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Tempered optimism: Advances in the precision medicine era for pediatric low-grade glioma

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Abstract

The clinical trial landscape of molecularly targeted treatments for pediatric low-grade glioma (pLGG) has created an exciting and hopeful era for both patients and clinicians alike. Despite numerous clinical trials investigating the use of targeted agents for pLGG, only two oral precision-based regimens for pLGG have received federal agency approval. However, enthusiasm surrounding recently completed early phase clinical trials has resulted in increased off-label prescribing practices beyond the federally-approved indications, despite a lack of phase 3 clinical trial data and an incomplete understanding of the long-term radiographic, functional outcomes, and toxicity for both approved and experimental therapies. These gaps in knowledge are critically important to consider when selecting therapies for patients with pLGG, as the prevention and reduction of late effects in pLGG survivors is crucial to prevent long-term morbidity. In this editorial by the clinical working group of the International pLGG Coalition, we discuss the landscape of molecularly targeted therapies for pLGG, outline the unanswered questions for the use of novel therapies in the management of pLGG, review the risks and benefits of early off-label use of targeted agents, and discuss the importance of patience and evidence-based clinical practice in the rapidly evolving era of precision medicine.

Key Points

- Gaps in knowledge remain regarding long-term efficacy and toxicity of precision-based therapies for pediatric low-grade glioma (pLGG).
- Adoption of novel agents for pLGG outside of approved indications or clinical trial setting requires careful consideration.

Pediatric low-grade glioma (pLGG) is the most common central nervous system tumor of childhood, representing 30%-40% of pediatric brain tumors.[1,2] Long-term survival rates for pLGG now exceed 90% with prognosis largely determined by tumor location and extent of surgical resection.[3,4] Yet while most children with pLGG will have favorable survival outcomes, many require intermittent treatment across childhood and into adulthood and suffer long-term sequelae of disease with chronic deficits in physical health and quality of life.[4,5] In the context of this chronic morbidity, increased emphasis has been placed on identifying novel therapies with equivalent or increased efficacy to cytotoxic chemotherapy and radiation but with decreased toxicity and less negative impact on quality of life.[6] The recent dramatic increase in understanding of the

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oncogenic drivers of pLGG has led to numerous interventional clinical trials of novel molecularly targeted therapies. Excitingly, a select few of these clinical trials have supported the first-ever federal approvals of oral precision-based therapies for pLGG, expanding treatment options beyond conventional chemotherapy and radiation.[7-9] However, while targeted therapies for pLGG are generating broad excitement, mature data for both the approved and experimental drugs is lacking, and off-label prescribing practices have increased despite this lack of understanding of long-term efficacy and toxicities. Further, many of these agents have been evaluated only in the context of early phase clinical trials for progressive or refractory pLGG and their role as frontline therapy is not yet defined.[8,10] Finally, the comparative effectiveness of many of these novel agents with well-studied, standard chemotherapy regimens is relatively unknown, as the requisite randomized clinical trials have not yet concluded or even been initiated. These unknowns are of utmost importance to consider when selecting therapies for patients with pLGG, as the prevention and mitigation of late effects in pLGG survivors is crucial to prevent long-term morbidity and negative impact on quality of life.[11] The objective of this editorial, developed by the clinical working group of the International pLGG Coalition (iPLGGc), is to provide an overview of the use of targeted agents for pLGG in the emerging era of precision-based therapy. This editorial was inspired by the robust debate and discussions surrounding the use of targeted therapies for pLGG at the 2024 iPLGGc meeting held in London, UK. The content of the manuscript is based on current evidence and ongoing discussions amongst multi-disciplinary members of the iPLGGc. The iPLGGc is a collaborative multi-disciplinary effort to address key issues in pLGG research and clinical care, including epidemiology, therapeutic development, and optimizing treatment strategies. Herein, we review the current landscape of molecularly targeted therapies for pLGG, highlight the unique challenges and unanswered questions in the management of pLGG with these novel therapies, consider the risks and benefits of early off-label use of targeted agents, and discuss the importance of equipoise in the rapidly evolving precision medicine landscape.

Molecular Landscape

PLGG represent a spectrum of distinct tumor subtypes with varying histology and molecular alterations.[12] Advances in molecular profiling techniques continue to refine our understanding and classification of these tumors, and in the recently updated 2021 WHO Classification of Tumors of the Central Nervous System, pLGG were further subdivided into three categories: pediatric-type diffuse LGG, circumscribed pLGG, and glioneuronal and neuronal tumors.[13] Prior versions of the WHO CNS classification categorized tumors primarily by histopathologic characteristics, whereas the WHO 2021 classification emphasizes integration of histology with molecular findings to increase diagnostic accuracy (Table 1).[13,14] The updated classification aligns with current trends in clinical practice, with increasing recognition of the importance of molecular characterization of pLGG for prognostication and selection of tumor-directed therapies.[15-17] Several recent large-scale efforts have described the spectrum of oncogenic drivers across pLGG subcategories, thereby expanding the opportunities for translation to targeted therapeutics.[12,17-21] Contrary to high-grade pediatric glioma, pLGG typically harbor a single oncogenic driver, most commonly resulting in hyperactivation of the mitogen activated protein kinase pathway (Table 1).[6] Approximately 50%-60% of sporadic pLGG harbor structural variants in the B-Raf proto-oncogene (*BRAF*) gene, such as the *KIAA1549*::*BRAF* fusion, which leads to constitutive activation of the MAPK pathway (Figure 1).[12] The second most common oncogenic driver, observed in 15 to 20% of pLGG, is a hotspot mutation in the *BRAF* gene (eg, $BRAF^{V600E}$ mutation).[12,22] Other common somatic alterations in sporadic pLGG include alterations in the fibroblast growth factor

Table 1. Prevalent molecular alterations described in the 2021 WHO Classification of Pediatric Diffuse Low-Grade Glioma, Circumscribed Astrocytoma Glioma, and Glioneuronal and Neuronal Tumors[a]

2021 WHO Classification		Characteristic alterations (frequency) [13,14]
Pediatric-type diffuse LGG	Diffuse low-grade glioma, *MAPK* pathway altered	BRAF p. V600E mutation (20%-40%)
		FGFR1 alterations (To be determined)
	Diffuse astrocytoma, *MYB*- or *MYBL1*-altered	MYB/MYBL1 structural variants (100%)
	Angiocentric glioma	MYB::QKI fusion (90%)
	Polymorphous low-grade neuroepithelial tumor of the young	BRAF p. V600E mutation (30%-40%)
		FGFR2/3 alterations (30%-40%)
Circumscribed astrocytic glioma	Pleomorphic xanthoastrocytoma	BRAF p. V600E mutation (80%-90%)
	Pilocytic astrocytoma	KIAA1549::BRAF fusion (70%-80%)
	Subependymal giant cell astrocytoma	TSC1/2 alterations (85%-95%)
	Astroblastoma, *MN1*-altered	MN1 structural variants (70%)
	Chordoid glioma	PRKCA p. D463H mutation (80%-90%)
Glioneuronal and neuronal tumors	Ganglioglioma	BRAF p. V600E mutation (40%-50%)
	Dysembryoplastic neuroepithelial tumor	FGFR1 internal tandem duplication (40%-60%)

[a]Abbreviations: LGG low grade glioma; BRAF B-Raf proto-oncogene; FGFR fibroblast growth factor receptor; MN1 meningioma 1; MYBL1 MYB proto-oncogene like 1; TSC tuberous sclerosis complex; PRKCA protein kinase C alpha.

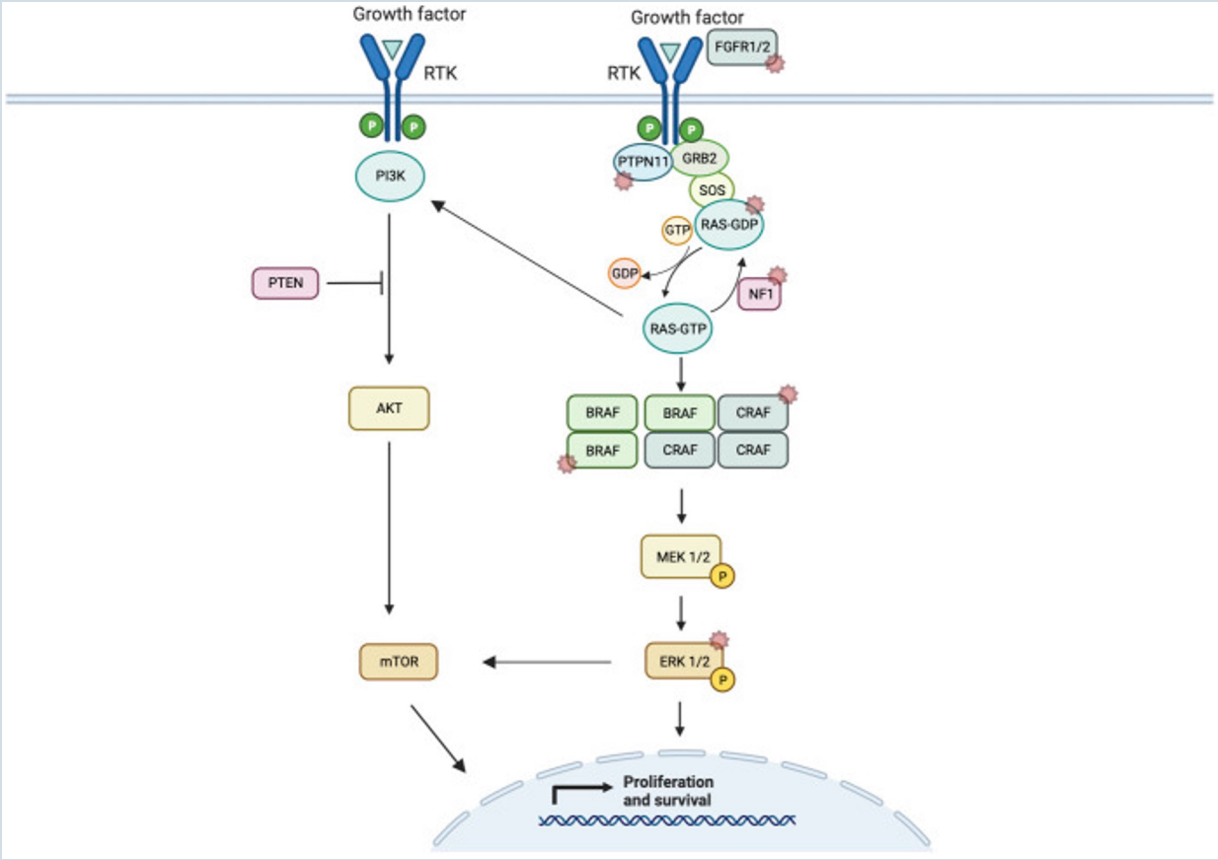

Figure 1. Schematic representation of Ras/MAPK pathway signaling. Starred pathways indicate alterations implicated in tumorigenesis (Figure reprinted with permission from Trinder et al[76]).

receptor (*FGFR*) gene, such as structural and single nucleotide variants of *FGFR1/2* including *FGFR1* tyrosine kinase domain duplication and *FGFR1*::*TACC1* fusion, resulting in activation of the RAS/MAPK and PI3K/AKT/mTOR pathways.[21] Rarer recurrent alterations have been identified in specific subtypes of pLGG such as *MYB/MYBL1* alterations in pediatric-type diffuse glioma.[12,17,23]

Select germline cancer predisposition syndromes result in an increased risk for the development of pLGG, with different prevalence rates of somatic oncogenic drivers in these populations.[24] Nearly 20% of children with the tumor predisposition syndrome neurofibromatosis type 1 (NF1) will be diagnosed with a LGG. The spectrum of molecular alterations in NF1-LGG is distinct from sporadic pLGG, with most NF1-pLGG harboring bi-allelic *NF1* inactivation as the only genetic abnormality. Only an estimated 11% of NF1-pLGG requiring biopsy or surgical intervention demonstrate additional mutations beyond the *NF1* gene, such as *FGFR1* variants.[19] As surgical biopsy is rarely performed prior to treatment of NF1-LGG and only a limited subset of NF1-LGG will ever require biopsy or resection, the incidence of these additional variants across all NF1-LGG is likely much lower. Therefore, the therapeutic approach to NF1-LGG is distinct from sporadic pLGG due to differences in natural history, molecular alterations, treatment response, and risk of associated toxicities.[25-27]

Treatment Approach

The treatment paradigm for pLGG has evolved significantly in recent decades, however surgical resection remains the mainstay of therapy for most patients with pLGG. The primary goal of surgery is to obtain a histopathologic diagnosis and achieve the maximal safe resection, as progression free and overall survival for completely resected pLGG is favorable with a low likelihood of tumor recurrence.[3,28] For the pLGG that are residual, recurrent, and/or not amenable to complete resection without significant morbidity, additional therapy is often required. There are several commonly utilized and well-studied frontline cytotoxic chemotherapy regimens, including carboplatin with vincristine (CV), carboplatin monotherapy, vinblastine (VBL) monotherapy, bevacizumab with or without irinotecan, and thioguanine, procarbazine, lomustine, and vincristine (TPCV).[29-33] At present, cytotoxic chemotherapy is considered the standard frontline treatment for children with symptomatic or progressive pLGG requiring therapy, with the exception of *BRAF*^{V600E}-mutated pLGG. In treatment-naïve, sporadic pLGG, 5-year PFS rates after frontline chemotherapy are approximately 40%.[30,31] Thus, over half of children with both sporadic and a substantial minority with NF1-associated pLGG may require additional treatment regimens for

progressive disease.[34] Radiation therapy, once a primary form of post-surgical adjuvant therapy, is now considered only after progression through multiple systemic and/or molecularly targeted treatment regimens. However, there is no standard of care for recurrent or progressive pLGG requiring additional therapy, and choice of therapy in this setting is often institution or even provider specific.

Historically, systemic treatment for progressive or recurrent pLGG was largely limited to intravenous cytotoxic chemotherapies. However, increased understanding of the molecular drivers of pLGG has unveiled several therapeutic targets in pLGG, with subsequent translation in numerous early phase clinical trials. Based on the prevalence of alterations involving the Ras-MAPK pathway, recent molecularly guided pLGG clinical trial efforts focused predominantly on therapeutic targets of this pathway. Excitingly, due to the successes of these efforts, two oral therapies have been recently approved by regulatory agencies for the treatment of pLGG. These include the type I RAF inhibitor dabrafenib in combination with the MEK inhibitor trametinib for frontline and subsequent treatment of *BRAF*^{V600E}-mutant pLGG, and the type II RAF inhibitor tovorafenib for recurrent/refractory pLGG with *BRAF* alterations.

Initial interest in the combination of BRAF and MEK inhibition for pLGG was largely derived from studies in adult cancers such as *BRAF*^{V600E}-altered melanoma. In the phase 1/2 study of dabrafenib plus trametinib for *BRAF*^{V600E}-altered relapsed/refractory pLGG, 25% (95% CI: 12-42) of evaluable participants achieved an objective response [OR; complete (CR) or partial response (PR)] with a PFS estimate of 36.9 months, compared to 15% OR (95% CI: 2-45) in participants treated with trametinib monotherapy.[9] In a subsequent trial randomizing participants to dabrafenib and trametinib versus CV for treatment-naïve *BRAF*^{V600E}-altered pLGG, participants receiving the targeted combination demonstrated an ORR (CR or PR) of 47% (34/73 participants) compared to ORR of 11% (4/37) receiving conventional chemotherapy.[7] Based on these impressive results, the Food and Drug Administration (FDA) and European Medicines Agency granted approval of dabrafenib in combination with trametinib in 2023 for the treatment of pediatric patients 1 year of age or older with *BRAF*^{V600E}-altered LGG, thereby establishing this regimen as a standard of care option for treatment naïve *BRAF*^{V600E}-altered pLGG requiring systemic therapy.[35]

In the recent phase 2 trial (FIREFLY-1) of the type II RAF inhibitor tovorafenib for participants with relapsed/refractory pLGG harboring alterations such as *BRAF*^{V600E}, *KIAA1549*::*BRAF* fusion, and other noncanonical BRAF oncoproteins, the ORR per Response Assessment in Pediatric Neuro-Oncology (RAPNO) criteria was 51% (95% CI: 40-63; 37% partial response, 14% minor response).[8] The ORR was nearly identical in tumors harboring BRAF fusions [52% (33/64); 95% CI: 39-64] versus *BRAF*^{V600E} mutations [50% (6/12); 95% CI: 21-79]; although the sample size of *BRAF*^{V600E} mutated tumors was relatively small. Based on these results, the FDA granted accelerated approval to tovorafenib in 2024 for patients 6 months of age and older with relapsed/refractory pLGG harboring a BRAF fusion or rearrangement or *BRAF*^{V600E} mutation.[36]

While the availability of new targeted treatment options for pLGG has created an exciting era for both patients and clinicians alike, there remain significant unknowns regarding the long-term outcomes of these agents, including the efficacy, durability of response, functional impact, and late effects. This also includes toxicity and impact on the natural history of the tumor, specifically whether these treatments alter expected tumor senescence. Importantly, while these novel therapies have demonstrated promise in early phase clinical trials for pLGG, hastened use and modification of existing treatment paradigms based on early interpretation of the literature may risk inferior long-term outcomes. Therefore, despite their exciting promise, caution should be exercised in the off-label use of targeted therapies. Clinicians should be aware of the current indications for use and limitations in the current data for these novel therapies. Overall, the pros and cons of early, off-label utilization of targeted agents should be carefully considered and are herein discussed.

Support for Early Utilization of Novel Targeted Therapies

The use of novel targeted therapies in pLGG, prior to completion of phase 3 studies or maturation of early phase clinical trial data, is gaining momentum and is supported by strong biological rationale and exciting early clinical trial data. Molecular profiling is increasingly feasible at diagnosis and initiating treatment with therapy tailored to the tumor's genetic driver may maximize therapeutic response while minimizing exposure to broad-spectrum cytotoxic agents. For example, the dabrafenib-trametinib combination showed clinical benefit (defined as complete or partial response or stable disease for 24 weeks or greater) in 86% of participants with *BRAF*^{V600E}-mutant pLGG, compared to 46% in those receiving conventional chemotherapy, thereby demonstrating clinical rationale for precision-based therapies in this population.[7] This precision medicine approach aligns with modern oncology principles and is becoming the standard of care in several adult and pediatric malignancies.

A major advantage of the targeted therapies is their oral administration, unlike traditional intravenous regimens. Oral medications can be taken at home, reducing the burden of frequent hospital and clinic visits and eliminating the need for central venous access. This home-based treatment model may improve quality of life for families and lower healthcare costs associated with frequent outpatient visits. It is particularly advantageous for families living far from pediatric oncology centers and in regions or countries with limited access to intravenous chemotherapy. Of note, the advantage of oral administration can also be a limitation; adherence to a daily oral therapy can be quite challenging and therapeutic drug monitoring to assess compliance is not standard of care. In addition, while most clinical trials are conducted in North America, Europe, and Australia, the majority of children with pLGG reside in low- and middle-income countries (LMICs), where access to traditional chemotherapy is often restricted. In such contexts, oral targeted therapies may offer a paradigm-shifting solution.[37] However, access to these therapies remains a significant barrier. In addition, the high cost of these novel agents is a serious constraint, and financial subsidies and industry incentives will be necessary to

allow for access for patients in these regions. Cost effectiveness analyses and patients' satisfaction comparisons conducted within both developed countries and LMICs are needed to further evaluate the routine use of these targeted agents.[38]

In both clinical trials and real-world practice, patients with *BRAF*-altered pLGG have shown significant tumor shrinkage and neurological improvement sometimes occurring rapidly after initiation of targeted treatments. In the randomized trial of dabrafenib and trametinib, most responses occurred within four months of treatment initiation.[7] Similarly, participants with pLGG treated with tovorafenib through FIREFLY-1 demonstrated a median time to response of 5.5 months.[39] Early tumor reduction can alleviate symptoms due to mass effect, such as headaches, visual impairment, and motor deficit, thereby improving quality of life and potentially reducing the need for interventions like shunt placement. In studies of tovorafenib, 31% (11/35) of participants with optic pathway glioma demonstrated improved visual acuity (VA), with VA per eye improving in 27% (14 of 52 eyes), thus mirroring rates of visual response observed with conventional chemotherapy. In the phase 2 study of dabrafenib and trametinib, VA per eye was improved in 34% (14 of 41 eyes) in the 25 patients treated with dabrafenib plus trametinib vs. 11 % improvement (2 of 18 eyes) in patients treated with chemotherapy.[7,40] However, it is important to note that these functional outcomes are based on limited participant numbers.

Finally, conventional chemotherapies are associated with well-known acute toxicities, including cytopenias and immunosuppression. Most patients treated with CV experience vincristine-induced neuropathy to varying degrees.[41] In contrast, targeted therapies exhibit a different spectrum of AEs, such as dermatological reactions, fever, or gastrointestinal disturbances, that are often grade 1 or 2. In the randomized trial of dabrafenib with trametinib versus CV for pLGG, grade 3 or higher AEs occurred in only 47% of the patients receiving targeted therapy compared to 94% of those receiving chemotherapy.[7] However, a grade 2 AE with an oral agent that is poorly managed may be more adherence-limiting than a brief grade 3 event with intravenous chemotherapy. Future, prospective multi-arm clinical trials will be required to explore the impact of this further.

Cons to Early Utilization of Targeted Therapies

It is important to note that outside of combination dabrafenib-trametinib for *BRAF*^{V600E}-mutant pLGG, the role of MAPK pathway inhibitors as *first-line* treatment in pLGG is still being actively evaluated in multiple prospective clinical trials (NCT04166409, NCT04923126, NCT05180825). However, given the promising responses observed in early-phase trials in the recurrent setting, there is increasing real-world incorporation of these novel therapies as upfront treatments for pLGG patients outside the trial setting, primarily through off-label prescribing of these drugs. Despite practitioners' increasing familiarity and comfort using these agents, there remain significant reservations about this practice given the many clinical and biologic questions that remain unanswered.

Risks

The acute toxicity profiles of MAPK-targeted agents are now well described in the pediatric setting, most commonly involving skin, gastrointestinal, cardiac, fatigue, weight gain, and rarely retinal toxicity. While these adverse effects (AE) are often felt to represent a more palatable toxicity profile than traditional chemotherapy, our understanding of the less common acute toxicities is still evolving, highlighting the need for continued study of both AE and patient reported outcomes in a controlled setting. For example, treatment with tovorafenib resulted in unexpected reductions in growth velocity in a proportion of participants enrolled on the phase 2 FIREFLY-1 trial.[8]This represented a new AE distinct from previously studied MAPK pathway inhibitors. It is postulated that the pharmacologic inhibition of CRAF, the primary RAF isoform expressed in hypertrophic chondrocytes, leads to suppression of linear growth velocity.[42] Data to date suggests this effect is reversible, with restoration of growth velocity observed in most participants, however the long-term implications on bone health are not yet fully understood, particularly for patients treated in peri-puberty.[42] Comparable experiences of unexpected toxicities in other targeted therapies emphasizes the need for cautious examination of agents in a trial setting.[43,44] For example, FGFR inhibitors unexpectedly caused serious bone toxicities (such as long bone fractures and slipped capital femoral epiphyses in the setting of increased growth velocity) in pediatric patients when used both off-label for *FGFR*-altered gliomas and in clinical trials in other disease settings.[45,46] This had not previously been appreciated in adult FGFR inhibitor studies or a phase 2 study enrolling patients 12 years and over, likely because most of those patients had fused growth plates and therefore had minimal vulnerability to this specific toxicity.[47] These toxicities were best observed and understood over time and within the context of controlled clinical trials.

It should also be noted that little is known about the long-term toxicity of these drugs, and it will be some years before this late effects data matures. In the adult population, BRAF inhibitors with and without MEK inhibitors have been used since the mid-2010s allowing for longer follow up than in pediatric trials. Importantly and unexpectedly, inhibitor use has been associated with the late development of malignant skin lesions, as well as other secondary conditions, including RAS-mutant leukemia and colorectal cancer.[48-50] It is postulated that these events are driven by RAF inhibitor-induced paradoxical MAPK pathway activation leading to non-mutant RAF isoform homo- and heterodimerization.[48-50] In children, use of BRAF and MEK inhibitors has been associated with the development of a variety of skin lesions, including reports of changes in melanocytic nevi, eruptive melanocytic nevi, and squamous cell carcinoma.[51,52] Given these observed late effects, there is concern in the field about the potential risk for late malignant transformation of these skin lesions, particularly with cumulative ultraviolet oncogenic exposure during childhood. For pLGG,

where long-term survival is excellent, preventing future treatment-related toxicities is of crucial importance and many are concerned that we do not yet know the long-term implications nor quantifiable risks of targeted inhibitor use in childhood.

Further justifying the investigation of these novel agents in controlled, trial-based settings are ongoing gaps in our biologic understanding of targeted agents, which can have unexpected implications. An important example of this is the experience of sorafenib, a multi-kinase inhibitor including RAF in its inhibitory profile, which was investigated in a phase 2 trial of patients with progressive pLGG. Of 11 patients enrolled, 9 (82%) experienced early tumor progression, prompting study termination.[53] It was subsequently demonstrated *in vitro* that type I RAF inhibition resulted in paradoxical activation of MAPK signaling in cell lines expressing *KIAA1549-BRAF* due to homodimerization and heterodimerization of nonmutant RAF isoforms.[54,55] Therefore, for the majority of pLGG which are driven by BRAF fusions, type I RAF inhibitors can cause paradoxical MAPK activation, resulting in tumor growth. Similar reasoning led to the exclusion of NF1-associated LGG in clinical trials of tovorafenib, as tumor acceleration was observed in preclinical models.[56] In the case of sorafenib, the confines of the clinical trial setting allowed for expedient identification of this AE, the appropriate halting of treatment, and comprehensive evaluation of the underlying cause. Crucially, had sorafenib been used off-label outside these clinical trial parameters, this paradoxical tumor growth would likely not have been captured or understood for a prolonged period, bypassing trial safety mechanisms and allowing unnecessary exposure to patients with a risk of significant unforeseen AEs.

Our incomplete understanding of the biologic implications of MAPK pathway inhibition also raises concern of theoretical impact of inhibitors on the phenomenon of disease senescence in early adulthood. It has been demonstrated that pLGG are comprised of cycling and senescent cell populations, differentially expressing MAPK programs, cell-cycle programs, and senescence programs, which in turn communicate with immune cells in a paracrine manner.[57,58] Interestingly, senescent programs are associated with cells expressing the highest levels of MAPK programs, such that MAPK pathway activity has been shown to cause oncogene-induced senescence.[59-61] This has raised theoretical concerns that inhibition of the MAPK pathway may interrupt the observed natural history of clinical senescence of these tumors in young adulthood. These concerns have, in part, led to clinical trials investigating the combination of chemotherapy with targeted agents (NCT04576117, NCT06381570). Whilst these processes are still very much under investigation, the question highlights the need for equipoise in the incorporation of targeted inhibitor therapies into clinical care, particularly off-label in the frontline setting.

Outstanding Questions

Duration of Treatment

In addition to the potential risks of MAPK inhibitor therapy, many other questions remain regarding the clinical utilization of these agents. First, the optimal duration of treatment with MAPK pathway inhibitors is unknown. While most pediatric trials have used a treatment duration of 24 months, this was not based on scientific rationale. Practitioners have therefore often adopted two years as a standard treatment duration, yet anecdotally many will treat *BRAF*^{V600E}-mutant pLGG for extended courses beyond this based on concern for recurrence and/or rebound growth. However, there is not yet data to determine whether shorter treatment courses would yield similar response rates and durability, or, conversely, whether extended courses are beneficial. Drawing from the adult melanoma experience, there is some data suggesting that BRAF +/- MEK inhibition can be successfully discontinued after a prolonged CR by imaging and ctDNA criteria.[62] However, there are significant impediments to applying this data to pLGG cohorts, including the different genetic and clinical features across tumor types, the rarity of CR in systemic treatment of pLGG, and a lack of validation of ctDNA in pLGG. Yet, the data highlights the potential for shorter treatment courses to be efficacious, particularly given that time to maximal response for targeted inhibitors in pLGG generally ranges between 3 and 12 months.[7-9,63] Ideally, the question of treatment duration will be incorporated into MAPK inhibitor trials moving forward. Additionally, the concept of intermittent dosing has been raised as a possible strategy to reduce prolonged drug exposure and associated toxicity.[64,65] Caution should certainly be exercised using this intermittent dosing strategy in pediatric patients, which is currently under investigation in a PNOC trial of intermittent versus continuous dosing of everolimus and trametinib for recurrent pediatric glioma (NCT04485559), and a United Kingdom trial of intermittent dosing of selumetinib in NF1-associated plexiform neurofibromas or optic pathway glioma (NCT03326388). Data from these trials may help inform future investigations for alternative dosing schema in this patient population.

Variability of Response and Treatment Failure

Another key area of MAPK inhibition which is not presently understood is the variability of response among histologically and molecularly similar tumors; it is unknown which clinical and molecular features are predictive of pLGG treatment response. In addition, response rates to targeted therapies for less common molecular alterations are largely unknown. Further, for many drugs mature data describing response durability is lacking even in the patient populations evaluated in the clinical trial setting, and as such, early response rates may not be representative of long-term efficacy. An example of this is demonstrated in the phase 2 trial of selumetinib for recurrent BRAF-altered and NF1-associated pLGG. The initial analysis reported a 2-year PFS of 70% for stratum 1 (patients with pilocytic astrocytoma with *KIAA1549: BRAF* fusion or *BRAF*^{V600E} mutation) and 96% for stratum 3 (NF1-LGG).[10,66] However, the recently reported longitudinal analysis revealed a 5-year PFS of 30.8% for stratum 1 and 54.2% for stratum 3; these PFS estimates are more equivocal with the 5-year PFS rates of traditional chemotherapy.[30,31,66]

An additional concern is the phenomenon of rebound growth. With increasing MAPK inhibitor experience, it has been observed that some tumors demonstrate rapid growth on discontinuation of the targeted agent. One retrospective multi-institutional series reported rapid progression in 13/17 (76.5%) of pLGG following cessation of targeted therapy with a median time to progression of 2.3 months (range 0.3-20.8 months).[16] Importantly, objective response to retreatment was seen in 8/9 (90%) of patients who were rechallenged with targeted therapy.[16] Another single-institution retrospective study showed rapid regrowth following cessation of BRAF and MEK inhibitor therapy in BRAF fusion/duplication and *BRAF*^{V600E} mutant tumors at a median of 2.38 and 2.86 months, respectively.[67] This study also showed that for *BRAF*^{V600E}-mutant tumors, the rapid growth peaked and then decreased spontaneously for an overall mean volumetric change of -14% compared to the baseline pre-treatment imaging.[67] This suggested that the "rebound" growth observed may represent a mixture of true progression and transient growth (pseudoprogression), and raises a question of whether rebound growth can be monitored for spontaneous regression, rather than being empirically retreated. The biologic underpinnings of this phenomenon are still being investigated. Early preclinical data from *BRAF*^{V600E}-mutant cell lines has demonstrated MAPK pathway overactivation following withdrawal of BRAF inhibitor *in vitro*, suggesting that rebound growth may not be solely due to rapid reactivation of the MAPK pathway but potentially from additional co-occurring mechanisms (such as accumulation of upstream activators due to loss of negative feedback on parallel pathways).[68] Recent preliminary data on patients with refractory pLGG entering a tovorafenib drug holiday showed durable tumor responses off treatment.[69] However, the median duration of these drug holidays was short (3 months), and ongoing data maturation is required to better inform optimal duration of treatment.

Whilst this phenomenon is still being interrogated, the real-world observation of rebound growth has prompted questions of whether drug tapering or alternative dosing strategies may reduce the risk of rebound or need for retreatment. Clinicians are variably adopting this practice; in fact, a recently published Canadian expert consensus guideline suggests a slow wean of MEK inhibitor followed by BRAF inhibitor for patients with *BRAF*^{V600E}-mutant glioma on dual targeted therapy.[70] Given the rapidly expanding use of targeted inhibitor therapy has in many ways outstripped the pace of formal investigation of this and other scientific questions, it is understandable that clinicians are having to rely on anecdotal experience and expert guidance to address evolving clinical issues that have not yet been thoroughly investigated. However, it should be cautioned that there is currently no firm preclinical or clinical data to support the practice of MAPK inhibitor drug tapering, and further active investigation in the preclinical and clinical trial settings are required to fully understand its role. An upcoming PNOC trial plans to investigate this question, with randomization of participants with *BRAF*^{V600E}-altered tumors to either a six-month taper of BRAF-targeted therapy or the conventional abrupt discontinuation of therapy (NCT07110246). Clearly, there are many outstanding questions about MAPK inhibitor therapy that require robust investigation in the controlled clinical trial setting.

Finally, while *BRAF* structural variants and single nucleotide variants are the most common somatic driving alterations of pLGG, a subset is driven by a variety of other alterations, both converging on the MAPK pathway (including *FGFR* alterations) and non-MAPK alterations (such as *MYB* and *MYBL1*). FGFR alterations, in particular, are the third most common somatic driver of pLGG, found in around 10% of tumors.[12] Given their interaction with the MAPK pathway and the lack of as-yet safe or approved FGFR-inhibitor therapy for FGFR-driven pLGG as mentioned above, MEK inhibitors have presented an enticing possible targeted option for FGFR-driven pLGG. And whilst there are several reports of patients with FGFR-driven pLGG being treated with MEK inhibitors (most commonly achieving stable disease as best response), there is not yet reliable, prospective efficacy data to justify the use of MAPK inhibitor therapy in FGFR-altered or other non-BRAF altered pLGG.[71]

Impact on Ongoing Clinical Trials and Future Directions

The excitement generated from the early phase clinical trial data of MEK inhibitors as an oral option for recurrent/refractory pLGG has resulted in the use of this therapy as a *front-line* treatment regimen before completing the requisite phase 3 trials. There are significant concerns that off-label utilization of MAPK targeted therapies is diverting patients from active, ongoing clinical trials. A key example of accrual failure potentially impacted by off-label use is the recent premature closure of enrollment to the Children's Oncology Group phase 3 randomized clinical trial for treatment-naïve NF1-associated pLGG (ACNS1831), with the primary objective to determine whether the efficacy of treatment with selumetinib as measured by event-free survival is non-inferior to treatment with carboplatin/vincristine. Even with activation across most COG participating sites, the study was unable to recruit the intended 140 participants to this crucial study. However, it should be noted that this was conceptualized as an international trial in collaboration with non-COG sites; a subsequent lack of expansion outside COG institutions, amongst other reasons, may have also hindered accrual. Early closure and incomplete accrual is not unique to ACNS1831, as there are several pitfalls in the current design and landscape of late phase clinical trials for pLGG. These limitations include competition for participant enrollment between clinicals trials, consortium, and pharmaceutical companies, a lack of child-friendly formulations, regulatory delays, and the aforementioned diversion of potential participants through off-label use of therapy prior to the appropriate maturation of prospective clinical trial data. Further, the management approach to NF1-LGG has shifted in recent years, with more patients initially undergoing active surveillance rather than initiating tumor-directed therapy, and this shift must be considered when designing NF1-LGG clinical trials. Overall, the pLGG community must work together and learn from prior clinical trial challenges and failures to address and overcome these limitations, as phase 3 studies are necessary to rigorously compare the efficacy and safety of a new treatment approach against the current standard. For example, despite the encouraging

phase 2 data of selumetinib for relapsed/refractory pLGG, it is important to acknowledge that by design, phase 2 trials determine only the safety, tolerability, and preliminary efficacy of a therapy in a target population and purposefully do not have sufficient statistical power to measure a clinically relevant primary outcome nor can results be directly compared to other standard therapies.[72] Second, these smaller cohorts may fail to capture the more infrequent, yet severe side effects that some patients may not be willing to accept compared to other well-studied front-line therapies. The small cohort sizes may also obscure a more robust understanding on how different histologic subtypes respond to treatment compared to an appropriately powered phase 3 trial.[73] Given the above, it is not surprising that nearly one-half of phase 3 trials ultimately fail due to lack of efficacy and nearly one-quarter fail due to safety despite promising results from phase 2 trials; these statistics should be considered when contemplating off-label, early utilization of these novel therapies.[74]

Furthermore, while MEK inhibitors have clearly demonstrated promise in phase 2 trials for pLGG, there are significant limitations when attempting to determine comparative effectiveness using PFS rates from historical clinical trial data. The PFS in the COG study (CCG9952) of CV for treatment naïve, sporadic pLGG was approximately 60% at 2-years compared to 70% in the phase 2 PBTC study of selumetinib for BRAF-aberrant recurrent/progressive pLGG.[10,30] This difference in 2-year PFS rates has led some to believe that selumetinib achieves more robust rates of PFS compared to CV, with some clinicians electing to prescribe MEK inhibitors as a frontline off-label therapy in place of conventional cytotoxic chemotherapy based on this quantitative difference. However, it is important to understand key differences between these studies, including but not limited to participant demographics, duration of therapy, durability of response, number of patients accrued, and timing of study evaluations. For example, the duration of therapy for CV is typically 14 months, thus at 2 years most participants treated with this combination would have been off therapy for greater than 6 months. In contrast, the duration of therapy for selumetinib in the PBTC clinical trial was 26 cycles or approximately 2 years, thus 2-year PFS is representative of progression rates at the end of protocol therapy. To cite 2-year PFS rates between the studies as a justification for use of selumetinib as frontline therapy may be nearsighted when considering these key differences. The concern regarding this interpretation of treatment outcomes is further highlighted by the recently reported 5-year PFS rates for the PBTC study of selumetinib, where 5-year PFS rates appear more equivocal with traditional cytotoxic chemotherapy as mentioned above (30.8% for non-NF1 and 54.2% for NF1 stratum compared to 39% for non-NF1 and 69% for NF1 at 5-years for the CV regimen).[30,66]

Perhaps more important than radiographic progression rates in patients with pLGG are functional response and quality of life measures. It is important to note that while crude assessments of visual outcomes were performed in the phase 2 selumetinib study, patient reported outcomes and quality of life assessments were *not* evaluated and differences have yet to be determined. Importantly, visual acuity was a co-primary outcome for tumors located within the optic pathway in the recently closed ACNS1831, with cognitive measures also an important secondary outcome. Unfortunately, early closure of ACNS1831 to accrual prohibits understanding of not only radiographic response but also the impact of selumetinib on key outcomes such as visual function and quality of life. With the early closure to enrollment of ACNS1831, it will remain unknown if MEK inhibitors have a role in frontline therapy for NF1-LGG, as completion of this phase 3 trial was necessary to directly compare these two therapies and determine if frontline MEK inhibitor therapy achieves non-inferior and/or superior outcomes to chemotherapy in terms of rates and durability of response, objective functional measures, and patient reported outcomes.

Overall, continued off-label prescribing practices without appropriate follow up in a clinical trial setting often delays acquisition of knowledge regarding efficacy and outcomes for the entire pLGG community. The iPLGGc would caution against off-label use and largely advocate for clinical trial enrollment when possible if considering initiation of novel targeted therapies without existing regulatory approval in pLGG, particularly in upfront use. However, the iPLGGc simultaneously acknowledges factors which may hinder clinical trial enrollment for individual patients, such as access to academic centers, logistical and travel challenges, financial constraints, and the psychosocial burden of trial enrollment. Overall, while hopeful that MAPK inhibitors will demonstrate at a minimum non-inferiority and expand options for patients with pLGG, cautious optimism should prevail until the necessary studies have been completed. For clinicians prescribing off-label targeted therapy, it is their responsibility to have a transparent, evidence-guided discussion with the patient and caregivers regarding the pros and cons of use and to confirm patient comprehension in order to facilitate true shared decision-making. When considering use outside of an interventional clinical trial, clinicians should also consider options for registry enrollment like the Securing Access to Innovative Therapies for Children, Adolescents, and Young Adults with Cancer Used Outside Clinical Trials (SACHA) study.[75] While this cohort study has demonstrated feasibility of toxicity and outcomes reporting with an observational study design for individuals receiving therapy through compassionate use or outside marketing authorization in France (NCT04477681), there remains a significant need for high-quality data collection through international, prospective observational studies to fully capture acute and long-term impact of these therapies.

Further, several prior studies have demonstrated that survivors of pediatric CNS tumors demonstrate decreased health-related quality of life, rates of employment, educational attainment, and independent living, however there is a paucity of adequately powered studies in the current era of molecular targeted therapies that granularly examine long-term outcomes and the interaction of histopathologic and molecular diagnosis, treatment approach, endocrine dysfunction, fertility, functional outcomes, financial toxicity, and quality of life. Future directions for the iPLGGc and pLGG community include an increased focus on functional outcomes and health-related quality of life for survivors of both untreated and treated pLGG through centralized protocols. This information will allow for further comparison of long-term outcomes for children treated with targeted versus conventional chemotherapy agents. An increased emphasis on the evaluation of late effects of therapy

including quality of life is readily appreciated based on the current number of large-scale studies examining these important outcomes both within and external to the iPLGGc, including the iPLGGc Quality of Life (QOL) study, the companion Neurofibromatosis Type 1 Optic Pathway Glioma and non-Optic Pathway Natural History studies, the Novartis Roll Over studies (including NCT03340506), the NF Clinical Trials Consortium Long-Term Outcomes study (NFEXTEND), and the Pediatric Neuro-Oncology Consortium Cognitive, Quality of Life (QOL), and Comprehensive Effects of Therapies study (PNOCCOMP). Each of these studies will provide invaluable information by which to benchmark outcomes for future emerging therapies. For example, the iPLGGc QOL study is an international, multi-center prospective study enrolling pLGG survivors greater than 5 years from their initial diagnosis regardless of current treatment status. The study design includes serial medical record data abstraction and patient- and caregiver-reported quality of life survey administration examining the functional, educational, and financial status of the participants through contemporaneous quality of life assessments and granular capture of economic data. In summary, the iPLGGc QOL and other studies examining late effects in pLGG survivors will address key gaps in current datasets and knowledge in the era of precision medicine.

Conclusion

In conclusion, the emergence of MAPK pathway targeted therapies marks a major advancement in the treatment of pediatric low-grade gliomas, particularly those harboring defined molecular alterations. Their use is supported by compelling evidence of profound clinical and radiologic responses, improved tolerability compared to conventional chemotherapy, and the convenience of oral, home-based administration. However, the integration of these therapies into the pLGG treatment paradigm, particularly in frontline management (beyond *BRAF*^{V600E}-mutated pLGG), requires careful consideration. Many questions remain regarding MAPK inhibitor therapies for pLGG, including optimal timing of therapy, treatment duration, drug tapering, and long-term efficacy, risks and toxicities. These questions will remain unanswered until ongoing biologic work and clinical trial investigation is completed with subsequent maturation of long-term follow up data.

Ultimately, while early use of targeted agents may provide substantial benefits in selected patients, the iPLGGc would caution equipoise in the adoption of these novel agents for pLGG outside of approved indications or the clinical trial setting, until the appropriate comparative clinical data has emerged supporting this. Their role should be defined within a broader therapeutic strategy that includes long-term follow-up, functional outcomes, and individualized goals of care. Precision medicine holds great promise, but must be balanced with clinical judgment, patient-centered considerations, and evolving evidence.

Keywords

clinical trial | low grade glioma | pediatric neuro-oncology | targeted therapy

Lay Summary

There is growing excitement about new targeted therapies for the treatment of pediatric lowgrade glioma (pLGG). However, only two of these targeted treatments have received regulatory approval, despite many being studied in clinical trials. Promising early clinical trial results from small studies have led some clinicians to prescribe these targeted therapies without regulatory approval. This raises concerns, as important questions remain about the long-term effectiveness and safety of these new medications. These knowledge gaps are especially important to consider in pLGG, as many children survive after diagnosis. This manuscript provides an evidence-focused review of targeted therapies for pLGG, with a specific emphasis on current knowledge gaps, the risks and benefits of prescribing these therapies without regulatory approval, and the importance of patience in clinical practice.

Author Contributions

C.K., S.P., P.P., M.J.F., D.H., L.K., P.B., and J.F. conceptualized the manuscript. All authors engaged in content discussion of manuscript. C.K., S.P., P.P. drafted the manuscript and contributed equally. M.J.F., D.H., and L.K. contributed equally. All authors read and approved the final version.

Conflict of Interest Statement

D.H., L.K., R.A.A., J.F., and M.J.F. serve as study chairs, co-chairs or study team members for multiple phase 2 and phase 3 clinical trials involving children with LGG. J.F. receives financial support from Children's Oncology Group to serve as study chair and serves on the unbranded educational speaker's bureau for Day One and served on a paid pediatric advisory board for Day One Biopharmaceuticals. R.A.A. receives funding from the NIH (CA180886-04S1 and CA23653) and Ozmosis for research and training activities for these clinical trials. D.H. has acted as a consultant for Alexion, AstraZeneca, Day One Biopharmaceuticals, Ipsen and Novartis. S.P. has served on advisory boards for Alexion, AstraZeneca, Bayer, EMD Serono, and Eisai. L.K. has acted as a consultant for BluePrint Medicine and Chimerix and is the institutional PI for clinical trials which receive clinical trial funding support from Day One Biopharmaceuticals, Novartis, Spring Works Therapeutics, Regeneron Pharmaceutical, Recursion Pharma. P.B. serves on the Board of Trustees for the Justice Resource Institute and has also served on paid advisory boards for QED Therapeutics and DayOne Biopharmaceuticals. D.T.W.J. has been on an advisory board for Day One Biopharmaceuticals and given an educational seminar for Ipsen Pharma. M.J.F. is on the advisory board for Alexion and SpringWorks and receives research support from Alexion, Array BioPharma, and Exelixis. A.V. serves as the co-PI for a clinical trial which receives clinical trial funding support from Spring Works Therapeutics. This editorial is the sole product of the authors, and no third party had input or gave support to its writing.

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References

1. Ostrom QT, Price M, Ryan K, et al. CBTRUS statistical report: pediatric brain tumor foundation childhood and adolescent primary brain and other Central nervous system tumors diagnosed in the United States in 2014-2018. *Neuro Oncol*. 2022;24:iii1-iii38. https://doi.org/10.1093/neuonc/noac161
2. Adel Fahmideh M, Scheurer ME. Pediatric brain tumors: descriptive epidemiology, risk factors, and future directions. *Cancer Epidemiol Biomarkers Prev*. 2021;30:813-821. https://doi.org/10.1158/1055-9965.EPI-20-1443
3. Bandopadhayay P, Bergthold G, London WB, et al. Long-term outcome of 4,040 children diagnosed with pediatric low-grade gliomas: an analysis of the surveillance epidemiology and end results (SEER) database. *Pediatr Blood Cancer*. 2014;61:1173-1179. https://doi.org/10.1002/pbc.24958
4. Zelt S, Cooney T, Yu S, et al. Disease burden and healthcare utilization in pediatric low-grade glioma: a United States retrospective study of

linked claims and electronic health records. *Neurooncol Pract*. 2024;11:583-592. https://doi.org/10.1093/nop/npae037

5. Traunwieser T, Kandels D, Pauls F, et al. Long-term cognitive deficits in pediatric low-grade glioma (LGG) survivors reflect pretreatment conditions-report from the German LGG studies. *Neurooncol Adv*. 2020;2:vdaa094. https://doi.org/10.1093/noajnl/vdaa094
6. Fangusaro J, Jones DT, Packer RJ, et al. Pediatric low-grade glioma: state-of-the-art and ongoing challenges. *Neuro Oncol*. 2024;26:25-37. https://doi.org/10.1093/neuonc/noad195
7. Bouffet E, Hansford JR, Garre ML, et al. Dabrafenib plus trametinib in pediatric glioma with BRAF V600 mutations. *N Engl J Med*. 2023;389:1108-1120. https://doi.org/10.1056/NEJMoa2303815
8. Kilburn LB, Khuong-Quang D-A, Hansford JR, et al. The type II RAF inhibitor tovorafenib in relapsed/refractory pediatric low-grade glioma: the phase 2 FIREFLY-1 trial. *Nat Med*. 2024;30:207-217. https://doi.org/10.1038/s41591-023-02668-y
9. Bouffet E, Geoerger B, Moertel C, et al. Efficacy and safety of trametinib monotherapy or in combination with dabrafenib in pediatric BRAF V600-mutant low-grade glioma. *J Clin Oncol*. 2023;41:664-674. https://doi.org/10.1200/JCO.22.01000
10. Fangusaro J, Onar-Thomas A, Young Poussaint T, et al. Selumetinib in paediatric patients with BRAF-aberrant or neurofibromatosis type 1-associated recurrent, refractory, or progressive low-grade glioma: a multicentre, phase 2 trial. *Lancet Oncol*. 2019;20:1011-1022. https://doi.org/10.1016/S1470-2045(19)30277-3
11. Fangusaro J, Avery RA, Fisher MJ, et al. Considering functional outcomes as efficacy endpoints in pediatric low-grade glioma clinical trials: an FDA educational symposium. *Clin Cancer Res*. 2024;30:2303-2308. https://doi.org/10.1158/1078-0432.CCR-23-3386
12. Ryall S, Zapotocky M, Fukuoka K, et al. Integrated molecular and clinical analysis of 1,000 pediatric low-grade gliomas. *Cancer Cell*. 2020;37:569-583.e5. https://doi.org/10.1016/j.ccell.2020.03.011e565.
13. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. *Neuro Oncol*. 2021;23:1231-1251. https://doi.org/10.1093/neuonc/noab106
14. Louis DN, Perry A, Reifenberger G, et al. The 2016 world health organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol*. 2016;131:803-820. https://doi.org/10.1007/s00401-016-1545-1
15. Manoharan N, Liu KX, Mueller S, Haas-Kogan DA, Bandopadhayay P. Pediatric low-grade glioma: targeted therapeutics and clinical trials in the molecular era. *Neoplasia*. 2023;36:100857. https://doi.org/10.1016/j.neo.2022.100857
16. Nobre L, Zapotocky M, Ramaswamy V, et al. Outcomes of BRAF V600E pediatric gliomas treated with targeted BRAF inhibition. *JCO Precis Oncol*. 2020;4https://doi.org/10.1200/PO.19.00298 :
17. Moreira DC, Qaddoumi I, Spiller S, et al. Comprehensive analysis of MYB/MYBL1-altered pediatric-type diffuse low-grade glioma. *Neuro Oncol*. 2024;26:1327-1334. https://doi.org/10.1093/neuonc/noae048
18. Zhang J, Wu G, Miller CP, et al.; St. Jude Children's Research Hospital–Washington University Pediatric Cancer Genome Project. Whole-genome sequencing identifies genetic alterations in pediatric low-grade gliomas. *Nat Genet*. 2013;45:602-612. https://doi.org/10.1038/ng.2611
19. Fisher MJ, Jones DTW, Li Y, et al. Integrated molecular and clinical analysis of low-grade gliomas in children with neurofibromatosis type 1 (NF1). *Acta Neuropathol*. 2021;141:605-617. https://doi.org/10.1007/s00401-021-02276-5
20. Sievert AJ, Jackson EM, Gai X, et al. Duplication of 7q34 in pediatric low-grade astrocytomas detected by high-density single-nucleotide polymorphism-based genotype arrays results in a novel BRAF fusion gene. *Brain Pathol*. 2009;19:449-458. https://doi.org/10.1111/j.1750-3639.2008.00225.x
21. Engelhardt S, Behling F, Beschorner R, et al. Frequent FGFR1 hotspot alterations in driver-unknown low-grade glioma and mixed neuronal-glial tumors. *J Cancer Res Clin Oncol*. 2022;148:857-866. https://doi.org/10.1007/s00432-021-03906-x
22. Lassaletta A, Zapotocky M, Mistry M, et al. Therapeutic and prognostic implications of BRAF V600E in pediatric low-grade gliomas. *J Clin Oncol*. 2017;35:2934-2941. https://doi.org/10.1200/JCO.2016.71.8726
23. Chung HJ, Rajan S, Wu Z, et al. MYB/MYBL1-altered gliomas frequently harbor truncations and non-productive fusions in the MYB and MYBL1 genes. *Acta Neuropathol*. 2024;148:54. https://doi.org/10.1007/s00401-024-02803-0
24. Kyritsis AP, Bondy ML, Rao JS, Sioka C. Inherited predisposition to glioma. *Neuro Oncol*. 2010;12:104-113. https://doi.org/10.1093/neuonc/nop011
25. Kotch C, de Blank P, Gutmann DH, Fisher MJ. Low-grade glioma in children with neurofibromatosis type 1: surveillance, treatment indications, management, and future directions. *Childs Nerv Syst*. 2024;40:3241-3250. https://doi.org/10.1007/s00381-024-06430-8
26. Kotch C, Brosius SN, De Raedt T, Fisher MJ. Updates in the management of Central and peripheral nervous system tumors among patients with neurofibromatosis type 1 and neurofibromatosis type 2. *Pediatr Neurosurg*. 2023;58:267-280. https://doi.org/10.1159/000529507
27. de Blank PMK, Gross AM, Akshintala S, et al. MEK inhibitors for neurofibromatosis type 1 manifestations: clinical evidence and consensus. *Neuro Oncol*. 2022;24:1845-1856. https://doi.org/10.1093/neuonc/noac165
28. Wisoff JH, Sanford RA, Heier LA, et al. Primary neurosurgery for pediatric low-grade gliomas: a prospective multi-institutional study from the children's oncology group. *Neurosurgery*. 2011;68:1548-1554. https://doi.org/10.1227/NEU.0b013e318214a66e
29. Packer RJ, Ater J, Allen J, et al. Carboplatin and vincristine chemotherapy for children with newly diagnosed progressive low-grade gliomas. *J Neurosurg*. 1997;86:747-754. https://doi.org/10.3171/jns.1997.86.5.0747
30. Ater JL, Xia C, Mazewski CM, et al. Nonrandomized comparison of neurofibromatosis type 1 and non-neurofibromatosis type 1 children who received carboplatin and vincristine for progressive low-grade glioma: a report from the children's oncology group. *Cancer*. 2016;122:1928-1936. https://doi.org/10.1002/cncr.29987
31. Lassaletta A, Scheinemann K, Zelcer SM, et al. Phase II weekly vinblastine for Chemotherapy-Naive children with progressive low-grade glioma: a Canadian pediatric brain tumor consortium study. *J Clin Oncol*. 2016;34:3537-3543. https://doi.org/10.1200/JCO.2016.68.1585
32. Gururangan S, Cavazos CM, Ashley D, et al. Phase II study of carboplatin in children with progressive low-grade gliomas. *J Clin Oncol*. 2002;20:2951-2958. https://doi.org/10.1200/JCO.2002.12.008
33. Gururangan S, Fangusaro J, Poussaint TY, et al. Efficacy of bevacizumab plus irinotecan in children with recurrent low-grade gliomas—a pediatric brain tumor consortium study. *Neuro Oncol*. 2014;16:310-317. https://doi.org/10.1093/neuonc/not154
34. Kotch C, Avery R, Getz KD, et al. Risk factors for treatment-refractory and relapsed optic pathway glioma in children with neurofibromatosis type 1. *Neuro Oncol*. 2022;24:1377-1386. https://doi.org/10.1093/neuonc/noac013
35. Barbato MI, Nashed J, Bradford D, et al. FDA approval summary: Dabrafenib in combination with trametinib for BRAFV600E mutation-positive low-grade glioma. *Clin Cancer Res*. 2024;30:263-268. https://doi.org/10.1158/1078-0432.CCR-23-1503
36. Singh S, Bradford D, Chatterjee S, et al. FDA approval summary: Tovorafenib for relapsed or refractory BRAF-altered pediatric low-grade glioma. *Clin Cancer Res*. 2025;31:1383-1389. https://doi.org/10.1158/1078-0432.CCR-24-3439
37. Ward R, Jones HM, Witt D, et al. Outcomes of children with low-grade gliomas in low- and middle-income countries: a systematic review. *JCO Glob Oncol*. 2022;8:e2200199. https://doi.org/10.1200/GO.22.00199

38. Abu Laban D, Alsharif A, Al-Hussaini M, et al. BRAF/MEK inhibitors use for pediatric gliomas; real world experience from a resource-limited country. *Front Oncol*. 2024;14:1417484. https://doi.org/10.3389/fonc.2024.1417484

39. Doz F, van Tilburg CM, Geoerger B, et al. Efficacy and safety of larotrectinib in TRK fusion-positive primary central nervous system tumors. *Neuro Oncol*. 2022;24:997-1007. https://doi.org/10.1093/neuonc/noab274

40. Nysom K, Kilburn LB, Leary SES, et al. Radiographic and visual response to the type II RAF inhibitor tovorafenib in children with relapsed/refractory optic pathway glioma in the FIREFLY-1 trial. *Neuro Oncol*. 2025;27:1341-1355. https://doi.org/10.1093/neuonc/noae274

41. Rosca L, Robert-Boire V, Delisle JF, Samson Y, Perreault S. Carboplatin and vincristine neurotoxicity in the treatment of pediatric low-grade gliomas. *Pediatr Blood Cancer*. 2018;65:e27351. https://doi.org/10.1002/pbc.27351

42. Kline C, Waanders AJ, Ziegler DS, et al. LGG-40. Type II RAF inhibitor tovorafenib in relapsed/refractory pediatric Low-Grade glioma (PLGG): reversible decreases in growth velocity In the phase 2 FIREFLY-1 trial. 2024;26:1522-8517.

43. Robinson GW, Kaste SC, Chemaitilly W, et al. Irreversible growth plate fusions in children with medulloblastoma treated with a targeted hedgehog pathway inhibitor. *Oncotarget*. 2017;8:69295-69302. https://doi.org/10.18632/oncotarget.20619

44. Kieran MW, Chisholm J, Casanova M, et al. Phase I study of oral sonidegib (LDE225) in pediatric brain and solid tumors and a phase II study in children and adults with relapsed medulloblastoma. *Neuro Oncol*. 2017;19:1542-1552. https://doi.org/10.1093/neuonc/nox109

45. Witt O, Sait SF, Diez BD, et al. Efficacy and safety of erdafitinib in pediatric patients with advanced solid tumors and FGFR alterations in the phase 2 RAGNAR trial. *JCO*. 2024;42:10002-10002. https://doi.org/10.1200/JCO.2024.42.16_suppl.10002

46. Farouk Sait S, Fischer C, Antal Z, et al. Slipped capital femoral epiphyses: a major on-target adverse event associated with FGFR tyrosine kinase inhibitors in pediatric patients. *Pediatr Blood Cancer*. 2023;70:e30410.

47. Pant S, Schuler M, Iyer G, et al.; RAGNAR Investigators. Erdafitinib in patients with advanced solid tumours with FGFR alterations (RAGNAR): an international, single-arm, phase 2 study. *Lancet Oncol*. 2023;24:925-935. https://doi.org/10.1016/S1470-2045(23)00275-9

48. Boussemart L, Routier E, Mateus C, et al. Prospective study of cutaneous side-effects associated with the BRAF inhibitor vemurafenib: a study of 42 patients. *Ann Oncol*. 2013;24:1691-1697. https://doi.org/10.1093/annonc/mdt015

49. Boussemart L, Girault I, Malka-Mahieu H, et al. Secondary tumors arising in patients undergoing BRAF inhibitor therapy exhibit increased BRAF-CRAF heterodimerization. *Cancer Res*. 2016;76:1476-1484. https://doi.org/10.1158/0008-5472.CAN-15-2900-T

50. Gibney GT, Messina JL, Fedorenko IV, Sondak VK, Smalley KS. Paradoxical oncogenesis—the long-term effects of BRAF inhibition in melanoma. *Nat Rev Clin Oncol*. 2013;10:390-399. https://doi.org/10.1038/nrclinonc.2013.83

51. Boull CL, Gardeen S, Abdali T, et al. Cutaneous reactions in children treated with MEK inhibitors, BRAF inhibitors, or combination therapy: a multicenter study. *J Am Acad Dermatol*. 2021;84:1554-1561. https://doi.org/10.1016/j.jaad.2020.07.044

52. Nicolaides T, Nazemi KJ, Crawford J, et al. Phase I study of vemurafenib in children with recurrent or progressive BRAF(V600E) mutant brain tumors: Pacific pediatric neuro-oncology consortium study (PNOC-002). *Oncotarget*. 2020;11:1942-1952. https://doi.org/10.18632/oncotarget.27600

53. Karajannis MA, Legault G, Fisher MJ, et al. Phase II study of sorafenib in children with recurrent or progressive low-grade astrocytomas. *Neuro Oncol*. 2014;16:1408-1416. https://doi.org/10.1093/neuonc/nou059

54. Poulikakos PI, Zhang C, Bollag G, Shokat KM, Rosen N. RAF inhibitors transactivate RAF dimers and ERK signalling in cells with wild-type BRAF. *Nature*. 2010;464:427-430. https://doi.org/10.1038/nature08902

55. Yaeger R, Corcoran RB. Targeting alterations in the RAF–MEK pathway. *Cancer Discov*. 2019;9:329-341. https://doi.org/10.1158/2159-8290.CD-18-1321

56. Rastogi S, Perino S, Lal-Nag M, Wang Y, Blackman SC, Venetsanakos E. Preclinical activity of the type II RAF inhibitor tovorafenib in tumor models harboring either a BRAF fusion or an NF1 loss-of-function mutation. *Cancer Res Commun*. 2025;5:668-679. https://doi.org/10.1158/2767-9764.CRC-24-0451

57. Reitman ZJ, Paolella BR, Bergthold G, et al. Mitogenic and progenitor gene programmes in single pilocytic astrocytoma cells. *Nat Commun*. 2019;10:3731. https://doi.org/10.1038/s41467-019-11493-2

58. Jacob K, Quang-Khuong DA, Jones DT, et al. Genetic aberrations leading to MAPK pathway activation mediate oncogene-induced senescence in sporadic pilocytic astrocytomas. *Clin Cancer Res*. 2011;17:4650-4660. https://doi.org/10.1158/1078-0432.CCR-11-0127

59. Selt F, Sigaud R, Valinciute G, et al. BH3 mimetics targeting BCL-XL impact the senescent compartment of pilocytic astrocytoma. *Neuro Oncol*. 2023;25:735-747. https://doi.org/10.1093/neuonc/noac199

60. Sigaud R, Stefanski A, Selt F, et al. Multi-omics dissection of MAPK-driven senescence unveils therapeutic vulnerabilities in KIAA1549::BRAF-fusion pediatric low-grade glioma models. *Signal Transduct Target Ther*. 2025;10:197. https://doi.org/10.1038/s41392-025-02279-8

61. Raabe EH, Lim KS, Kim JM, et al. BRAF activation induces transformation and then senescence in human neural stem cells: a pilocytic astrocytoma model. *Clin Cancer Res*. 2011;17:3590-3599. https://doi.org/10.1158/1078-0432.CCR-10-3349

62. Warburton L, Meniawy TM, Calapre L, et al. Stopping targeted therapy for complete responders in advanced BRAF mutant melanoma. *Sci Rep*. 2020;10:18878. https://doi.org/10.1038/s41598-020-75837-5

63. Hargrave DR, Bouffet E, Tabori U, et al. Efficacy and safety of dabrafenib in pediatric patients with BRAF V600 mutation-positive relapsed or refractory low-grade glioma: results from a phase I/IIa study. *Clin Cancer Res*. 2019;25:7303-7311. https://doi.org/10.1158/1078-0432.CCR-19-2177

64. Gonzalez-Cao M, Mayo de las Casas C, Oramas J, et al. Intermittent BRAF inhibition in advanced BRAF mutated melanoma results of a phase II randomized trial. *Nat Commun*. 2021;12:7008. https://doi.org/10.1038/s41467-021-26572-6

65. Algazi AP, Othus M, Daud AI, et al. Continuous versus intermittent BRAF and MEK inhibition in patients with BRAF-mutated melanoma: a randomized phase 2 trial. *Nat Med*. 2020;26:1564-1568. https://doi.org/10.1038/s41591-020-1060-8

66. Fangusaro J, Onar-Thomas A, Young Poussaint T, et al. A phase 2 PBTC study of selumetinib for recurrent/progressive pediatric low-grade glioma: strata 2, 5, and 6 with long-term outcomes on strata 1, 3, and 4. *Neuro Oncol*. 2025;27:2415-2428. https://doi.org/10.1093/neuonc/noaf065

67. Tsai JW, Choi JJ, Ouaalam H, et al. Integrated response analysis of pediatric low-grade gliomas during and after targeted therapy treatment. *Neurooncol Adv*. 2023;5:vdac182. https://doi.org/10.1093/noajnl/vdac182

68. Kocher D, Selt F, Valinciute G, et al. LGG-17. Preventing recurrence: targeting molecular mechanisms driving tumor growth rebound after MAPKi withdrawal in pediatric low-grade glioma. *Neuro Oncol*. 2024;26:1522-8517.

69. Perreault S, Khuong-Quang D-A, Kilburn LB, et al. CTNI-09. Type II RAF inhibitor tovorafenib in relapsed/refractory (R/R) pediatric low-grade glioma (PLGG): results from patients on a drug holiday (DH) in the phase 2 FIREFLY-1 trial. *Neuro-Oncology*. 2024;26:viii96-viii97. https://doi.org/10.1093/neuonc/noae165.0377

70. Erker C, Vanan MI, Larouche V, et al. Canadian consensus for treatment of BRAF V600E mutated pediatric and AYA gliomas. *Curr Oncol*. 2024;31:4022-4029. https://doi.org/10.3390/curroncol31070299

71. Apfelbaum AA, Morin E, Sturm D, et al. A diverse landscape of FGFR alterations and co-mutations suggests potential therapeutic strategies in pediatric low-grade gliomas. *Nat Commun*. 2025;16:7018. https://doi.org/10.1038/s41467-025-61820-z

72. Torres-Saavedra PA, Winter KA. An overview of phase 2 clinical trial designs. *Int J Radiat Oncol Biol Phys*. 2022;112:22-29. https://doi.org/10.1016/j.ijrobp.2021.07.1700

73. Packer RJ, Pfister S, Bouffet E, et al. Pediatric low-grade gliomas: implications of the biologic era. *Neuro Oncol*. 2017;19:750-761.

74. Harrison RK. Phase II and phase III failures: 2013-2015. *Nat Rev Drug Discov*. 2016;15:817-818. https://doi.org/10.1038/nrd.2016.184

75. Berlanga P, Ndounga-Diakou LA, Aerts I, et al. Measuring safety and outcomes for the use of compassionate and off-label therapies for children, adolescents, and young adults with cancer in the SACHA-France study. *JAMA Netw Open*. 2023;6:e2321568. https://doi.org/10.1001/jamanetworkopen.2023.21568

76. Trinder SM, McKay C, Power P, et al. BRAF-mediated brain tumors in adults and children: a review and the Australian and New Zealand experience. *Front Oncol*. 2023;13:1154246. https://doi.org/10.3389/fonc.2023.1154246

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