1. ABSTRACT

- **Title**

Prospective Observational Non-Interventional Study to Describe Characteristics and Management of Patients with Giant Cell Tumor of Bone Treated with XGEVA and its Use in Routine Clinical Practice in France

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- **Keywords**

Giant cell tumor of bone, denosumab, real-world evidence.

- **Rationale and Background**

Denosumab (XGEVA®) was shown to be effective in relieving pain and improving functional outcome in advanced giant cell tumor of bone (GCTB). It received approval for the treatment of adults and skeletally mature adolescents with GCTB that is unresectable or where surgical resection is likely to result in severe morbidity. This study provides real-world data on the characteristics of treated patients, the conditions of use of XGEVA, its impact on morbidity and patient-reported outcomes (PRO).

- **Research Question and Objectives**

The primary objective was to describe patient and disease characteristics of GCTB patients prior to XGEVA initiation. The secondary objectives were to describe treatment patterns, to evaluate effectiveness and to assess pain in GCTB patient who initiated XGEVA.

- **Study Design**

This is a multicenter, observational non-interventional, prospective study in GCTB patients receiving XGEVA.

- **Setting**

Patients were prospectively enrolled into the study from reference centers of the French Sarcoma Network between January 2018 and December 2019, only after documented evidence for the prescription of XGEVA had been obtained from a multidisciplinary meeting. Patients from other sites who initiated XGEVA treatment between January 2018 and December 2019 were retrospectively included until December 2020.

- **Subjects and Study Size, Including Dropouts**

Inclusion:

Adults (aged ≥ 18 years) or skeletally mature adolescents (aged ≥ 12 years and with weight ≥ 45 kg) with GCTB initiating a treatment with XGEVA as per French reimbursement criteria.

Exclusion:

Patients who had received prior treatment with denosumab (XGEVA or Prolia®) were excluded from the study.

According to expert opinion, the XGEVA GCTB target population is around 50 to 60 patients per year, and 25 to 40 patients were expected to be enrolled per year in the study.

- **Data Source(s) and Methods**

At each follow-up visit, the data collection was performed via a CRF by the investigator and via a patient self-reported questionnaire (BPI-SF).

The enrolment period for this study was 3 years. The first patient was enrolled on 19 February 2018, and the last patient was enrolled on 08 June 2020. Subjects who agreed to enter the study completed a baseline patient reported outcome (PRO) assessment before starting XGEVA. Patients from other sites who had initiated XGEVA treatment between January 2018 and December 2019 were also eligible to enrol into the study. These subjects could be retrospectively included until December 2020.The patient individual follow-up period was 5 years from XGEVA initiation, whether XGEVA was discontinued or not during the study period, to be able to assess treatment duration and capture retreatment with XGEVA if any.

- **Variables**

The variables for this final report were collected at inclusion and/or follow-up and included:

- Socio-demographic characteristics at XGEVA initiation.
- Disease characteristics including pulmonary metastasis at diagnosis and at initiation.
- History of GCTB targeting treatment at initiation and during the study period.
- XGEVA treatment patterns at initiation and during the study period, characterized in terms of dosage, frequency of injections, duration of treatment, XGEVA discontinuation including reason, number of XGEVA reintroductions, type and number of surgeries. The type of subsequent treatment targeting GCTB after XGEVA discontinuation will be described up to the defined end of study.
- Analgesic intake, type and reason for intake.
- BPI-SF scores at baseline and changes from baseline.
- Time to BPI-SF deterioration from initiation.
- Safety Information and Product Complaints / Adverse Drug Reactions (ADRs) and Serious Adverse Drug Reactions (SADRs).

- **Results**

Participants

Two population sets were analyzed in this study: the Modified Intent-To-Treat set (mITT1) which included all included subjects who had received at least one dose of XGEVA; i.e. at least one injection date or one XGEVA dosage is available, and the Modified Intent-To-Treat set for BPI SF analysis (mITT2) which included all mITT1 subjects with at least one available BPI-SF score at baseline.

Overall, 49 patients were screened in the study, with 45 included in the miTT1 set and 30 in the miTT2. Most patients were female in both population sets (29 [64.4%] patients in the mITT1 and 20 [66.7%] patients in the mITT2). The patients' age ranged from 15.4 to 65.5 years, with a median value of 36.0 years in mITT1, and from 17.4 to 61.2 years with a median value of 40.9 in mITT2. Median age of GCTB patients at the time of diagnosis was 35.3 years in mITT1 and 40.3 in mITT2.

Most patients were living at home, either with their family (33 [73.3%]) or alone (5 [11.1%]) in the mITT1, versus 22 [73.3%] and 5 [16.7%] in the mITT2, respectively. Secondary education was the education level most represented by patients in the mITT1 and mITT2 with 14 (31.1%) versus 12 (40.0%) patients, respectively, and with most patients being employed: (28 [62.2%]) versus (18 [60.0%]).

End of study data were available for 39 (86.7%) patients; among these, reasons for ending the study were lost to follow-up (4 patients [10.3%]), death (1 patient [2.6%]) and “other” (1 patient [2.6%]).

Tumor characteristics

Tumor characteristics at diagnosis

Mean (SD) time since diagnosis (i.e., between diagnosis and the first injection of XGEVA) was 5.5 (9.2) months.

For over half of the patients, tumors were located at the lower limb (55.6%), mainly the tibia (68.0%) and the femur (24.0%). In almost a third of patients, tumors were detected in the upper limb and shoulder (28.9%), mainly the radius (53.8%), the wrist joint (23.1%) and the humerus (15.4%). Tumors in the pelvis, sacrum or coccyx were less frequently reported (8.9%) as were tumors in the skull and facial bones (4.4%) and in the spine (4.4%).

The mean (SD) diameter of the tumor was 5.06 (1.93) cm. Soft tissue extension was observed in 40.0% of patients, fracture was observed in 11.1% of patients. No incidence of pulmonary metastasis was observed, although for 28.9% of patients, the occurrence of pulmonary metastasis was unknown.

Tumor characteristics at treatment initiation

Most patients had primary tumors at the time of treatment initiation with XGEVA (38/45 [84.4%]). Only 7 (15.6%) patients had recurrent tumors, with a mean (SD) of 1.3 (0.8) recurrences and a mean (SD) duration of 2.39 (1.18) months from last recurrence.

Of the 7 recurrent tumors, all were confirmed by MRI scans and 4 (57.1%) were biopsied. The mean (SD) diameter was 4.80 (2.55) cm (ranging from 2.5 to 9.0 cm). Soft tissue extension was observed in 3 (42.9%) patients and pulmonary metastasis in 1 (14.3%) patient. No fracture was observed in 6 (85.7%) patients and fracture was unknown in 1 (14.3%) patient.

Management of GCTB

History of GCTB targeting treatment

Before treatment initiation with XGEVA, 8/45 (17.8%) patients received tumor treatment. The treatment received was surgery for all of them. The mean (SD) time between the first surgery and XGEVA treatment initiation was 20.4 (14.2) months (ranging between 1.7 and 44.5 months). No treatment by bisphosphonates, chemotherapy, radiotherapy or other treatments were reported before XGEVA initiation.

Treatment exposure

The decision to initiate XGEVA treatment was taken by a multidisciplinary team meeting for 38/45 (84.4%) patients, as recommended by the Transparency Commission. For 5 (11.1%) patients, the decision to initiate XGEVA treatment was not taken by a multidisciplinary team, and for 2 (4.4%) patients this information was not known. Of the 45 patients in the mITT1, the tumor was potentially operable in 37 (82.2%) patients. A dosage of 120 mg XGEVA was prescribed for all patients and for all treatments.

Calcaemia was reported for 41 (91.1%) patients, and 37 (82.2%) patients were taking calcium supplementation.

Dental examination was reported for 34 (75.6%) patients of whom 20 (58.8%) patients had good dental condition and 14 (41.2%) required treatment by a specialist. Dental examination was unknown for 9 (20.0%) patients.

Finally, vitamin D supplementation was reported for 33 (73.3%) patients.

Treatment exposure during follow-up

Overall, patients had a median number of injections of 8 and ranged between 1 and 51. Median time between two injections was 5 weeks ranging between 3 and 9 weeks, more commonly (24/37 [64.9%]) spaced by less than 5 weeks. Cumulative duration of treatment was 11.6 (15.5) months.

A total of 33 (73.3%) patients discontinued XGEVA at least once during the study, with a mean (SD) time before discontinuation of 8.4 (7.6) months and a discontinuation duration of 7.6 (8.4) months. Reasons for discontinuation were mainly surgical interventions (16 [50.0%]) and classified as “other” (14 [43.8%]), only one case was allocated to an adverse event.

During follow-up, 31 patients (68.9%) underwent therapeutic surgery. The others received either definitive denosumab treatment for unresectable lesion or other reasons (n=14). Among patients who underwent therapeutic surgery and those who did not undergo surgery, the median [95% CI] number of injections was 6 [1; 34] and 21 [9; 37], respectively. The median time between injections was 4 weeks [3; 9] in the surgery group and 5 weeks [4; 5] in the no-surgery group. The cumulative duration of XGEVA treatment was 3.5 months [0.0; 33.4] for patients undergoing surgery and 16.8 months [6.2; 50.6] for patients without surgery. Treatment discontinuation and reasons for discontinuation were primarily associated with surgical interventions.

Effectiveness

TTP and PFS

Regarding time to progression (TTP) and progression free survival (PFS) from XGEVA initiation, 13 patients (28.89%) experienced progression; (Median) TTP and PFS [CI 95%] were not measurable (NR) [53.8-.]. Two-years progression-free survival rate were 72.9% in patients who underwent surgery and 85.7% in the other patients.

RFS

Regarding recurrence-free survival (RFS) in patients who underwent therapeutic surgery within one year after XGEVA initiation, (7 [33.33%] events); (Median) RFS [CI 95%] was (50.8) [17.4-.], disease control at 24 months concerned 11 (64.7%).

Analgesic intake

Almost half of the patients were taking analgesics (17 [47.2%]) at baseline. All patients who were taking analgesics did so to treat pain linked to the tumor and 2 (11.8%) patients to treat headaches. The most used analgesics were either Level I, non-morphine analgesics (12 [70.6%]) or Level II, weak opioid analgesics (10 [58.8%]). Analgesics intake according to occurrence of therapeutic surgery during follow-up involved overall 16 (48.5%) patients, with similar reasons for analgesic intake and type of analgesics taken.

At 24 months, one of 9 patients reported analgesic intake for pain linked to tumor in the no-surgery group. Data was not available for the therapeutic surgery group.

Patient reported outcomes

Patient reported outcome was based on BPI-SF scores.

BPI-SF scores at baseline

A total of 30 (88.2%) patients completed questionnaires at baseline. At baseline, 16 (53.3%) patients had moderate or severe pain scores. Overall, median pain severity score at baseline was 2.8, ranging from 0.0 to 6.5, with a high score representing a high pain severity score. Median pain interference score at baseline was (2.49), median: 4.5, ranging from 6.0 to 9.7, with a high score representing a high pain interference in daily life.

Pain severity score improvement

Median time to pain improvement, defined as 2 points or more decrease from baseline in worst pain score, was 2.6 (95% CI 1.9–3.8) months.

ADRs and SADRs

A total of 30 ADRs were reported in 12 (26.67%) patients, with one (2.22%) leading to treatment discontinuation. Osteonecrosis of the jaw (ADR of interest) was reported in one (2.22%) patient 37 months after XGEVA initiation which led to treatment discontinuation. No SADRs or ADRs leading to death were reported.

- **Discussion**

This study represents the first national, prospective, observational study, providing long-term data on patients with GCTB treated with XGEVA in routine practice in France. The socio-demographic characteristics of the patients enrolled in this study and their clinical and radiological disease characteristics before the initiation of XGEVA treatment were consistent with findings from previous clinical trials and reports in the literature. Median time to progression (TTP) was not reached in patients without surgery, as only 3 of 14 (21%) experienced response failure or metastasis—though these were not considered true relapses after expert review. In contrast, progression occurred in surgical patients (median TTP: 53.8 months), with seven local relapses after adjuvant denosumab and curettage/resection. Additionally, three patients treated with denosumab for prior relapse following curettage/resection appeared controlled without reoperation. Pain scores and analgesic intake generally decreased over time following XGEVA initiation. The treatment demonstrated an overall favorable safety profile, with adverse drug reactions occurring in a minority of patients; only one case led to treatment discontinuation due to osteonecrosis of the jaw, and no serious adverse events or deaths were reported.

The study provides real-world evidence of denosumab effectiveness in term of pain control and tumor response and safety in GCTB management in France, supporting its role in treating this rare disease.

- **Marketing Authorization Holder(s)**

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- **Names and Affiliations of Principal Investigators**

Principal investigators of study centers included in this final report are provided in section 3 of this report.