

**Best Pharmaceuticals for Children Act (BPCA)
Pediatric Oncology Core Working Group Conference Call
March 18, 2013
4:00 p.m.–4:45 p.m. ET**

Participants

Susan Blaney, M.D.
Martha Donoghue, M.D.
Lia Gore, M.D.
Mark Kieran, M.D., Ph.D.
Kate Matthay, M.D.
Gregory H. Reaman, M.D.
Patrick Reynolds, M.D., Ph.D.
Nita Seibel, M.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 this call was to discuss the following:

- Next planned Pediatric Subcommittee meeting: November 5–6, 2013
- Potential topics for discussion at the Pediatric Subcommittee meeting:
 - LEE011 (Novartis)
 - Anti-PD-1 or anti-PD-L1 antibodies; status of PD-L1 expression by pediatric tumors
 - Ipilimumab
- Update on the Pediatric Advisory Committee (PAC) meeting: March 14, 2013
- Proposal for Pediatric Studies Request (PPSR)/Written Request (WR) update: ipilimumab, denosumab, and LDE 225.

Next Planned Pediatric Subcommittee Meeting

Dr. Reaman explained that the Pediatric Subcommittee will not meet before November 5–6, 2013, due to conflict with the FDA Oncologic Drugs Advisory Committee (ODAC) scheduling commitments, which are further complicated by budgetary issues.

Topics for the Pediatric Subcommittee Meeting

The Subcommittee agreed that there were not many new agents of potential interest to discuss. The following agents have been proposed.

LEE011. Novartis has requested a discussion of LEE011—a CDK-4 and CDK-6 inhibitor. Based on preclinical studies, Novartis is considering development of LEE011 for a pediatric-specific indication, even before targeting an adult malignancy indication. Discussion of LEE011 has tentatively been added to the November meeting agenda. The potential pediatric indications for the agent are atypical teratoid rhabdoid tumor and neuroblastoma. The phase 1 trial has been submitted to institutional review boards at multiple institutions.

Anti-PD-1 or Anti-PD-L1 Antibodies; Status of PD-L1 Expression by Pediatric Tumors.

These agents are of interest because of their mechanism of action, potential applicability to pediatric cancers, and paucity of published data on the expression of PD-L1 or CD-274 by pediatric tumors other than some Hodgkin disease and non-Hodgkin lymphomas. Dr. Smith proposed that there should be some discussion on whether there are tissue microarrays available for screening of PD-L1 expression. Dr. Reaman asked whether such studies could be conducted before the November meeting. Dr. Smith replied that discussion with relevant Children's Oncology Group (COG) disease committees regarding tissue array screening would be sufficient. Information from various investigators on PD-L1 expression in a set of childhood cancers would be valuable for discussion at the meeting. Dr. Blaney agreed to contact relevant COG disease committee chairs regarding their interest in tissue microarray screening for PD-L1 expression by potentially relevant pediatric tumors. If there is significant expression and potential target tumors can be identified, the Subcommittee will consider inviting appropriate sponsors.

Ipilimumab. This agent is another possible topic for discussion not just for pediatric/adolescent melanoma indication but also, given its mechanism of action, for other pediatric tumors where immune effects might be targeted therapeutically. The agent's sponsor has expressed some interest in development for pediatric melanoma. The agent may have a broader applicability. Ipilimumab demonstrated significant toxicity in the phase 1 trial, particularly in older patients. The toxicity was age related. The dose used in children was higher than the dose used in adults. The phase 1 dose has been proposed as the recommended phase 2 dose. The agent is currently being evaluated for melanoma. Dr. Reaman asked whether there is any rationale to explore ipilimumab for its potential utility in diseases other than melanoma (for example, neuroblastoma). Dr. Sholler noted that Dr. Melinda Merchant at the National Cancer Institute (NCI), who has treated a few patients with neuroblastoma, may be able to provide input on the use of ipilimumab. Dr. Gore said there is an active phase 2 international trial, which has been slow to accrue patients. Dr. Matthay said she is not aware of any interest in evaluating ipilimumab for neuroblastoma.

Update on the PAC Meeting: March 14, 2013

Dr. Reaman provided an update on this meeting. Drugs that have been granted exclusivity are required to be presented for safety reviews. Pemetrexed (Alimta) was presented. The pediatric use of this agent has been minimal. Outside of the clinical trials that were part of the WR, only one international patient with a mesothelioma has been reported. No unusual/ unexpected toxicity was reported. This agent will be subjected to attenuated review. It will probably not have to be presented annually.

PPSR/WR Update: Ipilimumab, Denosumab, and LDE 225

PPSRs have been submitted for ipilimumab, denosumab, LDE 225, trametinib, and dabrafenib, and WRs are being considered or in process.

The U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have held bilateral discussions of erubulin. The sponsor of TH-302 has expressed interest in a bilateral FDA/EMA review of this agent. The potential role of TH-302 in pediatric cancer has not yet been determined. The FDA recommended that instead of a bilateral review, the agent be discussed in bilateral commentary to provide input as the sponsor works with investigators to develop a pediatric development plan. Dr. Blaney asked for clarification on the bilateral review process, specifically whether WRs have been developed for other agents. Dr. Reaman explained that the FDA and EMA timelines are not synchronized. Sometimes the FDA timeline can be arranged to accommodate the EMA timing constraints for making decisions about pediatric investigation plans (PIPs). The FDA has been flexible in working with the EMA. Because of the limited number of patients and the limited number of trials that can be conducted, the FDA and the EMA do not want competing drug development studies. The FDA and the EMA want to be synchronized, to the extent possible, with their review and decisions related to sponsor study plans.

Dr. Reaman explained that previously exclusivity could be granted based on phase 1 or phase 2 study results without a requirement of commitment to conduct phase 3 studies. The requirements are now changing. WRs are flexible about requirements for phase 3 study plans. Dr. Reaman said that some earlier WRs have used results from previously completed studies. If there is interest, a WR can be issued during or after phase 1 or phase 2 studies in adults. Although there is no requirement that a WR be issued in the early stages of drug development, there is flexibility in how and when WRs can be developed and issued. For example, randomized phase 3 registration trials can begin before or after the WRs have been issued. Pediatric exclusivity is granted only if a WR is issued and the requirements stated in the WR are fulfilled upon review by the Exclusivity Board. Trials can begin or be completed without a WR.

Although most WRs have originated from PPSRs from sponsors, the FDA can also develop and issue WRs if there is interest or a scientific rationale for doing so. Study concepts or letters of intent from the investigator community could constitute a PPSR submitted to the FDA, and a WR could be developed. Dr. Donoghue commented that a WR can be issued by the FDA if an investigator is interested in studying a particular drug, even without a PPSR. Details on the patient population and study design would help the FDA in developing the WR.

Dr. Reaman asked whether initiating the WR consideration and development by the FDA would be feasible, from a Cancer Therapy Evaluation Program perspective, as concepts and protocols for new agents are reviewed and approved by the Steering Committees. Dr. Smith explained that phase 2 or phase 3 studies submitted for concept review could trigger the process. Dr. Reaman replied to a question that if there is sufficient investigator interest but delay by sponsors—and there has been discussion among investigators, the NCI, and sponsors—a WR could be developed without a definitive phase 3 study design and EMA approval of PIPs. The FDA can

stipulate the timeframe in the WR. There is a template for the WR, which can be made available to the working group. The FDA is working to revise the WR template and finalize the process for evaluating PPSRs. Dr. Reaman noted that preclinical data or a scientific rationale are generally needed for PPSRs; adult study data are generally not required. This PPSR mechanism is not being extensively used for nononcologic diseases. Sponsors may not be using the PPSR mechanism if they are unaware of investigator community interest or potential pediatric indications.

Action Items:

- Dr. Blaney will contact relevant COG disease committee chairs regarding their interest in tissue microarray screening for PD-L1 expression.
- Working group members should send to Dr. Reaman suggestions for additional agents that can be discussed at the Pediatric Subcommittee meeting.