Emerging Therapeutic Strategies for Glioma: Insights from Recent Clinical Trials

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Abstract

Glioma, a form of central nervous system tumour, is currently one of the most common forms of cancer and remains one of the most challenging to approach with treatment; this form of cancer costs many lives if approached without innovative and effective treatment. Several medical professionals, pharmaceutical companies, and research teams work annually and repeatedly in medical environments to strive for medical advancements that further aid in the treatment of this cancer. These professionals have undertaken numerous endeavours and achieved notable successes over the years. A notable number of these advancements have been made through clinical trials. The paper will review clinical trials that are progressing through various stages, including those that are completed, active, and recruiting. This development in clinical trials will enable a practical judgment to draw conclusions and form an outlook on the development of therapeutic strategies for gliomas by leveraging insights from recent clinical trials.

Introduction

Brain tumours affect approximately 300,000 individuals worldwide each year, with central nervous system (CNS) tumours ranking as the fifth most common cancer overall and the third most common among children and young adults[1]. Around 28% of CNS tumours are malignant, and about 1 million people are currently living with a brain tumour diagnosis, although only 12% of adult patients survive beyond five years[1].

Gliomas are the most prevalent type of CNS tumour, arising from glial cells in the brain or spinal cord. They account for approximately six new cases per 100,000 individuals annually[1]. First described by Rudolf Virchow in 1848[2], gliomas became better understood in the early 20th century with the advancement of neurosurgical techniques that allowed for tumour excision and histological analysis[2]. These tumours are classified into four WHO grades based on histological and molecular features. Grade IV glioblastoma multiforme (GBM) is the most aggressive and is associated with a median survival of just one year. Lower-grade gliomas include astrocytomas, oligodendrogliomas, and oligoastrocytomas, which tend to have slower progression but remain clinically challenging[3,4].

Current treatment for gliomas typically involves a combination of surgery, radiation therapy, and chemotherapy[5,6]. Diagnosis often occurs during surgery, where tissue samples are analysed by a pathologist to inform the treatment strategy. Temozolomide (TMZ, Fig. 1), an oral alkylating agent, is a widely used chemotherapeutic drug. New agents such as Vorasidenib, as well as others including Afinitor, Carmustine, Lomustine, and Tovorafenib, are also under investigation for glioma treatment[5,7].

This paper presents a critical overview of four clinical trials exploring different aspects of glioma treatment: one completed trial evaluating a drug (Sorafenib)[8], another assessing a

radiation-based treatment plan[9], one ongoing trial testing Vorasidenib in patients with grade II gliomas and IDH1/2 mutations[10], and a recruiting surgical trial focused on treatment strategies for recurrent glioblastoma[11]. These examples offer a representative cross-section of current efforts to improve outcomes in glioma therapy. By examining these trials, this paper aims to compare their methodologies, endpoints, and implications for clinical practice, highlighting both current progress and future directions in the management of glioblastoma.

Main Text

The standard approach to treating gliomas typically involves a combination of surgery, radiotherapy, and chemotherapy. While pharmacological agents play a critical role in this multimodal strategy, they are often used in conjunction with other treatments rather than as standalone interventions. Historically, the development and application of systemic therapies for brain tumours have been limited, in part due to the challenge of delivering drugs across the blood–brain barrier (BBB)[11]. As a result, medications have traditionally played a secondary role to surgical and radiation-based treatments in glioma management.

However, clinical trials continue to explore and refine pharmacological strategies to improve therapeutic outcomes and shift perceptions about the role of medications in glioma care. Several chemotherapeutic and targeted agents have shown promise in this context. Temozolomide (TMZ, Fig. 1), for example, has become a mainstay in the treatment of gliomas, particularly glioblastoma multiforme[12]. It is an oral alkylating agent classified as a second-generation imidazotetrazine prodrug that undergoes spontaneous conversion to its active form under physiological conditions[13]. Temozolomide is typically administered alongside radiotherapy following surgical resection, a regimen that has demonstrated improved survival outcomes compared to radiotherapy alone. Despite this progress, the overall median survival for glioma patients remains approximately one year, underscoring the need for continued therapeutic innovation[13].

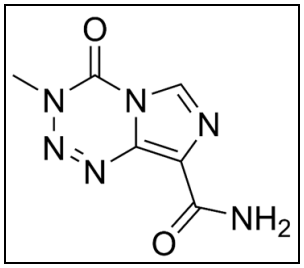

Figure 1. Chemical Structure of Temozolomide.

While pharmacological treatments are increasingly promising, the current standard of care for glioma remains multimodal, with surgical resection, radiotherapy, and chemotherapy forming the foundation of therapeutic intervention.

Diagnosis of gliomas, particularly glioblastoma, is tissue-based and guided by the most recent World Health Organisation (WHO) classification of CNS tumours. This includes histopathological evaluation, immunohistochemistry, and molecular testing[14]. Following a confirmed diagnosis, patients proceed to treatment.

Surgical resection remains the primary treatment strategy for gliomas of all grades. The goal is maximal safe resection of the tumour, ideally performed in specialised centres by experienced neurosurgeons[14]. When tumours are located in eloquent brain areas, an open biopsy may be necessary instead. Intraoperative imaging techniques are often employed to increase the precision and completeness of tumour removal.

Radiotherapy is another cornerstone of glioma treatment and is frequently used in combination with surgery. Studies have shown that the combination of surgery followed by radiotherapy significantly improves patient survival[14]. Radiotherapy is especially important in targeting residual tumour cells that cannot be removed surgically. High-precision radiotherapy allows for escalated dosing in the tumour region while minimising damage to surrounding healthy tissue[14]. However, the adoption of advanced radiation modalities requires further validation through controlled clinical trials.

Chemotherapy, most notably with TMZ, is also a widely used adjunct to surgery and radiotherapy, to achieve higher survival rates[15]. Chemotherapeutic protocols are implemented in accordance with regulatory guidelines, such as those from the European Organisation for Research and Treatment of Cancer (EORTC) and national health authorities.

Despite ongoing research and therapeutic advances, glioma treatment remains highly challenging. The median survival time for patients with high-grade glioma is still approximately one year, and many clinicians express concern over the slow pace of progress. One of the primary obstacles in developing effective brain cancer therapies is the blood–brain barrier (BBB), a protective physiological barrier that limits the entry of many systemic drugs into the brain[16,17]. Designing therapeutics that can effectively cross the BBB without compromising safety remains a major scientific and financial challenge. Moreover, gliomas, particularly glioblastoma, are inherently resistant to many conventional therapies, contributing to high recurrence rates and poor prognosis. Novel treatment strategies and clinical trials are therefore essential for overcoming these limitations and improving patient outcomes.

Clinical trials rigorously assess new medical approaches and innovations to ensure reliability and authenticity, using a structured format with distinct phases and characteristics, as outlined in Table 1A, which illustrates the key characteristics of clinical trials. Note that clinical trials vary and do not all follow the same principles and characteristics. Over the past five decades, approximately 1,300 clinical trials targeting central nervous system (CNS) tumours have been conducted in the United States[18]. However, many of these trials have faced methodological limitations that affect the reliability of their findings. Common issues include the

absence of control groups and the lack of randomisation, both of which compromise the scientific rigour of the study design[19].

Implementing control arms can be challenging in neuro-oncology trials, as patients may be reluctant to participate due to concerns about receiving a placebo or non-interventional care. Additionally, the logistical complexity and cost of randomised controlled trials, coupled with stringent eligibility criteria, can restrict patient enrolment and limit generalisability. These barriers represent a significant bottleneck in the development of robust, large-scale glioma trials.

To address these challenges, improved coordination between clinicians, research institutions, and regulatory bodies is essential. Streamlining trial accessibility and design will be critical for generating reliable, high-quality data. These issues will be revisited later in the paper during the evaluation of four selected clinical trials summarised in Table 1B: (1) Sorafenib in Newly Diagnosed High-Grade Glioma (completed, 2014)[8]; (2) Radiation Therapy in Treating Young Patients With Gliomas (completed, 2019)[9]; (3) INDIGO: Study of Vorasidenib (AG-881) in Participants With Residual or Recurrent Grade II Glioma With an IDH1 or IDH2 Mutation (active)[10]; (4) RESURGE: Surgery for Recurrent Glioblastoma (active, recruiting)[11].

Table 1. **A.** Characteristics of Clinical Trial Phases; **B.** Table summarising the clinical trials.

A.

	Phases				
	0 (Exploratory)	1	2	3	4
Description	First-in-man early trial to determine if the drug engages its suspected target	Initial safety evaluations determine safe dosage range, identify common side effects, and study the toxicity profile of the drug	Begin to explore efficacy while maintaining safety	First confirmation of safety and efficacy	Any trials conducted after FDA approval of the drug
Number of Subjects	10-15 healthy participants	20-80 healthy participants	100-300 participants with targeted medical condition	1000 - 3000 participants with targeted medical condition	Number of participants depends on trial endpoints
Dose	Single, low dose (<1% of dose calculated to produce a clinical effect)	Single dose, single ascending dose, multiple ascending dose	Multiple-dose trials, often conducted against a placebo	Multiple dose trials, ascending doses	Variable
Endpoints	Not expected to show clinical effect of significant adverse effects. Helps choose between competing chemical analogues for further study	Escalation of dose ends when unacceptable side effects occur; the previous dose is considered the maximum tolerated dose	Explores the clinical effects against the targeted condition and reveals less common side effects	Confirms clinical efficacy of the drug against the targeted condition and evaluates safety and side effects	Confirms clinical efficacy and safety and explores other possible drug uses; may be required as a condition of drug approval
Timing	Can be conducted with prior approval while the final IND review is pending	Together with Phase 0 trials, the first clinical trials were conducted in an IND process	Conducted after reporting to FDA of results of Phase 1 trials	Conducted after reporting to the FDA of results of Phase II trials	Conducted after the release o the drug by the FDA for marketing

B.

Characteristic	1	2	3	4
A: Enrolment Status	Complete (2014)	Complete (2018)	Active	Recruiting
B: Condition Studied	High-Grade Glioma	Low-grade Gliomas in young patients	Residual or recurrent Grade 2 glioma	Glioblastoma
C: Primary Endpoint	Establish the MTD of Sorafenib in combination with TMZ and RT	MFR: Determines how often the tumour recurs at the treatment margins.	Determine whether Vorasidenib offers effective treatment, measuring PFS	Compare survival outcome after surgery followed by adjuvant second-line therapy to no surgery followed by second-line therapy in recurrent glioblastoma.
D: Phase	Phase I	Phase II	Phase III	Phase II
E: Sponsor	(HUG) Geneva University Hospital	Children's Oncology Group	Institut de Recherches Internationales Servier	Insel Gruppe AG, University Hospital Bern
F: Allocation	Non-Randomised	NA	Randomised	Randomised
G: Blinding	Open-Label	Open-Label	Double-blind	NA
H: Number of Arms	Single Arm	Single Arm	Double Arm	Double Arm
I: Control Arm?	NO	NO	YES	NO
K: Sample Size	17 participants	92 participants	331 participants	120 (estimated)
L: Start Date	03-2009	11-2006	01-05-2020	2015
M: Completion Date	03-2012	31-12-2018	Estimated (05-2028)	NA
N: Result	MTD established; median PFS 7.9 months, OS 17.8 months	MFR -> 100% effective PFS like EFS (possible correlation) QOL no data	NA (ACTIVE)	NA (RECRUITING)

1. Sorafenib in Newly Diagnosed High-Grade Glioma

The phase I clinical trial, last updated in 2014, was conducted at the University Hospital of Geneva (Hôpitaux Universitaires de Genève, HUG) and aimed to assess the safety, tolerability, and optimal dosing of Sorafenib (Sb, Fig. 2) in combination with TMZ and radiation therapy (RT) in patients with newly diagnosed high-grade glioma[8,20]. Sorafenib, originally approved for the treatment of kidney and liver cancers, acts by inhibiting multiple kinases involved in tumour cell proliferation and angiogenesis[20].

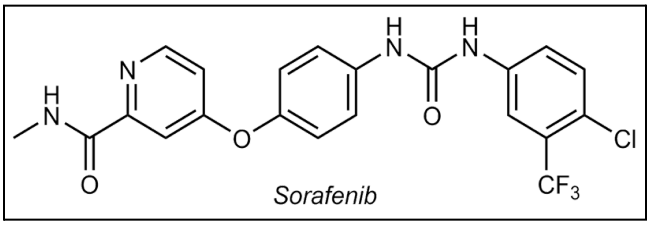

Figure 2. Chemical Structure of Sorafenib.

The trial included 17 adult patients with newly diagnosed high-grade glioma (Table 2). All patients underwent a standard course of radiotherapy (60 Gy in 2 Gy fractions) combined with daily TMZ (75 mg/m²). Sorafenib was administered in three escalating dose levels starting on day 8 of RT: 200 mg once daily (QD), 200 mg twice daily (BID), and 400 mg BID. Following the concurrent phase, patients entered a maintenance phase where they received TMZ (150–200 mg/m² on days 1–5 of a 28-day cycle) alongside Sb (400 mg BID). Dosage adjustments were made based on individual patient tolerance. Pharmacokinetic (PK) analyses were performed on day 8 (TMZ) and day 21 (TMZ + Sb)[20]. The trial identified 200 mg BID of Sorafenib as the maximum tolerated dose (MTD) in this regimen. Reported outcomes included a median progression-free survival (PFS) of 7.9 months and a median overall survival (OS) of 17.8 months[20].

Despite advances in glioblastoma therapy, the standard of care, surgical resection followed by RT and TMZ, typically yields a median survival of around 14 months. Therefore, novel treatment strategies are urgently needed. Given the known role of kinase-mediated pathways in glioma progression and treatment resistance, Sorafenib presents a rational candidate for combination therapy. Preclinical and early clinical data suggest that combining Sb with TMZ and RT may improve therapeutic outcomes.

Participants were enrolled based on eligibility criteria, including confirmed WHO grade II glioma or glioblastoma, age over 18 years, adequate health status, and capacity to provide informed consent. Patients were stratified into three cohorts based on Sb dosage. All participants who completed the concurrent treatment phase progressed to maintenance therapy. TMZ dose adjustments were made depending on the patient's tolerance during the initial treatment cycles, increasing from 150 to 200 mg/m² if tolerated.

Table 2. Patient Baseline Characteristics for the clinical trial on Sorafenib[20].

Patient	Sex	Age at diagnosis	Diagnosis	Type of resection	MGMT Status	ECOG at inclusion	Sorafenib adminstration in phase I part
Dose level 1							1 DLT
Patient 1	M	67.1	GBM	Incomplete	Unmethylated	0	DLT (thrombocytopenia grade 4)
Patient 2	M	37.3	GBM	Complete	Invalid test	0	Completed
Patient 3	F	62.4	GBM	Near complete	Unmethylated	0	Completed
Patient 4	F	64.0	GBM	Incomplete	Unmethylated	0	Completed (pulmonary embolism, grade 4)
Patient 5: screening failure							
Patient 6	M	43.3	GBM	Complete	Unmethylated	0	Completed
Patient 7	M	54.6	GBM	Incomplete	Unmethylated	0	Completed
Dose level 2							1 DLT
Patient 8: screening failure							
Patient 9	F	61.7	GBM	Near complete	Methylated	0	Completed
Patient 10	F	48.5	GBM	Incomplete	Methylated	0	Completed
Patient 11	M	62.5	GBM	Biopsy	Invalid test	1	Completed
Patient 15	F	25.1	GBM	Complete	Unmethylated	0	Completed
Patient 16	F	57.8	GBM	Biopsy	Not determined	0	Completed
Patient 17	F	45.3	OA grade 3	Biopsy	Not determined	0	DLT (thrombocytopenia grade 4)
Dose level 3							2 DLTs
Patient 12	F	41.2	GBM	Near complete	Unmethylated	0	Interrupted (pt's wish after hand-foot syndrome grade 3)
Patient 13	F	47.8	GBM	Incomplete	Methylated	1	DLT (hypercholesterolaemia and triglyceridaemia, grade 3)
Patient 14	F	69.9	GBM	Complete	Unmethylated	0	DLT (diarrhoea grade 4)

Abbreviations: DLT = dose-limiting toxicity; ECOG = Eastern Cooperative Oncology Group performance status; GBM = glioblastoma; MGMT = O6-methylguanine DNA-methyltransferase gene; OA = oligoastrocytoma.

All enrolled patients who received at least one dose of Sorafenib were monitored for safety through evaluation of vital signs, physical examinations, dose-limiting toxicities (DLTs), and laboratory parameters[20]. Notably, all participants experienced at least one treatment-related adverse event (Table 3). Based on the safety and tolerability data, the recommended dose of Sorafenib for further study was determined to be 200 mg BID, as administered in Cohort 2. The trial reported a median progression-free survival (PFS) of 7.9 months and a median overall survival (OS) of 17.9 months. Imaging revealed pseudoprogression in seven patients, a phenomenon where treatment-related inflammation or necrosis mimics tumour progression on radiographic scans[20].

Table 3. Adverse effects observed during the concomitant phase of the clinical trial 1[20].

Toxicity	Grade 1–2, *n*(%)	Grade 3, *n*(%)	Grade 4, *n*(%)	Grade 5, *n*(%)
Haematological-Thrombocytopenia	1 (6.6%)	3 (20%)	2 (13.3%)	0
Haematological-Lymphopenia	0	1 (6.6%)	2 (13.3%)	0
Haematological-Neutropenia	1 (6.6%)	1 (6.6%)	1 (6.6%)	0
Pulmonary embolism	0	0	1 (6.6%)	0
Cutaneous-Skin rash	6 (40%)	0	0	0
Cutaneous-Hand-foot syndrome	4 (26.6%)	2 (13.2 %)	0	0
Dyslipidemia	1 (6.6%)	1 (6.6%)	0	0
Diarrhoea	1 (6.6%)	1 (6.6%)	0	0
Constipation	0	1 (6.6%)	0	0
Hypertension	2 (13.3%)	2 (13.3%)	0	0
Heart rate abnormalities	4 (26.6%)	1 (6.6%)	0	0
Fatigue	3 (20%)	2 (13.3%)	0	0

% are expressed as number of events compared with the entire cohort of patients.

This Phase I clinical trial offers promising preliminary data on the safety and tolerability of Sorafenib in combination with temozolomide and radiotherapy for high-grade glioma. However, several limitations must be acknowledged. The absence of a control group is a significant limitation, as it restricts the ability to accurately evaluate the true efficacy of Sorafenib compared to standard treatment. Without a comparator arm, the clinical benefit of the intervention remains difficult to interpret. Future trials should incorporate randomised control arms to strengthen the validity and generalisability of the findings.

As expected for a Phase I study, the primary focus was on safety and dose optimisation rather than efficacy. Nonetheless, progression to larger Phase II and III trials will be necessary to confirm clinical benefit and assess outcomes across a broader patient population. A notable strength of the trial design is the use of multiple dosing cohorts, which enables systematic evaluation of dose-dependent effects and helps establish the maximum tolerated dose. This approach enhances the rigour of the dose-finding process and provides a solid foundation for future investigation.

In summary, although the lack of a control group limits the conclusions regarding efficacy, the trial successfully achieves its objectives for a Phase I study. Further research in controlled, larger-scale settings will be critical to establishing the clinical utility of Sorafenib in glioma treatment.

2. Radiation Therapy in Treating Young Patients with Gliomas

This clinical trial, completed in 2018, studied the effectiveness of radiation therapy (reduced-field conformal radiotherapy) in treating young patients with gliomas[9]. This clinical trial focused on determining the marginal failure rate (MFR) in young patients with low-grade gliomas treated with reduced-field conformal radiotherapy. On the side, the trial held many secondary objectives, including: determining Progression-free survival (PFS) and event-free survival (EFS), the quality of life (QOL) of patients going through this treatment and correlating the MIB-1 labelling index with PFS and overall survival (OS) of these patients. The study included 92 participants with low-grade glioma, aged from 3 to 20 years. To participate, participants had to have a life expectancy of more than a year, not be pregnant, and not have undergone prior radiotherapy.

This study consisted of a single arm where patients underwent reduced-field conformal radiation therapy 5 days a week for 6 weeks in the absence of disease progression or unacceptable toxicity[9]. The participants continue to be recorded and observed for an additional 5 years and are assessed to find primarily the MFR, and additionally the PFS, EFS, OS and QOL[9]. Ostensibly, this trial conducts realistic existing reduced-field conformal radiotherapy to treat Low-Grade Glioma and assesses how this treatment has affected the participant for the next 5 years. The study also focused on determining whether the MIB-1 labelling index can determine OS and/or MFR.

Notably, the participants' flow during this clinical trial (Fig. 3). Among the 92 patients who had participated, only 56 had completed it. Reasons for the inability to complete include death, absence from the program, withdrawal and inability to continue to follow the conditions of the trial. Evidently, since the main body of participants of this trial are minors, it is essential to account for the fact that the legal guardians of the minors must be in agreement with this trial at all times in order for their minor to continue in the program of this clinical trial. Such families, including the legal guardians of the minor, are expected to be living in significantly exigent conditions.

Arm/Group Title	Reduced-field Conformal Radiation Therapy
Arm/Group Description	Patients undergo reduced-field conformal radiation therapy 5 days a week for 6 weeks in the absence of disease progression or unacceptable toxicity. radiation therapy: Undergo 3D-CRT Undergo proton radiation therapy Undergo IMRT
Period Title: **Overall Study**	
Started	92
Completed	56
Not Completed	36
Reason Not Completed	
Death	7
Lost to Follow-up	18
Withdrawal by Subject	4
Ineligible	7

Figure 3. Participant flow recorded in the clinical trial: "Radiation therapy in treating young patients with glioma"[9].

After following up with the participants for five years, the trial yielded results in line with its objectives. For the MFR, in all 84 patients assessed during the 5-year time frame, the treatment was effective for all of them, excluding deaths from the count. This shows to be an acceptable MFR, showing the treatment is, to a greater extent, effective. As for the PFS, 85 patients were assessed, and the PFS (3 years) rate was shown to be 77.1% of the patients, living with the tumour without progression. Additionally, the same was recorded for EFS; the same 85 patients were assessed over the same 3 years, and the EFS (3-year) rate was also shown to be 77.1%. This means that the 77.1% may include the same patients included in the PFS count, representing a possible correlation between EFS and PFS. The same 85 patients were additionally involved in studies for the same 3 years for determining OS, which was shown to be at 94% of the patients, suggesting that a worsening of the condition without death is possible.

Regarding the QOL, no patients were analysed, as this was cancelled by the trial authorities due to unspecified reasons, as stated in the trial and the source. Moreover, 64 patients were assessed throughout the entire clinical trial, using the marker MIB-1 to determine whether it contributed to the aggressiveness of the disease. In this case, 3.1% of patients showed this, meaning that it does not have a significant correlation with the aggressiveness of the tumour. Additionally, these patients were tested to see if the MIB-1 correlated with the PFS. Only 1.08% of patients showed this, suggesting an insignificant correlation with the PFS.

This clinical trial provides impactful data on the realistic treatment's impact on patients, as determined by MFR, PFS, EFS, OS, and QOL. To effectively form comparisons with the previous clinical trial explored in this paper, contrasting this trial with the previous one is necessary. It becomes evident that this trial does not inhibit the same experimental aspects and

properties as the previous one. Elaborating on this point, the previous trial attempted to test and assess the effectiveness of a relatively new experimental treatment, Sb, on patients, aiming to determine the optimal dosage for maximum efficiency. Furthermore, this clinical trial treated patients with a real, tangible treatment currently used, and the trial focused on assessing how this treatment affected young patients with Low-Grade Glioma. Although there were no size limitations, this trial was designed as a Phase 2 study by choice, as there are no factors that limit its size.

While the trial is highly effective in achieving its goal, as mentioned, there is no apparent medical reason restricting its size, meaning that the results could have been more accurate if they had had more than 92 participants. This further emphasises the situation that only 56 of them completed the trial. However, the reason they are at 92 participants is understandable, if assessed differently. All participants had to be aged 3 to 20, and 93.5% of the participants were minors [8]. Minors have parents or guardians who are responsible for them, meaning that they are inevitably the ones who decide whether their respective child can participate in a clinical trial. This adds complications to the equation, as there are tangible reasons why parents would not want their minors to participate in a clinical trial. This is proven by the four who withdrew and the 18 participants who were lost during their follow-ups. Additionally, since this is a rare condition, it might have been challenging to find patients in this age group who have it. While it could have been greater, the results published in this Phase 2 trial are significant. Overall, this makes the trial highly effective in analysing the experience and results of a young patient with glioma undergoing radiation therapy.

3. Study of Vorasidenib in Participants With Residual or Recurrent Grade II Glioma with an IDH1 or IDH2 Mutation

Vorasidenib is an anti-cancer oral medication that could potentially be used to treat certain forms of Glioma[21]. It is essential to recognise that this medication remains investigational and is not yet a commonly used treatment for glioma. This trial is one of the studies investigating the potential use of this medication[22]. This trial focuses explicitly on its usage with the Grade II glioma, IDH1 or IDH2 mutation in patients above the age of 12 that have a Karnofsky Performance Scale (KPS) score (for participants ≥16 years of age) or Lansky Play Performance Scale (LPPS) score (for participants <16 years of age) of ≥80%[10]. This is common in glioma II patients, where their KPS or LPPS score is typically above 80%, as these grade II gliomas are usually associated with minimal symptoms rather than severe functional impairments.

This trial will consist of a randomised allocation between two arms: the first arm will receive a daily 40 mg dosage of Vorasidenib as an oral tablet. The other arm, the control arm, will receive a daily 40 mg oral tablet of a matching placebo drug[22]. The introduction of a placebo drug regularly introduces various complications when it comes to the enrolment of participants. The presence of a placebo drug frequently offsets a participant's decision to be enrolled in a trial, as they may not want to be placed in the placebo arm. This trial will measure the patients' PFS over the next 30 months, additionally measuring the time till subsequent intervention (TTNI).

TTNI is defined as the time from randomisation to the initiation of the first subsequent anticancer therapy (including Vorasidenib, for subjects randomised to placebo who subsequently cross over) or death due to any cause. TTNI is defined as the time from randomisation to the initiation of the first subsequent anticancer therapy (including Vorasidenib, for subjects randomised to placebo who subsequently cross over) or death due to any cause. The Tumour Growth Rate (TGR) will also be measured every 6 months up to 2 years and 9 months, as well as many other factors, including OS. The completion of this trial is still pending as it is active, but certain conclusions and results have been drawn to this instant, noting that this is not a complete project.

Results show that TTNI was significantly better in the Vorasidenib group, although the Vorasidenib group experienced more adverse effects (22.8% in the Vorasidenib arm vs 13.5% with placebo). Most importantly, the PFS had significantly improved with the Vorasidenib patients, where the placebo patients had an average PFS of 11.1 months, while the Vorasidenib arm had an average PFS of 27.7 months[22]. Noting that this trial is unfinished, and these results display results which are currently being processed, this trial has not been marked as "completed". To avoid potential bias, an evaluation is not conducted as part of this review.

4. Surgery for Recurrent Glioblastoma (RESURGE)

The primary objective of this randomised trial is to compare survival outcomes after surgery followed by adjuvant second-line therapy with those after no surgery followed by second-line therapy in patients with recurrent glioblastoma[11]. This trial focuses on the approach to treatment rather than the specific treatment used, and assesses the effectiveness of the surgery. It is currently recruiting patients for the trial to begin.

Participants must be at least 18 years of age, have a KPS score of 70 or higher, and have no contraindications for surgery. This trial will simply split its participants into two randomised groups; one group will receive surgery followed by treatment, while the other will receive treatment alone. They will assess and compare the OS, PFS, and Morbidity of Surgery.

Over the years, there has been a better balance between clinical trials assessing new treatments, such as those focusing on Sorafenib and Vorasidenib, and clinical trials evaluating current treatments, including those focusing on Surgery and Radiation therapy. This is a positive advancement that provides a more comprehensive view of medical advancements.

Conclusions and Outlook

In conclusion, a range of ongoing and recent clinical trials are actively addressing the treatment of gliomas and glioblastomas, regardless of whether the trials are completed, ongoing, or still recruiting participants. The four trials highlighted in this review exemplify the diverse modalities under investigation, ranging from targeted drugs and chemotherapy combinations to adjustments in radiation techniques and surgical strategies. This diversity underscores that glioma treatment is, and will remain for the foreseeable future, a multifaceted endeavour. No single approach is likely to cure these tumours; instead, improvements are emerging on multiple fronts. Our examination of the trials shows that pharmacological interventions (like kinase inhibitors and IDH inhibitors) and surgical/radiation interventions are both critical components of current research. In practical terms, this means the optimal management of gliomas involves a combination of therapies tailored to each patient's situation.

Notably, the Sorafenib trial (Trial 1) explored the addition of a novel drug to standard therapy. In contrast, the pediatric radiation trial (Trial 2) refined an existing treatment to make it safer for children. The Vorasidenib trial (Trial 3) targets a specific mutation, reflecting a move toward personalised medicine, and the RESURGE trial (Trial 4) evaluates treatment sequencing, emphasising that how we use treatments can be as crucial as what treatments we use. The fact that all these approaches are being pursued in parallel is a positive sign – a balanced portfolio of trials (ranging from drug discovery to optimisation of current care) is necessary for meaningful progress. Innovation in glioma therapy takes many forms, including the development of new drugs, finding the optimal combinations, refining the timing and method of surgery/radiation, and exploring tumour genetics to guide therapy.

Another important observation is that as treatments move through clinical trial phases, the focus gradually shifts. Early-phase trials often introduce experimental treatments and assess safety (as with Sorafenib). In contrast, later-phase trials and those in more common settings focus on refining efficacy and ensuring that treatments are both practical and safe. It becomes increasingly crucial to improve what is already being done – for instance, optimising dosage, reducing side effects, and comparing new treatments to the current standard. Our review also highlights various trial designs used: some trials were single-arm or non-randomised (due to practical or ethical reasons), while others were rigorously randomised and controlled. Each design has its role, and collectively they contribute knowledge that must be integrated. Going forward, maintaining a balance of trial types – early versus late-phase, experimental versus pragmatic, pediatric versus adult – will be necessary to efficiently and effectively advance the field.

Looking ahead, glioma research is increasingly moving toward personalised treatment strategies based on tumour genetics. Trials like INDIGO show that targeting specific mutations, such as IDH1 or IDH2, can significantly improve outcomes. Future care will likely rely on molecular profiles to guide therapy choices, aiming to improve effectiveness while reducing unnecessary toxicity.

Clinical trial design is also evolving to become more efficient and informative. Including control arms, adaptive designs, and biomarker-driven enrolment helps trials provide clearer evidence of treatment benefit. The RESURGE trial illustrates how optimising treatment strategies (such as when to perform surgery) is just as important as testing new drugs. There is also a need for more inclusive trials. Children and elderly patients are often underrepresented, although they may respond differently to treatment. Expanding trial access for these groups is essential to ensure that progress benefits all patients.

Finally, quality of life is becoming a central consideration. Treatments should not only extend survival but also maintain neurological function and everyday well-being. More trials are now incorporating patient-reported outcomes to reflect this priority.

Together, these developments indicate a shift in glioma care from merely extending life to enhancing the quality of life during and after treatment. With continued innovation, collaboration, and a strong focus on patient needs, glioma may one day be managed as a chronic condition, offering real hope for better outcomes.

Works Cited

1. Aron Cohen-Gadol, M. 72 Must-Know Brain Tumour Statistics (2024).

2. Martin-Villalba, A., Okuducu, A. F. & von Deimling, A. The evolution of our understanding on glioma. *Brain Pathol* **18**, 455–63 (2008).

3. Chengkai Dai & Eric C Holland. Glioma models. *ScienceDirect* (2001).

4. Wajeeha Aiman, David P. Gasalberti & Appaji Rayi. Low-Grade Gliomas. *National Library of Medicine* (2024).

5. Glioma Treatment. *Memorial Sloan Kettering Cancer Center* https://www.mskcc.org/cancer-care/types/glioma/glioma-treatment.

6. Mayo Clinic. Glioma. *Mayo Clinic* Preprint at https://www.mayoclinic.org/diseases-conditions/glioma/diagnosis-treatment/drc-20350255#:~:text=Glioma%20treatment%20usually%20begins%20with,recommended%20as%20the%20first%20treatment.

7. Drugs Approved for Brain Tumors. *National Cancer Insitute (NIH)* Preprint at https://www.cancer.gov/about-cancer/treatment/drugs/brain.

8. Sorafenib in Newly Diagnosed High Grade Glioma. Preprint at https://doi.org/NCT00884416 (2014).

9. Radiation Therapy in Treating Young Patients With Gliomas. Preprint at https://doi.org/NCT00238264 (2019).

10. Study of Vorasidenib (AG-881) in Participants With Residual or Recurrent Grade 2 Glioma With an IDH1 or IDH2 Mutation (INDIGO). Preprint at https://doi.org/NCT04164901 (2023).

11. Surgery for Recurrent Glioblastoma (RESURGE). Preprint at https://doi.org/NCT02394626 (2023).

12. Tomar, M. S., Kumar, A., Srivastava, C. & Shrivastava, A. Elucidating the mechanisms of Temozolomide resistance in gliomas and the strategies to overcome the resistance. *Biochim Biophys Acta Rev Cancer* **1876**, 188616 (2021).

13. Friedman, H. S., Kerby, T. & Calvert, H. Temozolomide and Treatment of Malignant Glioma 1.

14. Wick, W., Osswald, M., Wick, A. & Winkler, F. Treatment of glioblastoma in adults. *Ther Adv Neurol Disord* **11**, (2018).

15. Wick, W. *et al.* A novel tool to analyze MRI recurrence patterns in glioblastoma. *Neuro Oncol* **10**, 1019–24 (2008).

16. Pardridge, W. M. The blood-brain barrier: Bottleneck in brain drug development. *NeuroRx* **2**, 3–14 (2005).

17. Yalamarty, S. S. K. *et al.* Mechanisms of Resistance and Current Treatment Options for Glioblastoma Multiforme (GBM). *Cancers* vol. 15 Preprint at https://doi.org/10.3390/cancers15072116 (2023).

18. Smith, E. J. *et al.* Adult neuro-oncology trials in the United States over 5 decades: Analysis of trials completion rate to guide the path forward. *Neurooncol Adv* **6**, (2024).

19. Stephen J. Bagley. Glioblastoma Clinical Trials: Current Landscape and Opportunities for Improvement. *AACR Journals - Clinical Cancer Research* (2021).

20. Hottinger, A. F. *et al.* Phase I study of sorafenib combined with radiation therapy and temozolomide as first-line treatment of high-grade glioma. (2014) doi:10.1038/bjc.2014.209.

21. Lamb, Y. N. Vorasidenib: First Approval. *Drugs* **84**, 1325–1331 (2024).

22. Mellinghoff, I. K. *et al.* Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma. *N Engl J Med* **389**, 589–601 (2023).