

30 May 2017
EMA/210027/2017

Report: Paediatric strategy forum for anaplastic lymphoma kinase (ALK) inhibition in paediatric malignancies

30-31 January 2017

Introduction

Today there are rapid developments in the field of oncology medicines with more effective and innovative medicinal products becoming available to treat adult patients. However, children who need new therapeutic options do not easily have access to these innovative drugs. There is a high medical need and major efforts are being made to accelerate new drug development for children and adolescents with cancer. Against this landscape, constructive interactions between relevant stakeholders (patients/patient representatives, clinicians, academics, pharmaceutical companies and regulators) on topics requiring discussion are essential in advancing the best interests of children and adolescents with cancer¹. To fulfil this need, ACCELERATE and the EMA have created a multi-stakeholder Paediatric Strategy Forum.

A Paediatric Strategy Forum is a scientific meeting where information is shared to inform the best strategy to develop drugs in one paediatric cancer indication, or in several paediatric cancers driven by a similar biological pathway. The aim of the Forum is to facilitate potential subsequent decisions to develop and study medicines, thereby expediting the introduction of innovative treatments into the standard-of-care of children with rare cancers and potentially in the future, other paediatric conditions. In a Paediatric Strategy Forum the epidemiology, clinical features, biology and therapeutic needs of patients with a given disease (or multiple relevant disease types with a given molecular target) are reviewed. Pharmaceutical companies are invited to present their pre-clinical data pertaining to paediatric cancers, pharmacokinetic and safety data in adults and any available paediatric clinical data for their relevant compound(s). The output will be a summary from all participants of the topics discussed.

Paediatric Strategy Forum for ALK Inhibition

The first Forum focussed on anaplastic lymphoma kinase (ALK) as ALK is an important oncogene and target in several paediatric tumours (inflammatory myofibroblastic tumour [IMT], anaplastic large cell lymphoma [ALCL], neuroblastoma and rhabdomyosarcoma) with unmet therapeutic needs. However, the genetic alterations differ between the ALK driven malignancies (translocations, copy number gains,

mutations and native protein expression) or even within the same tumour type. There are many ALK inhibitors, however the number of children diagnosed with these ALK driven malignancies is very small. Therefore, the ALK inhibitor with the greatest possible therapeutic benefit and with the most suitable safety profile may vary according to the different malignancy. It is important to identify early in development which of the available ALK inhibitors has the greatest potential to become a new therapeutic option in each of these different malignancies. The challenge is to rationally develop ALK inhibitors in this competitive landscape in order to accelerate the availability of new effective therapeutic options for children and adolescents with ALK driven paediatric cancer.

The first proof-of-concept, innovative and collaborative pilot Paediatric Strategy Forum on ALK inhibition was a success, with representation from European and North American paediatric disease-specific and drug development experts, five pharmaceutical companies, (Ariad, Ignyta, Novartis, Pfizer, and Roche-Genentech), regulators from EU national competent authorities and the EMA (including Paediatric Committee (PDCO), Committee for Medicinal Products for Human Use (CHMP), Committee for Orphan Medicinal Products (COMP) and Scientific Advice Working Party (SAWP) members) and several patient representatives from Unite2Cure. The Forum provided a comprehensive overview of the biology and therapeutic needs with respect to ALK inhibition of paediatric patients with ALCL, IMT, neuroblastoma and rhabdomyosarcoma, and clinical and pharmacological data on six ALK inhibitors (crizotinib, ceritinib, lorlatinib, alectinib, entrectinib and brigatinib) in development.

Anaplastic large cell lymphoma:

Data clearly demonstrates that ALK inhibitors are active in relapsed paediatric ALCL with response rates of 90%. There is an unmet need in relapsed ALCL where ALK inhibitors could play an important role. The consensus of the cooperative groups (Children's Oncology Group [COG] and European Inter-group for Childhood Non-Hodgkin Lymphoma [EICNHL]) and clinicians present at the meeting is that an ALK inhibitor should now be studied in first-line therapy to improve the outcome of paediatric patients. The COG's ANHL12P1 study recruits patients with ALCL to receive crizotinib (in addition to an ALCL99 chemotherapy backbone) and the results are expected to be very informative. In the EICNHL's approach only "high risk" paediatric ALCL patients would receive an ALK inhibitor and clinicians regard the opening of this study as a very high priority. Unfortunately, so far no ALK inhibitor has been selected or agreed for use in this study. The efficacy and safety of long term use of ALK inhibitors is currently unknown and warrants further investigation. The goal of the cooperative groups, after these two trials, is an international collaborative front-line study with foreseeable accrual of 100 paediatric patients per year, as many questions about the best use of ALK inhibitors in ALCL in children remain as yet unanswered.

Inflammatory myofibroblastic tumour:

Presented data indicated that ALK inhibitors are active in recurrent or refractory/unresectable IMT. A meaningful and feasible approach, agreed by clinicians present would be an international clinical trial of ALK inhibition in IMT in children and adults jointly, with integrated study of tumour biology and re-biopsy at time of progression.

Neuroblastoma:

Inhibition of mutant *ALK* in neuroblastoma is complex and challenging. There are major differences between therapeutic targeting of full-length ALK in neuroblastoma and of ALK-fusion proteins in ALCL, IMT and lung cancer. In neuroblastoma, the frequency and type of ALK genomic aberrations differ between presentation and relapse and therefore the therapeutic needs may be different in patients at

presentation compared to relapse. Although, the R1275 mutation is more sensitive to ALK inhibition than F1174, the understanding is that they should be grouped together for therapy at present. Pre-clinical models are very useful in identifying single drugs or combinations to take forward into clinical trials. Combination approaches are being extensively explored to overcome *de novo* resistance in ALK driven neuroblastoma. Based on encouraging clinical data combining chemotherapy and crizotinib, COG is about to evaluate, in a front-line therapy neuroblastoma study, the integration of crizotinib to improve the outcome for patients with ALK mutations (ANBL1531). The International Society of Paediatric Oncology Europe Neuroblastoma Group (SIOPEN) will evaluate in a frontline randomised study the ALK inhibitor or combination that is most promising based on pre-clinical research and early phase clinical studies demonstrating a 50% or more response.

Rhabdomyosarcoma:

It was agreed that based on current evidence rhabdomyosarcoma is not a priority area for evaluation of ALK inhibitors, but the results of existing trials will be informative.

Summary:

ALK inhibitors are active in relapsed paediatric ALCL and recurrent IMT. The overall clinical consensus of the cooperative groups and the clinicians present was that ALK inhibitors should be accessible to children with relapsed ALCL and IMT and there is a need for a European trial in ALCL with an ALK inhibitor and an international trial in IMT with an ALK inhibitor. There are differences in risk/benefit profile between IMT/ALCL and neuroblastoma, as therapy may potentially be of a longer duration in IMT/ALCL. In view of the number of children available for clinical trials and that paediatric studies are already in progress, or will open soon, with four ALK inhibitors (crizotinib, ceritinib, lorlatinib and entrectinib [the latter also as a pan-TRK-inhibitor]), the Forum agreed that additional ALK inhibitors should be moved forward at present into paediatric clinical development only if robust pre-clinical data provide clear utility for paediatric tumours compared with other ALK inhibitors already in paediatric clinical trials.

Comparative, pre-clinical research was demonstrated to be informative, especially if undertaken in the same laboratories and using the same models. The results could inform the selection of a drug for clinical evaluation, for example identifying the comparative activity of available ALK inhibitors in F1174 mutation (a more resistant mutation) in neuroblastoma.

Clinical combination studies, for example CRISP (crizotinib in combination with vinblastine or temsirolimus) and NEPENTHE (NExt generation PErsonalized Neuroblastoma THERapy), with molecular profiling were strongly encouraged by the Forum as these may lead to enriched trials with predictive biomarkers.

General discussion:

There are many benefits of academia sponsoring studies of compounds from different pharma, however academic clinical trials should be designed and managed in order to use clinical trial data for regulatory purposes, and early input should be sought from regulators (through for example PDCO and SAWP). European, US and other international academic clinical cooperative groups should work closely together, by harmonizing clinical studies (e.g. due to low patient number) to accelerate development of new drugs. Global studies in rare populations should ideally be undertaken. Further discussions among stake-holders will be required to achieve this.

Conclusion

The Forum facilitated the sharing of knowledge and evidence to support the planning and regulatory aspects of paediatric drug development in the field of ALK inhibitors; however further discussions are needed to define how to accomplish some of the goals. As the underlying biology of ALCL, IMT and neuroblastoma greatly differs and is complex, it is probable that not all therapeutic needs identified in paediatric tumours are likely to be met with one drug. This pilot Forum demonstrated that the approach taken for the Paediatric Strategy Forums is feasible, can be highly relevant for paediatric cancer drug development and are supported by the participating stakeholders. Future Forums are planned for other relevant oncologic paediatric diseases and targets with a high unmet medical need in order to support the introduction of innovative treatments into the standard care of children with very rare cancers. Their occurrence at an earlier stage in the drug development process could harmonize class and disease specific developments.

ⁱ 1 Pearson AD, Herold R, Rousseau R, Copland C, Bradley-Gareluk B, Binner D, Capdeville R, Caron H, Carleer J, Chesler L, Geoerger B, Kearns P, Marshall LV, Pfister SM, Schleiermacher G, Skolnik J, Spadoni C, Sterba J, van den Berg H, Uttenreuther-Fischer M, Witt O, Norga K, Vassal G; Members of Working Group 1 of the Paediatric Platform of ACCELERATE. Implementation of mechanism of action biology-driven early drug development for children with cancer. Eur J Cancer. 2016; 62:124-31