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

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DRAFT GUIDANCE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

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs, including biologics, for the treatment of patients who have bacillus Calmette-Guerin (BCG)-unresponsive nonmuscle invasive bladder cancer (NMIBC).[2] The definition described by Lerner et al. 2015 is used to identify the patient population with BCG-unresponsive disease. 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] The pathological diagnosis and staging, risk stratification, and trial design, including assessment of appropriate clinical endpoints, are discussed. These issues were discussed at the Food and Drug Administration/American Urological Association Bladder Cancer Workshop held on May 6, 2013, and in more recent publications (Jarow, Lerner, et al. 2014; Jarow, Maher, et al. 2015).

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

[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.

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 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 Phase Development

Nonclinical studies and early phase development should be conducted to demonstrate antitumor activity and determine the optimal dose and schedule of the investigational drug. Although six weekly instillations of intravesical therapy has become a standard approach for the treatment of NMIBC, there are few data available to support this approach. Antitumor activity may be demonstrated in animal models and/or in patients with marker lesions or those who are scheduled for cystectomy.

Marker lesions are small areas (less than 3 centimeters (cm)) of low-grade papillary lesions that are biopsied and left in place. These lesions then can be examined for complete response to the investigational drug. The number of patients involved in such studies should be small, and these patients should be closely followed with resection of residual lesions after response has been determined. In addition to the assessment of drug activity in low-grade disease, sponsors should consider assessment of activity of the investigational drug in patients with BCG-unresponsive disease before late phase development.

Another option to assess antitumor activity is to administer an investigational drug to patients who are awaiting cystectomy. This allows examination of activity against higher risk disease and over the entire surface of the bladder. With this approach, there is only a limited window available for observation of antitumor activity because surgery should not be delayed. Further, these studies should not interfere with the use of neoadjuvant systemic chemotherapy whenever appropriate.

[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 http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

B. Late Phase Development

1. General Considerations

A key consideration for the recommended trial design and endpoints used to evaluate effectiveness for an investigational drug used to treat NMIBC is whether the patient has active disease at the time of enrollment. The preferred trial design in patients without active disease (disease was resected at or before trial entry) is a randomized, controlled trial using a time-to-event endpoint of recurrence-free survival. In contrast, patients with disease at trial entry, such as patients with carcinoma in situ (CIS), can be studied in either a randomized, controlled trial or single-arm trial. The natural history of BCG-unresponsive NMIBC (CIS with or without resected disease) is that, in the absence of a pharmacologic intervention or cystectomy, CIS will almost always persist. In this setting, a single-arm clinical trial with complete response rate as the primary endpoint can provide primary evidence of effectiveness to support a marketing application.

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

2. Trial Population and Entry Criteria

The trial entry criteria should be specifically defined in the trial protocol and well documented in the case report forms.

NMIBC includes the following stages (Edge, Byrd, et al. 2010):

- Ta: Noninvasive papillary disease
- T1: Tumor invades the subepithelial connective tissue
- Tis: Carcinoma in situ

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, Miller, et al. 2010).

Tumor stage and grade can be used to categorize an individual patient's risk of recurrence and progression. The following risk categories are commonly employed (Persad, Lamm, et al. 2008):

- **Low-risk tumors:** include all of the following features: small-volume (less than 3 cm), low-grade, pathological Ta lesions with no evidence of CIS

- **Intermediate-risk tumors:** include those that cannot be categorized as low-risk or high-risk

- **High-risk tumors:** include any of the following features: T1 lesions, high-grade disease, tumors larger than 3 cm, multiple or recurrent lesions, and CIS

For the purposes of this guidance, BCG-unresponsive disease is defined as (Lerner, Dinney, et al. 2015):

- Persistent high-grade disease or recurrence within 6 months of receiving at least two courses of intravesical BCG (at least five of six induction doses and at least two of three maintenance doses); or

- T1 high-grade disease at the first evaluation following induction BCG alone (at least five of six induction doses)

Most patients with intermediate- or high-risk NMIBC are treated with an induction course (six weekly instillations) with or without maintenance (three weekly instillations at 3 and 6 months and every 6 months thereafter for 1 to 3 years) of BCG (Lamm, Blumenstein, et al. 2000). Some tumors recur on therapy or after a short disease-free interval. Patients with BCG-unresponsive disease are extremely unlikely to benefit from further therapy with BCG and represent a unique population for study of new therapies.

To fully define the extent of disease at study entry, patients with T1 disease should undergo repeat resection or biopsy of the base of the lesion before study entry to ensure the absence of muscle-invasive disease (T2). Furthermore, patients with high-risk disease should undergo pelvic examination under anesthesia and imaging by computerized tomography or magnetic resonance imaging to rule out locally advanced disease. Patients with BCG-unresponsive disease can have completely resected disease, resected disease with CIS, or CIS alone at study entry. Patients should be staged before enrollment. Staging should include the use of bladder mapping and random biopsies in patients with CIS or high-grade papillary disease (Gudjonsson, Blackberg, et al. 2012). Urine cytology also should be obtained and evaluated.

Data should be collected concerning previous anticancer therapies, the dose and timing of administration, and the patient's response to each therapy. Patient sex, age, and race should be considered when enrolling patients in any clinical trial. In NMIBC, an effort should be made to include women and patients of all races. Because bladder cancer rarely occurs in children, a pediatric waiver request may be appropriate.

The role of central pathology in establishing patient eligibility should be discussed with the responsible review division. Fluorescence-guided cystoscopy also may be used to aid in patient selection. Whether white light or fluorescence-guided cystoscopy is used at baseline, the same method of assessment should be employed throughout the study of that individual patient.

3. Randomization, Stratification, and Blinding

Because the urologist performing the cystoscopy can affect both patient eligibility and outcome, sponsors should consider randomization by study site. In either a randomized or single-arm trial, sponsors should ensure that all participating urologists perform and document their examination of the bladder according to the protocol. Moreover, for either randomized or single-arm trials, sponsors should provide a plan to examine the effect of the urologist/investigator site on patient staging and outcome.

In a randomized trial that includes patients with CIS and resected papillary disease, patients should be stratified into patients with CIS alone and patients with CIS and resected papillary disease. Sponsors also should consider whether fluorescence-guided cystoscopy will be used in the examination of the bladder and may choose to stratify by this variable as well. Finally, sponsors should consider whether blinding is feasible in a randomized trial.

4. Dose Selection

Dose selection is critical to optimal patient treatment and to the success of a late phase trial. Sponsors should consider an exploration of dose and schedule during nonclinical studies and early phase clinical trials. Systemic exposure assessed in an early phase dose-selection trial may help evaluate and minimize safety concerns from potential systemic exposure after intravesicular administration. For investigational drugs administered systemically, it is important to consider the safety profile, activity, and pharmacokinetics of the drug in patients with nonmuscle invasive disease. These considerations can help guide selection of various dose levels and dosing regmimens for study in the trials intended to provide primary evidence of effectiveness. The doses used to treat nonmuscle invasive disease may be lower than the doses administered for the systemic treatment of 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 disease to a minimally effective drug as a concurrent control raises ethical concerns. Because effective drugs are not available and the alternative treatment is cystectomy, single-arm trials of patients with BCG-unresponsive CIS disease with or without papillary disease are appropriate. In general, these single-arm trials should use drugs that have shown activity in bladder cancer.

6. Efficacy Endpoints

The primary endpoint we recommend sponsors use in single-arm trials of patients with BCG-unresponsive disease is the complete response rate of CIS and its 95 percent confidence interval. The median duration of response also should be assessed. Complete response can be defined as negative urine cytology and no lesions on cystoscopy. If random biopsies of the bladder and prostatic urethra are performed, they should be negative. Partial response has not been defined in this disease setting because the area involved with CIS is difficult to quantitate; therefore, partial response should not be used as a response criteria in the assessment of patients with BCG-

unresponsive CIS. Furthermore, partial response is not a relevant endpoint because cystectomy would be indicated in patients with any remaining BCG-unresponsive CIS. Patients with both CIS and completely resected lesions can be assessed using this endpoint. That is, this endpoint would be used to assess the response of the remaining CIS. Adequate follow-up should be provided to establish the duration of response.

A delay in cystectomy should not be used as a primary endpoint in patients with BCG-unresponsive CIS. A delay of cystectomy is considered a direct patient benefit. However, in a single-arm study, variability in health care provider and patient preference can makes it difficult to interpret such a delay. Nevertheless, these data should be collected to provide supportive evidence. Patients with completely resected lesions, in the absence of CIS, also can be included in these trials but should not contribute to the primary endpoint. These patients should be included in the safety analysis.

Intravesical therapy is unlikely to affect the occurrence of upper tract disease and, therefore, the development of upper tract disease should not be included as an event in the assessment of the duration of response. Upper tract disease should be included as an event in systemic therapy trials. In both settings, the incidence of upper tract disease should be recorded and presented as a separate analysis. Further, in some situations, it may be reasonable to exclude the development of low-risk disease as an event. For example, a trial involving patients with BCG-unresponsive disease could include only high-risk disease as an event. In this clinical setting, low-risk disease would lead to transurethral resection while high-risk disease would lead to cystectomy, a much different clinical outcome. Nevertheless, the low-risk recurrences and the development of upper tract disease should be recorded and reported separately.

7. Trial Procedures and Timing of Assessments

During the conduct of a clinical trial, patients with NMIBC should be followed every 3 months with cystoscopy, directed biopsies, and urine cytology. The definition of complete response should be included in the protocol and should include the absence of lesions on cystoscopy or negative, for cause, biopsies along with negative urine cytology. Random biopsies at a specific time point(s) are not needed, but sponsors can choose to incorporate these into the study design. The number of random biopsies and the biopsy sites should be defined in the protocol.

With either approach, it is important to ensure that all participating urologists perform and document their examination of the bladder in a similar manner. A detailed protocol, as well as investigator meetings and trial initiation visits, can be used to standardize this approach.

Follow-up of urine cytology is critical in patients with BCG-unresponsive NMIBC. The clinical protocol should provide an algorithm for further workup of positive and indeterminate cytology. In addition, the clinical protocol should provide a statement of what constitutes an event. For example, the protocol would state whether a patient with no visible lesions, positive urine cytology (i.e., the presence of malignant cells), and negative random biopsies would still be considered to have a complete response. Note that the definition of an event used in the clinical trial setting may differ from the actual management of the patient.

8. Endpoint Adjudication

Sponsors should consult with the appropriate review division concerning the need for central pathology review of all patients, or in a representative sample, to assess and adjudicate the endpoint.

9. Statistical Considerations

For single-arm trials 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 clinically unimportant complete response rates on treatment. The median duration and lower bound of the 95 percent confidence interval for duration of complete response are also important. A high complete response rate is not meaningful if the duration is short.

Either early phase evidence of effect size or data from historical controls can be employed to calculate the sample size of the single-arm trial; however, a prespecified response rate (performance goal) is not required. 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 traditional approval or it may require a confirmatory trial postapproval.[5] A confirmatory, randomized trial in the same population often is not possible (e.g., BCG-unresponsive patients). It may be possible to provide confirmatory evidence of effectiveness in a different patient population. For example, a drug that demonstrates a complete response rate in patients with BCG-unresponsive disease also may be effective in patients who do not develop a complete response following their initial induction course of BCG. Patients could then be randomized to additional BCG or additional BCG plus the investigational drug. 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.

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 have been outlined above. 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 are encouraged to meet with the FDA to discuss details of their trial designs.

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

C. Other Considerations

1. Risk Management Considerations

The FDA cannot make a decision concerning a risk management plan before it reviews the data included in a biologics license application or new drug application. Sponsors should provide a plan to assess the long-term outcomes for 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 initiating clinical trials in patients with NMIBC, we recommend that nonclinical studies be used to optimize the dose and schedule of intravesicular drugs. The choice and use of nonclinical models will vary with the investigational drug and should be discussed with the appropriate review division. Nonclinical studies also can be used 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 intravesicular administration, the extent of systemic exposure in nonclinical studies following intravesicular administration can be used 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 disease). This should be discussed with the appropriate review division before the conduct of 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 Cellular & Gene Therapy Guidances Web page at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/default.htm.

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