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

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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Center for Drug Evaluation and Research (CDER)
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I. INTRODUCTION

This guidance provides recommendations to sponsors regarding the use of 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 the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research.

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

Nonmetastatic, castration-resistant prostate cancer is defined by rising prostate-specific antigen (PSA) despite castrate levels of testosterone and no radiographic evidence of distant 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) for recurrent disease and subsequent androgen deprivation therapy. Patients with nmCRPC can have a prolonged disease course from the detection of a rising PSA until

[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.

documentation of distant metastases or death. Such a prolonged assessment period (in which patients receive multiple therapies) with low event 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 (ODAC) in 2011, in which the committee acknowledged that endpoints that can be measured earlier in the course of disease, such as MFS, or in the time from randomization to distant radiographic disease or death would be useful to assess the treatment effect of products in patients with nmCRPC.[3] Additionally, ODAC noted that the transition from nmCRPC to radiographically detectable metastatic disease (e.g., bone disease) is a clinically relevant event that can be associated with morbidity and the need for additional medical interventions. Local progression events, in contrast, may be treated with local therapies, may never progress to distant disease, and may not lead to systemic morbidity. Thus, a large magnitude of treatment effect on MFS with an acceptable safety profile could be used to demonstrate clinical benefit and support product approval.

III. MFS CONSIDERATIONS

A. General Trial Design Considerations

Sponsors should consider the following for trial designs with MFS as an endpoint for nmCRPC product development:

- The sponsor should establish the definition of MFS before initiation of the trial, and the definition should not include local progression events.

- The sponsor should consider stratification by prior local definitive therapy (e.g., surgery, radiation), or lack of prior definitive therapy, and by PSA doubling time.

- The protocol should prespecify procedures to mitigate attrition of patients in both treatment arms who withdraw from the trial because of anxiety about persistently rising PSA values. Sponsors should plan for sensitivity analyses to assess the effect of patient discontinuation for reasons other than disease progression.

- Trials should exclude patients who could benefit from radiation therapy to the prostate or pelvis.

- The trial entry criteria should include the definition of castration-resistant disease.

[3] See the ODAC meeting material available at https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/default.htm.

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:

- The sponsor should prespecify acceptable imaging modalities and assessment frequencies.

- For trial entry criteria, the radiographic definition of nonmetastatic disease should be prespecified. For example, patients entering these trials may have enlarged pelvic lymph nodes, and the sponsor should provide criteria concerning the acceptable size of these nodes, etc., at trial entry.

- The sponsor 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). Solitary bone metastases should be confirmed with additional imaging. When confirmatory imaging is performed, the date of recurrence should be listed as the date the metastasis was first identified. Confirmation of the development of additional metastatic sites is not required in patients who develop multiple bone lesions or unequivocal visceral lesions.

- Imaging assessment frequency should be the same on all treatment arms. Asymmetrical frequencies may bias the assessment of MFS.

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

- We recommend a blinded independent central review (BICR) of imaging studies. If a sponsor does not want to use a full BICR review, the sponsor should discuss plans for an audit with FDA to assess potential assessment bias.

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:

- Sponsors should avoid interim analysis of efficacy because it may lead to over- or underestimation of the magnitude of MFS improvement.

- 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 evaluation.

- While FDA does not require demonstration of an OS benefit, at the time of final MFS analysis, the sponsor should conduct a formal interim analysis of OS. 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. In addition, FDA expects continued follow-up for final OS.

D. Considerations Related to Analyses of MFS

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

- The sponsor should detail in the protocol and statistical analysis plan (SAP) the methodology for assessing, measuring, and analyzing MFS .

- Missing data can complicate analysis of MFS. Procedures should be put in place to minimize missing data, and the sponsor should prespecify in the protocol and SAP methodology for analyzing incomplete and/or missing follow-up assessments, including rules for censoring observations.

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

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