Best Pharmaceuticals for Children Act (BPCA)
Pediatric Oncology Working Group Conference Call
April 8, 2015
4:00 p.m.–5:00 p.m. ET

Participants

Peter Adamson, M.D.
Amy Barone, M.D.
Gilbert Burckart, Pharm.D.
Martha Donoghue, M.D.
Lori Ehrlich, M.D.
Lia Gore, M.D.
Richard Gorlick, M.D.
Douglas Hawkins, M.D.
Rita Humeniuk, Ph.D.
Mark Kieran, M.D., Ph.D.
Leigh Marcus, M.D.
Kathleen Neville, M.D., M.S.
Julie Park, M.D.
Gregory H. Reaman, M.D.
C. Patrick Reynolds, M.D., Ph.D.
Nita Seibel, M.D.
Malcolm Smith, M.D., Ph.D.
Donna Snyder, M.D.
Perdita Taylor-Zapata, M.D.
Brenda Weigel, M.D., M.Sc.
Erica Wynn, M.D.

Purpose

The purpose of this call was to discuss the following items:

- Products of possible interest for discussion/presentation at the upcoming Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (ODAC) meeting
- Additional suggestions from Working Group members
- Off-patent products requiring improved labeling
- Other business

Opening Remarks

Dr. Reaman opened the call by welcoming several new members of the Working Group. He explained that these new participants (Drs. Julie Park, Kathleen Neville, Richard Gorlick, and Douglas Hawkins) would provide disease-specific, as well as general, expertise to help inform Working Group discussions. Dr. Reaman also introduced several new U.S. Food and Drug Administration (FDA) pediatric oncologist medical officers (Drs. Amy Barone and Lori Ehrlich,

as well as Drs. Leigh Marcus and Denise Casey), and pediatric pharmacologists from the FDA Office of Pharmacology and Office of Translational Sciences (Drs. Gilbert Burckart and Rita Humeniuk).

Pediatric Subcommittee of the ODAC Meeting: Products for Discussion

Dr. Reaman reiterated that the purpose of these calls is to provide an opportunity for the Working Group to discuss new and emerging pharmaceutical and biologic products that individual members might recommend for further discussion and that could be of particular interest for the pediatric oncology investigator community. Based on these discussions, FDA could then invite sponsors to come and present at the next Pediatric Subcommittee of the ODAC meeting in consideration of issuing a Written Request for any of these products.

Dr. Reaman stated that some of these products are further along in their development, while others are in much earlier stages of development. He also explained that there is no required or predetermined timeline for when the FDA would consider issuing a Written Request. Dr. Reaman asked Working Group members for their input and updates on the following products:

- Lenvantinib
- LIE704 (Novartis)
- PLX3397 (Plexicon)
- RO5509554 Emactuzumab (Roche)
- CBL0137
- PD-L1 inhibitors: MED14736 (AZ), MPDL3280A (Genentech)
- Telazoparib
- Olaratumab (PDGFR Ab; Lilly)
- Venetoclax

Lenvantinib. Dr. Reaman asked Dr. Marcus to comment on this product. Dr. Marcus explained that Lenvantinib is a multikinase inhibitor, given orally in tablet form, with several different forumulations. She noted that this product had promising indications for adults, suggesting potential use for pediatric cases, as well. Dr. Marcus listed adverse events (AEs) documented for this product, including fatigue, hypertension, diarrhea, myalgia, nausea/vomiting, decreased appetite, and weight loss. Serious adverse reactions were hypertension, seen in 5 percent of the adult patients taking the medication, and pneumonia, which occurred in 4 percent of the adult patients using this product. Based on these initial findings and because it can be given orally, Dr. Marcus suggested that this product warrants further investigation of use with children.

Dr. Weigel noted that a pediatric study is currently underway in Europe, and that the drug is being produced in 1-mg., 4-mg., and 10-mg. capsules. The developer very recently finished an adult suspension formulation, which could provide another “pediatric-accessible” option.

Dr. Reaman noted that as part of the Written Request, the developer would be required to develop a pediatric formulation.

Dr. Gorlick mentioned that the company that makes this product has approached the Bone Tumor Committee regarding moving ahead on an osteo-sarcoma-specific study. He explained that the manufacturer has already compiled some pre-clinical data.

Dr. Reaman recommended making Subcommittee presentations as broad as possible. He explained that discussing application to specific diseases becomes problematic because the FDA then has to develop competing product lists. He concluded that the Working Group was interested in further discussion of this agent.

LIE704 (Novartis). Dr. Reaman noted that this is a CDK4/6 inhibitor and that he had information that in *in vivo* models, this agent appears to be five times more potent than its predecessor inhibitor agent, currently being evaluated in children. Dr. Reaman also mentioned that there is decreased incidence of hepatotoxicity in adults.

Dr. Park noted that there was enthusiasm about an earlier Novartis product, which was studied in Atypical Teratoid/Rhabdoid Tumors (AT/RTs). She explained that Novartis was very specific about what it allowed in the study of that agent (a precursor to LIE704). Dr. Park also noted that because some pre-clinical data indicated possible application in other brain tumors, that it is likely that there is broader interest in both agents beyond the AT/RT patient population. She also pointed out that even though the first drug was somewhat disappointing, it was only evaluated as a single agent.

Dr. Kieran explained that the developer was interested in studying this agent in AT/RT because in pre-clinical experiments, inhibition of the pathway had a dramatic impact on both *in vivo* and *in vitro* functioning of those cells. He noted that the only data he has seen were presented at a meeting, and that this information was not detailed. He also mentioned that although the results were somewhat disappointing, there were some children with AT/RT with prolonged stable disease.

Participants were unsure about the manufacturer's intent to focus on further study of this drug, as well as commitments to study other compounds in diseases such as leukemia. Dr. Weigel suggested that there is real interest in multiple disease groups within the Children's Oncology Group (COG). She also pointed out that several studies are in a "holding pattern" regarding commitment to pediatric studies.

Dr. Reaman concluded that there is rationale for inviting further discussion of LIE704 and presentation to the Working Group.

PLX3397 (Plexicon). Dr. Reaman noted that Dr. Casey had suggested that the group consider this novel agent. He explained that this agent is a CSF1 inhibitor affects the tumor micro environment, resulting in epistasis. He stressed that this agent is in the very early stages of development, but that it displays novel mechanisms of action. Dr. Reaman noted that he is not aware of any pre-clinical pediatric tumor models, and asked the group to indicate whether or not they recommended this agent for further discussion and presentation before the Subcommittee.

Dr. Casey suggested that it would be interesting to review pre-clinical data to assess whether or not the impact is truly in the tumor micro environment. She emphasized that without pre-clinical data, it would difficult to take the next step in pursuing further discussion.

Dr. Gorlick mentioned that this agent has been investigated by Memorial as a potential colony stimulating factor 1 (CSF1) inhibitor in patients with pigmented villonodular synovitis (PVNS). Because this condition is rare, undertaking a pediatric PVNS study would be very challenging.

Dr. Reaman acknowledged that it was unclear if this agent would be restricted to patients with PVNS or if it had potential broader applicability to sarcomas in general. Dr. Smith indicated that the Pediatric Preclinical Testing Program (PPTP) currently does not have plans to evaluate this agent. He explained that the PPTP will not undertake any new studies until after new awards are made in July 2015. However, Dr. Smith noted that the Program will keep this agent on a list to consider at that point.

RO5509554 Emactuzumab (Roche) and PD-L1 inhibitors: MED14736 (AZ), MPDL3280A (Genentech). Dr. Reaman noted that RO5509554 Emactuzumab is one of several PD-L1 inhibitors that participants had decided to discuss as a group. He noted that pediatric studies of PD-1 inhibitors are being conducted, but that it is unclear if there is interest in examining other PD-L1 inhibitors. He also pointed out that several of these inhibitors are being reviewed "in house" and are in various stages of development.

Participants noted that Merck is planning a company-sponsored pediatric trial; Bristol-Myers Squibb (with Genentech) and the COG are also studying these agents. Dr. Smith explained that the Bristol-Myers Squibb study is a combination, starting with PD-1 and then adding PD-L1.

Dr. Reaman recommended that there is no need to include further discussion of these agents, given that they are currently being studied or will be studied.

CBL0137. Dr. Reaman explained that Dr. Donoghue had recommended this agent from Cleveland BioLabs. Dr. Donoghue briefly summarized information on this agent, noting that she found pre-clinical pediatric data very encouraging. This agent is available in intravenous (IV) or oral dosages. Preliminary data indicated promising results in neuroblastomas showing tumor stabilization. Clinical trials in adults are in the very early stages. She asked if any Working Group members had further or updated information from the developer.

Dr. Weigel agreed that there would be potential broad interest; she also indicated that the developer is interested in pursuing pediatric studies, but only after the data "mature" and they are further along in their adult trials.

Dr. Donoghue recommended revisiting discussion of this agent within the next 6 to 12 months. Dr. Reaman remarked that the next Subcommittee meeting is scheduled for September 2015, and that it may be better to consider further discussion and presentation until more pre-clinical data are available. Dr. Donoghue offered to contact the developer for updated information on their adult clinical trials.

Telazoparib. This agent is currently being studied in combination with temozolomide. Dr. Smith explained that a Phase I clinical trial is ongoing within COG, with a somewhat unique study design. He explained that COG found three study populations as particularly interesting.

Given that the Phase I study is underway, Dr. Reaman asked participants for their opinions on whether to wait until more results are available, or if the Working Group prefers to invite the developer to discuss other areas for potential clinical evaluation at the Subcommittee meeting.

Dr. Smith noted that Phase I will have some Phase II expansion. Dr. Reaman recommended because there are already plans for Phase II expansion that it may be more beneficial to wait until that expansion occurs. He emphasized, however, that invitations have yet to be issued to sponsors and if any Group members feel strongly about including this developer, they should contact him as soon as possible.

Olaratumab (PDGFR Ab; Lilly). Dr. Reaman noted that data have been compiled on activity in certain sarcomas (lipo and leiomyosarcomas). Although preliminary results have been fairly dramatic, he explained that he is unaware of any pre-clinical studies of sarcomas other than those histologic subgroups. However, given the degree of clinical activity, Dr. Reaman suggested that the Group might want to consider this agent for further discussion.

He asked Dr. Gorlick to discuss. He reported that the Eli Lilly product is being studied in a broad sarcoma trial, and that an industry-sponsored, pediatric Phase I trial is being planned. He agreed that this product may be worth further examination and discussion.

Venetoclax (Genentech/AbbVie). Dr. Reaman explained that the pharmaceutical firm is interested in developing this product for use in myeloid malignancies. He also wondered if there are other potential opportunities for evaluating this agent.

Dr. Reynolds mentioned that a number of accommodation studies are being conducted using ABT199. He explained that it does have some interesting synergies in neuroblastomas, and that some zenograph data should be available by the summer. Although it is very early, he noted that there will be at least one subset that will show some interesting synergies with agents that are already clinically active. He also noted that this agent, administered orally, shows significant promise. However, he is not sure when the developer will conduct pediatric studies.

Dr. Reaman noted that the sponsor will be contacted to determine if the developer is interested in making a presentation for the Pediatric Subcommittee.

Dr. Reaman reminded participants that the next meeting of the Pediatric Subcommittee ODAC is scheduled for September 9, 2015. They will begin preparing invitations to some of the sponsors described during this call. He will keep Working Group members apprised regarding the status of those invitations.

Other Products for Potential Future Discussion

Dr. Reaman asked participants to identify additional products to consider as possibilities for issuing a Written Request.

Dr. Reynolds referred to his March 1, 2015, paper in *Clinical Cancer Research* on MM-398, a nanoliposomal irinotecan preparartion. He mentioned that Level 3, Phase I study has already been completed, with very interesting data, and that the developer is moving ahead with plans for registration for pancreatic cancer. Dr. Reynolds recommended that the Working Group issue a Pediatric Written Request for this agent. He explained that the manufacturer, Merrimack, is developing several products that show a lot of promise for pediatric cancers.

Dr. Smith inquired if there are any MDM2 inhibitors or other agents that may warrant further review. Dr. Reaman mentioned that Roche had made a presentation to the Pediatric Subcommittee after the last Working Group meeting regarding their MDM2 inhibitor. Although there had been initial interest in exploring the Roche product further, especially in neuroblastomas and leukemia, Dr. Reaman has not heard further from Roche. He is unaware of any discussion between Roche and investigators regarding a Proposed Pediatric Study Request.

Dr. Gore explained that the current adult study has two cohorts — a solid tumor cohort and a leukemia cohort. She noted that the leukemia cohort is just opening. She also noted that they are seeing prolonged thrombocytopenia in adults being treated in the current study. Dr. Gore discussed the current agent, NP28903 (the first agent was NP 9112). She explained that NP28903 is the agent currently being evaluated by Roche.

She suggested that Roche is being cautious given these findings. Rather than not being interested in pediatric trials, she pointed out that the developer may be appropriately cautious. Dr. Reaman agreed that the developer is being cautious about the toxicities occurring in the current adult cohort, and that the sponsor had hoped that the second generation agent would be less myelo-suppressive than the first version.

Off-Patent Drugs

Dr. Reaman reported that a final agenda item was for the Group to discuss off-patent products for opportunities for issuing a Written Request to the NIH for drugs that are being used off label for which pediatric labeling is missing, insufficient, or inadequate. He noted that he is unaware of any new information on the status of this program on the feasibility of conducting additional studies in pediatric oncology.

Dr. Reaman mentioned that a priority list has been generated, particularly for agents that have become more-or-less the standard of care. However, to his knowledge, there has been little or no activity on moving ahead on pediatric product labeling. He also noted that there have been funding issues. Dr. Reaman will follow up with Dr. Zajicek and Dr. Taylor-Zapata and report back to the Working Group.

Next Scheduled Meeting

Dr. Reaman suggested adjusting the quarterly call schedules. Participants agreed to schedule the next call for June or early July 2015 (rather than as originally scheduled for May).

Dr. Reaman closed the meeting, and thanked Working Group members for their participation.

Action Items

- Dr. Reaman will follow up with Drs. Taylor-Zapata and Zajicek regarding updated information on the pediatric labeling program for off-patent drugs.
- Dr. Reaman will update the Working Group regarding invitations issued to product developers for further discussion and presentation at the upcoming Pediatric Subcommittee of the ODAC meeting,
- Dr. Reaman will schedule the next Working Group meeting; Circle will issue invitations to Working Group participants.