

**Best Pharmaceuticals for Children Act (BPCA)
Pediatric Oncology Working Group Conference Call
October 25, 2016
11:00 a.m. – 12:00 p.m. EDT**

Participants

Amy Barone, M.D.
Susan Blaney, M.D.
Patricia Dinndorf, M.D.
Steven Dubois, M.D.
Lori Ehrlich, M.D.
Lia Gore, M.D.
Mark Kieran, M.D., Ph.D.
E. Anders Kolb, M.D.
Ruby Leong, Pharm.D.
Leigh Marcus, M.D.
Gregory Reaman, M.D.
Malcolm Smith, M.D.
Perdita Taylor-Zapata, M.D.
Brenda Weigel, M.D., M.Sc.
Carolyn Yancey, M.D.

Purpose

The purpose of this call was to discuss the following:

- Introduction of new Pediatric Oncology Medical Officers and new Working Group (WG) members
- Update on the Erwinaze® shortage
- Plans for the upcoming Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (ODAC)
- Recommendations from the WG for additional products to be presented/discussed.

Introduction of Pediatric Oncology Medical Officers

Dr. Reaman opened the meeting by introducing four Pediatric Oncology Medical Officers who recently have joined the Food and Drug Administration (FDA) Office of Hematology and Oncology Products: Leslie Doros, M.D., Nicole Drezner, M.D., Margret Merino, M.D., Nicholas Richardson, M.D. Dr. Reaman also welcomed several new WG members: Alberto Pappo, M.D., Katherine Janeway, M.D., E. Anders Kolb, M.D., and Steven Dubois, M.D. Those individuals who were not able to join this conference call will be re-introduced at the next WG conference call.

Erwinaze® Shortage Update

Dr. Reaman next briefly discussed the current status of the availability of Erwinaze® (asparaginase *Erwinia chrysanthemi*). He pointed out that this product—used in treatment of patients with acute lymphoblastic leukemia (ALL)—has been in short supply for some time, most often resulting from manufacturing complications. Dr. Reaman explained that the most recent shortage is due to the presence of certain metallic and plant/vegetable particulates detected during final inspection of this product. Dr. Reaman emphasized that the FDA is continually monitoring this situation. Because of concerns regarding the nature of these impurities, the FDA has cautioned that new supplies of this product are currently limited, until the Agency receives more clarification and verification from the manufacturer, Jazz Pharmaceuticals, that the situation has been resolved and that the product is safe at which time FDA may exercise regulatory discretion to release product with special administration guidelines. Dr. Reaman noted that while he would gladly entertain questions from WG members, he could do so only without compromising the confidential nature of this situation.

Pediatric Subcommittee of the ODAC Agenda

Dr. Reaman confirmed that the next Pediatric Subcommittee of the ODAC has been tentatively scheduled for June 21 and 22, 2017. Dr. Reaman briefly reviewed the tentative agenda for the 2-day meeting, explaining that the agenda could be altered to a 1-day format, or possibly to allow for general sessions within the 2-day timeframe.

Dr. Reaman then asked participants for their input regarding products to be considered for discussion and presentation during the upcoming ODAC meeting. Dr. Reaman explained that a preliminary selection of the following products was created because they represented a cross-section of newly approved or products in development that potentially could be relevant and appropriate for pediatric cancers:

- Curaxin (CUDC-907): Curtis
- Avelumab: EMD Serono
- Midostaurin: Novartis
- AG-120 and AG-221: Ageos
- Prexasartinib (PLX 3397): Plexxicon
- CPX-351: Jazz
- Olaratumab: Lilly
- Onivyde (liposomal irinotecan): Merrimack
- Palbociclib: Pfizer
- LY2606368: Lilly

Curaxin (CUDC-907): Curtis

Dr. Reaman noted that some activity has been noted in the use of this product in solid tumors. Dr. Smith agreed that this product warrants further discussion. Dr. Weigel mentioned that this product has generated interest as a treatment for leukemia and neuroblastomas. She also noted

while considerable formulation development, both in oral and intravenous (IV) applications, has already occurred, that the focus has been on hematologic malignancies in adults. Dr. Kieran asked Dr. Smith if data have been compiled for other malignancies with similar pathways. Dr. Smith offered to send Dr. Kieran the article that presents this information. Based on the interest in this product raised by the WG, Dr. Reaman will contact the developer and invite them to present at the June 2017 meeting.

Avelumab: EMD Serono

Dr. Reaman next asked WG members to share their opinions regarding the value of evaluating yet another programmed cell death protein 1/programmed cell death ligand-1 (PD-1/PDL-1) inhibitor for pediatric cancers. Dr. Weigel acknowledged that presentation from the developer regarding pathways would be of interest. She also pointed out that with the “glut” of new products flooding the market, many of which warrant further evaluation, the challenge is to present a convincing argument for differentiating this product from other products already further along in development for use with pediatric cancers. Dr. Weigel offered that this product is not a priority. She added that unless other WG members could present a compelling argument for why this product is more advantageous than other similar products, she would not recommend this product for discussion at the June meeting. Dr. Reaman agreed, noting that he knew of no current information that would substantiate selecting this product over other similar products at this time.

Dr. Kieran agreed but also suggested that the WG might reconsider this position if a company has a series of, or number of, products in its portfolio that are ideal as a combination. Dr. Kieran also concurred that the WG is not particularly interested in presentation of another PD-1/PD-L1 single agent. Dr. Reaman offered to contact the developer to inquire if the company is developing the product for potential combination with another product. Pending response from the developer, presentation regarding this product will be “tabled.” Dr. Smith also noted that while the prospect of presenting products as combinations is interesting, he cautioned that these combinations would need to be viable and demonstrate promise for stimulating pediatric-specific response.

Midostaurin: Novartis

Dr. Reaman noted that as a result of some rather exciting data, there are plans to develop this product as a treatment for myeloma. The manufacturer has received a “break-through” designation. Dr. Kolb explained that while this product shows promise for acute myeloid leukemia (AML) treatment, this product is the least specific, there are others that would have a higher priority; they are in various stages of pediatric investigational plan (PIP) development and implementation, Dr. Kolb did acknowledge that the priority ranking could certainly change, moving this product higher on the list.

Dr. Gore noted that there was an early stage trial in Europe for this product and there are some dosing and toxicity data available. This information gives a starting point should the drug rise to the level of needing attention.

Dr. Reaman concluded that pending toxicity evaluations, the WG recommended postponing inviting the manufacturer to present at the June meeting, at least for the time being.

AG-120 and AG-221: Ageos

Dr. Reaman next solicited input from the WG regarding interest in inviting the developer of these two isocitrate dehydrogenase 1 (NADP+), soluble (IDH-1) mutant inhibitors to present at the June meeting. Dr. Kolb referred to current mutational frequency data among teens less than 16 years of age, compared with patients in the 16 – 40 age group and older adults. He indicated that for an adolescent and young adult (AYA) study, there would be interest in the manufacturer presenting these products. He noted there is always a challenge in identifying mutations that are not usually identified or studied in pediatric cases. Dr. Reaman agreed that there could be an opportunity to enroll teen-aged patients. Dr. Kieran mentioned that the company had not expressed interest in lowering the age of study participants, and the number of patients with brain tumors has never been large enough to run an independent study.

Dr. Gore added that there are considerable data on adult patients using AG-120, as well as more limited information on use of AG-221 among adults. She agreed that a presentation on the products themselves could be worthwhile. She cautioned, however, that currently there are not enough patients, even worldwide, to conduct an independent study.

Dr. Reaman asked Dr. Kieran to discuss the frequency of mutations in pediatric brain tumors. Dr. Kieran explained that determining the frequency depends on how these tumors are identified. Most are low-grade cortical gliomas, although some high-grade gliomas have been identified. There is a dramatic increase in frequency in late adolescence. He also explained that patients 10 years of age or older, are routinely tested for IDH-1. Currently, the usual pattern in adults seems to be low-grade gliomas transferring to high-grade. However, it is unclear if what investigators are seeing is early onset of adult or late onset of the pediatric form. Dr. Kieran also pointed out that the recent World Health Organization (WHO) classification of central nervous system (CNS) tumors is largely based on IDH-1, which is much less common in pediatrics. Subsequently, the new WHO criteria are less relevant to pediatrics. IDH-1 does not fit into initial assessment of tumors.

Dr. Kieran agreed that a presentation on AG-120 at the June 2017 meeting would be useful.

Prexasartinib (PLX 3397): Plexxicon

Dr. Reaman noted that this product has received “break-through” designation and there has been interest in further development of this colony-stimulating factor 1 (CSF-1) receptor/inhibitor. Dr. Kieran asked if any members of the WG could elaborate on the status of Novartis CSF-1 study. Dr. Weigel reported that the protocol has been significantly amended for this Phase I-Phase II study. She also cautioned that this product is targeted for a very specific “niche” market. Although more patients have been added, very few study participants are less than age 18. Dr. Weigel further noted that although other clinical trials are underway, she was not aware of any clinical data specific to CNS tumors.

Dr. Reaman concluded that the WG recommended putting presentation of this product “on hold” pending release of more Phase I study information.

CPX-351: Jazz

Dr. Reaman advised the WG that there is potential interest in developing a Written Request (WR) for this product. Dr. Kolb reported that dose-finding Phase I and Phase II has been completed, and that study results have yielded compelling data, with impressive responses in older adults. U.S. developers have been working with European colleagues and are geared to move forward. Dr. Kolb emphasized that there is definitely interest in this product, and that he highly recommended it for presentation. Dr. Reaman will move ahead on inviting the developer to the June 2017 ODAC meeting.

Olaratumab: Lilly

Dr. Reaman described this product, recently approved for treatment of soft-tissue sarcomas. He noted that there has been interest in evaluating this product in pediatrics. Dr. Reaman requested input from the WG regarding including presentation from the developer regarding the somewhat unusual decisions made about this ongoing Phase I study. Participants concurred that there was significant interest within the WG, and that presentation from the sponsor would be beneficial. Dr. Weigel agreed, noting that there has been tremendous interest in potential application of this product for several tumor types. She also indicated that there has been considerable discussion regarding the post Phase I and Phase II study design. Dr. Reaman will move ahead on inviting the developer to present at ODAC in June 2017.

Onivyde (liposomal irinotecan): Merrimack

Dr. Reaman reminded the WG that the developer had been invited to present at a previous ODAC meeting, but was forced to postpone. He also noted that Dr. Reynolds had endorsed inviting the developer to present based on pre-clinical data that had been previously issued. Dr. Reaman further noted the frequency of use of irinotecan in a number of pediatric tumors. Dr. Weigel agreed, emphasizing that it would be particularly worthwhile for the developer to discuss any data regarding potential advantages or plans to use this product combined with other products. Dr. Reaman will re-open the previous invitation to the developer for presentation in June.

Palbociclib: Pfizer

Dr. Reaman noted that he was unaware of any specific pediatric development plans for this product, a CD4/ CD6 inhibitor, but there are potential targets within the pediatric tumor spectrum that might be appropriate. Dr. Weigel explained that there has been considerable broad interest regarding this product, but that development is still in the somewhat formative stage regarding future PIPs. She suggested that there may be considerable more data being compiled, and that she supported inviting the developer to present in June.

LY2606368: Lilly

Dr. Reaman briefly commented on this product, noting that while there had been considerable initial interest about this product, the developer had indicated that it would be “premature” to present at the previous ODAC meeting. Dr. Weigel noted that there is still substantial interest in

this product both within the WG and within the developer company itself. She suggested that the developer might be willing to present at the June 2017 meeting. Dr. Reaman will follow up with the developer.

Other Products Recommended for Invitation to Present

Dr. Reaman asked WG participants for their recommendations for other products that would possibly warrant an invitation to present in June. He emphasized while there are several months before the agenda is finalized, there is considerable preparation involved, and that the presenting companies will need time to prepare briefings. Dr. Kolb indicated that he will forward information on other suggestions to Dr. Reaman.

Other Business/Closing Comments

Dr. Reaman next asked participants for input regarding any previous business or for callers to offer discussion regarding any new topics. He concluded by thanking callers for their participation, and noted that he will keep them apprised of the responses from developers/sponsors that will be invited to present at the June 2017 meeting.

Next Scheduled WG Meeting

The next quarterly meeting will occur Tuesday, February 7, 2017, at 11:00 a.m. Eastern Time.