October 20, 2025

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket No. FDA-2024-D-5850; Approaches to Assessment of Overall Survival in Oncology Clinical Trials; Guidance for Industry; Draft Guidance

To Whom It May Concern:

On behalf of LUNGevity Foundation, the nation's preeminent lung cancer nonprofit that funds research, provides education and support, and builds communities for the more than 230,000 Americans diagnosed with lung cancer each year[i] and over 600,000 Americans living with the disease[ii], we appreciate the opportunity to submit these comments to the U.S. Food and Drug Administration (FDA) regarding the Draft Guidance "**Approaches to Assessment of Overall Survival in Oncology Clinical Trials**."

Serving as a measure of both safety and efficacy, overall survival (OS) is a clinically relevant endpoint that not only provides information valuable to patients but can be pragmatically assessed with minimal burden to trial participants. Interpretation of OS, however, can be hampered by intercurrent events like crossover, the availability of which may be vital to facilitating trial enrollment and as an important means of providing patients access to novel effective therapies upon progression. Therefore, while we support the preference for OS data generation, regardless of the defined primary and secondary efficacy endpoints, to provide a more complete understanding of safety, we ask that the Agency balance the need for robust OS data and its interpretation with patient-centric factors, such as crossover, that improve patient experience and trial efficiency but may confound OS interpretation.

Impact of OS Requirements on Use of Crossover

Allowing crossover of trial participants from one arm to another upon progression, as well as the use of unequal randomization schemes (e.g., 2:1 investigational: control), can be seen more favorably by prospective trial participants, as the perception is an increased likelihood of receiving the investigational agent, and thus facilitate enrollment. This is particularly true in cases where few alternative treatment options exist. Offering the opportunity for crossover upon progression can also aid in participant retention and reduce asymmetric early dropout of participants in the control arm, which has proven challenging in recent oncology clinical trials and hinders result interpretations[iii]. The need for robust

patient enrollment and retention aided by these trial design elements are particularly critical for trials targeting smaller patient populations. Trials assessing therapies in rare biomarker-selected populations, for example, may struggle with slow enrollment given the relatively small pool of potential participants. Enrollment challenges in these cases may already be further compounded by other hurdles such as central testing requirements. Beyond the advantages to enrollment and retention, crossover can also importantly improve clinical outcomes as well as quality of life (QoL) for patients, even in the absence of significant improvement in overall survival and especially when alternative treatments have low tolerability.

According to the draft guidance, given the potential of crossover to impact the interpretation of OS results, its use should be limited except when other therapeutic options are limited. However, there are other scenarios not mentioned in the draft guidance wherein allowing crossover may be appropriate, including: when the time to reaching OS is relatively short and patients are unlikely to otherwise receive subsequent therapy post-progression; in assessments of investigational therapies with well-known efficacy wherein an OS benefit would be expected despite robust crossover; when the investigational therapy is approved in a later line of therapy; when similar drugs are available off-study, and others. While we understand the importance of limiting the use of factors like crossover that may confound OS interpretation, we stress the importance of balancing this concern with the value of crossover and the benefits it can provide to patients and request the Agency include further considerations for the appropriate use of crossover in the finalized guidance document.

Alternative and Supplementary Measures to OS as an Assessment of Harm

While OS can serve as a reliable measure of harm, given its potential confounding by intercurrent events, we encourage the consideration of alternative and/or supplementary measures of harm. Patient-reported outcomes (PROs), for instance, can be operationalized as a measure of harm and provide a clear patient-centric picture of treatment tolerability. Any guidance the Agency could provide on addressing any associated challenges with collection of these data (e.g., ensuring continued QoL data collection post-progression) could be valuable. Also, patient-level data on adverse events, clinical laboratory abnormalities, pharmacokinetic exposure, and other measures could provide important context to observed OS trends and provide a more detailed view of the overall safety profile. We encourage the FDA to include considerations for the use of alternative and supplementary measures to OS as an assessment of harm in the final guidance document.

Approaches to Handling OS Confounding by Intercurrent Events

The draft guidance provides direction on approaches, including the use of causal models, to adjust for intercurrent events, like crossover, in the evaluation of OS. Further details on the utility of specific adjustment methods (e.g., rank preserving structural failure time models (RPSFTM), inverse probability of censoring weights (IPCW), two-stage estimation (TSE)) in the final guidance could be valuable to trial sponsors. Furthermore, we request that the final guidance include information on how the FDA interprets high OS hazard ratios in studies with high rates of crossover, particularly when the investigational therapy does not have a notably worse toxicity profile than the control arm.[iv] Guidance on the usefulness of earlier safety and efficacy endpoints in determining acceptable levels of uncertainty regarding OS and other tools that could be employed to increase confidence in observed OS results (e.g., data from ongoing trials, real-world data) could also be provided. We request that the Agency provide further information on the handling of OS results in the face of confounding factors.

Clarity on Interim OS Analyses

The draft guidance recommends the inclusion of interim OS analyses for futility or harm in the protocol and statistical analysis plan (SAP) when appropriate. However, as the document also states, the use of immature OS data can cause uncertainty in treatment effect estimates. Though mature OS data would provide a clearer picture of a drug's safety profile, the need to wait for OS data to mature must be balanced with avoiding delays in the delivery of promising new treatment regimens to patients. This is particularly critical in early-stage disease in which waiting for mature OS data would be detrimental to efficient clinical trials.[v] We recommend the FDA include further guidance on the appropriate handling of immature OS data, including in the early-stage setting.

LUNGevity appreciates the opportunity to comment on this important draft guidance. OS measures provide insights into both the safety and efficacy of novel treatment regimens while imposing minimal burden to trial participants, making OS an important and clinically meaningful endpoint to patients. LUNGevity supports the Agency's expectation of OS as a prespecified safety endpoint, so long as this expectation is balanced with the continued ability to incorporate trial design elements that may confound OS interpretation but that improve trial efficiency and patient experience. With the proposed additional clarifications and considerations, we support the guidance. Please feel free to reach out to me at bmckelvey@lungevity.org with any questions.

Sincerely,

Brittany McKelvey

Brittany Avin McKelvey
Senior Director, Regulatory Policy
On Behalf of LUNGevity Foundation

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[i] Howlader N, Noone AM, Krapcho M, et al. (eds). SEER Cancer Statistics Review, 1975-2018, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2018/, based on November 2020 SEER data submission, posted to the SEER web site, April 2021.

[ii] Centers for Disease Control and Prevention. United States Cancer Statistics. Available at https://gis.cdc.gov/Cancer/USCS/#/Prevalence/

[iii] Oncologic Drugs Advisory Committee Meeting (October 5, 2023). U.S. Food and Drug Administration. Sotorasib for KRAS G12C Mutated Locally Advanced or Metastatic Nonsquamous Non-Small Cell Lung Cancer. Available at: https://www.fda.gov/media/172756/download

[iv] Rodriguez LR, Gormley NJ, Lu R, Amatya AK, Demetri GD, Flaherty KT, Mesa RA, Pazdur R, Sekeres MA, Shan M, Snapinn S, Theoret MR, Umoja R, Vallejo J, Warren NJH, Xu Q, Anderson KC. Improving Collection and Analysis of Overall Survival Data. Clin Cancer Res. 2024 Sep 13;30(18):3974-3982.

[v] Friends of Cancer Research. Enhancing Study Designs and Interpretation of Interim Overall Survival Data in Oncology Trials: Friends of Cancer Research White Paper, 2024. https://friendsofcancerresearch.org/publication/white-paper-enhancing-study-designs-and-interpretation-of-interim-overall-survival-data-in-oncology-trial/