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

RE: Approaches to Assessment of Overall Survival in Oncology Clinical Trials; Guidance for Industry, Docket Number: FDA-2024-D-5850

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the opportunity to provide comments to the U.S. Food and Drug Administration (FDA) in response to the Agency's draft guidance for industry on Approaches to Assessment of Overall Survival in Oncology Clinical Trials FDA-2024-D-5850.

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.

We thank the FDA for releasing draft guidance outlining the Agency's expectations and current thinking on the use of overall survival (OS) as an endpoint for oncology clinical trials. Many of our members are clinical researchers who design and run clinical trials. Thus clear, consistent guidance from the FDA is crucial to the success of their research. We provide the following comments for your consideration.

Clarifications:

Clarification from the FDA on the timeframe for OS as an endpoint in clinical trials would be helpful. Specifically, clinical trial sponsors would benefit from guidance on the expected duration of OS follow-up when the primary endpoint is a surrogate; the acceptable thresholds for completeness of survival data; and appropriate approaches for situations where treatment crossover is unavoidable. Additional guidance on how to adapt OS requirements in rare diseases or highly selective precision trials should also be included in any final guidance. These clarifications may help improve the feasibility of using OS as a primary study endpoint.

Overall Survival as an Endpoint in a Clinical Trial:

ASH appreciates that the draft guidance does not require overall survival (OS) to be the primary endpoint; however, it does recommend that OS be collected as a secondary or safety endpoint, with sufficient follow-up to rule out clinically meaningful harm. The Society supports the FDA's thinking that OS remains one of the most robust and unbiased clinical trial endpoints, serving as a safeguard against potentially misleading conclusions derived from surrogate markers. OS continues to be the gold standard when evaluating clinical benefit and long-term safety, particularly in oncology and hematologic malignancies. In indolent diseases such as early-stage

chronic lymphocytic leukemia (CLL) or chronic phase myeloproliferative neoplasms, surrogate endpoints like progression-free survival (PFS) often fail to capture late toxicities or unexpected survival advantages. Even when OS is not designated as the primary endpoint, collecting data on OS adds significant value from a patient-outcomes perspective. By pre-specifying OS as a primary endpoint, patient safety and accurate assessment of the real clinical impact of novel interventions can be effectively prioritized and investigated. For example, in acute myeloid leukemia (AML), some treatment regimens have demonstrated apparent benefits in terms of complete remission or PFS, but the benefits have not consistently translated into a true OS benefit, often due to cumulative toxicity or the limited efficacy of salvage therapies.

Another example of OS being valuable is in studies of allogeneic hematopoietic cell transplantation (HCT) where composite endpoints such as graft-versus-host disease–free relapse-free survival (GRFS) are often selected. GRFS is used in graft-versus-host disease (GVHD) prevention studies to measure the time from transplant until the first occurrence of grade III or grade IV of GVHD. In trials focused on reducing transplant-related toxicities, endpoints like GVHD-free survival may be prioritized as an endpoint while OS is considered secondary. These different approaches to a clinical trial are justified for certain scientific and practical reasons, but in all such cases OS data should still be systematically collected as either a primary, secondary, or a prespecified safety endpoint to ensure transparency and to guard against misleading drug trial conclusions.

Feasibility of Implementing this Guidance in a Trial Setting:

Overall, the Society believes the draft guidance is reasonable, applicable, and broadly feasible when designing clinical trials and conducting those trials in research settings. We support that the guidance establishes principles rather than creating rigid mandates such as emphasizing the importance of prespecifying OS, defining strategies for handling intercurrent events, and clarifying follow-up expectations. Additionally, the guidance provides information on safeguards that are critical to ensuring trial reliability and transparency, and the concepts in the guidance reflect current practice in oncology and hematology trials.

There are concerns about the practical application of certain provisions within the clinical trial setting. To illustrate these implementation challenges, members shared several examples.

One major challenge is the determination of how long patient follow-up is necessary to ascertain when OS as an endpoint has been met, while another is how to link OS directly to the investigational drug if the patient is or has taken multiple lines of therapy post-protocol. This is especially true in rare hematologic conditions. Additionally, competing risks such as severe infections or GVHD after transplantation may also obscure the impact of an investigational therapy. Rare disease studies and highly selected precision medicine trials pose additional feasibility challenges, as achieving sufficient sample size to demonstrate OS benefit is often unrealistic. Further considerations such as crossover considerations, statistical methods, indolent disease, and long term follow up are outlined in further detail below.

Crossover Study Considerations:

Another consideration is the frequent use of crossover (*a clinical trial in which all participants receive the same two or more treatments, but the order in which they receive them depends on the group to which they are randomly assigned)* in hematological trials. The Society supports the FDA's guidance on managing crossover, and subsequent therapies in OS analysis as appropriate. However, crossover trials may make interpreting OS data difficult, especially when a crossover study is used in clinical trials examining drugs used for immunotherapy, cellular therapy, or hematopoietic stem cell transplant, as these disease states often have delayed effects, and require multiple lines of therapy. For example, in trials with Bruton's tyrosine kinase and B-cell lymphoma 2 inhibitors in CLL or chimeric antigen receptor T-cell (CAR T-cell) therapies in aggressive lymphomas, crossover studies are common, which may dilute the survival effect. The Society also supports the FDA's emphasis on the importance of detailed documentation around the timing and reasons for crossover or subsequent therapies, to ensure transparent interpretation of survival outcomes. However, no final guidance should be overly restrictive regarding crossover studies as this could discourage enrollment in a clinical trial and conflict with any ethical obligations for clinicians to provide the best available treatment.

Statistical Methods Outlined in the Draft Guidance:

ASH believes the proposed statistical methods outlined in the guidance can be considered both appropriate and practical for real-world oncology trials, provided that their use is pre-specified in the study design, as such the Society recommends this point be stated clearly in the updated guidance. Additionally, ASH recommends that FDA clearly defines "futility" and "harm" in the final guidance as these terms mean something entirely different from a statistician's perspective. Traditional approaches, such as the Cox proportional hazards model and the log-rank test, remain suitable for conditions in which the assumption of proportional hazards is reasonably met, for example in AML or aggressive lymphomas. However, in situations where this assumption is not held, such as with immunotherapies or long-term maintenance strategies after hematopoietic stem cell transplantation, alternative approaches like Restricted Mean Survival Time (RMST) or landmark analyses provide a more reliable estimation of treatment effect and a more intuitive picture of survival differences. Additionally, causal inference methods designed to adjust for treatment crossover, such as the rank-preserving structural failure time model or inverse probability weighting, can offer valuable exploratory insights. Nonetheless, these methods rely on assumptions that cannot always be verified and therefore should complement but not replace the intention-to-treat principle as the primary analytic strategy.

Overall Survival Endpoints in Clinical Trials for Diseases with Long Survival Times or Indolent Progression:

Including OS data collection in clinical trials for diseases with long survival rates or indolent progression is challenging and could create a barrier to a timely regulatory decision for therapies used for these disease types as well as straining infrastructure and funding for clinical trials. For example, in conditions like CLL, follicular lymphoma, or early-phase myeloproliferative neoplasms, OS data can take a decade or more to mature. For these diseases, it is more feasible to use progression-free survival (PFS), minimal residual disease (MRD) negativity, or time to next treatment as primary study endpoints, while still collecting OS as a long-term safety measure. We believe that event-driven or predefined minimal follow-up strategies in the clinical trial may help capture meaningful OS data without delaying patient access to new therapies. Creative approaches such as leveraging disease registries, remote survival tracking, and using real-world data can also make long-term OS data collection more efficient.

We note that OS remains an important endpoint to fully understand the impact of a given therapy, even when survival differences may take years to emerge. In diseases like multiple myeloma or low-grade lymphomas, where patients may live many years after diagnosis, surrogate endpoints have been explored in trials, but OS data should still be collected to ensure that there are no late safety concerns or unexpected harm created by the treatment. Because competing risks, such as death from unrelated causes, can distort OS interpretation over time, follow-up duration and data analysis need to be carefully planned when designing a clinical trial. Finally, we suggest that the final guidance should set clear limits for OS follow-up and complementing OS data collection with disease-specific survival metrics which can help maintain study feasibility and interpretability without discouraging clinical research in indolent cancers.

Difficulties in Maintaining Long Term Follow-Up to Capture Overall Survival:

While we support the use of OS as a study endpoint, there are real-world challenges to capturing this data. Collecting and maintaining OS data over the long term presents significant logistical and methodological challenges. Ensuring complete and accurate follow-up is often difficult due to patient mobility, fragmented care, subsequent therapies, and limited access to mortality data. These barriers are especially pronounced in hematopoietic cell transplantation (HCT) and pediatric oncology trials where patients frequently transition between institutions or care systems. In adolescent and young-adult patients, long-term follow-up is especially difficult, as many are lost to tracking after care or their transition back to their primary care physician, which may compromise survival data quality. Clinical trial designs need to include effective strategies for capturing OS data like using multiple data sources to verify survival status, maintaining contact with patients through robust clinical trial retention plans, and then clearly distinguishing data that is collected between treatment completion and study follow-up.

Challenges to collecting OS data include following patients when they move, changing insurance coverage, or transitioning to non-affiliated providers, hospice, or community care.

Long-distance referrals and transitions from pediatric to adult care increase the likelihood of losing contact over time. Additionally, complex clinical pathways and subsequent therapies complicate the ability to attribute survival outcomes to the original study treatment. Many patients receive additional interventions such as CAR-T therapy, allogeneic stem cell transplantation, or newer targeted agents which make it difficult to attribute and interpret OS results from the original clinical trial therapy. We also believe that lack of financial resources and data limitations hinder long-term follow-up. Funding and infrastructure to support extended data collection are often insufficient, particularly in non-industry or academic studies. Additionally, deaths that occur outside the hospital system, or site of the original clinical trial are not always captured accurately due to limited or inconsistent access to national death registries, reducing the completeness and reliability of survival data.

Furthermore, capturing OS overtime has implications on the patient's quality of life; a factor that should not be discounted to the benefit of collecting this type of data. For example, GRFS is now supported as a more meaningful endpoint by many within the transplant community due to the significant impact that GVHD (and/or relapse) may have on a patient. While OS is important, there are too many nuances in clinical trials to make OS the primary endpoint in all studies, and it should not be inferred that OS is needed for regulatory approval. To do this has the potential to diminish the patient's voice in determining what is helpful and meaningful to them.

For these reasons, while the Society supports OS as an important clinical trial endpoint, the challenges we noted must be considered in trial design, and subsequent data collection.

Effects of Guidance on Oncology Clinical Trial Design:

If finalized, the recommendations would likely influence oncology trial design by encouraging more detailed and advanced planning around the OS endpoint. Investigators, prior to the start of the clinical trial, would need to pre-specify OS analysis plans that include harm detection rules, futility boundaries, and strategies for handling crossover and subsequent therapies within the estimated clinical trial framework. The creation of more robust follow-up protocols would need to be a key consideration in clinical trial designs to ensure that accurate and timely survival data points are captured. The guidance, if finalized seems to promote incorporating alternative statistical approaches, such as Restricted Mean Survival Time (RMST) and while setting clear plans for intercurrent events or non-proportional hazards, making OS analysis more deliberate and standardized across studies.

ASH notes that if the final guidance contains stricter guidelines, including a requirement for more longitudinal follow-up, this could make non-industry-sponsored or cooperative group trials harder to conduct, and significantly more costly. This may then shift the clinical trials and research currently being conducted by academic and independent researchers towards more industry-funded studies. We request that when the FDA is finalizing the guidance, these concerns are accounted for.

ASH appreciates the opportunity to provide these comments. ASH supports the concept of the guidance, and encourages the Agency to address the Society's feedback in the final version. We believe the draft guidance on the use of OS as a study endpoint is technically feasible and appropriate; however, we encourage the Agency to ensure the right balance between scientific study and patient-centered care. 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* or 202-776-0544) as your point of contact.

Sincerely,

Belinda R. Avalos, MD

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ASH President