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BRIEF COMMUNICATION

Denosumab for Patients With Persistent or Relapsed Hypercalcemia of Malignancy Despite Recent Bisphosphonate Treatment

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Hypercalcemia of malignancy (HCM), caused primarily by tumor-induced bone resorption, may lead to renal failure, coma, and death. Although HCM can be treated with intravenous bisphosphonates, patients may not respond or may relapse on therapy. Denosumab binds the bone resorption mediator RANKL. In this single-arm, open-label, proof-of-concept study, HCM patients with albumin-corrected serum calcium (CSC) levels greater than 12.5 mg/dL (Common Terminology Criteria for Adverse Events grade ≥3) despite recent intravenous bisphosphonate treatment received subcutaneous denosumab on days 1, 8, 15, and 29, and then every 4 weeks. The primary endpoint was the proportion of patients with CSC 11.5 mg/dL or less (grade ≤1) within 10 days of denosumab initiation. In a prespecified interim analysis, 15 patients received denosumab (median CSC = 13.6 mg/dL). Time to response and response duration were analyzed with Kaplan–Meier methods. All statistical tests were two-sided. By day 10, 12 patients (80%; 95% exact confidence interval [CI] = 52% to 96%) responded (CSC ≤11.5 mg/dL); median response duration was 26 days. Ten patients (67%; 95% exact CI = 38% to 88%) had complete responses (CSC ≤10.8 mg/dL) by day 10. Denosumab may offer a new treatment option for HCM. Clinicaltrials.gov identifier: NCT00896454.

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Hypercalcemia of malignancy (HCM) is a serious complication that occurs most commonly in patients with advanced cancer and indicates poor prognosis (1). Untreated, HCM can lead to renal failure, progressive mental impairment, coma, and death. HCM results primarily from tumor-driven increases in bone resorption (2–5). Mechanisms include osteolytic resorption in bony areas near malignant cell invasion and humoral hypercalcemia, in which parathyroid hormone–related protein secreted by malignant cells promotes increased bone resorption and renal calcium retention. HCM is often treated with intravenous bisphosphonates, but patients may not respond or may relapse on bisphosphonate therapy (6). In clinical studies of patients treated with zoledronic acid 4 mg or pamidronate, 24% relapsed and another 21% had an incomplete response to treatment (6).

The fully human monoclonal antibody denosumab binds the bone resorption mediator RANKL. In phase III studies, denosumab was shown to prevent skeletal-related events or HCM in patients with advanced malignancies involving bone (7–9). In these trials, patients with breast cancer had a 52% lower incidence of HCM with denosumab than with zoledronic acid (10). This study evaluated denosumab for treatment of HCM in patients who remained hypercalcemic despite recent intravenous bisphosphonate treatment, as indicated by albumin-corrected serum calcium (CSC) levels, which were calculated as {total serum calcium in mg/dL + [0.8 × (4 – serum albumin in g/dL)]}. We present results of the prespecified interim analysis from this study.

This open-label, single-arm study was initiated in November 2009; the cutoff date for this analysis was June 2011. The study included adults with solid tumors or hematologic malignancies who had received intravenous bisphosphonate 7 to 30 days before screening. Patients had CSC levels greater than12.5 mg/dL (3.1 mmol/L; Common

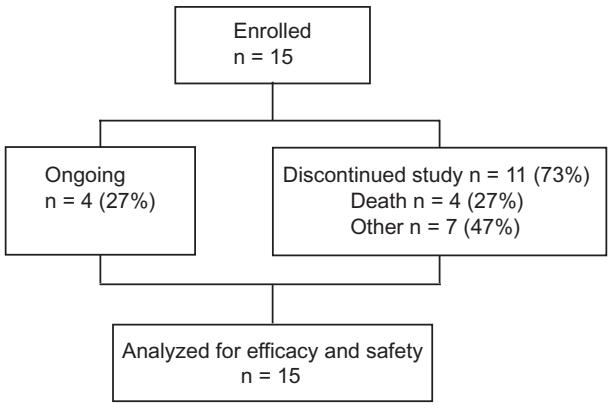

Figure 1. Study flow diagram. All 15 patients who enrolled in the study and received at least one dose of denosumab were included in the analyses. Other reasons for discontinuation include adverse events, progression of hypercalcemia, requirement for alternative cancer therapy, and consent withdrawal.

Table 1. Baseline characteristics*

Characteristic	Denosumab treatment group (n = 15)
Male sex, No. (%)	12 (80.0)
Ethnic group/race, No. (%)	
White	11 (73.3)
Black	2 (13.3)
Asian	1 (6.7)
Other	1 (6.7)
Age, y, median (range)	63 (40–79)
ECOG performance status, No. (%)	
1	4 (26.7)
2	6 (40.0)
3	3 (20.0)
4	2 (13.3)
Calcium level (albumin corrected), median (minimum, maximum), mg/dL†‡	13.6 (12.2, 16.3)†‡
PTHrP	
Median (minimum, maximum), pmol/L	3.6 (0.8–15.0)
Patients with PTHrP > 2 pmol/L, No. (%)	10 (66.7)
Patients reporting symptoms of HCM at baseline, No. (%)	9 (60.0)
Depressed level of consciousness	2 (13.3)
Anorexia	2 (13.3)
Nausea	2 (13.3)
Vomiting	2 (13.3)
Fatigue	2 (13.3)
Other§	6 (40.0)
Months of prior bisphosphonate use, median (minimum, maximum)	3 (1, 13)
Days from last intravenous bisphosphonate treatment to enrollment, median (minimum, maximum)	18 (8, 34)
Primary tumor type, No. (%)	
Hematologic malignancies	5 (33.3)
Chronic lymphocytic leukemia with Richter's transformation	2 (13.3)
Multiple myeloma	2 (13.3)
Non-Hodgkin lymphoma	1 (6.7)
Solid tumors	10 (66.7)
Breast	2 (13.3)
Non–small cell lung cancer	2 (13.3)
Neuroendocrine/carcinoid	2 (13.3)
Renal cell	2 (13.3)
Head and neck	1 (6.7)
Soft tissue sarcoma	1 (6.7)
Presence of bone metastasis at baseline, No. (%)	5 (33.3)
Concurrent chemotherapy at baseline, No. (%)	6 (40)

* ECOG = Eastern Cooperative Oncology Group; HCM = hypercalcemia of malignancy; PTHrP = parathyroid hormone–related protein

† If albumin is less than 4.0 g/dL, corrected serum calcium is calculated as {total serum calcium in mg/dL + [0.8 × (4 – serum albumin in g/dL)]}. If albumin is ≥4.0 g/dL, corrected serum calcium is equal to total calcium in mg/dL.

‡ The minimum baseline value is below the specified minimum for inclusion because local laboratory screening values were used to determine eligibility and may have differed from baseline values measured by the central laboratory.

§ Other symptoms reported by investigators include confusion, lethargy, constipation, dyspnea, general weakness, insomnolence, light-headedness, urinary frequency, and weight loss.

Terminology Criteria for Adverse Events [CTCAE] grade ≥3) at screening by local laboratory analyses and adequate liver function. Patients were excluded if they had benign hyperparathyroidism, hyperthyroidism, or adrenal insufficiency, or were on dialysis. Patients were also ineligible if they had received treatment with thiazides, calcitonin, mithramycin, or gallium nitrate within the window of expected therapeutic effect for each drug (physician determined) before screening or cinacalcet within 4 weeks before screening. Concurrent intravenous fluids, steroids, and chemotherapy were allowed. Each site's independent ethics committee or institutional review board approved the protocol; each patient provided written informed consent before participation. Patients received subcutaneous denosumab 120 mg on days 1, 8, 15, and 29, then every 4 weeks. Denosumab was discontinued if CSC was greater than12.5 mg/dL after four denosumab doses or by study day 57. CSC was measured by local laboratories to determine eligibility. On-study blood samples were collected on days 1, 2, 4, 8, 10, 15, 19, 23, and 29, then weekly until day 57 and monthly thereafter until the end of the study, and were analyzed by a central laboratory. Adverse events (AEs) were recorded throughout the study.

The primary endpoint was the proportion of patients with a response, defined as CSC 11.5 mg/dL or less (2.9 mmol/L; CTCAE grade ≤1) within 10 days after the first dose of denosumab. Secondary endpoints included response duration (defined as the number of days from the first occurrence of CSC ≤11.5 mg/dL to the last continuous CSC value ≤11.5 mg/dL) and the

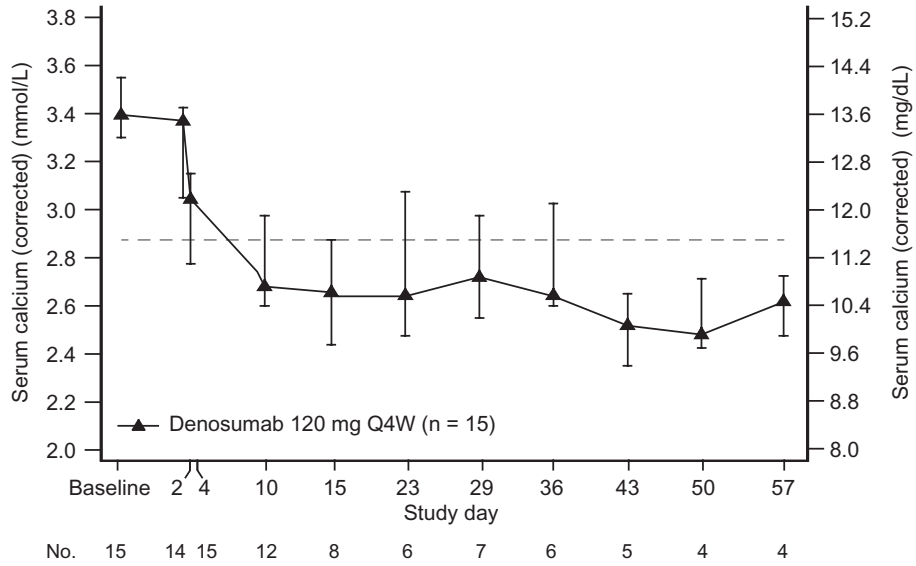

Figure 2. Median corrected serum calcium (CSC; mg/dL and mmol/L). **Error bars** represent the 25th and 75th percentiles (Q1, Q3). The **dashed horizontal line** represents the protocol-defined treatment response level (CSC ≤11.5 mg/dL [2.9 mmol/L]; Common Terminology Criteria for Adverse Events grade ≤1). The numbers at the bottom indicate the number of patients for whom a CSC value was available at each time point.

proportion of patients who experienced a complete response (CSC ≤10.8 mg/dL [2.7 mmol/L]) by day 10, consistent with previous studies (6). Patients analyzed received at least one dose of denosumab. This interim analysis was prespecified to occur after at least 10 denosumab-treated patients received at least two doses of denosumab and provided a serum sample for day 10 assessments. Descriptive statistics were employed, with 95% exact confidence intervals (CIs) for proportions of patients. For time to response and response duration, Kaplan–Meier estimates were employed, with 95% confidence interval values calculated using the bootstrap method. All statistical tests were two-sided.

Fifteen patients in the United States, France, and Poland were analyzed (Figure 1); Table 1 summarizes baseline patient characteristics. The patients' median age was 63 years; 80% were men. Five patients had hematologic malignancies; 10 had solid tumors. The median CSC level at baseline, measured by the central laboratory, was 13.6 mg/dL (3.4 mmol/L) (range = 12.2–16.3 mg/dL [3.1–4.1 mmol/L]. Patients' performance status was poor (Eastern Cooperative Oncology Group status ≥2) in 73% of patients; 60% of patients had HCM symptoms at baseline.

Twelve of the 15 patients (80%; 95% exact CI = 52% to 96%) responded to denosumab treatment with a CSC level 11.5 mg/dL or less; all responses occurred by day 10, and median time to response was 8 days (95% CI = 5 days to not estimable) (Figure 2). The median duration of response was 26 days (95% CI = 7 days to not estimable). By day 10, 10 patients (67%; 95% exact CI = 38% to 88%) had a complete response (CSC ≤10.8 mg/dL). Over the course of the study, 11 patients (73%) had a complete response, with a median time to complete response of 9 days (95% CI = 5 to 35 days). The median decrease in CSC from baseline at day 10 was 2.7 mg/dL (0.68 mmol/L).

Fourteen patients (93%) experienced AEs; 12 (80%) experienced serious AEs. Eight patients (53%) experienced fatal AEs, none of which were considered denosumab related by investigators. Seven patients (47%) discontinued the study or denosumab treatment because of AEs, none of which were considered treatment related. The most common AEs were nausea, hypercalcemia associated with cancer progression, and pyrexia; each of these occurred in three patients (20%).

In this proof-of-concept study of patients with advanced cancer and persistent hypercalcemia after incomplete response or relapse after recent bisphosphonate treatment, denosumab effectively lowered serum calcium to grade 1 or lower (≤11.5 mg/dL) in 80% of patients. The response was maintained for a median of 26 days, a clinically meaningful outcome given that patients entered this study with hypercalcemia of grade 3 and greater within a median of only 18 days after receiving the last dose of intravenous bisphosphonate. The safety profile of denosumab observed in this study was similar to that reported previously for denosumab and is consistent with an advanced cancer population.

This study also had some limitations. The study population was narrowly defined as patients who had persistent or relapsed HCM despite recent treatment with intravenous bisphosphonates, the current standard of care for HCM. It would not have been clinically appropriate to conduct a randomized controlled trial to compare denosumab with a treatment that had already proved ineffective for these patients; accordingly, a single-arm trial design including a small sample size was employed. These interim results suggest that denosumab may offer a new treatment option for HCM in this challenging population.

References

1. Stewart AF. Clinical practice. Hypercalcemia associated with cancer. *N Engl J Med*. 2005;352(4):373–379.
2. Burtis WJ, Wu T, Bunch C, et al. Identification of a novel 17,000-dalton parathyroid hormone-like adenylate cyclase-stimulating protein from a tumor associated with humoral hypercalcemia of malignancy. *J Biol Chem*. 1987;262(15):7151–7156.
3. Moseley JM, Kubota M, Diefenbach-Jagger H, et al. Parathyroid hormone-related protein purified from a human lung cancer cell line. *Proc Natl Acad Sci U S A*. 1987;84(14):5048–5052.
4. Strewler GJ, Stern PH, Jacobs JW, et al. Parathyroid hormonelike protein from human

renal carcinoma cells. Structural and functional homology with parathyroid hormone. *J Clin Invest*. 1987;80(6):1803–1807.
5. Wysolmerski JJ, Broadus AE. Hypercalcemia of malignancy: the central role of parathyroid hormone-related protein. *Annu Rev Med*. 1994;45:189–200.
6. Major P, Lortholary A, Hon J, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. *J Clin Oncol*. 2001;19(2):558–567.
7. Stopeck A, Lipton A, Body JJ, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. *J Clin Oncol*. 2010;28(35):5132–5139.
8. Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet*. 2011;377(9768):813–822.
9. Henry DH, Costa L, Goldwasser F, et al. 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. *J Clin Oncol*. 2011;29(9):1125–1132.
10. Martin M, Bell R, Bourgeois H, et al. Bone-related complications and quality of life in advanced breast cancer: results from a randomized phase III trial of denosumab versus zoledronic acid. *Clin Cancer Res*. 2012;18(17):4841–4849.

Notes

The study sponsor, Amgen Inc., designed the study in collaboration with the first author and other investigators. Amgen and the investigators collaborated in the collection, analysis, and interpretation of data, and the writing of the manuscript. All authors, including those employed by the sponsor, approved the submission of the manuscript for publication. Amgen provided the services of professional medical writers who assisted in manuscript development; this assistance is acknowledged in the manuscript. However, the authors accept full responsibility for the integrity of the reported data.

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