



Submitted by:
Eulena Horne, PharmD
Celgene Corporation
400 Connell Drive
Berkeley Heights, NJ 07922
Ph: 732-652-6594
Email: ehorne@celgene.com
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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 and Prescribing Information for POMALYST[®] (pomalidomide).

Specific Changes: Based on recent approval by the FDA, recommend the use of pomalidomide as a preferred salvage therapy option for patients with multiple myeloma.

FDA Clearance: POMALYST is indicated for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate. Clinical benefit, such as improvement in survival or symptoms, has not been verified.

Rationale: On February 8, 2013, the FDA approved POMALYST for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy.

This approval was based on results from a Phase II, randomized, open-label study evaluating pomalidomide plus low-dose dexamethasone (Pom/LoDex) or pomalidomide alone (Pom alone) in patients with relapsed multiple myeloma who were refractory to their last myeloma therapy and had received lenalidomide and bortezomib (MM-002 Trial) (POMALYST Prescribing Information).

Of the 221 patients that were evaluable for response, 29.2% (95% CI 21.0, 38.5) achieved a partial response or better in the Pom/LoDex arm compared to 7.4% (95% CI 3.3, 14.1) in the Pom alone arm. The median duration of response (DOR) for patients in the Pom/LoDex arm was 7.4 months (95% CI 5.1, 9.2) while the median has not yet been reached for the Pom alone arm.

In the study, 219 patients were evaluable for safety. The most common Grade 3 or 4 adverse events (AEs) (reported in $\geq 15\%$ of patients) in the Pom/LoDex arm versus the Pom alone respectively, were neutropenia (38% and 47%), anemia (21% and 22%), thrombocytopenia (19% and 22%), and pneumonia (23% and 16%).

Additional Studies

In addition, several other studies have been recently presented or published discussing the use of POMALYST in multiple myeloma patients relapsed/refractory to lenalidomide and bortezomib:

MM-002 (Updated Analysis)

Updated results of the pivotal MM-002 study described above were recently presented at the 54th Annual Meeting of the American Society of Hematology (ASH 2012) (Jagannath et al. 2012). With a median follow-up of 14.2 months, median progression-free survival (PFS), the primary end point of the study, was 4.6 months in the Pom/LoDex arm compared with 2.6 months in the Pom alone arm; (hazard ratio [HR], 0.67; $P=0.002$). Median DOR was 8.3 months in the Pom/LoDex arm compared with 8.8 months with Pom alone ($P=0.734$), and median overall survival (OS) was 16.5 months compared with 13.6 months ($P=0.609$), respectively. The OS of the Pom alone arm includes 59% of patients who received dexamethasone upon progression.

Phase III (MM-003)

A Phase III, multicenter, randomized, open-label study compared the efficacy and safety of Pom/LoDex (N=302) versus high-dose dexamethasone (HiDex) (N=153) in patients with multiple myeloma who were refractory to both lenalidomide and bortezomib (Dimopoulos et al. 2012). PFS was significantly longer in patients who received Pom/LoDex compared with those who received HiDex (median 3.6 months vs. 1.8 months; HR, 0.45; $P<0.001$). In addition, in a pre-specified interim analysis, Pom/LoDex demonstrated a statistically significant improvement in OS that crossed the upper boundary for superiority (median OS not reached vs. 7.8 months; HR, 0.53; $P<0.001$). As a result, the Data Monitoring Committee recommended that patients who had not yet progressed in the HiDex arm should be crossed over to Pom/LoDex. The most common hematologic Grade 3/4 AEs reported in the study for patients receiving Pom/LoDex were neutropenia (42%), anemia (27%) and thrombocytopenia (21%). Grade 3/4 non-hematologic AEs included infections (24%, including pneumonia in 9%), fatigue (5%), hemorrhage and glucose intolerance (3% each).

Phase II Studies

A Phase II study investigated 2 dosing regimens of combination pomalidomide (4 mg orally daily either Days 1-21 or Days 1-28 of each 28 day cycle) and dexamethasone (40 mg orally once weekly) in 84 patients with relapsed/refractory multiple myeloma (Leleu et al. 2013). Overall response rate (ORR) was 35% and 34% for patients in the 21 day and 28 day groups, respectively. With median follow-up of 23 months, median DOR, PFS, and OS were 7.3, 4.6, and 14.9 months across both groups, respectively. All patients experienced an AE with 89% (n=40, 21 day group; n=35, 28 day group) experiencing ≥ 1 Grade 3/4 AE. AEs were primarily due to myelosuppression

In addition, several complementary Phase II studies have been published evaluating the use of Pom/LoDex in multiple myeloma patients relapsed/refractory to lenalidomide and/or bortezomib:

- Lacy MQ, Allred JB, Gertz MA, et al. Pomalidomide plus low-dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: comparison of two dosing strategies in dual-refractory disease. *Blood* 2011; 118(11): 2970-5.
- Lacy MQ, Hayman SR, Gertz MA, et al. Pomalidomide (CC4047) plus low-dose dexamethasone as therapy for relapsed multiple myeloma. *Journal of Clinical Oncology* 2009; 27(30): 5008-14.
- Lacy MQ, Hayman SR, Gertz MA, et al. Pomalidomide (CC4047) plus low dose dexamethasone (Pom/dex) is active and well tolerated in lenalidomide refractory multiple myeloma (MM). *Leukemia* 2010; 24(11): 1934-9.

Your consideration of this submission is greatly appreciated.

Sincerely,



Eulena Horne, PharmD
Senior Manager, Global Medical Information



Yasir Nagarwala, MD
Executive Director, Medical Affairs Disease Lead – Multiple Myeloma

Cited References:

1. Dimopoulos MA, Lacy MQ, Moreau P, et al. Pomalidomide in Combination with Low-Dose Dexamethasone Demonstrates a Significant Progression Free Survival and Overall Survival Advantage, in Relapsed/Refractory MM: A Phase 3, Multicenter, Randomized, Open-Label Study [oral]. *Oral presented at: 54th Annual Meeting of the American Society of Hematology (ASH) 2012; December 8-11; Atlanta, GA; USA.*
2. Jagannath S, Hofmeister CC, Siegel DS, et al. Pomalidomide with Low-Dose Dexamethasone in Patients with Relapsed and Refractory Multiple Myeloma Who Have Received Prior Therapy with Lenalidomide and Bortezomib: Updated Phase 2 Results and Age Subgroup Analysis [oral]. *Oral presented at: 54th Annual Meeting of the American Society of Hematology (ASH) 2012; December 8-11; Atlanta, GA; USA.*
3. Lacy MQ, Allred JB, Gertz MA, et al. Pomalidomide plus low-dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: comparison of two dosing strategies in dual-refractory disease. *Blood* 2011; 118(11): 2970-5. <http://www.pubmed.gov/21690557>
4. Lacy MQ, Hayman SR, Gertz MA, et al. Pomalidomide (CC4047) plus low-dose dexamethasone as therapy for relapsed multiple myeloma. *Journal of Clinical Oncology* 2009; 27(30): 5008-14. <http://www.pubmed.gov/19720894>
5. Lacy MQ, Hayman SR, Gertz MA, et al. Pomalidomide (CC4047) plus low dose dexamethasone (Pom/dex) is active and well tolerated in lenalidomide refractory multiple myeloma (MM). *Leukemia* 2010; 24(11): 1934-9. <http://www.pubmed.gov/20827286>
6. 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: IFM 2009-02 [published online ahead of print, January 14, 2013]. *Blood* 2013. <http://www.pubmed.gov/23319574>
7. Pomalyst (pomalidomide) Prescribing Information. Summit, NJ: Celgene Corporation. February 2013