

NCCN Guidelines for Multiple Myeloma V.4.2018 – Follow-Up on 01/26/18

Guideline Page and Request	Panel Discussion/References	Institution Vote			
		YES	NO	ABSTAIN	ABSENT
<p><b>MYEL-4 and MYEL-E</b>                      Internal request: Review the FDA approval of denosumab for consideration in the guidelines.</p>	<p>Based upon review of the recent FDA approval, the panel consensus was to include denosumab as an option for all patients receiving primary myeloma therapy.</p> <p><a href="#">Denosumab Granted FDA Approval for MM.pdf</a></p>	18	1	1	6

<http://www.targetedonc.com/news/denosumab-granted-fda-approval-for-multiple-myeloma>

# Denosumab Granted FDA Approval for Multiple Myeloma

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Based on data from the phase III 482 study, denosumab (Xgeva) has been granted FDA approval for the prevention of skeletal-related events (SREs) in patients with multiple myeloma, according to Amgen, the developer of the RANK ligand inhibitor.



Results of the study, which were presented at the 16th International Myeloma Workshop in New Delhi, showed denosumab demonstrated noninferiority to zoledronic acid (Zometa) at delaying the time to the first SRE in patients with multiple myeloma (HR, 0.98; 95% CI, 0.85-1.14;  $P = .01$ ).

The median time to first on-study SRE was similar between the treatments, at 22.83 months with denosumab versus 23.98 months with the bisphosphonate zoledronic acid. The median progression-free survival was 10.7 month higher in the denosumab arm (HR, 0.82; 95% CI, 0.68-0.99;  $P = .036$ ). There was also a nonstatistically significant trend in overall survival (OS) favoring denosumab (HR, 0.90; 95% CI, 0.70-1.16;  $P = .41$ ).

"Up to 40% of patients remain untreated for the prevention of bone complications, and the percentage is highest among patients with renal impairment at the time of diagnosis," Noopur Raje, MD, director, Center for Multiple Myeloma, Massachusetts General Hospital Cancer Center, said in a statement. "Denosumab, which is not cleared through the kidneys, offers multiple myeloma patients bone protection with a convenient subcutaneous administration, providing patients with a novel treatment option."

Denosumab directly affects bone resorption through the inhibition of the RANK ligand, which is instrumental in the formation, function, and survival of osteoclasts. The monoclonal antibody was initially approved in 2010, based on a direct comparison with zoledronic acid for patients with prostate cancer, breast cancer, and other solid tumors. This trial also included patients with advanced multiple myeloma; however, the agent was not approved for this indication at that time, warranting the initiation of the 482 study.

The phase III 482 study, which began enrolling in April 2011, included 1718 patients with newly diagnosed multiple myeloma. There were 859 patients in each arm. The ECOG performance status was between 0 and 2 and all patients had adequate organ function. Creatinine clearance (CRCL) was  $\geq 30$  mL/min for all patients enrolled.

In the experimental arm, subcutaneous denosumab was administered at 120 mg along with an intravenous placebo. In the comparator arm, a subcutaneous placebo was administered along with zoledronic acid at 4 mg intravenously, with adjustments for renal function. Treatment was administered every 4 weeks in each arm.

Secondary endpoints of the study focused on superiority for the RANK ligand inhibitor versus the bisphosphonate for time to first SRE and time to first and subsequent SRE, which were defined as fracture, radiation to bone, surgery to bone, or spinal cord compression. In the initial analysis, these secondary endpoints were not met.

Adverse events (AEs) in the study were consistent with the known safety profile for denosumab. The most common AEs in the denosumab arm were diarrhea (33.5% vs 32.4% with zoledronic acid) and nausea (31.5% vs 30.4%).

Zoledronic acid has been a standard of care for patients with multiple myeloma for the prevention of SREs, since it was approved in 2002. In a 1018-patient study,<sup>1</sup> zoledronic acid reduced the risk of death by 22% and SREs by 25% compared with the bisphosphonate pamidronate in multiple myeloma. The median OS with zoledronic acid was 32.4 months compared with 23.4 months with pamidronate (HR, 0.78; 95% CI, 0.67-0.92).

In addition to other approvals, denosumab is currently indicated for the prevention of SREs in patients with bone metastases from a solid tumor, based upon 3 large studies comparing the agent with zoledronic acid in 5723 patients.<sup>2</sup> Across these trials, the median time to first SRE was 27.7 months with denosumab compared with 19.5 months with zoledronic acid (HR, 0.83; 95% CI, 0.76-0.90;  $P < .001$ ).

In the 3 trials, which used similar dosing schemes as the 482 study, the most common AEs were fatigue/asthenia, hypophosphatemia, and nausea. The most common AEs leading to discontinuation were osteonecrosis and hypocalcemia. Severe hypocalcemia, when vitamin D supplementation was utilized, was experienced by 3% of those treated with denosumab versus 1.4% with zoledronic acid. When supplements were not used, these rates were 3.9% and 1.0%, for denosumab and zoledronic acid, respectively.

Across the studies, renal-related dose adjustments or pauses were not required for patients taking denosumab. Eighteen percent of those in the zoledronic acid arm required a dose adjustment based on baseline CRCL levels. Once treatment had started, dosing pauses due to serum creatinine levels were required for 10% of patients in the zoledronic acid arm.

"Bone complications can be devastating for patients with multiple myeloma. Previously, treatment options for the prevention of bone complications were limited to bisphosphonates, which unlike Xgeva, are cleared by the kidneys," David M. Reese, MD, senior vice president of Translational Sciences and Oncology at Amgen, said in a press release. "We are pleased that the FDA has approved the expanded indication for Xgeva, providing a new option for patients and physicians, underscoring our commitment to advancing care for patients with multiple myeloma."

**References:**

1. Sanfilippo KM, Gage B, Luo S, et al. Comparative effectiveness on survival of zoledronic acid versus pamidronate in multiple myeloma. *Leuk Lymphoma*. 2015;56(3):615-621.
2. Lipton A, Fizazi K, Stopeck AT, et al. Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials. *Eur J Cancer*. 2012;48:3082-3092.

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