Submitted by:
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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 REVLIMID® (lenalidomide) in multiple myeloma (MM), specifically as it relates to the current scores contained within the 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 lenalidomide 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 ratings as follows:

- For lenalidomide/dexamethasone as primary therapy in non-transplant candidates, update efficacy, quality, and consistency score to 5
- For lenalidomide/dexamethasone in previously treated MM, update consistency score to 5

FDA Clearance: REVLIMID is a thalidomide analogue indicated for the treatment of patients with multiple myeloma in combination with dexamethasone. See the enclosed Revlimid Prescribing information for additional approved indications (Celgene Corporation, 2015).

Rationale for Proposed Changes:

Efficacy, Quality, and Consistency of Primary Therapy with Lenalidomide/Dexamethasone in Non-Transplant Candidates:

Significant and consistent survival advantages have been demonstrated across several randomized, controlled Phase III clinical trials of lenalidomide/dexamethasone in non-transplant patients in the front line setting, supporting the requested score changes for efficacy, quality and consistency.

In the Phase III pivotal study (MM-020, N=1623), the risk of progression or death was reduced by 28% with continuous lenalidomide/dexamethasone (Rd Continuous) treatment vs. fixed-cycle melphalan/prednisone/thalidomide (MPT); median progression free survival (PFS) was 25.5 vs 21.2 months, respectively (HR=0.72 [95% Confidence Interval (CI): 0.61-0.85, P<0.0001]) (Benboubker et al., 2014). At a median follow-up of 45.5 months, median overall survival (OS) was 58.9 months with Rd Continuous, 56.7 months with 18 cycles of lenalidomide/dexamethasone (Rd18) and 48.5 months with MPT (Rd Continuous vs. MPT, HR=.75 [95% CI, 0.62-0.90; P=.002]) (Facon et al., 2015).

In a Phase III landmark study (SWOG 0232, N=198), median PFS was 39 vs. 15 months (P=.001) in the lenalidomide/high dose dexamethasone (RD) vs. high-dose dexamethasone arms, respectively, and overall response rate (ORR) was 78% (63% ≥ very good partial response rate [VGPR]; 13% complete response [CR]) vs. 43% (16% ≥VGPR), P<0.001 (Zonder et al., 2011).

Similarly, significantly higher OS was observed in patients receiving lenalidomide/low-dose dexamethasone (Rd; 97%) vs. lenalidomide/high-dose dexamethasone (RD; 86%; P=.0002) in the Phase

III landmark (ECOG E4A03) study (Rajkumar et al., 2010). After 4 cycles, 68% of patients in the Rd arm and 79% in the RD arm (*P*=0.008) responded. At two years, the OS was 87% (95% CI: 81-93) vs. 75% (95% CI: 68-93), respectively.

Consistency with Lenalidomide/Dexamethasone in Previously Treated (Relapsed/Refractory) MM:

There has been minimal variability in outcomes for lenalidomide/dexamethasone vs. placebo/dexamethasone across two pivotal, registrational Phase III studies as well as several additional Phase III clinical trials. In the first Phase III study (MM-009), response and overall survival were significantly extended with lenalidomide/dexamethasone (ORR, 61.0%; median OS, 29.6 months) as compared with placebo/dexamethasone (ORR, 19.9% [*P* <0.001]; median OS, 20.2 months [*P* <0.001]) (Weber et al., 2007). The primary endpoint of median time to progression (TTP) was also significantly extended with lenalidomide/dexamethasone (11.1 months) as compared with placebo/dexamethasone (4.7 months [*P* <0.001]).

Similar outcomes were reported in the second Phase III study (MM-010) (Dimopoulos et al., 2007), with significantly extended response and survival reported with lenalidomide/dexamethasone (ORR, 60.2%; median OS, not reached) as compared with placebo/dexamethasone (ORR, 24.0% [*P* <0.001]; median OS, 20.6 months [*P* =0.03]). The primary endpoint of median TTP was again also significantly extended with lenalidomide/dexamethasone (11.3 months) as compared with placebo/dexamethasone (4.7 months [*P* <0.001]). Recently published data for Rd as part of triplet regimens (Stewart et al., 2015) (Dimopoulos et al., 2015) (Moreau et al., 2015) corroborate the efficacy and safety of Rd in RRMM and further support the consistency in outcomes in this patient population; as such, we recommend a change in consistency score from 4 to 5.

For additional information regarding the study designs, specific dosing, efficacy and safety results, please refer to the following enclosures submitted in support of the proposed changes: Benboubker et al. 2014, Dimopoulos et al. 2007, Facon et al. 2015, Dimopoulos et al. 2015, Moreau et al. 2015, Rajkumar et al. 2010, Stewart et al. 2015, Weber et al. 2007 and Zonder et al. 2011.

Your consideration of this submission is greatly appreciated.

Sincerely,

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Associate Director, Global Medical Information

Peg Squier
Vice President, Medical Affairs

CITED REFERENCES:

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