A Phase II Study of the Efficacy of Hypofractionated Radiation Therapy with Bevacizumab and Temozolomide Followed by Maintenance Temozolomide and Bevacizumab for Recurrent High-Grade Gliomas

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SYNOPSIS

Title	A Phase II Study of the Efficacy of Hypofractionated Radiation Therapy with Bevacizumab and Temozolomide Followed by Maintenance Temozolomide and Bevacizumab for Recurrent High-Grade Gliomas
Short Title	Radiation Therapy with Bevacizumab and Temozolomide for Recurrent Gliomas
Protocol Date	February 5, 2019, Amendment 11
Study Duration	3 years
Study Center(s)	Northwestern Memorial Hospital, Northwestern Medical Faculty Foundation, Edward Cancer Center, Northwestern Lake Forest Hospital, University of Chicago, Central Dupage Hospital, CDH-Delnor Health System d/b/a Cadence Health
Objectives	To determine the efficacy of concurrent radiation therapy, temozolomide, and bevacizumab followed by adjuvant temozolomide and bevacizumab in the setting of recurrent high grade gliomas, as measured by overall survival. Secondary endpoints will include progression free survival, toxicities, and the impact of this regimen on neurological symptoms.
Number of Subjects	77 total (40 GBM bevacizumab-naïve, 25 GBM bevacizumab-exposed, 6 anaplastic glioma bevacizumab-naïve, 6 anaplastic glioma bevacizumab-exposed).
Diagnosis and Main Inclusion Criteria	All patients will be diagnosed with recurrent high grade gliomas (glioblastoma or anaplastic glioma), and will be placed into groups 1-4 based on their histologic diagnosis and prior exposure to bevacizumab.
Treatment Summary	Patients will be given radiation therapy in 25 fractions over five weeks using a simultaneous integrated boost (SIB) technique. Concurrent temozolomide and bevacizumab will be given during radiation therapy, and adjuvant temozolomide and bevacizumab will be continued until the time of progression or toxicity.
Analysis Summary	Data will be analyzed using Kaplan-Meier curves for survival endpoints. Toxicity data will be summarized descriptively.

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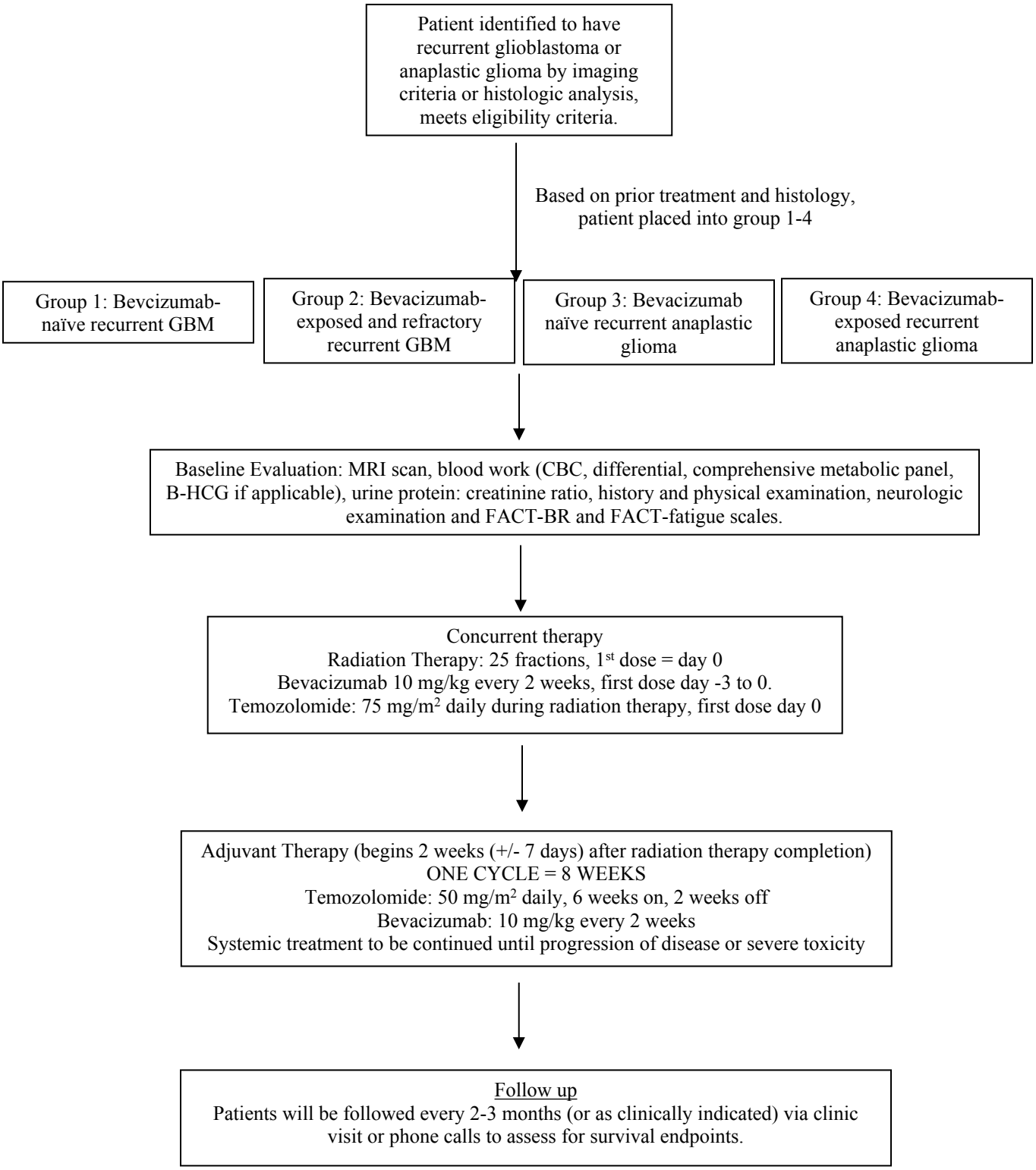
SCHEMA


Patient identified to have recurrent glioblastoma or anaplastic glioma by imaging criteria or histologic analysis, meets eligibility criteria.
Based on prior treatment and histology, patient placed into group 1-4
Group 1: Bevcizumab-naïve recurrent GBM
Group 2: Bevacizumab-exposed and refractory recurrent GBM
Group 3: Bevacizumab naïve recurrent anaplastic glioma
Group 4: Bevacizumab-exposed recurrent anaplastic glioma
Baseline Evaluation: MRI scan, blood work (CBC, differential, comprehensive metabolic panel, B-HCG if applicable), urine protein: creatinine ratio, history and physical examination, neurologic examination and FACT-BR and FACT-fatigue scales.
Concurrent therapy
Radiation Therapy: 25 fractions, 1st dose = day 0
Bevacizumab 10 mg/kg every 2 weeks, first dose day -3 to 0.
Temozolomide: 75 mg/m2 daily during radiation therapy, first dose day 0
Adjuvant Therapy (begins 2 weeks (+/- 7 days) after radiation therapy completion)
ONE CYCLE = 8 WEEKS
Temozolomide: 50 mg/m2 daily, 6 weeks on, 2 weeks off
Bevacizumab: 10 mg/kg every 2 weeks
Systemic treatment to be continued until progression of disease or severe toxicity
Follow up
Patients will be followed every 2-3 months (or as clinically indicated) via clinic visit or phone calls to assess for survival endpoints.

1 INTRODUCTION - BACKGROUND AND RATIONALE

1.1 High Grade Gliomas

High grade gliomas arise from astrocytes and oligodendrocytes. The most common type of malignant glioma is glioblastoma (GBM), which comprises 60% of gliomas. Other high grade gliomas include anaplastic astrocytoma, anaplastic oligodendroglioma, and anaplastic oligoastrocytoma, all of which are categorized as anaplastic gliomas.

The prognosis of patients with these diagnoses is poor. The overall survival (OS) rate for GBM is 27.2% at 2 years, 16.0% at 4 years, and 9.8% at 5 years with the standard treatment of surgical resection and adjuvant radiation therapy with concurrent and adjuvant temozolomide[1]. Patients generally undergo resection, followed by conformal radiation therapy (60 Gy) over 6 weeks with concurrent temozolomide followed by adjuvant temozolomide for a minimum of 6 months for responding patients. This regimen has also been used as "standard treatment" for patients with other forms of high grade gliomas, despite more limited data in this setting.

Addition of bevacizumab to standard first-line therapy has been shown to improve progression free survival (PFS) in the phase II setting compared to historical controls, but level 1 evidence for its use in the up-front setting does not exist, and such use is currently uncommon in most centers [2, 3]. In a single-arm study, 70 patients were treated with daily temozolomide (75 mg/m^2) and biweekly bevacizumab (10 mg/kg) with concurrent standard radiation therapy, followed by adjuvant temozolomide and bevacizumab. Median PFS was 13.6 months in the tri-modality therapy group and 7.6 months in a group of historical control patients [2]. Synergy of bevacizumab and temozolomide has been shown in several preclinical models [4-6]. Phase III studies of this combination in the first-line setting are currently in development.

1.2 Recurrent Disease – Systemic Agents

1.2.1 Clinical experience

Recurrent disease is almost universal in high grade gliomas [7, 8]. The current standard of care for recurrent GBM employs the use of the antiangiogenic agent bevacizumab. In the BRAIN study, a phase II, non-comparative, multicenter trial of 167 patients with recurrent GBM treated with bevacizumab alone (n=85) or in combination with irinotecan (n=82), those patients who received bevacizumab alone had a response rate of 25.9% with median duration of response of 4.2 months and 6 month PFS of 36%[9]. In an NCI-sponsored phase II study, 48 patients with recurrent GBM were treated with bevacizumab followed by bevacizumab with irinotecan at tumor progression. In these patients, the response rate was 19.6 % with a median duration of response of 3.9 months [10]. In the recurrent setting, cytotoxic chemotherapy such as CPT-11 or temozolomide is frequently combined with bevacizumab, resulting in somewhat higher response rates, and slightly

longer 6 month PFS (51% with CPT-11 plus bevacizumab in the BRAIN trial) [9, 11]. In several trials, the median survival ranges between 6.5 and 9.8 months In the randomized BRAIN trial, median survival was approximately 9 months for both cohorts; according to the literature, the composite median survival for recurrent GBM is approximately 8 months.

Attempts have also been made to salvage recurrent GBM with temozolomide alone [12] or in combination with bevacizumab[11], and the overall data suggest modest clinical activity with 6 month PFS of 23.9% with temozolomide alone, and 40% with the 2 agents combined. One year OS for those patients treated with temozolomide alone was 14.8-28.6%, depending on risk stratification group.

1.2.2 Dosing & safety

Several dosing schedules for bevacizumab and temozolomide have been employed. Bevacizumab has been given at 10 mg/kg every 2 weeks concurrent with and adjuvant to radiation therapy ([2, 9, 11]). Temozolomide has been dosed at 75 mg/m^2 [2] concurrent with radiation therapy. Adjuvant temozolomide dosing schedules have been more varied, and have included 150-200 mg/m^2/day for the first 5 days of a 28 day cycle [2, 13], as well as 100 mg/m^2/day for the first 21 days of a 28 day cycle[13]. Alteration of treatment schedule to continuous treatment with 50 mg/m^2/day in patients who have recurrent disease to has been shown to be a valuable therapeutic option [12].

Toxicity with combination therapy with bevacizumab and temozolomide has been moderate. The most common toxicities in the primary setting include cerebrovascular ischemia (9%), fatigue (20%), hypertension (11%), hyperglycemia (10%), hyponatremia (11%), proteinuria (11%), and venous thrombosis/pulmonary embolism (19%), GI bleed (3%), and GI perforation (3%) [2]. In the recurrent disease setting, re-challenge with temozolomide alone was associated with a 15.8% incidence of grade 3 lymphopenia and other grade 3-4 hematologic toxicities were uncommon. The most common non-hematologic toxicities included grade 3-4 nausea/vomiting (6.7%) and fatigue (5.8%) [12]. Treatment with bevacizumab alone in the recurrent disease setting was associated with a 46.4% incidence of grade 3 or higher adverse events, most commonly hypertension (8.3%) and convulsion (6.0%), along with arterial thromboembolism (2.4%), venous thromboembolism (3.6%), and grade 3 GI perforation (2.5%) [9]. Treatment with irinotecan in combination with bevacizumab in the recurrent glioblastoma setting was associated with increased side effects as compared to bevacizumab alone, with 65.8% of patients experiencing grade 3 or greater adverse events, the most common being convulsion (13.9%), neutropenia (8.9%), and fatigue (8.9%). Adverse events resulted in termination of bevacizumab treatment in 4.8% of the bevacizumab alone treatment group and 17.7% of the combination therapy group [9].

1.3 Recurrent Disease – Re-irradiation

Re-irradiation has also been investigated for patients with recurrent disease. There are several studies showing that radiation therapy may be delivered safely in this setting [14-16]. Some series suggest that those patients who receive bevacizumab and radiotherapy have improved response rates compared to those who receive either modality alone [17]. In 1 small single institution report of 25 patients (20 recurrent GBM and 5 recurrent anapalastic gliomas) treated with bevacizumab and hypofractionated radiotherapy (30 Gy in 5 fractions), the response rate for rGBM was 50% with 6 month PFS of 65% and median survival of 12.5 months; this was in a cohort of well selected patients with small volume recurrence (< 3.5 cm maximum diameter) [17]. Table 1 summarizes the above data.

Table 1. Efficacy of treatment options for patients with recurrent GBM

	Response Rate (%)	6 month PFS (%)	MS (months)
Bevacizumab Alone	28.2[9]	42.6[9]	9.2[9]
Bevacizumab + CPT-11	37.8[9]	50.3[9]	8.7[9]
Bevacizumab + Chemotherapy	34.1[18]	42[18]	7.2[13]
Temozolomide Alone		23.9[12]	7.2[13]
Radiation Therapy Alone		34.8[15]	11[14]
Bevacizumab + Radiation Therapy	50[17]	65[17]	12.5[17]

Most importantly, the above trial demonstrated the safety of re-irradiation. Three of 25 patients discontinued treatment with bevacizumab due to grade 3 toxicity related to bevacizumab, but no patients experienced radiation necrosis. In another study of re-irradiation alone in 108 patients with pulsed reduced dose rate radiotherapy(to a median of 50 Gy in 1.8-2 Gy fractions), 4 of 15 patients at the time of autopsy had notable radiation necrosis. No patients manifested obvious blindness from treatment[15]. In another group of 147 patients with recurrent GBM treated with hypofractionated radiation therapy (median dose 35 Gy in 3.5 Gy fractions), no patients experienced significant acute morbidity or required treatment breaks. One patient did experienc grade 3 late central nervous system (CNS) toxicity (headaches), but no patients required hospitalization or surgical intervention for toxicity [14].

1.4 Bevacizumab and Treatment of Radiation Necrosis

It is important to recognize the role of bevacizumab in treating and effectively reversing radiation-induced cerebral necrosis[19]. A randomized double-blind placebo-controlled trial with cross-over design of radiation therapy for radiation necrosis of the CNS involved 14 patients with radiation necrosis in the CNS with associated neurologic signs and symptoms. Five of 5 patients who were randomized to initial treatment with bevacizumab had improvement in their

neurologic signs and symptoms, and 7 of 7 who were initially randomized to the control group had no improvement. After crossover, all patients had symptomatic improvement. Bevacizumab is thought to be effective in treatment of central nervous system radiation necrosis by restoring the blood brain barrier which is made dysfunctional by radiation therapy, causing edema and neurologic symptoms.

1.5 Rationale for the Current Trial

Based upon the modest activity of all 3 treatment modalities (bevacizumab, temozolomide, and radiotherapy), possible synergy as demonstrated in several pre-clinical models, and data supporting that the use of bevacizumab is also likely protective against brain necrosis, we propose to combine these in a triple modality approach for patients with recurrent malignant glioma. Furthermore, the extensive use of this triple modality combination as first-line treatment in over 1000 newly diagnosed GBM patients supports the exploration of this same combination in the recurrent setting.

We propose to conduct a phase II trial of concurrent radiation, temozolomide, and bevacizumab followed by adjuvant temozolomide and bevacizumab in patients with recurrent high grade gliomas including GBM and anaplastic glioma. Patients will be stratified into 4 groups on the basis of histology and prior therapy: bevacizumab-naïve with recurrent GBM (Group 1), bevacizumab-exposed with refractory recurrent GBM (Group 2), bevacizumab-naïve with recurrent anaplastic glioma (Group 3), and bevacizumab-exposed with recurrent anaplastic glioma (Group 4). We will assess survival and toxicity endpoints for this regimen in the recurrent setting.

Since there is no standard re-irradiation dose, and attempts to hypofractionate the radiation dose seems to be safe and effective, we have chosen a modest but safe re-irradiation dose of 45 Gy using a simultaneous integrated boost (SIB) technique to increase the dose per fraction to the area of recurrent disease[14, 15, 17]. Bevacizumab dosing and schedule in both the primary and recurrent disease settings have been somewhat standard; thus we will utilize this standard dose of 10 mg/kg biweekly throughout both treatment periods [2, 9, 11]. We have chosen a temozolomide dose of 75 mg/m^2/day during the re-irradiation phase, followed by 50 mg/m^2/day in the adjuvant setting, as supported by the above trials [2, 12].

2 Objectives

2.1 Primary Objective:

The primary objective of this phase II study will be to determine the overall survival (OS) for patients with recurrent high grade malignant gliomas treated with concurrent radiation, temozolomide, and bevacizumab followed by adjuvant temozolomide and bevacizumab. OS is the most appropriate endpoint for this trial given that response rates are very low and do not serve as a useful surrogate. Additionally, PFS is confounded on the MRI due to changes consistent with

pseudoprogression, a well-described phenomenon in this disease.

2.2 Secondary Objectives:

Secondary objectives will include the following:

2.2.1 Determine the impact of this regimen on neurologic symptoms via FACT-Br and FACT-Fatigue scales and ECOG performance status.

2.2.2 Determine the safety profile of this regimen.

2.2.3 Determine the progression free survival (PFS) at 6 and 12 months (all patients) as well as at 3 months (bevacizumab-exposed patients only).

3 SELECTION OF PATIENTS

Potentially eligible patients will be identified by their treating physicians at each participating site; at the lead site, patients will be identified by the Neuro-Oncology outpatient clinic of Northwestern Medical Faculty Foundation or by the in-patient Neuro-Oncology service of Northwestern Memorial Hospital. Patients may also be referred to the Principal Investigator, Dr. Karan Dixit, at 312-695-0990, or to the local PI at each participating site.

Approximately 60 patients fitting the criteria listed above are seen per year at these locations. We estimate that we will accrue approximately 2-3 patients per month to this trial.

3.1 Inclusion Criteria

3.1.1 Patients must have histologically confirmed diagnosis of GBM or anaplastic glioma, WHO grade 3 or 4

3.1.2 Patients must have measurable or non-measurable (evaluable) disease recurrence.

3.1.2.1 Recurrence must be documented based on a combination of clinical and imaging parameters, consistent with routine clinical practice, with or without histologic confirmation.

3.1.2.2 Patients may have had any number of relapses and be eligible for the study.

3.1.3 Patients must have been previously treated with radiation therapy and temozolomide (bevacizumab-naïve – Groups 1 and 3) or radiation therapy, temozolomide and bevacizumab (bevacizumab-exposed – Groups 2 and 4). Therapy with these agents may be given together or sequentially in the past.

3.1.4 All patients may have had prior surgery, chemotherapy, and radiation therapy. Prior biologic therapy is permitted only for bevacizumab-exposed patients (Groups 2 and 4). Prior treatment with Gliadel is permitted for all groups.

3.1.5 For bevacizumab-naïve patients (Groups 1 and 3) a minimum of 6 months must have elapsed since completion of radiation therapy for study entry, and there is no minimum time since completion of last chemotherapy. For bevacizumab-exposed patients (Groups 2 and 4) no minimum time since completion of last radiation therapy, biologic agents, or chemotherapy will be required for study entry.

3.1.6 Patients must be 18 years or older.

3.1.7 Patients must have an ECOG performance status of ≤ 2.

3.1.8 Patients must have adequate bone marrow function (within 14 days prior to registration) defined as:

3.1.8.1 Hemoglobin ≥ 10

3.1.8.2 Platelets ≥ 100,000/mm^3

3.1.8.3 Absolute neutrophil count ≥ 1500/mm^3

3.1.9 Patients must have adequate liver function (within 14 days prior to registration) defined as:

3.1.9.1 Bilirubin ≤ 1.5 x upper limit of normal range

3.1.9.2 AST and ALT ≤ 3 x upper limit of normal range

3.1.10 Patients must have adequate renal function (within 14 days prior to registration) defined as:

3.1.10.1 BUN and Creatinine ≤ 1.5 x upper limit of normal range

3.1.10.2 Urine protein/creatinine ratio should be ≤ 1.

3.1.11 Patients' baseline blood pressure must be adequately controlled with or without antihypertensive medications prior to enrollment (systolic < 145 mmHg, diastolic < 90 mmHg).

3.1.12 Patients must have a baseline evaluation including history and physical examination with neurological evaluation and MRI of the brain (with and without gadolinium-based contrast), all completed within 30 days prior to initiation of treatment.

3.1.13 Female patients of child-bearing potential must have a negative pregnancy test within 14 days prior to enrollment on study. Child-bearing potential is defined as any female (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets one of the following criteria:

3.1.13.1 Has not undergone a hysterectomy or bilateral oophorectomy; **OR**

3.1.13.2 Has not been naturally postmenopausal for at least 12 consecutive months (i.e. has had menses at any time in the preceding consecutive 12 months).

3.1.14 Females of child-bearing potential and sexually-active males must consent to follow acceptable birth control methods to avoid contraception while on treatment.

3.1.15 All subjects must have given signed, informed consent prior to registration on study.

3.1.16 Patients previously treated outside of Northwestern must have their pathology slides sent to Northwestern for review and confirmation.
NOTE: A copy of the pathology report is sufficient for registration.

3.2 Exclusion Criteria

3.2.1 Patients who are pregnant or breast-feeding will NOT be eligible for participation.

3.2.2 Patients with a prior malignancy will NOT be eligible for participation aside from the following exception:

3.2.2.1 Patients who have had any curatively treated malignancy and have been disease free without treatment for 1 year prior to study entry ARE eligible for participation.

3.2.3 Patients with an active second malignancy (other than non-melanoma skin cancer or cervical cancer in situ) are NOT eligible for participation.

3.2.4 Patients with uncontrolled hypertension (≥ 145/90 mmHg) are NOT eligible for participation.

3.2.5 Patients who exhibit any other serious concurrent infection or other medical illness which would jeopardize their ability to receive the therapy outlined in this protocol with reasonable safety will NOT be eligible for participation.

The eligibility criteria listed above are interpreted literally and <u>cannot</u> be waived.

4 PATIENT REGISTRATION

Patients *may not* begin protocol treatment prior to registration. All patient registrations will be registered centrally through the Clinical Research Office (CRO) at Northwestern University before enrollment to study. Please contact the assigned Quality Assurance Monitor (QAM) or email the QA Department (croqualityassurance@northwestern.edu) for questions regarding patient registration.

4.1 Access to the Registration Program

Prior to registration, the eligibility checklist must be reviewed by the assigned QAM. The study coordinator will screen all subjects for potential registration via the Northwestern Oncology Trial Information System (NOTIS) using the web-based application, which can be found at: https://notis.nubic.northwestern.edu. Please note that a password is required to use this program and will be provided during site activation prior to training on the NOTIS system..

4.2 Registering a Patient

BEFORE a patient can be treated on study, please complete and submit the following items to confirm eligibility and receive a subject identification number:

- Patient's signed and dated informed consent form (upload to NOTIS).
- Eligibility checklist (signed and dated by the treating physician – upload to NOTIS)
- Eligibility eCRF (complete in NOTIS)
- Copy of the pathology report (upload in NOTIS).

Training on eCRF completion will be provided at the time of site activation. Please refer to the eCRF demonstration videos on the CRO website (https://www.cancertrials.northwestern.edu/collaborations/nu-iit-sites) for additional instructions on registering a patient.

4.3 Beginning Study Treatment

The QAM will review the registration, register the patient, assign a subject ID number, and send a confirmation of registration to study personnel.. Registration will then be complete and the patient may begin study procedures.

5 TREATMENT PLAN

5.1 Overview

This will be a phase II trial to assess the survival and toxicity associated with concurrent re-irradiation plus temozolomide and bevacizumab, followed by adjuvant temozolomide and bevacizumab in patients with recurrent high grade gliomas. A total of 77 patients will be enrolled on this trial. Patients will be stratified into 4 groups on the basis of histological diagnosis (GBM or anaplastic glioma) and prior therapies received (bevacizumab-naïve or bevacizumab-exposed). Treatment will be divided into 2 phases. The first phase (initial phase) will include all treatments (temozolomide and bevacizumab) given during (concurrently with) re-irradiation therapy, whereas the second phase (adjuvant phase) will consist of treatments (temozolomide and bevacizumab) given after re-irradiation therapy is completed. Re-

irradiation therapy will last for 5 weeks. One cycle of systemic therapy in the adjuvant phase will be defined as 8 weeks in duration. Cycles in the adjuvant phase may be spaced +/- 1 week apart. Patients will continue on adjuvant therapy until disease progression or removal due to toxicity. Overall survival will be the primary endpoint of this phase II trial.

5.2 Administration

5.2.1 Re-irradiation Therapy

The first day of re-irradiation therapy will be considered Day 0. Re-irradiation therapy will be given using a simultaneous integrated boost (SIB) technique, with a dose of 1.8 Gy per fraction for 25 fractions to a total dose of 45 Gy to the MR FLAIR abnormality (the T2 may substitute for FLAIR, if the FLAIR sequence is not available) as the clinical target volume (CTV), and simultaneously 2.2 Gy per fraction to a total dose of 55 Gy to a CTV of the enhancing disease on the MR MPRAGE sequence (or equivalent). There will be a minimal expansion from each CTV to planning target volume (PTV) of at most 2mm. At least 90% of each CTV should receive 90% of the prescribed dose. If standard SIB technique is not felt to be in the patient's best interest due to potential toxicity, then standard fractioned EBRT at 180-200 cGY will be used.

It is reasonable to assume that during the initial course of radiation therapy, the optic nerves and chiasm would have received approximately 50 Gy. Therefore, no more than an additional 20 Gy to the optic nerves or chiasm will be permitted during re-irradiation with the caveat that the total cumulative dose to these structures will not exceed 70 Gy.

Please note that proton therapy is an acceptable mode of radiotherapy for this study.

5.2.2 Temozolomide

Temozolomide will be administered orally, at the same time each day; the time of day may be selected according to the patient's and treating physician's discretion. The dose and frequency of administration will depend on the treatment phase (see below). Doses will be rounded to the nearest 5 mg. Patients will be instructed to take temozolomide on an empty stomach (no food 1 hour before or 1 hour after). Temozolomide tablets will be swallowed whole and may be taken with water. Patients will take compazine 5-10 mg, Zofran 4-8 mg, or Kytril 1-2 mg 30-40 minutes before temozolomide, as necessary. If vomiting occurs after taking temozolomide, the patient should not take a replacement dose on that same day. The patient should resume taking temozolomide at the next scheduled dose on the following day.

If a dose is missed, the patient should take the dose as soon as possible, but

only if there are 12 or more hours remaining before the next dose is due. If the next dose is due in less than 12 hours, the patient should skip the missed dose and take the next dose as scheduled. Patients will be given a study diary to record each dose of temozolomide, as well as any missed and/or vomited doses.

5.2.2.1 Initial Phase: During Re-irradiation Therapy
Temozolomide will be administered at a dose of 75 mg/m^2 per day. Treatment will begin on Day 0 and continue daily during re-irradiation therapy (7 days per week for a total of 5 weeks). The last day of temozolomide during the initial phase of treatment will be the last day of re-irradiation therapy.

5.2.2.2 Adjuvant Phase: After Re-irradiation Therapy
Temozolomide will be discontinued for 2 weeks (+/- 7 days) after re-irradiation therapy. Temozolomide will then be restarted at a dose of 50 mg/m^2 per day on a schedule of 6 weeks on, 2 weeks off for a total of 8 weeks per cycle. Subsequent cycles during this phase may occur +/- 1 week apart. Treatment will continue as long as there is no clinical or radiographic progression and no severe toxicity occurs. Please refer to Section 5.3 for dose delays and/or modifications to temozolomide.

5.2.3 Bevacizumab
Bevacizumab will be administered intravenously at a dose of 10 mg/kg every 2 weeks; the timing of the infusions will vary depending on the treatment phase (see below). Bevacizumab will be diluted in a total volume of 100 mL of 0.9% sodium chloride Injection, USP. Anaphylaxis precautions should be observed during drug administration. The dose will be based on current weight at each dosing time point. It is not necessary to correct dosing based on ideal weight.

For patients who are bevacizumab-naïve (Groups 1 and 3), the first dose will be delivered over a period of 30-90±15 minutes (per institutional practice). If the patient has been exposed to bevacizumab prior to study entry (Groups 2 and 4) without any infusion-associated adverse events, the first infusion may be delivered over a period of 30-60±10 minutes. If a patient experiences an infusion-associated adverse event, he/she may be premedicated for the next bevacizumab administration per institutional practice.

5.2.3.1 Initial Phase: During Re-irradiation Therapy
The first dose of bevacizumab will be given between Days -3 and 0, and will continue every 2 weeks (+/- 3 days) during re-irradiation therapy as long as no severe toxicity occurs.

5.2.3.2 Adjuvant Phase: After Re-irradiation Therapy
Bevacizumab will be continued every 2 weeks, with the first adjuvant dose occurring approximately 2 weeks (+/- 7 days) after re-irradiation therapy is complete. Patients will receive 4 infusions of bevacizumab per cycle (1 cycle = 8 weeks). Subsequent cycles during this phase may occur +/- 1 week apart. Treatment will continue as long as there is no clinical or radiographic progression and no severe toxicity occurs.

5.3 Dose Modifications

All toxicities will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

5.3.1 Temozolomide

5.3.1.1 Initial Phase Delays/Modifications
There will be no reductions to the temozolomide dose during the initial treatment phase. However, during re-irradiation therapy, dose delays may occur for specified toxicities (as noted below) for up to 7 days. Toxicity will be assessed weekly during the initial phase of treatment; assessment may occur more frequently as needed.

Temozolomide may be held for up to 7 days if any of the following is experienced during the initial phase:

5.3.1.1.1 Febrile neutropenia (any grade)

5.3.1.1.2 Grade 3 hematologic toxicity that, in the opinion of the investigator, is trending downward and has potential for further myelosuppression

5.3.1.1.3 Grade 4 hematologic toxicity (including a platelet count of < 25,000/mm3)

5.3.1.1.4 Any grade 3 or higher non-hematologic toxicity considered by the investigator to be related to temozolomide.

Please refer to Section 5.3.1.3 for conditions for re-starting temozolomide. *NOTE: Dose interruption or study discontinuation is **not** required for lymphopenia of any grade.*

5.3.1.2 Adjuvant Phase Delays/Modifications
During the adjuvant treatment phase, temozolomide will be given in 8-week cycles (daily administration for the first 6 weeks followed by 2 weeks off). Assessment of toxicity will occur prior to initiation of each cycle during the adjuvant phase; assessment may occur more frequently if toxicity occurs as noted below.

New cycles may be delayed up to 4 weeks if any of the following occurs:

5.3.1.2.1 Febrile neutropenia

5.3.1.2.2 Grade 3 hematologic toxicity that, in the opinion of the investigator, is trending downward and has potential for further myelosuppression

5.3.1.2.3 Grade 4 hematologic toxicity excluding lymphopenia (including a platelet count of < 25,000/mm^3)

5.3.1.2.4 Any grade 3 or higher non-hematologic toxicity considered by the investigator to be related to temozolomide.

Please refer to Section 5.3.1.3 for conditions for re-starting temozolomide. *NOTE: Dose interruption or study discontinuation is **not** required for lymphopenia of any grade.*

During the period that the treatment is delayed due to hematologic toxicity, the CBC will be repeated 1-2 times per week until the conditions for re-starting temozolomide are met. The temozolomide dose will then be reduced by 20% when it is re-started. Patients will be allowed up to 2 dose reductions by 20%; after 2 reductions, patients will be removed from the study due to toxicity.

Patients who require a toxicity-related treatment delay of > 4 weeks will also be removed from the trial. Patients who experience persistent grade 3 or higher hematologic or non-hematologic toxicity with a temozolomide dose of 50 mg/m^2 will be discontinued from the study.

5.3.1.3 Conditions for Re-starting Temozolomide

A new cycle of temozolomide therapy may begin when:

5.3.1.3.1 All drug-related non-hematologic toxicity (≥ grade 3) has resolved to ≤ grade 1

5.3.1.3.2 Patients with abnormal liver (AST/ALT/bilirubin) and renal function at baseline may receive treatment if the values have not risen by more than 1.5 x the upper limit for protocol eligibility

5.3.1.3.3 Hematologic toxicity has recovered to ANC ≥ 1500/mm^3, platelet count ≥ 100,000/mm^3, and Hgb >10 (may be given a transfusion to get > 10)

5.3.2 Bevacizumab

There will be no reductions to the dose of bevacizumab. There will be no difference in dosing between the initial and adjuvant phases of treatment for bevacizumab. If adverse events occur that require holding bevacizumab, the dose will remain the same once treatment resumes. Treatment may resume when all toxicities have resolved to ≤ grade 1. Up to 2 scheduled doses of bevacizumab may be missed, but treatment may not be held for > 6 weeks

due to toxicity. Please refer to Table 2 for adverse events requiring delays or permanent discontinuation of bevacizumab treatment. Regardless of the reason for holding bevacizumab treatment, the maximum allowable length of bevacizumab treatment interruption is 6 weeks.

Any toxicities related or possibly related to bevacizumab treatment should be managed according to standard medical practice. Discontinuation of bevacizumab will have no immediate therapeutic effect. Bevacizumab has a terminal half-life of 21 days; therefore, its continuation results in slow elimination over several months. There is no available antidote for bevacizumab.

Patients will be assessed clinically for toxicity prior to, during, and after each infusion. If unmanageable toxicity occurs because of bevacizumab at any time during the study, treatment with bevacizumab should be discontinued. Please refer to Table 2 below for guidelines regarding management of bevacizumab with regards to adverse events.

Table 2: Bevacizumab dose management due to adverse events

Event	Grade	Action to be Taken
Hypertension	1 or 2	No dose modification required.
	3	If not controlled to 150/100 mm/Hg with medication, discontinue bevacizumab.
	4 (including hypertensive encephalopathy)	Discontinue bevacizumab.
Hemorrhage: non-pulmonary & non-CNS events	1 or 2	No dose modification required.
	3	***Patients who are also receiving full-dose anticoagulation***: discontinue bevacizumab. ***All other patients***: hold bevacizumab until all of the following criteria are met: • Bleeding is resolved and Hgb is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence. ***Patients who experience a repeat Grade 3 hemorrhagic event will be discontinued from bevacizumab***.
(cont) **Hemorrhage: non-pulmonary & non-CNS events**	4	Discontinue bevacizumab.
Hemorrhage: pulmonary or CNS	1	***Patients who are also receiving full-dose anticoagulation***: discontinue bevacizumab. ***All other patients***: hold bevacizumab until all of the following criteria are met: • Bleeding is resolved and Hgb is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence.
	2, 3, or 4	Discontinue bevacizumab.
Venous thrombosis	1 or 2	No dose modification required.
	3 or 4	Hold bevacizumab. If the planned duration of full-dose anticoagulation is < 2 weeks, hold bevacizumab until the full-dose period is over.

		If the planned duration of full-dose anticoagulation is > 2 weeks, resume bevacizumab during the full-dose period if all of the following criteria are met: • The patient has an in-range INR if on warfarin; anticoagulant dosing must be stable prior to restarting bevacizumab treatment. • The patient must not have had a Grade 3 or 4 hemorrhagic event while on anticoagulation.
Arterial thromboembolic event (new onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, or any other arterial thromboembolic event)	Any grade	Discontinue bevacizumab.
Congestive heart failure (left ventricular systolic dysfunction)	1 or 2	No dose modifications required.
	3 or 4	Discontinue bevacizumab.
Proteinuria	1 or 2	No dose modifications required.
	3 (UPC > 3.5, urine collection > 3.5 g/24 hr)	Hold bevacizumab treatment until ≤ Grade 2, as determined by either UPC ration ≤3.5 or 24 hr collection ≤ 3.5 g.
	4 (nephrotic syndrome)	Discontinue bevacizumab.
GI perforation	Any grade	Discontinue bevacizumab.
Fistula	Any grade (TE fistula)	Discontinue bevacizumab.
	Other Grade 4 fistula	Discontinue bevacizumab.
Bowel obstruction	1	Continue bevacizumab for partial obstruction NOT requiring medical intervention.
	2	Hold bevacizumab for partial obstruction requiring medical intervention – resume upon complete resolution.
	3 or 4	Hold bevacizumab for complete obstruction. If surgery is necessary, patient may restart bevacizumab after full recovery from surgery if within allowed time frame and at the investigator's discretion.
Wound dehiscence	Any grade (requiring medical or surgical therapy)	Discontinue bevacizumab.
Reversible posterior leukoencephalopathy	Any grade (confirmed by MRI)	Discontinue bevacizumab.
Other unspecified bevacizumab-related adverse events	Grade 3	Hold bevacizumab until recovery to ≤ Grade 1.
	Grade 4	Discontinue bevacizumab.

5.3.2.1 Infusion reactions
Infusion of bevacizumab should be interrupted for subjects who develop dyspnea or clinically significant hypotension. Patients who experience Grade 3 or 4 allergic reaction/hypersensitivity, adult respiratory distress syndrome, or bronchospasm (regardless of grade) will be discontinued from bevacizumab treatment.

The infusion should be slowed to 50% or less or interrupted for patients who experience any infusion-associated symptoms not specified above. When symptoms have completely resolved, the infusion may be continued at no more than 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well-tolerated. Infusions may be restarted at the full rate during the next infusion.

5.3.3 Radiation Therapy
There will be no dose modifications to the radiation therapy treatment regimen.

5.4 Supportive Care Guidelines & Use of Concomitant Medications
All medications taken during study participation, including reasons for use, will be recorded in the appropriate eCRF. For all subsequent visits, all concomitant therapy that is continuing or has been added, discontinued, or had a dosage change since the previous visit must also be recorded.

5.4.1 **Antiemetic therapy** may be used as needed will be recorded. Compazine 5-10 mg may be taken 30-40 minutes prior to temozolomide administration. Alternately, Zofran 4-8mg or Kytril 1-2 mg may be used if nausea persists.

5.4.2 **Hematopoietic growth factors** (G-CSF) may be used per ASCO guidelines and at the investigator's discretion.

5.4.3 **Prophylactic antibiotics** for *Pneumocystis carinii* pneumonia (PCP) may be used for patients who are on corticosteroids. Options include Bactrim DS, 1 tablet 2x/week, Dapsone 50 mg/day, or inhaled Pentamidine 300 mg in 6 mL of sterile water by aerosol every 4 weeks.

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

5.4.5 **Anti-seizure medications** should be used as indicated.

5.4.6 **Febrile neutropenia** may be managed according to the institution's infections disease/ASCO guidelines. Measures may include appropriate laboratory testing (including blood and urine cultures) and the institution of broad-spectrum antibiotics. If a source for the fevers is not identified or the

fever resolves when the neutrophil count recovers, antibiotics may be discontinued and the patient observed. In this case, growth factors may be used.

5.4.7 If **neurosurgical intervention** is required for indications not related to tumor progression, these procedures must be documented, including indications for surgery, surgical operative note, and pathology report.

5.4.8 **Other therapies** considered necessary for the well-being of the patient may be given at the discretion of the investigator.

5.4.9 Any use of **complementary or alternative medications** should be cleared by the Principal Investigator.

5.5 Duration of Therapy

Patients will undergo approximately 5 weeks of concurrent re-irradiation therapy, temozolomide, and bevacizumab. Following this initial treatment phase, patients will receive adjuvant temozolomide and bevacizumab until clinical or radiologic disease progression or severe or intolerable toxicity as previously described. Patients will be evaluated weekly during the initial phase, and monthly during the adjuvant phase until disease progression or discontinuation due to toxicity.

5.5.1 Criteria for Discontinuation of Treatment

5.5.1.1 Clinical or radiographic disease progression. Patients will be treated clinically as indicated thereafter and will be tracked for survival.

5.5.1.2 Severe toxicity in which continuing treatment poses a safety risk. Please refer to Sections 5.3.1 and 5.3.2 for additional guidelines concerning treatment discontinuation due to toxicity.

5.5.2 Criteria for Withdrawal from Study

Patients who discontinue treatment for any reason, but have demonstrated stable disease or response from treatment, will be followed on study until disease progression unless one of the following occurs:

5.5.2.1 The patient or his/her legally authorized representative requests to discontinue protocol therapy or withdraws consent.

5.5.2.2 The decision is made by the treating physician to remove the patient from study due to patient non-compliance or lack of follow-up.

5.6 Follow-Up

Long-term follow-up after treatment discontinuation will occur every 2-3 months (or as clinically indicated) via clinic visit or phone calls; follow-up will continue until death to assess for survival endpoints.

Note: As of December 31, 2018, patients will no longer be followed and follow up information will not be collected.

6 ENDPOINT ASSESSMENT

Response to therapy will require completion of the initial phase of therapy (consisting of concurrent re-irradiation, temozolomide, and bevacizumab) with a follow up MRI scan that can be compared to the pre-treatment scan. Tumor measurements and assessments will be based on Updated Response Assessment Criteria of High Grade Gliomas- Neuro-Oncology Working Group (RANO criteria). Tumor assessments may include either a CT or MRI scan of the brain, however the same method should be used throughout the treatment period for each patient.

6.1 Definitions

6.1.1 Measurable Disease

Measurable disease is defined as bi-dimensionally measurable lesions with clearly defined margins by CT or MRI scan and 2 perpendicular diameters of at least 10 mm.

6.1.2 Nonmeasurable Disease (Evaluable disease)

Nonmeasurable disease is defined as either uni-dimensionally measurable lesions, masses with margins not clearly defined, or lesions with maximal perpendicular diameters less than 10 mm.

6.1.3 Overall Survival

Overall survival (OS) will be defined as the time from first re-irradation treatment until death from any cause.

Note: As of December 31, 2018, patients will no longer be followed and follow up information will not be collected.

6.1.4 Progression Free Survival

Progression free survival (PFS) will be defined as the time from the first study treatment to the first occurrence of disease progression or death.

Note: As of December 31, 2018, patients will no longer be followed and follow up information will not be collected.

6.2 Primary Endpoint

The primary objective is to determine the OS of patients on this study. Please refer to Section 6.1 for definition.

6.3 Secondary Endpoints

6.3.1 Change in neurological status

One secondary objective of this study is to determine the change in neurological status associated with this treatment regimen in this population. This will be assessed in several ways:

6.3.1.1 Examination
Changes in neurological and physical exam, as compared to baseline assessment.

6.3.1.2 Patient-reported outcomes
FACT-BR and FACT-fatigue scales will be obtained at baseline (pre-therapy) and at the time of each subsequent MRI or CT scan.

6.3.1.3 Performance Status
Patients will be graded according to ECOG Performance Status, at baseline, weekly during the initial phase of treatment, and then monthly during adjuvant treatment.

6.3.2 Safety profile
Another secondary objective is to determine the safety profile of this tri-modality approach. Toxicity will be assessed using the NCI CTCAE version 4.0 criteria (see appendices). Toxicity assessments will occur weekly during the initial phase of treatment, and then prior to the start of each cycle during the adjuvant phase of treatment. Assessments may occur more frequently if needed.

6.3.3 Determine the PFS
PFS will be calculated at the 6 and 12 month time points for all patients. For the bevacizumab-exposed patients (Groups 2 and 4), PFS will also be calculated at the 3 month timepoint. Please refer to 6.4 below for evaluation of response.

6.4 Evaluation of Response

Response will be evaluated using RANO criteria. If there are multiple contrast-enhancing lesions, a minimum of the 2 largest lesions should be measured, and the sum of the products of the perpendicular diameters of these lesions should be determined. A maximum of 5 of the largest lesions may be measured; the largest enlarging lesion(s) should be selected, with emphasis placed on lesions that allow reproducible repeated measurements.

For patients with recurrent disease who have multiple lesions of which only 1 or 2 are increasing in size, the enlarging lesions should be considered the target lesions for evaluation of response. The other lesions will be considered nontarget lesions and should also be recorded. Rarely, unequivocal progression of a nontarget lesion requiring discontinuation of therapy or development of a new contrast enhancing lesion may occur, even in the setting of stable disease or partial response in the target lesions. These changes would qualify as progression. Please refer to Table 3 below for response criteria and categories.

Table 3: Evaluation of Response by RANO Criteria

Criterion	Response Category			
	CR	**PR**	**SD**	**PD**
T1 gadolinium enhancing disease	None	≥ 50% ↓	< 50% ↓ but < 25% ↑	≥ 25% ↑
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑
New lesion	None	None	None	Present[1]
Corticosteroids	None	Stable or ↓	Stable or ↓	n/a
Clinical status	Stable or ↑	Stable or ↑	Stable or ↑	↓
Requirement for response	***All***	***All***	***All***	***Any[1]***

[1] Progression occurs when this criterion is present
↓ = decreased, ↑ = increased, CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease—If PD is unclear based on white matter changes, patients may be kept on trial

6.4.1 Pseudo-progression & Continuation of Treatment

Due to possible radiation effects using large dose per fraction, the initial scan 1 week following RT should NOT be used to declare progression. In the absence of neurologic worsening OR a new distant area of tumor, the initial post-radiation scan should not be used to declare progression. Progressive worsening on subsequent imaging studies usually distinguishes true progression from pseudo-progression. If true progression is determined by subsequent imaging, then the date of progression returns to the earlier date with increasing mass.

In the event that the radiographic changes are equivocal and it is unclear whether the patient is stable or has developed progressive disease, it is permissible to continue treatment and observe the patient closely, for example at 4 weekly intervals. If subsequent imaging studies demonstrate that progression has occurred, the date of progression should be the scan at which this issue was first raised.

7 STUDY PARAMETERS

	Screening[1]	Initial Phase[4]					Treatment Break[7]	Adjuvant Phase Cycles (1 cycle =8 weeks)		End of Treatment Visit[17]	Follow-Up[19]
	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5		D1 of each cycle	W3, W5, W7		
Re-irradiation[5]		X									
Temozolomide		X[6]						X[8]			
Bevacizumab		X[9]		X[9]		X[9]		X[10]	X[10]		
Informed consent	X										
Neurologic & physical examination & ECOG PS	X[2, 3]	X[3]		X		X		Monthly during each 8 week cycle		X	
Vital Signs[15]	X	X	X	X	X	X		X		X	
MRI with contrast or CT	X[11]						X[11]	X[11]		X	
Hematology[12]	X [2, 3]	X[3]		X		X		X		X	
Chemistries[13]	X										
Urine protein/creatinine ratio	X	X[18]					X[18]	X			
Urine Dip				X[18]		X[18]		X[18]	X[18]		
Pregnancy test [14]	X										
FACT-BR and FACT-fatigue scales[16]	X						X	X		X	
Symptom and toxicity assessment	X	X						X		X	
Survival Follow-up											X

[1] Unless otherwise noted, screening assessments must be done within 14 days prior to registration.

[2] Baseline examination must be done within 30 days of registration and will also include medical history and documentation of concomitant medications.

[3] If screening labs and history/physical were performed within 14 days prior to the first dose of bevacizumab, they do not need to be repeated.

[4] The initial phase of treatment will last approximately 5 weeks, and will begin with Day 0.

[5] Re-irradiation will begin on Day 0 and will consist of a dose of 45 Gy using a simultaneous integrated boost (SIB) technique; re-irradiation will consist of 25 fractions given over 5 weeks.

[6] Temozolomide will be administered orally at a dose of 75 mg/m^2 during the initial phase; temozolomide will begin on Day 0 and will continue daily throughout the initial phase (7 days/week for 5 weeks). Patients will take compazine 5-10 mg, Zofran 4-8 mg, or Kytril 1-2 mg 30-40 minutes before temozolomide, as necessary.

[7] There will be a 2 week (+/- 7 days) treatment break between the initial and adjuvant phases.

[8] Temozolomide will be administered orally at a dose of 50 mg/m^2 per day on a schedule of 6 weeks on, 2 weeks off for a total of 8 weeks per cycle during the adjuvant phase; treatment will continue until disease progression or discontinuation due to toxicity. Cycles during the adjuvant phase may be spaced +/- 1 week apart.

[9] Bevacizumab will be administered at a dose of 10 mg/kg IV; the 1st dose will occur between Days -3 and 0, and will continue every 2 weeks (+/- 3 days) during the initial phase.

[10] Bevacizumab will continue at a dose of 10 mg/kg IV every 2 weeks for a total of 4 infusions per cycle (1 cycle = 8 weeks) during the adjuvant phase; treatment will continue until disease progression or discontinuation due to toxicity. Cycles during the adjuvant phase may be spaced +/- 1 week apart.

[11] MRI/CT will be performed at baseline (within 30 days of registration), after the initial phase of treatment (approximately 1 week after the last dose of re-irradiation therapy), and then on Day 1 or within 7 days prior to each cycle of therapy during the adjuvant phase (1 cycle = 8 weeks). The same method of assessment should be used throughout for each patient.

[12] CBC with platelets and differential

[13] Comprehensive metabolic panel

[14] Females of child-bearing potential must have a negative serum or urine pregnancy test within 14 days of registration.

[15] Baseline vitals will include height, weight, BSA, B/P, pulse and temperature. All vitals during treatment will include weight, BSA, B/P, pulse and temperature.

[16] FACT BR and FACT-fatigue scales will be completed at baseline (within 14 days prior to registration) and then on D1 of each adjuvant cycle

[17] At time of treatment discontinuation (for any reason), patients will have final round of assessments; This is referred to as the end of treatment visit.

[18] Reflex UPC is required on Day 1 of Initial Phase. Urine dip may be performed thereafter during the Initial Phase on weeks when the patient is scheduled to receive bevacizumab (Weeks 3 and 5). If urine dip is < 2, treatment may proceed; if dip is ≥ 2, reflex UPC should be performed and results should be < 3.5 to proceed with treatment. Reflex UPC will be performed during the treatment break and during Week 1 of each cycle during the Adjuvant Phase. Urine dip may be performed prior to subsequent bevacizumab treatments during each cycle in the Adjuvant Phase. If urine dip is < 2, treatment may proceed; if dip is ≥ 2, reflex UPC should be performed and results should be < 3.5 to proceed with treatment.

[19]Patients will be followed at least once every 3 months (or as clinically indicated) via clinic visit or phone calls to assess for survival endpoints until death or patient is considered lost-to follow-up. **Note: As of December 31, 2018, patients will no longer be followed and follow up information will not be collected**.

8 DRUG FORMULATION AND PROCUREMENT

8.1 Temozolomide

8.1.1 Other Names

Temodar®, TMZ, Temodal®, methazolastone

8.1.2 Classification – type of agent

Temozolomide is an oral cytotoxic alkalyting agent.

8.1.3 Mode of Action

Temozolomide is not directly active but undergoes rapid non-enzymatic conversion at physiologic pH to the reactive compound MTIC. The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA. Alkylation (methylation) occurs mainly at the O6 and N7 positions at guanine. It has demonstrated activity against breast, ovarian, non-small cell lung, renal cell, colon, prostate and pancreatic cancer as well as melanoma and malignant glioma.

8.1.4 Storage and Stability

Temozolomide capusles are packaged in amber glass bottles and should be stored at 25°C (temperature excursions between 15-30°C are permitted). Refer to the product label for storage and stability information.

8.1.5 Protocol Dose

The dose for the initial (re-irradiation) phase of treatment will be 75 mg/m^2 taken orally starting on Day 0 (1^{st} day of re-irradiation treatment). Administration will continue throughout the initial phase (7 days/week for 5 weeks) followed by a 2 week (+/- 7 days) treatment break. Administration will resume during the adjuvant phase of treatment at a dose of 50 mg/m^2 per day on a schedule of 6 weeks on and 2 weeks off for a total of 8 weeks per cycle. Please refer to Section 5.3 for any applicable dose modifications.

8.1.6 Preparation

Temozolomide is supplied in white opaque, preservative-free capsules in a variety of dosage strengths. Doses should be rounded to the nearest 5 mg.

8.1.7 Protocol Administration

Temozolomide will be administered orally at the same time each day. Capsules should be swallowed whole with a glass of water. Absorption is affected by food, so patients will be instructed to fast before and after. Temozolomide may be administered on an empty stomach or at bedtime to reduce nausea and vomiting. A dose should not be repeated if vomiting occurs after administration. Capsules should not be opened or chewed.

Contact with skin should be avoided if capsules are accidentally opened or damaged.

8.1.8 Incompatibilities

Administration of valproic acid decreases oral clearance of temozolomide by about 5%. The clinical implication of this effect is not known.

8.1.9 Availability

Temozolomide is FDA-approved for the treatment of anaplastic astrocytoma and GBM. Locally-obtained, commercial supplies of temozolomide will be prescribed for this study (study will not provide this drug).

8.1.10 Side Effects

Side effects, according to the product information, may include:

8.1.10.1 Cardiovascular

Peripheral edema was reported in 11% of patients receiving temozolomide in clinical trials.

8.1.10.2 Dermatologic

Alopecia, rash and pruritus are described with the administration of temozolomide. Alopecia (grade 1 or 2) occurred in 9% of malignant melanoma patients receiving the 5-day regimen of temozolomide in 1 trial. Skin rashes may infrequently occur following therapeutic administration of temozolomide. Skin rash with pruritus has been described occasionally during oral therapy with temozolomide.

8.1.10.3 Endocrine/Metabolic

One case report describes ovarian suppression in a patient who received temozolomide. Hypercalcemia has been reported in approximately 1% of patients with the 5-day regimen of temozolomide.

8.1.10.4 Gastrointestinal Effects:

Constipation (incidence up to 33%) is described with the administration of temozolomide. Gastrointestinal bleeding, presumably related to thrombocytopenia, has been reported rarely with temozolomide therapy. Diarrhea and dysphagia have been reported in up to 16% of patients with temozolomide therapy. Nausea and vomiting occur in up to 75% of patients with temozolomide therapy, but is not usually severe (mostly grade 1 or 2); standard antiemetics have been effective in most patients. Less frequent adverse effects have included mucositis (up to

20%), stomatitis, anorexia (up to 40%) are described with the administration of temozolomide.

8.1.10.5 Hematologic

Anemia has been reported following therapeutic administration of temozolomide, and may be secondary to gastrointestinal bleeding. Anemia frequently coexists with neutropenia and thrombocytopenia, although it is generally less frequent and severe. Very rare cases of myelodysplastic syndrome and secondary malignancies, including myeloid leukemia have been observed.

8.1.10.6 Hepatic

Mild transaminitis (up to 40% of patients) and hyperbilirubinemia (up to 19%) have been reported; increases in alkaline phosphatase have also occurred in some patients. Grade 4 increases in bilirubin have been seen rarely. There are no cases of overt hepatotoxicity. Elevated hepatic enzymes are described with the administration of temozolomide.

8.1.10.7 Neurologic

During a phase I clinical trial of temozolomide in pediatric patients with advanced cancer, 14% of patients (n=16) reported mild to moderate ataxia. Headache is among the most commonly reported adverse effects with the use of temozolomide in clinical trials; headache has been reported in 41% of patients, with 6% of those patients experiencing a grade 3/4 headache, following temozolomide administration during a clinical efficacy trial. CNS effects occurring in greater than 5% of patients in clinical trials include anxiety, depression, insomnia, convulsions, paresis/hemiparesis, dizziness, coordination or gait disturbance, amnesia, paresthesia, somnolence, and ataxia. Causality is uncertain in many patients due to the underlying disease or other factors (eg, glioma, other drug therapy). Transient neurologic deterioration was estimated to have occurred in approximately 2% of temozolomide-treated patients (Rosenthal et al, 2002). Seizures were reported in 23% of patients, with anaplastic astrocytoma, who received temozolomide during a clinical trials (n=153), however it is unclear whether the seizures were drug-related or as a consequence of the patients' underlying disease.

8.1.10.8 Psychiatric

Anxiety, depression, and insomnia are described with the

administration of temozolomide.

8.1.10.9 Renal
Urinary tract infection and increased urinary frequency were reported in 8% and 6%, respectively, of patients receiving temozolomide in clinical trials.

8.1.10.10 Reproductive
Testicular function may be affected with the administration of temozolomide.

8.1.10.11 Respiratory
Upper respiratory tract infections, including pharyngitis, sinusitis, and rare cases of Pneumocystis carinii pneumonia (PCP) have been reported with the use of temozolomide.

8.1.10.12 Fatigue
Fatigue is among the most commonly reported adverse effect (34%) with the use of temozolomide in clinical trials, and is clearly drug-related. Fatigue with temozolomide therapy may be moderate to severe.

8.1.10.13 Infections disease
Opportunistic infections (eg, Pneumocystis carinii pneumonia (PCP)) have been reported rarely with the use of temozolomide

8.1.10.14 Teratogenicity/Effects in Pregnancy/Breastfeeding:
There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective). It is unknown if temozolomide crosses the placenta. Adequate, well-controlled studies have not been conducted in humans. Due to potential for adverse effects in the fetus, women of childbearing potential should be advised against becoming pregnant while taking temozolomide and in the 6 months following the end of treatment. For breastfeeding women, the Thomson Lactation Rating indicates that infant risk cannot be ruled out. The available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding.

8.1.11 Nursing implications
Monitor CBC carefully and report any significant changes to the treating

physician. Instruct patients to report signs/symptoms of infection, unusual bruising and bleeding to health care team.

Instruct patients to report any fever, cough, chest pain, or other signs of infection to the health care team.

Advise patients that a mild-moderate rash may be experienced.

Work with patients in energy conserving lifestyle methods to combat fatigue.

Encourage patients to increase fluid intake. Administer stool softeners or laxatives as ordered and monitor for their effectiveness.

8.2 Bevacizumab

8.2.1 Other Names

Avastin

8.2.2 Classification – type of agent

Bevacizumab is a vascular endothelial growth factor- specific angiogenesis inhibitor.

8.2.3 Mode of Action

Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in *in vitro* models of angiogenesis. Administration of bevacizumab to xenotransplant models of colon cancer in nude (athymic) mice caused reduction of microvascular growth and inhibition of metastatic disease progression.

8.2.4 Storage and Stability

Upon receipt of the study drug, vials are to be refrigerated at 2°C–8°C (36°F–46°F) and should remain refrigerated until just prior to use. DO NOT FREEZE. DO NOT SHAKE. Vials should be protected from light. Opened vials must be used within 8 hours. VIALS ARE FOR SINGLE USE ONLY. Vials used for 1 subject may not be used for any other subject. Once study drug has been added to a bag of sterile saline, the solution must be administered within 8 hours.

8.2.5 Protocol Dose

Bevacizumab will be administered at a dose of 10 mg/kg every 2 weeks (+/- 3 days). The first dose will occur between Days -3 and 0 during the initial phase of study treatment. During the

adjuvant phase of treatment, there will be 4 infusions per cycle.

8.2.6 Preparation
Bevacizumab will be diluted in a total volume of 100 mL of 0.9% Sodium Chloride Injection, USP.

8.2.7 **Protocol Administration**:
Administration will be as an intravenous infusion.

8.2.8 Incompatibilities
Bevacizumab should not be diluted in dextrose.

8.2.9 Availability
Bevacizumab is commercially available and will not be provided by the study.

8.2.10 Side Effects

8.2.10.1 Allergy/Immunology
Allergic reaction/hypersensitivity. infusion-related reactions.

8.2.10.2 Blood/Bone marrow
Leukopenia, neutropenia, thrombocytopenia

8.2.10.3 Cardiac
Hypertension/hypertensive crisis, cardiac ischemia/infarction, supraventricular arrhythmia, left ventricular dysfunction (congestive heart failure), hypotension, syncope

8.2.10.4 Constitutional symptoms
Asthenia, fever, rigors/chills, weight loss

8.2.10.5 Dermatology/skin
Exfoliative dermatitis, complications with wound healing, rash, skin ulceration, urticarial

8.2.10.6 Gastrointestinal
GI perforation and wound dehiscence, sometimes complicated by intra-abdominal abscesses, large bowel leakage, GI fistula, intestinal obstruction, intestinal necrosis, mesenteric venous occlusion, colitis, mucositis/stomatitis, nausea, vomiting, anorexia, constipation, diarrhea, heartburn/dyspepsia, dry mouth, taste disturbance.

8.2.10.7 Hemorrhage/Bleeding
Life-threatening or fatal pulmonary hemorrhage (primarily in lung cancer patients), CNS bleeding, GI hemorrhage, subarachnoid hemorrhage, hemorrhagic stroke, epistaxis (nose bleeds), vaginal bleeding, gum bleeding.

8.2.10.8 Infection
Infection with normal ANC.

8.2.10.9 Metabolic
Increased: alkaline phosphatase, ALT(SGPT), AST (SGOT), bilirubin, serum creatinine. Hyponatremia and hypokalemia.

8.2.10.10 Neurology
Cerebrovascular ischemia, dizziness, abnormal gait, confusion.

8.2.10.11 Ocular
Excessive lacrimation.

8.2.10.12 Pain
Abdominal pain, chest/thoracic pain, headache, arthralgias, myalgias, generalized.

8.2.10.13 Pulmonary/Upper respiratory
Dyspnea, cough, bronchospasm/wheezing, voice changes (hoarseness).

8.2.10.14 Renal/Genitourinary
Proteinuria, nephrotic syndrome

8.2.10.15 Vascular
Life-threatening and potentially fatal arterial thromboembolic events: cerebral infarction,transient ischemic attacks, myocardial infarction, angina. Venous thromboembolic events: deep vein thrombosis, intra-abdominal thrombosis

8.2.10.16 Reversible Posterior Leukoencephalopathy Syndrome
There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with RPLS, a rare neurologic disorder that

can present with the following signs and symptoms (among others): seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Brain imaging is mandatory to confirm the diagnosis of RPLS. In patients who develop RPLS, treatment of specific symptoms, including control of hypertension, is recommended along with discontinuation of bevacizumab. The safety of reinitiating bevacizumab therapy in patients previously experiencing RPLS is not known. [34,35].

8.2.11 Nursing Implications

Monitor CBC and platelets.

Monitor patient closely during infusion, for infusion related events and for bleeding.

Monitor blood pressure prior to each dose to assess for development of hypertension.

Instruct patient to monitor and report signs/symptoms of bleeding (nose bleeds, blood in sputum), wound healing problems, abdominal pain, thromboembolic problems (chest or leg pain, dyspnea, vision changes, severe headache, cough, swelling).

9 STATISTICAL CONSIDERATIONS

9.1 Endpoints

The primary endpoint in this phase II study will be overall survival (OS). Secondary endpoints will be hematologic and neurologic toxicities, progression free survival (PFS), and survival after re-irradiation.

9.2 Sample Size Justification & Assumptions

9.2.1 Glioblastoma (Groups 1 and 2)

Using the limited data available in similar groups of patients, as noted above in Table 1, those who have received systemic therapy alone have median survival ranging from 7.2-9.2 months [9, 13], and those who have received radiation seems to be in the range of 11-12.5 months [14, 17]. Those patients with GBM who are bevacizumab-naïve (Group 1) will presumably have improved overall outcomes compared to those who have been previously treated with bevacizumab (Group 2).

In Group 1, the primary hypothesis will be a 60% prolongation of survival (although we will measure survival as a hazard function, this is expected

to shift median from an anticipated 10 to 16 weeks. Using a one sample exponential survival model, to have at least 80% power to observe this delta, with a one-sided significance level of 0.1, a minimum of 22 patients will be required. This assumes 36 months of follow-up. Allowing for approximately 15% non-evaluability/drop-off, we anticipate a cohort size of 25.

In Group 2, the primary hypothesis will be a 50% prolongation of survival (although we will measure survival as a hazard function, this is expected to shift median from an anticipated 8 to 12 months). Using a one sample exponential survival model, to have at least 80% power to observe this delta, with a one-sided significance level of 0.1, a minimum of 34 patients will be required. This assumes 24 months of follow-up. Allowing for approximately 15% non-evaluability/drop-off, we anticipate a cohort size of 40.

9.2.2 Anaplastic Glioma (Groups 3 and 4)

There are no relevant clinical data to truly estimate the PFS in these patients. The purpose of enrolling these patients is to generate preliminary descriptive data and statistics for future clinical trial design. Therefore, in Groups 3 and 4, up to 6 patients will be enrolled in each group to determine response, PFS, and OS endpoints.

9.3 Analysis

Data will be analyzed using Kaplan-Meier curves for overall survival and the median survival will be determined from these curves.

9.4 Reporting and Exclusions

9.4.1 Evaluation of toxicity

All patients will be evaluable for toxicity from the time of their first treatment with bevacizumab, temozolomide, or radiation therapy.

9.4.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 8) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 8 usually designates the “unknown” status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria should be included in the main analysis of the survival and response endpoints. Patients in

response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-8 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals for response rate should also be provided.

10 ADVERSE EVENT MONITORING & REPORTING

This trial will be conducted in accordance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (see Appendices for link). The level of risk attributed to this study requires High Intensity Monitoring, as outlined in the DSMP. The assigned QAM, with oversight from the Data and Safety Monitoring Committee, will monitor this study in accordance with the study phase and risk level. Please refer to the Appendices for additional data submission instructions.

10.1 Adverse Event Monitoring

Collection and reporting of adverse event (AE) data is required as part of every clinical trial, and is done to ensure the safety of patients enrolled in this study as well as those who will enroll in future studies using similar agents. Toxicity will be assessed weekly during the initial phase of treatment and then prior to each cycle during the adjuvant phase (may be more frequently if needed), as described in Section 7.0. All adverse events will be reported on the appropriate eCRF (as outlined in Section 11.3) to the assigned QAM. Additionally, certain serious adverse events (SAEs) will be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

All patients experiencing an AE, regardless of its relationship to study drug, will be monitored until one of the following occurs:

- The AE resolves or the symptoms or signs that constitute the AE return to baseline.
- Any abnormal laboratory values have returned to baseline.
- There is a satisfactory explanation other than the study drug for the changes observed.
- Death.

10.2 Definitions & Descriptions

10.2.1 Adverse Event

An AE is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of an experimental intervention, whether or not related to the intervention.

Recording of AEs should be done in a concise manner using standard, acceptable medical terms. In general, AEs are not procedures or measurements, but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement. Preexisting conditions that worsen in severity or frequency during the study should also be recorded (a preexisting condition that does not worsen is not an AE). Further, a procedure or surgery is not an AE; rather, the event leading to the procedure or surgery is considered an AE.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the AE whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, "hepatitis" and not "elevated liver function tests" should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an AE, using appropriate medical terminology (e/g/ thrombocytopenia, peripheral edema, QT prolongation).

10.2.2 Severity of AEs

All adverse events will be graded according to the NCI's CTCAE version 4.0 (please see Appendices for link).

10.2.3 Serious Adverse Event

All SAEs, regardless of attribution, occurring from time of signed informed consent, through 30 days after the last administration of study drug, must be reported upon discovery or occurrence.

An SAE is any untoward medical occurrence that at any dose results in one of the following outcomes:

- **Results in *death*.**
  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
- **Is *life-threatening*.**

The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

- **Requires *in-patient hospitalization* or *prolongation of existing hospitalization* for ≥ 24 hours.**
- **Results in *persistent or significant disability or incapacity*.**
- **Is a *congenital anomaly/birth defect.***
- **Is an *important medical event*.**

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".

10.2.4 Exceptions to AE & SAE Definitions

Generally speaking, any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE, as described above. Likewise, any condition responsible for surgery should be documented as an AE if the condition meets the criteria for an AE. However, for the purposes of this study, neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as AEs or SAEs under the following circumstances:

10.2.4.1 Hospitalization or prolonged hospitalization is for a diagnostic or elective surgical procedure for a preexisting condition. Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.

10.2.4.2 Hospitalization or prolonged hospitalization is required to allow efficacy measurement for the study.

10.2.4.3 Hospitalization or prolonged hospitalization is required for study-directed therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the principal investigator.

10.2.4.4 Hospitalization or prolonged hospitalization is due to social reasons (i.e. awaiting transport home).

10.2.5 Unanticipated Problem Involving Risk to Subject or Others (UPIRSO)

In order for an adverse event to be reported to the Northwestern University IRB, it must qualify as a UPIRSO. In order to qualify as a UPIRSO, the event must meet <u>all three</u> of the following criteria:

10.2.5.1 The event must be unanticipated in terms of nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.).

10.2.5.2 The event must place the research subject or others at a different or greater risk of harm (including physical, psychological, economic, or social harm).

10.2.5.3 The event must be related or possibly related to participation in the study.

10.3 Adverse Event Reporting

10.3.1 Routine Reporting

All routine adverse events, such as those that are expected, or are unlikely or definitely not related to study participation, are to be reported on the appropriate eCRF. Routine AEs will be reviewed by the Data and Safety Monitoring Committee (DSMC) according to the study's phase and risk level, as outlined in the DSMP.

10.3.2 Determining if Expedited Reporting is Required

This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

1. Identify the type of adverse event using the NCI CTCAE v 4.0.
2. Grade the adverse event using the NCI CTCAE v 4.0.
3. Determine whether the adverse event is related to the protocol therapy.
   Attribution categories are as follows:
   - Definite: AE is clearly related to the study treatment.
   - Probable: AE is likely related to the study treatment.
   - Possible: AE may be related to the study treatment.
   - Unlikely: AE not likely to be related to the study treatment.
   - Unrelated: AE is clearly NOT related to the study treatment.
4. Determine the prior experience of the adverse event.
   Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:
   - the current protocol
   - the drug package insert
   - the current Investigator's Brochure

10.3.3 Expedited Reporting of SAEs/Other Events

10.3.3.1 Reporting to the Northwestern University QAM/DSMC

All SAEs must be reported to the assigned QAM within 24 hours of becoming aware of the event. Completion of the NU CRO SAE Form, provided as a separate document, is required.

The completed form should assess whether or not the event qualifies as a UPIRSO. The report should also include:

- Protocol description and number(s)
- The patient's identification number
- A description of the event, severity, treatment, and outcome (if known)
- Supportive laboratory results and diagnostics
- The hospital discharge summary (if available/applicable)

All SAEs will be reported to, and reviewed by, the DSMC at their next meeting.

10.3.3.2 Reporting to the Northwestern University IRB

- Any death of an NU subject that is unanticipated in nature and at least possibly related to study participation will be promptly reported to the NU IRB within 24 hours of notification.
- Any death of an NU subject that is actively on study treatment (regardless of whether or not the event is possibly related to study treatment)
- Any death of a non-NU subject that is unanticipated and at least possibly related and any other UPIRSOs will be reported to the NU IRB within 10 working days of notification.
- All other deaths of NU subjects not previously reported, other non-NU subject deaths that were unanticipated and unrelated, and any other SAEs that were not previously reported as UPIRSOs will be reported to the NU IRB at the time of annual continuing review.

11 RECORDS TO BE KEPT

Please refer to Appendix VI for detailed instructions regarding the entry and submission of data using eCRFs through NOTIS. Instructional videos are also available on the CRO website at: https://www.cancertrials.northwestern.edu/collaborations/nu-iit-sites.

In addition to the regular hospital chart, a separate patient folder will be kept which includes the patient's signed, dated informed consent document.

11.1 Patient Registration

Please refer to section 4.0 for detailed instructions.

11.2 Data Submission

Once subject is confirmed and enrolled to the study, the following eCRFs should be submitted to the assigned Quality Assurance Monitor through NOTIS according to the data submission schedule found in the appendices:

12 PATHOLOGY REQUIREMENTS

All patients who had surgery outside of Northwestern Memorial Hospital will be asked to submit their pathology for review at NMH for confirmation of diagnosis. A copy of the pathology report from the primary surgery is sufficient for registration. Biopsy proof of recurrent disease is not required. Dr. Qinwen Mao is the designated Neuro-Oncology Neuropathologist.

13 ADMINISTRATIVE, ETHICAL & REGULATORY CONSIDERATIONS

13.1 Conduct

This study will be conducted in accordance with the Declaration of Helsinki, Good Clinical Practices (GCP) guidelines and all applicable government regulations and Institutional research policies and procedures. The Principal Investigator or qualified designees are responsible for reporting all amendments, safety updates, and protocol violations. This study will be monitored in accordance with the Data Safety Monitoring Plan of the Lurie Cancer Center of Northwestern University and will abide by its policies and practices.

13.2 Amendments

The Principal Investigator will formally initiate all amendments to the protocol and/or informed consent. All amendment s will be subject to the review and approval of the appropriate local, institutional, and governmental regulatory bodies. Amendments will be distributed by the lead institution (Northwestern) to all affiliate sites upon approval by the Northwestern University IRB.

13.3 Informed Consent

The investigator is responsible for ensuring that no patient participates in any study-related examination or activity before that patient has given informed consent. The informed consent will be provided both through the written informed consent document and through verbal review of all information contained therein. Information provided in this way is to include potential benefits, aims of the study, potential harms or side effects and methods of the study. The patient will be given opportunity to ask questions about any aspect of the information and will be given time to review the information on their own. The patient may, after having been provided with this detailed written and verbal information, provide written consent. The patient will then be provided a copy of the executed informed consent for their reference. The patient is free to withdraw consent at any time and for any reason. The only consequence of consent withdrawal is that the patient is no longer able to participate in the study.

13.4 Protected Health Information

In accordance with the Health Information Portability and Accountability Act (HIPAA), patients who have provided written informed consent must also sign a subject authorization to release medical information to the study Sponsor and allow a regulatory authority, or Institutional Review Board access to subject's medical information relevant to the study. This authorization may be combined with the informed consent form in accordance with local institutional practice.

13.5 Participating Sites

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Research Office at Northwestern University:

- Signed and completed Letter of Invitation to participate in the study.
- Signed copy of Northwestern University's Data and Safety Monitoring Committee policy pertaining to data submission.
- A copy of the official IRB approval letter for the protocol and informed consent.
  NOTE: Informed consent form should be submitted to the Clinical Research Office for review/approval prior to submission to the local IRB.
- CVs and medical licensure for the local PI and any sub-investigators who will be involved in the study at the site.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation.

13.6 Data Management and Monitoring/Auditing

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to Appendix I). The level of risk attributed to this study requires High Intensity Monitoring, as outlined in the DSMP. The assigned QAM, with oversight from the Data and Safety Monitoring Committee, will monitor this study in accordance with the study phase and risk level. Please refer to the Appendix VI for additional data submission instructions.

13.7 Publication Policy

All potential publications and/or data for potential publications (e.g. manuscripts, abstracts, posters, clinicaltrials.gov releases) must be approved in accordance with the policies and processes set forth in the Lurie Cancer Center DSMP. The assigned QAM will prepare a preliminary data summary (to be approved by the DSMC) no later than 3 months after the study reaches its primary completion date (the date that the final subject is examined or receives an intervention for the purposes of final data collection for the primary endpoint). If the investigator's wish to obtain DSMC-approved data prior to this point (or prior to the point dictated by study design), the PI must send a written request for data to the QAM which includes justification. If the request is approved, data will be provided no later than 4 weeks after this request approval. The data will be presented to the DSMC at their next available meeting, and a final, DSMC-approved dataset will

be released along with any DSMC decisions regarding publication. The investigators are expected to use only DSMC-approved data in future publications. The investigators should submit a copies of the manuscript to the biostatistician to confirm that the DSMC-approved data are used appropriately. Once the biostatistician gives final approval, the manuscript may be submitted to external publishers.

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15 APPENDICES

15.1 Appendix I – Data and Safety Monitoring Plan

This trial will be conducted and monitored in accordance with the Data and Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University; a copy of the current DSMP can be obtained from the following link:

https://cancertrials.northwestern.edu/cpsrms/cpsrms-p-ps

Data is expected to be submitted according to requirements described in appendix VI. The QAM will review and assess each submitted eCRF for completeness, protocol adherence/compliance, toxicities or potential subject safety issues, and disease outcome and response. The QAM will routinely query study teams regarding any issues or for outstanding data. The QAM will present SAEs, protocol deviations, data summaries, and any other issues that may impact patient safety or data integrity to the DSMC on a semi-monthly basis.

15.2 Appendix II – CTCAE v 4.0

A copy of the NCI's Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0 and guidelines for use can be found at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

15.3 Appendix III – ECOG Performance Status

ECOG PERFORMANCE STATUS*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.*

15.4 Appendix IV – FACT-Br & FACT-Fatigue Scales

FACT-Br and FACT-Fatigue scales that will be used are attached as separate PDF documents.

15.5 Appendix V – Protocol History of Changes

Original IRB-Approved Version – November 2, 2011			
Amendment 1 – February 3, 2012 *Scientific Review Committee Approval – February 23, 2012*			
Section(s) Affected	***Prior Version***	***Amendment 1 Changes***	***Rationale***
Cover-page, Synopsis	No additional sites participating.	Adds Dr. William Broderick (Edward Cancer Center) and Dr. Joseph Imperato (Northwestern Lake Forest Hospital) as participating sites. Removes Dr. Virginia Diavolitsis from the list of Northwestern sub-investigators.	Administrative
7.0 (Study Parameters)	Chemistry panel tests required at baseline/screening but not marked on table.	Adds an "X" for chemistry panel tests at baseline/screening.	Corrects an error.
Amendment 2 – July 18, 2012 *Scientific Review Committee Approval – July 18, 2012*			
Section(s) Affected	***Prior Version***	***Amendment 2 Changes***	***Rationale***
Cover-page, Synopsis	Dr. Minesh Mehta listed as the PI 1. Drs. Raizer and Sean Grimm listed as sub-investigators. 2. n/a	1. Replaces Dr. Mehta with Dr. Jeffrey Raizer 2. Removes Dr. Raizer (now the PI) and Dr. Grimm and lists Dr. Priya Kumthekar. 3. Adds University of Chicago (Dr. M. Kelly Nicholas) as a	1. Dr. Mehta is leaving the institution. 2. Dr. Grimm is leaving the institution and Dr. Kumthekar has recently come on board. 3. Administrative

		participating site.	
Section 3.1 (Inclusion Criteria)	Lab parameters for baseline eligibility to have been within 14 days prior to ***initiation of study treatment.***	Revises lab parameters to have been within 14 days prior to ***study registration.***	This was done to correct an error and to align this section with Section 7.0 (Study Parameters)
Amendment 3 – August 30, 2012 *Scientific Review Committee Approval – September 19, 2012*			
Section(s) Affected	***Prior Version***	***Amendment 3 Changes***	***Rationale***
Cover-page, Synopsis	n/a	Adds Dr. Vinai Gondi (Central Dupage Hospital) as a participating site.	Administrative
Section 5.2.1 (Re-Irradiation Therapy)	n/a	Adds statement clarifying that proton therapy is an acceptable mode of radiotherapy for this study.	Clarification
Synopsis, Sections 5.1 (Treatment Overview) & 9.2 (Sample Size Justification & Assumptions)	Overall sample size listed as 80 subjects.	Corrects errors in the power analysis and adjusts sample size accordingly to 120 subjects.	Change necessitated to correct an error, as pointed out during review at an affiliate site.
Section 5.3.1.2 (Adjuvant Phase Delays/Modifications)	Stated that new cycles may be delayed up to 4 weeks in the event of Grade 4 hematologic toxicity (including a platelet count of < 25,000/mm^3)	Adds that this *excludes lymphopenia.*	Clarification
Amendment 4 – October 30, 2012 *Scientific Review Committee Approval – November 7, 2012*			
Section(s) Affected	***Prior Version***	***Amendment 4 Changes***	***Rationale***
5.1 (Treatment Plan –	Adjuvant cycles	Adds statements	Revised to allow

Overview), 5.2.2 (Temozolomide Administration), 5.2.3 (Bevacizumab Administration), 7.0 (Study Parameters)	occur every 8 weeks with no spacing between.	allowing cycles during the adjuvant phase of treatment to be spaced +/- 1 week apart.	flexibility in scheduling.
7.0 (Study Parameters)	MRI/CT to be performed at baseline (within 30 days of registration), after the initial phase of treatment (approximately 1 week after the last dose of re-irradiation therapy), and then prior to each new cycle of therapy during the adjuvant phase (1 cycle = 8 weeks).	Specifies that scans during the adjuvant phase will be done **on Day 1 or within 7 days prior** to each new cycle of therapy.	Added for clarity.
Amendment 5 – May 29, 2013 *Scientific Review Committee Approval – June 5, 2013*			
Section(s) Affected	***Prior Version***	***Amendment 5 Changes***	***Rationale***
Cover Page	CDH/ProCure were not listed as separate sites.	CDH and ProCure are now listed as two sites.	Administrative
Synopsis, 5.1 (Overview), 9.2 (Sample Size Justification & Assumptions)	Total accrual goal was 120 subjects.	Revises accrual goal to 77 subjects 40 GBM bevacizumab-naïve, 25 GBM bevacizumab-exposed, 6 anaplastic glioma bevacizumab-naïve, 6 anaplastic glioma bevacizumab-exposed).	This was revised at the request of the Data Monitoring Committee as a result of concerns over the slow accrual thus far.
3.0 (Selection of Patients)	Dr. Minesh Mehta still mentioned as the PI.	Replaces this with Dr. Jeffrey Raizer.	Administrative

3.1 (Inclusion Criteria), 3.2 (Exclusion Criteria)	Systolic blood pressure required to be <140 mmHg to be eligible.	Changed to require < 145 mmHg.	The PI determined that the previous requirement was too strict.
6.4 (Evaluation of Response)	n/a	Adds information regarding pseudoprogression, including how to distinguish between that vs. true progression and whether or not to continue treatment.	Added for clarity.
7.0 (Study Parameters)	1. Physical exam/ECOG score & hematology tests required weekly during the Initial (re-irradiation) phase. 2. n/a	1. Changes this to be required only during weeks when the patient is scheduled to receive bevacizumab (Weeks 3 and 5). 2. Adds a footnote clarifying when reflex UPC is required vs. when urine dip is acceptable throughout the initial phase, treatment break, and adjuvant phase of treatment. 3. Clarifies that if screening labs & physical were performed within 14 days prior to the first dose of bevacizumab, they do not need	Changes made to simplify the study schedule and avoid unnecessary tests/assessments.

		to be repeated.	
Amendment 6 – March 14, 2014 *Scientific Review Committee Approval – May 2, 2014*			
Section(s) Affected	***Prior Version***	***Amendment 6 Changes***	***Rationale***
Cover-page	Listed Drs. Levy, Batjer, and Getch as NU sub-investigators.	Removes Drs. Levy, Batjer, and Getch as NU sub-I's.	No longer at NU.
Cover-page, Synopsis	Referred to "CDH Proton Center, A Procure Center" as a participating site.	Changes this to "CDH-Delnor Health System d/b/a Cadence Health"	Administrative – needed to match contract language.
4.0 (Patient Registration)	Contained outdated language and instructions.	Updates language and instructions to reflect current practices and procedures. Adds use of the eligibility checklist.	Administrative
7.0 (Study Parameters)	n/a	Revises study parameters table to more clearly reflect the requirements.	Administrative
10.0 (Adverse Event Monitoring)	Contained outdated language and instructions.	Updates language and instructions to reflect current practices and procedures. Adds use of the NU CRO SAE form.	Administrative
11.0 (Records to be Kept)	Contained outdated language and instructions.	Updates language and instructions to reflect current practices and procedures.	Administrative
Appendices	n/a	Updates the DSMP link and information. Adds a whole new appendix VI to provide study-specific instructions for data submission.	Administrative

Amendment 7 – August 21, 2014 *Scientific Review Committee Approval – N/A*			
Section(s) Affected	***Prior Version***	***Amendment 6 Changes***	***Rationale***
7.0 (Study Parameters)	Deleted demarcation of required procedures in EOT column of parameters table.	Added demarcation of required procedures in EOT column in accordance with 5/29/2013 version of the protocol.	Administrative
Amendment 8 – April 1, 2015 *Scientific Review Committee Approval – April 15, 2015*			
5.2.1 (Re-irradiation Therapy)	n/a	Revised to add "If standard SIB technique is not felt to be in the patient's best interest due to potential toxicity, then standard fractioned EBRT at 180-200 cGY will be used."	Added radiation option for patients due to potential toxicity with standard SIB technique
9.2.1 (Statistical Considerations)	n/a	Revised to clarify that group 1 is bev-naïve GBM, and group 2 is bev-exposed GBM to be in line with the rest of the protocol.	Administrative
Amendment 9 – May 21, 2018 *Scientific Review Committee Approval – 5-23-2018*			
Section(s) Affected	***Prior Version***	***Amendment 9 Changes***	***Rationale***
Throughout Protocol	n/a	Formatting was updated	To align with the NU IIT template
Cover-page, Synopsis	Dr. Jeffrey Raizer listed as the PI	Replaces Dr. Raizer with Dr. Dixit Dr. Raizer is listed as Sub-I	Dr. Raizer will no longer serve as the PI.
	"Statistician"	"Biostatistician"	To align with NU IIT Template

	n/a	Version date was included	To align with NU IIT Template
Section 3.0 (Selection of Patients)	Dr. Raizer is mentioned as the PI.	Replaces this with Dr. Dixit.	Administrative
Section 10 (Adverse Event Monitoring & Reporting); Section 10.3.3.1 (Reporting to the Northwestern University QAM/DSMC); Section 13.5 (Participating Sites)	Data Monitoring Committee (DMC)	Data **and Safety** Monitoring Committee (DSMC)	Committee name has been changed.
Section 10.2 (Definitions & Descriptions); Section 10.3 (Adverse Event Reporting); 13.6 (Data Management and Monitoring/Auditing); Section 13.7 (Publication Policy)	n/a	Updated section with language from the NU IIT template	To align with NU IIT Template
Amendment 10 – September 11, 2018 *Scientific Review Committee Approval – 9/12/18*			
Section(s) Affected	***Prior Version***	***Amendment 10 Changes***	***Rationale***
Cover Page	Dr. Nicholas listed as PI at University of Chicago	Dr. Chmura listed as PI at University of Chicago	Administrative
	n/a	Addition of Dr. Rademaker's email address.	Administrative.
Amendment 11 – February 5, 2019 *Scientific Review Committee Approval –*			
Section(s) Affected	***Prior Version***	***Amendment 11 Changes***	***Rationale***
Section 5.6 (Follow-Up); Section 6.1.3 (Overall Survival); Section 6.1.4 (Progression Free Survival); Section 7 (Study Parameters); Appendix VI (Data	Patients followed until death	Included note "As of December 31, 2018, patients will no longer be followed and follow up information will not be collected."	Study PIs are already working on publication and not going to collect any more data.

Collection and Submission Guidelines)			

15.6 Appendix VI – Data Collection & Submission Guidelines

Study-specific instructions regarding the entry and submission of data using eCRFs through NOTIS will be provided at the time of training prior to study activation. In addition, instructional videos on data entry using NOTIS and eCRFs are available on the CRO's website at: https://www.cancertrials.northwestern.edu/working-with-the-cro. The Internal and Affiliate Data Compliance Policies of the Lurie Cancer Center's DSMC regarding will be strictly enforced.

Study Chart & eCRFs
In addition to the regular hospital chart, a separate patient folder will be kept which includes the patient's signed, dated informed consent document. Once a subject is confirmed and enrolled to the study, the following eCRFs should be submitted to the QAM through NOTIS.

Forms to be submitted prior to registration:
Please see Section 4.0 for all forms/documentation to be submitted prior to registration.

Forms to be submitted within 5 days of registration:
- Concomitant Medications Form: *updated to reflect the patients' information at the time of registration.*
- Adverse Event Forms: *update to reflect the adverse events that were present at baseline*
- On-Study Form: *dates and results of all baseline exams/tests/labs required to be performed prior to registration including:*
    - *Medical history*
    - *Physical exam (vitals, weight)*
    - *ECOG PS*
    - *CBC with platelets and differential, comprehensive metabolic panel*
    - *Pregnancy test (if applicable)*
    - *MRI or CT*
    - *Urine Protein/Creatinine Ratio*
- Study-specific document uploads:
    - RANO Spreadsheet Upload: *should reflect the measurements assessed at baseline*
    - FACT-BR and FACT-fatigue Uploads: *Upload the assessments from baseline*

Forms to be submitted after the Initial Phase of treatment:
- Labs Order Form: *There should be separate entries for weeks 3 and 5.*
- Adverse Events Form: *Should include all adverse events that occurred/were reported on a weekly basis through the initial phase.*
- Patient Vitals Form: *There should be separate entries for each weekly assessment conducted during this period.*
- Concomitant Medications Form: *Should be updated as necessary.*

- Treatment Log: *All doses of bevacizumab and temozolomide should be recorded for all treatment administered in the initial phase. A completed medication diary should be collected and uploaded under the treatment log.*
- RT Reports: *The radiation treatment summary should be uploaded to NOTIS at the end of RT.*

Forms to be submitted after the "treatment break":
- Labs Order Form: *Enter just Urine Protein/creatinine ratio.*
- RANO Spreadsheet Upload: *Upload the RANO spreadsheet for measurements assessed during treatment break.*
- FACT-BR and FACT-fatigue Uploads: *Upload the assessments performed during the treatment break.*

Forms to be submitted after every cycle (every 8 weeks) during the Adjuvant Phase:
- Labs Order Form
- Adverse Events Form: *Should include all adverse events that occurred/were reported during each cycle.*
- Patient Vitals Form: *These are to be performed monthly (there should be 2 entries submitted for each cycle).*
- Concomitant Medications Form: *Should be updated as necessary.*
- Treatment Log: *All doses of bevacizumab and temozolomide should be recorded for all treatment administered after each cycle. Completed medication diaries (2 monthly calendars for each cycle) should be collected and uploaded under the treatment log.*
- RANO Spreadsheet Upload: *Upload the RANO spreadsheet for measurements assessed after each cycle.*
- FACT-BR and FACT-fatigue Uploads: *Upload the assessments performed after each cycle.*

Forms to be submitted after the end-of treatment visit is conducted:
- Labs Order Form
- Adverse Events Form: *Should include all adverse events through the end of treatment visit*
- Patient Vitals Form
- Concomitant Medications Form: *Should be updated as necessary.*
- RANO Spreadsheet Upload: *Upload the RANO spreadsheet for measurements assessed at the end of treatment visit.*
- FACT-BR and FACT-fatigue Uploads: *Upload the RANO spreadsheet for measurements assessed at the end of treatment visit.*
- Off-treatment Form: *Complete part of this form within 1 week the subject's end of treatment visit.*

Forms to be completed during follow-up period:
- Survival Status Form: *Complete every 3 months until death or patient is lost to follow-up*
  Note: As of December 31, 2018, patients will no longer be followed and follow up

information will not be collected.

	Prior to registration	**Within 5 days of registration**	**After Initial Phase is Complete**	**After Treatment Break**	**After each Cycle of Adjuvant Phase**	**End of Treatment Visit**	**Follow-up**
Eligibility Form	X						
Informed Consent Form	X						
Pathology Report	X						
Eligibility Checklist	X						
On-Study Form		X					
Concomitant Medications Form		X[1]	X[5]	X[5]	X[5]	X[5]	
Patient Vitals Form			X[3]		X[8]	X	
Labs Order Form			X[3]		X[9]	X	
AE Form		X[2]	X	X	X	X	
Treatment form			X[4]		X[4]		
Medication Diary Upload			X[4]		X[4]		
RT Summary Upload			X[6]				
RANO Spreadsheet Upload		X[7]		X[10]	X[11]	X	
Off-Treatment Form						X[12]	
Survival Status Form							X[13]

1 Should reflect medications taken at baseline
2 Should reflect all AEs present at baseline
3May be entered at end of initial treatment phase, but should reflect vitals required after weeks 3 and 5
4 Bevacizumab and temozolomide doses to be entered and diary to be uploaded after pt returns completed medication diary for initial phase of treatment and each diary completed during adjuvant phase
5 Update as required
6 RT Treatment summary to be uploaded under "RT reports" after radiation is complete.
7 Should reflect assessment done at baseline.
8 To be completed after each cycle. There should be two entries submitted for monthly vitals required during the cycle.
9 To be completed after each cycle.
10 Should reflect assessment done during treatment break
11 Completed RANO spreadsheet should be uploaded for every cycle it's assessed in adjuvant phase.
12 Complete part of this form within 1 week the subject's end of treatment visit.
13 Complete every 3 months until death or patient is lost to follow-up. **Note: As of December 31, 2018, patients will no longer be followed and follow up information will not be collected.**