**Food and Drug Administration**
**Center for Drug Evaluation and Research**

**Final Summary Minutes of the Oncologic Drugs Advisory Committee Meeting**
**April 12, 2024**

**Location:** FDA and invited participants attended the meeting at FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. The public participated via an online teleconferencing and/or video conferencing platform, and the meeting presentations were heard, viewed, captioned, and recorded through an online video conferencing platform.

**Topic:** The Committee discussed the use of minimal residual disease (MRD) as an endpoint in multiple myeloma clinical trials, including considerations regarding timing of assessment, patient populations, and trial design for future studies that intend to use MRD to support accelerated approval of a new product or a new indication.

These summary minutes for the April 12, 2024 meeting of the Oncologic Drugs Advisory Committee of the Food and Drug Administration were approved on July 2, 2024 .

I certify that I attended the April 12, 2024 meeting of the Oncologic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

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| **/s/** | **/s/** |
| Takyiah Stevenson, PharmD | Grzegorz (Greg) S. Nowakowski, MD, FASCO |
| Acting Designated Federal Officer, ODAC | Acting Chairperson, ODAC |

**Summary Minutes of the Oncologic Drugs Advisory Committee Meeting**
**April 12, 2024**

The Oncologic Drugs Advisory Committee (ODAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on April 12, 2024. FDA and invited participants attended the meeting at FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. The public participated via an online teleconferencing and/or video conferencing platform, and the meeting presentations were heard, viewed, captioned, and recorded through an online video conferencing platform. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA, the Sylvester Comprehensive Cancer Center at University of Miami, and the International Independent Team for Endpoint Approval of Myeloma Minimal Residual Disease. The meeting was called to order by Grzegorz (Greg) S. Nowakowski, MD, FASCO (Acting Chairperson). The conflict of interest statement was read into the record by Takyiah Stevenson, PharmD (Acting Designated Federal Officer). There were approximately 1100 people in attendance. There were 8 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 the use of minimal residual disease (MRD) as an endpoint in multiple myeloma clinical trials, including considerations regarding timing of assessment, patient populations, and trial design for future studies that intend to use MRD to support accelerated approval of a new product or a new indication.

**Attendance:**
**Oncologic Drugs Advisory Committee Members Present (Voting):** Ranjana H. Advani, MD; Mark R. Conaway, PhD; Christopher H. Lieu, MD; Ravi A. Madan, MD; David E. Mitchell (*Consumer Representative*); Jorge J. Nieva, MD; Neil Vasan, MD, PhD

**Oncologic Drugs Advisory Committee Members Not Present (Voting):** Toni K. Choueiri, MD; William J. Gradishar, MD; Pamela L. Kunz, MD; Alberto S. Pappo, MD; Ashley Rosko, MD; Daniel Spratt, MD

**Oncologic Drugs Advisory Committee Member Present (Non-Voting):** Tara L. Frenkl MPH, MD (*Industry Representative*)

**Temporary Members (Voting):** Christopher Hourigan, DM, DPhil, FRCP; Thomas Martin, MD; Matthew J. Maurer, DMSc; Grzegorz (Greg) S. Nowakowski, MD, FASCO (*Acting Chairperson*); Michael A. Riotto (*Patient Representative*)

**FDA Participants (Non-Voting):** Richard Pazdur, MD; Marc Theoret, MD; Nicole Gormley, MD; Bindu Kanapuru, MD; Rachel Ershler, MD, MHS; Jonathan Vallejo, PhD; Jing Zhang, PhD

**Acting Designated Federal Officer (Non-Voting):** Takyiah Stevenson, PharmD

**Open Public Hearing Speakers:** Jenny Ahlstrom (HealthTree Foundation); Mary DeRome (Multiple Myeloma Research Foundation); Saad Usmani, MD; Surbhi Sidana, MD; Noopur Raje, MD; Vinay Prasad, MD, MPH; Linda Huguelet; Frank Morelli

***The agenda was as follows:***

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| Call to Order and Introduction of Committee | **Grzegorz (Greg) S. Nowakowski, MD, FASCO**<br>Acting Chairperson, ODAC |
| Conflict of Interest Statement | **Takyiah Stevenson, PharmD**<br>Acting Designated Federal Officer, ODAC |
| FDA Introductory Remarks | |
| Oncology Endpoint Development | **Nicole Gormley, MD**<br>Associate Director of Oncology Endpoint Development<br>Oncology Center of Excellence (OCE)<br>Director, Division of Hematologic Malignancies II (DHM II) Office of Oncologic Diseases (OOD)<br>Office of New Drugs (OND), CDER, FDA |
| Multiple Myeloma - Minimal Residual Disease (MRD) | **Bindu Kanapuru, MD**<br>Associate Director of Therapeutic Review<br>DHM II, OOD, OND, CDER, FDA |
| **INDUSTRY PRESENTATIONS** | **Sylvester Comprehensive Cancer Center, University of Miami** |
| Introduction | **C. Ola Landgren, MD, PhD**<br>Professor of Medicine<br>Chief, Division of Myeloma, Department of Medicine<br>Director, Sylvester Myeloma Institute<br>Co-Leader, Translational and Clinical Oncology Program<br>Paul J. DiMare Endowed Chair in Immunotherapy<br>Sylvester Comprehensive Cancer Center<br>University of Miami |
| Multiple Myeloma, Unmet Medical Need, and Role of MRD | **C. Ola Landgren, MD, PhD** |
| Data, Methodology, and Results | **Sean Devlin, PhD**<br>Associate Professor of Biostatistics<br>Associate Attending Biostatistician<br>Department of Biostatistics<br>Memorial Sloan Kettering Cancer Center |
| Summary and Clinical Conclusions | **C. Ola Landgren, MD, PhD** |

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| **INDUSTRY PRESENTATIONS** | **International Independent Team for Endpoint Approval of Myeloma Minimal Residual Disease (I2TEAMM)** |
| Introduction | **Brian G. M. Durie, MD**<br>Cedars-Sinai Comprehensive Cancer Center<br>Los Angeles, California |
| The Need for MRD Assessment | **Bruno Paiva, PhD**<br>Director of Flow Cytometry<br>Department of Hematology and Immunology<br>CIMA Laboratory Diagnostics<br>University of Navara, SPAIN |
| Meta-Analyses and Key Results | **Qian Shi, PhD**<br>Professor of Biostatistics and Oncology<br>Department of Quantitative Health Sciences<br>Mayo Clinic<br>Rochester, Minnesota |
| Conclusions | **Kenneth C. Anderson, MD**<br>Kraft Family Professor of Medicine<br>Dana-Farber Cancer Institute<br>and Harvard Medical School<br>Boston, Massachusetts |
| **FDA PRESENTATIONS** | |
| MRD to Support Accelerated Approval | **Rachel Ershler, MD, MHS**<br>Clinical Reviewer<br>DHM II, OOD, OND, CDER, FDA<br><br>**Jing Zhang, PhD**<br>Statistical Reviewer<br>Division of Biometrics IX<br>Office of Biostatistics<br>Office of Translational Sciences, CDER, FDA |
| **BREAK** | |
| Clarifying Questions | |
| **LUNCH** | |
| **OPEN PUBLIC HEARING** | |
| Questions to the Committee/ Committee Discussion | |
| **ADJOURNMENT** | |

***Questions to the Committee:***

1. **DISCUSSION:** Discuss the adequacy of the available data to support the use of minimal residual disease (MRD) as an accelerated approval endpoint in multiple myeloma (MM).

   ***Committee Discussion***: *Overall, the Committee agreed that the available patient level data and the biologic plausibility supported the use of MRD as an intermediate endpoint for accelerated approval in MM. Committee members acknowledged that MRD as an endpoint represents a major opportunity for acceleration of drug development in MM, particularly in the front-line setting. Several Committee members acknowledged that the studies and analyses conducted were well done and they had confidence in the data presented. Some Committee members expressed concern that clinical trials utilizing MRD may not capture the full toxicity profile of drugs being studied, and follow-up for long term outcomes like progression free survival (PFS) and overall survival (OS) and dose optimization will remain important. One member mentioned that more data may be needed to analyze MRD as an endpoint for later lines of therapy for relapsed/refractory MM. Please see the transcript for details of the Committee's discussion.*

2. **DISCUSSION:** Discuss whether the available data supports the use of MRD as an endpoint in the different MM disease settings.
   - Newly diagnosed MM
   - Relapsed/Refractory MM

   ***Committee Discussion***: *The majority of the Committee members concurred that the available data supports the use of MRD as an endpoint in both the newly diagnosed and relapsed/refractory MM disease settings. A few Committee members stated that the available data in the relapsed/refractory MM setting is weaker compared to the data in the newly diagnosed MM setting. Most members assessed that the data in both disease settings were adequate and pointed out that some of the analyses showing less association in relapsed/refractory MM were likely confounded by the smaller number of patients in those clinical trials. One Committee member noted that since the duration of remission gets shorter with each relapse more than four studies may be needed to demonstrate a difference in MRD negativity in this setting. Please see the transcript for details of the Committee's discussion.*

3. **DISCUSSION:** Discuss the acceptability of the timepoints for MRD assessment:
   - 9-months, 12-months, MRD negative complete response at any time
   - Requirement for assessment of durability

   ***Committee Discussion***: *The Committee generally agreed that the 9-month and 12-month timepoints were acceptable for MRD assessment. A couple of Committee members recommended that sustained MRD negativity may be helpful to assess durability. Several members commented that, while the proposed time points have been well studied, it is the responsibility of the clinician or researcher to decide whether to conduct additional MRD testing for additional timepoints or durability and correlation with long term outcomes. One*

*Committee member mentioned that while durability is important to assess, there is concern regarding the possibility of the burden for the patients being increased if researchers decide to conduct more frequent and ongoing bone marrow biopsies for a long period of time in order to add statistical power to a clinical trial. Another member commented that there should be flexibility and the best timepoint should be likely based on the trial, therapy, and setting. Please see the transcript for details of the Committee's discussion.*

4. **VOTE:** Does the evidence support the use of MRD as an accelerated approval endpoint in MM clinical trials?

   **Vote Result: Yes: 12 No: 0 Abstain: 0**

   ***Committee Discussion****: The Committee unanimously agreed that the evidence does support the use of MRD as an accelerated approval endpoint in MM clinical trials. A few Committee members acknowledged that MRD negativity may not correlate perfectly with clinical efficacy and overall survival. However, members agreed that the use of MRD in MM clinical trials to support accelerated approval is a reasonable approach. Other committee members stated their confidence that the design of FDA's Accelerated Approval Program will safeguard patient safety if drugs are given accelerated approval based on MRD as an endpoint. Please see the transcript for details of the Committee's discussion.*

The meeting was adjourned at approximately 3:20 p.m.