THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

DEPARTMENT OF MEDICINE

5841 S. Maryland Avenue, MC2115
Chicago, Illinois 60637-1470
Phone 773-702-4400 · Fax 773-702-0963

Section of Hematology/Oncology

Andrzej Jakubowiak, MD, PhD
Director, Myeloma Program
900 E. 57th St.
Rm 7146
Chicago, IL 60637
Phone773-702-4400, Fax 773-702-0963
ajakubowiak@medicine.bsd.uchicago.edu

Date of request: April 11, 2016
NCCN Guidelines Panel: Multiple Myeloma Panel

Dear Colleagues:

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 and consider changing the level of recommendation for primary therapy for transplant candidates with newly diagnosed multiple myeloma (NDMM) and adding as a new recommendation for primary therapy for non-transplant candidates.

Specific Changes:

I respectfully request consideration of the submitted data on carfilzomib in combination with lenalidomide and dexamethasone in newly diagnosed myeloma to support

(1) Changing the recommendation from Other Regimens for Primary Therapy to the Preferred Primary Therapy for Transplant Candidates and
(2) Including the regimen among the Other Regimens for Primary Therapy for Non-Transplant Candidates.
(3) Including these recommendations within the narrative section of the Guidelines (version V3.2016).

Relevant to this request, 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 therap.[1]

Carfilzomib is not currently approved by the US FDA In patients with newly diagnosed multiple myeloma (NDMM).

Rationale: Supportive data in NDMM for KRd in NDMM from one phase 1/2 trial (N = 53) and two phase 2 trials (N= 45 and N = 76).

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/m2.[1-3] 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 stringent complete response (sCR). The 3-year progression-free survival (PFS) was 79% and the 3-year overall survival (OS) was 96%,[2] and at more recent update 4-year PFS was 69% and 4-year OS 93%.[6] ln 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.[3] Grade 3/4 adverse events (AEs) occurring in $\geq$ 10% of patients were hyperglycemia, hypophosphatemia, thrombocytopenia, anemia, and neutropenia.

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 VGPR, and 98% achieved at least a PR.[4] One-year PFS for NDMM patients was 95%.[4] There were no grade 5 toxicities were reported In NDMM patients; lymphopenia, thrombocytopenia, and neutropenia were the most common grade 3/4AEs.[4] The dose was modified in 20 patients (44%); however, there was no discontinuation of study regimen due to treatment-related AEs.[4]

In a phase 2 study of KRd with autologous stem cell transplant (ASCT) in NDMM TE (N =76), 71% of patients achieved the primary outcome of sCR at the end of consolidation while 87% achieved sCR at the end of KRd maintenance.[6] The two-year PFS in patients who received ASCT was 98%.[6] The grade $\geq$ 3 AEs occurring in $\geq$ 5% of patients were lymphopenia, thrombocytopenia, leukopenia, thromboembolic event, anemia, and hyperglycemia.[5,6] Toxicities in the post-transplant setting appeared comparable to toxicities reported for study without transplant and overall comparable to those observed in the KRd arm in the ASPIRE trial.

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

1. 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.

2. 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 multiple myeloma. *Blood*. 2013;122(21) (Suppl): Abstract 3220.

3. 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.

4. 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.

5. Zimmerman TM, Griffith KA, Jasielec J, et al. Phase II MMRC trial of extended treatment with carfilzomib (CFZ), lenalidomide (LEN), and dexamethasone (OEX) plus autologous stem cell transplantation (ASCT) In newly diagnosed multiple myeloma (NDMM). J Clin Oncol 33, 2015 (suppl; abstr 8510).

6. 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.

Sincerely,

Andrzej J. Jakubowiak, MD, PhD
Professor of Medicine
Director, Myeloma Program
Section of Hematology/Oncology
University of Chicago Medical Center