Summary

Paediatric Strategy Forum for Medicinal Product Development of PI3K, mTOR, AKT and GSK3β Inhibitors in children and adolescents

ACCELERATE in collaboration with the European Medicines Agency
With participation of the Food and Drug Administration

The eleventh multi-stakeholder Paediatric Strategy Forum focussed on targeting the PI3K signalling pathway in paediatric and adolescent cancers with specific discussion of PI3K, mTOR, AKT and GSK3β inhibitors. As this pathway is constitutively activated or up-regulated in many paediatric cancers, it is a potentially important target for the development of new paediatric anti-cancer drugs. However, unique clinical toxicities of targeting this important metabolic pathway with PI3K/AKT/mTOR inhibitors may also occur, particularly when these drugs are combined with chemotherapies. A large array of inhibitors of this pathway have been developed and approved for adult cancers. Some have also received paediatric regulatory approval, although the optimal use of these inhibitors and how best to combine them with other agents commonly used in children is not yet fully understood. Furthermore, despite the large number of inhibitors and the relevance to paediatric cancers, inhibition of these targets has not to date had a major impact for children and adolescents. Moreover, at present only two front-line phase 3 trials have incorporated this class of drugs.

The meeting was held at the Dana-Farber Cancer Institute, Boston, Massachusetts on 3 and 4 April 2023. There were 146 participants, 48 in person, and 98 virtual. To provide a basis for discussion, academic experts first presented an overview of the biology of the pathway, genetic disorders driven by pathway mutations, successful experiences with PI3K / AKT inhibitors in adults, the genomic landscape in children and combination strategies. Potential lessons learnt from mTOR inhibitors were highlighted. Details of nine products inhibiting this pathway were presented by pharmaceutical companies: LOXO-783 (PIK3CA [H1047R]); copanlisib (PI3Kδ/α); navolisib (PI3K); gedatolisib (dual PI3K/mTOR); paxalisib (dual PI3K/mTOR); capivasertib (AKT); ipatasertib (AKT); miransertib (AKT) and 9-ING-41 (GSK3β). The Forum concluded with the patient advocates’ perspective and a multi-stakeholder strategic discussion. The discussion and conclusions focussed on seven main areas: i) the role of the PI3K pathway in paediatric cancer; ii) lessons learnt from the clinical evaluation of mTOR inhibitors; iii) how PI3K, mTOR, AKT and GSK3β inhibitors might fulfil unmet needs in childhood cancer; iv) challenges of PI3K inhibitors; v) identifying specific PI3K/AKT/mTOR inhibitors with the greatest benefit for children; vi) identifying optimal combinations and vii) how these inhibitors should be evaluated in a very rare patient populations.

The same mutations of the PI3K pathway genes occur in children as in adults (p.H1047, p.E545 p.E542), but they are significantly less frequent (11.6% of tumours in adults have PI3KCA mutations compared to 1.9% in children; 2% of cancers in adults have AKT mutations and 0.1% in children). Diffuse midline glioma is the childhood malignancy with the highest frequency of PI3KCA mutations (16-20%).

Everolimus, an mTOR inhibitor, has been approved for subependymal giant cell astrocytomas in patients with tuberous sclerosis complex. Everolimus and temsirolimus have been predominantly evaluated by academia, generally in empiric, mutation-agnostic, uncoordinated clinical trials with 44% of trials involving single centres. To date, almost 60% of these trials have studied mTOR inhibitors in combination with conventional chemotherapy, many without a biological rationale. Response rates to monotherapy (1.8%) and combinations have been very low, in children with relapsed cancers with the exception of those with low grade gliomas. Therefore, future trials of mTOR inhibitors in childhood cancer should not be conducted, unless there is a very strong biological rationale and supportive preclinical data.

Alpelisib, a PI3K alpha isoform inhibitor, has outstanding activity in children and adults with PIK3CA-related overgrowth syndrome and has been approved for this indication. PI3K inhibitors’ greatest potential role in childhood cancer is probably in diffuse midline glioma, where there is the highest frequency of PI3KCA mutations and a very substantial unmet clinical need. However, to date the major
barriers to the clinical translation of these inhibitors in both adults and children are i) limited single-agent activity as the pan PI3K inhibitors target both wild-type and mutant PI3K; ii) the problematic levels of toxicity with high blood glucose; iii) the effects being negated by high insulin levels and iv) central nervous system (CNS) penetration. Overall, this has resulted in very few completed studies in paediatrics and none in combination with other drugs.

With non-mutation specific inhibitors, a ketogenic diet, metformin, or SGLT2 inhibitors should be employed to overcome or prevent high insulin levels. These challenges can be overcome with new PI3K inhibitors which are mutation specific and therefore reduce toxicity from on-target PI3Kα wild-type activity. Paediatric studies should be undertaken with mutation-specific inhibitors in tumours with the relevant mutations.

Outside the very rare occasion where there is a mutation (~0.1%), the role of AKT in paediatric cancers remains unclear. Robust pre-clinical and clinical antitumor activity for GSK3β inhibitors have been reported in paediatric tumours. As these drugs have multiple effects, including immune modulation, further preclinical evaluation is required.

The appropriate combination, including with immunotherapy, must be based on disease biology, preclinical data and resistance mechanisms. Currently, there is a lack of models for evaluation of drugs such as 9-ING that have immunomodulatory activity and this presents a barrier to providing the preclinical rationale that is required to support the development of these immunomodulatory agents.

Advocates strongly agreed that a synergy of agents was necessary when combining novel/novel or novel/standard agent trials to maximize a potentially greater therapeutic impact. Advocates also urged analysing and combining data from every child participating in a clinical trial, including data from both positive and negative trials.

It was concluded that the scenario with the greatest probability of success would be evaluating mutation-specific, CNS-penetrant PI3K inhibitors in children with diffuse midline glioma. In view of the difficulties in the past assessing these inhibitors, investigations should focus on diffuse midline glioma as proof of concept. However, there are substantial challenges in evaluating these inhibitors in such a rare population with many competing trials. The aim should be on hypothesis-driven evidence generation focusing on the most suitable product. Innovative regulatory approaches supporting data generation for an indication, such as through an evolutionary, step wise PIP should be considered. Meaningful data generation through clinical trials, supported by compassionate access / expanded access and collecting and using real-world data could be explored as a means (if meaningful data available) to support innovative regulatory approaches to obtain an indication.