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Targeted Therapy in Pediatric Low-Grade Glioma

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Abstract Collectively, pediatric low-grade gliomas account for most brain tumors reported in children. Surgery is typically curable for operable lesions. However, more effective therapies are required for inaccessible tumors, both to overcome refractory disease and to minimize the toxicity associated with conventional adjuvant chemotherapy and radiotherapy regimens. Recent years have witnessed rapid improvements in our understanding of the molecular pathogenesis of several childhood tumors, including low-grade gliomas. As a result, several novel compounds targeting and inhibiting critical components of molecular signaling pathways purported to be overactive in the disease have been developed. This article summarizes the most recent literature evaluating such novel targeted agents in childhood low-grade gliomas.

Keywords Pediatric · Low-grade glioma · *BRAF* fusion · *BRAF* mutation · Subependymal giant cell astrocytoma · Phosphatidylinositol 3-kinase/AKT/mammalian target of rapamycin pathway · Antiangiogenic therapy · Bevacizumab

Introduction

Pediatric low-grade gliomas are the commonest group of brain tumors found in children, accounting for approximately 40 % of all reported cases [1]. With a combined annual incidence of up to 12 cases per million children in Western societies [2], the group comprises a spectrum of tumor subtypes with differing histopathological, demographic, and radiological features (Table 1). Pilocytic astrocytomas represent the largest recognized histological subgroup, although as many as one quarter of low-grade gliomas cannot be classified according to current World Health Organization criteria [3]. This reflects the heterogeneous spectrum of tumors encountered and, in turn, questions the suitability of the 'one treatment fits all' approach currently used when managing these lesions with conventional therapy.

Survival outcomes for pediatric low-grade gliomas are generally very good, although this is influenced by the degree of tumor resection, histological tumor classification, presence of disseminated disease, or concurrent diencephalic syndrome [4]. Indeed, long-term cure rates of over 90 % have been reported for cases achieving complete or near total tumor removals [5, 6]. However, excision is not feasible for symptomatic or growing midline gliomas of the hypothalamus/optic pathway and brainstem. In this context, chemotherapy has now become first-line therapy for the majority of affected children, particularly those with neurofibromatosis type 1 (NF1), in order to delay or avoid radiotherapy and its adverse sequelae [7–9]. The challenge for such chemotherapeutic strategies is to control subsequent tumor recurrence or progression, currently observed in up to two thirds of cases [10], and minimize inherent toxicity.

To address these issues, modern research has strived to increase our understanding of the biological pathogenesis of pediatric low-grade gliomas in order to improve on conventional treatments. Building on historical, observed associations with genetic predisposition syndromes such as NF1 and tuberous sclerosis, ongoing work has now led to the identification of deregulated genetic pathways underpinning tumor formation and to the development of molecularly targeted therapies that are hoped will improve efficacy at

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Table 1 Histopathological, radiological, and clinical features of principal pediatric low-grade gliomas as classified according to the 2007 World Health Organization (*WHO*) classification of tumors of the central nervous system [69]

Group	Subtype	WHO grade	Histology	Radiology(MRI)	Clinical
Astrocytic tumors	Pilocytic astrocytoma	I	Biphasic growth pattern with compacted glia and microcysts. Rosenthal fibers, eosinophilic granular bodies	Well demarcated. Often cystic with T2 hyperintense solid components. Typically marked contrast enhancement	Midline location: cerebellum, hypothalamus, optic pathway, brainstem, basal ganglia. Age: peak 5–9 years of age
	Pilomyxoid astrocytoma	I	Piloid cell features with angiocentric architecture, mucinous background. No biphasic pattern	T2 hyperintense solid component with extension into deep white and gray matter	Location: often suprasellar—hypothalamus, optic chiasm, third ventricle. Age: under 3 years/infancy
	Pleomorphic xanthoastrocytoma	II	Pleomorphic lipidized cells, abundant reticulin, eosinophilic granular bodies	Well demarcated. Can be cystic with an enhanced, mural nodule or occasionally solid (T2 hyperintense). Scalloping	Location: cerebral cortex and meninges. Age: typically adolescence
	Diffuse .astrocytoma	II	Typically fibrillary, diffuse infiltration, microcysts, mitoses and necrosis rare	Less well demarcated. Cyst and enhancement uncommon. T2 hyperintense, T1 hypointense or isointense	Location: typically cerebral hemispheres. Age: typically adolescence
	Subependymal giant cell astrocytoma	I	Large ganglion-like cells, mixed glial/neuronal cell differentiation	T1 hypointense or isointense, T2 hyperintense, contrast enhancement	Location: foramen of Munro. Association with TSC patients
Oligodendroglial tumors	Oligodendroglioma	II	Cells with round nuclei, honeycomb architecture, calcifications, dense capillary networks, cystic/mucoid degeneration	Well demarcated. Can be cystic. T1 hypointense. T2 hyperintense. Occasionally hemosiderin and calcification seen	Location: most often frontal lobe. Age: peak 6–12 years of age (uncommon in children)
Neuronal and mixed neuronal–glial tumors	Ganglioglioma	I	Dysplastic ganglion cells, variable neoplastic astrocytoma component	Variable cysts, contrast enhancement, calcification, and hemorrhage. Often T2 hyperintense and heterogeneous on T1 weighting	Location: temporal lobes. Age: Older childhood with mean age of 9–10 years
	Gangliocytoma	I	Multiple, large, dysplastic, multipolar neurons in groups	As for ganglioglioma	Location: often temporal lobe/hypothalamus. Age: second decade of life
	Desmoplastic infantile ganglioglioma	I	Poorly differentiated neuroepithelial and fibroblastic elements, prominent collagen and reticulin	Large cysts with enhanced peripheral solid component	Location: most often frontal, parietal, and temporal lobes Age: Infancy
	Dysembryoplastic neuroepithelial tumor	I	Multinodular, columnar cell arrangement, intercellular mucin, glioneuronal elements	Well demarcated. Intracortical thickening, T1 hypointensity, and T2 hyperintensity. Punctate enhancement	Location: most often medial temporal lobe/hemispheric. Age: Second decade of life

TSC tuberous sclerosis complex

minimal burden to normal, often developing, tissue. This article reviews the most recent principal literature evaluating such novel targeted agents for pediatric low-grade gliomas.

Downstream Drug Targeting of the RAS/RAF/Mitogen-Activated Protein Kinase Pathway

The most frequent genetic alterations identified in pediatric low-grade gliomas to date implicate *BRAF*, a downstream member of the RAF serine–threonine kinase family and a key regulator of the mitogen-activated protein kinase (MAPK) pathway responsible for controlling cell division, differentiation, and invasion (Fig. 1) [11].

Molecular work has shown that most pediatric pilocytic astrocytomas demonstrate a segmental duplication at chromosome band 7q34 [12, 13], resulting in a fusion transcript between the MAPK-activating domain of *BRAF* and another gene, *KIAA1549* [13, 14]. This oncogenic fusion is the commonest molecular anomaly reported in nonsyndromic pilocytic astrocytomas of childhood [3], particularly those located in the posterior fossa [3, 13, 15–17]. Although the fusion is typically not observed in patients with NF1 [18], the mutated NF1 protein also loses an inherent inhibitory effect on BRAF activity [19], thereby causing corresponding MAPK signaling activation. Paradoxically, recent studies have suggested that the presence of the *BRAF:KIAA1549* fusion may confer a less aggressive clinical phenotype, and is therefore associated with better outcome [18, 20], although this finding is not universal from comparative retrospective work [21, 22]. Molecular evaluation of a large, prospective clinical trial cohort is therefore required to accurately determine the true prognostic significance. Whether the fusion represents a potential drug target also remains unclear.

Although less common, point mutations of *BRAF* and other MAPK pathway members such as *KRAS* are also observed in pediatric low-grade glioma [13, 16, 22–25, 26•, 27]. The $BRAF^{V600E}$ mutation, resulting in the replacement of valine with glutamic acid at codon 600 of *BRAF*, is the most frequent reported. Indeed, in a recent study analyzing the presence of $BRAF^{V600E}$ mutations in 1,320 tumors of the central nervous system (CNS), this mutation was identified in approximately 9 % of extracerebellar pilocytic astrocytomas [26•]. Of note, the incidence was higher in other low-grade glioma subtypes, especially pleomorphic xanthoastrocytomas (66 %) and ganglioglioma (18 %), an observation confirmed by other groups [28–30].

A retrospective analysis of 198 pediatric low-grade gliomas reported a trend towards poorer progression-free survival for children with $BRAF^{V600E}$ mutated tumors [20], suggesting that targeting this anomaly therapeutically may improve

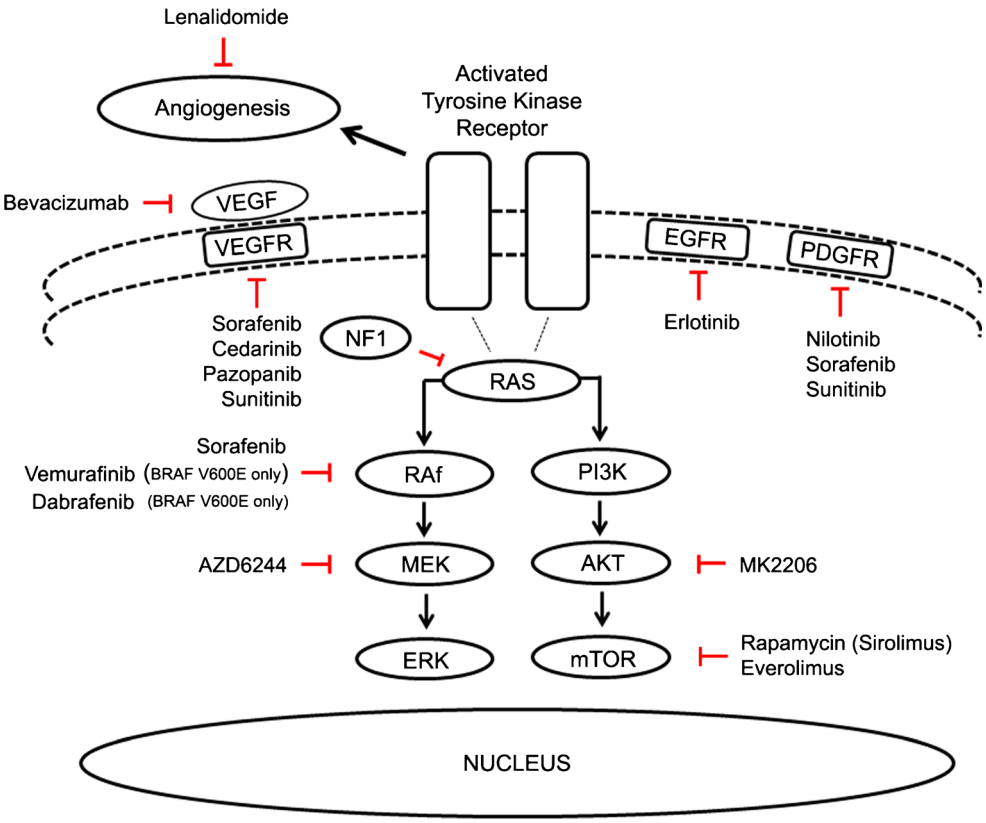

Fig. 1 Novel therapeutic agents targeting components of the cell signaling pathways frequently activated in pediatric low-grade gliomas. *EGFR* epidermal growth factor receptor, *ERK* extracellular-signal-regulated kinase, *NF1* neurofibromatosis 1, *mTOR* mammalian target of rapamycin, *PDGFR* platelet-derived growth factor receptor, *PI3K* phosphatidylinositol 3-kinase, *VEGF* vascular endothelial growth factor, *VEGFR* vascular endothelial growth factor receptor

patient survival outcomes. Indeed, novel agents inhibiting this mutation, such as vemurafenib and dabrafenib, have been developed. Although their use in childhood glioma therapy is emergent, a recent case report on the successful management of a pediatric ganglioglioma with vemurafenib provides a source for optimism [31•]. Early mutation screening to identify patients likely to benefit from these inhibitors is therefore fundamental and forms the basis of the current phase I/IIa international study of dabrafenib in children with *BRAF*^{V600E}-positive solid tumors, including low-grade gliomas (ClinicalTrials.gov Identifier NCT01677741).

Although the evolving era of novel *BRAF* inhibitors represents an exciting, potential paradigm shift in the management of childhood low-grade gliomas, clinicians are urged to temper enthusiasm for their universal efficacy. For instance, the value of such drugs against gliomas exhibiting the *BRAF:KIAA1549* fusion is unclear. A recent phase II study of sorafenib [a multi-kinase inhibitor targeting BRAF, vascular endothelial growth factor receptor, platelet-derived growth factor receptor (PDGFR), and c-KIT) in 12 children with recurrent low-grade gliomas, including three demonstrating *BRAF:KIAA1549* fusion, actually reported significant early progression rates, potentially indicating downstream paradoxical extracellular-signal-regulated kinase activation [32]. Likewise, resistance to vemurafenib analogues and subsequent growth activation in low-grade glioma cell lines expressing the *BRAF:KIAA1549* fusion have been observed in vitro [33, 34].

Other downstream inhibitors of the MAPK signaling cascade are also currently being evaluated in clinical trials. For instance, phase I and II studies of AZD6244, a small-molecule inhibitor of the MAPK activator kinases MEK1 and MEK2, are ongoing in children with recurrent or refractory low-grade gliomas (ClinicalTrials.gov Identifiers NCT01386450 and NCT01089101), after preclinical work demonstrated activity against pilocytic astrocytoma cell lines [35].

Downstream Drug Targeting of the Phosphatidylinositol 3-Kinase/Mammalian Target of Rapamycin Pathway

Another tyrosine-kinase-driven signaling cascade implicated in pediatric low-grade glioma pathogenesis is the phosphatidylinositol 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathway, which regulates cell growth, protein synthesis, and apoptosis [11]. The archetypical low-grade glioma associated with mTOR activation is the subependymal giant cell astrocytoma (SEGA) in patients with tuberous sclerosis complex (TSC).

TSC is an autosomal dominant genetic disorder characterized by germline mutations in two tumor suppressor genes–*TSC1* (hamartin) or *TSC2* (tuberin)—resulting in the development of benign tumors in multiple organ systems, including the brain, kidney, skin, heart, retina, and lungs [36]. These two genes encode the hamartin–tuberin protein complex, which in turn restricts downstream activation of mTOR; specifically the subunit mTOR complex 1. When the TSC genes are deficient, mTOR complex 1 is constitutively upregulated, with consequent abnormal cellular growth and proliferation [37]. Up to 15 % of TSC patients develop SEGAs, typically located adjacent to the intraventricular foramina of Munro, causing obstructive hydrocephalus [38, 39]. Historically, SEGAs required surgical resection if they caused symptomatic growth as they were resistant to conventional low-grade glioma chemotherapy therapy and radiation therapy [40]. However, the successful targeted treatment of SEGAs is now achievable, an evolution that represents the most significant advance for molecular therapy in pediatric low-grade gliomas to date [41, 42].

The first effective oral mTOR inhibitor in TSC-associated SEGA was reported in 2006, when five individuals all exhibited regression of their lesions following administration of the posttransplantation immunosuppressant sirolimus (rapamycin) [41]. Another mTOR inhibitor, everolimus, has also demonstrated efficacy against SEGAs. An initial, single-center, prospective, open-label study produced at least 30 % tumor volume reduction in 21 of 27 enrolled TSC patients, most of whom were below 18 years of age [42]. More recently, this effect was confirmed by Franz et al. [43••] through a double-blind, placebo-controlled randomized trial of 117 patients in which everolimus was analyzed against placebo. One third of those in the everolimus arm demonstrated a SEGA volume reduction of 50 % or more compared with none of the placebo group [43••]. As with preceding studies, tumor regrowth occurred on discontinuation of inhibitor therapy, but retreatment proved successful. Of interest, mTOR inhibition also appeared to have activity against other clinical manifestations of TSC such as skin lesions and renal angiomyolipomata [43••].

At present, the Food and Drug Administration has approved everolimus exclusively for the treatment of surgically unresectable SEGAs in the context of TSC. Nevertheless, several trials are now investigating the effect of mTOR inhibition on TSC-induced epilepsy (ClinicalTrials.gov Identifiers NCT01070316 and NCT01713946), neuropsychological disorders (ClinicalTrials.gov Identifier NCT01730209), and neurocognitive deficits (ClinicalTrials.gov Identifier NCT01954693).

Indeed, the benefit of mTOR inhibitors may not be exclusive to TSC-associated SEGA, with evidence of potential activity in other pediatric low-grade gliomas emerging. Proteomic and immunohistochemical analyses have shown that NF1-associated low-grade glioma subsets demonstrate differential levels of mTOR activation [44, 45], with pilocytic astrocytomas in particular demonstrating significantly elevated mTOR signaling [45, 46]. Evidence from neural stem cell

work has also suggested cross talk between the RAF and PI3K pathways, with downstream convergence at mTOR, which functions as a growth control center, activated by unique pathway-defined mechanisms (*MEK*-induced *TSC2* inactivation or *AKT* activation, respectively) [47].

Clinical work is now attempting to verify the in vitro implication that mTOR inhibitors could be effective agents against either sporadic or NF1-related pediatric low-grade gliomas. At present, the results are variable. A prospective, multi-institutional phase II study of everolimus in 23 non-NF1 children with recurrent or progressive low-grade gliomas has just been completed, with provisional encouraging results demonstrating either partial response (n=4) or stable disease (n=13) by the end of therapy in 74 % of the cohort [48]. Assessment of NF-1 associated gliomas is now under way (ClinicalTrials.gov Identifier NCT01158651). In contrast, another recent phase I/II study reported the use of rapamycin in combination with the epidermal growth factor receptor (EGFR) inhibitor erlotinib in 19 children with recurrent low-grade gliomas, eight of whom had NF-1 [49]. Although the combination was well tolerated, response rates were disappointing, with only one NF-1 patient demonstrating objective response and two children remaining progression free for longer than 18 months after treatment. These findings suggest that identifying future molecular predictors of response to these targeted inhibitors will be as important as evaluating the agents themselves.

Other members of the PI3K/mTOR pathway are also being targeted by novel inhibitors. For instance, a Children's Oncology Group (COG) phase I study of the AKT inhibitor MK2206 has just been completed for children with refractory solid tumors, including intracranial gliomas, after encouraging preclinical analysis (ClinicalTrials.gov Identifier NCT01231919); the results are awaited.

Upstream Targeting and Antiangiogenic Agents

The receptor tyrosine kinases (RTKs), such as vascular endothelial growth factor receptor, EGFR, and platelet-derived growth factor receptor (PDGFR), are mutual upstream members of both the BRAF/MAPK signaling pathway and the PI3K/mTOR signaling pathway (Fig. 1). They function as transmembrane regulators of key cellular processes such as proliferation, differentiation, and metabolism [50]. They also play a critical role in tumor angiogenic signaling, making them significant therapeutic drug targets for inhibition. Current novel agents used in this context are either monoclonal antibodies directed against growth factor ligands or inhibitors directly targeting the tyrosine kinase domains.

For refractory low-grade gliomas of childhood, the most evaluated agent with this function remains bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor [51, 52, 53•]. In almost all recorded pediatric cases (55 of 56), this has been administered in conjunction with the topoisomerase I inhibitor irinotecan. A recent phase II study of 14 children with recurrent or progressive disease evaluated bevacizumab-based therapy administered for a median duration of 12 months [51]. Twelve patients (86 %) demonstrated an objective response and/or clinical improvement with minimal toxicity. Although promising, progression occurred rapidly for almost all children on discontinuation of therapy. Nevertheless, retreatment proved feasible and effective. Another institutional study of bevacizumab and irinotecan in seven patients with refractory low-grade gliomas reported tumor shrinkage in six cases (86 %) [52]. The toxicity profile appeared tolerable, with the most frequent events being grade I proteinuria and hypertension.

A curtailed follow-up period for the above-mentioned studies restricted any meaningful progression-free survival analysis. To address this, the Pediatric Brain Tumor Consortium (PBTC) recently published a protracted phase II analysis of bevacizumab and irinotecan in 35 evaluable children with recurrent low-grade gliomas [53•]. Although the regimen was again relatively well tolerated (with adverse effects including hypertension, proteinuria, lethargy, and epistaxis), and disease stability was observed for over 80 % of the cohort after 6 months of therapy, making it a feasible therapeutic option, only two patients demonstrated a radiological response to therapy, and the 2-year progression-free survival rate was 48 %, comparable with but no better than that of current conventional strategies [53•, 54, 55]. Explanations for the discrepancy in response rates between this analysis and the preceding studies were elusive, but may reflect discrepant cohort size, drug dosing/scheduling, tumor histological features, and patient demographics. In addition, these findings suggest that radiological response to therapy cannot predict progression-free survival for these tumors. Prospective trials will be required to validate these findings and also evaluate any longer-term sequelae.

Small-molecule inhibitors of the VEGF receptor have also been developed and are currently being investigated by phase I feasibility studies in children. These include cediranib (ClinicalTrials.gov Identifier NCT00326664) and pazopanib (ClinicalTrials.gov Identifier NCT00929903). Sunitinib has also been investigated in such dose-escalation studies and, although dose-dependent cardiac toxicity precluded its widespread endorsement, it did produce disease stability for one child with a ganglioglioma [56]. As described previously, other RTK inhibitors already evaluated in the context of progressive pediatric low-grade glioma include the EGFR antagonist erlotinib [49] and the multi-kinase inhibitor sorafenib [32], and the PDGFR inhibitor nilotinib is currently being assessed in conjunction with conventional vinblastine as part of a European, open-label phase I/II study (ClinicalTrials.gov Identifier NCT01887522).

Antiangiogenic agents also represent an attractive option in treating CNS tumors as their mechanism of action, targeting intravascular endothelial cells, is not hindered by the blood–brain barrier. In addition to RTK inhibitors, other less-specific antiangiogenic agents or drug combinations have therefore been evaluated for pediatric low-grade gliomas. For instance, a phase I study of the oral thalidomide analogue lenalidomide by the PBTC recently reported either objective response ($n=2$) or prolonged disease stability for most of 26 children with previous refractory disease [57•]. The commonest toxicity was myelosuppression. As a result, a COG phase II randomized study of lenalidomide in children with recurrent or progressive optic pathway gliomas and pilocytic astrocytomas has now commenced, comparing a low-dose (20 mg/m^2) against a high-dose (115 mg/m^2) regimen; (COG trial ACNS1022, ClinicalTrials.gov Identifier cNCT01553149).

Preclinical work has also suggested that the metronomic administration of antiangiogenic agents may have more cytotoxic efficacy against tumor cells than the classic dose-intensive, interval scheduling of conventional chemotherapy [58–60]. To evaluate this hypothesis, a phase II trial of multiple agents with antiangiogenic properties (celecoxib, thalidomide, fenofibrate, cyclophosphamide, etoposide) given in a metronomic dosing schedule over 27 weeks was assessed in 101 children with recurrent CNS tumors, including 12 patients with low-grade glioma. Of these, nine (75 %) demonstrated stable disease or better, although only seven (58 %) were able to complete the full treatment, with adverse events primarily being hematological [61]. This suggests that further investigation of this approach is warranted in larger low-grade glioma cohorts, albeit with possibly fewer agents to reduce any accumulative toxicity.

High-Resolution Genomic Studies and Potential Therapeutic Targets

Other than the aforementioned mutations or duplications involving *BRAF* in certain types of tumor, few other genetic anomalies have been identified that may characterize other low-grade glioma subgroups. To address this, several international research groups have recently performed high-resolution tumor genomic analyses, including whole genome sequencing (WGS), reporting novel aberrations and possibly potential therapeutic targets [62–64].

One WGS analysis of 39 low-grade glioma/glioneuronal childhood tumors identified novel *BRAF*/*RAF1* abnormalities including *FXR1:BRAF*, *BRAF:MACF1*, and *QKI:RAF1* fusions [63], which supplemented previous work also identifying previously unknown MAPK gene fusions in pilocytic astrocytomas such as *SRGAP3:RAF1* and *FAM131B:BRAF* [16, 23, 65]. The study also reported a novel duplication in another RTK member, fibroblast growth factor receptor 1 (*FGFR1*). This was present in almost one quarter of diffuse (World Health Organization grade II) astrocytomas analyzed, a subgroup identified by this and another high-resolution genomic study to also be enriched for rearrangements of the transcription factor activator genes *MYB* and *MYBL1* [63, 64]. Recurrent activating mutations of *FGFR1* have also been reported in a noncerebellar subset of 96 pediatric pilocytic astrocytomas interrogated using WGS by the International Cancer Genome Consortium [62]. Duplication of *FGFR1* and MYB overexpression in low-grade gliomas has been shown to activate the BRAF/MAPK and PI3K/mTOR pathways [63], warranting their consideration as future therapeutic targets for inhibition as they have been used in other pediatric cancers [66–68].

Conclusion

Our understanding of low-grade glioma pathogenesis has improved in recent times. Nevertheless, the mechanistic action of conventional chemotherapy for pediatric low-grade gliomas remains largely unclear, in turn hindering accurate explanations and remedies for any subsequent drug resistance observed. In addition, the use of targeted molecular agents remains in its infancy. Although certain tumors such as pilocytic astrocytomas may well be caused by 'single pathway' disruption [62, 63], the pathogenesis of other lesions may implicate a cascade of multiple signaling pathways, such that exploiting a single aberration may ultimately prove unsuccessful. Tumor cells may also activate other escape mechanisms to confer therapeutic resistance. Indeed, identifying molecular predictors of response to this mode of treatment in large prospective cohorts remains necessary. It is therefore plausible that, for certain tumors, targeted agents will only be successful if they are combined with other conventional chemotherapeutic drugs or synergistic small-molecule inhibitors. Current clinical trials should provide more insight in this regard. More work is also required to elucidate the CNS penetrance of many novel inhibitors as clearly this will impact on their antitumor activity, irrespective of purported function. Additional matters to consider include the as yet unknown long-term toxicity profiles and impact on normal tissue development of these agents.

Nevertheless, we are in an exciting therapeutic era for children with low-grade gliomas, encouraging optimism among the pediatric neuro-oncology community, while raising new questions such as whether certain novel agents, for instance, in patients with TSC, should be considered for life. Ultimately, it is hoped that a targeted management strategy can improve long-term outcomes for the subset of affected children who are not cured by current approaches.

Compliance with Ethics Guidelines

Conflict of Interest John-Paul Kilday and Ute Katharina Bartels declare that they have no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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