Best Pharmaceuticals for Children Act (BPCA)
Pediatric Oncology Working Group Conference Call
November 3, 2015
11:00 a.m.–11:25 p.m. ET

Participants

Peter Adamson, M.D.
Amy Barone, M.D.
Meredith Chuk, M.D.
Martha Donoghue, M.D.
Lori Ehrlich, M.D.
Lori Gorski
Leigh Marcus, M.D.
Kate Mathhay, M.D.
Christy Osgood, M.D.
Julie Park, M.D.
Gregory H. Reaman, M.D.
C. Patrick Reynolds, M.D., Ph.D.
Donna Snyder, M.D.
Perdita Taylor-Zapata, M.D.
Brenda Weigel, M.D., M.Sc.
Anne Zajicek, M.D., Pharm.D.

Purpose

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

- Products for discussion/presentation at the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (ODAC) meeting, November 19, 8:00 a.m.–1:00 p.m.
  - lenvatinib (Eisai)
  - ABT-414 (AbbVie)
- Possible re-invites
  - olaratumab (Lilly)
  - CBL 0137 (Cleveland BioLabs)
  - PLX 3397 (Plexicon)
  - LIE704 (Novartis)
  - talazoparib
- PD-L1 inhibitors of interest
- Suggestions from the Working Group for its next meeting

Opening Remarks

Dr. Reaman reminded the call participants that the next Pediatric Subcommittee of the ODAC meeting will be on November 19. It will be a half-day meeting. Two products—lenvatinib and

ABT-414—will be presented in the morning. A number of companies that initially accepted the invitation cancelled due to other commitments on that date or were busy with filings for the products that were going to be discussed. Dr. Reaman noted that the U.S. Food and Drug Administration (FDA) expects approvals for a number of new oncologic products over the next 2 months.

Products for Discussion/Presentation at the Upcoming Pediatric Subcommittee of the ODAC Meeting

Lenvatinib. This agent is a multiple receptor tyrosine kinase inhibitor that was approved for refractory thyroid cancer. Eisai is interested in developing lenvatinib for sarcomas in adults. There have been some discussions of pediatric studies of lenvatinib and a phase 1 study that the Children's Oncology Group is conducting. If the investigator community is interested in lenvatinib, the FDA might consider developing and issuing a Written Request for pediatric studies of lenvatinib. At the meeting, the Pediatric Subcommittee could discuss potential pediatric studies for differentiated thyroid cancer and bone and soft tissue sarcomas. Dr. Marcus mentioned that the FDA Pediatric Subcommittee will be discussing the lenvatinib briefing package. Dr. Reynolds asked about nonclinical data showing that lenvatinib works in pediatric sarcoma. Dr. Marcus explained that Eisai has provided some *in vitro* data for lenvatinib-everolimus combination using a pediatric sarcoma xenograft model, which showed a synergistic effect in both bone and soft tissue sarcoma. Eisai has also provided some adult clinical data, which is included in the briefing package. Dr. Reaman noted that preclinical data from the briefing package will hopefully be discussed in greater detail at the Pediatric Subcommittee meeting.

ABT-414. ABT-414 is an antibody-drug conjugate against the epidermal growth factor receptor (EGFR). It recognizes a different epitope of the receptor than other EGFR antibodies. It is linked to midostaurin, and when the antibody is internalized, the cellular poison kills the tumor cells. The company is interested in developing ABT-414 for EGFR-positive high-grade gliomas and glioblastomas. Of adults, 40% to 50% demonstrate EGFR mutations. The EGFR mutation rate in children is probably less than 5%. The company would like to discuss a potentially novel approach: a nested pediatric study as part of an adult study. The company will share some preclinical and clinical data at the Pediatric Subcommittee meeting. The briefing package has been posted on the Federal Register. The drug's cerebral spinal fluid pharmacokinetics may be discussed at the meeting.

Possible Re-invites

Dr. Reaman asked the Working Group whether it is still interested in exploring any of the possible re-invites (olaratumab, CBL 0137, PLX 3397, LIE704, and talazoparib). He reported that the companies are interested and willing to present at some future time (after the November 19 meeting) if the Working Group is still interested. Dr. Adamson suggested that the Working Group explore setting priorities for these products. Dr. Reaman noted that the list can be readjusted. Dr. Reynolds recommended that the Working Group reconsider inviting Merrimack to present on MM-398. Dr. Reaman explained that he had invited Merrimack, but the company

responded that it is too premature to present on MM-398. However, now that the drug has an approved indication, MM-398 can be added to the list. Dr. Reynolds briefly discussed this agent's mechanism of action and clinical study results. He explained that MM-398 is of interest because it is a nanoliposomal formulation of irinotecan that generates SN-38 in the tumor that is more effective than other currently available clinical formulations.

PD-L1 Inhibitors of Interest. Dr. Reaman reported that Written Requests have been issued for PD-1 inhibitors, and there are now a number of PD-L1 inhibitors available. He asked the Working Group whether it has preferences for which PD-L1 inhibitors are of interest from an investigative perspective and whether the Working Group would like to invite sponsors to talk about these products. Dr. Reaman noted that the FDA has not received any pediatric study plans for these products to date. The Working Group could advise the FDA if there are clinical or pharmacologic attributes of these products that would make one a better choice over another. Dr. Weigel asked whether the Working Group should consider just MED14736 and MPDL3280A, which were discussed in the April 8 meeting, or other PD-L1 inhibitors. Dr. Reaman said the Working Group should consider all PD-L1 inhibitors.

Suggestions from the Working Group for Its Next Meeting

The Working Group will inquire about Merrimack's interest in presenting on MM-398. It will pursue the other products and re-invite the sponsoring companies. The Working Group will explore PD-L1 inhibitors of interest and make recommendations on which to discuss at the next meeting. Dr. Chuk previously mentioned that aldoxorubicin might be of interest. She asked whether this agent's safety profile had been discussed. The company had talked about the possibility of pediatric studies, but Dr. Chuk did not know the stage of interaction with the investigative community. She also asked whether the Working Group would be interested in discussing aldoxorubicin at its next meeting. Dr. Chuk agreed to send to the Working Group information on the results of the aldoxorubicin phase 2 trial.

Next Scheduled Meeting

The Working Group will meet again sometime after January 2016 and will hopefully meet on a quarterly basis.

Action Items

- Dr. Chuk will send to the Working Group information on the results of the aldoxorubicin phase 2 trial.
- Dr. Reaman will inquire about the sponsoring companies' interest in presenting at the next Pediatric Subcommittee of the ODAC meeting.