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Dear NCCN Multiple Myeloma Guidelines Panel:

On behalf of Celgene Corporation, we respectfully request the NCCN Guidelines Panel for Multiple Myeloma review the enclosed data for POMALYST® (pomalidomide) in multiple myeloma (MM), specifically as it relates to the current ratings contained within the NCCN Evidence Blocks.

Specific Changes: We conducted a review of the recently released NCCN evidence blocks for MM in relation to the breadth of evidence for pomalidomide in MM, including that which is referenced within the guidelines. Considering the NCCN definitions for the evidence block ratings, and based on the supporting evidence described in the Rationale section below, we request NCCN update the consistency rating for pomalidomide/dexamethasone in previously treated MM from 4 to 5.

FDA Clearance: POMALYST is a thalidomide analogue indicated, in combination with dexamethasone, for the treatment of 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:

Consistency of Pomalidomide/Dexamethasone in Previously Treated (Relapsed/Refractory) MM

Treatment with pomalidomide plus low-dose dexamethasone has demonstrated minimal variability in outcomes, consistent and substantial improvements in both progression free survival (PFS) and Overall Survival (OS) across multiple well-designed studies in relapsed/refractory MM (RRMM). These data herein are presented to support the requested change in NCCN Evidence Block consistency score from 4 to 5.

In the pivotal randomized, open-label, Phase III (MM-003) study of pomalidomide plus low-dose dexamethasone (Pom+LoDex; n=302) vs. high-dose dexamethasone (HiDex; n=153), the median progression free survival (PFS) was significantly longer with POM+LoDex (4.0 months) vs. HiDex (1.9 months; HR=.48; $P<.0001$) (San Miguel et al., 2013). The median overall survival (OS) was also significantly longer in the POM+LoDex group compared to the HiDex group (12.7 months vs. 8.1 months; HR=.74; $P=.0285$) (San Miguel et al., 2013).

Similarly, in the open-label, randomized Phase II registration study (MM-002) which compared Pom+LoDex (n=113) vs. pomalidomide alone (POM alone; n=108), the median PFS was 4.2 and 2.7 months, respectively (HR =0.68, $P =.003$) (Richardson et al., 2014). Overall response rates (ORRs) were 33% and 18% ($P = .013$), respectively, with median response duration of 8.3 and 10.7 months. Median OS was 16.5 and 13.6 months, respectively. Refractoriness to lenalidomide, or resistance to both lenalidomide and bortezomib, did not affect outcomes with POM+LoDex or POM alone.

In the Phase II IFM 2009-02 study of 84 patients with RRMM, ORR (\geq partial response [PR]) was demonstrated with both the 21-day (35%) and 28-day (34%) dosing regimens of pomalidomide (4 mg)

with dexamethasone (40 mg orally once weekly) (Leleu et al., 2013). As of data cut-off, 63% (53/84) of patients had died, including 25 (58%) patients in the 21-day and 28 (68%) patients in the 28-day groups.

Finally, although primarily designed to evaluate safety, a Phase IIIb (MM-010, STRATUS) study conducted in 682 RRMM patients further supports the efficacy of pomalidomide/dexamethasone in RRMM patients (Dimopoulos et al., 2015). ORR was 32.6%, with 0.6% complete response (CR), 7.6% very good partial response (VGPR) and 24.3% PR. Median PFS was 4.6 months and median OS was 11.9 months.

For additional information regarding the study designs, specific dosing, efficacy and safety results of these studies, please refer to the following enclosures submitted in support of the proposed changes: Leleu et al. 2013, Richardson et al. 2014 and San Miguel et al. 2013.

Your consideration of this submission is greatly appreciated.

Sincerely,



Associate Director, Global Medical Information



Peg Squier
Vice President, Medical Affairs

CITED REFERENCES:

1. Celgene Corporation. Pomalyst (pomalidomide) [Package Insert]. Summit, NJ: Celgene Corporation. <http://www.pomalyst.com/>.
2. Leleu X, Attal M, Arnulf B, et al. Pomalidomide plus low-dose dexamethasone is active and well tolerated in bortezomib and lenalidomide-refractory multiple myeloma: Intergroupe Francophone du Myelome 2009-02. *Blood*. 2013;121(11):1968-75. <http://www.ncbi.nlm.nih.gov/pubmed/23319574>.
3. Richardson PG, Siegel DS, Vij R, et al. Pomalidomide alone or in combination with low-dose dexamethasone in relapsed and refractory multiple myeloma: a randomized phase 2 study. *Blood*. 2014;123(12):1826-32. <http://www.ncbi.nlm.nih.gov/pubmed/24421329>.
4. San Miguel J, Weisel K, Moreau P, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2013;14(11):1055-66. <http://www.ncbi.nlm.nih.gov/pubmed/24007748>.