WHEN BONE METASTASES APPEAR, EVERYTHING CHANGES[1,2]

HER PROGNOSIS

HER PRIORITIES

HER TREATMENT

SHOULDN'T HER BONE-TARGETING AGENT CHANGE TOO?

Indications

XGEVA® is indicated for the prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors.

Important Safety Information

Hypocalcemia

- Pre-existing hypocalcemia must be corrected prior to initiating therapy with XGEVA®. XGEVA® can cause severe symptomatic hypocalcemia, and fatal cases have been reported. Monitor calcium levels, especially in the first weeks of initiating therapy, and administer calcium, magnesium, and vitamin D as necessary. Concomitant use of calcimimetics and other drugs that can lower calcium levels may worsen hypocalcemia risk and serum calcium should be closely monitored. Advise patients to contact a healthcare professional for symptoms of hypocalcemia.
- An increased risk of hypocalcemia has been observed in clinical trials of patients with increasing renal dysfunction, most commonly with severe dysfunction (creatinine clearance less than 30 mL/minute and/or on dialysis) and with inadequate/no calcium supplementation. Monitor calcium level and calcium and vitamin D intake.

Hypersensitivity

- XGEVA® is contraindicated in patients with known clinically significant hypersensitivity to XGEVA®, including anaphylaxis that has been reported with use of XGEVA®. Reactions may include hypotension, dyspnea, upper airway edema, lip swelling, rash, pruritus, and urticaria. If an anaphylactic or other clinically significant allergic reaction occurs, initiate appropriate therapy and discontinue XGEVA® therapy permanently.

Drug Products with Same Active Ingredient

- Patients receiving XGEVA® should not take Prolia® (denosumab).

Please see additional Important Safety Information throughout.

XGEVA®
(denosumab) injection
120 mg/1.7 mL vial

Now that she has bone metastases

Delay devastating bone complications* in your metastatic breast cancer patients with XGEVA®[3,4]

XGEVA® Q4W PREVENTED BONE COMPLICATIONS FOR > 2 YEARS[3,4]

~60%

of mBC patients were **free from bone complications** at 27 months (study end)

Median time for first on-study bone complication: 26.4 months for ZA, was not reached for denosumab

18%

risk reduction vs ZA

HR† =0.82
(95% CI: 0.71-0.95);
P=0.010‡

Study design: Based on a phase 3, double-blind, double-dummy, active-controlled trial comparing XGEVA® with ZA for the prevention of bone complications in patients with breast cancer and bone metastases (XGEVA®: n=1,026; ZA: n=1,020). Patients were randomized 1:1 to receive 120 mg XGEVA® subcutaneously (SC) every 4 weeks or 4 mg ZA intravenously (IV) every 4 weeks. Per label, the IV product was dose-adjusted for baseline creatinine clearance ≤ 60 mL/min. No dose adjustments were made and no doses were withheld, for increased serum creatinine for the SC product. **Median time from bone metastasis diagnosis to study randomization was 2 months.**[3,4]

The primary endpoint was noninferiority of time to first bone complication as compared with ZA. If the primary endpoint of noninferiority was met, the superiority test for secondary endpoints was conducted, including time to first bone complication and time to first and subsequent bone complications.[3,4]

*Bone complications, also known as skeletal-related events (SREs), are defined as radiation to the bone, pathologic fracture, surgery to bone, and spinal cord compression.[3]

†Hazard ratio (HR) is defined as the increase or decrease in likelihood of an event of interest (in this case, a bone complication for one group relative to a comparator group).

‡ *P* value for superiority.

CI, confidence interval; Q4W, every 4 weeks; ZA, zoledronic acid.

Important Safety Information (cont'd)

Osteonecrosis of the Jaw

- Osteonecrosis of the jaw (ONJ) has been reported in patients receiving XGEVA®, manifesting as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, or gingival erosion. Persistent pain or slow healing of the mouth or jaw after dental surgery may also be manifestations of ONJ. In clinical trials in patients with cancer, the incidence of ONJ was higher with longer duration of exposure.
- Patients with a history of tooth extraction, poor oral hygiene, or use of a dental appliance are at a greater risk to develop ONJ. Other risk factors for the development of ONJ include immunosuppressive therapy, treatment with angiogenesis inhibitors, systemic corticosteroids, diabetes, and gingival infections.
- Perform an oral examination and appropriate preventive dentistry prior to the initiation of XGEVA® and periodically during XGEVA® therapy. Advise patients regarding oral hygiene practices. Avoid invasive dental procedures during treatment with XGEVA®. Consider temporarily interrupting XGEVA® therapy if an invasive dental procedure must be performed.
- Patients who are suspected of having or who develop ONJ while on XGEVA® should receive care by a dentist or an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition.

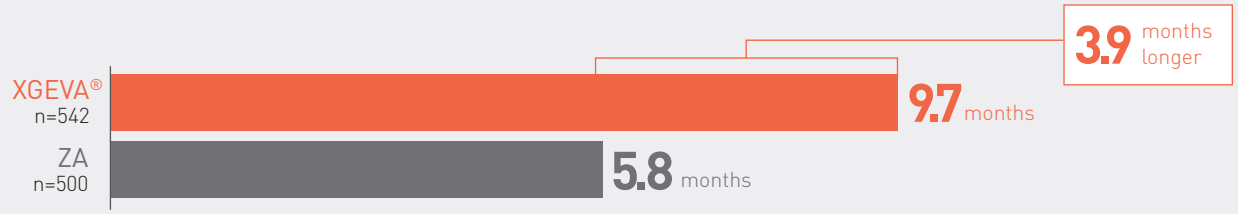
Start with XGEVA® at the first diagnosis of bone metastases[3,4]

Patients with bone complications frequently suffer from pain[5]

- 86% of patients with a bone complication experienced bone pain[§]

POST-HOC ANALYSIS: XGEVA® DELAYED PAIN FOR 3.9 MONTHS LONGER THAN ZA[6,**]

Median time to moderate/severe pain in advanced breast cancer patients[††,‡‡, §§]



- Results for castration-resistant prostate cancer patients[††]: XGEVA® (5.8 months) vs ZA (4.9 months)[7]
- Results for advanced solid tumor-only cancer patients (excluding multiple myeloma)[††]: XGEVA® (4.7 months) vs ZA (3.7 months)[8]
- Not adjusted for multiplicity or powered to assess efficacy in either arm

[§]Results collected from a retrospective study, which included 176 patients with breast cancer and bone metastases from 2008-2012. Bone complications were defined as: pathologic fracture, surgery to bone, radiation to bone, spinal cord compression, and hypercalcemia of malignancy.[5]
**Not included in US label.
[††]Time to moderate/severe worst pain was defined as the time to first post-baseline score of > 4 on the BPI-SF worst pain score in patients who had no/mild pain at baseline (BPI-SF worst pain score ≤ 4). Pain measures did not account for analgesic use.[6-9]
[‡‡]On a scale of 0 to 10. A score of ≤ 4 was considered no or mild pain and a score of > 4 was considered moderate or severe pain.[6-8]
[§§]Pain was measured every 4 weeks. Pain progression patient reported outcomes did not account for analgesic use.[6-8]
BPI-SF, Brief Pain Inventory (short form).

Important Safety Information (cont'd)

Atypical Subtrochanteric and Diaphyseal Femoral Fracture

- Atypical femoral fracture has been reported with XGEVA®. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution.
- Atypical femoral fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture. During XGEVA® treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Any patient who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patients presenting with an atypical femur fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of XGEVA® therapy should be considered, pending a risk/benefit assessment, on an individual basis.

Hypercalcemia Following Treatment Discontinuation in Patients with Giant Cell Tumor of Bone (GCTB) and in Patients with Growing Skeletons

- Clinically significant hypercalcemia requiring hospitalization and complicated by acute renal injury has been reported in XGEVA®-treated patients with GCTB and in patients with growing skeletons within one year of treatment discontinuation. Monitor patients for signs and symptoms of hypercalcemia after treatment discontinuation and treat appropriately.

Please see additional Important Safety Information throughout.

XGEVA®
(denosumab) injection
120 mg/1.7 mL vial

For superior prevention of bone complications vs ZA

Give her the XGEVA® difference right when she's diagnosed with bone metastases[3,4]

Visit **XGEVA.com/hcp/mBC** to learn more

Nearly **1.5 million people** worldwide have been treated with XGEVA®[10,*]

*Cumulative number of patients with cancer treated worldwide is calculated based on total global unit sales since 2010 and assumes patients received an average of 10 treatments.[3,10]

ZA, zoledronic acid.

XGEVA® (denosumab) injection
120 mg/1.7 mL vial

10 YEARS SERVING PATIENTS

Important Safety Information (cont'd)

Multiple Vertebral Fractures (MVF) Following Treatment Discontinuation

- Multiple vertebral fractures (MVF) have been reported following discontinuation of treatment with denosumab. Patients at higher risk for MVF include those with risk factors for or a history of osteoporosis or prior fractures. When XGEVA® treatment is discontinued, evaluate the individual patient's risk for vertebral fractures.

Embryo-Fetal Toxicity

- XGEVA® can cause fetal harm when administered to a pregnant woman. Based on findings in animals, XGEVA® is expected to result in adverse reproductive effects.
- Advise females of reproductive potential to use effective contraception during therapy, and for at least 5 months after the last dose of XGEVA®. Apprise the patient of the potential hazard to a fetus if XGEVA® is used during pregnancy or if the patient becomes pregnant while patients are exposed to XGEVA®.

Adverse Reactions

- The most common adverse reactions in patients receiving XGEVA® with bone metastasis from solid tumors were fatigue/asthenia, hypophosphatemia, and nausea. The most common serious adverse reaction was dyspnea. The most common adverse reactions resulting in discontinuation were osteonecrosis and hypocalcemia.
- For multiple myeloma patients receiving XGEVA®, the most common adverse reactions were diarrhea, nausea, anemia, back pain, thrombocytopenia, peripheral edema, hypocalcemia, upper respiratory tract infection, rash, and headache. The most common serious adverse reaction was pneumonia. The most common adverse reaction resulting in discontinuation of XGEVA® was osteonecrosis of the jaw.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

References: 1. American Cancer Society. *Cancer Facts & Figures 2020*. American Cancer Society; 2020. Accessed August 31, 2020. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf. **2.** Waks AG, Winer EP. Breast cancer treatment: a review. *JAMA*. 2019:321(3):288-300. **3.** XGEVA® (denosumab) prescribing information, Amgen. **4.** Stopeck AT, Lipton A, Body JJ, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. *J Clin Oncol*. 2010;28(35):5132-5139. **5.** Kuchuk I, Hutton B, Moretto P, et al. Incidence, consequences and treatment of bone metastases in breast cancer patients—experience from a single cancer centre. *J Bone Oncol*. 2013;2(4):137-144. **6.** Cleeland CS, Body JJ, Stopeck A, et al. Pain outcomes in patients with advanced breast cancer and bone metastases. *Cancer*. 2013;119(4):832-838. **7.** Brown JE, Cleeland C, Fallowfield L, et al. Pain outcomes in patients with bone metastases from castrate-resistant prostate cancer: results from a phase 3 trial of denosumab vs zoledronic acid. Poster presented at: 26th Annual EAU Congress; March 18-22, 2011; Vienna, Austria. Abstract 1091. **8.** Henry D, Vadhan-Raj S, Hirsh V, et al. Delaying skeletal-related events in a randomized phase 3 study of denosumab versus zoledronic acid in patients with advanced cancer: an analysis of data from patients with solid tumors. *Support Care Cancer*. 2014;22:679-687. **9.** Cleeland CS. The measurement of pain from metastatic bone disease: capturing the patient's experience. *Clin Cancer Res*. 2006;12(20 Pt 2):6236s-6242s. **10.** Data on file, Amgen; 2020.

AMGEN®