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REVIEW

Recent Advances in Targeted Therapies for Adult Gliomas

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Abstract

Purpose of Review Incorporation of molecular diagnostics has transformed the classification and risk stratification of adult gliomas, revealing a spectrum of therapeutically actionable targets. This review evaluates Food and Drug Administration (FDA)-approved and investigational targeted therapies and discusses the major challenges and future directions facing the field.

Recent Findings Landmark FDA approvals, such as vorasidenib for isocitrate dehydrogenase (IDH)-mutant gliomas, dabrafenib and trametinib for BRAF V600E-mutated gliomas, neurotrophic tyrosine receptor kinase (NTRK) inhibitors for NTRK fusion-positive tumors and dordaviprone for H3K27M-mutant diffuse midline gliomas, underscore a new era of targeted therapies in neuro-oncology. These molecularly-driven therapies deliver tangible clinical benefit to select subsets of patients with molecularly defined tumors. However, they are not curative, and tumors with these targetable alterations constitute a minority of adult gliomas. Novel agents targeting DNA repair and metabolic dependencies, and leveraging immune-based and advanced strategies of drug delivery, are under investigation.

Summary Targeted therapies have begun to transform the management of molecularly defined subsets of adult glioma, though their clinical benefits remain limited to date.

Keywords Glioma · Targeted therapy · IDH mutant · IDH wildtype · Glioblastoma · IDH inhibitor

Introduction

Gliomas are the most common primary malignant brain tumors in adults [1]. Their genetic heterogeneity and infiltrative nature present significant challenges, leading to limited therapeutic benefit from current therapies. In the last decade, the incorporation of molecular diagnostics, such as isocitrate dehydrogenase (IDH) mutations, has transformed the classification and prognostication of adult gliomas [2, 3]. However, translation of molecular insights into effective treatments has been slow, and survival outcomes, particularly for patients with IDH-wildtype (IDH-wt) glioma, remain poor. Encouragingly, this paradigm has begun to shift. Recent Food and Drug Administration (FDA) approvals have introduced the first targeted agents in gliomas, including vorasidenib for IDH-mutant (IDH-mut) diffuse gliomas, dabrafenib-trametinib for BRAF V600E-mutated gliomas, neurotrophic tyrosine receptor kinase (NTRK) inhibitors for NTRK fusion-positive tumors and dordaviprone for recurrent H3K27M-mutant diffuse midline gliomas. In this review, we outline the current classification and molecular landscape of adult gliomas and evaluate FDA-approved and investigational targeted therapies. We further consider evolving drug delivery strategies, persistent challenges that impede therapeutic progress and potential future directions.

Classification of Adult Gliomas

The classification of adult gliomas has undergone a paradigm shift over the last decade. Historically, the diagnosis of gliomas was based on histology [4, 5]. However, molecular classification was incorporated into the 2016 World Health Organization (WHO) Classification of Tumors of the Central Nervous System (CNS), and refined further in the 2021

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update [3, 6]. Together, these criteria introduced an "integrated diagnosis", where defining molecular alterations are considered alongside histopathology to designate distinct tumor types [3, 6].

In the latest 2021 WHO classification, *IDH1/2* mutation status is the primary molecular classifier of diffuse gliomas [6]. Glioblastoma (GBM) is a grade 4 tumor, defined by wild-type *IDH* alongside characteristic histologic features, including microvascular proliferation and necrosis or molecular features (*TERT* promoter mutation, *EGFR* amplification or chromosome 7 gain/10 loss) [6]. GBM is the most common malignant primary brain tumor in adults, accounting for approximately 51% of all malignant primary brain tumors and primarily affecting patients over 60 years old [1]. In contrast, IDH-mut gliomas are less common, accounting for roughly 15–20% of all adult gliomas, and are more prevalent in younger patients in their thirties and forties [1]. In IDH-mut glioma, co-deletion of the 1p and 19q chromosomal arms defines oligodendroglioma [6]. Oligodendrogliomas often harbor alterations in *TERT* promoter, *CIC*, *FUBP1* and *NOTCH1*, and are classified as grade 2 or 3 based on their histology [6]. IDH-mut, 1p/19q-intact tumors are classified as astrocytoma, typically harboring *ATRX* and *TP53* alterations and graded histologically as grade 2, 3 or 4 [6]. Notably, homozygous *CDKN2A/B* deletion in IDH-mut astrocytoma yields a grade 4 designation irrespective of histopathological features [6].

Besides GBM, IDH-wt adult gliomas include several "pediatric-type" diffuse gliomas and circumscribed gliomas that typically affect young adults and carry distinct molecular signatures. For instance, diffuse midline glioma (DMG), H3 K27-altered, is a grade 4 tumor defined by its midline location (e.g., thalamus, pons, spinal cord) and loss of H3K27 trimethylation, most commonly due to H3 K27M mutation (DMG-H3K27M) [6]. Examples of low grade circumscribed gliomas include pilocytic astrocytoma (PA) and pleomorphic xanthoastrocytoma (PXA) [6].

Molecular Landscape of Adult Gliomas

Beyond diagnostic classification, the molecular diversity of adult gliomas reveals distinct tumor biology and therapeutic vulnerabilities. In IDH-mut gliomas, *IDH1/2* mutations drive tumorigenesis [7, 8]. In contrast, IDH-wt gliomas, especially GBM, are characterized by complex molecular architectures involving frequent alterations in receptor tyrosine kinases (RTKs) (such as *EGFR*, *PDGFRA*, *FGFR*), RTK downstream cascades (including phosphatidylinositol 3-kinase–protein kinase B-mechanistic target of rapamycin (PI3K-AKT-mTOR) and mitogen-activated protein kinase (MAPK) pathways), cell cycle regulation and DNA damage response, resulting in marked pathway redundancy and cross-talk [9–11]. Targeted therapies in glioma have been designed either to directly inhibit oncogenic drivers, such as mutant *IDH1/2*, *EGFR* or *BRAF*, or to exploit vulnerabilities, such as DNA repair mechanisms or metabolic liabilities. Figure 1; Table 1 summarize key molecular pathways and therapeutic strategies in adult gliomas.

Targeted Therapies in Adult Gliomas

Historically, adult glioma management has relied on surgery, radiotherapy and cytotoxic chemotherapy. GBM is typically treated with maximal safe resection followed by chemoradiation, while IDH-mut gliomas have conventionally been managed with maximal safe resection followed by risk-adapted chemoradiation strategies based on tumor histology and grade [12, 13]. Given the limited benefit and toxicities associated with these regimens, interest in targeting specific molecular alterations has grown. In the sections that follow, we review FDA-approved targeted therapies for adult gliomas, examine supporting clinical trials, and highlight promising investigational agents. Table 2 summarizes pivotal trials that led to FDA approvals reporting glioma-specific data.

FDA-approved Targeted Therapies

Exploiting IDH Mutations – Mutant IDH Inhibitors

A majority of IDH-mut gliomas (over 90%) harbor a canonical heterozygous point mutation in *IDH1*, leading to an arginine-to-histidine substitution at amino acid 132 (IDH1 R132H), while a minority harbor non-canonical *IDH1* or *IDH2* mutations (Table 1) [2]. These gain-of-function mutations in *IDH1*/2 induce the accumulation of the oncometabolite D-2-hydroxyglutarate (D-2HG), leading to DNA and histone hypermethylation and tumorigenesis (Fig. 1; Table 1) [7, 14–16]. Mutant IDH inhibitors (mIDHis) had previously received FDA approval for treatment of IDH1/2-mut acute myeloid leukemia and IDH1-mut cholangiocarcinoma [17–19]. Building on promising preclinical studies, two mIDHis, ivosidenib and vorasidenib, advanced into clinical trials in patients with IDH-mut gliomas [12, 20].

In phase 1 trials, both ivosidenib (an oral mIDH1 inhibitor) and vorasidenib (a dual mIDH1/2 inhibitor) demonstrated clinical activity in recurrent or progressive pre-treated IDH-mut glioma [21–23]. In a randomized window-of-opportunity trial comparing these two mIDHis, both agents produced > 90% suppression of D-2HG production [24]. However, vorasidenib achieved superior brain penetration and slightly higher objective response rate (ORR) compared to ivosidenib (43% versus 36%), and was therefore selected

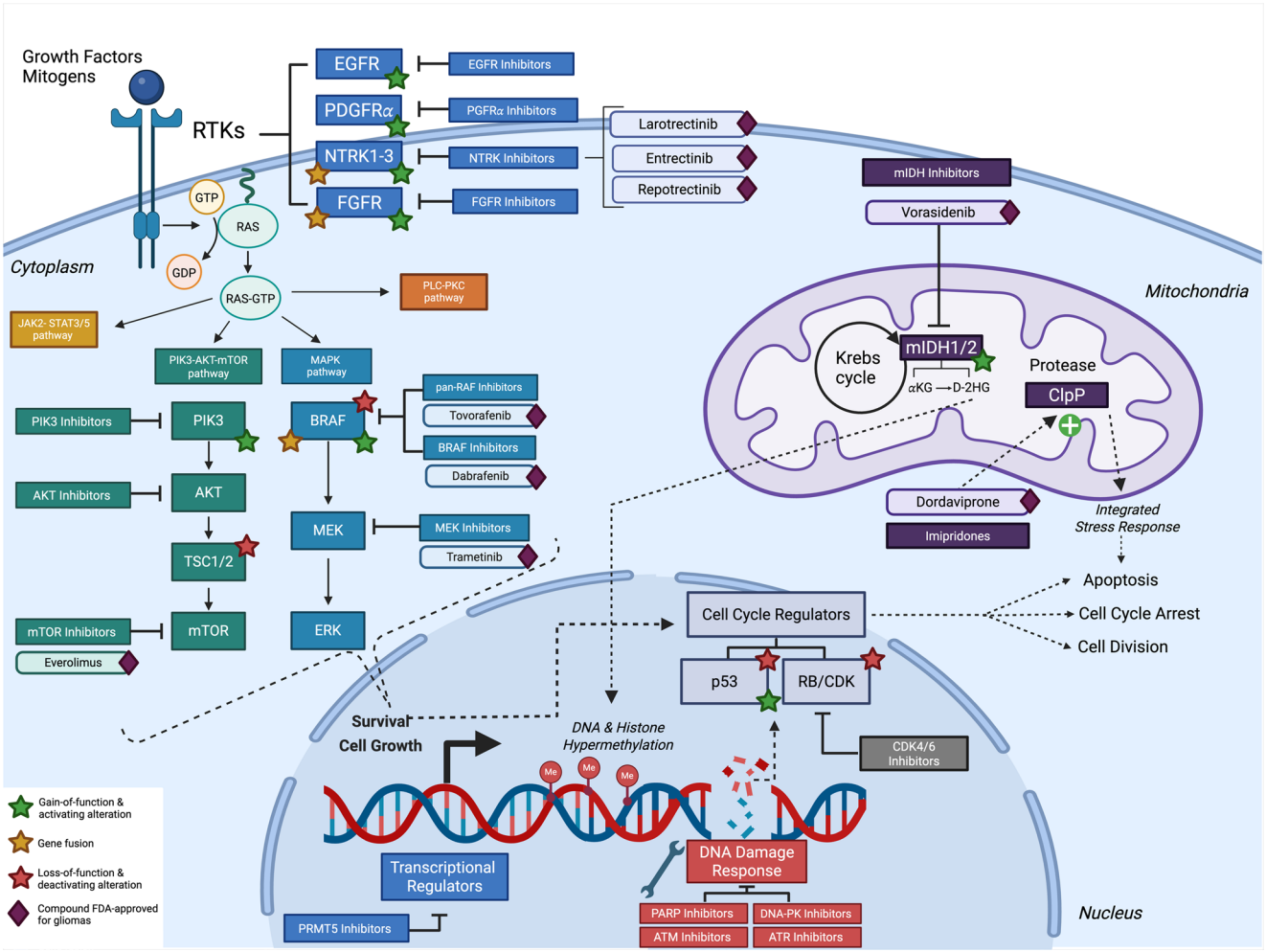

Fig. 1 Molecular landscape of adult gliomas: oncogenic pathways and targeted therapeutics. This schematic portrays key oncogenic signaling pathways and their genetic alterations in adult gliomas, with therapeutic agents, including Food and Drug Administration (FDA)-approved compounds (purple diamond) and investigational compounds, mapped onto specific targets. Genetic alterations are denoted as gain-of function or activating (green star), loss-of-function (red star), and gene fusions (yellow star). In IDH-mutant gliomas, the aberrant enzymatic production of D-2-hydroxyglutarate (D-2HG) drives widespread epigenetic changes, fostering tumorigenesis. In contrast, IDH-wildtype gliomas typically harbor frequent alterations in receptor tyrosine kinases (RTKs), including EGFR, PDGFRα, FGFR and NTRK. Activation of these RTKs by growth factors triggers downstream oncogenic cascades, including MAPK, PI3K-AKT-mTOR, JAK2-STAT3/5 and PLC/PKC, promoting unchecked cell proliferation, survival and therapeutic resistance. This schematic also highlights additional vulnerabilities, such as the mitochondrial protease ClpP, targeted by dordaviprone that induces integrated stress responses and apoptosis. Additional compounds targeting DNA damage response pathways (e.g., PARP, ATM, ATR and DNA-PK inhibitors), transcriptional regulation (PRMT5 inhibitors) and cell cycle control (CDK4/6 inhibitors) are mapped to relevant nodes, reflecting the diverse therapeutic strategies under investigation in adult gliomas. Created in BioRender. Lasica, A. (2026) https://BioRender.com/7x21409. Abbreviations: AKT – protein kinase B; αKG – alpha-ketoglutarate; ATM – ataxia-telangiectasia mutated; ATR – ataxia-telangiectasia and rad3-related; BRAF – B-Raf proto-oncogene; CDK4/6 – cyclin dependentkinase 4/6; ClpP – caseinolytic peptidase P; D-2HG – D-2-hydroxyglutarate; DNA-PK – DNA-dependent protein kinase; EGFR – epidermal growth factor receptor; ERK – extracellular signal-regulated kinase; FGFR – fibroblast growth factor receptor; JAK2-STAT3/5 – Janus kinase 2-signal transducer and activator of transcription 3/5; MAPK – mitogen-activated protein kinase; MEK – MAPK-kinase; mIDH1/2 – mutant isocitrate dehydrogenase 1/2; mTOR – mechanistic target of rapamycin; NTRK – neurotrophic tyrosine receptor kinase; PARP – poly (ADP-ribose) polymerase; PDGFRα – platelet-derived growth factor receptor alpha; PI3K – phosphoinositide 3-kinase; PKC – protein kinase C; PLC – phospholipase C, PRMT5 – protein arginine methyltransferase 5; p53 – tumor protein p53; RAS – rat sarcoma viral oncogene homolog; RB – retinoblastoma protein; RTK – receptor tyrosine kinase; TSC1/2 – tuberous sclerosis complex 1/2

for evaluation in the pivotal phase 3 INDIGO *(INvestigating vorasiDenIb in GliOma)* trial (Table 2) [24].

The INDIGO phase 3 trial was a double-blind, randomized, placebo-controlled study evaluating vorasidenib in 331 patients with residual or recurrent grade 2, non-enhancing IDH1/2-mut gliomas (Table 2) [25]. Participants were treatment-naïve except for prior surgery and were considered appropriate for a "watch-and-wait" approach. In the

Table 1 Targeted therapy opportunities in adult gliomas: molecular landscape and mechanistic rationale

Molecular Target			Genetic Alteration	Frequency& Predominant Tumor Type	Cellular Effects	Targeted Therapy
Targeting Genetic Alterations						
Cellular Metabolism	*IDH1/2*		Point mutations: IDH1: R132H > (R132C, R132S, R132L, R132G) [2] Point mutations: IDH2: R172K > (R172G, R172M) [2]	IDH1 R132H (>90%) Other IDH1/2 mut (>10%) [2]	↑ D-2HG → ↑ DNA methylation (G-CIMP); ↑ histone methylation; ↓ anti-tumor immune response [7, 8, 14, 15, 16]	mIDH Inhibitors
RTKs	*EGFR*		Focal amplification	45% IDH-wt GBM [87]	↑ PI3K-AKT-mTOR, MAPK and JAK2-STAT3/5 signaling → pro-survival and proliferation; reprogramming of vascular and immune niches	EGFR Inhibitors
			In-frame deletion: *EGFRvIII*	25–30% (>% in *EGFR*-amplified) IDH-wt GBM [87]		
	PDGFRA		Focal amplification	~15% IDH-wt GBM ~30% DMG-H3K27M [11]		PDGFRα Inhibitors
	FGFR		Fusions: e.g. FGFR3-TACC3 Focal amplification: FGFR3	~3–8% IDH-wt GBM [11, 97, 98]		FGFR Inhibitors
	NTRK1-3		Fusions: e.g. BCAN-NTRK1, BCR-NTRK2, and EML4-NTRK3 [56]	~0.5–2% (adult glioma) <~5% pediatric glioma: IDH-wt GBM + pediatric HGGs [11, 53, 54, 55]		NTRK Inhibitors
RTK Downstream Pathways	MAPK: *BRAF*		Point mutation: BRAF V600E [35]	~1–2% IDH-wt GBM; ~10–12% IDH-wt PA; ~60% IDH-wt PXA [36, 37]	Class I mutation: RAS-independent BRAF monomer → ↑ MEK/ERK signaling → pro-survival and proliferation [33, 34]	BRAF Inhibitors + MEK Inhibitors*; pan-RAF Inhibitors
			Fusion: KIAA1549-BRAF [33, 34]	~70% IDH-wt PA [36, 37]	Class II mutation: RAS-independent BRAF dimerization ↑ MEK/ERK signaling → pro-survival and proliferation [33, 34]	pan-RAF Inhibitors
	PI3K – AKT –mTOR	*PIK3CA*, *PIK3R1*	*PIK3CA*, Point mutations *PIK3R1;* Point mutations + in-frame or frameshift deletions/insertions	~5–10% IDH-wt GBM + IDH-mut [11]	↑ PI3K/AKT/mTOR signaling → pro-survival and proliferation	PI3K Inhibitors; PI3K/mTOR Inhibitors; AKT Inhibitors: mTOR Inhibitors
		PTEN	Point mutations + in-frame or frameshift deletions/insertions	~30% IDH-wt GBM [11]	↑ PI3K/AKT/mTOR signaling → pro-survival and proliferation	
		TSC1, *TSC2*	Point mutations *TSC2* > point mutations *TSC1*; *TSC1/2* deletions	~85% SEGA [113]	↑ mTOR1 signaling → pro-survival and proliferation	mTOR Inhibiors
Cell Cycle	RB/CDK pathway: *CDK4/6*		Focal amplification	CDK4~20%, CDK6 ~5% IDH-wt GBM [11]	↑ CDK4/6 activity → RB1 inactivation → ↑ cell proliferation (↑ G1 to S phase transition)	CDK4/6 Inhibitors
Transcriptional Regulation	*MTAP***		Homozygous deletion (co-occurs with *CDKN2A/B* deletion) [87, 88]	~30–50% IDH-wt GBM [11]	↑ MTA → PRMT5 inhibition (transcription regulator) → ↑ DNA damage sensitivity; ↓cell cycle control + gene regulation [89]	PRMT5 Inhibitors, MAT2A Inhibitors
Exploiting Molecular Vulnerabilities						
	Molecular Target		Molecular Function	Cellular Effects of Therapeutic Intervention		Targeted Therapy

Table 1 (continued)

Molecular Target		Genetic Alteration	Frequency& Predominant Tumor Type	Cellular Effects	Targeted Therapy
Apoptosis & Epigenetic Regulation	ClpP	ClpP → ↑ integrated stress response (ATF4/CHOP) → ↑ p53-independent apoptosis; ↓ cell survival signaling [63, 64,] ClpP → ↓OGDH + ↑α-KG → ↑ L-2HG via LDH [66]	↑ ClpP → ↑ integrated stress response → ↑ apoptosis [63, 64] ↑ ClpP → ↑ L-2HG via LDH → restoration of H3K27 trimethylation [66]		ClpP Inducer: Imipridones
DNA Damage Response	ATM	ATM → double-strand breaks repair [71]	↑ accumulation of genetic damage → genomic instability → apoptosis or cancer cell death [72]		ATM Inhibitors
	ATR	ATR → DNA repair coordination (incl. single-strand breaks) [71]			ATR Inhibitors
	DNA-PK	DNA-PK → double-strand breaks repair via non-homologous end joining [71]			DNA-PK Inhibitors
	PARP	PARP → single-strand breaks repair [71]			PARP Inhibitors

*MEK inhibitors are used in combination with BRAF inhibitors to reduce emergence of resistance

** Targeting tumors with homozygous *MTAP* deletion with PRMT5 inhibitors can be perceived as exploitation of metabolic vulnerability. However, as this vulnerability is genetically-driven, we included it in the 'Targeting Genetic Alteration' section

Abbreviations: ↑ – increase in activity; ↓ – decrease in activity; α-KG – alpha-ketoglutarate; ATF4 – activating transcription factor 4; ATM – ataxia-telangiectasia mutated; ATR – ataxia telangiectasia and rad3-related protein; BRAF – B-Raf proto-oncogene; CDK4/6 – cyclin-dependent kinase 4/6; CDKN2A/B – cyclin dependent kinase inhibitor 2A/B; CHOP – C/EBP homologous protein; ClpP – caseinolytic peptidase P; D-2HG – D-2-hydroxyglutarate; DNA-PK – DNA-dependent protein kinase; DMG-H3K27M – diffuse midline glioma, H3 K27M-mutant; EGFR – epidermal growth factor receptor; ERK – extracellular signal-regulated kinase; FGFR – fibroblast growth factor receptor; G-CIMP – glioma CPG island methylator phenotype; GBM – glioblastoma; HGGs – high grade gliomas; IDH – isocitrate dehydrogenase; JAK2-STAT3/5 – Janus kinase 2-signal transducer and activator of transcription 3/5; L-2HG – L-2-hydroxyglutarate; LDH – lactate dehydrogenase; MAPK – mitogen-activated protein kinase; MAT2A – methionine adenosyltransferase 2A, MEK – MAPK/ERK kinase; mIDH – mutant isocitrate dehydrogenase; MTA – methylthioadenosine; MTAP – methylthioadenosine phosphorylase; mut – mutant; NTRK – neurotrophic tyrosine receptor kinase; OGDH – oxoglutarate dehydrogenase; PA – pilocytic astrocytoma; PARP – poly (ADP-ribose) polymerase; PDGFRα – platelet-derived growth factor receptor alpha; PI3K-AKT-mTOR – phosphoinositide 3-kinase–protein kinase B–mechanistic target of rapamycin; PIK3CA – phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PIK3R1 – phosphoinositide-3-kinase regulatory subunit 1; PRMT5 – protein arginine N-methyltransferase 5; PTEN – phosphatase and tensin homolog; PXA – pleomorphic xanthoastrocytoma; RB/CDK – retinoblastoma protein /cyclin-dependent kinase; RTK – receptor tyrosine kinase; SEGA – subependymal giant cell astrocytoma; TSC1/2 – tuberous sclerosis complex 1/2; wt – wildtype

primary analysis, the vorasidenib cohort had significantly longer median progression-free survival (mPFS) of 27.7 months compared to mPFS of 11.1 months in the placebo cohort, alongside delayed time to next intervention (TTNI) and lower tumor growth rates for vorasidenib compared to placebo [25, 26]. Vorasidenib was well tolerated, and the most clinically significant adverse event was grade 3 or higher aminotransferase elevation in 9.6% of patients. With an additional six months of follow-up, vorasidenib demonstrated continued efficacy [27]. The INDIGO results led to FDA approval of vorasidenib in August 2024 for grade 2 IDH1/2-mut glioma following surgery.

The INDIGO trial is the first randomized study to demonstrate the efficacy of targeted therapy in IDH-mut gliomas, marking a significant advance in neuro-oncology. Although its impact on overall survival (OS) is not yet established, vorasidenib can prolong progression-free survival (PFS) and TTNI, thereby delaying chemoradiation and its associated toxicities [25, 28]. This is particularly relevant for younger patients, for whom preserving neurocognitive function and quality of life is paramount [29, 30].

The generalizability of INDIGO findings requires careful consideration. Though INDIGO only included tumors with measurable disease to allow for response assessment on MRI, vorasidenib is approved for use in gross-totally resected tumors, immediately after surgery. Vorasidenib is also approved for use regardless of MRI contrast enhancement, though INDIGO only included non-enhancing tumors. For patients with enhancing tumors, an individualized risk-benefit assessment is essential, informed by a multidisciplinary team and patient input [12, 28]. Additionally, the utility of vorasidenib across tumor grades remains an area of ongoing investigation, with preliminary evidence suggestive of a potential benefit in select non-enhancing grade 3 gliomas [12, 28].

Importantly, several outstanding questions remain, including the potential value of combining mIDHis with other treatments such as chemoradiation or immunotherapies; multiple clinical trials are underway to better characterize the benefits of these combination strategies [12]. The European Organization for Research and

Table 2 Landmark clinical trials leading to FDA approvals for targeted therapeutics for adult gliomas reporting on glioma-specific outcomes

Targeted Therapy Agent	Trial Name (NCT No.)	Trial Design &Phase	Glioma-only Study Population & Sample Size	Primary Endpoints	Glioma-only Results	FDA Approval Year	FDA Indication
Vorasidenib, mIDH1/2 inhibitor	INDIGO (NCT04164901) [25]	2-arm, double-blind, randomized, placebo-controlled, phase 3	Recurrent or residual, mIDH1/2 glioma, grade 2, measurable non-enhancing disease, treatment-naïve, ≥12 yrs (n=331)	PFS	Vorasidenib mPFS: 27.7 mo Placebo mPFS: 11.1 mo HR=0.39 (95% CI:0.27–0.56)	August 2024	Patients (≥12 yrs) with grade 2 IDH1/2-mutant glioma after surgery (biopsy or resection)
Dabrafenib, BRAF inhibitor/type I RAF inhibitor+Trametinib, MEK inhibitor	ROAR (NCT02034110) [43, 44]	1-arm, open-label, phase 2, basket trial	Recurrent or refractory BRAF V600E-mutant solid tumor (including gliomas), ≥18 yrs HGG: measurable disease, prior RT+CT or RT/CT, (n=45) LGG: non-enhancing measurable disease (n=13)	ORR	HGG: ORR: 33% mPFS*: 5.5 mo mOS: 17.6 mo DoR: 31.2 mo LGG: ORR: 54% mPFS*: not evaluable mOS: not evaluable mDoR: NR	June 2022	Patients (≥6 yrs) with unresectable or metastatic BRAF V600E-mutated solid tumors, including gliomas, who have progressed following prior treatment
	(NCT02124772) [46]	Multi-cohort, open-label, phase 1/2 trial	Refractory or recurrent childhood malignancies, including BRAF-mutated solid tumors such as gliomas, ≤18 yrs (n=49, assessed response; predominantly LGG)	RP2D	Trametinib ORR:15% mPFS: 16.4 mo mDoR: NR Dabrafenib+Trametinib ORR: 25% mPFS: 36.9 mo mDoR: 33.6 mo		
Tovorafenib, type II pan-RAF inhibitor	FIREFLY-1 (NCT04775485) [52]	1-arm, open-label, phase 2 trial	Relapsed or refractory BRAF-and RAF-altered pediatric LGG, >6 mo to <25 yrs (n=137)	ORR	As per RAPNO-LGG ORR: 51% mDoR:13.8 mo mTTR: 5.3 mo	April 2024	Patients (>6 months) with relapsed or refractory pediatric LGG with BRAF fusion, rearrangement, or V600 mutation
Larotrectinib, NTRK inhibitor	SCOUT (NCT02637687) NAVIGATE (NCT02576431)	1-arm, open-label, phase 1/2 trial 1-arm, open-label, phase 2 trial	Combined analysis (n=33): Adult (n=7) and pediatric (n=26) patients with NTRK fusion-positive CNS primary malignancies, recurrent or progressive [57]	ORR	ORR: 30% DoR% at 12mo: 75% PFS% at 12mo: 56% OS% at 12mo: 85% mTTR: 1.9mo	November 2018	Adult and pediatric patients with NTRK fusion-positive solid tumors either: metastatic malignancy or where surgical resection is likely to result in severe morbidity, and who have no satisfactory alternative treatments; OR whose cancer has progressed following treatment

Table 2 (continued)

Targeted Therapy Agent	Trial Name (NCT No.)	Trial Design &Phase	Glioma-only Study Population & Sample Size	Primary Endpoints	Glioma-only Results	FDA Approval Year	FDA Indication
Dordaviprone, D2DR antagonist, ClpP inducer	ONC006 (NCT02525692)	6-arm, open-label, phase 2 trial	Combined analysis ($n=50$): Adult ($n=46$) and pediatric patients: >2yrs ($n=4$) with recurrent, non-pontine and non-spinal DMG-H3K27M, >90 days post-RT, lesions measurable with RANO-HGG [67]	ORR	As per RANO-HGG ORR: 20% DCR: 40% mDOR:11.2 mo mTTR: 8.3 mo PFS% at 6mo: 35.1% mOS: 13.7mo	August 2025	Patients (≥1 yrs) with DMG-H3K27M with progressive disease following prior therapy
	ONC013 (NCT03295396)	2-arm, open-label, phase 2 trial					
	ONC014 (NCT03416530)	8-arm, open-label, phase 1 trial					
	ONC016 (NCT05392374)	Single-patient compassionate use program					
	ONC018 (NCT03134131)	Expanded access protocol					

*By investigator assessment

Abbreviations: BRAF – B-Raf proto-oncogene; CI – confidence interval; CNS – central nervous system; ClpP – caseinolytic protease P; CT – chemotherapy; DCR – disease control rate; DMG-H3K27M –diffuse midline glioma, H3K27M-mutant; DoR – duration of response; D2DR – dopamine subtype 2 receptor; HGG – high grade glioma; HR – hazard ratio; LGG – low grade glioma; mDOR – median duration of response; MEK – MAPK/ERK kinase; mIDH1/2 – mutant isocitrate dehydrogenase 1/2; mo – months; mOS – median overall survival, mPFS – median progression-free survival; mTTR – median time to response; NCT – national clinical trial number; NR – not reached; NTRK – neurotrophic tyrosine receptor kinase; ORR – objective response rate; OS – overall survival; PFS – progression-free survival; RANO-HGG – response assessment in neuro-oncology criteria for high-grade gliomas; RAPNO-LGG – response assessment in pediatric neuro-oncology in low grade glioma; RP2D – recommended phase 2 dose; RT – radiotherapy; RT/CT – concurrent chemoradiation; yrs – years

Treatment of Cancer (EORTC)-run placebo-controlled phase 3 VIGOR trial (NCT06809322) is evaluating vorasidenib as maintenance therapy after completion of first-line standard-of-care chemoradiotherapy in patients with grade 2 or 3 IDH-mut astrocytoma. In the United States, a placebo-controlled phase 3 trial sponsored by the Alliance for Clinical Trials in Oncology (NCT07215910) will assess vorasidenib in combination with adjuvant temozolomide (TMZ) following radiotherapy in patients with newly diagnosed grade 3 IDH-mut astrocytoma. Additionally, given the immunosuppressive effects of D-2HG, use of mIDHis to modulate the immune microenvironment has become the rationale for multiple ongoing trials. For example, a phase 1 trial of vorasidenib in combination with pembrolizumab (NCT05484622) for patients with recurrent IDH1-mut glioma is based on the rationale that mIDH inhibition may mitigate T-cell suppression and enhance the activity of immune-checkpoint blockade. Another phase 1 study, the ViCToRy trial (NCT05609994), is investigating vorasidenib in combination with an IDH1-specific peptide vaccine in patients with recurrent grade 2 or 3 IDH1-mut gliomas.

Other mIDHis under investigation include safusidenib, which has demonstrated activity in both enhancing and non-enhancing IDH-mut gliomas, with phase 2 studies ongoing (NCT05303519, NCT04458272, NCT05577416) [31]. Similarly, olutasidenib has shown preliminary signs of activity in high grade, enhancing tumors, supporting further evaluation in an ongoing phase 2 trial of olutasidenib plus TMZ following radiotherapy in newly diagnosed pediatric and young adult patients with grade 3 or 4 IDH1-mut gliomas (NCT06161974) [32]. Further details regarding these and other mIDHis and their clinical outcomes are reviewed elsewhere [12, 20].

Targeting MAPK pathway – BRAF, pan-RAF and MEK Inhibitors

Mutations in the B-Raf proto-oncogene (BRAF) are generally mutually exclusive with *IDH* mutations, and are grouped into three classes based on their kinase activity, dependence on dimerization and on RAS signaling [33, 34]. Class I mutations, in gliomas, exclusively the V600E point mutation, a valine-to-glutamic acid substitution, lead to RAS-independent active BRAF monomers [33–35]. The less frequent class II mutations lead to RAS-independent active BRAF dimers and include non-V600E alterations such as KIAA1549-BRAF gene fusions [33–35]. The rare class III mutations lead to a kinase-impaired BRAF that is dependent on upstream RAS activity and increases MAPK signaling through CRAF activation [34]. In adults, V600E mutations occur in only 1–2% of GBM, while PAs

and PXAs frequently harbor KIAA1549-BRAF fusions or V600E mutations (Table 1) [36, 37].

BRAF inhibitors (BRAFi) were originally developed and FDA-approved for the treatment of advanced melanoma harboring the BRAF V600E/K mutations, with subsequent clinical applications in other malignancies [38, 39]. The available compounds vemurafenib, dabrafenib and encorafenib are all classified as type I RAF inhibitors and demonstrate selectivity for class I mutations. The phase 2 VE-BASKET trial evaluated vemurafenib monotherapy in a subcohort of 24 adults with recurrent BRAF V600E-mutated gliomas of various grades, reporting ORR of 25% and a median overall survival (mOS) of 28.2 months [40]. However, therapeutic responses were heterogeneous: patients with low grade gliomas (LGGs) such as PXA achieved a higher ORR (42.9%), while high grade glioma (HGGs) group had an ORR of only 9.1%, underscoring the influence of histology on efficacy [40].

Despite these signals of clinical benefit, responses to BRAFi monotherapy in BRAF V600E-mutated gliomas were frequently transient due to acquired resistance (such as reactivation of downstream MAPK signaling) [39, 41]. The success of BRAFi and MEK inhibitors (MEKi) combination therapy in advanced melanoma relative to BRAFi alone provided a rationale for similar approaches in gliomas [42]. This mechanistic insight informed the design of the ROAR (*Rare Oncology Agnostic Research*) study, a phase 2 basket trial evaluating the efficacy of dabrafenib (BRAFi) and trametinib (MEKi) combination in patients with recurrent or progressive BRAF V600E-mutated gliomas and other rare malignancies [43, 44]. Among the glioma subcohort, ORR was 33% among HGGs (mPFS 5.5 months, mOS 17.6 months) and 54% among LGGs (mPFS not evaluable) (Table 2) [43, 44]. These findings, along with data from NCI-MATCH subprotocol H (NCT02465060) and pediatric cohort (NCT02124772), supported the tissue-agnostic FDA approval of dabrafenib plus trametinib in 2022 for adult and pediatric patients with BRAFV600-mutated solid tumors, including glioma, who have progressed following prior therapy (Table 2) [43–46]. In pediatric LGGs, the combination of dabrafenib and trametinib has also demonstrated efficacy in the first-line setting over standard-of-care chemotherapy in a randomized phase 2 trial, which led to 2023 FDA approval for its first-line use in this population [47]. In contrast, prospective data supporting upfront BRAFi/MEKi use in adults remains limited, particularly in HGGs, where the optimal timing of targeted therapy remains a topic of debate [48].

Of note, while BRAFi/MEKi combination can achieve meaningful clinical benefit, their real-world impact in adult gliomas is limited by the low prevalence of BRAF V600E mutations, especially in adult GBM. Additionally, the therapeutic benefit is highly dependent on tumor histology and is higher in LGGs patients [43, 44]. Of note, BRAFi/MEKi combinations are associated with frequent adverse events; nearly all patients report some toxicity, most commonly pyrexia, rash, fatigue and gastrointestinal symptoms [49]. While more serious ocular, cardiac or pulmonary complications are less common, careful monitoring is required [49].

Two additional notable limitations include suboptimal blood-brain barrier (BBB) penetration and frequent emergence of therapeutic resistance even with combination regimens [39, 41]. Consequently, newer compounds with enhanced CNS permeability are under investigation. A phase 2 trial evaluating next-generation BRAFi/MEKi combination of encorafenib and binimetinib in adults with recurrent HGGs suggested promising response rates, though interpretation is limited by a small sample size of five patients due to early administrative trial closure [50]. Additional phase 1 trials are evaluating brain-penetrant BRAFi/MEKi combinations including PF-07284890 ± binimetinib (NCT04543188) and ABM-1310 ± cobimetinib (NCT04190628) [51]. To address the issue of resistance, a new generation of agents is in development: paradox breaker BRAFis (e.g., plixorafenib/PLX8394), pan-RAF inhibitors/type II RAF inhibitors that also target class II mutations (e.g., tovorafenib) and ERK inhibitors targeting distal MAPK signaling nodes [34, 39]. Among these, tovorafenib is notable for superior CNS penetration and has demonstrated durable efficacy in the FIREFLY-1 trial for relapsed or refractory pediatric LGGs with BRAF V600E mutations, fusions or rearrangements, resulting in FDA approval in 2024 for patients 6 months of age and older, although efficacy data in adults remain limited (Table 2) [52]. The ongoing FIREFLY-2 phase 3 trial (NCT05566795) is further evaluating tovorafenib versus standard-of-care chemotherapy as first-line treatment in pediatric patients with BRAF-altered LGGs.

Leveraging *NTRK* Fusion Events - NTRK Inhibitors

NTRK genes (*NTRK1/2/3*), encoding tropomyosin receptor kinases (TrkA-C), are also implicated in gliomagenesis. *NTRK* gene fusions represent rare genomic alterations across solid tumors, including approximately 0.5–2% of adult gliomas and up to 5.3% of pediatric gliomas, most frequently in GBM and pediatric HGGs (Table 1) [11, 53–55]. Owing to their rarity, the development of tissue-agnostic NTRK inhibitor (NTRKi) therapies has paralleled that of BRAFi/MEKi, with clinical trials enrolling patients based on *NTRK* fusion status regardless of tumor type.

Larotrectinib, a highly selective, small-molecule inhibitor of TrkA-C, was the first NTRKi approved by the FDA in 2019 for NTRK fusion-positive solid tumors, based

on results from three multicenter, open-label, single-arm phase 1 and 2 trials: LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687) and NAVIGATE (NCT02576431) (Table 2) [56]. A pooled CNS-specific analysis of 33 patients with NTRK fusion-positive primary CNS tumors from the SCOUT and NAVIGATE trials demonstrated ORR of 30%, a 24-week disease control rate of 73% and tumor shrinkage in 82% of patients with measurable disease (Table 2) [57]. However, the study population was predominantly pediatric, with lower disease control rates observed in adults [57].

In addition to larotrectinib, entrectinib and repotrectinib are also FDA-approved for NTRK fusion-positive solid tumors. To date, no adult glioma-specific efficacy data have been published from the clinical trials that supported approval of either agent. For entrectinib, available evidence comes from adult case reports and from pediatric patients enrolled in studies such as STARTRK-NG (NCT02650401), where rapid and durable responses in pediatric solid tumors, including a small number of CNS tumors, were observed, although robust data specific to glioma are lacking; no glioma outcomes have yet been reported for repotrectinib [58–61].

Targeting Metabolic Vulnerability in Diffuse Midline Glioma, H3K27M: Dordaviprone

Dordaviprone (ONC201), first-in-class imipridone and a dopamine receptor D2 inhibitor, has emerged as a therapeutically relevant agent that exploits metabolic and epigenetic vulnerabilities, particularly in DMG-H3K27M [62]. Mechanistically, dordaviprone binds and hyperactivates the mitochondrial caseinolytic protease P (ClpP), triggering integrated stress response signaling and subsequent p53-independent apoptosis, leading to cell death (Fig. 1; Table 1) [63, 64].

Evidence of dordaviprone's activity in DMG-H3K27M emerged from a phase 2 study of molecularly unselected recurrent GBM patients, in which one early patient with a tumor harboring H3 K27M mutation achieved a durable radiographic response [65]. This led to focused studies of dordaviprone in DMG-H3K27M. The first aggregated efficacy analysis of dordaviprone in brainstem and thalamic DMG-H3K27M showed that patients treated shortly after radiation ($n = 35$) achieved mOS of 21.7 months compared to 12 months in historical controls [66]. Complementary in vitro and in vivo experiments demonstrated that dordaviprone reverses the loss of H3K27 trimethylation in H3K27M-DMG. This effect is mediated by increasing levels of the histone demethylase inhibitor L-2-hydroxyglutarate (L-2HG) (Table 1) [66].

Dordaviprone was further investigated in an integrated pooled analysis of a predominantly adult cohort of 50 patients with recurrent non-pontine H3K27M-DMG across five clinical trials (Table 2) [67]. All patients were enrolled at least three months after completion of radiation to decrease the likelihood of pseudoprogression. The ORR across the cohort was 20.0%, by RANO-HGG with mOS of 13.7 months and PFS rate at 6 months of 35.1% (Table 2) [67, 68]. This study led to the 2025 accelerated FDA approval of dordaviprone in patients with progressive DMG-H3K27M following prior therapy.

As DMG-H3K27M is a highly aggressive tumor with poor outcomes despite standard-of-care radiation, dordaviprone marks a significant advance. However, while current efficacy data are promising, they derive from pooled analyses of small, single-arm studies in recurrent disease and are limited by a lack of randomized controls, potential selection bias and restricted follow-up. The ongoing ACTION trial is a randomized, double-blind, placebo-controlled, international phase 3 study (NCT05580562) enrolling newly diagnosed adult and pediatric DMG-H3K27M patients after radiotherapy [69]. Given the FDA's accelerated approval of dordaviprone, patient recruitment in the United States was halted, as continuation of a placebo-controlled arm was deemed infeasible given the drug's commercial availability. In parallel, clinical trials evaluating dordaviprone-based combination therapies are also underway (NCT05009992) [70].

Promising Investigational Therapies

Targeting DNA Damage Response Pathways

DNA damage response (DDR) pathways are cellular mechanisms that maintain genomic stability in response to DNA damage [71]. Deficiencies in DDR pathways contribute to accumulating mutations and oncogenesis across cancers including glioma, but also confer vulnerability to radiation and alkylating chemotherapy [72]. In GBM, TMZ-induced DNA alkylation can lead to double-strand breaks (DSB) and cell death by mismatch repair-dependent mechanisms, especially in tumors with reduced activity (through promoter hypermethylation) of the DNA repair enzyme, O6-methylguanine-DNA methyltransferase (MGMT) [73, 74].

Recognizing the central role of DDR in tumor survival has led to the development of targeted therapeutics, most notably poly (ADP-ribose) polymerase (PARP), ataxia telangiectasia and rad3-related protein (ATR), DNA-dependent protein kinase (DNA-PK) and ataxia-telangiectasia mutated (ATM) inhibitors, that aim to selectively exploit defective DDR mechanisms in glioma cells for therapeutic advantage [71]. Additionally, combining targeted DDR blockade with DNA-damaging therapies, such as radiation or cytotoxic chemotherapy, may increase levels of unrepaired DNA

damage to achieve synthetic lethality - a strategy in which the simultaneous disruption of two critical survival pathways leads to cancer cell death.

A number of approaches to target DDR in glioma patients are under investigation. Promising agents include the ATM inhibitor AZD1390, now in phase 2/3 evaluation with radiation in GBM (NCT03970447), and DNA-PK inhibitor M3814 (nedisertib), currently at early clinical stages (NCT04555577), while ATR inhibitors remain untested in gliomas [75]. PARP inhibitors, FDA-approved in *BRCA*-mutated solid tumors such as breast and ovarian malignancies, are under ongoing investigation in GBM. Veliparib did not yield clinical benefit, while olaparib is being evaluated in newly diagnosed GBM with radiation, with or without TMZ, based on *MGMT* promoter methylation status [76–80]. Newer generation PARP inhibitors with improved brain penetration, such as niraparib are under clinical investigation in GBM as well (NCT06388733) [81].

In IDH-mut glioma, hypermethylation downstream of the oncometabolite D-2HG is hypothesized to create defects in homologous recombination that compromise DSB repair and may render tumors more vulnerable to PARP inhibition [82]. However, a phase 2 study of olaparib monotherapy in recurrent IDH-mut HGGs yielded only a 6% ORR [83]. More recently, a multicenter phase 1/2 trial with a window-of-opportunity cohort evaluated the use of another PARP inhibitor, pamiparib, in combination with metronomic low-dose TMZ in patients with recurrent grade 2–4 IDH-mut gliomas [84]. Although pamiparib achieved pharmacologically active intratumoral levels in both enhancing and non-enhancing tumors, the regimen did not yield clinically meaningful ORR. While a subset of patients achieved prolonged tumor stabilization, the regimen was further limited by cumulative hematologic toxicity [84]. Future efforts to target DDR mechanisms in glioma may focus on identifying biomarkers of response and rational combination regimens, with emerging next-generation PARP1-selective inhibitors (NCT05417594, NCT04910022) offering a potential approach to reduce the hematotoxicity burden of dual PARP1/2 inhibition [85, 86].

Synthetic Lethality-based Therapies in *MTAP*-deficient Tumors

Metabolic reprogramming and epigenetic modifications are tightly linked features of gliomas. Within this landscape, loss of the metabolic enzyme methylthioadenosine phosphorylase (MTAP) creates vulnerabilities that may be exploited for GBM therapy. *MTAP* homozygous deletion occurs in up to 30–50% of GBM, often co-occurring with *CDKN2A/B* deletion due to their proximity at the 9p21 locus [11, 87, 88]. MTAP catalyzes the first step in the methionine/adenine salvage pathway, essential for maintaining nucleotide and amino acid pools. Homozygous deletion of *MTAP* disrupts this process, leading to the buildup of methylthioadenosine (MTA), which acts as an inhibitor of protein arginine methyltransferase 5 (PRMT5), a key transcriptional regulator (Fig. 1; Table 1) [89]. This inhibition impairs gene regulation, disrupts cell cycle control and increases DNA damage sensitivity in MTAP-deficient cells. Synthetic lethality-based therapies exploit this vulnerability by targeting PRMT5 or related enzymes (e.g., MAT2A) in MTAP-deficient tumors [89, 90]. Figure 2 schematically depicts the MTAP–PRMT5 axis in MTAP-positive and MTAP-deficient glioma cells, illustrating how *MTAP* loss alters MTA metabolism and creates sensitivity to MAT2A and PRMT5 inhibition.

Early-generation PRMT5 inhibitors (e.g., TNG908; NCT05275478) and MAT2A inhibitors (e.g., AG-270; NCT03435250) have shown minimal activity [91]. Brain-penetrant PRMT5 inhibitors such as PRT811 have demonstrated acceptable safety but limited efficacy in HGGs [92]. Next-generation agents such as TNG456, BAY 3713372 and BGB58067, which are engineered for improved BBB penetration, are currently in early-phase trials in patients with *MTAP* deletion (NCT06810544; NCT06914128; NCT06589596).

Targeting Receptor Tyrosine Kinase Aberrations and Downstream Signaling

RTK pathways are frequently altered in glioma, especially in GBM (Table 1). Epidermal growth factor receptor (EGFR) is the most commonly altered RTK in GBM, most frequently by amplification (~45%) and activating mutations (~25%) (Table 1) [87]. The high prevalence of *EGFR* alterations renders it a desirable therapeutic target. Unfortunately, early-generation EGFR inhibitors have largely failed to demonstrate significant clinical benefits, while newer generation agents with improved BBB penetration, such as BDTX-1535 or ERAS-801, are under investigation, as detailed elsewhere [93–96]. Fibroblast growth factor receptor (FGFR) alterations, most frequently comprising FGFR-TACC fusions and *FGFR3* amplifications, occur in 3–8% of IDH-wt gliomas (Table 1; Fig. 1) [11, 97, 98]. Recent trials of FGFR inhibitors in patients with *FGFR* alterations have evaluated erdafitinib, infigratinib, fexagratinib, pemigatinib, futibatinib and zoligratinib [99–106]. While overall response rates in glioma patients remain modest, partial responses and periods of stable disease have been observed [99–106]. However, on-target side effects such as hyperphosphatemia, dermatologic, oral and ocular toxicities may be dose-limiting [99–107]. Given the rarity of *FGFR* alterations in glioma, most clinical studies to date have been limited by small sample sizes and heterogeneous patient

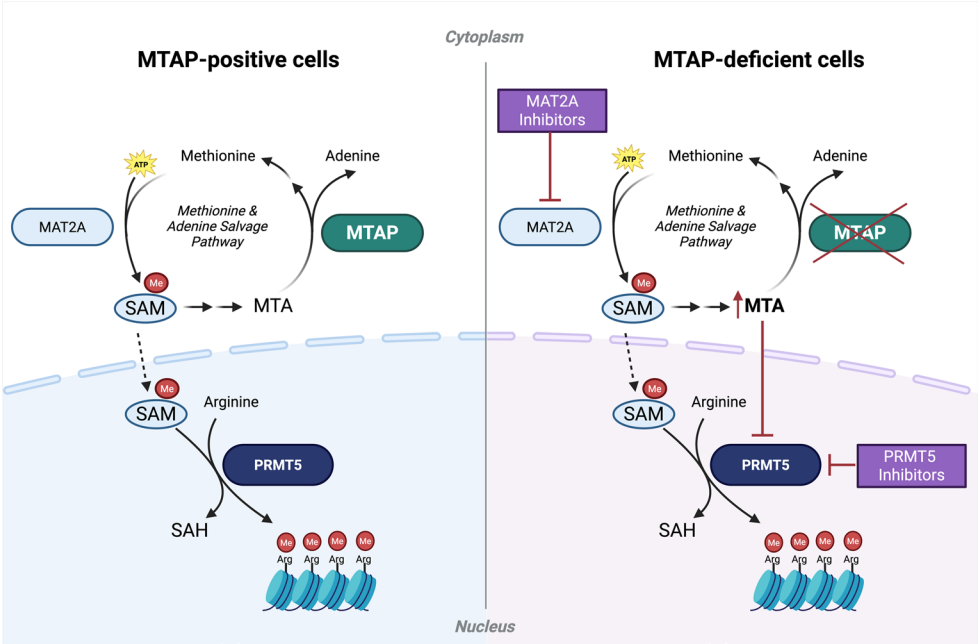

Fig. 2 MTAP–PRMT5 axis and targeted therapeutics in MTAP-deficient gliomas. Under physiological conditions (left panel), methylthioadenosine phosphorylase (MTAP) catalyzes the conversion of methylthioadenosine (MTA) to adenine and a methionine precursor within the methionine/adenine salvage pathway, thereby maintaining nucleotide and amino acid pools. Methionine is subsequently utilized by methionine adenosyltransferase 2A (MAT2A), together with adenosine triphosphate (ATP), to generate S-adenosylmethionine (SAM), the universal methyl group donor. After translocation into the nucleus, protein arginine methyltransferase 5 (PRMT5) transfers methyl groups from SAM to arginine residues on histone and non-histone substrates, contributing to transcriptional regulation. In MTAP-deficient cells (right panel), loss of MTAP leads to accumulation of MTA, which inhibits PRMT5 and consequently perturbs transcriptional programs, cell cycle regulation and increases sensitivity to DNA damage. This vulnerability can be exploited therapeutically through synthetic lethality: PRMT5 inhibitors further suppress PRMT5 activity and transcriptional regulation in tumor cells, promoting cell death. Similarly, MAT2A inhibitors limit SAM production and indirectly enhance MTA-mediated PRMT5 inhibition. Created in BioRender. Lasica, A. (2026) https://BioRender.com/icgu3dv. Abbreviations: Arg – arginine; ATP – adenosine triphosphate; MAT2A – methionine adenosyltransferase 2A; Me – methyl group; MTA – methylthioadenosine; MTAP – methylthioadenosine phosphorylase; PRMT5 – protein arginine methyltransferase 5; SAH – S-adenosylhomocysteine; SAM – S-adenosylmethionine

cohorts. Routine molecular testing for FGFR3-TACC3 fusions is likely to increase the identification of patients eligible for clinical trials and improve accrual [108]. Platelet-derived growth factor receptor A *(PDGFRA*) alterations, most commonly amplifications, are predominantly found in HGGs such as GBM (Table 1; Fig. 1) [11]. Recently, encouraging evidence from a case series indicated that avapritinib, a selective PDGFRA/KIT inhibitor, yields radiographic responses in some pediatric and young adult patients with *PDGFRA*-altered HGGs including GBM; however, clinical trials are still awaited [109].

Despite promising preclinical data, targeting the PI3K/AKT/mTOR pathway in GBM has not resulted in meaningful clinical benefit [110]. An exception is the mTOR inhibitor everolimus, which is FDA-approved for the treatment of unresectable subependymal giant cell astrocytoma (SEGA) in patients with tuberous sclerosis complex [111–113]. Similarly, cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, which target cell cycle dysregulation, have shown limited efficacy in GBM patients with *CDK4/6* amplification or *CDKN2A/B* homozygous deletion (Fig. 1; Table 1) [114].

Emerging Targeted and Immune-Based Delivery Modalities in Glioma Treatment

Recent advances in targeted therapies for gliomas have catalyzed the development of both innovative drug delivery and immune-based strategies, as the efficacy of new therapeutics is frequently limited by poor BBB penetration, intratumoral heterogeneity and an immunosuppressive microenvironment. Therapies such as antibody-drug conjugates (ADCs), radioligand therapies and chimeric antigen receptor (CAR) T cell approaches are being designed to address these long-standing challenges. These modalities actively leverage molecular profiling to identify actionable targets, facilitate tumor-specific delivery and aim to mitigate off-target toxicity, ultimately aiming to enhance therapeutic benefit.

Antibody-Drug Conjugates

ADCs consist of a tumor cell surface-specific monoclonal antibody attached to a potent cytotoxic payload by a chemical linker, enabling targeted drug delivery directly to tumor

cells and minimizing systemic toxicity [115]. Early trials in glioma patients targeted the *EGFR* axis, IL-13Rα2 receptor, IL-4, or transferrin, but these agents had limited success due to immunogenicity, unstable linkers and poor CNS delivery [116]. Over the past decade, advancements in ADC chemistry have led to a surge of interest in this therapeutic modality, resulting in multiple FDA approvals for ADCs across both solid tumors and hematologic malignancies [116].

Depatuxizumab mafodotin (Depatux-M) is an *EGFR*-targeted ADC that was evaluated in GBM. However, a large double-blind, placebo-controlled phase 3 INTELLANCE-1 trial, which evaluated Depatux-M combined with standard chemoradiation in adults with newly diagnosed, *EGFR*-amplified GBM, and INTELLANCE-2, a randomized phase 2 trial, evaluating Depatux-M and TMZ in recurrent *EGFR*-amplified GBM patients, both failed to demonstrate benefit [117, 118]. Other ADC targets, including B7-H3, GD2 and Trop-2, are being explored in gliomas [116, 119, 120]. Novel conjugation and delivery strategies, such as combination with focused ultrasound to increase BBB permeability or direct intratumoral infusion with convection-enhanced delivery, may potentially increase brain penetration and therapeutic efficacy [116].

Radioligand Therapy

Radioligand therapy (RLT) involves the delivery of cytotoxic radiation to tumor cells using a targeting peptide-ligand or antibody conjugated to a radionuclide [121]. As a branch of theranostics, RLT melds systemic radiation with precision targeting by exploiting molecular recognition of tumor-specific antigens. Unlike traditional targeted therapies, RLT relies on the presence of the molecular target within the tumor microenvironment and the achievement of sufficient intratumoral concentrations, rather than on the target's physiological function [121]. Key molecular targets in glioma under current investigation include: L-type amino acid transporter 1 (LAT1), somatostatin receptor 2 (SSTR2), prostate-specific membrane antigen (PSMA), gastrin-releasing peptide receptor (GRPR), each with dedicated early-phase clinical trials assessing agents like [^{131}I]IPA, [^{177}Lu]Lu-DOTA-TATE, [^{177}Lu]Lu-PSMA-617 and [^{177}Lu]-NeoB, respectively, in the setting of newly diagnosed and/or recurrent GBM; as reviewed in detail elsewhere [121]. These early trials aim to define the safety, efficacy and patient selection strategies required for successful RLT implementation in glioma care. Additionally, PARP has emerged as a distinct target, enabling delivery of cytotoxic radionuclides to DNA damage sites. Preclinical studies using radiolabeled PARP inhibitors, such as [^{123}I]I-CC1, have shown modest tumor growth delay in glioma xenograft models [122]. To advance RLT in neuro-oncology, overcoming BBB delivery challenges and managing neurotoxicity risks, particularly in patients with prior irradiation or neurological deficits, remains an important consideration for trial design and future implementation.

CAR T-cell Therapy

CAR T-cell therapy involves engineering patients' T cells to recognize and eliminate cells harboring a specific cell-surface tumor antigen [123]. Initially developed for hematological malignancies, it is now being explored in solid tumors including HGGs. Early-phase clinical trials targeting surface antigens, including EGFRvIII, IL-13Rα2, HER2, B7-H3, GD2 and EphA2, have demonstrated safety and feasibility of using CAR T-cells to target CNS tumors. Some patients experienced dramatic, though often transient, radiographic responses; however, interpretation of these data is limited by the small sample sizes enrolled in each study [124]. The major challenges impeding broader CAR T-cell therapy success in gliomas include pronounced antigen heterogeneity leading to immune escape, the immunosuppressive tumor microenvironment, limited CAR T-cell persistence, delivery barriers imposed by BBB and risks of neurotoxicity [124, 125]. To tackle these challenges, the field is pursuing next-generation strategies such as multi-antigen targeting (tandem/bispecific CARs or logic-gated circuits), CAR T-cells engineered to resist immunosuppression or secrete proinflammatory cytokines (armored CARs) and targeted delivery approaches to enhance efficacy and safety [124, 126]. Alongside CAR T-cell therapy, cancer vaccines represent another active area of immune-based strategies in glioma that aim to stimulate immune responses against tumor-specific antigens; these are reviewed in detail elsewhere [127–129].

Challenges in Targeted Therapy in Gliomas

Despite significant advances in our molecular understanding of gliomas, translating preclinical discoveries of targeted therapies into clinical benefit, especially in GBM, has proven challenging. One of the obstacles is penetration of the BBB, which limits the effective delivery of therapeutics into the tumor [130]. As a result, even therapies that demonstrate potent in vitro or in vivo anti-tumor activity may fail to achieve therapeutic concentrations in human brain tumors, as exemplified by the poor efficacy of early EGFR inhibitors [93, 94]. Recognition of these delivery challenges has led to the increased use of "window-of-opportunity" and phase 0 trials, where candidate drugs are administered pre-operatively and their concentrations are directly measured in resected tumor tissue, enabling pharmacokinetic and pharmacodynamic validation before proceeding to later

stage clinical trials [131]. Additionally, new methods to facilitate drug delivery across the BBB, including focused ultrasound, liposomal or nanoparticle formulations and convection-enhanced delivery, are under active investigation, but their clinical impact remains to be determined [130, 132].

The selection of viable targets is also hindered by the extraordinary spatial and temporal heterogeneity of gliomas, especially IDH-wt tumors [133, 134]. As a result, therapies focused on single aberrations may impact only a subset of tumor cells, enabling resistant clones to persist or emerge through rapid adaptation and phenotypic plasticity [135, 136]. Combination therapies targeting multiple pathways may be a way to subvert this adaptive plasticity, though this approach is limited by toxicity, especially given the high doses required to penetrate the BBB. Strategies to intervene earlier in the disease course, when heterogeneity and resistance may be more limited, may be fruitful. Additionally, the selection of appropriate molecular targets may be enhanced by integrative, multi-omic approaches, delineating key driver mutations, while the lack of robust preclinical models for drug testing may be ameliorated with tumor implantable in situ high-throughput pharmacophenotyping testing platforms [137, 138].

Lastly, designing effective clinical trials in neuro-oncology also presents substantial obstacles, with a limited patient population, inter- and intratumoral variability and response assessments complicated by pseudoprogression [139, 140]. Accordingly, new trial designs including adaptive platform trials using Bayesian adaptive randomization, such as GBM Agile (NCT03970447) or INSIGhT (NCT02977780), and the incorporation of external control datasets, offer a promising framework to accelerate drug evaluation and approval, though challenges in patient selection remain [114, 141].

Conclusions

The integration of molecular diagnostics has fundamentally redefined adult glioma classification, revealing actionable vulnerabilities and propelling a new era of targeted therapeutics in neuro-oncology. Recent FDA approvals, including vorasidenib for IDH-mut gliomas, dabrafenib-trametinib, and NTRK inhibitors for rare mutation-driven entities and dordaviprone for DMG-H3K27M, demonstrate that molecularly-driven therapies can offer meaningful clinical benefit in select subsets of glioma patients. For grade 2 IDH-mut gliomas, mutant IDH inhibition offers the possibility of delaying cytotoxic chemoradiation, though its impact on OS and its utility in grade 3 and enhancing disease is yet to be fully determined. In patients with IDH-wt gliomas, targeted therapies offer clinical benefit in select populations with actionable alterations such as BRAF V600E mutations or NTRK fusions; however, these alterations are rare, and the overall benefit remains limited. Therapeutic strategies under investigation include novel agents targeting DDR, RTK or metabolic dependencies, as well as immune-based and targeted drug delivery approaches. Persistent challenges include drug delivery barriers, intratumoral heterogeneity, rapid resistance and clinical trial complexity. Addressing these may expand the therapeutic benefit of targeted therapies to a broader population of patients with glioma.

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Declarations

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