



Submitted by:

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Date of request: March 24, 2021

NCCN Guidelines Panel: Multiple Myeloma

On behalf of Takeda Pharmaceutical Company Limited, I respectfully request the NCCN Multiple Myeloma Panel to review the enclosed published data from the phase III TOURMALINE-MM4 trial on the use of ixazomib maintenance after primary therapy in multiple myeloma patients who are not candidates for transplant.

Specific Change: Recommend adding ixazomib as a category 1 recommendation for maintenance therapy in multiple myeloma (MM) patients who are non-transplant candidates

FDA Clearance: Ixazomib in combination with lenalidomide and dexamethasone is approved by the US FDA for the treatment of patients with MM who have received at least one prior therapy, and this combination is listed as a preferred category 1 recommended therapy for previously treated MM in the Multiple Myeloma NCCN Guidelines Version 5.2021. Ixazomib maintenance in MM transplant candidates is also listed as a category 1 recommendation in the NCCN Guidelines. Ixazomib is not currently approved by the US FDA for use as single-agent maintenance.

Rationale: Maintenance therapy has emerged as an effective option to potentially delay progression and prolong survival in MM. Approved maintenance therapies for transplant-ineligible patients are currently not available. The phase III TOURMALINE-MM4 trial is a randomized, double-blind, placebo-controlled multicenter study evaluating the efficacy and safety of up to 2 years of single-agent ixazomib maintenance following standard of care (SOC) induction therapy in 706 transplant-ineligible MM patients. Data have been published in the *Journal of Clinical Oncology*; the trial is continuing for long-term follow-up.

Ixazomib maintenance therapy following SOC induction in non-transplant newly diagnosed MM patients showed a clinically meaningful 34.1% reduction in the risk of progression or death compared to placebo. At a median follow-up of 21.1 months, median PFS was 17.4 months with ixazomib vs 9.4 months with placebo (HR 0.659, 95% CI, 0.542–0.801, $p < 0.001$). Ixazomib also demonstrated PFS benefits in

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prespecified patient subgroups, including a statistically significant benefit in patients who achieved complete or very good partial responses to initial therapy induction (median PFS, 25.6 vs 12.9 months; HR, 0.586; $P < 0.001$), and benefits in patients with stage III disease, patients aged ≥ 75 years, and patients with expanded high-risk cytogenetics.

Ixazomib maintenance also resulted in PFS benefits vs placebo regardless of age or frailty score, with 25% to 47% reductions in the risk of progression or death vs placebo. In addition, statistically significant PFS benefits were seen with ixazomib vs placebo in patients who were MRD+ post-screening (HR 0.701; $p = 0.001$) and in patients with persistent MRD+ disease (HR 0.631; $p < 0.001$).

With ixazomib vs placebo, 36.6% vs 23.2% of patients had grade ≥ 3 treatment-emergent adverse events (TEAEs); 12.9% vs 8.0% discontinued treatment because of TEAEs. Common any-grade TEAEs included nausea (26.8% vs 8.0%), vomiting (24.2% vs 4.3%), and diarrhea (23.2% vs 12.3%). There was no increase in new primary malignancies (5.2% vs 6.2%); rates of on-study deaths were 2.6% vs 2.2%.

The following enclosures are submitted in support of the above proposal:

- Bringhen S, Pour L, Benjamin R, et al. Progression-Free Survival (PFS) Benefit Demonstrated and Quality of Life (QoL) Maintained across Age and Frailty Subgroups with the Oral Proteasome Inhibitor (PI) Ixazomib Vs Placebo As Post-Induction Maintenance Therapy in Non-Transplant Newly Diagnosed Multiple Myeloma (NDMM) Patients (Pts): Analysis of the TOURMALINE-MM4 Phase 3 Trial. *Blood* 2020; 136 (Suppl 1): 30-31.
- Dimopoulos MA, Špička I, Quach H, et al. Ixazomib as Postinduction Maintenance for Patients With Newly Diagnosed Multiple Myeloma Not Undergoing Autologous Stem Cell Transplantation: The Phase III TOURMALINE-MM4 trial. *J Clin Oncol* 2020; 38(34): 4030-4041.
- Paiva B, Manrique I, Giuliani N, et al. Prognostic Importance of Measurable Residual Disease (MRD) Kinetics and Progression-Free Survival (PFS) Benefit in MRD+ Patients (Pts) with Ixazomib Vs Placebo As Post-Induction Maintenance Therapy: Results from the Multicenter, Double-Blind, Phase 3 TOURMALINE-MM4 Trial in Non-Transplant Newly Diagnosed Multiple Myeloma (NDMM) Pts. *Blood* 2020; 136 (Suppl 1): 20-21.

Yours sincerely,



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