

# RADIATION THERAPY ONCOLOGY GROUP

## RTOG 0625

### A RANDOMIZED PHASE II TRIAL OF BEVACIZUMAB WITH IRINOTECAN OR BEVACIZUMAB WITH TEMOZOLOMIDE IN RECURRENT GLIOBLASTOMA

NCI-Supplied Agents: Bevacizumab (NSC 704865; IND 7921), Irinotecan (NSC 616348)

This is a collaborative effort with American College of Radiology Imaging Network (ACRIN) –  
*ACRIN Study Number 6677*

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RADIATION THERAPY ONCOLOGY GROUP

RTOG 0625

A RANDOMIZED PHASE II TRIAL OF BEVACIZUMAB WITH IRINOTECAN OR BEVACIZUMAB WITH TEMOZOLOMIDE IN RECURRENT GLIOBLASTOMA

SCHEMA (3/1/07)

S T R A T I F Y	Age	R A N D O M I Z E	Arm 1: Bevacizumab (q 2 weeks) plus temozolomide (days 1-21 of a 28-day cycle)  Arm 2: Bevacizumab (q 2 weeks) plus irinotecan (q 2 weeks) of a 28-day cycle
	1. <50 2. ≥50		
	Karnofsky performance status		
	1. 70-80 2. 90-100		

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

Patients with histologically proven glioblastoma who have failed external beam radiotherapy with temozolomide chemotherapy.

**Required Sample Size: 121 patients**

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**ELIGIBILITY CHECKLIST (3/1/07, 7/18/07)**

Case # \_\_\_\_\_

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- \_\_\_\_\_(Y) 1. Is there histologic proof of intracranial glioblastoma or gliosarcoma?
- \_\_\_\_\_(Y) 2. Is the patient  $\geq$  18 years of age?
- \_\_\_\_\_(Y) 3. Is the Karnofsky performance status  $\geq$  70?
- \_\_\_\_\_(Y) 4. Were a history and physical including neurologic examination done within 8 weeks of registration?
- \_\_\_\_\_(Y) 5. Is the systolic blood pressure  $\leq$  160 mg/Hg and/or diastolic pressure  $\leq$  90 mg?
- \_\_\_\_\_(Y) 6. Was a CBC/differential obtained within 14 days prior to registration and was bone marrow function within the parameters of Section 3.1 of the protocol?
- \_\_\_\_\_(Y) 7. Were required liver function studies done within 14 days prior to registration and were the results within the parameters of Section 3.1 of the protocol?
- \_\_\_\_\_(Y) 8. Were renal function studies done within 14 days prior to registration and were the results within the parameters of Section 3.1 of the protocol?
- \_\_\_\_\_(Y) 9. Is the urinalysis for urine protein creatinine (UPC) ratio within the parameters of Section 3.1 of the protocol?
- \_\_\_\_\_(Y) 10. Were the prothrombin time results within the parameters defined in Section 3.1 of the protocol?
- \_\_\_\_\_(N) 11. Is there evidence of active bleeding as defined in Section 3.1 of the protocol?
- \_\_\_\_\_(Y) 12. Did the patient receive prior temozolomide?
- \_\_\_\_\_(Y) 13. Has the patient recovered from toxic effects of prior therapy including chemotherapy, investigational drugs, non-cytotoxic agents, radiotherapy, and surgery as defined in Section 3.1 of the protocol?
- \_\_\_\_\_(Y) 14. Is there unequivocal radiographic evidence of tumor progression on MRI obtained 14 days prior to registration?
- \_\_\_\_\_(Y/N) 15. If the patient is receiving steroids, has dose been increased between the date of imaging and the date of registration?  
\_\_\_\_\_(Y) If yes, has a new baseline MRI been obtained prior to registration?

**Continued on next page**

RTOG Institution # \_\_\_\_\_

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**ELIGIBILITY CHECKLIST (3/1/07, 7/18/07)(12/11/07)**

Case # \_\_\_\_\_

(page 2 of 3)

- \_\_\_\_\_ (Y/N) 16. Has the patient had recent surgery for recurrent or progressive disease?  
\_\_\_\_\_ (Y) If yes, have all criteria regarding this surgery as defined in Section 3.1 of the protocol been met?
- \_\_\_\_\_ (Y) 17. If the patient is a woman of child bearing potential, has a negative  $\beta$ -HCG pregnancy test been documented 14 days prior to registration?
- \_\_\_\_\_ (Y) 18. Has the patient agreed to practice adequate contraception while on study?
- \_\_\_\_\_ (Y) 19. Has the patient signed a study-specific informed consent form prior to study entry?
- \_\_\_\_\_ (Y/N) 20. Is there history of prior malignancy?  
\_\_\_\_\_ (Y) If yes, does it meet the eligibility criteria in Section 3.2. of the protocol?
- \_\_\_\_\_ (N) 21. Is there known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies?
- \_\_\_\_\_ (N) 22. Does the patient have any of the severe, active comorbidities defined in Section 3.2 of the protocol?
- \_\_\_\_\_ (Y/N) 23. Has the patient been taking EIAEDS (enzyme-inducing antiepileptic drugs)?  
\_\_\_\_\_ (Y) If yes, have or will EIAED be discontinued 2 weeks prior to registration?
- \_\_\_\_\_ (N) 24. Does the patient have any condition that impairs his or her ability to swallow and retain oral medications as defined in Section 3.2 of the protocol?
- \_\_\_\_\_ (Y/N) 25. Has there been prior treatment with stereotactic radiosurgery, Gliadel wafer, or brachytherapy?  
\_\_\_\_\_ (Y) If yes, was confirmation of progressive disease based upon PET or Thallium scanning, MRI spectroscopy, or surgical documentation?
- \_\_\_\_\_ (N) 26. Does the patient have severely impaired renal function with estimated glomerular function rate  $<30\text{ml}/\text{mon}/1.73\text{m}^2$  and/or is the patient on dialysis?

**The following questions will be asked at study registration:**

- \_\_\_\_\_ 1. Name of institutional person registering this case?
- \_\_\_\_\_ (Y) 2. Has the Eligibility Checklist (above) been completed?
- \_\_\_\_\_ (Y) 3. Is the patient eligible for this study?
- \_\_\_\_\_ 4. Date the study-specific consent form was signed (must be prior to study entry)
- \_\_\_\_\_ 5. Patient's Initials (First Middle Last)
- \_\_\_\_\_ 6. Verifying Physician
- \_\_\_\_\_ 7. Patient's ID Number

**Continued on next page**

RTOG 0625

RTOG Institution # \_\_\_\_\_

RTOG 0625

**ELIGIBILITY CHECKLIST (3/1/07, 7/18/07, 8/9/07)**

Case # \_\_\_\_\_

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- \_\_\_\_\_ 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. Tissue kept for cancer research?
- \_\_\_\_\_ (Y/N) 19. Tissue kept for medical research?
- \_\_\_\_\_ (Y/N) 20. Allow contact for future research?
- \_\_\_\_\_ (Y/N) 21. Has the patient agreed to enroll in the advanced MRI imaging component study of ACRIN 6677
- \_\_\_\_\_ (18-49/≥50) 22. Age
- \_\_\_\_\_ (70-80/90-100) 23. Karnofsky performance status
- \_\_\_\_\_ 24. Medical oncologist's name
- \_\_\_\_\_ (Y/N) 25. Did the patient participate in RTOG 0525?  
\_\_\_\_\_ If yes, what was the case #?  
\_\_\_\_\_ (Y) If yes, was a central pathology review completed and found to have histologic proof of GBM?  
\_\_\_\_\_ (Y) If no, has the patient consented to submission of tissue for central pathology review?
- \_\_\_\_\_ (Y) 26. Has the patient agreed to have standard of care MRIs submitted for review at a central repository?

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

Completed by \_\_\_\_\_

Date \_\_\_\_\_

## **1.0 INTRODUCTION**

### **1.1 Study Overview**

The prognosis for patients with recurrent malignant glioma is poor. Patients with recurrent glioblastoma have a median survival of 4 months, despite attempts at administering a variety of chemotherapy regimens.<sup>1</sup> 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.<sup>2</sup> Further, some antiangiogenic treatments have been associated with the development of apoptosis within the tumor cells themselves. Additionally, recent studies suggest that prolonged exposure to lower doses of cytotoxic chemotherapy can provide antiangiogenic therapy, presumably by direct effect on endothelial cell viability.<sup>3</sup>

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.<sup>4</sup> "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).<sup>5</sup> 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.<sup>6-10</sup>

In most studies, bevacizumab was used in combination with traditional cytotoxic agents. Randomized trials confirm that there is benefit in combining bevacizumab with cytotoxic chemotherapy drugs compared with the cytotoxic regimen alone.<sup>11</sup> Although the mechanism of treatment enhancement is unknown, two main hypotheses have been proposed. The first 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 the 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.<sup>12,13</sup> A high objective response rate has been noted, and in some cases the responses appear to be durable. 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. Therefore, we plan to formally evaluate the efficacy of the combination of irinotecan and bevacizumab to determine if this regimen is potentially beneficial for patients with recurrent glioblastoma, in whom very few proven treatment regimens exist.

Metronomic treatment with lower dose, but prolonged administration, of cytotoxic chemotherapy may be an ideal treatment regimen to combine with bevacizumab. For malignant brain tumors, temozolomide may be the ideal agent. The drug has nearly 100% oral bioavailability and an excellent toxicity profile, and cumulative myelotoxicity is rare, permitting prolonged use.

Additionally, temozolomide does cross the blood-brain barrier and has been shown to have activity in malignant gliomas.<sup>14</sup>

However, as described below, on the basis of the recently reported phase III trial performed by the European Organisation for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC), the current standard of care for patients with newly diagnosed glioblastoma is radiation and concurrent temozolomide followed by adjuvant temozolomide.<sup>15</sup> As a successor to this study, the Radiation Therapy Oncology Group (RTOG) and EORTC recently launched protocol RTOG 0525/EORTC 26052\_22053. This new study will treat patients with newly diagnosed glioblastoma with concurrent radiation, and then patients will be randomized to either standard-dose temozolomide or a dose-dense schedule. The study proposed in this protocol will include patients who have undergone previous treatment with temozolomide, often defined as “temozolomide refractory,” to test the hypothesis that the planned schedule of combined bevacizumab and temozolomide will target angiogenesis, specifically tumor-related endothelial cells that are unlikely to be temozolomide resistant.

## **1.2 Bevacizumab (1/22/09)**

### **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 ( $k_d = 1.1 \text{ nM}$ ).<sup>16</sup> 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.<sup>16-18</sup>

### **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.<sup>10</sup>

### **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.<sup>16,18-20</sup> 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.<sup>20-22</sup> Associated with the antitumor activity of anti-VEGF MAbs were findings of reduced intratumorial 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.<sup>17</sup>

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.<sup>23</sup> 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 principle 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.<sup>24</sup> 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%.<sup>6,7</sup>

Bevacizumab has also been studied in renal cell cancer. In a 3-arm, double-blind, placebo-controlled phase II trial,<sup>9</sup> 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. 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.<sup>12</sup> 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). Vrendenbergh and colleagues presented the results of a phase II trial from Duke of 32 patients with recurrent malignant glioma (glioblastoma = 23, anaplastic glioma = 9) at the 2006 meeting of the American Society of Clinical Oncology.<sup>13</sup> They reported that 62% of patients had an objective radiographic response; the 6-month progression-free rate was 30%. Nine patients had treatment stopped because of medical complications, most commonly venous thrombosis. They report no significant intratumoral hemorrhage.

### **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<sup>14</sup> treated patients with recurrent glioblastoma with either temozolomide (200 mg/m<sup>2</sup> days 1-5 of a 28-day cycle) or procarbazine (150 mg/m<sup>2</sup> 28 day-on, 28-day off schedule). 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<sup>2</sup> 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.<sup>25</sup>

There were no published studies using temozolomide as a post-radiation adjuvant treatment. Stupp and colleagues performed a phase II trial in patients with newly diagnosed glioblastoma, administering a daily lower dose (75 mg/m<sup>2</sup>) 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<sup>2</sup> for days 1 to 5 of a 28-day cycle.<sup>26</sup> 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 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. 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 the June 2004 annual meeting of the American Society of Clinical Oncology, with the full report published in the *New England Journal of Medicine*.<sup>15</sup> This chemoradiation regimen has been widely accepted as the new standard of care for patients with newly diagnosed glioblastoma.

### **1.4 Irinotecan Overview**

Irinotecan is a topoisomerase I inhibitor that has shown benefit in a wide range of cancers including colon cancer and non-small cell lung cancer. Irinotecan is administered intravenously; although the parent compound has activity, metabolism of irinotecan by carboxylesterase results in the formation of SN-38 that has a thousand-fold increase in topoisomerase activity.<sup>27</sup> Several treatment schedules have been tested for systemic cancers as well as for gliomas. Schedules including weekly times 4, then 2 weeks off; every 3 weeks; and, more recently, every 2 weeks have been evaluated. As a single agent for gliomas, most series report only modest activity, with response rates reported from 15% to less than 5%.<sup>25,28,29</sup> However, a recent study suggests that irinotecan and temozolomide in combination has better activity than either agent alone. In this phase II study, an objective response rate of 22% was noted.<sup>30</sup>

One of the major issues with irinotecan is the concern regarding drug-drug interaction. Two studies clearly demonstrated that the clearance and metabolism of irinotecan is markedly enhanced in patients receiving drugs, primarily anticonvulsants that induce the hepatic cytochrome p450 system. In these studies, patients not on enzyme-inducing antiepileptic drugs (EIAEDs) required a much lower dose of drug to reach the maximum tolerated dose. The study by Prados et al<sup>31</sup> demonstrated that patients on EIAEDs reached the maximum tolerated dose at a dose of 750 mg/m<sup>2</sup> with every-3-week dosing compared with 350 mg/m<sup>2</sup> for those patients not on EIAEDs. Similarly, the work of Gilbert and colleagues<sup>32</sup> reported that the maximum tolerated

dose for patients on EIAEDs to be 412 mg/m<sup>2</sup> with the weekly times 4 schedule compared with 117 mg/m<sup>2</sup> for patients not on EIAEDs.

The major toxicity of irinotecan is diarrhea. Both an acute (occurring within minutes to hours of drug infusion) and a subacute form (starting within days of treatment) have been reported. Although the pathogenesis of each of these syndromes has not been fully delineated, effective treatment paradigms have been established for each. The acute syndrome is treated with intravenous atropine, whereas the subacute form is usually successfully managed with loperamide on a well-defined schedule and plan.

## **1.5 MR Spectroscopy, MR Perfusion, and Diffusion Imaging Overview**

Structural MRI remains the standard for assessment of recurrence of glioblastoma (and is an entrance criteria), and it is the standard method for assessment of 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, with enhancement (bright signal) indicating that there is micro-structural disruption. The Macdonald criteria<sup>34</sup> for response assessment are applied to post-gadolinium T1-weighted MRI in most studies of glioblastoma (primary or recurrent).

While structural MRI has become a mainstay for patient assessment, structural MRI typically provides very little mechanistic information. This is of prime interest in this trial, and a sub-study of sites will perform advanced MR imaging to gain insights into possible mechanisms of action of combined bevacizumab with chemotherapy. This question is important because each of the agents in this study when used alone in recurrent glioblastoma has not been shown substantial efficacy, but combination therapy appears to have substantial effect, at least radiographically.<sup>12,13</sup> Understanding how combination therapy might be effective will enable further advances in rational design of treatment.

Of particular interest is whether the observed radiographic response represents only a radiographic artifact such as that due to changes in vascular permeability but not tumor viability. Observers point out that VEGF blockade should decrease contrast enhancement by decreasing vascular permeability but might not affect the underlying glioblastoma itself, just its vascularity. Anti-VEGF therapy may synergistically kill tumor cells when coupled with cytotoxic therapy, or, on the other hand, anti-angiogenesis treatment may lead to vascular normalization that is not directly toxic but allows improved delivery of chemotherapy. This remains uncertain at the present time.

In the face of these questions, a number of methods might be considered to provide mechanistic information. A variety of imaging, tissue sampling, and other techniques might be considered. However, given that patients will already be undergoing MRI, advanced MRI techniques that can be easily added to the existing schedule of imaging are intrinsically attractive. Three such techniques will be used in this study: magnetic resonance spectroscopic imaging (MRSI or simply MRS), perfusion MRI, and diffusion MRI. MRS can provide chemical information about the microenvironment in and around a tumor, and could identify regression of cancer markers (eg, choline, lactate, etc.) that might suggest functional changes to the tumor.

Perfusion MRI can be used to quantify the passage of contrast agent into the tissue using a method called dynamic contrast enhanced or DCE-MRI. This method can provide estimates of the transfer constant of the agent across the vessel wall, termed K<sub>trans</sub>. Another complementary perfusion MRI method, dynamic susceptibility contrast or DSC-MRI can provide estimates of blood volume, blood flow, and with certain methods an estimate of average blood vessel size. Diffusion MRI, by measuring vasogenic and cytotoxic edema, can in certain settings identify early changes that suggest cytotoxicity. This is done by measuring the diffusion and assuming Gaussian diffusion that can be estimated by a tensor, hence the term diffusion tensor imaging (DTI).

While these imaging techniques can potentially provide this type of information, their use in multicenter trials of glioblastoma therapy is limited. As a result, this component of the study is exploratory and sites will be invited to participate but participation is voluntary.

## **2.0 OBJECTIVES**

### **2.1 Primary**

- 2.1.1 To determine the efficacy of the combination of bevacizumab and irinotecan as measured by the 6-month progression-free survival rate in patients with recurrent glioblastoma.
- 2.1.2 To determine the adverse event profile and tolerability of the combination of bevacizumab and temozolomide in patients with recurrent glioblastoma.

### **2.2 Secondary**

- 2.2.1 To determine the efficacy of the combination of bevacizumab and temozolomide as measured by the 6-month progression-free survival rate in patients with recurrent glioblastoma who have been previously treated with temozolomide.
- 2.2.2 To determine the efficacy of bevacizumab and irinotecan as measured by objective response in patients with measurable disease.
- 2.2.3 To determine the efficacy of bevacizumab and temozolomide as measured by objective response in patients with measurable disease who have been previously treated with temozolomide
- 2.2.4 To determine the toxicity profile and tolerability of the combination of bevacizumab and irinotecan in patients with recurrent glioblastoma.

### **2.3 Central MRI Review (7/18/07)**

- 2.3.1 To assess the agreement between local interpretation and central interpretation of the standard MRI on the 6-month progression-free survival.
- 2.3.2 To estimate the accuracy of local interpretation on the 6-month progression-free survival using central review as the reference standard.

### **2.4 Advanced MRI (7/18/07)**

- 2.4.1 To assess the potential role of perfusion MRI and MR spectroscopy imaging as an early indicator of response to the therapy after two weeks following initiation of treatment with bevacizumab.
- 2.4.2 To assess the potential role of perfusion MRI and MR spectroscopy imaging as a prognostic indicator based on images taken before treatment, 2 weeks following initiation of protocol treatment, and after every 2 cycles of treatment.

## **3.0 PATIENT SELECTION**

### **3.1 Conditions for Patient Eligibility (3/1/07, 7/18/07)**

- 3.1.1 Histologically proven intracranial glioblastoma or gliosarcoma. There must be pathologic or imaging confirmation of tumor progression or regrowth.
  - 3.1.1.1 Patients will be eligible if the original histology was low-grade glioma and a subsequent diagnosis of glioblastoma or gliosarcoma is made.
- 3.1.2 The patient must consent to submission of tissue for central pathology review (See Section 10).
  - 3.1.2.1 Patients who have already undergone central pathology review through their enrollment on another RTOG glioblastoma trial do not need to consent to having their material re-reviewed by the central pathologist for this study.
- 3.1.3 History and physical examination, including neurologic examination, within 8 weeks prior to registration.
- 3.1.4 Systolic blood pressure  $\leq$  160 mg Hg or diastolic pressure  $\leq$  90 mg Hg
- 3.1.5 Patients must be able to undergo brain MRI scans with intravenous gadolinium.
- 3.1.6 Unequivocal radiographic evidence for tumor progression by MRI as defined in Section 11.2.1.2 within 14 days prior to registration.
  - 3.1.6.1 Patients must be on a steroid dose that has been stable for at least 5 days. If the steroid dose is increased between the date of imaging and registration, a new baseline MRI is required.
- 3.1.7 Karnofsky performance status  $\geq$  70
- 3.1.8 Age  $\geq$  18
- 3.1.9 CBC/differential obtained 14 days prior to registration, with adequate bone marrow function defined as follows:
  - 3.1.9.1 Absolute neutrophil count (ANC)  $\geq$  1,500/mm<sup>3</sup>

- 3.1.9.2 Platelets  $\geq 100,000$  cells/mm<sup>3</sup>
- 3.1.9.3 Hemoglobin  $\geq 10.0$  gm/dL (Note: The use of transfusion or other intervention to achieve Hgb  $\geq 10.0$  is acceptable)
- 3.1.9.4 White blood cell count (WBC)  $\geq 3,000$ /mCL
- 3.1.10 Adequate liver function within 14 days prior to registration, defined as follows:
  - 3.1.10.1 SGOT [AST]  $< 2$  times the upper limit of normal
  - 3.1.10.2 Bilirubin  $\leq 1.6$  mg/dL
- 3.1.11 Adequate renal function within 14 days prior to registration, defined as follows: Creatinine  $< 1.5$  mg/dL
- 3.1.12 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.
 

**Note:** UPC ratio of spot urine is an estimation of the 24-hour urine protein excretion; a UPC ratio of 1 is roughly equivalent to a 24-hour urine protein of 1 gm. UPC ratio is calculated using one of the following formulas:

  - [urine protein]/[urine creatinine]: if both protein and creatinine are reported in mg/dL
  - [(urine protein) x0.088]/[urine creatinine]: if urine creatinine is reported in mmol/L
- 3.1.13 Prothrombin time/international normalized ratio (PT INR)  $< 1.4$  for patients not on warfarin
- 3.1.14 Patients on full-dose anticoagulants (e.g., warfarin or LMW heparin) must meet both of the following criteria:
  - 3.1.14.1 No active bleeding or pathological condition that carries a high risk of bleeding (e.g., tumor involving major vessels or known varices)
  - 3.1.14.2 In-range INR (usually between 2 and 3) on a stable dose of oral anticoagulant or on a stable dose of low molecular weight heparin
- 3.1.15 Patients must have received prior temozolomide.
- 3.1.16 Patients must have recovered from the toxic effects of prior therapy, and there must be a minimum time of:
  - 3.1.16.1 28 days from the administration of any investigational agent
  - 3.1.16.2 28 days from administration of prior cytotoxic therapy with the following exceptions:
    - 3.1.16.2.1 14 days from administration of vincristine
    - 3.1.16.2.2 42 days from administration of nitrosoureas
    - 3.1.16.2.3 21 days from administration of procarbazine
  - 3.1.16.3 7 days from administration of non-cytotoxic agents [e.g., interferon, tamoxifen, thalidomide, cis-retinoic acid, etc. (radiosensitizer does not count)]. Any questions related to the definition of non-cytotoxic agents should be directed to the study chair.
- 3.1.17 Patients having undergone recent resection of recurrent or progressive tumor must meet all of the following conditions:
  - 3.1.17.1 Patients must have recovered from the effects of surgery and a minimum of 28 days must have elapsed from the day of surgery to the day of registration. For core or needle biopsy, a minimum of 7 days must have elapsed prior to registration.
  - 3.1.17.2 Residual disease following resection of recurrent glioblastoma is not mandated for eligibility into the study. To best assess the extent of residual disease post-operatively, an MRI should be done no later than 96 hours in the immediate postoperative period or at least 4 weeks postoperatively, within 14 days prior to registration. If the “within 96-hour of surgery” scan is more than 14 days before registration, the scan needs to be repeated.
  - 3.1.17.3 Patients must have failed prior radiation therapy and must have an interval of  $\geq 42$  days from the completion of radiation therapy to registration.
- 3.1.18 Patients with prior therapy that included interstitial brachytherapy, Gliadel wafer, or stereotactic radiosurgery must have confirmation of true progressive disease, rather than radiation necrosis, based upon either PET or Thallium scanning, MRI spectroscopy, or surgical documentation of disease.
- 3.1.19 Patients must sign study-specific informed consent prior to registration.
- 3.1.20 Women of childbearing potential must have a negative  $\beta$ -HCG pregnancy test documented within 14 days prior to registration.
- 3.1.21 Women of childbearing potential and male participants must practice adequate contraception.
- 3.1.22 The patient must agree to have standard of care MRIs submitted for review at a central repository. (See Sections 5.2, 11.2.2.1, and 11.2.3).

### **3.2 Conditions for Patient Ineligibility (7/18/07,12/11/07)**

- 3.2.1 Prior invasive malignancy that is not the glioblastoma or gliosarcoma (except non-melanomatous skin cancer or carcinoma in situ of the cervix) unless the patient has been disease free and off therapy for that disease for a minimum of 3 years
- 3.2.2 Acute intratumoral hemorrhage on MR imaging. Patients with MR imaging demonstrating old hemorrhage or subacute blood after a neurosurgical procedure (biopsy or resection) will be eligible for treatment
- 3.2.3 Severe, active comorbidity, defined as follows:
  - 3.2.3.1 Transmural myocardial infarction or unstable angina within 6 months prior to study registration
  - 3.2.3.1 Evidence of recent myocardial infarction or ischemia by the findings of S-T elevations of  $\geq 2$  mm using the analysis of an EKG performed within 14 days of registration
  - 3.2.3.2 New York Heart Association grade II or greater congestive heart failure requiring hospitalization within 12 months prior to registration
  - 3.2.3.3 History of stroke or transient ischemic attack within 6 months
  - 3.2.3.4 Inadequately controlled hypertension (systolic blood pressure  $> 160$  mm Hg and/or diastolic blood pressure  $> 90$  mm Hg despite antihypertensive medication)
  - 3.2.3.5 History of cerebral vascular accident (CVA) within 6 months
  - 3.2.3.6 Serious and inadequately controlled cardiac arrhythmia
  - 3.2.3.7 Significant vascular disease (e.g., aortic aneurysm, history of aortic dissection)
  - 3.2.3.8 Clinically significant peripheral vascular disease
  - 3.2.3.9 Evidence of bleeding diathesis or coagulopathy
  - 3.2.3.10 Serious or non-healing wound, ulcer, or bone fracture
  - 3.2.3.11 History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days prior to registration
  - 3.2.3.12 Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to registration
  - 3.2.3.13 Anticipation of need for major surgical procedures during the course of the study
  - 3.2.3.14 Core biopsy within 7 days prior to registration
  - 3.2.3.15 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration
  - 3.2.3.16 Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 14 days prior to registration
  - 3.2.3.17 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.
    - 3.2.3.17.1 Patients cannot be receiving HAART therapy.
- 3.2.4 Pregnant or nursing women
- 3.2.5 Fertile men and women who are sexually active and not willing/able to use medically acceptable forms of contraception during therapy and for at least 6 months after the completion of bevacizumab therapy. This exclusion is necessary because the treatment involved in this study may be significantly teratogenic.
- 3.2.6 Known hypersensitivity of Chinese hamster ovary cell products or other recombinant human antibodies
- 3.2.7 Any condition that impairs ability to swallow pills (e.g., gastrointestinal tract disease resulting in an inability to take oral medication or a requirement for IV alimentation, prior surgical procedures affecting absorption, active peptic ulcer disease).
- 3.2.8 Patients cannot not be receiving EIAEDs nor any other CYP3A4 inducers such as rifampin or St. John's wort. A reference list of EIAEDs is provided in Appendix IV.
- 3.2.9 No disease that will obscure toxicity or dangerously alter drug metabolism.
- 3.2.10 Patients with severely impaired renal function with estimated glomerular filtration rate  $< 30$  mL/min/1.73m<sup>2</sup> and/or on dialysis.

### **4.0 PRETREATMENT EVALUATIONS/MANAGEMENT (2/10/09)**

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

**NOTE: Patients must be offered the opportunity to participate in the correlative components of the study, such as tissue/specimen submission.**

- If the patient consents to participate in the tissue/specimen component of the study, the site is required to submit the patient's specimens as specified in Section 10.0 of the protocol. **Note:** Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

- 4.1 The following laboratory tests: albumin, alkaline phosphatase, BUN, calcium, chloride, glucose, lipase, potassium, total protein, SGPT [ALT], sodium, and antiepileptic drug levels as appropriate.

## **5.0 REGISTRATION PROCEDURES**

### **5.1 Regulatory Pre-Registration Requirements (1/22/09, 2/10/09)**

5.1.1 **U.S. and Canadian sites** 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](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

#### 5.1.2 *Pre-Registration Requirements FOR CANADIAN INSTITUTIONS*

5.1.2.1 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.

#### 5.1.3 *Pre-Registration Requirements FOR NON-CANADIAN INTERNATIONAL INSTITUTIONS*

##### 5.1.3.1 **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](http://www.rtog.org/pdf_forms.html?members/forms=Intl_LOI_Form.doc)

##### 5.1.3.2 **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.

### **5.2 Image Quality Assurance Review for MR Imaging (3/1/07, 7/18/07)**

Test cases described below will be scans previously obtained using the typical protocol-required technical parameters on patients with evidence of brain tumor.

Each RTOG institution must complete an ACRIN 6677 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 (optional) 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. The ACRIN 6677 PSA is available on the ACRIN website, [http://www.acrin.org/6677\\_protocol.aspx](http://www.acrin.org/6677_protocol.aspx).

#### 5.2.1 *Standard of Care MR Imaging*

All RTOG institutions participating in this study should submit images for image quality assurance review for MRI studies through the ACRIN Imaging Management Center (IMC). The image quality assurance review process includes submission and approval of one (1) standard of care MRI of a brain tumor where parameters used closely match those listed in the technique chart. The technique chart can be found on the ACRIN website at [http://www.acrin.org/6677\\_protocol.aspx](http://www.acrin.org/6677_protocol.aspx).

#### 5.2.2 *Advanced MR Imaging Option*

Sites that choose to participate in the advanced imaging option must also submit MRI images using the advanced MRI parameters. Complete instructions for the image quality review process are included in the ACRIN 6677 Protocol Specific Application (PSA).

Institutional reimbursements to offset the costs associated with participation in the advanced imaging component of the trial are provided by a grant from NCI/CIP through ACRIN. Payment for participation in the imaging component of the trial is automatic, based upon submission of

the key data forms and images to ACRIN. Reimbursement guidelines are outlined in Appendix VIII.

### **5.3 Online Registration (3/1/07)**

Patients can be registered only after eligibility criteria are met. Once the patient is registered via the web to RTOG 0625, the case will be automatically registered to ACRIN 6677. A registration confirmation e-mail is automatically generated and sent to the registering site including the Confirmation of New Case Registration to 6677[A0] and an ACRIN 6677 patient-specific calendar. The system creates a case file in the study 6677 database at the DMC (Data Management Center) and generates a 6677 data submission calendar listing all data forms, images, and reports and the dates on which they are due.

The first cohort of 91 patients are to be randomized between the two treatment arms using a permuted block design with the 2:1 ratio, meaning that patients will be twice as likely to be assigned the bevacizumab and irinotecan arm as they would be assigned the bevacizumab and temozolomide arm. This unbalanced randomization is being done because of the study endpoints (see section 13 for more detail).

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://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp>).
- A representative from the institution must complete the Password Authorization Form at [www.rtog.org/members/webreg.html](http://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 and provides the treatment assignment. 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@phila.acr.org](mailto:websupport@phila.acr.org) or 800-227-5463 ext. 4189 or 215-574-3189.

In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask for the site’s user name and password. This information is required to assure that mechanisms usually triggered by web registration (e.g., drug shipment, confirmation of registration, and patient-specific calendar) will occur.



## **6.0 RADIATION THERAPY**

Not applicable to this study.

## **7.0 DRUG THERAPY**

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

**Protocol treatment must begin within 5 business days after registration.**

### **7.1 Treatment**

**7.1.1 Dose Definitions:** The dosing of bevacizumab will be based on actual body weight in kilograms. The dosing of temozolomide and irinotecan will be based on actual body surface area as calculated in square meters.

#### **7.1.1.1 Summary of chemotherapy dosing**

**Arm 1: Temozolomide plus Bevacizumab**

**Temozolomide:** (cycle 1) 75 mg/m<sup>2</sup> p.o. days 1-21 of a 28 day cycle; the dose of temozolomide can be increased to 100 mg/m<sup>2</sup> for cycle 2 and beyond if there is no myelotoxicity greater than grade 2 . Other dose modifications are outlined in section 7.5.2.5 below.

**Bevacizumab:** 10 mg/kg i.v. days 1 and 15 of a 28 day cycle. There are no planned dose escalations or reductions.

**Arm 2: Irinotecan plus Bevacizumab**

**Irinotecan:** 125 mg/m<sup>2</sup> iv days 1 and 15 of a 28 day cycle. Dose modifications are outlined in section 7.5.3.5 below.

**Bevacizumab:** 10 mg/kg i.v. days 1 and 15 of a 28 day cycle. There are no planned dose escalations or reductions.

#### **7.1.2 Administration Guidelines**

##### **7.1.2.1 Bevacizumab**

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, all subsequent infusions should be administered over the shortest period that was well tolerated.

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

1. When the bevacizumab infusion is complete, add an additional 50 mL of 0.9% sodium chloride for injection to the bevacizumab 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 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.

**7.1.2.1.1 Special cautions/safety issues:** Measurement of blood pressure and dipstick urinalysis should be performed prior to each dose of bevacizumab. Modification of dose or discontinuation of therapy should be considered if the patient experiences uncontrolled hypertension and/or dipstick urinalysis reveals > 2 gm proteinuria/24 hour.

##### **7.1.2.2 Temozolomide**

Temozolomide is administered orally as a single dosage each day. Nightly administration just before bedtime has been reported to improve tolerance. Dosing should occur at least 2 hours after eating and no food consumption should occur for at least 1 hour after administration.

Antiemetic use is recommended to be taken 30 minutes to 1 hour prior to drug administration. Most patients report optimal nausea control with use of oral serotonin receptor (5-HT<sub>3</sub>) antagonist, such as ondansetron.

- 7.1.2.3** Irinotecan  
Irinotecan is administered intravenously over 90 minutes. Patients are premedicated with either an oral or intravenous serotonin antagonist. Patients who develop acute diarrhea and abdominal cramping should receive atropine at a dose of 1 mg intravenously. Subsequent treatments with irinotecan should then include atropine at a dose of 1 mg intravenously 15-30 minutes prior to the administration of the irinotecan. See Section 9.1 for additional information.
- 7.1.3** Duration of Treatment
- 7.1.3.1** Bevacizumab and Temozolomide: Each cycle of treatment will be defined as 28 days, during which time 21 consecutive days of temozolomide (days 1-21) will be administered and bevacizumab will be given on days 1 and 15. Evaluation of treatment efficacy will occur after each 2 cycles of treatment. Patients demonstrating evidence of benefit as defined by stable or responding tumor will be treated for 12 cycles with the option of extending to a maximum of 24 cycles as long as continued benefit is seen and severe toxicity, as defined in Section 7.5, does not develop.
- 7.1.3.2** Bevacizumab and Irinotecan: Each cycle of treatment will be defined as 28 days, during which time both the irinotecan and bevacizumab will be administered on days 1 and 15. Bevacizumab administration will be performed prior to the irinotecan. Evaluation of treatment efficacy will occur after each 2 cycles of treatment. Patients demonstrating evidence of benefit as defined by stable or responding tumor will be treated for 12 cycles with the option of extending to a maximum of 24 cycles as long as continued benefit is seen and severe toxicity, as defined in Section 7.5, does not develop.
- 7.1.3.3** For Both Treatment Regimens: Doses held or missed because of either hematologic or non-hematologic toxicity developing during the treatment cycle will not be made up. For toxicities present at the planned initiation of a treatment cycle, the guidelines provided in Section 7.5. will hold.

**7.2** Bevacizumab Agent Information (rhuMAb VEGF, Avastin) [NSC # 704865; IND # 7921] (1/22/09)

Please refer to the package insert for comprehensive information.

- 7.2.1** Formulation  
Bevacizumab is a recombinant humanized 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. Approximate molecular weight is 149,000 daltons.
- 7.2.2** Availability  
Bevacizumab is supplied as a clear to slightly opalescent, sterile liquid ready for parenteral administration in two vial sizes:
- Each 100 mg (25 mg/mL – 4 mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP.
  - Each 400 mg (25 mg/ml – 16 mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP.
- 7.2.3** Pharmacokinetics  
Bevacizumab blocks the binding of VEGF to its receptors resulting in inhibition of angiogenesis.
- 7.2.4** Storage and Stability  
Upon receipt, bevacizumab should be refrigerated (2° to 8° C). Do not freeze. Do not shake. Shelf-life studies of rhuMAb VEGF are ongoing. The sterile single use vials contain no antibacterial preservatives. Therefore, vials should be discarded 8 hours after initial entry. Once diluted in 0.9% sodium chloride, solutions of bevacizumab must be administered within 8 hours.
- 7.2.5** Administration: The initial dose is delivered over 90 minutes. If there are no infusion-associated adverse events such as fever or chills, the next dose can be given over 60 minutes. If there are no infusion-associated adverse events such as fever or chills, the next dose and all subsequent doses can be given over 30 minutes.
- 7.2.6** Agent Ordering and Agent Accountability  
NCI supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained.) The CTEP assigned protocol number must be used for ordering all CTEP supplied

investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Agent may be requested by completing a Clinical Drug Request (NIH-986) and mailing it to the Drug Management and Authorization Section, PMB, DCTD, NCI, 9000 Rockville Pike, EPN Room 7149, Bethesda, MD 20892-7422 or faxing it to (301) 480-4612. For questions call (301) 496-5725.

**7.2.6.1 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.

**7.2.7 Agent Inventory Records** - The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record (DAR) Form, according to good clinical practices and NCI guidelines. (See the NCI Investigators' Handbook for Procedures for Drug Accountability and Storage.)

**7.2.8 Preparation**

Vials contain no preservatives and are intended for single use only. Place the calculated dose in 100 mL of 0.9% sodium chloride for injection.

7.2.9 *Adverse Events (12/11/07)*

**Comprehensive Adverse Events and Potential Risks List (CAEPR) for Bevacizumab (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.cancer.gov/reporting/adeers.html> for further clarification. The CAEPR does not provide frequency data; refer to the Investigator's Brochure for this information. Below is the CAEPR for Bevacizumab.

Version 1.2, June 19, 2007<sup>1</sup>

<b>Category (Body System)</b>	<b>Adverse Events with Possible Relationship to Bevacizumab (CTCAE v3.0 Term)</b>	<b>'Agent Specific Adverse Event List' (ASAEL)</b>
<b>ALLERGY/IMMUNOLOGY</b>		
	Allergic reaction/hypersensitivity (including drug fever)	<b><i>Allergic reaction/hypersensitivity (including drug fever)</i></b>
	Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	<b><i>Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)</i></b>
<b>BLOOD/BONE MARROW</b>		
	Hemoglobin	<b><i>Hemoglobin</i></b>
	Leukocytes (total WBC)	<b><i>Leukocytes (total WBC)</i></b>
	Neutrophils/granulocytes (ANC/AGC)	<b><i>Neutrophils/granulocytes (ANC/AGC)</i></b>
<b>CARDIAC ARRHYTHMIA</b>		
	Supraventricular arrhythmia NOS	<b><i>Supraventricular arrhythmia NOS</i></b>
	Ventricular fibrillation	
<b>CARDIAC GENERAL</b>		
	Cardiac ischemia/infarction	<b><i>Cardiac ischemia/infarction</i></b>
	Cardiac troponin I (cTnI)	
	Hypertension	<b><i>Hypertension</i></b>
	Hypotension	
	Left ventricular diastolic dysfunction	
	Left ventricular systolic dysfunction	
<b>CONSTITUTIONAL SYMPTOMS</b>		
	Fatigue (asthenia, lethargy, malaise)	<b><i>Fatigue (asthenia, lethargy, malaise)</i></b>
	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10 <sup>9</sup> /L)	<b><i>Fever (in the absence of neutropenia, where neutropenia is defined as ANC &lt;1.0 x 10<sup>9</sup>/L)</i></b>
	Rigors/chills	<b><i>Rigors/chills</i></b>
	Weight loss	
<b>DERMATOLOGY/SKIN</b>		
	Pruritus/itching	<b><i>Pruritus/itching</i></b>
	Rash/desquamation	<b><i>Rash/desquamation</i></b>
	Ulceration	
	Urticaria (hives, welts, wheals)	<b><i>Urticaria (hives, welts, wheals)</i></b>
	Wound complication, non-infectious	
<b>GASTROINTESTINAL</b>		
	Anorexia	<b><i>Anorexia</i></b>
	Colitis	
	Constipation	<b><i>Constipation</i></b>
	Diarrhea	<b><i>Diarrhea</i></b>
	Fistula, GI - Select	
	Heartburn/dyspepsia	<b><i>Heartburn/dyspepsia</i></b>
	Ileus (functional obstruction of bowel, i.e., neuroconstipation)	
	Leak (including anastomotic), GI: large bowel	
	Mucositis/stomatitis (functional/symptomatic) - Select	<b><i>Mucositis/stomatitis (functional/symptomatic) - Select</i></b>
	Nausea	<b><i>Nausea</i></b>
	Perforation, GI - Select	

<b>Category (Body System)</b>	<b>Adverse Events with Possible Relationship to Bevacizumab (CTCAE v3.0 Term)</b>	<b>'Agent Specific Adverse Event List' (ASAEL)</b>
	Ulcer, GI - Select	
	Vomiting	<b>Vomiting</b>
<b>HEMORRHAGE/BLEEDING</b>		
	Hemorrhage, GI - Select	<b>Hemorrhage GI - Select</b>
	Hemorrhage, CNS	<b>Hemorrhage, CNS</b>
	Hemorrhage, GU: vagina	<b>Hemorrhage, GU: vagina</b>
	Hemorrhage, pulmonary/upper respiratory: lung	<b>Hemorrhage, pulmonary/upper respiratory: lung</b>
	Hemorrhage, pulmonary/upper respiratory: nose	<b>Hemorrhage, pulmonary/upper respiratory: nose</b>
<b>INFECTION</b>		
	Infection with normal ANC or Grade 1 or 2 neutrophils - Select	
	Infection with normal ANC or Grade 1 or 2 neutrophils - Select (pelvis, peritoneal cavity, rectum, scrotum, skin, wound)	
<b>METABOLIC/LABORATORY</b>		
	Alkaline phosphatase	<b>Alkaline phosphatase</b>
	ALT, SGPT (serum glutamic pyruvic transaminase)	<b>ALT, SGPT (serum glutamic pyruvic transaminase)</b>
	AST, SGOT (serum glutamic oxaloacetic transaminase)	<b>AST, SGOT (serum glutamic oxaloacetic transaminase)</b>
	Bilirubin (hyperbilirubinemia)	<b>Bilirubin (hyperbilirubinemia)</b>
	Creatinine	
	Proteinuria	<b>Proteinuria</b>
<b>NEUROLOGY</b>		
	CNS cerebrovascular ischemia	<b>CNS cerebrovascular ischemia</b>
	Dizziness	<b>Dizziness</b>
	Neurology - Other: (Leukoencephalopathy syndrome including reversible posterior leukoencephalopathy syndrome [RPLS])	
<b>PAIN</b>		
	Pain - abdomen NOS	<b>Pain - abdomen NOS</b>
	Pain - chest/thorax NOS	<b>Pain - chest/thorax NOS</b>
	Pain - head/headache	<b>Pain - head/headache</b>
	Pain - joint	<b>Pain - joint</b>
	Pain - muscle	
	Pain - NOS	
<b>PULMONARY/UPPER RESPIRATORY</b>		
	Bronchospasm, wheezing	
	Cough	<b>Cough</b>
	Dyspnea (shortness of breath)	<b>Dyspnea (shortness of breath)</b>
	Fistula, pulmonary/upper respiratory - Select	
	Nasal cavity/paranasal sinus reactions	<b>Nasal cavity/paranasal sinus reactions</b>
	Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)	<b>Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)</b>
	Pulmonary/Upper Respiratory - Other (nasal-septal perforation)	
<b>RENAL/GENITOURINARY</b>		
	Fistula, GU - Select	
	Renal failure	
<b>SYNDROMES</b>		
	Cytokine release syndrome/acute infusion reaction	<b>Cytokine release syndrome/acute infusion reaction</b>
<b>VASCULAR</b>		
	Thrombosis/thrombus/embolism	<b>Thrombosis/thrombus/embolism</b>
	Visceral arterial ischemia (non-myocardial)	

<sup>1</sup>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 ADEERSMD@tech-res.com. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

Also reported on bevacizumab trials but with the relationship to bevacizumab still undetermined:

**BLOOD/BONE MARROW** - Idiopathic thrombocytopenia purpura; platelets

**CARDIAC GENERAL** - Cardiac arrest; pericardial effusion; pulmonary hypertension

**COAGULATION** - DIC

**DEATH** - Sudden death (cause unknown)

**DERMATOLOGY/SKIN** - Hypopigmentation

**GASTROINTESTINAL** - Rectal abscess/necrosis; small bowel obstruction; taste alteration

**METABOLIC/LABORATORY** - Hyperglycemia; hypoglycemia; hypomagnesemia; hyponatremia

**MUSCULOSKELETAL/SOFT TISSUE** - Aseptic necrotic bone; gait/walking; myasthenia gravis

**NEUROLOGY** - Aseptic meningitis; confusion; peripheral neuropathy; seizure; syncope

**OCULAR/VISUAL** - Cataract; watery eye

**PULMONARY/UPPER RESPIRATORY** - ARDS; pneumonitis/pulmonary infiltrates; pneumothorax

**RENAL/GENITOURINARY** - Urinary frequency

**Note:** Bevacizumab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

### **7.3 Temozolomide Agent Information (Temodar) (7/18/07, 2/10/09)**

Please refer to the package insert for comprehensive information.

#### **7.3.1 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, 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 lauryl sulfate NF.

#### **7.3.2 Mode of Action**

Alkylating agent of imidazotetrazinone class.

#### **7.3.3 Storage and Stability**

The capsules are packaged in 30 cc, 28 mm, 48 Type I amber glass bottles (30 capsules/bottle) and should be stored at 25°C but temperatures between 15 and 30 degrees centigrade are permissible. Capsules are stable for at least 30 months when stored in amber glass bottles at this temperature.

#### **7.3.4 Supply**

Commercially available.

#### **7.3.4.1 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.

#### **7.3.5 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<sub>max</sub> 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%.

#### **7.3.6 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 AIC 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<sup>2</sup>.

### 7.3.7 Special Populations

7.3.7.1 Creatinine Clearance: Population pharmacokinetic analysis indicates that creatinine clearance over the range of 36-130 mL/min/m<sup>2</sup> 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 (CL<sub>cr</sub> < 36 mL/min/m<sup>2</sup>).

Caution should be exercised when temozolomide is administered to patients with severe renal impairment. Temozolomide has not been studied in patients on dialysis.

7.3.7.2 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.

7.3.7.3 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.

7.3.7.4 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.

### 7.3.8 Drug-Drug Interactions

In a multiple dose study, administration of temozolomide with ranitidine did not change the C<sub>max</sub> 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<sub>2</sub>-receptor antagonists, or phenobarbital on the clearance of orally administered temozolomide.

### 7.3.9 Known Potential 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

7.3.10 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.

### 7.3.11 Contraindications

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

### 7.3.12 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.

#### **7.4 Irinotecan Agent Information (Camptosar, CPT-11) [NSC 616348] (2/10/09)**

Please refer to the package insert for comprehensive information.

##### **7.4.1 Chemistry**

Irinotecan hydrochloride trihydrate {CPT-11, (4S)-4, 11-diethyl-4-hydroxy-9-[(4-piperidinopiperidino) carbonyloxy]-1H-pyrano[3',4':6,7]indolizino[1,2-b]quino line-3, 14(4H, 12H)dione hydrochloride trihydrate} is a topoisomerase I inhibitor.

##### **7.4.2 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.

##### **7.4.3 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.

##### **7.4.4 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.

##### **7.4.5 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 CAMPTOSAR) 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.

##### **7.4.6 Supply**



Commercially labeled Irinotecan will be supplied by Pfizer and be distributed by the Pharmaceutical Management Branch (PMB). See sections 7.2.6 and 7.2.7 for ordering and handling instructions.

**7.4.6.1 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.

**7.5 Dose Modifications (7/18/07)**

**7.5.1 Bevacizumab**

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

**Treatment Modification for Bevacizumab-Related Adverse Events**

Event	CTCAE.v3.0 Grade	Action To Be Taken
<b>Allergic reactions</b>  or  <b>Acute infusional reactions/ cytokine release syndrome</b>	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 the Sections 7.1 and 7.2 for bevacizumab administration.  <b>For patients with grade 3 reactions</b> , bevacizumab infusion should be stopped and not restarted on the same day. At the physicians' discretion, bevacizumab may be permanently discontinued or re-instituted with premedications and at a rate of 90±15 min. <b>If bevacizumab is re-instituted, the patient should be closely monitored for a duration comparable to or longer than the duration of the previous reactions.</b>
	Grade 4	Discontinue bevacizumab
<b>Arterial Thrombosis</b> - Cardiac ischemia/ infraction - CNS ischemia (TIA, CVA) - any peripheral or visceral arterial ischemia/thrombosis	Grade 2 ( if new or worsened since bevacizumab therapy)	Discontinue bevacizumab
	Grade 3-4	Discontinue bevacizumab

Event	CTCAE.v3.0 Grade	Action To Be Taken
<b>Venous Thrombosis</b>	Grade 3 OR asymptomatic grade 4	<ul style="list-style-type: none"> <li>▪ Hold bevacizumab treatment. If the planned duration of full-dose anticoagulation is &lt; 2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over.</li> <li>▪ If the planned duration of full-dose anticoagulation is &gt;2 weeks, bevacizumab may be resumed during the period of full-dose anticoagulation <b>IF all</b> of the criteria below are met: <ul style="list-style-type: none"> <li>- 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</li> <li>- The subject must not have pathological conditions that carry high risk of bleeding (eg, tumor involving major vessels or other conditions)</li> <li>- The subject must not have had hemorrhagic events while on study</li> </ul> </li> <li>▪ If thromboemboli worsen/recur upon resumption of study therapy, discontinue bevacizumab</li> </ul>
	Grade 4 (symptomatic)	Discontinue bevacizumab
<b>Hypertension*</b>	[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 <b>but</b> diastolic BP < 100 mmHg	Begin anti-hypertensive therapy and continue bevacizumab
	-Grade 2-3 Symptomatic <b>OR</b> -Diastolic BP > 100 mmHg	<ul style="list-style-type: none"> <li>• Hold bevacizumab should until symptoms resolve <b>AND</b> BP &lt; 160/90mmHg*</li> </ul>
	Grade 4	Discontinue bevacizumab.
<b>Congestive Heart Failure</b>	Grade 3	<ul style="list-style-type: none"> <li>• Discontinue bevacizumab</li> </ul>
	Grade 4	Discontinue bevacizumab
<b>Proteinuria</b>	[Proteinuria should be monitored by urine analysis for urine protein creatinine (UPC) ratio prior to every other dose of bevacizumab]	
	UPC ratio < 3.5	Continue bevacizumab
	UPC ratio ≥ 3.5	Hold bevacizumab until UPC recovers to < 3.5
	Grade 4 or nephrotic syndrome	Discontinue bevacizumab
<b>Hemorrhage (CNS or pulmonary)</b>	Grade 2-4	<ul style="list-style-type: none"> <li>• Discontinue bevacizumab</li> </ul>
<b>Hemorrhage (non-CNS; non-pulmonary)</b>	Grade 3	<ul style="list-style-type: none"> <li>• Patients receiving full-dose anticoagulation should discontinue bevacizumab</li> <li>• For patients not on full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met: <ul style="list-style-type: none"> <li>- the bleeding has resolved and Hb is stable</li> <li>- there is no bleeding diathesis that would increase the risk of therapy</li> <li>- there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence.</li> </ul> </li> <li>• Patients who experience recurrence of grade 3 hemorrhage should discontinue study therapy</li> </ul>
	Grade 4	Discontinue bevacizumab
<b>RPLS</b> (reversible posterior leukoencephalopathy syndrome <b>or</b> <b>PRES</b> (posterior reversible encephalopathy syndrome))		<ul style="list-style-type: none"> <li>• <b>Hold bevacizumab in patients with symptoms/signs suggestive of RPLS; subsequent management should include MRI scans and control of HTN</b></li> </ul>

Event	CTCAE.v3.0 Grade	Action To Be Taken
		• <b>Discontinue bevacizumab upon diagnosis of RPLS</b>
<b>Wound dehiscence</b> requiring medical or surgical intervention		• <b>Discontinue bevacizumab</b>
<b>GI perforation, GI leak or fistula</b>		Discontinue bevacizumab
<b>Bowel obstruction</b>	Grade 2 requiring medical intervention	• Hold bevacizumab until complete resolution, with a minimum of 4 weeks after surgery.
	Grade 3-4	• Hold bevacizumab until complete resolution • If surgery is required, patient may restart bevacizumab after full recovery from surgery, and at investigator's discretion
<b>Other unspecified bevacizumab-related AEs</b> (except controlled nausea/vomiting).	Grade 3	Hold bevacizumab until symptoms resolve to $\leq$ grade 1
	Grade 4	• Discontinue bevacizumab • <b>Upon consultation with the study chair</b> , resumption of bevacizumab may be considered if a patient is benefiting from therapy and the grade 4 toxicity is transient, has recovered to $\leq$ 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)

## 7.5.2 Temozolomide

7.5.2.1 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 <sup>2</sup>	Remarks
- 2	35	Reduction if prior AE
-1	50	Reduction if prior AE
0	75	Starting dose for cycle 1, increase to 100 mg/m <sup>2</sup> for cycle 2 and beyond if no toxicity ≥ grade 3
+1	100	Highest possible dose level

7.5.2.2 First Cycle: Temozolomide will be started at a dose of 75 mg/m<sup>2</sup>/day.

7.5.2.3 Second Cycle: The dose of temozolomide will be determined according to: (1) non-hematologic AE during the preceding treatment cycle, as well as (2) the worst ANC and platelet counts.

7.5.2.4 Delay: On day 1 of each cycle (within the prior 72 hours), ANC ≥ 1.5 x 10<sup>9</sup>/L, platelet count ≥ 100 x 10<sup>9</sup>/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 temozolomide should be stopped.

7.5.2.5 Dose Escalations and Reductions: If, during the first cycle, all non-hematologic AEs observed were grade ≤ 2 (except alopecia, nausea and vomiting) and with platelets ≥ 100 x 10<sup>9</sup>/L and ANC ≥ 1.5 x 10<sup>9</sup>/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 temozolomide 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).

7.5.2.5.1 Dose reductions: If any non-hematologic AE observed was grade > 2 (except alopecia, nausea and vomiting) and/or if platelets < 50 x 10<sup>9</sup>/L and/or ANC < 1 x 10<sup>9</sup>/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 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) 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 Temozolomide-Related Adverse Events**

<b>Worst Treatment-Related Non-Hematologic AE (except for alopecia, nausea, and vomiting) During the Previous Cycles</b>	
<b>Grade</b>	<b>Dose Modification</b>
<b>0-2</b>	No dose modifications for non-hematologic AEs. Dose reductions based on ANC and platelet counts are applicable.
<b>3</b>	Reduce by one dose level (except alopecia, nausea, and vomiting).
<b>4</b>	Stop (except alopecia, nausea, and vomiting). Dose modifications based on ANC and platelet counts are not applicable.

**Worst Treatment-Related Hematologic AE During the Previous Cycle**

<b>Worst AE</b>		<b>Platelets</b>		
		<b>≥100 x 10<sup>9</sup>/L</b>	<b>50 – 99 x 10<sup>9</sup>/L</b>	<b>&lt; 50 x 10<sup>9</sup>/L</b>
<b>ANC</b>	<b>≥ 1.5 x 10<sup>9</sup>/L</b>	Dose unchanged	Dose unchanged	Reduce by 1 dose level
	<b>≥1 &amp; &lt;1.5 x 10<sup>9</sup>/L</b>	Dose unchanged	Dose unchanged	Reduce by 1 dose level
	<b>&lt; 1 x 10<sup>9</sup>/L</b>	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, 21 and 28 (± 48 hours) after the first daily dose of each adjuvant treatment cycle.

<b>Hematologic AE on Day 1 of Each Cycle (within the prior 72 hours before Day 1)</b>	
<b>AE</b>	<b>Delay</b>
<b>ANC &lt; 1.5 x 10<sup>9</sup>/L and/or Platelet count &lt; 100 x 10<sup>9</sup>/L</b>	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.

<b>Non-Hematologic AE (except for alopecia, nausea, and vomiting) On Day 1 of Each Cycle (within the prior 72 hours)</b>	
<b>Grade</b>	<b>Delay</b>
<b>2-3</b>	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 AE, then no escalation is possible.

**7.5.3 Irinotecan**

**7.5.3.1** 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.

<b>Dose Level</b>	<b>Dose mg/m<sup>2</sup></b>	<b>Remarks</b>
- 2	75	Reduction if prior AE
-1	100	Reduction if prior AE
0	125	-----

- 7.5.3.2** First Cycle: Irinotecan will be started at a dose of 125 mg/m<sup>2</sup> on days 1 and 15 of a 28-day cycle.
- 7.5.3.3** 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
- 7.5.3.4** Delay: On day 1 of each cycle (within the prior 72 hours), ANC  $\geq 1.5 \times 10^9/L$ , platelet count  $\geq 100 \times 10^9/L$ , and all grade 3 or 4 non-hematologic AEs (except for alopecia, nausea, and vomiting) must have resolved (to grade  $\leq 1$ ).
- 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.
- 7.5.3.5** Dose Reductions: If any non-hematologic AE observed was grade  $> 2$  (except alopecia, nausea, and vomiting) and/or if platelets  $< 50 \times 10^9/L$  and/or ANC  $< 1 \times 10^9/L$ , 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**

<b>Worst Treatment-Related Non-Hematologic AE (except for alopecia, nausea, and vomiting) During the Previous Cycles</b>	
<b>Grade</b>	<b>Dose Modification</b>
<b>0-2</b>	No dose modifications for non-hematologic AEs. Dose reductions based on ANC and platelet counts are applicable.
<b>3</b>	Reduce by one dose level (except alopecia, nausea and vomiting).
<b>4</b>	Stop (except alopecia, nausea and vomiting). Dose modifications based on ANC and platelet counts are not applicable.

**Worst Treatment-Related Hematologic AE During the Previous Cycle**

<b>Worst AE</b>		<b>Platelets</b>		
		$\geq 100 \times 10^9/L$	$50 - 99 \times 10^9/L$	$< 50 \times 10^9/L$
<b>ANC</b>	$\geq 1.5 \times 10^9/L$	Dose unchanged	Dose unchanged	Reduce by 1 dose level
	$\geq 1 \ \& \ < 1.5 \times 10^9/L$	Dose unchanged	Dose unchanged	Reduce by 1 dose level
	$< 1 \times 10^9/L$	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, 21 and 28 ( $\pm 48$  hours) after the first daily dose of each adjuvant treatment cycle.

Hematologic AE on Day 1 of Each Cycle (within the prior 72 hours before Day 1)	
AE	Delay
ANC < 1.5 x 10 <sup>9</sup> /L and/or Platelet count < 100 x 10 <sup>9</sup> /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-Hematologic AE (except for alopecia, nausea and vomiting) On the day 1 of Each Cycle (within the prior 72 hours)	
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 AE then no escalation is possible.

#### **7.6 Criteria for Discontinuation of Protocol Treatment**

- Progression of disease;
- Unacceptable adverse event 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 protocol treatment of temozolomide or irinotecan of > 4 weeks or bevacizumab delay of > 8 weeks.
- 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;

Patients discontinuing treatment should continue to be followed for study endpoints.

#### **7.7 Modality Review**

The Medical Oncology Co-Chair, Mark R. 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/Acceptable Variation, Not Per Protocol, and Not Evaluable**. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

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

#### **7.8 Adverse Events Reporting Guidelines (1/22/09)**

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, (MedDRA, version 9.0) for grading of all adverse events. A copy of the CTCAE v3.0 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 v3.0.

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](https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup)).

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

#### 7.8.1 Adverse Events (AEs) Definitions

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

The following guidelines for reporting adverse events (AEs) apply to **all** NCI/RTOG research protocols. AEs, as defined above, experienced by patients accrued to this protocol should be reported on the AE section of the appropriate case report form (see Section 12.1). **Note: AEs indicated in the AdEERS Expedited Reporting Requirements in text and/or table in Section 7.X 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.**

#### 7.8.2 Serious Adverse Events (SAEs) All SAEs that fit any one of the criteria in the SAE definition below must be reported via AdEERS. Contact the AdEERS Help Desk if assistance is required.

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

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

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

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

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

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

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

**All supporting source documentation indicated as being provided in the Additional Information Section of the AdEERS Report must be properly labeled with the study/case numbers and the date of the event and must be faxed to 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.

7.8.3

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

7.8.4

Adverse event reporting for magnetic resonance imaging protocol

For information regarding adverse event reporting for the imaging component of the protocol please refer to Appendix VII-ACRIN Advanced Imaging Adverse Event Reporting Instructions.

## 7.9 AdEERS Expedited Reporting Requirements (1/22/09)

CTEP defines expedited AE reporting requirements for phase 2 and 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).

### 7.9.1 Phase 2 Trials Utilizing an Agent Under a CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days<sup>1</sup> of the Last Dose of the Investigational Agent [Bevacizumab] in this Study ([Arms 1 and 2])

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5 <sup>2</sup>	Grades 4 & 5 <sup>2</sup>
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	without Hospitalization	Expected with Hospitalization	without Hospitalization	Unex-pected	Expected
<b>Unrelated Unlikely</b>	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
<b>Possible Probable Definite</b>	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
<p><sup>1</sup> Adverse events with attribution of possible, probable, or definite that occur <b>greater</b> 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:</p> <ul style="list-style-type: none"> <li>Grade 4 and grade 5 unexpected events</li> </ul> <p>AdEERS 10 calendar day report:</p> <ul style="list-style-type: none"> <li>Grade 3 unexpected events with hospitalization or prolongation of hospitalization</li> <li>Grade 5 expected events</li> </ul> <p><sup>2</sup> 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.</p> <p>Please see exceptions below under section entitled "Additional Instructions or Exceptions."</p> <p style="text-align: right;">March 2005</p>									

**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.

## 7.10 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](mailto: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: Antiepileptic medications should be used as indicated. However, only patients taking non-hepatic enzyme inducing antiepileptic drugs (non-EIAEDs) or no antiepileptic drugs are eligible to enroll on this trial. Patients must not be taking EIAEDs for at least 2 weeks prior to registration. See Appendix IV for a list of EIAEDs and non-EIAEDs.

During therapy, patients who were previously on a non-EIAED and need to change anticonvulsants should be started on another non-EIAED if at all possible. No delays in treatment would be required.

If patients who were previously on no anticonvulsants require initiation of an anticonvulsant, a non-EIAED should be used if at all possible.

If a patient is started on an EIAED while on the study and the patient has been randomized to the irinotecan containing arm, he/she should immediately be started on another non-EIAED and the EIAED should be tapered and discontinued as quickly as possible. The patient may continue the current irinotecan dose while a non-EIAED is re-started because an EIAED will increase the clearance of irinotecan, reducing rather than increasing any potential anti-tumor effect, and therefore any efficacy bias introduced would be negative rather than positive. The dates that the patient took an EIAED should be noted.

For those patients randomized to the temozolomide-containing arm, requirement for an EIAED will not require conversion to a non-EIAED, although when possible, treatment with a non-EIAED is strongly encouraged.

Patients who were previously on a non-EIAED, enrolled to the irinotecan arm, and need to permanently change anticonvulsants but who cannot change to another non-EIAED will be taken off study.

- 9.1.2** Analgesics: As needed.

- 9.1.3** Hematopoietic Growth factors: Permitted for grade 4 neutropenia or neutropenia with fever and should follow American Society of Clinical Oncology guidelines for their use.<sup>33</sup> Prophylactic use of growth factors is not allowed, nor can they be used to improve blood counts to allow initiation of treatment.

- 9.1.4** Nutritional Supplementation: Permitted.

- 9.1.5** Antacids: Permitted.

- 9.1.6** Calcium Supplements: Calcium supplements (e.g., calcium carbonate, 500 mg PO three times daily) may be required to maintain serum calcium levels above the lower limit of normal during chemotherapy treatment. Vitamin D supplements (e.g., ergocalciferol, 400 IU PO daily) may be appropriate for persistent hypocalcemia.

- 9.1.7** Antiemetics/Antidiarrheals: The nausea, vomiting, and diarrhea that may occur with irinotecan or temozolomide administration can generally be managed through the use of appropriate supportive measures [antiemetics (e.g., 5-HT<sub>3</sub> antagonists, benzodiazepines, prochlorperazine) and antidiarrheal medications (e.g., loperamide)]. Specific guidelines for the use of loperamide for the subacute (days after administration) form of irinotecan-induced diarrhea are provided below:

- Patients should not be given drugs with laxative properties.
- Loperamide should be started at the earliest sign of: (1) a loose stool, or (2) the occurrence of 1-2 more bowel movements than usual in 1 day, or (3) a significant

increase in stool volume or liquidity. Loperamide should be taken in the following manner:

- 4 mg at the onset of diarrhea and then 2 mg by mouth every 2 hours, around the clock until the patient is diarrhea free for at least 12 hours. Patients may take loperamide every 4 hours during the night.
- Patients should increase fluid intake to help maintain fluid and electrolyte balance during episodes of diarrhea.

For patients who develop acute diarrhea or abdominal cramping, atropine at a dose of 1 mg intravenously should be given. For future treatment with irinotecan, atropine at a dose of 1 mg intravenously should be given as a premedication 15-30 minutes prior to the administration of the irinotecan.

## **9.2 Non-Permitted Supportive Therapy**

**9.2.1** Anticoagulants/Medications that Inhibit Platelet Function: Hemorrhagic events can occur with bevacizumab treatment. For this reason, patients who require anticoagulants such as warfarin or low molecular weight heparin, bevacizumab should be stopped for a minimum of 2 weeks to monitor for bleeding with the institution of the anticoagulant and for warfarin to establish a dose that results in an INR in the 2-3 range. Any subsequent hemorrhage would mandate cessation of bevacizumab. If the patient requires any surgical (including dental) procedure while on study, bevacizumab should be stopped 4 weeks before the procedure and not reinstated until 2 weeks afterward or until adequate tissue healing.

**9.2.2.** Herbal Products: Discouraged.

## **10.0 TISSUE/SPECIMEN SUBMISSION**

**NOTE: Patients must be offered the opportunity to participate in the correlative components of the study, such as tissue/specimen submission.**

- If the patient consents to participate in the tissue/specimen component of the study, the site is required to submit the patient's specimens as specified in Section 10.0 of the protocol. **Note:** Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

### **10.1 Tissue/Specimen Submission (7/18/07, 1/22/09)**

The RTOG Biospecimen Resource at the University of California San Francisco acquires and maintains high quality specimens from RTOG trials. Tissue from each block is preserved through careful block storage and processing. The RTOG encourages participants in protocol studies to consent to the banking of their tissue. The RTOG Biospecimen Resource provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions. The RTOG Biospecimen Resource also collects tissue for Central review of pathology. Central review of tissue can be for eligibility and/or analysis.

In this study, tissue will be submitted for the purpose of central review of pathology (mandatory) and tissue banking (recommended). For patients who have consented to participate in the banking component of the study, see Appendix I.

### **10.2 Specimen Collection for Central Pathology Review for Eligibility (required) (7/18/07, 1/22/09)**

**10.2.1** For patients **WHO HAVE** undergone central pathology review through enrollment on another RTOG GBM trial: Re-submission of material for central pathology review is NOT necessary.

**10.2.2** For patients **WHO HAVE NOT** undergone central pathology review through enrollment on another RTOG GBM trial: **Submit the following material directly to Dr. Aldape (See Section 10.4):**

**10.2.2.1** One H & E stained slide containing tumor.

**10.2.2.2** A Pathology Report documenting that the submitted slides contain tumor; the report must include the RTOG protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

**10.2.2.3** A Specimen Transmittal Form stating that the tissue is being submitted for central review. The form must include the RTOG protocol number and the patient's case number. If a patient has

been enrolled on a previous RTOG GBM trial, please include the previous study and case number on the transmittal form.

**10.2.2.4** A Central Pathology Review Form

Once Dr. Aldape has completed central pathology review, he will return the slide to the RTOG Biospecimen Resource, where it will be retained for patients who consent to the banking component of the study (See Section 10.3) or returned to the institution that submitted it for non-consenting patients.

**10.3** **Specimen Collection for Tissue Banking (recommended but not required) (7/18/07, 1/22/09)**  
**Submit the following material directly to Dr. Aldape (See Section 10.4), who will forward it to the RTOG Biospecimen Resource:**

**10.3.1** A paraffin-embedded tissue block of the tumor or a 2-mm diameter core of tissue, punched from the tissue block containing the tumor with a skin punch and submitted in a plastic tube labeled with the surgical pathology number. NOTE: A kit with the punch, tube, and instructions can be obtained free of charge from the Biospecimen Resource. Block or core must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.

**10.3.2** A Pathology Report documenting that the submitted block or core contains tumor. The report must include the RTOG protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

**10.3.3** A Specimen Transmittal Form clearly stating that tissue is being submitted for the RTOG Biospecimen Resource for banking purposes. The form must include the RTOG protocol number and patient's case number. If a patient has been enrolled on a previous RTOG GBM trial, please include the previous study and case number on the transmittal form.

**10.4** **Specimen Submission Mailing Information (7/18/07)**

Submit materials for central review and tissue banking to:

**Ken Aldape, MD**  
**U.T. M. D. Anderson Cancer Center**  
**1515 Holcombe Blvd.**  
**Houston, TX 77030**  
**(713) 792-0634; FAX (713) 792-4049**  
[kaldape@mdanderson.org](mailto:kaldape@mdanderson.org)

**10.5** **Reimbursement**

RTOG will reimburse submitting institutions \$200 per case for a block or core of material. After confirmation from the RTOG Biospecimen Resource that appropriate materials have been received, RTOG Administration will prepare the proper paperwork and send a check to the institution. Pathology payment cycles are run twice a year in January and July and will appear on the institution's summary report with the institution's regular case reimbursement.

**10.6** **Confidentiality/Storage (1/22/09)**

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

**10.6.1** Upon receipt, the specimen is labeled with the RTOG protocol number and the patient's case number only. The RTOG 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.

**10.6.2** Specimens for tissue banking will be stored for an indefinite period of time. Specimens for central review will be retained until the study is terminated. If at any time the patient withdraws consent to store and use specimens for banking, the material will be returned to the institution that submitted it.

**11.0** **PATIENT ASSESSMENTS**

**11.1** **Study Parameters:** See Appendix II.

**11.2** **Measurement of Effect (3/1/07, 7/18/07,12/11/07)**

**11.2.1** *Antitumor Effect – Solid Tumors*

The primary endpoint of this study is 6-month progression free-survival. Therefore, measurable disease is not required for study entry. However, objective responses will be measured.

For the purposes of this study, patients should be re-evaluated for response every 8 weeks.

#### 11.2.1.1 Definitions

- Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with either bevacizumab and irinotecan or bevacizumab and temozolomide.
- Evaluable for 6-month progression-free survival: All patients will be evaluable for 6mPFS except those that are removed from the study before the end of cycle 1 for reasons other than clinical progression (such as toxicity). Patients who suffer clinical progression without radiographic confirmation of progression will be considered to have progressive disease in determination of 6mPFS.
- Evaluable for objective response (CR or PR) rate: Only those patients who have measurable disease present at baseline will be considered evaluable for response except those who are removed from the study before the end of cycle 1 for reasons other than clinical progression (such as toxicity). These patients will have their response classified according to the definitions stated below. Patients with measurable disease at study entry who suffer clinical progression without radiographic confirmation of progression will be considered to have progressive disease in determination of objective response rate.

#### 11.2.1.2 Disease Parameters and Response Criteria

Response and progression will be evaluated in this study using standard criteria for patients with malignant gliomas.<sup>34</sup> The major difference from RECIST<sup>35</sup> and other criteria for measuring response in solid tumors is the requirement that patients be on a stable or decreasing dose of corticosteroids when evaluating for response because of the potentially confounding impact of corticosteroids on contrast enhancement during brain tumor imaging. The tumor size will be measured in millimeters and is the largest cross-sectional area using perpendicular measurements of contrast enhancing abnormality.

- Complete response (CR): Complete disappearance of all enhancing tumor on consecutive MRI scans at least 1 month apart, off corticosteroids, and neurologically stable or improved.
- Partial response (PR):  $\geq 50\%$  decrease in size of enhancing tumor on consecutive MRI scans at least 1 month apart, corticosteroids stable or reduced, and neurologically stable or improved.
- Stable disease (SD): Does not qualify for CR, PR, or PD.
- Progression:  $\geq 25\%$  increase in the size of enhancing tumor or any new tumor; or neurologically worse, and steroids stable or increased.
- Best response: The best response will be defined as the best objective status (CR, PR, SD, or PD).

#### 11.2.1.3 Duration of Response

- Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).
- Duration of stable disease (SD): SD is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

#### 11.2.1.4 Progression-Free Survival

Progression-free survival is defined as the duration of time from start of treatment to time of progression or death.

#### 11.2.2 Magnetic Resonance Imaging Protocol

All patients will undergo MRI that conforms to the protocol described on the ACRIN website at [http://www.acrin.org/6677\\_protocol.aspx](http://www.acrin.org/6677_protocol.aspx). These scans include at each visit a pre- and post-gadolinium T1-weighted sequence to assess areas of breakdown of the blood-brain barrier. Each visit MRI will also include the additional standard MRI sequences: T2-weighted images, FLAIR images, diffusion-weighted (or diffusion tensor) images. 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. Standard of care MRI will occur at baseline and at every 2 cycles of treatment, but there will be no week 2 MRI. For those participating in the optional advanced MRI component of the trial, examinations will include perfusion MRI including dynamic contrast enhanced (DCE) and/or dynamic susceptibility contrast (DSC) sequences, diffusion MRI, and magnetic resonance spectroscopy. In the advanced imaging sub-study, imaging will be performed at the baseline visit, week 2, and after every 2 cycles of treatment. All patients (i.e., patients receiving either standard or advanced MRIs) will receive a final scan after the completion or termination of study treatment.

**Note:** Use of MultiHance is not permitted in the advanced MRI. It may be used in the standard MRI.

**11.2.2.1** MRI Site Imaging Quality Assurance Review

Information regarding MRI imaging quality assurance review process can be found at [http://www.acrin.org/6677\\_protocol.aspx](http://www.acrin.org/6677_protocol.aspx) and is also available in Appendix VI of the Protocol Specific Application (PSA). MRI exam sequences, both standard and advanced, will be collected and archived at ACRIN Headquarters for a post-trial centralized reader study.

**11.2.3** Central Magnetic Resonance Imaging QA and Assessment

Images will be assessed locally for progression. Images will also be transmitted electronically to ACRIN Headquarters (Refer to Section 2 in Appendix VI for image submission instructions). This will allow early quality assurance (adherence to protocol, adequacy of image quality). It will also facilitate later central review of all images done in a manner to minimize bias.

**11.2.4** Advanced Magnetic Resonance Imaging Assessment–Optional Advanced Imaging Sub-Study

Sites may have the option of participating in certain advanced imaging studies including the diffusion MRI, perfusion MRI, and MRS studies as mentioned in Section 11.2.2 and in Appendices V and VI.



## **12.0 DATA COLLECTION**

### **12.1 Summary of Data Submission to RTOG**

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.

<b><u>Item</u></b>	<b><u>Due</u></b>
Demographic Form (A5)	Within 4 weeks of study entry
Initial Evaluation Form (I1)	
Pathology Report (P1)	
Slides/Blocks (P2)	
Specimen Transmittal Form (ST)	
Central Pathology Review Form (P4)	
Follow-Up Form (F1)	Every 4 weeks while the patient is receiving treatment; every 8 weeks after treatment has been discontinued
Adverse Event Form (AE)	

### **12.2 Summary of Data Submission to ACRIN (MRI Data) (3/1/07, 7/18/07,12/11/07)**

Data should be submitted by mail or fax to:

**ACRIN Headquarters\***  
**RTOG/ ACRIN Protocol 0625/6677**  
**1818 Market Street, Suite 1600**  
**Philadelphia, PA 19103**  
**Attn: ACRIN Imaging Specialist**  
**FAX: 215-923-1737**

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

<b><u>Item</u></b>	<b><u>Due</u></b>
MRI Assessment ('M' forms) <sup>1*</sup>	Within 2 weeks of MRI scan
Advanced MRI Assessment ('V' forms) <sup>2*</sup>	Within 2 weeks of advanced MRI scans
MR Reports ('R' forms)	Within 2 weeks of standard or advanced MRI scan
MR Images ('N' forms)	Within 2 weeks of standard or advanced MRI scan

<sup>1</sup> To be completed by all sites with the MRI assessment.

<sup>2</sup> To be completed by sites participating in the advanced MRI component of the trial.

Please see Appendix VI for instructions for image submission. Instructions for the 0625/6677 image submission can be found on both RTOG and ACRIN websites, [www.rtog.org](http://www.rtog.org) and [www.acrin.org](http://www.acrin.org).

## **13.0 STATISTICAL CONSIDERATIONS**

### **13.1 Study Endpoints (7/18/07)**

#### **13.1.1 Primary**

**13.1.1.1** To estimate the 6-month progression-free survival (bevacizumab and irinotecan arm)

**13.1.1.2** To estimate the rate of treatment adverse events (bevacizumab and temozolomide arm)

#### **13.1.2 Secondary**

**13.1.2.1** To estimate the 6-month progression-free survival (bevacizumab and temozolomide arm)

**13.1.2.2** To estimate the rates of objective response (complete response, partial response, stable disease, progression) in both arms

**13.1.2.3** To estimate the rate of treatment adverse events (bevacizumab and irinotecan arm)

#### **13.1.3 Central MRI Review**

**13.1.3.1** To assess the agreement between local interpretation and central interpretation of the standard MRI on the 6-month progression-free survival.

**13.1.3.2** To estimate the accuracy of local interpretation on the 6-month progression-free survival using central review as the reference standard.

#### **13.1.4 Perfusion MRI and MRS Imaging Endpoints**

**13.1.4.1** To estimate the correlations between degree of cerebral blood volume (CBV), lactate to NAA (Lac/NAA) ratio, and patient response between baseline and 2 weeks following initiation of chemotherapy treatment with bevacizumab.

**13.1.4.2** To estimate the predictive values of CBV and Lac/NAA at baseline, 2 weeks following initiation of protocol treatment, and after every 2 cycles of treatment in assessing the 6-month progression-free survival.

### **13.2 Sample Size (7/18/07, 1/22/09)**

#### **13.2.1 Sample Size Derivation**

**13.2.1.1** Bevacizumab and Irinotecan Arm: The hypothesized baseline rate of 6-month progression-free survival comes from a database of 375 patients with recurrent high-grade glioma (150 anaplastic astrocytoma and 225 glioblastoma) enrolled in 8 previous phase II studies (in which none of the treatments were considered particularly effective). The proportion of glioblastoma patients remaining alive and free from progression at 6 months was 15% (95% confidence interval for ranged from 10% to 19%). We will set  $p_0$  to 20% as a conservative estimate of 6-month progression-free survival assuming the treatment combination is ineffective. We will set  $p_1$  to 35% (looking for an improvement of 15%). Error rates will be set at 10% for the false positive rate (alpha) and 10% for the false negative rate (beta). Based on the above design parameters, we will accrue a total of **60 patients** (assuming a 5% ineligible rate) to have the required 57 analyzable patients.

**13.2.1.2** Bevacizumab and Temozolomide Arm: As indicated in Section 1.2.4, studies using bevacizumab in recurrent gliomas have demonstrated an approximately 30% rate of treatment discontinuation due to treatment-related medical complications. We will set  $p_0$  as a 35% discontinuation rate of bevacizumab and temozolomide and  $p_1$  as 15%. Setting error rates at 0.1 for both alpha and beta, we will accrue **31 patients** (assuming 5% ineligible rate) to have the required 29 analyzable patients to assess the rate of discontinuation due to medical complications.

**13.2.1.3** In the event that temozolomide and bevacizumab arm is judged to be tolerable per Section 13.5.2, and if the number of patients who were alive at 6 months progression free is between 7 and 10 (7/29=24.1%; 10/29=34.5%), this arm will accrue an additional 30 patients (assuming 5% ineligibility rate) to have 28 analyzable patients. In so doing, will have a two-stage design as described by Fleming<sup>36</sup> with the same parameters as defined in Section 13.2.1.1 for the bevacizumab and irinotecan arm.

### **13.3 Randomization**

**13.3.1** Randomization will take place on this study in a 2:1 ratio between the bevacizumab and irinotecan arm and the bevacizumab and temozolomide arm. Patients will be randomized in a permuted block design using the method described by Zelen.<sup>37</sup>

**13.3.2** Patients will be stratified by age (< 50 years versus ≥ 50 years) and Karnofsky performance status (70-80 versus 90-100).

## **13.4 Analysis Plan (7/18/07)**

- 13.4.1** Primary Endpoint, Bevacizumab and Irinotecan Arm: The primary endpoint calculation will be done by taking the number of patients who have survived 6 months without progression of study disease after study registration in the numerator. The denominator will consist of all patients except those who were found retrospectively to be ineligible or who were lost to follow-up after less than 6 months. The determination of treatment efficacy will be made based on the following rules:
- 13.4.1.1** If 16 or more of the cases ( $16/57=28.1\%$ ) are progression free and alive at 6 months, we will reject the null hypothesis that the rate is no better than 20%.
- 13.4.1.2** If 15 or fewer of the cases ( $15/57=26.3\%$ ) are progression free and alive at 6 months, we will reject the alternative hypothesis that the rate is at least 35%.
- 13.4.2** Primary Endpoint, Bevacizumab and Temozolomide Arm: The primary endpoint calculation will be done by taking the number of patients who did not stop bevacizumab and temozolomide treatment due to medical complications in the numerator. The denominator will consist of all patients except those who were found retrospectively to be ineligible or who did not begin treatment. The determination of treatment efficacy will be made based on the following rules:
- 13.4.2.1** If 6 or fewer of the cases ( $6/29=20.6\%$ ) stop treatment due to medical conditions, we will reject the null hypothesis that the rate is at least 35%.
- 13.4.2.2** If 7 or more of the cases ( $7/29=24.1\%$ ) stop treatment due to medical conditions, we will reject the alternative hypothesis that the rate no more than 15%.
- 13.4.3** Secondary Endpoints
- 13.4.3.1** If the second group of patients have been entered onto the bevacizumab and temozolomide arm, the following rules are set for judging treatment efficacy:
- 13.4.3.1.1** If 15 or fewer of the cases ( $15/57=26.3\%$ ) are progression free and alive at 6 months, we will reject the alternative hypothesis that the rate is at least 35%.
- 13.4.3.1.2** If 16 or more of the cases ( $16/57=28.1\%$ ) are progression free and alive at 6 months, we will reject the null hypothesis that the rate is no better than 20%.
- 13.4.3.2** The crude incidence rates of patient response will be calculated for each arm of the study.
- 13.4.3.3** The crude incidence rates of severity of adverse events will be calculated for each arm of the study.
- 13.4.4** Statistical Methods for Central MRI Review
- 13.4.4.1** The agreement between local interpretation and central interpretation of the standard MRI on the patients' 6-month progression-free status will be assessed using a McNemar's test. The test will detect systematic inconsistency between local interpretation and central interpretation of the patients' 6-month progression-free status.
- 13.4.4.2** The sensitivity and specificity of the local interpretation of the 6-month progression-free survival will be estimated using the central review as the reference standard. In particular, for patients progressed at 6 months according to central review, the sensitivity of the local interpretation will be estimated and the exact confidence interval will be calculated. The specificity and the associated exact confidence interval of the local interpretation will be calculated in a similar way.
- 13.4.5** Statistical Methods for Perfusion MRI and MRS Imaging Analysis  
The analysis for perfusion MRI and MRS data will be exploratory in nature, aiming to assess the performance of perfusion MRI and MRS as a predictor of response to therapy and 6-month progression-free survival. As outlined in the protocol, MRI scans will be performed at baseline (T0), 2 weeks following initiation of protocol treatment (T1) and every 2 cycles (8 weeks) of chemotherapy with bevacizumab (T2) (See Appendix II). At each perfusion MRI scan, degree of cerebral blood volume (CBV) along with other perfusion parameters (such as peak height) will be derived. Similarly, at each MRS scan, lactate, NAA, creatine, choline, and other metabolites will be measured. Imaging parameters will be average for each ROI identified at MRI and then aggregated to the patient level. Only data at the patient level will be used to assess the sub-aims here, but if we have enough data from ROI level, further analysis utilizing different levels of data will be explored. Central reading data will be used in analyzing the two sub-aims listed, but the predictive values of primary interpretations at the sites will be also explored.

- 13.4.5.1** The changes in imaging parameters (CBV, Lac/NAA etc) from T0 will be assessed at T1 and T2. The correlations between imaging parameters and patient response will then be estimated based on the estimated changes. Cox proportional hazard models with time-varying imaging covariates (such as CBV, Lac/NAA, choline) will be fitted to identify imaging parameters useful in monitoring early disease progression. The patient response at T1 will be used as the response variable for the Cox proportional hazard models. The model will later be expended to include data from all T0, T1, and T2 and using patient response at T2 as the response variable.
- 13.4.5.2** Sensitivity, specificity and area under the ROC curve will be calculated for perfusion MRI and MRS separately using the 6-month progression status as the reference standard for the study overall and for each arm of study. For 6-month progression-free survival (binary outcome), a logistic regression will be fitted using CBV as the key independent response. Both CBV at T1 and the changes in CBV between T0 and T1 will be examined as predictors. Similarly, a separate logistic regression model will be fitted using MRS parameters (such as Lac/NAA and choline to creatine level). Time-dependent ROC curves analysis will be employed to assess the accuracy of the imaging parameters at the same time accounting for the presence of censored observations.<sup>38</sup>
- 13.4.6** Interim Analysis to Monitor the Study Progress: Interim reports 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; compliance rate of treatment delivery with the distributions of important prognostic baseline variables; and the frequencies and severity of treatment-related adverse events. The interim reports will not contain the results from of the efficacy endpoints (overall survival, progression-free survival, treatment response).
- 13.4.7** 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 by electronic means. Reports are due January 31, April 30, July 31, and October 31.

### **13.5 Patient Accrual (1/22/09)**

This trial is expected to accrue at least 15 cases per month by the third month that the study is open. At that rate, the study sample size should be reached in less than 9 months.

The study was closed temporarily on November 16, 2007, while data were evaluated for toxicity and response to determine whether there was sufficient evidence to proceed to the second stage accrual for the bevacizumab plus temozolomide arm. Among the 41 registered patients on this arm, 39 were eligible. Among the first 29 analyzable patients on this arm, 6 experienced treatment discontinuation due to treatment-related medical complications (4 additional patients experienced discontinuations, but they were not all related to treatment), and 11 experienced 6-month progression-free survival. The study design for this arm requires that if 6 or fewer patients experience drug discontinuation due to treatment-related complication and 7-10 patients experience 6-month progression-free survival among the first 29 analyzable patients, the bevacizumab/temozolomide arm will accrue an additional 30 patients (28 analyzable patients) to finish accrual of a total 57 eligible patients on that arm. The toxicity and efficacy data show the number of discontinuations (6) is at the borderline of the toxicity rule and the number of patients experiencing 6-month progression-free survival (11) exceeds the upper bound of the efficacy rule for continuing stage II accrual. In addition, there were 6 patients experiencing treatment discontinuation due to treatment-related complications among the 57 eligible patients on the bevacizumab/irinotecan arm and the discontinuation rate is 10.5% (6/57=10.5%), while the discontinuation rate on the bevacizumab/temozolomide arm is 20.7% (6/29=20.7%). More robust efficacy and safety data for the bevacizumab/temozolomide arm will be important in the current clinical trial setting. Therefore, the bevacizumab/temozolomide arm will accrue an additional 18 eligible patients (an additional 19 patients adjusting for a 5% ineligibility rate) to finish the total 57 eligible patients given that 39 eligible patients have already entered.

### **13.6 Inclusion of Minorities**

In conformance with the national Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we address this issue here, as we will also analyze treatment differences by gender, race, and ethnicity. The following table lists the

projected accrual for each racial and ethnic group based upon previous RTOG glioblastoma trials.

**Projected Distribution of Gender and Minorities**

	<b>Gender</b>		
<b>Ethnic Category</b>	<b>Females</b>	<b>Males</b>	<b>Total</b>
Hispanic or Latino	1	4	5
Not Hispanic or Latino	45	71	116
<b>Ethnic Category: Total of all subjects</b>	46	75	<b>121</b>
	<b>Gender</b>		
<b>Racial Category</b>	<b>Females</b>	<b>Males</b>	<b>Total</b>
American Indian or Alaskan Native	0	0	0
Asian	1	1	2
Black or African American	4	3	7
Native Hawaiian or other Pacific Islander	1	0	1
White	40	71	111
<b>Racial Category: Total of all subjects</b>	46	75	<b>121</b>

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**APPENDIX I (7/18/07, 8/9/07, 1/22/09, 2/10/09)**

**Informed Consent Template for Cancer Treatment Trials**  
**(English Language)**

**RTOG 0625**

**A Randomized Phase II Trial of Bevacizumab With Irinotecan or Bevacizumab With Temozolomide in Recurrent 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. Please take your time to make your decision about taking part. You may discuss 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 malignant brain tumor called glioblastoma that is growing or progressing despite treatment with radiation therapy and temozolomide.**

**Why is this study being done? (7/18/07, 1/22/09)**

This study is being done to determine if an investigational cancer treatment called bevacizumab combined with either the chemotherapy agent irinotecan or the chemotherapy agent temozolomide is effective in treating glioblastoma. In addition, the side effects and safety of these treatment combinations will be determined.

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.

**How many people will take part in the study?**

About 121 people will take part in this study.

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

Before you begin the study a full medical history and physical examination will be performed.

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or 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 will be taken to determine
  - Blood counts
  - Kidney function
  - Liver function
  - Electrolyte levels
- Pregnancy (if you are a woman of child-bearing potential)
- Electrocardiogram
- Urine evaluation for protein
- Magnetic resonance imaging

### **During the study ... (7/18/07, 1/22/09)**

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 tests and procedures. They are part of regular cancer care.

- Magnetic resonance imaging will be done after every 2 cycles of treatment (8 weeks)

You will need these tests and procedures that are part of regular cancer care. They are being done more often because you are in this study.

- Blood will be taken to determine
  - Blood counts
  - Kidney function
  - Liver function
  - Electrolyte levels

You will need this test to see how the study treatment is affecting your body.

- Urine evaluation for protein

If you have not already participated in a Radiation Therapy Oncology Group glioblastoma study that required this, your study doctor will need to send some of the 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.

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. Neither you nor your study doctor can choose the group you will be in.

If you are in group 1 (often called "Arm 1") you will receive the combination of bevacizumab and temozolomide. The bevacizumab is given by vein (intravenously) every two weeks. For the first treatment, you will receive the bevacizumab for a period of 90 minutes. If you don't experience fever or chills while you receive it, you will be able to receive the next bevacizumab treatments over a 60- or 30-minute period. This treatment arm contains temozolomide, a chemotherapy drug that was used for the initial treatment of your brain tumor. However, this drug is being tested in combination with bevacizumab to see if the treatment combination will generate tumor responses even when the tumor has previously not responded or stopped responding to the temozolomide. The temozolomide is given by mouth (orally) daily for 21 days, then 7 days without treatment. Four weeks is considered one treatment cycle.

If you are in group 1, you may also be asked to complete a medication diary while you are receiving temozolomide; this will help document when you take your medication and any side effects you experience.

If you are in group 2 (often called "Arm 2") you will receive the combination of bevacizumab and irinotecan. Both treatments are given by vein (intravenously) once every 2 weeks. For the first treatment, you will receive the bevacizumab for a period of 90 minutes. If you don't experience fever or chills while you receive it, you will be able to receive the next bevacizumab treatments over a 60- or 30-minute period. You will receive the irinotecan over a 90-minute period. Every 2 treatments (4 weeks) equals one cycle of treatment.

Initially, twice as many people will go on Arm 2 versus Arm 1. The main goal (primary objective) of Arm 1 is to determine the side effects of the combination of bevacizumab and temozolomide. The main goal (primary objective) of Arm 2 is to test whether the combination of bevacizumab and irinotecan is effective at treating glioblastoma. More patients are needed to determine the main goal of Arm 2 than are needed to determine the main goal of Arm 1. If the combination of bevacizumab plus temozolomide in Arm 1 has tolerable side effects, then more patients will be added to Arm 1 so that both arms will have an equal number of patients.

During each treatment, blood tests will be performed every 2 weeks to monitor blood counts, kidney function, liver function and electrolyte levels. Every 2 weeks, a urine test will be performed to determine if there is protein in the urine. Vital signs (blood pressure, pulse, temperature and respiratory rate) will be performed before each of the infusions of the bevacizumab.

Every 8 weeks, a brain MRI will be performed to evaluate the effect of treatment on your tumor. This MRI will include the administration of contrast ("dye") by vein to help the study doctors see the tumor.

### **Central Review**

If you agree to participate in the study, your routine MRI scans will be submitted for review at a central location to determine the changes in blood flow caused by the treatment. The reviews and test results will not be sent to you or your doctor and will not affect what therapy you receive on this trial. These central reviews are for research purposes only.

### **How long will I be in the study?**

You can take the bevacizumab and irinotecan or the bevacizumab and temozolomide for up to 2 years, as long as your tumor doesn't grow and you don't have side effects that prevent you from continuing the treatment. After you are finished taking the treatments, the study doctor will ask you to visit the office for follow-up exams for at least 1 month to ensure that any side effects of the treatment have resolved. In addition, after completing treatment, we would like to keep track of your medical condition for the rest of your life.

## **Can I stop being in the study?**

Yes. You can decide to stop at any time. Tell the 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 the study doctor if you are thinking about stopping so he or she can evaluate any risks from the treatment. 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.

The 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.

## **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, researchers 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 chemotherapy treatment. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

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 bevacizumab include those that are (7/18/07, 1/22/09):**

### **Very Likely**

- Nose bleeds
- High blood pressure - In most patients, blood pressure can be controlled with routine medications. Rarely, uncontrolled hypertension may lead to damage to the brain and other vital organ functions.
- Fatigue
- Rash
- Headache
- Soreness in mouth or throat

### **Less Likely**

- Dizziness
- Decrease in blood counts, which can lead to a risk of infection
- Anemia
- Low blood pressure
- Loss of appetite
- Weight loss
- Itching, hives, welts of the skin
- Ulcers (open sores of the skin or mucous membrane that shed inflamed dead tissue)
- Nausea and/or vomiting
- Inflammation of the colon, which can result in stomach cramps and/or diarrhea
- Obstruction of the bowel

- Mild to moderate bleeding in the tumor, stomach, intestines, vagina, or other parts of the body
- Blood clots in the veins: blood clots can occur in the veins of the leg and the lungs or other organs. These events can be life-threatening.
- Clots in the arteries, including stroke or heart attack. These conditions can be life-threatening or fatal. When several studies were looked at together, problems due to clots in arteries were increased about two-fold (up to 4-5%) in patients receiving chemotherapy plus bevacizumab compared to chemotherapy alone (about 2%). Patients who were elderly and with past history of clots in the arteries are at a greater risk for these problems.
- Leakage of protein in the urine, which can rarely lead to damage to the kidney
- Reactions associated with infusion of the bevacizumab: rash, chills, fever, rigor
- Watery eyes, nasal stuffiness
- Shortness of breath, cough, wheezing
- Pain in the stomach, chest, joints, or muscles and/or pain at the tumor site
- Constipation
- Hoarseness and/or change in or loss of voice

### **Rare But Serious**

- Serious or fatal bleeding from the tumor, brain, gut, vagina, or the lungs
- Fistulas (abnormal openings or passages between internal organs or from an internal organ to the surface of the body) in the lung and/or intestinal tract
- Nasal septum perforation: a hole in the wall that divides the inside of the nose, which could result in crusting in the nose, bleeding and/or discharge from the nose, and/or whistling on intake of air and which would require surgery to repair
- Bowel perforation and bowel anastomotic dehiscence. Bowel perforation occurs when an opening exists in the bowel wall allowing bowel contents to spill into the abdomen. Bowel anastomotic dehiscence is a breakdown in the surgical connection between two pieces of bowel. These events are rare but can lead to serious infection and require surgery to repair.
- Heart problems (including irregular heartbeats, fluid collections surrounding the heart, heart attack or heart failure)
  - Worsening of fluid within the tissues of the lung
  - Delayed or poor wound healing after surgery
  - Acute and/or severe allergic reactions that result in difficulty breathing or drop in blood pressure, and possible death
  - Reversible posterior leukoencephalopathy syndrome (RPLS) (<1%): RPLS is a medical condition related to leakiness of blood vessels in the brain and can cause confusion, blindness or vision changes, seizure and other symptoms, as well as changes in brain scans. This condition is usually reversible, but in rare cases, it is potentially life threatening and may have long-term effect on the brain function.
    - Reversible changes in the liver functions
    - Kidney failure
    - Sudden death of uncertain relationship to bevacizumab

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

#### **Likely**

- Nausea and/or vomiting
- Decreased appetite

- Headache
- Constipation
- Drowsiness/fatigue
- Inability to sleep

**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
- Itchiness
- Increased need to urinate
- Weakness
- Back pain
- Dizziness
- Tingling/burning in your arms and legs
- Anxiety
- Depression
- Stomach pain

**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 irinotecan include those that are:**

**Likely**

- 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 especially 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 severe 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 doctor. Should you become weak, lightheaded, or feel faint, call your doctor immediately. Don't take loperamide tablets unless you have loose or frequent stools or diarrhea.

#### **Less Likely**

- 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.

There have been deaths reported from these serious side effects. Although the risk of death is low, you should tell your doctor immediately if you experience any of these side effects.

**Reproductive risks:** Because the drugs in this study can possibly affect an unborn baby and infants, you should not become pregnant or father a baby or breast feed while you are 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, 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.

A pregnancy test is required for women with child-bearing potential before entry on the study is permitted.

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. However, it is still possible for you to become pregnant while you are taking temozolomide, so you must use appropriate birth control measures.

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 these treatment regimens will be more useful against cancer 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 these combinations of drugs as a treatment for cancer. 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 cancer without being in a study
- Taking part in another study
- Getting no treatment

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 are housed at RTOG Headquarters in a password-protected database. 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.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The Radiation Therapy Oncology Group (RTOG)

- American College of Radiology Imaging Network (ACRIN)/Center for Statistical Sciences
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- A qualified representative from a pharmaceutical collaborator

### **What are the costs of taking part in this study? (8/9/07)**

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.

Bevacizumab and irinotecan will be provided free of charge while you are participating in this study. However, if you should need to take bevacizumab and irinotecan much longer than is usual, it is possible that the free supply of these drugs given to the NCI could run out. If this happens, your study doctor will discuss with you how to obtain additional drugs from the manufacturer and you may be asked to pay for it.

If you are randomized to Arm 1, you will receive temozolomide through a commercial prescription.

Although the bevacizumab and irinotecan will be provided at no cost to you, you or your health plan may need to pay for costs of the supplies and personnel who give you the drug.

You will not be paid 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, \_\_\_\_\_ [investigator's name(s)], if you feel that you have been injured because of taking part in this study. You can tell the 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 the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

**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). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]**

**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 the following studies. Below, please mark your choice.

### *Consent Form for Use of Tissue for Research*

#### **About Using Tissue for Research (2/10/09)**

*You have had a biopsy or surgery that resulted in the diagnosis of a brain tumor. 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 cancer and other diseases. 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](http://www.rtog.org/tissue%20for%20research_patient.pdf)*

*The research that may be done with your tissue is not designed specifically to help you. It might help people who have cancer and other diseases in the future.*

*Reports about research done with your tissue will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.*

#### **Things to Think About**

*The choice to let us keep the left over tissue for future research is up to you. No matter what you decide to do, it will not affect your care or your participation in the main part of the study.*

*If you decide now that your tissue 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. Then any tissue that remains will no longer be used for research and 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 doctor/institution 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 is used for genetic research (about diseases that are passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records.*

*Your tissue will be used only for research and will not be sold. The research done with your tissue may help to develop new products in the future.*

## **Benefits**

*The benefits of research using tissue include learning more about what causes cancer 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 records. 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 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 or your participation in the main part of the study.*

*1. My tissue may be kept for use in research to learn about, prevent, or treat cancer.*

Yes                      No

*2. My tissue 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 Participation in Advanced MRI Study (7/18/07, 12/11/07)*

[LIMITED INSTITUTIONS: INSTITUTIONS QUALIFIED FOR ADVANCED MRI SUB-STUDY]

You will undergo MRI examinations as part of your regular treatment before and during the treatment to allow your doctors to determine the changes in blood flow caused by the treatment. You are being asked to participate in an additional advanced MRI 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 treatment. You will be scanned at the baseline visit, week 2, and every two cycles of chemotherapy. You will receive another MRI scan when you come off the study. Each examination takes between 45 and 60 minutes to complete. 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.

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.

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 “triple dose,” which is injected rapidly. Some but not all MRI contrast agents have been FDA-approved for triple dose, but triple 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 is a condition associated with the gadolinium contrast agent when there is severe kidney disease. Symptoms include tightening or scarring of the skin and organ failure. In some cases, it can be deadly. NSF has not been seen in patients with normal working kidneys or mild problems in kidney function. Prior to study entry, 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.

The results of the advanced and the standard of care 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. You can participate in the treatment part of the study without participating in the additional imaging study. You may also participate in the other optional research studies performed on your tumor even if you decide not to participate in the advanced imaging study.

If you decide to participate in the additional advance imaging 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). Copies of your MRI 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.

If I qualify, I agree to participate in the additional advanced MRI study that is being done for research as a part of this study.	
<b>Yes</b>	<b>No</b>

**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/AboutMRI.aspx>. 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/>**

**You will get a copy of this form. If you want more information about this study, ask your study doctor.**

**Signature**

**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 (3/1/07, 7/18/07, 8/9/07,12/11/07, 1/22/09)**

**STUDY PARAMETER TABLE**

	Pre-Study	Wk 2	Wk 4	Wk 6	Wk 8	Repeat testing as listed for weeks 2-8 for each subsequent 2 cycles				Off Study
						Wk 2	Wk 4	Wk 6	Wk 8	
<b>Cycle</b>		<b>1</b>		<b>2</b>		<b>Cycles 3, 5, 7 etc</b>		<b>Cycles 4, 6, 8 etc</b>		
Medical history	X									
Concurrent meds	X	X-----X								
Physical exam	X		X		X					X
Vital signs	X	X	X	X	X	X	X	X	X	X
Height	X									
Weight	X		X		X				X	X
Performance status	X		X		X				X	X
CBC w/diff, plts	X	X	X	X	X	X	X	X	X	X
Serum chemistry <sup>a</sup>	X	X	X	X	X	X	X	X	X	X
PT-INR	X		X <sup>b</sup>		X <sup>b</sup>		X <sup>b</sup>		X <sup>b</sup>	
Beta-HCG <sup>C</sup>	X									
EKG	X									
Adverse event evaluation		X-----X								X <sup>e</sup>
Urinary Protein Creatinine Ratio <sup>d</sup>	X		X		X		X		X	
Urine dipstick for protein	X	X	X	X	X	X	X	X	X	

MRI Assessments							
	Pre-Study	Wk 2	Wk 4	Wk 6	Wk 8	Repeat MRI after every 2 cycles	Off Study
Standard MRI <sup>f</sup>	X				X	X	X
Optional- Advanced MRI <sup>g</sup> (for those who are consented)	X	X			X	X	X

a: Albumin, alkaline phosphatase, total bilirubin, BUN, calcium, chloride, creatinine, glucose, lipase, potassium, total protein, SGOT[AST], SGPT[ALT], sodium.

b: For patients on systemic anticoagulation with warfarin

c: Serum or urine pregnancy test (women of childbearing potential).

d: Urine analysis for calculation of Urine Protein: Creatinine Ratio (UPC ratio) should be performed prior to each cycle or every other course of bevacizumab. If UPC ration is  $\geq 1$ , collection of 24 hour urine for measurement of urine protein level is recommended but not required. UPC ratio of spot urine is an estimation of the 24 urine protein excretion – a UPC ratio of 1 is roughly equivalent to a 24-hour urine protein of 1 gm. UPC ratio is calculated using on of the following formula:

- [urine protein]/[urine creatinine] – if both protein and creatinine are reported in mg/dL
- [(urine protein) x0.088]/[urine creatinine] – if urine creatinine is reported in mmol/L

e: Patients who have an on-going study agent-related serious adverse event upon study completion or at discontinuation from the study should be contacted by the investigator or his/her designee periodically until the event is resolved or determined to be irreversible.

f: Standard MRI will occur at baseline and at every 2 cycles (no 2-wk MRI) per standard of care until progression or discontinuation of treatment. An additional scan will be taken once the patient is off protocol treatment.

g: Patients in the advanced MRI imaging sub-study will have an advanced MR at baseline, during week 2, and after every 2 cycles. An additional scan will be taken once the patient is off protocol treatment.

**APPENDIX III (1/22/09, 2/10/09)**

**KARNOFSKY PERFORMANCE SCALE**

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



## APPENDIX IV

### EIAEDs and Non-EIAEDs

#### EIAEDs:

Carbamazepine	(Tegretol, Tegretol XR, Carbatrol)
Oxcarbazepine	(Trileptal)
Phenytoin	(Dilantin, Phenytek)
Fosphenytoin	(Cerebyx)
Phenobarbital	
Primidone	(Mysoline)

#### Non-EIAEDs:

Valproic acid	(Depakote, Depakene)
Gabapentin	(Neurontin)
Lamotrigine	(Lamictil)
Topiramate	(Topamax)
Tiagabine	(Gabatril)
Zonisamide	(Zonegran)
Levetiracetam	(Keppra)
Clonazepam	(Klonopin)
Clobazam	(Frisium)

**APPENDIX V (7/18/07,12/11/07)**

**MRI Technical Acquisition Instructions**

The current imaging parameters for this protocol are listed on the Imaging Transmittal Worksheet on the ACRIN website at [http://www.acrin.org/6677\\_protocol.aspx](http://www.acrin.org/6677_protocol.aspx).

## APPENDIX VI (3/1/07, 7/18/07,12/11/07)

### **Imaging Study Submission and Review**

Site imaging quality assurance for both the standard of care and 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. A detailed process for the imaging quality assurance review and approval is outlined in the RTOG and ACRIN websites, respectively, <http://www.rtog.org> and [http://www.acrin.org/6677\\_protocol.aspx](http://www.acrin.org/6677_protocol.aspx).

Registration criteria are outlined in Section 5.2. Eligible patients must have given written consent to participate in the advanced imaging (MRI and MRS) sub-study, and satisfy the eligibility criteria outlined in Section 3.0.

Guidelines and image submission requirements are outlined below in Section 2 of this appendix.

Images will be submitted to ACRIN via secure FTP for central review. The results of the review will not be returned to the institutions and will not effect patient participation in the therapeutic aspects of RTOG 0625 protocol, nor affect participation in other translational studies performed as a part of the study.

**NOTE:** Reimbursement for performance of the advanced imaging (MRI and MRS) sub-study (including submission of data) and for submission of the MRI images are outlined in Appendix VIII.

**NOTE:** For more detailed information, contact Jim Gimpel at [jgimpel@phila.acr.org](mailto:jgimpel@phila.acr.org) or Anthony Levering at [alevering@phila.acr.org](mailto:alevering@phila.acr.org).

#### 1. MR Image Quality Evaluations

##### 1.1 ACRIN Imaging Quality Assurance Review

##### 1.1.1 Institution MRI Scanners

- All institutions must utilize an ACRIN approved MRI Scanner prior to registering participants.

##### 1.1.2 Submission of Test Cases for Image Quality Assurance Review

- Submit for review one standard of care MRI exam to include the MRI sequences using the parameters listed on the Imaging Transmittal Worksheet available on the ACRIN website at [http://www.acrin.org/6677\\_protocol.aspx](http://www.acrin.org/6677_protocol.aspx).
- Additionally, sites that participate in the advanced imaging option will include MR spectroscopy, perfusion, and the dynamic contrast enhanced sequences done according to protocol using the parameters listed on the Imaging Transmittal Worksheet. Spectroscopy submissions must include raw data files, (e.g., P Files, .spar/.sdat files or .rda files), which can be sent via ftp. Vendor-specific instructions for locating and submitting raw MRS data can be found on the ACRIN website under Imaging Requirements are available at [http://www.acrin.org/6677\\_protocol.aspx](http://www.acrin.org/6677_protocol.aspx). **MRS raw data submissions must be named using the case#\_timepoint naming convention found in these instructions.**

##### 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 MRI images from each site.
- To facilitate accurate and timely submission of required MR imaging.

## 1.2 Imaging protocol

1.2.1 Imaging protocol can be found on the Imaging Transmittal Worksheet on the ACRIN website, [http://www.acrin.org/6677\\_protocol.aspx](http://www.acrin.org/6677_protocol.aspx), or on the RTOG website ([www.rtog.org](http://www.rtog.org)).

All Advanced MRI imaging will conform to the MRI imaging quality control standards as described on the ACRIN website, [http://www.acrin.org/6677\\_protocol.aspx](http://www.acrin.org/6677_protocol.aspx), or on the RTOG website ([www.rtog.org](http://www.rtog.org)).

## 2 MRI Image Submission Instructions

For Patients Enrolled in either the standard of care imaging or the advanced imaging (MRI and MRS)

sub-study:

2.1 Imaging exams should be submitted to the ACRIN-Image Management Center after each time-point/visit. Imaging submitted shall not include any additional imaging for which the participant has not consented at registration. A completed, signed Image Transmittal Worksheet MUST accompany all imaging exams submitted to ACRIN for each time-point. For exams submitted via the internet, 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, case number, date of exam(s), time point, and type of imaging. For further information or questions contact the Image Management Center at ACRIN at [imagearchive@phila.acr.org](mailto:imagearchive@phila.acr.org).

### 2.2 Electronic Transfer of MRI Images and Raw Spectroscopy Data:

Digitally generated image files in DICOM v3.0 and raw MRS data files can be transmitted to the ACRIN Image Management Center (IMC) via FTP directly to the image archive. Vendor-specific instructions for locating and submitting raw MRS data can be found on the ACRIN website under Imaging Requirements at [http://www.acrin.org/6677\\_protocol.aspx](http://www.acrin.org/6677_protocol.aspx).

For further assistance in utilizing the electronic image submission option or for questions regarding image transfer, contact the ACRIN Image Management Center at [imagearchive@phila.acr.org](mailto:imagearchive@phila.acr.org).

### 2.3 Removal of Confidential Participant Information

If DICOM is being used, please note that the header record on DICOM formatted image data, which often contains information identifying the participant by name, must be scrubbed before the image is transferred. This involves replacing the Participant Name tag with both the ACRIN and RTOG Institutional numbers, replacing Participant ID tag with both the ACRIN and RTOG case numbers, and putting the study number (ACRIN 6677/RTOG 0625) into the Other Participant ID tag. This can be performed using a customized software program or using a program available from ACRIN.

For further assistance in utilizing the electronic image submission option or for questions regarding image transfer, contact the ACRIN Image Management Center at [imagearchive@phila.acr.org](mailto:imagearchive@phila.acr.org).

### 2.4 CD Transfer

In the event that either DICOM capability or transfer of scrubbed image headers is not available, images may also be sent on a CD or other electronic medium for the ACRIN IMC to transfer to

the image archive. Please contact ACRIN prior to sending the media to confirm compatibility, particularly before your first case to Anthony Levering ([alevering@phila.acr.org](mailto:alevering@phila.acr.org); 215-574-3244).

## 2.5 Image Quality Control

A review of all MRI cases will be performed in order to ascertain the quality of image processing at the participating institutions. All MRI images will be sent promptly to the ACRIN image archive in Philadelphia to ensure adequate image quality control.

## APPENDIX VII (3/1/07, 7/18/07,12/11/07)

### **ACRIN Advanced Imaging Adverse Event Reporting Instructions**

#### **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 adverse event 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 adverse event.

#### **Definition of Serious Adverse Event**

Adverse events are classified as serious or non-serious. A Serious Adverse Event (**SAE**) is any adverse event 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 a serious adverse event);
- 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.

If there is any doubt whether the adverse event constitutes a serious adverse event, it should be considered and treated as serious and reported via AdEERS.

#### **Adverse Event Grading**

Grade refers to the severity (intensity) of the adverse event.

- 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**

#### **Adverse Event Attribution**

Attribution is the determination of whether an adverse event 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.

### **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.

### **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 adverse events through discussion and, as appropriate, by examination. Information on all expected and unexpected adverse events 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. adverse event log and/or progress notes of the study participant's chart, and retained at the site. These adverse events 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 MRI imaging, sites should follow standard of care practice per the local institution's policies and procedures.

### **Reporting of Adverse Events**

Prompt reporting of all adverse events is the responsibility of each investigator, clinical research associate, and nurse engaged in clinical research.

Routine reporting is defined as documentation of adverse events 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 MRI (MRI and MRS) component, immediate notification to ACRIN is also required. Routine reporting requirements also apply.

ACRIN will collect and report only those adverse events considered possibly, probably, or definitely related to the advanced imaging (MRI and MRS) 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 (MRI and MRS) sub-study and serious adverse events 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).

### **Expedited Reporting to NCI, RTOG, and/or ACRIN**

1. Investigator or investigator-designee must use expedited adverse event reporting for **deaths** (considered possibly, probably, or definitely related to the advanced imaging (MRI and MRS) sub-study) occurring during study participation and up to 30 days after the last study procedure.
2. All life-threatening/disabling unexpected adverse events (considered possibly, probably, or definitely related to the advanced imaging (MRI and MRS) sub-study) occurring during study participation and up to 30 days after the last study procedure will be reported within 24 hours, followed by a full report within five (5) calendar days of first knowledge of the event.
3. All hospitalizations (or prolongation of existing hospitalization) for adverse events with the severity (intensity) level of CTCAEv3.0 Grade 3, 4, 5 and attribution of possibly, probably, or definitely related to the advanced imaging (MRI and MRS) 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.
4. All other serious adverse events with attribution of possibly, probably, or definitely related to the advanced imaging (MRI and MRS) 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.
5. Significant new information and/or follow-up information (e.g., test results, autopsy, and discharge summary) on on-going serious adverse events should be promptly reported.

### **When to report an event in an expedited manner**

Some adverse events require 24-hour notification. Please complete a 24-Hour Notification Report via the NCI AdEERS website (<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 (MRI and MRS) 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 adverse event requires expedited reporting, submit a full AdEERS report within the timeframes outlined in table above. **NOTE:** Adverse events that meet the reporting requirements and occur within 30 days of the last dose of protocol treatment or procedure (advanced imaging (MRI and MRS) sub-study) must be reported on an expedited adverse event report form (using AdEERS).

For any adverse events that occur more than 30 days after the last dose of treatment or procedure (advanced imaging (MRI and MRS) 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 adverse event report form (using AdEERS).

**The following table summarizes the reporting requirements for AEs for the advanced imaging (MRI and MRS) sub-study:**



Adverse Events that occur during study participation (related to the advanced imaging (MRI and MRS) 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 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 adverse events with the severity (intensity) level of CTCAEv3.0 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 adverse event 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](mailto: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/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 (897-7402) and ACRIN (215-717-0936) for investigational component of the advanced MRI related events.

All expedited adverse event reports should be sent to your local Institutional Review Board (IRB). Adverse events 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 adverse events and serious adverse events and safety reports.

Other recipients of adverse event reports

AdEERS reports will be forwarded to the appropriate regulatory agencies and/or pharmaceutical company, if applicable.

## **APPENDIX VIII (3/1/07, 7/18/07)**

### **Imaging Reimbursement**

Reimbursement for participation in the standard and advanced imaging components of the study will be provided in two separate payments:

1. Institutions that submit images, imaging reports, and imaging data for the standard imaging component will be triggered for payment once **all** required MRI data has been received at ACRIN. The standard MRI payment is \$1562.00 (U.S.D).
2. Institutions that participate in the advanced imaging component will be triggered for payment once **all** required advanced MRI data has been received at ACRIN. The advanced MRI payment is \$6210.00 (U.S.D).
3. ACRIN will run a reimbursement report on a quarterly basis (Jan.-Mar.; Apr.-June; July-Sept.; Oct.-Nov.). Registered cases will be triggered for payment once all required MRI data has been received at ACRIN. Per case money will be issued by ACRIN. The grant has been provided by NCI/CIP through ACRIN.

The following conditions must be met before patient recruitment to the study:

- The institute has been deemed qualified by ACRIN as outlined in Section 5.2 and Appendix VI.
- The research rate (maximum of \$2,000 per case) is deemed acceptable by the IRB or Central Research Office.
- The research rates are reported to the institution's Financial Office and an account established in the RTOG investigator's name.
- The patient provides written consent and meets the eligibility criteria to participate in the Advanced MRI study.

Verification of patient registration to the ACRIN 6677 trial, submission of the MRI images and pre-study reports to ACRIN, and approval to reimburse will be given by ACRIN.

**NOTE:** Patients or their insurance companies are not to be billed for the one additional research Advanced MRI scans.

For additional information please refer to the ACRIN website, [http://www.acrin.org/6677\\_protocol.aspx](http://www.acrin.org/6677_protocol.aspx). The form is listed under protocol specific contents as 0625/0677 CRS.