Title	Effectiveness, Efficacy, and Safety of XGEVA® (denosumab) in Chinese Patients With Giant Cell Tumor of Bone (GCTB): a Systematic Literature Review
Protocol version identifier	*V1.0*
Date of last version of the protocol	*22-August-2022*
Therapeutic Area	Oncology
Product Reference	XGEVA® (denosumab)
Research Objectives	
Author	PPD *CfOR* PPD *CfOR* PPD *, Global Development*

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
AFF	Atypical Femoral Fracture
BTA	Bone Targeting Agent
CDE	Center for Drug Evaluation
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCTB	Giant Cell Tumor of Bone
NMPA	National Medical Products Administration
PK	Pharmacokinetics
ONJ	Osteonecrosis of the Jaw

2. ABSTRACT

- Title

  Effectiveness, efficacy, and safety of XGEVA® (denosumab) in Chinese patients with Giant Cell Tumor of Bone (GCTB): a systematic literature review

- Background and rationale:

  Globally, clinical and real-world evidence suggests that XGEVA® is both safe and efficacious for the treatment of adults and skeletally mature (defined as at least 1 mature long bone and had a body weight ≥ 45 kg) adolescents with GCTB that is unresectable or where surgical resection is likely to result in severe morbidity. However, a current review of evidence is needed to better understand the benefit: risk of XGEVA® among Chinese GCTB patients. This gap will be informed by an assessment of clinical and real-world evidence (RWE) from publicly available literature, relevant to establishing an understanding of the safety and effectiveness of XGEVA® in Chinese patients with GCTB.

- Objective(s) and research questions:

  The aim of this systematic review is to evaluate published evidence on the safety and clinical effectiveness of XGEVA® among mainland Chinese and Chinese patients in Taiwan, Hong Kong, and Macau with GCTB, and to characterize the benefit-risk profile associated with use of this drug in these Chinese GCTB patients, in context of the global body of evidence derived from XGEVA® treated GCTB patients.

- Study eligibility

  Published studies of XGEVA® for treatment of GCTB among skeletally mature Chinese adolescents (ages ≥ 12 years) and adults in China (including mainland China, Taiwan, Hong Kong, and Macau), will be included as long as any outcome of interest is reported (disease progression, response rate, recurrence, surgical downgrading, limb or joint complications requiring surgery, any safety endpoints). No restrictions will be placed on study design (randomized, observational), and studies with or without non-denosumab comparison groups will be eligible for inclusion.

- Study identification

  Chinese and English language terms for GCTB and XGEVA® (denosumab) mapped to subject headings will be searched in Sinomed, CNKI, 万方, MEDLINE, Epub Ahead of Print and In-Process & Other Non-Indexed Citations, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, Web of Science, Google Scholar for identification of all published reports as well as congress abstracts, pre-prints, and any clinical trial results not yet formally published. Additional databases and publication platforms specific to Chinese studies will be searched as guided by our BeiGene-Amgen partners and collaborative efforts.

- Study selection

  A total of six reviewers, in pairs of two, will independently screen titles and abstracts, and select records for full-text review: two reviewers for publications in Simplified Chinese, two reviewers for publications in Traditional Chinese, and two reviewers for publications in English. Selected articles identified via the title/abstract screening process will be retrieved, translated into English if needed, and reviewed by one team (Amgen U.S. CfOR team) for study eligibility and inclusion according to PICOS criteria. Disagreements between reviewers during title/abstract screening will be resolved after full-text review by consensus discussion and consultation with an independent seventh reviewer with clinical expertise in GCTB, who will make the final decision. Data abstraction

  All relevant information, qualitative and quantitative, will be extracted using the Data Extraction and Quality Assessment Form developed for this study based upon existing validated tools. The information will be copied into two pre-formatted tables (Appendix E. and Appendix F.), including one describing the study sample and another detailing the study-specific information on population, treatment regimens evaluated, outcome rates and measures of association, safety events, covariates accounted for in the analysis, and the quality assessment score.

- Assessment of methodological quality

  The Downs and Black checklist for assessment of methodological quality of randomized and non-randomized studies will be used to assess bias. The 27-item checklist, which is based upon quality of reporting, external validity, internal validity (bias and confounding) and statistical power, has been imported into the Data Extraction and Quality Assessment Form for ease of use with the included studies during the review process.

- Data synthesis (descriptive only)

  A qualitative synthesis of results will be performed, and a narrative summary provided in the text of the final report including a discussion of main findings in the context of the broader body of evidence on the safety and effectiveness of XGEVA® (denosumab) for GCTB among the global population.

3. AMENDMENTS AND UPDATES

None

4. BACKGROUND AND RATIONALE

4.1 Disease or Therapeutic Area

Giant cell tumor of bone (GCTB) is a rare, aggressive, histologically benign primary bone tumor that presents as an eccentric osteolytic lesion in the metaphyseal and epiphyseal portions of long bones or in the spine or sacrum. GCTB is the third most commonly encountered benign bone neoplasm, and accounts for significant disability and dysfunction. This disease typically occurs in young adults in the second or third decade of life. GCTB is also reported very rarely in the pediatric population, usually in skeletally mature adolescents (ie, after the epiphyseal plates have closed).

According to a 2015 study performed comparing Epidemiologic data between patients treated at Chinese Beijing Ji Shui Tan Hospital (JST) database and patients treated at the Mayo Clinic in Rochester Minnesota, in JST the most common histologic type of bone tumor was conventional osteosarcoma, accounting for 22.8% of all bone tumors (2097 of 9200), followed by GCTB (16.7%; 1536 of 9200) [1]. At the time of diagnosis of primary benign bone tumors, 63.0% of the Chinese JST patients were younger than 30 years. Overall, a higher incidence of GCTB was reported in the Chinese population which accounts for 30.7% of benign bone tumors and 16.7% of all bone tumors. A higher Male predominance has been reported in China [1,2].

GCTB is characterized by rapid growth, severe destruction of bone, and extension into the surrounding soft tissues. When left untreated, GCTB progresses resulting in complete destruction of the affected bone and massive tumor formation, which may lead to gross physical deformity, severe pain, loss of mobility and function, and potential loss of limb. Thus, the objectives of treatment are removal of the tumor to relieve symptoms, preservation of the adjacent joint and surrounding anatomic structures, and restoration of function to the affected extremity or spine.

GCTB typically occurs near the end of the long bones, the most commonly occurs in the long bones around the knee, wrist and shoulder [3]. GCTB affects young adults with peak incidence in the third decade of life (median age 20 to 40 years), and usually appears as a lytic geographic lesion with a non-sclerotic, yet well-defined margin that often extends to the subchondral bone. GCTB may be pathologically staged as a localized tumor (confined to bone), regional tumor (penetrating cortical bone which can result in displacement of the adjacent skeletal muscle), or metastatic tumor (either extra compartmental extension or metastasis). Patients with GCTB often present with pain

and mechanical difficulty resulting from bone destruction, limitation of joint motion, and have an increased risk for pathologic fracture.

In some cases, primary benign GCTB can metastasize to the lung (< 5%), and metastatic GCTB lung lesions may preserve benign histologic features or assume the character of a primary sarcoma: osteosarcoma, fibrosarcoma, malignant fibrous histiocytoma, or undifferentiated pleomorphic sarcoma. Although GCTB is classified as a benign lesion, the designation does not preclude aggressive clinical behavior with local recurrence rates ranging from in 10% to 75% of patients. If the tumor is located in the axial skeleton or the pelvis, surgery with curative intent may not be possible[4].

The diagnosis of GCTB requires a multidisciplinary and multi-modal approach with clinical and histopathologic evaluation combined with imaging studies (X-ray, magnetic resonance imaging [MRI], or computed tomography [CT] scans) in order to assess the integrity of the bony cortex, heterogeneity of tumor tissue content, extent of the lesion, and any extraosseous soft tissue invasion [5]. Although the vast majority of GCTB have benign histologic features, a small percentage present as a malignant GCTB with a more aggressive cytologic appearance. Because osteoclast-like giant cells can be present in many other conditions, including reactive conditions and other benign and malignant tumors, evaluation should be performed by a pathologist experienced in this field to exclude other diagnoses such as giant cell-rich osteosarcoma, brown tumor of hyperparathyroidism, etc. Staging requires chest imaging with either a non-contrast chest CT or x-ray.

Surgical therapy remains the mainstay of treatment for GCTB but has been associated with high rates of local tumor recurrence and significant complications. Giant cell tumors (GCTs) of bone often are treated with curettage, adjuvant therapy, and cementation [6]. The therapy of choice is extended intralesional curettage, augmented with high-speed burring of the tumor cavity, in order to maintain anatomic integrity of the involved bone and especially the articular surface, even in the setting of a pathologic fracture. En bloc resection of the involved bone typically lowers the risk of local recurrence but often necessitates prosthetic joint reconstruction which can be problematic in young adults especially with long-term follow-up. Adjuvant treatment is defined as a therapy applied after initial definitive surgical treatment for GCTB to prevent the recurrence of the disease and has been advocated in an attempt to reduce the rate of local recurrence, which can be as high as 50%. A wide variety of adjuvant options are commonly used, including preoperative embolization, water, hydrogen peroxide, phenol, cryotherapy,

argon beam coagulation, and bone cement; however, the efficacy of most remains unproven [7]. Metastatic disease does not usually respond well to chemotherapy and may cause death, although in many cases repeated surgical excision may be beneficial.

GCTB are dependent upon RANK ligand (RANK ligand [RANKL]) for growth. The RANKL pathway plays a key role in the pathogenesis of GCT. The GCTB lesion is characterized by multinucleated osteoclast-like giant cells and their precursors that express RANK and mononuclear stromal cells that produce and express RANKL [8]. RANKL-expressing stromal cells serve as the neoplastic component of the GCTB lesion and are hypothesized to recruit the cells that fuse to form the multinucleated osteoclast-like giant cells, which are responsible for the aggressive osteolytic activity of the tumor [5].

XGEVA® inhibits RANKL and was approved in June 2013 by the US FDA, in September 2014 by the EMA, and in May 2019 in China by the CDE-NMPA, as the first treatment for use in adults and skeletally mature adolescents with GCTB that are unresectable or where surgical resection is likely to result in severe morbidity.

XGEVA® also reduced the relative content of proliferative, densely cellular tumor stromal cells, replacing them with nonproliferative, differentiated, densely woven new bone[9]. XGEVA® can be a help to the oncologic surgeon by reconstituting a peripheral rim and switching the stage from aggressive to active or latent disease, but as tumor cells remain in the new-formed bone, the surgical technique of curettage has to be changed from gentle to more aggressive to avoid higher local recurrence rates,[10] and for patients with resectable GCTB, neoadjuvant XGEVA® therapy resulted in beneficial surgical downstaging, including either no surgery or a less morbid surgical procedure [11]. Neoadjuvant treatment is a treatment given before the surgical treatment to shrink a tumor before the main treatment and make the surgical therapy less aggressive and easier.

A multi-center study in Europe in 2013 reported 41% complete or partial response, and 58% stable disease after 7–20 doses of XGEVA® in the group that could not be resected surgically, and 58% complete or partial response and 41% stable disease was achieved in group that was planned to undergo surgery [9]. Interim results from a phase 2 study published in 2014 explored the effects of XGEVA® on pain and analgesic use in GCTB. It proved that most patients treated XGEVA® experienced clinically relevant decreases in pain within 2 months[12]. A study conducted in Canada published in 2016

showed the efficacy of XGEVA® in joint preservation for patients with GCTB[13]. In this study, all 20 patients experienced pain relief in the first month of treatment. All patients demonstrated a positive radiographic response with improved subchondral and cortical bone which allowed intralesional tumor resection and preservation of the joint and articular surface in 18 cases. Histological examination following XGEVA® revealed rarely detectable osteoclast-like giant cells. There was an obvious increase in osteoid matrix and woven bone which showed rare RANK staining amongst the mononuclear cells and only focal RANKL positivity. At median 30 months follow-up after resection, local tumor recurrence occurred in three patients. It proved that XGEVA® provides favorable and consistent clinical, radiographic, and pathologic responses which facilitates less aggressive surgical treatment, especially joint preservation. However, the local recurrence rate for GCTB following resection does not seem to be affected by XGEVA® and remains a concern[13]. A multicenter phase 2 trial in Japan demonstrated that XGEVA® has robust clinical efficacy in the treatment of GCTB[14]. The proportion of patients with an objective tumor response was 88% based on best response using any tumor response criteria. The proportion of patients with an objective tumor response using individual response criteria was 35% based on the modified RECIST criteria, 82% based on the modified EORTC criteria, and 71% based on inverse Choi criteria. The median time of study treatment was 13.1 months. XGEVA® was generally well tolerated in Japanese patients with GCTB. The safety profile of XGEVA® was consistent with that previously observed XGEVA® at this dose level[14].

The most frequently encountered adverse reactions (≥ 10%) were arthralgia, headache, nausea, back pain, fatigue, and pain in extremity. The most common serious adverse reactions were Osteonecrosis of the Jaw (ONJ) and osteomyelitis. The most common adverse reactions resulting in discontinuation of XGEVA® were ONJ, and tooth abscess or tooth infection. Safety and efficacy of XGEVA® for adults and skeletally mature adolescents with GCTB were predicted by the interim analysis of an open-label, parallel-group, phase 2 study published in 2013, which proved that of the 281 patients analyzable for safety, three (1%) had ONJ and 15 (5%) hypocalcemia. The most common grade 3-4 adverse events were hypophosphatemia, which occurred in nine (3%) patients, and anemia, back pain, and pain in extremities, each of which occurred in three patients (1%). Serious adverse events were reported in 25 (9%) patients. No treatment-related deaths were reported. Adverse events were consistent with the known

safety profile of XGEVA®. XGEVA® was associated with tumor responses and reduced the need for morbid surgery in patients with GCTB. The adverse reaction profile appeared similar in skeletally mature adolescents and adults.

4.2 Scope for Analysis

XGEVA® (denosumab) a human monoclonal antibody that specifically binds to and inhibits RANKL, was approved in June 2013 by the US FDA, and in September 2014 by the European Medicines Agency (EMA), as the first treatment for use in adults and skeletally mature adolescents with GCTB that is unresectable or where surgical resection is likely to result in severe morbidity. XGEVA® was approved as the first treatment for GCTB in China by the National Medical Products Administration-Center for Drug Evaluation (NMPA-CDE) in May 2019.

The rationale for this systematic literature review is to present additional clinical and real-world evidence (RWE) from all publicly available sources of literature, relevant to understanding the safety and effectiveness of XGEVA® in Chinese patients with GCTB, and to characterize the benefit: risk profile of XGEVA® in Chinese GCTB patients (mainland China, Taiwan, Hong Kong, and Macau), in the context of the GCTB global body of evidence, including East-Asian GCTB patients.

This systematic literature review will include randomized clinical trials (RCTs), case reports, observational studies published in peer reviewed journals, as well as RCTs and observational studies published as abstracts and/or posters at conferences and/or congresses.

5. OBJECTIVES

The objective of this systematic review is to evaluate published evidence on the safety and clinical effectiveness of XGEVA® among mainland Chinese and Chinese patients in Taiwan, Hong Kong, and Macau with GCTB, and to characterize the benefit-risk profile associated with use of this drug in these Chinese GCTB patients, in context of the global body of evidence of XGEVA® treated GCTB patients.

6. RESEARCH QUESTIONS

Based on a Systematic Literature Review of available evidence, is the use of XGEVA® in GCTB Chinese patients safe and effective?

7. METHODS FOR DATA COLLECTION

This systematic literature review will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and checklist to report search

methods and results[15]. Covidence software will be used to store and manage records and document all steps of the review process[16].

7.1 Study Eligibility

Inclusion Criteria: Literature that describes GCTB characteristics, use of XGEVA® , safety and effectiveness of XGEVA® in Chinese patients (mainland China, Taiwan, Hong Kong, Macau). Published RCTs (Single Arm; Phase I – IV), observational RWE studies, case reports, and SLRs and/or Meta-Analyses, published in Chinese (Simplified or Chinese) or English, where skeletally mature Chinese adolescents (ages ≥ 12 years) and/or adult Chinese patients are treated with XGEVA® for GCTB. Studies that address safety and effectiveness of XGEVA® in Chinese patients will be included.

Exclusion Criteria: Studies that are animal studies, or abstracts or publications superseded by more recent publications, and editorials or letter to editors.

PICOS Criteria:

P: Population:

- Skeletally mature Chinese adolescents (ages ≥ 12 years) or adult Chinese patients treated with XGEVA® (denosumab) for GCTB.
  - ☐ Salvageable
  - ☐ Unsalvageable

I: Intervention:

- XGEVA®

C: Comparator:

- N/A

O: Outcome:

- Disease (GCTB) progression [progression free survival; time to progression free survival; disease progression with new lung metastases]
- Recurrence (GCTB) [recurrence free survival; time to recurrence]
- Response Rate
- Limb or joint sparing surgical procedures (curettage)
- Surgical Downgrading
- Safety outcomes (Osteonecrosis of the Jaw [ONJ], Atypical Femoral Fracture [AFF], Hypocalcemia, Hypercalcemia)

S: Study Design:

- Studies will include RCTs (Single Arm; Phase I – IV), observational studies (retrospective; prospective; Case-Control), case reports, and systematic literature reviews (SLRs) and/or meta-analyses.

7.2 Study Identification

7.2.1 Identifying Citations (Literature Searches)

An initial search in English of PubMed (MEDLINE) will be conducted using the subject heading and text terms included in Appendix A. An additional search in the languages of Traditional Chinese and Simplified Chinese will be conducted using the search terms included in Appendix B, using Sinomed, CNKI, and 万方. Based on the initial search, retrieved articles will be reviewed for additional keywords and MESH terms. A subsequent electronic search will be conducted using the revised search strategy to ensure capture of all relevant publications. The final revised search strategy will be implemented in Sinomed, CNKI, and 万方, MEDLINE including Epub Ahead of Print and In-Process & Other Non-Indexed Citations, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and Cochrane Database of Systematic Reviews, Web of Science from Clarivate Analytics, and Google Scholar. The literature search will not be limited by publication date to ensure identification of all relevant studies up to the Current Date of SLR execution. This search strategy is designed to identify all formally published as well as "grey" literature from conference proceedings, such as abstracts and posters. In addition, reference lists of review articles will be manually searched.

7.3 Study Selection

Complete search results for each database will be exported to Endnote X9 and duplicate records removed. All unique records will then be exported to Covidence for screening eligibility based on PICOS criteria. Two reviewers for publications in Simplified Chinese, two reviewers for publications in Traditional Chinese, and two reviewers for publications in English, will independently screen titles and abstracts and select articles for full-text review. If any disagreement or uncertainty exists as to study eligibility based on the title and abstract, then the article will automatically move forward to full-text review. Full-text of selected articles based on title/abstract screening will be retrieved, and Chinese articles will be translated for full-text review in English. The Amgen U.S. CfOR team will perform full-text review of all selected articles for study eligibility and inclusion. Both reviewers will independently review and compare results, and any unresolved discrepancies will be adjudicated by a third reviewer with clinical expertise in GCTB.

Upon completion of the review process, inclusion or exclusion status of each record along with reason(s) for exclusion will be documented in Covidence in a data collection form adapted from the Cochrane Collaboration Data Collection Form and Downs and Black checklist for quality assessment [17] (Appendix C.). A consort diagram modeled after the PRISMA 2020 flow diagram template will be created to illustrate the search and selection process including number of records excluded at each step of screening and full-text review. (Appendix D.)

7.4 Data Abstraction

Relevant qualitative and quantitative data from each study included will be extracted into the Data Extraction and Quality Assessment Form (Appendix C.) and summarized in preformatted tables. Table 1. (Appendix E.) will summarize the study sample with percentages and proportions; Table 2 (Appendix F.) will present the data from each individual study including reference number, first author, publication year, data source, study design, sample size, study population (region, median age, disease stage, sites, salvageable or unsalvageable), time period of study conduct, treatment regimens, outcome measures (progression-/recurrence-free survival, response rate, surgical downgrading, limb or joint-sparing procedures, adverse events, serious adverse events), measures of association, adjustment variables, stratification, sensitivity analyses, and other relevant information. Study quality will be assessed using the Downs and Black checklist for assessment of methodologic quality of randomized and non-randomized studies [17], which is a numerical scoring system based on 27 items across 5 domains:

Methodologic Domain	**No. of Items**
Quality of reporting	10
Internal validity – bias	7
Internal validity – confounding	6
External validity	3
Statistical power	1
Total	**27**

Each item receives a score of 1 or 0 to indicate whether the criterion is met (yes, no/unclear). (See Appendix C., Bias Assessment, for detailed description of each item.) Scores are summed across all items to arrive at an overall quality score; thus the highest possible score is 27. Studies scoring higher than the median among the sample will be considered “better quality” versus those with lower scores.

8. DATA SYNTHESIS

8.1 Narrative Summary (Qualitative Synthesis)

Characteristics of the final sample of studies reviewed will be tabulated as described in the preceding section (Appendices E. and F.). A qualitative synthesis of results will be performed, and a narrative summary provided in the text of the final report. Descriptive information on the study sample will be presented including the range of sample sizes across studies, data sources and populations represented, years of study, geographical area and/or country, range of median age, number (percentages) of male and female patients, and study design (eg, prospective cohort, retrospective chart review, case-control, etc.), and the number of studies with and without a non-XGEVA® treatment arm or cohort group. Quantitative effectiveness data reported across studies will be summarized as the range of each outcome measure reported, according to treatment group. For example, the range of progression-free survival observed across all studies will be presented separately for patients who received XGEVA® containing regimens and for those who did not receive XGEVA® . Measures of causality or association, including attributable risk, relative risk (ie, hazard rate ratios), or odds ratios, will be summarized as the range of magnitude of effect associated with XGEVA® as compared to the referents. Any outcomes reported as percentages will also be summarized including, but not limited to, disease progression, recurrence, response rates, surgical downgrading, joint-sparing surgical procedures, adverse events, treatment-related toxicities, and treatment discontinuation, according to XGEVA® and non-XGEVA® treatment groups as available. In addition, findings from subgroup analyses and sensitivity analyses conducted will be presented and summarized.

Results of this systematic review will be placed in the context of the broader body of published evidence on the safety and effectiveness of XGEVA® for GCTB among the global population as compared to Chinese (mainland China, Taiwan, Hong Kong, and Macau) patients. A detailed discussion of the strengths and limitations of both the systematic review process, as well as the study sample, will provided.

9. STUDY LIMITATIONS

This systematic review is designed to gather data specific to GCTB patients in mainland China, Taiwan, Hong Kong, and Macau. Although the search strategy is intended to capture all published reports of studies of XGEVA® and GCTB among Chinese patients, there is no guarantee of complete capture of all studies conducted among the Chinese population.

10. ETHICAL AND REGULATORY CONSIDERATIONS

10.1 Adverse Events

No unpublished literature sources are being used with the aim of identifying and extracting patient-level data. The grey literature searches will be done to supplement the main database searches with respect to the targeted literature review objectives and the searches will be of publicly available material online. Reporting of individual adverse events (AE), product complaints (PCs) and other safety findings is not applicable for systematic literature reviews which involve published literature sources, as the safety data from the studies identified will have been previously reported to regulatory agencies, institutional review boards, and ethics committees in accordance with local regulations and routine pharmacovigilance practices.

10.2 Data Management and Quality Control Procedures

All steps outlined in section 7 for data collection will be utilizing templates outlined in the Appendix. All these completed forms will be kept with all other study documents, and all study inputs and outputs will be cross checked by the two study authors. Any discordant data will be evaluated by a third individual.

10.3 Subject Confidentiality

This study will comply with all applicable laws regarding subject privacy. No direct subject contact or collection of additional subject data will occur. Study results will be in tabular form and aggregate analyses that omits subject identification. Any publications and reports will not include subject identifiers.

11. ADMINISTRATIVE AND LEGAL OBLIGATIONS

11.1 Study Amendments and Study Termination

Amendments must be made only with the prior approval of BeiGene-Amgen. BeiGene-Amgen reserves the right to terminate participation in the study according to the study contract.

11.2 Study Documentation and Archive

Retention of study documents will be governed by the contractual agreement with the vendor and will be maintained pursuant to Amgen’s records retention schedule.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1 Publication Plan

This study will result in a peer reviewed publication.

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3, and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group alone does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review.

13. REFERENCES

1. Niu X, Xu H, Inwards CY, et al. Primary bone tumors: epidemiologic comparison of 9200 patients treated at Beijing Ji Shui Tan hospital, Beijing, China, with 10 165 patients at Mayo Clinic, Rochester, Minnesota. 2015;139(9):1149-1155.
2. Niu X, Zhang Q, Hao L, et al. Giant cell tumor of the extremity: retrospective analysis of 621 Chinese patients from one institution. 2012;94(5):461-467.
3. Sobti A, Agrawal P, Agarwala S, Agarwal MJAoB, Surgery J. Giant cell tumor of bone-an overview. 2016;4(1):2.
4. Chakravarti A, Spiro IJ, Hug EB, Mankin HJ, Efird JT, Suit HDJJ. Megavoltage radiation therapy for axial and inoperable giant-cell tumor of bone. 1999;81(11):1566-1573.
5. Lau CP, Huang L, Wong KC, Kumta SMJCtr. Comparison of the anti-tumor effects of denosumab and zoledronic acid on the neoplastic stromal cells of giant cell tumor of bone. 2013;54(6):439-449.
6. Skubitz KMJCtoio. Giant cell tumor of bone: current treatment options. 2014;15(3):507-518.
7. Balke M, Ahrens H, Streitbuerger A, et al. Treatment options for recurrent giant cell tumors of bone. 2009;135(1):149-158.
8. Branstetter DG, Nelson SD, Manivel JC, et al. Denosumab induces tumor reduction and bone formation in patients with giant-cell tumor of bone. 2012;18(16):4415-4424.
9. Chawla S, Henshaw R, Seeger L, et al. Safety and efficacy of denosumab for adults and skeletally mature adolescents with giant cell tumour of bone: interim analysis of an open-label, parallel-group, phase 2 study. 2013;14(9):901-908.
10. van der Heijden L, Dijkstra PS, Blay J-Y, Gelderblom HJEJoC. Giant cell tumour of bone in the denosumab era. 2017;77:75-83.
11. Rutkowski P, Ferrari S, Grimer RJ, et al. Surgical downstaging in an open-label phase II trial of denosumab in patients with giant cell tumor of bone. 2015;22(9):2860-2868.
12. Martin-Broto J, Cleeland CS, Glare PA, et al. Effects of denosumab on pain and analgesic use in giant cell tumor of bone: interim results from a phase II study. 2014;53(9):1173-1179.
13. Traub F, Singh J, Dickson BC, et al. Efficacy of denosumab in joint preservation for patients with giant cell tumour of the bone. 2016;59:1-12.
14. Ueda T, Morioka H, Nishida Y, et al. Objective tumor response to denosumab in patients with giant cell tumor of bone: a multicenter phase II trial. 2015;26(10):2149-2154.
15. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. International Journal of Surgery. 2021;88:105906.

16. Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. In.

17. Downs SH, Black NJJoE, Health C. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. 1998;52(6):377-384.

14. APPENDICES

14.1 Appendix A. English Terms and Phrases to be Used for the Literature Search

GCTB

((“Giant cell tumor” OR GCT) AND bone)

Osteoclastoma

(Osteolytic AND neoplas*)

“myeloid sarcoma”

Denosumab

XGEVA®

(Rankl* AND inhibitor)

Filter: Human

14.2 Appendix B. Chinese Language Terms and Phrases to be Used for the Literature Search

Chinese equivalent:

GCTB

((“Giant cell tumor” OR GCT) AND bone)

Osteoclastoma

(Osteolytic AND neoplas*)

骨巨细胞瘤

“myeloid sarcoma”

髓样肉瘤 OR 粒细胞肉瘤

Denosumab

地舒单抗 OR 地诺单抗

XGEVA®

(Rankl* AND inhibitor)

安加维 OR RANKL 抑制剂

Filter: Human

人类

14.3 Appendix C. Data Extraction and Quality Assessment Form

This form is adapted from the CDPLPG data collection form for intervention reviews for RCTs and non-RCTs, downloaded from https://dplp.cochrane.org/data-extraction-forms to meet MECIR standards for collecting and reporting information about studies for review, and analyzing their results (see MECIR standards C43 to C55; R41 to R45), and the Downs and Black checklist for assessment of methodologic quality and reporting of randomized and non-randomized studies,

Notes on using this form:

- Be consistent in order and style used to describe the information for each report.
- Record any missing information as unclear or not described, to make it clear that the information was not found in the study report(s).
- Include any instructions and decision rules on the data collection form, or in an accompanying document. It is important to practice using the form and give training to any other authors using the form.

General Information

Date form completed *(dd/mm/yyyy)*	
Name/ID of person extracting data	
Reference citation No.	
First author and year	
Report ID of other reports of this study including errata or retractions	
Publication type *(eg, full report, abstract, letter)*	
Notes:	

Study Eligibility

Study Characteristics	Eligibility criteria *(Insert inclusion criteria for each characteristic as defined in the Protocol)*	Eligibility criteria met? Yes	No	Unclear	Location in text or source *(pg & ¶/fig/table/other)*
Type of study	Randomised Controlled Trial	☐	☐	☐	
	Quasi-randomised Controlled Trial	☐	☐	☐	
	Single Arm Interventional	☐	☐	☐	
	Other clinical study (specify)	☐	☐	☐	
	Phase IV	☐	☐	☐	
	Observational	☐	☐	☐	
	Prospective Cohort	☐	☐	☐	
	Retrospective case-control	☐	☐	☐	
	Case series	☐	☐	☐	
	Claims database	☐	☐	☐	
	Registry	☐	☐	☐	
	Literature review	☐	☐	☐	
	Other (specify)	☐	☐	☐	
Participants	Chinese	☐	☐	☐	
	Skeletally mature	☐	☐	☐	
Types of intervention	Denosumab pre-surgery (curettage)	☐	☐	☐	
	Denosumab pre- and post-surgery				
Types of comparison	Curettage with no denosumab	☐	☐	☐	
Types of outcome measures	Progression- or Progression with new lung metastases or recurrence- free survival (time to progression or recurrence)	☐	☐	☐	
	Limb or joint-sparing procedure	☐	☐	☐	
	Safety outcomes: any AE	☐	☐	☐	
	Safety outcome: Osteonecrosis of the Jaw	☐	☐	☐	
	Safety outcome: Atypical Femoral Fracture	☐	☐	☐	
	Safety outcome: Hypocalcemia	☐	☐	☐	
INCLUDE ☐		EXCLUDE ☐			
Reason for exclusion					
Notes:					

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

Summary Data of Included Studies and Bias Assessment

Summary Data

Study Design	
Region	
Institution *(N of centers involved)*	
Date range of study *(including month, year)*	
Study population	
N *(total and by intervention and subgroup)*	
Age *(median, IQR)*	
Sites of GCTB *(specify, %)*	
Disease stages % *(specify system used)*	
Treatment regimens *(dosing, duration, route of admin, etc.)*	
Effectiveness Outcomes	
Progression-free survival *(median, 95% CI; % progressed)*	
Recurrent-free survival *(median, 95% CI; % recurrence, diagnostic criteria cited)*	
Limb or joint-sparing procedure by treatment arm and/or subgroup *(rates, %)*	
Measures of association *(eg, OR, HR, and 95% CI, adjusted or unadjusted)*	
Safety Outcomes	
Total AE %	
SAE rate % *(criteria cited)*	
Osteonecrosis of the Jaw %	
Atypical Femoral Fracture %	
Hypocalcemia %	

Other safety events reported % *(specify)*	
Covariates *(specify confounding factors and effect modifiers included)*	
NOTES:	

Bias Assessment

Domain	**Descriptions as stated in report/paper**	**Location in text or source** *(pg & ¶, fig/table/other)*	Yes/No/Unclear		
			Yes	No	Unclear
Reporting					
Aim of study *(Objective/hypothesis clearly described?)*			☐	☐	☐
Main Outcomes *(Clearly described in Intro and Methods?)*			☐	☐	☐
Population Characteristics *(Inclusion / exclusion criteria clearly described?)*			☐	☐	☐
Interventions *(Treatment clearly described?)*			☐	☐	☐
Distribution of confounders given			☐	☐	☐
Main findings *(Simple outcome data with denominators and numerators)*			☐	☐	☐

Random variability estimates provided *(Appropriate based on distribution eg, median [IQR] or mean [SD])*			☐	☐	☐
Reporting of AEs			☐	☐	☐
Reporting on patients lost to follow-up *(with characteristics)*			☐	☐	☐
Probability appropriately reported *(eg, p=0.035, rather than p<0.05 except where p<0.001)*			☐	☐	☐
External Validity					
Invited subjects representative of target population *(Did study identify source population and describe how participants were selected?)*			☐	☐	☐
Consented subjects are representative of target population *(Distribution similar between target population and study participants?)*			☐	☐	☐
Were study staff, places, facilities representative of the treatment that the majority of patients received?			☐	☐	☐
Internal Validity-Bias					
Blinding of subjects to intervention			☐	☐	☐
Blinding of study investigators and personnel			☐	☐	☐

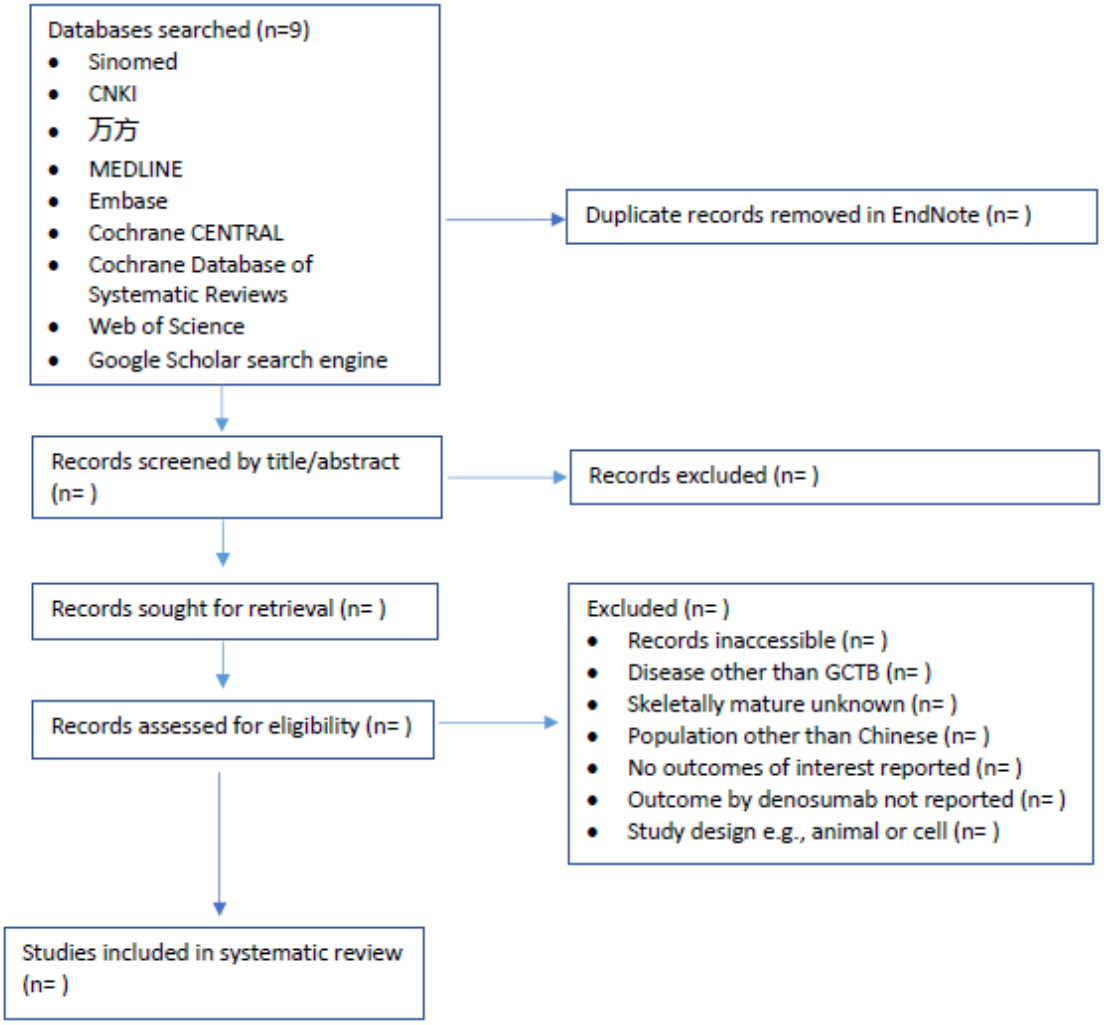
If any results were based on data dredging, was this made clear? *(Any analyses not planned at the outset should be clearly indicated)*			☐	☐	☐
In trials and cohort studies, analyses adjust for differences in length of follow-up; or in case-control studies, the time between intervention and outcome is the same for cases and controls.			☐	☐	☐
Statistical tests were appropriate for the data *(For example, non-parametric methods should be used for small samples sizes; if distribution of continuous data not described, assume appropriate)*			☐	☐	☐
Was compliance with intervention reliable?			☐	☐	☐
Were main outcome measures accurate? *(valid and reliable)*			☐	☐	☐
Internal Validity-Confounding (selection bias)					
Were patients in different intervention groups (cases and controls) recruited from the same population?			☐	☐	☐

Were patients in different intervention groups (cases and controls) recruited over the same time period?			☐	☐	☐
Randomization			☐	☐	☐
Was randomized treatment assignment concealed from patients and investigators until recruitment was complete and irrevocable?			☐	☐	☐
Adequate adjustment for confounding?			☐	☐	☐
Patients lost to follow-up were accounted for			☐	☐	☐
Power *(Power & sample size calculation was done and level of power achieved)*			☐	☐	☐
Total Score					

Notes: (Key conclusions of study authors, References to other relevant studies, Correspondence required for further study information)

* Downs and Black. J Epidemiol Community Health 1998; 52: 377-384

14.4 Appendix D. Figure 1. Flow Diagram of Study Screening and Selection



14.5 Appendix E. Table 1

Table 1. Characteristics of sample		
Characteristic	Statistics	References
Total N		
Study Design, N (%)		
Randomized Controlled Trial		
Quasi-randomized Controlled Trial		
Single Arm Interventional / Phase IV		
Prospective Cohort		
Retrospective case-control or case series		
Claims database		
Registry		
Literature review		
Data Source and Type, N (%)		
Single hospital or institution		
Multiple institutions		
Claims databases		
Medical records or registry		
Sample size		
Median (IQR)		
Greater than median, N (%)		
Treatment regimens evaluated, N (%)		
Denosumab pre-surgery (curettage)		
Denosumab pre- and post-surgery		
Curettage with no denosumab		
Outcomes, N (%)		
Progression- or recurrence-free survival		
Response Rate		
Surgical Downgrading		
Limb or joint-sparing procedure		
Safety outcomes: any AE		
Safety outcome: Osteonecrosis of the Jaw		
Safety outcome: Atypical Femoral Fracture		
Safety outcome: Hypocalcemia		
Safety outcome: Hypercalcemia		
Quality assessment		
Median score (IQR)*		
Score higher than median, N (%)		
* Downs and Black scale		

14.6 Appendix F. Table 2

Table 2. Summary of studies included in systematic review														
							Outcomes							
Ref No	First Author, Year	Study Design	Study Population	Time period of patient enrollment	Treatment Regimens	Salvageable or unsalvageable	PFS/RFS	Response Rate	Surgical downgrading	Limb/ joint-sparing procedures	Safety / AE, SAEs	Measures of Association	Confounders, Effect Modifiers	Quality Score

Abbreviations: PFS, progression-free survival; RFS, recurrence-free survival; AE, adverse event; SAE, serious adverse event