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

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Julia Beaver at 240-402-0489 or (CBER) the Office of Communication, Outreach, and Development at 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)
Center for Biologics Evaluation and Research (CBER)**

**October 2020
Clinical/Medical**

Bladder Cancer: Developing Drugs and Biologics for Adjuvant Treatment 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
Oncology Center of Excellence
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

**October 2020
Clinical/Medical**

Contains Nonbinding Recommendations

Draft — Not for Implementation

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	3
E.	Trial Analysis	4
F.	Interpretation of Trial Results	4

Contains Nonbinding Recommendations

Draft — Not for Implementation

1 **Bladder Cancer: Developing Drugs and Biologics for Adjuvant**
2 **Treatment**
3 **Guidance for Industry**
4
5
6

7
8 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
9 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not
10 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the
11 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible
12 for this guidance as listed on the title page.
13

14
15
16
17 **I. INTRODUCTION**
18

19 This guidance provides recommendations to sponsors regarding the development of drugs and
20 biologics,¹ regulated by CDER and CBER for the adjuvant treatment of muscle-invasive bladder
21 cancer. The guidance includes recommendations regarding eligibility criteria, choice of
22 comparator, follow-up imaging assessments, determination of disease recurrence, analyses of
23 disease-free survival (DFS), and interpretation of trial results. Although FDA may consider
24 endpoints other than DFS for the adjuvant treatment of muscle-invasive bladder cancer, this
25 guidance is focused on clinical trials with DFS as the primary efficacy endpoint.
26

27 In general, FDA's guidance documents do not establish legally enforceable responsibilities.
28 Instead, guidances describe the Agency's current thinking on a topic and should be viewed only
29 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
30 the word *should* in Agency guidances means that something is suggested or recommended, but
31 not required.
32
33

34 **II. BACKGROUND**
35

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

¹ 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).

Contains Nonbinding Recommendations

Draft — Not for Implementation

40 were discussed at an FDA-NCI public workshop held on November 27, 2017.² For information
41 regarding drug development for bacillus Calmette-Guérin (BCG)- unresponsive, nonmuscle-
42 invasive bladder cancer, see the guidance for industry *BCG-Unresponsive Nonmuscle Invasive*
43 *Bladder Cancer: Developing Drugs and Biologics for Treatment*.³

44
45

46 III. RECOMMENDATIONS

47
48
49

A. Trial Eligibility Criteria

50
51
52
53
54
55

- Patients with predominant urothelial carcinoma (UC) histology who have a component of variant histology should be included. Subset analyses should be performed to account for variations in response 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.

56
57
58
59

- Patients with microscopic positive margins without gross residual disease should be included when the clinical trial ensures that the number of patients at high-risk for recurrence achieves balance between arms through stratified randomization procedures.

60
61

- Patients with invasive upper-tract UC should be included.

62
63
64

- See section III.C for recommendations regarding imaging assessments relevant to eligibility criteria.

65
66
67
68
69
70

- 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 consensus guidelines. 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.

71
72
73
74
75

- 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.⁴

76
77
78
79

- 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.

² Apolo AB, Milowsky MI, Kim L, et al., 2019, Eligibility and Radiologic Assessment in Adjuvant Clinical Trials in Bladder Cancer, *JAMA Oncol*, epub ahead of print October 31, 2019, doi: 10.1001/jamaoncol.2019.41141.

³ February 2018. 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>.

⁴ 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.

Contains Nonbinding Recommendations

Draft — Not for Implementation

- 80 • Patients with residual or recurrent malignant disease should be excluded.
81
 - 82 ○ Any lesions that could possibly represent residual or recurrent bladder cancer on
83 imaging should be biopsied prior to enrollment, if safe and feasible, to assess for
84 the presence of malignant disease and to document eligibility.
85
 - 86 ○ When a biopsy is not safe or feasible, it may be necessary to use imaging to
87 establish absence of disease at baseline prior to enrollment to document
88 eligibility. The radiological definition of “no evidence of disease” should be
89 prespecified in the protocol. For example, for patients entering these trials with
90 enlarged lymph nodes or sub-centimeter lesions in the visceral organs that are not
91 amenable to biopsy, the protocol should contain criteria concerning the size or
92 other characteristics of these lesions that establish absence of disease for the
93 purpose of determining eligibility in the trial.
94
- 95 • A blinded independent central review (BICR) of baseline scans prior to study entry is
96 recommended to ensure the absence of metastatic disease.
97

B. Choice of Comparator

- 100 • The appropriate choice of comparator should be discussed with the FDA prior to study
101 initiation and should be consistent with standards of care and with practice patterns in the
102 community.
103

C. Imaging Assessments

- 104 • The protocol should specify acceptable methods of imaging acquisition, display, and
105 radiological interpretation technique for use in determination of DFS. The protocol
106 should specify that the same modality should be used throughout the trial for an
107 individual patient.
108
- 109 • Initial imaging studies should be completed within 4 weeks of trial enrollment.
110
- 111 • Imaging assessment frequency should be the same on all treatment arms as asymmetrical
112 frequencies may bias the assessment of DFS. The anticipated magnitude of effect on DFS
113 necessary to demonstrate clinical benefit should be considered in planning the frequency
114 of imaging assessments. The magnitude of DFS improvement should be substantially
115 greater than the imaging frequency for DFS to be interpretable.
116
117

D. Determination of Disease Recurrence

- 118
- 119 • The determination of disease recurrence for DFS should be based on the assessment by a
120 BICR.
121
- 122 • Radiological findings suggestive of disease recurrence should be supported by tumor
123 biopsies to confirm malignant disease, whenever safe and feasible.
124
125

Contains Nonbinding Recommendations

Draft — Not for Implementation

- 126 • The radiological definition of recurrence by site (e.g., tumor bed, lymph nodes, bone
127 metastases, visceral disease) should be prespecified, in case biopsy is not safe or feasible,
128 to confirm recurrence. The definition should include the location, size, and the number of
129 lesion(s) that define radiological recurrence. The definition should be applied uniformly
130 by investigators and the BICR to ensure consistency in criteria for recurrent disease in the
131 absence of histologic confirmation.
132
- 133 • The algorithm for assigning date of recurrence should be prespecified and consistently
134 applied. For example,
135
- 136 ○ When both an image and biopsy document recurrence, the earlier date should be
137 used for date of recurrence.
 - 138
 - 139 ○ When confirmatory imaging is required to document disease recurrence in the
140 absence of biopsy, the date of recurrence should be the date the lesion(s) was first
141 identified.
142
- 143 • New high-grade non-muscle-invasive tumors and all new muscle-invasive bladder cancer
144 tumors that develop in the remaining urothelium following resection should be DFS-
145 defining events. The designation of all other non-muscle invasive tumors as evidence of
146 disease recurrence should be discussed with the FDA prior to study initiation and pre-
147 specified in the protocol.
148
- 149 • Trials should specify if urine cytology will be used for post-operative surveillance in
150 patients who have remaining urothelium, and if so, the specific test and testing interval
151 required. Endoscopic surveillance procedures should be pre-specified.
152

E. Trial Analysis

- 153
- 154
- 155 • The protocol and statistical analysis plan (SAP) should contain a detailed description of
156 the trial assumptions and statistical methods for analysis of DFS and overall survival
157 (OS).
158
 - 159 • Procedures should be put in place to minimize missing data for DFS.
160
 - 161 • The SAP should specify the primary analysis and sensitivity analyses with different
162 censoring rules to evaluate the impact of missing observations, imaging assessment
163 frequency, and other factors on the results.
164

F. Interpretation of Trial Results

- 165
- 166
- 167 • Interim analyses of DFS are not recommended because immature data may lead to over-
168 or underestimation of magnitude of improvement.
169

Contains Nonbinding Recommendations

Draft — Not for Implementation

- 170
- 171
- 172
- 173
- 174
- 175
- 176
- 177
- 178
- 179
- The trial design (e.g., add-on design, active versus placebo control) and conduct, toxicity profile observed, study population, and the overall benefit-risk evaluation all factor in to the magnitude of improvement in DFS required to support drug approval.
 - While 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 final DFS 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. In addition, FDA expects continued follow-up to allow conduct of the final OS analysis.