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NCCN Guidelines Panel: Multiple Myeloma Panel

On behalf of Amgen Inc., I respectfully request the NCCN Multiple Myeloma panel members to review the enclosed data on the use of Kyprolis® (carfilzomib) in combination with pomalidomide and dexamethasone patients with relapsed and/or refractory multiple myeloma (RRMM) from investigator-initiated studies.

FDA Approval: Kyprolis® (carfilzomib) for Injection is approved by the US FDA:

- in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy.
- as a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy.[1]

Carfilzomib is not currently approved by the US FDA in combination with pomalidomide and dexamethasone in patients with RRMM.

New data was recently published and presented on June 3, 2016 at the 2016 Annual Meeting of the American Society of Clinical Oncology. These data are from a phase 1/2 trial (N = 55) combining carfilzomib (K) with pomalidomide (Pom) and dexamethasone (d) in patients with RRMM:

The trial was a phase 1/2 study of primarily proteasome inhibitor (PI)-naïve/sensitive RRMM patients. If patients were treated with KPomd in the second line, they were required to have lenalidomide refractory disease; if treated in the third line or later, they were required to be refractory to or have been exposed to lenalidomide previously.[1-3] Median time from diagnosis was 7.1 years, median number of prior lines of therapy was 2, and refractory disease was present in 75% of patients. In this study, the maximum tolerated dose (MTD) was established at K 20/27 mg/m^2 and Pom 4 mg. After 4 cycles, KPomd demonstrated a ≥ partial response (PR) of 77%. After a median of 7.2 cycles, KPomd resulted in a ≥ PR of 84%, ≥ minimal response (MR) of 91%, ≥ very good partial response (VGPR) of 26%, and complete response/near complete response (CR/nCR) of 12%. In the primary population (N = 35, with 23 patients with lenalidomide-refractory disease and 10 patients whose disease had progressed on lenalidomide maintenance), ≥ PR was 86% with 14 patients treated at the MTD at the cut-off date. After a median follow-up of 18 (range 1-39) months, median progression free survival (PFS) for all 55 pts enrolled was 12.9 months and the estimated 18 month overall survival (OS) was 86.5%. There were 9 dose-limiting toxicities, all of which were asymptomatic cytopenias (eight grade 3 neutropenias and one grade 4 thrombocytopenia). Grade (Gr) 3/4 hematologic adverse events (AEs) to date included neutropenia (21%) and thrombocytopenia (7%).[3] Non-hematologic toxicities (all grades) included fatigue (60%), infection (56%), and gastrointestinal (49%).

Additional supportive data for KPomd in RRMM is noted from a phase 1/2 study (ph 1, N = 32; ph 2, N = 79):

In the phase 1 portion of a phase 1/2 study of KPomd in RRMM, the time since initial diagnosis was 5.9 years (range 1.2-13), the median number of prior regimens was 6 (range 2-12), and 100% were refractory to lenalidomide. The MTD was established during the phase 1 portion (N = 32) at the initial dose level as K 20/27 mg/m^2, Pom 4 mg, and d 40 mg.[3] The overall response rate (ORR) was 50% and the clinical benefit rate (CBR), defined as greater than or equal to MR, was 66%. The median PFS was 7.2 months (95% confidence interval [CI]: 3-9 months) after a median follow-up of 26.3 months (range 1-37 months).[3] The median OS was 20.6 months (range, 11.9-28.7 months) with a 12-month OS rate of 67%. Hematologic AEs occurred in ≥ 60% of all patients, including 11 patients with grade ≥ 3 anemia. There were no reports of grade ≥ 3 peripheral neuropathy. Among the serious AEs were grade ≥ 3 pneumonia (n = 4), grade ≥ 3 acute renal failure (n = 3), and pulmonary emboli (n = 2), and congestive heart failure (n = 1).[3] In the phase 2 portion of the study (N = 79), the median time from diagnosis was 5.1 years, and the median number of prior regimens was 6 (range 2-15).[4] Patients received a median of 5 cycles (range 1-18 cycles). Responses, which were assessed in 67 out of 72 of patients, were the following: 1 CR, 18 VGPR, 24 PR, 11 MR, 11 stable disease (SD), and 2 progressive disease, associated with an ORR of 64%.[4] Efficacy was observed in all cytological abnormalities. The median PFS and OS were 12.0 and 16.3 months, respectively, for the entire cohort. The most common grade ≥ 3 AEs occurring in > 20% of patients included fatigue (48%), neutropenia (40%), anemia (34%), and thrombocytopenia (34%), and diarrhea (20%).[4]

Supporting Documentation: The following have been submitted in support of this request:

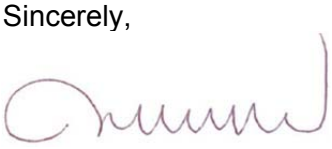
1. Rosenbaum CA, Kukreti V, Zonder J, et al. Phase 1b/2 study of carfilzomib, pomalidomide, and dexamethasone (KPd) in patients (pts) with lenalidomide-exposed and/or –refractory but proteasome inhibitor (PI)-naïve or –sensitive multiple myeloma: A Multiple Myeloma Research Consortium multi-center study. Bl*ood.* 2014;124. Abstract 2109.

2. Rosenbaum CA, Stephens LA, Kukreti V, et al. Phase 1/2 study of carfilzomib, pomalidomide, and dexamethasone (KPd) in patients (Pts) with relapsed/refractory multiple myeloma (RRMM): a multiple myeloma research consortium multicenter study. *J Clin Oncol.* 2016;34:Abstract 8007.

3. Shah JJ, Stadtmauer EA, Abonour R, et al. Carfilzomib, pomalidomide, and dexamethasone for relapsed or refractory myeloma. *Blood.* 2015;126(20):2284-2290.

4. Stadtmauer EA, Abonour R, Cohen AD et al. Phase I/II dose expansion of multi-center trial of carfilzomib, pomalidomide with dexamethaseon (Car-Pom-d) in patients with relapsed/refractory multiple myeloma. Blood, 2013;12(suppl21):Abstract 690.

Sincerely,



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