March 10, 2025

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

RE: Docket No. FDA-2024-D-2402-0002; Considerations for Including Tissue Biopsies in Clinical Trials; Guidance for Industry, Investigators, Institutions, and Institutional Review Boards; Draft Guidance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we appreciate the opportunity to submit these comments to the U.S. Food and Drug Administration (FDA) regarding the Draft Guidance "**Considerations for Including Tissue Biopsies in Clinical Trials**."

Tissue biopsies play an important role in lung cancer diagnosis, staging, and treatment decision-making. LUNGevity Foundation supports the use of tissue biopsies in clinical trials to ensure patients meet eligibility criteria, as well as to assess efficacy, if necessary. We support the FDA's position to not place additional risk and/or burden on patients by requirement of unnecessary tissue biopsies. We have conducted several research studies[iii,iv,v] including perspectives from patients, oncologists, radiologists, and pathologists to understand perceptions on biopsies in the clinical care of patients with lung cancer. Overall, patients are amenable to biopsies if there is actionability in the results and the reasoning for the biopsy is clearly explained. As patients with lung cancer now have the availability of multiple lines of treatments, patients are willing to undergo additional biopsies after treatment start, including at time of recurrence, if the results may inform participation in future clinical trials or treatments.[iv] The majority of surveyed oncologists (130 US-based oncologists from academic research centers, community cancer centers, and private practice) noted it was critical to explain the reasoning behind re-biopsy procedures to patients, which translated to an overwhelming patient willingness to undergo the re-biopsy.[iii] These findings support the concepts in the draft guidance for collection of tissue biopsies only if necessary and with clear justification (e.g., in informed consent procedures and patient provider communications). Below, we provide a few additional areas for clarification or expansion as the Agency finalizes the guidance.

Factors to Determine Level of Risk for Tissue Biopsies

The draft guidance highlights the need to consider the degree of risk involved in conducting the tissue biopsy, providing the contrast of a skin biopsy versus a brain biopsy. Additional examples with varying risk levels or factors that may determine the level of risk of the biopsy would be valuable, since the draft guidance notes that alternative approaches should be considered for "tissue sites that pose higher risk." Factors could include, for example, whether the biopsy involves general versus local anesthesia, or could differentiate between biopsies requiring hospitalization versus those performed in outpatient facilities.

Sampling Quantity within a Required Biopsy

The draft guidance focuses on which biopsies are critical and required, but does not make a distinction or elaborate on, within a single biopsy, the quantity that is required or critical. For example, a biopsy taken at a singular point in time could be one or multiple cores or one or multiple passes as part of a fine needle aspiration (FNA), which also will be dependent on the amount of tissue needed for a specific test. In addition to the concern that multiple biopsies are taken throughout a trial, multiple samples at a biopsy may also be needlessly taken. The obtainment of more tissue than necessary may increase the inherent risks of biopsy. The FDA should provide guidance and clarification that, within a single collection time point, no more than the necessary amount of tissue should be taken, and that sponsors should provide justification for the amount. As an example, an interdisciplinary qualitative study conducted by LUNGevity[vi] identified perceived challenges to obtaining percutaneous lung needle biopsy specimens for successful molecular testing in patients with advanced non-small lung cancer by radiologists and pathologists. There were wide differences in opinion regarding the best approach for judging sample adequacy and on the amount of sample necessary. This demonstrates the need for additional guidance to support sampling quantity.

Use of Existing Pathology Specimens

Patient tissue is extremely valuable. As patients with lung cancer live longer, they may participate in multiple clinical trials for multiple lines of therapy. Therefore, the ability for patients to have tissue available to be used for the next clinical trial for enrollment or biomarker status determination is paramount. The draft guidance notes that "including a required biopsy in the clinical trial protocol may be reasonable…if the information cannot be obtained from existing pathology specimens". Patients may needlessly have a biopsy performed due to the inability to locate existing specimens from other institutions or due to

the inability of patients or sponsors to obtain the past specimens due to ownership or access issues. We support clarity that attempts should be made to utilize existing pathological specimens before subjecting patients to additional biopsies.

Encouraging Research and Innovation

Lastly, while we support the Agency's overall goal of avoiding an undue burden on patients by not requiring biopsies for exploratory or non-key secondary endpoints, we also recognize the value of biopsies collected for specific research objectives to support innovation that may lead to future breakthroughs and more streamlined drug development processes. For example, the pooled analysis[vii] cited in FDA's final guidance as the main literature to validate the use of pathological complete response (pCR) as an intermediate endpoint for accelerated approval in breast cancer[viii] was supported by clinical trials in which pCR was a secondary or exploratory endpoint. We support the ability to conduct similar studies supporting validation of novel endpoints across cancer types in the future. While further study is needed to understand decision-making for trial participants to undergo an optional biopsy depending on its purpose, patients may be more inclined to undergo a biopsy to support an exploratory endpoint if they know how it will be used. We support optionality for biopsies for non-key secondary or exploratory endpoints to reduce unnecessary burdens for trial participants; patients should be able to remain on a trial regardless of their participation in these procedures. However, given the potential for these biopsies to support more efficient drug development and the delivery of novel therapies to patients in the future, trial participants should be made aware of the purpose of the biopsy and its potential benefits. We hope that the Agency can provide further guidance on how sponsors can clearly communicate the research objectives of the optional biopsies to encourage patient participation.

LUNGevity appreciates the opportunity to comment on this important guidance. Patients participating in clinical trials should not face the risks and burden of multiple tissue biopsies unnecessarily. The Agency's guidance on inclusion of tissue biopsies in clinical trials provides clarity on the collection and justification of these biopsies within a clinical trial setting. 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 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] rebiopsy-oncologist-perspective-white-paper.pdf
[iv] LUNGevity. Willingness for multiple biopsies to improve quality of lung cancer care: Understanding the patient perspective. 2016; https://lungevity.org/sites/default/files/file-uploads/rebiopsy-white-paper-march-2017_0.pdf. Accessed 2018, October 28
[v] Optimizing molecular testing of lung cancer needle biopsy specimens: potential solutions from an interdisciplinary qualitative study - PMC
[vi] Optimizing molecular testing of lung cancer needle biopsy specimens: potential solutions from an interdisciplinary qualitative study - PMC
[vii] Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis - The Lancet
[viii] download