Development of Cancer Drugs for Use in Novel Combination – Determining the Contribution of the Individual Drugs' Effects Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
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Guidance for Industry

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Development of Cancer Drugs for Use in Novel Combination – Determining the Contribution of the Individual Drugs' Effects Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations for characterizing the safety and effectiveness of individual drugs[2] for use in a novel combination regimen in treating cancer. Demonstrating the contribution of each drug to the overall treatment effect that is observed for the population is referred to as contribution of effect throughout this guidance. This guidance is intended for sponsors developing drugs for use in combination for the treatment of cancer. FDA believes the recommendations in this guidance relevant to demonstrating the contribution of the individual investigational drugs to the effect(s) of the combination are consistent with the requirements of 21 CFR § 300.50, "fixed-combination prescription drugs for humans" and the guidance expands on the recommendations in the 2013 guidance for industry *Codevelopment of Two or More New Investigational Drugs for Use in Combination* (the 2013 Codevelopment Guidance).[3]

This guidance reflects FDA's current thinking regarding the use of clinical data for demonstration of contribution of effect for the following types of novel combinations in oncology:

- Two (or more) investigational drugs[4] that have not been previously approved by FDA for any indication

[1] This guidance has been prepared by the Oncology Center of Excellence (OCE), Center for Drug Evaluation and Research (CDER), and Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] For the purposes of this guidance, the term *drug* includes both human drugs and biological products regulated by CDER and CBER.

[3] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[4] The scope of the 2013 Codevelopment guidance is limited to new investigational drugs that have not been previously developed for any indications. For the purpose of this guidance, *investigational drugs* refer to drugs that have not been approved by FDA but may have been previously developed for other indication(s).

- An investigational drug with a drug(s) approved for a different indication

- Two (or more) drugs approved for a different indication(s)

This guidance does not address contribution of effect in settings where an investigational drug is being developed in combination with a drug approved for the same indication for the purposes of comparing the approved drug to the combination (i.e., "add-on" trials to standard of care (SOC)) or to fixed combinations of previously approved drugs for the approved indication(s).

In addition, this guidance does not address safety or dosing considerations when designing trials to study two or more drugs when used in combination. Nor does it address the evaluation of safety data to support the benefit-risk of two or more drugs when used in combination. For more information on these concepts, refer to the 2013 Codevelopment Guidance.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

Combination therapy in oncology is an important treatment modality. Scientific advances have increased our understanding of the pathophysiological processes that underlie many cancers. This increased understanding has provided further impetus to develop new therapeutic approaches using combinations of drugs directed at multiple therapeutic targets to improve treatment response, minimize adverse events, or both. A novel combination of drugs may be considered for development when the necessity of each drug in the proposed combination is supported by a strong biologic rationale including the nonclinical characterization of each drug in the combination and early clinical evidence. Examples of such rationale include, but are not limited to:

- Drugs that inhibit distinct targets in the same molecular pathway or distinct steps in disease pathogenesis, provide inhibition of both a primary and compensatory pathway, or inhibit the same target at different binding sites to decrease resistance or allow use of lower doses to minimize overall toxicity.

- An investigational drug that is expected to have limited activity as monotherapy but may potentiate the treatment effect of the second drug in the combination (synergy) based on relevant nonclinical studies and/or short-term clinical studies on an established biomarker.

- Information from early clinical trials support limited or lack of efficacy of an individual drug(s) but the combination may provide a significant therapeutic advance that is superior to the individual drug(s).

Lack of appropriate animal models for development of oncology drugs in combination remains a challenge to adequately demonstrating contribution of effect. Additionally, because preclinical studies do not necessarily predict clinical activity of the drug, in most cases, clinical information will provide the most compelling rationale for the contribution of effect.

A critical aspect of codevelopment of novel combinations of oncology drugs is the characterization of the safety and effectiveness of the individual drugs in the combination because the benefit of using the individual drugs in combination is weighed against the added toxicity when they are used together. In some cases, the conventional approach to demonstrating contribution of effect by employing a standard factorial design may be infeasible (e.g., when monotherapy has limited activity in early clinical studies). When appropriate, it may be feasible to use alternative approaches, such as external data, i.e., data external to pivotal clinical studies intended to demonstrate efficacy to support evaluation of the contribution of each drug to the effect of the combination.[5]

Alternatives to a standard factorial design approach may be appropriate where preliminary clinical evidence with the combination suggests a large effect size is anticipated to impact a well-characterized outcome of interest that is superior to the effect of the monotherapies. Such approaches may accelerate development of novel combination regimens and decrease participant exposure to potentially less effective therapies. Ultimately, the studies used to isolate contribution of effect must be adequate and well controlled clinical investigations to meet the statutory requirements for substantial evidence.[6]

The recommendations in this guidance consider previous Agency discussions with sponsors, review of applications, and broader discussions with stakeholders,[7] which highlighted outstanding questions regarding considerations for the timing and approach of demonstrating contribution of effect in oncology drug development programs. The rapidly evolving science in oncology provides opportunities for drug development and the need for more and improved treatment options, including novel combination regimens consisting of drug(s) approved for different indications. This guidance includes considerations on a key aspect of codevelopment in oncology – use of external data for demonstrating the contribution of the individual drugs to the effect of a combination regimen. It expands on the recommendations on this topic in the 2013 Codevelopment Guidance and provides recommendations regarding demonstrating the contribution of effect for two additional combination drug development scenarios in oncology where at least one of the drugs has been previously approved for a different indication (i.e., a

[5] The recommendations in the draft guidance for industry *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products* (February 2023) may be helpful when considering the use of external data for patient-level comparisons to demonstrate the contribution of each drug to the overall effect. When final, this guidance will represent FDA's current thinking on this topic.

[6] See section 505(d) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(d)) and 21 CFR 314.126.

[7] Friends of Cancer Research March 14, 2019 Roundtable: Opportunities for Combination Drug Development: Data Sources and Innovative Strategies to Assess Contribution of Components. https://friendsofcancerresearch.org/events/combination-therapy-development-and-data-sources-assessing-drug-contributions-roundtable.

different cancer type or a different line of therapy in the same cancer): (1) an investigational drug combined with a drug(s) approved for a different indication and (2) two (or more) drugs approved for a different indication(s).

III. DEMONSTRATING CONTRIBUTION OF EFFECT IN DEVELOPMENT OF CANCER DRUGS FOR USE IN COMBINATION

A marketing application for a drug(s) for use in a novel combination regimen must demonstrate both the safety and effectiveness of the novel combination.[8] In addition, the application would provide the evidence to demonstrate that the individual components in the novel combination contribute to the treatment effect of the combination.[9] Sponsors developing cancer drugs for use in novel combinations are encouraged to consult the responsible FDA review division as early as possible (e.g., through a pre-investigational new drug application (IND) meeting) and frequently throughout the development process, particularly for complex development programs, to obtain feedback on acceptable approaches and potentially facilitate a streamlined strategy.[10] The amount and types of appropriate clinical data and trial designs required to support the assessment of the contribution of effect for each drug may vary from one development program to another depending on the context of disease and population, the availability and effectiveness of other treatments, the available preclinical and clinical data, the extent of clinical data for the individual drugs and the combination, and the complexity of the question(s) being investigated. A factorial design randomized trial, when feasible, is highly recommended to provide sufficient data to demonstrate the contribution of the individual drugs to the effect of the novel combination.

A. Factorial Designs to Demonstrate the Contribution of Effect

Traditional evaluation of novel combinations in oncology is accomplished using a multi-arm, randomized trial that includes a combination arm, the monotherapy arms, and a standard-of-care arm, where standard of care is not one of monotherapies (see Figure 1). This factorial trial design allows for characterization of the safety and effectiveness of each individual drug and the combination compared with standard of care while also demonstrating the contribution of the individual drugs to the efficacy demonstrated by the combination.

The 2013 Codevelopment Guidance discusses trial designs that can be used to demonstrate contribution to the effect of investigational drugs in various scenarios (i.e., when the individual drugs each have activity and can be administered separately, when the individual drugs cannot be administered separately, and when one individual drug is active and one has minimal activity with regards to efficacy as monotherapy) (see Section V.C of the 2013 Codevelopment Guidance). When each investigational drug in a novel combination regimen is active,

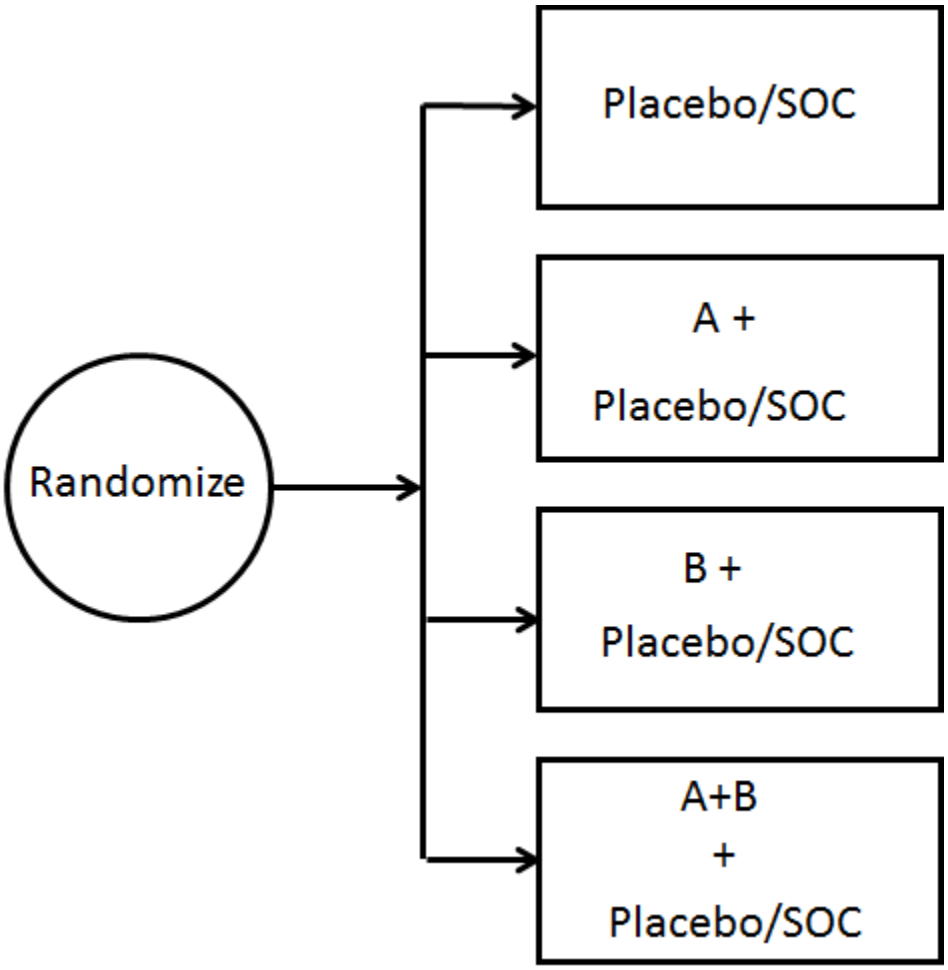
[8] Section 505(d) of the FD&C Act and section 351(a) of the Public Health Service Act. See also 21 CFR 314.126.

[9] See 21 CFR 300.50. FDA believes the recommendations in this guidance relevant to demonstrating the contribution of the individual investigational drugs to the effect(s) of the combination are consistent with the requirements of 21 CFR § 300.50, "fixed-combination prescription drugs for humans."

[10] See the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (September 2023). When final, this guidance will represent the FDA's current thinking on this topic.

randomized factorial trial designs that can demonstrate the contribution of each component to the effect of the combination are recommended.

Figure 1: Factorial Trial Design



In settings with evidence that one of the investigational drugs in a novel combination regimen is active not active by itself, a modified factorial design with three arms may be appropriate to isolate the contribution of each component to the effect of the combination.[11]

Use of an adaptive factorial trial design may promote efficiency in the development of novel combinations by initially randomizing all participants to the arms specified by factorial design, but allowing sponsors to drop potentially futile study arms in addition to other adaptations.[12] This decreases the overall number of participants needed for the trial, while also limiting the number of participants exposed to potentially less effective therapy. Adaptations and the

[11] Korn, EL, CJ Allegra, and B Freidlin, 2025, Phase III Evaluation of Treatment Combinations in Three-Arm Trials, JCO, 43(2):226-233.

[12] See the guidance for industry *Adaptive Designs for Clinical Trials of Drugs and Biologics* (December 2019).

statistical analysis plan should be pre-specified, with consideration of the overall type I error probability and respective power to detect a treatment effect.[13]

The primary endpoint of a trial intended to demonstrate contribution of effect for each component of a combination may be a persuasive pharmacodynamic/response biomarker that can provide direct evidence of a treatment effect for that cancer (e.g., overall response rate with duration of response information) and can be measured earlier than other clinical endpoints of importance such as progression-free (PFS) or overall survival. The limitations of this approach include the potential that all the components of a novel combination are not contributing (or are detrimental) to the long-term clinical outcome of interest, e.g., PFS or survival. The overall drug development program should demonstrate that the individual components contribute to the treatment effect of the novel combination; sponsors are therefore encouraged to discuss with the Agency the trial design and choice of endpoint intended to demonstrate contribution of each drug to the effect of the combination.

B. External Data to Demonstrate the Contribution of Effect

The rationale for use of external data to provide evidence of the contribution of effect for the individual drugs to the overall combination regimen can be supported by several factors. These include: 1) there is strong biological plausibility for the combination regimen, 2) the natural history of the disease is highly predictable, 3) the drug as a single agent has been demonstrated to not be as effective as compared with its use in combination with other classes of drugs, and/or 4) the magnitude of the treatment effect of the combination is expected to be large. To consider this approach, among other considerations, the external data should be from comparable populations studied across the combination and the components, contain detailed information on clinically relevant confounding variables, and use similar methods of response assessment and variable collection across the data sources. The limitations of comparisons with external data can include determination of appropriate endpoints for comparison. In general, the strengths and limitations associated with various types of external data should be considered, and any plan to use such data to support contribution of effect should be discussed in advance with the review division.

1. Suitability of External Data Source for Contribution of Effect

Sponsors conducting a trial of a combination relative to a control without a complete randomized factorial design (e.g., A+B vs. SOC), and using external data to support the comparative activity of the individual drugs, need to consider the appropriateness of the external data source. With complete, high-quality, patient-level data, it may be possible to conduct comparative analyses to estimate contribution of individual components to the treatment effect of the combination. For example, incorporating patient-level external data from a contemporaneous or previously conducted clinical trial to supplement or replace a single-agent arm(s) in a prospective study may allow for a direct comparative analysis for establishing contribution of components. In general, summary-level evidence from published clinical studies should be considered only hypothesis generating for a prospective trial. Data that are not fit for purpose as a comparator, regardless of whether the data are summary-level or patient-level, will only be appropriate for hypothesis generation.

[13] Ibid.

The suitability of a data source is determined by several factors related to the comparability of the trial arms. Factors may include, but are not limited to, the temporality of the treatment arms for use in assessment of contribution of components to the treatment effect, source population for participants, availability and similarity of inclusion and exclusion criteria including disease and line of treatment, and availability of trial participants' data. Sponsors should collect sufficient participant demographic and clinical characteristics to adequately assess the comparability of data sources, with special attention to balancing prognostic and predictive characteristics for internal validity of efficacy effect estimation.

When assessing fitness for purpose and determining whether to use external data to support contribution of effect, sponsors should consider the following non-exhaustive factors:

- Knowledge of natural history of the disease under consideration

- Availability of information on the background outcome (e.g., tumor response) rate with the use of standard of care when the novel combination regimen includes standard of care as a component

- Availability of patient-level data, with sufficient sample size and follow-up, including specific clinically relevant covariates to inform comparability of data sources as well as analytical plan

- Data provenance, traceability, and auditability of data sources to ensure the accuracy, reliability, and validity of key data elements[14,15]

- Extent of missing data, including information on key clinical covariates, and exposure and outcome ascertainment

- Ability to select participants for use in the evaluation of the drug(s) while remaining blinded to outcome

- Pre-specified statistical analysis plan for any comparison of the experimental combination therapy arm to a comparator to establish contribution of individual components to the treatment effect

Due to the potential limitations of the external data source – e.g., lack of comparable participant populations for the indication under consideration, variances in study conduct, and variability in endpoint assessment – comparisons between different data sources may or may not be appropriate. For example, in circumstances where baseline characteristics and/or disease status of participants in the external arms may differ from the characteristics of those participants in the trial assessing the investigational combination regimen, certain analytical methods, including

[14] See the guidance for industry *Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products* (December 2023).

[15] See the guidance for industry *Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products* (July 2024).

statistical methods for causal inference and/or Bayesian methodology, should be considered to account for known sources of bias and to improve the utility of the external data for cross-trial comparisons. However, these analytical methods do not account for all potential limitations associated with the use of external data to isolate the contribution of effect and should be interpreted with appropriate caution.

2. Selection of External Data Source for Contribution of Effect

The selection of a fit-for-purpose data source for establishing contribution of a component to the treatment effect is paramount in evaluating the strength of the evidence that can be generated from a comparison of efficacy endpoints. A traditional factorial randomized controlled trial with multiple arms to assess the effect of each component in a combination treatment provides the greatest strength of evidence for establishing contribution of effect (see Section III.A above). As an alternative design, randomized trials that borrow data from external sources to supplement a randomized arm intended to demonstrate contribution of effect (hybrid or augmented data), can provide adequate evidence of contribution to the treatment effect, but may also introduce some uncertainty in estimation of treatment effect with the inclusion of external data. Such approaches typically require careful evaluation prior to study initiation and sponsors should consult the relevant Review Division. When scientifically justified and when randomization to an arm to demonstrate contribution of effect would be infeasible, data from the following external sources can be considered to provide varying levels of evidence of contribution of effect depending on the relevance and reliability of the external data:

- External data from clinical trials (same setting, same indication) may offer a high degree of relevance, especially when clinical trials overlap in time and the data is contemporaneous, as compared with data from a previously conducted clinical trials which may introduce temporal biases

- Prospectively collected patient-level data (e.g., registry data) that includes demographics, disease characteristics, and treatment and outcomes of interest

- Other patient-level Real-World Data (RWD)[16] sources

- Summary-level evidence from previously published trials or from previously published observational (non-interventional) studies

3. Endpoint Considerations for Use of External Data

Appropriate endpoints and analyses thereof to demonstrate the contribution of each component will depend on the context of disease, trial design, and availability of clinical information. Differences in endpoints definitions and assessment methods (e.g., investigator assessment or blinded independent central review), and assessment schedules, may further limit comparisons across trials. In addition, prognostic characteristics are not accounted for in the absence of randomization. These limitations can make it difficult to draw conclusions on the contribution of

[16] For the purposes of this guidance, RWD are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

each of the drugs across trials, and a large magnitude of the treatment effect of the combination may need to be demonstrated on an endpoint to infer a treatment effect.

Sponsors should select the most appropriate endpoint(s) to demonstrate the contribution of components to the treatment effect. Whether the external data source can be used to demonstrate the contribution of effect will be dictated by the feasibility assessment of the available data source and the consistency with which such outcome data are collected/reported:

- Time-to-event endpoints may be subject to length time (or immortal-time or survival) bias for not only the baseline measurements, but also for the measurement of event time. The comparability of index date and follow-up time between arms should be cautiously considered.

- Overall survival is a well-defined and objective endpoint; however, certain real world data sources can be incomplete in collection of death data, and the outcome may be confounded by anti-cancer therapy that an individual receives subsequent to trial participation with the drug(s) of interest.

- Timing of assessments as well as the evaluation criteria for the determination of tumor measure-based endpoints, such as response or progression, should be comparable across treatment arms.

- Other endpoints such as patient-reported outcomes, or other measure of clinical outcomes and biomarkers, when validated, may also be considered.

C. General Development Program Considerations for Demonstrating Contribution of Effect

1. Two or More Investigational Drugs (Refer to the 2013 Codevelopment Guidance)

When each drug of a combination is an investigational drug, sponsors should evaluate the contribution of effect of the individual drugs as early as possible in development to inform the development of the combination. Knowledge of the contribution of effect will allow sponsors to consider whether a codevelopment approach is appropriate per the criteria recommended in the 2013 Codevelopment guidance. A factorial design to demonstrate the contribution of the components to the effect of the combination is highly recommended (refer to Section III.A of this guidance).

2. An Investigational Drug With a Drug Approved for a Different Indication

To develop an investigational drug in combination with a drug previously approved for a different indication, a randomized trial is highly recommended to provide sufficient data to demonstrate the contribution of the investigational drug and the approved drug to the effect of the novel combination. In addition, there is greater uncertainty with the use of an external data source in this type of novel combination drug development scenario to support contribution of each component to the treatment effect, particularly for:

- An investigational drug(s) where there has been no prior determination of safety of effectiveness in any indication

- Disease settings where identification of treatment effect is less reliable based on the natural history of the disease

- Novel combination regimens where the magnitude of treatment effect for the combination is modest

The type of external data source and strength of evidence required for demonstration of effect will depend on available information for one or both components of the novel combination regimen. A strong biologic rationale and nonclinical and/or early clinical evidence supporting the necessity of each drug in the novel combination may reduce uncertainties inherent in using comparisons with external data to demonstrate the contribution of the individual drug(s) to the effect of the combination. In such cases, external data from clinical trials investigating the previously approved drug(s) (approved for a different indication) as monotherapy in the same indication as that under evaluation for the novel combination regimen may be appropriate to demonstrate the contribution of effect.

Based on the limitations of external data, randomized trials performed earlier in the development program with assessment of overall response rate or another endpoint that demonstrates a persuasive direct treatment effect on the cancer are preferred for assessment of contribution of effect.

3. Two or More Drugs Approved Individually for Different Indication(s)

For a novel combination in which each drug is approved for a different indication(s), a randomized trial is recommended to provide sufficient data to demonstrate the contribution of each of the approved drugs to the effect of the novel combination as the efficacy and safety profiles would be unknown for the new indication. Extensive clinical experience and prior determinations of safety and effectiveness of the previously approved drugs (in other indications) may reduce the uncertainties with use of external data to support the contribution of effect. The appropriateness of the external data source to demonstrate the contribution of effect of a novel combination consisting of previously approved drugs for other indications will depend on the information available, such as:

- The similarity of the etiology (e.g., molecular aberration in the tumor) across cancers or clinical context of the disease

- The strength of the rationale based on the mechanism of action of the drug(s) for use of the combination in a specific disease

- The strength of evidence from the external data, including the adequacy of source and appropriateness of endpoint(s), demonstrating the contribution of effect of individual components in other indications

- The quantity of clinical data demonstrating the contribution of the individual components to the effect of the novel combination (e.g., demonstrated in multiple disease types)

- The clinical importance of the benefit (e.g., overall survival) demonstrated with the novel combination.