Cancer Clinical Trial Eligibility Criteria: Available Therapy in Non-Curative Settings

Guidance for Industry

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

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Cancer Clinical Trial Eligibility Criteria: Available Therapy in Non-Curative Settings Guidance for Industry[1]

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I. INTRODUCTION

This guidance provides recommendations to clinical investigators and sponsors regarding the inclusion of patients who have not received available therapy[2] (commonly referred to as existing treatment options) for their cancer in clinical trials of drugs[3] and biological products for the treatment of cancer in the non-curative setting (i.e., when there is no potential for cure or prolonged/near normal survival). For the purpose of this guidance, non-curative is generally defined as 1) unresectable, locally advanced, or metastatic disease in solid tumors or 2) hematologic malignancies with unfavorable long-term overall survival.

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[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] Refer to the guidance for industry *Expedited Programs for Serious Conditions – Drugs and Biologics* (May 2014) for a description of available therapy. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[3] For the purpose of this guidance, references to *drugs* include drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service Act (42 U.S.C. 262).

II. BACKGROUND

Under 21 CFR part 312, which applies to clinical investigations of drugs and biological products, FDA must determine that study subjects are not or would not be exposed to an unreasonable and significant risk of illness or injury (312.42(b)(1)(i) and (b)(2)(i)) to allow such trials to proceed. Therefore, in clinical trials evaluating investigational cancer drugs, eligibility criteria should generally include that patients should have received available therapy(ies) that offer the potential for cure in a substantial proportion of patients (e.g., available treatment for pediatric acute lymphoblastic leukemia, classic Hodgkin lymphoma, or testicular cancer). Alternatively, such available therapy should be administered to all patients in the trial, where the investigational drug is added to such therapy (i.e., add-on trial).

Particularly in the early stages of oncology drug development, eligiblity criteria have historically included that patients should have received a certain number of available therapy(ies) or all available treatment options considered clinical standard of care. This type of requirement can inadvertently limit patient access to clinical trials and preclude patients from participating. In the non-curative setting, it is reasonable for patients to receive an investigational drug(s) in lieu of available therapy, as long as patients have been provided adequate information about all therapeutic options to make an informed decision on trial participation.

III. RECOMMENDATIONS

When planning cancer clinical trials in the non-curative setting, sponsors should consider eligibility criteria as it pertains to available therapy(ies). FDA encourages sponsors to discuss their drug development plan with FDA early in development, including their approach to available therapy(ies) when developing eligibility criteria. In certain circumstances, FDA may request a specific approach for drug development. When designing cancer clinical trials, the following should be considered in the non-curative setting:

- Patients may be eligible for inclusion in trials of investigational drugs, including first-in-human trials, regardless of whether they have received available therapy in the non-curative setting. Among other considerations, sponsors must ensure the elements of informed consent, as required by 21 CFR part 50.25, are addressed, including "a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject".[4] The informed consent must clearly state that other treatment options known to confer clinical benefit exist, and must include discussion of reasonably foreseeable risks and any potential benefits associated with the investigational drug.[5]

[4] For additional information, see the guidance for industry *Placebos and Blinding in Randomized Controlled Cancer Clinical Trials for Drug and Biological Products* (August 2019).

[5] For additional information on informed consent, see 21 CFR part 50 and the draft guidance for IRBs, clinical investigators, and sponsors *Informed Consent Information Sheet* (July 2014). When final, this guidance will represent the FDA's current thinking on this topic.

- If interpretation of efficacy results requires a homogeneous patient population, evaluate patients who have received available therapy(ies) and patients who have not in separate cohorts. Alternatively, analyses of efficacy may be performed in pre-specified subgroup analyses, defined by prior receipt of available therapy(ies).

- In early stage dose escalation studies, it may be reasonable to evaluate safety in all patients without stratifying for prior receipt of available therapy(ies), if the potential toxicities of the investigational oncology product are not expected to differ across these patient subgroups.