Phase II Study of Border Zone Stereotactic Radiosurgery With Bevacizumab in Patients with Recurrent or Progressive Glioblastoma Multiforme

Protocol Number:	UPCI 13-063 (Genentech ML28725)
Principal Investigator:	Ajay Niranjan, M.D, MBA Department of Neurosurgery UPMC Presbyterian 200 Lothrop Street, F158 Pittsburgh, PA 15213 Phone: 412-647-6779; Email: niraax@upmc.edu
Clinical Research Coordinators	Melinda Vargas-Jaffe, RN, BSN Clinical Research Services UPMC Cancer Pavilion 5150 Centre Ave, Pittsburgh, PA 15232 Phone: 412-235-1320 Email: vargasjaffema@upmc.edu
	Sarah J. Anderson, RN , BSN Clinical Research Coordinator UPMC Cancer Pavilion 5150 Centre Avenue Pittsburgh, PA 15232 Phone: 412-647-8569 Email: andersonsj3@upmc.edu
	Lisa Baxendell, RN Department of Neurosurgery UPMC Presbyterian 200 Lothrop Street, F158 Pittsburgh, PA 15213 Phone: 412-647-4994 Email: decesx@upmc.edu
Statistician:	Daniel Normolle, PhD UPCI Biostatistics Shared Resource Facility Phone: 412-383-1591; E-mail: dpn7@pitt.edu
Version	November 23, 2016
IND#	Exempt

Table of Contents

1. PROTOCOL SUMMARY

Title: Phase II Study of Border Zone Stereotactic Radiosurgery with Bevacizumab in Patients with Recurrent or Progressive Glioblastoma Multiforme

Indication: Recurrent or Progressive Glioblastoma Multiforme

Objectives:
Primary Objective:

To assess the efficacy of Border Zone SRS with bevacizumab by overall survival in patients with recurrent or progressive glioblastoma following conventional management with surgery, fractionated radiation therapy, and chemotherapy.

Secondary Objectives:

1. To estimate progression-free and overall survival at 6 months
2. To evaluate the CNS toxicity of combined treatment, as measured by RTOG/EORTC Acute Radiation Morbidity Scoring and the NCI CTCAE v4.0 for late toxicity. Unacceptable toxicity will be considered to be irreversible grade 3 (severe), any grade 4 (life threatening) or grade 5 (fatal) RTOG CNS toxicity occurring within 3 months of GK.
3. To evaluate whether border zone SRS with bevacizumab improves tumor response or reduces radiosurgical toxicity compared to historical outcomes.
4. To evaluate the quality of life of border zone SRS with bevacizumab administration
5. To evaluate the potential value of magnetic resonance spectroscopy (MRS) in improvement of border zone target selection and detection of therapeutic response

Study Type: Interventional

Study Design: Single-arm, one-stage phase II trial for patients with recurrent glioblastoma.
Allocation: Non-Randomized
Endpoint Classification: Safety/Efficacy Study
Masking: Open Label
Primary Purpose: Treatment

Patient Numbers: A total of 40 patients with recurrent glioblastoma will be enrolled.

Summary of Patient Eligibility Criteria

Histological confirmation of glioblastoma; prior first-line treatment with surgery, fractionated radiation therapy, and chemotherapy for glioblastoma; age > 18 years; life expectancy >12 weeks; Karnofsky Performance Status ≥ 60; adequate organ function; signed patient informed consent; willingness to forego additional therapy until evidence of disease progression.

End Points

Primary: Overall survival (OS)
Secondary: Progression-free survival at 6 months (PFS-6) and overall survival at 6 months (OS), progression-free survival (PFS),
location of recurrence,
symptomatic adverse radiation effect (ARE) rate,
rate and type of adverse effects by bevacizumab,
reoperation rate, reoperation findings (estimated percentage of viable tumor vs. ARE),
QOL analysis

Project Summary in Lay Terms

Glioblastoma Multiforme (GBM) is the most common primary brain tumor in adults. Unfortunately, despite aggressive surgery, radiation therapy (RT) and chemotherapy, the prognosis for this disease is poor. It is our hypothesis that GBM is a "local" disease wherein treatment failure is due to failure to eradicate tumor cells in the pathways along which the tumor eventually spreads (the "border zone"). We hypothesize that treatment volume escalation will be successful at improving overall survival in patients with GBM when appropriate targeting and precision dose delivery is performed in a single treatment session. The 'border zone' of the tumor will be targeted for SRS (defined as a combination of the MRI volume of gadolinium enhancement plus up to 2 cm of the surrounding T 2 volume). This represents the volume of tumor infiltrated white matter and is the route of GBM spread. Bevacizumab, a monoclonal antibody to vascular endothelial growth factor (VEGF), has been used with safety and clinical success with concomitant chemotherapy in solid tumors, including GBM. We hypothesize that a combined approach of SRS with this VEGF inhibitor will be an effective strategy for GBM because bevacizumab will maximize the effects of radiation in the treated volume and potentially reduce radiation toxicity in the adjacent brain.

2. BACKGROUND/RATIONALE

Glioblastoma Multiforme (GBM) is the most common primary brain tumor in adults, with nearly 10,000 cases diagnosed annually in the United States. Unfortunately, despite aggressive surgery, radiation therapy (RT) and chemotherapy, the prognosis for this disease is poor. The expected five-year survival rate is less than 5%.[1] GBM is never a surgically curable lesion. The local control of the disease however has been improved markedly using image guided neurosurgical cytoreductive techniques followed by aggressive local therapy. Indeed, the resectability of the initial lesion correlates with survival.[2-3] In addition, the volume of locally recurrent disease correlates inversely with survival.[4] Recurrence and disease progression generally is adjacent to the surgical treatment volume.

Research has shown that glial cells mutate over time, become polarized, develop increasing local invasiveness, express genes that create proteins which cause breakdown of the extracellular matrix along white matter pathways, and develop actin contractility, in order to become motile. This motile behavior suggests a reappearance of the motile phenotype seen in glial cells migrating from the germinal matrix during embryonic development.[5] Indeed, there is a suggestion that if these mutated cells cannot migrate, they die. It is our hypothesis that GBM is a "local" disease whose treatment failure is due to neglect of the pathways along which the tumor eventually spreads (the "border zone"). It would be expected that treatment directed at local control would improve overall outcomes, as 90% of recurrences in malignant gliomas are located within 2 cm of the enhancing edge of the original tumor on CT scans[6-7] Indeed, many efforts at intensifying local radiation therapy suggest an improvement in outcome with higher doses. In an analysis of data from the Brain Tumor Study Group protocols, an improvement in median survival time was demonstrated with increasing RT dose (delivered conventionally): from 18 weeks without radiation, to 28 weeks with 50 Gy, 36 weeks with 55 Gy and 42 weeks with 60 Gy.[8] Unfortunately, efforts to increase radiation dose beyond 60 Gy did not improve outcomes but did increase toxicity. Fractionated stereotactic reirradiation for recurrent GBMs (performed with a median dose of 36 Gy in with fractions of 5 X 2 Gy/week) was associated with an additional median survival time of 8 months without severe radiation effects.[9]

Stereotactic radiosurgery (SRS) is a less-invasive treatment technique, and is usually performed on an outpatient basis. Numerous review articles discuss this delivery method.[10-12] The safety of SRS has been investigated by the RTOG in a phase I dose escalation study (RTOG 90-05) for the treatment of recurrent primary brain tumors and CNS metastases in patients who have previously received irradiation to the brain. The maximal tolerable dose based on overall toxicity was determined to be 24 Gy for <= 20mm tumors, 18 Gy for 21-30 mm tumors, and 15 Gy for 31-40 mm tumors.[13] Appropriate targeting is essential to improve the success of additional radiation techniques in treating GBM. It has become clear that treating the contrast enhancing portion of the tumor is insufficient in most cases. For example, image guided stereotactic biopsies have shown infiltrating tumor cells in the adjacent high T2 signal region around the contrast-enhancing tumor on MRI [14] In addition, work with glioma cell lines has shown that diffuse astrocytoma, and especially GBM, invade the brain preferentially along white matter fiber tracts.[15-17] Because this property is shared with human fetal brain cells that have been transplanted into the adult brain, it has been hypothesized that the migratory mechanisms of glioma cells may be related to embryonic development.[5] Spread along white matter pathways generally leads to contralateral spread via the corpus callosum, and diffuse, incurable disease.[17] Thus, based on the known invasive and migratory properties of glioma cells, it is not surprising that dose escalation focused on the contrast-enhancing portion of glioblastoma tumor has not been successful. In addition to the RTOG efforts at dose escalation with conventional techniques, a recently reported RTOG trial (RTOG 93-05) of upfront SRS to the contrast-enhancing portion of GBM failed to show a significant benefit for SRS over RT alone.[18]

Re-irradiation with SRS has been used in patients with focally recurrent glioblastoma because of its beneficial effect on survival. McDermott et al. [19] reported a series of 79 patients with recurrent glioblastoma treated with SRS at UCSF. The authors achieved a median survival of 40.6 weeks patients with glioblastoma and 61.6 weeks for those with recurrent anaplastic astrocytoma; similar results have been reported from other series [20-21]. Most single or multiple agent chemotherapy regimens used in this setting, in contrast, can only control disease progression an average of 8-24 weeks, with median survival expectation of only 20-42 weeks [22-25]. It is unusual to have an effective

response to additional chemotherapy, and treatment with these agents can be complicated by the systemic effects of treatment, such as myelosuppression, nausea, and anorexia.

Patterns of recurrence following SRS are similar to those reported for conventional radiation, with focal recurrence in 83.5% of patients [19]. Patients tend to fail within 1 to 2 cm from the contrast-enhancing edge of the lesion being treated, in keeping with the biology of this tumor, which is a highly infiltrative, invasive tumor. One potential reason for the high rate of subsequent local recurrence after radiosurgery at recurrence is inadequate targeting of viable tumor when radiosurgery is performed. It is standard practice to use the region of gadolinium enhancement on T1-weighted magnetic resonance imaging (MRI) as the basis for the treatment plan for SRS.

However, it is known that gadolinium enhancement does not correspond fully to active tumor; there are often regions of non-enhancing tumor that extend beyond the areas of contrast enhancement. These areas may be better defined using MRS; elevation of choline (Cho) levels and an increased ratio between choline and n-acetyl-acetate (NAA) correlate with tumor presence (26). In addition, selected reports suggest that the outcome of patients with recurrent gloiblastoma treated with SRS is correlated with the degree of overlap between treatment target (based on gadolinium-enhanced MRI) and presence of tumor as assessed by MRS (27-29). Areas of tumor detected by MRS that are not included in the SRS target volume are likely to recur, and that there is a trend toward poorer survival in these patients. We hypothesize that the use of a combination of gadolinium enhancement and elevated Cho:NAA ratio via MRS to determine the treatment target volume (the "border zone") for SRS may improve target selection during SRS for focally-recurrent glioblastoma.

Glioblastomas are innately hypoxic tumors with strong endogenous expression of vascular endotherial growth factor (VEGF) and VEGF receptors and consequently demonstrate vigorous angiogenesis. Bevacizumab, a humanized monoclonal antibody to VEGF, has been used with safety and clinical success with concomitant chemotherapy in solid tumors [26-28], including GBM [29-31]. Several reasons exist to combine bevacizumab and RT. These include the ability of antiangiogenic agents to sensitize tumor endothelium to RT by depletion of VEGF and the reduction of its pro-survival signaling.[32-33] Recently, a Phase II trial of single-agent bevacizmab at tumor progression in recurrent GBM patients who underwent conventional RT and temozolomide chemotherapy reported that six (12.5%) of 48 patients had drug-associated toxicity (five thromboembolic events, one bowel perforation). The median progression free survival (PFS) and overall survival (OS) was 16 weeks and 31 weeks, respectively. The 6 months PFS and OS was 29% and 57%, respectively.[34] We hypothesized that a combined approach of SRS with VEGF inhibitor would be an effective strategy for GBM because bevacizumab could maximize the effects of radiation and avoid radiation toxicity.

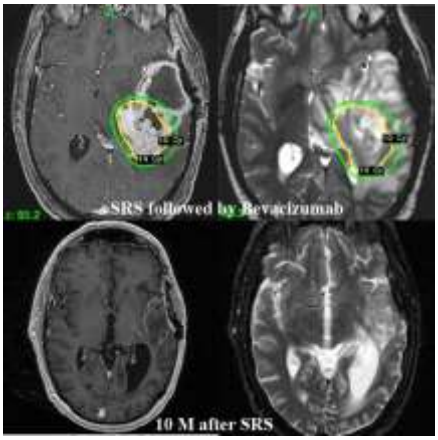


Figure. SRS followed by Bevacizumab
GBM patient who underwent surgical resection followed by fractionated RT and Temozolomide chemotherapy developed tumor progression. This patient underwent Gamma Knife radiosurgery (14 Gy/50% isodose) followed by Bevacizumab. The target was only Gd enhanced area with progression. The tumor was significantly smaller in size 10 months after SRS with Bevacizumab without adverse radiation effects.

Recently the University of Pittsburgh published a case-control study of salvage Gamma Knife stereotactic radiosurgery followed by bevacizumab for recurrent GBMs comparing to recurrent GBM without bevacizumab [35]. Compared with patients who did not receive bevacizumab, the patients who received bevacizumab had significantly prolonged PFS (6-months PFS: 73% vs. 58%, median PFS: 15 months vs 7 months, p=0.035) and OS (6-months OS: 100% vs. 89%, median OS: 18 months vs 12 months, p=0.005), and were less likely to develop an adverse radiation effect (9% vs 46%, p=0.037).

The significance of this research is that Border Zone SRS itself is a novel technique. We hypothesize that the addition of bevacizumab will reduce the risk of ARE in the volume treated by SRS, while having a direct therapeutic effect to the solid tumor itself. It is critical to study the safety, toxicity, and effectiveness of Border Zone SRS with bevacizumab. Volumetric maps of Border Zone radiosurgical volumes will be defined using T2 MRI. The greatest potential impact of this treatment paradigm is soon after conventional management of GBM (after initial surgery or biopsy, radiation therapy, and concomitant temozolomide chemotherapy) has been confirmed to fail.

Because of the high mortality of GBM, statistically significant data should become available within 3 years of the onset of the trial.

3. OBJECTIVES

Primary Objective:

To assess the efficacy of Border Zone SRS with bevacizumab as measured by overall survival in patients with recurrent or progressive glioblastoma following conventional management with surgery, fractionated radiation therapy, and chemotherapy.

Secondary Objectives:

- To evaluate progression free and overall survival at 6 months
- To evaluate the CNS toxicity of combined treatment, as measured by RTOG/EORTC Acute Radiation Morbidity Scoring and the NCI CTCAE v4.0 for late toxicity. Unacceptable toxicity will be considered to be irreversible grade 3 (severe), any grade 4 (life threatening) or grade 5 (fatal) RTOG CNS toxicity occurring within 3 months of GK.
- To evaluate whether border zone SRS with bevacizumab improves tumor response or reduces radiosurgical toxicity compared to historical outcomes.
- To evaluate the quality of life of border zone SRS with bevacizumab administration
- To evaluate the potential value of magnetic resonance spectroscopy (MRS) in improvement of border zone target selection and detection of therapeutic response.

4. STUDY DESIGN AND ELIGIBILITY CRITERIA

4.1 Study Design

This is a Non-Randomized Phase II trial. A total of 40 recurrent GBM patients will be enrolled into the trial and all will undergo Border Zone Stereotactic Radiosurgery (BZ-SRS) with bevacizumab. They will receive BZ-SRS and additionally receive bevacizumab (10 mg/kg) one day before and then at day 14 followed by 10 mg/kg/day every 14 days until progression. All patients enrolled in the study will be evaluated for progression-free survival, overall survival, symptomatic ARE, reoperation rate, reoperation findings (estimated percentage of viable tumor vs. ARE), quality of life evaluation, and toxicity.

4.2 Inclusion Criteria

1) Histologically confirmed glioblastoma multiforme, WHO grade IV astrocytoma.
2) Prior first-line treatment with surgery or biopsy followed by fractionated radiotherapy with concurrent temozolomide-containing chemotherapy is required for glioblastoma patients. Additional prior chemotherapy is allowed, without limitation on number of recurrences.
3) An interval of ≥ 2 months since completion of fractionated radiotherapy.
4) Age > 18 years
5) Life expectancy of at least 12 weeks.
6) Karnofsky Performance Status score (KPS) of ≥ 60 (Appendix 1).
7) Documented recurrent disease: Recurrent disease is defined either as radiological confirmation of the tumor, as an increase in tumor size of at least 25% based upon serial MR images, or as development of a new site of disease.
   - Tumor volume will be calculated using the sum of the largest cross-sectional perpendicular diameters of contrast-enhancing tumor, the sum of the largest cross-sectional perpendicular diameters of FLAIR abnormality, or as worsened spectroscopic characteristics for any tumor type (development of ≥ 2 new voxels with CNI ≥ 3, or ≥ 25% increase in the sum of the CNI ratios within a group of previously abnormal voxels [where abnormal is defined as CNI ≥ 3]).
   - Disease must be evaluable, but does not need to be measurable.
   - The target site for SRS does not need to be located in a previously-irradiated area.

8) Eligibility for stereotactic radiosurgery using MRI targeting: The decision to treat with stereotactic radiosurgery will be made by a consensus of the radiation oncology, neurosurgery and neuro-oncology providers or their alternates at the weekly Brain Tumor or Stereotactic Radiosurgery Tumor Conferences. All patients must have no restrictions to obtaining MRI with and without paramagnetic contrast.
9) BUN < 25 and Cr < 1.7
10) Adequate bone marrow, hepatic and renal function (ANC ≥1,500/μL, hemoglobin of ≥10.0 g/dL, platelet count of ≥100,000/L, aspartate aminotransferase/ alanine aminotransferase of ≤2.5 × upper limit of normal, serum bilirubin of ≤1.5 × upper limit of normal, urine protein and urine blood negative to trace on POCT urine dip to Proteinuria at screening as demonstrated by either: Urine Protein:Creatinine (UPC) ratio ≥ 1.0 at screening OR Urine dipstick for proteinuria ≥ 2+ (patients discovered to have ≥ 2+ proteinuria on dipstick urinalysis at baseline should undergo a 24 hour urine collection and must demonstrate ≤ 1g of protein in 24 hours to be eligible)

11) Negative pregnancy test at the time of SRS in any patient who could be pregnant.
12) Willingness to forego additional therapy until evidence of disease progression.
13) Signed and witnessed informed consent and signed authorization for the release of their protected health information.

4.3 Exclusion Criteria

1. General Medical Exclusions:
   1) Current, recent (within 4 weeks of the first infusion of this study), or planned participation in an experimental drug study.
   2) Active malignancy, other than superficial basal cell and superficial squamous (skin) cell, or carcinoma in situ of the cervix within last 3 years.
   3) Prior radiosurgery
   4) Prior intracavitary irradiation or Gliadel wafers.

2. Disease-Specific Exclusions:
   1) Inability to comply with protocol or study procedures
   2) Prior treatment with bevacizumab.
   3) Inability to undergo MRI with and without contrast administration.

3. Bevacizumab-Specific Exclusions:
   1) Inadequately controlled hypertension (defined as systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg).
   2) Prior history of hypertensive crisis or hypertensive encephalopathy.
   3) New York Heart Association (NYHA) Grade II or greater congestive heart failure.
   4) History of myocardial infarction or unstable angina within 6 months prior to Day 1.
   5) History of stroke or transient ischemic attack within 6 months prior to Day 1.
   6) Significant vascular disease (e.g., aortic aneurysm, requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Day 1.
   7) History of hemoptysis (>/= 1/2 teaspoon of bright red blood per episode) within 1 month prior to Day 1.
   8) Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation).
   9) Major surgical procedure, open biopsy, or significant traumatic injury within 14 days prior to Day 1 or anticipation of need for major non -cranial surgical procedure during the course of the study.
   10) Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to Day 1.
   11) History of abdominal fistula or gastrointestinal perforation within 6 months prior to Day 1.
   12) Serious, non-healing wound, active ulcer, or untreated bone fracture.
   13) Proteinuria as demonstrated by: (a) Urine protein: creatinine (UPC) ratio >/= 1.0 at screening OR (b) Urine dipstick for proteinuria >/= 2+ (patients discovered to have >/= 2+ proteinuria on dipstick urinalysis at baseline should undergo a 24 hour urine collection and must demonstrate </= 1g of protein in 24 hours to be eligible).
   14) Known hypersensitivity to any component of bevacizumab

15) Pregnancy (positive pregnancy test) or lactation. Use of effective means of contraception (men and women) in subjects of child-bearing potential.

4.4 Proposed SRS Target and Dose

Standard MRI Targeting

On the day of the SRS procedure, after application of an MRI compatible Stereotactic head frame, each patient will undergo stereotactic brain MRI. The target volume will be determined using commercially available radiosurgery software. The target volume will include up to 2 cm of the high T2 signal brain surrounding the contrast enhancing tumor. This volume may include signal change noted within the corpus callosum. The total SRS dose will depend on the target volume and the proximity of dose limiting adjacent critical structures, such as the optic nerve and brain stem.

Whenever feasible, the centers will have the option of using MRS during radiosurgery planning. One to 14 days before SRS procedure, patients at centers with MRS experience will undergo standard brain MRI and MRS). A choline to N-acetyl aspartate index (CNI) on MRS ≥ 3 is considered tumor metabolism (see 10.3). Depending on total T2 treatment volume, we will attempt to include the area of CNI ≥ 3 within the 50% isodose volume at the time of SRS procedure. The target volume will include up to 2 cm of the high T2 signal brain surrounding the contrast enhancing tumor. Using the preoperative MRS coregistered to the intraoperative MRI, we will adjust the SRS target volume. This volume may include signal change noted within the corpus callosum. The total SRS dose will depend on the target volume and the proximity of dose limiting adjacent critical structures, such as the optic nerve and brain stem.

Target definition:

Standard MRI targeting

1) Gadolinium enhanced area + all T2 hyper intensity area if it is $\leq$ 2 cm (maximum diameter):

Or

2) Gadolinium enhanced area + maximum 2 cm margin of T2 hyper intensity area if T2 hyper intensity areais > 2 cm.

Optional: Whenever feasible, at selected centers MRS will be used during radiosurgery planning. The area of CNI on MRS (1-14 days before SRS) ≥ 3 will be targeted provided that it falls within the volume limitation of up to 2 cm of T2 signal surrounding the contrast enhancing tumor volume.

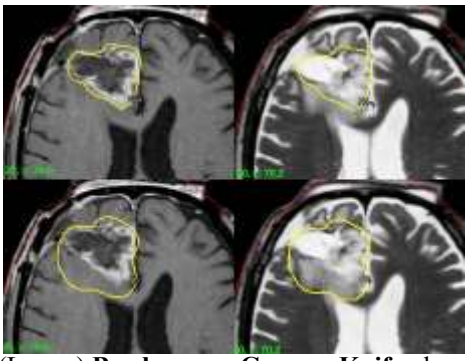


Figure. Border zone SRS
GBM patient who underwent surgical resection followed by fractionated RT and Temozolomide chemotherapy developed tumor progression.
(Upper) Gamma Knife planning for only Gd enhanced area. The target volume = 21.4 cc.
(Lower) **Border zone Gamma Knife** planning for Gd enhanced area + T2 hyper intensity area. The target volume = 42.6 cc.

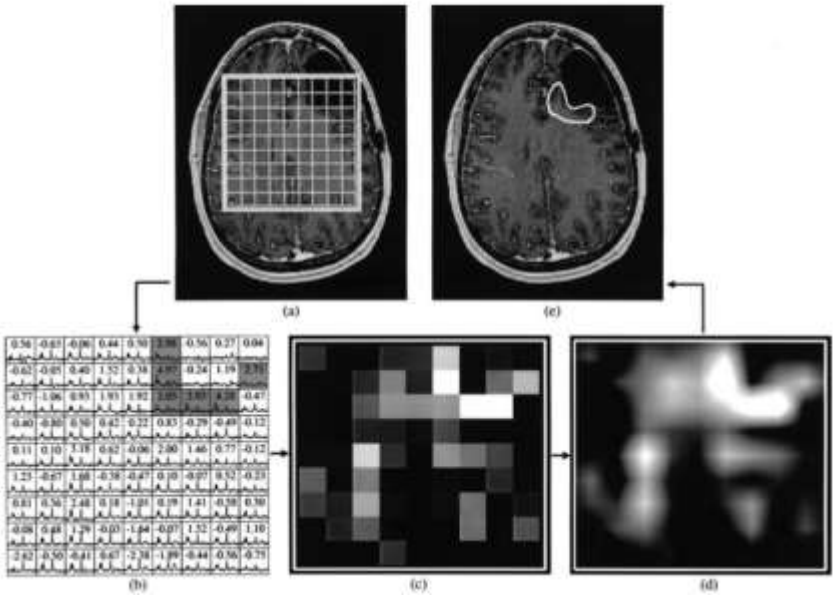


Figure. MRS targeting
The various steps in delineating the metabolic lesion. First, a 3D array of spectra is acquired (a) and the CNI for each voxel in the array of spectra is calculated (b) to produce a low-resolution CNI map (c). This map is resampled
to produce a high-resolution CNI map (d) that is contoured using a CNI value of 2. This contour is overlaid onto the reference image (e).
CNI = Cho/NAA index

J Neurosurg 101:467–475, 2004

Margin dose:
The dose will be prescribed to the isodose surface (50%) which encompasses the border zone of the tumor. The maximum dose will be normalized to the 100% and dose prescribed to the 50% isodose surface.

The 100% (maximum) dose will be recorded for each patient. The prescription dose shall be delivered to the 50% (maximum = 100%) isodose surface, and is defined as the minimum dose to the target volume. . This minimum dose shall be established by an examination of the target dose-volume histogram and the dose distribution on surrounding normal brain. Following doses are suggested however, these doses may need to be adjusted depending upon the interval period between the RT and radiosurgery. In case RT was completed less than 3 months ago these doses may need to be lowered.

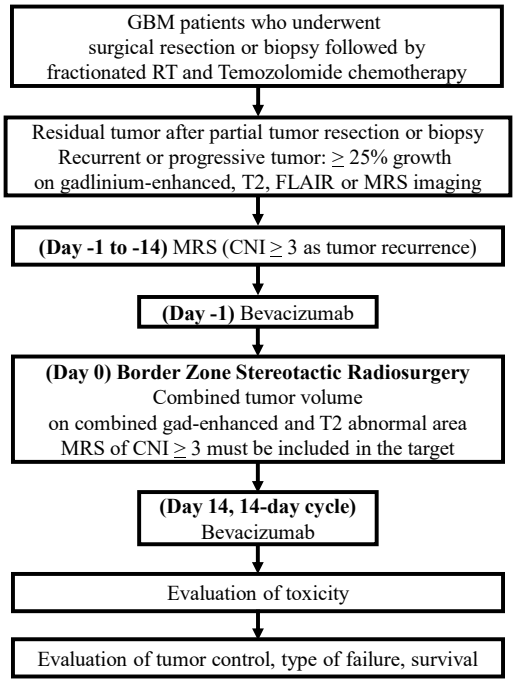
. Less than or equal to 8 cc: 18 Gy
8-15 cc: 16 Gy
16-30 cc: 14 Gy
31-35 cc: 12 Gy
36 cc or more: 10 Gy

4.5 Protocol Schema

a) Day -14 to -1: Patients will undergo MRS, at participating centers with MRS experience.

b) Day -1: Patients will be treated with bevacizumab 10 mg/kg 1 day before SRS.

c) Day 1: Patients will undergo Border Zone SRS.
Total dose of Border Zone SRS will depend on the size of the target volume and the proximity of adjacent



critical structures. When possible the target volume will include the edematous area surrounding the contrast enhancing tumor and the area of elevation of choline (Cho) levels and an increased ratio between choline and n-acetyl-acetate (NAA) in the MRS along the white matter pathways of spread ("border zone").

d) Fourteen days after SRS, patients will be treated with 14-day cycle of bevacizumab (10 mg/kg) until progression. Dose delays were allowed for reversible and preventable toxicity (See 4.5.2).

e) All patients will have an evaluation of SRS toxicity 6 months after SRS.

f) All patients will undergo a MRI in order to ascertain study eligibility, at the time of SRS, and then after every four cycles of bevacizumab. MRI scans will be assessed using both the historical subjective Levin criteria and the more recent objective Macdonald criteria (30, 31). The Levin criteria consider extent of gadolinium enhancement, edema, and mass effect in a global assessment of the scan compared with baseline. Response is scored as a complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) using RECIST criteria. In contrast, the Macdonald criteria use linear measurements of target lesion cross-sectional diameters to define response (Appendix 2-1). The RANO (Response Assessment in Neuro-Oncology) Response Criteria will be also used as updated response assessment criteria (Appendix 2-2) (40).

4.5.1 Bevacizumab administration

4.5.1.1 Rate of Infusion

The initial bevacizumab dose should be delivered over 90 minutes as a continuous IV infusion prior to all chemotherapy infusions. If the first infusion is tolerated without infusion-associated adverse events (fever and/or chills), the second infusion may be delivered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 minutes.

If a patient experiences bevacizumab infusion-associated adverse events, patient may receive pre-medication (acetaminophen, diphenhydramine, steroids or other medications given for symptom control) at the investigators' discretion, prior to the next bevacizumab infusion. If pre-medication is required, the infusion time may not be decreased for the subsequent infusion. However, if the next infusion is well tolerated with pre-medication, the subsequent infusion time may then be decreased by 30 minutes per infusion to a minimum infusion time of 30 minutes, as long as the patient continues to receive the same pre-medication.

If a pre-medicated patient experiences infusion-associated adverse events with the 60-minute infusion, all subsequent doses should be given over 90 minutes. Similarly, if a pre-medicated patient experiences infusion-associated adverse events with the 30-minute infusion, all subsequent doses should be given over 60 minutes.

A rate-regulating device should be used for all bevacizumab infusions. When the bevacizumab IV bag is empty, 50 mL of 0.9% sodium chloride injection, USP, should be added to the IV bag or an additional bag should be hung. An alternative method of flushing the infusion line would be to replace the empty bevacizumab infusion bag with a 50 mL bag of 0.9% sodium chloride injection

and infuse a volume equal to that of the tubing to ensure complete delivery of the bevacizumab. The infusion should be continued for a volume equal to that of the tubing to ensure complete delivery of the bevacizumab.

4.5.1.2 Anaphylaxis Precautions

Anaphylaxis precautions should be observed during bevacizumab administration.

The patient's blood pressure and heart rate should be monitored every 15 minutes during the first infusion.

Emergency agents including oxygen, oral and endotracheal airways, intubation equipment, epinephrine, antihistamines and corticosteroids should be available.

In the event of a suspected anaphylactic reaction during bevacizumab infusion, stop the bevacizumab infusion and apply a tourniquet proximal to the injection site, if possible, to slow systemic absorption of bevacizumab. Administer antihistamines, epinephrine, or other medications at the investigator's discretion.

4.5.1.3 Bevacizumab Infiltration

Should infiltration of the bevacizumab infusion occur, the following steps are to be taken:

- Discontinue the IV.
- If a significant volume of the bevacizumab infusion remains, restart the IV and complete the infusion.
- Treat the infiltration according to institutional guidelines for infiltration of a non-caustic agent.

4.5.1.4 Hypertension

Hypertension is a known and potentially serious adverse event associated with bevacizumab treatment. Patients should have their BP monitored closely during the first cycle of therapy and prior to each infusion of bevacizumab. Hypertensive mediation should be initiated or increased per routine practice.

4.5.1.5 Wound complications and surgery

The appropriate interval between the last dose of bevacizumab and elective surgery is unknown; however, the half-life of bevacizumab is estimated to be 20 days. The study will suspend bevacizumab for at least 28 days prior to elective surgery if needed because of continued tumor progression. In addition, bevacizumab should not be restarted until at least 4 weeks after major surgery provided that the wound has adequately healed.

NOTE: If, for any reason, patient is off bevacizumab for $\geq$ 4 weeks, Study Principal Investigator must be contacted, and the case discussed, before patient may resume protocol treatment.

Dose Modifications/Delays

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. Bevacizumab has a terminal half-life of 2 to 3 weeks; therefore, its discontinuation results in slow elimination over several months. There is no available antidote for bevacizumab.

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

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 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. Regardless of the reason for holding study drug treatment, the maximum allowable length of treatment interruption is 2 months.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 RPLS (confirmed by MRI) or hypertensive encephalopathy)	Discontinue bevacizumab.
Hemorrhage	
No dose modifications for grade 1/2 nonpulmonary and non-CNS events	
Grade ≥ 2 pulmonary or CNS hemorrhage or **tumor Related bleeding**	Discontinue bevacizumab.
Grade 3 nonpulmonary and non-CNS hemorrhage	All subjects will have study treatment 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	Discontinue bevacizumab.
Venous Thrombosis	
If patient develops DVT during study and requires full dose anticoagulation, bevacizumab will be discontinued.	

Table 1

Bevacizumab Dose Management due to Adverse Events (continued)

Arterial Thromboembolic event	
(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	Hold bevacizumab until resolution to Grade ≤ 1.

Grade 4	Discontinue bevacizumab.
Proteinuria	
No dose modifications for grade 1/2 events	
Grade 3 (UPC> 3.5, urine collection > 3.5 g/24 hr, or dipstick 4+)	Hold bevacizumab treatment until ≤ Grade 2, as determined by either UPC ratio ≤ 3.5 or 24 hr collection ≤ 3.5 g
Grade 4 (nephrotic syndrome)	Discontinue bevacizumab
GI Perforation	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 3/4	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 requiring medical or surgical therapy	Discontinue bevacizumab.
Other Unspecified Bevacizumab-Related Adverse Events	
Grade 3	Hold bevacizumab until recovery to ≤ Grade 1
Grade 4	Discontinue bevacizumab.

4.6 Sample Size

The sample size is justified in terms of the primary analysis, comparing the overall survival of the protocol participants to a historical control set of patients treated at this institution. The estimated survival function of the control set (246 events in 269 patients) is presented in Figure 4.6.1. A Monte Carlo simulation is used to estimate the power for increases in median OS of treated patients, compared to controls, from 0% to 100%. For each percent increase, 1000 bootstrap samples are drawn from the control set of size 269 (the simulated control sets) in addition to 1000 bootstrap samples of size 40 (the simulated treatment sets). Each survival time in the simulated treatment sets is increased by the given percentage. The, for each of the 1000 simulated trial results, the proportion of control-treatment pairs of sets for which the null hypothesis of no treatment effect is rejected (at α=0.10) by a proportional hazards (Cox) regression is determined. The result is the power curve in Figure 4.6.2, where it is seen that the expected power is in excess of 80% when the median overall survival in the treatment group exceeds 14.3 months, a 59% increase.

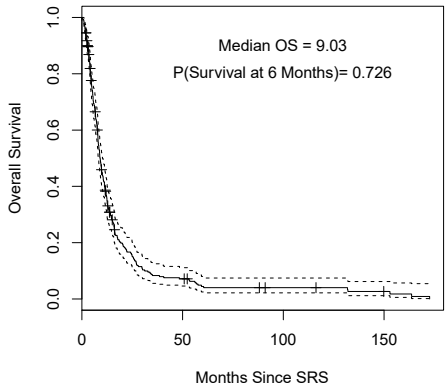


Figure 4.6.1 Estimated survival function of the control set.

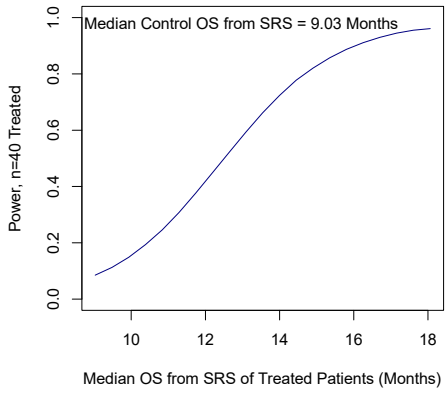


Figure 4.6.2 Power of primary analysis as a function of median survival in the treatment arm

5. PATIENT REGISTRATION

All patients who are consented will be entered into University of Pittsburgh Clinical Trial Management Application (CTMA) database.

6. STEREOTACTIC RADIOSURGERY TREATMENT PROTOCOL

6.1 General Plan:

All SRS procedures will be done at the participating NAGKC institutions. All patients considered for the protocol must have a lesion deemed suitable for stereotactic radiosurgery after presentation to a multidisciplinary Brain Tumor Conference and/or Stereotactic Radiosurgery Conference. SRS procedures must be done within 21 days of study registration.

6.2 Treatment Plan Requirements

Patient treatments will be planned using available radiosurgery dose planning software. The dose will be prescribed to the margin of target volume. The radiosurgery dose will be prescribed based on volume within the prescribed isodose surface according to the curve shown in Appendix 3.

6.3 Treatment Volume Definition

The target volume will include enhancing tumor plus up to 2 cm of the high T2 signal brain surrounding the contrast enhancing tumor.

7. CONCOMITANT MEDICATIONS

Patients may receive all concomitant therapy deemed necessary to provide adequate support, such as steroids or anticonvulsants; treatment with other anti-cancer agents or therapies is not permitted.

8. TOXICITY MANAGEMENT

8.1 Radiation Toxicity: Expected side effects of radiosurgery include adverse radiation effects (ARE) in the treatment region, or adjacent to it. Radiation toxicity will be divided into acute (within the first 90 days after treatment) and late (occurring more than 90 days after treatment) manifestations. Assessment of radiation toxicity will be done using the RTOG/EORTC Radiation Morbidity Scoring Scheme (see Appendix 6) for acute toxicity and the NCI CTCAE v4.0 (see http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf) for late toxicity. Patients who develop ARE may require treatment with steroids or surgical resection of the affected volume.

8.2 Hematologic Toxicity: All toxicities including hematologic due to bevacizumab therapy will be rated according to the NIH Common Toxicity Criteria (version 4.0).

8.3 Other Toxicities: All other toxicities and adverse events will also be recorded using the CTCAE v4.0.

9. SCHEDULE OF ASSESSMENTS

A flow chart of the study assessments is given in Appendix 4.

9.1 Screening Procedures

The following procedures will be conducted within 14-21 days prior to SRS. Registration is defined as the point after the patient signs the informed consent and prior to meeting all eligibility requirements..

- 9.1.1 Signed and witnessed informed consent within 30 days prior to registration
- 9.1.2 Medical history.
- 9.1.3 Physical and neurological examination including KPS, review of systems, vital signs, height, and weight.
- 9.1.4 Quality of life questionnaires
- 9.1.5 EKG (12-lead)
- 9.1.6 CBC, Serum Chemistry (albumin, alkaline phosphatase, total bilirubin, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT[AST], SGPT[ALT], sodium.), PT/INR and Urine Protein Creatinine Ratio (or point of care (POCT) urine dipstick for blood and protein)
- 9.1.7 Pregnancy test for women of child-bearing potential.

9.1.8 Contrast-enhanced Gd-DPTA MRI (may be MRI showing progression, even if performed more than 21 days prior to SRS)
9.19 MRS (at selected sites) – within 14 days of SRS
9.1.10 Stable or decreasing dose of steroids for at least 5 days.

9.2 Post SRS Study Procedures

9.2.1. Physical and neurological examination, including Karnofsky Performance Status score, review of systems, vital signs, height, and weight every 2 weeks.

9.2.2. All patients will undergo a gadolinium-enhanced MRI at baseline, and at 8-week intervals or after every 4 cycles.

9.2.3 Laboratory tests (complete blood counts, basic metabolic panel and urinary protein to creatinine ratio) will be obtained every 2 weeks or every cycle.

9.2.4 Imaging studies after every 4 cycles of post SRS bevacizumab at the 6-month toxicity evaluation. (The toxicity evaluation MRI may be part of the post Cycle 12 imaging.) If there is a question of worsening of the MRI at the time of other evaluations, the patient should undergo reevaluation with repeat MRI)

9.2.5 Quality of life questionnaires after the first 4 cycles of bevacizumab

9.3 Follow-up post 12 months SRS:

The following evaluations will be done one year after SRS, followed by every 3 months year two post SRS, then every 4 months for year 3 post SRS, then every 6 months thereafter:

9.3.1. Physical and neurological examination, including Karnofsky Performance Status score, review of systems, vital signs, height, and weight, as well as Quality of Life Questionnaires.

9.3.2. Gadolinium-enhanced MRI.

9.3.3 Laboratory tests (complete blood counts, basic metabolic panel and urinary protein to creatinine ratio)

If not being seen in-person otherwise, all patients who received treatment will be contacted via mail or telephone every two to three months to determine survival. A review of medical records or other official documentation are also acceptable to confirm patient status.

10.0. CRITERIA FOR EVALUATION

10.1 Clinical Neurological Examination

Neurological performance will be monitored by grading both symptoms and signs. Evaluation will be based on any changes in the neurological clinical exam in the interval since the last examination. Changes should be unrelated to post-ictal state or other unrelated events such as infection, and steroid requirement will be considered in the evaluation as well.

The following scale will be used to designate relative changes:

+2 = definitely better
+1 = possibly better
0 = unchanged
-1 = possibly worse
-2 = definitely worse

10.2 Brain Imaging

The following MRI protocol will be performed on each patient before treatment and with each subsequent imaging follow-up.: pre-contrast sagittal T1-weighted, axial and coronal T2 weighted imaging, diffusion-weighted, post-contrast axial and coronal T1-weighted imaging. From the MRI scan, the following parameters will be assessed: volumes of contrast enhancing lesion, T2 abnormality, as well as areas of restricted diffusion from ADC maps, . In addition, tumor and treatment related complications such as edema, hemorrhage, hydrocephalus, and degree of mass effect/midline shift will be assessed. Any new areas of contrast enhancing or T2 lesions will also be recorded.

Tumor response will be evaluated using RANO Criteria.

RANO Response Criteria				
Criterion	**CR**	**PR**	**SD**	**PD**
T1 gadolinium enhancing disease	None	≥ 50% ↓	< 50% -< 25% ↑	≥ 25% ↑*
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑*
New lesion	None	None	None	Present*
Corticosteroids	None	Stable or ↓	Stable or ↓	NA†
Clinical status	Stable or ↑	Stable or ↑	Stable or ↑	↓*
Requirement for response	All	All	All	Any*

10.3 MR Spectroscopy:

Whenever there is a question as to whether the appearance of the MRI represents true tumor progression versus treatment effect, the use of proton MR spectroscopy is encouraged at centers with MRS capability. Proton MR Spectroscopy will be performed using a three-dimensional (3D), multi-voxel technique. A region of interest to target the spectroscopic examination will be placed on the anatomic MRI abnormality defined on FLAIR and contrast-enhanced T1-weighted images. The maximal dimension of the 3D spectroscopic box will be 10x10x10mm. Spectroscopic data will be processed on an offline UNIX workstation using a program developed in-house that allows quantification of relative metabolite ratio index within a given spectroscopic voxel size of 1cc. The following metabolite ratio indices will be measured on a voxel-by-voxel basis: choline to N-acetyl aspartate index (CNI) and lactate and lipid index (LLI). A CNI ≥ 3 will be considered suspicious for tumor metabolism and LLI ≥ 3 in a region of CNI ≤ 2 will be considered suspicious for treatment effect.

10.4 Definition of Tumor Progression

If surgery is not done for histological confirmation, tumor progression will be defined by evaluating both traditional MRI sequences (gadolinium-enhanced T1 and T2) and spectroscopic data, as follows:

- Outside the area targeted by SRS:
    - Development of an area of new or increased (by $\geq 25\%$ in the product of two perpendicular diameters despite stable or increased steroid dose) gadolinium-enhanced T1 or FLAIR abnormality will be considered to be tumor progression.
    - If there is discordance between the traditional MRI (gadolinium-enhanced T1 or T2) and the spectroscopy (e.g. one modality is concerning for progression but the other is not), the MRI and MRS will be repeated in 1-2 months at the treating physician's discretion. If there remains concern for progression in either or both modalities (traditional MRI or MRS) on the second scan, the tumor will be considered to have progressed and the date of progression will be retrospectively determined to be the date of the initial scan demonstrating concerning changes.

- Within the area targeted by SRS:
    - The sum of the CNI ratios within the voxels considered abnormal (e.g. CNI ≥ 3) will be taken at the time of treatment planning and at the time of each follow-up MRI. If there is a $\geq 25\%$ increase in the sum relative to the smallest sum at baseline or subsequently, in an area of new or increased (by $\geq 25\%$ in the product of two perpendicular diameters despite stable or increased steroid dose) gadolinium-enhanced T1 MRI or T2 abnormality, this will be considered to be tumor progression.
    - If there is discordance between the traditional MRI (gadolinium-enhanced T1 or T2) and the spectroscopy (e.g. one modality is concerning for progression but the other is not), the MRI and MRS will be repeated in 1-2 months at the treating physician's

discretion. If there remains concern for progression in either or both modalities (traditional MRI or MRS) on the second scan, the tumor will be considered to have progressed and the date of progression will be retrospectively determined to be the date of the initial scan demonstrating concerning changes.

Regardless of imaging, failure to return for evaluation due to death or deteriorating condition will be considered progression, unless clearly unrelated to this tumor.

10.5 Overall Response

The overall response will be a combination of neurological and imaging status. Imaging findings will be emphasized, but will be interpreted with attention to steroid dosing and findings on neurological examination.

10.6 Progression-Free Survival

Because of the complexity of interpreting imaging changes in these patients, PFS will need to be retrospectively determined in many patients, based on clinical course and analysis of serial MRIs at later time points. For example, if a patient's 6-month MRI shows increased enhancement, it may not be obvious at that moment whether this represents adverse radiation effect, pseudo-progression or tumor progression. In that case, if clinically appropriate the patient will be followed, and an interval MRI will be done 8 weeks later. If the next MRI has stabilized or improved, the patient will be considered to have had radiation necrosis. If the MRI continues to worsen, additional imaging evaluation will be undertaken if possible, surgical evaluation will be considered, if appropriate, and the case will be discussed either at a multidisciplinary tumor board meeting or amongst the investigators to determine an appropriate course of action.

11. CRITERIA FOR TERMINATION

11.1 Conditions for Terminating the Study

The Principal Investigator may terminate the study for any of the following reasons:

a) Significant toxicities (see Safety Stopping Rule, 12.3)

b) If it becomes clear that the study treatment is ineffective (see Futility Stopping Rule, 12.5)

c) Once all data has been completed.

11.2 Conditions for Individual Patient Termination

The Principal Investigator may terminate the participation of an individual patient for any of the following reasons:

a) Disease progression
b) Need for exclusionary concurrent treatment
c) Withdrawal of informed consent
d) Protocol non-compliance
e) Loss to follow-up
f) Death

Patients are free to withdraw from the study at any time without giving a reason. Full documentation will be made of any withdrawals that may occur during the study. The Investigator will document the date of the withdrawal, the reason for withdrawal, if known, and the result of any assessments made at that time. Whenever possible, patients whose participation is terminated due to progression of disease will be followed for safety measurements as detailed in this protocol.

12. STATISTICAL CONSIDERATIONS

12.1 Study Design

This is a single-arm phase II trial to evaluate the safety, toxicity, and potential efficacy of bevacizumab combined with border zone stereotactic radiosurgery) and can be compared to the published results of bevacizumab alone). Forty patients with recurrent glioblastomas will be enrolled. Overall survival, progression-free survival and measures of toxicity and clinical response will be compared to a historical series of 297 patients (269 evaluable for overall survival and 219 evaluable for progression-free survival)) treated at this institution with gamma knife radiosurgery alone. A propensity-matched subset of that series will also be used as a comparison series.

12.2 Safety and Futility Stopping Rules

We intend to monitor adverse events on a monthly basis to determine if there are unacceptable toxicities. A formal stopping rule for safety will allow the possibility of terminating the trial early in the event that an excessive number of acute or late toxicities thought to be related to the treatment is observed. Specifically, we will look at acute toxicity when 10 and 20 patients have been enrolled and followed for acute toxicities for 90 days after SRS treatment. A 10% rate of acute toxicity is considered to be acceptable. If the number of patients experiencing acute toxicity thought to be related to treatment exceeds 2 out of 10 patients, or 4 out of 20 patients, the investigators will meet to discuss early termination of the trial.

Late toxicity will be assessed at least every 6 months, but will also be specifically assessed a year after the registration of the 10^{th} and 20th patients. 40% is considered to be an acceptable maximal late toxicity rate. If the number of patients experiencing late toxicity exceeds 6 out of 10 or 11 out of 20, the investigators will meet to discuss early termination of the trial.

The specific rule for safety stopping is based on the 1-sided lower 90% confidence interval for the probability of toxicity exceeding the respective acceptable rates. The probability of stopping under various true toxicity rates are given in Tables 1 and 2 below.

Table 1. Acute toxicity stopping rule

		Probability of stopping under various true acute toxicity rates								
# pts	Stop if >= toxicities	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
10	3	.07	.32	.62	.83	.95	.99	.99	.99	.99

20	5	.04	.37	.76	.95	.99	.99	.99	1	1

Table 2. Late toxicity stopping rule

		Probability of stopping under various true late toxicity rates								
# pts	Stop if >= toxicities	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9
10	7	<.001	.001	.01	.05	.17	.38	.65	.88	.99
20	12	<.001	<.001	.005	.06	.25	.60	.89	.99	.99

A futility analysis will be conducted when 20 recurrent glioblastoma patients have been enrolled to allow for the possibility of stopping the trial if progression-free survival is unacceptably low. Specifically, if more than 17 patients have progressed at the 6-month time point, the trial will be stopped for futility. If the true rate of PFS-6 is only 10% (under the null), there would be a 68% chance of stopping that arm of the trial early. On the other hand, if the true probability of being progression-free at 6 months is 25% (under the alternative), the chance of stopping that arm of the trial early would be 9%.

12.3 Endpoint Definitions and Statistical Analysis

Primary Endpoint:

To assess the efficacy of Border Zone SRS with bevacizumab by overall survival (OS) in patients with recurrent or progressive glioblastoma following conventional management with surgery, fractionated radiation therapy, and chemotherapy. OS is defined as number of days from the day of diagnosis until the date of death due to any cause. Patients who are lost to follow-up will be censored at the date of last contact. OS of protocol patients will be compared to the OS of 269 evaluable University of Pittsburgh historical controls (patients who were managed using standard treatment with gamma knife radiosurgery without Avastin) by means of a log-rank test applied to Kaplan-Meier estimates of the respective survival functions. The median OS of the historical control set is 18.1 months (95% CI: (17.0,19.6)). The same test will be applied to compare protocol patients and selected controls propensity-score matched on age and gender. If the proportionality assumption is not met, a time covariate will be created and the data will be analyzed via conditional multiple logistic regression models with time as a covariate.

Secondary Endpoints:

1. *Evaluate progression-free and overall survival at 6 months (PFS-6 and OS-6).* OS-6 is defined as the percentage of patients who remain alive as of 6 months from the date of radiosurgery; PFS-6 is defined in a similar fashion (see Section 10.4). Any patient who receives bevacizumab treatment will be included in the statistical analysis, except for patients who are followed for less than 6 months for reasons other than death. Cases will be compared with our internal historical controls (patients who were managed using standard treatment with gamma knife radiosurgery without Avastin). Fisher's exact test will be used to compare the proportion of protocol patients alive, and alive and disease-free at six months to the historical control set. The test will be repeated to compare protocol patients and the propensity-matched control set.

2. *To evaluate the CNS toxicity of combined treatment, as measured by RTOG/EORTC Acute Radiation Morbidity Scoring and the NCI CTCAE v4.0 for late toxicity.*
Unacceptable toxicity, considered to be irreversible grade 3 (severe), any grade 4 (life threatening) or grade 5 (fatal) RTOG CNS toxicity occurring within 3 months of GK, will be tabulated by grade. A cumulative logit modelwill be used to compare the distribution of Grad 3-5 toxicities to the full control set and the propensity score-matched controls. A similar model will be used to compare the RTOG/EORTC Acute Radiation Morbidity Scoring, a patient-level 0-4 scale, between both the full and propensity-matched protocol and control samples. The presence or absence of unacceptable toxicity will be compared by means of Fisher's exact test. Adverse events will be tabulated in the protocol patients by location and CTCAE grade.

3. *To evaluate whether border zone SRS with bevacizumab improves tumor response or reduces radiosurgical toxicity compared to historical outcomes.*
Tumor response is defined in Appendix 2. A cumulative logit model will be used to compare tumor response (complete response, partial response, stable disease or progression) between the protocol and historical control samples.

4. *To evaluate the quality of life of border zone SRS with bevacizumab administration.* The following assessments and instruments will be available at baseline and, after the first 4 cycles of bevacizumab and each follow up visit: Karnofsky score; Barthel's Index of Activities of Daily living; Center for Epidemiological Studies Depression Scale (CES-D); Functional Assessment of Cancer Therapy-Brain Specific (FACT-Br). These QoL assessments are not available from the control set, so the analyses will be descriptive, focusing on trends over time.

5. *To evaluate the potential value of magnetic resonance spectroscopy (MRS) in improvement of border zone target selection and detection of therapeutic response.* This is an exploratory aim comparing the derived treatment volumes between MRI and MRI+MRS in the current trial. The analyses will be descriptive, and there will be no comparison to the control sample.

12.4 Replacement of Patients

Patients who enroll but are unable to begin treatment will be replaced. Given that SRS is completed within a single session, any patient who initiates SRS will by definition complete treatment, so there will be no other indication for replacement of patients.

13. ETHICAL ASPECTS

13.1 Regulatory Considerations

This study will be reviewed University of Pittsburgh Institutional Review Board (IRB; see below).

13.2 Independent Ethics Committees/Institutional Review Board

This protocol and the informed consent will be approved by the University of Pittsburgh Institutional Research Board (IRB). The Principal Investigator is responsible for keeping the IRB advised of the progress of the study and of any changes made in the protocol prior to implementation. The Principal Investigator will also keep the IRB informed of any significant adverse reactions, and any protocol exceptions or deviations. Records of all study review and approval documents must be kept on file by the Principal Investigator and are subject to FDA inspection during or after completion of the study. The IRB will receive notification of the termination of the study.

14 SAFETY REPORTING OF ADVERSE EVENTS

14.1 Assessment of Safety

14.1.1 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 {study drug}, all events of death, and any study specific issue of concern.

14.1.2 Adverse Events

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 Glioblastoma Multiforme 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.

14.1.3 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).

14.2 Methods and Timing for Assessing and Recording Safety Variables

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

14.2.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of initiation of any study procedures" and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

14.2.2 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 reported appropriately. Each reported 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 {study drug}, 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 {study drug}; and/or the AE abates or resolves upon discontinuation of the {study drug} or dose reduction and, if applicable, reappears upon re-challenge.

No

Evidence exists that the AE has an etiology other than the {study drug} (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to {study drug} 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 (P.I.) 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 P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

14.3 Procedures for Eliciting, Recording, and Reporting Adverse Events

14.3.1 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?"

14.3.2 Specific Instructions for Recording Adverse Events

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

14.3.2.1 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.

14.3.2.2 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".

14.3.2.3 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").

14.3.2.4 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.

14.3.2.5 Pregnancy

If a female subject becomes pregnant while receiving investigational therapy or within 30 days) 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 the {study drug} should be reported as an SAE.

14.3.2.6 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 {study drug} 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.

14.3.2.7 Reconciliation

The Sponsor agrees to conduct reconciliation for the product. Genentech and the Sponsor 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 Sponsor 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.

14.3.2.8 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. See Appendix 7 for bevacizumab events of special interest for this study.

14.3.2.9 SAE Reporting

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

Fax Cover Sheet is located in Appendix 8

- 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 the 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 bevacizumab report Genentech.

Note: Investigators should also report events to the University of Pittsburgh IRB as per institutional guidelines.

14.3.3 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

14.3.3.1 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/medwatch/getforms.html

14.4 Publishing and FDA Reporting

14.4.1 Publishing

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.

Clinical Operations Contact:
Amber Lapp
Country Study Manager On Assignment with Genentech
P: 484-533-2019 Ext. 3051 Email: lappa@gene.com

14.4.2 FDA Reporting

Genentech is responsible for all FDA reporting. The PI will not submit reports directly to the FDA.

15. DATA SAFETY MONITORING PLAN

Investigator/Sub-investigators, regulatory, CRS management, clinical research coordinators, clinical research associates, data managers, and clinic staff meet monthly in disease center Data Safety Monitoring Boards (DSMB) to review and discuss study data to include, but not limited to, the following:

- serious adverse events
- subject safety issues
- recruitment issues
- accrual
- protocol deviations
- unanticipated problems
- breaches of confidentiality

All toxicities encountered during the study will be evaluated on an ongoing basis according to the NCI Common Toxicity Criteria version 4.0. All study treatment associated adverse events that are serious, at least possibly related and unexpected will be reported to the IRB. Any modifications necessary to ensure subject safety and decisions to continue, or close the trial to accrual are also discussed during these meetings. If any literature becomes available which changes the risk/benefit ratio or suggests that conducting the trial is no longer ethical, the IRB will be notified in the form of an Unanticipated Problem submission and the study may be terminated.

All study data reviewed and discussed during these meetings will be kept confidential. Any breach in subject confidentiality will be reported to the IRB in the form of an Unanticipated Problem submission. The summaries of these meetings are forwarded to the UPCI DSMC which also meets monthly following a designated format.

For all research protocols, there will be a commitment to comply with the IRB's policies for reporting unanticipated problems involving risk to subjects or others (including adverse events). DSMC progress reports, to include a summary of all serious adverse events and modifications, and approval will be submitted to the IRB at the time of renewal.

Protocols with subjects in long-term (survival) follow-up or protocols in data analysis only, will be reviewed twice a year rather than monthly.

Both the UPCI DSMC as well as the individual disease center DSMB have the authority to suspend accrual or further investigate treatment on any trial based on information discussed at these meetings.

All records related to this research study will be stored in a locked environment. Only the researchers affiliated with the research study and their staff will have access to the research records.

16. REFERENCES

1. Mahaley MS, Jr., Mettlin C, Natarajan N, Laws ER, Jr., Peace BB. National survey of patterns of care for brain-tumor patients. *J Neurosurg.* Dec 1989;71(6):826-836.

2. Nitta T, Sato K. Prognostic implications of the extent of surgical resection in patients with intracranial malignant gliomas. *Cancer.* Jun 1 1995;75(11):2727-2731.

3. Daneyemez M, Gezen F, Canakci Z, Kahraman S. Radical surgery and reoperation in supratentorial malignant glial tumors. *Minim Invasive Neurosurg.* Dec 1998;41(4):209-213.

4. Keles GE, Lamborn KR, Chang SM, Prados MD, Berger MS. Volume of residual disease as a predictor of outcome in adult patients with recurrent supratentorial glioblastomas multiforme who are undergoing chemotherapy. *J Neurosurg.* Jan 2004;100(1):41-46.

5. Demuth T, Berens ME. Molecular mechanisms of glioma cell migration and invasion. *J Neurooncol.* Nov 2004;70(2):217-228.

6. Hochberg FH, Pruitt A. Assumptions in the radiotherapy of glioblastoma. *Neurology.* Sep 1980;30(9):907-911.

7. Wallner KE, Galicich JH, Krol G, Arbit E, Malkin MG. Patterns of failure following treatment for glioblastoma multiforme and anaplastic astrocytoma. *Int J Radiat Oncol Biol Phys.* Jun 1989;16(6):1405-1409.

8. Walker M, Strike T, GE S. An analysis of dose-effect relationship in the radiotherapy of malignant gliomas. *Int J Radiat Oncol Biol Phys.* 1979;5(10):1725-1731.

9. Combs SE, Thilmann C, Edler L, Debus J, Schulz-Ertner D. Efficacy of fractionated stereotactic reirradiation in recurrent gliomas: long-term results in 172 patients treated in a single institution. *J Clin Oncol.* Dec 1 2005;23(34):8863-8869.

10. McKenzie MR, Souhami L, Podgorsak EB, Olivier A, Caron JL, Villemure JG. Photon radiosurgery: a clinical review. *Can J Neurol Sci.* May 1992;19(2):212-221.

11. Podgorsak EB. Physics for radiosurgery with linear accelerators. *Neurosurg Clin N Am.* Jan 1992;3(1):9-34.

12. Wu A. Physics and dosimetry of the gamma knife. *Neurosurg Clin N Am.* Jan 1992;3(1):35-50.

13. Shaw E, Scott C, Souhami L, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05. *Int J Radiat Oncol Biol Phys.* May 1 2000;47(2):291-298.

14. Kelly PJ, Daumas-Duport C, Kispert DB, Kall BA, Scheithauer BW, Illig JJ. Imaging-based stereotaxic serial biopsies in untreated intracranial glial neoplasms. *J Neurosurg.* Jun 1987;66(6):865-874.

15. Belien AT, Paganetti PA, Schwab ME. Membrane-type 1 matrix metalloprotease (MT1-MMP) enables invasive migration of glioma cells in central nervous system white matter. *J Cell Biol.* Jan 25 1999;144(2):373-384.

16. Giese A, Kluwe L, Laube B, Meissner H, Berens ME, Westphal M. Migration of human glioma cells on myelin. *Neurosurgery.* Apr 1996;38(4):755-764.

17. Pedersen PH, Edvardsen K, Garcia-Cabrera I, et al. Migratory patterns of lac-z transfected human glioma cells in the rat brain. *Int J Cancer.* Sep 15 1995;62(6):767-771.

18. Souhami L, Seiferheld W, Brachman D, et al. Randomized comparison of stereotactic radiosurgery followed by conventional radiotherapy with carmustine to conventional radiotherapy with carmustine for patients with glioblastoma multiforme: report of Radiation Therapy Oncology Group 93-05 protocol. *Int J Radiat Oncol Biol Phys.* Nov 1 2004;60(3):853-860.

19. McDermott M, W., Sneed PK, Chang S, M. *Results of Radiosurgery for Recurrent Gliomas.* Vol 11996.

20. Chamberlain MC, Barba D, Kormanik P, Shea WM. Stereotactic radiosurgery for recurrent gliomas. *Cancer.* Aug 15 1994;74(4):1342-1347.

21. Shrieve DC, Alexander E, 3rd, Wen PY, et al. Comparison of stereotactic radiosurgery and brachytherapy in the treatment of recurrent glioblastoma multiforme. *Neurosurgery.* Feb 1995;36(2):275-282; discussion 282-274.

22. de Groot JF, Gilbert MR, Aldape K, et al. Phase II study of carboplatin and erlotinib (Tarceva, OSI-774) in patients with recurrent glioblastoma. *J Neurooncol.* Oct 2008;90(1):89-97.

23. Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *J Clin Oncol.* Oct 1 2009;27(28):4733-4740.

24. Vredenburgh JJ, Desjardins A, Herndon JE, 2nd, et al. Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. *J Clin Oncol.* Oct 20 2007;25(30):4722-4729.

25. Wong ET, Hess KR, Gleason MJ, et al. Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials. *J Clin Oncol.* Aug 1999;17(8):2572-2578.

26. Levin VA, Crafts DC, Norman DM, Hoffer PB, Spire JP, Wilson CB. Criteria for evaluating patients undergoing chemotherapy for malignant brain tumors. *J Neurosurg.* Sep 1977;47(3):329-335.

27. Macdonald DR, Cascino TL, Schold SC, Jr., Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. *J Clin Oncol.* Jul 1990;8(7):1277-1280.

28. Prados MD, Lamborn K, Yung WK, et al. A phase 2 trial of irinotecan (CPT-11) in patients with recurrent malignant glioma: a North American Brain Tumor Consortium study. *Neuro Oncol.* Apr 2006;8(2):189-193.

29. Buckner JC. Factors influencing survival in high-grade gliomas. *Semin Oncol.* Dec 2003;30(6 Suppl 19):10-14.

30. Lamborn KR, Chang SM, Prados MD. Prognostic factors for survival of patients with glioblastoma: recursive partitioning analysis. *Neuro Oncol.* Jul 2004;6(3):227-235.
31. Therasse P, Le Cesne A, Van Glabbeke M, Verweij J, Judson I. RECIST vs. WHO: prospective comparison of response criteria in an EORTC phase II clinical trial investigating ET-743 in advanced soft tissue sarcoma. *Eur J Cancer.* Jul 2005;41(10):1426-1430.
32. Ahn GO, Brown JM. Matrix metalloproteinase-9 is required for tumor vasculogenesis but not for angiogenesis: role of bone marrow-derived myelomonocytic cells. *Cancer Cell.* Mar 2008;13(3):193-205.
33. Gorski DH, Beckett MA, Jaskowiak NT, et al. Blockage of the vascular endothelial growth factor stress response increases the antitumor effects of ionizing radiation. *Cancer Res.* Jul 15 1999;59(14):3374-3378.
34. Kreisl TN, Kim L, Moore K, et al. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. *J Clin Oncol.* Feb 10 2009;27(5):740-745.
35. Park KJ, Kano H, Iyer A, et al. Salvage Gamma Knife Stereotactic Radiosurgery Followed by Bevacizumab for Recurrent Glioblastoma Multiforme: A case-control study. *J Neurooncol.* 2011.
36. Nagai H, Kondziolka D, Niranjan A, Flickinger J, Lunsford L. Results following stereotactic radiosurgery for patients with glioblastoma multiforme. *Radiosurgery.* 2004;5:91-99.
37. Lamborn KR, Yung WK, Chang SM, et al. Progression-free survival: an important end point in evaluating therapy for recurrent high-grade gliomas. *Neuro Oncol.* Apr 2008;10(2):162-170.
38. Kim HT. Cumulative incidence in competing risks data and competing risks regression analysis. *Clin Cancer Res.* Jan 15 2007;13(2 Pt 1):559-565.
39. Collin C, Wade DT, Davies S, Horne V. The Barthel ADL Index: a reliability study. *Int Disabil Stud.* 1988;10(2):61-63.
40. Mahoney FI, Barthel DW. Functional Evaluation: The Barthel Index. *Md State Med J.* Feb 1965;14:61-65.
41. Wade DT, Collin C. The Barthel ADL Index: a standard measure of physical disability? *Int Disabil Stud.* 1988;10(2):64-67.
42. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol.* Apr 10 2010;28(11):1963-1972.

17. APPENDICES
Appendix 1: Karnofsky Performance Status

Normal: no complaints, no evidence of disease	100
Able to carry on normal activity; minor signs or symptoms of disease	90
Normal activity with effort; some signs or symptoms of disease	80
Cares for self; unable to carry on normal activity or to do active work	70
Requires occasional assistance but is able to care for most of his needs	60
Requires considerable assistance and frequent medical care	50
Disabled; requires special care and assistance	40
Severely disabled; hospitalization is indicated although death is not imminent	30
Very sick; hospitalization necessary	20
Moribund; fatal processes progressing rapidly	10
Dead	0

Appendix 2 Current Response Criteria for Malignant Gliomas

Appendix 2-1:

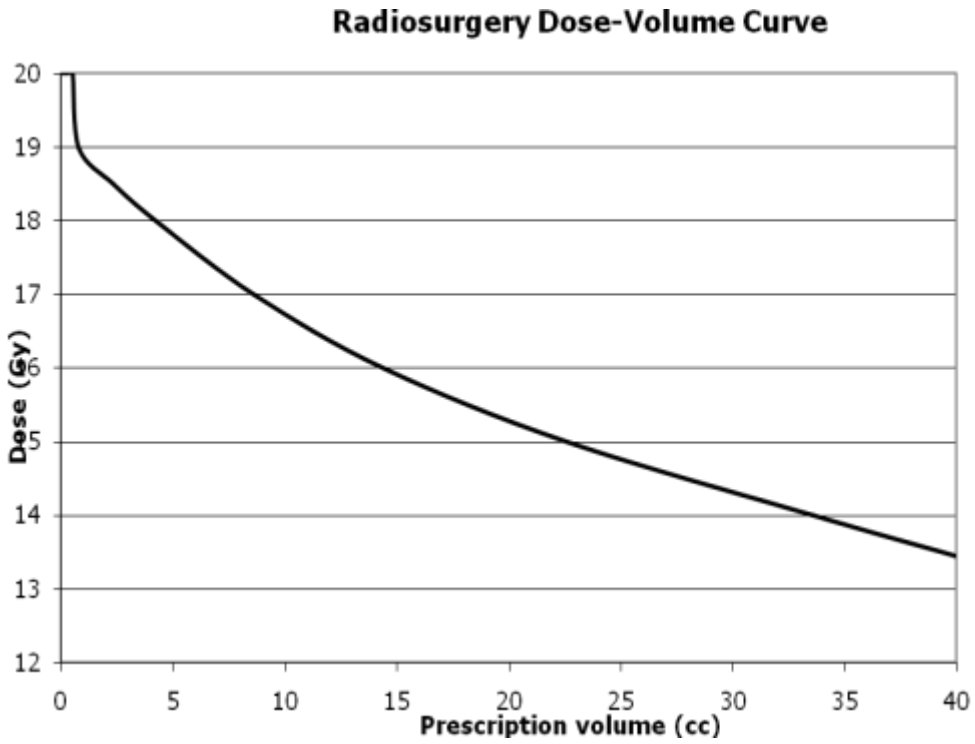
Current Response Criteria for Malignant Gliomas (Macdonald Criteria) [26-27]	
Response	Criteria
Complete response	Requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; no corticosteroids; and stable or improved clinically
Partial response	Requires all of the following: $\geq$ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no new lesions; stable or reduced corticosteroid dose; and stable or improved clinically
Stable disease	Requires all of the following: does not qualify for complete response, partial response, or progression; and stable clinically
Progression	Defined by any of the following: $\geq$ 25% increase in sum of the products of perpendicular diameters of enhancing lesions; any new lesion; or clinical deterioration

Appendix 2-2:

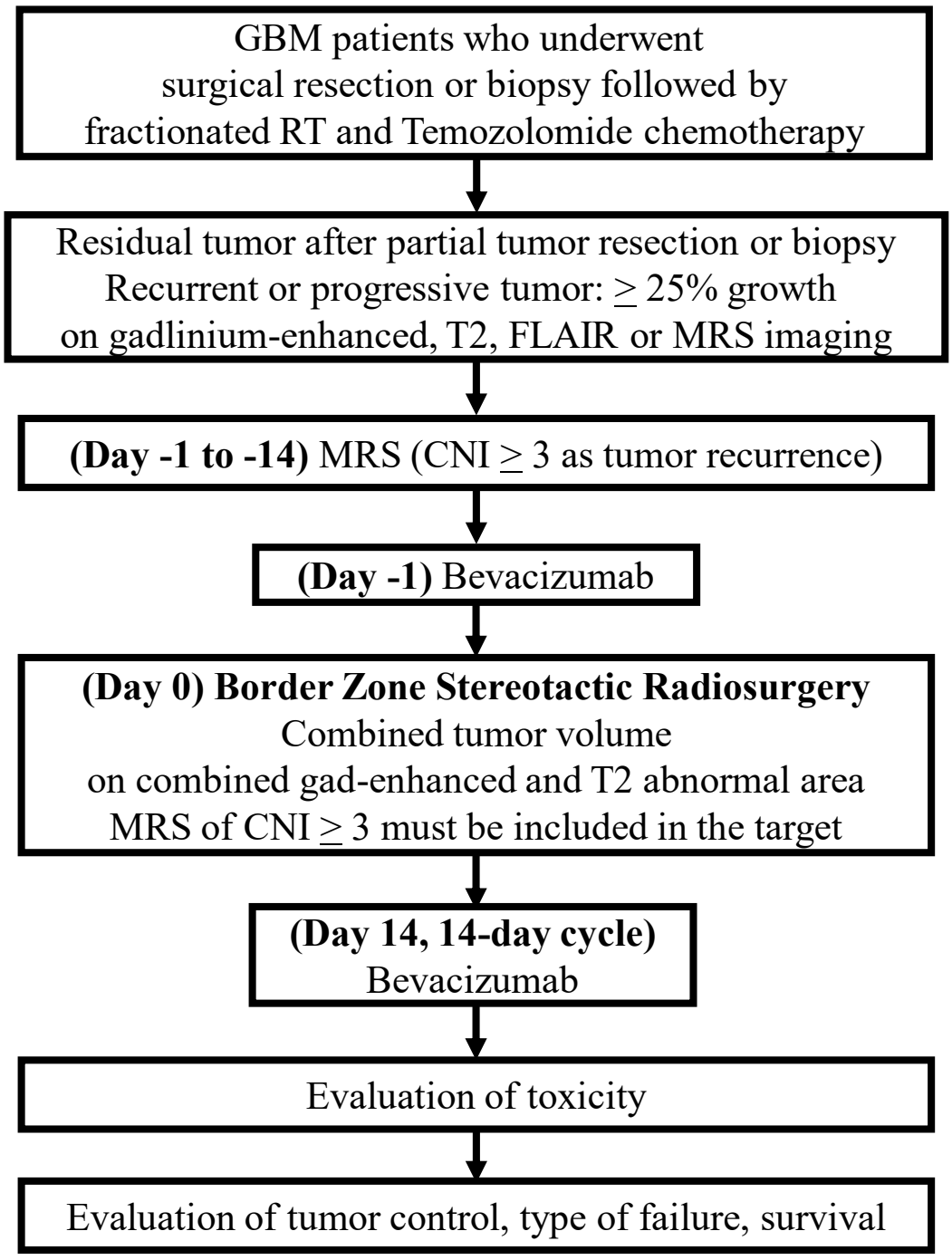
RANO (Response Assessment in Neuro-Oncology) Response Criteria[45]				
Criterion	complete response	partial response	stable disease	progressive disease
T1 gadolinium enhancing disease	None	≥ 50% decrease	< 50% decrease but < 25% increase	≥ 25% increase*
T2/FLAIR	Stable or decrease	Stable or decrease	Stable or decrease	Increase*
New lesion	None	None	None	Present*
Corticosteroids	None	Stable or decrease	Stable or decrease	NA†
Clinical status	Stable or increase	Stable or increase	Stable or increase	Decrease*
Requirement for response	All	All	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.				

Several reports have documented good outcome of Criteria for Response Assessment Incorporating MRI and Clinical Factors[42]	
Response	Criteria
complete response	Requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions; patients must be off corticosteroids (or on physiologic replacement doses only); and stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have a complete response; the best response possible is stable disease.
partial response	Requires all of the following: ≥50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of nonmeasurable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; the corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan; and stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have a partial response; the best response possible is stable disease.
stable disease	Requires all of the following: does not qualify for complete response, partial response, or progression; stable nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
progressive disease	Defined by any of the following: ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids*; significant increase in T2/FLAIR nonenhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy* not caused by comorbid events (eg, radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects); any new lesion; clear clinical deterioration not attributable to other causes apart from the tumor (eg, seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or changes in corticosteroid dose; failure to return for evaluation as a result of death or deteriorating condition; or clear progression of nonmeasurable disease.
NOTE. All measurable and nonmeasurable lesions must be assessed using the same techniques as at baseline. *Stable doses of corticosteroids include patients not on corticosteroids.	

Appendix 3 Radiosurgery Dose-Volume Curve



Appendix 4 Study Flowchart



Appendix 5 Study Schedule

Evaluations	Screening: Within 21 days of SRS	Within 14 days of SRS	1 day prior to SRS	SRS	Every Cycle (2 weeks) [g]	Every 4 Cycles (8 weeks) [g]	> 6 months post-SRS [h] follow up	> 12 months post-SRS [e] follow up
History and Physical	X				X			X
Neuro Exam + KPS	X				X			X
Vital signs	X				X			X
Height	X							
Weight	X				X			X
Quality of Life Questionnaires[l]	X					X[j]		X
EKG	X							
CBC	X				X			X
Serum chemistry[a]	X				X			X
Beta-HCG[b]	X							
PT-INR	X				X[c]			X[c]
Urine Protein Creatinine Ratio[d]	X				X			X
Adverse event evaluation					X		X	X
Bevacizumab [f]			X		X			
MRI with Gd-DPTA	X			X		X		X
MRS		X[k i]						

[a]Albumin, alkaline phosphatase, total bilirubin, BUN, calcium, chloride, creatinine, glucose potassium, total protein, SGOT[AST], SGPT[ALT], sodium.
[b]Serum or urine pregnancy test (women of childbearing potential).
[c]For patients on systemic anticoagulation with warfarin
[d]Urine analysis for calculation of Urine Protein: Creatinine Ratio (UPC ratio) should be performed. prior to each cycle. If UPC ration is > 1, collection of 24 hour urine for measurement of urine protein level is recommended but not required.
UPC ratio of spot urine is an estimation of the 24 urine protein excretion – a UPC ratio of 1 is roughly equivalent to a 24-hour urine protein of 1 gm. UPC ratio is calculated using on of the following formula:
- [urine protein]/[urine creatinine] – if both protein and creatinine are reported in mg/dL
- [(urine protein) x0.088]/[urine creatinine] – if urine creatinine is reported in mmol/L
Alternately, POCT urine dipstick for blood and protein can be be performed. If POCT urine dipstick, blood and protein need to be <+2 for treatment.

[e]Evaluations to be done every 3 months for one year, then every 4 months for one year, then every 6 months thereafter.
[f] bevacizumab (10 mg/kg) will be administered one day before SRS and then at **day 14** after SRS followed by 10 mg/kg/day every 14 days until progression
[g] +/- 2 days
[h] +/-3 days
[i] at MRS capable facilities; to be done 14 days prior to SRS

[j] at the end of the first 4 cycle visit only (i.e. at about week 8)
[k] research scans
[l] upon completion copies of the forms will be forwarded to the PI.

Appendix 6 RTOG/EORTC Acute Radiation Morbidity Scoring

RTOG/EORTC Acute Radiation Morbidity Scoring Scheme (Partial)

	[0]	[1]	[2]	[3]	[4]
SKIN	No change over baseline	Follicular, faint or dull erythema/ epilation/dry desquamation/ decreased sweating	Tender or bright erythema, patchy moist desquamation/ moderate edema	Confluent, moist desquamatiom other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
MUCOUS MEMBRANE	No change over baseline	Injection/ may experience mild pain not requiring analgesic	Patchy mucositis which may produce an inflammatory serosanguinitis discharge/ may experience moderate pain requiring analgesia	Confluent fibrinous mucositis/ may include severe pain requiring narcotic	Ulceration, hemorrhage or necrosis
EYE	No change	Mild conjunctivitis with or without scleral injection/ increased tearing	Moderate conjunctivitis with or without keratitis requiring steroids &/or antibiotics/ dry eye requiring artificial tears/ iritis with photophobia	Severe keratitis with corneal ulceration/ objective decrease in visual acuity or in visual fields/ acute glaucoma/ panopthalmitis	Loss of vision (unilateral or bilateral)
EAR	No change over baseline	Mild external otitis with erythema, pruritis, secondary to dry desquamation not requiring medication. Audiogram unchanged from baseline	Moderate external otitis requiring topical medication/ serious otitis medius/ hypoacusis on testing only	Severe external otitis with dischange or moist desquamation/ symptomatic hypoacusis/tinnitus, not drug related	Deafness
SALIVARY GLAND	No change over baseline	Mild mouth dryness/ slightly thickened saliva/ may have slightly altered taste such as metallic taste/ these changes not reflected in alteration in baseline feeding behavior, such as increased use of liquids with meals	Moderate to complete dryness/ thick, sticky saliva/ markedly altered taste	-------	Acute salivary gland necrosis
PHARYNX & ESOPHAGUS	No change over baseline	Mild dysphagia or odynophagia/ may require topical anesthetic or non-narcotic analgesics/ may require soft diet	Moderate dysphagia or odynophagia/ may require narcotic analgesics/ may require puree or liquid diet	Severe dysphagia or odynophagia with dehydration or weight loss(>15% from pre-treatment baseline) requiring N-G feeding tube, I.V. fluids or hyperalimentation	Complete obstruction, ulceration, perforation, fistula
LARYNX	No change over baseline	Mild or intermittent hoarseness/cough not requiring antitussive/ erythema of mucosa	Persistent hoarseness but able to vocalize/ referred ear pain, sore throat, patchy fibrinous exudate or mild arytenoid edema not requiring narcotic/ cough requiring antitussive	Whispered speech, throat pain or referred ear pain requiring narcotic/ confluent fibrinous exudate, marked arytenoid edema	Marked dyspnea, stridor or hemoptysis with tracheostomy or intubation necessary
CNS	No change	Fully functional status (i.e., able to work) with minor neurologic findings, no medication needed	Neurologic findings present sufficient to require home case/ nursing assistance may be required/ medications including steroids/anti-seizure agents may be required	Neurologic findings requiring hospitalization for initial management	Serious neurologic impairment which includes paralysis, coma or seizures>3 per week despite medication/hospitalization required (Patients with seizure disorders at baseline who have breakthrough seizures would not be considered to have a grade IV)

GUIDELINES: The acute morbidity criteria are used to score/grade toxicity from radiation therapy. The critera are relevant from day 1, the commencement of therapy, through day 90.

Appendix 7 Bevacizumab Related Events of Special Interest

- Hypertension ≥ grade 3
- Proteinuria ≥ grade 3
- GI perforation, abscesses and fistulae (any grade)
- Wound healing complications ≥ grade 3
- Haemorrhage ≥ grade 3 (any grade CNS bleeding; ≥ grade 2 haemoptysis)
- Arterial thromboembolic events (any grade)
- Venous thromboembolic events ≥ grade 3
- PRES (any grade)
- CHF ≥ grade 3
- Non-GI fistula or abscess ≥ grade 2

Appendix 8 Safety Reporting Fax Cover Sheet

Genentech
A Member of the Roche Group

SAFETY REPORTING FAX COVER SHEET

Genentech Supported Research

AE / SAE FAX No: (650) 225-4682

Alternate Fax No: (650) 225-5288

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]

Subject Initials (Enter a dash if patient has no middle name)	[ ] - [ ] - [ ]

SAE or Safety Reporting questions, contact Genentech Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

Version 1 31-May-2012