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NCCN Multiple Myeloma Panel: Request for review of selinexor (XPOVIO®) and dexamethasone in combination with bortezomib, pomalidomide, or daratumumab for use in previously treated multiple myeloma.

On behalf of Karyopharm Therapeutics, I am resubmitting our request to the NCCN Multiple Myeloma Panel to review the clinical studies[1-3] in support of oral selinexor and dexamethasone in combination with bortezomib, as well as additional combinations with pomalidomide and daratumumab for the treatment of patients with previously treated multiple myeloma (MM). Since our previous request (submitted May 29, 2020), the BOSTON phase 3 and STOMP phase 1/2b trials have been published in Lancet and European Journal of Haematology, respectively.[1-2]

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/bortezomib/dexamethasone (once weekly)"
- Under "Other Recommended Regimens":
  - Add the regimens: "Selinexor/daratumumab/dexamethasone" and "Selinexor/pomalidomide/dexamethasone"

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 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. This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.[4]

Clinical Rationale: Despite the number of treatment options available, nearly all patients with MM relapse and require novel therapies. The proteasome inhibitor (PI), bortezomib, in combination with dexamethasone (Vd) is standard therapy for patients with MM; however, the twice weekly dosing regimen is associated with high rates of neuropathy and requires twice weekly clinic visits, underscoring the need for more efficacious, convenient and less toxic treatment strategies.[5,6] The BOSTON study, the first phase 3 trial examining a novel triplet-Vd regimen including once weekly oral selinexor with *once weekly bortezomib* (SVd) versus standard twice weekly Vd in patients with RRMM, demonstrated that patients on the SVd regimen had a 47% increase in median progression-free survival (PFS) with a lower rate of peripheral neuropathy.[1] Similarly, triplet regimens including selinexor and dexamethasone in combination with daratumumab (SDd) and pomalidomide (SPd) have demonstrated deep and durable responses in patients with previously treated MM.[2,3] The introduction of oral selinexor in these novel combination regimens represents new, more convenient treatment options for patients with RRMM.

Summary of Literature: The phase 3 (randomized, controlled, open-label, global) BOSTON study enrolled 402 patients with MM after 1-3 prior therapies who were randomly assigned to *once* weekly oral selinexor plus *once* weekly bortezomib and low dose dexamethasone [SVd, n=195] or standard twice weekly bortezomib with dexamethasone (Vd, n=207).[1] Doses of bortezomib and dexamethasone were 40% and 25% lower, respectively, in the first 24 weeks of treatment on the SVd arm as compared with the standard Vd arm. A 4.47 month increase in median PFS (13.93 vs 9.46 months, HR 0.70, p=0.0075), a significantly higher overall response rate (ORR, 76.4% vs 62.3%, p=0.0012) and deep response rates (≥VGPR 44.6% vs 32.4%) were observed with SVd

compared to Vd. This benefit was observed across patient subgroups, including patients with high cytogenetic risk, those ≥ 65 years of age, patients who are frail, patients with renal impairment (creatinine clearance 30-60 ml/min), those who received 1 prior line of therapy, and patients with prior lenalidomide exposure. Time to next treatment was higher with SVd (16.1 vs 10.8 months, p=0.0012), and there were fewer deaths on the SVd arm (47) than on the Vd arm (62). The most frequent adverse events (AEs, grade ≥3) observed (SVd vs Vd) were thrombocytopenia (39.5% vs 17.2%), anemia (15.9% vs 9.8%), neutropenia (8.7% vs 3.4%) and fatigue (13.3% vs 1.0%). In general, AEs were reversible and effectively manageable with appropriate supportive care and dose modification. Compared with the higher doses of selinexor-dexamethasone used in the STORM study in patients with triple-class refractory disease, fewer grade 3/4 hematologic adverse events were observed with SVd in this study.[7] Notably, the rates of overall (32.3% vs 47.1%, p=0.0010) and grade ≥2 (21.0% vs 34.3%, p=0.0013) peripheral neuropathy were significantly lower with SVd compared to Vd. Peripheral neuropathy was the most common AE leading to treatment discontinuation (4.6% on SVd vs 7.4% on Vd). This is the first phase 3 study demonstrating a lower rate of peripheral neuropathy with a triplet Vd regimen versus Vd.[8,9]

Additional selinexor combination regimens have been investigated in the phase 1/2b (multicenter, open label) STOMP study, including selinexor/daratumumab/dexamethasone (SDd) and selinexor/pomalidomide/dexamethasone (SPd).[2,3] These combinations utilize once weekly selinexor and may provide unique options for patients with previously treated MM. In the STOMP SDd study, a total of 34 patients (32 evaluable) who had received ≥3 prior lines of therapy for MM, including a PI and an immunomodulatory drug (IMiD), or those whose disease was refractory to both a PI and IMiD were enrolled.[2] Patients (of whom 62% and 65% had MM refractory to bortezomib and lenalidomide, respectively) received oral selinexor twice weekly (60 mg, n=3) or once weekly (100 mg, n=31) in the expansion cohort (daratumumab-naïve patients only) with dexamethasone and daratumumab. The ORR was 73% in the daratumumab-naïve cohort (n=30), with a PFS of 12.5 months; responses were not observed in the 2 patients with daratumumab refractory disease. Common treatment-related grade 3/4 AEs included thrombocytopenia (47.0%), fatigue (17.6%), nausea (8.8%), anemia (32.4%) and neutropenia (26.5%), similar to the safety profile observed with selinexor and dexamethasone alone, and were effectively managed by dose modification and appropriate supportive care.[2,7] Relative to single agent activity (ORR of 26.2% with Sd and 29% with Dd), once weekly SDd demonstrates deep and durable responses in patients with heavily pretreated RRMM, the majority with disease refractory to bortezomib and lenalidomide.[7,10]

In the all oral STOMP SPd study, 48 patients (44 evaluable) who had received a median of 4 prior treatments for MM, including lenalidomide and a PI, were enrolled.[3] Selinexor was evaluated once or twice weekly (60 or 80 mg) with escalating doses of pomalidomide and dexamethasone. Among patients with pomalidomide-naïve/lenalidomide-refractory disease (n=32), an ORR of 56% and median PFS of 12.2 months were observed. For patients with disease refractory to lenalidomide *and* pomalidomide (n=13), the ORR was 36% and the median PFS was 4.2 months. Common grade 3/4 treatment-related AEs included neutropenia (54%), thrombocytopenia (33%), anemia (29%), leukopenia (15%), hyperglycemia (17%), pneumonia (17%), and fatigue (10%). This AE profile, with the majority of events being grade 1/2, was expected and manageable with appropriate dose modifications and supportive care. Based on these results, once weekly SPd represents an effective oral regimen for patients with pomalidomide-naïve/lenalidomide-refractory MM, exhibiting superior ORR and longer PFS when compared to Sd alone and to Pd in a similar population (31% ORR, 3.6 months median PFS).[11] This combination represents an all oral, PI-sparing regimen for patients whose MM is progressing on many of the available therapies.

Consistent with the novel mechanism of action of selinexor and as demonstrated by the deep and durable responses observed with SVd, SDd, and SPd, the introduction of selinexor to combination regimens represents three novel treatment options for patients with RRMM. The SVd regimen may have utility in the second line setting, particularly following daratumumab and lenalidomide, as this combination represents two novel mechanisms that can delay the repeated use of an IMID or anti-CD38 monoclonal antibodies. Furthermore, lower rates and severity of peripheral neuropathy seen with SVd is a significant benefit as pain can persist for months with negative impact on daily living.[12] The utility of once weekly oral selinexor in combination with currently approved backbone agents offers more convenience and significantly reduces clinical visits and associated risks. In particular, the all oral SPd regimen may be potentially associated with reduced economic burden, less time spent receiving treatment, as well as greater treatment compliance and patient-reported treatment satisfaction compared with injectable regimens.[13,14] Thus, novel combination regimens including oral selinexor may provide novel effective regimens that allow for reduced clinic visits for patients with previously treated MM.

Sincerely,

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