Cancer Clinical Trial Eligibility Criteria: Brain Metastases Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 is one in a series of guidances that provide recommendations regarding eligibility criteria for clinical trials of drugs or biological products[2] regulated by CDER and CBER for the treatment of cancer.[3,4] Specifically, this guidance includes recommendations regarding the inclusion of patients with brain metastases. This guidance is intended to assist stakeholders, including sponsors and institutional review boards, responsible for the development and oversight of clinical trials.

A clinical trial's eligibility criteria (for inclusion and exclusion) are essential components of the trial, defining the characteristics of the study population. Because there is variability in investigational drugs and trial objectives, eligibility criteria should be developed taking into consideration the mechanism of action of the drug, the targeted disease or patient population, the anticipated safety of the investigational drug, and the ability to recruit trial participants from the patient population to meet the objectives of the clinical trial. However, some eligibility criteria have become commonly accepted over time or used as a template across trials without clear scientific or clinical rationale. Unnecessarily restrictive eligibility criteria may slow patient

[1] This guidance has been prepared by the Oncology Center of Excellence, 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, references to drugs and drug and biological products include drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and biological drug products licensed under section 351 of the Public Health Service Act (42 U.S.C. 262).

[3] Topics of the other three guidances are related to eligibility criteria for patients with human immunodeficiency virus, hepatitis B virus, and hepatitis C virus infections; with organ dysfunction or with prior or concurrent malignancies; and regarding minimum age for pediatric patients.

[4] The recommendations in this guidance do not apply to trials designed specifically to assess the safety and efficacy of investigational drugs for the treatment of primary brain cancers (e.g., glioblastoma) or brain metastases.

accrual, limit patients' access to clinical trials, and lead to trial results that do not fully represent treatment effects in the patient population that will ultimately use the drug.[5,6]

Broadening cancer trial eligibility criteria can maximize the generalizability of trial results and the ability to understand the therapy's benefit-risk profile across the patient population likely to use the drug in clinical practice without jeopardizing patient safety.

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 guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Every year, approximately 70,000 patients living with cancer in the United States are diagnosed with brain metastases. The incidence of brain metastases is increasing in patients with certain malignancies such as melanoma, lung cancer, and breast cancer. However, patients with brain metastases have historically been excluded from clinical trials due to concerns of poor functional status, shortened life expectancy, or increased risk of toxicity.

Clinical trial eligibility criteria have either excluded all patients with known brain metastases or restricted enrollment to subgroups of those patients, such as those with treated and clinically stable brain metastases. Given the prevalence of brain metastases in patients with cancer, their systematic exclusion from clinical trials may result in the assessment of an investigational drug's efficacy or safety in a trial population that is not fully representative of the patient population that will be prescribed the drug in clinical practice. Designing clinical trials that include patients with brain metastases and including this information in the labeling promotes the safe and effective use of these products across a broader patient population likely to use the drug in clinical practice.

III. RECOMMENDATIONS

Thoughtful consideration should be given to the potential inclusion of patients with brain metastases. Patients with brain metastases should be included in clinical trials in a way that contributes to a greater understanding of the efficacy and safety profile of the investigational drug while maintaining patient safety. Patients with cancers that commonly metastasize to the brain (e.g., lung cancer, breast cancer, melanoma) should be included in early drug development trials, either in separate cohorts or in cohorts with planned subset analyses to assess preliminary

[5] Beaver JA, Ison G, Pazdur R, 2017, Reevaluating Eligibility Criteria- Balancing Patient Protection and Participation in Oncology Trials, NEJM, 376:1504-1505.

[6] Kim E, Bruinooge S, Roberts S, et al., 2017, Broadening Eligibility Criteria to Make Clinical Trials More Representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement, JCO, 35(33): 3737-3744.

efficacy and toxicity in patients with brain metastases. In cases where there is a strong rationale for exclusion, the rationale should be described in the trial protocol.

The eligibility criteria regarding patients with brain metastases should describe the eligibility for each of the following types of metastases:

- **Treated/stable metastases**- where patients have received prior therapy for their brain metastases and their central nervous system (CNS) disease is radiographically stable,

- **Active metastases**- where patients have new or progressive brain metastases at the time of study entry, and

- **Leptomeningeal metastases**- where patients have metastases in the leptomeningeal space, rather than in the parenchyma. Leptomeningeal disease (LMD) is a clinical diagnosis that is defined as positive cerebrospinal fluid (CSF) cytology or unequivocal radiologic or clinical evidence of leptomeningeal involvement.

A. Recommendations for inclusion of patients with treated/stable brain metastases

- Patients with treated/stable brain metastases should be included in trials of all phases unless there is a strong rationale to exclude such patients.

- In dose-finding studies and early exploratory studies, inclusion of patients with treated/stable brain metastases should not be dependent on whether the drug's pharmacological properties predict penetration of the brain-blood barrier.

- Patients should be neurologically stable prior to study entry to mitigate the uncertainty of correctly attributing CNS toxicity to drug or underlying disease. In addition, consider limiting enrollment to patients receiving a stable to decreasing corticosteroid dose during one week before study entry.

B. Recommendations for inclusion of patients with active brain metastases

- Patients with active brain metastases should not be automatically excluded and should be included if the treating physician determines that immediate CNS specific treatment is not required and is unlikely to be required.

- For drugs with known CNS toxicities, exclusion of patients with active brain metastases may be justified, especially early in drug development.

- There are several approaches for, and considerations regarding, inclusion of patients with active brain metastases in clinical trials, including:

1. Trial design

- Local therapy to brain metastases could be permitted followed by immediate enrollment once acute treatment-related toxicities have resolved.

- Dose-finding study

    - Strategies may include enrolling patients in a separate cohort early in clinical development, taking into consideration prior safety and efficacy data from similar drugs in class (if available). Additionally, dose-limiting toxicity (DLT) definitions and reporting should be prospectively designed and adapted for patients with active brain metastases.

- Single-arm, activity estimating study

    - Strategies may include enrolling patients in a separate cohort or enrolling patients in the overall study with a prespecified subset analysis for both safety and efficacy.

- Randomized studies with a time-to-event endpoint

    - Several study designs and mitigation strategies could be implemented for including patients with active brain metastases in later-phase studies. For example, enrolling patients in a parallel exploratory cohort to generate supportive safety and efficacy data who would not be included in the assessment of the primary efficacy endpoint, conducting pre-specified subset analyses, limiting enrollment of patients with active brain metastases to a predetermined number, designating brain metastases as a stratification factor, and incorporating early stopping rules for excess toxicity in patients with active brain metastases.

2. Investigational drug

- The inclusion of patients with active brain metastases early in drug development will facilitate the collection of data to inform the development of eligibility criteria in later-phase trials.

    - Examples of factors to consider when developing eligibility criteria regarding patients with active brain metastases include mechanism of

action, expected CNS penetration, preclinical and clinical data, and CNS-specific toxicity.

3. Disease characteristics

- The following characteristics would influence the risk-benefit of including patients with active brain metastases in trials and affect the amount of preliminary data required to consider inclusion of these patients: propensity for toxicities among different tumor types, the expected efficacy of local therapies to brain metastases, the disease course, and expected survival rates.

C. Recommendations for inclusion of patients with leptomeningeal metastases

- Patients with LMD should not be automatically excluded and should be included if the treating physician determines that immediate CNS specific treatment is not required and is unlikely to be required.

- Patients with LMD should be included in early-phase trials when the drug is anticipated to have CNS activity, is relevant for the primary tumor, and there is strong scientific rationale to support the likelihood of benefit, based on the understanding of molecular pathways or preclinical data.

- Patients with LMD should be included in later-phase trials.

D. Recommendations for exclusion of patients with brain metastases

- In early clinical development, for drugs with the potential to increase the risk of bleeding, patients with clinically symptomatic hemorrhage on brain imaging or receiving therapeutic anticoagulation should be excluded until preliminary evidence of safety is available demonstrating that participants would not be exposed to unreasonable risk.

- For drugs with the potential to lower seizure threshold, patients with a history of seizures within the past month should be considered for exclusion until preliminary evidence of safety is available demonstrating that participants would not be exposed to unreasonable risk.

- For drugs with potential cytochrome interactions, patients on certain enzyme-inducing antiepileptic drugs should be considered for exclusion until preliminary evidence of safety is available demonstrating that participants would not be exposed to unreasonable risk.

- For drugs whose efficacy may be compromised by concurrent corticosteroids, patients requiring corticosteroid use that exceeds a prespecified threshold should be considered for exclusion.

E. Baseline CNS screening

Providers have been reluctant to perform screening CNS imaging because detection of an asymptomatic lesion may preclude patient eligibility for a clinical trial. Expanding eligibility to include patients with brain metastases enables baseline imaging to be performed that does not result in automatic exclusion of all patients with brain metastases. Baseline CNS imaging should be obtained prior to enrollment to document brain tumor measurements and disease stability in patients with a known history of brain metastases. Additionally, baseline CNS imaging is recommended to determine if eligibility criteria are met:

- In populations where the risk of brain metastasis is high,
- If there are specific concerns related to inclusion of patients with brain metastases, and
- If an objective of the study is to evaluate the effect of the investigational drug on CNS-related outcomes.