Best Pharmaceuticals for Children Act (BPCA)
Pediatric Oncology Core Working Group Conference Call
June 27, 2013
2:00 p.m.–3:50 p.m. ET

Participants

Peter Adamson, M.D.
Martha Donoghue, M.D.
Lia Gore, M.D.
Lori Gorski, M.D.
Mark Kieran, M.D., Ph.D.
Gregory H. Reaman, M.D.
Patrick Reynolds, M.D., Ph.D.
Donna Snyder, M.D.
Malcolm Smith, M.D., Ph.D.
Erica Wynn, 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
- Topics for Subcommittee meeting
  - LEE011 (Novartis)
  - Anti PD-1 or anti-PD-L1 antibodies; Status of PD-L1 expression by pediatric tumors
  - Invited sponsors/products:
    - LEE011/Novartis*
    - Nivolumab/Bristol-Myers Squibb (BMS)
    - MK-3475/Merck*
    - Ipilumumab/BMS

    **accepted invitation*
- Working Group suggestions: Agents for future discussion
- Working Group input on U.S. Food and Drug Administration's (FDA's) collaboration on European Medicines Agency "standard" pediatric investigation plans (PIPs) for specific pediatric cancers
- Possible agents for written requests (WR) consideration to the National Institutes of Health (NIH).

Next Planned Pediatric Subcommittee Meeting

Dr. Reaman went over the agenda for the next Pediatric Subcommittee meeting. Two days are currently allotted, but there is a chance only 1 day will be used. The agenda includes discussion of two agents. First is Novartis' CDK-4 and CDK-6 inhibitor. Novartis approached the FDA about having this compound evaluated in rhabdoid tumors and possibly in neuroblastoma.

Novartis' representatives want to present their data and discuss their proposed clinical investigations at the Subcommittee meeting. Second are the PD-1 and PD-L1 antibodies. BMS was approached to talk about Nivolumab at the meeting, but the company has not given a definite confirmation of attendance. Merck, however, has confirmed and wants to discuss its MK-3475compound. It was hoped that there could also be discussion about use of BMS' Ipilumumab in adolescents and younger children, given the combination activity with that and the PD-1 antibodies in melanoma. BMS has had some discussions with the FDA about its plans and has submitted a proposed pediatric study request, but the FDA was uncomfortable with the dose that was being recommended. Thus, the conversation has been deferred until BMS has more experience with the larger dose in a greater number of adult patients, as well as pediatric patients. Dr. Reaman noted it may be useful to have some general discussion about these agents and therapeutically exploiting the immune system in pediatric oncology and inviting someone such as Dr. Paul Sondel to come give a brief presentation about the topic.

Dr. Gore noted that Eli Lilly has a CDK-4/CDK-6 inhibitor (LY2835219) and the company is trying to determine how to design a PIP. She said it may be interesting to look at this and the Novartis agents and see what the order of events will look like. It could be helpful to have some early discussions to see where companies are with the agents. Dr. Reaman said that when there are sponsors with competing products it can get tricky to have discussions, but the brief presentations they make at meetings do not divulge much proprietary information. Dr. Gore said Pfizer also has a compound called palbociclib that may be worth looking into. Dr. Smith said Genentech presented its anti-PD-L1 drug at the American Society of Clinical Oncology meeting, and Dr. Adamson noted that it is in an earlier stage than the Merck and BMS compounds. Dr. Gore said Genentech is not ready to move forward with pediatric studies of its anti-PD-L1 drug. She noted that there have not been any pediatric studies of this drug. Dr. Reaman said more time can be spent discussing each of these agents at the Subcommittee meeting.

Dr. Reaman asked for feedback about the idea of organizing a session about patient-reported outcomes (PROs) in pediatric clinical trials. He said the FDA is very focused on patient input and patient groups and on putting the information into study designs and endpoint considerations. There is a significant push to look at how well patients survive and how they feel afterward. It is an opportunity in pediatrics to look at a complex subject, given the varying age groups in that population. Dr. Reaman said he would like a workshop/presentation about this at the Subcommittee meeting and noted there is some activity around this topic at the Children's Oncology Group (COG). He was approached by Dr. David Freyer and Dr. Pam Hinds about trying to work with the FDA, but given the current economic climate at FDA, it would be difficult to fund a workshop. However, if it was done as part of an Oncologic Drugs Advisory Committee meeting there is a separate funding pool. Dr. Reaman asked for opinions and suggestions. Dr. Adamson said he does not know how much data currently exist in pediatrics, so it would depend on how long the session will be. Dr. Reaman said it may be good to highlight the gaps and discuss how to close them, because even with the abundance of adult data, the quality is sometimes suspect and difficult to interpret. There are pediatric PROs used in other disease areas that have more consistency in patient symptoms, but it may be worth at least looking at the topic within oncology. He said the topic may be more relevant to products for supportive care rather than cancer drugs. Dr. Reaman will talk with Dr. Hinds to find out how

much data are available. He noted that the scientists from the Office of Translational Science's labeling group (SEALD) were going to be invited to the meeting, because they are responsible for PRO evaluations at the FDA. He said perhaps a half day could be devoted to this topic.

Dr. Reaman said the FDA has a couple of standard PIPs from the pediatric committee of the EMA—one for acute lymphoblastic leukemia **(**ALL**)** and one for rhabdomyosarcoma. The EMA is working on these even though the FDA has not been a part of the process. He asked whether the FDA really wants to be involved when only limited information is available and plans are already being made for studies far in the future. He noted that many things could change in that course of time, amendments could be needed, and plans may be discontinued. Dr. Smith said he is concerned that the PIPs will continue with the same organizational structure and format, even though not a single child has been studied and studies are already being mapped out for the next decade. He said this is a waste of everyone's time and that there are much better ways to spend energy. He noted that until the EMA makes fundamental changes, there is not much the FDA can do to help serve the needs of children. Dr. Adamson agreed with this assessment and said the unintended consequences will increase, such as potentially having multiple PIPs that accomplish nothing. It is a very drug-centric, not disease-centric, approach to development. It was noted that the EMA may not have much flexibility to address this issue, because PIPS are required to have plans into phase 3. The FDA's WR process does not have that requirement, because the history of oncology products is well known. The FDA has an advantage with WR requirements as they allow for more flexibility in relation to future studies.

Dr. Gore said she participated in a meeting last fall when the potential model PIP for ALL was presented, and it was a very interesting process. She said a lot of discussion took place with the Innovative Therapies for Children with Cancer group related to how the Europeans want to try and define the issues for the model PIPs and guidelines. She said they have been rather thoughtful about the process and have consulted with North American investigators. Dr. Reaman said he did not think there was much North American involvement in the AML or rhabdomyosarcoma PIP, but Dr. Gore said she believes this is changing and that the studies are becoming more global. She said the EMA is trying to be more cognizant of potential risks. She said the discussion she was part of centered on biologic driving features, how stratification might occur, unique biologic features of subgroups, and what to recommend to pharmaceutical companies. The model ALL PIP discussion ensured that epidemiology and incidence, for example, for subgroups were clearly defined so study designs could take practical considerations into account, and this is an area that North American researchers could help with. Dr. Kieran said his experience with the EMA and PIPs has been similar. He said generally the drug companies come back asking whether what the EMA wants is doable or how studies can be modified to make the requirements work.

Dr. Reaman said he has not yet had a focused discussion with Dr. Ralf Herold but that he will talk with him to understand what flexibility there may be with the European legislation to make it feasible for the FDA to work with the EMA in a productive way. At this time, the best the FDA can do may be to help sponsors not be crippled by the demands placed on them due to unrealistic and nonfeasible requirements for some of the studies.

Dr. Reaman asked for suggestions for possible agents that are either off patent or that could be considered for WRs to the NIH. He asked what oncology drugs should be prioritized, which are frequently used drugs that have insufficient data to inform labeling, or which may have been studied in the wrong populations and should be further explored. Those suggested included:

- Prednisone
- Cyclophosphamide
- Vincristine
- Actinomycin D
- Daunomycin
- Methotrexate
- Azacytidine
- Etoposide
- Thalidomide.

It was asked whether the FDA is considering gathering original data out of COG trials. Dr. Reaman replied that the FDA has not said how further studies will be conducted, but that it wants to improve the labeling for some of the older cancer drugs. He noted an injectable methotrexate product is being developed for arthritis, and that the original methotrexate labeling is 50 years old. He asked Dr. Zajicek about the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD's) position around these studies and what is feasible. She said money is very tight this year because the budget was cut by about 10 percent due to the congressional sequestration. There is infrastructure with the Pediatric Trials Network, but this group does not have expertise in pediatric oncology. Any money for this type of study would need to come through the National Cancer Institute, but the NICHD is definitely interested. Dr. Smith said getting ideas about what drugs could be studied would be interesting. Dr. Kieran said researchers are using intrathecal etoposide for diseases such as primitive neuroectodermal tumors. Thus far it has been well tolerated and had dramatic results, but it is generally given along with systemic therapy, so the results are hard to isolate. Intrathecal etoposide is gaining more interest in Europe, and he believes this drug works better than many of the other brain tumor drugs. In addition, it does not need to be metabolized and does not include a preservative agent; it is water soluble. Dr. Gore noted that azacytidine is owned by Celgene, but it has no pediatric indication and was generic for a long time. She said she does not know what the regulatory responsibilities for the drug are at this point.

It was asked how to gain access to what is in the PIP decisions for the 104 oncology drugs. Dr. Reaman said they are public and are on the EMA website. Dr. Reaman will find the information for the group and noted that its information is more transparent than with the FDA's WRs.

Action Items:

- Dr. Reaman will speak with Dr. Hinds to find out how much data are available around PROs.
- Dr. Reaman will send the group information about how to access PIP decision information.
- Plans to pursue a WR to the NIH (NICHD) for etoposide studies will be discussed further.