American Association for Cancer Research®
FINDING CURES TOGETHER®

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-2024-D-5850 — "Approaches to Assessment of Overall Survival in Oncology Clinical Trials"

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cancer research, prevention, and cures, we express our appreciation for the opportunity to provide comments on the draft guidance "Approaches to Assessment of Overall Survival in Oncology Clinical Trials."

As a multidisciplinary coalition of academic investigators, clinicians, biostatisticians, 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 commends the U.S. Food and Drug Administration (FDA) for providing recommendations that clarify best practices for the analysis of overall survival (OS) in oncology clinical trials and for the agency's commitment to considering input from all parties involved in oncology drug development. We are encouraged that this draft guidance directly builds on insights from the 2023 FDA–AACR–ASA Workshop on Overall Survival in Oncology Clinical Trials, and incorporates many of the points highlighted in our joint 2024 article on Improving Collection and Analysis of Overall Survival Data.

Our comments are intended to provide additional context and highlight areas where further clarification could strengthen the guidance's scientific foundation, enhance operational feasibility, and safeguard patient interests.

1. Clarify and Emphasize the Intended Scope of the Guidance
AACR supports FDA's emphasis on pre-specifying OS assessments in randomized oncology trials, both as indicators of efficacy and safety. However, the draft could more clearly define its scope. While it states that the guidance applies broadly to randomized trials supporting marketing approval, it would be helpful to clarify whether this includes all randomized trials or only phase III trials with registrational intent.

2. Provide Nuanced Guidance on Interim Analyses for Futility and Harm
AACR agrees that interim analyses are vital for protecting participants but require careful implementation. In oncology, particularly with immunotherapies, early survival data are often immature. Multiple early looks can create misleading impressions of harm or futility, risking premature termination of promising therapies. AACR recommends that FDA emphasize the need for statistical justification and optimized timing for interim analyses. Clarifying when futility (lack of efficacy) versus harm (safety) analyses should be used would promote consistency. AACR also recognizes that event-driven analyses remain ideal; however, FDA could outline situations where time-based analyses may be appropriate, for example in diseases with prolonged survival, to provide sponsors practical flexibility while maintaining the intent of patient protection.

3. Align Overall Survival Safety Oversight with Data-Monitoring-Committee Practices
Independent Data Monitoring Committees (DMCs) are central to ongoing patient-safety oversight in oncology trials. Their charters typically include predefined rules for assessing safety and survival data. AACR encourages FDA to explicitly acknowledge this role and emphasize coordination, rather than duplication. Clarifying how OS monitoring can be integrated within established DMC processes could enhance transparency, efficiency, and impartiality while minimizing operational burden.

4. Maintain Flexibility and Clarity for Crossover Designs and Unequal Randomization
AACR strongly supports flexibility for crossover, which is often essential in life-threatening diseases or where treatment options are limited. Allowing patients on control arms access to investigational therapy after progression promotes enrollment, access, and trust. While crossover complicates OS analyses, validated tools (e.g., rank-preserving structural failure time model and inverse probability of censoring weighting) can address these challenges. AACR encourages FDA to emphasize pre-specification of analytic approaches and

transparent reporting of assumptions. Crossover may also be appropriate in trials where accrual or retention is challenging, not only where options are limited. Similarly, the Agency could clarify considerations for unequal randomization, which may aid recruitment but complicate analysis.

5. Expand Statistical Flexibility and Encourage Complementary Endpoints

AACR applauds FDA's call for rigorous pre-specification of statistical methods and estimands. This section could be strengthened by referencing complementary metrics such as restricted mean survival time, especially when proportional hazards assumptions do not hold. These methods, discussed at the 2023 FDA–AACR–ASA Workshop, are gaining wide acceptance. AACR also encourages FDA to acknowledge the value of patient-reported outcomes (PROs) and real-world survival data as contextual evidence that enrich OS interpretation, helping stakeholders assess both magnitude and quality of survival benefit.

6. Clarify Expectations for Defining and Evaluating Potential Harm

AACR supports FDA's goal of ensuring trials are adequately powered to rule out clinically meaningful detriment to survival. The final guidance could expand on how sponsors should define and justify harm thresholds, recognizing that tolerance for risk varies by disease severity and patient values. Flexibility in analytical methods (e.g., Bayesian or simulation-based modeling) should be encouraged, particularly when OS data are immature. The draft aligns with emerging international principles emphasizing proportionality, transparency, and patient-centered interpretation of outcomes. These frameworks advocate focusing trials on interventions that deliver tangible, meaningful improvements in OS and quality of life. AACR further recommends highlighting frameworks that quantify meaningful benefit, such as the ESMO Magnitude of Clinical Benefit Scale (MCBS v2.0). Encouraging sponsors to design and power studies around such thresholds would strengthen interpretability and patient relevance. Additionally, FDA should stress transparent reporting of follow-up duration and censoring in OS analyses. Reports should clearly include median and range of follow-up, proportion of censored patients by arm, and sensitivity analyses assessing the impact of censoring on OS results. These metrics are essential for evaluating data maturity and robustness.

7. Reinforce That Post-Hoc and Subgroup Analyses Are Exploratory

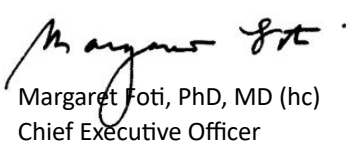
AACR agrees that subgroup analyses can identify effect modifiers or safety signals but should be interpreted cautiously. Post-hoc findings are inherently variable and should be considered hypothesis-generating. FDA may consider reinforcing that exploratory analyses should be guided by biological plausibility and, where appropriate, prospectively validated before informing labeling or indication restrictions. Strengthening guidance for pre-specification of key subgroups while allowing room for hypothesis-driven exploration will balance innovation with statistical rigor.

Conclusion

AACR applauds FDA's leadership in advancing the regulatory science of OS evaluation in oncology clinical trials. By refining recommendations on areas such as interim analyses, crossover design, harm thresholds, subgroup interpretation, and maintaining the flexibility to incorporate patient perspectives, the Agency will strengthen both the rigor and compassion that define modern cancer drug development. AACR values FDA's continued collaboration on regulatory science initiatives that advance and strengthen the scientific and patient-centered foundations of oncology drug development.

Sincerely,

Lillian Siu, MD, FRCPC
President



Margaret Foti, PhD, MD (hc)
Chief Executive Officer

Kenneth Anderson, MD
Chair, Regulatory Science and Policy Subcommittee