# RADIATION THERAPY ONCOLOGY GROUP

# RTOG 0825

# PHASE III DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL OF CONVENTIONAL CONCURRENT CHEMORADIATION AND ADJUVANT TEMOZOLOMIDE PLUS BEVACIZUMAB VERSUS CONVENTIONAL CONCURRENT CHEMORADIATION AND ADJUVANT TEMOZOLOMIDE IN PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA

**NCI-Supplied Agent: Bevacizumab (NSC 704865; IND 7921)**

**This is a collaborative effort with American College of Radiology Imaging Network (ACRIN)**
**ACRIN Study Number 6686** (7/20/09)

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**STUDY PARTICIPANTS** (8/2/10)

**Lead Group – Investigators from this Group should enroll patients through RTOG.**
RTOG

**Endorsing Group(s) – Investigators from these Groups must enroll patients through the CTSU.**
NCCTG, ECOG.

*The following Cooperative Groups have endorsed this trial via the CTSU Endorsement Plus Option:*
*NCCTG: Co-chair Dr. Kurt Jaeckle.*
*NCCTG members will enroll patients to this study via the CTSU. Institutions holding dual memberships in NCCTG and RTOG may credit either Group for enrollments, provided the credited PI is a member of the credited Group.*

**Ordering Group(s) – Investigators must have a current affiliation with one of these Groups to receive investigational agent and/or an Investigator's Brochure for this protocol.**
RTOG
CTSU

**Imaging Group – To participate in the ACRIN advanced imaging component, ACRIN investigators must have an affiliation with one of these Groups.**
RTOG
CTSU

**NOTE:** Sites participating through CTSU must apply for an RTOG username and password **immediately after registering**, to enable access to the Neurocognitive Training Procedure Letter on the 0825 forms section of the RTOG website. A user name and password can be obtained by completing the Password Authorization Form at www.rtog.org/members/webreg.html. See the CTSU logistics appendix for details.

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

Institutions not aligned with the RTOG will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix.

- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at http://members.ctsu.org
- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.
- **Patient enrollments** will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.
- Data management will be performed by the RTOG. **Case report forms** (with the exception of patient enrollment forms)**, clinical reports, and transmittals** must be sent to RTOG Headquarters unless otherwise directed by the protocol. Do not send study data or case report forms to CTSU Data Operations.
- **Data query and delinquency reports** will be sent directly to the enrolling site by the RTOG. Please send query responses and delinquent data to the RTOG and do not copy the CTSU Data Operations. Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP IAM account contact information current. This will ensure timely communication between the clinical site and RTOG Headquarters.

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**RADIATION THERAPY ONCOLOGY GROUP**

**RTOG 0825**

**PHASE III DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL OF CONVENTIONAL CONCURRENT CHEMORADIATION AND ADJUVANT TEMOZOLOMIDE PLUS BEVACIZUMAB VERSUS CONVENTIONAL CONCURRENT CHEMORADIATION AND ADJUVANT TEMOZOLOMIDE IN PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA**

**SCHEMA**

**STEP 1 REGISTRATION**

↓

**Central Pathology Tissue Screening**
- Histology confirmation
- Confirmation of adequacy of tissue for MGMT analysis and molecular profile
- NOTE: Tumor tissue must be received and central review confirmation completed before STEP 2 registration can occur.

↓

**STEP 2 REGISTRATION**

↓

(Initial 3 weeks of chemoradiation treatment)

Radiation (30 Gy in 2 Gy fractions)

Concurrent daily temozolomide (qd X 21 d)*

Analysis for MGMT methylation and molecular profile

↓

**STEP 3 REGISTRATION**

**RANDOMIZATION STEP: Must Occur by Day 10 After the Start of Radiation**

↓

**STRATIFY**
**MGMT Methylation Status:** Methylated vs. Unmethylated vs. Invalid
**Molecular Profile:** Favorable vs. Unfavorable vs. Undetermined

↓

**Arm 1**
(Final 3 weeks of chemoradiation)
Radiation (30 Gy in 2 Gy fx)* + daily TMZ
(qd x 21 d) + placebo q 2 wks (continues without stop)

4 weeks after completion of chemoradiation:
Temozolomide d 1-5 of 28-d cycle
+ placebo q 2 wks ; 12 cycle maximum**

↓

**Arm 2**
(Final 3 weeks of chemoradiation)
Radiation (30 Gy in 2 Gy fx)* + Daily TMZ
(qd x 21 d) + bevacizumab q 2 wks (continues without stop)

4 weeks after completion of chemoradiation:
Temozolomide d 1-5 of 28-d cycle + bevacizumab q 2 wks; 12 cycle maximum**

* Institution must be pre-credentialed. See Section 5.0.
**Bevacizumab at progression at physician discretion.
See Section 6.0 for complete radiation therapy details.
See Section 7.0 for complete drug therapy details.

**Patient Population**: (See Section 3.0 for Eligibility)

- Histopathologically confirmed glioblastoma (WHO Grade IV) **confirmed by central pathology tissue screening prior to step 2 registration**
- Tumor tissue that is **determined by central pathology tissue screening prior to step 2 registration** to be of sufficient size for analysis of MGMT status and determination of molecular profile
- The tumor must have a supratentorial component

**Required Sample Size**: 942 patients

**ACRIN 6686 Advanced Imaging Component for Participating Sites** (7/20/09)

**SCHEMA***

| **Advanced MR Imaging Time Points Table (Select Sites Only)** | | | | |
|---|---|---|---|---|
| | **T0—**Baseline† (within 0 to 5 Days prior to chemo-RT) | **T1—**Week 3 (within 0 to 3 days prior to placebo or bevacizumab initiation) | **T2—**Week 3 + 1 Day (must be completed same day or 1st day after placebo or bevacizumab begins) | **T3—**Week 10 (post-chemo-RT, during adjuvant phase) |
| Advanced Imaging: DSC-MRI and DCE- MRI | X | X | X | X |
| † Acute intracranial hemorrhage must have been ruled out prior to Baseline advanced imaging scan. | | | | |

*** See Section 11.3.2 for details and Appendix II: Study Parameter Table for a complete outline of all study procedures and timing.**

**Site Eligibility:** Pre-qualification of imaging scanners and images is required for advanced imaging component; all eligible potential participants recruited at advanced-imaging sites must be asked to consent to advanced imaging (see Appendix I).

**Required Sample Size for ACRIN Advanced Imaging Component**: 264 participants from the 942 RTOG-study patients.

**RTOG Institution #**
**RTOG 0825** **ELIGIBILITY CHECKLIST—STEP 1** (7/27/09)
**Case #** **(page 1 of 1)**

_____(Y) 1. Is the patient suspected to have glioblastoma or gliosarcoma (WHO Grade IV)?

**The following questions will be asked at Study Registration for STEP 1 Registration**:

**IMRT CREDENTIALING IS REQUIRED BEFORE REGISTRATION**
**NEUROCOGNITIVE CERTIFICATION IS REQUIRED BEFORE REGISTRATION**
**ADVANCED MRI SCANNER CERTIFICATION IS REQUIRED BEFORE REGISTRATION**
**FOR ADVANCED-IMAGING SITES**

_____ 1. Name of institutional person registering this case?

_____(Y) 2. Has the Eligibility Checklist (above for step 1) been completed?

_____(Y) 3. Will the patient's tissue be submitted for central review?

_____ 4. Date the patient provided study-specific consent prior to study entry

_____ 5. Patient's Initials (First Middle Last)

_____ 6. Verifying Physician
Due to the blinded nature of this study, with drug being provided through the Pharmaceutical Management Branch (PMB) of the NCI, extreme accuracy and consistency of physician information are required to achieve accurate and timely drug shipments. The shipping address for each per-patient shipment is automatically retrieved from the physician-specific information provided on the site's most recent Supplemental Investigator Data Form (IDF) on file with the PMB. (Please see Section 7.6.3.2 for detailed instructions related to IDF maintenance.) Please be certain the address of the local verifying physician you select from the drop down menu during registration is consistent with where the drug is expected to be received and that the physician has a valid NCI (CTEP ID) number. Please also be consistent in identifying the same verifying physician at each registration step [A0 (Step 1), A2 (Step 2), and A3 (Step 3)].

_____ 7. Patient's ID Number

_____ 8. Date of Birth

_____ 9. Race

_____ 10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)

_____ 11. Gender

_____ 12. Patient's Country of Residence

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

_____ 14. Patient's Insurance Status

_____ 15. Will any component of the patient's care be given at a military or VA facility?

_____ 16. Calendar Base Date

_____ 17. Registration/randomization date: This date will be populated automatically.

_____(Y/N) 18. Is the patient going to be treated with IMRT?

**RTOG Institution #**
**RTOG 0825**
**Case #**
*(assigned in Step 1)*

**ELIGIBILITY CHECKLIST—STEP 2** (8/2/10)


_____(Y) 1. Does the patient have histopathologically confirmed glioblastoma or gliosarcoma (WHO Grade IV) **confirmed by central pathology tissue screening**?

_____(Y) 2. Does the patient have tumor tissue that is **determined by central pathology tissue screening** to be of sufficient size for analysis of MGMT status and determination of molecular profile (as described in Section 10.2 and Appendix IV)?

_____(Y) 3. Does the tumor have a supratentorial component?

_____(Y) 4. Was a history/physical examination done within 14 days prior to registration?

_____(Y) 5. Has the patient recovered from the effects of surgery, postoperative infection, and other complications prior to study registration?

_____(Y) 6. Was a diagnostic contrast-enhanced MRI of the brain performed preoperatively and postoperatively prior to the initiation of radiotherapy?

_____(Y) 7. Was the postoperative scan performed within 28 days prior to step 1 registration?

_____(Y) 8. Was an MRI or CT scan (potentially in addition to the postoperative scan) obtained within 10 days prior to the start of radiation therapy that did not demonstrate significant postoperative hemorrhage defined as > 1 cm diameter of blood? If > 1 cm of acute blood is detected, the patient will be ineligible for this trial. The radiation planning MRI or CT scan may be used to determine presence of hemorrhage.
**DATE OF SCAN _____**

_____(Y) 9. Is there documentation of steroid doses or absence of ongoing steroid treatment within 14 days prior to registration?

_____(Y) 10. Is the Karnofsky performance status ≥ 70?

_____(Y) 11. Is the patient's age ≥ 18?

_____(Y) 12. Was a CBC/differential obtained within 14 days prior to registration on study, with adequate bone marrow function defined as follows:

- Absolute neutrophil count (ANC) ≥ 1,800 cells/$mm^3$
- Platelets ≥ 100,000 cells/$mm^3$
- Hemoglobin ≥ 10.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 10.0 g/dl is acceptable)

_____(Y) 13. Is there adequate renal function, as defined below:

- BUN ≤ 30 mg/dl within 14 days prior to study registration
- Creatinine ≤ 1.7 mg/dl within 14 days prior to study registration
- Urine protein screened by urine analysis for urine protein creatinine (UPC) ratio. For UPC ratio > 0.5, 24-hour urine protein should be obtained and the level should be < 1000 mg.

_____(Y) 14. Is there adequate hepatic function, as defined below:
- Bilirubin ≤ 2.0 mg/dl within 14 days prior to study registration
- ALT/AST ≤ 3 x normal range within 14 days prior to study registration

_____(Y) 15. Is the systolic blood pressure ≤ 160 mg Hg or diastolic pressure ≤ 90 mg Hg within 14 days prior to study registration?

_____(Y) 16. Was an electrocardiogram without evidence of acute cardiac ischemia done within 14 days prior study registration?

_____(Y) 17. Was prothrombin time/international normalized ratio (PT INR) < 1.4 for patients not on warfarin confirmed by testing within 14 days prior to study registration?

_____(Y/N) 18. Is the patient on full-dose anticoagulants (e.g., warfarin or low molecular weight heparin)?

_____(Y) 19. If yes, does the patient 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

_____(Y/N) 20. Did the patient provide study-specific informed consent prior to study entry?

_____(Y/NA) 21. Is this patient female and of child-bearing potential?
_____(Y) If yes, was a negative serum pregnancy test within 14 days prior to registration?

_____(Y/N) 22. Has the patient had prior invasive malignancy?
_____(Y) If yes, has the patient been disease free for >3 years?

_____(N) 23. Is the tumor a recurrent or multifocal malignant glioma?

_____(N) 24. Is there metastases detected below the tentorium or beyond the cranial vault?

_____(N) 25. Has there been prior use of chemotherapy or radiosensitizers for cancers of the head and neck region? Note that prior chemotherapy for a different cancer is allowable. Prior use of Gliadel wafers or any other intratumoral or intracavitary treatment are <u>not</u> permitted.

_____(N) 26. Has there been prior radiotherapy to the head or neck (except for T1 glottic cancer)?

_____(N) 27. Does the patient have severe, active co-morbidity, as defined below?

- Unstable angina and/or congestive heart failure within the last 6 months
- Transmural myocardial infarction within the last 6 months
- Evidence of recent myocardial infarction or ischemia by the findings of S-T elevations of ≥ 2 mm using the analysis of an EKG performed within 14 days of registration
- New York Heart Association grade II or greater congestive heart failure requiring hospitalization within 12 months prior to registration
- History of stroke, cerebral vascular accident (CVA) or transient ischemic attack within 6 months
- Serious and inadequately controlled cardiac arrhythmia
- Significant vascular disease (e.g., aortic aneurysm, history of aortic dissection) or clinically significant peripheral vascular disease
- Evidence of bleeding diathesis or coagulopathy
- Serious or non-healing wound, ulcer, or bone fracture or history of abdominal fistula, gastrointestinal perforation, intra-abdominal abscess major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to registration, with the exception of the craniotomy for tumor resection.
- 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 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.
- Active connective tissue disorders, such as lupus or scleroderma, that in the opinion of the treating physician may put the patient at high risk for radiation toxicity.
- Any other major medical illnesses or psychiatric impairments that in the investigator's opinion will prevent administration or completion of protocol therapy.

_____(N) 28. Has the patient been treated on any other therapeutic clinical protocols within 30 days prior to study entry or during participation in the study?

_____(N) 29. Has the patient been treated with temozolomide, bevacizumab, Gliadel wafers or any other intratumoral or intracavitary treatment?

_____(Y/N) 30. Is the **SITE** participating in the ACRIN 6686 advanced imaging component

_____(Y/N) If yes, did the **PATIENT** agree to participate in the ACRIN 6686 advanced imaging component?

If YES:

_____(N) Is the patient unable to undergo MRI (e.g., due to safety reasons, such as presence of a pacemaker)?

**The following questions will be asked at Study Registration for STEP 2 Registration**:

_____ 1. Name of institutional person registering this case

_____(Y/N) 2. Is the patient going to receive protocol treatment?
_____If no, provide the reason the patient cannot continue to Step 2:
1) progression of disease
2) patient refusal
3) physician preference
4) death
5) toxicity
6) other complicating disease
7) other, specify: _____

_____ 3. Patient's Initials (First Middle Last)

_____ 4. Verifying Physician
Due to the blinded nature of this study, with drug being provided through the Pharmaceutical Management Branch (PMB) of the NCI, extreme accuracy and consistency of physician information are required to achieve accurate and timely drug shipments. The shipping address for each per-patient shipment is automatically retrieved from the physician-specific information provided on the site's most recent Supplemental Investigator Data Form (IDF) on file with the PMB. (Please see Section 7.6.3.2 for detailed instructions related to IDF maintenance.) Please be certain the address of the local verifying physician you select from the drop down menu during registration is consistent with where the drug is expected to be received and that the physician has a valid NCI (CTEP ID) number. Please also be consistent in identifying the same verifying physician at each registration step [A0 (Step 1), A2 (Step 2), and A3 (Step 3)].

_____ 5. Patient's ID Number

_____ 6. Calendar Base Date (for Step 2)

_____ 7. Registration/randomization date: This date will be populated automatically (for Step 2)

_____(Y) 8. Has the Eligibility Checklist (in Step 2 above) been completed?

_____ 9. Medical oncologist

_____(Y/N) 10. Tissue/Blood/Urine kept for cancer research?

_____(Y/N) 11. Tissue/Blood/Urine kept for medical research?

_____(Y/N) 12. Allow contact for future research?

_____(Y/N) 13. Did the patient agree to participate in the quality of life component of the study?
_____If no, provide the reason from the following:
1) Patient refused due to illness
2) Patient refused for other reason: specify _____
3) Not approved by institutional IRB
4) Tool not available in patient's language
5) Other reason: specify_____

_____(Y) 14. Was an MRI or CT scan (potentially in addition to the postoperative scan) obtained within 10 days prior to the start of radiation therapy that did not demonstrate significant postoperative hemorrhage defined as > 1 cm diameter of blood? If > 1 cm of acute blood is detected, the patient will be ineligible for this trial. The radiation planning MRI or CT scan may be used to determine presence of hemorrhage.
**DATE OF SCAN** _____

_____(Y/N) 15. Is the **SITE** participating in the ACRIN 6686 advanced imaging component?
_____(Y/N) If yes, did the **PATIENT** agree to participate in the ACRIN 6686 advanced imaging component?
If YES:

_____(N) 16. Is the patient unable to undergo MRI (e.g., due to safety reasons, such as presence of a pacemaker)?

The Eligibility Checklist must be completed in its entirety prior to 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 _____

**RTOG Institution #**
**RTOG 0825**
**Case #**
*(assigned in Step 1)*

**ELIGIBILITY CHECKLIST-STEP 3** (8/27/09)
**(page 1 of 1)**

**The following questions will be asked at Study Registration for STEP 3 Registration**:

_____ 1. Name of institutional person registering this case

_____(Y/N) 2. Is the patient going to receive protocol treatment?
_____If no, provide the reason the patient cannot continue to Step 3:
1) progression of disease
2) patient refusal
3) physician preference
4) death
5) toxicity
6) other complicating disease
7) other, specify: _____

_____ 3. Patient's Initials (First Middle Last)

_____ 4. Verifying Physician
Due to the blinded nature of this study, with drug being provided through the Pharmaceutical Management Branch (PMB) of the NCI, extreme accuracy and consistency of physician information are required to achieve accurate and timely drug shipments. The shipping address for each per-patient shipment is automatically retrieved from the physician-specific information provided on the site's most recent Supplemental Investigator Data Form (IDF) on file with the PMB. (Please see Section 7.6.3.2 for detailed instructions related to IDF maintenance.) Please be certain the address of the local verifying physician you select from the drop down menu during registration is consistent with where the drug is expected to be received and that the physician has a valid NCI (CTEP ID) number. Please also be consistent in identifying the same verifying physician at each registration step [A0 (Step 1), A2 (Step 2), and A3 (Step 3)].

_____ 5. Patient's ID Number

_____ 6. Calendar Base Date (for Step 3)

_____ 7. Registration/randomization date: This date will be populated automatically (for Step 3)

_____ 8. Patient's weight in kg

**NOTE:** Sites participating through CTSU must apply for an RTOG username and password **immediately after registering**, to enable access to the Neurocognitive Training Procedure Letter on the 0825 forms section of the RTOG website. A user name and password can be obtained by completing the Password Authorization Form at www.rtog.org/members/webreg.html. See the CTSU logistics appendix for details.

# 1.0 INTRODUCTION

## 1.1 Overview

The prognosis for patients with glioblastoma remains grim, with most studies reporting a median survival of 10 to 12 months (Grossman and Batara 2004). These statistics have remained nearly unchanged since the seminal studies in the 1970s that confirmed the efficacy of external beam radiation. (Walker, Alexander et al. 1978) In those studies, the addition of chemotherapy (a nitrosourea) did not statistically improve survival compared with patients receiving radiation alone. At 2 years, less than 10% of patients were alive (Walker, Green et al. 1980). Subsequent meta-analyses of randomized trials of radiation versus radiation plus a nitrosourea-containing regimen showed only a modest improvement in 1-year survival in the patients receiving the combination regimen (Fine, Dear et al. 1993; Stewart 2002). However, Stupp and colleagues (Stupp, Dietrich et al. 2002) performed a phase II trial in patients with newly diagnosed glioblastoma, administering a daily lower dose (75 mg/m$^2$) of temozolomide every day during the course of radiation therapy, followed by 6 months of adjuvant chemotherapy at the standard single-agent dose of 200 mg/m$^2$ for days 1 to 5 of a 28-day cycle. These phase II results were promising, demonstrating an overall median survival of 16 months.

These results stimulated interest in a confirmatory phase III trial. This study, performed by the European Organisation for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC), randomized patients with newly diagnosed glioblastoma to receive either radiation therapy alone or concurrent radiation and temozolomide followed by 6 months of adjuvant temozolomide. The study demonstrated a statistically significant improvement in median survival for the combination treatment arm (12.1 vs 14.6 months) as well as a significant increase in 2-year survival (10% vs 26%). Eighty-eight percent of the patients received the full course of concurrent temozolomide with radiation. Approximately 40% of patients received the full 6 cycles of temozolomide after the completion of the radiation (adjuvant therapy). Tumor progression was the most prominent cause of treatment cessation. The chemoradiation treatment was well tolerated, with an incidence of grade 3 or 4 hematologic toxicity of < 4%. The results of this trial were first presented at ASCO in June 2004, with the full report published in the *New England Journal of Medicine* (Stupp, Mason et al. 2005). This chemoradiation regimen has been widely accepted as the new standard of care for patients with newly diagnosed glioblastoma. An update from this trial was presented at the 2007 meeting of the American Society for Therapeutic Radiology and Oncology, demonstrating a 10% 5-year survival rate in patients treated with the chemoradiation regimen and providing additional evidence of the efficacy of this therapy.

Additionally, correlative laboratory studies were performed using tumor tissue from patients enrolled on this clinical trial. An analysis of data evaluating the impact of MGMT expression on response and survival has demonstrated a correlation between methylation (inactivation) of the MGMT gene and response as well as overall prognosis (Hegi, Diserens et al. 2005). A statistically significant difference in outcome was found when MGMT gene promoter status was evaluated as an independent factor in the patients on the temozolomide-radiation arm. Patients with tumors demonstrating methylation of the MGMT gene had a significant improvement in median survival as well as in 2-year survival rate (46% vs 14%). These findings, along with the prior laboratory data demonstrating MGMT expression in tumors as a major mechanism of resistance to alkylating agents, strongly support the impact of MGMT expression on response to temozolomide in patients with glioblastoma. Given the potential prognostic importance of MGMT promoter methylation status in glioblastoma, several clinical trials are evaluating this marker as a randomization stratification factor. This evaluation mandates collection of tumor tissue blocks at study entry.

### 1.1.1 Angiogenesis and invasion in glioblastoma

Available treatments have been limited by problems with delivery to the tumor because of widespread tumor infiltration, the blood-brain barrier, and the rapid development of resistance to conventional cytotoxic agents. Therefore, there has been great interest in targeting the angiogenesis that is a prominent feature of the malignant gliomas, particularly the glioblastoma. Prior studies suggest that targeting the endothelial cells involved in tumor angiogenesis is not hampered by the development of resistance (Lund, Spang-Thomsen et al. 1998). Further, some antiangiogenic treatments have been associated with the development of apoptosis within the tumor cells themselves.

The two processes, angiogenesis and tumor cell invasion, are closely associated. In gliomas, vascular endothelial growth factor (VEGF) promotes both angiogenesis and invasion of tumor cells (Machein and Plate 2000). "Invasion" of endothelial cells into the tumor is an important component of the angiogenic process. Early clinical trials attempted to block the VEGF signal transduction pathway, usually by inhibiting the VEGF receptor and/or the downstream pathway. A variety of treatments including monoclonal antibody against the receptor and small molecule receptor tyrosine kinase inhibitors have been used, with only modest success in the treatment of systemic cancers. These approaches have shown even less efficacy in the treatment of glioblastoma, likely due to limited drug delivery to the target receptor at clinically relevant concentrations and target competition with the natural ligand. A treatment that utilizes an intravascular approach would eliminate the concerns regarding drug delivery through the blood-brain or blood-tumor barrier. Bevacizumab is a humanized monoclonal antibody against VEGF (VEGF-A) (Ferrara, Hillan et al. 2005). Intravenous administration of this agent has been shown to rapidly reduce the concentration of VEGF in the circulation. Extensive investigations of bevacizumab clearly demonstrate anticancer activity in a variety of systemic cancers, including renal cell carcinoma, non-small cell lung cancer, and colorectal cancer (Yang, Haworth et al. 2003; Hurwitz, Fehrenbacher et al. 2004; Willett, Boucher et al. 2004; Miller, Chap et al. 2005).

In most studies, bevacizumab was used in combination with traditional cytotoxic agents. Randomized trials suggest that there is benefit in combining bevacizumab with cytotoxic chemotherapy drugs compared with the cytotoxic regimen alone (Gille 2006). Although the mechanism of treatment enhancement is unknown, two main hypotheses have been proposed. The first hypothesis states that there is a synergy of activity with the cytotoxic chemotherapy along with the removal of circulating VEGF leading to endothelial cell apoptosis. The second hypothesis proposes that bevacizumab selectively inhibits angiogenesis and results in the loss of markedly aberrant and tortuous intratumoral neovasculature, causing a paradoxical improvement in perfusion and delivery of the cytotoxic agent to the tumor cells. Available data support both theories, and both mechanisms may be responsible for the proven benefit of bevacizumab in the wide spectrum of cancers tested to date.

There have been small series and anecdotal reports of patients with recurrent malignant glioma, predominantly glioblastoma, who have been treated with the combination of irinotecan and bevacizumab (Stark-Vance 2005; Vredenburgh, Desjardins et al. 2007). A high objective response rate has been noted, and in some cases the responses appear to be durable. For example, a recent phase II study in patients with recurrent glioblastoma combined bevacizumab with irinotecan (Vredenburgh, Desjardins et al. 2007). The investigators reported a 57% objective response rate and a 6-month progression-free survival rate of 46%. The results of both studies compare very favorably with single-agent temozolomide in patients with no prior temozolomide exposure, where objective tumor responses were reported in less than 6% of patients and the 6-month progression-free survival rate was 21% (Yung, Albright et al. 2000). Despite concerns regarding the potential for intratumoral hemorrhages, particularly in light of an early report of bleeding in a brain metastasis in a patient on a clinical trial with bevacizumab, the preliminary reports suggest that this complication is infrequent in gliomas. Similarly, the large trials of bevacizumab in colorectal, lung, and breast cancer suggest an increase in vascular thrombotic events, although the excess numbers appear to be arterial thromboses. Again, this problem has not been identified in the brain tumor population treated with bevacizumab.

A recent phase II study randomized patients with recurrent GBM to treatment with either bevacizumab alone or bevacizumab with CPT-11 (Cloughesy, Prados et al. 2008). A total of 163 patients were enrolled. Treatment was well tolerated; the most common serious adverse events were hypertension (8% in bevacizumab alone arm, 1% in the combination arm), fatigue (5% in bevacizumab alone arm and 6% in the combination arm), deep venous thrombosis (4% in bevacizumab alone and 8% in the combination

arm), and neutropenia (1% in bevacizumab alone and 9% in the combination arm). Overall response rate, as determined by independent radiology review, was 20% in the bevacizumab alone arm and 33% with the combination. The 6-month progression-free survival rate was 35% for bevacizumab alone and 50% for the combination. Although the study was not statistically powered to compare the two arms, these results suggest a response and progression-free rate benefit to the combination of bevacizumab with a cytotoxic agent.

Laboratory and clinical imaging studies also support the potential role of antiangiogenic agents in combination with both radiation therapy and chemotherapy (Batchelor, Sorensen et al. 2007). Contrary to the early concerns that these agents would markedly reduce blood flow and therefore delivery of oxygen (for radiation-induced free radical formation) and delivery of chemotherapy, studies now clearly demonstrate that antiangiogenic agents cause vascular normalization (Jain 2005). Tumors typically demonstrate extensive neovascularization that is characterized by tortuous vessels, poorly formed basement membranes, and often by saccular structures (dead ends) and large gaps between endothelial cells. Antiangiogenic agents have been shown to eliminate many of these poorly formed vascular components, resulting in an overall enhancement of blood supply to the tumor through a process called "vascular normalization."

## 1.2 Bevacizumab

### 1.2.1 Overview

Bevacizumab is a humanized IgG1 monoclonal antibody (MAb) that binds all biologically active isoforms of human VEGF(or VEGF-A) with high affinity ($k_d$ = 1.1 nM )(Presta, Chen et al. 1997). 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(Kim, Li et al. 1993; Presta, Chen et al. 1997; Brochure 2006).

### 1.2.2 Mechanism of Action

VEGF is one of the most potent and specific angiogenic factors, and it has been identified as a crucial regulator of both normal and pathological angiogenesis. VEGF is a secreted, heparin-binding protein that exists in multiple isoforms. Action of VEGF is primarily mediated through binding to the receptor tyrosine kinases VEGFR-1 (Flt-1) and VEGFR-2 (KDR/Flk-1). The biologic effects of VEGF include endothelial cell mitogenesis and migration, increased vascular permeability, induction of proteinases leading to remodeling of the extracellular matrix, and suppression of dendritic cell maturation. Neutralization of VEGF by A.4.6.1 or bevacizumab has been shown to inhibit the VEGF-induced proliferation of human endothelial cells in vitro and to decrease microvessel density and interstitial pressure in tumor xenografts in vivo. Preliminary results from a neoadjuvant trial in patients with rectal cancer demonstrated a decrease in blood perfusion/permeability and interstitial fluid pressure in tumors after one dose of bevacizumab (Willett, Boucher et al. 2004).

### 1.2.3 Preclinical Studies

The murine parent MAb of bevacizumab, A4.6.1, has demonstrated potent growth inhibition in vivo in a variety of human cancer xenograft and metastasis models, including those for SK-LMS-1 leiomyosarcoma, G55 glioblastoma multiforme, A673 rhabdomyosarcoma, Calu-6, and MCF-7 cell lines (Kim, Li et al. 1993; Presta, Chen et al. 1997; Borgstrom, Gold et al. 1999). The antitumor activity was enhanced with the combination of A4.6.1 and chemotherapeutic agents compared to either agent alone. Furthermore, combined blockage of the VEGF pathway and other growth factor pathways (e.g., EGFR or PDGFR) has also demonstrated additive effects in vivo (Shaheen, Ahmad et al. 2001; Bergers, Song et al. 2003). Associated with the antitumor activity of anti-VEGF MAbs were findings of reduced intratumoral endothelial cells and microcapillary counts as well as reduced vascular permeability and interstitial pressure

Nonclinical toxicology studies have examined the effects of bevacizumab on female reproductive function, fetal development, and wound healing. Fertility may be impaired in cynomolgus monkeys administered bevacizumab, which led to reduced uterine weight and endometrial proliferation as well as a decrease in ovarian weight and number of corpora lutea. Bevacizumab is teratogenic in rabbits, with increased frequency of fetal resorption as

well as specific gross and skeletal fetal alterations. In juvenile cynomolgus monkeys with open growth plates, bevacizumab induced physeal dysplasia that was partially reversible upon cessation of therapy. Bevacizumab also delays the rate of wound healing in rabbits, and this effect appeared to be dose dependent and characterized by a reduction of wound tensile strength.

**1.2.4** Clinical Studies

To date, over 3000 patients have been treated in clinical trials with bevacizumab as monotherapy or in combination regimens (Brochure 2006). The pharmacokinetics of bevacizumab have been characterized in several phase I and II clinical trials, with doses ranging from 1 to 20 mg/kg administered weekly, every 2 weeks, or every 3 weeks. The estimated half-life of bevacizumab is approximately 21 days (range 11-50 days). The predicted time to reach steady state was 100 days. The volume of distribution is consistent with limited extravascular distribution. The maximum tolerated dose of bevacizumab has not been determined; however, the dose level of 20 mg/kg was associated with severe headaches (Cobleigh, Langmuir et al. 2003). The dose schedule of either 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks is used in most phase II or III trials with only a few exceptions (e.g., the pivotal phase III trial in colorectal cancer, in which bevacizumab was given at 5 mg/kg every 2 weeks).

Clinical proof of efficacy for anti-VEGF therapy with bevacizumab has been provided by the pivotal phase III trial of bevacizumab (5 mg/kg every 2 weeks) in combination with bolus irinotecan/5-fluorouracil/leucovorin (IFL) in patients with untreated advanced colorectal cancer (Hurwitz, Fehrenbacher et al. 2004). In that study, the addition of bevacizumab to IFL was associated with an increase in objective responses (45% vs. 35%) and significant prolongations of both time to progression (10.6 vs. 6.2 months) and overall survival (20.3 vs. 15.6 months) compared with IFL. However, in the phase III trial in previously treated metastatic breast cancer, the addition of bevacizumab to capecitabine did not show a difference in time to progression despite an increase in the response rate from 9% to 20% (Miller, Chap et al. 2005).

Bevacizumab has also been studied in renal cell cancer. In a 3-arm, double-blind, placebo-controlled phase II trial, patients with previously treated stage IV renal cell cancer were randomized to high-dose bevacizumab (10 mg/kg every 2 weeks), low-dose bevacizumab (3 mg/kg every 2 weeks), or placebo (Yang, Haworth et al. 2003). The study demonstrated a highly significant prolongation of time to progression in the high-dose arm (4.8 months) compared with the placebo (2.6 months) (hazard ratio = 2.55, p = 0.0002); the low-dose arm was associated with a smaller difference in time to progression (3.0 months) of borderline significance. The tumor response rate was 10% in the high-dose arm but was 0% in the low-dose and placebo groups.

Additional clinical trials are ongoing in a variety of solid tumors and hematologic malignancies using bevacizumab as monotherapy or in combination with chemotherapy, radiation, or other targeted/biologic agents. Clinical trials have been reported using bevacizumab in combination with irinotecan to treat patients with recurrent malignant glioma.

Stark-Vance reported the first study in 2004 at the World Federation of Neuro-Oncology. Twenty-one patients were treated and an objective response rate, as determined by changes in cross-sectional area was demonstrated (Stark-Vance 2005). Treatment was reportedly well tolerated, although six patients were removed from the study because of medical issues, two of which were believed related to treatment (thrombosis and intestinal perforation). As described above, Vredenburgh and colleagues presented the results of 2 phase II trials from Duke University (Vredenburgh, Desjardins et al. 2007). The investigators reported a 57% objective response rate and a 6-month progression free survival rate of 46%. They report one intracranial hemorrhage among 35 treated patients and 4 incidents of thromboembolic complications.

In addition to the phase II study described above in patients with recurrent glioma, bevacizumab has been evaluated with concurrent radiation therapy and temozolomide. Preliminary data from the study by Lai and colleagues suggest that this combination is moderately well tolerated, although initiation of this combination regimen within 3 weeks of

craniotomy and tumor resection may be associated with a higher rate of wound healing problems (Lai, Filka et al. 2008). A more recent update of toxicity from the initial 52 patients of the planned 70 on this trial is provided in the table below:

Preliminary Toxicity Profile From the UCLA Clinical Trial

Number of patients in report 52 (of a planned 70 patient accrual)

| **Toxicity** | **Grade 3** | **Grade 4** |
|---|---|---|
| Bowel perforation | - | 2 |
| Fatigue | 1 | - |
| Gastrointestinal bleed | 2 | - |
| Renal failure | - | 4 |
| Craniotomy wound dehiscence/infection | 4 | - |
| Pulmonary embolus or deep vein thrombosis | 1 | 2 |
| Leukopenia | - | 1 |
| Neutropenia | - | 1 |
| Thrombocytopenia | - | 1 |
| Retinal detachment | 1 | - |
| Optic Neuropathy | - | 1 |
| Hypertension | 1 | - |

### 1.3 Temozolomide Overview

Temozolomide, an oral alkylating agent with good penetration of the central nervous system, has been evaluated in patients with glial malignancies. Initial studies evaluated the efficacy of temozolomide in patients with recurrent glioblastoma and anaplastic glioma. A large, randomized phase II study by Yung and colleagues treated patients with recurrent glioblastoma with either temozolomide (200 mg/m$^2$ days 1-5 of a 28-day cycle) or procarbazine (150 mg/m$^2$ 28 day-on, 28-day off schedule) (Yung, Albright et al. 2000). The study demonstrated only a modest objective response rate for both regimens (approximately 5%), but a superior 6-month progression-free survival rate for temozolomide (21% vs. 9%) was found. In the pre-radiation setting, a phase II study demonstrated a good objective response rate (complete plus partial response = 41%) in patients with glioblastoma during the four monthly cycles of treatment, using 200 mg/m$^2$ on days 1 to 5 of a 28-day cycle. However, the responses were not durable in many cases and the median progression-free survival rate was 3.8 months. Overall survival for patients on this study was 13.1 months, similar to most reports of treatment in newly diagnosed patients. This suggests that the neoadjuvant temozolomide chemotherapy likely had little overall benefit. However, these results did demonstrate definite activity of temozolomide for glioblastoma (Gilbert, Friedman et al. 2002).

There were no published studies using temozolomide as a post-radiation adjuvant treatment. As described above, Stupp and colleagues (Stupp, Dietrich et al. 2002) performed a phase II trial in patients with newly diagnosed glioblastoma, administering a daily lower dose (75 mg/m$^2$) of temozolomide every day during the course of radiation therapy, followed by 6 months of adjuvant chemotherapy at the standard single-agent dose of 200 mg/m$^2$ for days 1 to 5 of a 28-day cycle. These phase II results were promising, demonstrating an overall median survival of 16 months and stimulating interest in a confirmatory phase III trial. This study, performed by the EORTC and the NCIC, randomized patients with newly diagnosed glioblastoma to receive either radiation therapy alone or concurrent radiation and temozolomide followed by 6 months of adjuvant temozolomide. Treatment was well tolerated and the study demonstrated a statistically significant improvement in median survival, progression free survival, and 2-year survival rate for the combination treatment (Hegi, Diserens et al. 2005). This chemoradiation regimen has been widely accepted as the new standard of care for patients with newly diagnosed glioblastoma.

## 1.4 Central Storage of Imaging Studies

Central storage of critical imaging studies is an important component of successfully using a progression-free endpoint. Imaging studies will therefore be collected and stored by the American College of Radiology Imaging Network (ACRIN) in Philadelphia PA, for potential central review.

## 1.5 Health-Related Quality of Life and Neurocognitive Function

Health-related quality of life, symptom burden, and neurocognitive measures have been validated in the brain tumor population as additional indicators of treatment benefit. The EORTC core Quality of Life Questionnaire (QLQ-C30) and a Brain Cancer Module (BCM20) were developed and validated for use in this patient population (Osaba 1996). Extensive health-related quality of life data were obtained during 1 randomized phase II study comparing temozolomide with procarbazine in patients with recurrent glioblastoma (Yung 2000). This study, which used the EORTC QLC-C30/BCM20, demonstrated an improvement in most domains tested.

In addition to the randomized phase II trial described above, the EORTC QLQ-C30/BCM20 has become the standard and has been used in many large cooperative group trials. Recently there has been some concern that health-related quality of life assessments may reflect patient 'response shift,' as they frequently measure patient preferences and adjustment in terms of their function. Symptom assessment measures such as the M.D. Anderson Symptom Inventory Brain Tumor (MDASI-BT) have been specifically developed in patients with primary brain tumors to capture patient self reports of symptom severity and interference with daily activities. It has demonstrated reliability and validity in the primary brain tumor patient population, including predictive validity for tumor recurrence. This tool represents a modification of the widely used and validated MDASI, with particular attention to symptoms common in patients with brain tumors versus patients with stable disease (Armstrong et al., 2006).

Assessment of neurocognitive function provides unique information about neurologic function that frequently is not captured by self-report measures (Cull 1996). Brain tumors affect brain functioning, and interventions such as chemotherapy and radiation therapy may also impact on brain functions. Therefore, tumor recurrence, survival, and time to progression end points in a clinical trial may not fully describe the outcome of an intervention unless added information regarding neurocognitive function, health-related quality of life, and symptom assessments are also considered as therapeutic outcomes. The arguments for including neurobehavioral measures as an index for determining treatment outcomes for brain tumor patients have been recently reviewed (Weitzner 1997). The importance of these measures is underscored by the FDA indicating that 'improvement in neurocognitive function or delay in neurocognitive progression are acceptable endpoints' in clinical trials. Neurocognitive function has been demonstrated to predict tumor progression (Meyers 2003) and to independently predict survival for patients with central nervous system tumors (Meyers 2000, Meyers 2004, Taphoorn 2004). A brief, sensitive, repeatable, highly standardized battery of cognitive tests has been utilized in numerous brain tumor clinical trials (Groves 1999, Levin 2002). This battery has also been demonstrated to be practical in terms of cost and burden to the patient, with good compliance in multicenter trials (Meyers 2004).

Although recent clinical trials have demonstrated an improvement in survival with novel therapeutic regimens, patients diagnosed with GBM have a poor prognosis. An important endpoint in this study is to evaluate the neurocognitive, symptom and quality of life profile across the disease course. This includes assessments during the early phase when the majority of patients may demonstrate a differential treatment effect of one treatment approach relative to the other and during the late period when the subgroup of long term survivors may experience impact on their neurocognitive function, symptoms and quality of life.

Encephalopathy has been reported as an acute adverse side effect in glioma patients treated with bevacizumab and radiation. In addition, leukoencephalopathy has been reported in patients with systemic cancer treated with this agent. This study will provide an opportunity to collect this important data and have a control group that was not treated with this agent. As the incidence of this acute effect and its reversibility have not been defined, continued assessments in the

adjuvant period are warranted. By marrying these assessments with imaging, we will be able to study the correspondence between imaging and non-imaging biomarkers and distinguish changes that are treatment related from those associated with recurrent tumor.

An additional issue with this treatment is the reported change in the pattern of recurrence, from a localized mass to a more infiltrative pattern. The potential neurocognitive and neurologic symptom impact of this change has not yet been defined. Collecting this information on long-term survivors on this trial will provide an opportunity to document any impact on neurocognitive function, symptoms, and quality of life.

Although recent clinical trials have demonstrated an improvement in survival with novel therapeutic regimens, patients diagnosed with GBM have a poor prognosis. Management of these patients is complex, partly related to the neurologic sequelae of the disease and treatment. Building on the positive results of RTOG 0525, the availability of validated instruments provides an opportunity to prospectively assess the direct impact of treatment, both positive and negative, on patients. The evaluation of symptom burden, health-related quality of life, and neurocognitive function will assist in determining the net clinical benefit of this treatment approach.

## 1.6 Summary

This study represents a logical successor trial to the ongoing phase III trial, RTOG 0525, which compares conventional adjuvant temozolomide with dose-dense temozolomide (21 of 28 day schedule) in patients with newly diagnosed glioblastoma or gliosarcoma. RTOG 0525 is an international collaborative effort involving the RTOG, EORTC, and the NCCTG. Accrual has been robust, with the current accrual rate of over 60 patients per month. In addition, eligibility requirements mandate that a tumor tissue block be provided at the time of study entry to perform the MGMT gene promoter methylation analysis for stratification. Despite this potentially burdensome mandate, accrual has exceeded expectations.

Since the launching of RTOG 0525, there have been advances in identifying molecular profiles that may predict outcome independently of clinical factors and MGMT methylation status. As described in Section 13 the expression profile of the 9 genes may identify subcategories of tumor, distinguishing a “mesenchymal/angiogenic” profile from a proneural profile. Incorporation of this profile into the stratification design will balance the two treatment arms for this important prognostic factor and may permit prospective determination of optimal therapy based on tumor specific profiles.

## 1.7 ACRIN 6686 Advanced Imaging Component: Magnetic Resonance Perfusion and Dynamic Contrast-Enhanced Magnetic Resonance Imaging Overview (7/20/09)

Structural magnetic resonance imaging (MRI) remains the standard for assessment of glioblastoma and for assessment of treatment response. Specifically, contrast-enhanced T1-weighted MRI (using a gadolinium chelate as the contrast agent) allows the assessment of the integrity of the blood-brain barrier; enhancement indicates micro-structural disruption. The Macdonald criteria (Macdonald 1990) for response assessment are applied to post-gadolinium T1-weighted MRI in most studies of glioblastoma (primary or recurrent).

While it has become a mainstay for patient assessment, structural MRI typically provides little physiological information, particularly information about tumor angiogenesis. This is of prime interest in this trial given the mechanism of action of bevacizumab. Therefore, a subset of sites will perform baseline advanced imaging, including perfusion magnetic resonance (also called dynamic susceptibility-contrast or DSC-MRI) and dynamic contrast-enhanced MRI (DCE-MRI).

Of particular interest is whether baseline tumor angiogenesis levels, as measured by perfusion MRI, correlate with response to antiangiogenic therapy. Perfusion MRI can provide estimates of cerebral blood volume (CBV), blood flow, and—with certain methods—an estimate of average blood vessel size. Perfusion MRI therefore may be able to identify patient populations particularly likely or unlikely to respond to bevacizumab treatment. Specifically, high CBV (defined as CBV greater than 1.75 times normal brain CBV) at baseline has been shown to correlate with shorter survival independent of tumor grade (Law 2008), and degree of CBV has been shown to correlate with response to radiation therapy (Cao 2006). An imaging biomarker related to CBV would be

extremely valuable for patient selection and/or prognosis. Furthermore, there is some evidence that DCE-MRI, as quantified by the parameter $K^{trans}$, shows early changes after the initiation of anti-VEGF therapy (Batchelor 2007, Sorensen 2009). Early single-center data suggest the possibility of an early biomarker of response—that early changes in $K^{trans}$ correlate with survival.

Further, imaging tools have the potential to:

- Provide additional information about the microenvironment in and around the tumor;
- Identify regression of cancer markers suggestive of functional changes in the tumor;
- Quantify the passage of a contrast agent through the vessel wall of the tumor tissue (DCE-MRI in combination with DSC-MRI);
- Provide estimates of blood flow, blood volume, and (with certain methods) average blood vessel size;
- Measure vasogenic and cytotoxic edema;
- In certain settings, identify early changes that suggest cytotoxicity.

## 1.8 Biomarker, Imaging, Quality of Life Study Funding Program: Exploration of Imaging Response Criteria—A Companion Study to RTOG 0825/ACRIN 6686

(8/2/10)

Clinical trials using traditional cytotoxic therapies generally determine drug efficacy by assessing tumor response based on measures of tumor regression by computed tomography (CT) or MRI radiographic studies. Agents that produce a radiographic response are considered effective, either by a decrease in the size of the mass or stabilization of tumor growth. This assessment for cytotoxic drugs has proven to be adequate, as tumor regression has been correlated with prolonged survival (Eisenhauer et al, 1998). Cytostatic drugs that have specific molecular targets present a different challenge for clinicians. The use of imaging for the assessment of response to both cytotoxic and cytostatic therapies is now undergoing intense investigation and change. Advanced imaging modalities and algorithms are being used as biomarkers and surrogates for response assessment in oncology. With these technological advancements, a more accurate overall assessment of response to treatment is needed to determine the correlation between the size threshold change and survival.

### 1.8.1 Response Assessment: The Macdonald Criteria

In 1990, Macdonald et al recommended imaging-based criteria for response assessment in clinical trials of new therapies for malignant gliomas (Macdonald et, 1990). These criteria were modeled after guidelines used in general oncology, defined response as a measurable change in the size of the tumor, which, for convenience, has been generally assessed as the maximum cross-sectional tumor area. The criteria identified four "response" categories:

- Complete Response (CR): disappearance of all enhancing tumor on consecutive computed tomography or magnetic resonance imaging scans at least 1 month apart, off steroids, and neurologically stable or improved.
- Partial Response (PR): ≥50% reduction in size of enhancing tumor on consecutive CT or MRI scans at least 1 month apart, steroids stable or reduced, and neurologically stable or improved.
- Progressive Disease (PD): ≥25% increase in size of enhancing tumor or any new tumor on CT or MRI scans, or neurologically worse, and steroids stable or increased.
- Stable Disease (SD): all other situations.

Under this paradigm, response categorization is determined on the basis of changes in the cross-sectional area of a tumor on neuro-imaging (most typically MRI), coupled with both the clinical assessment of neurological status and corticosteroid utilization. The Macdonald criteria have been a useful guide to response assessment in the context of phase II trials of cytotoxic chemotherapies for recurrent malignant gliomas and facilitated communication in the comparison of clinical results. The criteria also marked the transition from a subjective interpretation of clinical and radiologic changes toward more objective based criteria (i.e., one that is auditable and less susceptible to local inadvertent bias). However, it has become apparent that the Macdonald criteria have certain shortcomings.

### 1.8.2 Shortcomings of the Macdonald Criteria

The current approach to determine response criteria was based on size changes. Unfortunately, the irregular shape of gliomas, which infiltrate the surrounding tissue and lack a more common spheroid shape found in other solid mass tumors, make measurement difficult. Furthermore, the criteria relied primarily on CT–based two-dimensional WHO response criteria and that two decades ago, found volume measurements were too technically difficult and "not the wisest choice for response assessment" (Macdonald et al, 1990). Technological advances have now established that volumetric assessment is feasible and more accurate than cross-sectional assessment (Chisholm et al, 1989; Sorensen et al, 2008). Additionally, the core of Macdonald's criteria includes changes in enhancement, which can be nonspecific and primarily reflects a disrupted blood-brain barrier. Enhancement can also be influenced by changes in corticosteroid dose and radiologic technique (Sorensen et al, 2008; Prados et al, 2006). A variety of non-tumoral processes (e.g., inflammation, seizure activity, postsurgical changes, and radiation necrosis) can also induce enhancement (Batchelor et al, 2007; Stark-Vance et al, 2005; Li et al, 200 ; Chi et al, 2007). As a result, changes in the enhancing area cannot be equated with changes in tumor size or proliferation. Furthermore, the Macdonald criteria assigned arbitrary numbers to the four response categories that have never been correlated to actual overall survival. Recent clinical trials with new targeted agents against gliomas have revealed these significant limitations in the end points used.

Most neuro-oncologists now rely on abnormalities visualized by gadolinium-enhanced MRI to establish response to treatment. Radiographic assessment of response determined by contrast enhancing tumor volume change is problematic with anti-angiogenic therapies (Chamberlain et al, 2009; Kreisl et al, 2009). The normalization of GBM vascularity from bevacizumab therapy results in a decrease of gadolinium contrast enhancement, normalization of tumor blood volume and perfusion, and improvement in peritumoral edema (Desjardins et al, 2008). This effect on edema is not surprising because VEGF is a potent mediator of vascular permeability (Kalbfleisch et al, 2002). Norden et al illustrated that in some cases, failure of antiangiogenic therapy initially appears as an increase in FLAIR signal before re-emergence of contrast enhancement. A recent study in recurrent disease reports an unusually high radiographic response rate (60%) with the combination of bevacizumab and irinotecan (Heagerty et al, 2000; Heagerty et al, 2005). However, it remains unclear whether this increased response rate translates into a true prolongation of survival (Hintze, 2006).

**1.8.3** RTOG 0825/ACRIN 6686: Assessing Important Changes to Volumetric Parameters

RTOG 0825 will collect MRI data in 942 patients with newly diagnosed GBM being treated with chemoradiation with or without bevacizumab targeted therapy. The RTOG 0825 will collect contrast-enhanced MRI pre-treatment, during the adjuvant phase, and after the completion of therapy. Out of this participant group, ACRIN 6686 will collect advanced DSC-MRI and DCE- MRI imaging on a subset of 264 participants. These images will be collected at different time points: prior to chemoradiotherapy, during chemoradiotherapy at early and later timepoints, and post chemoradiotherapy. The RTOG 0825/ACRIN 6686 study provides an ideal population to answer the question of what changes in volumetric parameters are important, with or without anti-VEGF treatments. The goal is to explore correlations between changes over time in size (1-D, 2-D and volumetric measurements) and overall survival. This study will utilize centrally stored images at ACRIN containing standard MRI, DSC-MRI, and DCE-MRI images from the RTOG 0825/ACRIN 6686. This correlation between tumor size by MRI analysis and overall survival will identify new potential biomarkers that may act as future prognostic indicators of disease progression and overall survival.

## 2.0 OBJECTIVES

### 2.1 Primary

To determine whether the addition of bevacizumab to temozolomide and radiation improves efficacy as measured by progression-free and/or overall survival.

### 2.2 Secondary

**2.2.1** To determine whether the tumor molecular profile conferring a mesenchymal/angiogenic phenotype is associated with a selective increase in benefit, as measured by either overall survival or progression-free survival, from the addition of bevacizumab.

**2.2.2** To compare and record the toxicities of the conventional and bevacizumab-containing regimens.

**2.3 Tertiary**

**2.3.1** The primary focus is to determine the differential acute effects associated with the addition of bevacizumab to temozolomide and radiation, as compared to the conventional arm, on measures of neurocognitive function, health-related quality of life, and symptoms during radiation and across the longitudinal progression-free interval..

**2.3.2** To determine the relationship of neurocognitive function, health-related quality of life, and symptoms, with progression-free and overall survival.

**2.3.3** To determine the association between tumor molecular profile (i.e., mesenchymal/angiogenic phenotype and proneural phenotype) and neurocognitive function, health-related quality of life, and symptoms.

**2.3.4** To describe the association between health-related quality of life as measured by the EORTC-QL30/BCM20 and mean symptom severity as measured by the MDASI-BT in patients enrolled in this study.

**2.3.5** To evaluate the relationship between self-reported neurocognitive function and objectively measured tests of NCF.

**2.4 ACRIN 6686 Imaging Objectives** (8/2/10)

**2.4.1** Primary Imaging Objectives

**2.4.1.1** To assess the association between overall survival and $K^{trans}$ change from T1 to T2.

**2.4.1.2** To assess the association between overall survival and spin echo CBV change from T1 to T2.

**2.4.2** Secondary Imaging Objectives

**2.4.2.1** To assess the association between progression-free survival and $K^{trans}$ change from T1 to T2.

**2.4.2.2** To assess the association between progression-free survival and spin echo CBV change from T1 to T2.

**2.4.2.3** To assess the association between values of $K^{trans}$ and spin echo CBV measured separately at T0 and at T1, and overall and progression-free survival.

**2.4.2.4** To assess the association between overall survival and $K^{trans}$ changes from T0 to T1 and from T2 to T3.

**2.4.2.5** To assess the association between overall survival and spin echo CBV changes from T0 to T1 and from T2 to T3.

**2.4.2.6** To assess the association between overall survival and apparent diffusion coefficient (ADC) change from T0 to T1.

**2.4.2.7** To assess the association between overall survival and ADC change from T1 to T2.

**2.4.2.8** To assess the association between progression-free survival and ADC change from T0 to T1.

**2.4.2.9** To assess the association between progression-free survival and ADC change from T1 to T2.

**2.4.2.10** To assess the association between T1 values of ADC and overall and progression-free survival.

**2.4.2.11** To assess the association between change in lesion size between T1 and T3, as measured by advanced MRI, and overall and progression-free survival.

**2.4.3** Aims for Biomarker, Imaging, Quality of Life Study Funding Program Supplement (8/2/10)

**2.4.3.1** To assess the association between measures of change in enhancing tumor size at week 22 and overall survival in participants with glioma receiving chemoradiotherapy with and without bevacizumab.

**2.4.3.2** To assess the association between measures of change in T2-based tumor size at week 22 and overall survival in participants with glioma receiving chemoradiotherapy with and without bevacizumab.

**2.4.3.3** To assess the association between changes in ADC values and overall survival in participants with glioma receiving chemoradiotherapy with and without bevacizumab.

## 3.0 PATIENT SELECTION

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

Sites participating in the advanced imaging component must offer all advanced imaging–eligible patients the opportunity to enroll in the ACRIN 6686 advanced imaging component of the RTOG 0825 study until the advanced imaging accrual objective is met. (7/20/09)

**3.1 Conditions for Patient Eligibility** (8/2/10)

**3.1.1** Histologically proven diagnosis of glioblastoma or gliosarcoma (WHO grade IV) **confirmed by central review prior to step 2 registration**

**3.1.2** Tumor tissue that is **determined by central pathology review prior to step 2 registration** to be of sufficient size for analysis of MGMT status and determination of molecular profile.

- Patients must have at least 1 block of tumor tissue; submission of 2 blocks is strongly encouraged to maximize the chances of eligibility. At least 1 cubic centimeter of tissue composed primarily of tumor must be present. (See Section 10.2 and Appendix IV for details.)
- CUSA (Cavitron ultrasonic aspirator)-derived material is not allowed; fresh frozen tumor tissue acquisition is encouraged.
- Diagnosis must be made by surgical excision, either partial or complete; stereotactic biopsy is not allowed because it will not provide sufficient tissue for MGMT analysis.
- The tumor tissue should be sent as soon as possible to maximize the likelihood of eligibility. Tumor tissue should be submitted by 4 weeks after the surgical procedure so that study registration and treatment can commence by the mandatory 5 week post-surgery outer limit as stipulated in Sections 6.0 and 7.0.
- Per Section 10.2, sites **must** submit tissue directly to Dr. Aldape in order to obtain the MGMT analysis. Patients from sites not following the protocol-specified process for obtaining MGMT results will be made ineligible.

**3.1.3** The tumor must have a supratentorial component.

**3.1.4** History/physical examination within 14 days prior to step 2 registration;

**3.1.5** The patient must have recovered from the effects of surgery, postoperative infection, and other complications before step 2 registration.

**3.1.6** A diagnostic contrast-enhanced MRI of the brain must be performed preoperatively and postoperatively prior to the initiation of radiotherapy. The postoperative scan must be performed within 28 days prior to step 1 registration.

**3.1.6.1** An MRI or CT scan (potentially in addition to the postoperative scan) must be obtained within 10 days prior to the start of radiation therapy and must not demonstrate significant postoperative hemorrhage defined as > 1 cm diameter of blood. If > 1 cm of acute blood is detected, the patient will be ineligible for this trial. The radiation planning MRI or CT scan may be used to determine presence of hemorrhage.

**3.1.6.2** Patients unable to undergo MR imaging because of non-compatible devices can be enrolled, provided pre- and postoperative contrast-enhanced CT scans are obtained and are of sufficient quality. Preoperative and postoperative scans must be the same type. Such patients cannot be enrolled into the advanced imaging component (see Section 3.2.10).

**3.1.7** Documentation of steroid doses within 14 days prior to step 2 registration.

**3.1.8** Karnofsky performance status ≥ 70;

**3.1.9** Age ≥ 18;

**3.1.10** CBC/differential obtained within 14 days prior to step 2 registration, with adequate bone marrow function defined as follows:

**3.1.10.1** Absolute neutrophil count (ANC) ≥ 1,800 cells/$mm^3$;

**3.1.10.2** Platelets ≥ 100,000 cells/$mm^3$;

**3.1.10.3** Hemoglobin ≥ 10.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 10.0 g/dl is acceptable.);

**3.1.11** Adequate renal function, as defined below:

**3.1.11.1** BUN ≤ 30 mg/dl within 14 days prior to step 2 registration.

**3.1.11.2** Creatinine ≤ 1.7 mg/dl within 14 days prior to step 2 registration.

**3.1.11.3** Urine protein screened by urine analysis for urine protein creatinine (UPC) ratio. For UPC ratio > 0.5, 24-hour urine protein should be obtained and the level should be < 1000 mg.

**3.1.11.3.1** UPC 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

**3.1.12** Adequate hepatic function, as defined below:

**3.1.12.1** Bilirubin ≤ 2.0 mg/dl within 14 days prior to step 2 registration

**3.1.12.2** ALT/AST ≤ 3 x normal range within 14 days prior to step 2 registration

**3.1.13** Systolic blood pressure ≤ 160 mg Hg or diastolic pressure ≤ 90 mg Hg within 14 days prior to step 2 registration

**3.1.13.1** Electrocardiogram without evidence of acute cardiac ischemia within 14 days prior to step 2 registration

**3.1.14** Prothrombin time/international normalized ratio (PT INR) < 1.4 for patients not on warfarin confirmed by testing within 14 days prior to step 2 registration.

**3.1.14.1** 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 (between 2 and 3) on a stable dose of oral anticoagulant or on a stable dose of low molecular weight heparin

**3.1.15** Patient must provide study specific informed consent prior to study entry.

**3.1.16** Women of childbearing potential and male participants must practice adequate contraception.

**3.1.17** For females of child-bearing potential, negative serum pregnancy test within 14 days prior to step 2 registration

### 3.2 Conditions for Patient Ineligibility (8/2/10)

**3.2.1** Prior invasive malignancy (except for non-melanomatous skin cancer) unless disease free for ≥ 3 years. (For example, carcinoma in situ of the breast, oral cavity, and cervix are all permissible).

**3.2.2** Recurrent or multifocal malignant gliomas

**3.2.3** Metastases detected below the tentorium or beyond the cranial vault.

**3.2.4** Prior chemotherapy or radiosensitizers for cancers of the head and neck region; note that prior chemotherapy for a different cancer is allowable, except prior temozolomide or bevacizumab. Prior use of Gliadel wafers or any other intratumoral or intracavitary treatment are not permitted. See Section 3.2.1.

**3.2.5** Prior radiotherapy to the head or neck (except for T1 glottic cancer), resulting in overlap of radiation fields.

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

**3.2.6.1** Unstable angina and/or congestive heart failure within the last 6 months

**3.2.6.2** Transmural myocardial infarction within the last 6 months

**3.2.6.3** Evidence of recent myocardial infarction or ischemia by the findings of S-T elevations of ≥ 2 mm using the analysis of an EKG performed within 14 days of step 2 registration

**3.2.6.4** New York Heart Association grade II or greater congestive heart failure requiring hospitalization within 12 months prior to step 2 registration

**3.2.6.5** History of stroke, cerebral vascular accident (CVA) or transient ischemic attack within 6 months

**3.2.6.6** Serious and inadequately controlled cardiac arrhythmia

**3.2.6.7** Significant vascular disease (e.g., aortic aneurysm, history of aortic dissection) or clinically significant peripheral vascular disease

**3.2.6.8** Evidence of bleeding diathesis or coagulopathy

**3.2.6.9** Serious or non-healing wound, ulcer, or bone fracture or history of abdominal fistula, gastrointestinal perforation, intra-abdominal abscess major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to step 2 registration, with the exception of the craniotomy for tumor resection.

**3.2.6.10** Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration

**3.2.6.11** Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of step 2 registration

**3.2.6.12** Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for liver function and coagulation parameters are not required for entry into this protocol.

**3.2.6.13** 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.

**3.2.6.14** Active connective tissue disorders, such as lupus or scleroderma, that in the opinion of the treating physician may put the patient at high risk for radiation toxicity.

**3.2.6.15** Any other major medical illnesses or psychiatric impairments that in the investigator's opinion will prevent administration or completion of protocol therapy.

**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** Pregnant or lactating women, due to possible adverse effects on the developing fetus or infant due to study drug.

**3.2.9** Patients treated on any other therapeutic clinical protocols within 30 days prior to study entry or during participation in the study.

**3.2.10** **For ACRIN 6686 Advanced Imaging:** Inability to undergo MRI (e.g., due to safety reasons, such as presence of a pacemaker).

## 4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

Not applicable to this study.

## 5.0 REGISTRATION PROCEDURES (8/27/09)

**NOTE:** Sites participating through CTSU must apply for an RTOG username and password **immediately after registering**, to enable access to the Neurocognitive Training Procedure Letter on the 0825 forms section of the RTOG website. A user name and password can be obtained by completing the Password Authorization Form at www.rtog.org/members/webreg.html. See the CTSU logistics appendix for details.

### 5.1 Pre-Registration Requirements (7/20/09)

**5.1.1** ***Regulatory Pre-Registration Requirements***

**5.1.1.1** **U.S. and Canadian institutions** must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206), along with the completed CTSU-IRB/REB Certification Form, http://www.rtog.org/pdf_file2.html?pdf_document=CTSU-IRBCertifForm.pdf, prior to registration of the institution's first case:

- IRB/REB approval letter;
- IRB/REB approved consent (English Version)
- IRB/REB assurance number

**5.1.1.2** *Pre-Registration Requirements FOR CANADIAN INSTITUTIONS*

**5.1.1.2.1** Prior to clinical trial commencement, Canadian institutions must complete and fax to the CTSU Regulatory Office (215-569-0206) Health Canada's Therapeutic Products Directorates' Clinical Trial Site Information Form, Qualified Investigator Undertaking Form, and Research Ethics Board Attestation Form.

**5.1.1.3** *Pre-Registration Requirements FOR NON-CANADIAN INTERNATIONAL INSTITUTIONS*

**5.1.1.3.1** **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/pdf_forms.html?members/forms=Intl_LOI_Form.doc

**5.1.1.3.2** **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.

Prior to registration of an institution's first case, international sites must submit a copy of approval from their FDA equivalent to import bevacizumab for this study. Documentation must be faxed to both of the following:

- PMB at fax 301-480-4612
- RTOG Headquarters at fax 215-574-0300.

**5.1.2 *Pre-Registration Requirements for IMRT Treatment Approach***

**5.1.2.1** In order to utilize IMRT on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements are available on the Radiological Physics Center (RPC) web site at http://rpc.mdanderson.org/rpc/; select "Credentialing" and "RTOG." To determine if these requirements have already been met, select "Credentialing Status Inquiry."

An IMRT phantom study with the RPC must be successfully completed (if the institution has not previously met this credentialing requirement on another RTOG IMRT Head and Neck study). 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.

**5.1.2.2** The institution or investigator must complete a new IMRT facility questionnaire and set up an SFTP account for digital data submission, both of which are available on the ATC 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.

**5.1.3 *Pre-Registration Requirements for 3D-CRT Treatment Approach***

**5.1.3.1** 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 to this study.

**5.1.3.2** 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.

**5.1.4 *Pre-Registration Requirements for Neurocognitive Function Testing Certification***

**NOTE: Sites must offer English-speaking participants the opportunity to participate in the neurocognitive function component of this study.**

Institutions with patients participating in the quality of life/neurocognitive function components of this study must meet certification requirements for administering neurocognitive assessments. Upon review and successful completion of the Neurocognitive Certification, Dr. Wefel will notify both the certified examiner and RTOG Headquarters that the examiner has successfully completed this requirement.

See Appendix V for certification requirements.

**5.1.5 ACRIN 6686 Pre-Registration Requirements for Advanced MRI Certification (only for sites participating in the advanced imaging component**

Each institution must complete an American College of Radiology Imaging Network (ACRIN) 6686 Protocol Specific Application (PSA). The PSA will request each center to identify a radiologist with standard and advanced neuro-MRI experience to oversee implementation of the standard and advanced MRI components of the protocol. In addition, the PSA will also request information on the staff and equipment that will be used to acquire image data for the protocol.

Each advanced-imaging site must be pre-qualified for the trial by demonstrating the ability to perform and electronically transfer MRI scans per protocol specifications. Centers already qualified previously for an RTOG/ACRIN study (e.g., RTOG 0625/ACRIN 6677) do not need to re-

qualify to participate in this study. The central repository is located at ACRIN Imaging Management Center in Philadelphia, PA. The qualification process includes submission and approval of at least one (1) standard-of-care MRI of a brain tumor where parameters used match those in Appendix XII, as well as at least one imaging examination performed according to the protocol parameters for advanced imaging referenced in Appendix XII. Institutional reimbursements to offset the costs associated with MR perfusion and DCE-MRI are provided by a grant from NCI/CIP through ACRIN. Detailed technical acquisition parameters are available on the ACRIN web site at http://www.acrin.org/6686_protocol.aspx.

Payment for participation in the imaging component of the trial is automatic, based upon submission of the key data forms and confirmation of the quality of images submitted to ACRIN. The ACRIN 6686 PSA is available on the ACRIN web site at http://www.acrin.org/6686_protocol.aspx.

## 5.2 Summary of Registration Procedures

Once the patient has been determined to meet pre-registration requirements, this study incorporates a 3-step registration process.

**Step 1** of registration entails an initial registration for tissue pathology tissue screening.

- The site will register the patient and will then submit tissue to Dr. Aldape (see Section 10). A pathology screening form (P4), pathology materials, and pathology report must be submitted to Dr. Aldape per Section 10.
- Dr. Aldape will evaluate the tissue to confirm that the histology is GBM and that there is adequate tissue to perform MGMT analysis and molecular profiling.
- If the histology is GBM and there is adequate tissue, the site may proceed to Step 2 registration.
- See Section 5.3 for online registration procedures.

**NOTE**: During this time institutions must verify by MRI or CT that < 1 cm of blood is in the tumor cavity. If the treatment planning scan will be used for this, the treatment planning must be completed prior to Step 2 registration. See Section 3.1.6 for details.

**Step 2** of registration entails a second registration for obtaining MGMT status and molecular profiling.

- Upon notification of 2nd step patient registration, Dr. Aldape will initiate the processes for tissue analysis for MGMT analysis and molecular profiling.
- RTOG HQ will notify institutions once the MGMT and molecular profiling test results have been received and the 3rd step of registration can be done. (It may take several weeks after the submission of tissue for the MGMT and molecular profiling results to be available.)
- See Section 5.3 for online registration procedures.

**Step 3** of registration entails a third registration, at which time randomization will occur.

- A blinded treatment assignment will then be provided along with a new data submission calendar.
- Should the patient experience significant toxicity from pre-randomization treatment and not proceed to be randomized, step 3 of registration must still be completed.
- See Section 5.3 for online registration procedures.

## 5.3 Online Registration (8/27/09)

Patients can be registered only after eligibility criteria are met.

Each individual user must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:

- The investigator and research staff must have completed Human Subjects Training and been issued a certificate (Training is available via http://phrp.nihtraining.com/users/login.php).

- A representative from the institution must complete the Password Authorization Form at www.rtog.org/members/webreg.html (bottom right corner of the screen), and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

An institution can register the patient by logging onto the RTOG web site (http://www.rtog.org), going to "Data Center Login" and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient's record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study's database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

Institutions can contact RTOG web support for assistance with web registration: websupport@acr-arrs.org or 800-227-5463 ext. 4189 or 215-574-3189

## 6.0 RADIATION THERAPY/FUNCTIONAL IMAGING (7/20/09)

**Note: Intensity Modulated RT (IMRT) Is Allowed**
**Modality chosen at registration must be used for the entire course of treatment.**

**Treatment must begin > 3 weeks and ≤ 5 weeks after surgery.**

### 6.1 Dose Specifications and Schedule

For both IMRT and 3D-CRT plans, one treatment of 2 Gy will be given daily 5 days per week for a total of 60 Gy over 6 weeks. All portals shall be treated during each treatment session. Doses are specified such that at least 95% of the PTV shall receive 100% of the prescribed dose; DVHs are necessary to make this selection.

### 6.2 Technical Factors

Treatment shall be delivered with megavoltage machines of a minimum energy of 6 MV photons. Selection of the appropriate photon energy (ies) should be based on optimizing the radiation dose distribution within the target volume and minimizing dose to non-target normal tissue. Source skin distance for SSD techniques or source axis distance for SAD techniques must be at least 80 cm. Electron, particle, or implant boost is not permissible. IMRT delivery will require megavoltage radiation therapy machines of energy ≥ 6 MV.

### 6.3 Localization, Simulation, and Immobilization

The patient shall be treated in the supine or other appropriate position for the location of the lesion. A head-holding device to ensure adequate immobilization during therapy and ensure reproducibility is strongly recommended. Simulation may include a dedicated radiotherapy simulator or a virtual simulation using a treatment planning CT. Fusion with MR images is strongly recommended, whenever feasible.

For patients accrued to the protocol, treatment verification and documentation should be carried out, at least for the first treatment fraction, and more frequently, based on institutional

policy; weekly verification is common. We suggest orthogonal images for documenting isocenter setup accuracy for the first fraction. These orthogonal images can be obtained with film or EPID. Other imaging techniques are possible, for example, the BrainLab ExacTrac system that uses two orthogonal imaging panels irradiated with KV x-rays. Another example is the volume images obtained with cone-beam CT, or helical tomotherapy or any other CT capability that is integrated with the treatment unit.

## 6.4 Treatment Planning/Target Volumes

Treatment plans may include opposed lateral fields, a wedge pair of fields, rotation, or multiple field techniques. Intensity-modulated inverse-planned approaches are permitted. Any of the methods of IMRT (including tomotherapy) may be used, subject to protocol localization and dosimetry constraints. CT-based treatment planning is necessary to assure accuracy in the selection of field arrangements. MRI-fusion for accurate target delineation is strongly recommended.

**6.4.1** **Initial Target Volume**: Target volumes will be based upon postoperative-enhanced MRI. Preoperative imaging should be used for correlation and improved identification. Two planning target volumes (PTV) will be defined, as outlined below. The initial gross tumor volume (GTV1) will be defined by either the T2 or the FLAIR abnormality on the post-operative MRI scan. This must also include all postoperative-enhanced MRI enhancement, and the surgical cavity. The initial clinical target volume (CTV1) will be the GTV plus a margin of 2 cm. If no surrounding edema is present, the initial planning target volume (PTV1) should include the contrast-enhancing lesion (and should include the surgical resection cavity) plus a 2.5-cm margin. The CTV1 margin may be reduced to 0.5 cm around natural barriers to tumor growth such as the skull, ventricles, falx, etc, and also to allow sparing of the optic nerve/chiasm, if necessary. The initial planning target volume (PTV1) is an additional margin of 3 to 5 mm, depending upon localization method and reproducibility, at each center. PTV margins account for variations in set-up and reproducibility. Reducing PTV margins to modify organ at risk (OAR) dose(s) is not generally permissible. However, OAR must be defined, along with a planning risk volume (PRV) for each OAR. Each PRV will be its OAR plus 3 mm. In the event that an OAR is in immediate proximity to a PTV such that dose to the OAR cannot be constrained within protocol limits, a second PTV ($PTV_{overlap}$), defined as the overlap between the PTV1 and the particular PRV of concern, may be created. Dose to the $PTV_{overlap}$ must be as close as permissible to 46 Gy while not exceeding the OAR dose limit.

**6.4.2** **Boost Target Volume**: The boost gross tumor volume (GTV2) will be defined by the contrast-enhanced T1 abnormality on the post-operative MRI scan. This must also include the surgical cavity margins. The boost clinical target volume (CTV2) will be the GTV plus a margin of 2 cm. The CTV2 margin may be reduced to 0.5 cm around natural barriers to tumor growth such as the skull, ventricles, falx, etc, and also to allow sparing of the optic nerve/chiasm, if necessary. The boost planning target volume (PTV2) is an additional margin of 3 to 5 mm, depending upon localization method and reproducibility, at each center. PTV margins account for variations in set-up and reproducibility. Reducing PTV margins to modify organ at risk (OAR) dose(s) is not generally permissible. However, OAR must be defined , along with a planning risk volume (PRV) for each OAR. Each PRV will be its OAR plus 3 mm. In the event that an OAR is in immediate proximity to a PTV such that dose to the OAR cannot be constrained within protocol limits, a second PTV ($PTV_{overlap}$), defined as the overlap between the PTV2 and the particular PRV of concern, may be created (the overlap is the intersection between the PTV1 and the PRV). Dose to the $PTV_{overlap}$ must be as close as permissible to 14 Gy while not exceeding the OAR dose limit.

**6.4.3** **Dose Guidelines**: The initial target volume will be treated to 46 Gy in 23 fractions. After 46 Gy, the conedown or boost volume will be treated to a total of 60 Gy, with seven additional fractions of 2 Gy each (14 Gy boost dose).

Isodose distributions for the initial target volume (PTV1) and the conedown target volume (PTV2) are required on all patients. A composite plan is required showing the respective target volumes. The following composite isodose lines should be included: 66 Gy (when 66 Gy dose regions exist in the tumor), 60 Gy, 57 Gy, 48 Gy, 44 Gy and 40 Gy. The inhomogeneity within the target volume shall be kept to ± 10% of the prescribed dose.

The minimum dose to the target volume should be kept within 10% of the dose at the center of the volume. Doses are specified such that at least 95% of the PTV shall receive 100% of the prescribed dose; DVHs are encouraged to make this selection. The use of vertex fields requires either a diagram or a photograph of the treatment position to be submitted to RTOG Headquarters.

### 6.5 Dose Limitation to Critical Structures

In addition to the above defined GTVs, CTVs and PTVs the lenses of both eyes, both retinae, both optic nerves, the optic chiasm, and the brainstem must be defined. The maximum point (defined as a volume greater than 0.03 cc) doses permissible to the structures are listed in the table below.

| Critical Structure | Maximum Dose |
|---|---|
| Lenses | 7 Gy |
| Retinae | 50 Gy |
| Optic Nerves | 55 Gy |
| Optic Chiasm | 56 Gy |
| Brainstem | 60 Gy |

### 6.6 Compliance Criteria (8/2/10)

**6.6.1** Per Protocol
95% of PTV2 is covered by 60 Gy
99% of PTV2 is covered by 54 Gy

**6.6.2** Variation Acceptable
90% of PTV2 is covered by 60 Gy
97% of PTV2 is covered by 54 Gy

**6.6.3** Deviation Unacceptable
<90% of PTV2 is covered by 60 Gy
<97% of PTV2 is covered by 54 Gy

**6.6.4** Up to 5 days of treatment interruption are permitted for any reason. Interruptions of 6 to 7 treatment days will be considered an acceptable protocol violation. For interruptions of 8 days or greater, an unacceptable deviation will be assigned.

### 6.7 R.T. Quality Assurance Reviews

The Principle RT Investigator, Minesh Mehta, MD, in concert with other assigned Radiation Oncologist/s will perform an RT Quality Assurance Review. These reviews will be ongoing and performed remotely or at the RTOG semi-annual meetings as well as at RTOG Headquarters. The final cases will be reviewed within 6 months after this study has reached the target accrual.

### 6.8 Radiation Therapy Adverse Events

**6.8.1** 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.

**6.8.2** Early Delayed

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

**6.8.3** Late Delayed

Possible late delayed effects of radiotherapy include radiation necrosis, endocrine dysfunction, and radiation-induced neoplasms. 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.

**6.9 Radiation Therapy Adverse Event Reporting**

See Section 7.0.

**6.10 ACRIN 6686 Functional Imaging: Advanced Imaging of Glioblastomas and Timeline** (8/2/10)

**6.10.1** Study participants will undergo DSC-MRI and DCE-MRI at four time points:

- T0: Baseline (corresponding to 0–5 days before the initiation of chemoradiation);
- T1: Week 3 of the study (corresponding to 0–3 days before the commencement of bevacizumab therapy or placebo in the respective arm);
- T2: after T0 at Week 3 + 1 day (corresponding to 1 day after the commencement of bevacizumab therapy or placebo in the respective arm); and
- T3: at Week 10 of the study (corresponding to 7 weeks after the commencement of bevacizumab therapy or placebo in the respective arm).

**6.10.2** Because of the expense and challenge of performing such studies, only 264 of the 942 participants will undergo advanced imaging. Sites will be limited to those who pre-qualify their imaging techniques through ACRIN for quality. Once a site is qualified, it is **mandatory** for that site to offer the advanced imaging series to all advanced imaging–eligible participants until 264 patients are enrolled. Once 264 participants are enrolled to the advanced imaging component of the trial, advanced-imaging sites may conduct standard imaging on additional study participants until all 942 participants are enrolled.

## 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.**

**Treatment must begin > 3 weeks and ≤ 5 weeks after surgery.**

**7.1 Code Breaks** (8/2/10)

**NOTES**

- The results of the MGMT and 9-gene profile analyses will not be revealed to physicians or patients.
- The site should have the study case number and initials available when requesting unblinding.

**7.1.1** In the Event of Evidence of Tumor Progression During or After Protocol Treatment

If the patient has evidence of tumor progression during or after protocol therapy, the code will be broken and the treatment arm will be released to the treating physician so that the appropriate therapy can be instituted. A Code Breaking Form (CX) must be completed (See Section 12.1). The RTOG Code Breaking Officer will respond to your request within 3 business days. [**NOTE**: The Radiology Review Form (SR) reporting progression **must** be completed to trigger the Code Breaking Form (CX).]

**7.1.2** Emergency Safety Unblinding

Emergency unblinding will only be considered for a life-threatening event or extraordinary clinical circumstance for which knowledge of drug assignment will affect clinical judgment.

During business hours (8:30 AM to 5 PM ET), call RTOG Headquarters at **215-574-3150** and ask to speak to the Study Statistician. For after hours, weekends, and holidays, call **215-459-3576**.

**7.2 Pre-Randomization Temozolomide During Concomitant Radiation Therapy**

**7.2.1** Temozolomide will be administered continuously from day 1 of radiotherapy to the last day of radiation at a daily oral dose of 75 mg/m$^2$ for a maximum of 49 days. The drug will be administered orally 1 hour before each session of radiotherapy during weekdays (Monday through Friday). During weekends without radiotherapy (Saturday and Sunday), the drug will be taken in the morning.

**7.2.2** The dose will be determined using actual body surface area (BSA) as calculated in square meters at the beginning of the concomitant treatment. The BSA will be calculated from the height

obtained at the pretreatment visit and the weight obtained at the visit immediately before the first day of treatment. Capsules of temozolomide are available in 5, 20, 100, 140, 180, and 250 mg. The daily dose will be rounded to the nearest 5 mg.

**7.2.3** Patients will be instructed to swallow the capsules whole, in rapid succession, without chewing them. If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The capsules should be taken on an empty stomach, therefore a minimum of 2 hours after eating and with no food consumption for at least 1 hour after temozolomide administration. Although, nightly administration just before bedtime has been reported to improve tolerance, the low daily dose administered during radiation is very well tolerated and administration in the morning before radiation dosing is required for this protocol. Administration of the higher dosing regimen during the adjuvant phase of the protocol should be performed using the nightly administration.

**7.2.4** Antiemetic prophylaxis is usually not required for the continuous daily dosing schedule (during radiation). However, prophylaxis with a 5-$HT_3$ antagonist is recommended prior to administration of the first few temozolomide doses and should be administered orally 30 to 60 minutes before temozolomide treatment. Most patients report optimal nausea control with the use of a 5-$HT_3$ antagonist. Routine use of antiemetics is recommended during the adjuvant phase of treatment.

## 7.3 Post-Randomization Temozolomide and Bevacizumab/Placebo During Concomitant Radiation Therapy (7/20/09)

**7.3.1 Temozolomide treatment will continue uninterrupted using the treatment guidelines provided above in Section 7.2.**

**7.3.2** Bevacizumab/placebo will be administered intravenously on days 1 and 15 of each 28-day cycle, at the beginning of the 4th week of radiation.
Bevacizumab/placebo day 1 will be given with RT fraction 16, 17, or 18 (ie, 32, 34 or 36 Gy).
Bevacizumab/placebo day 15 will be given with RT fraction 26, 27, or 28 (ie, 52, 54 or 56 Gy).

**7.3.3** A dose of bevacizumab/ placebo will be administered at the beginning of the second week after completion of radiation. The next dose of bevacizumab/placebo is to be given concurrently(same day) as the initiation of the first cycle of the post-radiation temozolomide. Any toxicity-related delays in the initiation of temozolomide will also result in a delay in the dosing of the bevacizumab/placebo treatment.

**7.3.4** The dose will be 10 mg/kg of actual body weight.

**7.3.4.1** The dose will be determined using body weight determined at the beginning of each treatment cycle. The daily dose will be rounded to the nearest 5 mg. The exact dose administered should be recorded in the CRF.

**7.3.4.2** The initial dose should be administered over a minimum of 90 minutes. If no adverse reactions occur, the second dose should be administered over a minimum of 60 minutes. If no adverse reactions occur after the second dose, all subsequent doses should be administered over a minimum of 30 minutes. If infusion-related adverse reactions occur, subsequent treatments should include premedication as outlined in Section 7.3.4.3 below and the next infusion should be given over a minimum of 90 minutes. If the second infusion is well tolerated with the use of a premedication regimen, an attempt can be made to reduce the time of the next infusions. The next dose should be administered over a minimum of 60 minutes. If no adverse reactions occur after this dose, an attempt can be made to administer the next dose over a minimum of 30 minutes. All subsequent infusions should be administered over the shortest period that was well tolerated.

To insure complete delivery of bevacizumab/placebo, the IV infusion line must be flushed with 0.9% sodium chloride. The following are two recommended methods for flushing the bevacizumab/placebo IV infusion line:

1. When the bevacizumab/placebo infusion is complete, add an additional 50 mL of 0.9% sodium chloride for injection to the bevacizumab/placebo infusion bag. Continue the infusion until a volume equal to that of the volume contained in the tubing has been administered.
2. Replace the empty bevacizumab/placebo infusion bag with a 50 mL bag of 0.9% sodium chloride for injection and infuse a volume equal to the volume contained in the tubing.

Please note: the flush is not included in the total recommended infusion times.

**7.3.4.3** *Precautions*

- General: Prior to each treatment, the patient should be carefully assessed with special attention to blood pressure, proteinuria, bleeding and cardiovascular events, as well as symptoms or signs of bowel perforation and reversible posterior leukoencephalopathy syndrome (RPLS). Decisions for retreatment or dose modification/interruption should follow the dose modification guidelines in Section 7.8.
- Infusional reactions: Routine premedication is not required for the first dose of bevacizumab. If infusional reactions occur, acetaminophen, diphenhydramine, steroids or other medications may be given for symptom control and for premedication as needed. Anaphylactic precautions should be observed during bevacizumab administration.
- Hypertension: Patients should have blood pressure monitored prior to each infusion of bevacizumab. Hypertensive medication should be initiated or increased for optimal blood pressure control according to standard public heath guidelines.
- Surgery and wound complication issues and surgery: The appropriate interval from discontinuation of bevacizumab to subsequent elective surgery required to reduce the risk of impaired wound healing has not been determined. Decision on such an interval should take into consideration the half-life of bevacizumab. It is generally recommended that bevacizumab should be discontinued at least 4-8 weeks prior to major elective surgery. In addition, bevacizumab should not be restarted until at least 4 weeks after major surgery provided that the wound has adequately healed; in cases of high risk procedures such as liver resection, thoracotomy or neurosurgery, it is recommended that bevacizumab be resumed no earlier than 8 weeks after surgery.
  **Craniotomy site must be adequately healed and free of drainage or cellulitis, and the underlying cranioplasty must appear intact.**

***NOTE: If significant toxicity from concomitant treatment persists over 8 weeks from the time of completion of the radiation, the patient should be removed from protocol treatment.***

**7.4 *Post-Radiation Temozolomide*** (8/2/10)

**7.4.1** Temozolomide will be administered orally once per day for 5 consecutive days (days 1-5) of a 28-day cycle. The starting dose for the first cycle will be 150 mg/m$^2$/day, with a single dose escalation to 200 mg/m$^2$/day in subsequent cycles if no treatment-related adverse events > grade 2 are noted.

The start of the first cycle will be scheduled 28 days ± 3 days after the last day of radiotherapy. The start of all subsequent cycles (2-12) will be scheduled every 4 weeks (28 days ± 3 days) after the first daily dose of temozolomide of the preceding cycle.

**7.4.2** The dose will be determined using the BSA calculated at the beginning of each treatment cycle. The BSA will be calculated from the height obtained at the pretreatment visit and from the weight obtained at the visit immediately before each cycle. Capsules of temozolomide are available in 5, 20, 100, 140, 180, and 250 mg. The daily dose will be rounded to the nearest 5 mg. The exact dose administered should be recorded in the CRF. Each daily dose should be given with the least number of capsules.

**7.4.3** Prior to each treatment cycle with temozolomide a complete blood count (CBC) will be obtained (within 72 hours prior to dosing). Patients will be instructed to fast at least 2 hours before and 1 hour after temozolomide administration. Water is allowed during the fast period. Patients will be instructed to swallow the capsules whole, in rapid succession, without chewing them. Treatment should be given at night.

**7.4.4** If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose.

**7.4.5** Antiemetic prophylaxis with a 5-HT$_3$ antagonist is strongly recommended and should be administered 30 to 60 minutes before temozolomide administration. See Section 9.1.

**7.4.6** Patients will be treated with post-radiation temozolomide for 6 cycles unless there is evidence of tumor progression (defined in Section 11) or treatment-related toxicity (defined in Section 7.8). Patients demonstrating continued benefit from the adjuvant treatment (temozolomide plus bevacizumab or temozolomide plus placebo) can continue treatment to a maximum of 12 cycles.

**7.4.7** Pneumocystis carinii prophylaxis is **required** during the radiation phase (see Section 9.1.4).

**7.4.8** Duration of Treatment

Patients will be treated with post-radiation temozolomide and bevacizumab/placebo for 6 cycles unless there is evidence of tumor progression or treatment-related toxicity. At the completion of 6 cycles, patients may receive up to an additional 6 cycles of treatment (therefore, a maximum of 12 cycles) if treatment has been well tolerated and at least one of the following criteria are met:

- Serial MR studies show continued tumor response as evidenced by reduction in tumor size
- The patient demonstrates progressive improvement in overall performance status
- The patient demonstrates clinical improvement by improvement in neurologic function
- The patient demonstrates ongoing treatment benefit by a decreasing requirement of corticosteroids

## 7.5 Temozolomide Agent Information (Temodar, Temodal)

Please refer to the package insert for comprehensive information.

**7.5.1** *Formulation*

Other Names: - methazolastone; Temozolomide is supplied in white opaque, preservative-free, two-piece, hard gelatin capsules of the following p.o. dosage strengths: 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg. Each capsule contains drug substance in combination with lactose, anhydrous NF, colloidal silicon dioxide NF, sodium starch glycolate NF, tartaric acid NF, and stearic acid NF. The capsule shells contain gelatin NF, titanium dioxide USP, and sodium lautyl sulfate NF.

**7.5.2** *Mode of Action*

Alkylating agent of imidazotetrazinone class.

**7.5.3** *Storage and Stability*

The capsules are packaged in amber glass bottles and should be stored at 25 °C. Temperature excursions between 15 and 30 °C are permissible. Refer to the commercially labeled bottles for expiration dating.

**7.5.4** *Pharmacokinetics*

Temozolomide is rapidly and completely absorbed after oral administration; peak plasma concentrations occur in 1 hour. Food reduces the rate and extent of temozolomide absorption. Mean peak plasma concentration and AUC decreased by 32% and 9%, respectively, and $T_{max}$ increased 2-fold (from 1.1 to 2.25 hours) when temozolomide was administered after a modified high-fat breakfast.

Temozolomide is rapidly eliminated with a mean elimination half-life of 1.8 hours and exhibits linear kinetics over the therapeutic dosing range. Temozolomide has a mean apparent volume of distribution of 0.4 L/kg (%CV=13%). It is weakly bound to human plasma proteins; the mean percent bound of drug-related total radioactivity is 15%.

**7.5.5** *Metabolism and Elimination*

Temozolomide is spontaneously hydrolyzed at physiologic pH to the active species, 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC) and to temozolomide acid metabolite. MTIC is further hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC), which is known to be an intermediate in purine and nucleic acid biosynthesis and to methylhydrazine, which is believed to be the active alkylating species. Cytochrome P450 enzymes play only a minor role in the metabolism of temozolomide and MTIC. Relative to the AUC of temozolomide, the exposure to MTIC and ACI is 2.4% and 23%, respectively. About 38% of the administered temozolomide total radioactive dose is recovered over 7 days; 37.7% in urine and 0.8% in feces. The majority of the recovery of radioactivity in urine is as unchanged temozolomide (5.6%), AIC (12%), temozolomide acid metabolite (2.3%), and unidentified polar metabolites(s) (17%). Overall clearance of temozolomide is about 5.5 L/hr/$m^2$.

**7.5.6** *Special Populations*

**7.5.6.1** Creatinine Clearance: Population pharmacokinetic analysis indicates that creatinine clearance over the range of 36-130 mL/min/$m^2$ has no effect on the clearance of temozolomide after oral administration. The pharmacokinetics of temozolomide have not been studied in patients with severely impaired renal function (CLcr < 36 mL/min/$m^2$).
Caution should be exercised when temozolomide is administered to patients with severe renal impairment. Temozolomide has not been studied in patients on dialysis.

**7.5.6.2** Hepatically Impaired Patients: In a pharmacokinetic study, the pharmacokinetics of temozolomide in patients with mild to moderate hepatic impairment (Child's-Pugh Class I-II) were similar to those observed in patients with normal hepatic function. Caution should be exercised when temozolomide is administered to patients with severe hepatic impairment.

**7.5.6.3** Gender: Population pharmacokinetic analysis indicates that women have an approximately 5% lower clearance (adjusted for body surface area) for temozolomide than men. Women have higher incidences of grade 4 neutropenia and thrombocytopenia in the first cycle of therapy than men.

**7.5.6.4** Age: Population pharmacokinetic analysis indicates that age (range 19-78 years) has no influence on the pharmacokinetics of temozolomide. In the anaplastic astrocytoma study population, patients 70 years of age or older had a higher incidence of grade 4 neutropenia and grade 4 thrombocytopenia in the first cycle of therapy than patients under 70 years of age. In the entire safety database, however, there did not appear to be a higher incidence in patients 70 years of age or older.

**7.5.7** *Drug-Drug Interactions*

In a multiple dose study, administration of temozolomide with ranitidine did not change the $C_{max}$ or AUC values for temozolomide or MTIC. Population analysis indicates that administration of valproic acid decreases the clearance of temozolomide by about 5%. The clinical implication of this effect is not known. Population analysis failed to demonstrate any influence of co-administered dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, $H_2$-receptor antagonists, or phenobarbital on the clearance of orally administered temozolomide.

**7.5.8** *Adverse Events*

Hematologic: Thrombocytopenia, leukopenia, myelodysplastic syndrome
Gastrointestinal: Nausea, vomiting, anorexia
Hepatic: Elevated liver enzymes (reversible)
Skin: Rash
Neurologic: Convulsions, weakness on one side of the body, abnormal coordination, paralysis
Other: Constipation, diarrhea, stomatitis, fatigue, decreased performance status, headache

**7.5.9** Temozolomide is potentially mutagenic and should be handled with appropriate precautions by both staff and patients. Capsules should not be opened. If capsules are accidentally opened or damaged, rigorous precautions should be taken with the capsule contents to avoid inhalation or contact with the skin or mucous membranes. Procedures for proper handling and disposal of anticancer drugs should be considered**.**

**7.5.10** *Contraindications*

Temozolomide is contraindicated in patients who have a history of a hypersensitivity reaction to any of its components or to DTIC.

**7.5.11** *Pregnancy Category D*

Temozolomide may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. **Women of childbearing potential should be advised to avoid becoming pregnant during therapy with temozolomide.**

Treatment of a man with temozolomide may increase the risk of birth defects if he causes a woman to become pregnant while he is taking temozolomide. Men treated with temozolomide may have difficulty causing a woman to become pregnant after their treatment is completed. Men receiving temozolomide should be directed to use effective contraception while they are being treated. There is insufficient data to know what the risk of subsequent problems with fertility will be. Similarly, women who are treated with temozolomide may have difficulty becoming pregnant in the future and may at be at increased risk of having children with birth defects. There is insufficient evidence to determine what the risk of these complications will be.

**7.5.12** *Supply*

Commercially available.

**7.5.12.1** **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.

**7.6 Bevacizumab Agent Information Bevacizumab (NSC #704865) (IND #7921)/Placebo** (8/2/10)

**Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling (301) 496-5725 Monday through Friday between 8:30 am and 4:30 pm Eastern Time. You may also contact PMB via e-mail at PMBAfterHours@mail.nih.gov.**

**7.6.1** *Investigator Brochure*

All investigators who receive a copy of the protocol should also obtain a copy of the Investigator's Brochure (IB). IB's are available from the Pharmaceutical Management Branch, CTEP, DCTD, NCI and may be obtained by emailing the IB Coordinator (ibcoordinator@mail.nih.gov) or by calling the IB Coordinator at 301-496-5725.

**7.6.2** *Clinical Supplies*

Bevacizumab (NSC 704865) and matching placebo will be provided free of charge by Genentech and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

Bevacizumab and matching placebo will be supplied in 4 mL fill glass vials each containing 100 mg (Bevacizumab) or 0 mg (Placebo for Bevacizumab) of bevacizumab. In the future, only 400 mg vials of bevacizumab or placebo for 400 mg bevacizumab will be available. At that time, bevacizumab and matching placebo will be supplied in 16 mL fill glass vials each containing 400 mg (Bevacizumab) or 0 mg (Placebo for Bevacizumab) of bevacizumab. The blinded, patient-specific vials will be sealed in a cardboard box with a tamper-evident seal.

For **BLINDED (bevacizumab or placebo) THERAPY**, each box of bevacizumab / placebo will be labeled with …

- the protocol number (i.e., "RTOG-0825")
- the box number (e.g., "Box 1 of 2" and "Box 2 of 2")
- the number of vials (e.g., "45 vials")
- the study case number assigned by RTOG at the time of patient registration
- the patient initials (i.e., **F**irst initial, **M**iddle initial, **L**ast initial [e.g., "FML"])
- the agent identification (i.e., "Bevacizumab 100 mg or Placebo" or "Bevacizumab 400 mg or Placebo")
- a blank line for the pharmacist to enter the patient's name
- storage instructions (i.e., "Store in refrigerator [2 – 8°C]. Do not freeze. Do not shake.")
- emergency contact instructions
- a Julian date

For **OPEN-LABEL bevacizumab THERAPY**, each box of open-label bevacizumab will be labeled with …

- the protocol number (i.e., "RTOG-0825")
- the box number (e.g., "Box 1 of 2" and "Box 2 of 2")
- the number of vials (e.g., "45 vials")
- the study case number assigned by RTOG at the time of patient registration
- the patient initials (i.e., **F**irst initial, **M**iddle initial, **L**ast initial [e.g., "FML"])
- the agent identification (i.e., "Bevacizumab 100 mg" or Bevacizumab 400 mg")
- a blank line for the pharmacist to enter the patient's name
- storage instructions (i.e., "Store in refrigerator [2 – 8°C]. Do not freeze. Do not shake.")
- emergency contact instructions
- a Julian date

The Julian date indicates the day the box was labeled and shipped and is composed of the last two digits of the calendar year (e.g., 2006 = 06, 2007 = 07) and a day count (e.g., January 1 = 001, December 31 = 365). For example, a box labeled and shipped on January 1, 2006 would have a Julian date of '06001' and a box labeled and shipped on December 31, 2007 would have a Julian date of '07365'. The Julian date will be used by PMB for recalls. When a lot expires, PMB will determine the last date the expired lot was shipped and will recall all vials (i.e., both Bevacizumab and Placebo) shipped on or before that date thus eliminating any chance of

breaking the blind. The Julian date can be documented in the "Lot Number" field on the Investigational Agent Accountability Record.

**7.6.3** *Drug Ordering*

Due to the blinded nature of this study, with drug being provided through the Pharmaceutical Management Branch (PMB) of the NCI, extreme accuracy and consistency of physician information are required to achieve accurate and timely drug shipments. The shipping address for each per-patient shipment is automatically retrieved from the physician-specific information provided on the site's most recent Supplemental Investigator Data Form (IDF])on file with the PMB. (Please see Section 7.6.3.2 for detailed instructions related to IDF maintenance.) Please be certain the address of the local verifying physician you select from the drop down menu during registration is consistent with where the drug is expected to be received and that the physician has a valid NCI (CTEP ID) number. Please also be consistent in identifying the same verifying physician at each registration step [A0 (Step 1), A2 (Step 2), and A3 (Step 3)].

**BLINDED (bevacizumab or placebo) THERAPY (Active and Placebo Arms)**

**No blinded starter supplies will be available for this phase.** Blinded, patient-specific clinical supplies will be sent to the registering investigator at the time of randomization. This randomization will be performed electronically during registration (see Section 5). The study case number electronically assigned during registration must be recorded by the registering institution for proper study medication dispersion. Once a patient has been electronically registered an auto-generated email message will transmit a clinical drug request for that patient to the PMB. This request will be processed by the PMB the next business day and shipped the following business day. All shipments will be sent on blue ice by FedEx (generally one to two day delivery). Thus, if a patient is registered on Monday, RTOG would enter a clinical drug request for that patient on Monday and PMB would process the request on Tuesday and ship the drug on Wednesday. Both United States and Canadian sites could expect to receive their order either Thursday or Friday. All other international sites should allow for a *minimum* of four (4) days for the shipment to arrive from the day that PMB receives the order. Note that PMB will only send blue ice shipments on Monday through Thursday for delivery on Tuesday through Friday. Thus, if a patient is registered on Wednesday, the order will be processed on Thursday and shipped the following Monday for delivery on Tuesday or Wednesday. The initial request will be for a sufficient number of vials to **complete the final 3 weeks of concurrent radiation, temozolomide and bevacizumab or placebo** (i.e., **a 6 week supply at 10mg/kg IV every two weeks**) **and the one dose of bevacizumab or placebo between the end of radiation treatment and beginning of adjuvant temozolomide plus bevacizumab or placebo treatment** based on the patient's weight in "kg" provided by RTOG at the time of patient registration. When the third dose is administered (i.e., four weeks before the adjuvant temozolomide and bevacizumab or placebo are needed), sites may reorder an additional **2 cycles** (i.e., **an 8 week supply at 10mg/kg IV every two weeks**) by completing an NCI Clinical Drug Request form and faxing it to the PMB at 301-480-4612. The NCI Clinical Drug Request form is available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. The protocol number (i.e., RTOG-0825), the assigned study case number, the patient initials (e.g., "FML"), the number of vials remaining from the previous shipment, and the patient's weight (in "kg") should be entered on each order. All drug orders will be shipped directly to the physician registering the patient.

**RTOG-0825 Shipment Schedule**

| Patient Randomized With RTOG | Initial e-Order Transmitted by RTOG | Initial e-Order Received and Approved by PMB | Initial Order Shipped By PMB | Initial Order Received at Site * |
|---|---|---|---|---|
| Monday | Monday | Tuesday | Wednesday | Thursday |
| Tuesday | Tuesday | Wednesday | Thursday | Friday |
| Wednesday | Wednesday | Thursday | Monday | Tuesday |
| Thursday | Thursday | Friday | Monday | Tuesday |
| Friday | Friday | Monday | Tuesday | Wednesday |

*** arrival time approximate and will be longer for international sites/shipments sent by Federal Express.**

**NOTE: At the time of disease progression, ALL remaining clinical supplies of blinded bevacizumab / placebo should be returned to PMB (see "Drug Returns" below).**

**OPEN LABEL bevacizumab treatment**

**In order to obtain open – label clinical supplies, patients must be unblinded with the RTOG Data Management Center (see section 11.6.1) at the time of disease progression.**

**No open label starter supplies will be available.** Open-label, patient-specific clinical supplies will be sent to the registering investigator at the time the patient is unblinded. This unblinding will be performed by RTOG Headquarters. **The study case number will NOT change.** Once the patient has been unblinded, the treating institution will electronically submit a Salvage Treatment Guideline Questionnaire **(SX)** (see Section 12.1); submission of the SX will trigger an auto-generated email message transmitting a clinical drug request to the PMB. This request will be processed by the PMB the next business day and shipped the following business day. All shipments will be sent on blue ice by FedEx (generally one to two day delivery). Thus, if the SX form is completed on Monday, the clinical drug request for that patient would be transmitted on Monday evening and PMB would process the request on Tuesday and ship the drug on Wednesday. Both United States and Canadian sites could expect to receive their order either Thursday or Friday. Note that PMB will only send blue ice shipments on Monday through Thursday for delivery on Tuesday through Friday. Thus, if an SX form is completed on Wednesday, the order will be processed on Thursday and shipped the following Monday for delivery on Tuesday or Wednesday. The initial request will be for a sufficient number of vials to complete **2 cycles** (i.e., **an 8 week supply at 10mg/kg IV every two weeks**) based on the patient's weight in "kg" provided by RTOG at the time the patient is unblinded. When the fourth dose is administered (i.e., two weeks before the next cycle is needed), sites may reorder an additional **2 cycles** (i.e., **an 8 week supply at 10mg/kg IV every two weeks**) by completing an NCI Clinical Drug Request form and faxing it to the PMB at 301-480-4612. The NCI Clinical Drug Request form is available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. The protocol number (i.e., RTOG-0825), the assigned study case number, the patient initials (e.g., "FML"), the number of vials remaining from the previous shipment, and the patient's weight (in "kg") should be entered on each order. All drug orders will be shipped directly to the physician registering the patient.

**NOTE: At the time of disease progression, ALL remaining clinical supplies of open-label bevacizumab should be returned to PMB (see "Drug Returns" below).**

**7.6.3.1** **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. Before drug can be provided your institution must comply with all pre-registration

requirements and certifications and provide all necessary documentation listed in your LOI Approval Notification document.

**7.6.3.2** **Detailed Instructions Related to Investigator Data Form (IDF) Maintenance**

The Principal Investigator (or authorized designee listed by the Investigator on the site's most recent Supplemental Investigator Data Form [IDF] on file with the PMB) at each participating institution will be the recipient of the bevacizumab from NCI's Pharmaceutical Management Branch (PMB) for this study. The updated version (11/10/03) of each institution's Drug Authorization Review and Tracking System (DARTS) will require selecting a designee from the individuals listed on the IDF. The information on the IDF is linked to the Investigator during the annual Investigator registration process, which maintains the validity of the Investigator NCI (CTEP ID) number. This process must be current or completed before a drug order can be triggered for that investigator. Any changes to this information will require updating the first two pages of the IDF, having the Investigator sign the revised IDF, and returning it to the PMB via fax at 301-402-4870. Questions about the process should be directed to the PMB at 301-496-5725 Monday through Friday from 8:30 – 4:30 Eastern Time. For a blinded study such as this, PMB policy requires the drug be shipped directly to the address on file on the IDF for the selected verifying physician. This is an automatic process and can not be altered after the fact. If the physician's NCI (CTEP ID) number is invalid or inaccurate the shipment will be rejected.

**7.6.4** *Drug Transfers*

Vials **MAY NOT** be transferred from one patient to another patient or from one protocol to another protocol. All other transfers (e.g., a patient moves from one participating clinical site to another participating clinical site, the responsible investigator at a given clinical site changes) must be approved **in advance** by the PMB. To obtain an approval for transfer, investigators should complete and submit to the PMB (fax number 301-402-0429) a Transfer Investigational Agent Form available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. The study case number and the patient initials (e.g., "FML") should be entered in the "Received on NCI Protocol No." and the "Transferred to NCI Protocol No." fields in addition to the protocol number (i.e., "RTOG-0825").

**7.6.5** *Drug Returns*

**Only unopened clinical supplies should be returned to the PMB.** When it is necessary to return study drug (e.g., sealed vials remaining when a patient completes blinded therapy, sealed vials remaining when a patient completes open-label therapy, sealed vials remaining when a patient permanently discontinues protocol treatment, expired vials recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Drug List available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. The study case number, the patient initials (e.g., "FML"), and the Julian date should be entered in the "Lot Number" field. A separate line item is required for each study case and for each agent (e.g., blinded "bevacizumab / placebo", open label "bevacizumab") being returned.

**7.6.6** *Drug Accountability*

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. A separate NCI Investigational Agent Accountability Record must be maintained for each study case number on this protocol. Sites should start a separate study case-specific accountability record for the open-label portion of treatment.

**7.6.7** *Description*: Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody, consisting of 93% human and 7% murine amino acid sequences. The agent is composed of human IgG framework and murine antigen-binding complementarity-determining regions. Bevacizumab blocks the binding of vascular endothelial growth factor (VEGF) to its receptors resulting in inhibition of angiogenesis.

**7.6.8** *How Supplied:* "Bevacizumab" and "Placebo" are supplied as a clear to slightly opalescent, sterile liquid ready for parenteral administration. For "Bevacizumab", each 100mg (25mg/mL – 4mL fill) and 400 mg (25 mg/mL – 16 mL) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP. For "Placebo", each 0mg (0mg/mL – 4mL fill or 16 mL fill) glass vial contains phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP.

**7.6.9** *Storage and Stability*: Bevacizumab and placebo for bevacizumab are shipped on blue ice for next day delivery. On receipt, bevacizumab and placebo for bevacizumab should be stored in the refrigerator ($2^{o}$ to $8^{o}$C) and should remain refrigerated until just prior to use. Do not freeze. Do not shake. Shelf-life studies of bevacizumab are continuing. Investigators will be notified when lots have expired. The sterile single use vials contain no antibacterial preservatives; therefore, vials should be discarded eight hours after initial entry.

**7.6.10** *Preparation*: Vials contain no preservative and are intended for single use only. The calculated dose should be placed in a 100 mL of 0.9% Sodium Chloride for Injection. Once diluted in 0.9% Sodium Chloride for Injection, the bevacizumab solution must be administered within 8 hours. **NOTE: Each vial of bevacizumab/placebo will be labeled with the intended study case number. Please verify that all of the study case labels match the study case for which the dose is being prepared.**

**7.6.11** *Administration*: Bevacizumab/placebo is administered intravenously as a continuous infusion. The initial dose should be administered over a minimum of 90 minutes. If no adverse reactions occur after the initial dose, the second dose should be administered over a minimum of 60 minutes. If no adverse reactions occur after the second dose, all subsequent doses should be administered 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.

To ensure complete delivery of bevacizumab/placebo, the IV infusion line must be flushed with 0.9% Sodium Chloride for Injection. Please note that this flush is not included in the infusion times. The following are two recommended methods for flushing the bevacizumab/placebo IV infusion line:

- When the bevacizumab/placebo infusion is complete, add an additional 50mL of 0.9% Sodium Chloride for Injection to the bevacizumab/placebo infusion bag. Continue the infusion until a volume equal to that of the volume contained in the tubing has been administered.
- Replace the empty bevacizumab/placebo infusion bag with a 50mL bag of 0.9% Sodium Chloride for Injection and infuse a volume equal to the volume contained in the tubing.

**7.6.12** *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 Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.info.nih.gov/protocolDevelopment/default.htm#adverse_events_adeers for further clarification. Below is the CAEPR for bevacizumab (rhuMAb VEGF).

**Version 2.1, May 4, 2010**[1]

| **Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 4.0 Term)** | | | **EXPECTED AEs FOR ADEERS REPORTING Agent Specific Adverse Event List (ASAEL)** |
|---|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** | ***Expected*** |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | | | |
| | Anemia | | ***Anemia*** |
| | | Blood and lymphatic system disorders - Other (renal thrombotic microangiopathy) | |
| CARDIAC DISORDERS | | | |
| | | Acute coronary syndrome | |
| | | Heart failure | |
| | | Left ventricular systolic dysfunction | |
| | | Myocardial infarction | ***Myocardial infarction*** |
| | Supraventricular tachycardia | | ***Supraventricular tachycardia*** |
| | | Ventricular arrhythmia | |
| | | Ventricular fibrillation | |
| EAR AND LABYRINTH DISORDERS | | | |
| | Vertigo | | |
| GASTROINTESTINAL DISORDERS | | | |
| | Abdominal pain | | ***Abdominal pain*** |
| | Colitis | | |
| | Constipation | | ***Constipation*** |
| Diarrhea | | | ***Diarrhea*** |
| | Dyspepsia | | ***Dyspepsia*** |
| | | Gastrointestinal fistula[2] | |
| | Gastrointestinal hemorrhage[3] | | ***Gastrointestinal hemorrhage***[3] |
| | | Gastrointestinal perforation[4] | |
| | | Gastrointestinal ulcer[5] | |
| | Ileus | | |
| | Mucositis oral | | ***Mucositis oral*** |
| Nausea | | | ***Nausea*** |
| Vomiting | | | ***Vomiting*** |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | | |
| Fatigue | | | ***Fatigue*** |
| | Infusion related reaction | | ***Infusion related reaction*** |
| | Non-cardiac chest pain | | ***Non-cardiac chest pain*** |
| | Pain | | ***Pain*** |
| IMMUNE SYSTEM DISORDERS | | | |

| | | | |
|---|---|---|---|
| | Allergic reaction | | ***Allergic reaction*** |
| | | Anaphylaxis | |
| INFECTIONS AND INFESTATIONS | | | |
| | Infection[6] | | ***Infection[6]*** |
| | Infections and infestations - Other (peri-rectal abscess) | | |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | | | |
| | | Gastrointestinal anastomotic leak | |
| | Wound dehiscence | | ***Wound dehiscence*** |
| INVESTIGATIONS | | | |
| | Alanine aminotransferase increased | | ***Alanine aminotransferase increased*** |
| | Alkaline phosphatase increased | | ***Alkaline phosphatase increased*** |
| | Aspartate aminotransferase increased | | ***Aspartate aminotransferase increased*** |
| | Blood bilirubin increased | | ***Blood bilirubin increased*** |
| | Cardiac troponin I increased | | |
| | Neutrophil count decreased | | ***Neutrophil count decreased*** |
| | Weight loss | | ***Weight loss*** |
| | White blood cell decreased | | ***White blood cell decreased*** |
| METABOLISM AND NUTRITION DISORDERS | | | |
| | Anorexia | | ***Anorexia*** |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | | | |
| | Arthralgia | | ***Arthralgia*** |
| | Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia)[7] | | |
| | Myalgia | | |
| NERVOUS SYSTEM DISORDERS | | | |
| | Dizziness | | ***Dizziness*** |
| Headache | | | ***Headache*** |
| | | Intracranial hemorrhage | ***Intracranial hemorrhage*** |
| | | Ischemia cerebrovascular | ***Ischemia cerebrovascular*** |
| | | Reversible posterior leukoencephalopathy syndrome | |
| | Syncope | | |
| RENAL AND URINARY DISORDERS | | | |
| | Acute kidney injury | | |
| | Hematuria | | ***Hematuria*** |
| | Proteinuria | | ***Proteinuria*** |
| | | Renal and urinary disorders - Other (Nephrotic Syndrome) | |
| | | Renal and urinary disorders - Other (renal failure) | |
| | | Urinary fistula | |
| REPRODUCTIVE SYSTEM AND BREAST DISORDERS | | | |
| | | Vaginal fistula | |
| | Vaginal hemorrhage | | ***Vaginal hemorrhage*** |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | | | |
| | | Bronchopleural fistula | |
| | | Bronchopulmonary hemorrhage | |
| | Cough | | ***Cough*** |
| | Dyspnea | | ***Dyspnea*** |
| | Epistaxis | | ***Epistaxis*** |
| | Hoarseness | | ***Hoarseness*** |

| | | | |
|---|---|---|---|
| | | Respiratory, thoracic and mediastinal disorders - Other (nasal-septal perforation) | |
| | Respiratory, thoracic, and mediastinal disorders - Other (rhinitis) | | ***Respiratory, thoracic, and mediastinal disorders - Other (rhinitis)*** |
| | | Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula) | |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | | | |
| | Pruritus | | ***Pruritus*** |
| | Skin and subcutaneous tissue disorders - Other (rash) | | ***Skin and subcutaneous tissue disorders - Other (rash)*** |
| | Urticaria | | ***Urticaria*** |
| VASCULAR DISORDERS | | | |
| Hypertension | | | ***Hypertension*** |
| | Thromboembolic event | | ***Thromboembolic event*** |
| | | Vascular disorders - Other (arterial thromboembolic event)[8] | |

[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 includes: 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 includes: 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 perforation includes: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Jejunal perforation, Rectal perforation, Small intestinal perforation, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[5]Gastrointestinal ulcer includes: Duodenal ulcer, Esophageal ulcer, Gastric ulcer and other sites under the GASTROINTESTINAL DISORDERS SOC.

[6]Infection includes all 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

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

[8]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
**GASTROINTESTINAL DISORDERS** - Small intestinal obstruction
**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Gait disturbance; Sudden death NOS
**HEPATOBILIARY DISORDERS** - Hepatic failure
**INFECTIONS AND INFESTATIONS -** Infections and infestations - Other (aseptic meningitis)
**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); Osteonecrosis of jaw
**NERVOUS SYSTEM DISORDERS** - Dysgeusia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure
**PSYCHIATRIC DISORDERS** - Confusion
**RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** - Adult respiratory distress syndrome; Pneumonitis; Pneumothorax; Pulmonary hypertension
**SKIN AND SUBCUTANEOUS TISSUE DISORDERS -** 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.

### 7.7 Accountability

Drug accountability records must be maintained at all sites according to good clinical practices and NCI guidelines. Please see Section 7.6.6 for additional considerations related to bevacizumab/placebo accountability.

### 7.8 Dose Modifications (8/2/10)

**7.8.1** *Bevacizumab*

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

**7.8.1.2** Concomitant bevacizumab (or placebo), if radiotherapy is interrupted:
If radiotherapy has to be temporarily interrupted for medical reasons unrelated to the bevacizumab (or placebo) administration, then treatment with every 2 week bevacizumab (or placebo) should be stopped until recovery (≤ grade 2 toxicity by CTC version 3). If radiotherapy has to be temporarily interrupted for technical reasons unrelated to bevacizumab (or placebo) administration, then treatment with every- 2=-week bevacizumab (or placebo) should continue.

**Treatment Modification for Bevacizumab- (or Placebo-) Related Adverse Events**

| Event | CTCAE.v3.0 Grade | Action To Be Taken |
|---|---|---|
| **Allergic reactions**<br><br>**or**<br><br>**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 (or placebo) administration.<br><br>**For patients with grade 3 reactions**, bevacizumab (or placebo) 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 at a rate of 90±15 min. **If bevacizumab (or placebo) 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 (or placebo) |
| **Arterial Thrombosis**<br>- Cardiac ischemia/ infraction<br>- CNS ischemia (TIA, CVA)<br>- any peripheral or visceral arterial ischemia/thrombosis | Grade 2 ( if new or worsened since bevacizumab therapy) | Discontinue bevacizumab (or placebo) |
| | Grade 3-4 | Discontinue bevacizumab (or placebo) |
| **Venous Thrombosis** | | |
| | Grade 3<br>OR<br>asymptomatic grade 4 | ▪ Hold bevacizumab (or placebo) treatment. If the planned duration of full-dose anticoagulation is < 2 weeks, bevacizumab (or placebo) should be held until the full-dose anticoagulation period is over.<br>▪ If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab (or placebo) may be resumed during the period of full-dose anticoagulation **IF** all of the criteria below are met:<br>- 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 (or placebo)<br>- The subject must not have pathological conditions that carry high risk of bleeding (eg, tumor involving major vessels or other conditions)<br>- The subject must not have had hemorrhagic events while on study<br>▪ If thromboemboli worsen/recur upon resumption of study therapy, discontinue bevacizumab (or placebo) |
| | Grade 4 (symptomatic) | Discontinue bevacizumab (or placebo) |
| **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**<br>-Diastolic BP > 100 mmHg | • Hold bevacizumab (or placebo) until symptoms resolve **AND** BP < 160/90mmHg* |
| | Grade 4 | Discontinue bevacizumab (or placebo) |

| Event | CTCAE.v3.0 Grade | Action To Be Taken |
|---|---|---|
| **Congestive Heart Failure** | Grade 3 | • Discontinue bevacizumab (or placebo) |
| | 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(or placebo) ] | |
| | UPC ratio < 3.5 | Continue bevacizumab (or placebo) |
| | UPC ratio ≥ 3.5 | Hold bevacizumab (or placebo)until UPC recovers to < 3.5 |
| | Grade 4 or nephrotic syndrome | Discontinue bevacizumab (or placebo) |
| **Hemorrhage (CNS or pulmonary)** | Grade 2-4 | • Discontinue bevacizumab (or placebo) |
| **Hemorrhage (non-CNS; non-pulmonary)** | Grade 3 | • Patients receiving full-dose anticoagulation should discontinue bevacizumab (or placebo)<br>• For patients not on full-dose anticoagulation, hold bevacizumab(or placebo) until ALL of the following criteria are met:<br>- the bleeding has resolved and Hb is stable<br>- there is no bleeding diathesis that would increase the risk of therapy<br>- there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence.<br>• Patients who experience recurrence of grade 3 hemorrhage should discontinue study therapy |
| | Grade 4 | Discontinue bevacizumab (or placebo) |
| **RPLS** (reversible posterior leukoencephalopathy syndrome **or PRES** (posterior reversible encephalopathy syndrome) | | • **Hold bevacizumab** (or placebo) **in patients with symptoms/signs suggestive of RPLS; subsequent management should include MRI scans and control of HTN**<br>• **Discontinue bevacizumab** (or placebo) **upon diagnosis of RPLS** |
| **Wound dehiscence** requiring medical or surgical intervention | | •**Discontinue bevacizumab**(or placebo) |
| **GI perforation, GI leak or fistula** | | Discontinue bevacizumab (or placebo) |
| **Bowel obstruction** | Grade 2 requiring medical intervention | • Hold bevacizumab (or placebo) until complete resolution, with a minimum of 4 weeks after surgery. |
| | Grade 3-4 | • Hold bevacizumab (or placebo)until complete resolution<br>• 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 (or placebo) until symptoms resolve to ≤ grade 1 |
| | Grade 4 | • Discontinue bevacizumab(or placebo)<br>• **Upon consultation with the study chair,** resumption of bevacizumab (or placebo) 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)

**7.8.2** *Temozolomide*

**7.8.2.1** Temozolomide During Concomitant Radiation Therapy:

No dose reduction will be made, but delay or discontinuation of temozolomide administration will be decided weekly according to hematologic and non-hematologic adverse events (AEs), as specified below.

If the administration of temozolomide has to be interrupted, the radiotherapy will proceed normally. Missed doses of temozolomide will not be made up at the end of radiotherapy. The total number of days and total dose of temozolomide will be recorded on the Treatment Summary Form (TF).

If one or more of the following are observed:

- ANC < $1.0 \times 10^9$/ L
- Platelet count < $75 \times 10^9$/L
- Grade 3 non-hematologic AE (except alopecia, nausea and vomiting while on maximal antiemetic therapy, and fatigue)

then treatment with concomitant temozolomide will be withheld until all of the following conditions are met:

- ANC ≥ $1.0 \times 10^9$/L
- Platelet count ≥ $75 \times 10^9$/L
- Grade ≤ 1 non-hematologic AE (except alopecia, nausea and vomiting, and fatigue)

In case of hematologic AE as defined above, a complete blood count (CBC) should be performed at least twice weekly. In case of non-hematologic AE, the patient should be assessed at least weekly with relevant laboratory test(s). As soon as all of the above conditions are met, the administration of temozolomide will resume at the same dose as used initially.

If one or more of the following are observed:

- ANC < $0.5 \times 10^9$/L (Grade 4)
- Platelet count < $25 \times 10^9$/L (Grade 4)
- Grade 4 non-hematologic AE (except alopecia, nausea and vomiting unless the patient has failed maximal antiemetic therapy, and fatigue)

then treatment with concomitant temozolomide should be **stopped**.

If the duration of radiotherapy exceeds 7 weeks, then concomitant treatment with temozolomide should be stopped after 49 days of temozolomide treatment.

***Summary of Temozolomide Delay or Discontinuation During Concomitant Radiation Therapy***

| AE | Value | Grade | Action |
|---|---|---|---|
| ANC | ≥ 0.5 and < $1.0 \times 10^9$/L | 2, 3 | **Delay** temozolomide until:<br>---ANC > $1.0 \times 10^9$/L<br>---Platelet > $75 \times 10^9$/L<br>---Non-hem AE ≤ 1 |
| Platelet count | ≥ 50 and < $75 \times 10^9$/L | 2, 3 | |
| Non-hematologic (except alopecia, nausea/vomiting unless on maximal antiemetic therapy) | NA | 3 | |
| ANC | < $0.5 \times 10^9$/L | 4 | **Stop** concomitant temozolomide |
| Platelet count | < $25 \times 10^9$/L | 4 | |
| Non-hematologic (except alopecia, nausea/vomiting) | NA | 4 | |

**7.8.2.1.1** *Concomitant temozolomide, if radiotherapy is interrupted*

If radiotherapy has to be temporarily interrupted for technical or medical reasons unrelated to the temozolomide administration, then treatment with daily temozolomide should continue. If radiotherapy has to be permanently interrupted then treatment with daily temozolomide should stop. Temozolomide can resume with the initiation of the adjuvant phase of treatment.

**7.8.2.2** Post-Radiation (Adjuvant) Temozolomide

Dosing is based on adverse events (AEs) during the prior treatment cycle. If multiple AEs are seen, the dose administered should be based on the dose reduction required for the most severe grade of any single AE.

| Dose Level | Temozolomide Dose, $mg/m^2$/day | Remarks |
|---|---|---|
| -2 | 100 | Reduction if prior AE |
| -1 | 125 | Reduction if prior AE |
| 0 | 150 | Starting dose cycle 1 (adjuvant) |
| +1 | 200 | Escalated dose at cycle 2, for cycles 2-12 in absence of AE |

**Delay**

On day 1 of each cycle (within the prior 72 hours), ANC ≥ 1.5 x $10^9$/L, platelet count ≥ 100 x $10^9$/L and all treatment-related grade 3 or 4 non-hematologic AEs (except alopecia, nausea, and vomiting) must have resolved (to grade ≤ 1).

If AEs persists, treatment should be delayed by 2 weeks for up to 4 consecutive weeks, so that the temozolomide dosing can coincide with the administration of the bevacizumab or placebo. If, after 4 weeks of delay, all AEs have still not resolved: then any further adjuvant treatment with temozolomide should be stopped.

**Dose escalation**

If, during the first cycle, all non-hematologic AEs observed were grade ≤ 2 (except alopecia, nausea and vomiting) and with platelets ≥ 100 x $10^9$/L and ANC ≥ 1.5 x$10^9$/L: then the temozolomide dose should be escalated to dose level 1 and this dose should be used as the starting dose for subsequent cycles. If treatment after cycle 1 has to be delayed because of ongoing non-hematologic AEs of grade ≥ 2, then no escalation is possible. If the dose was not escalated at cycle 2, then the dose should not be escalated in further cycles (3-12).

**Dose reductions**

If any non-hematologic AE observed was grade > 2 (except alopecia, nausea and vomiting) and/or if platelets < 50 x $10^9$/L and/or ANC < 1 x $10^9$/L, then the dose should be reduced by one dose level. For patients who would require dose reductions to a dose level < 100 $mg/m^2$/day, temozolomide will be stopped. Also, if any of the same non-hematologic grade 3 AE recurs (except alopecia, nausea and vomiting) after reduction for that AE, then temozolomide will be stopped.

If any treatment-related non-hematologic AE observed was grade 4 (except alopecia, nausea and vomiting) then adjuvant temozolomide treatment should be stopped.

*Subsequent cycles (3-12):* Any dose reductions of temozolomide will be determined according to (1) non-hematologic AE during the preceding treatment cycle, as well as (2) (2) the nadir (lowest/worst) ANC and platelet counts observed. No dose escalation should be attempted. The same dose reductions as for the second cycle should be applied.

*Important:* If the dose was reduced or delayed for adverse events, there will be no dose escalation.

The reason(s) for dose reduction and/or delay must be documented in the CRF.

***Summary of Dose Modification or Discontinuation During Post-Radiation Temozolomide***

| **Worst Non-Hematologic AE (except alopecia, nausea and vomiting) During the Previous Cycles** | |
|---|---|
| **Grade** | **Dose Modification** |
| **0-2** | No dose modifications for non-hematologic AEs. Dose escalations (only for cycle 2) or reductions based on ANC and platelet counts are applicable. |
| **3** | Reduce by one dose level (except alopecia, nausea and vomiting). Dose modifications (escalations or reductions) based on ANC and platelet counts are not applicable. No further escalation is possible. If the same non-hematologic grade 3 AE recurs (except alopecia, nausea and vomiting) after reduction for that AE, then stop. |
| **4** | Stop (except alopecia, nausea and vomiting). Dose modifications (escalations or reductions) based on ANC and platelet counts are not applicable. |

| **Nadir Values** | | **Platelets** | | |
|---|---|---|---|---|
| | | **≥100 x $10^9$/L** | **50 – 99 x $10^9$/L** | **< 50 x $10^9$/L** |
| **ANC** | **≥ 1.5 x $10^9$/L** | Escalation to DL 1 (cycle 2 only) | Dose unchanged | Reduce by 1 dose level |
| | **≥1 & <1.5 x $10^9$/L** | Dose unchanged | Dose unchanged | Reduce by 1 dose level |
| | **< 1 x $10^9$/L** | Reduce by 1 dose level | Reduce by 1 dose level | Reduce by 1 dose level |

**Note:** A complete blood count must be performed 21 days (± 48 hours) after the first daily dose of each adjuvant treatment cycle.

| **Hematologic AE on Day 1 of Each Cycle (within 72 hours before)** | |
|---|---|
| **AE** | **Delay** |
| **ANC< 1.5 x $10^9$/L and/or Platelet count < 100 x $10^9$/L** | Delay up to 4 weeks until all resolved. If unresolved after 4 weeks then stop. If resolved, dose delay/reductions based on non-hematologic AEs are applicable. If treatment has to be delayed for AEs, then no escalation is possible. |

| **Non-Hematological AE (except for alopecia, nausea and vomiting) on Day 1 of Each Cycle (within 72 hours before)** | |
|---|---|
| **Grade** | **Delay** |
| **2-3** | Delay up to 4 weeks until all resolved (to grade ≤ 1). If unresolved after 4 weeks, then stop. If resolved, dose delay/reductions based on ANC and platelets are applicable. If treatment has to be delayed for AEs, then no escalation is possible. |

## 7.9 Modality Review

This study will undergo a full review. After 50 patients have been accrued on the study and at least 8 months have passed since the last patient of this cohort has been enrolled, the Medical Oncology Co-Chair, Mark Gilbert, 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**; **variation, acceptable**; **deviation unacceptable**; **not evaluable for chemotherapy review**; or, **incomplete chemotherapy**. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year. Similar reviews will occur for each of the next 50 patient cohorts with the same timing until the initial 200 patients have been evaluated for compliance and eligibility issues.

## 7.10 Adverse Events (11/29/10)

**NOTE: For information regarding adverse events and reporting for the ACRIN 6686 advanced imaging component of the protocol, see Appendix XV.**

**Beginning December 31, 2010,** this study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for AdEERS reporting of adverse events. A copy of the CTCAE v4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). The CTEP home page also can be accessed from the RTOG web page at http://www.rtog.org/regulatory/regs.html. All appropriate treatment areas should have access to a copy of the CTCAE v4.0. **All AE reporting on the study case report forms will continue to use CTCAE version 3.0.**

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).

In the rare occurrence when Internet connectivity is lost, an AE report may be submitted using CTEP's Adverse Event Expedited Report-Single Agent or Multiple Agent paper template (available at http://ctep.cancer.gov) and faxed to 301-230-0159. 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 on a paper template or a 24-hour notification phoned in must be entered electronically into AdEERS by the original submitter at the site

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/members/toxicity/main.html) 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.

### 7.10.1 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: Expedited Adverse Event Reporting Requirements. December 2004.]

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 7.10 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.**

### 7.10.2 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 III Studies: All unexpected potentially related SAEs**

**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.

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 both the NCI at 301-230-0159 and 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.

### 7.10.3 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 using the NCI/CTEP Secondary AML/MDS Report Form available at http://ctep.cancer.gov/forms/index.html. The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification (RTOG study/case numbers). This form will take the place of a report via the AdEERS system and must be faxed to the Investigational Drug Branch, FAX 301-230-0159, and mailed to RTOG Headquarters (address below) within 30 days of AML/MDS diagnosis.

| RTOG Headquarters |
|---|
| AML/MDS Report |
| 1818 Market Street, Suite 1600 |
| Philadelphia, PA 19103 |

### 7.11 AdEERS Expedited Reporting Requirements (7/20/09)

**NOTE: For information regarding adverse events and reporting for the ACRIN 6686 advanced imaging component of the protocol, see Appendix XV.**

CTEP defines expedited AE reporting requirements for phase 3 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).

**Phase 3 Trials Utilizing an Agent Under a CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days[1] of the Last Dose of the Investigational Agent (Bevacizumab/Placebo) in this Study**

| | Grade 1 | Grade 2 | Grade 2 | Grade 3 | | Grade 3 | | Grades 4 & 5[2] | Grades 4 & 5[2] |
|---|---|---|---|---|---|---|---|---|---|
| | Unexpected and Expected | Unexpected | Expected | Unexpected with Hospitalization | Unexpected without Hospitalization | Expected with Hospitalization | Expected without Hospitalization | Unexpected | Expected |
| **Unrelated Unlikely** | Not Required | Not Required | Not Required | 10 Calendar Days | Not Required | 10 Calendar Days | Not Required | 10 Calendar Days | 10 Calendar Days |
| **Possible Probable Definite** | Not Required | 10 Calendar Days | Not Required | 10 Calendar Days | 10 Calendar Days | 10 Calendar Days | Not Required | 24-Hour; 5 Calendar Days | 10 Calendar Days |

[1] **Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:**

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

- Grade 4 and Grade 5 unexpected events

AdEERS 10 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

**Please see exceptions below under section entitled "Additional Instructions or Exceptions."**

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**Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. "On study" is defined as during or within 30 days of completing protocol treatment.**

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

**Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 3 Trials Utilizing an Agent under a CTEP IND:**

Grade 3-4 (with or without hospitalization) myelosuppression (platelets, neutrophils, leukocytes, hemoglobin) do NOT require expedited AdEERS reporting.

## 7.12 Clinical Trials Agreement

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies)

(hereinafter referred to as ”Collaborator(s)”) and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the “Intellectual Property Option to Collaborator” (http:// ctep.cancer.gov/industry) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient’s family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data”.):

   a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

   b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

   c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order.. Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator’s confidential and proprietary data, in addition to Collaborator(s)’s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be

forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Regulatory Affairs Branch, CTEP, DCTD, NCI
Executive Plaza North, Suite 7111
Bethesda, Maryland 20892
FAX 301-402-1584
Email: anshers@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

## 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: Anticonvulsants may be used as clinically indicated. Doses at study entry and at specific time points of the treatment must be recorded.

**NOTE**: The use of hepatic cytochrome p450 enzyme inducing anticonvulsants (EIAEDs) as outlined in Appendix XA will alter dosing of irinotecan if used as a component of treatment for patient participating in the unblinded component of treatment (see Section 11.6.1 and Appendix X). EIAED use does NOT change dosing of temozolomide, bevacizumab or placebo.

**9.1.2** Corticosteroids: Corticosteroids may be administered at the treating physician's discretion. Doses at study entry and at specific time points of the treatment must be recorded.

**9.1.3** Antiemetics: Prophylactic antiemetics may be administered at the treating physician's discretion. Guidelines for antiemetic prophylaxis with a 5-$HT_3$ antagonist are specified in Sections 7.2 and 7.3.

**9.1.4** Pneumocystis Carinii Prophylaxis:

Both corticosteroid therapy and continuous temozolomide therapy induce lymphocytopenia. Patients receiving any of these drugs or both concomitantly are at an increased risk for opportunistic infections. Therefore, a prophylaxis against *P. carinii* pneumonia is required for all patients receiving temozolomide during radiotherapy: trimethoprim-sulfamethoxazole (Bactrim forte®, Bactrim DS®) 1 tablet 3 times per week or monthly pentamidine inhalations (300 mg via aerosol monthly) or dapsone 100 mg po each day (except in patients with G6-PD deficiency). Prophylaxis is recommended to continue for the duration of radiotherapy, regardless of the lymphocyte count. After completion of the chemoradiation, patients with a lymphocyte count < 500/$mm^3$ should have CD4 quantification. If the CD4 is < 200, then prophylaxis is recommended to continue and the CD4 should be quantified on a monthly basis. If the lymphocyte count is ≥ 500 or the CD4 is > 200, then prophylaxis can be stopped.

### 9.2 Non-Permitted Supportive Therapy

**9.2.1** Growth factors are not permitted to induce elevations in neutrophil count for the purposes of: (1) administration of temozolomide on the scheduled dosing interval; (2) allowing treatment with temozolomide at a higher dose; or (3) avoiding interruption of the treatment during concomitant radiotherapy.

**9.2.2** No other investigational drugs will be allowed during the "blinded phase" of the study. Patients participating on the unblinded component may be allowed to use other investigational drugs after discussion with one of the study principal or co-principal investigators.

**9.2.3** Surgical procedures for tumor debulking, other types of chemotherapy, and immunotherapy or biologic therapy must not be used. Further, additional stereotactic boost radiotherapy is not allowed. If any of these treatments are required, the patient will not receive further therapy with temozolomide and bevacizumab or placebo according to this protocol. All further therapy is at the treating physicians discretion, but should be recorded in the CRF.

**9.2.4** Erythropoietin may not be administered because of possible synergistic toxicity with bevacizumab.

## 10.0 TISSUE/SPECIMEN SUBMISSION

### 10.1 General Information

This study requires mandatory central pathology review prior to registration (See Section 10.2). In addition, tissue of consenting patients will be stored at the RTOG Biospecimen Resource at the University of California San Francisco for tissue banking and translational research (strongly encouraged but not mandatory) (See Section 10.3).

The RTOG Biospecimen Resource 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.

### 10.2 Specimen Collection for Central Pathology Tissue Screening for Eligibility (Step-1 Registration)

Central pathology tissue screening is **mandatory** for this study and must occur in conjunction with Step 1 Registration. Dr. Ken Aldape will perform a pathology review for every case. The pathology review will consist of: (1) confirmation that the histologic features meet the WHO criteria for GBM; and (2) confirmation that the tissue is of sufficient size for analysis of MGMT status and determination of molecular profile.

Tissue specimens should be taken from pre-study diagnostic open biopsy or surgical resection. The following materials are required:

**10.2.1** Representative tissue blocks that contain diagnostic viable tumor.

As a guide, at least 1 cubic centimeter of tissue composed primarily of tumor must be present. Note that the tissue blocks composed primarily of either normal tissue or necrotic tissue are inadequate for molecular analysis, as it depends on the presence of viable tumor tissue. In cases where a single block has insufficient tumor, tissue for multiple blocks can be combined to ensure specimen adequacy. If Dr. Aldape determines that the block that was sent is insufficient, he will contact the site in an attempt to obtain additional tissue which could render the patient eligible, *provided there is sufficient time prior to randomization*. Given the narrow time frame for patient evaluation, *submission of at least 2 blocks is highly encouraged to maximize the chances of eligibility*. One or both blocks will be returned upon request. Examples of adequate and inadequate samples are shown in Appendix IV.

**10.2.2** A Pathology Report documenting that the submitted material contains tumor; the report must include the RTOG protocol number and the patient's initials. 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.

**10.2.3** A Specimen Transmittal Form listing pathology materials being submitted for Central Tissue Evaluation and a Pre-Randomization Pathology Submission Form (P4) completed by the local pathologist must be included in the pathology submission. These forms must include the RTOG protocol number and the patient's initials.

**10.2.4** An accompanying H&E is encouraged for rapid diagnosis but is not required. If an H&E is included, Dr. Aldape will use this for the review. If it is not included, Dr. Aldape will cut a section from the paraffin block, stain this with H&E, and use that slide for the review.

**10.2.5** Send pathology material by overnight mail directly to:

**Ken Aldape, M.D.**
**Department of Pathology, Box 85, Room G1.3563**
**UT MD Anderson Cancer Center**
**1515 Holcombe Blvd.**
**Houston, TX 77030**
**(713) 792-0634**
**FAX (713) 792-4049**
**kaldape@mdanderson.org**
**rtogpath@gmail.com**

- Include on the P4 form the name, telephone number, and fax number of the person to notify with the results of the tissue evaluation.
- Shipments must be made Monday through Thursday.
- Notify Dr. Aldape by email (please use both email addresses) on or before the day of submission: (1) that a case is being submitted for review; (2) the name of the contact person; (3) when to expect the sample; and (4) the overnight shipping carrier and tracking number.
- Dr. Aldape will email the appropriate contact person from the submitting institution with the results and will fax a copy of the completed form to the institution and to RTOG Headquarters. **If Dr. Aldape is given the proper email notification, review is guaranteed within 3 business days of receipt of the tumor block.**
- Since there is a narrow time window within which the review must be completed, submission of tumor blocks should be done as soon as possible to ensure sufficient time for review. *Dr. Aldape must receive the tumor block within 4 weeks of surgery to allow time for review and molecular testing. Samples received after this time will not be accepted in most cases*.
- If the patient does not meet eligibility requirements, *all* tissue and forms will be returned to the participating submitting institution.

**10.2.6** After confirming histopathologic diagnosis and adequacy of tissue for MGMT methylation analysis and molecular profiling, Dr. Aldape will inform the site that the patient can register to the trial.

**10.2.7** Upon patient registration, Dr. Aldape will cut sections for DNA/RNA isolation, send material for MGMT methylation analysis and perform the molecular profile test.

**10.2.8** When Dr. Aldape has completed the molecular profile and has been notified that the MGMT methylation test has been completed and was successful, he will: (1) send remaining materials to the RTOG Biospecimen Resource for consenting patients (see next section); or (2) return remaining materials to the submitting institution for non-consenting patients.

**10.3 Specimen Collection for Tissue Banking (Strongly Encouraged)** (8/2/10)
***[For patients who have consented to participated in this component of the study (See Tissue Consent of Appendix I)]***

**NOTE: Patients must be offered the opportunity to participate in the banking components of the study.** If the patient consents to participate in the tissue/specimen component of the study, the site is required to submit the patient's specimens for banking as detailed below.

**Sites are not permitted to delete the banking component from the protocol or from the sample consent.**

**10.3.1** Submission of frozen tissue is strongly encouraged to maximize the information gained from this trial. When available, frozen tissue should be sent on dry ice to the RTOG Biospecimen Resource as indicated in Section 10.3.3 and Appendix VIII. The RTOG Biospecimen Resource will supply kits for frozen tissue. To request a kit, contact the Biospecimen Resource at RTOG@UCSF.EDU or by phone at 415-476-7864.

**10.3.2** Tissue Blocks (collected and shipped per Section 10.2)
Dr. Aldape will send remaining tissue of consenting patients to the RTOG Biospecimen Resource. The Biospecimen Resource will punch tissue for banking. If desired, the remaining tissue will be sent back to the submitting institution.

**10.3.3** Serum, Plasma, Whole Blood, and Urine

- *Serum/plasma/whole blood* should be collected within 28 days prior to treatment. If a site misses this collection, the site can collect the whole blood aliquots at any time the patient is being seen for treatment or follow-up.

- *Urine* should be collected: (1) within 28 days prior to treatment; (2) 1-month following start of radiation therapy; and (3) on day 28 of the first post-radiation chemotherapy cycle.

- The following must be provided in order for the case to be evaluable for the Biospecimen Resource: A Specimen Transmittal Form documenting the date of collection of the serum, plasma, whole blood, and/or urine; the RTOG protocol number, the patient's case number, and method of storage, for example, stored at -80° C, must be included.

- See Appendix VII for detailed collection instructions, including information pertaining to collection kits. **Note:** Kits include a label for shipping.

- Submit materials to:

  **U.S. Postal Service Mailing Address: For Non-frozen Specimens Only**
  **RTOG Biospecimen Resource**
  **University of California San Francisco**
  **Campus Box 1800**
  **1657 Scott Street, Room 223**
  **San Francisco, CA 94143-1800**

  **Courier Address (FedEx, UPS, etc.): For Frozen Specimens**
  **RTOG Biospecimen Resource**
  **University of California San Francisco**
  **1657 Scott Street, Room 223**
  **San Francisco, CA 94115**

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

**10.4 Storage Conditions** (9/29/09)

Store frozen biospecimens at -80° C (-70°C to -90°C) until ready to ship on dry ice.
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 1 week (please ship out Monday-Wednesday only).

**- OR:**

- Samples can be stored in dry ice for up to 1 week, replenishing daily (please ship out on Monday-Wednesday only).

**- OR:**

- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only).

Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

## 10.5 Summary of Specimen Submission (8/2/10)

| Specimen | Collected When | Submitted As | Shipped How |
|---|---|---|---|
| **REQUIRED for Central Pathology Review** | | | |
| 1 block | From pre-study open biopsy or surgical resection | Paraffin-embedded block | Overnight mail to Dr. Aldape prior to registration |
| **STRONGLY ENCOURAGED for Central Pathology Review** | | | |
| 1 or more *additional* blocks | From pre-study open biopsy or surgical resection | Paraffin-embedded block | Overnight mail to Dr. Aldape prior to registration |
| Slide | From pre-study open biopsy or surgical resection | H&E stained slide | Overnight mail to Dr. Aldape Prior to registration |
| **STRONGLY ENCOURAGED for Tissue Banking** | | | |
| Tissue block; frozen tissue | From pre-study open biopsy or surgical resection | Frozen tissue | Overnight mail on dry ice to RTOG Biospecimen Resource at any time with notification; request collection kit from RTOG Biospecimen Resource |
| SERUM: 5-10 mL of whole blood in each of 2 red-top tubes and centrifuge | Pre-treatment | Frozen serum samples containing a minimum of 0.5 mL per aliquot in 1 mL cryovials | Frozen on dry ice to RTOG Biospecimen Resource via overnight carrier |
| PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/lavender top) and centrifuge | Pre-treatment | Frozen plasma samples containing a minimum of 0.5 mL per aliquot in 1 mL cryovials | Frozen on dry ice to RTOG Biospecimen Resource via overnight carrier |
| DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/lavender top), mix and aliguot | Pre-treatment. If pre-treatment time point is missed then this specimen can be collected at any time the patient comes in for treatment or follow-up. | Frozen whole blood samples containing a minimum of 0.5 mL per aliquot in 1 mL cryovials | Frozen on dry ice to RTOG Biospecimen Resource via overnight carrier |
| 5-15 mL clean-catch urine | Baseline, during radiation therapy, and 1-month following radiation therapy | Minimum of 5 mL unpreserved urine aliquotted into one-two 15 mL polypropylene tubes | Frozen on dry ice to RTOG Biospecimen Resource via overnight carrier |

## 10.6 Reimbursement (for Tissue Banking) (8/2/10)

RTOG will reimburse institutions for submission of protocol-specified biospecimen materials sent to the RTOG 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 & Case Credit Schedule found on the RTOG Web site (http://www.rtog.org/pdf_document/RTOG_STUDY_LIST.pdf). Biospecimen payments will be processed quarterly and will appear on the institution's summary report with the institution's regular case reimbursement.

### 10.7 Confidentiality/Storage

(See the RTOG Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/tissuebank/tissuefaq.html for further details.)

**10.7.1** 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.

**10.7.2** Specimens for tissue banking will be stored for an indefinite period of time. Specimens required for central review will be retained until the study is terminated. 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.

### 10.8 Planned Correlative Studies

Using banked frozen and formalin-fixed paraffin-embedded blocks, serum, and urine, efforts will be made to investigate possible predictive and prognostic biomarkers using high-throughput genetic, epigenetic (global methylation), and molecular analysis on the signal transduction, angiogenic, DNA Repair, and metabolic levels, respectively. These findings could ultimately shed additional insights into the underlying mechanisms of therapeutic resistance of GBMs and future strategies to overcome these putative resistance mechanisms.

## 11.0 PATIENT ASSESSMENTS: See Appendix II for a Summary of Assessments and Time Frames

### 11.1 Quality of Life Assessments (English Translations Not Available for This Protocol; enrollment restricted to English-speaking participants)

**NOTE: Sites must offer English-speaking participants the opportunity to participate in the quality of life component of this study.**

**11.1.1** EORTC Quality of Life Questionnaire-Core 30/Brain Cancer Module-20 (EORTCQLQ30/BCM20)

The EORTC QLQ-C30/BCM20 were developed and validated for use in this patient population. The QLQ-C30 is a 30-item self-report questionnaire that has patients rate the items on a 4-point scale, with 1 "not at all" to 4 "very much." The instrument measures several domains, including physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, fatigue, pain, nausea and vomiting, and several single items (dyspnea, insomnia, anorexia, constipation, diarrhea, and financial impact). The BCM20 consists of 4 scales comprised multiple items (future uncertainty, visual disorder, motor dysfunction, communication deficit) and 7 single items (headache, seizures, drowsiness, hair loss, itching, difficulty with bladder control, and weakness of both legs). The combined instrument takes an average of 8 minutes to complete by patients with primary brain tumors (Osaba 1996).

**11.1.2** M. D. Anderson Symptom Inventory Brain Tumor Module (MDASI-BT)

The MDASI-BT was developed and validated for use in this patient population. It consists of 23 symptoms rated on an 11-point scale (0 to 10) to indicate the presence and severity of the symptom, with 0 being "not present" and 10 being "as bad as you can imagine." Each symptom is rated at its worst in the last 24 hours. Symptoms included on the instrument include those commonly associated with cancer therapies, those associated with increased intracranial pressure, and those related to focal deficits. The MDASI-BT also includes ratings of how symptoms interfered with different aspects of a patient's life in the last 24 hours. These interference items include: general activity, mood, work (includes both work outside the home and housework), relations with other people, walking, and enjoyment of life. The interference items are also measured on 0-10 scales. The average time to complete the MDASI-BT by patients with primary brain tumors is 5 minutes (Armstrong in press).

## 11.2 Neurocognitive Function Assessments (English Translations Not Available for This Protocol; enrollment restricted to English-speaking participants)

**NOTE: Sites must offer English-speaking participants the opportunity to participate in the neurocognitive function component of this study.**

The healthcare professional (e.g., nurse, psychologist) who is responsible for test administration in this study must be pre-certified by Dr. Wefel. See Section 5.1.4 and Appendix V for details.

The tests in the neurocognitive test battery were selected because they are widely used standardized psychometric instruments that have been shown to be sensitive to the impact of cancer and the neurotoxic effects of cancer treatment in other clinical trials (Meyers 2004). The tests have published normative data that takes into account age, and where appropriate, education and gender.

The tests are given by certified site administrators, and the total time for the cognitive assessment is approximately 20 minutes, as follows:

| **Cognitive Domain** | **Test** | **Administration Time** (minutes) |
|---|---|---|
| Memory | Hopkins Verbal Learning Test-Revised (HVLT-R) | 5 |
| Cognitive Processing Speed | Trail Making Test, Part A | 3 |
| Executive Function | Trail Making Test, Part B | 5 |
| Verbal fluency | Controlled Oral Word Association Test (COWAT) | 5 |

**11.2.1** Hopkins Verbal Learning Test-Revised (HVLT-R)
The patient is asked to recall a list of 12 words over three trials. After a delay of 20 minutes, the patient is asked to spontaneously recall the words. The patient is then asked to identify the list words from distractors. There are six alternate forms of this test to minimize practice effects. The test measures learning memory retrieval, and memory consolidation processes. This measure has been widely used in clinical trials (Benedict 1998).

**11.2.2** Trail Making Test, Part A
This is a test of visual-motor cognitive processing speed, requiring the patient to connect dots in numerical order from 1 to 25 as fast as possible (Reitan 1992).

**11.2.3** Trail Making Test, Part B
This test is similar to Trail Making Test Part A, with the additional requirement of shifting mental set (an executive function). The patient connects dots alternating numbers and letters as fast as possible (Reitan 1992).

**11.2.4** Controlled Oral Word Association Test (COWAT)
This is a test of phonemic verbal fluency. The patient is asked to produce as many words as possible in 60 seconds beginning with a specified letter. There are two alternate forms of this test (Benton 1989).

## 11.3 CT/MRI Review (7/20/09)

**11.3.1** For Standard Imaging
The serial CT/MRI will be examined at the institution by an independent reviewer (i.e., a neuroradiologist who is not a co-investigator on this study and who is not involved in the patient's care). The evaluation of the scans will be compared to and correlated with the patient's clinical course. (**NOTE**: CT option ONLY for patients unable to undergo MR imaging because of non-compatible devices, provided that preoperative and postoperative scans are the same type.)

**11.3.2** For ACRIN 6686 Advanced Imaging MRI (for sites participating in the advanced imaging component)

**Note**: Use of MultiHance or Vasovist is not permitted in the advanced MRI (due to albumin binding).

A sub-set of sites will be pre-qualified to conduct advanced MRI sequences at 1.5 Tesla or 3 Tesla (preferred) for their participant patient population. For this Advanced Imaging, each visit MRI will also include the additional standard MRI sequences: T2-weighted images, FLAIR images, diffusion-weighted (or diffusion tensor) images, and 3D T1 volumetric imaging. Contrast agent application will be performed before the T1-weighted post contrast scan. Contrast is administered at the standard dose of 0.1 mmol/kg of standard Gd agent, intravenous injection for the DCE-MRI, and also 0.1 mmol/kg for the DSC-MRI. For the advanced MRI component of the trial, examinations will include perfusion MRI, including DCE and DSC sequences.

In the Advanced Imaging sub-study, DCE- and DSC-MRI will be performed at four time points:

- **T0:** At Baseline, within 0 to 5 days prior to initiation of chemoradiation;
- **T1:** At Week 3, within 0 to 3 days before the initiation of bevacizumab or placebo;
- **T2:** At same day of or 1 day after the first dose of bevacizumab or placebo (Week 3 + 1 Day or "Day 22"); and
- **T3:** At Week 10 of the study, 4 weeks after ending chemoradiation, during the adjuvant phase of the study.

Per protocol, each patient will also receive standard-of-care MRI scans every 2 months and one additional MRI scan after study exit to confirm progression.

**11.3.2.1** Advanced MRI Site Imaging Quality Assurance Review

Sites involved in Advanced Imaging must be pre-qualified for image quality per guidelines in Section 5.1.5 of the protocol. Information regarding the MRI quality assurance review process for Advanced Imaging can be found at http://www.acrin.org/6686_protocol.aspx, in Appendix XIV (Section 2.4), in the Protocol Specific Application (PSA), and in Section 5.1.5 of the protocol. Advanced MRI exam sequences will be collected and archived at ACRIN Headquarters for a post-trial centralized reader study.

*Central Advanced MRI QA Review and Assessment:* Advanced images will be assessed locally for quality and for disease progression. Patient-specific information will be removed from the image prior to submission. Advanced images will be transmitted electronically to ACRIN Headquarters. (Refer to Section 2 in Appendix XIV for image submission instructions.) This will allow early quality assurance (adherence to protocol, adequacy of image quality). Ongoing quality assessment in the ACRIN Core Lab will facilitate any revisions needed for this Advanced Imaging. It will also facilitate later central review of all images in a manner to minimize bias.

## 11.4 Measurement of Response [NOTE: A Radiology Review Form (SR) must be signed by the MD and submitted per Section 12.1] (8/2/10)

The primary measure of response will be by serial measures of the product of the two largest cross-sectional diameters. 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 http://ctep.cancer.gov/guidelines/recist.html for further details.

**11.4.1** *Complete Response **(CR)***: Circumstance when the enhancing tumor is no longer seen by neuroimaging, with the patient off all steroids or on adrenal maintenance only; CR will be coded only if confirmed by a second CT/MR scan performed a minimum of 4 weeks after the initial scan coding a response.

**11.4.2** *Partial Response **(PR)***: Decrease of > 50% in the product of two diameters. **Patients should be receiving stable or decreasing doses of steroids.** PR will be coded only if confirmed by a second CT/MR scan performed a minimum of 4 weeks after the initial scan.

**11.4.3** *Minor Response **(MR)***: Decrease in diameter products of < 50%. **Patients should be receiving stable or decreasing doses of steroids.** This will not need a confirmatory scan.

**11.4.4** *Stable Disease **(SD)***: Circumstance when the scan shows no change. Patients should be receiving stable or decreasing doses of steroids. This will not need a confirmatory scan.

**11.4.5** *Progression **(P)***: A > 25% increase in tumor area (two diameters) provided that the patient has not had his/her dose of steroids decreased since the last evaluation period. This will not need a confirmatory scan. A concomitant decrease in steroid dose will rule out a progression designation during the first 2 months after completion of XRT.

**11.4.6** *Pseudo-progression*: Recent studies have demonstrated that imaging studies performed soon (1 to 3 months) after the completion of the concurrent chemoradiation may demonstrate an increase in the enhancing abnormality after administration of intravenous contrast that is the result of an increase of blood-brain barrier permeability leading to an increase in contrast leakage. This is NOT tumor progression, as these effects will resolve over several months and the term "pseudo-progression" has been used to describe this phenomenon. Therefore, in the absence of neurologic worsening OR a new distant area of tumor, the initial post-chemoradiation scan should NOT be used to declare progression. Progressive worsening on subsequent imaging studies usually distinguishes true progression from pseudo-progression.

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

## 11.5 Criteria for Evaluation of Therapy Effectiveness (7/20/09)

**11.5.1** 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.)

**11.5.2** 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.

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

**11.5.4** Toxicities will be measured using the CTCAE criteria, version 3.0.

## 11.6 Criteria for Discontinuation of Protocol Treatment

- Progression of disease during the "blinded component" of the protocol; (note that patients would potentially be eligible for unblinded bevacizumab and approved combination regimens with bevacizumab – see 11.6.1 and following sections)
- 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/flowsheet, and RTOG Headquarters data management must be notified;
- A delay in drug therapy > 4 weeks for temozolomide or > 8 weeks for bevacizumab (or placebo) as described in Section 7.8.
- The patient may withdraw from the study at any time for any reason. The institution must notify RTOG Headquarters Data Management about this in writing and follow the guidelines set forth in the RTOG procedure manual.

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

**11.6.1** *Administration of Unblinded (Open-Label) Bevacizumab at Disease Progression*
Patients with progressive disease either during or after protocol treatment may receive bevacizumab as a single agent or in a combination regimen. See Appendix X for details.

## 11.7 Reader Study Design for Biomarker, Imaging, Quality of Life Study Funding Program (8/2/10)

**11.7.1** All available imaging time-points from the 942 cases enrolled into the study will be interpreted centrally, including both the conventional imaging arm cases from RTOG 0825 and advanced imaging arm cases from ACRIN 6686. The methods for analyzing these images will be standardized and are more fully described in the next paragraph. This will include initial visual assessments, but the manual quantitative measurements and semi-automated analyses of regions of interest will provide the majority of work and address the specific aims of the study (see Section 2.4.3).

All cases will be reviewed by board-certified radiologists with fellowship training and experience in neuro-radiology. A pair of radiologists will individually interpret the standard imaging cases from the master RTOG study and will provide the one dimensional (1-D), two dimensional (2-D), and volumetric (3-D) measurements using the facilities of the ACRIN Core Laboratory. Two neuro-radiologists will perform readings at different reading sessions to ensure that the interpretations will remain independent and the readers will perform each analysis in the case set. If readings are discordant, a third radiologist will adjudicate and determine the measurement category for the dataset. The cases will be randomly selected and a technologist will assist the reader by preparing the MRI studies for presentation and by recording the measurements. The readers will be blinded to the order of the scans but will interpret the data from all time points available. This approach will ensure that images are appropriately compared and will limit the confusion from differences in boundaries. Reader bias will be decreased by alternating temporal sequence, blinding any previous interreader results, and suppressing survival outcomes. No intrareader variability has been designed for this analysis. Some RTOG 0825 participants will participate in the advanced imaging from the ACRIN 6686 sub-study, and the central review of those data also will use two neuro-radiologists to determine the 1-D, 2-D, and 3-D measurements of those scans (possibly even the same two neuro-radiologists). Therefore, we will use ACRIN 6686 interpretations when possible to avoid duplicating effort, and both data sets will be combined and used in the statistical analysis.

**11.7.2** Data collected during the central sessions include: image quality, 2-D measurements of tumor area using the MacDonald criteria based on the 2-D T1 post-contrast sand T2 FLAIR series, 3-D measurement of tumor volume based on the 3-D T1 post-contrast series, 3-D measurement of tumor volume based on the T2 FLAIR series, and response assessments based on 2-D T1 measurements, 3-D T1 measurements, and 3-D T2 measurements. In addition, we plan to incorporate the Vasari common data elements for the baseline scan for each case.

**11.7.3** Tumor contours (3-D post-gadolinium volumetric contouring and 2-D FLAIR volumetric contouring) will be performed *a priori* by two sets of two ACRIN technologists, again using the procedures in place at the ACRIN Core Lab currently. Each set of two technologists will be paired with one of the central readers, and technologists will perform their contours blinded to the imaging time-point.

## 12.0 DATA COLLECTION (8/2/10)

**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

**Summary of Data Submission FOR PROTOCOL TREATMENT**

| Item | Due |
|---|---|
| Pre-Registration Pathology Submission Form **(P4)** | Within 4 weeks after surgery |
| Demographic Form **(A5)** | Within 2 weeks of registration |
| Pathology Report **(P1)** | Within 2 weeks of registration |
| Specimen Transmittal Form **(ST)** | Within 2 weeks of registration |
| Initial Evaluation Form **(I1)** | Within 2 weeks of registration |
| Quality of Life Assessments<br>▪ EORTC QLQ30/BCM20<br>▪ MDASI-BT | At registration, Wk 6, Wk 10, Wk 22, Wk 34, Wk 46, and Wk 62 (with Wks 22, 34, 46, and 62 coinciding with MRI evaluation during treatment). Thereafter, in conjunction with MRI at follow-up. |
| NCF Assessments (See Appendix V)<br>▪ HVLT-R<br>▪ Trail Making Test Part A<br>▪ Trail Making Test Part B<br>▪ COWAT | At registration, Wk 6, Wk 10, Wk 22, Wk 34, Wk 46, and Wk 62 (with Wks 22, 34, 46, and 62 coinciding with MRI evaluation during treatment). Thereafter, in conjunction with MRI at follow-up. |
| Treatment Summary Form **(TF)** | At the end of the first 3 weeks of RT; after completion of the remaining 3 weeks of RT (3rd dose of bevacizumab/placebo must be included); and at the end of each post-RT adjuvant cycle |
| Follow-Up Form **(F1)*** | At the conclusion of protocol therapy, then q 3 months X 1 year, q 4 months X 1 year; then q 6 months. Also at the time of progression/relapse and death. |
| Radiology Review Form **(SR)*** | Protocol treatment: Within 1 week of the start of cycles 1, 4, 7, & 10 & 1 month after final cycle; at progression |
| Operative Reports **(S2)**, Surgical Reports **(S5)** (for subsequent surgery) | As applicable |
| Autopsy Report **(D3)** | As applicable |

**Summary of Data Submission FOR SALVAGE TREATMENT**

| Item | Due |
|---|---|
| Radiology Review Form **(SR)*** | At 2nd progression, then within 1 week of the start of cycles 1, 4, 7, 10 & 1 month after final cycle<br><br>**NOTE**: The SR reporting progression **must** be completed to trigger the CX |
| Salvage Treatment Guideline Questionnaire **(SX)** | As soon as the treatment code is received and the decision is made to receive salvage treatment |
| Code Breaking Form **(CX)** | As soon as progression is confirmed |
| Salvage Treatment Summary Form **(SF)** | Monthly during salvage treatment for each cycle |

## 12.2 Summary of Dosimetry Digital Data Submission FOR PROTOCOL TREATMENT (Submit to ITC; see Section 12.2.1) (9/29/09)

| Item | Due |
|---|---|
| **Preliminary Dosimetry Information (DD)**<br>†Digital Data Submission – Treatment Plan submitted to ITC via SFTP account exported from treatment planning machine by Physicist<br>Digital data submission includes the following:<br>• CT data, critical normal structures, all GTV, CTV, and PTV contours<br>• Digital beam geometry for initial and boost beam sets<br>• Doses for initial and boost sets of concurrently treated beams<br>• Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan<br><br>Digital Data Submission Information Form **(DDSI)** – Submitted online (Form located on ATC web site, http://atc.wustl.edu/forms/DDSI/ddsi.html)<br><br>Hard copy isodose distributions for total dose plan as described in QA guidelines†<br><br>**NOTE: Sites must notify ITC via e-mail (itc@castor.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".** | Within 1 week of RT start |
| **Final Dosimetry Information**<br>Radiotherapy Form **(T1)**<br>Daily Treatment Record **(T5) [copy to HQ and ITC]**<br>Modified digital patient data as required through consultation with Image-Guided Therapy QA Center | Within 1 week of RT end |

†Available on the ATC web site, http://atc.wustl.edu/

**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@castor.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**

## 12.3 Image Scan Submission to ACRIN (for ALL cases) (8/2/10)

**ATTENTION:** Sites are to submit **all cases** to ACRIN for image archiving. This is **not** be confused with the ACRIN 6686 Advance Imaging Component.

**NOTE: Sites with patients participating in the ACRIN 6686 advanced imaging component should also refer to Appendix XIV for advanced image scan submission.**

Imaging examinations must be submitted to the ACRIN-Image Management Center (IMC) immediately after each time point in accordance with the chart below.

A completed, signed Image Transmittal Worksheet (ITW) MUST accompany all imaging exams submitted to ACRIN IMC for each time-point. The Image Transmittal worksheet can be found on the ACRIN web site for this study under Protocol Summary Table at http://www.acrin.org/6686_protocol.aspx.

For exams submitted via electronic transmission, complete this worksheet and fax to (215) 923-1737. For exams submitted via media, complete this worksheet and include with the media shipment. Please affix a label to the jacket of the media to include: study name, site name, NCI inst., code, case no., date of exam, time point, and type of imaging. Do not affix labels directly to the disk.

Images on CD or DVD-ROM, should be shipped to:

**ACRIN Image Archive**
**American College of Radiology**
1818 Market Street, Suite 1600
Philadelphia, PA 19103
Attn: RTOG 0825

ACRIN can provide software (TRIAD) for installation on a PC at your site that collects, anonymizes and submits image sets from your MRI system or from your PACS. The images are “DICOM pushed” either from the MRI system or from the PACS to the PC on which the software is installed. This software anonymizes and encrypts images as they are transferred via FTP to the ACRIN image archive. For more information, see **https://triad.acr.org**.

TRIAD Image Submission software PC requirements:

1. Network capability to transmit data from a scanner to a linked workstation, PC, or PACS
2. A Windows XP PC available to transmit data (patient data, MR and PET image data) to ACRIN:
   a. Operating System Windows XP Pro
   b. Access to the Internet: Internet Explorer
   c. Minimum of 50 GB available hard drive
   d. At least 1 GB RAM
   e. Ability to view PDF documents

3. Software utilities required:
   a. Windows Installer 3.1
   b. Microsoft .NET framework 2.0
   c. MDAC Type 2.8
   d. MS SQL 2005 Express

**Please contact the TRIAD help desk (Triad-Support@ acr-arrs.org) or 215-940-8820 regarding installation requirements and to arrange the installation of TRIAD software prior to first accrual.**

**For questions regarding site qualification, image acquisition or image submission, contact Jim Gimpel RT(R)(MR), lead technologist for this trial at: imagearchive@ acr-arrs.org or 215-574-3238.**

| Item | Due |
|---|---|
| Pre-operative and post-operative scans **(MR)** **Each scan must be accompanied by an ITW MRI submission form** | Within 1 week of RT start |
| Post-operative scan for detection of hemorrhage (if applicable) **(MR)** **Each scan must be accompanied by an ITW MRI submission form** | Within 1 week of RT start |
| Scans obtained during adjuvant treatment phase [*Before initiation of cycle 1, 4, 7 (if administered), 10 (if administered) within 72 hrs prior to d 1 & 1 mo after final cycle completion*] **(MR)** **Each scan must be accompanied by an ITW MRI submission form** | Within 1 week of obtaining scan |
| Progression scan **(MR)** **Each scan must be accompanied by an ITW MRI submission form** | Within 1 week of obtaining scan |

## 12.4 ACRIN 6686 Summary of Data Submission for Sites with Patients Participating in the Advanced Imaging Component (7/20/09)

**NOTE: ALL sites should also refer to Section 12.3 for submission instructions for standard MR images.**

**Refer to Appendices XIII and XIV for detailed instructions for advanced MR image submissions.**

### 12.4.1 General Imaging Data

All imaging data forms will be entered through ACRIN's Data Center. The web address is www.acrin.org.

### 12.4.2 Clinical Data Submission

**12.4.2.1** Upon successful registration to RTOG of participants consented to the advanced MRI option, an ACRIN case-specific calendar will be generated. This calendar lists all forms and designated reports required by protocol along with form due dates at ACRIN's Data Management Center (DMC). The calendars are available 24 hours a day on the ACRIN website and will be updated as the study proceeds to reflect data that have been received, due dates for queries about unclear data, deadlines for follow-up reports of adverse events, or changes in the protocol that change the data being collected or the timeframe. The research associate may use the calendar as a case management tool for data submission and follow-up scheduling. The investigative site is required to submit data according to protocol as detailed on each participant's ACRIN calendar.

**12.4.2.2** To submit data via the ACRIN web site, the appropriate investigator-designated research staff will log in to the Data Center through the ACRIN web site with the pre-assigned user name and password. Case report forms will be available on the web site at http://www.acrin.org/6686_protocol.aspx. Each web form is separated into modules; each module must be completed sequentially in order for the internal programming to be accurate. The user selects the link to the appropriate form and enters data directly into the web-based form. As information is entered into the web form application, various logic checks will be performed. These logic checks look for data that are missing, out of range, or in the wrong format (e.g. character data in a field requiring numeric responses). Such errors will be detected as soon as the user attempts to either submit the form or move to the next data element. The user will not be able to finalize form transmission to the DMC until all data entered pass these logic checks. Forms that are not completed in one sitting can still be submitted and completed at a later date. The form will remain available on the web until the "Complete Form" button is depressed.

**12.4.2.3** Once data entry of a form is complete, and the summary form is reviewed for completeness and accuracy, the investigator or the research staff presses the "Complete Form" button on the form summary screen and the data is transferred into the clinical database. No further direct revision of the submitted data is allowed after this point. E-mail confirmation of web data entry is automatically generated and sent to the site investigator or research associate listing all of the data generated and just submitted. Should a problem occur during transmission and the e-mail confirmation of data submission is not received, the investigator or research associate should contact the DMC for resolution of the submission.

**12.4.2.4** If technical problems prevent access to the Data Center website, sites will be unable to enter data. The site RA or investigator should notify the DMC if a problem with the Data Center is encountered. All sites will be notified through an ACRIN broadcast message when access to the web data entry is unavailable and the estimated time when access will be restored. The investigative site should wait until access is restored to submit data.

**12.4.3 Data Security**

The registration and data collection system has a built-in security feature that encrypts all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system is controlled by a sequence of identification codes and passwords.

**12.4.4 Electronic Data Management**

**12.4.4.1** Data received from the web-based forms are electronically stamped with the date and time of receipt by the ACRIN server; the data are then entered into the database. A protocol-specific validation program is used to perform more extensive data checks for accuracy and completeness. Complementary validation programs are initiated at the Biostatistics and Data Management Center (BDMC) that are more comprehensive than those built into the web-based data entry screens. The BDMC will run thorough cross-form validations, frequency distributions to look for unexpected patterns in data, and other summaries needed for study monitoring. The validation program generates a log of errors which is managed by the DMC Data Manager (DM). The program is frequently updated to incorporate exceptions to rules so that subsequent validity checks minimize the time DMC spends resolving problems. All communication with the participating sites is handled by the DMC.

**12.4.4.2** If missing or problematic data is detected, the DM sends an Additional Information Request (Z1 query letter) to the site RA or investigator specifying the problem and requesting clarification. The DM updates the participant's data submission calendar with the Z1 due date to notify the site RA or investigator of when a response is expected. The calendar will be updated upon receipt of the query response.

**12.4.5 Missing and Delinquent Data Submission**

In addition to providing the investigator a data collection calendar for each case, the DMC periodically prompts institutions for timely submission of data through the use of a Forms Due Report. This report lists data items (e.g. forms, reports, and images) that are delinquent. It is distributed at regular intervals via the electronic mail system to both the RA and the investigator at each site. In addition to prompting clinicians to submit overdue data, the Forms Due Report helps to reconcile the DMC's case file with that of the RA and/or investigator. Future Forms Due Reports may be sent on an as-needed basis in addition to past due reports. The site investigator or RA may use the Forms Due and Future Due Reports as a case management tool. At any time, sites may run their own Forms Due Reports using the Site Operations Tool on the ACRIN website.

**12.4.6 Data Quality Assurance**

**12.4.6.1** The Biostatistics Center (BC) at Brown University will maintain a study database at its site for monitoring data quality and for performing analyses. These data are drawn directly from the permanent database at the DMC. The transfer of data between the DMC and the BC have been validated through a series of checks consisting of roundtrip data verification in which data are sent back and forth to verify that the sent data are equivalent to the received data. These checks are repeated at random intervals during the course of a given study. Any discrepancies and other data quality issues will be referred to the DMC for resolution, since only the DMC can correct the data file. No changes to the data will be made at the BC.

**12.4.6.2** Data will be monitored to assess compliance with the protocol and to look for unforeseen trends that may be indicative of procedural differences among clinical sites. If patterns are discovered in the data that appear to arise from causes specific to an institution, the DMC will contact the site to resolve the problem. The ACRIN Protocol Development and Regulatory Compliance (PDRC) Department will be involved in this process as needed. If the BDMC and PDRC cannot reconcile the problem with the site, it will be brought to the ACRIN Quality Assurance (QA) Committee for further discussion and resolution.

## 13.0 STATISTICAL CONSIDERATIONS (7/20/09)

**NOTE: See Section 13.7 for Statistical Considerations for ACRIN 6686 Advanced Imaging Component**

### 13.1 Study Endpoints

**13.1.1** Composite Primary Endpoint

**13.1.1.1** Overall survival, defined as the interval from randomization to death due to any cause.

**13.1.1.2** Progression-free survival, defined as the interval from randomization to progression or death, whichever occurs first

**13.1.2** Secondary Endpoint

**13.1.2.1** Treatment-related toxicity.

**13.1.3** Tertiary Endpoints (Exploratory)

**13.1.3.1** Quality of life measured by the M.D. Anderson symptom inventory brain tumor module (MDASI-BT tool) and EORTC Quality of Life Questionnaire-Core/Brain Cancer Module( QLQ-C30/BCM20)

**13.1.3.2** Neurocognitive function measured by the Hopkins Verbal Learning Test-Revised(HVLT-R), Trail Making Test Part A, Trail Making Test Part B, Controlled Oral Word Association Test (COWAT)

**13.1.3.3** *Rationale for the designation of tertiary endpoints*

RTOG 0525 successfully achieved large scale incorporation of multidimensional patient outcome assessments with excellent accrual and retention, based on early review of submitted data, of malignant glioma patients. However, patient outcome data (i.e., neurocognitive function, symptom and health-related quality of life measures) from this trial are not yet available. Limited published data exist concerning the effects of bevacizumab with and without temozolomide on these endpoints as well. Despite the lack of empirical data, anecdotal clinical evidence is emerging suggesting that there is reason to believe that the addition of bevacizumab may result in measurable effects on patient well-being that is not captured by MRI imaging changes alone.

Performance status is inadequate as a proxy for formal measurement of neurocognitive function, symptoms and health-related quality of life. Thus, we plan to incorporate the same multidimensional set of measures into RTOG 0825 that were utilized in RTOG 0525. This multidimensional set includes measurement of neurocognitive function, symptoms, and health-related quality of life to establish the

nature and extent of differences associated with the addition of bevacizumab therapy to standard concurrent chemoradiation with temozolomide followed by adjuvant temozolomide in these endpoints. Patient participation in this component of the trial will be optional, as it was in RTOG 0525, and thus these endpoints will be considered exploratory to generate future hypotheses to be tested.

## 13.2 Sample Size (8/2/10)

### 13.2.1 Treatment Comparison: Sample Size Derivation and Power Justification

Concurrent chemoradiation and standard temozolomide dose maintenance, serving as the control arm in an ongoing phase III study RTOG 0525, will continue to serve as the control arm in this proposed design. The composite primary endpoint of RTOG 0825 tests overall survival for the hypothesized hazard ratios of **0.75** and progression-free survival for the hypothesized hazard ratios of 0.70. The hazard ratios compare the bevacizumab-containing regimen to the control arm. The sample size calculation will address whether the addition of bevacizumab to concurrent chemoradiation and standard temozolomide will improve overall and/or progression-free survival in patients with glioblastoma. The statistical power is set as 0.8 and the significance levels for overall and progression-free survival are 0.023 and 0.002 (both one-sided), respectively, to maintain the overall significance level of 0.05 at the time of final overall survival analysis. The null hypothesis for overall survival is that both arms will have a median survival time of 14 months. The alternative hypothesis for overall survival is that patients receiving the experimental regimen will have a median survival time of at least 18.7 months, corresponding to a 25% relative hazard reduction. Using a one-sided test with alpha of 0.023 and four planned analyses (three interim analyses when 25%, 50% and 75% cumulative information for overall survival is available and one final analysis when complete information for overall survival is available), a total of **390** deaths are required to detect the hypothesized survival difference with 80% power. Assuming median time for progression-free survival of 6.7 and 9.6 months for the control and experimental arms, respectively, in order to maintain the overall type I error of 0.025 (one-sided) for this study the progression-free survival difference will be tested at the one-sided significance level of 0.002. The trial will be declared positive if either the overall or progression-free survival comparison of the treatments is statistically significant favoring the bevacizumab-containing arm at 0.023 and 0.002, respectively. A total of **612** analyzable patients are required. Guarding against up to a 5% ineligibility rate and another 10% non-randomization rate due to progression, death, or refusal the final targeted accrual for this study will be **720** cases. Based upon the analysis of the first 360 patients entered, the rate of patients not being randomized due to ineligibility, insufficient tissue, progression, patient refusal, or other reasons was very much underestimated (35% vs. originally projected 15%). So a slightly higher nonrandomized rate of 35% was adopted to recalculate the targeted sample size for the study. With that rate **942** patients would have to be entered in order to have 612 patients randomized.

If the RTOG 0525 results determine that intensified temozolomide maintenance is better than standard temozolomide maintenance, both arms of RTOG 0825 will be modified through a protocol amendment to include intensified temozolomide maintenance. However, the primary hypothesized hazard ratios for overall and progression-free survival will remain same.

### 13.2.2 Molecular Profile: Power Justifications

Endpoints for the molecular correlative studies will be overall survival and progression-free survival. Endpoints will be measured within each treatment arm, as well as the study as a whole. For planning purposes, it is assumed that patient accrual will not be discontinued before the trial reaches its final analysis. Molecular profile is a stratification variable in this study; therefore, it is projected that all randomized patients will be available for molecular profile evaluation. It is expected that >90% patients will be classified as having either favorable or unfavorable molecular profile and less than 10% will be indeterminate; therefore, a total of 550 patients (275 per treatment arm) will be available for the molecular profile analysis focusing on the favorable and unfavorable groups. Patients with indeterminate molecular profile will be analyzed separately.

The hypothesis to be tested is the prognostic value of molecular profile for overall survival in patients within and across the different treatment regimens. Patients will be divided into two groups: one with mesenchymal-angiogenic phenotype (unfavorable) and the other with proneural phenotype (favorable). It is expected that **70% to 80%** of patients will be in the mesenchymal-angiogenic group (unfavorable) based upon previous studies (submitted to NEJM; See Appendix XI).

The equation described by Schoenfeld was used to calculate statistical power for univariate analyses:

Number of failures = $(z_{1-\alpha/2} + z_{1-\beta})^2 / (\ln HR)^2 \, w \, (1 - w)$, where:

$z_{1-\alpha/2}$ = normal deviate for the significance level
$z_{1-\beta}$ = normal deviate for the statistical power
HR = hazard ratio comparing unfavorable risk group (mesenchymal-angiogenic group) to favorable risk group (proneural phenotype)
w = prevalence rate of unfavorable risk group

Table 13.1 shows statistical powers to detect hazard ratios for survival of 2.0, 2.25, and 2.5, as well as hazard ratio detections with 80% and 90% power for prevalence rates of 70%, 75%, and 80%. When the proposed analysis is performed, we expect approximately **179 and 211** deaths on the bevacizumab-containing arm and the control arm, respectively, among a total of **390** deaths on both arms if the study results show a positive treatment. After excluding patients with indeterminate molecular profile, we expect approximately **161, 190, and 351** deaths with molecular profile determination on the bevacizumab-containing arm, the control arm, and combined arms, respectively. The significance level is set at 0.05. As seen in below, in each comparison there will be greater than 95% statistical power to detect a hazard ratio of 2 or bigger, as reported for molecular profile by Aldape et al (submitted to NEJM). Statistical power is calculated at a significance level of 0.05 (two-sided) for the experimental arm, the standard arm, and whole study if the overall survival for this study is positive.

Table 13.1: Statistical power and hazard ratio detection between two molecular profile groups under various scenarios of prevalence within and across treatment regimens

| | Number of events | Prevalence | Hazard Ratio | | | 80% power HR detection | 90% power HR detection |
|---|---|---|---|---|---|---|---|
| | | | 2.0 | 2.25 | 2.5 | | |
| Experimental arm | 161 | | | | | | |
| | | 70% | 0.98 | 0.99 | 0.99 | 1.62 | 1.75 |
| | | 75% | 0.96 | 0.99 | 0.99 | 1.67 | 1.80 |
| | | 80% | 0.94 | 0.98 | 0.99 | 1.74 | 1.89 |
| Standard arm | 190 | | | | | | |
| | | 70% | 0.99 | 0.99 | 0.99 | 1.56 | 1.67 |
| | | 75% | 0.98 | 0.99 | 0.99 | 1.60 | 1.72 |
| | | 80% | 0.96 | 0.99 | 0.99 | 1.66 | 1.80 |
| Whole study | 351 | | | | | | |
| | | 70% | 0.99 | 0.99 | 0.99 | 1.39 | 1.46 |
| | | 75% | 0.99 | 0.99 | 0.99 | 1.41 | 1.49 |
| | | 80% | 0.99 | 0.99 | 0.99 | 1.45 | 1.54 |

This study will also determine whether the addition of bevacizumab to temozolomide and radiation enhances treatment efficacy (overall and progression-free survival) compared with conventional temozolomide and radiation in patients with favorable and unfavorable molecular profiles. Table 13.2 demonstrates statistical power to detect the hazard ratios between the two treatment regimens for survival of 0.75, 0.67, and 0.5, as well as hazard ratio detections with 80% power for prevalence rates of 30%, 25%, and 20% for the favorable group (70%, 75%, and 80% for the unfavorable group). The hazard ratios here still compare the bevacizumab-containing regimen to the standard temozolomide and radiation arm. Assuming that the hazard ratio of 2.0 for overall survival between the unfavorable and favorable profile groups, observed from Dr. Aldape's laboratory, still holds true in this study, when the proposed final analysis for overall survival is performed (390 deaths/351 deaths with molecular profile determination), we expect approximately 76, 63, and 49 deaths in the favorable group (275, 288, 302 deaths in the unfavorable group) with prevalence rates for unfavorable molecular profile of approximately 70%, 75%, and 80%. The significance level is set as 0.05 (two-sided). As seen in Table 13.2, within the unfavorable group, there will be greater than 90% power to detect a hazard ratio of 0.67 or less and modest power (> 60% power) to detect a hazard ratio of 0.75 or bigger; conversely, there will be modest power to detect a hazard ratio of 0.5 or less and inadequate power

to detect a hazard ratio of 0.67 or bigger within the favorable group.

Table 13.2: Statistical power and hazard ratio detection between two treatment groups under various scenarios of prevalence within two molecular profile groups

| | Prevalence | Number of events | Hazard Ratio | | | 80% power HR detection |
|---|---|---|---|---|---|---|
| | | | 0.75 | 0.67 | 0.5 | |
| Favorable molecule profile group | | | | | | |
| | 30% | 76 | 0.23 | 0.42 | 0.85 | 0.53 |
| | 25% | 63 | 0.20 | 0.36 | 0.78 | 0.49 |
| | 20% | 49 | 0.16 | 0.29 | 0.67 | 0.45 |
| Unfavorable molecular profile group | | | | | | |
| | 70% | 275 | 0.65 | 0.91 | 0.99 | 0.71 |
| | 75% | 288 | 0.67 | 0.93 | 0.99 | 0.72 |
| | 80% | 302 | 0.69 | 0.94 | 0.99 | 0.72 |

**13.2.3** MDASI-BT/EORTQLQ30/BCM20 and Neurocognitive Function Evaluation: Statistical Power Considerations

The meaningful effect size for quality of life tools is still in debate. Cohen's widely used rules of thumb for interpreting the magnitude of difference define 0.8 standard deviation (SD) as a "large" effect size, 0.5 SD as a "median" effect size, and 0.2 SD as a " small" effect size (Cohen 1988). Consensus from the literature seems to indicate that 0.5 SD is a conservative estimate of an effect size that is likely to be clinically meaningful. In the absence of other information, the 0.5 SD is a reasonable and scientifically supportable estimate of a meaningful effect. Effect size below 0.5 SD, supported by data regarding the specific characteristics of a particular quality of life assessment or application, may also be meaningful (Sloan 2005). This discussion is also very applicable to the MDASI-BT/EORTQLQ30/BCM20 and the neurocognitive function tools. For planning purposes, we will assume 35% of enrolled patients will not be randomized to either the experimental or standard arm; therefore among the 942 enrolled patients there will be 612 patients potentially eligible for the quality of life and neurocognitive function components.

Because patient participation in any of these components is not mandatory, we expect that 30% to 50% of patients will participate in the quality of life/neurocognitive component for this study, with baseline and 6 week data submission, given the experience of the quality of life/neurocognitive function endpoints in the ongoing RTOG 0525. Briefly, with a sample size of 92, 123, and 153 per treatment arm, we will have 92%, 97%, and 99% power to detect an effect size difference of 0.5 between the two treatment groups at the significance level of 0.05 (two-sided) in the selected scores/subscales of the MDASI-BT, EORTQLQ30/BCM20QLQ, and neurocognitive function tools, respectively. Table 13.3 shows the power for the treatment comparison under various effect sizes and proportions of patients with data submission for MDASI-BT, EORTQLQ30/BCM20QLQ, and neurocognitive function tools.

The treatment comparison with regard to MDASI-BT, EORTQLQ30/BCM20QLQ, and neurocognitive function tools between baseline and 10 weeks is also of interest. Assuming that 10% of patients with baseline and 6 week data submission will not be available with information at 10 weeks due to disease progression, death, or other reasons, there will be 82, 110, and 137 patients per arm with baseline and 10 week data for the MDASI-BT, EORTQLQ30/BCM20QLQ, and neurocognitive function tools, respectively, with the previous assumed rates of participation in this component of the study. Table 13.4 shows the statistical power for the treatment comparison in terms of the MDASI-BT, EORTQLQ30/BCM20, and neurocognitive function tools, between baseline and 10 weeks. These treatment comparisons will be considered exploratory in nature, and no effort will be made to control for the overall significance level.

Table 13.3: Power of the treatment comparison at alpha = 0.05 (two-sided) between baseline and 6 week data

| Effect size detection in standard deviation | Proportion of randomized patients with MDASI-BT, EORTQLQ30/BCM20, neurocognitive function data (corresponding number of patients per treatment arm) | | |
|---|---|---|---|
| | 30% (92) | 40%(123) | 50%(153) |
| 0.80 | 0.99 | 0.99 | 0.99 |
| **0.50** | **0.92** | **0.97** | **0.99** |
| 0.40 | 0.76 | 0.87 | 0.93 |
| 0.33 | 0.60 | 0.73 | 0.80 |

Table 13.4: Power of the treatment comparison at alpha = 0.05 (two-sided) between baseline and 10 week data

| Effect size detection in standard deviation | Proportion of randomized patients with MDASI-BT, EORTQLQ30/BCM20, neurocognitive function data (corresponding number of patients per treatment arm) | | |
|---|---|---|---|
| | 30% (82) | 40%(110) | 50%(137) |
| 0.80 | 0.99 | 0.99 | 0.99 |
| **0.50** | **0.88** | **0.95** | **0.98** |
| 0.40 | 0.72 | 0.83 | 0.90 |
| 0.33 | 0.55 | 0.68 | 0.77 |

## 13.3 Patient Accrual (8/2/10)

The average monthly accrual rate to RTOG 0525 for the same patient population was 50 cases and approximately 80% were from RTOG and NCCTG institutions. In light of these rates, the projected accrual rate for this study will be 40 cases per month (480 per year). During the first 6 months following activation, little accrual is anticipated while the trial is being approved by institutional IRBs; therefore we expect that the study should meet its targeted sample size in 24 months. If the total accrual during months 13 through 18 of the study is ≤ 20% of the targeted accrual (≤ 8 cases per month), the protocol will be discontinued per NCI-CTEP accrual guidelines for phase III studies. If the total accrual is between 21% and 49%, the protocol will continue to accrue subject to approval of the RTOG Data Monitoring Committee (DMC) and NCI-CTEP. If continued, the study must accrue at least 50% of targeted accrual (> 20 cases per month) during months 22 through 24 to remain open beyond 2 years.

Given the planned analyses of patients within the unfavorable and favorable molecular profile subgroups, the proportion of patients who will not be able to be assessed for molecular profile (indeterminate) will need to be closely monitored, and this will be reported at regular intervals (see Section 13.5.6). Likewise, the proportion of patients who are deemed retrospectively ineligible or not randomized will also be regularly monitored. After the first 360 patients have been entered, these two rates will be formally evaluated to assure that enough patients with determined molecular profile will be accrued. If the rate with undetermined molecular profile is greater than 15% or if the rate of ineligibility or failure to be randomized is greater than 20%, an amendment increasing the study sample size will be proposed to the RTOG Brain Steering Committee.

The analysis for June 2010 RTOG semi-annual meeting showed that, based on the first 360 enrolled patients, the percentage of patients not being randomized due to a variety of reasons was higher than what we projected (35% vs. 15%). Thus, a greater of number of patients must be initially enrolled in order to achieve the originally targeted sample size of 612 patients for randomized comparison between these two treatment arms. This is not a protocol-stipulated interim efficacy or futility analysis. In order to achieve the targeted sample size for randomized comparison after adjusting for the higher nonrandomized rate of 35%, 942 patients will have to be initially enrolled in the study. The study should meet its targeted sample size within 26 months after initial study activation based on the current observed monthly accrual of 40~50 cases.

## 13.4 Patient Randomization (8/27/09)

The randomization to bevacizumab or placebo will occur by Wednesday (cycle 1, day 10) of week 2 of radiation. Patients will be stratified by MGMT methylation status (methylated vs. unmethylated vs. invalid) and by tumor molecular profile (metagene score: favorable vs. unfavorable vs. undetermined). This results in 9 strata, and randomization will be conducted within each stratum. The treatment allocation scheme described by Zelen (Zelen 1974) will be used because it balances patient factors other than

institution. For the first 60 patients, two of every three patients in each stratum will be randomized to the experimental arm to minimize the number of patients assigned to that arm if the addition of bevacizumab to chemoradiation proves to be too toxic. For the next 60 patients, one of every three patients in each stratum will be randomized to the experimental arm to balance out the treatment assignments between the two arms. After that, patients will be assigned with equal probability to each arm in each stratum, resulting in equal allocation for the trial overall.

## 13.5 Analysis Plan (8/27/09)

### 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. Differences in observed severities of toxicities (grade 3+) between groups will be tested using a chi square test.

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. 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.

Statistical analysis will also be performed to identify the effect of molecular profile on overall and progression-free. In univariate analysis, the log-rank test will be used to test for overall and progression-free survival differences between the favorable and unfavorable risk groups. Multivariate analysis will be performed using the Cox proportional hazard model for both outcomes to determine if molecular profile is an independent prognostic factor and possibly a predictive factor for the use of bevacizumab. The covariates evaluated for the multivariate models are: assigned protocol treatment; MGMT methylation status; molecular profile; RTOG RPA risk class; and the interactions of treatment with methylation status, molecular profile, and RPA class.

In addition, there will be two subset analyses comparing the two treatments: one subset of patients with both MGMT unmethylated status and an unfavorable molecular profile (~35% of patients), and a second subset of patients with both MGMT methylated status and a favorable molecular profile (~10% of patients). In the first subset, it is hypothesized that the biggest positive effect on outcome for the bevacizumab arm will be seen. The rationale for this hypothesis is that we find the most aggressive tumors (those with the most unfavorable metagene scores) are also the most angiogenic (Phillips, Kharbanda et al. 2006.) In the second subset, it is hypothesized that there will be little positive, or possibly a negative, effect on outcome for the bevacizumab arm. The rationale for these hypotheses is that patients with favorable metagene scores will show a good response to standard therapy, a response that will not be appreciably improved by the addition of bevacizumab. Therefore, it is also necessary to consider the power justifications for the interactions between received treatment, MGMT status, and molecular profile. There are two levels for treatment: standard temozolomide and bevacizumab-containing regiment. There are four levels for the different combinations of MGMT status and molecular profile. Therefore, the 2*4 factorial design was used to test this interaction in Table 13.5.

Table 13.5: Hypothesized hazard rates, hazard ratios, and expected death numbers at each different combination of MGMT methylation status and molecular profile

| | MGMT Methylated | | MGMT unmethylated | |
|---|---|---|---|---|
| | Favorable molecular profile | Unfavorable molecular profile | Favorable molecular profile | Unfavorable molecular profile |
| Hypothesized hazard rate (median survival time in months): | | | | |
| Standard TMZ | 0.0134(51.9) | 0.0401(17.3) | 0.0286(24.2) | 0.0924(7.5) |
| Bevacizumab-containing | 0.012(57.7) | 0.0286(24.2) | 0.0241(28.8) | 0.0573(12.1) |
| Hypothesized hazard ratio (standard vs. bevacizumab-containing) | 1.12 | 1.40 | 1.19 | 1.61 |
| Prevalence of each subgroup | 10% | 15% | 10% | 35% |
| Expected death number with 18 month accrual and 16 additional follow-up | | | | |
| Standard TMZ | **9** | **28** | **15** | **92** |
| Bevacizumab-containing | **8** | **23** | **13** | **78** |

The monthly accrual rate of 40 patients (34 analyzable patients) for 18 months with an additional 16 months of follow-up will result in 390 deaths, the required death number for the final analysis for overall survival. Given the prevalence of the 4 subgroups in this study population, the hypothesized hazard rates and median survival times for each cell in the combinations of treatments and subgroups in Table 13.5, at the time of final analysis for overall survival the expected death numbers in each cell are listed in rows 8-9. According to Peterson and George's method for sample size and power justification for testing the interaction for time-to-failure outcome (Peterson B. and George SL, 1993), there is **19%** power to detect the interactions based on the hypothesized hazard ratios among the 4 subsets at the time of protocol-specified analysis. In addition, according to the expected deaths number in each cell, for the subset of patients with both MGMT unmethylated status and an unfavorable molecular profile (~35% of patients), there is **86%** power to detect the survival hazard ratio of **1.6** or greater at the final analysis time.

**13.5.2** Statistical Methods for Symptoms, Quality of Life, and Neurocognitive Function

**13.5.2.1** *Neurocognitive, Symptom and HRQOL Change*

The mean scores from different tools will be calculated at baseline, 6 weeks, and 10 weeks after registration; the arms with and without bevacizumab will be compared using the two-sample t-test. If the parametric assumptions are not met, then the Mann-Whitney test will be used.

Longitudinal data analysis will also be performed to change trend of scores over time across the two treatment arms using hierarchical formulation of the linear mixed model. The model will include initial performance status, age, and type of surgery.

**13.5.2.2** *Time to Neurocognitive, Symptom and HRQOL Progression*

Neurocognitive failure is defined as the first cognitive failure on any of the following tests: the HVLT-R for Free Recall, Delayed Recall and Delayed Recognition; the COWAT; and the Trail Making Test Part A or B. Cognitive failure for each test is defined as a change in a score that meets or exceeds the Reliable Change Index (RCI) value for each test indicating a performance that is worse than the patient's personal baseline score. For the MDASI-BT, a change in symptom severity of 1 point will be classified as the minimum clinically meaningful change. Mean symptom severity and mean symptom interference will also be calculated and assessed for significance in relation to treatment. For the EORTC QLQ30/BN20, differences of at least 10 points will be classified as the minimum clinically meaningful change in a HRQOL measure. For example, an increase of 10 points or more on a functional scale would mean a moderate improvement, whereas a decrease of 10 points or more would be interpreted as moderate worsening. Furthermore, a rise in a symptom score means deterioration. Changes of less than 10 points will be regarded as no change or as clinically irrelevant, and changes of more than 20 points will be considered large effects.

The cumulative incidence approach will be used to estimate the median time to neurocognitive failure to account for the competing risks of disease progression and death. Similar approaches will be used

for symptom and HRQOL data. Gray's test will be used to test for a statistically significant difference in the distribution of neurocognitive failure times at the alpha=0.05 level (Gray RJ. 1988). The null and alternative hypotheses are:

$H_0: S_1(t) = S_2(t)$ vs. $H_A: S_1(t) \neq S_2(t)$
where $S_i(t)$ is the distribution of time to neurocognitive failure for patients in arm i

In addition, the Cox proportional hazards regression model will be used to determine hazard ratios and 95% confidence intervals for the treatment difference. Unadjusted ratios and ratios adjusted for stratification variables and other covariates of interest will be computed.

**13.5.2.3** *Prediction of Overall Survival and Progression-Free Survival*

The multivariate Cox proportional hazards model will be used to determine if one or more baseline scores from the MDASI-BT, the EORTC QLQ-C30/BCM20, and the neurocognitive function tools have prognostic impact on overall and progression-free survival after accounting for tumor-related and sociodemographic variables and protocol treatment.

**13.5.2.4** *Molecular Correlative Translational Research*

Multivariate regression models will be utilized to model the association between tumor molecular profile (i.e., mesenchymal/angiogenic phenotype and proneural phenotype) and neurocognitive, symptom, and HRQOL outcomes.

**13.5.2.5** *Missing Data*

Participation in the quality of life/neurocognitive function component is not mandatory in this study. However, if patients agree to participate in this component, adherence to the component assessment schedule will be encouraged through reminders from participating institutions. Completion of all scheduled assessment is part of the routine delinquency assessment for participating institutions. The Statistics and Data Management Center staff will monitor proportions of missing quality of life/neurocognitive function information in each treatment arm at different assessment points. In spite of these efforts, missing data is to a certain extent expected. If data on half of the patients who remain eligible during the long-term follow-up portion of the study is not able to be collected, data collection will be suspended. The information from patients with missing data will be reviewed in to determine whether the data analyses will be biased. Patients with missing data will be reviewed for the distributions of treatment arms and patient characteristics. Mean scores on the primary items will be compared for patients with and without missing data at different assessment points to identify whether missing data was preceded by a significant decline in the scores. Mean scores by assessment time for cohorts stratified by baseline score quartile will also be compared to investigate if the missingness is consistent with an ignorable missing data process (missing at random). If no missing data mechanism can be detected, the data will be analyzed assuming missing data is at random and the appropriate imputation for missing values will be conducted. The imputation methods may include: the missing value can be imputed from the variable mean of the completed cases, or it can be imputed from the mean conditional on observed values of other variables, or multiple imputation. If the missing data mechanism appears to be present, we will use appropriate analytic strategies to control for the potential bias and, if possible, to impute the missing data. The possible strategies for imputation and analyses will depend on the severity of the missing data problem and missing pattern. The imputation methods may include: worse-case scenario, use of mean response for individuals who withdraw from the trial from either all or similar (matched) patients remaining in the trial, last observation carry forward, or multiple imputation. The data can also are analyzed using pattern mixture models to estimate separate estimates for the outcome within strata based on the missing data pattern, and then combining estimates in a specialized way to yield appropriate an overall effect estimate( Little R and Rubin D. 2002). Sensitivity analyses based on the varying assumptions about the missing data mechanisms will also be conducted.

**13.5.3** Special Interim Toxicity Analysis

Since there is limited experience with bevacizumab added to concurrent radiation therapy with temozolomide for the treatment of patients with GBM, a special interim analysis will be performed to assure that this new regimen is safe. There is particular concern with a possibly unacceptable increase in the incidence of the following grade 3+ adverse events (regardless of attribution to protocol treatment) because of the addition of bevacizumab:

1) Hemorrhage [CTCAE v3.0 category *Hemorrhage/Bleeding*, any term]

2) Wound dehiscence [CTCAE v3.0 term *Wound complication, non-infectious*]

3) Encephalitis [CTCAE v3.0 terms *Leukoencephalopathy (radiographic findings)* and *Encephalopathy*]

4) Pulmonary emboli and/or deep venous thrombosis [CTCAE v3.0 terms *Thrombosis/thrombus/embolism* and *Thrombosis/embolism (vascular access-related)*]

5) Myelosuppression (grade 4-5 neutrophils or platelets) [CTCAE v3.0 terms Neutrophils/granulocytes (ANC/AGC), Platelets]

In addition, the dosage reduction of temozolomide (< 80% of protocol-defined dose) when given with radiation will also be evaluated as an indirect measure of toxicity, and patient tolerance will be considered as an adverse event for this analysis. Hemorrhage, wound dehiscence, and encephalitis will be considered local complications while pulmonary emboli and/or deep venous thrombosis, myelosuppression, and dose reduction will be considered non-local complications.

This special interim analysis will be performed twice: once after 20 patients are entered on the experimental arm and once after 40 patients are entered on the experimental arm. Initially, two of every three patients will be randomized to the experimental arm to minimize the number of patients assigned to that arm if the addition of bevacizumab to chemoradiation proves to be too toxic. The data for the first and the second special interim analyses would be available 8.5 and 9.5 months, respectively, after study activation. These time points would allow sufficient time for the induction chemoradiation to be completed, the assessment of adverse events to be done at 4 weeks post-treatment as specified in the protocol prior to start of maintenance therapy, the data to be processed, and the slow accrual in the first six months during which institutions obtain IRB approvals.

The baseline rates for these 6 adverse events, regardless of attribution in this study, are based upon the interim analysis of the ongoing phase III trial, RTOG 0525, for the June 2008 RTOG semiannual meeting. At the time of the analysis, for the 487 eligible patients enrolled before June 1, 2007, 472 patients had information regarding adverse events following chemoradiation prior to the start of maintenance therapy. With respect to local complications, only two patients (<1%) had encephalitis, three patients (1%) had hemorrhage, and no patients had wound complication. With respect to the non-local complications, 35 patients (7%) had pulmonary emboli and/or deep venous thrombosis, 40 patients (8%) had grade 4 or 5 myelosuppression, and 78 patients (18%) had (>20%) dose reduction. It should be noted that there was no specific question on the data collection form for any of these six events. This may have resulted in some underreporting of these adverse events, but the degree of underreporting is felt to be minimal.

For evaluation of the three local complications, incidence of 1% for encephalitis and wound complication, incidence of 2% for hemorrhage, and an incidence of 5% for occurrence of any of them are used as control. If the incidence of patients with each of the three local adverse events is 10% higher (e.g., 1% to 11%), on the bevacizumab arm or if the incidence of patients with at least one of the individual 3 adverse events increases from 5% to 15% on the bevacizumab arm then all pertinent local adverse events will be reviewed by the study chairs, the RTOG DMC, and the study statistician.

For evaluation of the three non-local adverse events, an incidence of 20% will be used for (>20%) dose reduction, an incidence of 10% will be used for (grade 4+) myelosuppression, and an incidence of 9% will be used for pulmonary emboli and/or deep venous thrombosis. If the incidence of patients with each of the three non-local adverse events is 10% higher (e.g., 9% to 19%) on the bevacizumab arm, then all pertinent non-local adverse events will be reviewed by the study chairs, the RTOG DMC, and the study statistician.

Following each special interim analysis of local and/or non-local adverse events, the study chairs, RTOG DMC, and study statistician will make a recommendation to the RTOG Brain Steering Committee, RTOG Research Strategy Committee, and CTEP for their consideration. These Committees jointly will decide the future course of action for the study (such as deleting the bevacizumab entirely from the chemoradiation as outlined in the modified schema below). With 20 patients treated on the experimental arm at the time of first analysis, it should be noted that if the true adverse event rates are 5% or less [(1% or less), (2% or less), (9% or less), (10% or less), (20% or less)] there is less than a 2% chance [0.2% chance, 1%

chance, 10% chance, 5% and 9% chance] that the chemoradiation regimen with bevacizumab added will be identified as unacceptable, assuming a binomial distribution with a one-sided test. With 40 patients at the time of the second analysis, it should be noted that if the true adverse event rates are 5% or less [(1% or less), (2% or less), (9% or less), (10% or less), (20% or less)] there is less than a 1% chance [0.1 % chance, 1% chance, 3% chance, 2% and 5% chance] that the chemoradiation regimen with bevacizumab added will be identified as unacceptable. If the concurrent radiation plus temozolomide plus bevacizumab regimen is judged to have an unacceptable toxicity profile, the bevacizumab will simply be dropped from the chemoradiation treatment component.

**13.5.4** Significance Testing for Early Termination and Reporting

Interim treatment comparisons will be performed when we observe 25% (98 deaths), 50% (195 deaths), and 75% (293 deaths) of the 390 required maximum number of deaths. The three analyses will be done on an intent-to-treat basis, with all eligible cases being included in the treatment arm to which they were randomized regardless of what treatment the patients actually received. The primary endpoint of overall survival will be tested in each interim analysis. The efficacy will be tested using a Haybittle-Peto method for early rejection of the null hypothesis to stop for superiority. Critical values used in the sequential analyses will preserve an overall alpha level of 0.025 (one-sided) for the study, with 0.023 for overall survival and 0.002 for progression-free survival. Futility will be tested using the lower boundary based on testing the alternative hypothesis at one-sided 0.005 alpha level, as recommended by Freidlin and Korn (Freidlin B and Korn EL 2002). The Z-score futility boundaries will be evaluated as $-2.576 + \log(1.33) * sqrt(d/4)$, where $-2.576$ corresponds to $Z_{(0.005)}$, 1.33 corresponds to the hazard ratio of control arm to the experimental arm, d is the total observed number of deaths. The significance levels, superiority boundary and Z-score futility boundary for early stopping are as follows in Table 13.6.

If the true hazard ratio of control arm to experimental arm is 1.33 (0.75 for experimental to control arm), then the probability of stopping by first, second, and third interim analysis to reject the null hypothesis is 0.048, 0.108 and 0.142, respectively. The superiority boundaries were chosen to preserve an overall one-sided type I error of 0.023, ignoring the futility boundary. The stopping for futility does not inflate the type I error probability and the futility boundary also does not result in any significant loss of power.

Table 13.6: Interim analysis for overall survival

| Interim Test number | Percent Information | Number of Events | p-value for Efficacy | Superiority Boundary | p-value for Futility | Futility boundary |
|---|---|---|---|---|---|---|
| **1** | **25%** | **98** | **<0.001** | **3.09** | **<0.005** | **-1.16** |
| **2** | **50%** | **195** | **<0.001** | **3.09** | **< 0.005** | **-0.58** |
| **3** | **75%** | **293** | **<0.001** | **3.09** | **<0.005** | **-0.14** |

The progression-free survival endpoint will be tested only once, either when the test statistics from overall survival comparisons cross the pre-specified boundaries in the interim analysis or at the final OS analysis, whichever occurs first. If the interim superiority bound for the overall survival comparison is crossed, indicating the superiority for the experimental arm, the responsible statistician may recommend early reporting of the results and/or stopping accrual (if applicable). At the same time, progression-free survival outcomes will be examined to provide additional treatment information. If the interim futility boundary for the overall survival comparison is crossed, indicating that the overall survival is less likely to prove superior for the experimental arm, the progression-free survival outcome will be examined for efficacy and futility. The futility boundary for progression-free survival is based on testing the alternative hypothesis for progression-free survival at the one-sided 0.005 level. The Z-score futility boundaries will be evaluated as $-2.576 + \log(1.43) * sqrt(pfse/4)$, where $-2.576$ corresponds to $Z_{(0.005)}$, 1.43 corresponds to the hazard ratio of control arm to the experimental arm in terms of progression-free survival, and pfse is the total observed number of progression-free survival events. If both overall and progression-free survival futility boundaries are crossed, we will recommend terminating the trial; otherwise, we will recommend continuing the trial due to the consideration of progression-free survival outcomes.

At each protocol-planned interim analysis, the results from the test assessing the treatment efficacy and 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 p-value is less than the nominal value specified in a sequential design for either efficacy or futility. 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.

**13.5.5** Significance Testing for Final Analysis

The final analysis will be done 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 final analysis will occur at the next RTOG meeting after there have been at least 390 deaths reported. If the observed p-value (one-sided) at the time of the final analysis is ≤ 0.0221, we will reject the null hypothesis that the two treatments have a common survival. If the progression-free survival endpoint has not been tested before, the progression-free survival analysis will also be conducted; if the observed p-value (one-sided) is less than 0.002, we will reject the null hypothesis that the two treatments have the same progression-free survival. According to the projected number of progression-free survival events (512) at the time of final analysis for overall survival, there will be 87% power to detect the hypothesized hazard ratio of 0.70 for progression-free survival. A sensitivity analysis will be performed to study the impact on the progression-free survival analysis due to censoring. Two extreme scenarios about censored cases will be considered. One is that censored cases experience events immediately after they are censored. This corresponds to the hypothesis that censored cases are those that tend to be at high risk of a progression-free survival event. The opposite one is that censored cases have longer times to events than anyone else in the sample. This corresponds to the hypothesis that censored cases are those tend to be at low risk of a progression-free survival event.

**13.5.6** Interim Analysis to Monitor the Study Progress

Interim reports with statistical analyses will be prepared twice per year until the initial paper reporting the treatment results has been submitted. In general, the interim reports will contain information about the patient accrual rate with a projected completion date for the accrual phase; rates of patient exclusion rates due to ineligibility and failure to be randomized following registration; compliance rate of treatment delivery with the distributions of important prognostic baseline variables including MGMT methylation status and molecular profile; the frequencies and severity of treatment-related adverse events by treatment arm; the assay performance with regard to turn-around time (defined as the time between the dates of tissue collection and randomization) and failure rate (defined as the percentage of assays that fall in the undetermined category). The assay performance with regard to reproducibility over time will be performed on the first 100 samples; therefore, the results will also be included in interim reports when available. 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.

**13.5.7** Interim Analysis of Efficacy Results

As mentioned in Section 13.5.4, the efficacy results of this study will be reviewed by the RTOG DMC three times. At such times, the DMC will be presented with a report as in Section 13.5.6 with the addition of a blinded comparison of overall survival. The study statistician will also make a recommendation to the Committee based upon the observed results at the time of the analysis. If the boundary for rejecting the null hypothesis is crossed while the study is still open to patient accrual, the statistician will recommend immediately closing the study to accrual.

**13.5.8** Statistical Analysis Plan for the Post-Progression Component

The statistical analysis for the post-progression component will be exploratory in nature, aiming to asses the rates of progression-free survival, overall survival, and adverse events (grade 3+) in patients receiving different treatment options on the unblinded (post-progression) component of the study. Progression-free survival will be measured from the start of post-progression treatment to the date of first progression or death or, otherwise, the last follow-up date on which the patient was reported alive. Overall survival will be measured from the start of post-progression treatment to the date of death or, otherwise, the last follow-up date on which the patient was reported alive.

**13.5.9** 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 (8/2/10)

In conformance with the national Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we address this issue here, as we will also analyze treatment differences by gender, race, and ethnicity. Table 13.7 lists the projected accrual for each racial and ethnic group based upon a previous RTOG GBM trial (patients enrolled from RTOG and NCCTG institutions for RTOG 0525).

**Table 13.7: Projected Distribution of Gender and Minorities**

| | Gender | | |
|---|---|---|---|
| **Ethnic Category** | **Females** | **Males** | **Total** |
| Hispanic or Latino | 14 | 26 | 40 |
| Not Hispanic or Latino | 364 | 469 | 833 |
| Unknown | 32 | 37 | 69 |
| **Ethnic Category: Total of all subjects** | 410 | 532 | 942 |
| | | | |
| **Racial Category** | | | |
| American Indian or Alaskan Native | 2 | 1 | 3 |
| Asian | 9 | 6 | 15 |
| Black or African American | 7 | 12 | 19 |
| White | 385 | 503 | 888 |
| More than one race | 2 | 1 | 3 |
| Unknown | 5 | 9 | 14 |
| Racial Category: Total of all subjects | 410 | 532 | 942 |

## 13.7 Statistical Considerations for ACRIN 6686 Advanced Imaging Component (8/2/10)

### 13.7.1 Sample Size

A total of 264 participants will be enrolled in the Advanced Imaging sub-study. In each of the sites participating in ACRIN 6686, consecutive cases will be recruited without reference to their randomization status. Accrual to the study will continue until the overall projected sample size of 264 is reached. After these 264 participants are enrolled in the trial, advanced-imaging sites will conduct standard imaging on any additional study participants until all 942 trial participants are enrolled. Assuming 5% attrition of the original sample, we expect that the analysis set will include 250 participants.

Results from Cox regression analyses of data from a series of patients undergoing anti-VEGF therapy (with cediranib) for glioblastoma were used to guide the sample size considerations for this imaging sub-study (Batchelor 2007). In particular, in separate univariate models the coefficient of change in $K^{trans}$ (in logarithmic scale) was 0.57 (HR = 1.76) and the coefficient of change (ratio) in spin echo CBV was -2.59 (HR = 0.075). The standard deviations of the two predictors in this cohort were 0.94 and 0.15, respectively.

The sample size for the Advanced MRI sub-study was computed to permit adequate power to detect a hazard ratio in a neighborhood of the projected values, within each arm. The following table presents computations of statistical power to detect a coefficient for $K^{trans}$ change of the indicated magnitude, using a two-sided test at level 0.05. The hazard ratios corresponding to the values of the coefficient considered in the table range from 1.50 to 1.76. The standard deviation of the predictor was conservatively assumed to vary from 0.9 to 0.94, based on the preliminary data. In line with the main study, the overall event rate was assumed to vary from 0.6 to 0.65. Computations were carried out using PASS (Hinze J. [2008] PASS 2008, NCSS, LLC, Kaysville, Utah).

| Power | Sample Size | Coefficient | Stand. Dev. of Predictor | Event Rate |
|---|---|---|---|---|
| 0.89171 | 125 | 0.410 | 0.900 | 0.600 |
| 0.91585 | 125 | 0.410 | 0.940 | 0.600 |
| 0.94796 | 125 | 0.460 | 0.900 | 0.600 |
| 0.96285 | 125 | 0.460 | 0.940 | 0.600 |
| 0.97805 | 125 | 0.510 | 0.900 | 0.600 |
| 0.98580 | 125 | 0.510 | 0.940 | 0.600 |
| 0.99191 | 125 | 0.560 | 0.900 | 0.600 |
| 0.99532 | 125 | 0.560 | 0.940 | 0.600 |
| 0.91406 | 125 | 0.410 | 0.900 | 0.650 |
| 0.93499 | 125 | 0.410 | 0.940 | 0.650 |
| 0.96178 | 125 | 0.460 | 0.900 | 0.650 |
| 0.97367 | 125 | 0.460 | 0.940 | 0.650 |
| 0.98527 | 125 | 0.510 | 0.900 | 0.650 |
| 0.99089 | 125 | 0.510 | 0.940 | 0.650 |
| 0.99510 | 125 | 0.560 | 0.900 | 0.650 |
| 0.99732 | 125 | 0.560 | 0.940 | 0.650 |

The following table presents computations of statistical power to detect a coefficient of change in spin echo CBV of the indicated magnitude, using a two-sided test at level 0.05. The hazard ratios corresponding to the values of the coefficient considered in the table range from 0.075 to 0.1. The standard deviation of the predictor was conservatively assumed to vary from 0.12 to 0.15, based on the preliminary data.

| Power | Sample Size | Coefficient | Stand. Dev. of Predictor | Overall Event Rate |
|---|---|---|---|---|
| 0.77097 | 125 | -2.600 | 0.120 | 0.600 |
| 0.83328 | 125 | -2.600 | 0.130 | 0.600 |
| 0.88344 | 125 | -2.600 | 0.140 | 0.600 |
| 0.92184 | 125 | -2.600 | 0.150 | 0.600 |
| 0.70339 | 125 | -2.400 | 0.120 | 0.600 |
| 0.77097 | 125 | -2.400 | 0.130 | 0.600 |
| 0.82891 | 125 | -2.400 | 0.140 | 0.600 |
| 0.87651 | 125 | -2.400 | 0.150 | 0.600 |
| 0.80299 | 125 | -2.600 | 0.120 | 0.650 |
| 0.86142 | 125 | -2.600 | 0.130 | 0.650 |
| 0.90676 | 125 | -2.600 | 0.140 | 0.650 |
| 0.94008 | 125 | -2.600 | 0.150 | 0.650 |
| 0.73762 | 125 | -2.400 | 0.120 | 0.650 |
| 0.80299 | 125 | -2.400 | 0.130 | 0.650 |
| 0.85740 | 125 | -2.400 | 0.140 | 0.650 |
| 0.90061 | 125 | -2.400 | 0.150 | 0.650 |

**13.7.2 Statistical Analysis Methods**

Study participants in both arms will undergo DCE-MRI and DSC-MRI at four time points during the study, corresponding to Baseline (T0), Week 3 (T1), Week 3 + 1 Day or "Day 22" (T2), and Week 10 (T3) as described in Section 11.3.2. Section 1.7 describes the background significance of DCE-MRI and DSC-MRI in evaluating treatment response. $K^{trans}$ will be used as the primary metric from the DCE-MRI scan and spin echo CBV will be used as the primary metric from the perfusion MRI scan to assess progression-free and overall survival as described in Section 2.4 and below.

**13.7.2.1** Analysis Plan

**13.7.2.1.1** *Primary Aims*

**13.7.2.1.1.1** To assess the association between overall survival and $K^{trans}$ change from T1 to T2.

**13.7.2.1.1.2** To assess the association between overall survival and spin echo CBV change from T1 to T2.

Overall survival will be estimated for the entire Advanced Imaging cohort of this sub-study and separately for the two arms using Kaplan Meir curves. The main analysis for each of the two primary aims will be based on Cox regression models, in which the response will be overall survival and the predictors will be change in $K^{trans}$ or spin echo CBV as a continuous variable, treatment arm as a binary indicator, and the interaction between treatment and MRI predictor. In a secondary analysis, each MRI predictor will be assessed using time-dependent ROC curves for the prediction of survival at pre-specified time points (Heagerty 2000).

**13.7.2.1.2** *Secondary Aims*

**13.7.2.1.2.1** To assess the association between progression-free survival and $K^{trans}$ change from T1 to T2.

**13.7.2.1.2.2** To assess the association between progression-free survival and spin echo CBV change from T1 to T2.

**13.7.2.1.2.3** To assess the association between T1 values of $K^{trans}$ and spin echo CBV measured separately at T0 and T1, and overall and progression-free survival.

**13.7.2.1.2.4** To assess the association between overall survival and $K^{trans}$ changes from T0 to T1 and from T2 to T3.

**13.7.2.1.2.5** To assess the association between overall survival and spin echo CBV changes from T0 and T1 and from T2 to T3.

**13.7.2.1.2.6** To assess the association between overall survival and apparent diffusion coefficient (ADC) change from T0 to T1.

**13.7.2.1.2.7** To assess the association between overall survival and ADC change from T1 to T2.

**13.7.2.1.2.8** To assess the association between progression-free survival and ADC change from T0 to T1.

**13.7.2.1.2.9** To assess the association between progression-free survival and ADC change from T1 to T2.

**13.7.2.1.2.10** To assess the association between T1 values of ADC with overall and progression-free survival.

**13.7.2.1.2.11** To assess the association between change in lesion size between T1 and T3, as measured by advanced MRI, and overall and progression-free survival.

The analysis for each of the secondary aims will be carried out similarly to the analysis of the primary aims. For example for secondary aims 1 and 2, Cox regression models will be used with the same predictors as in the primary aims but with progression-free survival as the response.

**13.7.2.3** **Aims for Biomarker, Imaging, Quality of Life Study Funding Program Supplement** (8/2/10)

Aims 1 and 2 (see below) will assess the ability of several imaging based markers to predict overall survival within each of the arms of the study. These markers will represent the change between baseline and 22 weeks in measurements derived by imaging. The marker of primary interest will be the volumetric (3-D) tumor measurement on post gadolinium T1-weighted imaging for Aim 1 and the corresponding 3-D tumor measurement on T2-weighted imaging for Aim 2.

The primary analytic approach will be based on Cox regression models in which the marker change between baseline and 22 weeks will be the independent variable of interest, with other covariates as indicated in the application. We will also pursue analyses using time-dependent ROC methods.

**13.7.2.3.1** *Aim 1*: To assess the association between measures of change in enhancing tumor size at week 22 and overall survival in participants with glioma receiving chemoradiotherapy with and without bevacizumab.

Two general approaches will be used in the analysis for this aim. First, Cox regression modeling will be used in which the response variable will be overall survival and the predictors will be measures of tumor size, including 1-D measurements, 2-D measurements, and volumetric (3-D) measurements on post-gadolinium T1 weighted

imaging (Kalbfleisch et al, 2008). Models will be fitted separately for each randomization arm. For each of these measures, the change between baseline and 22 weeks is of primary interest as predictor of overall survival. However other time points (e.g., 3 months) will also be considered. Models will be fitted for each marker separately as well as for combinations of markers. Covariates identified in the RTOG 0825 protocol will be assessed and include the assigned protocol treatment, MGMT methylation status, molecular profile, RTOG RPA risk class, and the interactions of treatment with methylation status, molecular profile, and RPA class. Relevant patient characteristics (age, initial Karnofsky performance index, tumor MGMT status, etc.) will be included. The c-statistic will be used to assess model fit and cross-validation will be employed.

Second, time dependent ROC analysis will be used to assess the ability of each marker to predict survival at fixed time points (1, 2, and 3 years) In this analysis, ROC curves for each marker will be estimated at each time point (Heagerty et al, 2000; Heagerty et al, 2005). In addition to providing an overall assessment of the predictive performance of the marker, the estimated ROC curves will be used to determine marker threshold values for optimal prediction of survival at the designated timepoints. Comparison of markers will be made using the area under the respective ROC curves (Hintze, 2006).

**13.7.2.1.3.2** *Aim 2*: To assess the association between measures of change in T2-based tumor size at week 22 and overall survival in participants with glioma receiving chemoradiotherapy with and without bevacizumab.

The research questions for this Aim are similar to those in Aim 1 but will use T2-based measurements, again with 1-D, 2-D, and volumetric 3-D measurements. The analytic strategy will be similar to Aim 1.

**13.7.2.1.3.3** *Aim 3*: To assess the association between changes in ADC values and overall survival.

In this analysis, the markers of interest will be measures of the change in ADC values from baseline to specific timepoints during the study. The analytic strategy will be similar to Aim 1.

**13.7.2.3.4** *Power Calculations*

In order to perform power calculations for these aims, we utilized the assumptions made in the protocol on survival and expected events for each arm. However, we do not have information from previous studies on the predictive performance of the markers we plan to explore. Thus, we computed the statistical power to detect a difference in post–week 22 (5.08 months) survival between groups defined by a dichotomized marker.

Following the study protocol, we assumed that 612 cases with analyzable data will be available. We also assumed a median survival of 14 months for the control arm and 18.7 for the experimental arm. According to the protocol, approximately 211 deaths are expected in the control arm and 179 in the experimental arm. Assuming now an exponential survival distribution, we calculate that approximately 78% of cases in the control arm and 83% of cases in the experimental arm will survive past 22 weeks. Using the protocol projection of 612 analyzable cases and assuming they will be equally distributed between the arms, we project that about 238 analyzable cases will have survived past 22 weeks on the control arm and about 254 in the experimental arm. The expected number of deaths after the 22 weeks time point would then be 143 in the control arm and 127 in the experimental arm.

Using these assumptions we performed power computations for the ability of markers to predict overall survival for participants who survived past 22 weeks. The computations were done separately within each arm. Because we do not have access to any information from previous studies, we performed power computations for two group comparisons, defined by a threshold in the values of the marker. We assumed that the dichotomizing of the marker will generate a “high risk” and a “low risk” group, with the prevalence of the high risk group ranging from 50% (median split on the values of the marker) to 80%. Power was then computed for a level 0.05 logrank test, separately within each of the two arms of the study.

The following table presents the computed power by arm, for a range of values of the hazard ratio and the prevalence of the high risk group. As shown in the table, the available sample size within each arm provides adequate power to detect hazard ratios of 1.75 or more under most of the prevalence configurations we considered. Hazard ratios around 2 are considered reasonable for biomarker studies, and so these power calculations suggest our proposal is adequately powered.

| Power Control Arm | Power Treatment Arm | Hazard Ratio | Prevalence |
|---|---|---|---|
| 0.76178 | 0.71222 | 1.75 | 0.8 |
| 0.86422 | 0.82258 | 1.75 | 0.7 |
| 0.90545 | 0.87010 | 1.75 | 0.6 |
| 0.91621 | 0.88295 | 1.75 | 0.5 |
| 0.91190 | 0.87777 | 2 | 0.8 |
| 0.96659 | 0.94705 | 2 | 0.7 |
| 0.98204 | 0.96903 | 2 | 0.6 |
| 0.98540 | 0.97411 | 2 | 0.5 |
| 0.99221 | 0.98496 | 2.5 | 0.8 |
| 0.99887 | 0.99718 | 2.5 | 0.7 |
| 0.99967 | 0.99903 | 2.5 | 0.6 |
| 0.99978 | 0.99932 | 2.5 | 0.5 |
| 0.99950 | 0.99862 | 3 | 0.8 |
| 0.99997 | 0.99990 | 3 | 0.7 |
| 1.00000 | 0.99998 | 3 | 0.6 |
| 1.00000 | 0.99999 | 3 | 0.5 |

The propensity of GBM to invade brain tissue makes surgical resection a formidable challenge for neurosurgeons seeking to minimize neurologic morbidity. The occurrence of brain shift after the dura is opened, such as the egress of cerebrospinal fluid, gravity, brain edema, and change in positions of intracranial structures, further complicates optimal surgery (Nabavi et al, 2001). Historically, complete resections have been reported in approximately 20% of cases in surgical series with postoperative imaging (Albert et al, 1994; Barker et al, 1996; Kowalczuk et al, 1997; Simpson et al, 1993; and Vecht et al, 1990). Therefore, the Study Team anticipates that, in the large majority of participants (80% or more), there will be residual disease post surgery that may be measured radiographically.

Aims 1 and 2 will examine the ability of the change from baseline to 22 weeks to predict overall survival. When the change is measured as a fraction of the baseline value of the marker, the analysis can be done only with participants that have non-zero values of the marker at baseline. This setting is the primary interest to the proposed study, and so only participants with measurable tumor will be in the main analysis. We present here a second power calculation if there were to be a 20% reduction in our sample size due to this inclusion. These power calculations suggest that even with a 20% reduction in sample size there is adequate power to detect a hazard ratio of at least 2.

| Power Control Arm | Power Treatment Arm | Hazard Ratio | Prevalence |
|---|---|---|---|
| 0.66547 | 0.61514 | 1.75 | 0.8 |
| 0.78042 | 0.73217 | 1.75 | 0.7 |
| 0.83263 | 0.78803 | 1.75 | 0.6 |
| 0.84715 | 0.80398 | 1.75 | 0.5 |
| 0.84128 | 0.79751 | 2 | 0.8 |
| 0.92348 | 0.89208 | 2 | 0.7 |
| 0.95211 | 0.92801 | 2 | 0.6 |
| 0.95904 | 0.93711 | 2 | 0.5 |
| 0.97454 | 0.95831 | 2.5 | 0.8 |
| 0.99412 | 0.98829 | 2.5 | 0.7 |
| 0.99769 | 0.99480 | 2.5 | 0.6 |
| 0.99831 | 0.99603 | 2.5 | 0.5 |
| 0.99687 | 0.99322 | 3 | 0.8 |
| 0.99968 | 0.99907 | 3 | 0.7 |
| 0.99992 | 0.99974 | 3 | 0.6 |
| 0.99995 | 0.99983 | 3 | 0.5 |

Importantly, we note that the majority of participants will still have measurable disease on T2 imaging, as surgeons resect the T1 post-gadolinium abnormality but not the T2 abnormality. Therefore, the power analysis for Aim 2 presented above remains valid, as Aim 2 will not need to drop participants due to lack of measurable disease. We also note that our planned exploratory analyses may be able to overcome the lack of measurable disease at baseline. For example, when the change is measured by the difference in values between baseline and week 22, the analysis can include all participants.

Published data support that gross total resection leads to a better survival result than a lesser resection of simple debulking (Lacroix et al, 2001). Stummer et al (2008) addressed several factors which may influence the degree of resection and concurrently influence survival, such as “resectability” and the prognostic factors that may influence surgical decisions. These factors may concurrently influence survival, and so we agree that resection status should be given consideration as an independent, prognostic variable for survival in any study on newly diagnosed GBM and we will perform this as a secondary, exploratory analysis. We note that even with the potential reduction in sample size for Aim 1, this study will have a larger study population than any other GBM study in the literature and the clinical relevance of this work will be very high.

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# APPENDIX I

## RTOG 0825

## PHASE III DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL OF CONVENTIONAL CONCURRENT CHEMORADIATION AND ADJUVANT TEMOZOLOMIDE PLUS BEVACIZUMAB VERSUS CONVENTIONAL CONCURRENT CHEMORADIATION AND ADJUVANT TEMOZOLOMIDE IN PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. We recognize that this study is very complex; please take your time to make your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have a brain tumor that is a glioblastoma.

**Why is this study being done?**
A recent study demonstrated that combining a drug called temozolomide with radiation treatment and following this treatment with temozolomide treatment improved tumor control compared with radiation alone. Therefore, the combination of temozolomide with radiation followed by temozolomide alone has become the standard of care for patients with glioblastoma. Bevacizumab is an antiangiogenic agent, which means that it can interrupt the body's ability to grow new blood vessels, causing tumors to shrink. There is also information that demonstrates that bevacizumab may eliminate poorly formed blood vessels in tumors, resulting in improved blood flow. This improved blood flow may result in better delivery of chemotherapy agents. There are preliminary studies that suggest that combining chemotherapy drugs with bevacizumab may be better than either the chemotherapy agent alone or bevacizumab alone for treating some types of tumors. The study doctors want to see whether this will be true for glioblastoma.

The purpose of this study is to determine whether the addition of bevacizumab to the standard chemoradiation will further improve the outcome. This study will find out what effects, good and/or bad, this change in treatment has on you and on your tumor compared with standard treatment. Bevacizumab has not been approved by the US Food and Drug Administration for the treatment of glioblastoma.

In addition, this study will try to determine whether the response to the bevacizumab and the overall outcome depend on a genetic pattern (molecular profile) in the tumor. After you register for the study, a sample of your tumor tissue will be submitted to a central laboratory to confirm that your tumor is a glioblastoma and to determine the molecular profile (genetic analysis) of the tumor tissue. The molecular profile will look at whether your tumor has certain combinations of the following genes that have been found to be important in determining response to glioblastoma treatment: MGMT, AQP1, CHI3L1, EMP3, GPNMB, IGFBP2, LGALS3, OLIG2, PDPN, RTN1. This information will be used to place you in one of the study

arms in a way that makes sure that the number of patients with these gene combinations is balanced in each group (stratification). The molecular profile results will be used for research purposes only and will not be given to you or your study doctor.

**How many people will take part in the study?** (8/2/10)
About 942 people will take part in this study.

**What will happen if I take part in this research study?**

***Before you begin the study…***
You will need to have the following exams, tests, and procedures to find out if you can be in the study. These exams, tests, and procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Blood work for blood counts and biochemistry
- MRI scan of your brain (an image of your brain produced by magnetic rays) [NOTE: If unavailable, a CT scan, which takes computerized images of your brain, may be done instead]
- Pregnancy test if indicated

***During the study…*** (8/27/09)
If the exams, tests, and procedures show that you can be in the study, and you choose to take part, then you will need the following exams, tests, and procedures. They are part of regular cancer care.

- MRI (or CT) scan of your brain
- Blood work for blood counts as well as kidney and liver function
- Documentation of any side effects you are experiencing from treatment

MRI/CT scans, blood work, and documentation of side effects will be repeated throughout the study so that your study doctor can monitor you. Your study doctor will send your MRI/CT scans to a central agency. Radiologists may look at those scans to evaluate your response to the treatment. Your name and other information that may identify you by name will be removed from the scans.

You will also be asked to complete a medication diary while you are receiving treatment; this will help document when you take your medication and any side effects you experience.

When you enter the study, your study doctor will need to send the block of tumor tissue obtained at the time of your brain tumor surgery to a central pathology site. There, a pathologist will confirm that the tumor is a glioblastoma and will also determine whether there is adequate tumor tissue to perform the analysis for genetic (molecular) profile. If the tumor is not a glioblastoma and/or if the tissue is not adequate for performing the molecular analyses, you will not be able to continue on the study.

You will begin the study treatment by taking temozolomide at the same time that you receive radiation therapy. You will take temozolomide capsules orally every morning (7 days a week) for a maximum of 7 weeks. You may need to take several temozolomide capsules for each dose, since the exact dose you receive depends on your body weight. You will take each dose with an 8-ounce glass of water on an empty stomach at least 1 hour before eating. You should

not open or split the capsules, and you should swallow them whole and never chew them. You should store the temozolomide at room temperature, away from excessive heat, moisture and light and away from children and pets.

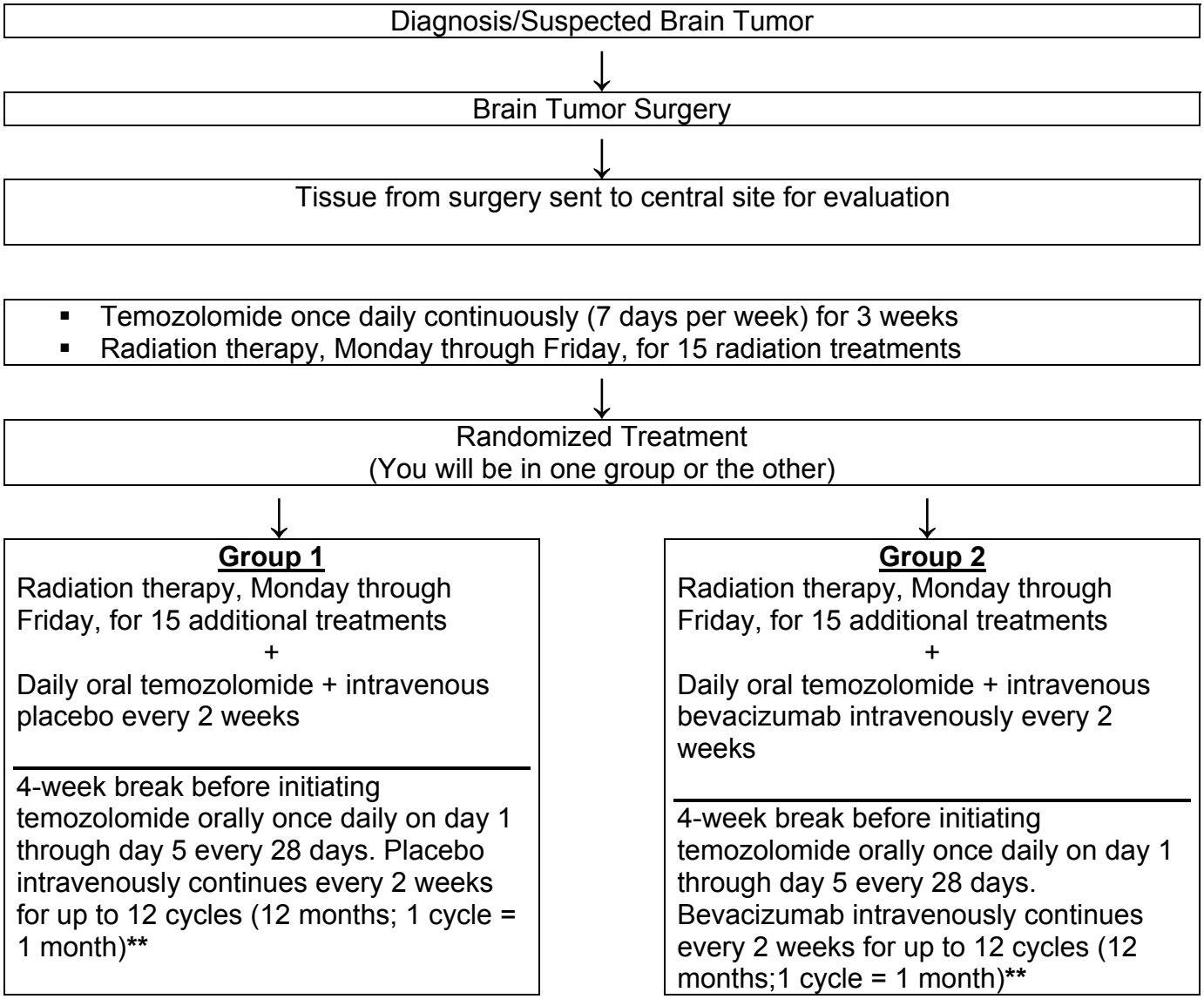
You will receive radiation therapy Monday through Friday for a total of 30 radiation treatments.

By day 3 of week 2 during your radiation treatment, you will be “randomized” into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. During initial accrual to the study (for the first 60 patients randomized), you will have a 2 in 3 (67%) chance of being placed in the group that includes bevacizumab and a 1 in 3 (33%) chance of being placed in the group that includes placebo. Subsequently (after 60 patients have been randomized), you will have a 1 in 3 (33%) chance of being placed in the group that includes bevacizumab and a 2 in 3 (67%) chance of being placed in the group that includes placebo. After enrollment between the two treatment arms is balanced (after 120 patients have been randomized to either the bevacizumab or placebo group), you will have an equal chance of being placed in either group. You will begin the randomized part of your treatment with the 4$^{th}$ week of radiation therapy.

You will receive an intravenous treatment of either bevacizumab or placebo every 2 weeks beginning during week 4 of radiation and continuing until the end of the temozolomide treatment. This includes during radiation treatment, for the 4 week rest between radiation and the restart of temozolomide until the completion of the adjuvant (after radiation) temozolomide treatment. You will take temozolomide every evening on day 1 through day 5 every 28 days for up to 12 cycles (48 weeks; 1 cycle = 4 weeks).

*See next page for Study Plan chart.*

**Study Plan**
Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.




**If your disease gets worse while you are receiving protocol treatment or afterwards, you will be offered the possibility of receiving bevacizumab, either alone or in combination with temozolomide or irinotecan. Your study doctor will discuss these options with you.*

**When I am finished taking the study treatment…**
You will be followed at regular check-ups, including MRI or CT scans, every 3 months after completing treatment for the first year, then every 4 months for the second year, and then every 6 months for the rest of your life.

**How long will I be in the study?**
You will receive radiation plus temozolomide for a maximum of 7 weeks. The intravenous treatment will start at the beginning of the fourth week of radiation. You will then be asked to take temozolomide and the intravenous treatment for up to 12 months following completion of

radiation. The exact amount of time you take the post-radiation temozolomide and intravenous treatment will depend on your response to the drug.

After you are finished taking the temozolomide, the study doctor will ask you to visit the office or clinic for follow-up exams every 3 months after completing treatment for the first year, then every 4 months for the second year, and then every 6 months for the rest of your life.

**Can I stop being in the study?**
Yes. You can decide to stop at any time. Tell your study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell your study doctor if you are thinking about stopping, so he or she can evaluate any risks from the temozolomide and radiation. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

Your study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

**Will I find out which treatment I received?**
If your disease gets worse either while you are receiving protocol treatment or afterwards, you and your study doctor will be able to find out whether you were assigned to the placebo or bevacizumab arm. You will then be offered the possibility of receiving unblinded bevacizumab, regardless of the arm you were assigned to. Your study doctor will discuss with the possible treatments you can receive with unblinded bevacizumab. They are:

- Bevacizumab alone
- Bevacizumab with temozolomide
- Bevacizumab with irinotecan

**What side effects or risks can I expect from being in the study?**
You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the drugs. In some cases, side effects can be serious, long lasting, or may never go away. A severe side effect rarely may be life threatening. Although the risk of death is low, you should tell your study doctor immediately if you experience any of these side effects.

All side effects will be treated in the best way possible and this may involve anti-nausea medications, hospitalization for antibiotics, platelet transfusions, stool softeners or laxatives, and steroids or antihistamines for allergic reactions. There are guidelines for reducing the doses of chemotherapy drugs or eliminating them altogether should you experience serious or intolerable side effects. To avoid potential drug interactions, you should consult your physician or pharmacist before taking any new medications, including over the counter (non-prescription) medications.

You should talk to your study doctor about any side effects that you have while taking part in the study.

**Risks and side effects related to the radiation include those that are:**

**Likely**

- Scalp redness or soreness
- Hair loss, which may be temporary or permanent
- Ear/ear canal reactions, possibly resulting in a short-term hearing loss
- Fatigue
- Lethargy
- Temporary aggravation of brain tumor symptoms such as headaches, seizures, or weakness

**Less Likely**

- Mental slowing
- Permanent hearing loss
- Cataracts
- Behavioral change
- Nausea
- Vomiting
- Temporary worsening of existing neurological deficits, such as decreased vision, drowsiness, and weakness of your arms and legs
- Endocrine problems causing abnormalities in the level of some hormones related to changes to the pituitary gland
- Dry mouth or altered taste

**Rare but Serious**

- Severe local damage to normal brain tissue, a condition called necrosis (tissue deterioration). Radiation necrosis can mimic recurrent brain tumor and may require surgery for diagnosis and treatment.
- Injury to the eyes with the possibility of blindness
- Development of other tumors (either benign or malignant)

**Risks and side effects related to temozolomide include those that are:** (7/20/09)

**Likely**

- Nausea and/or vomiting
- Decreased appetite
- Headache
- Constipation
- Drowsiness/Fatigue
- Inability to sleep
- Hair loss

**Less Likely**

- Decrease in blood counts that may cause infection, bleeding, and bruising
- Diarrhea
- Fever
- Sores in your mouth
- Rash
- Elevated liver enzymes (reversible)

- Swelling in your arms and legs
- Memory loss
- Confusion
- Itchiness
- Increased need to urinate
- Weakness
- Back pain
- Dizziness
- Tingling/burning in your arms and legs
- Anxiety
- Depression
- Stomach pain
- Blurred vision

**Rare but Serious**

- Decreased ability to carry out daily activities
- Convulsions
- Weakness on one side of your body
- Abnormal coordination
- Paralysis
- Myelodysplastic syndrome (problem with the bone marrow that causes decreased production of red cells, white cells, or platelets that can sometimes turn into blood cancer)

**Risks and side effects related to bevacizumab include those that are** (8/2/10)**:**

**Likely**

- Diarrhea
- Nausea or the urge to vomit
- Vomiting
- Fatigue or tiredness
- Headache or head pain
- High blood pressure

**Less Likely**

- Lack of enough red blood cells (anemia)
- Fast heartbeat usually originating in an area located above the ventricles
- Feeling of spinning or whirling
- Belly pain
- Inflammation (swelling and redness) of the large bowel (colon)
- Constipation
- Heartburn
- Bleeding in some organ(s) of the digestive tract
- Partial or complete blockage of the small and/or large bowel. Ileus is a functional rather than actual blockage of the bowel.
- Irritation or sores in the lining of the mouth
- Reaction that can occur during or following infusion of the drug. The reaction may include fever, chills, rash, low blood pressure, and difficulty breathing.
- Chest pain not heart-related

- Pain
- Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing.
- Infection
- Infection (collection of pus) around the rectum
- Premature opening of a wound along surgical stitches after surgery
- Increased blood level of a liver enzyme (ALT/SGPT)
- Increased blood level of a liver or bone enzyme (alkaline phosphatase)
- Increased blood level of a liver enzyme (AST/SGOT)
- Increased blood level of a liver pigment (bilirubin) often a sign of liver problems
- Increased blood level of a heart muscle protein (troponin I) indicating damage to the heart muscle
- Decreased number of a type of white blood cell (neutrophil/granulocyte)
- Weight loss
- Decrease in the total number of white blood cells (leukocytes)
- Loss of appetite
- Joint pain
- Abnormal changes in the growth plate that may affect the growth of long bones in very young children. This side effect appeared to be reversible after the treatment was stopped but has not been assessed with long-term use of the bevacizumab drug.
- Muscle pain
- Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)
- Fainting
- Sudden decrease of kidney function
- Blood in the urine
- More protein leaking into the urine than usual, often a sign of kidney disease
- Bleeding in the vagina
- Cough
- Shortness of breath
- Nose bleed
- Hoarseness
- Stuffy nose
- Itching
- Skin rash
- Hives
- Formation of a blood clot that plugs the blood vessel; blood clots may break loose and travel to another place, such as the lung

**Rare But Serious**

- Damage of or clots in small blood vessels in the kidney that can cause complications, some of which are serious including abnormal destruction of red blood cells (hemolysis) or platelets (that help to clot blood) and kidney failure
- Collection of signs and symptoms that indicate sudden heart disease in which the heart does not get enough oxygen. Sudden symptoms such as chest pain, shortness of breath, or fainting could indicate heart disease and should be reported right away. Signs such as abnormal EKG and blood tests can confirm damage to the heart.

- Heart failure: inability of the heart to adequately pump blood to supply oxygen to the body
- Decrease in heart's ability to pump blood during the "active" phase of the heartbeat (systole)
- Heart attack caused by a blockage or decreased blood supply to the heart
- Irregular heartbeat resulting from an abnormality in the one of the lower chambers of the heart (ventricle)
- Ventricular fibrillation: irregular heartbeat that involves the lower chambers of the heart (ventricles) that results in uncoordinated contraction of the heart; life threatening and potentially fatal, needing immediate attention
- Gastrointestinal fistula: Abnormal hole between an organ of the digestive tract and another organ or tissue
- Gastrointestinal perforation : A tear or hole in the stomach or gut that can lead to serious complications and may require surgery to repair
- Sore (ulcer) somewhere in the digestive tract
- Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing, and loss of consciousness.
- Leakage from stomach due to breakdown of an anastomosis (surgical connection of two separate body structures)
- Bleeding in the brain
- Stroke caused by decreased blood flow to the brain
- Abnormal changes in the brain that can cause a collection of symptoms including headache, confusion, seizures, and vision loss associated with MRI imaging findings (RPLS)
- A condition in which the kidneys leak a large amount of protein into the urine that can cause complications including swelling and kidney failure
- Kidney failure
- Abnormal hole between part of the urinary system and another organ or tissue
- Abnormal hole between the vagina and another organ or tissue
- Abnormal hole between the lower breathing tube and the body cavity that surrounds the lungs
- Bleeding from the lungs
- Hole in the wall that separates the nostrils of the nose
- Abnormal hole between the breathing tube (windpipe) and the tube that goes from mouth to stomach through which food passes (esophagus). This is life-threatening and potentially fatal.
- Blockage or narrowing of a blood vessel (artery) that can cause damage or loss of function including a heart attack or stroke

***(NOTE: For patients with worsening disease after initial protocol treatment who opt to receive bevacizumab in combination with irinotecan)***

**Risks and side effects related to irinotecan include those that are:**

**<u>Likely</u>**

- Delayed diarrhea (occurring within hours of receiving study drug and lasting up to 5-7 days)
- Abdominal cramping, including delayed abdominal cramping (stomach pain that can last for 5-7 days)
- Nausea and vomiting
- Lack of appetite
- Sweating
- Flushing
- Runny nose
- Teary eyes
- Hair loss
- Weakness
- Decrease in blood cells (due to the drug preventing your body from making and keeping new blood cells)
- Sudden urge to have a bowel movement occurring shortly after the irinotecan infusion. *Note:* Dehydration has occurred as a consequence of diarrhea, particularly when associated with severe vomiting. Diarrhea that occurs at a time when the white blood cell count is low can be <u>especially</u> dangerous, which can make you more susceptible to severe infections that could be life-threatening. Should you experience a fever or other sign of infection when your white blood cell count is very low, you may need to be admitted to the hospital for precautionary measures and receive intravenous antibiotics until your blood cell counts rise to safe levels.

  Diarrhea has been the most frequent <u>*severe*</u> side effect associated with receiving irinotecan. When severe diarrhea has occurred, some patients have had to be admitted to the hospital to receive intravenous fluids until the diarrhea resolved (usually in 5-7 days). With early recognition and proper treatment, the likelihood of severe diarrhea may be decreased. In order to minimize the severity of the diarrhea, you are advised to follow these directions:
  1. Be aware of your bowel movements. If they become softer than usual or if you have any increase in the number of bowel movements over what is normal for you, begin taking loperamide tablets right away.
  2. Take two loperamide (Imodium) tablets immediately after the onset of diarrhea or increased frequency of bowel movements, and then take one tablet every two hours until you have been without a bowel movement for 12 hours straight. At night, you may take two tablets every four hours so that you won't have to wake up so often. Make sure that you drink plenty of fluids (soups, juices, etc.) to replace the fluids lost in the bowel movements. If your soft bowel movements or diarrhea do not stop within 36 hours, call your study doctor. Should you become weak, lightheaded, or feel faint, call your study doctor immediately. Don't take loperamide tablets unless you have loose or frequent stools or diarrhea.

**<u>Less Likely</u>**

- Mouth sores
- Frequent bowel movements (sometimes with blood noted in your bowel movements)
- Redness or irritation of your skin at infusion sites

**Rare but Serious**

- Lung problems with symptoms shortness of breath, nonproductive (dry) cough, and abnormal chest x-ray
- Abnormal blood, kidney and liver lab results, which could indicate serious blood, kidney, or liver problems

*Note*: If you are on a blood thinner (warfarin), you will need to be monitored for any interaction between irinotecan and warfarin. If you have any bleeding or bruising, you should let your physician know.

**Patients undergoing treatment with radiation and temozolomide are at increased risk of developing a specific type of pneumonia (lung infection) called Pneumocystis. There are specific antibiotic treatments that are given during the radiation and temozolomide treatments to reduce the chance of developing this pneumonia. Risks and side effects related to each antibiotic treatment (either trimethoprim-sulfamethoxazole or pentamidine or dapsone) to prevent Pneumocystis pneumonia include the following** (7/20/09)

***Trimethoprim-sulfamethoxazole***

**Likely**

- Itching
- Rash

**Less Likely**

- Decreased hemoglobin level (anemia)
- Feeling of general discomfort or uneasiness
- Fever
- Nausea
- Vomiting

**Rare but Serious**

- Low white blood cell count, which may cause problems with infection
- Low blood platelet count, which may cause problems with bruising, bleeding, and blood clotting
- Temporary abnormalities in liver function tests, which may cause fatigue and skin discoloration
- Aplastic anemia (a form of anemia in which the bone marrow dramatically decreases or stops blood cell production)
- Other abnormalities in blood tests
- Liver irritation resembling hepatitis
- Problems with kidney function, which may lead to increased urination and kidney failure
- Pseudomembranous colitis (a diarrheal disease that can occur in patients taking antibiotics and can cause watery diarrhea, fever, and abdominal cramping)

- Stevens-Johnson syndrome (a severe skin reaction similar to a bad burn that can involve the lining of the mouth and eye)

***Pentamidine***

**Likely**

- Bronchospasm (difficulty breathing due to the squeezing of breathing passages in the lungs)
- Cough
- Shortness of breath
- Chills
- Rash
- Chest pain
- Headache
- Increased potassium levels in your blood

**Less Likely**

- Metallic taste, which may lead to decreased appetite

**Rare but Serious**

- Dizziness
- Abnormal heart rhythms
- Low blood pressure
- Low white blood cell count, which may cause problems with infection
- Low blood platelet count, which may cause problems with bruising, bleeding, and blood clotting
- Low red blood cell count, which may cause fatigue
- Low blood sugar
- High blood sugar
- Pancreatitis (inflammation of the pancreas that is severe enough to cause symptoms like belly pain, vomiting, nausea)
- Kidney damage
- Liver irritation resembling hepatitis
- Vomiting
- Fever
- Fatigue
- Severe allergic reactions
- Collapsed lung

***Dapsone***

**Less Likely**

- Abdominal pain
- Nausea
- Vomiting
- Kidney injury
- Vertigo (spinning sensation)
- Blurred vision
- Tinnitus (noises or buzzing in the ears)
- Fever

- Headache
- Lupus-like syndrome (might include joint pain, aching, rashes, fever, sores in the mouth, kidney injury), which usually resolves when drug is stopped
- Numbness, pins and needles, and loss of strength and coordination in the hands and feet due to injury to nerves in the arms and legs. Usually this improves if the dapsone is stopped.
- Low red blood cell count, caused by speeding up the break down of red cells. If you develop this problem dapsone will be stopped.

**Rare but Serious**

- Retinal and optic nerve damage, which may cause permanent visual loss or blindness
- Pancreatitis (inflammation of the pancreas that is severe enough to cause symptoms like belly pain, vomiting, nausea)

Reproductive risks:
You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breast feed a baby while on this study. Also, because bevacizumab remains in your body for weeks to months, you should continue to use adequate contraceptive measures and avoid nursing a baby for at least 6 months after your last dose of bevacizumab or placebo, although the optimal or the maximal time required for drug clearance cannot be precisely predicted. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. If you are a woman of childbearing age, and have not been surgically sterilized (tubal ligation or hysterectomy), you must have a pregnancy test before enrolling in this study.

Temozolomide may make it harder for a woman to become pregnant or for a man to cause a woman to become pregnant even after the chemotherapy has been completed. There is not enough information about temozolomide in men and women of childbearing age who subsequently try to have children to know how likely problems will be.

For more information about risks and side effects, ask your study doctor.

**Are there benefits to taking part in the study?**
Taking part in this study may or may not make your health better. While researchers hope the addition of bevacizumab to the established treatment will be more useful against your brain tumor compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help researchers learn more about bevacizumab as a treatment for brain tumors. This information could help future cancer patients.

**What other choices do I have if I do not take part in this study?**
Your other choices may include:

- Getting treatment or care for your brain tumor without being in a study; this could include the standard therapy arm of this trial (radiation plus temozolomide followed by temozolomide)
- Taking part in another study

- Getting no treatment other than close observation and follow-up
- Surgery alone or surgery in combination with radiation treatment and/or other chemotherapy drugs

Talk to your study doctor about your choices before you decide if you will take part in this study.

**Will my medical information be kept private?**

Data will be housed at the Radiation Therapy Oncology Group (RTOG) Headquarters in a password-protected database. If your study doctor is a member of the North Central Cancer Treatment Group (NCCTG), your data will also be kept in a confidential file at NCCTG as applicable. We will do our best to make sure that the personal information in your medical records will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- RTOG
- Qualified representatives of Genentech, the company that makes bevacizumab
- Local institutional research boards
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- The American College of Radiology Imaging Network (ACRIN) [the central agency that is storing your MRI/CT scans so that radiologists can evaluate your response to the treatment]
- The central institutional review board (CIRB)

**What are the costs of taking part in this study?**

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment. The study agent, bevacizumab or placebo, will be provided free of charge while you are participating in this study. However, if you should need to take the study agent much longer than is usual, it is possible that the supply of free study agent that has been supplied to the NCI could run out. If this happens, your study doctor will discuss with you how to obtain additional drug from the manufacturer and you may be asked to pay for it. Your health plan may need to pay for costs of the supplies and personnel who give you the bevacizumab or placebo.

You will not receive payment for taking part in this study. For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage

You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

**What happens if I am injured because I took part in this study?**
It is important that you tell your study doctor_____*[investigators/ name(s)],* if you feel that you have been injured because of taking part in this study. You can tell your study doctor in person or call him/her at _____ *[telephone number]*.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

**What are my rights if I take part in this study?**
Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

A Data Safety Monitoring Board will be regularly meeting to monitor safety and other data related to this study. The Board members may receive confidential patient information, but they will not receive your name or other information that would allow them to identify you by name.

**Who can answer my questions about the study?**
You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor_____ *[name(s)]* at_____ *[telephone number].*

For questions about your rights while taking part in this study, call the_____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *[telephone number].*

**Where can I get more information?**
You may call the National Cancer Institute's Cancer Information Service at:
1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov.cancerinfo/

**Please note: This section of the informed consent form is about additional research that is being done with people who are taking part in the main study. You may take part in this additional research if you want to. You can still be a part of the main study even if you say "no" to taking part in this additional research. You can say "yes" or "no" to each of the following studies.**

Quality of Life/Neurocognitive Function Study

We want to know your view of how your life has been affected by cancer and its treatment. This "quality of life/neurocognitive function" sub-study looks at how you are feeling physically and emotionally during your cancer treatment. It also looks at how you are able to carry out your day-to-day activities. Patients participating in the main part of the study will be asked to participate by having their symptoms, quality of life, and neurocognitive function evaluated.

This information will help doctors better understand how patients feel during treatments and what effects the medicines are having. In the future, this information may help patients and doctors as they decide which medicines to use to treat cancer.

If you agree to participate in this part of the study, you will be asked to complete a neurocognitive assessment and two quality of life questionnaires at the following times throughout the main part of the study:

- When you register for the study;
- At weeks 6, 10, 22, 34, 46, and 62 of your study treatment; and
- Thereafter, at the same time that you receive your follow-up MRI (or CT) scan (every 3 months after completing treatment for the first year, then every 4 months the second year, and then every 6 months).

The quality of life questionnaires and the symptom assessment will take approximately 30 minutes to complete. If any questions make you feel uncomfortable, you may skip those questions and not give an answer.

If you decide to take part in this sub-study, the only thing you will be asked to do is fill out the questionnaires and undergo the assessment. You may change your mind about completing the questionnaires and undergoing the assessment at any time. You may stop participating in this part of the study at any time without affecting your care or your participation in the main part of the study.

Just like in the main study, we will do our best to make sure that your personal information will be kept private.

Please circle your answer.

I choose to take part in the Quality of Life/Neurocognitive Function Study. I agree to fill out the Quality of Life/Neurocognitive Function Questionnaires.

YES NO

Consent Form for Use of Tissue, Blood, and Urine for Research

**About Using Tissue, Blood, and Urine for Research** (8/2/10)
You have had surgery to see if you have cancer. Your doctor has removed some tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care. We plan to examine the block of tumor tissue to confirm that the tumor is a glioblastoma and to use the tissue to evaluate the genetic (molecular) profile. These studies are essential components of the clinical trial and therefore permission to use the tissue block for this purpose is mandatory.

We would like to keep some of the tissue that is left over for future research. If you agree, this tissue will be kept and may be used in research to learn more about brain tumors. Please read the information sheet called "How is Tissue Used for Research" to learn more about tissue research. This information sheet is available to all at the following web site:
http://www.rtog.org/tissue%20for%20research_patient.pdf

As a result of your participation in the trial, you also will have blood tests performed before you start treatment. We would like to keep for future research about three tablespoons of the blood taken at that time. If you agree, this blood will be kept and may be used in research to learn more about cancer and other diseases.

In addition, we would like to keep some of your urine for future research. We would collect your urine at the following times: before you start treatment, 1 month after you start treatment with radiation and temozolomide, and 1 month after you start the randomized part of the trial. We would keep about five tablespoons of urine at each of these times. If you agree, the urine will be kept and may be used in research to learn more about cancer and other diseases.

The research that may be done with your tissue, blood, and urine is not designed specifically to help you. It might help people who have brain tumors and other diseases in the future. Reports about research done with your tissue, blood, and urine will not be given to you or your doctor. These reports will not be put in your health record. This research will not have an effect on your care.

**Things to Think About**
The choice to let us keep the left over tissue, blood, and urine for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your tissue, blood, and urine can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue, blood, and urine. Then any tissue that remains will be returned to the institution that submitted it.

In the future, people who do research may need to know more about your health. While the Radiation Therapy Oncology Group may give them reports about your health, it will not give

them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue, blood, and urine are used for genetic research. Even if your tissue, blood, and urine are used for this kind of research, the results will not be put in your health records.

Your tissue, blood, and urine will be used only for research and will not be sold. The research done with your tissue, blood, and urine may help to develop new products in the future.

**Benefits**
The benefits of research using tissue, blood, and urine include learning more about what causes brain tumors and other diseases, how to prevent them and how to treat them.

**Risks**
The greatest risk to you is the release of information from your health record. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

**Making Your Choice**
Please read each sentence below and think about your choice. After reading each sentence circle "Yes" or "No". If you have any questions, please talk to your study doctor or nurse, or call our research review board at [IRB's phone number]_____.

No matter what you decide to do, it will not affect your care. If you agree that your tissue, blood, and urine may be used for research, you can change your mind at any time if you give a written request to your study doctor.

1. My tissue, blood, and urine may be kept for use in research to learn about, prevent, or treat brain tumors.

Yes No

2. My tissue, blood, and urine may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes No

3. Someone may contact me in the future to ask me to take part in more research.

Yes No

## Consent Form for ACRIN 6686: Advanced Imaging Sub-Study

*[LIMITED INSTITUTIONS: Potential participants at advanced imaging–qualified institutions must be asked to consider the Advanced MR component and, if amenable, consent to the advanced imaging sequence]*

**About Advanced Imaging in the Study** (8/2/10)
In addition to the standard imaging you are being asked to undergo in the RTOG 0825 study, you are being asked to participate in an advanced MRI study. A total of 264 patients will be included in the advanced imaging portion of the study.

Researchers hope that the advanced MRI will help them learn more about how blood is supplied to the cancer and the tumor's response to the investigational treatment. The advanced MRI will take more time to complete (each examination takes between 45 and 60 minutes) than the regular MRI examinations.

*Advanced imaging will take place at four (4) time points:*

*Within 5 days of starting chemoradiation*

↓

*Within a couple of days of receiving either placebo or bevacizumab*

↓

*The day of or the day after you receive the placebo or bevacizumab*

↓

*Seven weeks later, after you have received several cycles of the study treatment (after you are done with chemoradiation)*

MRI examinations require that you lie flat in the MR scanner while imaging is performed. During this time, you will receive an intravenous (through a tube placed in a vein in your arm) medication, called gadolinium that helps doctors see areas of blood flow to tumors.

**Risks** (8/2/10)
*MRI.* For most patients, there are no specific risks associated with MRI scanning, but some may experience anxiety, stress, claustrophobia, or discomfort. You will not be allowed to have an MRI scan if you have certain types of metallic or electrical devices (such as a pacemaker or certain aneurysm clips) placed in your body. If you had previous surgery to your heart or brain, doctors will determine whether the MRI is safe for you. You will not be allowed to have an MRI if you have any metal pieces in your brain, spinal cord, or eyes. If your job has ever placed you at risk for exposure to metallic fragments (such as metal working or welding), doctors will perform an x-ray of your eyes prior to the study to determine that MRI is safe for you.

*Gadolinium Contrast Agent.* The gadolinium used during the MRI is an FDA-approved MRI contrast agent with very few side effects. The dose used in the advanced MRI tests is "double dose," which is injected rapidly. Some but not all MRI contrast agents have been FDA-approved for double dose, but double dose of all of these agents has been used in many hospitals around the world without evidence of negative effects from the increased dose. Approximately 2 percent of participants experience some side effects with the use of

gadolinium; however, they are mostly mild (nausea, headache, hives, temporary low blood pressure).

Serious side effects are very rare. In very rare cases a condition called nephrogenic systemic fibrosis (NSF)/nephrogenic fibrosing dermopathy (NFD) has been reported. NSF and NFD are conditions associated with the gadolinium contrast agent that affects people who have severe kidney disease. Symptoms include tightening or scarring of the skin and organ failure. In some cases, NSF and NFD can be deadly. These conditions have not been seen in patients with normal working kidneys or mild problems in kidney function. Prior to study entry and throughout the study and your treatment, we will determine if your kidneys are working properly in order to make sure the gadolinium contrast agent is safe for you. You will receive prompt medical attention for any reactions to the contrast agent.

**Benefits**

You will not directly benefit from the results of the advanced imaging study, but we hope that the results will help other people with brain cancer in the future. The results of the advanced MRI central reviews will not be sent to you or your doctor and will not be used to determine your treatment. You or your insurance company will not be charged for these MRI scans.

**Making Your Choice**

If you decide to participate in the study, these advanced images will be part of the study. We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the American College of Radiology Imaging Network (ACRIN) in Philadelphia, PA. Copies of your MR images will be permanently kept on file at ACRIN. This information will be used for research purposes only. All identifying information will be taken off of the films to maintain confidentiality. Future research studies may be conducted on other aspects of the data collected during the study. At this time it is not known what type of studies may be conducted. Some possibilities may be issues affecting patient care or future studies of a medical or non-medical nature.

**Where Can I Get More Information?**

For more information about MRI scans you can go to ACRIN's Web site at http://www.acrin.org/files/mri_description.doc. You or your doctor can print a description of MRI scans from this Web site.

You may call the National Cancer Institute's Cancer Information Service at:
1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

**Please circle your answer.**

If I qualify, I choose to take part in the ACRIN 6686 advanced MRI study that is being done for research as a part of the RTOG 0825 treatment study.

**Yes** **No**

You will get a copy of this form. If you want more information about this study, ask your study doctor.

I have been given a copy of all__*[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

_____

Participant

_____

Date

## APPENDIX II: STUDY PARAMETER TABLE (8/2/10)

| | Pre-Treatment | | | | During Chemo-RT | | | | Adjuvant Phase | | After Therapy Completion |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | As soon as possible after surgery | ≤ 28 d prior to step 2 registr-ation | ≤ 14 d prior to step 2 registr-ation | ≤ 1 wk prior to registration | Wkly | q 2 wks | Mnthly | Wk 6 | Before initiation of cycle 1, 4, 7 (if administered), 10 (if administered) within 72 hrs prior to d 1 & 1 mo after final cycle completion | d 28 (± 3 d) of each cycle | q 3 mos for 1 yr, then q 4 mos for 1 yr, then q 6 mos |
| Tissue eval for histology & sample adequacy | X | | | | | | | | | | |
| History/physical | | | X | | | | | | X | | X |
| Standard Imaging: Contrast-enhanced MRI** | | X | | | | | | | X | | X |
| Advanced Imaging: DSC- and DCE- MRI (for consenting pts at advanced sites) | | | | 1 scan within 5 days of chemo-RT initiation | 2 scans at week 3 only† | | | | Week 10 only† | | |
| MRI/CT (blood detection) | | | | X** | | | | | | | |
| Steroid dose documentation | | | X | | | | | | | X | |
| Performance status | | | X | | | | | | | X | |
| CBC w/ diff, ANC, platelets, Hgb | | | X | | | X | | | X*** | And at d 21 (± 48h) of each cycle | |
| BUN | | | X | | | X | | | X*** | X | |
| Creatinine | | | X | | | X | | | X*** | X | |
| Urine protein UPC ratio | | | X | | | X | | | X*** | X | |
| Bilirubin | | | X | | | X | | | X*** | X | |
| ALT/AST | | | X | | | X | | | X*** | X | |
| CD4 count | | | | | | If lympho-cyte count <500 $mm^3$ | | | If lymphocyte count <500 $mm^3$*** | If lympho-cyte count <500 $mm^3$ | |

| | Pre-Treatment | | | | During Chemo-RT | | | | Adjuvant Phase | | After Therapy Completion |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | As soon as possible after surgery | ≤ 28 d prior to step 2 registr-ation | ≤ 14 d prior to step 2 registr-ation | ≤ 1 wk prior to registr-ation | Wkly | q 2 wks | Mnthly | Wk 6 | Before initiation of cycle 1, 4, 7 (if administered), 10 (if administered) within 72 hrs prior to d 1 & 1 mo after final cycle completion | d 28 (± 3 d) of each cycle | q 3 mos for 1 yr, then q 4 mos for 1 yr, then q 6 mos |
| Systolic/diastolic blood pressure | | | | | | X | | | X*** | X | |
| PT INR (pts not on warfarin) | | | X` | | | | | | | | |
| PT INR (pts on full-dose anticoagulants) | | | X | | | | X | | X*** | X | |
| EKG | | | X | | | | | | | | |
| Serum pregnancy test (if applicable) | | | X | | | | | | | | |
| Informed consent | | X | | | | | | | | | |
| Tumor response eval | | | | | | | | | X | | |
| Adverse event eval | | | | | X | | | | | X | |
| Tissue for banking (for consenting pts) | X | | | | | | | | | | |
| Blood for banking (for consenting pts) | | 28 d prior to treatment | | | | | | | | | |
| Urine for banking (for consenting pts) | | 28 d prior to treatment | | | | | At 1 mo only | | | 1st cycle only | |
| Quality of Life (for consenting pts)*<br>▪ EORTCQLQ30/ BCM20<br>▪ MDASI-BT | | | | X | | | | X | X | | X |
| Neurocognitive Function (for consenting pts)*<br>▪ HVLT-R<br>▪ Trail Making A<br>▪ Trail Making B<br>▪ COWAT | | | | X | | | | X | X | | X |

* See NC/QOL Endpoint Diagram at the end of Appendix V for details.
** See Section 3.1.6 for details.
*** Prior to cycle 1 of adjuvant (pre-adjuvant treatment assessment)
† See Section 11.3.2 for details.

For clarification purposes of ACRIN 6686 Advanced Imaging time points: (7/20/09)

| **ACRIN 6686 Advanced MR Imaging Time Table† (Select Sites Only)** | | | | |
|---|---|---|---|---|
| | Baseline | Week 3 | Week 3 + 1 Day | Week 10 |
| Advanced Imaging: DSC-MRI and DCE- MRI | X | X | X | X |
| † See Section 11.3.2 for details. | | | | |

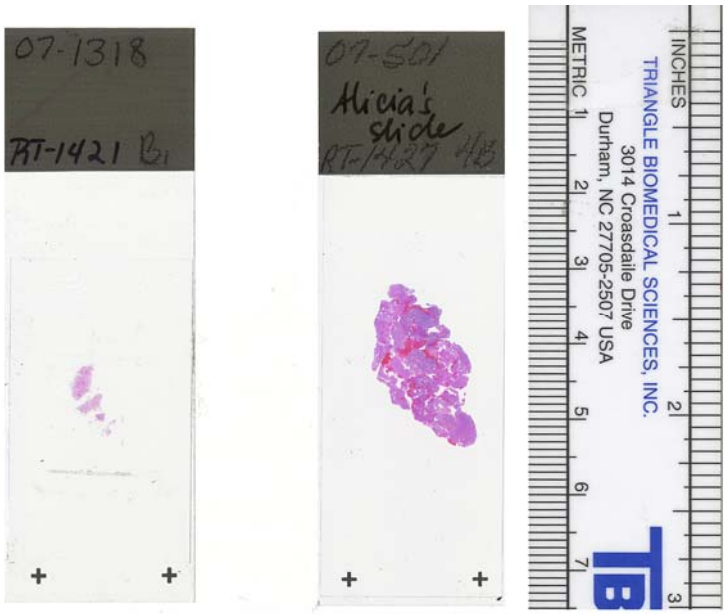
## APPENDIX III

### 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 IV

### EXAMPLES OF ADEQUATE AND INADEQUATE TISSUE SAMPLES




Examples of inadequate (*left*) and adequate (*right*) tissue samples for study entry. In both cases a slide was cut from the submitted block and stained with H&E. Even though the slide on the left had tissue diagnostic of glioblastoma, the amount of tumor will be insufficient for molecular testing.

## APPENDIX V (9/29/09)

## CERTIFICATION AND ADMINISTRATION PROCEDURES FOR THE NEUROCOGNITIVE TEST BATTERY

### STEP 1 – EXAMINER CERTIFICATION FOR RTOG 0825

Institutions with patients participating in the quality of life/neurocognitive function components of this study must meet certification requirements for administering neurocognitive assessments. The healthcare professional (e.g., nurse, psychologist) who is responsible for test administration in this study must be pre-certified by Dr. Wefel (See Section 5.1.4). Examiners who have completed the full certification procedure to perform these tests for RTOG 0525, 0534 or 0614 during the past 6 months do not need to complete the full certification procedure again, but the certification worksheet for 0825 must be faxed to Dr. Wefel for documentation purposes with information regarding the examiners prior certification (protocol number, date of certification). If these criteria are met, each examiner and RTOG will be notified of the examiner's recertification status for 0825. Examiners who have not completed the full certification procedure for RTOG 0525, 0534 or 0614 within the past 6 months must complete the full certification procedure to be recertified to ensure continued familiarity with study procedures.

Prior to registering and/or testing a patient, potential examiners must:

(1) Read Section 11.2 of the protocol
(2) Read Appendix V (Certification and Administration Procedures for the Neurocognitive Test Battery)
(3) Go to the RTOG web site and use your username and password to access the link entitled, "Neurocognitive Training Procedure Letter" on the 0825 forms section of the RTOG website. This letter will provide you with the web address for the training video.
(4) Obtain copies of the HVLT-R, TMT and COWA from the RTOG website
(5) Watch the training video
(6) Complete the training video post test
(7) Complete a "practice" assessment
(8) Complete the Certification Worksheet (Appendix VI)
(9) All materials (i.e., post test, completed practice assessment and scoring forms, certification worksheet) must be faxed to Dr. Wefel, who will review it and correct any procedural errors with the trainee.
(10) If the trainee demonstrates competency, he/she will be notified of the certification approval to administer the tests to study subjects as part of RTOG 0825. A certification approval notice will be sent to RTOG for the registration process and to ensure that only RTOG 0825-approved examiners are testing subjects on protocol RTOG 0825.
(11) **After you are certified, please fax all neurocognitive test and summary forms for the first study patient you test on RTOG 0825 to Dr. Wefel (713-794-4999) for centralized review.**

### STEP 2 – ALTERNATE TEST FORMS/VERSIONS

Two of the tests to be administered have alternate forms or versions in order to reduce the effects of practice. See the table below for the versions to be administered at each session. The forms should continue to be alternated in this order for the duration of the study. The forms packet will contain alternate versions of these neuropsychological tests.

| TEST | ≤ 1 week prior to registration | Week 6 of RT/TMZ | Prior to cycle 1 | Prior to cycle 4 | Prior to cycle 7 | Prior to cycle 10 | 1 month after completion of final cycle | Post-treatment follow-up phase |
|---|---|---|---|---|---|---|---|---|
| HVLT-R | Form 1 | Form 2 | Form 3 | Form 4 | Form 5 | Form 6 | Form 1 | Continue to alternate in order |
| COWAT | 'C-F-L' | 'P-R-W' | 'C-F-L' | 'P-R-W' | 'C-F-L' | 'P-R-W' | 'C-F-L' | Continue to alternate form |

## STEP 3 — TEST INSTRUCTIONS AND ADMINISTRATION PROCEDURES

**Additional comments:**

1. Testing must be completed in one session. Test instructions must be followed verbatim with every patient at every study visit. All tests should be completed in black pen.
2. Tests should be administered in the following order to every patient and at every study visit: HVLT-R Part A (Learning Trials); Trail Making Test Part A; Trail Making Test Part B; COWAT; HVLT-R Part B (Delayed Recall); and the HVLT-R Part C (Delayed Recognition).
3. You may fill the delay interval between COWAT and HVLT-R Part B (Delayed Recall) with HRQOL and Symptom questionnaires.
4. Follow the instructions on the Forms Packet Index before submission of forms to RTOG.
5. Please keep all original test forms. In the event of questions, contact Dr. Wefel. Copies of the test forms and summary sheets for the first case from each certified examiner must be faxed for review to Dr. Wefel (713-794-4999). Additional test forms are not submitted to Dr. Wefel nor to RTOG Headquarters. Results remain on file at the institution as source documentation pending request for submission by RTOG or a study chair.
6. All test results are recorded on the Neurocognitive Evaluation Summary Form (CS), which is found in the Forms Packet. Study/case-specific labels must be applied to all forms.
7. Patients should not be given copies of their tests to avoid learning the material between test administrations.
8. Before dismissing the patient, thank the patient for his/her cooperation.
9. In the event that a patient cannot complete a given test, please write the reason(s) on the test form AND the Neurocognitive Evaluation Summary Form (CS).

### 1. HOPKINS VERBAL LEARNING TEST - REVISED (HVLT-R)

This test has three parts and six alternate forms:
**Part A - Free Recall:** Complete the three learning trials first
**Part B - Delayed Recall:** Complete after a 20 minute delay that includes administration of Trail Making Tests and COWAT as well as HRQOL and symptom self-report measures if appropriate
**Part C - Delayed Recognition:** Complete immediately after Delayed Recall

**Part A – Free Recall: Trial 1**
**Examiner*: "I am going to read a list of words to you. Listen carefully, because when I am through, I'd like you to tell me as many of the words as you can remember. You can tell them to me in any order. Are you ready?"***

- Read the words at the rate of one word every 2 seconds.

***Examiner: "OK. Now tell me as many of those words as you can remember*."**

- Check off the words the patient recalls on the form.
- If a word is said that is not in the list (*for example, "intrusion"*), do not write that word on the form and say nothing to the patient about the word not being on the list.
- There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
- If not, move on to trial 2. Later, you can record the number of words that were correctly repeated on the summary form.

**Part A – Free Recall: Trial 2**
**Examiner*: "Now we are going to try it again. I am going to read the same list of words to you. Listen carefully, and tell me as many of the words as you can remember, in any order, including the words you told me the first time."***

- Read the words at the rate of one word every 2 seconds.
- Check off the words the patient recalls on the form.
- If a word is said that is not in the list (*for example, "intrusion"*), do not write that word on the form and say nothing to the patient about the word not being on the list.
- There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.

- If not, move on to trial 3. Later, you can record the number of words that were correctly repeated on the summary form.

**Part A – Free Recall: Trial 3**

**Examiner*: "I am going to read the list one more time. As before, I'd like you to tell me as many of the words as you can remember, in any order, including all the words you've already told me."***

- Read the words at the rate of one word every 2 seconds.
- Check off the words the patient recalls on the form.
- If a word is said that is not in the list (*for example, "intrusion"*), do not write that word on the form and say nothing to the patient about the word not being on the list.
- There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
- Do not tell the respondent that recall of the words will be tested later.
- Record the time on the clock that you *complete* 'Part A – Free Recall' (for example, 10:00 am) on the designated space on the HVLT-R form.

## 2. TRAIL MAKING TEST [Timed Test]

**Part A – Sample*:*** The Sample for Part A must be completed/attempted by each patient and every assessment. Place the Sample A worksheet flat on the table, directly in front of the patient *(the bottom of the worksheet should be approximately six inches from the edge of the table).* Give the patient a black pen and say:

**Examiner*: "On this page* (point) *are some numbers. Begin at number 1* (point to 1) *and draw a line from 1 to 2* (point to 2), *2 to 3* (point to 3)*, 3 to 4* (point to 4), *and so on, in order, until you reach the end* (point to the circle marked END). *Draw the lines as fast as you can. Ready, begin."***

If the patient completes Sample A correctly and in a manner demonstrating that s/he understands what to do, proceed immediately to Test A. If the patient makes a mistake on Sample A, point out the error and explain it. The following explanations of mistakes serve as illustrations:

- ***"This is where you start (point to number 1)"***
- ***"You skipped this circle (point to the circle omitted)"***
- ***"You should go from number 1 to 2, 2 to 3, and so on, until you reach the circle marked END"***

If it is clear that the patient intended to touch a circle but missed it, do not count it as an omission. Remind the patient, however, to be sure to touch the circles. If the patient still cannot complete Sample A, take his/her hand and guide him/her through the trail using the opposite end of the pen, lightly touching the worksheet to avoid making marks on he copy. Then say:

**Examiner*: "Remember, begin at number 1 (*point to 1*) and draw a line from 1 to 2 (*point to 2*), 2 to 3 (*point to 3*), 3 to 4 (*point to 4*) and so on, in order, until you reach the circle marked END (*point*). Do not skip around, but go from one number to the next in proper order. Remember to work as fast as you can. Ready, begin."***

If the patient does not succeed, or it becomes evident that s/he cannot do the task, DISCONTINUE testing and indicate the corresponding reason on the Trail Making Data Sheet. If the patient completes Sample A correctly and appears to understand what to do, proceed immediately to Part A.

**Part A – Test:** After the patient has completed Sample A, place the Part A test worksheet directly in front of the patient and say:

**Examiner*: "Good! Let's try the next one. On this page are numbers from 1 to 25. Do this the same way. Begin at number 1 (*point*) and draw a line from 1 to 2 (*point to 2*), 2 to 3 (*point to 3*), 3 to 4 (*point to 4*) and so on, in order, until you reach the circle marked END (*point*). Do not skip around, but go from one number to the next in proper order. Remember to work as fast as you can. Ready, begin."***

- Start timing as soon as the instruction is given to "begin"
- Watch closely in order to catch any errors as soon as they are made. If the patient makes an error, call it to his/her attention immediately and have him/her proceed from the point the mistake occurred
- The patient must complete the test in 3 minutes or less

- DO NOT STOP TIMING UNTIL HE/SHE REACHES THE CIRCLE MARKED "END"
- If the patient does not complete the test within 3 minutes terminate the testing. The test can also be discontinued if the patient is extremely confused and is unable to perform the task. Collect the worksheet and complete the Trail Making Data Sheet indicating the reason the test was terminated and the last correct number reached on the test.
- If the patient successfully completes the test collect the worksheet and record the time to completion on the Trail Making Data Sheet in minutes and seconds. Then say, **"*That's fine. Now we'll try another one."***

**Part B – Sample:** The Sample for Part B must be completed/attempted by each patient and every assessment. Place the Sample B worksheet flat on the table, directly in front of the patient (the bottom of the worksheet should be approximately six inches from the edge of the table) and say:
**Examiner*: "On this page (*point*) are some numbers and letters. Begin at number 1 (*point to 1*) and draw a line from 1 to A (*point*), A to 2 (*point to 2*), 2 to B (*point to B*), B to 3 (*point to 3*), 3 to C (*point to C*) and so on, in order, until you reach the end (*point to the circle marked END*). Remember, first you have a number (*point to 1*), then a letter (*point to A*), then a number (*point to 2*), then a letter (point to B), and so on. Draw the lines as fast as you can. Ready, begin."***

If the patient completes Sample B correctly, and in a manner demonstrating that s/he understands what to do, proceed immediately to Part B. If the patient makes a mistake on Sample B, point out the error and explain it. The following explanations of mistakes serve as illustrations:

- ***"You started with the wrong circle. This is where you start (point to number 1)"***
- ***"You skipped this circle (point to the circle omitted)"***
- ***"You should go from number 1 (point) to A (point), A to 2 (point to 2), 2 to B (point to B), B to 3 (point to 3) and so on, until you reach the circle marked END (point)"***

If it is clear the patient intended to touch a circle but missed it, do not count it as an omission. Remind the patient, however, to be sure to touch the circles. If the patient still cannot complete Sample B, take their hand and guide them through the trail using the opposite end of the pen, lightly touching the worksheet to avoid making marks on the copy. Then say:
**Examiner*: "Now you try it. Remember, begin at number 1 (*point to 1*) and draw a line from 1 to A (*point to A*), A to 2 (*point to 2*), 2 to B (*point to B*), B to 3 (*point to 3*) and so on, in order, until you reach the circle marked END (*point*). Ready, begin."***

If the patient does not succeed or it becomes evident that s/he cannot do the task, DISCONTINUE testing and indicate the corresponding reason on the Trail Making Test Data Sheet. If the patient completes Sample A correctly and appears to understand what to do, proceed immediately to Part A.

**Part B – Test:**
After the patient has completed Sample B, place the Part B Worksheet directly in front of the patient and say:
**Examiner*: " Good! Let's try the next one. On this page are both numbers and letters. Do this the same way. Begin at number 1 (*point*) and draw a line from 1 to A (*point to A*), A to 2 (*point to 2*), 2 to B (*point to B*), B to 3 (*point to 3*), 3 to C (*point to C*) and so on, in order, until you reach the circle marked END (*point*). Remember, first you have a number (*point to 1*), then a letter (*point to A*), then a number (*point to 2*), then a letter (*point to B*), and so on. Do not skip around, but go from one circle to the next in the proper order. Draw the lines as fast as you can. Ready, begin."***

- Start timing as soon as the instruction is given to "begin"
- Watch closely in order to catch any errors as soon as they are made. If the patient makes an error, call it to his/her attention immediately and have him/her proceed from the point the mistake occurred - do NOT start from the beginning
- The patient must complete the test in 5 minutes or less
- DO NOT STOP TIMING UNTIL HE/SHE REACHES THE CIRCLE MARKED "END"
- Collect the worksheet and record the time to completion on the Trail Making Test Data Sheet in minutes and seconds
- If the patient does not complete the test within 5 minutes terminate the testing. The test can also be discontinued if the patient is extremely confused and is unable to perform the task. Collect the worksheet and complete the Trail Making Test Data Sheet indicating the reason the test was terminated and the last correct number or letter reached on the test.

- At the top of both Sample forms and both Test forms please write: patient initials, RTOG case number, date of evaluation, institution name, name of certified tester, and the certified tester's phone number.

**3. CONTROLLED ORAL WORD ASSOCIATION TEST (COWAT) [Timed Test]**

This test has three parts (letters) and two alternate forms.

**Examiner*: "I am going to say a letter of the alphabet, and I want you to say as quickly as you can all of the words that you can think of that begin with that letter. You may say any words at all, except proper names such as the names of people or places. So you would not say 'Rochester' or 'Robert'. Also, do not use the same word again with a different ending, such as 'Eat,' and 'Eating.'***

***"For example, if I say 's,' you could say 'son', 'sit,' 'shoe,' or 'slow.' Can you think of other words beginning with the letter 's'?"***

Wait for the patient to give a word. If it is a correct response, say ***"good"***, and ask for another word beginning with the letter "s". If a second appropriate word is given, proceed to the test itself.

If the patient gives an inappropriate word on either occasion, correct the patient, and repeat the instructions. If the patient then succeeds, proceed to the test.

If the patient fails to respond, repeat the instructions. If it becomes clear that the patient does not understand the instructions or cannot associate, stop the procedure, and indicate the reason(s) on the scoring sheet and the Neurocognitive Evaluation Summary Form (CS).

If the patient has succeeded in giving two appropriate words beginning with the demonstration letter, say:

**Examiner*: "That is fine. Now I am going to give you another letter and again you say all of the words beginning with that letter that you can think of. Remember, no names of people or places, just ordinary words. Also, if you should draw a blank, I want you to keep on trying until the time limit is up and I say STOP."***

***"You will have a minute for each letter. The first letter is '___'"*** (see scoring sheet).

**Allow exactly one minute for each letter**

- If the patient discontinues before the end of the time period, encourage him/her to try to think of more words.
- If he/she is silent for 15 seconds, repeat the basic instruction and the letter (e.g., **"Tell me all the words you can think of that begin with a "c"**).
- No extension on the time limit is made in the event that instructions are repeated.
- Continue the evaluation with the remaining two letters, allowing one minute for each.

Recording and Scoring:

- The record sheet provides lines on which the patient's responses can be entered *(e.g., write in the word that is said by the patient)*. Record all patient responses verbatim. If his/her speed of word production is too fast to permit verbatim recording, a "+" should be entered to indicate a correct response.
- Incorrect responses should be struck through with a line and then initial and date in the margin next to the error.
- If the patient provides more responses than there are lines on the record sheet, place check marks in the boxes to indicate correct responses only.
- Count all the correct responses. The number of correct words should be indicated below each column on the recording sheet and on the Neurocognitive Evaluation Summary Form (CS) that is sent to the RTOG.

Comments on scoring:

- Note: It can be helpful for the first several patients and for patients known to be fast with their word production to tape record the session for transcription at a later time.

- The instructions include a specific prohibition against giving proper names or different forms of the same word. Therefore, inflections of the same word *(e.g., eat-eating; mouse-mice; loose-loosely; ran-run-runs)* are not considered correct responses.
- Patients often give both a verb and a word derived from the verb or adjective *(e.g., fun-funny; sad-sadness)*. These are not considered correct responses. On the other hand, if the word refers to a specific object *(e.g., foot-footstool; hang-hanger),* it would be counted as a correct answer.
- Many words have two or more meanings *(e.g., foot; can; catch; hand)*. A repetition of the word is acceptable IF the patient definitely indicates the alternative meaning to you.
- Slang terms are OK if they are in general use.
- Foreign words *(for example, pasta; passé; lasagna)* can be counted as correct if they can be considered part of the lexicon of the relevant language, the criterion being their listing in a standard dictionary of that language. <u>All incorrect and repeated responses MUST be crossed out with one single line, initialed and dated. Additionally, all duplicate entries that have been verified to have different meanings must be marked "ok", initialed and dated. Refer to the descriptions above for guidelines for acceptability. Add the total number of correct responses in each column and input the totals where indicated on the COWAT worksheet.</u>
- If the test is discontinued or omitted, please mark this on the bottom of the test form and indicate the reason on the Neurocognitive Evaluation Summary Form (CS)

**4. <u>HOPKINS VERBAL LEARNING TEST - REVISED (HVLT-R)</u>**

**<u>Part B – Delayed Recall</u>**

- ***<u>DO NOT READ THE WORD LIST AGAIN</u>*.**
- <u>Record the time on the clock that you *start* 'Part B – Delayed Recall' (for example, 10:20 am) on the designated space on the HVLT-R form.</u>
- Administer 'Part B – Delayed Recall' <u>after</u> completing <u>all</u> Trail Making Tests and the COWAT. There should be at least <u>20 minutes</u> between 'Part A' and 'Part B' of the HVLT-R. If the time is too short, allow the patients to complete a questionnaire.

**Examiner: "*Do you remember that list of words you tried to learn before? Tell me as many of those words as you can remember."***

- Check the box on the corresponding line of the HVLT-R worksheet for each word the patient accurately recalls.
- If a word is said that is not in the list (*for example, "intrusion"*), do not write that word on the form and say nothing to the patient about the word not being on the list.
- There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
- If not, record the number of words that were correctly recalled on the summary form.

**<u>Part C – Delayed Recognition</u>**

**Examiner*: "Now I'm going to read a longer list of words to you. Some of them are words from the original list, and some are not. After I read each word, I'd like you to say "Yes" if it was on the original list or "No" if it was not. Was [<u>word</u>] on the list?"***

- <u>Read the words from the top of the columns down.</u>
- Check either the "**Y"** (Yes) or "**N"** (No) box next to each word to indicate the patient's response.
- Guessing is allowed.
- If the test is discontinued or omitted, please mark this on the bottom of the test form and indicate the reason on the Neurocognitive Evaluation Summary Form (CS).
- The score for this portion of the HVLT-R is the number of list words (i.e., words that in CAPS) correctly identified ("yes" response) minus the number of non-list words (i.e., words in lower case) incorrectly identified ("yes" response). Therefore, the actual score can range from –12 *(<u>no list words</u> identified and <u>all non-list words</u> identified)* to +12 *(<u>all list words</u> identified and <u>no non-list words</u> identified)*.

## NC/QOL ENDPOINT FLOW DIAGRAM

| Surgery | Registration | | Wk4 | Wk6 | Wk10 | Wk12 | Wk14 | Wk16 | Wk18 | Wk20 | Wk22 | Wk24 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Start XRT TMZd | Randomize Bevacizumab Placebo | Finish XRT TMZd | Start TMZ C1 | B/P | B/P TMZ C2 | B/P | B/P TMZ C3 | B/P | B/P TMZ C4 | B/P |
| | NC/QOL MRI | | | NC/QOL | NC/QOL MRI | | | | | | NC/QOL MRI | |

| Wk26 | Wk28 | Wk30 | Wk32 | Wk34 | Wk36 | Wk38 | Wk40 | Wk42 | Wk44 | Wk46 | Wk48 | Wk50 | Wk52 | Wk54 | Wk62 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| B/P TMZ C5 | B/P | B/P TMZ C6 | B/P | B/P TMZ C7 | B/P | B/P TMZ C8 | B/P | B/P TMZ C9 | B/P | B/P TMZ C10 | B/P | B/P TMZ C11 | B/P | B/P TMZ C12 | |
| | | | | NC/QOL MRI | | | | | | NC/QOL MRI | | | | | NC/QOL MRI |

## After Therapy Completion Follow-Up Schedule

| Post Tx Year 1 Month 3 | Post Tx Year 1 Month 6 | Post Tx Year 1 Month 9 | Post Tx Year 1 Month 12 | Post Tx Year 2 Month 4 | Post Tx Year 2 Month 8 | Post Tx Year 2 Month 12 | Post Tx Year 3 Month 6 | Post Tx Year 3 Month 12 |
|---|---|---|---|---|---|---|---|---|
| NC/QOL MRI | NC/QOL MRI | NC/QOL MRI | NC/QOL MRI | NC/QOL MRI | NC/QOL MRI | NC/QOL MRI | NC/QOL MRI | NC/QOL MRI |

**TMZd** = temozolomide daily during radiation; **TMZ** = 5/28 adjuvant temozolomide
**B/P=** bevacizumab or placebo
**NC/QOL=** neurocognitive and quality of life battery

## **APPENDIX VI** (8/27/09)

### CERTIFICATION WORKSHEET FOR TEST ADMINISTRATOR

This appendix is available on the RTOG web site, www.rtog.org, next to the protocol.

## APPENDIX VII (8/2/10): BLOOD/URINE COLLECTION

## RTOG BLOOD COLLECTION KIT INSTRUCTIONS

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

Kit contents:

- One Red Top tube for serum
- One Purple Top EDTA tube for plasma
- One Purple Top EDTA tube for Whole Blood
- Twenty (20) 1 ml cryovials
- Biohazard bags (3)
- Absorbent shipping material (3)
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Pre-paid shipping label(s)
- UN1845 DRY Ice and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal Form
- Kit Instructions

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

- ❑ Label as many 1ml cryovials (up to 10) as serum collected. Label them with the RTOG study and case number, collection date and time, 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 serum collected (up 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.**

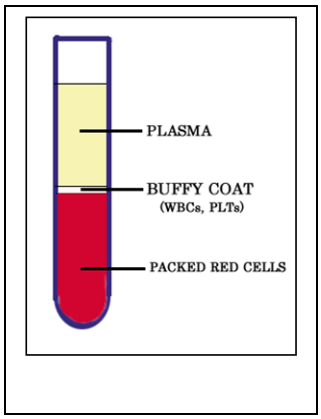
**Plasma (If requested): Purple Top EDTA tube #1**

- ❑ Using four (4) or more 1 ml cryovials, label them with the RTOG study and case number, collection date and time, 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 greater than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot 0.5 ml plasma into each cryovial labeled with RTOG study and case numbers, collection date/time, time point collected and clearly mark specimen as "plasma".
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.**




**Whole Blood For DNA (if requested): Purple Top EDTA tube #2**

- ❑ Using four (4) or more 1 ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovial(s) "blood".

Process:

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 labeled "blood" as possible, Clearly mark the tubes with date/time of collection and time point collected.
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. See below for storage conditions.

**PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.**

**Freezing**

- ☐ Freeze Blood samples in a -80C Freezer or on Dry Ice or snap freeze in liquid nitrogen.

**Storage**

- ❑ 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 Mon-Tues).

  - OR:
  - Samples can be stored in plenty of Dry Ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only- Canada Mon-Tues).

  - OR:
  - Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only- Canada Mon-Tues).
- ❑ 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 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 Email RTOG@ucsf.edu or call (415)476-7864

**Shipping Address :**

**FedEx/UPS/Courier address** (all courier packages & frozen samples)
RTOG Biospecimen Resource
UCSF
1657 Scott Street, Room 223
San Francisco, CA 94115
Contact # 415.476.7864

## RTOG URINE COLLECTION KIT INSTRUCTIONS

**This Kit contains:**

- One (1) Sterile Urine collection cup
- Two 15 ml polypropylene centrifuge tubes
- Two 7 ml disposable plastic Transfer pipets
- Biohazard bags
- Absorbent Paper Towel
- Parafilm for sealing outside of tubes
- UN3373 (Biohazardous material) and UN1895 (Dry Ice) Stickers

**Urine Specimens:**

Preparation for collecting **Urine:**

- A clean catch urine specimen will be collected.

Process

- 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 10-12 mls of Urine into each of two 15 ml polypropylene centrifuge tubes (transfer pipets are provided in kit). 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”.
- Place Urine Tubes into biohazard bag and seal the bag
- Store specimens frozen at -20°C or -80°C until ready to ship.

**Shipping Instructions for all specimens:**

**Urine Specimens**: Urine Tubes must be wrapped in an absorbent material (e.g., paper towels) and placed in an airtight plastic freezer bag (i.e., re-sealable bag).
Urine specimens may be sent in batches, if within 30 days of collection, but make sure each case is in a separate bag. Pack the frozen specimens in a heavy grade Styrofoam box with dry ice (7-10 lbs. minimum). Seal the box with plastic tape. All paperwork should be placed in a plastic bag, sealed, and taped to the outside of the Styrofoam box. Pack the Styrofoam box in a cardboard box. Place UN3373 and UN1895 Stickers on outside of cardboard box.
Note: Specimens requiring specific infectious precautions should be clearly labeled, with specific sources of infectious concerns listed, if known.

Send specimens by overnight express to the address below. Specimens only should be shipped Monday – Wednesday (US Sites) and Mon-Tues (Canadian sites) to prevent thawing due to delivery delays.
Saturday or holiday deliveries cannot be accepted. Samples received thawed will be discarded, and a notification will be sent immediately to the Principal Investigator and Clinic Research Assistant of the submitting institution. The institution should send a subsequent sample, collected as close as possible to the original planned collection date.

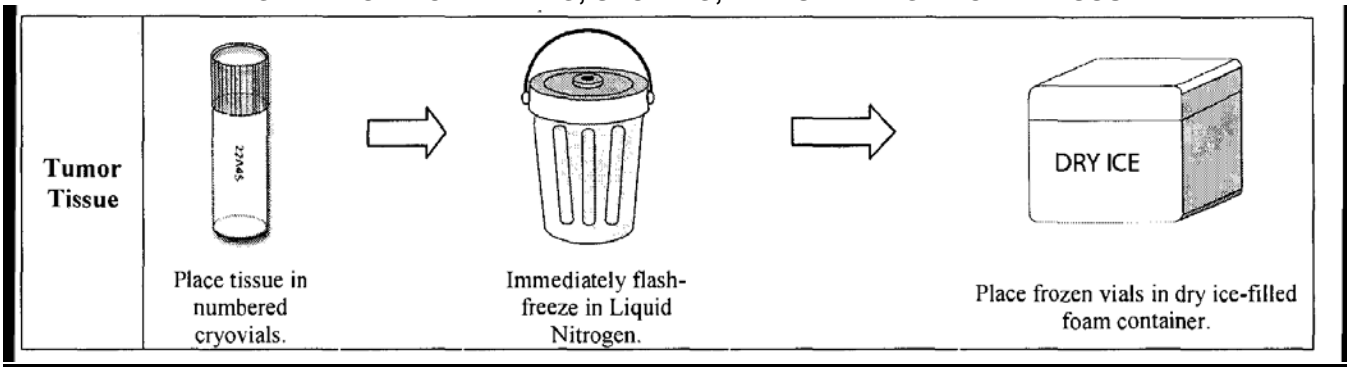
**Ship: Specimens and all paper work as follows:**

**Courier Address (FedEx, UPS, etc.): For Frozen Specimens**
**RTOG Biospecimen Resource**
**University of California San Francisco**
**1657 Scott Street, Room 223**
**San Francisco, CA 94115**

- **For questions,** please Email RTOG@ucsf.edu or call (415)476-7864

## APPENDIX VIII

### DIAGRAM FOR COLLECTING, STORING, AND SHIPPING FROZEN TISSUE



**APPENDIX IX** (8/27/09)

## CTSU LOGISTICS

## ADDRESS AND CONTACT INFORMATION FOR RTOG-0825

| **To submit site registration documents:** | **For patient enrollments:** | **Submit study data directly to the RTOG unless otherwise specified in the protocol:** |
|---|---|---|
| CTSU Regulatory Office<br>1818 Market Street, Suite 1100<br>Philadelphia, PA 19103<br>Phone - 1-888-823-5923<br>Fax – 215-569-0206 | CTSU Patient Registration<br>Voice Mail – 1-888-462-3009<br>Fax – 1-888-691-8039<br>Hours: 9:00 AM – 5:30 PM Eastern Time, Monday – Friday (excluding holidays)<br><br>[For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301-704-2376. Please use the 1-888-462-3009 number for ALL other CTSU patient enrollments.] | RTOG Headquarters<br>1818 Market Street, Suite 1600<br>Philadelphia, PA 19103<br><br>Please do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions. |
| **For patient eligibility questions:**<br>Contact the RTOG Research Associate for Protocol, Data Management section at 215-574-3214.<br>**For treatment-related questions:**<br>Correspond by e-mail (preferred) or by phone with the study chair designated on the protocol cover page. | | |
| **For questions unrelated to patient eligibility, treatment, or data submission** contact the CTSU Help Desk by phone or e-mail:<br>CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative. | | |
| **The CTSU Public Web site** is located at: www.ctsu.org<br><br>**The CTSU Registered Member Web site** is located at: http://members.ctsu.org | | |

## CANCER TRIALS SUPPORT UNIT (CTSU) PARTICIPATION PROCEDURES

*REGISTRATION/RANDOMIZATION*

Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSU. 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, 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 CTSU 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 at http://members.ctsu.org

All forms and documents associated with this study can be downloaded from the RTOG-0825 Web page on the CTSU registered member Web site (http://members.ctsu.org). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS.

**Requirements for RTOG-0825 site registration:**

- CTSU IRB Certification
- 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 sites enrolling through the CTSU an RT Facilities Inventory From 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.

**Pre-study requirements for patient enrollment on RTOG-0825**

- Patient must meet all inclusion criteria, and no exclusion criteria should apply.
- Patient has signed and dated all applicable consents and authorization forms.
- All baseline laboratory tests and prestudy evaluations performed within the time period specified in the protocol.
- Sites must meet the technology requirements for either the IMRT or 3D-CRT treatment approaches.
- This protocol requires a 3-Step registration process. Pathology materials for central pathology review, MGMT analysis and molecular profiling must be submitted within four weeks of surgery per section 10.2 of the protocol. Once results have been obtained, sites may proceed with registration to Step 2. Sites will also be notified when the MGMT analysis is complete and when they can proceed with registration to Step 3.

*CTSU Procedures for Patient Enrollment*

1. Contact the CTSU Patient Registration Office by calling 1-888-462-3009. Leave a voicemail to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs, e.g. within one hour, call the registrar cell phone at 1-301-704-2376.

2. Complete the following forms:

Step 1:
- CTSU Patient Enrollment Transmittal Form
- RTOG-0825 Step 1 Eligibility Checklist

Step 2:
- CTSU Patient Enrollment Transmittal Form
- RTOG 0825 Step 2 Eligibility Checklist

Step 3:
- CTSU Patient Enrollment Transmittal Form
- RTOG 0825 Step 3 Eligibility Checklist

3. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 9:00 a.m. and 5:30 p.m., Mon-Fri, Eastern Time (excluding holidays); however, please be aware that RTOG registration hours end at 4:30 pm Eastern Time. The CTSU registrar will check the investigator and site information to ensure that all regulatory requirements have been met. The registrar will also check that forms are complete and follow-up with the site to resolve any discrepancies.

4. Once investigator eligibility is confirmed and enrollment documents are reviewed for compliance, the CTSU registrar will contact the RTOG (**within the confines of RTOG's registration hours**) to obtain assignment of a unique patient ID (to be used on all future forms and correspondence). Patients will be randomized to only if a

diagnosis of GBM has been confirmed and upon conclusion of the MGMT analysis. The CTSU registrar will confirm registration by fax or email.

NOTE: Upon completion of Step 1 registration, institutions must verify by MRI or CT that < 1 cm of blood is in the tumor cavity. If the treatment planning scan will be used for this, the treatment planning must be completed prior to registration to Step 2. See protocol section 3.1.6 for details

**Randomization must occur by day 10 after the start of radiation.**

5. Sites participating through CTSU must apply for an RTOG username and password **Immediately after registering**, to enable access to the Neurocognitive Training Procedure Letter on the 0825 forms section of the RTOG website.. A user name and password can be obtained by completing the Password Authorization Form at www.rtog.org/members/webreg.html.

*DATA SUBMISSION AND RECONCILIATION*

1. All case report forms (CRFs) and transmittals associated with this study must be downloaded from the RTOG-0825 web page located on the CTSU registered member Web site (http://members.ctsu.org). Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.

2. Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and transmittals to RTOG Headquarters unless an alternate location is specified in the protocol. Do not send study data to the CTSU.

3. The RTOG Headquarters will send query notices and delinquency reports to the site for reconciliation. Please send query responses and delinquent data to the RTOG and do not copy CTSU Data Operations. Each clinical site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP IAM account contact information current. This will ensure timely communication between the clinical site and the RTOG.

**SPECIAL MATERIALS OR SUBSTUDIES**

**Specimen Collection for correlatives or banking (Protocol Section 10.3):**

- Collect, prepare, and submit specimens as outlined in the protocol
- Do not send specimens, supporting clinical reports, or transmittals to the CTSU
- CTSU Institutions qualify for specimen reimbursement as described in Section 10.6 of the protocol. Payments will be made in accordance with RTOG's pathology payment cycle and forwarded to the enrolling sites by the Cooperative Group credited with the accrual.

**Specimen Banking:**

- Provided patient consent is obtained and sent to the investigator, specimens for tissue banking will be stored for an indefinite period of time. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it. See Section 10.7.2

**Quality of Life and Neurocognitive Assessments:**

- Please consult protocol section 11.0 for specific information regarding QOL and neurocognitive patient assessments.

**Radiation Therapy (Protocol Section 6.0):**

- Please consult section 6.0 of the protocol for specific information regarding radiation therapy.

**NOTE**: Radiation Therapy quality assurance is required for this protocol. Please see protocol section 12.2. for required submissions. **Radiation therapy must begin > 3 weeks and ≤ 5 weeks after surgery.**

*SERIOUS ADVERSE EVENT (SAE) REPORTING*

1. CTSU sites must comply with the expectations of their local Institutional Review Board (IRB) regarding documentation and submission of adverse events. Local IRBs must be informed of all reportable serious adverse reactions.

2. CTSU sites will assess and report adverse events according to the guidelines and timelines specified in the protocol. You may navigate to the CTEP Adverse Event Expedited Report System (AdEERS) from either the Adverse Events tab of the CTSU member homepage (http://members.ctsu.org) or by selecting Adverse Event Reporting Forms from the document center drop down list on the RTOG-0825 web page.

3. Do not send adverse event reports to the CTSU.

**DRUG PROCUREMENT**

Investigational Agents: Bevacizumab

Commercial Agents: Temozolomide

1. Information on drug formulation, procurement, storage and accountability, administration, and potential toxicities are outlined in section 7.0 of the protocol.

2. You may navigate to the drug forms by selecting Pharmacy Forms from the document center drop down list on the RTOG 0825 Web page.

**REGULATORY AND MONITORING**

**Study Audit**

To assure compliance with Federal regulatory requirements [CFR 21 parts 50, 54, 56, 312, 314 and HHS 45 CFR 46] and National Cancer Institute (NCI)/ Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity, all protocols approved by NCI/CTEP that have patient enrollment through the CTSU are subject to audit.

Responsibility for assignment of the audit will be determined by the site's primary affiliation with a Cooperative Group or CTSU. For Group-aligned sites, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment. For CTSU Independent Clinical Research Sites (CICRS), the CTSU will coordinate the entire audit process.

For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation provided that Group has an active clinical trials program for the primary disease type being addressed by the protocol. Per capita reimbursement will be issued by the credited Group provided they have endorsed the trial, or by the CTSU if the Group has not endorsed the trial.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up are available for download from the CTSU Operations Manual located on the CTSU Member Web site.

**Health Insurance Portability and Accountability Act of 1996 (HIPAA)**

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-U.S. HIPAA guidelines are provided in the HIPAA Authorization Form located on the CTSU website.

The HIPAA Privacy Rule does not affect participants from outside the United States. Authorization to release Protected Health Information is NOT required from patients enrolled in clinical trials at non-US sites.

**Clinical Data Update System (CDUS) Monitoring**

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. The sponsoring Group fulfills this reporting obligation by electronically transmitting to CTEP the CDUS data collected from the study-specific case report forms.

## APPENDIX X (8/2/10)

### PROVISIONS FOR UNBLINDED (OPEN-LABEL) BEVACIZUMAB AT DISEASE PROGRESSION

**NOTES**

- **The results of the MGMT and 9-gene profile analyses will not be revealed to physicians or patients.**
- **For salvage treatment, progression must be diagnosed by imaging only.**

## 1.0 SUMMARY

**1.1** Patients with progressive disease either during or after protocol treatment may receive unblinded bevacizumab as:

- A single agent,
- In combination with irinotecan, or
- In combination with temozolomide.

**NOTE: No other investigational agents are permitted.**

**1.2** Bevacizumab will be supplied to the patient free of charge via CTEP/PMB (see Section 7.6.3 of the full protocol).

**1.3 Steps to Receive Open-Label Bevacizumab**

**1.3.1** Radiology Review Form (SR) is completed electronically confirming progression.

**1.3.2** Code Breaking Form (CX) is completed electronically to request the treatment code.

**1.3.3** The treatment code will be supplied to the treating physician noted on the CX form by RTOG Headquarters (Normally, within 3 business days of CX receipt).

**1.3.3** Once the treatment code has been received, the decision to receive unblinded bevacizumab will be made by the patient and treating physician.

**1.3.4** The treating institution will then electronically submit a Salvage Treatment Guideline Questionnaire (SX), which will trigger an auto-generated email message transmitting a clinical drug request to the PMB. Open-label supplies will not be sent until the SX form has been submitted. (see Section 7.6.3 of the full protocol).

**1.4** Toxicity and efficacy will be monitored for all patients receiving unblinded bevacizumab.

## 2.0 PRE-TREATMENT EVALUATIONS/ELIGIBILITY GUIDELINES

**2.1** Pre-therapy evaluations must occur as described in Appendix XA below.
**NOTE:** An MRI scan must be performed within 2 weeks prior to starting salvage treatment.

**2.2** Patients receiving unblinded bevacizumab treatment must meet the following criteria:

**2.2.1** The patient must not receive any chemotherapy, radiotherapy, or other treatment intended as an anti-cancer therapy since the protocol based therapy (RT, temozolomide +/- bevacizumab/placebo) on the blinded component of the study.

**2.2.2** The patient must have recovered from the effects of surgery, postoperative infection, and other complications.

- If the patient has undergone re-resection or other neurosurgical procedure including stereotactic or open biopsy: An MRI or CT scan must be obtained and must not demonstrate significant postoperative hemorrhage defined as > 1 cm diameter of blood. If > 1 cm of acute blood is detected, the patient may not receive unblinded bevacizumab.

**2.2.3** Karnofsky performance status ≥ 60

**2.2.4** CBC/differential, with adequate bone marrow function defined as follows:

- Absolute neutrophil count (ANC) ≥ 1,500 cells/$mm^3$;

- Platelets ≥ 100,000 cells/$mm^3$;
- Hemoglobin ≥ 10.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 10.0 g/dl is acceptable.);

**2.2.5** Adequate renal function, as defined below:
- BUN ≤ 30 mg/dl
- Creatinine ≤ 1.7 mg/dl
- Urine protein screened by urine analysis for urine protein creatinine (UPC) ratio. For UPC ratio > 0.5, 24-hour urine protein should be obtained and the level should be < 1000 mg.

**2.2.6** Adequate hepatic function, as defined below:
- Bilirubin ≤ 2.0 mg/dl
- ALT/AST ≤ 3 x normal range

**2.2.7** Systolic blood pressure ≤ 160 mg Hg or diastolic pressure ≤ 90 mg Hg

**2.2.8** Electrocardiogram without evidence of acute cardiac ischemia

**2.2.9** Prothrombin time/international normalized ratio (PT INR) < 1.4 for patients not on warfarin confirmed by testing

**2.2.10** 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 (between 2 and 3) on a stable dose of oral anticoagulant or on a stable dose of low molecular weight heparin

**2.2.11** Women of childbearing potential and male participants must practice adequate contraception

**2.2.12** For females of child-bearing potential, negative serum pregnancy test

## 3.0 DRUG THERAPY

### 3.1 Open-Label Bevacizumab Options

Open-label bevacizumab may be administered in one of three ways:
- Bevacizumab alone (see Section 3.2 of this Appendix)
- Bevacizumab with temozolomide (see Section 3.3 of this Appendix)
- Bevacizumab with irinotecan (see Section 3.4 of this Appendix)

**NOTES: No other investigational agents are permitted.**

**It is recommended that patients who receive bevacizumab plus temozolomide during initial protocol therapy be considered for either bevacizumab with irinotecan or a treatment regimen outside of this protocol.**

### 3.2 Bevacizumab

**3.2.1** ***Treatment Specifications***

The dose of bevacizumab will be 10 mg/kg delivered intravenously. There will be no dose reduction allowed 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.

Monitoring and treatment modifications should be performed as outlined in Section 7.8.1.2 of the full protocol and Appendix XA below.

**3.2.2** ***Bevacizumab Agent Information*:** See Section 7.6 of the full protocol.

**3.2.3** ***Supply:*** Bevacizumab will be supplied to the patient free of charge via CTEP/PMB (see Section 7.6.3 of the full protocol for details).

**3.2.4** ***Accountability:*** Sites should start a separate study case-specific accountability record for the open-label portion of treatment.

### 3.3 Bevacizumab Plus Temozolomide

**3.3.1** ***Treatment Specifications***

Bevacizumab will be given as described in Section 3.2 of this Appendix.

Temozolomide will be administered on days 1-5 of a 28-day cycle. Starting dose will be at 150 mg/m$^2$, with the possibility of dose escalation to 200 mg/m$^2$, as specified in Section 7.4 of the full protocol.

Monitoring and treatment modifications should be performed as outlined in Section 7.4 of the full protocol.

**3.3.2** ***Temozolomide Agent Information:*** See Section 7.5 of the full protocol

**3.3.3** ***Temozolomide Supply*:** Commercially available.

## 3.4 Bevacizumab Plus Irinotecan (CPT-11)

### 3.4.1 *Treatment Specifications*

Bevacizumab will be given as described in Section 3.2 of this Appendix.

As discussed in Section 1.1.1 of the full protocol, there have been several phase II trial combining bevacizumab with irinotecan. This combination is therefore permitted using open-label bevacizumab.

Irinotecan will be administered as follows:

Dosing is based on adverse events (AEs) during the prior treatment cycle. If multiple AEs are seen, the dose administered should be based on the dose reduction required for the most severe grade of any single AE.

| Dose Level | Dose mg/m$^2$ for patients NOT taking EIAEDs | Dose mg/m$^2$ for patients taking EIAEDs | Remarks |
|---|---|---|---|
| - 2 | 75 | 200 | Reduction if prior AE |
| -1 | 100 | 275 | Reduction if prior AE |
| 0 | 125 | 340 | ---------- |

First Cycle: for patients not taking EIAEDs (Appendix XB below), irinotecan will be started at a dose of 125 mg/m$^2$ on days 1 and 15 of a 28-day cycle. For patients taking EIAEDs, irinotecan will be started at a dose of 340 mg/m$^2$.

Second Cycle: The dose of irinotecan will be determined according to: (1) non-hematologic AE during the preceding treatment cycle, as well as (2) the worst ANC and platelet counts

Delay: On day 1 of each cycle (within the prior 72 hours), ANC ≥ 1.5 x 10$^9$/L, platelet count ≥ 100 x 10$^9$/L, and all grade 3 or 4 non-hematologic AEs (except for alopecia, nausea, and vomiting) must have resolved (to grade ≤ 1).

If AEs persists, treatment should be delayed by 1 week for up to 4 consecutive weeks. If, after 4 weeks of delay, all AEs have still not resolved: then any further treatment with irinotecan should be stopped.

Dose Reductions: If any non-hematologic AE observed was grade > 2 (except alopecia, nausea, and vomiting) and/or if platelets < 50 x 10$^9$/L and/or ANC < 1 x 10$^9$/L, then the dose should be reduced by one dose level. Patients who require more than two dose reductions will have treatment stopped.

If any treatment-related non-hematologic AE observed was grade 4 (except alopecia, nausea and vomiting) then adjuvant temozolomide treatment should be stopped.

*Subsequent cycles (3-12):* Any dose reductions of irinotecan will be determined according to (1) non-hematologic AE during the preceding treatment cycle, as well as (2) the lowest ANC and platelets observed. No dose escalation should be attempted. The same dose reductions as for the second cycle should be applied. *Important:* If the dose was reduced or delayed for AEs, there will be no dose escalation in subsequent treatment cycles.

***Summary of Dose Modifications or Discontinuation for Irinotecan-Related Toxicity***

| **Worst Treatment-Related Non-Hematologic AE (except for alopecia, nausea, and vomiting) During the Previous Cycles** | |
|---|---|
| **Grade** | **Dose Modification** |
| **0-2** | No dose modifications for non-hematologic AEs. Dose reductions based on ANC and platelet counts are applicable. |
| **3** | Reduce by one dose level (except lymphopenia, alopecia, nausea and vomiting). |
| **4** | Stop (except lymphopenia, alopecia, nausea and vomiting). Dose modifications based on ANC and platelet counts are not applicable. |

**Worst Treatment-Related Hematologic AE During the Previous Cycle**

| **Worst AE** | | **Platelets** | | |
|---|---|---|---|---|
| | | **≥100 x $10^9$/L** | **50 – 99 x $10^9$/L** | **< 50 x $10^9$/L** |
| **ANC** | **≥ 1.5 x $10^9$/L** | Dose unchanged | Dose unchanged | Reduce by 1 dose level |
| | **≥1 & <1.5 x $10^9$/L** | Dose unchanged | Dose unchanged | Reduce by 1 dose level |
| | **< 1 x $10^9$/L** | Reduce by 1 dose level | Reduce by 1 dose level | Reduce by 1 dose level |

**Note:** A complete blood count must be performed on days 14, and 28 (± 48 hours) after the first daily dose of each treatment cycle.

**3.4.2** ***Irinotecan Agent Information***

Please refer to the package insert for comprehensive information.

*Chemistry:* Irinotecan hydrochloride trihydrate {CPT-11, (4S)-4, 11-diethyl-4-hydroxy-9-{(4-piperidinopiperidino) carbonyloxy}-IH-pyroano{3',4':6,7}indolzino{1,2-b}quino line-3, 14(4H, 12H)dione hydrochloride trihydrate} is a topoisomerase I inhibitor.

*Formulation:* The drug is supplied in two forms: 2 mL vials containing 40 mg of drug and 5 mL vials containing 100 mg of drug. The drug is supplied in brown vials and appears as a pale-yellow-to-yellow crystalline powder and pale yellow transparent solution when reconstituted.

*Administration:* Irinotecan will be diluted with D5W to a total volume of 500 ml and infused intravenously over 90 minutes. Nothing else should be added to the bag.

*Storage and Stability:* Irinotecan vials must be stored in a cool, dry place, protected from light in a locked cabinet accessible only to authorized individuals. It is stable to the expiration date

on its labeling. Irinotecan is stable for at least 24 hours in glass bottles or plastic bags after reconstitution with D5W.

*Adverse Events*
Virtually all phase I and II studies of irinotecan have reported neutropenia and/or late diarrhea (diarrhea occurring more than 8 hours after irinotecan administration) as the dose-limiting toxicities (depending upon the schedule). Other commonly observed adverse events include nausea and vomiting, anorexia, abdominal cramping, alopecia, asthenia, lymphocytopenia, and anemia.

Dehydration has occurred as a consequence of diarrhea, particularly when associated with severe vomiting. Patients may have an acute syndrome of lacrimation, diaphoresis, abdominal cramping, and diarrhea (early diarrhea) during or shortly after irinotecan administration; this syndrome is thought to be cholinergically mediated. Prophylactic or therapeutic administration of atropine should be considered in patients experiencing cholinergic symptoms. Each patient should be instructed to have loperamide readily available and to begin treatment for late diarrhea (generally occurring more than 24 hours after administration of irinotecan) at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normally expected for the patient. One dosage regimen for loperamide used in clinical trials (note: this dosage regimen exceeds the usual dosage recommendations for loperamide) consisted of the following: 4 mg at the first onset of late diarrhea and then 2 mg every 2 hours until the patient is diarrhea-free for at least 12 hours. During the night, the patient may take 4 mg of loperamide every 4 hours. Premedication with loperamide is not recommended. The use of drugs with laxative properties should be avoided because of the potential for exacerbation of diarrhea.

Sporadic cases of pulmonary toxicity, manifested as shortness of breath, nonproductive cough, and transient infiltrates on chest X-ray have been reported. Infrequent occurrences of mucositis or colitis (sometimes with gastrointestinal bleeding) have been observed. Occasionally, abnormalities of serum creatinine, hepatic enzymes, or thrombocytopenia have been observed. irinotecan may cause local irritation at infusion sites. Extravasation necrosis of the skin has not been reported in US studies.

**3.4.3** ***Irinotecan Supply*:** Commercially available.

## 4.0 ADVERSE EVENT REPORTING

See Section 7.10 of the full protocol.

## **APPENDIX XA** (8/27/09)

### STUDY PARAMETER TABLE FOR UNBLINDED BEVACIZUMAB TREATMENT

| | Before initiation of cycle 1, 4, 7 (if administered), 10 (if administered) within 72 hrs prior to d 1 & 1 mo after final cycle completion | d 28 of each cycle (± 3 d) |
|---|---|---|
| | | |
| History/physical | X | |
| Contrast-enhanced MRI/CT | X** | |
| MRI/CT (blood detection) | ** | |
| Steroid dose documentation | | X |
| Performance status | | X |
| CBC w/ diff, ANC, platelets, Hgb | X* | X |
| BUN | X* | X |
| Creatine | X* | X |
| Urine protein | X* | X |
| Bilirubin | X* | X |
| ALT/AST | X* | X |
| CD4 count | X* | If lymphocyte count <500 $mm^3$ |
| Systolic/diastolic blood pressure | X* | X |
| PT INR (pts on full-dose anticoagulants) | X* | X |
| Tumor response evaluation | X | |
| Adverse event evaluation | | X |

* Also prior to cycle 1 of adjuvant (pre-adjuvant treatment assessment)

**The initial, pre-cycle 1 MRI scan must be performed within 2 weeks prior to starting salvage treatment. This imaging will also be used to detect blood in tumor or brain prior to initiation of treatment.

## APPENDIX XB

### PERMITTED AND NON-PERMITTED ENZYME INDUCING ANTIEPILEPTIC DRUGS (EIAEDS) USE WITH IRINOTECAN DURING OPEN-LABEL BEVACIZUMAB ADMINISTRATION

The following agents are potential hepatic enzyme inducing antiepileptic drugs (EIAEDs) and should not be used:

Carbamazepine (Tegretol, Tegretol XR, Carbatrol)
Oxcarbazepine (Trileptal)
Phenytoin (Dilantin, Phenytek)
Fosphenytoin (Cerebyx)
Phenobarbital
Pentobarbital
Primidone (Mysoline)

The following agents are acceptable (non-EIAEDs):

Valproic acid (Depakote, Depakene, Depacon)
Gabapentin (Neurontin)
Lamotrigine (Lamictal)
Topiramate (Topamax)
Tiagabine (Gabitril)
Zonisamide (Zonegran)
Levetriacetam (Keppra)
Clonazepam (Klonopin)
Clonozam (Frisium)

## APPENDIX XI

## CLASSIFIER, CUTOFFS, AND FAILURE RATES FOR 9-GENE PREDICTOR ASSAY

**Description of classifier and weighting of molecular variables**

The classifier is based on 9 individual gene assays, where the expression of each gene is measured and a composite "metagene" score is calculated for each tumor sample. To optimize predictive models, each variable was weighted according to its individual strength of association. In concept, variables with a stronger association with outcome were weighted more heavily than variables with a lesser association. To accomplish this, the estimate of the Cox proportional hazards coefficient (ß) was determined in a univariate analysis for each variable. This coefficient was then used as the weighting factor to calculate a metagene score according to the formula

$$\sum_{1}^{i} \beta_i V_i$$

where ß is the Cox regression coefficient and V is the variable in question.

Variables and weighting factors are shown in the table below. Note that of the 9 genes, 7 have positive weighting factors, indicating that elevated expression was associated with poor outcome and the remaining 2 have negative weighting factors, indicating that overexpression was associated with improved outcome.

| Variable | ß |
|---|---|
| AQP1 | 0.15 |
| CHI3L1 | 0.12 |
| EMP3 | 0.13 |
| GPNMB | 0.20 |
| IGFBP2 | 0.22 |
| LGALS3 | 0.13 |
| OLIG2 | -0.15 |
| PDPN | 0.19 |
| RTN1 | -0.20 |

**Cutoffs to determine favorable from unfavorable metagene scores**

Recursive partitioning analysis using survival as a continuous variable was used to determine the best cutoff for metagene scores. This led to 2 groups with a cutoff of approximately 75% high/unfavorable metagene scores versus the remaining 25% with low/favorable metagene scores. For this reason, the cutoff used to determine favorable from unfavorable metagene scores will be the 75$^{th}$ percentile, with 75% of patients expected to have unfavorable scores and the remaining 25% expected to have favorable scores. Weighted metagene scores are shown in the table below. For space considerations, the 1$^{st}$-ranked, last-ranked, and every 10$^{th}$ score is shown, along with the designation as favorable or unfavorable.

Table: Examples from the 169-sample set of weighted metagene scores and designation as favorable or unfavorable.

| Weighted metagene score | Rank | Dichotomization |
|---|---|---|
| 3.97 | 1 | unfavorable |
| 2.21 | 10 | unfavorable |
| 1.53 | 20 | unfavorable |
| 1.25 | 30 | unfavorable |
| 1.01 | 40 | unfavorable |
| 0.68 | 50 | unfavorable |
| 0.53 | 60 | unfavorable |
| 0.43 | 70 | unfavorable |
| 0.20 | 80 | unfavorable |
| 0.06 | 90 | unfavorable |
| -0.07 | 100 | unfavorable |
| -0.27 | 110 | unfavorable |
| -0.46 | 120 | unfavorable |
| -0.78 | 130 | favorable |
| -1.34 | 140 | favorable |
| -2.38 | 150 | favorable |
| -4.07 | 160 | favorable |
| -7.33 | 169 | favorable |

**Failure rates**

The failure rate of the multigene predictor was assessed using 180 consecutive samples of archival paraffin tissues from MD Anderson files. Success was determined based on the average $C_t$ value of the control genes. When assessing quantitative reverse transcription-polymerase chain reaction assays, the $C_t$ value is inversely correlated with the amount of amplifiable RNA species. We find that high $C_t$ values (greater than 33 cycles) represent unacceptably low amount of RNA such that they are not accurately measured. For this reason, we calculate the average $C_t$ values of the three control genes since these genes are relatively uniformly expressed across GBM samples. Using this criteria 169 of the 180 evaluable samples passed this threshold and were considered acceptable, with the remaining 11 (7%) considered failures. This failure rate estimation may be at the high end because the samples used for this evaluation were up to 10 years old and it established that nucleic acid from older paraffin blocks is of lower quality. Based on these data, we estimate a maximum failure rate for RTOG 0825 samples of 5%-10%.

## **APPENDIX XII** (7/20/09)

## STANDARD MR IMAGING GUIDELINES

Tumor evaluations (baseline and post therapy)

*MRI*

MRI of the head can be performed at either 1.5T or 3.0T, with dedicated head coil. Localizing sequences per institutional routine that allow for all three planes to be visualized can be used, provided they are sufficient to define the anterior commisure-posterior commisure line. Note, axial imaging plane refers to imaging parallel to the AC-PC line.

Pre-contrast imaging series should include the following:

T1 Spin Echo
- Plane: axial
- FOV: 220-240 mm
- Phase direction: L-R
- Phase FOV: 75%
- Slice thickness: 5mm (1mm gap)
- TR: 400-600 ms
- TE: ≤ 15 ms
- Matrix: 256 (frequency) x 192 (phase)
- NEX/NSA: 1

Diffusion weighted imaging
- Plane: axial
- FOV: 220-240 mm
- Phase direction: L-R
- Phase FOV: 75%
- Slice thickness: 5mm (1mm gap)
- TR: minimum
- TE: minimum
- b value ~1000 (at least three directions, b = 0 images obtained as well)
- Matrix: 128 x 128 or greater
- NEX/NSA: 1 or more

T2 Fast Spin Echo
- Plane: axial
- FOV: 220-240 mm
- Phase direction: L-R
- Phase FOV: 75%
- Slice thickness: 5mm (1mm gap)
- TR: 2500-4500 ms
- TE: 100-130 ms
- ETL/Turbo factor: 13-25
- Matrix: 512 (frequency) x 256 (phase)
- NEX/NSA: 2

FLAIR (1.5T)
- Plane: axial
- FOV: 220-240 mm

- Phase direction: L-R
- Phase FOV: 75%
- Slice thickness: 5mm (1mm gap)
- TR: 10000 ms
- TE: 100-150 ms
- TI: 2000 ms
- Matrix: 256 (frequency) x 192 (phase)
- NEX/NSA: 1

FLAIR (3.0T)
- Plane: axial
- FOV: 220-240 mm
- Phase direction: L-R
- Phase FOV: 75%
- Slice thickness: 5mm (1mm gap)
- TR: 10000 ms
- TE: 70-130 ms
- TI: 2500 ms
- Matrix: 256 (frequency) x 192 (phase)
- NEX/NSA: 1

Gadolinium based contrast should then be administered per institutional routine. The post-contrast imaging must be performed in the plane that the pre-contrast imaging was obtained in (axial, as indicated here). Post-contrast imaging should also be acquired in at least one additional plane (e.g. coronal, or sagittal). 3D T1-weighted volumetric imaging (e.g., SPGR or MPRAGE) with 1.5mm isotropic voxel size or better should be considered as well.

T1 Spin Echo post-contrast (axial)
- Plane: axial
- FOV: 220-240 mm
- Phase direction: L-R
- Phase FOV: 75%
- Slice thickness: 5mm (1mm gap)
- TR: 400-600 ms
- TE: ≤ 15 ms
- Matrix: 256 (frequency) x 192 (phase)
- NEX/NSA: 1

T1 Spin Echo post-contrast (coronal)
- Plane: coronal
- FOV: 220-240 mm
- Phase direction: L-R
- Phase FOV: 75%.
- Slice thickness: 5mm (1mm gap)
- TR: 400-600 ms
- TE: ≤ 15 ms
- Matrix: 256 (frequency) x 192 (phase)
- NEX/NSA: 1

T1 Spin Echo post-contrast (sagittal)
- Plane: sagittal
- FOV: 220-240 mm
- Phase direction: A-P
- Phase FOV: 100%.

- Slice thickness: 5mm (1mm gap)
- TR: 400-600 ms
- TE: ≤ 15 ms
- Matrix: 256 (frequency) x 192 (phase)
- NEX/NSA: 1

T1 volumetric imaging post contrast (MPRAGE/SGPR)

- Plane: sagittal
- FOV: 240-260 mm
- Phase direction: A-P
- Phase FOV: 100%.
- Slice thickness: ≤ 1.5 mm
- TR: 2400-2600 ms
- TE: minimum
- TI: 1100 ms
- Matrix: 256 x 256
- NSA/NEX: 1

*CT*

In cases where MRI is contraindicated, CT can substitute for MRI. CT should be performed with iodinated contrast material per institutional routine. CT scan should be a minimum of 5 mm slice thickness.

Hemorrhage exclusion scanning:

CT or MRI must be performed within one week prior to second step registration (study enrollment after confirmation of glioblastoma pathology by central pathology review) to delineate the presence and degree of hemorrhage. If CT scanning is used, non-contrast scanning must be performed. The hemorrhage exclusion scan can be identical to the baseline tumor assessments scan (if using CT, then both pre-contrast and post-contrast CT must be performed). If a separate hemorrhage exclusion scan is performed in addition to the baseline tumor assessment scan, contrast-enhanced imaging is not required.

## APPENDIX XIII (7/20/09)

## ACRIN 6686 ADVANCED MRI TECHNICAL ACQUISITION GUIDELINES

### Site Selection

The advanced MR imaging described in this appendix will be undertaken at a limited number of pre-qualified sites per the qualification instructions posted on the ACRIN web site for the advanced imaging sub-study at: http://www.acrin.org/6686_protocol.aspx.

### Technical Parameters

Technical parameters for both standard and advanced imaging, as well as instructions for site pre-qualification can be found on the web at http://www.acrin.org/6686_protocol.aspx. Site qualification for the advanced imaging sub-study must be met prior to registering any eligible participants. All MRI studies should be performed on a scanner that has submitted images for pre-enrollment central review and has been approved for use in this study as described in this appendix. All studies must be performed according to the protocol performed during pre-qualification.

Participants will undergo follow-up scanning on the same exact scanner serially.

**Advanced MRI Imaging at 1.5 Tesla or 3.0 Tesla in order of acquisition:**

1. 3-plane localizer/scout
2. T1-weighted pre contrast (spin echo)
3. T2-weighted axial
4. Fluid-attenuated inversion recovery (FLAIR) axial
5. DCE-MRI
6. Diffusion Weighted Imaging/Diffusion Tensor Imaging (DWI/DTI)
7. DSC-MRI
8. T1-weighted post contrast 3D volumetric (gradient echo)
9. T1-weighted post contrast (spin echo)

### DCE Perfusion MRI Technique

The DCE-MRI component requires a T1 mapping sequence consisting of multiple series done at varying flip angles prior to the contrast enhanced series. An injection of 0.1 mmol/kg of gadolinium contrast agent + saline flush is administered after approximately 30 seconds of baseline imaging during the subsequent contrast enhanced series.

### DSC Perfusion MRI Technique

The DSC perfusion component of the MRI requires a dynamic image acquisition during rapid injection of a 0.1 mmol/kg Gd contrast agent / saline flush. The DCE-MRI series will be run prior to this DSC perfusion series. In this order, the DCE series with a gadolinium dose of 0.1 mmol/kg will have served as a pre-load for the DSC acquisition to minimize T1 leakage effects.

## APPENDIX XIV (7/20/09)

## ACRIN 6686 ADVANCED MR IMAGING ACQUISITION AND IMAGE SUBMISSION

**NOTE:** Detailed technical parameters for imaging, as well as instructions for site pre-qualification for Advanced Imaging, can be found on the web at http://www.acrin.org/6686_protocol.aspx The advanced MR imaging described in this appendix will be undertaken at a limited number of pre-qualified sites per the qualification instructions posted on the ACRIN web site at: http://www.acrin.org/6686_protocol.aspx.

Sites performing Advanced Imaging must be able to perform all of the required advanced series. A detailed process for the imaging quality assurance review and approval is outlined on the RTOG and ACRIN web sites, respectively, http://www.rtog.org and http://www.acrin.org/6686_protocol.aspx.

Eligible patients must have given written consent to participate in the Advanced Imaging (MRI) sub-study and satisfy the eligibility criteria.

Image submission requirements are outlined below in section 2 of this appendix.

Images will be submitted to ACRIN via secure FTP (sFTP) for approval by the central quality reviewer. The results of this review will be returned to the institutions prior to site participation.

**NOTE:** For more detailed information, contact Jim Gimpel at jgimpel@acr-arrs.org.

### 1 MR Image Quality Evaluations

#### 1.1 ACRIN Imaging Quality Assurance Review

##### 1.1.1 Institution MRI Scanners

- All institutions must have an ACRIN-approved MRI scanner qualified prior to registering participants.

##### 1.1.2 Submission of Test Cases for Image Quality Assurance Review

- Submit for review one MRI exam performed per protocol using the parameters available on the ACRIN web site at http://www.acrin.org/6686_protocol.aspx.
- Additionally, sites that participate in the advanced imaging option will include, DSC-MRI and DCE-MRI sequences according to protocol using the parameters listed in the Imaging Guidelines available on the ACRIN web site.

##### 1.1.3 Image Quality Assurance Review Rationale

- To establish a communication link between ACRIN, RTOG, and sites.
- To establish a mechanism for transferring images to ACRIN, e.g., internet, CD, DVD, etc.
- To ensure high quality standardized MR images from each site.
- To facilitate accurate and timely submission of required MR imaging.

### 1.2 Imaging Protocol

Imaging protocol can be found along with the Imaging Transmittal Worksheet on the ACRIN web site, http://www.acrin.org/6686_protocol.aspx, or on the RTOG web site (www.rtog.org).

All advanced MR imaging will conform to the MRI quality control standards as described on the ACRIN web site, http://www.acrin.org/6686_protocol.aspx, and on the RTOG web site (www.rtog.org).

## 2 MRI Submission Instructions

All imaging exams must be submitted to the ACRIN Image Management Center immediately following each time point/visit. Imaging submitted must not include any additional imaging for which the participant has not consented at registration.

A completed, signed Imaging Transmittal Worksheet (ITW) MUST accompany all imaging exams submitted to ACRIN for each time point. The ITW must be completed and faxed to 215-923-1737 at the time the images are being submitted. For exams submitted via media, this worksheet must be completed and included with the media shipment. Please affix a label to the jacket of the media to include: study name, site name, case number, date of exam(s), time point, and type of imaging.

### 2.1 MR Image Submission

ACRIN can provide software for anonymization and sFTP of DICOM image data. This software, TRIAD, can be installed and configured for radiology sites participating in ACRIN protocols. For more information on TRIAD software, contact the ACRIN Image Management Center at imagearchive@acr-arrs.org or the TRIAD helpdesk at Triad-Support@acr-arrs.org.

### 2.2 Removal of Confidential Participant Information

The header record on DICOM formatted image data often contains information identifying the participant by name and must be scrubbed before the image is transferred. This involves replacing the Participant Name tag with the ACRIN institution ID, replacing Participant ID tag with the ACRIN case number, and putting the study number (RTOG 0825/ACRIN 6686) into the Other Participant ID tag.

For further assistance in utilizing TRIAD for anonymization, about submission, or for other questions regarding image transfer, contact the ACRIN Image Management Center at imagearchive@acr-arrs.org.

### 2.3 CD Transfer

Images may also be sent on CD-ROM or other electronic medium for the ACRIN Image Management Center to transfer to the image archive. Please contact Jim Gimpel (jgimpel@acr-arrs.org; 215-574-3238) at ACRIN prior to your media submission to confirm compatibility before your first case.

### 2.4 Image Quality Control

All image submissions will be subject to ongoing quality control review by the ACRIN Image Management Center. In addition, a central quality review will be formally

conducted on the first standard imaging submission and the first two advanced submissions from each participating institution, including a review by the central quality investigator for the trial. A random sampling of 10% of the remaining cases will be reviewed thereafter.

Prompt submission of all image data is essential to ensure adequate image quality control.

## APPENDIX XV (11/29/10)

### ACRIN 6686 Advanced Imaging Adverse Event Reporting Instructions

### 1.0 Definition of Adverse Event

An Adverse Event **(AE)** is any untoward, undesired, unplanned medical occurrence in a participant, and does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding or physiological observation), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). Any symptom, sign, illness, or experience that develops or worsens in severity during the course of the study, including intercurrent illnesses or injuries, should be regarded as an AE.

### 2.0 Definition of Serious Adverse Event

AEs are classified as serious or non-serious. A Serious Adverse Event **(SAE)** is any AE that results in any of the following outcomes:

- Death;
- Life-threatening (refers to any adverse event that places the subject at immediate risk of death from the event as it occurred; life-threatening event does not include an event that, had it occurred in a more severe form, might have caused death, but as it actually occurred, did not create an immediate risk of death);
- Inpatient hospitalization and/or prolongation of an existing hospitalization (hospitalization is defined as lasting 24 hours or longer. Emergency room visits are not considered serious until one of the above criteria is met. Any elective hospitalization for a pre-existing condition that has not worsened does not constitute an SAE;
- Results in persistent or significant disability or incapacity (substantial disruption in a person's ability to conduct normal daily living activities);
- A congenital anomaly or birth defect (in offspring); or
- Other medically important event.

Important medical events are those based upon appropriate medical judgment that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above.

### 3.0 Adverse Event Grading

Grade refers to the severity (intensity) of the AE.

**1 – Mild:** AE is noticeable to the participant but does not interfere with routine activity.

**2 – Moderate:** AE interferes with routine activity but responds to symptomatic therapy and/or rest

**3 – Severe:** AE significantly limits the subject's ability to perform routine activities despite symptomatic therapy

**4 – Life-threatening or disabling**

**5 – Death/Fatal**

### 4.0 Adverse Event Attribution

Attribution is the determination of whether an AE is related to the advanced imaging study.

Attribution categories are:

| | | |
|---|---|---|
| **Definite** | – | AE **is clearly related** to the study treatment or procedure. |
| **Probable** | – | AE **is likely related** to the study treatment or procedure. |
| **Possible** | – | AE **may be related** to the study treatment or procedure. |
| **Unlikely** | – | AE **is doubtfully related** to the study treatment or procedure. |
| **Unrelated** | – | AE **is clearly NOT related** to the study treatment or procedure. |

## 5.0 Expected Adverse Events for Advanced Imaging Study:

MRI Scan:

- Anxiety/Stress
- Claustrophobia
- Discomfort.

Gadolinium:

- Allergic reaction to contrast agent
- Headache
- Nausea
- Vomiting
- Rash
- Temporary low blood pressure
- Nephrogenic Systemic Fibrosis (NSF)/Nephrogenic Fibrosing Dermopathy (NFD).

NOTE: Precautions should be exercised for patients with a history of grand mal seizures, severely impaired renal function or hemolytic anemia. The very unlikely possibility of a reaction, including anaphylactic or cardiovascular reactions, should be considered especially for patients with a known sensitivity to Gd or history of asthma. Nephrogenic Systemic Fibrosis (NSF) or Nephrogenic Fibrosing Dermopathy (NFD) (kidney disorders), may occur in patients with moderate to end-stage kidney disease after they have had a MRI scan with gadolinium-based contrast agent.

Needle Placement**:**

- Minor discomfort;
- Bleeding;
- Infection;
- Bruising.

## 6.0 Recording of Adverse Events

At each contact (site visit and/or telephone) with the study participant, the investigator or investigator-designee must seek information on AEs through discussion and, as appropriate, by examination. Information on all expected and unexpected AEs considered possibly, probably, definitely related to the advanced imaging (MRI and MRS) sub-study with the severity level of grades 3, 4, 5 should be recorded immediately into the source document, e.g. AE Log and/or progress notes of the study participant's chart, and retained at the site. These AEs will also be recorded in the AE CRF and reviewed by the principle site investigator in real time to determine grade and attribution of the event. For the standard MR imaging, sites should follow standard of care practice per the local institution's policies and procedures.

## 7.0 Reporting of Adverse Events

Prompt reporting of all AEs is the responsibility of each investigator, clinical research associate, and nurse engaged in clinical research.

Routine reporting is defined as documentation of AEs on source documents and AE CRF, and submission to RTOG for preparation of a report for Data and Safety Monitoring Committee (DSMC) review, quarterly reports to CDUS, and the final study report.

Expedited reporting is defined as immediate notification of NCI and RTOG. If reporting an event related to the Advanced Imaging (DCE-MRI and DSC-MRI) component, immediate notification to ACRIN is also required. Routine reporting requirements also apply.

ACRIN will collect and report only those AEs considered possibly, probably, or definitely related to the Advanced Imaging (DCE-MRI and DSC-MRI) sub-study that occur during study participation and up to 30 days after the last study procedure. Local IRBs and/or institutions may stipulate additional adverse events reporting based upon their review of the protocol.

All expected and unexpected adverse events considered possibly, probably, or definitely related to Advanced Imaging (DCE-MRI and DSC-MRI) sub-study and SAEs will be documented in the study participant's chart and AE CRFs, in addition to meeting all study-specific reporting requirements of ACRIN, NCI/CIP, and the local IRB (per local IRB policy).

## 8.0 Expedited Reporting to NCI, RTOG, and/or ACRIN

**8.1** Investigator or investigator-designee must use expedited AE reporting for **deaths** (considered possibly, probably, or definitely related to the Advanced Imaging [DCE-MRI and DSC-MRI] sub-study) occurring during study participation and up to 30 days after the last study procedure.

**8.2** All life-threatening/disabling unexpected AEs (considered possibly, probably, or definitely related to the Advanced Imaging [DCE-MRI and DSC-MRI] sub-study) occurring during study participation and up to 30 days after the last study procedure will reported within 24 hours, followed by a full report within five (5) calendar days of first knowledge of the event.

**8.3** All hospitalizations (or prolongation of existing hospitalization) for AEs with the severity (intensity) level of CTCAE (4.0) grade 3, 4, 5 and attribution of possibly, probably, or definitely related to the Advanced Imaging (DCE-MRI and DSC-MRI) sub-study must be reported within ten (10) calendar days of first knowledge of the event, in addition to documentation in patient chart and AE CRF. However, if the event is grade 4 or 5 and unexpected, it must be reported within 24 hours, followed by a full report within five (5) calendar days.

**8.4** All other SAEs with attribution of possibly, probably, or definitely related to the Advanced Imaging (DCE-MRI and DSC-MRI) sub-study which include AEs that results in persistent or significant disability or incapacity, or congenital anomaly (birth defect) in the offspring of the study participant must be reported within ten (10) calendar days of first knowledge of the event during study participation and up to 30 days after the last study procedure, in addition to documentation in patient chart and AE CRF.

**8.5** Significant new information and/or follow-up information (e.g., test results, autopsy, and discharge summary) on on-going SAEs should be promptly reported.

### 8.6 When to Report an Event in an Expedited Manner

Some AEs require 24-hour notification. Please complete a 24-Hour Notification Report via the NCI AdEERS web site (http://ctep.cancer.gov/reporting/adeers.html) within 24 hours of learning of the event. The full AdEERS report must be completed and submitted via AdEERS within 5 calendar days.

If the AdEERS system is down, a 24-hour notification call must be made to TRI 301-897-1704 and ACRIN 215-717-2763 for any AE related to the Advanced Imaging (DCE-MRI and DSC-MRI) sub-study. Once the system is restored, a 24-hour Notification Report must be entered into the AdEERS system by the original submitter of the report at the site.

When an AE requires expedited reporting, submit a full AdEERS report within the timeframes outlined in the table below. **NOTE:** AEs that meet the reporting requirements and occur within 30 days of the last dose of protocol treatment or procedure (Advanced Imaging [DCE-MRI and DSC-MRI] sub-study) must be reported on an expedited AE report form (using AdEERS).

For any AEs that occur more than 30 days after the last dose of treatment or procedure (Advanced Imaging [DCE-MRI and DSC-MRI] sub-study), only those that have an attribution of possibly, probably, or definitely AND meet the reporting requirements as described in the table below must be reported on an expedited AE report form (using AdEERS).

The following table summarizes the reporting requirements for AEs for the Advanced Imaging [DCE-MRI and DSC-MRI] sub-study:

| **Adverse Events that occur during study participation (related to the Advanced Imaging (DCE-MRI and DSC-MRI) sub-study)** | **Type of Report** | | |
|---|---|---|---|
| | **Routine Reporting** | **Expedited— Written in 10 days** | **Telephonic Report to NCI-CIP, RTOG, and/or ACRIN within 24 hours of first knowledge of AE** |
| **Grade 3 (Attribution of possible, probable, or definite)** | **X** Expected and Unexpected | | |
| **Hospitalization/Prolongation of hospitalization** (Attribution of possible, probable, or definite)** | **X** Expected and Unexpected | **X** Unexpected | |
| **Grade 4 (Attribution of possible, probable, or definite)** | **X** Expected and Unexpected | **X** Unexpected | |
| **Death (Attribution of possible, probable, or definite)** | **X** Expected and Unexpected | **X** Expected and Unexpected | **X** Expected and Unexpected |

****All unexpected hospitalizations (or prolongation of existing hospitalization) for AEs with the severity (intensity) level of CTCAE v 4.0 grade 3, 4, or 5 with attribution of possible, probable or definite.**

Assignment of grades (severity level) and attribution for each AE is to be completed at the institution by the Investigator.

This study requires that expedited AE reporting use the NCI's Adverse Expedited Reporting System (AdEERS). The NCI's guidelines for AdEERS can be found at http://ctep.cancer.gov. For questions regarding the use of the AdEERS application, please contact the NCI Technical Help Desk: 301-840-8202. For general questions regarding completion of AdEERS reports or submissions, email CIPAEReporting@tech-res.com or call the AdEERSMD helpline at 301-897-7497.

An AdEERS report must be submitted to RTOG/ACRIN and the appropriate regulatory agencies by one of the following methods:

- Electronically submit the report via the AdEERS Web-based application located at http://ctep.cancer.gov, **or**
- If the AdEERS system is down, fax the completed NCI Adverse Event Expedited Report – Single Agent or Multiple Agents for the investigational component of the DCE-MRI/DSC-MRI adverse events (paper template located at http://ctep.cancer.gov) to TRI (301-897-7402) and ACRIN (215-717-0936).

**NOTE:** Paper copies of AdEERS reports will only be accepted if the AdEERS system is down. Once the system is restored, a report submitted on a paper template must be entered into the AdEERS system by the original submitter of the report at the site.

Any supporting or follow up documentation must be faxed to TRI (301-897-7402) and ACRIN (215-717-0936) for investigational component of the Advanced Imaging (DCE-MRI and DSC-MRI) related events.

All expedited AE reports should be sent to your local Institutional Review Board (IRB). AEs not requiring expedited reporting are normally reported to your local IRB in an annual report and/or continuing review. Please refer to your local institution's IRB policies regarding AEs and SAEs and safety reports.

### 9.0 Other Recipients of AE Reports

**AdEERS reports will be forwarded to the appropriate regulatory agencies and/or pharmaceutical company, if applicable.**