



Submitted by:
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Date of request: December 2, 2018
NCCN Guidelines Panel: Multiple Myeloma

On behalf of Takeda Pharmaceutical Company Limited, we respectfully request the NCCN Multiple Myeloma Panel to review the enclosed data from the TOURMALINE-MM3 trial on the use of single-agent ixazomib (NINLARO) as maintenance therapy following induction, high-dose therapy, and transplantation for patients with multiple myeloma.

Specific Changes:

- Recommend inclusion of ixazomib as a suggested Category 1 Preferred Regimen for Maintenance Therapy

FDA Clearance: Ixazomib in combination with lenalidomide and dexamethasone is approved by the US FDA for the treatment of patients with multiple myeloma who have received at least one prior therapy and this combination is listed as a category 1 recommended therapy for previously treated multiple myeloma in the Multiple Myeloma NCCN Guidelines Version 1.2019. Ixazomib is not currently approved by the US FDA as a maintenance therapy.

Rationale: The phase 3, double blind, placebo controlled, TOURMALINE-MM3 study randomized patients with newly diagnosed multiple myeloma to receive ixazomib (N=395) or placebo (N=261) maintenance therapy for 2 years following induction, high-dose therapy and transplantation.

Data from a median follow-up of 31 months in the TOURMALINE-MM3 study were presented orally at the 2018 Annual Meeting of the American Society of Hematology (ASH) and are in press with *The Lancet*, with an anticipated online publication date of Monday, December 10, 2018. Single-agent ixazomib maintenance demonstrated a 28% reduction in the risk of progression/death, corresponding to a 39% improvement in PFS. Depth of response improved during maintenance in 46% of patients in the ixazomib arm versus 32% in the placebo arm. Among patients who were positive for minimal residual

disease at study entry, 12% in the ixazomib arm converted to MRD-negativity, while 7% in the placebo arm converted. No increase in second malignancies was noted with ixazomib therapy; 3% in each arm. In the ixazomib and placebo groups, 27% versus 20% had serious adverse events.

The following enclosure is submitted in support of the above proposal:

- Dimopoulos MA, et al. "Maintenance Therapy With the Oral Proteasome Inhibitor (PI) Ixazomib Significantly Prolongs Progression-Free Survival (PFS) Following Autologous Stem Cell Transplantation (ASCT) in Patients With Newly Diagnosed Multiple Myeloma (NDMM): Phase 3 TOURMALINE-MM3 Trial", oral presentation at the 2018 Annual Meeting of the American Society of Hematology.

Yours sincerely,

A handwritten signature in blue ink, appearing to read "Stephen J. Noga". The signature is fluid and cursive, with a large, stylized initial "S" and a long, sweeping underline.

Stephen J. Noga, MD, Ph.D.
Vice President, U.S. Medical Affairs - Oncology