

RANDOMIZED TRIAL

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Denosumab Treatment for Giant Cell Tumor of the Spine Including the Sacrum

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Study Design. This was a subanalysis of an international, multicenter, open-label study.

Objective. The aim of this study was to assess the efficacy and safety of denosumab in a subset of patients with giant cell tumors of bone (GCTB) of the spine including the sacrum from an international, open-label, single-arm, phase 2 study (ClinicalTrials.gov: NCT00680992).

Summary of Background Data. Standard GCTB treatment is surgical removal, either by curettage or resection, combined with intraoperative adjuvant therapy; however, some sites may not be amenable to resection (e.g., skull, spine).

Methods. Adults or skeletally mature adolescents with pathologically confirmed GCTB of the spine including the sacrum, and radiologically measurable evidence of active disease, were included. Patients received denosumab (120 mg subcutaneously) once every 4 weeks during the treatment phase, with loading

doses on days 8 and 15 of the first cycle. Patients had surgically unsalvageable GCTB (Cohort 1), had planned surgery expected to result in severe morbidity (Cohort 2), or were enrolled from a previous GCTB study (Cohort 3).

Results. Overall, 132 patients were included in the safety analysis (103 in Cohort 1, 24 in Cohort 2, and five in Cohort 3); 131 patients were included in the efficacy analysis. Kaplan-Meier estimated probabilities of disease progression or recurrence were 3% (95% confidence interval [CI], 0.0–6.2) at year 1 and 7.4% (95% CI, 2.1–12.7) at years 3 and 5 in Cohort 1, and not estimable in Cohorts 2 and 3. Of 23 patients (Cohort 2) with surgery planned at baseline, 10 (43%) had on-study surgery; of these, one patient had reported disease progression or recurrence after the on-study surgery. Clinical benefit was reported in 83% of patients overall (all cohorts).

Conclusion. Results from the analysis suggest that denosumab is potentially effective treatment for patients with GCTB of the spine including the sacrum. The adverse event profile was consistent with the full study population.

Key words: bone malignancies, clinical trial, denosumab, GCTB, giant cell tumor of bone, open-label, receptor activator of nuclear factor-kappa B (RANK), sacrum, spine, unresectable disease.

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patients (38%) treated with one-stage surgery and in five of 10 patients (50%) treated with two-stage surgery.⁶ Conventional chemotherapy is rarely used for treatment of spinal and sacral GCTBs because of inadequate response and unacceptable toxicity. Radiotherapy has been employed for incomplete excision of spinal GCTB, but risks of spinal cord myelitis and malignant transformation have been reported.⁷ Alternatively, selective serial embolization of sacral GCTB may offer local tumor control, but a recurrence rate of 31% has been reported at 10 years (43% at 15 and 20 years).⁸

Osteoclast-like giant cells express receptor activator of nuclear factor-kappa B (RANK); stromal cells, thought to be the neoplastic component of GCTB, express RANK ligand (RANKL).^{9,10} RANKL drives osteoclast formation, function, and survival¹⁰; excessive RANKL expression is associated with GCTB.¹¹ Denosumab (XGEVA, Amgen Inc., Thousand Oaks, CA), a fully human monoclonal antibody that inhibits RANKL, is approved for the treatment of adults and skeletally mature adolescents with GCTB that is unresectable or where surgical resection is likely to result in severe morbidity.¹²

The objective of this study was to assess the efficacy and safety of denosumab in a subset of patients with GCTB of the spine including the sacrum from an international, open-label, single-arm, phase 2 study.^{13,14}

MATERIALS AND METHODS

Study Design and Patients

A subset of patients with GCTB of the spine including the sacrum from an international, open-label, single-arm, phase 2 study (Figure 1) were analyzed; adults (≥ 18 years of age) or skeletally mature adolescents ≥ 12 years of age with weight ≥ 45 kg and pathologically confirmed GCTB and radiologically measurable evidence of active disease ≤ 1 year before enrollment, and a Karnofsky performance score

$\geq 50\%$ were included.^{13,14} Patients with other current GCTB-specific treatments (*e.g.*, radiation, chemotherapy, or embolization) or bisphosphonates, known or suspected current diagnosis of underlying malignancy or Paget disease, or known diagnosis of second malignancy within ≤ 5 years were excluded.

Patients received denosumab (120 mg subcutaneously) once every 4 weeks, with additional doses administered on study days 8 and 15 of the first cycle; those who enrolled from a previous GCTB study¹⁵ continued on denosumab 120 mg subcutaneously every 4 weeks. For all patients, treatment continued until disease progression, absence of clinical benefit, patient decision to withdraw, or complete tumor resection.¹³ On-study retreatment was allowed for patients with a tumor response to denosumab but who were not currently receiving denosumab (*i.e.*, in the case of recurrent disease while the patient was in the safety follow-up phase). Follow-up continued until patients completed a minimum of 60 months on study, or until death or loss to follow-up, whichever came first. All patients were to be adequately supplemented with ≥ 500 mg calcium and ≥ 400 IU vitamin D daily (except in patients with preexisting hypercalcemia). The primary objective was to evaluate the safety profile of denosumab in patients with GCTB; secondary objectives included evaluation of time to disease progression in patients with unsalvageable GCTB and evaluation of the proportion of patients who did not require surgery by month 6 in those with salvageable GCTB. The study protocol was approved by an independent ethics committee or institutional review board for each center; patients provided written informed consent. The study is registered with ClinicalTrials.gov (NCT00680992).

Spine Including the Sacrum Subset Analyses

The efficacy and safety of denosumab in patients with GCTB of the spine (cervical, thoracic, or lumbar vertebrae) including

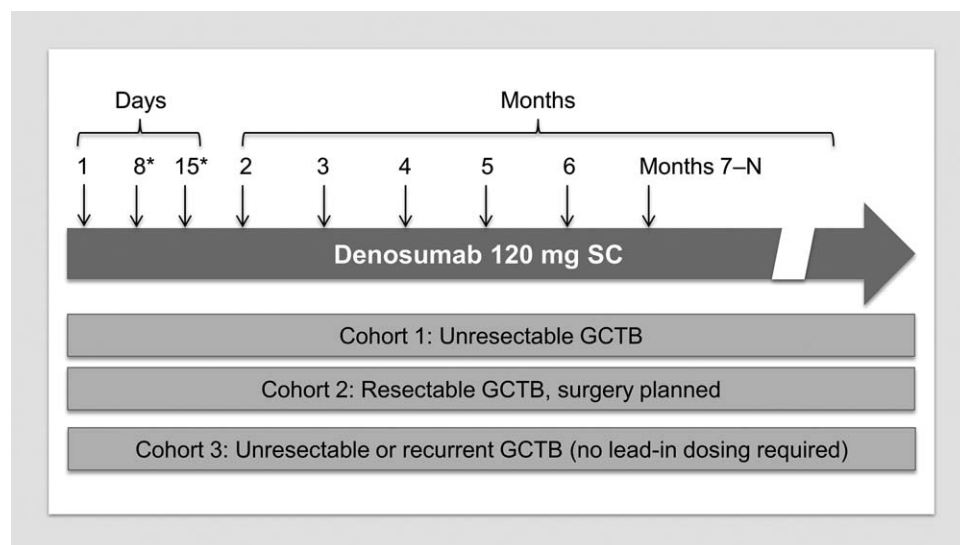


Figure 1. Study design for administration of denosumab to patients with giant cell tumor of the bone. *Lead-in dosing for patients starting on denosumab. GCTB indicates giant cell tumor of bone; SC, subcutaneous.

the sacrum who received one or more denosumab doses were evaluated through the data cutoff date for the final analysis (August 15, 2018). Patients were divided into three cohorts: surgically unsalvageable disease (Cohort 1), surgically salvageable disease (Cohort 2), and surgically unresectable disease re-enrolling from the pilot GCTB study¹⁵ (Cohort 3).

Imaging was obtained based on regional standard of care by investigators to assess disease status, and results were summarized descriptively per investigators' local standard practice. The protocol did not specify a predefined standardized criteria for tumor assessment, and there was no specified imaging schedule of assessment. This was left to investigator discretion and local standards of care.

Case report forms were used to record patients' symptoms, pain, activity, functional effects, drug use, and other information (*e.g.*, work status, disability). Investigator-assessed disease status (complete response, partial response, stable disease, and progressive disease) and clinical benefit were evaluated. Disease status was assessed at baseline, then every 4 weeks during the treatment phase of the study, and at 6 and 12 months of safety follow-up, and was based on multiple factors, including assessment of clinical response, imaging response, physical examination, and clinical benefit. Disease status and clinical benefit results were based on best response reported during the assessment period per the investigator's opinion based on clinical observation. Patient-reported outcomes (PROs) for pain were measured using the Brief Pain Inventory (short form; BPI-SF) at baseline, at days 8 and 15, then every 4 weeks from weeks 5 to 25, and every 12 weeks thereafter.

Safety was evaluated by assessing changes in laboratory variables and the nature, frequency, severity, relationship to

investigational product, and outcome of all adverse events (AEs). Treatment-emergent, treatment-related, serious, serious treatment-related, and fatal AEs, as well as AEs leading to investigational product discontinuation and/or study withdrawal, were grouped by preferred term and system organ class according to the Medical Dictionary for Regulatory Activities version 21.0.

Statistical Analysis

Efficacy analyses included all eligible patients with GCTB of the spine including the sacrum who received one or more doses of denosumab. Patients not meeting key inclusion or exclusion criteria (*e.g.*, pathologically confirmed GCTB, known or suspected diagnosis of underlying malignancy) were excluded from the efficacy analysis. For time-to-event outcomes, Kaplan-Meier (KM) estimates (two-sided 95% confidence intervals [CIs]) of quartiles and/or event probability at various time points were summarized. Safety analyses included all enrolled patients who received one or more doses of denosumab. Statistical analyses in this study were descriptive; no formal hypothesis was tested.

RESULTS

Patients

Overall, 132 patients with GCTB were included in the safety analysis for this spine including the sacrum subset (Table 1); 103 in Cohort 1, 24 in Cohort 2, and five in Cohort 3. Most patients were female ($n = 86$; 65%), and the median (range) age was 32 (13–83) years. Most lesions occurred in the

TABLE 1. Patient Demographics and Disease Characteristics (Spine Including the Sacrum Patients) in Safety Analysis Dataset

Characteristic	Cohort 1 (N = 103)	Cohort 2 (N = 24)	Cohort 3 (N = 5)	Total Patients (N = 132)
Female, n (%)	66 (64.1)	16 (66.7)	4 (80.0)	86 (65.2)
Male, n (%)	37 (35.9)	8 (33.3)	1 (20.0)	46 (34.8)
Age, median (range), y	32.0 (13–83)	29.5 (14–73)	33.0 (22–63)	32.0 (13–83)
Target lesion location, n (%)				
Sacrum	65 (63.1)	14 (58.3)	2 (40.0)	81 (61.4)
Thoracic vertebrae	17 (16.5)	4 (16.7)	2 (40.0)	23 (17.4)
Cervical vertebrae	13 (12.6)	1 (4.2)	0	14 (10.6)
Lumbar vertebrae	8 (7.8)	5 (20.8)	1 (20.0)	14 (10.6)
Presentation, n (%)				
Recurrent unresectable	43 (41.7)	0	3 (60.0)	46 (34.8)
Primary unresectable	60 (58.3)	0	2 (40.0)	62 (47.0)
Primary resectable	0	18 (75.0)	0	18 (13.6)
Recurrent resectable	0	6 (25.0)	0	6 (4.5)
Received at least one dose of denosumab				
Doses received, median (IQR)	48.0 (34.0–74.0)	20.0 (16.0–58.5)	65.0 (55.0–78.0)	46.5 (27.5–69.5)
Months on trial, median (IQR)	70.0 (43.4–87.5)	60.7 (21.8–73.9)	87.4 (80.2–90.0)	69.1 (40.9–86.4)

IQR indicates interquartile range.

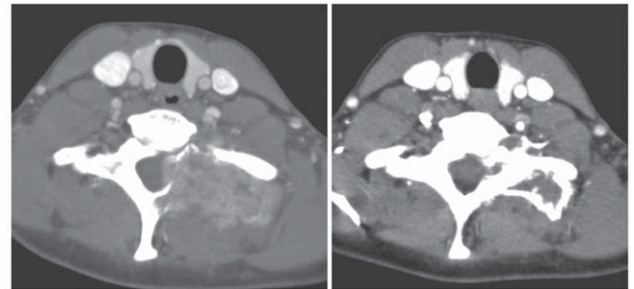
sacrum (n = 81; 61%) and presented as recurrent unresectable (n = 46; 35%) or primary unresectable (n = 62; 47%) lesions; only patients in Cohort 2 had surgically salvageable disease (primary resectable, n = 18; recurrent resectable, n = 6). The median (interquartile range [IQR]) number of denosumab doses received during the entire treatment period (including the initial treatment and retreatment phases) was 46.5 (27.5–69.5); most patients (n = 97; 73%) received 31 or more doses, and only four patients (3%) received ≤10 (range, 5–116) doses. Patients in Cohort 1 received a median (IQR) of 48.0 (34–74) doses over the entire treatment period and patients in Cohort 2 received 20.0 (16.0–58.5) doses.

The median (IQR) number of months on trial (including treatment and safety follow-up phases) was 69.1 (40.9–86.4). Over the study duration, denosumab was discontinued in all patients, primarily for administrative reasons, protocol-specified criteria, or other reasons (*e.g.*, end of trial) (Table 2). One patient in Cohort 2 was found to be misdiagnosed with primary malignant GCTB, which violated eligibility criteria; thus, the patient was excluded from the efficacy analysis (N = 131).

Tumor Responses

Computed tomography images displaying representative responses to denosumab in the spine and sacrum are shown in Figure 2A and B, respectively. For those with surgically unresectable disease, 13 patients (13%) in Cohort 1 had a best post-baseline outcome of complete response, 37 (36%) had partial response, 52 (51%) had stable disease, and one patient (1%) had disease progression; for Cohort 3, three patients (60%) had partial response and two (40%) had

Axial contrast-enhanced CT images through the upper thoracic spine

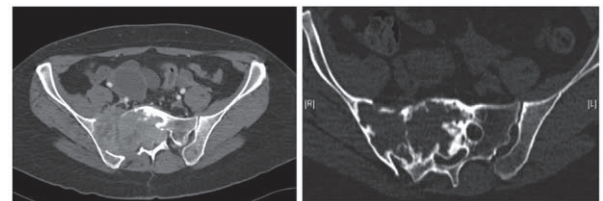


Pretreatment, showing destruction of the left T-2 lamina and transverse process, with tumor invading the spinal canal.

Following 4 months of treatment, the soft tissue mass has diminished. There is reconstitution of cortex around the entire lesion, with internal mineralization. The canal is now tumor-free.

A

Axial CT images through the upper sacrum



Pretreatment, showing destruction of the sacral promontory and right sacral ala, including the S1 neural foramen. The tumor has crossed the sacroiliac joint and invaded the posterior iliac wing. The posterior sacral canal is filled with tumor.

Following 4 months of treatment, the lesion shows not only extensive peripheral mineralization, but the sacral canal has reconstituted. The anterior soft tissue mass is smaller. The promontory is now partially calcified.

B

Figure 2. Response to denosumab in spine (A) and sacrum (B). CT indicates computed tomography.

TABLE 2. Reasons for Treatment Phase Discontinuation (Spine Including the Sacrum Patients) in Safety Analysis Dataset

	Cohort 1 (N = 103)	Cohort 2 (N = 24)	Cohort 3 (N = 5)	Total Patients (N = 132)
Discontinued treatment phase, n (%)	103 (100.0)	24 (100.0)	5 (100.0)	132 (100.0)
Administrative decision	32 (31.1)	10 (41.7)	2 (40.0)	44 (33.3)
Protocol-specified criteria*	10 (9.7)	8 (33.3)	0	18 (13.6)
End of trial	14 (13.6)	1 (4.2)	1 (20.0)	16 (12.1)
Consent withdrawn	10 (9.7)	1 (4.2)	0	11 (8.3)
Adverse event	9 (8.7)	0	1 (20.0)	10 (7.6)
Other	9 (8.7)	1 (4.2)	0	10 (7.6)
Disease progression	6 (5.8)	1 (4.2)	0	7 (5.3)
Lost to follow-up	6 (5.8)	1 (4.2)	0	7 (5.3)
Pregnancy	2 (1.9)	0	1 (20.0)	3 (2.3)
Requirement for alternative therapy	3 (2.9)	0	0	3 (2.3)
Noncompliance	1 (1.0)	1 (4.2)	0	2 (1.5)
Death	1 (1.0)	0	0	1 (0.8)

*Patients had complete resection.

TABLE 3. Investigator-determined Disease Status With Best Post-Baseline Response

Cohort*	Complete Response, n (%)	Partial Response, n (%)	Stable Disease, n (%)	Disease Progression, n (%)
Cohort 1 (N = 103)	13 (12.6)	37 (35.9)	52 (50.5)	1 (1.0)
Cohort 2 (N = 23)	11 (47.8)	8 (34.8)	4 (17.4)	0
Cohort 3 (N = 5)	0	3 (60.0)	2 (40.0)	0
Cohorts 1 and 2 (N = 126)	24 (19.0)	45 (35.7)	56 (44.4)	1 (0.8)
All Cohorts (N = 131)	24 (18.3)	48 (36.6)	57 (43.5)	1 (0.8)

*N = Number of patients in efficacy analysis set with GCTB of the spine (cervical, thoracic, or lumbar vertebrae) including the sacrum.

Response was determined by investigator based on best response reported during the assessment period per the investigator's opinion based on clinical observation. All 131 patients in the efficacy analysis set had one or more evaluations of post-baseline disease status (based on investigator opinion). If multiple responses were present, the best response was used. Patients in Cohort 2 who had complete resection were considered as complete response. Percentages based on n/N.

stable disease (Table 3). For those patients with surgically salvageable disease (Cohort 2), complete resection was considered a complete response; 11 patients (48%) had an investigator-reported best post-baseline outcome of complete response, eight (35%) had partial response, and four (17%) had stable disease. Nine of 103 (8.7%) of unresectable Cohort 1 patients and none of the 28 cohort 2 or 3 patients experienced disease progression during the initial treatment phase. KM estimates of the probability of Cohort 1 patients experiencing disease progression or recurrence during the initial treatment phase were 3.0% (95% CI, 0–6.2) at year 1 and 7.4% (95% CI, 2.1–12.7) at years 3 and 5 (95, 69, and 36 patients were in the Cohort 1 risk set at years 1, 3, and 5, respectively), and not estimable in Cohorts 2 and 3; over Cohorts 1 and 2, the estimated probability of patients without disease progression or recurrence was 93.6% at year 5 (40 patients were in the combined Cohorts 1 and 2 risk set at year 5).

Of the 104 patients who discontinued denosumab for reasons other than death, lost to follow-up, disease progression, or withdrawal of consent, 16 (15%) had disease progression or recurrence after discontinuation (12 [15%] from Cohort 1 and four [19%] from Cohort 2), with a 25th percentile time of 23.0 months across Cohorts 1 and 2 (95% CI, 10.28–not estimable; median not estimable).

Surgical Outcomes

All 23 eligible patients in Cohort 2 had planned on-study surgery at baseline: 10 patients (43%) ultimately underwent surgery, whereas 13 patients (57%) did not have surgery. The median time to surgery in Cohort 2 was 9.2 months (95% CI, 3.9–12.9).

For the 10 patients who had surgery, the median (IQR) number of denosumab doses received before surgery was 11.5 (9.0–17.0). All 10 patients achieved complete surgical resection, after which one of 10 patients (10%) had recurrence of disease. The KM estimate of the probability of disease progression or recurrence after on-study surgery was 14.3% (95% CI, 0–40.2) at 24 months. Four of the 10 patients (40%) were able to undergo a less morbid procedure than planned at baseline (Supplemental Table 1, <http://links.lww.com/BRS/B650>).

Clinical Benefit

Clinical benefit was reported for 109 of the 131 patients (83%) in the efficacy analysis set (Table 4). Pain reduction was reported by 97 patients (74%), improved mobility by 57 patients (44%), improved function by 50 patients (38%), and other benefits reported by the investigator (such as symptom control or overall clinical impression) were reported for 18 patients (14%). Results were similar for the individual cohorts (Cohorts 1 and 2).

TABLE 4. Clinical Benefit

Cohort*	Clinical Benefit, n (%)	Pain Reduction, n (%)	Improved Mobility, n (%)	Improved Function, n (%)	Other, n (%)
Cohort 1 (N = 103)	87 (84.5)	77 (74.8)	46 (44.7)	39 (37.9)	13 (12.6)
Cohort 2 (N = 23)	19 (82.6)	18 (78.3)	10 (43.5)	9 (39.1)	5 (21.7)
Cohort 3 (N = 5)	3 (60.0)	2 (40.0)	1 (20.0)	2 (40.0)	0
Cohorts 1 and 2 (N = 126)	106 (84.1)	95 (75.4)	56 (44.4)	48 (38.1)	18 (14.3)
All cohorts (N = 131)	109 (83.2)	97 (74.0)	57 (43.5)	50 (38.2)	18 (13.7)

*N = Number of patients in efficacy analysis set with GCTB of the spine (cervical, thoracic, or lumbar vertebrae) including the sacrum who had a post-baseline clinical benefit evaluation.

Response was determined by investigator based on best response reported during the assessment period per the investigator's opinion based on clinical observation.

For an individual patient, within each category, if multiple responses were present in the same time frame, the best response was presented. Percentages based on n/N.

Overall, 69 of 121 patients (57%) with PROs (53/94 in Cohort 1, 15/22 in Cohort 2, and one of five in Cohort 3) had moderate or severe worst pain at baseline (BPI-SF worst pain scores >4 points); 65 of 69 patients with PROs (94%) had a clinically meaningful reduction in pain severity (*i.e.*, a two-or-more-point decrease in BPI-SF pain score), including 49 (93%) in Cohort 1, 15 (100%) in Cohort 2, and one (100%) in Cohort 3. The KM estimate of median time to a two-or-more-point decrease in worst pain score was 0.5 months (95% CI, 0.49–0.62).

During the trial, increasing proportions of patients shifted from strong opioid use (analgesic score ≥ 3) at baseline to nonopioid analgesic/weak opioid use (analgesic score ≤ 2). In 60 patients overall receiving strong opioids at baseline, a shift to nonopioid/weak opioid was observed in 25% (14/57) at week 21, and this shift increased with subsequent evaluations (*e.g.*, 36% [19/53] at week 49, 44% [20/45] at week 97, and 44% [18/41] at week 157). Few patients shifted from no/low analgesic use to strong opioid use during the treatment phase (<5% overall at the majority of assessments).

AEs

The most common treatment-emergent AEs (TEAEs) were back pain (49%) and fatigue (31%; Table 5). Forty-seven patients (36%) experienced serious TEAEs; 15 (11.4%) experienced serious treatment-related TEAEs. Thirteen patients (10%) experienced TEAEs leading to denosumab discontinuation, 10 (8%) were considered treatment-related. There were two fatalities, which were not considered to be treatment-related; one was circulatory collapse in an 82-year-old, and the other was malignant transformation to sarcoma in a patient who was subsequently found to have pathologically proven preexisting malignancy (*i.e.*, misdiagnosis of the primary malignant GCTB). Eleven patients (8%) had positively adjudicated osteonecrosis of the jaw (ONJ; nine in Cohort 1 and one each in Cohorts 2 and 3; Table 5). The median (IQR) time to onset of ONJ was 44.5 (32.2–78.4) months overall and 40.9 (32.2–64.1) months in Cohort 1 (time to onset was 55.0 and 79.1 months for the individuals in Cohorts 2 and 3, respectively). ONJ onset was preceded by tooth extraction in six patients, history of radiation to the head and neck in one patient, dental appliance/denture use in two patients, and/or oral infection in four patients; there was no history of prior bisphosphonate use in any patient (per protocol). As of the data cutoff, ONJ had resolved in four (36%) of 11 cases. Overall, no new safety signals were identified in patients with GCTB of the spine including the sacrum who received denosumab.

DISCUSSION

In this subset analysis from a phase 2 study of GCTB of the spine including the sacrum with a median follow-up of nearly 6 years, investigator-determined complete response, partial response, or stable disease occurred in all but one patient. Duration of response was robust for most patients, with an estimated 93% of patients with unresectable disease

(Cohort 1) having no progression or recurrence at 5 years in the initial treatment phase. Although the cohort with surgically salvageable disease (Cohort 2) was relatively small, one of 10 patients (10%) had recurrence after on-study surgery, with an estimated 86% of patients having no progression or recurrence at 2 years. The median time to recurrence after surgery (*i.e.*, complete response) was not reached; the 25th percentile time to recurrence was 16.1 months, and the probability of disease progression or recurrence after on-study GCTB surgery was 28% at month 24. Notably, more than half of the patients with resectable sacral or spinal tumors achieved excellent disease control and elected to continue denosumab treatment in lieu of undergoing surgery. In addition, 14 patients from Cohort 1 initially judged to have unresectable disease had on-study surgery; of these, four patients (29%) had recurrence. This may explain the unexpected observation that a small number of patients in Cohort 1 had a best investigator-determined outcome of complete response, since complete response in the absence of complete surgical resection would not have been expected. Clinical benefit was reported for 83% of all patients; almost all patients experienced a rapid reduction in pain, and approximately half experienced an improvement in mobility. Given the rarity of the GCTB of the spine and sacrum, it would be difficult to undertake a randomized assessment of surgery versus denosumab in these patients; however, our results appear to support the role of denosumab as a potential alternative to surgery in patients with GCTB in sites not amenable to resection.

Results from this subset analysis are consistent overall with those observed in the full GCTB study population.^{13,14} In the overall population, clinical benefit was reported for 79% of patients and tumor response of stable disease or better was >99%. The safety profile of this analysis was consistent with other studies with antiresorptive therapies^{16–19}; the most common AEs were back pain and fatigue. Rates of positively adjudicated ONJ (8% *vs.* 5%) were slightly higher than the overall study population, likely reflecting the longer duration of therapy in this largely unresectable group of patients. The incidence of ONJ seen in patients with unresectable lesions of the spine including the sacrum (Cohort 1) was similar to that observed in the overall study subset (9% *vs.* 8%).

Although this analysis reports on a subset of patients from the largest and only prospective trial to date in GCTB,^{13,14} there remain some limitations. Due to the rarity of this disease and because the trial included patients with unresectable disease for which there is no standard medical treatment, a single-arm design with no comparator agent or placebo was used. Also, since the study population was relatively high risk at baseline (most patients had at least one recurrence or unresectable lesions), the results here may not be widely applicable to all GCTB patients with disease in the spine including the sacrum. Additionally, the open-label design may have biased investigator assessments (*e.g.*, disease status, clinical benefit, timing, surgery scope). Furthermore, time to disease progression was

TABLE 5. Adverse Events

AEs, n (%)	Cohort 1 (N = 103)	Cohort 2 (N = 24)	Cohort 3 (N = 5)	All Patients (N = 132*)
Treatment-emergent AEs (TEAEs)				
All TEAEs	99 (96.1)	23 (95.8)	5 (100)	127 (96.2)
Serious TEAEs	40 (38.8)	4 (16.7)	3 (60.0)	47 (35.6)
Fatal TEAEs	1 (1.0)	1 (4.2)	0	2 (1.5)
TEAEs leading to denosumab discontinuation	11 (10.7)	1 (4.2)	1 (20.0)	13 (9.8)
Grade ≥ 3 TEAEs	51 (49.5)	8 (33.3)	3 (60.0)	62 (47.0)
Treatment-related TEAEs [†]				
All treatment-related TEAEs	69 (67.0)	15 (62.5)	4 (80.0)	88 (66.7)
Serious treatment-related TEAEs	13 (12.6)	1 (4.2)	1 (20.0)	15 (11.4)
Fatal treatment-related TEAEs	0	0	0	0
Treatment-related TEAEs leading to denosumab discontinuation	9 (8.7)	0	1 (20.0)	10 (7.6)
Grade ≥ 3 TEAEs	18 (17.5)	6 (25.0)	0	24 (18.2)
TEAEs reported in $\geq 10\%$ of all patients				
Back pain	50 (48.5)	11 (45.8)	4 (80.0)	65 (49.2)
Fatigue	32 (31.1)	7 (29.2)	2 (40.0)	41 (31.1)
Pain in extremity	31 (30.1)	6 (25.0)	3 (60.0)	40 (30.3)
Arthralgia	30 (29.1)	3 (12.5)	3 (60.0)	36 (27.3)
Nausea	28 (27.2)	5 (20.8)	1 (20.0)	34 (25.8)
Headache	26 (25.2)	4 (16.7)	4 (80.0)	34 (25.8)
Constipation	23 (22.3)	4 (16.7)	0	27 (20.5)
Musculoskeletal pain	18 (17.5)	5 (20.8)	4 (80.0)	27 (20.5)
Nasopharyngitis	20 (19.4)	3 (12.5)	2 (40.0)	25 (18.9)
Edema peripheral	19 (18.4)	4 (16.7)	1 (20.0)	24 (18.2)
Toothache	18 (17.5)	3 (12.5)	1 (20.0)	22 (16.7)
Hypophosphatemia	14 (13.6)	4 (16.7)	2 (40.0)	20 (15.2)
Vomiting	15 (14.6)	2 (8.3)	2 (40.0)	19 (14.4)
Pyrexia	13 (12.6)	2 (8.3)	2 (40.0)	17 (12.9)
Paresthesia	14 (13.6)	3 (12.5)	0	17 (12.9)
Abdominal pain	15 (14.6)	0	1 (20.0)	16 (12.1)
Hypoesthesia	14 (13.6)	2 (8.3)	0	16 (12.1)
Muscle spasms	13 (12.6)	2 (8.3)	1 (20.0)	16 (12.1)
Urinary tract infection	14 (13.6)	0	1 (20.0)	15 (11.4)
ONJ	13 (12.6)	0	1 (20.0)	14 (10.6)
Diarrhea	13 (12.6)	1 (4.2)	0	14 (10.6)
Weight increased	11 (10.7)	2 (8.3)	1 (20.0)	14 (10.6)
AEs of interest [‡]				
Positively adjudicated ONJ	9 (8.7)	1 (4.2)	1 (20.0)	11 (8.3)
Serious	8 (7.8)	1 (4.2)	1 (20.0)	10 (7.6)
Malignancy [§]	4 (3.9)	0	0	4 (3.0)
Serious	3 (2.9)	0	0	3 (2.3)
Hypercalcemia occurring >30 days following discontinuation of denosumab	1 (1.0)	1 (4.2)	0	2 (1.5)
Serious	1 (1.0)	1 (4.17)	0	2 (1.5)
Positively adjudicated atypical femur fracture	1 (1.0)	0	0	1 (0.8)
Serious	0	0	0	0

AE indicates adverse event; ONJ, osteonecrosis of the jaw; TEAE, treatment-emergent AE.

*N = patients who received one or more doses of denosumab.

[†]Treatment-related TEAEs include those AEs where the investigator has indicated that there is a possible relationship with denosumab treatment.

[‡]For positively adjudicated ONJ, positively adjudicated atypical femur fracture, and malignancy, AEs of interest include all TEAEs and AEs after the treatment-emergent period. For hypercalcemia, AEs of interest include AEs that occurred after 30 days following the last dose of denosumab in the initial treatment phase.

[§]Amgen conducted an independent external expert review of all malignancy in GCTB-reported events, including pathologic and imaging review. Seven patients found to have malignancy present in the pre-enrollment tumor biopsy were considered eligibility deviations and were not counted as new malignancy in GCTB.

assessed using imaging and histopathology based on the investigator's localized standard of care; this means that the approach to assessment of time to disease progression may have varied across the centers included in this study. Finally, due to the small size of Cohorts 2 and 3, no comparisons of the outcomes between the different cohorts should be made.

In conclusion, efficacy and safety profiles of denosumab in patients with GCTB of the spine including the sacrum appear to be consistent with those of denosumab in the overall GCTB population and in other advanced bone malignancies. Results from the analysis suggest that denosumab is a potentially useful treatment for patients with GCTB of the spine including the sacrum.

➤ Key Points

- ❑ Results from this subanalysis of an international, multicenter, open-label study suggest that denosumab is potentially effective for patients with GCTB of the spine including the sacrum.
- ❑ In this subset analysis with a median follow-up of nearly 6 years, investigator-determined complete response, partial response, or stable disease occurred in all but one patient.
- ❑ More than half of the patients with resectable sacral or spinal tumors achieved excellent disease control and elected to continue denosumab treatment in lieu of undergoing surgery.
- ❑ The safety profile in the subset of patients with GCTB of the spine including the sacrum was consistent with the full study population and no new safety signals were identified.

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Data Sharing: Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: <http://www.amgen.com/datasharing>.

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