

**Best Pharmaceuticals for Children Act (BPCA)  
Pediatric Oncology Working Group Conference Call  
May 10, 2016  
11:00 a.m.–11:45 a.m. ET**

**Participants**

Peter Adamson, M.D.  
Amy Barone, M.D.  
Susan Blaney, M.D.  
Patricia Dinndorf, M.D.  
Martha Donoghue, M.D.  
Lori Ehrlich, M.D., Ph.D.  
Aviva Krauss, M.D.  
Leigh Marcus, M.D.  
Kate Matthay, M.D.  
Christy Osgood, M.D.  
Julie Park, M.D.  
Gregory Reaman, M.D.  
C. Patrick Reynolds, M.D., Ph.D.  
Malcolm Smith, M.D.  
Donna Snyder, M.D.  
Brenda Weigel, M.D., M.Sc.  
Anne Zajicek, M.D., Pharm.D.

**Purpose**

The purpose of this call was to discuss the following:

- Plans for the upcoming Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (ODAC)
- Recommendations from the Working Group (WG) for additional products to be discussed

**Pediatric Subcommittee of the ODAC Agenda**

Dr. Reaman began the meeting by briefly reviewing the tentative agenda for the upcoming Pediatric Subcommittee of the ODAC, scheduled for June 28 and June 29, 2016. He explained that initially six products were to be discussed. However, one of the pharmaceutical sponsors, Merrimack Pharmaceuticals, notified the U.S. Food and Drug Administration (FDA) that it would be unable to present and discuss Liposomal irinotecan at the June meeting. Dr. Reaman briefly reviewed the schedule and the five products that will be presented during the upcoming session:

Day 1: ABT-199 (Venetoclax)  
Day 1: Tazometostat  
Day 1: Atezolizumab

Day 2: Loxo-101

Day 2: Entrectinib

The afternoon of the second day will include a general discussion of the benefits/risk assessment of surgical biopsies of diffuse intrinsic pontine glioma (DIPG) to assess molecular phenotype to select appropriate, molecularly-targeted drugs for treatment.

Dr. Reaman noted that his office has been engaged in discussions with the Center for Devices and Radiologic Health (CDRH) regarding this topic and that several Investigational New Drug (IND) applications in-house are currently evaluating agents in this particular tumor and requirement for biopsies. He noted that Dr. Skip Nelson from the Office of Pediatric Therapeutics will address this issue. Other presentations from CDRH staff are planned: Dr. Mark Kieran will present the neuro-oncology perspective. Two pediatric neurosurgeons, Dr. Nalin Gupta and Dr. Jeffrey Leonard, also are scheduled to present.

Dr. Reaman explained that a 2009 Advisory Committee discussed the issue of biopsies of tumors for biology studies. At that time, there were mixed positions regarding this matter; but current thinking is that the potential for direct clinical benefit related to identifying an appropriate targeted therapy for a particular patient is more obvious.

Dr. Reaman noted that the June 28/29 meeting also will include an open hearing to provide an opportunity for members of the public to offer comments and to allow for subsequent discussion among the committee members.

Finally, he reminded the WG that the ODAC meeting will be Webcast, and that WG members are encouraged to participate remotely, if possible.

### **Follow up Discussion**

Dr. Reaman was asked to clarify the intent of the proposed presentations, given that most of the agents being presented are already in Phase 1 pediatric trials. He reiterated that Written Requests (WRs) are NOT required for pediatric phase 1 trials and that some key goals include:

- Determining direction for post-Phase 1 activities and processes
- Delineating the rationale for issuing a WR from the product sponsors
- Clarifying what those trials should look like, including defining the target population.

Dr. Reaman also reminded the WG that several of these sponsors had been previously invited to present, but they had declined and opted to wait until they had an opportunity to compile more data from adult findings before presenting to the Pediatric Subcommittee of the ODAC. Also, while typically these presentations are made before a Phase 1 study commences, Dr. Reaman noted that there is a benefit to knowing that a Phase 1 study is already underway.

Dr. Smith asked for clarification of the current policy regarding the scope of WRs, in particular, how far these WRs would extend into Phase 2 and Phase 3.

Dr. Reaman noted that the WR is intended to provide as much information as feasible to inform product labeling, and possibly lead to an indication (supplemental application) for that agent in a particular pediatric cancer. The results of Phase 1 studies (if they haven't already been submitted to the Agency) are generally included in the WR. Depending on discussions within the FDA's Office of Hematology and Oncology Products on plans and details related to Phase 2 evaluation or even expanding the Phase 1 study with disease-specific cohorts could be considered as part of the WR. Any consideration for more definitive studies based on the results of dose-finding and activity-estimating studies, as well as descriptions of possible comparators for controlled studies, also could be included in a WR.

Dr. Reaman noted that these WRs are being issued early in the process so that results of Phase 1 and Phase 2 studies can be assessed to determine whether there is merit to continuing a specific study or to provide the sponsor the opportunity to amend or eliminate the requirement. He emphasized that the ultimate goals are to:

1. Get appropriate, relevant products evaluated in pediatric populations
2. Inform labeling for providers on dose and toxicity of relevant products which are being used in children
3. Hopefully approve a product for pediatric indication.

Dr. Smith noted that only a limited number of randomized or controlled trials can be studied in a specific disease. This translates into consequences for agents that aren't going to be studied.

Dr. Reaman pointed out that the WRs are amendable. If the results of Phase 1 indicate that pursuing Phase 2 and Phase 3 are unrealistic or impossible, those factors are certainly taken into consideration. All agents considered for presentation have been recommended as being of interest. A WR will be issued only if an agent is deemed appropriate for further study.

He also pointed out that this legislative initiative is the only relevant program currently available to get studies of cancer drugs and biologic products conducted in pediatric populations.

Dr. Weigel asked for clarification of the status of the agents being presented vis-à-vis pediatric investigational plans (PIPs).

Dr. Reaman noted that presenters will be asked to discuss the status of PIPs to assess the opportunity to make WRs and PIPs parallel and collaborative rather than competing processes. He pointed out that monthly international, regulatory phone calls with the European Medicines Agency (EMA), Health Canada, Japan's Pharmaceuticals and Medical Devices Agency, and Australia's Therapeutic Goods Administration have already been occurring to discuss products that are being evaluated under WRs and PIPs. He noted that the FDA and EMA have been quite successful in suggesting single/complementary studies whenever possible. He also mentioned that they have used data from studies conducted as part of PIPs or part of a WR.

## **Other Products of Interest**

Dr. Reaman asked WG members if there are other high-priority products that they would recommend adding to the agenda of future Pediatric Subcommittee ODAC meetings. Dr. Smith mentioned that a Lilly CHK1 inhibitor Phase 1 study of single-agent activity for adults has just gotten underway, generating some possible interest, but it is still very early in the process. He suggested that the study of CDK 4/6 inhibitor also might show potential for including on the agenda for future discussion by the WG. Dr. Smith also suggested considering the issue of combined myelosuppressive therapy.

Dr. Reaman noted that there has been discussion within the FDA regarding the significant challenge given the large number of these agents. He also pointed out that currently, no WRs have been issued for any of the PD-L1 inhibitors.

The FDA is looking to WG members for their input for how to approach this issue, especially given the low level of neo-antigen expression on pediatric tumors. Dr. Reaman emphasized that input from the WG is particularly important. The Agency does not want to issue a WR for a study that cannot be done, or for a study already underway, or if the mechanism of action is not relevant for pediatric tumors. He also pointed out that these studies will have to include biomarker evaluation. All of these are issues that the WG can help in addressing/resolving.

Dr. Reaman asked if there are other PD-L1s that are further ahead in pediatric development. Dr. Smith noted that he is not aware of any at the present time.

Dr. Reynolds briefly described a just-published report of an incomplete trial of off-patent drugs. Because of some compelling non-clinical data compiled during the course of the initial study, he noted that investigators are interested in completing the study. He inquired if the BPCA could be used to move this study forward. Dr. Reynolds will send Dr. Zajicek further information, and they will discuss this study outside this call.

### **Pediatric Research Equity Act (PREA)**

Dr. Reaman next discussed possible plans to change to the scope of PREA, which mandate pediatric evaluation. To date, no oncology drug has triggered PREA. However, language has been introduced and legislation is being considered by Congress to amend PREA to require evaluation of oncology drugs that are molecularly targeted and that appear to be of relevance for one or more pediatric cancers. He noted that the limited number of patients and limited number of targets identified to date, as well as the multiple drugs that are being developed, present potential consequences. One of which is prioritization of evaluation of products being developed. Dr. Reaman asked the group for their feedback on their willingness to participate as advisors to the FDA in prioritizing products for evaluation due to potential changes to PREA statutory language.

Several WG members voiced their willingness to participate. Dr. Smith agreed that this type of support would make optimum use of the WG. He also requested clarification from the Steering Committee regarding the entire process of involving the WG. He asked that the process become formalized, with members' roles clearly articulated.

While Dr. Reaman noted that he was just gauging WG member interest at this time, he agreed that if the process moves forward, it will definitely warrant a well-defined directive, especially for Committee members who are Government employees. He also reiterated that his office will seek advice from the Office of the Chief Counsel and Office of Regulatory Policy, and will keep WG members apprised regarding the PREA follow up.

### **Closing Comments**

Dr. Reaman ended the discussion by urging WG members to continue to identify and bring forward new products that they feel have merit for following up with the product sponsors for presentation and discussion at future Subcommittee meetings.

### **Next Scheduled Meeting**

The next quarterly Working Group call is scheduled for Tuesday, August 2, 2016 at 11:00 a.m. Eastern Time.