Extended Efficacy and Safety of Denosumab in Breast Cancer Patients with Bone Metastases Not Receiving Prior Bisphosphonate Therapy

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Abstract

Purpose: Denosumab, a fully human monoclonal antibody to RANKL, suppresses bone resorption. This study evaluated the effects of denosumab in i.v. bisphosphonate (IV BP) – naïve patients with breast cancer-related bone metastases.

Experimental Design: Eligible women (n = 255), stratified by type of antineoplastic therapy, were randomized to 1 of 5 blinded denosumab cohorts or an open-label IV BP cohort. Denosumab was administered s.c. every 4 weeks (30, 120, or 180 mg) or every 12 weeks (60 or 180 mg) through 21 weeks. Final efficacy results for up to 25 weeks are reported, including percentage change from baseline in urine N-telopeptide corrected for creatinine (uNTx/Cr) and incidence of skeletal-related events (SRE). Safety results are reported through the end of follow-up (up to 57 weeks).

Results: At week 13 and 25, the median percent changes in uNTx/creatinine (Cr) among patients with measurable uNTx were -73% and -75% for the pooled denosumab groups and -79% and -71% for the IV BP group. Among patients with ≥1 postbaseline measurement of uNTx at week 25, 52% (109 of 208) of denosumab-treated patients and 46% (19 of 41) of IV BP – treated patients achieved ›65% uNTx/Cr reduction. On-study SREs occurred in 12% (26 of 211) of denosumab-treated patients and 16% (7 of 43) of IV BP – treated patients. Overall rates of adverse events were 95% in denosumab and IV BP groups. No denosumab-related serious or fatal adverse events occurred.

Conclusions: In IV BP – naïve breast cancer patients with bone metastases, denosumab suppresses bone turnover and seems to reduce SRE risk similarly to IV BPs, with a safety profile consistent with an advanced cancer population receiving systemic therapy.

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Approximately three-quarters of women who have metastatic breast cancer develop bone metastases (1–4), which can result in complications such as skeletal-related events (SRE), including fracture, spinal cord compression, and hypercalcemia (1, 5). In patients with breast cancer and bone metastases, bone turnover markers such as urine N-telopeptide (uNTx) are also elevated, predicting an increased risk of skeletal complications, disease progression, and death (6–8).

Cancer-induced bone metastases are characterized by a continuous cycle of tumor growth and osteolysis, marked by the activity of receptor activator of nuclear factor-κB ligand (RANKL), a key mediator of osteoclast differentiation, function, and survival (9–11). Binding of RANKL to the surface of osteoclasts stimulates increased bone resorption and the release of growth factors that trigger a continuing cycle of bone destruction and tumor cell proliferation (12). RANKL also promotes migration of RANK-expressing tumor cells to bone (13).

Bone metastases are treated with antineoplastic treatments, radiation, and i.v. bisphosphonates (IV BP). Although IV BPs such as zoledronic acid, pamidronate, and ibandronate can be effective in the treatment of complications from bone

metastases, not all patients respond to IV BP treatment. In addition, the dosage and use of IV BPs in some patients are limited by renal toxicity and osteonecrosis. Additional therapies are needed to treat patients with bone metastases.

Denosumab is a fully human monoclonal antibody that binds and neutralizes RANKL (14), thereby inhibiting osteoclast function and bone resorption. Denosumab provides a potential option for the treatment of bone loss caused by bone metastases, multiple myeloma, or osteoporosis. A single s.c. dose of denosumab suppressed bone turnover for up to 6 months in postmenopausal women with low bone mass and for up to 12 weeks in patients with multiple myeloma or breast cancer (14, 15).

This trial investigated the efficacy and safety of denosumab in IV BP–naïve patients with breast cancer and bone metastases and compared the results with those observed in patients treated with IV BPs. Thirteen-week results were previously described (16). Here, we report final efficacy results of the study at week 25, including reductions in markers of bone turnover and the proportion of patients experiencing SREs. We also report on final results of off-treatment safety follow-up through week 57.

Patients and Methods

Design. In this phase 2, randomized, partially double-blinded, active-controlled, international, multicenter, multidose, parallel group study, patients were stratified by the type of antineoplastic treatment received at baseline: hormone therapy or chemotherapy (including patients who received both). Patients in each stratum were randomized in a 1:5 ratio to receive open-label IV BP (zoledronic acid, pamidronate, or ibandronate) every 4 wk (Q4W) or s.c. injections of denosumab Q4W (30, 120, or 180 mg) or every 12 wk (Q12W; 60 or 180 mg). During the 32-wk off-treatment follow-up period, patients in all treatment groups had the option of receiving IV BPs, which are considered standard-of-care therapy.

The primary end point of the study, reported previously, was the percentage change from baseline to week 13 in uNTx/Cr (16). Additional efficacy end points were the percentage change from baseline to week 25 in uNTx/Cr, the proportion of patients who achieved a >65% reduction in uNTx/Cr from baseline, and the median time to achieve this reduction. A reduction of >65% is the average percentage decrease reported in the literature for patients with bone metastases treated with IV BPs (17–20). The percentage of patients experiencing an SRE (fracture, surgery or radiation to bone, or spinal cord compression) while on the study was also evaluated. Safety parameters summarized were the incidence of treatment-emergent adverse events (AE), the incidence of acute-phase AEs (a flu-like syndrome of combined fever, chills, flushing, bone pain, arthralgias, and myalgias), changes from baseline in laboratory values for albumin-adjusted calcium, serum Cr, liver enzymes, and electrolytes; and development of antidenosumab antibodies.

Patients. The study, conducted at 56 centers in Europe, North America, and Australia, enrolled women who had breast cancer with radiologic evidence of bone metastases. Patients were at least ages 18 y and ambulatory, with adequate organ function, and an Eastern Cooperative Oncology Group status of 0, 1, or 2; they had not previously received IV BPs and had no evidence of impending fracture in weight-bearing bones. Key exclusion criteria included pregnancy; disorders associated with abnormal bone metabolism; brain metastases; prior malignancy except for breast cancer, basal cell carcinoma, or cervical carcinoma *in situ*; current therapy with chronic systemic corticosteroids; or receipt of calcitonin, parathyroid hormone-related peptides, mithramycin, strontium ranelate, or gallium nitrate within 8 wk of randomization. All patients provided written informed consent before enrollment, and the study was approved by the Institutional Review Board or Ethics Committee for each site.

Procedures. Treatments were administered on day 1 and Q4W thereafter through week 21. Patients received either s.c. injections (denosumab and placebo to maintain blinding to dose) or i.v. infusions of bisphosphonates, administered according to the country-specific product information insert. All patients were instructed to take 500 mg calcium and 400 IU vitamin D daily.

Patients were followed for a total of 57 wk: 25 wk of treatment and 32 wk of follow-up. Serum chemistries and denosumab serum concentrations were measured on study day 1 and periodically through the treatment period. Antidenosumab antibodies were measured by ELISA at week 1 and at scheduled intervals through the treatment and follow-up periods. Medical and medication history were recorded; physical examinations, assessment of Eastern Cooperative Oncology Group status, monitoring of vital signs, weight and height measurements, electrocardiograms, and collection of urine and blood were done periodically throughout the study. The effect of denosumab on bone resorption was assessed by measurement of uNTx/Cr levels in the second morning void of urine. The baseline value for uNTx/Cr was established before initial dosing; measurements were collected at week 1 and at scheduled intervals through the treatment and follow-up periods. Off-treatment follow-up included four visits for assessment of uNTx/Cr levels and safety evaluations. AEs, other laboratory values, and concomitant medications were recorded and assessed at all study visits. AEs associated with an acute-phase reaction were monitored and using Medical Dictionary for Regulatory Activities 9.0 preferred search terms.

Statistical analyses. This study was planned for a sample size of 240 patients (40 patients in each of 6 treatment arms), providing a 95% confidence interval of the primary end point within $\pm$5.1%, assuming a 10% drop-out rate and a 15.7% SD for the pooled patient group. Statistical tests were descriptive evaluations of differences between groups; statistical testing to calculate *P* values was not planned for this study because of the small sample size. The study included a control arm to further characterize the effects of denosumab. Percentage changes in uNTx/Cr from baseline were calculated for all patients who were randomized, received at least one dose of study drug, and had measurements of uNTx/Cr at baseline (pretreatment) and postbaseline. A Kaplan-Meier analysis was done to determine the time from randomization to >65% reduction in uNTx/Cr and time from randomization to first on-study SRE. All patients who were randomized and received at least one dose of denosumab or IV BP were included in the safety analysis.

Results

Demographics and baseline characteristics. A total of 255 women with breast cancer who had bone metastases were enrolled. All patients received denosumab or IV BP and were evaluated for efficacy and safety, except for 1 patient randomly assigned to the denosumab 120-mg Q4W cohort who was not treated because of a low baseline hemoglobin concentration. Most patients (87% of the denosumab group and 84% of the IV BP group) had received all scheduled treatments at the time of the week 25 visit, and more than two-thirds of patients (70% denosumab and 67% IV BP) attended the final safety follow-up visit at week 57. Overall baseline demographics, which been previously described (16), were balanced among all cohorts (Table 1).

Bone metabolism. All doses of denosumab resulted in suppression of uNTx/Cr; suppression was seen as early as 2 weeks after administration of the initial dose and continued through week 25 (Fig. 1A and B). At week 13 (the primary end point), the median percentage change from baseline was -73% in the pooled denosumab cohort and -78% in the IV BP cohort. Similar suppression of uNTx/Cr was seen at week 25 among

patients with measurable uNTx, for both the pooled denosumab group and the IV BP group: -75% for denosumab-treated patients and -71% for the IV BP group. The suppression of uNTx/Cr did not seem to be affected by the type of antineoplastic therapy that patients received (hormonal therapy or chemotherapy). At week 25, among patients with at least 1 postbaseline measurement of uNTx, 52% of denosumab-treated patients had a uNTx/Cr reduction of >65%, as did 46% of IV BP-treated patients (Fig. 1C). The median time to achieve a reduction of uNTx/Cr >65% seemed to be similar among treatment groups (9-13 days; Fig. 1D), with the exception of the denosumab 180 mg Q12W dose group (30 days). As was observed at 13 weeks (16), uNTx/Cr remained suppressed in patients who received denosumab Q4W but not in all patients in the Q12W dose groups.

The levels of other markers of bone turnover (type 1 serum-C telopeptide, bone-specific alkaline phosphatase, tartrate-resistant acid phosphatase 5b, procollagen 1 NH_2-terminal peptide, and osteocalcin) were also suppressed by denosumab and IV BPs at week 25 (Fig. 2). Suppression was seen as early as week 2 for serum-C telopeptide, procollagen 1 NH_2-terminal peptide, and bone-specific alkaline phosphatase, and by week 13 for bone-specific alkaline phosphatase and osteocalcin.

SREs. By week 25, the proportion of patients who experienced at least 1 SRE was similar among patients who received denosumab (12%) and those who received IV BPs (16%). Most

Table 1. Baseline demographics and disease characteristics of study population

	IV BP (*n* = 43)	Denosumab					
		30 mg Q4W (*n* = 42)	120 mg Q4W (*n* = 42)	180 mg Q4W (*n* = 43)	60 mg Q12W (*n* = 42)	180 mg Q12W (*n* = 43)	All Denosumab (*n* = 212)
Sex, *n* (%)							
Female	43 (100)	42 (100)	42 (100)	43 (100)	42 (100)	43 (100)	212 (100)
Age in years—mean (SD)	52 (11)	57 (11)	57 (11)	58 (14)	59 (12)	58 (9)	58 (11)
ECOG status—*n* (%)							
0	19 (44)	26 (62)	26 (62)	23 (54)	28 (67)	32 (74)	135 (64)
1	20 (46)	15 (36)	15 (36)	18 (42)	11 (26)	11 (26)	70 (33)
2	4 (9)	1 (2)	1 (2)	1 (2)	3 (7)	0 (0)	6 (3)
3	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	1 (<1)
Hormone receptor status,* *n* (%)							
Negative	4 (9)	7 (17)	8 (19)	4 (9)	6 (14)	8 (19)	33 (16)
Positive	30 (70)	25 (60)	24 (57)	28 (65)	26 (62)	26 (60)	129 (61)
Unknown	9 (21)	10 (24)	10 (24)	11 (26)	10 (24)	9 (21)	50 (24)
Time since original diagnosis in years—median (min, max)	3.1 (0.0, 15.6)	3.5 (0.0, 16.0)	2.2 (0.1, 32.8)	3.3 (0.0, 18.5)	3.6 (0.0, 26.1)	3.3 (0.1, 14.5)	3.3 (0.0, 32.8)
Time since bone metastases in months—median (min, max)	2.1 (0.3, 26.9)	2.5 (0.4, 26.3)	1. 8 (0.5, 36.5)	2.5 (0.3, 65.5)	1.8 (0.3, 206.2)	1.8 (0.1, 95.7)	1.9 (0.1, 206.2)
Bone metastases >2—*n* (%)	34 (79)	34 (81)	32 (76)	34 (79)	28 (67)	28 (65)	156 (74)
Total number of previous SREs, *n* (%)							
0	28 (65)	27 (64)	29 (69)	23 (54)	26 (62)	35 (81)	140 (66)
1	14 (33)	13 (31)	11 (26)	19 (44)	12 (29)	6 (14)	61 (29)
≥2	1 (2)	2 (5)	2 (5)	1 (2)	4 (10)	2 (5)	11 (5)
eGFR median (min, max)	98.7 (51.1, 160.2)	92.4 (46.2, 169.8)	92.3 (54.2, 158.1)	83.3 (51.0,144.1)	88.2 (55.4, 200.9)	88.6 (29.0, 139.6)	88.8 (29.0, 200.9)
Baseline uNTx/Cr (nmol/L/mmol/L) median (Q1, Q3)	49.1 (22.7, 111.6)	44.0 (22.9, 86.0)	63.5 (31.9, 124.6)	45.8 (24.7, 79.3)	57.1 (35.5, 131.1)	41.1 (23.7, 106.6)	46.0 (25.2, 103.3)
Baseline sCTx (ng/mL) median (Q1, Q3)	0.58 (0.39, 0.70)	0.56 (0.36, 0.77)	0.60 (0.41, 0.87)	0.60 (0.34, 0.92)	0.56 (0.35, 0.98)	0.47 (0.22, 0.72)	0.56 (0.34, 0.84)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate; Q1, first quartile; Q3, third quartile; sCTx, serum C-telopeptide.
*Tumors were screened for expression of the estrogen receptor or progesterone receptor.

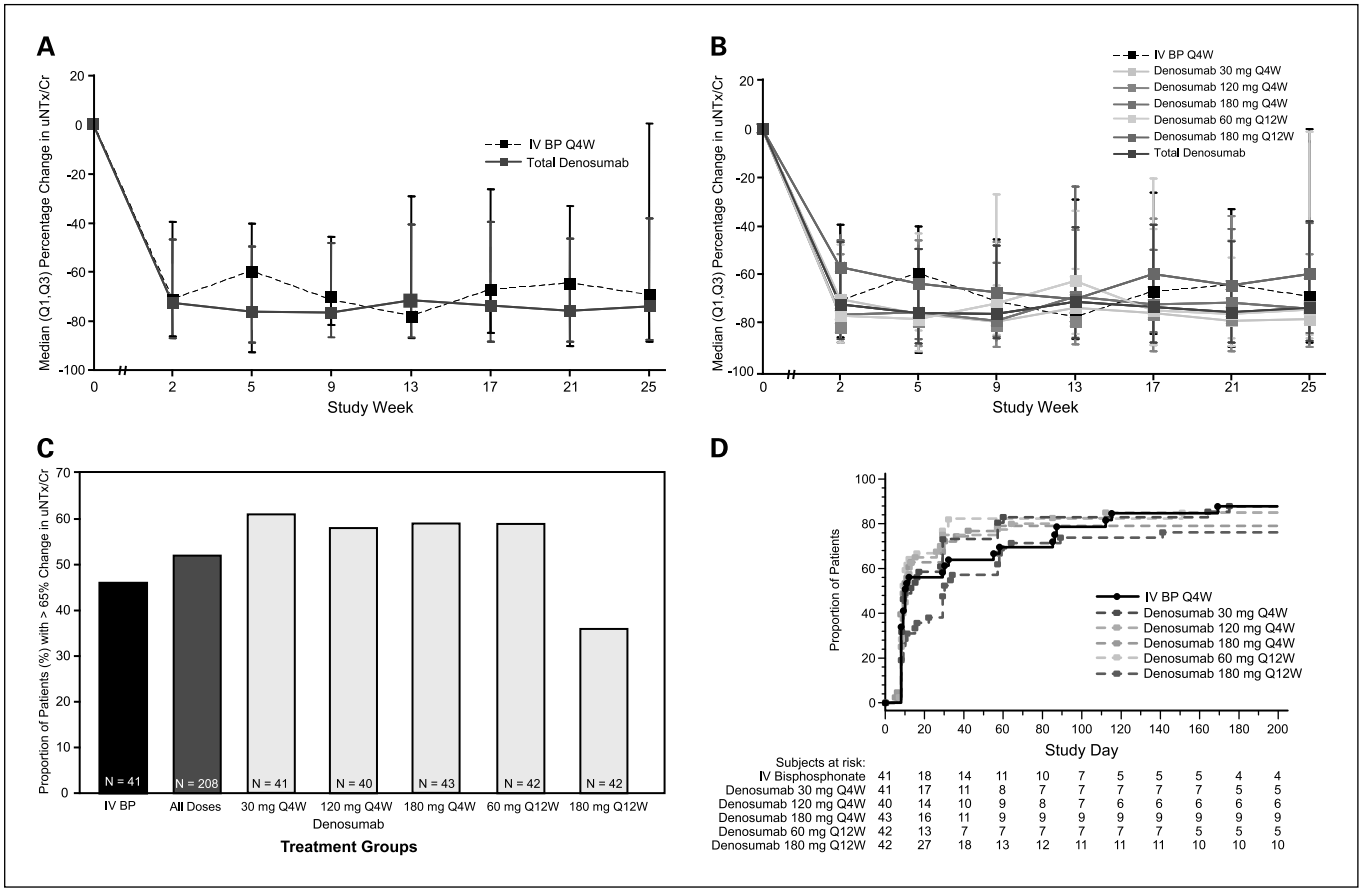

Fig. 1. All doses of denosumab resulted in suppression of uNTx/Cr; suppression was seen at the first study visit after administration of the initial dose and continued through week 25 (*A*). At week 25, the median percentage change from baseline in uNTx was similar in both treatment groups (*B*). At week 25, 52% of denosumab-treated patients had a uNTx/Cr reduction of >65%, as did 46% of IV BP – treated patients (*C*). A Kaplan-Meier analysis shows that the time to a uNTx/Cr reduction of >65% was similar in all treatment groups, except for the denosumab 180 mg Q12 dose group (*D*).

SREs (85% in the denosumab group and 86% in the IV BP group) occurred during the first 13 weeks of the study (Fig. 3).

Safety

Clinical parameters. As expected in patients being treated for advanced cancer, 95% of patients in both the denosumab and IV BP treatment groups reported AEs (Table 2). The most common AEs among patients receiving denosumab were nausea (22%), vomiting (17%), and diarrhea (17%). Among patients receiving IV BPs, the most common AEs were arthralgia (30%), asthenia (28%), and nausea (23%). The incidence of AEs in the denosumab group did not seem to be dose related.

The incidence of serious AEs was similar for all denosumab and IV BP cohorts (Table 2), with no serious AEs attributed to denosumab or IV BPs. Serious infections were reported in 5 (12%) IV PB – treated patients and 11 (5%) patients treated with denosumab. Osteonecrosis of the jaw was not reported by any patients in this study. Over the course of treatment and follow-up, 8 (19%) IV BP – treated patients and 32 (15%) denosumab-treated patients died; most deaths were attributed to breast cancer or its complications, and none were considered related to denosumab or IV BP. None of the treatment-related AEs experienced by denosumab patients were considered severe or serious, but two IV BP – treated patients experienced treatment-related AEs (asthenia and pain) that were considered severe. No binding or neutralizing antidenosumab antibodies were detected in any patients.

Acute-phase AEs associated with a flu-like syndrome were reported more often by patients receiving IV BPs than by those receiving denosumab: 18 (8%) denosumab-treated patients and 14 (33%) IV BP – treated patients during the first 3 days after initial denosumab or IV BP treatment, and 56 (26%) of denosumab-treated patients and 21 (49%) of IV BP – treated patients during the first 4 weeks after initial treatment.

Laboratory parameters. Laboratory values for calcium, Cr, liver enzymes, and electrolytes of patients in all cohorts were as expected and have been reported previously (16). Neither denosumab nor IV BPs seemed to have a marked effect on renal function, as measured by changes in serum Cr level and estimated glomerular filtration rate.

Discussion

In this study of IV BP – naïve patients, all doses of denosumab rapidly suppressed uNTx/Cr. Consistent with the results observed at 13 weeks, patients who received denosumab Q4W continued to experience uNTx/Cr suppression throughout the duration of the study treatment period, whereas evidence of escape from suppression was noted in some

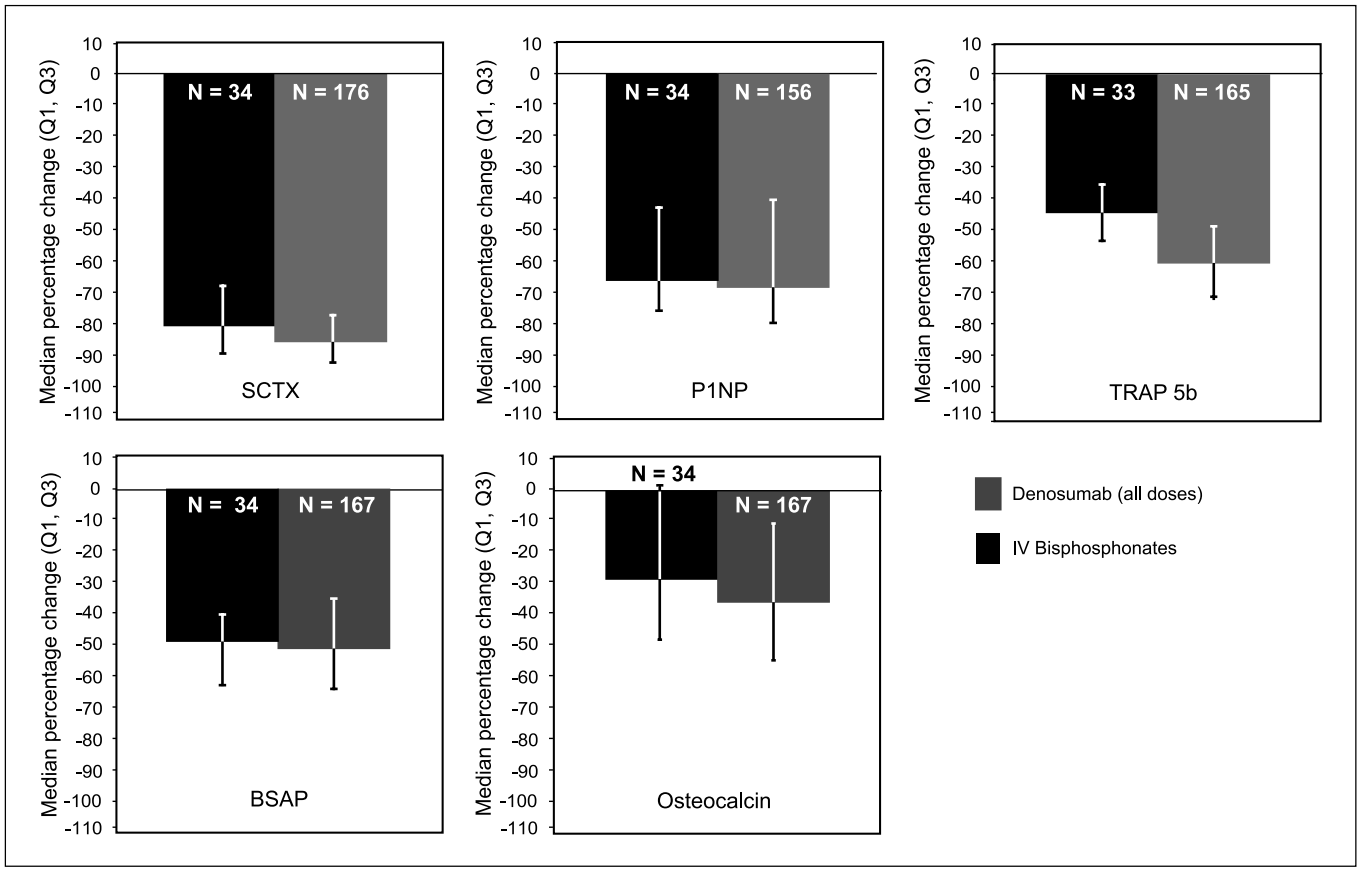

Fig. 2. Levels of the bone turnover markers serum C telopeptide (*SCTX*), procollagen 1 NH_2-terminal peptide (*P1NP*), tartrate resistant acid phosphatase 5b (*TRAP 5b*), bone-specific alkaline phosphatase (*BSAP*), and osteocalcin were suppressed by denosumab and IV BPs.

patients who received denosumab every 12 weeks. Denosumab treatment also caused suppression of other markers of bone turnover, including serum-C telopeptide, bone-specific alkaline phosphatase, and osteocalcin. Although no comparison with placebo was done in this study, the time to first on-study SRE seemed to be similar for patients in the denosumab and IV BP cohorts, suggesting that denosumab may also reduce the incidence of SREs. This phase 2 study of a range of doses and treatment schedules was designed to yield estimates on primary and secondary end points for each of the treatment arms. Tests of significance comparing treatment arms on these end points were not done because the study was not designed (powered) for these comparisons. Large, adequately powered, head-to-head studies comparing denosumab with zoledronic acid are

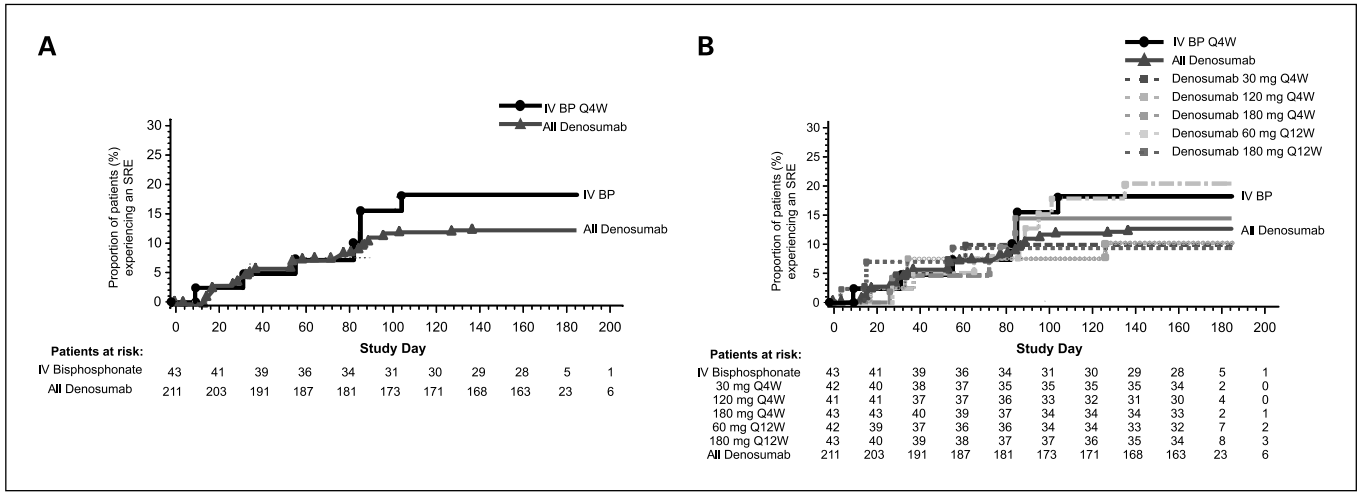

Fig. 3. By the end of the study, 26 patients (12%) in the denosumab groups and 7 patients (16%) in the IV BP group had experienced at least 1 SRE.

Table 2. Summary of AEs by week 57

	IV BP (n = 43) n (%)	Denosumab					
		30 mg Q4W (n = 42)	120 mg Q4W (n = 41)	180 mg Q4W (n = 43)	60 mg Q12W (n = 42)	180 mg Q12W (n = 43)	All Denosumab (n = 211)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
No of patients reporting serious AEs	15 (35)	11 (26)	19 (46)	16 (37)	14 (33)	15 (35)	75 (36)
Number of patients reporting any AEs, n (%)	41 (95)	39 (93)	39 (95)	40 (93)	41 (98)	41 (95)	200 (95)
Treatment-related AEs, n (%)	13 (30)	12 (29)	8 (20)	12 (28)	5 (12)	8 (19)	45 (21)
Serious treatment-related AEs, n (%)	0 (0)	0 (0)	0 (0)*	0 (0)	0 (0)	0 (0)	0 (0)*
Withdrawals from the study because of AEs, n (%)	1 (2)	0 (0)	0 (0)	1 (2)	3 (7)	1 (2)	5 (2)
Deaths, n (%)	8 (19)	4 (10)	6 (15)	8 (19)	6 (14)	8 (19)	32 (15)
AEs reported by >10% of patients							
Nausea	10 (23)	10 (24)	9 (22)	11 (26)	7 (17)	10 (23)	47 (22)
Vomiting	8 (19)	11 (26)	7 (17)	6 (14)	7 (17)	5 (12)	36 (17)
Diarrhea	7 (16)	9 (21)	9 (22)	6 (14)	5 (12)	6 (14)	35 (17)
Asthenia	12 (28)	9 (21)	9 (22)	5 (12)	6 (14)	5 (12)	34 (16)
Back pain	4 (9)	7 (16)	9 (22)	5 (12)	4 (10)	5 (12)	30 (14)
Fatigue	5 (12)	7 (17)	5 (12)	5 (12)	6 (14)	5 (12)	28 (13)
Headache	8 (19)	4 (10)	6 (15)	6 (14)	8 (19)	4 (9)	28 (13)
Bone pain	8 (19)	3 (7)	8 (20)	6 (14)	5 (12)	4 (9)	26 (12)
Constipation	7 (16)	7 (17)	5 (12)	6 (14)	4 (10)	4 (9)	26 (12)
Arthralgia	13 (30)	3 (7)	4 (10)	9 (21)	5 (12)	3 (7)	24 (11)
Anemia	2 (5)	3 (7)	4 (10)	2 (5)	8 (19)	6 (14)	23 (11)
Pain in extremity	8 (19)	6 (14)	4 (10)	7 (16)	2 (5)	2 (5)	21 (10)
Cough	7 (16)	5 (12)	6 (15)	2 (5)	3 (7)	2 (5)	18 (8)
Pyrexia	9 (21)	2 (5)	5 (12)	4 (9)	3 (7)	4 (9)	18 (8)
Edema, peripheral	6 (14)	2 (5)	1 (2)	3 (7)	2 (5)	6 (14)	14 (7)
Dyspnea	5 (12)	1 (2)	5 (12)	4 (9)	1 (2)	1 (2)	12 (6)

*One serious treatment-related AE in the 120-mg Q4W denosumab group (pyrexia) was recorded, but it was determined to be unrelated to treatment after the study database was locked.

being done to provide a more accurate estimate of the effect of denosumab treatment on the risk of SREs.

The incidence of AEs was similar among the IV BP and denosumab treatment groups. Patients receiving denosumab reported fewer cases of AEs resembling a flu-like syndrome and fewer acute-phase reactions than patients receiving IV BPs. This difference is as expected because the inhibition of RANKL (the mechanism of action of denosumab) does not result in the release of cytokines that might stimulate an acute-phase reaction. Overall, the safety profile of patients in this study is similar to that expected in patients with advanced cancer receiving systemic chemotherapy or hormonal therapy.

The data presented in this study confirm the results reported at 13 weeks (16) and support further investigation of targeted inhibition of RANKL by denosumab as a potential treatment for bone destruction associated with metastatic cancer. Large phase 3 trials of denosumab 120 mg Q4W are in progress.

Disclosure of Potential Conflicts of Interest

S. Jun, M. Peterson, A. Kinsey, and G. Gao are employees of Amgen; A. Paterson, R. Coleman, R. de Boer, J. Body, and A. Lipton have received honoraria from Amgen; A. Lipton has received honoraria from Novartis; J. Body has received consulting fees from Amgen and Novartis.

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