American Association for Cancer Research®
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615 Chestnut Street | 17th Floor
Philadelphia, PA 19106-4404
215-440-9300 | 215-440-9313 Fax
www.AACR.org | @AACR | facebook.com/AACR.org

Food and Drug Administration
Division of Dockets Management
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: Docket No. FDA-2025-D-2616. — "Minimal Residual Disease and Complete Response in Multiple Myeloma: Use as Endpoints To Support Accelerated Approval"

To Whom it May Concern:

On behalf of the American Association for Cancer Research (AACR), the world's oldest and largest scientific organization dedicated to accelerating cancer research, prevention, and cures, the AACR Regulatory Science and Policy Subcommittee expresses our appreciation for the opportunity to provide comments on the draft guidance "Minimal Residual Disease and Complete Response in Multiple Myeloma: Use as Endpoints To Support Accelerated Approval."

As a multidisciplinary coalition of academic investigators, clinicians, industry partners, and patient advocates, AACR is deeply committed to ensuring that regulatory frameworks evolve in parallel with scientific innovation and the lived realities of people with cancer. AACR applauds the U.S. Food and Drug Administration (FDA)'s efforts to spur innovation in drug development, in this case by clarifying best practice approaches for the use of minimal residual disease (MRD) and complete response (CR) as endpoints to support accelerated approval in multiple myeloma (MM), and for its continued consideration of external thought leadership towards improved outcomes for patients with cancer. Particularly, we are encouraged by FDA's longstanding efforts in novel endpoint development, and are thrilled to continue to work with the FDA on this topic through efforts such as the recent FDA-AACR Approach to Novel Oncology Endpoint Development Workshop. Our comments below largely request additional context and highlight areas where further clarification could enhance uptake of the suggestions provided in the guidance in pursuit of safe, innovative drug development.

1. **Outline Clear Contexts of Use for MRD in MM Drug Development**

One clear learning from the aforementioned FDA-AACR workshop on novel endpoint development was that endpoints need to be validated in specific contexts. For example, combining multiple datasets across different drug classes or clinical settings within an endpoint validation effort was generally thought to lead to difficulties in interpreting the outcome. While we appreciate the draft guidance's mention of clinical settings in which MRD is currently not supported, including precursor conditions, extramedullary disease, and maintenance settings, it would be valuable for FDA to explicitly state whether the existing data supports use across therapeutic modalities. If there are specific scenarios where more data is indeed needed to support the use of MRD as an endpoint for accelerated approval in MM, it would be useful if required data and the phase of development where it should be discussed with FDA were described.

2. **Clarify Parameters Used to Define MRD**

The guidance provides examples of varying landmarks for analysis of MRD, including 9-months, 12-months, or best MRD. It would be helpful if FDA clearly stated some considerations sponsors could take into account when determining these timepoints. Further, FDA should clarify whether these examples were chosen with intention for sponsors to harmonize around them, or whether they were chosen as potential examples. Additionally, the guidance states that MRD should be defined within the context of a complete response (CR), and that MRD should be evaluated within a specified time window of CR. A more concrete discussion of parameters that can aid sponsors in selecting this time window, as well as any potential flexibilities for when operational or clinical difficulties cause aligning these measurements to be difficult, would be appreciated. Although this draft guidance clearly focuses on bone marrow MRD assessment using flow cytometry or sequencing, it would also support innovation if FDA could address the potential for other upcoming approaches such as circulating tumor DNA or mass spectrometry.

3. Additional Considerations Regarding MRD Rate Calculations

It is stated in the guidance that the denominator used for MRD rate calculations should be all treated patients in single-arm trials, or the intent-to-treat population in randomized trials. In the March 2023 Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics Guidance for Industry, it is stated that "for a response-based endpoint, the analysis to support accelerated approval could be based on a pre-specified number of initially randomized patients…." We believe it would aid drug developers if FDA expanded upon the statements in this guidance to clarify a rationale for this potential discrepancy, or aligned the language with previous guidance.

Additionally, the guidance indicates that the assumed magnitude of treatment difference for MRD negativity rate within randomized trials and the MRD negativity rate proposed for single-arm trials, "should consider the toxicity of the therapy to inform benefit-risk." Given that sponsors may not understand the toxicity profile of a given agent during the trial design stage, as early safety evaluations in oncology generally do not include hypothesis testing, this may be difficult to implement for some therapeutics. More detail regarding how to take toxicity into account to determine these rates at the design stage would be welcomed.

4. Provide Further Guidance on Trial Design and Statistical Considerations

Several clarifications and additional details could provide sponsors with greater direction when designing trials, including when designing statistical analyses. While FDA does highlight that randomized trials are preferred, it would be valuable if FDA could provide input on parameters that would influence when single-arm trials using MRD or CR as primary endpoints may be acceptable, especially given that the guidance frequently references the possibility of use in both single-arm or randomized trials. Additionally, it would further support development in this space if FDA reassured sponsors that submissions based on MRD for accelerated approval will be adequate even in the absence of efficacy analyses of progression-free survival or OS (overall survival). This is because sponsors generally submit OS information at the time of any submission as part of safety assessments, but such time-to-event endpoints will likely be immature at the time of submission for accelerated approval, and allocating alpha for these early interim analyses may impact final analyses. This is particularly relevant as this guidance highlights a one-trial approach.

The guidance also highlights that sponsors should outline strategies for handling missing data, but does not provide further details that may be specific to MRD assessments. It would be helpful if it was stated whether different potential reasons for missingness, such as assay failures or missed assessments, should be uniformly classified as MRD positive or whether sensitivity analyses that differentiate various types of missing data might be acceptable. Finally, this guidance invokes aspects of the previous FDA guidance "Considerations for Generating Clinical Evidence from Oncology Multiregional Clinical Development Programs," particularly when discussing that the control arm of a randomized trial using MRD should be consistent with standard of care in the United States. Additional information regarding how these guidances interact, such as whether there are any specific strategies that would be particularly effective to mitigate the impacts of varying standards of care around the world in a multi-regional clinical trial utilizing MRD, would improve understanding of both guidances.

Conclusion

AACR applauds FDA's leadership in the development and validation of novel endpoints for use in oncology clinical trials. While already a strong document that outlines clear recommendations for the use of MRD as an endpoint for accelerated approval in MM, we believe that addressing the comments provided herein will improve its actionability and implementation by sponsors. We look forward to continued collaboration with FDA on the development and implementation of novel endpoints in oncology clinical trials in service of providing patients with access to safe, effective drugs as rapidly as possible.

Sincerely,

Kenneth Anderson, MD
Chair, Regulatory Science and Policy Subcommittee
The American Association for Cancer Research