Best Pharmaceuticals for Children Act (BPCA)
Pediatric Oncology Working Group Conference Call
February 2, 2021
12:00 p.m.–1:00 p.m. (EST)

Participants

Kristin Baird, M.D.
Najat Bouchkouj, M.D.
Diana Bradford, M.D.
Gilbert Burckart, Pharm.D.
Martha Donoghue, M.D.
Ira Dunkel, M.D.
Lori Ehrlich, M.D.
Dionna Green, M.D.
E. Anders Kolb, M.D.
Leigh Marcus, M.D.
Margret Merino, M.D.
Cara Rabik, M.D., Ph.D.
Gregory Reaman, M.D.
C. Patrick Reynolds, M.D., Ph.D.
Nita Seibel, M.D.
Sonia Singh, M.D.

Purpose

Dr. Reaman noted that the purpose of the call was to reexamine the working group (WG) directive within the BPCA legislative mandate. He began by reviewing key discussion topics for the meeting:

- Impact of the Food and Drug Administration (FDA) Reauthorization Act (FDARA) Sec. 504 [Research to Accelerate Cures and Equity (RACE) for Children Act] on BPCA and the Written Request (WR) mechanism for oncology products
- Participant input for consideration for inclusion in the Pediatric Subcommittee of Oncologic Drugs Advisory Committee (ODAC) and the BPCA WG agenda
- WG recommendations for issuance of WRs for approved oncology drugs and possible re-purposing
- WG recommendations for WRs from the National Institutes of Health (NIH) for off-patent oncology products.

Dr. Reaman explained that before enactment of the RACE for Children Act as part of FDARA Sec.504, there were no PREA requirements to impact pediatric oncology drug development. As a result, Pediatric Oncology WG meetings evolved as a forum to discuss development of specific products of interest for pediatrics and as a mechanism to inform the Agency about issuing WRs early in the development timeline by engaging with sponsors to submit Proposed Pediatric Study Requests (PPSRs)., With implementation of the RACE for Children Act, there

is now a requirement to test all new adult oncology drugs in children when the molecular targets are relevant to a particular childhood cancer. As a result of this mechanism, Dr. Reaman noted that within the past year, there have been 25 commitments to evaluate drugs early in pediatric populations.

Dr. Reaman urged participants to apply their WG experience and expertise to identify additional opportunities for future WG consideration, especially those external to FDA. The organization depends in large part on the insight of non-FDA participants to identify clinically unmet needs in pediatric oncology.

Dr. Reaman alerted participants that open public workshops will be held May 11-May 12, 2021. He pointed out that while previous Pediatric Subcommittee Meetings of the ODAC focused on products of interest for pediatric development, that need is less obvious. The first day of the May workshops will focus on the pediatric Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™) and its use within clinical trials. They will look at whether that information might help inform patient assessment of tolerability and toxicity. During the second day, the workshops will focus on "real-world" data and potential use in regulatory decision-making. They will also address issues such as the impact of design choices for randomized clinical trials, how to utilize external controls, in recognition of the innate limitations of the patient population.

Dr. Reaman noted that there has been a great deal of recent interest in studying drug combinations. Single-agent therapy has never been the optimal best approach. He suggested that a better approach might be to issue WRs for already-developed drugs combined with recently approved, or not-yet approved, drugs.

Dr. Reynolds cited the example of p53-reactivator APR-246. He explained that recent data indicate that this product works well with irinotecan across disease models and types. However, because it failed to meet its endpoint for myelodysplastic syndromes (MDS), the sponsor pulled back from further study.

Using this example, Dr. Reynolds asked if there would be opportunities for an WR to be issued to incentivize sponsors. For this particular drug, he noted that activity difference is highly significantly beneficial in Alternative Lengthening of Telomeres (ALT) tumors but there is also activity in telomerase tumors. Continued study using a different endpoint would be beneficial.

Dr. Reaman briefly reviewed FDA's current process of working with sponsors, noting that for the past 10 years, the intent has been to be as accommodating as possible. He explained that in the current process, the sponsor initiates a proposed pediatric study request, and the FDA issues the WR. To encourage communication and cooperation among FDA and sponsors, FDA has been inviting sponsors to present at meetings of the ODAC Pediatric Advisory Subcommittee to determine if there is relevance to pediatric studies. He cautioned participants about the challenge of bringing together sponsors with the same in-class products. Ensuring that there is no potential conflict of interest or compromise of proprietary information often requires onerous and time-consuming waivers. Dr. Reaman also stressed the importance of buy-in from the Clinical

Investigator (CI) community, especially given the reluctance of CIs to engage in pediatric studies.

In reference to acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL), Dr. Kolb noted that there are a number of menin inhibitors moving forward in the drug development process. A few years ago, the study of FLT3 inhibitors presented some challenges due to testing limitations. He noted the importance of ensuring that developers have feasible plans moving forward, as industry competition in a small population will make it difficult to ensure there are enough children to be tested on these new drugs.

Dr. Reaman mentioned past FDA correspondence with Syndax to discuss their menin inhibitor, which was discussed at the last Subcommittee meeting. A phase 1 study in adults and children is ongoing. He noted that with the new PREA requirement, there is less interest and less urgency in having sponsors voluntarily participate in these types of meetings.

Dr. Reaman suggested that this group may play a role with industry in discussing drugs that were approved before the requirement was put in place where there may still be an opportunity to discuss the potential for pediatric testing.

Dr. Reynolds asked if there were a way to use the WR process to expand opportunities for combination therapies. Dr. Reaman explained that in certain scenarios for combination studies, two companies would each receive the same WR for a new single-study combination of two drugs that still have patent life remaining. In other scenarios, an existing drug may be studied with a new agent. In this case, the WR would be issued to the sponsor of the new agent. There must be biologic rationale for the combination.

Dr. Reaman explained that suggestions would also be solicited from the investigator community regarding interesting/promising combinations. WRs for off-patent drugs could be coordinated through NIH. In all scenarios, sponsor incentives remain in place.

While programs such as ComboMATCH may offer some opportunities, Dr. Reynolds noted that such studies may be limited due to the exclusion of combining a new agent with a cytotoxic agent. Dr. Reaman pointed out that there may be other ways to initiate combination studies, other than ComboMATCH.

Dr. Reaman asked participants for their input regarding pediatric oncology drugs that should be studied and in those cases, the appropriate sponsor could be invited to present at an ODAC meeting. He asked that WG members notify the group if they become aware of drugs that might benefit from further discussions, as well as if there are drugs where a sponsor abandons development but there is still interest in the pediatric community. A mechanism for studying off-patent drugs is available under the BPCA program. If there are any off-patent oncology drugs that should be studied, that information can be conveyed to NICHD who manages the program.

Dr. Reynolds asked if the WR mechanism may be eliminated given the new PREA requirement. Dr. Reaman replied that he expects the WR incentive to remain and in fact, there may be increased opportunities for WRs in the future.

Dr. Kolb reported that he and the Children's Oncology Group (COG) AML Committee have begun conversations with Sutro Pharmaceuticals regarding studies targeting menin inhibitors in AML. Specifically, anti-CD74-ADC is an investigational antibody-drug conjugate currently in Phase 1 or Phase 1B development. Folate receptor 1 alpha ADC is another target of interest. Sutro Pharmaceuticals has indicated interest in further development but has limited knowledge about pediatric drug development for these AML targets.

Dr. Reynolds mentioned that AstraZeneca is looking at ataxia telangiectasia mutated (ATM)-kinase inhibitors. He suggested that there may be potential to reach out to the company to initiate meetings/presentations, targeting all cancers.

Dr. Kolb further noted that meeting regulatory requirements and complying with National Cancer Institute (NCI)-funded cooperative agreements are potential disincentives/confounders for sponsors.

Dr. Reynolds again referred to ComboMATCH, suggesting that it would be advantageous if ComboMATCH would be willing to accept novel investigational agents combined with well-known cytotoxic agents to obtain proof of concept data across ages and disease types on market driven trials. Dr. Reaman agreed to raise this issue on an upcoming meeting between FDA and NCI's Cancer Therapy Evaluation Program.

Dr. Seibel explained that although not directly involved in ComboMATCH, she agreed that the combination-type study design may offer the flexibility needed in pediatric study populations. On the other hand, she cautioned that the current ComboMATCH design criteria could possibly preclude pediatric populations.

There is not always total consensus among NCI and FDA or between NCI and drug development sponsors. Dr. Reaman explained that FDA tries to align with NCI regarding studies of drugs that may have potential in the pediatric subject area. He pointed out that FDA engages in discussions with NCI regarding alignment of study design and meeting statutory guidelines for labeling directives.

Dr. Reynolds noted that information "silos" remain a challenge. He offered to reach out to Dr. Jeff Moscow for more information on ComboMATCH. Dr. Seibel suggested inviting Dr. Moscow to participate in upcoming WG calls. Dr. Reaman also encouraged the group to explore alternative mechanisms to studying combination therapies.

Next Scheduled Meeting

The next quarterly WG conference call is scheduled for Tuesday, May 4, 2021 at 11:00 AM EDT.