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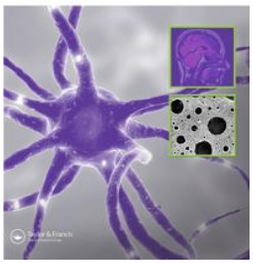

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REVIEW ARTICLE

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Practical management of BRAF inhibitors in glioma: toxicity and resistance

Danielle Bazer[a], Abiola A. Ayanlaja[b,c] and Karisa C. Schreck[b,c]

[a]Department of Neurology, Cooper University Health Care, Camden, NJ, USA; [b]Department of Neurology, Johns Hopkins School of Medicine, Baltimore, MD, USA; [c]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA

ABSTRACT

BRAF inhibitors have advanced treatment for patients with BRAF-altered high and low-grade glioma (HGG and LGG, respectively). Clinically-available therapies are effective but require selection by mutation type and careful, proactive toxicity management to maximize patient quality of life and treatment duration. While pediatric LGG patients often experience durable responses, adults with LGG and patients with HGG frequently develop treatment resistance and disease progression while on treatment. Strategies to prevent or overcome resistant disease are under active preclinical and clinical investigation. This review serves as a primer to BRAF-altered therapy in glioma, outlines best practices for using available BRAF inhibitors, and highlights emerging therapeutic approaches aimed at improving outcomes in resistant disease. It serves as a forward-looking, practical guide for clinicians treating patients with BRAF-altered glioma.

ARTICLE HIGHLIGHTS

1. BRAF inhibitors are effective in both pediatric and adult low- and high-grade gliomas (LGG and HGG), but treatment should be tailored to the specific BRAF alteration (Table 1).
2. Dabrafenib combined with trametinib is FDA-approved for BRAF V600E-mutant gliomas, while tovorafenib is approved for pediatric LGGs harboring BRAF V600 mutations or BRAF fusions.
3. Proactive management, including anticipatory guidance and dose reduction for some patients, is essential to mitigate toxicity and avoid treatment interruptions.
4. Tumor progression can occur during treatment interruptions or drug cessation; however, some patients may respond to BRAF inhibitor rechallenge.
5. Emerging strategies focus on combination with other therapies including radiation, autophagy inhibitors, additional targeted agents, and others to overcome acquired resistance.
6. Next-generation BRAF inhibitors—including paradox breakers, dimer disruptors, and protein degraders—are under clinical investigation (Table 2).

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KEYWORDS
High-grade glioma; low-grade glioma; BRAF; targeted therapy; BRAF inhibitor; MEK inhibitor; tovorafenib; dabrafenib

1. Introduction

Breakthroughs in brain cancer therapies have been limited over the past 20 years, despite significant advances for small molecule inhibitors and immunotherapy in other solid tumors. The notable positive exception has been for subgroups of gliomas with targetable oncogenic driver mutations such as v-Raf murine sarcoma viral oncogene homolog B (*BRAF)* or isocitrate dehydrogenase (*IDH1/2*) [1]. Oncogenic *BRAF* alterations result in constitutive kinase activity and loss of negative feedback inhibition, permitting dysregulated ERK signaling [2,3]. The most common BRAF alteration in cancers, a single-nucleotide variant at p.V600E confers constitutive kinase activity without the need for dimerization [4]. Other common alterations include rearrangements, which are particularly common in pediatric low-grade glioma (pLGG), and result in kinase activity that is dependent on dimerization but independent from upstream RAS activation [2,5]. Small molecule inhibitors of mutant BRAF (BRAFi), alone or in combination with small molecule inhibitors of the downstream kinase MEK (MEKi), successfully inhibit ERK signaling and tumor growth across many cancers [6,7].

Targetable BRAF alterations occur in many glioma subgroups, most notably in pLGG where 72% of tumors harbor a BRAF alteration (Figure 1A) [8]. Low-grade

CONTACT Karisa C. Schreck ksolt1@jhmi.edu Department of Neurology, Johns Hopkins School of Medicine, 201 N Broadway, Viragh #9179 Baltimore MD 21287, USA.

Table 1. Patient characteristics, responses, and common toxicities of BRAF inhibitors evaluated in clinical trials of patients with gliomas.

	Dabrafenib + Trametinib (Wen)	Dabrafenib + Trametinib (Bouffet)	Vemurafenib (Kaley)	Encorafenib + Binimetinib (Schreck)	Tovorafenib (Kilburn)
Trial enrollment (years)	4/17/2014-7/25/2018	9/2018-12/2020	Not Reported	1/2020-11/2021	4/22/21-1/26/23
Age in years (median, range)	HGG: 42 (range 18–72), LGG 33 (range 18–58)	10 (1-17)	32 (18-81)	27 (22-77)	9 (1-24)
Sex (male/female)	27/31	40/33	6.0/18.0	2.0/3.0	73/64
Tumor pathology	HGG: GBM, aPXA, AA. LGG: anglioglioma, PXA, DA.	PA, GG, LGG, other	PXA, malignant diffuse glioma, other	PXA, GBM	pediatric LGG
RR - HGG (%)	33	N/A	9	80	N/A
RR - LGG (%)	69	47	43 (PXA), 33 (other)	N/A	53
Median duration of treatment (mo)	HGG: 14.9, 14.2 months (dabrafenib, trametinib). LGG: 27.3, 26.7 months (dabrafenib, trametinib)	17.4	PXA: NR, malignant diffuse glioma: 11.9, and other: 28.2.	10 (DOR)	15.8
PFS (mo)	3.8 (HGG), NR (LGG)	20.1	5.5	9.4	19.4
Most Common TRAEs ($\geq$20%)from FDA Package Insert	Pyrexia, fatigue, nausea, rash, chills, headache, hemorrhage, cough, vomiting, constipation, diarrhea, myalgia, arthralgia, edema	Pyrexia, rash, headache, vomiting, musculoskeletal pain, fatigue, diarrhea, dry skin, nausea, hemorrhage, abdominal pain, dermatitis acneiform	Arthralgia, rash, alopecia, fatigue, photosensitivity, nausea, pruritus, skin papilloma	fatigue, nausea, vomiting, abdominal pain, arthralgia	rash, hair color changes, fatigue, viral infection, vomiting, headache, hemorrhage, pyrexia, dry skin, constipation, nausea, dermatitis acneiform, upper respiratory tract infection
Serious TRAEs (CTCAE Gr $\geq$ 3) from FDA package insert	Cutaneous squamous cell carcinomas (2%), new melanoma (<1%), intracranial hemorrhage (0.6%), cardiomyopathy (6%), uveitis (2%), fever (5%), skin toxicity (<1%), hyperglycemia (2%)	Serious bleeding (3.6%), cerebral hemorrhage (0.6%), cardiomyopathy (9%), uveitis (1.2%), pyrexia (17%), skin toxicity (1.8%), vomiting (4.2%), hyperglycemia (<1%)	Cutaneous squamous cell carcinomas (24%), malignant new melanoma (2.1%), rash (7%), photosensitivity (3%), liver function test elevation (6%), uveitis (2.1%), creatinine elevation (1.2%)	cutaneous squamous cell carcinoma (2.6%), left ventricular dysfunction (1.6%), liver function test elevation (6%), hemorrhage (3.2%), intracranial hemorrhage (1.6%), uveitis (4%), QT prolongation (0.5%)	serious bleed (5%), intratumoral hemorrhage (9%), rash (12%), photosensitivity (0.6%), liver function test elevation (4%), decreased growth velocity (5%), pyrexia (4%), vomiting (4%), decreased hemoglobin (15%)

AA = anaplastic astrocytoma, DA = diffuse astrocytoma, GBM = glioblastoma, GG = ganglioglioma. LGG = low-grade glioma, HGG = high-grade glioma, NR = not reached, PA = pilocytic astrocytoma, PXA = pleomorphic xanthoastrocytoma.

Table 2. Ongoing targeted therapy clinical trials enrolling patients with BRAF-altered gliomas.

NCT number	Phase	Age requirment (years)	Tumors	Drug(s)	Mechanism of action
NCT06610682	I	> 18	Glioma	Plixorafenib	BRAF paradox breaker
	0	> 18	BRAFi recurrent glioma	Plixorafenib	BRAF paradox breaker
NCT06712875	I/II	1-26.0	Glioma	Dabrafenib, Trametinib, Nivolumab	MAPK inhibitor and anti-PD-1
NCT06326411	I	1-30.0	Solid Tumors with MAPK alterations	NST-628	pan-RAF/MEK molecular glue
NCT04566393	Expanded Access	> 12	Solid Tumors with MAPK alterations	Ulixertinib	MEK inhibitor
NCT05355701	I	>16	BRAF altered solid tumors	PF-07799933	BRAF inhibitor
NCT06270082	I	> 18	RAS- or RAF-altered solid tumors	IK-595	MEK/RAF inhibitor
NCT05786924	I	> 18	Solid tumors harboring BRAF mutations	BDTX-4933	pan-RAF inhibitor
NCT04589845	II	All	Solid tumors	Belvarafenib (and others)	pan-RAF inhibitor

gliomas in adult patients harbor BRAF alterations in 2-5% of cases. In high-grade gliomas, approximately 3% of adult and 5–10% pediatric HGG demonstrate a BRAF alteration [9,10]. The BRAFV600E alteration is the most prevalent BRAF alteration in adult gliomas and in HGG, while BRAF rearrangements, most commonly *KIAA1549-BRAF,* are more prevalent in pLGG [8,11,12]. Despite their relative rarity, BRAF alterations are enriched in certain glioma subgroups including pilocytic astrocytoma, pleomorphic xanthoastrocytoma, ganglioglioma, and epithelioid glioblastoma (Figure 1B) [8,13].

BRAF-targeted therapy is FDA-approved for gliomas based on positive clinical trials in patients with pediatric low-grade glioma (pLGG), adult LGG, and high-grade glioma (HGG). The BRAFi, dabrafenib, in combination with the MEKi, trametinib, is effective in the first line setting for people with pLGG, as well as for those with recurrent/refractory LGG and HGG having a BRAFV600E mutation [14,15]. A second BRAFi/MEKi inhibitor combination, encorafenib with binimetinib, has shown positive responses in patients with treatment-refractory BRAFV600E-mutant HGG, providing a potential, off-label tool for clinical use [16]. Vemurafenib monotherapy has also demonstrated positive benefit in children and adults with HGG and LGG [17,18]. Unfortunately, dabrafenib and other BRAFi in the same class (encorafenib, vemurafenib) are largely ineffective for gliomas with other BRAF point mutations or for BRAF rearrangements/fusions due to their specificity. Tovorafenib, a type 2 BRAF inhibitor capable of binding to and inhibiting the function of BRAFV600 mutants as well disrupting dimerization, demonstrates clinical responses and benefit in children with relapsed/recurrent pLGG with BRAFV600E or rearrangements [19].

While a substantial step forward for people with BRAF-altered gliomas, BRAFi are not curative, and resistance can occur. Resistance to targeted therapy can occur from the start of treatment (*de novo* due to intrinsic resistance*)* or emerge over the course of treatment, even after a durable response. Resistance can develop through additional genomic alterations that evade ERK suppressive therapy (acquired resistance), or through changes in signaling networks evading or overcoming targeted therapy (adaptive resistance) [20–22]. Resistance has been observed more commonly in adults and in patients with HGG, likely due to other co-occurring alterations conferring resistance (e.g., *NF1, KRAS, PI3CA)* or overall poor prognosis (i.e., *CDKN2A/B)* [8,13,15].

In this manuscript, we describe best practices to improve tolerability and evade therapeutic resistance using clinically-available BRAF inhibitors, as well as novel approaches in development. This is intended to be a practical guide to clinicians caring for patients with BRAF-altered glioma.

2. Maximizing the benefit of FDA-approved targeted therapy for gliomas

Currently, there are two BRAF targeted therapies specifically approved for brain tumors (Table 1). The combination therapy of dabrafenib and trametinib carries a tumor-agnostic approval for both unresectable or metastatic solid tumors with BRAFV600E mutations in patients aged 6 years or older, as well as an approval for LGG in patients aged 1 year or older in both the USA and Europe [23,24]. Response rates to dabrafenib/trametinib range from 33 to 69% in children and adults with LGG, to 31-56% in adults and children with HGG or glioblastoma, respectively [14,15,25].

Tovorafenib, a type II RAF inhibitor, is effective at inhibiting oncogenic BRAFV600 mutations and BRAF rearrangements. It demonstrated a response rate of 53% in patients aged 0–21 with relapsed/refractory pediatric low-grade gliomas (included minor responses as part of this response rate) and is approved by the

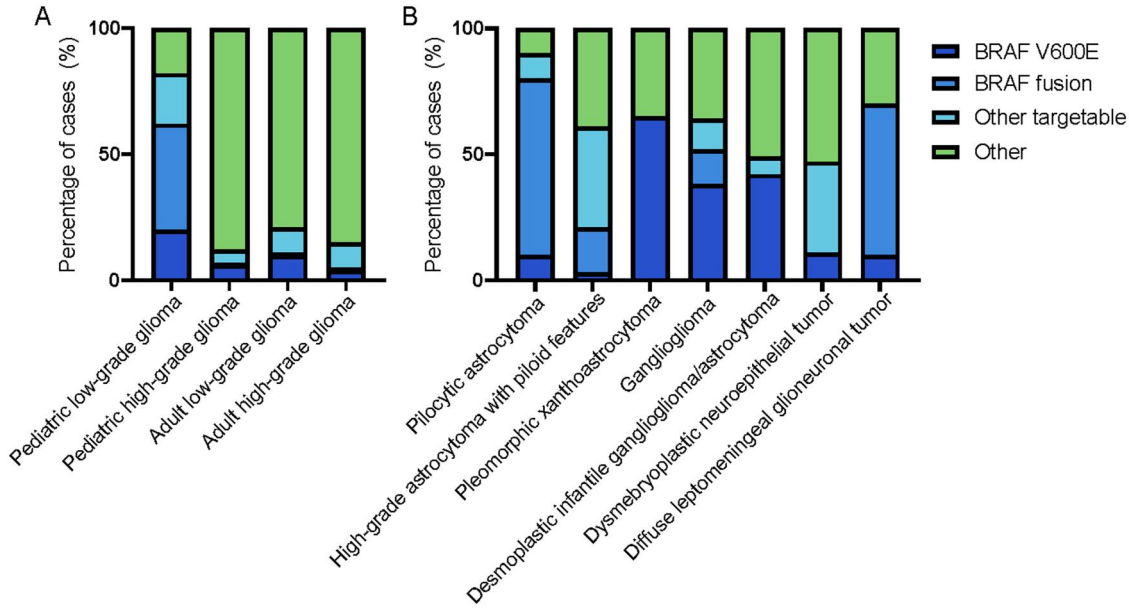

Figure 1. Relative frequency of BRAF and other targetable alteration types by tumor type across A) adult and pediatric ages with high- and low-grade gliomas or B) tumor types in which BRAF alterations occur frequently.

FDA for individuals aged 6 months or older with BRAF-altered, relapsed/refractory LGG (pending authorization in EMA) [19]. Notably, tovorafenib shows efficacy for patients who received a prior BRAFi or MEKi as well, with a 71% response rate. Its efficacy in HGG or adult patients with LGG is unclear [26,27].

While BRAF inhibitors benefit patients with LGG and HGG, a patient's experience while on therapy is likely affected by adverse drug reactions. Dabrafenib/trametinib is commonly associated with pyrexia, chills, fatigue, rash, nausea, vomiting, diarrhea, abdominal pain, peripheral edema, headache, arthralgia, night sweats, decreased appetite, constipation, and myalgia, which are also seen in patients with HGG/LGG [28]. In a clinical trial of adults with glioma, adverse events led to dose reduction in 8% of patients, dose interruptions in 41% of patients, and permanent discontinuation in 9% of patients [15]. For pediatric patients with HGG, response rates can be as high as 56% [25]. This is reflective of the overall clinical experience in solid cancers with dabrafenib/trametinib, where 57% of patients experience dose interruptions, 28-65% experience dose reductions, and 12-24% of patients discontinue drug for toxicity [29–32]. In a pediatric study, 79% of patients underwent dose adjustments or interruptions for toxicity [14]. Of note, the incidence of adverse events generally does not correlate with response to treatment or outcome [33].

Tovorafenib is associated with similar toxicities, most commonly rash, hair color changes, fatigue, viral infections, vomiting, headache, hemorrhage, pyrexia, dry skin, constipation, nausea, dermatitis acneiform, upper respiratory tract infection, reduced growth velocity, and a rare risk of intratumoral hemorrhage (7%) [34,35]. These adverse events led to dose reduction in 24% of patients and dose interruptions in 37% of patients on study, with drug discontinuation due to toxicity in 7% [19]. Given its recent FDA approval, real world data on tolerability are still emerging.

2.1. Optimizing tolerability of dabrafenib/trametinib

While 90% of patients on BRAF-targeted therapy experience drug-related toxicities, the bulk of these are low grade (CTCAE Grade 1–2) toxicities that can be managed supportively, enabling patients to remain on therapy [29,36]. Anticipatory guidance and close follow-up are critical to maximize tolerability, particularly early in treatment. Judicious dose reductions can ameliorate toxicity while maintaining benefit. Lastly, switching between agents within a class can be effective at improving particularly challenging toxicity [37,38].

2.2. Anticipatory guidance and resources

Given the known toxicity profiles for dabrafenib and trametinib, patients should be provided with anticipatory guidance and resources to guide them during their treatment. For example, pyrexia with or without associated features such as hypotension, dehydration, and/or renal failure have a different treatment paradigm [39,40]. Pyrexia without associated systemic

features requires only a drug hold with the ability to resume once the fever effervesces, however, a drug hold and dose reduction is necessary when there are concurrent, associated features [39,40]. Anti-inflammatory drugs can help with symptom management and in the setting of recurrent pyrexia, corticosteroids can help ameliorate symptoms and prevent further dose reductions [41]. In addition to fevers, dabrafenib/trametinib cause additional inflammatory toxicities and for all, aggressive early management is key for tolerability.

Anticipatory guidance regarding additional consultants and surveillance monitoring can improve compliance and help avoid some toxicities. For example, regular dermatologic and ophthalmologic evaluations every 3–6 months can establish a baseline and identify early signs of complications or toxicity [41]. A baseline echocardiogram can document a patient's left ventricular ejection fracture and provide data for repeat evaluation 1 month after treatment initiation and every 2–3 months while on treatment as appropriate [39,40].

The National Health Service (NHS) provides useful leaflets for patients to remain informed about their therapy [42]. The Canadian Consensus Statement also provides further guidance, specifically for dabrafenib and trametinib induced pyreixa [43].

2.3. Dose reduction

Dose reductions can help to improve tolerability, though this must be balanced against a potential for decreased efficacy. In some cases re-escalation may be warranted once a patient adjusts to the medication. For combination therapies, such as dabrafenib/trametinib, providers should first consider reducing the dose of the agent most likely responsible for the intolerable side effect. The FDA package inserts include guidance for specific dose reductions, though if dosing goes below 1 mg daily of trametinib or 50 mg twice daily of dabrafenib, the drugs should be discontinued as the risk of resistance without any benefit is presumed to be high [39,40]. Tovorafenib can also be reduced for toxicity per manufacturer's instructions [44].

2.4. Timing

It is clear that drug cessation or drug holds, even briefly, can lead to rapid disease progression in HGG [32]. Even in the setting of severe toxicity, prolonged cessation of more than a week should be avoided when possible [41,45]. In patients with melanoma, several randomized phase II studies evaluated the role of intermittent versus continuous dosing and found that continuous dosing shows superior efficacy and progression-free survival [46–48]. This was true across multiple drug combinations, with one study demonstrating a PFS of 9 vs 5.5 months for continuous versus intermittent dosing [46]. While intermittent versus continuous dosing has not been evaluated in gliomas, these results suggest that intermittent treatment regimens should not be used as a means to improve tolerability as intermittent dosing promotes resistance.

Following targeted therapy discontinuation for toxicity, rechallenging with BRAFi/MEKi at disease progression is an effective approach in some solid cancers. A systematic review and meta-analysis found that 65% of patients with advanced melanoma will achieve disease control (partial response and stable disease) when rechallenged following progression during a dose-hold [37]. An objective response rate as high as 43% can be achieved with a rechallenge of therapy [49]. Responses to re-challenge have also been documented in patients with gliomas [32].

2.5. Optimizing choice of agents

BRAF targeted therapy should be selected in a mutation-specific fashion. Type 1 BRAFi (i.e., dabrafenib) are not effective against BRAF fusions and can result in paradoxical activation and tumor progression. Tovorafenib is effective in recurrent pLGG with BRAFV600 or BRAF fusions, while dabrafenib is ineffective in tumors with BRAF fusions. Notably, tovorafenib shows efficacy in patients with pLGG who had received prior BRAF or MEK inhibitor therapy, suggesting it can be used as a salvage therapy in the setting of progression [19]. Preliminary study results suggest benefit in adults with BRAF or CRAF fusion positive HGG as well [50]. However, there are no published efficacy data on patients with BRAF-V600 mutant HGG and further studies will be necessary to define the role of tovorafenib in patients with HGG.

BRAF targeted therapy may also be modulated based on toxicity. Successful intra-class switching for toxicity has been described in several solid cancers [38,51–53]. Should a patient have pyrexia secondary to dabrafenib and trametinib that interferes with continuous dosing, one could consider switching to encorafenib and binimetinib, which is not approved for brain tumors or for a tumor-agnostic indication. When comparing the published studies on melanoma brain metastases, encorafenib and binimetinib had similar outcomes to dabrafenib and trametinib [54,55]. In a small study examining encorafenib and binimetinib for

patients living with glioma, there were no grade 3 or 4 treatment-related adverse events for pyrexia [16]. These data suggest that in some cases, intraclass switching of BRAF/MEKi could be an option for symptom management.

2.6. Considerations for discontinuing targeted therapy at the time of progression

The time and mechanism for BRAFi discontinuation is unclear. In patients with HGG who progress on therapy, withdrawal may result in rapid progression and clinical decline [32,56,57]. As a result, the time to transition to a new regimen should be minimized or therapies may be overlapped. In patients with pLGG, rapid radiographic progression can occur as well, with some cases representing true disease progression and others representing establishment of a new stable baseline [57]. The appropriate duration of therapy in pLGG is unclear, and the pediatric community is working to develop data-driven guidelines for V600E and fusion altered pLGG [58].

3. Emerging targeted approaches for BRAF-mutant glioma

Resistance to BRAF-targeted therapy is common in patients with HGG and adult patients with LGG, even those whose cancers respond for a period of time [15,16]. Here, we focus on therapeutic approaches under evaluation in clinical trials as well as emerging practices for treatment-refractory or high-risk patients.

3.1. First-line BRAF inhibitor therapy in HGG and LGG

Given the efficacy of BRAFi in the recurrent setting, there is interest in identifying whether earlier treatment with BRAFi would provide more durable responses. Based on a randomized phase 2 study in children with newly diagnosed pediatric LGG requiring therapy, dabrafenib/trametinib is superior to standard chemotherapy [14]. Overall response was higher (47% vs 11%, $p < 0.001$) and progression-free survival was longer (20.1 vs 7.4 months, HR 0.31; 95% CI 0.17 to 0.55) in those treated with targeted therapy compared to chemotherapy. This trial included children with LGG in whom therapy was clinically indicated, and does not generalize to patients in whom clinical surveillance is recommended. Based on these data, dabrafenib combined with trametinib can be used first-line therapy in pLGG, including the AYA population (which may extend to < 39 years of age). An ongoing clinical trial of tovorafenib is also evaluating its role in first-line therapy for RAF-altered pLGG [59].

In HGG, the majority of case reports and retrospective cohort studies describe first-line treatment with BRAF inhibitors in combination with or following radiation (see section below). There are two reports in the literature of adults with anaplastic PXA treated with BRAF-targeted therapy alone in the first line setting after progression from low-grade [13,60]. There are also several cases of pediatric patients with HGG treated with BRAF-targeted therapy in the first-line setting [61]. For patients with secondarily-progressive or relatively indolent HGG in whom there is some reluctance to start with radiotherapy (e.g., due to widely disseminated disease or a relatively indolent clinical course), first-line treatment with BRAF/MEK targeted inhibitors may be reasonable. Patients should be counseled regarding the tolerability of this approach. In our single-institution experience, many adults with HGG progress after drug is held in the recurrent setting, suggesting this may be a chronic therapy until resistance emerges. There is room for a well-designed pre-irradiation clinical trial in order to identify the potential efficacy of this approach [62].

3.2. First-line BRAF inhibitor therapy combined with radiation therapy for HGG

Preclinical data in a variety of models demonstrate BRAFi have a radiosensitizing effect on BRAF-mutant cancer cells [63–66]. Murine intracranial HGG models also show synergy between BRAFi/MEKi and radiotherapy [67]. A retrospective study of children with HGG treated with BRAFi, primarily in combination with radiotherapy showed improvement in survival compared to historical controls, and no serious toxicities attributable to combination with radiotherapy [61]. Similar data do not exist for adults with HGG, which are known to have inferior overall survival and decreased response to BRAF-targeted therapy compared to children [13]. An ongoing study in the Children's Oncology Group is evaluating the efficacy of dabrafenib and trametinib following radiation therapy for children and young adults (<26 years) with BRAFV600E mutant HGG (NCT03919071). In the study, patients are treated with radiotherapy followed after a one-month washout by 24 months of therapy with dabrafenib and trametinib. Results will be critical to understand the role of dabrafenib and trametinib in the first line setting for patients with HGG.

3.3. Preventing resistance through autophagy inhibition

Autophagy, the process of engulfing and degrading a cell's own components, is increased in BRAF mutant cancers and facilitates tumor progression and therapeutic resistance [68,69]. BRAFV600E mutant pediatric gliomas exhibit high rates of induced autophagy compared to wildtype tumors, and inhibiting autophagy increases sensitivity to BRAFi [70]. Moreover, autophagy inhibition is effective in the setting of multiple unique resistance mechanisms that arise against BRAFi [21]. Combining BRAFi with FDA-approved drugs that function as autophagy inhibitors (i.e., chloroquine or hydroxychloroquine) enhances growth inhibition and tumor regression in preclinical models of glioma and other ERK dependent cancers [71,72].

A phase I/II clinical trial for metastatic BRAFV600 mutant melanoma evaluated the recommended phase 2 dose and early efficacy of hydroxychloroquine combined with BRAFi/MEKi [73]. Hydroxychloroquine 600 mg orally twice daily with dabrafenib and trametinib was the recommended phase 2 dose, but the study did not meet its prespecified efficacy endpoint of PFS at 12 months, possibly due to early trial closure.

An ongoing Phase 1/2 study is evaluating the safety and efficacy BRAF inhibition with hydroxychloroquine in patients aged < 30 whose gliomas have progressed on prior targeted therapy (NCT04201457). Patients with V600E alterations receive dabrafenib/trametinib with hydroxychloroquine, while those with BRAF fusions receive trametinib with hydroxychloroquine. The safety and recommended phase 2 dose of hydroxychloroquine (20 mg/kg/day divided twice daily) with trametinib has been confirmed and enrollment of the efficacy cohort is nearing completion [74].

3.4. Paradox breakers and dimer disruptors

A different class of BRAFi known as paradox breakers selectively inhibit BRAF-V600E and mutant-BRAF containing dimers by binding to one promoter and disrupting function of the other [75,76]. They thereby prevent paradoxical MAPK pathway activation in normal tissues, potentially increasing the therapeutic index and preventing escape and resistance [77,78].

Plixorafenib (PLX8394, FORE8394) is a paradox breaker that inhibits signaling in BRAF-V600E or BRAF-fusion cancers without reactivating the upstream MAPK pathway (Table 2) [79]. Plixorafenib has been administered to more than 100 patients as part of the Phase 1/2a dose optimization study, with reasonably good tolerability. Of the thirteen patients with gliomas, 4/9 high-grade gliomas and 2/4 LGG showed response [80]. A phase 2 study for participants with BRAF-fusion solid tumors (including gliomas) or rare BRAF V600-mutated solid tumors, melanoma, thyroid, or recurrent primary CNS tumors is ongoing internationally (NCT05503797). Additionally, a study to develop CSF and plasma biomarkers for response to plixorafenib is ongoing in patients with HGG recurrent following prior dabrafenib/trametinib (NCT06610682).

Additional pan-RAF inhibitors, RAF-MEK molecular glue, and BRAF-degraders are also being evaluated in preclinical and clinical studies [76,81]. The RAF-MEK molecular glue, avuotometinib, recently received accelerated approval by the FDA for KRAS-mutated, recurrent low-grade serous ovarian cancer, and early phase clinical trials are in progress for patients with glioblastoma (NCT06630260). BRAF protein degraders are also in pre-clinical and clinical development, with some compounds having potential blood-brain barrier penetration [82,83].

4. Future directions for targeted therapy in BRAF-altered glioma

4.1. Approaches that deepen ERK pathway inhibition

MAPK-ERK signaling dependence in BRAF-mutant cancers can be exploited through strategies that augment the depth of pathway inhibition (vertical inhibition). Inhibitors of the downstream target, ERK1/2, have been developed with one drug (ulixertinib) having reached Phase 2 studies and granted expanded access through the FDA [84]. Additional ERK inhibitors are in development and may demonstrate increased specificity with decreased negative-feedback mediated rebound [85–87]. Other small molecule inhibitors targeting MAPK-ERK signaling such as SOS1 inhibitors and pan-RAS inhibitors may also hold potential as combinations that enhance vertical inhibition. The primary concern for this approach has been on-target, off-tissue toxicity due to profound inhibition of ERK signaling in normal tissues.

The phosphatase SHP2 (encoded by *PTPN11*) has emerged as a central node in MAPK activity in glioma, serving as a convergence point for receptor tyrosine kinase (RTK)-mediated RAS activation. Preclinical studies in melanoma and *NF1*-deficient cancers demonstrated that SHP2 inhibition (SHP2i) could enhance efficacy of MEKi and decrease compensatory feedback activation of RAS signaling [88]. By targeting SHP2, this strategy aims to disrupt a common escape route exploited by tumors, offering a mechanism to prolong ERK pathway

suppression. The combination of a BRAFi and an allosteric SHP2i have been evaluated in a clinical trial of patients with colorectal cancer (NCT04294160) [89]. In preclinical studies, adding a SHP2i to BRAFi overcomes resistance in BRAF-mutant HGG [90]. Preclinical data showed increased suppression of ERK activity, prolonged pathway inhibition *in vitro*, and significantly delayed tumor growth *in vivo* in heterotopic models. A variety of SHP2i have been developed or are currently in clinical development, with likely having brain penetration [80,91].

4.2. Immunotherapy approaches in BRAF-mutant gliomas

In immunosensitive cancers such as melanoma, BRAF mutant tumors show high sensitivity to immunotherapy. In preclinical models, BRAF inhibitors decrease both PD-L1 expression on tumor cells and recruitment of myeloid-derived suppressor cells, hence, priming the tumor microenvironment for immune checkpoint blockade [92,93]. Combinatorial therapy with BRAF/MEKi and PD-1 blocking therapy (pembrolizumab) may lead to enhanced progression-free survival, durable response rates, and overall survival in patients with melanoma [94,95].

In patients with glioblastoma, the presence of a MAPK pathway alteration such as *BRAF* or *PTPN11* is associated with improved response to immune checkpoint inhibitors and prolonged survival on retrospective analysis [96]. In preclinical glioma models, BRAFi/MEKi induces PDL-1 expression, and adding a PD-1 inhibitor to BRAFi/MEKi prolongs survival in murine models [97].

For patients living with gliomas, there is an enrichment for immunotherapy response with MAPK pathway alterations, yielding improved response rates as well as overall survival [96]. Contributing to this phenomenon may be the elevation of PD-L1 expression in BRAF-mutant gliomas [97]. The combination of BRAF targeted therapy with anti-PD1 therapy is currently being evaluated in pediatric gliomas (NCT06712875).

5. Conclusion and future perspective

Patients with BRAF-altered gliomas have an increasing array of targeted therapy options available to them. Currently available therapies are effective in LGG and some HGG, but come with toxicity that needs to be managed thoughtfully and proactively in order to maximize patient quality of life and duration of therapy. Additional clinical trials and preclinical research are ongoing to evaluate novel drug combinations (Table 2). It is likely an increasingly sophisticated array of targeted therapy combinations will become available for patients with BRAF mutant gliomas and solid cancers over the next 5–10 years. These will allow patients access to multiple lines of life-extending therapy. Growing evidence suggest a paradigm shift, such a combination with chemotherapy or immunotherapy, will be necessary for durable disease control and could lead to true breakthroughs.

Author contributions

Karisa C. Schreck – Conceptualization, Writing- Reviewing and Editing, Supervision, Project administration. Danielle Bazer – Conceptualization, Writing - Original Draft, Writing - Review & Editing, Visualization. Abiola A. Ayanlaja - Writing - Original Draft, Writing - Review & Editing, Visualization

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