The Preston Robert Tisch Brain Tumor Center
Duke University Medical Center

Title

Phase II Trial of Bevacizumab, Radiation Therapy and Temodar followed by Bevacizumab and Temodar with Continuation of Bevacizumab Beyond Progression (BBP-Bevacizumab Beyond Progression)

Study Drugs

Bevacizumab (Avastin)
Temozolomide (Temodar)

Support Provided By

Genentech, Inc.

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2 Background

2.1 Disease Background

There is an unmet clinical need for the therapy of malignant gliomas with a median survival of <20 months despite available therapies. The current standard of care is radiation therapy with daily temozolomide followed by 6 cycles of temozolomide.[1] Vascular endothelial growth factor (VEGF) is present on the cell surface and around malignant gliomas.[2, 3] It appears that the presence of vascular endothelial growth factor is a prognostic growth factor with more VEGF expression correlating with a poor prognosis.[4, 5] Monoclonal antibodies to VEGF have inhibited growth of malignant gliomas in a mouse xenograft.[6] Bevacizumab is a humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor. Bevacizumab has been shown to have acceptable toxicity and efficacy in colorectal, non-small cell lung, renal carcinomas and glioblastoma in a multitude of studies.[7-11]

2.2 Bevacizumab Clinical Experience

Bevacizumab has been studied in a multitude of Phase I, II, and III clinical trials in more than 5000 patients and in multiple tumor types. In addition, data are available from 3,863 patients enrolled in two post-marketing studies in metastatic colorectal cancer (CRC). Approximately 130,000 patients have been exposed to bevacizumab as a marketed product or in clinical trials. The following discussion summarizes bevacizumab's safety profile and presents some of the efficacy results pertinent to this particular trial. Please refer to the bevacizumab Investigator Brochure for descriptions of all completed Phase I, II, and III trials reported to date.

Arnold and al. were the first to show in a randomized study that bevacizumab plus chemotherapy continued beyond progression significantly prolongs the overall survival and progression-free survival of metatastic colorectal cancer patients.[12] In a large phase III study (AVF2107g) in patients with metastatic colorectal cancer, the addition of bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF), to irinotecan/5-fluorouracil/leucovorin (IFL) chemotherapy resulted in a clinically and statistically significant increase in duration of survival, with a hazard ratio of death of 0.67 (median survival 15.6 vs. 20.3 months; $p < 0.001$). Similar increases were seen in progression-free survival (6.2 vs. 10.6 months; $p < 0.001$), overall response rate (35% vs. 45%; $p < 0.01$) and duration of response (7.1 vs. 10.4 months; $p < 0.01$) for the combination arm versus the chemotherapy only arm (bevacizumab Investigator Brochure, October 2005).

Based on the survival advantage demonstrated in Study AVF2107g, bevacizumab was designated for priority review and was approved on 26 February 2004 in the United States for first-line treatment in combination with IV 5-FU–based chemotherapy for subjects with metastatic colorectal cancer.

Additional data from Phase III trials in metastatic CRC (E3200), non-small cell lung cancer (NSCLC; E4599), and metastatic breast cancer (E2100) have also demonstrated clinical benefit from bevacizumab when added to chemotherapy. In Study E3200, the addition of bevacizumab to FOLFOX chemotherapy resulted in improved overall survival compared with FOLFOX alone

(13.0 vs. 10.8 months, respectively, HR = 0.75; $p < 0.01$) in a population of previously treated CRC patients.

There was also improved overall survival in first-line NSCLC patients (E4599) treated with carboplatin/paclitaxel + bevacizumab compared with chemotherapy alone (12.3 vs. 10.3 months, respectively; HR = 0.80; $p = 0.003$). The results from this trial were the basis for FDA approval of bevacizumab for use in combination with carboplatin + paclitaxel as first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic, non-squamous NSCLC in October 2006. Finally, patients with untreated metastatic breast cancer (E2100) who received bevacizumab in combination with weekly paclitaxel had a marked improvement in PFS compared with chemotherapy alone (13.3 vs. 6.7 months, respectively; HR = 0.48; $p < 0.0001$) (see the Bevacizumab Investigator Brochure for additional details).

2.2.1 Safety Profile

In the initial Phase I and II clinical trials, four potential bevacizumab-associated safety signals were identified: hypertension, proteinuria, thromboembolic events, and hemorrhage. Additional completed Phase II and Phase III studies of bevacizumab as well as spontaneous reports have further defined the safety profile of this agent. Bevacizumab-associated adverse events identified in phase III trials include congestive heart failure (CHF) primarily in metastatic breast cancer, gastrointestinal perforations, wound healing complications, and arterial thromboembolic events (ATE). These and other safety signals are described in further detail as follows and in the bevacizumab Investigator Brochure.

Hypertension: An increased incidence of hypertension has been observed in patients treated with bevacizumab. Grade 4 and 5 hypertensive events are rare. Clinical sequelae of hypertension are rare but have included hypertensive crisis, hypertensive encephalopathy, and reversible posterior leukoencephalopathy syndrome (RPLS).[13, 14]

There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating bevacizumab therapy. Therefore, caution should be exercised before initiating bevacizumab therapy in these patients. Monitoring of blood pressure is recommended during bevacizumab therapy. Optimal control of blood pressure according to standard public health guidelines is recommended for patients on treatment with or without bevacizumab.

Temporary interruption of bevacizumab therapy is recommended in patients with hypertension requiring medical therapy until adequate control is achieved. If hypertension cannot be controlled with medical therapy, bevacizumab therapy should be permanently discontinued. Bevacizumab should be permanently discontinued in patients who develop hypertensive crisis or hypertensive encephalopathy.

Proteinuria: An increased incidence of proteinuria has been observed in patients treated with bevacizumab compared with control arm patients. In the bevacizumab-containing treatment arms of clinical trials (across all indications), the incidence of proteinuria (reported as an adverse event) was up to 38% (metastatic CRC Study AVF2192g). The severity of proteinuria has ranged from asymptomatic and transient events detected on routine dipstick urinalysis to nephrotic

syndrome; the majority of proteinuria events have been grade 1. NCI-CTC Grade 3 proteinuria was reported in up to 3% of bevacizumab-treated patients, and Grade 4 in up to 1.4% of bevacizumab-treated patients. The proteinuria seen in bevacizumab clinical trials was not associated with renal impairment and rarely required permanent discontinuation of bevacizumab therapy. Bevacizumab should be discontinued in patients who develop Grade 4 proteinuria (nephrotic syndrome).

Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. There is evidence from the dose-finding, Phase II trials (AVF0780g, AVF0809s, and AVF0757g) suggesting that Grade 1 proteinuria may be related to bevacizumab dose.

Proteinuria will be monitored by urine protein:creatinine (UPC) ratio at least every 6 weeks. If the UPC ratio is not available, a dipstick urinalysis may be used to allow treatment to proceed.

Thromboembolic Events: Both venous and arterial thromboembolic (TE) events, ranging in severity from catheter-associated phlebitis to fatal, have been reported in patients treated with bevacizumab in the colorectal cancer trials and, to a lesser extent, in patients treated with bevacizumab in NSCLC and breast cancer trials.

Venous thromboembolism (including deep venous thrombosis, pulmonary embolism, and thrombophlebitis: In the phase III pivotal trial in metastatic CRC, there was a slightly higher rate of venous TE events in patients treated with bevacizumab plus chemotherapy compared with chemotherapy alone (19% vs. 16%).

In Study AVF2107g, a Phase III, pivotal trial in metastatic CRC, VTE events, including deep venous thrombosis, pulmonary embolism, and thrombophlebitis, occurred in 15.2% of patients receiving chemotherapy alone and 16.6% of patients receiving chemotherapy + bevacizumab.

The incidence of NCI-CTC Grade ≥ 3 venous VTE events in one NSCLC trial (E4599) was higher in the bevacizumab-containing arm compared to the chemotherapy control arm (5.6% vs. 3.2%). One event (0.2%) was fatal in the bevacizumab-containing arm; not fatal events were reported in the carboplatin/paclitaxel arm (see Bevacizumab Investigator Brochure).
In metastatic CRC clinical trials, the incidence of VTE events was similar in patients receiving chemotherapy + bevacizumab and those receiving the control chemotherapy alone.

In clinical trials across all indications the overall incidence of VTE events was 2.8%–17.3% in the bevacizumab-containing arms compared with 3.2%–15.6% in the chemotherapy control arms. The use of bevacizumab with chemotherapy does not substantially increase the risk of VTE event compared with chemotherapy alone. However, patients with metastatic CRC who receive bevacizumab and experienced a VTE event may be at higher risk for recurrence of VTE event.

Arterial Thromboembotic Events: An increased incidence of ATE events was observed in patients treated with bevacizumab compared with those receiving control treatment. ATE events

include cerebrovascular accidents, myocardial infarction, transient ischemic attacks (TIAs), and other ATE events. In a pooled analysis of data from five randomized Phase II and III trials (mCRC [AVF2107g, AVF2192g, AVF0780g]; locally advanced or metastatic NSCLC [AVF0757g]; metastatic breast cancer [AVF2119g]), the incidence rate of ATE events was 3.8% (37 of 963) in patients who received chemotherapy + bevacizumab compared with 1.7% (13 of 782) in patients treated with chemotherapy alone. ATE events led to a fatal outcome in 0.8% (8 of 963) of patients treated with chemotherapy + bevacizumab and 0.5% (4 of 782) of patients treated with chemotherapy alone. Cerebrovascular accidents (including TIAs) occurred in 2.3% of patients treated with chemotherapy + bevacizumab and 0.5% of patients treated with chemotherapy alone. Myocardial infarction occurred in 1.4% of patients treated with chemotherapy + bevacizumab compared with 0.7% of patients treated with chemotherapy alone (see the Bevacizumab Investigator Brochure for additional details).

Aspirin is a standard therapy for primary and secondary prophylaxis of arterial thromboembolic events in patients at high risk of such events, and the use of aspirin ≤ 325 mg daily was allowed in the five randomized studies discussed above. Use of aspirin was assessed routinely as a baseline or concomitant medication in these trials, though safety analyses specifically regarding aspirin use were not preplanned. Due to the relatively small numbers of aspirin users and arterial thromboembolic events, retrospective analyses of the ability of aspirin to affect the risk of such events were inconclusive. However, similarly retrospective analyses suggested that the use of up to 325 mg of aspirin daily does not increase the risk of grade 1-2 or grade 3-4 bleeding events, and similar data with respect to metastatic colorectal cancer patients were presented at ASCO 2005.[15] Further analyses of the effects of concomitant use of bevacizumab and aspirin in colorectal and other tumor types are ongoing.

Gastrointestinal perforation Patients with metastatic carcinoma may be at increased risk for the development of gastrointestinal perforation and fistula when treated with bevacizumab and chemotherapy. Bevacizumab should be permanently discontinued in patients who develop gastrointestinal perforation. A causal association of intra-abdominal inflammatory processes and gastrointestinal perforation to bevacizumab treatment has not been established. Nevertheless, caution should be exercised when treating patients with intra-abdominal inflammatory processes with bevacizumab. Gastrointestinal perforation has been reported in other trials in non-colorectal cancer populations (e.g., ovarian, renal cell, pancreas, breast, and NSCLC) and may be higher in incidence in some tumor types.

Fistula: Bevacizumab use has been associated with serious cases of fistulae including events resulting in death. Fistulae in the GI tract are common (1%–10% incidence) in patients with metastatic CRC, but uncommon (0.1%–1%) or rare (0.01%–0.1%) in other indications. In addition, fistulae that involve areas of the body other than the GI tract (e.g., tracheoesophageal, bronchopleural, urogenital, biliary) have been reported uncommonly (0.1%–1%) in patients receiving bevacizumab in clinical studies and postmarketing reports. Events were reported at various timepoints during treatment, ranging from 1 week to > 1 year following initiation of bevacizumab, with most events occurring within the first 6 months of therapy.

Permanently discontinue bevacizumab in patients with tracheoesophageal fistulae or any Grade 4 fistula. Limited information is available on the continued use of bevacizumab in patients with other fistulae. In cases of internal fistula not arising in the GI tract, discontinuation of bevacizumab should be considered.

Wound healing complications: Wound healing complications such as wound dehiscence have been reported in patients receiving bevacizumab. In an analysis of pooled data from two trials in metastatic colorectal cancer, patients undergoing surgery 28-60 days before study treatment with 5-FU/LV plus bevacizumab did not appear to have an increased risk of wound healing complications compared to those treated with chemotherapy alone.[16] Surgery in patients currently receiving bevacizumab is not recommended. No definitive data are available to define a safe interval after bevacizumab exposure with respect to wound healing risk in patients receiving elective surgery; however, the estimated half-life of bevacizumab is 21 days. Bevacizumab should be discontinued in patients with severe wound healing complications.

If patients receiving treatment with bevacizumab require elective major surgery, it is recommended that bevacizumab be held for 4–8 weeks prior to the surgical procedure. Patients undergoing a major surgical procedure should not begin or restart bevacizumab until 4 weeks after that procedure (in the case of high-risk procedures such as liver resection, thoracotomy, or neurosurgery, it is recommended that chemotherapy be restarted no earlier than 6 weeks and bevacizumab no earlier than 8 weeks after surgery).

In the study of patients with relapsed glioblastoma (study AVF3708g), the incidence of post-operative wound healing complications (craniotomy site wound dehiscence and cerebrospinal fluid leak) was 3.6% in patients treated with single-agent Avastin and 1.3% in patients treated with Avastin plus irinotecan.

Hemorrhage: Overall, grade 3 and 4 bleeding events were observed in 4.0% of 1132 patients treated with bevacizumab in a pooled database from eight phase I, II, and III clinical trials in multiple tumor types (bevacizumab Investigator Brochure, October 2005). The hemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumor-associated hemorrhage (see below) and minor mucocutaneous hemorrhage.

Tumor-Associated Hemorrhage: Major or massive pulmonary hemorrhage or hemoptysis has been observed primarily in patients with NSCLC. Life-threatening and fatal hemoptysis was identified as a bevacizumab-related adverse event in NSCLC trials. These events occurred suddenly and presented as major or massive hemoptysis. Among the possible risk factors evaluated (including squamous cell histology, treatment with anti-rheumatic/anti-inflammatory drugs, treatment with anticoagulants, prior radiotherapy, bevacizumab therapy, previous medical history of atherosclerosis, central tumor location, and cavitation of tumors during therapy), the only variables that showed statistically significant correlations with bleeding were bevacizumab therapy and squamous cell histology.

GI hemorrhages, including rectal bleeding and melena have been reported in patients with CRC, and have been assessed as tumor-associated hemorrhages.

Tumor-associated hemorrhages were also seen rarely in other tumor types and locations, including a case of CNS bleeding in a patient with hepatoma with occult CNS metastases and a patient who developed continuous oozing of blood from a thigh sarcoma with necrosis.

Mucocutaneus Hemorrhage: Across all bevacizumab clinical trials, mucocutaneous hemorrhage has been seen in 20%-40% of patients treated with bevacizumab. These were most commonly NCI-CTC Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in bevacizumab treatment regimen.

There have also been less common events of minor mucocutaneous hemorrhage in other locations, such as gingival bleeding and vaginal bleeding.

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.[13, 14]

Congestive heart failure: In clinical trials CHF was observed in all cancer indications studied to date, but predominantly in patients with metastatic breast cancer. In the Phase III clinical trial of metastatic breast cancer (AVF2119g), 7 (3%) bevacizumab-treated patients experienced CHF, compared with two (1%) control arm patients. These events varied in severity from asymptomatic declines in left ventricular ejection fraction (LVEF) to symptomatic CHF requiring hospitalization and treatment. All the patients treated with bevacizumab were previously treated with anthracyclines (doxorubicin cumulative dose of 240–360 mg/m^2). Many of these patients also had prior radiotherapy to the left chest wall. Most of these patients showed improved symptoms and/or left ventricular function following appropriate medical therapy.[17]

In a randomized, Phase III trial of patients with previously untreated metastatic breast cancer (E2100), the incidence of LVEF decrease (defined as NCI-CTC Grade 3 or 4) in the paclitaxel + bevacizumab arm was 0.3% versus 0% for the paclitaxel alone arm.

No information is available on patients with preexisting CHF of New York Heart Association (NYHA) Class II–IV at the time of initiating bevacizumab therapy, as these patients were excluded from clinical trials.

Prior anthracyclines exposure and/or prior radiotherapy to the chest wall may be possible risk factors for the development of CHF. Caution should be exercised before initiating bevacizumab therapy in patients with these risk factors.

A Phase II trial in patients with refractory acute myelogenous leukemia reported 5 cases of cardiac dysfunction (CHF or LVEF decrease to < 40%) among 48 patients treated with sequential cytarabine, mitoxantrone, and bevacizumab. All but 1 of these patients had significant prior exposure to anthracyclines as well.[18]

Other studies in patients with various tumor types and either a history of anthracycline exposure or concomitant use with bevacizumab are ongoing.

Patients receiving concomitant anthracyclines or with prior exposure to anthracyclines should have a baseline MUGA scans or echocardiograms (ECHOs) with a normal LVEF.

Neutropenia: Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone.[19]

Additional Adverse Events: See the bevacizumab Investigator Brochure for additional details regarding the safety experience with bevacizumab.

2.3 Bevacizumab for Malignant Gliomas

Given the synergism with irinotecan and bevacizumab for colorectal carcinomas, the combination has been studied in gliomas. In a study of 21 patients, the combination of irinotecan and bevacizumab produced a 43% response rate, with acceptable toxicity.[20] The response rate is significantly higher than irinotecan alone and any other therapy for recurrent glioma. There were two serious adverse events, one intracranial hemorrhage and one bowel perforation. At the Duke Brain Tumor Center, we have treated 68 patients on an IRB approved Phase 2 Study under a FDA IND with irinotecan and bevacizumab, and there were two CNS hemorrhages, one asymptomatic hemorrhage after ten cycles and the other after eight cycles and the patient was started on enoxaparin two weeks prior to the hemorrhage for a DVT. There was acceptable toxicity in the phase II trial. The response rate was 59%, and the 6-month progression-free survival was 43% in GBMs, which are some of the best results seen to date.[21] A follow-up randomized phase II trial of bevacizumab alone vs. bevacizumab and irinotecan confirmed the activity of bevacizumab, which led to accelerated approval of single agent bevacizumab for recurrent GBM by the FDA in May 2009.[7] We completed a phase II trial of bevacizumab, radiation therapy and temozolomide, followed by bevacizumab, irinotecan and temozolomide for newly diagnosed GBMs, and the median PFS was 14 mos, which is more the doubled the median PFS in the Stupp trial.[1] The regimen was well tolerated with one treatment-related death during radiation therapy and encouraging early overall survival results. We have enrolled 125 patients, and two died of toxicity during the post-radiation phase, one from a pulmonary embolus and the other from sepsis. At a median follow-up of 16 mos for the original 75 patients enrolled, 80% remain alive compared with a median OS of 15 mos in the Stupp trial with radiation and temozolomide followed by temozolomide.

2.4 Bevacizumab and Radiation Therapy

Bevacizumab may reverse some of the tissue hypoxia around tumor cells, making radiation therapy more effective. A radioresistant tumor can become radiosensitive with the addition of

agents that block VEGF activity or prevent VEGF intracellular signaling.[22-24] VEGF blockade by bevacizumab reduces tumor hypoxia, interstitial pressure, increases chemotherapy drug delivery and optimizes radiation therapy.[25-27] Bevacizumab has been combined with radiation therapy and chemotherapy in rectal and pancreatic carcinomas, with acceptable toxicity and a suggestion of improved tumor control.[28, 29]

2.5 Rationale for Study Design

Given the possible synergism with irinotecan and bevacizumab for colorectal carcinomas, the combination has been studied in gliomas. In a study of 21 patients, the combination of irinotecan and bevacizumab produced a 43% response rate, with acceptable toxicity.[20] The response rate is significantly higher than irinotecan alone and any other therapy for recurrent glioma. There were two serious adverse events, one intracranial hemorrhage and one bowel perforation. At the Duke Brain Tumor Center, we have treated over 1000 glioblastoma patients with a bevacizumab-containing regimen, and there is marked clinical benefit and acceptable toxicity. Our initial study looking at the combination of bevacizumab and irinotecan for patients with recurrent glioblastoma published in 2007 found impressive response rates and survival and corroborated the earlier experience of Starks-Vance.[20, 21]

We completed a study for newly diagnosed glioblastoma that utilized bevacizumab, radiation therapy and temozolomide followed by 6 months of bevacizumab, irinotecan and temozolomide.[30] In addition, the group at UCLA published a study with bevacizumab, radiation therapy and temozolomide followed by 12 months of bevacizumab and temozolomide for newly diagnosed glioblastoma.[31] These two phase II studies reported acceptable toxicity and a suggestion of improved survival compared to historical controls, and led to two large phase III randomized, placebo controlled studies of the addition of bevacizumab for newly diagnosed glioblastoma patients. The current proposal builds on the encouraging results of the addition of bevacizumab to the standard therapy for newly diagnosed glioblastoma patients. Two critical questions remain- the role of bevacizumab maintenance and bevacizumab at the time of progression in a patient previously treated with bevacizumab at the time of initial diagnosis. In addition, a retrospective analysis of data collected at our center from patients with recurrent disease suggests that continuation of bevacizumab at the time of progression may improve overall survival in comparison with cessation of bevacizumab.[32]

3 Objectives

3.1 Primary Objective

To assess the effect on overall survival of continuing bevacizumab treatment after disease progression in patients treated with bevacizumab from the time of first diagnosis of grade IV malignant glioma.

3.2 Secondary Objective

To describe the toxicity of bevacizumab, 10 mg QOW, in combination with radiation therapy and daily Temodar, followed by bevacizumab and 5-day Temodar with continuation of bevacizumab beyond progression.

To assess the effect on progression-free survival of continuing bevacizumab treatment after disease progression in patients treated with bevacizumab from the time of initiation of treatment to the first occurrence of progression, or death

3.3 Exploratory Objective

To describe patient-reported quality of life outcomes of patients who continue to receive bevacizumab beyond progression

4 Study Design

4.1 Overview

This is a Phase II trial of bevacizumab, radiation therapy (XRT) and Temodar (temozolomide), followed by bevacizumab and Temodar, then bevacizumab maintenance and continuation of bevacizumab beyond progression for newly diagnosed patients with malignant gliomas.

4.2 Outcome Measures

The patients will undergo a baseline MRI, as well as a MRI at the beginning of every other cycle during post chemoradiotherapy treatment to determine response and progression.

4.2.1 Primary efficacy outcome measure

Overall survival

4.2.2 Secondary efficacy outcome measure

Progression-free survival

4.2.3 Safety outcome measures

Incidence and severity of CNS hemorrhage and systemic hemorrhage

Incidence of grade ≥ 4 hematologic and ≥ 3 non-hematologic toxicities

4.2.4 Quality of life outcome measure

Patient-Reported Outcomes (PROs) as assessed by standardized and validated questionnaires including: Quality of Life (Functional Assessment of Cancer Therapy-Brain); Fatigue (Functional Assessment of Cancer Therapy-Fatigue); Cognition (Functional Assessment of Cancer Therapy-Cognition), Depression (Beck Depression Inventory); Epworth Sleepiness Scale, Pittsburgh Sleep Quality Index, Godin Leisure-Time Exercise Questionnaire short scale

Functional Capacity (Six-minute walk test)

Neurocognitive Function (a computerized neurocognitive test battery called CNS Vital Signs®)

5 Safety Plan

5.1 Bevacizumab-specific Monitoring during Parts A and B

A number of measures will be taken to ensure the safety of patients participating in this trial. These measures will be addressed through exclusion criteria (see Section 6.2) and routine monitoring as follows.

Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, blood pressure, and laboratory measurements. Patients will be evaluated for adverse events, serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study.

Specific monitoring procedures are as follows:

- Hypertension will be monitored through routine evaluation of blood pressure prior to each bevacizumab treatment. Optimal control of blood pressure according to standard public health guidelines is recommended for patients on treatment with or without bevacizumab.
- Proteinuria will be monitored by urine dipstick or 24 hour urine at least every cycle.
- If patients on treatment with bevacizumab require elective major surgery, it is recommended that bevacizumab be held for 6 weeks prior to the surgical procedure. Patients undergoing a major surgical procedure should not begin/restart bevacizumab until 4 weeks after that procedure (in the case of high risk procedures such as liver resection, thoracotomy, or neurosurgery, it is recommended that chemotherapy be restarted no earlier than 2 weeks and bevacizumab no earlier than 6 weeks after surgery).

Bevacizumab may be given by the local oncologists under the direction of the Duke investigators. The Duke investigators will review all the laboratory data and order the treatment. The local oncologist will be an agent of the Duke investigators, and just administer the therapy; the Duke investigators will be responsible for all the research data.

5.2 Temodar

The patients will receive standard anti-emetic therapy to prevent temozolomide-induced nausea and vomiting. Patients will have a CBC weekly and serum chemistries every four weeks.

5.2.1 Temodar administration during XRT

Temodar should be initiated within 5 days of the start of external beam radiotherapy but must not be started until the following initiation criteria are met:

a. ANC $\geq$ 1,500/µl
b. Platelet count $\geq$ 125,000/µl
c. Adequate hepatic function - SGOT and total bilirubin $\leq$2 x upper limit of normal
d. Adequate renal function – serum creatinine $\leq$ 1.5 mg/dl

Complete blood count (CBC) with differential should be measured weekly and complete metabolic panel (CMP) should be monitored every other week during XRT with concurrent daily

Temodar. Temodar will be held if thrombocytopenia (grade 3), neutropenia (grade 4) or grade 4 non-hematologic toxicity attributable to Temodar develop. CBC/diff and/or CMP levels will be followed more frequently as clinically indicated in patients who develop abnormalities that surpass the above guidelines. Temodar may resume when the following re-treatment criteria are met: ANC ≥ 1,000 cells/µl, platelets ≥ 100,000 cells/µl. However, the Temodar dose will be modified according to the following table:

Temodar Dose at Toxicity	Modified Dose
75 mg/m^2	50 mg/m^2

If a patient experiences dose toxicity as defined above at 50 mg/m^2 during XRT, Temodar will be held for the duration of the remaining external beam radiotherapy but may be resumed upon completion of XRT on the 28-day dosing schedule once the above-defined initiation criteria are met.

See sections 7.2 and 7.3 for the Temodar and bevacizumab safety plan post-radiation therapy.

6 Study Population

The patients will have a newly diagnosed brain tumor with a histologic diagnosis of grade 4 malignant glioma (glioblastoma or gliosarcoma). If the patient had a prior surgical procedure, the patient must be within 8 weeks of the last major surgical procedure, craniotomy, open biopsy, or stereotactic biopsy.

6.1 Inclusion Criteria

- Patients with histologically confirmed WHO Grade IV primary malignant glioma (glioblastoma or gliosarcoma);
- Patients ≥ 18 years of age;
- An interval of at least 2 weeks, but not ≥ 8 weeks between prior surgical procedure and initiation of treatment;
- Karnofsky Performance Status (KPS) ≥ 60%
- Laboratory Values:
    - Platelet Count ≥ 125,000 cells/µL
    - Absolute neutrophil count (ANC) ≥ 1,500 cells/µL
    - Adequate renal function indicated by all of the following:
        - Serum creatinine ≤ 1.25 x ULN or calculated creatinine clearance ≥ 50 ml/min
        - Urine dipstick for proteinuria < 2+ unless a 24-hour urine protein < 1 g of protein is demonstrated
    - PT and aPTT ≤ 1.5 x ULN within 14 days prior to starting any protocol specific treatment. The use of full-dose oral or parenteral anticoagulants is permitted as long as the PT or aPTT is within these limits. In order to begin treatment with bevacizumab, the patient has to be on a stable dose of anticoagulants for at least two weeks prior to the first bevacizumab treatment.

- Patients will sign an IRB-approved informed consent form.
- Female patients must not be pregnant or breast-feeding. Female patients of childbearing potential (defined as < 2 years after last menstruation or not surgically sterile) must use a highly effective contraceptive method (allowed methods of birth control, [i.e. with a failure rate of < 1% per year] are implants, injectables, combined oral contraceptives, intra-uterine device [IUD; only hormonal], sexual abstinence or vasectomized partner) during the trial and for a period of > 6 months following the last administration of trial drug(s). Female patients with an intact uterus (unless amenorrhea for the last 24 months) must have a negative serum pregnancy test within 7 days prior to first study treatment.
- Fertile male patients must agree to use a highly effective contraceptive method (allowed methods of birth control [i.e. with a failure rate of < 1% per year] include a female partner using implants, injectables, combined oral contraceptives, IUDs [only hormonal], sexual abstinence or prior vasectomy) during the trial and for a period of > 6 months following the last administration of trial drugs.

6.2 Exclusion Criteria

- Any prior treatment for any grade glioma, including, but not limited to gliadel wafers, immunotherapy (including vaccine therapy), radiation therapy or chemotherapy, irrespective of grade of the tumor (*NOTE*: 5-aminolevulinic acid (ALA)-mediated photodynamic therapy administered prior to surgery to aid in optimal surgical resection is not considered a chemotherapy agent.);
- Co-medication that may interfere with study results; e.g. immuno-suppressive agents other than corticosteroids;
- Active infection requiring intravenous antibiotics;
- Prior or current treatment with bevacizumab or other anti-angiogenic treatment (i.e. anti-VEGF or VEGFR therapies or tyrosine kinase inhibitors) for any condition;
- Treatment with any other investigational agent within 28 days or 2 investigational agent half-lives (whichever is longer) prior to first study treatment;
- Prior, unrelated malignancy requiring current active treatment with the exception of cervical carcinoma in situ and adequately treated basal cell or squamous cell carcinoma of the skin;
- Evidence of > Grade 1 CNS hemorrhage on post-operative MRI scan, unless repeat MRI or CT performed prior to initiating bevacizumab shows stable grade 1 or resolving (< grade 1) CNS hemorrhage.

<u>Bevacizumab-Specific Exclusion Criteria:</u>

- Inadequately controlled hypertension (defined as systolic blood pressure >150 mmHg and/or diastolic blood pressure > 100 mmHg) within 28 days of first study treatment;
- Prior history of hypertensive crisis, hypertensive encephalopathy, reverse posterior leukoencephalopathy syndrome (RPLS);
- Prior history of gastrointestinal perforation or abscess;
- Clinically significant (i.e. active) cardiovascular disease, for example cerebrovascular accidents ≤ 6 months prior to study enrollment, myocardial infarction ≤ 6 months prior to study enrollment, unstable angina, New York Heart Association (NYHA) Grade II or

greater congestive heart failure (CHF), or serious cardiac arrhythmia uncontrolled by medication or potentially interfering with protocol treatment;

- History or evidence upon physical/neurological examination of central nervous system disease (e.g. seizures) unrelated to cancer unless adequately controlled by medication or potentially interfering with protocol treatment;
- Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent arterial thrombosis) within 6 months prior to start of study treatment. Any previous venous thromboembolism > NCI CTCAE Grade 3;
- History of pulmonary hemorrhage/hemoptysis ≥ grade 2 (defined as ≥ 2.5 mL bright red blood per episode) within 1 month of first study treatment;
- History or evidence of inherited bleeding diathesis or significant coagulopathy at risk of bleeding (i.e. in the absence of therapeutic anticoagulation);
- Current or recent (within 10 days of study enrollment) use of aspirin (>325 mg/day), clopidogrel (>75 mg/day) or equivalent. Prophylactic use of anticoagulants is allowed;
- Surgical procedure (including open biopsy, surgical resection, wound revision, or any other major surgery involving entry into a body cavity) or significant traumatic injury within 28 days prior to first study treatment, or anticipation of need for major surgical procedure during the course of the study;
- Minor surgical procedure, e.g. stereotactic biopsy, within 7 days of first study treatment; placement of a vascular access device, within 2 days of first study treatment;
- History of intracranial abscess within 6 months prior to first study treatment;
- History of active gastrointestinal bleeding within 6 months prior to first study treatment;
- Serious, non-healing wound, active ulcer, or untreated bone fracture;
- Known hypersensitivity to any component of bevacizumab or any of the study drugs;

7 Study Conduct

7.1 Treatment Plan

This is a Phase II trial of bevacizumab, radiation therapy (XRT) and Temodar (temozolomide), followed by bevacizumab and Temodar then bevacizumab maintenance with continuation of bevacizumab beyond progression for newly diagnosed patients with Grade 4 malignant gliomas. Patients will receive bevacizumab and Temodar and XRT treatment (Part A), then bevacizumab and Temodar for 12 cycles (Part B). If the patient remains stable throughout Part B of the study, they will continue on bevacizumab alone, i.e. 10 mg/kg q o week (Part C). If the patient's disease progresses during either Part B or Part C of the study, the patient will always receive their Duke treating physician's best bevacizumab-based treatment regimen (Part D), unless contraindicated by toxicity.

Bevacizumab doses may be given by the local oncologists under the direction of the Duke investigators. The Duke investigators will review all the laboratory data and order the treatment by faxing the orders to the oncologist. The orders that are sent to the local oncologist will contain a bevacizumab dose that is rounded to the nearest 100mg to mimic the Duke standard of practice in bevacizumab dosing. Due to the multiple local oncology offices that are being used and due to the fact that each office will differ in their standard practice, it will not be considered a reportable

deviation if the local oncologist does not round the dose of the bevacizumab. The local oncologist will be an agent of the Duke investigators, and just administer the therapy; the Duke investigators will be responsible for all the research data. The study coordinator will send the local oncologist a letter giving specific details of the study, including what regular laboratory tests need be performed, and requesting all laboratory results be faxed to the coordinator, along with all information related to toxicities or adverse events. If labs are not provided in a timely fashion, the study coordinator will contact the local oncologist's office to obtain them. See section 8.1.2 for bevacizumab administration.

The patient population will include up to 68 patients.

7.2 Drug Administration/Dosing Schedule

During Part A of the study, patients will receive standard radiation therapy and daily Temodar, 75 mg/M^2, for six-seven weeks, beginning a minimum of 2 weeks and not > 8 weeks post-operatively. Bevacizumab (10 mg/kg every 2 weeks) will be given concurrently with radiation therapy and daily Temodar, beginning a minimum of 4 weeks following the last surgical procedure.

If there is no evidence of progression 2-4 weeks after radiation therapy, but not greater than 8 weeks, the patients start Part B of the study and will receive up to 12 cycles of bevacizumab and Temodar. The bevacizumab will be administered 10 mg/kg q o week on approximately days 1 and 15. The Temodar will be 200 mg/m^2 daily for 5 days, days 1-5 of each cycle. Each cycle will be 4 weeks. The dose of Temodar will be reduced to 150 mg/m^2 if the patient has a grade 3 thrombocytopenia, grade 4 neutropenia or grade 4 non-hematologic toxicity that the investigators attribute to Temodar. After 12 cycles of bevacizumab and Temodar, if the patient's disease is stable, he/she will begin Part C of the study, bevacizumab-only therapy (see Section 7.2.2).

Whenever a patient has evidence of progression (during either Part B or Part C of the study), treatment will be terminated and the patient will begin Part D of the study involving the Duke treating physician's best bevacizumab-based treatment (see Section 7.2.3).

7.2.1 Radiation Therapy: Dose Definition and Schedule

External beam radiation therapy (XRT) should begin 2-8 weeks after surgery. One treatment of 1.8 -2Gy will be given daily, 5 days per week, (30-33 fractions over less than seven weeks) for a total of 59-60Gy. All portals shall be treated during each treatment session. Doses are prescribed at the maximum isodose line encompassing the target volume.

7.2.2 Bevacizumab Only (Part C)

Bevacizumab will be continued at 10 mg/kg approximately every 2 weeks or 15 mg/kg approximately every 3 weeks. Ideally, infusions will not be given more than 2-3 days early. Infusions can be given late, if needed, based on re-treatment criteria, scheduling issues, holidays, etc. These adjustments in the infusion dates will not be considered reportable deviations. Cycles will ideally be approximately 8 weeks long for patients on 10mg/kg dosing and approximately 9 weeks long for patients on 15mg/kg dosing, however, the cycle lengths may be adjusted per the Duke treating physician based on the patient's response to the treatment.

7.2.3 Treatment at Progression (Part D)

At the time of progression, the patient will receive bevacizumab-based therapy containing bevacizumab in combination with a chemotherapy and/or biologic agent, as determined by the Duke treating physician and patient, as long as there are no contraindications to bevacizumab (see Table 1 and Section 10). The bevacizumab-based therapy may not, however, be within the context of another clinical trial.

7.3 Re-Treatment Criteria

7.3.1 Part B- Initiation of each cycle will require:

- ANC $\geq$ 1,000 cells/µl
- Platelets $\geq$ 100,000 cells/µl
- AST, bilirubin, creatinine $\leq$ 2.0 x upper limit of normal
- Resolution of any grade 3 or greater toxicity felt to be possibly, probably or definitely attributable to the study regimen to grade 1 or pre-treatment baseline.
- Proteinuria < 4+ on urinalysis or $\leq$ 3.5g protein in a 24-hour urine collection

7.3.2 Re-treatment criteria for Part C

- Platelets $\geq$ 50,000 cells/µl
- Proteinuria < 4+ on urinalysis or $\leq$ 3.5g protein in a 24-hour urine collection

7.3.3 Re-treatment criteria for Part D

This will be determined by the patient's treating physician at Duke, as appropriate for the bevacizumab-based treatment regimen.

7.4 Quality of Life Assessments

Quality of Life will be assessed using standardized and validated questionnaires. These questionnaires include Functional Assessment of Cancer Therapy-Brain (FACT-BR) scale[33], Functional Assessment of Cancer Therapy-Fatigue (FACIT-Fatigue) subscale, version 4,[34] Functional Assessment of Cancer Therapy-Cognition (FACT-Cog) subscale,[35] Epworth Sleepiness Scale (ESS)[36], Pittsburgh Sleep Quality Index (PSQI)[37], Godin Leisure-Time Exercise Questionnaire short scale[38], and Beck depression inventory (BDI).[39]

Functional capacity will be assessed using 6-minute walk test.[40] The patient will be instructed to walk at their fastest pace and to cover the longest possible distance over 6 minutes under supervision of trained personnel. Distance walked will be determined in a measured corridor and performed according to ATS guidelines.

Neurocognitive testing will include the performance on the following testing using a computerized battery CNS Vital Signs®.[41] Normative data is available for this testing through CNS Vital Signs® and patients' performance will be compared to this normative data.

All quality of life, functional capacity, neurocognitive assessments will be completed at baseline, after radiation therapy (Part A), and then approximately every 6 months (in correlation with the Duke visit) during Part B, Part C, and Part D of the study.

7.5 Miscellaneous

Steroids and anti-emetics will be administered as clinically warranted. Attempts will be made to keep the steroid dose stable or lower prior to the next MRI.

7.6 Suggested Image Acquisition

Imaging evaluation of patients in this study will be performed as part of the treatment assessment and to determine progression free survival as described in section 7.7. Generally, brain MRI with and without gadolinium-based contrast agents will be performed unless contraindicated, in which case brain CT with and without iodinated contrast-agent will be performed.

7.6.1 MR image acquisition

The MR evaluation of these patients will be performed with and without gadolinium-based contrast agents and using the routine clinical protocol, with the exception listed below. The routine clinical protocol must at minimum include T1-weighted images obtained in the axial plane both before and after the administration of contrast agent; T1-weighted imaging after the administration of contrast agent in either the sagittal or coronal plane; and T2-weighted or FLAIR imaging in the axial plane. For all of these sequences, a slice thickness of 5mm or less and an interslice gap of 3mm or less will be used. Full recommended dose of gadolinium-based contrast agent will be generally be used, although half-dose of contrast agent may be used for patients with mild renal impairment as directed by local imaging guidelines.

For those patients that undergo MR imaging at Duke University Medical Center and Duke University Health system affiliated centers, an additional MR imaging procedure designed to better evaluate the margins of mildly enhancing tumor margins may be used. The imaging procedure will include a sagittal T1-weighted 3D acquisition (isotropic voxel size of 1.5mm or less) obtained before the administration of contrast agent. An identical sequence will be performed after the administration of contrast agent. The latter images will be reformatted into isotropic coronal images. The additional imaging will be acquired on studies performed on MR imaging units which have been pre- approved by the study team for use for the research imaging protocol.

MR contraindications: MRI is the imaging modality of choice for patients evaluated in this study; however, patients may be excluded from MR imaging due to criteria in place at the sites where imaging is performed. As a general rule, patients with cardiac pacemakers, intraorbital metallic foreign bodies, neurostimulators, aneurysms, and/or significant claustrophobia may be excluded from MR imaging. If the patient is excluded from brain MR imaging or is unable to receive gadolinium-based contrast agents due to allergy, brain CT with and without administration of iodinated contrast agent can be performed as an alternative.

7.6.2 CT image acquisition

For patients who cannot receive a brain MRI with gadolinium-based contrast agents, a brain CT with and without iodinated contrast agent will be performed using the standard site clinical protocol. The routine clinical protocol must include axial images with a slice thickness of no more than 5mm.

7.7 Response Criteria

The imaging response criteria described below will be used by the treating physician to assess the patient while in clinic and will take into consideration their clinical status, corticosteroid use and imaging assessment. The criteria described below serve as a guideline for the treating physician while in clinic, and does not represent the need to describe response rate by the study team. Therefore, no formal measurements will be made for study purposes and the CTRAF form will not be completed.

Stable Disease: Neurological exam is at least stable and maintenance corticosteroid dose not increased, and MRI/CT imaging does not meet the criteria for Progressive Disease. In order to classify this category of response as a clinical benefit, Stable Disease status must be maintained for at least 8 weeks for patients on this study.

Progressive Disease: Progressive neurological abnormalities or worsening neurological status not explained by causes unrelated to tumor progression (e.g. anticonvulsant or corticosteroid toxicity, electrolyte disturbances, sepsis, hyperglycemia, etc.) **OR** ≥25% increase in the bi-dimensional measurement of enhancing or non-enhancing tumor on MR/CT when compared to nadir **OR** a new area of enhancement or FLAIR consistent with tumor progression. The RANO criteria will be used to determine progression and pseudo-progression, as defined by Wen et al., 2010, below.[42]

Criterion	Stable Disease (SD)	Progressive Disease (PD)
T1 gadolinium enhancing disease	< 50% ↓ but < 25% ↑	≥ 25% ↑ *
T2/FLAIR	Stable or ↓	↑ *
New lesion	None	Present *
Corticosteroids	Stable or ↓	Not applicable **
Clinical status	Stable or ↑	↓ *
Requirement for response	All	Any *

*Progression occurs when this criterion is present.
**Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

8 Study Medication

8.1 Bevacizumab

8.1.1 Description

Bevacizumab is a clear to slightly opalescent, colorless to pale brown, sterile liquid concentrate for solution for intravenous (IV) infusion. Bevacizumab may be supplied in 5-cc (100-mg) and 20-cc (400-mg) glass vials containing 4 mL or 16 mL bevacizumab, respectively (all at 25 mg/mL). Vials contain bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection (SWFI), USP. Vials contain no preservative and are suitable for single use only.

For further details and molecule characterization, see the bevacizumab Investigator Brochure.

Bevacizumab will be provided by Genentech for use in this study.

8.1.2 Administration

Bevacizumab will be diluted in 0.9% Sodium Chloride Injection, USP, to a total volume of 100 mL. Administration will be given as a continuous IV infusion. Anaphylaxis precautions should be observed during study drug administration. It is not necessary to correct dosing based on ideal weight.

The initial dose will be delivered over 90±10 minutes. The 2nd dose may be delivered over 60±10 minutes. All subsequent infusions may be delivered over 30±10 minutes. It will not be considered a reportable deviation if the local oncologist chooses to infuse the bevacizumab over a longer period of time than the recommended infusion times listed above.

If a subject experiences an infusion–associated adverse event, he or she may be premedicated for the next study drug infusion; however, the infusion time may be increased to 60 minutes for the subsequent infusion at the discretion of the investigator. If the next infusion is well tolerated with premedication, the subsequent infusion time may then be decreased by 30±10 minutes as long as the subject continues to be premedicated. If a subject experiences an infusion-associated adverse event with the 60-minute infusion, all subsequent doses should be given over 90±15 minutes. Similarly, if a subject experiences an infusion-associated adverse event with the 30-minute infusion, all subsequent doses should be given over 60±10 minutes.

8.1.3 Storage

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.

8.1.4 Dose modification and toxicity management

There are no reductions in the bevacizumab dose. If adverse events occur that require holding bevacizumab, the dose will remain the same once treatment resumes.

Any toxicities associated or possibly associated with 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 discontinuation results in slow elimination over several months. There is no available antidote for bevacizumab.

Subjects should be assessed clinically for toxicity for each infusion. If unmanageable toxicity occurs because of bevacizumab at any time during the study, treatment with bevacizumab should be discontinued.

Infusion Reaction: Infusion of bevacizumab should be interrupted for subjects who develop dyspnea or clinically significant hypotension. Subjects who experience a NCI CTCAE v. 4.0

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 will be slowed to 50% or less or interrupted for subjects who experience any infusion-associated symptoms not specified above. When the subject's 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 cycle.

Adverse events requiring delays or permanent discontinuation of bevacizumab are listed in Table 1.

Table 1: Bevacizumab Dose Management Due to Adverse Events

Event	Action to be Taken
Hypertension No dose modifications for grade 1/2 events	
Grade 3	If not controlled to 150/100 mmHg with medication, discontinue bevacizumab.
Grade 4 (including hypertensive encephalopathy)	Discontinue bevacizumab.
Hemorrhage No dose modifications for grade 1/2 non-pulmonary and non-CNS events	
Grade 3 non-pulmonary and non-CNS hemorrhage	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have study bevacizumab held until all of the following criteria are met: • The bleeding has resolved and hemoglobin 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. Subjects who experience a repeat Grade 3 hemorrhagic event will be discontinued from receiving bevacizumab.
Grade 4 non-pulmonary or non-CNS hemorrhage	**Discontinue bevacizumab.**

Grade 1 pulmonary or CNS hemorrhage	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have bevacizumab held until all of the following criteria are met: • The bleeding has resolved and hemoglobin 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.
Grade 2, 3, or 4 pulmonary or CNS hemorrhage	**Discontinue bevacizumab.**
Venous Thrombosis No dose modifications for grade 1/2 events	
	Hold study drug treatment. If the planned duration of full-dose anticoagulation is <2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab may be resumed during the period of full-dose anticoagulation if all of the following criteria are met: • The subject must have an in-range INR (usually between 2 and 3) if on warfarin; LMWH, warfarin, or other anticoagulant dosing must be stable prior to restarting bevacizumab treatment. • The subject 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, and any other arterial thromboembolic event)	
Any grade	**Discontinue bevacizumab.**
Congestive Heart Failure (Left ventricular systolic dysfunction) No dose modifications for grade 1/2 events	
Grade 3	**Discontinue bevacizumab.**
Grade 4	**Discontinue bevacizumab.**
Proteinuria No dose modifications for grade 1/2 events	

Grade 3 (Urine protein dipstick 4+, or urine collection > 3.5 g/24 hr)	Hold bevacizumab treatment until ≤ Grade 2, as determined by either urine dipstick ≤ 3+, or 24 hr collection ≤ 3.5 g
Grade 4 (nephrotic syndrome)	**Discontinue bevacizumab**
GI Perforation	**Discontinue bevacizumab.**
Fistula	
Any grade (TE fistula)	**Discontinue bevacizumab.**
Grade 4 fistula	**Discontinue bevacizumab.**
Bowel Obstruction Grade 1	Continue patient on study for partial obstruction NOT requiring medical intervention.
Grade 2	Hold bevacizumab for partial obstruction requiring medical intervention. Patient may restart upon complete resolution.
Grade 3 or 4	Hold bevacizumab for complete obstruction. If surgery is necessary, patient may restart bevacizumab after full recovery from surgery, and at 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 Grade 4	Hold bevacizumab until recovery to ≤ Grade 1 **Discontinue bevacizumab.**

8.2 Temozolomide (Temodar)

8.2.1 Description

(SCH 52365, temozolomide, NSC-362856, 8-Carbamoyl-3-methylimidazol[5,1-d]-1,2,3,5-tetrazine-4-(3H)-one, CCRG 81045, M&B 39831). Temodar is commercially available and not provided in this study.

8.2.2 Formulation

Temodar is supplied as a machine-filled, white opaque, preservative-free, two-piece, hard gelatin capsule available in 250 mg, 180 mg, 140 mg, 100 mg, 20 mg, and 5 mg strengths. Refer to Investigator Brochure for contents of the formulation. Temodar capsules are packaged in 30 cc, 28 mm 480 Type 1 amber glass bottles containing 30 capsules of 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, or 250 mg strengths.

8.2.3 Storage

Temodar capsules should be stored between 2°C to 30°C. Commercial supply and packaging will be used.

8.2.4 Administration

Temodar is administered orally on an empty stomach. The drug is approximately 100% bioavailable. The dose should be rounded to the nearest 5 mg. Effects of food on product absorption are not yet known. **DO NOT OPEN CAPSULES. DO NOT MIX WITH FOOD. DO NOT CHEW CAPSULES.**

Temodar at a dose of 75mg/m^2 po daily will be started within the first 5 days of external beam radiation. Temodar will be held for grade 3 thrombocytopenia, grade 4 neutropenia, or grade 4 non-hematologic toxicity secondary to Temodar. Temodar will be re-started at 50 mg/m^2 after resolution of the toxicity, or $\leq$ grade 1. If the grade 3 thrombocytopenia, grade 4 neutropenia, or grade 4 non-hematologic toxicity secondary to Temodar recurs at 50 mg/m^2, Temodar will be held during radiation therapy, but may resume after radiation therapy if the patient meets the treatment criteria.

Beginning approximately 2-3 weeks after the last radiation treatment, Temodar will be given at 200 mg/m^2 daily the first 5 days of each 28-day cycle. The dose of Temodar will be reduced to 150 mg/m^2 if the patient had grade 3 thrombocytopenia, grade 4 neutropenia, or grade 4 non-hematologic toxicity secondary to Temodar. If the patient has grade 3 thrombocytopenia, grade 4 neutropenia, or grade 4 non-hematologic toxicity secondary to Temodar at 150 mg/m^2 daily, the Temodar will be reduced to 100 mg/ m^2 daily, which will be the last dose reduction. If the toxicity recurs at 100 mg/m^2 daily, Temodar will be discontinued.

8.2.5 Toxicities

Temodar has been well tolerated by both adults and children with the most common toxicity being mild myelosuppression. Other, less likely, potential toxicities include nausea and vomiting, constipation, headache, alopecia, rash, burning sensation of skin, esophagitis, pain, diarrhea, lethargy, and hepatotoxicity. Hypersensitivity reactions have not yet been noted with Temodar. As is the case with many anti-cancer drugs, Temodar may be carcinogenic. Rats

given Temodar have developed breast cancer. The significance of this finding for humans is not presently known.

8.2.6 Packaging and labeling

Temodar is manufactured by Schering-Plough and commercial drug will be used:

- Product Identity: Temozolomide (SCH 52365)
- Bottles of dose strength of 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, or 250 mg

8.3 Radiation Therapy and Chemotherapy

8.3.1 External Beam Radiation Therapy – Standard of Care

Guidelines and final radiation therapy plan to be completed by treating radiation oncologist. Below are guidelines that will be given to the local radiation oncologist, however, if the local radiation oncologist feels that a variation of this plan is better for the patient, then the radiation oncologist may use his/her plan.

8.3.1.1 Dose definition and schedule

External beam radiation therapy (XRT) should begin 2-6 weeks after surgery. One treatment of 1.8-2Gy will be given daily, 5 days per week, (30-33 fractions over less than seven weeks) for a total of 59-60Gy. All portals shall be treated during each treatment session. Doses are prescribed at the maximum isodose line encompassing the target volume. IMRT is allowed.

8.3.1.2 Physical factors

Treatment shall be delivered on megavoltage machines of energy ranging from 4 to 18 MV photons. Selection of the appropriate photon energy(ies) should be based on optimizing the RT dose distribution within the target volume and minimizing dose to non-target normal tissue. Photon energies > 10 MV should be utilized only in dual energy beam arrangements using at least one beam with energy < 10 MV. Source skin distance for SSD techniques or source axis distance for SAD techniques must be at least 80 cm.

8.3.1.3 Localization, simulation, and immobilization

The patient shall be treated in the supine or another appropriate position for the location of the lesion. A head-holding device that is transparent to x-rays and provides adequate immobilization must be utilized at all times during planning and therapy to ensure reproducibility.

The initial target volume shall include the contrast-enhancing lesion and surrounding edema (if it exists) demonstrated on the pre-operative T2-weighted MRI plus a 2.0-cm margin. If no surrounding edema is present, the initial target volume should include the contrast-enhancing lesion plus a 2.5-cm margin. This primary target volume will be treated to 45 Gy in 25 daily fractions, at 1.8 Gy per fraction.

The boost volume will be based on the post-operative contrast-enhanced T1-weighted MRI performed during treatment planning. After 45 Gy, the boost volume will include the contrast-enhancing lesion plus a 1.5-cm margin or, if minimal contrast-enhancing lesion is present at a portion of the resection cavity on MRI, the surgical defect plus a 2.0-cm margin, whichever is greater at that segment of the MRI image. The boost volume will be treated to an additional 14.4

Gy in 8 daily fractions, 1.8 Gy per fraction. This will bring the total target dose to 59.4 Gy in 33 fractions.

All parts of the target volumes are to receive at least 95% but no more than 112% of the dose at the prescription isodose line, with at least 95% of the target volumes receiving at least 100% of the prescribed dose. However, coverage as low as 90% of the boost target volume receiving at least 90% of the prescribed dose is acceptable if needed to meet the dose limitations to critical structures, described below(8.3.1.5).

8.3.1.4 Treatment planning and safety

Treatment plans may include opposed lateral fields, a wedge pair of fields, rotation, or multiple-field techniques, including intensity-modulated radiotherapy (IMRT). MRI-guided 3D treatment planning is necessary to assure accuracy in the selection of field arrangements. Isodose distributions for the primary and boost target volume are required on all patients, including those treated with parallel-opposed fields. A composite plan is required showing the respective target volumes. The inhomogeneity across the target volume shall be kept to a minimum. The maximum dose should be no higher than 112% of the dose at the prescription isodose line.

Possible side effects include swelling of the brain, hair loss, localized skin irritation, low blood counts, fatigue, memory loss, hearing loss, nausea and/or vomiting, loss of appetite, headaches, radiation necrosis (death of tissue or skin), and secondary cancer.

8.3.1.5 Dose limitations to critical structures

The lens and cervical spine must be shielded from the direct beam at all times. The maximum dose to the optic apparatus (optic chiasm, optic nerves, eyes) must be limited to 54 Gy, and the brain stem limited to 60 Gy. During radiation therapy, patients will recive Temozolomide 75 mg/m^2/day as described below (8.3.2)

8.3.2 Temodar administration

Patients will receive 75 mg/m^2 of Temodar on a continuous daily schedule throughout the course of external beam radiotherapy. Temodar should be initiated within 5 days of the start of external beam radiotherapy but must not be started until the following initiation criteria are met:

a. ANC $\geq$ 1,500/µl;
b. Platelet count $\geq$ 125,000/µl
c. Adequate hepatic function - SGOT and total bilirubin < 2 x upper limit of normal
d. Adequate renal function – serum creatinine $\leq$ 1.5 mg/dl

Complete blood count (CBC) with differential should be measured weekly and complete metabolic panel (CMP) should be monitored every other week during XRT with concurrent daily Temodar. Temodar will be held if thrombocytopenia (grade 3), neutropenia (grade 4) or grade 4 non-hematologic toxicity attributable to Temodar develop. CBC/diff and/or CMP levels will be followed more frequently as clinically indicated in patients who develop abnormalities that surpass the above guidelines. Temodar may resume when the above initiation criteria are met, but the temozolomide dose will be modified according to the following table:

Temodar Dose at Toxicity	Modified Dose
75 mg/m^2	50 mg/m^2

If a patient experiences dose toxicity as defined above at 50 mg/m^2 during XRT, Temodar will be held for the duration of the remaining external beam radiotherapy but may be resumed upon completion of XRT on the 28-day dosing schedule once the above-defined initiation criteria are met.

9 Clinical and Laboratory Evaluations

9.1 Pre-treatment evaluations

- Vital signs, including blood pressure (within 2 weeks of starting treatment)
- History and physical exam including a full neurologic exam at baseline Duke visit.
- CBC with diff, CMP, PT, PTT (within 2 weeks of starting treatment), Beta-HCG if appropriate (Beta-HCG must be performed within 48 hours of starting study drug)
- Urinalysis (within 2 weeks of starting treatment)
- Baseline MRI of the brain (or CT if unable to have MRI) within eight weeks of starting treatment
- Baseline assessments of Quality of Life, Functional Capacity, and Neurocognitive Testing (at baseline Duke visit).

9.2 Evaluations During Radiation Treatment (Part A)

Blood pressure	Before each dose of bevacizumab
CBC with differential	Weekly
CMP	Before each dose of bevacizumab
Urine dipstick for protein on a spot urinalysis	Once per month
Quality of Life Assessments	At the end of XRT
Functional Capacity Assessments	At the end of XRT
Neurocognitive Testing	At the end of XRT

9.3 Evaluations During Part B

Blood pressure	Before each dose of bevacizumab
CBC with differential	Every 2 weeks
CMP	Prior to every cycle
Urine dipstick for protein on a spot urinalysis	Prior to every cycle
Physical Exam, including a full neurologic exam	Prior to every other cycle
MRI of the brain (or CT if unable to have MRI)	Prior to every other cycle
Toxicity assessment	Continuous
Quality of Life Assessments	Every 6 months

Functional Capacity Assessments	Every 6 months
Neurocognitive Testing	Every 6 months

9.4 Evaluations During Bevacizumab Only (Part C)

Blood pressure	Before each dose of bevacizumab
CBC with differential	Prior to every cycle
CMP	Prior to every cycle
Urine dipstick for protein on a spot urinalysis	Prior to every cycle
Physical Exam, including a full neurologic exam	Prior to every other cycle
MRI of the brain (or CT if unable to have MRI)	Prior to every other cycle
Toxicity assessment	Continuous
Quality of Life Assessments	Every 6 months
Functional Capacity Assessments	Every 6 months
Neurocognitive Testing	Every 6 months

9.5 Evaluations During Bevacizumab-based Therapy After Progression (Part D)

Blood pressure	Before each dose of bevacizumab
CBC with differential	Prior to every cycle
CMP	Prior to every cycle
Urine dipstick for protein on a spot urinalysis	Prior to every cycle
Physical Exam, including a full neurologic exam	Prior to every other cycle
MRI of the brain (or CT if unable to have MRI)	Prior to every other cycle
Toxicity assessment	Continuous
Quality of Life Assessments	Every 6 months
Functional Capacity Assessments	Every 6 months
Neurocognitive Testing	Every 6 months

10 Treatment Discontinuation

In addition to the guidelines presented in Table 1, patients may be discontinued from treatment at any time at the discretion of the investigator. Specific reasons for discontinuation from treatment are:

- Subject decides to withdraw
- Protocol non-compliance
- Patients will be discontinued from treatment for specific adverse events as described in Table 1.
- The treating physician feels that another treatment option is better for the patient.

Patients that are discontinued from the treatment portion of the study may remain on study (if they are not receiving additional treatment) and will be followed for adverse events and survival. The patients will continue to follow the return schedule, if possible, unless the treating physician recommends a different schedule.

11 Study Discontinuation

Patients will be discontinued from the study if they enroll into another study or if other treatment outside of this study is needed. Those patients will continue to be followed for survival until death or withdrawal of consent. Patients may also be discontinued from the study for protocol non-compliance. Those patients will continue to be monitored for survival.

12 Safety Reporting of Adverse Events

12.1 Assessment of Safety

12.1.1 Specification of Safety Variables

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) that are considered related to bevacizumab, all events of death, and any study specific issue of concern.

Adverse events (AE) will use the descriptions and grading scales found in the revised NCI Common Toxicity Criteria (CTC). This study will utilize the CTC version 4.0 for adverse event reporting. All appropriate treatment areas should have access to a copy of the CTC version 4.0.

12.2 Definition of Adverse Event

12.2.1 Adverse Event (AE)

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with malignant glioma that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).

If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.

Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

12.2.2 Serious Adverse Events

An AE should be classified as an SAE if the following criteria are met:

- It results in death* (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

* Since participants may remain on study treatment with bevacizumab well past initial disease progression, (i.e. part D of the study) it is expected that patients may die while still being treated or within 30 days of being treated with bevacizumab. Deaths that are attributed to disease progression while participants are in Part D of the study, will be recorded as an AE, but will not be reported as an SAE.

12.3 Methods and Timing for Assessing and Recording Safety Variables

The investigator is responsible for ensuring that all AEs and SAEs that are observed during the study are collected and reported, if applicable, to the Duke IRB and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

12.3.1 Adverse Event Recording Period

The study period during which all AEs and SAEs must be recorded, begins after informed consent is obtained and initiation of study treatment and ends after the last administration of study treatment or study discontinuation/termination, whichever is earlier. In addition, SAEs that occur within the 30 days after the last administration of study treatment or study discontinuation/termination will be reported to both the Duke IRB and Genentech. Deaths that occur during the 30 days after the last administration of study treatment or study discontinuation/termination will only be reported if the death is attributed to the study treatment. Deaths due to disease progression, or other non-study treatment related reasons, will not be reported as an SAE.

12.3.2 Assessment of Adverse Events

All AEs and SAEs, whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means, will be recorded appropriately. Each recorded AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria, if applicable, suspected relationship to the study drug (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes

There is a plausible temporal relationship between the onset of the AE and administration of the bevacizumab, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the bevacizumab; and/or the AE abates or resolves upon discontinuation of the bevacizumab or dose reduction and, if applicable, reappears upon re-challenge.

No

Evidence exists that the AE has an etiology other than the bevacizumab (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to bevacizumab administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert or current Investigator Brochure.

Unexpected adverse events are those not listed in the Package Insert or current Investigator Brochure (I.B.) or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the insert or I.B. For example, under this definition, hepatic necrosis would be unexpected if the insert or I.B. only referred to elevated hepatic enzymes or hepatitis.

12.4 Procedures for Eliciting, Recording, and Reporting Adverse Events

12.4.1 Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation timepoints should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

12.4.2 Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is ok to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

Deaths

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death." Deaths due to disease progression after a patient has entered part D of the study treatment will not be reported as an SAE.

Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

Pregnancy

If a female subject becomes pregnant while receiving investigational therapy or within 6 months after the last dose of study drug, a report should be completed and expeditiously submitted to the Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to bevacizumab should be reported as an SAE.

Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior bevacizumab exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE.

Reconciliation

The Investigator agrees to conduct reconciliation for the product. Genentech and the Investigator will agree to the reconciliation periodicity and format, but agree at minimum to exchange monthly line listings of cases received by the other party. If discrepancies are identified, the Investigator and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution.

AEs of Special Interest (AESIs)

AEs of Special Interest are defined as a potential safety problem, identified as a result of safety monitoring of the Product.

Bevacizumab Events of Special Interest are:

- Hypertension greater than or equal to Grade 3
- Proteinuria greater than or equal to Grade 3
- Gl perforation, abscesses and fistulae (any grade)
- Wound healing complications greater than or equal to Grade 3
- Haemorrhage greater than or equal to Grade 3 (any grade CNS bleeding; greater than or equal to Grade 2 haemoptysis)
- Arterial Thromboembolic events (any grade)
- Venous thromboembolic events greater than or equal to Grade 3
- PRES (any grade)
- CHF greater than or equal to Grade 3
- Non-Gl fistula or abscess greater than or equal to Grade 2

SAE Reporting to Genentech

Investigators must report all SAEs to Genentech within the timelines described below. The completed Medwatch/case report should be faxed immediately upon completion to Genentech Drug Safety at:

(650) 225-4682
OR
(650) 225-5288

- Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.
- Serious AE reports that are related to the bevacizumab and AEs of Special Interest (regardless of causality) will be transmitted to Genentech within fifteen (15) calendar days of the Awareness Date.
- Serious AE reports that are unrelated to the bevacizumab will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.

Additional Reporting Requirements to Genentech include the following:

- Any reports of pregnancy following the start of administration with bevacizumab will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.
- All Non-serious Adverse Events originating from the Study will be forwarded in a quarterly report to Genentech.

SAE Reporting to Duke IRB

In the event of an adverse event the first concern will be for the safety of the subject.

Only adverse events that the Duke Sponsor-Investigator determines to be serious, unanticipated, and related or possibly/probably (i.e. more likely than not) related to the research must be reported to the Duke IRB. Those adverse events will be submitted in the electronic IRB (eIRB) system, according the following guidelines:

- Report within 24 hours of learning about any subject's death that was unanticipated and more likely related to the research than unrelated;
- Report within 5 business days of learning about any serious, unanticipated, and related or possibly/probably related adverse event;
- Report within 10 business day of learning about any other unanticipated problem or event that was more likely related to the research than unrelated.

12.4.3 MedWatch 3500A Reporting Guidelines

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

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up Information

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

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

Occasionally, Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom and adverse event was reported. For questions regarding

SAE reporting, you may contact the Genentech Drug Safety representative noted above or the MSL assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A (Mandatory Reporting) form is available at http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm

13 Statistical Considerations

13.1 Study Design and Sample Size Justification

A single-arm phase II trial is proposed in which 68 patients newly diagnosed with glioblastoma or gliosarcoma will receive the following treatment regimen: bevacizumab-Temodar and XRT treatment then bevacizumab and Temodar for 12 months followed by bevacizumab alone; at the time of failure, the patient will always receive bevacizumab-based treatment regimens, unless contraindicated by toxicity. The goal of this study is to determine whether continued administration of bevacizumab after initial disease progression is worthy of further investigation. The primary basis for this assessment will be overall survival, with data from Duke's newly diagnosed bevacizumab-Temodar-CPT11 study used as the historical benchmark for this assessment. In that study, the median survival was 21 months.

The following power calculation is generated under the following assumptions:

- Type I error rate = $\alpha = 0.1$ (one-tailed)
- Accrual Rate $\approx$ 11 patients per month
- Accrual period = 6 months
- Total patient accrual = 68 patients
- Follow-up period = 28 months
- Exponential survival
- No loss to follow-up

Under these assumptions, there is 80% power to detect a hazard ratio of 0.71 assuming a one-tailed test conducted at the 0.10 level of significance. Such an improvement in overall survival is characterized by an increase from a median survival of 21 months within the historical cohort to 29.5 months.[43] The calculator for one-arm survival sample size and power as found on www.crab.org was used in this determination.

13.2 Analytic Methods

The product limit estimator developed by Kaplan and Meier will be used to describe overall survival and progression-free survival. Overall survival is defined as the time between initiation of treatment and death, or censored at last follow-up if the patient has not died. Progression-free survival (PFS) is defined as the time between initiation of treatment and the first occurrence of progression or death. PFS will be censored at last known follow-up if the patient remains alive without disease progression.

For each type of toxicity observed, the maximum grade experienced by each patient will be tabulated overall and for each 6-month period of follow-up.

The mean change between baseline and each follow-up assessment for QOL and functional capacity will be computed.

13.3 Toxicity Monitoring

Given that both long- and short-term toxicities are of interest in this study, it is not feasible to suspend accrual while toxicity is assessed as is often done in phase I trials. If the following criteria are satisfied or there are other reasons for concern about the safety of patient treatment (e.g. treatment-related toxic death), accrual will be suspended and data will be carefully reviewed to determine if accrual should be permanently terminated or the protocol modified. These guidelines have not been adjusted for differential length of follow-up of accrued patients.

For the purpose of toxicity monitoring, the occurrence of ≥ grade 2 CNS hemorrhage or grade 4 or 5 non-hematologic toxicity is defined as being unacceptable. One of the more common "unacceptable" adverse events observed with brain tumor patients treated with and without bevacizumab are venous thromboembolisms (VTEs). Simanek (2007, Neuro-Oncology) reports a cumulative probability of VTEs of 21% after 3 months and 26% after 12 months among patients with high-grade glioma. VTE incidence is generally in the range of 20-30% over the course of the disease (Jenkins, 2010). Clinical studies of bevacizumab usage typically until initial disease progression have reported VTE rates of 10-20% (Friedman, 2009; Fine, 2009; Vredenburgh, 2007). With many VTEs being considered unacceptable, one would expect that an unacceptable toxicity rate of approximately 25% if long-term treatment with bevacizumab did not increase the changes for unacceptable toxicity. Therefore, "unacceptable" toxicity rates of 25% or less are considered desirable, while rates of 45% or greater are considered as undesirable. The statistical hypothesis that will be considered in defining monitoring rules differentiates between a 5% (null hypothesis) and 20% (null hypothesis) rate of unacceptable toxicity.

Tabulated below are the conditions under which accrual will be temporarily suspended and data carefully reviewed to determine the appropriate action, including permanent study termination, continuation with patient accrual after appropriate amendment, or continuation with patient accrual with no modification of the protocol. Accrual will also be suspended whenever a death occurs that is possibly, probably, or definitely related to protocol treatment.

Number of patients accrued	Number of patients with unacceptable toxicity requiring accrual suspension
8-12	>4
13-15	>5
16-18	>6
19-21	>7
22-24	>8

25-28	>9
29-32	>10
33-37	>11
38-42	>12
43-49	>13
50-60	>14
>60	>15

These guidelines have not been adjusted for differential length of follow-up of accrued patients. The probability of accrual suspension as a function of the true unacceptable toxicity rate is tabulated below based upon simulation studies. These statistics were generated assuming toxicity outcome was known at the time of accrual, and ignored issues such as time to toxicity, accrual rate, and length of follow-up.

Underlying unacceptable toxicity Rate	Probability of accrual suspension
0.1	0.004
0.15	0.03
0.2	0.10
0.25	0.22
0.3	0.39
0.35	0.56
0.4	0.72
0.45	0.85
0.5	0.92

Every 6 months the toxicity experienced by patients accrued to this study will be summarized and reviewed regardless of the number of patients accrued to determine whether the overall toxicity profile of treatment is unacceptable or not.

14 Study Management: Data Safety and Monitoring Plan

14.1 Audits and Inspections

Authorized representatives of the Institutional Review Board (IRB) or Duke Cancer Institute (DCI) may visit the center to perform audits or inspections, including source data verification. The purpose of such an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements.

14.2 Data Safety and Monitoring

This clinical research study will be monitored both internally by the PI and externally by the Duke University Medical Center Cancer Center's Protocol Review and Monitoring System in accord with their NCI-approved "Institutional Protocol Monitoring Procedures and Guidelines for NIH-sponsored Research Involving Human Subjects." In terms of internal review, the PI will continuously monitor and tabulate adverse events (see Section 13.3). Appropriate reporting to the Duke University Medical Center IRB will be made. If an unexpected frequency of grade III or IV events occur, depending on their nature, action appropriate to the nature and frequency of these adverse events will be taken. This may require a protocol amendment or potentially closure of the study. The PI of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

- Interim analyses occur as scheduled;
- Stopping rules for toxicity and/or response are met;
- Risk/benefit ratio is not altered to the detriment of the subjects;
- Appropriate internal monitoring of adverse events and outcomes is done;
- Over-accrual does not occur;
- Under-accrual is addressed with appropriate amendments or actions;
- Data are being appropriately collected in a reasonably timely manner.

External review of this protocol begins with an initial review by the Cancer Protocol Committee (CPC), which performs a risk assessment of the trial. The PI will abide by their assessment of the level of risk, which will determine the intensity of subsequent external monitoring. Documentation of this assessment will be maintained. Formal, independent monitoring will be conducted by the DCI Monitoring Team.

The DCI Monitoring Team will conduct monitoring visits to ensure subject safety and to ensure that the protocol is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, good clinical practice, and applicable regulatory requirements. As specified in the DCI Data and Safety Monitoring Plan, the DCI Monitoring Team will conduct routine monitoring after the third subject is enrolled, followed by annual monitoring of 1 – 3 subjects until the study is closed to enrollment and subjects are no longer receiving study interventions that are more than minimal risk.

The DCI Safety Oversight Committee (SOC) will perform annual reviews on findings from the DCI Monitoring Team visit and additional safety and toxicity data submitted by the Principal Investigator.

Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns and may be initiated upon request of DUHS and DCI leadership, the CPC, the Safety Oversight Committee (SOC), the sponsor, the Principal Investigator, or the IRB. All study documents must be made available upon request to the DCI Monitoring Team and other authorized regulatory authorities, which may include but is not limited to the National Institute of Health, National Cancer Institute, and the FDA. Every reasonable effort will be made to maintain confidentiality during study monitoring.

This phase II study is limited to Duke University Medical Center. Routine monitoring will be carried out via a monthly team conference among investigators during which toxicity data, including all SAEs, will be reviewed and other issues relevant to the study such as interim assessment of accrual, outcome and compliance with study guidelines will be discussed. Monitoring will be carried out on an ongoing basis. . The severity, relatedness and whether or not the event is expected will be reviewed via email.

14.3 Data Collection

The study coordinator and investigators are responsible for ensuring that the eligibility checklist is completed in a legible and timely manner for every patient enrolled on study. This form will be maintained in the patient's clinical chart at the Preston Robert Tisch Brain Tumor Center at Duke (PRTBTC). Any errors on source data should be lined through, but not obliterated, with the correction inserted, initialed and dated by the study coordinator or PI. All source documents will be available for inspection by the FDA, DUHS IRB, and the Duke Cancer Institute Safety Oversight Committee.

Patient data will be entered into an Oracle Clinical database created and maintained by DUMC CCIS. The data are backed up daily and stored on a secure medical center server. The PI, study investigators, study statisticians, clinical research coordinator and data coordinator for the study are the only individuals who will have access to the web-based Oracle application. All study personnel with data editing rights will have documented training.

14.3.1 Study Close-out

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

Avastin Protocols
Email: avastin-gsur@gene.com
Fax : 650-745-0978

14.4 Retention of Records

All documentation of adverse events, records of study drug receipt and dispensation, patient records, regulatory documents and all correspondence will be kept for at least 2 years after the study is closed, as required by the FDA.

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Appendix A: Schedule of Events in Part A of the Study

		Weeks During Radiation Therapy					
	Pre-treatment evaluations	1	2	3	4	5	6
Blood pressure[a]	X	X[a]		X[a]		X[a]	
H&P with neurological assessment	X						
CBC with differential	X	X	X	X	X	X	X
CMP[a]	X	X		X		X	
PT, PTT	X						
Beta-HCG, if appropriate (within 48 hours)	X						
Urinalysis[b]	X				X		
MRI[c]	X						
Quality of Life Assessments[d]	X						
Bevacizumab[e]		X[e]	X[e]	X[e]	X[e]	X[e]	X[e]
Radiation Therapy (XRT)[f]		X	X	X	X	X	X
Temodar[g]		X	X	X	X	X	X

[a] Blood pressure and CMP should be obtained prior to each dose of bevacizumab.
[b] Urinalysis will be obtained once per month.
[c] MRI with and without contrast (or CT if unable to have MRI) within 8 weeks of starting treatment.
[d] Includes quality of life and functional capacity assessments, as well as neurocognitive testing. These assessments will also be obtained at the end of radiation therapy.
[e] Bevacizumab will be administered approximately every other week (but is listed on the table under each week since the treatment may start on an even or odd numbered week).
[f] Radiation therapy will be administered 5 days/week for approximately 6.5 weeks.
[g] Temodar will be taken daily.

Appendix B: Schedule of Events in Part B of the Study

		Cycles 1, 2, 3, 4, …12[a]			
	Post- XRT[b]	1	2	3	4
Blood pressure[c]		X	X	X	X
H&P with neurological assessment[d]		X		X	
CBC with differential[e]		X	X	X	X
CMP[f]		X	X	X	X
Urinalysis[f]		X	X	X	X
MRI[d]		X		X	
Toxicity Assessment	Continuous				
Quality of Life Assessments[g]		X			
Bevacizumab[h]		X	X	X	X
Temodar[i]		X	X	X	X

[a] Each cycle is 4 weeks long. Subjects can receive up to 12 cycles.
[b] If there is no evidence of progression 2-4 weeks after XRT, but not greater than 8 weeks, subjects will start Part B of the study.
[c] Blood pressure should be obtained prior to each dose of bevacizumab.
[d] H&P with neurological assessment and MRI should be obtained prior to the beginning of every other cycle.
[e] CBC with differential should be obtained every 2 weeks.
[f] CMP and urinalysis should be obtained prior to the beginning of every cycle.
[g] Includes quality of life and functional capacity assessments, as well as neurocognitive testing. Assessments will occur after XRT and then every 6 months.
[h] Bevacizuamb will be administered approximately every other week during a cycle on approximately Days 1 and 15.
[i] Temodar will be taken on Days 1-5 of each cycle.

Appendix C: Schedule of Events in Part C of the Study (Bevacizumab Only)

	Cycles 1, 2, 3, 4, …12[a]			
	1	2	3	4
Blood pressure[b]	X	X	X	X
H&P with neurological assessment[c]	X		X	
CBC with differential[d]	X	X	X	X
CMP[d]	X	X	X	X
Urinalysis[d]	X	X	X	X
MRI[c]	X		X	
Toxicity Assessment	Continuous			
Quality of Life Assessments[e]	X			
Bevacizumab[f]	X	X	X	X

[a] Cycle lengths may vary based on the dosing schedule and per the treating physician. The cycle lengths can be increased or decreased per the treating physician based on the patient's response to treatment.
[b] Blood pressure should be obtained prior to each dose of bevacizumab.
[c] H&P with neurological assessment and MRI should be obtained at the beginning of every other cycle.
[d] CBC with differential, CMP, and urinalysis should be obtained prior to the beginning of every cycle.
[e] Includes quality of life and functional capacity assessments, as well as neurocognitive testing. Assessments will occur every 6 months.
[f] Bevacizuamb will be administered approximately every other week during a cycle on approximately Days 1 and 15 (unless the treatment regimen calls for different timing of bevacizumab per the treatment physician). At the time of progression, the patient will begin Part D of the study and receive bevacizumab-containing therapy (alone or with chemotherapy and/or biologic agents), as long as there are no contraindications to bevacizumab.

Appendix D: Schedule of Events in Part D of the Study (Bevacizumab-based Therapy)

	Cycles 1, 2, 3, 4, …12[a]			
	1	2	3	4
Blood pressure[b]	X	X	X	X
H&P with neurological assessment[c]	X		X	
CBC with differential[d]	X	X	X	X
CMP[d]	X	X	X	X
Urinalysis[d]	X	X	X	X
MRI[c]	X		X	
Toxicity Assessment[a]	Continuous			
Quality of Life Assessments[e]	X			
Bevacizumab[f]	X		X	

[a] Cycle lengths may vary based on the dosing schedule and per the treating physician. The cycle lengths can be increased or decreased per the treating physician based on the patient's response to treatment.

[b] Blood pressure should be obtained prior to each dose of bevacizumab.
[c] H&P with neurological assessment and MRI should be obtained at the beginning of every other cycle.
[d] CBC with differential, CMP, and urinalysis should be obtained prior to the beginning of every cycle.
[e] Includes quality of life and functional capacity assessments, as well as neurocognitive testing. Assessments will occur every 6 months.
[f] At the time of progression, the patient will receive bevacizumab-containing therapy (alone or with chemotherapy and/or biologic agents), as long as there are no contraindications to bevacizumab.