

**Best Pharmaceuticals for Children Act (BPCA)
Pediatric Oncology Core Working Group Conference Call
October 12, 2012
2:30 p.m.–3:15 p.m. ET**

Participants

Peter C. Adamson, M.D.
Maryam Fouladi, M.D., M.Sc.
Lia Gore, M.D.
Mark Kieran, M.D., Ph.D.
Kate Matthay, M.D.
Erica Radden, M.D.
Gregory H. Reaman, M.D.
Patrick Reynolds, M.D., Ph.D.
Nita Seibel, M.D.
Amir H. Shahlaee, M.D.
Malcolm Smith, M.D., Ph.D.
Perdita Taylor-Zapata, M.D.
Anne Zajicek, M.D., Pharm.D.

Purpose

The purpose of this call was to introduce working group members and discuss the following:

- Agents to be discussed at the December 4 Pediatric Subcommittee meeting, agents under consideration for Written Requests (WRs), and other agents
- The composition of the working group and charge to members
- Recommendations for Special Government Employees (SGEs) and members of the Pediatric Subcommittee of the U.S. Food and Drug Administration (FDA) Oncologic Drugs Advisory Committee (ODAC).

Introduction of Members

Dr. Reaman explained that the working group has been expanded to include some individuals from the pediatric and maternal health staff in the FDA Office of New Drugs who are liaisons and have the expertise to implement provisions of pediatric legislation—the BPCA and the Pediatric Research Equity Act. He and the other members introduced themselves:

- Dr. Reaman is Associate Director of the Office of Hematology and Oncology Products at the FDA and is responsible for coordination and oversight of the Pediatric Subcommittee of ODAC.
- Dr. Adamson is from Children’s Hospital of Philadelphia and is chair of the Children’s Oncology Group (COG).
- Dr. Fouladi is with Cincinnati Children’s Hospital and chairs the Pediatric Brain Tumor Consortium.

- Dr. Kieran is director of neuro-oncology at Dana Farber Cancer Institute and Boston Children’s Hospital.
- Dr. Gore is with Children’s Hospital Colorado and is part of the Pediatric Oncology Experimental Therapeutics Investigators’ Consortium.
- Dr. Radden is one of the representatives from the pediatric/maternal health staff at the FDA.
- Dr. Reynolds directs the Cancer Center at Texas Tech University Health Sciences Center and serves on an advisory committee for the Cancer Prevention and Research Institute of Texas.
- Dr. Shahlaee is one of the medical officers at the FDA and is a member of the sarcoma/melanoma team.
- Dr. Seibel is with the Clinical Investigations Branch of the Clinical Trials and Translational Research Advisory Committee, National Cancer Institute.
- Dr. Taylor-Zapata is a medical officer for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and coordinates the National Institutes of Health (NIH) part of the BPCA prioritization process.
- Dr. Smith is with the NCI’s Cancer Therapy Evaluation Program and is program director for COG, the Phase 1 Consortium, and the Pediatric Brain Tumor Consortium.

Composition of Working Group and Charge to Members

Dr. Reaman said the FDA is trying to utilize the infrastructure that has been afforded to the agency and the NIH through the NICHD for implementation of the BPCA and to use the infrastructure that was developed primarily for review of off-patent drugs for which submission of WRs might be appropriate for evaluation of agents for children with cancer. To accelerate and facilitate pediatric drug investigation, the strategy is to not wait until drugs are off patent or even approved for adult cancer indications without thinking about pediatric investigation. The FDA Safety and Innovation Act passed several months ago now stipulates there be early discussion of pediatric evaluation plans and that they occur at the end of phase 2 meetings when industry sponsors meet with the agency to discuss their applications. This working group was created to inform members about agents the FDA is aware of due to applications that have come in—generally not for pediatric applications but for agents that may have some applicability to pediatric cancer—and to then seek working group members’ advice and recommendations for drugs that could be considered for pediatric evaluation that can be discussed at the Pediatric Subcommittee of ODAC meetings with sponsors.

Dr. Reaman said the WR process has not been as transparent as it could be; much of the specific information in WRs is confidential. Unfortunately, the FDA’s public Web site has only information related to those sponsors that have accepted WRs and in cases where study reports have been accepted and approved and where exclusivity has been granted. However, studies are in progress for a large number of agents, and there are plans for the FDA Web site to become more transparent about which companies have been issued WRs for which agents and provide information about those studies. The next Pediatric Subcommittee meeting is scheduled for December 4, which unfortunately is the same day and time as the BPCA annual meeting.

Dr. Reaman shared information about four drugs that will be discussed at the December Pediatric Subcommittee meeting:

- Volasertib—a polo-like kinase inhibitor being developed for acute myelogenous leukemia (AML); there is a new drug application (NDA) for AML in adults.
- Blinatumomab.
- Trametinib—a MEK inhibitor being developed for V600 E mutated melanoma both as a single agent and in combination with a BRAF inhibitor. The sponsor is interested in studying the drug in children with melanoma, and the FDA is trying to determine whether there is interest in evaluating it in other pediatric cancers where MEK may be a significant target to consider.
- TH-302—an alkylating agent whose activity is significantly enhanced in hypoxic situations. There has been some interesting and significant activity in a variety of tumors. An NDA exists for use in adults, and the drug might be worth exploring for pediatrics.

During the December 4 meeting, there will be a brief presentation by industry sponsors, followed by clarifying questions and discussion about whether the investigator community is interested in studying these agents and what potential study designs might look like.

Also on this meeting agenda are the following agents currently under consideration for WRs:

- Denosumab, for which a WR is being developed with a phase 2 study for giant cell tumor of bone in adults and skeletally mature adolescents; a second study is being developed for osteosarcoma for older adolescents who are not necessarily skeletally mature but who meet significant bone age requirements appropriate for males and females, with an expectation that if the drug is shown effective in phase 2 study, a definitive study would be developed in the front-line adjuvant metastatic setting.
- Pazoponib, a VEGF inhibitor, is being developed for adults with soft tissue sarcomas, and there is consideration for extending study of the drug to the pediatric age group, again because of activity seen in sarcomas.

Dr. Matthay said there are some preclinical data from Toronto with pazoponib for neuroblastoma and that the drug may be active in other solid tumors. Dr. Smith said there was limited testing, and the focus was on sarcomas. He believes the data were published but he will have to check and make sure. Dr. Reaman said that may be information worth bringing to light at the time of the ODAC meeting if there is interest from COG or elsewhere in expanding to a broader based phase 2 study. It was noted that there may be a neuroblastoma cohort in the phase 2 studies run by the COG. Dr. Matthay said a study was published about oral topotecan in mouse models.

Dr. Reaman discussed two other agents with a limited degree of potential. First, ponatinib is a multi-tyrosine kinase inhibitor (TKI) that is being developed in refractory imatinib/dasatinib/nilotinib resistant chronic myelogenous leukemia (CML). It appears to inhibit EGF receptor, as well as VEGF, and seems to have a more toxic profile than related drugs. He mentioned this drug so the working group members could think about it and perhaps provide some feedback. Dr. Gore said there is an active pediatric investigational plan for ponatinib that was approved by the European Medicines Agency (EMA) in June 2012; the sponsor has outlined a series of pediatric trials to look at the drug in pediatrics. She discussed toxicity with regard to pancreatitis. Most patients experiencing toxicity in studies were enrolled at a single institution. When that one institution was eliminated, the drug was better tolerated than imatinib and

desatinib. Dr. Reaman noted that hypertension is associated with this agent, as well as thrombotic complications and myocardial infarctions. There is a lot of concern about the toxicity profile. The FDA was aware of pancreatitis, and these other toxicities have emerged more recently. He asked Dr. Gore whether the studies were looking in CML or other pediatric tumors, given the broad scope of activity. Dr. Gore said the pediatric investigation protocol that was approved was for two pediatric studies: first was a classic all-comers study for solid tumors, with the opportunity to enroll leukemia patients if available, and second was a Ph+ disease study specifically for CML in a Ph+ acute lymphoblastic leukemia (ALL) cohort.

Dr. Reaman next discussed omacetaxine mepesuccinate (also known as HHT), which was studied in the COG Phase 1 Consortium perhaps 20 years ago. There was not much interest in this drug because not a lot of activity was demonstrated; nevertheless, it is being proposed for potential approval for second- or third-line CML in adults who are resistant to at least two of the three approved TKIs. Dr. Reaman asked that the working group members please pass along any interest in this drug.

Dr. Reaman mentioned one other WR that is in development for LDE225, an inhibitor of the hedgehog pathway in medulloblastoma. He then opened the discussion to other agents members are aware of or might be interested in that could be put on the agenda for the next pediatric ODAC meeting in mid-spring 2013.

- Dr. Kieran said in addition to LDE225, two other drugs were recently approved to go ahead with pediatric phase 1 studies: the PI3 kinase inhibitor BKM120 from Novartis and dabrafenib, a GSK BRAF inhibitor, which is about to start phase 1 next month.
- Dr. Fouladi said there is an Eli Lilly sonic hedgehog inhibitor that is just about to go into phase 1. She will look up the number.
- Dr. Seibel said one to consider is the Biomar PARP inhibitor (BMN-673); the company is planning to do a phase 1 study in pediatrics with it.
- Dr. Kieran mentioned cabazitaxel, a taxane. It is just starting phase 1 for solid tumors and brain tumors.
- Dr. Gore said that Cell Therapeutics has a cardiac-sparing anthracycline called Pixantrone that is coming forward as well.
- Dr. Kieran mentioned a drug called Xercept that just completed phase 1 testing for radiation-induced edema in the brain tumor setting. This agent is from Celtic Pharma, which plans to go to phase 2.

Composition of Oncology Working Group

Dr. Reaman brought up the question of whether the composition of the group is broad enough or too broad. Several FDA staff have been included to keep as many people as possible in the loop, but he wanted to have enough involvement from the investigator community. There was a suggestion about having a lay advocate, as there is on the Pediatric Subcommittee of ODAC. Dr. Reaman asked for input from the group about that suggestion and whether other people should be considered for addition to the group.

Dr. Zajicek said it would be nice to have a lay advocate on the working group. Dr. Reaman said they would move forward and see about adding an advocate. An advocate who is already an SGE is required to agree to follow the confidentiality agreement.

Recommendations for SGEs and Members of Pediatric Subcommittee of ODAC

Dr. Reaman discussed getting recommendations for SGEs for members of the Pediatric Subcommittee of ODAC. The current ODAC has a number of fixed members, but there are several hundred SGEs who are medical oncologists, radiation oncologists, and other specialists, and about 15 pediatric oncologists are on the list. Some have special expertise that would be helpful to the subcommittee. Dr. Reaman asked the working group members to think about whether they might be interested in being considered for the subcommittee or whether they can recommend other people who might be interested. The vetting process is more onerous than many processes that deal with conflict of interest; there are detailed queries about relationships with industry, especially pharmaceutical sponsors. It would be helpful to have a broader pool of qualified individuals to serve on the subcommittee.

Dr. Reaman agreed to share the current list of SGEs with the group. He will send the list to Brandy Weathersby of Circle Solutions, Inc., who will send it out to the group members. Ms. Weathersby will also collect suggestions from the working group members for potential SGEs.

Dr. Reaman encouraged group members to let him know about drugs for which they are interested in submitting a WR.

Action Items:

- Dr. Reaman will forward the current list of SGEs who serve on the Pediatric Subcommittee of ODAC to Ms. Weathersby to send to the group members.