
Bladder Cancer: Developing Drugs and Biologics for Adjuvant Treatment Guidance for Industry

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

**June 2022
Clinical/Medical**

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TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	BACKGROUND	1
III.	RECOMMENDATIONS	2
	A. Trial Eligibility Criteria	2
	B. Choice of Comparator	3
	C. Imaging Assessments	3
	D. Determination of Disease Recurrence	4
	E. Trial Analysis	4
	F. Interpretation of Trial Results	5

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I. INTRODUCTION

This guidance provides recommendations to sponsors regarding the development of drugs and biological products² regulated by CDER and CBER for the adjuvant treatment of muscle-invasive bladder cancer. The guidance includes recommendations regarding eligibility criteria, choice of comparator, follow-up imaging assessments, determination of disease recurrence, analyses of disease-free survival (DFS), and interpretation of trial results. Although FDA may consider endpoints other than DFS for the adjuvant treatment of muscle-invasive bladder cancer, this guidance is focused on clinical trials with DFS as the primary efficacy endpoint.

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

Significant variability exists in the design, conduct, and analysis of trials for the adjuvant treatment of bladder cancer, including the eligibility criteria, radiological disease assessments, the definition of disease recurrence, and the date used to define the DFS endpoint. Consistency in these aspects within and across trials may facilitate interpretation of trial results. These issues

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

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were discussed at an FDA-National Cancer Institute (NCI) public workshop held on November 28, 2017.^{3, 4}

III. RECOMMENDATIONS

A. Trial Eligibility Criteria

- Patients with predominant urothelial carcinoma (UC) histology who have a component of variant histology should be included. Detailed pathology information including histology should be prospectively captured.
- We encourage the enrollment of patients with microscopic positive margins without gross residual disease but sponsors should account for potential heterogeneity with regard to treatment effect and risk for recurrence.
- Patients with invasive upper-tract UC should be included.
- See section III.C for recommendations regarding imaging assessments relevant to eligibility criteria.
- If patients who received neoadjuvant therapy prior to study entry are eligible, eligibility criteria should ensure that such patients received adequate neoadjuvant therapy, consistent with current standard of care. Eligibility criteria for patients who have not received standard of care neoadjuvant treatment should be based on post-cystectomy pathologic stage and should be pre-specified in the protocol.
- Eligibility criteria defining “cisplatin ineligibility” that includes: Eastern Cooperative Oncology Group performance status (ECOG-PS) 2, creatinine clearance (CrCl) < 60 mL/min, grade ≥ 2 hearing loss, grade ≥ 2 neuropathy, or New York Heart Association (NYHA) class III heart failure, should be pre-specified.⁵
- The protocol should require documentation of tumor stage, grade, extent, and the number of lymph nodes sampled at the time of cystectomy to ensure eligibility criteria are met. Case report forms should be designed to capture this information.

³ Apolo AB, Milowsky MI, Kim L, et al., 2019, Eligibility and Radiologic Assessment in Adjuvant Clinical Trials in Bladder Cancer, *JAMA Oncol*, 5(12):1790-1798.

⁴ For information regarding drug development for bacillus Calmette-Guérin (BCG)-unresponsive, nonmuscle-invasive bladder cancer, see the guidance for industry *BCG-Unresponsive Nonmuscle Invasive Bladder Cancer: Developing Drugs and Biologics for Treatment* (February 2018). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

⁵ Galsky MD, Hahn NM, Rosenberg J, et al., 2011, Treatment of Patients with Metastatic Urothelial Cancer “Unfit” for Cisplatin-Based Chemotherapy, *JCO*, 29(17):2432-2438.

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- Patients with residual or recurrent malignant disease should be excluded.
 - Any lesions that could possibly represent residual or recurrent bladder cancer on imaging should be biopsied prior to enrollment, if safe and feasible, to assess for the presence of malignant disease and to document eligibility.
 - When a biopsy is not safe or feasible, it may be necessary to use imaging to establish absence of residual or recurrent disease at baseline prior to enrollment to document eligibility. The radiological definition of “no evidence of disease” should be prespecified in the protocol. For example, for patients entering these trials with enlarged lymph nodes or sub-centimeter lesions in the visceral organs that are not amenable to biopsy, the protocol should contain criteria concerning the size or other characteristics of these lesions that establish absence of disease for the purpose of determining eligibility in the trial.
- A large number of discrepancies between investigator and blinded independent central review (BICR) with respect to presence of disease on baseline imaging may interfere with interpretation of results. Consider determination of eligibility based on absence of disease by BICR.

B. Choice of Comparator

The appropriate choice of comparator should be discussed with the FDA prior to study initiation and should be consistent with standards of care and with practice patterns in the U.S.

C. Imaging Assessments

- The protocol should specify acceptable methods of imaging acquisition, display, and radiological interpretation technique for use in determination of DFS. The protocol should specify using the same modality throughout the duration of the trial for an individual patient.
- Initial imaging studies should be timed to allow for stabilization of post-surgical imaging and is recommended to be completed within 4 weeks prior to trial enrollment.
- Imaging assessment frequency should be the same on all treatment arms as asymmetrical frequencies may bias the assessment of DFS. The anticipated magnitude of effect on DFS necessary to demonstrate clinical benefit should be considered in planning the frequency of imaging assessments. The magnitude of DFS improvement should be greater than the imaging frequency for DFS to be interpretable.

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D. Determination of Disease Recurrence

- We recommend the determination of disease recurrence for DFS be based on the assessment by a BICR. If it is based on investigator assessment, it should include a BICR audit.
- Radiological findings suggestive of disease recurrence should be supported by tumor biopsies to confirm malignant disease, whenever safe and feasible.
- The radiological definition of recurrence by site (e.g., tumor bed, lymph nodes, bone metastases, visceral disease) should be prespecified, in case biopsy is not safe or feasible, to confirm recurrence. The definition should include the location, size, and the number of lesion(s) that define radiological recurrence. The definition should be applied uniformly by investigators and the BICR to ensure consistency in criteria for recurrent disease in the absence of histologic confirmation.
- The method for assigning date of recurrence should be prespecified and consistently applied. For example,
 - When both an image and biopsy document recurrence, the earlier date should be used for date of recurrence.
 - When confirmatory imaging is required to document disease recurrence in the absence of biopsy, the date of recurrence should be the date the lesion(s) was first identified.
- New high-grade non-muscle-invasive tumors and all new muscle-invasive bladder cancer tumors that develop in the remaining urothelium following resection should be DFS-defining events. The designation of all other non-muscle invasive tumors as evidence of disease recurrence should be discussed with the FDA prior to study initiation and pre-specified in the protocol.
- Trials should specify if urine cytology will be used for post-operative surveillance in patients who have remaining urothelium, and if so, the specific test and testing interval required. Endoscopic surveillance procedures should be pre-specified.

E. Trial Analysis

- The protocol and statistical analysis plan (SAP) should contain a detailed description of the trial assumptions and statistical methods for analysis of DFS and overall survival (OS).
- Procedures should be put in place to minimize missing data, especially for DFS.

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- The SAP should specify the primary analysis and sensitivity analyses with different censoring rules to evaluate the impact of missing observations, imaging assessment frequency, and other factors on the results.
- Subset analyses should be performed to account for variations in outcomes if sufficient numbers of patients with a component of variant histology are enrolled. Those with pure non-UC histology (e.g., mixed endocrine/small cell tumors), if included, should be analyzed separately.

F. Interpretation of Trial Results

- Interim analyses of DFS to stop for effectiveness are not recommended because immature data may lead to over- or underestimation of magnitude of improvement. A study designed with interim analyses should be discussed with the Agency prior to initiation. Adequate follow-up of the study population prior to efficacy assessment should be carefully considered.
- There is not a single threshold for the magnitude of improvement in DFS required to support drug approval. Instead, whether the data support both a conclusion of substantial evidence of effectiveness and a favorable benefit-risk evaluation depends on several factors including, but not limited to, the trial design (e.g., add-on design, active vs. placebo control), trial conduct, study population, magnitude and type of clinical benefit, and the toxicity profile observed.
- Although FDA approval does not require demonstration of an OS benefit, the protocol and SAP should include a plan for a formal interim analysis of OS at the time of DFS analysis. To support a favorable benefit-risk assessment, this analysis should provide assurance that OS is not adversely affected by the treatment. In addition, FDA expects continued follow-up to allow conduct of the final OS analysis.