Neuro-Oncology Advances
8(S2), vdaf007, 2026 | https://doi.org/10.1093/noajnl/vdaf007

RAS/MAPK inhibition in pediatric gliomas

Anfal Jasem M. Alshammari, Darren Hargrave, and Anirban Das

All author affiliations are listed at the end of the article.

Corresponding Author: Anirban Das, MBBS, MD, DM, Paediatric Neuro-Oncology Unit, Division of Haematology/Oncology, Department of Paediatrics, University of Toronto, Genetics-Genome Biology Program and Brain Tumor Research Center, The Hospital for Sick Children, 555 University Avenue, Toronto, ON, M5G 1X8, Canada (anirban.das@sickkids.ca).

Abstract

Unresectable pediatric low-grade glioma is a chronic disease that can cause significant morbidity in young patients. Historically, treatment has mainly involved chemotherapy, with many patients needing multiple lines of treatment for a recurring/relapsing disease. Orally administered inhibitors targeting the rat sarcoma virus (RAS)/mitogen-activated protein kinase (MAPK) pathway, which is the most frequently altered pathway in this disease, have resulted in a new era in the management and care for these patients. Some drugs have been already approved for specific indications, based on improved response rates in comparison to chemotherapy regimens. In this manuscript, we review the current landscape of RAS/MAPK-inhibitor use in sporadic, pediatric low-grade, and select subsets of high-grade gliomas. We summarize the recently completed trials that led to the approvals, as well as ongoing and upcoming trials investigating upfront use, combinatorial approaches, and newer agents. We highlight some of the unique challenges the neuro-oncology community is facing in this new age of targeted therapies, including a distinct set of toxicities, current unknowns, including the optimal duration of treatment, durability of response, mechanisms of tumor rebound and resistance, and the long-term impact of therapy. We conclude by focusing on some of the needed areas for research and clinical applications relevant to this patient population in the coming decade.

Key Points

- Oral RAS/mitogen-activated protein kinase inhibitors have been established as an important treatment modality for pediatric low-grade glioma (PLGG).
- The combination of dabrafenib and trametinib is Food and Drug Administration approved for treatment in *BRAF*;p.V600E mutant PLGG, while tovorafenib is approved for relapsed and refractory PLGG harboring a *BRAF* fusion or rearrangement, or *BRAF*;p.V600E mutation. Ongoing trials are investigating upfront use in BRAF-fused patients, combination approaches for refractory disease, and newer agents.
- The early successes have also opened a new set of challenges, with unique side effects, as well as unknowns regarding treatment duration, resistance mechanisms, and long-term effects of treatment, that will be the focus for research in the coming years.

Central nervous system (CNS) tumors are the most common solid tumors in children and are the leading cause of childhood cancer-related mortality and morbidity.[1] Tumors harboring a glial morphology (gliomas) are the most frequent type, yet the most varied tumors affecting the CNS. The most recent 2021 World Health Organization (WHO) classification for CNS tumors (5th edition) divides glial and glioneuronal tumors into 6 groups.[2] In this manuscript, we will be focusing on the WHO subgroups of pediatric-type, diffuse low-grade, and high-grade gliomas, as well as circumscribed astrocytic gliomas, that are biologically driven, or associated with aberrations in the rat sarcoma virus-rapidly accelerated fibrosarcoma-mitogen-activated

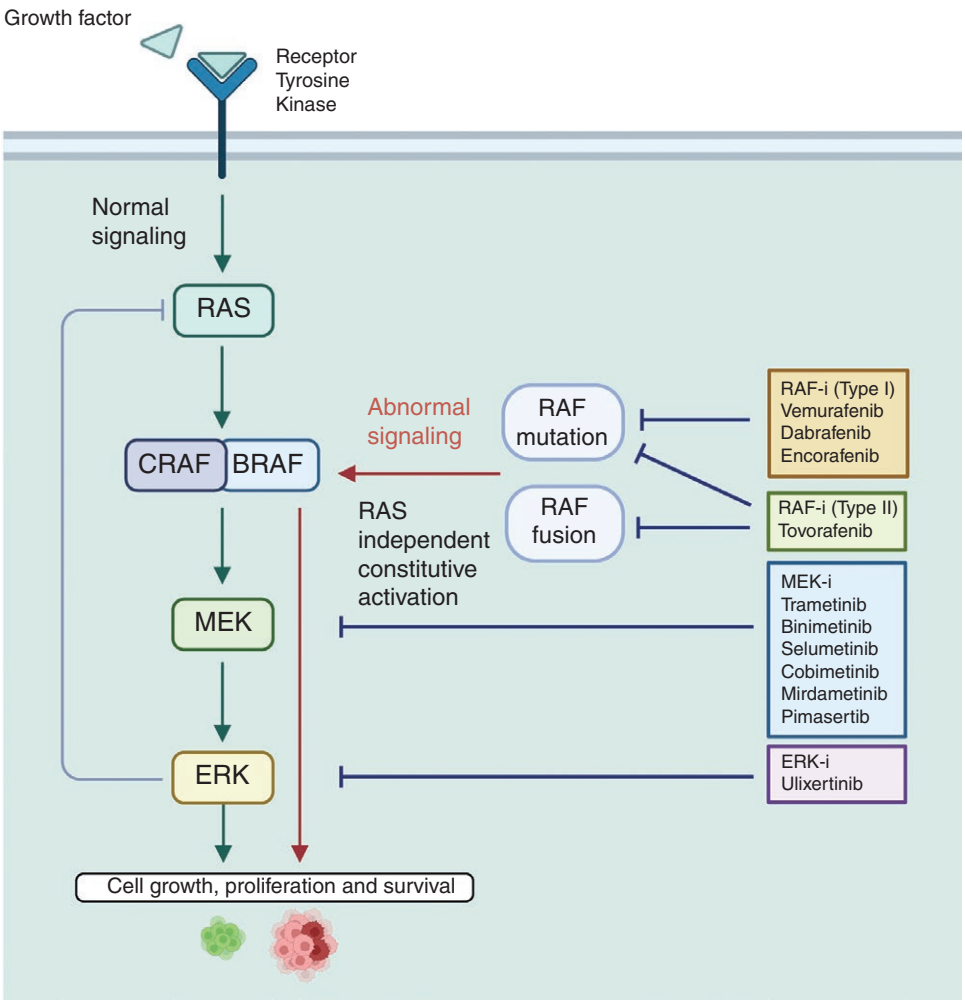

Figure 1. The Ras-Raf-MEK-ERK or MAPK pathway in normal cells, the effects of abnormal signaling, and the sites of actions of different inhibitor classes. Abbreviations: RAS: Rat sarcoma virus; RAF: rapidly accelerated fibrosarcoma; MEK: Mitogen-activated protein kinase; ERK: extracellular signal-regulated kinase; i: inhibitor. Figure made with Biorender.com.

protein kinase kinase-extracellular signal-regulated kinase (Ras-Raf-MEK-ERK) pathway, also simply termed as the mitogen-activated protein kinase (MAPK) pathway.[3]

The MAPK pathway is involved in transmitting extracellular signals from the membrane to intracellular destinations impacting diverse cellular functions including development, differentiation, proliferation, and death (Figure 1).[3] It is one of the canonical pathways that is dysregulated across different cancer types. Therefore, it has also been a focus of targeted drug development in oncology since the turn of this century, which has accelerated further over the last decade. Different inhibitors have been approved as monotherapies and combinations in melanoma, subsets of colon, and lung cancer, and histiocytic neoplasms.[3]

In this review, we will summarize the recent successes and challenges with therapies against different targets in the MAPK pathway, as it pertains to pediatric low-grade (PLGG) and high-grade (PHGG) gliomas. First, we focus on PLGG, highlighting the important role of the RAS/MAPK pathway in the disease biology (Figure 1), reviewing the available data on different inhibitor classes (RAF, MEK, and ERK inhibitors) and their activities in distinct PLGG subsets, their toxicities and other emerging challenges, and end the manuscript by the role of RAS/MAPK inhibition in select subsets of PHGG. Patients with germline neurofibromatosis type 1 (NF1), who have a characteristic clinical phenotype in terms of development, location, and outcomes of PLGG and other tumors like plexiform neurofibromas, and have been successfully treated with MEK-inhibitors over the last decade,[4,5] will be discussed in a separate review within the current series of manuscripts and will not be discussed in the index manuscript.

RAS/MAPK Targeted Therapy for Sporadic PLGG

While PLGG is curable with surgery, unresectable tumors arising in and around critical structures, including the optic pathway and hypothalamic regions, and other deeper brain

structures, were historically treated with chemotherapy. The goal was to stabilize the disease and preserve function, even in the absence of objective responses in the majority of cases.[6] While overall survival (OS) with these approaches exceeded 90%, 5-year progression-free survival (PFS) across chemotherapy regimens was < 50%.[6] This meant that patients would often need to undergo multiple courses of treatment with different chemotherapy regimens with successive and additive morbidities from both the disease and its therapy. Importantly, although effective for disease control, radiation therapy is currently seldom favored by most physician groups as a treatment modality in PLGG due to its devastating long-term adverse effects,[7–10] except in rare and multiply recurrent and refractory cases.

Identifying Targetable Molecular Aberrations in PLGG

Several landmark genomic efforts have systematically mapped somatic driver events across PLGG, confirming that it is largely driven by single-driver genetic events, and characterized in over 90% of cases by aberrant activation of MAPK pathway signaling.[11] Structural variants in the BRAF gene are the most common somatic driver event. Most frequently, these structural variants lead to the expression of a fusion protein that contains the 3′ terminal BRAF kinase, with the uncharacterized protein KIAA1549 representing the most common fusion partner, leading to an abnormal *KIAA1549-BRAF* fusion transcript. The next common subset harbors single nucleotide variants (SNVs) in the *BRAF* gene, most frequently the oncogenic *BRAF*;p.V600E mutation (15%–20%). Other MAPK drivers identified include non-canonical *BRAF* fusions, SNVs other than *BRAF*;p.V600E, *RAF1* fusion, aberrations in *KRAS,* and other genes in the MAPK pathway. Mutations and abnormal fusion transcripts lead to constitutive RAS-independent activation of the MAPK pathway resulting in Raf-driven oncogenic growth and cell proliferation (Figure 1). Activation of the MAPK pathway also exerts an anti-apoptotic influence, drives cell cycle progression, plays a role in the degradation of the extracellular matrix, promotes angiogenesis, interfaces with other signaling pathways including the phosphoinositide 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathway, and causes dysregulation of autophagy, which combine to drive tumor growth.[3]

The second most frequent group of sporadic PLGG are those that harbor fibroblast growth factor receptor family gene alterations (~7%).[11] However, these tumors can also commonly harbor second (and sometimes third) SNVs that converge on regulators of MAPK or mTOR signaling, including the *PTPN11*, *PIK3CA*, and *NF1* genes. The role of these additional mutations in gliomagenesis is unclear, as are the effects of targeting these alterations for effective tumor control. Rarer subtypes harbor recurrent alterations in receptor tyrosine kinase genes (such as *neurotrophic tyrosine receptor kinase*, *anaplastic lymphoma kinase*, *c-ros proto-oncogene 1*, *mesenchymal epithelial transition*, *rearranged during transfection*, *KIT proto-oncogene, receptor tyrosine kinase*, and *platelet-derived growth factor receptor alpha*; 4%) and non-MAPK oncogenes (such as *myeloblastosis (MYB)/MYB proto-oncogene like (MY1)* and *isocitrate dehydrogenase 1/2 (IDH1/2);* 5%).[11] Therefore, understanding of the specific aberrations driving the tumor is critical for choice and success of targeted therapies.

Currently, the successful use of MAPK pathway inhibitors is limited to the first and largest group of PLGG that are proven to harbor genomic variants, either an RAF-mutation or an abnormal fusion, that then lead to the aberrant activation of the RAS/MAPK pathway. Depending on the site and mechanism of action, currently available inhibitors can be classified as RAF-inhibitors (Type I, that bind to active conformation of the abnormal RAF protein blocking its catalytic activity, but can induce dimerization of drug-bound BRAF with CRAF leading to paradoxical downstream activation in RAF-wild type cells, versus Type II that bind to the inactive conformation of RAF protein and despite inducing RAF dimerization, bind to both RAF dimer partners and catalytically inhibit both promoters), MEK-inhibitors, and ERK-inhibitors (Figure 1). We will start this review by summarizing the successes of various agents in the last decade for the treatment of these tumors.

Efficacy of MEK-Inhibitors in BRAF-Fused PLGG

Selumetinib, an oral MEK1/2 inhibitor is available in capsule form, was first tested by the Pediatric Brain Tumor Consortium for recurrent/refractory PLGG in phase 1 and 2 trials. Among sporadic BRAF-fused PLGG patients, objective response rates between 35% and 56% were noted, with a 2-year PFS of ~70%.[4,12,13] In recurrent optic pathway and hypothalamic gliomas, 80% achieved disease stability or partial response, with a 2-year PFS of 78% with visual improvement in > 20% of patients in this multiply treated cohort of patients.[13] Current clinical trials are investigating whether the addition of chemotherapy (vinblastine) to selumetinib can improve outcomes for progressive PLGG (NCT04576117), and whether selumetinib can outperform chemotherapy (vincristine and carboplatin) in a randomized clinical trial for upfront treatment of newly diagnosed sporadic PLGG (NCT04166409; Table 1).

Trametinib is another oral MEK1/2 inhibitor that has the advantage of the availability of a liquid formulation and has been reported to have similar efficacy in recurrent/refractory BRAF-fused PLGG in the recurrent/refractory setting.[14] Case reports have suggested efficacy even in the otherwise difficult-to-treat, disseminated BRAF-fused PLGG.[15] A phase 2 randomized clinical trial in France (NCT05180825) is comparing trametinib against chemotherapy (vinblastine) in the frontline setting in patients with PLGG.

Other MEK-inhibitors including cobimetinib,[16] binimetinib,[17] and mirdametinib[18] have shown similar response rates in recurrent/refractory PLGG in early-phase clinical trials, and additional studies and data are expected in the coming years (Table 1).

Efficacy of Targeted Therapy for *BRAF*;p.V600E Mutant PLGG

Retrospective analyses had suggested inferior outcomes for *BRAF*;p.V600E mutant PLGG following chemotherapy as compared to BRAF-fused patients, providing an early impetus to move forward with targeted therapies.[19] The

Table 1. Summary of Active Clinical Trials for Inhibitors for RAS/MAPK-Altered Gliomas

No.	Clinical trial	Disease/Population	Trial Description	Recruiting	Expected End Date
Upfront therapy for new diagnoses					
1	NCT04166409	PLGG	Selumetinib vs standard-of-care carboplatin and vincristine in newly diagnosed PLGG.	Yes	31-12-2026
2	NCT05566795	PLGG	LOGGIC/FIREFLY-2: a phase 3, randomized, international multicenter trial of Day101 monotherapy vs standard-of-care chemotherapy(vinblastine) in PLGG harboring an activating RAF alteration as upfront therapy.	Yes	03-2030
3	NCT05180825	PLGG	MEK inhibitor (trametinib) vs chemotherapy vinblastine in non NF1 PLGG as upfront therapy.	Yes	01-12-2031
4	NCT04923126	PLGG	Evaluation of mirdametinib in children, adolescents, and young adults with low-grade glioma.	Yes	06-2031
5	NCT03919071	PHGG	Dabrafenib combined with trametinib after radiation therapy in treating patients with newly diagnosed V600E mutant PHGG as upfront therapy.	Yes	30-09-2027
Recurrent/Progressive/Refractory disease					
1	NCT04576117	PLGG	Selumetinib alone vs selumetinib and vinblastine in progressive/recurrent PLGG.	Yes	30-12-2026
2	NCT06381570	PLGG	Pilot study of vinblastine and tovorafenib in patients with recurrent/progressive RAF PLGG (Victory).	Yes	21-03-2029
3	NCT04201457	PLGG and PHGG	A trial of dabrafenib, trametinib, and hydroxychloroquine for patients with recurrent LGG or HGG with a BRAF aberration.	Yes	30-06-2029
4	NCT05503797	Pediatric and adult gliomas	A study to assess the efficacy and safety of FORE8394 (plixorafenib) in participants with cancer harboring BRAF alterations.	Yes	28-08-2026
5	NCT06159478	low grade glioma (LGG)/adults	Binimetinib in patients with BRAF fusion-positive low-grade glioma or pancreatic cancer (perfume).	Yes	28-02-2027
6	NCT05804227	LGG/adults	Window-of-opportunity trial of ulixertinib for MAPK-activated low-grade gliomas in adults.	Yes	22-09-2027
7	NCT05768178	LGG and HGG/adults	Determine trial treatment arm 05: vemurafenib in combination with cobimetinib in adult patients with BRAF positive cancers.	Yes	10-2029
8	NCT06610682	LGG and HGG/adults	Feasibility of CSF and plasma ctDNA in BRAF-altered glioma during treatment with plixorafenib combined with cobicostat in refractory *BRAF*;p.V600E gliomas.	Starting 15-11-2024	15-05-2027
Long-term effects					
1	NCT03975829	PLGG	An open label, multi-center roll-over study to assess long-term effect in pediatric patients treated with Tafinlar (dabrafenib) and/or Mekinist (trametinib).	Yes	29-05-2026

oral BRAF inhibitors dabrafenib and vemurafenib demonstrated anti-tumor efficacy in early-phase clinical trials.[20–22] Specifically, the objective response rate for dabrafenib was 44% and 1-year PFS was 85% in recurrent/refractory patients.[20] In a retrospective study, targeted therapy outperformed chemotherapy with a 3-year PFS of 49.6% versus 29.8%.[23] Importantly, it was observed that while a MEK-inhibitor like trametinib also has activity in *BRAF*;p.V600E mutant PLGG,[24] these specific BRAF inhibitors were noted to paradoxically activate MAPK pathway signaling in BRAF-fused and BRAF-wild-type tumors, and possibly in healthy normal cells.[25] Studies from adult oncology in melanoma suggested that a combination of dabrafenib and trametinib could lead to improved efficacy and mitigate risk of resistance and some toxicities of BRAF-inhibitor monotherapy, including the risk of secondary skin cancers.[26,27] This provided the impetus for combination studies in PLGG. A randomized clinical trial recently demonstrated the superior efficacy of dabrafenib + trametinib in comparison to chemotherapy (vincristine + carboplatin) as first-line treatment, in terms of both objective response (47% vs 11%) and median PFS (20 vs 7 months).[28] However the choice of combination dabrafenib + trametinib, which is currently US Food and Drug Administration (FDA) approved for this indication, versus dabrafenib monotherapy is still an ongoing discussion for front-line therapy in the neuro-oncology community, with some groups still favoring the latter due to possible better compliance and lower cost of monotherapy treatment.[29]

A novel BRAF inhibitor, plixorafenib, that is uniquely designed to disrupt BRAF dimers and evade paradoxical MAPK pathway activation has been tested in both V600 and non-V600 BRAF-altered gliomas in adults and has been reported to have a favorable safety profile as compared to

Table 2. Side Effects Reported With the Currently Most Frequently Used RAS/MAPK Inhibitors in Pediatric Patients

Drug	Side Effects Observed in > 15%–20% of Patients	Serious Adverse Effects With ≥ 1% Prevalence	Other Side Effects
Selumetinib	Pyrexia, dry skin, acneiform rash, stomatitis, paronychia, hair changes (thinning/lightening), diarrhea, headache, anemia, elevated creatine kinase, hypoalbuminemia, elevated liver enzymes, increased creatinine decreased ejection fraction.	Retinal detachment, retinal vein occlusion, acute kidney injury, hypoxia.	Weight gain, facial edema, peripheral edema, nausea, abdominal pain, influenza-like illness, skin infections/ ulcerations, epistaxis, hematuria, electrolyte imbalance, increased amylase and lipase.
Trametinib	Rash, dermatitis acneiform, diarrhea, fatigue, peripheral edema, nausea/vomiting, hair thinning/ loss.	Cellulitis, pulmonary embolism, pneumonitis, reduced ejection fraction.	Dry skin, paronychia, stomatitis, hypertension, abdominal pain, musculoskeletal pain, headache, hemorrhage, cough, lymphedema, elevated liver enzymes and creatine kinase, decreased blood counts.
Dabrafenib	Pyrexia, headache, rash, hyperkeratosis, palmar-plantar erythrodysaesthesia, fatigue, nausea, alopecia, diarrhea, arthralgia, edema, hyponatremia.	Atrial fibrillation, squamous cell carcinoma, venous thromboembolism, reduced ejection fraction, chorioretinopathy.	Reduced appetite, dry skin, cellulitis, myalgia, constipation, hyperglycemia, hypophosphatemia, hemophagocytic lymphohistiocytosis.
Trametinib and Dabrafenib	Pyrexia, fatigue, nausea, headache, rash, chills, diarrhea, vomiting, arthralgia, myalgia, peripheral edema, hypertension, haemorrhage.	Decreased ejection fraction, hypotension, cellulitis, chorioretinopathy, venous thromboembolism.	Abdominal pain, constipation, dry skin, dermatitis acneiformis, weight gain, decreased blood counts, elevated liver enzymes, hyperglycemia, sarcoidosis.
Tovorafenib	Hair color change maculopapular rash, anemia, fatigue, vomiting, headache, hemorrhage, pyrexia, dry skin, diarrhea, nausea, dermatitis acneiform, paronychia, weight loss, elevated creatine kinase, elevated liver enzymes, hypophosphatemia.	Tumor hemorrhage, seizure, pericardial effusion.	Decreased growth velocity, photosensitivity reactions, decreased blood counts, electrolyte imbalance.

dabrafenib.[30] A phase 2 study (NCT05503797) is currently recruiting both adults and older children with *BRAF*;p.V600E and *BRAF*-fused CNS tumors (Table 1).

Efficacy of Type II RAF Inhibitors for MAPK-Altered PLGG

Tovorafenib is an oral, CNS-penetrant, type II RAF inhibitor that has activity against both oncogenic BRAF fusion, as well as *BRAF*;p.V600 mutations, without the paradoxical activation seen with traditional BRAF-inhibitors. In phase 2 clinical trial for relapsed/refractory RAF-altered PLGG, tovorafenib demonstrated an overall response rate of > 50% in both BRAF-fused and mutant tumors, including in patients previously treated on prior BRAF/MEK inhibitors, with median PFS > 19-months, leading to FDA approval for this indication.[31] The availability of a liquid formulation, a weekly dosing regimen (in contrast to daily doses for other available BRAF/MEK inhibitors) and lack of food effect, may make drug compliance easier for young patients.

Ongoing clinical trials include a phase 3 randomized clinical trial against chemotherapy (vinblastine or vincristine + carboplatin as investigator's choice) in the front-line setting (NCT05566795), and a combination study with chemotherapy (vinblastine) for recurrent/ progressive PLGG harboring an RAF alteration (NCT06381570). Notably, a combination study of tovorafenib and MEK1/2 inhibitor pimasertib (NCT04985604) has been recently terminated due to limited tolerance in adults with refractory tumors. Another novel "pan-RAF" inhibitor, belvarafenib,[32] has been tested recently in adults and adolescents in a clinical trial (NCT04589845) and results are awaited.

ERK-Inhibitor in MAPK-Altered PLGG

Ulixertinib is a reversible, ATP-competitive, ERK1/2 inhibitor that had shown preclinical efficacy in PLGG.[33] As reactivation of ERK signaling is a common driver for resistance after treatment with BRAF and MEK-inhibitors, the clinical development of ERK-inhibitors are of considerable interest. Ulixertinib was recently tested in a phase 2 trial for refractory pediatric cancers (NCT03698994). Though demonstrating no objective responses, a best response of stable disease lasting > 6 months was observed in 2 patients with PLGG and *BRAF*-fusion, and a patient with glioneuronal tumor with *BRAF*;p.V600E.[34] A PLGG-specific trial is underway in adults (NCT05804227;Table 1).

Current and Emerging Challenges With MAPK-Inhibitor Treatment for PLGG

Adverse effects.—The acute toxicity profile for MEK and BRAF-inhibitors as a class has been well-studied over the past decade and also reported now across different pediatric studies (Table 2).[35] Data from adults suggest that female patients may be at higher risk of some of the

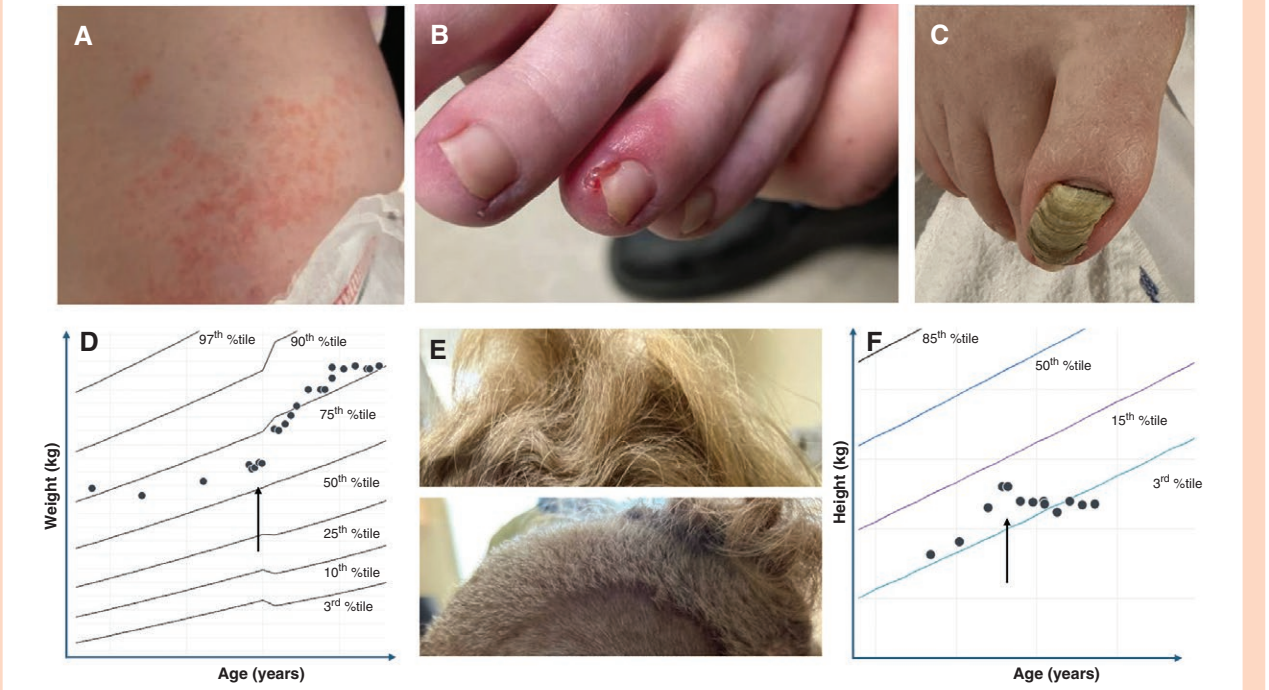

Figure 2. Common adverse effects of RAS/MAPK inhibition in children with low-grade gliomas. (A) Maculopapular rash; (B) Paronychia; (C) Discoloration and disfigurement of nails mimicking onychomycosis; (D) Rapid weight gain in a child after initiation of MEK-inhibitor; (E) Change in the color of hair after initiation of a pan-RAF inhibitor; (F) Lack of gain of height and decrease in growth velocity after initiation of a pan-RAF inhibitor.

treatment-related adverse effects. Cutaneous toxicities are frequent and include acneiform reactions, eczematous rash, dermatitis, panniculitis, keratosis-pilaris, and paronychia[36] (Figure 2A–C). If not proactively and adequately managed, this can add to significant morbidity, and hence needs specialized multi-disciplinary care. This involves adequate hygiene and preventive measures, counseling, specialized nursing care and support, as well as early dermatological review and intervention for severe cases.[36] Recent consensus guidelines have been published and focus on preventative and hygiene measures, and include the use of topical followed by systemic steroids, with or without antimicrobial treatment, in a graded manner, dependent on the severity.[37] A monoclonal antibody targeting interleukin-4 was recently reported to be an effective treatment for eczematous lesions and allowed sparing of steroids and successful rechallenge of MEK-inhibitors in patients with intractable cutaneous adverse effects.[38] Additional studies are needed in the future.

Gastrointestinal side effects including stomatitis, nausea, and diarrhea can develop with the use of BRAF/MEK-inhibitors, but are usually symptomatically managed, after excluding bleed and symptomatic colitis.[39] Pyrexia, edema, weight gain (Figure 2D), fatigue, liver enzyme, and creatine kinase elevation are usually manageable conservatively but may need temporary holding and/or dose modifications. Regular cardiac and ophthalmological review is mandatory to monitor for rare yet significant events including reduced ejection fraction and retinal detachment.[40–42]

The common acute adverse effects of the type II RAF inhibitor tovorafenib included hair color change (Figure 2E), anemia, elevated creatine kinase, and cutaneous reactions. Importantly, a reversible decrease in growth velocity (Figure 2F), and an increased incidence of intra-tumoral hemorrhage were reported. Pyrexia, diarrhea, and weight gain were reported to be less common than MEK/BRAF inhibitors, and no signs of ocular and cardiac toxicity were reported.[31]

Long-term side effects of MAPK inhibition in children are unknown and will need ongoing studies (like NCT03975829) and post-marketing surveillance. BRAF-inhibitor use in adults has been linked to benign and malignant skin pathologies.[27] While reports of squamous cell carcinoma exist in children,[21] whether younger patients on chronic therapy with these agents, have similar or different risks than adults, is yet to be conclusively determined.[20] Additionally, chronic immunological side effects of such inhibitors have been described in adults, including sarcoid-like reactions,[43] and as case reports in children.[44] The treating pediatric neuro-oncologists need to be aware of such emerging, albeit rare, immunological toxicities, given the increasing understanding of immune effects of MAPK inhibition.[45,46]

Duration of Treatment

Currently, the optimal duration of treatment with MAPK inhibitors in PLGG is unknown. Many of the clinical trials had chosen an arbitrary cutoff of 2 years.[47] But it is becoming

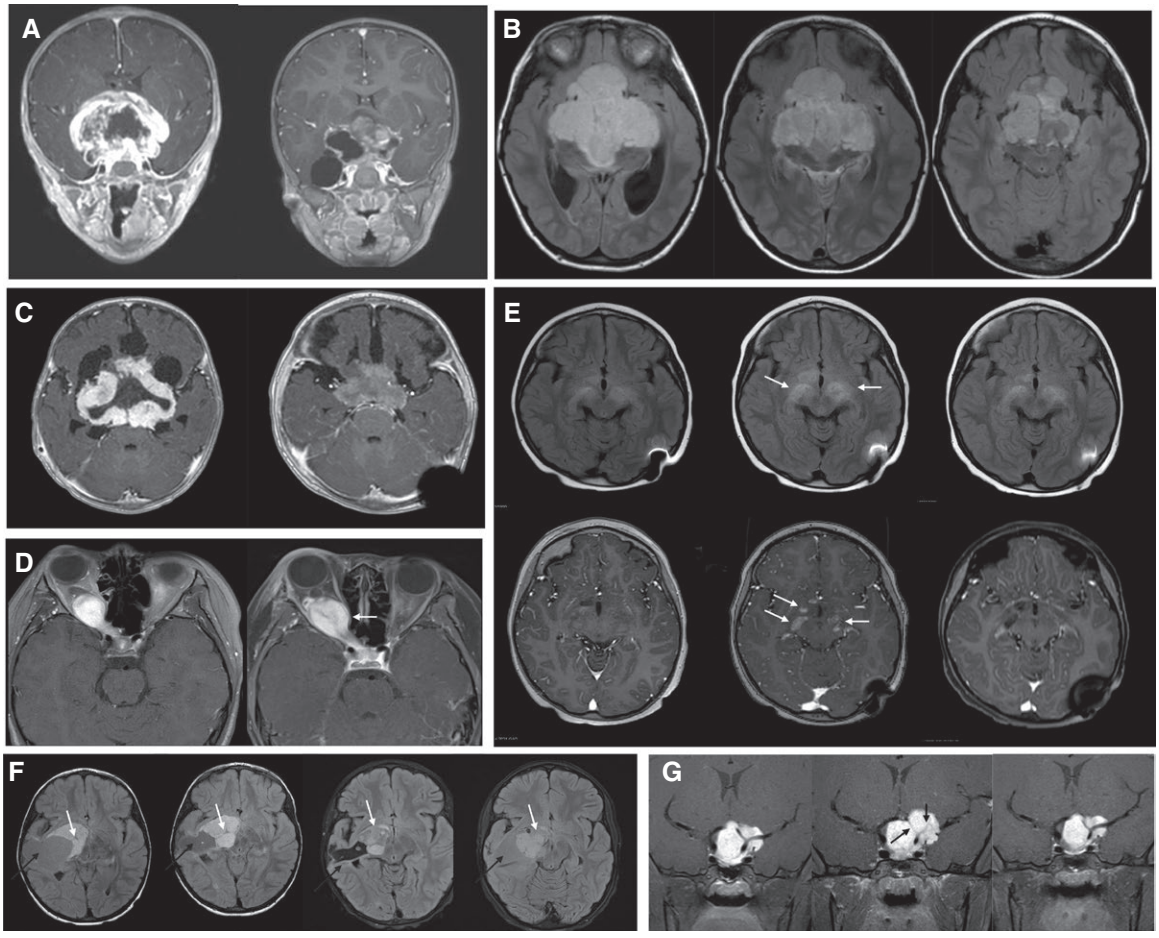

Figure 3. Varied response dynamics and trajectories following RAS/MAPK inhibition in pediatric low-grade gliomas. (A) Response to MEK-inhibitor within 3 months of treatment initiation in a patient with chemotherapy-refractory PLGG with a *KIAA1549-BRAF* fusion transcript. (B) A more typical slower response to MEK-inhibition in a chemotherapy refractory, BRAF-fused low-grade glioma, with slow and continued reduction of tumor dimensions at 6 and 12 months after start of treatment. (C) Relatively rapid radiological response within 2 months of initiation of dabrafenib monotherapy in a chemotherapy refractory, progressive, PLGG with *BRAF*;p.V600E. (D) True, sustained progression (white arrow) of an isolated optic nerve glioma with BRAF-fusion following MEK-inhibitor treatment over consecutive scans, suggesting intrinsic resistance to this treatment. (E) A child with PLGG with *BRAF*;p.V600E and initial response to dabrafenib and trametinib had to stop drugs due to toxicity, leading to rapid "rebound" growth (white arrows; T2/FLAIR sequences above and T1-contrast enhanced sequences below) and clinical deterioration withing weeks of treatment interruption. Concomitant management of toxicity while reinitiating targeted therapy led to radiological response and clinical improvement. (F) A child with chemotherapy-refractory, progressive *BRAF*-fused PLGG with a solid (white arrow) and cystic (black arrow) component causing pressure effects, was managed with insertion of an Ommaya reservoir for the cyst decompression, and initiated on MEK-inhibitor. Response was demonstrated over time, in terms of reduction of both the solid and cystic components, and treatment was stopped after prolonged disease stability was observed on serial imaging (image 3). However both components demonstrated slow and sustained re-growth over the next year (image 4) as the patient remained off-treatment, suggesting need for re-treatment. (G) Initial increase in dimensions of a BRAF-fused PLGG on a pan-RAF inhibitor, as seen by the increase in size and obliteration of intervening blood vessels (black arrows), which started to response after continuation of the same treatment over the next couple of months, akin to a pseudo-progression like phenomenon.

clearer that longer durations of therapy may be needed for many patients.[48] Inter-patient variability for response exists and is currently not well understood (Figure 3A–D). While relatively rapid response within months of treatment initiation can occur (Figure 3A), MEK-inhibitor treatment for BRAF-fused gliomas typically follow a slower trajectory for objective response, requiring several months and sometimes even a year or more of treatment (Figure 3B). In contrast, responses to BRAF and pan-RAF inhibitors may be observed within the early weeks to months of treatment initiation (Figure 3C). A small subset of patients can unfortunately demonstrate progression following targeted therapy (Figure 3D).

Durability of response can also be variable. Both rapid tumor rebound (within 3 months of stopping drug; Figure 3E), and a slower recurrence regrowth (usually ≥ 6 months after stopping treatment; Figure 3F) are well described.[49] This frequently mandates a drug rechallenge or additional therapies. There is emerging data to suggest that response to rechallenge may be suboptimal as compared to response during the primary therapy in some patients.[50] As complete drug holidays can therefore be challenging,

a unique approach suggested by a Canadian expert group involves slow "weaning" of the drug dose in patients with *BRAF*;p.V600E PLGG after a longer duration (36 months) of treatment.[29] A similar approach is under development for patients with BRAF-fused tumors. The goal would be to offset the risk of rapid tumor regrowth, while allowing patients to reduce their dose to achieve either a slower wean-off, or reach a lower dose that achieves disease stability, but limits toxicity. Stringent follow-ups are needed to see if such a strategy becomes successful.

Resistance

A significant tumor growth or development of a new metastatic lesion while on MAPK-inhibitor treatment would imply drug resistance.[49] However, it is important to note that the phase 2 tovorafenib trial did note subsequent tumor shrinkage after initial radiographic progression in a subset of patients, akin to the pseudo-progression phenomenon noted following immunotherapy[31] (Figure 3G). However once true resistance (either intrinsic or acquired after a definite duration of treatment) is confirmed, different therapeutic approaches are needed.[3] While mechanisms of MAPK-inhibitor resistance in PLGG are not yet well established, data from adult cancers generically suggest that this can be either through reactivation of the MAPK pathway, or other parallel pathways, genomic/transcriptional changes in the tumor, and changes in the microenvironment.[3,51,52] A subset of MAPK-inhibitor pretreated patients showed responses to tovorafenib, suggesting that a different inhibitor with a broader or different mechanism of action can work for some patients.[31] However others would need combinatorial approaches to overcome resistance. Current trials in refractory PLGG are investigating a combination of targeted and chemotherapy (NCT04576117, NCT06381570; Table 1). Another approach has been to overcome autophagy-associated MAPK-inhibitor resistance as described in adults,[53] by combining hydroxychloroquine with BRAF and MEK-inhibitors in progressive and refractory PLGG (NCT04201457). Ongoing research is investigating the intricate relationship between the MAPK pathway, oncogene-induced senescence, and the tumor microenvironment in PLGG.[54] Attempts to predict MAPK-inhibitor sensitivity in PLGG suggests that not only pathway inhibition in the tumor cells, but also in the immune microenvironment, may play a substantial role in response to inhibitor treatment, as well as for phenomenon like tumor rebound after treatment interruption.[52,55] These observations will probably allow more combinatorial approaches harnessing novel vulnerabilities in the PLGG microenvironment in the near future.

RAS/MAPK Targeted Therapy in Specific Subgroups of PHGG

Targeted Therapy in *BRAF*;p.V600E Mutant PHGG

This subset accounts for 5%–10% of PHGG.[56] Despite having relatively favorable outcomes as compared to other PHGG subsets, it is still ultimately a fatal disease. In a phase 2 trial in relapsed/refractory V600-mutant PHGG, the combination of dabrafenib and trametinib demonstrated superior objective response rates (56%), with a median duration of response of 22 months, as compared to historical controls.[57] Retrospective reviews have suggested that upfront use of targeted therapy could improve outcomes in comparison to historical controls, with a 3-year PFS of up to 65%.[58,59] In addition, a small clinical trial for V600-mutant PHGG in adults using encorafenib + binimetinib reported encouraging radiographic responses.[60] An open phase 2 clinical trial (NCT03919071) is currently investigating the post-radiation upfront treatment of V600-mutant PHGG with dabrafenib + trametinib. Interestingly, a case report suggested that for patients who progress, re-irradiation while continuing targeted therapy can be safe and effective.[61] Whether other combinations including immune checkpoint inhibitors can further add to efficacy in this disease subset as seen in melanoma by harnessing the effects of BRAF/MEK inhibition on the tumor microenvironment,[62] and some case reports of adult high grade gliomas (HGG),[63] this will need to be evaluated systematically in the pediatric population in the future.

MAPK Inhibition in Other PHGG

A subset of diffuse midline glioma driven by H3.3K27M mutations, which defines these tumors as high-grade irrespective of their morphology, demonstrate co-occurrence of mutations in the MAPK pathway, including co-mutations in *BRAF* and *FGFR1*.[64,65] This subset may be commoner at older ages and has been reported to have better OS (median 3 years) as compared to other DMGs.[65] A preclinical study recently demonstrated that despite in vitro sensitivity to MEK-inhibitors in DMG harboring MAPK alterations, there was lack of response in patient-derived xenograft models and in patients. However, a combinatorial approach using trametinib and dasatinib demonstrated synergism.[66] Similarly preclinical studies suggested that combined PI3K and MEK-inhibition may be effective in DMG.[67] It remains to be seen if such combinatorial approaches can be translated to benefit in human patients in well-designed clinical trials.

PHGG driven by DNA-replication repair deficiency (RRD) harbor hypermutation and microsatellite instability but only a subset responds to anti-programmed cell death protein 1 (PD1) monotherapy.[68] A preclinical study demonstrated oncogenic addiction to the RAS-MAPK pathway in the backdrop of hypermutation in RRD-HGG and response in preclinical studies to MEK-inhibitors.[69] This was translated to a pilot cohort of patients where MEK-inhibitor demonstrated synergism with anti-PD1 in patients progressing on anti-PD1 treatment by demonstrating radiological response and prolonged survival.[68] The peripheral immune response was synergized as well with the combination.[68] Further studies are needed to see if this approach can be beneficial to a larger number of patients with RRD-HGG.

Future Directions

Early successes with targeted therapy inhibiting the RAS/MAPK pathway in PLGG have ushered in an exciting new era for patients with this disease, that while usually not

fatal, caused significant long-term and chronic morbidities in patients whose disease could but be surgically resected. There is optimism in the neuro-oncology community for not only improved response rates as compared to chemotherapy, but also salvage of lost function, for example, improvement in vision in patients with optic pathway disease,[13] especially with early use of inhibitor treatment in the future. However, it has also become clear that despite PLGG being a "single pathway" disease, most patients will need long-term treatment, and a subset will not respond, or acquire resistance. While familiarity in the physician and nursing community with a set of toxicities which are distinct from chemotherapy like cutaneous issues has allowed better management, long-term effects in terms of toxicity, and impact on tumor senescence for oncologic outcomes, are unknown. Rare and emerging adverse effects suggest that meticulous follow-ups are needed for young patients on long-term treatment with these inhibitors. The next decade will need strive to further improve our understanding of MAPK inhibition in pediatric gliomas, focusing not only on objective responses and survival, but also patient-reported, functional, psychological, and neuro-cognitive outcomes, ongoing surveillance for late and emerging toxicities, identifying predictors of response and mechanisms of resistance, and developing combinatorial approaches to achieve durability of disease control.[47,70] In parallel, these therapies would need to be made more accessible and measures taken to curtail their effects on health economy, as these oral therapies can be a game-changer for the current dismal outcomes for patients with PLGG in low and middle-income countries.[71] Lastly, for PHGG, RAS/MAPK inhibition can be an important adjunct and need to be systematically studied in combination clinical trials involving standard-of-care radiation and other emerging treatments, and hope remains that this will improve survival steadily in this fatal disease.

Keywords

BRAF inhibition | high-grade glioma | low-grade glioma | MEK inhibition | targeted therapy

Conflict of interest statement

DH has received funding from Alexion/Astra Zeneca, Day One Biotherapeutics, Ipsen, and Novartis. AD has served on the Servier Canada advisory board outside the scope of this work.

Supplement sponsorship

This article appears as part of the supplement "Targeted Therapies in Pediatric Brain Tumors," sponsored by Day One Biopharmaceuticals.

Affiliations

Department of Paediatrics, University of Toronto and Hospital for Sick Children, Toronto, Canada (A.J.M.A.; A.D.); Developmental Biology and Cancer Department, University College London and Great Ormond Street Institute of Child Health, London, UK (D.H.)

References

1. Hossain MJ, Xiao W, Tayeb M, Khan S. Epidemiology and prognostic factors of pediatric brain tumor survival in the US: evidence from four decades of population data. *Cancer Epidemiol.* 2021;72:101942.
2. 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(8):1231–1251.
3. Bahar ME, Kim HJ, Kim DR. Targeting the RAS/RAF/MAPK pathway for cancer therapy: from mechanism to clinical studies. *Signal Transduct Target Ther.* 2023;8(1):455.
4. 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(7):1011–1022.
5. Gross AM, Wolters PL, Dombi E, et al. Selumetinib in children with inoperable plexiform neurofibromas. *N Engl J Med.* 2020;382(15):1430–1442.
6. Fangusaro J, Jones DT, Packer RJ, et al. Pediatric low-grade glioma: state-of-the-art and ongoing challenges. *Neuro Oncol.* 2024;26(1):25–37.
7. Armstrong GT, Liu Q, Yasui Y, et al. Long-term outcomes among adult survivors of childhood central nervous system malignancies in the Childhood Cancer Survivor Study. *J Natl Cancer Inst.* 2009;101(13):946–958.
8. Neglia JP, Robison LL, Stovall M, et al. New primary neoplasms of the central nervous system in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *J Natl Cancer Inst.* 2006;98(21):1528–1537.
9. 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(7):1173–1179.
10. Krishnatry R, Zhukova N, Guerreiro Stucklin AS, et al. Clinical and treatment factors determining long-term outcomes for adult survivors of childhood low-grade glioma: a population-based study. *Cancer.* 2016;122(8):1261–1269.
11. Ryall S, Zapotocky M, Fukuoka K, et al. Integrated molecular and clinical analysis of 1,000 pediatric low-grade gliomas. *Cancer Cell.* 2020;37(4):569–583.e5.
12. Banerjee A, Jakacki RI, Onar-Thomas A, et al. A phase I trial of the MEK inhibitor selumetinib (AZD6244) in pediatric patients with recurrent or refractory low-grade glioma: a Pediatric Brain Tumor Consortium (PBTC) study. *Neuro Oncol.* 2017;19(8):1135–1144.
13. Fangusaro J, Onar-Thomas A, Poussaint TY, et al. A phase II trial of selumetinib in children with recurrent optic pathway and hypothalamic low-grade glioma without NF1: a Pediatric Brain Tumor Consortium study. *Neuro Oncol.* 2021;23(10):1777–1788.
14. Perreault S, Larouche V, Tabori U, et al. SYST-04. TRAM-01: a phase 2 study of trametinib for patients with pediatric glioma with activation of the MAPK/ERK pathway. *Neurooncol Adv.* 2021;3(Supplement_4):iv9–iv9.
15. Castellano-Damaso S, Vazquez-Gomez F, Moreno-Carrasco JL, et al. Continuous response despite reduced dose of trametinib as single agent in an adolescent with a relapsed disseminated pediatric low-grade glioma KIAA1549-BRAF fusion positive: a case report and review of the literature. *Front Oncol.* 2024;14:1381354.
16. Trippett T, Toledano H, Campbell Hewson Q, et al. Cobimetinib in pediatric and young adult patients with relapsed or refractory solid tumors (iMATRIX-cobi): a multicenter, phase I/II study. *Target Oncol.* 2022;17(3):283–293.
17. Robison N, Pauly J, Malvar J, et al. LTBK-04. LATE BREAKING ABSTRACT: MEK162 (binimetinib) in children with progressive or

recurrent low-grade glioma: a multi-institutional phase II and target validation study. *Neuro-Oncology.* 2022;24(Supplement_1):i191–i192.
18. Robinson GW, Vinitsky A, Bag AK, et al. LGG-53. Results from the phase 1 and phase 1 expansion cohorts of SJ901: a phase 1/2 trial of single-agent mirdametinib (PD-0325901) in children, adolescents, and young adults with low-grade glioma. *Neuro-Oncology.* 2024;26(Supplement_4):129.
19. 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(25):2934–2941.
20. 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(24):7303–7311.
21. 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(21):1942–1952.
22. Kaley T, Touat M, Subbiah V, et al. BRAF inhibition in BRAF(V600)-mutant gliomas: results from the VE-BASKET study. *J Clin Oncol.* 2018;36(35):3477–3484.
23. Nobre L, Zapotocky M, Ramaswamy V, et al. Outcomes of BRAF V600E pediatric gliomas treated with targeted BRAF inhibition. *JCO Precis Oncol* 2020;4:PO.19.00298.
24. 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(3):664–674.
25. Sievert AJ, Lang SS, Boucher KL, et al. Paradoxical activation and RAF inhibitor resistance of BRAF protein kinase fusions characterizing pediatric astrocytomas. *Proc Natl Acad Sci U S A.* 2013;110(15):5957–5962.
26. Robert C, Grob JJ, Stroyakovskiy D, et al. Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. *N Engl J Med.* 2019;381(7):626–636.
27. Peng L, Wang Y, Hong Y, et al. Incidence and relative risk of cutaneous squamous cell carcinoma with single-agent BRAF inhibitor and dual BRAF/MEK inhibitors in cancer patients: a meta-analysis. *Oncotarget.* 2017;8(47):83280–83291.
28. Bouffet E, Hansford JR, Garre ML, et al. Dabrafenib plus trametinib in pediatric glioma with BRAF V600 mutations. *N Engl J Med.* 2023;389(12):1108–1120.
29. Erker C, Vanan MI, Larouche V, et al. Canadian consensus for treatment of BRAF V600E mutated pediatric and AYA gliomas. *Curr Oncol.* 2024;31(7):4022–4029.
30. de la Fuente M, Butowski N, Taylor J, et al. CTNI-76. Efficacy of BRAF inhibitor plixorafenib (FORE8394) in recurrent, primary central nervous system tumors (PCNST). *Neuro-Oncology.* 2023;25(Supplement_5):v95–v95.
31. Kilburn LB, Khuong-Quang DA, 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(1):207–217.
32. Gonzalez M, Lebert B, Campion S, Aguilar-Bonilla A, Smith A. TRLS-13. Novel PAN-RAF inhibitor belvarafenib as a promising targeted therapy for BRAF-altered pediatric low-grade gliomas. *Neuro-Oncology.* 2023;25(Supplement_1):i82–i82.
33. Sigaud R, Rösch L, Gatzweiler C, et al. The first-in-class ERK inhibitor ulixertinib shows promising activity in mitogen-activated protein kinase (MAPK)-driven pediatric low-grade glioma models. *Neuro-Oncology.* 2022;25(3):566–579.
34. Vo KT, Sabnis AJ, Williams PM, et al. Phase II study of ulixertinib in children and young adults with tumors harboring activating mitogen-activated protein kinase pathway alterations: APEC1621J of the National Cancer Institute-Children's Oncology Group Pediatric MATCH Trial. *JCO Precis Oncol.* 2024;8:e2400103.
35. Garutti M, Bergnach M, Polesel J, et al. BRAF and MEK inhibitors and their toxicities: a meta-analysis. *Cancers (Basel).* 2022;15(1):141.
36. 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(6):1554–1561.
37. Azizi AA, Hargrave D, Passos J, et al. Consensus recommendations on management of selumetinib-associated adverse events in pediatric patients with neurofibromatosis type 1 and plexiform neurofibromas. *Neurooncol Pract.* 2024;11(5):515–531.
38. Gu S, Dusza SW, Dunkel IJ, et al. Dupilumab for the treatment of dermatologic adverse events associated with MEK and EGFR inhibitors. *J Clin Oncol.* 2023;41(16_suppl):3143–3143.
39. Gelsomino F, Di Federico A, Tardio ML, et al. Drug-induced colitis on BRAF and MEK inhibitors for BRAF V600E-mutated non-small cell lung cancer: a case report. *Invest New Drugs.* 2022;40(1):190–193.
40. Glen C, Tan YY, Waterston A, et al. Mechanistic and clinical overview cardiovascular toxicity of BRAF and MEK inhibitors: JACC: cardiooncology state-of-the-art review. *JACC CardioOncol.* 2022;4(1):1–18.
41. Jeng-Miller KW, Miller MA, Heier JS. Ocular effects of MEK inhibitor therapy: literature review, clinical presentation, and best practices for mitigation. *Oncologist.* 2024;29(5):e616–e621.
42. Mettler C, Monnet D, Kramkimel N, et al. Ocular safety profile of BRAF and MEK inhibitors: data from the World Health Organization pharmacovigilance database. *Ophthalmology.* 2021;128(12):1748–1755.
43. Anastasopoulou A, Diamantopoulos PT, Skalioti C, et al. The diagnosis and management of sarcoid-like reactions in patients with melanoma treated with BRAF and MEK inhibitors. A case series and review of the literature. *Ther Adv Med Oncol.* 2021;13:17588359211047349.
44. Wilhelmsson M, Chun FJ, Yeung RSM, et al. Sarcoid-like reaction in a child following prolonged therapeutic exposure to dabrafenib and trametinib for BRAF V600E mutated hypothalamic/chiasmatic glioma. *Pediatr Blood Cancer.* 2023;70(11):e30619.
45. McKeown T, Renzi S, Larouche V, et al. LGG-51. Systemic immune toxicity of BRAF and MEK-inhibitors in children: a Pan-Canadian series. *Neuro-Oncology.* 2024;26(Supplement_4):0–0.
46. Ascierto PA, Dummer R. Immunological effects of BRAF+MEK inhibition. *Oncoimmunology.* 2018;7(9):e1468955.
47. Mueller S, Fangusaro J, Thomas AO, et al. Consensus framework for conducting phase I/II clinical trials for children, adolescents, and young adults with pediatric low-grade glioma: guidelines established by the International Pediatric Low-Grade Glioma Coalition Clinical Trial Working Group. *Neuro Oncol.* 2024;26(3):407–416.
48. Selt F, van Tilburg CM, Bison B, et al. Response to trametinib treatment in progressive pediatric low-grade glioma patients. *J Neurooncol.* 2020;149(3):499–510.
49. O'Hare P, Cooney T, de Blank P, et al. Resistance, rebound, and recurrence regrowth patterns in pediatric low-grade glioma treated by MAPK inhibition: a modified Delphi approach to build international consensus-based definitions-International Pediatric Low-Grade Glioma Coalition. *Neuro Oncol.* 2024;26(8):1357–1366.
50. Bajin IY, Siddaway R, Levine A, et al. LGG-50. Poor response to MEKI re-initiation in pediatric low-grade glioma after treatment discontinuation. a PLGG taskforce study. *Neuro-Oncology.* 2024;26(Supplement_4):0–0.
51. Kun E, Tsang YTM, Ng CW, Gershenson DM, Wong KK. MEK inhibitor resistance mechanisms and recent developments in combination trials. *Cancer Treat Rev.* 2021;92:102137.
52. Pensabene JM, Perez NM, Yazejian RM, Moziak K, Martin AM. LGG-46. MEKI with mirdametinib: exploring adaptive signaling pathway

dynamics and immune modulation in pediatric gliomas. *Neuro-Oncology.* 2024;26(Supplement_4):0–0.

53. Mehnert JM, Mitchell TC, Huang AC, et al. BAMM (BRAF autophagy and MEK inhibition in melanoma): a phase I/II trial of dabrafenib, trametinib, and hydroxychloroquine in advanced BRAFV600-mutant melanoma. *Clin Cancer Res.* 2022;28(6):1098–1106.
54. Sigaud R, Brummer T, Kocher D, Milde T, Selt F. MOST wanted: navigating the MAPK-OIS-SASP-tumor microenvironment axis in primary pediatric low-grade glioma and preclinical models. *Childs Nerv Syst.* 2024;40(10):3209–3221.
55. Sigaud R, Albert TK, Hess C, et al. MAPK inhibitor sensitivity scores predict sensitivity driven by the immune infiltration in pediatric low-grade gliomas. *Nat Commun.* 2023;14(1):4533.
56. Mackay A, Burford A, Carvalho D, et al. Integrated molecular meta-analysis of 1,000 pediatric high-grade and diffuse intrinsic pontine glioma. *Cancer Cell.* 2017;32(4):520–537.e5.
57. Hargrave DR, Terashima K, Hara J, et al.; Investigators involved in the high-grade glioma cohort. Phase II trial of dabrafenib plus trametinib in relapsed/refractory BRAF V600-mutant pediatric high-grade glioma. *J Clin Oncol.* 2023;41(33):5174–5183.
58. Rosenberg T, Yeo KK, Mauguen A, et al. Upfront molecular targeted therapy for the treatment of BRAF-mutant pediatric high-grade glioma. *Neuro Oncol.* 2022;24(11):1964–1975.
59. Arbour G, Ellezam B, Weil AG, et al. Upfront BRAF/MEK inhibitors for treatment of high-grade glioma: a case report and review of the literature. *Neurooncol Adv.* 2022;4(1):vdac174.
60. Schreck KC, Strowd RE, Nabors LB, et al. Response rate and molecular correlates to encorafenib and binimetinib in BRAF-V600E mutant high-grade glioma. *Clin Cancer Res.* 2024;30(10):2048–2056.
61. Bergeron Gravel S, Bouffet E, Tabori U, Hawkins C, Tsang DS. Re-irradiation with concurrent BRAF and MEK inhibitor therapy. *Pediatr Blood Cancer.* 2021;68(5):e28838.
62. Adams R, Coumbe JEM, Coumbe BGT, et al. BRAF inhibitors and their immunological effects in malignant melanoma. *Expert Rev Clin Immunol.* 2022;18(4):347–362.
63. Wagle N, Sharma A, Nguyen M, et al. Neoadjuvant combination treatment with checkpoint inhibitors, chemotherapy, and BRAF/MEK inhibitors for BRAF(V600E) glioblastoma results in sustained response: a case report. *Neurooncol Adv.* 2024;6(1):vdae110.
64. Roberts HJ, Ji S, Picca A, et al. Clinical, genomic, and epigenomic analyses of H3K27M-mutant diffuse midline glioma long-term survivors reveal a distinct group of tumors with MAPK pathway alterations. *Acta Neuropathol.* 2023;146(6):849–852.
65. Auffret L, Ajlil Y, Kergrohen T, et al. DIPG-43. Clinical and molecular characteristic of a new subtype OF DMG, H3K27-altered with MAPK-activating co-driver mutations. *Neuro-Oncology.* 2023;25(Supplement_1):i22–i23.
66. Izquierdo E, Carvalho DM, Mackay A, et al. DIPG harbors alterations targetable by MEK inhibitors, with acquired resistance mechanisms overcome by combinatorial inhibition. *Cancer Discov.* 2022;12(3):712–729.
67. Chang R, Tosi U, Voronina J, et al. Combined targeting of PI3K and MEK effector pathways via CED for DIPG therapy. *Neurooncol Adv.* 2019;1(1):vdz004.
68. Das A, Fernandez NR, Levine A, et al. Combined immunotherapy improves outcome for replication-repair-deficient (RRD) high-grade glioma failing anti-PD-1 monotherapy: a report from the International RRD Consortium. *Cancer Discov.* 2024;14(2):258–273.
69. Campbell BB, Galati MA, Stone SC, et al. Mutations in the RAS/MAPK pathway drive replication repair-deficient hypermutated tumors and confer sensitivity to MEK inhibition. *Cancer Discov.* 2021;11(6):1454–1467.
70. 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(11):2303–2308.
71. Moreira DC, Bouffet E, Qaddoumi I. The greatest challenge for pediatric low-grade glioma. *Neuro Oncol.* 2024;26(5):975–976.