Amgen
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
Direct Dial: 800-772-6436
Fax : 866-292-6436

Submitted by:
Phuong Khanh Morrow, MD, FACP
Executive Medical Director
Amgen Inc.
One Amgen Center Drive, MS 38-2-B
Thousand Oaks, CA 91320-1799
pmorrow@amgen.com

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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 lenalidomide and dexamethasone in newly diagnosed patients who are either transplant and/or non-transplant candidates 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 patients with newly diagnosed multiple myeloma (NDMM).

New data was recently published and presented on June 10, 2016 at the 21st annual meeting of the European Hematology Association. These data are from a phase 2 trial (N = 72) with carfilzomib (K) with lenalidomide (R) and dexamethasone (d) in patients with NDMM:
In the current phase 2 study of KRd with or without autologous stem cell transplant (ASCT) in transplant-eligible (TE) patients with NDMM, 76 patients are enrolled with 72 patients evaluable.[3] At the end of 8 cycles, stringent complete response (sCR) was 72% for KRd with ASCT (n=50) vs 30% for KRd without ASCT (n=44). At the end of 18 cycles, sCR was 88% in the KRd with ASCT arm (n=26), vs 51% in the KRd without ASCT arm (n=41). At median follow-up of 17.8 months, 2-year progression-free survival (PFS) was 99% for KRd with ASCT vs 92% for KRd without ASCT at median follow-up of 47.5 months. In the KRd arm with ASCT, minimal residual disease (MRD) measured by multiparameter flow cytometry (MFC) was negative in 94% of pts tested (n=31) at the end of cycle 8 and in 95% of pts tested (n=19) at the end of cycle 18. In the KRd w/o ASCT arm, 4-year PFS was 69% overall, 78% in MRD-negative pts vs 60% in MRD-positive/unknown pts by MFC, and 100% in pts with MRD-negative status by next-generation sequencing.[3] The types and rates of adverse events (AEs) pre- and post-ASCT were comparable to AEs in KRd without ASCT. The grade ≥ 3 AEs occurring in ≥ 5% of patients were lymphopenia, thrombocytopenia, leukopenia, thromboembolic event, anemia, and hyperglycemia.[1,2]

Additional supportive data exists with KRd in NDMM from one phase 1/2 trial (N = 53) and one phase 2 trial (N= 45):
In a phase 1/2 study of KRd in patients with NDMM transplant-eligible (TE)/-ineligible (TI) (N = 53) the carfilzomib dose range was 20 to 36 mg/m^2.[4-6] Among all patients (N = 53) after a median of 24 KRd cycles, 64% of patients achieved at least a complete response (CR) and 55%

achieved sCR. The 3-year PFS was 79% and the 3-year overall survival (OS) was 96%.[5] In a sub-analysis of elderly patients aged ≥ 65 years (n = 23), 100% achieved at least a partial response (PR), 79% of patients had at least a CR, and 65% a sCR after a median of 24 cycles.[6] Grade 3/4 AEs occurring in ≥ 10% of patients were hyperglycemia, hypophosphatemia, thrombocytopenia, anemia, and neutropenia.[4]

In a phase 2 study of KRd with extended lenalidomide in NDMM and smoldering MM TE/TI (N = 45), all patients with NDMM 56% achieved CR/sCR, 89% achieved at least a very good partial response (VGPR), and 98% achieved at least a PR.[7] One-year PFS for NDMM patients was 95%.[7] There were no grade 5 toxicities were reported in NDMM patients; lymphopenia, thrombocytopenia, and neutropenia were the most common grade 3/4 AEs.[7] The dose was modified in 20 patients (44%); however, there was no discontinuation of study regimen due to treatment-related AEs.[7]

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

1. Zimmerman TM, Griffith KA, Jasielec J, et al. Phase II MMRC trial of extended treatment with carfilzomib (CFZ), lenalidomide (LEN), and dexamethasone (DEX) plus autologous stem cell transplantation (ASCT) in newly diagnosed multiple myeloma (NDMM). J Clin Oncol 33, 2015 (suppl; abstr 8510).
2. Jakubowiak AJ, Griffith K, Jasielec JK, et al. Carfilzomib (CFZ, Kyprolis®), lenalidomide (LEN, Revlimid®), and dexamethasone (DEX) (KRd) combined with autologous stem cell transplant (ASCT) shows improved efficacy compared with KRd without ASCT in newly diagnosed multiple myeloma (NDMM). *Clin Lymph Myel and Leukemia*. 2015 Vol. 15, e42. In: International Myeloma Workshop. 2015; Abstract OP-003.
3. Jakubowiak AJ, Raje N, Vij R, et al. Improve efficacy after incorporating autologous stem cell transplant (ASCT) into KRd treatment with carfilzomib (K), lenalidomide (R), and dexamethasone (d) in newly diagnosed multiple myeloma. Presented at: 21st European Hematology Association Annual Meeting; June 9-12, 2016; Copenhagen, Denmark. Abstract S101.
4. Jakubowiak AJ, Dytfeld D, Griffith KA, et al. A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. *Blood.* 2012;120:1801-1809.
5. Jasielec J, Dytfeld D, Griffith KA, et al. Predictors of treatment outcome with the combination of carfilzomib, lenalidomide, and low dose dexamethasone in newly diagnosed mulitple myeloma. *Blood*. 2013;122(21)(Suppl):Abstract 3220.
6. Dytfeld D, Jasielec J, Griffith KA, et al. Carfilzomib, lenalidomide, and low-dose dexamethasone in elderly patients with newly diagnosed multiple myeloma. *Haematologica.* 2014;99:e162-e164.
7. Korde N, Roschewski M, Zingone A, et al.. Treatment with carfilzomib-lenalidomide-dexamethasone with lenalidomide extension in patients with smoldering or newly diagnosed multiple myeloma. *JAMA Oncol*. 2015;1:746-754.

Sincerely,

Phuong Khanh Morrow, MD, FACP
Executive Medical Director