Special Report

Clinical Trial Design for the Development of New Therapies for Nonmuscle-invasive Bladder Cancer: Report of a Food and Drug Administration and American Urological Association Public Workshop

Jonathan P. Jarow, Seth P. Lerner, Paul G. Kluetz, Ke Liu, Rajeshwari Sridhara, Dean Bajorin, Sam Chang, Colin P. N. Dinney, Susan Groshen, Ronald A. Morton, Michael O'Donnell, Diane Zipursky Quale, Mark Schoenberg, John Seigne, and Bhadrasain Vikram

OBJECTIVE To summarize the discussion at a public workshop, cosponsored by the U.S. Food and Drug Administration (FDA) and the American Urological Association, reviewing potential trial designs for the development of new therapies for non–muscle-invasive bladder cancer (NMIBC). There have been only 3 drug approvals for NMIBC in the last 30 years, and product development for this disease has been stymied by difficulties in trial design and patient accrual.

METHODS A workshop evaluating potential trial design for the development of therapies for NMIBC was held in San Diego, CA, in May 2013. Invited experts representing all stakeholders, including urology, medical oncology, radiation oncology, industry, and patient advocates, discussed development of products for all risk strata of NMIBC.

RESULTS The panel responded to specific questions from the FDA, discussing eligibility criteria, efficacy endpoints, and trial design for patients with a mix of high-grade papillary disease and carcinoma in situ, Bacillus Calmette-Guerin (BCG)-refractory disease, and intermediate-risk disease. Panel members also addressed the magnitude of response that would be clinically meaningful for various disease strata and trial design options for perioperative intravesical chemotherapy instillation at the time of resection of bladder tumors.

CONCLUSION Expert commentary provided by panel members will inform a planned FDA guidance on pathways for drug and biologic development for NMIBC and will be discussed at meetings of the FDA's Oncologic Drugs Advisory Committee. FDA intends to develop a set of principles that can be used to promote the development of new products for this disease. UROLOGY 83: 262–265, 2014. Published by Elsevier Inc.

Financial Disclosure: *The authors declare that they have no relevant financial interests.*

From the Office of Hematology and Oncology Products, Food and Drug Administration, Silver Spring, MD; Scott Department of Urology, Baylor College of Medicine Medical Center, Houston, TX; the Office of Cellular, Tissue and Gene Therapies, Center for Biologics Evaluation and Research, Food and Drug Administration, Silver Spring, MD; the Division of Biometrics V, Office of Biostatistics, CDER, Food and Drug Administration, Silver Spring, MD; Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY; the Department of Urologic Surgery, Vanderbilt University Medical Center, Nashville, TN; the University of Texas MD Anderson Cancer Center, Houston, TX; the Department of Preventive Medicine, USC Norris Comprehensive Cancer Center, USC/Keck School of Medicine, Los Angeles, CA; the American Medical Systems, Minnetonka, MN; the University of Iowa, Iowa city, IA; the Bladder Cancer Advocacy Network, Bethesda, MD; the Johns Hopkins University School of Medicine, Baltimore, MD; Dartmouth-Hitchcock Medical Center and Norris Cotton Cancer Center, Lebanon, NH; and the National Cancer Institute, Bethesda, MD

Reprint requests: Jonathan P. Jarow, M.D., Food and Drug Administration, Office of Hematology and Oncology Products, Silver Spring, MD 20993. E-mail: Jonathan.jarow@fda.hhs.gov

Submitted: July 12, 2013, accepted (with revisions): October 20, 2013

The U.S. Food and Drug Administration (FDA) has partnered with the American Urological Association to hold public workshops evaluating potential trial designs to support the development of drugs, biologics, and devices to treat localized genitourinary cancers. These workshops are designed to engage key opinion leaders and stakeholders who understand the unique problems associated with trial design and product development for these diseases. Issues highlighted at these workshops will be brought to the Oncologic Drugs Advisory Committee (ODAC), statutory advisory body of FDA for review of oncology drugs. Discussions at both the workshops and ODAC will inform guidance that FDA is preparing on clinical trial design for localized bladder cancer product approvals.

0090-4295/14/$36.00
http://dx.doi.org/10.1016/j.urology.2013.10.030

The most recent of these workshops was held on May 6, 2013, in San Diego, CA, to consider clinical trial design for non–muscle-invasive bladder cancer (NMIBC). The panel consisted of recognized experts from urology, medical oncology, radiation oncology, industry, and patient representatives, along with FDA officials. The discussion was facilitated by Jonathan P. Jarow, M.D., Medical Officer from the Office of Oncology Drug Products at FDA's Center for Drug Evaluation and Research.

The workshop focused on identifying pathways for the development of new products for the treatment of NMIBC, with a special focus on trial designs for each risk strata and effect sizes that would be clinically meaningful. In addition, panelists identified key areas about which knowledge is limited and proposed areas that would benefit from further study.

MATERIALS AND METHODS

The workshop consisted of 3 formal presentations by panel members covering the following topics: regulatory basis of drug and biologics approval, statistical issues including time to event analysis and noninferiority design, and review of the level 1 evidence of the effect size of Bacille Calmette-Guerin (BCG) therapy. These presentations were followed by discussion of 5 specific questions posed by the FDA (Fig. 1). The FDA questions also served as a starting point for a wide-ranging discussion.

FDA's questions addressed clinical trial design elements related to the development of products for high-risk disease, BCG-refractory disease, intermediate-risk disease, and perioperative chemotherapy instillation. Discussion focused on multiple trial design features, including patient eligibility criteria, diagnostic testing, efficacy endpoints, and the magnitude of effect that would be considered clinically meaningful. The panel's discussion and responses to the FDA questions are summarized in the following section.

1. Is it appropriate to conduct trials with a mix of patients with carcinoma in situ, papillary disease, and both? How can we design a trial that mixes these patient populations that measures treatment effect using a single endpoint with a time to event analysis?
2. What is the appropriate comparator for a randomized trial in patients with BCG-refractory NMIBC (CIS and/or papillary)?
3. Is the natural history of patients with BCG-refractory CIS defined well enough to design a single-arm trial? If yes, what would you consider a clinically meaningful magnitude of effect for complete response and duration?
4. Is it feasible to conduct a randomized trial that employs no treatment or placebo as the control arm in any risk strata of patients with NMIBC? For patients in whom there are therapies with proven benefit, how long is it safe to delay therapy? Alternatively, in the setting of a neoadjuvant trial, what is the longest period that it is safe to delay cystectomy?
5. What would you recommend as the primary endpoint (i.e., time to event or recurrence-free survival rates) and what magnitude of benefit is clinically meaningful?

Figure 1. Food and Drug Administration questions for panel members.

RESULTS

Trial Design for Patients With High-risk NMIBC

- There was broad consensus that trials might include a mix of patients with high-grade papillary disease, carcinoma in situ (CIS), and both.
- The preferred primary endpoint for these trials would be time to event using failure to achieve a complete response in patients with CIS and recurrence in patients with CIS or papillary disease as the events.
- The placebo-controlled trials of BCG were discussed. Although these trials demonstrate a favorable risk-benefit profile for BCG, they are not helpful in estimating the effect size over placebo when using contemporary dosing schedules and risk stratification. The panel concluded that a single-arm trial or noninferiority design using BCG as the comparator is not feasible.
- Patients with papillary disease should undergo re-resection and site-directed biopsies to rule out muscle invasion and determine the presence of CIS, respectively.[1,2]
- Duration of follow-up should be at least 18-24 months.
- Adjuncts to visualization of bladder tumors such as fluorescent agents might be used but it would not be practical to mandate them at this time.[3,4]

Trial Design for Patients With BCG-refractory NMIBC

- The panel defined BCG-refractory disease as patients who received 2 induction courses of BCG, induction plus maintenance (usually within 6 months), or were intolerant of BCG.[5-7]
- The panel could not agree on a standard of care for the treatment of these patients to use as a control arm but did agree that additional BCG is not appropriate.
- There was broad consensus that a placebo arm was inappropriate for ethical and practical reasons.
- There was discussion by the panel of the use of physician choice for a comparator in a randomized controlled trial in this patient population.
- There was broad consensus by the panel that provided the results were robust, a single-arm trial could provide sufficient evidence of benefit. For patients with BCG-refractory CIS, the panel felt that an initial complete response rate of 40%-50% at 6 months and a durable response rate of at least 30% for 18-24 months with the lower bound of the 95% confidence interval excluding 20% could be clinically meaningful.[8]
- There was discussion on how to handle a patient who recurred with low-grade papillary disease and whether to call them a failure without development of a consensus.
- There was no discussion of what would be an acceptable level of response/recurrence-free interval for patients with BCG-refractory papillary disease without CIS.

Placebo-controlled Trials

- There was broad consensus by the panel that a placebo control could be used in low-risk patients.
- Most of the panel did not favor use of placebo control in other risk strata with the following exceptions:
  - ➢Using the paradigm of neoadjuvant chemotherapy for patients undergoing radical cystectomy,[9] an

intravesical agent could be compared with a placebo or active control using pathologic response as the primary endpoint. The majority of the panel thought it would be safe to delay cystectomy for 3 months.[10] A minority thought cystectomy could be safely delayed for up to 6 months in this patient population.[11]

➢There was broad consensus that a placebo control could be used in an add-on trial design, for example, BCG plus X vs BCG plus placebo.

Perioperative Intravesical Chemotherapy Instillation

- There was broad consensus that trials evaluating perioperative intravesical chemotherapy should be performed with a time to event analysis for recurrence with a follow-up period of at least 2 years.[12,13]
- Placebo control was considered appropriate.
- The panel defined a clinically meaningful result as an absolute reduction of at least 15% event rate or a hazard ratio of 0.70.
- The panel suggested that future trials consider stratification of patients on the basis of primary vs recurrent disease.[14]

CONCLUSION

Summaries and presentations from this workshop are posted on the FDA Web site (http://www.fda.gov/Drugs/NewsEvents/ucm348373.htm). The conclusions by the panel members will be discussed at subsequent ODAC meetings and will inform any future FDA's guidance on bladder cancer product development. Ultimately, FDA intends to work toward establishing a set of principles that can be used to define efficacy standards for drugs used to treat NMIBC.

References

1. Babjuk M, Burger M, Zigeuner R, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2013. *Eur Urol.* 2013;64:639-653.
2. American Urological Association. Hall, MC, Chang, SS, Dalbagni, G, et al. Guideline for the management of nonmuscle invasive bladder cancer: (Stages Ta, T1 and Tis): Update (2007). Available at: http://www.auanet.org/education/guidelines/bladder-cancer.cfm. Accessed July 2013.
3. Fradet Y, Grossman HB, Gomella L, et al. A comparison of hexaminolevulinate fluorescence cystoscopy and white light cystoscopy for the detection of carcinoma in situ in patients with bladder cancer: a phase III, multicenter study. *J Urol.* 2007;178:68-73.
4. Grossman HB, Gomella L, Fradet Y, et al. A phase III, multicenter comparison of hexaminolevulinate fluorescence cystoscopy and white light cystoscopy for the detection of superficial papillary lesions in patients with bladder cancer. *J Urol.* 2007;178:62-67.
5. Gallagher BL, Joudi FN, Maymi JL, et al. Impact of previous bacille Calmette-Guerin failure pattern on subsequent response to bacille Calmette-Guerin plus interferon intravesical therapy. *Urology.* 2008;71:297-301.
6. Joudi FN, Smith BJ, O'Donnell MA. Final results from a national multicenter phase II trial of combination bacillus Calmette-Guerin plus interferon alpha-2B for reducing recurrence of superficial bladder cancer. *Urol Oncol.* 2006;24:344-348.
7. Rosevear HM, Lightfoot AJ, Birusingh KK, et al. Factors affecting response to bacillus Calmette-Guerin plus interferon for urothelial carcinoma in situ. *J Urol.* 2011;186:817-823.
8. Steinberg G, Bahnson R, Brosman S, et al. Efficacy and safety of valrubicin for the treatment of Bacillus Calmette-Guerin refractory carcinoma in situ of the bladder. The Valrubicin Study Group. *J Urol.* 2000;163:761-767.
9. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med.* 2003;349:859-866.
10. Badalato GM, Gaya JM, Hruby G, et al. Immediate radical cystectomy vs conservative management for high grade cT1 bladder cancer: is there a survival difference? *BJU Int.* 2012;110:1471-1477.
11. Luciani LG, Neulander E, Murphy WM, et al. Risk of continued intravesical therapy and delayed cystectomy in BCG-refractory superficial bladder cancer: an investigational approach. *Urology.* 2001;58:376-379.
12. Abern MR, Owusu RA, Anderson MR, et al. Perioperative intravesical chemotherapy in non-muscle-invasive bladder cancer: a systematic review and meta-analysis. *J Natl Compr Canc Netw.* 2013;11:477-484.
13. Sylvester RJ, Oosterlinck W, van der Meijden AP. A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. *J Urol.* 2004;171:2186-2190.
14. Gudjonsson S, Adell L, Merdasa F, et al. Should all patients with non-muscle-invasive bladder cancer receive early intravesical chemotherapy after transurethral resection? the results of a prospective randomised multicentre study. *Eur Urol.* 2009;55:773-780.

EDITORIAL COMMENT

For the urologic oncology community, the massive unmet need for therapeutics in bladder cancer throughout the disease spectrum is widely recognized. For patients with non—muscle-invasive bladder cancer (NMIBC), this issue is best illustrated by the following: 3 drug approvals in 30 years, in contrast to 5 new drugs approved for castration-resistant metastatic prostate cancer in the last 3 years. There are many reasons for this dismal performance, including limited interest by big (and little) pharma and a rather poor track record of completion of clinical trials in urothelial cancer. NMIBC is inherently problematic to study in the context of clinical trials in no small part because of a lack of consensus on trial end points both from a clearly clinical and regulatory perspective. The present report summarizes the work at a joint Food and Drug Administration and American Urological Association meeting, whose goal was to reach some consensus on potential trial designs and end points, to "jump start" efforts for the development of novel therapeutics. The focus, appropriately, was on both high-risk NMIBC and BCG-refractory carcinoma in situ (CIS). For the latter setting, there appeared to be broad consensus that there is no standard comparator for a randomized trial, and perhaps of more importance, that an initial complete response rate of 40%-50% at 6 months and a durable response rate of at least 30% for 18-24 months, with the lower bound of the 95% confidence interval excluding 20% could be

clinically meaningful — which I interpret to mean as a potentially approvable endpoint. With respect to trial design for patients with high-risk NMIBC, there was consensus that the preferred primary endpoint for these trials should be time to event, using failure to achieve a complete response in patients with CIS and recurrence in patients with CIS or papillary disease as the events. This joint effort of the American Urological Association and Food and Drug Administration is encouraging but requires follow-up action from the urologic oncology community to "encourage" our colleagues in pharma to explore this area of unmet need with renewed enthusiasm, especially given a potential window of opportunity for drug development in trials with end points that are more broadly accepted, which could potentially lead to regulatory approval.

Robert Dreicer, M.D., M.S., F.A.C.P., F.A.S.C.O.,
Department of Solid Tumor Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH

http://dx.doi.org/10.1016/j.urology.2013.10.031
UROLOGY 83: 264—265, 2014. Published by Elsevier Inc.