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The Oncologist, 2023, **28**, 1005–e1104
https://doi.org/10.1093/oncolo/oyad196
Advance access publication 14 July 2023
Clinical Trial Results

Denosumab in Giant Cell Rich Tumors of Bone: An Open-Label Multicenter Phase II Study

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Abstract

Background: Since giant cell tumors of bone (GCTB) and other giant cell rich tumors of bone (GCRTB) share the histological presence of osteoclastic giant cells and expression of RANK/RANKL, we hypothesized that GCRTB will respond similarly to denosumab as GCTB. The primary objective of this study was to determine the efficacy of denosumab in patients with GCRTB that have recurred or require morbid surgery.

Methods: In this open-label, multicenter, phase II trial, patients with GCRTB were included (June 2018-March 2020). Recruitment was stopped because of low accrual. Patients received denosumab (120 mg) subcutaneously (SC) on day 1 of every 4-week cycle with a loading dose of 120 mg SC on days 8 and 15.

Results: Three patients were enrolled. One withdrew consent before start of study. The remaining patients had central giant cell granuloma of the jawbone (CGCG). Median treatment duration was 15 cycles (range 12-18). In both subjects, improvement in ossification of lesions was seen. Median follow-up was 28.5 months (range 20-37). One patient developed a recurrence for which surgery was performed.

Conclusion: Due to critical emerging real-world data of denosumab in GCRTBs, the study was prematurely stopped and not supportive of use of denosumab for this indication. (ClinicalTrials.gov Identifier: NCT03605199).

Key words: giant cell rich tumor of bone; denosumab; aneurysmal bone cyst; giant cell granuloma; systemic therapy.

Lessons Learned

- Given the high activity of denosumab in giant cell tumors of bone (GCTB), this trial aimed to explore the activity in other giant cell rich tumors of bone (GCRTB).
- As the use of denosumab in GCTB declined and due to critical emerging real-world data of denosumab in GCRTBs, the study was prematurely stopped and not supportive of use of denosumab for this indication.

Discussion

This open-label, multicenter, single arm, phase II study aimed to investigate the safety and efficacy of denosumab in giant cell rich tumors of bone (GCRTB), including aneurysmal bone cysts (ABC) and giant cell granuloma (GCG).

Three subjects were enrolled; one withdrew consent and the remaining 2 subjects started and completed the trial (Table 1). Both subjects had central giant cell granuloma of the jaw (CGCG) that would otherwise require morbid surgery, which is the current treatment standard. Median treatment duration on trial was 15 months; further continuation of trial treatment was not expected to provide more clinical benefit, as lesions showed no further increase in ossification (Fig. 1). Median follow-up after discontinuation of denosumab on trial was 28.5 months (range 20-37). After 7 months follow-up, a recurrence was seen in subject 2 for which a resection was performed and maintenance dose of adjuvant denosumab was started off-study (120 mg every 3 months, after 3 months reduced to 60 mg every 3 months). Subject 1 was started on a maintenance dose of 60 mg every 3 months directly following trial treatment, and no recurrence was seen at last follow-up. No serious adverse events or adverse events of interest (atypical femoral fracture, osteonecrosis of the jaw, malignancy) were reported during the study.

Two phase II trials on denosumab for GCTB reported stable disease in the majority of patients, high pathological response rates and less morbid or no surgery was needed after RANKL inhibition.[1,2] Several initial case reports and series

Received: 26 February 2023; Accepted: 14 June 2023.

Table 1. Patient, tumor, and treatment characteristics.

	Salvageable cohort
Subjects, *n*	2
Females, *n*	2
Age, years (median, range)	40.5 (40-41)
Disease type, *n*	
ABC	0
CGCG	2
ECOG performance status, *n*	0: 1
	1: 1
Duration of treatment, cycles (median, range)	15 (12-18)
Reason stop treatment, *n*	
Decision study doctor	2
Best response, *n*	
Clinical benefit/stable pain score	1
Radiological response	
RECIST response	0
Increased ossification	2
Underwent surgery, *n*	0
Follow-up duration, months (median, range)	28.5 (20-37)
Recurrences, *n*	1
Surgery performed	1
Adverse events, *n* (% of total pts)	
Hypophosphatemia, grades 1-2	1 (50%)
Nausea, grades 1-2	1 (50%)
Arthralgia, grades 1-2	1 (50%)

Abbreviations: ABC: aneurysmal bone cyst; CGCG: central giant cell granuloma of the jaw; ECOG: European Cooperative Oncology Group; RECIST: response evaluation in solid tumors.

supported the use of denosumab in ABC and CGCG with comparable results. However, more recent literature suggests higher recurrence rates after cessation of denosumab treatment, due to latency of the neoplastic cell population and/or suboptimal intralesional curettage in the intensely ossified bone.[3-7]

The study closed prematurely, and we are not able to draw any conclusions on the efficacy or safety of denosumab in GCRTB based on the available data. The accrual of patients was slow due to the rarity of the studied diseases, and meanwhile critical emerging real-world data of denosumab in GCRTBs emerged that do not support the of use of denosumab as described in our study protocol.

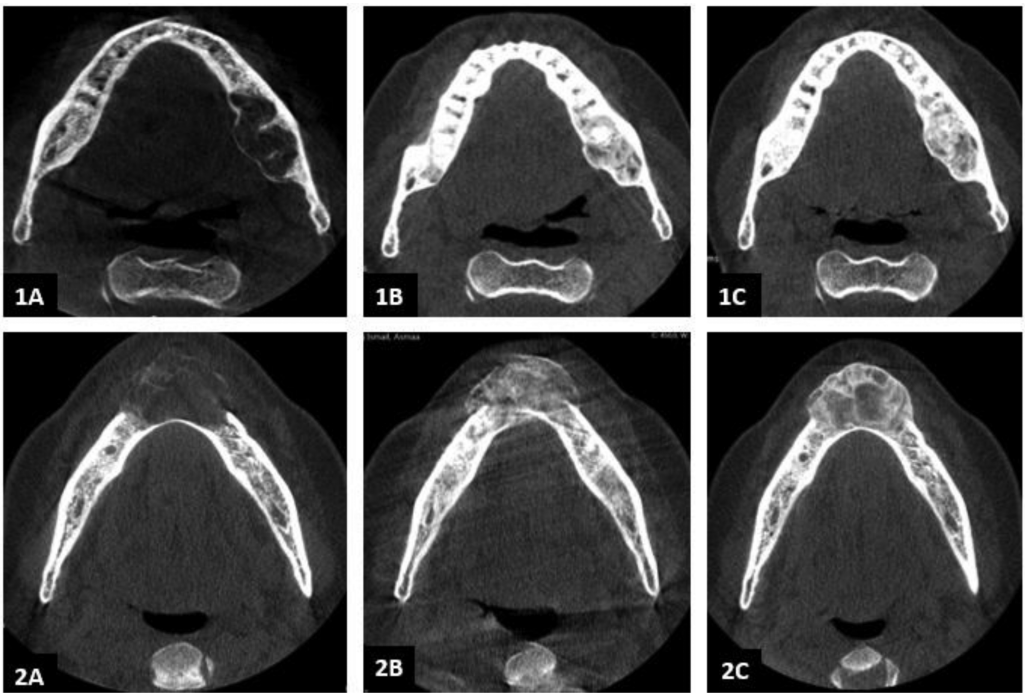

Figure 1. CT images of patient 1. (**1A**) patient 1 baseline CT; central giant cell granuloma (CGCG) body of the left mandible, (**1B**) patient 1 after 3 cycles; cortical thickening and central ossification, (**1C**) patient 1 after 10 cycles; increased ossification 80%. (**2A**) patient 2 baseline CT; CGCG of the anterior mandible, (**2B**) patient 2 after 3 cycles; cortical thickening and central ossification of the affected mandible, (**2C**) patient 2 after 6 cycles; further increase of ossification.

Trial Information	
Disease	Giant cell rich tumors of bone (other than giant cell tumors of bone (GCTB))
Stage of disease/treatment	Recurrent, advanced
Prior therapy	None or surgery
Type of study	Phase II, single arm
Primary endpoint	• Salvageable disease: avoidance of surgery, performance of less morbid surgery compared to planned surgical procedure at baseline. • Unsalvageable disease: disease control (combined endpoint: radiological response, no progression after one year and stable pain score).
Secondary endpoints	Safety, recurrences after surgery, symptomatic improvement, time to surgery, time to recurrence after surgery, progression-free survival
Investigator's analysis	Active but results overtaken by other developments

Additional Details of Endpoints or Study Design

In this open-label, multicenter, phase II trial subjects with giant cell rich tumors of bone (GCRTB) that would require morbid surgery or with GCRTB that have recurred after previous surgery were treated with denosumab.

We intended to include patients with GCRTB including aneurysmal bone cysts (ABC), giant cell granulomas (GCG) and other nonmalignant giant cell rich lesions of bone. Patients were to be divided into 2 cohorts: salvageable and unsalvageable GCRTB.

The primary objectives of the study were to evaluate avoidance of surgery and performance of less morbid surgical procedure compared with the planned surgical procedure at baseline in subjects with salvageable GCRTB during the study. For subjects with unsalvageable tumors, the objective was to evaluate disease control: radiological response assessed by combined RECIST, PET, inverse Choi when available and/or no progression (based on clinical disease assessment) at one year in combination with stable pain score defined as ≤1 point increase on "worst pain" question in Brief Pain Inventory-Short Form (BPI-SF). For subjects that were to undergo surgical tumor resection, denosumab treatment would be discontinued after surgery. In all other cases, denosumab treatment would be continued for a maximum of up to 3 years as long as ongoing clinical benefit was derived from treatment; treatment would be stopped at confirmation of disease progression.

Target number of patients was not reached due to premature closure of the trial due to slow accrual and emerging real-world data (RWD).

Drug Information	
Generic/working name	Denosumab
Company name	Amgen
Drug type	Monoclonal antibody
Drug class	RANK ligand inhibitors
Dose	120
Unit	Milligrams (mg)
Route	Subcutaneous (sc)
Schedule of administration	On day 1 of every 4-week cycle with a loading dose of 120 mg SC on days 8 and 15 of the first cycle. All subjects received daily supplements of 500 mg calcium and 400 IU of vitamin D, except in case of preexisting hypercalcemia.

Patient Characteristics: Unsalvageable Cohort*	
Number of patients, male	0
Number of patients, female	2
Stage	Advanced
Age, years, median (range)	40.5 (40-41)
Number of prior systemic therapies	0
Performance status: ECOG	0: 1 1: 1 2: 0 3: 0 4: 0
Cancer types or histologic subtypes	Giant cell granuloma of the jaw,2

*Complete baseline demographic and disease characteristics are presented in Tables 1 and 2.

Primary Assessment Method	
Title	Disease control (combined endpoint: radiological response, no progression after one year and stable pain score).
Number of patients screened	3
Number of patients enrolled	3

Primary Assessment Method

Number of patients evaluable for toxicity	2
Number of patients evaluated for efficacy	2
Evaluation method	Disease control evaluated by imaging and pain score on BPI-SF
Outcome notes	Response assessment imaging: see Tables 1 and 2 for patient, tumor, and treatment characteristics and Fig. 1 for CT images. Response assessment pain score: not performed, insufficient data available.

Adverse Events

Adverse events, CTCAE v5.0	Grades 1-2 *n* (% of total pts)	Grade ≥ 3 *n* (% of total pts)	All grades *n* (% of total pts)
Hypoophosphatemia	1 (50%)	—	1 (50%)
Nausea	1 (50%)	—	1 (50%)
Arthralgia	1 (50%)	—	1 (50%)

Assessment, Analysis, and Discussion

Completion	Study terminated prior to completion
Investigator's assessment	Active but results overtaken by other developments

Giant cell rich tumors of bone (GCRTB) other than giant cell tumor of the bone (GCTB) are a distinct group of rare benign bone and cartilage tumors composed of aneurysmal bone cyst (ABC), giant cell granuloma (GCG), osteoblastoma, chondroblastoma, and chondromyxoid fibroma among others.[8-11] Although these tumors are heterogenic in epidemiology and presentation, all harbor osteoclastic giant cells as important histopathologic feature. Surgery is the standard treatment approach in these tumors when they cause unacceptable morbidity.[12]

Denosumab is a fully human monoclonal IgG2 antibody that binds with high affinity and specificity to the soluble and cell membrane-bound forms of human RANKL. Denosumab binding prevents the activation of RANK and inhibits the formation, activation, and survival of osteoclasts. As a consequence, bone resorption and tumor-induced bone destruction are reduced.[13]

Since the histological presence of osteoclastic giant cells and expression of RANK/RANKL is something GCTB and all other GCRTB have in common, we hypothesized that GCRTB will show the same response to denosumab as previously seen in classical GCTB. This study aimed to investigate the effect of denosumab in subjects diagnosed with GCRTB that would require morbid surgery or is recurrent after prior surgery. The primary objectives of this study were to evaluate avoidance of surgery and performance of less morbid surgery than originally planned in the subject group with salvageable disease. For subjects with unsalvageable tumors, the objective was to evaluate disease control (combined endpoint: radiological response assessed by combined RECIST,[14] PET,[15] inverse Choi[16] when available and/or no clinical progression at 1 year in combination with stable pain score defined as ≤1 point increase on "worst pain" question in Brief Pain Inventory Short Form (BPI-SF) pain score).[17]

During recruitment, all cases centrally reviewed at the Dutch Committee for Bone Tumours were screened for inclusion. Only 3 subjects were enrolled; one withdrew consent and the remaining 2 subjects started and completed the trial. Both subjects had CGCG of the jaw that would otherwise require morbid surgery. Median treatment duration on trial was 15 months; for both subjects, continuation of trial treatment was not expected to provide any more clinical benefit as lesions showed no further increase in ossification (Fig. 1). There was insufficient data collected to assess a change in pain score. Median follow-up after discontinuation of denosumab on trial was 28.5 months (range 20-37). After 7 months follow-up, a recurrence was seen in subject 2 for which a resection was performed, and maintenance dose of adjuvant denosumab was started off-study (120 mg every 3 months, after 3 months reduced to 60 mg every 3 months). Subject 1 was started on a maintenance dose of 60 mg every 3 months directly following trial treatment, and no recurrence was seen at last follow-up. No serious adverse events or adverse events of interest (atypical femoral fracture, osteonecrosis of the jaw, malignancy) were reported during the study.

We also report 2 additional eligible patients who received a similar regime of denosumab for CGCG before the study was open for recruitment, both of whom have given consent to publish their anonymous data (Table 3). The first patient (patient 3), a 56-year old male, was treated with denosumab during 8 months. Imaging showed increased ossification of the lesion while on-treatment (Fig. 2). Eleven months after discontinuation of denosumab a recurrence was observed within the ossified mass after which denosumab was reintroduced with a good response seen after 3 months. A maintenance dose of denosumab was started of 60 mg every 6 months, and no recurrence was seen during follow-up of 3 years.

The second patient treated off-study (patient 4), a 42-year old female, was diagnosed with a CGCG of the right hemimaxilla in 2014 and started denosumab treatment. Six months later imaging demonstrated a volume reduction, and she discontinued treatment after 1 year. In 2019, she reported pain, and a recurrence was seen on imaging (Fig. 3). Reinitiation of monthly denosumab stabilized the lesion, and however radiologically, no increased ossification was seen. After 1 year of monthly denosumab, the patient remains on maintenance treatment with 3-monthly injections. Unfortunately, she developed bilateral atypical femoral fractures as side effect of long-term denosumab use, for

which a prophylactic intramedullary nail stabilization was performed and maintenance dose of denosumab tapered to 60 mg every 6 months.

Two phase II trials on denosumab for GCTB reported stable disease in the majority of patients, high pathological response rates and less morbid or no surgery was needed after RANKL inhibition.[1,2] Several initial case reports and series supported the use of denosumab in ABC and CGCG with comparable results.[9,18-29] However, more recent literature suggests higher recurrence rates after cessation of denosumab treatment, due to latency of the neoplastic cell population and/or suboptimal intralesional curettage in the intensely ossified bone.[3-7] A recent case series in CGCG reports high-response rates after one year of definitive treatment with denosumab, but a progression-free survival rate of only 22.6% at 5 years moreover demonstrating that response is not durable once off-treatment.[30]

Furthermore, the optimal treatment duration in the neoadjuvant setting as well as in the setting of definitive treatment is unsure. Longer treatment with denosumab is associated with dose-dependent osteonecrosis of the jaw and atypical femoral fractures.[31,32] Transformation of GCTB to malignant bone tumors like osteosarcoma has been reported, linked to prior radiation therapy, sampling errors, initial misdiagnosis but also after the use of denosumab.[33-37] A possible explanation could be immunosuppression leading to malignant transformation due to RANKL inhibition increasing susceptibility to oncogenes and negative effects on T- and B-cell differentiation and dendritic cell survival.[35] There is currently an ongoing search for the optimal indications, dosing, and treatment duration to overcome these aforementioned significant limitations.[38]

The study closed prematurely and we are not able to draw any conclusions on the efficacy or safety of denosumab in GCRTB based on the available data. The accrual of patients was slow due to rarity of the studied diseases, and meanwhile critical emerging real-world data of denosumab in GCRTBs emerged that do not support the of use of denosumab as described in our study protocol.

Acknowledgments

This study was sponsored by Leiden University Medical Center. The Medical Ethics Committee Leiden The Hague Delft provided Institutional Review Board approval.

Funding

This work was supported by Amgen (ISS 20159990).

Conflict of Interest

The authors indicated no financial relationships.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Figures and Tables

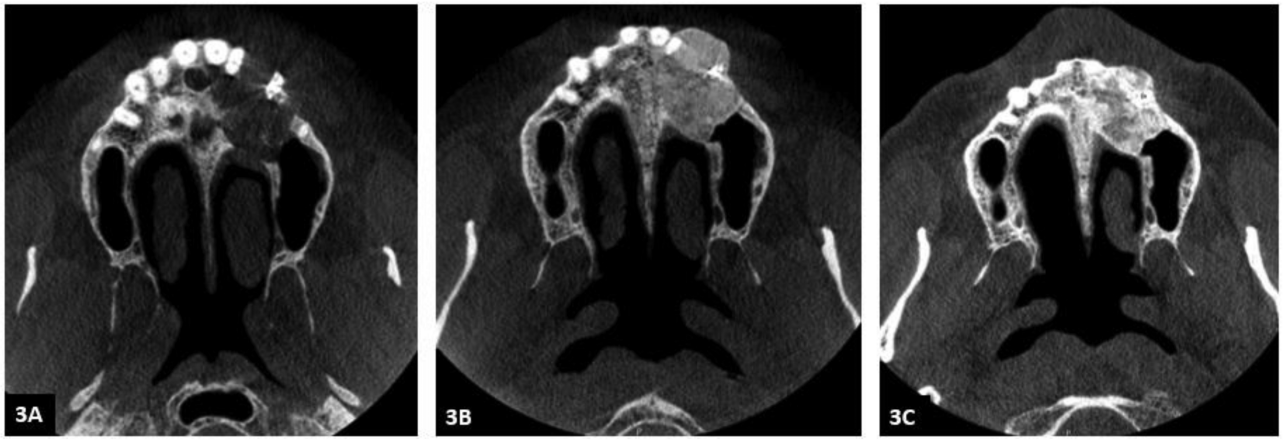

Figure 2. CT images patient 3 (treated outside of study). (**3A**) baseline CT; central giant cell granuloma (CGCG) left hemimaxilla, (**3B**) after 4 cycles; ossification of affected area, (**3C**) 11 months after discontinuation of denosumab with new developing central lucency in the ossified mass indicating a recurrence of the CGCG.

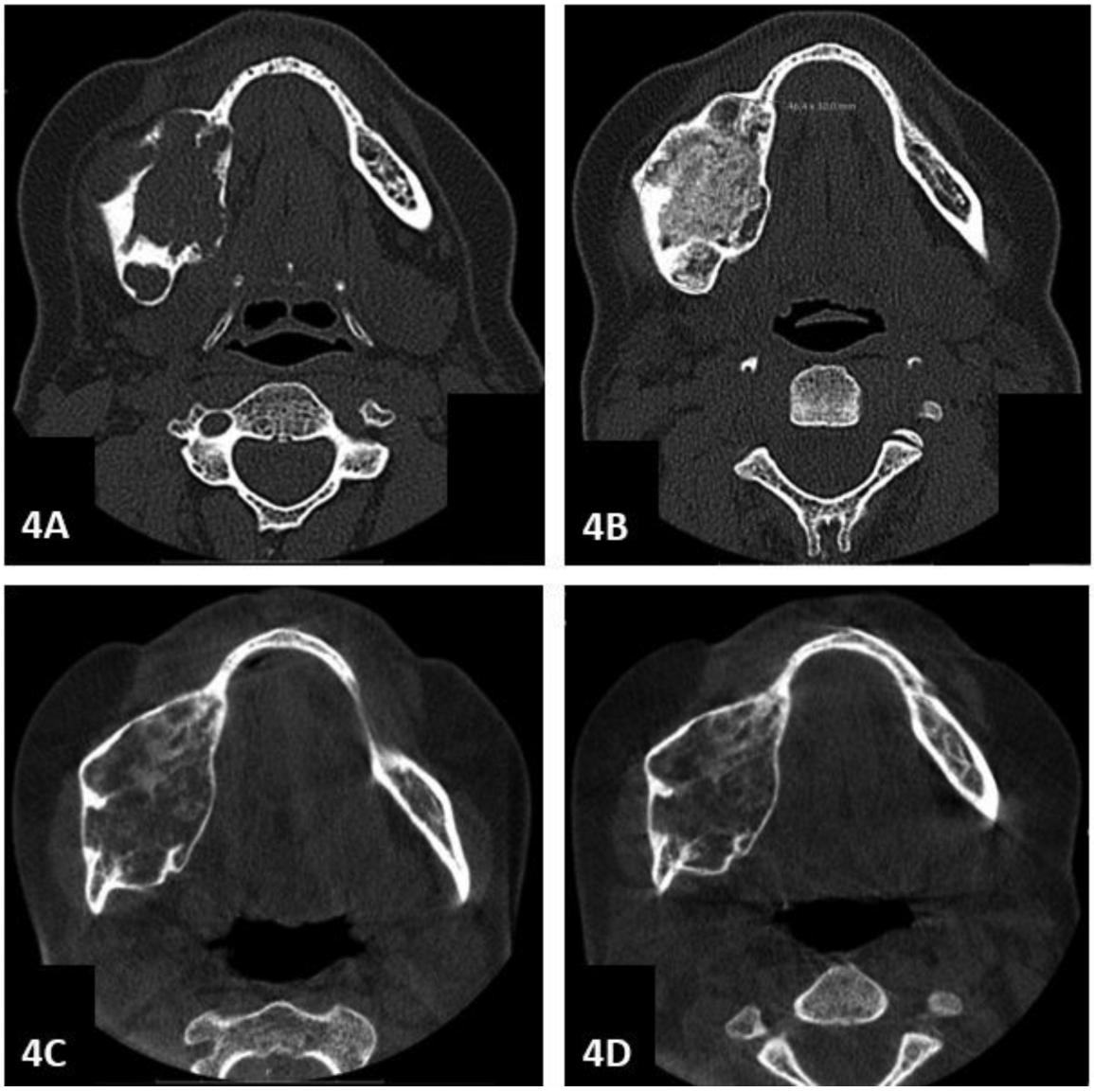

Figure 3. CT images patient 4 (treated outside of study). (**4A**) baseline CT; central giant cell granuloma (CGCG) body of the right mandible, (**4B**) after 6 cycles; ossification of the affected right hemimandible, (**4C**) 5 years after discontinuation of denosumab; decreased ossification and lytic process right mandible, indicating recurrence of CGCG, (**4D**) after one year of treatment, stable lesion, no increase in ossification.

Table 2. Patient, tumor, and treatment characteristics, including 2 real-world data patients.

Subjects, *n*	4
Females, *n*	3
Age, years (median, range)	41.5 (40-56)
Disease type, *n*	
-ABC	0
-CGCG	4
ECOG Performance status, *n*	0: 3
	1: 1
Duration of treatment, cycles (median, range)	12 (8-18)
Reason stop treatment, *n*	
-Decision treating physician	4
Best response, *n*	
-Clinical benefit/stable pain score	1
-Radiological response	
◦RECIST response	0
◦Increased ossification	4
Underwent surgery, *n*	0
Follow-up duration, months (median, range)	36.5 (20-96)
Recurrences, *n*	3
-Surgery performed	1
-Denosumab reintroduced	2
Adverse events, *n* (% of total pts)	
-Hypophosphatemia, grade 1-2	1 (25%)
-Nausea, grade 1-2	1 (25%)
-Arthralgia, grade 1-2	1 (25%)
-Atypical femur fracture	1 (25%)

Abbreviations: ABC: aneurysmal bone cyst; CGCG: = central giant cell granuloma of the jaw; ECOG: European Cooperative Oncology Group; RECIST: response evaluation in solid tumors.

Table 3. Adverse events.*

Adverse events	Grades 1-2 *n* (% of total pts)	Grade ≥ 3 *n* (% of total pts)	All grades *n* (% of total pts)
Hypophosphatemia	1 (50%)	—	1 (50%)
Nausea	1 (50%)	—	1 (50%)
Arthralgia	1 (50%)	—	1 (50%)

*Common Terminology Criteria of Adverse Events (CTCAE) version 5.0.