Takeda Oncology
40 Landsdowne Street
Cambridge, MA 02139
direct: 617.551.3693
mobile: 410.419.7359
Email: stephen.noga@takeda.com

Date of request: March 27, 2020
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 on the use of ixazomib in combination with daratumumab, lenalidomide, and dexamethasone in newly diagnosed multiple myeloma (MM) patients. We also request review of the enclosed data on ixazomib in combination with daratumumab and dexamethasone in unfit and frail patients with newly diagnosed MM.

Specific Changes:

- Recommend inclusion of ixazomib plus daratumumab, lenalidomide, and dexamethasone as a suggested Category 2A regimen for Newly Diagnosed Multiple Myeloma
- Recommend inclusion of ixazomib plus daratumumab and dexamethasone as a suggested Category 2A regimen for Newly Diagnosed Multiple Myeloma

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 3.2020. Ixazomib is not currently approved by the US FDA in newly diagnosed MM or in combination with daratumumab.

Rationale: The phase II MC1686 trial treated 78 newly diagnosed multiple myeloma patients (both transplant-eligible and -ineligible) with 12 cycles of ixazomib plus daratumumab, lenalidomide, and dexamethasone, followed by ixazomib and daratumumab maintenance for 24 cycles or until progression. Patients in Arm A (n=38) received all four drugs throughout induction, while patients in Arm B (n=40) discontinued dexamethasone after the first 2 cycles. In both arms, there was a confirmed overall response rate of ≥95%, with rapid responses that deepened over initial cycles of therapy. This trial used mass

spectrometry–based immunofixation, which is significantly more sensitive than standard immunofixation and may lead to lower complete response rates than observed with less sensitive assays. In Arm B, 28% of patients were MRD-negative. The 12-month PFS and OS in Arm B were 90% and 100%, respectively. There were low rates of dose reductions in both arms, and no impact on stem cell collection.

The phase II HOVON 143 trial is studying the IMiD-free combination of ixazomib plus daratumumab and dexamethasone induction plus maintenance in newly diagnosed MM patients who are unfit or frail; this is one of the few clinical trials specifically designed for this population. Efficacy and safety data were presented for the first 23 unfit and 23 frail patients in a planned interim analysis, along with preliminary mortality data for all 132 patients included in the trial. Among 23 unfit patients, there was an overall response of 74% to induction, with a median progression-free survival of 23 months; toxicity was manageable. Among 23 frail patients, the overall response rate was 78%, with a median progression-free survival of 12 months. The preliminary early mortality rate was 2% (1/65) among unfit patients and 9% (6/67) in frail patients, primarily due to vulnerability and infections.

The following enclosures are submitted in support of the above proposal. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of some of these publications.

- Kapoor P, et al. Phase 2 Trial of Daratumumab, Ixazomib, Lenalidomide, and Modified Dose Dexamethasone in Patients with Newly Diagnosed Multiple Myeloma. Blood (2019) 134 (Supplement_1): 864.
- Kumar S, et al. Phase 2 Trial of Ixazomib, Lenalidomide, Dexamethasone and Daratumumab in Patients with Newly Diagnosed Multiple Myeloma. Blood (2018) 132 (Supplement 1): 304.
- Stege CAM, et al. Tolerability and Efficacy of Ixazomib-Daratumumab-Low Dose Dexamethasone in Unfit and Frail Newly Diagnosed Multiple Myeloma Patients. Blood (2019) 134 (Supplement_1): 695.

Yours sincerely,

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