November 18, 2024

Division of Dockets Management (HFA-305)
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. FDA-2024-D-3163; Considerations for Generating Clinical Evidence from Oncology Multiregional Clinical Development Programs, Guidance for Industry—Draft Guidance

To Whom It May Concern:

On behalf of the 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we appreciate the opportunity to submit these comments to the U.S. Food and Drug Administration (FDA) regarding the draft guidance "**Considerations for Generating Clinical Evidence from Oncology Multiregional Clinical Development Programs**."

As part of our mission to improve outcomes for patients diagnosed with lung cancer, LUNGevity supports and engages in efforts to improve the efficiency of clinical trial conduct. By accessing a larger pool of potential trial participants, multiregional clinical trials (MRCTs) can accelerate trial enrollment, thus shortening drug development timelines and expediting the delivery of novel therapies to patients. LUNGevity appreciates the FDA's issuance of the draft guidance on the appropriate generation of clinical evidence from MRCTs intended to support an FDA marketing application. Providing clarity on FDA's expectations for MRCT data collection can help ensure these trials are run with minimal hurdles and delays.

Diversity in MRCT Populations with Rare Molecular Subtypes

While we recognize the importance of ensuring that MRCT data reflect the diversity of the U.S. patient population to support FDA approval, this requirement may pose significant challenges in trials involving rare molecular subtypes of cancer. Targeted therapies have revolutionized the treatment of rare lung cancer subtypes, particularly those characterized by certain mutations or fusions in non-small cell lung cancer (NSCLC), offering significant clinical benefits with fewer side effects. **We urge the FDA to consider flexibility around requirements for representativeness of trial populations for MRCTs focused on rare subtypes, where achieving demographic diversity may be difficult.** Maintaining appropriate flexibility will be critical in ensuring continued progress in delivering effective therapies to these unique patient populations.

Pragmatic Elements in MRCT Design

Incorporating pragmatic clinical trial elements, such as broadening eligibility criteria and reducing the number and/or frequency of assessments, can facilitate enrollment of a diverse, U.S.-representative patient population. Pragmatic approaches not only reduce the burden on participants—facilitating the inclusion of historically underrepresented groups—but also enable greater participation by community-based clinical sites, as encouraged by the draft guidance.

That said, sponsors often encounter regulatory inconsistencies across regions, particularly around the adoption of pragmatic elements. For instance, stricter safety data collection requirements in the European Union may limit the inclusion of these elements in MRCT protocols. **We recommend that the FDA engage with global regulatory authorities to align expectations on the utility and acceptability of pragmatic elements in oncology trials, fostering broader international consistency.**

Considerations for Post-Progression Therapies and Crossover

We appreciate the FDA's recognition of potential regional disparities in access to subsequent therapies for patients who progress while participating in an MRCT. Variable availability of post-progression therapies across regions can complicate the interpretation of overall survival (OS), particularly in MRCTs implementing crossover to allow control arm patients to access experimental therapies. **We request additional clarity on how the FDA evaluates overall survival (OS) data in the context of such regional disparities. Specifically, we ask the FDA to clarify when OS data would be required for marketing applications and how the Agency would assess potential confounding factors in MRCTs.** Providing sponsors with explicit guidance upfront will help streamline trial design and data interpretation.

LUNGevity appreciates the opportunity to provide input on this important guidance. Clarifying expectations for MRCT data used to support FDA marketing applications will further reinforce the ability of these trials to expedite the availability of innovative therapies for patients. We welcome the chance to collaborate further and provide additional patient-centric perspectives.

Please feel free to contact me at **aeferris@lungevity.org** with any questions or for further discussion.

Sincerely,

Andrea Stern Ferris
President and Chief Executive Officer
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/.