FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Oncologic Drugs Advisory Committee (ODAC) Meeting
FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503)
10903 New Hampshire Avenue, Silver Spring, Maryland
February 26, 2019

QUESTIONS

NDA 212306

Selinexor tablets

Applicant: Karyopharm Therapeutics Inc.

PROPOSED INDICATION: In combination with dexamethasone, for the treatment of patients with relapsed refractory multiple myeloma who have received at least three prior therapies and whose disease is refractory to at least one proteasome inhibitor, at least one immunomodulatory agent, and an anti-CD38 monoclonal antibody.

BACKGROUND

Significant advances have been made in the treatment of multiple myeloma (MM) in recent decades, however, it is not considered curable, and most patients will eventually relapse and are likely to develop refractory disease. Treatment of relapsed/refractory multiple myeloma (RRMM) remains challenging. In general, the duration of remission shortens with each subsequent line of therapy, and patients who become refractory to the major classes of available anti-myeloma therapies have poor outcomes.

NDA 212306 for selinexor is primarily based on Part 2 of the phase 2b trial, KCP-330-012 (STORM). STORM was a single arm trial of combination therapy. Patients with RRMM received selinexor in combination with dexamethasone. Part 2 enrolled 123 patients with RRMM who had received at least 3 prior therapies, including an alkylating agent, bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab, and a glucocorticoid, and whose disease was considered triple-class refractory, i.e., refractory to at least one proteasome inhibitor (bortezomib and/or carfilzomib), at least one immunomodulatory agent (lenalidomide and/or pomalidomide), and an anti-CD38 mAb (daratumumab). The primary endpoint was overall response rate (ORR; defined as the proportion of patients with a partial response (PR) or better).

EFFICACY

The modified intent-to-treat (mITT) population included 122 patients with triple-class refractory MM enrolled in Part 2 of STORM who met all eligibility criteria and received at least one dose of selinexor and dexamethasone. The ORR was 25.4% (95% CI: 18%, 34.1%) with a median duration of response (DOR) of 4.4 months (range 0.8 to 9.0 months). Responses included 2 patients with stringent complete response (sCR), 6 patients with very good partial response (VGPR), and 23 patients with PR.

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QUESTIONS (cont.)

SAFETY

The safety analysis was primarily based on 123 patients enrolled and treated on STORM Part 2. All patients (100%) experienced at least one treatment-emergent adverse event (TEAE), 93.5% experienced at least one severe (Grade 3–4) TEAE, and 60.2% experienced at least one serious adverse event (SAE). Of the 23 deaths that occurred on or within 30 days of study treatment in Part 2 of STORM, 13 (10.6%) were due to disease progression, and 10 (8.1%) were due to a fatal TEAE. Most patients (88.6%) required at least one dose modification due to a TEAE and 28.5% of patients permanently discontinued study treatment due to a TEAE.

The most common TEAEs (occurring in at least 20% of patients) in Part 2 were anemia (65.9%), leukopenia (30.9%), neutropenia (38.2%), thrombocytopenia (71.5%), constipation (22%), diarrhea (42.3%), nausea (69.9%), vomiting (37.4%), fatigue (72.4%), weight decreased (48.8%), decreased appetite (53.7%), hyponatremia (35%), and dyspnea (21.1%).

ISSUES:

- STORM was a single arm trial of combination therapy. Selinexor demonstrated essentially no single agent activity in the phase 1 trial (1 response among 56 patients treated). Dexamethasone has a historical response rate between 10-27%. It is difficult to isolate the treatment effect of selinexor in the STORM trial.
- Treatment with Selinexor is associated with significant toxicity.
    - There was a high rate of severe TEAEs, SAEs, and TEAEs resulting in death in the STORM trial.
    - A randomized, controlled trial in patients with relapsed/refractory AML demonstrated a worse overall survival trend.
- The safety profile and high rate of dose modifications suggest that the optimal dose may not have been identified.

QUESTIONS

1. **DISCUSSION:** Discuss whether the KCP-330-012 (STORM) data are conclusive to allow for an adequate assessment of the safety and efficacy in the proposed patient population, and whether selinexor provides a benefit that outweighs the risks.

2. **VOTE:** Should the approval of selinexor be delayed until results of the randomized phase 3 trial, BOSTON, are available?