Submitted by:
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Dear NCCN Multiple Myeloma Guidelines Panel Members:

On behalf of Celgene Corporation, we respectfully request that the NCCN Guidelines Panel for Multiple Myeloma review the enclosed data on the use of POMALYST® (pomalidomide) in combination with bortezomib and dexamethasone in patients with previously treated multiple myeloma (MM).

Specific Changes: Recommend an update to the guidelines regarding previously treated MM to reflect the Phase I study of the triplet combination, pomalidomide/bortezomib/dexamethasone (PVD), in patients with relapsed/refractory MM (RRMM).

FDA Clearance: POMALYST is a thalidomide analogue indicated, in combination with dexamethasone, for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of completion of the last therapy (Celgene Corporation, 2015).

Rationale for Proposed Change:
The addition of triplet combinations to the treatment landscape for multiple myeloma has expanded the therapy options for patients with RRMM in later lines of treatment where there is an unmet medical need. The use of pomalidomide in combination with existing agents such as bortezomib and dexamethasone (PVD) represents a triplet regimen which has demonstrated activity in patients with high risk disease.

The triplet combination of pomalidomide/bortezomib/dexamethasone (PVD) has been evaluated in patients with relapsed/refractory multiple myeloma (RRMM) in 2 early phase studies (Richardson et al., 2015b) (Lacy et al., 2014) and is being evaluated in an ongoing Phase III study (Richardson et al., 2015a).

The first study was a multi-center, Phase I dose escalation study (MM-005) which evaluated the efficacy and tolerability of PVD in 34 patients with lenalidomide (LEN)-refractory and proteasome inhibitor (PI)-exposed myeloma (median age, 58.5 years; median of 2 prior therapies; 56% received ≥2 prior therapies) (Richardson et al., 2015b). Response was achieved in approximately two-thirds of patients (overall response rate [ORR], 65%) and was durable for a median of 7.4 months. Most common Grade 3/4 adverse events (AEs) were mainly hematologic, including neutropenia (44%) and thrombocytopenia (26%). Additionally, AEs were generally less frequent with subcutaneous (SC) vs. intravenous (IV) bortezomib. The maximum tolerated dose from this study (pomalidomide 4 mg on Days 1-14, bortezomib 1.3 mg/m^2 IV or SC on Days 1, 4, 8 and 11 for Cycles 1-8 then on Days 1 and 8 for Cycles 9+ and dexamethasone 20 mg [10 mg for patients >75 years] on Days 1-2, 4-5, 8-9 and 11-12 for Cycles 1-8 then on Days 1-2 and 8-9 for Cycles 9+) is being evaluated in the ongoing Phase III (MM-007 OPTIMISMM) study in 782 patients (Richardson et al., 2015a). The primary endpoint of the Phase III study is progression-free survival (PFS) with a secondary endpoint of overall survival; results have not yet been reported.

In a Phase I/II study, 50 patients with LEN-refractory MM (median age, 66 years; median of 3 prior therapies) received pomalidomide 4 mg on Days 1-21, bortezomib 1.0 mg/m^2 (or 1.3 mg/m^2 in Dose

Level 2) IV on Days 1, 8, 15 and 22 and dexamethasone 40 mg on Days 1, 8, 15 and 22 in 28-day cycles (Lacy et al., 2014). Response rates were high (81%), including among high risk patients (82%). Patients remained progression-free for a median of 17.7 months, with 72% of patients progression-free. At a median follow-up of 9 months, 96% of patients were alive and 66% of patients remained on study. The most common AEs, at least possibly treatment-related, were cytopenias although the majority of these were Grade 1/2. Deep venous thrombosis/pulmonary embolism (DVT/PE) was uncommon, occurring in only 1 patient.

The following enclosures are submitted in support of the above proposed changes: Lacy et al., 2014; Richardson et al., 2015b.

Your consideration of this submission is greatly appreciated.

Sincerely,

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Associate Director, Global Medical Information

Peg Squier
Vice President, US Medical Affairs

Cited References:

1. Celgene Corporation. Pomalyst (pomalidomide) [Package Insert]. Summit, NJ: Celgene Corporation. http://www.pomalyst.com/.
2. Lacy MQ, Laplant BR, Laumann KM, et al. Pomalidomide, Bortezomib and Dexamethasone (PVD) for Patients with Relapsed Lenalidomide Refractory Multiple Myeloma (MM) [Oral]. Oral presented at: 56th Annual Meeting and Exposition of the American Society of Hematology (ASH); December 6-9, 2014; San Francisco, CA, USA.
3. Richardson P, Bensmaine A, Doerr T, Wang J, Zaki M. MM-007: A Phase 3 Trial Comparing the Efficacy and Safety of Pomalidomide (POM) bortezomib (BORT) and Low-Dose Dexamethasone (LoDEX [PVD]) Versus BORT and LoDEX (VD) in Subjects With Relapsed or Refractory Multiple Myeloma (RRMM) [Poster]. Poster presented at: 2015 Annual Meeting of the American Society of Clinical Oncology (ASCO); May 29-June 2, 2015a; Chicago, IL USA.
4. Richardson PG, Hofmeister C, Raje NS, et al. A Phase 1, Multicenter Study of Pomalidomide, Bortezomib, and Low-Dose Dexamethasone in Patients with Proteasome Inhibitor Exposed and Lenalidomide-Refractory Myeloma (Trial MM-005) [Meeting Abstract]. Presented at: 57th Annual Meeting and Exposition of the American Society of Hematology (ASH); December 5-8, 2015b; Orlando, FL, USA. Abstract # 3036.