4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2020-D-0938]

Evaluating Cancer Drugs in Patients with Central Nervous System Metastases; Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a final guidance entitled "Evaluating Cancer Drugs in Patients with Central Nervous System Metastases; Guidance for Industry." The guidance document provides recommendations regarding the design of clinical trials of drugs and biological products regulated by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (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. The guidance includes study design recommendations regarding the patient population, available therapy, prior therapies, assessment of CNS disease, study endpoints, and leptomeningeal disease. The guidance announced in this notice finalizes the draft guidance of the same title dated August 2020.

DATES: The announcement of the guidance is published in the *Federal Register* on **[INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].**

ADDRESSES: You may submit either electronic or written comments on Agency guidances at any time as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2020-D-0938 for "Evaluating Cancer Drugs in Patients with Central Nervous System Metastases." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

Submit written requests for single copies of the guidance to the Office of Communication, Outreach and Development, Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist the office in

processing your requests. The guidance may also be obtained by mail by calling CBER at 1-800-835-4709 or 240-402-8010. See the SUPPLEMENTARY INFORMATION section for electronic access to the guidance document.

FOR FURTHER INFORMATION CONTACT: Shanthi Marur, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 2369, Silver Spring, MD 20993-0002, 240-402-6373; or Stephen Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993-0002, 240-402-7911.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a document entitled "Evaluating Cancer Drugs in Patients with Central Nervous System Metastases." This guidance provides recommendations for sponsors designing clinical trials of drugs and biological products regulated by CDER and CBER that are intended to support product labeling describing the antitumor activity in patients with CNS metastases from solid tumors originating outside the CNS. Specifically, the guidance includes recommendations regarding the patient population, available therapy, prior therapies, assessment of CNS disease, study endpoints, and leptomeningeal disease. The guidance describes that CNS metastases should be evaluated in the context of the entire disease burden and discusses how treatment effects may be described in drug labeling. The recommendations pertain to clinical trials for systemic anticancer drugs where patients with CNS metastases are included in the study population. These recommendations are also applicable to trials conducted exclusively in patients with CNS metastases.

CNS metastases are associated with significant morbidity and mortality and development of therapeutic products for patients with CNS metastases is needed. FDA has participated in efforts to facilitate drug development for patients with CNS metastases, including a March 2019 "Workshop on Product Development for CNS Metastases." Stakeholders at this meeting stated

there is a need for further FDA guidance on specific topics, including identifying optimal study endpoints. Study design challenges for CNS metastases include uncertainty regarding optimal endpoints, lack of standardized response assessments, understanding how CNS metastases are evaluated in the context of the entire burden of metastatic disease to characterize a drug's potential benefit (e.g., timing of CNS radiographic assessments relative to other sites of metastases), and interpreting radiographic response in the setting of recent radiation therapy or surgery. This guidance is intended to provide recommendations on these study design challenges.

In the *Federal Register* of August 27, 2020 (85 FR 53007), FDA announced the availability of the draft guidance "Evaluating Cancer Drugs in Patients with Central Nervous System Metastases" dated August 2020. FDA received several comments on the draft guidance and those comments were considered as the guidance was finalized. A summary of changes includes: clarification on the number of stratification factors the protocol should specify in order to minimize bias, confirmation of the version of Response Evaluation Criteria in Solid Tumours (RECIST) that should be referred to when evaluating CNS disease, clarification that both CNS and systematic duration of response should be captured and the addition of a 6-month timepoint, and the addition of progression-free survival in patients with brain metastasis as another measurement to be reported when CNS is a common metastatic site. In addition, editorial changes were made to improve clarity. The guidance announced in this notice finalizes the draft guidance dated August 27, 2020.

This guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The guidance represents the current thinking of FDA on "Evaluating Cancer Drugs in Patients with Central Nervous System Metastases." 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.

II. Paperwork Reduction Act of 1995

While this guidance contains no collection of information, it does refer to previously approved FDA collections of information. Therefore, clearance by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3521) is not required for this guidance. The previously approved collections of information are subject to review by OMB under the PRA. The collections of information in 21 CFR part 312 have been approved under OMB control number 0910-0014; the collections of information in 21 CFR part 314 have been approved under OMB control number 0910-0001; the collections of information in 21 CFR part 601 have been approved under 0910-0338; and the collections of information in 21 CFR 201.56 and 201.57 have been approved under OMB control number 0910-0572.

III. Electronic Access

Persons with access to the internet may obtain the guidance at either https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances or https://www.regulations.gov.

Dated: June 28, 2021.

Lauren K. Roth,

Acting Principal Associate Commissioner for Policy.

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