Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Oncologic Drugs Advisory Committee Meeting
February 26, 2019

Location: FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland

Topic: The committee discussed new drug application (NDA) 212306 for selinexor tablets, application submitted by Karyopharm Therapeutics Inc. The proposed indication (use) for this product is 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.

These summary minutes for the February 26, 2019 Oncologic Drugs Advisory Committee (ODAC) meeting of the Food and Drug Administration were approved on March 5, 2019.

I certify that I attended the February 26, 2019 Oncologic Drugs Advisory Committee meeting of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/
Lauren D. Tesh, PharmD, BCPS
Designated Federal Officer
ODAC

/s/
Brian I. Rini, MD, FACP
Chairperson
ODAC

Final Summary Minutes of the Oncologic Drugs Advisory Committee (ODAC) Meeting
February 26, 2019

The Oncologic Drugs Advisory Committee (ODAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on February 26, 2019, at the FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Karyopharm Therapeutics Inc. The meeting was called to order by Brian I. Rini, MD, FACP (Chairperson). The conflict of interest statement was read into the record by Lauren D. Tesh, PharmD, BCPS (Designated Federal Officer). There were approximately 175 people in attendance. There were seventeen (17) Open Public Hearing (OPH) speaker presentations.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda: The committee discussed new drug application (NDA) 212306 for selinexor tablets, application submitted by Karyopharm Therapeutics Inc. The proposed indication (use) for this product is 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.

Attendance:

Oncologic Drugs Advisory Committee Members Present (Voting): Massimo Cristofanilli, MD, FACP; Susan Halabi, PhD; Christian S. Hinrichs, MD; Heidi D. Klepin, MD, MS; Vassilliki A. Papadimitrakopoulou, MD; Alice T. Shaw, MD, PhD; Brian I. Rini, MD, FACP (Chairperson); Thomas S. Uldrick, MD, MS

Oncologic Drugs Advisory Committee Member Present (Non-Voting): Phuong Khanh (P.K.) Morrow, MD, FACP (Industry Representative)

Oncologic Drugs Advisory Committee Members Not Present (Voting): Philip C. Hoffman, MD; Grzegorz S. Nowakowski, MD; Alberto S. Pappo, MD; Courtney J. Preusse, MA; Gregory J. Riely, MD, PhD

Temporary Members (Voting): David Harrington, PhD, MA; Randy W. Hawkins, MD (Acting Consumer Representative); Clifton C. Mo, MD; Natalie Compagni Portis, PsyD, MFT (Patient Representative); Gita Thanarajasingam, MD

FDA Participants (Non-Voting): Richard Pazdur, MD; Ann Farrell, MD; Nicole Gormley, MD; Andrea C. Baines, MD, PhD

Designated Federal Officer (Non-Voting): Lauren D. Tesh, PharmD, BCPS

Open Public Hearing Speakers: Dan Vogl, MD, MSCE; Cynthia Chmielewski; Robin Tuohy on behalf of Aldo Del Col; Jenny Ahlstrom (Myeloma Crowd); Diane Moran (International Myeloma Foundation); Deborah Graff; Michael Tuohy; Anne Quinn Young, MPH (Multiple Myeloma Research Foundation); Ajay K. Nooka, MD MPH FACP; Sharon Studzienko; Ignacy Studzienko; Nashat Y. Gabrail, MD (Gabrail Cancer Center); Michael Walsh; Stephanie Fox-Rawlings, PhD (National Center for Health Research); Paul Ahlstrom; Anne Stovell; Robin Tuohy

The agenda was as follows:

Call to Order and Introduction of Committee	**Brian I. Rini, MD, FACP** Chairperson, ODAC
Conflict of Interest Statement	**Lauren D. Tesh, PharmD, BCPS** Designated Federal Officer, ODAC
Introductory Comments	**Nicole Gormley, MD** Clinical Team Leader Division of Hematology Products (DHP) Office of Hematology and Oncology Products (OHOP) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Karyopharm Therapeutics Inc.**
Introduction	**Tanya Lewis** Senior Vice President, Global Regulatory Affairs Karyopharm Therapeutics
Unmet Need in Triple-Class-Refractory MM	**Paul Richardson, MD** Clinical Program Leader and Director of Clinical Research Jerome Lipper Multiple Myeloma Center Dana Farber Cancer Institute Boston, Massachusetts RJ Corman Professor of Medicine Harvard Medical School
Efficacy	**Jatin Shah, MD** Senior Vice President, Clinical Development Karyopharm Therapeutics
Safety	**Michael Kauffman, MD, PhD** CEO and Chief Medical Officer Karyopharm Therapeutics

APPLICANT PRESENTATIONS (CONT.)

Clinical Perspective	**Sundar Jagannath, MD** Director of the Multiple Myeloma Program and Professor of Medicine The Tisch Cancer Institute Mount Sinai, New York
Conclusion	**Sharon Shacham, PhD** President and Chief Scientific Officer Karyopharm Therapeutics

FDA PRESENTATION

NDA 212306: Selinexor	**Andrea C. Baines, MD, PhD** Clinical Reviewer DHP, OHOP, OND, CDER, FDA

Clarifying Questions

BREAK

OPEN PUBLIC HEARING

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

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.

   Committee Discussion*: A lot of the committee members noted that the data are inconclusive to allow for an adequate assessment of the safety and efficacy in the proposed patient population, and therefore, it was undeterminable whether selinexor provides a benefit that outweighs the risks. One committee member noted that there was a lot of missing data from patients in the STORM study, and that selinexor was not tolerated by many patients as shown by the high frequency of dose modifications and discontinuations. It was also noted that randomized trials are needed when there is significant toxicity associated with a product and tolerability is a concern. There was a thought that dexamethasone may have contributed to some of the benefits seen in the STORM trial. Furthermore, there was discussion that selinexor's contribution to the treatment effect in the STORM trial could not be determined because of the single arm trial design. However, one committee member noted that patients in the STORM trial are likely steroid refractory and the dose of dexamethasone in the STORM study is lower than what was used historically, and therefore, it is extremely unlikely*

that the 25% response rate was due to dexamethasone alone. It was also noted that an active drug would be expected to result in an improvement in quality of life, which was not clearly demonstrated in the STORM trial, with the caveat that the data collected regarding quality of life/patient-reported outcomes was very limited. Please see the transcript for details of the Committee discussion.

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

   Vote Result: Yes: 8 No: 5 Abstain: 0

   ***Committee Discussion**: Eight committee members voted "Yes", indicating that the approval of selinexor should be delayed until results of the randomized phase 3 trial, BOSTON, are available. These members noted that data from the STORM trial does not meet the FDA regulatory standards needed to prove the safety and effectiveness of selinexor. The five committee members who voted "No" noted that patients need options for this indication and selinexor should be granted accelerated approval now. Please see the transcript for details of the Committee discussion.*

   The meeting was adjourned at approximately 5:00 p.m.