Best Pharmaceuticals for Children Act (BPCA)
Pediatric Oncology Conference Call
November 7, 2023
11:00 a.m.–12:00 p.m. (EST)

Participants

Amy Barone, M.D.
Diana Bradford, M.D.
Gilbert Burckart, Pharm.D.
Rosane Charlab Orbach, Ph.D.
Martha Donoghue, M.D.
Nicole Drezner, M.D.
Steven DuBois, M.D.
Elizabeth Duke, M.D.
Lori Ehrlich, M.D.
Beth Fox, M.D.
Julia Glade Bender, M.D.
Kamar Godder, M.D.
Lia Gore, M.D.
Doug Hawkins, M.D.
Emily Jen, M.D.
Andy Kolb, M.D.
Margret Merino, M.D.
Julie Park, M.D.
Lauren Price, Pharm.D.
Cara Rabik, M.D., Ph.D.
Nicholas Richardson, M.D.
Marjilla Seddiq, M.D.
Nita Seibel, M.D.
Stacy Shord, Pharm.D.
Sonia Singh, M.D.
Perdita Taylor-Zapata, M.D.
Brenda J Weigel, M.D., M.Sc.
Kristin Wessel, M.D.
Joanna Yi, M.D.

ACCELERATE Paediatric Strategy Forum on Cyclin Dependent Kinase (CDK) Inhibitors in Children and Adolescents–Post Meeting Discussion

The call largely focused on a summary of research presented at the October 23 ACCELERATE Paediatric Strategy Forum on Cyclin Dependent Kinase (CDK) Inhibitors in Children and Adolescents, group member input on this data, and recommendations for future research.

CDK 4/6 Inhibitors

CDK 4/6 inhibitors are highly active in adults, particularly in breast cancer, in combination with hormonal therapy. Similar to the experience in pediatrics, there hasn't been much single agent activity with this class, with the exception of abemaciclib.

Although this class of inhibitors is relevant to pediatrics, there hasn't been much observed dramatic activity with this class of agents, either as a single agent, or in combination with traditional chemotherapy.

There was some discussion surrounding identification of predictive biomarkers for this class of agents, but nothing showing major promise was discussed.

Pediatric preclinical models have predicted cytostatic activity but there are limitations with existing pre-clinical data, in terms of the depth of the models and restriction of the assessment. A more comprehensive multi-omic analysis is recommended to fully elucidate pre-clinically how these CDK 4/6 inhibitors might be beneficial in pediatrics.

CDK 4/6 inhibitors are currently being studied in the ESMART trial (in combination with chemotherapy) and in trials of abemaciclib and ribociclib. Pediatric Written Requests have been issued for palbociclib, abemaciclib, and ribociclib.

Based on the aggregate data presented, Dr. Martha Donoghue noted that it may not be beneficial to initiate new trials of these agents without more compelling pre-clinical or clinical data to support thoughtful integration of CDK 4 inhibitors in pediatrics. It may also be useful for sponsors to consider participating in a pre-submission meeting to discuss potential new pediatric development of CDK 4/6 inhibitors and transcriptional inhibitors.

Dr. Nita Seibel noted that there are a number of irinotecan, temozolomide, and CDK 4/6 inhibitor trials currently in process. She referred to pre-clinical data presented at the meeting by Dr. David Teachey, and asked if more trials might be needed in certain cancers such as malignant peripheral nerve sheath tumors (MPNST), certain subtypes of medulloblastoma, and T-cell hematologic malignancies.

Dr. Donoghue noted that while temozolomide-irinotecan is a common choice, she is uncertain if that is just the backbone that is typically used in this relapse refractory setting. She questioned whether there is compelling data supporting other combinations that may be more fruitful, when combining with a CDK 4/6 inhibitor.

Dr. Brenda Weigel agreed that there is not much data to support additional single agent studies in any indication at this time. She commented on the combination of classic cytotoxic agents and noted that if the pre-clinical data supports it, it might be worth looking at novel-novel combinations with CDK 4/6 inhibitors or novel-immunotherapy combinations. She noted that it is early to consider novel-immunotherapy combinations but this is something potentially of interest, pending additional data.

Dr. Donoghue commented that an example presented at the meeting on trilaciclib was interesting, as it seemed to be protective against hematologic toxicity, rather than necessarily adding synergistic activity. The survival data presented was in a very specific scenario where it was administered along with a short burst of chemotherapy.

Dr. Julia Glade Bender inquired about potentially bringing the FDA, EMA, and sponsors together for a follow up meeting, to enhance coordination and collaboration as new data is acquired. These types of meetings can fit into existing EMA or FDA meeting mechanisms; however, there may be sponsor hesitancy due to concerns regarding disclosure of proprietary information with respect to Written Requests. Sponsors may be more willing to have a combined pre-submission meeting with the EMA since the infrastructure is a bit more transparent. Dr. Donoghue will be meeting with Dominik Karres (EMA) to follow up on the best way to bring people together.

Dr. Joanna Yi referenced Dr. Teachey's presentation of pre-clinical data combined with immunotherapy, suggesting additional laboratory assessments could be added into existing trials to capture immune effects. She noted that there is existing pre-clinical data of this pathway being a key contributor to a lot of cancers, however, it is very easy to develop resistance mechanisms. CDK 4/6 inhibitors work well in hormone-mediated cancers like breast and prostate cancers. The UK Institute of Cancer Research (ICR) is developing a neuroblastoma trial combining cis-retinoic acid (cis-RA) with a CDK 4/6 inhibitor based on interesting pre-clinical data.

Dr. Doug Hawkins reflected on the fact that this is a drug class that is being used to treat breast cancer in combination with hormonal therapy, and wondered if it might not have applicability to other types of cancer. Perhaps cis-RA might be applicable as a targeted therapy, but he is curious if breast cancer is somewhat of an outlier in this sense.

Dr. Hawkins also noted that given the evidence of predominantly cytostatic activity, perhaps the focus should be on areas where there is an incredibly high unmet need, rather than more common pediatric indications. One that stood out in particular is MPNST, for which there are no effective therapies. He suggested looking into novel-novel combination therapies in areas such as this one where there are no effective standard therapies.

Dr. Rosane Charlab-Orbach commented on the lack of known oncologic biomarkers in both adults and pediatrics. There is a need for proteomic and epigenomic data, adding an additional layer of complexity. She also noted that non-clinical data does not always translate to clinical data and identification of a potential biomarker.

Dr. Donoghue noted that while there are limitations to the predictive ability of pre-clinical models translating to what is seen in the clinic, pre-clinical models predicted stable disease, rather than tumor shrinkage. More work is needed, and resources need to be evaluated to determine how they can be applied to pre-clinical work.

In summary, more preclinical work is needed, and it needs to be determined how best to apply resources to the pre-clinical work.

Transcriptional CDK Inhibitors

Dr. Donoghue moved on to address transcriptional CDK inhibitors discussed at the ACCELERATE meeting. Early data was presented for KB-0742, a CDK 9 inhibitor, with clinical responses seen in some rare subtypes of sarcoma. The ITCC-P4 is evaluating this further preclinically in combination with chemotherapy, though data are limited at this point.

Overall, there seems to be excitement with this class, partly because mechanistically it appeared that these might be less toxic and potentially more active in inducing apoptosis in certain types of fusion-driven tumors. The dual inhibition of CDK 2 & 9 with fadraciclib could be synergistic with some early data suggesting potential in temozolomide-resistant neuroblastoma.

CDK 4 selective inhibitors show less potential for heme toxicity, which means that higher levels of exposure are possible, allowing for higher exposures than with other CDK 4/6 inhibitors. More pre-clinical work and exploration needs to be done in pediatrics.

Dr. Glade Bender is also optimistic about potential use of transcriptional CDK inhibitors in pediatrics. She referenced a presentation at the meeting that addressed the pharmacokinetics of the molecule and testing of the MYC hypothesis.

There was also interest in bridging the gap on the adolescent/young adult (AYA) translocation-driven sarcomas relatively early, and work on a pediatric formulation to bring down to MYC-amplified tumors in younger patients (such as MYC-amplified osteosarcoma, medulloblastoma, etc.). There seems to be enough pre-clinical and early clinical data to suggest starting this research. Dr. Bender suggested pediatric in vivo work as a next step. The ITCC-P4 may be currently evaluating KB-0742 in combination with chemotherapy.

Dr. Yi commented that pediatric cancers have few genomic alterations but are transcriptionally deregulated. Kronos Bio is studying KB-0742 in adults and Dr. Charles Lin is interested in its potential use in pediatrics. There is a good understanding of the pharmacokinetic-pharmacodynamic (PKPD) relationship, so that the drug can effectively hit its target, without impacting other cells in the body that also use CDK 9. Kronos is using gene assay panels to evaluate pharmacodynamics and evaluating genes that they believe can be affected.

Dr. Park also opined that there is enthusiasm for studying fadraciclib in pediatric neuroblastoma. Dr. Weigel noted that pre-clinical data presented at the ACCELERATE meeting on fadraciclib (CDK 2 & 9 combination) was impressive, especially in temozolomide-resistant neuroblastoma. There was a lot of data presented in reference to neuroblastoma and other MYC-driven tumors.

Regarding CDK 4/6 inhibitors, Dr. Weigel raised the question of biomarker dose-exposure relationships and selectivity. CDK 4 inhibitors have limited data available, but it might be interesting to look at from a drug development perspective.

Dr. Weigel also noted that for all of these compounds, engaging with partners very early on in the development process would be beneficial. In particular, it is important to involve FDA, EMA,

and the drug development companies as early as possible, before development plans are finalized. Dr. Donoghue described 'Type F' meetings, which occur within 30 days of being requested, which sponsors can request to discuss their initial pediatric study plans with the FDA. It's not common for academia or subject matter experts to join these meetings, but it might be useful for sponsors to involve more people at this early stage.

Dr. Seibel commented that the irinotecan-temozolomide backbone may not be as useful in the future, particularly with a new neuroblastoma protocol being developed, as many patients will receive an extended induction with irinotecan temozolomide. To look at these agents, it would be useful to come up with a way to combine this in a new population of neuroblastoma patients. Dr. Julie Park agreed that this chemotherapy backbone may not be as useful as potential novel-novel combinations. Dr. Glade Bender stated that at the ACCELERATE meeting, someone mentioned that fadraciclib is planned for investigation through the ESMART platform.

Written Requests

Dr. Donoghue shared that the following three Written Requests were issued by FDA in the past two years: ribociclib (2/22); selpercatinib (6/23); and alpelisib (2/23).

HER2-ADCs

The final discussion covered Human Epidermal Growth Factor Receptor 2 Antibody Drug Conjugates (HER2-ADCs). There are a few HER2-ADCs approved in adults, primarily in lung cancer and breast cancer.

Trastuzumab Deruxtecan Findings

Pre-clinical studies of trastuzumab deruxtecan were conducted by the Pediatric Preclinical Testing Consortium (PPTC) which found relatively high HER2 mRNA expression in osteosarcoma, Wilms tumor, malignant rhabdoid tumor, and ependymoma. In osteosarcoma, there is primarily cytoplasmic staining, rather than membranous staining, whereas there was weak to moderate membranous staining from malignant rhabdoid tumor (MRT) and Wilms tumor (WT). In vivo data looked promising with some prolonged event-free survival in six of seven osteosarcoma models, one out of one ATRTs, two out of two extracranial rhabdoid tumors, and three out of three Wilms tumor models. Six out of seven osteosarcoma models showed progressive disease. MRT, ATRT, and WT showed promising prolonged MCRs.

It was noted that although RNA sequence data from xenograft models showed variable/broad expression across tumor types, precisely determining protein expression levels is challenging because HER2 amplification is not the primary event driving protein levels in pediatric tumors. The degree of protein expression did not consistently correlate with RNA expression or response. IHC models may need further optimization and validation across pediatric tumors.

The study shows potential across a wide variety of tumor types, though there remains some uncertainty about the significance of the staining pattern for HER2, with membranous staining being more common in adult tumors compared to cytoplasmic staining in osteosarcoma, in particular. That correlation of response and degree of HER2 expression may not be possible.

Dr. Donoghue asked for the group's feedback on if it is now appropriate to begin studying anti-HER2-ADCs in pediatrics, and if so, which tumor types would be most applicable.

Dr. Steven DuBois asked about a current osteosarcoma trial being done with the Pediatric Early Phase Clinical Trials Network (PEP-CTN). Dr. Seibel noted that the study is complete, but being kept open so additional disease strata can be added. The study completed accrual to the first stage but did not meet criteria to move to the second stage. Dr. Seibel and Dr. Bender noted that while initial response in osteosarcoma might not be encouraging, there remains interest in looking at more rare tumor types where there might be potential for activity, perhaps as a biomarker-driven basket trial. There has been some difficulty obtaining the drugs for study due to supply issues, however. The group universally agreed that there is interest in pursuing this class in some of the rarer tumor types, particularly those for which there is some pre-clinical data and some anecdotal data of response.

Dr. Charlab-Orbach asked about the osteosarcoma study previously discussed, inquiring as to if HER2 was measured in the tumor samples, and what was seen in terms of HER2 expression. Dr. Seibel responded that the one patient who had stabilization of disease had the lowest detection of HER2.

Conclusion

Dr. Donoghue reminded participants to share topics and agenda items for future meetings, along with suggestions on the best ways to encourage early interactions with companies.

The next call will be held February 6, 2024, at 11:00 AM EST.