Journal of Neuro-Oncology
https://doi.org/10.1007/s11060-020-03529-1

TOPIC REVIEW

# Molecular markers and targeted therapy in pediatric low-grade glioma

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Received: 3 April 2020 / Accepted: 4 May 2020


## Abstract

**Introduction** Recently discovered molecular alterations in pediatric low-grade glioma have helped to refine the classification of these tumors and offered novel targets for therapy. Genetic aberrations may combine with histopathology to offer new insights into glioma classification, gliomagenesis and prognosis. Therapies targeting common genetic aberrations in the MAPK pathway offer a novel mechanism of tumor control that is currently under study.

**Methods** We have reviewed common molecular alterations found in pediatric low-grade glioma as well as recent clinical trials of MEK and BRAF inhibitors.

**Results** In this topic review, we examine the current understanding of molecular alterations in pediatric low-grade glioma, as well as their role in diagnosis, prognosis and therapy. We summarize current data on the efficacy of targeted therapies in pediatric low-grade gliomas, as well as the many unanswered questions that these new discoveries and therapies raise.

**Conclusions** The identification of driver alterations in pediatric low-grade glioma and the development of targeted therapies have opened new therapeutic avenues for patients with low-grade gliomas.

**Keywords** Pediatric brain tumor · Low-grade glioma · Targeted therapy · Molecular markers

## Introduction

Recent scientific advances have redefined the biological landscape of pediatric low-grade gliomas (pLGG). The identification of molecular alterations, most commonly in the MAPK pathway, that drive tumor growth in many of these tumors has led to novel classification of many of these tumors based on the combination of histopathology and genetic abnormalities. These advances have paved the way for targeted therapies that have significantly expanded the therapeutic options for children with pLGG and may change the standard management of these diseases in the future.

## Epidemiology and clinical management

Low-grade gliomas account for roughly one-third of all pediatric brain tumors and are the most common brain tumor in children [1, 2]. pLGG frequently arise in the posterior fossa but may develop throughout the brain and spine particularly in supratentorial or midline structures. Although histologically similar, low-grade gliomas occurring in children are biologically distinct from their adult counterparts.

Outcomes following treatment of pLGG are generally excellent, with 10-year overall survival of 96% for pilocytic astrocytoma and 85% for other low-grade gliomas [3]. However, despite the excellent prognosis, patients are frequently left with residual deficits caused by either their tumors or tumor-targeting therapies. These may include neurosensory deficits, endocrinopathies, motor weakness, and difficulty with coordination or cognition [4]. As a result, current therapy is designed to maintain this excellent prognosis while enhancing functional outcomes and reducing therapy-related complications.

Complete surgical resection, when feasible, may be curative for pLGG, but even incomplete resection may lead to prolonged tumor dormancy [5]. For gliomas that cannot be treated with surgery alone, additional therapy may be used

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Published online: 12 May 2020

to halt tumor progression. Radiotherapy for pLGG results in excellent 5-year progression free and overall survival of 87% and 96% [6]; however, radiotherapy is often avoided in young children with low-grade glioma due to substantial late effects and risk of second malignancy [6–8]. Instead, chemotherapy is frequently used in young children with progressive or incompletely resected low-grade glioma to delay or obviate the need for radiotherapy. Carboplatin-based regimens are frequently relied upon as frontline therapy and have demonstrated 3-year progression free survival between 52 and 83% [9–11]. Alternative chemotherapy regimens, including vinblastine or the combination of thioguanine, procarbazine, lomustine and vincristine (TPCV), among others, have also been used with similar efficacy [12–16]. Although survival remains excellent for children with pLGG, recurrent or progressive tumors may require multiple treatment regimens which may lead to cumulative adverse events and deficits.

## pLGG morphology

pLGGs exhibit a broad spectrum of histopathologies generally characterized by glial or mixed glial-neuronal morphological features. The vast majority lack overtly high-grade findings such as necrosis, elevated mitotic activity, or glomeruloid microvascular proliferation, and accordingly are classified as either WHO grade I or II [17]. Specific histopathological patterns that have historically corresponded to WHO-defined disease entities include pilocytic and pilomyxoid astrocytoma, which together represent the most common pLGGs, along with pleomorphic xanthoastrocytoma (PXA), ganglioglioma, and dysembryoplastic neuroepithelial tumor (DNET) [18] (Fig. 1a–f). Recent integrated molecular profiling has facilitated the delineation of additional diagnostic subclasses such as angiocentric glioma, polymorphous low-grade neuroepithelial tumor of the young (PLNTY; Fig. 1g), and isomorphic diffuse glioma [19–21]. Nevertheless, equivocal and/or overlapping histological patterns can hamper definitive morphologic classification [22], even at the level of distinguishing classically circumscribed lesions (e.g. pilocytic astrocytoma, ganglioglioma) from their more infiltrative counterparts (e.g. PLNTY, isomorphic diffuse glioma, diffuse glioma). Descriptive terms, such as low-grade glioma, low-grade astrocytoma, or low-grade glioneuronal tumor are often employed in these contexts. Moreover, infiltrative pLGG variants (e.g. low-grade diffuse gliomas), particularly in adolescents and young adults, must be effectively distinguished from their more prognostically ominous adult counterparts, the diffuse astrocytoma and oligodendroglioma, to ensure appropriate clinical management.

These considerations underscore the singular importance of molecular markers for the optimal classification pLGGs and clinical management of affected patients. As in many other areas of cancer biology, comprehensive molecular profiling has greatly clarified the molecular pathogenesis of different pLGG variants, while also revealing avenues for therapeutic development [23]. We describe the most clinically impactful pLGG-associated molecular alterations below. As we shall see, many exhibit notable and even disease-defining levels of enrichment in association with specific histopathological patterns (Table 1). However, few if any are entirely restricted to one morphological entity. As such, precise pairings of molecular alterations and cellular histiogeneses likely underlie the biological distinctions delineating pLGG entities.

## BRAF abnormalities

Abundant work has repeatedly implicated mitogen-activated protein kinase (MAPK) pathway alterations as central to the pathogenesis of multiple pLGG variants [24, 25]. Among other functions, the MAPK signaling network conveys cellular growth and proliferation cues from receptor tyrosine kinases (RTKs) to downstream transcriptional and metabolic effectors [26], and genes encoding many of its core components are recurrently altered across the broad spectrum of human neoplasia [27]. The B-Raf proto-oncogene (*BRAF*) encodes the MAPK pathway constituent most frequently altered in pLGG, with two specific gene abnormalities predominating over all others. The activating valine to glutamic acid mutation (*BRAF* V600E) exhibits notable promiscuity in its strong associations with PXA (> 60%) [28, 29], ganglioglioma (18–45%) [28, 30, 31], and other pLGG entities (e.g. pilocytic astrocytoma, PLNTY) [20, 28, 30]. Oncogenic fusions coupling the constitutively active C-terminal domain of *BRAF* with *KIAA1549* represent a second highly recurrent pLGG-associated *BRAF* alteration, arising in the majority of pilocytic astrocytomas [32, 33]. As such, although primarily restricted to this one histopathological pattern, *KIAA1549-BRAF* fusions are the single most frequent molecular alteration impacting pLGG. A variety of "non-canonical" fusions coupling BRAF with alternative partners have also been described, albeit at much lower frequency [23]. While these fusions are thought to have similar biological consequences to *KIAA1549-BRAF* and also arise primarily in pilocytic astrocytoma, the precise anatomical localization, patient age distribution, and histopathological pattern exhibited by their associated tumors are somewhat more variable than those seen in canonical pilocytic astrocytoma. Above and beyond *BRAF* V600E and *BRAF* fusions, rare pLGG cases documenting *BRAF* duplications and alternative point mutations have also been reported [34, 35].

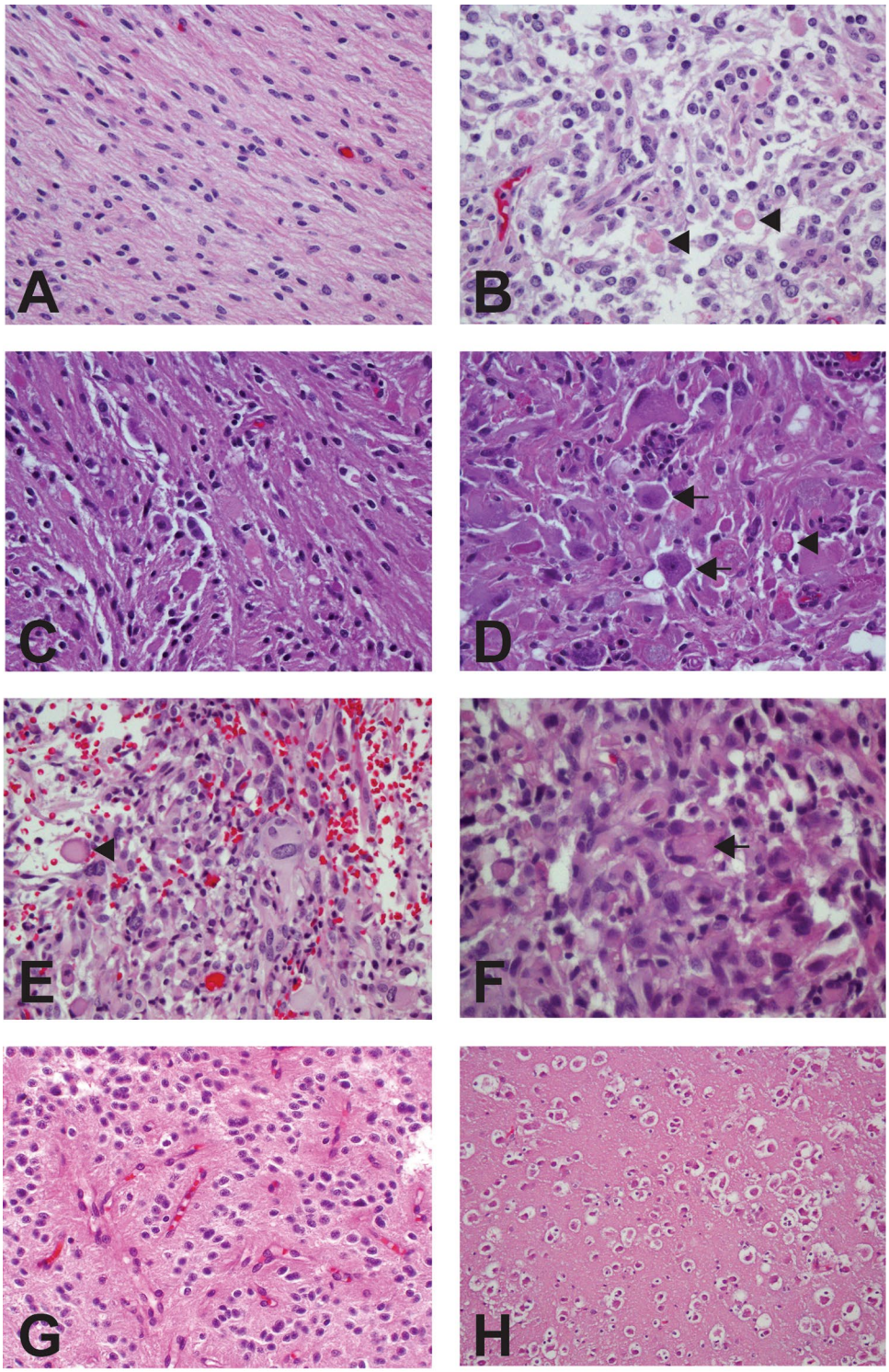


**Fig. 1** Morphological features of pediatric low-grade glioma. Pilocytic astrocytomas exhibit biphasic architecture, with packed "piloid" regions consisting of bipolar astrocytic tumor cells (**a**) admixed with more loosely arranged areas in which tumor cells demonstrate more stellate morphology (**b**). Eosinophilic granular bodies (arrowheads) and Rosenthal fibers are characteristic. Gangliogliomas exhibit variable combinations of glial and neuronal morphologies (**c**–**d**). Gangliocytic forms (arrows) and eosinophilc granular bodies (arrowheads) are characteristic. PXAs consist of pleomorphic astrocytic tumor cells (**e**–**f**) that often exhibit xanthomatous vacuolization (arrow) along with eosinophic granular bodies (arrowhead). While variable in their histopathology, PLNTYs typically exhibit features similar to low-grade oligodendrogliomas with round to oval nuclear monomorphism and perinuclear halos (**g**). MVNTs characteristically demonstrate areas of gangliocyte-like cells with abundant eosinophilc cytoplasm and neuronal nuclear morphology loosely arranged within a vacuolated background (**h**)

## FGFR abnormalities

Abnormalities involving fibroblast growth factor receptor (*FGFR*) genes represent highly recurrent molecular alterations across a broad spectrum of pLGG [24]. *FGFR* family genes (*FGFR1-4*) encode highly conserved receptor tyrosine kinases (RTKs) that signal through the MAPK as well as phosphoinositide-3-kinase (PI3K) molecular networks downstream [36]. Fusions coupling the extracellular N-terminus of FGFR with the intracellular C-terminus of several different partner genes (e.g. *TACC1*, *TACC2*, *TACC3*, *CTNNA3*, *KIAA1598*), characterize multiple pLGG variants,

**Table 1** Molecular alterations commonly found in pediatric low-grade glioma

| Molecular alteration | Commonly associated diagnosis |
|---|---|
| BRAF V600 | Pleomorphic Xanthroastrocytoma, Ganglioglioma, pilocytic astrocytoma, PLNTY |
| *KIAA1549BRAF* and other *BRAF* fusion | Pilocytic astrocytoma |
| FGFR fusions and point mutations | Pilocytic astrocytoma, PLNTY, extraventricular neurocytoma, DNET, glioneuronal tumors, rosette forming glioneuronal tumor |
| NF1 | Pilocytic astrocytoma, diffuse astrocytoma, frequently of the optic pathway |
| KRAS mutations | Pilocytic astrocytoma |
| CRAF fusions | Pilocytic astrocytoma |
| MAP2K1 activating mutations | Multinodular vacuolating neuronal tumor |
| MYB fusions and amplifications | Angiocentric glioma |
| MYB and MYBL1 abnormalities | Diffuse astrocytoma and isomorphic diffuse astrocytoma |

and are thought to function through enhanced dimerization of the chimeric receptor, which in turn activates downstream signaling [37]. *FGFR3* fusions (most commonly *FGFR3-TACC3*), are recurrent alterations in IDH-wild type high-grade gliomas [38], but have also been reported in PLNTYs, as have multiple distinct *FGFR2* fusions (*FGFR2-KIAA1598* and *FGFR2-CTNNA3*) [20]. *FGFR2-CTNNA3*, in particular, has thus far only been identified as a potential oncogenic driver in PLNTY. Analogous fusions involving *FGFR1* are primarily associated with pilocytic astrocytomas [24], as well as low-grade neuroepithelial tumors classified as extraventricular neurocytomas [39]. Tyrosine kinase domain point mutations in *FGFR1* (N546K and N656E) are most commonly seen in DNET, glioneuronal tumors, and extracerebellar and midline variants of pilocytic astrocytoma, a subset of which may arise in association with the neurocutaneous syndrome encephalocraniocutaneous lipomatosis [40–43]. Early evidence suggests that *FGFR1*-mutant and *FGFR1*-fused pilocytic astrocytomas behave unfavorably relative to *BRAF*-altered counterparts [44]. *FGFR1* point mutations also represent defining molecular alterations in the rare rosette forming glioneuronal tumor (RGNT) [40]. Finally, genetic duplications of the *FGFR1* tyrosine kinase domain (*FGFR1-TKDD*) have been reported in low-grade diffuse gliomas as well as pLGGs with DNET, pilocytic astrocytoma, PXA, or even RGNT architecture [24, 41, 42, 45, 46].

## Other MAPK pathway abnormalities

A variety of other molecular alterations involving MAPK constituents also serve to upregulate pathway signaling in the context of pLGG. *NF1* encodes a negative regulator of Ras GTPases (e.g. KRAS, HRAS, NRAS) [47], important drivers of MAPK signaling. Germline loss-of-function mutations in *NF1* cause the tumor predisposition syndrome Neurofibromatosis Type I, which can feature both pilocytic and diffuse pLGG [48–51]. These gliomas have a predilection for the optic pathway and characteristically exhibit indolent behavior. Germline and sporadic *NF1* mutations are also associated with high-grade glioma, though the biology and mutational profile of these lesions appears to be distinct from their low-grade counterparts [48].

Activating mutations in *KRAS* and fusions involving the *BRAF* homologue *CRAF* arise in small minorities of pilocytic astrocytomas, and appear to function through MAPK pathway activation [24, 32, 42, 52–54]. Fusions involving the RTK-encoding genes *NTRK1-3* have been also reported in rare instances of pLGG [24, 42, 55], with their underlying biology reminiscent of *FGFR*-fused disease variants [56]. Finally, activating mutations in the MAPK pathway constituent *MAP2K1* are highly recurrent in multinodular vacuolating neuronal tumor (MVNT; Fig. 1h)[57], an unusual ganglioglioma variant [58]. Interestingly, a minority of MVNTs harbor unusual *BRAF* point mutations and *FGFR* fusions [57], highlighting once more the importance of MAPK signaling in pLGG pathogenesis.

## MYB/MYBL1 abnormalities

The myb proto-oncogene and myb-proto-oncogene like 1 genes (*MYB* and *MYBL1*) encode related transcription factors that regulate proliferation and differentiation in a variety of progenitor cell lineages [59]. Activating *MYB* abnormalities include 3′ fusion events, most commonly *MYB-QKI*, and whole gene amplification [21, 24]; both mechanisms have the effect of increasing levels of the transcribed MYB protein. By contrast, *MYBL1* is altered primarily by partial genetic duplication with truncation of the C-terminal regulatory domain [60]. pLGGs harboring *MYB* and *MYBL1* alterations tend to arise in young children and localize primarily to the cerebral hemispheres [61]. Histopathologically, *MYB* fusions and amplifications are defining molecular alterations in angiocentric glioma and both *MYB* and *MYBL1*

abnormalities are enriched in low-grade diffuse astrocytomas [24, 55], a subset of which likely represent the recently described isomorphic diffuse glioma [19].

## Other abnormalities of prognostic relevance

While most pLGGs behave indolently, specific subsets exhibit a more aggressive clinical course associated with recurrence and malignant progression. Recent work has revealed a defined set of molecular abnormalities enriched in these poorly performing subpopulations. An aggressive variant of pilocytic astrocytoma, termed anaplastic astrocytoma with piloid features (AAP), shares driving MAPK pathway activation with its low-grade counterpart [62]. However, its landscape of molecular alterations differs somewhat, featuring higher levels of *NF1* mutations at the expense of the *BRAF* and *FGFR1* abnormalities more commonly seen in conventional pilocytic astrocytoma. Moreover, AAPs are highly enriched in deletions involving cyclin dependent kinase inhibitor 2A (*CDKN2A*) and loss-of-function mutations in α-thalassemia mental retardation X-linked (*ATRX*) [62, 63]. The *CDKN2A* locus encodes two tumor suppressors, INK4A and ARF, that regulate the crucial retinoblastoma and p53 networks respectively [64], and *ATRX* inactivation has been repeatedly associated with pathological telomere maintenance, enabling cellular immortality [65, 66]. That both alterations confer aggressive behavior in pilocytic astrocytoma is not surprising, given their established associations with a variety of malignancies within and outside of the central nervous system (CNS) [67]. *CDKN2A* deletions are also highly recurrent features of anaplastic PXAs, where they invariably pair with driving *BRAF* alterations, most commonly *BRAF* V600E [68]. Interestingly, while *ATRX* mutations are relatively infrequent in anaplastic PXAs, activating alterations in *TERT*, either promoter mutations or amplification events, are highly recurrent. *TERT* encodes the catalytic core component of telomerase, the enzymatic activity chiefly responsible for adding DNA repeat sequences to telomeres [69, 70]. As such, enhanced *TERT* expression essentially phenocopies ATRX inactivation, promoting telomere maintenance and enabling unregulated cell division.

## Epigenetics

Comprehensive genomic characterization has in many cancers revealed a hitherto unappreciated prevalence of molecular alterations directly impacting the cellular epigenome [71], an amalgamation of DNA modifications, histones and their associated marks, and other chromatin binding factors that together directly regulate underlying gene expression. Epigenomic dysfunction has been implicated as a driving factor in multiple primary brain tumors, including gliomas [72]. Mutations involving isocitrate dehydrogenase 1 and 2 (*IDH1* and *IDH2*) and the H3.3 histone encoding genes *H3F3A* and *HIST1H3B* are particularly notable in this regard. IDH mutations induce a global DNA and histone hypermethylation phenotype, through the production of the oncometabolite 2-hydroxyglutarate [73, 74], while H3.3 mutations directly impact associated histone marks, chromatin accessibility, and underlying gene expression [75, 76]. While the results of these disruptive events are complex and cell type specific, a fundamental rewiring of normal developmental programs appears to underlie at least a significant portion of their gliomagenic sequelae. Despite the central roles played by IDH and H3.3 mutations in the biology of adult and/or high-grade glioma variants, these molecular alterations are only infrequently associated with pLGG. Specifically, recent reports have identified H3.3 K27M mutations in small subsets pilocytic astrocytoma and glioneuronal tumor [63, 77–79], all of which appear to behave more aggressively than non H3.3-mutant counterparts. Nevertheless, these pLGG variants are associated with more extended patient survival than typically seen in H3.3-mutant high-grade glioma.

More generally, epigenomic profiles have come to represent key disease markers in pLGG and across the spectrum of primary CNS neoplasia. In particular, global DNA methylation profiling delineates unique "fingerprints" that, in many cases, define brain tumor entities and have laid the groundwork for the systematic classification of pLGG [80]. Indeed, recent work has employed global methylation profiling in the characterization of isomorphic diffuse glioma [19], PLNTY [20], and AAP [62]. We expect that analogous strategies will continue to clarify the precise taxonomy of pLGGs in the coming years.

## Novel targeted therapies for pLGG

The discovery of driving genetic alterations in pLGG has led to targeted therapies, particularly focused on the MAPK pathway that is frequently altered in these tumors.

Selumetinib (AZD6244) is one orally available MEK1/2 inhibitor which has been extensively studied in pLGG. In a phase 1 study of selumetinib in 38 children with recurrent and refractory pLGG, the recommended phase 2 dose (R2PD) was determined to be 25 mg/m$^2$/dose twice daily [81]. Among 25 patients treated at the RP2D, 5 (20%) had a partial response and 2-year PFS was 69%. This data led to an ongoing phase 2 trial of selumetinib in children with progressive/recurrent glioma among six biologically and histologically-defined strata. Some data from this trial is now available. Among children with progressive/recurrent

pilocytic astrocytoma not associated with NF1 but with a BRAF alteration (KIAA1549BRAF fusion or BRAFV600 point mutation), 36% achieved a sustained partial response and the 2-year progression-free survival was 70%. Among children with NF1 and recurrent/progressive low-grade glioma, 40% achieved a sustained partial response and the 2-year progression free survival was 96% [82]. The most frequent grade 3/4 adverse events included elevated CPK (10%) and rash (10%). Strata containing tumors without BRAF alterations among children without NF1 have not been reported, but have demonstrated sufficient responses ($\geq 2$ responses among 16 subjects) to expand this cohort. These early reports suggest that MEK inhibitors may be effective in patients without commonly identified BRAF aberrations, potentially due to unidentified mutations that accelerate the MAPK pathway and are amenable to MEK inhibition. As a result of these studies, the Children's Oncology Group is conducting two phase 3 studies investigating selumetinib as frontline therapy for pLGG (ACNS1831 (clinicaltrials.gov identifier NCT03871257) and ACNS1833 (NCT04166409) which include children with and without NF1, respectively).

Trametinib, binimetinib, and cobimetinib are among other MEK inhibitors currently being investigated for use in pLGG [83, 84]. Published experience with these agents in low-grade glioma is more limited. However in early clinical trials of trametinib and binimetinib that included children with low-grade glioma, partial response and stable disease were frequently reported [83, 84]. Most MEK inhibitors seem to share common adverse events, including maculopapular or acneiform rash, paronychia, and diarrhea. MEK inhibitors have also been associated with cardiac dysfunction and ocular toxicities, although these have been observed mostly in adults [81, 85]. It is unclear how the frequency and severity of individual toxicities may differ between agents, or which agent will prove most efficacious against pLGG.

Direct inhibitors of BRAF, such as dabrafenib and vemurafenib, may be another promising therapy for pLGG. These agents are potent and selective inhibitors of BRAF kinases, and dramatic responses have been reported in pLGG that contain $BRAF^{V600}$ mutations [86, 87]. Ongoing studies are currently investigating the use of BRAF inhibitors for BRAF mutant pLGG (NCT02684058, NCT01748149). First-generation BRAF inhibitors (such as dabrafenib and vemurafenib) that target monomeric forms of BRAF should not be used for tumors with BRAF fusion where paradoxical activation may occur [88]. Fortunately, second-generation BRAF inhibitors bypass this effect and may be used for BRAF fusions or mutations. Early clinical trials with these agents are ongoing (NCT 03429803, NCT02428712) but may show promise [89].

## Conclusion

As our understanding of molecular drivers of pLGG expands, many questions of how best to treat these tumors remain unanswered. Current studies will develop our understanding of MEK inhibitors, as well as the management of related toxicities. Because pLGG may be associated with significant morbidity, it will be important that these studies compare not only radiographic progression but also quality of life, toxicities and functional outcomes between conventional and targeted regimens to maximize these outcomes for patients. Understanding late effects of novel targeted therapies will be equally important as most children will survive their disease. Many pLGG will recur once targeted therapies are discontinued, prompting the question of how durable remissions can be achieved and how prolonged therapy may affect developing children. Finally, while many tumors may respond to MEK inhibition, new therapies or combinations outside the MAPK pathway may be required as novel tumor drivers are identified. The identification of driving alterations in pLGG and the development of targeted therapies have changed the treatment of childhood glioma. However, we have just begun to explore the new landscape of pLGG and what it may mean for future therapies.

**Author contributions** All authors contributed to the study conception and design. The first draft of the manuscript was written by PdB and JTH, and MF provided critical revisions of the work. All authors commented on previous versions of the manuscript, and read and approved the final manuscript.

**Funding** The authors have nothing to declare.

## Compliance with ethical standards

**Conflicts of interest** The authors declare they have no conflicts of interest.

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