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NCCN Multiple Myeloma Guideline Panel:

On behalf of Onyx Pharmaceuticals, Inc., I respectfully request the NCCN Multiple Myeloma Guideline Panel to consider reviewing the enclosed data for the inclusion of carfilzomib (Kyprolis™) in the Multiple Myeloma treatment guidelines as primary therapy for patients who are transplant candidates.

Specific Changes: Recommend the addition of carfilzomib as an option for primary therapy for patients with active (symptomatic) myeloma who are eligible for transplant in combination with lenalidomide and dexamethasone.

FDA Clearance: Kyprolis™ (carfilzomib) is a proteasome inhibitor indicated for the treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy.<sup>1</sup> Kyprolis™ is not approved for primary therapy of multiple myeloma by the FDA.

Rationale: The safety and efficacy of carfilzomib in combination with lenalidomide and dexamethasone as primary therapy for patients with multiple myeloma were evaluated in two single-arm trials.

The first study, a multicenter phase 1/2 trial conducted by the MMRC and published by Dr. Jakubowiak and colleagues, evaluated the combination of carfilzomib, lenalidomide and dexamethasone (CRd) in newly diagnosed multiple myeloma patients.<sup>2</sup> Carfilzomib 36 mg/m<sup>2</sup> with lenalidomide 25 mg/day days 1-21 and dexamethasone 40 mg weekly for cycles 1-4 then decreased to 20 mg weekly for cycles 5-8 (28 day cycles). After 8 cycles, patients received CRd every other week (days 1, 2 and 15, 16 of 28 day cycles) for 8 cycles. After 24 cycles of therapy, single-agent lenalidomide was recommended off study. The best response in this trial of 53 evaluable patients was ≥ PR 98%, ≥ VGPR 81%, and ≥ nCR 62% (sCR 42%) after a median of 12 cycles. The PFS rate was 97% at 12 months and 92% at 24 months. The most common grade 3/4 toxicities in ≥ 10% of patients included hypophosphatemia (25%), hyperglycemia (23%), anemia (21%), thrombocytopenia (17%) and neutropenia (17%).

The second trial was conducted at the NIH and was recently presented by Dr. Korde at the 54<sup>th</sup> Annual Meeting and Exposition of the American Society of Hematology in Atlanta, GA.<sup>3</sup> This phase 1/2 trial also evaluated the CRd combination in newly diagnosed multiple myeloma patients. The dosing in this study was carfilzomib 20/36 mg/m<sup>2</sup> (20 mg/m<sup>2</sup> on days 1 and 2 of cycle 1 only) on days 1, 2, 8, 9, 15, and 16, with lenalidomide 25 mg/day on days 1-21 and dexamethasone 20 mg days 1, 2, 8, 9, 15, 16, 22, and 23 for cycles 1-4, then decreased to 10 mg for cycles 5-8 (28 day cycles). After 8 cycles of treatment, patients received 12 cycles of lenalidomide 10 mg/day days 1-21. The primary

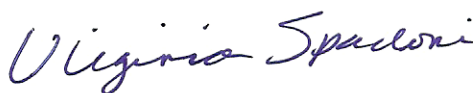
objective was the rate of  $\geq$  grade 3 neuropathy, and the secondary objectives included many correlative studies as well as response rate, progression free survival, overall survival and duration of response. Data from stage 1 of this 2 stage design phase 2 trial included 20 response-evaluable patients. With regard to the primary objective, no patient developed  $\geq$  grade 3 neuropathy. The best response for PR or better (ORR) was 95% and the nCR/sCR rate was 75% after a median of 7 cycles administered. The median time to sCR was 4.5 cycles, and 10 patients that achieved a nCR/sCR there were evaluated by flow cytometry, all were MRD negative. The most common grade 3/4 toxicities in  $\geq$  10% of patients included lymphopenia (60%), LFT elevation (20%), fatigue (15%),rash/pruritis (15%), dyspnea (10%), heart failure (10%). Patients continue to be accrued to the second stage of this study.

Additional studies have been conducted and presented utilizing carfilzomib in combination with other agents for the primary therapy of patients with multiple myeloma. Other combinations studied include carfilzomib with melphalan and prednisone in transplant ineligible patients,<sup>4</sup> carfilzomib with cyclophosphamide and dexamethasone in elderly patients,<sup>5</sup> carfilzomib with thalidomide and dexamethasone in transplant eligible patients<sup>6</sup> and carfilzomib with cyclophosphamide, thalidomide and dexamethasone in transplant eligible patients as well.<sup>7</sup>

The following articles and presentations are submitted in support of this proposed change.

1. Kyprolis™ [Prescribing Information]. Onyx Pharmaceuticals, Inc., South San Francisco, CA. July 2012.
2. Jakubowiak AJ, Dytfield 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.
3. Korde N, Zingone A, Kwok M, *et al.* Phase II clinical and correlative study of carfilzomib, lenalidomide, and dexamethasone (CRd) in newly diagnosed multiple myeloma (MM) patients. Presented at the 54<sup>th</sup> Annual Meeting and Exposition of the American Society of Hematology in Atlanta, GA, Abstract #732, December 10, 2012. <https://ash.confex.com/ash/2012/webprogram/Paper49008.html>
4. Kolb B, Hulin C, Caillot D, *et al.* Phase I/II study of carfilzomib plus melphalan-prednisone (CMP) in elderly patients with de novo multiple myeloma. Presented at the 2012 American Society of Clinical Oncology Annual Meeting, Chicago, IL. June 3, 2012. Abstract #8009. [http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst\\_detail\\_view&confID=114&abstractID=96240](http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=114&abstractID=96240)
5. Palumbo A, Bringhen S, Villani O, *et al.* Carfilzomib, cyclophosphamide and dexamethasone (CCd) for newly diagnosed multiple myeloma (MM) patients. Presented at the 54<sup>th</sup> Annual Meeting and Exposition of the American Society of Hematology in Atlanta, GA, Abstract #730, December 10, 2012. <https://ash.confex.com/ash/2012/webprogram/Paper46801.html>
6. Sonneveld P, Asselbergs E, Zweegman S, *et al.* Carfilzomib combined with thalidomide and dexamethasone (CTD) is an highly effective induction and consolidation treatment in newly diagnosed patients with multiple myeloma (MM) who are transplant candidate. Presented at the 54<sup>th</sup> Annual Meeting and Exposition of the American Society of Hematology in Atlanta, GA, Abstract #333, December 10, 2012. <https://ash.confex.com/ash/2012/webprogram/Paper47825.html>
7. Mikhael JR, Reeder CB, Libby EN, *et al.* Results from the phase II dose expansion of cyclophosphamide, carfilzomib, thalidomide and dexamethasone (CYCLONE) in patients with newly diagnosed multiple myeloma. Presented at the 54<sup>th</sup> Annual Meeting and Exposition of the American Society of Hematology in Atlanta, GA, Abstract #445, December 10, 2012. <https://ash.confex.com/ash/2012/webprogram/Paper52680.html>

Regards,



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