Submitted by:
Mona Patel, PharmD
Global Medical Information
Celgene Corporation
86 Morris Avenue
Summit, NJ 07901
Ph: 908-679-7658
Email: mopatel@celgene.com
Date of Request: April 12, 2018

Dear NCCN Multiple Myeloma Guidelines Panel Members:

On behalf of Celgene Corporation, we respectfully request that the NCCN Guidelines Panel for Multiple Myeloma review recently presented data regarding the use of REVLIMID® (lenalidomide) in patients with high-risk smoldering myeloma.

Specific Change: We request inclusion within the Guidelines, information on the combination of lenalidomide/carfilzomib/dexamethasone (KRd) for high-risk smoldering myeloma as induction therapy followed by autologous stem cell transplant (ASCT), KRd consolidation and lenalidomide/dexamethasone maintenance therapy.[1]

FDA Status: REVLIMID is a thalidomide analogue indicated for the treatment of patients with MM in combination with dexamethasone and as maintenance therapy in patients with MM following autologous hematopoietic stem cell transplantation. REVLIMID is not approved for the treatment of high-risk smoldering myeloma. Please see the enclosed REVLIMID Prescribing Information.[2]

Rationale for Proposed Addition:
There are limited clinical studies which have assessed treatments for high-risk smoldering myeloma using a consistent definition for high-risk criteria. The following recently presented data by Mateos et al. adds additional evidence into this data gap.[1] In the Phase II multicenter, open-label, single-arm study (GEM-CESAR), 90 high-risk smoldering myeloma patients received KRd induction therapy followed by ASCT, KRd consolidation then maintenance therapy with lenalidomide/dexamethasone for up to 2 years.

Thirty-five patients were evaluable after KRd consolidation therapy with a 60% MRD negativity rate. In the 29 patients evaluable after the maintenance phase, ORR was 100%; including 83% sCR, 7% CR and 7% VGPR. The median follow-up was 10 months (range, 1-28) and at 28 months, PFS was 94% and OS was 98%. The most common (≥5%) Grade 3/4 toxicities in the induction phase were infections (10%), skin rash (9%) and thrombocytopenia (5%); common (≥5%) Grade 3/4 toxicities in the consolidation and maintenance phases included neutropenia (9% in both phases). Similarly, Kazandjian et al. presented data for KRd in high risk smoldering myeloma (N=18) from a Phase II study where patients were given KRd for 8 cycles followed by lenalidomide maintenance for 24 cycles; transplant eligible patients underwent stem cell collection after ≥4 cycles.[3] At a median follow up of 43.3 months, the ORR was 100%. There are many other data evaluating lenalidomide-containing regimens in high-risk smoldering myeloma.[4, 5, 6, 7, 8]

A copy of the references, along with the prescribing information is enclosed for your review. Your consideration of this submission is greatly appreciated.

Sincerely,

Mona Patel, PharmD
Associate Director, Global Medical Information

Thorsten Sperber, M.Sc.
Executive Director, US Medical Affairs

Reference List

1. Mateos M-V, Martinez-Lopez J, Rodriguez-Otera P, Ocio E, al et. Curative Strategy for High-Risk Smoldering Myeloma (GEM-CESAR): Carfilzomib, Lenalidomide and Dexamethasone (KRd) As Induction Followed By HDT-ASCT, Consolidation with Krd and Maintenance with Rd [Oral]. Oral presented at: 59th Annual Meeting and Exposition of the American Society of Hematology (ASH); December 9-12, 2017; Atlanta, GA, USA.
2. Celgene Corporation. Revlimid (lenalidomide) [Package Insert]. Summit, NJ: Celgene Corporation. http://www.revlimid.com/.
3. Kazandjian D, Korde NS, Roschewski M, et al. Sustained High Rates of Complete Response and Minimal Residual Disease Negativity after 8 Cycles of Carfilzomib (CFZ), Lenalidomide (LEN), and Dexamethasone (DEX) Followed By 2 Years of Lenalidomide Maintenance (CRd-R) in Patients with High-Risk Smoldering Multiple Myeloma: Updated Results of Clinical and Correlative Phase 2 Study [Meeting Abstract]. Presented at: 58th Annual Meeting and Exposition of the American Society of Hematology (ASH); December 3-8, 2016; San Diego, CA, USA. Abstract # 3339.
4. Mateos M-V, Hernandez M-T, Giraldo P, et al. Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. *N Engl J Med*. 2013;369(5):438-47. http://www.ncbi.nlm.nih.gov/pubmed/23902483.
5. Mateos M-V, Hernandez M-T, Giraldo P, et al. Lenalidomide plus dexamethasone versus observation in patients with high-risk smouldering multiple myeloma (QuiRedex): long-term follow-up of a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2016;17(8):1127-36. http://www.ncbi.nlm.nih.gov/pubmed/27402145.
6. Mateos M-V, Hernandez M-T, Giraldo P, et al. Sustained Overall Survival Benefit with Lenalidomide Plus Dexamethasone Versus No Treatment in Patients with Smoldering Myeloma at High Risk of Progression to Myeloma: Long Term Analysis [Meeting Abstract]. Presented at: 58th Annual Meeting and Exposition of the American Society of Hematology (ASH); December 3-8, 2016; San Diego, CA, USA. Abstract # 3308.
7. Lonial SMD, Jacobus S, Weiss MMDP, Fonseca RMD, Dhodapkar MVMD, Rajkumar SVMD. 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 [Meeting Abstract]. Presented at: 55th Annual Meeting of the American Society of Hematology (ASH); December 7-10, 2013; New Orleans, LA, USA. Abstract # 3174.
8. Ghobrial I, Caola A, Henrick P, et al. PHASE II TRIAL OF COMBINATION OF ELOTUZUMAB, LENALIDOMIDE, AND DEXAMETHASONE IN HIGH-RISK SMOLDERING MULTIPLE MYELOMA [Meeting Abstract]. Presented at: 22nd Congress of the European Hematology Association (EHA); June 22-25, 2017; Madrid, Spain. Abstract # S779.