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NCCN Guidelines Panel: Multiple Myeloma

On behalf of Amgen Inc., I respectfully request the NCCN Multiple Myeloma panel members to review the enclosed data from the phase 3 CANDOR study, which demonstrated that carfilzomib (Kyprolis®) in combination with daratumumab and dexamethasone (twice weekly DKd56) significantly prolonged progression-free survival (PFS) and reduced the risk of progression or death by 37% compared with carfilzomib and dexamethasone (Kd) in patients with relapsed or refractory multiple myeloma (RRMM) who had received 1-3 prior lines of therapy.[1]

The CANDOR study[1] confirmed the efficacy and tolerability of DKd in the management of RRMM previously reported in phase 1b EQUULEUS/MMY1001 study (N=85). EQUULEUS evaluated once weekly DKd70 in patients with RRMM who had received 1-3 prior lines of therapy.[2] The unadjusted and adjusted propensity score comparison of CANDOR and EQUULEUS showed similar efficacy in terms of overall response rate (ORR) and PFS in the twice weekly DKd56 (CANDOR) and once weekly DKd70 (EQUULEUS) groups. The safety of DKd56 and DKd70 was consistent with the known safety profiles of individual study treatments.[3] The incidence of treatment-emergent grade 3 or higher, serious, and fatal adverse events was higher in the DKd arm compared to the Kd arm in the CANDOR study.[1]

FDA has approved both once weekly and twice weekly dosing of Kyprolis for the DKd combination based on the CANDOR and EQUULEUS data. [4]

Specific Requested Changes: We respectfully request your consideration to include the once weekly and twice weekly DKd regimens in the list of preferred treatment options for the treatment of RRMM.

FDA Approval:
Kyprolis is approved by the US FDA[4]:

- In combination with dexamethasone, with lenalidomide plus dexamethasone, or with daratumumab plus dexamethasone for the treatment of adult patients with RRMM who have received one to three lines of therapy.
- As a single agent for the treatment of patients with RRMM who have received one or more lines of therapy.

Rationale:
CANDOR (twice weekly DKd vs Kd study) is a phase 3, randomized, open-label, multicenter trial that compared Kyprolis® plus IV daratumumab and dexamethasone (DKd) to Kyprolis and dexamethasone (Kd) in patients with RRMM who had received 1-3 prior lines of therapy. A total of 466 patients were randomized 2:1 to receive DKd (n=312) or Kd (n=154) twice weekly for 28-day cycles until disease progression or unacceptable toxicity. Kyprolis was administered on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle (20 mg/m^2 on days 1 and 2 during cycle 1 and 56 mg/m^2 thereafter). The primary endpoint was PFS. Select secondary endpoints included ORR, minimal residual disease negative-complete response (MRD[-]CR) rate, overall survival, and safety.[1,4]

After a median follow-up of approximately 17 months, treatment with DKd resulted in a 37% reduction[1] in the risk of progression or death in patients with RRMM (hazard ratio = 0.63; 95% CI, 0.46 to 0.85; 2-sided *P* = 0.0027, 1-sided *P* = 0.0014). The median PFS for patients treated with DKd had not been reached, compared to a median PFS of 15.8 months for Kd treated patients.[1,4] The PFS benefit was generally consistent across prespecified subgroups of clinical interest, including lenalidomide-exposed and lenalidomide-refractory patients. For lenalidomide-exposed patients, median PFS was not reached in the DKd group vs 12.1 months in the Kd group (hazard ratio = 0.53; 95% CI, 0.34 to 0.82). Similarly, median PFS was not reached in the DKd group versus 11.1 months in the Kd group for patients who were lenalidomide-refractory at any prior line of treatment (hazard ratio = 0.47; 95% CI, 0.29 to 0.78).[1]

ORR was 84% in the DKd group vs 75% in the Kd group, complete response (CR) was 28% in the DKd group vs 10% in the Kd group, partial response (PR) was 15% in the DKd group vs 26% in the Kd group, and very good PR (VGPR) was 41% in the DKd group vs 38% in the Kd group. MRD[-]CR rate at 12 months was 12% in the DKd group vs 1.3% in the Kd group and MRD[-]CR rate was 14% in the DKd group vs 3.2% in the Kd group.[4]

Grade 3 or higher treatment-emergent adverse events (TEAE) were reported in 82% of patients in the DKd group and 74% of patients in the Kd group. Adverse events leading to treatment discontinuation in 22% of patients in the DKd group and 25% of patients in the Kd group. Treatment-emergent fatal adverse events occurred in 10% of patients in the KdD group and 5% of patients in the Kd group.[1]

Once-weekly dosing of DKd was demonstrated in the EQUULEUS study, a phase 1b, open-label, multi-cohort study (N=85) which evaluated the combination of once weekly Kyprolis with IV daratumumab and dexamethasone in patients with RRMM who had received 1-3 prior lines of therapy. Kyprolis was administered weekly on Days 1, 8, and 15 of each 28-day cycle (20 mg/m^2 on day 1 during cycle 1 and 70 mg/m^2 thereafter). Safety and tolerability of DKd were evaluated as primary endpoints. Median PFS was not reached for DKd in the overall population and was 25.7 months for lenalidomide-refractory patients.[2] ORR was 81%; CR or better was 35%, PR was 13% and VGPR was 33%. The most common grade 3/4 treatment-emergent adverse events were thrombocytopenia (32%), lymphopenia (25%), anemia (21%), and neutropenia (21%). Deaths due to TEAEs occurred in 3.5% of patients.[4] Results from the EQUULEUS study set a precedent for the phase 3 CANDOR study and provided the rationale for the once weekly dosing of DKd.

Supporting Documentation: The following are submitted in support of this request:

1. Dimopoulos M, Quach H, Mateos MV, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study. *Lancet* 2020;396:186-97.
2. Chari A, Martinez-Lopez J, Mateos MV, et al. Daratumumab plus carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma. *Blood* 2019;134:421-31.
3. Leleu X, Beksac M, Chou T, et al. Efficacy and safety of carfilzomib, dexamethasone, daratumumab (KdD) twice-weekly at 56 mg/m^2 and once-weekly at 70 mg/m^2 in relapsed or refractory multiple myeloma (RRMM): Cross-study comparison of candor and MMY1001. *J Clin Oncol*. 2020;38:8526-26.
4. Kyprolis® (carfilzomib) prescribing information, Amgen.

Sincerely,

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