Paediatric Strategy Forum for Medicinal Product Development of Epigenetic Modifiers in children
ACCELERATE in collaboration with the European Medicines Agency
with participation of the Food and Drug Administration
23 and 24 January 2020

Summary

Context: The fifth multi-stakeholder Paediatric Strategy Forum, organised by ACCELERATE in collaboration with the European Medicines Agency (EMA) with participation of the Food and Drug Administration (FDA) was held in Philadelphia and focused on epigenetic modifiers in children and adolescents. As most mutations in paediatric malignancies influence chromatin associated protein or transcription factors and paediatric cancers are driven by developmental gene expression, targeting epigenetics (or chromatin-based control of gene expression) is a very important therapeutic approach in paediatric cancer. The RACE Act in the USA will be implemented in August 2020. As there are many epigenetic targets on the FDA Paediatric Molecular Targets List, paediatric development of epigenetic modifiers should be considered early.

The Forum: The specific aims of the Forum were:- i) to identify epigenetic targets or mechanisms of action relevant to paediatric cancers and ii) to define the landscape for paediatric drug development of epigenetic modifiers. DNA methyltransferase inhibitors/hypomethylating agents and histone deacetylase (HDAC) inhibitors were largely excluded from discussion as the aim was to discuss those targets for which therapeutic agents are early in development.

Seventy two participants (in person) from both North America and Europe (academic experts, patient advocates from Children's Cause for Cancer Advocacy, Coalition Against Childhood Cancer, Alex's Lemonade Stand, KickCancer, Solving Kids' Cancer and the Andrew McDonough B+ Foundation; EMA [including the Paediatric Committee] and FDA regulators) and representatives from 11 biopharmaceutical companies discussed the scientific rationale for the epigenome to be a therapeutic target across all paediatric malignancies

A comprehensive overview of the scientific rationale for epigenetic modifiers in paediatric leukaemia, central nervous system tumours and solid tumours was presented as well as the pharmacological and clinical information on seventeen compounds being developed as epigenetic modifiers.

Conclusions of the Forum: The epigenetic landscape is an evolving field and is highly relevant to many paediatric cancers; the biology is elegant and new targets are emerging constantly. Targeting epigenetics is considered a very important therapeutic approach in paediatric malignancy, which has yet to achieve its full potential, as, many targets do not yet have drugs available. A combination approach is critical for many epigenetic modifiers (e.g. EZH2 and EED) and exploration of the optimum combination should be underpinned by extensive pre-clinical research in advance of clinical translation. The Forum greatly encouraged more extensive pre-clinical research. Eight classes of medicinal products were discussed and prioritised, based on the level of science to support early evaluation in children: menin, DOT1L, EZH2, EED, BET, PRMT5, LSD1 inhibitors and retinoic acid receptor alpha agonists. Menin inhibitors should be moved rapidly into paediatric development, in view of their biological rationale, pre-clinical activity and ability to fulfil an unmet clinical need. A follow up multi-stakeholder meeting focusing on BET inhibitors will be held to define how to prioritise the multiple compounds in clinical development that may need to be evaluated in children and evaluate their specific roles. As epigenetic modifiers are early in development, there is a major opportunity to define the landscape of epigenetic modifiers in order that efficient and optimum plans for their evaluation in children and adolescents are developed. A detailed manuscript describing the conclusions of the Forum is in preparation.

With the kind support of