



May 25, 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 Dr. Fashoyin-Aje:

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 year¹ and the more than 400,000 Americans living with the disease², we appreciate the opportunity to submit comments on the draft guidance “Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics” (Docket No. FDA-2023-D-0110).

LUNGevity thanks the Food and Drug Administration (FDA) Oncology Center of Excellence (OCE) for its willingness to embrace the accelerated approval pathway (AAP), which has provided millions of patients with cancer access to promising therapies years before they would have been available through regular approval. The AAP has had an outsized, positive impact on the lung cancer community, in particular those with non-small cell lung cancer (NSCLC). There have been 21 accelerated approvals for NSCLC indications since 2003, two-thirds of which have been converted to full approvals and only one of which has been withdrawn³. In an evaluation of clinical benefit of drugs approved through the AAP, early access to two NSCLC therapies—alectinib and pemetrexed—was estimated to have conferred more than 189,000 additional life years (compared to accepted alternative treatments at the time of accelerated approval) across the roughly 587,000 patients who received the medicines⁴. Although we realize that not every disease community has experienced such favorable outcomes as a result of the AAP, including patients with small cell lung cancer, LUNGevity offers these comments from a privileged position of expectation of continued benefit from the use of the AAP in oncology drug development.

We commend the OCE for its willingness to engage with drug developers, clinical investigators, and patient advocates in the leadup to publishing the draft guidance to identify opportunities and challenges—both general and disease-specific—for designing clinical trials to support accelerated approval. One such effort, the multi-stakeholder working group convened by Friends of Cancer Research

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 Friends of Cancer Research Accelerated Approvals dashboard. <https://friendsofcancerresearch.org/accelerated-approvals-in-oncology-1992-present/>. Accessed 5/12/2023.

⁴ Partnership for Health Analytic Research. July 2022. “Issue Brief: Clinical Benefits of Accelerated Approval.” <https://www.pharllc.com/publication/clinical-benefits-of-accelerated-approval/>. Accessed 5/19/2023.



(FOCR) over the summer and fall of 2022, produced a white paper⁵ highlighting considerations specific to the one-trial approach discussed on pages 5-7 of the guidance, which may be helpful to cite or include. Specifically, Figure 2 is a useful visual representation of clinical trial milestones in the one- vs two-trial approaches for accelerated approval, and Appendix 2 provides important considerations on timing of endpoint readouts under different scenarios. Having this additional context, or something similar, would help guide sponsors as they consider whether, and which approach for, accelerated approval is appropriate for the investigation they are planning.

LUNGEvity was appreciative to see that single-arm trials may still be an acceptable means of predicting clinical benefit for accelerated approval. Many of the accelerated approvals for NSCLC indications are based on data from single-arm trials and we would not want this important mechanism closed off for future evaluations. It would be useful for the guidance to offer more detail on what the OCE considers “clinical and regulatory context(s)” that would and would not merit use of single-arm trials. For example, in Appendix 1 of the white paper on trial design approaches for accelerated approval⁵, the FOCR working group cited the case study of abemaciclib + fulvestrant for HR+/HER2- advanced or metastatic breast cancer, for which it notes “FDA discourag[ed] a single-arm trial to support accelerated approval with a separate RCT to confirm benefit.” Including this or similar examples and outlining what factors contributed to the Agency’s discouragement would provide valuable insight into their thinking and help companies evaluate their own plans to use single-arm trials, even if the circumstances are not identical.

We also recommend the inclusion of more detail in the guidance regarding how alternative trial designs can be leveraged to support accelerated approval. Master protocol studies, in which one trial is designed to evaluate multiple hypotheses⁶, may prove to be attractive alternatives to traditional, stand-alone trials—especially for rare diseases and/or diseases with multiple subgroups—by offering efficiencies for patients, sponsors, and regulators alike. Stakeholders would benefit from understanding how identified design and statistical considerations for master protocols⁷ apply in an accelerated approval setting.

Similarly, it would be helpful for FDA to outline the applicability of real-world and/or external data in trials intended to support accelerated approval. The recent draft guidance on external control arms⁸ should feature prominently in the current guidance given its relevance to the discussion on single-arm trials. More broadly, providing an understanding of what the Agency considers to be appropriate uses of evidence generated from real-world data for both single-arm and randomized controlled trials in the context of accelerated approval would be welcomed.

⁵ Friends of Cancer Research. “Accelerating Investigation of New Therapies in Earlier Metastatic Treatment Settings.” Annual Meeting 2022.

⁶ Woodcock J, LaVange LM. “Master protocols to study multiple therapies, multiples diseases, or both.” *N Engl J Med.* 2017; 377:62-70.

⁷ “Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics. Guidance for Industry.” <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/master-protocols-efficient-clinical-trial-design-strategies-expedite-development-oncology-drugs-and-biologics>.

⁸ “Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products. Draft Guidance for Industry.” <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-design-and-conduct-externally-controlled-trials-drug-and-biological-products>.



The importance of the AAP to patients cannot be overstated. Drugs approved through this pathway have provided hope and, crucially, time. LUNGEvity applauds the OCE for championing the use of the AAP as well as undertaking critical evaluations of both its benefits and shortcomings. We appreciate the need for high standards for evidence and outcomes for drugs being considered for accelerated approval in order to ensure, to the extent possible, patient safety and benefit. Overall, LUNGEvity supports the considerations presented in the draft guidance, including the recommendation to have the confirmatory trials open and enrolling/-ed at the time of an accelerated approval decision when a two-trial approach is used; from a patient perspective, this makes sense to speed enrollment to the second trial. We do, however, think the document would benefit from including additional detail in the areas outlined above. 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,

A handwritten signature in blue ink that reads "Andrea Stern Ferris".

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.