Evaluating Cancer Drugs in Patients with Central Nervous System Metastases

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Shanthi Marur at 240-402-6373 or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence
Center for Drug Evaluation and Research (CDER)
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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

The purpose of this guidance is to describe FDA's recommendations for clinical trial designs of cancer drugs or biological products[2] regulated by CDER and CBER that are intended to support product labeling describing the antitumor activity in patients with central nervous system (CNS) metastases from solid tumors originating outside the CNS.

FDA's current thinking regarding inclusion of patients with brain metastases in clinical trials is addressed in the guidance for industry *Cancer Clinical Trial Eligibility Criteria: Brain Metastases*.[3]

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

The solid tumors that most often metastasize to the CNS are small cell and non-small cell lung cancers, breast cancer, melanoma, and renal cancers.[4] CNS metastatic disease includes parenchymal metastases to the brain or spinal cord, as well as leptomeningeal disease (LMD)

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

[2] For purposes of this guidance, references to drugs include drugs approved under section 505 of the FD&C Act (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service Act (42 U.S.C. 262).

[3] July 2020. 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] Nayak L, Lee EQ, Wen PY, 2012, Epidemiology of Brain Metastases, Curr Oncol Rep, 14(1): 48-54.

involving the pia, subarachnoid leptomeninges, and cerebrospinal fluid (CSF). LMD may present with or without concurrent parenchymal disease and represents widespread dissemination of cancer cells throughout the CNS.

Metastatic cancer is a systemic disease; therefore, evaluation of the effectiveness of cancer drugs includes consideration of whether the cancer is controlled at all disease sites. The potential for benefit of a drug as assessed by tumor shrinkage of CNS lesions is uninterpretable without information regarding tumor shrinkage at extra-CNS disease sites. Furthermore, evaluation of anti-tumor activity, particularly durability of tumor response in the CNS may not be attributable solely to the investigational drug, as treatment would generally be changed at the time of extra-CNS disease progression in patients with evidence of stable or responding CNS lesions. The recommendations below reflect the challenges in assessing the potential benefit of systemic therapies at a single disease site in patients with disease in, or at risk for disease progression in, CNS and extra-CNS sites.

III. CLINICAL TRIAL DESIGN CONSIDERATIONS

The recommendations discussed below pertain to clinical trials for systemic anticancer drugs where patients with CNS metastases are included in the study population and CNS anti-tumor activity is intended to be described in product labeling. These recommendations are also applicable to trials conducted exclusively in patients with CNS metastases.

A. Patient Population

FDA recognizes that treatment of CNS metastases presents several challenges and unique considerations (e.g., circumventing the blood-brain barrier); however, CNS disease should not be evaluated in isolation from metastatic disease in the rest of the body. FDA will evaluate effects of systemic drugs on CNS metastases in the context of the entire burden of metastatic disease, regardless of whether the trial was conducted exclusively in patients with CNS metastases or where only a subset of patients has CNS metastases. Therefore, efficacy claims based on endpoints measuring CNS activity alone may not be appropriate. For example, evaluation of the clinical significance of overall response rates or progression-free survival (PFS) that considers only CNS disease sites (CNS-ORR or CNS-PFS, respectively) is difficult to interpret as it does not take into account extra-CNS metastatic disease. Likewise, a labeling indication specifically for treatment of CNS metastases alone may not be appropriate. Where anti-tumor activity has been demonstrated in both the CNS and extra-CNS sites of disease, treatment effects on CNS metastases may be described in Section 14 ("Clinical Studies") of the product label.

B. Available Therapy

For the purposes of determining whether an expedited program is an appropriate regulatory pathway for a given drug, an available therapy for a metastatic solid tumor would be an available therapy[5] for CNS metastases of that solid tumor, unless otherwise specified in the labeling for

[5] For the definition of available therapy, see section III.B of the guidance for industry *Expedited Programs for Serious Conditions – Drugs and Biologics* (May 2014).

that therapy (e.g., the drug is contraindicated for CNS metastases). For example, since alectinib is approved for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC), alectinib is considered available therapy for the treatment of patients with CNS metastases from ALK-positive NSCLC.

C. Prior Therapies

FDA recommends that trial designs incorporate the following elements regarding therapies that subjects may have received prior to enrolling in the trial:

- Case report forms should be designed to capture information on all prior CNS-directed treatments such as surgery, stereotactic radiosurgery (SRS), or whole brain radiation therapy (WBRT), including the dates of such therapy and response to therapy at baseline.

- The protocol should specify the interval between completion of CNS radiation therapy (RT) and study entry as an eligibility criterion. The interval should be of sufficient duration to allow attribution of treatment effects to the study intervention, and to reduce the likelihood of enrolling patients with radiographic post-RT pseudoprogression. In most cases, an interval of at least 12 weeks may suffice, unless there is reasonable certainty of disease progression supported by additional information (e.g., histologically proven, new disease outside the RT field) prior to that time.

- The protocol should specify appropriate stratification factors for randomization to minimize bias based on prior therapy(ies) (e.g., treated vs. untreated CNS metastases at baseline; presence or absence of CNS metastases at baseline).

D. Assessment of CNS Metastases

- Magnetic resonance imaging (MRI) with gadolinium contrast is the preferred imaging modality for tumor assessment.[6]

- The protocol should require baseline imaging evaluation of the CNS in all enrolled patients to identify patients with CNS disease prior to initiation of protocol-specified therapy.

- The protocol should apply accepted standard response criteria for evaluation of CNS disease (e.g., Response Assessment in Neuro-Oncology – Brain Metastases [RANO-BM]). Any proposed modifications or adaptations to standard response criteria should be adequately justified.

- The protocol should require on-study imaging assessments for CNS disease at the same time points as those for extra-CNS disease. Any unscheduled disease assessments (e.g., due to clinical worsening) should include evaluation of both CNS and extra-CNS disease.

[6] Lin NU, Lee EQ, Aoyama H, et al., 2015, Response assessment criteria for brain metastases: proposal from the RANO group, Lancet Oncology, 16(6): e270–e278.

- Sponsors should provide a radiology charter describing the imaging modalities, sequences, and other standardized parameters that should be applied at all trial sites.

- The protocol and the radiology charter should specify the conditions under which previously radiated lesions may be included as target lesions (e.g., documentation of progressive disease).

- Case report forms should capture data at baseline and during the study on variables that may impact interpretation of radiographic response, including presence or change in neurological symptoms, concurrent steroid use/change in steroid use, and concurrent anti-seizure medications/change in anti-seizure medications.

E. Study Endpoints

The selection of the appropriate endpoint to evaluate CNS activity of a systemic drug will depend in part on the study population, including whether the trial is intended to evaluate only patients with CNS metastases.[7] The following study endpoints may be considered:

- Time-to-event endpoints

  - As discussed in the guidance for industry *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics,* data derived from externally controlled trials are seldom reliable for time-to-event endpoints and those endpoints should therefore be evaluated in randomized, internally controlled trials.

- Overall Survival (OS):

  - OS can generally only be evaluated in randomized controlled trials.

  - As it is challenging to accurately attribute death to CNS disease, death due to any cause should be used to determine OS.

- Endpoints based on tumor assessment:

  - Key efficacy endpoints based on tumor assessments should incorporate evaluation of both CNS and extra-CNS disease (see III.A). Specifically, the ORR and PFS should be determined based on evaluation of all metastatic disease, regardless of whether it occurs in the CNS or extra-CNS.

  - When the primary endpoint is based on tumor assessment, it should be verified by independent, blinded central review with neuro-radiology expertise. Where necessary and when supported by adequate justification, a random sample-based blinded central

[7] For additional information on study endpoints, see the guidance for industry *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* (December 2018).

review auditing approach could be used; such an approach should include a pre-specified auditing plan with a strategy to detect potential assessment bias.

- Capture duration of response (DoR). The proportion of patients with durable responses at specific time points (e.g., 12-month DoR) may also be described.

- CNS-RR may be uninterpretable in a population with recent CNS-directed therapy such as RT; therefore, responses should be reported based on time from prior RT (e.g., < 3 months, < 6 months).

- Time to CNS progression or CNS-PFS may be uninterpretable due to censoring of patients at the time of extra-CNS progression or death, resulting in a large number of censored patients or disproportionate censoring. For solid tumors where the CNS is a common metastatic site, the incidence of CNS as first site of progression, alone or with concurrent extra-CNS progression, may be reported.

F. Leptomeningeal Disease (LMD)

- For the purposes of this guidance, FDA considers LMD to be a disease of the entire CNS compartment. Clinical trials intended to evaluate drug effects on LMD should also evaluate CNS parenchymal disease and efficacy claims will be based on assessment of disease in the entire CNS unless there is a biological rationale for why a product may affect LMD preferentially (e.g., local delivery to the CSF).

- LMD can be identified based on imaging or CSF analysis; however, clinical symptoms should also be evaluated and followed. The presence of at least one site of MRI evaluable disease amendable to repeat assessment is preferred to establish and evaluate LMD.

  - Patients with suspected LMD by clinical symptoms only (without imaging findings), should undergo CSF analysis to substantiate the diagnosis of LMD.

  - Responses should be confirmed by follow-up imaging or cytology depending on how the diagnosis was established.