

**Best Pharmaceuticals for Children Act (BPCA)
Pediatric Oncology Working Group Conference Call
February 6, 2018
11:00 a.m. – 11:45 a.m. (EST)**

Participants

Peter Adamson, M.D.
Kristin Baird, M.D.
Amy Barone, M.D.
Susan Blaney, M.D.
Najat Bouchkouj, M.D.
Diana Bradford, M.D.
Gilbert Burckart, Pharm.D.
Patricia Dinndorf, M.D.
Martha Donoghue, M.D.
Leslie Doros, M.D.
Steven Dubois, M.D.
Ira Dunkel, M.D.
Lori Ehrlich, M.D.
Rachel Ershler, M.D.
Dionna Green, M.D.
Mark Kieran, M.D., Ph.D.
E. Anders Kolb, M.D.
Aviva Krauss, M.D.
Ruby Leong, Pharm.D.
Leigh Marcus, M.D.
Kathleen Neville, M.D., M.S.
Christy Osgood, M.D.
Julie Park, M.D.
Gregory Reaman, M.D.
C. Patrick Reynolds, M.D., Ph.D.
Hari Cheryl Sachs, M.D.
Nita Seibel, M.D.
Malcolm Smith, M.D.
Perdita Taylor-Zapata, M.D.
Ashley Ward, M.D.
Brenda Weigel, M.D., M.Sc.

Purpose

This conference call focused on the following topics:

- Review of the Food and Drug Administration Reauthorization Act (FDARA) 2017 changes relevant to the Pediatric Research Equity Act (PREA); implications for pediatric cancer drug development
- Upcoming Workshops and Meetings
 - Friends of Cancer Research Workshop on Molecular Targets in Pediatric Cancer
 - Public Meeting on Development of a List of Molecular Targets Relevant to Pediatric Cancer, April 20, 2018
 - Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (ODAC)/Open Public Meeting on Implementation of FDARA 2017
- Potential Products for WG consideration

Discussion

Dr. Reaman welcomed call participants, including several FDA Pediatric Oncology Medical Officers.

FDARA 2017/PREA: New Statutory Requirements

Dr. Reaman began by briefly reviewing key components of the FDARA 2017 that have, or will, impact PREA. He pointed out that previously, PREA statutory directives had no direct effect on pediatric cancer drug development. However, as of August 18, 2020, sponsors with applications for new products—even if developed primarily for adult malignancies, but that address a target—that may have relevance to one or more pediatric cancers—will be required to submit an initial Pediatric Study Plan. This plan will describe the sponsor’s process for evaluating the drug in a pediatric population or provide justifications for waiving that requirement. Dr. Reaman provided several examples of such justifications, such as population of patients is too small, disease does not exist in the pediatric population, product does not represent a meaningful improvement over available therapeutic options for children with the disease, or the drug is too toxic and an appropriate drug formulation has not yet been developed.

Dr. Reaman pointed out that these statutory changes are good news; they provide new opportunities for earlier evaluations of novel agents in the pediatric space. However, he also acknowledged some potential unfavorable consequences, including the possibility of having too many agents, particularly agents of the same class, to study in a limited pediatric population. He also emphasized the need to require thoughtful consideration of how these pediatric provisions will be implemented. Dr. Reaman also described those rare situations where a drug is being developed for an adult cancer, and where there may be pediatric patients. Those situations have previously triggered an “orphan exemption.” Under FDARA 2017, those exemptions no longer exist. Pediatric investigation now must be included for drugs developed for conditions such as Hodgkin’s disease, or for some histology-agnostic indications.

Dr. Kieran asked for clarification regarding the stage of drug development during which the pharmaceutical companies will have to prepare and submit this plan.

Dr. Reaman explained that the drug sponsor will be required to submit an initial pediatric study plan within 60 days after the Phase 2 meeting that the drug sponsor has with the Agency. He noted that with implementation of some internal streamlining there may be no EOP2 meeting; the aim is as early as possible. Dr. Reaman also pointed out that the law also includes provisions for life-threatening diseases. He further noted that the sponsor can request and the Agency has to comply with that request, to meet immediately after Phase 1 to discuss the pediatric study plan.

Dr. Kieran also asked for clarification of the process in a situation where a disease does not exist in a pediatric population.

Dr. Reaman explained that now the trigger is a relevant molecular target, not an indication. Unlike in the past, when an indication was a justification for sponsors to request a waiver due to infeasibility of studies, now sponsors will be required to justify why a target to which a drug is directed is not relevant to a pediatric tumor.

Dr. Dubois asked how this change could affect previous products in Phase 1 trials.

Dr. Reaman explained that this change affects only those products whose New Drug Applications (NDAs), or Biologic License Applications (BLAs) are submitted after August 18, 2020. For those products already granted waivers, FDA is continuing to operate within current PREA provisions. Dr. Reaman also noted that the Agency already has had initial meetings with sponsors to alert them to the upcoming changes. Most importantly, although they may submit pediatric study plans and request waivers, it is possible if their application is submitted after August 18, 2020, that the justification for the waiver may disappear and that the sponsor may be required to conduct studies in the pediatric population.

Dr. Reaman also noted that the legislation mandates the Agency to develop a molecular target list. Obviously, the FDA will seek input from the National Cancer Institute (NCI) and from members of the clinical, translational, and basic research community.

Friends of Cancer Research/NCI/FDA Workshop on Molecular Targets in Pediatric Cancer

Dr. Reaman explained that Friends of Cancer Research has volunteered to sponsor an initial discussion and lead a workshop on Molecular Targets in Pediatric Cancer. The Workshop, planned for February 20, 2018, in Washington, DC, will provide a forum for attendees to discuss the framework for how to designate whether or not a target is appropriate for inclusion on the planned list. Envisioned as a scientific discussion, a multi-stakeholder planning committee is working on compiling a background document and developing an agenda.

During the Workshop, participants will discuss plans/processes for updating/maintaining the Molecular Target List on a regular basis, as required in the Act (and for processes for posting

changes/additions to the list on the FDA web site). Dr. Reaman suggested other considerations that should be addressed likely with include ultimate implementation of these provisions based on relative numbers of patients, toxicity profiles, potential benefits/risks.

Dr. Reaman noted that many of the call participants may have already received an invitation to the meeting, and that approximately 80 participants have already registered for the Workshop.

Public Meeting on Development of a List of Molecular Targets Relevant to Pediatric Cancer

Dr. Reaman reported that the FDA will conduct an FDARA-mandated open public meeting scheduled for April 19, 2018. Conducted at the FDA's Silver Spring, MD, campus, this meeting will provide an opportunity for participants to review/discuss the list of molecular targets relevant to pediatric cancer. Dr. Reaman explained, as mentioned above, that the preliminary list compiled with the NCI, includes 182 targets related to specific gene abnormalities. The list includes targets related to integral cell molecules, cell-surface antigens; targets related to tumor stroma or immune cells that may be related to infiltrating lymphocytes, or non-specific targets with known molecular mechanisms of action.

During the April meeting, participants are also expected to discuss ways for updating the Molecular Targets List on a regular basis, including procedures involving the transfer process among sponsors and investigators. The agenda also will include discussion regarding methods for better engaging stakeholders at national/international scientific meetings, and holding sessions in concert with ODAC meetings.

Dr. Reaman explained that the April meeting is being held to address industry confusion and concerns resulting in regulatory uncertainty as a result of changes to the mandated changes to PREA language.

Pediatric Subcommittee of ODAC Meeting/Open Public meeting on Implementation of FDARA 2017

Dr. Reaman noted that this meeting is scheduled for June 19–20, 2018, also held at the FDA Silver Spring, MD, campus. He indicated that this meeting will focus on providing an opportunity for participants to offer additional input/advice on the Molecular Targets List, as well as attendees' suggestions on finalizing the regular updating process. Most importantly, participants will be asked to offer their advice on how same in class agents should be prioritized for evaluation in the pediatric population, given that it is impossible to study all inhibitors currently being developed. Finally, the meeting also will seek participants' recommendations for enhancing and expanding collaboration on this subject between FSA and EMA and other international colleagues w/ collaborations.

Dr. Kieran asked if it would be possible for the WG to obtain a copy of the list of 182 agents on the list:

Dr. Reaman explained that it likely would be possible to provide the WG with a copy of the list before the public meeting. However, he cautioned that the list is currently very much a work-in-progress, and he would welcome any input from the WG. Dr. Reaman also explained that once there is consensus on the framework, the Agency will move forward in finalizing the initial list, including incorporating WG input. He reiterated that the list will most likely take a disease-agnostic approach, given that many targets cross histologies. He asked call participants for their comments/questions about the process for developing the list.

Dr. Dubois asked if the list would include molecular phenotypes that may have more than one molecular target within them. Dr. Reaman indicated that such a phenotype would be included. He pointed out that there is no requirement that because a target is on a list of potentially relevant targets, that pediatric studies have to be conducted on that agent. Also, although an agent is not on the list, it does not mean that the Agency could not require pediatric evaluation. Dr. Reaman also pointed out the likelihood that there will not be sufficient information to warrant an informed decision, resulting in a recommendation to defer a decision about whether or not study is warranted.

Possible Products for Consideration

Dr. Reaman mentioned that in addition to 1 day to review and discuss the target list and implementation of FDARA provisions, the June meeting also will include a ½ day session to discuss products of interest for issuing Written Requests (WRs). He explained that in the past, the Agency sent out invitations to industry sponsors to present and discuss their products as warranting consideration for issuing a WR. He also explained that several sponsors have indicated that these presentations on some of these products would be premature, but that the sponsor would be interested in presenting in the future.

Dr. Reaman then updated WG participants on the status of the following products that were previously discussed as possible presenters at future Pediatric Subcommittee of ODAC meetings:

- CUDC-907 (Curis): in pediatric phase I study; when first contacted, the sponsor indicated at that time that it was premature to present. The sponsor has been contacted again; the Agency is waiting for their response.
- PLX3397 (Plexxikon): not interested.
- ASTX 029 (Astex): sent an invitation, awaiting response from sponsor.
- Curaxin: resend invitation.
- Cemiplimab: do not send invitation at this time.
- Tegavivint: no specific pediatric development plan at this time; not a major player in pediatric oncology. Dr. Dubois suggests that there might be some interest to warrant inviting the sponsor to present; Dr. Weigel concurred.
- Epacadostat (BMS): product could be considered in combination with other agents, but does not have a formal pediatric development plan in place. However, this product may be of some interest. Dr. Weigel indicated that developer has a Pediatric Investigation Plan (PIP) in place, as well as a letter of intent (LOI). She noted that the sponsor is very interested in pediatric development; she thinks the product has potential for wide applicability.

Dr. Reaman asked participants for additional suggestions. In regards to Epcadostat, Dr. Smith pointed out that there will be a number of other agents that will warrant interest. Dr. Smith recommended that it might be helpful to bring a group together to define the “end game” and determine how many Immuno-oncology agents the group needs to review and assess.

Dr. Reaman welcomed the recommendation. He suggested that FDA should sponsor a workshop, in late spring/early summer 2018 to determine a more formal review structure, for example, whether or not to require verification of mutational burden as part of the enrichment strategy when evaluating these agents. Dr. Reaman called for volunteers to lead coordination of this workshop.

Dr. Neville asked for clarification regarding sponsors’ position regarding prioritizing the review of these products. Dr. Reaman agreed that any prioritization plan should clearly involve the pharmaceutical industry. He also emphasized that the FDA would have to direct involvement in this process. The Agency will follow direction from industry and the investigator community.

Dr. Smith mentioned ASTX 029; clarifying what is the target for this product. Dr. Reaman indicated that he will follow up with Dr. Smith. He noted that this product is very early in development; one pre-clinical paper has been published to date. It may be premature to consider this product at this time.

Dr. Reaman asked participants for additional suggestions for products to include in the June 2018 meeting.

Dr. Kieran asked if any transcriptional inhibitors, such as the one currently being developed by AstraZeneca, are far enough along to warrant discussion.

Other Business/Concluding Remarks

Dr. Reaman thanked Dr. Neville for volunteering to assist in coordinating the proposed late spring/early summer workshop on product review process. He also invited other WG members to volunteer in the prioritization effort.

Dr. Reaman reminded WG members to email him any additional sponsors/products that they would like to invite to the June 2018 meeting or future Pediatric Subcommittee of ODAC meetings.

Next Scheduled Call

The next WG conference call is scheduled for Tuesday, May 1 at 11:00 a.m. (EST).