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Review

Paediatric strategy forum for medicinal product development of PI3-K, mTOR, AKT and GSK3β inhibitors in children and adolescents with cancer

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ABSTRACT

Phosphatidylinositol 3-kinase (PI3-K) signalling pathway is a crucial path in cancer for cell survival and thus represents an intriguing target for new paediatric anti-cancer drugs. However, the unique clinical toxicities of targeting this pathway (resulting in hyperglycaemia) difficulties combining with chemotherapy, rarity of mutations in childhood tumours and concomitant mutations have resulted in major barriers to clinical translation of these inhibitors in treating both adults and children. Mutations in *PIK3CA* predict response to PI3-K inhibitors in adult cancers. The same mutations occur in children as in adults, but they are significantly less frequent in paediatrics. In children, high-grade gliomas, especially diffuse midline gliomas (DMG), have the highest incidence of *PIK3CA* mutations. New mutation-specific PI3-K inhibitors reduce toxicity from on-target PI3-Kα wild-type activity. The mTOR inhibitor everolimus is approved for subependymal giant cell astrocytomas. In paediatric cancers, mTOR inhibitors have been predominantly evaluated by academia, without an overall strategy, in empiric, mutation-agnostic clinical trials with very low response rates to monotherapy. Therefore, future trials of single agent or combination strategies of mTOR inhibitors in childhood cancer should be supported by very strong biological rationale and preclinical data. Further preclinical evaluation of glycogen synthase kinase-3 beta inhibitors is required. Similarly, even where there is an AKT mutation (~0.1 %), the role of AKT inhibitors in paediatric cancers remains unclear. Patient advocates strongly urged analysing and conserving data from every child participating in a clinical trial. A priority is to evaluate mutation-specific, central nervous system-penetrant PI3-K inhibitors in children with DMG in a rational biological combination. The choice of combination, should be based on the genomic landscape e.g. *PTEN loss* and resistance mechanisms supported by preclinical data. However, in view of the very rare populations involved, innovative regulatory approaches are needed to generate data for an indication.

1. Introduction

Mutations of the phosphoinositide 3-kinase (PI3-K) signalling pathway are rare in paediatric malignancies (about 1–2 % of tumours), however the pathway is constitutively activated or up-regulated in many paediatric cancers. This raises questions about the importance of this target for the development of new paediatric anti-cancer drugs [1,2]. In addition, unique clinical toxicities of targeting this important metabolic pathway with PI3-K/AKT/mTOR inhibitors have been observed in adults, particularly when these drugs are combined with chemotherapies [3]. A large array of inhibitors of this pathway have been developed and approved for adult cancers, yet very few have received paediatric regulatory approval. In addition, the optimal use of these inhibitors and how best to combine them with other agents commonly used in children is not fully understood. Furthermore, despite the large number of inhibitors and the apparent relevance to paediatric cancers, inhibition of these targets has not to date had a major impact for most children and adolescents and, at present, only four front-line phase 3 trials have incorporated this class of drugs [4–7].

The eleventh multi-stakeholder Paediatric Strategy Forum [8–17] organised by ACCELERATE [18,19] in collaboration with the European Medicines Agency (EMA) and with the participation of the US Food and Drug Administration (FDA) focussed on targeting the PI3-K signalling pathway in paediatric and adolescent cancers with specific discussion of PI3-K, mTOR, AKT and glycogen synthase kinase-3 beta (GSK3β) inhibitors.

The meeting was held at the Dana-Farber Cancer Institute, Boston, Massachusetts, United States on 3 and 4 April 2023. There were 146 participants, 48 in person, and 98 virtual from 27 countries: 83 international clinical paediatric oncology and biology experts from Europe, the United States (US), Canada, Japan, Australia, Africa and Asia; an expert in adult anti-cancer drug development; 26 representatives from eight pharmaceutical companies (Actuate Therapeutics, AstraZeneca, Bayer, Celcuity, Genentech, Kazia Therapeutics, LOXO/Eli Lily, Merck); 22 patient advocates from Europe, the US and Nigeria (representatives from Alan B. Slifka Foundation, Andrew McDonough B+ Foundation, Children's Cancer Cause, Coalitional Against Childhood Cancer, Dorcas Cancer Foundation, The EVAN Foundation, Imagine for Margo, National Brain Tumor Society, Nikita, Paediatric Brain Tumor Foundation of the US, Rally Foundation for Childhood Cancer Research, Solving Kids' Cancer [US], Swiss DIPG, Zoé4life and Childhood Cancer International Europe); 15 regulators from the EMA (including the Paediatric Committee [PDCO]) and national competent authorities within the EU regulatory network and US FDA as observers; and two organisers. To provide a basis for discussion, academic experts first presented an overview of the biology of the pathway, genetic disorders driven by pathway mutations, successful experiences with PI3-K/AKT inhibitors in adults, the genomic landscape in children and combination strategies. Potential lessons learnt from mTOR inhibitors were highlighted. Details of ten PI3-K, AKT and GSK3β inhibitors were presented by companies or academic investigators. The Forum concluded with the patient advocates' perspective and a multi-stakeholder strategic discussion.

2. Biology of the PI3-K/AKT/mTOR pathway

PI3-K is a lipid kinase that phosphorylates phosphatidylinositol-4,5-bisphosphate (PIP2) at the 3 position to generate a membrane embedded second messenger phosphatidylinositol- 3,4,5-trisphosphate (PIP3) [20]. PIP3 was found to be the optimal substrate for the tumour suppressor protein, phosphatase and TENsin homolog (PTEN) [21], which is the second most frequently lost tumour suppressor gene in human cancers. An overview of the pathway is shown in Fig. 1.

Insulin binds to the insulin tyrosine kinase receptor which then phosphorylates insulin receptor substrate at sites optimal for binding to PI3-K and generates PIP3. Insulin increases glycogen production, protein synthesis, glucose uptake and reduces the transcription of gluconeogenesis in all cells. PTEN dephosphorylates PIP3 thereby inhibiting this pathway activation. In summary, growth factors (PDGF, IGF1 and others) and hormones (e.g. insulin) activate PI3-K and drive growth and cell survival through glucose uptake and metabolism and PTEN counteracts [22].

Activating mutations, amplifications, or both of *PIK3CA*, the gene for PI3-K, most frequently occur in women's cancers (uterine, cervical, breast and ovarian) and colorectal cancers. Most human cancers have either PTEN loss, *PIK3CA* mutations, amplifications, or both [23,24].

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In addition, in *PIK3CA*-related overgrowth syndromes (PROS), mosaic activating mutations in *PIK3CA* (the same as in malignancy) result in localized hypertrophy, illustrating that, while *PIK3CA* mutations alone are not enough to cause cancer, they can serve to accelerate tissue growth [25].

PI3-K is a dimer composed of p85 and p110α subunits. There are oncogenic mutations (most frequently E453/E545 mutated p110α) in the catalytic subunit of PI3-K, and in H1047R p110α (40 %), which result in strong activation of the insulin pathway [26–29].

AKT phosphorylates tuberous sclerosis complex 2 (*TSC2*) and loss of *TSC2* causes hyper-activation of the downstream mammalian target of rapamycin (mTOR) pathway, resulting in the tuberous sclerosis complex (TSC). Subependymal giant cell astrocytomas (SEGAs) associated with TSC are treated with mTOR inhibitors [30].

In mice and humans, PI3-K inhibition increases blood glucose and induces over-secretion of insulin, which may be relevant to tumour control. The PI3-K inhibitor, BKM120, results in cell death in organoid cultures of *PIK3CA* mutant endometrial cancer, but in the presence of insulin the cells survive as insulin protects from BKM120-induced cell death [31]. High insulin levels therefore override the effects of PI3-K inhibition. Approaches to reduce glucose levels without exogenous insulin include: metformin (suppressing glycogenesis in the liver), SGLT2 inhibitors (inhibiting reabsorption of glucose in the kidney) and a ketogenic (very low carbohydrate, high fat) diet. In mouse models, a ketogenic diet is the most effective approach to keep insulin levels low and cause tumour regression with a PI3-K inhibitor. This anti-tumour effect is abrogated by the addition of insulin. SGLT2 inhibitors were the second most effective strategy [31]. High insulin levels therefore override the effects of PI3-K inhibition. In the phase Ib study of alpelisib (BYL719), a PI3-Kα-specific inhibitor, responses were observed and metformin or sodium-glucose cotransporter-2 (SGLT2) inhibitor was administered, to control drug-induced elevated glucose levels and no patients received insulin [32]. In contrast, a phase 1 trial of taselisib allowed insulin for glucose control and no responses were observed [33]. Clinical trials are ongoing combining PI3-K inhibitors and a ketogenic diet in endometrial cancer, lymphoma and HER2 negative breast cancer.

There are now specific inhibitors of the *H1047R* mutant form of *PIK3CA* [34]. Since wild-type PI3-K is less inhibited by these mutation-specific inhibitors, these are thought to not cause hyperglycaemic effects.

In conclusion, high serum insulin levels protect tumour cells from PI3-Kα inhibitors, so maintaining low serum glucose and insulin during therapy is critical for tumour killing with these drugs. Specific inhibitors of the mutant form of *PIK3CA* (i.e. *H1047R)* do not raise serum insulin and are far more effective in pre-clinical trials.

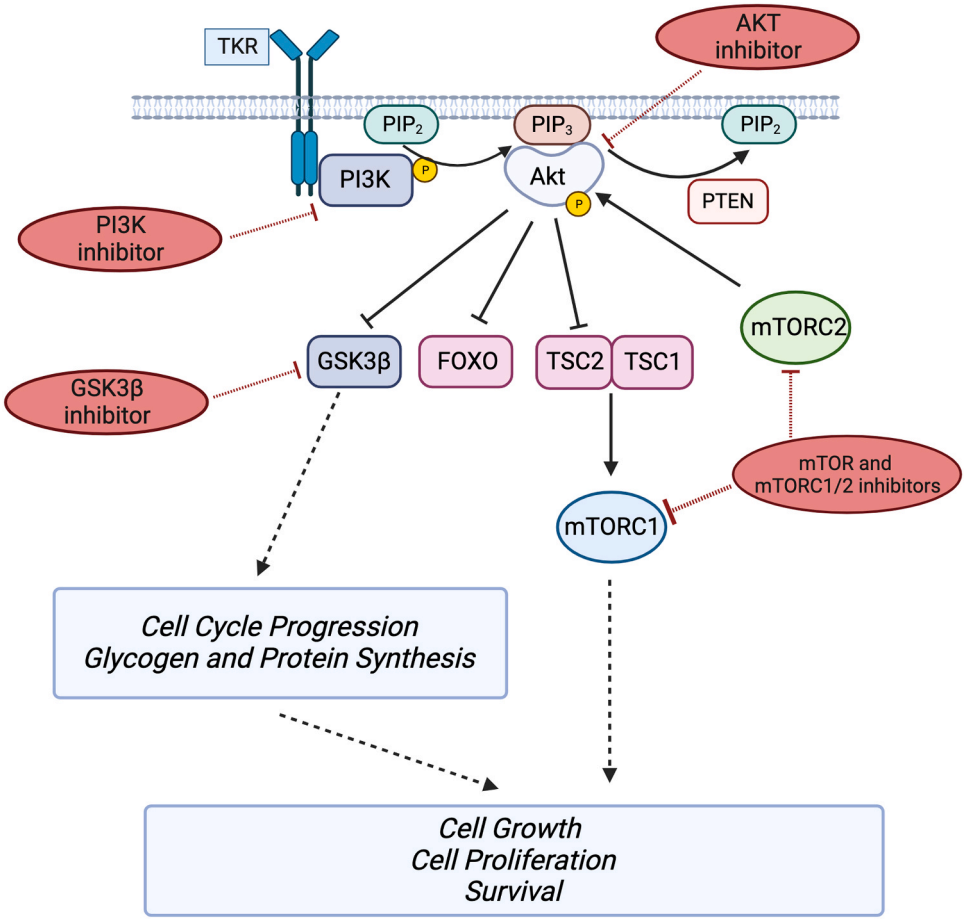

Fig. 1. Schematic overview of the PI3K/AKT/mTOR pathway. Activation of tyrosine kinase receptors (TKR) results in the activation/recruitment of phosphatidylinositol 3-kinase (PI3K) to the cell membrane, which in turn phosphorylates phosphatidylinositol-4,5-biphosphonate (PIP2) to phosphatidylinositol-3,4,5-biphosphonate (PIP3). PIP3 interacts with and activates AKT which in turn phosphorylates and inhibits glycogen synthase kinase-3 beta (GSK3B) leading to cell cycle progression and alterations in protein and glycogen synthesis. Similarly, activated AKT inhibits FOXO1 and tuberous sclerosis complex 2 (TSC2). In turn, inhibition of TSC2 leads to activation of the mammalian target of rapamycin complex 1 (mTORC1). All of these signalling pathways result in increased cell proliferation, growth, and survival. The mammalian target of rapamycin complex 2 (mTORC2) can also activate AKT. The tumour suppressor phosphatase and TENsin homolog (PTEN) inactivates PIP3 back to PIP2. Created with BioRender.com.

3. Lessons learnt from genetic disorders driven by pathway mutations - PIK3CA-related overgrowth syndromes (PROS)

A mosaic gain of function *PIK3CA* mutation is responsible for the majority (80 %) of overgrowth syndromes [25,35–38]. In 2018, alpelisib, a PI3-K α isoform inhibitor, was demonstrated to have substantial activity in a patient with PROS [39]. The mechanism of the response was confirmed in a PROS mouse model, which responded to alpelisib and progressed on withdrawal of alpelisib [40].

EPIK-P1, a retrospective chart review, provided real-world data of patients with PROS and a confirmed *PIK3CA* mutation who received alpelisib under a managed access programme [41]. Out of 57 patients, 37.5 % had a reduction of $\geq$ 20 % and 74.2 % had any reduction in target lesion volume; no patients progressed and symptoms improved. The dose administered was 250 mg/day in contrast to the single agent maximum tolerated dose of 400 mg/ day [42], indicating that as PI3-K is the driver, a lower dose was sufficient to achieve therapeutic benefit. Based on EPIK-P1, alpelisib was granted accelerated FDA approval in April 2022 for patients over two years of age with PROS [43]. Recently, infants (< 2 years) with PROS have responded to alpelisib [44].

EPIK-P2 [45] is an ongoing trial randomising alpelisib and placebo, followed by crossover for patients receiving placebo. In addition, the biology of the differences in clinical manifestations of *PIK3CA* mutation and response to alpelisib between different tissues is being elucidated [46,47].

4. Lessons learnt from genetic disorders driven by pathway mutations - Proteus syndrome and AKT inhibition

Proteus syndrome is an ultra-rare (estimated to affect ~300 individuals globally) mosaic overgrowth disorder caused by an *AKT1* mutation during development [48]. It is almost always an AKT^{E17K} mutation and leads to a heterogenous spectrum of severity and manifestations of Proteus syndrome most commonly causing bony overgrowth and cerebriform connective tissue nevi (CCTN) [49] but also changes in skin, bone, soft tissues and viscera and predisposing to tumours. Miransertib, a pan-AKT inhibitor [50], was shown to decrease phospho-AKT and downstream signalling in patient derived fibroblasts [51]. The phase 1 pharmacodynamic study of six individuals with Proteus syndrome demonstrated a 50 % reduction in phospho-AKT in affected tissue from five individuals at a dose of about 5 % used in oncology trials, and clinical improvement [52]. Subsequently, a study to evaluate the effect of miransertib on the manifestations of Proteus syndrome has been opened [53]. In view of the rarity and heterogeneity, a randomised study was not considered feasible and therefore a single arm design, with real world data to inform control estimates is being used and will require only 10 individuals with a 70 % response.

5. Lessons learnt from successful adult oncology development of PI3-K inhibitors

Development of PI3-K inhibitors in adult malignancies has followed the principles of i) what is the target gene/protein? ii) is there a biomarker? and iii) what is the disease of interest? (should the development be disease specific or disease agnostic)? However, it has been challenging, predominantly due to agent toxicity and the need for combinations.

Mutations in *PIK3CA* are common actionable alterations in breast, colorectal, endometrial, ovarian and gastric cancers, and selected central nervous system (CNS) tumours [54]. Unlike in PROS, most *PIK3CA* mutations do not dramatically activate the protein and do not automatically result in cancer. Very high levels of the oncogenic protein are required to cause malignancy and a secondary, cooperative event, for example PTEN alteration, or sometimes other mutations are required [55–57]. Usually, the cooperative event is in a different pathway or collateral event.

PI3-K has four isoforms (α, β, γ, and δ) and there has been increasing selectivity in the development of PI3-K inhibitors [28]. Pan-PI3-K/mTOR inhibitors (apitolisib, BEZ235, GSK21264580), pan-PI3-K (buparlisib, copanlisib, pictilisib, pilaralisib) were generally toxic, with gedatolisib (pan-PI3-K/mTOR) and copanlisib (pan--PI3-K/mTOR) less so. The PI3-K β-sparing inhibitor (taselisib) [33] had high δ activity and caused chronic colitis, which was predicted from the mouse model [58,59]. The α isoform-specific inhibitor (alpelisib) tended to be less toxic, active against mutant and wild type α PI3-K, but inactive against β, γ, and δ, nor mTOR [60]. There is also a β-isoform-specific inhibitor (AZD8186) and more selective inhibitors (GDC-0077 [mutant –p110α]). More recently, new mutation specific PI3-K inhibitors RLY-2608 [mutant α], STX-478 [*H1047X*], LOXO-783 [*H1047R*]) reduce toxicity from on-target PI3Kα wild-type activity. As a result, these agents can be successfully combined with other inhibitors and are high priority to develop.

In the first trial of alpelisib (BYL719) in *PIK3CA*-altered solid tumours (BYL719X2101), there were limited response rates, in contrast to the early results of BRAF inhibitors in *BRAF* mutated and driven cancers [42]. Sequencing of tumours of non-responder patients almost always demonstrated concomitant mutations in other genes whereas responders (mostly, ER-positive breast cancer patients) lacked other mutations [61]. This highlights that the disease context is very important.

In vivo investigations showed that PI3-K inhibition in breast cancer enhanced oestrogen receptor function. [62] Therefore subsequent trials combined oestrogen receptor and PI3-Kα inhibition with alpelisib and fulvestrant (a selective oestrogen receptor degrader) [63]. In the SOLAR 1 trial, the combination of alpelisib and fulvestrant was superior to placebo and fulvestrant, with greater benefit in second rather than first line therapy [64]. These findings emphasize the concept of the right patient at the right time with the right treatment. Other combinations including CDK 4/6 inhibitors (the third important target in ER-positive breast cancer) are being evaluated [65,66].

Investigations of metastases from a tumour that initially responded to BYL719 revealed loss of PTEN by two different genetic alterations [67]. Moreover, resistance developed in response to a first line therapy can generate resistance to secondary therapies simultaneously. For example, acquired PTEN loss mediates cross-resistance to CDK4/6 and PI3-Kα inhibitors [68]. One current hypothesis is that multiple agents given concomitantly to vertically inhibit the pathway will be more effective than sequential administration; however, toxicity is the major challenge [69]. The recently developed mutant specific inhibitors RLY-2608 [70], STX-478 [71] and LOXO-783 [72] show efficacy with less toxicity.

AKT inhibitors are being investigated in clinical trials and are well tolerated. Encouraging levels of activity have been reported in patients with cancers harbouring AKT^{E17K} mutations, which supports the use of biomarker-driven patient selection in the future clinical development of these products. In the FAKTION trial (capivasertib and fulvestrant), capivasertib predominantly benefited patients with tumours with alterations in the pathway compared to the non-altered subgroup [73,74]. These results with AKT inhibitors need to be verified in Phase 3 trials.

In summary, *PIK3CA* mutations can be successfully targeted in adult tumours. Improving the therapeutic window is key to improving PI3-Kα anti-tumour activity [75] and the new mutation-specific inhibitors offer great potential. AKT inhibitors may have similar potential in AKT-altered tumours. The choice of concomitant combination therapy should be based on the molecular landscape and knowledge of the resistance mechanisms. These data are critical to understanding the appropriate development pathway in the paediatric population.

6. Genomic landscape in children and potential genomic predictors for activity

In adults, *PIK3CA* mutations occur in 11.6 % of all tumours and the most frequent of these are p.H1047 (34 %), p.E545 (27 %) and p.E542

(14 %) [76,77]. In contrast, in paediatric cancers, *PIK3CA* is mutated in only about 1–2 %, of tumours. The mutations are located within the same hotspots across adult and paediatric tumours [78,79]. Loss or mutation of PTEN occurs in 0.9 % of paediatric malignancies and other mutations of the PI3-K pathway are even less common (PIK3R1 [0.8 %], mTOR [0.7 %], TSC 1 [0.6 %], TSC 2 [0.6 %], AKT1 [0.5 %], AKT2 [0.2 %] and AKT3 [0.6 %]) [78,79].

Data from St Jude Children's Research Hospital PeCanPortal demonstrate a 1 % (61/5800) incidence of *PIK3CA* mutations in paediatric malignancies [80]. High-grade gliomas have the highest incidence of mutations and diffuse midline gliomas (DMG) have the highest proportion of *PIK3CA* mutations (17.5 % [10/57]), compared to 2.7 % (37/1378) of all CNS tumours and 6 % (4/67) of non-brain stem high-grade gliomas [80]. Approximately 5–6 % of DMG have a *H1047R* mutation [81] (5.7 % [8/140] Inform series personal communication D Jones).

An arm of National Cancer Institute–Children's Oncology Group (COG) Paediatric MATCH on the PI3-K pathway is investigating the use of samotolisib in patients with either *TSC1*, *TSC2*, *mTOR*, *PIK3R1*, *PIK3CA* mutations or *PTEN* mutation and loss [82]. Overall, the incidence of these mutations was similar to those previously reported; notably 40 % of tumours also had a MAPK pathway mutation [82].

7. Development of mTOR inhibitors in children

mTOR inhibitors were the first PI3-K-AKT-mTOR pathway inhibitors evaluated in children. The first generation of mTOR inhibitors included everolimus, temsirolimus, sirolimus (rapamycin), ridaforolimus, umirolimus, zotarolimus and the second generation were ATP-competitive mTOR kinase inhibitors including mTORC1/2 dual inhibitors (torin-1, torin-2, vistusertib) and mTOR/PI3-K dual inhibitors (paxalisib, samotolisib, SF-1126).

Everolimus was first approved in 2009 by the FDA and the EMA for renal cell carcinoma in adults. It was approved for SEGA in TSC in children and adults in 2010 in the US and in 2011 in Europe. The FDA has approved paediatric formulations for SEGA and TSC seizures.

Based on a review of clinicaltrials.gov [83] and PubMed [84], since 2000 there have been 59 trials with everolimus which allowed inclusion of paediatric patients (below 18 years of age), 34 (58 %) were for an oncological condition and 25 (44 %) for a non-oncological condition. Most of the trials for an oncological condition had an academic sponsor (31/34), with only three sponsored by industry. Moreover, most (30) were early phase/phase 2 trials. Four late phase trials have evaluated mTOR inhibitors: a Phase 3 COG ARST1431 evaluating temsirolimus in intermediate-risk rhabdomyosarcoma (academic) [4]; EXIST-1, evaluating everolimus in SEGA in TSC (Novartis) [5], BIOMEDE evaluating everolimus and radiotherapy versus erlotinib and radiotherapy versus dasatinib and radiotherapy in biomarker selected patients with diffuse intrinsic pontine glioma (DIPG) (academic) [6] and BIOMEDE2 evaluating everolimus and radiotherapy compared to ONC201 and radiotherapy in DIPG (academic) [7]. The substantial imbalance of early to late phase trials indicates that most combinations or indications do not progress to front-line evaluation. Fourteen of the 34 oncological trials were single centre trials, with only two intercontinental. The first trial opened in 2004 with maximum number of trials opened in 2011 and 2012 and some trials were still opening in 2022.

The results of fifteen clinical trials of everolimus in paediatric cancer have been published: eight for CNS tumours [85–92] (SEGA in TSC [2] [91,92]), three for solid tumours [93–95], two for haematological malignancies [96,97] and two agnostic/mutation-driven [98,99]. With single agent therapy, the overall response rates for SEGA were 78 % (61/78), for low grade gliomas - objective response rate (ORR) 11 % (5/45), stable disease (SD) 49 % (22/45) and for solid tumours - ORR 1.8 % (1/57), SD 28 % (16/570). In combination, the response rates were 22 % with vemurafenib in BRAF positive tumours [99], 33 % with vorinostat in Hodgkin's lymphoma [97] and 86 % with chemotherapy in ALL [96], however there was no activity with ribociclib or bevacizumab [89,90,95,98].

There is a similar pattern with temsirolimus as with everolimus. From 2005 to 2016, there have been 32 trials for paediatric cancer with 97 % (31) academic sponsored, 6 % (2) late-phase, 44 % (14) single centre and 91 % (29) combination trials.

8. Products discussed at the Forum Paediatric Investigation Plans (PIPs) and details of completed paediatric trials

Ten medicinal products – alpelisib, LOXO-783, copanlisib, inavolisib, gedatolisib, paxalisib, capivasertib, miransertib, ipatasertib and 9-ING-41 were discussed (Table 1).

As of April 2023, there are two published agreed PIPs for PI3-K and mTOR inhibitors in oncological indications: copanlisib (PI3-Kδ/α inhibitor) with an indication of relapsed or refractory neuroblastoma, Ewing sarcoma, osteosarcoma or rhabdomyosarcoma including in combination with chemotherapy; everolimus (mTOR inhibitor) for the treatment of patients with SEGA associated with TSC. As mentioned previously there is a PIP for alpelisib (PI3-Kα inhibitor) with an indication for treatment of PROS. There are no published agreed PIPs for AKT and GSK3β inhibitors (Table 2).

Details of completed, discontinued and ongoing paediatric trials of PI3-K, mTOR, AKT and GSK3β inhibitors are shown in Table 3. In summary, there are 95 relevant paediatric trials, 18 with PI3-K inhibitors, 7 with AKT, 66 with mTOR, and 4 GSK3 inhibitors, involving 21 products (12 PI3-K, 4 AKT, 3 mTOR, 2 GSK3 inhibitors). Most 56 % (53/95) are combination trials, particularly for mTOR inhibitors, 73 % (48/66).

9. Combination strategies

Sequencing cancer cell lines in the paediatric cancer dependency project highlighted important differences between paediatric and adult tumours with PI3-K pathway mutations. There was no enrichment of PI3-K pathway dependencies compared to adult tumours [100]. Thus, in paediatric cancer, distinct from PROS, there is a low a priori expectation of single agent activity, therefore it is crucial to consider how these inhibitors can be used as combination partners.

To date, there have been no completed chemotherapy combination trials with PI3-K or AKT inhibitors, in contrast to many completed chemotherapy combination trials with mTOR inhibitors.

There are two broad rationales for use of inhibitors as combination partners; a) synthetic lethality with novel agents - unfortunately there

Table 1
PI3-K, mTOR, AKT and GSK3β inhibitors discussed at the Forum.

Product	Target	Paediatric clinical trials (recruiting)	Paediatric Investigation Plan (PIP)	Company
Alpelisib[a]	PI3-Kα	3(2)[b]	+	Novartis
Copanlisib	PI3-Kδ/α	1(1)	+	Bayer
Inavolisib	PI3-K	0		Genentech
LOXO-783	PIK3CA (H1047R)	0		LOXO/Eli Lily
Gedatolisib	Dual PI3-K/mTOR	0		Celcuity
Paxalisib	Dual PI3-K/mTOR	1(1)		Kazia Therapeutics
Capivasertib	AKT	0		AstraZeneca
Miransertib	AKT	3(2[c,d])		Merck
Ipatasertib	AKT	3(1)		Genetech
9-ING-41	GSK3β	3 (1)		Actuate Therapeutics

[a] Presented by an academic investigator; b PROS and megalencephaly-capillary malformation polymicrogyria syndrome; c Active, but not recruiting; recruiting trial for Proteus syndrome

Table 2
Published PIPs agreed for PI3-K, mTOR, AKT and GSK3β inhibitors, PIP for alpelisib (PI3-Kα inhibitor) with an indication for treatment of PROS.

Product	Copanlisib (Bayer)	Everolimus (Novartis)
PIP	Modified PIP 2020 (EMEA-001757-PIP02-15-M02)	Modified PIP 2014 for SEGA (EMEA-000019-PIP02-07-M05) Modified PIP for TSC (EMEA-000019-PIP08-12-M03) and for solid transplants (EMEA-000019-PIP06-09-M05) [Waivers for thoracic neuroendocrine tumor 2015, for carcinoid tumors 2008, for renal cell carcinoma and pancreatic NET 2007]
MoA	PI3-Kδ/α	mTOR
Condition	Treatment of all conditions included in the category of malignant neoplasms (except haematopoietic and lymphoid tissue)	Treatment of subependymal giant cell astrocytoma
PIP Indication	Treatment of children with a relapsed or refractory neuroblastoma, Ewing sarcoma, osteosarcoma or rhabdomyosarcoma including at first relapse, in combination with chemotherapy.	Treatment of patients with subependymal giant cell astrocytomas (SEGA) associated with tuberous sclerosis complex (TSC)
Waiver	0-6 months	None
Deferral	By 2027	By 2015
Formulation	Powder for solution for infusion, intravenous use	Tablet Dispersible tablet
Clinical	Open-label, non-controlled, dose escalating - PK, PD, safety and activity of copanlisib in relapsed/refractory solid tumour or lymphoma (6mo-18y) Expansion phase in relapsed/refractory neuroblastoma, osteosarcoma, rhabdomyosarcoma, Ewing (6mo-18y) Randomised, controlled – safety and efficacy of copanlisib + anticancer therapy in relapsed/refractory neuroblastoma, osteosarcoma, rhabdomyosarcoma, Ewing 6mo-18y)	Relative bioavailability study between intact 1 mg tablet and 1 mg tablet dispersed in water in adults Bioequivalence study between intact 1 mg tablet and 5 mg dispersible tablet in adults. Randomised, double-blind, placebo-controlled, parallel-group, dose-titration, comparative, multi-centre study → PK, safety, tolerability and activity of everolimus in children (0-18y).

PK - pharmacokinetic, PD, - pharmacodynamic

are no known examples relevant to the PI3-K pathway; b) additivity/synergy with combination partners. There are several examples of this:

i. *Enhancing chemosensitivity*: a combination of irinotecan and temozolomide with temsirolimus with a 16 % response rate [101]. COG ARST0921 comparing bevacizumab versus temsirolimus with a vinorelbine and cyclophosphamide backbone demonstrated a superior event free survival (EFS) with temsirolimus, although there was no difference in response rate and overall survival [102]. Based on this, COG ARST1431 evaluated vincristine, dactinomycin and cyclophosphamide alternating with vincristine and irinotecan with or without temsirolimus in rhabdomyosarcoma [4]. COG ANBL1221 compared dinutuximab versus temsirolimus with an irinotecan and temozolomide backbone and dinutuximab was found to be superior [103]. This highlights that disease context matters. In ESMART, vistusertib (TORC1/2 inhibitor) was given as monotherapy in Arm E or in combination with topotecan and temozolomide in Arm F [104]' but these arms were terminated prematurely. Similar to other combinations, the dose of the novel agent and the backbone chemotherapy had to be reduced because of toxicity and no responses were observed. In ALL, everolimus and a four-drug induction [96] and temsirolimus with cyclophosphamide/etoposide have been evaluated and found to be safe. [105]. However, it is unknown if responses rates would have been the same without an mTOR inhibitor; this highlights the value of randomised trials.

ii. *Increased DNA damage*: there are no published paediatric combinations with DNA damage repair inhibitors nor with radiotherapy, although one trial is ongoing [106].

iii. *Combinations with anti-angiogenic inhibitors:* there is a completed, but not yet published paediatric trial of everolimus and lenvatinib in paediatric cancers [107]. A published trial of everolimus and sorafenib in adults with recurrent osteosarcoma reported a 6-month PFS 45 % [108]. This compared favourably to 29 % with sorafenib monotherapy [109] and 12 % at 4-months in COG phase 2 pooled experience [110]. Several trials of sirolimus with metronomic chemotherapy demonstrated that the combination was tolerable [111,112], but with limited antitumor activity. Similar results were obtained with everolimus and bevacizumab [95].

iv. *Vertical inhibition: abrogating signalling at other nodes in axis:* currently there is no clear evidence of a therapeutic benefit with vertical inhibition. The best example is a combination of IGF-1R inhibitors and temsirolimus. Two studies reported 12 % and 15 % response rates in Ewing sarcoma [113,114], which is similar to those seen with an IGF-1R inhibitor alone. In a study of the combination in all histologies, no responses were seen [115]. Combination therapy produced greater toxicity than expected with each single agent. A trial of the AKT inhibitor perifosine and temsirolimus had no responses [116].

v. *Target signalling in two pathways*: an adult trial combining trametinib and temsirolimus was unable to identify a recommended phase two dose [117], however, there is an ongoing paediatric trial of the combination [118].

vi. *Dual inhibition of cell cycle*: three trials of a mTOR and CDK4/6 inhibitor [88,89] including a trial with molecular enrichment [98], again demonstrated that reduced doses were required when used in combination therapy. In addition, in two trials combining ribociclib and everolimus in recurrent CNS tumours. These data are critical to understanding the appropriate development pathway in the paediatric population including DIPG and high grade gliomas, there were no responses and a median of survival in DIPG was similar to registry data [88,89]. In a molecularly enriched population, when ribociclib was combined with topotecan and temozolomide there were no objective responses, but 14.3 % of the patients had stable disease. When ribociclib was combined with everolimus again there were no objective responses but 41.2 % had stable disease, albeit a significant leukemic blast reduction was noted in a patient with T-ALL that exhibited genetic activation of both pathways [98].

There are several ongoing paediatric trials of combination products that target multiple pathways with one agent: samotolisib (dual PI3-K/mTOR inhibitor) in Paediatric MATCH [82]; paxalisib (CNS penetrant dual PI3-K/mTOR inhibitor) for midline glioma [119]; two trials of fimepinostat (dual HDAC/PI3-K inhibitor) [120,121]. The trial of SF1126 (dual PI3-K/mTOR inhibitor) for neuroblastoma was terminated [122].

In summary, many trials are based on empiricism. Combination doses have been identified, but often at lower dose(s) than the single agent recommended dose due to toxicity. There are some signals of combination activity in ALL, osteosarcoma, and rhabdomyosarcoma. However, as there are very few randomised trials, the contribution of the mTOR inhibitor is difficult to ascertain and there are no predictive biomarkers to guide trial development.

Table 3
Summary of completed and ongoing paediatric trials of PI3K, AKT and GSK3β inhibitors.

Product (Company)	Target	Paediatric Trials				
		Name - NCT	Phase	Treatment	Indication	Status (Study Start)
Paxalisib (Kazia) [106]	Dual PI3-K/ mTOR	NCT05009992	2	Paxalisib + ONC201 + RT	DIPG	Recruiting (2021)
Samotolisib (Eli Lilly)[82]	Dual PI3-K/ mTOR	NCT03213678	2	Monotherapy	Relapsed/refractory solid tumors, NHL, HCL with TSC or PI3K/mTOR mutations	Active, not recruiting (2017)
SF-1126 (SignalRX) [122]	Dual PI3-K/ mTOR	NCT02337309	1	Monotherapy	Relapsed/refractory neuroblastoma	Terminated (2015)
Copanlisib (Bayer) [138]	PI3-K δ/α	NCT03458728	1/2	Monotherapy	Relapsed/refractory solid tumors or lymphoma	Recruiting (2018)
Duvelisib (Secura Bio)[139]	PI3-Kδ/γ	NCT02028039	2	Monotherapy	Relapsed/refractory ALL	Withdrawn (2013)
Alpelisib (Novartis) [45,140,141]	PI3-K α	NCT05577754	2	Monotherapy	Megalencephaly-capillary Malformation Polymicrogyria Syndrome (MCAP)	Not yet recruiting (2022)
		NCT04980833	2	Monotherapy	PIK3CA-related overgrowth spectrum (PROS)	Recruiting (2022)
		NCT04589650	2	Monotherapy	PIK3CA-related overgrowth spectrum (PROS)	Recruiting (2021)
Idelalisib (Gilead) [142,143]	PI3-K δ	NCT03349346	1	Idelalisib + CT (RICE)	B-cell lymphoma	Withdrawn (2019)
		NCT01393106	2	Monotherapy	R/R Hodgkin lymphoma	Completed (2011)
Leniolisib (Pharming) [144–147]	PI3-K δ	NCT05693129	3	Monotherapy	Activated PI3Kdelta Syndrome (APDS)	Recruiting (2023)
		NCT05438407	3	Monotherapy	Activated PI3Kdelta Syndrome (APDS)	Not yet recruiting (2022)
		NCT02435173	2/3	Monotherapy	APDS or Common Variable Immunodeficiency	Completed (2015)
		NCT02859727	2/3	Monotherapy	Activated PI3Kdelta Syndrome (APDS)	Active, not recruiting (2016)
Umbralisib (Rhizen) [148,149]	Dual PI3-Kδ /CK1ε	NCT03364231	2	Monotherapy	NHL (Waldenstrom Macroglobulinemia)	Completed (2017)
		NCT03207256	2	Umbralisib + Ublituximab	CLL or NHL	Terminated (2017)
Fimepinostat (Curis) [120,121]	PI3-K α/β/δ &HDAC 1/2/3/10	NCT03893487	1	Fimepinostat + surgery	DIPG or HGG	Active, not recruiting (2019)
		NCT02909777	1	Fimepinosta	Solid tumors (including neuroblastoma), lymphoma, or brain tumors.	Active, not recruiting (2016)
Ceralasertib (AZ) [150]	Dual ATR/PI3-K-related kinase	NCT04417062	2	Monotherapy	R/R osteosarcoma	Recruiting (2020)
Mirasentib (Merck) [53,151,152]	AKT	NCT03094832		Monotherapy	PIK3CA-related overgrowth spectrum (PROS)	Terminated (2017)
		NCT04980872	2	Monotherapy		Active, not recruiting (2021)
		NCT04316546	2	Monotherapy	Proteus syndrome	Recruiting (2022)
MK-2206 (Merck) [153]	AKT	NCT01231919	1	Monotherapy	R/R solid tumors or leukemia	Completed (2011)
TAS-117 (Taiho) [154]	AKT	NCT04770246	2	Monotherapy	Advanced/MTX solid tumors + /- germline PTEN inactivating mutations	Recruiting (2021)
Ipatasertib (Roche) [155]	AKT	TAPISTRY NCT04589845	2	Monotherapy	Advanced/MTX solid tumors	Recruiting (2021)
9-ING-41 (Actuate) [156–158]	GSK3β	NCT04239092	1	Monotherapy	R/R malignancies	Recruiting (2020)
		NCT05116800	2	9-ING-41 + CT (gemcitabine/docetaxel)	Advanced/MTX sarcoma	Withdrawn (2022)
		NCT04906876	2	9-ING-41 + CT (gemcitabine/docetaxel)	Advanced/MTX sarcoma in adolescents/ adults	Withdrawn (2021)
Tideglusib (AMO) [159]	GSK3β	NCT03692312	2/3	Monotherapy	Congenital myotonic dystrophy	Recruiting (2021)

CNS – central nervous system; DIPG – diffuse intrinsic pontine glioma; HRR - homologous recombination repair, NHL – non Hodgkin's lymphoma, HCL - Hodgkin's lymphoma, DDR - DNA Damage Response, HR - homologous recombination, RMS – rhabdomyosarcoma, RP2D – recommended phase 2 dose, SRCT – small round cell tumour

10. Discussion

10.1. Patient advocates' perspective

Patient advocates noted that the development of alpelisib for PROS reinforced lessons on how each research participant's data can add value to understanding the biology and treatment of paediatric cancers. Further, this example leads advocates to urge tighter collaborations among academic researchers and provides a model to address the needs of patients with rare paediatric cancers. It also demonstrated once again how advocates' early engagement in companies' planning can be beneficial to ensure that trial design meets the unmet needs of patients.

Advocates appreciated that while current technologies are critical to molecularly identify patients who might benefit from novel agents, they urged the use of new techniques for selecting patients for trials beyond molecular pathways. They encouraged greater consideration of the unique features of paediatric cancers (e.g. tumour microenvironment and cells' tendency to differentiate) to increase the validity of nonclinical research necessary for evaluating new paediatric indications.

While advocates supported some low-risk strategies, such as dietary interventions, to inhibit certain pathways critical for tumour growth, they strongly agreed that combining novel/novel or novel/standard agent are required to achieve the greatest therapeutic impact. Novel agents are expected to be more promising, but drugs repurposed based on adult clinical and preclinical data should be considered only with strong rationale. Finally, advocates noted that when investigators consider a drug for paediatric cancer evaluation, its expected lifespan in a company needs to be deeply understood so that trials are completed and that the research participation of each child with cancer is valued.

10.2. Specific themes

10.2.1. Role of the PI3-K pathway in paediatric cancer

PI3-K is associated with many genes that drive tumour formation. Mutations in *PIK3CA* predict response to PI3-K inhibitors in adult cancers [3], indicating that targeting of *PIK3CA* mutation is crucial. However, mutations of the pathway are rare (1.9 %) in paediatrics, with DMG having the highest frequency of PI3KCA mutations (16–20 %).

10.2.2. Lessons learnt from the clinical evaluation of mTOR inhibitors

mTOR inhibitors are effective, and everolimus, has been approved for the treatment of SEGA. Everolimus and temsirolimus have been predominantly evaluated in paediatric cancer by academia, generally in empiric, mutation-agnostic, uncoordinated clinical trials many without a clear biological rationale. Moreover, most trials did not enrich for a PI3K pathway activated study population. Response rates to monotherapy and combinations have been generally very low in children with relapsed cancers, with the exception of those with low grade gliomas. Moreover, due to lack of randomisation, it is uncertain how much of any observed activity in combination trials is due to mTOR inhibition. Lack of evidence of single-agent activity does not justify opening of combination trials as, generally, it is uncommon for additional meaningful clinical benefit to be observed for combinations in which an agent lacking evidence of single agent activity is evaluated [123–125]. Therefore, future trials of mTOR inhibitors in childhood cancer should be appropriately powered and not conducted unless there is a strong biological rationale and supportive preclinical data that demonstrate the potential for clinically meaningful benefit (e.g. regression of established tumours in preclinical in vivo models). To date, dual mTORC1/2 inhibitors have not been evaluated in detail in paediatrics. For example, the development of the TORC1/2 vistusertib was halted early due to a drug-intrinsic failure to engage the target, but not necessarily due to a lack of effect of dual TORC inhibition. Evaluation of novel anticancer therapies and combinations should be developed based on mechanism of action and robust preclinical evaluation and may include data from adult clinical trials.

10.2.3. Challenges of PI3-K inhibitors

To date the major barriers to the clinical translation of these inhibitors in both adults and children have been: i) limited single-agent activity as the pan PI3-K inhibitors target both wild-type and mutant PI3-K; ii) limiting toxicities including high blood glucose; iii) the effects being negated by high insulin levels and iv) lack of CNS penetration. Overall, this has resulted in very few completed studies in paediatrics and none in combination with other drugs.

With non-mutation specific inhibitors, a ketogenic diet, metformin, or SGLT2 inhibitors could be employed to overcome or prevent high insulin levels. Additionally, these challenges may be reduced with new mutation-specific PI3-K inhibitors with reduced toxicity from off-target PI3-Kα wild-type activity. Paediatric studies should be undertaken with mutation-specific inhibitors in tumours with the relevant mutations, acknowledging the rarity of such tumours.

10.2.4. How can PI3-K, mTOR, AKT and GSK3β inhibitors fulfil unmet needs in childhood cancer and which inhibitors are of the highest value for children?

The greatest potential role for PI3-K inhibition in childhood cancer is probably in DMG, where there is the highest frequency of *PIK3CA* mutations and a very substantial unmet clinical need. In view of the historical difficulties assessing these inhibitors, investigations should focus on DMG as proof of concept with mutation-specific CNS-penetrant inhibitors. However, the major challenge is the low frequency of the mutations (5–6 % of DMG have a *H1047R* mutation) and therefore there must be patient selection.

In addition, DMGs harbouring PIK3CA mutations showed increased sensitivity to the DRD2 antagonist and ClpP agonist ONC201, suggesting that PI3-K/Akt signalling promotes metabolic adaptation to ONC201-mediated disruption of mitochondrial energy homeostasis in DMGs [126]. However, there are emerging data that PI3-K may be a general dependency in DMG irrespective of PIK3CA status. Using a cancer cell line atlas and multiomics analyses, a substantial difference in PIK3CA gene dependency has been reported in paediatric compared to adult high grade gliomas [127]. Most paediatric high-grade gliomas (including DMGs) are highly sensitive to PI3-K inhibition compared with adult lines. However, unlike adult cancers (for example breast cancer) where PIK3CA mutations predict PIK3CA dependence, PIK3CA mutation did not predict response to PI3-K inhibition in paediatric high grade glioma cell lines [127]. In addition, in patient tumours there is a relative high frequency of alterations in AKT and PTEN. Therefore, an alternative approach to evaluate PI3-K inhibitors in DMG would be a less focused, not mutation specific, strategy, though this may be of limited utility for mutation-specific compounds with little off-target activity. The results of Combination Therapy for the Treatment of Diffuse Midline Gliomas (NCT05009992) evaluating paxalisib, ONC201 and radiotherapy in diffuse intrinsic pontine glioma are awaited.

Outside the very rare occasion where there is a mutation (~0.1 %), the role of AKT in paediatric cancers remains unclear. Robust preclinical anti-tumour activity for GSK3β inhibitors have been reported in paediatric tumours. As these drugs have, in addition to effect on the PI3-K pathway, multiple effects, including immune modulation (increases NK cell activity, regulates expression of immune checkpoints in tumours (PD-1, LAG-3, TIGIT), up-regulates MHC in MHC null or low tumour cell lines and decreases TCR clonality and increases specific T cell clonotypes), further preclinical evaluation is required to understand which patients are most likely to benefit. However, currently there is a lack of models for evaluation of drugs such as 9-ING41 that have immunomodulatory activity, and this presents a challenge to providing the pre-clinical rationale that is required to support the development of these immunomodulatory agents. The results of the ongoing clinical trial (NCT04239092) will demonstrate the toxicity profile and initial activity, but trials of biological rational combinations are required. TORC1/2 inhibitors have been studied in a few paediatric trials, however their results to date in children and adults do not prioritise their further evaluation, although there is pre-clinical activity in neuroblastoma [128].

A further potential role of inhibitors of the pathway relates to targeting MYCN protein. GSK3β regulates the phosphorylation status of T58, which is critical to the oncogenic activity of MYC proteins [129]. Degradation of MYCN is required for terminal differentiation of neuronal precursors [130]. Aberrant PI3-K/mTOR activity in neuroblastoma correlates with poor outcome [131], drives oncogenic stabilization of MYCN [132] and could be targeted by clinical PI3-K pathway inhibitors. However, destabilising of MYCN protein as an approach to target MYCN has not been evaluated in the clinic.

10.2.5. Optimal combinations

To date, paediatric combination trials with PI3-K inhibitors have generally been empiric and not based on tumour biology, in contrast to studies in advanced breast cancer. An appropriate combination, including with immunotherapy, must be based on disease biology, preclinical data, and resistance mechanisms. The choice of combination therapy should be based on the molecular landscape and knowledge of concomitant mutations in other genes, therefore molecular profiling of DMGs with *H1047R* mutations is high priority. The optimal combination in DMG will be discussed at the thirteenth Paediatric Strategy Forum on DMG in May 2023. The combinations assessed to date have demonstrated unique and increased toxicities, necessitating lower doses than used in monotherapy. An industry-supported, academic-sponsored platform trial with compounds from different pharmaceutical companies may be an approach. With very few randomised trials the contribution of, for example, mTOR inhibitors, is difficult to ascertain. To isolate the efficacy and toxicity contributed by a PI3-K pathway

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

- Mutations in PIK3CA encoding PI3-K are the most common actionable alterations in all cancers
- PI3-K is a potentially important target for the development of new paediatric anti-cancer drugs

- Major barriers to clinical translation are:
  - Unique clinical toxicities – hyperglycaemia
  - Difficulties combining with chemotherapy
  - Rarity of mutations (1% of paediatric malignancies have a *PIK3CA* mutation, DMGs have the highest proportion 17.5% and approximately 5-6% of DMG have a *H1047R* mutation
  - Concomitant mutations

- As a result of these barriers PI3-K inhibitors have not had yet a major impact in paediatric cancer
- Mutations in PIK3CA predict response to PI3-K inhibitors in adult cancers

- Alpelisib, a PI3-Kα inhibitor, has activity in PIK3CA-related overgrowth syndrome therapy
- New mutation-specific PI3-K inhibitors reduce toxicity from on-target PI3-Kα wild-type activity
- Understanding the genomic landscape of the tumours and resistance mechanisms is key for rational combinations
- Evaluation of mutation-specific, CNS-penetrant PI3-K inhibitors in children with DMG and should be prioritised
- Innovative regulatory approaches are needed to support data generation for mutation-specific, CNS-penetrant PI3-K inhibitors in DMG, such as the currently piloted 'stepwise' PIP
- Combination therapy should be based on the molecular landscape and knowledge of concomitant mutations in other genes - molecular profiling of DMGs with *H1047R* mutations is high priority
- Emerging data suggest that PI3-K may be a general dependency in DMG irrespective of *PIK3CA* status
- mTOR inhibitor everolimus has been approved for subependymal giant cell astrocytomas
- mTOR inhibitors have been predominantly evaluated by academia, without an overall strategy, with very low response rates to monotherapy
- Future trials of mTOR inhibitors in childhood cancer should not be conducted without very strong biological rationale and supportive preclinical data.
- Further preclinical evaluation is required for GSK3β inhibitors to explore their immunomodulatory effect and role in modulating MYCN protein
- Even where there is an AKT mutation (~0.1%), the role of AKT inhibitors in paediatric cancers remains unclear

inhibitor, a randomised trial is needed comparing the partner with and without the PI3-K inhibitor**.**

10.2.6. Strategy for evaluating these inhibitors in a very rare population

The scenario with the greatest probability of success is an evaluation of a mutation-specific, CNS-penetrant PI3-K inhibitors in children with DMG. In view of past difficulties, investigations should focus on DMG as proof of concept. There are substantial challenges in such a rare population with many competing trials. The aim should be on hypothesis-driven evidence generation focusing on the most suitable product. Innovative regulatory approaches such as the currently piloted "stepwise" PIP supporting data generation should be considered [133]. Meaningful data generation in clinical trials, and use of real-world data could support innovative regulatory approaches to obtain an indication. Furthermore, in view of global development, there should be simultaneous regulatory submissions of PIPs and initial Paediatric Study Plans to the EMA and the FDA, respectively, to facilitate early regulatory interactions and discussions among regulatory agencies e.g. at the Paediatric Cluster [134–137].

11. Conclusion

PIK3CA mutations should be targeted, but improving the therapeutic window of PI3-Kα inhibition is key to increasing anti-tumour activity and the new mutation specific inhibitors are expected to offer greater potential.

There is a low a priori expectation of single agent activity, therefore it is crucial to consider how these inhibitors can be used as combination partners. The choice of concomitant combination therapy should be based on the molecular tumour/disease landscape, concomitant mutations in other genes and knowledge of the resistance mechanisms. Evaluation of mutation-specific, CNS-penetrant PI3-K inhibitors in children with DMG should be prioritised and innovative regulatory approaches are needed in view of the rarity of the population.

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RB is an employee of Genentech, A Member of the Roche Group, South San Francisco, CA USA. JC is an employee of Bayer Healthcare Pharmaceuticals, Whippany, NJ, USA. SGD has received consulting fees for advisory board participation from Amgen, Bayer, InhibRx, and Jazz and travel funding from Loxo, Roche, and Salarius. JF is an employee of Kazia Therapeutics. IG an employee of Celcuity. HK is an employee of Loxo Oncology at Lilly. DL is an employee of Merck Sharp & Dohme. AM is an employee of Actuate. MEM has receiving consulting fees for advisory board participation from Ymabs Therapeutics, Recordati and travel funding from Bayer. KN has received consulting fees for advisory board participation from Y-mAbs, EUSA Pharma and Bayer, fees for teaching from Bayer and serving on a data monitoring committee from Lilly. ADJP has consulted for Lilly, Norgine and Developmental Therapeutics Consortium Limited and been an advisor for Amgen. All remaining authors have declared no conflicts of interest.

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