Incorporating Targeted Therapy Into Neuro-Oncology Practice

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OVERVIEW

The integration of targeted therapies into neuro-oncology is revolutionizing the management of primary CNS malignancies. Advances in sequencing technologies and the incorporation of molecular alterations into CNS tumor classification have led to more precise tumor prognosis and enabled the identification of actionable oncogenic drivers. However, challenges such as drug delivery, tumor and microenvironment heterogeneity, and limitations of preclinical models complicate the selection of effective therapies. This review presents a comprehensive framework for optimizing drug selection in neuro-oncology. We discuss strategies to enhance drug development and improve clinical trial success, including window-of-opportunity trials and advanced imaging techniques. Additionally, we highlight recent advances in the treatment of isocitrate dehydrogenase–mutant gliomas, focusing on the INDIGO study and its role in the regulatory approval of vorasidenib. The review also examines the use of MAPK inhibitors, from BRAF inhibitors to PAN-RAF inhibitors, in both pediatric and adult patients, as well as novel investigational agents. Finally, we explore emerging targeted therapies for rarer oncogenic drivers, such as FGFR and NTRK alterations, emphasizing the need for CNS-specific drug development strategies.

INTRODUCTION

The management of CNS malignancies remains a significant challenge due, in part, to intertumoral, intratumoral, and microenvironmental heterogeneity, limited availability of preclinical models, and the complexities of CNS drug delivery. Additional limitations in clinical trial design include difficulties in powering trials for regulatory approval when patient populations are small, the absence of standard-of-care treatment for randomization in certain rare tumors, and the inclusion of both primary and secondary CNS tumors in basket studies. However, recent advances in next-generation sequencing technologies are reshaping CNS tumor classification. These technologies, along with various computational tools, have not only facilitated the identification of several potentially actionable oncogenic driver mutations but also spurred the development of targeted therapies aimed at these alterations. This manuscript outlines systematic approaches for optimizing drug selection in the treatment of CNS malignancies. It offers a practical overview of integrating targeted therapies into neuro-oncology practice, highlighting both currently approved treatments and strategies under investigation.[1–4]

LIMITATIONS TO SELECTION OF CNS-ACTIVE DRUGS

Biological Barriers to CNS Drug Delivery

CNS drug delivery is challenged by unique biological barriers, including the blood-brain barrier (BBB), tumor and microenvironment heterogeneity, and limitations of preclinical models. The BBB, formed by endothelial cells and astrocytic endfeet connected by tight junctions, prevents over 95% of drugs from reaching the brain parenchyma.[5–7] By contrast, the cerebrospinal fluid (CSF) barrier is formed by fenestrated capillaries embedded in connective tissue stroma and surrounded by secretory epithelium, and enables selective nutrient and drug movement into the CSF (Fig 1).[5] Because of their vastly different permeability profiles, pharmacokinetics (PK) measurements in brain parenchyma and CSF are not interchangeable. For instance, isocitrate dehydrogenase (IDH) inhibitor vorasidenib could be erroneously deemed a poor CNS drug candidate based solely on its CSF concentrations, which are approximately 200-fold lower than in the brain parenchyma.[8]

CNS PK are further complicated by the brain-tumor barrier, which disrupts the BBB and exhibits heterogeneous

PRACTICAL APPLICATIONS

- Next-generation sequencing, along with computational tools, has led to more accurate classification of CNS tumors and the identification of several potentially actionable oncogenic alterations.
- CNS drug delivery remains a significant challenge in neuro-oncology, primarily because of the blood-brain barrier, tumor and microenvironmental heterogeneity, and limitations of preclinical models.
- Vorasidenib should be considered after biopsy or resection in patients with WHO grade 2 *mIDH* glioma who are not in immediate need for radiotherapy and/or chemotherapy.
- The efficacy of vorasidenib in higher-grade gliomas, its role in maintenance therapy, potential in combination with chemotherapy, and long-term outcomes remain unknown.
- Targeted therapies may offer an effective and durable therapeutic option in highly selected glioma patients with druggable molecular alterations (BRAF and NTRK).

permeability because of efflux pump upregulation, astrocyte reprogramming, and leaky capillaries.[9] Because BBB breakdown enhances gadolinium contrast on magnetic resonance imaging (MRI), measuring tumor drug concentrations only in contrast-enhancing regions can severely overestimate drug BBB permeability. By contrast, tumor regions that are less accessible to locoregional therapies often have intact BBB and therefore lower drug levels.[10,11]

Furthermore, these tumors present high intratumoral and intertumoral heterogeneity in neoplastic and nonneoplastic compartments, low lymphocyte infiltration, and a high abundance of myeloid subsets, which together create a highly protumorigenic immunosuppressive microenvironment. Additionally, these compartments exhibit dynamic changes with tumor progression and therapeutic interventions.[12]

Limitations of Preclinical PK Models

Preclinical models often fail to recapitulate the composition of the human brain. The mouse brain has over 25,000 times less white matter than the human brain, with a disproportionately lower white-to-gray-matter ratio (8:92 in mice *v* 45:55 in humans; Fig 1).[13] Most drugs administered through the bloodstream have drastically lower levels in the physiologically less perfused white matter relative to the gray matter.[14-17] As a result, murine models tend to overestimate brain drug penetration.

Orthotopic xenograft models also tend to artificially perturb the BBB and fail to replicate the infiltrative growth patterns of gliomas, while traditional glioma cell lines may lose genotypic fidelity to the source tumor, reducing their clinical relevance.[18-20] IDH-mutated (IDHm) glioma cell lines are particularly difficult to culture, making these models limited in availability and reliability.[21] CNS metastasis models are less affected by these limitations since their hematogenous spread can be replicated through intracardiac or intracarotid injection. These models also tend to be well demarcated and retain driver mutations much more similarly to their real-world counterparts yet remain underutilized.[22-24]

Overall, these nuances underscore the critical need for a paradigm shift toward integrating in vivo human data and developing noninvasive PK tools to enhance drug selection for CNS oncology trials and ultimately for personalized medicine.

A SYSTEMATIC APPROACH TO PREDICT CNS DRUG ACTIVITY AND ITS PRACTICAL APPLICATION

In 2020, the Adult Brain Tumor Consortium (ABTC) established baseline criteria for drugs to be considered suitable for efficacy trials.[25] According to these, drugs that work through direct drug-tumor interaction must accumulate at therapeutic concentrations within the target tumor volume. As most primary brain tumors, and even micrometastatic systemic cancers, invade areas in the brain with partially, or fully intact BBB, assessing drug penetration beyond contrast-enhancing regions is crucial. Therefore, three key PK parameters should be considered when evaluating a drug's potential CNS activity:

1. Effective concentration (eg, IC_{50}, IC_{90}, etc) against the target cancer type
2. Maximum plasma concentration (C_{max}) at the maximum tolerated dose (MTD) in humans
3. Drug concentration in non–contrast-enhancing brain regions in humans measured directly or indirectly.

A 2022 analysis of genotypically targeted drugs against glioblastoma found that CNS drug selection is based on incomplete data.[26] Only one drug (ribociclib) had all three required parameters, including measurements from nonenhancing tumor regions in humans. Expanding the data set to include PK information from contrast-enhancing tumor in humans increased data completeness to 11% (six drugs). When animal brain PK data were included, this rose to 33%. However, the majority of drugs did meet two of the three criteria, allowing the least-promising candidates for CNS use to be eliminated.

To address missing information, the following inference strategies can be applied:

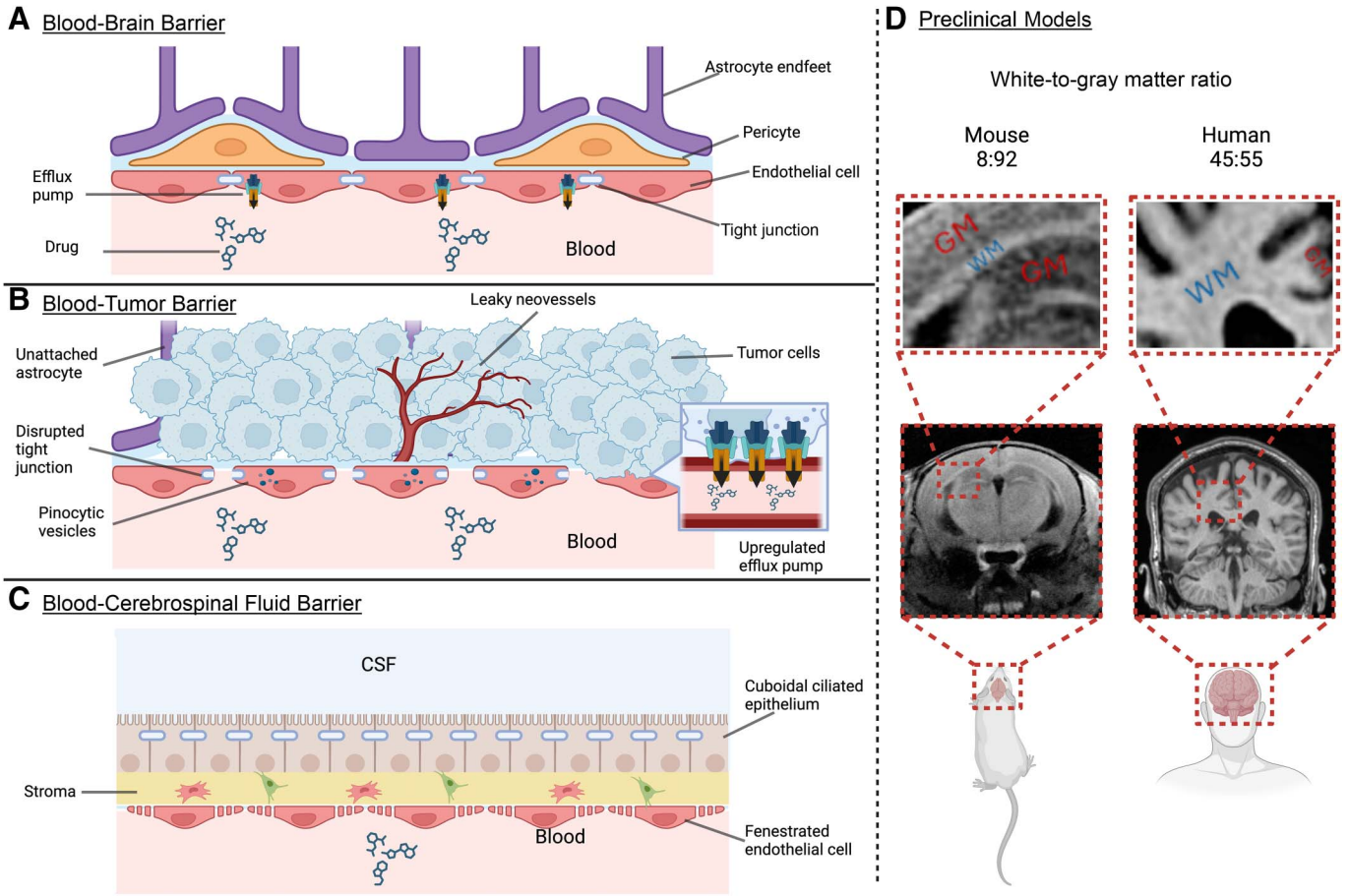

FIG 1. Limitations to selection of CNS-active drugs. (A) Normal blood-brain barrier with tight junctions, pericyte cells, astrocyte endfeet, and efflux pumps prevents over 95% of drugs reaching brain parenchyma. (B) Blood-tumor barrier with disrupted tight junctions, pinocytic vesicles, upregulated efflux pump, leaky neovessels, and unattached astrocyte endfeet. (C) Blood-cerebrospinal fluid-barrier with fenestrated endothelial cell, stroma, and cuboidal ciliated epithelium. (D) Preclinical models overestimate brain drug penetration because of a lower white-to-gray matter ratio in mice compared to humans. CSF, cerebrospinal fluid; GM, gray matter; WM, white matter.

1. If IC_{50} for the target cancer and the human plasma C_{max} are known, the required brain-to-plasma ratio can be estimated.
2. If brain drug concentration is known at MTD, it defines the upper limit of IC_{50} threshold for efficacy for the target tissue.
3. If IC_{50} for the target cancer and animal brain-to-plasma concentrations are known, but human PK data are missing, blood measurements in early-phase trials can determine whether therapeutic brain levels are feasible.

For instance, if a drug's plasma C_{max} is tenfold lower than the IC_{50}, it would need to accumulate over tenfold higher in the brain than in plasma—an unlikely scenario. However, highly potent drugs (eg, IC_{50} in the nanomolar range) may remain effective despite low CNS penetration.[26,27] A real-world example is tovorafenib, which demonstrated an IC_{50} of approximately 0.5 μM in *NF1* and *BRAF* mutated glioma cell lines,[28] and a 24% plasma-to-brain ratio in normal mouse brain.[29] Its human plasma C_{max} of 13.6 μM far exceeds the levels necessary for therapeutic brain levels, thus predicting clinical efficacy as shown in the FIREFLY-1 trial for pediatric low-grade *BRAF*-mutated glioma.[30,31]

FUTURE METHODS TO GENERATE DATA TO ENHANCE CNS-ACTIVE DRUG SELECTION

Expanding Publicly Accessible PK and PD Data

There is an urgent need to expand publicly available data sets on IC_{50}, and human PK and pharmacodynamics (PD). Pharmacogenomic tools such as CellMiner NCI-60[32,33] and the Genomics of Drug Sensitivity in Cancer tool[34,35] provide valuable IC_{50} data but require expansion. High-throughput screening platforms using 3D chip–based models could significantly accelerate data acquisition.[36] High-throughput screening can also be applied to test drug synergy.[37]

Integrating PK/PD Data Into Early-Phase Clinical Trials

Tissue-based assessments in early-phase clinical trials can bridge critical gaps in human brain PK/PD data. Window-of-opportunity trials (WoO), in which patients receive therapeutic drug doses before surgical intervention, allow for ex vivo PK/PD analysis.[38] Examples include microdialysis studies measuring unbound drug in vivo, showing at least

5-fold lower drug concentration in nonenhancing, compared with contrast-enhancing brain tumor regions for multiple drugs.[10,11] Overall WoO studies represent the most accurate method for establishing human PK/PD profiles, but their invasiveness, high costs, and the need for specialized expertise limit their broader implementation.

Advancing Noninvasive PK Imaging

Noninvasive imaging offers an alternative to some surgical studies, enabling drug biodistribution analysis in vivo. Positron emission tomography (PET) is the most sensitive PK imaging modality, capable of picomolar-level drug quantification.[39] PET is often used to guide the selection of CNS-active agents, such as osimertinib from a cohort of EGFR inhibitors on the basis of its superior brain penetration.[40] However, PET requires radiolabeling, which can alter PK, is costly, and entails regulatory hurdles for investigational new drug approval, making it most viable when integrated early on from preclinical drug development.[39,41]

Alternatively, MRI-based techniques allow drug detection without chemical modification, eliminating the regulatory and financial barriers but at the cost of sensitivity and often specificity. MR spectroscopy (MRS) directly detects drugs or metabolites with unique spectral profiles when present at millimolar concentrations.[42-46] Chemical exchange saturation transfer (CEST) MRI amplifies sensitivity by targeting the exchangeable protons of the target compound, allowing submillimolar in vivo detection of chemotherapeutics, such as methotrexate or gemcitabine, and can be used to detect colocalized substances such as albumin as used in nab-paclitaxel.[47,48]

PD-Based Imaging for Drug Selection

PD imaging can track tumor response through on-target or off-target effects providing indirect PK insights as well. Ideal PD markers should respond within hours after administration, correlate with both tumor and target tissue, and be reproducible. Examples include changes in tracer uptake in response to a drug targeting a metabolic modulator pathway as seen in [^{18}F] fluorodeoxyglucose (FDG) uptake reduction mammalian target of rapamycin (mTOR) inhibition,[49,50] or amino acid (FET) uptake reduction in IDHm inhibitor therapy.[51] MRS can determine PK/PD when the drug-induced metabolite both in tumor (eg, lactate) and in normal brain (eg, glutamate) as seen with dichloroacetate.[52] MRS can also detect IDHm inhibitor–induced reduction in R(-)-2-hydroxyglutarate (2HG) levels many months before changes in growth trajectories.[46,53] CEST MRI can detect pH changes and thus predict responses to drugs that modulate acidity such as HIF2-alpha inhibitors.[54] Finally, multiparametric approaches, combining PET, diffusion MRI, and CEST MRI, have been used to track antitumor responses, as seen with the PiK3C/mTOR1/2 inhibitor paxalisib (GDC-0084).[50] These biomarkers could aid in patient enrichment strategies for clinical trials, identifying responders early.

Enhancing Sensitivity for Early Efficacy Signals

PD sensitivity can be improved by comparing pretreatment and on-treatment growth rates. This allows patients to serve as their own controls and thus reduces the sample size required to detect early efficacy signals.[53,55,56]

TARGETED THERAPY FOR PATIENTS WITH *IDH*-MUTANT GLIOMA

Vorasidenib Drug Development

*IDH*m gliomas are diffusely infiltrating primary brain tumors characterized by somatic mutations in the *IDH1* or *IDH2* genes. Despite the standard treatment approach, which includes surgery, radiation therapy, and chemotherapy—each associated with short-term and long-term toxicities—these tumors inevitably recur.[57]

Mutations in the *IDH* genes are early events in gliomagenesis, leading to the loss of the normal enzyme's ability to catalyze the conversion of isocitrate to α-ketoglutarate (α-KG). These mutations also confer a gain of function, enabling the nicotinamide adenine dinucleotide phosphate hydrogen (NADPH)–dependent reduction of α-KG to 2HG. The resulting loss of NADPH and α-KG, coupled with the accumulation of the oncometabolite 2HG, drives a variety of oncogenic processes in glioma.[58-60] As a result, targeting 2HG depletion by directly inhibiting the mutant IDH enzyme has become a highly promising therapeutic strategy.[61]

mIDH inhibitors are FDA-approved for various indications and have been studied for glioma treatment. Ivosidenib and olutasidenib are approved for relapsed or refractory (RR) AML with *IDH1* mutations, while enasidenib is approved for RR AML with *IDH2* mutations. Additionally, ivosidenib is approved for newly diagnosed *IDH1*-mutant AML in patients ineligible for intensive chemotherapy, as well as for unresectable, locally advanced, or metastatic *IDH1*-mutant cholangiocarcinoma.

Vorasidenib, a brain-penetrant, dual mIDH inhibitor, demonstrated good tolerability in a phase I dose-escalation study involving 52 patients with recurrent glioma. Dose-limiting toxicities, including elevated transaminase levels, were observed at doses ≥100 mg but were reversible. Vorasidenib demonstrated preliminary antitumor activity in these patients. The protocol-defined objective response rate (ORR) in the nonenhancing glioma patients was 18%, including one partial response and three minor responses, with a median progression-free survival (PFS) of 36.8 months (95% CI, 11.2 to 40.8). By contrast, patients with enhancing glioma had a median PFS of 3.6 months (95% CI, 1.8 to 6.5) with no confirmed radiographic responses.[62] A summary of published studies including targeted therapies in gliomas is provided in Table 1.

To evaluate the biological potential and identify the optimal IDH inhibitor and dose for a phase III study, a perioperative phase I trial was conducted with vorasidenib (10 or 50 mg once daily) and ivosidenib (500 mg once daily or 250 mg twice daily) in 49 patients with recurrent *IDH*-mutant gliomas requiring tumor resection. The primary end point was the concentration of 2HG in resected tumors. A remarkable reduction of over 90% in 2HG levels was observed in patients treated daily doses of vorasidenib 50 mg and ivosidenib 500 mg, while the effect was less pronounced at lower doses of vorasidenib and ivosidenib 250 mg twice daily. Given its demonstrated brain penetrance and more consistent 2HG suppression, vorasidenib was selected to be tested in the phase III INDIGO trial.[63]

In INDIGO, a double-blind, phase III trial, patients with nonenhancing grade 2 m*IDH* glioma who had undergone no previous treatment other than surgery were randomly assigned to oral vorasidenib (40 mg once daily, n = 168) or matched placebo (n = 163). At a median follow-up of 14.2 months, 226 patients (68.3%) continued to receive vorasidenib or placebo. PFS, the primary end point, was significantly improved in the vorasidenib group compared with the placebo group (median PFS, 27.7 months *v* 11.1 months; hazard ratio [HR] for disease progression or death, 0.39; [95% CI, 0.27 to 0.56; $P < .001$]). At the time of progression, patients had the option to cross over to the experimental arm, which may preclude the analysis of survival benefit. In patients with pretreatment/on-treatment scans available (n = 123), vorasidenib reduced tumor growth rate (pretreatment: 13.2% [95% CI, 10.3 to 16.3] *v* on-treatment −3.3% [95% CI, −5.2 to −1.2]), while no significant change was observed with placebo (pretreatment: 18.3% [95% CI, 15.0 to 21.7] *v* on-treatment 12.2% [95% CI, 9.5 to 14.9]; difference of slopes changes 11.0 [95% CI, 4.5 to 17.8]; $P < .001$).[64] There was no difference in health-related quality of life between the two groups, and no notable changes in neurocognitive function were observed (median follow-up was 14.2 months). No significant difference in seizure frequency or severity was seen at 14.2 months.[75] More mature data reveal an increase in seizure frequency in the placebo group, likely indicative of tumor growth.[76]

Vorasidenib in Clinical Practice

Indications—What Do We Know and What We Do Not Know

The results of the INDIGO study are exciting, and, probably, one of the most promising results we have seen in glioma trials in recent years. How should we translate the results from this selected study population into daily clinical practice? How do we select patients who will benefit from vorasidenib without jeopardizing survival?

Translated from the INDIGO study, it is clear that patients with predominantly non–contrast-enhancing grade 2 m*IDH* glioma, who have undergone resection or biopsy 1-5 years before the start of vorasidenib and provided there is no immediate need for treatment with radiotherapy (RT) and/or chemotherapy, have a prolonged PFS with vorasidenib compared with placebo. Both m*IDH* astrocytoma and oligodendroglioma benefit, with HR for PFS of 0.47 (95% CI, 0.29 to 0.75) and 0.32 (95% CI, 0.18 to 0.57), respectively.[64]

One important unanswered question is whether the benefit of PFS applies only to grade 2 tumors or if patients with grade 3 gliomas also benefit from treatment with vorasidenib. The histologic criteria for grading are subjective, resulting in high interobserver variability.[77] Furthermore, there is significant spatial and temporal heterogeneity in the tumors, and no significant differences in survival outcome are found in grade 2 versus grade 3 tumors after treatment with RT and chemotherapy.[78-80] Recent work by Elia et al[81] showed that in a highly selected group of grade 3 gliomas, a watch-and-wait policy after radical resection appears to be feasible. All in all, grade most likely is a biological continuum rather than a black and white difference between grade 2 and 3. If so, some patients with grade 3 nonenhancing gliomas might also benefit from vorasidenib.[82]

Many other questions remain unanswered: are there selected groups of patients with enhancing tumors who could still benefit from vorasidenib? What is the right timing for treatment with vorasidenib? The INDIGO study is limited to the 1-5 years' interval after surgery for initiating treatment, in patients with measurable residual disease. What should be done for patients without measurable residual disease after surgery? Is there a role for a neoadjuvant setting, are combinations with RT and/or chemotherapy possible, and is there a role for maintenance therapy after RT and/or chemotherapy? Some of these questions will hopefully be answered in planned trials, yet-to-be-planned trials, or (inter)national registries (Table 2).[83]

Practical Management

The recommended dose of vorasidenib is 40 mg once daily. Available pills are 40 mg or 10 mg to allow for dose reductions. The most common side effects of vorasidenib are elevated liver enzymes, headache, fatigue, and gastrointestinal complaints. Elevated liver enzymes have the most practical implications. In INDIGO, 29.9% of patients in the vorasidenib arm had their treatment temporarily interrupted and 10.8% required a dose reduction; in 3.6%, it was permanently discontinued. In daily practice, this means frequent monitoring of liver enzymes is required: current recommendations are every 2 weeks for the first 2 months, and then once per month as long as the patient is on vorasidenib. It is key to educate the patients and caregivers regarding commonly used hepatotoxic drugs such as acetaminophen and healthy dietary habits. There are limited data on vorasidenib use during pregnancy or lactation, and animal data suggest teratogenicity. Adequate birth control is advised for both female and male patients while on treatment, and breastfeeding should be avoided. For imaging

TABLE 1. Overview of Targeted Therapy Clinical Trials in Gliomas: Published Data

Drug and Trial	Design (phase, patients)	Outcomes	Toxicities ≥Grade 3
IDH inhibitors			
Vorasidenib[62] NCT02481154	I, F-I-H N = 52 *mIDH1/2* gliomas	ORR Nonenhancing glioma: 18% Enhancing glioma: 0% PFS: 7.5 months	ALT increase: 5% AST increase: 3% Fatigue: 2% Nausea: 2%
Vorasidenib and ivosidenib[63] NCT03343197	I, perioperative N = 24 surgical candidate grade 2/3 mIDH1-R132H CNS tumors	[2-HG] reduction Vorasidenib 50 mg: 92.6% Ivosidenib 500 mg: 91.1% ORR Vorasidenib 50 mg: 42.9% Ivosidenib 500 mg: 35.7%	Vorasidenib 50 mg ALT increase: 7% HypoPhos: 7% Ivosidenib 500 mg HypoNa: 6%
INDIGO trial Vorasidenib[64] NCT04164901	III N = 331 residual/recurrent grade 2 *mIDH* glioma	PFS: 27.7 months vorasidenib *v* 11.1 months placebo HR, 0.39 (95% CI, 0.27 to 0.56; *P* < .001) TTNI: NR vorasidenib *vs* 17.8 months placebo HR, 0.26 (95% CI, 0.15 to 0.43; *P* < .001)	ALT increase: 9% AST increase: 4% GGT increase: 3% Fatigue: 0.6%
Olutasidenib[65] NCT03684811	Ib/II N = 26 relapsed mIDH1-R132 glioma	ORR 8%	ALT increase: 12% AST increase: 12% HypoPhos: 4% Nausea: 4%
Ivosidenib[66] NCT02073994	I N = 66 relapsed *mIDH1* glioma	ORR Nonenhancing glioma: 4% Enhancing glioma: 0%	HypoPhos: 3%
Safusidenib[67] NCT04458272	I, F-I-H N = 47 relapsed mIDH1-R132 glioma	ORR Nonenhancing glioma: 33% Enhancing glioma: 17% PFS Nonenhancing glioma: NR Enhancing glioma: 10.4 weeks	ANC decrease: 12.8% ALT increase: 6.4% AST increase: 4.3% HypoPhos: 4% Diarrhea: 4%
BAY1436032[88] NCT02746081	I, F-I-H n = 45 mIDH1-R132 glioma (39 LGG, 16 grade 4 astrocytoma)	ORR LGG: 11% Grade 4 astrocytoma: 0%	ALT increase: 4% Lipase increase: 2% Nausea: 2%
LY3410738[87] NCT04521686	I, F-I-H n = 27 *mIDH1* gliomas	ORR Enhancing glioma: 13%	Anemia: 3% HypoNa: 3% Cholangitis 3%
MAPK inhibitors			
ROAR trial Dabrafenib-trametinib[68] NCT02034110	II n = 58 BRAF V600E gliomas (45 HGG, 13 LGG)	ORR LGG: 54% HGG: 33% PFS LGG: NR HGG: 3.8 months	Fatigue: 9% ANC decrease: 9% Neutropenia: 5% AST increase: 3% Pyrexia: 2% ALT increase: 2%
Dabrafenib-trametinib[69] NCT02684058	II randomized *v* SOC chemotherapy N = 110 BRAF V600 pediatric LGG	ORR: 47% dabrafenib/trametinib *v* 11% SOC chemotherapy RR, 4.31 (95% CI, 1.7 to 11.2; *P* < .001) PFS: 20.1 months dabrafenib/trametinib *v* 7.4% SOC chemotherapy HR, 0.31 (95% CI, 0.17 to 0.55; *P* < .001)	Neutropenia: 10% Pyrexia: 8% Increase weight: 7% ALT increase: 5% ANC decrease: 5% AST increase: 3%
FIREFLY-1 trial Tovorafenib[30] NCT04775485	II N = 137 *BRAF* altered pediatric LGG (101 KIAA1549:BRAF fusion, 22 BRAF V600E)	ORR BRAF fusion: 69% BRAF mutation: 50% Previous MAPKi: 71% MAPKi naïve: 61%	CPK increase: 12% Anemia: 10% Rash: 8% Decreased growth velocity: 5% ALT increase: 5% AST increase: 3%
Other			
RAGNAR trial Erdafitnib[70] NCT04083976	II n = 37 mFGFR gliomas (30 HGG, 7 LGG)	ORR LGG: 29% HGG: 10%	Stomatitis: 12% Anemia: (8%) Hand-foot syndrome: 6% HyperPhos: 5% ALT increase: 5% HypoNa: 4% Onycholysis: 3%

(continued on following page)

TABLE 1. Overview of Targeted Therapy Clinical Trials in Gliomas: Published Data (continued)

Drug and Trial	Design (phase, patients)	Outcomes	Toxicities ≥Grade 3
TARGET trial Fexagratinib[71] NCT02824133	I/II N = 12 FGFR-TACC fusion positive relapse HGG	PFS 6 months: 25% (95% CI, 5 to 57) PFS: 1.4 months (95% CI, 9 to 67) ORR: 8% (1 partial response)	Stomatitis: 8% ALT increase: 8% Hyperglycemia: 8% Lymphopenia: 8%
SCOUT and NAVIGATE trial Larotrectinib[72] NCT02637687, NCT02576431	I/II pooled analysis n = 33 NTRK fusion–positive CNS tumors (26 < 18 years)	ORR <18 years: 38% >18 years: 0% PFS 18.3 months (95% CI, 6.7 to NE)	Dysphagia: 6% Memory impairment: 6% Vomiting: 3% ANC decrease: 3% Irritability: 3%
STARTRK-NG Entrectinib[73] NCT02650401	I/II n = 16 NTRK fusion–positive CNS tumors <22 years	ORR 50%	Weight gain: 16% ANC decrease: 16% Neutropenia: 7% ALT increase: 4%
Everolimus[74] NCT00411619	I/II N = 28 definitive TSC and growing SEGA	Reduction of tumor volume at 6 months ≥30%: 75% ≥50%: 32% DOR 67.8 months (4.7-83.2)	Stomatitis: 4% Sinusitis: 4% WBC decrease: 4%

Abbreviations: [2-HG] = 2-hydroxyglutarate concentration; ANC, absolute neutrophil count; CPK, creatine phosphokinase; DOR, duration of response; F-I-H, first-in-human; GGT, gamma-glutamyl transferase; HGG, high-grade glioma; HR, hazard ratio; IDH, isocitrate dehydrogenase; LGG, low-grade glioma; MAPKi, MAPK inhibitor; mFGFR, mutant FGFR; mIDH, mutant IDH; NE, not estimable; NR, not reached; ORR, objective response rate; PFS, progression-free survival; RR, risk ratio; SEGA, subependymal giant cell astrocytoma; SOC, standard-of-care; TSC, tuberous sclerosis complex; TTNI, time to next intervention.

follow-up, a MRI brain with gadolinium sequences is recommended every 3 months for the first 3 years, and thereafter at least every 6 months.[84,85]

Other IDH Inhibitors

Although ivosidenib exhibits relatively low brain penetration in preclinical models, potentially limiting its efficacy for *IDH*-mutant glioma, ivosidenib is very potent, with an IC_{50} measured below 10 nM and it has been shown to reduce intratumoral 2HG levels by more than 90%.[63] In a phase I trial that included 66 patients with recurrent *IDH1*-mutant gliomas, ivosidenib 500 mg once per day demonstrated good tolerability. Antitumor activity in 31 enhancing tumors resulted in no complete or partial responses and 45% stable disease. In nonenhancing tumors (n = 35), there was one partial response (4%) and 85% stable disease.[66] In a cohort of 30 patients with *IDH*-mutant glioma (n = 21 grade 2), off-label use of ivosidenib demonstrated good tolerability. Antitumor activity in 22 nonenhancing tumors resulted in 12 stable diseases, five minor responses, and three partial responses. Seizure frequency was stable or improved in most patients.[86]

In an early-phase study of recurrent or progressive *IDH1*m gliomas, olutasidenib 150 mg twice daily, a brain-penetrant selective inhibitor of mIDH1 demonstrated a disease control rate (ORR plus stable disease) of 48% with responses in enhancing gliomas.[65] Furthermore, investigational agents such as safusidenib, BAY1436032, and LY3410738 have shown objective responses in early-phase clinical trials involving patients with enhancing and/or nonenhancing *IDH*-mutant gliomas.[67,87,88]

As expected with the use of these epigenetic drugs, reduction in tumor growth rates and volume reductions may be observed many months after treatment initiation.[53,89]

EMERGING THERAPEUTICS FOR RARE ONCOGENIC DRIVERS

RAS-RAF-MEK-ERK Pathway

Alterations in the RAS-RAF-MEK-ERK signaling pathway are among the most common oncogenic events in cancer. BRAF is a serine/threonine kinase that, in its nonmutant state, is activated by RAS, triggering BRAF homodimerization or heterodimerization. This activation leads to downstream signaling through MEK and ERK, resulting in the activation of nuclear transcription factors responsible for cell proliferation.[90] BRAF alterations can be categorized into three functional classes. Class I mutations, which include the *BRAF* V600 mutations, are characterized by RAS-independent monomer signaling and account for over 90% of BRAF alterations in cancer (Fig 2).[91] The prevalence of the V600E mutation varies across CNS tumors, being present in 60% of pleomorphic xanthoastrocytomas, 40% of gangliogliomas, 2% of adult low-grade gliomas (LGG), and 1%-2% of glioblastomas.[92,93] By contrast, Class II mutations rely on RAS-independent dimerization for signaling and encompass a variety of mutations and fusions, such as the BRAF:KIAA1549 fusion, which is found in up to 70% of

TABLE 2. Ongoing Molecularly Targeted Therapy Trials in Gliomas

Trial Name and NCT Number	Treatment	Patient Population	Design (phase and comparator)
IDH inhibitors			
ViCToRy NCT05609994	Vorasidenib + PEPIDH1M vaccine	Adult patients with recurrent mIDH1 LGG	I
NCT06478212	Vorasidenib + temozolomide	Age ≥12 years with mIDH1/2 gliomas	Ib/II
NCT05484622	Vorasidenib + pembrolizumab	Adult patients with recurrent or progressive mIDH1 grade 2/3 gliomas	I
VIGOR NCT06809322	Vorasidenib	Adult patients with mIDH1/2 grade 2/3 gliomas after first-line chemoradiation	III Placebo
NCT06161974	Olutasidenib + temozolomide	Age 12-39 years with mIDH1 HGG	I
NCT04521686	LY3410738 monotherapy and in combination with chemotherapy or durvalumab	Adult patients with relapsed mIDH1/2 gliomas	I
NCT02381886	IDH305	Adult patients with IDH1 R132 gliomas	I
NCT05577416	Safusidenib	Adult patients with mIDH1 LGG before surgery	I
NCT05303519	Safusidenib	Adult patients with recurrent mIDH1 grade 2/3 gliomas	II
NCT03030066	Safusidenib	Adult patients with recurrent IDH1 R132 gliomas	I Japan only
NCT04458272	Safusidenib	Treatment-naïve adult patients with IDH1 R132 grade 2 gliomas	II Japan only
MAPK inhibitors			
NCT06712875	Dabrafenib/trametinib + nivolumab Trametinib + nivolumab	Age ≤26 years with pediatric LGG/HGG KIAA1549:BRAF fusion or BRAF V600 pediatric LGG/HGG	II
NCT04201457	Dabrafenib/trametinib + hydroxychloroquine	Age ≤ 30 years with BRAF V600 LGG/HGG or BRAF duplication or fusion LGG	I/II
NCT03919071	Dabrafenib/trametinib	Age 3-25 years with mBRAF V600 HGG after chemoradiation	II
NCT03363217	Trametinib	Age ≤25 years with progressive LGG NF1, KIAA1549:BRAF fusion and MAPK/ERK activating mutation	II
NCT06666348	Mirdametinib + vinblastine	Age 2-25 years with pediatric LGG with KIAA1549:BRAF fusion or MAPK alterations other than BRAF V600E	I/II
VICTORY NCT06381570	Tovorafenib + vinblastine	Age ≤25 years with progressive BRAF/CRAF altered LGG	I
LOGGIC/FIREFLY-2 NCT05566795	Tovorafenib	Age ≤25 years with RAF activating alteration LGG	III SOC chemotherapy
FIRELIGHT-1 NCT04985604	Tovorafenib Tovorafenib + pimasertib	Age ≥12 years. Recurrent solid tumors with BRAF and MAPK alterations	I/II
NCT05503797	Plixorafenib (FORE8394)	Age ≥ 10 years with recurrent BRAF V600E gliomas	II
NCT04166409	Selumetinib	Age 2 to 21 years with BRAF V600E LGG	III Vincristine + Carboplatin
Perfume NCT06159478	Binimetinib	Age ≥12 years with recurrent BRAF rearranged LGG	II Japan only
NCT02285439	Binimetinib	Age ≤18 years with BRAF rearranged and other MAPK alterations LGG	I/II
NCT05804227	Ulixertinib	Age ≥18 years with mNF1 grade 1 to 3 glioma or grade 2/3 oligodendroglioma	I
Other			
NCT05859334	Erdafitinib	Age ≥18 years with progressive FGFR-TACC fusion–positive IDH-WT gliomas	II

(continued on following page)

TABLE 2. Ongoing Molecularly Targeted Therapy Trials in Gliomas (continued)

Trial Name and NCT Number	Treatment	Patient Population	Design (phase and comparator)
FIGHT-209 NCT05267106	Pemigatinib	Age ≥18 years with progressive FGFR 1-3 alterations gliomas	II
NCT04655404	Larotrectinib	Age ≤21 years with NTRK fusion HGG	I
NCT06558691	Entrectinib	Age <3 years with NTRK or ROS1 HGG	II

Abbreviations: HGG, high-grade gliomas; IDH, isocitrate dehydrogenase; LGG, low-grade gliomas; mBRAF, mutant BRAF; mIDH, mutant IDH; mNF1, mutant NF1; SOC, standard-of-care; WT, wild type.

pediatric pilocytic astrocytomas. The role of BRAF alterations as a predictive and prognostic biomarker in gliomas is still to be determined.[94-96]

Class I BRAF inhibitors, such as dabrafenib and vemurafenib, demonstrated unprecedented response rates in early clinical trials for BRAF V600-mutant melanoma.[97,98] However, development of secondary cutaneous neoplasms was observed, attributed to the paradoxical activation of BRAF wild-type (WT) dimers and ERK signaling.[99] To mitigate this effect, combination therapy with MEK inhibitors, such as trametinib, was introduced, resulting in a decreased incidence of proliferating skin lesions and improved therapeutic efficacy.[100] Dabrafenib/trametinib combination received FDA approval as a tissue-agnostic treatment for advanced solid tumors harboring BRAF V600E mutation, including adult and pediatric LGG and high-grade gliomas (HGG) and for first-line treatment of patients with pediatric BRAF V600E LGG who require systemic therapy. Data to support its use in primary CNS tumors come mainly from two studies. The phase II ROAR basket trial included adult patients with recurrent BRAF V600E mutant HGG and LGG. The ORR and median duration of response (DoR) were 33% (95% CI, 20 to 49) and 36.9 months (95% CI, 7.4 to 44.2) for the HGG cohort (n = 45), and 69% (95% CI, 39 to 91) with DoR not reached for the LGG cohort (n = 13), respectively.[68] The second study focused on pediatric LGG patients. In the first-line setting, a randomized phase II trial included 110 pediatric patients with diagnosis of BRAF V600x (96% V600E)-mutant LGG who were randomly assigned to dabrafenib/trametinib versus standard-of-care carboplatin plus vincristine. ORR for the dabrafenib/trametinib versus chemotherapy groups were 46% versus 11%, respectively, and median PFS was 20.1 months (95% CI, 12.8 to not evaluable) with dabrafenib/trametinib and 7.4 months (95% CI, 3.6 to 11.8) with chemotherapy (HR, 0.31 [95% CI, 0.17 to 0.55], $P < .001$). Most frequent tumor types were pilocytic astrocytoma (37%) and ganglioglioma (33%).[69] The safety profile observed in these

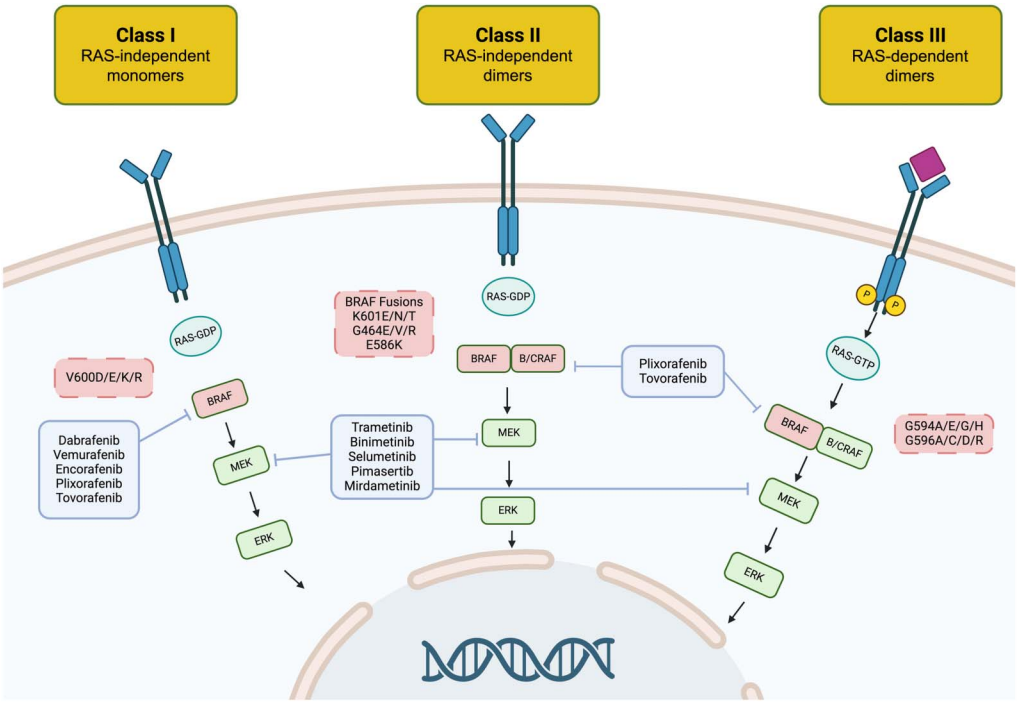

FIG 2. BRAF functional classes and their inhibitors.

trials was consistent with that reported in previous studies. The most common toxicities of grade 3 or higher included pyrexia, fatigue, and decreased neutrophil count. Permanent discontinuation because of adverse effects was below 10%.[68,69] Additionally, a reduction in left ventricular ejection fraction of 10% or greater was observed in 6% of patients receiving the combination treatment, warranting periodic cardiac evaluation. Similarly, uveitis was reported in 2% of patients across the trials, requiring monitoring.[101]

Tovorafenib is a novel, CNS-penetrant, first-in-class, FDA-approved BRAF type II inhibitor, which targets both BRAF V600 mutations and BRAF fusions without paradoxical activation of the MAPK pathway. The phase II FIREFLY-1 trial evaluated tovorafenib monotherapy in children, adolescents, and young adults with refractory or relapsed *BRAF*-altered pediatric LGG or advanced solid tumors, including patients who had previously received treatment with BRAF or MEK inhibitors. The study included 137 patients, with most tumors harboring BRAF:KIAA1549 fusions (74%) and *BRAF* V600E mutations (16%). ORR for tumors with *BRAF* fusions and *BRAF* mutations were 69% and 50%, respectively, with 17% complete responses in the entire cohort. Interestingly, ORR for previously treated patients with MAPK inhibitors was 71% compared with 61% for MAPK inhibitor–naïve patients. The most frequent treatment-related adverse events grade ≥3 were elevated creatine phosphokinase (12%), anemia (11%), and rash (8%). Other clinically significant adverse events included hair color changes (76%), which may have a notable psychosocial impact, particularly in younger patients, and decreased growth velocity (12%), with varying degrees of recovery after treatment discontinuation. Additionally, intratumoral hemorrhage was observed in 15 patients; however, the association between tovorafenib and tumor-related bleeding remains uncertain.[30] The main limitation of this study is the lack of randomization. However, this design illuminates some alternative trial designs that may support registration when the traditional approaches, such as large, randomized trials, are unfeasible.

The LOGGIC/FIREFLY-2 trial (ClinicalTrials.gov identifier: NCT05566795) is an ongoing study evaluating tovorafenib in comparison with chemotherapy in the first-line treatment of pediatric LGG. The FIRELIGHT-1 trial (ClinicalTrials.gov identifier: NCT04985604) focuses on patients with relapsed solid tumors, including CNS malignancies, harboring BRAF fusions or other MAPK pathway alterations. This trial includes two treatment arms: tovorafenib monotherapy and in combination with MEK inhibitor pimasertib. These ongoing and upcoming studies with tovorafenib will provide additional insights into the role of this drug in this heterogeneous population (Table 2).

Similarly, plixorafenib (FORE8349) is an experimental, oral, highly selective BRAF inhibitor that targets V600 and non-V600 alterations by disrupting BRAF monomers and BRAF-BRAF/BRAF-CRAF heterodimers without paradoxical activation of the MAPK pathway.[102] A phase I/IIa trial that included 113 patients with advanced solid tumors supported the CNS activity of plixorafenib, demonstrating an ORR of 66.7% (95% CI, 29.9 to 92.5) in nine patients with *BRAF* V600-mutant MAPK-naïve primary CNS tumors.[103] The most common adverse event was grade 1 to 2 liver function test changes. Interestingly, and most likely related to its novel mechanism of action, plixorafenib demonstrated a benign safety profile when compared with approved BRAF inhibitors, including no uveitis, retinal detachment, left ventricular ejection fraction or secondary skin cancers, and only grade 1 rash and pyrexia. This safety profile translates in better tolerability and decreases patient burden as serial dermatology and ophthalmology evaluations as well as echocardiograms are not required. These early-phase results led to the ongoing NCT05503797 FORTE Phase II basket study, which enrolls patients age 10 years and older into four subprotocols, including advanced solid and CNS tumors with BRAF fusions and BRAF V600 mutant recurrent CNS tumors.

As BRAF alterations evolve as druggable biomarkers in CNS tumors, and novel and safer brain-penetrant inhibitors are developed, upcoming trials should address the best treatment sequence for patients with BRAF-altered CNS tumors,[96] especially for adult patients with HGG, in which first-line treatments have remained basically unchanged for over two decades.[104]

NTRK

NTRK genes encode for a family of tropomyosin receptor kinase (TRK) proteins that, when activated, promote cell proliferation and survival.[105-107] *NTRK* gene fusions result in a constitutively active protein and are found in about 1% of adult and 3%-5% of pediatric gliomas and in up to 40% of pediatric nonbrainstem HGG.[108,109] NTRK mutations or amplification have been associated with a lack of response with some NTRK inhibitors. However, NTRK fusions have been associated with remarkable responses leading to regulatory approval. Larotrectinib is a selective inhibitor of TRK that has been approved as tumor-agnostic therapy for adult and pediatric patients whose tumors harbor a NTRK fusion and have no satisfactory alternative treatment on the basis of data from three single-arm clinical trials: LOXO-TRK-14001 (ClinicalTrials.gov identifier: NCT02122913), SCOUT (ClinicalTrials.gov identifier: NCT02637687), and NAVIGATE (ClinicalTrials.gov identifier: NCT02576431).[110] Evidence of its utility in CNS primary tumors comes from a pooled analysis from early phase trials that included 33 patients, mostly pediatric (n = 26). ORR was 38% (95% CI, 16 to 49) for pediatric patients, with three (9%) complete responses and seven (21%) partial responses. Interestingly there were no responses in adult patients. Median PFS for the whole cohort was 18.3 months (95% CI, 6.7 to not estimable).[72]

Entrectinib is another potent TRK inhibitor that was specifically designed to cross the BBB, with reported preclinical

brain/plasma concentrations ratio of 0.43.[111] Intracranial activity was confirmed in early-phase trial including patients with CNS metastases.[112] The STARTRK-NG phase I/II trial included 16 pediatric patients with primary brain tumors with NTRK *(n = 11)*, *ROS1 (n = 4)*, or ALK *(n = 1)* fusions, three patients in the *NTRK* group had a complete response, and two had a partial response.[73] Among them, a patient with epithelioid glioblastoma achieved a complete response and had DoR of 25 months. Interestingly, in the *ROS1* fusion–positive subgroup, one patient with a H3 K27M diffuse midline glioma had a complete response with a DoR of 22 months and partial responses were seen in two participants.[73] So far, evidence for entrectinib in adult patients with CNS tumors comes from case reports.[113,114] In concordance with physiologic function of TRK (A/B/C), NTRK inhibitors show a unique toxicity profile that includes weight gain, nociception and memory impairment, ataxia, as well as fatigue, hallucinations, and decreased neutrophil count.[72,73,115]

Mammalian Target of Rapamycin

Subependymal giant cell astrocytoma (SEGA) is a rare type of circumscribed astrocytic glioma that seems to arise from the subependymal nodules in patients with tuberous sclerosis complex (TSC). TSC is an autosomal dominant genetic disorder that can affect multiple systems, caused by mutations in *TSC1* or *TSC2* genes.[116] Approximately 10% of patients with TSC develop SEGA.[117] As a result of these mutations, mTOR complex 1 is constitutively upregulated, leading to cell proliferation.[118] A phase I to II study included 28 adult and pediatric patients with diagnosis of TSC and growth of SEGA, who were treated with the mTOR inhibitor, everolimus. A significant reduction in the tumor volume was seen at 6 months, with 21 (75%) patients having a reduction of ≥30% and nine (32%) of ≥50%.[74] On the basis of the results of this study, everolimus obtained regulatory approval by FDA. These findings were confirmed by a long-term follow-up report of this study that showed a median duration of treatment of 67.8 months (4.7-83), and 52% and 61% volume reductions of ≥50 and ≥30%, respectively.[119] Interestingly, no patient required surgery during the treatment period, and everolimus demonstrated to be a long-term safe medication.

FGFR

FGFR alterations, including mutations and fusions, contribute to cellular proliferation and tumorigenesis. FGFR1 mutations are predominantly observed in pediatric gliomas but can also be found in both LGG and HGG. By contrast, FGFR2 and FGFR3 alterations primarily occur as fusions, with FGFR3-TACC3 fusions being almost exclusively detected in adult HGG.[120] FGFR-TACC chromosomal translocations describe the fusions of tyrosine kinase coding domain of the *FGFR* gene to the coiled-coil domain of TACC. FGFR3-TACC3 (F3T3) is the most recurrent gene fusion in cancer and the most prevalent type of gene fusion in adult glioma. Because of their histopathologic and molecular features, it has been suggested that F3T3 gliomas represent a unique entity among *IDH* WT gliomas. F3T3 gene fusion is present in 3%-6% of *IDH* WT gliomas and is an independent predictor of a favorable outcome in these tumors (independent of tumor grading).[121] F3T3 fusion is a potent oncogene that confers sensitivity to FGFR inhibitors. Of note, the F3T3 fusion is retained in recurrent glioblastoma.[121-124] Erdafitinib is a potent FGFR1-4 inhibitor approved for the treatment of FGFR-altered urothelial carcinoma. Clinical evidence regarding its activity in CNS tumors comes from the phase II RAGNAR trial that included 30 heavily pre-treated patients with HGG and 7 with LGG. To note, this trial allowed patients with a variety of alterations, including mutations and fusions. ORR for HGG and LGG was 10% and 29%, respectively, DOR was not reached. Interestingly, two patients from the HGG cohort, whose tumors had F3T3 fusion had partial responses and one of them had a 24-month ongoing partial response at data cutoff.[70] Tumor heterogeneity, especially in glioblastoma, has been one of the major causes, for which promising treatments fail to show significant benefits in clinical trials.[71] Consequently, two ongoing phase II trials have been specifically designed to evaluate the efficacy of erdafitinib in glioma patients with FGFR alterations. NCT05859334 ETCTN 10559 is recruiting patients with recurrent IDH-wildtype gliomas with a F3T3 fusion to receive treatment with erdafitinib. Whereas FIGHT-209 (ClinicalTrials.gov identifier: NCT05267106) included patients with glioblastomas and other CNS tumors with FGFR 1-3 fusions or mutations.

CONCLUSION

A CNS-specific framework for drug selection is essential to improving clinical trial success in neuro-oncology. Inadequate preclinical models and a reliance on data from only contrast-enhancing tumor regions tend to overestimate drug penetration. Expanding human PK/PD data through WoO trials, microdialysis, and imaging advances will enable more accurate drug prioritization. In the interim, systematic data–driven screening can identify agents with low CNS activity early, preventing ineffective trials and streamlining drug development.

Tumor profiling is becoming an essential component of the diagnostic workup for patients with primary CNS tumors.[125] Consequently, assays with broad gene panels may identify targetable oncogenic drivers in these tumors. However, the prevalence of driver alterations proven to be actionable other than IDH is below 10% in gliomas,[126] the exception being BRAF alterations, with the BRAF-KIAA1549 fusion observed in up to 70% of pediatric pilocytic astrocytoma and the BRAF V600E mutation detected in approximately 60% of pleomorphic xanthoastrocytoma.[127,128]

In addition to the fact that designing and executing registrational clinical trials for these rare tumors with oncogenic drivers poses significant challenges, the obstacle of BBB

permeability further complicates the treatment of CNS tumors. However, data from studies such as Indigo and FIREFLY demonstrated that these studies are feasible and can end on new treatment options for our patients. In neuro-oncology practice, advocating for tumor profiling is crucial, as identifying these rare but targetable alterations can offer brain tumor patients more effective treatments with fewer side effects. Ongoing clinical trials will further clarify the role and best timing to incorporate these therapeutic strategies during the disease course.

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