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Efficacy and safety of JMT103 in patients with bone metastases from solid tumors: A randomized Phase Ib clinical trial

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Abstract

This study aimed to assess the efficacy and safety of three dosing regimens of JMT103 in patients with bone metastases from solid tumors. Eligible patients were randomly assigned to receive JMT103 subcutaneously, 120 mg every 4 weeks (Cohort 1), 120 mg every 8 weeks (Cohort 2), or 180 mg every 8 weeks (Cohort 3) for up to 49 weeks. The primary endpoint was change from baseline to Week 13 in creatinine-adjusted urinary N-telopeptide (uNTx/Cr). Two hundred and ninety-five patients were randomized, and 293 received at least one dose of JMT103, of whom 96 were assigned to Cohort 1, 97 were assigned to Cohort 2, and 100 were assigned to Cohort 3. The median (interquartile range) percentage reduction in uNTx/Cr at

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Week 13 was 80.0% (49.9%, 93.4%) in Cohort 1, 73.0% (34.5%, 94.0%) in Cohort 2, and 75.7% (40.4%, 92.0%) in Cohort 3, respectively. On-study skeletal-related events were reported by 3.1% of patients in Cohort 1, 6.2% in Cohort 2, and 7.0% in Cohort 3. Treatment-emergent adverse events occurred in 289 patients, 162 of whom were deemed treatment-related. The most common treatment-related adverse events were hypocalcemia (23.2%), hypophosphatemia (22.9%), and increased aspartate transaminase (11.9%). JMT103 demonstrated a good safety and a strong suppression of the bone turnover markers.

KEYWORDS
bone metastases, JMT103, RANK ligand

What's New?

Bone metastases are common in a variety of cancer types, causing increased pain and worse outcomes. Suppression of bone turnover, such as with the monoclonal antibody denosumab, results in fewer skeletal complications and improved prognosis. Here, the authors demonstrate the safety and efficacy of a similar antibody, JMT103. Like denosumab, JMT103 targets the receptor activator of nuclear factor-kB ligand (RANKL). In patients with bone metastases, subcutaneous JMT103 was well tolerated and strongly suppressed bone turnover markers.

1 | INTRODUCTION

The bone is one of the most common sites of cancer metastases.[1] The incidence of bone metastases ranged from 5% to 95% and was particularly high in patients with breast cancer, prostate cancer, and myeloma.[2,3] Bone metastases are associated with serious skeletal complications, such as pain, hypercalcemia, fracture, and spinal cord compression, bringing a tremendous burden and causing poorer prognosis in cancer patients.[4]

The primary mechanism of bone metastases is interference with bone turnovers and can be classified as osteolytic, osteoblastic, or mixed.[5] Osteolytic metastases are the most common type of bone metastases, characterized by increased bone resorption and lytic (destructive) lesions.[6] The receptor activator of nuclear factor-kB (RANK) and RANK ligand (RANKL) signaling pathway is essential in osteoclast function and formation. In the tumor environment, RANKL was hypersecreted by osteoblasts and stromal cells to promote osteoclastogenesis and osteolytic lesions.[7] Inhibiting the RANK and RANKL pathway could significantly suppress bone resorption and relieve bone metastasis symptoms.[8]

The current standard of treatment for bone metastasis includes surgery, radiotherapy, and bone-modifying agents (such as bisphosphonates and denosumab).[9] Denosumab is an IgG2 fully human monoclonal antibody against RANKL. Previous studies have demonstrated that denosumab could correct elevated bone turnover markers, reduce the risk of skeletal-related events (SREs), and decrease bone pain effectively,[10–12] and was superior to zoledronic acid in the prevention of SREs.[13] However, previous studies have reported disulfide scramble in human IgG2 monoclonal antibody,[14,15] which could contribute to product heterogeneity during therapeutic monoclonal antibody product development.[16] JMT103 is a novel, fully humanized monoclonal anti-RANKL antibody that shares the same Fab arms as denosumab but with Fc end switches from IgG2 to IgG4. IgG4 possesses unique properties that prevent the formation of large complexes and the activation of effector functions to act as a safe "blocking antibody."[17,18]

The previous Phase I study of JMT103 showed robust and sustained suppression of bone resorption biomarkers with good safety results.[19] In our Phase Ib trial, we aimed to evaluate the efficacy and safety of JMT103 in patients with bone metastases from solid tumors and establish a recommended dose for further Phase III study.

2 | PATIENTS AND METHODS

2.1 | Study design and patients

In this randomized, multi-center, open-label, Phase Ib study, eligible patients were randomly assigned to one of the three dose cohorts: 120 mg every 4 weeks (Q4W, Cohort 1), 120 mg every 8 weeks (Q8W, Cohort 2), or 180 mg Q8W (Cohort 3) using an interactive web response system. The randomization schedule was prepared by an individual independent of the study team. Randomization was stratified by cancer type (breast cancer, prostate cancer, or other solid tumors) and prior use of bisphosphonates (yes or no).

Eligible patients were aged 18 years or older with histologically or cytologically confirmed solid tumors and had radiographic evidence (by x-ray, computed tomography, magnetic resonance imaging, or positron emission tomography-computed tomography) of at least one bone metastasis within 3 months prior to randomization. Additional

inclusion criteria were adequate organ function, albumin-adjusted serum calcium concentration ≥ the lower limit of normal, Eastern Cooperative Oncology Group performance status 0–2, and a life expectancy of at least 6 months. Main exclusion criteria were current or previous osteonecrosis or osteomyelitis of the jaw; unhealed dental or oral surgery wounds; acute dental or jaw disease requiring surgery or scheduled invasive dental surgery during the study period; planned radiation or surgery to bone; untreated, symptomatic, or actively progressing central nervous system metastases; bone metabolic diseases (such as Paget's disease, Cushing's syndrome, and hyperprolactinemia); rheumatoid arthritis; parathyroid disorders; and previous use of anti-RANKL antibodies. The full list of inclusion and exclusion criteria is provided in the supplemental methods.

2.2 | Procedures

Patients received subcutaneous injections of JMT103 120 mg Q4W (Cohort 1), 120 mg Q8W (Cohort 2), or 180 mg Q8W (Cohort 3) for up to 49 weeks. Patients in Cohort 1 received a total of 13 doses, and those in Cohort 2 and Cohort 3 received a total of seven doses. Dose adjustments were not allowed. In addition, daily supplements of vitamin D (at least 400 International Unit (IU)) and calcium (500 mg) were given to all patients.

The dose selection of JMT103 was based on the results of the Phase I study, which demonstrated that JMT103 was safe at 1.0–3.0 mg/kg and provided effective suppression of bone turnover markers to a level similar to that previously reported for denosumab.[19]

Blood samples for pharmacokinetic analysis were collected post-dose on study Day 1 and pre-dose on Weeks 9, 17, 25, 33, 41, and 90 days after the last dose or withdrawal. Blood samples for biomarker analysis were collected pre-dose on study Day 1, at Weeks 5, 13, 25, 37, 49, and 90 days after the last dose or withdrawal. Blood samples for immunogenicity analysis were collected pre-dose on study Day 1, at Week 5 (for Cohort 1) or at Week 9 (for Cohort 2 and 3), and 90 days after the last dose or withdrawal. Urine samples for biomarker analysis were collected pre-dose on study Day 1, on Weeks 5, 9, 13, 17, 21, 25, 37, 49, and 90 days after the last dose or withdrawal.

Skeletal assessments by radiographic imaging (x-ray, computed tomography, or magnetic resonance imaging) were scheduled at baseline and every 3 months thereafter to assess the bone metastatic sites, pathological fractures, and spinal cord compression; unscheduled imaging was allowed if the attending physician indicated.

Oral examinations were performed at baseline, Weeks 25 and 90, days after the last dose or withdrawal. The pain severity within the past 24 h was assessed on study Days 1 and 15, at Weeks 13, 25, 37, 49, and 90 days after the last dose or withdrawal, using the Brief Pain Inventory-Short Form (BPI-SF). Pain severity was rated on an 11-point scale (0, no pain; 1–4, mild pain; 5–6, moderate pain; and 7–10, severe pain). A minimal 2-point change from the baseline BPI-SF score was considered a clinically meaningful reduction.[20]

Laboratory assessments, physical examination, on-study SREs, treatment-emergent adverse events (TEAEs), and concomitant dedication were recorded throughout the study period. Adverse events were coded using the Medical Dictionary for Regulatory Activities (version 25.1), and the severity of adverse events was graded according to the Common Terminology Criteria for Adverse Events (version 5.0).

2.3 | Endpoints

The primary endpoint was the percentage change from baseline to Week 13 in creatinine-adjusted urinary N-telopeptide (uNTx/Cr). The secondary endpoints included the occurrence of on-study SREs, the change of pain severity as per BPI-SF, the change from baseline in serum C-telopeptide of crosslinked collagen type I (sCTX-I) and bone alkaline phosphatase (bALP), the presence of anti-JMT103 antibody, and safety.

2.4 | Statistical analysis

The sample size for this study was not determined from power analysis. Assuming the response rate was more than 50%[19] (response was defined as achieving a more than 65% reduction in uNTx/Cr[21] from baseline to Week 13), 95 patients per cohort (285 patients in total) could provide a relatively tight range of 95% Confidence Interval (CI) of the primary endpoint (±10%), considering a relatively large standard deviation for the primary endpoint.

The full analysis set (FAS) included all patients who underwent randomization, received at least one dose of JMT103 and had at least one available post-baseline endpoint result. Safety analysis set (SS) included all patients who received at least one dose of JMT103. The baseline characteristics, bone turnover biomarkers, and efficacy were analyzed in the FAS. The safety outcomes were analyzed in the SS.

Descriptive statistics (such as count, percentage, mean, standard deviation, median, minimum, and maximum) were used to measure demographic parameters, baseline characteristics parameters, Pharmacokinetics (PK) parameters, and safety outcomes as appropriate. The Kaplan–Meier method was used for time-to-event endpoints, and 95% CIs were estimated for each group. Hazard ratios (using Cohort 3 as a reference) and the corresponding 95% CIs were estimated using a stratified Cox regression model. All statistical analyses were done by SAS software (version 9.4) unless otherwise stated.

3 | RESULTS

3.1 | Patient disposition

Between November 3, 2020, and March 31, 2023, a total of 423 patients were screened; 295 were randomized; and 293 received at least one dose of JMT103. The distribution of patients between

the groups was cohort 1: $n = 96$, cohort 2: $n = 97$, and cohort 3: $n = 100$. As of March 31, 2023, of the patients who underwent randomization, 148 (50.2%) completed the study, and 147 (49.8%) discontinued it (Figure 1).

The demographic and baseline characteristics were generally balanced among the three dose cohorts (Table 1). A total of 63.5% of the patients were female, and the mean (standard deviation [SD]) age was 57.9 (10.7) years, with a mean (SD) Body Mass Index (BMI) of 23.9 (3.5) kg/m^2. The most common tumor types were breast cancer (49.5%) and prostate cancer (15.0%). And 186 (63.5%) had previously used bisphosphonates.

3.2 | Efficacy

3.2.1 | Bone metabolism

The change in uNTx/Cr by study week in all patients and patients with breast cancer and prostate cancer is shown in Figures 2 and S1. Reduction in uNTx/Cr was observed in all three cohorts as early as study Week 5 (the 1st assessment) and well-maintained through Week 49. The median percent reduction in uNTx/Cr from baseline to Week 13 was 80.0% (interquartile range [IQR]:49.9%, 93.4%) in Cohort 1, 73.0% (IQR: 34.5%, 94.0%) in Cohort 2, and 75.7% (IQR: 40.4%, 92.0%) in Cohort 3, respectively. For patients with breast cancer, the median percent reduction in uNTx/Cr from baseline to Week 13 was 79.5% (IQR: 40.7%, 93.1%) in Cohort 1, 69.7% (IQR: 34.1%, 89.5%) in Cohort 2, and 74.6% (IQR: 41.6%, 89.7%) in Cohort 3; for patients with prostate cancer, the median percent reduction in uNTx/Cr from baseline to Week 13 was 85.0% (IQR: 42.4%, 95.1%) in Cohort 1, 72.8% (IQR: 66.2%, 94.8%) in Cohort 2, and 92.3% (IQR: 59.4%, 97.2%) in Cohort 3, respectively.

Overall, 58.3% of patients in cohort 1 achieved a more than 65% reduction in uNTx/Cr from baseline to Week 13, compared with 50.5% of patients in cohort 2 and 51.0% of patients in cohort 3.

Similar reductions were also observed in other bone turnover markers, sCTX-I and bALP (Figures S2 and S3). At study Week 13, levels of sCTX-I decreased by a median of 81.7% (IQR: 60.3%, 94.1%) in Cohort 1, 81.6% (IQR: 48.5%, 92.8%) in Cohort 2 and 77.5% (IQR: 29.8%, 94.4%) in Cohort 3; and bALP decreased by 27.1% (IQR: 3.4%, 45.9%) in Cohort 1, 26.4% (IQR: 7.0%, 50.7%) in Cohort 2, and 18.7% (IQR: 2.9%, 35.4%) in Cohort 3, respectively.

3.2.2 | Skeletal-related events

During the 49-week treatment period, the percentage of patients experiencing an on-study SRE was 3.1% (3 out of 96) in Cohort 1, 6.2% (6 out of 97) in Cohort 2, and 7.0% (7 out of 100) in Cohort 3. The most common SRE was fracture (Table S1), and the median time to the first on-study SRE was not estimable.

3.2.3 | Pain severity

The percentage of patients with meaningful improvement (a decrease ≥2 points) in the worst pain score was similar among the three dose cohorts throughout the study (Figure 3). Among the patients with a baseline BPI-SF pain score ≥2 points, 22 (61.1%) in Cohort

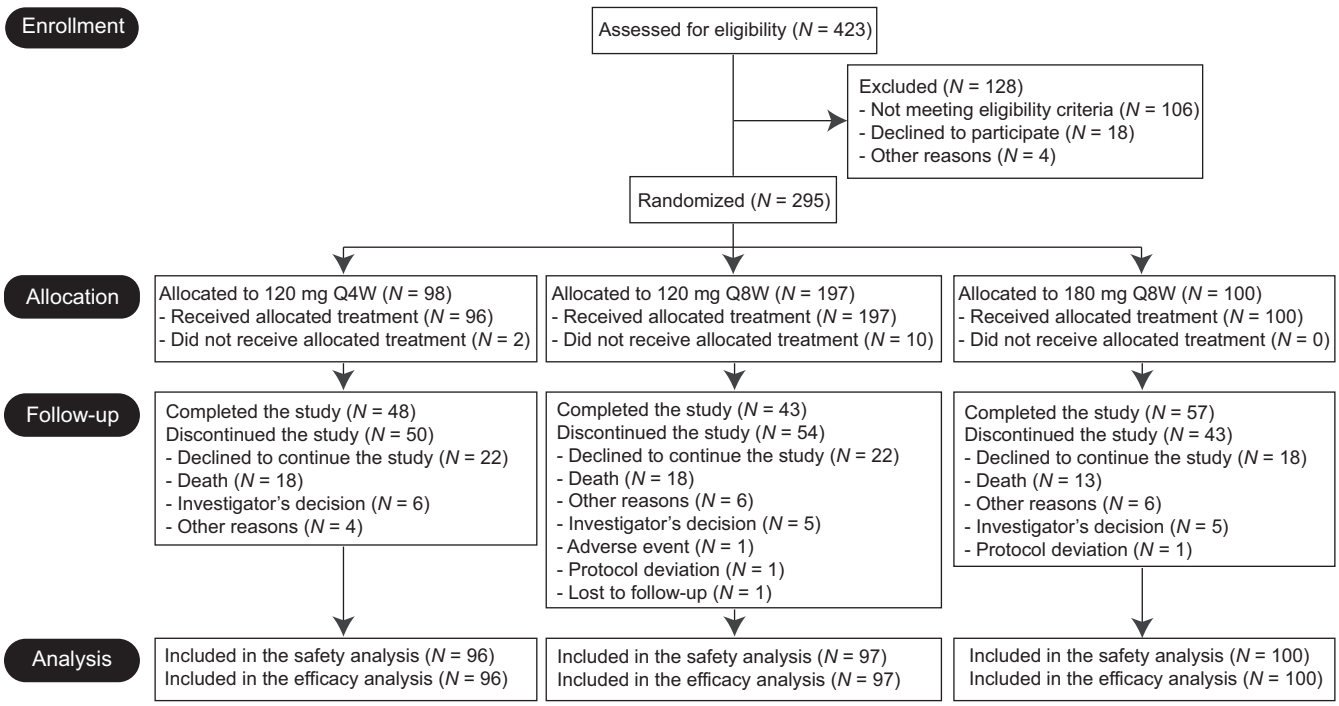

FIGURE 1 Patient disposition.

TABLE 1 Demographic and disease characteristics of patients at baseline (full analysis set).

Characteristic	120 mg Q4W (*N* = 96)	120 mg Q8W (*N* = 97)	180 mg Q8W (*N* = 100)
Age, years, mean (SD)	57.7 (10.6)	57.4 (10.9)	58.5 (10.5)
Sex			
Male	37 (38.5)	31 (32.0)	39 (39.0)
Female	59 (61.5)	66 (68.0)	61 (61.0)
Body mass index, kg/m^2, mean (SD)	23.7 (3.3)	24.2 (4.1)	23.7 (3.2)
Eastern Cooperative Oncology Group (ECOG) performance status			
0	40 (41.7)	36 (37.1)	35 (35.0)
1	54 (56.3)	57 (58.8)	63 (63.0)
2	2 (2.1)	4 (4.1)	2 (2.0)
Tumor type			
Prostate cancer	15 (15.6)	13 (13.4)	16 (16.0)
Breast cancer	46 (47.9)	49 (50.5)	50 (50.0)
Other cancers[a]	35 (36.5)	35 (36.1)	34 (34.0)
No. of prior systemic treatments			
1 line	76 (79.2)	80 (82.5)	77 (77.0)
2 lines	25 (26.0)	33 (34.0)	34 (34.0)
3 lines	15 (15.6)	18 (18.6)	10 (10.0)
>3 lines	12 (12.5)	8 (8.2)	8 (8.0)
Type of prior systemic treatments			
Prior chemotherapy	71 (74.0)	66 (68.0)	60 (60.0)
Prior endocrine therapy	47 (49.0)	39 (40.2)	52 (52.0)
Prior targeted therapy	30 (31.3)	16 (16.5)	23 (23.0)
Prior immunotherapy	3 (3.1)	6 (6.2)	3 (3.0)
Time since the diagnosis of bone metastases, days, median (IQR)	157.0 (50.0, 573.0)	195.5 (41.5, 503.5)	155.0 (40.0, 492.0)
Number of bone metastases per patient, median (IQR)	2 (1, 3)	2 (1, 4)	3 (1, 4)
Sites of bone metastases			
Spine	77 (80.2)	79 (81.4)	79 (79.0)
Rib	51 (53.1)	54 (55.7)	56 (56.0)
Pelvis	56 (58.3)	57 (58.8)	60 (60.0)
Femur	16 (16.7)	22 (22.7)	29 (29.0)
Other sites	37 (38.5)	41 (42.3)	44 (44.0)

Note: Data are expressed as count (percentage) unless otherwise specified. *N*, count.
Abbreviations: IQR, interquartile range; Q4W, every 4 weeks; Q8W, every 8 weeks; SD, standard deviation.
[a]Other cancers include submaxillary gland tumor, lung cancer, gastric cancer, cervix cancer, thymoma, thymic carcinoma, nasopharyngeal carcinoma, colorectal cancer, anal cancer, ampullary cancer, bladder cancer, renal cancer, liver cancer, and malignant mixed mesodermal tumor.

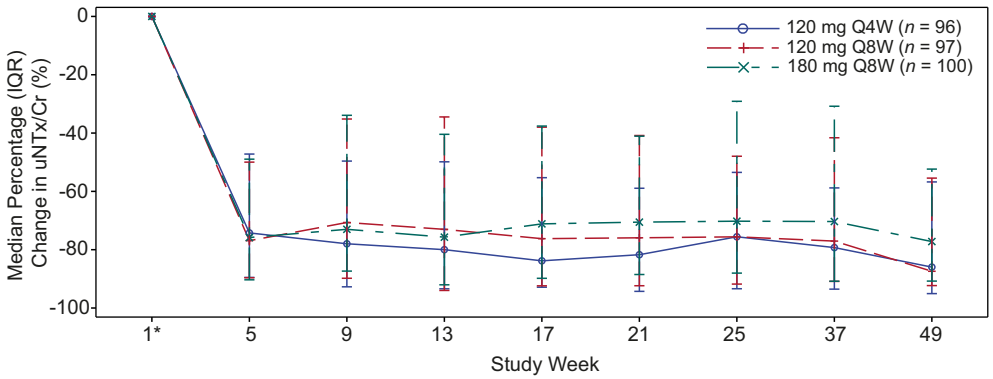

FIGURE 2 Median percentage change (IQR) from baseline in creatinine-adjusted urinary N-telopeptide (uNTx/Cr). *Baseline.

1, 17 (45.9%) in Cohort 2, and 22 (53.7%) in Cohort 3 already had a clinically meaningful improvement in pain score on the first visit on Day 15. Ameliorating pain severity was also similar among the three cohorts (Figure S4). The proportion of patients with no pain increased from 52.6% at baseline to 79.1% at Week 49 in Cohort 1, 45.7% to 61.9% in Cohort 2, and 47.4% to 58.5% in Cohort 3.

3.3 | Safety

Two hundred ninety-three patients who received at least one dose of JMT103 were included in the safety analysis (96 patients in Cohort 1, 97 in Cohort 2, and 100 in Cohort 3). The median of the total exposure of JMT103 was 1440 (IQR: 720, 1560) mg in Cohort 1, 720 (IQR: 360, 840) mg in Cohort 2, and 1260 (IQR: 720, 1260) mg in Cohort 3.

In total, 289 (98.6%) of 293 patients reported at least one TEAE, of whom 157 patients reported grade ≥3 TEAEs and 82 reported serious TEAEs (Table 2). A summary of TEAEs with a frequency of ≥10% in at least one cohort is provided in Table 3. The incidence of all-grade or grade ≥3 TEAEs was similar across all cohorts (Table 3). The most common TEAEs (all grades) were white blood cell count decreased ($n = 132$, 45.1%), anemia ($n = 125$, 42.7%), neutrophil count decreased ($n = 120$, 41.0%), hypocalcemia ($n = 83$, 28.3%), aspartate aminotransferase increase ($n = 82$, 28.0%), and hypophosphatemia ($n = 79$, 27.0%). The percentage of patients reporting hypocalcemia was numerically lower in Cohort 1. Hypocalcemia was reported by 22 (22.9%) patients in Cohort 1, 31 (32.0%) in Cohort 2, and 30 (30.0%) in Cohort 3. The incidence of grade ≥3 hypocalcemia was low: 0 in Cohort 1, 3 (3.1%) in Cohort 2, and 3 (3.0%) in Cohort 3.

Treatment-related adverse events (TRAEs) were experienced by 162 patients. No apparent differences were observed for the

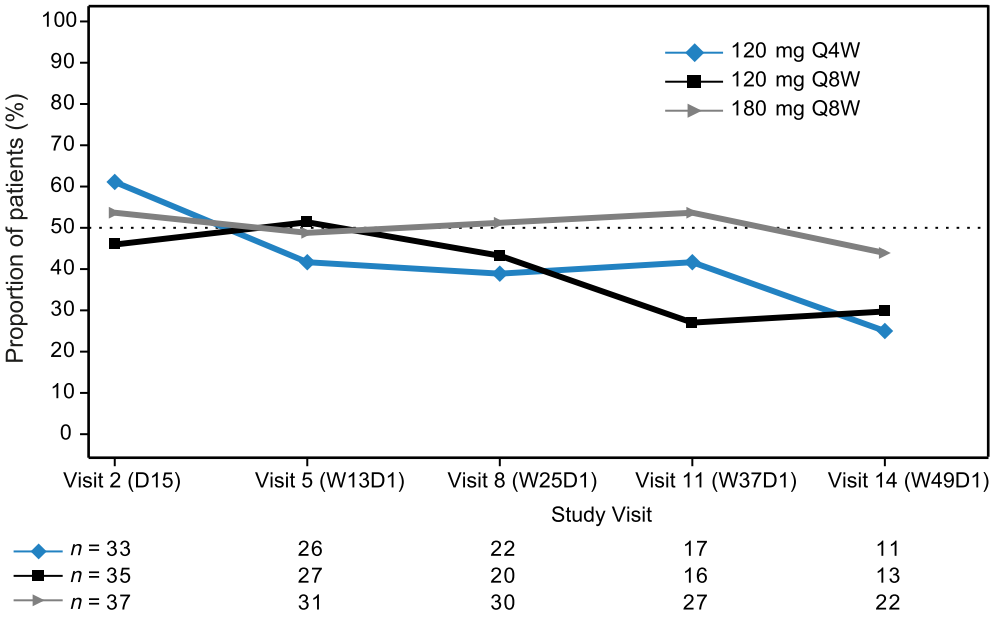

FIGURE 3 Proportion of patients who experienced a clinically relevant improvement in pain score among patients with a baseline Brief Pain Inventory-Short Form pain score ≥2 points. n = number of patients with BPI-SF pain score data at each timepoint.

TABLE 2 Overall safety summary.

	120 mg Q4W ($N = 96$)	120 mg Q8W ($N = 97$)	180 mg Q8W ($N = 100$)
TEAEs	96 (100.0)	96 (99.0)	97 (97.0)
Grade ≥3 TEAEs	54 (56.3)	56 (57.7)	47 (47.0)
Serious TEAEs	27 (28.1)	33 (34.0)	22 (22.0)
TEAEs leading to permanent discontinuation	7 (7.3)	7 (7.2)	4 (4.0)
TEAEs leading to treatment interruption	10 (10.4)	9 (9.3)	5 (5.0)
TRAEs	50 (52.1)	53 (54.6)	59 (59.0)
Grade ≥3 TRAEs	6 (6.3)	15 (15.5)	8 (8.0)
Serious TRAEs	2 (2.1)	1 (1.0)	1 (1.0)
TRAEs leading to permanent discontinuation	0	0	1 (1.0)
TRAEs leading to treatment interruption	2 (2.1)	1 (1.0)	0

Note: Data are expressed as count (percentage). *N*: count. Safety analysis set included all patients who received at least one dose of the study drug.
Abbreviations: Q4W, every 4 weeks; Q8W, every 8 weeks; TEAEs, treatment-emergent adverse events; TRAEs, treatment-related adverse events.

TABLE 3 Treatment-emergent adverse events in ≥10% of patients (safety summary).

	120 mg Q4W ($N = 96$)		120 mg Q8W ($N = 97$)		180 mg Q8W ($N = 100$)	
	All grades	≥Grade 3	All grades	≥Grade 3	All grades	≥Grade 3
Any	96 (100.0)	54 (56.3)	96 (99.0)	56 (57.7)	97 (97.0)	47 (47.0)
White blood cell count decreased	48 (50.0)	18 (18.8)	42 (43.3)	12 (12.4)	42 (42.0)	10 (10.0)
Anemia	39 (40.6)	0	43 (44.3)	0	43 (43.0)	0
Neutrophil count decreased	45 (46.9)	17 (17.7)	34 (35.1)	14 (14.4)	41 (41.0)	16 (16.0)
Hypocalcemia	22 (22.9)	0	31 (32.0)	3 (3.1)	30 (30.0)	3 (3.0)
Aspartate aminotransferase increase	25 (26.0)	2 (2.1)	27 (27.8)	2 (2.1)	30 (30.0)	3 (3.0)
Hypophosphatemia	24 (25.0)	0	24 (24.7)	1 (1.0)	31 (31.0)	0
Alanine aminotransferase increased	23 (24.0)	2 (2.1)	28 (28.9)	0	25 (25.0)	0
Platelet count decreased	27 (28.1)	6 (6.3)	21 (21.6)	7 (7.2)	25 (25.0)	6 (6.0)
Weight decreased	23 (24.0)	2 (2.1)	23 (23.7)	0	20 (20.0)	4 (4.0)
Hypokalemia	14 (14.6)	3 (3.1)	22 (22.7)	4 (4.1)	22 (22.0)	2 (2.0)
Urinary tract infection	16 (16.7)	0	17 (17.5)	0	17 (17.0)	1 (1.0)
Gamma-glutamyl transferase increased	18 (18.8)	6 (6.3)	13 (13.4)	5 (5.2)	17 (17.0)	4 (4.0)
Hypoalbuminemia	14 (14.6)	0	15 (15.5)	0	18 (18.0)	0
Hyperglycemia	13 (13.5)	0	16 (16.5)	0	16 (16.0)	0
Hypertriglyceridemia	8 (8.3)	1 (1.0)	12 (12.4)	2 (2.1)	22 (22.0)	4 (4.0)
Blood lactate dehydrogenase increased	14 (14.6)	0	14 (14.4)	0	13 (13.0)	0
Asthenia	19 (19.8)	2 (2.1)	10 (10.3)	1 (1.0)	10 (10.0)	1 (1.0)
Malignant neoplasm progression	13 (13.5)	7 (7.3)	15 (15.5)	11 (11.3)	10 (10.0)	5 (5.0)
Proteinuria	9 (9.4)	1 (1.0)	14 (14.4)	0	13 (13.0)	0
Diarrhea	12 (12.5)	0	12 (12.4)	0	10 (10.0)	0
Blood bilirubin increased	9 (9.4)	1 (1.0)	15 (15.5)	5 (5.2)	9 (9.0)	2 (2.0)
Hyponatremia	9 (9.4)	1 (1.0)	14 (14.4)	4 (4.1)	10 (10.0)	0
Weight increased	13 (13.5)	0	10 (10.3)	1 (1.0)	9 (9.0)	1 (1.0)
Blood alkaline phosphatase increased	9 (9.4)	0	14 (14.4)	1 (1.0)	9 (9.0)	1 (1.0)
Hyperuricemia	7 (7.3)	0	13 (13.4)	0	9 (9.0)	0
Constipation	8 (8.3)	0	11 (11.3)	0	10 (10.0)	0
Lymphocyte count decreased	12 (12.5)	4 (4.2)	8 (8.2)	3 (3.1)	8 (8.0)	2 (2.0)
Hypercholesterolemia	7 (7.3)	0	8 (8.2)	0	11 (11.0)	0
Upper respiratory tract infection	11 (11.5)	0	9 (9.3)	0	6 (6.0)	1 (1.0)
Decreased appetite	12 (12.5)	1 (1.0)	9 (9.3)	1 (1.0)	3 (3.0)	0
Back pain	5 (5.2)	0	4 (4.1)	0	10 (10.0)	0

Note: Data are expressed as count (percentage). *N*: count. Treatment-emergent adverse events are summarized by preferred term according to MedDRA for events occurring in ≥10% of patients in the safety analysis set that occurred. Safety analysis set included all patients who received at least one dose of the study drug.
Abbreviations: Q4W, every 4 weeks; Q8W, every 8 weeks.

incidence of TRAEs across different dose cohorts (Table S2). The most common TRAEs were hypocalcemia ($n = 68$, 23.2%), hypophosphatemia ($n = 67$, 22.9%), increased aspartate transaminase ($n = 35$, 11.9%), increased alanine aminotransferase ($n = 29$, 9.9%), and increased gamma-glutamyl transferase ($n = 24$, 8.2%).

Overall, serious treatment-emergent adverse events (SAEs) occurred in 82 (28.0%) patients, including 27 (28.1%) in Cohort 1, 33 (34.0%) in Cohort 2, and 22 (22.0%) in Cohort 3 (Table S3). No apparent dose dependency was observed. Four SAEs were judged as being possibly related to the study drug, including infective pneumonia ($n = 1$, 0.3%) and blood creatine phosphokinase increased ($n = 1$, 0.3%) in Cohort 1, anemia ($n = 1$, 0.3%) in Cohort 2, osteomyelitis ($n = 1$, 0.3%) in Cohort 3.

At database lock, a total of 40 (13.7%) deaths occurred within 90 days of the last dose of JMT103; 20 (6.8%) were due to unknown causes, 14 (4.8%) were due to disease progression, and 6 (2.0%) were due to TEAEs, of which one case in Cohort 1 was attributed to a treatment-related SAE (infective pneumonia).

In total, 268 patients were tested for anti-drug antibody (ADA) at baseline and after administration of JMT103. Only one (1%) patient in Cohort 2 tested negative at baseline but turned positive after having JMT103.

4 | DISCUSSION

In this randomized, multi-center, open-label, Phase Ib study of 293 cancer patients with bone metastasis, JMT103 showed strong suppression of bone turnover markers and a comparable safety profile to denosumab.

As demonstrated in previous studies,[21–24] suppression of bone turnover, which correlates with inhibition of osteoclast function, was predictive of fewer skeletal complications and a better prognosis in patients with bone metastasis. In the previous studies of denosumab in patients with bone metastasis, the median change of uNTx/Cr from baseline to Week 13 ranged from 40% to 78%.[11,21,24] The study of QL1206, a denosumab biosimilar, also showed a similar reduction in uNTx/Cr in Chinese patients, with a median change of uNTx/Cr from baseline to Week 13 of −75%.[25] The median reduction in uNTx/Cr at Week 13 was numerically greater with 120 mg Q4W (80.0%) versus 120 mg Q8W (73.0%) and 180 mg Q8W (75.7%). Since no relationship analysis between the pharmacokinetic of JMT103 and uNTx/Cr was planned in our study, we could only make the assumption that the difference in the reduction in uNTx/Cr for these three cohorts might be attributed to lower trough concentration of JMT103 in 120 mg Q8W and 180 mg Q8W.

A summarized report by Lipton and colleagues showed that the pooled incidence was 32.6% (934 out of 2862) from three Phase III trials of denosumab in patients with bone metastases, with a median time to first on-study SRE of 27.6 months.[26] In our study, only 16 on-study SREs occurred, and fewer patients in 120 mg Q4W cohort (3/96) had on-study SREs compared with those in the 120 mg Q8W (6/97) and 180 mg Q8W cohorts (7/100). The median time to first on-study SRE was not estimable. A previous study has confirmed that there was a positive correlation between decreased uNTx levels and reduced risk of SREs in patients with bone metastases,[27] which seems to be consistent with our findings. The relatively short study period may result in inadequate capture of the SREs, so a more extended follow-up period will be helpful for further elucidating the benefits of preventing SREs.

In addition to preventing SREs, pain relief or delaying pain worsening is especially important for maintaining quality of life in patients with bone metastases. In our study, more patients in the 120 mg Q4W cohort (79.1%) achieved no pain at Week 49 compared with those in the 120 mg Q8W (61.9%) and 180 mg Q8W cohorts (58.5%). The greater effect on pain of JMT103 120 mg Q4W over 120 mg Q8W and 180 mg Q8W was consistent with its reduction in bone turnover markers, which may be explained by its ability to suppress cancer-induced bone destruction. In the patients who had moderate or severe pain at baseline, the median time to meaningful improvement in the worst pain score was 0.5 month (IQR 0.5, 5.5) in patients in the 120 mg Q4W cohort. It is anticipated that additional pain-related indicators, including the time to pain worsening and the time to first use of opioid-type analgesic drugs, will be examined to assess the effect of JMT103 on pain palliation in future research.

In the pooled safety analysis of the three Phase III trials of denosumab (at 120 mg Q4W),[26] 96.2% of patients reported at least one TEAE. The most common TEAEs of Denosumab were nausea (30.8%), anemia (27.1%), fatigue (27.1%), back pain (25.3%), and decreased appetite (23.1%). The incidence of ≥ grade 3 hypocalcemia was 3.1%, and osteonecrosis of the jaw (ONJ) was 1.8%. In our study, the incidence of any-grade TEAEs was similar to that of denosumab, and the incidence of nausea (8.2%), back pain (6.5%), and decreased appetite (8.2%) was all numerically low, as well as the ≥ grade 3 hypocalcemia. The incidence of ≥ grade 3 hypocalcemia was as low as 2.0% in our study, with zero incidence in Cohort 1 (at 120 mg Q4W). No ONJ and no injection site reactions were reported. The potential reasons for no ONJ observed might be as follows: firstly, since the presence of delayed healing following invasive dental procedures was identified as a potential risk factor for the development of ONJ. Therefore, we excluded those patients based on their dental examination findings; secondly, previous studies[28,29] showed that the incidence rate of ONJ increased with denosumab therapy duration: the incidence of ONJ under denosumab was 0.9% in the first year, 6.2% in the second, 13.6% in the third, and 16.2% in subsequent years. JMT103 might have a lower risk of ONJ based on the 2-year results in this study. Long-term data are warranted to confirm these findings. The occurrence of ADA was also low after having JMT103, indicating a low immunogenicity. Overall, JMT103 was well tolerated in patients, which was consistent with findings from our preliminary Phase I study.[19]

Theoretically, besides the presence of disulfide scramble in IgG2,[14,15] IgG4 also exhibits unique characteristics that prevent the formation of large complexes and the activation of effector functions.[17,18] Despite the lack of observed safety advantages of JMT103 in our study, conducting investigations with an expanded sample size and an extended study period are warranted to find out its potential safety benefits.

In summary, the percentage of reduction in bone turnover marker, uNTx/Cr, was numerically greater when administered at 120 mg Q4W (80.0%) compared to 120 mg Q8W (73.0%) and 180 mg Q8W (75.7%). Additionally, the response rate of uNTx/Cr throughout the study was numerically higher with 120 mg Q4W versus 120 mg Q8W and 180 mg Q8W. Despite similar overall safety profiles among the three dosing regimens of JMT103, the incidence of hypocalcemia was numerically lower with 120 mg Q4W versus 120 mg Q8W and 180 mg Q8W. After assessing the benefit–risk evaluation of the three dose levels of JMT103, 120 mg Q4W was determined as the recommended dose.

Our study presented a few limitations, including the relatively short study period, which is too short to evaluate the full impact on SREs. A further limitation relates to statistical methods; no specific hypothesis testing was used to compare cohorts. In addition, this study did not include a standard of care as a control, so the

interpretation of the treatment effects should be cautious. A large, Phase III, randomized controlled study (NCT06221072) is ongoing to compare JMT103 120 mg Q4W and zoledronic acid in patients with advanced solid tumors bone metastases.

In conclusion, JMT103 demonstrated robust suppression in bone turnover markers and a good safety profile in patients with bone metastases from solid tumors. The recommended dose was 120 mg Q4W.

AUTHOR CONTRIBUTIONS

Ran Ran: Data curation; writing – original draft; formal analysis. **Hongtao Li:** Data curation; writing – review and editing. **Tao Sun:** Data curation; writing – review and editing. **Huan Zhou:** Data curation; writing – review and editing. **Aimin Zang:** Data curation; writing – review and editing. **Hongqian Guo:** Data curation; writing – review and editing. **Hua Xie:** Data curation; writing – review and editing. **Shikai Wu:** Data curation; writing – review and editing. **Yong Yan:** Data curation; writing – review and editing. **Xing Yin:** Data curation; writing – review and editing. **Hailin Xiong:** Data curation; writing – review and editing. **Hong Li:** Data curation; writing – review and editing; conceptualization; writing – review and editing; formal analysis. **Jing Yuan:** Software; formal analysis; writing – review and editing. **Juan Wang:** Formal analysis. **Huiping Li:** Conceptualization; formal analysis; writing – review and editing. **Jin Li:** Conceptualization; writing – review and editing; formal analysis.

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CONFLICT OF INTEREST STATEMENT

Juan Wang, Hong Li, and Jing Yuan are employees of CSPC ZhongQi Pharmaceutical Technology (Shijiazhuang) Co., Ltd. All other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The datasets (including de-identified individual data) generated during the current study are available from the corresponding author upon request. Requestors will need to submit a proposal to the corresponding author and sign a data access agreement to gain access to the data.

ETHICS STATEMENT

The study was approved by the Independent Ethics Committee at each study site and conducted following the Declaration of Helsinki and Good Clinical Practices. Written informed consent was obtained from all patients before enrollment. This study is registered with ClinicalTrials.gov: NCT04630522.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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