Phase II Study of Laser Interstitial Thermal Therapy (LITT) in Recurrent Glioblastoma

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1.0 OBJECTIVES

1.1 Primary Objective

Determine the disease control rate at 6 months in patients with recurrent glioblastoma or isocitrate dehydrogenase (IDH)-wildype anaplastic astrocytoma treated with LITT at recurrence, followed by salvage chemotherapy.

1.2 Secondary Objectives

1.2.1 Estimate overall survival (OS) of patients with recurrent glioblastoma, or IDH-wildtype anaplastic astrocytoma treated with LITT at tumor recurrence, followed by salvage chemotherapy.

1.2.2 Estimate time to progression (TTP) of patients with recurrent glioblastoma, or IDH-wildtype anaplastic astrocytoma that are treated with LITT at tumor recurrence, followed by salvage chemotherapy.

1.2.3 Analyze volumetric data consisting of thermal damage threshold lines and overall tumor volume to determine any role of 'extent of ablation' in outcomes (OS and/or TTP).

1.2.4 Characterize the safety profile of LITT followed by treatment with lomustine chemotherapy in the recurrent disease setting, using the CTCAE version 4.0.

1.2.5 Assess the long-term steroid requirements following LITT.

1.2.6 Determine the radiographic evolution of LITT-treated glioblastoma over time, using conventional MRI (T1 pre and post-contrast images, T2-weighted images (T2WI), Fluid attenuating inversion recovery (FLAIR) images) and advanced brain tumor imaging (ABTI) [MR perfusion [dynamic susceptibility contrast (DSC), dynamic contrast enhancement (DCE) and arterial spin labeling (ASL)], MR- diffusion, and MR spectroscopy), to include quantitative tumor metrics (volumetric extent of ablation and RANO criteria).

1.2.7 Analyze health care utilization as measured by length of hospital stay following LITT (including inpatient rehabilitation care).

1.2.8 Evaluate patients' functional status (using the Karnofsky Performance Score (KPS) and the occurrence of symptoms (using the MD Anderson Symptom Inventory-Brain Tumor Module (MDASI-BT(English)) self-reporting tool), and correlate to disease progression and tolerance to treatment.

1.3 Exploratory Objectives

1.3.1 Identify correlative tumor and peripheral blood molecular markers that impact outcomes, etc, and identify inflammatory/immunologic markers to assess neoantigen expression, etc, if sufficient tissue is available.

1.3.2 Identify and characterize changes in tumor tissue following LITT, by analyzing and comparing pre- and post-procedure tissue samples, if sufficient tissue is available.

2.0 BACKGROUND

2.1 Glioblastoma

Glioblastoma (GBM) is the most common and the most aggressive primary adult brain tumor. Prognosis for patients with glioblastoma is quite dismal despite aggressive treatment. The current standard of care consists of maximal safe surgical resection, followed by 6 weeks of concurrent chemoradiation with daily temozolomide, followed by 6 4-week cycles of adjuvant temozolomide, with many patients remaining on treatment for 12 cycles. The overall median survival for patients with glioblastoma is less than 15 months [21]. Following disease progression, therapy most commonly consists of second-line chemotherapy, although radiation therapy, and/or surgery are also considerations. The response to single or multiple-agent chemotherapy is poor, with a response rate of 6%, 6-month progression-free survival rates for patients with recurrent GBM of 15% and median survival of 6 months [26]. Interestingly, although histologically grade 3 gliomas, patients with IDH wildtype anaplastic astrocytomas seem to have similar prognosis to patients with glioblastoma, and likely benefit from similar treatments.

Studies have shown a correlation between initial resection of glioblastoma and survival, with gross-total resection of tumor independently associated with longer survival [11]. Subtotal resection of tumor may still provide symptomatic benefits [11]. Tumors in deep or eloquent regions of brain are often not amenable to resection due to high risk of neurologic morbidity, and patients with these tumors most often only undergo biopsy. Over 70% of patients are not candidates for a complete resection due to a variety of factors [7]. Unfortunately, without initial cytoreductive surgery, radiation and chemotherapy appear to have more limited benefit [11, 12, 18]. Due to volume of tumor and associated edema, patients who have undergone biopsy only may be more likely to require long-term, high-dose corticosteroid treatment, and may experience shorter survival, compared to patients undergoing gross-total resection. At MD Anderson Cancer Center, for patients with good performance status and unresectable (biopsy-only) glioblastoma, the median survival is about 10 months. These findings suggest a need for an alternate cytoreductive treatment modality.

2.2 Laser Interstitial Thermal Therapy

LITT is a minimally invasive procedure for destroying tissue using heat generated through light absorption [3, 4]. Laser induced hyperthermia as a cytoreductive treatment option has been present since the 1980s [1]. Laser-induced thermal therapy was used as a treatment

for a range of different brain pathologies [10, 16, 22]. However, limitations in monitoring and controlling the extent of thermal damage delivered during treatment prevented this modality from being widely used until recently [13]. MR-thermography based on the temperature dependence of the proton resonance frequency (PRF) now allows for real-time image guidance of the extent of thermal damage from lasing [8]. Technologic advances such as this, as well as laser probe design, surgical navigation, and computer algorithms predictive of tissue kill, have allowed for a resurgence in the use of LITT for brain tumor cytoreduction [15]. The NeuroBlate System® (Monteris Medical Corporation, Plymouth, MN) is one such LITT device. NeuroBlate received FDA 510k clearance (K081509) in May 2009 without any specific limitations for intracranial use [13]. This was followed by a successful first in human study [19].

The LITT equipment manufactured as the NeuroBlate System uses a diode laser which transfers energy to the target tissue via a CO2 gas-cooled, side-firing probe [13]. The NeuroBlate system also includes a tool for obtaining biopsy of tumor tissue. The lasing is planned and controlled via the NeuroBlate System computer workstation using proprietary software under real-time MR-thermography guidance. The real-time extent of thermal ablation is calculated based on an algorithm of heat kill of cells (a relationship between time and temperature) demonstrated as thermal damage threshold (TDT) lines. A yellow TDT line encircles the area of tissue heated to an equivalent of 43 degrees Celsius for at least 2 minutes and a blue TDT line encircles the tissue heated to an equivalent of 43 degrees Celsius for at least 10 minutes, or to a higher temperature for a shorter interval [19].

Interactions between the laser and tissue are mostly thermal and rely on the power applied by the laser. The optical fiber emits photons that are absorbed by tumor chromophores causing excitation and release of thermal energy [20]. Maintaining the temperature above a critical threshold causes protein denaturation and irreversible tissue coagulation. Damage is produced in the tissue due to extrinsic properties of the laser and intrinsic properties of the target tissue [5]. The lesions produced by LITT are due to the combined effects of internal thermal generation and heat conduction [15].

LITT was first popularized as a percutaneous means of killing malignant hepatic and renal lesions [15]. Several animal studies using LITT to treat tumors in vivo, followed by clinical trials, have established the feasibility of LITT in treating intracranial tumors [15]. LITT has been used previously in the ablation of cerebral metastasis, with safety and efficacy demonstrated in small studies [3]. There are limited published studies describing clinical outcomes in patients with glioblastoma treated with LITT. Schwarzmaier et al studied 16 patients with recurrent GBM treated with LITT. They reported a 6.9 month median survival after LITT, relatively better than the historical control; no permanent neurologic deficits were reported [17]. More recently, Sloan et al conducted a phase I trial with 10 patients with high-grade glioma, using NeuroBlate for the LITT procedure. Median OS was 10.5 months after LITT; no deaths were reported related to the procedure [19]. The authors conclude from their phase I study that LITT therapy for recurrent glioblastoma is safe. In the largest series to date, Mohammadi et al retrospectively reviewed 34 patients with high-

grade glioma who underwent the LITT procedure with NeuroBlate, either as upfront or salvage treatment. This study showed some improvement in median progression free survival, although the median overall survival was not yet reached [13]. This study found that more complete coverage of tumor by TDT lines improved PFS and suggested that this can be likened to the extent of resection concept in surgery.

There is little data in the literature regarding the role of the extent of tumor coverage by LITT thermal energy on outcomes for patients with glioblastoma. However, there is literature reporting improved outcomes in patients with extensive surgical resections. There is a suggestion that the improved survival correlated with "extent of surgical resection" can be achieved by the "extent of hyperthermic ablation." [13]

2.3 Salvage treatment of recurrent glioblastoma

Second-line chemotherapy is the most common treatment modality in recurrent glioblastoma. At recurrence, a minority of patients are eligible for repeat resection or re-irradiation which may pose challenges, although repeat resection may be associated with a survival advantage [6]. Necrosis and cognitive impairment can occur with re-irradiation, and increased risk of infection and worsening neurologic status is more likely in patients undergoing repeat resection. Efficacy of second-line chemotherapy, as noted above, is very limited. Options include treatment with bevacizumab (FDA approved humanized monoclonal antibody that targets the vascular endothelial growth factor), rechallenging with temozolomide or other cytotoxic drugs including lomustine, and experimental targeted therapies and immunotherapies.

Nitrosoureas are commonly used as treatment for glioblastoma. Beginning in 1968, investigators studied single-agent chemotherapy in the treatment of brain tumors [24]. In the 1970s, the Brain Tumor Study group defined carmustine, a nitrosourea agent, as the standard against which newer forms of therapy were compared. Unfortunately, most patients quickly develop resistance to carmustine, and thus there have been modest improvements in survival rates with its use [2]. Lomustine (CCNU), also a nitrosourea agent, is pharmacologically similar to carmustine and is used in the treatment of certain neoplastic diseases. Lomustine has been shown to be useful as a single agent or in combination therapy with other approved chemotherapy agents in both primary and metastatic brain tumors. Study results for single-agent use of lomustine in the treatment of recurrent malignant gliomas in adults have been summarized by Hildebrand [9] with overall tumor response rates of 19% to 44% (partial response [PR] + stable disease [SD]) with length of remission of 6 to 8 months. A recent large meta-analysis of 364 studies describing 24,193 patients with high-grade glioma treated with lomustine either as single agent or in combination with other agents revealed a survival gain of 5.3 months [25].

Although lomustine alkylates DNA and RNA, this agent is not cross resistant with other alkylators. In a recent phase III trial of enzastaurin versus lomustine in the treatment of recurrent glioblastoma, some temozolomide resistant glioblastoma patients responded to lomustine treatment (response rate of 4.3% but a 6-month PFS of 19% [23]; indicating

there is non-overlapping resistance with temozolomide. Due to high lipid solubility and the relative lack of ionization at physiological pH, lomustine crosses the blood-brain barrier quite effectively. Common and severe adverse events include bone marrow suppression (most notably thrombocytopenia and leukopenia).

2.4 Rationale for this trial

Surgical extent of resection has been shown to have an impact on glioma outcomes, with patients with unresectable or subtotally resected tumors being at a suspected disadvantage with regard to outcomes. Tumor progression may be heralded by new imaging changes and/or neurologic symptoms. These symptoms may require additional medications such as corticosteroids which may lead to additional symptoms (e.g. steroid myopathy) and a reduction in quality of life. A multi-institutional nonrandomized retrospective study suggests LITT may improve progression free survival in patients with unresectable glioblastoma, and a first-in-humans phase I trial found LITT to be safe, and promising in terms of efficacy [19]. Improving progression-free survival may prevent degradation of quality of life.

With this in mind, we propose treating patients with recurrent glioblastoma, with LITT followed by salvage chemotherapy with lomustine, a second-line chemotherapy agent in patients with recurrent glioblastoma who have failed temozolomide treatment. Patients with known IDH-wildtype anaplastic astrocytomas (grade 3 gliomas), with suspected recurrence, will also be considered for inclusion, as these tumors may be similarly aggressive and lack viable treatment options. The aim of the study is to improve disease control rate at 6 months in this cohort of patients with recurrent glioblastoma.

2.5 Rationale for secondary objectives

2.5.1 Rationale for evaluating survival

It has been suggested that the cytoreductive effect of hyperthermia may be equivalent to surgical debulking [13], in other words, extent of ablation is potentially equivalent to extent of resection.

2.5.2 Rationale for analyzing volumetric data consisting of thermal damage threshold (TDT) lines and overall tumor volume.

The goal is to correlate the extent of laser thermal ablation with outcome (OS and TTP). Volumetric data will allow a quantitative measurement of extent of ablation.

2.5.3 Rationale for imaging correlates

LITT's mode of action induces tissue damage by thermal ablation. Some tissue damage continues to occur even after the completion of the procedure. A systematic analysis of the evolution of these changes over time on imaging studies, and their correlation with

outcome, will help us evaluate how these changes evolve and impact the assessment of tumor progression.

2.5.4 Rationale for evaluating the safety profile

Previous studies have found LITT to be a safe procedure for patients with brain tumors. We will gather more data on the safety of LITT, in the context of recurrent glioblastoma, and salvage chemotherapy.

2.5.5 Rationale for analyzing quality of life, functional status, and health care utilization

Patients with recurrent brain tumors often experience reduced quality of life, poor functional status and increased health care utilization. We will determine whether the use of LITT can preserve quality of life and functional status in recurrent disease, and lower the extent of hospitalization and health care utilization.

2.6 Rationale for exploratory objectives

Tumor tissue and peripheral blood will be evaluated in our trial with the objective of identifying correlative biomarkers of response and outcome. Collection of tumor tissue may allow for the evaluation of molecular and immunologic markers linked to response to therapy and survival in subsets of patients. Tumor tissue (biopsy) will be collected immediately pre- and post-procedure to inform the changes imparted on brain tumor tissue by thermal ablation.

3.0 DRUG AND DEVICE INFORMATION

3.1 Device name: NeuroBlate System®

The laser probe is available in two diameters (3.3 mm and 2.2 mm) and is internally cooled using CO2 gas. The laser energy (1064 nm) exits the probe almost perpendicularly (side-firing probe) through a sapphire tip. The laser source is a 12-W pulse mode diode laser (1064 nm, cycle of 1.6 seconds in on mode and 2.2 seconds in off mode).

The NeuroBlate System monitors and visually reports the temperature of tissue and the thermal dose. By convention the temperature commonly used in reporting experimental thermal dosage equivalence is 43°C. Tissues exposed to temperatures of 43°C or higher for ≥ 60 minutes initiate apoptosis and die within 48 hours. Tissues exposed to 43°C for shorter periods of time have a decreased level of damage, which has been refined empirically through preclinical testing and canine and porcine models (unpublished data, Monteris Medical, Inc.).

The NeuroBlate software determines the likelihood of eventual cell death across the monitored tissue following laser thermal therapy [17].

3.1.1 Risks

The risks of LITT therapy are low in the treatment of brain tumors, as has been documented in several small studies (Hawasli, 2012; Schroeder, 2013, Missios, 2013). In a few patients, temporary or permanent mild neurological deterioration (typically some manifestation of paresis) was observed, along with occasionally focal seizures. In general, the overall functionality (Karnofsky scores) was not reduced by the LITT treatment. Improvements in survival have been suggested following LITT therapy, equivalent to those observed following surgical resection (median = 11.2 months). With the recent availability (FDA clearance and market release) of the NeuroBlate® System, neurosurgeons managing this group of patients have an additional option. The minimally invasive approach of the NeuroBlate® System procedure with the non-ionizing ablation is an attractive alternate intervention to address the therapeutic needs of these subjects. In the NeuroBlate® System therapy First-in-Humans Phase 1 Clinical Trial for Recurrent Glioblastoma, the procedure appeared to be a new, safe method of ablating deep hemispheric recurrent GBM (Sloan, 2013). The device offers neurosurgeons precise control over thermal dosing into target tissues sufficient to induce near immediate tissue necrosis. The procedure was well tolerated and most subjects could be safely discharged after 24-48 hours without significant pain in the surgical area, nausea or headache. No infections related to the LITT procedure were observed within 6 months of the procedure (Hawasli, 2012; Schroeder, 2013, Missios, 2013). The impact of the NeuroBlate® System procedure on the QoL of patients with brain tumors or brain metastases is limited by the small collective clinical experience using the NeuroBlate® System therapy. Due to the recent introduction of NeuroBlate® System therapy, its effective incorporation in standard clinical practice of patients with newly diagnosed glioblastoma is unknown.

Risks are classified as follows:

Risk	Mild	Moderate	Severe
Likely risks (>5%)	Fever Low or high blood pressure Headache Fatigue, drowsiness	Bleeding into or around the brain Swelling of the tissue in the brain Increased size of abnormal area due to the treatment Pain at the biopsy site Nausea or vomiting	
Less likely risks (1-5%)	Depression of anxiety Agitation Blurry vision Small transient strokes (TIA) Reaction to anesthesia or other drugs	Seizures Difficulty speaking Loss of muscle coordination to one or more parts of the body Injury to blood vessels Pneumonia	Injury to brain tissue Loss of nerve function to a part of the body Stroke Blood clots to other parts of the body

	Wound healing difficulties	Fluid in the lungs or other lung abnormalities Infection, local or general	Air bubbles to the lungs or other parts of the body
Rare risks (<1%)	Anemia Abnormal blood cell counts	Loss of mental function Personality changes Unconsciousness Heart attack	Death Failure of brain to regulate body systems

As with any surgical procedure, the NeuroBlate® System involves some risks. The following potential risks or discomforts may be associated with the surgical procedure or the NeuroBlate System. In addition, the list includes possible risks associated with the use of the NeuroBlate System in the GBM population. The frequency and severity of adverse events can vary, and may necessitate additional medical intervention, including surgery.

- Agitation
- Anemia
- Aneurysm
- Anxiety
- Aphasia
- Ataxia or loss of body coordination
- Atelectesis
- Bacteremia or sepsis
- Bleeding into or around the brain
- Blurry vision/visual disturbance
- Cerebral infarction
- Coma
- Complete or incomplete hemiparesis
- Death
- Decrease energy
- Deep venous thrombosis
- Depression
- Difficulty hearing
- Difficulty speaking
- Difficulty swallowing
- Difficulty walking
- Drowsiness
- Edema
- Failure of central regulation
- Fever
- Headache
- Hypertension
- Hypotension

- Increased seizures frequency/duration or severity
- Infection, local or generalized
- Injury to blood vessels
- Injury to brain tissue
- Insomnia (e.g. sleep problems)
- Intestinal toxicity
- Loss of mental function
- Muscle weakness
- Myocardial infarction
- Nausea/vomiting
- Nerve paralysis
- Obtundation
- Paralysis
- Personality or cognitive changes (e.g. mood, memory, attention and thinking ability)
- Permanent neurological deficit
- Pneumonia
- Presence of new type of seizure
- Pain at incision site
- Pulmonary or other air embolism
- Reaction to anesthesia or other drugs
- Status epilepticus
- Stroke or transient ischemic attack (TIA)
- Thromboembolism
- Tingling or numb sensations in the body
- Tissue damage
- Unconsciousness
- Wound dehiscence

3.1.2 The training for the operator to use LITT equipment

LITT is FDA-approved for intracranial use. All users undergo standard training provided by the company, Monteris. The surgeons performing this procedure are already experienced users of LITT (over 120 cases combined). Deployment of the laser probe into the tumor is exactly the same as performing a stereotactic biopsy (i.e. using computer-assisted navigation technique for implanting a stereotactic biopsy needle), which is standard training during neurosurgery residency. As far as mitigating damage to normal tissue, thermal damage maps are monitored in real time and points are selected on normal tissue that enable the user to immediately stop treatment should those structures reach damaging temperatures.

3.2 Drug Name: Lomustine (CCNU)

Lomustine is one of the nitrosoureas used in the treatment of certain neoplastic diseases. It is 1-(2-chloro-ethyl)-3-cyclohexyl-1-nitrosourea. It is a yellow powder with the empirical formula of C9H16ClN3O2 and a molecular weight of 233.71. Lomustine is soluble in 10% ethanol (0.05 mg per mL) and in absolute alcohol (70 mg per mL). Lomustine is relatively insoluble in water (<0.05 mg per mL). Inactive ingredients in lomustine capsules are magnesium stearate and mannitol, and may additionally contain wheat starch and talc. Lomustine is commercially available in 10 mg, 40 mg and 100 mg capsules for oral administration. Doses of lomustine should be rounded down to the nearest 10 mg.

3.2.1 Chemical Name: 1-(2-chloro-ethyl)-3-cyclohexyl-1-nitrosourea

3.2.2 Molecular Formula: C9H16ClN3O2

3.2.3 Molecular Weight: 233.71

3.2.4 Appearance: yellow powder

3.2.5 How Supplied: Lomustine is commercially available in 10 mg, 40 mg and 100 mg capsules for oral administration.

3.2.6 Formulation: Lomustine is soluble in 10% ethanol (0.05 mg per mL) and in absolute alcohol (70 mg per mL). It is relatively insoluble in water (<0.05 mg per mL). Inactive ingredients in lomustine capsules are magnesium stearate and mannitol, and may additionally contain wheat starch and talc.

3.2.7 Mechanism of Action: Nitrosourea antineoplastic agents are alkylating agents.
This class of drugs work by inhibiting DNA replication, RNA transcription, and nucleic acid function. The drug is believed to inhibit DNA replication, RNA transcription, and nucleic acid function. Lomustine also may modify cellular proteins. Specifically, lomustine possesses a chloroethyl group that alkylate nucleic acids and cell proteins and form DNA-DNA or DNA-protein crosslinks, which lead to the global effects of impaired nucleic acid functioning. As compared to carmustine, lomustine is less likely to form isocyanates leading to diminished carbamoylation effects; although lomustine metabolites exhibit increased alkylating activity. Cells resistant to other alkylating agents are probably resistant to lomustine.

3.2.8 Pharmacology/Pharmacokinetics:
A. Absorption: The drug is rapidly absorbed across the GI tract following oral administration, or across the skin following topical administration. The exact bioavailability is unknown, but nearly complete oral absorption occurs in 30 minutes. Orally-administered lomustine is rapidly and totally converted to metabolites by first-pass metabolism in the liver. Essentially all of an oral dose is metabolized within 1 hour; some of these metabolites may be active

B. Distribution: The drug distributes throughout the body tissues. Because of the high lipid solubility and the relative lack of ionization at physiologic pH, lomustine crosses the blood-brain barrier quite effectively; however, only lomustine's metabolites can be detected in the CSF. CSF concentrations are >= 50% of plasma concentrations.

C. Metabolism & Elimination: The half-life of lomustine metabolites ranges from 16 hours to 2 days

D. Excretion: Following the administration of radio-labeled lomustine at oral doses of 30—100 mg/m2, about half of the radioactivity was excreted in the urine in the form of metabolites within 24 hours. Most of the metabolites are eliminated slowly in the urine.

E. Effect of Renal Impairment: There is no dosage adjustment provided in the manufacturer's labeling.

F. Effect of Hepatic Impairment: There is no dosage adjustment provided in the manufacturer's labeling.

3.2.9 Human Toxicology:

A. Bone marrow suppression (e.g., thrombocytopenia, leukopenia, and anemia) has been commonly reported with lomustine therapy; thrombocytopenia and leukopenia are dose-limiting toxicities. Patients receiving lomustine are at increased risk for serious bleeding and infection. Delayed and cumulative myelosuppression (pancytopenia) may occur, typically between 4 to 6 weeks following a dose, and may persist for 1 to 2 weeks; therefore, do not administer recommended doses of lomustine sooner than every 6 weeks. Monitor blood counts weekly for at least 6 weeks after a dose. Duration of suppression may be longer after repeated doses. A lomustine dose reduction may be necessary based on nadir blood counts. Following a lomustine 130 mg/m2 dose, 65% of patients experienced white blood cell (WBC) counts below 5000 cells/mm3 and 36% had WBC counts less than 3000 cells/mm3.

B. Gastrointestinal (GI) adverse events such as nausea and vomiting have been reported 3 to 6 hours after oral lomustine doses; loss of appetite (anorexia) may also occur. Symptoms usually last less than 24 hours. Prophylactic antiemetic administration and taking lomustine on an empty stomach may help to prevent these GI side effects. Stomatitis has also been reported infrequently with lomustine therapy.

C. Elevated hepatic enzymes (e.g., increased transaminase and alkaline phosphatase levels) and hyperbilirubinemia have been reported with lomustine therapy. Hepatotoxicity was typically reversible. Monitor liver function tests periodically during lomustine therapy.

D. Renal adverse events (e.g., progressive azotemia, decrease in kidney size, and renal failure (unspecified)) have been reported in patients receiving large cumulative doses after prolonged lomustine therapy. Kidney damage has also been reported infrequently in

patients receiving lower total lomustine doses. Monitor kidney function tests periodically during lomustine therapy.

E. Pulmonary toxicity (e.g., pulmonary infiltrate and/or pulmonary fibrosis) has been reported rarely with lomustine therapy. Pulmonary toxicity typically occurs 6 months or longer after starting lomustine therapy; however, delayed onset pulmonary fibrosis has been reported up to 17 years after treatment in patients who received related nitrosoureas in childhood and early adolescence (1—16 years) combined with cranial radiotherapy for intracranial tumors. Additionally, pulmonary toxicity has been typically reported following cumulative lomustine doses of greater than 1100 mg/m2, but there was 1 report of pulmonary toxicity occurring at a cumulative dose of 600 mg. Obtain baseline pulmonary function studies and monitor pulmonary function tests frequently tests during treatment. Patients with baseline predicted Forced Vital Capacity (FVC) or Carbon Monoxide Diffusing Capacity (DLCO) below 70% are particularly at risk for toxicity.

F. Secondary malignancy (e.g., acute leukemia and bone marrow dysplasia) has been reported with prolonged nitrosourea therapy.

G. Alopecia has also been reported infrequently with lomustine therapy.

H. Optic atrophy and visual impairment (e.g., blindness) have been reported infrequently with lomustine therapy.

I. Neurological adverse reactions such as disorientation, lethargy, ataxia, and dysarthria have occurred with lomustine therapy.

3.2.10 Clinical Pharmacokinetic Properties: See Section 3.2.8

3.2.11 Administration: Lomustine will be administered orally as described in the treatment plan.

3.2.12 Supplier: Lomustine (Gleostine) is available commercially.

3.2.13 Agent Distribution: Lomustine (Gleostine) will be supplied through the patients' insurance provider.

4.0 ELIGIBILITY CRITERIA

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects with regards to gender or race. Males and females will be recruited with no preference to gender. No exclusion to this study will be based on race. All patients who meet the following eligibility criteria must be registered with the University of Texas MD Anderson Cancer Center.

4.1 General Inclusion Criteria

A. Patients must have suspected recurrent supratentorial grade IV glioblastoma (or grade III IDH-wildtype anaplastic astrocytoma), for which a complete surgical resection is unsafe due to location, shape, or size of the tumor.

Diagnosis of recurrence will be established by biopsy and frozen section immediately prior to initiating LITT procedure. If findings on frozen section are not consistent with recurrence (glioblastoma or recurrent IDH-wildtype anaplastic astrocytoma), decision to proceed with LITT procedure will be at the discretion of the neurosurgeon (only patients with histologically-proven recurrent tumor will be evaluable for efficacy).

B. All patients must sign an informed consent indicating that they are aware of the investigational nature of this study. Patients must have signed an authorization for the release of their protected health information. Patients must be registered prior to treatment on study.

C. Patients must be $\geq$ 18 years old.

D. Patients must have a Karnofsky Performance Score (KPS) >60.

E. Patients must have received standard of care therapy with chemoradiation with temozolomide followed by adjuvant chemotherapy with temozolomide. Patients may have received one additional chemotherapy regimen (other than lomustine) in addition to adjuvant temozolomide prior to study entry (patients at either first or second recurrence are eligible).

F. In the context of this clinical trial, a lesion suitable for LITT is single, enhancing, supratentorial, at least 2 cm from inner table of skull over the hemispheric convexity, and >1 cm, but <= 5 cm in cross-sectional dimension, including thalamic tumor ($\leq$ 3 cm).

G. Patients must have stable cardiovascular, neurovascular and neurological status, and be considered surgical candidates, as determined by any relevant pre-operative assessments, at the neurosurgeon's discretion.

H. Patients must not be receiving concurrent anti-tumor treatment and must have recovered from toxicity of prior treatment. Minimum interval required: 1) >6 weeks following nitrosourea chemotherapy; 2) >4 weeks after recovering from any non-nitrosourea drug or systemic investigational agent; 3) >2 weeks after receiving any non-cytotoxic anti-tumor drug; 4) > 4 weeks after receiving radiation therapy (>12 weeks following upfront concurrent chemoradiation); 5) >2 weeks following Optune device use.

I. Patients must not have previously undergone an intracranial LITT procedure.

J. Patients must have adequate bone marrow function (WBC $\geq$ 3,000/µl, ANC $\geq$ 1,500/mm^3, platelet count of $\geq$ 100,000/mm^3, and hemoglobin $\geq$ 10 gm/dl), adequate liver function (SGOT and bilirubin < 2 times ULN), and adequate renal function (creatinine < 1.5 mg/dL) before starting therapy. These tests must be performed within 14 days (+ 3 working days) prior to registration. Eligibility level for hemoglobin and platelets may be reached by transfusion.

K. Women of childbearing potential must have a negative B-HCG documented within 7 days prior to registration and must agree to practice adequate contraception as defined below.

Non-childbearing potential (i.e., physiologically incapable of becoming pregnant), includes any female who has had:

1. A hysterectomy
2. A bilateral oophorectomy
3. A bilateral tubal ligation
4. Is post-menopausal:
   Subjects not using hormone replacement therapy (HRT) must have experienced total cessation of menses for $\geq$ 1 year and be greater than 45 years in age, OR, in questionable cases, have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value < 40pg/mL (<140 pmol/L).

   Subjects using HRT must have experienced total cessation of menses for >= 1 year and be greater than 45 years of age OR have had documented evidence of menopause based on FSH and estradiol concentrations prior to initiation of HRT.

Childbearing potential includes any female who has had a negative serum pregnancy test within 7 days of study registration, and agrees to use adequate contraception. Acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follows:

1. Complete abstinence from sexual intercourse for 14 days before starting treatment, through the treatment, and for at least 1 month after the last dose of temozolomide.
2. Oral contraceptive, either combined or progestogen alone. A second barrier method is required during the first month of treatment with oral contraceptives.
3. Injectable progesterone
4. Implants of levonorgestrel.
5. Estrogenic vaginal ring.
6. Percutaneous contraceptive patches.
7. Intrauterine device (IUD) or intrauterine system (IUS) with a documented failure rate of less than 1% per year.
8. Male partner sterilization (vasectomy with documentation of azoospermia)

prior to the female subject's entry into the study, and this male is the sole partner for that subject.

9. Double barrier method: condom and an occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/film/cream/suppository).

Female participants who are lactating should discontinue nursing prior to the first dose of temozolomide and should refrain from nursing throughout the treatment period and for 42 days following the last dose of lomustine.

4.2 General Exclusion Criteria

A. Patients must not have received treatment with bevacizumab.

B. Patients must not have had prior treatment of glioblastoma with stereotactic radiosurgery, brachytherapy, or carmustine-impregnated wafers (Gliadel).

C. Patients must not have symptoms attributed to mass effect of the tumor (despite corticosteroid treatment) that would be better treated with debulking surgery, or wherein surgical debulking in the first 30 days following LITT procedure would be anticipated for symptom management.

D. Patients unable to undergo MRI are not eligible.

E. Patients with progression of multifocal tumors or tumors involving the posterior fossa (brainstem and cerebellum) will be excluded, as will patients where the anticipated treatment margin will be within 5 mm of critical intracranial structures (e.g., primary branches of cerebral vessels, dural sinuses, hypophysis or cranial nerves).

F. Patients may not have undergone previous treatment with lomustine.

G. Patients must not have any significant medical illnesses that in the investigator’s opinion cannot be adequately controlled with appropriate therapy or would compromise the patient’s ability to tolerate this therapy.

H. Patients with a history of any other cancer (except non-melanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission and off of all therapy for that disease for a minimum of 3 years are ineligible.

I. Patients must not have active infection or serious intercurrent medical illness.

J. Patients must not be pregnant/breast feeding and must agree to practice adequate contraception (see 4.1.K)

K. Patients must not have uncontrolled hypertension (systolic >180 mm hg or diastolic > 100 mg Hg), angina pectoris, cardiac dysrhythmia, or recent (within 6 weeks) intracranial hemorrhage

5.0 STATISTICAL FACTORS

There will be an accrual of approximately 34 patients. Accrual to the trial may be increased to 37 (10%) patients to ensure a sufficient number of evaluable patients for the primary objective of the study. Patients removed due to toxicity are evaluable and these patients will be considered treatment failures for the primary efficacy outcome. Patients who undergo LITT but do not complete salvage chemotherapy will still be evaluable. However, patients with pre-LITT biopsy not consistent with recurrent glioblastoma or recurrent IDH-wildtype anaplastic astrocytoma will not be evaluable for efficacy and will be replaced.

6.0 TREATMENT PLAN

6.1 General

All patients who meet eligibility criteria must be registered before initiating the study procedure.

A. Patients will be monitored for hematologic or serologic evidence of myelosuppression, hepatic injury, renal injury, and electrolyte disturbances and for clinical evidence of other toxicity as is described in section 8.0.

B. G-CSF Administration:

Routine prophylactic use of G-CSF is not permitted. However, therapeutic use in patients with serious neutropenic complications, such as sepsis, may be considered at the investigator’s discretion.

C. Supportive Care:

a. Corticosteroids should be used in the smallest dose to control symptoms of cerebral edema and mass effect, and discontinued if possible.

b. Anti-seizure medications should be used as indicated.

c. Febrile neutropenia may be managed according to the institution's Infectious Disease guidelines. Measures may include appropriate laboratory testing, including blood and urine cultures and the institution of broad-spectrum antibiotics. If a source for the fever is not identified or the fever resolves when the neutrophil

count recovers, antibiotics may be discontinued and the patient observed.

d. Antiemetics. The use of antiemetics will be left to the investigators' discretion. Prophylactic treatment with 5-HT3 receptor antagonists is recommended.

e. Other Concomitant Medications.

Therapies considered necessary for the well-being of the patient may be given at the discretion of the investigator. Other concomitant medications should be avoided except for analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems. All concomitant medications must be recorded. Pneumocystis jiroveci pneumonia (PJP, previously carinii, PCP) – prophylaxis is required ONLY for patients during concurrent chemoradiation. During adjuvant and salvage chemotherapy, all patients, particularly if on steroids, should be observed closely for lymphopenia. Prophylaxis for PJP may be considered at the investigator's discretion if the total lymphocyte count is ≤ 200.

D. Other Anticancer or Experimental Therapies:

No other anticancer therapy (including chemotherapy, hormonal treatment or immunotherapy) of any kind is permitted during the study period. No other drug under investigation may be used concomitantly with the study drug.

E. Surgery:

If neurosurgical management is required for reasons other than tumor progression, these procedures must be documented, including the indications for surgery, the surgical operative note and pathology report. If surgery is required for suspected progression and pathology reveals only treatment effect, the patient can continue treatment with lomustine at the discretion of the treating physician, once recovered from surgery.

6.2 Treatment Plan Overview

This will be a prospective, single-center study. All eligible participants with recurrent glioblastoma (see study criteria, section 4.0) will undergo thermal ablation of tumor utilizing the LITT procedure. Diagnosis of glioblastoma will be determined histologically (frozen section) by biopsy, prior to LITT procedure. Diagnosis will be confirmed upon full neuropathological review (for determination of evaluability for efficacy). It is acceptable for biopsy to occur immediately prior to LITT procedure, establishing presence of viable tumor by histological analysis of frozen section performed by a neuropathologist. If there is uncertainty as to the exact pathological diagnosis, or if frozen section is not consistent with glioblastoma, LITT procedure will either proceed at the discretion of the neurosurgeon or be delayed until full neuropathological review is completed. Blood (within 24 hours of procedure) and tissue (pre-ablation biopsy) will be obtained and banked for corollary

studies. If possible, post-ablation biopsy will also be obtained, immediately following the procedure, for comparison of tissue and banking for corollary studies. LITT procedure will be followed by salvage lomustine.

The surgeon will perform the LITT procedure in the MD Anderson Cancer Center MRI BrainSuite operating room, using real-time MRI with thermography (heat mapping) and proprietary software. The patient will undergo post-procedural neurologic assessment and follow up MRI within 48 hours of the procedure. The patient will present for outpatient follow up neurological assessment 14 days (+/- 3 business days) following the procedure. The patient will be evaluated for appropriateness to begin salvage therapy with lomustine, to start 14-35 days following the procedure. Choice of salvage chemotherapy is limited to lomustine, to standardize the treatment plan. The patient's neurological status MRI scans will be reassessed at regular intervals. The patient will complete a quality of life self-assessment at regular intervals. Steroid dose will be documented at time of each neurologic assessment/MRI scan. Toxicity will be monitored. Should the patient's tumor progress per the RANO criteria, or the patient develop toxicity on treatment regimen, further management decisions will be made per the treating physician.

6.3 Number of Patients and Study Duration

An estimated 3 patients can be accrued per month, with accrual completed in about 12 months, with an additional 12 months of follow-up.

Total accrual to the trial will be increased by 10% to ensure a sufficient number of evaluable patients for the primary objective of the study.

The total study duration is estimated at 24 months.

6.4 Study Design/Treatment Schedule

Within 24 hours prior to the procedure, the patient will undergo pre-operative trajectory site and skull entry point planning MRI. MRI sequences will include FLAIR, T2*, diffusion-weighted, and T1-weighted volume spoiled gradient-recalled acquisition in the steady state, and in some cases diffusion tensor imaging, to further evaluate nearby critical white matter tracts. The eloquence of the tumor will be graded according to the criteria of Sawaya et al (see Appendix), and tumor dimensions and volume will be calculated (see below).

In the MD Anderson Cancer Center MRI BrainSuite operating room, after induction of general anesthesia, a Mayfield 3-point fixation apparatus is attached to the patient's head and a trajectory guidance device, modified to secure the laser probe control mechanism, is attached to the skull. The patient then undergoes a brain biopsy. Standard biopsy technique will be used. Approximately 4 cores will be obtained from each biopsy. Before proceeding with LITT, the diagnosis will be established by histological analysis of frozen section. If there is uncertainty as to the exact pathological diagnosis, LITT procedure will either

proceed at the discretion of the neurosurgeon or delayed until full neuropathological review is completed. Diagnosis will be confirmed upon full neuropathological review (for determination of evaluability for efficacy). Blood (within 24 hours of procedure) and tissue (at pre-ablation biopsy) will be obtained and banked for corollary studies. If possible, post-ablation biopsy will also be obtained, immediately following the procedure, for comparison of tissue and banking for corollary studies. These studies will include exploratory determination of tumor markers and blood-based biomarkers.

LITT will be delivered directly to the tumor by a neurosurgeon, using the rigid, gas-cooled, side-firing or diffusion tip NeuroBlate laser probe. The surgeon manually segments the tumor using NeuroBlate software and the T1-weighted planning images. Temperature reference points are identified. Treatment is monitored using real-time MRI thermometry as well as proprietary software providing predictive thermal feedback. The surgeon will control the rotation and depth of the probe, to tailor tissue coagulation. The surgeon will optimize the delivery of the dose to the tumor, while minimizing dose to surrounding brain tissue. Disposition of thermal energy outside the tumor into the cisterns, ventricles, sulci, and subarachnoid space is permitted at the discretion of the surgeon. Application of laser energy at multiple angles and depths as required is permitted. The probe is advanced and retracted to treat planes within the tumor until maximum coverage of the prescribed thermal injury is achieved. Laser ablation is stopped manually by the surgeon when it is thought that the predicted thermal ablation zone is sufficient, or stopped automatically if any monitored limits are exceeded.

The patient will undergo post-operative follow-up neurologic assessment (including KPS) and MRI (details of sequences outlined below) within 48 hours of the procedure. If the patient is stable, they may be discharged within 48 hours of the procedure, following MRI. Symptomatic, treatment-related edema may be treated with corticosteroids.

All patients will be monitored throughout the study for safety and toxicityIf the patient reports new or worsening neurologic deficits, signs/symptoms of increased intracranial pressure, or a decline in KPS, CT head will be performed as indicated. If there is evidence of new or worsening edema, a trial of steroids may be prescribed, per the treating physician. Hemorrhage or other clinical or radiographic evidence of toxicity will be managed as appropriate. Toxicity will be graded 1-5 according to the National Cancer Institute Terminology Criteria for Adverse Events v4.0, with a score of 1 indicating mild adverse effects, a score of 2 moderate adverse effects, a score of 3 severe adverse effects, and a score of 4 life-threatening adverse effects (see Appendix).

Patients will be monitored for toxicity in the 2 week period following LITT and then for an additional 4 weeks, which may include a period during which a patient is receiving chemotherapy.

Patients will undergo followup clinic visit on post-operative day 14 (+/- 3 days).

Following a 14-35 day post-surgical interval, patients may be eligible to initiate treatment

with single-agent lomustine for up to 6 cycles.

For all patients, RANO criteria will be used to determine response to treatment.

Patients will undergo follow-up evaluation including neurologic examination, adverse effects, and MRI sequences at intervals as detailed below. Patients will be followed until death. KPS and steroid dose will be documented at time of each neurologic assessment.

Beginning with the first post-operative scan, all MRI imaging will incorporate the conventional MRI (T1 pre and post-contrast images, T2-weighted images (T2WI), Fluid attenuating inversion recovery (FLAIR) images) and advanced MRI (MR perfusion [dynamic susceptibility contrast (DSC), dynamic contrast enhancement (DCE) and arterial spin labeling (ASL)], MR- diffusion, and MR spectroscopy) sequences. Imaging post-processing and evaluation will include but is not be limited to modified RANO criteria, advanced quantitative imaging and volume tumor metrics, and voxel-by-voxel (texture, heterogeneity, energy, etc) imaging analysis. Pre-operative imaging will include contrast-enhanced T1-weighted volumetric images, which are transferred to proprietary software, and probe trajectory and skull entry point are planning. DTI-FT may be added to identify nearby critical white matter tracts. Intra-operative imaging will include MR-thermography and TDT lines. For all imaging, the amount of edema will be graded quantitatively with a score of 0 (no detectable edema), 1 (moderate edema without significant shift), or 2 (severe regional edema with mass effect or shift). Tumor dimensions and volume (detailed below) will also be calculated. Tumor progression will be defined according to the RANO criteria (see section 9.3).

6.5 Evaluation and treatment schedule for salvage chemotherapy

14-35 days following the procedure, if deemed medically stable, participants will initiate treatment with lomustine. The baseline examination before initiation of chemotherapy will include MRI (within 48 hours post-procedure and 14 days (+/- 3 days) post-procedure), full blood counts and blood chemistry tests (BUN, creatinine, electrolytes, liver function tests), and a physical examination that includes KPS.

One cycle of lomustine is defined as 6 weeks. Patients will undergo comprehensive evaluation with MRI scan along with neurologic assessment to include KPS following each cycle (6 weeks) of lomustine. Chemotherapy prescription or orders will be provided based on outlined parameters and assessment of toxicities during the previous cycle.

6.6 CBC Monitoring Parameters

Lomustine
CBC and differential and BUN/creatinine will be checked every 2 weeks during a 6 week cycle, and must be checked on day 42 (+/- 2 days), prior to initiating a new cycle. LFTs will be performed on day 42 (+/- 2 days), prior to initiating a new cycle.

6.7 Post-procedural inflammatory changes

If prior to the next scheduled MRI, the patient develops signs of increased intracranial pressure (ie. confusion, new/worsening headache, nausea & vomiting), new or worsening of neurological deficits, and/or KPS decreases to < 70 and likely is attributable to the experimental treatment, the patient will undergo CT head or MRI brain with and without contrast to ensure there is no hemorrhage, new/worsening edema or other acute event. Corticosteroids may be initiated in the case of symptomatic edema. If CT head is negative for a hemorrhage, significant edema or cerebrospinal fluid obstruction, and the addition or increase of dexamethasone does not improve symptoms, an MRI brain with and without contrast is warranted to better assess for signs of edema or other abnormalities.

6.8 Disease Progression

If disease progression occurs outside of the area of the initial LITT procedure, further management will be at the discretion of the treating physician. Repeat LITT therapy near to prior LITT site may be performed but patients will be considered to have progression according to the protocol endpoints. Data on subsequent therapy will be collected when possible.

6.9 Doses

1. Salvage Therapy

A. Lomustine

Lomustine will be administered orally on an empty stomach before bed (2 hours after or 1 hour before food). Lomustine will be administered every six weeks on day 1 of every 6 week cycle. While the recommended dose of lomustine for patients with recurrent GBM is 100-130 mg/m2 (Wick, 2010), we chose to initiate lomustine at 90 mg/m2 for the first cycle, as this is the routine initial dose in our clinical practice for patients with recurrent GBM. This is the dose typically tolerated in our patient population, in terms of myelosuppression. The dose of lomustine may be increased to 110 mg/m2 starting with the second cycle, at the treating physician's discretion, as long as patient has not required dose modification for toxicity. A treatment window of +/- 3 days is acceptable. Patients receiving lomustine should receive premedication with ondansetron, granisetron or other anti-emetic medication at the treating physician's discretion. Doses of lomustine will be rounded down to the nearest 10 mg.

Dose Level	**Lomustine**
+1	110 mg/m2
0 (Starting)	90 mg/m2
-1	67.5 mg/m2
-2	45 mg/m2

6.10 Dose modifications for toxicity

6.10.1 Salvage Treatment with Lomustine
For hematological toxicity

Nadir After Prior Dose Absolute Neutrophil Count (ANC) ($x10^9$/L)	**Platelets ($x10^9$/L)**	**Percentage of Starting Dose to be Given**
	> 100,000	100%
LLN - 1.5	75,000-99,999	100%
1.5 – 1.0	25,000-74,999	75%
<1.0	< 25,000	50%

A repeat course of lomustine should not be given until circulating blood elements have returned to acceptable levels (platelets above 100,000/mm3; or absolute neutrophil count ≥ 1500/mm3). This usually occurs within 6 weeks. Blood counts should be monitored weekly and repeat courses should not be given before 6 weeks because the hematologic toxicity is delayed and cumulative. Growth factor support is permitted. Lomustine may be dose reduced a maximum of 2 times.

For nonhematologic toxicity

For nonhematologic toxicity ≥CTCAE Grade 3, treatment should be delayed until resolution to less than or equal to the patient's baseline value before proceeding. Dose reductions for nonhematologic toxicities will be based on the previous dose level administered. If, after restarting therapy, the patient does not have recurrence of the event after 42 days of therapy, the patient may be reescalated to the full dose at the discretion of the investigator. Upon toxicity resolution to Grade 1 or less, lomustine treatment will resume as follows:

a. Nausea and/or vomiting: treatment may resume without dose reduction. Grade 3 or 4 nausea and/or vomiting should be managed with appropriate changes in antiemetic regimen. Additionally, the dose of lomustine may be split over 3 days if necessary.
b. Grade 3 transaminase elevations that return to baseline by Day 1 of the next cycle: treatment may resume without delay or dose reduction.
c. For pulmonary toxicities: Patients will be assessed with pulmonary function tests, discontinuation and as clinically indicated during the course of therapy.

d. Other Grade 3 or 4 nonhematologic toxicities considered study drug related: a 25% dose reduction should be administered for the first dose reduction and a 50% dose reduction for the second reduction, if deemed appropriate by the treating physician.

7.0 PRE-TREATMENT EVALUATION

7.1 General Requirements

7.1.1 A complete history and neurological examination (to include documentation of KPS as well as MRI (see section 6).

7.1.2 Pre-study laboratory tests shall include CBC, differential, platelets, BUN, serum creatinine, bilirubin, ALT, AST, PT/INR, and serum pregnancy test for women of childbearing potential. Pre-study laboratory tests must be obtained within 14 days of registration. HCG must be obtained within 14 days of registration, in women of child-bearing potential. Further pre-operative labs will be obtained at the discretion of the surgeon.

7.1.3 Patients must undergo pre-operative risk stratification/evaluation.

7.1.4 Documentation of suspected recurrent tumor diagnosis. Following biopsy (which may be performed immediately prior to LITT procedure), tissue slides must be submitted for neuropathologic review (See section 12). Decision to proceed with LITT will be per the discretion of the neurosurgeon. If there is uncertainty as to the exact pathological diagnosis, or if frozen section is not consistent with glioblastoma, LITT procedure will either proceed or be delayed until full neuropathological review is completed.

8.0 EVALUATION DURING STUDY

(See Study Calendar in Appendix)

8.1 General Requirements

8.1.1 Within 24 hours prior to the procedure, the patient will undergo pre-operative trajectory site and skull entry point planning MRI. If taking corticosteroids, the patient must be on a stable or decreasing dose for at least 5 days, prior to MRI.

8.1.2 A real-time brain MRI with heat mapping will be performed during the LITT procedure, along with proprietary software providing predictive thermal damage feedback.

8.1.2 Blood will be collected within 24 hours prior to the LITT procedure. Blood will be banked for exploratory analysis. Blood will also be collected approximately every 2 weeks while the patient is undergoing treatment with lomustine.

8.1.3 Tumor tissue will be collected at pre-ablation and post-ablation biopsy (when feasible) and banked for correlative analysis.

8.1.4 A brain MRI and neurologic assessment including KPS will be performed within 48 hours following completion of the LITT procedure.

8.1.5 A brain MRI and neurologic assessment including KPS will be performed on day 14 (+/- 3 days) following completion of the LITT procedure.

8.1.6 A brain MRI and neurologic assessment including KPS will be performed every 6 weeks (every cycle) while on lomustine chemotherapy.

8.1.7 All relevant information regarding drug doses, concomitant medications, and doses, measurable lesions with measurements, tumor response, laboratory examinations, and treatment-related toxicities will be documented in the patient's medical record and flow sheets. Corticosteroid use must be documented.

8.1.8 A complete physical and neurologic exam (to include documentation of KPS) will be performed prior to initiation of every cycle of chemotherapy.

8.1.9 Determination of progression of disease (as defined in Section 9.4).

a. RANO criteria will be used to determine progression.

b. Patients who discontinue treatment due to progression will be followed for survival every 3 months (+/- 14 days)*.

c. Patients who come off therapy for reasons other than progression will be followed every 3 months (+/- 6 weeks) until progression or institution of new anti-tumor therapy. They should then be followed for survival every 3 months (+/- 14 days)*.

* if the patient is unable to return for a clinic visit, the follow up may be conducted via letter or phone call from research staff to inquire regarding interim health history. Information will be recorded. All patients will be followed until death or loss-to-follow-up. Attempts to avoid loss of follow-up, including letters and phone call, will be implemented by research nurse.

8.1.10 Laboratory Assessment

During the salvage chemotherapy phase with lomustine, CBC with differential and BUN/creatinine will be obtained every 2 weeks (+/- 3 days), and LFTs will be performed prior to each (6 week) cycle.

8.1.11 An end-of treatment visit will ideally include history and exam, and MRI to document status of disease.

9.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

9.1 Primary Endpoint

9.1.1 Disease control rate at 6 months: Defined as the percentage of evaluable (See Section 5.0) patients that have at least stable disease or better at 6 months after the LITT procedure. RANO criteria will be used to determine progression.

9.2 Secondary Endpoints

9.2.1 Overall survival time, defined as the time from the enrollment until the time of death. Patients who are alive will be censored at the time of last contact. .

9.2.2 Time to progression (TTP) is defined as the time from study enrollment until the time of first disease progression, relapse, or death due to disease (event). Patients who are alive without progression or relapse will be censored at the time of last contact. Patients who died without progression will be censored at death.

9.2.3 Safety and toxicity of LITT by determination of adverse events and surgical complications within 2 weeks of the procedure, plus an additional 4 weeks (to account for potential delayed inflammatory changes and initiation of subsequent treatment). Safety for LITT procedure will be defined as the absence of severe clinical toxicity as determined by the CTCAE version 4.0, within 6 weeks of the procedure, and/or absence of acute events (ie, significant hemorrhage or brain herniation) documented on imaging. Severe toxicity will also be defined as a drop of 20 points or more in KPS and not amenable to corticosteroids, and likely attributable to the procedure, or symptomatic hemorrhage, increased brain edema resulting in herniation/impending herniation, and/or significant neurologic decline not amenable to corticosteroids. Safety and toxicity will be reassessed again throughout the duration of the study.

9.2.4 Analysis of volumetric data consisting of thermal damage threshold lines and overall tumor volume and analysis of radiographic evolution of LITT treated glioblastoma, by serial MRI for analysis of the chronological sequence of the lesion’s evolution.

9.2.5 Evaluate functional status and the occurrence of symptoms, using the Karnofsky Performance Score (KPS) and the MDASI-BT (English) self-reporting tool, respectively.

9.2.6 Analysis of health care utilization as measured by length of hospital stay post-op, readmission, and time to home (include inpatient rehab care).

9.3 Exploratory Endpoints

9.3.1 To identify peripheral blood and tumor tissue molecular biomarkers associated with response to LITT based therapy, as measured by progression-free survival and overall survival, and to obtain exploratory data regarding tumor tissue inflammatory/immunologic profile.

9.3.2 To determine changes in tumor tissue pre- and post-procedure, to evaluate the impact of the procedure on brain tumor tissue.

9.4 Definitions of Response (Based on RANO Criteria)

RANO Criteria:

Criterion	CR	PR	SD	PD***
T1 gadolinium enhancing disease	None	≥ 50% ↓	< 50% ↓ but < 25% ↑	≥25%↑
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑*
New Lesion	None	None	None	Present
Corticosteroids	None	Stable or ↓	Stable or ↓	NA**
Clinical Status	Stable or ↑	Stable or ↑	Stable or ↑	↓*
Requirement for Response	All	All	All	Any*

Abbreviations: RANO, Response Assessment in Neuro-Oncology; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; FLAIR, fluid-attenuated inversion recovery; NA, not applicable.

* Progression occurs when this criterion is present. To be considered progressive disease, increase in T2/FLAIR should occur on stable or increasing doses of corticosteroids compared to baseline scan or best response following initiation of therapy, and should not be due to co-morbid events (e.g. radiation therapy, demyelination, ischemic injury, infection, seizures, post-operative changes, or other treatment effects).

**Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

*** this criteria only pertains to assessment of progression >12 weeks following completion of chemoradiation.

The primary measure of imaging response will be based on serial measures of the product of the two largest cross-sectional diameters. For patients with <0.5mm of enhancing tissue in two cross-sectional diameters in each of two perpendicular slices on the baseline scan, progression will be defined when enhancement is >1cm in two cross-sectional diameters in each of two perpendicular slices.

9.4.1. Measurable Disease: Bidimensionally measurable lesions with clearly defined margins by MRI scan.

9.4.2 Evaluable Disease: Unidimensionally measurable lesions, masses with margins not clearly defined.

9.4.3 Non-Evaluable Disease: Not Applicable for response evaluation.

9.4.4. Objective Status, To Be Recorded at Each Evaluation: If there are too many measurable lesions to measure at each evaluation, choose the largest two to be followed before a patient is entered on study. The remaining lesions will be considered evaluable for the purpose of objective status determination. Unless progression is observed, objective status can only be determined when ALL measurable and evaluable sites and lesions are assessed.

9.5 Best Response: This will be calculated from the sequence of objective statuses.

For patients with all disease sites assessed every evaluation period, the best response will be defined as the best objective status as measured according to Section 9.4 If the response does not persist at the next regular scheduled MRI, the response will still be recorded based on the prior scan, but will be designated as a non-sustained response. If the response is sustained, e. g. still present on the subsequent MRI, it will be recorded as a sustained response, lasting until the time of tumor progression. Best response is unknown if the patient does not qualify for a best response or increasing disease and if all objective status determinations before progression are unknown.

9. 6 Neurological Exam: Although not used for determining response, it is useful to evaluate improvement in the neurologic exam, (as compared to the baseline assessment), that should coincide with objective measurement of tumor size.

+1	Better
0	Unchanged
-1	Worse
B	Baseline

9.7 Performance Status: Patients will be graded according to Karnofsky Performance Status (see Appendix 16.2).

9.8 Time to Progression: From date of enrollment in study to the date of first observation of progressive disease, death due to disease (event), or early discontinuation of treatment.

9.9 Overall Survival: Time from initial tumor diagnosis (definitive surgical resection or biopsy) to death from any cause.

10.0 CRITERIA FOR REMOVAL FROM STUDY

10.1 Criteria for Removal from Study:

a. Biopsy sample prior to planned LITT procedure does not meet pathological inclusion criteria.

b. Administration of 6 cycles of salvage therapy with lomustine.

c. Progression of disease (as defined in Section 9.4)

Patients must be followed by MRI and will be removed from study if unequivocal progression (per RANO criteria) is documented after any cycle of treatment. Patients with stable disease, partial or complete response will continue on therapy as defined in Section 6.0.

d. Unacceptable toxicity (see Section 6.10)

e. The patient may withdraw from the study at any time for any reason.

f. Medical or psychiatric illness which in the investigator's judgment renders the patient incapable of further therapy.

g. Treatment delay due to toxicity greater than 8 weeks measured from the start of the preceding cycle.

10.2 All reasons for discontinuation of treatment must be documented in the flow sheets.

11.0 STATISTICAL CONSIDERATIONS

11.1 Overview

In this prospective, single-arm phase II study, we will estimate the disease control rate at 6 months in patients with recurrent GBM, who are treated with LITT and followed by salvage therapy with lomustine.

Simon's optimal two-stage design (Simon, 1989) will be employed to evaluate the effect of the study regimen on disease control rate at 6 months. A disease control rate of 10% or lower is considered a failure and the new regimen will be rejected under this circumstance, and we would like to improve this rate to 25%. Given type I error rate of 0.1 and type II error rate of 0.20, Simon's optimal two-stage design requires to enroll 13 patients in the first stage. Up to 6 months of suspension of accrual is needed to evaluate the disease control in these 13 patients. The study will be stopped and the new regiment will be declared as ineffective if 0 or 1 patient remains disease control at 6 months. The accrual will only continue when at least 2 disease controls at 6 months have been observed, at which time 21 additional patients will be accrued to reach a total of 34 patients. By the end of the study, the null hypothesis will be rejected if 6 or more patients remain disease control and the study regimen will be considered promising. Given these boundaries, the probability of stopping the trial early is 62% and the expected sample sizes will be 21 if the true disease control rate is 10%.

11.2 Toxicity Monitoring

Patients will be monitored by cohorts of 10 patients for severe toxicities (drop in KPS > 20 points which is attributed to the procedure and not amenable to corticosteroids, and/or symptomatic hemorrhage or increased brain edema resulting in herniation/impending herniation attributed to the procedure and not amenable to corticosteroids, and/or National Cancer Institute Terminology Criteria for Adverse Events v4.0 grade of 3-4 attributable to the procedure or procedure and chemotherapy) within 2 weeks + 6 weeks in which period that patients receive the LITT procedure and 1 cycle of chemotherapy (total of 8 to 10 weeks). Specifically, we will stop the trial if there is a high probability of observing the severe toxicity rate TOX_E >30%, i.e., $Pr(TOX_E > 30\%|Data)>90\%$.

Given this rule and the prior for severe toxicity rate as beta(0.3, 0.7), we will stop the study and claim the treatment is too toxic if the number of patients in each group with severe toxicities/total of number of patients treated >= 6/10, 9/20, and 13/30. The operating characteristics of for these stopping rules are in Table 2.

Table 2: Operating Characteristics for the Stopping Rule (5000 Simulations)

True Toxicity Rate	Probability Stop Early	Average Sample Size
0.20	1.4%	33.7
0.30	15.0%	31.7
0.40	52.8%	25.9

11.3 Analysis Plan:

Data of variables of interest including patients' demographic, clinical characteristics, length of hospital stay following LITT, peripheral blood and tumor tissue molecular biomarkers, and inflammatory/immunologic profile will be summarized using standard descriptive statistics, such as mean, standard deviation, median, and range for continuous variables, frequency and proportion for categorical variables. Correlation will be assessed among continuous variables using Pearson or Spearman correlation coefficient, whichever is appropriate. Association between categorical variables will be examined by Chi-Squared test or Fisher's exact test when appropriate. Wilcoxon rank-sum test or Kruskal-Wallis test will be used to examine the difference on continuous variables between or among patient's characteristic groups. Overall survival (OS) and Time to progression (TTP) will be estimated using the Kaplan-Meier method and the comparison between or among patient's characteristic groups will be evaluated by log-rank test. The Cox regression model may be applied to assess the effect of covariates of interest on OS and TTP. The disease control rate at 6 months will be estimated along with 95% confidence intervals. Toxicity data and the long-term steroid requirements will be summarized by frequency tables. KPS and MDASI-BT data will be obtained at baseline, after procedure, and with every imaging visit thereafter. We will summarize the MDASI-BT at each time point using descriptive statistics and evaluate the change of MDASI-BT over time and its correlation with response and/or treatment tolerance using linear mixed models, where random effects will be used to account for within-subject correlations. The radiographic evolution of LITT-treated glioblastoma quantitatively measured by MRI and ABTI, tumor metrics, peripheral blood and tumor tissue molecular biomarkers, and inflammatory/immunologic profile at each time point will be summarized using descriptive statistics and presented graphically and the change of it will also be evaluated using linear mixed models. We may also evaluate the association between the change in peripheral blood/tumor tissue molecular biomarkers/inflammatory/immunologic profile and response status.
Other statistical methods may be applied when appropriate.

References:

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11.4 Evaluability

The study will be conducted as an intent-to-treat study. All patients who had the laser probe

inserted into the brain will be evaluable for inclusion in the analysis, provided that histology confirms recurrent glioblastoma or IDH wildtype-anaplastic astrocytoma (per the criteria outlined in section 12). This is the case regardless of losses before the outcome is measured due to dropout or noncompliance. To be evaluable for inclusion in the toxicity stopping rule patients must have had the laser probe inserted into the brain.

12.0 DISCIPLINE REVIEW

12.1 Pathology Review

a. Following LITT, slides from the biopsy must be submitted for review if not previously done. The purpose of this review is to verify the histologic diagnosis.
b. Biopsy tissue must be verified by the neuropathologist to represent viable glioblastoma (or anaplastic astrocytoma, if IDH-wildtype).
c. For samples representing mixed viable tumor and radiation necrosis, biopsy tissue must be verified by the neuropathologist to contain at least 30% viable, mitotically-active glioblastoma (or anaplastic astrocytoma, if IDH-wildtype) to be considered representative of recurrent disease. If unable to obtain percentage, recurrent disease will be determined per expert opinion of neuropathologist.

12.2 Radiology Review

All MRI scans will be obtained and interpreted at MD Anderson Cancer Center.

13.0 SAFETY ASSESSMENTS AND TOXICITY MONITORING

All patients will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, CNS observations, physical examination findings, and spontaneous reports of adverse events reported to the investigator by patients. All toxicities encountered during the study will be evaluated according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and recorded prior to each course of therapy. Life-threatening toxicities that are unexpected and assessed to be possibly related to the study agent should be reported immediately to the study coordinator, Institutional Review Board (IRB), and those that are unexpected and assessed to be possibly related to the study agents should also be reported to the FDA.

Adverse Device Effect

An adverse device effect (ADE) is an AE related to the use of the study device. This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment or operation, or any malfunction of the medical device. This definition also includes any event from an error in usage or from intentional misuse of the medical device.

Serious Adverse Device Effect

A serious adverse device effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Anticipated Serious Adverse Device Effect

An anticipated serious adverse device effect is an effect which by its nature, incidence, severity or outcome, has been identified in the risk analysis report.

Unanticipated Serious Adverse Device Effect

An unanticipated serious adverse device effect (USADE) is a serious adverse effect, which by its nature, incidence, severity or outcome, has not been identified in the current version of the risk analysis report, protocol or application (including a supplementary plan or application). USADEs are also commonly called unanticipated adverse device effects (UADE), as defined in 21 CFR 812.3 (s).

Device Malfunction

A device malfunction is defined as a failure of a device to meet its performance specification or otherwise perform as intended per IFU.

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded on the Adverse Event Case Report Form and followed as appropriate. An adverse event is any undesirable sign, symptom or medical condition occurring after starting study drug (or therapy) even if the event is not considered to be related to study drug.

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment (any procedures specified in the protocol). Adverse events occurring before starting study treatment but after signing the informed consent form are recorded on the Baseline Evaluations_Adverse Events Case Report Form. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy, and are also recorded on the Adverse Events Case Report Form.

A serious adverse event is any adverse drug experience at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions in a patient who has never had seizure activity in the past that do not result in inpatient

hospitalization, or the development of drug dependency or abuse.

Events not considered to be serious adverse events are hospitalizations for the purposes of this protocol and include:

- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition;
- Treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen;
- Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

Pregnancy, although not itself a serious adverse event, should also be reported on serious adverse event form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.

The study will utilize the Cancer Therapy Evaluation Program (BTTC) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 for Toxicity and Adverse Event reporting.

All serious adverse events that are unexpected and assessed to be possibly related to the study agents must be reported to the FDA by the lead investigator (or their designee) as a 15-day post-marketing 'Alert Report'. An unexpected adverse event is one that is not already described in the study agent Investigator Brochure(s). The lead principal investigator (or their designee) also has the obligation to report serious adverse events to their IRB, This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences.
SAEs should be recorded on a MedWatch Form FDA 3500A. The MedWatch form can be downloaded from the www at:

http://www.fda.gov/medwatch/how.htm

MedWatch 3500A Reporting Guidelines:

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome, if known
- Supportive laboratory results and diagnostics

- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up information:

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted (The subject identifiers are important so that the new information is added to the correct initial report)

Assessing Causality:

Investigators are required to assess whether there is a reasonable possibility that the study agent/s caused or contributed to an adverse event. The following general guidance may be used.

Yes: If the temporal relationship of the clinical event to the study agent/s administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

No: If the temporal relationship of the clinical event to the study agent/s administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

Adverse events will be classified as follows:

- Definitive (certain): conclusive evidence beyond reasonable doubt that the AE can be attributed to radiation and/or temozolomide.
- Probable (likely): evidence is clearly in favor of attributing the AE to radiation and/or temozolomide.
- Possible (indeterminate): evidence is indeterminate for attributing the AE to radiation and/or temozolomide or an alternate cause.
- Not related: conclusive evidence beyond reasonable doubt that the AE can be attributed to causes other than radiation and/or temozolomide.

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15.0 APPENDIX

15.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE version 4.0 for Toxicity and Adverse Event reporting. A copy of the CTCAE version 4.0 can be downloaded from the www at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

15.2 Karnofsky Performance Status (KPS) and Neurological Function

Patient's performance status and Neurologic Functions will be graded according to the following scales:

Karnofsky Performance Status

KPS 100	Normal; no complaints; no evidence of disease
KPS 90	Able to carry on normal activity; minor signs or symptoms of disease
KPS 80	Normal activity with effort; some sign or symptoms of disease
KPS 70	Cares for self; unable to carry on normal activity or do active work
KPS 60	Requires occasional assistance, but is able to care for most personal needs
KPS 50	Requires considerable assistance and frequent medical care
KPS 40	Disabled; requires special care and assistance
KPS 30	Severely disabled; hospitalization is indicated, although death no imminent
KPS 20	Very sick; hospitalization necessary; active support treatment is necessary
KPS 10	Moribund; fatal processes progressing rapidly
KPS 0	Dead

Neurologic Function

+1	Better
0	Unchanged
-1	Worse
B	Baseline

15.3 Summary of specimen requirements and collection

Tissue or Specimen	**Time of Collection**
Plasma	Baseline and then every 6 or 8 weeks.
PBMCs	Baseline, and then every 6 or 8 weeks.
Tumor tissue (also collect plasma and PBMCs)	At the time of surgery

PBMC and Plasma Collection and Processing:
Collect 2-8 mL CPT tubes into a BD Vacutainer CPT™ tube with Sodium Citrate (Becton Dickinson product #362761). Plasma and PBMC aliquots will be generated using standard laboratory processing procedures. Please contact research technician from Dr. de Groot's laboratory when samples are collected. Pager number 713-834-6209, or 713-606-0213.

Tumor tissue collection and processing
At the time of tumor resection, the collaborating neurosurgeon will collect fresh tumor tissue (depending on tissue availability given the likelihood that the patient will have a limited tumor biopsy) along with a sample of patient blood as described above. DNA and RNA will be extracted from tumor tissue and analyzed for genomic alterations, when possible.

15.4 Standard monitoring plan to be used for all Phase II protocols at M. D. Anderson Cancer Center

The Institutional Review Board of the University of Texas M. D. Anderson Cancer Center (Cancer Center) has reviewed and approved the following Data and Safety Monitoring Plan for all Phase I and Phase II clinical trials conducted at the Cancer Center.

During the protocol review and approval process, the IRB determines the level of safety monitoring required for each protocol on a case by case basis. The minimum monitoring requirements include investigator monitoring of patient safety, adverse event (AE) reporting in compliance with IRB, NCI and FDA guidelines and participation in the Continuing Review process with the IRB. For protocols that are determined by the IRB to be of higher risk, the investigator will be required to report on patient safety after treating a small number of patients before being allowed to accrue more participants. This number will be determined at the time the protocol is approved by the IRB. Studies that are blinded, multi-center, high-risk or involve vulnerable populations will be monitored by our Data and Safety Monitoring Board (DSMB). The outcome of IRB and DSMB safety reviews are conveyed to the Principal Investigator (PI) via the administrative support staff in the Office of Protocol Research (OPR).

For all protocols conducted at the Cancer Center, the principal investigator is responsible for submitting AEs to the IRB. The Cancer Center's policy for AE submission has been defined and approved by the IRB and must be included as an appendix to all protocols. AEs are submitted to OPR, entered into the Protocol Data Management System (PDMS) and forwarded to the designated IRB vice chairperson for review. Attached to each AE, is a listing of all prior AEs submitted for that protocol. Any comments, questions or changes the IRB requests to the protocol as a result of this review are conveyed to the investigator. The investigator response and protocol modification process is monitored by the IRB vice chairperson and OPR support staff. The vice chairperson presents the report on AE review to the full committee at the next IRB meeting.

All protocol participants must be registered in the PDMS. Eligibility questions for each protocol are databased and must be answered in the system before it will accept each registration. If any answer indicates the participant does not completely meet eligibility PDMS provides a prompt and an explanation is required. These are reviewed monthly by the Vice President for Research Administration to assure each explanation addresses the appropriate eligibility issue. For NCI sponsored studies, the system does not allow registration of participants with less than complete eligibility. The date in the current informed consent document is displayed to ensure only the most current IRB approved version is used. Consent date, registration date, off study date, and evaluability data are required for all registrants.

15.5 Guidelines for Filing Reports of Adverse Experiences at M. D. Anderson

A. 21 CFR 312.32

Serious Adverse Experience (SAE) –Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity – a substantial disruption of a person's ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Unexpected Adverse Drug Experience - Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. Unexpected, as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

B. MDA Policy and Procedure for reporting of adverse experiences (Includes both commercial and investigational drugs):

- All clinical protocols should include a list of the expected and anticipated events or hospitalizations relating to the study regimen. If an expected or anticipated event is documented in the protocol, then it does not have to be reported as an SAE.

(Example: Expected Grade 4 myelosuppression needs only to be reported as part of the study results)

- All events falling under the definition of serious adverse event that are not listed in the protocol as being expected or anticipated, and occurring within 30 days following the last treatment date, must be reported to the sponsor within the specified time frame stated in the protocol.

- All deaths with possible, probable or definite attribution to the study drug, device, or intervention must have a written report submitted to the Institutional Review Board (IRB) via OPR within one working day (24 hours) of knowledge of the event.

- All serious adverse events other than that stated above must have a written report submitted to the Institutional Review Board (IRB) via OPR within 5 working days of knowledge of the event.

- If necessary, the sponsor is then required to notify the Food and Drug Administration (FDA) within 7 calendar days.

- All unexpected adverse experiences that are classified as Grade 4 must be reported by following the guidelines listed above.

- Known reactions classified as Grades 1-3 do not need to be reported. However, these toxicities should be submitted as part of the study results.

C. Adverse Experience Reporting Forms:

Attached is the MDACC severe adverse event reporting form. This form should be utilized if MDACC is the sponsor, the study is a non-sponsored study, or the sponsor does not provide an appropriate reporting form.

If the study sponsor requires a protocol specific SAE form to be completed, then that form may be use for IRB submission as long as the MDACC protocol number and patient medical record number is written at the top of the front page.

D. External Adverse Experiences / Safety Reports

All external adverse events/safety reports received from the sponsor should be submitted to the IRB through the Office of Protocol Research. The "External Adverse Event Report" can be located under section 1 of the OPR Forms Manual, and should be utilized as the cover sheet for this submission.

15.6 Classification of Tumor Eloquence (from Sawaya et al, 1998)

Grade I: Noneloquent Brain	Grade II: Near-eloquent Brain[a]	Grade III: Eloquent Brain
Frontal or temporal polar lesion	Near motor or sensory cortex Near calcarine fissure	Motor/sensory cortex Visual center
Right parieto-occipital lesions	Near speech center Corpus callosum	Speech center Internal capsule
Cerebellar hemisphere lesions	Near dentate nucleus Near brain stem	Basal ganglia Hypothalamus/thalamus Brain stem Dentate nucleus

[a] Near-eloquent brain, based on preoperative magnetic resonance imaging scans, includes tumors in the supplementary motor area.

15.7 Informed Consent

15.8 Study Calendar

				Salvage Chemotherapy**			End of Treatment	Follow-up10			
				Cycles 1 -6							
	Screening	LITT	Post-LITT clinic visit	Day 1***	Day 15	Day 29		3 Mons	6 Mons	9 Mons	12 Mons
	<28 days prior to registration	≤ 7 days following registration	14 days post-LITT (±3)		± 3 days	± 3 days	±6 weeks	±6 weeks	±6 weeks	±6 weeks	±6 weeks
Eligibility Assessment1	X										
Informed Consent	X										
Medical History Review	X		X	X			X	X	X	X	X
Medications Review	X		X	X			X	X	X	X	X
Serum Pregnancy Test (bHCG)3	X2		X	X							
Physical Exam	X	X	X	X			X	X	X	X	X
Neurological Exam	X	X4	X	X			X	X	X	X	X
KPS	X	X4	X	X			X	X	X	X	X
MRI	X	X5, X6, X7	X	X			X	X	X	X	X
Hematology2	X2		X	X	X	X					
Chemistry2	X2		X	X	X	X					

LFTs	X2		X	X							
MDASI-BT (English)	X		X	X			X	X	X	X	X
NeuroBlate System procedure (LITT/thermal ablation)		X									
Blood sample for corollary studies (5-10 ml)		X8									
Tissue samples for corollary studies		X9									
Lomustine			X*	X							
Adverse Event Assessment		X	X	X	X	X	X	X	X	X	X

	*Lomustine to start between 14-35 days following LITT (at physician's discretion); Tests/procedures (except MRI) indicated under "Day 1" must be repeated if lomustine initiated > 3 days following Day 14 visit
	** Up to 6 cycles of lomustine, on day 1 of a 42 day cycle
	***a) Tests/procedures within 3 days before starting; b) a) Cycle 1 day 1 to start between 14-35 days following LITT; For C1D1, tests/procedures (except MRI) indicated under "Day 1" must be repeated if lomustine initiated > 3 days following Day 14 visit
	1. Recurrent GBM will be confirmed by biopsy prior to or on day of LITT procedure
	2. Labs (including bHCG) should be obtained within 14 days prior to registration
	3. Serum Pregnancy test (bHCG) only required for females of child-bearing potential unless the patient is confirmed as post-menopausal or surgically sterile
	4. Post-operative follow-up neurologic assessment (including KPS) within 48 hours of procedure
	5. Within 24 hours prior to the procedure, the patient will undergo pre-operative trajectory site and skull entry point planning MRI

	6. Intra-op MRI will be completed as part of the LITT set-up
	7. Post-LITT MRI should be completed within 48 hours after LITT procedure
	8. Blood sample to be obtained within 24 hours of procedure, for banking and corollary studies
	9. Pre- and post-ablation biopsy tissue samples, when feasible, for banking and corollary studies
	10. For patients discontinuing therapy for reasons other than tumor progression. Patients who discontinue therapy for tumor progression will be contacted by research staff every 3 months (+/- 14 days) to inquire regarding interim health history(if unable to return for a clinic visit)