

**Best Pharmaceuticals for Children Act (BPCA)
Pediatric Oncology Conference Call
May 3, 2022
11:00 a.m.–11:40 a.m. (EDT)**

Participants

Amy Barone, M.D.
Diana Bradford, M.D.
Rosane Charlab Orbach, Ph.D.
Martha Donoghue, M.D.
Elizabeth Duke, M.D.
Ira Dunkel, M.D.
Lori Ehrlich, M.D.
Jason Fangusaro, M.D.
Beth Fox, M.D.
Julia Glade Bender, M.D.
Kamar Godder, M.D.
Lia Gore, M.D.
Richard Gorlick, M.D.
Doug Hawkins, M.D.
Emily Jen, M.D.
Margret Merino, M.D.
Julie Park, M.D.
Gregory Reaman, M.D.
Marjilla Seddiq, M.D.
Nita Seibel, M.D.
Sonia Singh, M.D.
Malcolm Smith, M.D.
Perdita Taylor-Zapata, M.D.
Jim Whitlock, M.D.
Joanna Yi, M.D.
Megan Zimmerman, M.D.

Welcome

Dr. Gregory Reaman began the call by welcoming new members to the group. He noted that the group has a large U.S. Food and Drug Administration (FDA) presence and welcomes recommendations from members of the Children's Oncology Group (COG) and outside the FDA to recommend additional participants who may want to join these discussions in the future.

Review of Planned Pediatric Subcommittee of ODAC May 11-12, 2022

The Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (ODAC) will meet May 11 and 12, 2022. The meeting will consist of two general sessions, both of which will be held in conjunction with regulatory colleagues from the European Medicines Agency (EMA). The first day will focus on developing a consistent conceptual framework for same in class products for full waivers of pediatric investigations.

The Research to Accelerate Cures and Equity (RACE) for Children Act now requires early investigation in the pediatric population of appropriate targeted drugs. An unintended consequence has been the development of multiple “me-too drugs” developed by industry, for which drug study may not be necessary.

The FDA has been addressing this on an ad hoc basis. There is some instruction in the implementation guidance to be a bit more transparent on the specific characteristics (e.g., a clinical activity where adults have more favorable toxicity profile, superior pharmacologic characteristics, whether the drug penetrates the central nervous system, etc.). Further discussion surrounding these areas will take place. It is important to align with EMA when, for example, multiple applications are received for PI3-Kinase Delta Isoform Inhibitors for multiple myeloma and B cell malignancies, and waiver justifications must be reviewed.

The second day of the meeting will focus on a discussion of early end of induction response to chemotherapy in frontline patients with neuroblastoma. The discussion will focus on whether or not this could be used as a drug development biomarker. It has been established as a response biomarker but could potentially be considered an early endpoint, or intermediate endpoint, that might facilitate more rapid development of drugs in neuroblastoma.

Dr. Jim Whitlock asked a question regarding participation from Health Canada at the meeting. Dr. Reaman noted that no one from Health Canada will be participating as a speaker, but the meetings are open to the public so it's likely that representatives from Health Canada will attend.

Opportunities for Written Requests for Combination Studies

The discussion next focused on opportunities for written requests, in particular for combination studies. Dr. Reaman noted that there are some existing applications for the study of combinations of products for specific diseases. It might be appropriate to invite those sponsors to present their ideas. He asked the group for recommendations of specific products or specific combinations of products (approved or not yet approved), that might be reasonable candidates for written requests for pediatric studies.

Participants were asked to consider drugs including those that may be under investigation within the Pediatric Early Phase Clinical Trials Network (PEP-CTN), in a COG developmental therapeutics program, or as part of the Pediatric Brain Tumor Consortium (PBTC).

Dr. Lia Gore commented that there are many potentially exciting new compounds – both cell therapies and targeted agents – but it has been a challenge to understand how to subtract what is assumed to be baseline “backbone” toxicity, and how to assess novel agents that are being introduced to older “backbones” of therapy that are modest, but not as curative.

Dr. Reaman agreed this is a valid concern in need of further discussion. There are a number of fairly common “backbone” regimens used in the solid tumor arena, across a number of different diseases. It would be useful to add an investigational agent to those “backbones” and design a study so that there could be a mechanism by which contribution of effect, as well as contribution to toxicity, can be addressed. Such a study might require randomization in order to accurately

assess drug response, though there may be difficulty in securing investigators, and patients/families who are willing to participate in such studies.

Dr. Gore asked about the allowability of historic comparison to those “backbones” versus contemporary randomization. Dr. Reaman replied that this would be allowed only if there is sufficient patient level data that has been appropriately captured, managed, curated, and that could be used to evaluate the response to that common “backbone.” Due to limitations in availability and quality of data, this information is not always clear. It would be appropriate to further discuss these issues within the context of individual disease settings and individual clinical scenarios.

Dr. Ira Dunkel asked if requests for combinations would require both agents to be held by the same company. Dr. Reaman replied that it would be preferable in many instances, but it is not required. If one has an investigational agent, and there is a desire for exclusivity, or if it's an approved drug that still has some patent life, and there's a desire for exclusivity, having products from a single company would make sense. But there are situations, particularly for older products that are the standard of care utilized with an investigational agent, that could be subject to a written request. Written requests have been issued for combinations of agents that are the assets of different companies.

Dr. Julia Glade-Bender commented that her group has been studying DNA Damage Response (DDR) pathway agents, mainly as single agents. In order to best take advantage of this class of agents, it would be beneficial to induce some DNA damage with a conventional agent. However, industry contacts tend to feel that a single agent Phase I dose confirmation trial is needed first. She asked for feedback on the idea of a first cycle of a single agent with the addition of chemotherapy for patients with stable disease or less response in the second cycle. In this scenario, there would be a window of opportunity to see if there is single agent activity, but researchers can quickly move to a combination, if needed, even in the same patient.

Dr. Reaman agreed that this would provide not only an opportunity for a window to evaluate any potential single agent activity or efficacy, but also single agent toxicity. FDA and industry members would likely be open to considering this type of study design.

Dr. Beth Fox commented on concepts for combination therapies, noting that in the pediatric population, only one schedule can logically be studied. She asked for feedback on how to prioritize that schedule in the context of a combination study, and what areas should be evaluated for FDA consideration.

Dr. Reaman suggested looking not only at scheduling, but at dose within a fixed schedule. There are cases where the recommended Phase II doses in adults eventually become approved doses, though they are not necessarily the optimal doses. It is important when conducting a pediatric investigation to have some assurance that the most effective, least toxic doses, are being used, in addition to evaluating scheduling. Designs that could look at both would be worth considering.

Dr. Malcolm Smith noted that a discussion surrounding IO combinations would be relevant. His team is working on an IO trial now with combination in the PEP-CTN. A conversation would be

useful to discuss how many different drugs can be combined with PD-1 inhibitors. Dr. Reaman suggested including this as part of a more general combination discussion to address not only IO drugs in combination with more conventional cytotoxics, or targeted drugs, but even combinations of IO drugs. Dr. Reaman noted that there are a number of adult applications with PD-1 inhibitors in combination with anti-TIGIT products, anti-LAG-3, and CD47 that are worth further discussion.

Dr. Smith noted that these are primarily being developed in adults, in tumors for which PD-1 antibodies and anti PD-1 agents are effective. He asked what would be needed to provide rationale to study such a combination in a pediatric cancer where anti PD-1 agents have either little activity or such a small amount of activity that it's of minimal interest.

Dr. Reaman replied that there have been some adult applications for the combination of anti PD-1 and anti-TIGIT in adult diseases, where there has been minimal or marginal evidence of PD-1 anti PD-1 activity, with the hypothesis that using both together will increase activity. When looking at these applications and the potential for an early pediatric investigation as part of an initial pediatric study plan, comments to sponsors are typically evaluating them in those few pediatric diseases where there has been evidence of anti PD-1 activity. It is important to assess whether that can be evaluated to see if there is a synergy or added efficacy with the combination.

Dr. Smith noted that if one or more of these combinations can take a non-responsive tumor to anti PD-1 and make it responsive, it is crucial to understand the rationale for the mechanism for why it became responsive. Without that understanding, it would be difficult to translate that mechanism to a pediatric cancer.

Dr. Julia Glade-Bender suggested that antibody-drug conjugates (ADCs) might be a prime class of agents to consider for combinations. These are being given predominantly as single agents, but, seeing how effective brentuximab has been, combinations would be worth considering.

Dr. Reaman asked that anyone aware of specific disease committees with interest in exploring those kinds of studies notify him, as they might provide a stimulus for including sponsors in a joint discussion about potential interest in exploring those kinds of combinations.

Update on FNIH PPP and Molecular Target “Prioritization”

Dr. Reaman shared background on work between the National Cancer Institute (NCI), FDA, and the Foundation for the NIH (FNIH) to develop a public-private partnership (PPP). This PPP was initially viewed as an opportunity to promote academic-industry collaboration in preclinical investigation of promising agents using pediatric-specific animal models and existing PDX models, new PDX models, PDX models in rare diseases, orthotopic models, and other new approaches to evaluate immuno-oncology drugs.

Funding was provided to facilitate pediatric-specific animal models for testing and to make them publicly available, when appropriate. This has now transformed into an opportunity to not only spur collaboration in the preclinical investigation space, but to also evaluate priority of relevant targets.

This prioritization has helped to spur pre-clinical studies in investigation both through the NCI pivot program, and potentially with the EU's [ITCC-P4](#) preclinical platform. A series of quarterly meetings are being planned where investigators and other interested parties will look at available data on relevance. The first meeting will focus on MDM2, EZH2 or ezrin, and CD47 as the three targets of interest. Academic investigators and sponsors will identify the targets to prioritize for the next meeting. The hope is that this will help identify the best uses of preclinical testing resources and to work with companies to do the most informative preclinical testing.

Action Items

Dr. Reaman invited group members to recommend individuals from outside the FDA who might be interested in participating in some of these discussions.

Participants should reach out to Dr. Reaman with additional combinations of interest.

Next Call

The next call will be held Tuesday, August 2 at 11:00 AM Eastern Time.