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Point/counterpoint: Upfront BRAF inhibition for adult BRAF-mutant high-grade gliomas

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Background

Gliomas classified as CNS WHO grade 3 and 4 (herein referred to as HGG) are aggressive, fast-growing tumors with a poor prognosis and limited therapeutic options.[1] Given their rapid progression, there is a critical clinical need for immediate adjuvant treatment following surgery. For decades, focal radiation therapy, with or without chemotherapy, has been the standard of care for patients with these tumors, though its effectiveness varies.[2]

Recent advances in molecular profiling have identified distinct subtypes of HGG with specific genetic alterations.[3] Testing for BRAF and IDH alterations currently holds the greatest clinical significance in gliomas based on the identification of clinically relevant targetable alterations.[4] The *BRAF*^{V600E} mutation, which is classified as ESCAT evidence tier I according to the ESMO Scale for Clinical Actionability of Molecular Targets,[4] is detectable by most sequencing panels. In addition, BRAF alterations are considered as characteristic features of several glioma subtypes in the 2021 WHO Classification of Tumors of the Central Nervous System and should therefore be routinely assessed.[1]

The *BRAF*^{V600E} mutation is more commonly found in pediatric low-grade gliomas, but also occurs in older adolescent and adult patients.[5] The exact incidence of BRAF alterations in HGG remains under study, but large datasets estimate the percentage to be around 3–5% in adult patients.[3,6] However, the prevalence of this mutation varies by tumor type, with reported frequencies of 69% in epithelioid glioblastoma, 38% in anaplastic pleomorphic xanthoastrocytoma (aPXA), and 46% in anaplastic ganglioglioma.[5] While *BRAF*^{V600E} is considered a driver mutation in pediatric gliomas, which typically harbor few additional alterations, adult gliomas often exhibit activation of other pathways, and *BRAF*^{V600E} may represent a bystander mutation in some of these cases.

The development of targeted therapies, including BRAF and MEK inhibitors, has introduced promising new treatment options for these difficult-to-treat tumors with *BRAF*^{V600E} mutation. Based on the efficacy of BRAF inhibition in other cancers harboring the *BRAF*^{V600E} mutation, such as melanoma,[7] BRAF inhibitors (BRAFi) have begun to be utilized for the treatment of HGGs since the early 2010s.[8]

A recent publication highlights the use of neoadjuvant and pre-radiation chemotherapy (PRC) across cancer types, in contrast to its relative paucity in GBM specifically.[9] Despite the available data on the effectiveness of both standard treatments (radiation therapy and chemotherapy) and targeted therapies, such as BRAF and MEK inhibitors, for HGGs, there is ongoing debate regarding the optimal treatment strategy. Specifically, the question remains whether targeted therapy should be used in the upfront setting (following or in lieu of radiation therapy) or be reserved for recurrence.

Summary of the Evidence in Adult and Pediatric Patients

Case Reports and Review of the Literature

Several pediatric and adult case reports have demonstrated the efficacy of BRAFi, either as monotherapy or in combination with MEK inhibitors (MEKi), in patients who failed standard treatments involving radiation and chemotherapy.[10] Some cases reported remarkable radiographic and clinical improvements.

In 2022, Arbour et al. reviewed published cases of HGG with *BRAF*^{V600E} mutations treated with BRAFi with or without MEKi.[10] They identified 32 patients with a median age of 22.5 years (range: 1.5–50 years). Best responses were reported in 31 patients, including 4 complete responses (CR) (13%), 23 partial responses (PR) (74%), 2 cases of stable disease (SD) (7%), and 2 cases of progressive disease (PD) (7%).

The most comprehensive compilation of treatment cases to date is a systematic review analyzing the prevalence of *BRAF*^{V600} mutations in gliomas and responses to BRAFi treatment from case reports and clinical trials.[11] Among 394 *BRAF*^{V600}-mutant gliomas treated with BRAFi from 130 publications, 97 adult HGG cases showed CR, PR, SD, and PD in 6 (6%), 31 (32%), 27 (28%), and 33 (34%) patients, respectively. This was similar to the 25 pediatric HGG cases when accounting for cohort size, which showed CR, PR, SD, and PD in 4 (16%), 10 (40%), 4 (16%), and 7 (28%) patients, respectively.

Retrospective Cohort Studies

Additionally, larger, retrospective series have demonstrated the efficacy of BRAF-targeted therapy in recurrent HGG. A bi-institutional cohort of 10 adults with relapsed HGG (4 glioblastoma, 6 aPXA) revealed 50% of patients ($n = 5$) with clinical benefit for at least four months, and 40% remained on therapy for 20 months or longer.[12] This is similar to what has been reported in a separate cohort of 11 heavily pretreated pediatric patients (6 glioblastoma, 2 anaplastic ganglioglioma, 2 aPXA, and 1 anaplastic astrocytoma).[13] Though detailed treatment courses were not provided, all patients had prior radiation therapy, and 9 received systemic therapy. Four patients (36%) responded, including 1 CR and 3 PR.

There are no data for first-line treatment with targeted therapy in the adult HGG population. Drawing from the pediatric experience, a series of 19 pediatric HGG patients with *BRAF*^{V600E} mutations were treated with targeted therapy in the first-line setting.[14] The vast majority ($n = 16$, 84%) received upfront radiation therapy followed by BRAFi ± MEKi, while three underwent biopsy with upfront targeted therapy alone. The overall response rate (ORR) was 64%, with CR and PR observed, and only one case of PD. Their study demonstrated an 18-month progression-free survival (PFS) of 83% compared to 42% in a historical *BRAF*-mutant cohort, and a 3-year overall survival (OS) of 82% versus 44% in the same cohort.

Clinical Trials

Four studies, including two in adults, have demonstrated the efficacy of BRAFi ± MEKi for gliomas with *BRAF*^{V600E} mutations. While a randomized trial for first-line treatment of pediatric low-grade gliomas demonstrated that the combination of BRAFi and MEKi was superior to standard chemotherapy,[15] no similar randomized studies exist for patients with HGG.

Uncontrolled open-label trials have demonstrated the efficacy of BRAFi. Hargrave et al. investigated dabrafenib and trametinib in pediatric HGG with *BRAF*^{V600E} mutations.[16] Patients received at least one prior treatment (radiation and/or chemotherapy) before targeted therapy. The ORR was 56%, with a higher response rate (67%) in grade 3 PXA. Most responses occurred within 4 months by independent assessment. Treatment was well-tolerated, with only one patient discontinuing treatment due to adverse effects. Dose reductions were required in 32% (dabrafenib) and 17% (trametinib) of cases. The 12-month PFS was 44%, and OS was 33%.

In adults, the VE-Basket trial evaluated vemurafenib in 24 patients with *BRAF*^{V600E} mutation-positive gliomas of all grades, including 11 malignant diffuse glioma (six glioblastoma and five anaplastic astrocytoma), 7 PXA, three anaplastic ganglioglioma, two pilocytic astrocytoma, and one high-grade glioma, not otherwise specified.[17] The ORR was 25% (42% for PXA, 9% for malignant diffuse gliomas). For the entire cohort, they reported an ORR of 25% including CR; PR; SD; PD in 1 (4%); 5 (21%), 10 (42%); and 5 (21%), respectively. The confirmed clinical benefit was 38%. The median PFS was 5.5 months with a median OS for all patients was 28.2 months. The ORR was higher with PXA (42%), and median OS was not reached. Ten patients required one or more vemurafenib dose reductions, and only one discontinued treatment as a result of intolerable adverse effects.

Similarly, the ROAR study investigated dabrafenib and trametinib in 45 adult HGG patients (31 glioblastoma (69%), 5 PXA grade 3 (11%), 5 anaplastic astrocytoma (11%), 1 anaplastic ganglioglioma (2%), 1 anaplastic oligodendroglioma (2%), 1 astroblastoma (2%), and 1 undifferentiated (2%)).[18] All except one received prior radiation therapy, and all but three received at least one line of prior chemotherapy. The ORR was 33% (3 CR, 12 PR), with stable disease in 22% and PD in 42%. Median duration of investigator-assessed response was 36.9 months and 13.6 months by independent radiology review. The median OS of 17.6 months for the entire HGG cohort (13.7 months for glioblastoma and 45.2 months for other HGG subtypes). Adverse events led to dose reductions in 22 (38%) patients, interruptions in 24 (41%) patients, and permanent discontinuation in five (9%) patients (three in the HGG cohort [headache, decreased ejection fraction, and cardiac conduction disorder]).

Recently, a small, prematurely terminated phase 2 study evaluated encorafenib and binimetinib in 5 adults with HGG (1 glioblastoma, 4 PXA grade 3).[19] All had received prior radiation and had one or more recurrences (up to five). The ORR was 80% (2 CR, 2 PR), with a median PFS of 9.4 months and median OS of 14.6 months in the entire cohort. Adverse events led to treatment discontinuation in one patient (20%, cilioretinal artery occlusion), and one patient had a dose reduction for grade 4 elevated creatine phosphokinase (CPK). Table 1 provides an overview on trials, retrospective studies, and case reports.

Ongoing trials are not listed above and include the Phase 1/2a study of plixorafenib in *BRAF*^{V600E} altered tumors, currently enrolling recurrent primary CNS tumors (NCT02428712). In addition, for the purposes of this review, we did not include studies that only enrolled patients with pediatric LGG. One such study worth highlighting is the Phase 2 FIREFLY-1 trial (PNOC026; NCT04775485), which showed rapid and clinically meaningful responses to tovorafenib, a type II RAF inhibitor, in pediatric patients and adolescent and young adults with recurrent pLGG.[20]

The Need for Further Evidence on Upfront BRAFi in HGG

While the studies summarized above indicate encouraging responses to BRAFi in both children and adults, they are limited by small sample sizes. In addition, the above

studies were conducted in patients with recurrent disease, and no study has directly compared upfront BRAFi to the standard of care in adult patients with HGG, making it unclear whether BRAFi should be used in the upfront setting. In this context, we outline key arguments both for and against upfront BRAFi in HGG, with the aim of informing future research, clinical trial design, and clinical practice.

Point: The Case for BRAF and MEK Inhibition in the First-line Setting for HGG with *BRAF*^{V600E} Mutation

Benefit of BRAFi May be Amplified in First-line Setting

While encouraging responses to BRAF inhibitors in HGG have been reported in single-arm phase 2 basket studies by the Adult Brain Tumor Consortium,[19] the VE-Basket trial[17] and the ROAR trial,[18] these included only recurrent glioma patients. It should be noted that the response rate in recurrent HGG is much lower than in CNS WHO grade 2 gliomas—9–80% based on the studies summarized in Table 1. The duration of response is also shorter, 3.8–9.4 months, albeit in recurrent HGG. It is possible that a fraction of patients with newly diagnosed HGG, particularly older adults, will be insensitive to BRAF-targeted therapy.[18] However, based on the treatment-refractory nature of HGG, the potential disease-shrinking benefit of targeted therapy, and the overall high tolerability of targeted therapy, we believe consideration of BRAF targeted therapy in the first line is warranted for carefully selected newly diagnosed HGG patients, in particular younger patients.

Delaying Time to Next Intervention

Specifically for patients with non-glioblastoma HGG, radiation therapy could be delayed or omitted in certain cases in favor of treatment with upfront BRAFi. This strategy is particularly appealing both in patients where radiation poses a higher risk for toxicity (eg, large tumors, leptomeningeal disease) or, conversely in cases where HGG is less aggressive (eg, gross total resection). Given the rapid response to BRAFi plus MEKi (typically within three to six months), treatment efficacy can be assessed early, and regularly, with the option of salvage radiation, re-resection, or systemic chemotherapy in the event of clinical or radiographic progression. The argument to delay radiation applies particularly to grade 3 PXA, which may have a more favorable prognosis than other HGG subtypes and is also more prone to leptomeningeal dissemination, favoring BRAF-targeted therapy. These complex decisions should be discussed in multidisciplinary tumor boards and involve comprehensive patient and family discussions.

Safety Considerations for Concurrent or Adjuvant BRAFi with Radiation

The safety of BRAFi in combination with or following radiation therapy needs to be better elucidated. On one hand, in highly symptomatic patients with significant tumor burden, rapid initiation of BRAFi and MEKi (before or with concurrent radiation therapy), could help to control disease symptoms. On the other, prior reports suggested increased cutaneous toxicity when combining BRAFi or MEKi with radiation. While the risk may be tolerable and small relative to the overall risks of treatment, it warrants consideration.[21] Safety of adjuvant BRAFi following radiation is currently being evaluated, along with efficacy, in a clinical trial (NCT03919071), including pediatric, adolescent, and young adult patients.

Special Populations: Younger Patients

It is recognized that the adolescent and young adult population (age, 15–39 years) encompass adult and pediatric type gliomas.[22] In this population, the incidence of *BRAF*^{V600E} mutation-positive gliomas is higher than in older adults and may reflect distinct tumor types and prognosis. Retrospective data suggest that patients 18–35 with glioblastoma carrying a *BRAF* alteration have significantly improved overall survival compared to older patients.[12] In the ROAR trial, 96% of the HGG patients were in the 18-65 age group, and patients aged 18 to < 40 years had a higher response rate compared to patients ≥ 40 (ORR: 41% vs 17%).[18] In this population, where survivorship may be prolonged, and where toxicities of chemotherapy and radiation need to be minimized, upfront BRAFi may represent an effective and quality-of-life enhancing approach to achieve control of their disease.[23] Long-term toxicity may influence treatment duration, and an indefinite course can be psychologically distressing or impact family planning for some patients. Upfront discussion of these considerations should be included when initiating first-line targeted therapy.

Special Populations: MGMT-unmethylated BRAF-altered HGG

A significant subset of adult HGG patients with *BRAF*^{V600E} mutation receive a histological diagnosis of glioblastoma, and currently, regardless of age, have a dismal prognosis. In large retrospective cohorts, the presence of a *BRAF*^{V600E} alteration did not intrinsically confer an improved outcome in the setting of standard chemo-radiation and prior to the adoption of BRAF-inhibition.[12]

Methylation of the O6-methylguanine-DNA methyltransferase promoter (*MGMT*) in glioblastoma has been associated with a clinical benefit from the current standard of care with the Stupp protocol. However, this addition of adjuvant temozolomide in the setting of *MGMT*-unmethylated glioblastoma, which represents 55–60% of all glioblastoma may not confer any additional benefit,[24,25] and clinical trial options are often sought for these patients. As such, the case could be made to incorporate BRAF-targeted therapy into the first-line setting for a subset of *MGMT*-unmethylated HGG.

Conclusion: Pro Side

Based on the treatment-refractory nature of HGG, the potential disease-shrinking benefit of targeted therapy, and

Table 1. Studies and Case Reports on $BRAF^{V600E}$-mutant Gliomas Treated with BRAF Inhibitors

Category	Reference	Study	Population/ intervention	Key Finding	Level of Evidence
Case Reports	Andrews et al., 2022[11]	Systematic review of case reports	Adult and pediatric patients with BRAF V600E-mutant glioma	394 BRAF V600-mutant gliomas from 130 publications.97 adult HGG with ORR: CR (6.2%), PR (32.0%), SD (27.8%), PD (34.0%). 25 pediatric HGG with ORR: CR (16%), PR (40%), SD (16%), PD (28%).	Level 4
	Arbour et al., 2022[10]	Systematic review of case reports	Adult and pediatric patients with BRAF V600E-mutant HGG	32 HGG patients; ORR: CR (12.9%), PR (74.2%), SD (6.5%), PD (6.5%).	Level 4
Retrospective Studies	Schreck et al., 2023[12]	Retrospective, multi-institutional study	Multi-insititutional cohort of adult and pediatric patients with BRAF-altered glioma	296 gliomas with BRAF alteration. 10 adults with recurrent HGG; 50% showed clinical benefit for ≥ 4 months; 40% remained on therapy for 20 + months.	Level 3
	Nobre et al., 2020[13]	Retrospective, multi-institutional study (pediatric)	Multi-insititutional cohort of pediatric patients with BRAF-altered glioma	67 patients with pediatric LGG and HGG. 11 patients with HGG; ORR: CR (1), PR (3); all received prior radiation therapy.	Level 3
	Rosenberg et al., 2022[14]	Retrospective, multi-institutional study (pediatric)	Pediatric HGG treated with BRAF ± MEK inhibitors at first-line	19 pediatric patients; ORR: 64.3%; 18-month PFS: 83%, 3-year OS: 82%.	Level 3
Prospective Studies and Clinical Trials	Hargrave et al., 2023[16]	Phase 2 trial (pediatric)	Relapsed pediatric HGG treated with dabrafenib plus trametinib	56.1% ORR; better response in grade 3 PXA (66.7%); 12-month PFS: 44.1%, OS: 32.8%.	Level 1
	Kaley et al., 2018[17]	Basket trial (adult)	Nonrandomized, multicohort study for glioma treated with vemurafenib	24 patients; ORR: 25% (PXA: 42%, malignant diffuse gliomas: 9%); median PFS: 5.5 months, median OS: 28.2 months.	Level 1
	Wen et al., 2022[18]	Phase 2 trial (adult)	Relapsed adult glioma treated with dabrafenib plus trametinib	45 HGG patients; ORR: 33% (CR: 3, PR: 12); median PFS: 3.8 months; median OS: 17.6 months.	Level 1
	Schreck et al., 2024[19]	Phase 2 trial (adult)	Relapsed HGG treated with encorafenib and binimetinib	5 adults; ORR: 80% (CR: 2, PR: 2); median PFS: 9.4 months, median OS: 14.6 months.	Level 1

Abbreviations: CR = complete response; HGG = high-grade glioma; ORR = overall response rate; PD = progressive disease; PR = partial response; PXA = pleomorphic xanthoastrocytoma; SD = stable disease.

the overall high tolerability of targeted therapy, we believe that BRAF targeted therapy in the first line could be an effective strategy in carefully selected patients, and that future trials should explore this strategy. Specifically, incorporating BRAF targeted therapy in the first line with radiation for *MGMT* unmethylated glioblastoma needs to be considered as an alternative to adjuvant chemotherapy. First-line BRAF targeted therapy in place of radiation may also be a reasonable option for non-glioblastoma HGGs that carry a better prognosis, are younger at diagnosis, and may benefit from delaying radiation. The duration of BRAFi/MEKi combination therapy following radiation therapy is subject to debate and warrants further investigation.

Counterpoint: The Case Against BRAF and MEK Inhibition in the First-line Setting for HGG with *BRAF*^{V600E} Mutation

Toxicity

Discussion of upfront treatment with BRAFi needs to include the potential burden of toxicity/adverse events and the need for daily medication compliance. Common adverse effects include dermatologic reactions (rash, photosensitivity, pruritus), gastrointestinal symptoms (diarrhea, nausea), and systemic effects such as fatigue and fever, particularly with combination therapy.[7,18,26] Serious complications require close monitoring. Cardiotoxicity, including left ventricular dysfunction, is linked to BRAFi and MEKi.[27] Venous thromboembolism, particularly deep vein thrombosis and pulmonary embolism, is another significant risk.[28] Ocular toxicity, such as retinal vein occlusion, and paradoxical squamous cell carcinomas due to MAPK activation, further complicate treatment.[29] Lastly, emerging toxicities with more novel inhibitors, such as the type II RAF inhibitor tovorafenib (hair color changes, elevated CPK, anemia)[20] and plixorafenib (liver function test changes)[30] will also need to be assessed in larger real-world cohorts.

Resistance

One of the most significant challenges associated with BRAF inhibition, particularly when it is used as an upfront treatment, is the potential for the development of resistance at any point of treatment from initiation to late in the treatment course. The ROAR study showed an ORR of ≥ 50% across all cohorts, but only an ORR of > 30% in *BRAF*^{V600E} mutation-positive HGG. The decreased response of BRAFi in the HGG cohort is thought to be attributed to the fact that *BRAF* mutations are not the primary drivers of some high-grade tumors, but rather passenger mutations, and the fact that *BRAF* mutational heterogeneity does exist, among different tumor sites of a single patient and/or even within a single tumor (intratumor heterogeneity). This hypothesis is supported by the frequent presence of other mutations that may contribute to the tumor's pathogenesis in *BRAF* mutation-positive gliomas. Other genetic alterations (eg, a gain in chromosome 7q, a high mutational burden, NF1 deletion, mTOR activation, ARAF/CRAF amplification, the homozygous loss of *CDKN2A*, amplification of CDK4, TERT upregulation or ATRX downregulation, epigenetic modulation, and DNA repair abnormalities) are often found alongside *BRAF* mutations.[12,31] Even in high-grade gliomas that do respond, resistance frequently emerges over time and much more frequently than in low-grade gliomas, resulting in a limited duration of benefit from targeted therapy. It is unclear whether treatment in the first-line setting would prolong the benefit or lead to emergent resistance at the same rate. Multiple mechanisms of acquired resistance limiting therapeutic benefit have been described, including elevated expression of the kinases CRAF, COT1, or mutant *BRAF*, activating mutations in *N-RAS*, *MEK1*, or *AKT1*, aberrant splicing of *BRAF*, activation of phosphatidylinositol-3-OH kinase (PI3K) via the loss of PTEN, and persistent activation of receptor tyrosine kinases, including platelet-derived growth factor receptor β (PDGFRβ), insulin-like growth factor IR (IGF-IR), and EGF receptor (EGFR).[32,33]

Risks of Using BRAF Inhibitors in the Upfront Setting

If BRAF inhibitors are utilized in the upfront setting, this may result in delays in initiating standard-of-care therapies such as radiation and chemotherapy, which—unlike BRAF inhibitors—have been shown to be effective in improving PFS and OS for most patients with newly diagnosed HGG.[2] For example, studies have shown that delaying radiation therapy can negatively affect overall survival in patients with HGG.[34] Thus, in the absence of clear clinical trial evidence that demonstrates that BRAF inhibitors are effective in improving outcomes and in the context of some clinical trials showing that two-thirds of patients with HGG can fail BRAF inhibition, potentially delaying radiation therapy to trial BRAF inhibition in the upfront setting is particularly concerning. Ultimately, the potential harm incurred with postponing radiation therapy in favor of pursuing BRAF inhibition first may be considered unacceptable for most patients with HGG.

Durability of Response

Although approximately one-third of patients with *BRAF*-mutant glioblastoma experience (often dramatic) responses to BRAF inhibiton, the durability of these responses is limited. In the ROAR trial, PFS was only 3.8 months,[18] indicating that acquired resistance mechanisms eventually develop, complicating long-term disease control.

Financial Burden and Accessibility

In addition to the clinical concerns about using BRAFi in the upfront setting for HGG, there are several practical challenges surrounding the accessibility and financial feasibility of utilizing BRAFi at the time of diagnosis as a frontline therapy. Without definitive evidence endorsing these drugs as a first-line treatment, it is highly likely that

many insurance providers may refuse to cover the costs of these medications. Even when reimbursement is available, the financial burden associated with these therapies could remain substantial.

BRAFi, especially when combined with MEKi, are expensive drugs, with annual costs often exceeding $150,000 USD.[35] Prolonged use exacerbates this financial strain, contributing to financial toxicity. This includes accumulating medical debt, loss of income, and psychological stress. It is possible that patients of lower socioeconomic status, minorities, and other marginalized populations may not have access to or be able to afford this treatment in an equitable manner.

Conclusion: Con Side

When compared to standard-of-care radiotherapy and chemotherapy, these limitations raise critical questions about the efficacy, accessibility, and sustainability of care with using BRAF inhibition in the upfront setting, particularly when the long-term benefits of BRAF inhibitors remain uncertain. In the absence of convincing evidence, we recommend BRAF inhibition to be reserved for the setting of recurrence until more robust data can be obtained from clinical trials specific to HGG in adults.

Future Directions

Defining Optimal Treatment Strategies

A major question is whether upfront BRAFi should replace or complement standard therapy. Pediatric studies suggest benefits of upfront BRAFi approaches; however, HGG are more aggressive in adults. Given their distinct clinical practices, most pediatric neuro-oncologists have adopted targeted therapies as part of the upfront treatment for both low- and high-grade gliomas, whereas adult neuro-oncologists have approached this strategy with more caution, often awaiting further clinical evidence. Prospective trials must determine whether BRAFi should be used before or after radiotherapy, particularly in *MGMT*-unmethylated tumors. Additionally, combinations of BRAFi with radiation and/or immunotherapy could be further investigated.

Overcoming Resistance Mechanisms

Acquired resistance limits the efficacy of BRAFi, with tumors developing alternative survival pathways. Future strategies should explore combination therapies such as BRAFi/MEKi with CDK4/6 inhibitors, PI3K/mTOR inhibitors, or immune checkpoint blockade. Adaptive dosing strategies and combination with other drugs may also help sustain responses.

Patient Selection and Biomarker Development

Not all BRAF-mutant HGGs respond equally to targeted therapy, highlighting the need for better patient stratification. Co-occurring mutations in CDKN2A/B, NF1, and TERT promoter may impact therapeutic response. Identifying which patients benefit most from upfront BRAFi versus standard therapy will be critical for personalized treatment.

Bridging Pediatric and Adult Data

Most evidence for BRAF inhibition comes from pediatric studies, but translating these findings to adults is challenging due to differences in tumor biology. Pediatric patients often receive prolonged BRAFi treatment, while the feasibility of long-term therapy in adults remains uncertain. These differences and their biological basis need to be further elucidated.

Clinical Trials

Randomized trials would be the strongest approach to evaluate the efficacy of upfront BRAFi. However, conducting such trials in adults is extremely challenging—if not unfeasible—due to the low frequency of BRAF mutations and the need to screen large patient populations. A platform in which one could efficiently assess molecular and clinical eligibility post-operatively in newly diagnosed HGG with subsequent close monitoring of response and rapid transition to radiochemotherapy in case of failure is one proposed solution to this challenge.[36] In addition, leveraging external data could significantly enhance the design of trials investigating upfront BRAFi in HGG. Externally controlled trial designs allow for the integration of well-matched historical or real-world patient-level data in registry studies like EORTC-2013-BTG (GLIORARE, NCT05259605) to contextualize treatment effects observed in smaller or single-arm studies. This approach can reduce required sample sizes and support more informed early-phase decision-making.[37] The latter appears particularly well suited for rare molecular subtypes like BRAF-mutant HGG. In addition to prospective trials evaluating upfront BRAFi, other key areas of research include combination strategies targeting resistance mechanisms, long-term safety and quality-of-life studies. Finally, molecular stratification and biomarker refinement will be needed to identify optimal responders.

In conclusion, the development of targeted therapies has introduced a promising new modality for treating *BRAF*^{V600E} mutation-positive HGG. While clinical trials and retrospective studies have shown encouraging response rates, key challenges remain, including establishing optimal treatment sequencing, elucidating resistance mechanisms, identifying biomarker-driven patient selection, and promoting long-term efficacy. Each patient is unique, and current therapeutic options should be carefully evaluated in multidisciplinary tumor boards and discussed with the patient and their family, while further evidence is awaited.

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