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Efficacy and safety of JMT103 in patients with unresectable or surgically-challenging giant cell tumor of bone: a multicenter, phase Ib/II study

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This was a multicenter, single-arm, open-label, phase Ib/II study (NCT04255576), aimed to evaluate the efficacy and safety of JMT103 in patients with unresectable or surgically-challenging giant cell tumor of bone (GCTB). JMT103 (2 mg/kg) was administered subcutaneously every four weeks, with loading doses on days 8 and 15. The primary endpoint was the objective tumor response rate (OTR) based on best response, defined as the proportion of patients who achieved elimination of at least 90% of the giant cells or radiologic complete or partial response per the modified Inverse Choi density/size (mICDS) or modified European Organization for Research and Treatment of Cancer (mEORTC) within 12 weeks. Secondary endpoints included objective response rate (ORR) per mICDS and mEORTC, and safety. A total of 139 patients were enrolled, and 135 were analyzed for efficacy. OTR, determined by the independent review committee (IRC) was 93.3% (95% CI 87.7-96.9). Treatment-related adverse events occurred in 90 (64.7%) patients, with hypophosphatemia and hypocalcemia being the most common. No serious treatment-related adverse events were observed. Thus, JMT103 demonstrates potential as a therapeutic option for GCTB.

Giant cell tumor of bone (GCTB) is a rare primary osteolytic bone tumor that typically arises from the epiphyseal portions of long bones, the spine, or the sacrum[1–3], accounting for approximately 5% of primary bone tumors[4–6]. In China, the annual incidence of GCTB (about 1.49-2.57 per million) was higher than in the United States[7,8], which might reflect a younger population in China[9]. Most patients present with pain, swelling, decreased joint motion, and disability[9,10]. GCTB is destructive and locally aggressive, damaging the bone and nearby soft tissue, causing substantial morbidity, and occasionally metastasizing (as much as 6%), most frequently to the lung (3%-4%) due to hematogenous dissemination[11–13].

While surgical removal remains the standard curative treatment for GCTB, local recurrence is high (estimated 10%-40%), indicating that complete resection is frequently not achieved[13,14]. Patients with unresectable GCTB have limited treatment options. Denosumab, a monoclonal anti-receptor activator of nuclear factor-kappa B (RANK) ligand

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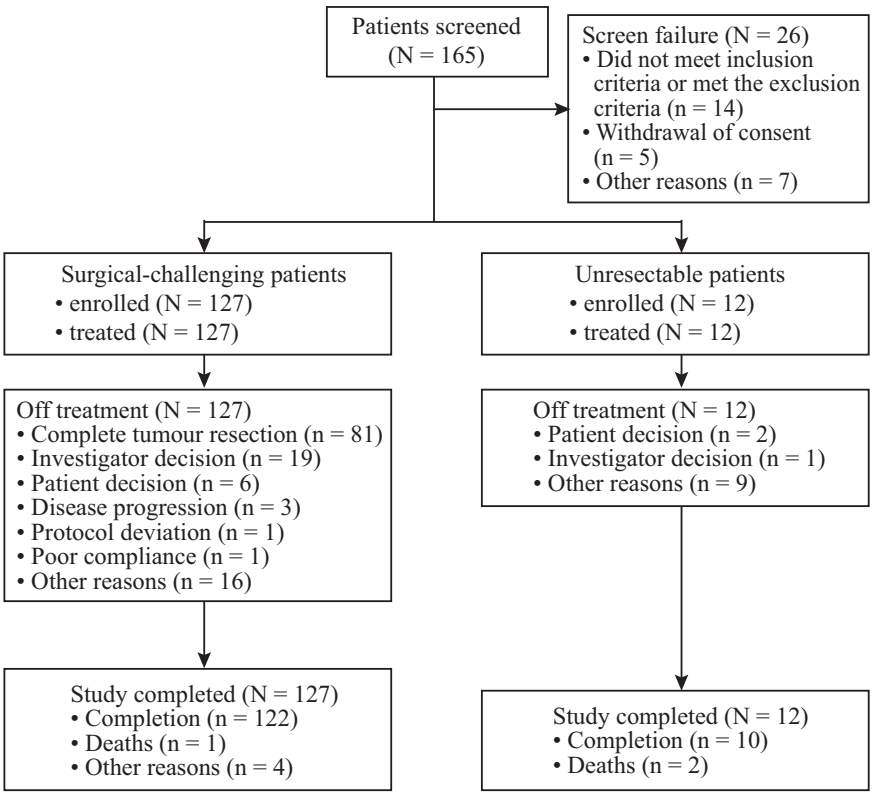

Fig. 1 | Patient disposition. A total of 139 patients were enrolled, including 127 surgical-challenging patients and 12 unresectable patients. At the time of database lock (14 July 2023), all patients had discontinued treatment and completed the study. The most common reason for treatment discontinuation was complete surgical resection of the tumor.

(RANKL) antibody, is one preferred treatment for unresectable GCTB[15,16]. Although the role of RANK-RANKL-mediated signaling in GCTB remains incompletely understood, it has been proposed that inhibition of this pathway inhibits GCTB-induced osteolysis. Several studies have suggested that denosumab effectively reduces tumor size, restores bone density, provides pain relief, and downstages surgery[17–20]. However, excessive sclerotic bone and thickened cortex resulting from long-term (≥ 25 weeks) preoperative denosumab treatment made it difficult to delineate the surgical margin, leading to increased recurrence and malignant transformation[21,22]. The risk of osteonecrosis of the jaw (ONJ) also increased with prolonged denosumab treatment[23]. Although a few published clinical experiences have suggested that a shorter treatment duration (3-4 months) of preoperative denosumab was beneficial in GCTB treatment[24,25], its efficacy remains to be established.

JMT103 is an innovative fully-humanized monoclonal antibody that shares the same Fab arms as denosumab, with the Fc end switched from IgG2 to IgG4[26]. Previous investigations have highlighted the presence of disulfide scrambling in human IgG2 monoclonal antibodies[27,28], which may contribute to product heterogeneity during therapeutic monoclonal antibody product development[29]. Since our target is to inhibit RANK-RANKL signaling, the "blocking antibody" IgG4 may present better safety profiles than IgG2 by avoiding formation of large complexes that can trigger effector functions[30]. Our phase I study of JMT103 in patients with bone metastases also demonstrated that suppression of bone resorption biomarkers by JMT103 was rapid, significant, and sustained[31].

Given these promising results from previous studies, we aimed to assess the efficacy and safety of JMT103 in patients with unresectable or surgically-challenging GCTB in this phase Ib/II study. Here we report the results of this phase Ib/II study (NCT04255576) showing the efficacy and manageable safety profile of JMT103, which suggest that JMT103 has the potential as a therapeutic option for GCTB.

Results

Patients

Between May 22, 2020, and June 15, 2023, 165 patients were screened, and 139 patients were enrolled. At the time of database lock (July 14, 2023), all patients (100%) had discontinued treatment and completed the study. The most common reason for treatment discontinuation was complete surgical resection of the tumor (Fig. 1). All 139 patients were included in the safety analysis set (SS), 135 were included in the full analysis set (FAS). One was excluded from the FAS because of a diagnosis of chondroblastoma, and the remaining three were excluded because they did not meet the criteria for unresectable or surgically-challenging GCTB.

The patients' demographic and baseline characteristics were summarized in Table 1. The median age of patients in the FAS was 33 years (range 18.0–67.0; Table 1). More than half of the patients ($n = 71$, 52.6%) were female. Most patients ($n = 124$, 91.9%) had surgically challenging GCTB (96 were primary and 28 were recurrent), and 11 (8.1%) had unresectable GCTB. The primary sites of GCTB lesions included the lower extremities, upper extremities, spine, sacrum, and pelvis.

Efficacy

In the FAS, the independent review committee (IRC)-reported objective tumor response rate (OTR) based on best response in any of the three prespecified criteria was 93.3% (95% CI 87.7–96.9; Table 2). The investigator-reported OTR was 92.6% (95% CI 86.8–96.4), consistent with the results of IRC assessment. Within 12 weeks of treatment, the median time to response (TTR) was 0.95 (IQR 0.89–1.05) months per modified Inverse Choi density/size (mICDS) and 2.60 (IQR 2.00–2.76)

Table 1 | Demographics and baseline characteristics (FAS)

	All patients (*N* = 135)
Age, years, median (range)	33.0 (18.0–67.0)
Sex (female)	71 (52.6)
ECOG performance status	
0	52 (38.5)
1	78 (57.8)
2	5 (3.7)
Primary tumor site	
Lower extremity	57 (42.2)
Upper extremity	34 (25.2)
Spine or sacrum	30 (22.2)
Pelvis	10 (7.4)
Other	4 (3.0)
Metastatic	
Yes	11 (8.1)
No	124 (91.9)
Metastatic site	
Lung	10 (7.4)
Lower extremity	1 (0.7)
Other	0
GCTB disease status	
Primary resectable[a]	96 (71.1)
Primary unresectable	5 (3.7)
Recurrent resectable[a]	28 (20.7)
Recurrent unresectable	6 (4.4)
Previous treatment for GCTB	
Surgery	42 (31.1)
Bisphosphonates	4 (3.0)
Chemotherapy	1 (0.7)
Time from diagnosis to first treatment, median (IQR) months	0.76 (0.46, 12.06)

Data are presented as n (%) unless otherwise specified.
IQR interquartile range, *ECOG* Eastern Cooperative Oncology Group, *GCTB* giant cell tumor of bone.
[a]Resectable means surgically-challenging.

Table 2 | Summary of best tumor response (FAS)

	IRC-reported (*N* = 135)	Investigator-reported (*N* = 135)
OTR, % (95% CI)	93.3 (87.7, 96.9)	92.6 (86.8, 96.4)
Best response within 12-week treatment per mICDS criteria		
Complete response	0	0
Partial response	110 (81.5)	102 (75.6)
Stable disease	25 (18.5)	32 (23.7)
Progressive disease	0	0
Not evaluable	0	0
Not available	0	1 (0.7)
TTR, median (IQR) months	0.95 (0.89, 1.05)	0.95 (0.89, 1.05)
Best response within 12-week treatment per mEORTC criteria		
Complete response	4 (3.0)	2 (1.5)
Partial response	91 (67.4)	89 (65.9)
Stable disease	17 (12.6)	18 (13.3)
Progressive disease	1 (0.7)	3 (2.2)
Not evaluable	0	0
Not available	22 (16.3)	23 (17.0)
TTR, median (IQR) months	2.60 (2.00, 2.76)	2.60 (2.00, 2.76)
Histological response throughout the study[a]		
Response[b]	56 (41.5)	
Non-response	4 (3.0)	
Not available[c]	75 (55.6)	

Data are presented as *n* (%) unless otherwise specified.
The Clopper-Pearson method was used to calculate 95% CIs.
IRC Independent Review Committee, *OTR* objective tumor response rate, *TTR* time to first objective response, *IQR* interquartile range, *mICDS* modified Inverse Choi density/size, *mEORTC* modified European Organization for Research and Treatment of Cancer.
[a]Responses were assessed in an independent central laboratory.
[b]Response defined as elimination of at least 90% of giant cells relative to baseline.
[c]Histological responses not available consisted of cases without consent to collect tissue specimens, valid baseline specimens, or post-treatment specimens.

months by modified European Organization for Research and Treatment of Cancer (mEORTC) in both IRC and investigator's assessments (Table 2). Furthermore, 116 (88.1%) patients achieved a decrease in target lesion size, 119 (88.4%) experienced an increase in tumor density, and 107 (79.3%) achieved a decrease in the sum of the maximum standardized uptake values within 12 weeks of treatment (Fig. 2).

Tumor responses throughout the study are summarized in Table S1 (Supplemental data). According to the IRC assessment, the objective response rate (ORR) and disease control rate (DCR) as per mICDS were 85.9% (95% CI 78.9-91.3) and 100.0% (95% CI 97.3-100.0), respectively; the ORR and DCR as per mEORTC were 80.0% (95% CI 72.3-86.4) and 93.3% (95% CI 87.7-96.9), respectively (Table S1 in Supplemental data). Based on the investigator's assessment, the ORR and DCR as per the mICDS were 80.0% (95% CI 72.3-86.4) and 99.3% (95% CI 95.9-100.0), respectively, and the ORR and DCR as per the mEORTC were 77.0% (95% CI 69.0-83.8) and 91.1% (95% CI 85.0-95.3), respectively (Table S1 in Supplemental data). The median time to disease progression (TTP) was not reached (Fig. S1 in Supplemental data). No patient with a complete or partial response exhibited subsequent progressive disease by the end of the study.

The mean reduction in worst pain score from baseline increased over time in patients with a Brief Pain Inventory-Short Form (BPI-SF) pain score > 0 at baseline. Pain interfered less with daily functioning over time among the 91 patients with a baseline BPI-SF pain score ≥ 2 points, and 28 (30.8%) patients showed a clinically relevant decrease in pain score on day 8. Notably, among 37 patients with baseline worst pain score > 4, 17 (45.9%) achieved pain score ≥ 2 decrease on day 8. More than half the patients showed a clinically relevant decrease in pain from the first month to the last BPI-SF evaluation (Fig. S2 in Supplemental data).

Two bone-resorption biomarkers, uNTx/Cr and sCTx, were rapidly, substantially, and steadily suppressed (Fig. S3 in Supplemental data). The median reductions in concentration were 77.9% (IQR 64.5–87.4) for uNTx/Cr and 76.9% (IQR 53.4–86.9) for sCTx on day 8, and the magnitudes of reduction were sustained from day 8 onward.

Safety

One hundred and thirty-nine patients received at least one dose of JMT103. The median duration of treatment was 86.0 days (IQR 84.0-308.0), and the median number of doses was 5.0 (IQR 5.0-12.0). Of the 139 patients, 127 (91.4 %) reported at least one treatment-emergent adverse events (TEAEs), 90 (64.7 %) of which were attributed to the study drug (Table 3). The most common TEAEs (all grades, ≥10%) were anemia (*n* = 37, 26.6%), hypophosphatemia (*n* = 36, 25.9%), hypocalcemia (*n* = 32, 23.0%), alanine aminotransferase elevation (*n* = 19, 13.7%), white blood cell count elevation (*n* = 17, 12.2%), and upper respiratory tract infection (*n* = 15, 10.8%). The most common treatment-related TEAEs (TRAEs, ≥10%) were hypophosphatemia (*n* = 33, 23.7%) and hypocalcemia (*n* = 23, 16.5%).

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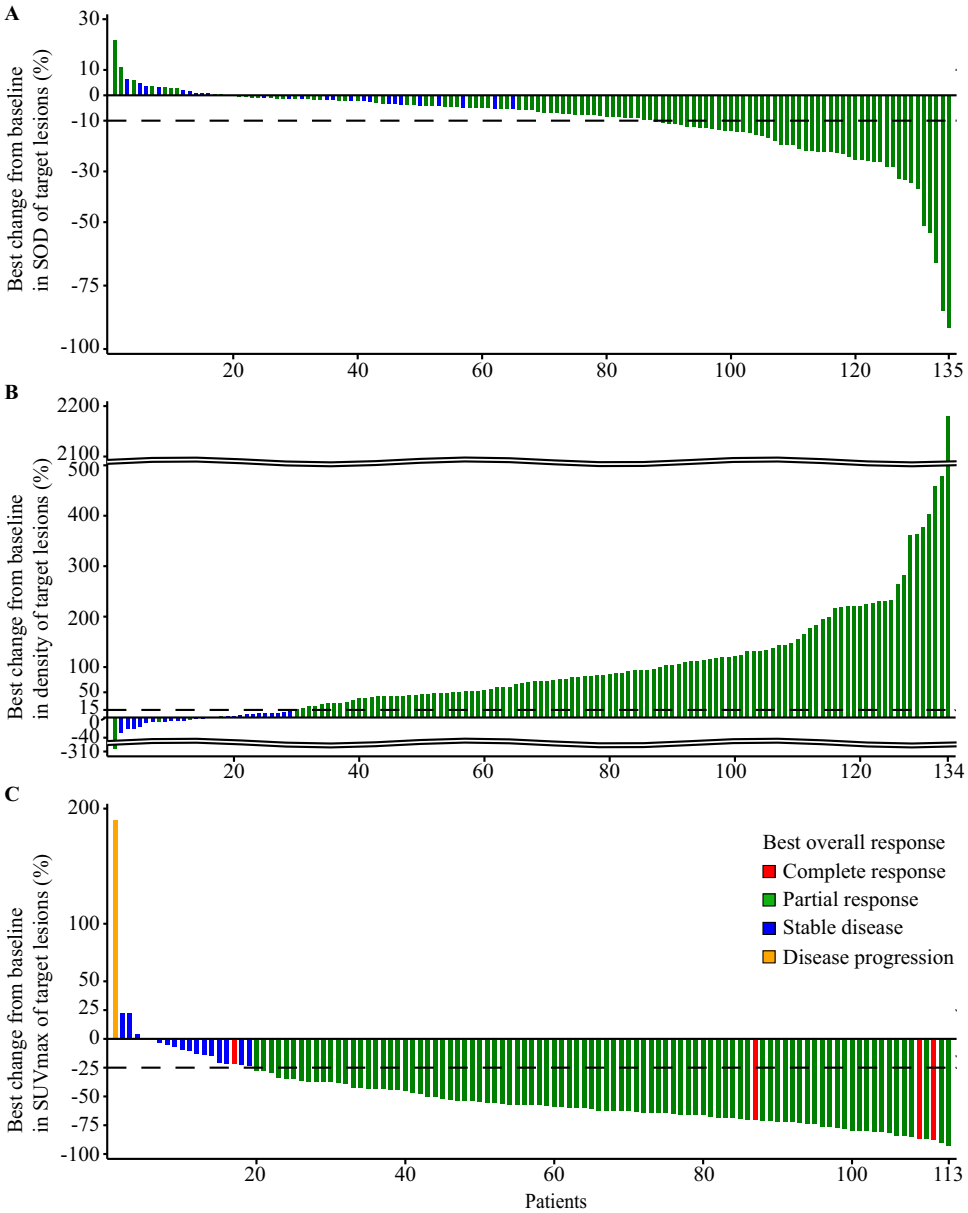

Fig. 2 | Waterfall plots showing anti-tumor activity within 12 weeks. A Best percentage change from baseline in SOD assessed by IRC per mICDs. **B** Best percentage change from baseline in tumor density assessed by IRC per mICDs. **C** Best percentage change from baseline in SUVmax assessed by IRC per mEORTC. Patients with at least one on-study target-lesion assessment were included. If any radiological procedure was different and not interchangeable with the procedure at screening, the percentage change from baseline could not be calculated and was not displayed. The dashed line indicates the threshold of partial response for the corresponding criteria. Source data are provided as a Source Data file. IRC Independent Review Committee, SOD sum of the target lesion diameter, CT computed tomography, SUVmax sum of the maximum standardized uptake value, mICDS modified Inverse Choi density/size, mEORTC modified European Organization for Research and Treatment of Cancer.

Eight (5.8%) patients reported TEAEs that lead to temporary interruption of JMT103 (Table S2 in Supplemental data). None of the patients reported TEAEs that led to permanent discontinuation of treatment.

Grade ≥3 TEAEs occurred in 23 (16.5%) patients, with anemia in 10 (7.2%) patients being the most common grade ≥3 TEAEs (Table 3). Three (2.2%) patients reported grade-3 TRAEs, including hypomagnesemia ($n = 2$, 1.4%), increased aspartate aminotransferase levels ($n = 1$, 0.7%), and hypertension ($n = 1$, 0.7%). No patients reported grade-4 or grade-5 TRAEs. Eight (5.8%) patients reported treatment-emergent serious adverse events (SAEs) (Table S3 in Supplemental data), but none were deemed treatment-related, and their clinical conditions resolved after short hospitalizations. One patient (0.7%) reported an adverse event of special interest (AESI) (grade 2 allergic dermatitis), which was determined to be treatment related and resolved with anti-allergy therapy.

One patient with a giant unresectable GCTB experienced metabolic acidosis and hemorrhagic shock after surgery due to a large abdominal mass and comorbid bilateral hydronephrosis, then died a day later. Although it occurred during the safety observation period, the investigators reviewed this case carefully and determined the AE causality to be unrelated to the study drug. Two patients died during the safety follow-up period due to disease progression.

In the SS, all 139 patients were tested for anti-drug antibodies (ADA) at enrollment, with 132 tested after JMT103 administration. One patient (0.7%) tested positive at baseline but tested negative after JMT103. Two patients (1.4%) with negative results at baseline tested positive within 90 days from the end of treatment (EOT).

Table 3 | Summary of adverse events (SS)

	All grades (*N* = 139)	Grade 3-4[a] (*N* = 139)
Any TEAEs	127 (91.4)	23 (16.5)
TEAEs occurring in ≥5% of patients		
Anemia	37 (26.6)	10 (7.2)
Hypophosphatemia	36 (25.9)	0
Hypocalcemia	32 (23.0)	0
Alanine aminotransferase elevation	19 (13.7)	0
White blood cell count elevation	17 (12.2)	0
Upper respiratory tract infection	15 (10.8)	1 (0.7)
Hypermagnesemia	13 (9.4)	2 (1.4)
C-reactive protein increased	13 (9.4)	0
Periodontal disease	13 (9.4)	0
COVID-19	12 (8.6)	0
Hypoalbuminemia	12 (8.6)	1 (0.7)
Dental caries	11 (7.9)	0
Aspartate aminotransferase elevation	11 (7.9)	1 (0.7)
Pyrexia	11 (7.9)	0
Weight increased	10 (7.2)	0
Neutrophil count elevation	9 (6.5)	0
Blood bilirubin elevation	8 (5.8)	1 (0.7)
Cough	7 (5.0)	0
Hypomagnesaemia	7 (5.0)	2 (1.4)
Hyperuricemia	7 (5.0)	0
Pain in extremity	7 (5.0)	0
Any TRAEs	90 (64.7)	3 (2.2)
TRAEs occurring in ≥5% of patients		
Hypophosphatemia	33 (23.7)	0
Hypocalcemia	23 (16.5)	0
Alanine aminotransferase elevation	12 (8.6)	0
Periodontal disease	11 (7.9)	0
Hypermagnesemia	9 (6.5)	0
Aspartate aminotransferase elevation	7 (5.0)	1 (0.7)

TEAE was defined as an adverse event that occurred from the first dose to 97 days after the last dose or an adverse event that started pre-dose but worsened post-dose (CTCAE grade increased).
SS safety analysis set, *TEAEs* treatment-emergent adverse events, *TRAE* treatment-related adverse events.
[a]No patients reported grade 5 TEAE.

Discussion

This is a clinical trial to assess the efficacy and safety of JMT103 in patients with unresectable or surgically-challenging GCTB. In this trial, JMT103 exhibited high OTRs (93.3% for IRC assessment, and 92.6% for investigator's assessment), stable and sustained effects on pain relief and bone resorption, and a manageable safety profile with no unexpected safety concerns.

Previous studies of denosumab also showed impressive tumor response rates, ranging from 71% to 88% with a median TTR of 2.8 to 3.2 months[23,32–34], suggesting that targeting the RANKL/RANK pathway is a valid therapeutic strategy for GCTB (regardless of differences in study design). Consistent with previous studies on denosumab[9,32,33,35], our results provide further evidence to support the use of anti-RANKL therapy for unresectable or surgically-challenging GCTB.

Although extensive studies have been conducted with denosumab and long-term follow-up results have been published[23,33], key questions regarding anti-RANKL treatment still need to be answered. Due to the lack of guidance and regulation on treatment duration, controversy over preoperative treatment duration has arisen and urgently needs to be addressed.

In our study, scheduled imaging and uniform assessments by the IRC were performed prospectively. Based on clinical experience with short-term denosumab treatment[24,25,36], we placed a 12-week limit on radiological responses to emphasize the efficacy of short-term treatment. Most objective tumor responses were observed at the first tumor assessment, confirming the fast onset antitumor effect of JMT103 and suggesting that a shorter duration of preoperative JMT103 can exert promising clinical, radiological, and histological antitumor effects.

Several studies have raised the possibility of increased local recurrence after curettage due to unclear boundaries between the tumor and normal tissues after long-term denosumab use[21,37]. Thus short-term anti-RANKL treatment may be recommended. Theoretically, short-term anti-RANKL treatment can benefit patients by preventing excessive bone sclerosis and by reducing recurrence. In our study, we performed curettage after short-term JMT103 treatment (median time to curettage, 2.94 months). Until the time of database lock, no recurrence after resection was observed. However, a longer follow-up period is needed to further document recurrence after JMT103.

The optimal assessment method for GCTBs is another unanswered question. In our study, we used mICDS, mEORTC, and histological examination to assess tumor response, but did not use RECIST 1.1, mainly because most GCTB patients did not meet the special requirements for soft tissue components in bone lesions[38]. ICDS criteria are initially proposed for gastrointestinal stromal tumors suitable for settings where tumor shrinkage is unable to predict clinical benefit[39]. EORTC, as metabolic criteria, offer advantages in assessment of tumors with obscure margins and complex structures[40,41]. The readouts per ICDS and EORTC correlated well with the clinical benefits observed in GCTB patients[35]. In our study, three different response criteria were employed to capture different aspects of GCTB tumor response, including ossification, vascularization, and cell morphology. Further research is required to develop standardized criteria for bone tumor assessment.

The types and frequencies of adverse events were consistent with those reported for treatment of bone metastases from solid tumors[31]. The most common TRAEs in the previous study were hypophosphatemia and hypocalcemia. The patient who died during the safety observation period was reported to have massive intraoperative hemorrhage (9000 mL) during surgery for a large abdominal mass, comorbid bilateral hydronephrosis, metabolic acidosis, and hemorrhagic shock. He was transferred to the Intensive Care Unit and underwent emergency interventions but died one day later. Based on the above information, the investigator concluded that metabolic acidosis and hemorrhagic shock were not related to JMT103 treatment. No new safety concerns that could be attributed to JMT103 were raised by the time of data cutoff. No grade ≥3 hypophosphatemia and hypocalcemia were reported, but serum phosphate and calcium should be monitored during treatment[42,43]. Moreover, no patients reported ONJ, one of the most common TRAEs and treatment-related SAEs in the denosumab-treated patients[23]. The lack of occurrence of ONJ is probably related to the shorter-term treatment with JMT103, as we have learned that the frequency of ONJ increases with increasing denosumab exposure[23]. Also, the occurrence of ONJ needs to be confirmed with further study. Overall, our results indicate that JMT103 has a good safety profile.

Our study has several limitations. Due to its single-arm design, our results must be interpreted with caution[44]. To reduce the risk of bias, we designed a retrospective real-world study that included denosumab and non-treated patients as external controls (NCT05402865). A multicenter, randomized, double-blind, active-controlled phase 3 trial is also planned to compare JMT103 with denosumab to evaluate the differences in safety and efficacy in GCTB (NCT05813665). Another limitation is that the follow-up period was relatively short. It remains

unclear whether the long-term outcomes of JMT103 and postoperative recurrence require further investigation.

In conclusion, these findings suggest that JMT103 has therapeutic potential for unresectable and surgically-challenging GCTB, and displays a good safety profile. Further investigation of JMT103 treatment is warranted.

Methods

Patients

This study was conducted in accordance with Good Clinical Practice guideline and the Declaration of Helsinki. The study protocol was approved by Independent Ethics Committees at all study sites, including Beijing Ji Shui Tan Hospital, West China Hospital, Sichuan University, Peking University Third Hospital, The First Affiliated Hospital of Sun Yat-Sen University, Fudan University Shanghai Cancer Center, Sun Yat-sen University Cancer Center, Qilu Hospital of Shandong University, Liaoning Cancer Hospital & Institute, Hunan Cancer Hospital, The Fourth Medical Center, Chinese PLA General Hospital, The Second Affiliated Hospital of Air Force Medical University, Yunnan Cancer Hospital, Cancer Hospital Affiliated to Guangxi Medica University, The First Affiliated Hospital of Fujian Medical University, Henan Cancer Hospital, Xi'an HongHui Hospital, The Second Affiliated Hospital Zhejiang University School of Medicine, The Third Hospital of Hebei Medical University, The Affiliated Cancer Hospital of Guizhou Medical University, Tianjin Medical University Cancer Institute & Hospital, Shengjing Hospital of China Medical University, Peking University Cancer Hospital, Harbin Medical University Cancer Hospital, Second hospital of Shanxi Medical University and registered at *ClinicalTrials.gov* (NCT04255576, date of registration: February 5 2020). Written informed consent was obtained from all patients before enrollment.

Eligible patients (≥18 years) had pathologically confirmed unresectable GCTB (defined as a tumor that could not be entirely removed by surgery because: (1) it was large, deep in location, and complex in anatomy, and invaded the crucial structures (e.g., the main blood vessels, spinal cord, or cauda equina nerve, or viscera); and (2) it had extensive distant metastases) or surgically-challenging GCTB (defined as a tumor can be completely removed by surgery, but the planned surgery may cause serious dysfunction or complications because: (1) the tumor invaded the joint or adjacent articular cartilage; (2) the curettage was unavailable and needs prosthesis replacement; (3) the tumor was recurrent, and the extent of the tumor is difficult to identify; (4) the tumor located in the sacrum, pelvis, or spine; (5) the surgery may lead to limb necrosis and amputation) designated by the treating surgeon. Criteria included an Eastern Cooperative Oncology Group (ECOG) status of 0-2 and a serum albumin corrected calcium concentration ≥ lower limit of normal.

Key exclusion criteria were a history or current evidence of osteomyelitis or ONJ, unhealed dental or oral surgery wounds, acute tooth or jaw disease requiring oral surgery, or planned invasive dental surgery during the study period; known bone metabolic diseases, such as hypoparathyroidism or hyperparathyroidism, hypothyroidism or hyperthyroidism, and Paget's disease; known history of a malignant tumor within the five years of study enrollment (except for curable tumors such as skin basal cell carcinoma under complete excision and breast/cervical carcinoma in situ); current anti-tumor treatment (such as radiotherapy, chemotherapy, and arterial embolization); concurrent treatment with bisphosphonates; and previous treatment with anti-RANKL antibodies. The full lists of inclusion and exclusion criteria are provided in study protocol (Supplementary Note).

Study design and procedures

This was a multicenter, single-arm, open-label, phase Ib/II study conducted at 24 centers (Table S4 in Supplemental data) in China between May 22, 2020, and June 15, 2023. JMT103 was administered subcutaneously at a dose of 2 mg/kg every four weeks, with loading doses administered on days 8 and 15. Dose adjustments were not permitted. Patients without preexisting hypercalcemia were instructed to consume at least 400 IU vitamin D and 500 mg calcium daily. The study treatment was continued until disease progression, complete tumor resection, intolerable toxicity, withdrawal by the patient, or absence of clinical benefit based on the investigators' clinical judgment occurred (whichever occurred first).

Tumor assessments were performed every four weeks for the first 12 weeks, every 12 weeks for up to 49 weeks, and every 24 weeks thereafter until disease progression or end of the study (EOS). EOS was defined as 24 months after the last patient's enrollment, or the time determined by the investigator. Unscheduled assessments were permitted, if deemed clinically necessary. Radiological imaging was carried out through computed tomography (CT), magnetic resonance imaging (MRI), and ^{18}F-fluorodeoxyglucose positron emission tomography (PET) scans of target lesions and nontarget lesions at each center. A CT scan (or MRI when CT was unsuitable) was performed every four weeks for the first 12 weeks, every 12 weeks up to 49 weeks, and every 24 weeks thereafter until disease progression or EOS. PET was performed at 12 weeks and was scheduled according to the investigator's instructions. If available, pre- and post-treatment tissue samples were collected (preferably by surgical resection). All radiological tumor assessments were performed by the IRC and investigators. Histopathological analysis was done using the biopsy before treatment and within 12 weeks after treatment or postoperative specimen and histopathological tumor responses were assessed in an independent central laboratory.

Patient-reported pain and its interference with daily functioning were assessed before administration of JMT103 on days 1, 8, and 15, every four weeks for up to 6 months, and every 12 weeks thereafter until EOT. The worst pain severity within the past 24 hours was assessed at each evaluation visit using the BPI-SF. A minimal 2-point change from baseline BPI-SF score was considered a clinically meaningful reduction.

Urine and blood samples were collected prior to dosing on days 1, 8, 15, and 29, every four weeks for up to 6 months, and every eight weeks thereafter, for biomarker analyses. Blood samples were collected prior to dosing on days 1, 57, and 90 after EOT for ADA analysis.

TEAEs were recorded throughout the safety observation period (from the first dose to 90 days after EOT). The predefined AESIs were grade 3 or greater hypocalcemia (defined as serum calcium < 7.0 mg/dL or 1.75 mmol/L; ionized calcium < 0.9 mmol/L), grade 3 or greater hypophosphatemia (defined as a low concentration of phosphates in the blood, and severe or medically significant but not immediately life-threatening or life-threatening consequences; hospitalization or prolongation of existing hospitalization), injection site reaction, hypercalcemia after EOT, ONJ, and hypersensitivity. For patients who discontinued JMT103 or dropped out of the study, safety follow-up visits were scheduled within 90 days after EOT or before initiating a new antitumor treatment, whichever occurred first.

Outcomes

The primary endpoint was histopathological or radiological OTR based on best response evaluated using the following response criteria: (1) elimination of at least 90% of giant cells relative to baseline[45]; (2) radiologic complete or partial response of the target lesion within 12 weeks, as per mICDS[39] or mEORTC[46] criteria (Table S5 in Supplemental data). Response was deemed to have occurred if either criterion was met. Secondary endpoints included ORR and DCR throughout the study, TTP, changes in BPI-SF score, uNTx/Cr, and sCTx concentrations, safety, and immunogenicity. Safety was assessed on the basis of the intensity or frequency of TEAEs, SAEs, AESIs, and ADA. The TEAEs were recorded using the Medical Dictionary for Regulatory Activities (version 24.0) and graded according to NCI Common

Terminology Criteria for Adverse Events (version 5.0). A full list of objectives and endpoints is provided in the protocol (Supplemental Protocol); not all endpoints are reported in this paper.

Statistical analyses

In all, 6–12 patients were predetermined to be enrolled in the phase Ib study for safety assessment. For the phase II study, referring to the results of denosumab treatment[33,34], we assumed that the observed OTR of JMT103 would range from 50% to 80%. A sample size of 100 patients would limit the maximum width of the exact two-sided 95% CI to approximately 20% when the observed OTRs were 50%–80%. Considering an attrition rate of 20%, 125 patients were enrolled.

The FAS and SS included all patients who received at least one dose of JMT103. Patients incorrectly enrolled in the study were excluded from the FAS. Efficacy was analyzed using the FAS. Safety was analyzed using the SS. Bone metabolic biomarkers were characterized in the pharmacodynamic analysis set, which included patients with evaluable pharmacodynamic results.

Descriptive statistics (count, percentage, median, minimum, and maximum) were used to measure demographic factors, baseline disease characteristics, and safety outcomes, as appropriate. The OTR, ORR, and DCR were reported as percentages with 95% confidence intervals (CI calculated using the Clopper-Pearson method). The Kaplan-Meier method was applied to estimate median TTP, with 95% CIs estimated using the Brookmeyer-Crowley method with log-log function transformation to achieve a normal approximation. All statistical analyses were based on observed data using SAS software (version 9.4, SAS Institute, Cary, North Carolina, USA) without imputing missing values.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Data supporting the findings of this study are available in the article, its Supplementary information, the source data file. All de-identified patient-level data are available under restricted access, not for commercial use. Access can be obtained by contacting corresponding authors (X-H Niu, niuxiaohui@263.net) and all requests will be evaluated by corresponding author, the institutional review board and Shanghai JMT-Bio Technology Co., Ltd. A signed data access agreement with the sponsor is required before data sharing. The complete protocol is available in the Supplementary Note. The remaining data are available within the Article, Supplementary Information or Source Data file. Source data are provided with this paper.

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Author contributions

H.X. and X.N. conceived and designed the study. H.X., Y.Z., L.L., J.S., W.Y., J.W., J.M.L., X.Z., G.H., W.B., Z.G., Y.X., J.H.L., W.Y., Z.T., W.Z., G.Z., Z.Y., D.W., J.Y., Z.F., C.L., G.Q., Q.Z., F.W., W.L., and C.T. enrolled the patients and contributed to data acquisition. J.Y. and H.L. contributed to the data analysis. H.L., H.X., and Y.Z. provided the administrative and technical support. H.X. and X.N. supervised the study. H.X. wrote the first draft of the manuscript. All authors reviewed the data analyses, contributed to data interpretation, revised the manuscript, and all authors approved the manuscript for submission.

Competing interests

J.Y. and H.L. are employees of the CSPC Pharmaceutical Group Limited. All other authors declare no competing interests.

Additional information

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