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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 phase IV US-MM6 study on the use *i*n-class transition from bortezomib-based induction to all-oral ixazomib plus lenalidomide and dexamethasone (IRd) in transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM). As an oral regimen, IRd is suitable for home-based patients; the medications can be delivered to and taken at patients' homes and follow-up can be conducted via telemedicine when travel is an issue.

Specific Changes: Recommend inclusion of *i*n-class transition (*I*CT) of bortezomib-based induction to IRd as a suggested Category 2A Regimen as Primary Therapy for Non-Transplant Candidates

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 multiple myeloma; however, IRd is listed as an "other recommended regimen" for non-transplant candidates in the NCCN guidelines.

Rationale: Proteasome inhibitor (PI)-based therapy is a standard of care for non-transplant NDMM patients. However, long-term treatment, which is associated with improved outcomes, is often challenging in routine clinical practice outside of strictly controlled clinical trials. This disparity may be due to various factors such as older age, high comorbidity burden, socioeconomic status, ethnicity/racial differences, poor treatment adherence, burden of repeated IV/SC administration; cost; and toxicity (e.g. peripheral neuropathy with bortezomib). Additionally, patients may have difficulty with travel to receive treatment at a clinic (e.g. due to environmental conditions, travel restrictions, or social/family situations), and some patients may prefer to continue treatment outside of a hospital or clinic setting. With the aim of increasing PI-based treatment adherence and duration while maintaining quality of life (QoL), the US

MM-6 Phase IV community-based study (NCT03173092) is investigating a transition after 3 cycles of IV/SC bortezomib-based induction to all-oral IRd.

As of April 2019, 55 patients had been enrolled at 16 community study sites. The median age was 72 years (range 49-90), with 42% of patients aged ≥75 years. Forty percent of patients had ISS stage III disease, and patients had numerous comorbidities (most commonly hypertension, anemia, fatigue, renal/urinary disorders, GERD, and cardiac disorders). At a median follow-up of 6 months, 73% of patients remained on therapy.

The overall response rate was 65% following transition to IRD. Twenty-one patients (36%) had deepening of their responses after transitioning to IRd, including an 18% increase in ≥CR. The preliminary 6-month PFS rate was 91% from start of IRD and 96% from start of bortezomib-based induction. The safety profile of IRd was in line with that reported in previous ixazomib studies. The most common grade 3 adverse events (AEs) were 7% each pneumonia and syncope; the most common all-grade AEs were diarrhea, peripheral neuropathy, fatigue, cough, and nausea. Preliminary electronic patient-reported outcomes and actigraphy data from the study suggest that long-term treatment does not impact health-related quality of life measures or patient activity levels and sleep duration.
A manuscript is currently in preparation with data for 84 patients enrolled as of October 2019 and shows similar trends and no new safety signals. Nearly 100 of the planned 160 patients are currently enrolled.

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

- Rifkin RM, et al. Long-Term Proteasome Inhibitor (PI) Therapy in Community Patients (Pts) with Newly Diagnosed Multiple Myeloma (NDMM) Transitioning from Bortezomib (Btz)-Based to Ixazomib-Based Induction: Results from the US MM-6 Study in the Real World (RW) Setting. Blood (2019) 134 (Supplement_1): 1882.
- Noga SJ, et al. Real-World Treatment Patterns and Patient-Related Factors Including Quality of Life, Medication Adherence, and Actigraphy in Community Patients with Newly Diagnosed Multiple Myeloma Transitioning from Bortezomib to Ixazomib: The US MM-6 Community-Based Study. Blood (2019) 134 (Supplement_1): 3168.

Yours sincerely,

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