

Virginia Spadoni, Pharm.D., BCOP
Director, Medical Communications
Onyx Pharmaceuticals, Inc.
249 E. Grand Avenue
South San Francisco, CA 94080
650-266-2106
gspadoni@onyx.com

July 30, 2012

NCCN Multiple Myeloma Guideline Panel:

On behalf of Onyx Pharmaceuticals, Inc., I respectfully request the NCCN Multiple Myeloma Guideline Panel to review the enclosed data and package insert for the inclusion of carfilzomib (Kyprolis™) in the Multiple Myeloma treatment guidelines for patients requiring salvage therapy.

Specific Changes: Recommend the addition of carfilzomib as an option for Salvage Therapy for patients with multiple myeloma.

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.¹

Rationale: The safety and efficacy of carfilzomib were evaluated in a single-arm, multicenter clinical trial (003-A1). Two hundred and sixty-six patients with relapsed multiple myeloma who had received at least 2 prior therapies (including bortezomib and thalidomide and/or lenalidomide) were enrolled. The primary endpoint was the overall response rate (ORR) as determined by Independent Review Committee assessment using International Myeloma Working Group (IMWG) criteria. The ORR (stringent complete response [sCR] + complete response [CR] + very good partial response [VGPR] + partial response [PR]) was 22.9% (95% CI: 18.0, 28.5) for the safety population (N = 266) and 23.7% (95% CI: 18.7-29.4) for the response-evaluable population (n=257).^{1,2} The median duration of response (DOR) was 7.8 months (95% CI: 5.6, 9.2).¹ The ORR and DOR were consistent across subgroups analyzed including those refractory and/or intolerant to available therapies.² Clinical benefit response (CBR) rate (≥ minimal response [MR] according to IMWG and European Group for Blood and Marrow Transplantation [EBMT] criteria) was a secondary endpoint. The CBR rates for the safety population (n=266) and the response-evaluable population (n=257) were 36% and 37% respectively.^{2,3}

The safety and efficacy of carfilzomib in the treatment of patients with multiple myeloma is supported by data from additional trials in patients with relapsed and/or refractory disease (Studies 003-A0, 004, and 005),⁴⁻⁶ This includes data in bortezomib-naïve patients with relapsed and/or refractory myeloma (004 part 2) treated with single-agent carfilzomib at 20 mg/m² in cycle one and 27 mg/m² in subsequent cycles (n = 67) who demonstrated an ORR of 52%.⁵ Additionally, carfilzomib has been studied in combination with lenalidomide and dexamethasone (006) in patients with relapsed myeloma (n = 51).⁷ These patients demonstrated an ORR of 78%.⁷

The most common adverse reactions (incidence of 30% or greater) to carfilzomib observed in clinical trials of patients with multiple myeloma (n = 526) were fatigue, anemia, nausea, thrombocytopenia, dyspnea, diarrhea, and pyrexia.¹ For additional safety information, please refer to the enclosed package insert.¹

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. Siegel DS, *et al.* A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. *Blood* blood-2012-05-425934; published ahead of print July 25, 2012, doi:10.1182/blood-2012-05-425934.
3. Onyx Presentations, Kyprolis™ (carfilzomib) for injection, for the June 20, 2012 Meeting of the Oncologic Drugs Advisory Committee. Available at : <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM310859.pdf> Accessed on 7/30/2012.
4. Siegel D, *et al.* Results of PX-171-003-A0, part 1 of an open-label, single-arm, phase 2 study of carfilzomib in patients with relapsed and refractory multiple myeloma. Abstr#9236. Poster presentation at the Joint ECCO 15-34th ESMO Multidisciplinary Congress, September 20-24, 2009; Berlin, Germany. (manuscript in progress)
5. Vij R, *et al.* An open-label, single-arm, phase 2 (PX171-004) study of single-agent carfilzomib in bortezomib-naïve patients with relapsed and/or refractory multiple myeloma. *Blood*. 2012;119:5661-5670.
6. Niesvizky R, *et al.* Carfilzomib pharmacokinetics, safety, and activity in patients with relapsed or refractory multiple myeloma and renal dysfunction. Abst#1530. Poster presentation at the 16th Congress of European Hematology Association, June 9-12, 2011; London, UK.
7. Niesvizky R, *et al.* An update on the phase 1b/2 dose-escalation study of carfilzomib with lenalidomide and low-dose dexamethasone in patients with relapsed or refractory multiple myeloma. Presented at the 16th Congress of European Hematology Association; June 9-12, 2011; London, UK. Abstract#1531/Poster#0295.

Regards,



Virginia Spadoni, Pharm.D, BCOP
Director, Medical Communications
Global Scientific Affairs