denosumab and zoledronic acid, respectively; $P = .004$). Overall survival (HR, 0.95; 95% CI, 0.81 to 1.11; $P = .49$) and disease progression (HR, 1.00; 95% CI, 0.89 to 1.11; $P = .93$) were similar between study groups (Fig 3).

Denosumab treatment resulted in greater suppression of bone turnover markers compared with zoledronic acid. At study week 13, levels of uNTx/Cr decreased by a median 80% with denosumab compared with 68% with zoledronic acid ($P < .001$). Levels of BSAP decreased by a median 44% with denosumab compared with 37% with zoledronic acid ($P < .001$).

Safety

Rates of overall, severe (Common Terminology Criteria of Adverse Events [CTCAE] grade ≥ 3), and serious AEs (eg, life-threatening or requiring hospitalization) were similar between groups (Table 2). These AEs were mostly reflective of toxicities related to concomitant therapies (eg, chemotherapy) or complications of underlying cancer. No patients developed detectable levels of neutralizing antidenosumab antibodies.

An analysis of all AEs was performed using Fisher's exact test to identify between-group differences with a nominal *P* value < .05 (Fig 4) by MedDRA preferred terms. Because this analysis does not include adjustments for multiple comparisons, it should be considered exploratory in nature. Twenty AEs with nominal *P* value < .05 were identified: 18 were more common with zoledronic acid, including pyrexia, bone pain, arthralgia, renal failure, and hypercalcemia; two

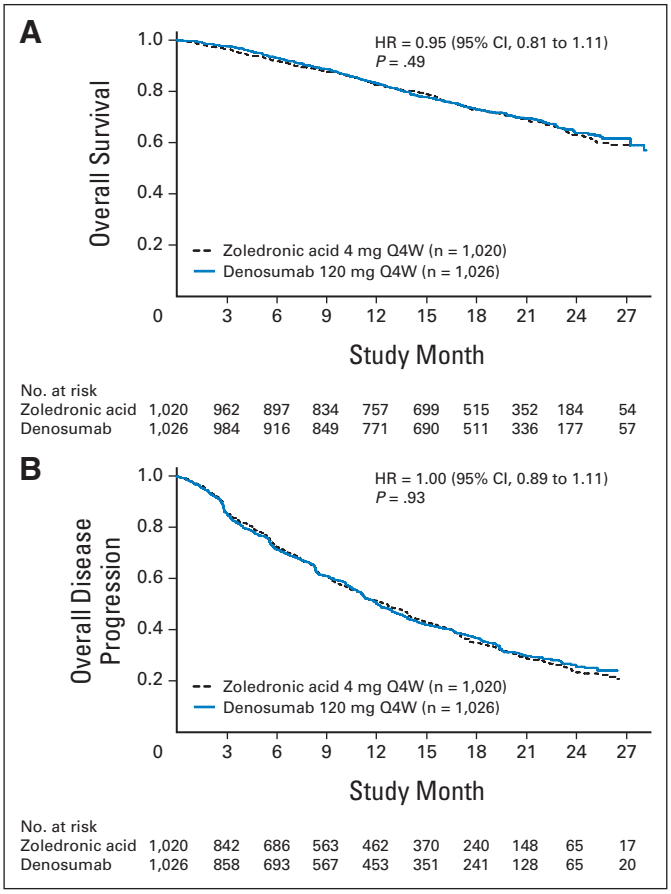

Fig 3. Kaplan-Meier estimates of (A) overall survival and (B) time to disease progression by treatment group. Drugs were administered every 4 weeks. HR, hazard ratio; Q4W, every 4 weeks.

were more common with denosumab, including toothache and hypocalcemia. Toothache was not associated with the development of ONJ.

Analyses for AEs potentially associated with acute-phase reactions (flu-like syndrome including pyrexia, chills, flushing, bone pain, arthralgias, and myalgias), renal toxicity, and ONJ were also performed (Table 2). Acute-phase reactions occurring within the first 3 days after treatment were 2.7 times more common with zoledronic acid.

AEs potentially associated with renal toxicity (8.5% *v* 4.9%; $P = .001$), especially severe (2.2% *v* 0.4%) and serious renal AEs (1.5% *v* 0.2%), occurred more frequently with zoledronic acid. The incidence of renal AEs among patients with baseline renal clearance ≤ 60 mL/min was also higher in the zoledronic acid group (20.0%) than in the denosumab group (5.9%), and a greater proportion of patients had decreases in their baseline creatinine clearance from ≥ 60 mL/min to < 60 mL/min with zoledronic acid (16.1%) compared with denosumab (12.7%).

Expected decreases in serum calcium, phosphorus, and total alkaline phosphatase were observed in both groups. Decreases in serum calcium were generally mild, transient, and not associated with clinical sequelae. ONJ occurred infrequently (20 [2.0%] denosumab *v* 14 [1.4%] zoledronic acid). Rates of ONJ were not statistically significantly different between groups ($P = .39$). ONJ occurred as early as 6

Table 2. Adverse Events

Adverse Event	Zoledronic Acid Q4W (4 mg) (n = 1,013) No.	%	Denosumab Q4W (120 mg) (n = 1,020) No.	%
Overall safety summary				
Any adverse event	985	97.2	977	95.8
Adverse events occurring with ≥ 20% frequency in either group				
Nausea	384	37.9	356	34.9
Fatigue	324	32.0	301	29.5
Arthralgia	291	28.7	250	24.5
Back pain	264	26.1	241	23.6
Pyrexia	247	24.4	170	16.7
Bone pain	238	23.5	186	18.2
Vomiting	238	23.5	212	20.8
Anemia	232	22.9	192	18.8
Diarrhea	207	20.4	231	22.6
Dyspnea	190	18.8	222	21.8
Pain in extremity	222	21.9	204	20.0
Headache	214	21.1	197	19.3
Constipation	205	20.2	176	17.3
CTCAE grade ≥ 3 adverse events	635	62.7	609	59.7
CTCAE grade ≥ 3 adverse events occurring with ≥ 5% frequency in either group				
Neutropenia	93	9.2	87	8.5
Dyspnea	61	6.0	82	8.0
Anemia	68	6.7	69	6.8
Fatigue	63	6.2	62	6.1
Adverse events leading to treatment discontinuation	125	12.3	98	9.6
Serious adverse events	471	46.5	453	44.4
Adverse events of interest				
Infectious adverse events*	494	48.8	473	46.4
Infectious serious adverse events*	83	8.2	71	7.0
New primary malignancy	5	0.5	5	0.5
Adjudicated positive ONJ†	14	1.4	20	2.0
Resolved	6 of 14	42.9	10 of 20	50.0
Ongoing	1 of 14	7.1	2 of 20	10.0
Continued until death	5 of 14	35.7	5 of 20	25.0
Unknown‡	2 of 14	14.3	3 of 20	15.0
Local infection	9 of 14	64.3	10 of 20	50.0
Surgical treatment	7 of 14	50.0	7 of 20	35.0
Limited surgery	7 of 14	50.0	7 of 20	35.0
Bone resection	0	0	0	0
Acute phase reactions (first 3 days)§	277	27.3	106	10.4
Adverse events potentially associated with renal toxicity¶	86	8.5	50	4.9
Adverse events potentially associated with renal toxicity occurring with ≥ 1% frequency¶				
Increased blood creatinine	41	4.0	31	3.0
Renal failure	25	2.5	2	0.2
CTCAE grade ≥ 3 adverse events potentially associated with renal toxicity	22	2.2	4	0.4
Serious adverse events potentially associated with renal toxicity	15	1.5	2	0.2

Abbreviations: Q4W, every 4 weeks; CTCAE, Common Terminology Criteria of Adverse Events, Version 3.0; ONJ, osteonecrosis of the jaw.

*Based on Medical Dictionary for Regulatory Activities (MedDRA) v12.0 System Organ Class categorization "infections and infestations."

†As of February 2010.

‡Consent withdrawn, lost to follow-up, status unknown at time of death, or current status unknown.

§Defined as flu-like syndrome including pyrexia, chills, flushing, bone pain, arthralgias, and myalgias that have been associated with intravenous bisphosphonate use, per prescribing information for zoledronic acid.

¶Includes increased blood creatinine, hypercreatininemia, oliguria, renal impairment, proteinuria, renal failure, decreased urine output, decreased creatinine renal clearance, acute renal failure, abnormal renal function test, anuria, increased blood urea, and chronic renal failure.

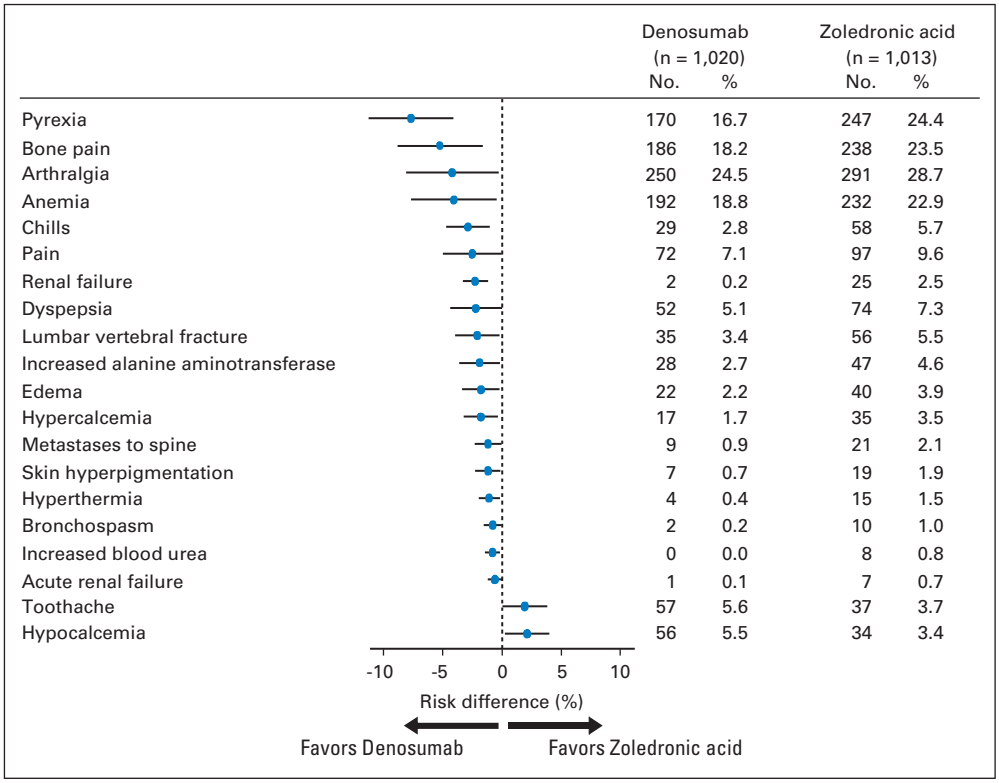

Fig 4. Forest plot of adverse events with between-group differences with an unadjusted $P < .05$ (Fisher's exact test).

months after random assignment. The cumulative incidence in the denosumab and zoledronic acid groups, respectively, was 0.8% and 0.5% at 1 year, 1.9% and 1.2% at 2 years, and 2.0% and 1.4% at 3 years. Known risk factors for ONJ, including history of dental extraction, poor oral hygiene, or use of dental appliance occurred in 18 (90%) of 20 and 10 (71%) of 14 patients in denosumab and zoledronic acid groups, respectively. Fifteen (75%) denosumab-treated and 11 (79%) zoledronic acid-treated patients who developed ONJ were receiving or had received chemotherapy, and four (29%) patients in the zoledronic acid group (*v* zero in the denosumab group) had received prior oral bisphosphonate therapy for osteoporosis. Antiangiogenic therapy has also been associated with an increased risk of ONJ.[29-31] Four (20%) ONJ events in the denosumab group and two (14%) in the zoledronic acid group occurred in patients receiving antiangiogenic therapy. As of February 2010, 10 (50%) denosumab-treated patients and six (43%) zoledronic acid–treated patients had resolution of the ONJ event; 10 (50%) denosumab-treated patients and nine (64%) zoledronic acid–treated patients reported local infection; and seven patients in each group (35%, denosumab; 50%, zoledronic acid) reported undergoing limited surgical procedures such as debridement and sequestrectomy.

DISCUSSION

This study demonstrated that monthly subcutaneous injection of 120 mg of denosumab is superior to monthly intravenous infusion of 4 mg of zoledronic acid at delaying or preventing SREs in patients with breast cancer metastatic to bone. Denosumab significantly reduced the risk of first on-study SRE and subsequent SREs compared with zoledronic acid. Improved efficacy with denosumab was observed as early as 6 months, with absolute differences between the two treatments continuing to increase throughout the study. The improvement in efficacy over zoledronic acid suggests that greater inhibition of osteoclast-induced bone resorption by denosumab, as evident by increased suppression of bone turnover markers, translates into improved clinical outcomes (ie, prevention of SREs).

The risk of renal toxicity is a known AE associated with use of intravenous bisphosphonates[9] and certain chemotherapies. Therefore, management of renal function requires a balance between bisphosphonate use with specific cancer therapies such as platinum-based chemotherapy and other nephrotoxic agents such as antibiotics. Despite dose adjustments per the zoledronic acid prescribing information, the incidence of AEs potentially associated with renal toxicity was still higher and declines in creatinine clearance were more frequently observed with zoledronic acid therapy. Denosumab elimination is likely through nonspecific catabolism in cells of the reticuloendothelial system similar to that of other therapeutic monoclonal antibodies and is not reliant on renal function.[32] Thus, denosumab represents a therapeutic option for patients with bone metastases who have chronic renal failure and renal insufficiency and for those with metastatic breast cancer receiving nephrotoxic platinum-based chemotherapy regimens.

Acute-phase reactions (flu-like symptoms) occurred almost three times more frequently with zoledronic acid than with denosumab. These flu-like symptoms represent an added burden for patients and require greater monitoring and potential treatment following zoledronic acid therapy. Hypocalcemia, a known AE of drugs that reduce bone remodeling, occurred more frequently with

denosumab. Most of these events occurred within the first 6 months after initiating treatment, likely because of the initial reduction in serum calcium commonly observed with denosumab or zoledronic acid, and were generally not associated with symptoms or clinical consequence. No AEs of hypocalcemia were reported as fatal, and grade 3 or 4 AEs of hypocalcemia were similar between groups (1.6%, denosumab; 1.2%, zoledronic acid).

This trial provides additional insight into the incidence of ONJ. Both groups had similar albeit small numbers of patients who experienced ONJ at a fairly constant rate throughout the trial. Known risk factors for ONJ, including prior dental extractions, poor oral hygiene, and dentures, were present in the vast majority of on-study ONJ cases, indicating that patients at risk may be identified. Although additional safety events associated with long-term denosumab use may still be elucidated, these results demonstrate a favorable risk-benefit profile.

In conclusion, denosumab was superior to zoledronic acid for delaying or preventing SREs and has several potentially beneficial characteristics for patients, including the avoidance of renal toxicity and acute phase reactions and the convenience of a subcutaneous injection. Our results support the use of denosumab as a potential novel treatment option for the management of bone metastases in breast cancer patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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