BCG-Unresponsive Nonmuscle Invasive Bladder Cancer: Developing Drugs and Biologics for Treatment

Guidance for Industry

U.S. Department of Health and Human Services
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Center for Drug Evaluation and Research (CDER)
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TABLE OF CONTENTS

Contains Nonbinding Recommendations

BCG-Unresponsive Nonmuscle Invasive Bladder Cancer: Developing Drugs and Biologics for Treatment Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. 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. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the development of drugs, including biologics, for the treatment of patients who have bacillus Calmette-Guérin (BCG)-unresponsive nonmuscle invasive bladder cancer (NMIBC).[2] This guidance is intended for pharmaceutical sponsors, the academic community, and the public and provides a framework, based on current Food and Drug Administration (FDA) thinking, to facilitate the development of drugs to treat this patient population.[3] This guidance discusses pathological diagnosis and staging, risk stratification, and trial design, including assessment of appropriate clinical endpoints. These issues were discussed at the FDA/American Urological Association Bladder Cancer Workshop held on May 6, 2013, and in published literature (Jarow et al. 2014; Jarow et al. 2015).

Many of the general principles elucidated in this guidance also apply to development of drugs for other forms of NMIBC. Nevertheless, the specific recommendations for trial design and endpoints contained herein may not necessarily apply, and sponsors should discuss with the FDA development plans for drugs intended to treat other forms of NMIBC or for muscle invasive, locally advanced, or metastatic bladder cancer.

This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical*

[1] This guidance has been prepared by the Division of Oncology Products 1 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 *drugs* include both human drugs and biological products unless otherwise specified.

[3] In addition to consulting guidances, sponsors are encouraged to contact the division to discuss specific issues that arise during the development of drugs for the treatment of BCG-unresponsive NMIBC.

Principles for Clinical Trials and *E10 Choice of Control Group and Related Issues in Clinical Trials*, respectively.[4]

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. DEVELOPMENT PROGRAM

A. Early Product Development

Sponsors should conduct nonclinical studies to assess toxicity in animal models (see section II.C.2., Nonclinical Safety Considerations). We also recommend that sponsors conduct nonclinical studies to demonstrate antitumor activity in NMIBC and to determine the optimal dose and schedule of the investigational drug. Although six weekly instillations of intravesical therapy have become a standard dosing regimen for the treatment of patients with NMIBC, few data are available to support this approach. Once sponsors complete the animal studies, we recommend that sponsors examine antitumor activity as well as the optimal dose and schedule in an early phase clinical trial. One option is to assess antitumor activity in patients with marker lesions that can be safely left in place after resection of other areas of NMIBC.

Sponsors developing investigational drugs for BCG-unresponsive NMIBC should also consider assessing antitumor activity in a small number of patients who are awaiting radical cystectomy for BCG-unresponsive NMIBC. With this approach, only a limited window of time is available for observation of antitumor activity because surgery should not be delayed. In addition, these trials should not interfere with the use of neoadjuvant systemic chemotherapy whenever appropriate.

B. Late Phase Development

1. General Considerations

Whether the patient has active disease at the time of trial enrollment is a key consideration for the recommended trial design and endpoints used to evaluate the effectiveness of an investigational drug treating NMIBC. For patients without active disease (disease was resected at or before trial entry), FDA recommends a randomized, controlled trial design using a time-to-event endpoint such as recurrence-free survival. In contrast, patients with carcinoma in situ (CIS) at trial entry can be studied in either a randomized, controlled trial or a single-arm trial. In the absence of pharmacologic intervention or cystectomy, BCG-unresponsive CIS (a type of NMIBC), with or without resected disease, will persist and progress. In BCG-unresponsive

[4] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

NMIBC, a single-arm clinical trial with complete response rate and duration of response as the primary endpoint can provide primary evidence of effectiveness to support a marketing application. Sponsors can include patients with completely resected lesions and no evidence of CIS in these single-arm trials but should not include them in the evaluation of the primary efficacy endpoint. However, sponsors should include these patients in the safety analysis.

The use of systemic, as opposed to intravesical, therapy has been proposed for the treatment of patients with BCG-unresponsive NMIBC. Given the potential for the increased risks associated with the use of systemic therapies, sponsors should limit early phase trials to patients with few treatment options. Patients with BCG-unresponsive NMIBC are appropriate because their treatment options are limited and the current alternative is cystectomy.

2. Trial Population and Entry Criteria

Sponsors should specifically define the trial entry criteria in the trial protocol and document in detail the treatment history in the case report forms.

For the purposes of this guidance, BCG-unresponsive disease is defined as being at least one of the following:

- Persistent or recurrent CIS alone or with recurrent Ta/T1 (noninvasive papillary disease/tumor invades the subepithelial connective tissue) disease within 12 months of completion of adequate BCG therapy

- Recurrent high-grade Ta/T1 disease within 6 months of completion of adequate BCG therapy

- T1 high-grade disease at the first evaluation following an induction BCG course (Steinberg et al. 2016)

In this context, adequate BCG therapy is defined as at least one of the following:

- At least five of six doses of an initial induction course plus at least two of three doses of maintenance therapy

- At least five of six doses of an initial induction course plus at least two of six doses of a second induction course

Sponsors have some flexibility in the use of 6 and 12 months to define BCG-unresponsive NMIBC. For example, a patient whose first assessment occurs 9 months (rather than 3 months) after initiation of his or her second course of BCG and who is found to have high-grade Ta/T1 disease could be considered BCG-unresponsive. Sponsors should specify this within the protocol and discuss this with the appropriate review division.

Patients with BCG-unresponsive NMIBC are extremely unlikely to benefit from further therapy with BCG and represent a unique population for the study of new therapies. The standard of care

for these patients is radical cystectomy; however, many of these patients prefer to avoid cystectomy despite the potential risk of progression to muscle-invasive or metastatic disease. Patients who refuse cystectomy can enter into trials of investigational therapies. Sponsors should inform all patients of the risk of tumor progression and/or recurrence. Further, sponsors should follow these patients regularly so that patients with persistent or recurrent disease can discontinue investigational drugs and proceed to other therapies.

Patients with BCG-unresponsive NMIBC may have recurred with either papillary disease or CIS or both, and their disease status at the time of trial entry may include completely resected disease, resected disease with CIS, or CIS alone. The 2004 World Health Organization/International Society of Urologic Pathology classification system is the preferred system for tumor grading. This system categorizes tumors as papillary urothelial neoplasm of low malignant potential, low-grade, or high-grade (Miyamoto et al. 2010). Before initiating the trial, sponsors should assess and discuss with the FDA the need for central pathology review of tissue and urine cytology to determine patient eligibility and patient outcomes.

Because the methods of a urologist performing the cystoscopy can affect both patient eligibility and outcome, sponsors should ensure that all participating urologists perform and document their bladder examinations according to the protocol. Investigators should fully characterize a patient's disease status at trial entry. Bladder mapping and random biopsies in patients with CIS should be performed before trial entry (Gudjonsson et al. 2012). Sponsors should also obtain urine cytology. The FDA considers use of biomarkers for further risk stratification exploratory at this time. To fully define the extent of disease at trial entry, sponsors should have patients with T1 disease undergo resection of the base of the lesion (the biopsy should contain muscle fibers) before trial entry to ensure the absence of muscle-invasive disease. Furthermore, for patients with high-risk disease undergoing transurethral resection of their bladder tumors, we recommend pelvic examination under anesthesia to rule out the presence of locally advanced disease. Sponsors should use imaging by computerized tomography or magnetic resonance to further evaluate patients for the presence of locally advanced disease.

Sponsors should collect data on the patient's previous anticancer therapies, the dose and timing of administrations, and the patient's responses to each therapy. Sponsors should attempt to enroll patients who reflect the clinically relevant patient population in regard to age, gender, race, and ethnicity. Sponsors should attempt to include women and patients of all races and ethnicities. Because bladder cancer rarely occurs in children, a pediatric waiver request may be appropriate.

3. Randomization, Stratification, and Blinding

Sponsors should stratify the analysis of randomized trials that include patients with CIS based on the type of disease (CIS alone or CIS with resected papillary disease) at trial enrollment. Sponsors should consider whether blinding is feasible in a randomized trial. Sponsors should stratify the analysis of randomized trials that include patients with resected papillary disease by the type of disease (e.g., Ta, T1, and grade) at trial enrollment.

4. Dose Selection

Dose selection is critical to an optimal risk-benefit balance and to the success of a late phase trial. Systemic exposure following intravesical therapy should be assessed during initial clinical trials to evaluate and help mitigate safety concerns. Sponsors should consider the safety profile, activity, and pharmacokinetics of systemically administered investigational drugs in patients with NMIBC. These considerations help guide the selection of dose levels and dosing regimens for patients with NMIBC who may have a lower risk tolerance than patients with other indications for which the drug is being developed, such as metastatic disease. These doses may be different than those used to treat metastatic disease.

5. Single-Arm vs. Randomized, Controlled Trial Design

Single-arm trials are appropriate in clinical settings where a randomized, controlled trial is either unethical or not feasible. Randomizing patients with BCG-unresponsive NMIBC to a placebo or minimally effective drug as a concurrent control raises ethical concerns. Currently, single-arm trials are appropriate for assessment of therapies for patients with BCG-unresponsive disease (CIS with or without resected papillary disease) because, currently, no effective medical therapies are available and the only alternative is radical cystectomy. Sponsors should use randomized trials in clinical settings in which an active or placebo control or a time to event endpoint is appropriate. If effective therapies become available in BCG-unresponsive NMIBC, a randomized trial may be appropriate.

6. Efficacy Endpoints

The primary efficacy endpoint in single-arm trials of patients with BCG-unresponsive NMIBC should be the complete response rate in patients with CIS. Sponsors should consider the complete response rate in the context of the duration of response. Complete response rate can only be determined in those patients who have disease at trial entry (patients with CIS) with or without resected papillary disease. Because partial response has not been defined in this disease setting, sponsors should not use it as a response criterion. Sponsors should discuss with the appropriate review division the minimum duration of follow-up (and, thus, the minimum duration of response) before submitting an application.

For single-arm trials of patients with BCG-unresponsive disease, the FDA defines a complete response as at least one of the following:

- Negative cystoscopy and negative (including atypical) urine cytology
- Positive cystoscopy with biopsy-proven benign or low-grade NMIBC and negative cytology

For intravesical therapies without systemic toxicity, the FDA includes, in the definition of a complete response, negative cystoscopy with malignant urine cytology if cancer is found in the upper tract or prostatic urethra and random bladder biopsies are negative.

Intravesical instillation does not deliver the investigational drug to the upper tract or prostatic urethra. Therefore, the development of disease in these areas cannot be attributed to a lack of activity of the investigational drug. Thus, sponsors can consider patients with new malignant lesions of the upper tract or prostatic urethra who have received intravesical therapy to have achieved a complete response in the primary analysis. However, sponsors should record these lesions and conduct sensitivity analyses in which these patients are not considered to have achieved a complete response.

Systemic therapies are expected to have a treatment effect throughout the urinary tract. Therefore, a patient who received systemic therapy cannot be considered to have a complete response if the patient has a malignant lesion(s) in the upper tract or prostatic urethra.

For the purposes of determining the duration of a complete response, the FDA defines a recurrence as findings on follow-up that no longer meet the above definition for a complete response. The protocol should provide a plan for the evaluation of patients with suspicious urine cytology. Suspicious cytology does not include the presence of atypical cells. This plan should specify how a suspicious urine cytology will affect the initial definition of complete response and the duration of complete response. For example, the plan may include repeat cytologies or random bladder biopsies. Regardless of the prespecified plan, all investigators should evaluate suspicious urine cytology in the same manner.

The goal of therapy in patients with BCG-unresponsive NMIBC is to avoid cystectomy. The development of low-risk/low-grade papillary lesions does not affect the decisions regarding cystectomy because these patients can be treated with transurethral resection alone. Therefore, for the purposes of these trials, sponsors should consider patients with low-risk/low-grade lesions to have achieved a complete response and to have maintained this response (following resection of these low risk/low-grade papillary lesions) in the primary analysis. However, sponsors should record these lesions and conduct sensitivity analyses in which these patients are not considered to have achieved a complete response.

Although delay in radical cystectomy is considered a direct patient benefit, the variations in patient and health care provider preferences can confound the interpretation of this endpoint in randomized trials and particularly in single-arm trials. Nevertheless, sponsors should collect these data, which may provide supportive evidence of effectiveness. In addition, sponsors should assess disease progression to muscle-invasive and/or metastatic disease.

In general, sponsors should use the complete response rate as the primary endpoint for treatment of CIS. However, the trial design should prespecify whether patients with CIS who do not achieve a complete response at their 3-month assessments should discontinue the investigational drug(s) because of the risk of progression. Sponsors should consider the patient's disease history, type of disease present at 3 months (e.g., T1), and the mechanism of action of the investigational drug(s). At 3 months, patients with BCG-unresponsive CIS at study entry who are found to have new, T1 high-grade disease with or without CIS and patients with persistent CIS who did not have a disease-free interval should discontinue the investigational drug(s). Sponsors should discuss these issues with the FDA during the development of the trial design.

7. Trial Procedures and Timing of Assessments

During the conduct of a clinical trial, patients with BCG-unresponsive NMIBC should be followed every 3 months for 2 years, then every 6 months for 2 years, and then annually with cystoscopy, directed biopsies, and urine cytology. The FDA recommends random bladder biopsies at a specific time point(s) (e.g., 6 months, 18 months, etc.), but these are not required. The protocol should address the number of random biopsies and the biopsy sites.

8. Endpoint Adjudication

Sponsors should consult with the appropriate FDA review division regarding the need for central pathology review of biopsy specimens and/or cytology for all patients or a representative sample.

9. Statistical Considerations

For single-arm trials of patients with BCG-unresponsive NMIBC in patients with CIS that use complete response rate as the primary endpoint, the lower bound of the 95 percent confidence interval around the observed response rate should rule out a clinically unimportant complete response rate. The median duration of complete response is also important. A high complete response rate is not meaningful if the response duration is short. The sponsor should discuss with the appropriate review division the minimum duration of response at the time of NDA or BLA submission. Patients participating in the trial should continue to be followed for the development of a complete response and for duration of complete response.

Sponsors can use either early phase evidence of effect size or data from historical controls to calculate the sample size of the single-arm trial; however, the FDA does not require or recommend a prespecified response rate. The natural history of CIS is well understood, and the complete response rate is negligible in the absence of therapy.

10. Accelerated Approval (Subpart H and Subpart E) Considerations

A development program that assesses complete response rate in a single-arm trial may be appropriate for regular approval, or it may require a confirmatory trial after approval.[5] A confirmatory, randomized trial in the same population often is not possible (e.g., patients with BCG-unresponsive NMIBC). Sponsors may be able to provide confirmatory evidence of effectiveness in a different patient population. Potential trial designs include randomized trials comparing the investigational drug to BCG in treatment-naïve high-risk disease or as add-on therapy to BCG (BCG plus/minus investigational drug) in patients who recur after an initial induction course of BCG. The need for a confirmatory trial and its design can be discussed at a separate, end-of-phase 2 meeting held during the conduct of a single-arm trial. On occasion, long-term follow-up from the same trial can satisfy a confirmatory study obligation under accelerated approval.

[5] 21 CFR part 314, subpart H, and part 601, subpart E.

11. Risk-Benefit Considerations

The approval of a marketing application is based on a favorable risk-benefit assessment. The key elements in the planning and conduct of these trials are outlined above. These issues were discussed at the FDA/American Urological Association Bladder Cancer Workshop held on May 6, 2013. The International Bladder Cancer Group addressed similar issues in a recent publication (Kamat et al. 2016).

For therapies that have greater toxicity (e.g., systemic therapies), substantially greater efficacy might be needed to achieve an overall favorable risk-benefit assessment. Sponsors of clinical trials using either intravesical or systemic therapy should meet with the FDA to discuss trial design details.

C. Other Considerations

1. Risk Management Considerations

The FDA cannot make a decision concerning a risk management plan before reviewing the data included in a biologics license application or new drug application. Sponsors should provide a plan to assess the long-term outcomes of patients receiving the investigational drug. For example, a long-term study or trial to assess bladder capacity may be needed if there was a signal in premarketing studies that the investigational drug caused bladder fibrosis.

2. Nonclinical Safety Considerations

Before sponsors initiate clinical trials in patients with NMIBC, we recommend that sponsors use nonclinical studies to optimize the dose and schedule of intravesical drugs. A sponsor's choice and use of nonclinical models will vary with the investigational drug. The sponsor should discuss this with the appropriate review division. Sponsors also can use nonclinical studies to ensure that systemic therapies are active at the mucosal surface of the bladder and to justify the potential risks associated with systemic therapies. For drugs intended for intravesical administration, sponsors can use the extent of systemic exposure in nonclinical studies following intravesical administration to determine the need for evaluation of systemic toxicity. If systemic exposure is low, histological evaluation may be limited to locally exposed tissues. Similarly, if systemic exposure of the active substance is equivalent to or less than that of an approved route of administration for the same active substance, histological evaluation also may be limited to locally exposed tissues. The recommendations for and timing of additional nonclinical studies depends upon the available nonclinical and clinical data, the nature of the toxicities observed, and the patient population (e.g., more advanced NMIBC such as BCG-unresponsive NMIBC). Sponsors should discuss this with the appropriate review division before conducting a clinical trial using either a systemic or intravesicular drug in patients with NMIBC.

For recommendations on the substance and scope of nonclinical information needed to support clinical trials for cell therapy and gene therapy products, see the guidances for industry *Preclinical Assessment of Investigational Cellular and Gene Therapy Products*, *Clinical Considerations for Therapeutic Cancer Vaccines*, and *Recommendations for Microbial Vectors Used for Gene Therapy*.[6]

[6] These guidances are available on the FDA's Cellular & Gene Therapy Guidances web page at https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/default.htm.

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