September 15, 2025

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

RE: Docket No. FDA-2025-D-1071; Development of Cancer Drugs for Use in Novel Combination—Determining the Contribution of the Individual Drugs' Effects; Guidance for Industry; Draft Guidance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we appreciate the opportunity to submit these comments to the U.S. Food and Drug Administration (FDA) regarding the Draft Guidance "**Development of Cancer Drugs for Use in Novel Combination—Determining the Contribution of the Individual Drugs' Effects**."

This draft guidance is particularly relevant to our lung cancer community, given the rapid pace of combination therapy development, notably in non-small cell lung cancer (NSCLC) in which combination regimens are needed to overcome resistance seen with both targeted therapies and immunotherapies. A clear understanding of the Agency's expectations for clinical trials supporting the approval of combination regimens is vital to maintain an accelerated and productive pace in combination therapy development for patients who are refractory to available therapies. LUNGevity applauds the FDA's issuance of the draft guidance to provide further clarification on demonstrating the contribution of individual drugs to a combination regimen's overall effects.

Determination of the contribution of effect for a combination's individual components is important to ensure each agent is necessary for the overall regimen's clinical benefit and to avoid unnecessary toxicity. However, the need to have rigorous demonstration of the contribution of effect must be adequately balanced with feasibility concerns with the overall complexity of the clinical trial. This is important not only to ensure efficient trial conduct (e.g., minimizing enrollment hurdles) but also, in some cases, to maintain equipoise and minimize the number of patients exposed to likely inefficacious therapies in instances when one component is expected to have minimal efficacy alone.

Since 2021 LUNGevity Foundation has engaged in several multi-stakeholder discussions specifically related to this topic in an effort to understand the scientific, clinical, and regulatory factors influencing clinical trial designs needed to demonstrate the contribution of effect for combinatorial treatments for non-small cell lung cancer (NSCLC). These include hosting a workshop and subsequent launch of a working group including industry experts, key opinion leaders, and regulatory officials to discuss key considerations for combinatorial clinical trial designs, specifically to address resistance to PD-1/PD-(L)1 pathway inhibition. Output from those efforts was published in 2023[iii]. A key theme throughout these activities was the sense that additional regulatory guidance in this area would be helpful and welcome. Informed by these discussions, we provide the following areas for additional clarification and expansion by the Agency for consideration this guidance document is finalized.

Data Supporting the Contribution of Effect

The draft guidance highlights the "context of disease and population" as a consideration to inform the amount and types of appropriate clinical data and trial designs to support the assessment of contribution of effect. Additional granularity and/or examples provided by the Agency regarding these factors would be helpful. For example, the appropriate evidence package for demonstrating contribution of effect will likely be different for an agent in the combination in which the indication of interest is within the same cancer type (e.g., moving up from second line to frontline or studying the agent in an earlier stage of disease), compared to an indication in a different tumor type for a previously approved combination regimen. One could consider that additional pre-clinical or clinical evidence could be necessary to support the agent's use and contribution of effect in a different tumor type compared to the same tumor type. However, the guidance does not make this distinction and lists "context of disease and population" broadly.

Pertaining to external data, the draft guidance highlights examples of rationale for use of external data to demonstrate contribution of effect. This includes when a single agent is not expected to be as effective compared to its use in combination with other drug classes. This scenario can be illustrated by the example of combining novel agents without a primarily immunologic mechanism of action with PD-(L)1 pathway blocking agents, which evidence suggest may synergize to benefit patients with immune checkpoint inhibitor (ICI)-refractory NSCLC[iii]. A key challenge is assessing the contribution of effect of the novel agent and that of the switching the PD-(L)1-targeting agent, particularly given the low likelihood that switching PD-(L)1-targeted agents alone will provide clinically significant benefit and thus the minimal equipoise of a PD-(L)1 monotherapy arm. We believe this type

of scenario would warrant use of external data for assessing contribution of effect rather than factorial design, and we request that the Agency provide such specific examples and include associated recommendations in the final guidance wherever possible.

Additionally, it may be beneficial for the FDA to create a tool kit, similar to the Oncology Dosing Tool Kit[iv], to help stakeholders identify and justify the clinical data that could be used to support the assessment of contribution of effect for combination therapies. Similarly to the dosing tool kit, a systematic template for sponsors listing the types of data (e.g., pre-clinical, early clinical, registrational trial, external data) that may be leveraged to support the assessment of contribution of effect and the sponsors' justification for its use can help instigate early discussions with the Agency on the appropriateness of the data sources.

Additional Clarification on Appropriate Endpoint Selection

The guidance highlights the use of pharmacodynamic/response biomarkers, citing overall response rate (ORR) with duration of response contextual information to demonstrate contribution of effect with the advantage of providing earlier readouts compared to long-term endpoints such as PFS or OS. However, the draft guidance later mentions the caveat that an ORR advantage would not necessarily indicate clinical benefit and brings into question the ability to use early endpoints for demonstrating contribution of effect. We request the Agency provide a clearer statement of the reliability of early endpoints like ORR in demonstrating contribution of effect, as early endpoints provide valuable information, particularly in indications where long-term clinical endpoints would take a considerable time to reach maturity.

Further, the draft guidance outlines potential limitations related to the comparability of endpoints used across trials in the acceptability of external data to assess contribution of effect. The draft guidance notes, in the presence of such limitations, that a "large magnitude of the treatment effect" of the combination may be needed to overcome these limitations to support the use of the combination. The draft guidance also uses the term "modest" elsewhere in the document to qualify treatment effects. What constitutes a "large" or "modest" treatment effect is not defined in the guidance, and assumed definitions of effect may vary significantly depending on the disease and treatment context. For example, a "modest" effect may still be meaningful in an indication with few viable treatment options, whereas a modest effect with a combination may not be practice changing in indications with multiple treatment options. Further clarification from the Agency on defining "large" versus "modest" treatment effects would be helpful and support the intricacies of meaningful drug development.

Additional Clarification on Types of External Data

The draft guidance cites the high relevance of external data from clinical trials in the same setting and indication for assessing contribution of a combination's components, though it does not speak to opportunities to leverage trial data from the same tumor type but in other lines or settings (e.g., moving from second to first line, from metastatic to locally advanced disease). While trial data in the same indication would be optimal, data in a different indication may be useful, particularly if the safety and efficacy profile is likely to be similar. In a different but related context, accelerated approvals have been converted to full approvals based on results from confirmatory trials conducted in a different indication (e.g., line of therapy or stage of disease) than that for which an accelerated approval was given. While we recognize potential caveats (e.g., the potential difference in drug activity between different lines of therapy, particularly when a patient has been treated with a drug from the same class), it seems possible to leverage trial data from the same tumor type in a different indication to support the assessment of contribution of effect.

Furthermore, consideration or additional clarification in the guidance on the acceptability of the use of external trial data from other in-class agents would be valuable, as these data could similarly be useful in providing context of an agent's treatment effects. We ask the Agency to include information on the potential, as well as the limitations, of these kinds of external clinical trial data.

Also, the draft guidance underscores the importance of using external data from "comparable populations" analyzed across the combination regimen and its individual components. We request additional details on how comparability is defined, with examples of parameters for its assessment, encompassing both demographic and clinical factors. For example, previous trial data generated outside of the intended indication may include differing proportions of patients based on biomarker status than the intended indication, and this may impact the data's utility in demonstrating contribution of effect.

Pre-Clinical Evidence Generation

As noted in the draft guidance, the development of novel combinations can be supported by strong biologic rationale which may be derived from nonclinical characterization of each drug. The FDA has recently signaled moving away from animal testing[v], and, as noted in the guidance, there is a lack of appropriate animal models for drug combination development in oncology. Therefore, additional clarity is needed on acceptable designs for pre-clinical studies generating data that may serve as rationale (e.g., pharmacodynamic data) for the development of new combinations, as well as on the amount of pre-clinical data deemed to be appropriate to show sufficient activity.

Furthermore, while the draft guidance focuses on the use of preclinical and early clinical data to support efficacy signals for combinations, the document should also consider language to support the use of such data in elucidating the safety and toxicity profile of a novel combination. The draft guidance could also elaborate on how external data can be used to understand the influence of individual components on the overall tolerability of a combination, especially when a component is not being studied as a monotherapy in the indication being studied to ensure that patients are not exposed to undue toxicities.

Statistical Considerations

We request that the final guidance provide more information on the FDA's expectations surrounding statistical analyses of studies assessing combination regimens. Further clarity on when formal statistical comparisons between arms will be required, including those leveraging external data, would be helpful.

Contribution of Effect Assessment within the Oncology Development Landscape

It is important that sponsors have clear and practical plans for their development of combination drug regimens, taking into consideration not only adequately assessing contribution of each component to overall treatment effects. For example, although dosage optimization is not addressed in the draft guidance, sponsors may face significant logistical challenges when assessing contribution of components to a combination's overall treatment effect while also exploring multiple dosages.

Similarly, trials assessing perioperative combination therapy regimens may be particularly challenging to conduct. In July 2024, the Agency's Oncologic Drug Advisory Committee (ODAC) voted in favor of a proposed requirement that trial design proposals for perioperative regimens for resectable NSCLC include adequate assessment of the contribution of each (neoadjuvant and adjuvant) treatment phase. As a four-arm factorial trial design would be the optimal assessment of both contribution of phase for a perioperative regimen, as well as of contribution of components for 2-drug combination, trials assessing perioperative drug combinations could become extremely complex. However, three perioperative immunotherapy regimens have been approved in NSCLC, all of which included an ICI + chemotherapy combination in the neoadjuvant phase[vi,vii,viii]. We request that the final guidance include considerations on assessment of contribution of effect alongside contribution of phase and dose optimization efforts.

LUNGevity appreciates the opportunity to comment on this important draft guidance. In the rapidly changing landscape of oncology drug development, combination therapies play an increasingly important role. Ensuring the appropriateness of each agent in the combination

to the contribution of the overall treatment effect is crucial for patients to not be unreasonably exposed to additional toxicities. The Agency's guidance on demonstration of contribution of effect and potential clinical trial designs and use of external data to support this demonstration will help support robust and meaningful trials in this space. 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 McKelvey

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] Zhang T, Forde PM, Sullivan RJ, Sharon E, Barksdale E, Selig W, Ebbinghaus S, Fusaro G, Gunenc D, Battle D, Burns R, Hurlbert MS, Stewart M, Atkins MB. Addressing resistance to PD-1/PD-(L)1 pathway inhibition: considerations for combinatorial clinical trial designs. J Immunother Cancer. 2023 May;11(5):e006555.

[iv] U.S. FDA. Oncology Dosing Tool Kit. https://www.fda.gov/about-fda/oncology-center-excellence/oncology-dosing-tool-kit

[v] FDA News Release (April 10, 2025): FDA Announces Plan to Phase Out Animal Testing Requirement for Monoclonal Antibodies and Other Drugs. https://www.fda.gov/news-events/press-announcements/fda-announces-plan-phase-out-animal-testing-requirement-monoclonal-antibodies-and-other-drugs.

[vi] FDA approves neoadjuvant/ adjuvant pembrolizumab for resectable non-small cell lung cancer. Oct 16, 2023. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-neoadjuvant-adjuvant-pembrolizumab-resectable-non-small-cell-lung-cancer

[vii] FDA approves neoadjuvant/adjuvant durvalumab for resectable non-small cell lung cancer. Aug 15, 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-neoadjuvantadjuvant-durvalumab-resectable-non-small-cell-lung-cancer

[viii] FDA approves neoadjuvant/adjuvant nivolumab for resectable non-small cell lung cancer. Oct 03, 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-neoadjuvantadjuvant-nivolumab-resectable-non-small-cell-lung-cancer