Pediatric Gliomas
Molecular Landscape and Emerging Targets

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KEYWORDS

• Targeted therapy • Molecular genetics • Pediatric glioma • Histone mutation
• Diffuse midline glioma • Next-generation sequencing

KEY POINTS

- Molecular genetic characterization of pediatric gliomas identifies oncogenic pathways and potential therapeutic targets.
- The MAPK and PI3K pathways are highly active in pediatric glioma biology.
- Mechanisms of oncogenesis unique to pediatric forms of glioma may lead to unique therapeutic opportunities.
- Genetic alterations identified through next-generation exome sequencing have yielded targeted therapeutics currently in clinical trials.
- Adequate drug penetration, sensitivity of brain tissue to treatment-associated toxicities, and a multiplicity of mechanisms of resistance present significant challenges to effective treatment.

CURRENT TREATMENT STRATEGIES AND PROGNOSIS

Pediatric Low-Grade Gliomas

Pediatric low-grade gliomas (pLGGs) are the most common brain tumors in children.[1,2] PLGGs generally are slow growing and devoid of malignant features. Anatomic location appears to correlate with genetic landscape. These tumors are clinically and genetically distinct from the low-grade gliomas seen in adults and must be treated as such. PLGGs broadly include all World Health Organization (WHO) grade I and grade II gliomas: pilocytic astrocytoma (PA), dysembryoplastic neuroepithelial tumor (DNET), ganglioglioma (GG), pleomorphic xanthoastrocytoma (PXA), subependymal giant cell astrocytoma (SEGA), and diffuse astrocytoma (DA), among others.

PLGGs generally portend a favorable prognosis and often can be cured by surgical resection alone.[3] PAs are the most benign of pLGGs, with 10-year overall survival rates of 96% and recurrence rates of 10% to 20%.[4,5] Where complete surgical resection is not possible, however, treatment of these tumors can be lengthy and complex, with risks of tumor progression, malignant transformation, and non-negligible treatment-related neurologic deficits, visual impairment, and endocrine dysfunction.[3,5]

Surgical resection is the mainstay of treatment in pLGGs, undertaken when feasible and safe to perform with curative intent.[5] Debulking procedures are reserved most frequently for symptomatic relief. When considering systemic therapies and radiation treatment, a balance must be maintained

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between the likelihood of tumor control, and minimizing long-term treatment-related morbidity because pLGGs typically are slow-growing, rarely undergo malignant transformation, and portend a long overall survival.[6] Four scenarios typically are encountered in pLGG: (1) tumors in surgically accessible locations (most of which are cured by resection alone); (2) tumors in high-consequence locations hostile to surgical resection; (3) Neurofibromatosis type 1 (NF1) patients with optic pathway gliomas, which typically are observed and are managed surgically only after significant symptomatic tumor progression refractory to other treatment modalities; and (4) tuberous sclerosis (TS) patients with SEGAs, for which mechanistic target of rapamycin (mTOR) inhibitors and surgery yield excellent results.[1,3]

A majority of pLGGs harbor a single driver alteration within a cluster of commonly altered genes and alterations. A majority of sporadic pLGG cases carry *KIAA1549:BRAF* and *BRAF*^{V600E} gene mutations[7]; however, chemotherapies utilized for pLGG patients are limited to traditional agents, and targeted molecular therapies are only in their nascency.[3,5] Radiotherapy generally offers improved progression-free survival for many pLGG types but potentially at the cost of worsening overall survival.[3] Importantly, radiotherapy is avoided in the setting of germline cancer predisposition syndromes, such as NF1, and in very young patients (<3 years old) due to an extremely high risk of endocrine dysfunction, neurologic deficits, developmental delay, impaired vision, and radiation-induced malignancies.[2]

Pediatric High-Grade Gliomas

Pediatric high-grade gliomas (pHGGs) often are divided into diffuse midline glioma (DMG), essentially all H3K27M mutants,[8,9] and the non-brainstem pHGGs, which include H3G34R/V gliomas (**Fig. 1**).[10,11] Although histopathologic features are similar, the malignant gliomas seen in children are distinct from those seen in adult patients in many important ways. Whereas the classical adult forms of glioblastoma most frequently are diseases of copy number alteration, pHGGs frequently carry somatic point mutations. pHGGs often involve chromothripsis and a hypermutator phenotype, referring to combinations of multiple somatic and potentially germline mutations involved in DNA repair.[12] Next generation sequencing (NGS) has identified some overlap between WHO low-grade and high-grade gliomas in terms of genetic alterations, and the prognostic value of WHO grading in pediatric glioma potentially is diminished, in favor of molecular genetic characterization.[13–17] Two main subtypes of pHGG are marked by somatic *H3-3A* gene mutations.[18–20]

The H3G34R/V glioma subtype displays distinct characteristics that differentiate it from the better-characterized DMGs. H3G34R/V gliomas occur most typically in adolescent children and young adults, whereas DMG presents most commonly in early childhood. H3G34R/V gliomas typically are supratentorial and lobar in location, in contrast with the midline DMGs that occur in rhombencephalic and diencephalic structures. Concurrent *TP53* and *ATRX/DAXX* alterations are frequent in H3G34R/V gliomas and are thought to contribute to its CpG island promotor hypomethylated phenotype, whereas concurrent *TP53* mutations also accompany DMGs but without the same perturbations in chromatin remodeling, alternative lengthening of telomeres, or CpG island promotor methylation.[18–20]

Extent of resection is correlated directly to prognosis in pHGG[21]; however, as in adult glioblastoma, radiotherapy, with or without alkylating chemotherapy agents, remains the primary treatment modalities in pHGGs.[10,11,22] Advances in treatment have been few—none of the 68 clinical trials in DMG between 1984 and 2014 has conferred any survival benefits relative to radiation alone.[1,10,23] Chemotherapy agents commonly employed in young children to treat pHGG include vincristine, carboplatin, temozolomide, and thiotepa,[2,22] although evidence for survival benefit is scant. Therefore, pHGGs remain a devastating diagnosis with a poor overall prognosis, with an estimated 2-year survival of less than 20%.[10,12,24] DMGs in particular carry a median survival of less than 1 year.[4,10,11,22,25–27] The gain-of-function oncogenic p53 protein has a significant effect on 5-year progression-free survival in pHGG—44% with low mutant p53 expression compared with 17% with high p53 expression.[6,12] Specific to pHGG cases, other factors contributing to treatment challenges include a population of slow-cycling stem cells and new mutations gained on evolution toward recurrence.[28]

MOLECULAR LANDSCAPES WITH PROMISING THERAPIES

mTOR Pathway Inhibition for Subependymal Giant Cell Astrocytoma in Tuberous Sclerosis

Two germline disorders are associated strongly with the development of pLGGs. The intracranial manifestations of TS, including SEGAs, are thought to arise from germline *TSC1* or *TSC2* gene mutations, sometimes compounded by somatic Phosphoinositide 3-kinase/Protein kinase

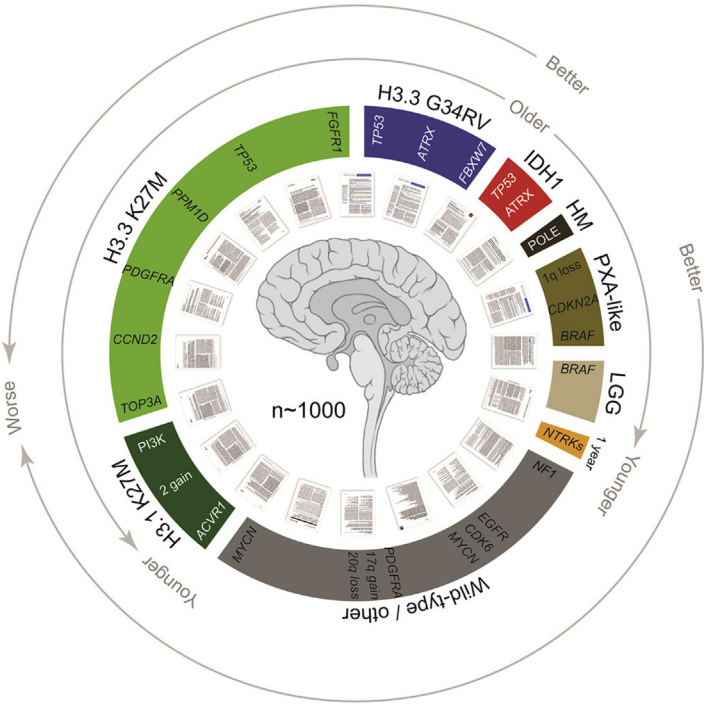

Fig. 1. Molecular patterns and clinical features of pediatric glioma subtypes It has become increasingly apparent that pHGG differ from their adult counterparts, with molecular profiling studies carried out over the last 6–7 years having incrementally identified key genetic and epigenetic differences in pHGG associated with distinct ages of onset, anatomical distribution, clinical outcome, and histopathological and radiological features. The outer ring represents relative frequencies of the pediatric gliomas with most common molecular genetic alterations associated with each subgroup. Subgroups are arranged and labelled by median age at presentation and overall survival prognosis. Original data from the German Cancer Research Center in Heidelberg aligned with published data from other studies. (*From* Mackay A, et. al. Pediatric High-Grade and Diffuse Intrinsic Pontine Glioma. Cancer Cell. 32(4):520-537.e5. https://doi.org/10.1016/j.ccell.2017.08.017; with permission.)

B/mTOR (PI3K/Akt/mTOR) pathway mutations (Fig. 2).[29] Patients with TS are at increased risk of developing SEGAs in early childhood, thought to result from loss of heterozygosity in the same chromosomal region containing the *TSC1* or *TSC2* mutation.

Despite the name, SEGAs should not be confused with astrocytomas. Rather, they are distinct entities with a unique molecular genetic pathogenesis and serve as a paragon for targeted molecular therapy. Everolimus, an mTOR inhibitor, and rapamycin have demonstrated seizure control benefit and reduction in tumor volume in TS patients with SEGAs (see Fig. 2).[1,3,30–32]

mTOR Pathway Inhibition for Low-Grade Glioma in NF1

Twenty percent of NF1 patients manifest hypothalamic/optic pathway pLGGs.[33] The *NF1* gene encodes neurofibromin, a Ras-Guanosine triphosphate (GTP)ase–activating protein that regulates Mitogen-activated protein kinase/ extracellular receptor kinase (MAPK/ERK) activity through Ras. When mutated, Ras regulation is disrupted, causing constitutive activation of both MAPK and PI3K pathways, thus leading to tumorigenesis (see Fig. 2).[34] Histologically, these tumors appear consistent with PAs; however, in NF1 patients, these hypothalamic/optic pathway PAs demonstrate a less aggressive natural history than sporadic hypothalamic/optic pathway PAs.[35]

NF1-deficient malignant gliomas have shown initial responsiveness to mitogen-activated kinase kinase (MEK or MAP2K) inhibitors, such as selumetinib[36]; however, only a partial response has been observed in NF1-associated pLGGs.[37] Promising findings have been mentioned from preclinical studies with Akt-mediated or MEK-mediated mTOR inhibition.[38]

Targeting Mitogen-Activated Protein Kinase (MAPK) Signaling in BRAF-Mutant Glioma

MAPK signaling is known to affect cell proliferation, differentiation, migration, and cell death. Recently, 2 large, whole-genome sequencing studies identified genomic alterations in MAPK pathways to be the most common molecular characteristic in pLGGs.[5,39,40] Almost all PAs harbor a single-hit somatic mutation involving the MAPK signaling pathway without any additional mutations—a single-pathway disease.[41] *BRAF*, an early transducer in the MAPK pathway, is the most frequently mutated gene in PAs; 90% of cerebellar PAs and 50% of supratentorial PAs have a noted alteration in the *BRAF* gene.[5,42]

The most common point mutation in PAs is the $BRAF^{V600E}$ mutation, identified in 17% of pLGGs.[43] This mutation seems to demonstrate some

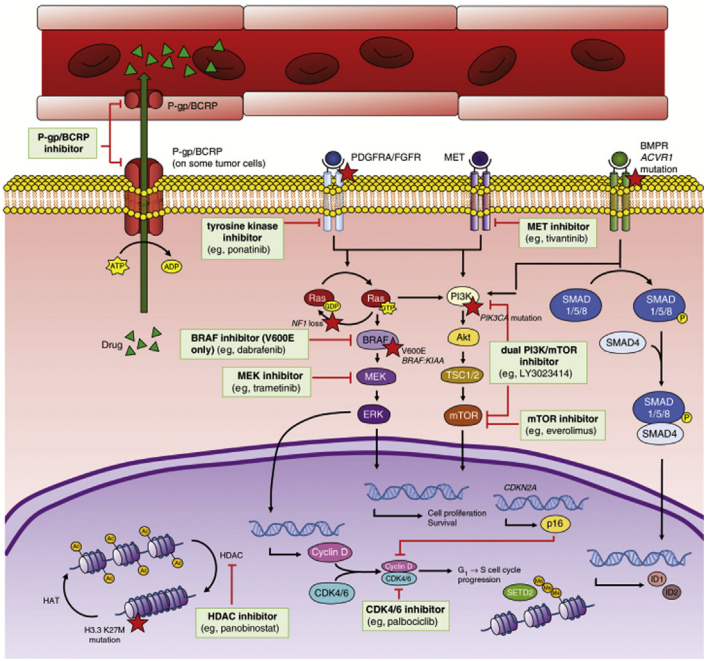

Fig. 2. Schematic of key pathways in pediatric glioma, including the frequent efflux of drugs from CNS tissue by efflux proteins, such as P-glycoprotein (P-gp) and breast cancer resistance protein. ACVR1, activin A receptor type 1; Akt, protein kinase B; BMPR, bone morphogenetic protein receptor; G1, gap 1 phase; HAT, histone acetyltransferase; ID1/2, inhibitor of DNA binding 1/2; MET, MET RTK; p16, cyclin-dependent kinase inhibitor 2A (protein); Ras, Ras family GTPase; S, synthesis phase; SETD2, SET domain containing 2; SMAD1/5/8, mothers against decapentaplegic homolog 1/5/8; SMAD4, mothers against decapentaplegic homolog 4. (*From* Miklja Z, Pasternak A, Stallard S, et al. Molecular profiling and targeted therapy in pediatric gliomas: review and consensus recommendations. *Neuro Oncol*. February 2019. https://doi.org/10.1093/neuonc/noz022 [81]; with permission. (Figure 1 in original).)

specificity to tumor location and is present in approximately 20% of extracerebellar PAs versus only 2% of posterior fossa PAs.[44] *BRAF*^{V600} mutations are not limited to PAs, and are, in fact, more common among other forms of pLGG, although they are seen sparsely among low-grade gliomas in adults.[40] Certain pediatric tumors are far more likely to carry *BRAF* alterations; *BRAF*^{V600} mutations have been found in an estimated 66% of PXAs,[44] 18% to 58% of GGs,[44–46] 30% of DNETs,[45] and 44% of desmoplastic infantile GGs/astrocytomas.[47]

PLGG patients harboring *BRAF*^{V600} mutations are likely to have a worse prognosis than those with wild-type *BRAF*, particularly in the setting of a concurrent *CDKN2A* deletion.[43] Although common in adults, malignant transformation is rare in pLGG. Among secondary pHGG, a majority have been found to harbor this particular combination of genetic alterations.[48] *CDKN2A* deletion was identified in 25% of pLGGs with the *BRAF*^{V600E} mutation, 60% of PXAs, and 16.7% of GGs.[43] The downstream effects include unopposed MAPK pathway activation and dysregulation of neuroglial cell proliferation via the mTOR pathway (see **Fig. 2**).[49]

Much clinical effort has focused on targeting *BRAF* mutations. Clinical trials of the first-generation BRAF inhibitor dabrafenib reported up to 44% responsiveness in pLGGs,[50] with subsequent studies echoing these results.[1,3,51] On the other hand, sorafenib, a multikinase inhibitor with impact on the activity of both wild-type BRAF and *BRAF*^{V600E}, caused rapid tumor progression due to paradoxic ERK activation.[52] Unfortunately, most of these therapies have not been as effective against *BRAF*^{V600E} tumors as with the *KIAA1549:BRAF* fusion tumors, and novel targeted drugs effective for both are required. Importantly, MAPK reactivation by Ras-independent activation of MEK and ERK or from EGFR signaling has resulted in eventual resistance to BRAF inhibitors.[53] Combinations of a BRAF inhibitor with MEK, EGFR, ERK, and EGFR inhibition are strategies that have begun testing in the clinical setting to prevent BRAF escape.

The second most common point mutation in supratentorial PAs involves *FGFR1* mutations.[39] These gene alterations appear to be common in gliomas of the nonastrocytic lineage, such as DNET and oligodendroglioma.[1,49,54] FGFR1 dysfunction triggers unregulated activation of both the PI3K and MAPK/ERK pathways.[1,49,54] Similarly, *ROS1* and anaplastic lymphoma kinase (ALK) fusions also result in constitutive activation of Ras/MAPK, PI3K, and Janus kinase (JAK)/signal transducer and activator of transcription proteins (STAT) pathways.[42] These alterations are seen mostly in infants and younger children, for both pLGGs and pHGGs.[42]

Immunotherapy

A comprehensive review of immunomodulatory therapies for pHGGs is beyond the scope of this topic. Particular examples of molecular genetic

targets of immunotherapy, however, serve to highlight the potential for future development. Chheda and colleagues demonstrated that cloned T-cell receptors could bind a presented antigen encompassing the H3K27M mutant peptide[55] and, in the corresponding peptide vaccine trial, identified a selective systemic expansion of H3K27M-reactive cytotoxic T lymphocytes in response to vaccination.[56]

EMERGING TARGETS AND THERAPIES UNDER INVESTIGATION

In developing targeted molecular therapies, 3 general approaches are common: (1) identification of patient populations who may benefit from existing targeted pharmaceuticals; (2) creating targeted therapies based on the molecular genetic profile of a particular patient population; and (3) individualizing treatment regimens to target molecular genetic findings specific to a patient's tumor.

Histone Alterations and Inhibitors of Histone Deacetylases

In pHGGs, mutations are estimated to involve histone modification or chromatin remodeling even more frequently than cell-cycle regulation and receptor tyrosine kinase (RTK)/Ras/PI3K signaling (see **Fig. 1**).[12] The H3K27M H3.3 (*H3-3A*) and H3.1 (*HIST1H3A/B/C*) are mutually exclusive events that result in loss of H3K27M trimethylation and hyperacetylation of the epigenome[10,24] and, ultimately, a variety of post-translational epigenetic alterations. H3.1K27M mutants tend to occur only in the brainstem and frequently are associated with *ACVR1* mutations (see **Fig. 1**). H3.3K27M mutants are found both in the pons or other midline intracranial locations, including the thalamus, and frequently co-occur with *TP53* and *FGFR1* mutations (see **Fig. 1**).[4,42]

One mechanism of oncogenesis appears to involve a shift of the downstream kinase to its active conformation and subsequent increased activity of bromodomain and extraterminal (BET) protein BRD4 which, in turn, activates an acetyltransferase, known as cyclic AMP response element–binding protein (CREB), and stimulates DMG super enhancer-driven oncogenes.[12,25]

The second described oncogenic mechanism is inhibition of 2 (PRC2) by sequestering enhancer of zeste homolog 2 (EZH2), thus interrupting histone H3 methylation and impacting downstream gene regulation.[1,26,57,58] The extent of PRC2 inhibition appears to depend on the concentration of H3K27M,[57] although PRC2 remains inhibited even after dissociation from chromatin.[57] This results in a significant decrease in global trimethylation of wild-type H3K27 and ultimately in unregulated proliferation of DMG cells.[10,57,59] At the same time, unusually high acetylation occurs at certain repetitive elements in the chromatin, boosting gene expression and stimulating, among many other possible foci, MYC-driven immune evasion.[24]

Several drugs targeting these epigenetic changes have been proposed, specifically that alter histone trimethylation, acetylation, or phosphorylation. Various mechanisms have been explored, including inhibition of H327 demethylase and methyltransferase to target trimethylation, inhibition of histone deacetylase (HDAC) and BET to target acetylation, and inhibition of phosphatase-related enzymes to target phosphorylation.[60] A phase I clinical trial describes achieving in vivo inhibition of H3K27M-mutant gliomatosis with panobinostat, an HDAC inhibitor (see **Fig. 2**).[22,61] This class of drugs (including vorinostat, entinostat, and valproic acid) currently is part of multiple phase I clinical trials, as monotherapy and in combination with other drugs, and via various delivery modalities to address systemic toxicity.[1,11]

Additional epigenetic therapies in early stages of development include a histone H3K27 demethylase inhibitor, EZH2 inhibitors, and CBP or BET bromodomain inhibitors.[1,25] Gene editing studies using cell culture of pediatric gliomas also has revealed that both K27M and G34R mutations cause gliomagenesis by inducing genes in the NOTCH pathway, raising the possibility of gamma secretase inhibitor targets among these tumors.[62]

In contrast to H3K27M DMGs, H3G34R/V gliomas are even less understood, and mechanisms of oncogenicity remain largely unknown. Early studies identify N-MYC up-regulation, H3K36 hypomethylation, and dysregulated telomere lengthening.[1,10,13,54] H3G34 R/V tumors also often harbor ATRX/DAXX mutations, which encode proteins that form part of a chromatin-remodeling complex that is essential for histone H3.3 incorporation into telomeres and heterochromatin.[4,6,10,42]

Growth Factor Mutations and Kinase Inhibitors

The remaining pHGGs with wild-type *BRAF*, *IDH*, and *H3-3A* demonstrate significant intratumoral heterogeneity, implicating many potential oncogene drivers.[4,28] Pharmacologic ACVR1 inhibitors are being investigated as a potential DMG therapy (see **Fig. 2**).[63] The *ACVR1* gene encodes a bone morphogenic protein type I receptor and initially was identified as part of fibrodysplasia ossificans progressive syndrome, although it does not predispose to cancer in that disease.[64] The BMP pathway plays an important role in regulating differentiation

and proliferation of astrocytic cells.[63] The mutation is found only in a minority of DMGs and likely is not an independent oncogenic driver.[10,12,64,65] The *ACVR1* mutation is associated with younger age, increased survival, and *HIST1H3B*, *PIK3CA*, and *PIK3R1* mutations (see **Fig. 1**).[12,13,64] The latter 2, along with mutations in growth factor receptor genes (ie, Platelet Derived Growth Factor Receptor Alpha (*PDGFRA*), *EGFR*, *FGFR*, and *ACVR1*), altered *PTEN* promoter methylation, and overexpression of *YB1*, all are known to act through amplification of cell proliferation via the RTK/Ras/PI3K pathway (see **Fig. 2**).[2,4,6,10,64]

Fusion Proteins and Other Potential Targets

The most common somatic alterations seen in infants appear to be gene fusion events. Many of the fusion genes involved in pHGGs appear to affect the MAPK pathway, and some are targetable by existing drugs. Among these, neurotrophic tyrosine kinase (*NTRK*)*1/2/3* fusion events appear to be extremely common,[12,39,40] as are *ALK, ROS1*, and mesenchymal epithelial transition factor (*MET*) gene fusions.[66] *RTK* gene fusions in infant gliomas of differing histologies have been reported.[67–76] Additionally, studies have found *MYBL1* amplification and/or rearrangement (41% of DAs) and *MYB-QKI* fusion (87% of angiocentric gliomas) to have a predilection for astrocytic pLGGs.[1,49,54] Alterations in the *MYB* gene lead to structural changes, possibly driving oncogenesis, although the mechanism is not fully understood.[13] Certain DAs exhibit concomitant *BRAF* alterations.

Mutations in transcription regulators, such as MYC amplification, have been described and lend themselves to a poor prognosis.[1,2,10,12] The *PPM1D* gene, often overexpressed in medulloblastoma, has been found to affect a gain-of-function in DMG that attenuates activity of p53 and DNA damage protein *CHK2*.[10,13,77,78] Other genes contributing to p53 function with mutation potential include *CHK2* and *ATM*.[13] *TP53* mutations are more common in DMG but also can occur in hemispheric pHGG (see **Fig. 1**).[64] Finally, 59% of pHGG carry mutations leading to cell-cycle dysregulation, including *TP53* and G1 checkpoint regulators (*CCND*1, *CCND*2, and *CCND*3; *CDK4*; and *CDK6*) (see **Fig. 2**).[2,12,64]

Second-generation ALK inhibitors (ceritinib, alectinib, brigatinib, and ensartinib) have exhibited favorable efficacy and safety profiles, with lorlatinib having the best intracranial activity.[2] Other ongoing clinical trials for pHGGs include TRK inhibitors (larotrectinib),[2,12,68] with promising results so far in mouse models without additional mutations required, and PDGFRA inhibitors (crenolanib and dasatinib), the latter also being investigated in combination with c-MET (a MET proto-oncogene) and ALK inhibitor crizotinib (see **Fig. 2**).[1,2,77,79] Increased sensitivity to palbociclib, a CDK4/6 inhibitor, was observed in H3K27M versus wild-type tumors.[80]

CLINICAL CHALLENGES AND FUTURE DIRECTIONS

- Low-grade gliomas in children pose the unique challenge of balancing the opportunity for long-term tumor control with protection from treatment-induced morbidity in the highly sensitive central nervous system.
- Higher-grade gliomas in children pose perhaps the greatest challenge in pediatric oncology today. Therapeutic options are limited due to toxicity and morbidity. Molecular heterogeneity and intrinsic mechanisms of treatment resistance result in universal recurrence. The relative scarcity of these tumors makes developing therapies difficult to assess through clinical trials.
- Molecular genetic profiling of pediatric gliomas has identified valuable prognostic information, has confounded previously held assertions regarding the biology of these entities, and has identified targeted therapy options.
- Radiotherapy generally should be avoided in patients younger than 3 years of age as well as in patients with genomic tumor predisposition, such as NF1, due to high risk of developmental delay, neurologic deficits, vision impairment, endocrine dysfunction, and radiation-induced malignancies.
- It is recommended to analyze each brain tumor sample for the presence of a BRAF alteration because there are promising therapies on the horizon against this oncogenic driver.

SUMMARY

The clinical impact of prior investigational therapy trials in pediatric glioma has been limited. The standard of care for many of these tumors remains unchanged over decades, with stagnant survival outcomes. Molecular genetic characterization of pediatric gliomas already, in a short amount of time, has revealed new potential therapeutic targets, many of which already are under investigation in clinical trials. Although understanding of the exact mechanisms linking genetic and epigenetic alterations in pediatric gliomas has only begun to scratch the surface, tremendous progress has been made in the past decade. Lessons learned from NGS efforts include the existence of significant intratumoral and intertumoral heterogeneity

and the value of employing combined targeted therapies to simultaneously affect multiple prominent oncogenic pathways. Furthermore, transition to an integrated histopathologic-molecular genetic approach to pediatric glioma characterization is likely to alter the therapies offered to patients. Improved understanding of cellular mechanisms and gene expression regulation will guide investigatory efforts to identify the most effective, and least toxic, therapies for these devastating pathologies.

CLINICS CARE POINTS

- Low-grade gliomas in children pose the unique challenge of balancing the opportunity for long-term tumor control with protection from treatment-induced morbidity in the highly sensitive central nervous system.
- Molecular genetic profiling of pediatric gliomas has identified valuable prognostic information, has confounded previously held assertions regarding the biology of these entities, and has identified targeted therapy options.
- Higher-grade gliomas in children pose perhaps the greatest challenge in pediatric oncology today. Therapeutic options are limited due to toxicity and morbidity. Molecular heterogeneity and intrinsic mechanisms of treatment resistance result in universal recurrence. The relative scarcity of these tumors makes developing therapies difficult to assess through clinical trials.
- It is recommended to analyze each brain tumor sample for the presence of a BRAF alteration because there are promising therapies on the horizon against this oncogenic driver.
- Radiotherapy generally should be avoided in patients younger than 3 years of age as well as in patients with genomic tumor predisposition, such as NF1, due to high risk of developmental delay, neurologic deficits, vision impairment, endocrine dysfunction, and radiation-induced malignancies.

DISCLOSURE

The authors have no conflicts relevant to this manuscript to disclose. The authors of this article have no financial conflict of interest to disclose.

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