March 20, 2023

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

Submitted electronically via http://www.regulations.gov

Dear Sir or Madam:

On behalf of LUNGevity Foundation, the nation's preeminent lung cancer nonprofit organization that funds research, provides education and support, and builds communities for the more than 230,000 Americans diagnosed with lung cancer each year[1] and the more than 400,000 Americans living with the disease[2], we appreciate the opportunity to submit comments on the draft guidance "Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases" (Docket No. FDA-2022-D-2827).

Delivering cutting-edge, safe, and effective therapies to patients is the shared responsibility of drug developers, clinicians, regulators, and patient advocates. Embedded in this mission is the tension between moving as quickly as possible to address the life-threatening set of diseases that is cancer and taking the time to weigh all benefits and risks of investigational therapies, including patients' quality of life and ability to function while taking them, before putting them on the market. With this in mind, we commend the Food and Drug Administration (FDA) Oncology Center of Excellence (OCE) for continuing to strive for a more innovative, patient-centric oncologic drug development paradigm by asking sponsors to think critically about how they arrive at the recommended dosage to be included in labelling. Although we are not convinced of the utility and necessity of all the recommendations put forth in the guidance, we appreciate the Center's call to collect and evaluate a wide array of data for the dose finding process.

Specifically, LUNGevity was pleased to see mention in the guidance of including patient-reported outcomes (PROs) in early phase dose finding trials as one factor for assessing tolerability. Patient insights can provide a depth of understanding about side effect burden and drug tolerability that cannot be replicated with clinician-reported outcomes, as has been shown in the literature.[3] However, it is critical that patients **understand**—not just that they are informed

[1] National Cancer Institute Surveillance, Epidemiology, and End Results Program, Cancer Stat Facts: Lung and Bronchus Cancer. https://seer.cancer.gov/statfacts/html.lungb.html. Accessed 9/26/2022.
[2] Centers for Disease Control and Prevention. United States Cancer Statistics. https://gis.cdc.gov/Cancer/USCS/#/NationalPrevalence/. Accessed 9/26/2022.
[3] Brundage, Michael D., Joseph L. Pater, and Benny Zee. "Assessing the reliability of two toxicity scales: implications for interpreting toxicity data." *JNCI: Journal of the National Cancer Institute* 85.14 (1993): 1138-1148.

of—how and when PRO data will be used and the importance of providing honest, accurate answers to PRO questions in order for their full benefit to be realized.[4]

We believe the primary value of PRO data is their ability to identify and inform management of lower grade, yet persistent, symptomatic side effects. If PRO data are thoughtfully captured during the dose finding process, they could help to manage side effects and mitigate risk in later phases of drug development. While we appreciate the reference to the draft Guidance for Industry "Core Patient-Reported Outcomes in Cancer Clinical Trials (June 2021)" for purposes of instrument selection and assessment frequency, it should be noted that the strategy outlined within that guidance is intended for registration trials. It would likely be sufficient in these early phase trials, to consider collecting only unobservable symptomatic side effects (e.g., nausea, constipation, neuropathy, etc.).

LUNGevity does, however, recognize the potential infrastructure and logistical challenges capturing patient experience data in early phase trials may pose, especially for smaller biotechnology companies who are often the ones shepherding promising drug candidates through phase I.[5] Moreover, we acknowledge the reality, especially in oncology, that many drug candidates that succeed in phase I will not survive the development pipeline all the way to the New Drug Application stage,[6] and the resulting reluctance to invest in PROs if resources are limited. Some of these challenges may be attenuated by thoughtfully selecting a very limited set of appropriate PRO measure items on symptomatic side effects that could be used to assess the totality of tolerability. For example, Shepshelovich et al. collected side effect information using the PRO-CTCAE at just three time points in a phase I study, which, with 91% of the planned PRO assessments fully completed,[7] was found in a subsequent study to be sufficient to identify additional side effects that would have been missed, some entirely by clinician report (e.g., sexual health like vaginal dryness, cognition, and visual disturbances).[8]

We appreciate the Center's advice to work "with patients and other key stakeholders including patient advocacy groups…(who) will provide valuable input on important safety and tolerability

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Basch, Ethan, et al. "Adverse symptom event reporting by patients vs clinicians: relationships with clinical outcomes." *JNCI: Journal of the National Cancer Institute* 101.23 (2009): 1624-1632.

[4] Basu Roy U, King-Kallimanis B, Kluetz PG et al. "Learning from Patients: Reflections on Use of Patient-Reported Outcomes in Lung Cancer Trials." JTO. 2018 (13) 1815-1817. https://doi.org/10.1016/j.jtho.2018.09.003.

[5] Kneller, R. The importance of new companies for drug discovery: origins of a decade of new drugs. *Nat Rev Drug Discov* **9**, 867–882 (2010). https://doi.org/10.1038/nrd3251

[6] Takebe T, Imai R, Ono S. The Current Status of Drug Discovery and Development as Originated in United States Academia: The Influence of Industrial and Academic Collaboration on Drug Discovery and Development. Clin Transl Sci. 2018 Nov;11(6):597-606. doi: 10.1111/cts.12577.

[7] Shepshelovich, Daniel, et al. "Feasibility assessment of using the complete Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) item library." *The oncologist* 24.4 (2019): e146-e148.

[8] Veitch ZW, Shepshelovich D, Gallagher C, Wang L, Abdul Razak AR, Spreafico A, Bedard PL, Siu LL, Minasian L, Hansen AR. Underreporting of Symptomatic Adverse Events in Phase I Clinical Trials. J Natl Cancer Inst. 2021 Aug 2;113(8):980-988. doi: 10.1093/jnci/djab015

considerations" (lines 190-192). However, LUNGevity would like to see additional detail on when and how sponsors should engage these groups to ensure meaningful insights are gathered to help guide the PRO strategy on high-level concepts. Once the side effect profile is better characterized, it is worthwhile to re-engage patients and advocates to clarify the relative importance of specific side effects to the targeted patient population so that those can then be included in the PRO measurement strategy moving forward.

Finally, LUNGevity is concerned that terminology used in this guidance and for Project Optimus, namely, dose optimization and optimal dose over-promises. Even though the Center is careful to include the potential plural with "dosage(s)" throughout the guidance, the word "optimal" denotes a singular best, just as "optimization" is the process of arriving at the best. This terminology is misleading for patients, who may believe that with dose optimization in place, drug toxicities and dose reductions will be things of the past. However, in reality, no dose will be "best" for everyone regardless of how carefully and with how much information it was selected. We suggest OCE adopt more practical language, such as "dose selection," and be candid about what the new expectations for arriving at the recommended dose will—and will not—mean for patients.

LUNGevity supports the overall intent of the OCE's dose optimization initiative. Through our work to transform clinical trials to make them more friendly to patients, we are examining all aspects of trial design and conduct to identify areas in need of a fresh approach. Modernizing the dose selection process to account for new drug modalities and mechanisms of action, and weighing the impact of persistent, low-grade adverse events on patients' quality of life, are valuable and necessary efforts and we applaud the Center for putting them front-and-center. However, we want to ensure that the process does not become overly prescriptive in the name of patient centricity and does allow for flexibility to accommodate disease- and population-specific considerations. Please feel free to reach out to me at 240-454-3100 or aeferris@lungevity.org if you have any questions or would like to engage me or my staff in further dialogue.

Sincerely,

Andrea Stern Ferris
President and Chief Executive Officer
LUNGevity Foundation

ABOUT LUNGEVITY: LUNGevity's mission is to improve outcomes for people diagnosed with lung cancer. Our goals are three-fold: (1) to accelerate research to patients that is meaningful to them; (2) to empower patients to be active participants in their care and care decisions; and (3) to help remove barriers to access to high quality care. We have the largest lung cancer survivor network in the country and actively engage with them to identify, understand, and address unmet patient needs. We also have a world class Scientific Advisory Board and Health Equity Council that guide the programs and initiatives of the organization.