



Submitted by

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Date of request: July 22, 2019

NCCN Multiple Myeloma Panel

Request for review of recent FDA approval for selinexor (XPOVIO®) for use in combination with dexamethasone for relapsed/refractory multiple myeloma.

On behalf of Karyopharm Therapeutics, I respectfully request the NCCN Multiple Myeloma Panel to review the enclosed FDA approved label¹ and clinical studies²⁻⁵ in support of selinexor in combination with dexamethasone for the treatment of patients with relapsed/refractory multiple myeloma.

Suggested Changes: We respectfully ask the NCCN Panel to consider the following:

MYEL-E (page 3 of 3), "Therapy for Previously Treated Multiple Myeloma":

- Under "Preferred Regimens":
 - Add the regimen: "Selinexor/dexamethasone"
 - Add footnote: "Indicated for the treatment of patients who have received at least three prior therapies and who are refractory to a PI, immunomodulatory agent, and CD38 monoclonal antibody."

FDA Clearance: XPOVIO is a nuclear export inhibitor indicated in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least 2 immunomodulatory agents, and an anti-CD38 monoclonal antibody. This indication is approved under accelerated approval based on response rate.¹

Clinical Rationale: Patients whose disease is refractory to an anti-CD38 monoclonal antibody, and have had more than three prior therapies have a median progression-free survival (PFS) of 2.2 to 3.1 months, while those with triple-class refractory disease have a median overall survival (OS) of 3.5 months.^{6,7} In the STORM study, all 123 patients enrolled received at least three prior therapies and had triple-class refractory disease (disease refractory to a PI, immunomodulatory agent, and CD38 monoclonal antibody), which is the same patient population suggested above for NCCN guidelines. Selinexor plus dexamethasone demonstrated clinically meaningful activity (26.2% overall response rate (ORR) and 15.6 months median OS among the 39% of patients with minimal response or better) in patients who had triple-class refractory disease with a manageable safety profile.^{2,3} Primary outcomes of ORR and the safety profile are similar between the entire study population with triple-class refractory disease and the subset of patients that were penta-refractory to bortezomib, carfilzomib, lenalidomide,

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pomalidomide, and daratumumab (which was the basis of approval). Therefore, the risk-benefit profile of selinexor-dexamethasone in patients with triple-class refractory myeloma is the same as the subset of patients with penta-refractory myeloma in the label. This novel regimen provides a new option for patients and is the first to receive FDA approval for patients who are refractory daratumumab.¹

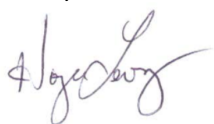
Literature for Refractory Disease: Approval of selinexor and low-dose dexamethasone is based on data from the phase 2b STORM clinical trial.²⁻⁴ Part 2 of the STORM study enrolled 123 patients whose disease was triple-class refractory including refractoriness to at least one PI, IMiD, and an anti-CD38 monoclonal antibody.^{2,3} Patients enrolled had rapidly progressive disease entering the study, as the 73% of patients with available data had a median increase in disease burden of 22% between screening and the first day of cycle 1 of therapy (median 12 days). Patients also received a median of 7 prior glucocorticoid-containing regimens (range: 3-18). The ORR with selinexor plus low-dose dexamethasone, as determined by a 4-physician independent review committee, was 26.2%, including 2 minimal residual disease negative (MRD-) stringent complete responses. The two patients who had previously received CAR-T therapy also achieved partial responses. Overall, median OS was 8.6 months; median PFS and duration of response were 3.7 months and 4.4 months, respectively.^{2,3} Median OS was 15.6 months among the responders (complete, partial, or minimal response). The above data set has been accepted for publication by the *New England Journal of Medicine*. A Cox proportional hazards regression analysis was performed to assess the survival impact of selinexor and low-dose dexamethasone in the triple-class refractory setting compared with a cohort of 69 patients from the Flatiron Health Analytic Database (FHAD).⁸ Despite being more heavily pretreated and having a higher frequency of high-risk disease, patients who received selinexor plus dexamethasone in STORM had higher median OS than patients in the FHAD cohort who had not received selinexor plus dexamethasone (10.4 vs 5.2 months; HR, 0.49; P=0.0241).⁸

Part 1 of the STORM trial enrolled 79 heavily pretreated patients who had received at least 3 prior lines of therapy.⁴ Treatment with selinexor plus low dose dexamethasone was administered twice weekly. Patients were categorized into two cohorts; cohort 1 included 48 patients who were double-class refractory to PI (bortezomib, carfilzomib) and IMiD (lenalidomide, pomalidomide). Cohort 2 evaluated 31 patients who were triple-class refractory. The ORR was 21% in the double-class refractory cohort and 20% in the triple-class refractory cohort. The median PFS and OS were 2.3 and 9.3 months, respectively.⁴ The overall STORM data were consistent with an earlier Phase 1 trial that demonstrated a 22% ORR with selinexor plus low-dose dexamethasone in patients with heavily pretreated multiple myeloma.⁵

Selinexor plus dexamethasone has a well-defined and manageable safety profile with no major end organ (cardiac, pulmonary, hepatic, renal, neuropathy, or mucositis) toxicity. The most common grade 3 or 4 adverse events were thrombocytopenia (53.7%), anemia (29.3%), fatigue (18.7%), neutropenia (18.7%), hyponatremia (16.3%), leukopenia (13%), and nausea (9.8%).^{2,3} The majority of these events are transient, reversible, and are not typically associated with clinical sequelae such as bleeding or infection. These side effects can be effectively managed with early intervention of supportive care, dose reduction and modification.

Thank you for your consideration.

Sincerely,



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References (enclosed):

1. XPOVIO™ (selinexor) oral prescribing information. Karyopharm Therapeutics.
2. Chari A, et al. Results of the pivotal STORM study (Part 2) in penta-refractory multiple myeloma (MM): deep and durable responses with oral selinexor plus low dose dexamethasone in patients with penta-refractory MM. *Blood*. 2018;132:598.
3. Chari A, et al. Results of the pivotal STORM study (Part 2): Deep and durable responses with oral selinexor plus low dose dexamethasone in patients with penta-exposed and triple class refractory MM. Oral Presentation. ASH Annual Meeting. December 3, 2018. Abstract:598.
4. Vogl DT, et al. Selective inhibition of nuclear export with oral selinexor for treatment of relapsed or refractory multiple myeloma. *J Clin Oncol*. 2018;36(9):859-866.
5. Chen C, et al. Safety and efficacy of selinexor in relapsed or refractory multiple myeloma and Waldenstrom macroglobulinemia. *Blood*. 2018;131(8):855-863.
6. Pick M, et al. Daratumumab resistance is frequently in advanced-stage multiple myeloma patients irrespective of CD38 expression and is related to dismal prognosis. *Eur J Haematol*. 2018;100(5):494-501.
7. Lakshman A, et al. Efficacy of daratumumab-based therapies in patients with relapsed, refractory multiple myeloma treated outside of clinical trials. *Am J Hematol*. 2017;92(11):1146-1155.
8. Richardson PG, et al. Overall survival (OS) with oral selinexor plus low dose dexamethasone (Sd) in patients with triple class refractory multiple myeloma (TCR-MM). *J Clin Oncol*. 2019;37(suppl):8014.