

**Best Pharmaceuticals for Children Act (BPCA)
Pediatric Oncology Core Working Group Conference Call
January 22, 2013
11:00 a.m.–12:00 p.m. ET**

Participants

Peter C. Adamson, M.D.
Martha Donoghue, M.D.
Lia Gore, M.D.
Lori Gorski
Erica Radden, M.D.
Gregory H. Reaman, M.D.
Patrick Reynolds, M.D., Ph.D.
Amir H. Shahlaee, M.D.
Giselle Sholler, M.D.
Malcolm Smith, M.D., Ph.D.
Perdita Taylor-Zapata, M.D.
Anne Zajicek, M.D., Pharm.D.

Purpose

The purpose of the call was to update the group on the December meeting of the U.S. Food and Drug Administration (FDA) Oncologic Drugs Advisory Committee (ODAC) Pediatric Subcommittee.

Discussion

Dr. Reaman said that the ODAC Pediatric Subcommittee primarily discussed four agents.

Volasertib. This agent, a polo-like kinase 1 inhibitor, is being developed in adults for the treatment of acute myelogenous leukemia (AML) in patients who are not candidates for intensive induction therapy. Given its mechanism of action—interfering with mitosis—a broader area of development would have been anticipated. This agent is being evaluated for other tumors, such as pancreatic and other gastrointestinal cancers. However, because of the agent’s activity in AML, the company is interested in this indication in adults.

Used in combination with low-dose cytarabine (ara-C), the major toxicity of volasertib is myelosuppression. The subcommittee agreed that there was significant evidence of activity; with combination therapy, remission occurred in more than 30 percent of patients. The subcommittee recommended that any early-phase, dose finding study be conducted in a broader population, not just in children with relapsed/refractory AML. Should preclinical studies support investigation of volasertib outside AML, further studies may be needed.

The European Medicines Agency (EMA) is also entertaining a Pediatric Investigation Plan (PIP) on the use of volasertib combined with intensive reinduction therapy. The EMA and the FDA are providing bilateral commentary to the sponsor. A concern is that intensive combination therapy may be difficult to pursue because volasertib is myelosuppressive. The subcommittee did not feel that low-dose ara-C would be the regimen of choice except for relapse patients following transplant. There is no other population of children with AML who are not candidates for intensive therapy. The plan includes phase 1 studies of volasertib in refractory solid tumors and leukemias and phase 2 studies of the agent in combination with intensive therapy for relapsed AML.

Blinatumomab. This agent, now developed by Amgen, is being developed for the treatment of acute lymphocytic leukemia (ALL). The antibody is a bidirectional T-cell engager (BiTE) that is anti-CD3 and anti-CD19 for B cell lymphoid leukemia.

There is significant experience with blinatumomab in adults, primarily in non-Hodgkin lymphoma and recently in ALL. A number of studies are ongoing in adults with ALL who are minimal residual disease-positive at the end of induction. There is a phase 1 study, with plans to extend the study in the pediatric population. The FDA seeks input as to whether or not a Written Request (WR) should be considered, given the ongoing early-phase pediatric investigation. There is interest in looking at this agent in a relapsed/refractory pediatric population and in high-risk populations not yet defined.

Dr. Reaman asked whether there was interest in developing a WR for blinatumomab. Dr. Gore asked about Amgen's intentions, based on the ODAC meeting. Dr. Reaman said that the ODAC is interested in evaluating the agent more extensively than the current Children's Oncology Group (COG) study. Dr. Gore asked whether the new relapse study was discussed. Dr. Smith said that a randomized study in the first relapse population was discussed and favorably considered. Amgen gave no formal feedback at the meeting. The COG early concept will help define Amgen's intentions.

Dr. Reaman said the FDA would like to facilitate the process and harmonize plans for this agent with EU efforts. There may be an opportunity to accelerate the process and interest Amgen with the prospect of exclusivity. If there is a way the FDA can help, the FDA should know sooner rather than later. Dr. Gore said that more information would be available after the data monitoring committee meeting and cohort review at the end of February. Dr. Reaman said that the COG plans could be incorporated into the studies requested in the WR.

Trametinib. This MEK inhibitor is being developed in combination with the BRAF inhibitor for melanoma, dabrafenib. The subcommittee was interested in this agent, given the mitogen-activated protein (MAP) kinase pathway involvement in a number of pediatric tumors. The subcommittee discussed the sponsor's early pediatric development plan, which evaluated a broad spectrum of tumors. There was no prospective assessment of MAP-kinase pathway activation for tumor selection; the assessment would be done after phase 1 and 2 studies despite the readily available pathological materials.

The subcommittee discussed focusing on tumors that are associated with NF-1. Concern was raised about an active investigation of another MEK inhibitor in plexiform neurofibromas and other NF-1-related tumors. The patient population may not be able to support investigations of multiple agents.

The subcommittee discussed the use of trametinib as a single agent in melanoma, where there is significantly more activity when combined with dabrafenib. The subcommittee supported investigating a combined approach in a pediatric population yet to be defined. There were concerns about the sponsor's plan to evaluate trametinib in adolescents with unresectable melanoma by extrapolation. It is not clear that incidence of BRAF V600E mutations or the biology of BRAF-mutated melanoma is the same in adolescents and adults. The subcommittee recommended that trametinib should be studied, not extrapolated, in the adolescent population to evaluate efficacy. The subcommittee preferred evaluation of the combined agents over evaluation of trametinib alone.

TH-302. This agent, which is bromated isophosphoramidate, is activated in the setting of hypoxia. TH-302 is being developed in adults with soft tissue sarcomas of various histologies. It has a relatively favorable toxicity profile, other than myelosuppression. There were concerns about developing this agent in relapsed/refractory sarcomas in pediatrics. One concern is adding TH-302 to other myelosuppressive agents. Another concern was the plan to combine TH-302 with anthracycline in adults since most pediatric patients with sarcoma have had anthracycline as part of front-line therapy, so this combination may not be appropriate to pursue in pediatrics.

There was some confusion as to how similar TH-302 is to ifosfamide. The subcommittee agreed that TH-302 should not be viewed as a less toxic replacement for ifosfamide, given the agent's unique mechanism of activation. However, TH-302 could be explored as treatment for a number of tumors, including sarcomas of soft tissue and bone, neuroblastoma, and brain tumors, although only about 2 percent of this agent crosses the blood-brain barrier. The subcommittee also discussed whether TH-302 could be developed in the adjuvant setting. This issue is being explored in adults. In micrometastatic lesions there is a significant degree of hypoxia, and the sponsor feels that the agent would be active in that setting. Combination studies with inhibitors of angiogenesis should be considered.

Dr. Reaman asked about evaluation of TH-302 in the Pediatric Preclinical Testing Program (PPTP). Dr. Smith said that the PPTP discussed the agent with the company, but studies have not been conducted yet. The agent appears to be truly hypoxia activated and has a different toxicity pattern than other alkylating agents, particularly with skin toxicities. The challenge is determining where hypoxia is the rate-limiting step in pediatric cancers.

Dr. Reaman said there were no immediate plans for TH-302, which is owned by a small company. The company is developing the agent in the European Union as well and would like to have a unified approach to a pediatric development plan.

Other Agents. Dr. Reaman discussed other agents for which the FDA is working on WRs. He asked about denosumab. Dr. Donoghue said that the FDA issued a WR to Amgen in late

November or early December, primarily for investigation of the agent in two pediatric/young adult diseases. The first is giant-cell tumor of the bone, where resection is not possible or would have high morbidity or mortality. The second disease is osteosarcoma. The WR included a single-arm study to assess activity and safety of denosumab as part of monotherapy in patients with recurrent osteosarcoma. The WR also included conduct of a randomized study of denosumab as part of combination therapy in osteosarcoma, depending on the results of the first study. Amgen accepted the terms of the WR.

Dr. Reaman said that a WR is in development for LDE225, a smoothed inhibitor of the sonic hedgehog pathway in medulloblastoma.

A proposed pediatric study request (PPSR) has been sent to the sponsor for ponatinib, a multi-targeted tyrosine kinase inhibitor (TKI) with major activity in the mutated BCR-ABL kinase. The FDA did not feel the PPSR was adequate, but there might be interest given that the agent is highly active, particularly in chronic myelogenous leukemia (CML) that develops resistance to other BCR-ABL inhibitors. Dr. Reaman asked whether there was interest in developing ponatinib for treatment of other pediatric tumors because it inhibits c-KIT as well as platelet-derived growth factor receptor and vascular endothelial growth factor. The FDA would be interested in feedback from the group.

Dr. Gore said that a PIP agreed to two studies of ponatinib: a phase 1 study of solid tumors and leukemia and a phase 2 study of Philadelphia (Ph)-positive disease. She thought that the phase 1 study would be company-sponsored and conducted in the United States and Canada. The phase 2 study would be international, primarily in Europe and North America. Dr. Gore said she thought the pediatric protocol had been drafted and would be circulated for comments, with the phase 1 study opening late in the second quarter or early in the third quarter of 2013. The phase 2 study would be in recurrent or refractory disease and have two cohorts—one CML and one Ph-positive ALL. Patients with resistant or intolerant disease will be accepted.

Advisors for the ODAC Pediatric Subcommittee. Dr. Reaman asked the group to recommend advisors for the Pediatric Subcommittee. Brandy Weathersby of Circle Solutions, Inc., distributed the current list of advisors before the call. Many advisors are inactive because they are often unavailable or cannot participate due to seniority and involvement with pharmaceutical sponsors. This group could recommend advisors who have a significant role in COG or one of the other research networks but who are not committee chairs and do not have in-depth involvement with pharmaceutical sponsors. Participants should e-mail their recommendations to Ms. Weathersby.

Agents for Future Consideration. Dr. Reaman asked the group to recommend additional agents that the FDA should consider for pediatric development or discuss at future ODAC meetings.

Model PIPs. Dr. Gore asked about the EU effort to develop model PIPs for disease groups. Dr. Reaman said that he discussed the disease-oriented PIPs with Dr. Ralf Herold, who shared some of the templates. The FDA is interested in developing similar models in the United States, and

harmonization should not be limited to the regulatory agencies but should involve the investigator and stakeholder communities.

Dr. Gore noted that some sponsors are developing pediatric studies without input from pediatric experts, and the studies do not serve the drug, patients, or disease. Pediatric experts should be involved early in the process. There is a backlog of studies that will not be completed because they are not attractive to the pediatric oncologists who put patients in studies.

Dr. Reaman said that disease-specific templates would need some flexibility. He agreed that some sponsors are developing PPSRs with limited input from pediatric experts and without assessing the feasibility of the study design or enrollment. Requirements and plans should be harmonized with the EMA.

Dr. Smith asked how disease-specific PIPs could address phase 3 studies that may not begin for several years. Dr. Gore said that she attended one meeting on the PIP for ALL. The meetings are different for different disease groups. At the ALL meeting, there was a comprehensive plan, but the specifics of the phase 3 studies were not discussed in detail. Some agents that would fall into that model PIP would be small molecule inhibitors or multi-TKIs, and some of them are more classic cytotoxics. The endpoints for each of those studies might look very different. The meeting she attended did not discuss that level of detail. The endpoints may need to be rather fluid, based on a number of factors that cannot be predicted when the PIP is put in place.

Before the committee convened to develop the PIP, the EMA had called for a randomized study of 600 patients with Ph-positive ALL. The committee noted that such a study would require 25 years to recruit patients. It is important for the EMA to have reasonable expectations for the patient populations. One goal of the model PIP meetings is to incorporate epidemiology and biology to ensure that entry criteria reflect patient populations.

Dr. Reaman said that Dr. Smith raised a good point. There are opportunities to get tripped up by the templates because the PIP process is different than the process in the United States. There are different timelines for amending PIPs. It is difficult to describe in detail studies that will not begin enrollment for 5 or 6 years, given how rapidly the environment changes, competing agents are developed, and the biology advances. In WRs, there are very stringent criteria for phase 2 studies, but less detail is required for phase 3 studies because changes may be needed.

Action Items:

- Participants should e-mail their recommendations for advisors to the ODAC Pediatric Subcommittee to Ms. Weathersby.