




Advances in Targeted Therapies for Pediatric Brain Tumors

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Abstract

Purpose of Review Over the last years, our understanding of the molecular biology of pediatric brain tumors has vastly improved. This has led to more narrowly defined subgroups of these tumors and has created new potential targets for molecularly driven therapies. This review presents an overview of the latest advances and challenges of implementing targeted therapies into the clinical management of pediatric brain tumors, with a focus on gliomas, craniopharyngiomas, and medulloblastomas.

Recent Findings Pediatric low-grade gliomas (pLGG) show generally a low mutational burden with the mitogen-activated protein kinase (MAPK) signaling presenting a key driver for these tumors. Direct inhibition of this pathway through BRAF and/or MEK inhibitors has proven to be a clinically relevant strategy. More recently, MEK and IL-6

receptor inhibitors have started to be evaluated in the treatment for craniopharyngiomas. Aside these low-grade tumors, pediatric high-grade gliomas (pHGG) and medulloblastomas exhibit substantially greater molecular heterogeneity with various and sometimes unknown tumor driver alterations. The clinical benefit of different targeted therapy approaches to interfere with altered signaling pathways and restore epigenetic dysregulation is undergoing active clinical testing. For these multiple pathway-driven tumors, combination strategies will most likely be required to achieve clinical benefit.

Summary The field of pediatric neuro-oncology made tremendous progress with regard to improved diagnosis setting the stage for precision medicine approaches over the last decades. The potential of targeted therapies has been clearly demonstrated for a subset of pediatric brain tumors. However, despite clear response rates, questions of sufficient blood-brain barrier penetration, optimal dosing, treatment duration as well as mechanisms of resistance and how these can be overcome with potential combination strategies need to be addressed in future investigations. Along this line, it is critical for future trials to define appropriate endpoints to assess therapy responses as well as short and long-term toxicities in the growing and developing child.

Introduction

Central nervous system (CNS) tumors are the most common type of solid tumors in children [1]. Traditionally, standard therapy for these tumors consists of surgery and/or chemotherapy as well as radiotherapy. Even though there is a growing number of pediatric brain tumors in which tumor growth can be controlled or even cured, these therapies expose children to high doses of chemotherapy and radiation, leading to long-term effects that negatively impact quality of life [2]. Therefore, therapeutic approaches that target specific molecular tumorigenic pathways (Fig. 1) and pose fewer side effects are needed in the clinical management of pediatric brain tumors.

Over the last decade, the understanding of the molecular biology of pediatric brain tumors has expanded due to the emergence of genomic platforms [3–5, 6••]. This has led to more narrowly defined molecular tumor

subgroups and created a new opportunity for targeted therapies (Table 1). Even in tumors that were mainly treated with surgery and/or radiotherapy, e.g., craniopharyngiomas, new insights into oncogenic upregulation of signaling pathways are now being used for biology-derived therapeutic interventions. Besides the growing number of trials testing these targeted agents (Table 2), several recent studies have demonstrated the feasibility and utility of incorporating molecular profiling into the daily clinical care of children with brain tumors, allowing treatment decision-making based on specific molecular alterations in real time [7, 8•].

In this article, we will highlight the latest advances and challenges of implementing targeted therapies into the clinical management of pediatric brain tumors with a focus on gliomas, craniopharyngiomas, and medulloblastomas.

Low-Grade Gliomas

Pediatric low-grade gliomas (pLGGs) are the most common childhood CNS tumors, accounting for approximately one-third of pediatric brain tumors [9]. Pediatric LGGs are a heterogeneous group of lesions histologically classified as WHO grade I–II tumors, including but not limited to pilocytic astrocytoma (PA), diffuse astrocytoma, subependymal giant cell astrocytoma (SEGA), and pleomorphic xanthoastrocytoma (PXA) (Table 1) [3]. Prognosis for pLGG is generally very

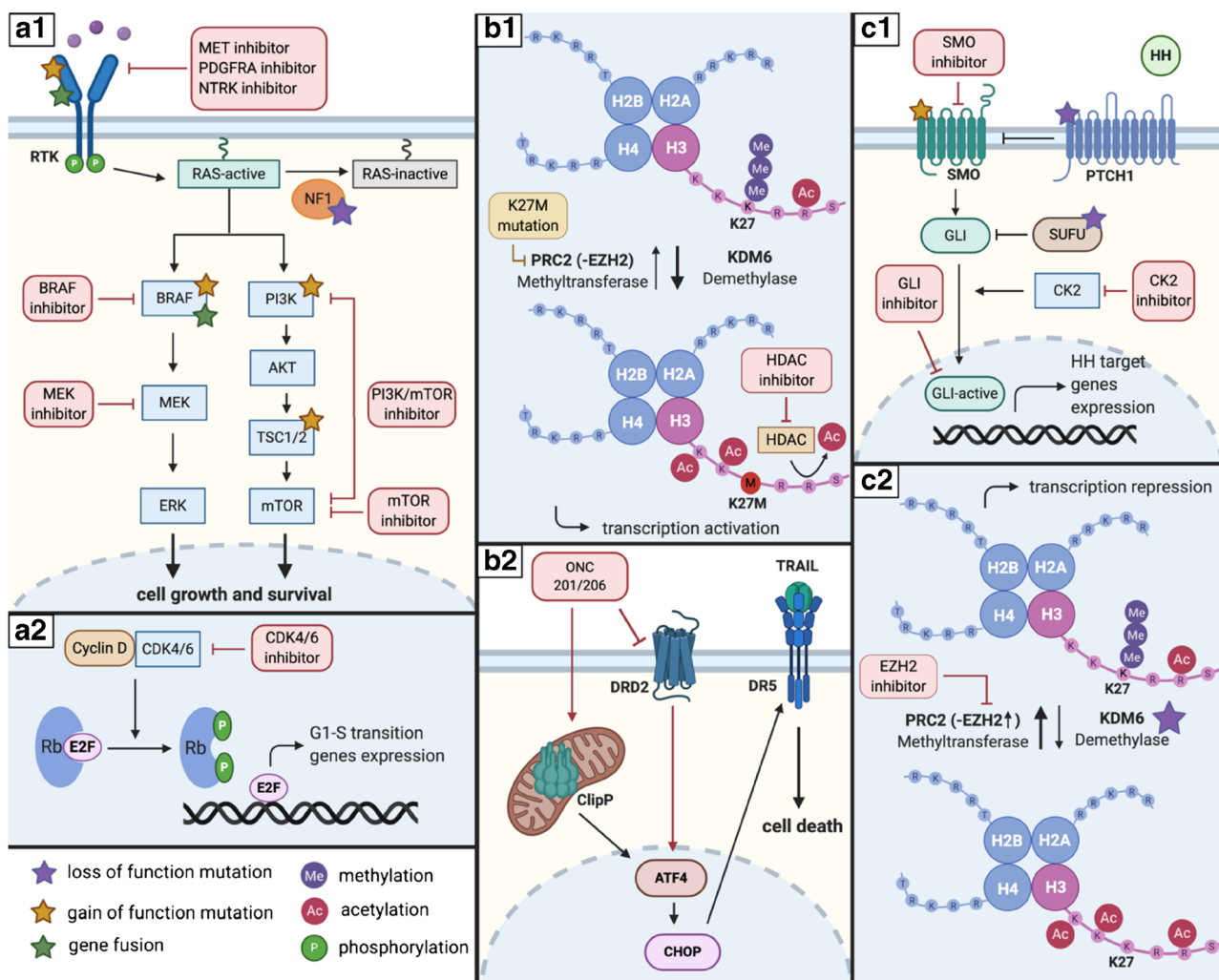


Fig. 1. Important signaling pathways and their inhibitors in pediatric brain tumors (**A**: pLGG, pHGG and craniopharyngioma; **B**: diffuse midline glioma; **C**: medulloblastoma). **A1** Constitutive RAS/MAPK and RAS/PI3K/AKT/mTOR pathway activation and corresponding inhibitors. Pathway activation takes place through paracrine stimulation (craniopharyngioma), activating mutation/fusion in *RTK*, *BRAF*, *PI3K* and *TSC1/2* or loss of *NF1* (pHGG, pLGG) and propagates cell growth and cell survival. **A2** CDK4/6 inhibition prevents cell cycle progression from the G1 phase to the S phase. **B1** Epigenetic modifications in H3K27M mutated DMGs and HDAC inhibition. The mutated histone site H3K27M inactivates PRC2. The resulting hypomethylation at H3K27 enhances oncogenic transcription activation at these loci. By inhibiting HDAC, histone tail poly-acetylation can be achieved and partially rescue H3K27M-induced global hypomethylation, by counteracting PRC2 inhibition. **B2** ONC inhibition pathway in DIPG. ONC drugs are thought to induce apoptosis either by antagonizing DRD2 receptors, or through targeting and activating the mitochondrial ClpP protein. Regardless, both mechanisms result in ATF4 increased expression. ATF4-driven CHOP expression results in TRAIL pathway activation by recruiting DR5 receptors which leads to cell death. **C1** Alterations in the hedgehog signaling pathway in SHH medulloblastomas and corresponding inhibitors. In the absence of HH ligand, PTCH1 inhibits SMO and hedgehog signaling does not take place. In the activated HH pathway (e.g. through HH binding, gain of function mutation in SMO or loss of function mutation in *PTCH1/SUFU*) the transcription factor GLI is activated resulting in the expression of HH targeted genes. **C2** Epigenetic modifications in Group 4 medulloblastomas and EZH2 inhibition. The over-expressed EZH2 (catalytic subunit of PRC2) methylates H3K27 and thereby promotes repression of transcription at these loci. The subsequent repression of tumor suppressor genes is further enhanced by the loss of function of the mutated demethylase KDM6A. EZH2 inhibitors are used to repeal this repressive methylation signature. (Figure created with BioRender.com)

Table 1. Histological/molecular subgroups of pediatric brain tumors and their therapeutically important molecular alterations

Disease	WHO Grade	Tumor subgroup	Molecular alteration	Targeted therapy	Therapeutic agent (example)
Glioma	I-II	Pilocytic astrocytoma	BRAF-fusion/NF1-loss	BRAF inhibitor MEK inhibitor mTOR inhibitor	Dabrafenib selumetinib everolimus
		Pleomorphic xanthoastrocytoma	BRAF-mutation	BRAF inhibitor MEK inhibitor	Dabrafenib selumetinib
	III-IV	Subependymal giant-cell astrocytoma	TSC1/2- mutation	mTOR inhibitor	Everolimus
		Hemispheric high-grade glioma (anaplastic astrocytoma, glioblastoma)	IDH-mutation	IDH inhibitor PARP inhibitor	AG-120 BGB-290
Cranio-pharyngioma	I	Diffuse midline glioma Adamantinomatous	NTRK-fusion	NTRK inhibitor	Larotrectinib
			BRAF-mutation	BRAF inhibitor /MEK inhibitor	Dabrafenib/trametinib
			MET-fusion/ amplification	MET inhibitor	PLB1001
			PDGFRA- mutation/ amplification	PDGFRA inhibitor	Dasatinib
			PIK3CA mutation	mTOR inhibitor ± PI3K inhibitor	LY3023414 paxalisib
			H3K27M	HDAC inhibitor DRD2/ Ctip	Panobinostat ONC201
			CTNNB1-mutation	MEK inhibitor (only in vitro)	Trametinib
			IL-6R upregulation	IL-6-R inhibitor	Tocilizumab
			BRAF-mutation	BRAF inhibitor MEK inhibitor	Vemurafenib/cobimetinib
			CTNNB1-mutation		
Medullo-blastoma	IV	Papillary WNT	SMO/ PTCH1/ SUFU-- mutation	SMO inhibitor GLI inhibitor CK2 inhibitor BET protein inhibitor	Vismodegib/sonidegib ATO sunitasertib (CX-4945) JQ1
			HDAC2 over-expression	HDAC inhibitor	Fimepinostat
	Group 3	SHH	GFI1/GFI1B-enhancer hijacking	LSD1 inhibitor	GSK-LSD1
			HDAC2 over-expression	HDAC inhibitor	Fimepinostat
	Group 4	SHH	EZH2 over-expression/ KDM6A-mutation	EZH2 inhibitor	Tazemetostat
			GFI1/GFI1B-enhancer hijacking	LSD1 inhibitor	GSK-LSD1
			HDAC2 over-expression	HDAC inhibitor	Fimepinostat

Table 2. Molecular targets and their corresponding clinical trials for pediatric brain tumors

Molecular target	Drug	Disease	Upfront/recurrent	Trial	Phase
BRAF	Vemurafinib	Glioma (BRAF-mut)	Recurrent	NCT01748149	1
	PLX8394	Solid tumor (BRAF-mut)	Recurrent	NCT02428712	1/2
	TAK-580	LGG	Recurrent	NCT03429803	1/2
MEK	Selumetinib	LGG (NF1 associated)	Upfront	NCT03871257	3
	Selumetinib	LGG (non-NF1 associated)	Upfront	NCT04166409	3
	MEK162	LGG (NF1 or BRAF-fusion)	Recurrent	NCT02285439	1/2
	Trametinib	LGG (NF1 or BRAF-fusion)	Recurrent	NCT03363217	1/2
BRAF/MEK	Dabrafenib/ trametinib	LGG (BRAF-mut)/ HGG	Upfront/recurrent	NCT02684058	2
	trametinib	HGG (BRAF-mut)	Upfront	NCT03919071	2
	Vemurafenib/cobimetinib	PCP (BRAF-mut)	Upfront	NCT03224767	2
IDH	AG881	Glioma (IDH-mut)	Recurrent	NCT02481154	1
	AG-120	Glioma (IDH-mut)	Recurrent	NCT02073994	1
PARP	BGB-290	LGG/HGG (IDH-mut)	Recurrent/upfront	NCT03749187	1
CDK4/6	Palbociclib-isthionate	CNS-tumors	Recurrent	NCT02255461	1
	Abemaciclib	HGG	Recurrent	NCT02644460	1
	Ribociclib	CNS-tumors	Recurrent	NCT03434262	1
NTRK	Larotrectinib	Solid tumors (incl. CNS)	Recurrent	NCT03213704	2
	Larotrectinib	Solid tumors (incl. CNS)	Recurrent	NCT02637687	1/2
	Larotrectinib	Solid tumors (incl. CNS)	Recurrent	NCT02576431	2
	Entrectinib	Solid tumors (incl. CNS)	Recurrent	NCT02650401	1/2
MET	PLB1001	HGG	Recurrent	NCT02978261	1
PI3K/mTOR	LY3023414	Solid tumors (incl. CNS)	Recurrent	NCT03213678	2
	Paxalisib	DMG	Upfront	NCT03696355	1
HDAC	Panobinostat	DIPG	Recurrent	NCT02717455	1
	Panobinostat	HGG (H3K27M)	Recurrent/upfront	NCT03632317	1
	Fimepinostat	HGG, medulloblastoma	Recurrent/upfront	NCT03893487	1
	MTX110	DIPG	Upfront	NCT03566199	1/2
DRD2/ClpP	ONC201	HGG (H3K27M)	Recurrent/upfront	NCT03416530	1
IL-6 receptor	Tocilizumab	ACP	Recurrent/upfront	NCT03970226	1
SMO receptor	Vismodegib	MB	Upfront	NCT01878617	2
CK2	Silmitasertib (CX-4945)	MB	Recurrent	NCT03904862	1/2
EZH2	Tazemetostat	CNS-tumors	Recurrent	NCT03155620	2
BET proteins	BMS-986158	Solid tumors (incl. CNS)	Recurrent	NCT03936465	1

favorable, with 10-year overall survival (OS) between 85 and 96% [10]. If feasible, initial therapy for these low-grade tumors often relies on maximal safe surgical resection. Historically, unresectable pLGGs, or those that progressed after initial resection, were retreated with additional therapies consisting often of cytotoxic chemotherapy or, if unavoidable, radiation therapy [9].

Pediatric LGGs show a low mutational burden and are generally considered to be a single molecular pathway disease. The main molecular pathway affected in these tumors is the mitogen-activated protein kinase (MAPK) signaling cascade (Fig. 1). The most frequent alterations affecting this pathway include BRAF fusions or the point mutation BRAF V600E [6••, 11, 12]. Alterations within the PI3K/AKT/mTOR signaling pathway have also been described driving tumorigenesis in pLGGs (Fig. 1) [13].

TSC1/2 Mutations and mTOR Inhibitors

The first and well-established targeted therapy for pediatric brain tumors refers to the use of everolimus for SEGAs in patients with tuberous sclerosis complex (TSC). TSC is a genetic neurocutaneous syndrome caused by inactivating mutations in the *TSC1* or *TSC2* gene. About 10% of patients with TSC develop these slow-growing, low-grade SEGAs, which mainly arise in the periventricular area [14].

TSC1 and *TSC2* encode the proteins tuberin and hamartin, respectively. These proteins form the tuberin-hamartin complex, which negatively regulates the mTOR pathway. By consequence, mutations in either *TSC1* or *TSC2* lead to unchecked activation of mTOR and thereby drive cell proliferation and survival (Fig. 1) [15]. Krueger et al. showed that the mTOR inhibitor everolimus safely and significantly reduced tumor volume of SEGAs [16]. Even after 5 years, everolimus remained well-tolerated and continued to demonstrate sustained effect on tumor volume reduction. The treatment is now a US Food and Drug Administration-approved therapy for SEGAs and is considered the standard of care of these tumors if surgical resection is not feasible [17].

Loss of NF1 and mTOR/MEK Inhibitors

More recently, everolimus has also been used for the treatment of PAs. These tumors are the principal CNS neoplasm associated with the tumor predisposition syndrome Neurofibromatosis type 1 (NF1) [3]. The *NF1* gene encodes the neurofibromin protein, which acts in the MAPK pathway as a GTPase for RAS, thereby facilitating the deactivation of RAS (Fig. 1). Patients with NF1 have only one wildtype copy of the *NF1* gene. Subsequent functional loss of this single wildtype *NF1* gene results in overactivity of the Ras effector pathways via the RAS/MAPK or RAS/PI3K/AKT/mTOR pathway [18, 19]. Therefore, these NF1-associated pLGG tumors seem to benefit from MAPK signaling blockage by MEK inhibitors like selumetinib [20]. On the other hand, Ullrich et al. recently showed that patients with recurrent/progressive NF1-associated pLGG undergo significant disease stability or shrinkage by successfully blocking the RAS/PI3K/AKT/mTOR signaling pathway with mTOR inhibitor everolimus [21••]. Since everolimus is very well tolerated and therefore provides a good quality of life for patients, a follow-up study from the Pacific Pediatric Neuro-Oncology Consortium (PNOC) is enrolling children with recurrent LGG and actively investigating tissue biomarkers of response (PNOC001; NCT01734512).

BRAF Alterations (Mutation/Fusion) and BRAF/MEK Inhibitors

BRAF gene alterations are frequently observed in pLGGs such as PAs, gangliogliomas (GGs) or PXAs. The BRAF gene encodes the serine/threonine kinase B-Raf, a downstream effector in the MAPK signaling pathway (Fig. 1) [3, 22].

PAs, the most common glial tumor in children, harbor a tandem duplication of 7q34 involving the BRAF gene in > 70% of cases. Due to this duplication, the N-terminal regulatory region of BRAF is replaced by the N-Terminus of the KIAA1549 protein resulting in KIAA1549-BRAF fusion protein, which forms BRAF dimers and constitutively activates the MAPK pathway [3, 12].

On the other hand, PXAs show constitutive activation of the MAPK signaling pathway by an amino acid substitution of valine to glutamate (V600E mutation) within the BRAF gene, leading to a monomeric BRAF oncoprotein. Even though the BRAF V600E mutation is common in PXA (> 60%), it also occurs in other pLGGs such as PA (2–9%) and GGs (up to 18%) [23]. Since KIAA1549-BRAF fusion and the BRAF V600E mutation are key oncogenic drivers in pLGGs, they represent a particularly good target for either MEK or BRAF inhibitors [22, 24].

Dabrafenib, a BRAF V600E inhibitor, has been described as a promising treatment option in BRAF V600E-mutated PXAs in single cases [25]. Hargrave et al. demonstrated in a phase I/II trial a meaningful clinical benefit of dabrafenib in relapsed or refractory BRAF V600E pLGGs, where 44% of the tumors radiographically responded to this targeted therapy [26]. Nicolaidis et al. reported that vemurafenib was well tolerated in a phase I trial for a selected group of recurrent/refractory BRAF V600E mutated brain tumors with good responses as well [27] (PNOC002; NCT01748149).

However, BRAF V600E inhibitors can lead to paradoxical activation of the MAPK pathway in tumor cells with BRAF wildtype or cells harboring BRAF fusions [28–30], demonstrating the critical issue selecting the correct patient population for such therapies. Besides adequate patient selection, the effects of paradoxical MAPK pathway activation have been overcome with the use of second-generation BRAF inhibitors like TAK-580 (also known as MLN2480). TAK-580 is a pan-RAF inhibitor and an equipotent antagonist of BRAF mutated (monomeric) and BRAF fusion (dimeric) oncoproteins. Beside the capacity to eliminate the paradoxical activation of the MAPK pathway, this second-generation pan RAF inhibitor also harbors a favorable blood-brain barrier penetration compared with first-generation agents and an agreeable administration schedule with once weekly dosing [31•]. Clinical trials, under development and in progress, will examine the use of second-generation BRAF inhibitors in children and adults with BRAF-mutated malignancies (NCT03429803, NCT02428712).

With regard to paradoxical activation of MAPK signaling and the potential toxicity of BRAF inhibitors, there have also been efforts to target more downstream MAPK pathway components, such as MEK. MEK inhibitor selumetinib has proven to be an effective and reasonably well tolerated orally available inhibitor for the treatment of pLGGs [32]. Fangusaro et al. recently demonstrated that the use of single-agent selumetinib for BRAF-altered recurrent PAs resulted in a sustained partial tumor response rate of 36% (9/25 patients) and for NF1-associated recurrent pLGGs in one of 40% (10/25 patients) [20]. While other phase I/II trials investigate alternative MEK inhibitors (NCT02285439, NCT03363217) in the recurrent setting, two phase III trials testing selumetinib for newly diagnosed patients. In these phase III trials, selumetinib will be compared with standard chemotherapy with carboplatin/vincristine for patients with NF1-associated pLGG (NCT03871257) or with non-NF1 pLGG (NCT04166409). Along these lines, another phase III study, the LOGGIC trial, will randomize also newly diagnosed pLGG (non-NF1) participants to chemotherapy (carboplatin/vincristine vs. weekly vinblastine) vs. trametinib. This trial

will use both functional endpoints as well as overall and progression free survival to compare treatment benefit. These studies will answer the question how these targeted inhibitors compare to standard chemotherapy regimens with the important aspect of taking functional endpoints into consideration.

In addition to single-agent use of BRAF or MEK inhibitors, the combination of both MAPK pathway inhibitors has been used with promising results in the treatment of other tumors. In recent years, the combined use of BRAF and MEK inhibitors for the treatment of BRAF V600E mutated melanomas has shown significant OS benefit without increasing overall toxicity [33]. Published 5-year follow-up data also support these findings from a long-term perspective [34]. With regard to pLGG, Zhang et al. showed in vitro as well as in vivo that combined BRAF and MEK inhibition prevents rebound MAPK activation, resulting in enhanced antitumor efficacy [35]. This combinatorial targeting approach is now in clinical trials for pLGG as well as high-grade glioma (NCT02684058, NCT03919071).

Other promising combinatory targeting strategies to target the MAPK pathway and address the potential escape mechanisms of acquired resistance to single-agent MAPK pathway therapies include using a mTOR inhibitor along with MEK inhibition. Two independent studies were able to show the preclinical potency of combinatorial targeting with MEK and mTOR inhibitors, which will be tested in an upcoming trial for recurrent pLGGs within PNOG (PNOG021; NCT04485559) [36, 37••].

High-Grade Gliomas

Pediatric high-grade gliomas (pHGGs) include WHO grade III and grade IV tumors and comprise approximately 10–15% of all primary brain tumors in children (Table 1) [3]. Unfortunately, the prognosis for pHGGs has been stagnant despite several decades of clinical trial investigations. Survival remains extremely poor with a median OS of 10 to 18 months, resulting in one of the leading causes of pediatric cancer deaths [3]. Standard of care for pHGG historically relies on maximal safe surgical resection followed by adjuvant chemotherapy and focal radiation [38].

Although the histopathological appearance of pHGG overlaps with their adult counterparts, pediatric HGGs harbor different genetic alterations and should therefore be considered separate tumor entities [4, 39]. Based on the regional occurrence, pHGG can be separated into midline and non-midline, hemispheric HGGs. Midline tumors occur in the thalamus, brainstem, or spine. Malignant midline gliomas are referred to as diffuse midline gliomas (DMGs) that also include diffuse intrinsic pontine gliomas (DIPGs). Over 70% of these DMGs harbor recurrent mutations in genes encoding histone H3 variants including histone H3.3 (H3F3A) and H3.1 (HIST1H3B and HIST1H3C). Therefore, the new WHO classification introduced a new entity referred to as diffuse midline glioma, H3K27 mutant. In contrast, the H3G34R/V (glycine to arginine or valine) missense mutations can mainly be found in hemispheric HGGs and rarely in DMGs [39, 40]. As expected, compared with pLGGs, pHGG exhibit substantially greater genetic heterogeneity. Genetic analyses of pHGG have uncovered frequent molecular alterations targeting receptor tyrosine kinase (RTK) signaling pathways (e.g., PDGFRA, MET, FGFR1, PIK3CA, BRAF) and cell cycle regulation (e.g., TP53, ATRX, CDK4/6, CDKN2A)

(Table 1) [4, 5]. However, some of these genetic changes tend to occur within subgroups of pHGGs. For example, DIPGs harbor recurrent somatic mutations in *ACVR1* (35%), while infant hemispheric HGGs encompass tumors driven by *NTRK*, *ALK*, *ROS1*, and *MET* fusions [41, 42]. A detailed understanding of these different molecularly distinct subtypes of pHGGs will be critical when assessing treatment responses or failures as these alterations might impact outcome.

IDH Mutation and PARP Inhibitors

In adults, HGGs are currently subdivided into either *IDH* wildtype or *IDH* mutant gliomas [3]. The *IDH* mutation is also present in a subset of pediatric patients, suggesting that these lesions may be biologically similar to malignant adult gliomas [43, 44].

The normal function of isocitrate dehydrogenase (*IDH*) enzymes is to catalyze the conversion of isocitrate to α -ketoglutarate in the citric acid cycle. Nearly all known *IDH1/2* alterations are heterozygous missense mutations that confer a neomorphic activity on the encoded *IDH* enzymes, such that they convert the α -ketoglutarate to the oncometabolite 2-hydroxyglutarate (2HG) [45]. There is growing evidence that 2HG affects chromatin methylation and cellular differentiation [46]. It is also assumed that 2HG promotes deficiency in homologous recombination (HR) within the *IDH*-mutated cancer cells [47].

For adults, a number of clinical trials are investigating the benefit of *IDH1* inhibitors in *IDH* mutant gliomas, hoping that these patients would benefit from reduction of the oncometabolite 2HG (NCT02481154, NCT02073994). In contrast, the finding that *IDH1/2* mutations induce a HR defect within tumor cells led to the concept of exploiting rather than inhibiting the effects of the *IDH* mutation through the use of poly(adenosine 5'-diphosphate-ribose) polymerase (PARP) inhibition [48••]. Normal cells can tolerate DNA damage generated by PARP inhibition because of an efficient HR mechanism. Meanwhile, *IDH* mutated cancer cells demonstrate a deficient HR pathway and are thus unable to repair double-strand breaks efficiently [47]. Exploiting the concept of synthetic lethality, a current phase I trial is evaluating the side effects and best dose of the CNS penetrant PARP inhibitor, BGB-290, in combination with temozolomide in treating adolescents and young adults with *IDH1/2*-mutant grade I-IV gliomas (PNOC017; NCT03749187).

BRAF Mutation and BRAF/MEK Inhibitors

BRAF point mutations are present in about 10–15% of pHGG [49]. It is assumed that these tumors may represent a subset of pLGG that transformed into secondary high-grade gliomas [50]. The BRAF mutations often co-occur with deletions of CDK inhibitor 2A (*CDKN2A*) and together contribute to dysregulated cellular proliferation [51]. These tumors are associated with modestly improved OS when compared with primary HGGs [5].

Case reports and series have revealed promising results using BRAF inhibitors as monotherapy or, more recently, in combination with MEK inhibitors for BRAF V600E mutant pHGG tumors [52–54]. In a case series of 3 patients, Toll et al. showed that the combination of BRAF V600E and MEK inhibitor therapy is an effective and safe treatment option for children with these BRAF V600E mutated HGG [49]. Clinical trials are now testing this strategy for newly diagnosed and recurrent BRAF V600E mutant HGGs (NCT02684058, NCT03919071).

The combination of a BRAF inhibitor with a CDK4/6 inhibitor, which prevents progression from the G1 phase to the S phase of the cell cycle (Fig. 1), has shown improved survival in human xenograft models of pHGG with BRAF V600E mutation and CDKN2A homozygous loss compared with single-agent therapy [55]. This combination has not yet been evaluated in clinical trials in pHGG but may represent a promising targeted therapeutic strategy option for patients harboring both alterations. Currently, two phase I clinical trials are evaluating the safety and efficacy of CDK4/6 inhibitor monotherapy in pediatric tumors, including pHGGs (NCT02255461, NCT02644460).

Receptor Tyrosine Kinase (RTK) Signaling Aberrations and NTRK, MET, and PI3K/mTOR Inhibitors

Common signaling pathways that are activated in pHGGs include RTK/PI3K/AKT/mTOR and MAPK cascades. These pathways are activated through different mutations, fusions, or amplifications with genes coding for RTKs. In addition, the PI3K/AKT/mTOR pathway is also activated by other somatic variations such as the PIK3CA mutation, coding for the intracellular signal transducer PI3K (Fig. 1) [56]. Recent studies suggest that a large subset (20–30%) of pediatric patients with pHGG have mutations and/or amplifications of platelet-derived growth factor receptor alpha (*PDGFRA*) [4]. Other in-frame fusions of RTK genes involve the *ALK*, *ROS1*, *FGFR*, *MET*, and *NTRK* genes, and one recent study revealed *MET* fusions in 10% and *MET* amplification in 3–7% of pHGG [4, 57]. Lastly, neurotrophic receptor kinase gene (*NTRK*) fusions have been identified in up to 40% of hemispheric HGG in infants [4, 41, 42].

Several case reports have been published demonstrating the efficacy of targeting *ROS1*, *FGFR*, *NTRK*, and *MET* gene fusions in pHGGs [57–60], but with regard to the proof of efficacy, data from clinical trials is lacking for many of these RTK inhibitors. Success in *NTRK* fusion inhibition is largely drawn from larotrectinib, a highly selective TRK inhibitor that is well tolerated in pediatric patients and has shown significant antitumor activity in patients with TRK fusion positive cancers [61]. Clinical trials to further assess the efficacy and safety of larotrectinib in up-front and recurrent pediatric malignancies, including pHGGs, are ongoing (NCT03213704, NCT02637687, NCT02576431). Along these lines, a phase 1 study using entrectinib, a new-generation CNS-penetrant oral inhibitor of ALK/ROS1/NTRK kinases, has been successfully concluded in refractory CNS tumors harboring alterations in these kinases [62, 63]. A phase II trial investigating the safety and efficacy of entrectinib is ongoing (NCT02650401).

Bender et al. were also able to show that MET inhibitors suppress MET-driven tumor growth in xenograft models and achieved partial response with the targeted inhibitor, crizotinib, in a pediatric patient bearing an MET fusion expressing glioblastoma [57]. Furthermore, the selective MET inhibitor, PLB1001, is currently being tested in a clinical trial for PTPRZ1-MET fusion gene positive recurrent HGG (NCT02978261).

The development of PI3K inhibitors for patients harboring a PI3K activating mutation (e.g., PIK3CA mutation) has been difficult due to severe side effects [64]. For pediatric patients harboring such a mutation, the targeted utilization of everolimus has been applied and, more recently, LY3023414, a dual PI3K

and mTOR inhibitor, is undergoing investigation (NCT03213678). Furthermore, paxalisib (GDC-0084) is another PI3K/mTOR inhibitor, which has recently proven to penetrate the blood-brain barrier and showed a metabolic partial response, by FDG-PET, in up to 26% of adult HGG patients [65]. A first-in-pediatric study is currently examining the safety and preliminary antitumor activity of paxalisib in DMGs (NCT03696355).

H3K27M Mutation and Histone Deacetylase (HDAC) Inhibitors

Trimethylation at H3K27 (H3K27me₃) is associated with transcriptionally silenced chromatin (Fig. 1). The H3K27M mutation in DMG prevents methylation by the repressive histone methyl transferase (HMT) complex PRC2, which results in hypomethylation of H3K27 leading to transcriptional activity at these loci (Fig. 1) [66]. In order to re-establish the balance of these post-translational modifications, it has been shown that in H3K27M mutant tumors, the histone 3 tail poly-acetylation can partially rescue H3K27M-induced hypomethylation, by re-enabling PRC2-mediated histone methylation [67, 68]. By inhibiting histone deacetylase (HDAC), for example, with panobinostat, poly-acetylation can be achieved, and increased global H3K27 trimethylation can be observed (Fig. 1) [69]. Currently, the safety of panobinostat and other HDACs for the use in DIPG patients are being evaluated in phase 1/2 trials (NCT02717455, NCT03632317, NCT03893487). Due to the fact that panobinostat and other HDAC inhibitors have poor blood-brain barrier penetration, a new water-soluble formulation (MTX110), which can be delivered directly to the tumor through convection-enhanced delivery, has been developed [70] and is currently being tested in a clinical trial for DIPG (PNOC015; NCT03566199).

H3K27M Mutation and the Imipridone, ONC201

In addition to HDAC inhibitors, the small anti-cancer imipridone, ONC201, has shown preliminary but promising pre-clinical and clinical results in H3K27M mutated pHGG. ONC201 is thought to induce cell death through pro-apoptotic TRAIL pathway activation either by antagonizing dopamine receptor D2 (DRD2) or by targeting and activating the mitochondrial caseinolytic protease P (ClpP) protein (Fig. 1) [71, 72].

Recent preclinical data demonstrate that ONC201 is most potently cytotoxic to H3K27M mutant glioma cells with reduced activity against wild-type cells [73]. Among the 17 patients included in a Phase II clinical trial of oral ONC201 in adult patients with recurrent glioblastoma, one 22-year-old patient harbored a biopsy-proven H3K27M mutated thalamic high-grade tumor and showed radiological tumor regression of approximately 80% [74]. Hall et al. successfully used ONC201 in a pediatric case of H3K27M-mutated DIPG and were able to detect a significant radiological as well as clinical response [75]. These promising results for ONC201 are currently being investigated in a clinical trial for H3K27M-mutated pHGG (NCT03416530).

Craniopharyngiomas

Craniopharyngiomas (CPs) are histologically WHO grade I tumors with two clinicopathological variants (adamantinomatous [ACPs] and papillary [PCPs]) that harbor distinct phenotypes and genetic alterations

(Table 1) [3]. Even though CPs are histologically benign, they are locally aggressive tumors in the sellar region, which may cause devastating visual, neurological, and endocrine deficits. ACP is the more prevalent subtype and has a bimodal age distribution, with incidence peaks between ages 5–15 years and 45–60 years, whereas rare cases during the neonatal period have been reported [76]. PCP, on the other hand, has been classically considered an adult entity peaking between 40 and 55 years of age [77] and few pediatric cases being reported [78].

In general, CPs have traditionally been treated with surgery and/or radiotherapy. Although the 10-year survival with these approaches is very good (ranging from 64 to 92%), in the case of tumor progression or recurrence, the therapeutic options are limited. Even with surgery or radiotherapy, CPs can cause high morbidity and predispose children to a life of severe disability across different organ systems [79, 80].

The recent increase in knowledge of the molecular pathology of these tumors and development of animal models have led to promising new possibilities for the use of specific targeted therapies in the upfront and adjuvant treatment of CPs [81].

BRAF Mutation and BRAF/MEK Inhibitors in PCP

Nearly all PCPs harbor the BRAF V600E mutation [82]. These findings have led to a number of case reports using BRAF and/or MEK inhibitors for CPC [83–85]. These case reports support the potential benefit of BRAF inhibitors with or without the combination of MEK inhibitor in the treatment of recurrent PCP. In all described cases, at least a transient tumor response has been observed. For the first time, Jurtali et al. administered the BRAF V600E inhibitor, dabrafenib, as a neoadjuvant treatment in a 21-year-old male prior to surgery and found a >80% reduction of tumor size [86].

However, to further evaluate the efficacy of and tumor resistance to these BRAF and MEK targeting agents, the results of prospective clinical trials are needed. Currently, the neoadjuvant treatment combination of BRAF inhibitor, vemurafenib, with the MEK inhibitor, cobimetinib, is being evaluated in a phase II trial in patients harboring BRAF V600E mutated craniopharyngiomas (NCT03224767).

WNT/ β -Catenin Signaling and MEK Inhibitors in ACP

The most frequently observed mutations in ACPs are located in the *CTNNB1* gene (encoding β -catenin) [87]. These mutations affect regulatory amino acids that include phosphorylation sites that normally allow quick degradation of β -catenin. By consequence, β -catenin accumulates and mediates WNT pathway signaling. Even though the majority of ACPs have somatic activating mutations in *CTNNB1*, the cellular accumulation of β -catenin is limited to only a small proportion of cells (referred to as β -catenin-accumulating cell clusters) [88••, 89]. Insight into the functional significance of the β -catenin-accumulating cell clusters suggest that these cells potentially drive tumor growth and invasion into the surrounding tissue by secretion of factors (e.g., fibroblast growth factor (FGF), epithelial growth factor (EGF), and platelet-

derived growth factor (PDGF)) in a paracrine manner [88••, 89]. Along these lines, Apps et al. were able to show that even though ACPs do not carry mutations in the MAPK pathway components, this pathway was activated in mice and human APC cells next to these paracrine active cluster cells [88••].

One in vitro study inhibiting the MAPK pathway in APCs using the MEK inhibitor, trametinib, demonstrated reduced proliferation and increased apoptosis in both mouse and human ACP tumors [88••]. These results suggest that MEK inhibition could also provide a clinically viable treatment in ACP tumors.

Unfortunately, the direct inhibition of the activated WNT/ β -catenin pathway has not been translated into novel targeted therapies yet, due to the difficulty of targeting this pathway without causing unacceptable toxicity [90].

IL-6 Receptor Inhibitor in ACP

Other transcriptional molecular analyses of ACPs have revealed a high expression of immune-related genes. Beside other immunomodulators, these studies demonstrated highly upregulated levels of IL-6 receptor (IL-6R) and IL-6 in cyst fluid and solid tumor tissue, suggesting a critical role in ACP pathogenesis [91, 92]. From a therapeutic perspective, IL-6R can be targeted by tocilizumab, a humanized monoclonal antibody, that has already been used in pediatric oncology (FDA approved for children older than 2 years for the treatment of juvenile idiopathic arthritis and cytokine release syndrome).

Grob et al. recently reported the first use of tocilizumab alone or in combination with bevacizumab for the treatment of cystic ACP in two pediatric patients. In both cases, the cystic portion of the tumor responded. When the patient on tocilizumab monotherapy progressed, bevacizumab was added as a cystic targeted therapy. Even though the role of bevacizumab as a monoclonal antibody that binds to vascular endothelial growth factor (VEGF) and results in inhibition of new blood vessel formation remains unclear in ACP patients [93], clinical benefit was seen in these patients. An early phase 1 trial with tocilizumab for children with ACP has been initiated with the first phase of the trial to confirm that drug is able to reach the tumor. If the clinical results are favorable and tocilizumab shows penetration of the tumor, the trial will expand to a feasibility phase, where tocilizumab will be administered every 2 weeks for up to 2 years (NCT03970226).

Medulloblastomas

Medulloblastomas (MB) are highly aggressive (WHO grade IV) embryonal tumors of the posterior fossa and comprise 15–20% of pediatric CNS tumors, making up the most common malignant pediatric brain tumor [3]. Classification into four molecular subgroups (wingless-activated [WNT], sonic hedgehog-activated [SHH], Group 3, and Group 4) has improved treatment stratification and provided rationale for introduction of targeted therapies (Table 1) [94–96]. Standard therapy for medulloblastoma comprises surgical resection, craniospinal irradiation (for children > 3–5 years of age), and multiagent chemotherapy. However, novel treatment strategies are greatly needed to reduce treatment-related morbidity and provide curative options for high-risk patients, including those with metastatic dissemination, *TP53*-mutated/SHH MB, or relapsed/progressive MB.

Inhibitors of the SHH Pathway

The sonic hedgehog (SHH) pathway has been the most explored in MB and thus far numerous targets have been identified [97] (Fig. 1). SHH MB are prevalent across the entire age spectrum, with a bimodal distribution and age peaks in both infancy and adulthood. There are four molecular subtypes within the SHH subgroup, each with distinct clinical characteristics and outcome [96]. Whereas adult SHH MB are typically driven by *PTCH*, *SMO* mutations, and/or *TERT* promoter mutations, infant SHH MB comprise 2 subtypes, including a group of patients with poor prognosis harboring alterations such as *SUFU* mutations and *PTEN* loss. School-aged children, on the other hand, commonly have *TP53* mutations, which are associated with very high risk of treatment failure and early relapse [98]. SHH MB in adolescents and adult patients also commonly harbor mutations of U1 spliceosomal small nuclear RNAs (snRNAs) [99].

Given the heterogeneity within SHH-driven MB, multiple targeted or combination treatment strategies are warranted. The first targeted therapies to advance into clinical trials were the smoothed receptor (SMO) inhibitors, which target the SHH signaling pathway early in transduction [100–102]. Vismodegib (GDC-0449) and sonidegib (LDE225), both SMO inhibitors, have been investigated for their use in recurrent SHH-driven medulloblastoma and the addition of vismodegib to standard chemotherapy is currently being investigated for selected, newly diagnosed SHH MB patients (SJMB12; NCT01878617). In a meta-analysis evaluating clinical trials of vismodegib and sonidegib, both inhibitors were well tolerated and showed antitumor activity against SHH MB but not against other MB subgroups. In this study, sonidegib appeared to have higher efficacy, especially in pediatric patients [103•]. Unlike adult MB, infant and childhood SHH-driven MB often exhibit mutations downstream of *PTCH* and are thus unlikely to respond to SMO inhibitors [104]. Furthermore, inhibition of growth plate fusion upon treatment with these agents raises concern for their application in children [105, 106••] and acquired resistance is frequent, limiting their use as a monotherapy [107].

Alternative targeting strategies focusing on other downstream targets, such as *GLI* transcriptional factors, or combination therapies, are in development [108–110]. Arsenic trioxide (ATO), which is already approved by the FDA for treatment of acute promyelocytic leukemia, interferes with *GLI* transcription factors and in combination with itraconazole has shown efficacy *in vitro* and *in vivo* in SMO inhibitor-resistant medulloblastoma [109, 111]. Casein kinase 2 (CK2) is critical for *GLI2* activity in SHH-driven medulloblastoma, and CK2 inhibitors were shown to impair proliferation [112] and sensitize MB cells to temozolomide [113]. One of these inhibitors, silmitasertib (CX-4945), is currently being tested in a phase I/II trial for recurrent SHH-MB (NCT03904862). Development of specific inhibitors for CDK 4/6 also offers potential use in treatment of medulloblastoma [114]. An ongoing phase I trial (NCT03434262) investigates several combination therapies for recurrent pediatric CNS tumors, including CDK 4/6 inhibitor ribociclib in combination with trametinib or sonidegib for SHH MB.

Targeting MYC-Amplified Medulloblastomas

Children with Group 3, *MYC*-amplified MB commonly present with metastatic disease and respond poorly to current treatment protocols. Using *MYC*-driven murine and human MB cell models, high-throughput drug profiling studies have identified the combination of pemetrexed and gemcitabine [115] as well as antagonists of the PI3K and HDAC pathway [116] as promising agents for treatment of *MYC*-driven MBs. Pemetrexed and gemcitabine are currently being investigated in newly diagnosed patients with Group 3 and Group 4 MB (NCT01878617).

In a subset of Group 3 and Group 4 MBs, tumors are driven by *MYC* in cooperation with growth factor independent genes *GFI1* and *GFI1B*, which are overexpressed due to “enhancer hijacking” events [117]. These tumors critically depend on lysine-specific histone demethylase (LSD1) function in order to block genes for neural commitment and differentiation [118]. Genetic ablation of this enzyme impairs tumor growth in vivo; hence LSD1 inhibitors may be another therapeutic strategy for Group 3 and 4, *GFI*-driven MB.

Epigenetic Drivers as Targets in Medulloblastoma

Other strategies targeting epigenetic alterations have been explored in medulloblastoma. Histone demethylase, KDM6A, is found to be mutated in Group 4 medulloblastoma resulting in elevated H3K27me3 and recruitment of repressive PRC2 complex, with EZH2 as its catalytic subunit (Fig. 1). This recruitment represses lineage differentiation genes and leads to maintenance of proliferative stem cell signatures [119]. Overexpression of EZH2 and subsequent repression of tumor suppressor genes has been found in many cancers, including non-WNT/non-SHH medulloblastoma [120]. Several EZH2 inhibitors show anti-cancer effects in cell lines and mouse models [121] and the EZH2 inhibitor, tazemetostat, is in a clinical phase 2 trial for a variety of recurrent tumors in children, including medulloblastoma (NCT03155620).

Having a near ubiquitous role in cancers, HDACs belong to the best studied epigenetic modifiers. Several HDAC inhibitors are in clinical trials for pediatric brain tumors (mostly HGG/DMG, as discussed above). For medulloblastoma, HDAC2 has been observed to be overexpressed in SHH, Group 3, and Group 4 subgroups, and its ablation reduced tumorigenicity in cell lines [122]. Fimepinostat, a dual HDAC and PI3K Class I inhibitor, is currently under investigation in a target validation clinical trial to assess blood-brain barrier penetration in children with pediatric brain tumors, including children with recurrent medulloblastoma (PNOC016; NCT03893487).

BET family of bromodomain proteins recognize histone acetylation and trigger gene expression, including super-enhancer-regulated cancer genes [123]. The BET protein inhibitor, JQ1, represses tumor growth in SHH-medulloblastoma cells, by reducing *GLI1* and *GLI2* expression [124]. Similar effects are seen in Group 3 medulloblastoma cells, where BET inhibition leads to downregulation of *MYC* expression [125]. Other BET inhibitors are currently under investigation for pediatric solid tumors (NCT03936465).

Discussion

Over the recent years, our understanding of the molecular biology of pediatric brain tumors has vastly improved. This has led to more narrowly defined

subgroups of these tumors and created new potential targets for molecularly driven therapies, even extending to tumors that have historically been treated with surgery and radiotherapy, such as craniopharyngiomas. Further, since the early 2000s, initial successes in the clinical implementation of targeted therapy such as everolimus for SEGAs have been demonstrated. However, the promising advances in targeted therapies for pediatric brain tumors also lead to challenges that the pediatric neuro-oncology community still has to address.

Enhancing Drug Delivery to the Brain Tumor

In order to identify effective targeted therapies, the blood-brain barrier (BBB) penetration and the distribution within the brain and tumor tissue need to be considered. A number of different strategies have been developed to overcome these barriers and improve the delivery of therapeutic agents to cancer cells. These methods range from chemically disrupting the BBB itself to modifying the therapy agents and their carriers [126]. Another emerging and promising method entails the temporary mechanical opening of the BBB in a targeted and localized manner by MR-guided focused ultrasound (MRgFUS) to support drug delivery [127]. An alternative strategy to deliver drugs directly into the tumor tissue, bypassing the BBB entirely, is performed by convection-enhanced delivery (CED) through stereotactically placed catheters [70]. Broad applications of such targeted deliveries are still missing, but early studies support feasibility and safety [128].

Clinical Study Endpoints Beyond Tumor Response

With the growing number of targeted therapies entering the clinic, it is critical to define appropriate endpoints to assess therapy responses as well as short- and long-term toxicities. Currently, therapy response in clinical trials for pediatric brain tumors is mainly based on radiographic tumor response and clinical endpoints like overall survival (OS), progression-free survival (PFS), or event-free survival (EFS) depending on the specific tumor type. Functional outcomes, such as ophthalmologic, neurocognitive, neurofunction, and quality of life (QOL) assessments, are often not included as primary study endpoints. These endpoints though, potentially having more direct patient relevance, especially since image-based responses remain challenging to evaluate correctly in many pediatric tumor types. Additionally, while other exciting upcoming modalities, e.g. patient derived liquid biopsy analysis, may help to more adequately predict early tumor response [129], they lack sufficient assessment of the functional response to therapy and QOL aspects for the growing and developing child. Therefore, to help providers and patients perform more accurate risk/benefit analyses when deciding and comparing therapeutic options, incorporation of functional endpoints and QOL assessments into clinical trial design will be crucial.

Resistance Mechanisms and Combinational Targeted Therapies

Strong driver mutations, such as the commonly altered MAPK pathway in pLGG, have been proven to be a particularly good target for direct inhibitors such as MEK inhibitors. However, despite clear response rates in this setting, many questions remain unsolved: What is the optimal dosing? How long should patients be treated with these targeted inhibitors? What are the mechanisms of resistance and how can these be overcome with potential combination

strategies? Aside from pLGGs, most other pediatric CNS tumors exhibit substantially greater molecular heterogeneity and likely various tumor driver alterations or yet unknown drivers. Hence, wide genomic profiling for these tumors will be crucial for correct subclassification and implementation of targeted treatment strategies. There are now many examples that such assessments can be integrated in real time and should be considered the standard. Even for entities that generally only allow the collection of small stereotactic biopsies such as DIPG, genomic-based, real-time multiagent therapy approaches for treatment are feasible [7]. The increased understanding of the molecular make up of tumors allows response assessment in a defined context, which will be critical for future successes.

Conclusion

The field of pediatric neuro-oncology made tremendous progress with regard to improved diagnosis setting the stage for precision medicine approaches over the last decades. The potential of targeted therapies has been clearly demonstrated for a subset of pediatric brain tumors. However, despite clear response rates, questions of sufficient blood-brain barrier penetration, optimal dosing, treatment duration, as well as mechanisms of resistance and how these can be overcome with potential combination strategies need to be addressed in future investigations. Along this line, it is critical for future trials to define appropriate endpoints to assess therapy responses as well as short- and long-term toxicities in the growing and developing child.

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Compliance with Ethical Standards

Conflict of Interest

None of the authors declare any conflict of interest.

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