RADIATION THERAPY ONCOLOGY GROUP

RTOG 0837

RANDOMIZED, PHASE II, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF CONVENTIONAL CHEMORADIATION AND ADJUVANT TEMOZOLOMIDE PLUS CEDIRANIB VERSUS CONVENTIONAL CHEMORADIATION AND ADJUVANT TEMOZOLOMIDE PLUS PLACEBO IN PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA

NCI-Supplied Agent: Cediranib (NSC 732208, IND 72740)

This is a collaborative effort with American College of Radiology Imaging Network (ACRIN)
ACRIN Study Number 6689

ACRIN 6689 IND Imaging Agent: 3'-deoxy-3'-[^{18}F] Fluorothymidine (NSC 743144, IND 71260)

Study Chairs

Principal Investigator/Medical Oncology
Tracy Batchelor, MD
Center for Neuro-Oncology
Yawkey 9E
Massachusetts General Hospital
55 Fruit Street
Boston, MA 02114
617-724-8770/FAX 617-643-2591
tbatchelor@partners.org

Radiation Oncology
Arnab Chakravarti, MD
Dept. of Radiation Oncology
Arthur G. James Comprehensive Cancer Center and
Richard J. Solove Research Institute
The Ohio State University Medical School
300 W. 10th Ave. Room 080B
Columbus, OH 43210
614-366-4671/Fax 614-293-4044
arnab.chakravarti@osumc.edu

Neuropathology/Correlative Biology
(not responsible for patient care)
Ken Aldape, MD
U.T. M. D. Anderson Cancer Center
1515 Holcombe Blvd.
Houston, TX 77030
713-834-6228/FAX 713-792-3573
kaldape@mdanderson.org
rtogpath@GMail.com

Medical Physics
Murshed Hossain, PhD
Dept. of Radiation Oncology
Fox Chase Cancer Center
333 Cottman Avenue
Philadelphia, PA 19111
215-728-3895/FAX 215-728-4789
murshed.hossain@fccc.edu

Neurosurgery
Costas G. Hadjipanayis, MD, PhD
Department of Neurological Surgery
Emory University School of Medicine
Winship Cancer Institute
1365C Clifton Road
Altanta, GA 30322
404-778-3091/FAX 404-778-4472
chadjip@emory.edu

Senior Statistician
Meihua Wang, PhD
Radiation Therapy Oncology Group/ACR
1818 Market Street, Suite 1600
Philadelphia, PA 19013
215-574-3207/FAX 215-928-0153
mwang@acr-arrs.org

ACRIN Principal Investigator/Advanced Imaging
A. Gregory Sorensen, MD
A.A. Martinos Center for Biomedical Imaging
Mail code CNY149-2301
Building 149, 13th Street
Boston, MA 02129
617-726-3914/FAX 617-726-7422
sorensen@nmr.mgh.harvard.edu

ACRIN Statistician
Constantine Gatsonis, PhD
Center For Statistical Sciences
Brown University, Box G-S121-7
121 South Main Street
Providence, RI 02912
401-863-9183/FAX 401-863-9182
gatsonis@stat.brown.edu

Activation Date: February 26, 2010
Version Date: August 26, 2010
Includes Amendments 1-2
(Broadcast September 14, 2010)
Update Date: September 14, 2010

RTOG Headquarters
1-800-227-5463, ext. 4189

INDEX

RADIATION THERAPY ONCOLOGY GROUP

RTOG 0837

Randomized, Phase II, Double-Blind, Placebo-Controlled Trial Of Conventional Chemoradiation And Adjuvant Temozolomide Plus Cediranib Versus Conventional Chemoradiation And Adjuvant Temozolomide Plus Placebo In Patients With Newly Diagnosed Glioblastoma

SCHEMA

STEP 1 REGISTRATION

↓

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

↓

Analysis for MGMT Methylation

STRATIFY
RPA Class: III vs. IV vs. V
MGMT Methylation Status: Methylated vs. Unmethylated vs. Invalid

↓

STEP 2 REGISTRATION

↓

RANDOMIZE

Arm 1	**Arm 2**
Placebo qd x 3 days	Cediranib qd x 3 days
↓	↓
Radiation (60 Gy in 2 Gy fx) + daily TMZ (qd x 42 d) + placebo qd	Radiation (60 Gy in 2 Gy fx) + daily TMZ (qd x 42 d) + cediranib qd
↓	↓
Placebo qd x 28 days	Cediranib qd x 28 days
↓	↓
Temozolomide d 1-5 of 28-d cycle + placebo qd ; 12 cycles maximum	Temozolomide d 1-5 of 28-d cycle + cediranib qd; 12 cycles maximum

See Section 6.0 for complete radiation therapy details.
See Section 7.0 for complete drug therapy details.

Patient Population: (See Section 3.0 for Eligibility)
- Histopathologically confirmed glioblastoma (WHO Grade IV) **confirmed by central review prior to Step 2 registration**
- Tumor tissue that is **determined by central pathology review prior to Step 2 registration** to be of sufficient size for analysis of MGMT status.
- The tumor must have a supratentorial component

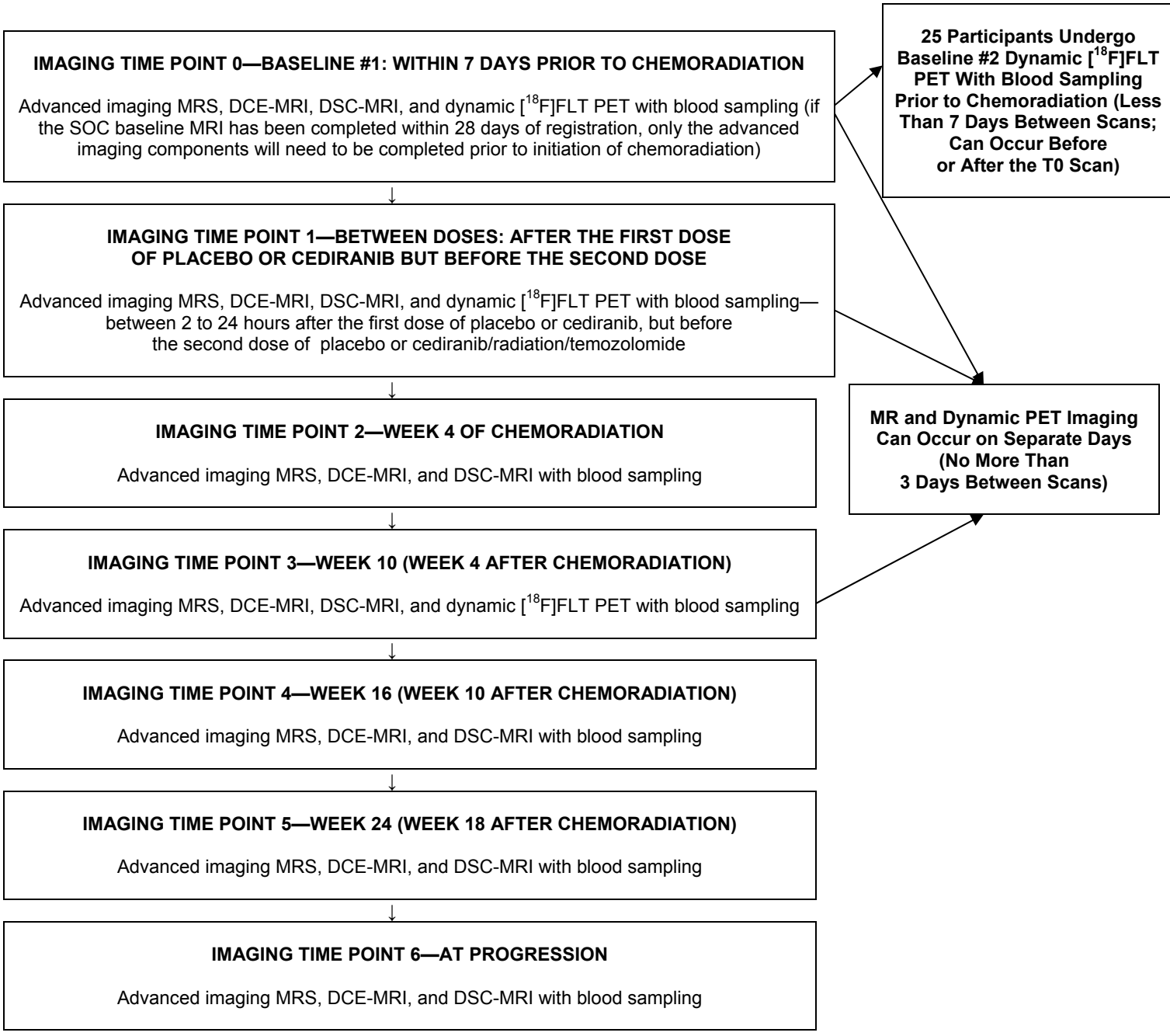
Required Sample Size: 177

For ACRIN 6689 Advanced Imaging Schema, see next page.

ACRIN 6689

Advanced Imaging Component Time Points
(All Advanced-Imaging Eligible Patients Recruited to RTOG 0837 at Participating Sites [Until 51 Accrued])

SCHEMA*



MRS, magnetic resonance spectroscopy; MRI, magnetic resonance imaging; DCE-MRI, dynamic contrast-enhanced MRI; DSC-MRI, dynamic susceptibility-contrast MRI (perfusion MRI); [^{18}F]FLT, 3'-deoxy-3'-[^{18}F] Fluorothymidine; PET, positron emission tomography.

NOTE: For this protocol, "PET" may comprise PET, PET/CT, or MR-PET.

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

ACRIN 6689 Site Eligibility: Pre-qualification of MR and PET imaging scanners and images is required for advanced imaging component; all imaging-eligible participants recruited at advanced-imaging sites must consent to advanced imaging until all 51 participants are accrued (see Appendix I).

Required Sample Size for ACRIN 6689 Advanced Imaging Component: 51 participants from the 177 RTOG-study patients recruited at advanced-imaging sites will undergo the advanced imaging component if they are eligible for imaging. A total of 25 participants will undergo a second [^{18}F]FLT PET scan (Baseline #2) prior to initiation of chemotherapy; specifically, the first 5 participants from each advanced-imaging site will undergo the second [^{18}F]FLT PET scan until 25 participants have completed advanced imaging.

RTOG Institution #
RTOG 0837 **ELIGIBILITY CHECKLIST—STEP 1** (9/14/10)
Case # **(page 1 of 2)**

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

IMRT CREDENTIALING IS REQUIRED BEFORE REGISTRATION
ADVANCED MRI AND PET SCANNER CERTIFICATION IS REQUIRED BEFORE REGISTRATION FOR ACRIN 6689 ADVANCED-IMAGING SITES

The following questions will be asked at study registration for STEP 1:

_____ 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) [If no middle initial, use hyphen]

_____ 6. Verifying Physician

Due to the blinded nature of this study, with drug being provided through the Pharmaceutical Management Branch (PMB) of the NCI, extreme accuracy and consistency of physician information are required to achieve accurate and timely drug shipments. The shipping address for each per-patient shipment is automatically retrieved from the physician-specific information provided on the site's most recent Supplemental Investigator Data Form (IDF) on file with the PMB. (Please see Section 7.3.9.2 for detailed instructions related to IDF maintenance.) Please be certain the address of the local verifying physician you select from the drop down menu during registration is consistent with where the drug is expected to be received and that the physician has a valid NCI (CTEP ID) number. Please also be consistent in identifying the same verifying physician at each registration step [A0 (Step 1) and A2 (Step 2)].

_____ 7. Patient's ID Number

_____ 8. Date of Birth

_____ 9. Race

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

_____ 11. Gender

_____ 12. Patient's Country of Residence

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

_____ 14. Method of Payment

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

_____ 16. Calendar Base Date

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

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

_____(Y) 19. Was the tumor tissue collected within 28 days after the surgical procedure prior to registration?

RTOG Institution #
RTOG 0837
Case #
(assigned in Step 1)

ELIGIBILITY CHECKLIST—STEP 2 (8/26/10)
(page 1 of 5)

_____(Y) 1. Is there histologically proven diagnosis of glioblastoma or gliosarcoma (WHO grade IV) confirmed by central review prior to step 2 registration?
_____(N) If yes, was the material obtained through CUSA (Cavitron ultrasonic aspirator)?
_____(N) If yes, was the material obtained by stereotactic biopsy?

_____(Y) 2. Has the tumor a supratentorial component?

_____(Y) 3. Was a history/physical exam performed within 14 days prior to registration?

_____(Y) 4. Has the patient recovered from the effects of surgery, post-operative infection, and other complications before study registration?

_____(Y) 5. Was a diagnostic contrast-enhanced MRI of the brain performed preoperatively and postoperatively prior to 1st step registration.
_____(Y) Was the postoperative scan performed within 28 days prior to 1st step registration?

_____(Y) 6. Is there documentation of steroid doses/concurrent medications within 14 days prior to registration?

_____(Y) 7. Karnofsky performance status ≥ 70 within 14 days prior to registration?

_____(Y) 8. Age ≥ 18?

_____(Y) 9. CBC/differential obtained within 14 days prior to registration?
_____(Y) If yes, is absolute neutrophil count (ANC) ≥ 1,800 cells/mm^3?
_____(Y) If yes, is the platelet count ≥ 100,000 cells/mm^3?
_____(Y) If yes, is hemoglobin ≥ 10.0 g/dl?

_____(Y) 10. Adequate renal function?
_____(Y) If yes, is BUN ≤ 30 mg/dl within 14 days prior to registration?
_____(Y) If yes, is creatinine ≤ 1.7 mg/dl within 14 days prior to registration?
_____(Y) If yes, is urine protein screened by urine analysis for urine protein creatinine (UPC) ratio?
_____(Y/N) Is UPC ratio > 0.5?
_____(Y) If yes for UPC > 0.5, is 24-hour urine protein obtained and the level is < 1000 mg?

_____(Y) 11. Adequate hepatic function?
_____(Y) If yes, is bilirubin ≤ 2.0 mg/dl within 14 days prior to registration?
_____(Y) If yes, is ALT/AST ≤ 3 x normal range within 14 days prior to registration?

_____(Y) 12. Is systolic blood pressure ≤ 150 mm Hg or diastolic pressure ≤90 mm Hg within 14 days prior to study registration in the presence or absence of a stable regimen of anti-hypertensive therapy?

_____(Y) 13. Is prothrombin time/international normalized ratio (PT INR) < 1.4 for patients not on warfarin confirmed by testing within 1 week of registration?

_____(Y/N) 14. Is patient on full-dose anticoagulants (e.g., warfarin or LMW heparin)?
_____(Y) If yes, is there active bleeding or pathological condition that carries a high risk of bleeding (e.g., tumor involving major vessels or known varices)?
_____(Y) If yes, is INR in range ((usually between 2 and 3) on a stable dose of oral anticoagulant or on a stable dose of low molecular weight heparin?

_____(Y) 15. Did patient provide study specific informed consent form prior to study entry?

_____(Y) 16. Woman of childbearing potential or male participant using adequate contraception?

_____(Y/N/A) 17. Negative serum pregnancy test within 14 days prior to registration?

_____(Y/N/A) 18. Pregnant or lactating woman?

_____(Y/N) 19. Prior invasive malignancy (except for non-melanomatous skin cancer?
_____(Y) If yes, was patient disease free for ≥ 3 years

_____(N) 20. Recurrent or multifocal malignant gliomas?

_____(N) 21. Prior chemotherapy or radiosensitizers for cancers of the head and neck?

_____(N) 22. Prior radiotherapy to the head or neck (except for T1 glottic cancer), resulting in overlap of radiation fields?

_____(N) 23. Unstable angina and/or congestive heart failure requiring hospitalization?

_____(N) 24. Transmural myocardial infarction within the last 6 months?

_____(N) 25. Evidence of recent myocardial infarction or ischemia by the findings of S-T elevations of ≥ 2 mm using the analysis of an EKG performed within 14 days of registration?

_____(N) 26. New York Heart Association grade II or greater congestive heart failure requiring hospitalization within 12 months prior to registration?

_____(N) 27. History of stroke, cerebral vascular accident (CVA) or transient ischemic attack within 6 months?

_____(N) 28. Serious and inadequately controlled cardiac arrhythmia?

_____(N) 29. Significant vascular disease (e.g., aortic aneurysm, history of aortic dissection) or clinically significant peripheral vascular disease?

_____(N) 30. Evidence of bleeding diathesis or coagulopathy?

_____(N) 31. Serious or non-healing wound, ulcer, or bone fracture or history of abdominal fistula, gastrointestinal perforation, intra-abdominal abscess major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to registration, with the exception of the craniotomy for tumor resection?

_____(N) 32. Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration?

_____(N) 33. Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration?

_____(N) 34. Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for liver function and coagulation parameters are not required for entry into this protocol?

_____(N) 35. 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?

_____(N) 36. Active connective tissue disorders, such as lupus or scleroderma, which in the opinion of the treating physician may put the patient at high risk for radiation toxicity?

_____(N) 37. Any other major medical illnesses or psychiatric impairments that in the investigator's opinion will prevent administration or completion of protocol therapy?

_____(N) 38. Prior allergic reaction to temozolomide?

_____(N) 39. Patient treated on any other therapeutic clinical protocols within 30 days prior to study entry or during participation in the study?

_____(N) 40. History of allergic reactions attributed to compounds of similar chemical or biologic composition to cediranib?

_____(N) 41. Mean QT_c > 500 msec (with Bazett's correction) in screening electrocardiogram or history of familial long QT syndrome or other significant ECG abnormality noted within 14 days of treatment?

_____(N) 42. Patient receiving concurrent VEGF inhibitors?

_____(N/Y) 43. Patient on enzyme-inducing anti-epileptic drugs (EIAED)?
See Appendix VI for a list of acceptable anti-epileptic drugs that cause modest or no induction of hepatic metabolic enzymes.
_____(Y) If yes, was the last dose of EIAED administered at least 14 days before the first dose of cediranib?

_____(Y/N) 44. Is the **SITE** participating in the ACRIN 6689 advanced imaging component?
If Y:
_____(Y) Did the **PATIENT** consent to participate in the ACRIN 6689 advanced imaging component? (mandatory for all imaging-eligible patients at participating sites until accrual target is reached for ACRIN 6689)
_____(Y/N) Is the patient able to undergo MRI and PET (a patient may be disqualified due to safety reasons, such as presence of a pacemaker, or weight limitations of the machines)?
_____(Y/N) Is the patient able to tolerate two (2) intravenous (IV) lines, one (1) in each arm?
_____(Y/N) Does the patient have any history of allergic reactions attributed to compounds of similar chemical or biological composition to gadolinium or [^{18}F]FLT contrast agents?

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

_____ 1. Name of institutional person randomizing this case

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

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

_____ 4. Verifying Physician
Due to the blinded nature of this study, with drug being provided through the Pharmaceutical Management Branch (PMB) of the NCI, extreme accuracy and consistency of physician information are required to achieve accurate and timely drug shipments. The shipping address for each per-patient shipment is automatically retrieved from the physician-specific information provided on the site's most recent Supplemental Investigator Data Form (IDF) on file with the PMB. (Please see Section 7.3.9.2 for detailed instructions related to IDF maintenance.) Please be certain the address of the local verifying physician you select from the drop down menu during registration is consistent with where the drug is expected to be received and that the physician has a valid NCI (CTEP ID) number. Please also be consistent in identifying the same verifying physician at each registration step [A0 (Step 1) and A2 (Step 2)].

_____ 5. Patient's ID Number

_____ 6. Calendar Base Date (for Step 2)

_____ 7. Randomization date: This date will be populated automatically (for Step 2).

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

_____ 9. Medical oncologist

_____(Y/N) 10. Have you obtained the patient's consent for his or her tissue to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 11. Have you obtained the patient's consent for his or her blood to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 12. Have you obtained the patient's consent for his or her urine to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 13. Have you obtained the patient's consent for his or her tissue to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?

_____(Y/N) 14. Have you obtained the patient's consent for his or her blood to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?

_____(Y/N) 15. Have you obtained the patient's consent for his or her urine to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?

_____(Y/N) 16. Have you obtained the patient's consent to allow someone from this institution to contact him or her in the future to take part in more research?

_____(<50/≥50) 17. Age

_____(70-80/90-100) 18. Karnofsky performance status

_____(partial or total resection/biopsy) 19. Prior surgery

_____(0, 1 / 2, 3, 4) 20. Neurologic function

_____(Y/N) 21. Is the **SITE** participating in the ACRIN 6689 advanced imaging component?

If Y:

_____(Y) Did the **PATIENT** consent to participate in the ACRIN 6689 advanced imaging component? (mandatory for all imaging-eligible patients at participating sites until accrual target is reached for ACRIN 6689)

_____(Y/N) Is the patient able to undergo MRI and PET (a patient may be disqualified due to safety reasons, such as presence of a pacemaker, or weight limitations of the machines)?

_____(Y/N) Is the patient able to tolerate two (2) intravenous (IV) lines, one (1) in each arm?

_____(Y/N) Does the patient have any history of allergic reactions attributed to compounds of similar chemical or biological composition to gadolinium or [^{18}F]FLT contrast agents?

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 Background

An estimated 51,410 primary brain tumors were diagnosed in the United States in 2007 and 40% of these tumors were gliomas. Glioblastoma (GBM) accounted for 50.7% of all gliomas diagnosed from 1998-2002 (CBTRUS2008). The prognosis for patients with glioblastoma remains poor, with most studies reporting a median survival of 10 to 15 months (Wen 2008). At 5 years, less than 5% of patients are alive. Meta-analyses of randomized trials of radiation versus radiation plus a nitrosourea-containing regimen showed only a modest improvement in 1-year survival in the patients receiving the combination regimen (Fine 1993, Stewart 2002). In addition to tumor progression, some patients stopped treatment because of adverse effects such as myelosuppression and/or progressive pulmonary dysfunction as a consequence of nitrosourea-induced pulmonary fibrosis. Therefore, the disappointing results achieved with adjuvant chemotherapy for glioblastoma may be the combined consequence of modest treatment activity and premature treatment cessation because of toxicity.

1.2 Temozolomide and Radiation

Temozolomide, an oral alkylating agent with good penetration of the central nervous system and a favorable toxicity profile, is now considered standard therapy for patients with newly diagnosed glioblastoma (Stupp 2005). The efficacy of temozolomide in combination with radiation (chemoradiation) was established in a randomized phase III study conducted by the European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC). In this study Stupp and colleagues administered a daily dose (75 mg/m^2) of temozolomide during the course of radiation therapy, followed by 6 months of adjuvant chemotherapy at the standard single-agent dose of 200 mg/m^2 for days 1 to 5 of a 28-day cycle. This experimental arm was compared to a standard arm in which patients received only radiation. 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 hematological toxicity of < 4% (Stupp 2005). In correlative studies conducted as part of the EORTC-NCIC phase III trial the impact of MGMT expression on response and survival was assessed. Expression of the MGMT protein mediates resistance to alkylating chemotherapeutic agents like temozolomide by repairing the covalent crosslinks in DNA produced by these drugs. MGMT can be inactivated by methylation of the gene promoter and this occurs spontaneously in approximately half of all glioblastomas. A statistically significant difference in survival was found when MGMT gene promoter status was evaluated as an independent factor in the patients on the chemoradiation arm. Patients with tumors demonstrating methylation (inactivation) of the MGMT gene had a significant improvement in median survival as well as in 2-year survival rate (46% vs 14%). These findings, and those from other studies, strongly support the impact of MGMT expression on response to temozolomide in patients with glioblastoma (Hegi 2005, Esteller 2000). Several strategies have been used to modulate MGMT activity. These include specific MGMT inhibiting agents, such as O6-benzylguanine. To date, these strategies have been limited by excessive myelosuppression as a consequence of MGMT inhibition in normal hematopoietic elements (Quinn 2005). However, early laboratory studies have demonstrated that temozolomide is also a substrate for MGMT and prolonged high-dose exposure results in sustained inhibition of the MGMT activity (Wick 2007). An ongoing study of "dose-dense" versus standard-dose post-radiation adjuvant temozolomide (RTOG 0525) is currently being conducted in the RTOG based on the hypothesis that "dose-dense" temozolomide (temozolomide administered for 21 out of 28 days) will deplete MGMT and enhance the cytotoxic effects of the drug.

1.3 Angiogenesis as a Therapeutic Target

Solid tumors, regardless of their type or cellular origin, require vascularization to grow beyond minimal size. Angiogenesis is the process by which new capillary blood vessels extend from established blood vessels creating additional vascular supply. This allows most solid tumors to grow beyond a limiting size by facilitating delivery of nutrients to the tumor and removal of waste products (Folkman, 1985; Plate, et al. 1994; Weinstat-Saslow, et al. 1994; Folkman, 1995; Parangi, et al. 1996). During tumor angiogenesis, previously quiescent endothelial cells separate from their

basement membrane and begin to migrate toward the tumor cells in response to secretion of angiogenic factors such as the vascular endothelial growth factors. In this way, a blood supply to the proliferating tumor cells is established and a vascularized tumor is formed. It has been hypothesized that specific inhibition of tumor-induced angiogenesis should prevent the growth of many types of solid tumors, as well as prevent their metastatic potential, thereby providing a novel approach for the treatment of cancers (Fan, et al. 1995; Seed 1996; Augustin 1998).

The VEGF family of soluble growth factors consists of five related proteins that have been implicated in angiogenesis (VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E), four of which occur in the human genome (VEGF-A, VEGF-B, VEGF-C, VEGF-D). There are three VEGF receptors (VEGFR1, VEGFR2, and VEGFR3) that play important roles in the angiogenesis of numerous solid malignancies, including glioblastoma. The VEGF family of endothelial growth factors is considered to play a key role in angiogenic processes and has been shown to be secreted by tumor cells and tumor stromal cells (such as macrophages or fibroblasts) (Fukumura, et al. 1998; Fong, et al 1999; Wood, et al. 2000; Bold, et al. 2000; Fabbro, et al. 2002). Tumor angiogenic and lymphangiogenic signals are transmitted via three tyrosine kinase cell surface receptors [VEGFR1 (Flt-1), VEGFR2 (KDR), and VEGFR3 (Flt-4)] located on the host vascular endothelial cells, monocytes/macrophages, and hematopoietic precursors. Because VEGF receptors (VEGFRs) are only up-regulated in endothelial cells of newly forming vessels in tumors, a potential target for anti-tumor therapy will be the VEGFR tyrosine kinases. Inhibition of VEGF-induced angiogenic and lymphangiogenic signals will selectively target the tumor-associated vessels, since cell division of endothelial cells in the normal vasculature is a very rare event. VEGF (also known as vascular permeability factor, VPF) is also a potent inducer of vascular permeability and may play a key role in tumor-associated brain and solid organ edema, ascites and malignant effusions (Fong, et al. 1999). VEGF has also been shown to interfere with the maturation of dendritic cells and may therefore inhibit immune responses against VEGF-secreting tumors. Several molecules, some of which are polypeptide growth factors, affect angiogenesis. A series of low molecular weight inhibitors of VEGFR tyrosine kinases are currently under clinical development (Wood, et al. 2000; Bold, et al. 2000; Drevs, et al. 2000). These inhibitors block VEGF activity in both *in vivo* and *in vitro* models of angiogenesis (Fong, et al. 1999; Wood, et al. 2000; Bold, et al. 2000), inhibiting tumor angiogenesis, tumor growth, and the formation of metastasis in rodent tumor models. VEGF inhibitors are, in general, better tolerated than conventional cytotoxic agents. However, VEGF inhibitors may interfere with important physiological processes (wound healing, menstrual cycle, pregnancy, and fetal development), which may restrict usage in specific patient populations. Elevations in blood pressure have also been observed with VEGF inhibitors and may be due to decreased levels of nitric oxide caused by inhibition of VEGF. In patients with hypertension or risk factors for hypertension, there are decreased levels of nitric oxide in the endothelium, which may tend to exacerbate the effect of VEGF inhibition.

1.4 Normalization of Tumor Vasculature

The mechanism by which anti-angiogenic therapies exert an anti-tumor effect has not been well established. The traditional notion is that anti-angiogenesis represents a pruning of the tumor vasculature and that the tumor is thereby deprived of essential nutrients and oxygen. However, it is now recognized that anti-angiogenic therapies may achieve their anti-neoplastic effect by mechanisms other than simple destruction and pruning of tumor vasculature. Furthermore, it is possible that different mechanisms are operative at different time points during anti-angiogenic therapy and that different mechanistic theories are not mutually exclusive. The vascular network within a solid tumor is abnormal and characterized by dilated, leaky vessels lacking pericyte coverage and with abnormally thickened basement membranes. These structural abnormalities lead to physiological changes within the tumor including hypoxia, acidosis and increased tumor interstitial pressure. Moreover, it has been demonstrated that these highly permeable, dilated vessels are not effective conduits for delivery of drugs into the tumor matrix. It has been demonstrated both in pre-clinical models and a phase II trial in patients with rectal cancer that treatment with anti-VEGF therapies “normalizes” tumor vasculature as measured by reduced microvessel density; reduced mean blood vessel diameter; enhanced pericyte coverage; reduced basement membrane thickness; reduced tumor interstitial pressure and reduced permeability of tumor vasculature (Winkler, et al 2004; Willett, et al 2004). However, with continuation of anti-VEGF therapy these functional and structural changes revert back to an abnormal state. Thus, there appears to be a “normalization window” during which delivery of chemotherapeutics might be

optimized. Furthermore, it has been demonstrated that oxygen delivery to the tumor is enhanced during the "normalization window" with a reduction in the hypoxic tumor fraction during this period (Winkler, et al 2004). The combination of anti-VEGFR2 therapy with fractionated radiation during the "normalization window" results in a greater than additive effect on growth inhibition of human gliomas (Winkler, et al 2004). Furthermore, the co-administration of the anti-VEGF antibody, bevacizumab, with cytotoxic chemotherapy increases the effectiveness of chemotherapy in patients with colorectal cancer (Hurwitz, et al 2004). In a study conducted at the Massachusetts General Hospital Cancer Center patients with rectal cancer treated with bevacizumab, showed decreased microvascular density (MVD) and interstitial fluid pressure in the post-therapy period (Willett, et al. 2004). In this study bevacizumab was also associated with an increase in the fraction of vessels with pericyte coverage. The decrease in IFP and the increase in the fraction of vessels with pericyte coverage support the normalization hypothesis (Jain 2005).

1.5 Glioblastoma and Angiogenesis

Tumor angiogenesis is an important target in glioblastoma as endothelial proliferation is a diagnostic criterion for this disease. The classical characteristics of glioblastoma include marked angiogenesis with microvascular proliferation and severe hypoxia with tumor necrosis (Valk, et al. 1992; Rampling, et al. 1994; Plate, et al. 1995). Gene expression profiles of high-grade gliomas have identified distinct prognostic subclasses including a neuronal phenotype associated with longer survival and a mesenchymal phenotype associated with shorter survival and robust angiogenesis (Phillips, et al. 2006).

Two major problems currently plague the non-surgical treatment of glioblastoma. First, physiological barriers impede the delivery of conventional and novel therapeutics. Second, drug resistance resulting from genetic and epigenetic mechanisms reduces the effectiveness of available drugs. Anti-angiogenic therapy has the potential to circumvent these problems. This therapy targets the tumor vasculature, derived from local and circulating endothelial cells that are considered genetically stable. The fact that a large number of cancer cells depend upon a small number of endothelial cells for their growth and survival might also amplify the therapeutic effect. Prior studies have demonstrated the potential benefit of anti-angiogenic therapies in patients with recurrent glioblastoma (Fine, et al. 2003). VEGF receptor 1 (VEGFR1 or FLT-1 [fms-like tyrosine kinase 1]) and VEGF receptor 2 (KDR [kinase insert domain-containing receptor]) are highly co-expressed on endothelial cells of glioblastoma. It has been hypothesized that VEGF is secreted by glioblastoma cells and acts to stimulate endothelial cells through paracrine mechanisms (Steiner, et al. 2004). Angiogenesis in glioblastoma is driven by high levels of VEGF (Shweiki, et al. 1992; Holash, et al. 1999) via VEGFR2 (Millauer, et al. 1994). VEGFR2 is the major mediator of several physiological and pathological effects of VEGF-A on endothelial cells, including proliferation and survival, migration and permeability. However, as noted previously, VEGF-induced angiogenesis does not lead to mature, functional vessels: glioma vessels are dilated, tortuous, disorganized, have a high permeability, and are characterized by abnormal microvascular density (Plate, et al. 1995; Zagzag, et al. 1999; Guo, et al. 2003). Furthermore, levels of VEGF protein as well as mRNA correlate with the histological grade and microvascular density of gliomas (Samoto, et al. 1995; Schmidt, et al. 1999).

Reduction of tumor vessel permeability and tumor interstitial pressure as consequences of normalization with anti-VEGF therapy may provide multiple salutary effects in patients with glioblastoma. The normalization window may represent the optimal time during which multiple therapeutic agents may be most effective. In addition to the possibility of more efficient delivery of oxygen and chemotherapeutics these physiological effects may also reduce tumor-associated brain edema, mass effect and intracranial pressure. These effects may improve neurological function and allow better clinical tolerance of fractionated radiation, as a well known adverse effect of radiation is tumor edema and tumor necrosis. In fact, there is anecdotal evidence that combined temozolomide and fractionated radiation may enhance the risk of tumor edema and necrosis. Thus, in addition to the possibility of an enhanced anti-neoplastic effect there is also the potential of a potent and beneficial anti-edema effect with anti-VEGF therapy for patients with newly diagnosed GBM.

1.6 Prior Studies of VEGF Inhibitors in Glioblastoma

In addition to a study of cediranib monotherapy for recurrent GBM (see below under Preliminary Studies) there have been other studies VEGF inhibitors that have demonstrated potential efficacy in the glioblastoma patient population.

PTK787 (vatalanib) is an oral pan-VEGFR tyrosine kinase inhibitor which also inhibits PDGFR-ß. PTK787 has been combined with other chemotherapeutic agents in patients with recurrent glioblastoma. In one study PTK787 was combined with either lomustine or temozolomide. In 23 patients treated with PTK787 and lomustine there were 3 dose limiting toxicities (neutropenia, 2 patients; transaminase elevation, 1 patient) and the dose of PTK787 was reduced to 750mg/day. In another study PTK787 was combined with temozolomide for treatment of patients with recurrent glioblastoma. In 37 patients treated with PTK787 (from 500mg/day up to 1500mg/day) and temozolomide (200mg/m^2 x 5 days) there was 1 dose limiting toxicity and the MTD was not reached. The median time to progression for patients treated with temozolomide and PTK787 was 15.7 weeks (96% CI 8.6, 18.3), which compared favorably to historical controls. In all 51 patients (PTK787 + temozolomide; PTK787 + lomustine) evaluable for radiographic response there were 4 partial responses (3 on PTK787/ZK 222584 + temozolomide and 1 on PTK787 + CCNU) and 27 patients had stable disease. (Reardon, et al. 2004).

Bevacizumab, a humanized IgG1 monoclonal antibody to VEGF administered intravenously, was combined with irinotecan in a phase II study of 35 patients with recurrent glioblastoma (Vredenburgh, et al 2007). In this trial 23 patients were treated every other week with bevacizumab (10mg/kg) and irinotecan (125mg/m^2 for patients not taking enzyme-inducing anti-epileptic drugs or 340mg/m^2 for patients taking enzyme-inducing anti-epileptic drugs) and 12 patients were treated with bevacizumab (15mg/kg) every 21 days and irinotecan on days 1, 8, 22, 29. The radiographic response proportion in this study was 57% (20/35 patients), the median progression-free survival was 24, the median OS was 42 weeks and the proportion of patients alive and without disease progression at 6 months (APF6) was 46%. Eleven patients were removed from the study due to thromboembolism, fatigue and proteinuria. In a study of bevacizumab monotherapy (10mg/kg) every 2 weeks in 48 patients with recurrent glioblastoma the radiographic response proportion was 35% (17/48), the median progression-free survival was 16 weeks, the median OS was 31 weeks and the APF6 was 29% (Kreisl, et al 2009). The most common toxicities were hypertension (12.5%), thromboembolic events (12.5%), hypophosphatemia (6%) and thrombocytopenia (6%). Six patients (12.5%) were removed from the study due to toxicity.

1.7 Cediranib

Cediranib (AZD2171, Recentin) (NSC 732208, IND 72740), an orally available small molecule, is a potent inhibitor of receptor tyrosine kinases (RTKs), which influence the effects of a key angiogenic factor, VEGF-A. VEGF is implicated in tumor blood vessel formation and in disease progression in a wide range of solid tumor malignancies. The effective half-life of cediranib in humans is 22 hours (12.5 – 35.4 hours). Expression of this factor is increased by diverse stimuli, which include proto-oncogene activation and hypoxia, with the hypoxic state frequently occurring in solid tumors because of inadequate perfusion. In addition to its angiogenic role, VEGF also profoundly increases the permeability of the vasculature and thereby potentially contributes to tumor progression – a leaky tumor endothelium enhances nutrient and catabolite exchange and represents less of a barrier to tumor cell migration during metastasis. With the goal of suppressing neovascularization and thus inhibiting tumor growth and metastasis, numerous anti-angiogenic agents have been developed. In contrast to many of these intravenously administered anti-angiogenic agents, a recently emerging class of novel orally administered VEGF TK inhibitors including cediranib has been developed (Hennequin, et al. 1999; Wedge, et al. 2000; Wedge, et al. 2002).

Two high-affinity receptors for VEGF with associated TK activity have been identified on human vascular endothelium, KDR (kinase insert domain-containing receptor = VEGFR2) and Flt-1 (fms-like tyrosine kinase 1 = VEGFR1). Although the relative contributions of KDR and Flt-1 signaling in mediating tumor progression have not been elucidated, a number of studies suggest that KDR performs a predominant role. Cediranib is a potent inhibitor of both KDR (IC_{50} <0.002 microM) and Flt-1 (IC_{50} = 0.005 microM) and shows activity versus c-kit, platelet-derived growth factor receptor

beta (PDGFR-β), and Flt-4 at nanomolar concentrations. It has been shown that cediranib potently and selectively inhibits VEGF-stimulated human umbilical cord vascular endothelial cell (HUVEC) proliferation with an IC_{50} of 4 nM (Ogilvie et al. 2004). These authors have also demonstrated the agent's profound inhibitory effect on vessel area, length, and branching at subnanomolar concentrations using a modified fibroblast/endothelial cell co-culture system. The effects of cediranib on hemodynamic parameters have been studied in an athymic rat xenograft model of human colorectal carcinoma (SW620) using perfusion-permeability dynamic contrast-enhanced magnetic resonance imaging (pp-DCE-MRI) (Bradley, et al. 2004). This method clearly demonstrated that in this model, cediranib significantly reduced vascular permeability by 80% ($P<0.005$) and vascular volume by 68% ($P<0.05$).

1.7.1 Nonclinical Efficacy of Cediranib

The effect of cediranib was studied in athymic nu/nu mice bearing established subcutaneous human tumor xenografts of diverse histologies [SW620 (colon), PC-3 (prostate), Calu-6 (lung), SKOV-3 (ovarian), and MDA-MB-231 (breast)]. Animals were administered cediranib orally (PO) at doses ranging from 0.75 to 6 mg/kg/day (2.25-18 mg/m^2/day) in a constant volume of 0.1 ml/10 g body weight for 24-28 days. Cediranib produced a statistically significant inhibition of tumor growth in all human tumor types examined when dosed at 1.5 mg/kg/day (4.5 mg/m^2/day) or higher.

The murine renal cell carcinoma (RENCA) model, which rapidly (generally within 10 days) metastasizes to the lung and abdominal lymph nodes, has also been used for cediranib efficacy studies (Drevs, et al. 2004). In experiments incorporating a vehicle control, cediranib (at a dose of 6.3 mg/kg/day PO) reduced primary tumor growth, metastasis, and microvessel density more potently than any other previously studied VEGF RTK inhibitor reported in the literature.

Using a transgenic mouse model in which multiple mammary tumors spontaneously develop after two pregnancies, investigators studied the temporal effects of cediranib administration (Klinowska, et al. 2004). When dosed with cediranib (0.75 to 6 mg/kg/day PO) at the time early lesions start to develop, the number of tumor foci was not affected, but their growth was inhibited. When tumors were well established before cediranib was given (at doses of 3 and 6 mg/kg/day), dose-dependent growth inhibition occurred as well as tumor regression. Further details of the non-clinical efficacy of cediranib can be found in the investigator's brochure.

1.7.2 Nonclinical Pharmacology and Toxicology of Cediranib

Nonclinical pharmacology and toxicology, company-sponsored, cediranib studies have been conducted in rats, dogs, and cynomolgus monkeys. In rats and dogs, oral bioavailability is high, but absorption is relatively slow, with peak plasma concentration (C_{max}) of the agent seen 4-6 hours after PO dosing. Plasma concentrations and exposure are generally linear over the dose ranges studied in rats. Cediranib is excreted in the feces (>70% of the dose) of rats, dogs, and cynomolgus monkey after both PO and intravenous administration. Fecal excretion was the predominant route of elimination (>70% of the dose) in both rat, dog and cynomolgus monkey after both oral and intravenous administration. Elimination was rapid in rats and monkeys with over 75% of the dose being recovered in the first 48 hours; in dogs excretion was slightly slower but again substantially complete by 7 days.

Over the dose ranges examined in the rat, plasma concentrations and exposure generally increased in proportion to dose; however, in monkeys, plasma cediranib concentration-time profiles obtained following a single oral dose indicated that systemic exposure increased in a greater than dose-proportional manner over the dose range 0.05 to 2.5 mg/kg.

Protein binding of cediranib (90 to 95%) was relatively high across all species examined and was independent of concentration (range: 0.03 to 10 mcg/ml) and gender. Cediranib was approximately 95% bound to human plasma proteins, with human serum albumin and α_1-acid glycoprotein accounting for most of this binding.

VEGF has three major biological activities in endothelial cells of rats and primates of the age groups used in the nonclinical studies. It is an important angiogenic factor, a potent physiological mediator of vascular tone (specifically of vasodilation), and a potent modulator of

capillary permeability inducing endothelial cell fenestrations. VEGF receptor inhibition was therefore considered to be the cause of many of the pathophysiological changes encountered.

Vascular (myocarditis, choroid plexus) and renal (glomerulosclerosis and tubular degeneration) pathologies have been observed in rat, dog, and primate dosed with cediranib which are considered to be consistent with lesions induced by hypertension, although a direct effect by cediranib on these tissues cannot be excluded. Pathological findings were also seen in the adrenal glands (degenerative cortical changes), pancreas (acinar epithelial cell necrosis), thyroid (follicular epithelial cell atrophy), liver (hepatocyte necrosis), and biliary system (cholangitis and bile duct proliferation and bile duct cholangitis) of the rat. In addition in the primate, changes were seen in the gallbladder (mucosal hypertrophy) and bile duct (hyperplasia/hypertrophy).

Cediranib did not induce rat hepatic microsomal P450 activity but caused a 40 to 60% reduction in CYP1A activity at the 2.5 mg/kg dose level. Inhibition studies *in vitro* using human hepatic microsomal protein gave IC_{50} values for cediranib against CYP2D6, CYP3A4 testosterone, and CYP3A4 midazolam of 32.9, 16.2, and 21.4 mcg/ml, respectively. For CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, and CYP2E1, the IC_{50} values were outside the concentration range of cediranib examined. As the clinically relevant plasma concentration of cediranib has not yet been determined, any possible effect on compound clearance and drug interaction is currently unknown. Further details of the nonclinical pharmacology and toxicity of cediranib can be found in the investigator's brochure.

1.7.3 Clinical Studies of Cediranib

The safety, tolerability, efficacy, and pharmacokinetics (PK) of cediranib are currently being evaluated in monotherapy and combination studies in patients with solid tumors and metastatic liver disease (Study 2171IL/0001), in relapsed or refractory acute myeloid leukemia (Study 2171IL/0002), and in elderly patients with metastatic prostate adenocarcinoma (Study 2171IL/0003). A detailed description of the preliminary data from these studies is provided in the investigator's brochure.

In Study 2171IL/0001, patients received cediranib at doses ranging from 0.5 to 60 mg. Patient cohorts received a single dose of cediranib followed by a 7-day washout period then started a 28-day cycle of daily doses of the agent at the same dose level they received initially. In this study cediranib was well tolerated at doses up to and including 45 mg/day. The 60 mg dose of cediranib appeared to be less well tolerated and was associated with an increased frequency of adverse events, dose interruptions, and increases in serum thyroid stimulating hormone (TSH). The most frequently reported adverse events (AEs) in Study 2171IL/0001 were fatigue (13/36 [36%]), nausea (13/36 [36%]), diarrhea (10/36 [28%]), and vomiting (10/36 [28%]). Three serious adverse events (SAEs) including an abnormal liver function test, hypertension, and hypoglycemia were considered to be related to cediranib. AstraZeneca reported that the patients with events of hypertension and hypoglycemia recovered, while the patient with an abnormal liver function test improved while on trial. Increases in mean arterial blood pressure (MAP) were observed for at least one time point in several patients across all of the cediranib doses studied. No clinically relevant changes in electrocardiogram parameters, heart rate, or laboratory parameters have been observed. AstraZeneca reports that while only limited and preliminary safety data are currently available from the other three studies, those data also suggest that cediranib is well tolerated.

Preliminary cediranib PK data from two phase 1 clinical studies (Study 2171IL/0001 and 2171IL/0003) have established that following a single dose, cediranib is orally available with C_{max} ranging from 1 to 8 hours post dosing. Concentrations declined in an apparent bi-exponential manner thereafter with a $t_{½lz}$ ranging from 12.5 to 35.4 hours. Steady-state plasma concentrations were predicted by the single dose PK with the grand arithmetic mean temporal change parameter value being 1.07. This observation supports the concept that there are no time-dependent PK changes. Dose proportionate increases in C_{max}, $C_{max,\ ss}$, AUC, and AUC_{ss} provide no evidence to reject linear PK for single and multiple cediranib doses ranging from 0.5 to 60 mg. The PK profile of cediranib supports once-daily oral dosing.

Initial assessments from phase 1 study in patients with solid tumors and metastatic liver disease (Study 2171IL/0001) have produced encouraging indications of potential biological efficacy in the patient population studied. Reductions in blood flow in hepatic metastases were detected by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), and initial biomarker assessments (VEGF and VEGF-R2) have been encouraging. In addition, AstraZeneca reports that one ovarian cancer patient had a minor-partial response in lung and liver metastases, while a colorectal cancer patient had a minor response.

Based on evidence from animal data with cediranib (vascular and renal pathology) and results from the phase 1 clinical studies, it appears that the agent will produce hypertension in man. Because hypertension seen in animals has been abrogated by nifedipine, the change is thought to be mechanistically related to inhibition of VEGF signaling, although a direct toxicological effect on the blood vessels and kidneys cannot be excluded. The potential for hypertensive changes following cediranib administration is additionally supported by evidence from the use of other anti-angiogenic agents in the clinic. For these reasons, patients should be monitored frequently for changes in blood pressure and renal function (blood urea nitrogen, creatinine, and urinary protein). There is also a potential for myocardial injury.

Certain physiological processes other than endothelial cell growth are dependent on VEGF signaling, so inhibition of this growth factor may have implications for the use of cediranib in selected patient populations. Pediatric studies with cediranib should be undertaken with caution because the agent increases the zone of hypertrophy in the epiphyseal growth plates thus preventing ossification during long bone growth. Cediranib interferes with normal reproductive processes and completely prevents fetal development in rats at a dose of 2.5 mg/kg/day. For this reason, women of childbearing potential should have a negative pregnancy test before treatment with cediranib is initiated. In rat studies, cediranib significantly inhibited endochondral ossification and corpora lutea formation (Wedge, et al. 2004).

1.7.4 Rationale for Evaluation of Cediranib in Glioblastoma

Preclinical studies have demonstrated that blocking VEGF signaling pathways can inhibit the growth of glioblastoma. For example, using DC101, a monoclonal antibody against VEGFR2, there is inhibition of glioma angiogenesis and growth (Kunkel, et al. 2001). Additionally, targeting the VEGF pathway not only holds the promise of destroying tumor vessels, but can also potentially improve the efficacy of additional radiation and chemotherapy. It has been demonstrated that anti-VEGFR2 therapy combined with fractionated radiation has a greater than additive effect on growth inhibition of experimental, ectopic and orthotopic human gliomas (Gorski, et al. 1999; Lee, et al. 2000; Kozin, et al. 2001,Winkler, et al. 2004). Moreover, a clinical trial has demonstrated that co-administration of the anti-VEGF antibody bevacizumab increases the efficiency of established cytotoxic therapy for colorectal cancer patients (Hurwitz, et al. 2004). Finally, as noted previously, PTK787 and bevacizumab (with irinotecan), inhibitors of VEGF signalling, have demonstrated potential efficacy in patients with glioblastoma.

Cediranib was the subject of a phase II trial in recurrent glioblastoma patients not taking enzyme-inducing anti-epileptic drugs. A report of the first 16 consecutive patients enrolled onto this study was published in *Cancer Cell* (Batchelor, et al. 2007). These data have been updated for all 30 patients with respect to efficacy outcomes as enumerated below. The dose of cediranib monotherapy in this study was 45mg/day by mouth once daily. Patients had received and failed prior standard therapy with resection or biopsy followed by radiation and temozolomide. Toxicity in the first 16 recurrent glioblastoma patients treated with cediranib was modest with expected toxicities of hypertension, fatigue, dysphonia, elevation of TSH and palmar/plantar erythema. Only one of the first 29 recurrent glioblastoma patients treated with cediranib had the drug discontinued because of toxicity – fatigue. No intratumoral or intracerebral hemorrhages were observed during the course of cediranib treatment in this recurrent glioblastoma population. Using volumetric techniques, most recurrent glioblastoma patients showed diminished tumor contrast enhancement after a single dose of cediranib despite an aggressive growth rate of approximately 1% in tumor enhancement volume per day prior to treatment initiation. A reduction of tumor enhancement volume of more than 50%

(partial response) was observed in 17/30 (56.7%) patients and 25% to 50% (minor response) in 6/30 (20%) patients. Thus, 23/30 (76.7%) patients experienced a 25-95% reduction in tumor contrast enhancement in response to cediranib monotherapy. The median progression-free survival and overall survival for these 31 patients was 117 days and 227 days, respectively, which compares favorably to the progression-free and overall survival, 63 days and 175 days, respectively, reported from an historical database (Wong, et al. 1999). Similar to other anti-angiogenic therapies that target only tumor endothelium, monotherapy with cediranib may not improve overall survival compared to other reported trials, suggesting the need to combine cytotoxic therapies with cediranib (lower bound of 95% confidence interval for median overall survival was 136 days, compared to a median overall survival of 175 [95% CI: 147, 196] days from an historical database (Wong, et al., 1999). Clinical and radiographic data from the first 16 patients strongly support an anti-edema effect of cediranib. Among the 16 patients who were receiving corticosteroids during treatment with cediranib, 15 had their corticosteroid dose reduced and 5 had their corticosteroids discontinued. Moreover, significant reductions in ADC, FLAIR and Ve served as imaging corroboration of an anti-edema effect. The challenge remains how to optimally combine cediranib with other therapeutics that target glioblastoma (Jain, et al. 2006). This will be the subject of the current study.

1.7.5 Rationale for Cediranib Combination With Chemoradiation

Temozolomide is an imidazotetrazinone with activity attributed to the formation of a reactive methyldiazonium cation and methylation of O6-guanine in DNA. Clinical responses to temozolomide are closely linked to the activity of O6-methylguanine-DNA-methyltransferase (MGMT), a DNA repair protein which removes O6-alkylguanine adducts in DNA (Wedge, et al. 1996). Features of temozolomide that are attractive for use in CNS tumors include excellent oral bioavailability and good penetration of the blood-brain barrier (BBB) (Newlands, et al. 1997). The activity of temozolomide is highly dependent on the dosing schedule, with multiple administrations being more effective than a single dose. It is administered orally at 150-200 mg/m^2 daily for five days on a four-week cycle. Peak plasma concentration is achieved within 30-60 minutes of oral administration and the compound has an elimination half-life of one to two hours. Elimination is largely via renal excretion as intact drug and a carboxylic acid metabolite which has equivalent cytotoxicity. Myelosuppression, which is dose limiting at 1200 mg/m^2, and nausea and vomiting are the most frequent adverse events. In a randomized clinical trial of daily temozolomide (75 mg/m^2) + radiation versus radiation alone in adults with newly diagnosed GBM the patients who received temozolomide and radiation versus radiation had improved progression free survival (6.9 months versus 5.0 months, $p < 0.0001$); overall survival (14.6 months versus 12.1 months, $p < 0.0001$) and 2-year survival (26.5% versus 10.4%, $p < 0.0001$). (Stupp, et al. 2005). Based on this randomized trial the standard for care for newly diagnosed GBM has changed with concurrent radiation and temozolomide as the new standard. New agents tested in the newly diagnosed GBM setting should include both temozolomide and radiation as modern standard of care for GBM.

Combined treatment of tumors with anti-angiogenesis agents like angiostatin, a proteolytic fragment of plasminogen, and ionizing radiation (IR) has demonstrated potentiation of the cytotoxic effect against endothelial cells and an increased anti-tumor effect (Mauceri, et al. 1998; Gorski, et al 1998). Inhibition of the VEGF receptor by SU5416, an Flk-1 kinase inhibitor, reversed radiation resistance of refractory tumor blood vessels and enhanced the toxicity of radiation (Geng, et al 2001). Down-regulation of the PI3K/Akt pathway by PTK787 sensitizes cells to IR. One study demonstrated that combined treatment with daily, fractionated IR and PTK787 resulted in a significant, supra-additive, anti-tumor effect on human SW480 adenocarcinoma tumor xenografts in an *in vivo* mouse model. In this same study there was no immediate or long-term additive toxicity observed (Hess, et al 2001). There are several potential levels of cooperation between anti-angiogenesis agents and IR with respect to tumor control. IR targets both tumor cells and endothelial cells and also enhances expression of VEGF as part of an induced stress response in the tumor. Anti-angiogenic agents may down-regulate the VEGF-dependent proliferation of tumor microvasculature and block IR-induced survival pathways mediated by VEGF (Hess, et al 2001). Thus, there is a good rationale to combine certain anti-angiogenic agents with IR in an effort to achieve improved tumor control. There have been no human studies of radiation and cediranib to date.

The induction of a normalization window by cediranib affords a potential opportunity to enhance delivery of temozolomide to the GBM in a combination study as proposed. Moreover, the potential to diminish tumor hypoxia by improving oxygen delivery to tumor cells may sensitize the cells to the cytotoxic effects of ionizing radiation.

1.7.6 Enzyme-Inducing Antiepileptic Drugs and Cediranib

In human studies cediranib, at concentrations comparable with those detected in clinical studies, does not cause significant inhibition CYP isozymes (CYP1A2; CYP2A6; 2C8; 2C9; 2C19; 2E1). No significant drug interactions of cediranib with co-administered agents that affect the hepatic microsomal cytochrome system are expected. However, in the absence of phase I studies of cediranib and enzyme-inducing anti-epileptic drugs we have elected to exclude patients on EIAED from this study.

1.8 Rationale for Correlative Biospecimen Studies

The investigators leading this proposal have extensive pre-clinical and clinical experience in the evaluation of angiogenesis inhibitors in patients with cancer. It has been hypothesized that normalization of tumor endothelium may improve delivery of oxygen and therapeutic agents to the tumor. In patients with newly diagnosed glioblastoma normalization of tumor vasculature could increase oxygen delivery to the tumor and, consequently, enhance the sensitivity of tumor cells to the cytotoxic effects of radiation. Moreover, normalization of tumor vasculature may also improve delivery of the cytotoxic drug, temozolomide, to the tumor. In this study we propose to analyze the tumor tissue obtained at the time of resection prior to treatment with cediranib for gene expression patterns (Mesenchymal versus neuronal), MGMT promoter methylation status, microvascular density (MVD), basement membrane and pericyte coverage, angiopoietin-1 and -2 expression to stratify patients (MGMT) and to determine whether these biological parameters may be predictive of response to therapy with cediranib, temozolomide and radiation.

In this study we also propose to collect blood at serial time points for the assessment of circulating endothelial cells (CECs) and progenitor cells and plasma proteins. Some of the most promising and most studied biomarkers for antiangiogenic therapy are the blood circulating endothelial cells (Bertolini, et al. 2003). In rectal cancer patients it has been demonstrated that bevacizumab decreased tumor microvascular density and the number of viable CECs, consistent with an antivascular effect (Willett, et al. 2004; Willett, et al. 2005). Whether these changes have predictive value for the combined bevacizumab-chemoradiation regimen is currently being investigated in an ongoing phase II trial. In recurrent glioblastoma patients, we found that viable CEC number increased significantly with tumor volume at four time points (days 1, 28, 56 and 112) during cediranib monotherapy. In addition, viable CEC levels (evaluated at eight time points during treatment) were significantly higher in the patients who experienced disease progression during cediranib therapy compared to patients without progression at day 112 (Batchelor, et al. 2007). No such correlation was seen for CPCs. Rather, as mentioned above, a significant rise in CPCs was observed during drug interruptions (Batchelor, et al. 2007). These findings suggested a differential role for CPCs versus viable CECs in the assessment of clinical outcomes. These data also emphasized the critical importance of using multiple viability and cell surface markers to identify these distinct populations and differentiate them from other blood circulating cells, such as non-viable CECs (Mancuso, et al. 2001) (likely shed by the tumor endothelium during therapy) or mature hematopoietic cells (Duda, et al. 2007).

Tumor– or systemic-derived angiogenic factors are readily detectable in plasma and urine by standard and multiplexed ELISA assay. Collaborators on this study are investigating plasma angiogenic proteins in more than a dozen phase I-II oncology trials. So far, it has been observed that the plasma levels of VEGF and PlGF are significantly increased in rectal cancer patients receiving bevacizumab (Willett, et al. 2005). Others have reported similar observations in cancer patients treated with a variety of anti-VEGF receptor TKIs (e.g., vatalanib, sunitinib), and have also observed a decrease in soluble VEGFR2 levels in plasma (Motzer, et al 2006). Collectively, these clinical correlative data strongly suggest a potential “pharmacodynamic biomarker” value for these three plasma markers. Another group reported that baseline sICAM1 levels in plasma predicted response to bevacizumab with chemotherapy in metastatic lung cancer patients (Dowlati, et al. 2006). Of great interest for the field would be to identify biomarkers that predict disease progression

through anti-VEGF therapy. Although in the rectal cancer patients we were unable to identify significant changes in bFGF, our data from the phase II trial of cediranib in recurrent glioblastoma patients showed a significant correlation between bFGF and Tie-2 and tumor progression (Batchelor, et al 2007). These differences may be due to the excellent clinical response in rectal cancer patients, or to disease or agent-specificity.

Expertise with respect to the tissue and blood assays cited above exists at our collaborating institutions and much of the data cited above including the Willett, et al. study and the phase II cediranib study was generated by collaborators on this study proposal.

1.9 ACRIN 6689 Rationale for Imaging of Glioblastomas (8/26/10)

1.9.1 MRI in Neuro-oncology

Structural magnetic resonance imaging (MRI) remains the standard for assessment of glioblastoma and for assessment of treatment response. MRI can provide excellent anatomical detail of brain tumors. Imaging in neuro-oncology can assist in the refinement of pre-operative differential diagnosis, give more precise anatomical localization for operative planning, detect response to treatment and identify tumor progression, and possible treatment-related side effects (Henson, et al., 2005). Advances in MRI techniques have provided better diagnostic and prognostic data information and may act as surrogate biomarkers of physiological and pathological processes. Although MRI can clearly detect the presence of certain cancers once they are macroscopic mass lesions, the specificity of MRI, MR spectroscopy (MRS), or other MR-based techniques need better definition to be incorporated into routine clinical practice. New techniques that allow analysis of the chemical composition of tumor tissue, capillary density, and the diffusion of water have great potential but are not yet well validated. Until these techniques are fully established at multicenter clinical trials to confirm reproducibility, MRI will remain secondary to pathology in the final diagnostic evaluation (Sorensen, 2006).

1.9.2 ACRIN 6689 Advanced MR Imaging: MRS, DSC-MRI, DCE-MRI With Blood Collection

While structural MRI remains the standard for assessment of glioblastoma, MRS has been used extensively to study brain cancer. With its near-spherical shape and relative lack of motion, MRI imaging of the brain confers several technical advantages. Single-center studies have shown that MRS can retrospectively distinguish high-grade gliomas (grade 3/4) from low-grade lesions (grade 1/2) (Fountas, et al., 2004). Other studies have investigated the value of MRS in the diagnosis of pediatric tumors and distinguished primary tumors from metastatic lesions (Tzika, et al., 2002). As a predictor of survival, MRS was also used to compare MRS measures with that of more invasive standard clinicopathological measures to predict length of survival in patients with supratentorial gliomas (Kuznetsov, et al., 2003). Additionally, *in vivo* MRS can be used to monitor disease progression and has showed sufficient spatial resolution and chemical specificity to allow distinction of recurrent tumor from radiation effects in patients with treated gliomas (Rabinov, et al., 2002). MRS can provide chemical information about the microenvironment in and around a tumor, and could identify regression of cancer markers (e.g., choline, lactate, etc.) that might suggest functional changes to the tumor. However, there is not yet a published large multicenter study demonstrating any added benefit of MRS over MRI in diagnosis or monitoring of brain cancer progression.

Radiographic studies of different tumors have shown in vivo angiogenesis as far back as 1939 (Ide, 1939). With the increased tumor blood flow seen in lesions, MRI methods to measure tumor tissue blood flow have been of significant research interest. MRI perfusion imaging of the brain was developed in the late 1980s (Villringer, et al., 1988) on the basis of the first-pass imaging of a gadolinium contrast agent and its resultant magnetic susceptibility effects on T2 and T2* as it passed through the compartmentalized brain vessels with their blood-brain barrier (Sorensen, 2006). Dynamic susceptibility contrast (DSC) demonstrated the ability to measure blood volume in brain tumors and now can provide blood flow as well as blood volume measurements (Ostergaard, Sorensen, et al., 1996, Ostergaard, Weisskoff, et al., 2006). Numerous single center studies have documented the correlation between tumor blood volume and lesion grade in the brain (Aronen, et al., 2000). The full relationship between tumor blood flow and tumor blood volume may be a novel way of evaluating the effect of anti-angiogenic agents in clinical trials.

DCE-MRI is another technique which allows the noninvasive assessment of microcirculatory characteristics of lesions. The DCE-MRI methodology is based on the rapid diffusion of a small contrasting molecule such as a Gd-chelate complex (Knopp, et al., 2003). Correlative work has demonstrated that the signal intensity relates to the vascular density within the lesion and that the rate of enhancement characterizes the vascular fenestration and functional permeability (Knopp, et al., 1994 and Brix, et al., 1999). DCE-MRI was initially used to characterize the microcirculatory properties of a lesion and has been shown to be a robust technique to monitor changes during and after therapeutic interventions. Several studies have used DCE-MRI for monitoring chemotherapy as well as radiation therapy, and more recent applications are monitoring experimental immunogenic or anti-angiogenic therapies. While structural MRI has become a mainstay for patient assessment, it typically provides little physiological information, particularly information about tumor angiogenesis. These advanced MRI applications of MRS, DCE-MRI, and DSC-MRI provide additional information on top of morphology for oncologic applications for the clinical implementation of functional assessment.

This is of prime interest in this trial given the mechanism of action of cediranib. Therefore, a subset of sites will perform baseline advanced imaging, including perfusion magnetic resonance (DSC-MRI and DCE-MRI). Of particular interest is whether baseline tumor angiogenesis levels, as measured by perfusion MRI, correlate with response to anti-angiogenic therapy. Perfusion MRI can provide estimates of cerebral blood volume (CBV), blood flow, and—with certain methods—an estimate of average blood vessel size. Perfusion MRI therefore may be able to identify patient populations particularly likely or unlikely to respond to cediranib treatment. Specifically, high CBV (defined as CBV greater than 1.75 times normal brain CBV) at baseline has been shown to correlate with shorter survival independent of tumor grade (Law, et al., 2008), and degree of CBV has been shown to correlate with response to radiation therapy (Cao, et al., 2006). An imaging biomarker related to CBV would be extremely valuable for patient selection and/or prognosis. Furthermore, there is some evidence that DCE-MRI, as quantified by the parameter K^{trans}, shows early changes after the initiation of anti-VEGF therapy (Batchelor, et al., 2007). Early single-center data suggest the possibility of an early biomarker of response—that early changes in K^{trans} correlate with survival. Further, imaging tools have the potential to provide additional information about the microenvironment in and around the tumor. In evaluating the efficacy of pan-VEGF inhibitors such as cediranib, imaging can provide estimates of blood flow, blood volume, and (with certain methods) average blood vessel. In addition to measuring vasogenic and cytotoxic edema or identifying early changes indicative of cytotoxicity, this study will help identify the different mechanisms of action of cediranib in combination therapy with temozolomide and radiation therapy in treating glioblastomas.

Sorensen et al. reported at-least transient radiographic response to cediranib in 30 of 31 participants and created the “vascular normalization index” by combining advanced imaging findings with circulating biomarkers (Sorensen, et al., 2009). Changes in K^{trans}, microvessel volume, and circulating collagen IV were combined to create a “vascular normalization index” that closely correlated with patient outcome measures—after a single dose of cediranib. These values were found to be significantly predictive of response, as measured by progression-free and overall survival, in patients with recurrent glioblastoma. Blood collection and advanced MRI in this study will continue to assess the relationship between imaging, circulating biomarkers, and the effects of cediranib on progression-free and overall survival; circulating biomarkers will be evaluated with normalization of structure and function of glioblastoma vessels seen on functional MRI.

1.9.3 ACRIN 6689 [^{18}F]FLT-PET in Neuro-oncology

Tumor cellular proliferation can be assessed non-invasively by positron emission tomography (PET). 3'-deoxy-3'-^{18}F fluorothymidine ([^{18}F]FLT) is a structural analog of the DNA constituent, thymidine and has been proposed to investigate cellular proliferation with PET. Although [^{18}F]FLT is not incorporated into DNA, it is trapped in the cell due to phosphorylation by thymidine kinase, a part of the proliferation pathway. As such, it has potential as a marker of proliferating tumor in proportion to the DNA synthesis rate. Therefore, [^{18}F]FLT is proposed as a radiolabeled imaging probe for in vivo assessment of cellular proliferation in malignant tumors using PET. Although [^{18}F]FLT studies are designed to characterize [^{18}F]FLT as a tracer of cellular proliferation in the primary tumor, the comparison of [^{18}F]FLT images with other clinical imaging and with disease progression will provide initial data about [^{18}F]FLT's ability to depict

regional tumor proliferation and distant metastases. Significant correlations between quantitative [^{18}F]FLT uptake and Ki-67 immunohistochemistry have been demonstrated in extracranial tumors. In gliomas, relative [^{18}F]FLT uptake appears greater than [^{18}F]FDG uptake and correlates with Ki-67 cellular proliferation in gliomas. In NCI-sponsored trials, FLT was found to be a safe radiotracer for quantifying proliferation in the human cancer setting (Spence, et al., 2008). Kinetic analysis of [^{18}F]FLT in patients with newly diagnosed high-grade gliomas was used to determine the proliferation rate in vivo (Ulrich, et al., 2008). The potential of [^{18}F]FLT kinetic analysis for the early prediction of clinical outcome and response to therapy remains promising and needs to be further investigated in a larger trial. The evaluation of therapy effectiveness of individual molecular-targeted approaches may benefit from [^{18}F]FLT kinetic analysis and [^{18}F]FLT-PET may be well suited to evaluate brain tumor response to chemotherapeutic agents.

Initial tumor response in patients receiving chemoradiotherapy in brain cancer is generally determined at the completion of therapy. While there is some promising evidence that mid treatment [^{18}F]FDG-PET imaging may be predictive of subsequent tumor response (Pottgen, et al., 2006), the tendency of [^{18}F]FDG to accumulate in inflammatory tissues can complicate the interpretations of mid-therapy images. Preliminary data suggests that early [^{18}F]FLT PET is better able to predict response to therapy, as [^{18}F]FLT uptake has been shown to correlate with cellular proliferation (Leyton, et al., 2005; Chen, et al., 2005; Smycek-Gargya, et al., 2004; Schwartz, et al., 2003), and not uptake significantly in inflammatory tissue (Van Waarde, et al., 2004). The primary objective of this study is to determine which [^{18}F]FLT uptake parameters best correlate with early tumor response to chemoradiotherapy in patients.

Because [^{18}F]FLT is not readily permeable across the blood–brain barrier (BBB), BBB disruption significantly affects the uptake of FLT in the brain and in brain tumors (Muzi, et al., 2005; Jacobs, et al., 2005; Ullrich, et al., 2008). Since the BBB may be damaged by both the tumor and therapy, kinetic analysis of [^{18}F]FLT images is critical for brain tumor imaging to be able to separate the effect of BBB disruption on transport (K1) versus retention on the basis of phosphorylation by thymidine kinase (flux, Ki). Recent data showing that [^{18}F]FLT flux, but not simple measures of uptake such as SUV, correlate with outcome underscores this point. This will be especially critical in the proposed study, given the apparent effects of drugs like cedarinib on BBB transport, as evidenced by contrast-enhanced MRI changes. To be able to perform kinetic analysis, blood sampling is necessary to obtain the [^{18}F]FLT blood clearance function, which serves as the input for kinetic modeling (Spence et al., 2009; Muzi et al., 2006).

1.9.4 Previous Human Studies with [^{18}F]FLT

The pharmacology of FLT is based on its action as an inhibitor of DNA synthesis (Langen, Graetz et al., 1972; Langen, Kowollik et al., 1972). Intracellular metabolism of FLT produces nucleotides that inhibit endogenous DNA polymerases because they lack a 3'-hydroxyl substituent. This results in premature chain termination of DNA synthesis (Mathes, et al., 1988; Mathes, et al, 1987). These biochemical properties can account for FLT's prominent hematological and liver toxicity (Sundseth, et al.,1996; Flexner et al., 1994; Faraj, et al., 1994). The pharmacology of FLT closely parallels that of the widely used prescription HIV-antiviral drug azidothymidine (AZT) (Lundgren, et al.,1991; Kong, et al., 1992). Both FLT and AZT are 3'-deoxythymidine analogs that act as inhibitors of DNA synthesis and are cleared from the body in the same way. However, FLT is significantly more cytotoxic than AZT in test cell lines (Faraj, et al., 1992). Cellular uptake of FLT and thymidine is greater than that of AZT. Transport of FLT and thymidine across cell membranes occurs by active transport and passive diffusion (Kong, et al., 1992).

Several preliminary studies using [^{18}F]FLT imaging in human subjects have been performed in Germany and the United States (UCLA, University of Washington in Seattle, Wayne State University). The imaging protocols were pre-approved by their respective regulatory committees and conducted under the RDRC process or under NCI IND, with patients receiving between 1.4 and 13 mCi of [^{18}F]FLT. The group in Seattle, which has the most experience with this agent in the US, has performed numerous studies in patients with lung cancer as well as a few in patients with primary brain tumors. Their findings demonstrate the feasibility and merit of tumor imaging with [^{18}F]FLT. [^{18}F]FLT PET showed increased uptake in tumor lesions outside the liver

or bone marrow (standardized uptake value [SUV] 4-7), which were delineated from surrounding tissue (SUV 0.5-2).

Previous published manuscripts using [^{18}F]FLT human imaging in the brain studies

Investigator (year)	Year	Organ System	N	mCi injected	MBq Injected	Specific Activity
Spence (2008)	2008	Brain	12 (a)	4.2 – 5.2	154-192	>1.25 Ci/umol
Ullrich (2008)	2008	Brain	13 (b)		111-370 (322±85)	Not reported
Hatakeyama (2008)	2008	Brain	41	3.5 - 6.4	129-236 (161)	Not reported
Chen (2007)	2007	Brain	21 (c)	0.05 mCi/kg	2.0 MBq /kg	Not reported
Schiepers (2007)	2007	Brain	9 (c)	0.04 mCi/kg	1.5 kg	Not reported
Muzi (2006)	2006	Brain	12 (a)	5	185	7.4 GBq/umol
Saga (2006)	2006	Brain	25	10	370	Not reported
Yamamoto (2006)	2006	Brain	10	4	104-202	37-222 GBq/umol
Jacobs (2005)	2005	Brain	23 (c)	8.6	111-370 (321)	Not reported
Chen (2005)	2005	Brain	25	4.7	141-218 (174)	~74 Bq/mmol
Choi (2005)	2005	Brain	26 (c)	10	370	3.2-7.7 Ci/umol

(a) There appears to be an overlap of two patients reported in the Muzi 2006 and Spence 2008 manuscripts.
(b) There appears to be an overlap of two patients reported in the Ullrich 2008 and Jacobs 2005 manuscripts.
(c) The Chen 2005, Chen 2007, and Schiepers manuscripts appear to represent a total of 34 unique patients.

2.0 OBJECTIVES

2.1 Primary

To determine if the addition of cediranib to chemoradiation treatment enhances treatment efficacy as measured by the 6-month progression-free survival rate

2.2 Secondary

2.2.1 To determine if the addition of cediranib to chemoradiation treatment enhances treatment efficacy as measured by overall survival.

2.2.2 To determine if the addition of cediranib to chemoradiation treatment enhances treatment efficacy as measured by progression-free survival.

2.2.3 To determine if there is an association between tumor MGMT gene methylation status and treatment response and outcome.

2.2.4 To compare and record the toxicities of the cediranib + chemoradiation arm versus the chemoradiation arm.

2.2.5 To evaluate whether 6-month progression-free survival is associated with overall survival.

2.3 ACRIN 6689 Advanced Imaging Objectives

2.3.1 Primary

To assess the association between overall survival and change in each of the following markers: K^{trans}, gradient echo CBV, and [^{18}F]FLT Ki and K1, from T0 to T1.

2.3.2 Secondary

2.3.2.1 To assess the association between progression-free survival and change in each of the following markers: K^{trans}, gradient echo CBV, and [^{18}F]FLT Ki and K1 from T0 to T1.

2.3.2.2 To assess the association between overall survival and change in each of the following markers: K^{trans}, gradient echo CBV, and [^{18}F]FLT Ki and K1 from T1 to T3.

2.3.2.3 To assess the association between progression-free survival and change in each of the following markers: K^{trans}, gradient echo CBV, and [^{18}F]FLT Ki and K1, from T1 to T3.

2.3.2.4 To assess the association between overall and progression-free survival and the T0 values of each of the following markers: K^{trans}, gradient echo CBV, and [^{18}F]FLT Ki and K1.

2.3.2.5 To assess the relationship between [^{18}F]FLT Ki and K1 and markers of tumor proliferation, both cross-sectionally and longitudinally.

2.3.2.6 To evaluate the reproducibility of [^{18}F]FLT Ki and K1 measurements.

2.3.2.7 To assess the association between overall and progression-free survival and the change in the "vascular normalization index" between T0 and T1. The vascular normalization index combines serum collagen IV level and K^{trans} (as defined in Sorensen et al., 2009).

3.0 PATIENT SELECTION

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

Imaging-eligible participants at advanced imaging sites must be consented to the ACRIN 6689 advanced imaging component (MRS, DCE-MRI, DSC-MRI, and dynamic [^{18}F]FLT PET with blood sampling) until all 51 participants are accrued.

3.1 Conditions for Patient Eligibility (8/26/10)

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

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

- Patients must have at least 1 block of tumor tissue; submission of 2 blocks is strongly encouraged.
- CUSA (Cavitron ultrasonic aspirator)-derived material is not allowed; fresh frozen tumor tissue acquisition is encouraged.
- Diagnosis must be made by surgical excision, either partial or complete; stereotactic biopsy is not allowed because it will not provide sufficient tissue for MGMT analysis.
- The tumor tissue must be sent as soon as possible to maximize the likelihood of eligibility. Tumor tissue **may not be submitted later than 28 days after the surgical procedure**, because tissue analysis will not be able to be performed in time for treatment to commence by the mandatory 6-week post-surgery outer limit as stipulated in Sections 6 and 7. **Submission of tissue earlier than 28 days post-surgery is highly recommended.**

3.1.3 The tumor must have a supratentorial component.

3.1.4 History/physical examination, including neurologic examination with MMSE, within 14 days prior to registration;

3.1.5 The patient must have recovered from the effects of surgery, post-operative infection, and other complications before study registration.

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

3.1.7 Documentation of steroid doses/concurrent medications within 14 days prior to registration.

3.1.8 Karnofsky performance status ≥ 70 within 14 days prior to registration;

3.1.9 Age ≥ 18;

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

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

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

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

3.1.11 Adequate renal function, as defined below:

3.1.11.1 BUN ≤ 30 mg/dl within 14 days prior to study registration.

3.1.11.2 Creatinine ≤ 1.7 mg/dl within 14 days prior to study registration.

3.1.11.3 Urine protein screened by urine analysis for urine protein creatinine (UPC) ratio within 14 days prior to registration. For UPC ratio > 0.5, 24-hour urine protein should be obtained and the level should be < 1000 mg.

3.1.12 Adequate hepatic function, as defined below:
3.1.12.1 Bilirubin ≤ 2.0 mg/dl within 14 days prior to study registration
3.1.12.2 ALT/AST ≤ 3 x normal range within 14 days prior to study registration
3.1.13 Systolic blood pressure ≤ 150 mm Hg or diastolic pressure ≤ 90 mm Hg within 14 days prior to study registration in the presence or absence of a stable regimen of anti-hypertensive therapy.
3.1.14 Prothrombin time/international normalized ratio (PT INR) < 1.4 for patients not on warfarin confirmed by testing within 1 week of registration.
3.1.14.1 Patients on full-dose anticoagulants (e.g., warfarin or LMW heparin) must meet both of the following criteria:
- No active bleeding or pathological condition that carries a high risk of bleeding (e.g., tumor involving major vessels or known varices)
- In-range INR (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 Patient must provide study specific informed consent prior to study entry.
3.1.16 Women of childbearing potential and male participants must practice adequate contraception.
3.1.17 For females of child-bearing potential, negative serum pregnancy test within 14 days prior to registration.

3.2 Conditions for Patient Ineligibility

3.2.1 Prior invasive malignancy (except for non-melanomatous skin cancer) unless disease free for ≥ 3 years. (For example, carcinoma in situ of the breast, oral cavity, and cervix are all permissible).
3.2.2 Recurrent or multifocal malignant gliomas
3.2.3 Metastases detected below the tentorium or beyond the cranial vault.
3.2.4 Prior chemotherapy or radiosensitizers for cancers of the head and neck region; note that prior chemotherapy for a different cancer is allowable (except temozolomide or cediranib). Prior use of Gliadel wafers or any other intratumoral or intracavitary treatment are not permitted. See Section 3.2.1.
3.2.5 Prior radiotherapy to the head or neck (except for T1 glottic cancer), resulting in overlap of radiation fields.
3.2.6 Severe, active co-morbidity, defined as follows:
3.2.6.1 Unstable angina and/or congestive heart failure requiring hospitalization
3.2.6.2 Transmural myocardial infarction within the last 6 months
3.2.6.3 Evidence of recent myocardial infarction or ischemia by the findings of S-T elevations of ≥ 2 mm using the analysis of an EKG performed within 14 days of registration
3.2.6.4 New York Heart Association grade II or greater congestive heart failure requiring hospitalization within 12 months prior to registration
3.2.6.5 History of stroke, cerebral vascular accident (CVA) or transient ischemic attack within 6 months
3.2.6.6 Serious and inadequately controlled cardiac arrhythmia
3.2.6.7 Significant vascular disease (e.g., aortic aneurysm, history of aortic dissection) or clinically significant peripheral vascular disease
3.2.6.8 Evidence of bleeding diathesis or coagulopathy
3.2.6.9 Serious or non-healing wound, ulcer, or bone fracture or history of abdominal fistula, gastrointestinal perforation, intra-abdominal abscess major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to registration, with the exception of the craniotomy for tumor resection.
3.2.6.10 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration.
3.2.6.11 Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration
3.2.6.12 Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for liver function and coagulation parameters are not required for entry into this protocol.
3.2.6.13 Acquired immune deficiency syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive.
3.2.6.14 Active connective tissue disorders, such as lupus or scleroderma, which in the opinion of the treating physician may put the patient at high risk for radiation toxicity.

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

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

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

3.2.9 Prior allergic reaction to temozolomide.

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

3.2.11 History of allergic reactions attributed to compounds of similar chemical or biologic composition to cediranib

3.2.12 Mean QT_c >500 msec (with Bazett's correction) in screening electrocardiogram or history of familial long QT syndrome or other significant ECG abnormality noted within 14 days of treatment

3.2.13 Patients receiving concurrent VEGF inhibitors are prohibited from participating in this study

3.2.14 Patients must not be on enzyme-inducing anti-epileptic drugs (EIAED). Patients may be on non-enzyme inducing anti-epileptic drugs (NEIAED) or may not be taking any anti-epileptic drugs. In patients who have previously been on EIAED there must be at least a 14 day period since the last dose of an EIAED before the first dose of cediranib. See Appendix VI for a list of acceptable AEDs that cause modest or no induction of hepatic metabolic enzymes.

3.2.15 **For ACRIN 6689 Advanced Imaging**

3.2.15.1 Inability to undergo MRI or PET (e.g., due to safety reasons, such as presence of a pacemaker, or weight limitations of the machines).

3.2.15.2 Any history of allergic reactions attributed to compounds of similar chemical or biological composition to gadolinium or [^{18}F]FLT contrast agents.

3.2.15.3 Inability to tolerate two (2) intravenous (IV) lines, one (1) in each arm.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

4.1 Required Evaluations/Management

Note that failure to perform one or more of these tests may result in assessment of a protocol violation.

4.1.1 ECHO/MUGA: Patients at increased risk of compromised left ventricular ejection function (LVEF) must have an ECHO/MUGA done at screening to help identify compromised LVEF should it occur.

4.1.2 EKG: Within 14 days prior to registration

4.1.3 Serum Chemistry: Complete metabolic panel, magnesium, LDH, phosphorous within 14 days prior to registration

4.1.4 Troponin T or I: Within 14 days prior to registration

4.1.5 TSH, Free T4: Within 14 days prior to registration

5.0 REGISTRATION PROCEDURES

5.1 Pre-Registration Requirements (8/26/10)

5.1.1 Regulatory Pre-Registration Requirements

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

- IRB/REB approval letter;
- IRB/REB approved consent (English Version)
  ***Note**: Institutions must provide certification of consent translation to RTOG Headquarters
- IRB/REB assurance number

5.1.1.2 *Pre-Registration Requirements FOR CANADIAN INSTITUTIONS*

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

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

NOT APPLICABLE: This study is not open to Non-Canadian International Institutions.

5.1.2 Pre-Registration Requirements for IMRT Treatment Approach

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

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

5.1.2.2 The institution or investigator must complete a new IMRT Facility Questionnaire and send it to RTOG for review prior to entering any cases, and/or set up an SFTP account for digital data submission, both of which are available on the Image-Guided Center (ITC) web site at http://atc.wustl.edu.

Upon review and successful completion of the "Dry-Run" QA test, the ITC will notify both the registering institution and RTOG Headquarters that the institution has successfully completed this requirement. RTOG Headquarters will notify the institution when all requirements have been met and the institution is eligible to enter patients onto this study.

5.1.3 Pre-Registration Requirements for 3DCRT Treatment Approach

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

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

5.1.4 ACRIN 6689 Pre-Registration Requirements for Advanced MRI and Dynamic [^{18}F]FLT PET Certification (for sites participating in the advanced imaging component only)

Each institution must complete an American College of Radiology Imaging Network (ACRIN) 6689 Protocol Specific Application (PSA). The PSA will request each center to identify a radiologist with advanced neuro-MRI and PET experience to oversee implementation of the advanced MRI and PET components of the protocol. In addition, the PSA will also request information on the staff and equipment that will be used to acquire image data for the protocol.

Each advanced-imaging site must be pre-qualified for the trial by demonstrating the ability to perform and electronically transfer MRI and PET scans per protocol specifications. Sites must be capable of performing dynamic [^{18}F]FLT PET imaging and blood sampling. Centers already qualified for RTOG 0625/ACRIN 6677 or RTOG 0825/ACRIN 6686 do not need to re-qualify their MR scanners to participate in this study. The central repository for all study images (advanced MRI and PET) is located at ACRIN Core Laboratory in Philadelphia, PA. The qualification process includes submission and approval of at least one (1) imaging examination performed according to the protocol parameters for advanced MR and PET imaging, referenced in Appendices IX and X. Qualification instructions and detailed technical acquisition parameters are available on the ACRIN web site at http://www.acrin.org/6689_imagingmaterials.aspx.

Payment for participation in the imaging component of the trial is automatic, based upon complete submission of the key data forms, and confirmation of the quality of images submitted to ACRIN.

The ACRIN 6689 PSA is available on the ACRIN web site at http://www.acrin.org/6689_protocol.aspx.

5.2 Summary of Patient Registration Procedures

Once the patient has been determined to meet pre-registration pathology requirements, this study incorporates a 2-step registration process.

Step 1 of registration entails an initial registration as detailed in Sections 5.1 and 5.3.

- The site will register the patient and will then submit tissue to Dr. Aldape (see Section 10). A pathology screening form (P4), pathology materials, and pathology report must be submitted to Dr. Aldape per Section 10.
- Dr. Aldape will evaluate the tissue to confirm that the histology is GBM and that there is adequate tissue to perform MGMT analysis.
- Dr. Aldape will initiate the processes for tissue analysis for MGMT analysis and send tissue to Oncomethylome.
- RTOG HQ will notify institutions once the MGMT test results have been received and the randomization process can be done.
- See Section 5.3 for online registration procedures.

Step 2 will consist of randomization.

- A unique patient ID (e.g., 0837-999) will be assigned along with a new data submission calendar.
- Should the patient experience significant toxicity from pre-randomization treatment and not proceed to be randomized, step 2 of registration must still be completed.
- See Section 5.3 for online registration procedures.
- **NOTE: No blinded starter supplies will be available for this study.** Initial blinded, patient-specific clinical supplies of cediranib/placebo will be shipped from the Pharmaceutical Management Branch (PMB) to the registering investigator at the time of patient randomization and should arrive within 7 to 10 days of randomization (see Section 7.3).

5.3 Registration

Patients can be registered only after eligibility criteria are met.

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

- The investigator and research staff must have completed Human Subjects Training and been issued a certificate (Training is available via http://phrp.nihtraining.com/users/login.php).
- A representative from the institution must complete the Password Authorization Form at www.rtog.org/members/webreg.html (bottom right corner of the screen), and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

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

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient’s record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study’s database at the DMC (Data Management

Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

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

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

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/FUNCTIONAL IMAGING (8/26/10)

Note: Intensity Modulated RT (IMRT) Is Allowed

The same treatment modality must be used for the entire course of treatment.

Treatment must begin > 3 weeks and ≤ 6 weeks after craniotomy.

6.1 Dose Specifications and Schedule

For both IMRT and 3D conformal therapy (3DCRT) plans, one treatment of 2.0 Gy will be given daily 5 days per week for a total of 60.0 Gy over 6 weeks. All portals shall be treated during each treatment session. Doses are specified such that at least 95% of the PTV shall receive 100% of the prescribed dose; DVHs are necessary to make this selection.

6.2 Technical Factors

Treatment shall be delivered with megavoltage machines of a minimum energy of 6MV or greater. Selection of the appropriate photon energy (ies) should be based on optimizing the radiation dose distribution within the target volume and minimizing dose to non-target normal tissue. 100 cm SAD is required. Electron, particle, or implant boost is not permissible. IMRT delivery will require megavoltage radiation therapy machines of energy ≥ 6 MV.

6.3 Localization, Simulation, and Immobilization

The patient shall be treated in the supine or other appropriate position for the location of the lesion. A head-holding device to ensure adequate immobilization during therapy and ensure reproducibility is strongly recommended. Simulation must be either CT or MR-based. Fusion with MR images is required for the planning process.

For patients accrued to the protocol, treatment verification and documentation should be carried out, at least for the first treatment fraction, and more frequently, based on institutional policy; weekly verification is common. We suggest orthogonal images for documenting isocenter setup accuracy for the first fraction. These orthogonal images can be obtained with film or EPID. Other imaging techniques are possible, for example, the BrainLab ExacTrac system that uses two orthogonal imaging panels irradiated with KV x-rays. Another example is the volume images obtained with cone-beam CT, or helical Tomotherapy or any other CT capability that is integrated with the treatment unit.

6.4 Treatment Planning/Target Volumes

Treatment plans may include opposed lateral fields, a wedge pair of fields, rotation, or multiple field techniques. Intensity-modulated inverse-planned approaches are permitted. Any of the methods of IMRT may be used, subject to protocol localization and dosimetry constraints. Institutions previously credentialed for the use of IMRT and intending to use volume arc dose delivery will be asked to re-credential with this technology. CT-based treatment planning is necessary to assure

accuracy in the selection of field arrangements. MRI-fusion for accurate target delineation is required.

6.4.1 Initial Target Volume

Target volumes will be based upon postoperative-enhanced MRI. Preoperative imaging should be used for correlation and improved identification. Two planning target volumes (PTV) will be defined, as outlined below. The initial gross tumor volume (GTV1) will be defined by either the T2 or the FLAIR abnormality on the post-operative MRI scan. This must also include all postoperative-enhanced MRI enhancement, and the surgical cavity. The initial clinical target volume (CTV1) will be the GTV plus a margin of 2.0 cm. If no surrounding edema is present, the initial planning target volume (PTV1) should include the contrast-enhancing lesion (and should include the surgical resection cavity) plus a 2.5-cm margin (an additional margin of 3.0 to 5.0 mm should be added, depending upon localization method and reproducibility, at each center) The two PTV margins represent inter-fraction and intra-fraction setup uncertainties respectively. The CTV1 margin may be reduced to 0.5 cm around natural barriers to tumor growth such as the skull, ventricles, falx, etc, and also to allow sparing of the optic nerve/chiasm, if necessary. Reducing PTV margins to modify organ at risk (OAR) dose(s) is not generally permissible. However, OAR must be defined (see Section 6.5), along with a planning risk volume (PRV) for each OAR. Each PRV will be its OAR plus 3.0 mm. In the event that an OAR is in immediate proximity to a PTV such that dose to the OAR cannot be constrained within protocol limits, a second PTV ($PTV_{overlap}$), defined as the overlap between the PTV1 and the particular PRV of concern, may be created. Dose to the $PTV_{overlap}$ must be as close as permissible to 46 Gy while not exceeding the OAR dose limit.

6.4.2 Boost Target Volume

The boost gross tumor volume (GTV2) will be defined by the contrast-enhanced T1 abnormality on the post-operative MRI scan. This must also include the surgical cavity margins. The boost clinical target volume (CTV2) will be the GTV plus a margin of 2.0 cm. The CTV2 margin may be reduced to 0.5 cm around natural barriers to tumor growth such as the skull, ventricles, falx, etc, and also to allow sparing of the optic nerve/chiasm, if necessary. The boost planning target volume (PTV2) may include an additional margin of 3.0 to 5.0 mm, depending upon localization method and reproducibility, at each center. PTV margins account for variations in set-up and reproducibility. Reducing PTV margins to modify organ at risk (OAR) dose(s) is not generally permissible. However, OAR must be defined, along with a planning risk volume (PRV) for each OAR. Each PRV will be its OAR plus 3.0 mm. In the event that an OAR is in immediate proximity to a PTV such that dose to the OAR cannot be constrained within protocol limits, a second PTV ($PTV_{overlap}$), defined as the overlap between the PTV2 and the particular PRV of concern, may be created. Dose to the $PTV_{overlap}$ must be as close as permissible to 14 Gy while not exceeding the OAR dose limit.

6.4.3 Dose Guidelines

The same treatment modality must be used for the entire course of treatment.

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

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

The minimum acceptable dose within PTV1 will be 43 Gy, and in the PTV2 volume, it will be 57 Gy. Doses are specified such that at least 95% of the PTV shall receive 100% of the prescribed dose; DVHs are necessary to make this selection.

6.5 Dose Limitation to Critical Structures

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

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

6.6 Documentation Requirements

At completion of treatment, the following should be forwarded to RTOG Headquarters: daily treatment record, and the radiotherapy summary per Section 12.2.

6.7 Compliance Criteria

6.7.1 For all patients, as mentioned above, two PTV prescriptions, PTV1 and PTV2 will be used and the prescription isodose (46 Gy for PTV1 and 14 Gy for PTV2) must cover >95% of the PTV volume; therefore, the total dose in the PTV2 volume will be 60 Gy. The minimum acceptable dose within PTV1 will be 43 Gy, and in the PTV2 volume, it will be 57 Gy . If the minimum dose falls below 43 Gy, but remains at or above 42 Gy for PTV1, and below 57 Gy, but above 55 Gy for PTV2, an acceptable variation will be assigned. If the minimum dose falls below these parameters, an unacceptable deviation will be assigned. The maximum dose for the PTV1 should not exceed 51 Gy for any volume that is greater than 0.03 cc, and similarly, for PTV2, the maximum dose should not exceed 66 Gy. If the maximum dose for PTV1 exceeds 51 Gy but does not exceed 53 Gy, an acceptable variation will be assigned. If the maximum dose for PTV2 exceeds 66 Gy but does not exceed 68 Gy, an acceptable variation will be assigned. If the maximum doses exceed these parameters, an unacceptable deviation will be assigned.

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

6.8 R.T. Quality Assurance Reviews

The Radiation Oncology Co-Chair, Arnab Chakravarti, MD, along with other assigned radiation oncologists, will perform an RT Quality Assurance Review. These reviews will be ongoing. The final cases will be reviewed within 6 months after the study has reached the target accrual.

6.9 Radiation Therapy Adverse Events

6.9.1 Acute

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

6.9.2 Early Delayed

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

6.9.3 Late Delayed

Possible late delayed effects of radiotherapy include radiation necrosis, endocrine dysfunction, and radiation-induced neoplasms. In addition, neurocognitive deficits, which could lead to mental slowing and behavioral change, are possible. Permanent hearing impairment and visual damage are rare. Cataracts can be encountered.

6.10 Radiation Therapy Adverse Event Reporting

See Section 7.8 and 7.9.

6.11 ACRIN 6689 Advanced Imaging of Glioblastomas and Timeline (8/26/10)

6.11.1 Advanced imaging study participants will consent to undergo **MRS, DSC-MRI, and DCE-MRI, with blood collection prior to imaging, at seven (7) time points:**

- T0: Baseline (within 7 days prior to initiation of chemoradiation)
- T1: Between doses (within 2 to 24 hours after the first dose of placebo or cediranib, but prior to the second dose of placebo or cediranib/radiation/TMZ);
- T2: Week 4 of chemoradiation;
- T3: Week 10 (Week 4 after completion of chemoradiation);
- T4: Week 16 (Week 10 after completion of chemoradiation);
- T5: Week 24 (Week 18 after completion of chemoradiation); and
- T6: Progression (whenever disease progression occurs; progression is defined as > 25% increase in tumor area [two diameters]).

6.11.2 All 51 consenting advanced-imaging study participants will undergo dynamic **[^{18}F]FLT PET with blood sampling at three (3) time points**; a subset of 25 participants consenting to advanced imaging will undergo **a fourth dynamic [^{18}F]FLT PET (Baseline #2) with blood sampling (the first 5 participants accrued at each site will undergo this scan until 25 scans are completed):**

- T0: Baseline #1 (within 7 days prior to initiation of chemoradiation);
- T0.1: Baseline #2 (prior to initiation of chemoradiation); must be completed within 7 days of the T0 scan, but can occur before or after the T0 MRI scan.
- T1: Between doses (within 2 to 24 hours after the first dose of placebo or cediranib, but prior to the second dose of placebo or cediranib/radiation/TMZ); and
- T3: Week 10 (Week 4 after completion of chemoradiation).

NOTE: "PET" may refer to PET, PET/CT, or MR-PET depending on the site.

6.11.3 Because of the expense and challenge of performing such studies, only 51 of the 177 participants will undergo advanced imaging. Sites will be limited to those who pre-qualify their MR and PET imaging techniques through ACRIN for quality. **Once a site is qualified, the advanced imaging series will be completed for all imaging-eligible participants at qualified sites until 51 patients are accrued.** Until 25 participants total have completed double-baseline dynamic PET imaging (Baseline #1 and Baseline #2), the first 5 participants enrolled for the advanced imaging at each of the 5 advanced imaging sites will undergo the second baseline dynamic [^{18}F]FLT PET (prior to initiation of chemoradiation). Once 51 participants consent and are enrolled to the advanced imaging component of the trial, advanced-imaging sites may consent remaining participants to standard imaging only until all 177 participants are enrolled.

6.12 ACRIN 6689 Investigational Imaging Agent Information—Advanced imaging ([^{18}F]FLT for Dynamic PET Scans)

6.12.1 Agent Description: [^{18}F]FLT (NSC 743144, IND 71260)

(FLT is being supplied according to the National Cancer Institute [NCI] Investigational New Drug [IND] application. Please refer to the Investigator Brochure for comprehensive information.)

3'-deoxy-3'-[^{18}F]fluorothymidine: [^{18}F]FLT (MW 243) is a structural analog of the DNA constituent, thymidine (Figure 1). It is a radiolabeled imaging agent that has been proposed for investigating cellular proliferation with positron emission tomography (PET). Since FLT is not incorporated into DNA, due to phosphorylation by thymidine kinase, (a part of the proliferation pathway) FLT-monophosphate (FLT-MP) is trapped in the cell. As such, it has the potential to image proliferating tumor in proportion to the DNA synthesis rate. Pilot clinical studies and nonclinical studies in animals suggest that FLT may have desirable properties as an imaging probe for quantifying cellular proliferation with PET. Therefore, FLT is proposed as a radiolabeled imaging probe for quantifying cellular proliferation in malignant tumors with PET.

6.12.2 Chemical Structure

[^{18}F]FLT has not been marketed in the United States and, to the best of our knowledge; there has been no marketing experience with this drug in other countries. The radiopharmaceutical product, [^{18}F]FLT is the only active ingredient and it is dissolved in a solution of ≤ 10 mL of 92% 0.01 M phosphate buffered saline (PBS): 8% ethanol (v:v). The drug solution is stored at room temperature in a gray butyl septum sealed, sterile, pyrogen-free glass vial with an expiration time of 8 hours. The injectable dose of [^{18}F]FLT for most studies will be approximately 175 MBq (5 mCi) at the time of

injection. In the dose of [^{18}F]FLT only a small fraction of the FLT molecules are radioactive. The amount of injected drug is ≤ 0.61 µg/mL (≤ 2.5 nmol/mL) of FLT. [^{18}F]FLT is administered to subjects by intravenous injection of ≤ 10 mL. There is no evidence that nonradioactive and radioactive FLT molecules display different biochemical behavior.

Figure from the investigator's brochure (dated 7-24-08)

6.12.3 Final Product Specifications

The drug is composed of a small amount of [^{18}F]FLT that is labeled with radioactive ^{18}F at the 3'-position on the sugar ring with a specific activity ranging < 200 Ci/mmol at the time of injection. The radiopharmaceutical product, [^{18}F]FLT is the only active ingredient and it is dissolved in a solution of ≤ 10 mL of 92% 0.01 M phosphate buffered saline (PBS): 8% ethanol (v:v). [^{18}F]FLT is administered to subjects by intravenous injection (≤ 10 mL). Doses are calculated based on subject weight (0.07) mCi/Kg) and radioactivity content (upper limit of 5.0 mCi).

6.12.4 Pharmacological and Physical Characteristics

The pharmacology of FLT is based on its action as an inhibitor of DNA synthesis (Langen, et al.,1969; Langen, et al., 1972; Matthes, et al., 1988). Intracellular metabolism of FLT produces nucleotides that inhibit endogenous DNA polymerases because they lack a 3'-hydroxyl substituent. This results in premature chain termination of DNA synthesis (Matthes, et al., 1987; Sundseth, et al., 1996). These biochemical properties can account for FLT's prominent hematological and liver toxicity in treatment studies. The proposed PET tracer studies using approximately 6 µg single dose [^{18}F]FLT are significantly lower than the oral 0.125 mg/kg or 2 mg/day multi dose used in the human studies (Flexner, et al., 1994; Faraj, et al., 1994; Sundseth, et al., 1996; Katlama, et al., 2004).The pharmacology of FLT closely parallels that of the widely used prescription HIV-antiviral drug azidothymidine (AZT) (Lundgren, et al., 1991; Kong, et al., 1992). Both FLT and AZT are 3'-deoxythymidine analogs that act as inhibitors of DNA synthesis and are cleared from the body in the same way. However, FLT is significantly more cytotoxic than AZT in test cell lines (Faraj, et al., 1994). Cellular uptake of FLT and thymidine is greater than that of AZT. Transport of FLT and thymidine across cell membranes occurs by active transport and passive diffusion (Kong, et al., 1992).

6.12.5 Mechanism of Action

The pharmacologic mechanism of FLT closely parallels that of the widely used prescription HIV-antiviral drug AZT (Lundgren, et al., 1991; Kong, et al., 1992). Both FLT and AZT are 3'-deoxythymidine analogs that act as inhibitors of DNA synthesis and are cleared from the body in the same way. However, FLT is significantly more cytotoxic than AZT in test cell lines (Faraj, et al., 1994). Cellular uptake of FLT and thymidine is greater than that of AZT. Transport of FLT and thymidine across cell membranes occurs by active transport and passive diffusion (Kong, et al.,1992).

6.12.6 Toxicity of FLT in Humans

FLT was investigated as an anti-AIDS drug in humans (Flexner, et al., 1994). Toxic effects and death were reported for some subjects who received FLT during randomized concentration-controlled trials during a 16-week treatment of oral multi-dosing. Doses of 0.125 mg/Kg every 12h produced a mean cumulated drug exposure (AUC12: area under curve) of 417 ng-h/mL. At this level, serious (grade 3) hematologic toxicity occurred in 6 of 10 subjects. At 300 ng-h/mL, grade 2 or greater (fall in hemoglobin to < 9.4 g/dL) developed within 4 weeks in 9 of 12 subjects. At 200 ng-h/mL almost no clinically significant anemia developed, but dose-limiting granulocytopenia (< 750 granulocytes/mm3) occurred in 5 of 15 subjects. Mild peripheral neuropathy occurred in 2 of

10 subjects at 50 ng-h/mL, but was not dose-limiting. FLT drug trials were terminated after the unexpected death of 2 subjects of hepatic failure. One patient assigned to 200 ng-h/mL developed progressive liver failure and died after 12 weeks of FLT therapy. A second subject, who received a fixed dose of 10 mg/day, developed progressive liver failure and died at about the same time. All surviving subjects were followed closely for 4 weeks after stopping FLT and none had evidence of clinically significant liver disease or other adverse effects. Overall, 25 of the 44 subjects receiving at least two doses of FLT completed the 16 week study without clinically significant adverse effects.

FLT (Alovudine) was withdrawn from development for several years, and then reinvestigated for multi-drug resistant HIV infection. Fifteen patients with multi-drug resistance HIV received 7.5 mg each day for 28 days along with their ongoing therapy (Katlama, et al.,2004). No serious adverse events were observed. In a randomized, double-blind, placebo-controlled study by the same group, 51 patients received 0.5 mg, 1.0 mg, or 2.0 mg daily for 28 days in addition to their routine therapy; 21 patients received placebo (Ghosn, et al., 2008). No unexpected adverse events were observed, and no serious AEs were attributed to the study drug.

No adverse events have been reported for [^{18}F]FLT at the strength to be used for this study. Non-radioactive FLT has been investigated as an anti-AIDS drug, and reversible peripheral neuropathy was observed in subjects exposed to 50 ng-h/mL plasma over a course of 16 weeks (15µg/kg q12h). The FLT dose anticipated for this study will be <6.1µg for a single injection. Assuming a 70kg individual, the maximum concentration of FLT would be expected to be equivalent to 0.29 ng-h/mL. The radiation exposure associated with this study is comparable to the dose for other widely used clinical nuclear medicine procedures.

In a 2007 study performed at the University of Washington, Turcotte et al assessed the toxicity of [^{18}F]FLT in 20 patients with proven or suspected diagnosis of non-small cell lung cancer. Blood samples from multiple time points before and after [^{18}F]FLT PET were assayed for comprehensive metabolic panel, total bilirubin, complete blood and platelet counts. A standard neurological examination was also performed by a qualified physician for each patient before and immediately after [^{18}F]FLT PET. No side effects were reported by patients or witnessed. No change in the neurological status of patients was observed.

The group in Seattle also recently published the results from safety studies performed in patients with recurrent glioma (Spence, et al., 2008). Twelve patients were injected with 0.07 mCi/kg (5mCi maximum) of [^{18}F]FLT (specific activity 1.25 Ci/umol) and were closely monitored for three hours afterward. Additional follow-up was performed at 1 day post- and 1 month post-injection. Their findings showed no evidence of toxicity at this dose. Monitoring of vital signs and ECG, review of systems, neurological assessments, and laboratory evaluations revealed no evidence of adverse effects. Notably, no signs or symptoms of peripheral neuropathy were observed in any patient at any time.

6.12.7 Dosimetry

The dose of FLT to be administered in this imaging trial is 1400-fold lower than the dose that led to serious toxicity in the studies described above. A summary of the relevant human dosimetry for 2 different voiding scenarios from the investigator's brochure is included in the table below. For more details, the reader is referred to the investigator's brochure.

Human dosimetry estimates

Organ of Interest	Men (mrad/mCi)	mGy/MBq	Women (mrad/mCi)	mGy/MBq
Total Body Dose	Scenario 1 (46)	1.23E-02	Scenario 1 (58)	1.56E-02
	Scenario 2 (47)	1.26 E-02	Scenario 2 (59)	1.59 E-02
Bladder	Scenario 1 (662)	1.79E-01	Scenario 1 (646)	1.74E-01
	Scenario 2 (293)	7.91E-02	Scenario 2 (287)	7.76E-02
Liver	Scenario 1 (167)	4.51E-02	Scenario 1 (238)	6.42E-02
	Scenario 2 (168)	4.54 E-02	Scenario 2 (239)	6.45 E-02

Scenario 1: Single bladder voiding at 6 h after [^{18}F]FLT administration with a 10% post-voiding bladder residual decayed to infinity. This scenario assumed no urine reaccumulation after 6 h.

Scenario 2: First bladder voiding at 2 h after [^{18}F]FLT administration with a 10% post-voiding residual; urine reaccumulation between 2 and 6 h at a rate determined by the bladder curve fit; second bladder voiding at 6 h with a 10% post-voiding residual decayed to infinity. This scenario assumed no urine reaccumulation after 6 h. The first scenario is conservative, whereas the second has a more realistic voiding scheme.

6.12.8 Previous Human [^{18}F]FLT Imaging Studies

Several preliminary studies using [^{18}F]FLT imaging in human subjects have been performed in Germany and the United States (UCLA, University of Washington in Seattle, Wayne State University). The imaging protocols were pre-approved by their respective regulatory committees and conducted under the RDRC process or under NCI IND, with patients receiving between 1.4 and 13 mCi of [^{18}F]FLT. The group in Seattle, which has the most experience with this agent in the US, has performed numerous studies in patients with lung cancer as well as a few in patients with primary brain tumors. Their findings demonstrate the feasibility and merit of tumor imaging with [^{18}F]FLT. [^{18}F]FLT PET showed increased uptake in tumor lesions outside the liver or bone marrow (standardized uptake value [SUV] 4–7), which were delineated from surrounding tissue (SUV 0.5–2). The Investigator's Brochure contains a full summary of published manuscripts reporting [^{18}F]FLT human imaging studies.

6.12.9 [^{18}F]FLT Administered Dose

The administered dose will be 0.07 mCi/kg with a maximum of 5 mCi. The drug solution is stored at room temperature in a gray butyl septum sealed, sterile, pyrogen-free glass vial and is labeled with its expiration time. In the dose of [^{18}F]FLT, only a small fraction of the FLT molecules are radioactive. The amount of injected drug is ≤ 6.1 µg (≤ 25 nmol per dose) of FLT. [^{18}F]FLT is administered to subjects by intravenous injection of ≤ 10 mL. There is no evidence that nonradioactive and radioactive FLT molecules display different biochemical behavior.

6.12.10 Quality Assurance, Quality Control, and Storage

FLT is being supplied according to the NCI IND application. In accordance with regulations, the radioisotope vendor conducts several quality control tests on the [^{18}F]FLT product prior to release for human administration. Once delivered to the participating institution, doses will be stored in the appropriate storage area in the nuclear medicine facility until they are administered to the patient.

6.12.10.1 *Drug Ordering*

[^{18}F] FLT will be purchased from a commercial vendor of radioisotopes in most cases. The vendor must be authorized within the NCI IND. The investigator or the investigator-designee will order patient doses of [^{18}F]FLT. The investigative radiopharmaceutical [^{18}F]FLT solution will be shipped to the site the same day the participant is to be injected.

The investigational pharmacist or qualified nuclear medicine technologist at the participating institution will be the responsible party designated by the investigator.

[^{18}F]FLT can only be synthesized on site if the chemistry manufacturing and control procedures are filed within the NCI IND.

6.12.10.2 *Drug Returns*

If for any reason the study imaging is unable to be completed, sites will allow the radioactivity of the [^{18}F]FLT solution to decay and then discard it appropriately per site's policies and procedures. A copy of the policy should be available upon request.

6.12.10.3 *Drug Accountability*

The investigator or the investigator-designee must maintain a detailed record of receipt, disposition, and destruction dates of [^{18}F]FLT solution, using the Drug Accountability Record form available on the ACRIN web site (www.acrin.org/6689_protocol.aspx) or by calling the ACRIN 6689 project manager.

7.0 DRUG THERAPY (8/26/10)

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

Treatment must begin > 3 weeks and ≤ 6 weeks after craniotomy for glioblastoma resection.

7.1 Code Breaks (2/26/10)

The decision to break the code (unblind) must be based on a life-threatening event or extraordinary clinical circumstance for which knowledge of drug assignment will affect clinical judgment. The code will not be broken solely for disease progression. Unblinding can also be performed for emergency situations (such as accidental ingestion by others) for patients receiving doses to use at home.

The RTOG SOP for emergency study arm unbinding addresses the procedure by which a double-blinded treatment code for a patient participating on an RTOG study is broken in the event an emergency treatment decision needs to be made with the knowledge of drug assignment. This SOP will be followed to break the code for this study, and the procedure described therein is as follows:

During business hours (8:30 AM to 5 PM ET), call RTOG Headquarters at 215-574-3150 and ask to speak to the Study Supporting Statistician. For after hours, weekends, and holidays, call 215-459-3576 and speak to the Unblinding Officer of the RTOG Regulatory Compliance Department. The Study Supporting Statistician or Unblinding Officer determines if the above unblinding criteria have been met. If the unblinding criteria have been met, the requester's information on the Request for Unblinding Form will be documented and the treatment information will be given to the requester. If a consensus can not be reached between the requesting physician and the Statistician/RTOG Unblinding Officer as to whether the situation warrants unblinding, the Group Chair or his designee will be contacted to make the final determination.

7.2 Treatment (8/26/10)

7.2.1 Dose Definition

Treatment will be administered on an outpatient basis. Based on data from prior studies of cediranib in combination with chemotherapy the best tolerated dose of cediranib in combination with temozolomide + radiation and with post-radiation temozolomide will be 20mg/day.

Cediranib or placebo will begin 3-6 weeks after craniotomy and 3 days before the radiation and temozolomide and is then administered continuously until disease progression, dose-limiting toxicity or patient decision to withdraw from the study.

Cediranib or placebo will be administered in combination with daily temozolomide during the 6 weeks of the chemoradiation phase of this study. Cediranib or placebo will continue as monotherapy for 4 weeks after conclusion of chemoradiation and will then be administered in combination with temozolomide for 24 weeks (6 cycles) and up to 48 weeks (12 cycles) as per Section 7.2.5. In the first post-radiation cycle of combination cediranib or placebo + temozolomide, the temozolomide will be administered at 150mg/m^2/day on days 1-5 of the 28-day cycle. If this combination is well-tolerated the temozolomide dose will be increased to 200mg/m^2/day on days 1-5 of the 28-day cycle for cycles 2-6.

Weeks 1-6	Weeks 7-10	Weeks 11-58
Cediranib/placebo (Weeks 1-6) (20mg/day) + Radiation (Weeks 1-6) + Temozolomide (Weeks 1-6) (75mg/m^2/day)	Cediranib/placebo (20mg/day)	Cediranib/placebo (20mg/day) + Temozolomide (150 to 200 mg/m^2/day d1-5 every 28 days

NOTE: No blinded starter supplies will be available for this study. Initial blinded, patient-specific clinical supplies of cediranib / placebo will be shipped from the Pharmaceutical Management Branch (PMB) to the registering investigator at the time of patient randomization and should arrive within 7 to 10 days of randomization (see Section 7.3).

7.2.2 Technique of Administration

7.2.2.1 Cediranib or placebo will administered 3 days prior to the start of temozolomide and radiation. Temozolomide and radiation will start on the same day.

7.2.2.2 In this study temozolomide at 75mg/m^2 will be administered to patients for 42 consecutive days during treatment with radiation and cediranib/placebo. Temozolomide will then be administered at a dose of 150-200mg/m^2 for 6 months in the post-radiation phase. Temozolomide has been administered to glioblastoma patients as a continuous daily dose in combination with fractionated radiation over a course of 6 weeks (42 consecutive days). The oral dose when administered with radiation has been 75mg/m^2.

7.2.2.3 The dose of temozolomide will be determined using actual body surface area (BSA) as calculated in square meters at the beginning of the concomitant treatment. The BSA will be calculated from the height obtained at the pretreatment visit and the weight obtained at the visit immediately before the first day of treatment. Capsules of temozolomide are available in 5, 20, 100, 140, 180, and 250 mg. The daily dose will be rounded to the nearest 5 mg.

7.2.2.4 Typically, an anti-emetic is administered 30 minutes prior to temozolomide and can be taken as needed for the next few days for chemotherapy-induced nausea or vomiting. Ondansetron or granisetron are the recommended anti-emetics for use in this study . The recommended dose of granisetron is a 2mg oral dose 30 minutes before taking the temozolomide. The recommended dose of ondansetron is an 8mg oral dose 30 minutes before taking the temozolomide. Temozolomide is best tolerated when administered to patients with an empty stomach. Therefore, many patients choose to take nothing by mouth after going to bed and to take the anti-emetic followed by temozolomide on an empty stomach the following morning. Patients should not eat or drink for 1 hour after administration of temozolomide.

7.2.2.5 Patients have complete blood counts done weekly when taking the continuous daily doses of temozolomide. Patients should not be administered temozolomide unless the absolute neutrophil count is > 1500 and the platelet count is > 100,000.

7.2.2.6 Patients should be instructed to take the daily dose of cediranib/placebo and temozolomide at approximately the same time each day. Patients should have fasted for a minimum of 2 hours prior to any doses of cediranib/placebo or temozolomide. Patients should fast for another 1 hour after taking cediranib/placebo and temozolomide. Patients should first take the anti-emetic followed 30 minutes later by cediranib/placebo immediately followed by temozolomide. Each daily dose of cediranib/placebo and temozolomide should be taken with a glass of water and consumed within 15 minutes. Patients should be instructed to swallow the tablets whole and not chew them. Radiation should occur between 2-6 hours after the cediranib/placebo and temozolomide dosing, ideally within 2-4 hours.

7.2.2.7 Grapefruit and grapefruit juice should be avoided while on this protocol.

7.2.2.8 Vomited or missed doses of cediranib/placebo or temozolomide will NOT be replaced. If vomiting occurs during the course of treatment, NO re-dosing of the patient is allowed before the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be noted in the adverse events section of the CRF.

7.2.3 Post-Radiation Temozolomide

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

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

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

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

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

7.2.3.4 Antiemetic prophylaxis with a 5-HT_3 antagonist is strongly recommended and should be administered 30 to 60 minutes before temozolomide administration. (See Sections 7.2 and 9.1)

7.2.3.5 Patients will be treated with post-radiation temozolomide for 12 cycles unless there is evidence of tumor progression or treatment-related toxicity.

7.2.3.6 Pneumocystis carinii prophylaxis is required in all patients during the radiation/temozolomide phase (weeks 1-6 and in patients with lymphopenia [See Section 9.1] after week 6).

7.2.4 Drug Interruption/Drug Holiday

In the event that temozolomide or cediranib/placebo (or both) must be held during the chemoradiation phase of treatment the radiation may continue unless there is a problem with wound healing or wound dehiscence, there is related radiation toxicity or there is grade IV thrombocytopenia. The radiation will also be held until resolution of toxicity in any of the latter situations. Radiation may be held up to 2 weeks before the patient must be removed from the protocol. The maximum duration that cediranib/placebo may be interrupted is 14 days.

7.2.5 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment with cediranib/placebo and temozolomide may continue for up to 12 monthly cycles maximum after radiation ends or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

7.3 Cediranib (AZD2171, Recentin) (NSC 732208)(IND 72740)/Placebo

Please refer to the Investigator's Brochure for comprehensive information.

Investigators with an affiliation with RTOG may request an Investigator's Brochure by emailing the Pharmaceutical Management Branch's IB Coordinator at <ibcoordinator@mail.nih.gov> and providing …

- the investigator's full name (first, middle, last)
- the investigator's NCI investigator number
- the agent name (i.e., "cediranib")
- the NSC (i.e., "732208")
- the protocol (i.e., "RTOG-0837")
- the requester's name, email address, and phone number

7.3.1 Drug Description

Chemical Name: 4-[(4-Fluoro-2-methyl-1*H*-indol-5-yl)oxy]-6-methoxy-7-(3-pyrrolidin-1- ylpropoxy) quinazoline maleate

Other Names: AZD2171, cediranib, Recentin®, AZD2171 maleate

CAS Registry Number: 288383-20-0 (for the free base)

Molecular Formula: $C_{25}H_{27}FN_4O_3 \cdot C_4H_4O_4$

Molecular Weight: 566.59 as maleate salt (450.52 as free base)

Approximate Solubility: The aqueous solubility of AZD2171 has been measured as 0.0006 mg/mL for the free base (distilled water, pH 8.1 at 25°C) and 1.9 mg/mL for the maleate salt (distilled water, pH 4.4 at 25°C).

7.3.2 Mode of Action

AZD2171 is a highly potent inhibitor of vascular endothelial growth factor receptor (VEGFR) tyrosine kinase activity, which may inhibit vascular endothelial growth factor-A (VEGF) driven angiogenesis and, as a consequence, constrain solid tumor growth.

7.3.3 How Supplied

For this study, "AZD2171" and matched "Placebo" will be supplied as round, beige film-coated tablets for oral administration. The 20mg (starting dose) tablets are 8mm in diameter and the 15mg (reduced dose) tablets are 7mm in diameter. Each tamper-evident, child-resistant, 75mL, square, white, opaque high-density polyethylene (HDPE) bottle contains 35 tablets.

For "AZD2171", each tablet contains either 15mg or 20mg of cediranib maleate with mannitol, dibasic calcium phosphate anhydrous, sodium starch glycolate, microcrystalline cellulose, and magnesium stearate. For the matched "Placebo", each tablet contains mannitol, dibasic calcium phosphate anhydrous, sodium starch glycolate, microcrystalline cellulose, and magnesium stearate. For "AZD2171" and "Placebo", the film coat consists of hypromellose 2910, polyethylene glycol 400, red iron oxide, yellow iron oxide, black iron oxide, and titanium dioxide.

7.3.4 Storage and Stability

AZD2171 is shipped at room temperature by US Priority Mail. On arrival, intact bottles should be stored at controlled room temperature [20° to 25°C (68 to 77°F)] and protected from light.

Shelf-life studies of AZD2171 are continuing and investigators will be notified when lots have expired.

7.3.5 Route of Administration

Oral. AZD2171 tablets should be taken either 1 hour before or 2 hours after meals.

7.3.6 Adverse Events and Potential Risks (4/5/10)

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Cediranib (AZD2171, NSC 732208)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.info.nih.gov/protocolDevelopment/default.htm#adverse_events_adeers for further clarification. *Frequency is provided based on 681 patients.* Below is the CAEPR for cediranib (AZD2171).

Version 2.9, February 19, 2010[1]

Adverse Events with Possible Relationship to Cediranib (AZD2171) (CTCAE 4.0 Term) [n= 681]			**EXPECTED AEs FOR ADEERS REPORTING Agent Specific Adverse Event List (ASAEL)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	***Expected***
CARDIAC DISORDERS			
		Left ventricular systolic dysfunction	
ENDOCRINE DISORDERS			
	Hyperthyroidism		
	Hypothyroidism		***Hypothyroidism***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain***
	Anal mucositis		***Anal mucositis***
	Constipation		***Constipation***
Diarrhea			***Diarrhea***
	Dry mouth		***Dry mouth***
	Dysphagia		***Dysphagia***
	Mucositis oral		***Mucositis oral***
	Nausea		***Nausea***
	Rectal mucositis		***Rectal mucositis***
	Small intestinal mucositis		***Small intestinal mucositis***
	Vomiting		***Vomiting***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue***
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
	Investigations - Other (increased blood erythropoietin)		
	Investigations - Other (increased thyroid stimulating hormone)		***Investigations - Other (increased thyroid stimulating hormone)***
	Neutrophil count decreased		
	Platelet count decreased		
	Weight loss		***Weight loss***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia***
	Dehydration		***Dehydration***

NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness***
	Headache		***Headache***
		Leukoencephalopathy	
		Reversible posterior leukoencephalopathy syndrome	
RENAL AND URINARY DISORDERS			
	Proteinuria		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough***
	Dyspnea		***Dyspnea***
	Laryngeal mucositis		***Laryngeal mucositis***
	Pharyngeal mucositis		***Pharyngeal mucositis***
	Tracheal mucositis		***Tracheal mucositis***
	Voice alteration		***Voice alteration***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Palmar-plantar erythrodysesthesia syndrome		***Palmar-plantar erythrodysesthesia syndrome***
VASCULAR DISORDERS			
Hypertension			***Hypertension***
		Vascular disorders - Other (arterial thrombosis)	

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

Also reported on cediranib (AZD2171) trials but with the relationship to cediranib (AZD2171) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Leukocytosis
CARDIAC DISORDERS - Acute coronary syndrome; Chest pain - cardiac; Myocardial infarction
EAR AND LABYRINTH DISORDERS - Tinnitus; Vertigo
ENDOCRINE DISORDERS - Endocrine disorders - Other (thyrotoxicosis)
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Colitis; Dyspepsia; Enterocolitis; Esophagitis; Flatulence; Gastric perforation; Ileus; Oral pain; Rectal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Fever; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatic failure; Hepatic hemorrhage; Hepatic pain
IMMUNE SYSTEM DISORDERS - Allergic reaction
INFECTIONS AND INFESTATIONS - Gum infection; Lung infection; Sepsis; Skin infection; Soft tissue infection; Urinary tract infection
INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; Cardiac troponin T increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; GGT increased; Investigations - Other (decreased thyroxine); Lymphocyte count decreased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Bone pain; Chest wall pain; Generalized muscle weakness; Muscle weakness lower limb; Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Dysgeusia; Encephalopathy; Intracranial hemorrhage; Ischemia cerebrovascular; Lethargy; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Somnolence; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Confusion; Insomnia
RENAL AND URINARY DISORDERS - Acute kidney injury; Hematuria
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Irregular menstruation

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Epistaxis; Hypoxia; Pharyngolaryngeal pain; Pleural effusion; Pneumonitis; Pneumothorax
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Hyperhidrosis; Nail loss; Pruritus; Purpura; Rash maculo-papular
VASCULAR DISORDERS - Hematoma; Hypotension; Thromboembolic event

Note: Cediranib (AZD2171) 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.

7.3.7 Cediranib General Concomitant Medication and Supportive Care Guidelines

7.3.7.1 *Blood Pressure*

Frequent blood pressure monitoring is important in patients receiving cediranib. Experience to date suggests that increases in blood pressure may occur following dosing with cediranib for a number of weeks and that these increases usually occur within the first 4 weeks of therapy. Patients will have their blood pressure measured at each clinic visit. At the discretion of the treating physician patients may be required to have more frequent monitoring by a health care professional (primary care physician, etc). Section 7.6.3 includes specific guidelines on the management and, if appropriate, dose modifications for treatment-emergent hypertension.

7.3.7.2 *Renal Function*

Renal function (creatinine and urinary protein) should be frequently monitored as suggested by the pathologic changes noted in animal studies and evidence from studies of other anti-angiogenic agents. Specific guidelines for management of proteinuria are outlined in Section 7.3. The following potentially nephrotoxic agents should be used with extreme caution and only if absolutely necessary during treatment with cediranib: vancomycin, amphotericin, and pentamidine

7.3.7.3 *Cardiac Function*

Patient levels of troponin T or troponin I should be monitored because of the potential for myocardial injury with cediranib. In patients who develop cardiac dysfunction the dose will be modified according to the LVEF Dose Modification Schedule in Section 7.6.4 below. Patients who develop symptomatic heart failure while on study will have the cediranib discontinued.

7.3.7.4 *Drug Interactions*

Because there is a potential for interaction of cediranib with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies.

7.3.7.5 *Thyroid Function*

Cediranib therapy has been associated with increases in TSH. In the majority of patients this has not resulted in reductions in either total thyroxine or free T4 to below the lower limit of the normal range, but clinical hypothyroidism has been reported in a small number of patients. Patients have responded to replacement therapy without the need for stopping or reducing the dose of cediranib. Replacement levothyroxine should be given when clinically indicated to normalize the thyroxine level to within the normal range, and before the patient becomes clinically symptomatic. Replacement levothyroxine therapy may also be considered in patients with TSH increases (and thyroxine levels within the normal range), together with adverse events and symptoms suggestive of incipient hypothyroidism. Thyroid function should be monitored frequently and the dose of levothyroxine should be titrated as required.

7.3.7.6 *Reversible Posterior Leukoencephalopathy*

At the time of writing this protocol, cases of Magnetic Resonance Imaging (MRI)-confirmed RPLS have rarely been reported in patients receiving cediranib in clinical studies. RPLS is a rare syndrome affecting vascular endothelial cells in the brain that may lead to capillary leak and edema, and was first described in 1996 (Hinchey et al 1996). It has been associated with a number of conditions, including renal failure, hypertension, fluid retention, and the use of cytotoxic or immunosuppressive drugs. It has also been reported rarely in association with the use of VEGF inhibitors including bevacizumab and sunitinib. The syndrome can present in a variety of non-specific ways, including headache, seizures, lethargy, confusion, blindness and other visual and neurological disturbances. Hypertension may be present, but is not necessary for the diagnosis of RPLS. Magnetic Resonance Imaging (MRI) is the most sensitive imaging modality to detect RPLS and is recommended in suspected cases to confirm the diagnosis. RPLS is reversible upon removal of any possible precipitating factors and control of hypertension.

7.3.8 Clinical Supplies

Cediranib (NSC 732208/CTEP IND #72,740) and matching Placebo will be provided free of charge by AstraZeneca and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

Cediranib and matching Placebo will be supplied in bottles containing 35 – 20mg tablets (Cediranib 20mg) or 35 - 0mg tablets (Placebo for Cediranib 20mg) with a child-resistant cap and a tamper-evident seal. In addition, to support dose reductions, Cediranib and matching Placebo will also be supplied in bottles containing 35 – 15mg tablets (Cediranib 15mg) or 35 - 0mg tablets (Placebo for Cediranib 15mg). Each blinded, patient-specific bottle will be labeled with …

- the protocol number (i.e., "RTOG-0837")
- the bottle number (i.e., "Bottle 1 of 3", "Bottle 2 of 3", and "Bottle 3 of 3")
- the number of tablets (i.e., "35 tablets")
- the patient ID number (e.g., "0837-999"; where ""0837" represents the RTOG designated protocol number and "999" represents the unique patient identifier assigned by RTOG at randomization)
- the patient initials (i.e., first initial, middle initial, last initial [e.g., "FML"])
- the agent identification (i.e., "Cediranib 20mg or Placebo" OR "Cediranib 15mg or Placebo")
- a blank line for the pharmacist to enter the patient's name
- administration instructions (i.e., "Take 1 tablet once daily.")
- storage instructions (i.e., "Store at room temperature (20ºC to 25ºC; 66ºF to 77ºF) and protect from light.")
- emergency contact instructions
- a Julian date

The Julian date indicates the day the bottle was labeled and shipped and is composed of the last two digits of the calendar year (e.g., 2010 = 10, 2011 = 11) and a day count (e.g., January 1 = 001, December 31 = 365). For example, a bottle labeled and shipped on January 1, 2010 would have a Julian date of '10001' and a bottle labeled and shipped on December 31, 2011 would have a Julian date of '11365'. The Julian date will be used by PMB for recalls. When a lot expires, PMB will determine the last date the expired lot was shipped and will recall all bottles (i.e., both cediranib and placebo) shipped on or before that date thus eliminating any chance of breaking the blind.

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling (301) 496-5725 Monday through Friday between 8:30am and 4:30pm Eastern Time or by emailing <PMBAfterHours@mail.nih.gov> anytime.

7.3.9 Drug Orders

Due to the blinded nature of this study, with drug being provided through the Pharmaceutical Management Branch (PMB) of the NCI, extreme accuracy and consistency of physician information is required to achieve accurate and timely drug shipments. The shipping address for each per-patient shipment is automatically retrieved from the physician-specific information provided on the investigator's most recent Supplemental Investigator Data Form (IDF) on file with the PMB. (Please see Section 7.3.9.2 for detailed instructions related to IDF maintenance.) Please be certain the address of the local verifying physician you select from the drop down menu during registration is consistent with where the drug is expected to be received and that the physician has a valid NCI (CTEP ID) number. Please also be consistent in identifying the same verifying physician at each registration step [A0 (Step 1) and A2 (Step 2)].

No blinded starter supplies will be available for this study. Blinded, patient-specific clinical supplies will be sent to the registering investigator at the time of the step 2 randomization and should arrive within approximately 7 to 10 days. Patients will be randomized by the RTOG Coordinating Center in Philadelphia, PA. The assigned patient ID number must be recorded by the registering institution at the time of randomization for proper clinical supply dispersion. Once a patient has been randomized, the RTOG Coordinating Center will electronically transmit a clinical drug request for that patient to the PMB. This request will be entered and transmitted by the RTOG

Coordinating Center the day the patient completes the step 2 randomization and will be processed by PMB the next business day and shipped the following business day. Shipments within the United States will be sent by US Priority Mail (generally two to three day delivery) and shipments to Canada will be sent by FedEx (generally one to two day delivery). Thus, if a patient is registered on Monday, RTOG would enter a clinical drug request for that patient on Monday and PMB would process that request on Tuesday and ship the drug on Wednesday. United States clinical sites could expect to receive their order approximately Friday or Monday (depending on the US Mail service) and Canadian clinical sites could expect to receive their order either Thursday or Friday. Shipments to United States clinical sites can be expedited (i.e., receipt on Thursday in example above) by the provision of an express courier account name and number to the RTOG Coordinating Center at the time the patient is randomized.

The initial request will be for **3 – 35 tablet bottles** of Cediranib **20mg** or matched placebo (a sufficient quantity to support **weeks 1 to 6** [radiation therapy + temozolomide + cediranib] AND **weeks 7 to 10** [cediranib alone] at a dose of one – 20mg tablet once daily). Eight weeks (two months) after the initial electronic request (i.e., two weeks before needed), sites may reorder an additional **3 - 35 tablet bottles** of Cediranib **20mg** (a **3 – cycle / 12 week [weeks 11 to 22, 23 to 34, 35 to 46, and 47 to 58]) supply** at a dose of one – 20mg tablet once daily) by completing an NCI Clinical Drug Request form and faxing it to the PMB at 301-480-4612. The NCI Clinical Drug Request form is available on the CTEP home page (http://ctep.cancer.gov). The assigned patient ID number (e.g., “0837-999”) and the patient initials (e.g., "FML") should be entered in the "Patient or Special Code" field and the number of bottles remaining should be entered in the “Your Current Inventory” field.

Special Ordering Procedures for Patients Requiring a Dose Reduction. If the patient is **dose reduced** from cediranib **20mg** once daily TO cediranib **15mg** once daily (see Section 7.5.3), an NCI Clinical Drug Request form must be completed and faxed to PMB to obtain the cediranib 15mg and matched placebo tablets. Be sure to specify “Cediranib 15mg / Placebo” in the “Strength” field. **Please indicate the date and the week of therapy of the dose reduction in the comments field** (see section 7.2.1).

All drug orders will be shipped directly to the registering physician at the shipping address provided on their current Supplemental Investigator Data Form (IDF) on file with CTEP. The registering investigator must maintain an active investigator registration status with CTEP, DCTD through the annual submission of an FDA Form 1572 (Statement of Investigator), a Curriculum Vitae, a Supplemental Investigator Data Form (IDF), and a Financial Disclosure Form (FDF).

RTOG-0837 Shipment Schedule

Patient Randomized with RTOG	Initial e-Order Transmitted by RTOG	Initial e-Order Received and Approved by PMB	Initial Order Shipped by PMB	Initial Order Received at Site *
Monday	Monday	Tuesday	Wednesday	US Priority Mail
Tuesday	Tuesday	Wednesday	Thursday	US Priority Mail
Wednesday	Wednesday	Thursday	Friday	US Priority Mail
Thursday	Thursday	Friday	Monday	US Priority Mail
Friday	Friday	Monday	Tuesday	US Priority Mail

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

The authorized shipping designee listed by the verifying investigator in box 10 of their most recent Supplemental Investigator Data Form [IDF] on file with the PMB will be the recipient of the per-patient cediranib or matched placebo shipments from NCI’s Pharmaceutical Management Branch (PMB) for this study. The information on the IDF is linked to the investigator during their annual investigator registration process, which maintains the validity of the investigator NCI (CTEP ID) number. This process must be current or completed before a drug order can be triggered for an investigator. Any changes to this information will require updating the first two pages of the IDF, having the investigator sign the revised IDF, and returning it to the PMB via fax at 301-402-4870. Questions about the process should be directed to the PMB at 301-496-5725 Monday through Friday from 8:30 – 4:30 Eastern Time.

For a blinded study such as this, PMB policy requires the drug be shipped directly to the address on file on the IDF for the selected verifying physician. This is an automatic process and can not be altered after the fact. If the physician's NCI (CTEP ID) number is invalid or inaccurate the shipment will be rejected.

7.3.10 Drug Transfers

Bottles may **NOT** be transferred from one patient to another patient or from one protocol to another protocol. All other transfers (e.g., a patient moves from one participating clinical site to another participating clinical site, the registering investigator for a given patient changes) must be approved in advance by the PMB. To obtain an approval for transfer, investigators should complete and submit to the PMB (fax number 301-480-4612) a Transfer Investigational Agent Form available on the CTEP home page (http://ctep.cancer.gov). The patient ID number (e.g., "0837-999") and the patient initials (e.g., "FML") should be entered in the "Received on NCI Protocol No." and the "Transferred to NCI Protocol No." fields in addition to the protocol number (i.e., "RTOG-0837").

7.3.11 Drug Returns

Only undispensed clinical supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed bottles remaining when a patient permanently discontinues protocol treatment, expired bottles recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Drug List available on the CTEP home page (http://ctep.cancer.gov). The patient ID number (e.g., "0837-999") and the patient initials (e.g., "FML") should be entered in the "Lot Number" field. A separate line item is required for each patient ID (e.g., "0837-999") being returned. **Dispensed bottles with remaining tablets should be documented in the patient-specific NCI Investigational Agent Accountability Record (i.e., logged is as "returned by patient" and logged out as "destroyed on site") and destroyed on site in accordance with institutional policy**.

7.3.12 Drug Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the CTEP home page (http://ctep.cancer.gov). A separate NCI Investigational Agent Accountability Record must be maintained for each patient ID number (e.g., "0837-999") on this protocol. It is recommended that the combination Julian date / order number in the upper right hand corner of the patient-specific bottle label be recorded as the lot number.

7.3.13 Emergency Unblinding

In the event of an emergency or severe adverse reaction necessitating identification of the medication for the welfare of the patient, please contact RTOG Headquarters per Section 7.1.

RTOG will require the protocol number (i.e., "RTOG-0837"), the patient ID number (e.g., "0837-999"), and the patient initials (e.g., "FML") to unblind the patient. Please note that, if a patient is emergently unblinded, he/she is considered to be off-therapy and must discontinue protocol treatment.

7.3.14 Compliance

Patients will be required to return all bottles of study medication at the end of each cycle. The number of tablets remaining should be documented and recorded on the pill diary and TF form (available on the forms section of the RTOG website).

A pill diary must be distributed to each patient at the beginning of protocol treatment and must be checked on a regular basis during patient visits for compliance to protocol treatment. A template of the pill diary is posted on the RTOG website (http://www.rtog.org/pdf_forms.html?members/forms=pilldiary1.pdf) as a tool for participating sites. Any other institutional pill diary templates may be used, and the choice will be left at the discretion of the treating physician.

7.4 **Temozolomide** (Temodar, Temodal)

Please refer to the package insert for comprehensive information.

7.4.1 Formulation

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

and stearic acid NF. The capsule shells contain gelatin NF, titanium dioxide USP, and sodium lautyl sulfate NF.

7.4.2 Mode of Action

Alkylating agent of imidazotetrazinone class.

7.4.3 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.

7.4.4 Pharmacokinetics

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

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

7.4.5 Metabolism and Elimination

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

7.4.6 Special Populations

7.4.6.1 *Creatinine Clearance*

Population pharmacokinetic analysis indicates that creatinine clearance over the range of 36-130 mL/min/m^2 has no effect on the clearance of temozolomide after oral administration. The pharmacokinetics of temozolomide have not been studied in patients with severely impaired renal function (CLcr < 36 mL/min/m^2).

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

7.4.6.2 *Hepatically Impaired Patients*

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

7.4.6.3 *Gender*

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

7.4.6.4 *Age*

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

7.4.7 Drug-Drug Interactions

In a multiple dose study, administration of temozolomide with ranitidine did not change the C_{max} or AUC values for temozolomide or MTIC. Population analysis indicates that administration of

valproic acid decreases the clearance of temozolomide by about 5%. The clinical implication of this effect is not known. Population analysis failed to demonstrate any influence of co-administered dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H_2-receptor antagonists, or phenobarbital on the clearance of orally administered temozolomide.

7.4.8 Adverse Events

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

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

7.4.10 Contraindications

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

7.4.11 Pregnancy Category D

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

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

7.4.12 Supply

Commercially available.

7.5. Dose Modifications

7.5.1 Definition of Dose Limiting Toxicity

A dose-limiting toxicity defined as a clinically significant adverse event or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications/temozolomide and occurs during the first 6 weeks, following the first dose of cediranib in the chemoradiation, phase I study, and meets any of the following criteria:

1. Hematological toxicities:

   CTCAE grade 4 neutropenia (ANC including bands < 0.5×10^9/L)

   CTCAE grade ≥ 3 thrombocytopenia

   Note: Dose limiting hematological toxicities, as defined above, are more likely due to temozolomide and will be attributed to temozolomide. The dose adjustment will occur in the temozolomide dose first (see below) with cediranib potentially adjusted for subsequent dose-limiting hematological toxicities.

2. Renal toxicity:

   Serum creatinine ≥ 2.0 x ULN

3. Hepatic Toxicity

≥ grade 3 bilirubin elevation

≥ grade 3 AST or ALT elevation for any duration

4. All other clinically significant NCI common terminology criteria, adverse events version 3.0

≥ grade 2 hypertension

Any hypertension requiring urgent management

≥ grade 3 ataxia, dizziness or other neurotoxicities

Diagnosis of posterior leukoencephalopathy

Total visual loss

≥ grade 2 proteinuria on dip stick reading confirmed by a 24-hour urine collection with a protein ≥ 1 gram

≥ grade 2 hematuria

Clinically significant surgical wound dehiscence/breakdown

Occurrence of clinically significant grade 3 or 4 adverse events

≥ grade 3 vomiting or grade 3 nausea despite the use of standard anti-emetics

≥ grade 3 diarrhea despite the use of optimal anti-diarrheal medications

Headaches are frequent in the brain tumor population and are usually due to diffuse increased intracranial pressure or compression of pain-sensitive intracranial structures (example: dura). The oncologists participating in this study are experienced clinicians accustomed to evaluation of brain tumor patients with headaches. Each patient with a headache is approached individually with a systematic assessment as to the etiology of the pain. Appropriate tests might include vital signs; CT or MRI scans or other investigations. If, in the opinion of the treating oncologist, the headache is due to cediranib the toxicity will be graded as above and, if ≥ grade 3, it will be defined as a DLT.

Seizures are also a common complication associated with brain tumors. As noted in the preceding paragraph each patient will be approached individually and assessment for the cause of the seizure will be performed. If, in the opinion of the treating oncologist, the seizure is due to cediranib the toxicity will be graded and, if ≥ 2, it will be defined as a DLT.

7.5.2 Temozolomide

7.5.2.1 *Temozolomide During Concomitant Radiation Therapy*

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

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

If one or more of the following are observed:

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

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

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

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

If one or more of the following are observed:

- ANC < 0.5 x 10^9/L (Grade 4)
- Platelet count < 25 x 10^9/L (Grade 4)
- Grade 3 or 4 non-hematologic AE (except alopecia, nausea and vomiting unless the patient has failed maximal antiemetic therapy, and fatigue)

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

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

Summary of Temozolomide Delay or Discontinuation During Concomitant Radiation Therapy

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

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

7.5.2.2 *Post-Radiation (Adjuvant) Temozolomide*

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

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

Delay

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

If AEs persists, treatment should be delayed by 1 week for up to 4 consecutive weeks. If, after 4 weeks of delay, all AEs have still not resolved: then any further adjuvant treatment with temozolomide should be stopped.

Dose escalation

If, during the first cycle, all non-hematologic AEs observed were grade ≤ 2 (except alopecia, nausea and vomiting) and with platelets ≥ 100 x 10^9/L and ANC ≥ 1.5 x10^9/L: then the temozolomide dose should be escalated to dose level 1 and this dose should be used as the starting dose for subsequent cycles. If treatment after cycle 1 has to be delayed because of ongoing non-hematologic AEs of grade ≥ 2, then no escalation is possible. If the dose was not escalated at cycle 2, then the dose should not be escalated in further cycles (3-12).

Dose reductions

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

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

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

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

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

Summary of Dose Modification or Discontinuation During Post-Radiation Temozolomide

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

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

Note: A complete blood count must be performed 21 days (± 48 hours) and 28 days (± 48 hours) after the first daily dose of each adjuvant treatment cycle.

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

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

7.5.3 Cediranib

In the event of grade 3 or higher non-hematological toxicity attributed to cediranib the dose of cediranib will be modified as stipulated below. Management of hypertension is specified in Section 7.5.5. Adverse events (AEs) should be treated with the appropriate maximum supportive care, and dose reductions should be clearly documented in the case report form. One dose reduction will be allowed for the cediranib and placebo as below.

Cediranib Dose	*Dose Reduction 1*	
20mg/day	15mg/day	Discontinue

The maximum duration that cediranib may be held for toxicity is for 14 days. If a dose reduction of cediranib is required during chemoradiation (weeks 1-6) (i.e. 20mg/day to 15mg/day) then the dose-reduced level of cediranib (i.e. 15mg/day) will be continued for the remainder of the study.
If cediranib is held for reasons other than toxicity (for example, surgery) then the drug may be restarted even after being held for > 14 days when it is safe to do so in the opinion of the treating physician.

NOTE: Please see Section 7.3.9, Special Ordering Procedures for Patients Requiring a Dose Reduction, for instructions on ordering replacement "Cediranib 15mg or Placebo" clinical supplies if your patient is dose reduced from "cediranib 20mg tablets" to "cediranib 15mg tablets.

7.5.4 General Management of Adverse Events Attributed to Cediranib

Observation	Action
AE resolves promptly with supportive care	Maintain dose level
1. Grade 3 or higher (non-hematological) or grade 4 (hematological) AE related to cediranib and lasting > 5 days that does not resolve to grade 2 or below despite maximum supportive care for ≤ 48 hours. 2. Lower grade but related AEs	Reduce one dose level*
AE does not resolve to grade 2 or below after treating patient at the lowest cediranib dose (*i.e*., 10 mg qd) reduced dose level.	In general, remove patient from study
* Alternatively and if medically appropriate, investigators may choose to hold dose for up to 14 days or withdraw patient from study.	

7.5.5 Management of Hypertension

Increases in blood pressure (BP) and cases of hypertension have been associated with many drugs acting on the VEGF pathway. The proposed mechanism for this increase is through inhibition of VEGF-induced peripheral vasodilation. Hypertension following cediranib treatment has been seen in animal studies as well as clinical trials. In some studies the incidence of hypertension is highest within the first few weeks of therapy. Specific guidance for management of this AE is provided below. Blood pressure will be measured as part of the routine assessment of patients conducted by health care professionals and outlined below.

Hypertension management protocol for emergent hypertension

Hypertension severity	Actions
Mild to moderate hypertension: BP 140/90 mmHg on 2 consecutive occasions >24 hours apart OR Increase in diastolic pressure by ≥20 mmHg or to ≥100 mmHg or increase in systolic pressure to ≥150 mmHg	1. Repeat reading at least 1 hour later. If isolated increase, increase BP monitoring to twice weekly by health professional or daily home monitoring. **Continue cediranib[a] at the same dose.** 2. If confirmed by second reading, **continue cediranib at the same dose** and initiate monotherapy with a long acting dihydropyridine calcium-channel blocker (eg, nifedipine, amlodipine, felodipine) at low dose. • If calcium channel blocker is contraindicated, use selective β-blocker first line. • Monitor BP daily by health professional until it stabilizes. 3. If BP >140/90 mmHg after 24 hours INCREASE the first agent to the full dose and consider adding an additional agent in combination (eg, selective β-blocker, low dose combined alpha- and β-blocker, thiazide diuretic [angiotensin converting enzyme inhibitors or angiotensin receptor blockers if specific indication]). 4. If BP >140/90 mmHg after a further 24 hours, add an additional agent if the patient is only on one new agent or increase to full doses of the 2-drug combination. 5. If BP >160/95 mmHg and is static or increasing after a further 48 hours, temporarily stop cediranib and continue anti-hypertensive therapy under close supervision. 6. Restart cediranib at the same dose (with maintenance anti-hypertensive therapy) when BP ≤140/90 mmHg. Monitor BP at least every 2 days by health professional until steady state is reached (7 days) and BP stabilized. 7. If BP increases to >160/95 mmHg, follow step 5 and restart cediranib but with the tablets at 1 dose lower than the starting dose when BP<140/90 mmHg. 8. If BP increases to >160/95 mmHg, follow step 5 and restart cediranib but with the tablets at 2 doses lower than the starting dose when BP<140/90 mmHg. 9. If BP increases to >160/95 mmHg after 2 dose reductions despite anti-hypertensive therapy, permanently stop cediranib.

Hypertension management protocol for emergent hypertension

Hypertension severity	Actions
Severe hypertension: Increase in diastolic pressure to ≥110 mmHg or increase in systolic pressure to ≥180 mmHg on 2 readings >1 hour apart	1. Temporarily stop cediranib and consider if hospitalization is necessary. 2. Initiate treatment with a 2-drug combination including a calcium channel blocker licensed for use in severe hypertension, tailored to the patient's underlying conditions and previous anti-hypertension treatment. 3. If there is evidence of target-organ damage, intravenous therapy should be considered while continuing oral therapy. 4. Nitrates may adversely affect the therapeutic mechanism of action of cediranib but should be used if clinically indicated. 5. Restart cediranib but with the tablets at 1 dose lower than the starting dose (with maintenance antihypertensive therapy) when BP ≤140/90 mmHg. Monitor BP at least every 2 days by health professional until steady state is reached (7 days) and BP stabilized. 6. If BP >160/95 mmHg and is increasing after 48 hours, temporarily stop cedirainib and continue anti-hypertensive therapy under close supervision. 7. Restart cediranib but with the tablets at 2 doses lower than starting dose (with maintenance antihypertensive therapy) when BP ≤140/90 mmHg. Monitor BP at least every 2 days by health professional until steady state is reached (7 days) and BP stabilized. 8. If BP increases to >160/95 mmHg after 2 dose reductions despite antihypertensive therapy, permanently stop cediranib.

The development of hypertension in patients treated with cediranib is generally an early event, usually occurring in the first 4 weeks of treatment. In a minority of patients hypertension can also occur later in a treatment schedule.

The rigorous monitoring of BP and adherence to the hypertension management guidelines are necessary in order to achieve optimal hypertension control. It is recommended that patients are monitored approximately weekly for the first 4 weeks of treatment with cediranib.

Patients on prolonged treatment with cediranib should have their blood pressure checked monthly. Patients on prior anti-hypertensive therapy may be particularly at risk of developing moderate or severe hypertension on cediranib.

Therefore, patients with pre-existing hypertension or on anti-hypertensives are likely to benefit from having their BP management optimized before starting cediranib.

For all BP thresholds described in this protocol, a trigger level is considered to be met if either the systolic and/or the diastolic pressure reach the threshold. If the threshold is recorded at home, it must be confirmed by a healthcare professional as defined above before commencing any treatment.
CLEAR reasons for progressing to the next step in the management protocol must be documented.
When managing mild to moderate hypertension, the following principles should be noted:

Cediranib may cause rapid increases in BP in some patients. Patients who are already on anti hypertensive agents may be at higher risk of developing moderate or severe hypertension. In such patients, care should be taken to ensure blood pressure is well controlled to <140/90mmHg prior to

commencing cediranib. This may mean adding or increasing doses of calcium channel blockers prior to commencing cediranib.

Calcium-channel blockers are the first line agents of choice.

If calcium channel blockers are contraindicated, ACE inhibitors; Angiotensin receptor antagonists or β-blockers are alternative agents.

Increase anti-hypertensives to maximum doses and add additional agents as required.

It is recommended that no more than 2 additional drugs are added in a 48 hour period before temporarily stopping cediranib.

The following cautions and contraindications should be noted:

Calcium-channel blockers: use with caution in patients with tachyarrhythmias, aortic stenosis, unstable angina or congestive cardiac failure and may cause headache.

Short-acting dihydropyridines such as diltiazem or verapamil should be avoided since they may precipitate abrupt fall in BP and increase risk of myocardial ischemia, infarction or stroke.

Beta-blockers: contraindicated in patients with asthma, chronic obstructive pulmonary disease and A-V block; they should be used with caution in patients with peripheral vascular disease and glucose intolerance and may cause fatigue.

If diuretics are to be used, thiazides rather than loop diuretics are recommended.

A record of the management of hypertension will be maintained.

CTC grade 3 should NOT be assigned to hypertension AEs on the basis of the number of drugs used according to this protocol to treat mild-moderate hypertension since this is a proactive treatment approach. CTC grade 3 should be assigned **if hypertension is not controlled after 48 hours of per-protocol anti-hypertensive therapy.**

The definitions provided in the following table should be used to record the severity of increases in BP:

Severity of increases in BP – Modified CTCAE grading of hypertension AEs

CTC grade	Definition
1	Asymptomatic, transient (<24 hr) increase by >20 mmHg (diastolic) or to >150/100 mmHg if previously within normal limits; intervention not indicated
2	Recurrent or persistent (>24 hr) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 mmHg if previously within normal limits; monotherapy may be indicated
3	CTC grade 3 should not be assigned to hypertension AEs on the basis of the number of drugs used according to this protocol to treat mild-moderate hypertension, since this is a pro-active treatment approach. CTC grade 3 should be assigned if **grade 2 hypertension is not controlled after 48 hours of per-protocol anti-hypertensive treatment**
4	Life threatening consequences (eg, hypertensive crisis)
5	Death

7.5.6 Management of Proteinuria

Although patients with > 1+ proteinuria at entry are ineligible, increases in proteinuria may occur during treatment and should be managed as follows:

Management of Proteinuria

Proteinuria Value	Monitoring	Dose modification
≥ 1+ (dipstick or equivalent routine laboratory analysis)	Perform the following tests: • 24-hour urine collection for total protein and creatinine • microscopic examination of fresh urine • urine protein electrophoresis (at first occurrence of >1+ proteinuria only)	See below.
Based on results of the 24-hour urine collection:		
<1g protein (24-hour collection)	Continue dipstick or equivalent routine laboratory analysis	Continue planned dose
≥1g but ≤2g protein (24-hour collection)	Perform 24-hour urine collection (total protein, creatinine) prior to day 1 of each subsequent cycle of therapy (q4w) until total protein is <500 mg/24 hours.	Decrease one dose level; continue treatment
>2 g protein (24-hour collection)	Perform 24-hour urine collection (total protein, creatinine) weekly until proteinuria is <2g.	Hold cediranib. When protein is <2g/24 hours, resume treatment at one lower dose level.
	Perform 24-hour urine collection (total protein, creatinine) prior to day 1 of each subsequent cycle of therapy (q4w).	Continue until patient is off study.

7.5.7 Dose Modification for Left Ventricular Dysfunction

LVEF DOSE MODIFICATION TABLE

Asymptomatic Decrease in LVEF

The decision to continue or hold cediranib/placebo is based on the LVEF as it relates to the institution's lower limit of normal (LLN) and change in ejection fraction from screening (LVEF as measured at registration) according to the following table:

Relationship of LVEF to institution's LLN	**LVEF Decrease < 10%**	**LVEF Decrease 10-15%**	**LVEF Decrease ≥ 16%**
Normal	Continue	Continue	Continue and repeat MUGA/ECHO within 1-2 cycles
1-5% below LLN	Continue and repeat MUGA/ECHO within 1-2 cycles	Continue and repeat MUGA/ECHO within 1-2 cycles	HOLD and repeat MUGA/ECHO within 1-2 cycles
≥ 6% below LLN	Continue and repeat MUGA/ECHO within 1-2 cycles	HOLD and repeat MUGA/ECHO within 1-2 cycles	HOLD and repeat MUGA/ECHO within 1-2 cycles

Discontinue cediranib/placebo if:

Two consecutive HOLD categories occur.

Three intermittent HOLD categories occur (at the discretion of the investigator, STUDY DRUG may also be permanently discontinued prior to the occurrence of 3 intermittent HOLD categories).

If LVEF is maintained at a "Continued and repeat MUGA/ECHO" or improves from a HOLD to a "Continue and repeat MUGA/ECHO" category, additional MUGA scans/echocardiograms prior to the next scheduled MUGA/ECHO will be at the discretion of the investigator.

Symptomatic Cardiac Events

Discontinue cediranib/placebo if:

A patient has symptoms of congestive heart failure (CHF) and a diagnosis of CHF is confirmed.

A patient has myocardial infarction.

Patients who discontinue cediranib/placebo due to cardiac toxicity may continue chemotherapy at the investigator's discretion.

7.5.8 Management of Diarrhea

Diarrhea should be treated at an early stage (Common Toxicity Criteria Adverse Event (CTCAE) Grade 1) with loperamide or similar agent. The patient should be given a prescription to take as required at home.

If Common Toxicity Criteria Adverse Event (CTCAE) Grade 2 diarrhea occurs despite medication with loperamide and is present at the time of the next cycle of chemotherapy, the cediranib should be held and the patient should be monitored weekly. If it then resolves to Grade 1 within a week, cediranib can be re-started with no dose reduction. If Grade 2 diarrhea recurs in a subsequent cycle despite medication with loperamide the cediranib should be held and the patient monitored frequently. If it then resolves to Grade 1 within a week the cediranib can be re-started with dose reduction by one level. If it persists for a further week cediranib should be discontinued.

For CTCAE Grade 3-4 diarrhea refractory to oral anti-diarrheal medication, all treatment will be held. If ≥ CTCAE Grade 3 diarrhea persists for > 2 weeks, cediranib should be discontinued. If the toxicity resolves to ≤ CTCAE Grade 1, then the cediranib may be restarted but reduced by one dose level. If ≥ CTCAE Grade 3 diarrhea recurs at the reduced dose cediranib should be discontinued.

7.6 Modality Review

The Medical Oncology Chair, Tracy Batchelor, 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 Chair, Tracy Batchelor, M.D., will perform a Quality Assurance Review after complete data for the first 20 cases enrolled has been received at RTOG Headquarters. Dr. Batchelor 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.

7.7 Clinical Trials Agreement

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as ”Collaborator(s)”) and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the “Intellectual Property Option to Collaborator” (http:// ctep.cancer.gov/industry) contained within the terms of award, apply to the use of the Agent(s) in this study:

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

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

   a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the

proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

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

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

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

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

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

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

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

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

7.8 Adverse Events

This study will utilize the descriptions and grading scales found in the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) for grading all adverse events. The CTEP Active Version of the CTCAE is identified and located on the CTEP web site at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.

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

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

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 7.8 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

7.9 AdEERS Expedited Reporting Requirements

NOTE: For information regarding adverse events and reporting for the ACRIN 6689 advanced imaging component of the protocol, see Section 7.10.

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).

Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days[1] of the Last Dose of the Investigational Agent [Cediranib/Placebo] in this Study and a Commercially Available Agent

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

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

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

- Grade 4 and Grade 5 unexpected events

AdEERS 10 calendar day report:

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

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

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

March 2005

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 <u>24 hours</u> of learning of the event followed by a complete AdEERS report within <u>5 calendar days</u> of the initial 24-hour report.
  - "10 calendar days" - A complete AdEERS report on the AE must be submitted within <u>10 calendar days</u> 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.

<u>Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a CTEP-IND and a Commercially Available Agent:</u>

Not applicable.

7.10 ACRIN 6689 Advanced Imaging Adverse Event Reporting Requirements (8/26/10)

Adverse Event Reporting must follow the guidelines below. The ACRIN Adverse Event Reporting Manual [May 2008 version or latest revision—available on the ACRIN web site] provides additional details and may be consulted as a reference, but does not supersede AE reporting as specified in this protocol. The AdEERS electronic AE reporting system is to be used for AE reporting of AdEERS qualified events unless unavailable. AE data is to be entered into the AdEERS electronic system if it meets AdEERS criteria (see Section 8.0 for AdEERS reporting criteria), even when it has been manually captured and/or manually submitted due to system unavailability (see manual process below).

7.10.1 Definition of Adverse Event

An Adverse Event **(AE)** is any untoward, undesired, unplanned medical occurrence in a participant, and does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding or physiological observation), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). Any symptom, sign, illness, or experience that develops or worsens in severity during the course of the study, including intercurrent illnesses or injuries, should be regarded as an AE.

Abnormal results of diagnostic procedures are considered to be AEs if the abnormality:

- results in study withdrawal;
- is associated with a serious adverse event (SAE);
- is associated with clinical signs or symptoms;
- leads to additional treatment or to further diagnostic tests;
- is considered by the investigator to be of clinical significance.

7.10.2 Definition of Serious Adverse Event

AEs are classified as serious or non-serious. A Serious Adverse Event **(SAE)** is any AE that results in any of the following outcomes:

- Death;
- A life-threatening event (refers to any AE that places the participant at immediate risk of death from the event as it occurred; life-threatening event does not include an event that, had it occurred in a more severe form, might have caused death, but as it actually occurred, did not create an immediate risk of death);
- Inpatient hospitalization and/or prolongation of an existing hospitalization (hospitalization is defined as lasting 24 hours or longer). Emergency room visits are not considered serious until one of the above criteria is met. Any elective hospitalization for a pre-existing condition that has not worsened does not constitute an SAE;
- 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.

Medically important 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 participant and may require intervention to prevent one of the other serious outcomes noted above.

7.10.3 Adverse Event Grading

Grade refers to the severity (intensity) of the AE. An AE is graded using the current version of the Common Terminology Criteria for Adverse Events (CTCAE), or the following categories (if the term does NOT appear in the current version of the CTCAE):

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 participant's ability to perform routine activities despite symptomatic therapy

4 – Life-threatening or disabling

5 – Death/Fatal

7.10.4 Adverse Event Attribution

Attribution is the determination of whether an AE is related to the advanced imaging and the investigational imaging agent.

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.

7.10.5 Expected and Unexpected Adverse Events

AEs may be **expected** or **unexpected**:

An **expected AE** is one that is described in the protocol, the ICF, or the investigator's drug brochure, even if such an event would be considered extremely rare.

An **unexpected AE** is one that has not been described in the protocol, the ICF, or the investigator's drug brochure.

7.10.6 Expected Adverse Events

7.10.6.1 IV Needle Placement for Contrast Agent Administration and Blood Sampling:

Hemorrhage (hematoma at the injection site);

Pain at the injection site;

Minor discomfort;

Bleeding;

- Infection (catheter related infection) at the injection site;
- Bruising.

7.10.6.2 Advanced MR Imaging:

- Anxiety/stress;
- Claustrophobia;
- Discomfort.

Gadolinium:

- Allergic reaction to contrast agent;
- Headache;
- Nausea;
- Vomiting;
- Rash/hives;
- Temporary low blood pressure;
- Nephrogenic Systemic Fibrosis (NSF)/Nephrogenic Fibrosing Dermopathy (NFD).

NOTE: Precautions should be exercised for participants 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 participants with a known sensitivity to Gd or history of asthma. Nephrogenic Systemic Fibrosis (NSF) or Nephrogenic Fibrosing Dermopathy (NFD) (kidney disorders), may occur in participants with moderate to end-stage kidney disease and in participants with renal dysfunction due to the hepatorenal syndrome or in the perioperative liver transplantation period after they have had a MRI scan with Gd-based MR contrast agents (GBMCA).

NSF causes fibrosis of the skin and connective tissues throughout the body. Participants develop skin thickening that may prevent bending and extending joints, resulting in decreased mobility of joints. NSF

usually starts in the lower extremities. Fibrosis can also develop in the diaphragm, muscles in the thigh and lower abdomen, and lung vessels.

Reference: FDA/Center for Drug Evaluation and Research. May 23, 2007 (www.fda.gov/cder/drug/infopage/gcca/qa_200705.htm).

7.10.6.3 [^{18}F]FLT PET Scans

No AEs have been reported for [^{18}F]FLT PET at the strength to be used for this study. Non-radioactive FLT has been investigated as an anti-AIDS drug and in some instances of reversible peripheral neuropathy were observed in participants exposed to 50 ng-h/mL plasma over a course of 16 weeks (15µg/kg q12h).

The FLT dose anticipated for this study will be <6.1µg for a single injection. Assuming a 70kg individual, the maximum concentration of FLT would be expected to be equivalent to 0.29 ng-h/mL. Refer to the [^{18}F]FLT Investigator Drug Brochure for details.

Participants will be monitored for AEs during each [^{18}F]FLT PET imaging session; vital signs (temperature, blood pressure, heart rate, and respiratory rate) will need to be recorded prior to injection of the [^{18}F]FLT agent and after completion of the [^{18}F]FLT PET. AEs are defined as any signs of illness or symptoms that have appeared or worsened since the infusion of [^{18}F]FLT.

At the beginning and end of the [^{18}F]FLT PET imaging session and 24 hours afterward, participants will be questioned regarding any appearance or change in signs and symptoms and will have the opportunity to add any signs/symptoms that are not listed.

[^{18}F]FLT:

- Respiratory difficulties;
- Flushing;
- Dizziness;
- Itching/rash;
- Other symptoms that could be secondary to an anaphylactic reaction.

PET Scan:

Anxiety/stress;

Discomfort;

Claustrophobia.

7.10.6.4 Expected Adverse Events Associated With Radiation Risks

While the radiation dosage for PET scanning varies with the part of the body being scanned, the exposure for this examination is approximately 2000 to 2800 millirems (depending on whether PET only or PET is used). The radiation dose from the PET has not been shown to have any adverse effects.

7.10.7 Recording of Adverse Events

At each contact (site visit and/or telephone) with the study participant, the investigator or investigator-designee must elicit, through open ended questioning (e.g. “How are you feeling?”) information on AEs. Participants should be evaluated clinically. Information on reportable AEs should be recorded immediately into the source document (e.g. ACRIN AE Log and/or progress notes of the participant’s study chart) and retained at the site.

7.10.8 Reporting Requirements of Adverse Events

7.10.8.1 The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. A copy of the most current version of CTCAE can be downloaded from the CTEP web site: http://ctep.cancer.gov/reporting/ctc.html.

7.10.8.2 Prompt reporting of all AEs is the responsibility of each investigator, investigator-designee, clinical research associate, and/or nurse engaged in clinical research. Anyone uncertain about whether a particular AE should be reported should contact the ACRIN headquarters at 215-574-3150 and ask for the ACRIN AE Coordinator for assistance.

7.10.8.3 Assignment of grades and attribution for each AE/SAE must be completed by the site principal investigator or investigator-designee.

7.10.8.4 All AEs/SAEs must be documented in the participant's study chart, AE form, and events that qualify for AdEERS must be submitted through the electronic-AdEERS (e-AdEERS) system in the required timeframes, as specified in the table below.

7.10.8.5 Routine reporting is defined as documentation of AEs on source documents and AE CRF, and submission to RTOG for preparation of a report for RTOG/ACRIN Data and Safety Monitoring Committee (DSMC) review, quarterly reports to CDUS, and the final study report.

7.10.8.6 Expedited reporting is defined as immediate notification of NCI and RTOG/ACRIN. If reporting an expedited AE, immediate notification to ACRIN is also required. Routine reporting requirements also apply.

7.10.8.7 ACRIN will collect and report all serious and non-serious, expected and unexpected imaging AEs related to the advanced imaging component of the study - MRS, DCE-MRI, DSC-MRI and/or [^{18}F]FLT PET during study participation and up to 30 days after the last study procedure.

7.10.8.8 All reportable AEs/SAEs must 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).

7.10.8.9 Advanced Imaging Adverse Events

TABLE A. AdEERS Reporting Requirements for Advanced Imaging Adverse Events

	Grade 1	Grade 2			Grade 3				Grade 4		Grade 5	
	Unexpected and Expected	Unexpected		Expected	Unexpected		Expected		Un-expected	Expected	Un-expected	Expect-ed
		with Hospital-ization	without Hospital-ization		with Hospital-ization	without Hospital-ization	with Hospital-ization	without Hospital-ization				
Unrelated Unlikely	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	Not Required	10 Calendar Days	10 Calendar Days	Not Required	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days	24-Hour; 5 Calendar Days	10 Calendar Days

Hospitalization is defined as initial hospitalization or prolongation of hospitalization for ≥ 24 hours, due to adverse event.

7.10.8.10 [^{18}F]FLT Imaging Agent Adverse Events
Reporting Requirements for Adverse Events That Occur Within 24 Hours (± 4 Hours) of the Administration of the Investigational Agent: [^{18}F]FLT

TABLE B. AdEERS Reporting Requirements for Adverse Events That Occur Within 24 Hours (± 4 Hours) of the Last Use of the Investigational Agent: [^{18}F]FLT Held Under CIP IND

	Grade 1	Grade 2		Grade 3				Grades 4 & 5
				Unexpected		Expected		
	Unexpected and Expected	Unexpected	Expected	with Hospital-ization	without Hospital-ization	with Hospital-ization	without Hospital-ization	Unexpected and Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	24-Hour; 5 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days

Hospitalization is defined as initial hospitalization or prolongation of hospitalization for ≥ 24 hours, due to adverse event.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to agent administration or other cause must be provided.

7.10.8.11 All SAEs that are still ongoing at the end of the study must be followed up to determine, to the degree possible, the final outcome. Any SAE that occurs after the study period and is considered to be possibly related to the study procedures or study participation should be recorded and reported immediately

7.10.9 Expedited Reporting to NCI, RTOG, and/or ACRIN

Some AEs require 24-hour notification. Please complete a 24-Hour Notification Report via the AdEERS web site (http://ctep.cancer.gov/reporting/adeers.html) within 24 hours of learning of the event. The full AdEERS report must be completed and submitted via AdEERS. Refer to Section 8.0 for reporting details.

If the AdEERS system is down, a 24-hour notification call must be made to TRI at 301-897-1704 and ACRIN at 215-717-2763. Once the system is restored, a 24-hour Notification Report must be entered into the AdEERS system by the original submitter of the report at the site.

When an AE requires expedited reporting, submit a full AdEERS report within the timeframes outlined in the table below. **NOTE:** AEs that meet the reporting requirements and occur within 30 days of the imaging procedures related to the Advanced Imaging sub-study must be reported on an expedited AE report form (using AdEERS).

Assignment of grades (severity level) and attribution for each AE is to be completed at the institution by the Investigator.

This study requires that expedited AE reporting use the NCI Adverse Expedited Reporting System (AdEERS). The NCI guidelines for AdEERS can be found at http://ctep.cancer.gov. For questions regarding the use of the AdEERS application, please contact the NCI Technical Help Desk: 301-840-8202. For general questions regarding completion of AdEERS reports or submissions, email CIPAEReporting@tech-res.com or call the AdEERSMD helpline at 301-897-7497.

An AdEERS report must be submitted to RTOG/ACRIN and the appropriate regulatory agencies by one of the following methods:

- Electronically submit the report via the AdEERS Web-based application located at http://ctep.cancer.gov, **or**
- If the AdEERS system is down, fax the completed NCI Adverse Event Expedited Report – Single Agent or Multiple Agents for the investigational component of the Advanced Imaging—MRS, DCE-MRI, DSC-MRI, and [^{18}F]FLT PET—adverse events (paper template located at http://ctep.cancer.gov) to TRI (301-897-7402) and ACRIN (215-717-0936).

NOTE: Paper copies of AdEERS reports will only be accepted if the AdEERS system is down. Once the system is restored, a report submitted on a paper template must be entered into the AdEERS system by the original submitter of the report at the site.

Any supporting or follow up documentation must be faxed to TRI (301-897-7402) and ACRIN (215-717-0936) for investigational component of the Advanced Imaging (MRS, DCE-MRI, DSC-MRI, and [^{18}F]FLT PET) related events.

Please refer to your local institution's IRB policies regarding AEs and SAEs and safety reports.

7.10.10 Other Recipients of AE Reports

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

8.0 SURGERY

Not applicable to this protocol.

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

For this study, patients may be on no anti-epileptic drugs (AED) or on non-enzyme inducing anti-epileptic drugs (NEIAED). See Appendix VI for acceptable NEIAEDs. If a patient on this study protocol needs to have an AED started or needs to have a second AED added then only NEIAED should be used. There must be a ≥ 14 day period from discontinuation of an EIAED and initiation of cediranib therapy. In the event that an enzyme-inducing anti-epileptic drug *must* be used for patient on study the patient will be removed from the protocol.

9.1.2 Antiemetics

Ondansetron or granisetron are recommended 30 minutes prior to the dose of cediranib and temozolomide. The recommended dose of granisetron is a 2mg oral dose 30 minutes before taking the temozolomide. The recommended dose of ondansetron is an 8mg oral dose 30 minutes before taking the temozolomide. Repeat doses of granisetron may be repeated as needed. Granisetron may not be on the formulary at some participating sites and patients at these sites must be given a prescription for the drug to be dispensed at an outside pharmacy in the event it is prescribed.

9.1.3 Anticoagulants

Anticoagulants, including warfarin and low-molecular weight heparin, are allowed for venous thromboembolic events or other conditions that require anticoagulation.

9.1.4 Antidiarrheals

Diarrhea should be treated at an early stage (Common Toxicity Criteria Adverse Event (CTCAE) Grade 1) with loperamide or similar agent. The patient should be given a prescription to take as required at home. For CTCAE Grade 3-4 diarrhea refractory to oral anti-diarrheal medication, cediranib will be held. If ≥ CTCAE Grade 3 diarrhea persists for > 2 weeks, cediranib should be discontinued. If the toxicity resolves to ≤ CTCAE Grade 1, then the cediranib will be restarted and the dose reduced. If ≥ CTCAE Grade 3 diarrhea recurs cediranib should be discontinued.

9.1.5 Analgesics

Analgesics are allowed at the discretion of the treating physician.

9.1.6 Hematopoietic Growth Factors

Routine prophylactic use of granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GBM-CSF) is not recommended on this trial. Therapeutic G-CSF use in patients with serious neutropenic complications such as tissue infections, sepsis syndrome, fungal infection, etc., may be given at the investigator's discretion.

9.1.7 Herbal products

No data exists regarding the interaction of cediranib with commonly used herbal or non-traditional medications. Patients should be instructed not to use such medications while receiving cediranib therapy.

9.1.8 Nutritional supplementation

Nutritional supplements are allowed at the discretion of the treating physician.

9.1.9 PCP Prophylaxis

Trimethoprim-Sulfamethoxazole (TMP/SMX) as one double-strength table by mouth three times per week (MWF) or an alternative as determined by the treating physician (atovaquone or dapsone) is required as prophylaxis against opportunistic pulmonary infection during the period of radiation plus temozolomide. After completion of the chemoradiation, patients with a lymphocyte count < 500/mm^3 should have CD4 quantification. If the CD4 is < 200, then prophylaxis is recommended to continue and the CD4 should be quantified on a monthly basis. If the lymphocyte count is ≥ 500 or the CD4 is > 200, then prophylaxis can be stopped. However, if in the opinion of the treating physician, the patient may benefit from continuation of TMP/SMX (example: patient on long-term corticosteroids) the medication may be continued. Pentamidine is NOT allowed due to the potential of this drug to prolong the QT interval.

9.1.10 Corticosteroids

Postoperatively, corticosteroids should be tapered to a stable dose as determined by the clinical status of the patient. **However, patients must be maintained on a stable corticosteroid regimen for 5 days prior to their baseline MRI scan.** The lowest required steroid dose should be maintained throughout the duration of the study in order to eliminate steroid effects as a confounding variable in the interpretation of serial brain imaging studies. Corticosteroid doses can be tapered as clinically indicated if the patient appears to be responding to therapy as judged by serial scans. Corticosteroid dose may, of course, be increased in the event of clinical deterioration or at the discretion of the attending physician. In the event of suspected clinical deterioration, repeat brain imaging is recommended.

9.1.11 Thyroid Replacement

Replacement levothyroxine should be given when clinically indicated to normalize the thyroxine level to within the normal range, and before the patient becomes clinically symptomatic. Replacement levothyroxine therapy may also be considered in patients with TSH increases (and thyroxine levels within the normal range), together with adverse events and symptoms suggestive of incipient hypothyroidism. Thyroid function should be monitored frequently and the dose of levothyroxine should be titrated as required.

9.1.12 Phosphorous Replacement

Replacement for phosphorous depletion is allowed and may consist of oral or intravenous replacement depending on the clinical situation. Hypophosphatemia should not be considered a dose-limiting toxicity until maximal medical replacement has been attempted.

9.1.13 Although the following medications are not contraindicated on this study, each should be used with extreme caution, due to potential nephrotoxic effects: vancomycin, amphotericin, and pentamidine.

9.2 Non-permitted Supportive Therapy

Enzyme-inducing anti-epileptic drugs are not permitted in this trial.

10.0 TISSUE/SPECIMEN SUBMISSION

10.1 Tissue/Specimen Submission

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

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

10.2 Specimen Collection For Central Review For Eligibility (Step 1 Registration) (Mandatory) (8/26/10)

Central pathology review is mandatory for this study and must occur as soon as Step 1 registration is complete. Dr. Ken Aldape will perform a pathology review for every case. The pathology review will consist of: (1) confirmation that the histologic features meet the WHO criteria for GBM; and (2) confirmation that the tissue is of sufficient size for analysis of MGMT status.

Tissue specimens should be taken from pre-study surgical resection; stereotactic biopsy is not allowed. The following materials are required:

10.2.1 Representative tissue blocks that contain diagnostic viable tumor.

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

10.2.2 A Pathology Report documenting that the submitted material contains tumor; the report must include the RTOG protocol number and the patient's initials. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

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

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

10.2.5 Send pathology material by overnight mail directly to:

Ken Aldape, M.D.
Department of Pathology, Box 85, Room G1.3563
UT MD Anderson Cancer Center
1515 Holcombe Blvd.
Houston, TX 77030
(713) 792-834-6228
FAX (713) 792-3573
kaldape@mdanderson.org
rtogpath@gmail.com

- Include on the P4 form the name, telephone number, and fax number of the person to notify with the results of the tissue evaluation.
- Shipments must be made Monday through Thursday.
- Notify Dr. Aldape by email (please use both email addresses) on or before the day of submission: (1) that a case is being submitted for review; (2) the name of the contact person; (3) when to expect the sample; and (4) the overnight shipping carrier and tracking number.
- Dr. Aldape will email the appropriate contact person from the submitting institution with the results and will fax a copy of the completed form to the institution and to RTOG Headquarters. **If Dr. Aldape is given the proper email notification, review is guaranteed within 3 business days of receipt of the tumor block.**
- Since there is a narrow time window within which the review must be completed, submission of

tumor blocks should be done as soon as possible to ensure sufficient time for review. *Dr. Aldape must receive the tumor block within 28 days of surgery to allow time for review and molecular testing. Samples received after this time will not be accepted*.

- If the patient does not meet eligibility requirements, *all* tissue and forms will be returned to the participating submitting institution.

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

10.2.7 Upon patient registration, Dr. Aldape will cut sections for DNA/RNA isolation and send material for MGMT methylation analysis.

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

10.3 Specimen Collection for Tissue Banking (Strongly Encouraged) (8/26/10)

[For patients who have consented to participated in this component of the study (See Tissue Consent of Appendix I)]

10.3.1 Dr. Aldape will send remaining tissue (collected and shipped per Section 10.2) of consenting patients to the RTOG Biospecimen Resource. The Biospecimen Resource will punch tissue for banking. If return of a block is desired, please email Dr. Aldape (rtogpath@gmail.com) indicating your request.

10.3.2 Submission of frozen tissue is strongly encouraged in order to maximize the information gained from this trial. When available, frozen tissue should be collected as described in Appendix VII and be sent on dry ice to the RTOG Biospecimen Resource at the address below. The RTOG Biospecimen resource will supply kits for frozen tissue. To request a kit, contact the Biospecimen Resource at RTOG@UCSF.EDU or by phone at 415-476-7864.

10.3.3 Serum, Plasma, Whole Blood, and Urine

- Serum, plasma, and urine should be collected pretreatment, week 5, and at 1 and 6 months post-treatment.
- Whole blood should be collected pretreatment only.
- The following must be provided to the RTOG Biospecimen Resource: A Specimen Transmittal Form documenting the date of collection of the serum, plasma, whole blood and/or urine; the RTOG protocol number, the patient's case number, and method of storage, for example, stored at -20° C, must be included.
- See Appendices VII and VIII for detailed instructions, including information pertaining to collection kits.

10.3.4 Storage Conditions

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

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

OR:

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

OR:

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

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

10.3.5 Submit materials for tissue banking to:

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

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

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

10.4 Summary of Specimen Submission Details (8/26/10)

Specimen	Taken When	Submitted As	Shipping
REQUIRED for Central Pathology Review			
1 block	From pre-study open biopsy or surgical resection	Paraffin-embedded block	Prior to registration Overnight mail to Dr. Aldape
STRONGLY ENCOURAGED for Central Pathology Review			
1 or more *additional* blocks	From pre-study open biopsy or surgical resection	Paraffin-embedded block	Prior to registration Overnight mail to Dr. Aldape
Slide	From pre-study open biopsy or surgical resection	H&E stained slide	Prior to registration Overnight mail to Dr. Aldape
STRONGLY ENCOURAGED for Tissue Banking and Translational Research			
Frozen tissue	From pre-study open biopsy or surgical resection	Snap freeze tissue samples in liquid nitrogen. *(If no liquid nitrogen is available, freeze on dry ice.)* Store at –70 to –80° C	Post registration Overnight mail on dry ice to RTOG Biospecimen Resource
Serum	Pretreatment, week 5, 1 month post-treatment, 6 months post-treatment	Aliquot 0.5 ml serum into 1 ml cryovials (up to 10) Store at –80° C	Frozen on dry ice to RTOG Biospecimen Resource via overnight carrier
Plasma	Pretreatment, week 5, 1 month post-treatment, 6 months post-treatment	Aliquot 0.5 ml plasma into 1ml cryovials (up to 10) Store at –80° C	Frozen on dry ice to RTOG Biospecimen Resource via overnight carrier
Whole blood	Pretreatment	Aliquot 1.0 ml blood into 1 ml cryovials (up to 5) Store at –80° C	Frozen on dry ice to RTOG Biospecimen Resource via overnight carrier
Urine	Pretreatment, week 5, 1 month post-treatment, 6 months post-treatment	Two 10 ml urine aliquots in 2 sterile 15 ml polypropylene centrifuge tubes. Store frozen at -20 or 80° C	Frozen on dry ice to RTOG Biospecimen Resource via overnight carrier

10.5 Reimbursement for Tissue Banking (8/26/10)

RTOG will reimburse institutions for submission of protocol-specified biospecimen materials sent to the Biospecimen Resource at the University of California San Francisco and other protocol-specified collection repositories/laboratories. After confirmation from the RTOG Biospecimen Resource or other designated repository/laboratory that appropriate materials have been received, RTOG Clinical Trials Administration will authorize payment according to the schedule posted with the Reimbursement and Case Credit Schedule found on the RTOG web site

(http://www.rtog.org/pdf_document/RTOG_STUDY_LIST.pdf). Biospecimen payments will be processed quarterly and will appear on the institution's summary report with the institution's regular case reimbursement.

10.6 Confidentiality/Storage

(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 Biospecimen Resource database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

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

10.7 Translational Research

Since cediranib is an antiangiogenic agent, it will be useful to test whether markers of angiogenesis are specific predictors of response to this agent. Samples will be tested for molecular markers of angiogenesis, including expression of VEGF using a real-time quantitative PCR assay. In addition, since proliferation of vascular elements is a fairly direct demonstration of ongoing angiogenesis, immunohistochemistry for the Ki-67 antigen, using the MIB-1 antibody, will be performed, and the proliferation index (of the vascular components only) will be determined. The studies indicated here as well as possible exploratory studies to be performed on either leftover paraffin tissue or frozen tissue sent directly to the RTOG Biospecimen Resource, will be not take priority over the main study objectives and will be performed only if there is sufficient tissue available following the pathology review and MGMT analysis.

10.8 ACRIN 6689 Blood Collection and Blood Sampling (Prior to MR and During Dynamic [^{18}F]FLT PET Scans—at All Time Points) (8/26/10)

10.8.1 Blood will be drawn from all advanced-imaging participants prior to imaging at each MR imaging time point. Two vials of blood (less than 20 mL) will be collected at each time point from each of the 51 sub-study participants. Blood collection can occur at the time of intravenous catheter placement for gadolinium administration or per the NOTE below. Specimens will be discarded after processing is completed. Blood samples will be collected and delivered to an ACRIN-certified laboratory for analysis of circulating biomarkers. See the Biomarker Process Manual posted to www.acrin.org/6689_imagingmaterials.aspx.

10.8.2 This study will use blood samples taken during [^{18}F]FLT PET scans to obtain FLT blood clearance function and to calibrate and correct an image-based blood clearance curve based on the level of FLT in venous blood close to the end of the study when there are no arterial-venous differences. This is needed for kinetic analysis and modeling. Metabolites also may be evaluated. Blood will be drawn from all advanced-imaging participants during the dynamic [^{18}F]FLT PET scans. Blood sampling will occur at 3 time points during each scan. Blood samples will not be collected by ACRIN centrally, but will be locally processed same-day. Specimens will be discarded after processing is completed. **Exact time documentation of collection of blood sampling is key for this portion of the protocol.** Time will need to be recorded using a standard global time piece for the study. Minutes and seconds will be recorded and reported. See Appendix XI and www.acrin.org/6689_imagingmaterials.aspx for details.

NOTE: On days when both the MR and PET scans are being performed, the same intravenous (IV) catheter can be used for blood collection related to the MR and PET scans as described above. Note that for [^{18}F]FLT PET, two IV lines are needed, as it is not feasible to perform blood sampling and [^{18}F]FLT infusion through the same catheter.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters: See Appendix II.

11.2 MRI Review (standard MRI for all cases)

11.2.1 The serial MRI will be examined at the institution by an independent reviewer (i.e., a neuroradiologist who is not a co-investigator on this study and who is not involved in the patient's care). The evaluation of the scans will be compared to and correlated with the patient's clinical course.

11.2.2 All standard MRI exams will be submitted to the ACRIN Imaging Core Laboratory for central review for determination of progression-free survival. Central analysis will be performed by each of two readers on all eligible examinations. Images will be assessed using MacDonald criteria for progression versus response on 2D T1 and T2 weighted images. A third reader will adjudicate in the event of discordance. Reads will be performed after all time points have been collected for the case, and results of the central read will be provided to RTOG for further analysis.

11.3 Measurement of Response [NOTE: A Radiology Review Form (SR) must be signed by the radiologist and submitted per Section 12.1]

The primary measure of response will be by serial measures of the product of the two largest cross-sectional diameters. Response will also be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [JNCI 92(3): 205-216, 2000]. See http://ctep.cancer.gov/guidelines/recist.html for further details.

11.3.1 Complete Response (CR)

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

11.3.2 Partial Response (PR)

Decrease of > 50% in the product of two diameters with the patient off all steroids, or on adrenal maintenance only; PR will be coded only if confirmed by a second MR scan performed a minimum of 4 weeks after the initial scan.

11.3.3 Minor Response (MR)

Decrease in diameter products of < 50% with the patient off all steroids, or on adrenal maintenance only. This will not need a confirmatory scan.

11.3.4 Stable Disease (SD)

Circumstance when the scan shows no change. Patients should be receiving stable or decreasing doses of steroids. This will not need a confirmatory scan.

11.3.5 Progression (P)

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

11.4 Criteria for Evaluation of Therapy Effectiveness

11.4.1 Tumor response and regrowth can frequently be difficult to measure directly. Serial neurological exams and MRI scans may provide a guide to the actual course. Time interval to progression will be measured from registration until deterioration is documented by the individual investigator using these guides.

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

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

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

11.5 Criteria for Discontinuation of Protocol Treatment

NOTE: See Section 11.6.7 for criteria for discontinuation of ACRIN 6689 Advanced Imaging Study

- Progression of disease;
- Unacceptable toxicity to the patient (at the discretion of the treating physician) — Reasons for removal must be clearly documented on the appropriate case report form/flowsheet, and RTOG Headquarters data management must be notified;
- A delay in drug therapy due to toxicity > 14 days as described in Section 7.5.

- The patient may withdraw from the study at any time for any reason. The institution must notify RTOG Headquarters Data Management about this in writing and follow the guidelines set forth in the RTOG procedure manual.

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

11.5.1 Administration of Medications at Disease Progression

Cediranib/placebo and temozolomide will be discontinued at the time of disease progression.

11.6 ACRIN 6689 Advanced MRI and Dynamic [^{18}F]FLT PET with Blood Sampling Overview (only for sites participating in the advanced imaging component) (8/26/10)

11.6.1 Advanced MRI Pre-qualification and Overview

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

A sub-set of sites will be pre-qualified to conduct advanced MRI sequences at 1.5 Tesla or 3 Tesla (preferred) for all imaging-eligible patients at qualified sites until the 51-participant target has been reached. For this Advanced Imaging, each visit MRI will also include the additional standard MRI sequences: T2-weighted images, FLAIR images, diffusion-weighted (or diffusion tensor) images, and 3D T1 volumetric imaging. Contrast agent application will be performed before the T1-weighted post contrast scan. Contrast is administered at the standard dose of 0.1 mmol/kg of standard Gd agent, IV injection for the DCE-MRI, and also 0.1 mmol/kg for the DSC-MRI.

Blood collection (two vials, less than 20 mL) prior to imaging at each MR time point can be drawn at the time of IV placement for gadolinium injection. The blood collected will be submitted to an ACRIN-certified laboratory for analysis of circulating biomarkers. See the Biomarker Process Manual posted to www.acrin.org/6689_imagingmaterials.aspx. On days when the [^{18}F]FLT PET is also being performed, the same IV catheter intended for blood sampling during the PET scan can be used for the pre-MR blood collection. For the advanced MRI component of the trial, examinations will include perfusion MRI, including DCE and DSC sequences.

In the Advanced Imaging sub-study, MRS, DCE-MRI, and DSC-MRI with blood sampling will be performed at seven (7) time points:

- T0: Baseline (within 7 days prior to initiation of chemoradiation);
- T1: Between doses (within 2 to 24 hours after the first dose of placebo or cediranib, but prior to the second dose of placebo or cediranib/radiation/TMZ);
- T2: Week 4 of chemoradiation;
- T3: Week 10 (Week 4 after completion of chemoradiation);
- T4: Week 16 (Week 10 after completion of chemoradiation);
- T5: Week 24 (Week 18 after completion of chemoradiation); and
- T6: Progression (whenever disease progression occurs; progression is defined as > 25% increase in tumor area [two diameters]).

NOTE: Renal function must be assessed within 28 days prior to each MRI time point to ensure creatinine is 1.7 mg/dL or lower prior to gadolinium administration.

11.6.2 Dynamic [^{18}F]FLT PET Pre-qualification and Overview

11.6.2.1 Participant must be scanned on PET scanners that have been qualified by the ACRIN PET Core Laboratory per the protocol-specific instructions posted on the ACRIN web site at: www.acrin.org/CORELABS/PETCORELABORATORY/PETQUALIFICATION/tabid/485/Default.aspx.

11.6.2.2 A dedicated PET scanner or hybrid PET/CT scanner is mandatory. The PET scanner must be capable of performing both emission and transmission images in order to allow for attenuation-corrected PET scan images. The ability to calculate standardized uptake values (SUVs) is mandatory.

11.6.2.3 Serial scans of the same participant must be done on the same scanner for this study.

11.6.2.4 The PET scanner must be kept calibrated in accordance with the manufacturer's recommendations. The scanner should routinely be assessed for quantitative integrity and stability by being tested using various imaging protocols on a standard phantom. For SUV

measurements, this assessment should include a comparison against a dose calibrator to ensure accuracy; that is, a comparison of absolute activity measured versus the measured activity injected, should be performed.

11.6.2.5 The PET scanner calibrations should be routinely verified according to manufacturer recommendations. The scanner should be assessed regularly for quantitative integrity and stability by scanning a standard quality control phantom with the same acquisition and reconstruction protocols used for study participants. The SUV verification measurements must include the dose calibrator used to measure the doses of study participants to ensure that the dose calibrator and PET scanner are properly cross calibrated, i.e. the dose measured in the dose calibrator and injected into the phantom matches the results obtained from analysis of the phantom images.

11.6.2.6 A daily quality control (QC) check must be performed at the beginning of the day, including PET scanner and dose calibrator in accordance with the manufacturer recommendations. If any of the QC results are outside of the manufacturer's guidelines, the study must be rescheduled and the problem rectified before scanning any patients.

11.6.2.7 All 51 advanced-imaging study participants will undergo dynamic [^{18}F]FLT PET and blood sampling at three (3) time points; a subset of 25 participants consenting to advanced imaging will undergo a fourth dynamic [^{18}F]FLT PET (Baseline #2) with blood sampling (the first 5 participants accrued at each site will undergo this scan until 25 scans are completed):

- T0: Baseline #1 (within 7 days prior to initiation of chemoradiation);
- T0.1: Baseline #2 (prior to initiation of chemoradiation); must be completed within 7 days of the T0 scan, but can occur before or after the T0 MRI scan;
- T1: Between doses (within 2 to 24 hours after the first dose of placebo or cediranib, but prior to the second dose of placebo or cediranib/radiation/TMZ); and
- T3: Week 10 (Week 4 after completion of chemoradiation).

NOTE: "PET" may refer to PET, PET/CT, or MR-PET depending on the site.

11.6.3 Pre-Scan Participant Preparation

11.6.3.1 There will be no deliberate fasting prior to injection for the participant of the study.

11.6.3.2 Participant's height and weight must be measured using calibrated and medically-approved devices (not verbally relayed by the participant).

11.6.3.3 Two (2) IV catheter access lines (18 or 20 gauge is preferred) are placed, one in each arm—one for the [^{18}F]FLT injection and the other for blood sampling during the scan.

11.6.3.4 The dose of [^{18}F]FLT will be <6.1µg for a single injection. Assuming a 70kg individual, the maximum concentration of [^{18}F]FLT would be expected to be equivalent to 0.29 ng-h/mL.

11.6.3.5 A saline flush should follow the [^{18}F]FLT injection.

11.6.3.6 The exact time of calibration of the dose should be recorded using a global time piece consistently used throughout the study for time recording; the exact time of injection should be noted and recorded to permit correction of the administered dose for radioactive decay. In addition, any of the dose remaining in the tubing or syringe, or that was spilled during injection, should be recorded. The injection should be performed through an IV catheter and 3-way stopcock.

11.6.3.7 AEs will be solicited in open-ended fashion (i.e., "how are you feeling?") at this time.

11.6.4 Dynamic [^{18}F]FLT PET Imaging

11.6.4.1 Single field-of-view dynamic imaging must begin after [^{18}F]FLT injection. Imaging start time should be recorded using the global time piece for the study (see Section 11.6.3 for description). [^{18}F]FLT must be infused over one minute using a syringe pump.

11.6.4.2 An attenuation scan should be performed after emission scanning. The transmission scan should be a low-dose CT scan for the PET/CT or a transmission scan for PET-only devices. The transmission scan type, length, etc. should exactly match that used in the calibration and qualification procedure.

NOTE: "PET" may refer to PET, PET/CT, or MR-PET depending on the site.

11.6.4.3 During the dynamic emission scan, three (3) venous blood samples are obtained at 15, 30, and 60 minutes. Blood must be drawn from the IV that was not used for the [^{18}F]FLT injection. The exact time of the blood draws should be recorded using the standard global time piece for the study.

11.6.4.4 Whole blood samples of 1mL each are counted in a multichannel gamma well counter that is calibrated in units of cpm/uCi (see Appendix XI for well counter cross-calibration instruction and Appendix XI for blood sampling procedures).

11.6.4.5 The exact time that each blood sample is counted should be recorded using the global time piece.

11.6.5 Well-Counter Calibration/Blood Sampling with [^{18}F]FLT PET: Pre-Qualification and Sampling Guidelines

In this study, we will use blood samples taken during [^{18}F]FLT PET scans to determine the FLT blood clearance function and perform kinetic analysis for subsequent modeling. Metabolites also may be evaluated. ***Exact time of collection is key for this protocol.*** Time will need to be recorded from a global resource to be used throughout the study. Preferably, minutes and seconds will be recorded and reported.

11.6.5.1 *Well-Counter Calibration*

See Appendix X for well counter cross calibration details.

As a pre-qualification measure, sites will need to demonstrate appropriate well-counter cross calibration.

Well counter cross calibration should be completed prior to each PET scan. Should issues arise with cross-calibration, the imaging study must be rescheduled and the problem rectified before scanning the participant at that time point.

An Excel document to assist in calculations during cross calibration is provided online at www.acrin.org/6689_imagingmaterials.aspx.

11.6.5.2 *Blood Sampling*

See Appendix X for additional procedural details.

Blood will be drawn at three time points from all advanced-imaging participants during the 90-minute dynamic [^{18}F]FLT PET imaging sequence (venous samples are obtained at 15, 30, and 60 minutes). Sites are expected to process the blood samples locally and discard the specimens after processing.

NOTE: Dose calibrators are not permitted for blood sample counting. All samples should be counted in a scintillation well counter designed to count low-level gamma-emitting radioactivity.

11.6.6 Advanced MRI and Dynamic [^{18}F]FLT PET Site Imaging Quality Assurance Review

Sites involved in Advanced Imaging must be pre-qualified for image quality per guidelines in Section 5.1.5 of the protocol. Information regarding the MRI quality assurance review process for Advanced Imaging can be found at www.acrin.org/6689_imagingmaterials.aspx, in Appendix VIII (Section 2.4), in the Protocol Specific Application (PSA), and in Section 5.1.5 of the protocol. Advanced MRI exam sequences will be collected and archived at ACRIN Headquarters for a post-trial centralized reader study.

Central Advanced MRI and Dynamic [^{18}F]FLT PET QA Review and Assessment: Advanced MRI and PET images will be assessed locally for quality and for disease progression. Patient-specific information will be removed from the image prior to submission. Advanced MR and PET images will be transmitted electronically to ACRIN Headquarters. (Refer to Section 2 in Appendix XI for image submission instructions.) This will allow early quality assurance (adherence to protocol, adequacy of image quality). Ongoing quality assessment in the ACRIN Core Lab will facilitate any revisions needed for this Advanced Imaging. It will also facilitate later central review of all images in a manner to minimize bias.

11.6.7 Criteria for Discontinuation of ACRIN 6689 Advanced Imaging Study

If a participant is unable to complete advanced imaging sequences for the following reasons, the individual will need to be replaced to ensure 51 participants' data are accrued:

- Allergic reaction from gadolinium or [^{18}F]FLT radiotracers;
- Participant missing any of the first three (3) advanced imaging time points—T0, T1, or T2—for any reason, including toxicity.

12.0 DATA COLLECTION

Data should be submitted to:

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

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

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

12.1 Summary of Data Submission (2/26/10)

SEE SECTION 12.3 FOR ALL IMAGING SUBMISSION

Item	Due
Pre-Registration Pathology Submission Form **(P4)**	Within 4 weeks after surgery
Demographic Form **(A5)**	Within 2 weeks after registration
Initial Evaluation Form **(I1)**	Within 2 weeks after registration
Pathology Report **(P1)**	Within 2 weeks after registration
Specimen Transmittal Form **(ST)**	Within 2 weeks after registration
Treatment Summary Form **(TF)**	After completing chemo + RT; after 1 month of single-agent cediranib/placebo; and then monthly during temozolomide plus cediranib/placebo. (1 month = one 28-day "cycle," for a maximum of 12 cycles).
Follow-Up Form **(F1)**	At the conclusion of protocol therapy, then q 3 months X 1 year, q 4 months X 1 year, then q 6 months. Also at 26 weeks after registration and at the time of progression/relapse and death.
Radiology Review Form **(SR)**	After completing scans prior to odd # cycles, response confirmation, and at progression
Operative Reports **(S2)**, Surgical Reports **(S5)** (for subsequent surgery)	As applicable
Autopsy Report **(D3)**	As applicable

12.2 Summary of Dosimetry Digital Data Submission (Submit to ITC; see Section 12.2.1) (2/26/10)

SEE SECTION 12.3 FOR ALL IMAGING SUBMISSION

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

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

12.2.1 *Digital Data Submission to ITC*

Digital data submission may be accomplished using media or the Internet.

For network submission: The SFTP account assigned to the submitting institution by the ITC shall be used, and e-mail identifying the data set(s) being submitted shall be sent to:

itc@wustl.edu

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

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

12.3 ALL CASES (RTOG and ACRIN): Standard Image Scan Submission to ACRIN

Prompt submission of all image data is essential to ensure adequate image quality control.

Instructions for image submission and anonymization, as well as information regarding Quality Control are available at www.acrin.org/6689_imagingmaterials.aspx.

12.4 Advanced Image Scan Submission to ACRIN - ONLY For Sites PARTICIPATING in the Advanced Imaging Component

Refer to Appendix XI for detailed instructions for advanced MR and PET image submissions.

12.4.1 General Imaging Data

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

12.4.2 Clinical Data Submission

Upon successful registration to RTOG of participants consented to the advanced MRI and dynamic [^{18}F]FLT PET option, an ACRIN case-specific calendar will be generated. This calendar lists all forms and designated reports required by protocol along with form due dates at ACRIN's Data Management Center (DMC). The calendars are available 24 hours a day on the ACRIN web site and will be updated as the study proceeds to reflect data that have been received, due dates for queries about unclear data, deadlines for follow-up reports of adverse events, or changes in the protocol that change the data being collected or the timeframe. The research associate may use the calendar as a case management tool for data submission and follow-up scheduling. The investigative site is required to submit data according to protocol as detailed on each participant's ACRIN calendar.

To submit data via the ACRIN web site, the appropriate investigator-designated research staff will log in to the Data Center through the ACRIN web site with the pre-assigned user name and password. Case report forms will be available on the web site at http://www.acrin.org/6689_protocol.aspx. Each web form is separated into modules; each module must be completed sequentially in order for the internal programming to be accurate. The user selects the link to the appropriate form and enters data directly into the web-based form. As information is entered into the web form application, various logic checks will be performed. These logic checks look for data that are missing, out of range, or in the wrong format (e.g. character data in a field requiring numeric responses). Such errors will be detected as soon as the user attempts to either submit the form or move to the next data element. The user will not be able to finalize form transmission to the DMC until all data entered pass these logic checks. Forms that are not completed in one sitting can still be submitted and completed at a later date. The form will remain available on the web until the "Complete Form" button is depressed.

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

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

12.4.3 Data Security

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

12.4.4 Electronic Data Management

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

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

12.4.5 Missing and Delinquent Data Submission

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

12.4.6 Data Quality Assurance

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

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

13.0 STATISTICAL CONSIDERATIONS

NOTE: See Section 13.7 for Statistical Considerations for ACRIN 6689 Advanced Imaging Component.

13.1 Study Endpoints

13.1.1 Primary Endpoint

6-month progression-free survival rate.

13.1.2 Secondary Endpoints

13.1.2.1 Overall survival, defined as the interval from randomization to death due to any cause

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

13.1.2.3 Treatment-related toxicity, measured by CTCAE, v.4.0.

13.2 Sample Size

13.2.1 Treatment Comparison: Sample Size Derivation and Power Justification

Concurrent chemoradiation and standard temozolomide dose maintenance, serving as the control arm in an ongoing phase III study RTOG 0525, will continue to serve as the control arm in this proposed design. The sample size calculation will address whether the addition of cediranib to concurrent chemoradiation and standard temozolomide will improve the 6-month progression-free survival rate in patients with glioblastoma compared to the standard arm (control arm). The null hypothesis is that the progression-free survival rates for both arms are 50%. The alternative hypothesis is that patients receiving the experimental regimen will have a 6-month progression-free survival rate of 66%. The study will be a randomized phase II screening trial as proposed by Rubinstein, et al. The randomization of experimental and standard arms is set as 2:1. With 150 eligible subjects, there will be 80% power to detect a 16% increase in 6-month progression-free survival at a significance level of 0.15, using a one-sided Z test for two proportions. Guarding against up to 15% patients not eligible for randomization due to insufficient tissue, progression, death, or other reasons, the final targeted accrual for this study component will be 177 cases.

13.2.2 Association Between MGMT Status and Survival: Power Justifications

A retrospective analysis of EORTC 26981/22981 - NCIC trial CE.3 in GBM showed that patients with methylated MGMT promoter had significantly improved survival as compared to patients with unmethylated MGMT promoter (HR = 2.5) and this effect was also seen when the comparison was done by treatment arm (Hegi et al 2005). Endpoints for the correlative studies will be overall survival and progression-free survival. Endpoints will be measured within each treatment arm, as well as the study as a whole. For planning purposes, it is assumed that patient accrual will not be discontinued before the trial reaches its final analysis. MGMT methylation status is a stratification variable in this study; therefore, it is projected that all randomized patients will be available for MGMT methylation evaluation. Based on the prevalence of MGMT methylation status in RTOG 0525 with same patient population, it is expected that 30%, 60% and 10% patients will be classified as having methylated, unmethylated and indeterminate respectively.

The correlative analyses will be performed after patients have a minimum of 20 month follow-up. At that time, we expect approximately **53, 32, and 85** deaths with MGMT methylated/unmethlyated status on the experimental arm, the control arm, and combined arms respectively, if the study results show a positive treatment (30% reduction in the hazard of death and median survival of 20 months). Patients with MGMT indeterminate status will be analyzed separately. The table below shows statistical powers to detect hazard ratios for survival of 2.0, 2.25, 2.5 and 3.0 between MGMT methylated and unmethylated groups, as well as hazard ratio detections with 80% power. As seen in below, in the comparisons of experimental arm, standard arm and combined arms, there will be around or greater than 80% statistical power to detect a hazard ratio of 2.25, 3, and 2 or bigger between MGMT unmethylated and methlyated groups, respectively. Statistical power is calculated at a significance level of 0.05 (two-sided) for the experimental arm, the standard arm, and whole study if the overall survival for this study is positive.

Statistical Power And Hazard Ratio Detection Between Methylated and Unmethylated Groups Within and Across Treatment Regimens

	Number of Patients	Number of patients under methylated and unmethylated groups	Number of events under methylated and unmethylated groups	Statistical power for the HR of				80% power HR detection
				2.0	2.25	2.5	3	
Experimental arm	100	90	53	66%	**79%**	88%	96%	2.3
Standard arm	50	45	32	45%	57%	68%	**83%**	2.9
Whole study	150	135	85	**85%**	94%	97%	99%	1.9

13.3 Patient Accrual

The average monthly accrual rate to RTOG 0420 (a phase II single-arm study) for the same patient population was 15 cases during the whole accrual period and 22 cases excluding the first 6 months during which IRB approvals were obtained in individual institutions. The monthly accrual rate to RTOG 0525 (a randomized phase III study) for the same patient population was 41 cases during the whole accrual period and 46 cases excluding the first 6 months. Because of the time for local IRB approval and competition for patient accrual to RTOG 0825 (a randomized phase III GBM trial), it is projected that there will be no patient accrual in the first 4 months. Patient accrual will gradually increase for the next 8 months. During months 13 through 18, the study accrual will be between 5 and 8 cases per month. Patient accrual will reach 15 cases per month at 2 years after activation. According to this projection, it will take 30 months to reach the target accrual. If the total accrual during months 13 through 18 of the study is ≤ 20% of the targeted accrual (≤ 1 cases per month), the protocol will be discontinued per NCI-CTEP accrual guidelines. If the total accrual is between 21% and 49%, the protocol will continue to accrue subject to approval of the RTOG Data Monitoring Committee (DMC) and NCI-CTEP. If continued, the study must accrue at least 50% of the targeted accrual (> 7.5 cases per month) during months 22 through 24 to remain open beyond 2 years.

13.4 Stratification and Randomization

The randomization will occur in a 2:1 ratio between cediranib and placebo arm. The RTOG has previously performed a recursive partitioning analysis of patients with glioblastoma and has identified four distinct prognostic groups based upon age, performance status, extent of pretreatment surgery, neurological function, and mental status. Patients on this study will be classified either as class III (age <50 and KPS 90-100), class IV (age <50 and KPS <90 **OR** age ≥ 50 and partially or total resected with no worse than minor neurofunction impairment), or class V (Age ≥ 50 years and KPS 70-100 and underwent prior partial or total tumor resection with worse than minor neurofunction impairment, **OR** Age ≥ 50 years and KPS 70-100 and underwent prior tumor biopsy only, **OR** Age ≥ 50 years, KPS <70). In addition to RPA class, patients will be stratified by MGMT methylation status (methylated vs. unmethylated vs. indeterminate). Patients will be randomized in a permuted block design using the method of described by Zelen (Zelen 1974).

13.5 Analysis Plans

13.5.1 Statistical Methods

The difference in 6-month progression-free survival rates between the two treatments will be tested using Z test for two proportions (Ott 1993). Overall and progression-free survival rates will be estimated using the Kaplan-Meier method (Kaplan 1958), and differences between treatment arms will be tested in the log rank test (Mantel 1966). Overall survival will be measured from the date of randomization to the date of death or, otherwise, the last follow-up date on which the patient was reported alive. Progression-free survival will be measured from the date of randomization to the date of first progression or death or, otherwise, the last follow-up date on which the patient was reported alive. Differences in observed severities of toxicities (grade 3+) between groups will be tested using a chi square test.

Multivariate analyses with the Cox proportional hazard model (Cox 1972) for overall and progression-free survival will be performed with the stratification variables as fixed variables to assess the treatment effect adjusting patient-specific risk factors. The covariates evaluated for the multivariate models are: assigned protocol treatment, MGMT methylation status, RPA risk class and other prognostic factors. Proportional hazard assumptions will be checked using different graphical or time-varying coefficients testing methods. If the data clearly do not follow proportional hazards, other statistical models will be used to fit the data instead. Possible alternatives are to use the stratified Cox proportional hazard model, accelerated failure model, or partition the time axis into sections where proportional hazard assumption holds. Statistical analysis will also be performed to identify the effect of MGMT methylation status on overall and progression-free survival. The log-rank test will be used to test for overall and progression-free survival differences between different groups.

13.5.2 Interim Futility Analysis

The interim futility analysis will be performed when 50% of the total patients (75 eligible patients) have a minimum of 6-months of follow-ups and finish the 6-month progression-free evaluation. The analysis will be performed on an intent-to-treat basis, with all eligible cases included in the treatment arm to which they were randomized regardless of what treatment the patients actually received. The primary endpoint of the 6-month progression-free survival rate will be tested. The futility will be tested using the conditional probability under the alterative hypothesis of detecting the hypothesized treatment benefit favoring the experimental arm at the final analysis given the observed data. The results from testing the treatment futility will be reported to the RTOG DMC. The responsible statistician may recommend early reporting of

the results and/or stopping accrual (if applicable) of the trial if the conditional power is less than 0.1. The accrual rate, treatment compliance, safety of the treatments, and the importance of the study are also considered in making such a recommendation. The results will be reported to the RTOG DMC with the treatment blinded. The DMC will then make a recommendation about the trial to the RTOG Group Chair.

13.5.3 Interim Analysis to Monitor Study Progress

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

a) the patient accrual rate with a projected accrual completion date
b) accrual by institution
c) the pretreatment characteristics of accrued patients including MGMT methylation status
d) the frequency and severity of toxicities
e) the results of any completed study chair modality reviews

The interim reports will not contain the results from the treatment comparisons with respect to the efficacy endpoints (6-month progression-free survival rate, overall survival, progression-free survival, treatment response). The RTOG DMC will review the accrual to the study and the rate of adverse events on the study at least twice per year until the initial results of the study have been presented to the scientific community.

13.5.4 Significance Testing for Final Analysis

The final analysis will be performed on an intent-to-treat basis, such that all eligible cases on the study will be included in the arm to which they were randomized regardless of what treatment the patients actually received. The analysis to report the final results of treatment will be undertaken when each randomized patient has been potentially followed for a minimum of 6 months. A one-sided Z test for two proportions at the 0.15 significance level will be performed to test the difference in 6-month progression-free survival rates between the two treatment arms. If the P value is less than protocol-specified 0.15 (one-sided), the study statistician will reject the null hypothesis and conclude that the experimental arm has a better 6-monfth progression-free survival rate than the standard arm, therefore supporting the development of a phase III trial comparing this regimen to the current standard at that time. All information reported in the interim analyses to monitor the study progress (Section 13.5.3) and the treatment compliance with respect to radiation and chemotherapy will also be included in the final report.

13.5.5 CDUS Tracking

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

13.6 Gender and Minorities

In conformance with the national Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, both men and women of all races and ethnic groups are eligible for this study. We will also analyze treatment differences by gender, race, and ethnicity. The table below lists the projected accrual for each racial and ethnic group based upon a previous RTOG GBM trial (patients enrolled from RTOG and NCCTG institutions for RTOG 0525).

Projected Distribution of Gender and Minorities

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	3	5	8
Not Hispanic or Latino	74	95	169
Ethnic Category: Total of all subjects	77	100	**177**
	Gender		
Racial Category	**Females**	**Males**	**Total**
American Indian or Alaskan Native	0	0	0
Asian	2	1	3
Black or African American	2	2	4
White	73	97	170
More than one race	0	0	0
Other	0	0	0
Racial Category: Total of all subjects	77	100	177

13.7 Statistical Considerations for ACRIN 6689 Advanced Imaging Component (8/26/10)

13.7.1 Primary Endpoint

13.7.1.1 To assess the association between overall survival and change in each of the following markers: K^{trans}, gradient echo CBV and [^{18}F]FLT Ki and K1, from T0 to T1.

13.7.2 Secondary Endpoints

13.7.2.1 To assess the association between progression-free survival and change in each of the following markers: K^{trans}, gradient echo CBV, and [^{18}F]FLT Ki and K1 from T0 to T1.

13.7.2.2 To assess the association between overall survival and change in each of the following markers: K^{trans}, gradient echo CBV and [^{18}F]FLT Ki and K1 from T1 to T3.

13.7.2.3 To assess the association between progression-free survival and change in each of the following markers: K^{trans}, gradient echo CBV, and [^{18}F]FLT Ki and K1, from T1 to T3.

13.7.2.4 To assess the association between overall and progression-free survival and the T0 values of each of the following markers: K^{trans}, gradient echo CBV, and [^{18}F]FLT Ki and K1.

13.7.2.5 To assess the relationship between [^{18}F]FLT Ki and K1 and markers of tumor proliferation, both cross-sectionally and longitudinally.

13.7.2.6 To evaluate the reproducibility of [^{18}F]FLT Ki and K1 measurements.

13.7.2.7 To assess the association between overall and progression-free survival and the change in the "vascular normalization index" between T0 and T1.

13.7.3 Sample Size

A total of 51 participants will be enrolled in the Advanced Imaging sub-study and will be apportioned to the study arms in the same proportions as the main study randomization. Assuming 5% attrition of the original sample, we expect that the analysis set will include 51 participants, 17 of which will be in Arm 1 and 34 in Arm 2 of the study. The moderate sample size for this Advanced Imaging sub-study *will permit a primarily hypothesis generating analysis*.

For the MRI markers, preliminary data were available from a series of patients undergoing anti-VEGF therapy (with cediranib) for glioblastoma. In separate univariate Cox regression models the coefficient of change in K^{trans} (in logarithmic scale) was 0.57 (HR = 1.76) and the coefficient of change (ratio) in spin echo CBV was -2.59 (HR = 0.075). The standard deviations of the two predictors in this cohort were 0.94 and 0.15, respectively.

The following table presents computations of statistical power to detect a coefficient for K^{trans} change of the indicated magnitude, using a two-sided test at level 0.05. The hazard ratios corresponding to the values of the coefficient considered in the table range from 1.7 to 1.76. The standard deviation of the predictor was assumed to vary from 0.92 to 0.96, based on the preliminary data. In line with the main study, the overall event rate was set at 0.64. Computations were carried out using PASS (Hinze J. [2008] PASS 2008, NCSS, LLC, Kaysville, Utah).

Power	Sample Size	Reg. Coeff.	Sd of predictor	Event rate
0.796	51	0.53	0.92	0.64
0.812	51	0.53	0.94	0.64
0.828	51	0.53	0.96	0.64
0.824	51	0.55	0.92	0.64
0.840	51	0.55	0.94	0.64
0.855	51	0.55	0.96	0.64
0.850	51	0.57	0.92	0.64
0.865	51	0.57	0.94	0.64
0.878	51	0.57	0.96	0.64

The following table presents computations of statistical power to detect a coefficient of change in spin echo CBV of the indicated magnitude, using a two-sided test at level 0.05. The hazard ratios corresponding to the values of the coefficient considered in the table range from 0.05 to 0.08. The standard deviation of the predictor was assumed to vary from 0.14 to 0.17. The power will be above 80% only if the hazard ratio is somewhat lower than the point estimate of 0.075 obtained from the preliminary data.

Power	Sample Size	Reg. Coeff.	SD of predictor	Event rate
0.670	51	-3.0000	0.1400	0.6400
0.729	51	-3.0000	0.1500	0.6400
0.783	51	-3.0000	0.1600	0.6400
0.830	51	-3.0000	0.1700	0.6400
0.640	51	-2.9000	0.1400	0.6400
0.700	51	-2.9000	0.1500	0.6400
0.755	51	-2.9000	0.1600	0.6400
0.804	51	-2.9000	0.1700	0.6400
0.610	51	-2.8000	0.1400	0.6400
0.670	51	-2.8000	0.1500	0.6400
0.726	51	-2.8000	0.1600	0.6400
0.776	51	-2.8000	0.1700	0.6400
0.579	51	-2.7000	0.1400	0.6400
0.638	51	-2.7000	0.1500	0.6400
0.694	51	-2.7000	0.1600	0.6400
0.746	51	-2.7000	0.1700	0.6400
0.548	51	-2.6000	0.1400	0.6400
0.606	51	-2.6000	0.1500	0.6400
0.662	51	-2.6000	0.1600	0.6400
0.714	51	-2.6000	0.1700	0.6400
0.516	51	-2.5000	0.1400	0.6400
0.572	51	-2.5000	0.1500	0.6400
0.628	51	-2.5000	0.1600	0.6400
0.680	51	-2.5000	0.1700	0.6400

In the absence of preliminary data for [^{18}F]FLT, we considered the power for comparing overall survival among participants divided by the median values of change in each of the two FLT markers (Ki and K1). Under assumptions about accrual time and follow-up as specified in the main study, the proposed sample size would provide power 0.8 to detect a hazard ratio of 0.36 between the two groups, for each of the two markers.

13.7.4 Statistical Analysis Methods

Study participants in both arms will undergo MRS, DCE-MRI, and DSC-MRI with blood sampling at seven (7) time points during the study, corresponding to Baseline (T0); between doses—after first dose of placebo or cediranib, but before second dose of placebo or cediranib/radiation/TMZ (T1); Week 4 of chemoradiation (T2); Week 10, or Week 4 after completion of chemoradiation (T3); Week 16, or Week

10 after completion of chemoradiation (T4); Week 24, or Week 18 after completion of chemoradiation (T5); and at time of progression (T6) as described in Section 11.6. Study participants in both arms will undergo dynamic [^{18}F]FLT PET with blood sampling at three to four (3 to 4) time points during the study, corresponding to Baseline (T0), Baseline #2 for a subset of 25 participants only (T0.1), between doses (T1), and at Week 10, or Week 4 after completion of chemoradiation (T3). Section 1.9 describes the background significance of MRS, DCE-MRI, DSC-MRI, and dynamic [^{18}F]FLT PET in evaluating treatment response. NAA/Cho will be used as the primary metric from the MRS scan; K^{trans} will be used as the primary metric from the DCE-MRI scan; spin echo CBV will be used as the primary metric from the perfusion MRI scan; and tumor SUV will be used as the primary metric from the dynamic [^{18}F]FLT PET to assess progression-free and overall survival as described in Section 2.3 and below.

13.7.5 Statistical Analysis Plan

13.7.5.1 *Primary Aim*

To assess the association between overall survival and change in each of the following markers: K^{trans}, gradient echo CBV, and dynamic [^{18}F]FLT uptake, from T0 to T1.

As noted above, due to the limited sample size, the Advanced Imaging sub-study will be primarily hypothesis generating. Overall survival will be estimated for the entire cohort of this sub-study and separately for the two arms using Kaplan-Meir curves. In the main analysis, each marker will be evaluated separately. First, participants will be divided into two groups using median split of the marker values and survival curves for these groups will be compared. Second, Cox regression models will be used, in which the response will be overall survival and the predictors will be the particular marker (entered as a continuous variable), treatment arm as a binary indicator, and the interaction between treatment and the marker. In a secondary analysis, each marker will be assessed using time-dependent ROC curves for the prediction of survival at pre-specified time points (Heagerty 2000). Also in a secondary analysis, a multivariate Cox regression modeling will be used to examine all markers together.

13.7.5.2 *Secondary Aims*

13.7.5.2.1 *To assess the association between progression-free survival and change in each of the following markers: K^{trans}, gradient echo CBV, and [^{18}F]FLT Ki and K1 from T0 to T1.*

13.7.5.2.2 *To assess the association between overall survival and change in each of the following markers: K^{trans}, gradient echo CBV and [^{18}F]FLT Ki and K1 from T1 to T3.*

13.7.5.2.3 *To assess the association between progression-free survival and change in each of the following markers: K^{trans}, gradient echo CB,V and [^{18}F]FLT Ki and K1, from T1 to T3.*

13.7.5.2.4 *To assess the association between overall and progression-free survival and the T0 values of each of the following markers: K^{trans}, gradient echo CBV, and [^{18}F]FLT Ki and K1.*

The analytic approach for Secondary Aims 1-4 will be similar to the approach used for the Primary Aim. For example for Secondary Aim 1, Cox regression models will be used with the same predictors as in the primary aim but with progression-free survival as the response. Similarly, time-depended ROC curves will be estimated for the prediction of progression-free survival at prespecified time points.

13.7.5.2.5 *To assess the relationship between [^{18}F]FLT Ki and K1 and markers of tumor proliferation, both cross-sectionally and longitudinally*.

Cross-sectional assessments of the relation between [^{18}F]FLT Ki and K1 and markers of tumor proliferation will be conducted at each time point for which pairs of measures are available. The analysis will examine the pattern of correlation between [^{18}F]FLT Ki and K1 and each marker of tumor proliferation, using graphical displays and regression modeling. Nonlinear regression models will be considered as needed. The longitudinal covariation of [^{18}F]FLT Ki and K1 and markers of tumor proliferation will also be examined using graphical displays and longitudinal regression modeling.

13.7.5.2.6 *To evaluate the reproducibility of [^{18}F]FLT Ki and K1 measurements*.

For this aim, [^{18}F]FLT Ki and K1 measurements will be taken twice on a subset of the participants. After graphical exploration of the data, the Intraclass Correlation Coefficient will be used to quantify reproducibility.

13.7.5.2.7 *To assess the association between overall and progression-free survival and the change in the "vascular normalization index" between T0 and T1*.

The analytic approach for this aim will be similar to that for the Primary Aim, with the vascular normalization index as the marker value.

REFERENCES

Abu-Hajir, M, Rand SD, Kruwer HG, et al. Noninvasive assessment of neoplastic angiogenesis: the role of magnetic resonance imaging. *Semin Thromb Hemost*. 2003;29:309-315.

Akella, NS, Twieg DB, Mikkelsen T, et al. Assessment of brain tumor angiogenesis inhibitors using perfusion magnetic resonance imaging: quality and analysis results of a phase I trial. *J Magn Reson Imaging*. 2004;20:913-922.

Aronen HJ, Pardo FS, Kennedy DN, et al. High microvascular blood volume is associated with high glucose uptake and tumor angiogenesis in human gliomas. *Clin Cancer Res*. 2000;6:2189-2200.

Augustin H. Antiangiogenic tumour therapy: will it work? *TIPS*. 1998;19:216-222.

Batchelor TT, Sorensen AG, di Tomaso E, et al. AZD2171, a pan-VEGF and PDGF receptor tyrosine kinase inhibitor, normalizes tumor vasculature and alleviates edema in glioblastoma patients. *Cancer Cell*. 2007;11:83-95.

Bertolini F, Paul S, Mancuso P, et al. Maximum tolerable dose and low-dose metronomic chemotherapy have opposite effects on the mobilization and viability of circulating endothelial progenitor cells. *Cancer Res*. 2003;63:4342-4346.

Bold G, Altmann KH, Frei J, et al. New anilino-phthalazines as potent and orally well-absorbed inhibitors of the VEGF receptor tyrosine kinase useful as antagonists of tumor driven angiogenesis. *J Med Chem*. 2000;43:2310-2323.

Bradley DP, Tessier JT, Checkley DR, et al. The VEGF signaling inhibitors ZD6474 and AZD2171 compromise hemodynamic parameters in an SW620 human colon tumor model: an analysis using perfusion-permeability dynamic contrast-enhanced magnetic resonance imaging (pp-DCE-MRI). *Proc Am Assoc Cancer Res*. 2004;A4552.

Brix G, Schreiber W, Hoffmann U, et al. Methodological approaches to quantitative evaluation of microcirculation in tissues with dynabasis of contrast enhancement in breast tumors. *J Magn Reson Imaging.* 1999;10: 260-266.

Cao Y, Tsien CI, Nagesh V, et al. Survival prediction in high-grade gliomas by MRI perfusion before and during early stage of RT. *Int J Radiat Oncol Biol Phys*. 2006;64:876-885.

CBTRUS (2008) Statistical report: primary brain tumors in the United States, 2000-2004. Published by the Central Brain Tumor Registry of the United States.

Chen W, Cloughesy T, Kamdar N, et al. Imaging proliferation in brain tumors with 18F-FLT PET: comparison with 18F-FDG. *J Nucl Med*. 2005;46:945-952.

Chen W, Delaloye S, Silverman DHS, et al. Predicting Treatment Response of Malignant Gliomas to Bevacizumab and Irinotecan by Imaging Proliferation with [18F] Fluorothymidine. *J Clin Oncol.* 2007;25:4714-4721.

Choi SJ, Kim JS. [18F]3'-deoxy-3'-fluorothymidine PET for the diagnosis and grading of brain tumors. *Eur J Nucl Med Mol Imaging*. 2005;32:653-659.

Cox DR. Regression models and life-tables. *J Royal Statistical Society.* 1972 (Series B);34:187-202

Curran WJ, Scott CB, Horton J, et al. Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. *J Natl Cancer Inst.* 1993; 85:704-710.

Drevs J, Hofmann I, Hugenschmidt H, et al. Effects of PTK787/ZK 222584, a specific inhibitor of vascular endothelial growth factor receptor tyrosine kinases, on primary tumor, metastasis, vessel density, and blood flow in a murine renal cell carcinoma model. *Cancer Res*. 2000;60:4819-4824.

Drevs, J, Esser N, Wedge SR, et al. Effect of AZD2171, a highly potent VEGF receptor tyrosine kinase inhibitor, on primary tumor growth, metastasis and vessel density in murine renal cell carcinoma. *Proc Am Assoc Cancer Res*. 2004;A4554.

Dowlati R, Gray DH., Johnson JH, et al. Prospective correlative assessment of biomarkers in E4599 randomized phase II/III trial of carboplatin and paclitaxel ± bevacizumab in advanced non-small cell lung cancer (NSCLS). *Proc Am Soc Clin Oncol*. 2006;24:3705.

Duda DG, Cohen KS, Scadden DT. et al. A protocol for phenotypic detection and enumeration of circulating endothelial cells and circulating progenitor cells in human blood. *Nat Protoc*. 2007 ;2:805-810.

Esteller M, Garcia-Foncillas J, Andion E, et al. Inactivation of the DNA-repair gene MGMT and the clinical response of gliomas to alkylating agents. *N Engl J Med*. 2000;343:1350-1354.

Fabbro D, Parkinson D, Matter A. Protein tyrosine kinase inhibitors: new treatment modalities? *Curr Opin Pharmacol*. 2002;2:3743-81.

Fan TP, Jaggar R, Bicknell R. Controlling the vasculature: angiogenesis, anti-angiogenesis and vascular targeting of gene therapy. *Trends Pharmacol Sci*. 1995;16:57-66.

Fine HA, Dear KB, Loeffler JS, et al. Meta-analysis of radiation therapy with and without adjuvant chemotherapy for malignant gliomas in adults. *Cancer.* 1993;71:2585-2597.

Fine HA, Wen, PY, Viscosi E. et al. Phase II trial of thalidomide and carmustine for patients with recurrent high-grade gliomas. *J Clin Oncol*. 2003 ;21 :2299-2304.

Flexner C, van der Horst C, Jacobson MA, et al. Relationship between plasma concentrations of 3'-deoxy-3'-fluorothymidine (alovudine) and antiretroviral activity in two concentration-controlled trials. *J Infect Dis*. 1994;170:1394-1403.

Folkman J. Tumor angiogenesis. *Adv Cancer Res*. 1985;43:175-203.

Folkman J. Angiogenesis in cancer, vascular, rheumatoid and other diseases. *Nat Med*. 1995:1:27-31.

Fong TA, Shawver LK, Sun L, et al. SU5416 is a potent and selective inhibitor of the vascular endothelial growth factor receptor (Flk-1/KDR) that inhibits tyrosine kinase catalysis, tumor vascularization, and growth of multiple tumor types. *Cancer Res*. 1999;59:99-106.

Fountas KN, Kapsalaki EZ, Vogel RL, et al. Noninvasive histologic grading of solid astrocytomas using proton magnetic resonance spectroscopy. *Stereotact Funct Neurosurg*. 2004;82:90-97.

Fukumara D, Xavier R, Chen Y. et al. Tumor induction of VEGF promoter activity in stromal cells. *Cell*. 1998;94:715-725.

Geng L, Donnely E, McMahon G, et al. Inhibition of vascular endothelial growth factor receptor signaling leads reversal of tumor resistance to radiotherapy. *Cancer Res*. 2001;61:2413-2419.

Gorski DH, Mauceri HJ, Salloum RM, et al. Potentiation of the antitumor effect of ionizing radiation by brief concomitant exposures to angiostatin. *Cancer Res*. 1998;58:5686-5689.

Gorski DH, Beckett MA, Jaskowiak NT, et al. Blockage of the vascular endothelial growth factor stress response increases the antitumor effects of ionizing radiation. *Cancer Res*. 1999;59: 3374-3378.

Gray RJ. A class of K-sample test for comparing the cumulative incidence of a competing risk. *Ann Statist*. 1988;16:1141-1154.

Guo P, Hu B, Gu W, et al. Platelet-derived growth factor-B enhances glioma angiogenesis by stimulating vascular endothelial growth factor expression in tumor endothelia and by promoting pericyte recruitment. *Am J Pathol*. 2003;162:1083-1093.

Hatakeyama T, Kawai N, Nishiyama Y, et al. 11C-methionine (MET) and 18F-Fluorothymidine (FLT) PET in patients with newly diagnosed glioma. *Eur J Nucl Med Mol Imaging*. 2008;35:2009-2017.

Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med*. 2005;352:997-1003.

Hennequin LF, Thomas AP, Johnstone C, et al. Design and structure-activity relationship of a new class of potent VEGF receptor tyrosine kinase inhibitors. *J Med Chem*. 1999;42:5369-5389.

Henson JW, Gaviani P, Gonzalez RG, MRI in treatment of adult gliomas. *Lancet Oncol*. 2005;6:167-175.

Hess C, Vuong V, Hegyl I, et al. Effect of VEGF receptor inhibitor PTK787/ZK222548 combined with ionizing radiation on endothelial cells and tumour growth. *British J Cancer.* 2001;85:2010-2016.

Hinchey J, Chaves C, Appignani B, et al. A reversible posterior leukoencephalopathy syndrome. *N Engl J Med*. 1996;334:494-500.

Holash J, Maisonpierre PC, Compton D, et al. Vessel cooption, regression, and growth in tumors mediated by angiopoietins and VEGF. *Science*. 1999;284:1994-1998.

Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med*. 2004;350: 2335-2342.

Ide A, Baker N, Warren S. Vascularization of the Brown Pearce rabbit epithelioma transplant as seen in the transparent ear chamber. *Am J Roengenol*. 1939;42:891-899.

Jacobs AH, Thomas A. 18F-fluoro-L-thymidine and 11C-methylmethionine as markers of increased transport and proliferation in brain tumors. *J Nucl Med*. 2005;46:1948-1958.

Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. *Science*. 2005;307:58-62.

Jain RK, Duda DG, Clark JW, et al. Lessons from phase III clinical trials on anti-VEGF therapy for cancer. *Nat Clin Pract Oncol*. 2006;3:24-40.

Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958;53:457-481.

Klinowska TC, Jackson JA, Farrington PM, et al. AZD2171, a highly potent inhibitor of VEGF receptor tyrosine kinase activity, inhibits the growth of spontaneous mammary tumors in the MMTV-neu transgenic mouse. *Proc Am Assoc Cancer Res*. 2004;A4540.

Katlama Ch, Ghosn J, Tubiana R, et al. MIV-310 reduces HIV viral load in patients failing multiple antiretroviral therapy: results from a 4-week phase II study. *AIDS*. 2004;18:1299-1304.

Knopp MV, von Tengg-Kobligk H, Choyke PG, et al. (Gd-DTPA) to visualize neoangiogenic induced vascular changes functional magnetic resonance imaging in oncology for diagnosis and therapy monitoring, Molecular *Cancer Therapeutics*. 2003;2:419-426.

Knopp MV, Weiss E, Sinn HP, et al. Measurement of capillary permeability from the Gd enhancement curve: a comparison of bolus and constant infusion injection methods. *Magn Reson Imaging*. 1994;12:81-91.

Kong XB, Zhu QY, Vidal PM, et al. Comparisons of anti-human immunodeficiency virus activities, cellular transport, and plasma and intracellular pharmacokinetics of 3'-fluoro-3'-deoxythymidine and 3'-azido-3'-deoxythymidine. *Antimicrob Agents Chemother.* 1992;36:808-818.

Kozin S. Boucher VY, Hicklin DJ, et al. Vascular endothelial growth factor receptor-2-blocking antibody potentiates radiation-induced long-term control of human tumor xenografts. *Cancer Res*. 2001;61:39-44.

Kreisl TN, Kim L, Moore K, et al. Phase II trial of single-agent bevacizumab followed by bevicizumab plus irinotecan at tumor progression in recurrent glioblastoma. *J Clin Oncol*. 2009;27:740-745.

Kunkel P, Ulbricht U, Bohlen P, et al. Inhibition of glioma angiogenesis and growth in vivo by systemic treatment with a monoclonal antibody against vascular endothelial growth factor receptor-2. *Cancer Res*. 2001;61:6624-6628, 2001.

Kuznetsov YE, Caramanos Z, Antel SB, et al: Proton magnetic resonance spectroscopic imaging can predict length of survival in patients with supratentorial gliomas. *Neurosurgery*. 2003;53:565-576.

Langen P, Etzold G, Hintsche R, et al. 3'-Deoxy-3'-fluorothymidine, a new selective inhibitor of DNA synthesis. Acta *Biol Med Germ*. 1969;23:759-766.

Langen P, Kowollok G, Etzold G, et al. The phosphorylation of 3'-deoxy-3'-fluorothymidine and its incorporation into DNA in a cell free system from tumor cells. *Acta Biol Med Germ*. 1972;29:483-494.

Law M, Young RJ, Babb JS, et al. Gliomas: predicting time to progression or survival with cerebral blood volume measurements at dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging. *Radiology*. 2008;247:490-498.

Lee CG, Heijn M, di Tomaso E, et al. Anti-Vascular endothelial growth factor treatment augments tumor radiation response under normoxic or hypoxic conditions. *Cancer Res*. 2000 ;60:5565-5570.

Leyton J, Latigo JR, Perumal M, et al. Early detection of tumor response to chemotherapy by 3 '-deoxy-3 '-[(18) F]fluorothymidine positron emission tomography: The effect of cisplatin on a fibrosarcoma tumor model in vivo. *Cancer Res*. 2005;65:4202-4210.

Little RJA, Rubin DB. *Statistical Analysis With Missing Data*. 2nd ed. Hoboken, NJ: John Wiley & Sons, Inc; 2002.

Lundgren B, Bottiger D, Ljungdahl-Stahle E, et al. Antiviral effects of 3'-fluorothymidine and 3'-azidothymidine in cynomolgus monkeys infected with simian immunodeficiency virus. *J Acquir Immune Defic Syndr*. 1991 ;4:489-498.

Mancuso P, Burlini V, Pruneri G, et al. Resting and activated endothelial cells are increased in the peripheral blood of cancer patients. *Blood*. 2001;97:3658-3661.

Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chem Rep*. 1966;5:163-170.

Matthes E, Lehmann Ch, Scholz D, et al. Phosphorylation, anti-HIV activity and cytotoxicity of 3'-fluorothymidine. *Biochem Biophys Res Comm*. 1998;153:825-831.

Matthes E, Lehmann Ch, Scholz D, et al. Inhibition of HIV-associated reverse transcriptase by sugar modified derivatives of thymidine 5'-triphosphate in comparison to cellular DNA polymerases. *Biochem Biophys Res Comm*. 1987;148:78-85.

Mauceri HJ, Hanna NN, Beckett MA. Combined effects of angiostatin and ionizing radiation in antitumor therapy. *Nature*. 1998;394:287-291.

Millauer B, Shawver L, Plate KH, et al. Glioblastoma growth inhibited in vivo by a dominant-negative Flk-1 mutant. *Nature.* 1994;367:576-579.

Motzer RJ, Michaelson MD, Redman BG, et al. Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2006;24:16-24.

Muzi M, Vesselle H. Kinetic analysis of 3'-deoxy-3'-fluorothymidine PET studies: validation studies in patients with lung cancer. *J Nucl Med*. 2005;46:274-282.

Muzi M, Spence AM, O'Sullivan F, et al. Kinetic analysis of 3'-deoxy-3'-18F-fluorothymidine in patients with gliomas. *J Nucl Med.* 2006;47:1612-1621.

Newlands ES, Stevens MF, Wedge SR, et al. Temozolomide: a review of its discovery, chemical properties, pre-clinical development and clinical trials. *Cancer Treat Rev*. 1997;23:35-61.

Ogilvie DJ, Kendrew J, Barrt ST, et al. AZD2171, a highly potent inhibitor of VEGF receptor signaling in primary human endothelial cells, exhibits broad-spectrum activity in tumor xenograft models. *Proc Am Assoc Cancer Res*. 2004;A4553.

Ostergaard L, Sorensen AG, Kwong KK, et al. High resolution measurement of cerebral blood flow using intravascular tracer bolus passages, part II: Experimental comparison and preliminary results. *Magn Reson Med*. 1996;36:726-736.

Ostergaard L, Weisskoff RM, Chesler DA, et al. High resolution measurement of cerebral blood flow using intravascular tracer bolus passages, part I: Mathematical approach and statistical analysis. *Magn Reson Med.* 1996;36:715-725.

Ott L. An introduction to statistical methods and data analysis. Belmont, Calif.: Duxbury Press, 1993.

Parangi S, O'Reilly M, Christofori G, et al. Antiangiogenic therapy of transgenic mice impairs de novo tumor growth. *Proc Natl Acad Sci U S A*. 1996;93:2002-2007.

Phillips HS, Kharbanda S, Chen R, et al. Molecular subclasses of high-grade glioma predict prognosis, delineate a pattern of disease progression, and resemble stages in neurogenesis. *Cancer Cell*. 2006;9:157-173.

Plate KH, Breier G, Risau W. Molecular mechanisms of developmental and tumor angiogenesis. *Brain Pathol*. 1994;4:207-218.

Plate KH, Mennel HD Vascular morphology and angiogenesis in glial tumors. *Exp Toxicol Pathol.* 1995;47:89-94.

Pottgen C, Levegrun S, Theegarten D, et al. Value of F-18-fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography in non-small-cell lung cancer for prediction of pathologic response and times to relapse after neoadjuvant chemoradiotherapy. *Clin Cancer Res*. 2006;12:97-106.

Quinn JA, Desjardins A, Weingart J, et al. Phase I trial of temozolomide plus O6-benzylguanine for patients with recurrent or progressive malignant glioma. *J Clin Oncol*. 2005;23:7178-7187.

Rabinov JD, Lee PL, Barker FG, et al. In vivo 3-T MR spectroscopy in the distinction of recurrent glioma versus radiation effects: Initial experience. *Radiology*. 2002;225:871-879.

Rampling R, Cruickshank G, Lewis AD, et al. Direct measurement of PO2 distribution and bioreductive enzymes in human malignant brain tumors. *Int J Radiat Oncol Biol Phys*. 1994;29:427-431.

Reardon D, Friedman H, Yung WKA, et al. A phase I/II trial of PTK787/ZK 222584 (PTK/ZK), a novel, oral angiogenesis inhibitor, in combination with either temozolomide or lomustine for patients with recurrent glioblastoma multiforme. *Proc Am Soc Clin Oncol*. 2004;23:110.

RECIST criteria. *JNCI*. 2000;92:205-216.

Rubinstein LV, Korn EL, Freidlin B, et al. Design issues of randomized phase II trials and a proposal for phase II screening trials. *J Clin Oncol*. 2005;23:7199-7206.

Samoto K, Ikezaki K, Ono M, et al. Expression of vascular endothelial growth factor and its possible relation with neovascularization in human brain tumors. *Cancer Res*. 1995;55:1189-1193.

Schmidt NO, Westphal M, Hagel C, et al. Levels of vascular endothelial growth factor, hepatocyte growth factor/scatter factor and basic fibroblast growth factor in human gliomas and their relation to angiogenesis. *Int J Cancer*. 1999;84:10-8.

Schwartz JL, Tamura Y, Jordan R, et al. Monitoring tumor cell proliferation by targeting DNA synthetic processes with thymidine and thymidine analogs. *J Nucl Med*. 2003;44:2027-2032.

Schiepers Ch, Chen W, Dahlbom M, et al. [18F]-Fluorothymidine kinetics of malignant brain tumors. *Eur J Nucl Med Mol Imaging*. 2007;34:1003-1011.

Seed MP. Angiogenesis inhibition as a drug target for disease: an update. *Expert Opin Investig Drugs*. 1996;5:1617-1636.

Shweiki D, Itin A, Soffer D, et al. Vascular endothelial growth factor induced by hypoxia may mediate hypoxia-initiated angiogenesis. *Nature*. 1992;359:843-845.

Smyczek-Gargya B, Fersis N, Dittmann H, et al. PET with [18F]fluorothymidine for imaging of primary breast cancer: a pilot study. *Eur J Nucl Med Mol Imaging*. 2004;31:720-724.

Sorensen G. Magnetic resonance as a cancer imaging biomarker. *J Clin Oncol*. 2006;24:3274-3281.

Sorensen AG, Batchelor TT, Zhang W-T, et al. A "vascular normalization index" as potential mechanistic biomarker to predict survival after a single dose of cediranib in recurrent glioblastoma patients. *Cancer Res*. 2009;69:5296-5300. Epub 2009 Jun 23.

Spence AM, Muzi M, Link JM, et al. NCI-sponsored trial for the evaluation of safety and preliminary efficacy of FLT as a marker of proliferation in patients with recurrent gliomas: safety studies. *Mol Imaging Biol*. 2008;10:271-280.

Spence AM, Muzi M, Link JM, et al. NCI-sponsored trial for the evaluation of safety and preliminary efficacy of 3'-deoxy-3'-[(18)F]fluorothymidine (FLT) as a marker of proliferation in patients with recurrent gliomas: preliminary efficacy studyies. *Mol Imaging Biol*. 2009;Mar 27. [Epub ahead of print]

Steiner HH, Karcher S, Mueller MM, et al. Autocrine pathways of the vascular endothelial growth factor (VEGF) in glioblastoma multiforme: clinical relevance of radiation-induced increase of VEGF levels. *J Neurooncology*. 2004;66:129-138.

Stewart LA. Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomized trials. *Lancet.* 2002;359:1011-1018.

Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352:987-996.

Sundseth R, Joyner SS, Moore JT, et al. The anti-human immunodeficiency virus agent 3'-fluorothymidine induces DNA damage and apoptosis in human lymphoblastoid cells. *Antimicrob Agents Chemother.* 1996 ;40:331-335.

Turcotte E, Wiens LW, Grierson JR, et al. Toxicology evaluation of radiotracer doses of 3'-deoxy-3'-[18F]fluorothymidine (18F-FLT) for human PET imaging: laboratory analysis of serial blood samples and comparison to previously investigated therapeutic FLT doses. *BMC Nucl Med.* 2007;7:3.

Tzika AA, Zarifi MK, Goumnerova L, et al. Neuroimaging in pediatric brain tumors: Gd-DTPA enhanced, hemodynamic, and diffusion MR imaging compared with MR spectroscopic imaging. *AJNR Am J Neuroradiol*. 2002;23:322-333.

Ullrich R, Backes H, Li H, et al. Glioma proliferation as assessed by 3'-fluoro-3'-deoxy-L-thymidine positron emission tomography in patients with newly diagnosed high-grade glioma. *Clin Cancer Res*. 2008 ;14:2049-2055.

Valk PE, Mathis CA, Prados MD, et al. Hypoxia in human gliomas: demonstration by PET with fluorine-18-fluoromisonidazole. *J Nucl Med*. 1992;33:2133-2137.

van Waarde A, Cobben DC, Suurmeijer AJ, et al. Selectivity of 18F-FLT and 18F-FDG for differentiating tumor from inflammation in a rodent model. *J Nucl Med*. 2004;45:695-700.

Villringer A, Rosen BR, Belliveau JW, et al. Dynamic imaging with lanthanide chelates in normal brain: contrast due to magnetic susceptibility effects. *Magn Reson Med*. 1988;6:164-174.

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

Wedge SR, Newlands ES. O6-benzylguanine enhances the sensitivity of a glioma xenograft with low O6-alkylguanine-DNA alkyltransferase activity to temozolomide and BCNU. *Br J Cancer*. 1996;73:1049-1052.

Wedge SR, Ogilvie DJ, Dukes M, et al. ZD4190: an orally active inhibitor of vascular endothelial growth factor signaling with broad-spectrum antitumor efficacy. *Cancer Res*. 2000;60:970-975.

Wedge SR, Ogilvie DJ, Dukes M, et al. ZD6474 inhibits vascular endothelial growth factor signaling, angiogenesis, and tumor growth following oral administration. *Cancer Res*. 2002;62:4645-4655.

Wedge SR, Kendrew J, Valentine PJ, et al. VEGF receptor tyrosine kinase inhibitor AZD2171 inhibits VEGF signaling, angiogenesis, and tumor growth *in vivo*. *Proc Am Assoc Cancer Res*. 2004;A4555.

Weinstat-Saslow D, Steeg PS. Angiogenesis and colonization in the tumor metastatic process: basic and applied advances. *FASEB J*. 1994;8:401-407.

Wen PY, Kesari S. Malignant gliomas in adults. *N Engl J Med*. 2008;359:492-507.

Wick A, Felsberg J, Steinbach JP, et al. Efficacy and tolerability of temozolomide in alternating weekly regimen in patients with recurrent glioma. *J Clin Oncol*. 2007;25:3357-3361.

Willett CG, Boucher Y, di Tomaso E, et al. Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer. *Nat Med*. 2004;10:145-147.

Willett CG, Boucher Y, Duda DG, et al. Surrogate markers for antiangiogenic therapy and dose-limiting toxicities for bevacizumab with radiation and chemotherapy: continued experience of a phase I trial in rectal cancer patients. *J Clin Oncol*. 2005;23:8136-8139.

Winkler F, Kozin SV, Tong RT, et al. Kinetics of vascular normalization by VEGFR2 blockade governs brain tumor response to radiation: Role of oxygenation, angiopoietin-1, and matrix metalloproteinases. *Cancer Cell*. 2004;6:553-563.

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

Wood JM. Inhibition of vascular endothelial growth factor (VEGF) as a novel approach for cancer therapy. *MEDICINA*. 2000;60:41-47.

Wood J, Bold G, Buchdunger E, et al. PTK787/ZK222584, a novel and potent inhibitor of VEGF receptor tyrosine kinases, impairs VEGF-induced responses and tumor growth after oral administration. *Cancer Res*. 2000;60:2178-2189.

Yamamoto Y, Wong TZ, Turkington TG, et al. 3'-Deoxy-3'-[F-18]Fluorothymidine positron emission tomography in patients with recurrent glioblastoma multiforme: comparison with GD-DTPA enhanced magnetic resonance imaging. *Mol Imaging Biol*. 2006;8:340-347.

Zagzag D, Hooper A, Friedlander DR, et al. In situ expression of angiopoietins in astrocytomas identifies angiopoietin-2 as an early marker of tumor angiogenesis. *Exp Neurol*. 1999;159: 391-400.

Zelen M. The randomization and stratification of patients to clinical trials. *J Chron Dis*. 1974;27:365-375.

APPENDIX I
RTOG 0837

Informed Consent Template for Cancer Treatment Trials
(English Language)

Randomized, Phase II, Double-Blind, Placebo-Controlled Trial Of Conventional Chemoradiation And Adjuvant Temozolomide Plus Cediranib Versus Conventional Chemoradiation And Adjuvant Temozolomide Plus Placebo In Patients With Newly Diagnosed Glioblastoma

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. 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 type of brain tumor known as a glioblastoma.

Why is this study being done? (8/26/10)

Standard treatment for patients with glioblastoma is temozolomide plus radiation followed by temozolomide alone. The purpose of this study is to determine whether the addition of an experimental medication, cediranib, to standard treatment will improve the outcome of treatment. Cediranib is designed to attack the blood vessels in glioblastoma. The study will find out what effects, good or bad, cediranib has on your tumor.

In addition, this study will try to determine whether the response to cediranib and the overall outcome depend on whether or not the tumor contains a particular genetic material called the MGMT gene. The MGMT is a protein in the tumor that may make your tumor resistant to temozolomide. After you register for the study, a sample of your tumor tissue will be submitted to a central laboratory to confirm that your tumor is a glioblastoma and to see whether your tumor has the MGMT gene. If you agree to participate in the study, this information will be used to place you in one of the study arms in a way that makes sure that the number of patients with the MGMT gene is balanced in each group (stratification).

In a study investigating cediranib in patients with recurrent glioblastoma, cediranib did not improve time to disease progression compared with standard treatment for recurrent glioblastoma. However, cediranib remains investigational in patients with newly diagnosed glioblastoma and may improve outcome in patients whose disease was not previously treated.

How many people will take part in the study?

About 177 people will take part in this study.

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

Before you begin the study …

You will need to have the following exams, tests 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.

- Physical and neurological examination
- MRI
- Blood tests
- Urine test
- Electrocardiogram (EKG)

During the study …

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.

- Physical and neurological examinations. These will be done about every other week for the first 10 weeks of treatment and about every month during treatment thereafter
- MRI scans. These will be done about every 2 months during treatment
- Blood tests to measure blood counts, electrolyte levels, and liver function. These will be done about every week for the first 6 weeks of treatment and about every 2 to 3 weeks during treatment thereafter

You will need these tests and procedures to see how the study is affecting your body.

- Blood tests to see how your thyroid and heart muscle are functioning .These will be done at Weeks 2 and 3 of the study. About 1/2 to 1 teaspoon of blood will be taken each time.
- Urine tests to see how your kidney is functioning. These will be done at Weeks 2, 5, 7, 8, and 11 of the study. About 1 teaspoon of urine will be collected each time.
- Electrocardiogram to check for possible changes in your heart rhythm. This will be done at Week 2 of the study.

You will also be asked to complete a medication diary while you are receiving treatment; this will help document when you take your medication and any side effects you experience. You will be asked to bring this diary with you to each visit, so you and your study doctor can review it together.

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

If the central pathology review indicates that your tumor is a glioblastoma with adequate tissue to perform the MGMT analysis, 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. You will have a 1 in 3 (33%) chance of being placed in group 1, and you will have a 2 in 3 (67%) chance of being placed in group 2.

If you are in group 1 (often called "Arm A"):
You will receive the standard treatments for glioblastoma—radiation and oral temozolomide— plus an oral placebo medication. A placebo is an inactive pill that looks exactly like an active pill. In this trial, the placebo will look exactly like the cediranib pill that patients randomized to group 2 will receive.

You will receive the placebo continuously throughout your treatment with radiation and temozolomide as follows: You will first receive the placebo every day for 3 days. You will then receive radiation therapy once per day on Monday through Friday, for a total of 30 treatments, plus temozolomide every day for 42 days and placebo every day for 42 days.

When you have finished the radiation part of your treatment, you will stop taking the temozolomide for 28 days but will continue taking the placebo every day. After 28 days, you will continue the daily placebo and will re-start temozolomide for 5 days per week every 28 days. You will take the placebo and temozolomide in this way for up to 12 months.

Treatment will be on an outpatient basis.

If you are in group 2 (often called "Arm B"):
You will receive the standard treatments for glioblastoma—radiation and oral temozolomide—plus the experimental medication, oral cediranib.

You will receive cediranib continuously throughout your treatment with radiation and temozolomide as follows: You will first receive cediranib every day for 3 days. You will then receive radiation therapy one per day on Monday through Friday, for a total of 30 treatments, plus temozolomide every day for 42 days and cediranib every day for 42 days.

When you have finished the radiation part of your treatment, you will stop taking the temozolomide for 28 days but will continue taking cediranib every day. After 28 days, you will continue taking daily cediranib and will re-start temozolomide for 5 days per week every 28 days. You will take cediranib and temozolomide in this way for up to 12 months.

Treatment will be on an outpatient basis.

This study will be “double blind.” This means that you and your study doctor will not know whether you are assigned to group 1 (standard treatment plus placebo) or group 2 (standard treatment plus cediranib).

Study Plan

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

Diagnosis/Suspected Brain Tumor

↓

Brain Tumor Surgery

↓

Tissue from surgery sent to central site for evaluation

↓

Randomized Treatment
(You will be in one group or the other)

↓

Group 1

Oral placebo daily for 3 days

↓

Radiation therapy, Monday through Friday, for 30 treatments
+
Oral temozolomide daily for 42 days
+
Oral placebo daily for 42 days

↓

Oral placebo daily for 28 days

↓

Oral temozolomide daily on days 1 through 5 every 28 days for up to 12 cycles (48 weeks; 1 cycle = 28 days = 4 weeks)
+
Oral placebo daily for up to 12 cycles (48 weeks; 1 cycle = 28 days = 4 weeks)

↓

Group 2

Oral cediranib daily for 3 days

↓

Radiation therapy, Monday through Friday, for 30 treatments
+
Oral temozolomide daily for 42 days
+
Oral cediranib daily for 42 days

↓

Oral cediranib daily for 28 days

↓

Oral temozolomide daily on days 1 through 5 every 28 days for up to 12 cycles (48 weeks; 1 cycle = 28 days = 4 weeks)
+
Oral cediranib daily for up to 12 cycles (48 weeks; 1 cycle = 28 days = 4 weeks)

When you are finished taking the study treatment…
You will be followed at regular check-ups, including MRI scans, every 3 months after completing treatment for the first year, then every 4 months for the second year, and then every 6 months thereafter.

How long will I be in the study?
You will receive treatment on the study for up to about 14 months. After you are finished taking the treatment, your study doctor will ask you to visit the office for follow-up exams indefinitely.

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

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

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

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 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 the radiation include those that are:

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

Less Likely
- Neurocognitive problems, including memory deficits, that could be permanent
- Permanent hearing loss
- Cataracts
- Behavioral change

- Nausea
- Vomiting
- Temporary worsening of existing neurological deficits, such as decreased vision, drowsiness, and weakness of your arms and legs
- Endocrine problems related to changes to the pituitary gland
- Dry mouth or altered taste

Rare but Serious

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

Risks and side effects related to the cediranib include those which are: (4/5/10)

Likely

- Diarrhea
- Fatigue or tiredness
- High blood pressure

Less Likely

- Abnormally high level of thyroid gland hormone
- Abnormally low level of thyroid gland hormone
- Belly pain
- Irritation or sores in the lining of the anus
- Constipation
- Dry mouth
- Difficulty swallowing
- Irritation or sores in the lining of the mouth
- Nausea or the urge to vomit
- Irritation or sores in the lining of the rectum
- Irritation or sores in the lining of the small bowel
- Vomiting
- Increased blood level of a liver enzyme (ALT/SGPT)
- Increased blood level of a liver enzyme (AST/SGOT)
- Increased levels of a substance involved in the production of red blood cells
- Increased levels of a substance (thyroid stimulating hormone) involved in the function of the thyroid gland, which indicates an underactive thyroid
- Decreased number of a type of white blood cell (neutrophil/granulocyte)
- Decreased number of a type of blood cell that help to clot blood (platelet)
- Weight loss
- Loss of appetite
- Dehydration (when your body does not have as much water and fluid as it should)
- Dizziness (or sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking)
- Headache or head pain
- More protein in the urine than usual, often a sign of kidney disease
- Cough
- Shortness of breath

- Irritation or sores in the lining of the voice box
- Irritation or sores in the lining of the throat
- Irritation or sores in the lining of the windpipe
- Voice change
- Swelling and redness of the skin on the palms of the hands and soles of the feet

Rare but Serious

- Decreased in heart's ability to pump blood during "active" phase of the heartbeat (systole)
- Progressive necrosis (tissue death) of a part (the white matter) of the brain without inflammation (swelling and redness)
- Collection of symptoms including headache, confusion, seizures, and vision loss associated with imaging findings (MRI, CT Scan)
- Blood clot in a blood vessel (artery)

Cediranib 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.

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, while cells, or platelets that can sometimes turn into blood cancer)

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. If you are a woman of childbearing age, and have not been surgically sterilized (tubal ligation or hysterectomy), you must have a pregnancy test before enrolling in this study.

Temozolomide may make it harder for a woman to become pregnant or for a man to cause a woman to become pregnant even after the chemotherapy has been completed. There is not enough information about temozolomide in men and women of childbearing age who subsequently try to have children to know how likely problems will be.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While researchers hope cediranib will be more effective at delaying or preventing progression compared to standard treatment, there is no proof of this yet. We do know that the information from this study will help researchers learn more about cediranib 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:

- Qualified representatives of AstraZeneca, the pharmaceutical collaborator
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- The Radiation Therapy Oncology Group (RTOG)
- The American College of Radiology Imaging Network (ACRIN) (for patients participating in the advanced imaging component of this study, ACRIN 6689)

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

The study agent, cediranib or placebo, will be provided free of charge while you are participating in this study. However, although this would be expected to occur infrequently, if you should need to take the study agent much longer than is usual, it is possible that the supply of free study agent that has been supplied to the NCI could run out. If this happens, your study doctor will discuss with you how to obtain additional drug from the manufacturer and you may be asked to pay for it.

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 your study doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

A Data Safety Monitoring Board will be regularly meeting to monitor safety and other data related to phase I, I/II, and II RTOG clinical trials. The Board members may receive confidential patient information, but they will not receive your name or other information that would allow them to identify you by name.

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.]*

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). *[*Only applies to sites using the CIRB.]*

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 study. Below, please mark your choice.

Consent Form for Use of Tissue, Blood, and Urine for Research

About Using Tissue for Research
You have had a biopsy (or surgery) to see if you have cancer. Your doctor will have removed some tissue to do some tests. The results of these tests will be used to plan your care.

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

We would like to collect some blood for future research. We would collect your blood at the following times: before you start treatment, at week 5, and at 1 and 6 months after you complete. We would keep about three of teaspoons of blood at each of these times. If you agree, this blood will be kept and may be used in research to learn more about cancer and other diseases.

In addition, we would like to collect some of your urine for future research. We would collect your urine at the following times: before you start treatment, at week 5, and at 1 and 6 months after you complete treatment. We would keep about five tablespoons of urine at each of these times. If you agree, the urine will be kept and may be used in research to learn more about cancer and other diseases.

The research that may be done with your tissue, blood, and urine is not designed specifically to help you. It might help people who have 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, blood, and urine can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue, blood, and urine. Then any tissue that remains will no longer be used for research and will be returned to the institution that submitted it, and blood and urine will be destroyed.

In the future, people who do research may need to know more about your health. While the Radiation Therapy Oncology Group may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue, blood, and urine are used for genetic research (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, blood, and urine 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, blood, and urine 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.

1. My specimens may be kept for use in research to learn about, prevent, or treat cancer, as follows:
   - Tissue☐Yes ☐ No
   - Blood ☐Yes ☐ No
   - Urine ☐Yes ☐ No

2. My specimens 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), as follows:
   - Tissue☐Yes ☐ No
   - Blood ☐Yes ☐ No
   - Urine ☐Yes ☐ No

3. Someone may contact me in the future to ask me to take part in more research.
   ☐Yes ☐ No

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or **TTY: 1-800-332-8615**

You may also visit the NCI Web site at http://cancer.gov/

- **For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/**
- **For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/**

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.]*

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 I CON'T (8/26/10)
RTOG 0837/ACRIN 6689

Informed Consent Template for Cancer Treatment Trials
(English Language Inclusive of Advanced Imaging Sub-Study)

Randomized, Phase II, Double-Blind, Placebo-Controlled Trial Of Conventional Chemoradiation And Adjuvant Temozolomide Plus Cediranib Versus Conventional Chemoradiation And Adjuvant Temozolomide Plus Placebo In Patients With Newly Diagnosed Glioblastoma

[LIMITED INSTITUTIONS: Potential participants at advanced imaging–qualified institutions must consent to the Advanced MR and [^{18}F]FLT PET imaging component with blood collections if the patient is imaging eligible. This Informed Consent Form Template contains the therapeutic and imaging components of the RTOG 0837 and ACRIN 6689 trial]

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 type of brain tumor known as a glioblastoma.

Why is this study being done?

Standard treatment for patients with glioblastoma is temozolomide plus radiation followed by temozolomide alone. The purpose of this study is to determine whether the addition of an experimental medication, cediranib, to standard treatment will improve the outcome of treatment. Cediranib is designed to attack the blood vessels in glioblastoma. The study will find out what effects, good or bad, cediranib has on your tumor. One way that your study doctors will find this out is by using advanced imaging technology, along with an investigational imaging agent. They will help the study doctors to see what is happening inside your body while you are taking the cediranib or a placebo.

In addition, this study will try to determine whether the response to cediranib and the overall outcome depend on whether or not the tumor contains a particular genetic material called the MGMT gene. The MGMT is a protein in the tumor that may make your tumor resistant to temozolomide. After you register for the study, a sample of your tumor tissue will be submitted to a central laboratory to confirm that your tumor is a glioblastoma and to see whether your tumor has the MGMT gene. If you agree to participate in the study, this information will be used to place you in one of the study arms in a way that makes sure that the number of patients with the MGMT gene is balanced in each group (stratification).

In a study investigating cediranib in patients with recurrent glioblastoma, cediranib did not improve time to disease progression compared with standard treatment for recurrent glioblastoma. However, cediranib remains investigational in patients with newly diagnosed glioblastoma and may improve outcome in patients whose disease was not previously treated.

How many people will take part in the study?

About 177 people will take part in this study. About 50 of those participants will participate in advanced imaging using MR (magnetic resonance) and PET/CT (positron emission tomography and computer tomography) with blood sampling.

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

Before you begin the study …

You will need to have the following exams, tests 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.

- Physical and neurological examination
- MRI
- Blood tests
- Urine test
- Electrocardiogram (EKG)

These scans are not part of regular cancer care and are being done because you are in this study.

- MR scans using advanced techniques and contrast imaging agents and blood collection prior to the scan
- PET/CT using an investigational radiotracer called [^{18}F]FLT; blood sampling will be done during these scan and you will need to have two (2) intravenous catheters—tubes used to access your veins—for these scans (one [1] placed in a vein in each arm)

During the study …

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.

- Physical and neurological examinations. These will be done about every other week for the first 10 weeks of treatment and about every month during treatment thereafter
- MRI scans. These will be done about every 2 months during treatment
- Blood tests to measure blood counts, electrolyte levels, and liver function. These will be done about every week for the first 6 weeks of treatment and about every 2 to 3 weeks during treatment thereafter

You will need these tests and procedures to see how the study is affecting your body.

- Blood tests to see how your thyroid and heart muscle are functioning .These will be done at Weeks 2 and 3 of the study. About 1/2 to 1 teaspoon of blood will be taken each time.

- Urine tests to see how your kidney is functioning. These will be done at Weeks 2, 5, 7, 8, and 11 of the study. About 1 teaspoon of urine will be collected each time.
- Electrocardiogram to check for possible changes in your heart rhythm. This will be done at Week 2 of the study.

You will have the following imaging and blood collection procedures during the course of the study. Your treating doctors and research team will do their best to limit the number of additional visits needed for you to complete the advanced MRI and PET scans.

- Seven (7) MRI scans using the contrast imaging agent called gadolinium. Some of these scans will be completed the same day as your standard imaging. At least one (1) scan will require an additional visit for you to be part of the ACRIN 6689 advanced imaging sub-study;
- Three (3) to four (4) PET scans using an investigational imaging agent called [^{18}F]FLT; these may mean additional visits as part of the study;
- Blood collection—taken prior to the every MRI scan, equaling less than 20 mL (two vials of blood) each time, and three times during each PET scan, totaling 3 mL (less than three teaspoons) each time.
- Intravenous (IV) catheters—tubes used to access your veins—one (1) to two (2) IV catheters, possibly one [1] placed in a vein in each arm, for the imaging agents and blood collection.

You will also be asked to complete a medication diary while you are receiving treatment; this will help document when you take your medication and any side effects you experience. You will be asked to bring this diary with you to each visit, so you and your study doctor can review it together.

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

If the central pathology review indicates that your tumor is a glioblastoma with adequate tissue to perform the MGMT analysis, 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. You will have a 1 in 3 (33%) chance of being placed in group 1, and you will have a 2 in 3 (67%) chance of being placed in group 2.

The FLT agent used for PET imaging is an investigational agent. The advanced MRI scans are also investigational in that study doctors are still learning about how the image results can be best applied to help patients. The techniques themselves for the MRI and PET scans are proven effective. In other words, the study doctors know how to do the images well; they are not yet sure how the images will best be used.

If you are in group 1 (often called "Arm A"):
You will receive the standard treatments for glioblastoma—radiation and oral temozolomide— plus an oral placebo medication. A placebo is an inactive pill that looks

exactly like an active pill. In this trial, the placebo will look exactly like the cediranib pill that patients randomized to group 2 will receive.

You will receive the placebo continuously throughout your treatment with radiation and temozolomide as follows: You will first receive the placebo every day for 3 days. You will then receive radiation therapy once per day on Monday through Friday, for a total of 30 treatments, plus temozolomide every day for 42 days and placebo every day for 42 days.

When you have finished the radiation part of your treatment, you will stop taking the temozolomide for 28 days but will continue taking the placebo every day. After 28 days, you will continue the daily placebo and will re-start temozolomide for 5 days per week every 28 days. You will take the placebo and temozolomide in this way for up to 12 months.

Treatment will be on an outpatient basis.

If you are in group 2 (often called "Arm B"):
You will receive the standard treatments for glioblastoma—radiation and oral temozolomide—plus the experimental medication, oral cediranib.

You will receive cediranib continuously throughout your treatment with radiation and temozolomide as follows: You will first receive cediranib every day for 3 days. You will then receive radiation therapy one per day on Monday through Friday, for a total of 30 treatments, plus temozolomide every day for 42 days and cediranib every day for 42 days.

When you have finished the radiation part of your treatment, you will stop taking the temozolomide for 28 days but will continue taking cediranib every day. After 28 days, you will continue taking daily cediranib and will re-start temozolomide for 5 days per week every 28 days. You will take cediranib and temozolomide in this way for up to 12 months.

Treatment will be on an outpatient basis.

This study will be “double blind.” This means that you and your study doctor will not know whether you are assigned to group 1 (standard treatment plus placebo) or group 2 (standard treatment plus cediranib).

Treatment Study Plan

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

Diagnosis/Suspected Brain Tumor

↓

Brain Tumor Surgery

↓

Tissue from surgery sent to central site for evaluation

↓

Randomized Treatment
(You will be in one group or the other)

↓

Group 1

Oral placebo daily for 3 days

↓

Radiation therapy, Monday through Friday, for 30 treatments

+

Oral temozolomide daily for 42 days

+

Oral placebo daily for 42 days

↓

Oral placebo daily for 28 days

↓

Oral temozolomide daily on days 1 through 5 every 28 days for up to 12 cycles (48 weeks; 1 cycle = 28 days = 4 weeks)

+

Oral placebo daily for up to 12 cycles (48 weeks; 1 cycle = 28 days = 4 weeks)

Group 2

Oral cediranib daily for 3 days

↓

Radiation therapy, Monday through Friday, for 30 treatments

+

Oral temozolomide daily for 42 days

+

Oral cediranib daily for 42 days

↓

Oral cediranib daily for 28 days

↓

Oral temozolomide daily on days 1 through 5 every 28 days for up to 12 cycles (48 weeks; 1 cycle = 28 days = 4 weeks)

+

Oral cediranib daily for up to 12 cycles (48 weeks; 1 cycle = 28 days = 4 weeks)

When you are finished taking the study treatment…

You will be followed at regular check-ups, including MRI scans, every 3 months after completing treatment for the first year, then every 4 months for the second year, and then every 6 months thereafter.

About Advanced Imaging in the Study

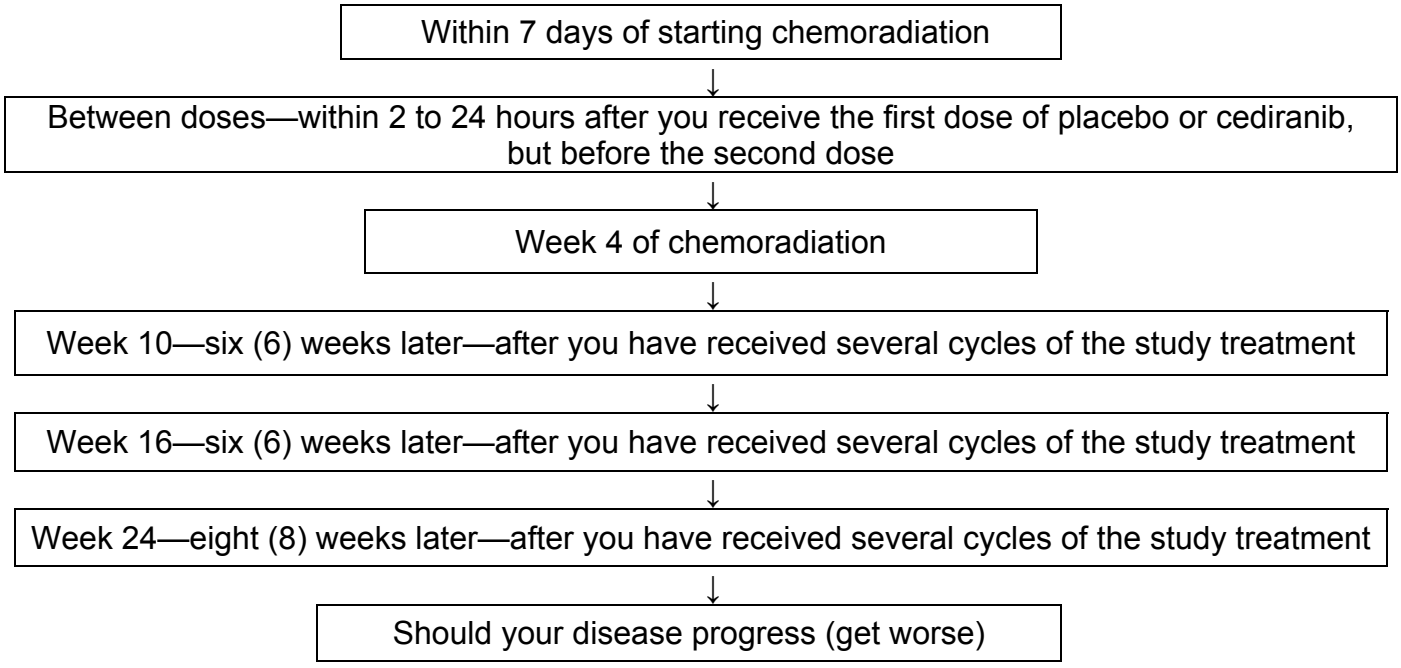
Researchers hope that the advanced imaging using MRI and PET will help them learn more about how blood is supplied to the cancer and what is happening inside your body while you are taking the cediranib or a placebo. The advanced MRI will take more time to complete (each examination takes between 45 and 60 minutes) than the regular MRI examinations. Blood will be collected prior to each of the MRI examinations. The PET imaging includes an investigational agent called FLT and blood collection. Your doctors will do their best to perform the PET scans on the same days as you receive your MR examinations.

Your study doctors hope that the blood collected during the trial will tell them more about how the study treatments and the FLT used for the PET scan react in the body. In the future, it is hoped the MRI and FLT PET scans performed before and after the start of chemotherapy treatment will allow doctors to tell in advance whether the tumor will respond well to treatment. Several studies using MRI and FLT PET at other institutions have shown promising results.

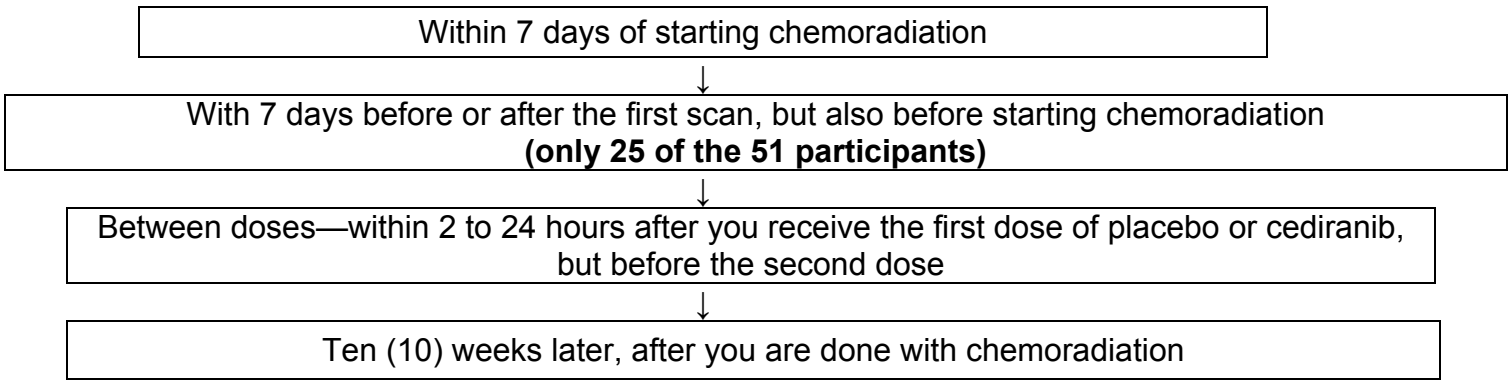
Descriptions of the timing for each scan can be found on the following pages.

Imaging Study Plan

If you agree to participate, you will have six or seven (6 or 7) advanced MR scans with blood collection prior to each scan:



Also, you will have three or four (3 or 4) PET scans with blood collection during each scan:



At least three (3)—and perhaps more—of these scans may require additional visits just for the ACRIN 6689 advanced-imaging sub-study. All other imaging will be completed at the same time as standard imaging required during your treatment. Your treating doctors and research team will do their best to limit the number of additional visits needed for you to complete this advanced imaging.

For the MRI examinations, you will need one (1) to two (2) intravenous (through a tube placed in a vein in your arm) catheters. Research staff may be able to use only one (1) intravenous catheter if blood is collected immediately prior to giving you the gadolinium. If you have MR and PET scans the same day, you may have two (2) intravenous catheters. In one, you will receive the imaging contrast agent, called gadolinium, that helps study doctors see areas of blood flow

to tumors. In the other one, two vials of blood will be collected, less than 20 mL. During this time, you will be required to lie flat in the MR scanner while imaging is performed.

During the FLT PET scan, you will need two (2) intravenous lines to receive an intravenous investigational imaging agent, called FLT, and for blood collection. The intravenous catheters will be placed, one in each of your arms. In one arm, your study doctors will inject the FLT investigational contrast agent; in the other arm, three (3) tubes of blood about 1 mL each (totaling about 1 teaspoon for all 3 blood collections) will be taken during your PET scan for future study.

If you are having the MR and PET imaging the same day, you will only need two (2) intravenous catheters for the entire day of imaging.

How long will I be in the study?
You will receive treatment on the study for up to about 14 months. After you are finished taking the treatment, your study doctor will ask you to visit the office for follow-up exams indefinitely.

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

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

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

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 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 the radiation include those that are:

<u>Likely</u>
- Scalp redness or soreness
- Hair loss, which may be temporary or permanent

- Ear/ear canal reactions, possibly resulting in a short-term hearing loss
- Fatigue
- Lethargy
- Temporary aggravation of brain tumor symptoms such as headaches, seizures, or weakness

Less Likely
- Neurocognitive problems, including memory deficits, that could be permanent
- Permanent hearing loss
- Cataracts
- Behavioral change
- Nausea
- Vomiting
- Temporary worsening of existing neurological deficits, such as decreased vision, drowsiness, and weakness of your arms and legs
- Endocrine problems related to changes to the pituitary gland
- Dry mouth or altered taste

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

Risks and side effects related to the cediranib include those which are: (9/14/10)

Likely
- Diarrhea
- Fatigue or tiredness
- High blood pressure

Less Likely
- Abnormally high level of thyroid gland hormone
- Abnormally low level of thyroid gland hormone
- Belly pain
- Irritation or sores in the lining of the anus
- Constipation
- Dry mouth
- Difficulty swallowing
- Irritation or sores in the lining of the mouth
- Nausea or the urge to vomit
- Irritation or sores in the lining of the rectum
- Irritation or sores in the lining of the small bowel
- Vomiting
- Increased blood level of a liver enzyme (ALT/SGPT)
- Increased blood level of a liver enzyme (AST/SGOT)
- Increased levels of a substance involved in the production of red blood cells
- Increased levels of a substance (thyroid stimulating hormone) involved in the function of the thyroid gland, which indicates an underactive thyroid

- Decreased number of a type of white blood cell (neutrophil/granulocyte)
- Decreased number of a type of blood cell that help to clot blood (platelet)
- Weight loss
- Loss of appetite
- Dehydration (when your body does not have as much water and fluid as it should)
- Dizziness (or sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking)
- Headache or head pain
- More protein in the urine than usual, often a sign of kidney disease
- Cough
- Shortness of breath
- Irritation or sores in the lining of the voice box
- Irritation or sores in the lining of the throat
- Irritation or sores in the lining of the windpipe
- Voice change
- Swelling and redness of the skin on the palms of the hands and soles of the feet

Rare but Serious

- Decreased in heart's ability to pump blood during "active" phase of the heartbeat (systole)
- Progressive necrosis (tissue death) of a part (the white matter) of the brain without inflammation (swelling and redness)
- Collection of symptoms including headache, confusion, seizures, and vision loss associated with imaging findings (MRI, CT Scan)
- Blood clot in a blood vessel (artery)

Cediranib 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.

Cediranib 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.

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, while cells, or platelets that can sometimes turn into blood cancer)

Risks and side effects related to MRI scan include those that are:

Likely
- Anxiety/stress;
- Discomfort;
- Claustrophobia.

Risks and side effects related to the Gadolinium contrast agent used in the advanced MRI scans include those that are:

Less Likely
- Headaches;
- Hives/rash;
- Vomiting
- Temporary low blood pressure;
- Nausea.

Less Likely, but Serious
- Allergic reactions.

Very Rare
- Nephrogenic systemic fibrosis (NSF)/Nephrogenic Fibrosing Dermopathy (NFD). 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.

Risks and side effects related to PET include those that are:

Likely

- Anxiety/stress;
- Discomfort;
- Claustrophobia.

For more information on PET scans, you can go to ACRIN's web site at: http://www.acrin.org/PATIENTS/ABOUTXRAYSANDSCANS/tabid/135/Default.aspx. You or your doctor can print a description of PET scans from this web site.

About risks and side effects related to the [^{18}F]FLT investigational imaging agent used in the PET imaging, including:

[^{18}F]FLT is an investigational imaging agent used in the PET scan; it has been given to more than 700 people. None of these people reported any side effects. Because [^{18}F]FLT is an investigational imaging agent, other unknown side effects may occur in this study. As with any other medication, serious allergic reactions can also occur.

- Respiratory difficulties;
- Flushing;
- Dizziness;
- Itching/rash;
- Other symptoms that could be secondary to an anaphylactic reaction.

Risks and side effects related to the Intravenous Catheter Placement include those that are:

Likely

- Minor discomfort;
- Pain.

Less Likely

- Bleeding;
- Infection;
- Bruising.

Radiation risks related to the PET include:

<<Each site may need to modify this section to quote the correct PET dosimetry for its own PET scanner in accordance with its own institutional policies and procedures. The following language and dosing range is an example only.>>

For example:

Your PET scan does involve exposure to radiation in order to monitor your tumor status and your response to treatment. If you live in the United States, you receive about 300 millirem of radiation each year. It comes from space and the earth around you. This is called "background radiation." A "millirem" (mrem) is a unit used to measure doses of radiation.

These scans will expose you to radiation. The radiation dose to your whole body from each of your PET scans will range from about 540 millirem (for PET only scanners) to 1745 mrem (for PET scanners). This dose can vary from person to person.

The risk of harm from this amount of radiation is low, and no harmful health effects are expected. However, your risk of harmful effects may increase if you are exposed to more procedures that involve radiation. If you have more procedures that expose you to radiation, risks of harm may include getting a new cancer or changes in your genes. As you may need to have other x-rays or scans for your care, ask your doctor(s) about the need for other x-rays or scans and the associated risks.

In previously studied patients, we have not noticed any appreciable side effects nor did the patients complain of any as a direct result of the tests. But if you notice anything differently, please feel free to contact the investigators.

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. If you are a woman of childbearing age, and have not been surgically sterilized (tubal ligation or hysterectomy), you must have a pregnancy test before enrolling in this study.

Temozolomide may make it harder for a woman to become pregnant or for a man to cause a woman to become pregnant even after the chemotherapy has been completed. There is not enough information about temozolomide in men and women of childbearing age who subsequently try to have children to know how likely problems will be.

We do not know the effects of [^{18}F]FLT in pregnancy. You will need to inform your study doctor or research staff if you are pregnant or suspect that you may be pregnant. If you are pregnant, you will not be able to participate in this study. If you are unsure, you will need to have a negative pregnancy result per the usual standard of care prior to enrolling and/or prior to imaging in this trial.

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 cediranib will be more effective at delaying or preventing progression compared to standard treatment, there is no proof of this yet. We do know that the information from this study will help researchers learn more about cediranib as a treatment for cancer. This information could help future cancer patients.

You will not directly benefit from the results of the advanced imaging study, but we hope that the results will help researchers and other people with brain cancer in the future. The results of the advanced MR and PET scans will not be sent to you or your doctor and will not be used to determine your treatment. The blood collected prior to the MRI and during the FLT PET scans will not directly benefit you but may help other people with cancer in the future.

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 *and standard-of-care imaging only* 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.

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 ACRIN in Philadelphia, PA. Copies of your MR and PET images will be permanently kept on file at ACRIN. This information will be used for research purposes only. Blood samples will be processed and thrown out after processing. All identifying information will be taken off of the images and the vials of blood to maintain confidentiality.

Future research studies may be conducted on data and images 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. The results of future research will not be reported to you nor will they specifically help you. But, future research may help people who have a brain tumor or other diseases.

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

- Qualified representatives of AstraZeneca, the pharmaceutical collaborator
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- The Radiation Therapy Oncology Group (RTOG)
- The American College of Radiology Imaging Network (ACRIN)

What are the costs of taking part in this study?
You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

The study agent, cediranib or placebo, will be provided free of charge while you are participating in this study. However, although this would be expected to occur infrequently, if you should need to take the study agent much longer than is usual, it is possible that the supply of free study

agent that has been supplied to the NCI could run out. If this happens, your study doctor will discuss with you how to obtain additional drug from the manufacturer and you may be asked to pay for it.

You or your insurance company will not be charged for the seven (7) advanced MR scans nor the three (3) or four (4) [^{18}F]FLT PET scans, including the additional blood collected.

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.

Will I be paid for being in the study?

The National Cancer Institute (NCI) allows reasonable reimbursement for travel expenses and time away from work associated with trial participation. If you are eligible to enroll in the study, you will receive a total of $<<Institution to provide appropriate amount—sites can determine a per-visit rate of $45 to $75 based upon appropriateness for their institution >> upon completion of the study as compensation for time and travel associated with your participation in this research study. There are approximately nine advanced imaging scans for this trial; the number of unique visits depends on your standard-of-care treatment. If, for whatever reason, you do not complete all the research-related imaging scans, you will be given $<<Institution to provide appropriate amount—sites can determine a per visit rate of $45 to $75 based upon appropriateness for their institution>> per each research-related scan completed.

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 your study doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

A Data Safety Monitoring Board will be regularly meeting to monitor safety and other data related to phase I, I/II, and II RTOG clinical trials. The Board members may receive confidential patient information, but they will not receive your name or other information that would allow them to identify you by name.

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 more information about MRI scans you can go to ACRIN's Web site at www.acrin.org/files/mri_description.doc. You or your doctor can print a description of MRI scans from this Web site.

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.]*

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). *[*Only applies to sites using the CIRB.]*

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 RTOG 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.

Blood collection and sampling during the ACRIN imaging sub-study is mandatory, so you will not be opting out of these elements by marking "no" below.

You can say "yes" or "no" to the following study. Below, please mark your choice.

Consent Form for Use of Tissue, Blood, and Urine for Research

About Using Tissue for Research
You have had a biopsy (or surgery) to see if you have cancer. Your doctor will have removed some tissue to do some tests. The results of these tests will be used to plan your care.

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

We would like to collect some blood for future research. We would collect your blood at the following times: before you start treatment, at week 5, and at 1 and 6 months after you complete. We would keep about three of teaspoons of blood at each of these times. If you agree, this blood will be kept and may be used in research to learn more about cancer and other diseases.

In addition, we would like to collect some of your urine for future research. We would collect your urine at the following times: before you start treatment, at week 5, and at 1 and 6 months after you complete treatment. We would keep about five tablespoons of urine at each of these times. If you agree, the urine will be kept and may be used in research to learn more about cancer and other diseases.

The research that may be done with your tissue, blood, and urine is not designed specifically to help you. It might help people who have 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, blood, and urine can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue, blood, and urine. Then any tissue that remains will no longer be used for research and will be returned to the institution that submitted it, and blood and urine will be destroyed.

In the future, people who do research may need to know more about your health. While the Radiation Therapy Oncology Group may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue, blood, and urine are used for genetic research (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, blood, and urine 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, blood, and urine 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.

1. My specimens may be kept for use in research to learn about, prevent, or treat cancer, as follows:
   - Tissue☐Yes ☐ No
   - Blood ☐Yes ☐ No
   - Urine ☐Yes ☐ No

2. My specimens 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), as follows:
   - Tissue☐Yes ☐ No
   - Blood ☐Yes ☐ No
   - Urine ☐Yes ☐ No

3. Someone may contact me in the future to ask me to take part in more research.
   ☐Yes ☐ No

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or **TTY: 1-800-332-8615**

You may also visit the NCI Web site at http://cancer.gov/

- **For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/**
- **For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/**

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.]*

If I qualify, my signature below indicates that I choose to participate in the advanced MR and PET imaging studies that are being done for research as a part of this study (RTOG 0837/ACRIN 6689).

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: STUDY PARAMETER TABLE (8/26/10)

	Pre-Treatment			During Chemo/RT (Wks 1-6)		During Cediranib/ Placebo Monotherapy (Wks 7-10)		During Cediranib/ Placebo + TMZ (Wks 11+)		Follow-Up	
	≤28 d prior to registration	≤14 d prior to registration	≤ 7d prior to registration	Wkly	Wks 2 & 4	≤ 7 d prior to start	Wk 8	≤ 7 d prior to start of q cycle	≤ 7 d prior to start of q odd cycle	Q3 mos for 1 y & at Wk 26, q 4 mos for 1 y, then q 6 mos	1 mo & 6 mos post treatment
Performance status		X			X	X	X	X			
Vital signs		X									
Height		X									
Weight		X			X	X		X			
History/physical		X			X	X	X	X			
Neurological exam (including MMSE)		X			X	X	X	X		X	
Steroid dose documentation		X		X		X	X	X			
Concurrent meds		X		X		X	X	X			
AE evaluation				X		X	X	X			
CBC w/ diff		X		X		X	X	And on d 21 & 28 (+/- 2 d)			
BUN		X									
Creatinine		X									
Urinalysis		X			≤ 7 d prior to cediranib start & Wk 5	X	X	X			

	Pre-Treatment			During Chemo/RT (Wks 1-6)		During Cediranib/ Placebo Monotherapy (Wks 7-10)		During Cediranib/ Placebo + TMZ (Wks 11+)		Follow-Up	
	≤28 d prior to registration	≤14 d prior to registration	≤ 7d prior to registration	Wkly	Wks 2 & 4	≤ 7 d prior to start	Wk 8	≤ 7 d prior to start of q cycle	≤ 7 d prior to start of q odd cycle	Q3 mos for 1 y & at Wk 26, q 4 mos for 1 y, then q 6 mos	1 mo & 6 mos post treatment
Bilirubin		X									
ALT/AST		X									
CD4 count						If absolute lympho-cyte count on CBC is <500 mm^3		X			
Serum chemistry: Complete metabolic panel, magnesium, LDH, phosphorous*		X		X		X	X	X			
Systolic/diastolic blood pressure											
PT/INR, PTT			X								
Pregnancy test (if applicable)		X									
Troponin T or I*		X			Wks 2 & 3						
TSH, Free T4*		X			Wk 2	X		Cycles 1 & 2 only			
ECHO/MUGA (pts at increased risk of LVEF)*	X										
EKG*		X			Wk 2						
Standard contrast-enhanced MRI* (all pts)	X								X	X	

	Pre-Treatment			During Chemo/RT (Wks 1-6)		During Cediranib/ Placebo Monotherapy (Wks 7-10)		During Cediranib/ Placebo + TMZ (Wks 11+)		Follow-Up	
	≤28 d prior to registration	14 d prior to registration	≤ 7d prior to registration	Wkly	Wks 2 & 4	≤ 7 d prior to start	Wk 8	≤ 7 d prior to start of q cycle	≤ 7 d prior to start of q odd cycle	Q3 mos for 1 y & at Wk 26, q 4 mos for 1 y, then q 6 mos	1 mo & 6 mos post treatment
ACRIN 6689 Advanced Imaging MRS, DCE-MRI, and DSC-MRI with Blood Sampling (for all imaging-eligible pts at advanced sites)				See Time Table Below							
ACRIN 6689 Advanced Imaging Dynamic [^{18}F]FLT-PET with Blood Sampling (for all imaging-eligible pts at advanced sites)				See Time Table Below							
Tissue for banking (for consenting pts)	X										
Serum for banking (for consenting pts)	X				Wk 5						X
Plasma for banking (for consenting pts)	X				Wk 5						X
Whole blood for banking (for consenting pts)	X										
Urine for banking (for consenting pts)	X				Wk 5						X

* See Sections 3.1 and 4.1 for details and exceptions.

ACRIN 6689 MR and Dynamic PET Study Time Table: For All Imaging-Eligible Participants) at Qualified Sites Only (51 Total Are Accrued)

	T0: Baseline (Pre-Chemo/RT)	**T1:** Between Doses (2 to 24 Hours After 1st Dose/ Before 2nd Dose)	**T2:** Week 4 of Chemo/RT	**T3:** Week 10	**T4:** Week 16	**T5:** Week 24	**T6:** At Time of Progression
Advanced MR: MRS, DCE-MRI, and DSC-MRI with Blood Collection **(Select Sites Only)**	X	X	X	X	X	X	X
Dynamic [^{18}F]FLT PET with Blood Sampling at 3 Time Points **(Select Sites Only)**	X†	X		X			

† A second baseline (Baseline #2) dynamic [^{18}F]FLT PET with blood sampling at 3 time points will be conducted on 25 of the 51 ACRIN 6689 advanced imaging-site participants prior to initiation of therapy. See Sections 1.9.2 and 11.6.2 for details.

NOTE: "PET" may refer to PET, PET/CT, or MR-PET depending on the site.

ACRIN 6689 MR and Dynamic PET Study Procedures Table

Study Procedure	**T0:** Baseline #1 Within 7 Days Prior to Chemo/RT	**T0.1:** Baseline #2 **1st 5 Patients at Each Site (25 Total)** Completed Within 7 Days of the T0 Scan	**T1:** Between Doses (2 to 24 Hours After 1st Dose/ Before 2nd Dose of Placebo or Cediranib)	**T2:** Week 4 of Chemo/RT	**T3:** Week 10 (Week 4 After Completion of Chemo/RT)	**T4:** Week 16 (Week 10 After Completion of Chemo/RT)	**T5:** Week 24 (Week 18 After Completion of Chemo/RT)	**T6:** At Time of Progression
Urine Pregnancy Test for Women of Childbearing Potential	X	X	X	X	X	X	X	X
[^{18}F]FLT PET Scan								
Daily QC Check, Including PET Scanner and Dose Calibrator	X	X	X		X			

Measure Height and Weight (Verbally Relayed by Participant is Not Allowed)	X	X	X		X			
Pre-PET Scan QC Check of Well Counter Cross Calibration	X	X	X		X			
Vital Signs (Before [^{18}F]FLT Administration and After PET Scan)	X	X	X		X			
Place 2 IV Catheters (1 in Each Arm)	X	X	X		X			
Administer [^{18}F]FLT	X	X	X		X			
Dynamic [^{18}F]FLT PET with Blood Sampling at 3 Time Points†	X	X	X		X			
Note Exact Time of Blood Sample Collections and Sample Analyses*	X	X	X		X			
AE(s) Assessment With Telephone Follow-Up 24 Hours Post-[^{18}F]FLT PET Injection†	X	X	X		X			
Advanced MRI Scans								
Obtain Creatinine Levels for GFR within 28 Days prior to MRI‡	X		X	X	X	X	X	X
Place 1 IV Catheter	X		X	X	X	X	X	X
MRS, DCE-MRI, and DSC-MRI with Blood Collection (20 mL Prior to Scan)	X		X	X	X	X	X	X

* The exact time of calibration of the [^{18}F]FLT dose should be recorded using a global time piece consistently used throughout the study for time recording; the exact time of injection should be noted and recorded to permit correction of the administered dose for radioactive decay. In addition, any of the dose remaining in the tubing or syringe, or that was spilled during injection, should be recorded. The injection should be performed through an IV catheter and 3-way stopcock.

† A phone call will be made to participants at 24 hours (± 4 hours) after the [^{18}F]FLT injection to elicit AEs using open-ended questions. In the event an AE is reported, concomitant medication details from the 2 weeks prior to the event and/or during the time of the reported AE will need to be collected.

‡ To be completed if the creatinine levels were not completed within 28 days of registration and within 28 days prior to each Visit including an MRI scan with Gd contrast.

APPENDIX III

KARNOFSKY PERFORMANCE SCALE

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

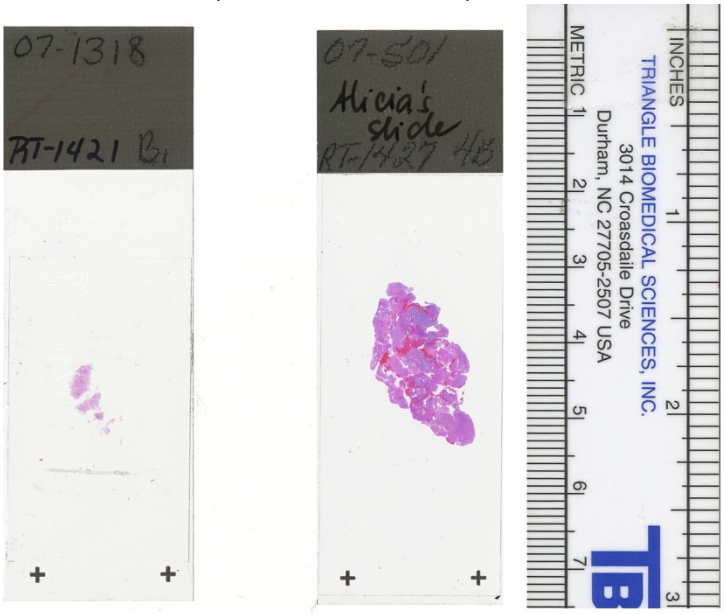
APPENDIX IV

NEUROLOGIC FUNCTION STATUS

0	**No neurologic symptoms; fully active at home/work without assistance**
1	**Minor neurologic symptoms; fully active at home/work without assistance**
2	**Moderate neurologic symptoms; fully active at home/work but requires assistance**
3	**Moderate neurologic symptoms; less than fully active at home/work and requires assistance**
4	**Severe neurologic symptoms; totally inactive requiring complete assistance at home or in institution--unable to work**

APPENDIX V

EXAMPLES OF ADEQUATE AND INADEQUATE TISSUE SAMPLES



These photographs of H & E slides show examples of acceptable and non-acceptable tissue submissions for the clinical protocol. The example on the left shows a sample of insufficient tissue size (approximately 0.3 cm^2). On the right the sample measures approximately $2cm^2$ which is sufficient for this clinical protocol.

APPENDIX VI

ACCEPTABLE ANTIEPILEPTIC DRUGS THAT CAUSE MODEST OR NO INDUCTION OF HEPATIC METABOLIC ENZYMES

Generic Name	Trade Name
Gabapentin	Neurontin
Lamotrigine	Lamictal
Valproic Acid	Depakote, Depakene
Felbamate	Felbatol
Levetiracetam	Keppra
Tiagibine	Gabitril
Topiramate	Topamax
Zonisamide	Zonegran

APPENDIX VII (8/26/10)

RTOG FROZEN TISSUE KIT INSTRUCTIONS*

This Kit is for processing and shipping of frozen tissue specimens.

Kit contents:

- Biohazard pads/wipes 4" x 4" (orange)
- Five (5) 5-mL cryovials
- Disposable scalpel blades
- Disposable forceps
- Biohazard bags
- Absorbent shipping material
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Prepaid shipping label
- UN 3373 Label
- UN 1895 Dry Ice Sticker

Preparation and Processing of Fresh Frozen Tissue:

- ❑ On sterile cutting board, lay out the underpads.
- ❑ Keep biohazard wipes nearby to keep area clean throughout process.
- ❑ Label cryovials with RTOG study and case numbers
- ❑ Using provided disposable scalpel, evenly cut tissue into up to 3-5 separate pieces (Note: if a frozen core was obtained, do not cut but send it whole).
- ❑ Use forceps to place each piece of tissue into individual 5-mL cryovials.
- ❑ Snap freeze tissue samples in liquid nitrogen, a dry ice slurry (dry ice with 95% ethanol or isopentane), or directly on dry ice.
- ❑ Once frozen, place all of the cryovials into biohazard bag
- ❑ Use RTOG provided labels to label bag (provided when patient is registered).

PLEASE MAKE SURE EVERY SPECIMEN IS LABELED.

Storage and Shipping:

Freezing and Storage

- ❑ Store at -80°C (-70°C to -90°C) until ready to ship.
  If a -80°C Freezer is not available,
  - Samples can be stored short term in a -20° C Freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only- Canada Mon-Tues).

  - OR:
  - Samples can be stored in plenty of Dry Ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only- Canada Mon-Tues).

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

Shipping/Mailing:

- ❑ Include all RTOG paperwork in pocket of biohazard bag.
- ❑ Place specimens and the absorbent shipping material in Styrofoam cooler filled with dry ice (at least 7lbs- if appropriate; double-check temperature sample shipping temperature). Place Styrofoam cooler into outer cardboard box, and attach shipping label to outer cardboard box.
- ❑ *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified.*
- ❑ Send frozen specimens via overnight courier to the address below. Specimens should only be shipped Monday through Wednesday (Monday-Tuesday for Canada) to prevent thawing due to delivery delays.
- ❑ Saturday or holiday deliveries cannot be accepted. Samples can be stored frozen until ready to ship.
- ❑ For Questions regarding collection/shipping or to order a Frozen Tissue Kit, please contact the RTOG Biospecimen Resource:

Courier Address (FedEx, UPS, etc.): For all frozen specimens
RTOG Biospecimen Resource at UCSF
1657 Scott Street, Room 223,
San Francisco, CA 94115

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

APPENDIX VIII (8/26/10)

RTOG BLOOD COLLECTION KIT INSTRUCTIONS

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

Kit contents:

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

Preparation and Processing of Serum, Plasma and Whole Blood:

A) Serum (if requested): Red Top Tube

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

Process:

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

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

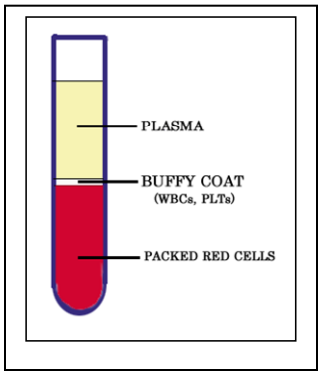
B) Plasma (If requested): Purple Top EDTA tube #1

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

Process:

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

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED,
and include collection Timepoint on STF.



C) Whole Blood For DNA (If requested): Purple Top EDTA tube #2

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

Process:

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

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

Storage and Shipping:

Freezing and Storage:

- ❑ Freeze Blood samples in a -80C Freezer or on Dry Ice or snap freeze in liquid nitrogen.

- ❑ Store at –80°C (-70°C to -90°C) until ready to ship.

If a -80°C Freezer is not available,

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

- OR:

- Samples can be stored in plenty of Dry Ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only- Canada Mon-Tues).

- OR:

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

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

Shipping/Mailing:

- ❑ Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- ❑ Include all RTOG paperwork in a sealed plastic and tape to the outside top of the Styrofoam box.
- ❑ Wrap frozen specimens of same type (i.e., all serum together, plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). ***Add padding to avoid the dry ice from breaking the tubes.***

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

Shipping Address : **FedEx/UPS/Courier address (For all frozen samples)**

RTOG Biospecimen Resource at UCSF
1657 Scott Street, Room 223
San Francisco, CA 94115

Contact Phone 415.476.7864

APPENDIX IX (8/26/10)

RTOG URINE COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of Urine Specimens

Kit Contents:

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

Preparation and Processing of Urine Specimens:

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

Storage and Shipping:

Freezing and Storage

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

OR:

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

Shipping/Mailing

- ❑ Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- ❑ Include all RTOG paperwork in a sealed plastic and tape to the outside top of the Styrofoam box.
- ❑ Place sealed specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). ***Add padding to avoid the dry ice from breaking the tubes.***
- ❑ Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.
- ❑ *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice. Add padding to avoid the dry ice from breaking the tubes.*
- ❑ Samples received thawed will be discarded, and a notification will be sent immediately to the Principal Investigator and Clinic Research Assistant of the submitting institution. The institution should send a subsequent sample, collected as close as possible to the original planned collection date.
- ❑ For questions regarding ordering, collection, or shipping a Urine Collection Kit, please Email RTOG@ucsf.edu or call (415)476-7864

Shipping Address : **FedEx/UPS/Courier address** **(For all frozen samples)**

RTOG Biospecimen Resource at UCSF
1657 Scott Street, Room 223
San Francisco, CA 94115

Contact Phone 415.476.7864

APPENDIX X

ACRIN 6689

ADVANCED MRI TECHNICAL ACQUISITION GUIDELINES

Site Selection

The advanced MR imaging described in this appendix will be undertaken at a limited number of pre-qualified sites per the qualification instructions posted on the ACRIN web site for the advanced imaging sub-study at: www.acrin.org/6689_imagingmaterials.aspx.

Technical Parameters

The Advanced Imaging Manual, as well as instructions for site pre-qualification, can be found on the web at www.acrin.org/6689_imagingmaterials.aspx. Scanner qualification for the advanced imaging sub-study must be met prior to registering any eligible participants. All MRI studies should be performed on a scanner that has submitted images for pre-enrollment central review and has been approved for use in this study as described in this appendix. All studies must be performed according to the protocol performed during pre-qualification.

Participants will undergo follow-up scanning on the same exact scanner serially using precisely the same parameters. Additional scanners will require additional qualification.

Advanced MRI Imaging at 1.5 Tesla or 3.0 Tesla in order of acquisition:

1. 3-plane localizer/scout
2. T1-weighted pre contrast (spin echo)
3. T2-weighted axial
4. Fluid-attenuated inversion recovery (FLAIR) axial
5. T1 mapping (5 series) and DCE-MRI
6. Diffusion Weighted Imaging/Diffusion Tensor Imaging (DWI/DTI)
7. DSC-MRI
8. T1-weighted post contrast 3D volumetric (gradient echo)
9. T1-weighted post contrast (spin echo)
10. MR Spectroscopy

DCE Perfusion MRI Technique

The DCE-MRI component first requires a T1 mapping sequence consisting of 5 series done at varying flip angles (30, 20, 15, 10, and then either 2 or 5, the lowest available on the scanner) prior to the contrast enhanced series. Slab prescription shall be sufficient to cover the tumor in its entirety (~6cm).

The dynamic series then follows. This series MUST be no longer than 3.5 to 6 seconds per phase and run for approximately 5 to 5.5 minutes. An injection of 0.1 mmol/kg of gadolinium contrast agent + saline flush is then administered after 30 seconds of baseline imaging.

The parameters of the T1 mapping sequence are the same as for the main DCE sequence, but are a single phase using 2 averages (NEX/NSA) instead of 1. Injection is done at 5cc/sec with a 20cc saline flush.

Imaging must be acquired as an axial 3D using an orthogonal axial (non-obliqued) prescription. The slab location of the pre-contrast T1 mapping sequences must match the slab location of the dynamic series. Parameters below represent 1.5T imaging. Please contact the ACRIN Core Laboratory for assistance with 3T adaptation.

T1 Mapping (5 series):
Parameters as listed below for dynamic imaging, except T1 maps will use 2 averages (NEX) and a flip angle (30, 20, 15, 10, and 2)

Dynamic acquisition at 1.5T:

Sequence Type	3D FLASH/ MPRAGE or SPGR
Plane	Axial (AC-PC)
TR [ms]	3.0 to 8.6
TE [ms]	Minimum (2.1 to 4.11)
Flip Angle	20-35
Field of view [mm]	256
Phase field of view [%]	75 to 100
Repetitions	50 (for main DCE only)
Slice thickness [mm]	3 to 5
Spacing (gap) [mm]	0
Number of slices/locs per slab (reconstructed)	16 to 20
Acquisition Matrix	256 x 128 to 256
Phase encoding direction	A/P or R/L
Number of averages (NEX/NSA) **Injection** **Time per phase** **Total scan Time**	1 **At 30 seconds in; 5cc/sec + flush** **3.5 – 6 seconds** **5 minutes minimum**

DSC Perfusion MRI Technique

The DSC perfusion component of the MRI study requires a dynamic image acquisition during rapid injection of a 0.1 mmol/kg Gd contrast agent with saline flush, both at 5cc/second. The gadolinium administered for the DCE-MRI series which precedes this DSC series will have served as a pre-load for the DSC acquisition to minimize T1 leakage effects.

Sequence Type	2D EPI
Plane	Axial (AC-PC)
TR [ms]	1300-1500
TE [ms]	30-40 (Gradient Echo), 60-105 (Spin Echo)
Field of view [mm]	220-240
Repetitions	120
Flip Angle [degrees]	90
Phase field of view [%]	100
Slice thickness [mm]	5
Spacing (gap) [mm]	0-2.5
Number of slices	10-15
Acquisition Matrix	128
Phase encoding direction	A/P
Number of averages	1

MR Spectroscopy Technique

Multi-voxel axial sequence with a minimum 16 x 16 matrix and 160mm FOV.

Detailed instructions for advanced imaging are in the Advanced Imaging Manual, available online at www.acrin.org/6689_imagingmaterials.aspx.

APPENDIX XI

ACRIN 6689

DYNAMIC [^{18}F]FLT PET TECHNICAL ACQUISITION, WELL COUNTER CROSS CALIBRATION, AND BLOOD SAMPLING GUIDELINES

Supplemental materials that support the dynamic [^{18}F]FLT PET imaging sequence, well counter cross calibration, and blood sampling are available on the ACRIN web site at the ACRIN 6689 Protocol web page (www.acrin.org/6689_protocol.aspx).

Types of materials posted include:

- Technical parameters for the PET imaging sequence.
- Step-by-step instructions for routine well counter calibration.
- An Excel spreadsheet for cross calibration.
- Specific time lines for PET imaging and blood sampling procedures.
- Instructions for blood sampling processing and data submission.

For more information related to the trial, contact the ACRIN 6684 Contact Personnel link on the above-mentioned Web page for a list of protocol team members at ACRIN Headquarters and their roles.

APPENDIX XII

ACRIN 6689

MRI AND PET IMAGE SUBMISSION

NOTE: Detailed technical parameters and instructions for site pre-qualification for advanced imaging, can be found in Appendices IX and X as well as on the web at http://www.acrin.org/6689_imagingmaterials.aspx The advanced MRI and dynamic [^{18}F]FLT PET scans with blood sampling described in this appendix will be undertaken at a limited number of pre-qualified sites per the qualification instructions posted on the ACRIN web site at: http://www.acrin.org/6689_protocol.aspx.

Sites performing advanced imaging must be able to perform all of the required advanced series and blood collections.

Imaging-eligible participants recruited at sites performing advanced imaging must undergo advanced imaging until total accrual for this sub-study is complete. Eligible patients must have given written consent (see Appendix I) to participate in the Advanced Imaging (MRS, DCE-MRI, DSC-MRI, and dynamic [^{18}F]FLT PET with blood collection) sub-study and satisfy the eligibility criteria.

A detailed process for the imaging quality assurance review and approval is outlined on the ACRIN web site at, http://www.acrin.org/6689_imagingmaterials.aspx. Image submission requirements are outlined below in Section 2 of this appendix. Images will be submitted to ACRIN via secure FTP (sFTP) for approval by the central quality reviewer. The results of this review will be returned to the institutions prior to site participation.

NOTE: For more detailed information, contact Jim Gimpel at jgimpel@acr-arrs.org.

1 MR and PET Image Quality Evaluations

1.1 ACRIN Imaging Quality Assurance Review

1.1.1 Institution MR and PET Scanners

- All institutions must have an ACRIN-approved MRI scanner and an ACRIN-approved PET scanner qualified prior to registering participants.

1.1.2 Submission of Test Cases for Image Quality Assurance Review

- Submit for review one (1) advanced MRI exam and one (1) dynamic [^{18}F]FLT PET scan performed per protocol using the parameters available on the ACRIN web site at: http://www.acrin.org/6689_imagingmaterials.aspx.
- Additionally, sites that participate in the advanced imaging option will include MRS, DSC-MRI, and DCE-MRI sequences with blood collection, as well as [^{18}F]FLT PET scans with blood collection according to protocol, using the parameters listed in the Imaging Guidelines available on the ACRIN web site.

1.1.3 Image Quality Assurance Review Rationale

- To establish a communication link between ACRIN, RTOG, and sites.
- To establish a mechanism for transferring images to ACRIN, e.g., internet, CD, DVD, etc.
- To ensure high quality standardized MR and PET images from each site.
- To facilitate accurate and timely submission of required MR and PET imaging.

1.2 Imaging Protocols

Imaging protocol can be found along with the Imaging Transmittal Worksheet (ITW) on the ACRIN web site, http://www.acrin.org/6689_imagingmaterials.aspx.

All advanced MR imaging will conform to the MRI quality control standards as described on the ACRIN web site (http://www.acrin.org/6689_imagingmaterials.aspx).

All [^{18}F]FLT PET imaging will conform to the PET quality control standards as described on the ACRIN web site: http://www.acrin.org/6689_imagingmaterials.aspx.

2 MR and PET Image Submission Instructions

All advanced imaging exams must be submitted to the ACRIN Core Laboratory immediately following each time point/visit. Imaging submitted must not include any additional imaging for which the participant has not consented at registration.

A completed, signed ITW *MUST* accompany all imaging exams submitted to ACRIN for each time point. The ITW must be completed and faxed to 215-923-1737 at the time the images are being submitted. For exams submitted via media, this worksheet must be completed and included with the media shipment. Please affix a label to the jacket of the media to include: study name, site name, case number, date of exam(s), time point, and type of imaging.

2.1 MR and PET Image Submission

ACRIN can provide software for anonymization and sFTP of DICOM image data. This software, TRIAD, can be installed and configured for radiology sites participating in ACRIN protocols. For more information on TRIAD software, contact the ACRIN Core Laboratory at imagearchive@acr-arrs.org or the TRIAD helpdesk at Triad-Support@acr-arrs.org.

2.2 Removal of Confidential Participant Information

The header record on DICOM formatted image data often contains information identifying the participant by name and must be scrubbed before the image is transferred. This involves replacing the Participant Name tag with the ACRIN institution ID, replacing Participant ID tag with the ACRIN case number, and putting the study number (RTOG 0837/ACRIN 6689) into the Other Participant ID tag.

For further assistance in utilizing TRIAD for anonymization, about submission, or for other questions regarding image transfer, contact the ACRIN Core Laboratory at imagearchive@acr-arrs.org.

2.3 CD Transfer

Images may also be sent on CD-ROM or other electronic medium for the ACRIN Core Laboratory to transfer to the image archive. Please contact Jim Gimpel (jgimpel@acr-arrs.org; 215-574-3238) at ACRIN prior to your media submission to confirm compatibility before your first case.

2.4 Image Quality Control

All image submissions will be subject to ongoing quality control review by the ACRIN Core Laboratory. In addition, a central quality review will be formally conducted on the first two advanced submissions from each participating institution, including a review by the central quality investigator for the trial. A random sampling of 10% of the remaining cases will be reviewed thereafter.

Prompt submission of all image data is essential to ensure adequate image quality control.