Document Coversheet

Title:	Phase II Study of Neoadjuvant Chemoradiation for Resectable Glioblastoma (NeoGlio)
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Phase II Study of Neoadjuvant Chemoradiation for Resectable Glioblastoma (NeoGlio)

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Amendment 04 25July2022

Summary of Changes

PI Change from Dr Anand Mahadevan to Dr Michel Lacroix

Amendment 03 08Apr2022

Summary of Changes

Page 19 Post-Radiation, Post- OP Temozolomide Dosing

Changed Second paragraph, "treatment-related adverse events >grade2" to '>grade 1"

Page 20, under Dose Modifications; deleted 2nd paragraph; added Table 2 to the 3rd paragraph section.

Added Table 1 to support Dose modifications for Temozolomide during Concomitant RT

Page 22, under Dose reductions; first sentence, changed '(by 25mg/sqm)" to (by 50mg/sqm)"

Page 23/24, added Tables 2, 3 and 4 for reference.

Page 25, second paragraph, added 'if known' to G6-PD deficiency reference; 3rd paragraph, deleted reference to CD4 monitoring every 2 weeks, and entire section, "During the adjuvant…";
Added, 'If G-6PD is tested positive, administer Bactrim SS daily or Bactrim DS MWF. Atovaquone may be used in patients with sulfa allergy"

Section 5.6 Study Time and Events Table:

Removed test for CD4 and footer – this is done at physician discretion and is standard care.

Amendment 02 13Jul2021

Summary of Changes

Page 24, Test Table corrections: Moved CD4 to be done at 'Pre-Surgery' and not 'during surgery'; Added footnote 'e' to clarify Adjuvant treatment to be done no later than 4 to 6 weeks from surgery. Added to column header.

Page 17, 18, 19 and 20, corrected 'superscript in lab grading values;

Consent form: The test schedule has been updated to match the protocol V7.13.2021 with the above changes.

Amendment 01 22Feb2021

Summary of changes to Protocol:

Page 1 – Administrative changes

Section 5.4.1 and 5.4.2– Clarified duration of participation to 26 months.

Section 5.5.5 – Clarified Post radiation and post operative TMZ timepoint.

Increased the cycles from 6 to **up to 12**.

Section 5.6 – Clarified CRT weeks from 1-6 to **1-7;** added 'Pre-Surgery' column to clarify timepoints of tests and Questionnaires; removal of Questionnaire timepoints under 'Surgery' ; clarified weeks to Surgery from 8-10 to **8-12**; Clarified Adjuvant Treatment is from one month after surgery to give patients time to heal post surgery.

REDCAP (MDASI-BT): updated details of data collection of adjuvant treatment timepoints to track any dosing changes.

Informed Consent form changes:

Test table, page 3 – updated columns of Weeks 1-6 to *1-7;* Weeks 8-10 to *8-12;* addition of biopsy timepoint and deletion of QOL collection; Addition Pre-Surgery column for MRI ; QOL, AE and blood draw time points; Clarified Adjuvant Treatment column to 'one month after surgery' instead of after 'initiation of RT'; addition of QOL at follow up.

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1 ABBREVIATIONS USED IN THE PROTOCOL

Abbreviation	Term
AE	Adverse event
ASL	Arterial Spin Labelling
CRT	Chemoradiotherapy
EGFR	Epidermal Growth Factor Receptor
EOR	Extent of Resection
GBM	Glioblastoma
GIRB	Geisinger IRB
HGG	High Grade Glioma
IDH	Isocitrate Dehydrogenase
IRB	Institutional Review Board
KPS	Karnofsky Performance Status
MGMT	Methyl Guanine Methyl Transferase
SAE	Serious Adverse Event
TMZ	Temozolamide

2 ABSTRACT

High grade gliomas, particularly glioblastoma, are the most common malignant primary brain tumors in adults(1). Surgical resection, when feasible, offers the best chance of alleviating the mass effect and increasing the likelihood of durable local control. Whether tumors are resected or deemed unresectable, the standard definitive treatment for high grade glioma is involved field radiation with concurrent and adjuvant temozolomide chemotherapy(2). Additional therapy with anti-VEGF therapies(3, 4) and wearable devices such as alternating electric fields(5) have improved progression free and overall survival modestly.

Unfortunately, most patients recur in the region of the primary tumor, ultimately leading to neurological progression and death in a majority of patients(6). One hypothesis for this progression in the region of the primary tumor has been the persistence of resistant clones, including glioma stem cells(7).

Neoadjuvant, preoperative chemo radiation has consistently shown improvements in local disease control or organ preservation in many cancers including head and neck(8), esophageal(9), rectal(10), bladder cancers(11) and sarcomas(12), leading to improvements in overall survival and limb or organ preservation.

Preoperative therapy has not been well studied in resectable glioblastoma. This study attempts to prospectively assess the feasibility and efficacy of preoperative chemoradiation in improving local control, as this is the predominant mode of failure in these patients leading to poor outcomes.

We plan to do this interventional study in two phases using the Simon two-stage Phase II study design(13). Please see section 5.9 on statistical analysis and plan. In the initial stage if there are no more than 3 unanticipated events after 9 patients, an additional 15 patients will be treated in the second stage of this Phase II study. If no more than 9 of the overall 24 patients overall progress in 8 months the study treatment would be considered significant and worthwhile studying in a future randomized phase III study, comparing preoperative study treatment with standard of care post postoperative chemoradiation to evaluate progression free and overall survival as the end point.

3 BACKGROUND AND SIGNIFICANCE

Malignant gliomas are the most common primary central nervous system tumor in adults, and glioblastoma multiforme (GBM) represents the most aggressive and prevalent subtype of these tumors(6). Approximately 12,000 cases of GBM are diagnosed in the United States each year, and the incidence of GBM has been increasing over the past decade, with the peak occurrence after the age of 40(1, 14).

Despite surgery, conventional radiotherapy, and chemotherapy, the median survival for GBM remains poor at approximately 15-16 months in contemporary series(15). Although adjuvant chemoradiotherapy has been shown to increase survival, the predominant pattern of failure remains local(16).

3.1 Surgery

Surgical resection of GBMs after diagnosis is used to relieve mass effect, confirm the diagnosis pathologically, and set the stage for multimodal adjunctive therapy(17). Lacroix et al. reported on the outcomes of 416 patients with newly diagnosed and recurrent GBMs(18). The authors found that an extent of resection of 98% or more was associated with improved survival. More recently, Marko et al. reported the outcomes of 500 newly diagnosed GBM patients undergoing initial resection(19). With modern surgery, significant survival benefits were observed with resection of as little as 78% but increased as the extent of resection approached 100%, at which point median overall survival exceeded 16 months (compared with 12.2 months for the entire cohort).

3.2 Adjuvant Chemoradiation

After surgical resection of all or part of the tumor, radiation therapy with concurrent and adjuvant temozolomide remains the most effective single standard adjuvant treatment for newly diagnosed GBMs(2).

Chemoradiation is often employed to treat unresectable or sub totally resected GBM. Radiating native GBM is not uncommon as many tumors are not safely resectable due to its location in eloquent brain. Also, surgical resection is often performed in patients who recur after initial definitive treatment with chemo radiation. Hence, this approach of

chemoradiation of native glioblastomas and surgical resection after prior chemoradiation is not entirely new. However, planned neoadjuvant chemoradiation prior to immediate surgical resection in glioblastoma is the novel approach.

3.3 Local Failure

Although radiation therapy prolongs median survival, most patients eventually experience infield recurrences that ultimately lead to death. Increasing doses of conventional radiation therapy beyond the standard of 60 Gy is limited by potential toxicity to the normal brain and has not resulted in improved survival(20). Furthermore, complications of radiation correlate directly with the overall target volume treated. In all disease sites comparing preoperative versus postoperative adjuvant radiation, preoperative treatment volumes are consistently smaller. Considering that 90% of recurrences in malignant gliomas are located within 2 cm of the enhancing edge of the original tumor on scans and that the occurrence of multicentric disease or metastatic spread is rare(21), treatments that increase the dose or dose effectiveness to a localized tumor without increasing radiation to the adjacent normal brain tissue are attractive approaches that may improve the therapeutic ratio. However, no significant impact has been made over the last few decades on improvements in local control and survival beyond standard adjuvant chemoradiation. In other disease sites with resectable local disease, where local recurrence is a significant problem, neoadjuvant therapy has consistently shown improvement in local control of up to 50%.

3.4 Neoadjuvant Therapy

Delivering CRT in the neoadjuvant setting has the promise to remedy the pitfalls associated with adjuvant CRT approaches that results in delays and poor compliance. Postoperative complications may limit compliance with adjuvant CRT. Earlier delivery of full-dose CRT therapy to eliminate marginal micro metastatic disease has the potential to decrease the risk of disease progression and improve disease-related outcomes(22). Improved local control and decreased toxicity has been consistently demonstrated with preoperative CRT in esophagogastric(23), pancreatic(24), rectal(25), bladder(26) and soft tissue sarcomas(27) and thereby leading in many instances with improved survival (esophageal and rectal cancer) and organ preservation (larynx and bladder cancer).

3.5 Stem cell hypothesis in Glioblastomas

A promising new approach to treat glioblastoma proposes targeting cancer stem cells. The cancer stem cell hypothesis proposes that cancers derive from a small fraction of cancer cells that constitute a reservoir of self-sustaining cells with the exclusive ability to divide asymmetrically to self-renew and maintain the tumor. These stem-cell-like cancer cells make up just a small fraction of the malignant cells in many solid tumors, but they are solely responsible for propagating the disease in laboratory models. They were first isolated from glioblastomas by the expression of CD133 that marks neural stem and progenitor cells. The existence of glioblastoma stem cells (GSCs) and the discovery of vascular stem cell niches in the normal brain suggest a further sinister role for the tumor vascular bed: the formation of abnormal stem cell niches that maintain the cancer stem cells(28). As well as regulating stem cell proliferation and cell-fate decisions, niches also have a protective role, shielding stem cells from environmental insults. Thus, GSCs are inherently radio-resistant and might be protected further from conventional therapies by factors within the vascular niche, enabling these cells to reform a tumor mass following an initial clinical response(29). Due to intrinsic resistance, there is a suggestion that GSCs are preferentially enriched after traditional chemo radiation. Also, there is emerging data of upregulation of CD133 cell population after standard chemo radiation(30). Treatments aimed to disrupt and remove stem cell niches after standard therapy with surgical resection could prove to be beneficial in glioblastoma outcomes.

4 HYPOTHESIS AND SPECIFIC AIMS

4.1 Hypothesis

After standard treatment of GBM with resection and adjuvant therapy, local failure the dominant pattern of failure. Neoadjuvant therapy consistently provides the potential for improved local control and removal of residual stem cell niches. The hypothesis is that earlier institution of neoadjuvant chemoradiation therapy in GBM would improve local control and potentially overall survival.

Involved field radiation is often employed to treat unresectable or sub totally resected GBM. Radiating native GBM is not uncommon as many tumors are not safely resectable due to its location in eloquent brain. Also, surgical resection is often performed in patients who recur

after initial definitive treatment with chemo radiation. Hence, this approach of chemoradiation of native glioblastomas and surgical resection after prior chemoradiation is not entirely new. However, planned neoadjuvant chemoradiation prior to immediate surgical resection in glioblastoma is a novel approach.

4.2 Specific Aim 1

Feasibility of neoadjuvant therapy in GBM to improve local control (local progression free survival) without significant impact of preoperative chemotherapy and radiation on surgical resection.

4.3 Specific Aim 2

To determine the progression free survival with this approach.
Assess the impact of improvements in local control on overall survival.

5 STUDY DESIGN

5.1 Description

We plan to do this interventional study in two phases using the Simon two stage Phase II study design(13). Please see section 5.9 – Statistical methods. Given the novel approach of an existing treatment scheme, this two-stage design allows for safety and efficacy evaluation to proceed to the complete phase II study.

If the median progression free survival (PFS) in this study, meets significance at the completion of this study, it would form the basis to continue as a randomized phase III study with PFS as the primary study objective and overall survival as the secondary objective.

5.2 Study Population

5.2.1 Approximate Number of Subject

Approximately 30 Geisinger subjects will participate in this initial Phase II study.

5.2.2 Inclusion Criteria

1. Newly diagnosed GBM with histopathological confirmation.

2. Surgically suitable for subtotal or gross total resection as determined by central review.
3. KPS>70
4. No contraindication for chemoradiation.
5. >18 years of age.
6. CBC/differential obtained within 28 days prior to registration, with adequate bone marrow function defined as follows:
    a. Absolute neutrophil count (ANC) ≥ 1,500 cells/mm3;
    b. Platelets ≥ 100,000 cells/mm3;
    c. Hemoglobin ≥ 8.0 g/dl (Note: the use of transfusion or other intervention to achieve Hgb ≥8.0 g/dl is acceptable)
7. Adequate hepatic function within 28 days prior to registration, as defined below:
    a. ALT and AST ≤ 3 x ULN
    b. Bilirubin ≤ 1.5 ULN
8. Negative serum pregnancy test obtained for females of child-bearing potential within 28 days prior to step 2 registration.
9. Ability to get multiplanar contrast enhanced MRI

5.2.3 Exclusion Criteria

1. Recurrent, unresectable or multifocal malignant gliomas.
2. Any site of distant disease (for example, drop metastases from the GBM tumor site)
3. Prior radiation or chemotherapy or radiosensitizers for cancers of the brain and head and neck region; note that prior chemotherapy for a different cancer is allowable (except temozolomide).
4. Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.
5. Patents treated on any other therapeutic clinical protocols within 30 days prior to registration.
6. Inability to undergo MRI (e.g., due to safety reasons, such as presence of a pacemaker, or severe claustrophobia).
7. Severe, active co-morbidity, defined as follows:
    a. Transmural myocardial infarction within the last 6 months prior to registration
    b. History of recent myocardial infarction 1month prior
    c. New York Heart Association grade II or greater congestive heart failure requiring hospitalization within 3 months prior to registration.

d. Serious or non-healing wound, ulcer or bone fracture or history of abdominal fistula, intra-abdominal abscess requiring major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to registration, with the exception of the craniotomy for surgical resection
e. Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration
f. Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for coagulation parameters are not required for entry into this protocol.
g. Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration
h. Acquired immune deficiency syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is because the treatments involved in this protocol may be significantly immunosuppressive with potentially fatal outcomes in patients already immunosuppressed.
i. Any other severe immunocompromised condition.
j. Active connective tissue disorders, such as lupus or scleroderma that in the opinion of the treating physician may put the patient at high risk for radiation toxicity.
k. End-stage renal disease (i.e. on dialysis or dialysis has been recommended).
l. Any other major medical illnesses or psychiatric treatments that in the investigator's opinion will prevent administration or completion of protocol therapy.

5.3 Recruitment

All patients seen by the Neuro-Oncology team in the Geisinger health system for fulfillment of the eligibility criteria will be invited to participate in the study. Nurse coordinators and clinical research staff would identify these patients for screening.

5.4 Study Duration

5.4.1 Approximate Duration of Subject Participation

The median progression-free survival for these patients is in the order of 8-12 months, and the median overall survival is in the order of 14-18 months. Subject participation will be from

registration to progression, death or 26 months after the enrollment of the last study participant. This includes registration, study treatment, postoperative phase, adjuvant therapy, and follow-up.

5.4.2 Approximate Duration of Study

We estimate at least 15 patients a year will be enrolled in this study. With further follow-up of at least 26 months from registration to assess the progression free survival, this Phase II study would be completed in 3 years. The end of the study is the last visit of the last subject or end of collection of data from the patient's electronic health record or whichever is last.

5.5 Procedures

All Procedures including, biopsy, pathology, radiology, radiation therapy, chemotherapy, surgery, adjuvant therapy, follow up and salvage therapy, would be standard of care for this study population and disease. The experimental part of the study would be this selection of resectable patients and sequencing neoadjuvant chemoradiation prior to surgery.

5.5.1 Registration:

Patient registration can occur only after evaluation for eligibility is complete, and eligibility criteria have been met. Patients must have signed and dated all applicable consents and authorization forms.

5.5.2 Imaging

Patients will undergo standard multiparametric baseline MRI imaging at presentation, following biopsy/prior to initiation of chemo radiation, at,Pre-surgery, following surgery, and as otherwise indicated for surgical or therapy planning, then every 2 months after surgery for follow up. Imaging sequences should include a minimum of 2D diffusion-weighted imaging, T2, and FLAIR, imaging as well as 3D-IR GRE T1-weighted imaging before and after intravenous administration of 0.1 ml/kg gadobutrol (Gadavist). Dynamic susceptibility contrast perfusion imaging should be performed whenever possible using an additional 0.1 ml/kg preload injection. For each patient, if possible, serial imaging should be performed on the same scanner on which the baseline scan was obtained.

5.5.3 Immunohistopathological/Molecular Confirmation

Histopathological confirmation of a glioblastoma is required eligibility criteria for the study. This would be performed with routine stereotactic or open biopsy (preferably stereotactic with minimal skin wound). This would be at a standard of care procedure.

Synoptic description should include the presence of necrosis or vascular proliferation in the setting of a malignant glioma. IDH1, MGMT promoter methylation, EGFR amplification, TP53, and ATRX status are minimum requirements in the pathological evaluation.

5.5.4 **Radiation therapy (Standard of care)**

3DCRT and IMRT are allowed. IMRT with a simultaneous integrated boost with Fixed-gantry IMRT, helical tomotherapy, or VMAT can be used. All photon treatments shall be delivered with megavoltage machines of a minimum energy of 6 MV photons. Selection of the appropriate photon energy(ies) should be based on optimizing the radiation dose distribution within the target volume and minimizing dose to non-target normal tissue. Source-to-skin distance for SSD techniques or source-to-axis distance for SAD techniques must be at least 80 cm.

Patients will be treated in a supine position and immobilized with a thermoplastic mask and headrest. Additional immobilization devices such as a bite block are permitted.
A planning CT scan will be obtained of the cranial contents and will be fused with the MRI scans.

Definition of Target Volumes and Margins:
3D Conformal or Sequential IMRT
CTV_4600: CTV to receive 46 Gy in 23 fractions
PTV_4600: PTV to receive 46 Gy in 23 fractions
CTV_6000: CTV to receive 60 Gy in 30 fractions
PTV_6000: PTV to receive 60 Gy in 30 fractions

IMRT Dose painted
CTV_5100: CTV to receive 51 Gy in 30 fractions
PTV_5100: PTV to receive 51 Gy in 30 fractions
CTV_6000: CTV to receive 60Gy in 30 fractions
PTV_6000: PTV to receive 60 Gy in 30 fractions

Margin Definitions
CTV_4600 and CTV_5100 - Either the T2 or FLAIR abnormalities on the MRI scan, inclusive of all contrast-enhancing T1 abnormality on the MRI, plus a margin of 1-2 cm, which may be reduced around natural barriers to tumor growth such as the skull, ventricles, falx, etc. If no

surrounding edema is present, CTV should include MRI enhancement plus a 2-cm margin, with reductions permitted as described above.
CTV_6000 - Contrast-enhancing T1 abnormality plus a margin of 1-2 cm. The CTV_6000 margin may be reduced around natural barriers to tumor growth such as the skull, ventricles, falx, etc.
PTV_4600, PTV_5100- In general the PTV is the CTV plus a geometric 4 mm expansion in all dimensions. PTV may extend beyond bony margins and the skin surface.

Dose Prescription:
>95% of the volume to receive at least 4600cGy (PTV_4600), 5100cGy (PTV_5100) or 6000cGy (PTV_6000) respectively. D95 of up to 95% will be allowed to meet OAR (Organs at risk dose constraints. D95 of 95-90% would a be minor violation. D95<90% is not allowed.

Treatment Planning Priorities
1. Spinal Cord
2. Brain Stem core
3. Brain Stem surface
4. Optic Chiasm PRV
5. Optic Nerve L PRV and Optic Nerve R PRV
6. PTV_4600
7. PTV_6000
8. Brain
9. Retina L and Retina R
10. Lens L and Lens R

For photon IMRT plans, patient specific QA is highly recommended. QA is performed by delivering the plan onto a phantom and measuring the dose using an ion chamber array or other 2D/3D device. Measured dose distribution will be compared to planned dose distribution using a Gamma criterion of 3% dose difference and 3mm distance to agreement. For plans with highly modulated dose distributions a 5% dose difference and 3mm distance to agreement criterion may be used. The pass rate should be at least 90% measured for the entire plan.

Daily image-guided radiation therapy (IGRT) is required for this protocol.

5.5.5 Drug therapy – Temozolomide (Standard of Care)

Refer to the package insert for detailed pharmacologic and safety information of Temozolomide

Dosing

Temozolomide During Concomitant Radiation Therapy

Protocol treatment must preferably begin on the same day as the first fraction of radiotherapy (+/- 48 hours allowed for logistic reasons). Temozolamide will be administered continuously from day 1 of radiotherapy to the last day of radiation at a daily oral dose of 75 mg/m^2 for a maximum of 49 days. The drug will be administered orally daily during radiotherapy, as best tolerated by the patient. During weekends without radiotherapy (Saturday and Sunday), the drug will be taken in the morning. The dose will be determined using actual body surface area (BSA) as calculated in square meters at the beginning of the concomitant treatment. The BSA will be calculated from the height obtained at the pretreatment visit. Capsules of temozolomide are available in 5, 20, 100, 140, 180, and 250 mg. The daily dose will be rounded to the nearest 5 mg.

Post-Radiation – Post Operative Temozolomide

The start of the first cycle will be scheduled as soon as patient recovered from surgery and surgical wound has healed, but no later than 4 to 6 weeks from surgery. After the first post surgery visit to start TMZ (Cycle 1, Month 1), all subsequent cycles (2-12) will be scheduled every 4 weeks (28 days ± 3 days) after the first daily dose of temozolomide of the preceding cycle.

In all treatment arms, temozolomide will be administered orally once per day for 5 consecutive days (days 1-5) of a 28-day cycle, up to 12 cycles. Patients demonstrating continued benefit from the adjuvant temozolomide can continue treatment to a maximum of 12 cycles. The starting dose for the first cycle will be 150 mg/m^2/day, with a single dose escalation to 200 mg/m^2/day in subsequent cycles if no treatment-related adverse events > grade 1 are noted.
28 days (-3/+5) days after the last day of radiotherapy.

The dose will be determined using the BSA calculated at baseline. The BSA will be re-calculated at the pretreatment visit and if a change in more than 10% in weight has occurred, the dose of temozolomide must be adjusted according to the new BSA. Capsules of temozolomide are available in 5, 20, 100, 140, 180, and 250 mg. The daily dose will be rounded to the nearest 5

mg. The exact dose administered should be recorded in the CRF. Each daily dose should be given with the least number of capsules.

Prior to each treatment cycle with temozolomide a complete blood count (CBC) will be obtained (within 72 hours prior to dosing). Patients will be suggested to fast at least 2 hours before and 1 hour after temozolomide administration. Water is allowed during the fast period. Patients will be instructed to swallow the capsules whole, in rapid succession, without chewing them. Treatment should be given at night. If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose.
Antiemetic prophylaxis with a 5-HT3 antagonist is strongly recommended and should be administered 30 to 60 minutes before temozolomide administration.
Patients will be treated with post-radiation post-operative temozolomide for 6-12 cycles unless there is evidence of tumor progression or treatment-related toxicity
Pneumocystis carinii prophylaxis is strongly recommended during the radiation phase
Hepatic toxicity including liver failure has been observed in patients enrolled in clinical studies utilizing temozolomide. In addition, liver toxicity may occur several weeks or more after initiation of treatment or after temozolomide discontinuation. For patients with significant liver dysfunction, the risks and benefits of treatment continuation should be carefully considered.

Dose Modifications
Temozolomide During Concomitant Radiation Therapy
No dose reduction will be made but delay or discontinuation of temozolomide administration will be decided weekly according to hematologic and non-hematologic adverse events (AEs), as specified below. If the administration of temozolomide must be interrupted, the radiotherapy will proceed normally. Missed doses of temozolomide will not be made up at the end of radiotherapy. The total number of days and total dose of temozolomide will be recorded. If the duration of radiotherapy exceeds 7 weeks, then concomitant treatment with temozolomide should be stopped after 49 days of temozolomide treatment. If radiotherapy must be temporarily interrupted for technical or medical reasons unrelated to the temozolomide administration, then treatment with daily temozolomide should continue. If radiotherapy must be permanently interrupted, then treatment with daily temozolomide should stop. Temozolomide can resume with the initiation of the adjuvant phase of treatment. See Table Below:

TABLE 1: Temozolomide Dosing Interruption or Discontinuation During Concomitant Radiotherapy and Temozolomide

Toxicity	TMZ Interruption*	TMZ Discontinuation
Absolute Neutrophil Count	greater than or equal to 0.5 and less than 1.5 x 10^9/L	less than 0.5 x 10^9/L
Platelet Count	greater than or equal to 10 and less than 100 x 10^9/L	less than 10 x 10^9/L
CTC Nonhematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 2	CTC Grade 3 or 4

*Treatment with concomitant TMZ could be continued when all of the following conditions were met: absolute neutrophil count greater than or equal to 1.5 x 10^9/L; platelet count greater than or equal to 100 x 10^9/L; CTC nonhematological toxicity less than or equal to Grade 1 (except for alopecia, nausea, vomiting).
TMZ=temozolomide; CTC=Common Toxicity Criteria.

Adjuvant treatment can be resumed if hematologic adverse events resolve (platelet > 100 x 10^9/L and ANC > 1.5 x 10^9/L) during the interval from the completion of chemoradiation to the time for initiation of adjuvant chemotherapy.
Cases of hepatic injury, including fatal hepatic failure, have been observed in patients enrolled in clinical studies utilizing the agent temozolomide. In addition, it was noted that liver toxicity may occur several weeks or more after initiation of treatment or after temozolomide discontinuation. For patients with significant liver function abnormalities, the risks and benefits of treatment continuation should be carefully considered Reference TABLE 2 below.

TABLE 2: Temozolomide Dose Levels for Maintenance Treatment

Dose Level	Dose (mg/m^2/day)	Remarks
-1	100	Reduction for prior toxicity
0	150	Dose during Cycle 1
1	200	Dose during Cycles 2-6 in absence of toxicity

Post-Radiation Post-Operative (Adjuvant) Temozolomide
Dosing is based on adverse events (AEs) during the prior treatment cycle. If multiple AEs are seen, the dose administered should be based on the dose reduction required for the most severe grade of any single AE.
On day 1 of each cycle (within the prior 72 hours), ANC ≥ 1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L and all treatment-related grade 3 or 4 non-hematologic AEs (except nausea and vomiting unless the patient has failed maximal antiemetic therapy and fatigue) must have resolved (to grade ≤ 1).
If these re-treatment parameters are not met, the treatment will be delayed to a maximum of 4 consecutive weeks. If, after 4 weeks of delay, re-treatment parameters are not met: then any further adjuvant treatment with temozolomide should be stopped.

Dose escalation

If, during the first cycle, all treatment-related non-hematologic AEs observed were grade ≤ 2 (except nausea and vomiting unless the patient has failed maximal antiemetic therapy and fatigue) and with platelets ≥ 100 x 10^9/L and ANC ≥ 1.5 x10^9/L: then the temozolomide dose should be escalated to dose level 1 and this dose should be used as the starting dose for subsequent cycles. If treatment after cycle 1 has to be delayed because of ongoing non-hematologic AEs of grade ≥ 2, then no escalation is possible. If the dose was not escalated at cycle 2, then the dose should not be escalated in further cycles.

Dose reductions

If any treatment-related non-hematologic AE observed was grade > 2 (except nausea and vomiting unless the patient has failed maximal antiemetic therapy and fatigue) and/or if platelets < 50 x 10^9/L and/or ANC < 1 x 10^9/L, then the dose should be reduced by one dose level (by 50mg/sqm – i.e. 150-100mg/sqm)). For patients who would require dose reductions to a dose level < 100 mg/m^2/day, temozolomide will be stopped. Also, if any of the same non-hematologic grade 3 AE recurs (except nausea and vomiting unless the patient has failed maximal antiemetic therapy and fatigue) after reduction for that AE, then temozolomide will be stopped.

If any treatment-related non-hematologic AE observed was grade 4 (except nausea and vomiting unless the patient has failed maximal antiemetic therapy and fatigue) then adjuvant temozolomide treatment should be stopped.

Subsequent cycles (3-12): Any dose reductions of temozolomide will be determined according to (1) non-hematologic AE during the preceding treatment cycle, as well as (2) the nadir (lowest/worst) ANC and platelet counts observed. No dose escalation should be attempted. The same dose reductions as for the second cycle should be applied.

If the dose was reduced or delayed for adverse events, there will be no dose escalation.

The reason(s) for dose reduction and/or delay must be documented. Reference TABLES 2, 3 and 4 below.

TABLE 2: Temozolomide Dose Levels for Maintenance Treatment

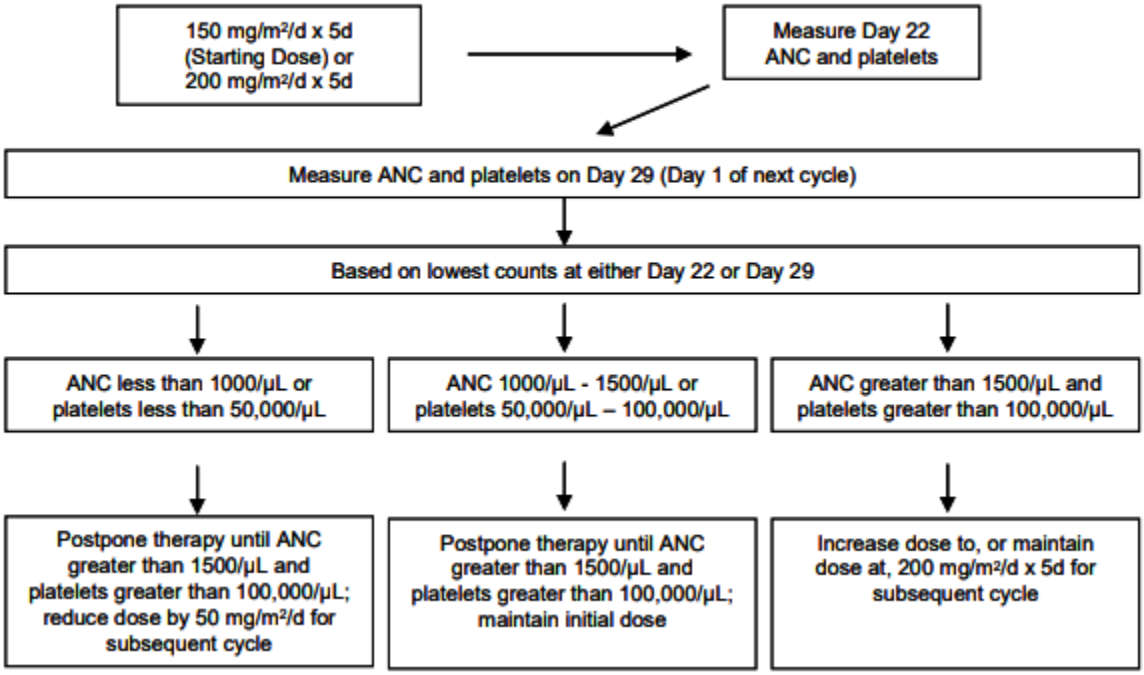
Dose Level	Dose (mg/m^2/day)	Remarks
-1	100	Reduction for prior toxicity
0	150	Dose during Cycle 1
1	200	Dose during Cycles 2-6 in absence of toxicity

TABLE 3: Temozolomide Dose Reduction or Discontinuation During Maintenance Treatment

Toxicity	Reduce TMZ by 1 Dose Level*	Discontinue TMZ
Absolute Neutrophil Count	less than 1.0 x 10^9/L	See footnote†
Platelet Count	less than 50 x 10^9/L	See footnote†
CTC Nonhematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 3	CTC Grade 4†

*TMZ dose levels are listed in **Table 2**.
†TMZ is to be discontinued if dose reduction to less than 100 mg/m^2 is required or if the same Grade 3 nonhematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction.
TMZ=temozolomide; CTC=Common Toxicity Criteria.

TABLE 4: Dosing Modification Table



5.5.7 Other therapies (Standard of Care)

Permitted Supportive Therapy
All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

Anticonvulsants: Anticonvulsants may be used as clinically indicated. The regimen and dosing schedule at study entry and any subsequent changes in the anticonvulsant regimen and/or dosing schedule must be recorded. EIAED use does NOT change dosing of temozolomide.

Corticosteroids: Corticosteroids may be administered at the treating physician's discretion. Doses at study entry must be recorded per Appendix I. The goal is to use the lowest clinically necessary dose of corticosteroids.

Antiemetics: Prophylactic antiemetics may be administered at the treating physician's discretion.

Pneumocystis Carinii Prophylaxis:
Both corticosteroid therapy and continuous temozolomide therapy induce lymphopenia. Patients receiving any of these drugs or both concomitantly are at an increased risk for opportunistic infections.
Therefore, prophylaxis against P. carinii pneumonia is recommended for all patients receiving temozolomide during radiotherapy: trimethoprim-sulfamethoxazole 1 tablet 3 times per week or monthly pentamidine inhalations (300 mg via aerosol monthly) or dapsone 100 mg po each day (except in patients with G6-PD deficiency, if known). Prophylaxis is strongly recommended to continue for the duration of radiotherapy, regardless of the lymphocyte count.

In addition, daily temozolomide has been associated with selective CD4 lymphopenia (Su, Sohn, et al., 2014). Throughout chemoradiotherapy, it is strongly recommended that all patients have CD4 quantification prior to initiation of chemoradiotherapy, at 4 weeks during chemoradiotherapy, at completion of chemoradiotherapy, and in follow up per physician choice. If the CD4 is < 200 prior to or during chemoradiotherapy, then P. carinii prophylaxis is required. If the lymphocyte count is ≥ 500 or the CD4 is > 200, then P. carinii prophylaxis is strongly recommended but not mandatory.
.

If G-6PD is tested positive, administer Bactrim Single Strength once daily or Bactrim Double Strength tablet 3 times weekly(Monday Wednesday Friday). Atovaquone may be used in patients with sulfa allergy.

Non-Permitted Supportive Therapy

Growth factors are not permitted to induce elevations in neutrophil count for the purposes of: (1) administration of temozolomide on the scheduled dosing interval; (2) allowing treatment with temozolomide at a higher dose; or (3) avoiding interruption of the treatment during concomitant radiotherapy.

No other investigational drugs or devices will be allowed.

Surgical procedures for tumor debulking, other types of chemotherapy, and immunotherapy or biologic therapy must not be used. Further, additional stereotactic boost radiotherapy is not allowed. All further therapy is at the treating physicians' discretion but should be recorded in the CRF.

Carmustine wafers, TTF (tumor treating fields) or any form of brachytherapy is not permitted prior to study entry or while the patient is on this study.

5.5.8 Quality of Life assessments:

Symptom Burden
Four subscales (symptom severity, symptom interference, neurologic factor, and cognitive factor score) as well as certain individual items (fatigue, neurologic factor items, and cognitive factor items) of the MDASI-BT will be analyzed. For discrete time point analyses, the change from baseline to each follow-up time point (2, 4, 6, and 12 months from the start of treatment) will be evaluated.

To assess the prognostic ability of baseline symptom severity, symptom interference, fatigue, neurologic factor items, and neurocognitive factor items on time to neurocognitive decline, the cause-specific Cox proportional hazards regression model will be used (Cox 1972).

Assessment of Quality Adjusted Survival
Quality-adjusted survival can be defined by the weighted sum of different time episodes added up to a total quality-adjusted life-year [U= sum of quality (q_i) of health states K times the duration (s_i) spent in each health state] (Glasziou 1990):

$$\mathbf{U} = \sum_{i=1} \mathbf{q_i s_i}$$

We will use Glasziou's multiple health-state (Q-TwiST) models to use the repeated measures of EQ-5D-5L. Because Glasziou's method incorporates longitudinal QOL data into an analysis of quality-adjusted survival, the health stated model must be constructed on the following assumptions:

A1) QOL is independent from treatment.
A2) A health state is independent from previous states.
A3) Proportionality of quality-adjusted duration and duration of the actual state of health

Assumption A1 can be checked by plotting QOL over time according to treatment, and the t-test can be used to compare the mean QOL scores of each treatment arm.
Assumption A2 can be checked by comparing the QOL for patient groups in a given health state where the groups are defined by duration of previous health state experience using a regression model. Suitable checks for assumption A3 at minimum would be a simple plot. If data does not support these assumptions, we will use a method which uses the longitudinal QOL data directly. We will use the 5-item utility score in EQ-5D-5L for the health outcomes analysis.

5.6 Study Time and Events Table

Study Procedure	Screening	CRT	Pre-Surgery	Surgery	Adjuvant Treatment for 12 mos. from 4 to 6 weeks after surgery	Follow-up
Study Interval	Day-1 to -21	Weeks 1-7		Weeks 8-12	Every 2 mos. (28 day cycle)	Every 3 mos. after 12 mos. timepoint
Medical history and Examination	X					X
Screening, Labs, pregnancy	X					
Informed consent	X					
Biopsy	X			X		
Temozolomide Dosing[a]	X				X	
RT Planning	X					
Radiation Therapy + Temozolomide		X				
Surgery				X		
Adjuvant Temozolomide					X[e]	
MRI	X		X		X	X
Weight	X	X		X	X	X
CBC/d[b]	X	X	X	X	X	X
QOL Questionnaires (MDASI-BT)	X		X		X	X
Concomitant medication Review	X	X			X	X
Adverse events Review[d]	X	X	X	X	X	X

a Temozolomide will continue in the adjuvant setting for a total of 12 weeks
b CBC/d weekly during neoadjuvant CRT +/- 3 days, and pre-surgery
c From the time of informed consent to the end of the study, 26 months.
d. Adjuvant Temozolomide (C1) schedule no later than 4 to 6 weeks from surgery

5.7 Primary Endpoints

Phase II Simon Stage 1: No study related undue toxicity or progression in the first stage patients: Toxicity is defined as: progression precluding surgery, unanticipated neurological decompensation, non-completion of neoadjuvant therapy (other than protocol defined dose adjustments or discontinuation), treatment related delay of > 6 weeks to surgery, and/or major unforeseen surgical complication requiring repeat surgical intervention including other than non-life- threatening infection like meningitis/encephalitis or septicemia.

Phase II Stage 2 (Entire Cohort): Progression Free Survival: defined as MRI defined progression (increasing FLAIR, enhancement, diffusion and or perfusion) 3 months after completion of therapy (to allow for excluding pseudo progression) OR clinical progression with new or worsening neurological symptoms related to the tumor (by MRI or clinical correlation with location) and not due to non-tumor or study related symptoms.

5.8 Secondary Endpoints

Overall survival.

5.9 Statistics

The study staff with the assistance of the Biostatistics core, will perform the statistical analysis.

5.9.1 Statistical Analysis Plan

The Simon two-stage design will be used.
The median progression-free survival of these patients with current standard of care therapy is in the range of 6-8 months (6.9 months in the standard of care). With the proposed trial of surgical resection of the tumor after chemotherapy and radiation the median progression free survival is anticipated to be approximately 11-12 months from subset analysis of available literature and based on prior data on other disease sites. In other words, the 7-month local progression rates is anticipated to decrease from 50% to 25%, or progression free survival improve from 50-75%
Due to assessment of unanticipated adverse events with this novel sequencing of established treatment, a Simon two-stage phase II study design would be used to proceed with the study treatment after meeting prespecified events in the initial phase, with goal being to determine whether the new treatment paradigm is sufficiently promising to warrant a major controlled clinical evaluation against the standard therapy

5.9.2 Statistical Power and Sample Size Considerations

In the Simon two-phase design of this study, if:
p0 = progression rate of Standard of care = 0.5 (null Hypothesis)
p1= Progression after study treatment = 0.25
OR
p0= non-progression rate of 0.5
p1= non-progression rate of 0.75
With a
Prespecified Type1 error rate $\alpha \leq 0.05$
Prespecified Power ≥ 0.8

For non-progression being the response:
The null hypothesis that the true response rate p0=50% will be tested against a one-sided alternative. In the first stage n1=11 patients will be accrued. If there are r1=6 or fewer patients responding (i.e. don't progress) in these n1==11 patients, the study will be stopped. Otherwise n-n1=14 additional patients will be accrued to a total of n=25. The null hypothesis will be rejected if r2+1=17 or more responses (If >17 of 25 patients do not progress in 7 months) are observed in the (n=25) patients. This design yields a type 1 error rate of 0.05 and a power of 80% when the true response rate (non-progression at 7 months) is >75%.

After completion of 25 patients followed at least for 7 months of the last patient treated, Primary and secondary endpoints will be evaluated and reported.

5.10 Data Management

5.10.1 Data Collection and Storage

Data will be collected this study team and will be scheduled in partial protected computerized in locked offices.

5.10.2 Records Retention

Study records will be retained for Geisinger policy for the duration of the study and for 6 years thereafter.

6 SAFETY MONITORING

6.1 Adverse Event Reporting

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for adverse event (AE) reporting. The CTCAE version 5.0 is located on the CTEP website at
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm
Clinical adverse events (AEs) will be monitored throughout the study. The date and time of onset and outcome, course, intensity, action taken, and causality to study treatment will be assessed by the study PI. All AEs will be reported to the institutional review board (IRB) per the Unanticipated Problem Policy Definitions
Given the nature and end points of the feasibility part of the study, the PI would report every 3 months to an independent Data Safety Monitoring Board (DSMB) from the Cancer Institute who will review the AE data.
An **adverse event** (AE) is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiologic observations occurring in a person given a drug or test in a clinical study.
All treatment interventions in this study are standard of care.

Radiation Therapy Adverse Events
Acute
Expected adverse events include hair loss, fatigue, and erythema or soreness of the scalp. Potential acute toxicities include nausea and vomiting as well as temporary aggravation of brain tumor symptoms such as headaches, seizures, and weakness. Reactions in the ear canals and on the ear should be observed and treated symptomatically; these reactions could result in short-term hearing impairment. Dry mouth or altered taste has been occasionally reported.
Early Delayed
Possible early delayed radiation effects include lethargy and transient worsening of existing neurological deficits occurring 1-3 months after radiotherapy treatment.
Late Delayed
Possible late delayed effects of radiotherapy include radiation necrosis, leukoencephalopathy, endocrine dysfunction, and radiation-induced neoplasms. In addition, neurocognitive deficits, which could lead to mental slowing and behavioral change, are possible. Permanent hearing impairment and visual damage are rare. Cataracts can be encountered.

Temozolamide side effects are elaborated under drug therapy.

A **serious adverse event** (SAE) is an AE that:

- Results in death.
- Is life-threatening (see below).
- Requires inpatient hospitalization or prolongation of an existing hospitalization (see below).
- Results in a persistent or significant disability or incapacity (see below).
- Results in cancer.
- Results in a congenital anomaly or birth defect.
- Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Life-threatening refers to immediate risk of death as the event occurred per the reporter. A life-threatening experience does not include an experience, had it occurred in a more severe form, might have caused death, but as it actually occurred, did not create an immediate risk of death. For example, hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life-threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.

Hospitalization is official admission to a hospital. Hospitalization or prolongation of a hospitalization constitutes criteria for an AE to be serious; however, it is not in itself considered an SAE. In absence of an AE, a hospitalization or prolongation of a hospitalization should not be reported as an SAE by the participating investigator. This is the case in the following situations:

- The hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol.

- The hospitalization or prolongation of hospitalization is part of a routine procedure followed by the center (eg, stent removal after surgery). This will be recorded in the study file.

In addition, a hospitalization for a preexisting condition that has not worsened does not constitute an SAE.

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions.

If there is any doubt about whether the information constitutes an SAE, the information is treated as an SAE.

A **protocol-related adverse event** is an AE occurring during a clinical study that is not related to the study treatment but is considered by the investigators to be related to the research conditions, ie, related to the fact that a subject is participating in the study. For example, a protocol-related AE may be an untoward event occurring during a washout period or an event related to a medical procedure required by the protocol.

6.2 Recording and Reporting

A subject's AEs and SAEs will be recorded and reported from the signing of the informed consent form to withdrawal from study or death.

6.3 Unanticipated Problem reporting

Dr Michel Lacroix, the study PI will notify GIRB of all study SAEs in accordance with policy guidelines. If an SAE has not resolved at the time of the initial report, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) will be submitted to GIRB. An SAE will be followed until either resolved or stabilized.

7 PROTECTION OF HUMAN SUBJECTS

7.1 Informed Consent

The investigator will provide for the protection of the subjects by following all applicable regulations. The informed consent form will be submitted to the IRB for review and approval. The following conditions would not apply:

- Assent, alteration or waiver of authorization, waiver of consent, waiver of consent, or waiver of documentation of consent
- Subjects who do not have adequate capacity to give consent

Before any procedures specified in this protocol are performed, a subject must:

- Be informed of all pertinent aspects of the study and all elements of informed consent.
- Be given time to ask questions and time to consider the decision to participate.
- Voluntarily agree to participate in the study.
- Sign and date an IRB-approved informed consent form.

7.2 Protection of Human Subjects Against Risks

All the interventions in this study are standard of care. Hence there are no treatment related study related risks. However, there may be unforeseen the risks due to the sequence of treatment which is novel in this study. The purpose of this prospective study is to analyze if sequencing of standard of care makes is safe and could make a favorable difference as it has in other malignancies.

There are always potential risks related to loss of confidentiality (e.g., loss of insurance or employment, etc.) and all standard precautions will be taken to minimize the risks (eg. password protected files, encryption, locked cabinets)

7.3 Data Monitoring Plan

The initial Feasibility Phase of the study may be limited to 10 patients. If 3 or more of these patients experience unexpected toxicities, the study will be discontinued. A data monitoring committee formulated specifically for the study would review the project from the Feasibility Phase to Phase II of the project.

8 PUBLICATION PLAN

Data analysis from the completion of the feasibility phase and the Phase II study will be presented in national and international meetings and presented for publication in peer reviewed journals.

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