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-2025-D-1071, "**Development of Cancer Drugs for Use in Novel Combination-Determining the Contribution of the Individual Drugs' Effects**"

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education, and collaboration, we express our sincere appreciation for the opportunity to provide comments on the FDA's draft guidance, "Development of Cancer Drugs for Use in Novel Combination-Determining the Contribution of the Individual Drugs' Effects." 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.

We appreciate the thoughtful expansion of recommendations beyond the 2013 Co-development Guidance to address combinations involving investigational drugs and/or previously approved agents for different indications. The evaluation of the contribution of individual components in combinatorial cancer therapies holds tremendous potential for transforming our understanding of treatment mechanisms and accelerating the development of life-saving therapies.

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 FDA for providing clarity on this important issue. However, we respectfully offer the following recommendations to strengthen the draft guidance and ensure its feasibility, scientific rigor, and ethical grounding:

1. Clarify the Scope and Primary Objective of the Guidance
While the guidance briefly notes that its primary objective is to evaluate the contribution of individual components to a combination's efficacy, this point is currently embedded in the text and could be overlooked. Making this point unambiguous will ensure readers understand that safety, dosing, and other aspects of drug development are not the focus of this document and are addressed elsewhere. This framing will help sponsors design programs with the appropriate evidentiary focus, avoid unnecessary safety-related duplications, and align expectations early in development.

2. Provide Clearer Criteria for Deviating from Full Factorial Designs
While factorial trials remain the preferred approach, their feasibility is often limited by large sample size requirements, particularly in rare cancers or biomarker-defined subpopulations, and by limited monotherapy activity. We urge FDA to specify quantitative or qualitative thresholds for effect size that would justify alternative designs (e.g., adaptive, hybrid, or external control–based approaches); to clarify, for three- or four-arm trials, which pairwise comparisons are primary and must be powered (e.g., A+B vs SOC/placebo) to guide efficient trial planning; and to address the acceptability of unequal randomization schemes (e.g., 3:1:1:1) to reduce patient exposure to potentially less effective monotherapies. The CheckMate 227 trial, for example, demonstrates that when feasible, factorial designs can yield high-quality evidence for confirmation of efficacy (COE) while still accommodating biomarker-defined subgroups. It evaluated nivolumab plus ipilimumab in advanced non-small cell lung cancer (NSCLC) using a multi-part, partially factorial design.[1] Patients were stratified by PD-L1 expression and randomized across various treatment arms, enabling direct comparison of multiple combinations and monotherapies. This design provided robust evidence of the contribution of individual components and supported FDA approval of the combination.

1. Hellmann MD, et al. N Engl J Med. 2019;381:2020-2031

3. Address Ethical Considerations When Monotherapies Are Clearly Inferior

In cases where early data or strong biological rationale indicate that a combination meaningfully outperforms standard therapies in overall or progression-free survival, it may be ethically inappropriate to randomize patients to suboptimal monotherapy arms. We recommend explicit guidance on when omission of monotherapy arms is justified. Exposing patients to arms with anticipated inferior outcomes can compromise patient welfare, reduce trial acceptability among investigators and participants, and slow accrual. Moreover, in rare or refractory cancers where treatment options are extremely limited, the ethical implications of such randomization are magnified, as patients may not have subsequent opportunities to access the superior therapy outside the trial setting. We recommend that FDA provide explicit criteria or a decision-making framework for when omission of monotherapy arms is justified.

4. Strengthen Recommendations on Use of External Data

We support the use of high-quality, patient-level external data when factorial designs are infeasible. To ensure rigor and transparency, we recommend defining "complete" and "high-quality" external datasets, including minimum covariate, endpoint, and follow-up requirements; encouraging mandatory public sharing of patient-level trial data to enable such analyses; addressing harmonization of endpoint definitions and assessment schedules across internal and external datasets, particularly for imaging-based measures; and, discussing acceptable statistical methods (e.g., causal inference, Bayesian approaches) to mitigate biases inherent in external control comparisons. KEYOTE-146, which evaluated pembrolizumab + lenvatinib combination in advanced endometrial carcinoma, demonstrated how external data can support approval.[2] This study received accelerated FDA approval in 2019 without a randomized control arm in the pivotal trial. Instead, FDA relied heavily on historical and real-world data from patients treated with standard agents (e.g., doxorubicin, paclitaxel) to contextualize the observed overall response rate (approximately 38%) and the durability of those responses. This example illustrates how carefully selected, high-quality external data can provide compelling evidence for contribution of effect when traditional randomized trials are infeasible. The combination later received regular FDA approval in 2021 following completion of the phase III KEYNOTE-775/Study 309.[3]

5. Incorporate Toxicity and Therapeutic Index into COE Evaluation

While this guidance focuses on demonstrating the efficacy contribution of each component in a novel combination, the ultimate regulatory decision is grounded in a benefit–risk assessment. In clinical practice, efficacy gains that come at the cost of significant added toxicity may undermine the real-world utility of a regimen, particularly in cancers with multiple therapeutic options. For example, when veliparib, a PARP inhibitor, was combined with cyclophosphamide, tolerability issues required a 75–90% dose reduction of veliparib compared with its use as monotherapy.[4] This example underscores the importance of evaluating the therapeutic index when determining the clinical utility of a combination regimen. We recommend that the COE framework explicitly integrate therapeutic index considerations, balancing incremental efficacy against the severity, reversibility, and manageability of adverse events. This would align COE assessment with the clinical decision-making process oncologists navigate daily, in which treatment selection frequently depends on tolerability and its impact on patients' quality of life.

6. Provide Specific Pathways for Rare Cancers and Molecularly Defined Populations

In rare cancers and narrowly defined molecular subgroups, patient populations are often extremely limited. This scarcity makes it challenging to conduct adequately powered factorial trials that assess the contribution of each component in a novel combination. Without alternative evidentiary pathways, the development of promising therapies in these settings risks being delayed or halted due to feasibility constraints rather than a lack of scientific or clinical merit. We recommend that FDA outlines pragmatic, fit-for-purpose strategies for demonstrating COE in these populations.

7. Specific Comments on Draft Guidance Text

Line Numbers	Comment	Proposed New or Edited Language
212–215	The discussion of hypothesis generation seems out of scope for a guidance focused on determining treatment effects.	We recommend removing these lines or rephrasing to emphasize that only fit-for-purpose data are suitable for direct comparisons.

2. KEYNOTE-146/Study 111; Makker V, et al. J Clin Oncol. 2020;38:2981-2992

3. KEYNOTE-775. J Clin Oncol. 2023 Jun 1;41(16):2904-2910

4. Randomized Trial of Oral Cyclophosphamide and Veliparib in High-Grade Serous Ovarian, Primary Peritoneal, or Fallopian Tube Cancers, or BRCA-Mutant Ovarian Cancer. *Clin Cancer Res*. 2015;21(7):1574-1582. doi:10.1158/1078-0432.CCR-14-2565

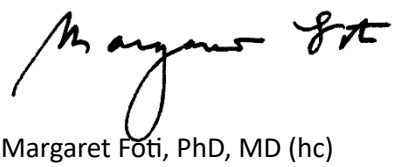
223	"Efficacy effect estimation" may be unnecessarily narrow since other sections also highlight safety.	We recommend replacing "efficacy effect estimation" with the broader term "effect estimation" to align terminology across the document.
244	The phrase "selection of participants" may be misinterpreted as implying prospective recruitment.	Consider revising to "selection of participants' data" to more clearly reflect retrospective or external dataset use.
258	The term "cross-trial" may exclude valuable real-world data sources.	We recommend using "cross-study" instead of "cross-trial" to reflect a broader evidentiary base, inclusive of RWD.
261	The limitation of analytical methods is relevant to study design as well as interpretation.	We suggest replacing "interpretation" with "employed," so that the caution applies to both the design and analysis stages.
316	Post-trial follow-up could be strengthened by integrating real-world data sources.	We recommend adding language (to the bullet on line 323 or a new bullet) that linkage to trial participants' health records, using privacy-preserving record linkage systems, may facilitate the collection of treatment exposures, confounders, and outcomes. In some cases, such data could also help quantify and adjust for differences in patient characteristics and design elements across treatment arms.

The AACR appreciates FDA's efforts to address this critical aspect of oncology drug development. By clarifying design expectations, strengthening external data standards, and incorporating ethical and rare disease considerations, the final guidance will better support innovative, scientifically sound, and patient-centered development of novel cancer drug combinations.

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

Sincerely,

Lillian Siu, MD, FRCPC
President



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