



Submitted by

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NCCN B-Cell Lymphomas Panel

Request for review of selinexor (XPOVIO®) for use in relapsed or refractory diffuse large B-cell lymphoma.

On behalf of Karyopharm Therapeutics, I respectfully request the NCCN B-Cell Lymphomas Panel to review the enclosed FDA approved label¹ and clinical studies^{2,3} in support of single agent oral selinexor for the treatment of patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL).

We believe that for patients ineligible for intensive therapies, selinexor, with its overall response rate of 28% (median duration of response [DOR] 9.3 months) and complete response rate of 12% (median DOR 23 months), represents a reasonable oral option that does not require prolonged clinic visits or unusual monitoring.³

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

BCEL-C (page 2 of 4), "Second-line and Subsequent Therapy (non-candidates for transplant)":

- Under "Preferred regimens":
 - Add the regimen: "Selinexor"
 - Add footnote: "Selinexor may be used for the treatment of patients with relapsed or refractory DLBCL who have received at least two prior therapies."

FDA Clearance: XPOVIO is a nuclear export inhibitor indicated:¹

- In combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody.
- For the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy.

These indications are approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Clinical Rationale: The long-term outlook for patients with heavily pretreated relapsed or refractory DLBCL (RR DLBCL) who are not candidates for autologous stem cell transplantation (ASCT) or chimeric antigen receptor (CAR)

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T cell therapy, or those who relapse after ASCT, remains poor. Despite the emergence of treatment options, the median survival for patients with RR DLBCL who have received at least 2 prior regimens is ≤ 6 months.⁴⁻⁶ The SADAL study, one of the largest clinical trials evaluating patients with RR DLBCL who are not candidates for ASCT (or CAR-T) therapy, demonstrated an overall response rate (ORR) of 28.3% and median overall survival (OS) of 9.1 months in patients treated with single-agent oral selinexor.³ As outlined in the summary below, oral selinexor represents a new treatment option for patients with RR DLBCL.

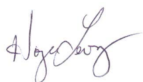
Summary of Literature: The phase 2b SADAL study enrolled 267 patients with RR DLBCL who had received 2 to 5 lines of prior therapy and who had disease progression post-ASCT or who were not candidates for ASCT.³ Patients in the modified intent-to-treat (mITT) population (60 mg selinexor arm, n=127) were heavily pretreated with disease progression at study entry, including 41% who received ≥ 3 prior regimens and 30% with prior ASCT. In addition, patients enrolled had poor prognostic factors including 50% with non-GCB subtype, and 72% with disease refractory to the most recent systemic therapy. The ORR for patients treated with selinexor was 28%, including 15 (12%) complete responses (*note that in the USPI, a revised mITT population of n=134 is included with an ORR of 29% and 18 (13%) complete responses*¹). Among patients with a GCB subtype, the ORR was 34% compared to 21% in non-GCB disease. Overall, median OS was 9.1 months (median OS was not reached in patients with a \geq partial response (PR) and 18.3 months in patients who had stable disease), median progression-free survival was 2.6 months, and median duration of response was 9.3 months (23.0 months in patients with a complete response). Clinical response was observed across patient subgroups despite age, prior therapy, DLBCL subtype, prior ASCT therapy, or refractory status. For example, the ORR was comparable between patients who were ≥ 70 years old (25% of enrolled patients, ORR=25%) and the overall study population. Furthermore, selinexor enabled CAR-T therapy in patients (n=3) who previously progressed following ASCT and were ineligible for CAR-T. These overall results are consistent with observations from a Phase 1 study where single agent selinexor demonstrated an investigator-assessed ORR of 31% and complete response rate of 6% in patients with heavily pretreated DLBCL.²

The majority of adverse events associated with selinexor in the SADAL study were generally reversible and effectively managed with dose modifications and standard supportive care.³ These adverse events are similar to those reported in previous selinexor trials in multiple myeloma, including STORM, but occurring generally with less frequency and severity as expected with the lower dose of selinexor used in SADAL.⁷ The most common grade 3 or 4 adverse events observed in the SADAL study were thrombocytopenia (46%), neutropenia (24%), anemia (22%), fatigue (11%), hyponatremia (8%), and nausea (6%). Furthermore, there were no grade ≥ 3 bleeding events associated with thrombocytopenia.

Despite the poor prognosis of patients with RR DLBCL who have received at least 2 prior regimens, these results indicate that selinexor is an oral, single-agent treatment option that shows a durable, clinical response in this patient population. The availability of an oral agent for the treatment of patients with either GCB or non-GCB subtypes of DLBCL could be an important addition to our currently available therapies, particularly in the context of reducing time spent in medical clinics.

Thank you for your consideration.

Sincerely,



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References (enclosed):

1. XPOVIO™ (selinexor) oral prescribing information. Karyopharm Therapeutics.
2. Kuruvilla J, Savona M, Baz R, *et al.* Selective inhibition of nuclear export with selinexor in patients with non-Hodgkin lymphoma. *Blood* 2017; **129**: 3175–83.
3. Kalakonda N, Maerevoet M, Cavallo G, *et al.* Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm multinational phase 2 trial. *Lancet Haematol* Jul 2020; **7**: E511-522.
4. Crump M, Neelapu SS, Farooq U, *et al.* Outcomes in refractory diffuse large B-cell lymphoma: Results from the international SCHOLAR-1 study. *Blood* 2017; **130**: 1800–8.
5. Ansell SM, Minnema MC, Johnson P, *et al.* Nivolumab for relapsed/refractory diffuse large B-cell lymphoma in patients ineligible for or having failed autologous transplantation: A single-arm, phase II study. *J Clin Oncol* 2019; **37**: 481–9.
6. Sehn LH, Herrera AF, Flowers CR, *et al.* Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *J Clin Oncol* 2019; : JCO1900172.
7. Chari A, Vogl DT, Gavriatopoulou M, *et al.* Oral selinexor-dexamethasone for triple-class refractory multiple myeloma. *N Engl J Med* 2019; **381**: 727–38.