Best Pharmaceuticals for Children Act (BPCA)
Pediatric Oncology Conference Call
November 2, 2021
12:00 p.m.–1:00 p.m. (EDT)

Participants

Peter Adamson, M.D.
Diana Bradford, M.D.
Martha Donoghue, M.D.
Leslie Doros, M.D.
Ira Dunkel, M.D.
Julia Glade-Bender, M.D.
Francis Green, Pharm.D.
Ruby Leong, Pharm.D.
Leigh Marcus, M.D.
Margret Merino, M.D.
Christy Osgood, M.D.
Julie Park, M.D.
Aaron Pawlyk, Ph.D.
Cara Rabik, M.D., Ph.D.
Gregory Reaman, M.D.
Nicholas Richardson, M.D.
Nita Seibel, M.D.
Sonia Singh, M.D.
Malcolm Smith, M.D.
Perdita Taylor-Zapata, M.D.
Brenda Weigel, M.D., M.Sc.
Joanna Yi, M.D.

Purpose

Dr. Reaman began the meeting by recapping the previously discussed reorientation and redirection of the objectives and mission of the group, in light of the implementation of Section 504 (RACE for Children Act) of the FDA Reauthorization Act of 2017 (FDARA), which amended the Pediatric Research Equity Act (PREA). Previously, the primary motivation for meeting was to identify products in early development, or that might be applicable to development in the pediatric population, and potential candidates for the FDA to issue Written Requests. In these instances, sponsors were invited to present at Oncologic Drugs Advisory Committee (ODAC) subcommittee meetings and subcommittee members would in turn determine the feasibility of issuing Written Requests.

Prior to the RACE for Children Act implementation, BPCA was the only piece of legislation directed at drug development for children that could be used for pediatric cancer medications.

This new mechanism offers more opportunities to require companies to conduct early phase studies, designed to evaluate dose, toxicity, and signal of activity.

Dr. Reaman noted that there were some products not discussed prior to August 2020, when the new legislation went into effect and invited the group to discuss recently approved drugs, or drugs that are in later phases of development, that might be potential candidates of interest for issuing Written Requests. These drugs could potentially be discussed at the pediatric subcommittee of ODAC meeting in May 2022. Of note, Written Requests can be issued without sponsors presenting, but the opportunity for the conversation among the investigator community is useful.

He also noted that in general, drugs are evaluated as single agents through these programs, but there may be opportunities to consider combinations (i.e., investigational drug in combination with an approved drug, two investigational drugs, or two approved drugs within the context of a Written Request). He then asked Dr. Brenda Weigel to give an update on the NCI PEP-CTN program.

NCI PEP-CTN

Dr. Weigel presented on behalf of herself as well as Dr. Beth Fox who could not attend this call due to another commitment. She began by sharing a list of studies that are active or in development that do not have Written Requests. She noted there is also a cohort of fully-funded industry studies, many of which already have Written Requests, but did not plan to address these in detail.

She began by describing the following active studies:

- PEPN2011: Tegavivit (Wnt/β-catenin inhibitor)
  This study recently activated with the first patient enrolling this week. This medication has been studied in adults, predominantly in desmoid tumors. It is well tolerated and administered via weekly IV. Dose-limiting toxicity (DLT) was not reached in the adult Phase 1 study. The dose was selected based on pharmacokinetics (PK); there was no biomarker used to determine dose. Data from four different groups showed responses in desmoid tumors in adults with both partial response and stable disease.

  Preclinical pediatric data from four different groups is available in osteosarcoma, Ewing sarcoma, and lymphoma. The data is unpublished but demonstrates relevance in pediatrics. The current trial will include a Phase 1 dose escalation in solid tumors, as well as multiple planned Phase 2 expansion cohorts of this single agent study. The plan is to start with the adult recommended Phase 2 dose with a planned de-escalation, along with the potential to escalate if needed. This decision will be based on PK and toxicity.

- PEPN1812: Flotetuzemab (CD123 X CD3)
  This study targets 2nd or greater relapsed acute myeloid leukemia (AML) and is not biomarker-selected, so CD 123 expression is not required; it is ubiquitously expressed on AML.

  The study involves increasing dosage during the first week and continuing it at the highest dose level. The adult recommended phase starting dose was 500 nanograms per kilo per day with the second dose level at 700 nanograms per kilo per day. Dr. Weigel explained that the toxicity was noted, and cytokine release syndrome has been an issue. Dose-limiting toxicities have been noted in first and subsequent cycles in both dose levels.

  The study has been paused for assessment. There is a planned Phase 2 study through LLS PEDAL in the AML relapse population.

- ADVL1414: Selinexor
  This study has completed accrual and is a first in class selective inhibitor of nuclear export. This study had two dose escalations. For Part A, dose escalation was first defined on a dosing schedule of twice weekly and was then revised to a weekly schedule. Part B was a dose expansion in high grade gliomas.

  The interest in this study was in the CNS population. The toxicities demonstrated here were predominantly hematologic and thrombocytopenic. PK was also completed. The lower dose of the twice weekly administration was thought to be not sufficient to penetrate to the CNS, hence the higher doses weekly, which was further explored.

  The study has completed accrual to dose finding as well as part B and is awaiting results from the Phase 2 expansion. The recommended Phase 2 dose has been defined and there is a Phase 2 COG study planned in Diffuse Intrinsic Pontine Glioma (DIPG), expected to open in early 2022.

- ADVL1514: nab-rapamycin
  There were two cycles for this study. Cycle one was a single agent given on days one and eight and cycle two was given in combination with temozolomide and irinotecan. In this study, researchers needed to de-escalate twice. The main toxicity, both as a single agent and in combination, was thrombocytopenia. The study is currently closed, with the PK and pharmacodynamics (PD) pending. The recommended Phase 2 dose has been defined as DL-2 15 mg/m^2. There is discussion with the Bone Tumor committee of a possible study in Ewing sarcoma, but this decision is pending PK and PD data.

Dr. Weigel went on to describe PEP-CTN Studies in Development:

- PEPN2111: CBL0137
  A study was conducted in adults and the main toxicities noted were myelosuppression and photosensitivity. A two-phase single agent study is planned with Phase 1 in a rolling

six design. Phase 2 is based on preclinical data and will have two cohorts: a progressive/recurrent DIPG/ Diffuse Midline Glioma (DMG) cohort, and a relapsed/refractory osteosarcoma cohort.

The study will begin slightly below the adult recommended Phase 2 dose due to the toxicity of myelosuppression, and then escalating or de-escalating accordingly. PK and PD are planned with activation scheduled in December 2022.

- PEPN2113: Uproleselan (opening soon)
  This e-selectin inhibitor will be studied for relapsed refractory AML, for second or greater relapse. E-selectin is found on a subset of AML blasts as a membrane-bound protein. Downs syndrome patients are eligible to participate. The study is biomarker driven and requires greater than 30% e-selectin ligand expression on myeloid blasts.

  This medication will be given with chemotherapy. A single agent will be administered on the first day and will be studied in combination with AraC and fludarabine on days 2-6. PK will be studied for the single agent as well as the combination.

  This will be a rolling six design evaluating the potential for two dose levels. Planned activation is early 2022.

- PEPN2112: Elimusertib
  This is Phase 1/2 study of a novel ATR inhibitor. Preclinical data is available in Ewing sarcoma and alveolar rhabdomyosarcoma targeting deaf domain receptor alterations. This is an oral agent. Phase 1 will define the recommended Phase 2 dose as a single agent. Phase 2 will involve 3 cohorts: Ewing sarcoma, alveolar rhabdomyosarcoma, and a disease agnostic cohort defined by specific DDR abnormalities.

  Planned activation is in early 2022.

- PEPN2121: tiragolumab and atezolizumab
  This is a Phase 2 study of a novel combination of tiragolumab and atezolizumab. Tiragolumab is a T cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif (ITIM) domain (TIGIT) inhibitor and atezolizumab works against programmed cell death-ligand 1 (PD-L1). This is a novel combination in pediatrics, targeting SMARCB1 & SMARCA4 deficient tumors.

  Preclinical data suggests that that SMARCB1 tumors are uniquely sensitive to the combination of PD-L1 and TIGIT inhibition, with multiple responses noted in the adult studies to date. In a randomized Phase 2 study in adults, there was improvement in survival and overall response rate in non-small cell lung carcinoma.

  The planned cohorts are malignant rhabdoid tumor, poorly differentiated chordoma, epithelioid sarcoma, atypical teratoid rhabdoid tumors, renal cell carcinoma, and other

SMARCB1 & SMARCA4 deficient tumors. The study will include a safety phase for patients under 12 years old, but will enroll adults as well as children.

Planned activation is in early 2022.

Dr. Reaman agreed that these studies represent opportunities for Written Requests, both for single agent and combination formulations. He asked the group for any additional thoughts on products for group discussion.

Dr. Donoghue commented on the tiragolumab and atezolizumab overview, noting that there has been a lot of recent development in the non-small cell lung cancer space for a checkpoint inhibitor plus an anti-TIGIT. She appreciated the comments related to the ABI drug and found information on the toxicity profile in children and dose de-escalation informative.

Dr. Reaman commented on selinexor with radiation and a potential opportunity for treatment of newly diagnosed DIPG. Flotetuzemab is also of significant interest in the AML space as part of the PEDAL study that could potentially be conducted as an international program with the European AML group. He noted that tegavivit is also of potential interest and asked the group for feedback on inviting some of the sponsors to present on these drugs.

Dr. Glade-Bender noted that there was a suspension early on in the selinexor trial which precluded researchers from testing the drug in younger patients, and particularly for diseases for which they were very interested like Wilms' tumors and neuroblastoma.

Dr. Reaman responded that BPCA and Written Requests do offer some options, with respect to formulations. If there is, in fact, interest in evaluating this in a pediatric population, and if a pediatric appropriate formulation is feasible, then one of the requirements of the Written Requests is to make that formulation available not only for investigational purposes, but also for commercial purposes, if the results of the planned studies are positive.

Written Requests generally are required to address all potential pediatric indications, so there could be an opportunity to do so via this mechanism. Drugs that are fairly recently approved, with significant patent life, could appropriately incentivize a sponsor.

Dr. Glade-Bender commented that an extemporaneous formulation is now approved, but the approval came too late for this trial. So, it will be available for the DIPG study going forward.

Dr. Reaman then asked Dr. Glade-Bender to comment on the NCI/COG ComboMATCH Program.

NCI ComboMATCH

Dr. Glade-Bender noted that ComboMATCH is the follow-up study to the MATCH trial, testing the premise that combinations are more likely to provide clinical benefit than single agents. The study will also test a hypothesis that the preclinical data from in vivo models can predict clinical

benefit. This is a challenge for pediatrics, because there has been less preclinical testing that meets the appropriate bar of evidence.

ComboMATCH eligibility will be determined by standard of care genetic testing, through the National Cancer Institute (NCI) Clinical Laboratory Network, although centralized patient treatment assignment will be provided by the NCI. Initially, each NCI Clinical Trials Network (NCTN) group was to have its own protocol with two to seven substudies each, but that is still pending at this time.

The preliminary plan was for each study to have a molecularly or histology-defined cohort and to test a drug combination or single agent in multiple cohorts. This was based on the original plan to have multiple master protocols under one larger platform. However, from an operational standpoint, this may not be feasible. The pediatric studies may, in fact, have their own master protocol, more akin to the pediatric NCI MATCH.

Dr. Glade-Bender noted that NCI planned to provide some central support including the Molecular Diagnostics Network and the Precision Medicine Analysis and Coordination Center for treatment assignment. She explained that all trials were to be conducted on the CTEP IND and all agents would be brought in under CRADA. CTEP will provide scientific review of all the studies and the NCI-CIRB will be the IRB of record.

The concept development process is a bit complicated, beginning with the ComboMATCH Agents and Genes Working Group and involving multiple layers of review, including the NCI statistics group, the precision medicine group, and the biomarker group, and the Scientific Council.

For this study, the selection criteria included in vivo evidence of anti-tumor activity in at least two relevant models, with additive or synergistic activity. Activity needed to be analogous to clinical benefit, including not just statistically significant slowing of growth rate, but regressions, as well. Additionally, clinical evidence of tolerability of the combination was required and biomarkers for enrichment needed to be part of Standard of Care genomic sequencing panels.

Dr. Glade-Bender noted that it has been difficult to identify drug combinations that are novel, while also meeting the bar of having sufficient in vivo and clinical evidence. The Mitogen-activated protein kinase (MAPK) pathway is the most common molecular aberration to enroll in pediatrics on the on the MATCH study.

In looking at the adult ComboMATCH, there was some hope of applying some of the studies to pediatrics, but the ones that will be opening soon are for diseases not typically found in pediatrics (e.g., triple negative breast cancer). Dr. Park asked if there could be a specific pediatric arm embedded into the adult trials. Dr. Glade-Bender agreed this is a good idea, but the studies are not yet underway and there is hesitation to add another element that might slow down enrollment. This is something to consider for the future.

Dr. Glade-Bender shared information on a Phase 2 protocol of the combination of a MEK inhibitor selumetinib, with the pan-RAF inhibitor DAY101. This study recently completed accrual, but unfortunately, there was very little activity on the single agent selumetinib. The idea here was that when a MEK is inhibited, the negative feedback is inhibited as well. Preclinical evidence showed that in RAS-mutated rhabdomyosarcoma, the combination of a pan-RAF inhibitor and a MEK inhibitor could induce regression and stable disease.

Dr. Glade-Bender further explained that this study showed clinical evidence for tolerability of selumetinib, from a Phase 2 and low-grade glioma for day 101. The prediction is that the majority of the tolerability issues will be related to skin toxicity. The plan with this trial is to do a safety run using a rolling six design starting at the recommended Phase 2 doses of each of the drugs with one dose reduction. Once a tolerated dose is achieved, the Phase 2 study would have four cohorts: low grade glioma, RAF-altered malignant tumors, RAS-altered malignant tumors, and NF1 malignant tumors.

In response to a participant question, Dr. Glade-Bender clarified that none of these patients will have demonstrated activity to a single agent. She explained that for the molecular or histology cohorts where there has been single agent activity, those arms will be in treatment exposed patients of a single agent. But, for example, for patients with RAS-mutant tumors where there has been no evidence of activity or NF1 Mutant malignancies, those agents will not have to be prior exposed.

Dr. Dunkel asked if those that have pre-exposure to the agent must have progressed on the agent. He asked what would happen if they electively stopped the drug and progressed off of the agent.

Dr. Glade-Bender explained that for the low-grade gliomas, the BRAF V600Es need to have progressed on a BRAF V600E inhibitor. For the fusions, they need to have progressed on a MEK inhibitor, and for a deletion or a deleterious mutation in NF1, they need to have progressed on a on a MEK inhibitor. She clarified that the NF1 strata that is separate is for non-low grade glioma NF deleted tumors, like malignant peripheral nerve sheath tumor, which have not responded to anything.

Dr. Reaman asked if there was commitment from the sponsors for this particular drug. Dr. Glade-Bender confirmed that both AstraZeneca and Day One Biopharmaceuticals were very excited by the idea of this trial.

Dr. Reaman noted that there is no current precedent, at least in oncology, for issuing Written Requests to more than one sponsor, but agreed this is something worth considering, particularly since there are multiple indications that may be addressed here.

Dr. Glade-Bender reiterated that the combinations do not need to be two novel drugs or two biologics. Many of the concepts in adults were combining with chemotherapy. In some cases, there may be only one new agent, combined with a cytotoxin.

Next Scheduled Meeting

Dr. Reaman thanked the group for their participation and adjourned the call. The next meeting will be held February 1, 2022 at 11:00 AM EST.