

**Best Pharmaceuticals for Children Act (BPCA)
Pediatric Oncology Conference Call
May 2, 2023
11:00 a.m.–12:00 p.m. (EDT)**

Participants

Amy Barone
Diana Bradford
Gilbert Burckart
Martha Donoghue
Nicole Drezner
Elizabeth Duke
Lori Ehrlich
Beth Fox
Julia Glade Bender
Kamar Godder
Lia Gore
Richard Gorlick
Doug Hawkins
Andy Kolb
Margret Merino
Lauren Price
Cara Rabik
Nicholas Richardson
Marjilla Seddiq
Nita Seibel
Stacy Shord
Sonia Singh
Perdita Taylor-Zapata
Brenda Weigel
Joanna Yi

Welcome

Dr. Martha Donoghue began the call by welcoming participants, reviewing the agenda, and reminding attendees to share any feedback they have for future discussion topics for this group.

**4/23 ACCELERATE Paediatric Strategy Forum on PI3K, AKT, mTOR and GSK3B
Pathway Inhibitors – Post-Meeting Discussion**

Dr. Donoghue recapped the April 2023 ACCELERATE Paediatric Strategy Forum for Medicinal Product Development of PI3K, AKT, mTOR and GSK3 β Pathway Inhibitors in Children and Adolescents (<https://www.accelerate-platform.org/>).

Discussions at the meeting addressed the fact that many single-center mTOR inhibitor studies done over the years did not show significant anti-tumor activity. Many of these studies were single-agent studies. A strong biologic rationale and preclinical data is needed prior to

conducting future studies. One potential study is vandetanib/everolimus for the treatment of ACVR1-mutant DIPG.

P13K Inhibitors

Many of the alterations in PI3K and AKT are shared between pediatric and adult tumors. Alterations in pediatrics are much rarer. In terms of PI3K inhibitors, newer agents tend to be more mutation-specific, which could be good in terms of controlling side effects, such as hyperglycemia, but can pose more difficulties in terms of making an already rare population even rarer.

There was also discussion of the dual PI3K/mTOR inhibitors being of interest as well as the importance of CNS penetration given the potential application in DIPG tumors.

The consensus was that additional information should be acquired before proceeding with additional studies of these drugs. For example, it would be useful to review readouts from the Pediatric MATCH trial subprotocol (samotolisib) as well as the St. Jude trial of paxalasisib prior to conducting additional studies.

There was a presentation about alpelisib for the treatment of PIKCA-related overgrowth spectrum (PROS) which demonstrated an interesting contrast between the utility of a single agent PI3K inhibitor in a “non-malignant” tumor that's tied to a single genetic alteration without resistance mechanisms as opposed to the experience in pediatric cancers, for which limited activity has been shown to date.

AKT Inhibitors

Attendees learned about the development program of miransertib for Proteus. There is a single arm study being conducted at NIH, looking at an endpoint of reduction in the growth rate of cerebriiform connective tissue nevus (CCTN) plantar lesions. There is also an ongoing study of ipatasertib, another AKT inhibitor.

GSK3 β Inhibitors

Some information was shared regarding GSK3 β inhibitors (9-ING-41) but there is limited information about this class of agents at this time.

Strategy Forum Takeaways

There was discussion at the meeting on the importance of pre-clinical data and the opinion that pediatric trials should not be conducted in the absence of demonstrated tumor reduction in pre-clinical models. Many of these drugs are likely to be cytostatic and would be better used in combinations.

There are challenges in studying these drugs efficiently given the rarity of pediatric cancers, accentuated for mutation-specific inhibitors. Suggested takeaways include:

- Maximally leverage adult experience
- N of 1 studies
- Learning from expanded access
- Global strategy
- Use of CT DNA

At this time, there is not an urgency to study these drugs beyond the studies that are already ongoing. However, pre-clinical work should be thoughtfully considered as science evolves, prior to conducting clinical studies.

Discussion

Dr. Brenda Weigel agreed that pre-clinical work is necessary and also that single agent studies should be limited, given the low prevalence of specific cancer mutations. It is a challenge to identify how many DIPG studies are needed, given the rarity of the population impacted. The emphasis on combinations is important, but if there's no single agent activity, compelling data is needed to justify combination studies. There is an unmet need to study drugs for this patient population due to the devastating prognosis, but some prioritization is needed to determine how many and which studies should occur.

Dr. Donoghue agreed that single agents are unlikely to be effective in the DIPG population and that combination studies would be ideal. Dr. Doug Hawkins added that given the rarity of specific pediatric cancer mutations, the clinical trials system fails to effectively study tumors with a lower frequency of alterations.

Dr. Hawkins also commented on the relative distribution of single institution studies versus collaborative studies and suggested that data be presented on these trends at a future ACCELERATE meeting. Many single institution studies can lead to duplication of effort and parallel work, whereas collaborations across institutions could result in much more efficient studies.

Lastly, Dr. Hawkins noted that the medical oncology perspective at the meeting was useful. One of the key takeaways was that dual pathway inhibition is essential. This is something lacking in many current studies and that would have been useful when designing existing studies.

Dr. Lia Gore commented on the special considerations of the DIPG patient population, notably, the inability or unwillingness of many patients to travel for study-related visits. She agreed that a move away from single-institution studies would be appropriate to ease the process of trials and data collection, in a way that is patient and family friendly. One of the upcoming ACCELERATE forums will focus on DIPG specifically.

Dr. Donoghue agreed that a more pragmatic approach to studying DIPG would be useful, to include simpler trials, more decentralization, more diversified, patient-centric studies, etc.

Dr. Beth Fox noted that this forum is uniquely positioned to think about the U.S. role relative to the global need to evaluate drugs in children. She noted that single institution studies are often favored due to easier access to the drugs being studied; it can be much more difficult for a home institution to get access to investigational drugs through participation in a multi-institutional study.

Dr. Fox also commented on the increase in single-patient IND requests and how this positions researchers to think about full-scale drug development. This includes both access to patients and regulatory approval.

Dr. Donoghue commented on the concept of leveraging data from expanded access. From a regulatory perspective, it is a somewhat complicated and difficult topic, because the primary purpose of expanded access is to treat patients; it is very different from a study. If data is collected that might be used for a future drug development program, it may be difficult to justify the expanded access designation. In general, both the FDA and patient families want every bit of data that can be gleaned from treatment to be used to expedite development of new effective treatments, so it is important to find an appropriate way to do this. She suggested that sponsors offer their own expanded access programs. This would make it easier to consolidate information rather than trying to pull out multiple single-patient INDs. Sponsors should think in advance about some type of data collection or consent, so that data can be accessed afterwards if needed.

Dr. Donoghue noted that the FDA is currently working on a paper which will provide the FDA perspective on issues with expanded access. It is expected to be published later in 2023.

Dr. Julia Glade Bender agreed that it would be nice to have the option to marry single-patient access to a registry, so that it could somehow be followed in parallel. It is important to find ways to more quickly move studies to a combination phase, noting that the ESMART trials did so more quickly and were also more successful in terms of accruals than U.S. precision medicine platforms. A more flexible platform could allow more data to be obtained earlier in the process.

Dr. Glade Bender referenced the TAPUR study which looked at approved drugs in non-approved indications for the adult cancer population, in an effort to expand indications. She suggested that something similar would be useful in pediatrics. Dr. Hawkins commented that there had been an invitation for pediatric/adolescent participation in the TAPUR study but there was essentially no pediatric participation.

Written Requests

Dr. Donoghue reviewed the FDA Written Request process. The Best Pharmaceuticals for Children Act (BPCA) provides a financial incentive to companies to voluntarily conduct pediatric studies under a Pediatric Written Request (WR). These WRs provide an additional 6 months of exclusivity, attaching to all existing exclusivities and patents for the drug moiety. WRs do not require positive studies or a pediatric indication. A sponsor may request the FDA to issue a WR by submitting a Proposed Pediatric Study Request (PPSR) or FDA may issue a WR without a PPSR.

A sponsor may submit a PPSR which contains the rationale for studies and detailed study designs (clinical and nonclinical) and plans for age-appropriate formulation development if one is needed. Reports of studies outlined in WRs need to be submitted. The FDA goal is to issue the WR as early in the drug development process as possible, ideally before NDA/BLA submission.

FDA considerations in reviewing a PPSR include:

- What is the public health benefit?
- Are the study designs feasible? Are they sufficient to support dosing, safety, and efficacy?

- Have all populations and conditions been addressed?
- Are there other products already approved for the indication?

PPSRs generally require multiple rounds of review and discussion with a company. Frequent negotiation points include:

- Samples size
- Number of studies
 - Need to address indications that are most likely to benefit from drug/biologic
- Study Scope
- Pediatric formulation development
- Balance feasibility with getting maximum amount of useful data for labeling

Once a WR is issued, it can be amended by the company or the FDA, but both parties must agree. Amendment requests include extending the timeframe outlined for submission, modification of patient populations, elements of study design, etc. There are often many amendments during the lifecycle of a WR.

The sponsor must notify FDA within 180 days of receipt of the WR whether they agree to the terms or not. If they agree, they must indicate when studies will be initiated; if they decline, they must indicate why.

Reports of studies outlined in WRs must be submitted within the designated timeframe of the WR. In general, exclusivity requests must be submitted to the NDA/BLA, along with proposed labeling changes, at least 15 months before the patent/exclusivity expires. FDA reviews the reports within 6 months or less to make a decision about exclusivity. Pediatric exclusivity attaches to existing patent protection or exclusivity that would otherwise expire 9 months or more after exclusivity is granted.

Helpful resources pertaining to Written Requests were shared:

- Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, And Cosmetic Act: Frequently Asked Questions on Pediatric Exclusivity (505A): <https://www.fda.gov/drugs/development-resources/qualifying-pediatric-exclusivity-under-section-505a-federal-food-drug-and-cosmetic-act-frequently>
- Written Requests Issued: <https://www.fda.gov/drugs/development-resources/written-requests-issued>
- Exclusivity Granted: <https://www.fda.gov/drugs/development-resources/pediatric-exclusivity-granted>
- List of Determinations Including Written Request: <https://www.fda.gov/drugs/development-resources/list-determinations-including-written-request>

Dr. Joanna Yi asked about a possible scenario where a company declines the terms in a WR. Dr. Donoghue clarified that, in that case, the company may still conduct any studies they'd like to do, as long as they are reasonable. However, the WRs are generally accepted so this has not been an issue.

Dr. Donoghue did note that sometimes the opposite happens – a Written Request is issued, but too much time has passed and the studies cannot be completed before the end of the exclusivity timeframe.

Dr. Glade Bender asked about the relationship between a PPSR and an Initial Pediatric Study Plan (iPSP) and how the timelines for each work together. Dr. Donoghue clarified that the requirement for an iPSP to be submitted is tied to an end of Phase 2 meeting (for the adult indication). Typically these need to be submitted within 60 days of the meeting, if not sooner.

iPSPs are often submitted earlier in the process, and in many cases the pediatric studies are approved and initiated before the drug is approved for adults. The PPSR submission/issuance of a WR can occur any time during the development timeframe, although it generally doesn't occur until after the iPSP. The WR can include the initial iPSP-mandated study as long as there are also additional studies being required in the WR beyond the initial one. The WR cannot include any study from which data has already been submitted.

Dr. Andy Kolb shared that he's been in active discussions with companies about clinical trials as they are going through the WR process, but the companies do not always share details of the WR. He suggested that more communication would be useful at this stage, including a meeting to discuss the contents of the PPSR or the WR, and request that investigator representatives join. Alternatively, if there is a way to encourage companies to close the loop internally (medical staff communicating with regulatory staff), that would help as well.

Dr. Donoghue encouraged participants to share any drug names or future topics that they would like to discuss at the next meeting.

Following the meeting, the meeting slides were distributed (5/2/2023 @ 12:15 PM EDT) as well as a list of recent WRs (5/3/2023 @ 11:00 AM EDT).

The next call will be held August 1, 2023 at 11:00 AM EDT.