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Review

Paediatric Strategy Forum for medicinal product development in mitogen-activated protein kinase pathway inhibitors ACCELERATE in collaboration with the European Medicines Agency with participation of the Food and Drug Administration

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Abstract As the mitogen-activated protein kinase (MAPK) signalling pathway is activated in many paediatric cancers, it is an important therapeutic target. Currently, a range of targeted MAPK pathway inhibitors are being developed in adults. However, MAPK signals through many cascades and feedback loops and perturbing the MAPK pathway may have substantial influence on other pathways as well as normal development. In view of these issues, the ninth Paediatric Strategy Forum focused on MAPK inhibitors.

Development of MAPK pathway inhibitors to date has been predominantly driven by adult indications such as malignant melanoma. However, these inhibitors may also target unmet needs in paediatric low-grade gliomas, high-grade gliomas, Langerhans cell histiocytosis, juvenile myelomonocytic leukaemia and several other paediatric conditions. Although MAPK inhibitors have demonstrated activity in paediatric cancer, the response rates and duration of responses needs improvement and better documentation. The rapid development and evaluation of combination approaches, based on a deep understanding of biology, is required to optimise responses and to avoid paradoxical tumour growth and other unintended consequences including severe toxicity. Better inhibitors with higher central nervous systempenetration for primary brain tumours and cancers with a propensity for central nervous system metastases need to be studied to determine if they are more effective than agents currently being used, and the optimum duration of therapy with MAPK inhibition needs to be determined.

Systematic and coordinated clinical investigations to inform future treatment strategies with MAPK inhibitors, rather than use outside of clinical trials, are needed to fully assess the risks and benefits of these single agents and combination strategies in both front-line and in the refractory/relapse settings. Platform trials could address the investigation of multiple similar products and combinations. Accelerating the introduction of MAPK inhibitors into front-line paediatric studies is a priority, as is ensuring that these studies generate data appropriate for scientific and regulatory purposes. Early discussions with regulators are crucial,

particularly if external controls are considered as randomised control trials in small patient populations can be challenging.

Functional end-points specific to the populations in which they are studied, such as visual acuity, motor and neuro psychological function are important, as these outcomes are often more reflective of benefit for lower grade tumours (such as paediatric low-grade glioma and plexiform neurofibroma) and should be included in initial study designs for paediatric low-grade glioma. Early prospective discussions and agreements with regulators are necessary.

Long-term follow-up of patients receiving MAPK inhibitors is crucial in view of their prolonged administration and the important involvement of this pathway in normal development.

Further rational development, with a detailed understanding of biology of this class of products, is crucial to ensure they provide optimal benefit while minimising toxicity to children and adolescents with cancer.

1. Introduction

Activating somatic mutations of the mitogen-activated protein kinase (MAPK) pathway are frequently associated with paediatric tumours and malignancies where there are currently unmet needs [3,4,12]. The *BRAF* V600E mutation occurs in approximately 7% of all human cancers [5]. A range of targeted MAPK pathway inhibitors has been developed, evaluated and approved in adult malignancies such as malignant melanoma [6], G12C mutation positive non-small cell lung cancer [7] and colorectal cancer [8], but only one inhibitor (Koselugo® [selumetinib]) has received specific regulatory approval in children [9–12]. RAF inhibitors have demonstrated activity in paediatric low-grade gliomas (pLGG) [13–16], paediatric high-grade gliomas (pHGG) [17,18], Langerhans cell histiocytosis (LCH) [19] and select solid tumours [20]. MEK inhibitors have also been active in plexiform neurofibroma [9–12], pLGG [21,22], LCH [23] and some subtypes of leukaemia/juvenile myelomonocytic leukaemia (JMML) [24], but definitive activity in other paediatric tumours has not been clearly demonstrated. The complexity and differences in the (epi)genomic landscape of different childhood tumours likely predict this variation in response to MAPK pathway (RAS, MEK, ERK) inhibition with targeted agents [4].

In view of the importance of the MAPK pathway in paediatric tumours and malignancies and the number of targeted pathway inhibitors currently being evaluated in adults and children, it was considered timely to hold a Paediatric Strategy Forum to focus on the role of these inhibitors in children. The Forum was organised by ACCELERATE [25,26] in collaboration with the European Medicines Agency (EMA) with the participation of the Food and Drug Administration (FDA) and built on the format and ethos of previous Forums aiming to evaluate science, facilitate dialogue and share information [27–33].

The Paediatric Strategy Forum focused on the key issues in the ongoing development of inhibitors of the MAPK pathway in paediatric oncology. Specifically, it addressed: (i) What are the unmet needs with existing MAPK pathway inhibitors?; (ii) How to better utilise existing MAPK pathway inhibitors (duration, schedule, alone or in combinations)?; (iii) What are the best end-points for MAPK pathway inhibitor trials for different indications?; (iv) Can predictive biomarkers for treatment response and resistance be identified to answer these questions and answers? The Forum also highlighted the crucial importance of formulation and different pharmacokinetic and pharmacodynamic properties, including central nervous system (CNS) penetration and short- and long-term toxicities of these targeted agents.

The meeting was held virtually on 28 and 29 March 2022 with 206 participants: 98 international paediatric oncology experts from Europe, US, Canada, Australia, South America, Japan and India; 47 representatives from ten pharmaceutical companies in Europe and the US (Alexion/AstraZeneca, BioMed Valley Discoveries, Boehringer-Ingelheim, Day One Biopharmaceuticals, Merck & Co., Inc. Rahway, NJ, USA, Novartiş Pierre Fabre, Roche, SpringWorks Therapeutics); 14 patient advocates from Europe, the US and Canada (representatives from Andrew McDonough B^{+} Foundation, Children's Cancer Cause, Coalition Against Childhood Cancer, HistioCure Foundation, Histiocytosis Association, Imagine for Margo, NGO Karkinaki Awareness for Childhood and Adolescent Cancer, Paediatric Brain Tumour Foundation, Solving Kids' Cancer, Solving Kids' Cancer UK, Swedish Childhood Cancer Fund, Zoé4life and Childhood Cancer International–Europe); 25 regulators from the EMA (including the Paediatric Committee [PDCO]) and national competent authorities within the EU regulatory network, European Health Technology Assessment [HTA] bodies, US FDA and Health Canada as observers;

the ACCELERATE Operations Coordinator. An overview of the biology of the MAPK pathway and a review of the current trials, plans and unmet needs in pLGG, pHGG, LCH and leukaemia were presented by academic experts. The details of seventeen inhibitors of the MAPK pathway were presented by industry representatives. The Forum concluded with the patient advocate perspectives and a multi-stakeholder strategic discussion.

2. Biology of the MAPK pathway

The MAPK signalling cascade is commonly altered in cancer and is crucial in normal development [1–3]. MAPK signalling also impacts many other pathways and feedback loops, especially the PI3K/AKT/mTOR pathway (Fig. 1). Therefore, perturbing the MAPK pathway may have substantial influence on other pathways.

The MAPK pathway is frequently activated through somatic events across a number of paediatric cancers, including JMML [34], acute myeloid leukaemia (AML) pLGG [35–37], pHGG [39,40], LCH [41], sarcoma, fusion-negative rhabdomyosarcoma [42], neuroblastoma [43] and osteosarcoma [2,3,44]. Neurofibromatosis type 1 (NF1), the most frequent hereditary cancer predisposition syndrome associated with MAPK pathway activation, is a genetic disease characterised by having a heterozygous pathogenic *NF1* variant [45]. Neurofibromin (encoded by the *NF1* gene) negatively regulates RAS activation [46]. The most common NF1-associated tumours include LGG, HGG, plexiform neurofibromas and malignant peripheral nerve sheath tumours [47].

pLGG is an example of a disease of aberrant MAPK signalling with *BRAF* being the most frequently altered gene. In most tumours, there is only one driver event, which is most commonly a structural variant that leads to pathway activation; less frequently, oncogenic *BRAF* point mutations occur [35–38]. The most common *BRAF* rearrangement results in loss of the N' terminal negative regulatory domain and replacement by another gene, most commonly *KIAA1549,* with the fused gene resulting in an activated BRAF kinase [35–40]. The next most frequent alteration is the *BRAFV600E* hotspot mutation which results in constitutive activation of the BRAF kinase. Alterations in the FGFR family represent the second most common group of somatic alterations and affect *FGFR1* or *FGFR2* [48]. Alterations in the *FGFR1* gene include tandem duplications, point mutations and fusions. Tumours with *FGFR1* point mutations frequently have co-occurring point mutations that are predicted to activate the MAPK or mTOR signalling pathway, which often include *PTPN11*, *PIK3CA* or loss-of-function *NF1* alterations. In addition, oncogene-induced senescence (robust and sustained anti-proliferative response brought about by oncogenic signalling resulting from an activating mutation of an oncogene, or the inactivation of a tumour-suppressor gene [49]) and its associated secretory phenotype, as well as the tumour microenvironment, are important modulators of tumour growth, behaviour and response to therapy.

Kinase inhibitors have been successful in the therapy of malignant melanoma, including BRAF, MEK and ERK inhibitors targeting the MAPK pathway; PI3K, AKT or mTOR inhibitors targeting the PI3K pathway and some newer FGFR inhibitors are in development [50]. However, it is essential to understand the biology of these oncogenic pathways, as there are risks of paradoxical signalling activation via feedback loops with targeting of some nodes. For example, preclinical studies of *BRAF* V600E-mutated pLGG cell lines treated with a type 1 BRAF inhibitor are effective in switching off MAPK signalling, while treatment with the same BRAF inhibitor in *BRAF KIAA1549*-rearranged cells can cause paradoxical pathway activation

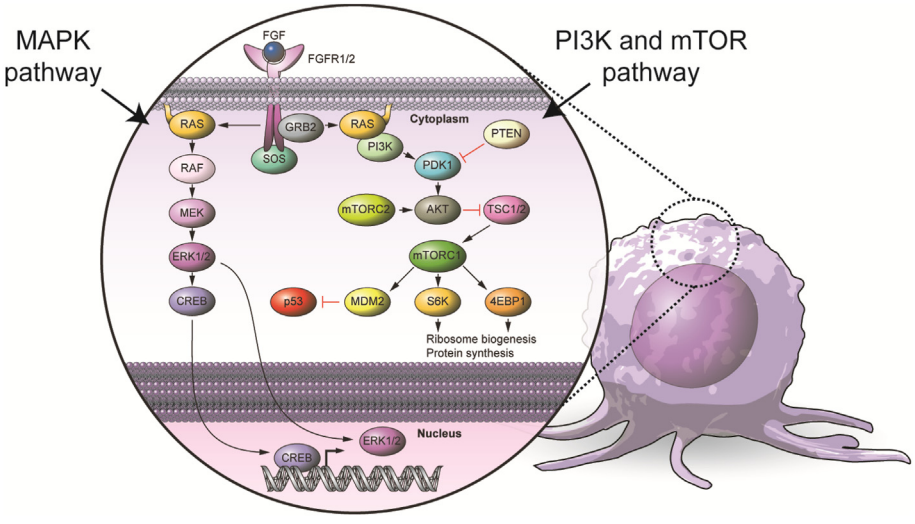

Fig. 1. MAPK, PI3K and mTOR pathways.

and an increase in cell growth [51]. Paradoxical activation of MAPK signalling led to unexpected tumour growth in a clinical trial evaluating the kinase inhibitor sorafenib for children with pLGGs, leading to early termination of the clinical trial [52].

The highly conserved MAPK pathway plays a critical role in the regulation of normal development across a large range of cell and tissue types, including (but not limited to) placental development, immune differentiation, angiogenesis, cardiovascular development and neurogenesis [53,54]. In the developing brain, MEK expression is essential for the regulation of gliogenesis [55]. Conversely, the loss of MEK1 is embryonic lethal due to anomalies in placental development, while the combined loss of MEK1 and MEK2 is also incompatible with postnatal survival, with effects across several tissues. Similarly, the loss of specific RAS and RAF isoforms in knock-out mice are also associated with an array of developmental defects [56]. While the effects of MAPK signalling in development have been widely evaluated, the sequelae of MAPK inhibition and thus long-term effects on childhood development remain unknown.

In summary: (i) the MAPK pathway is one of the most commonly altered pathways across childhood cancers; (ii) drugs targeting different components of the pathway may enable precision medicine approaches; (iii) a deeper understanding of the biology of the pathway is required to prevent potential for paradoxical cancer cell growth and to select the patient populations most likely to benefit from treatment and to avoid toxicity.

2.1. MAPK pathway inhibitors in pLGG

Approximately 3500 patients present with pLGG per year in North America and Europe. Currently, 90% of these patients survive with 50% cured by surgery alone [57]. However, the 5-year progression-free survival (PFS), after chemotherapy, is less than 50% with many patients receiving multiple lines of therapies in an attempt to avoid radiotherapy and associated substantial long-term sequelae [58,59]. The World Health Organisation classification of pLGG is evolving with the inclusion of molecular data rather than simple morphological grading [60]. pLGG is one of the six paediatric malignancies in the World Health Organisation Global Childhood Cancer Initiative to be addressed to save one million lives of children with cancer by 2030 [61]. **The current unmet needs** in pLGG are to minimise morbidity and to maximise quality of life by replacing chemotherapy with presumably less toxic, more effective targeted therapy. In addition to overall survival and PFS, new clinical end-points have also been proposed by international cooperative groups for inclusion in trial designs. These include visual acuity, quality of life, motor and neuropsychological functioning since the majority of these children will survive well into adulthood yet may suffer significant risk for reduced quality of life and compromise function in these realms. The ongoing and completed trials of inhibitors of the MAPK pathway in pLGG are shown in Tables 1 and 2. The inhibition of MEK results in partial responses (≥50%

Table 1
Summary of ongoing trials in newly diagnosed/recurrent pLGG with MAPK pathway inhibitors.

Trial	Study start	Population	Intervention
Newly diagnosed disease			
Tadpole G (NCT02684058) [16,68]	2017	Newly diagnosed *BRAF* V600E-mutant pLGG	Randomised phase 2 - dabrafenib (BRAFi) + trametinib (MEK1/2i) versus carboplatin and vincristine
COG ACNS1831 (NCT03871257) [106]	2019	Untreated *NF1*-associated pLGG	Phase 3 - carboplatin + vincristine versus selumetinib (MEK1/2i)
COG ACNS1833 (NCT04166409) [107]	2020	Untreated non-*NF1* and non-*BRAF* V600E mutant pLGG	Phase 3 - carboplatin + vincristine versus selumetinib (MEK1/2i)
LOGGIC (In Preparation)		Newly diagnosed non-*NF1* mutant pLGG patients who need further treatment after initial operation	Phase 3 - MAPK inhibitor versus physician's choice
MEKTRIC (NCT05180825) [108]	2022	Newly diagnosed non-*NF1*, *BRAF* wild-type pLGGs	Randomised phase 2 - trametinib(MEK1/2i) versus weekly vinblastine
Recurrent or Progressive disease			
PNOC026/DAY101-001/FIREFLY-1 (NCT04775485) [109]	2021	Recurrent or progressive *BRAF*-mutant pLGG	Phase 2 - Tovorafenib [DAY101] (Pan-RAFi)
PBTC-055 (NCT04201457) [71]	2019	Recurrent or progressive *BRAF*-mutant pLGG or pHGG	Phase 1/2 - dabrafenib (BRAFi), trametinib (MEK1/2), hydroxychloroquine
COG ACNS1931 (NCT04576117) [110]	2021	Recurrent or Progressive pLGG	Phase 3 - selumetinib versus selumetinib + vinblastine (MEK1/2i)
Paediatric MATCH (NCT03155620) [111]	2017	Ras/Raf pathway activated tumours	Phase 1/2 - ulixertinib (ERK1/2i)
Phase I/II MEK162 Ras/Raf Pathway Activated Tumours (NCT02285439) [112]	2016	Ras/Raf pathway activated tumours	Phase 1/2 - MEK162
SJ901 (NCT04923126) [113]	2021	Recurrent or progressive pLGG	Phase 1/2 - mirdametinib (MEK1/2i)
PNOC021 (NCT04485559) [114]	2020	Recurrent or Progressive pLGG	Phase 1 - trametinib (MEK1/2i) and everolimus

Table 2
Summary of completed trials in recurrent pLGG with MAPK pathway inhibitors (no trials in newly diagnosed pLGG).

Trial	Date Study start and end	Population	Intervention
Recurrent or Progressive disease			
PNOC014[a] (NCT03429803) [15,115]	2018–2024	Recurrent or progressive solid or CNS tumours with activated RAS/RAF/MEK/ERK pathway	Phase 1 – DAY101
PBTC-029[a] (NCT01089101) [21,116]	2010–2025	Recurrent or refractory pLGG	Phase 1/2 - Selumetinib
NYU 10–00561[b] (NCT01338857) [52,117]	2011–2013	Recurrent or progressive LGG (including NF-1)	Phase 2 - Sorafenib
Novartis 116540[c] (NCT02124772) [118]	2015–2020	Recurrent or refractory malignancies with V600 mutations	Phase 1/2 – Trametinib alone or trametinib plus dabrafenib

[a] Active, not recruiting (i.e., study end date is the projected primary completion date).
[b] Terminated - ineffective.
[c] Completed.

tumour reduction by RANO criteria) in 30–40% of recurrent pLGG [21,22,62], and similar results have been obtained with BRAF inhibitors in BRAF V600-mutated pLGG [6,13,18] and BRAF/MEK combinations [16]. A randomised trial in BRAF V600–mutant pLGG has demonstrated superior overall response rate, clinical benefit rate and median PFS with dabrafenib and trametinib compared to carboplatin and vincristine [16]. However, not all patients remain in continuous partial response after stopping therapy and tumour rebound may occur following treatment cessation. Both better inhibitors, with, for example, higher CNS penetration and better combination therapies, are likely required to drive deeper and more durable responses. However, inhibitors with higher CNS penetration need to be studied to determine if they are more effective than agents currently being used. In addition, tumour microenvironmental factors including senescence-related pathways likely modulate treatment response to MAPK inhibitors and may provide opportunities for novel single agent and combination therapies [63–65]. With increasing understanding of disease biology, it is appreciated that pLGGs are very heterogeneous tumours [66], most clearly depicted in the difference between those pLGG arising in patients with NF1 compared to the rest of the population. This molecular heterogeneity demands that predictive biomarkers are discovered and understood to better select specific patients for tailored therapy. Understanding rebound and resistance are key future goals. At present, the optimal duration of therapy is unknown with response persisting in some patients after drug discontinuation whilst others experience tumour regrowth or progression. The current pragmatic approach is to treat clinical benefit until loss of clinical benefit or for a certain specific duration (typically approximately 2 years) and then stopping therapy. In view of the prolonged administration, the involvement of this pathway in normal development and the life expectancy of patients into adulthood, a better understanding of the late effects of patients receiving MAPK inhibitors is required. Ancillary and integrated biological studies will hopefully allow the understanding of which patients require further therapy. Currently, there are several studies open or in the late stages of planning for both newly diagnosed and recurrent pLGG and completed studies (Tables 1 and 2). For the future, an industry-supported, academic-sponsored international platform trial that provides clinical trial data that can be used for licensing purposes and with early input from regulators, could address the investigation of multiple similar products and combinations in small patient populations. Within the same overall trial structure, products from different pharmaceutical companies and different mechanisms of action could be evaluated using an adaptive design and products for further evaluation could be identified.

2.2. MAPK pathway inhibitors in pHGG

Approximately 1150 patients present each year in North America and Europe with pHGG. Similar to pLGG, the classification of pHGG is evolving with inclusion of molecular data rather than simple morpholohistological grading [60]. *BRAF* V600E mutations occur in approximately 6% of pHGG (70 patients per year in Europe and North America) (mostly midline or hemispheric tumours) and confer a better prognosis [39,67] with 67% 5-year PFS with conventional chemotherapy and radiotherapy [39]. **The current unmet needs** in *BRAF*-mutated pHGG are to identify more effective therapies that would increase survival and in the long-term, ultimately, to reduce or avoid radiation therapy entirely. In one study, BRAF inhibition with dabrafenib resulted in a maximum tumour reduction of ≥50% in 68% of patients with pHGG, but this was of short duration (median PFS 7.4 months) [13]. Combination approaches are required, and studies are planned or ongoing of BRAF and MEK inhibitors (dabrafenib + trametinib [NCT02684058 [68], NCT03919071 [69]], binimetinib + encorafenib [≥18years] [NCT03973918 [70]], dabrafenib + trametinib + hydroxychloroquine [NCT04201457 [71]]). In newly diagnosed and recurrent pHGG, there has been a retrospective, multi-institutional review of patients with BRAF-mutant pHGG treated off-label with BRAF inhibitors with or without MEK inhibitors, confirming activity [72].

Responses were observed and the authors concluded that adjuvant randomised trials of BRAF inhibitors in adult and paediatric low-grade and high-grade gliomas were needed. Similarly to LGG, inhibitors with higher CNS penetration need to be evaluated. The key future focus is to improve overall survival of these patients by determining optimal inhibitor combinations and ascertain if treatment response/resistance [40,73] depends on blood brain barrier penetrance, secondary mutations, tumour morphology or other specifics of the tumour's molecular landscape.

2.3. MAPK pathway inhibitors in plexiform neurofibromas in NF1

Approximately 66,000–110,000 individuals in the US have NF1 [74]. They have a 30–50% risk of developing plexiform neurofibromas (20,000–55,000) [47]. In a condition where previously effective medical therapies were lacking, treatment with the MEK inhibitor, selumetinib, has resulted in 68% of patients achieving a confirmed partial response (tumour volume decreases from baseline of ≥20% by volumetric analysis of the MRI); 82% of these having a durable response (>1 year). The median time to initial response is 8 cycles (32 weeks) (range, 4 to 20) with a median time to best response being 16 cycles (range, 4 to 36) [9–11]. Selumetinib (Koselugo®) as monotherapy is indicated for the treatment of paediatric patients 2 years of age and older in the United States (and 3 years of age and older in the European Union) with NF 1 who have symptomatic, inoperable plexiform neurofibromas [12]. Mirdametinib is an investigational agent which has been shown to be active in adolescents and adults with plexiform neurofibromas [75]. Preliminary data suggests plexiform neurofibromas respond to other MEK inhibitors as well [76]. **The current unmet needs** are to increase the number of patients who achieve partial response (as defined above), to obtain greater tumour volume reduction (as currently there are very few tumours which shrink more than 30%), to make responses more durable (most tumours regrow after stopping treatment), and to define schedules, e.g. intermittent dosing that reduce toxicity while maintaining efficacy with improved functional and quality of life outcomes, e.g. motor function and tumour-related pain. MAPK, including KRAS inhibitors, with better safety and efficacy profiles, used as monotherapy or in combination may also have a role.

2.4. MAPK pathway inhibitors in LCH

Approximately 800 children present each year in North America, Europe and Australia with LCH, which is similar in incidence to paediatric Hodgkin lymphoma and AML. LCH is therapeutically classified either as low-risk single system, low-risk multisystem and high-risk multisystem disease (classically involving spleen, bone marrow and/or liver) with response to initial chemotherapy guiding further treatment for patients with multi-focal disease [77]. Generally, overall survival is very good (85% at 5 years for high-risk disease) [78] but disease eradication is achieved in <50% of patients with front-line therapy, and further attempts at curative therapy result in increased risk of morbidity and mortality [79]. LCH-neurodegenerative syndrome (dysarthria, dysmetria, learning and behaviour difficulties, and brain MRI changes) occurs in 5–10% of patients and currently does not have an effective therapy [80]. Conversely, some patients with low-risk disease may be over treated with conventional chemotherapy. **The current unmet needs are** to eliminate the risk of death in high-risk patients, improve treatment efficacy, reduce morbidity from treatment failure and/or chronic therapy and prevent and/or effectively treat LCH-neurodegenerative syndrome. Activating somatic MAPK pathway mutations are identified in almost all cases of LCH, with BRAF V600E as the most common, followed by activating mutations in MAP2K1 (which encodes MEK1). Alternative *BRAF* mutations, tyrosine kinase receptor gene mutations and *ARAF* mutations have also been reported [81]. BRAF inhibitors have been used off label in about 100 patients in international observational cohorts receiving vemurafenib or dabrafenib [19,82]. MAPK inhibitors are very efficient in achieving rapid clinical remission in LCH, and resistance to therapy is extremely rare [82]. However, there are high rates (>75%) of rapid reactivation/progression with cessation of MAPK pathway inhibitors [82]. Molecular remission is not obtained with monotherapy as evaluated by high sensitivity peripheral blood or bone marrow studies [82–84] and additional or combination therapy is likely needed to eradicate subsets of mutated cells. A combination of BRAF and MEK inhibitors (trametinib with dabrafenib) has been evaluated [85]. New therapeutic approaches are needed for three situations: high-risk disease, LCH–neurodegenerative syndrome and low-risk recurrent LCH. A possible therapeutic schema is initial treatment with MAPK pathway inhibition, then chemotherapy followed by further MAPK pathway inhibition. The optimum duration of therapy with MAPK inhibition needs to be determined. There is a need for the systematic development of treatment strategies including MAPK inhibitors rather than the current widely spread off-label use in order to assess the risks and benefits of various agents and combination strategies for front-line and salvage settings. An intercontinental trial in high-risk disease could generate knowledge. Given the current evidence, it is crucial that MAPK inhibitors move forward into front-line and studies are appropriately designed and conducted to generate data suitable to support regulatory evaluation and approval.

2.5. MAPK pathway inhibitors in leukaemia

Approximately 150 children present each year in North America and Europe with JMML, where an excessive production of the monocytes infiltrate other organs including the spleen, liver, lung and gastrointestinal tract. Currently, allogeneic haematopoietic stem cell transplant is considered the only curative treatment and is usually delivered following antecedent chemotherapy for cytoreduction and disease control. Virtually, all patients with JMML have a MAPK pathway mutation [34]. In ADVL1521 (Phase II study of MEK inhibition with trametinib in children with relapsed or refractory JMML) (NCT03190915 [86]), 5 of 10 patients enrolled have had an objective response (1 complete response, 4 partial responses) and 2 patients have had prolonged stable disease [24]. However, no molecular responses as evidenced by decreased RAS pathway mutational burdens have been recorded in treated patients. A subsequent trial in North America, TACL2020-004, (in planning) will risk-stratify patients with newly diagnosed JMML to therapy based on genotyping and methylation analysis. Lower-risk patients [1 mutation and low DNA methylation] will receive azacitidine and trametinib. Higher-risk patients [>1 mutation and intermediate or high methylation] will receive azacitidine and trametinib, chemotherapy and allogeneic transplant. If successful, this approach may allow for a paradigm shift in 'definitive therapy' for these children with high-risk disease.

In acute lymphoblastic leukaemia, the most common childhood cancer, 30–50% of children have a subclonal mutation in the MAPK pathway [87,88]. RAS mutations can appear or disappear from diagnosis to relapse, and their prognostic significance remains unknown. Patients with RAS mutations have a higher risk/incidence of CNS relapse, so this is an area of medical need. The ongoing SeluDex trial (NCT03705507) [89] is evaluating the role of MEK inhibition with selumetinib in combination with dexamethasone in relapsed or refractory acute lymphoblastic leukaemia [89,90]. Recruitment to this trial has proven challenging in the present era of available chimeric antigen-receptor T-cell therapy, commercially or clinical trials [90]; however, responses have been noted and the early reports show reasonable tolerability and feasibility. Finally, 43% of paediatric patients with AML have a MAPK pathway mutation at diagnosis [91]. It has been reported that RAS mutation variant allele frequency often increases at relapse, suggesting a role as a driver or disease modifier. Combination approaches of a MEK inhibitor and chemotherapy are under consideration for a clinical trial in children with RAS-mutant AML.

3. Products discussed at the Forum and Paediatric Investigation Plans and Written Requests

Seventeen medicinal products (selumetinib (Koselugo®), dabrafenib (Tafinlar®), trametinib (Mekinist®), vemurafenib (Zelboraf®), cobimetinib (Cotellic®), encorafenib (Braftovi®), binimetinib (Mektovi®), tovorafenib [DAY101], belvarafenib, pimasertib, ulixertinib, BI 1701963, BI 3011441, BI 1823911, GDP pan-KRAS inhibitor, mirdametinib and BGB-3245 were discussed at the Forum (Table 3).

As of March 2022, there were 7 published Paediatric Investigation Plans (PIP) agreed for selumetinib

Table 3
MAPK inhibitor medicinal products discussed at the Paediatric Strategy Forum.

Product	Target	Adult Marketing Authorisation	Paediatric Marketing Authorisation	Paediatric Investigation Plan	Company
Selumetinib (Koselugo®)]	MEK1/2	+	+	+	Alexion/AstraZeneca/Merck & Co., Inc., Rahway, NJ
Dabrafenib (Tafinlar®)	BRAF	+		+	Novartis
Trametinib (Mekinist®)	MEK1/2	+		+	Novartis
Vemurafenib	BRAF	+		Full waiver	Roche
Cobimetinib (Cotellic®)	MEK1/2	+		+	Roche
Encorafenib (Braftovi®)	BRAF	+		+	Pierre Fabre.
Binimetinib (Mektovi®)	MEK1/2	+		+	Pierre Fabre.
Tovorafenib [DAY101]	Pan-RAF			+	Day One Biopharmaceuticals
Belvarafenib	Pan-RAF			–	Roche
Pimasertib	MEK			–	Day One Biopharmaceuticals
Ulixertinib	ERK1/2			–	BioMed Valley Discoveries
BI 1701963	SOS1::KRAS				Boehringer-Ingelheim
BI 3011441	MEK1/2			–	Boehringer-Ingelheim
BI 1823911	$KRAS^{G12C}$			–	Boehringer-Ingelheim
GDP pan-KRAS inhibitor	Pan-KRAS			–	Boehringer-Ingelheim
Mirdametinib	MEK1/2			–	SpringWorks Therapeutics
BGB-3245	Pan-RAF			–	MapKure [joint venture of Spring Works/BeiGene]

(Koselugo®), dabrafenib (Tafinlar®) and trametinib (Mekinist®), cobimetinib (Cotellic®), encorafenib (Braftovi®) and binimetinib (Mektovi®) and tovorafenib (DAY101). Two of these PIPs are for combination therapy (dabrafenib + trametinib; encorafenib + binimetinib). The indications of the PIPs are disease-specific: melanoma with *BRAF* V600 mutations (n = 3); thyroid cancer (n = 1); NF-1 (plexiform neurofibroma) (n = 1); glioma with BRAF V600 (n = 1); LGG with *BRAF* fusion (n = 1). Two indications are histology agnostic: solid tumours with BRAF V600 (1) and solid tumours with RAS/RAF/MEK pathway activation (2) (Table 4). The agreed initial PIP for vemurafenib (Zelboraf®) in adolescent patients for the treatment of melanoma was later modified into a Product Specific Waiver in all age groups in the same condition on the grounds of 'clinical studies are not expected to be of significant therapeutic benefit to or fulfil a therapeutic need of the specified paediatric subset' [92].

4. Discussion

4.1. Patient advocates' perspectives

Patient advocates were concerned about the potential adverse developmental impact and late toxic effects of MAPK pathway inhibitors. They believed it was essential that companies, academic researchers and regulators pay particular attention to late effects on children's development as monotherapy, and especially, combination therapy trials are developed. Late effects of therapy in adults may not be considered as companies develop agents for adult malignancies, but it is essential that this risk is considered in children. Patient advocates feel a special urgency about children with brain tumours, who often already live their entire lives with neurological sequelae from disease and treatment, as their families struggle with their care both short- and long-term.

Advocates urged that researchers come together with industries and regulators, perhaps in a dedicated meeting, to create new functional outcome measures that should include neurocognitive and endocrine changes in addition to PFS. Advocates' input in creating such measures will add considerable value.

Common challenges are emerging about how to evaluate MAPK inhibitors as research uncovers deeper biological understanding of pHGG, pLGG, LCH and leukaemia. Variability in response to MAPK inhibitors shines a spotlight on the need for biomarkers to distinguish patients whose disease will respond differently. While patient advocates understand the challenges that small patient subsets create for trial design and patient recruitment, they support novel trial designs that are more finely tuned to the biology of patients' disease profiles, e.g. platform and tumour agnostic trials, and the proposed JMML trial in which genotyping precedes disease classification and treatment. In addition, advocates urged that no paediatric data be wasted and that clinicians analyse and make public data from off label and compassionate use that may yield fresh insights. Further, advocacy groups strongly endorsed and have helped financially support the conduct of international trials to address small patient populations, as exemplified in pLGG and LCH.

Multiple therapeutic opportunities make it even more important that tumour biology determines which agents are evaluated in children. Families and patients trust investigators and regulators, in collaboration with companies, to plan paediatric trials governed not only by what agents are available but also by the latest and best scientific insights. Any commitment to evaluating one specific therapy in a small patient population can effectively eliminate other potentially more promising opportunities for these patients.

5. General themes

5.1. Biology

Understanding specific tumour biology is critical, especially as the MAPK pathway is tightly connected to other signalling pathways. There may be unforeseen consequences if biology is not well understood, such as compensatory signalling up the regulation of alterative pathways and paradoxical tumour growth [51,52]. It is important to understand which feedback loops will be triggered by inhibiting one pathway and which other pathways could be co-inhibited for potentially synergistic effects. Furthermore, the importance of the MAPK pathway in normal development, especially glial differentiation, must be considered. The combinations of MAPK pathway inhibitors should be developed based on the mechanism of action, cancer biology and robust preclinical evaluation. The selection of combinations with compelling biological and clinical rationale for evaluation in children is essential given the rarity of paediatric cancers and the mismatch between the immense numbers of combinations that are available for testing compared to the number of clinical trials that can be conducted.

5.2. Trial design and regulatory considerations

Front-line academic trials of new products should be designed to generate data sufficient for regulatory decision making on benefit/risk assessment and there should be early discussion between academia, industry and regulators [26]. This is especially important if evaluating a new product is challenging in a randomised clinical trial. Trials submitted to fulfil regulatory requirements (e.g. PIPs and initial Paediatric Study Plans [iPSPs]) should be aligned with those designed prospectively by academic cooperative groups to be practice changing.

Table 4
Published PIPs agreed for MAPK inhibitors.

Product	Selumetinib (AZ/ Merck)	Dabrafenib + Trametinib (Novartis)	Dabrafenib mesylate (Novartis)	Trametinib dimethyl sulfoxide (Novartis)	Cobimetinib (Roche)	Vemurafenib (Roche)	Encorafenib + Binimetinib (Pierre Fabre)	DAY101 (DayOne)
PIP	Modified PIP Aug19 (EMEA-001585-PIP01-13-M03)	PIP Oct20 (EMEA-001147-PIP02-20 & EMEA-001177-PIP02-20)	Modified PIP Oct20 (EMEA-001147-PIP01-11-M07)	Modified PIP Oct20 (EMEA-001177-PIP01-11-M06)	Modified PIP, Mar21 (EMEA-001425-PIP01-13-M05)	Initial PIP decision in Aug16 2011. (EMEA-000978-PIP01-10-M01) Modified 2016 Product Specific Waiver in melanoma"	Modified PIPs Mar18 - EMEA-001588-PIP01-13-M01 & EMEA-001454-PIP03-15-M01	PIP Dec20, EMEA-002763-PIP01-20
MoA	MEK1, ERK1/2	BRAF + MEK1/2	BRAF	MEK1/2	MEK1	(B)RAF	BRAF inhibitor & MEK1/2 inhibitor	PanRAF kinase inhibitor
Condition	Melanoma, NF-1, thyroid cancer	Glioma	Melanoma, solid malignant tumours (excluding melanoma)	Melanoma, malignant neoplasms (except melanoma, haematologic, glioma)	Malignant neoplasms (except haematologic) with Ras, Raf or MEK pathway activation	Melanoma	Melanoma	Paediatric LGG
PIP Indication	NF1 - inoperable plexiform neurofibromas Selumetinib + radioactive iodine therapy for HR differentiated thyroid cancer	Glioma with BRAF V600 mutations	Melanoma with BRAF V600 activating mutations (adolescents) Solid tumours with BRAF V600 activating mutations (children)	Melanoma with BRAF V600 activating mutations (adolescent) Solid malignant tumour with known or expected RAS, RAF or MEK pathway activation (children)	Paediatric solid malignant tumour with Ras, Raf or MEK pathway activation, R/R	Melanoma in adolescents - waiver on the grounds of "clinical studies not expected to be of significant therapeutic benefit to or fulfil a therapeutic need of the specified paediatric subset"	Encorafenib + binimetinib with unresectable or metastatic melanoma with BRAF V600 mutations (>12 y)	LGG with BRAF fusion: R/R Newly diagnosed with unresectable/sub-totally resected
Waiver	NF1: 0−1 y; Thyroid cancer: 0 −12 y; Melanoma: 12−18 y	0-1 y	Melanoma: 0−12 y; Solid tumours: 0−1 y	Melanoma: 0−12 y; Solid tumours: 0−1 month	0−6 months	0−18 years	0-12 y	0−6 months
Deferral	By September 2022	By December 2021	By June 2022	By June 2022	By July 2020	N/A	By June 2023	By July 2030
Formulation	Age-appropriate oral dosage form Capsule, hard	Capsule, hard Dispersible tablet	Capsule, hard Dispersible tablet	Film-coated tablet Powder for oral solution	Film-coated tablet Age-appropriate oral formulation	Film-coated tablet	Capsule, hard Age-appropriate oral dosage form	Tablet Age-appropriate paediatric formulation
Clinical	**NF1 - inoperable plexiform**	**Advanced BRAF V600-mutant glioma:**	**Melanoma & Solid tumours:**	**Melanoma & Solid tumours**:	**R/R solid tumours with Ras, Raf or MEK**	N/A	**Unresectable or metastatic BRAF V600 mutant**	Low-grade gliomas and

(*continued on next page*)

Table 4 (*continued*)

Product	Selumetinib (AZ/ Merck)	Dabrafenib + Trametinib (Novartis)	Dabrafenib mesylate (Novartis)	Trametinib dimethyl sulfoxide (Novartis)	Cobimetinib (Roche)	Vemurafenib (Roche)	Encorafenib + Binimetinib (Pierre Fabre)	DAY101 (DayOne)
	neurofibromas: • Single-arm → safety, toxicity, PK and activity (3–18 y) • Non-controlled, multiple-dose → PK, PD, safety, acceptability and activity (2–18 y). • Placebo-controlled, double-blind, randomised-withdrawal → PK, safety, tolerability and activity (1–7 y) • **Thyroid Cancer:** N/A	Open-label - safety and efficacy of dabrafenib + trametinib (1–18 y)	• Single agent - safety, tolerability, PK and MTD (1–18 y) in advanced BRAF V600-mutant solid tumours. • Randomised, single dose 3-way cross-over relative bioavailability study in normal adult healthy volunteers. **Melanoma (BRAF V600-mutant):** Measure (modelling and simulation) to demonstrate that PK, PD, and efficacy in adolescents (12–18 y) are similar to that in adults	• Open-label, single agent, dose escalation trial → safety, tolerability, PK, PD in R/R solid malignant tumours (1 mo-18 y) • Relative bioavailability study in adults.	**pathway activation:** Multiple dose 2-stage trial to evaluate PK, safety and activity of cobimetinib (6 months-18 y) (GO29665/ NCT02639546)		**melanoma**: Multicentre, open-label → PK, safety, tolerability, and preliminary evidence of activity of binimetinib + encorafenib (12–18 y)	other RAS/RAF/ MEK/ERK pathway-activated tumours: dose finding study Relapsed or progressive low-grade gliomas harbouring BRAF fusions: open0label, single-arm trial→PK, safety, and activity of DAY101 (6m-18y) Newly diagnoses unresectable or sub-totally resected low-grade glioma harbouring BRAF fusions: randomised trial →safety and efficacy of DAY101 (6m-18y)

With the increasing alignment between regulators in Europe and the US, there should be simultaneous regulatory submissions of individual PIPs and iPSPs to the EMA and FDA, respectively, including a suggestion for discussion at cluster calls [93–96]. Clinical trials should be designed to generate data supporting scientific, regulatory and payers (e.g. health technology assessment bodies in Europe) decision making, leading to regulatory approval with access for all children to the medicinal products.

5.2.1. Toxicity

In general, MEK inhibitors have been well tolerated with most toxicities being grade 1 and 2 with rare grade 3 and higher toxicities [22,97–99]. Currently, there has not been detailed comparison of the toxicity of differing MEK inhibitors, similarly data on long-term toxicity are lacking. Likewise, with BRAF inhibitors, grade 3 adverse effects are also rare and tend to be maculopapular rash, arthralgia and absence of pigment in the hair with the most frequent adverse effects being fatigue[13,14,15]. In a randomised trial in pLGG of dabrafenib and trametinib compared to carboplatin and vincristine, there were less grade $\geq$3 adverse events with dabrafenib and trametinib [16]. In the future, quality of life of patients and patient-reported outcome assessment of the MAPK pathway inhibitors need to be assessed and clearly reported. Patient-reported outcomes have been used in the paediatric oncology application to the FDAs for selumetinib [100]. Furthermore, e-patient-reported outcomes hopefully can provide more accurate reporting of adverse events and the better evaluation of impact of those that are symptomatic [101].

5.3. Long-term follow-up

Long-term follow-up of patients receiving any new medicinal product is important so that survivors and their families, clinicians and regulatory agencies are informed of the long-term effects of treatment, including the potential for secondary malignancies. As the optimal duration of therapy is currently unknown and because the pathway is involved in normal development processes (especially glial differentiation), long-term follow-up assumes an even greater importance. It is crucial to know late effects which occur after five years or even longer as well as more short-term events. The ACCELERATE long-term follow-up initiative proposes an international and inter-company, harmonised and sustainable data registry of early and late adverse effects of new anti-cancer products, including MAPK pathway inhibitors [102]. This will provide informative data of the long-term safety to support the best use of these therapies, inform families and clinicians of the long-term effects of treatment in order to guide their decision making and support fulfilling regulatory requirements of the marketing authorisation holders.

5.4. Paediatric formulation

In view of the age of patients who may potentially benefit from MAPK pathway inhibitors and for whom prolonged administration is required, the development of oral 'child-friendly' formulations (especially palatable suspensions or liquid formulations) of the medicinal product that are appropriate to be administered to young children is critical.

6. Specific themes

6.1. Better use of existing MAPK pathway inhibitors

Generally, monotherapy with a MAPK pathway inhibitor will result in a clinically relevant response rate in tumours with only one molecular driver [103]. However, for LCH and leukaemias, a molecular remission will likely not be obtained and when the MAPK inhibitor is discontinued, disease can recur as with pLGG and LCH. Therefore, there is a need for 'deeper' molecular, as well as clinical, responses. Multi-drug approaches are also required, which may be via combination with another MAPK inhibitor or, targeted agent, with chemotherapy. In other situations, where there are multiple mutations (e.g. pHGG with *BRAFV600E* and other mutations), MAPK inhibitors result in a 60–70% short duration response, after which resistance occurs. Studies are being carried out of combinations with BRAF and MEK inhibitors, and the results of these are awaited. In the absence of adult data, the design of such trials would be optimised if there were a randomised comparison between monotherapy and combination therapy rather than a retrospective comparison of response rates (e.g. the ROAR trial of dabrafenib plus trametinib in adult patients with *BRAFV600E*-mutant low-grade and high-grade glioma; NCT0203411 [104]). To accelerate drug development cross-company, cross-product combined analyses of toxicity would be invaluable.

Generally, MAPK inhibitors with higher CNS penetration are preferred for diseases affecting the brain, e.g. CNS tumours or metastatic disease to the brain from other cancers, and this is an important attribute of any inhibitor. Better brain penetration should reduce peripheral toxicity, as less systematic exposure is required to deliver sufficient drug to the brain/target tissue. The theoretical concern that higher CNS penetrance will lead to a greater incidence of CNS adverse events must be monitored. The width of the therapeutic window will depend on the magnitude of oncogene addiction of the tumour cells to aberrant MAPK signalling versus normal cells. However, MAPK inhibitors which have a higher CNS penetrance need to be studied

to determine if they are more effective than agents currently being used. As it is not possible to define the optimal biological dose in CNS tumours due to the inability to biopsy tumour tissue for pharmacodynamic assessment, dose escalation strategies should ideally target the pharmacokinetically defined exposure obtained in adults or, if that is not feasible, the maximum tolerated dose. Furthermore, it is conceivable that therapeutic plasma levels may vary according to tumour types, particularly between extra- and intra-cranial tumours. Pharmacodynamic and pharmacokinetic studies should be undertaken with the objective of relating these parameters to both efficacy and toxicity.

The optimal duration of therapy is currently unknown, may differ in different disease types and clinical evidence demonstrates that some patients relapse whilst others do not after discontinuation of therapy. It is proposed that patients are treated for an empirical duration from the best response or start of treatment and then treatment is discontinued. Ancillary biological studies must be integrated into trials to understand the heterogeneity in biology, monitor development of mutations and to inform rational duration of treatment and potential for development of resistance. Alternative approaches could be intermittent dosing or integrating other therapeutic modalities.

6.2. Best endpoints for MAPK pathway inhibitor trials for different diseases

In the tumour entities where MAPK inhibitors are being currently evaluated, there is a need to include additional end-points to overall survival and PFS. The number of patients in whom the cancer recurs after the discontinuation of therapy and the patterns of recurrence should also be captured. With CNS tumours, especially pLGG, visual function, quality of life, patient reported outcomes, motor function and neuropsychological functioning are invaluable and important endpoints in the evaluation of innovative therapies. For these end-points to be considered by regulators, early discussions with regulatory agencies are required, involving academia, industry and patient advocates. A further challenge is defining appropriate end-points in LCH, particularly LCH-neurodegenerative syndrome.

6.2.1. Identifying the optimal MAPK inhibitors and combinations

There are a range of inhibitors of the MAPK pathway, including: type 1 RAF^{V600}, type 2 pan-RAF, MEK1, MEK1/2, ERK1/2, SOS1, $KRAS^{G12C0}$ and pan-KRAS. Clinical trials need to be designed very carefully to ensure robust data are obtained regarding the optimal agents to take forward. For example, the benefits and role of ERK1/2 inhibitors require clarification. New generation BRAF inhibitors are very promising but clinical data are very early and in small numbers of patients. The theoretical benefits of type 2 pan-RAF inhibitors compared to type 1 monomeric inhibitors have been postulated and demonstrated non-clinically, but they have not yet been confirmed in clinical trials. Peer-reviewed articles are eagerly awaited describing efficacy and toxicity.

6.3. Coordination of evaluation of products in development

With an increasing number of MAPK pathway inhibitors under or entering clinical evaluation with the intention of regulatory submissions, but a relatively small potential paediatric population with RAS/MAPK pathway-mutant diseases, international coordination is required to develop a strategy to identify the most effective drugs for children. The general proposed regulatory strategy, where there are multiple products of the same class, is that there is a consolidated agreement by industry and academia regarding which product or products, based on current evidence, is considered to have the highest potential to address unmet medical needs and minimises toxicity. This product(s) should then be advanced into paediatric development and submitted for regulatory approval, usually as part of PIP or iPSP, without delay (i.e. without a deferral). Part of this prioritisation discussion, however, also includes the need to decide on the sequence based on scientific arguments in which (any) other available (or emerging) products should be developed in reference to the one decided to move forward into development. The development of these products should be foreseen in sequence and in dependency so that as soon as a development is completed (either due to futility or efficacy); others are already prepared for evaluation. Regulatory tools like deferrals are in place to facilitate this within PIPs. Such consolidated prioritisation strategies allow fulfilment of the respective regulatory requirements, improves efficiency and is of benefit to children with malignancy. In the case of MAPK inhibitors, the development of some products is too advanced to employ this strategy now.

6.4. Patient access to MAPK inhibitors

MAPK inhibitors have the potential to make a substantial difference in several childhood malignancies and fulfil current unmet needs. Patients need access to new drugs which require both regulatory and payer (health technology assessment bodies) approval. One very important issue is that these new drugs are more costly than conventional therapy. The cost effectiveness of these innovative approaches needs to be robustly demonstrated to payers (e.g. health technology assessment bodies). Frequently, robust data about the effectiveness of established/standard therapies are not available for regulatory and health technology

assessment bodies purposes, creating a need to generate robust real-world evidence in this domain.

6.5. Evaluation of MAPK inhibitors in pLGG

MAPK inhibitors have the potential to fulfil unmet needs in pLGG and their development should be accelerated. The results of ongoing trials of single agents, and especially combinations in newly diagnosed patients are awaited and these will inform the field. Going forward, international coordination of trials in pLGG will be crucial to ensure progress is made rapidly and repetition is minimised. Defining the benefit of MAPK inhibitors compared to current standard of care, including economic evaluation, will establish how MAPK inhibitors could be practice changing treatments. Evaluating MAPK inhibitors with the greatest CNS penetration is of critical importance, although other characteristics of agents may also be important in defining the therapeutic window for MAPK inhibitors for LGG. Investigating the optimal MAPK inhibitors in a platform trial could be advantageous in identifying which to take forward to future front-line trials. Understanding biology in greater depth, including the role of promoting senescence versus blocking proliferation in the treatment of pLGG tumours, will allow predictive biomarkers to be identified to dissect the heterogeneous nature of the tumours, enabling therapy to be tailored. Similarly, biological studies will increase the understanding of rebound, resistance, optimal duration of therapy and late toxic effects. Validating new endpoints (e.g. visual acuity, quality-of-life, motor function, neuro-psychological function) and agreeing upon them prospectively with regulators for clinical trials are additional important goals.

6.6. Evaluation of MAPK inhibitors in pHGG with BRAF V600E mutations

Combination approaches are required, utilising inhibitors with the highest CNS penetration when feasible and safe. MAPK inhibitors are being incorporated in front-line therapy of pHGG with *BRAF* V600E mutations, with radiation therapy [67] and the results are awaited.

6.7. Evaluation of MAPK inhibitors in LCH

A high priority is to carry out intercontinental prospective trials evaluating the role of MAPK inhibitors in relapsed high-risk LCH (e.g. inclusion in a modified stratum III of the LCH IV trial: second-line therapy for high-risk). The substantial toxicity of current chemotherapeutic approaches further highlights the need for these approaches. Knowledge of the efficacy of MAPK inhibitors is not being systematically gained with the current substantial off-label use. There is a clear unmet need for companies to work in partnership with established histiocyte-focused cooperative groups to generate scientific knowledge that could be used for regulatory purposes. The second high priority in LCH is a trial that systematically investigates the value of MAPK inhibitors in LCH-neurodegenerative, especially since this devastating condition is not curable with the currently available chemotherapy and/or immunomodulation.

6.8. Evaluation of MAPK in RASopathies and other solid tumours

MAPK inhibitors will highly likely have a major role in other RASopathies caused by germline pathogenic variants in genes that encode RAS pathway proteins in addition to NF1, including malignant peripheral nerve sheath tumours, Noonan syndrome, cardiofaciocutaneous syndrome and Costello syndrome [105]. The role of MAPK inhibitors in other solid tumours (neuroblastoma and rhabdomyosarcoma [42,43]) is more complicated, in view of the complex genomic landscape and long pipeline of agents already under investigation. This is exemplified in the paediatric MATCH phase 2 trial Arm E which evaluated selumetinib in tumours harbouring activating MAPK pathway genetic alterations, but excluded LGG. Selumetinib demonstrated limited efficacy, indicating that pathway mutation status alone is insufficient to predict response to selumetinib [103].

7. Conclusions

In view of the MAPK signalling cascade being frequently activated across paediatric cancers, the development of successful therapeutic approaches to inhibit the pathway and monitoring validated functional endpoints in treated children with MAPK-pathway driven diseases are critical goals. Understanding specific tumour biology is crucial to develop the optimal combinations, to avoid paradoxical growth and to prevent unintended consequences including severe acute and late toxicity. The development of MAPK pathway inhibitors to date has been predominantly driven by adult indications. However, these inhibitors can address unmet paediatric needs in pLGG, pHGG, LCH, plexiform neurofibroma, JMML and potentially other paediatric tumours Box 1.

The rapid development and evaluation of combination approaches (ideally combining agents which each) show single agent activity and non-overlapping toxicity is required to optimise responses and to achieve more profound molecular and clinical responses. Furthermore, determining the optimal duration of therapy is important; treatment for an empirical, but well defined duration with integrated ancillary biological studies should facilitate establishing the rational duration of

Box 1. Text box of key conclusions of the Paediatric Strategy Forum

- The mitogen-activated protein kinase (MAPK) signalling pathway is activated in many paediatric cancers
- It is an important therapeutic target
- MAPK also signals through many other cascades and their feedback loops, and perturbing the MAPK pathway may have substantial influence on other pathways
- Development of MAPK pathway inhibitors to date has been predominantly driven by adult indications (e.g. malignant melanoma)
- MAPK inhibitors can address many unmet needs in paediatric low-grade gliomas, paediatric high-grade gliomas, Langerhans cell histiocytosis, plexiform neurofibroma and juvenile myelomonocytic leukaemia
- Although MAPK inhibitors have demonstrated activity, breadth and depth of responses need to be improved
- Better inhibitors with higher central nervous system penetration for cancers located in the brain need to be studied to determine if they are more effective than agents currently being used
- Rapid development and evaluation of combination approaches is required to optimise responses
- Understanding specific tumour biology is crucial to develop the optimal combinations, to avoid paradoxical growth and to prevent unintended consequences including severe toxicity
- Optimum duration of therapy with MAPK inhibition needs to be determined, by rationally designed studies
- Systematic and coordinated development of treatment strategies with MAPK inhibitors, rather than off-label use is needed to assess the risks and benefits of these agents and combination strategies in front-line and salvage settings.
- Platform trials could have an important role
- There is a major need for the international coordination of evaluation of products in development, in view of their number and a relatively small potential paediatric population, with RAS/MAPK pathway-driven diseases
- Accelerating the introduction of MAPK inhibitors into front-line studies is a priority, as is ensuring that these studies generate data appropriate for regulatory purposes
- Early discussions with regulators are crucial, in designing trials
- Additional functional end-points e.g. visual acuity, quality-of-life, motor function and neuro-psychological function are important so that these agents benefit children with paediatric low-grade gliomas and should be included in initial designs and agreed upon prospectively with regulators
- Long-term follow-up of patients receiving these inhibitors is crucial in view of their prolonged administration and the involvement of the pathway in normal development

treatment. Accelerating the introduction of MAPK inhibitors into front-line studies is a priority, as is ensuring that these studies generate data appropriate for regulatory purposes. Early discussion with regulators is crucial, particularly if randomised control trials are challenging to perform.

Additional end-points of function and quality of life (as these outcomes are often more reflective of benefit for lower grade tumours such as paediatric low-grade glioma and plexiform neurofibroma) should be included in initial study designs for pLGG and agreed upon prospectively with regulators.

8. Participants

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Long-term follow-up of patients receiving MAPK pathway inhibitors is particularly crucial in view of the prolonged administration that is currently required and the involvement of the MAPK pathway in normal development. Currently, late sequelae of therapy are unknown and determining these are critically important especially in good prognosis tumours. The ACCELERATE long-term follow-up initiative should provide an appropriate infrastructure to accomplish this important task.

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