RADIATION THERAPY ONCOLOGY GROUP

RTOG 1205

RANDOMIZED PHASE II TRIAL OF CONCURRENT BEVACIZUMAB AND RE-IRRADIATION VERSUS BEVACIZUMAB ALONE AS TREATMENT FOR RECURRENT GLIOBLASTOMA

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Protocol Agents

Agent	Supply	NSC #	IND #
Bevacizumab	Commercial	704865	N/A

Participating Sites

☐ US Only
☐ Canada Only
☒ US and Canada
☒ International/Non North American

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RTOG 1205

Randomized Phase II Trial of Concurrent Bevacizumab and Re-Irradiation Versus Bevacizumab Alone as Treatment for Recurrent Glioblastoma

SCHEMA

Bevacizumab-Naïve Recurrent GBM Patients:

STRATIFY	Age 1. <50 2. ≥50 Karnofsky performance status 1. 70-80 2. 90-100 Recent resection 1.Yes 2. No/biopsy only	**RANDOMIZE**	Arm 1: Bevacizumab alone q 2 weeks (control arm) Arm 2: Hypofractionated radiotherapy 35 Gy in 10 fractions with concurrent Bevacizumab q 2 weeks (experimental arm)

See Section 5.0 for radiation therapy credentialing requirements. See Section 7.0 for details/doses of bevacizumab.

Patient Population: (See Section 3.0 for Eligibility)
Patients with recurrent glioblastoma or variant (gliosarcoma or giant cell glioblastoma etc).

Required Sample Size: 178

ELIGIBILITY CHECKLIST (11/5/12)
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_____(Y) 1. Does the patient have histologically proven diagnosis of glioblastoma or variants per section 3.1.1?

_____(Y/NA) 2. Does patient have progression on contrast-enhanced MRI/CT within 14 days prior to registration as defined in section 3.1.1, bullet 1?

_____(Y/N) 3. Is there an interval of 6 months or greater between completion of prior radiotherapy and registration?
_____ (Y) If No, was one or more of the criteria in section 3.1.1 a, b or c met?

_____(Y/N) 4. Does the patient have a prior history of standard dose CNS radiation as defined in section 3.1.2?
_____ (Y) If No, was one or more of the criteria in section 3.1.1 a, b or c met?

_____(Y/NA) 5. Has patient recovered from the toxic effects of prior therapy?

_____(Y/NA) 6. If patient received prior investigational agent(s) and/or prior cytotoxic therapy was there a minimum time of 28 days prior to registration? With the exceptions of vincristine (minimum time of 14 days), nitrosoureas (minimum time of 42 days) and procarbazine (minimum time of 21 days)

_____(Y/N) 7. Did the patient have a recent resection (within 30 days prior to registration) of the glioblastoma?
If Y:
_____(Y) Has the patient recovered from the effects of surgery?
_____(Y/NA) Has a minimum of 7 days elapsed for core or needle biopsy?
_____(Y) Was a postoperative scan performed within 30 days prior to registration and within 96-hours post surgery?

_____(Y) 8. Was a history and physical examination completed within 14 days prior to registration?

_____(Y) 9. Is the Karnofsky performance status greater than or equal to 70 within 14 days prior to registration?

_____(Y) 10. Is the patient's age ≥18?

_____(Y) 11. Was a CBC with differential obtained within 14 days prior to registration with adequate bone marrow function as defined in section 3.1.8?

_____(Y) 12. Is there adequate liver and renal function within 14 days prior to registration as defined in section 3.1.8?

_____(N) 13. Does the patient have proteinuria within 14 days of registration as defined in section 3.1.9?

_____(N/NA) 14. Is the patient pregnant or nursing?

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_____(Y/NA) 15. Was a pregnancy test done within 7 days before registration?

_____(Y/NA) 16. Is the patient willing to practice effective contraception while on study treatment and 6 months after? (women of childbearing potential and men)

_____(Y/N) 17. Is the patient on full dose anticoagulants?
If Y:
_____ (N) Does the patient have active bleeding or a pathological condition that carries a high risk of bleeding?
_____ (Y) Is there an in-range INR (usually between 2 and 3) on a stable dose of oral anticoagulant or on a stable dose of low molecular weight heparin?

_____(Y) 18. Did the patient provide study-specific informed consent prior to study entry?

_____(N) 19. Has the patient had more than 2 relapses?

_____(N) 20. Is there multifocal, infratentorial or leptomeningeal evidence of recurrent disease?

_____(N) 21. Does the patient have a recurrent or persistent tumor greater than 5 cm in maximum diameter??

_____(N) 22. Has the patient had prior therapy with an inhibitor of VEGF or VEGFR (including bevacizumab)?

_____(Y/N) 23. Has the patient had prior invasive malignancy (except non- melanomatous skin cancer)?
If Y:
_____ (Y) Has the patient been disease free for a minimum of 1 year

_____(N) 24. Does the patient have severe active co-morbidity as in defined in 3.2.6.?

_____(N) 25. Does the patient have prior allergic reaction to the study drug (Bevacizumab)?

_____(N) 26. Does the patient have prior history of hypertensive crisis or hypertensive encephalopathy?

_____(N) 27. Does the patient have a history of a non-healing wound, ulcer or bone fracture within 90 days (3 months) prior to registration?

_____(N) 28. Has the patient had gastrointestinal bleeding or any other hemorrhage/bleeding event CTCAE, v.4 grade 3 or greater within 30 days prior to registration?

_____(N) 29. Has the patient had major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to registration (with the exception of craniotomy)?

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<u>The following questions will be asked at Study Registration</u>:
IMRT CREDENTIALING AND IGRT CREDENTIALING (for reduced margins only) IS REQUIRED BEFORE REGISTRATION. PROTON CREDENTIALING IS REQUIRED IF USING PROTONS.

_____ 1. Institutional person randomizing case.

_____(Y) 2. Has the Eligibility Checklist been completed?

_____(Y) 3. In the opinion of the investigator, is the patient eligible?

_____ 4. Date informed consent signed

_____ 5. Patient Initials (First Middle Last)

_____ 6. Verifying Physician

_____ 7. Patient ID

_____ 8. Date of Birth

_____ 9. Race

_____ 10. Ethnicity

_____ 11. Gender

_____ 12. Country of Residence

_____ 13. Zip Code (U.S. Residents)

_____ 14. Method of Payment

_____ 15. Any care at VA or Military Hospital?

_____ 16. Calendar Base Date

_____ 17. Randomization date

_____ 18. Medical oncologist's name

_____(Y/N) 19. Have you obtained the patient's consent for his or her tissue to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 20. Have you obtained the patient's consent for his or her blood to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 21. Have you obtained the patient's consent for his or her urine to be kept for use in research to learn about, prevent, treat, or cure cancer?

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_____(Y/N) 22. Have you obtained the patient's consent for his or her tissue to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?

_____(Y/N) 23. Have you obtained the patient's consent for his or her blood to be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

_____(Y/N) 24. Have you obtained the patient's consent for his or her urine to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?

_____(Y/N) 25. Have you obtained the patient's consent to allow someone from this institution to contact him or her in the future to take part in more research?

_____ 26. Patient's age (<50/≥50):
(1) <50
(2) ≥50

_____ 27. Karnofsky performance status:
(1) 70-80
(2) 90-100

_____ 28. (Y/N-biopsy only): Recent resection

_____ (Y/N) 29. Did the patient participate in a previous RTOG GBM trial that collected MGMT methylation status?
If yes, what was the RTOG study number?
If yes, what was the patient ID number on the RTOG trial mentioned above?

_____(Y/N) 30. Did the patient have MGMT analysis performed as routine care by a treating physician outside of an RTOG GBM trial (or that was collected during an RTOG trial but **not required** per protocol)?
If yes, what was the result of MGMT analysis?
(1) Methylated
(2) Unmethylated
(3) Invalid

_____(Y/N) 31. Will IGRT be used for patient positioning?

_____(Y/N) 32. Will IGRT be used for patient positioning and margin reduction?

33. Specify treatment techniques/machine:
(1) 3D-CRT
(2) IMRT
(3) Cyberknife
(4) Protons

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The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by _____ Date _____

1.0 INTRODUCTION

1.1 Overview

Glioblastoma is the most common lethal primary brain tumor in adults (Brandes 2003). Despite optimal treatment including surgery, chemotherapy, and radiation, median survival of patients with glioblastoma is 14 months. The majority of patients will develop recurrence at a median of 8 months post treatment (Stupp 2005).

Patients with recurrent glioblastoma have poor prognoses and have been treated with various modalities including resection, chemotherapy, or re-irradiation. Prior phase II chemotherapy trials were associated with a 6-month progression-free survival of 15% and a median survival of 25 weeks (Wong 1999, Carson 2007). In 2009, bevacizumab, a humanized monoclonal antibody which targets VEGF, was approved by the FDA as a single agent for recurrent glioblastoma.

Vascular proliferation is a notable feature in glioblastoma; therefore, targeting the vascular endothelial growth factor (VEGF) is a logical treatment approach (Jain 2007). Anti-VEGF therapy can inhibit new vessel growth, lead to vascular regression and vascular normalization, as well as directly affect tumor cell function (Ellis 2008). Antiangiogenic therapies rapidly normalize leaky abnormal tumor vessels and therefore decrease vasogenic edema as well as the patient's dependence on corticosteroids. This effect may lead to significant improvement in the patient's quality of life (Vredenburgh 2010).

Several clinical trials have evaluated the safety and efficacy of bevacizumab alone or in combination with chemotherapy in recurrent gliomas. A single-institution phase II trial demonstrated increased response rates and prolonged 6-month progression-free survival (Vredenburgh 2007a; Vredenburgh 2007b). Thirty-two patients with recurrent grade III-IV glioma (Vredenburgh 2007a) received bevacizumab and irinotecan, showing promising activity with a 6-month progression-free survival of 38%. The median overall survival limited to grade IV patients was 9.2 months.

In a phase II trial, 48 heavily pretreated recurrent glioblastoma patients received single-agent bevacizumab, with a median progression-free survival of 16 weeks, 6-month progression-free survival of 29%, and a response rate of 35% based on Macdonald criteria (Kreisl 2009). A subsequent randomized, non-comparative phase II trial (BRAIN study) was performed and led to the FDA approval of single-agent bevacizumab. Patients with recurrent glioblastoma in first or second relapse were randomized to either bevacizumab 10 mg/kg every 2 weeks alone (85 patients) or in combination with irinotecan (82 patients). The estimated 6-month progression-free survival rate was 42.6% and 50.3%, respectively. Median overall survival was 9.2 and 8.7 months, respectively. The majority of patients in this trial had partial or complete resection (91.8% and 91.5%, respectively). A minority of patients (8% and 13%, respectively) were enrolled ≤3 months following radiotherapy, while 20% and 10%, respectively, were enrolled ≤3 months following surgery. Overall, treatment was well tolerated; adverse events related to bevacizumab included hypertension, fatigue, and deep vein thrombosis. There was no clear increase in efficacy with the addition of irinotecan; however, there was increased toxicity (Friedman 2009). Despite the significant increase in response rates and 6-month progression-free survival with single-agent bevacizumab, the median overall survival remains 8 to 9 months.

Several phase II trials have attempted to combine bevacizumab with other chemotherapy agents, with no significant improvement in outcome. These agents include daily low-dose temozolomide, etoposide, erlotinib, and nitrosourea. In fact, these trials identified increased toxicity with no improvement in efficacy (Verhoeff 2010; Gilbert 2009; Hasselbach 2010; Reardon 2009; Sathornsumetee 2010). Response rates to chemotherapy following bevacizumab failure are exceptionally poor. Salvage chemotherapy provided only transient tumor control with an estimated 6-month progression-free survival of 2% (Quant 2009). Enrollment in a clinical trial for patients with recurrent glioblastoma should be the standard clinical practice and highlights the pressing need to identify novel strategies.

Salvage re-irradiation has long been offered as a treatment modality (Hudes 1999, Kim 1997, Laing 1993, Grosu 2005, Lederman 2000). Prior results obtained from over 300 glioblastoma patients confirmed a 6-month progression-free survival ranging from 28% to 39% and a median 1-year overall survival of 26% ranging from 18% to 46% (Combs 2005, Nieder 2008, Fogh 2010). However, recent advances in RT techniques including fractionated stereotactic radiotherapy (FSRT), protons, and IMRT, now allow for highly conformal treatment, which has the potential to significantly reduce the toxicity associated with re-irradiation (Fogh 2010).

Several studies report an improvement in 6-month functional status as well as a reduction and discontinuation of corticosteroid usage (Laing 1993; Kim 1997; Nieder 2008; VanderSpek 2008). Late CNS toxicity was uncommon especially following FSRT. Combs et al reported on 172 recurrent gliomas with a median time from RT to re-radiation of 10 months. Median tumor size for glioblastoma tumors was 47.7 cc. RT dose was 36 Gy in 2 Gy fractions given 5 fractions per week. Progression-free survival for 59 glioblastoma patients following re-irradiation was 5 months, with a median overall survival of 8 months. Factors associated with improved outcome included histology, extent of initial resection, and age at primary diagnosis. Treatment was well tolerated, with 1 incidence of radiation necrosis (Combs 2005).

Fogh et al reported on 147 high-grade glioma patients treated with FSRT delivering 35 Gy in 10 fractions. Median time to re-irradiation was 8 months. Somewhat surprisingly, and in contrast with other reports, patients who received irradiation within 6 months of initial diagnosis did not demonstrate an inferior survival. Median tumor volume was 22 cc. Eighty-four patients underwent salvage surgery prior to re-irradiation. Forty-eight patients received concurrent chemotherapy such as temozolomide. Median survival was 11 months. Treatment was well tolerated. Multivariate analysis suggested younger age and smaller tumor volumes were associated with improved outcome (Fogh 2010).

There is a clear rationale for combining bevacizumab with re-irradiation to increase the therapeutic ratio through increased antitumor and antivascular effects (Provencio 2010; Lee 2000). Preclinical data suggest that VEGF is up-regulated in response to radiation; therefore, the use of antiangiogenic agents combined with radiation may sensitize both tumors and associated vasculature to RT (Gorski 1999). Preclinical studies have demonstrated that antiangiogenic agents may uniquely target the radio-resistant and highly tumorigenic cancer stem cells by disrupting vascular niches harboring cancer stem cells (Hovinga 2010). Due to its potential radioprotective effects, especially the phenomenon of vascular stabilization, the addition of bevacizumab may also reduce the toxicity associated with re-irradiation by reducing risk of radiation necrosis (Levin 2011). Several phase II and phase III trials have reported on the initial safety and tolerability of combining bevacizumab and temozolomide with radiotherapy in primary glioblastoma patients (Lai 2010; Vredenburgh 2011).

Preliminary evidence suggests improved outcome with the addition of concurrent and adjuvant bevacizumab to re-irradiation. Gutin et al published results regarding 25 patients with recurrent grade III-IV gliomas using FSRT and concurrent bevacizumab; with a reported 6-month progression-free survival of 65% and median overall survival of 12.5 months. Median time to radiation was 15 months. Enhancing tumor volume was ≤ 3.5 cm in maximum diameter. Treatment was well tolerated. There was no incidence of radiation necrosis and no additional need for corticosteroids following radiation (Gutin 2009).

The Duke group recently reported its single-institution retrospective data on 63 patients with recurrent high-grade gliomas, including 49 glioblastoma patients treated with re-irradiation using SRS techniques combined with bevacizumab therapy. The treatment regimen was noted to be well tolerated. Median time to re-irradiation was 19.6 months. Mean number of systemic therapies prior to SRS was 3.6 and mean number of therapies following SRS was 2.9. Median target volume was 4.8 cc. The 1-year overall survival in glioblastoma patients who received adjuvant (concurrent with or after SRS) bevacizumab was 50% vs. 22% for patients not receiving adjuvant

bevacizumab (p= 0.005). Both age < 50 years and performance status > 70 were associated with improved overall survival (Cuneo 2011).

Retrospective single-institutional experience in high-grade glioma patients treated with FSRT using 36 Gy in 18 fractions, with concurrent bevacizumab, followed by maintenance bevacizumab was recently reported. Overall survival appeared better in patients receiving bevacizumab (12.1 months) than those who had received either re-irradiation alone or concurrent with temozolomide (8.0 months). Treatment was well tolerated, with no incidence of radiation necrosis and one incidence of wound dehiscence (Niyazi 2010).

Based on the long history and clinical experience of re-irradiation of recurrent glioblastoma, we wish to obtain prospective multi-institutional safety and efficacy data regarding the combination of bevacizumab and re-irradiation in improving overall survival in bevacizumab-naïve recurrent glioblastoma patients.

Therefore, the primary aim of this study is to provide preliminary evidence of an overall survival benefit with the addition of re-irradiation in combination with bevacizumab for patients with recurrent glioblastoma in a multi-institutional setting, in the context of a phase II randomized trial that will require further confirmation in a phase III trial.

1.1.1 Significance of the Current Study

RTOG 1205 is important in potentially changing the paradigm of treatment in recurrent glioblastoma. Despite numerous randomized chemotherapy studies as well as novel targeted agents studied to date, no regimens have shown significant improvement in overall survival compared to bevacizumab alone. Single-agent bevacizumab is currently the mainstay of treatment in recurrent glioblastoma, but the overall survival remains limited at approximately 8 to 9 months. Responses to therapy following bevacizumab failures are extremely poor. Preclinical data suggest that a resistant and invasive phenotype develops following bevacizumab failure, and salvage therapy remains ineffective in this context; therefore, this latter patient group will NOT be included in our trial.

The goal of this study is to test the hypothesis that re-irradiation combined with an effective targeted agent, bevacizumab, will improve the overall survival of bevacizumab-naïve recurrent glioblastoma patients. This trial will also be the first prospective multi-institutional study to evaluate survival, response, and patterns of failure following re-irradiation. Further, if this trial is positive, the implication is that higher radiotherapy doses are potentially feasible and safe, and therefore, the addition of bevacizumab and re-irradiation in recurrent gliomas may provide the preliminary proof of principle to further study dose-escalated radiation in combination with bevacizumab in the upfront treatment of glioblastoma. Additionally, this trial could also potentially set the stage for testing additional chemotherapeutic and/or targeted agents with radiation in the recurrent glioblastoma setting. This could provide preliminary clinical data to move promising agents in the upfront setting in a more efficient manner.

1.2 Safety, Efficacy, and Rationale for Combination of Bevacizumab and Re-Irradiation

The safety and efficacy of hypofractionated stereotactic irradiation in combination with bevacizumab for recurrent glioblastoma was reported by Gutin et al (2009). The results were promising, with a 6-month progression-free survival of 65% and a median overall survival of 12.5 months. There were no incidences of radiation necrosis noted and there was no need for additional corticosteroids following treatment. The treatment was also safe and well tolerated. Grade 3 toxicity, including intratumor hemorrhage, wound dehiscence, and bowel perforation, was noted in 12% of patients. Retrospective results of hypofractionated stereotactic radiation alone using 35 Gy in 10 fractions in 147 high-grade glioma patients were reported by Fogh et al (2010). Median survival was 11 months. This underscores the safety and tolerability of this approach.

RTOG 0625, a phase II randomized study of bevacizumab and irinotecan or temozolomide, enrolled 123 patients and was recently published in abstract form (Gilbert 2009). ACRIN 6637

provided central review of all pre-treatment MRIs. Analysis of the pre-treatment MRI confirmed that over 90% of cases had an initial post-contrast T1 MRI tumor diameter of 5 cm or less. A statistical analysis was performed using this inclusion criteria (limiting to 5 cm or less), and demonstrated a median overall survival of 9.4 months for patients receiving bevacizumab and temozolomide and 7.6 months for patients receiving bevacizumab and irinotecan (Wang, RTOG 0625 summary analysis unpublished data). This preliminary analysis confirms the median survival of recurrent glioblastoma treated with bevacizumab at approximately 9 months and a basis for the inclusion of tumors limited in size to 5 cm diameter.

Re-irradiation using the newer SRS techniques delivers higher doses of irradiation to a considerably more precise target volume, in a single fraction, and with a steep dose gradient beyond the tumor. In several series reporting on these novel SRS techniques, overall survival was 9 to 11 months. Because of the potential CNS toxicity associated with a single-fraction treatment or treatment with very few fractions of large dose per fraction, patients selected for this therapy must have small, limited volume recurrences. Fractionation leads to improvement of the therapeutic ratio by reducing the risk to normal tissues compared with single-fraction treatments, especially for larger tumors (3 to 5 cm) (Brenner 1997, Cho 1999). The linear quadratic (LQ) model has been used to calculate the biological equivalent dose using a tumor alpha/beta ratio of 10 Gy (Mayer 2008). The effect on late normal tissue was calculated using an alpha/beta ratio of 3 Gy. The proposed schema in this study of 35 Gy in 10 fractions was directly compared to the 30 Gy in 5 fractions used by Gutin et al and was predicted using biologic modeling to have similar antitumor efficacy (47.2 versus 48 Gy with alpha-beta of 10 Gy). However, the 35 Gy in 10 fractionation scheme is much more favorable in regards to risk of late normal tissue toxicity and is likely better tolerated for larger tumors.

2.0 OBJECTIVES

2.1 Primary Objective

To establish an improvement in overall survival in recurrent GBM patients receiving bevacizumab and re-irradiation compared with patients receiving bevacizumab alone.

2.2 Secondary Objectives

2.2.1 To estimate and compare the rate of objective response in patients with measurable disease.
2.2.2 To estimate and compare the 6-month progression-free survival rate.
2.2.3 To estimate and compare progression-free survival.
2.2.4 To estimate and compare the rate of treatment adverse events.
2.2.5 To estimate and compare the rate of ≥grade 3 acute or delayed CNS toxicity.

3.0 PATIENT SELECTION

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED

3.1 Conditions for Patient Eligibility

3.1.1 Histopathologically proven diagnosis of glioblastoma or variants (gliosarcoma, giant cell glioblastoma etc). Patients will be eligible if the original histology was lower-grade glioma and a subsequent diagnosis of glioblastoma or gliosarcoma is made.

- Patients who did not have recent surgery for their glioblastoma must have shown unequivocal radiographic evidence for tumor progression by contrast-enhanced MRI scan (or CT scan for patients with non-compatible devices) within 14 days prior to registration as defined in Section 11.4.1.

- Patients must have passed an interval of 6 months or greater between completion of prior radiotherapy and registration. If patients have not passed an interval of at least 6 months, they may still be eligible if they meet one or more of the following criteria:
  a) New areas of tumor outside the original radiotherapy fields as determined by the investigator, or
  b) Histologic confirmation of tumor through biopsy or resection, or
  c) Nuclear medicine imaging, MR spectroscopy, or MR perfusion imaging consistent with true progressive disease, rather than radiation necrosis obtained within 28 days of

registration AND an interval of at least 90 days between completion of radiotherapy and registration.

- Patients unable to undergo MR imaging because of non-compatible devices can be enrolled provided CT scans are obtained and are of sufficient quality. Patients without non-compatible devices may not use CT scans performed to meet this requirement.

3.1.2 Prior history of standard dose CNS radiation of 60 Gy in 30 fractions or 59.4 Gy in 1.8 Gy fractions, or equivalent or lower doses.

- Patients who have received prior treatment with non-standard RT dose and fractionation, interstitial brachytherapy, stereotactic radiosurgery, etc. are eligible as long as the criterion in 3.1.1 a, b, or c is met.

3.1.3 Patients must have recovered from the toxic effects of prior therapy, and there must be a minimum time of 28 days prior to registration from the administration of any investigational agent or prior cytotoxic therapy with the following exceptions:

- 14 days from administration of vincristine
- 42 days from administration of nitrosoureas
- 21 days from administration of procarbazine

3.1.4 Patients having undergone recent resection of their glioblastoma (within 30 days prior to registration) must have recovered from the effects of surgery. For CNS related core or needle biopsies, a minimum of 7 days must have elapsed prior to registration.

- Residual disease following resection of recurrent glioblastoma is not mandated for eligibility into the study. To best assess the extent of residual disease post-operatively, a post-operative MRI scan (or CT scan for patients with non-compatible devices) must be performed within 30 days prior to registration and should be within 96 hours post surgery (although 24 hours would be optimum).

3.1.5 History/physical examination, including neurologic examination, within 14 days prior to registration

3.1.6 Karnofsky performance status ≥ 70 within 14 days prior to registration

3.1.7 Age ≥ 18

3.1.8 CBC/differential obtained within 14 days prior to registration, with adequate bone marrow function. Adequate bone marrow reserve as follows:

- Absolute neutrophil count (ANC) ≥ 1,500 cells/mm^3
- Platelets ≥ 100,000 cells/mm^3
- Hemoglobin ≥ 9.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 9.0 g/dl is acceptable.)

3.1.9 Acceptable liver (total bilirubin ≤ 2.0 mg/dL, and SGOT or AST ≤ 2.5 times the upper limit of normal) and renal function (serum creatinine ≤ 1.8 mg/dL) within 14 days prior to registration.

- Urine protein: creatinine (UPC) ratio < 1.0 within 14 days prior to registration **OR** urine dipstick for proteinuria ≤ 2+ (patients discovered to have > 2+ proteinuria on dipstick urinalysis at baseline must have a UPC ratio done that is <1.0 to be eligible. If the UPC ratio is ≥ 1.0 then the patients should undergo a 24-hour urine collection and must demonstrate ≤ 1g of protein in 24 hours to be eligible).

  Note: UPC ratio of spot urine is an estimation of the 24-hour 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 one of the following formulas:
  - ☐ [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

3.1.10 Patients must not be pregnant (positive pregnancy test) or breast feeding; pregnancy test must be done within 7 days prior to registration. Effective contraception (men and women) must be used in patients of child-bearing potential while on study treatment and for 6 months after.

3.1.11 Patients on full-dose anticoagulants (e.g., warfarin or LMW heparin) must meet both of the following criteria:

- No active bleeding or pathological condition that carries a high risk of bleeding (e.g., tumor involving major vessels or known varices)
- In-range INR (usually between 2 and 3) on a stable dose of oral anticoagulant or on a stable dose of low molecular weight heparin

3.1.12 Patient must be able to provide study-specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility

3.2.1 More than two relapses

3.2.2 Multifocal, infratentorial, or leptomeningeal evidence of recurrent disease

3.2.3 Recurrent or persistent tumor greater than 5 cm in maximum diameter

3.2.4 Prior therapy with an inhibitor of VEGF or VEGFR (including bevacizumab)

3.2.5 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 1 year (for example, carcinoma *in situ* of the breast, oral cavity, or cervix are all permissible).

3.2.6 Severe, active co-morbidity, defined as follows:

- Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months prior to registration
- Transmural myocardial infarction within the last 6 months prior to registration
- History of stroke or transient ischemic attack within 6 months prior to registration.
- Significant vascular disease (e.g., aortic aneurysm, history of aortic dissection) or clinically significant peripheral vascular disease.
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration
- Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration
- Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for liver function other than screening panel (Section 3.1) and coagulation parameters are not required for entry into this protocol.
- Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients.

3.2.7 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

3.2.8 Prior allergic reaction to the study drug (Bevacizumab)

3.2.9 Prior history of hypertensive crisis or hypertensive encephalopathy.

3.2.10 History of a non-healing wound, ulcer, or bone fracture within 90 days (3 months) prior to registration

3.2.11 Gastrointestinal bleeding or any other hemorrhage/bleeding event CTCAE, v. 4 grade 3 or greater within 30 days prior to registration

3.2.12 Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to registration (with the exception of craniotomy)

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

NOTE: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Highly Recommended Evaluations

4.1.1 Baseline MR diffusion and perfusion imaging is optional but strongly recommended as further confirmation that the GTV is related to tumor and not radiation effect. The same type of enhanced scan, i.e., MRI or CT, should be used throughout the period of protocol treatment for tumor measurement. See also Section 11.1.3.

4.1.2 The MGMT methylation status as a predictor of outcome will be obtained for the following patient groups:

- Patients who have already had MGMT performed prior to registration into an RTOG GBM trial collecting MGMT methylation status.
- Patients who have had MGMT analysis performed as routine care by a treating physician outside of an RTOG GBM trial.

5.0 REGISTRATION PROCEDURES

5.1 Pre-Registration Requirements for Image-Guided Radiotherapy (IGRT) Treatment Approach

5.1.1 Institutions that plan to utilize PTV margins of less than 5 mm will also be required to complete image-guided radiotherapy (IGRT) credentialing for brain.

In order to utilize IGRT for margin reduction (see Section 6.3), the center must be credentialed for its use. This means the institution must have met technology requirements and have provided the baseline physics information. This information is available on the Advanced Technology Consortium (ATC) web site, http://atc.wustl.edu. The ATC is in part comprised of RTOG RT Quality Assurance, the Image-Guided Therapy Center (ITC) at Washington University, and the Radiological Physics Center (RPC) at MD Anderson Cancer Center.

In order to become credentialed for brain IGRT, the institution must have already become credentialed for either 3DCRT and/or IMRT. Institutions that have not been credentialed by the RTOG to perform 3DCRT and/or IMRT MUST apply for 3DCRT and/or IMRT credentialing as described below in Sections 5.2 and 5.3.

5.1.2 *IGRT Credentialing Process*

- IGRT credentialing for brain (review of at least one case) will be required for institutions utilizing PTV margins of less than 5 mm (See Section 6.3). The first step is for the institution or investigator to complete a new Facility Questionnaire and/or set up an SFTP account for digital data submission, both of which are available on the ATC web site at http://atc.wustl.edu.
- Next, the institution must submit a series of daily treatment images along with a spreadsheet of IGRT data from an anonymized brain cancer patient. See the ATC web site, http://atc.wustl.edu, for the spreadsheet. This series must include a minimum of 5 daily pre-treatment images obtained on sequential treatment days. Pre-treatment images may include three-dimensional (3D) volumetric images (either fan- or cone-beam CT with Megavoltage (MV) or kilovoltage (kV) x-ray or Orthogonal (MV or kV) 2D images. These images and the spreadsheet will be reviewed by the Study Chair, Christina Tsien, MD, and the Medical Physics Co-chair, Martha Matuszak, PhD, prior to certification.

5.2 Pre-Registration Requirements for IMRT Treatment Approach

5.2.1 In order to utilize IMRT on this study (this includes all CyberKnife treatments), the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements or determining if they already have been met are available on the Radiological Physics Center (RPC) web site. Visit http://rpc.mdanderson.org/rpc and select “Credentialing” and “Credentialing Status Inquiry”.

An IMRT phantom study with the RPC must be successfully completed (if the institution has not previously met this IMRT credentialing requirement). Instructions for requesting and irradiating the phantom are available on the RPC web site at http://rpc.mdanderson.org/rpc/; select “Credentialing” and “RTOG”. Upon review and successful completion of the phantom irradiation, the RPC will notify both the registering institution and RTOG Headquarters that the institution has completed this requirement. Subsequently, RTOG Headquarters will notify the institution that the site can enroll patients on the study.

5.2.2 The institution or investigator must complete a new Facility Questionnaire including the IMRT section and send it to RTOG for review prior to entering any cases, and/or set up an SFTP account for digital data submission, both of which are available on the Image-Guided Center (ITC) web site at http://atc.wustl.edu. Upon review and successful completion of the “Dry-Run” QA test, the ITC will notify both the registering institution and RTOG Headquarters that the

institution has successfully completed this requirement. RTOG Headquarters will notify the institution when all requirements have been met and the institution is eligible to enter patients onto this study.

5.3 Pre-Registration Requirements for 3D-CRT Treatment Approach

5.3.1 Only institutions that have met the technology requirements and that have provided the baseline physics information that are described in 3D-CRT Quality Assurance Guidelines may enter patients onto this study.

5.3.2 The new Facility Questionnaire (one per institution, available on the ATC website at http://atc.wustl.edu) is to be sent to RTOG for review prior to entering any cases. Upon review and successful completion of a "Dry-Run" QA test, the ITC will notify both the registering institution and RTOG Headquarters that the institution has successfully completed this requirement. RTOG Headquarters will notify the institution when all requirements have been met and the institution is eligible to enter patients onto this study. Institutions that have previously enrolled patients on 3D-CRT trials of this same disease site may enroll patients on this study without further credentialing.

5.4 Pre-Registration Requirements for Proton Treatment Approach

5.4.1 *Proton Credentialing Process*

Proton therapy may be used on this protocol. Investigators using proton therapy must comply with the NCI proton guidelines for the Use of Proton Radiation Therapy in NCI Sponsored Cooperative Group Clinical Trials, which are available on the websites of the RPC (http://rpc.mdanderson.org), ATC (http://atc.wustl.edu), and QARC (http://www.qarc.org). These requirements include, but are not limited to, completion of a proton facility questionnaire, a successful RPC site visit, which identifies the proton technique(s) which can be used, annual monitoring of the proton beam calibration, e.g. RPC's monitoring program, and successful digital data submission to the ITC.

5.4.2 Dose will be reported in Gy (RBE), where 1 Gy(RBE) = proton dose Gy x RBE (radiobiological effective dose), RBE = 1.1.

5.4.3 Radiation doses shall be prescribed using the protocol specified definitions for GTV and CTV. For set-up uncertainties and target motion, additional margin (including proximal and distal), smearing, and range of modulation will be added on a per beam basis. Proton treatment plans will be based upon a CT scanner for which the institution has defined an imaging protocol for protons which establishes the relationship between the CT number and the stopping power ratios.

5.4.4 The RPC will coordinate the completion of the proton therapy use approval process in conjunction with the appropriate other Quality Assurance Offices for any additional protocol specific credentialing requirements. The RTOG will review the documentation provided by the RPC and credential institutions to participate in this protocol.

5.4.5 Additional credentialing requirements for this protocol may be found on the RPC web site (http://rpc.mdanderson.org/rpc/) by selecting "Credentialing" and "RTOG".

5.4.6 Proton resources for this protocol include:

Michael T. Gillin, PhD
Professor
The University of Texas
MD Anderson Cancer Center
Department of Radiation Physics
713-563-2507/Fax: 713-563-2545
mgillin@mdanderson.org

Anita Mahajan, MD
University of Texas MD Anderson Cancer Center
1515 Holcombe Boulevard
Houston, TX 77030
713-563-2350
amahajan@mdanderson.org

5.4.7 If protons are to be used, review and successful completion of the **"Dry-Run" QA** test using protons is required, the RPC will notify both the registering institution and RTOG Headquarters that the institution has successfully completed this requirement for protons

There are no proton protocol specific credentialing requirements for this protocol.

5.5 Regulatory Pre-Registration Requirements

5.5.1 This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch (PMB), CTEP, DCTD, NCI. These forms are available on the CTSU registered member web site or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org.

Requirements for RTOG 1205 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet
- CTSU RT Facilities Inventory Form

NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the Radiological Physics Center (RPC) monitoring program. For non-lead group institutions an RT Facilities Inventory Form must be on file with CTSU. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility.

5.5.2 **In addition to the requirements noted above, all institutions** must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206); study- related regulatory documentation also may be e-mailed to the CTSU at CTSURegulatory@ctsu.coccg.org. This must be done prior to registration of the institution's first case:

- IRB/REB approved consent (English and native language versions*****)
  ***Note**: Institutions must provide certification/verification of IRB/REB consent translation to RTOG Headquarters (described below).
- IRB/REB assurance number renewal information as appropriate.

Non-English Speaking Canadian and Non-North American Participating Sites Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved RTOG will accept, at a minimum, a verified translation. A verified translation consists of the actual REB approved consent document in English and in the native language, along with a cover letter on organizational/letterhead stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

5.5.3 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS

Prior to clinical trial commencement, Canadian institutions must complete and fax (215-569-0206) or e-mail (CTSURegulatory@ctsu.coccg.org) the following Health Canada forms to the CTSU Regulatory Office:

- Clinical Trial Site Information Form,
- Qualified Investigator Undertaking Form, and
- Research Ethics Board Attestation Form.

5.5.4 Pre-Registration Requirements FOR NON-CANADIAN INTERNATIONAL INSTITUTIONS

- ***For institutions that do not have an approved LOI for this protocol*:**
  International sites must receive written approval of submitted LOI forms from RTOG Headquarters prior to submitting documents to their local ethics committee for approval. See http://www.rtog.org/Researchers/InternationalMembers.aspx .
- ***For institutions that have an approved LOI for this protocol*:**
  All requirements indicated in your LOI Approval Notification must be fulfilled prior to enrolling patients to this study.

5.6 Registration

5.6.1 Online Registration

Patient registration can occur only after pre-treatment evaluation is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

All site staff (RTOG and CTSU Sites) will use OPEN to enroll patients to this study. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' web site https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPPA authorization form (if applicable).

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.
- To perform registrations on protocols for which you are a member of the RTOG, you must have an equivalent 'Registrar' role on the RTOG roster. Role assignments are handled through the Groups in which you are a member.
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.
- **NOTE**: **If you are enrolling as a non-RTOG site**: Prior to beginning the enrollment, call the RTOG Randomization desk at 215-574-3191 or 215-574-3192 to obtain an RTOG, non-Lead Group, site-specific institution number.

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

5.6.2 In the event that the OPEN system is not accessible, participating sites can register a patient by calling RTOG Headquarters, at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask the site to fax in the eligibility checklist and will need the registering individual's e-mail address and/or return fax number. This information is required to assure that mechanisms usually triggered by the OPEN web registration system (e.g. drug shipment, confirmation of registration, and patient-specific calendar) will occur.

6.0 RADIATION THERAPY

Note: Intensity Modulated RT (IMRT) Is Allowed.

Protons are permitted for institutions which have been approved and credentialed for protons, as protons may reduce the volume of normal tissue which will be re-irradiated. (If protons are used, to avoid delays resulting from unplanned equipment availability, photon therapy may be administered instead of proton therapy.)

6.1 Dose Specifications

6.1.1 Photons: Treatment shall consist of 35 Gy delivered in 10 fractions. Target coverage and homogeneity limits and deviations are listed in Table 1.

6.1.2 Protons - Absorbed dose: Doses are expressed in units of RBE-weighted absorbed dose, D_{RBE}. For protons the RBE is taken to be 1.1. D_{RBE} = 1.1 x D, where D represents the absorbed dose in Gy. Treatment shall consist of 35 Gy(RBE) delivered in 10 fractions. Target coverage and homogeneity limits and deviations are listed in Table 1.

Table 1. Target Coverage and Dose Limits

Dose Metric	Per Protocol	Variation Acceptable	Deviation Unacceptable
Volume of PTV covered by the prescription dose photons 35 Gy – protons 35 Gy(RBE)	Greater than or equal to 95% of the PTV should receive greater than or equal to photons 35 Gy – protons 35 Gy(RBE)	Greater than or equal to 90% of the PTV receiving greater than or equal to photons 35 Gy – protons 35 Gy(RBE)	Less than 90% of the PTV receiving greater than or equal to photons 35 Gy – protons 35 Gy(RBE)
Minimum dose to the PTV (0.03 cc)	Greater than or equal to 29.75 Gy (85% of the prescription dose) – protons 29.75 Gy(RBE)	Greater than or equal to 28 Gy (80% of the prescription dose) – protons 28 Gy(RBE); Minimum doses of less than 28 Gy are acceptable if they occur due to OAR/PTV overlap	Less than 28 Gy (80% of the prescription dose) – protons 28 Gy(RBE); Minimum doses of less than 28 Gy are unacceptable unless they occur in regions of OAR/PTV overlap
Maximum dose to the PTV (0.03 cc)	Less than or equal to 42 Gy (120% Rx Dose) – protons 42 Gy(RBE)	Less than or equal to 45.50 Gy (130% Rx Dose) – protons 45.50 Gy(RBE)	Greater than 45.50 Gy (130% Rx Dose) – protons 45.50 Gy(RBE)

6.2 Technical Factors [Equipment, energies]

The 10 treatment fractions of 3.5 Gy each will be delivered on consecutive treatment days (typically 5 fractions per week). Any FDA cleared external beam radiation delivery system may be used (including conventional linear accelerators, cyberknife systems, tomotherapy, proton therapy, etc.). Imaging for treatment planning will be obtained with the patient in the same position and immobilization device as for treatment. All patients will be positioned via a combination of rigid immobilization and daily image guidance to ensure positioning accuracy of 3 mm or better, and of a magnitude that justifies the PTV margin applied (the participating institutions must document the immobilization and localization methods applied).

6.3 Localization, Simulation, and Immobilization

MRI and/or CT scanning, with injected contrast, are required for treatment planning. At least one of these scans must be of the patient immobilized in treatment position, and with image resolution of no worse than 1.5 mm x1.5 mm x 3 mm. Immobilization must be rigid (e.g. thermoplastic masks). For daily treatment, localization will include the steps of a) immobilization with the same device used for simulation, and b) daily image guidance using at a minimum orthogonal pairs of radiographs aligned to DRRs as a computer-assisted process (CT-CBCT alignment is permitted as well). Institutions utilizing PTV margins of less than 5 mm are required to undergo IGRT credentialing for brain (see Section 5.1).

6.4 Treatment Planning/Target Volumes

A GTV will be defined using the CT and/or MRI images. The post-operative resection cavity will be outlined if no residual enhancing tumor is noted. A CTV expansion of no more than 5 mm is optional for lesions measuring less than 3.5 cm in maximum diameter or if this is a new lesion, but must be reported when used. Otherwise, no additional CTV expansion will be added. A PTV expansion that is justified based on image guidance and immobilization will be applied. Regardless of immobilization and localization methods, the PTV expansion should be no smaller than 3 mm. As noted in Section 6.3, institutions utilizing PTV margins of less than 5 mm are required to undergo IGRT credentialing for brain (see Section 5.1) and utilize computer-assisted daily IGRT for all treatment fractions.

If protons are used, an adjustment must be made within the treatment planning process to take into account of range uncertainties along the beam direction, following the established practice at the specific proton facility, which should be based on the recommendations contained in ICRU 78, paragraph 5.1.4.4.

Treatment planning using multiple, non-coplanar beams or arc-based therapy is advised. IMRT based planning is allowed. To ensure dose calculation accuracy, the minimum field size used should be consistent with the minimum field size commissioned for use at the institution and should not be smaller than 2 cm x 2 cm. In any case, the objective of treatment planning is to ensure sufficient dose conformity that the normal tissue constraints are met.

6.5 Critical Structures

Normal tissues to be contoured will include the brain, brainstem, optic nerves and chiasm. Planning risk volume (PRV) expansions (minimum of 3 mm) should be utilized for optic nerves and chiasm. Special consideration should be given to avoid doses greater than the prescription dose within the scalp as well as limiting the exit dose through the oral cavity and mucosa. The treatment parameters should be modified to optimize the conformity of the prescription isodose volume to the target volume while minimizing dose to critical structures. There are two scenarios for normal tissues limits: (1) previous radiation to the local area including critical organs at risk and (2) no previous radiation to the local area or organs at risk. The limits for both scenarios are given in Table 2.

Table 2. Normal Tissue Dose Limits

Dose Metric	Per Protocol	Variation Acceptable	Deviation Unacceptable
Scenario (1): Previous radiation to the local area including critical organs at risk			
Maximum Dose to PRV for Optic Nerves and Chiasm (0.03 cc)	Less than or equal to 20 Gy photons – 20 Gy(RBE) protons	Greater than 20 Gy but less than or equal to 25 Gy photons – 25 Gy(RBE) protons	Greater than 25 Gy photons – 25 Gy(RBE) protons
Maximum Dose to Brainstem (0.03 cc)	Less than or equal to 24 Gy photons – 24 Gy(RBE) protons	Greater than 24 Gy but less than or equal to 30 Gy photons – 30 Gy(RBE) protons	Greater than 30 Gy photons – 30 Gy(RBE) protons
Scenario (2): No previous radiation to the local area or critical organs at risk			
Maximum Dose to PRV for Optic Nerves and Chiasm (0.03 cc)	Less than or equal to 35 Gy (the prescription dose) photons – 35 Gy(RBE) protons	Greater than 35 Gy but less than or equal to 36.75 Gy (105 % of the prescription dose) photons – 36.75 Gy(RBE) protons	Greater than 36.75 Gy (105% of the prescription dose) photons – 36.75 Gy(RBE) protons
Maximum Dose to Brainstem (0.03 cc)	Less than or equal to 35 Gy (the prescription dose) photons – 35 Gy(RBE) protons	Greater than 35 Gy but less than or equal to 36.75 Gy (105 % of the prescription dose) photons – 36.75 Gy(RBE) protons	Greater than 36.75 Gy (105 % of the prescription dose) photons – 36.75 Gy(RBE) protons

6.6 Documentation Requirements

At the completion of treatment, the following should be forwarded to RTOG Headquarters: daily treatment record and the radiotherapy summary per Section 12.1. In addition, CT/MRI documentation must be submitted per Section 12.2. Isodose distributions should be displayed on orthogonal planes or, if not possible, on multiple transverse slices through each target.

6.7 Compliance Criteria

See Tables 1 and 2 for target and normal tissue compliance criteria.

6.8 R.T. Quality Assurance Reviews

The Radiation Oncology Co-Chair, Christina Tsien, M.D., will perform an RT Quality Assurance Review of cases on an ongoing basis. The final cases will be reviewed within 6 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at RTOG Headquarters, whichever occurs first. These reviews will be ongoing and performed at the RTOG semi-annual meetings as well as at RTOG Headquarters.

6.9 Radiation Therapy Adverse Events

6.9.1 Acute

Expected acute radiation-induced toxicities include hair loss, fatigue, and erythema or soreness of the scalp. Potential acute toxicities include nausea and vomiting as well as temporary aggravation of brain tumor symptoms such as headaches, seizures, and weakness. Reactions in the ear canals and on the ear should be observed and treated symptomatically; these reactions could result in short-term hearing impairment. Dry mouth or altered taste have been occasionally reported.

6.9.2 Early Delayed

Possible early delayed radiation effects include lethargy and transient worsening of existing neurological deficits occurring 1-3 months after radiotherapy treatment.

6.9.3 Late Delayed

Possible late delayed effects of radiotherapy include risk of radiation necrosis, and endocrine dysfunction. In addition, neurocognitive deficits, which could lead to mental slowing and

behavioral change, are possible. Permanent hearing impairment and visual damage are rare. Cataracts can be encountered.

6.10 Radiation Therapy Adverse Event Reporting

See Section 7.6.

7.0 DRUG THERAPY

Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual.

Protocol treatment must begin within 14 days after registration.

7.1 Treatment

7.1.1 Dose Definition

Bevacizumab will be administered at a dose of 10 mg/kg every 2 weeks. Doses will be adjusted if there is a > 10% change in weight.

7.1.2 Technique of Administration

Bevacizumab will be administered intravenously per institutional guidelines with associated pre-medications.

7.1.3 Duration of Treatment

Initial cycle of bevacizumab must start within 14 days of registration. A deviation of +/- 3 days is permitted. If beyond this timing period, the imaging and work-up will need to be repeated. Subsequent bevacizumab doses may be given every 14 days apart +/- 3 days due to holidays, etc. Treatment may be held for > grade 3 toxicities as defined in Section 7.3.

Arm 1: Patients randomized to the bevacizumab alone arm will be administered bevacizumab every 2 weeks until disease progression.

Arm 2: Patients randomized to the bevacizumab and re-irradiation arm will receive an initial induction dose of bevacizumab (alone without radiation). It will then be followed by concurrent bevacizumab and radiation at the next dose which is administered 14 days later. This will allow additional time for radiation therapy planning especially in symptomatic patients. Concurrent bevacizumab cycle may be given either on the day prior to start of radiation or on day 1 of radiation. Bevacizumab will then be continued every 2 weeks until disease progression.

7.2 Bevacizumab Agent Information

Consult the package insert for further details.

7.2.1 Description and Packaging

Bevacizumab is a humanized IgG1 monoclonal antibody (MAb) that binds all biologically active isoforms of human VEGF (or VEGF-A) with high affinity (kd = 1.1 nM). The antibody consists of a human IgG1 framework and the antigen-binding complementarity-determining regions from the murine anti-VEGF MAb A.4.6.1.16-18. Vials contain bevacizumab with phosphate, trehalose, polysorbate 20, and sterile water for injection (SWFI), USP.

7.2.2 Administration

Bevacizumab should be administered as a continuous intravenous infusion using a rate–regulating device per institutional guidelines with associated pre-medications. Do not administer as an IV push or bolus.

Administer the initial dose over a minimum of 90 minutes. If no adverse reactions occur, administer the second dose over a minimum of 60 minutes. If no adverse reactions occur after the second dose, administer subsequent doses over a minimum of 30 minutes. If infusion-related adverse reactions occur, all subsequent infusions should be administered over the shortest period that was well tolerated.

7.2.3 Storage

Vials contain no preservative and are suitable for single use only.

7.2.4 Supply

Commercially available.

- **Non-Canadian International Institutions**
  Please refer to your LOI Approval Notification. Your institution will be responsible for acquiring any drug noted in the protocol as commercially available and not provided for the study.

7.2.5 Adverse Events

Comprehensive Adverse Events and Potential Risks list (CAEPR) For Bevacizumab (rhuMAb VEGF, NSC 704865)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via AdEERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification.

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.2, October 21, 2011[1]

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 4.0 Term)			**Specific Protocol Exceptions to Expedited Reporting (SPEER)** (formerly known as ASAEL)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr. 3)***
		Blood and lymphatic system disorders - Other (renal thrombotic microangiopathy)	
	Febrile neutropenia		***Febrile neutropenia (Gr. 3)***
CARDIAC DISORDERS			
		Acute coronary syndrome	
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction	
	Supraventricular tachycardia		***Supraventricular tachycardia (Gr. 3)***
		Ventricular arrhythmia	
		Ventricular fibrillation	
EAR AND LABYRINTH DISORDERS			
	Vertigo		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr. 3)***

	Colitis		***Colitis (Gr. 3)***
	Constipation		***Constipation (Gr. 3)***
	Diarrhea		***Diarrhea (Gr. 3)***
	Dyspepsia		***Dyspepsia (Gr. 2)***
		Gastrointestinal fistula[2]	
	Gastrointestinal hemorrhage[3]		***Gastrointestinal hemorrhage[3] (Gr. 2)***
	Gastrointestinal obstruction[4]		
		Gastrointestinal perforation[5]	
		Gastrointestinal ulcer[6]	
	Ileus		
	Mucositis oral		***Mucositis oral (Gr. 3)***
	Nausea		***Nausea (Gr. 3)***
	Vomiting		***Vomiting (Gr. 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		***Fatigue (Gr. 3)***
	Infusion related reaction		***Infusion related reaction (Gr. 2)***
	Non-cardiac chest pain		***Non-cardiac chest pain (Gr. 3)***
	Pain		***Pain (Gr. 3)***
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		***Allergic reaction (Gr. 2)***
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection[7]		***Infection[7] (Gr. 3)***
	Infections and infestations - Other (peri-rectal abscess)		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Gastrointestinal anastomotic leak	
	Wound dehiscence		***Wound dehiscence (Gr. 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr. 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr. 3)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr. 3)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr. 2)***
	Cardiac troponin I increased		
	Neutrophil count decreased		***Neutrophil count decreased (Gr. 3)***
	Weight loss		***Weight loss (Gr. 3)***
	White blood cell decreased		***White blood cell decreased (Gr. 3)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr. 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr. 3)***
	Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia)[8]		
	Myalgia		***Myalgia (Gr. 3)***
	Osteonecrosis of jaw[9]		
NERVOUS SYSTEM DISORDERS			

	Dizziness		***Dizziness (Gr. 2)***
	Headache		***Headache (Gr. 3)***
		Intracranial hemorrhage	
		Ischemia cerebrovascular	
	Peripheral sensory neuropathy[10]		
		Reversible posterior leukoencephalopathy syndrome	
	Syncope		
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
	Hematuria		***Hematuria (Gr. 3)***
	Proteinuria		***Proteinuria (Gr. 2)***
		Renal and urinary disorders - Other (Nephrotic Syndrome)	
		Urinary fistula	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
Reproductive system and breast disorders - Other (ovarian failure)[11]			
		Vaginal fistula	
	Vaginal hemorrhage		***Vaginal hemorrhage (Gr. 3)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Allergic rhinitis		***Allergic rhinitis (Gr. 3)***
		Bronchopleural fistula	
		Bronchopulmonary hemorrhage	
	Cough		***Cough (Gr. 3)***
	Dyspnea		***Dyspnea (Gr. 2)***
	Epistaxis		***Epistaxis (Gr. 3)***
	Hoarseness		***Hoarseness (Gr. 3)***
		Respiratory, thoracic and mediastinal disorders - Other (nasal-septal perforation)	
		Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Pruritus		***Pruritus (Gr. 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr. 2)***
	Urticaria		***Urticaria (Gr. 2)***
VASCULAR DISORDERS			
Hypertension			***Hypertension (Gr. 3)***
	Thromboembolic event		***Thromboembolic event (Gr. 3)***
		Vascular disorders - Other (arterial thromboembolic event)[12]	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Gastrointestinal fistula may include: Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Rectal fistula, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[3]Gastrointestinal hemorrhage may include: Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Intra-abdominal hemorrhage, Oral hemorrhage, Rectal hemorrhage, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[4]Gastrointestinal obstruction may include: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[5]Gastrointestinal perforation may include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Jejunal perforation, Rectal perforation, Small intestinal perforation, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[6]Gastrointestinal ulcer may include: Duodenal ulcer, Esophageal ulcer, Gastric ulcer, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[7]Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

[8]Metaphyseal dysplasia was observed in young patients who still have active epiphyseal growth plates.

[9]Cases of osteonecrosis of the jaw (ONJ) have been reported in cancer patients in association with bevacizumab treatment, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates.

[10]Increased rate of peripheral sensory neuropathy has been observed in trials combining bevacizumab and chemotherapy compared to chemotherapy alone.

[11]Ovarian failure, defined as amenorrhea lasting 3 or more months with follicle-stimulating hormone (FSH) elevation (≥30 mIU/mL), was increased in patients receiving adjuvant bevacizumab plus mFOLFOX compared to mFOLFOX alone (34% vs. 2%). After discontinuation of bevacizumab, resumption of menses and an FSH level <30 mIU/mL was demonstrated in 22% (7/32) of these women. Long term effects of bevacizumab exposure on fertility are unknown.

[12]Arterial thromboembolic event includes visceral arterial ischemia, peripheral arterial ischemia, heart attack, and stroke.

Also reported on Bevacizumab (rhuMAb VEGF) trials but with the relationship to Bevacizumab (rhuMAb VEGF) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (idiopathic thrombocytopenia purpura); Disseminated intravascular coagulation
CARDIAC DISORDERS - Pericardial effusion
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Gait disturbance; Sudden death NOS
HEPATOBILIARY DISORDERS - Hepatic failure
INFECTIONS AND INFESTATIONS - Infections and infestations - Other (aseptic meningitis)

INVESTIGATIONS - Platelet count decreased
METABOLISM AND NUTRITION DISORDERS - Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Musculoskeletal and connective tissue disorder - Other (aseptic necrotic bone); Musculoskeletal and connective tissue disorder - Other (myasthenia gravis)
NERVOUS SYSTEM DISORDERS - Dysgeusia; Peripheral motor neuropathy; Seizure
PSYCHIATRIC DISORDERS - Confusion
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Pneumonitis; Pneumothorax; Pulmonary hypertension
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Palmar-plantar erythrodysesthesia syndrome; Skin ulceration
Note: Bevacizumab (rhuMAb VEGF) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.3 Bevacizumab Dose Modifications

7.3.1 First dose: The dose of bevacizumab will be 10 mg/kg delivered intravenously. There will be no dose reduction for bevacizumab. Treatment should be interrupted or discontinued for certain adverse events, as described below. If bevacizumab is interrupted for ANY reason for > 8 weeks, the patient should discontinue bevacizumab therapy on protocol.

Treatment Modification for Bevacizumab-Related Adverse Events

Event	CTCAE.v4.0 Grade	Action To Be Taken
Allergic reactions **or** **Acute infusional reactions/ cytokine release syndrome**	Grade 1-3	If infusion-related or allergic reactions occur, premedications should be given with the next dose and infusion time may not be reduced for the subsequent infusion. Follow the guidelines in Section 7.3 for bevacizumab administration. **For patients with grade 3 reactions**, bevacizumab infusion should be stopped and not restarted on the same day. At the physicians' discretion, bevacizumab may be permanently discontinued or re-instituted with premedications and administered no faster than 60 minutes. **If bevacizumab is re-instituted, the patient should be closely monitored for a duration comparable to or longer than the duration of the previous reactions**.
	Grade 4	Discontinue bevacizumab
Arterial Thrombosis - Cardiac ischemia/ infraction - CNS ischemia (TIA, CVA) - any peripheral or visceral arterial ischemia/thrombosis	Grade 2 (if new or worsened since bevacizumab therapy)	Discontinue bevacizumab
	Grade 3-4	Discontinue bevacizumab

Venous Thrombosis		
	Grade 3 OR asymptomatic grade 4	▪ Hold bevacizumab treatment. If the planned duration of full-dose anticoagulation is < 2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over. ▪ If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab may be resumed during the period of full-dose anticoagulation **IF** <u>all</u> of the criteria below are met: - The subject must have an in-range INR (usually 2-3) on a stable dose of warfarin or be on a stable dose of heparin prior to restarting bevacizumab - The subject must not have pathological conditions that carry high risk of bleeding (eg, tumor involving major vessels or other conditions) - The subject must not have had hemorrhagic events while on study ▪ If thromboemboli worsen/recur upon resumption of study therapy, discontinue bevacizumab
	Grade 4 (symptomatic)	Discontinue bevacizumab
Hypertension*	[Treat with antihypertensive medication as needed. The goal of BP control should be consistent with general medical practice]	
	Grade 1	Consider increased BP monitoring
	Grade 2 asymptomatic **but** diastolic BP < 100 mmHg	Begin anti-hypertensive therapy and continue bevacizumab
	-Grade 2-3 Symptomatic **OR** -Diastolic BP > 100 mmHg	• Hold bevacizumab until symptoms resolve **AND** BP < 160/90mmHg*
	Grade 4	Discontinue bevacizumab
Congestive Heart Failure	Grade 3	• Discontinue bevacizumab
	Grade 4	Discontinue bevacizumab
Proteinuria	[Proteinuria should be monitored by urine analysis for urine protein creatinine (UPC) ratio prior to every other dose of bevacizumab]	
	UPC ratio < 3.5	Continue bevacizumab
	UPC ratio <u>≥</u> 3.5	Hold bevacizumab until UPC recovers to < 3.5
	Grade 4 or nephrotic syndrome	Discontinue bevacizumab
Hemorrhage (CNS or pulmonary)	Grade 2-4	• Discontinue bevacizumab

Hemorrhage (non-CNS; non-pulmonary)	Grade 3	• Patients receiving full-dose anticoagulation should discontinue bevacizumab • For patients not on full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met: - the bleeding has resolved and Hb is stable - there is no bleeding diathesis that would increase the risk of therapy - there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence. • Patients who experience recurrence of grade 3 hemorrhage should discontinue study therapy
	Grade 4	Discontinue bevacizumab
RPLS (reversible posterior leukoencephalopathy syndrome **or PRES** (posterior reversible encephalopathy syndrome)		• **Hold bevacizumab in patients with symptoms/signs suggestive of RPLS; subsequent management should include MRI scans and control of HTN** • **Discontinue bevacizumab upon diagnosis of RPLS**
Wound dehiscence requiring medical or surgical intervention		•**Discontinue bevacizumab**
GI perforation, GI leak or fistula		Discontinue bevacizumab
Bowel obstruction	Grade 2 requiring medical intervention	• Hold bevacizumab until complete resolution, with a minimum of 4 weeks after surgery.
	Grade 3-4	• Hold bevacizumab until complete resolution • If surgery is required, patient may restart bevacizumab after full recovery from surgery, and at investigator's discretion
Other unspecified bevacizumab-related AEs (except controlled nausea/vomiting).	Grade 3	Hold bevacizumab until symptoms resolve to ≤ grade 1
	Grade 4	• Discontinue bevacizumab • **Upon consultation with the study chair,** resumption of bevacizumab may be considered if a patient is benefiting from therapy and the grade 4 toxicity is transient, has recovered to ≤ grade 1 and unlikely to recur with retreatment

***Current CTCAE definitions used by CTEP:**

- Grade 1: asymptomatic, transient (< 24 hours) increase by > 20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not indicated
- Grade 2: recurrent or persistent (> 24 hours) or symptomatic increase by > 20 mmHg (diastolic) or to > 150/100 if previously WNL; monotherapy may be indicated
- Grade 3: requiring more than one drug or more intensive therapy than previously
- Grade 4: life threatening (eg, hypertensive crisis)

7.4 Modality Review

The Neuro-Oncology Co-Chair, Jeffrey Raizer, M.D., will perform a Chemotherapy Assurance Review of all patients who receive or are to receive chemotherapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 12.1. The scoring mechanism is: **Per Protocol/Acceptable Variation, Not Per Protocol, and Not Evaluable**. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

The Neuro-Oncology Co-Chair, Jeffrey Raizer, M.D., will perform a Quality Assurance Review after complete data for the first 20 cases enrolled has been received at RTOG Headquarters. Dr. Raizer will perform the next review after complete data for the next 20 cases enrolled has been received at RTOG Headquarters. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at RTOG Headquarters, whichever occurs first.

7.5 Adverse Events

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for AdEERS reporting of adverse events (AEs). **All AE reporting on the study case report forms (CRFs) should follow grading criteria instructions on the specific CRF.** The CTCAE version 4.0 is identified and located on the CTEP web site at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

All adverse events (AEs) as defined in the tables below will be reported via the AdEERS (Adverse Event Expedited Reporting System) application accessed via the CTEP web site (https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup).

Serious adverse events (SAEs) as defined in the tables below will be reported via AdEERS. Sites also can access the RTOG web site (http://www.rtog.org/ResearchAssociates/AdverseEventReporting.aspx) for this information.

In order to ensure consistent data capture, serious adverse events reported on AdEERS reports also must be reported on an RTOG case report form (CRF). In addition, sites must submit CRFs in a timely manner after AdEERS submissions.

A 24-hour notification is to be made to CTEP by telephone at 301-897-7497 only when internet connectivity is disrupted. Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into AdEERS by the original submitter at the site.

7.5.1 Adverse Events (AEs)

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. January 2005; http://ctep.cancer.gov/reporting/adeers.html]

The following guidelines for reporting adverse events (AEs) apply to **all** NCI/RTOG research protocols. AEs, as defined above, experienced by patients accrued to this protocol should be reported on the AE section of the appropriate case report form (see Section 12.1). **Note: AEs indicated in the AdEERS Expedited Reporting Requirements in text and/or table in Section 7.6 also must be reported via AdEERS.**

NOTE: If the event is a Serious Adverse Event (SAE) [see next section], further reporting will be required. Reporting AEs only fulfills Data Management reporting requirements.

7.5.2 Serious Adverse Events (SAEs)

All SAEs that fit any one of the criteria in the SAE definition below must be reported via AdEERS. Contact the AdEERS Help Desk if assistance is required.

Certain SAEs as outlined below will require the use of the 24 Hour AdEERS Notification:

- **Phase II & III Studies: All unexpected potentially related SAEs**
- **Phase I Studies: All unexpected hospitalizations and all grade 4 and 5 SAEs regardless of relationship**

Definition of an SAE: Any adverse experience occurring during any part of protocol treatment and 30 days after that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Any pregnancy occurring on study must be reported via AdEERS as a medically significant event.

Pharmaceutically supported studies will require additional reporting over and above that which is required by CTEP.

SAEs (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable, or definite) should be reported via AdEERS.

All supporting source documentation indicated as being provided in the Additional Information Section of the AdEERS Report must be properly labeled with the study/case numbers and the date of the event and must be faxed to the RTOG dedicated SAE FAX, 215-717-0990, before the five or ten-calendar-day deadline to allow RTOG to comply with the reporting requirements of the pharmaceutical company/companies supporting the RTOG trial. The RTOG Case Number without any leading zeros should be used as the Patient ID when reporting via AdEERS. Non-RTOG intergroup study and case numbers must also be included, when applicable. Submitted AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient's case number as the patient ID when reporting via AdEERS.

SAE reporting is safety related and separate and in addition to the Data Management reporting requirements as outlined in the previous AE reporting section. **Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as "expedited reporting NOT required" must still be reported for safety reasons and to fulfill the obligations of RTOG to the pharmaceutical company/companies supporting the RTOG trial. Sites must bypass the "NOT Required" assessment and complete and submit the report. The AdEERS System allows submission of all reports regardless of the results of the assessment. Note:** Sites must select the option in AdEERS to send a copy of the report to the FDA or print the AdEERS report and fax it to the FDA, FAX 1-800-332-0178.

7.5.3 Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)

AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the AdEERS system within 30 days of AML/MDS diagnosis. If you are reporting in CTCAE version 4, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment-related secondary malignancy.

7.6 AdEERS Expedited Reporting Requirements

CTEP defines expedited AE reporting requirements for phase 1 trials as described in the table below. **Important:** All AEs reported via AdEERS also must be reported on the AE section of the appropriate case report form (see Section 12.1).

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via AdEERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitaliz-ation</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

NOTE: Deaths clearly due to progressive disease should **NOT** be reported via AdEERS but rather should be reported via routine reporting methods (e.g., CDUS and/or CTMS).

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a CTEP-IND [or Non-CTEP IND]:
Not applicable.

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy

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

9.1.1 Anticonvulsants: No limitations in type of anti-convulsants used.

9.1.2 Antiemetics: Prophylactic medications are not needed. For nausea, anti-emetics may be used based on the treating physician's preference.

9.1.3 Anticoagulants: These may be used for the treatment of DVT's or PE's if they occur. Preference should be given for LMW Heparins, but Coumadin is allowed.

9.1.4 Antidiarrheals: Used as needed per treating physician's discretion.

9.1.5 Analgesics: Used as needed per treating physician's discretion.

9.1.6 Hematopoietic Growth Factors: Used as needed per treating physician's discretion.

9.1.7 Herbal products: Are allowed but patients should inform treating physician and these should be recorded.

9.1.8 Nutritional supplementation: Are allowed but patients should inform treating physician and these should be recorded.

9.2 Non-permitted Supportive Therapy

9.2.1 Patients should avoid the use of medications that have anti-oxidant properties during radiation.

10.0 TISSUE/SPECIMEN SUBMISSION

NOTE: Patients must be offered the opportunity to participate in the correlative components of the study, such as tissue/specimen submission or quality of life assessment. If the patient consents to participate in the tissue/specimen component of the study, the site is required to submit the patient's specimens as specified in Section 10.0 of the protocol. Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

10.1 Tissue/Specimen Submission

The RTOG Biospecimen Resource at the University of California San Francisco acquires and maintains high quality specimens from RTOG trials. Tissue from each block is preserved through careful block storage and processing. The RTOG encourages participants in protocol studies to

consent to the banking of their tissue. The RTOG Biospecimen Resource provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions.

In this study, tissue will be submitted to the RTOG Biospecimen Resource for the purpose of tissue banking and translational research (highly recommended).

10.2 Specimen Collection for Banking and Translational Research (Highly Recommended)
For patients who have consented to participate in the component of the study.

The following must be provided in order for the case to be evaluable for the Biospecimen Resource:

10.2.1 Tissue (For collection, processing and shipping information please see Specimen Collection Summary below and Appendix III.)

- One H&E stained slide
- A paraffin-embedded tissue block of the tumor or a 2 mm diameter core of tumor tissue, punched from the tissue block containing the tumor with a punch tool and submitted in a plastic tube labeled with the surgical pathology number. **Note:** A kit with the punch, tube, and instructions can be obtained free of charge from the Biospecimen Resource. Block or core must be clearly labeled with the pathology identification number that corresponds to the Pathology Report (see below).
- A Pathology Report documenting that the submitted block or core contains tumor. The report must include the RTOG protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.
- A Specimen Transmittal Form (STF) clearly stating that tissue is being submitted for the RTOG Biospecimen Resource; if for translational research, this should be stated on the form. The form must include the RTOG protocol number and patient's case number.

10.2.2 Blood and Urine (For collection, processing and shipping information please see Specimen Collection Summary below and Appendix III.)

A Specimen Transmittal Form documenting the type of Biospecimen, the date of collection of the biospecimen; the RTOG protocol number, the patient's case number, time point of study, and method of storage, for example, stored at -80° C, must be included.

10.2.3 Storage Conditions for All Specimens

Store frozen specimens at -80° C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:

- Samples can be stored short term in a -20° C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday).

  OR:
- Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

  OR:
- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

Please indicate on the STF the storage conditions used and time stored.

10.2.4 Specimen Collection Summary

Specimens for Banking/Translational Research			
Specimens taken from patient:	**Collected when:**	**Submitted as:**	**Shipped:**
Representative H&E stained slides of the primary tumor	Pre-treatment	H&E stained slide	Slide shipped ambient
A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment or a 2 mm diameter core of tissue, punched from the tissue block with a punch tool	Pre-treatment	Paraffin-embedded tissue block or punch biopsy	Block or punch shipped ambient or on a cold pack to prevent blocks from melting during warm weather.
SERUM: 5-10 mL of whole blood in 1 red-top tube and centrifuge	(1) Pre-treatment (2) Post treatment (at 6 weeks)	Frozen serum samples containing 0.5 mL per aliquot in 1 mL cryovials (five to ten)	Serum sent frozen on dry ice via overnight carrier
PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/ lavender top) and centrifuge	(1) Pre-treatment (2) Post treatment (at 6 weeks)	Frozen plasma samples containing 0.5 mL per aliquot in 1 mL cryovials (five to ten)	Plasma sent frozen on dry ice via overnight carrier
DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/ lavender top) and mix	(1) Pre-treatment (Note: if site missed this timepoint they may collect whole blood at any timepoint or follow up visit, but this must be noted on the ST Form)	Frozen whole blood samples containing 1.0 mL per aliquot in 1 mL cryovials (three-five)	Whole blood sent frozen on dry ice via overnight carrier
10-20 mL clean-catch urine	(1) Pre-treatment (2) Post treatment (at 6 weeks)	Two 5-10 mL urine aliquots in 2 sterile 15 ml polypropylene centrifuge tubes. Store frozen at -20° or 80° C	Urine sent frozen on dry ice via overnight carrier

10.2.5 Submit materials for Specimen Banking, Translational Research as follows:

U. S. Postal Service Mailing Address: For Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

Questions: 415-476-RTOG (7864)/FAX 415-476-5271; RTOG@ucsf.edu

10.3 Reimbursement

RTOG will reimburse institutions for submission of protocol specified biospecimen materials sent to the Biospecimen Resource at the University of California San Francisco and other protocol-specified collection repositories/laboratories. After confirmation from the RTOG Biospecimen

Resource or other designated repository/laboratory that appropriate materials have been received, RTOG Clinical Trials Administration will authorize payment according to the schedule posted with the Reimbursement and Case Credit Schedule found on the RTOG web site (http://www.rtog.org/LinkClick.aspx?fileticket=Csxzt1v1hEk%3d&tabid=323). Biospecimen payments will be processed quarterly and will appear on the institution's summary report with the institution's regular case reimbursement.

10.4 Confidentiality/Storage

(See the RTOG Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/Researchers/BiospecimenResource/BiospecimenResourceFAQs.aspx for further details.)

10.4.1 Upon receipt, the specimen is labeled with the RTOG protocol number and the patient's case number only. The RTOG Biospecimen Resource database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.4.2 Specimens for tissue banking will be stored for an indefinite period of time. Specimens for the translational research component of this protocol will be retained until the study is terminated, unless the patient has consented to storage for future studies. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters: See Appendix I. See below for additional details.

11.1.1 Urine should be assessed via dipstick or random urine creatinine and protein before each dose of bevacizumab.

11.1.2 Vital signs should be assessed before each dose of bevacizumab (on treatment day) to make sure there is no increase in blood pressure.

11.1.3 MR diffusion and perfusion imaging at 8 and 24 weeks post-treatment start is optional but strongly recommended. Repeat MR diffusion and perfusion imaging at progression is optional but strongly recommended as further confirmation of true tumor progression and not radiation necrosis.

11.2 Measurement of Response

The primary measure of response will be by serial measures of the product of the two largest cross-sectional diameters using MacDonald Criteria. Response will also be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [JNCI 92(3): 205-216, 2000], see Section 11.4.

11.2.1 Complete Response (CR)

Requires all of the following: complete disappearance of the measurable enhancing lesion sustained for at least 4 weeks; no new lesions; and no corticosteroids.

11.2.2 Partial Response (PR)

Requires all of the following: ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of the measurable enhancing lesion sustained for at least 4 weeks; no new lesions; and stable or reduced corticosteroid dose.

11.2.3 Stable Disease (SD)

Requires all of the following: does not qualify for complete response, partial response, or progression and is receiving stable or decreasing doses of steroids. This will not require a confirmatory scan.

11.2.4 Progression (P)

Defined by any of the following: ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions provided that the patient has not had his/her dose of steroids decreased since the last evaluation period; and any new lesions. This will not require a confirmatory scan. A concomitant decrease in steroid dose will rule out a progression designation during the initial 12 weeks after completion of RT.

11.2.5 Pseudo-progression

Due to possible radiation effects using large dose per fraction, the initial scan 6 weeks following RT should NOT be used to declare progression. In the absence of neurologic worsening OR a new distant area of tumor, the initial post-radiation scan should not be used to declare progression. Progressive worsening on subsequent imaging studies usually distinguishes true progression from pseudo-progression.

11.2.6 If true progression is determined by subsequent imaging, then the date of progression returns to the earlier date with increasing mass.

11.3 Criteria for Evaluation of Therapy Effectiveness

11.3.1 Tumor response and regrowth can frequently be difficult to measure directly. Serial neurological exams and CT/MRI scans may provide a guide to the actual course. Time interval to progression will be measured from registration until deterioration is documented by the individual investigator using these guides. The patient should consistently be followed with the same diagnostic imaging study (CT or MRI). (**NOTE**: CT option ONLY for patients unable to undergo MR imaging because of non-compatible devices.)

11.3.2 Overall survival will be measured from registration until death. Progression-free survival will be measured from registration until the first occurrence of progression or death.

11.3.3 The quality of survival will be measured by neurological functional classification and performance status.

11.3.4 Toxicities will be measured using the CTCAE criteria, version 4.0.

11.4 RANO Response Criteria

Efficacy determinations using RANO response criteria (Wen 2010) also will be obtained.

11.4.1 Response Criteria

Radiographic response should be determined in comparison to the tumor measurement obtained at pretreatment baseline for determination of response, and the smallest tumor measurement at either pretreatment baseline or following initiation of therapy for determination of progression. The tables below outline the criteria for radiographic changes following therapy and summarize RANO response criteria. In the event that the radiographic changes are equivocal and it is unclear whether the patient is stable or has developed progressive disease, it is permissible to continue treatment and observe the patient closely, for example at 4 weekly intervals. If subsequent imaging studies demonstrate that progression has occurred, the date of progression should be the scan at which this issue was first raised.

All measurable and non-measurable lesions should be assessed using the same techniques as baseline. Ideally patients should be imaged on the same MRI, or least with the same magnet strength, for the duration of the study to reduce difficulties in interpreting changes.

All measurable and non-measurable lesions must be assessed using the same techniques as baseline.

Criteria for Response Assessment Incorporating MRI and Clinical Factors

Complete Response:

Requires all of the following:

a) Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks.
b) No new lesions.
c) Stable or improved non-enhancing (T2/FLAIR) lesions.
d) Patients must be off corticosteroids (or on physiologic replacement doses only).
e) Stable or improved clinically.

Note: Patients with non-measurable disease only cannot have a complete response. The best response possible is stable disease.

Partial Response:

Requires all of the following:

a) Greater than or equal to 50% decrease compared to baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks.
b) No progression of non-measurable disease.
c) No new lesions.
d) Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan.
e) The corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan.
f) Stable or improved clinically.

Note: Patients with non-measurable disease only cannot have a partial response. The best response possible is stable disease.

Stable Disease:

Requires all of the following:

a) Does not qualify for complete response, partial response, or progression.
b) Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to 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.
c) Stable clinically.

Progression:

Defined by any of the following:

a) Greater than > 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared to the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids.*
b) Significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared to baseline scan or best response following initiation of therapy,* not due to co-morbid events (e.g. radiation therapy, demyelination, ischemic injury, infection, seizures, post-operative changes, or other treatment effects).
c) Any new lesion.
d) Clear clinical deterioration not attributable to other causes apart from the tumor (e.g. seizures, medication side effects, complications of therapy, cerebrovascular events, infection, etc.) or changes in corticosteroid dose.
e) Failure to return for evaluation due to death or deteriorating condition.
f) Clear progression of non-measurable disease.

*Stable doses of corticosteroids include patients not on corticosteroids

Summary of RANO Response Criteria

Criterion	CR	PR	SD	PD[#]
T1-Gd +	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*

Abbreviations: RANO, Response Assessment in Neuro-Oncology; CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; FLAIR, fluid-attenuated inversion recovery; ↓ = decrease; ↑ = increase

[#] Progression occurs when any of the criteria with * is present.

NA**: Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

11.4.2 Efficacy Assessments

- *Progression free survival (PFS)* will be defined from the time the patient enters the study until there is clinical or radiographic evidence of progressive disease (see definition of PD above).
- *Overall survival (OS)* will be defined from the time the patient enters the study to the date of death. Patients not known to have died will be censored for survival as of the last date known alive.
- *PFS and overall survival* will be estimated by using the Kaplan-Meier method.
- The primary endpoint for this study is overall survival.

11.5 Criteria for Discontinuation of Protocol Treatment

- Progression of disease (See Section 11.2)
- Unacceptable toxicity to the patient (at the discretion of the treating physician) — Reasons for removal must be clearly documented on the appropriate case report form/flow sheet, and RTOG Headquarters data management must be notified.

If protocol treatment is discontinued, follow up and data collection will continue as specified in the protocol.

12.0 DATA COLLECTION

Data should be submitted to:

RTOG Headquarters*
1818 Market Street, Suite 1600
Philadelphia, PA 19103

***If a data form is available for web entry, it must be submitted electronically.**

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

12.1 Summary of Data Submission

Item	Due
Demographic Form **(A5)** Initial Evaluation Form **(I1)** Pathology Report **(P1)**	**Within 2 weeks after registration**
Treatment Form **(TF)**	At completion of each 8-week period (4 doses of bevacizumab per TF form if no protocol modification)
Follow-up Form **(F1)**	At the time of progression and at death. AFTER progression or treatment discontinuation: every 2 months for 1 year, then every 6 months for 1 year, then annually.
MRI scans and Reports (MR, ME)	Pre-study (see Section 12.2) Progression on CD to HQ

For protocols involving submission to ITC:

12.2 Summary of Dosimetry Digital Data Submission (Submit to ITC; see Section 12.2.1)

Item	Due
Preliminary Dosimetry Information (DD)	
Digital Data Submission – Treatment Plan submitted to ITC via SFTP account exported from treatment planning machine by Physicist Digital data submission includes the following: • CT data, critical normal structures, all GTV, CTV, and PTV contours • Digital plan • Digital dose • Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose	Within 1 week of start of RT

plan **(DV)**

Digital Data Submission Information Form **(DDSI)** – Submitted online (Form located on ATC web site, http://atc.wustl.edu/forms/DDSI/ddsi.html)

Hard copy isodose distributions for total dose plan **(T6)**

MRI SUBMISSION
Pre-study MRI (the Scan used to delineate the target volumes for planning. Submit the entire series and specify on the DDSI form which one was used for planning)

NOTE: Sites must notify ITC via e-mail (itc@wustl.edu) after digital data is submitted. The e-mail must include study and case numbers or, if the data is phantom, "dry run" or "benchmark".

Final Dosimetry Information — Within 1 week of RT end
Radiotherapy Form **(T1) [copy to HQ and ITC]**
Daily Treatment Record **(T5) [copy to HQ and ITC]**
Modified digital patient data as required through consultation with Image-Guided Therapy QA Center

NOTE: ALL SIMULATION AND PORTAL FILMS AND/OR DIGITAL FILM IMAGES WILL BE KEPT BY THE INSTITUTION AND ONLY SUBMITTED IF REQUESTED.

12.2.1 *Digital Data Submission to ITC*

Digital data submission may be accomplished using media or the Internet.
For network submission: The SFTP account assigned to the submitting institution by the ITC shall be used, and e-mail identifying the data set(s) being submitted shall be sent to:

itc@wustl.edu

For media submission: Please contact the ITC about acceptable media types and formats.
Hardcopies accompanying digital data should be sent by mail or Federal Express and should be addressed to:

Image-Guided Therapy Center (ITC)
ATTN: Roxana Haynes
4511 Forest Park, Suite 200
St. Louis, MO 63108
314-747-5415
FAX 314-747-5423

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary Endpoint

Overall Survival, defined as the interval from randomization to death due to any cause.

13.1.2 Secondary Endpoints

- Objective response
- 6-month progression-free survival
- Progression-free survival, defined as the interval from randomization to progression or death, whichever occurs first
- Treatment adverse events
- Grade 3 acute or delayed CNS toxicity

13.2 Sample Size and Power Justification

The primary objective of this study is to determine whether re-irradiation plus bevacizumab (experimental arm) will improve the overall survival compared to bevacizumab alone (control arm). The design will be a randomized phase II screening trial as proposed by Rubinstein et al (2005). The randomization of experimental and control arms is 1:1. The null hypothesis is that the overall survival for both arms is 9 months, based on data from RTOG 0625/ACRIN 6677 and the BRAIN study. The alternative hypothesis is that patients receiving IMRT plus bevacizumab will have an improvement in overall survival to 13 months, based on the Gutin data. With 160 eligible subjects, there will be 80% power to detect a 31% reduction in the hazard ratio to 0.69 at the significance level of 0.10 (one-sided). Analysis will be performed when 135 events (deaths) are reported, expected to occur 16 to 21 months after trial closure. Guarding against up to a 10% ineligibility rate, **the final target accrual for this study will be 178 cases**.

13.3 Patient Accrual

Based on the monthly accrual for a prior RTOG recurrent glioblastoma phase II study (RTOG 0625), this study is projected to accrue 10 cases/month. Therefore, the target accrual should be completed within 22 months of study activation, allowing slow accrual in the first 6 months. If the average monthly accrual (6 months after trial activation) is less than 5 patients, the study will be re-evaluated with respect to feasibility.

13.4 Patient Stratification and Randomization

A randomized phase II trial will be conducted for bevacizumab-naïve recurrent GBM patients. Age and Karnofsky performance status (KPS) are demonstrated to be prognostic of survival for recurrent GBM (Carson 2007). In addition, previous RTOG recurrent GBM trials (RTOG 0625, 0627) show that age, KPS, and resection type have prognostic value in overall survival. Therefore, for this RTOG recurrent GBM study, patients will be stratified by age (<50 vs. ≥50), KPS (70-80 vs.90-100), and resection type (yes vs. no/biopsy only), and then randomized to either the control arm or experimental arm in a permuted block design using the method described by Zelen (1974).

13.5 Analyses Plans

13.5.1 Statistical Methods

Overall and progression-free survival rates will be estimated using the Kaplan-Meier method (Kaplan 1958), and differences between treatment arms will be tested in the log-rank test (Mantel 1966). Overall survival will be measured from the date of randomization to the date of death or, otherwise, the last follow-up date on which the patient was reported alive. Progression-free survival will be measured from the date of randomization to the date of first progression or death or, otherwise, the last follow-up date on which the patient was reported alive.

Objective response rate, grade 3+ toxicities rate, acute or delayed CNS toxicity rate, and 6-month progression-free survival rate, will be estimated using an exact binomial distribution together with 95% confidence interval. The difference between the 2 groups will be tested using a chi square test. In terms of grade 3+ toxicity and acute/delayed toxicity, all patients receiving any protocol

treatment (bevacizumab or combination of RT with bevacizumab) should be included. For the statistical comparison of the primary endpoint (overall survival), the type I error is set as 0.1 (1-sided), while for all the secondary endpoints, the statistical comparison between groups will serve as an exploratory purpose without multiple comparison adjustment, with type I error of 0.05 (2-sided) for each comparison.

Multivariate analyses with the Cox proportional hazard model (Cox 1972) for overall and progression-free survival will be performed with the stratification variables as fixed variables to assess the treatment effect adjusting patient-specific risk factors. The covariates evaluated for the multivariate models are assigned protocol treatment, tumor volume at the time of treatment, time since original diagnosis, stratification factors, and other prognostic factors. Proportional hazard assumptions will be checked using different graphical or time-varying coefficients testing methods. If the data clearly do not follow proportional hazards, other statistical models will be used to fit the data instead. Possible alternatives are to use the stratified Cox proportional hazard model, accelerated failure model, or partition the time axis into sections where proportional hazard assumption holds.

13.5.2 Interim Toxicity and Futility Analysis

Due to a possible increased incidence of grade 3+ CNS toxicity (possibly, probably, or definitely related to treatment) occurring during the first 6 months post RT in the experimental arm, a special interim analysis will be performed after the first 20 patients enrolled to the experimental arm have a minimum 6-month follow-up. If the incidence of grade 3+ CNS toxicity (based on RTOG 0625) is 20% higher, or 30%, in the experimental arm, the trial will be halted due to lack of safety. The interim toxicity analysis results will be reported to the RTOG DMC. The DMC will then make a recommendation about the trial to the RTOG Group Chair.

The interim futility analysis will be performed when 50% of the required events (68 deaths) are reported. The analysis will be performed on an intent-to-treat basis, with all eligible cases included in the treatment arm to which they were randomized regardless of what treatment the patients actually received. The primary endpoint, overall survival, will be tested. The futility will be tested using the conditional probability under the alterative hypothesis of detecting the hypothesized treatment benefit favoring the experimental arm at the final analysis given the observed data. The results from testing the treatment futility will be reported to the RTOG DMC. The responsible statistician may recommend early reporting of the results and/or stopping accrual (if applicable) of the trial if the conditional power is less than 0.1. The accrual rate, treatment compliance, safety of the treatments, and the importance of the study are also considered in making such a recommendation. The results will be reported to the RTOG DMC with the treatment blinded. The DMC will then make a recommendation about the trial to the RTOG Group Chair.

13.5.3 Interim Analysis to Monitor Study Progress

Interim reports with statistical analyses are prepared every 6 months until the initial manuscript reporting the treatment results has been submitted. The reports contain:

- The patient accrual rate with a projected accrual completion date
- Accrual by institution
- The pretreatment characteristics of accrued patients
- The frequency and severity of toxicities
- The results of any completed study chair modality reviews

The interim reports will not contain the results from the treatment comparisons with respect to the efficacy endpoints (overall survival, progression-free survival, treatment response). The RTOG DMC will review the accrual to the study and the rate of adverse events on the study at least twice per year until the initial results of the study have been presented to the scientific community.

13.5.4 Significance Testing for Final Analysis

The final analysis will be performed on an intent-to-treat basis, such that all eligible cases on the study will be included in the arm to which they were randomized regardless of what treatment the patients actually received. The analysis to report the final results of treatment comparison between the experimental arm and the control arm will be undertaken when 135 events (deaths) have been reported. A one-sided log-rank test will be performed to test the difference in overall

survival between the two treatment arms. If the p value is less than protocol-specified 0.10 (one sided), the study statistician will reject the null hypothesis and conclude that the experimental arm (re-radiation plus bevacizumab) is promising in prolonging overall survival, therefore supporting the development of a confirmatory phase III trial comparing this regimen to the current standard treatment. All information reported in the interim analyses to monitor the study progress (above) and the treatment compliance with respect to re-radiation and chemotherapy will also be included in the final report.

13.5.5 This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

13.6 Gender and Minorities

In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, both men and women of all races and ethnic groups are eligible for this study. We will also analyze treatment differences by gender, race, and ethnicity. The following table lists the projected accrual for each racial and ethnic group based upon previous RTOG recurrent GBM trials.

Projected Distribution of Gender and Minorities

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	10	13	23
Not Hispanic or Latino	67	88	155
Ethnic Category: Total of all subjects	77	101	178
	Gender		
Racial Category	**Females**	**Males**	**Total**
American Indian or Alaskan Native	1	1	2
Asian	3	3	6
Black or African American	6	6	12
Native Hawaiian or other Pacific Islander	1	1	2
White	66	90	156
Racial Category: Total of all subjects	77	101	178

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APPENDIX I: STUDY PARAMETER TABLES
(See Sections 3.0; 4.0; and 11.1 for additional details.)

Pre-Treatment Assessments

Assessment	Within 30 days prior to registration	Within 14 days prior to registration	Within 7 days prior to registration
Histopath dx		X	
History		X	
Physical		X	
Neurological exam		X	
Tumor imaging MRI/CT scan (pts **without** recent resection)*		X	
Tumor imaging MRI/CT scan (pts **with** recent resection)*	And within 96 h post-surgery		
Karnofsky status		X	
CBC w/ differential		X	
Bilirubin SGOT or AST		X	
Serum creatinine		X	
Urine protein: creatinine or urine dipstick		X	
Serum pregnancy test (if applicable)			X
MR diffusion and perfusion imaging (optional but strongly recommended)		X	
MGMT methylation status		X	
Tissue, blood, urine for banking (if patient consents)		X	

*****See Section 3.1.4 for details.

Assessments During Treatment

Assessment	q8 weeks (± 3 days)	At 8 weeks, 24 weeks, and progression
Physical	RT arm: weekly during RT Non-RT arm: q8 weeks	
Neurological exam	X	
Tumor imaging MRI/CT scan	X	
Karnofsky status	X	
CBC w/ differential	X	
Urine protein: creatinine or urine dipstick	X (See 11.1)	
MR diffusion and perfusion imaging (optional but strongly recommended)		X
Blood pressure monitoring	X (See 11.1; done prior to each drug dose)	
AE evaluation	X	

Follow-Up Assessments

Assessments	After treatment discontinuation or progression: q8 weeks for 1 year, then q6 months for 1 year, then annually (± 2 weeks). (See Section 12.1 for details)
Physical	X
Karnofsky status	X
Blood, urine for banking (if patient consents)	At 6 weeks post-treatment (± 3 days)
AE evaluation	X

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

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

APPENDIX III

Appendices for RTOG Biospecimen Collection *(as specified by the protocol)*.

RTOG FFPE Specimen Plug Kit Collection
RTOG Blood Collection Kit Instructions
RTOG Urine Collection Kit Instructions

Shipping Instructions:

U.S. Postal Service Mailing Address: For FFPE or Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen or Trackable Specimens
RTOG Biospecimen Resource
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

- Include all RTOG paperwork in pocket of biohazard bag.
- Check that the Specimen Transmittal Form (STF) has the consent boxes checked off.
- Check that all samples are labeled with the RTOG study and case number, and include date of collection as well as collection time point (e.g., pretreatment, post-treatment).

- **FFPE Specimens:**
  - Slides should be shipped in a plastic slide holder/slide box. Place a small wad of padding in top of the container. If you can hear the slides shaking it is likely that they will break during shipping.
  - FFPE Blocks can be wrapped in paper or placed in a cardboard box with padding. Do not wrap blocks in with bubble wrap or gauze. Place padding in top of container so that if you shake the container the blocks are not shaking. If you can hear the slides shaking it is likely that they will break during shipping.
  - Slides, Blocks, or Plugs can be shipped ambient or with a cold pack either by United States Postal Service (USPS) to the USPS address (94143) or by Courier to the Street Address (94115). **Do NOT ship on Dry Ice**.

- **Frozen Specimens:**
  - Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified.
  - Place specimens and absorbent shipping material in Styrofoam cooler filled with dry ice (at least 7 lbs). There should be plenty of dry ice under and above the specimens. If the volume of specimens is greater than the volume of dry ice then ship in a larger Styrofoam box, or two separate boxes. Any Styrofoam box can be used, as long as it is big enough.
  - Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
  - Send frozen specimens via overnight courier to the address above. Specimens should only be shipped Monday through Wednesday (Monday-Tuesday for Canada) to prevent thawing due to delivery delays. Saturday or holiday deliveries cannot be accepted. Samples can be stored frozen at -80° C until ready to ship.

- **For Questions regarding collection/shipping please contact the RTOG Biospecimen Resource by e-mail: RTOG@ucsf.edu or phone: 415-476-RTOG(7864) or Fax: 415-476-5271.**

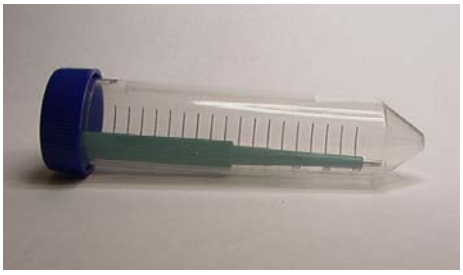
RTOG FFPE SPECIMEN PLUG KIT INSTRUCTIONS

This Kit allows sub-sampling of an FFPE block for submission to the RTOG Biospecimen Resource. The plug kit contains a shipping tube and a punch tool.

Step 1
If the block is stored cold, allow it to equilibrate for 30 minutes at room temperature. Place the punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate the plug from the block. Then pull the punch tool out of the block. The punch should be filled with tissue sample.

Step 2
Label the punch tool with the proper specimen ID. DON'T remove specimen from the punch.

Use a separate punch tool for every specimen. Call or e-mail us if you have any questions or need additional specimen plug kits.



Step 3
Once punch tool is labeled, place in shipping tube and mail to address below. Please do not mix specimens in the same tube.

We will remove core specimen from the punch, embed in a paraffin block, and label with specimen ID.

***NOTE:** If your facility is uncomfortable obtaining the plug but wants to retain the tissue block, please send the entire block to the RTOG Biospecimen Resource and we will sample a plug from the block and return the remaining block to your facility. Please indicate on the submission form the request to perform the plug procedure and return of the block.
Ship specimen plug kit, specimen in punch tool, and all paperwork to the address below. For Questions regarding collection/shipping or to order an FFPE Specimen Plug Kit, please contact the RTOG Biospecimen Resource by e-mail: RTOG@ucsf.edu or call 415-476-RTOG(7864)/Fax 415-476-5271.

U.S. Postal Service Mailing Address: **For Non-frozen Specimens Only** **RTOG Biospecimen Resource** **University of California San Francisco** **Campus Box 1800** **2340 Sutter Street, Room S341** **San Francisco, CA 94143-1800**	**Courier Address (FedEx, UPS, etc.):** **For Frozen Specimens or Trackable shipments** **RTOG Biospecimen Resource** **University of California San Francisco** **2340 Sutter Street, Room S341** **San Francisco, CA 94115**

RTOG BLOOD COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of serum, plasma, or whole blood *(as specified by the protocol)*:

Kit contents:

- One Red Top tube for serum (A)
- One Purple Top EDTA tube for plasma (B)
- One Purple Top EDTA tube for Whole Blood (C)
- Twenty-five (25) 1 ml cryovials
- Biohazard bags (3) and Absorbent shipping material (3)
- Styrofoam container (inner) and Cardboard shipping (outer) box
- UN1845 DRY Ice Sticker and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal Form (STF) and Kit Instructions

PREPARATION AND PROCESSING OF SERUM, PLASMA AND WHOLE BLOOD:

(A) Serum (if requested): Red Top Tube

- ❑ Label as many 1ml cryovials (5 to 10) as necessary for the serum collected. Label them with the RTOG study and case number, collection date, time, and time point, and clearly mark cryovials "serum".

Process:

1. Allow one red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the STF.
3. Aliquot 0.5 ml serum into as many cryovials as are necessary for the serum collected (5 to 10) labeled with RTOG study and case numbers, collection date/time, protocol time-point collected (e.g. pretreatment, post-treatment), and clearly mark specimen as "serum".
4. Place cryovials into biohazard bag and immediately freeze at -70 to -90° C, and store frozen until ready to ship. See below for storage conditions.
5. Store serum at -70 to -90° C until ready to ship on dry ice. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the STF.

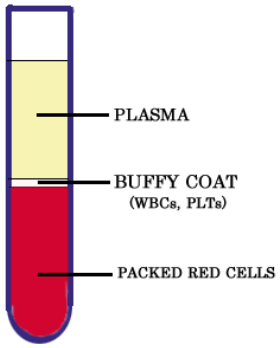
(B) Plasma (If requested): Purple Top EDTA tube #1

- ❑ Label as many 1ml cryovials (5 to 10) as necessary for the plasma collected. Label them with the RTOG study and case number, collection date, time, and time point, and clearly mark cryovials "plasma".

Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the STF..
3. If the interval between specimen collection and processing is anticipated to be more than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot 0.5 ml plasma into as many cryovials as are necessary for the plasma collected (5 to 10) labeled with RTOG study and case numbers, collection date/time, time point collected and clearly mark specimen as "plasma". Avoid pipetting up the buffy coat layer.
5. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C.
6. Store frozen plasma until ready to ship on dry ice.
7. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the STF.



(C) <u>Whole Blood for DNA (if requested): Purple Top EDTA tube #2</u>

- ❑ Label as many 1ml cryovials (3 to 5) as necessary for the whole blood collected..Label them with the RTOG study and case number, collection date/time, and time point, and clearly mark cryovials "blood".

<u>Process</u>:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
2. Carefully pipette and aliquot 1.0 ml blood into as many cryovials as are necessary for the blood collected (3 to 5) labeled with RTOG study and case numbers, collection date/time, time point collected and clearly mark specimen as "blood".
3. Place cryovials into biohazard bag and freeze immediately at -70 to -80° Celsius.
4. Store blood samples frozen until ready to ship on dry ice.
5. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on STF.

<u>Freezing and Storage</u>:

- ☐ Freeze Blood samples in a -80°C Freezer or on Dry Ice or snap freeze in liquid nitrogen.
- ❑ Store at –80°C (-70°C to -90°C) until ready to ship.
  If a -80°C Freezer is not available,
  - Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).

  <u>OR</u>:
  - Samples can be stored in plenty of dry ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only; Canada: Monday-Tuesday only).

  <u>OR</u>:
  - Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
- ❑ Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

<u>Shipping/Mailing</u>:

- ❑ Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- ❑ Include all RTOG paperwork in a sealed plastic bag and tape to the outside top of the Styrofoam box.
- ❑ Wrap frozen specimens of same type (i.e., all serum together, plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard

bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). ***Add padding to avoid the dry ice from breaking the tubes.***

- ❑ Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.
- ❑ *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice.* ***Add padding to avoid the dry ice from breaking the tubes.***
- ❑ **For questions regarding collection, shipping or to order a Blood Collection Kit, please e-mail RTOG@ucsf.edu or call (415)476-7864.**

Shipping Address:

Courier Address (FedEx, UPS, etc.): For all Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
For questions, call 415-476-RTOG (7864) or e-mail: RTOG@ucsf.edu

RTOG URINE COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of urine specimens.

Kit Contents:

- One (1) Sterile Urine collection cup
- Two 7 ml disposable pipettes
- Absorbent paper towel
- Two 15 ml polypropylene centrifuge tubes
- Biohazard bags
- Parafilm for sealing outside of tubes

Preparation and Processing of Urine Specimens:

Process:

- A clean catch urine specimen will be collected. To collect the specimen, use the following instructions:
  - Males should wipe clean the head of the penis and females need to wipe between the labia with soapy water/cleansing wipes to remove any contaminants.
  - After urinating a small amount into the toilet bowl to clear the urethra of contaminants, collect a sample of urine in the collection cup.
  - After 10-25 mL urine has been collected, remove the container from the urine stream without stopping the flow of urine.
  - Finish voiding the bladder into the toilet bowl.
- Aliquot 5-10 mls of Urine into each of two 15 ml polypropylene centrifuge tubes (disposable pipets are provided in the kit). Do not fill with more than 10 mls to avoid cracking of tubes due to expansion during freezing. Replace the cap and tighten on the tubes. Make sure the cap is not cross-threaded or placed on incorrectly or leaking will occur.
- Use parafilm to seal the cap around the outside rim of the urine tube to prevent leakage.
- Discard remaining Urine and collection cup.
- Label the specimen with the RTOG study and case number, collection date and time, time point of collection, and clearly mark specimens as “urine”.
- Wrap Urine Tubes with absorbent material (paper towels) and place into biohazard bag and seal the bag. Freeze and store Urine samples in a -20°C or -80°C freezer until ready to ship.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED with RTOG study and case numbers, collection date/time, and time point collected (e.g. pretreatment, post-treatment).

Storage and Shipping:

Freezing and Storage:

- ❑ Urine specimens may be sent in batches or with other frozen biospecimens, if within 30-60 days of collection. Store at -20°C or -80°C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:
  - Samples can be stored short term in a -20° C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).

  OR:
  - Samples can be stored in plenty of Dry Ice for up to one week, replenishing daily (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
  - Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

Shipping/Mailing:

- ❑ Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- ❑ Include all RTOG paperwork in a sealed plastic bag and tape to the outside top of the Styrofoam box.
- ❑ Place sealed specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). ***Add padding to avoid the dry ice from breaking the tubes.***
- ❑ Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.

- *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice.* ***Add padding to avoid the dry ice from breaking the tubes.***
- Samples received thawed will be discarded, and a notification will be sent immediately to the Principal Investigator and Clinical Research Assistant of the submitting institution. The institution should send a subsequent sample, collected as close as possible to the original planned collection date.
- **For questions regarding ordering, collection, or shipping of a Urine Collection Kit, please e-mail RTOG@ucsf.edu or call (415)476-7864 or fax (415) 476-5271.**

Shipping Address: FedEx/UPS/Courier address (For all frozen samples)
RTOG Biospecimen Resource at UCSF
2340 Sutter Street, Room S341, San Francisco, CA 94115
Contact Phone: (415) 476-RTOG(7864)