CHAPTER ELEVEN

Emerging interventional treatments in the management of pediatric brain tumors

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Abstract

Recent advancements in the molecular understanding of pediatric brain tumor biology have significantly contributed to the development of innovative therapeutic strategies aimed at improving clinical outcomes for affected children. These scientific breakthroughs have facilitated the identification of specific molecular targets and signaling pathways integral to the oncogenesis of pediatric brain tumors, thereby enabling the design of targeted therapies that disrupt these pathogenic processes.

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Furthermore, the incorporation of immunotherapy and precision medicine approaches has unveiled novel therapeutic avenues, offering the potential for more efficacious and less toxic treatment modalities. As research in this domain continues to progress, these cutting-edge therapeutic interventions are anticipated to enhance survival rates and improve the quality of life for pediatric patients. This review delineates emerging interventional treatments in pediatric brain tumor management and examines the persistent challenges within the field.

1. Introduction

Pediatric brain tumors represent a significant challenge in oncology, being the leading cause of cancer-related mortality in children (Miller et al., 2021). Despite advances in surgical techniques, radiation, and chemotherapy, the prognosis for many pediatric brain tumors remains poor, necessitating the exploration of novel therapeutic approaches (Kulubya et al., 2022).

Over the past two decades, strides in the molecular understanding of brain tumor biology have revolutionized the landscape of treatment strategies. By elucidating the genetic and epigenetic alterations driving tumorigenesis, researchers have identified distinct molecular targets and signaling pathways that are crucial in the pathogenesis of these malignancies (Kulubya et al., 2022). This has facilitated the development of targeted therapies designed to specifically disrupt oncogenic processes, offering the promise of more precise and less toxic treatment options.

Moreover, Neurosurgical innovations have included the use of laser interstitial thermal therapy, focused ultrasound and sonographic therapy for treatment of brain tumors. The principles of these innovative approaches for tissue ablation are well understood from the application of a heat or waves via radiant light energy, the associated cell death from heating, and advanced magnetic resonance imaging (MRI) to monitor and guide the ablation. However, initial response and long-term control for specific tumor types are not well established in the field. Furthermore, the unique pathologies common to pediatric brain tumors lags behind our adult counterparts in the extant literature. It is expected for these innovative approaches to play a more significant role in pediatric neuro-oncology, but if that becomes upfront therapy, limited to recurrent or residual disease, or in combination with targeted medical therapy to facilitate breaking down the blood-brain barrier for more efficacious drug deliver remains to be determined.

This chapter aims to explore the latest advancements in molecular targeting and therapeutic innovations, highlighting their implications for improving survival rates and quality of life in pediatric patients, while also addressing the ongoing challenges in this rapidly evolving field.

2. Advancements in the molecular biology of pediatric brain tumors

The 2021 World Health Organization (WHO) classification of central nervous system tumors now integrates histopathologic and molecular data, reflecting significant advancements in the molecular characterization of these tumors (Louis et al., 2021). Pediatric low-grade gliomas (pLGGs) exemplify the forefront of research into brain tumor molecular alterations. They are increasingly recognized as a "single pathway disease," primarily driven by genetic changes that consistently activate the mitogen-activated protein kinase (MAPK) pathway, which plays a fundamental role in cellular processes, including proliferation, differentiation, and survival, and its dysregulation is a critical factor in tumorigenesis (Ziegler et al., 2024).

A pivotal discovery in 2008 identified a tandem duplication within the BRAF kinase gene, resulting in the KIAA1549-BRAF fusion protein, which leads to constitutive activation of the MAPK pathway and promotes oncogenesis (Jones et al., 2008). Subsequent studies have identified a range of additional genetic alterations within this pathway. Notably, point mutations such as BRAF V600E lead to the persistent activation of the BRAF protein kinase. Additionally, gene fusions involving other kinases, such as RAF1 and FGFR1, have been detected, highlighting the genetic heterogeneity contributing to MAPK pathway dysregulation in pLGGs (Ryall et al., 2020). These molecular insights have significant implications for the advancement of targeted therapeutic strategies. The precise characterization of genetic alterations driving the growth of pediatric low-grade gliomas (pLGGs) has enabled the development of therapies specifically targeting these oncogenic pathways, culminating in the approval of treatment modalities by the FDA (Manoharan et al., 2023). The identification and understanding of these genetic drivers have facilitated a precision medicine approach, allowing for the customization of treatments based on the tumor's molecular profile.

While the elucidation of molecular alterations in pLGGs has spurred the development of innovative therapeutics, the discovery of driver histone

mutations and associated epigenetic modifications in pediatric high-grade gliomas (pHGGs) has not yet translated into significant therapeutic advancements (Schwartzentruber et al., 2012). Mutations in histone genes, such as H3K27M and H3G34R/V, alter chromatin architecture and gene expression, playing a crucial role in pHGGs pathogenesis (Kasper & Baker, 2020; Weinberg et al., 2017). Despite these discoveries, translating this knowledge into effective treatment options remains challenging due to the complexity of epigenetic regulation and the aggressive nature of pHGGs.

Advances in understanding medulloblastoma and rare embryonal brain tumors, once classified as primitive neuroectodermal tumors (PNETs), have been significant (Lazow et al., 2022). High-throughput genomic and proteomic technologies have facilitated detailed methylomic and transcriptomic analyses, revealing medulloblastoma as a biologically diverse spectrum rather than a singular disease. This has led to the identification of four distinct molecular subgroups: WNT-activated, SHH-activated, Group 3, and Group 4, each characterized by specific DNA methylation patterns, copy number variations, somatic mutations, and cytogenetic profiles (Sarvode & Gajjar, 2023). This molecular stratification is crucial for contemporary medulloblastoma clinical trials, which aim to tailor therapies to the unique molecular and clinical features of each subgroup.

The term "PNET" has become obsolete, as tumors previously grouped under this category have been redefined into more precise classifications based on molecular characteristics. The WHO's 2016 update eliminated the PNET classification, introducing more specific categories including "Atypical teratoid rhabdoid tumor (ATRT), embryonal tumors with multilayered rosettes (ETMR), pineoblastoma, CNS neuroblastoma, FOXR2-activated, CNS tumor with BCOR internal tandem duplication and embryonal tumors not otherwise specified (NOS)" (Sturm et al., 2016). This paradigm shift underscores the critical role of genetic and molecular profiling in the accurate classification and treatment of CNS embryonal tumors.

Ependymoma represents another tumor entity where genetic sequencing has revealed distinct molecular features, leading to the identification of ten different ependymal tumor subtypes defined by location. These subtypes correlate with clinical behavior and outcomes, providing a more nuanced understanding of the disease (Kresbach et al., 2022). Several genomic features have been recognized to impact prognosis, such as the gain of chromosome 1q, in posterior fossa A tumors (Merchant et al., 2019), and MYCN amplification, particularly in spinal ependymomas

(Raffeld et al., 2020), are associated with a poorer prognosis. The 2021 WHO CNS5 classification reflects a shift towards a molecular-based classification system, moving away from traditional grading (Louis et al., 2021).

Recent advancements in the molecular understanding of CNS germ cell tumors have significantly enhanced our knowledge of their origins and key pathogenic factors. These tumors are characterized by chromosomal abnormalities and alterations in pathways such as MAPK and AKT/mTOR, alongside global hypomethylation. Such insights are pivotal in advancing precision medicine approaches, allowing for the development of targeted therapies tailored to the tumor's unique molecular profile, thereby improving treatment efficacy (Zhou et al., 2024).

In the realm of craniopharyngiomas, significant progress has been made in identifying critical pathogenic mechanisms and therapeutic targets of Adamantinomatous Craniopharyngiomas (ACP). The dysregulation of the MAPK/ERK and programmed cell death pathways has opened up new therapeutic possibilities. With PD-1 expression playing a role in tumorigenesis, current efforts are focusing on evaluating targeted inhibitors with the potential to redefine standard treatment strategies, highlighting the importance of reducing dysfunction associated with both the disease and its treatment effects (Shatara & Abdelbaki, 2025).

Despite these molecular advancements in pediatric brain tumors, translating them into improved treatment strategies and outcomes remains a challenge, underscoring the ongoing need for dedicated research and collaborative efforts to bridge the gap between molecular understanding and clinical application.

3. Novel therapeutic approaches in pediatric brain tumors

In recent years, substantial progress has been achieved in the development of therapeutic compounds, driven by new insights into cellular pathways, oncogenic driver mutations, and cancer cell mechanisms. These targeted therapies function by either directly inhibiting these pathways or by activating the immune system to facilitate the destruction of cancer cells. This category of therapies includes small-molecule inhibitors, monoclonal antibodies, and adoptive cellular immunotherapy. Tables 1 and 2 summarize the completed and ongoing novel approaches in children with brain tumors.

Table 1 Overview of completed and ongoing studies in pediatric CNS tumor therapies: targeted and epigenetic approaches completed studies.

Study focus	Therapeutic agent (s)	Patient group	Key findings
Completed studies			
PBTC-029	Selumetinib	Sporadic optic pathway gliomas and hypothalamic LGGs	Achieved a 24 % partial response rate, with 56 % of patients experiencing prolonged stable disease.
Novartis Phase II trial: NCT02684058	Dabrafenib, Trametinib	BRAF V600E mutant pLGGs	Showed a response rate of 47 % and a 1-year progression-free survival rate of 67 %, leading to FDA approval.
EXIST trial	Everolimus	Subependymal giant cell astrocytoma (SEGA) in TSC patients	Reported > 50 % reduction in SEGA volume compared to placebo with a favorable safety profile.
NCT02684058	Dabrafenib, Trametinib	BRAF V600E mutant recurrent pediatric HGGs	Demonstrated a 56.1 % ORR, improved progression-free and overall survival.
PBTC-047	Panobinostat	DMG, DIPG	Limited tolerability due to myelosuppression; no significant clinical benefits.
NCT01076530	Vorinostat, Temozolomide	Ependymoma, Ganglioglioma, High-grade glioma	Partial response in ependymoma; stable disease in other cases.
NCT03893487	Vorinostat, Bortezomib	Various CNS Tumors	No objective tumor responses observed.
PBTC-026	Vorinostat, Isotretinoin	Embryonal Tumors	Well-tolerated; 5-year PFS of 55 %, OS of 61 %.
MATCH APEC1621C	Tazemetostat	SMARCB1/SMARCA4 loss tumors	Demonstrated stable disease in ATRT patient; no significant tumor shrinkage.
PNOC015	Panobinostat (CED delivery)	DIPG	Demonstrated technical feasibility of CED delivery; efficacy results inconclusive.

Study Focus	Therapeutic Agent(s)	Patient Group	Study Details
Ongoing studies			
FIREFLY-2 (Tovorafenib Study)	Tovorafenib	pLGGs	Evaluating tovorafenib in the upfront setting for pLGG.
LOGGIC Study	Vincristine/carboplatin vs. vinblastine vs. Tovorafenib	Initial therapy of LGG	European study examining outcomes for initial therapy of LGG.
Children's Oncology Group Study ACNS1723	BRAF and MEK Inhibitors	Pediatric BRAF-mutant HGG	Evaluating as adjuvant therapy following radiation (NCT03919071).
PNOC-021	Trametinib, Everolimus	Recurrent gliomas	Evaluating combination of trametinib and everolimus in recurrent gliomas.
PNOC022	ONC201, Paxalisib	Diffuse midline glioma	Evaluating combination therapy pre-radiation, post-radiation, or at progression.
ROVER Phase 1/2	Avapritinib	Pediatric patients with relapsed/refractory tumors driven by KIT or PDGFRA	Assessing safety, pharmacokinetics, and efficacy (NCT04773782).

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Table 1 Overview of completed and ongoing studies in pediatric CNS tumor therapies: targeted and epigenetic approaches completed studies. (*cont'd*)

Study Focus	Therapeutic Agent(s)	Patient Group	Study Details
PNOC016	Fimepinostat	CNS Tumors	Showed blood-brain barrier penetration; well-tolerated with common myelosuppression.
NCT03936465	BMS-986158 and BMS-986378	Solid Tumors, Lymphomas, CNS Tumors	Aims to establish phase II dosing and assess safety.
ACTION trial (NCT05580562)	ONC201 (Dordaviprone)	DMG	Improved outcomes compared to historical controls; ongoing studies for efficacy and safety.

Table 2 Overview of completed and ongoing studies in pediatric CNS tumor therapies: immunotherapeutic approaches.

Therapy type	Agent/approach	Trial phase	Trial ID	Patient population	Key scientific outcomes/ findings
Oncolytic Viral Therapies	HSV-1 Variant (HSV1716)	Phase I	**NCT02031965**	Pediatric High-Grade Gliomas (pHGGs)	Trial terminated early due to limited enrollment; preclinical studies showed reduced tumor cell migration and invasion.
	HSV-1 Variant (G207)	Phase I	**NCT02457845**	Recurrent Supratentorial pHGGs	Demonstrated safety and tolerability; 11 of 12 patients exhibited radiographic, neuropathologic, or clinical responses; median OS of 12.2 months.
		Phase II	**NCT04482933**	Pediatric Brain Tumors	Ongoing trial assessing combination of G207 with radiotherapy to enhance therapeutic efficacy.
	Adenovirus (Delta-24-RGD)	Phase I	**NCT03178032**	Newly Diagnosed DIPG	Demonstrated safety; median OS of 17.8 months; notable long-term survival in a subset of patients.

(continued)

Table 2 Overview of completed and ongoing studies in pediatric CNS tumor therapies: immunotherapeutic approaches. (*cont'd*)

Therapy type	Agent/approach	Trial phase	Trial ID	Patient population	Key scientific outcomes/ findings
	Poliovirus Chimera (PVSRIPO)	Phase I	**NCT03043391**	Recurrent pHGGs	Primarily focused on safety; preliminary evidence of efficacy with one patient achieving long-term survival.
	Measles Virus (Edmonston strain)	Phase I	**PNOC-005, NCT02962167**	Recurrent Medulloblastoma and ATRT	Safety confirmed; observed immunomodulatory effects correlated with antiviral tumor activity.
Immune Checkpoint Inhibitors	Nivolumab	Various	**NCT02992964, NCT04323046**	Relapsed or refractory cancers with high TMB/ MMRD	Positive clinical and radiological outcomes in hypermutated GBM; ongoing studies exploring neoadjuvant and combination approaches to enhance immune responses.
	Pembrolizumab	Phase I/II	**NCT02332668**	Advanced melanoma or PD-L1 positive pediatric tumors	Interim data show an objective response rate of 5.9 %; partial responses observed in a subset of patients, including those with malignant rhabdoid tumor.

	Nivolumab + Ipilimumab	Phase II	**NCT04416568**	SMARCB1-deficient tumors	Evaluating combination therapy efficacy; typically low mutational burden tumors with minimal initial response to ICIs.
Cancer Vaccines	Dendritic Cell Vaccines	Various	**NCT01326104, NCT03334305, NCT04911621**	Pediatric Brain Tumors	Generally well-tolerated; some patients with high-grade gliomas and ATRT showed prolonged survival; ongoing trials to refine vaccine strategies.
	Peptide-Based Vaccines	Various	**PNOC007, NCT01795313, NCT04978727**	Pediatric High-Grade Gliomas	Promising early immune activation; trials exploring synergy with PD-1 inhibitors to counteract T-cell exhaustion observed post-vaccination.
	RNA-Based Vaccines	Phase I	**NCT04573140**	Pediatric High-Grade Gliomas	Investigating mRNA vaccine adaptability across diverse patient HLA haplotypes; potential for broad applicability in pediatric oncology.

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Table 2 Overview of completed and ongoing studies in pediatric CNS tumor therapies: immunotherapeutic approaches. (*cont'd*)

Therapy type	Agent/approach	Trial phase	Trial ID	Patient population	Key scientific outcomes/ findings
Monoclonal Antibodies	BiTEs, Radio-immunotherapy	Various	**NCT05064306, NCT04743661**	Pediatric CNS Tumors	Ongoing studies focusing on optimizing delivery and enhancing tumor targeting efficacy; strategies include targeting B7-H3 and EGFR with radio-conjugates.
CAR T-Cell Therapy	GD2, HER2, B7-H3 CAR T-cells	Various	**NCT04185038, NCT03500991, NCT04196413**	Pediatric CNS Tumors	Promising preclinical efficacy; phase trials assessing safety and therapeutic potential; ongoing efforts to improve intratumoral delivery and overcome antigen escape.

3.1 Targeted small-molecule inhibitors

3.1.1 MPAK-pathway inhibitors

Pediatric LGGs exemplify how detailed molecular characterization can effectively guide therapeutic strategies. These tumors often exhibit genetic alterations in the Ras-MAPK pathway, particularly BRAF V600E mutations and KIAA1549-BRAF fusions (Manoharan et al., 2023; Ryall et al., 2020). This molecular profile makes them amenable to targeted inhibition, marking a significant evolution in treatment approaches. The development of small-molecule inhibitors targeting these dysregulated signaling proteins has become a focal point in clinical research, with BRAF inhibitors like vemurafenib and dabrafenib, alongside MEK inhibitors such as trametinib and selumetinib, showing promising efficacy in early-phase clinical trials.

The chronic nature of pLGGs, characterized by indolent growth and long-term survivability, necessitates a balanced treatment approach that ensures efficacy while minimizing treatment-related morbidity. Surgical resection remains the primary treatment modality, offering a potential cure when complete tumor removal is achieved (Wisoff et al., 2011). However, for patients with unresectable or recurrent tumors, chemotherapy has traditionally been used, albeit with a modest 5-year progression-free survival rate of approximately 45–55 % (Fangusaro et al., 2023). The advent of targeted therapies offers a potential paradigm shift, focusing not only on the reduction of cytotoxic exposure but also on the preservation of neurocognitive function and quality of life.

Central to advancing treatment options for pLGGs is the focus on targeting the hyperactivation of the Ras-MAPK pathway. This focus has yielded significant progress with RAF and MEK inhibitors, many of which have received FDA approval or are undergoing clinical evaluation. For example, selumetinib, a selective small molecule inhibitor, was tested in a phase 2 trial through the Pediatric Brain Tumor consortium (PBTC) and achieved a 24 % partial response rate, with 56 % of patients experiencing prolonged stable disease in cases of sporadic optic pathway gliomas (OPG) and hypothalamic LGGs (Fangusaro et al., 2021).

Type 1 RAF (BRAF) inhibitors, such as dabrafenib and vemurafenib, have been extensively studied in pLGGs harboring BRAF V600E mutations. The Pediatric Neuro-Oncology Consortium (PNOC) conducted a Phase 1/2 trial to assess vemurafenib, which showed early signs of safety and potential efficacy as a monotherapy, with radiographic outcomes indicating one complete response, five partial responses, and thirteen

instances of stable disease among patients (Nicolaides et al., 2020). The ongoing Phase 2 study aims to provide a more comprehensive assessment of the objective response rate.

Conversely, dabrafenib, when combined with the MEK inhibitor trametinib, has shown significantly improved outcomes in BRAF V600E mutant pLGGs (Wahid et al., 2024). In a Phase 2 study, this combination therapy achieved a response rate of 47 % and a 1-year progression-free survival rate of 67 %, substantially outperforming standard chemotherapy regimens (Bouffet et al., 2023). These results led to the FDA's approval of this combination as a first-line treatment for pediatric patients with pLGGs and a BRAF V600E mutation, representing a major advancement in therapeutic options for this patient population.

Further expanding the arsenal of targeted therapies, tovorafenib, an oral, selective, CNS-penetrant type II RAF inhibitor, was recently FDA-approved for use in patients aged six months and older with relapsed or refractory pLGGs harboring a BRAF fusion, rearrangement, or BRAF V600 mutation. This approval was based on results from the Phase 2 FIREFLY-1 (PNOC026; NCT04775485) trial, which showed a median progression-free survival of 13.8 months and a median duration of response of 16.6 months according to Response Assessment in Pediatric Neuro-Oncology "RAPNO" criteria (Kilburn et al., 2024). The ongoing FIREFLY-2 (NCT05566795) Phase 3 trial is currently evaluating tovorafenib in the upfront setting for pLGG. There is a European study, LOGGIC, examining the outcomes for vincristine/carboplatin vs. vinblastine vs. tovorafenib for initial therapy of LGG as well (NCT05566795).

In contrast, the effectiveness of targeted therapy for HGGs in pediatric patients has been limited. The current standard treatment for newly diagnosed patients involves maximal surgical resection followed by focal radiotherapy for those aged three years and older, along with chemotherapy. However, the overall response rates (ORRs) are less than 20 %, and the 5-year survival rates are dismal, highlighting the urgent need for advancements to improve outcomes in these tumors (Erker et al., 2024; Yoel et al., 2024).

The BRAF V600E mutation is found in approximately 5–10 % of pediatric HGGs (Mackay et al., 2017). While its prognostic significance remains uncertain, this mutation is predominantly observed in favorable histologic subtypes of pediatric HGG (Nobre & Bouffet, 2022). A Phase II study using dabrafenib and trametinib at recurrence demonstrated an ORR

of 56.1 %, with a median duration of response of 22.2 months. The median progression-free survival (PFS) and overall survival (OS) were 9 months and 32.8 months, respectively (Hargrave et al., 2023).

Moreover, in a retrospective multi-institutional review found that using BRAF inhibitors, with or without MEK inhibitors, in BRAF V600E mutant HGGs, significantly improved PFS and OS, compared to historical cohorts, suggesting the advantage of employing small-molecule targeted inhibitors as upfront therapy (Rosenberg et al., 2022). The Children's Oncology Group (COG) is currently investigating this approach by evaluating BRAF and MEK inhibitors as adjuvant therapy following radiation for pediatric BRAF-mutant HGG (NCT03919071).

The involvement of the MAPK signaling pathogenesis in the tumorigenesis of ACPs is currently being evaluated in multiple clinical trials using tovorafenib (NCT05465174/PNOC029), and Binimetinib (NCT05286788/CONNECT2108).

3.1.2 PI3K/mTOR inhibitors

The PI3K/mTOR signaling pathway is critically involved in the pathogenesis pLGGs and pHGGs, where it governs key processes of cellular growth and proliferation. Activation of cell surface receptors by ligands such as growth factors or cytokines triggers the recruitment of PI3K to the cell membrane, resulting in the accumulation of phosphatidylinositol-3,4,5-bisphosphate (PIP3). This cascade leads to the phosphorylation and activation of the serine/threonine kinase Akt. Akt then inhibits the tuberin-hamartin (TSC) complex, effectively lifting the inhibition on mTOR and promoting cellular proliferation and survival (Rogers et al., 2017; Siegel et al., 2025).

Therapeutic strategies frequently target the PI3K or mTOR components, particularly in conditions like tuberous sclerosis complex (TSC)—an autosomal dominant disorder that predisposes individuals to tumor development in multiple organs, including the brain, heart, kidneys, skin, and retina. Subependymal giant cell astrocytoma (SEGA) is a type of LGG that occurs in approximately 15 % of TSC patients, often forming near the foramen of Monro and potentially leading to obstructive hydrocephalus. Historically, surgical resection was the primary mode of therapy (Man et al., 2024). However, the mTOR inhibitor everolimus has been approved by the FDA based on the pivotal phase 3 EXIST trials, which reported a greater than 50 % reduction in SEGA volume in the treatment group compared to none in the placebo group, with a favorable safety profile (Curatolo et al., 2018; Franz et al., 2014; Franz et al., 2013; Franz et al., 2016; Franz et al., 2006; Jóźwiak et al., 2016).

In contrast, similar efficacy has not been observed in non-TSC pLGGs. A phase 2 trial of everolimus monotherapy for recurrent or progressive pediatric LGG showed a partial response in only 13 % of patients (Wright et al., 2021). Furthermore, another study demonstrated no significant correlation between PI3K/mTOR pathway activation and treatment response (Haas-Kogan et al., 2023). Low response rates were also observed in trials involving recurrent NF1-associated LGG treated with everolimus (Ullrich et al., 2020).

Pre-clinical studies have shown that combining mTOR inhibitors with agents like the MEK inhibitor trametinib and carboplatin may have synergistic effects (Arnold et al., 2020). An ongoing phase 1 study (PNOC-021, NCT04485559) is evaluating the combination of trametinib and everolimus in recurrent gliomas, exploring the interaction between the MAPK and PI3K/mTOR pathways for potential combination therapies.

Alterations in the PI3K/mTOR pathway, such as AKT and PIK3CA mutations or PTEN loss, have been identified in H3K27-altered diffuse midline glioma (Duchatel et al., 2024; Mackay et al., 2017). Samotolisib, an ATP-competitive inhibitor of PI3K isoforms, mTOR, and DNA-PK, was tested in pediatric patients with these genetic alterations but showed no significant antitumor activity as a single agent, suggesting the need for combination approaches (Laetsch et al., 2024).

Paxalisib, another novel CNS-penetrant PI3K/mTOR inhibitor, has demonstrated efficacy in preclinical models of diffuse midline glioma when used with other agents (Jackson et al., 2023; Wen et al., 2020). It is part of an ongoing clinical trial (PNOC022/NCT05009992) with ONC201, an oral ClpP agonist. In this trial, patients aged 2–39 years were enrolled pre-radiation, post-radiation, or at progression. They received ONC201 and paxalisib, with pharmacokinetic and biologic samples collected. Results indicate that the combination is generally well-tolerated. The median overall survival (OS) from diagnosis is 13.2 months for pre-radiation patients, 15.8 months for those post-radiation, and 8.8 months for those at progression, with further analyses of pharmacokinetics, circulating tumor DNA, metabolic signatures, survival, and tumor response underway (Kline et al., 2024).

3.1.3 Receptor tyrosine kinase inhibitors

Receptor tyrosine kinases (RTKs) are essential components of cellular signaling, acting as transmembrane glycoproteins that mediate communication between the extracellular environment and intracellular pathways.

These receptors are activated upon binding with specific extracellular ligands, such as growth factors, hormones, cytokines, and neurotrophic factors (De Meyts, 2015; Tomuleasa et al., 2024). This binding induces dimerization of the RTKs, leading to autophosphorylation of specific tyrosine residues within their cytoplasmic domains. This phosphorylation event is crucial as it creates docking sites for a variety of intracellular signaling proteins, effectively initiating a cascade of downstream signaling pathways (Sun et al., 2016; Yao et al., 2017). The RAS/MAPK/ERK and PI3K/AKT pathways are among the primary pathways activated by RTKs, playing significant roles in cell proliferation, differentiation, survival, and metabolism (Tomuleasa et al., 2024; Xu & Huang, 2010).

The structural diversity of RTKs allows them to be classified into distinct subfamilies, including the epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), and others. Each subfamily is characterized by unique ligand specificities and structural motifs that determine their functional roles in various physiological processes (Du & Lovly, 2018; Lemmon & Schlessinger, 2010; Pulivarthi et al., 2023). Dysregulation of RTK signaling is a common feature in many cancers, including pediatric brain tumors, where it contributes to tumorigenesis and disease progression. This dysregulation often results from mutations, amplifications, or overexpression of RTKs, leading to continuous activation of signaling pathways that promote uncontrolled cell growth and survival (Bache et al., 2004; Saraon et al., 2021).

Alterations in RTK family members, alongside histone mutations, represent a significant area of focus in pHGG, often exhibiting amplification of the platelet-derived growth factor receptor A (PDGFRA)-driven signaling, while adult high-grade gliomas (HGG) often exhibit overexpression of EGFR (Bredel et al., 1999; Paugh et al., 2011; Paugh et al., 2010). This amplification of PDGFRA leads to the activation of the PI3K/mTOR or MAPK signaling pathways, which are pathways linked to poor prognoses in these pediatric tumors (Koschmann et al., 2016; Paugh et al., 2013; Zhang et al., 2007). Consequently, RTKs are considered promising therapeutic targets, with ongoing research aimed at developing inhibitors that can effectively disrupt these aberrant signaling pathways.

3.1.3.1 PDGFR inhibitors

Dasatinib has emerged as a promising PDGFRA inhibitor, especially in pHGG with PDGFRA amplification. In vitro studies utilizing cell lines

from young patients have demonstrated robust growth-inhibitory effects, with IC50 values in the nanomolar range. While its effectiveness is reduced in models lacking receptor amplification, dasatinib's moderate ability to penetrate the blood-brain barrier and its potent inhibition of PDGFR signaling make it a viable option for treating pHGGs with PDGF pathway alterations (Koschmann et al., 2016; Ravi et al., 2021; Schwark et al., 2022). Additionally, dasatinib has shown synergistic effects when combined with therapies such as the mTOR inhibitor everolimus, resulting in extended survival in preclinical studies and improved outcomes in small clinical cohorts (Miklja et al., 2020).

Avapritinib, a selective inhibitor of both wild-type and mutant PDGFRA, is specifically designed to target activation loop mutations like PDGFRA D842V, and it exhibits higher specificity for PDGFRA and KIT compared to dasatinib (Evans et al., 2017). Approved in the United States for adults with unresectable or metastatic gastrointestinal stromal tumors (GIST) harboring PDGFRA exon 18 mutations and advanced systemic mastocytosis (Chi et al., 2021), avapritinib's excellent central nervous system penetration makes it a promising candidate for pHGG treatment. Both preclinical and clinical experiences have demonstrated significant tumor growth reduction and enhanced survival (Mayr et al., 2023; Trissal et al., 2023), which has led to the initiation of the ROVER phase 1/2 multicenter, open-label trial (NCT04773782). The study is currently evaluating the safety, pharmacokinetics, and efficacy of avapritinib in pediatric patients aged 2 to under 18 years with relapsed or refractory tumors driven by KIT or PDGFRA signaling, including H3K27M-mutant gliomas (Abbou et al., 2024; Chi et al., 2021; Koschmann et al., 2023).

3.1.3.2 EGFR inhibitors

EGFR is a pivotal member of the ErbB family of TKRs, playing a significant role in regulating essential cellular activities such as migration, differentiation, and proliferation (Sievers et al., 2021; Wells, 1999). Mutations and amplifications in the EGFR gene are frequently observed in a variety of tumors, including glioblastoma multiforme (GBM) and bithalamic and other midline pHGGs, and significantly dictate the effectiveness of EGFR inhibitors (Mondal et al., 2020).

A major challenge in treating brain tumors with EGFR inhibitors is ensuring adequate penetration of the CNS. First-generation tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib have demonstrated limited success due to their poor CNS penetration did not significantly enhance

survival rates compared to historical controls. Despite promising preclinical results, second-generation inhibitors also failed to yield significant clinical benefits (Fouladi et al., 2013; Macy et al., 2017; Mayr et al., 2025; Pollack et al., 2011; Qaddoumi et al., 2014). However, third-generation inhibitors like osimertinib have shown enhanced CNS penetration (Ballard et al., 2016), leading to exploration of osimertinib in pHGG, showing potential benefits, notably those with EGFR exon 20 insertions, demonstrating slower disease progression (Mondal et al., 2020). Furthermore, recent research underscores EGFR's role in cancer metabolism, revealing that EGFR mutations can influence metabolic pathways, thereby contributing to tumor resistance against metabolic drugs (He et al., 2021). This insight suggests that combining EGFR inhibitors with metabolic modulators might provide a novel strategy for overcoming resistance in brain tumors (Schwark et al., 2022).

3.1.3.3 FGFR inhibitors

Fibroblast growth factor receptors (FGFRs 1–4) are frequently pediatric gliomas, with FGFR1 being the most frequent alteration and the focus of targeted therapeutic strategies (Parker et al., 2014; Porta et al., 2017). The pan-FGFR inhibitor erdafitinib has shown promising preclinical and clinical activity in gliomas harboring FGFR mutations. In phase II trial involving solid tumors, including pediatric gliomas, erdafitinib elicited partial responses (Lee et al., 2023; Witt et al., 2024). Nevertheless, the efficacy of FGFR inhibitors can be compromised by cancer cells' ability to develop resistance through alternative mutations or signaling pathways, prompting the inclusion of patients with FGFR mutations or fusions in MEKi trials based on MAPK pathway upregulation (Szymczyk et al., 2021; Vanan et al., 2023).

The selective FGFR inhibitor Debio1347 was investigated in a case series involving five glioma patients (three with pLGG and two with pHGG), where two patients (one with pLGG and one with pHGG) experienced sustained partial responses. However, the treatment raised concerns regarding toxicity, particularly skeletal issues such as increased linear growth velocity and joint complications in skeletally immature patients, as well as metabolic side effects (Farouk Sait et al., 2021).

Multi-kinase inhibitors like ponatinib and lenvatinib, although not exclusively specific to FGFR, have demonstrated the potential to inhibit FGFR pathways involved in tumor development. Ponatinib, known for its CNS penetration (Ravi et al., 2021), exhibited antiproliferative effects in

vitro and has been used off-trial for individual cases with FGFR-activating mutations (Linzey et al., 2017; Schwark et al., 2022; Vanan et al., 2023). However, ponatinib did not demonstrate significant clinical efficacy in adult GBM (Lee et al., 2019).

3.1.3.4 NTRK inhibitors

Neurotrophic tropomyosin receptor kinase (NTRK) gene fusions are implicated in the constitutive activation of TRK receptors, driving tumorigenesis in various gliomas (Gambella et al., 2020). NTRK fusions are particularly common in pediatric gliomas, notably up to 40 % of infant high-grade gliomas (Lang et al., 2022; Moreira et al., 2024). NTRK inhibitors have emerged as a promising class of targeted therapies for pediatric CNS tumors with NTRK gene fusions.

The first-generation multi-kinase inhibitor, entrectinib, exhibits efficacy against NTRK, ALK, and ROS1 fusions, making it well-suited for the treatment of infant HGG. In early-phase clinical trials, entrectinib demonstrated rapid and durable responses in CNS tumors harboring NTRK fusions (Desai et al., 2022; Robinson et al., 2020; Robinson et al., 2019). These findings led to the FDA accelerated approval of entrectinib for pediatric patients with NTRK fusion-positive tumors in 2019 (Blauel & Laetsch, 2022).

Larotrectinib, another first-generation inhibitor with high selectivity for NTRK, has shown substantial antitumor activity as well as the ability to penetrate the CNS. In the SCOUT and NAVIGATE clinical trials, larotrectinib achieved tumor reduction ranging 75–80 % of patients and is currently being evaluated in the upfront treatment for newly diagnosed pHGGs with NTRK fusions (NCT04655404, NCT02637687) (Doz et al., 2022; Hong et al., 2020; Laetsch et al., 2018).

Resistance to these inhibitors frequently arises due to "on-target" mutations within the kinase domain, hindering drug binding. Second-generation inhibitors like selitrectinib and repotrectinib are being explored in such settings. Additionally, resistance may involve "off-target" mechanisms, particularly the activation of the MAPK pathway, indicating that the combination of NTRK inhibitors with MEK inhibitors could provide therapeutic advantages (Blauel & Laetsch, 2022; Cocco et al., 2019; Drilon, 2019; Shulman & DuBois, 2020).

3.1.3.5 MET inhibitors

The Mesenchymal-epithelial transition (MET) receptor, involved in cellular growth and angiogenesis, is frequently altered in gliomas, correlating

with adverse clinical outcomes (Schwark et al., 2022; Siegel et al., 2025). While capmatinib demonstrated limited activity in adult GBM trials (van den Bent et al., 2020), the MET inhibitor bozitinib (PLB-1001) was tested in 18 recruited pHGG patients, with two showing partial responses and an overall median progression-free survival (PFS) of 3 months (Hu et al., 2018). Crizotinib is being investigated in combination with other therapeutic modalities, such as temozolomide and radiotherapy for newly diagnosed GBM (NCT02270034), and with dasatinib in pHGGs, including DIPG (NCT01644773) (Gibson et al., 2021). Although both clinical trials have been completed, the findings have not yet been available. Nonetheless, in a phase I trial involving 25 recurrent pHGG patients, crizotinib, combined with dasatinib, resulted in frequent dose-limiting toxicities and no objective radiologic responses (Broniscer et al., 2018). These findings underscore the need for further exploration of combination therapies to enhance the efficacy of MET inhibitors in glioma treatment.

3.1.3.6 VEGF inhibitors

Vascular endothelial growth factor (VEGF) is a critical mediator of angiogenesis in high-grade gliomas, and as such, VEGF inhibitors have been extensively researched for their ability to disrupt tumor angiogenesis (Kaur & Roy, 2024). Bevacizumab, a monoclonal antibody targeting VEGF, is widely utilized in pediatric CNS tumors, particularly in pLGGs and optic pathway gliomas. In these contexts, bevacizumab, either as monotherapy or in combination with irinotecan, has demonstrated sustained radiographic responses and improvements in visual acuity (Couec et al., 2012; Gururangan et al., 2013; Packer et al., 2009).

In neurofibromatosis type 2 (NF-2)-associated vestibular schwannoma, bevacizumab has demonstrated potential benefits, including improved auditory function and disease stabilization. However, further studies are required to optimize its dosing regimen and therapeutic strategies (Lu et al., 2019; Plotkin et al., 2009; Tops et al., 2025).

Bevacizumab has also been investigated in adult and pediatric HGGs with mixed results. Bevacizumab has demonstrated improved PFS in GBM but has not overall survival when used as monotherapy (Kaka et al., 2019). In children, The HERBY trial, which included non-brainstem WHO grade III or IV gliomas, reported no difference in event-free survival (EFS) with the addition of bevacizumab to standard treatment. Nevertheless, improved EFS was observed in tumors with high CD8+ lymphocytic infiltration, suggesting a potential biomarker for bevacizumab responsiveness (Grill et al., 2018;

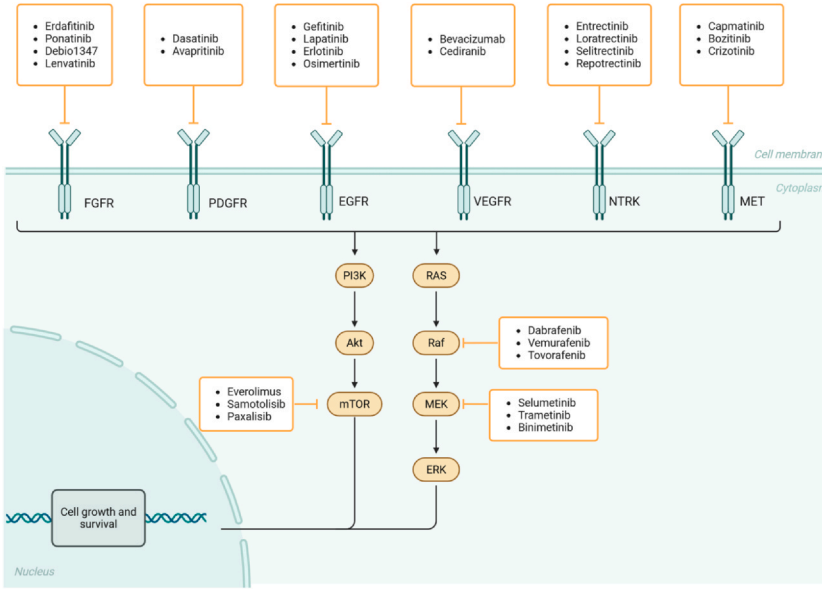

Fig. 1 Diagram illustrating the MAPK, mTOR, and RTK cellular signaling pathways, highlighting targets for therapeutic intervention.

Mackay et al., 2018). Similarly, the combination of bevacizumab with irinotecan in pHGGs did not yield additional benefits (Gururangan et al., 2010).

Other VEGFR inhibitors, such as cediranib, have had limited success in clinical trials, underscoring the necessity for developing more effective therapeutic approaches (Batchelor et al., 2013).

In summary, while RTK inhibitors offer a promising avenue for glioma treatment, challenges such as CNS penetration and resistance mechanisms persist. Ongoing research is crucial to enhance the efficacy of these therapies and improve patient outcomes in both pediatric and adult populations. Fig. 1 outlines the MAPK, mTOR, and RTK cellular signaling pathways, emphasizing the key targets for therapeutic intervention.

3.2 Epigenetic alterations and inhibitors

Epigenetic modifications, which modulate gene expression without altering the DNA sequence, play a pivotal role in cancer development. These modifications encompass DNA methylation, histone acetylation, ubiquitinylation, demethylation, deacetylation, and the involvement of non-coding RNAs (Alencastro Veiga Cruzeiro et al., 2021; Lu et al., 2020). Fig. 2 illustrates the diverse epigenetic mechanisms present in pediatric brain tumors.

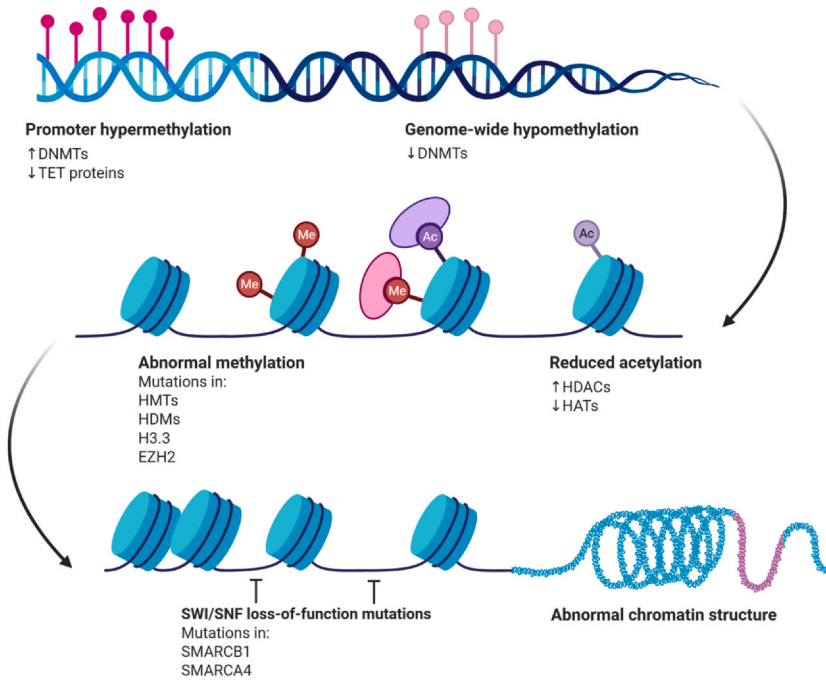

Fig. 2 Diagram illustrating the epigenetic modifications in pediatric brain tumors.

Post-translational modifications of histones influence gene expression by modifying chromatin structure, either condensing it to suppress transcription or relaxing it to facilitate transcription, thereby providing a reversible mechanism of gene regulation (Skouras et al., 2023). For example, mutations such as H3F3A p.K27M and p.G34R alter histone methylation patterns, contributing to oncogenesis (Sun et al., 2020).

In medulloblastoma, epigenetic modifications are pivotal in the differentiation of subtypes. Specifically, groups 3 and 4 are characterized by the overexpression of EZH2, an increase in H3K27me3, and a reduction in H3K4 methylation. Additionally, the regulation of the WNT pathway and the epigenetic function of SHH in activating bivalent genes are noteworthy (Roussel & Stripay, 2018).

Aberrant epigenetic regulation plays a crucial role in the pathogenesis of atypical teratoid rhabdoid tumors (ATRT), primarily through the inactivation of the SMARCB1 gene, a key component of the mSWI/SNF chromatin-remodeling complex. This inactivation disrupts normal neural differentiation by altering chromatin structure and gene expression, contributing to the

tumor's development and highlighting potential therapeutic targets, such as DNA methylation and histone modification pathways (Huhtala et al., 2024).

Ependymomas exhibit distinct epigenetic changes, such as elevated global H3K4me3 levels linked with oncogenes like Cyclin D1 (CCND1) and Erb-B2 Receptor Tyrosine Kinase 2 (ERBB2), which contribute to therapeutic resistance (Lewis et al., 2019; Skouras et al., 2023). In supratentorial ependymomas, the ZFTA-RELA fusion protein acts within the permissive epigenetic landscape of radial glial cells to maintain oncogenic transcriptional programs. Meanwhile, posterior fossa ependymomas are characterized by EZHIP overexpression, leading to a decrease in the repressive H3K27me3 mark, thereby promoting tumorigenesis through altered metabolic and transcriptional pathways (Kardian & Mack, 2024).

EZH2, a component of the Polycomb Repressive Complex 2, is involved in H3K27 trimethylation, a marker of gene repression. Inhibiting EZH2 can disrupt these repressive marks, potentially reactivating tumor suppressor genes and inhibiting tumor growth (Sneeringer et al., 2010). This strategy is promising in tumors like atypical teratoid tumors and rhabdoid tumors, where EZH2 dysregulation plays a role. Tazemetostat, an FDA-approved EZH2 inhibitor for epithelioid sarcoma and follicular lymphoma, reduces H3K27me3 levels and reactivates tumor-suppressing genes (Straining & Eighmy, 2022). In the NCI-COG pediatric MATCH APEC1621C study, tazemetostat was used for tumors with SMARCB1 or SMARCA4 loss, demonstrating stable disease in one ATRT patient, although no objective tumor shrinkage was observed (Chi et al., 2023). Similarly, 3-Deazaneplanocin A (DZNep) degrades PRC2 complex proteins and reduces H3K27 trimethylation. In PFA- ependymoma models, DZNep treatment led to decreased EZH2 expression and improved survival (Mack et al., 2014).

Histone deacetylases (HDACs) are enzymes that catalyze the removal of acetyl groups from histone proteins, leading to chromatin condensation and subsequent gene silencing. By inhibiting HDACs, chromatin structure can be relaxed, facilitating gene activation. HDAC inhibitors (HDACis) such as panobinostat and vorinostat have been studied for their therapeutic potential in CNS tumors (Perla et al., 2020). In preclinical models, panobinostat demonstrated efficacy by reducing tumor proliferation and enhancing survival rates. However, in a phase 1 clinical trial (PBTC-047, NCT02717455), the tolerability of panobinostat in pediatric patients with diffuse midline glioma (DMG) and diffuse intrinsic pontine glioma (DIPG) was limited, with significant myelosuppression as the primary dose-limiting

toxicity, which impeded drug administration and dose escalation. Furthermore, the trial did not report any significant clinical benefits (Monje et al., 2023). The limited penetration of the blood-brain barrier also posed a considerable obstacle. The phase 1 targeted validation study (PNOC015; NCT03566199) explored the feasibility of using convection-enhanced delivery (CED) to administer panobinostat directly to DIPG tumors. Although the study demonstrated the technical feasibility of this delivery method, efficacy results were inconclusive due to the small sample size and challenges related to drug distribution within the tumor (Mueller et al., 2023). Nonetheless, panobinostat (Farydak) was withdrawn from the United States market in March 2022, after its approval was revoked.

Fimepinostat is a novel oral agent that functions as a potent dual inhibitor of both pan-HDAC and PI3K. In the target validation study PNOC016, it demonstrated the ability to penetrate the blood-brain barrier in pediatric patients with CNS tumors. Intratumoral levels of fimepinostat or its metabolites were detectable in most patients. The drug was generally well-tolerated, with myelosuppression being the most common adverse effect, occurring in approximately one-third of patients (Kline et al., 2024). Further analyses are ongoing, including pharmacodynamic correlation, survival analyses, and circulating tumor DNA evaluation.

Vorinostat, an HDAC inhibitor, has been evaluated in multiple phase I clinical trials. In one study (NCT01076530), vorinostat was combined with temozolomide, showing tolerability and resulting in a partial response in a patient with ependymoma, and stable disease in cases of ependymoma, ganglioglioma, and high-grade glioma (Hummel et al., 2013). Conversely, another phase I trial (NCT03893487) combining vorinostat with bortezomib did not yield any objective tumor responses (Muscal et al., 2013). Recently, PBTC-026 (NCT00867178) assessed the feasibility and safety of adding vorinostat and isotretinoin to an intensive chemotherapy regimen for newly diagnosed embryonal tumors, demonstrating that this combination was well-tolerated and feasible, with a five-year progression-free survival of 55 % and overall survival of 61 %. Molecular characterization offered additional prognostic insights, especially for high-risk groups such as group 3 medulloblastoma, indicating the need for further research into the efficacy of these novel agents (Leary et al., 2022). Despite these varied outcomes, HDAC inhibitors continue to be a significant area of research due to their potential to target epigenetic modifications in cancer.

Bromodomain and Extra Terminal (BET) inhibitors, such as JQ1 and I-BET151, have demonstrated significant efficacy in inhibiting bromodomain interactions with acetylated lysine residues. These compounds have shown potential in preclinical models by effectively crossing the blood-brain barrier, reducing histone H3 lysine 27 acetylation (H3K27ac) levels, promoting cellular differentiation, and decreasing tumor growth in DIPG and medulloblastoma (Groves et al., 2022). Currently, a pediatric clinical trial (NCT03936465) is underway to evaluate two BET inhibitors, BMS-986158 and BMS-986378 (CC-90010), aiming to establish recommended phase II dosing and assess safety in patients under 21 years of age with relapsed or refractory solid tumors, lymphomas, or central nervous system tumors. These inhibitors are being explored for their potential broader application in the treatment of pediatric solid tumors.

ONC201 (Dordaviprone), a small molecule initially identified for its potential in targeting dopamine receptor D2, has garnered significant attention over the past decade as a possible treatment for diffuse midline glioma (DMG), particularly in cases with the H3K27M mutation. This mutation disrupts the normal trimethylation of histone H3, promoting oncogenic signaling. ONC201's mechanism of action includes upregulating the TNF-related apoptosis inducing ligand (TRAIL) pathway, inducing apoptosis through inhibition of Akt and MEK pathways, and more recently, disrupting the TCA cycle within mitochondria. This disruption inhibits histone lysine demethylases, leading to an increase in genomic H3K27me3, which may counteract the effects of the H3K27M mutation (Hansford et al., 2024; Venneti et al., 2023).

Clinical exploration of ONC201 began with anecdotal reports and early phase studies suggesting its potential efficacy in DMG, particularly in patients with the H3K27M mutation(Chi et al., 2017). A notable case from a phase II trial in 2016 highlighted a partial response in a young adult with recurrent glioblastoma, sparking interest in its application for DMG. Subsequent studies, including a phase I pediatric trial involving 22 patients, reported median progression-free survival (PFS) of 20.4 weeks and overall survival (OS) of 53.8 weeks in non-recurrent cases, although these results were confounded by prior radiotherapy treatments (Gardner et al., 2022). Venneti et al., pooled data from ONC201–014 (NCT03416530) and ONC201-018 (NCT03134131), indicated improved outcomes compared to historical controls (Venneti et al., 2023). Ongoing studies, including PNOC022 (NCT05009992) (Kline et al., 2024) and the international phase 3 ACTION trial (NCT05580562), a randomized, double-blind,

placebo-controlled, parallel-group study (Arrillaga-Romany et al., 2024), will be crucial to determining the drug's true efficacy and safety profile, amidst a backdrop of high patient and family hopes for a breakthrough in DMG treatment.

3.3 Cell-cycle alterations and inhibitors

Cyclin-dependent kinases (CDKs), particularly CDK4 and CDK6, are pivotal in cell cycle regulation, facilitating the G1 to S phase transition through phosphorylation of the retinoblastoma protein (Rb). These kinases are negatively regulated by the tumor suppressor protein P16, encoded by the CDKN2A gene, which induces G1 cell cycle arrest. Homozygous deletions of CDKN2A lead to unchecked CDK4/6 activity, promoting unregulated cell division and contributing to oncogenesis in cancers such as BRAF V600E gliomas and IDH-wildtype high-grade gliomas (HGGs). These deletions correlate with poorer clinical outcomes, serving as independent adverse prognostic markers in V600E-mutant pediatric low-grade gliomas (pLGG) (Mills et al., 2017; Ryall et al., 2020).

CDK4/6 inhibitors, including palbociclib, ribociclib, and abemaciclib, are small-molecule agents that mimic P16's function, inducing cell cycle arrest by targeting the dysregulated CDK4/6 pathways prevalent in cancers (Mills et al., 2017). Palbociclib has exhibited antitumor efficacy in preclinical models of pediatric brain tumors, such as brainstem gliomas and astrocytomas harboring specific mutations, and is under clinical investigation for Rb-positive central nervous system (CNS) tumors (Barton et al., 2013). A phase I trial (PBTC-042) assessing palbociclib in pediatric patients with progressive or refractory brain tumors found the drug to be well-tolerated, with myelosuppression, particularly grade 3/4 neutropenia and leukopenia, as the primary dose-limiting toxicities. However, despite its safety profile, the trial did not observe any objective responses, highlighting limited efficacy as a monotherapy in this setting (Van Mater et al., 2021).

Ribociclib, known for its effective CNS penetration, was also well-tolerated in a phase I/II clinical trials pHGG, DIPG, and refractory CNS tumors, yet did not yield significant clinical benefits, potentially due to cell-cycle reactivation following drug cessation (DeWire et al., 2020; Geoerger et al., 2017). This outcome has spurred investigations into combination therapies (NCT03355794), combining ribociclib with everolimus, which demonstrated therapeutic concentrations in CSF and tumor tissues (DeWire et al., 2022; DeWire et al., 2021). The ongoing Phase II TarGeT-A trial (NCT05843253) further explores these combinatorial approaches.

Abemaciclib's blood-brain barrier permeability making it a viable candidate for treating DIPG and other malignant brain tumors (Liang et al., 2020).

Beyond CDK inhibitors, aurora kinase inhibitors like AT9283 and alisertib are being evaluated for their potential in targeting mitosis-related aurora kinases, with preclinical studies indicating potential benefits for pediatric brain tumors. Alisertib has demonstrated efficacy in neuroblastoma and rhabdoid tumor models (Venkataraman et al., 2012). However, a phase II trial involving pediatric patients with refractory or recurrent solid tumors and acute leukemias revealed a limited objective response rate of less than 5 %, despite achieving target pharmacokinetic concentrations and demonstrating tolerability (Mossé et al., 2019). Moreover, Wee1 kinase inhibitors, such as AZD1775, are being investigated to enhance cancer cell sensitivity to DNA-damaging agents by disrupting the G2/M checkpoint, with current studies focusing on their combination with radiation therapy for DIPG (Mueller, Cooney, et al., 2022; Mueller et al., 2014).

3.4 SHH alterations and inhibitors

The Hedgehog/Glioma-associated oncogene homolog (HH/GLI) pathway is crucial for various processes during embryonic development, such as cerebellar maturation and tissue regeneration. Sonic hedgehog (SHH), a key component of this pathway, is vital for normal cerebellar development (Carballo et al., 2018). However, its constitutive activation can lead to tumorigenesis. The Hedgehog pathway involves the transmembrane receptor PATCH (PTCH1), which, when bound, releases its inhibition of smoothened (SMO), a protein that activates downstream pathways by binding to the suppressor of fused (SUFU). This induces the nuclear translocation of activators Gli1 and Gli2, and a repressor Gli3, regulating the expression of targets like Cyclin D and MYC involved in cell survival, proliferation, and differentiation. Mutations in this pathway drive the initiation and progression of the SHH subtype of medulloblastoma and other solid tumors, leading to the development of targeted therapies against SHH, SMO, and Gli proteins (Siegel et al., 2025; Wireko et al., 2024).

SMO inhibitors, including vismodegib and sonidegib, have been extensively researched. Vismodegib, the most prevalent SMO inhibitor, has demonstrated limited efficacy in SHH-activated medulloblastoma, particularly in patients with PTCH1 mutations. In a phase I trial (PBTC-025, NCT00822458), vismodegib elicited a tumor response in 1 of 3 of

patients with recurrent or refractory SHH-MB, although this was short-lived (Gajjar et al., 2013). In two phase II trials evaluating the efficacy of vismodegib in recurrent medulloblastoma (PBTC-025B and PBTC-032), three adult patients with SHH-subgroup medulloblastoma (SHH-MB) exhibited sustained objective responses, defined as a complete or partial response maintained for at least eight weeks, while one pediatric patient also demonstrated a sustained response; progression-free survival (PFS) was significantly longer in patients with SHH-MB compared to those with non-SHH-MB, with genomic analysis revealing that favorable responses were associated with PTCH1 loss of heterozygosity, whereas non-responsiveness correlated with downstream mutations such as those in SUFU and GLI2, highlighting the importance of genomic profiling in predicting treatment efficacy (Robinson et al., 2015). However, resistance due to SMO mutations and downstream alterations, combined with significant adverse effects like irreversible growth plate fusion in young patients, limits its use (Robinson et al., 2017). To address these issues, alternative delivery methods, such as intraventricular administration, are being explored to minimize systemic toxicity (Kresbach et al., 2024).

Sonidegib, a second-generation SMO inhibitor, is under phase I/II trials for recurrent, highly metastatic SHH-amplified medulloblastoma. Preliminary findings show a 50 % overall response rate in children with activated SHH pathways, including four complete and one partial response (Kieran et al., 2017). Nonetheless, resistance persists, often stemming from SMO mutations and alternative pathway activations like PI3K/Akt/mTOR (Buonamici et al., 2010).

Other SMO inhibitors, including HhAntag and bis-amide compounds, have demonstrated efficacy against vismodegib-resistant SMO both in vitro and in vivo (Slika et al., 2024). Furthermore, the strategic combination of SMO inhibitors with other therapeutic agents, such as those targeting downstream effectors like GLI in SMO-mutated resistant medulloblastoma, may counteract resistance mechanisms (Slika et al., 2024).

3.5 Monoclonal antibodies and adoptive cellular immunotherapy

The immune system has long been a pivotal component in combating cancer, with immunotherapy experiencing substantial progress over recent decades across various tumor types, including pediatric malignancies (Capitini et al., 2010; Zhang & Zhang, 2020). However, the translation of these advances to pediatric central nervous system (CNS) tumors has been

constrained by their unique clinical, biological, and immunosuppressive attributes, which have historically impeded the application of immunotherapeutics. Pediatric CNS tumors are distinguished from their adult counterparts by unique molecular and immunological characteristics, defined by specific oncogenic drivers and epigenetic modifications that present potential targets for neoantigen-based vaccines (Grabovska et al., 2020).

Additionally, the tumor microenvironment (TME) in pediatric CNS tumors is a complex and dynamic entity that significantly influences tumorigenesis, progression, and therapeutic resistance. It is characterized by a high concentration of immunosuppressive cytokines such as transforming growth factor-beta (TGF-β) and interleukin-10 (IL-10), which augment regulatory T cell (Treg) function and suppress effector T cell activity, thereby establishing an immunosuppressive niche that impedes effective antitumor immune responses. The TME also comprises a heterogeneous population of immune cells, such as myeloid-derived suppressor cells (MDSCs) and M2-polarized macrophages, which contribute to immune evasion, whereas antigen-presenting cells such as dendritic cells and M1-polarized macrophages, which facilitate antitumor immunity, are often deficient (Yao et al., 2023). Moreover, the tumor stroma and aberrant vasculature play critical roles in modulating immune cell infiltration and spatial distribution, potentially inducing hypoxic conditions that favor immune escape mechanisms. The antigenic landscape of the TME is shaped by distinct genetic and epigenetic alterations, providing opportunities for targeted immunotherapy via neoantigen expression (Wu et al., 2024). Furthermore, the expression of immune checkpoint molecules, notably programmed death-ligand 1 (PD-L1), is a hallmark of these tumors, contributing to immune suppression and representing viable targets for therapeutic intervention (Cui et al., 2024). The metabolic profile of the TME, influenced by factors such as indoleamine 2,3-dioxygenase (IDO) activity, can further impair T cell functionality, while systemic immune tolerance poses significant barriers to the activation and trafficking of tumor-specific T cells (Munn & Mellor, 2013). An in-depth understanding of these components is imperative for the development of effective immunotherapeutic strategies tailored to the unique challenges posed by pediatric CNS malignancies.

Current immunotherapeutic modalities include oncolytic viral therapies, immune checkpoint inhibitors (ICIs), antibody-mediated therapies, cancer vaccines, adoptive cellular therapies. These approaches have been applied to pediatric brain tumors with varying degrees of success, as summarized below.

3.5.1 Oncolytic viral therapies

Oncolytic viral therapies are gaining significant traction as innovative cancer treatments, particularly at the intersection of biological and immunotherapies. These therapies leverage viruses that can naturally target cancer cells or are genetically modified to enhance their specificity for cancer. have the unique ability to transform 'cold' tumors into 'hot' ones by activating proinflammatory pathways within the tumor microenvironment. This capability is particularly beneficial for pediatric central nervous system (CNS) tumors, which often have low tumor mutational burdens and minimal immune cell infiltration.

Herpes Simplex Virus (HSV) Variants: Clinical trials have investigated two significant HSV-1 variants, HSV1716 and G207, for their potential in treating pediatric brain tumors. HSV1716, which is engineered to lack the neurovirulence factor ICP34.5 (Garcia-Moure et al., 2024), has shown in preclinical studies to effectively reduce the migration and invasion of tumor cell lines in pHGGs and DIPG models. Treatment with HSV1716 decreased the invasive growth patterns in an orthotopic xenograft DIPG model, suggesting its potential to inhibit the typical infiltrative growth of these tumors (Cockle et al., 2017). However, a phase I trial for pHGGs (NCT02031965) was ended prematurely after enrolling only two patients, and the findings have not been published. Another HSV-1 variant, G207, which includes additional genetic modifications (Garcia-Moure et al., 2024), was tested in a phase I trial (NCT02457845) with 12 pediatric patients suffering from recurrent supratentorial pHGGs, demonstrating that G207 was safe and well-tolerated. Notably, 11 out of 12 patients showed radiographic, neuropathological, or clinical responses, achieving a median overall survival of 12.2 months (Friedman et al., 2021). These promising results have led to the initiation of a phase II trial to further assess G207 in combination with radiotherapy (NCT04482933).

Adenovirus-Based Therapies: Delta-24-RGD (DNX-2401) is a modified adenovirus designed to selectively replicate in tumor cells, and it has shown promising results in preclinical pHGG and DIPG (Martínez-Vélez et al., 2019), ATRT and embryonal tumors human xenograft mouse models (Garcia-Moure et al., 2021). A phase I trial (NCT03178032) for newly diagnosed DIPG who received a single dose of DNX-2401 followed by standard radiotherapy, demonstrating safety and a median OS of 17.8 months, with three patients experienced long-term survival (Gállego Pérez-Larraya et al., 2022). Another adenovirus variant, ICOVIR17K (VCN-01), has been enhanced for tumor selectivity and viral spread,

showing efficacy in preclinical CNS-PNET models (Garcia-Moure et al., 2019). While clinical trials in pediatric brain tumors are yet to be conducted, its preclinical success underscores its potential.

Poliovirus Chimeras (PVSRIPO), a genetically modified poliovirus, was evaluated in a phase I trial (NCT03043391) for recurrent pHGGs. This trial focused primarily on safety, yet it provided some indications of efficacy, with one patient achieving long-term survival (Thompson et al., 2023). Similarly, A phase I (PNOC-005, NCT02962167) involving the attenuated Edmonston strain of the measles virus for recurrent medulloblastoma and ATRT demonstrated the safety of administering the virus directly into the tumor bed or subarachnoid space, as well as immunomodulation changes correlating with anti-viral tumor effect (Kline et al., 2024).

Other Viruses: Additional OVs, such as the Seneca Valley Virus, Myxoma Virus, Vaccinia Virus and Vesicular Stomatitis Virus have shown potential in preclinical CNS tumor models due to their ability to cross the blood-brain barrier and target tumor cells, offering further avenues for innovative treatments (Garcia-Moure et al., 2024).

3.5.2 Immune checkpoint inhibitors

Immune checkpoint inhibitors (ICIs) are humanized monoclonal antibodies designed to inhibit interactions involving PD-1, PD-L1, and CTLA-4 on tumor and immune cells, with the goal of reactivating antitumor immune responses and sustaining T cell activation. These agents have demonstrated significant efficacy in adult cancers, such as metastatic melanoma and non-small cell lung cancer (Melaiu et al., 2022). However, their application in pediatric CNS tumors is limited by factors including immune senescence, the blood-brain barrier, and low PD-L1 expression, except in cases with mismatch-repair deficiency (Das et al., 2022; Hwang et al., 2018).

A study by Bouffet et al. highlighted positive clinical and radiological outcomes in hypermutated, recurrent glioblastoma multiforme (GBM) treated with nivolumab (Bouffet et al., 2016). The NCT02992964 trial evaluated nivolumab in pediatric patients with relapsed or refractory cancers characterized by high tumor mutation burden (TMB) and/or mismatch repair deficiency (MMRD). Among the 11 patients studied, the best overall response rate was 50 %, with delayed immune responses contributing to prolonged survival, despite an initial objective response rate of 20 %. The median overall survival was 23.7 months, with a two-year survival rate of 50 %, and a median progression-free survival of 3.6 months.

The treatment was generally well-tolerated, although some patients experienced significant adverse effects, such as grade 3 pancreatitis (Das et al., 2023).

Several ongoing clinical trials are exploring alternative dosing schedules, neoadjuvant approaches, and combination therapies. For instance, the PNOC019 trial (NCT04323046) is examining the immunological and systemic alterations induced by administering nivolumab as a neoadjuvant treatment before surgical intervention. Additionally, the KEYNOTE-051 study (NCT02332668) is assessing pembrolizumab in children with advanced melanoma or PD-L1 positive advanced, relapsed, or refractory solid tumors or lymphoma. An interim analysis revealed an objective response rate of 5.9 %, with partial responses in eight patients, including one with a malignant rhabdoid tumor (Geoerger et al., 2020).

The NCT04416568 phase II trial is evaluating the combination of nivolumab and ipilimumab in pediatric and young adult patients with SMARCB1-deficient tumors. Although these tumors are typically mutationally quiet, isolated reports suggest minimal response to ICI therapy (Tran et al., 2023). Other studies include the use of nivolumab with metronomic chemotherapy (NCT03585465) and a pilot study targeting hypermutant cancers (NCT02992964). These trials aim to enhance ICI efficacy by considering factors like tumor mutational burden and PD-L1 expression (Hwang et al., 2022).

Despite the promise of ICIs in pediatric oncology, their efficacy remains variable, necessitating further research to optimize treatment strategies. This includes exploring combination therapies and stratifying patients based on molecular and immunological profiles. Overcoming challenges posed by the blood-brain barrier and developing innovative delivery methods, such as focused ultrasound or intratumoral administration, are critical areas for ongoing investigation. Additionally, understanding the role of tumor mutational burden and microsatellite instability (MSI) as biomarkers for ICI efficacy remains a promising avenue for improving treatment outcomes (Foster et al., 2023; Hwang et al., 2022; Zhang et al., 2024).

3.5.3 Cancer vaccines

Cancer vaccines work by harnessing the immune system to specifically target and destroy cancer cells through recognition of tumor-associated antigens (TAAs) or tumor-specific antigens (TSAs). These antigens are either overexpressed in cancer cells or arise from mutations unique to these cells, allowing the immune system to distinguish them from normal tissues

(Lin et al., 2022). There are several types of cancer vaccines, including dendritic cell (DC) vaccines, peptide-based vaccines, and mRNA vaccines. DC vaccines involve loading dendritic cells with TAAs or TSAs ex vivo, which are then reintroduced into the patient to activate T cells, particularly cytotoxic T lymphocytes (CTLs), that target tumor cells. Peptide-based vaccines use short sequences of amino acids that correspond to specific antigens, which are presented by antigen-presenting cells to stimulate an immune response. mRNA vaccines deliver genetic instructions to cells to produce specific antigens, mimicking a natural infection without the risk of live pathogens. This process activates T cells, leading to the destruction of tumor cells and the formation of memory T cells for long-term immunity (Makker et al., 2023). Cancer vaccines aim to overcome tumor immune evasion mechanisms and provide a specific, durable immune response with potentially fewer side effects than traditional therapies.

Four studies have highlighted the use of autologous dendritic cells (DCs) pulsed with tumor lysate or RNA obtained from surgical procedures in pediatric brain tumors (Ardon et al., 2010; Benitez-Ribas et al., 2018; Caruso et al., 2004; Lasky et al., 2013). The combined results demonstrated that the vaccines were generally well-tolerated, with no significant adverse events reported. However, due to the small sample sizes and the primary emphasis on safety, these studies were unable to provide conclusive evidence on the treatment's efficacy. In the largest cohort of the HGG-IMMUNO trial, no patients with medulloblastoma (MB) or primitive neuro-ectodermal tumor (PNET) survived, but there were subgroups showing favorable responses, with seven high-grade glioma (HGG) patients and two atypical teratoid rhabdoid tumor patients surviving up to seven years of follow-up (Ardon et al., 2010). Currently, vaccine trials utilizing dendritic cells are ongoing for medulloblastoma and HGG (Re-MATCH trial; NCT01326104), HGG (ACTION trial; NCT03334305), as well as HGG and diffuse intrinsic pontine glioma (DIPG) (ADDICT-pedGLIO, NCT04911621).

Peptide-based vaccines are designed to stimulate immune responses by presenting synthetic peptides that mimic specific tumor antigens. These vaccines are often enhanced with adjuvants such as polyinosinic-polycytidylic acid stabilized by lysine and carboxymethylcellulose (poly-ICLC) to boost immune activation (Foster et al., 2019). In early trials involving pediatric high-grade gliomas, vaccines targeting tumor-associated antigens like EphA2, IL13Rα2, and survivin have yielded promising results. Among the participants, 24 out of 26 experienced disease stabilization or partial

responses, with improved survival particularly noted in those exhibiting pseudoprogression. Another study with patients who had relapsed high-grade gliomas showed specific immune activation in 9 out of 10 participants, although clinical benefits were limited, possibly due to the tumor's immunosuppressive environment (Pollack et al., 2016; Pollack et al., 2014). PNOC conducted a trial with an H3.3K27M-specific peptide vaccine combined with poly-ICLC for HLA-A2-restricted patients with diffuse midline gliomas (PNOC007, NCT02960230). Although overall survival was similar to historical controls, a subset of patients with expanded vaccine-induced cytotoxic T cells demonstrated a median survival of over 16 months. This study underscored the potential advantages of combining the vaccine with anti-PD-1 therapy, as peripheral PD-1+ CD8+ T cells showed signs of exhaustion after vaccination (Mueller, Taitt et al., 2022). Current trials include CONNECT1906 (NCT05096481), which is evaluating a highly immunogenic CMV-directed peptide vaccine (PEP-CMV) in pediatric brain tumors. Additionally, a phase I trial is assessing a peptide vaccine with an immunoadjuvant for recurrent ependymoma (NCT01795313), and another trial is testing SurVaxM, which targets survivin, in various pediatric brain tumors (NCT04978727).

RNA-based vaccines, which have garnered considerable attention following their success during the COVID-19 pandemic, present significant potential across diverse patient haplotypes. Unlike some peptide vaccines that are constrained by HLA restrictions, mRNA vaccines can potentially offer broader applicability across different patient populations. This adaptability is being further investigated in trials like PNOC020 (NCT04573140), which aim to expand the use of mRNA vaccines in pediatric high-grade gliomas (Foster et al., 2023).

3.5.4 Monoclonal antibodies

Monoclonal antibodies are designed to bind specific tumor antigens, primarily modulating immune responses. The success of monoclonal antibodies targeting the HER-2 tyrosine kinase receptor in breast cancer treatment underscores their potential applicability in other malignancies, such as CNS cancer stem cells and medulloblastoma, where HER-2 is also overexpressed. However, the effectiveness of these therapies is often hindered by the blood-brain barrier (BBB) (Hingorani et al., 2022; Norris et al., 2022).

To address this limitation, bi-specific T-cell engagers (BiTEs) have been developed. BiTEs are engineered by fusing two single-chain variable

fragments (scFvs)—one targeting the CD3 receptor on T cells and the other binding to a tumor-specific antigen. This design facilitates the recruitment of T cells to tumor cells, thereby enhancing immune responses (Huehls et al., 2015). EGFRvIII-specific BiTEs, for instance, have demonstrated potent immune activation in adult CNS tumors and are currently under investigation for pediatric brain cancers, although they have not yet advanced to clinical trials (An et al., 2018; Hwang et al., 2022).

Monoclonal antibodies are also being leveraged for the delivery of radioimmunotherapy and immunotoxins. For example, antibodies targeting B7-H3 and EGFR have been conjugated to isotopes or toxins, such as Pseudomonas exotoxin, to target tumor-specific antigens (Heiss et al., 2019; Souweidane et al., 2018). This approach has shown promise in pediatric brainstem gliomas, although it requires precise catheter placement. In contrast, treatment of leptomeningeal metastases is more feasibly achieved using intraventricular reservoirs, as demonstrated by successful dispersion of 131I-omburtamab (Basu et al., 2022; Prasad et al., 2024; Tringale et al., 2023). Ongoing studies aim to further evaluate and optimize these strategies for improved clinical outcomes (NCT05064306, NCT04743661).

3.5.5 CAR T cell therapy

Chimeric Antigen Receptor (CAR) T-cell therapy represents a significant advancement in adoptive cell therapy for pediatric central nervous system (CNS) tumors, which typically exhibit low mutational burdens. CAR T-cells are genetically modified to express receptors that specifically target tumor-associated antigens, thereby enhancing their cytotoxic efficacy. The modularity of CAR constructs permits rapid adaptation to various tumor antigens, and the incorporation of co-stimulatory domains in second-generation and subsequent CAR designs has markedly enhanced their therapeutic effectiveness (Hwang et al., 2022; Ronsley, Bertrand et al., 2024).

Despite limited clinical success to date in pediatric CNS tumors, recent studies have yielded promising outcomes. For instance, the application of GD2-specific CAR T-cells in DMG has shown impressive tumor clearance in preclinical models (Monje et al., 2025; Mount et al., 2018). Initial phase studies have confirmed the safety and feasibility of intracerebroventricular infusions, which can improve CAR T-cell distribution and efficacy, even allowing for multiyear repeated dosing (Majzner et al., 2022; Vitanza et al., 2021; Vitanza et al., 2025; Vitanza et al., 2023). Current trials, including those targeting B7-H3 (NCT04185038), HER2 (NCT03500991), and GD2 (NCT04196413), are actively investigating the efficacy of these therapies in pediatric populations.

Moreover, the development of multi-antigen targeting strategies is underway to address challenges such as tumor heterogeneity and antigen escape. Trials like BrainChild-04 (NCT05768880) are designed to assess the effectiveness of these innovative approaches. Although initial results are promising, showing evidence of immune activation and tumor response, the field remains in its early stages (Ronsley, Seidel et al., 2024). Continued research is essential to optimize delivery methods, enhance patient outcomes, and broaden the clinical applications of CAR T-cell therapies in pediatric neuro-oncology.

Although these therapies are still in their nascent stages, they underscore the critical need for ongoing research to refine delivery methods and improve patient outcomes. Alongside these advancements, innovative interventional treatments are also gaining momentum, including laser interstitial thermal therapy (LITT), convection-enhanced delivery (CED), and sonodynamic therapy. The following section of the chapter will explore these therapies in greater detail.

4. Laser interstitial thermal therapy for pediatric brain tumors

Laser interstitial thermal therapy (LITT) is a minimally invasive surgical technique for the ablation of soft tissue. LITT is novel as a neurosurgical technique owing to how it leverages the principles of laser physics and tissue thermodynamics to achieve targeted tissue ablation guided by advanced MRI temperature monitoring technology (Chen et al., 2021). There are multiple platforms for LITT therapy that are FDA cleared to necrotize or coagulate soft tissue in organs of the human body including the brain. The general technique is invariably referred to by similar names including LITT, MRI guided LITT (MRgLITT), and stereotactic laser ablation (SLA); all of which refer to the same general technique and referred to as LITT for the remainder of this text. LITT as a neurosurgical technique has seen a rise in clinical utilization over the recent decades (Patel & Kim, 2020). Its use among neurosurgeons supported by clinical research reporting its safety and efficacy led to the creation of two new Category Level 1 CPT® codes for LITT that went into effect in 2022. One code (61736) to be used for a simple lesion treated with a single trajectory, and the second code (61737) for complex lesion(s) treated with multiple trajectories. The need for a new code reflects its relatively novel nature

among our neurosurgical armamentarium in that it is an ablative technique that relies on the stereotactic delivery of focused light energy. Ablative techniques in general are not new in neurosurgery. Other technologies used for ablation include electrical, chemical, microwave, high intensity focused ultrasound, and have been employed for functional and pain disorders with well documented efficacy (Franzini et al., 2019). However, these pre-existing ablation technologies are sufficiently different from LITT as a thermal ablation monitored by real-time MRI thermometry. Despite novel ablation and monitoring, the stereotactic aspect of the technique is not foreign. Because of this familiarity, adoption of LITT as a surgical technique can be readily adopted by most neurosurgeons.

The typical steps of the procedure begin with stereotactic placement of a fiber-optic catheter into the target tissue. Such stereotaxy is a familiar to most neurosurgeons in various forms. LITT is not limited to a specific stereotactic approach and therefore can be accomplished with frame based, frameless, robot assisted, or other technique most familiar to the surgeon or most appropriate for the specific pathology without impacting the fundamental laser ablation process. The implanted laser fiber is then used to heat the target tissue by delivery of laser light energy at the tip of the catheter. This laser energy generates heat and induces thermal damage and coagulative necrosis in a predictable volume around the site of laser application (Remick et al., 2020). One practical aspect of a thermal ablation technique is the need for active cooling of the laser fiber and sheath through which it is delivered. Cooling technique varies depending on which LITT platform is being used and includes circulation of saline for Medtronic Visualase and circulation of CO_2 for Monteris NeuroBlate (Awad & Kaiser, 2022). The ClearPoint Prism system does not require a cooling system (Wilson et al., 2024). In addition, tissue heating is further controlled by modulating the magnitude of laser energy being emitted. The precision of thermal ablation is made possible by real-time magnetic resonance imaging (MRI) guided thermometry, which measures the change in temperature in the surrounding tissue volume and is used to ensure the accurate delineation of treatment margins (Zhu et al., 2017). Many techniques for MRI thermometry exist, but the most commonly utilized by current LITT platforms relies on a shift measured from the proton resonance frequency (PRF) signal to determine temperature change during ablation (Poorter et al., 1995; Yuan et al., 2012). By obtaining a baseline measurement of the PRF signal prior to ablation at a known body temperature, the subsequent change in temperature associated with laser energy

deposition can be calculated by from the measured a PRF shift (PRFS) from baseline and an absolute temperature change inferred. The MRI thermometry is calculated per voxel and transformed into a color scale image for display in real-time as an overlay on the typical anatomic images (e.g., T1 or T2 weighted image) (Blackwell et al., 2022). The thermometry data spatially aligned to anatomic imaging allows the treating neurosurgeon to guide the extent of LITT ablation (Keefe et al., 2024). The combination of well controlled thermodynamics via modulation of the laser power with the ability for real-time temperature monitoring allows for precise control of the ablation being performed.

The term LASER stands for Light Amplification by Stimulated Emission of Radiation, and it involves the generation of a coherent beam of light. Coherence of laser light indicates all photons have the same phase and wavelength allowing the light to be highly focused as a narrow beam and delivered over a long distance across various media. These properties permit light energy to be emitted at high intensity with high specificity. This high-intensity light is produced by exciting electrons in a gain medium (Geavlete et al., 2016). In LITT, YAG (yttrium-aluminum-garnet) and diode lasers are commonly employed due to their efficient light emission in the near-infrared spectrum (Salem et al., 2019). The Monteris NeuroBlate system uses a Neodymium-doped YAG laser to produce a 1064 nm wavelength light, which penetrates biological tissues effectively. The Medtronic Visualase system uses tuned diode lasers to emit light in a range of wavelengths between 800 nm and 980 nm (Salem et al., 2019). These specific wavelengths are chosen because to maximize tissue penetration and absorption characteristics for effective thermal therapy.

The transformation of light energy into heat in LITT is facilitated by the absorption properties of biological tissues. As laser light is absorbed by chromophores within the tissue, including water and hemoglobin, the energy is converted into heat through a process known as the photothermal effect. This heat elevates the temperature of the targeted tissue to induce thermal damage. The extent of tissue damage is carefully controlled by manipulating both the intensity of the laser energy and the exposure duration (de Brito et al., 2022). Predicting cell death induced by LITT is dependent on the thermodynamics of heat transfer within the tissue and the cellular response to elevated temperatures (Despa et al., 2005). The combination of heat magnitude and exposure time, which is the area under the curve of the time-temperature curve, is used to predict the extent of the thermal damage and subsequent cell death. At temperatures ranging from

50 °C to 100 °C, proteins denature, cellular membranes rupture, and irreversible coagulative necrosis occurs. A thermal damage estimate (TDE) can be quantitatively predicted using the Arrhenius rate equation, which relates temperature and exposure duration to the probability of cell death (Brace, 2011; Dewhirst et al., 2003). Calculating TDEs for each voxel allows additional generated images to be overlaid on anatomic images as a binary volume predicting tissue death. Maximizing overlap of the TDE for cell death with the tumor volume is the goal of the neurosurgeon for treating pediatric brain tumors. To further reduce the risk of damage to neighboring critical structures, preoperative adjuncts such as diffusion tensor imaging (DTI) or functional magnetic resonance imaging (fMRI) can be employed (Fig. 3). Consequently, LITT is particularly advantageous for treating tumors located in challenging, deep-seated regions of the brain where traditional surgical approaches pose a high risk of morbidity (Fig. 4).

MRI-guided LITT has shown promising results in epilepsy surgery, particularly for patients with well-defined, localized epileptogenic zones that are refractory to pharmacological treatment. For instance, in cases of mesial temporal lobe epilepsy, LITT can effectively target and ablate the seizure focus while preserving critical structures such as the hippocampus and surrounding medial temporal lobe, which are crucial for cognitive functions (Willie et al., 2014). LITT saw early and more widespread

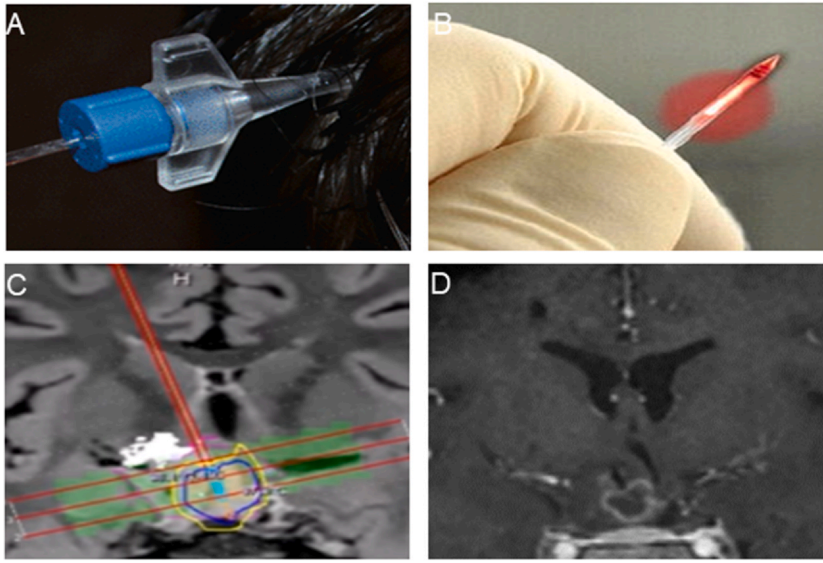

Fig. 3 Stereotactic laser ablation procedure and monitoring.

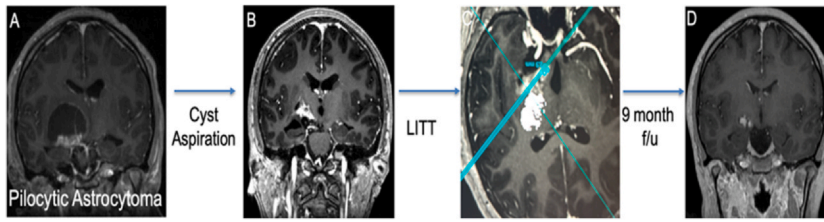

Fig. 4 Longitudinal imaging of thalamopeduncular pilocytic astrocytoma treatment with stereotactic laser interstitial thermal therapy (LITT) in a 9-year-old patient.

adoption in epilepsy than it has in neuro-oncology. Uncertainty in how thermal ablation may affect tumor tissue differently raised concerns despite the abundance of evidence in how thermal ablation causes cell death in normal tissues.

However, the minimally invasive, safe, cost-effective, and versatile nature of laser interstitial thermal therapy (LITT) (Chen et al., 2024; Dhawan et al., 2020; Gurses et al., 2024), has driven its increasing adoption in adults for the treatment of various oncologic pathologies, including primary and metastatic brain tumors, and radiation necrosis (Ahluwalia et al., 2019; Kamath et al., 2017; Kim et al., 2020; Shah et al., 2020; Shao et al., 2020). In both newly diagnosed and recurrent glioblastoma (GBM), LITT has demonstrated outcomes comparable to historical open surgical studies (de Groot et al., 2022). Furthermore, evidence suggests that LITT can transiently increase blood-brain and blood-tumor barrier permeability for up to 30 days (Salehi et al., 2020), thereby creating a therapeutic window to deliver agents that otherwise fail to penetrate the brain. For instance, in a phase II trial, Butt et al. reported that combining LITT with low-dose doxorubicin in patients with recurrent GBM improved overall survival (OS) compared to historical controls treated with bevacizumab (Butt et al., 2021).

In pediatric cases, though evidence remains limited, LITT has shown promising results. The first application of LITT in pediatric brain tumors was reported in 2011 for the treatment of a supratentorial primitive neuroectodermal tumor (Jethwa et al., 2011). Subsequent studies have expanded its use to various pediatric tumor types, including LGGs, HGGs, ependymomas, medulloblastomas, and others (Boop et al., 2023; Feroze et al., 2020; Pehlivan et al., 2021; Spacca et al., 2023; Zeller et al., 2021). In the largest multi-center retrospective study with total 86 patients (10 high grade, 76 low grade) who underwent LITT, 83.1 % of low-grade and

57.1 % of high-grade tumors showed a decrease in volume at last follow-up (Arocho-Quinones et al., 2023). However, LITT has yet to be systematically or prospectively studied in direct, head-to-head comparisons with surgical resection for tumor indications. Further research is necessary to establish non-inferiority between open resection and LITT. The most common complications of LITT include temporary or permanent neurologic deficits (8.82–35.5 % and 2.17–7.14 %, respectively), cerebral edema, seizures, and intracranial hemorrhage (0.98–14.2 %) (Holste & Orringer, 2020). Hemorrhage is thought to result from passage of the fiber or stereotactic biopsy. Special considerations are required when using LITT in very young patients (<2 years old), as the immaturity of the skull may prevent the placement of fixation pins for stereotaxis or cranial bolts for laser fixation. Nonetheless, technical workarounds for these challenges have been described in the literature (Hooten et al., 2019; Lee et al., 2021).

5. Convection-enhanced delivery for pediatric brain tumors

Convection-Enhanced Delivery (CED) was first described in the early 1990s by Edward Oldfield and colleagues at the National Institutes of Health (Bobo et al., 1994). Developed to overcome the challenges posed by the blood-brain barrier (BBB), CED involves stereotactic placement of one or more catheters directly into the targeted brain region. These catheters are connected to an external infusion pump, which creates a pressure gradient to drive the therapeutic infusate into the extracellular space. Unlike diffusion-based methods, which typically achieve tissue penetration of only a few millimeters, CED can facilitate drug distribution up to several centimeters from the infusion site. By bypassing the BBB, CED enables higher local drug concentrations while minimizing systemic exposure and associated side effects. Moreover, it accommodates a broad range of therapeutic agents, including chemotherapeutics, imaging tracers, proteins, viral vectors, liposomes, and nanoparticles (Mehta et al., 2017).

A key determinant of CED efficacy is the volume of distribution (Vd). Insufficient Vd may result in incomplete tumor coverage, compromising therapeutic outcomes. To address this, researchers have explored co-infusion with imaging agents such as gadolinium, enabling real-time visualization of Vd via magnetic resonance imaging (MRI). However, differences in molecular weight and lipophilicity between imaging agents

Table 3 Overview of clinical trials involving convection-enhanced delivery (CED) in pediatric brain tumors.

Study ID	Study phase	Treatment/agent	Patient population	Findings	Current status
NCT03086616 (PNOC009)	Phase 1	Irinotecan Liposome Injection	DIPG	Repurposed using CED of liposomal form to increase delivery and reduce toxicity in DIPG.	Completed
NCT03566199 (PNOC015)	Phase 1	MTX110 (Panobinostat)	DIPG	7 Patients received MTX110 with gadoteridol across 7 dose levels. A total of 48 CED infusions were performed. 3 patients experienced dose-limiting toxicities; 4 grade 3 treatment-related adverse events were noted. Median OS: 26.1 months. Tumor coverage ranged from 35.6 % to 81.0 %. Increased infusions negatively impacted QoL.	Completed
NCT01502917	Phase 1	I124-Omburtamab	DIPG	Maximum tolerated activity: 6 mCi (222 MBq). Mean total absorbed dose in lesion: 35.2 ± 18 cGy/MBq. High lesion-to-whole-body absorbed dose ratio: 816. 11 patients with grade 3 CNS toxicities, no grade 4 or 5. Median survival: 15.29 months. Survival rates: 65.4 % at 1 year, 18.4 % at 2 years, 11.7 % at 3 years.	Completed

(continued)

Table 3 Overview of clinical trials involving convection-enhanced delivery (CED) in pediatric brain tumors. (*cont'd*)

Study ID	Study phase	Treatment/agent	Patient population	Findings	Current status
NCT03178032	Phase 1	DNX−2401, Oncolytic Viral Therapy	DIPG	12 Patients received DNX−2401, followed by radiotherapy. Adverse events included headache, nausea, vomiting, fatigue, hemiparesis, and tetraparesis. Tumor size reduction was observed in 9 patients, with a partial response in 3 and stable disease in 8. Median survival: 17.8 months. T-cell activity changes were noted.	Completed
NCT01906385	Phase 1/2	186RNL	Recurrent Ependymoma or HGG (Ages 6−21)	Phase 1 dose-finding study followed by expansion cohorts. Part 1 will enroll up to 24 subjects to determine the maximum feasible dose (MFD) of 186RNL administered by CED. Tumor size and concentration of infusate will be escalated in each cohort (A-D). Part 2 will evaluate 186RNL in 2 expansion cohorts: Cohort 2 A for recurrent ependymoma and Cohort 2B for recurrent HGG. Primary endpoints: ORR for Cohort 2 A and progression free survival for Cohort 2B.	Ongoing

and therapeutic compounds can limit predictive accuracy, warranting further investigation. More recently, positron emission tomography (PET) with radiolabeled therapeutics has emerged as a more precise strategy for assessing Vd and optimizing infusion parameters (D'Amico et al., 2021; Kreatsoulas et al., 2024; Stine & Munson, 2019).

CED has shown particular promise in preclinical models of pediatric brain tumors, especially diffuse midline glioma (DMG), due to its capacity to bypass the intact BBB and facilitate targeted drug delivery to the brainstem (Lin et al., 2019; Singleton et al., 2017; Tsvankin et al., 2020). Studies have reported improved survival with CED-delivered therapies such as dasatinib (Tsvankin et al., 2020) and Panobinostat (Hennika et al., 2017) in H3.3K27M DMG models. Encouraged by these findings, several clinical trials are now assessing the safety and feasibility of intratumoral CED in children. Early data suggest a survival advantage compared to historical controls (Mueller et al., 2023; Souweidane et al., 2025; Souweidane et al., 2021). Table 3 presents a summary of CED clinical trials and findings in children with brain tumors.

Despite its advantages, CED is limited by the need for surgical intervention and hospitalization for each administration. Although repeat CED sessions are feasible and well-tolerated, long-term treatment remains challenging. To address this, recent advances have demonstrated the feasibility of chronic CED using an implantable, abdominally placed pump capable of delivering multiple treatment sessions over several weeks (Spinazzi et al., 2022). This approach may enable sustained therapy through subcutaneous refilling of the drug reservoir.

6. Focused ultrasound (FUS) and sonodynamic therapy in pediatric brain tumors

Focused ultrasound (FUS) is a non-invasive therapeutic modality that utilizes high-frequency sound waves to precisely target tissues within the body. Its mechanisms and applications are diverse, ranging from thermal ablation to mechanical disruption. FUS operates by propagating ultrasound waves that create alternating cycles of compression and rarefaction within tissues. When these waves converge at a focal point, they produce a localized increase in energy density, which can be modulated to achieve specific therapeutic effects. Integration with real-time MRI guidance enhances the precision and safety of FUS procedures by enabling accurate targeting and continuous monitoring

(Rao et al., 2023). Depending on the frequency and intensity of the ultrasound waves, FUS can induce either thermal or non-thermal biological effects. High-intensity focused ultrasound (HIFU), typically operating at frequencies above 650 kHz, generates thermal energy sufficient to ablate targeted tissue, including both normal and neoplastic structures. In contrast, low-intensity focused ultrasound (LIFU), operating at lower frequencies (e.g., ~220 kHz), produces mechanical effects such as cavitation, which can transiently disrupt the BBB. This allows for enhanced delivery of therapeutic agents to otherwise inaccessible regions of the brain (Chesney et al., 2024; Meng et al., 2022). The clinical application of LIFU for BBB disruption was first demonstrated in patients with Alzheimer's disease in 2018, showing successful and reversible BBB opening while meeting primary safety endpoints (Lipsman et al., 2018). More recently, a clinical trial demonstrated that LIFU, when combined with aducanumab, an anti-amyloid-β antibody, resulted in reduction of amyloid-β plaque burden, indicating therapeutic efficacy in neurodegenerative disease (Rezai et al., 2024). In pediatric neuro-oncology, LIFU is being actively investigated as a method to enhance drug delivery to malignant brain tumors. One ongoing clinical trial (NCT05630209) is evaluating the safety and efficacy of LIFU-mediated BBB disruption to facilitate doxorubicin delivery in patients with diffuse midline glioma (DMG) (Chesney et al., 2024).

Sonodynamic therapy (SDT) leverages the ability of low-intensity focused ultrasound (LIFU) to induce cavitation-mediated chemical reactions for therapeutic benefit. Traditionally, photosensitizing agents—compounds that generate reactive oxygen species (ROS) upon light activation—have been studied extensively for their cytotoxic effects in tumors. SDT builds on this principle by employing the fact that some of these agents can also be activated by ultrasound, specifically LIFU, offering the key advantage of non-invasive delivery to deep brain targets (Bader et al., 2025). A notable strategy under clinical investigation (NCT05123534) for pediatric DMG patients involves the combination of LIFU with aminolevulinic acid hydrochloride (ALA HCl), a prodrug that is metabolized into protoporphyrin IX (PpIX)—a photosensitizer preferentially accumulated by tumor cells. In this approach, LIFU is delivered at a frequency insufficient to cause direct thermal ablation but adequate to activate PpIX and trigger ROS generation, thereby inducing tumor cell necrosis and apoptosis through non-thermal mechanisms (Chesney et al., 2024). This technique holds promise as a novel, targeted therapeutic modality for deep-seated brain tumors, including those in pediatric populations. Table 4 provides a summary of ongoing clinical trials using FUS in pediatric patients with brain tumors.

Table 4 Overview of clinical trials involving focused ultrasound (FUS) in pediatric brain tumors.

Trial identifier	Study focus	Patient population	Methodology	Primary objectives
NCT03028246	HIFU for tumor ablation	Pediatric patients with benign centrally located tumors	Utilizes Insightec ExAblate 4000 Type 1.0 system	Assess safety, adverse events, and tumor volume reduction
NCT05123534	LIFU and SDT for DIPG	Pediatric patients with DIPG	Combines SONALA-001 (ALA HCl) with ExAblate 4000 Type 2.0	Evaluate safety, tolerability, and preliminary efficacy
NCT05630209	LIFU for BBB disruption	Pediatric DIPG patients undergoing chemotherapy	Uses ExAblate 4000 Type 2.0 to enhance doxorubicin delivery	Monitor safety, assess BBB disruption efficacy, and tumor response

7. Conclusion

The advent of innovative treatments such as LITT, FUS, sonographic therapy, and targeted therapies, marks a significant advancement in the management of pediatric brain tumors. These techniques offer promising alternatives to traditional surgery and radiation by providing precise, minimally invasive options that minimize damage to healthy tissues. LITT employs laser-induced heat for targeted ablation, FUS utilizes sound waves for both thermal and non-thermal therapeutic effects, and sonographic therapy combines ultrasound with sensitizing agents to selectively target tumor cells. Targeted therapy focuses on specific molecular markers within tumor cells, allowing for highly specific treatment that disrupts cancer cell growth pathways. Combinatorial therapies, which integrate multiple treatment modalities, can enhance efficacy by attacking tumors from different angles and reducing the likelihood of resistance. Together, these therapies hold the potential to enhance treatment outcomes and improve quality of life for children facing the challenges of brain tumors. As research continues, these modalities may become essential components of pediatric neuro-oncology, offering new avenues of effective treatment strategies.

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