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NCCN Guidelines Panel: Multiple Myeloma/Systemic Light Chain Amyloidosis/Waldenström's Macroglobulinemia Panel

Specific Request: In response to the NCCN's request for more information, Amgen Inc. is respectfully resubmitting a request for the NCCN Multiple Myeloma/Systemic Light Chain Amyloidosis/Waldenström's Macroglobulinemia Panel to review the enclosed data and consider modifying pages MYEL-H and MS-41 of the Multiple Myeloma guidelines to include that exploratory analyses of phase 3 trial data suggest patients with newly diagnosed multiple myeloma intending to undergo autologous stem cell transplant (ASCT) may receive a progression-free survival (PFS) benefit when administered XGEVA instead of zoledronic acid to prevent skeletal-related events.

FDA Approval: XGEVA® (denosumab) is indicated for[1]:

- Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors
- Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity
- Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy

Rationale: Up to 90% of patients who are newly diagnosed with multiple myeloma develop detectable bone lesions,[2] which can lead to skeletal-related events (SREs) such as pathologic bone fracture, radiation to bone, surgery to bone, and spinal cord compression.[3] XGEVA® and bisphosphonates (such as zoledronic acid) are both approved for the prevention of SREs in patients with multiple myeloma. These bone-targeting agents act to prevent SREs by different mechanisms. Bisphosphonates bind to hydroxyapatite in bone and inhibit bone breakdown by inducing osteoclast cells to undergo apoptosis.[4] XGEVA® is a monoclonal antibody that binds to and neutralizes RANK ligand, which leads to osteoclast inhibition and a reduction in bone resorption.[5]

The ability of XGEVA® and zoledronic acid to delay SREs was compared in a phase 3 double-blind, double-dummy, randomized active-controlled trial in 1,718 patients with newly diagnosed multiple myeloma.[6] Though XGEVA® and zoledronic acid had comparable efficacy in terms of time to first on-study SRE (primary endpoint) and overall survival, an exploratory endpoint analysis showed that PFS was longer in the XGEVA® arm by 10.7 months (hazard ratio 0.82, 95% CI: 0.68 to 0.99; descriptive $P = 0.036$).[6]

Because this unexpected PFS result suggested that RANK ligand inhibition might provide an antimyeloma effect, additional PFS analyses were performed on data from the phase 3 trial to identify patient subgroups that may benefit most from XGEVA® therapy.[7] These exploratory, post-hoc analyses were performed according to intent to undergo ASCT, induction therapy, renal function, and age. Results from these analyses indicated that the PFS benefit seen with XGEVA® relative to zoledronic acid was most pronounced in the ASCT-intent subgroup. In this subgroup, the median PFS in the XGEVA® arm was 46.1 months compared with 35.7 months in the zoledronic acid arm (hazard ratio 0.65; 95% CI: 0.49 to 0.85; descriptive $P = 0.002$).[7] In the ASCT-intent subgroup, the strongest PFS benefit with XGEVA® therapy relative to zoledronic acid was seen in patients who received frontline triplet induction therapy or a bortezomib-only induction regimen. The authors of the study hypothesized that the improved PFS observed with XGEVA® may be due to a more complete osteoclast inhibition via RANK ligand neutralization that, in turn, decreases osteoclast stimulation of myeloma growth and reactivation of myeloma cells.[6,7]

The large PFS benefit seen with XGEVA® compared with zoledronic acid in these exploratory analyses led to the inclusion of this finding in the recently updated guidelines on treatment of multiple myeloma-related bone disease from the Bone Working Group of the International Myeloma Working Group.[8] These guidelines state how XGEVA® "might prolong progression-free survival in patients with newly diagnosed multiple myeloma and multiple myeloma-related bone disease who are eligible for autologous stem-cell transplantation (grade B recommendation)."[8]

Summary: Thank you for considering the enclosed material on how patients with newly diagnosed multiple myeloma intending to undergo ASCT may receive a PFS benefit when treated with XGEVA® to inhibit osteoclast function instead of zoledronic acid.

Supporting Documentation: Please find attached the accompanying reprints in support of this request:

- Raje N, et al. Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomised, controlled, phase 3 study. Lancet Oncol 2018;19:370-81.
- Terpos E, et al. Denosumab compared with zoledronic acid on PFS in multiple myeloma: exploratory results of an international phase 3 study. Blood Adv 2021;5:725-36.
- Terpos E, et al. Treatment of multiple myeloma-related bone disease: recommendations from the Bone Working Group of the International Myeloma Working Group. Lancet Oncol 2021;22:e119-e30.

Sincerely,

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REFERENCES

1. XGEVA® (denosumab) prescribing information. Thousand Oaks, CA: Amgen Inc; June 2020.
2. Roodman GD. Pathogenesis of myeloma bone disease. Leukemia 2009;23:435-41.
3. Costa L, Badia X, Chow E, Lipton A, Wardley A. Impact of skeletal complications on patients' quality of life, mobility, and functional independence. Support Care Cancer 2008;16:879-89.

4. Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. Mayo Clin Proc 2008;83:1032-45.
5. Body JJ, Facon T, Coleman RE, et al. A study of the biological receptor activator of nuclear factor-kappaB ligand inhibitor, denosumab, in patients with multiple myeloma or bone metastases from breast cancer. Clin Cancer Res 2006;12:1221-8.
6. Raje N, Terpos E, Willenbacher W, et al. Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomised, controlled, phase 3 study. Lancet Oncol 2018;19:370-81.
7. Terpos E, Raje N, Croucher P, et al. Denosumab compared with zoledronic acid on PFS in multiple myeloma: exploratory results of an international phase 3 study. Blood Adv 2021;5:725-36.
8. Terpos E, Zamagni E, Lentzsch S, et al. Treatment of multiple myeloma-related bone disease: recommendations from the Bone Working Group of the International Myeloma Working Group. Lancet Oncol 2021;22:e119-e30.