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NCCN Guidelines Panel: Multiple Myeloma

On behalf of Takeda Pharmaceutical Company Limited, I respectfully request the NCCN Multiple Myeloma Panel to review the enclosed data on the use of NINLARO (ixazomib) in combination with lenalidomide and dexamethasone as first-line therapy for transplant-ineligible patients with multiple myeloma. NINLARO is a registered trademark of Millennium Pharmaceuticals, Inc. Millennium Pharmaceuticals, Inc. is a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

Specific Changes:
Inclusion of new phase 1/2 data on the use of ixazomib plus lenalidomide-dexamethasone in the NCCN Clinical Practice Guidelines (NCCN Guidelines™) for Multiple Myeloma (version V2.2016); specifically, the inclusion of:

- Ixazomib/lenalidomide/dexamethasone as a suggested Preferred Regimen for Primary Therapy for Non-Transplant Candidates, on slide MYEL-D (1 of 2)

In addition, we suggest the inclusion of the new data and associated references within the narrative section of the Guidelines, specifically on pages MS-15–19 of version V2.2016, where the current data on Preferred Primary Therapy Regimens for Non-Transplant Candidates are included.

FDA Clearance: NINLARO 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. Ixazomib is not currently approved by the US FDA for the treatment of previously untreated patients with multiple myeloma.

Rationale: Data from the phase 1/2 C16005 (NCT01217957) clinical trial of weekly oral ixazomib plus lenalidomide-dexamethasone in patients with previously untreated multiple myeloma were published in *Lancet Oncology* in 2014 and preliminary long-term follow-up data were presented at the 2014 Annual Meeting of the American Society of Hematology (ASH), describing the efficacy and safety of the regimen in this setting.

Supportive data:

- A total of 65 patients were enrolled (50 to phase 2 who received a fixed dose of ixazomib 4.0 mg), of whom 42 patients did not receive ASCT
    - 25 patients received all 12 planned cycles of triplet therapy and proceeded to receive single-agent ixazomib as maintenance.
- At the initial analysis, the overall response rate (ORR) was 92%, including 58% very good partial response or better (≥VGPR) and 27% complete/stringent complete response (CR/sCR).
    - In 42 evaluable patients not receiving ASCT, the ORR was 88%, including 60% ≥VGPR and 24% CR/sCR.
- At the preliminary long-term follow-up analysis, the median progression-free survival among all 50 patients treated in phase 2 was 28.7 months.
- At the initial analysis, grade ≥3 adverse events (AEs) were reported in 75% of patients, with 63% reporting drug-related grade ≥3 AEs; these included:
    - Skin and subcutaneous tissue disorders (17% drug-related grade 3–4), neutropenia (12%), fatigue (9%), thrombocytopenia (8%), diarrhea, hypokalemia, lymphopenia, peripheral neuropathy, vomiting (each 6%), hypertension, hypophosphatemia, leukopenia, and nausea (each 5%).
- Serious AEs were reported in 43% of patients.

The following enclosures are submitted in support of the above proposed changes:

- Kumar SK, et al. Safety and tolerability of ixazomib, an oral proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma: an open-label phase 1/2 study. Lancet Oncol 2014;15(13):1503–12.
- Kumar S, et al. Long-term ixazomib maintenance is tolerable and improves depth of response following ixazomib-lenalidomide-dexamethasone induction in patients (pts) with previously untreated multiple myeloma (MM): Phase 2 study results. Blood 2014;124(21):abstract 82; data from oral presentation at the 2014 Annual Meeting of ASH.
- NINLARO® (ixazomib) capsules, for oral use. United States prescribing information, issued November 2015.

Yours sincerely,

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