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Review

Second Paediatric Strategy Forum for anaplastic lymphoma kinase (ALK) inhibition in paediatric malignancies
ACCELERATE in collaboration with the European Medicines Agency with the participation of the Food and Drug Administration

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Abstract The first (2017) and sixth (2021) multistakeholder Paediatric Strategy Forums focused on anaplastic lymphoma kinase (ALK) inhibition in paediatric malignancies. *ALK* is an important oncogene and target in several paediatric tumours (anaplastic large cell lymphoma [ALCL], inflammatory myofibroblastic tumour [IMT], neuroblastoma and hemispheric gliomas in infants and young children) with unmet therapeutic needs. ALK tyrosine kinase inhibitors have been demonstrated to be active both in *ALK* fusion-kinase positive ALCL and IMT. *ALK* alterations differ, with fusions occurring in ALCL, IMT and gliomas, and activating mutations and amplification in neuroblastoma. While there are many ALK inhibitors in development, the number of children diagnosed with ALK driven malignancies is very small.

The objectives of this ALK Forum were to (i) Describe current knowledge of ALK biology in childhood cancers; (ii) Provide an overview of the development of ALK inhibitors for children; (iii) Identify the unmet needs taking into account planned or current ongoing trials; (iv) Conclude how second/third-generation inhibitors could be evaluated and prioritised; (v) Identify lessons learnt from the experience with ALK inhibitors to accelerate the paediatric development of other anti-cancer targeted agents in the new regulatory environments.

There has been progress over the last four years, with more trials of ALK inhibitors opened in paediatrics and more regulatory submissions. In January 2021, the US Food and Drug Administration approved crizotinib for the treatment of paediatric and young adult patients with relapsed or refractory ALCL and there are paediatric investigation plans (PIPs) for brigatinib and for crizotinib in ALCL and IMT.

In ALCL, the current goal is to investigate the inclusion of ALK inhibitors in front-line therapy with the aim of decreasing toxicity with higher/similar efficacy compared to present first-line therapies. For IMT, the focus is to develop a joint prospective trial with one product in children, adolescents and adults, taking advantage of the common biology across the age spectrum. As approximately 50% of IMTs are *ALK*-positive, molecular analysis is required to identify patients to be treated with an ALK inhibitor. For neuroblastoma, crizotinib has not shown robust anti-tumour activity. A focused and sequential development of ALK inhibitors with very good central nervous system (CNS) penetration in CNS tumours with *ALK* fusions should be undertaken.

The Forum reinforced the strong need for global academic collaboration, very early involvement of regulators with studies seeking possible registration and early academia-multicompany engagement. Innovations in study design and conduct and the use of 'real-world data'

supporting development in these rare sub-groups of patients for whom randomised clinical trials are not feasible are important initiatives. A focused and sequenced development strategy, where one product is evaluated first with other products being assessed sequentially, is applicable for ALK inhibitors and other medicinal products in children.

1. Introduction

Paediatric Strategy Forums are multistakeholder scientific meetings where information is shared in a pre-competitive setting to inform the best approach to develop drugs in one paediatric cancer indication or in several paediatric cancers driven by a similar biological pathway. These Forums aim to facilitate potential subsequent clinical investigation strategies to develop medicines and possibly inform regulatory decisions, thereby expediting the introduction of innovative treatments into the standard-of-care of children with rare cancers. Paediatric Strategy Forums [1–4] have been successful in evaluating preclinical and clinical research and providing an opportunity for constructive interactions between relevant stakeholders (patient advocates, clinicians, academic experts, biotechnology/pharmaceutical companies and regulators) on topics early and late in development.

The first Paediatric Strategy Forum in 2017 [5] focused on anaplastic lymphoma kinase (ALK) as *ALK* is an important oncogene and target in several paediatric tumours [6] (inflammatory myofibroblastic tumour [IMT] [7,8], anaplastic large cell lymphoma [ALCL] [9,10], and neuroblastoma [11–14]) with unmet therapeutic needs [5]. However, the genetic alterations differ, with *ALK* fusions occurring in ALCL and IMT and mutations and amplifications in neuroblastoma [6–14]. The proportion of patients with ALCL and IMT with tumours that harbour an *ALK* alteration is high (50–90%), with a lower proportion of neuroblastoma patients with *ALK* alterations (14%). Although there are many ALK inhibitors in development, the absolute number of children diagnosed with these *ALK* driven malignancies is very small, even when the frequency of *ALK* in that disease is relatively high (e.g. ALCL). Relapsed neuroblastomas have an increased mutation burden, including in the ALK-RAS-MAPK pathways, suggesting that *ALK* mutations may exist as subclonal populations at diagnosis that subsequently drive disease resistance and relapse [15–17]. The rarity of IMT compounded by fusions involving kinases other than ALK (e.g., ROS1, NTRK, RET and PDGFRB [7,18–21]) presents a further challenge. The ability to target the full-length *ALK* mutant proteins expressed in neuroblastoma tumours is more challenging than *ALK*-fusion proteins (ALCL/IMT), and the relative sensitivity to pharmacologic ALK inhibition differs significantly between these disease entities (ALCL/IMT compared to neuroblastoma) [22]. Furthermore, some entities require central nervous system (CNS) penetration of the drug. In this context, the ALK inhibitor with the highest level of effectiveness and with the most suitable safety profile may vary according to the target disease indication. It is important to identify early in development the available ALK inhibitors that may have the greatest potential to become a new therapeutic option in genomically characterised subsets of each of these different malignancies. The challenge is to rationally and efficiently develop ALK inhibitors for several diseases with differing needs in this competitive landscape in order to accelerate the availability of the most effective new therapeutic options for children and adolescents with an ALK driven paediatric cancer.

In the four years since the first Forum on ALK inhibition, the landscape of ALK inhibitors had evolved, and it was, therefore, considered timely to hold a second multistakeholder Paediatric Strategy Forum on ALK in 2021.

The objectives of this second Forum were to (i) Describe current knowledge of ALK biology in childhood cancers; (ii) Provide an overview the development of ALK inhibitors for children; (iii) Identify the unmet needs with planned or current ongoing trials; (iv) Discuss how second/third-generation inhibitors could be evaluated sequentially and prioritised if appropriate; (v) Identify lessons learnt from the experience with ALK inhibitors to accelerate the paediatric development of other anti-cancer targeted agents in the new regulatory environments. The latter two objectives are also relevant to other medicinal products with a very small target population. Given the limited number of paediatric patients with *ALK* driven malignancies, the evaluation and prioritisation of second/third-generation products are particularly relevant. Further, the Research to Accelerate Cures and Equity (RACE) for Children Act and the FDARA amendments to section 505B of the FD&C Act were implemented in the USA in August 2020, which mandates that an original new drug application for an ALK inhibitor contain a report of a molecularly targeted paediatric cancer investigation due to the relevance of ALK in paediatric cancers unless a deferral or waiver is granted [23]. The ongoing evaluation by the European Union on both the paediatric and

orphan regulations [24] and the recent European Pharmaceutical Strategy [25] will potentially further enhance the regulatory environment in Europe.

The second Paediatric Strategy Forum on ALK inhibition was organised by ACCELERATE, in collaboration with the European Medicines Agency (EMA), with the participation of the Food and Drug Administration (FDA). It was held virtually on 14 and 15 January 2021, with 78 participants: 38 international academic experts; 19 representatives from 5 companies (Pfizer, Roche/Genentech, Takeda, Turning Point Therapeutics and Xcovery); 7 patient advocates (representatives from Andrew McDonough B + Positive Foundation, Children's Cancer Cause, Coalition Against Childhood Cancer, Imagine for Margo, KidsvCancer, Solving Kids' Cancer UK, and Zoé4life); 11 regulators from the FDA and EMA as observers and three organisers. The Forum included an overview of medicinal products discussed in 2017 plus two additional products, followed by presentations of the current status of ALK inhibitors and unmet needs in ALCL, IMT, neuroblastoma and CNS tumours (an emergent area of relevance since the 2017 meeting), concluding with a strategic discussion and patient advocate perspective.

2. Conclusions of the first Paediatric Strategy Forum in 2017

The Paediatric Strategy Forum in 2017 concluded that *ALK* is an important oncogenic driver in ALCL [9,10], IMT [7,8] and neuroblastoma [11–14]. It was also agreed that, based on the evidence available at the time, rhabdomyosarcoma was not a high priority area for the evaluation of ALK inhibitors [26]. At that time, ALK tyrosine kinase inhibitors had been clearly demonstrated to be active both in ALCL and IMT[27,28] based on published data, although no agents had been yet approved for these indications. The overall consensus of academia, patient advocates and industry representatives present was that ALK inhibitors should be accessible to children with relapsed ALCL and IMT. Due to the molecular differences between IMT/ALCL and neuroblastoma [29], it was agreed that different medicinal products may produce optimal activity in the different disease entities (Fig. 1). Studies were already in progress, or were soon to open, with four ALK inhibitors (crizotinib [30,31], ceritinib [32], lorlatinib [33] and entrectinib [34,35] [the latter also as a pan- TRK/ROS1 -inhibitor]); the findings of some of these trials have since been presented or published and confirmed initial findings. The different effect of ALK inhibitors in ALK mutant proteins expressed in neuroblastoma compared to ALK-fusion proteins (ALCL/IMT) has been demonstrated by the different objective response rates (ORR) observed. Crizotinib resulted in an ORR of 90% and 86 for ALCL and IMT, respectively [30] in contrast to 15% for neuroblastoma [36]. Similarly, for ceritinib, there is an ORR of 75% and 70% for ALCL and IMT, in contrast to 20% for neuroblastoma [32].

Comparative, preclinical research was demonstrated to be informative, especially if undertaken in the same laboratories and using the same models, and verification and validation of findings independently were important. It was proposed that the results of this research could inform the selection of a drug for clinical evaluation, for example, identifying the comparative activity of available ALK inhibitors in neuroblastoma harbouring the ALK F1174L gain of function mutation (which confers resistance to ALK inhibition). There were encouraging preclinical results demonstrating the activity of lorlatinib against *ALK* mutant proteins in neuroblastoma in 2017 [37,38]. Clinical combination studies, for example, CRISP (crizotinib in combination with vinblastine in ALCL or temsirolimus in neuroblastoma and rhabdomyosarcoma) [39] and NEPENTHE (NExt generation PErsonalised Neuroblastoma THErapy) [40], with molecular profiling were strongly encouraged by the Forum as these may lead to enriched trials with predictive biomarkers. There were no agreed paediatric investigation plans (PIPs) for ALK inhibitors at that time, and the academic, industry and patient advocate participants of the Forum strongly recommended that data for crizotinib in ALCL and IMT should be filed for regulatory purposes.

Since the first Forum targeting ALK, many other approaches in addition to ALK tyrosine kinase inhibitors has been explored. As ALK protein is expressed on the surface of the majority of neuroblastoma cells, with or without germline or somatic ALK mutations, but not on normal tissue, this provides an opportunity to target ALK by an immunological approach [41]. The description of the ALK ligand [42,43,44] may have an impact on ALK expression and activation and these approaches. Both CAR T-cells targeting ALK [45] and more recently an antibody-drug conjugate directed (ADC) to ALK [46] have been developed and investigated preclinically.

3. Current status of ALK inhibitors, unmet needs in 2021 and future directions

3.1. Anaplastic large cell lymphoma (ALCL)

Current status: In North America, Japan, Australia and Europe combined, each year, there are approximately 150 paediatric patients with newly diagnosed ALCL, of whom approximately 5–6 have CNS involvement, and 40–50 patients relapse. A variety of different intensive chemotherapy approaches result in a 5-year event free survival (EFS) of 65–75% [46–54]. The results of the Children's Oncology Group (COG) trial (ANHL12P1), which evaluates the efficacy of crizotinib and

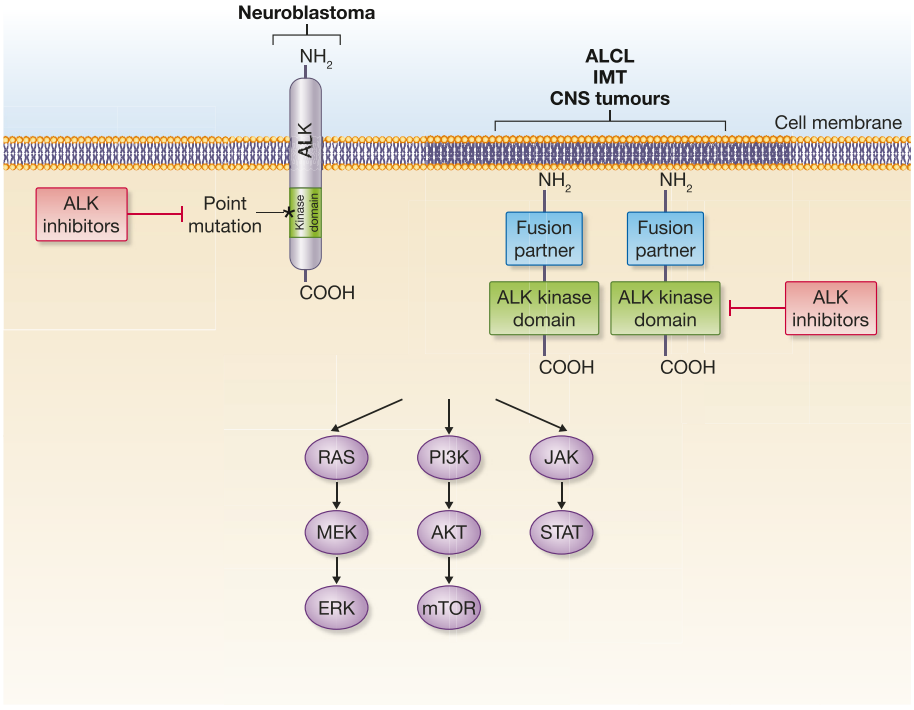

Fig. 1. Mechanism of action and downstream changes in the signalling of ALK inhibition.

brentuximab vedotin when each is individually combined with chemotherapy at diagnosis, are becoming available [55,56]. Multimodality relapse strategies with consolidation using allogeneic haematopoietic stem cell transplantation for most patients are effective, resulting in 5-year post-relapse survival of >50% and overall survival (OS) of 77% [57–59]. Monotherapy with ALK inhibitors in relapse is effective and reaches 70–90% response rates with manageable toxicity [28–32,60–62]. However, there is concern about disease recurrence after stopping monotherapy [63] (albeit the published data is in case reports) and the possible need for long-term/lifelong therapy. Therefore, potential long-term toxicity assumes even greater importance. It is unknown if resistance will eventually develop. Crizotinib was recently approved (January 2021) in the US by the FDA for the treatment of paediatric patients one year of age and older and young adults with relapsed or refractory systemic ALCL. Brigatinib is in the process of being evaluated in a clinical trial in relapsed and refractory ALCL. Crizotinib is also being evaluated in combination with vinblastine for patients with ALCL in the academic-sponsored Innovative Therapies for Children with Cancer (ITCC) - CRISP study [38]. It remains to be seen whether such a combination will be tolerable or not.

Future directions: An important question to be addressed is whether patients with newly-diagnosed ALCL can be cured by ALK-inhibitors given for a limited time. The current goal is to investigate the inclusion of ALK inhibitors in front-line therapy with the aim of decreasing toxicity with higher/similar efficacy compared to present first-line therapies. With an effective relapse strategy, ALCL is an ideal malignancy to change the paradigm for a targeted agent to become the cornerstone of front-line therapy. Relatively small, well-coordinated pilot studies moving ALK inhibitors to front-line with major cooperation between industry, cooperative groups and regulators are required. COG is considering amending its ongoing ANHL12P1 front-line clinical trial to evaluate brentuximab vedotin in combination with an ALK inhibitor [56]. Evaluating single drug ALK inhibitors or the combination of an ALK inhibitor with a less toxic chemotherapy regimen addresses the question of whether it is possible that therapy with an ALK inhibitor may not require an extended period of administration. A strategy to switch ALK inhibitors may be needed if resistance develops; hence, the development of assays that will detect minimal residual disease or emerging resistance is integral to these efforts. Possible long-term side-effects in developing children will be particularly important to capture, especially if continued therapy is required. The academic, industry and patient representatives concluded that currently, there is no need for additional ALK kinase inhibitors clinical studies for the treatment of ALCL in children. However, the risk of CNS recurrence requires the evaluation of an ALK inhibitor with good CNS penetrançe which may lead to increased CNS disease control, as well as increased risk for CNS-related toxicities. In this respect, other ALK inhibitors (alectinib, brigatinib and lorlatinib) have better CNS

penetration than crizotinib [64–66]. Trial designs need to acknowledge the low patient numbers and the existing well-known historical data on outcome with chemotherapy [46,47,49–54], which is consistent over time.

3.2. Inflammatory myofibroblastic tumour (IMT)

Current status: ALK inhibitors have been demonstrated to be active in IMT [28,30–32,67,68], a disease for which there is no known curative therapy unless the tumour can be widely resected. The biology of IMT is heterogeneous, including several alternative different gene-fusions [7,8,19–21]; however, investigations to date demonstrate that the biology of IMTs in adult and paediatric patients is superimposable [7,8,19–21]. Approximately half of IMTs harbour *ALK* rearrangement [7]. It is possible that in newly diagnosed localised diseases, long-term therapy is not required, especially after macroscopic complete resection following response to ALK inhibition [68]. However, in unresectable or metastatic disease, this paradigm is likely to be different. There is still uncertainty on the optimal duration of therapy. Additional data on the natural history of the disease and the effect of chemotherapy has been generated over the last four years [69,70]. However, the major deficit in knowledge arises because very small numbers of patients have been enrolled in multiple trials with small separate data sets, and there are concerns about drug approval and access to ALK inhibitors for patients with IMTs.

Future directions: The key challenge is to overcome the inclusion of a very small number of patients in multiple different trials. There is a need for a global approach; access to ALK inhibitors and the development and regulatory pathway for IMT should include children, adolescents and adults. The focus should be on a joint prospective trial with one product (with the largest amount of high-quality data and robust response data as there are no known major differences in efficacy or toxicity in this setting) developed in children, adolescents and adults, taking advantage of the common biology across the age spectrum. Other products should be evaluated sequentially, as warranted. A systematic review of existing literature, collection of previously accumulated data from past clinical trials into a common database, and a prospective plan for registry collection may be undertaken. As approximately 50% of IMT are *ALK*-positive [7,18–20] molecular analysis is required to identify patients to be treated with an ALK inhibitor at initial presentation and to identify other targetable fusions, including ROS, NTRK, RET and PDGFRB. Preclinically brentuximab vedotin, targeting CD30, has single-agent activity in epithelioid inflammatory myofibroblastic sarcoma (eIMS). These tumours have an *ALK* fusion (mostly ALK-RANBP2 fusion) in a very high percentage of cases and very aggressive behaviour with a high risk of relapse [71–73]. Furthermore, the combination of crizotinib and brentuximab vedotin is more active in eIMS than the single agents, supporting the future development of this and other combinations clinically [74]. FDG-PET imaging may play an important role in monitoring the response to therapy and surveillance of these patients [30]. The ongoing efforts to obtain regulatory approval for an ALK inhibitor in IMT were strongly encouraged.

3.3. Neuroblastoma

Current status: Activating ALK mutations and amplifications are detected in approximately 10% and 4.5% of neuroblastoma tumours, respectively, at the time of diagnosis. In both a retrospective COG study and a prospective International Society of Paediatric Oncology European Neuroblastoma Group (SIOPEN) trial, ALK alterations correlate with inferior survival [29,40,75]. There is a limited response to monotherapy with the first-generation ALK inhibitor crizotinib in relapse [27,32,76], but the response rate is higher in preclinical models when combined with chemotherapy [77]. The effect of crizotinib combined with chemotherapy is currently being studied in patients with newly diagnosed high-risk neuroblastoma with tumours harbouring *ALK* activating mutations or amplifications in a COG trial - ANBL1531 [77]. In comparison to the first-generation ALK inhibitor crizotinib, lorlatinib is more potent and has a broader spectrum of effectiveness across neuroblastoma *ALK* mutant proteins, including the crizotinib-resistant F1174L and F1245 hotspot mutations [36,37] and has CNS penetrance. In addition, preliminary data from a New Approaches to Neuroblastoma Therapy (NANT) consortium Phase I trial demonstrates that lorlatinib is tolerable, alone and in combination with chemotherapy (cyclophosphamide and topotecan), and has evidence of activity in neuroblastoma [33,36,37]. In this trial, the neurocognitive toxicities observed in adults were not seen in younger children, despite delivering doses above the FDA approved adult dose. A transatlantic (COG and SIOPEN) front-line collaboration evaluating lorlatinib combined with chemotherapy (TITAN- Transatlantic Integration Targeting ALK in Neuroblastoma) for this very rare population is in the advanced stages of planning and will be implemented in 2021 [78,79]. This is underpinned by extensive, transatlantic, correlative biomarker analyses. The different backbone chemotherapies and the choice of appropriate controls are some of the challenges facing this approach.

Future directions: The efficacy and safety of lorlatinib need to be determined in front-line patients with *ALK* aberrations in combination with chemotherapy. The clinical significance of sub-clonal mutations and the emergence of potential varying mechanisms of resistance requires further investigation, and this will be a

component of the TITAN initiative [15–17,78,79]. Studies are also ongoing to detect ALK variants in ctDNA and to evaluate the possible emergence of resistant clones in case of secondary resistance [80]. A clear therapeutic strategy, including combinations and ALK-immunotherapeutics [45] for patients who relapse on lorlatinib is needed to form the basis of future therapies.

3.4. CNS tumours

Current status: Several gene fusions involving *ALK* fusions are present in hemispheric gliomas in infants and young children [81,82]. Although the outcome of patients with these tumours is favourable with current therapies, there is an unmet need to avoid both extensive surgery and irradiation in vulnerable young patients. It is critical that timely genomic/transcriptomic assessment of infant tumours with assays capable of detecting *ALK* fusions be performed, and therefore, access to diagnostics is essential. It is estimated that approximately 40–60 paediatric patients are diagnosed each year with these tumours in Europe and North America; however, this number is uncertain due to the currently insufficient implementation of upfront genomic assessments that detect the numerous different fusion transcripts that have been reported. A clinical trial with alectinib (second-generation ALK inhibitor) is being opened in Europe and North America for *ALK*-fusion solid tumours, including CNS tumours. The primary goal is to rapidly determine the efficacy of this approach and to evaluate whether resistance develops, and if so, its mechanism. Second and third line ALK inhibitors have increased CNS penetration compared to first-generation compounds, which provides an important opportunity to evaluate this treatment in CNS tumours with ALK fusions. There is a concern about the extreme rarity of this condition to support the conduct of multiple trials. The intent to obtain regulatory approval for an ALK inhibitor in paediatric CNS tumours should be part of the development plan.

Future directions: Diagnostic sequencing, using techniques that will detect fusions such as whole-genome sequencing, RNA sequencing or specific assays of CNS tumours in infants and young children, is key since *ALK* fusion partners and breakpoints vary [81,82]. The academic, industry and patient representatives concluded that to overcome the concern about very few patients in multiple trials, a focused and sequential development of ALK inhibitors in CNS tumours with *ALK* fusions should be adopted, giving priority to inhibitors with high CNS penetrance. In this approach there should be agreement by all involved stakeholders (industry, patient advocates and academia) based on scientific arguments and on current evidence to identify the product that is considered to have the highest potential to address unmet medical needs. The sequence in which other available (or emerging) products should be developed or deferred should be agreed upon, based on considerations of their potential to address unmet medical needs, so that as soon as a development of one ALK inhibitor is completed (either due to futility or efficacy), another ALK inhibitor has been identified as ready and prepared for evaluation. Engagement with regulatory agencies in a consolidated effort early in development is critical and international cooperation is mandatory. The challenge of evaluating innovative medicinal products in very small populations where patients are scattered among numerous institutions was also highlighted as an issue requiring new approaches. If ALK inhibitors are demonstrated to be active, their role in front-line therapy of infants or young children with hemispheric gliomas with ALK-fusions should be rapidly evaluated.

3.5. ALK inhibitors discussed at the forum

Crizotinib, lorlatinib, brigatinib, alectinib, entrectinib, ceritinib, ensartinib, repotrectinib and TPX-0131 were discussed at the meeting. Ensartinib is a second-generation ALK and ROS1 tyrosine kinase inhibitor with demonstrated activity against ALK, ROS1 fusions, and preclinical efficacy in tumours harbouring common neuroblastoma ALK missense mutations (including the crizotinib resistant F1174L). It has good CNS penetrance and exhibits a differentiated tyrosine kinase inhibitor profile from alectinib and brigatinib [83]. TPX-0131, is a next-generation ALK inhibitor and is a compact macrocycle, which exerts activity preclinically against a broad spectrum of acquired and resistant mutations in non-small cell lung cancer. The current status of ALK inhibitors in clinical development is summarised in Tables 1 and 2.

4. Discussion

There has been progress over the last four years, with more trials of ALK inhibitors opened in paediatrics and more regulatory submissions. Crizotinib has been approved for paediatric patients with relapsed or refractory ALK-fusion positive ALCL by the FDA, and there are PIPs for brigatinib and crizotinib in ALCL and IMT. However, ten years elapsed between the FDA approval of crizotinib for lung cancer in 2011 and the highly relevant FDA approval for crizotinib for ALCL in 2021. This delay was not due to substantially different toxicity and safety profile in children compared to adults, but a result of drug development in children being driven by the adult indication and not, at that stage, a mechanism of action approach. Crizotinib is also being studied in front-line neuroblastoma; however, lorlatinib is more potent and has a broader spectrum of effectiveness across neuroblastoma *ALK* mutant

Table 1
Current status of ALK inhibitors in clinical development.

Product	Paediatric Phase I	ALCL	IMT	Neuroblastoma	CNS tumours	PIP	Comments
Crizotinib	[d]	[d]	[d]	[d]		[a,b]	CRISP study crizotinib and temsirolimus in neuroblastoma and crizotinib and vinblastine in ALCL
Lorlatinib	[d]			[d]			
Brigatinib	[e]	[e]	[e]			[d]	
Alectinib	[d]		[d]		Fusion only	[e]	
Ensartinib	[d]	[d]	[d]	[d]	[d]		
Repotrectinib	[d,c]						Initially ALK, ROS1, or NTRK1-3. Primary focus is now in ROS1 and NTRK1-3
Entrectinib	[f]	[f]	[f]	[f]	[f]	[f]	Focus on NTRK/ROS1
Ceritinib	[f]	[f]	[f]	[f]			No further planned paediatric development

[a] Approved in relapsed or refractory ALCL by FDA.
[b] PIP ALCL &IMT.
[c] Phase 2 ongoing for subjects 12 years and older; X no longer in development for paediatric ALK alterations.
[d] Completed or ongoing.
[e] Planned.
[f] No longer in development for paediatric ALK alterations.

proteins and will be evaluated in front-line trials in neuroblastoma. A trial with alectinib in *ALK*-fusion CNS tumours is opening, and a trial of brigatinib in ALCL and IMT is in the later stages of planning. ALK inhibitors may also fulfil an unmet need in children in a spectrum of rare tumours where *ALK*-rearrangement has been identified, e.g. juvenile myelomonocytic leukaemia, acute myeloid leukaemia, large B cell lymphoma, medullary thyroid cancer [84–88]. It is increasingly likely that such tumours will be identified with increased access to broad-scale diagnostic genomic and RNA-based analyses and that *ALK*-rearrangements may also be found in other tumours. In the future, these rare tumours will need to be studied in molecularly driven disease agnostic platform clinical trials.

There are issues with ALK inhibitors that are applicable to the development of other medicinal products in very small paediatric populations: (i) very small patient numbers in multiple trials result in a challenge to complete these trials and gain regulatory approval in a meaningful timescale; (ii) complexity regarding how and when second/third-generation products should be evaluated and prioritised; (iii) the importance of rigorous preclinical investigation and translating these findings into clinical trials; (iv) accelerating the time from early to late-phase clinical trials; (v) evaluating combination therapies earlier; (vi) lack of clarity regarding how real-world evidence can be used when randomised pivotal studies are not possible to provide comparator/control data.

Challenges that remain for the development of ALK inhibitors in paediatrics include how to most effectively combine these products with other therapeutic agents and establish their role in the standard of care therapy. Addressing these challenges will rely on close global interaction between all stakeholders.

As with all innovative medicines for malignancies, which occur in young children, the development of oral formulations of the medicinal product that can be administered to children (e.g. granules, mini-tablets, suspensions or liquid formulations) is also critical.

A systematic approach to comprehensively molecularly profile paediatric tumours will identify those patients who could benefit from therapy with ALK inhibitors and other targeted medicinal products. Basket trials such as the COG-NCI Paediatric MATCH [89] are informative approaches to obtain preliminary data about new products in a variety of tumour types with specific molecular and genetic alterations and histology-agnostic treatment strategies.

Acute and long-term toxicity: The acute toxicity profile of ALK inhibitors in current development appears to be acceptable; lung toxicity with brigatinib, hepatic toxicity with ceritinib, the potential for increased rate of thrombotic events for some ALK inhibitors when combined with intensive chemotherapy regimens used for ALCL [90], and CNS effects, including neurocognitive adverse events possible with lorlatinib and in children with CNS tumours, need to be continually reviewed. If there is a need for chronic administration, then, in addition, potential long-term effects (ocular toxicity and endocrine issues) will need to be addressed. CNS toxicities particularly require close evaluation for ALK inhibitors with greater CNS penetrance. Given the young age of many patients, especially those with ALK-

Table 2
ALK inhibitors discussed at the Second Paediatric Strategy Forum 2021.

Product	Company	Ongoing paediatric trials
Crizotinib	Pfizer	• ITCC-053: A phase 1B of crizotinib either in combination or as single agent in pediatric patients with ALK, ROS1 or MET positive malignancies (CRISP) (EUDRACT 2015-005437-53) • ANHL12P1: A Randomized Phase 2 Trial of Brentuximab Vedotin or Crizotinib in Combination with Chemotherapy for Newly Diagnosed Patients with ALCL (NCT01979536)[a] • ANBL1531: A Phase 3 Study of ^{131}I-Metaiodobenzylguanidine (^{131}I-MIBG) or Crizotinib Added to Intensive Therapy for Children with Newly Diagnosed High-Risk Neuroblastoma (NCT03126916)[b]
Lorlatinib	Pfizer	• NANT 2015-02: A Phase 1 Study of Lorlatinib, an Oral Small Molecule Inhibitor of ALK/ROS1, for Patients with ALK-driven Relapsed or Refractory Neuroblastoma (NCT03107988) • ANBL1531:A Phase 3 Study of ^{131}I-Metaiodobenzylguanidine (^{131}I-MIBG) or ALK Inhibitor Therapy Added to Intensive Therapy for Children with Newly Diagnosed High-Risk Neuroblastoma (NCT03126916)[b] • HR-NBL2: High-Risk Neuroblastoma Study 2 of SIOP-Europe-Neuroblastoma (SIOPEN) (NCT04221035)[c] • B7461036: Real World Data Collection Pediatric Neuroblastoma Treated With Lorlatinib (NCT04753658)
Brigatinib	Takeda	• An Open-Label, Phase 1/2 Dose Escalation and Expansion Trial to Evaluate Pharmacokinetics, Safety, and Efficacy of Brigatinib as Monotherapy in Pediatric and Young Adult Patients with ALK+ Anaplastic Large Cell Lymphoma (ALCL), Inflammatory Myofibroblastic Tumors (IMT) or Other Solid Tumors[d]
Alectinib	Roche/ Genentech	• Phase 1/2, open-label, multicenter study evaluating the safety, PK and efficacy of alectinib in pediatric patients with ALK fusion-positive solid or CNS tumors from whom prior treatment has proved to be ineffective or from whom there is no curative standard treatment available (NCT04774718)
Entrectinib	Roche/ Genentech	• Study Of Entrectinib (Rxdx-101) in Children and Adolescents With Locally Advanced Or Metastatic Solid Or Primary CNS Tumors And/Or Who Have No Satisfactory Treatment Options (STARTRK-NG)(NCT02650401)
Ceritinib	Novartis	None
Ensartinib	Xcovery	• Pediatric NCI-COG MATCH trial: Phase 2 subprotocol of Ensartinib in pediatric and young adult patients with tumors harboring ALK or ROS1 genomic alterations (NCT03155620)
Repotrectinib	Turning Point Therapeutics	• CARE: A Study of Repotrectinib in Pediatric and Young Adult Subjects Harboring ALK, ROS1, OR NTRK1-3 Alterations (NCT04094610) - Focus - ROS1 or NTRK1-3
TPX-0131	Turning Point Therapeutics	Preclinical[e]

[a] Crizotinib arm is closed to enrolment.
[b] Ongoing, future amendment planned to change crizotinib to lorlatinib.
[c] Ongoing, future amendment planned to include lorlatinib.
[d] Planned.
[e] FORGE-1: A Study of TPX-0131, a Novel Oral ALK Tyrosine Kinase Inhibitor, in Patients With ALK+ Advanced or Metastatic NSCLC. (NCT04849273) in adults only.

aberrant neuroblastoma and gliomas, neurocognitive development will need to be monitored. Acute and long-term toxicity are important elements in the decision-making process. There is thus a need for a global, co-ordinated and effective prospective collection of data on long-term side-effects and ACCELERATE as a Working Group addressing this issue [91].

4.1. Issues applicable beyond ALK inhibition

Real-World Evidence: Randomised clinical trials should always be undertaken, if possible, to obtain evidence to determine new standards of therapy. In very rare subgroups where randomised pivotal studies are not possible, for example, evaluating the role of ALK inhibitors in CNS tumours, IMT, and neuroblastoma, real-world evidence (provided through different mechanisms, including registries and other real-world data sources that have patient-level data) may in the future support development strategies, including characterising the natural history of the disease. There are methodological concerns with pooling data from different sources because there may be important differences with respect to processes for data capture, variable definition and temporality that make pooling inadvisable. Therefore, the use of real-world evidence as an external control requires that the data be reliable and fit-for-purpose and that the risk of bias be adequately mitigated such that iterative, close interaction between relevant stakeholders with appropriate expertise is needed for successful implementation of this approach. There is an ACCELERATE Working Group on this topic [92].

Companion diagnostics: The opinion of academics, patient advocates and representatives from industry was

Text box of key conclusions of the Paediatric Strategy Forum

- *ALK* is an important oncogene and target in several paediatric tumours (IMT, ALCL, and a subset of neuroblastomas and hemispheric gliomas in infants and young children).
- ALK inhibitors have been clearly demonstrated to be active both in ALCL and IMT.
- Genetic alterations differ with *ALK* fusions occurring in ALCL, IMT and gliomas, and missense mutations and amplifications in neuroblastoma.
- The number of children diagnosed with these ALK driven malignancies is very small.
- Crizotinib is now approved in the US and brigatinib is in the process of being evaluated in a clinical trial, for children with relapsed or refractory ALCL. At present, there is no need for additional ALK kinase inhibitors for ALCL as the current evidence indicates that newer inhibitors offer no therapeutic benefit to children, compared to established ALK inhibitors.
- Acute and long-term toxicity are important elements in the decision-making process.
- The risk of CNS recurrence in ALCL requires the evaluation of an ALK inhibitor with good CNS penetrance
- Approximately 50% of IMT are *ALK*-positive and there are several different gene-fusions, however the biology of IMTs in adult and paediatric patients is the same.
- The focus should be on a joint prospective trial in IMT with one product developed in children, adolescents and adults, taking advantage of the common biology across the age spectrum. Other products should be evaluated sequentially.
- *ALK* mutations (~10%) and amplifications (~4.5%) in high-risk neuroblastoma confer a poor outcome.
- In relapsed neuroblastoma there is limited response to monotherapy with first generation ALK inhibitors.
- In comparison to first generation ALK inhibitors lorlatinib is more potent with a broader spectrum of effectiveness across neuroblastoma ALK mutant proteins that are resistant to first generation inhibitors, and it is tolerable and has demonstrated activity in neuroblastoma
- The efficacy and toxicity of lorlatinib in combination with chemotherapy needs to be determined in front-line protocols for patients with neuroblastoma with *ALK* aberration
- Diagnostic sequencing at first presentation of CNS tumours in infants and young children is required to detect *ALK* fusion.
- A focused and sequential development of ALK inhibitors in CNS tumours with *ALK* fusions should be adopted and inhibitors with the highest potential to address unmet medical needs given priority. The sequence in which other available products should be developed or deferred should be agreed, so that as soon as a development is completed (either due to futility or efficacy) others are already prepared for evaluation
- There needs to be a process established for 'living prioritisation' for prioritisation of ALK inhibitors
- Global academic collaboration, very early involvement of regulators with studies seeking registration, early academia-multi company–patient advocacy engagement, agreement for sequenced development efforts and registry set-ups for collection of 'real world data' supporting development efforts are critical factors.
- Simultaneous coordinated PIP/iPSP submissions to the EMA and FDA requesting discussion at paediatric cluster calls and a Common Commentary are strongly recommended.

that specific companion diagnostics should not be mandated to accelerate the introduction of innovative medicines into standard practice. Instead, the expansion of precision oncology programs in paediatric oncology, including comprehensive DNA and RNA sequencing, will help to rapidly identify therapeutically targetable tumour genetic alterations, including *ALK* alterations, and avoid the inefficiencies and expense of serial single-gene testing. Furthermore, sample collections such as circulating tumour DNA from plasma should be strongly encouraged to enable sequential analyses under targeted therapies [80,93,94].

Evaluation and prioritisation of second/third-generation products: Second/third-generation products should be evaluated and prioritised if needs are not currently met, e.g. there is a need for: (i) a more efficacious medicinal product; (ii) an inhibitor with better CNS penetration if required; (iii) an inhibitor with less toxicity; (iv) an inhibitor that can be combined with other products.; (v) age-appropriate paediatric formulation. This is a dynamic and living multistakeholder process, which requires ongoing evaluation; for example, if a resistance mechanism is identified or a condition is associated with *de novo* resistance mutations (e.g., in neuroblastoma, there may be indications for a second-/third-generation product or combination based on preclinical studies). The sequence in which other available (or emerging) products should be developed or deferred could be agreed upon and/or discussed in real-time as data is generated, so that as soon as development for one ALK inhibitor in a specific cancer type is completed (either due to futility or efficacy) others agents are already prepared for evaluation. There needs to be a process established for 'living prioritisation' as has been done for acute myeloid leukaemia [3] and mature B cell malignancies [1]. Finally, while this Forum was focused on ALK tyrosine kinase inhibitors, other strategies to target ALK in paediatric malignancies will need to be considered over time, given that ALK has now been shown to be a tractable target across multiple paediatric cancers.

Clinical trials and regulatory approval: The participants of the Forum agreed that very early involvement of regulators in clinical trials of innovative medicines for which regulatory approval may ultimately be sought is

absolutely critical for optimal efficiency. Trial design (randomised versus non-randomised), identification of appropriate "control" populations (historical versus contemporaneous) and comparisons with the standard of care, and international collaboration/consensus on backbone therapies were considered critical issues. Moreover, accurate assessment and capture of safety findings to potentially inform labelling are essential. Similarly, planning the trials with the involvement of Health Technology Assessment (HTA) bodies in Europe and other jurisdictions is important. By aligning scientific, regulatory and HTA requirements from the inception of a clinical trial, drug development will be accelerated, and the fewest number of patients will need to be enrolled in clinical trials to obtain sufficient evidence for scientific and regulatory purposes. Clinical development plans for such products should always have an 'intent-to-file' [95], which significantly impacts how trials are designed from their initial inception. The participants encouraged the sponsors of trials to be transparent and submit simultaneous coordinated PIP and initial Paediatric Study Plan (iPSP) applications to the EMA and FDA, respectively, and to propose discussion at the Paediatric Cluster, which could lead to a Common Commentary [96]. The Paediatric Cluster is a monthly teleconference between FDA and EMA, with Japan's PMDA, Health Canada being observers and Australia's Therapeutic Goods Administration as active participants in some clusters. The clusters aim at cooperation on special topics and therapeutic areas identified as requiring an intensified exchange of information and collaboration. The Common Commentary is a tool to inform sponsors of products (submitted to both FDA and EMA) discussed at the paediatric cluster.

4.2. Patient Advocate's perspective

Patient advocates applauded companies' willingness to engage and collaborate with academic researchers and the focus on international trials exemplified by cooperation between SIOPEN and COG. The hope is that such collaboration will accelerate the availability of *ALK*-based paediatric treatments. Innovative approaches are needed to address trial design and access to trials, especially in small populations where patients are likely to be scattered among numerous institutions treating children. Real-world data could be of benefit by providing comparator/control data in very rare sub-groups, where randomised pivotal studies are not possible. Early discussion of such approaches with regulators is crucial. Researchers and companies should learn and share lessons from, the ALK experience as similar themes may develop in future Paediatric Strategy Forums with other targetable alterations. Patient advocates were concerned that the needs of children are not driving continued therapeutic development, especially when adult data do not look promising. They were also concerned with time lags in developing new drugs and patients' access to new drugs (especially for rare subsets of disease), short and long-term toxic effects of therapies, and urged companies and academic researchers to engage families and advocates early to help with study design challenges. The ultimate goal is to provide hope for families and to cure children and adolescents with cancer with the fewest and least significant short-term and long-term side-effects. For this, global academic collaboration and strengthening the ongoing early academia-multicompany engagement is critical.

5. Conclusions

ALK is an important target in ALCL, IMT, a subset of neuroblastomas and CNS tumours. ALK inhibition achieves remission in relapsed ALCL. However, whether relapsed disease may be cured by ALK inhibitors and if it can be employed effectively in newly diagnosed children to cure them while reducing treatment toxicity requires further rigorous evaluation. A consolidated strategy to establish the role of ALK inhibitors in IMT and support their approval in IMT, a focused and sequential approach for evaluation of ALK inhibitors in CNS tumours and a scientific and regulatory strategy for ALK inhibitors in ALK-driven neuroblastoma are required. This will provide access to ALK inhibitors for patients who can benefit. Data from current trials for ALK inhibitors should be evaluated before clinical trials for new drugs targeting ALK aberrations with characteristics similar to those of the products tested in clinical trials are initiated in children. Combination approaches, for example, brentuximab or vinblastine in combination with crizotinib or other ALK-inhibitors, should be evaluated to underpin the next generation of studies for ALCL [61]. Conclusions about the activity of ALK inhibition produced by a multitargeted tyrosine kinase inhibitor and prioritisation of classes of medicinal products should be agreed upon in a multistakeholder forum. Given the limited number of patients and the evolving molecular subsets of ALK driven malignancies, studies using innovative trial designs with an international scope, such as platform trials, may be informative approaches to obtain preliminary data.

A follow-up meeting of academic and industry participants will be held to define how to prioritise in very small patient subgroups the multiple compounds in clinical development that could be evaluated in children with cancer.

Overall, the Forum reinforced the very strong need for global academic collaboration in both preclinical and clinical investigations, very early involvement of regulators with studies seeking registration, early academia-multicompany engagement, agreement for sequential development efforts, involvement of patient advocates early in study design and registry set-ups (and/or data pooling of existing registries) to allow for

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the collection of 'real-world data' supporting development and registration efforts.

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Conflict of interest statement

EB is an employee of Day One Biopharmaceuticals and was an employee of Pfizer. HC is an employee of Hoffmann-La Roche. SGD has consulted for Bayer and received travel expenses from Loxo Oncology, Roche, and Salarius. FD is the European principal investigator of the Roche Alectinib study and participated in

advisory boards for Bayer, BMS, Roche, Celgene, LOXO Oncology, Servier and Tesaro and received travel expenses from Bayer, BMS, Roche and consultancy from Servier and received funding for research projects from Onxeo, Synth-Innove. LVM has consulted for Bayer and participated in advisory boards for BMS and Tesaro, and been a Data Monitoring Committee Member for Eisai and Merck. YM is an employee of Takeda Pharmaceuticals International. YPM has been a consultant for Pfizer. KN participated in advisory boards, consulted and taught for Bayer, Y-mAbs, and EUSA. GS is an employee of Xcovery. ADJP has participated in advisory boards for Novartis, Takeda, Merck, Lilly and Celgene and consulted for Lilly and Developmental Therapeutics Consortium Limited. KW is an employee of Pfizer. WW has consulted for Takeda and participated in an advisory board for Takeda Pharmaceuticals International. ZFZ is an employee of Turning Point Therapeutics. All remaining authors have declared no conflicts of interest.

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