

**Best Pharmaceuticals for Children Act (BPCA)
Pediatric Oncology Core Working Group Conference Call
May 23, 2012
12:00 p.m.–1:00 p.m. ET**

Participants

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Susan M. Blaney, M.D.
Beth Durmowitz, M.D.
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Lia Gore, M.D.
Mark Kieran, M.D., Ph.D.
Lisa Mathis, M.D.
Erica Radden, M.D.
Gregory H. Reaman, M.D.
Patrick Reynolds, M.D., Ph.D.
Victor Santana, M.D.
Amir H. Shahlaee, M.D.
Giselle Sholler, M.D.
Malcolm Smith, M.D., Ph.D.
Perdita Taylor-Zapata, M.D.

Purpose

The purpose of the call was to

- Discuss objectives of the Oncology Drug Advisory Committee's (ODAC's) Pediatric Subcommittee (PSC) meeting planned for November 2012
- Consider Pediatric Oncology Core Working Group recommendations of drugs to be discussed at the PSC meeting
- Discuss a larger meeting likely to be required by reauthorized pediatric legislation addressing current status of Written Request (WR) submissions and consideration of potential pediatric studies in response to Pediatric Research Equity Act (PREA) as well as approaches to facilitate earlier consideration of candidate drug and biologic products for evaluation in children.

Introductions

- Dr. Blaney is at the Texas Children's Cancer Center, Baylor College of Medicine, and is Vice Chair of the Children's Oncology Group (COG) and directs its Phase 1 Consortium.
- Dr. Gore works at the Children's Hospital of Colorado, University of Colorado. She is a member of the Pediatric Oncology Experimental Therapeutics Investigators' Consortium (POETIC).
- Dr. Kieran is affiliated with the Dana-Farber Cancer Institute, Boston Children's Hospital, Harvard Medical School and is the Harvard Principal Investigator for POETIC.

- Dr. Reynolds is Director, School of Medicine Cancer Center, Texas Tech University Health Sciences Center. He is involved with the New Approaches to Neuroblastoma Therapy, the COG, and the Statewide Clinical Trials Network of Texas.
- Dr. Santana is a practicing oncologist at St. Jude Children's Research Hospital.
- Dr. Sholler is affiliated with the Van Andel Research Institute and Helen DeVos Children's Hospital. She is chair of the Neuroblastoma and Medulloblastoma Translational Research Consortium.
- Dr. Adamson is at the Children's Hospital of Philadelphia. He is chair of the COG.
- Dr. Durmowitz is a medical officer with the Pediatric and Maternal Health staff in the Office of New Drugs, Center for Drug Evaluation and Research (CDER), FDA.
- Dr. Radden is a medical officer with the Pediatric and Maternal Health Staff, Office of New Drugs, CDER, FDA.
- Dr. Reaman is Associate Director of the Office of Hematology and Oncology Products (OHOP), FDA.
- Dr. Smith is with the Cancer Therapy Evaluation Program, National Cancer Institute.
- Dr. Mathis is Associate Director, Pediatric and Maternal Health Staff, Office of New Drugs, CDER, FDA.

Objectives of the November PSC Meeting

Dr. Reaman discussed the impact of the BPCA program on the development of new drugs for childhood cancer. The BPCA program has had an impressive impact on pediatric drug development in general. Its history of developing pediatric oncology products is not as impressive. Since the BPCA was enacted 10 years ago, more than 50 WRs have been issued and 15 or 16 agents have been granted pediatric exclusivity. The number of drugs approved for pediatric cancer indications has not been as large as anticipated. Challenges for developing pediatric oncology drugs remain. Dr. Reaman said there need to be changes in the FDA's review of Proposed Pediatric Study Requests (PPSRs) as well as reviews of Investigational New Drug Applications and New Drug Applications (NDAs) of new molecular entities for potential pediatric relevance. Input from experts is needed to help the FDA make determinations as to when inquiries are made about investigation plans for promising pediatric oncology drugs.

In an effort to make the BPCA program work better for children with cancer, the FDA has refocused and changed the objective of the PSC meetings. Previously the subcommittee met annually and focused on broad topic areas. The PSC's new exclusive focus will be on the prioritization of agents for which there is potential interest within the pediatric investigator community to evaluate and consider for submission of WRs. The PSC will now meet twice a year. Scheduling has been a problem because of the number of applications for new molecular entities to ODAC. The PSC's next meeting is scheduled for November 6 or 7.

The PSC is seeking input on the agents that may be of interest for investigation or evaluation in the pediatric population in order to begin submitting WRs to sponsors long before oncology drugs are approved for adult indications. There is flexibility as to when the WRs can be submitted. Dr. Reaman noted that the European Medicines Agency (EMA) requires Pediatric Investigation Plans (PIPs) to be submitted early in the drug development. He said the FDA could

consider development and submission of WRs at the end of phase 2 meetings rather than waiting until NDAs are submitted or approved.

Recommendations of Drugs to Be Discussed at the November PSC Meeting

During its April 9 meeting, the working group discussed a number of agents, including a new IGF receptor antibody. Other agents of potential interest that were discussed were the hedgehog inhibitors, Vismodegib and LDE225, and Pazaponib. The PSC would like input on agents of interest to investigators in order to plan the agenda for the November meeting. A notice will be posted in the *Federal Register*, which will allow sponsors to submit their candidate agents for discussion. The OHOP has discussed Aflibercept, Sorafenib, and some of the new MEK and C-met inhibitors.

Dr. Reaman noted that OHOP meets regularly with the EMA's oncology committee and knows the pediatric oncology agents that have gone through the PIP process and the proposals that have been approved, as well as those that have been deferred. Most of the agents are for adult indications. The FDA and the EMA are working to coordinate activities so that studies are not duplicated and to recommend consideration of international studies to sponsors when appropriate.

Dr. Reaman explained that the WR process can originate from companies that are submitting PPSRs. WRs can also originate from the FDA. In some cases, companies are waiting until a product has been studied by others before submitting the PPSR. The FDA is working to have WRs submitted earlier in the process. The timing of the WR depends on the agent and its potential pediatric indication. Companies are not required to submit a pediatric plan in response to a WR. Those that are interested in pediatric products will ask for a WR by submitting a PPSR. Drug exclusivity is the incentive for the companies to conduct pediatric studies. The FDA would like to be the driving force for WRs, instead of the companies. Dr. Blaney noted that the EMA's PIP process has become the driving force for clinical trials of pediatric oncology drugs. Dr. Reaman stated that this could easily be addressed by earlier consideration of WRs for specific products since many of the EMAs PIPS are deferred and/or waived and the Agency's timeline is far more flexible than the rigid EMA process.

Dr. Mathis explained that the FDA cannot require pediatric studies of oncology products under PREA because PREA studies have to be indication specific. However, there is a provision in PREA that can force a company to conduct a pediatric study if it turns down a WR issued under BPCA. The FDA has not attempted to do this, and its ability to force such studies is unknown. Dr. Mathis said that the earlier WRs can be issued in the drug development process, the quicker the FDA will be able to align its activities with the EMA. Issuing WRs earlier will also help identify earlier those companies that are not willing to conduct pediatric studies.

In response to questions from Dr. Smith, Dr. Reaman said WRs apply to both oncologic drugs and biologic agents. Requirements for clinical development plans in the WR are flexible and variable. In general, two studies are required. Historically, for oncology products, phase 2 studies have been required, with a sponsor commitment that if a drug demonstrates activity, further

development would continue with definitive randomized studies, if necessary. Dr. Reaman explained that the requirements for oncology drugs WRs are less stringent as those for other clinical areas given the small patient numbers, the life threatening nature of the clinical indication, and the diversity of cancer diagnoses in childhood. The FDA requires that studies of pediatric oncology drugs provide information on pharmacokinetics and toxicity; data on the recommended phase 2 dose, the optimum biologic dose, or planned therapeutic dose; and plans for formulation. The FDA is currently revising the guidance for pediatric oncology drug studies.

Dr. Mathis said the list of drugs for which WRs have been issued is on the FDA Web site. The WRs do not become public until the studies have been submitted and reviewed. Once the WRs have been reviewed, they are posted on the Web site. Information about PIPs accepted for pediatric oncology drugs is publicly available on the EMA Web site. Information is also publicly available for PIPs that are denied or withdrawn.

Dr. Adamson proposed that the working group review the WR and PIP lists, develop a list of pediatric oncology agents of interest, and discuss them during the next conference call. The working group could also list indications and tumors of interest. Dr. Reaman said that investigators can work with drug sponsors to amend WRs, if necessary. PIPs can also be amended.

In conclusion, Dr. Reaman noted the following pediatric oncology agents of interest: C-met inhibitor, MEK inhibitor, ombrabulin, LDE 225, hedgehog inhibitor, TH3, Regorafenib, Sorafenib, Aflibercept, and radio-labeled MIBG. These agents can be put on the agenda for the November PSC meeting.

Action Items:

- Dr. Mathis will send lists existing WRs and PIPs for pediatric oncology drugs to the working group.
- The working group will review the WR and PIP lists and develop a list of pediatric oncology agents of interest.