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Phase 1, Dose Escalation, Nonrandomized, Open-Label, Clinical Trial Evaluating the Safety and Preliminary Efficacy of Allogenic Adipose-Derived Mesenchymal Stem Cells for Recurrent Glioblastoma: A Clinical Trial Protocol

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GENERAL INFORMATION

Protocol Title

Phase 1, Dose Escalation, Non-Randomized, Open Label, Clinical Trial Evaluating the Safety and Preliminary Efficacy of Allogenic Adipose-Derived Mesenchymal Stem Cells (AMSCs) For Recurrent Glioblastoma

Registry

This study is registered in ClinicalTrials.Gov (NCT05789394)

Study Dates

June 2023 to present.

Sponsor/Funding Agency

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Institutional Approvals

Mayo Clinic Institutional Review Board, IRB No: (21–004561) and U.S. Food and Drug Administration Investigational New Drug, IND No: (27651)

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Abstract

Background and Objectives: Despite standard of care with maximal safe resection and chemoradiation, glioblastoma is the most common and aggressive type of primary brain cancer. Surgical resection provides a window of opportunity to locally treat gliomas while the patient is recovering, and before initiating concomitant chemoradiation. To assess the safety and establish the maximum tolerated dose of adipose-derived mesenchymal stem cells (AMSCs) for the treatment of recurrent glioblastoma (GBM). Secondary objectives are to assess the toxicity profile and long-term survival outcomes of patients enrolled in the trial. Additionally, biospecimens will be collected to explore the local and systemic responses to this therapy.

Methods: We will conduct a phase 1, dose escalated, non-randomized, open label, clinical trial of GBM patients who are undergoing surgical resection for recurrence. Up to 18 patients will receive intra-cavitary application of AMSCs encapsulated in fibrin glue during surgical resection. All patients will be followed for up to 5 years for safety and survival data. Adverse events will be recorded using the CTCAE V5.0.

Expected Outcomes: This study will explore the maximum tolerated dose (MTD) of AMSCs along with the toxicity profile of this therapy in patients with recurrent GBM. Additionally, preliminary long-term survival and progression-free survival outcome analysis will be used to power further randomized studies. Lastly, CSF and blood will be obtained throughout the treatment period to investigate circulating molecular and inflammatory tumoral/stem cell markers and explore the mechanism of action of the therapeutic intervention.

Discussion: This prospective translational study will determine the initial safety and toxicity profile of local delivery of AMSCs for recurrent GBM. It will also provide additional survival metrics for future randomized trials.

Keywords

Human Mesenchymal Stem Cells; Prospective; Stem Cell; Stromal Cell; Window of Opportunity

RATIONALE AND BACKGROUND INFORMATION

Glioblastoma (GBM) is the most common and aggressive form of primary brain cancer.[1] The yearly incidence rate of GBM in the United States is estimated to be 3.19 per 100,000 population.[1, 2] Though current standard therapies, which include maximal safe resection, radiation, and concomitant adjuvant chemotherapy have reduced mortality rates significantly, the median overall survival (OS) remains 15 months[3–6], while progression-free survival (PFS) post-treatment remains 4–6 months.[7–10] Despite the aggressive approaches, there is almost a 100% recurrence rate.[11] Such limitations have resulted in a surge of more directed aggressive approaches towards GBM.[12]

Surgery presents an opportunity to deliver local therapy and bypass the blood-brain barrier.[13–17] While conventional therapy involves a waiting period of 4–6 weeks after resection before initiating chemoradiation, intraoperative treatment allows for immediate intervention. Furthermore, approximately one quarter of recurrent glioblastoma patients are eligible for a second surgical procedure[4, 18–20], creating a critical time-frame to introduce targeted therapies that can improve outcomes at recurrence. Such timely intervention may potentially arrest disease or prolong survival outcomes.

The etiology of treatment failure in GBM is complex. One significant factor contributing to this is the difficulty in achieving effective delivery of agents due to the blood-brain barrier.[21–23] Despite effective delivery, some tumors may develop mutational advantages that render them resistant to treatment.[3, 12, 24] This is further exacerbated by tumor-mediated immune evasion through multiple mechanisms, including indirect changes in the tumoral microenvironment and directed immune-suppression imposed by the tumor itself.[25, 26] Notwithstanding such complexities, the ability of these malignant cells to migrate and invade neural tissue remains a significant challenge. Studies have shown the presence of tumoral cells beyond the contrast-enhancing portion of the tumor (thus causing high rates of local recurrence)[27–29], and demonstrating an ability to migrate long distances into the contralateral side and recur distally to the primary site.[29–31] Hence, to effectively tackle the aggressive characteristics of GBM, a therapeutic with multi-modal functions may counter the tumor's migrative, evasive and immunosuppressive properties. Once such emergent strategy is exploiting the potential use of Mesenchymal Stem Cells (MSCs) for the treatment of glioblastoma.[32–37] Numerous studies have demonstrated the non-oncogenic nature of MSCs in GBM models.[32, 33, 35–41] MSCs are a safe therapeutic option as they migrate and co-localize with tumor cells that remain in the tumor borders of those that have migrated distally.[33, 35] Moreover, MSCs have been demonstrated to be hypo-immunogenic and possess immunomodulatory properties, which could potentially lead to clinical improvement in GBM patients by reducing malignancy-induced inflammation.[38, 42, 43]

We hypothesize that the local delivery of AMSCs into the surgical cavity prior to surgical closure is feasible, safe, and could improve the long-term outcomes of recurrent GBM, and

posit that AMSC treatment may decrease the progression rate and invasiveness of malignant cells in these patients. The primary objective of this protocol is to assess the safety of AMSCs delivery to the surgical cavity of recurrent GBM. The study will collect data to assess the initial effectiveness of AMSC treatment, which will be used to complement further investigations. Correlative studies will also be conducted to gain insight into the mechanism of action underlying this approach.

STUDY GOALS AND OBJECTIVES

Primary Goals:

1. To establish the maximum tolerated dose (MTD) of locally delivered AMSCs in patients with recurrent GBM.

Secondary Goals:

1. To assess the safety and toxicity profile of locally delivered AMSCs in patients with recurrent GBM.
2. To assess OS in recurrent GBM patients treated with locally delivered AMSCs.
3. To assess PFS in recurrent GBM patients treated with locally delivered AMSCs.

Correlative Research:

1. To explore the systemic immune response after application of AMSCs through cytokine analysis on peripheral blood samples.
2. To explore the local changes on the brain parenchyma by analyzing tissue at recurrence.
3. To explore the presence of AMSCs on brain tissue at recurrence.

STUDY DESIGN

This is a phase 1, open label, non-randomized, dose escalation, 3+3 design, clinical trial to evaluate the safety and preliminary efficacy of AMSCs for recurrent GBM applied to the resection cavity at the time of surgical resection (Figure 1). This study consists of three different dose levels (Level 1: 5×10^6 AMSCs, Level 2: 10×10^6, and Level 3: 20×10^6) and up to 18 patients will be enrolled in the trial. The selection criteria can be found in Table 1.

METHODOLOGY

Study Agent

AMSCs will be produced in the (human cell therapy laboratory (HCTL) at Mayo Clinic Florida) following current good manufacturing practices (cGMP).[44] Briefly, lipoaspirates from a healthy female donor will be used to obtain the AMSCs. The adherent fraction of the lipoaspirate is expanded using the Quantum® Cell Expansion System (Terumo BCT, Inc.) to create an initial Master Cell Bank (MCB) of Cells that is fully characterized. The AMSC Product is generated by further expanding individual samples from the MCB stock using the Quantum until the time of cryopreservation. Doses of the final cryopreserved product is

formulated in 1mL of CryoStor CS5 (Sigma-Aldrich). At the day of clinical use, cells will be thawed, washed, resuspended in 1ml of lactate ringer solution (LRS, Baxter Healthcare Corp), and delivered directly to the operating room for application (Figure 2).

Surgical Procedure

Participants will be screened for eligibility during outpatient consults. Once enrolled, all patients will undergo maximal safe resection for recurrent glioblastoma. After resection is complete, while in the operating room before closure, cells will be encapsulated in an FDA-approved fibrin glue (TISSEEL, Baxter Healthcare Corp), and applied locally to the resection cavity (Figure 2). The fibrin glue serves as an extracellular matrix to support cell survival. Viability and survival studies of the AMSCs will be published elsewhere once study is complete. All patients will undergo implantation of an ipsilateral Ommaya reservoir (Natus Medical Inc.) at the time of surgery to obtain CSF samples for correlative studies.

AMSC + Fibrin Glue Mix Preparation

A prepackaged 4ml fibrin glue (TISSEEL, Baxter Healthcare Corp) will be used. Under sterile conditions, the surgeon will remove 1ml of thrombin (component 2) from the fibrin glue applicator (Figure 3A). Then, cell suspension (1ml) will be injected into the thrombin barrel using an 18-gauge needle (Figure 3B). The fibrin glue applicator is then completed following manufacturers' instructions (Figure 3C). This mixture will yield a final volume of 4ml consisting of 2ml fibrinogen + 1ml thrombin + 1m cell mixture.

Correlative Research Studies

Participants will undergo a 10ml blood draw within 24h before surgical procedure, within 24h after surgical procedure, 1 month after surgical procedure, and 2 months after surgical procedure. A CBC with differential and inflammatory cytokines (Interferon (INF)-γ, INF-a, TNF-a, IP-10, monocyte chemoattractant protein (MCP)-1, MCP-4, macrophage inflammatory protein-1b, interleukin (IL)-2, IL-4, IL-6, IL-7, IL-10, IL-12, IL-13 and IL-15) will be measured.

Participants will undergo a 10ml CSF aspiration through the Ommaya reservoir at the time of surgery, and weeks 1, 2, 3, and 4 after treatment. Inflammatory cytokines will be measured (INF-γ, INF-a, TNF-a, IP-10, MCP-1, MCP-4, macrophage inflammatory protein-1b, IL-2, IL-4, IL-6, IL-7, IL-10, IL-12, IL-13 and IL-15). Circulating tumor DNA (ctDNA) will be quantified and measured. An exploratory bioinformatics analysis will be obtained to quantify the presence of AMSCs within the CNS through genetic material analysis.

All participants will be consented to provide mandatory tissue specimens for research at the time of surgery and at recurrence (either reoperation or postmortem). Postmortem samples will be processed at the MCF brain bank. Immunohistochemistry for immune infiltration (CD4+, CD8+, CD163+, PD1+, and Sox2+) will be assessed.

Additionally, we will obtain clinical data along with tissue, blood, and CSF from institutional controls ((IRB# 16–008485)) enrolled in our brain tumor tissue biobank

(Quiñones-Hinojosa et al. 2023, under review)[45] to assess the effect of treatment with AMSCs vs. untreated controls.

DISCUSSION

This is a first-in-human clinical trial evaluating intratumoral application of AMSCs for recurrent glioblastoma. Upon study completion, the safety and maximum tolerated dose of intratumoral AMSCs for glioblastoma will be established. The knowledge will enable the performance of late phase clinical trials to evaluate the efficacy of this therapy for recurrent GBM and potentially design protocols for newly diagnosed disease. Moreover, the collection of preliminary efficacy data on long term survival of these patients will allow for an adequate calculation of statistical power for future studies.

Ultimately, this study will offer valuable insight into the mechanism of action of AMSCs and streamline the development of targeted cellular biotherapeutics for future studies. Results from this study will corroborate prior preclinical research, by our group and others, which demonstrated the survival advantages of nanoengineered and virally transduced MSCs secreting bone morphogenic protein 4 (BMP-4), tumor necrosis factor (TNF)-related apoptosis inducing ligand (TRAIL)[32, 35, 46], interleukin 12 (IL-12)[47], as well as further the work performed on nanoengineered and encapsulated MSCs in recurrent GBM (Al-Kharboosh et al. 2023, under review)[48]. The outcomes of this work will empower future studies that leverage the AMSC's innate ability to migrate towards malignant glioma cells.

TRIAL STATUS

This study is active and open for enrollment.

SAFETY CONSIDERATIONS

All patients enrolled in this study will receive standard of care and supportive disease measures at the discretion of the treating neuro-oncologist. All adverse events will be collected on patients throughout the study. For adverse events, we will use the CTCAE v5.0. Toxicities will be assessed for 28 days after treatment and are defined as any grade ≥3 that has prolonged for more than 7 days and that is not expected from any of the established complications of a neurosurgical procedure. In case of any occurrence, patient will remain under observation with supporting measures for at least 7 days or until the toxicity has resolved. The first 3 patients will be enrolled at the starting dose level. If no DLTs are seen, the next 3 patients will be enrolled at the next higher dose level. If at least 1 patient develops a DLT, 3 additional patients will be enrolled and treated at the same dose level. If a DLT is seen in at least 1 of these additional patients, the MTD will have been exceeded (MTD is defined as the dose of AMSCs at which ≤1 of 6 subjects experience a DLT), and further accrual will cease to this cohort. In case the MTD is exceeded, the dose will be de-escalated to the previous dose level where a DLT was not observed.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment that satisfy the following stopping rules:

1. ≥1 death within 7 days of AMSC application that is at least possibly related to the study agent across all treated subjects.
2. ≥1 SAE that is at least possibly related to the study agent occurring in 2 or more patients in a single dose level.
3. ≥3 SAEs that are at least possibly related to the study agent occurring in a single dose level.

FOLLOW UP

Patients will be seen in patient 24h (±24h) after the surgical procedure to obtain relevant medical history and AE collection. A postoperative MRI will be taken while the patient is hospitalized within 24 hours (±24h) of the procedure. Patients will then be seen as outpatient 1 week (±4 days), 2 weeks (±4 days), 3 weeks (±4 days), and 4 weeks (±4 days) after the procedure to obtain relevant medical history, AE collection, and biospecimen samples. Patients will then be seen for follow up every 2 months (±7 days) until progression of disease as defined by iRANO or until 1 year from registration. Patients will then be followed for survival. Other therapies for recurrent GBM will not be restricted and will be dictated at the discretion of the treating neuro-oncologist or radiation-oncologist.

DATA MANAGEMENT AND STATISTICAL ANALYSIS

Data collection for this study will be done exclusively through the Medidata Rave® clinical data management system (Medidata Solutions Inc.). All the relevant results pertaining to toxicity, MTD, response, timed endpoints and laboratory correlates will be examined in an exploratory and hypothesis-generating fashion.

A total of 6 patients treated at the MTD will be sufficient to identify common toxicities at the MTD. For instance, those toxicities with an incidence of at least 25% will be observed with a probability of at least 82% ($1-(1–0.25)^6$).

QUALITY ASSURANCE

(Mayo Clinic Florida is a National Cancer Institute Designated Comprehensive Cancer Center), and all patients will undergo a multi-disciplinary approach by neurosurgery, neuro-oncology, and radiation oncology throughout the study. Patient confidentiality will be kept throughout the study and data will be kept in an encrypted database following federal standards.

The study underwent thorough review for safety by the FDA through an IND application, by multiple neuro-oncology and cell therapy cancer center subcommittees, scientific review by the neuro-oncology committee, and finally by IRB to ensure appropriate scientific procedures.

EXPECTED OUTCOMES

We expect to find the MTD of AMSCs for the treatment of recurrent GBM to establish the safety of this therapy for GBM. At the same time, we intend to find a preliminary sign of

efficacy to power and design a larger phase 2 study. Furthermore, the correlative research will allow us to further understand the effects and the anti-brain cancer mechanisms of AMSCs.

DURATION OF THE PROJECT

We expect to complete enrollment within the first 6 months after activation and patients will be followed until progression of disease or until one year after treatment.

PROJECT MANAGEMENT

Trial oversight will be maintained by the study principal investigator as well as with oversight from the (Mayo Clinic IRB, DSMB, and the Mayo Clinic Comprehensive Cancer Center).

ETHICS

This study protocol, informed consent, and preclinical data were reviewed and approved by the (Mayo Clinic) Institutional Review Board (IRB) and the FDA through an IND application. Prior to enrollment, all patients will undergo informed consent and can withdraw from the study at any point.

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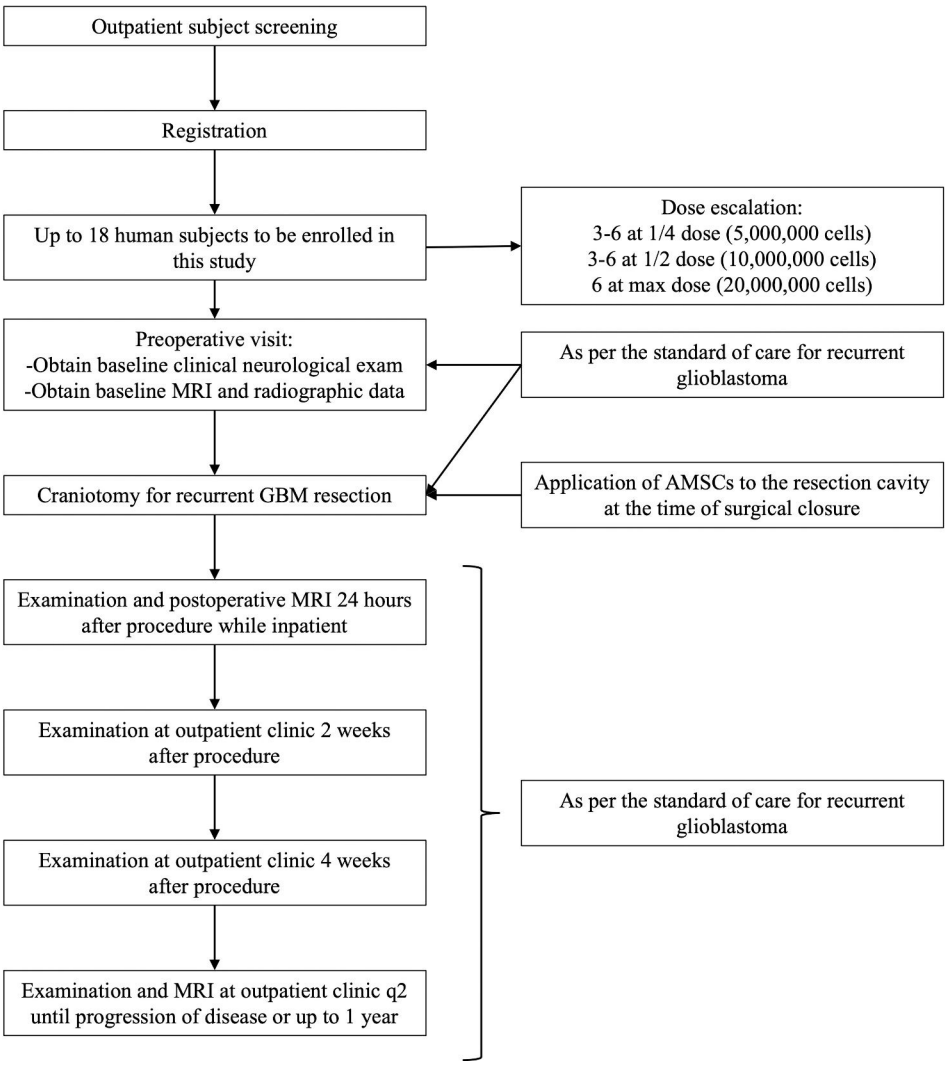

Figure 1.
Study design flow chart.

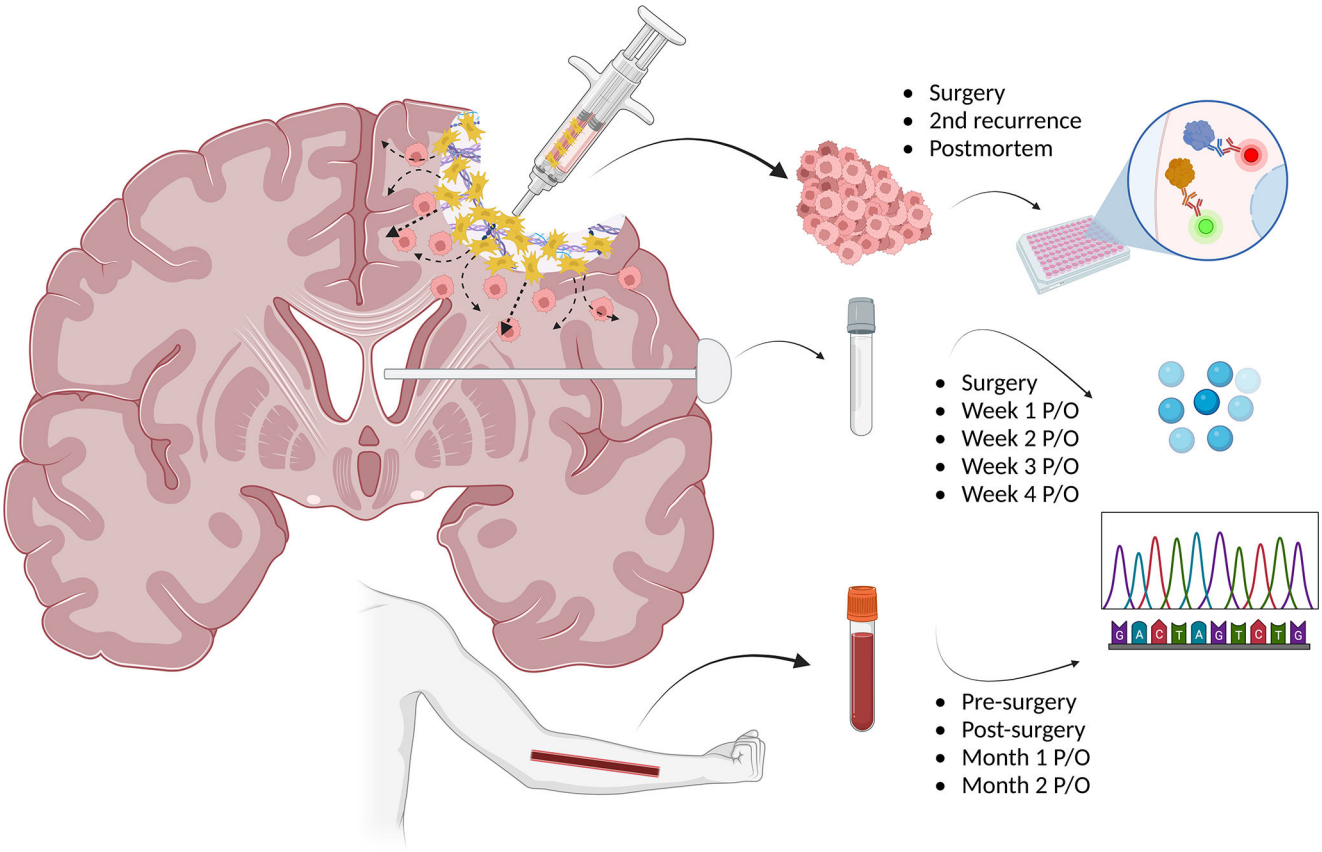

Figure 2.

Visual schematic of study procedures and correlative research (with time points). Patients will undergo intraoperative delivery of AMSCs encapsulated in fibrin glue to the resection cavity immediately after tumor excision. An ipsilateral CSF reservoir will also be placed at the time of surgery and will be used to collect CSF samples throughout the study. Tissue will undergo immunohistochemistry to evaluate immune infiltration and the long-term presence of AMSCs within the tissue. An inflammatory cytokine profile and next generation sequencing will be performed in all CSF and blood samples.

Figure 3.

Fibrin glue + AMSC mixture preparation. (**A**) Under sterile conditions, the surgeon will remove 1ml of thrombin (component 2) from the fibrin glue applicator. (**B**) Then, cell suspension (1ml) will be injected into the thrombin barrel using an 18-gauge needle. (**C**) The fibrin glue applicator is then built following manufacturers' instructions. This mixture will yield a final volume of 4ml consisting of 2ml fibrinogen + 1ml thrombin + 1m cell mixture.

Table 1.

Selection Criteria

Inclusion Criteria	**Exclusion Criteria**
Participants ≥18 years <65 years of age	Patients who are undergoing biopsy only or non-eligible for a surgical intervention
KPS ≥60	Previous treatment with Bevacizumab
Negative pregnancy test done <7 days prior to registration, for persons of childbearing potential only	Radiographic evidence of leptomeningeal disease
Patients with a previous histological diagnosis of GBM that show recurrence at the same location, who are candidates to- and will undergo a redo craniotomy for excision of recurrent tumor.	
Patients have undergone previous standard of care as outlined by Stupp et al. (2004) which include maximal safe resection followed by concomitant radiation therapy and chemotherapy with oral temozolomide.	
Adequate organ function as assessed by the following laboratory values ≤3 weeks prior to registration: a. Serum creatinine and urea ≤2 times the upper limit of normal. b. ALT, AST and alkaline phosphatase ≤ 3 times the upper limit of normal, and bilirubin ≤ 2.5 mg/dL. c. Prothrombin time ≤ 1.5 times upper limit of normal d. INR and PTT ≤ 1.5 times the upper limit of normal. e. Hemoglobin ≥ 9 g/dL f. Platelets ≥ 100×10^9/L g. Absolute Neutrophil Count (ANC) ≥1.5×10^9/L.	
Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study)	
Patient or legal guardian is able to fully understand and provide written and verbal consent for the protocol	
Willingness to provide mandatory blood specimens for correlative research	
Willingness to provide mandatory tissue specimens for correlative research	
Willingness to undergo Ommaya reservoir placement and provide CSF samples for correlative research	