

Submitted by:
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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 on the use of POMALYST® (pomalidomide) in combination with dexamethasone and carfilzomib in patients with previously treated multiple myeloma (MM).

Specific Changes: Recommend an update to the guidelines regarding previously treated MM to reflect results from two Phase I/II studies of the triplet combination pomalidomide/dexamethasone/carfilzomib described herein.

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

The addition of triplet combinations to the treatment landscape for multiple myeloma has expanded the therapy options for patients with RRMM in later lines of treatment. Despite tremendous progress, there continues to be an unmet medical need. The triplet combination of pomalidomide/dexamethasone/carfilzomib (PdC) has demonstrated activity in 2 Phase I/II studies in patients with relapsed/refractory multiple myeloma (RRMM) (Shah et al., 2013; Shah et al., 2015) (Rosenbaum et al., 2014).

The first Phase I/II study enrolled RRMM patients who were refractory to prior lenalidomide (LEN) (Shah et al., 2013; Shah et al., 2015). The maximum tolerated dose (MTD) was established as the starting dose of carfilzomib 20/27 mg/m² (20 mg on Days 1 and 2 of Cycle 1 then 27 mg) on Days 1-2, 8-9 and 15-16, pomalidomide 4 mg/day on Days 1-21 and dexamethasone 40 mg on Days 1, 8, 15 and 22 of a 28-day cycle. Response rates increased from the Phase I portion (N=32; overall response rate [ORR]; ≥ partial response [PR], 50%; clinical benefit rate [CBR]; ≥ minor response [MR]), 66%) to the Phase II portion (N=79; ORR, 70%; CBR, 83%), as did overall survival (OS; Phase I, 67% at 1 year vs. Phase II, not reached at 18 months). Responses were durable (median, 17.7 months) and patients remained progression-free for a median of 9.7 months. Treatment-related hematologic adverse events (AEs; all grades) included: neutropenia (34%), anemia (32%), thrombocytopenia (28%) and febrile neutropenia (4%). Other AEs (>15%) included fatigue (42%), dyspnea (28%), muscle spasms (18%) and diarrhea (16%).

The second Phase Ib/II study enrolled 26 RRMM patients in earlier stages of the disease, including a primary study population of proteasome inhibitor (PI)-naïve or -sensitive patients who were previously treated with LEN and/or were LEN-refractory (Rosenbaum et al., 2014). As the MTD was not reached in the Phase I portion, the enrollment for Phase II at the time of reporting was at Dose Level 3 (carfilzomib 20/27 mg/m², pomalidomide 4 mg and dex 40/20 mg weekly for cycles 1-4/5-8). Response rates were high (evaluable patients: ORR, 72%; CBR, 84%; primary study population: ORR, 77%; CBR, 91%),

achieved rapidly (\geq PR after 1 cycle, 52%) and improved with treatment (\geq PR, 79% and CBR, 89% after 4 cycles). Hematologic AEs (all grades) were reported as reversible and included neutropenia (23%), thrombocytopenia (19%) and anemia (27%). PdC-related Grade 1/2 peripheral neuropathy was reported in 35% of patients.

The following enclosures are submitted in support of the above proposed changes: Shah et al., 2013; Shah et al., 2015; Rosenbaum et al., 2014.

Your consideration of this submission is greatly appreciated.

Sincerely,



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Associate Director, Global Medical Information



Peg Squier
Vice President, US Medical Affairs

Cited References:

1. Shah JJ, Stadtmauer EA, Abonour R, et al. A Multi-Center Phase I/II Trial of Carfilzomib and Pomalidomide with Dexamethasone (Car-Pom-d) in Patients with Relapsed/Refractory Multiple Myeloma [Oral]. Oral presented at: 55th Annual Meeting of the American Society of Hematology (ASH); December 7-10, 2013; New Orleans, LA, USA.
2. Shah JJ, Stadtmauer EA, Abonour R, et al. Carfilzomib, pomalidomide, and dexamethasone (CPD) in patients with relapsed and/or refractory multiple myeloma. *Blood*. 2015. <http://www.ncbi.nlm.nih.gov/pubmed/26384354>.
3. Rosenbaum CA, Kukreti V, Zonder J, et al. Phase 1b/2 Study of Carfilzomib, Pomalidomide, and Dexamethasone (KPd) in Patients (Pts) with Lenalidomide-Exposed and/or -Refractory but Proteasome Inhibitor (PI)-Naïve or -Sensitive Multiple Myeloma: A Multiple Myeloma Research Consortium Multi-Center Study [Poster]. Poster presented at: 56th Annual Meeting and Exposition of the American Society of Hematology (ASH); December 6-9, 2014; San Francisco, CA, USA. <https://ash.confex.com/ash/2014/webprogram/Paper76549.html>