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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 carfilzomib (Kyprolis™) in the Multiple Myeloma treatment guidelines.

Specific Changes: Recommend including reference to the need to infuse doses of carfilzomib > 27 mg/m<sup>2</sup> intravenously over 30 minutes (either as a footnote to carfilzomib/lenalidomide/dexamethasone in the primary therapy section, or in the manuscript section of the Multiple Myeloma Guidelines).

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 approved to be administered intravenously over 2-10 minutes by the FDA.

Rationale: In rats, administration as a 30-minute infusion significantly improved tolerability of carfilzomib as compared to a rapid IV bolus.<sup>2,3</sup> Based on these findings, carfilzomib is administered intravenously over 30 minutes in clinical trials evaluating doses > 27 mg/m<sup>2</sup>.

This consistent with how carfilzomib was administered in the two front line trials that support the use of carfilzomib/lenalidomide/dexamethasone (CRd) as primary therapy.<sup>4,5</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. Jiang J, Kirk CJ, Muchamuel T, and Lee S. The benefits of irreversibility: infusion administration of carfilzomib results in potent proteasome inhibition and improved safety in animals. Presented at the 102<sup>nd</sup> Annual Meeting of the American Association for Cancer Research, Orlando, FL, Abstract #2607, April 2-6, 2011.  
<http://www.abstractsonline.com/Plan/ViewAbstract.aspx?sKey=1d39c323-ee6a-4d6c-ba64-bb04c6d004d2&cKey=54c42db5-0293-45e0-a1e1-9174bcc55fb5&mKey=%7b507D311A-B6EC-436A-BD67-6D14ED39622C%7d>
3. Papadopoulos K, Siegel DS, Singhal S, *et al.* Phase 1b evaluation of the safety and efficacy of a 30-minute IV infusion of carfilzomib in patients with relapsed and/or refractory multiple myeloma. Presented at the 52<sup>nd</sup>

Annual Meeting and Exposition of the American Society of Hematology in Orlando, FL, Abstract #3024, December 4 -7, 2010.

<http://abstracts.hematologylibrary.org/cgi/content/abstract/116/21/3024?maxtoshow=&hits=10&RESULTFORMAT=&fulltext=carfilzomib+infusion&searchid=1&FIRSTINDEX=0&volume=116&issue=21&resourcetype=HWCIT>

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. <http://bloodjournal.hematologylibrary.org/content/120/9/1801.full.pdf+html?sid=52427f70-1820-4728-9112-51844619ea05>
5. 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>

Regards,



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