



Submitted by:

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Dear NCCN Multiple Myeloma Guidelines Panel:

On behalf of Celgene Corporation, we respectfully request that the NCCN Guidelines Panel for Multiple Myeloma review and consider the recently published data regarding the use of REVLIMID<sup>®</sup> (lenalidomide) for the treatment of high-risk smoldering multiple myeloma (SMM).

**Specific Changes:** Consider inclusion of data demonstrating that, for patients with high-risk smoldering multiple myeloma, early intervention with lenalidomide in combination with dexamethasone followed by maintenance therapy with lenalidomide significantly delayed the time to progression to symptomatic disease and resulted in an overall survival benefit. These data also show that early intervention is not associated with unacceptable toxicity in this population. In addition, we respectfully request an update to the discussion of smoldering multiple myeloma on page MS-6 of the Multiple Myeloma Clinical Practice Guidelines to reflect the results presented in this publication.

**FDA Clearance:** REVLIMID is indicated for the treatment of (Revlimid Prescribing Information):

- Multiple myeloma, in combination with dexamethasone, in patients who have received at least one prior therapy
- Patients with transfusion-dependent anemia due to low- or intermediate-1 risk myelodysplastic syndromes (MDS) associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities
- Patients with mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib

**Rationale:**

The PETHEMA trial represents the first randomized, open-label, multicenter Phase III study, recently published in the *New England Journal of Medicine*, to investigate whether early treatment with lenalidomide/dexamethasone (Len/Dex) prolongs the time to progression (TTP) in smoldering multiple myeloma (SMM) patients at high risk of progression to active MM (Mateos et al. 2013). Patients (n=125, with n=119 evaluable for response) were randomized to receive either Len/Dex or no treatment (observation only). Patients on the Len/Dex study arm received nine 28-day cycles of lenalidomide 25 mg/day on Days 1-21 in combination with dexamethasone 20 mg on Days 1-4 and 12-15; followed by continued lenalidomide maintenance treatment at a dose of 10 mg on Days 1-21 every month for 2 years.

- At a median follow-up of 40 months (range, 27-57 months), treatment with Len/Dex resulted in a significantly longer median TTP to symptomatic disease compared to no treatment (TTP was not reached in the Len/Dex arm compared to 21 months in the observation arm; HR 0.18; 95% CI, 0.09-0.32;  $P < .001$ ).
- Overall Survival (OS) at 3 years was significantly higher in the Len/Dex arm compared to the observation arm (94% vs. 80%) (HR 0.31; 95% CI, 0.10-0.91;  $P = 0.03$ )
- Len/Dex demonstrated an overall response rate (ORR) after induction of 79%, including 14% CR. ORR following maintenance therapy improved to 90%, including 26% CR.
- The most common (>2%) Grade 3 Adverse Events (AEs) in the Len/Dex arm included asthenia (6%), infection (6%), neutropenia (5%), and rash (3%). Grade 1/2 deep vein thrombosis (DVT) was noted in 3 patients, 2 of whom had received prophylactic oral anticoagulation or aspirin. One patient had a Grade 5 AE (respiratory infection).

*Additional Data*

- A Phase II single arm pilot study evaluated the combination of carfilzomib 20/36 mg/m<sup>2</sup> on Days 1, 2, 8, 9, 15 and 16; lenalidomide 25 mg on Days 1-21 and dexamethasone 20/10mg on Days 1, 2, 8, 9, 15, 16, 22 and 23 for eight 28-day cycles in 10 high risk SMM patients (Landgren 2013).
  - After a median of 5.5 cycles (range, 2-9 cycles), 87.5% (n=7) of 8 evaluable patients obtained  $\geq$ VGPR (100% ORR). Among 5 patients with near CR (nCR), CR, or stringent CR (sCR), 4 were MRD-negative by flow cytometry.
  - Grade 3/4 hematologic AEs included lymphopenia (n=2), anemia (n=1), neutropenia (n=1) and thrombocytopenia (n=1). Grade 3/4 non-hematologic AEs included heart failure (n=1), rash/pruritus (n=2) and LFT elevation (n=1).
- A Phase II initial safety and toxicity study of single agent lenalidomide 25 mg/day on Days 1-21 for 6 28-Day cycles evaluated the potential benefit of early intervention in a high risk smoldering population. The study met its prespecified safety endpoints to allow for the Phase III expansion (Lonial et al. 2012).

Your consideration of this submission is greatly appreciated.

Sincerely,



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Cited References:

1. Landgren CO. Pilot Study: Carfilzomib, Lenalidomide, and Dexamethasone in High Risk Smoldering Multiple Myeloma [oral]. *Oral presented at: 14th Biennial International Myeloma Workshop (IMW) - International Myeloma Society* 2013; April 3-7; Kyoto; Japan.
2. Lonial S, Jacobus S, Weiss M, et al. Phase II Trial of Initial Safety and Toxicity Prior to the Phase III Trial of Lenalidomide Versus Observation Alone in Patients with Asymptomatic High-Risk Smoldering Multiple Myeloma (E3A06): A Trial Coordinated by the Eastern Cooperative Oncology Group [abstract]. *Proceedings of the 54th Annual Meeting of the American Society of Hematology (ASH)* 2012;.December 8-11; Atlanta, GA; USA: Abstract #4079.  
<https://ash.confex.com/ash/2012/webprogram/Paper54692.html>
3. Mateos MV, Hernandez MT, Giraldo P, et al. Lenalidomide plus Dexamethasone for High-Risk Smoldering Multiple Myeloma. *New England Journal of Medicine* 2013; 369(5): 438-47.  
<http://www.nejm.org/doi/full/10.1056/NEJMoa1300439>
4. Revlimid (lenalidomide) Prescribing Information. Summit, NJ: Celgene Corporation.  
<http://www.revlimid.com/>