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Randomized, Double-Blind Study of Denosumab Versus Zoledronic Acid in the Treatment of Bone Metastases in Patients With Advanced Cancer (Excluding Breast and Prostate Cancer) or Multiple Myeloma

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A B S T R A C T

Purpose
This study compared denosumab, a fully human monoclonal anti-receptor activator of nuclear factor kappa-B ligand antibody, with zoledronic acid (ZA) for delaying or preventing skeletal-related events (SRE) in patients with advanced cancer and bone metastases (excluding breast and prostate) or myeloma.

Patients and Methods
Eligible patients were randomly assigned in a double-blind, double-dummy design to receive monthly subcutaneous denosumab 120 mg (n = 886) or intravenous ZA 4 mg (dose adjusted for renal impairment; n = 890). Daily supplemental calcium and vitamin D were strongly recommended. The primary end point was time to first on-study SRE (pathologic fracture, radiation or surgery to bone, or spinal cord compression).

Results
Denosumab was noninferior to ZA in delaying time to first on-study SRE (hazard ratio, 0.84; 95% CI, 0.71 to 0.98; $P = .0007$). Although directionally favorable, denosumab was not statistically superior to ZA in delaying time to first on-study SRE ($P = .03$ unadjusted; $P = .06$ adjusted for multiplicity) or time to first-and-subsequent (multiple) SRE (rate ratio, 0.90; 95% CI, 0.77 to 1.04; $P = .14$). Overall survival and disease progression were similar between groups. Hypocalcemia occurred more frequently with denosumab. Osteonecrosis of the jaw occurred at similarly low rates in both groups. Acute-phase reactions after the first dose occurred more frequently with ZA, as did renal adverse events and elevations in serum creatinine based on National Cancer Institute Common Toxicity Criteria for Adverse Events grading.

Conclusion
Denosumab was noninferior (trending to superiority) to ZA in preventing or delaying first on-study SRE in patients with advanced cancer metastatic to bone or myeloma. Denosumab represents a potential novel treatment option with the convenience of subcutaneous administration and no requirement for renal monitoring or dose adjustment.

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INTRODUCTION

Patients with metastatic bone disease or myeloma frequently experience osteoclast-mediated bone destruction, resulting in clinically important complications such as fracture, need for radiation or surgery to bone, spinal cord compression, or hypercalcemia.[1,2] These complications, collectively known as skeletal-related events (SREs),[3-6] lead to pain and decreased quality of life.[7]

Bisphosphonates are frequently administered as part of the overall management of patients with bone metastases to delay or prevent SREs.[8-15] Zoledronic acid (Zometa, Novartis Pharmaceuticals, East Hanover, NJ) has been shown to be effective compared with placebo in prolonging time to first SRE in patients with advanced cancer (excluding breast or prostate) and bone metastases (median delay to first SRE approximately 2 months).[14] Zoledronic acid has also been shown to be effective in

reducing skeletal complications in patients with multiple myeloma or breast cancer and bone metastases in similar degree to pamidronate.[16]

Despite appropriate treatment with zoledronic acid, SREs still occur in patients with bone metastases with their attendant morbidity.[13,16] There are also limitations to intravenous (IV) zoledronic acid use. Renal complications occur frequently in patients with advanced cancer for a variety of reasons (eg, after use of platinum-based chemotherapy or antibiotics).[17-19] Antiresorptive treatment with bisphosphonates can further exacerbate renal impairment in these patients.[20,21] Per Zometa prescribing information, zoledronic acid is not indicated for patients with creatinine clearance lower than 30 mL/min, and must be dose adjusted if creatinine clearance is lower than 60 mL/min, or withheld to minimize the risk for renal failure if creatinine levels rise during treatment.[20] Zoledronic acid has also been associated with occurrence of an acute flu-like syndrome, particularly after the first dose, and with development of osteonecrosis of the jaw (ONJ).[20,22] Alternate therapeutic options that further reduce the occurrence of SREs and minimize potential toxicities are needed. In clinical trials of denosumab (XGEVA; Amgen, Thousand Oaks, CA), there have been no requirements for renal monitoring or dose adjustment, nor have acute-phase reactions been attributed to use of denosumab.

It is hypothesized that tumor cells in the bone lead to increased expression of receptor activator of nuclear factor kappa-B ligand (RANKL) on osteoblasts and their precursors. RANKL is an essential mediator of osteoclast function, formation, and survival.[8,23,24] Excessive RANKL-induced osteoclast activity results in resorption and local bone destruction (with evidence of elevated levels of bone turnover markers), leading to SREs.[11,25]

Denosumab is a fully human monoclonal antibody that binds to and neutralizes RANKL, thereby inhibiting osteoclast function and preventing generalized bone resorption and local bone destruction. Denosumab has been studied in two phase II trials of patients with bone metastasis and advanced cancer and in one phase II trial with myeloma.[26-28] These studies showed that treatment with denosumab at doses ranging from 30 to 180 mg administered every 4 or 12 weeks was associated with rapid and sustained suppression of bone turnover markers and delay of SREs similar to that seen with IV bisphosphonates.

In this phase III study, we evaluated the efficacy and safety of denosumab compared with zoledronic acid in patients with solid tumors and bone metastases or with osteolytic lesions from myeloma.

PATIENTS AND METHODS

Patients

Eligible patients were ≥ 18 years old with histologically or cytologically confirmed solid tumors (except breast and prostate) or myeloma and had radiographic evidence (by x-ray, computed tomography, or magnetic resonance imaging) of at least 1 bone metastasis or osteolytic lesion. Creatinine clearance ≥ 30 mL/min and an Eastern Cooperative Oncology Group performance status ≤ 2 were required at study entry. Key exclusion criteria included prior treatment with IV bisphosphonates, planned radiation or surgery to bone, and unhealed dental/oral surgery.

Study Design

In this international phase III, randomized, double-blind, active-controlled trial denosumab was compared with zoledronic acid for the treatment of established bone metastases in patients with advanced cancer or myeloma. Eligible patients were randomly assigned 1:1 by interactive voice response system to receive either subcutaneous injections of denosumab 120 mg and an IV infusion of placebo every 4 weeks (Q4W), or a single, 15-minute minimum IV infusion of zoledronic acid 4 mg (dose adjusted for renal impairment) and a subcutaneous injection of placebo Q4W. The random assignment schedule was prepared by an individual independent of the study team. Random assignment was stratified by tumor type (non–small-cell lung cancer [NSCLC], myeloma, or other), previous SRE (yes or no), and systemic anticancer therapy at enrollment (yes or no). Enrollment in the myeloma stratum was limited to 10% of the total study population.

The dose of the IV product was adjusted at baseline if creatinine clearance was ≤ 60 mL/min (using the Cockcroft-Gault formula[29]), and administration of IV product was withheld for any patient who experienced a rise in serum creatinine, per the Zometa prescribing information[20]; re-exposure to IV product was only permitted when serum creatinine returned to within 10% of the baseline value.

Daily supplementation with ≥ 500 mg calcium and ≥ 400 U vitamin D was strongly recommended. Specific anticancer therapy and other concomitant medications or treatments were allowed.

Patients in this trial provided written informed consent before any study-specific procedure. The study was approved by the institutional review board or local ethics committee for each study site. Patients were observed for survival for 2 years after the last dose of blinded investigational product.

Assessment of Outcomes

The primary analysis was conducted 34 months after enrollment initiated. SRE was defined as pathologic fracture, spinal cord compression, or radiation or surgery to bone. Fractures were identified in a blinded manner by two or more expert radiologists through central imaging review based on skeletal surveys obtained every 12 weeks or on unscheduled radiographic assessments performed to evaluate bone complications during routine care. Spinal cord compression reported by investigators was also confirmed in a blinded manner by central imaging review. Radiation to bone was given to control pain or treat or prevent pathologic fractures, or to treat or prevent spinal cord compression. Surgery to bone included procedures to prevent imminent fractures or spinal cord compression or to set/stabilize fractures.

At regular intervals, an external data monitoring committee reviewed safety and efficacy data.

Study End Points

The primary end point was time to first on-study SRE comparing denosumab with zoledronic acid for noninferiority. Secondary efficacy end points, evaluated only if noninferiority was demonstrated, were superiority tests comparing denosumab and zoledronic acid for time to first on-study SRE and time to first-and-subsequent SRE (multiple-event analysis). A subsequent SRE was defined as an event occurring ≥ 21 days after the previous SRE.

Safety end points included the incidence of treatment-emergent adverse events (AEs) and serious AEs (SAEs), changes in laboratory values, and incidence of antidenosumab antibodies (binding and neutralizing). All AEs were coded using the Medical Dictionary for Regulatory Activities version 12.0 system. Patients were evaluated on study day 1 and Q4W thereafter. Oral examinations were conducted at baseline and every 6 months thereafter. Potential ONJ events were adjudicated by an independent, blinded ONJ adjudication committee of external experts using a predetermined case definition of ONJ as a lesion occurring in the oral cavity with exposed alveolar or palatal bone where gingival or alveolar mucosa is normally found, persisting for longer than 8 weeks without prior therapeutic head/neck radiation.[30] Resolution of ONJ was considered to have occurred if there was mucosal healing with covering of the area of exposed bone.

Exploratory end points included bone turnover markers (measured at baseline and week 13), overall survival, and overall disease progression.

Statistical Analysis

The planned sample size was 1,690 patients (845 patients per treatment arm). Assuming a true hazard ratio (HR) of 0.9, 745 patients with at least one SRE would provide sufficient power to detect noninferiority of denosumab to zoledronic acid, based on a synthesis approach[31] designed to demonstrate that denosumab preserves ≥ 50% of the effect of zoledronic acid. Assuming a true HR of 0.8 for both secondary end points and a correlation coefficient of 0.6

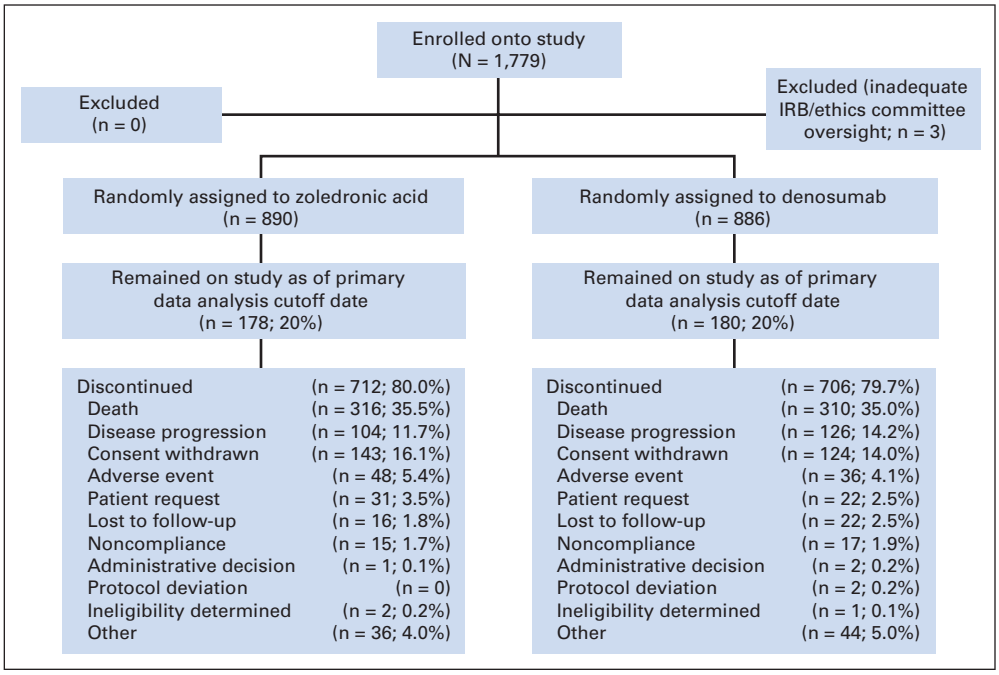

Fig 1. Patient disposition. IRB, institutional review board.

between the end points, 745 patients with SREs would provide sufficient power to detect superiority of denosumab for at least one secondary end point.

In this intention-to-treat analysis, time to first SRE was analyzed using a Cox model, and time to first-and-subsequent SRE was analyzed using the Andersen and Gill approach.[32] To control the significance level at .05, the secondary efficacy end points were tested only if the null hypothesis of the primary end point was rejected, and the Hochberg approach was used to adjust for the multiple secondary end points. The significance level for each exploratory efficacy end point was .05 without adjusting for multiplicity. All statistical testing was two sided. The van Elteren test stratified by stratification factors was used to compare between-group percent changes from baseline to week 13 in urine N-telopeptide corrected for urine creatinine (uNTx/Cr) and bone-specific alkaline phosphatase levels. A full description of the methodology used for statistical analysis appears in the Appendix (online only).

Incidence rates for treatment-emergent AEs are summarized for patients who received ≥ 1 dose of investigational product. The proportion of patients with positively adjudicated ONJ was compared using Fisher's exact test by treatment group in prespecified fashion. An exploratory analysis of AEs without adjustments for multiple safety comparisons is also presented. Assessments for antidenosumab antibodies were conducted using screening methods previously described.[33]

Statistical analysis was conducted by Amgen in Thousand Oaks, CA. The lead investigators assisted with review and interpretation of the analyses.

RESULTS

Patients

Patient enrollment occurred between June 2006 and May 2008 from 321 centers worldwide (890 zoledronic acid, 886 denosumab; Fig 1). Baseline characteristics were generally balanced between treatment groups, except for sex, age group, and the presence of visceral metastases (Table 1). Cancer therapies administered before random assignment included chemotherapy in 87% of patients, surgery in 46%, radiotherapy in 38%, and other therapies in 2% of patients. Prior bisphosphonate use was 3% in both treatment arms (n = 28, zoledronic acid; n = 24, denosumab). Median time (quartile [Q]1, Q3) on-study was approximately 7 months (Q1, 3; Q3, 14) in both treatment arms. The median number (Q1, Q3) of doses administered was 7.0 (Q1, 4.0; Q3, 14.0) for zoledronic acid and 7.0 (Q1, 4.0; Q3, 15.0) for denosumab, with cumulative drug exposure of 651.9 patient-years for zoledronic acid and 675.3 patient-years for denosumab. At the date of primary data analysis, approximately 20% of patients remained on-study in each treatment arm. Study discontinuations were primarily attributed to death (35%), withdrawal of consent (15%), or disease progression (13%).

Efficacy

Denosumab was noninferior to zoledronic acid in delaying time to first on-study SRE (HR, 0.84; 95% CI, 0.71 to 0.98; $P = .0007$, representing 16% reduction in hazard; Fig 2). The median time to first on-study SRE was 20.6 months for denosumab and 16.3 months for zoledronic acid. After adjustment for multiple comparisons using the Hochberg procedure to test for superiority for time to first SRE, the P value was .06 (.03 before adjustment) and therefore did not reach statistical significance. Time to first-and-subsequent SRE (multiple events) analysis demonstrated a rate ratio of 0.90 for denosumab compared with zoledronic acid (95% CI, 0.77 to 1.04; $P = .14$; 10% rate reduction; Fig 3), which was not statistically significant.

Overall survival (HR, 0.95; 95% CI, 0.83 to 1.08; $P = .43$) and disease progression (HR, 1.00; 95% CI, 0.89 to 1.12; $P = 1.0$) were similar between treatment groups (Fig 4).

Patients treated with denosumab experienced a greater suppression of bone turnover markers than with zoledronic acid. Between baseline and study week 13, levels of uNTx/Cr decreased by a median of 76% for denosumab (n = 546) and 65% for zoledronic acid (n = 543; $P < .001$) and bone-specific alkaline phosphatase

Table 1. Baseline Demographics and Characteristics

Demographic or Characteristic	Zoledronic Acid 4 mg Q4W (n = 890) No.	%	Denosumab 120 mg Q4W (n = 886) No.	%
Male sex	552	62	588	66
Median age, years	61		60	
Range	22-87		18-89	
≥ 65 years	336	38	299	34
ECOG status				
0	236	27	240	27
1	492	55	508	57
2	157	18	136	15
Missing	5	< 1	2	< 1
Primary tumor type				
Non–small-cell lung cancer	352	40	350	39
Multiple myeloma	93	10	87	10
Other	455	50	449	51
Prior SRE*	446	50	440	50
Median time from initial diagnosis of bone metastasis to randomization, months	2		2	
Minimum	0		0	
Maximum	130		152	
Prior anti-neoplastic treatment	855	96	845	95
Systemic anti-cancer therapy	770	87	767	87
Radiotherapy	353	40	324	37
Surgery	406	46	409	46
Other	20	2	15	2
Presence of visceral metastases	448	50	474	54
Liver	167	19	171	19
Lung	162	18	239	27
Other	340	38	319	36

Abbreviations: Q4W, every 4 weeks; ECOG, Eastern Cooperative Oncology Group; SRE, skeletal-related events.
*Based on random assignment.

decreased by 37% for denosumab (n = 578) and 29% for zoledronic acid (n = 581; $P < .001$).

The effect of denosumab on time to first on-study SRE relative to zoledronic acid by tumor stratification factors resulted in an HR of 0.84 for NSCLC (95% CI, 0.64 to 1.10; $P = .20$); 1.03 for myeloma (95% CI, 0.68 to 1.57; $P = .89$); and 0.79 for other solid tumors (95% CI, 0.62 to 0.99; $P = .04$), with an interaction test between tumor type and treatment ($P = .5$). An ad hoc analysis examining overall survival for the same three strata demonstrated an HR of 0.79 for NSCLC (95% CI, 0.65 to 0.95), 2.26 for myeloma (95% CI, 1.13 to 4.50), and 1.08 for other solid tumors (95% CI, 0.90 to 1.30).

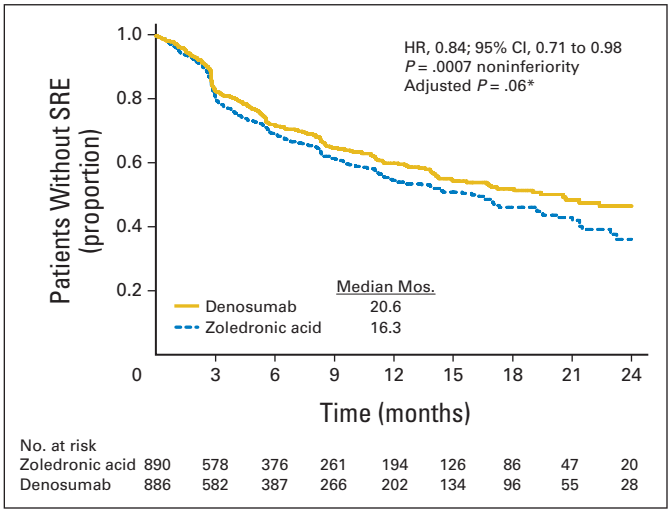

Fig 2. Kaplan-Meier estimate of time to first on-study skeletal-related events (SREs). HR, hazard ratio. (*) Adjusted for multiplicity.

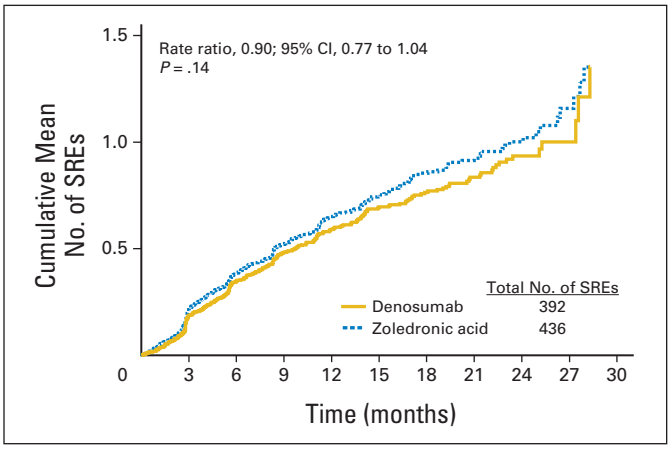

Fig 3. Time to first-and-subsequent on-study skeletal-related events (SREs; multiple event analysis*), which is represented as the cumulative mean number of SRE over time. *P* value adjusted for multiplicity. (*) Events that occurred at least 21 days apart.

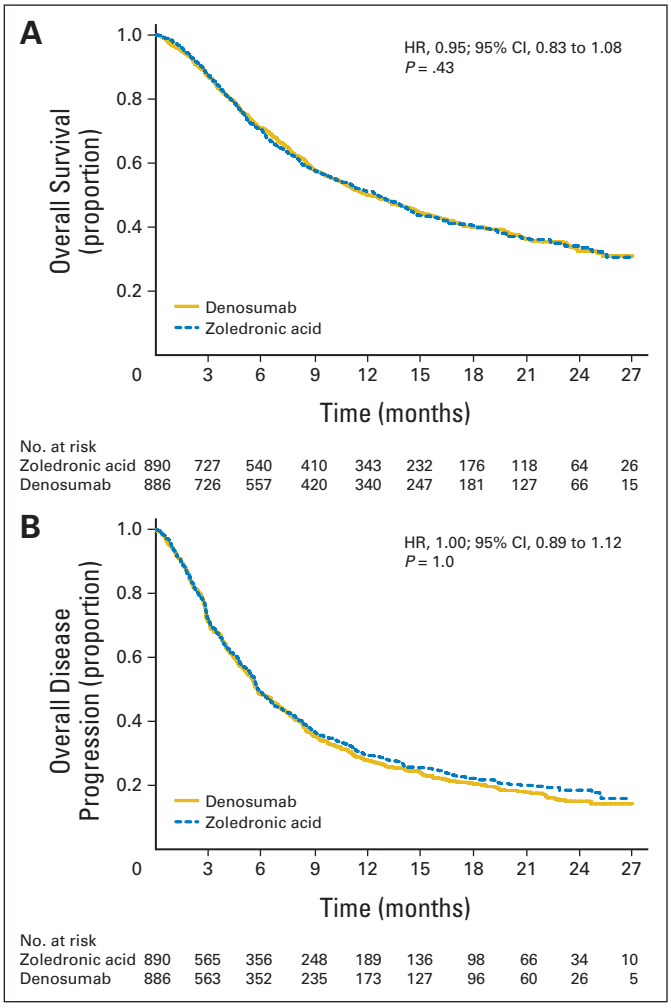

Fig 4. Kaplan-Meier estimates of (A) overall survival and (B) time to disease progression by treatment group. HR, hazard ratio.

Safety

Patients in both treatment groups experienced similar rates of overall AEs (Table 2). Rates of infectious AEs and SAEs were, respectively, 39.7% for zoledronic acid versus 40.8% for denosumab and 13.4% for zoledronic acid versus 14.6% for denosumab. New primary malignancy occurred in three patients (0.3%) receiving zoledronic acid and in five patients (0.6%) receiving denosumab. All patients with drug hypersensitivity were receiving drugs known to be associated with hypersensitivity reactions (eg, taxane chemotherapies).

Adverse events of hypocalcemia occurred more frequently with denosumab (10.8% denosumab; 5.8% zoledronic acid). Hypocalcemia is expected, as RANKL inhibition by denosumab targets osteoclasts specifically. In general the clinical consequences of hypocalcemia were not observed.

Centrally determined grade 3 and 4 decreases in albumin-adjusted calcium values were reported in nine patients (1.0%) receiving zoledronic acid and 20 patients (2.3%) receiving denosumab. IV calcium was administered at some point on-study to 2.7% of patients receiving zoledronic acid and 5.7% receiving denosumab.

For AEs of cardiac arrest, two (67%) of three for zoledronic acid and 10 (83%) of 12 for denosumab were noncardiovascular in nature and appeared associated with death from cancer progression, cancer-related complications, or unknown causes as noted by blinded external adjudication.

No patients developed neutralizing antidenosumab antibodies.

Positively adjudicated ONJ occurred with cumulative incidence rates in the zoledronic acid and denosumab groups of, respectively, 0.6% and 0.5% at 1 year, 0.9% and 1.1% at 2 years, and 1.3% and 1.1% at 3 years ($P = 1.0$). Among patients who developed ONJ, oral risk factors known to be associated with ONJ, such as tooth extraction, poor oral hygiene, or use of dental appliances occurred on study in 10 patients (n = 11; 91%) receiving zoledronic acid and seven (n = 10; 70%) receiving denosumab. Seven (64%) and six patients (60%) were receiving chemotherapy in the zoledronic acid and denosumab arms, respectively. Six patients (54%) on zoledronic acid and one patient (9%) on denosumab were receiving antiangiogenic therapy.[34-36] No patient in either arm had previously received bisphosphonates. As of April 2010, ONJ had resolved in three patients (27%) on zoledronic acid and four patients (40%) on denosumab. Five patients in each arm (45% zoledronic acid; 50% denosumab) reported local infection, six patients (55%) receiving zoledronic acid and four patients (40%) receiving denosumab underwent limited surgical procedures such as debridement and sequestrectomy, and one patient (10%) receiving denosumab who had a previous history of osteomyelitis underwent bone resection.

AEs associated with acute-phase reactions within the first 3 days after dose 1 of investigational product occurred in 14.5% of patients receiving zoledronic acid versus 6.9% receiving denosumab. Examples include pyrexia (5.9% zoledronic acid; 0.5% denosumab), fatigue (2.1% zoledronic acid; 1.0% denosumab), and arthralgia (1.9% zoledronic acid; 0.7% denosumab).

Initial dose adjustments of zoledronic acid to levels lower than 4 mg occurred per the Zometa product label for 152 patients (17.3%) who had baseline creatinine clearance lower than 60 mL/min. Doses of zoledronic acid were withheld because of elevated serum creatinine in 78 patients (8.9%; 344 total doses). No dose adjustments or dose withholding for renal function were required for denosumab. Despite these label-mandated dosing precautions for zoledronic acid in patients with impaired renal function, overall renal AEs occurred in 10.9% of patients receiving zoledronic acid and 8.3% receiving denosumab. In patients with a baseline creatinine clearance lower than 60 mL/min (n = 162 zoledronic acid; 151 denosumab), renal AEs occurred in 21.6% of patients receiving zoledronic acid compared with 11.3% receiving denosumab. On-study abnormal serum creatinine levels (National Cancer Institute Common Toxicity Criteria grading 1 to 4) were observed in 23.9% of patients receiving zoledronic acid versus 16.5% of patients receiving denosumab.

DISCUSSION

In this phase III trial, monthly subcutaneous injection of denosumab 120 mg was noninferior to monthly IV infusion of zoledronic acid 4 mg in delaying or preventing SREs across a broad range of tumor types, with denosumab showing a trend toward superiority for time to first on-study SRE.

Patients who experience one SRE are more likely to experience subsequent skeletal complications.[37] In this study, the rate at which subsequent SREs occurred with denosumab was lower than that for the zoledronic acid group although this was not statistically significant.

Table 2. Adverse Events

Parameter	Zoledronic Acid 4 mg Q4W (n = 878) No.	Zoledronic Acid 4 mg Q4W (n = 878) %	Denosumab 120 mg Q4W (n = 878) No.	Denosumab 120 mg Q4W (n = 878) %	Unadjusted P*
Overall safety summary					
Adverse events	842	95.9	841	95.8	1.00
Adverse events occurring with ≥ 20% frequency in either arm					
Nausea	266	30.3	248	28.2	.37
Anemia	286	32.6	242	27.6	.03
Dyspnea	200	22.8	220	25.1	.29
Fatigue	220	25.1	211	24	.66
Constipation	214	24.4	191	21.8	.21
Vomiting	183	20.8	186	21.2	.91
Back pain	196	22.3	173	19.7	.20
Asthenia	180	20.5	172	19.6	.68
Anorexia	195	22.2	165	18.8	.09
Pyrexia	182	20.7	139	15.8	.01
CTC grade 3, 4, or 5 adverse events	702	80	673	77	.10
Serious adverse events	581	66	552	63	.16
Adverse events leading to treatment discontinuation	109	12	91	10	.20
Adverse events of interest					
Acute phase reactions (first 3 days)	127	14.5	61	6.9	< .001
Adjudicated positive ONJ	11	1.3	10	1.1	1.00
Infectious adverse events†	349	39.7	358	40.8	.70
Infectious serious adverse events†	118	13.4	128	14.6	.54
New primary malignancy	3	0.3	5	0.6	.73
Renal adverse events‡	96	10.9	73	8.3	.07
Increased blood creatinine	43	4.9	29	3.3	.12
Renal failure	25	2.8	20	2.3	.55

Abbreviations: Q4W, every 4 weeks; CTC, National Cancer Institute Common Toxicity Criteria; ONJ, osteonecrosis of the jaw.
*Not adjusted for multiplicity.
†Based on Medical Dictionary for Regulatory Activities version 12.0 System Organ Class categorization infections and infestations.
‡Includes blood creatinine increased, renal failure, renal failure acute, proteinuria, blood urea increased, renal impairment, urine output decreased, anuria, oliguria, azotemia, hypercreatininemia, creatinine renal clearance decreased, renal failure chronic, and blood creatinine abnormal.

Denosumab also suppressed uNTx to a greater extent than zoledronic acid, demonstrating its more potent antiresorptive effects and supporting the clinical observations for the SRE end points.

Overall survival and disease progression were similar between treatment arms. Although differences in survival for both NSCLC and multiple myeloma were observed in a post hoc analysis, these may be due to differences in prognostic variables at study entry in this highly heterogeneous population or due to differences in specific antineoplastic treatments on-study. These findings warrant further investigation and analysis is ongoing.

Consistent with the more potent antiresorptive effect of denosumab compared with zoledronic acid, hypocalcemia occurred more frequently with denosumab. However, most of the hypocalcemia reported represented asymptomatic, low blood calcium values and only a small percentage were either symptomatic or required supplementation with IV calcium.

ONJ occurred infrequently and the clinical characteristics were similar in both treatment groups; most were associated with known risk factors of tooth extractions, poor oral hygiene, or dental appliance use or on-study chemotherapy use. There was evidence of resolution of the ONJ on-study based on mucosal covering of exposed bone.

Despite appropriate adjustments of the zoledronic acid dosing regimen for renal function, there was still evidence of an excess of renal AEs with zoledronic acid in this study. It is noteworthy that denosumab has no limitations with respect to renal impairment as it is a monoclonal antibody and is eliminated by intracellular catabolism in phagocytes, similar to the clearance mechanism of other therapeutic monoclonal antibodies with no evidence of renal effects.[38,39]

As would be expected based on the known adverse effect profile of zoledronic acid there was a substantially higher frequency of an initial flu-like syndrome in the zoledronic acid group. These events can be medically relevant in the clinic setting and represent an added burden to patients.

In conclusion, denosumab, with its novel mode of action and targeted nature, administered as a monthly subcutaneous injection represents a potential new treatment option for the management of bone metastases across a broad range of tumor types without the need for IV administration or renal monitoring, and without the burden of acute-phase reactions experienced by many patients receiving zoledronic acid.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Statistical Analysis

The primary and secondary efficacy analyses included the full (intention to treat) analysis set of all randomly assigned patients.

The primary end point was analyzed using a Cox model with treatment groups as the independent variable and stratified by the factors used to balance randomization. The noninferiority test for the primary end point used a synthesis approach.[32] Directly comparing zoledronic acid and placebo, the estimate of the effect of zoledronic acid relative to placebo was based on three historical trials and a three-step approach. First, data from a solid tumor trial of placebo versus zoledronic acid (Rosen LS, et al: J Clin Oncol 21:3150-3157, 2003) provided an initial estimate of the hazard ratio for placebo relative to zoledronic acid. Second, data from two myeloma trials (placebo *v* pamidronate [Berenson JR, et al: N Engl J Med 334:488-493, 1996] and zoledronic acid *v* pamidronate[16]) were combined to obtain a second estimate of the hazard ratio for placebo relative to zoledronic acid. Third, the results of the previous two steps were combined to obtain an overall estimate of the hazard ratio. To demonstrate that denosumab preserved at least 50% of the effect of zoledronic acid, these historical data were combined with the estimate of the effect of denosumab relative to zoledronic acid from this trial. If the CI for this estimate excluded zero, then denosumab would be declared noninferior to zoledronic acid. Subsequently, the results of the Cox model were used directly to determine if denosumab was superior to zoledronic acid.

For time to first-and-subsequent on-study SRE, the Andersen and Gill (Anderson PK, et al: Ann Stat 10:1100-1120, 1982) approach was used. To control the overall type I error for multiple comparisons, both secondary end points were tested simultaneously using the Hochberg procedure (Westfall PH, et al: SAS Institute Inc, Cary, NC, 1999).

For time to overall survival and time to disease progression analyses, Kaplan-Meier curves and hazard ratios ($\pm$ 95% CI) were calculated of denosumab compared with zoledronic acid using a proportional hazard model stratified by stratification factors and including treatment groups, age, sex, time from primary diagnosis of primary cancer to first evidence of metastatic disease, time from initial diagnosis to first bone metastasis, visceral metastasis (yes or no), and baseline Eastern Cooperative Oncology Group status as independent variables (Cox DR: Journal of Royal Statistical Society, Series B 34:187-220, 1972).