Approved Targeted Treatments for Pediatric Brain Tumors

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OVERVIEW

Advances in molecular and genomic techniques have significantly improved our understanding of pediatric brain tumors and enabled the development of targeted therapies directed at specific genetic alterations. The emergence of these therapies is reshaping the management of pediatric brain tumors, offering the potential for more effective and personalized treatment strategies, with reduced toxicity and improved clinical outcomes. This paradigm shift in pediatric neuro-oncology is still at an early stage but is expected to lead to substantial changes in clinical practice in the coming years. Clinical research has already resulted in the approval of several targeted agents, particularly for tumors driven by alterations in the MAP kinase pathway. These successes underscore the importance of integrating molecular diagnostics into routine care. This review summarizes the clinical development and regulatory approval of targeted therapies in pediatric brain tumors. It also addresses key challenges in the design and conduct of clinical trials in this unique population, including small patient numbers. In addition, several critical questions remain unresolved, such as the optimal duration of therapy, the durability of responses, mechanisms of resistance, and the long-term effects of these treatments in children. Finally, this review discusses issues related to access and equity, particularly the availability of these often-costly therapies in low- and middle-income countries, which remains a significant barrier to their global implementation.

Pediatric brain tumors are the leading causes of cancer-related morbidity and mortality in high-income countries. Collectively, they represent a diverse group of neoplasms that differ significantly from their adult counterparts in terms of biology, clinical behavior, and response to therapy.

The management of pediatric brain tumors has evolved over the past century, beginning with the introduction of surgery approximately 100 years ago. Radiation therapy emerged in the 1950s as a treatment for malignant brain tumors, followed by the introduction of chemotherapy in the late 1970s. Although these approaches have improved survival rates for certain tumor types, current treatment, in particular radiotherapy, are often associated with significant long-term toxicities, including neurocognitive impairment, endocrine dysfunction, and secondary malignancies. These adverse effects are particularly debilitating in infants and young children.[1] Consequently, there has been a growing emphasis on developing more precise and less toxic therapeutic strategies, leading to the emergence of targeted therapies as a promising paradigm in pediatric neuro-oncology.

In 2000, the first successful report of imatinib in the treatment of chronic myeloid leukemia[2] led to the development of multiple clinical trials based on the hypothesis that targeting specific genetic alterations could control tumor progression. However, most early clinical trials of targeted therapies failed to demonstrate clear clinical benefit.[3]

Targeted therapies are designed to specifically inhibit genetic alterations involved in tumor growth and progression. The development of this new generation of treatments has been enabled by advances in genomic and molecular profiling, which have facilitated the identification of key mutations, signaling pathways, and/or epigenetic changes unique to pediatric brain tumors. The aim of this chapter is to provide a comprehensive review of current knowledge on recently approved targeted therapies in pediatric brain tumors and to evaluate their impact on clinical management. The role of immunotherapies (immune checkpoint inhibitors, vaccines, and CAR T cell) will not be addressed.

TARGETING mTOR IN PATIENTS WITH SUBEPENDYMAL GIANT CELL ASTROCYTOMA

Mammalian target of rapamycin (mTOR) was first identified in 1993 by Kunz et al.[4] Approximately 10 years later, it was discovered that the protein products (hamartin and tuberin) of the genes responsible for tuberous sclerosis (*TSC1* and *TSC2*) form a dimer whose primary function is to inhibit mTOR.[5] Mutations in these genes result in hyperactivation of mTOR, which is responsible for the tumors and hamartomas typical of tuberous sclerosis (TS).

PRACTICAL APPLICATIONS

- Targeted therapies have demonstrated efficacy in pediatric glial tumors, particularly in tumors driven by alterations in the MAP kinase pathway.
- Historically, everolimus has been the first approved targeted drug to treat subependymal giant cell astrocytomas associated with tuberous sclerosis complex.
- The combination of dabrafenib and trametinib has been approved for the first-line systemic treatment of BRAF V600–mutated pediatric low-grade glioma, while tovorafenib is currently approved for the management of recurrent/refractory pediatric low-grade gliomas harboring a *BRAF* fusion or rearrangement or a BRAF V600 mutation.
- The NTRK inhibitors larotrectinib and entrectinib have been approved for the management of patients with solid tumors harboring a *NTRK* gene fusion, and vorasidenib for pediatric patients age 12 years and older with IDH1/2-mutated low-grade glioma.
- Although these approvals represent a paradigm shift in the management of these conditions, the introduction of targeted therapies also brings new challenges and uncertainties, including optimal treatment duration, mechanisms of resistance, and long-term effects.

Based on this knowledge, and the availability of the mTOR inhibitors rapamycin, and later everolimus, these agents were first used to treat the manifestations of TS in 2003. Case reports demonstrated reduction in size of both renal angiomyolipomas and subependymal giant cell astrocytomas associated with TS (Fig 1).[6,7] An open-label, single-center study (CRAD2485, NCT00411619) of everolimus to treat giant cell astrocytomas was conducted. In this study, all treated patients experienced a reduction in size of their giant cell astrocytoma. Adverse effects were typical of those seen with mTOR inhibitors use for other indications, for example, organ transplantation. The most common adverse effects were mucositis and upper respiratory infections. Based on these data, the US Food and Drug Administration (FDA) approved everolimus for the treatment of giant cell astrocytoma through sub-part H based on this single study.[8] These results were later confirmed in multicenter, double-blind, placebo-controlled studies: EXIST 1 for astrocytomas (ClinicalTrials.gov identifier: NCT00789828), EXIST 2 for angiomyolipomas (ClinicalTrials.gov identifier: NCT00790400), and EXIST 3 for epilepsy (ClinicalTrials.gov identifier: NCT01713946).

Currently, mTOR inhibitors are approved for the treatment of multiple manifestations of TS: giant cell astrocytomas, renal angiomyolipomas, epilepsy, lymphangioleiomyomatosis (destructive cystic remodeling of the lung resulting in pulmonary failure), and cutaneous angiofibromas. Other uses include treatment of developmental disabilities and autism, as well as reduction of hemodynamically significant fetal cardiac rhabdomyomas. Fetal rhabdomyomas are treated by administering rapamycin to the mother primarily in the late second and third trimesters. This has been undertaken in numerous patients without disruption of fetal growth or significant maternal adverse effects.[9,10]

Unlike preexisting therapies such as resective surgery or antiseizure medications, regardless of the specific indication, when an mTOR inhibitor is initiated in a patient with TS, it can be expected to provide benefit for all of a patient's disease manifestations. As such, mTOR inhibitors truly represent a disease-modifying therapy for a genetic disease for which symptomatic treatment was previously the only option.

THE TARGETING OF BRAF ALTERATIONS IN PEDIATRIC GLIOMAS

Most pediatric low-grade gliomas (pLGGs) are driven by one single genetic alteration involving the MAP kinase pathway. The most common alteration is the BRAF-KIIA1549 fusion, while the BRAF V600 mutation is less frequent. These alterations lead to activation of the downstream MEK/ERK, which in turn leads to cell proliferation.[11] Targeting pLGGs with MEK, BRAF, and pan-RAF inhibitors has been one of the most significant advances in pediatric neuro-oncology over the past two decades. These are oral medications with a clear benefit in terms of quality of daily life compared with standard chemotherapy. Clinical trials have demonstrated the efficacy and safety of these agents. Various drugs—including selumetinib, cobimetinib, vemurafenib, binimetinib, mirdametinib, dabrafenib, and trametinib—have been evaluated in clinical studies.[12-18]

A randomized trial (ClinicalTrials.gov identifier: NCT02684058) compared the combination of dabrafenib (D) and trametinib (T) with standard chemotherapy (vincristine and carboplatin) in pediatric patients with BRAF V600–mutated pLGG who were scheduled to received first-line therapy.[19] The trial enrolled 110 patients (73 in the D + T arm and 37 in the chemotherapy arm). The median follow-up at the time of the publication was 18.9 months. The trial showed a significant difference in the overall response rate (ORR) between D + T (47%) versus chemotherapy (11%; $P < .001$). The median progression-free survival (PFS) was 20.1 months for D + T versus 7.4 months for chemotherapy (hazard ratio, 0.31), and among patients with tumors involving the optic pathway, visual acuity improved in 34% of eyes in the D + T group compared with 11% in the chemotherapy group. Based on these results, the FDA approved this combination for the treatment of pLGG harboring the BRAF

V600 mutation. However, trametinib and dabrafenib monotherapies are not approved for use in pediatric patients.

Tovorafenib, an oral, selective, CNS-penetrant type II RAF inhibitor, was approved in 2024 following the results of the phase II FIREFLY-1 trial in patients with recurrent or refractory low-grade glioma associated with BRAF alterations.[21] This trial included patients age 6 months to 25 years with RAF-altered relapsed or refractory pLGG. The trial enrolled 137 patients, with a median number of three previous lines of treatment, including 83 (61%) who had previously received MEK and/or BRAF inhibitors. The ORR using the RAPNO criteria was 51% (37% partial responses and 14% minor responses) without any difference between patients with or without previous exposure to MEK/BRAF inhibitors. One important issue highlighted in the FIREFLY-1 trial is the potential impact of tovorafenib on growth velocity. In this study, 18% of enrolled patients experienced a decrease in growth velocity of more than one standard deviation. Notably, this finding was not associated with evidence of advanced bone age or premature closure of the growth plates. In a subset of patients who discontinued tovorafenib, partial recovery of growth velocity was observed. This signal warrants careful monitoring, and particular attention is being given to growth outcomes in the ongoing FIREFLY-2 trial.

Several randomized trials are currently ongoing to compare targeted therapies with standard-of-care chemotherapy. NCT04166409 uses the MEK inhibitor selumetinib in previously untreated LGG not associated with BRAF V600E mutations or systemic neurofibromatosis type 1 (NF1), while the aim of NCT05566795 is to compare tovorafenib with standard-of-care chemotherapy. One can expect the results of these trials to lead to a paradigm shift in the first-line management of unresectable pLGG. However, the recent closure of NCT03871257, a trial of selumetinib versus carboplatin/vincristine in patients with NF1 pLGG, due to low accrual is leaving the NF1 population without any prospect of accelerated approval of targeted treatment for NF1-associated pLGG, despite evidence of efficacy in early clinical trials.

Although clinical trials are ongoing, the criteria for defining superiority of a treatment in pLGG remain unclear. Although response rates to these inhibitors may appear superior to those observed with standard-of-care chemotherapy, data on the long-term benefits of targeted therapies in pLGG are still needed. pLGG is a chronic disease, and the experience with chemotherapy has shown that most patients eventually develop disease progression after a single line of treatment. It is not uncommon for patients with pLGG to receive multiple lines of chemotherapy to achieve a sustained tumor control. Early observations also suggest that many patients may experience further progression after discontinuation of targeted therapy.[12]

BRAF alterations are also observed in pediatric high-grade gliomas (pHGGs) and 5%-10% of pHGGs harbor the BRAF V600E mutation. Improvements in diagnosis and classification, and correlations with survival have suggested that this alteration is associated with more favorable outcome. A phase II study evaluated the combination of dabrafenib plus trametinib in 41 patients with relapsed/refractory BRAF V600–mutant pHGG and reported a 56% ORR, with a median duration of response of 22.2 months and a median overall survival (OS) of 32.8 months.[22] A retrospective review of 19 patients with pHGG treated with off-label BRAF ± MEK inhibitors as part of their initial therapy reported a 3-year PFS and OS of 65% and 82%, respectively, and suggested a survival benefit compared with a historical control cohort of patients with BRAF-mutant pHGG treated with conventional therapy.[23] In 2022, the combination of dabrafenib and trametinib received accelerated FDA approval in tumor-agnostic indication for use in adult and pediatric patients (age ≥1 year) with BRAF V600E–mutated unresectable or metastatic solid tumors with no viable alternative therapy.

Future clinical trials of BRAF and MEK inhibitors should focus on determining the optimal duration of treatment, as well as exploring alternative administration strategies, such as treatment holidays or intermittent dosing schedules. These approaches may help preserve therapeutic efficacy while maintaining durable tumor control. Identification of mechanisms of resistance are also important, particularly for patients with BRAF V600–mutated pHGG.

TARGETING OTHER ALTERATIONS IN PEDIATRIC GLIAL TUMORS

Other targetable alterations have been identified in pLGG and pHGG, including NTRK, ALK, and ROS1 fusions, fibroblast growth factor receptor (FGFR) fusion and mutation, and KRAS mutation. The efficacy of targeting H3K27M remains to be confirmed (see below).

NTRK gene fusions have been identified in up to 5.3% of pHGG and 2.5% of pLGG.[25,26] The prevalence of these alterations is higher in young children, particularly in infantile hemispheric gliomas, where the fusion frequency is identified in up to 20%.[27]

Larotrectinib is a highly selective small molecule inhibitor of TRKA, TRKB, and TRKC. Despite limited CNS penetration, larotrectinib showed an ORR of 37% in a cohort of 38 patients with CNS tumors (33% in pHGG and 42% in PLGG).[28,29] The median time to response was 1.9 months and the median duration of response was 17 months. Entrectinib is a CNS-penetrant oral inhibitor of TRKA, TRKB, TRKC, ROS1, and ALK. The STARTRK-NG trial included 20 patients with NTRK-fused CNS tumors. The ORR was 50%, with a median time to response of 1.9 months and a median duration of response of 25.4 months.[30] Based on these promising data, both drugs were FDA approved for the treatment of adult and pediatric patients with solid tumors harboring a *NTRK* gene fusion where surgical resection is likely to result in severe morbidity and who have no satisfactory alternative

treatments or have progressed after treatment. Interestingly, these approvals were granted based on the results of single-arm trials with a limited number of patients. However, durability of responses to first-generation NTRK inhibitors is limited by acquired resistance, including on-target NTRK mutations, bypass resistance, or off-target resistance mechanisms. Repotrectinib is a next-generation ROS1/NTRK inhibitor designed to address on-target resistance mutations. Clinical trials are ongoing to assess the efficacy of this compound.

Data on the efficacy of ALK and ROS1 inhibitor in pediatric gliomas are sparse and the conduct of clinical trials is challenging, considering the rarity of these alterations. Case reports have described spectacular and sustained responses to ALK inhibitors (alectinib and lorlatinib) and ROS1 inhibitors (entrectinib) in infants and young children, after failure of chemotherapy.[31-33] However, at this time, crizotinib is the only ALK inhibitor approved in children.

Although FGFR inhibitors appear to have some efficacy in pediatric gliomas, their development has been limited by the high toxicity of these agents in children. *FGFR* is involved in phosphate metabolism, bone growth, and tissue homeostasis, and major bone toxicity has been observed in a limited trial of the FGFR inhibitor Debio1347.[34,35] Interestingly, MEK inhibitors have shown some efficacy in patients with FGFR alteration[36] (Fig 2). Similarly, responses to MEK inhibitors have been reported in pLGG patients with KRAS mutations.[38]

The use of targeted agents in very young children raises concerns regarding potential long-term effects. The NTRK pathway plays a critical role in normal brain development, and the consequences of its prolonged inhibition remain uncertain. These considerations underscore the need for careful, long-term follow-up in this particularly vulnerable population.

TARGETING H3K27M MUTATION IN DIFFUSE MIDLINE GLIOMAS

Dordaviprone is among the most recently FDA-approved targeted therapies for pediatric and adolescent/young adult brain tumors, receiving accelerated approval in August 2025 for the treatment of recurrent H3K27m-altered diffuse midline gliomas (DMG).[39] The agent is a first-in-class oral small molecule that acts as a dopamine D2 receptor antagonist and ClpP agonist.[40,41] Mechanistically, it has been shown to restore H3K27 trimethylation loss, a molecular hallmark of DMG, suggestive of disease-selective activity.[42]

FDA accelerated approval of dordaviprone was based on reanalysis of a published data set[43] using updated follow-up and RANO 2.0 criteria[44] with blinded central review. The data set included patients with recurrent H3K27m-mutant DMG from five early-phase and expanded-access studies meeting prespecified eligibility criteria, which excluded diffuse intrinsic pontine glioma (DIPG), spinal cord tumors, and patients with cerebrospinal fluid (CSF) dissemination of disease. The ORR was 22% (95% CI, 12 to 36), with a median duration of response of 10.3 months (95% CI, 7.3 to 15.2).[1] Clinically meaningful corticosteroid dose reductions and improvement in performance status were observed in a subset of patients.[43] The toxicity profile was favorable, with 20% of patients experiencing treatment-related grade 3 adverse events (AEs), most commonly fatigue. No grade 4 or higher treatment-related events were reported.[5,45]

Although dordaviprone represents the first FDA-approved systemic therapy for H3K27m-altered DMG and provides a treatment option for patients with recurrent disease and

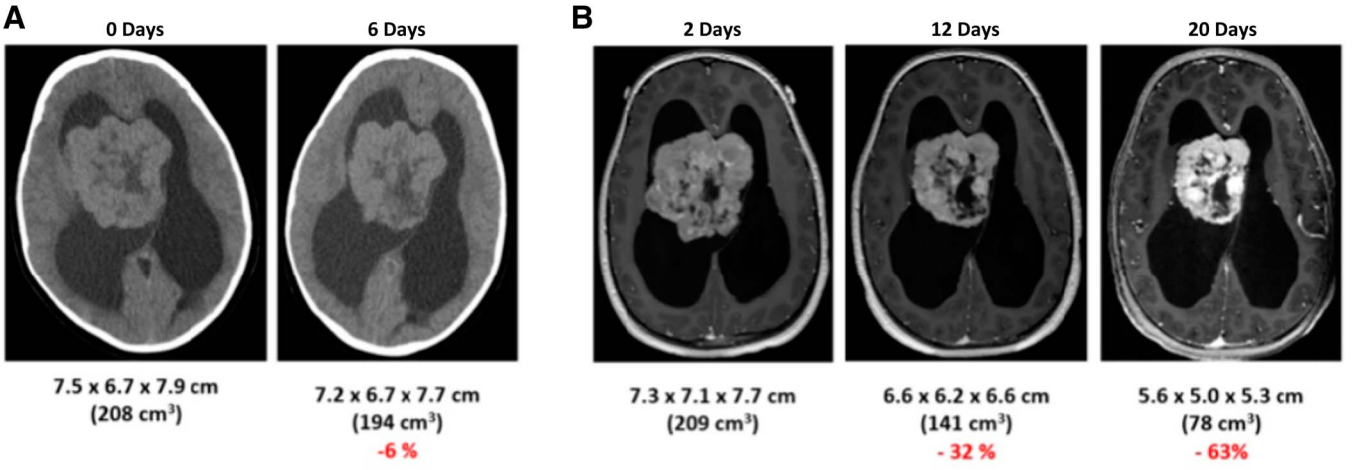

FIG 1. Acute SEGA response to everolimus. (A) Serial CT scans and (B) MRI scans obtained at various time intervals from presentation to the emergency department. The patient was acutely symptomatic from hydrocephalus and judged not to be a candidate for resection. Numbers in red represent percent reduction in volume from baseline. Adapted from the study by Arroyo et al.[37] CT, computed tomography; MRI, magnetic resonance imaging.

otherwise extremely limited alternatives, the ORR remains modest, and the available data are derived from single-arm studies. Additionally, pediatric patients comprise only 6% of the data set used for the US dordaviprone label. This reflects, in part, prespecified eligibility criteria that excluded DIPG as well as the earlier initiation of adult relative to pediatric trials, and inclusion into the data set as patients enrolled onto their corresponding trial up to a cap of 50 patients. These factors raise questions regarding the generalizability of results to pediatric populations. Confirmation of efficacy will be essential, and full approval is pending results of the randomized phase III ACTION (ClinicalTrials.gov identifier: NCT05580562) trial[45] with additional evidence in DIPG expected from BIOMEDE 2.0 (ClinicalTrials.gov identifier: NCT05476939) and PNOC022 (ClinicalTrials.gov identifier: NCT05009992). Dordaviprone represents a meaningful and promising therapeutic advance in a disease with significant unmet need and provides a much-needed option in clinical practice today, although confirmatory studies will be critical to define its long-term role.

IDH1 INHIBITORS

In August 2024, the FDA approved vorasidenib, an isocitrate dehydrogenase-1 (IDH1) and isocitrate dehydrogenase-2 (IDH2) inhibitor, for adult and pediatric patients age 12 years and older with grade 2 astrocytoma or oligodendroglioma with a susceptible IDH1 or IDH2 mutation, after surgery, including biopsy, subtotal resection, or gross total resection. This approval was based on the results of the INDIGO trial (ClinicalTrials.gov identifier: NCT06809322) that showed that vorasidenib significantly improved PFS and delayed the time to next intervention compared with placebo in a population of 331 randomly assigned patients.[46] Children age 12 years and older were eligible for the trial. However, only one pediatric patient was enrolled and data on the efficacy of vorasidenib in IDH1/2-mutated low-grade glioma in children are lacking. Although the incidence of these tumors is low in the pediatric population, a recent report by Bennett et al described unique characteristics of IDH-mutated astrocytomas in this age group, with a high proportion of patients with underlying predisposition syndromes, such as replication repair deficiency or Li-Fraumeni syndrome.[47]

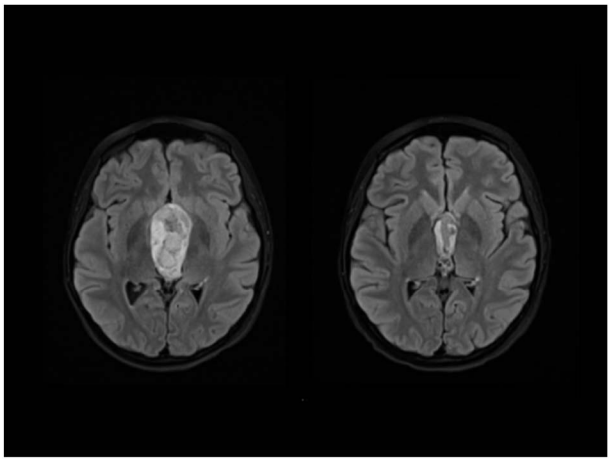

FIG 2. Pediatric low-grade glioma of the hypothalamic/chiasmatic region, associated with an FGFR1 mutation. The patient had further progression after two lines of chemotherapy. Left: before initiation of the oral MEK inhibitor trametinib, right: after 18 months of trametinib.

TARGETED THERAPY IN OTHER PEDIATRIC CNS TUMORS

Although the development of targeted therapies in pediatric glioma represents one of the most notable successes of precision medicine in pediatric oncology, progress in other pediatric brain tumors has so far been more modest, and, to our knowledge, no targeted therapies have yet received regulatory approval specifically for pediatric use.[48-54]

Clinical trials of Sonic Hedgehog inhibitors (SHHi) have demonstrated some activity in both pediatric and adult patients with recurrent medulloblastoma. However, response rates have been limited, with a study of vismodegib reporting responses in 15% of adults and only 8.3% of pediatric patients.[48] Higher response rates were observed in a phase I trial of sonidegib, with five responses among 10 patients with SHH-subgroup medulloblastoma.[49] Despite these encouraging signals, both trials identified significant growth plate toxicity in prepubertal patients, leading to the discontinuation of further development in this population.[49,50] Alternative approaches, including intraventricular administration, are currently being explored.[51,52]

Efforts to target the molecular consequences of INI1 loss in atypical teratoid/rhabdoid tumors (ATRT) have led to clinical evaluation of agents such as alisertib, an aurora kinase inhibitor, and tazemetostat, an EZH2 inhibitor. Although early results with alisertib were promising,[52] these findings were not confirmed in a subsequent phase II trial, which reported a response rate of only 3%.[53] NCT02601937 evaluated tazemetostat in INI-1–deficient tumors and reported a response rate of 24% in a cohort of 21 patients with ATRT.[54] However, the further clinical development of tazemetostat has recently been discontinued due to safety concerns.

TARGETED THERAPIES AND ACCESS IN LOW- AND MIDDLE-INCOME COUNTRIES

Although targeted therapies are increasingly incorporated into contemporary treatment paradigms in high-income countries, implementation of precision neuro-oncology remains uneven across low- and middle-income countries (LMICs), largely due to limitations in molecular diagnostics, drug affordability, and access to clinical trials.

Limited access to molecular diagnostics remains one of the most important barriers to the use of targeted therapy in LMICs. Data from the Asian-Oceanian region highlight substantial gaps in molecular testing capacity. Among

centers in lower-middle-income settings, in-house next-generation sequencing capability is available in fewer than 10% of institutions, while fluorescence in situ hybridization and Sanger sequencing are available in approximately 29% and 10%-15% of centers, respectively.[55] Access to DNA methylation profiling, which is increasingly used for molecular classification of CNS tumors, remains largely restricted to specialized reference laboratories. Even where diagnostic infrastructure exists, financial barriers and lack of reimbursement frequently limit routine clinical use, resulting in many children receiving treatment based primarily on histopathologic diagnosis.

Beyond diagnostic and therapeutic barriers, treatment abandonment remains a major challenge in pediatric oncology across many LMIC settings, with reported rates ranging from 10%-30% in some regions. Socioeconomic constraints, treatment costs, and geographic barriers to specialized care contribute substantially to these disparities.[56] Pediatric neuro-oncology programs in Brazil and Argentina have strengthened multidisciplinary care pathways and research collaboration, while emerging initiatives across sub-Saharan Africa are working to expand diagnostic capacity and training in neuro-oncology.[57]

International collaborations have also helped expand access to modern therapies. Networks such as the Pediatric Neuro-Oncology Consortium and global collaborative initiatives focused on constitutional mismatch repair deficiency have facilitated clinical trial participation and improved recognition of rare molecular tumor subtypes.[58,59]

Improving drug affordability is another key priority. The increasing availability of biosimilars and locally manufactured biologics may help expand access to modern therapies in LMIC settings. For example, the introduction of locally developed nivolumab biosimilars in India, including products developed by Zydus Lifesciences, represents an important step toward improving affordability and access to immune checkpoint inhibitors in resource-constrained health systems.[60]

Targeted therapies directed at key oncogenic pathways in gliomas, including MAPK pathway inhibitors (dabrafenib, trametinib, and tovorafenib) and IDH inhibitors, are increasingly incorporated into clinical management, although access to these agents remains limited in many LMIC settings (Table 1).

LESSONS LEARNED FROM TARGETED THERAPIES IN PEDIATRIC CNS TUMORS

In addition to the growing evidence supporting the efficacy of targeted therapies in pediatric CNS tumors, the development of clinical trials specifically designed for children has helped address age-specific challenges. Unlike adults, who typically receive fixed dosing, children exhibit a wide range of weight and body surface area, necessitating flexible dosing strategies. The development of age-appropriate formulations has therefore been essential. In particular, the ability—or inability—of young children to swallow capsules must be considered. To address this, liquid formulations of trametinib, dabrafenib, entrectinib, and larotrectinib have been developed, enabling administration in younger patients. Tovorafenib and selumetinib are available in sprinkle formulations, allowing for precise dose adjustments and administration with small amounts of liquid or food. Everolimus tablets can be dispersed in water before administration, creating an oral suspension suitable for pediatric use.

In this context, close collaboration between industry and clinical trial networks has been essential to advancing pediatric drug development programs. Such partnerships have enabled the conduct of clinical trials in rare diseases, which require the coordination of multiple, often international, centers to achieve adequate enrollment and robust data. This collaborative model has also fostered the emergence of dedicated pediatric drug development teams within industry, led by experts who understand the unique biology of childhood cancers, as well as the critical differences in factors such as body weight, pharmacokinetics, and metabolism that distinguish pediatric patients from adults.

Interestingly, it has also become evident that some agents traditionally considered to have limited CNS penetration—such as larotrectinib,[61] trametinib,[62] and vemurafenib,[63] all of which are substrates of P-glycoprotein—have nonetheless demonstrated remarkable efficacy in pediatric brain tumors.

FUTURE DIRECTIONS

Although major progress has been seen in the targeted treatment of glial tumor, there is a critical need to expand the spectrum of targeted therapies in other tumors, in particular embryonal tumors. Trials of alisertib or tazemetostat in atypical teratoid rhabdoid tumors have triggered hope that has not been translated in survival benefit.[53,54] Clinical trials are ongoing in craniopharyngioma.[64] However, there is an urgent need to focus on challenging entities such as embryonal tumors with true rosettes, or MYC-amplified and SHH TP53–mutated medulloblastoma. Resistance to targeted treatment is an important another problem that needs to be addressed. Finally, the integration of new tools such as liquid biopsies needs to be addressed. CSF ctDNA is likely to become an alternative to traditional tissue biopsies. Incorporation of such technique into prospective clinical trials of targeted therapies will be important to clarify its potential contribution in terms of diagnosis, eligibility for clinical trials, and monitoring during treatment.[65]

CONCLUSIONS

This review highlights the potential of targeted therapies to transform the management of pediatric brain tumors by

TABLE 1. Approved Targeted Therapies in Pediatric CNS Tumors and Challenges With Their Implementation in LMICs

Drug	Molecular Target	Key Pediatric CNS Evidence	Typical Dose (trial data)	Major Access Challenges in LMICs
Trametinib	MEK1/2 inhibitor	Activity in pediatric low-grade gliomas with MAPK pathway alterations[3]	Approximately 0.025 mg/kg once daily (≥6 years); approximately 0.032 mg/kg once daily (<6 years)[3]	Requires molecular diagnostics; high cost; limited availability
Dabrafenib + trametinib	BRAF V600E + MEK inhibition	Improved response and PFS *v* chemotherapy in pediatric BRAF V600E LGG[2]	Weight-based dosing[2]	Limited BRAF testing availability; reimbursement challenges
Selumetinib	MEK1/2 inhibitor	Activity in MAPK pathway–driven tumors[10]	Approximately 25 mg/m^2 twice daily[10]	Limited availability and cost barriers
Tovorafenib	Type II RAF inhibitor	Activity in relapsed/refractory pediatric LGG with BRAF alterations[4]	Once weekly oral dosing[4]	Newly approved therapy with limited global access
Vorasidenib	IDH1/2 inhibitor	INDIGO trial showed improved PFS in IDH-mutant grade 2 gliomas[5]	40 mg once daily[5]	Requires IDH testing; limited LMIC availability
Immune checkpoint inhibitors (eg, nivolumab)	PD-1 inhibition	Activity in hypermutant/MMRD gliomas[8]	Weight-based IV dosing[8]	High cost globally; biosimilar development (eg, Zydus nivolumab) may improve affordability

Abbreviations: IDH, isocitrate dehydrogenase; LGG, low-grade glioma; LMICs, low- and middle-income countries; MMRD, mismatch repair deficiency; PFS, progression-free survival.

tailoring treatment to their unique molecular characteristics. However, despite the promise of targeted therapies in pediatric brain tumors, several challenges remain. Tumor heterogeneity, both within and between patients, can lead to variable responses and the development of resistance to targeted agents. Additionally, many targeted therapies that have shown efficacy in extra-CNS tumors have limited ability to penetrate the blood-brain barrier, reducing their effectiveness in treating patients with pediatric brain tumor. One major concern is the long-term safety of these treatments in children. Beyond the approval of these agents, there is a need to collect follow up data, as the introduction of these new therapies is still recent. Addressing these challenges will require continued research, including the development of novel agents, combination therapies, and strategies to overcome resistance mechanisms.

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