American Association for Cancer Research®
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Food and Drug Administration
Division of Dockets Management
5630 Fishers Lane, Rm. 1061
Rockville, MD, 20842

Re: Docket No. FDA-2024-D-2402, "**Considerations for Including Tissue Biopsies in Clinical Trials; Draft Guidance for Industry, Investigators, Institutions, and Institutional Review Boards**"

To Whom It May Concern:

On behalf of the American Association for Cancer Research (AACR), the world's oldest and largest scientific organization dedicated to cancer research, education, and collaboration, we express our sincere appreciation for the opportunity to provide comments on the FDA's draft guidance, "Considerations for Including Tissue Biopsies in Clinical Trials." We recognize the significant impact this guidance will have on advancing cancer research and clinical trials, and we commend the agency's commitment to enhancing the integrity of clinical research while ensuring that regulatory frameworks support both scientific progress and patient safety.

The inclusion of tissue biopsies in clinical trials holds tremendous potential for transforming our understanding of cancer and accelerating the development of life-saving therapies. We believe this draft guidance represents an important step toward enhancing scientific rigor, improving patient outcomes, and fostering innovation in drug development. The AACR strongly supports the FDA's initiative to incorporate tissue biopsies as a tool to advance personalized medicine, better understand tumor biology, and identify biomarkers to guide therapeutic decision-making.

As a consortium of academic clinical investigators, industry professionals, and patient advocates committed to innovative cancer research, we share many of the concerns raised in the guidance, and we thank the FDA for providing clarity on this important issue. However, we respectfully offer the following comments and recommendations to further strengthen the guidance and address potential challenges in its implementation:

1. Alignment Between FDA and NCI Terminology
We recommend aligning the FDA's approach with the National Cancer Institute's (NCI) established frameworks and terminology, which could facilitate clearer communication across the research community. In particular, the NCI's use of "integral," "integrated," and "exploratory" biomarkers provides a well-established model for defining the role of biomarkers and biopsies in clinical trials. Incorporating these terms could lead to more consistent language and expectations for trial sponsors, investigators, and regulatory agencies.

2. Feasibility of Non-Integral Analyses with Respect to Optional Biopsies
The draft guidance suggests that tissue biopsies be optional in the clinical protocols when used to evaluate non-key secondary and exploratory endpoints. This patient-centered approach is appreciated, as it seeks to expand access and prevent unintended harm. However, we are concerned that making such biopsies optional may limit the ability to conduct thorough analyses of integrated and exploratory biomarkers. Without adequate tissue samples, critical mechanistic insights may be lost, potentially affecting the overall scientific value of the trial. We urge the FDA to consider how the optional nature of non-essential biopsies could impact the quality and completeness of these analyses. Some evidence

suggests that optional biopsies result in fewer biopsies collected, and, consequently, less biopsy data reported. This could lead to statistically underpowered analyses and uninterpretable results. We hope that the FDA can address this concern.

Additionally, while we agree that trial protocols should clearly state the rationale for including biopsies, we encourage stronger requirements for reporting biopsy-related adverse events and greater support for the broader reporting of biopsy-derived data. As part of Project Optimus, integrating pharmacodynamic (PD) data in dose decision-making is a priority, and obtaining this data often requires looking at select biomarkers and/or drug levels within the tumor. This cannot be assessed through peripheral blood draws alone and requires biopsy specimens for a more comprehensive PD assessment.

3. Categorization of Endpoints and Concerns of Increased Burden

We seek further clarity on how the FDA intends to define and categorize "key" versus "non-key" endpoints. Specifically, if sponsors elevate non-key secondary endpoints to "key" to mandate biopsies, this could inadvertently increase the burden on participants and clinical trial personnel. For example, biomarkers like PD-L1 expression on tumor cells are commonly used to determine patient eligibility or predict therapy response. While PD-L1 expression may be considered a "key" endpoint in some trials, in others, it may be a secondary or non-key endpoint, still requiring biopsies to explore its use as a biomarker or monitor immune response over time. We encourage the FDA to provide additional guidance on how "key" endpoints are designated, ensuring biopsies are only required when scientifically interrogating an endpoint, without placing undue strain on patients or trial personnel.

The AACR appreciates the FDA's thoughtful approach in drafting this guidance on tissue biopsies in clinical trials. We support the agency's efforts to enhance the scientific rigor and patient-centric nature of clinical trials and believe this draft guidance represents an important step forward. However, we urge the FDA to consider the potential challenges associated with limiting mandatory biopsy requirements, clarify the terminology used for endpoints, and provide further flexibility in the use of biomarkers.

We acknowledge that patients for whom obtaining a biopsy may pose significant risks should not be denied access to novel therapeutic interventions. However, this can be more clearly defined within the context of the protocol and biostatistical requirements for endpoint assessment. For example, it could involve allowing such patients while ensuring a sufficient number of participants to account for those who are unable to undergo a biopsy. These adjustments will help ensure that tissue biopsies are used in a way that maximizes both scientific value and patient safety.

Thank you for your unwavering commitment to advancing cancer research and regulatory science. We look forward to ongoing collaboration with the FDA to further refine this important guidance.

Sincerely,

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