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A Phase II Trial of Low Dose Fractionated Radiation Therapy as a Chemo-Potentiator of Salvage Temozolomide for Recurrent Anaplastic Astrocytoma and Glioblastoma Multiforme

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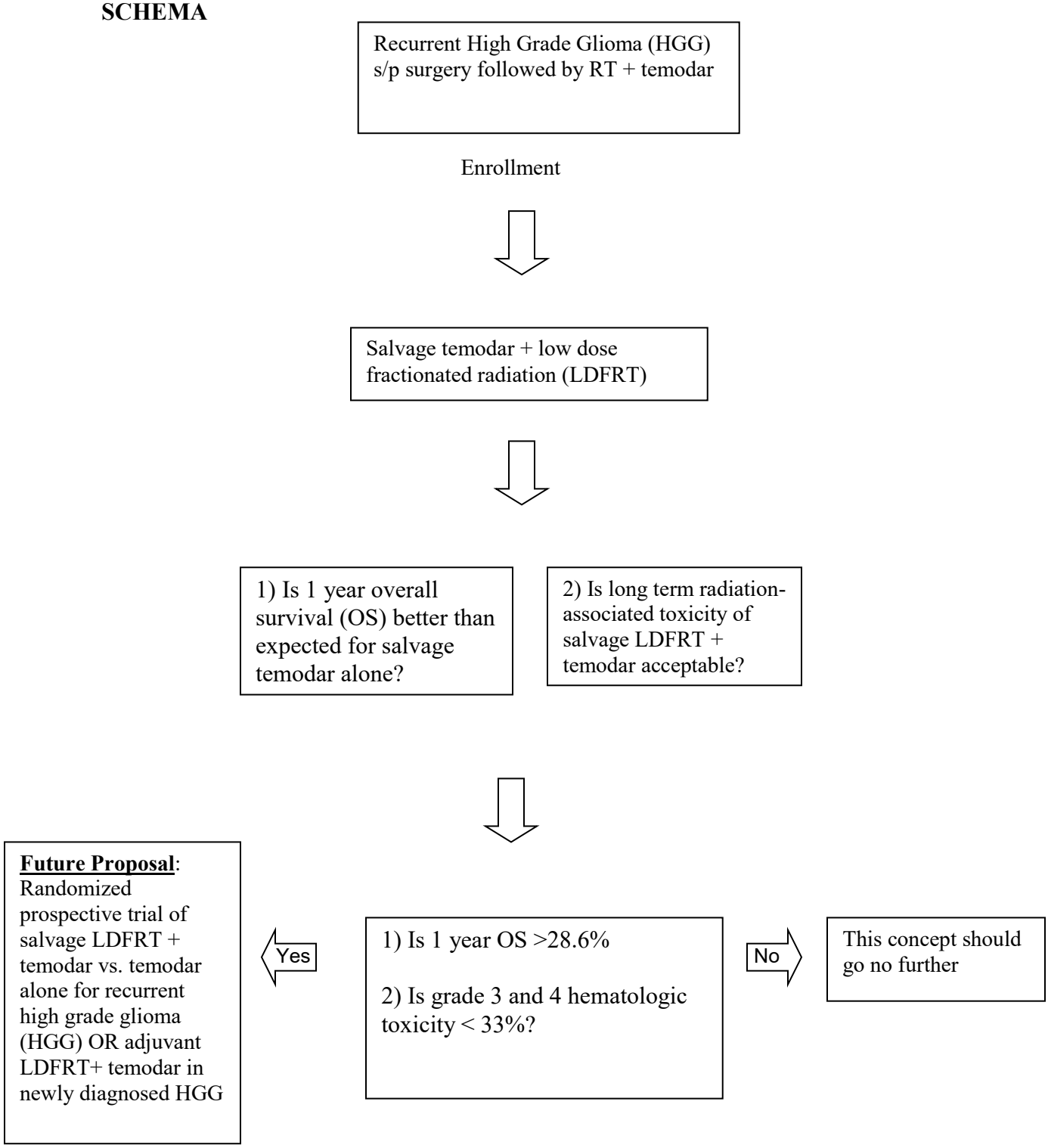
SCHEMA



For the purpose of this clinical trial High Grade Glioma (HGG) will only include Anaplastic Astrocytoma and Glioblastoma Multiforme.

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1.1.2 Secondary Objectives

To estimate the acute and late radiation-associated neurologic toxicity of salvage LDFRT + temozolomide.

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2. BACKGROUND

2.1 Study Disease

High grade glioma (HGG) is one of the most lethal forms of human cancer (1). The standard of care at the time of initial diagnosis of HGG consists of surgical resection followed by adjuvant radiation therapy and temozolomide chemotherapy, based on

the results of a randomized controlled trial which demonstrated a significant improvement in overall survival with the addition of temozolomide to adjuvant radiation therapy alone (1). Although this study was performed in patients with GBM, the results are widely applied to patients with anaplastic astrocytoma (AA) who are treated with the same paradigm. Despite recent advances in the treatment of HGG, the diagnosis remains essentially incurable and the tumor will recur in the vast majority of patients.

Management of patients with recurrent HGG remains controversial. Accepted treatment options include temozolomide alone, repeat radiation therapy with concurrent temozolomide, or a clinical trial. The response rate to second line therapies is limited and when effective the durability of response is generally poor. Improvements in salvage therapeutic options for HGG are therefore critical.

2.2 LDFRT Rationale

Numerous studies have shown that the slope of the cell survival curve is greater at very low doses of radiation than at the higher doses of radiation which are conventionally employed in the clinic (2-8). The mechanism behind this phenomenon known as hyper-radiation sensitivity appears to be two-fold. First, low doses of radiation do not induce cellular repair mechanisms such as ATM and mismatch repair that are typically activated with clinically relevant doses of radiation (2,9,10). Second, very small fractions of radiation manage to induce pro-apoptotic pathways without inducing pro-survival cascades that are activated with higher doses (11,12). Studies have shown that hyper-radiation sensitivity persists following multiple fractions of radiation (13) and that the effect is greatest in cells in the G2/M phase. Experiments in glioma cell lines have suggested that the point of maximum radiation hypersensitivity occurs with fractions of approximately 0.4-0.5 Gy.

In spite of these data, low dose fractionated radiation therapy (LDFRT) is not typically employed in the clinic because in order to use it as a primary modality, patients would need to be treated with multiple fractions of radiation per day for many months, and this is not feasible. However, in vitro and in vivo studies have suggested that LDFRT may be used to potentiate full dose chemotherapy, decreasing the development of resistance found with standard doses of radiation and chemotherapy (11-14). Recent data in U87 glioblastoma cells suggest that LDFRT may be used to sensitize cells to the effects of temozolomide. Specifically, Gupta et al. (15) demonstrated that the slope of the cell survival curve is greater following treatment with temozolomide plus LDFRT (0.5 Gy x 4 fractions, 8 hours apart) compared with temozolomide plus 2 Gy of radiation. The mechanism behind this effect remains to be elucidated.

The concept of low dose fractionated radiation therapy as a chemotherapy-sensitizer has been previously evaluated in humans in the context of early phase clinical trials in other disease sites, and the results have been optimistic. Arnold et al. (16) performed a phase II trial in patients with stage III and IV squamous cell carcinoma of the head and neck in which they used 0.8 Gy fractions of radiation twice daily to sensitize patients to induction chemotherapy with carboplatin and taxol. They enrolled forty

patients and report an overall response rate of 82% (13% complete response, 69% partial response), which is better than otherwise expected. In addition, they performed a second phase II trial in the same patient population using 0.5 Gy fractions of radiation twice daily to sensitize cells to carboplatin and taxol, and again report a favorable overall response rate of 88% (38% complete response, 50% partial response) (16). The authors propose further evaluation of the regimen in a randomized controlled trial.

Similarly positive results using LDFRT for chemotherapy sensitization were reported by Regine et al. (17) who performed a phase I/II trial of LDFRT plus gemcitabine in patients with unresectable or metastatic gastrointestinal tumors. The median overall survival time was 10 months, which is better than historical data might predict for these aggressive tumors.

A recent phase 2 trial evaluated ultrafractionated radiation therapy (3 daily doses of 0.75 Gy to a total dose of 67.5 Gy) without temozolomide in patients with newly diagnosed unresectable GBM (Beauchesne 2010). The results of this study were optimistic with no grade III or IV CNS toxicity, and PFS and OS which were superior to conventional RT alone based on historical controls.

Given the promising preclinical and clinical data, the purpose of this trial is to examine the safety and efficacy of LDFRT as a chemo-potentiator of temozolomide in patients with recurrent HGG.

2.2 Temozolomide

Temozolomide is a chemotherapeutic agent which is a standard component of treatment of patients with both newly diagnosed and recurrent HGG. The drug is an orally administered alkylating agent that interferes with DNA replication in a schedule-dependent manner. The therapeutic benefit of the drug depends on its ability to alkylate or methylate DNA at the N-7 or O-6 position of guanine residues, which results in DNA damage and cell death. Some tumor cells produce an enzyme called O-6-methylguaninine methyltransferase (MGMT) which repairs the DNA damage and decreases the therapeutic benefit of temozolomide (18). Epigenetic silencing of MGMT by some tumor cells prevents synthesis of the enzyme resulting in tumors that are more sensitive to killing by temozolomide. Similarly, MGMT presence in HGG cells predicts for poor response to the drug. Toxicities associated with temozolomide include nausea, vomiting, infertility, teratogenicity, alopecia, fatigue, headache, constipation, anorexia, convulsions, rash, hemiparesis, diarrhea, asthenias, fever, dizziness, coordination abnormal, viral infection, amnesia, insomnia, lymphopenia, thrombocytopenia, neutropenia, and leucopenia, allergic reactions.

2.3 Amendment February 2017:

The hypothesis of this study is low dose radiation hypersensitivity wherein very low doses of radiation in the range of 0.3-0.8 Gy actually demonstrate greater cell kill than more traditional radiation doses in the range of 1.8-3 Gy, seemingly because pro-

apoptotic pathways are activated while damage repair pathways are not (2-8).

To date, a total of 22 patients have been enrolled. Unexpectedly, the majority of patients have experienced substantial increases in contrast enhancement and edema as a result of treatment, which have then stabilized for many months. Figure 1 shows an example patient. Note the increase in contrast enhancement and edema at 3 months which then stabilizes and is markedly improved at month 11.

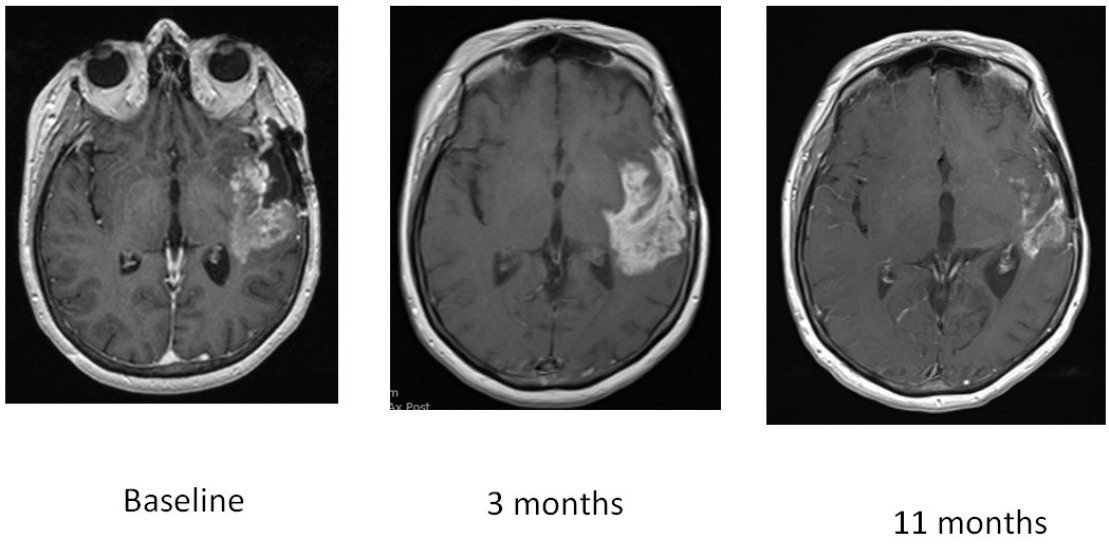

Figure 1: T1 post-gadolinium MRI images at baseline, 3 months and 11 months following initiation of management accordingly to J11120.

The phase 1 component of the study is completed and all patients are being treated according to cohort 1. In general patients have tolerated treatment well with 5 patients with SAEs attributable to the study treatment (fatigue in 2 patients, and lymphocytopenia, aphasia, cognitive disturbance each in 1 patient). Two of 22 patients had pathologically confirmed radionecrosis.

This unanticipated pseudo-progression type response renders our original primary objective of response rate inappropriate. With this amendment we wish to change the primary objective to one year overall survival and enroll the remaining nine patients. The current one year OS is 45.1% (80% CI: 28.2%, 60.9%), the median OS is 9.5 months (median follow-up of 12.7 months) and the median PFS is 4.0 months. Given that patients on this trial have been treated without any severe toxicities, it would be informative to determine if it is possible that there may be a delayed treatment effect that would indicate further study was warranted. Since overall survival is the most definitive endpoint for a clinical trial, we would like to estimate this outcome with the full sample size of 31 and potentially use this information as a reference in a future

clinical trial.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have recurrent GBM or anaplastic astrocytoma.

3.1.2 The diagnosis of GBM or anaplastic astrocytoma must be histologically confirmed.

3.1.3 Patients must have been previously treated with surgical resection (any extent okay) and radiation therapy plus temozolomide

3.1.4 Patients must be at least 12 months from completion of radiation therapy (to be consistent with the "rechallenge" group from Perry et al. JCO 2010 where the median time from completion of adjuvant radiation therapy to the time of progression was 19.69 months).

3.1.5 At least 2 months from completion of temozolomide (to be consistent with the the "rechallenge" group from Perry et al. JCO 2010)

3.1.6 Because no data regarding the effects of LDRT in patients <18 years of age, children are excluded from this study but will be eligible for future pediatric trials. 18 years.

3.1.7 ECOG performance status $\leq$2 (Karnofsky $\geq$60%, see appendix A).

3.1.8 There must be measurable disease on MRI.

3.1.9 Patients must have normal organ and marrow function as defined below:

- leukocytes	$\geq$3,000/mcL
- absolute neutrophil count	$\geq$1,500/mcL
- platelets	$\geq$100,000/mcL
- total bilirubin	within normal institutional limits
- AST(SGOT)/ALT(SGPT)	$\leq$2.5 X institutional upper limit of normal
- creatinine	within normal institutional limits
OR	
- creatinine clearance	$\geq$60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

3.1.10 If a woman is of child-bearing potential, a negative urine or serum pregnancy test must be demonstrated prior to treatment. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) for the duration of study participation and

for up to 12 weeks following the study. Should a women become pregnant or suspect she is pregnant while participating in this study she should inform her treating physician immediately.

3.1.11 Ability to understand and the willingness to sign a written informed consent document.

3.1.12 Temozolomide re-treatment is planned by the treating neuro-oncologist.

3.1.12 The most recent brain tumor pathology obtained for the patient must be glioblastoma or anaplastic astrocytoma.

3.2 Exclusion Criteria

3.2.1 Patients who are unable to receive MRIs will be excluded from the study since MRIs will be critical in monitoring the efficacy of therapy.

3.2.2 Patients may not be receiving any other investigational cancer treatment agents at the time of enrollment.

3.2.3 Patients may not have previously failed treatment with salvage temozolomide.

3.2.4 Patients may not have previously failed treatment with a VEGF inhibitor.

3.2.5 Patients may not have previously been treated with >1 course of radiotherapy to the brain.

3.2.6 Patients may not have previously been treated with radiosurgery to the brain.

3.2.7 Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.8 Pregnant and/or breastfeeding women are excluded. Women of child-bearing potential who are unwilling or unable to use and acceptable method of birth control to avoid pregnancy for the entire study period and up to 12 weeks after the study are excluded. Male subjects must also agree to use effective contraception for the same period as above.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

Eligible patients will be entered on study centrally at the Johns Hopkins Hospital by the Study Coordinator.
To register a patient, the following documents should be completed by the research nurse or data manager and sent to the Coordinating Center Study Coordinator via fax or email.

- Copy pathology report
- Source documentation verifying eligibility
- Eligibility checklist
- Signed patient consent form
- HIPAA authorization form

If the patient is deemed eligible for the study, the Study Coordinator will register the patient and assign a study number.

5. TREATMENT PLAN

5.1 Temozolomide

All patients will receive temozolomide (150 to 200 mg per square meter for 5 days during each 28 day cycle) for a total of 1 year or until the time of disease progression. After one year of follow-up, further chemotherapy or biologic therapy is permitted at the provider's discretion. Therapy will be recorded, but the patient will not be removed from the study. Risks of temozolomide include nausea, vomiting, infertility, teratogenicity, alopecia, fatigue, headache, constipation, anorexia, convulsions, rash, hemiparesis, diarrhea, asthenias, fever, dizziness, coordination abnormal, viral infection, amnesia, insomnia, lymphopenia, thrombocytopenia, neutropenia, and leucopenia, allergic reactions.

5.1.1 Therapy Modifications

Delay, reduction, or discontinuation of temozolomide administration will be decided according to hematological and non-hematological adverse events (AE), as specified below. If the administration of temozolomide has to be interrupted, radiotherapy will be delayed, as well. Missed doses of temozolomide will not be made up after the end of radiotherapy. Blood work will be checked weekly, based on the discretion of the treating Medical Oncologist.

If radiotherapy has to be temporarily interrupted for technical or medical reasons, unrelated to the temozolomide administration, then treatment with temozolomide may continue.

5.2 Low Dose Fractionated Radiation Therapy (LDFRT)

All patients will receive 0.5 Gy of radiation therapy twice daily (at least 6 hrs. apart). This study will include a safety run-in component. If > 33% of patients in the initial cohort of 6 experience grade 3 or greater hematologic toxicity (attribution of possible or above) according to the NCI Common Toxicity Criteria version 4, then a dose reduction will occur following the schedule listed below. Otherwise, following a 1 month waiting period after the first cycle of adjuvant LDFRT plus temozolomide for the first cohort of patients, the phase 2 study will open for full accrual. Patients will receive radiation with the first six 28-day cycles of temozolomide.

Safety Run-in Dose Reduction Schedule	
Cohorts	Radiation Schedule
Cohort 1	0.5 Gy bid on days 1-5 of temozolomide
Cohort 2	0.5 Gy bid on days 1-4 of temozolomide
Cohort 3	0.5 Gy bid on days 1-3 of temozolomide
Cohort 4	0.5 Gy bid on days 1 & 2 of temozolomide

6 patients will be enrolled in the initial cohort. Dose reduction will occur if >2 patients experience dose limiting toxicity.

5.2.1 **Definition of Dose-Limiting Toxicity**

Toxicity will be recorded according to the NCI Common Toxicity version 4. Dose limiting toxicity will be considered grade 3 or greater hematologic toxicity (attribution of possible or above) according to this scale. The criteria are available online at the Cancer Therapy Evaluation Program website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

5.2.2.1.Radiation Treatment Planning

5.2.2.1 Simulation

All patients will undergo CT simulation preferably with intravenous contrast. In addition they will undergo MRI simulation with T1 with gadolinium sequence. They will be treated in a supine position using an aquaplast mask system for immobilization. CT image data will be reconstructed in approximately 3 mm slice thickness and manually co-registered with the T1 post-gadolinium MRI.

5.2.2.2 Target Delineation

The gross tumor volume (GTV) will be contoured using the simulation CT scan and fused T1 with gadolinium sequence MRI. The clinical tumor volume (CTV) will include the GTV plus approximately 0.5-1.5 cm margin. The planning tumor volume (PTV) will include the CTV plus approximately 0.5 cm margin.

5.2.2.3 Normal Tissues

Organs at risk including the eyes, lens, optic nerves, optic chiasm, brainstem, and spinal cord will be contoured on the planning CT scan. Dose to adjacent structures will be limited as much as possible and dose will be recorded. All patients will have been previously irradiated, however the maximum dose delivered in this protocol will be 30 Gy in 0.5 Gy fractions which is below the radiation tolerance typically allowed in patients undergoing repeat irradiation for HGG.

5.2.2.4 Equipment

Patients will be treated using a megavoltage linear accelerator with nominal beam energy of 6 MV.

5.2.2.5 **Beam Verification**

Either daily on-line cone beam CT guidance or weekly portal imaging will be used for precise patient setup.

5.2.3 **Therapy Modifications**

For radiation therapy interruptions of up to and including 14 days, irradiation should be completed to the full prescribed dose. On the last day, the total number of fractions and the reasons for interrupting therapy must be documented.

If radiation therapy interruption goes beyond 14 days, the patient will be removed from the protocol treatment. Resumption and completion of additional radiation or chemotherapy treatment will then be at the discretion of the treating medical oncologist and radiation oncologist.

Treatment may be postponed for re-evaluation of disease. Participants may require further biopsies to confirm disease status. If results reveal stable disease, participants will continue protocol intervention.

5.2.4 **Risks of Radiation**

Short term toxicities of radiation therapy include fatigue, alopecia, erythema or irritation of the skin, dry skin, headaches, worsening of current symptoms, edema of brain requiring steroids, ear pain or discomfort, damage to the baby if patient is or becomes pregnant, seizures, neurologic deficits depending on tumor location, edema of brain requiring surgery, death. Long term toxicities include memory loss, cataracts, edema of the brain requiring steroids, vision loss, hearing loss, necrosis of brain requiring surgery second tumor or cancer caused by radiation.

5.3 **Duration of Therapy**

In the absence of treatment delays due to adverse events, LDFRT will be administered with the first 6 cycles of temozolomide and temozolomide will continue for a total of 1 year and or until one of the following criteria applies:

X Disease progression,

X Intercurrent illness that prevents further administration of treatment,

X Unacceptable adverse event(s),

X Patient decides to withdraw from the study, or

X General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.4 Duration of Follow Up

Patients will be followed until the time of death or until circumstances prevent the patient from presenting for additional follow-up.

5.5 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.3 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form. Patients will continue to be followed for overall survival. Data from medical oncology, including MRI reports and additional chemotherapy, will be collected until time of death.

6. CORRELATIVE/SPECIAL STUDIES

Not applicable.

7. STUDY CALENDAR

See Appendix D. Baseline evaluations and imaging are to be conducted within 4 weeks prior to start of protocol therapy. Every effort should be made to adhere to the protocol timeline as closely as possible, but if studies are delayed or missed as a result of unavoidable conflicts such as hospitalization at an outside facility, deteriorating of patient status, or other adversity precluding presentation for evaluation, it will not be considered a protocol deviation. Toxicity assessments that cannot be done in person will be completed over the phone.

In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for in person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

8. MEASUREMENT OF EFFECT

Patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated approximately every 8 weeks.

8.1 Antitumor Effect

Response and progression will be evaluated in this study using the international criteria proposed by the Response Assessment in Neuro-Oncology Working Group (RANO) (19).

8.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with LDFRT.

Evaluable for objective response. Only those patients who have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

8.1.2

8.1.3 Methods for Evaluation of Disease

All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to evaluate patients at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

MRI: T1 with gadolinium, T2 and FLAIR sequence MRI techniques should be performed with cuts of 5 mm or less in slice thickness contiguously.

Corticosteroid use: Dosages of corticosteroids will be recorded at baseline as well as follow-up visits and will be incorporated into the response criteria.

Clinical examination: Neurologic deficits and symptoms will be recorded at baseline as well as follow-up visits and will be incorporated into the response criteria.

8.1.4 Progression-Free Survival

Progression free survival will be measured from the date of initiation of salvage treatment to the date of documented progressive disease according to the RANO criteria (19).

8.1.5 Overall Survival (OS)

OS is defined as the duration of time from start of treatment to time of death from any cause.

8.1.6 Pseudo-progression

Pseudo-progression will be defined and MRI changes including T1 post-gadolinium, T2 or T2 variants such as FLAIR imaging, with or without clinical deterioration and/or increase in dexamethasone dose which stabilizes or reverses on later evaluations without a change in oncologic intervention.

8.1.7 **Toxicity**

Toxicity will be monitored according to the criteria outlined in section 5.2.1.

9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

9.1.1 **Study Design**

This is a nonrandomized, open label, single institution phase II trial with a safety run-in to evaluate the safety and efficacy of LDFRT plus temozolomide in patients with recurrent HGG previously treated with surgical resection followed by adjuvant radiation therapy plus temozolomide.

The original primary objective of this study was response rate where a CR+PR rate below 10% was considered clinically insignificant whereas a CR+PR rate above 25% was considered clinically significant using the temozolomide re-challenge group B3 of the Perry et al. JCO 2010 study as a comparator. Response rate was considered an appropriate primary objective since this was considered a predominantly chemotherapy based trial. We did not anticipate radiation-induced MRI changes (pseudo-progression) given the very low doses of radiation that are prescribed in this clinical trial.

As of 2/10/2017, 22 patients had been treated on study. At the time of the interim analysis, there were no clinical responses. Given the unexpected number of patients experiencing pseudo-progression on this study, and the possible implications of this for assessing response rate or progression free survival (PFS), the primary objective of this study is being changed to one year overall survival (OS). The current one year OS is 45.1% (80% CI: 28.2%, 60.9%). The median OS at this time is 9.5 months with a median follow-up of 12.7 months. When stratifying by tumor type there is no statistically significant difference in outcomes by group. The 17 patients with glioblastoma have a 1 year overall survival of 33% (80% CI: 13%-79%) and the 1 year overall survival for the 5 patients with anaplastic astrocytoma is 60% (80% CI: 13%-79%). These data suggest that early termination of the study due to futility is not warranted and support the revision of the primary endpoint to allow completion of the study with the originally intended sample size.

9.1.2 Endpoints

9.1.2.1 Safety Run-In

9.1.2.1.1 Primary Endpoint

Dose-limiting toxicity (DLT) is defined as hematologic toxicity during the month following cycle #1 of temozolomide plus LDFRT grade ≥3 by NCI common toxicity criteria version 4. All patients who receive any amount of LDFRT will be evaluable for toxicity. The recommended phase II dose will be the highest dose yields ≤ 33% DLT rate.

9.1.2.1.2 Secondary Endpoint

Radiation-associated neurologic toxicity of LDFRT plus temozolomide using the RTOG/EORTC acute (≤3 months) and late (>3 months) radiation morbidity scoring criteria at 3, 6 and 12 months following completion of therapy. Since the total radiation dose to the brain is low and delivered in very small fractions, the likelihood of radiation associated toxicity is expected to be low. The radiation-induced necrosis rate is less than 5% in patients with recurrent gliomas re-irradiated to a median dose of 36 Gy using conventional 2 Gy fractions (Combs JCO 2005). However, we will be collecting late radiation toxicity data and if there are four patients with radiation related symptomatic necrosis believed to be a result of the LDFRT, the trial will be suspended to accrual and a safety review by the institutional DSMB will be requested.

9.1.2.1 Phase II

Amended Primary Objective: Estimate one year OS in patients treated with LDFRT + temozolomide for recurrent GBM.

9.1.2.1.1 Primary Endpoint: OS will be measured from initial salvage starting date to the date of death.

9.1.2.1.2 Secondary Endpoints:

9.1.2.1.1.1.1 **PFS-6:** The definition of progression will be based on RANO criteria (19). Progression free will be measured from initial salvage starting date to the date of progressive disease is defined (documented).

9.1.2.1.1.1.1 Occurrence of pseudoprogression at any time point will be recorded as a binary variable for each patient (yes/no)

9.1.2.1.1.1.2

Use NCI common toxicity criteria (version 4, see section 5.2.1) to record the toxicity of LDFRT plus temozolomide for each patient associated with the treatment. All patients who receive any amount of LDFRT will be evaluable for toxicity.

1.2.1.1.1.3 Use the RTOG/EORTC acute and late radiation morbidity scoring criteria (see appendix B and C) to record the toxicity of LDFRT plus temozolomide for each patient with recurrent HGG. All patients who receive any amount of LDFRT will be evaluable for toxicity.

9.1 Sample Size/Accrual Rate

9.2.1 Sample Size

9.2.1.1 **Safety run-in**

A minimum of 6 and up to 24 patients will be enrolled for the safety run-in study at an accrual rate of 1 patients per month at the starting dose 0.5 Gy twice daily on days 1-5 of temozolomide. The exact number of patients will depend on the number of dose levels in this phase.

9.2.1.2 **Phase II**

Amended Primary Objective: The amended primary objective of the study is one year OS. The current one year OS after 22 patients have been enrolled and followed for a median of 12.7 months is 41.5% (80% CI: 25%, 68%). The one year OS for the historical reference used for this study, TMZ alone (Perry JCO 2010), was reported as 28.6%. Claiming improvement in one year OS within the context of a protocol with an amended primary objective would not be justified, however, the lower bound of the current 80% confidence interval is fairly promising compared to the historical estimate. Additional follow-up of the current patients and completing enrollment to the sample size of 31 will allow us to estimate one year OS with greater precision: width of current CI 0.33 versus simulated mean width of 0.23, Table 1. A one year OS with a lower bound of an 80% CI greater than 28% would be considered sufficiently promising for further study.

Table 1. Lower bound and mean width of 80% CI for one year OS based on 500 simulations with a sample size of 31

Simulated true 12 mo. OS	Simulations with lower bound > 28.6%	Mean width of 80% CI:
0.30	**19.8%**	**0.21**
0.35	**38.6%**	**0.22**
0.40	**59.0%**	**0.22**
0.47	**82.8%**	**0.23**
0.50	**93.4%**	**0.23**
0.55	**98.0%**	**0.23**

Original Primary Objective: The primary objective of this trial is to evaluate the therapeutic efficacy of LDFRT plus temozolomide in patients with recurrent HGG. A true (partial or complete) response rate below 10% is considered clinically insignificant and a true (partial or complete) response rate above 25% clinically is considered clinically significant. A 2-stage design will be used to follow for early termination if there is strong early evidence to support the null hypothesis that the true response rate is at most 10%. The alternative hypothesis is that the true response rate is at least 25%. A total of 31 patients will yield 80% power to detect a response rate (PR+CR) of 25% compared to a 10% rate among patients treated by TMZ alone (Perry JCO 2010) at a one-side alpha level of 0.1. Note that in this study (Perry JCO 2010) the outcomes for the "rechallenge" GBM group was comparable to the AA group.

In the first stage, if 2 or fewer patients of the first 20 accrued to the study show response (PR+CR), the study will be terminated. Otherwise, the study will continue to a second stage with additional 11 patients to a total of 31 patients. If 6 or more out of the 31 patients had PR or CR, the LDFRT plus temozolomide will be considered efficacious and recommended for future comparative study. The estimated probability of early stopping for null is 68%. The probability of early stopping under the alternative hypothesis is 9%. The 6 patients from the selected phase II dose enrolled in the safety run-in will count towards the phase II trial, so that the minimum number of patient for the study is 31 and the maximum is 49.

Safety Monitoring:

Early stopping for toxicity: according to observed severe adverse event (about 5% necrosis rate) that related to RT from the study with higher RT dose than this study among re-radiation HGG patients (Combs JCO 2005), it is very unlikely this low RT dose study will yield DLTs or later RT toxicity as necrosis. However, the study will monitor SAEs (RT related DLTs or Necrosis) continuously through the trial. Assuming the low dose RT related SAE rate follows a binomial distribution. In general, the trial enrollment will be suspend for safety consultation if a posterior probability of SAE rate exceeding 0.2 is great than 60%. The prior for this monitoring rule is a Beta distribution assuming a mean SAE rate of 5%.

The safety stopping rule and the operating characteristics are shown below and there are based on 5000 simulations:

SAE event in 2 out of 3 patients. Pr(Risk>0.2| Data) = 0.6
SAE event in 3 out of 6 patients. Pr(Risk>0.2| Data) = 0.7
SAE event in 4 out of 9 patients. Pr(Risk>0.2| Data) = 0.76
SAE event in 4 out of 12 patients. Pr(Risk>0.2| Data) = 0.62
SAE event in 5 out of 15 patients. Pr(Risk>0.2| Data) = 0.69
SAE event in 6 out of 18 patients. Pr(Risk>0.2| Data) = 0.74
SAE event in 6 out of 21 patients. Pr(Risk>0.2| Data) = 0.63
SAE event in 7 out of 24 patients. Pr(Risk>0.2| Data) = 0.69
SAE event in 8 out of 27 patients. Pr(Risk>0.2| Data) = 0.74
SAE event in 8 out of 30 patients. Pr(Risk>0.2| Data) = 0.65
SAE event in 9 out of 35 patients. Pr(Risk>0.2| Data) = 0.64
SAE event in 10 out of 40 patients. Pr(Risk>0.2| Data) = 0.63
SAE event in 11 out of 45 patients. Pr(Risk>0.2| Data) = 0.62
SAE event in 13 out of 55 patients. Pr(Risk>0.2| Data) = 0.61

Operating characteristics:

Underline true SAE rate	Probability declare unsafe	Average sample size
0.10	3.3	160
0.15	18.4	140
0.20	60.5	91
0.30	99.7	24
0.35	100	17

All SAEs or toxicity events will be tabulated by type and grade based on NCI CTC Version 4.0 for toxicity and adverse events. SAEs with an attribution of possible or above will be evaluated for early stopping. Proportion of individual type of SAE event will be estimated using the binomial distribution along with 95% confidence interval (exact method).

9.2.1.3 **Accrual**

We anticipate enrollment of approximately 1-2 patients per month to the protocol with accrual completed in approximately 3-4 years.

9.2.1.4 **Stratification Factors**

There will be no stratification factors upon initial enrollment in the protocol.

9.3 **Statistical Methods of Analysis**

9.3.1 **Safety/Toxicity:** NCI CTC version 4.0 will be used for scoring the toxicity and adverse events. The severity and frequency of the toxicity will be tabulated by the tested dose or doses using descriptive statistics. The proportions of patient who experienced grade 3 or above toxicities will be estimated, along with 95%

confidence intervals by each type of toxicity.

9.3.2 **Pseudo-progression:** The proportion of patients who had pseudo-progression will be reported with 95% confidence intervals.

9.3.2 **PFS-6:** The definition of progression will be based on RANO criteria (19). Progression free will be measured from initial salvage starting date to the date of progressive disease is defined (documented). The proportion of PFS-6 will be estimated along with 95% confidence intervals using the exact binomial method.

9.3.3 **OS**: the survival time is defined from the date of treatment start to the date of death. Patients who have not died by the analysis data cut-off date will be censored at their last date known to be alive. The Kaplan-Meier method will be used to estimate one year survival, and median survival along with 80% confidence intervals.

9.3.4 **Radiation Toxicity:** descriptive statistics will be used to summarize radiation toxicity based on the RTOG/EORTC acute and late radiation morbidity scoring criteria (see appendix B and C) for all patients who had any radiation treatment in this study.

10. ADVERSE EVENTS AND RECORDING

10.1 Definition of Adverse Event (AE)

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition during or following an exposure to a treatment, whether or not considered causally related to the treatment. An undesirable medical condition may be symptoms (headache, nausea), signs (tachycardia, enlarged liver), or abnormal results of an investigation (MRI, laboratory finding). In clinical trials, from the time of signing an informed consent, an AE may include an undesirable medical condition, occurring at any time, even if no trial treatment has been administered.

10.2 Radiation Related Adverse Events

All radiation related adverse events will be recorded on the local toxicity case report forms.

10.3 Chemotherapy Related Adverse Events

The adverse events (both hematologic and non-hematologic) that patients experience due to chemotherapy will be recorded on appropriate case report forms only if they are greater than or equal to grade 3, result in a delay in treatment, or are required to be reported per institutional guidelines.

11. SERIOUS ADVERSE EVENTS (SAE) AND REPORTING

11.1 Serious Adverse Event

11.1.1 Definition of Serious Adverse Event

A serious adverse event is an AE occurring at any point during a clinical trial that fulfills one or more of the following criteria:

- Results in death.
- Is immediately life threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Is a congenital abnormality or birth defect.
- Unexpected event that cause harm or place person at a greater risk of harm than was previously known or recognized, and which was possibly related to the research. Unexpected means that the event was not described in the consent form or the event exceeded the expected severity.
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

11.2 SAE Reporting Guidelines for Johns Hopkins Hospital

All SAE, with the exception of death, must be reported to the Johns Hopkins Hospital Institutional Review Board (JH-IRB) within 10 working days of the principal investigator learning of the event. Reporting for the death of a patient which was unexpected (i.e.: not related to a risk of participation that was listed in the protocol or the consent document, and was more likely than not to be caused by the research procedure/intervention, must be reported to the JH-IRB within 3 working days of when the principal investigator receives the report of the death. Reporting for death of a participant that was expected due to the nature of the patient's underlying disease or condition, or identified as caused by a possible risk of the study procedure/intervention as described in this protocol or consent form, must be reported to the JH-IRB within 10 working days from the time the principal investigator learns of the event. If death occurs 30 days after the participant has stopped or completed their study treatment, the principal investigator does not have to report the death until the time of continuing review.

12. DATA AND SAFETY REPORTING/ REGULATORY CONSIDERATIONS

12.1 Data Quality Monitoring

The SKCCC Compliance Monitoring Program will provide external monitoring for JHU affiliated sites in accordance with SKCCC DSMP (Version 6.0, 02/21/2019). The SMC Subcommittee will determine the level of patient safety risk and level/frequency of monitoring

12.2 Data Safety Monitoring Plan

The SKCCC Compliance Monitoring Program will provide external monitoring for JHU affiliated sites in accordance with SKCCC DSMP (Version 6.0, 02/21/2019). The SMC Subcommittee will determine the level of patient safety risk and level/frequency of monitoring

12.3 Data Reporting

12.3.1 Method

Data will be collected on Case Report Forms (CRFs). These CRFs will be completed by the study coordinator. The CRFs for each subject will be kept in a separate research binder. Along with each completed CRF there will be corresponding source documentation filed for verification. The Principal Investigator, Research Study Nurse, and Study Coordinator will informally meet on a regular basis to make sure that the trial is progressing as mandated by the protocol. The CRO will audit this trial per their standards to ensure and verify that the protocol is be carried out according to specs as well as to verify that data included on subject CRFs are accurate. Exit reports generated as a result of these CRO audits will be forwarded to both the Safety Monitoring Committee as well as to the adjudicating IRB of record for review.

12.3.2 Responsibility for Submissions

Not applicable.

12.4 CTEP Multicenter Guidelines

Not applicable.

12.5 Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA)

Not applicable

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APPENDIX A

Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B:
RTOG Acute Morbidity Scoring Criteria

Organ	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Skin	No change over baseline	Faint erythema, epilation, dry desquamation, or decreased sweating	Tender or bright erythema, patchy moist desquamation, moderate erythema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
Eye	No change over baseline	Mild conjunctivitis with or without scleral injection, increased tearing	Moderate conjunctivitis with or without keratitis requiring steroids and/or antibiotics, dry eye requiring artificial tears, iritis with photophobia	Severe keratitis with corneal ulceration, objective decrease in visual acuity or in visual fields, acute glaucoma, panopthalmitis	Loss of vision (unilateral or bilateral)
Ear	No change over baseline	Mild external otitis with erythema, pruritis, secondary to dry desquamation not requiring medication. Audiogram unchanged over baseline.	Moderate external otitis requiring topical medication, serous otitis media, hypoacusis on testing only	Severe external otitis with discharge or moist desquamation, symptomatic hypoacusis, tinnitus, not drug related	Deafness
CNS	No change over baseline	Fully functional status with minor neurologic findings, no medications needed	Neurologic findings present sufficient to require home care. Nursing care may be required. Medications including	Neurologic findings requiring hospitalization for initial management	Serious neurologic impairment which included paralysis, coma, or seizures, despite medications. Hospitalization

			steroids and/or anti-seizure agents		required
Hematologic WBC (x1000)	≥ 4.0	3.0 - <4.0	2.0 - <3.0	1.0 - <2.0	<1.0
Platelets (x 1000)	≥ 100	75 - <100	50 - <75	25 - <50	<25 or spontaneous bleeding
Neutrophils	≥ 1.9	1.5 - <1.9	1.0 - <1.5	0.5 - <1.0	<0.5 or sepsis
Hematocrit (%)	≥ 32	28 - <32	<28	Packed cell transfusion required	N/A

APPENDIX C:
RTOG Late Radiation Morbidity Scoring Criteria

Organ	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Skin	None	Slight atrophy, pigmentation change, some hair loss	Patchy atrophy, moderate telangiectasia, total hair loss	Marked atrophy, gross telangioectasia	Ulceration	Death directly related to late radiation effect
Subcutaneous Tissue	None	Slight induration and loss of subcutaneous fat	Moderate fibrosis but asymptomatic. Slight field contracture. <10% linear reduction	Severe induration and loss of subcutaneous tissue. Field contracture >10% linear measurement	Necrosis	
Spinal Cord	None	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurologic findings at or below cord level treated	Mono-, para-, quadra-plegia	
Brain	None	Mild headache, slight lethargy	Moderate headache, great lethargy	Severe headaches, severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures, paralysis, coma	
Eye	None	Asymptomatic cataract, minor corneal ulceration of keratitis	Symptomatic cataract, moderate corneal ulceration, minor retinopathy or glaucoma	Severe keratitis, severe, retinopathy or detachment, severe glaucoma	Panopthalmitis, blindness	

APPENDIX D: STUDY CALENDAR

Cycles 1 – 6: Radiation and Temodar

	Pre-Study[1]	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 14	Wk 15	Wk 16	Wk 17	Wk 18	Wk 19	Wk 20	Wk 21	Wk 22	Wk 23	Wk 24
LDFRT[2]		X				X				X				X				X				X			
Temozolomide		X				X				X				X				X				X			
Informed consent	X																								
Demographics	X																								
Medical history[3]	X	X				X				X				X				X				X			
Physical exam	X																								
Vital signs	X																								
Height	X																								
Weight	X																								
Performance status	X	X				X				X				X				X				X			
CBC with diff[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CMP[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NCI Common Toxicity Criteria	X	X				X				X				X				X				X			
RTOG Acute/Late Morbidity Criteria[5]	X	X				X				X				X				X				X			
MRI[6]	X								X								X								X
B-HCG	X																								

[1] Baseline evaluations and imaging are to be conducted within 4 weeks prior to start of protocol therapy.

[2] Patients receive temozolomide (150 to 200 mg per square meter) and 0.5 Gy of radiation therapy twice daily (at least 6 hrs. apart) for 5 days during each 28 day cycle for a total of 6 cycles or until the time of disease progression. Cycles 1 through 6 will always start on a Monday.

[3]Medical history should be a complete history at pre-study evaluation, but later histories may be interval toxicity evaluations only.

[4]Laboratory tests will be requested and performed at the discretion of the patient's medical oncologist.
[5]Use RTOG Acute Toxicity Criteria during RT and for first 6 months following completion of RT. Use RTOG Late Toxicity Criteria at baseline and at scheduled intervals 6 months following completion of RT.
[6]MRI imaging will be performed approximately every 2 months during temozolomide and then according to the schedule outlined above. MRI sequences must include at a minimum T1 with gadolinium, T2 and FLAIR sequences. Other sequences may be obtained at the provider's discretion. An MRI which is delayed or missed as a result of the deterioration of the patient's clinical condition or other adversity will not be considered a protocol violation.

Cycles 7 – 12: Temodar Only and Follow up

	Wk 25	Wk 26	Wk 27	Wk 28	Wk 29	Wk 30	Wk 31	Wk 32	Wk 33	Wk 34	Wk 35	Wk 36	Wk 37	Wk 38	Wk 39	Wk 40	Wk 41	Wk 42	Wk 43	Wk 44	Wk 45	Wk 46	Wk 47	Wk 48	3 MFU	6 MFU	12 MFU[6]
Temozolomide	X				X				X				X				X				X						
Interval medical history	X				X				X				X				X				X				X	X	X
Physical exam																									X[4]	X[4]	X[4]
Performance status	X				X				X				X				X				X				X	X	X
CBC with diff[1]	X				X				X				X				X				X				X	X	X
CMP[1]	X				X				X				X				X				X				X	X	X
NCI Common Toxicity Criteria	X				X				X				X				X				X						
RTOG Acute/Late Morbidity Criteria[2]	X				X				X				X				X				X				X	X	X
MRI[3]								X								X								X	X	X	X

[1]Laboratory tests will be requested and performed at the discretion of the patient's medical oncologist.
[2]Use RTOG Acute Toxicity Criteria during RT and for first 6 months following completion of RT. Use RTOG Late Toxicity Criteria at baseline and at scheduled intervals 6 months following completion of RT.
[3]MRI imaging will be performed approximately every 2 months during temozolomide and then according to the schedule outlined above. MRI sequences must include at a minimum T1 with gadolinium, T2 and FLAIR sequences. Other sequences may be obtained at the provider's discretion. An MRI which is delayed or missed as a result of the deterioration of the patient's clinical condition or other adversity will not be considered a protocol violation.
[4]The physical exams at follow-up may be focused neurological examinations
[5]Follow-Up appointments are permitted a +/- 10 day tolerance window

[6]Continue patient follow-up with interval histories and MRI until the time of patient death. After 12 months following completion of temozolomide, follow-up histories and imaging will be at the provider's discretion.