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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) as a single agent or in combination with dexamethasone as therapy for patients with previously treated multiple myeloma (MM). 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 phase 1 and phase 2 data on the use of single-agent ixazomib and ixazomib with dexamethasone in the NCCN Clinical Practice Guidelines (NCCN Guidelines™) for Multiple Myeloma (version V2.2016); specifically, the inclusion of:

- Ixazomib ± dexamethasone as a suggested Preferred Regimen for Previously Treated Multiple Myeloma, on slide MYEL-D (2 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-29–35 of version V2.2016, where the current data on Preferred Regimens for Previously Treated Multiple Myeloma 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 as a single agent or in combination with dexamethasone.

Rationale: Data from two phase 1 studies (Kumar, Blood 2014, n=60 and Richardson, Blood 2014, n=60) of single-agent ixazomib in patients with relapsed and/or refractory MM (median of 4 prior lines of therapy, both studies) were published in Blood in 2014. Data from a phase 2 study of ixazomib ± dexamethasone in patients with relapsed MM not refractory to bortezomib (median of 4 prior lines of therapy) were published in Blood Cancer Journal in 2015 (n=33) and updated at the 2015 Annual Meeting of the American Society of Hematology (ASH) (n=70).

Supportive data from phase 1 studies of single-agent ixazomib:

- The maximum tolerated dose (MTD) of ixazomib was 2.0 mg/m^2 on a twice-weekly schedule and 2.97 mg/m^2 on a weekly schedule.
- On the weekly schedule (Kumar, Blood 2014) in the 30 evaluable patients treated at the

MTD, the partial response or better (≥PR) rate was 27%.
    - In 50 evaluable patients treated in the dose-escalation phase and expansion cohorts, the ≥PR rate was 18%, another 2% had a minimal response (MR), and 30% had stable disease (SD).
- In 55 evaluable patients on the twice-weekly schedule (Richardson, Blood 2014), ≥PR rate was 15%, and the rate of SD or better was 76%.
- Grade ≥3 AEs were reported in 78% (drug-related in 62%) of patients on the twice-weekly schedule and 65% (53%) of patients on the weekly schedule.
- Common drug-related grade ≥3 AEs were thrombocytopenia (37%), neutropenia (17%), and skin and subcutaneous tissue disorders (8%) on the twice-weekly schedule, and thrombocytopenia (33%), neutropenia (18%), and diarrhea (17%) on the weekly schedule.
- Peripheral neuropathy (PN) was reported in 17% (drug-related in 12%) of patients, with no grade 3 events, on the twice-weekly schedule. On the weekly schedule drug-related PN was reported in 20% of patients (2% grade 3).

Supportive data from phase 2 study of ixazomib ± dexamethasone:

- In arm A, 33 patients with relapsed MM received weekly ixazomib 5.5 mg and had dexamethasone added for suboptimal response (67% of patients); in arms B and C, 70 patients were randomized to receive ixazomib 4.0 or 5.5 mg on a weekly schedule in combination with dexamethasone 40 mg weekly (n=35 each arm).
- In arms A, B, and C, the ≥PR rate was 34%, 31%, and 51%, respectively; median duration of response was 17.4, 16.7, and 16.3 months
- Grade 3 and 4 AEs were seen in 59% and 19% of patients respectively in arm A. Grade ≥3 AEs possibly related to treatment were seen in 21% and 54% of patients in arms B and C, respectively.
- In arm A, grade 1 and 2 PN possibly related to the drug was reported in 8 and 5 patients, respectively.
- In arms B and C, PN possibly related to ixazomib was reported in 55% (all grade 1/2) and 43% (2 patients grade 3) of patients, respectively.

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

- Richardson PG, et al. Phase 1 study of twice-weekly ixazomib, an oral proteasome inhibitor, in relapsed/refractory multiple myeloma patients. Blood 2014;124(7):1038–46.
- Kumar SK, et al. Phase 1 study of weekly dosing with the investigational oral proteasome inhibitor ixazomib in relapsed/refractory multiple myeloma. Blood 2014;124(7):1047–55.
- Kumar SK, et al. Phase 2 trial of ixazomib in patients with relapsed multiple myeloma not refractory to bortezomib. Blood Cancer J 2015;4:e338.
- Kumar SK, et al. Randomized phase 2 trial of two different doses of ixazomib in patients with relapsed multiple myeloma no refractory to bortezomib. Blood 2015;126(21):abstract 3050; data from 2015 ASH Annual Meeting abstract and poster presentation.
- NINLARO® (ixazomib) capsules, for oral use. United States prescribing information, issued November 2015.

Yours sincerely,
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