Nonmetastatic Castration-Resistant Prostate Cancer: Considerations for Metastasis-Free Survival Endpoint in Clinical Trials

Guidance for Industry

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

August 2021
Clinical/Medical

Nonmetastatic Castration-Resistant Prostate Cancer: Considerations for Metastasis-Free Survival Endpoint in Clinical Trials

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

and/or

Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

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

August 2021
Clinical/Medical

Contains Nonbinding Recommendations

TABLE OF CONTENTS

Contains Nonbinding Recommendations

Nonmetastatic Castration-Resistant Prostate Cancer: Considerations for Metastasis-Free Survival Endpoint in Clinical Trials Guidance for Industry[1]

I. INTRODUCTION

This guidance provides recommendations to sponsors about using metastasis-free survival (MFS) as an endpoint in clinical trials for nonmetastatic castration-resistant prostate cancer (nmCRPC) development programs for drug or biological products[2] regulated by FDA.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, 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

Nonmetastatic castration-resistant prostate cancer is defined by rising prostate-specific antigen (PSA) despite castrate levels of testosterone and no radiographic evidence of metastatic disease. Despite earlier detection of localized prostate cancer and advances in surgical and radiation techniques, many patients will continue to have rising PSA after local therapy (e.g., surgery, radiation), subsequent salvage therapies (if received for locally recurrent disease), and subsequent androgen deprivation therapy. Patients with nmCRPC can have a prolonged disease course following the detection of a rising PSA until documentation of distant metastases or death. Such a prolonged assessment period (in which patients may receive multiple therapies)

[1] This guidance has been prepared by the Office of Hematology and Oncology Products in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *products* include both human drugs and biological products unless otherwise specified.

with low death rates may make the use of overall survival (OS) impractical as a primary endpoint to support approval of products in this disease setting.

These issues were discussed at an Oncologic Drugs Advisory Committee meeting in 2011, during which the committee acknowledged that endpoints that can be measured earlier in the course of disease, such as MFS, defined as the time from randomization to distant radiographic disease or death, would be useful in assessing the treatment effect of products in patients with nmCRPC.[3] Additionally, the Oncologic Drugs Advisory Committee noted that the transition from nmCRPC to radiographically detectable metastatic disease (e.g., bone or visceral disease) is a clinically relevant event that can be associated with morbidity and the need for additional medical interventions. Conversely, local progression events may be treated with local therapies, may never progress to distant disease, and may not lead to systemic morbidity. Thus, a large treatment effect on MFS with an acceptable safety profile could demonstrate clinical benefit and support product approval.

III. METASTASIS-FREE SURVIVAL CONSIDERATIONS

A. General Trial Design Considerations

Sponsors should consider the following in trials using MFS as an endpoint for nmCRPC product development programs:

- Sponsors should establish the definition of MFS before initiating the trial, and the definition should exclude local progression events (e.g., progression in pelvic lymph nodes below the aortic bifurcation).

- Sponsors should consider stratification of randomization by prior local definitive therapy (e.g., surgery, radiation), or lack of prior definitive therapy, and by PSA doubling time (with timing and number of PSA measurements specified before trial initiation).

- The protocol should prespecify procedures to reduce attrition in both treatment arms caused by patients who withdraw from the trial because of concern about persistently rising PSA values (e.g., PSA blinding or targeted patient and investigator education). Sponsors should plan for sensitivity analyses to assess the effect of patient discontinuation for reasons other than disease progression.

- A superiority trial design should be used.

- Trials should exclude patients who could benefit from local therapy (e.g., surgery or radiation) to the prostate or pelvis. Such patients could be enrolled after completing local therapy if their PSA continues rising and meets trial entry criteria for castration-resistant prostate cancer and minimum PSA value.

[3] See the Oncologic Drugs Advisory Committee meeting material, available at https://www.fda.gov/advisory-committees/human-drug-advisory-committees/oncologic-drugs-advisory-committee.

- The trial entry criteria should include and justify the definition of castration-resistant disease, including the maximum allowable serum testosterone and the minimum absolute PSA value for eligibility.

B. Imaging Considerations

Sponsors should consider the following for imaging modalities and assessments in clinical trials with MFS as an endpoint for nmCRPC product development:

- Sponsors should prespecify acceptable imaging modalities and assessment frequencies. The same modalities should be used in the same patients for the duration of the trial. Imaging assessment frequency should also be the same on all treatment arms, as asymmetrical frequencies may bias the assessment of MFS.

- For trial entry criteria, sponsors should prespecify and justify the radiographic definition of nonmetastatic disease. For example, patients entering these trials may have enlarged pelvic lymph nodes, so sponsors should provide criteria concerning the acceptable size and location of these nodes at trial entry.

- Sponsors should prespecify the radiographic definition of local disease/local progression (e.g., pelvic lymph nodes) and metastatic disease (e.g., distant lymph nodes, bone metastases, visceral disease). Sponsors should confirm solitary bone metastases with additional imaging. When confirmatory imaging is performed, the date of recurrence should be the date when the metastasis was first identified. Evidence of unequivocal progression (e.g. development of multiple bone lesions or unequivocal visceral lesions) may not require confirmation.

- For MFS to be interpretable, the expected magnitude of improvement in MFS should be substantially greater than the imaging frequency.

FDA recommends a blinded independent central review of imaging studies to assess any potential assessment bias. Sponsors may also consider using an audit where a random sample of scans are sent for independent review. Sponsors should seek advice from the Agency about the design of an audit for MFS.

C. Considerations Related to Interpretation of Trial Results

Sponsors should consider the following for interpreting results of clinical trials with MFS as an endpoint for nmCRPC product development:

- Interim efficacy analyses of MFS are discouraged because these may lead to over- or underestimation of the magnitude of MFS improvement. Adequate follow-up of the study population before efficacy assessment should be carefully considered so as not to risk significant probability of over- or underestimation of the magnitude of benefit.

Sponsors should meet with the Agency to discuss a study designed with interim analyses before initiation.

- The acceptable magnitude of improvement in MFS required to support drug approval will depend primarily on the trial design (e.g., add-on design, active control versus placebo control), toxicity profile, enrolled population, and overall benefit-risk assessment.

- Although FDA does not require demonstration of an OS benefit, sponsors should conduct a formal interim analysis of OS at the time of final MFS analysis. To support a favorable benefit-risk assessment, this analysis should demonstrate a favorable numeric trend and provide assurance that OS is not adversely affected by the treatment. Sponsors should also plan for a long-term follow-up and analysis of OS. If the study has only limited power to show an OS benefit, the sponsor should seek advice on the length of follow-up needed.

- Sponsors may collect patient-reported outcome (PRO) and other clinical outcome assessment data to inform the benefit-risk assessment. If PROs are planned, sponsors should focus collection and analysis on the following domains: symptomatic adverse events, disease-related symptoms, and physical function. Sponsors are encouraged to meet with FDA to discuss their PRO development strategies. For further guidance on patient-focused drug development, see the guidance for industry *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input* (June 2020).[4]

D. Considerations Related to Analyses of MFS

Sponsors should consider the following for analyses of MFS in clinical trials for nmCRPC product development:

- Sponsors should describe in the protocol and statistical analysis plan the precise methodology for assessing, measuring, and analyzing MFS.

- Missing data can complicate analyzing MFS. Sponsors should put in place procedures to minimize missing data, and they should prespecify in the protocol and statistical analysis plan methodology for analyzing incomplete and/or missing follow-up assessments, including rules for censoring observations.

- The statistical analysis plan should specify the primary analysis and one or more sensitivity analyses to evaluate the effect of missing observations on the results.

- Sponsors can consider additional analyses of progression-free survival (including both local and metastatic progression) to support the primary MFS analysis.

[4] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.