American Society of Hematology
Helping hematologists conquer blood diseases worldwide

2026
President
Robert Negrin, MD
Stanford University
269 W. Campus Drive
Stanford, CA 94305
Phone: 650-868-8065

President-Elect
Cynthia Dunbar, MD
2127 California Street, NW
Washington, DC 20008
Phone: 202-819-6806

Vice President
Alison Loren, MD, MSCE
University of Pennsylvania
3400 Civic Center Boulevard
Philadelphia, PA 19104
Phone: 215-662-4859

Secretary
Jennifer Brown, MD, PhD
Dana-Farber Cancer Institute
450 Brookline Avenue
Boston, MA 02215
Phone: 617-632-5847

Treasurer
Joseph Mikhael, MD, FRCPC, MEd
Translational Genomics Research Institute
City of Hope Cancer Center
445 N. Fifth Street
Phoenix, AZ 85004
Phone: 602-343-8445

Councillors
Jennifer Holter-Chakrabarty, MD
Adam Cuker, MD, MS
Chancellor Donald, MD
Christopher Flowers, MD, MS
H. Leighton Grimes, PhD
Mary Horowitz, MD
Charlotte Niemeyer, MD
Mikkael Sekeres, MD, MS

Executive Director
Martha Liggett, Esq.

March 20, 2026

Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Submitted electronically via Regulations.gov

RE: Minimal Residual Disease and Complete Response in Multiple Myeloma: Use as Endpoints to Support Accelerated Approval; Draft Guidance for Industry; Availability [Docket No. FDA-2025-D-2616]

Dear Dr. Makary,

The American Society of Hematology (ASH) appreciates the opportunity to provide comments to the U.S. Food and Drug Administration (FDA) in response to the Agency's draft guidance for industry on Minimal Residual Disease and Complete Response in Multiple Myeloma: Use as Endpoints To Support Accelerated Approval (FDA-2025-D-2616). The Society thanks the FDA for the Agency's thoughtful and timely approach to this topic.

ASH represents more than 18,000 clinicians and scientists committed to studying and treating blood and blood-related diseases. These disorders encompass malignant hematologic disorders such as leukemia, lymphoma, and multiple myeloma, as well as classical hematology (non-malignant) conditions like sickle cell disease. In addition, hematologists are pioneers in demonstrating the potential of treating various hematologic diseases and continue to be innovators in the fields of stem cell biology, transfusion medicine, and gene and cell therapies. ASH membership is comprised of basic, translational, and clinical scientists, as well as physicians providing care to patients.

The Society thanks the FDA for releasing draft guidance outlining the Agency's expectations and current thinking on the use of Minimal Residual Disease (MRD) and Complete Response (CR) as endpoints to support accelerated approval in Multiple Myeloma (MM) trials. Many ASH members are clinical researchers who develop and participate in clinical trials, and clear, consistent guidance from the FDA is crucial to the success of their trials. We provide the following comments for your consideration.

ASH enthusiastically supports the FDA's guidance on allowing the use of MRD and CR as endpoints to support accelerated approval in MM trials. We believe that the draft guidance is consistent with the available evidence and will support continued innovation in MM treatment. Using MRD and CR as surrogate endpoints for progression-free survival (PFS) and overall survival (OS) will help address the challenge of increasing duration of response that slow trial timelines, facilitating ongoing and future clinical trials to make faster regulatory decisions and accelerate patient access to new therapies.

MRD and CR as Endpoints to Support Accelerated Approval in Multiple Myeloma Trials
We agree that MRD and CR can be used as endpoints to support accelerated approval in MM trials, although long-term endpoints like PFS or OS should still be collected as recommended in the guidance. ASH notes that in the draft guidance on line 97, "the randomized trial should be designed to adequately assess long-term clinical endpoints such as PFS or overall response rate as key objectives." We agree that collecting PFS as a long-term clinical endpoint should be a key objective, as stated on line 97. The statement goes on to suggest on lines 98-99 that "even if not a key objective, OS should be evaluated as a secondary endpoint or as a safety endpoint", to which we have no concerns. However, we would request that the FDA clarify the suggestion of overall response rate (ORR) as a long-term endpoint, as we believe that ORR and MRD are achieved at similar intervals and thus does not make a good long-term endpoint. The FDA could consider including OS as a more appropriate long-term clinical endpoint as a key objective along with PFS.

Overall, the guidance reflects the current state of knowledge regarding MRD and CR as potential endpoints. For instance, the correlation between MRD status and long-term outcomes is clear for most patients, making MRD not only a valuable trial endpoint but also an important tool in clinical practice for assessing treatment efficacy and prognosis. Patients with very good partial response (VGPR) generally do not appear clinically different from those who achieve CR or MRD-negative status in terms of symptoms or complications. Therefore, having MRD as an endpoint will be helpful to determine whether therapies being tested can achieve higher rates of MRD negativity, which is expected to translate into improved long-term outcomes, including longer freedom from disease complications, delayed need for more intensive therapy, and improved overall survival.

ASH urges the FDA to consider guidance acknowledging other emerging technologies (e.g., peripheral blood mass spectrometry), which early data suggest may show associations with long-term outcomes comparable to bone marrow–based MRD assessments. While the evidence may still be evolving, the guidance could include information about the types of data that would be required for peripheral blood–based approaches to be considered acceptable endpoints in the future.

Assessment of MRD Negativity
ASH agrees that MRD negativity should be assessed at a threshold of at least 1 in 10^5 residual tumor cells as this is appropriate and feasible for technology that is currently available. However, we recommend that FDA continue to be flexible and nimble as more data become available.

We also recommend that the FDA take into consideration some of the technical requirements for MRD assessments that may create practical limitations. Platforms such as clonoSEQ require a calibration sample, which can constrain trial design and reduce the clinical relevance or representativeness of enrolled populations. For example, trials evaluating maintenance or consolidation strategies ideally enroll patients after they have already responded to prior therapy, but identifying the necessary calibration sequence often requires reliable access to historical specimens. Because such samples are not always available, sponsors may instead enroll patients earlier, such as at the time of initial MM diagnosis, which can inadvertently skew study populations toward patients treated at academic centers and those who are healthier and more likely to meet eligibility criteria at diagnosis rather than at the maintenance or consolidation timepoint when the investigational intervention begins. Alternatively, flow cytometry does not face the same calibration constraints as clonoSEQ, but it remains less standardized in the United States than in Europe. Encouraging greater standardization of sensitive flow cytometry approaches in the United States could help address these limitations and improve evaluability for patients who lack adequate calibration samples for sequencing-based MRD assays.

Assessment of CR
ASH agrees with the requirement of having an independent review committee for assessment of CR. Given the nuance in interpretation of serum markers, having an independent review committee seems appropriate for trials where CR is being used as a primary endpoint for accelerated approval. ASH also agrees that CR should be assessed as an overall rate rather than at a specific time. This is appropriate since the criteria for CR that rely on serum paraprotein measurements evolve on a variable timeframe compared to bone marrow assessments. For instance, a patient may meet the bone marrow criteria for CR at the defined response assessment timepoint but it may take several months longer for the serum criteria for CR to be satisfied. Such a patient should be permitted to count as having a CR once the serum criteria are met.

Potential Consideration of Other Designs
ASH recommends that FDA considers other trial designs 1) to address concerns about toxicities that occur during longer follow up beyond the MRD assessment; and 2) for patients with progressive disease that is refractory to all effective therapies and for whom there is no standard therapy. The Society encourages FDA to consider amending the guidance to emphasize the importance of long-term follow-up for patients treated with novel therapies, given the potential for delayed toxicities and refractory disease. The Agency should also ensure that both short- and long-term toxicities are fully captured, which may not occur in the context of MRD-driven studies.

Lastly, the guidance implies a preference for randomized trials and MRD and CR endpoints in evaluation of new therapies. While this is reasonable, ASH asks that FDA consider cases where most enrolled patients in a trial have refractory MM. Even with all the recent progress in the field, patients commonly face progressive disease that is refractory to all effective therapies and there are patients for whom there is no standard therapy with established safety and efficacy. For such patients, partial response is often lifesaving. If the study has enrolled patients who were refractory to all standard therapies, overall response rate with an acceptable safety profile in a single-arm study should remain an acceptable endpoint for accelerated approval. We do not think that the approval should require proof of superiority to an established therapy, if the intended use is in patients refractory to that established therapy.

ASH appreciates the opportunity to provide these comments. We support the guidance and encourage the FDA to address the Society's feedback in the final version. Please consider ASH a resource; we would be pleased to provide additional information or support. If you have any questions, please use ASH Director of Government Relations and Public Health, Stephanie Kaplan (skaplan@hematology.org) as your point of contact.

Sincerely,

Robert Negrin, MD
President