Denosumab in patients with giant-cell tumour of bone: a multicentre, open-label, phase 2 study

Sant Chawla, Jean-Yves Blay, Piotr Rutkowski, Axel Le Cesne, Peter Reichardt, Hans Gelderblom, Robert J Grimer, Edwin Choy, Keith Skubitz, Leanne Seeger, Scott M Schuetze, Robert Henshaw, Tian Dai, Danielle Jandial, Emanuela Palmerini

Summary

Background Giant-cell tumour of bone (GCTB) is a rare, locally aggressive osteoclastogenic stromal tumour of the bone. This phase 2 study aimed to assess the safety and activity of denosumab in patients with surgically salvageable or unsalvageable GCTB.

Methods In this multicentre, open-label, phase 2 study done at 30 sites in 12 countries we enrolled adults and skeletally mature adolescents (aged ≥12 years) weighing at least 45 kg with histologically confirmed and radiographically measurable GCTB, Karnofsky performance status 50% or higher (Eastern Cooperative Oncology Group status 0, 1, or 2), and measurable active disease within 1 year of study enrolment. Patients had surgically unsalvageable GCTB (cohort 1), had surgically salvageable GCTB with planned surgery expected to result in severe morbidity (cohort 2), or were enrolled from a previous study of denosumab for GCTB (cohort 3). Patients received 120 mg subcutaneous denosumab once every 4 weeks during the treatment phase, with loading doses (120 mg subcutaneously) administered on study days 8 and 15 to patients in cohorts 1 and 2 (patients in cohort 3 did not receive loading doses). The primary endpoint was safety in terms of the type, frequency, and severity of adverse events; secondary endpoints included time to disease progression from cohort 1 and the proportion of patients without surgery at month 6 for cohort 2. The safety analysis set included all enrolled patients who received at least one dose of denosumab. This study is registered with ClinicalTrials.gov, number NCT00680992, and has been completed.

Findings Between Sept 9, 2008, and Feb 25, 2016, 532 patients were enrolled: 267 in cohort 1, 253 in cohort 2, and 12 in cohort 3. At data cutoff on Feb 24, 2017, median follow-up was 58·1 months (IQR 34·0–74·4) in the overall patient population, and 65·8 months (40·9–82·4) in cohort 1, 53·4 months (28·2–64·1) in cohort 2, and 76·4 months (61·2–76·5) in cohort 3. During the treatment phase, the most common grade 3 or worse adverse events were hypophosphataemia (24 [5%] of 526 patients), osteonecrosis of the jaw (17 [3%], pain in extremity (12 [2%]), and anaemia (11 [2%]). Serious adverse events were reported in 138 (26%) of 526 patients; the most common were osteonecrosis of the jaw (17 [3%]), anaemia (6 [1%]), bone giant cell tumour (6 [1%]), and back pain (5 [1%]). 28 (5%) patients had positively adjudicated osteonecrosis of the jaw, four (1%) had atypical femur fracture, and four (1%) had hypercalcaemia occurring 30 days after denosumab discontinuation. There were four cases (1%) of sarcomatous transformation, consistent with historical data. Ten (2%) treatment-emergent deaths occurred (two of which were considered treatment-related; bone sarcoma in cohort 2 and sarcoma in cohort 1). Median time to progression or recurrence for patients in cohort 1 during the first treatment phase was not reached (28 [11%] of 262 patients had progression or recurrence). 227 (92%; 95% CI 87–95) of 248 patients who received at least one dose of denosumab in cohort 2 had no surgery in the first 6 months of the study.

Interpretation The types and frequencies of adverse events were consistent with the known safety profile of denosumab, which showed long-term disease control for patients with GCTB with unresectable and resectable tumours. Our results suggest that the overall risk to benefit ratio for denosumab treatment in patients with GCTB remains favourable.

Funding Amgen.

Introduction

Giant-cell tumour of bone (GCTB) is a rare, locally aggressive osteoclastogenic stromal tumour of the bone.[1,2] Although GCTB is considered benign, the tumours can destroy the bone and extend into the surrounding soft tissue, causing pain, substantial morbidity, and occasionally metastasis.[3,4] Standard curative treatment is surgical removal, either by curettage or resection; however, some sites might not be amenable to resection (eg, skull and spine), and local recurrence can occur at any site.[3] Local recurrence after surgery is estimated to occur in 15–50% of patients, with a higher prevalence after curettage than after en-bloc resection.[3,5,6] For patients with surgically unsalvageable GCTB, treatment options are scarce and might not be curative or could have substantial morbidity.

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Sarcoma Oncology Center, Santa Monica, CA, USA (S Chawla MD); **Department of Medicine, Centre Léon Bérard Cancer Center & Université Claude Bernard Lyon, Lyon, France** (Prof J-Y Blay MD); **Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie Institute-Oncology Center, Warsaw, Poland** (Prof P Rutkowski MD); **Medical Oncology, Institut Gustave Roussy, Villejuif, France** (A Le Cesne MD); **Department of Oncology and Palliative Care, Helios Klinikum Berlin-Buch, Berlin, Germany** (P Reichardt MD); **Department of Medical Oncology, Leiden University Medical Center, Leiden, Netherlands** (Prof H Gelderblom MD); **Royal Orthopaedic Hospital, NHS Foundation Trust, Birmingham, UK** (Prof R J Grimer MB BS); **Division of Hematology & Oncology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA** (E Choy MD); **Department of Medicine, University of Minnesota, Minneapolis, MN, USA** (Prof K Skubitz MD); **UCLA Health System, Los Angeles, CA, USA** (Prof L Seeger MD); **Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA** (Prof S M Schuetze MD); **Department of Orthopedic Surgery (Orthopedic Oncology), Medstar Georgetown Orthopedic Institute and Washington Cancer Institute, Washington, DC, USA** (Prof R Henshaw MD); **Amgen Inc, Thousand Oaks, CA, USA** (T Dai PhD, D Jandial MD);

and Chemotherapy Unit, IRCCS Istituto Ortopedico Rizzoli/Department of Experimental, Diagnostic and Specialty Medicine, Università di Bologna, Bologna, Italy
(E Palmerini MD)

Correspondence to:
Dr Emanuela Palmerini, Chemotherapy Unit, IRCCS Istituto Ortopedico Rizzoli/Department of Experimental, Diagnostic and Specialty Medicine, Università di Bologna, Bologna 40136, Italy
emanuela.palmerini3@unibo.it

Research in context

Evidence before this study

We searched PubMed and Ovid when the study was being planned in 2005–06, with the terms "giant cell tumor of bone," "giant cell tumor," "bone neoplasms," "bone cancer," "osteoclastoma," "chemotherapy," "radiation therapy," "embolization," and "surgery" for publications in the English language related to treatment of patients with giant-cell tumour of bone (GCTB). No date restriction was applied. At the time of study design (2006), no papers related to denosumab in GCTB had been published, and no other studies showed conclusive evidence of an antitumour effect in patients with surgically unsalvageable disease. A phase 2 proof-of-concept study by Thomas and colleagues in 2010 showed tumour response at 25 weeks in 30 of 35 patients with GCTB who were given denosumab. The interim analysis of the present phase 2 study was published in 2013 by Chawla and colleagues and studied 282 patients enrolled between Sept 9, 2008, and March 25, 2011, for a median follow-up of 13 months.

Added value of this study

Our study reports the primary analysis results of the phase 2 study of denosumab in 532 patients with GCTB, which, to our knowledge, is the largest clinical trial so far in this disease. This study shows the long-term safety and activity of denosumab, with a median follow-up of 58·1 months (IQR 34·0–74·4). Most patients had radiological response and clinically meaningful decreases in pain scores. The incidence of osteonecrosis of the jaw or atypical femur fracture increased with increasing denosumab exposure. This study also provides data about analgesic use, and provides pharmacokinetic data from 188 denosumab samples from 15 adults and ten adolescent patients.

Implications of all the available evidence

Medical treatments for patients with locally advanced or metastatic GCTB are scarce and need to balance the risk of recurrence with functional outcomes. This study shows the utility of long-term denosumab in patients with GCTB. The proportion of patients who achieved clinical benefit (complete response, partial response, and stable disease) was high: 507 (>99%) of 509 patients. With respect to management of patients treated long-term with denosumab, the risks of osteonecrosis of the jaw, atypical femoral fracture, and postdiscontinuation hypercalcaemia need to be considered. Several patients with misdiagnosed GCTB were identified, highlighting the need for careful pathology review by bone pathologists and monitoring tumour response to treatment.

GCTB contains osteoclast-like giant cells and stromal cells; within biopsied tumours from patients with GCTB, osteoclast-like giant cells are found at the perimeter of areas of bone erosion.[7] The spindle-like stromal cells are the neoplastic component of GCTB owing to their ability to proliferate readily.[7] *H3F3A* mutations are frequent in GCTB.[8] Giant cells express receptor activator of nuclear factor-kappa β (RANK), whereas stromal cells express RANK ligand (RANKL).[9,10] RANKL drives osteoclast formation, function, and survival,[10] and excessive RANKL expression causes an increase in bone lysis and destruction.[11]

Denosumab, a human monoclonal antibody that inhibits RANKL, is approved for the treatment of adults and skeletally mature adolescents with GCTB that is unresectable or when surgical resection is likely to result in severe morbidity.[12–14] Results from phase 2 studies have shown tumour responses to denosumab as assessed by radiology and histology (reduction of multinucleated giant cells).[13,14] The objective of this study was to assess the safety and activity of denosumab in adult and skeletally mature adolescent patients with surgically salvageable or unsalvageable GCTB, the interim results of which have been previously published.[14]

Methods

Study design and participants

This is the primary analysis of a multicentre, open-label, phase 2 study done at 30 sites in 12 countries (appendix p 2). The data cutoff date (Feb 24, 2017) ensured that all patients enrolled in the pharmacokinetic substudy (which started after all patients enrolled in the main study were already accrued) had the opportunity to complete 12 months of denosumab treatment. The methods (appendix pp 43–112) and results from an interim analysis (data cutoff March 25, 2011) have been published previously.[14] The study was approved by each site's independent ethics committee or institutional review board.

Briefly, eligible patients were adults or skeletally mature adolescents (aged ≥12 years) weighing at least 45 kg with pathologically confirmed GCTB, a Karnofsky performance status of 50% or higher (or Eastern Cooperative Oncology Group status 0, 1, or 2), and measurable active disease within 1 year of study enrolment. Active disease was defined as imaging per local standard of care of osteolysis within the tumour or increasing symptoms such as pain, in conjunction with histopathology showing evidence of giant cells. Patients were not permitted to have current use of alternative therapies for GCTB. Patients with a known or suspected diagnosis of sarcoma, non-GCTB giant-cell-rich tumours, brown cell tumour of bone, or Paget disease; patients with a history or current evidence of osteonecrosis or osteomyelitis of the jaw; or those who required oral surgery or had unhealed dental or oral surgery were excluded. All patients provided written, informed consent.

After enrolment, patients were divided into three cohorts on the basis of surgical salvageability (cohorts 1 and 2) or current participation in an Amgen GCTB study

See Online for appendix

(NCT00396279); cohort 3, which was pragmatically added as a follow-up of a previous open-label, phase 2 study[13]), which were assigned at study entry (appendix p 40). Cohort 1 included patients with surgically unsalvageable tumours, such as sacral or spinal GCTB, or multiple lesions, including pulmonary metastases. Cohort 2 included patients with surgically salvageable disease in which a complete resection was feasible, but whose planned on-study surgery was associated with severe morbidity such as joint resection, limb amputation, hemipelvectomy, or a high risk of complications, including loss of major nerve or vascular structures. Cohort 3 included rollover patients who were participating in another study of unresectable GCTB[9] who were eligible to enrol.

Procedures

Patients received 120 mg denosumab subcutaneously once every 4 weeks, with loading doses (120 mg subcutaneously) administered on study days 8 and 15 to patients in cohorts 1 and 2 (patients in cohort 3 did not receive loading doses). Patients who had complete tumour resection (cohort 2) received adjuvant denosumab for six doses after pathological confirmation of partial response or complete response. For all other patients, treatment continued until disease progression, recommendation of discontinuation by the investigator or sponsor, absence of clinical benefit according to investigator judgment, patient decision, pregnancy, or administration of any disallowed treatments (eg, bisphosphonates). Study visits for all assessments occurred every 4 weeks for all cohorts until the end of treatment, with additional visits on days 8 and 15 of the first cycle for patients in cohorts 1 and 2. For patients who discontinued denosumab, safety follow-up visits were done every 6 months after the end-of-treatment visit (approximately 4 weeks after the last dose of denosumab) for the first year and then every 12 months thereafter. Dose adjustments were not permitted. Patients received concomitant supplements containing at least 500 mg calcium and 400 IU vitamin D.

On-study retreatment was allowed for patients who showed a tumour response to denosumab and were not receiving denosumab treatment (eg, in the case of recurrent disease while the patient was in the safety follow-up phase). The retreatment decision, including use of the loading dose and discontinuation of therapy, was handled on a case-by-case basis, and previous authorisation from the sponsor was required. Patients were required to satisfy all inclusion and exclusion criteria before being considered for retreatment and stayed in their originally assigned cohort. On May 15, 2013, a protocol amendment defined the end of the clinical trial as being when patients who were enrolled through November, 2012, had completed a minimum of 60 months on study, or until death or loss to follow-up, whichever occurred first.

All key efficacy and disease status assessments were determined by the investigator, based on patient evaluation, including imaging results, physical examination, and evaluation of pain and function. and were not reviewed centrally. Disease status and clinical benefit were assessed every 4 weeks while on treatment and were based on physical examination, patients' reports of symptoms (clinical benefit, including pain reduction, improved mobility, and improved function), and radiological imaging assessments (plain films, and CT, MRI, and ^{18}F-fluorodeoxyglucose PET scans) summarised descriptively per investigators' local standard practise. There were no predefined standardised criteria for tumour assessment, and there was no specified imaging schedule of assessment. Tumour response was generally based on multiple factors, including imaging assessment, clinical symptoms, and physical examination. Unless otherwise noted, all efficacy endpoints were assessed during the on-study period (ie, denosumab treatment during the initial treatment phase and excluded retreatment periods for patients who entered retreatment after a period of safety follow-up observation).

For patient-reported outcomes, case report forms were used to record patients' symptoms, pain (using the Brief Pain Inventory–Short Form [BPI-SF] questionnaire), activity, functional effects, concomitant medication use, treatments related to GCTB, and other information (eg, work status and disability). The range of the BPI-SF was from 0 (no pain) to 10 (worst pain), with ratings of 1–4 corresponding to mild pain, 5–6 to moderate pain, and 7–10 to severe pain. For patients in cohort 2, the timing and type of surgical intervention were also recorded and compared with the planned surgery at baseline. Potential morbidity of the planned surgery was determined by risk and extent of the procedure, such as joint resection, limb amputation, hemipelvectomy, or was high risk based on the extent or location of the lesion. Whether less morbid surgery (ie, surgery that was associated with less functional compromise or decreased morbidity compared to the planned procedure) was feasible was decided by the treating surgeon on the basis of clinical expertise and local practice standards for presentation at multidisciplinary tumour boards. Adverse events and laboratory abnormalities were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE; version 3.0). All reports of malignancy underwent independent expert review.

Safety information for all adverse events was collected every 4 weeks during the treatment period; during the safety follow-up period, only information about non-serious and serious adverse events of interest, and serious adverse events was collected. Serious adverse events were defined as adverse events that were fatal, life-threatening (ie, placed the patient at immediate risk of death), necessitated admission to hospital or prolongation of stay in hospital, resulted in persistent or clinically significant disability or incapacity, congenital anomalies or birth

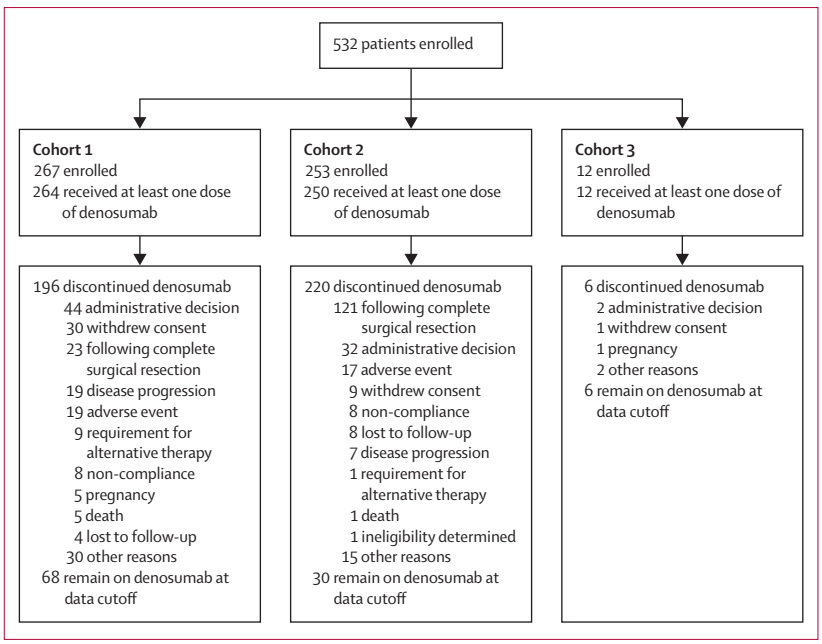

***Figure 1*: Trial profile**
Surgery type for the 245 eligible patients in cohort 2 were surgery (n=90), curettage (n=90), en-bloc resection (n=30), other (n=13), joint or prosthesis replacement (n=10), en-bloc excision (n=4), joint resection (n=4), amputation (n=2), and marginal excision (n=2).

defects, or other significant medical hazards. The incidence of adverse events was summarised according to the current Medical Dictionary for Regulatory Activities (version 19.1).

Outcomes

The primary endpoint was to characterise the safety profile of denosumab in terms of the type, frequency, and severity of adverse events, and laboratory abnormalities for each cohort. Secondary endpoints were time to disease progression for cohort 1, the proportion of patients without any surgery at month 6 for cohort 2, and serum denosumab pharmacokinetics (trough concentrations) in adolescent and adult patients with GCTB enrolled in the pharmacokinetic substudy. Prespecified exploratory endpoints included investigator-assessed tumour response, time to disease progression or recurrence in all patients, time to surgery for cohort 2, time to disease progression after discontinuation of denosumab, time to disease progression or recurrence after on-study GCTB surgery in cohort 2, time to disease recurrence for patients with complete clinical response, the proportion of patients who were able to undergo a less morbid surgical procedure compared with the planned procedure at baseline for cohort 2, clinical benefit, changes in pain score from baseline as measured by the BPI-SF questionnaire, and analgesic use (a full list of objectives and endpoints is in the appendix p 3; not all exploratory endpoint are reported in this paper).

Statistical analysis

The study sample size was determined by the anticipated number of patients with GCTB who would qualify for the study and could be recruited at the enrolling sites (approximately ten patients across all sites per month). In 2011, a protocol amendment increased the planned study enrolment size from 375 patients to approximately 500 patients. We subsequently estimated that around 530 patients would participate in the study. No hypothesis testing was done in this study, so there was no formal sample size requirement, and no power calculation was done.

The safety analysis set included all enrolled patients who received at least one dose of denosumab. The efficacy analysis set included all enrolled patients who were eligible for the study and received at least one dose of denosumab. Patients with inclusion or exclusion deviations of pathologically confirmed giant-cell tumour or known or suspected diagnosis of underlying malignancy were excluded from the efficacy analysis set as eligiblity deviations after enrolment. Pharmacokinetic analyses were done in adolescent and adult patients enrolled in the pharmacokinetic substudy who received at least one dose of denosumab, and who had a baseline pharmacokinetic measurement and at least one post-baseline pharmacokinetic measurement. Summary statistics for serum concentrations of denosumab and change from baseline (absolute and percentage change) were provided at scheduled visits. Treatment-emergent adverse events include all adverse events that occurred from the first dose in the initial treatment phase to the end of the initial treatment phase (or for patients who entered retreatment, from the first dose date in the initial treatment phase through any follow-up previous to a retreatment, until the end of retreatment phase). Adverse events that occurred after the treatment-emergent period are summarised separately.

For time-to-event endpoints, the Kaplan-Meier method was used to estimate the survival function, quartiles (median and IQR) with two-sided 95% CIs, and event rates at various timepoints with two-sided 95% CIs using SAS (version 9.2).

This study is registered with ClinicalTrials.gov, number NCT00680992.

Role of the funding source

The study was designed by the authors in collaboration with the sponsor (Amgen). The authors and sponsor were responsible for data collection, and the sponsor was responsible for data analysis. The authors and sponsor were involved in data interpretation, development of the report, and the decision to submit for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Sept 9, 2008, and Feb 25, 2016, 532 patients were enrolled in the treatment phase of the study: 267 in cohort 1, 253 in cohort 2, and 12 in cohort 3. 526 (99%) of

532 patients received at least one dose of denosumab (figure 1). At data cutoff (Feb 24, 2017), 104 (20%) of 526 patients remained on denosumab. Among the 422 (80%) patients who discontinued denosumab, common reasons for discontinuation included protocol-specified criteria relating to complete surgical resection of the tumour or administrative decision (mostly due to transfer to commercially available denosumab after approval by the US Food and Drug Administration in 2013, and by the European Medicines Agency in 2014; figure 1).

More than half of patients were women, with a median age of 33 years (IQR 25–45; table 1). Lesion locations in cohort 1 were primarily in the sacrum, lung, and vertebrae; in cohort 2, patients had GCTB tumours located primarily in the tibia, femur, and radius (appendix p 4). All cases of disease in the lungs were unresectable because of tumour number, size, or location. Median follow-up, including retreatment and safety follow-up, was 58·1 months (IQR 34·0–74·4) overall, and 65·8 months (40·9–82·4) in cohort 1, 53·4 months (28·2–64·1) in cohort 2, and 76·4 months (61·2–76·5) in cohort 3. Median exposure to denosumab was 32·0 doses (IQR 17·0–59·0) overall and 43·0 doses (24·0–68·0) in cohort 1, 20·5 doses (15·0–43·0) in cohort 2, and 66·0 doses (39·5–79·0) in cohort 3.

The median duration of the treatment-emergent period was 44·4 months (IQR 23·8–69·3) for cohort 1, 20·1 months (13·4–45·6) for cohort 2, 71·4 months (48·9–76·5) for cohort 3, and 32·3 months (16·3–59·9) for all cohorts combined. The most commonly reported treatment-emergent adverse events of any grade and across all cohorts were arthralgia, back pain, fatigue, pain in extremity, and headache (table 2), and the most common treatment-related and treatment-emergent adverse events were fatigue, hypophosphataemia, and headache (appendix pp 5–6). 46 (9%) of 526 patients had adverse events that led to discontinuation of denosumab (appendix p 21), with investigator-reported osteonecrosis of the jaw in 15 (3%) patients and sarcoma, pain in jaw, bone sarcoma, and tooth infection (all ≤1% each) being the most commonly reported adverse treatment-emergent events leading to treatment discontinuation overall. 29 (6%) of 526 patients had treatment-emergent treatment-related adverse events that led to discontinuation of denosumab (appendix p 22), including investigator-reported osteonecrosis of the jaw (in 14 [3%] patients) and pain in jaw and sarcoma (each in 2 [<1%] patients). The percentages of patients with commonly reported adverse events of any grade or severity were generally slightly higher in cohort 1 than in cohort 2 (table 2).

Serious treatment-emergent adverse events were reported in 138 (26%) of 526 patients (appendix p 23); the most common were investigator-reported osteonecrosis of the jaw, anaemia, bone giant cell tumour, and back pain (appendix pp 5–6). 42 (8%) of 526 patients had treatment-related serious treatment-emergent adverse events (appendix p 24), with the most common being investigator-reported osteonecrosis of the jaw, osteomyelitis, hypercalcaemia, osteonecrosis, sarcoma, and osteitis. 183 (35%) of 526 patients had treatment-emergent adverse events of CTCAE grade 3

	Cohort 1 (n=267)	Cohort 2 (n=253)	Cohort 3 (n=12)	All patients (n=532)
Sex				
Men	113 (42%)	111 (44%)	7 (58%)	231 (43%)
Women	154 (58%)	142 (56%)	5 (42%)	301 (57%)
Ethnicity or race				
White or Caucasian	221 (83%)	208 (82%)	11 (92%)	440 (83%)
Black or African–American	17 (6%)	13 (5%)	0	30 (6%)
Hispanic or Latino	13 (5%)	13 (5%)	1 (8%)	27 (5%)
Asian	11 (4%)	14 (6%)	0	25 (5%)
Native Hawaiian or other Pacific Islander	0	1 (<1%)	0	1 (<1%)
Other	5 (2%)	4 (2%)	0	9 (2%)
Longest dimension of target lesion, mm (median [IQR])	56·7 (31·5–90·5)	60·0 (41·2–80·0)	29·0 (14·0–67·0)	59·0 (35·0-84·0)
Adolescents*	14 (5%)	14 (6%)	0	28 (5%)
Age, years (median [IQR])	33 (25–46)	34 (25–44)	31 (25–48)	33 (25–45)
GCTB type				
Primary resectable	0	168 (66%)	0	168 (32%)
Primary unresectable	92 (34%)	0	2 (17%)	94 (18%)
Recurrent resectable	0	85 (34%)	0	85 (16%)
Recurrent unresectable	175 (66%)	0	10 (83%)	185 (35%)
Previous surgery for GCTB	182 (68%)	94 (37%)	0	276 (52%)
Planned surgery				
No surgery planned	267 (100%)	0	0	267 (50%)
Curettage	0	30 (12%)	0	30 (6%)
Marginal excision	0	2 (<1%)	0	2 (<1%)
En-bloc excision	0	10 (4%)	0	10 (2%)
En-bloc resection	0	88 (35%)	0	88 (17%)
Joint resection	0	36 (14%)	0	36 (7%)
Joint or prosthesis replacement	0	27 (11%)	0	27 (5%)
Amputation	0	42 (17%)	0	42 (8%)
Hemipelvectomy	0	11 (4%)	0	11 (2%)
Other	0	7 (3%)	0	7 (1%)
Not applicable†	0	0	12 (100%)	12 (2%)
Karnofsky performance status score				
40%	1 (<1%)	0	0	1 (<1%)
50%	4 (2%)	0	0	4 (<1%)
60%	14 (5%)	1 (<1%)	0	15 (3%)
70%	29 (11%)	24 (10%)	0	53 (10%)
80%	56 (21%)	51 (20%)	1 (8%)	108 (20%)
90%	86 (32%)	85 (34%)	1 (8%)	172 (32%)
100%	77 (29%)	92 (36%)	8 (67%)	177 (33%)
Not applicable†	0	0	2 (17%)	2 (<1%)

Data are n (%), unless otherwise indicated. GCTB=giant-cell tumour of bone. *Skeletally mature adolescents defined as patients aged 12–17 years with radiographical evidence of at least one mature long bone (ie, closed epiphyseal plates) and weighing at least 45 kg. †Not expected or available for patients in cohort 3.

Table 1: **Patient demographics and baseline characteristics**

	Cohort 1 (n=264)				Cohort 2 (n=250)				Cohort 3 (n=12)			
	Grades 1–2	Grade 3	Grade 4	Grade 5	Grades 1–2	Grade 3	Grade 4	Grade 5	Grades 1–2	Grade 3	Grade 4	Grade 5
Arthralgia	92 (35%)	4 (2%)	1 (<1%)	0	76 (30%)	1 (<1%)	0	0	6 (50%)	0	0	0
Back pain	93 (35%)	4 (2%)	0	0	41 (16%)	2 (1%)	0	0	5 (42%)	0	0	0
Fatigue	79 (30%)	1 (<1%)	0	0	59 (24%)	0	0	0	2 (17%)	0	0	0
Headache	72 (27%)	3 (1%)	0	0	49 (20%)	2 (1%)	0	0	5 (42%)	0	0	0
Pain in extremity	70 (27%)	8 (3%)	0	0	55 (22%)	3 (1%)	0	0	2 (17%)	1 (8%)	0	0
Nausea	64 (24%)	0	0	0	48 (19%)	0	0	0	1 (8%)	0	0	0
Nasopharyngitis	50 (19%)	0	0	0	23 (9%)	0	0	0	3 (25%)	0	0	0
Toothache	38 (14%)	1 (<1%)	0	0	22 (9%)	0	0	0	4 (33%)	0	0	0
Diarrhoea	38 (14%)	0	0	0	18 (7%)	0	0	0	2 (17%)	0	0	0
Vomiting	36 (14%)	0	0	0	24 (10%)	0	0	0	4 (33%)	0	0	0
Paraesthesia	36 (14%)	0	0	0	10 (4%)	0	0	0	0	0	0	0
Constipation	35 (13%)	0	0	0	21 (8%)	0	0	0	0	0	0	0
Musculoskeletal pain	33 (13%)	6 (2%)			18 (7%)	1 (<1%)	0	0	4 (33%)	0	0	0
Cough	33 (13%)	0	0	0	15 (6%)	0	0	0	5 (42%)	0	0	0
Upper respiratory tract infection	30 (11%)	0	0	0	13 (5%)	0	0	0	4 (33%)	0	0	0
Peripheral oedema	29 (11%)	0	0	0	13 (5%)	1 (<1%)	0	0	1 (8%)	0	0	0
Asthenia	28 (11%)	0	0	0	14 (6%)	0	0	0	4 (33%)	0	0	0
Abdominal pain	27 (10%)	3 (1%)	0	0	15 (6%)	1 (<1%)	0	0	2 (17%)	0	0	0
Hypophosphataemia	22 (8%)	14 (5%)	0	0	14 (6%)	8 (3%)	0	0	2 (17%)	1 (8%)	1 (8%)	0
Anaemia	14 (5%)	5 (2%)	4 (2%)	0	5 (2%)	2 (<1%)	0	0	1 (8%)	0	0	0
Osteonecrosis of jaw	10 (4%)	12 (5%)	0	0	2 (<1%)	5 (2%)	0	0	0	0	0	0

Data are n (%). Shown are grades 1–2 adverse events occurring in at least 10% of patients in either cohort 1 or 2, and grade 3–5 adverse events occurring in at least 2% of patients in either cohort 1 or 2. Grade 1–2 adverse events occurring in at least 5% of all patients and all grade 3 or worse adverse events are shown in the appendix pp 7–20.

Table 2: **Most frequent treatment-emergent adverse events by grade**

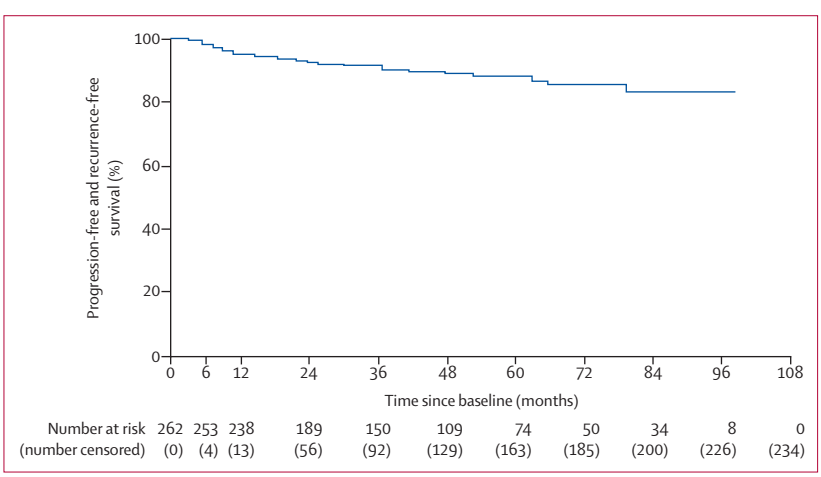

Figure 2: **Time to disease progression or recurrence (first treatment phase) for patients in cohort 1 (n=262)**

or worse (appendix pp 25–28), and 69 (13%) patients had grade 3 or worse treatment-emergent adverse events considered to be treatment related (appendix p 29), the most common of which were hypophosphataemia and investigator-reported osteonecrosis of the jaw. Ten (2%) of 526 patients had treatment-emergent fatal adverse events (appendix pp 5–6, 30), two of which were considered possibly treatment related (bone sarcoma in cohort 2 and sarcoma in cohort 1).

For the 348 patients who remained on the trial after the treatment-emergent period (the safety follow-up phase; median duration 23·3 months [IQR 11·8–39·2] for cohort 1, 17·8 months [11·5–39·2] for cohort 2, 11·2 months [10·6–17·4] for cohort 3, and 19·5 months [11·5–39·2] for all cohorts combined), 116 (33%) reported adverse events (38 [25%] in cohort 1, 77 [40%] in cohort 2, and one [20%] in cohort 3; appendix p 31). The most commonly reported adverse events in this period for all cohorts combined included GCBT (in 18 [5%] of 348 patients), arthralgia (14 [4%]), back pain (seven [2%]), nausea (seven [2%]), and pain in extremity (six [2%]). 48 (14%) of 348 patients had serious adverse events after the treatment-emergent period, including GCTB (in 12 [3%] patients) and anaemia, death, and osteonecrosis of the jaw (three [1%] each).

The most frequently reported adverse event of interest was positively adjudicated (osteonecrosis of the jaw determined by external independent adjudication by two expert dentists or oral surgeons) osteonecrosis of the jaw in 28 (5%) of 526 patients (21 [8%] in cohort 1 and seven [3%] in cohort 2), 21 (4%) of which were considered serious. At a median of 43 denosumab doses (IQR 23–67) in cohort 1 and 20 doses (15–43) in cohort 2, exposure-adjusted incidence of confirmed osteonecrosis of the jaw was 1·6 (95% CI 1·1–2·4) per 100 patient-years overall (ie, across cohorts 1 and 2) and was higher after

3 years on study; 0·0 (95% CI 0·0–0·0) during the first year, 1·6 (0·6–3·5) in the second year, 0·7 (0·1–2·6) in the third year, 4·7 (2·2–8·6) in the fourth year, 3·2 (1·0–7·5) in the fifth year, and 2·2 (0·6–5·6) after 5 years. Onset of osteonecrosis of the jaw was preceded by a tooth extraction in 16 (57%) of 28 cases or an oral infection in 14 (50%) cases. Additionally, six patients (21%) with osteonecrosis of the jaw had previously used zoledronic acid. During evaluation and treatment of suspected osteonecrosis of the jaw, denosumab was discontinued in 14 patients, temporarily withheld in nine, and continued in five patients. The condition resolved (defined by complete mucosal coverage in the absence of symptoms) in 15 (54%) of 28 cases (ten [48%] of 21 in cohort 1 and five [71%] of seven in cohort 2) and the frequency of resolution was generally similar regardless of whether denosumab was discontinued, temporarily interrupted, or continued (data not shown). For other adverse events of interest, four (<1%) patients in cohort 1 had adjudicated positive atypical femur fracture (all occurred after 48 months of denosumab treatment) and four (<1%; two in cohort 1 and two in cohort 2) had hypercalcaemia that occurred after 30 days after the last dose of denosumab (all occurred between 4 and 9 months after the last denosumab dose, two cases were recurrent).

Malignancy in GCTB was another event of interest. 20 (4%) of 526 patients with a potential diagnosis of malignancy on study were identified: 12 (5%) of 264 patients in cohort 1 and eight (3%) of 250 patients in cohort 2. Each case was reviewed by an independent expert panel; 15 (3%) of 526 were pathologically confirmed (n=8) or highly suspected (n=7) to be misdiagnoses of benign GCTB at baseline and the remaining five cases were determined to be sarcomatous transformation of previous histologically benign GCTB (n=4; 1%) or secondary malignant GCTB (n=1; <1%; appendix p 32).

Most patients in cohort 1 did not have investigator-determined disease progression during the first treatment phase. 28 (11%) of 262 treated patients had disease progression during the first treatment phase, and the median time to disease progression or recurrence was not reached (figure 2). The Kaplan-Meier estimates of the probabilities for disease progression or recurrence during the treatment period for cohort 1 were 1·9% (95% CI 0·3–3·6) at week 25, 3·9% (1·5–6·3) at week 49, and 6·5% (3·4–9·6) at week 98.

Overall, 132 (50%) of 262 patients in cohort 1 discontinued denosumab without disease progression (ie, patients who had a post-baseline disease status evaluation and whose reason for discontinuing denosumab was not due to death or lost to follow-up, disease progression, or withdrawal of consent). 34 (26%) of these 132 patients had disease progression or recurrence after discontinuation of denosumab; the median time to progression was 39·0 months (95% CI 21·0 to not estimable). The Kaplan-Meier estimates for the probability of recurrence after discontinuation of denosumab were 23·6% (95% CI 14·9–32·4) at 1 year, 42·3% (30·0–54·7) at 2 years, and 45·9% (32·5–59·4) at 3 years.

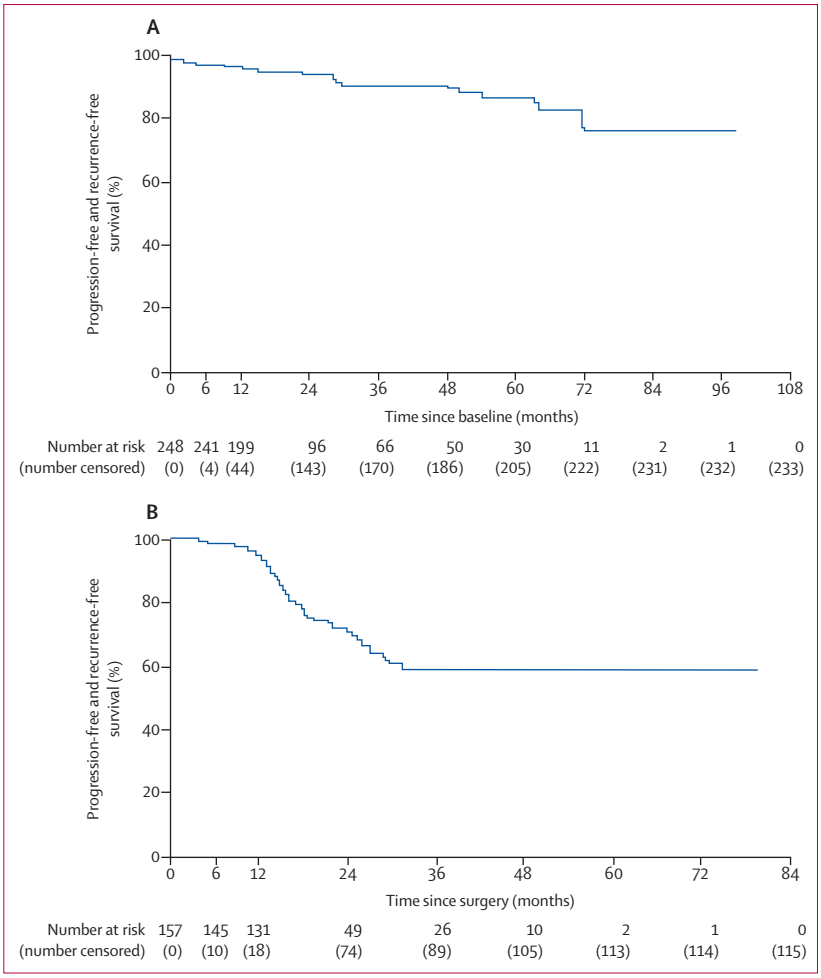

Figure 3: **Time to disease progression or recurrence in cohort 2**
(A) Time to disease progression or recurrence (first treatment phase) for all patients in the efficacy analysis set in cohort 2 (n=248). (B) Time to disease progression or recurrence since on-study GCTB surgery for 157 patients in cohort 2 who underwent surgery (includes all follow-up, including safety follow-up, up to the end of the trial; most progression or recurrence occurred during the safety follow-up). GCTB=giant-cell tumour of bone.

The Kaplan-Meier estimates of the probabilities for disease progression or recurrence during the first treatment phase for patients in all cohorts combined were 1·6 (95% CI 0·5–2·7) at week 25, 3·0 (1·5–4·5) at week 49, and 5·3 (3·2–7·4) at week 98. Median time to disease progression or recurrence for all cohorts combined was not reached (95% CI was not estimable).

Most patients in cohort 2 who received at least one dose of denosumab had no surgery for GCTB during the first 6 months of the study (227 [92%] of 248; 95% CI 87–95). Kaplan-Meier estimates for the proportion of patients in cohort 2 without disease progression (exploratory endpoint) or recurrence are shown in figure 3A. 157 (63%) of 248 patients ultimately underwent on-study surgery

	Patients with clinical benefit	Pain reduction	Improved mobility	Improved function	Other
Cohort 1 (n=262)	209 (80%)	170 (65%)	108 (41%)	92 (35%)	42 (16%)
Cohort 2 (n=248)	197 (79%)	164 (66%)	109 (44%)	79 (32%)	39 (16%)
Cohort 3 (n=11)	5 (46%)	4 (36%)	3 (27%)	4 (36%)	2 (18%)
Cohorts 1 and 2 (n=510)	406 (80%)	334 (66%)	217 (43%)	171 (34%)	81 (16%)

Data are n (%). n=number of patients in the efficacy analysis set.

Table 3: **Investigator-reported clinical benefit**

	Patients with post-baseline disease status evaluation	Complete response	Partial response	Stable disease	Disease progression
Cohort 1 (n=262)	262 (100%)	38 (15%)	115 (44%)	108 (41%)	1 (<1%)
Cohort 2 (n=248)	247 (>99%)	151 (61%)	58 (24%)	37 (15%)	1 (<1%)
Cohort 3 (n=11)	11 (100%)	0	6 (55%)	5 (46%)	0
Cohorts 1 and 2 (n=510)	509 (>99%)	189 (37%)	173 (34%)	145 (29%)	2 (<1%)

Data are n (%). n=number of patients in the efficacy analysis set.

Table 4: **Investigator-reported disease status with best post-baseline response**

for GCTB (appendix p 39), with a median estimated time to surgery of 9·2 months (95% CI 8·5–10·5). 42 (27%) of these 157 patients had disease progression or recurrence after on-study GCTB surgery; median time to disease progression or recurrence was not estimable. The Kaplan-Meier estimates of the probability of disease progression or recurrence after on-study surgery for GCTB in cohort 2 were 5·6% (95% CI 1·8–9·4) at year 1, 28·1% (19·8–36·5) at year 2, and 40·8% (30·2–51·3) at year 3 (figure 3B). 31 (34%) of 90 patients undergoing curettage and six (12%) of 51 patients undergoing excisional procedures had disease recurrence; median time to disease recurrence was not reached in either of these groups of patients (appendix p 41).

Overall, 187 (75%) of 248 patients in cohort 2 discontinued denosumab without disease progression; 46 (25%) of these 187 patients had disease progression or recurrence (median time to progression was not reached). The Kaplan-Meier estimates for the probability of recurrence after discontinuation of denosumab were 18·2% (95% CI 12·1–24·4) at 1 year, 34·3% (25·1–43·5) at 2 years, and 42·0% (31·2–52·8) at 3 years.

Most patients (about 80%) given denosumab had clinical benefit, defined as investigator-reported pain reduction, improved mobility, or improved function (table 3). Pain reduction was the most commonly reported clinical benefit in cohorts 1 and 2. Most patients showed improved or stable radiological changes over time (appendix p 33).

Most patients had an investigator-determined best response of stable disease or better during the on-treatment and post-treatment periods (table 4). 118 (48%) of 248 patients had complete response during the on-treatment period and about a third of these patients had subsequent progressive disease, locally recurrent disease, or relapse (38 [32%] of 118 in cohort 2); Kaplan–Meier-estimated median time to recurrence in these patients was not reached. Most patients with a planned surgical procedure (in cohort 2) were able to avoid surgery or have a less morbid procedure than was initially planned (appendix p 38); 90 (37%) of 245 patients with planned on-study surgery not in lungs or soft tissue ended up having no surgery and 106 (44%) had a less morbid procedure. Most patients (107 [96%] of 112) with planned major surgery (hemipelvectomy, amputation, joint or prosthesis replacement, and joint resection) did not undergo their planned procedure (appendix p 38). Native joint preservation was observed in 26 (96%) of 27 patients with a planned joint or prosthesis replacement and 31 (89%) in 35 patients with a planned joint resection or fusion. 39 (25%) of 157 patients in cohort 2 underwent a second on-study GCTB surgery (not in lung or soft tissue) over a Kaplan–Meier-estimated median time of 51·8 months (95% CI 34·3–not estimable).

110 (45%) of 246 patients in cohort 1 and 120 (51%) of 237 patients in cohort 2 had moderate or severe worst pain (BPI-SF worst pain score >4) at baseline. Median times to 2-point or more decrease from baseline in worst pain score were 1·0 (95% CI 0·6–1·9) month for cohort 1, 0·5 (0·5–1·0) month for cohort 2, and 19·4 (1·0, not estimable) months for cohort 3 (appendix pp 34, 42). These improvements persisted for the duration of patients' participation during the on-study period; at least 62% (134 of 218) of patients overall reported a clinically meaningful reduction in worst pain at week 5 and at all subsequent evaluations (appendix p 34).

Increasing proportions of patients shifted from strong opioid use (analgesic score ≥3) at baseline to non-opioid analgesic or weak opioid use (analgesic score ≤2). In the total 123 patients across all cohorts who were receiving strong opioids at baseline, a shift to non-opioid or weak opioid was observed in 27% (31 of 117) at week 21, and this proportion increased over subsequent evaluations (appendix p 35). Very few patients shifted from no or low analgesic use to strong opioid use during the on-study period (appendix p 36).

Study results for adolescent patients were consistent with those for the larger overall (all-patient) population (appendix p 37). A total of 188 denosumab samples were collected from 15 adult and 10 adolescent patients. Individual and mean denosumab concentrations were generally similar between adults and adolescents (appendix pp 43–45).

Discussion

This study represents a prospective clinical trial in 532 patients with GCTB, which, to our knowledge, is the largest so far in this disease setting. Common adverse events were consistent with the known safety profile of denosumab.[13,14] Overall, the percentages of patients with commonly reported adverse events were

generally slightly higher in cohort 1 than in cohort 2, which is probably attributable to the longer exposure to denosumab in cohort 1 than in cohort 2.

The frequency of positively adjudicated osteonecrosis of the jaw increased with increasing denosumab exposure, and was preceded by a tooth extraction in 75% and oral infection in 50% of cases. These results highlight the need for regular preventive dental hygiene visits and maintenance of good oral health,[12] which reduces the occurrence and risk of this adverse event.[15] More than half of the positively adjudicated cases of osteonecrosis of the jaw had resolved by the data cutoff. For patients who require invasive dental procedures while on treatment, denosumab treatment should be stopped before the procedure and not resumed until the mucosa has fully healed.[12] Reports of positively adjudicated atypical femur fracture were rare, but all occurred after long-term (>4 years) exposure to denosumab. During denosumab treatment, patients should be advised to report any new or unusual thigh, hip, or groin pain, and suspected atypical fracture should be ruled out in patients presenting with these symptoms.[12] Hypercalcaemia after treatment discontinuation was rare, but emphasises the need for monitoring of signs and symptoms of hypercalcaemia within the first year after treatment discontinuation, including periodic assessment of serum calcium and evaluation of the patient's need for ongoing calcium and vitamin D supplementation.[12,16]

The frequency of confirmed sarcomatous transformation in our study (1%) was not higher than the 2% that has been previously reported.[17–22] No biological evidence exists to support a causal association between malignancy and denosumab treatment. However, these findings suggest that careful radiological and pathological expert evaluation of the tumour is warranted before treatment; *H3F3A* mutational testing can be useful to differentiate GCTB from giant cell-rich sarcomas.[8] Close radiographical and clinical evaluation during the initial few months of treatment is also warranted, as evidenced by many misdiagnosed patients showing no expected radiological intratumoural calcifications and recurrent or progressive pain, expected as a consequence of the mechanism of action of denosumab in the GCTB lesion. Malignant transformation is more common in patients who have had previous radiotherapy than in those who had not received previous radiotherapy,[23] and therefore should be considered during the close monitoring period.

In patients with unresectable disease (cohort 1), denosumab provided long-term disease control; only 11% of patients had disease progression during the on-study period and median time to progressive disease was not reached. However, patients do risk relapse after stopping denosumab (approximately 25% of patients in this study). A reduced dose of denosumab or less frequent administration of drug for maintenance in patients with unresectable disease might be possible; the phase 2 REDUCE study (NCT03620149) aims to answer this question.

Most of the resectable patients (cohort 2) had no surgery for GCTB during the first 6 months; overall, 79% had clinical benefit with neoadjuvant denosumab and 37% avoided surgery. Many had advanced disease at baseline considered manageable only by amputation or hemipelvectomy; for these patients, avoidance of surgery and resulting morbidity is an important benefit (80% had no surgery or a less invasive procedure). The frequency of recurrence after curettage was higher than after excisional procedures, an observation consistent with previous studies that reported rates of 25–50% for curettage and 0–5% for en-bloc resection.[3,5] The high incidence of relapse after curettage underscores the need for a different treatment strategy in some resectable cases. A recent analysis[24] reported a local recurrence in 11 (44%) of 25 patients who were given denosumab compared with seven (21%) of 34 patients in a case-matched group who were not given denosumab. However, the incidence of recurrence decreased after denosumab therapy with curettage that covered the complete tumour margin before treatment (six [26%] of 23 using this method). Denosumab reduces the relative content of highly proliferative tumour stromal cells, replacing them with non-proliferative osteoid bone matrix and densely woven new bone, making it difficult to accurately define the extent of tumour before treatment.[9]

Several unanswered questions remain in the management of GCTB that this study was not designed to address. For unresectable patients, other studies[25] have similarly reported that prolonged treatment with denosumab produces sustained tumour control and clinical benefit (median treatment time was 54 months); however, 40% of patients discontinuing denosumab had tumour progression after a median of 8 months. The duration of therapy for such patients thus shows that at least some patients might require longer-term denosumab therapy for tumour control; a reduced dose density for long-term denosumab maintenance therapy (120 mg every 3 months) is being evaluated in patients with unresectable GCTB (NCT03630149). Although we do know that best response to denosumab can be expected within 3–6 months, no predictors of progression after discontinuation are available.

Among resectable cases, open questions remain regarding which tumours are most likely to benefit from neoadjuvant treatment, the optimal duration of neoadjuvant treatment, or even which tumours might be eligible for exclusive treatment by denosumab. Nevertheless, neoadjuvant denosumab, administered for a relatively short period (approximately 3–6 months), is a suggested option for treatment of initially locally advanced, high-risk tumours to facilitate complete surgical resection or avoid mutilating surgery.[24,26] Additionally, the added benefit of postoperative denosumab therapy as used in this protocol, as well as the

optimal duration or utility after complete tumour resection, remains unanswered. Further study of patients most likely to benefit from denosumab in these setting is warranted.

In patients with moderate to severe pain at baseline (about half of patients), rapid reduction in pain severity was observed, as well as a reduction in strong opioid use. These results extend those from the interim pain and analgesic use results.[27]

Our findings are consistent with those of the interim analysis, and provide additional data on pain and opioid use.[14] Our additional data did not suggest any new safety signals associated with denosumab and confirm its long-term safety and activity in a large group of patients. These findings are also consistent with an analysis of patients with GCTB given denosumab outside of clinical trials in terms of adverse events, response, misdiagnosis, and recurrence after surgery.[26]

This study is limited by the absence of a control group, dictated by the rarity of the disease, and the absence of a standardised disease assessment or schedule. Another limitation is that no predefined standardised criteria were used for disease or tumour response assessment and, therefore, consistency cannot be guaranteed across study sites. Nonetheless, we were able to recruit a large number of patients in this rare indication, with a long median time on treatment and duration of follow-up, which helps to strengthen our findings. In previously published studies[28] on patients with advanced cancer with bone metastases receiving denosumab for prevention of bone complications (at the same dose and schedule as that used in this trial), denosumab was used for approximately 24 months; thus, this study provides additional safety information about more prolonged treatment. Our study showed that osteonecrosis of the jaw is dose dependent and occurs more frequently in patients with dental comorbidities. A further trial is planned to investigate the potential for maintenance denosumab dosing to limit the risk for osteonecrosis of the jaw while maintaining disease control, especially in patients who might need extended long-term therapy for unresectable GCTB. Additional strengths of this study include the fact that we have reported disease status and clinical benefit data in the skeletally mature adolescent population, which was similar to the adult patients in the study.

In conclusion, our data show that the type and frequencies of adverse events were consistent with the known safety profile of denosumab. A higher incidence of osteonecrosis of the jaw is expected with longer-term use of denosumab; long-term denosumab treatment therefore requires strict patient monitoring and early treatment of osteonecrosis of the jaw according to guidelines.[29] The use of denosumab in patients with GCTB shows good safety and long-term disease control for patients with both unresectable and resectable tumours. Although the risks of long-term therapy, including osteonecrosis of the jaw and atypical femur fracture, need to be considered, the overall risk to benefit ratio of denosumab treatment in patients with GCTB remains highly favourable.

For more on **Amgen's data sharing policies** see https://wwwext.amgen.com/science/clinical-trials/clinical-data-transparency-practices/

Contributors

SC, J-YB, PR, ALC, PR, HG, RJG, EC, KS, SMS, RH, and EP conceived and designed the study and collected data. All authors analysed and interpreted the data and were involved in the development, review, and approval of the manuscript.

Declaration of interests

SC has received research grants from Amgen, Roche, Cytrx Corporation, Threshold Pharmaceuticals, GlaxoSmithKline, Ignyta, Immune Design, Tracon Pharma, Karyopharm Therapeutics, SARC, and Janssen. J-YB has received research grants and honoraria from Novartis and Amgen. PR has served on advisory boards for Novartis, Bristol-Myers Squibb, MSD, Amgen, Roche, and Blueprint Medicines; and has received honoraria for lectures from Pfizer, Novartis, Bristol-Myers Squibb, MSD, Amgen, Roche, and Blueprint Medicines. ALC has received personal fees from Novartis, Pfizer, Lilly, Eisai, and PharmaMar. PR has received personal fees from Novartis, Pfizer, Bayer, PharmaMar, Clinigen, Lilly, Deciphera, Merck, Roche, and Amgen. RJG has received grants and personal fees from Amgen for serving on the scientific advisory board for this trial. EC has received research grants and consulting fees from Amgen for this study; research grants from Novartis, AstraZeneca, Eisai, Daiichi, EMD Serono, Sanofi, and Janssen; and consulting fees from EMD Serono and Sanofi. KS has received research grants and consulting fees from Amgen for this study. SMS has received research grants from Amgen, Daiichi-Sankyo, and Janssen for this study; personal fees from Amgen, Daiichi-Sankyo, and Janssen; and research grants from Lilly, Karyopharm, Adaptimmune, and BluePrint Medicines. RH received research support from his institution, MedStar Health, for this study. TD and DJ are employed by and own stock in Amgen. EP has received fees from Amgen for this study; personal fees from Lilly and Daiichi Sankyo; non-financial support from Bristol-Myers Squibb, Pfizer, and Daiichi Sankyo; and travel support from Pharmamar and Takeda. All other authors declare no competing interests.

Data sharing

There is a plan to share data. This might include de-identified individual patient data for variables necessary to address the specific research question in an approved data sharing request; also related data dictionaries, study protocol, statistical analysis plan, informed consent form, or clinical study report. Data sharing requests relating to data in this manuscript will be considered after the publication date and after this product and indication (or other new use) have been granted marketing authorisation in both the USA and Europe, or after clinical development discontinues and the data will not be submitted to regulatory authorities. There is no end date for eligibility to submit a data sharing request for these data. Qualified researchers can submit a request containing the research objectives, the Amgen product(s) and Amgen study or studies in scope, endpoints or outcomes of interest, statistical analysis plan, data requirements, publication plan, and qualifications of the researcher(s). In general, Amgen does not grant external requests for individual patient data for the purpose of re-evaluating safety and efficacy issues already addressed in the product labelling. A committee of internal advisors reviews requests. If not approved, requests can be further arbitrated by a Data Sharing Independent Review Panel. Requests that pose a potential conflict of interest or an actual or potential competitive risk might be declined at Amgen's sole discretion and without further arbitration. Upon approval, information necessary to address the research question will be provided under the terms of a data sharing agreement. This can include anonymised individual patient data or available supporting documents, containing fragments of analysis code where provided in analysis specifications. Further details are available online.

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