

**RADIATION THERAPY ONCOLOGY GROUP**

**RTOG 0913**

**PHASE I/II TRIAL OF CONCURRENT RAD001 (EVEROLIMUS) WITH  
TEMOZOLOMIDE/RADIATION FOLLOWED BY ADJUVANT RAD001/TEMOZOLOMIDE IN  
NEWLY DIAGNOSED GLIOBLASTOMA**

**Study Chairs**

Principal Investigator/Radiation Oncology

Prakash Chinnaiyan, MD  
H. Lee Moffitt Cancer Center and Research Institute  
SRB3  
12902 Magnolia Drive  
Tampa, FL 33612  
813-745-3425/FAX 813-745-3829  
[Prakash.Chinnaiyan@moffitt.org](mailto:Prakash.Chinnaiyan@moffitt.org)

Neuropathology

Amy M. Rojiani, MD, PhD  
Department of Pathology-BF-104  
Medical College of Georgia  
1120 Fifteenth Street,  
Augusta, GA 30912-3600  
[arojiani@mcg.edu](mailto:arojiani@mcg.edu)  
706-721-2923/706-721-2358

Co-Principal Investigator/Neuro-Oncology

Patrick Y. Wen, MD  
Dana-Farber/Brigham and Women's Cancer Center  
44 Binney Street, Boston, MA 0115  
617-632-2166/FAX 617-632-4773  
[pwen@partners.org](mailto:pwen@partners.org)

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-arrrs.org](mailto:mwang@acr-arrrs.org)

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

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PHASE I/II TRIAL OF CONCURRENT RAD001 (EVEROLIMUS) WITH TEMOZOLOMIDE/RADIATION FOLLOWED BY ADJUVANT RAD001/TEMOZOLOMIDE IN NEWLY DIAGNOSED GLIOBLASTOMA

SCHEMA

PHASE I

**STEP 1 REGISTRATION**  
**Central Pathology Review**

- Histology confirmation

NOTE: Tumor tissue must be received and central review confirmation completed before STEP 2 registration can occur.



**STEP 2 REGISTRATION**



ARM 1: RAD001 2.5 mg/day\*  
ARM 2: RAD001 5 mg/day\*  
ARM 3: RAD001 10 mg/day\*

Radiation Therapy:

2.0 Gy x 30 fractions, 5 days/week x 6 weeks for a total dose of 60.0 Gy.

Concurrent RAD001 During Radiation Therapy:

Daily during radiation therapy; 1 hour prior to radiation and in the morning on weekends.

Concurrent Temozolomide During Radiation Therapy:

Daily during radiation therapy; 1 hour prior to radiation and in the morning on weekends.

28-Day Break

Post-Radiation RAD001:

Daily for up to 12 cycles, starting 28 days after the completion of radiation therapy.

Post-Radiation Temozolomide:

Daily for 5 days every 28 days for up to 12 cycles, starting 28 days after the completion of radiation therapy.

\* Dose refers to RAD001 when delivered during radiation. Post-radiation RAD001 dose will start at 10 mg/day.

## PHASE II

### **STEP 1 REGISTRATION Central Pathology Review**

- Histology confirmation
- Confirmation of adequacy of tissue for MGMT and pAKT/pMTOR analysis

NOTE: Tumor tissue must be received and central review confirmation completed before STEP 2 registration can occur.

### **STEP 2 REGISTRATION Stratify by RPA Class: III vs. IV vs. V**

### **RANDOMIZE**

#### **Arm 1**

##### Radiation Therapy:

2.0 Gy x 30 fractions, 5 days/week x 6 weeks for a total dose of 60.0 Gy.

##### Concurrent Temozolomide During Radiation Therapy:

Daily during radiation therapy; 1 hour prior to radiation and in the morning on weekends.

##### Post-Radiation Temozolomide:

Daily for 5 days every 28 days for up to 12 cycles, starting 28 days after the completion of radiation therapy.

#### **Arm 2**

##### Radiation Therapy:

2.0 Gy x 30 fractions, 5 days/week x 6 weeks for a total dose of 60.0 Gy.

##### Concurrent RAD001 During Radiation Therapy:

Daily during radiation therapy; 1 hour prior to radiation and in the morning on weekends.

##### Concurrent Temozolomide During Radiation Therapy:

Daily during radiation therapy; 1 hour prior to radiation and in the morning on weekends.

##### Post-Radiation RAD001:

Daily for up to 12 cycles, starting 28 days after the completion of radiation therapy.

##### Post-Radiation Temozolomide:

Daily for 5 days every 28 days for up to 12 cycles, starting 28 days after the completion of radiation therapy.

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 proven diagnosis of glioblastoma (WHO Grade IV) **confirmed by central pathology review prior to Step 2 registration**

Tumor tissue available for correlative studies (PHASE II ONLY, See Section 10)

**Required Sample Size:** 246 patients

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**ELIGIBILITY CHECKLIST—STEP 1**  
**(page 1 of 1)**

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

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

**IMRT CREDENTIALING IS REQUIRED BEFORE REGISTRATION**

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

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(assigned in Step 1)

**ELIGIBILITY CHECKLIST—STEP 2**  
(page 1 of 4)

- \_\_\_\_\_ (Y) 1. Does the patient have histopathologically confirmed glioblastoma or gliosarcoma (WHO Grade IV) **confirmed by central pathology tissue screening**?
- \_\_\_\_\_ (Y/NA) 2. Does the patient have tumor tissue available for correlative studies (Required ONLY in phase II portion, as described in Sections 3.1 and 10)?
- \_\_\_\_\_ (Y) 3. Does the tumor have a supratentorial component?
- \_\_\_\_\_ (Y) 4. Has the patient recovered from the effects of surgery, postoperative infection, and other complications?
- \_\_\_\_\_ (Y) 5. Was a diagnostic contrast-enhanced MRI or CT scan of the brain performed preoperatively and postoperatively prior to the initiation of radiotherapy?
- \_\_\_\_\_ (Y) 6. Was the postoperative scan performed within 28 days prior to study registration?
- \_\_\_\_\_ (Y) 7. Were the preoperative and postoperative scans the same type?
- \_\_\_\_\_ (Y) 8. Was a history/physical examination done within 14 days prior to registration?
- \_\_\_\_\_ (Y) 9. Was a neurological examination done within 14 days prior to registration?
- \_\_\_\_\_ (Y) 10. Is there documentation of steroid doses within 14 days prior to registration?
- \_\_\_\_\_ (Y) 11. Is the Karnofsky performance status  $\geq 70$ ?
- \_\_\_\_\_ (Y) 12. Is the patient's age  $\geq 18$ ?
- \_\_\_\_\_ (Y) 13. Was a CBC/differential obtained within 14 days prior to registration on study, with adequate bone marrow function defined as follows:  
Absolute neutrophil count (ANC)  $\geq 1,800$  cells/mm<sup>3</sup>
- Platelets  $\geq 100,000$  cells/mm<sup>3</sup>
  - Hemoglobin  $\geq 10.0$  g/dl (Note: The use of transfusion or other intervention to achieve Hgb  $\geq 10.0$  g/dl is acceptable)
- \_\_\_\_\_ (Y) 14. Was prothrombin time/international normalized ratio (PTT INR)  $\leq 1.5$  confirmed by testing within 14 days prior to study registration?  
(Note: Anticoagulation is allowed if target INR  $\leq 1.5$  on a stable dose of warfarin or on a stable dose of LMW heparin for  $> 2$  weeks at the time of enrollment)
- \_\_\_\_\_ (Y) 15. Is there adequate renal function, as defined below:
- BUN  $\leq 30$  mg/dl within 14 days prior to study registration
  - Serum Creatinine  $\leq 1.5$  x ULN within 14 days prior to study registration
- \_\_\_\_\_ (Y) 16. Is there adequate hepatic function, as defined below:
- Bilirubin  $\leq 1.5$  x normal range within 14 days prior to study registration
  - ALT  $\leq 2.5$  x normal range within 14 days prior to study registration
  - AST  $\leq 2.5$  x normal range within 14 days prior to study registration

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**ELIGIBILITY CHECKLIST—STEP 2**  
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- \_\_\_\_\_ (Y) 17. Is fasting cholesterol  $\leq$  300 mg/dL OR  $\leq$  7.75 mmol/L AND triglycerides  $\leq$  2.5 x ULN?  
(Note: If one or both of these thresholds are exceeded, the patient can only be included after initiation of appropriate lipid lowering medication)
- \_\_\_\_\_ (Y/NA) 18. Is this patient female and of child-bearing potential?  
\_\_\_\_\_ (Y) If yes, was a negative serum pregnancy test done within 14 days prior to registration?  
\_\_\_\_\_ (N) If yes, is she breastfeeding?
- \_\_\_\_\_ (Y/NA) 19. If this patient is a woman of child-bearing potential or a male, has she/he agreed to practice adequate contraception?
- \_\_\_\_\_ (Y) 20. Did the patient provide study-specific informed consent prior to registration?
- \_\_\_\_\_ (Y/N) 21. Has the patient had prior invasive malignancy?  
\_\_\_\_\_ (Y) If yes, has the patient been disease free for >3 years?
- \_\_\_\_\_ (N) 22. Is the tumor a recurrent or multifocal malignant glioma?
- \_\_\_\_\_ (N) 23. Is there metastases detected below the tentorium or beyond the cranial vault?
- \_\_\_\_\_ (N) 24. Has there been prior use of Gliadel wafers or any other intratumoral or intracavitary treatment?
- \_\_\_\_\_ (N) 25. Has there been prior radiotherapy to the head or neck (except for T1 glottic cancer), resulting in overlap of radiation therapy fields?
- \_\_\_\_\_ (N) 26. Has there been prior use of chemotherapy or radiosensitizers for cancers of the head and neck region? Note that prior chemotherapy for a different cancer is allowable, except prior temozolomide or RAD001.
- \_\_\_\_\_ (N) 27. Has there been prior radiation therapy or chemotherapy for glioblastoma?
- \_\_\_\_\_ (N) 28. Does the patient have severe, active co-morbidity, as defined below?
- Symptomatic congestive heart failure of New York heart Association Class III or IV
  - Unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction within the last 6 months, serious uncontrolled cardiac arrhythmia or any other clinically significant cardiac disease
  - Severely impaired lung function as defined as spirometry and DLCO that is 50% of the normal predicted value and/or O<sub>2</sub> saturation that is 88% or less at rest on room air
  - Uncontrolled diabetes as defined by fasting serum glucose >1.5 x ULN
  - Active (acute or chronic) or uncontrolled severe infections requiring intravenous antibiotics
  - Liver disease such as cirrhosis, chronic active hepatitis or chronic persistent hepatitis
  - Acquired immune deficiency syndrome (AIDS) based upon current CDC definition or known HIV seropositivity; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with HIV/AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive.
  - Active connective tissue disorders, such as lupus or scleroderma, that in the opinion of the treating physician may put the patient at high risk for radiation toxicity
  - Other major medical illnesses or psychiatric impairments that in the investigator's opinion will prevent administration or completion of protocol therapy

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**ELIGIBILITY CHECKLIST—STEP 2**  
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- \_\_\_\_\_ (N) 29 Has there been prior allergic reaction to temozolomide?
- \_\_\_\_\_ (N) 30. Has the patient received prior treatment with an mTOR inhibitor (e.g., sirolimus, temsirolimus, everolimus) or has a known hypersensitivity to these agents or their excipients?
- \_\_\_\_\_ (N) 31. Has the patient been treated on any other therapeutic clinical protocol?
- \_\_\_\_\_ (N) 32. Has the patient any impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of RAD001 (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)?
- \_\_\_\_\_ (Y/N) 33. Is the patient receiving enzyme-inducing anti-epileptic drugs (EIADs)? (See Appendix V)  
(Y) If yes, has the patient discontinued their use at least 14 days prior to registration?
- \_\_\_\_\_ (N) 34. Has the patient a history of deep vein thrombosis or pulmonary embolism?

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

- \_\_\_\_\_ (Y/N) 1. Is the patient going to receive protocol treatment?  
\_\_\_\_\_ If no, provide the reason the patient cannot continue to step 2:  
1) insufficient tissue  
2) checklist failure, specify: \_\_\_\_\_  
3) progression of disease  
4) patient refusal  
5) physician preference  
6) death  
7) toxicity  
8) other complicating disease  
9) other, specify: \_\_\_\_\_
- \_\_\_\_\_ 2. Patient's Initials (First Middle Last)
- \_\_\_\_\_ 3. Verifying Physician
- \_\_\_\_\_ 4. Patient ID
- \_\_\_\_\_ 5. Calendar Base Date
- \_\_\_\_\_ 6. Randomization date: This date will be populated automatically (for Step 2).
- \_\_\_\_\_ (Y) 7. Has the Eligibility Checklist (in Step 2 above) been completed?
- \_\_\_\_\_ 8. Medical oncologist's name
- \_\_\_\_\_ (Y/N) 9. 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) 10. 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) 11. 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?





## **1.0 INTRODUCTION**

### **1.1 Background**

There are approximately 18,500 cases of newly diagnosed primary brain malignancies per year, with the most aggressive form, glioblastoma (GBM), being the most common. Although the incidence of GBM is low when compared to such cancers as lung, prostate, and breast, because this disease is rapidly fatal and generally affects young and otherwise healthy individuals, they are among the most devastating malignancies in terms of average years of life lost<sup>1</sup>. The median survival is generally less than one year from the time of diagnosis, and even in the most favorable situations, a majority of patients die within two years.<sup>2,3</sup>

Standard therapy has consisted of surgical resection to the extent that is safely feasible, followed by radiotherapy. Unfortunately, nearly thirty years of cooperative-group trials have done little in furthering clinical gains in this disease. An overwhelming majority of patients recur locally and eventually succumb to uncontrolled disease progression despite delivering high doses of radiation to the tumor.<sup>3</sup> Despite the discouraging historical context involving GBM management, novel therapeutic strategies offering clinical gains have emerged. A survival benefit in GBM has recently been published by the European Organization for Research and Treatment of Cancer (EORTC).<sup>2</sup> This regimen, which is now the current standard of care in newly diagnosed GBM patients, consists of concomitant low dose temozolomide with radiation, followed by high dose adjuvant temozolomide. Despite representing progress, this approach still does not offer cure to these patients, as long-term prognosis remains poor. Therefore, new agents need to be identified that target specific pathways contributing towards GBM resistance that can be integrated, and enhance the cytotoxic effects of, the radiation/temozolomide regimen to achieve further clinical gains in GBM.

### **1.2 Targeting Both Tumor and Its Associated Microenvironment Through mTOR**

#### **1.2.1 PI3K/Akt/mTOR Pathway**

The phosphatidylinositol 3' kinase (PI3K) signaling pathway provides critical information for tumor survival, proliferation, and motility.<sup>4,5</sup> Stimulation initiates a signaling cascade that ultimately results in the phosphorylation and activation of mTOR through the potent pro-survival signal Akt. Aberrant activation of the PI3K pathway appears to play a significant role in GBM pathogenesis and its associated therapeutic resistance. Chakravarti et al demonstrated that the PI3K pathway was associated with increasing tumor grade, decreased levels of apoptosis, and adverse clinical outcome in glioma.<sup>4</sup> In GBM, activated PI3K, AKT and S6K were identified in 75%, 66%, and 56% of specimens, respectively, suggesting this pathway would be an attractive target in this disease.

A variety of growth factor networks may stimulate this PI3K/Akt/mTOR pathway, including EGFR, which overexpressed or constitutively activated in 50-60% of GBM.<sup>6</sup> In addition, activation of this pathway is often by virtue of phosphatase and tensin homologue gene (PTEN) mutation. PTEN is a tumor suppressor gene that encodes a phosphatase, dephosphorylating PIP3 to PIP2. If PTEN is mutated, PIP3 accumulates and co-recruits PDK1 and Akt to the cell membrane, resulting in phosphorylation and constitutive activation of Akt.<sup>7</sup> Retrospective analyses suggest 50-70% of GBM patients have mutated or loss of PTEN, providing further rationale for targeting this pathway in GBM.<sup>5</sup>

#### **1.2.2 Angiogenesis**

Targeting the tumor microenvironment through angiogenesis has been a dominant theme in anti-cancer therapy over the last decade. Specifically, GBM is characterized by florid angiogenesis.<sup>8</sup> Although several molecular mechanisms contribute towards tumor angiogenesis, the vascular endothelial growth factor (VEGF) pathway seems particularly important and has been a prominent therapeutic target in cancer treatment.<sup>8,9</sup> Along these lines, clinical gains appear promising in GBM with the integration of bevacizumab, which is a monoclonal antibody that binds to and inhibits the activity of VEGF. Vredenburgh et al noted an objective response rate of 57% and a 6-month progression-free survival of 46% in recurrent GBM, which is remarkable when compared to benchmark response rates of 6% and 6-month progression-free survival of 15% from salvage cytotoxic regimens.<sup>10</sup>

The mTOR pathway has recently been shown to play a contributory role in regulating angiogenesis. Activation of mTOR causes upregulation of VEGF through both transcriptional<sup>11</sup>

and translational regulation.<sup>12,13</sup> Further, a seminal work recently identified mTOR to play a central role linking inflammation with tumor angiogenesis.<sup>14</sup> IKK-beta, a major downstream kinase in the TNF-alpha inflammatory-signaling pathway, physically interacts with and phosphorylates TSC1, resulting in suppression. This IKK-beta mediated TSC1 suppression activates the mTOR pathway, enhancing angiogenesis and tumor development.<sup>14</sup>

Based on these fundamental biologic processes, investigators have evaluated the capacity of mTOR inhibitors to serve as anti-angiogenic agents. Guba et al demonstrated the capacity of rapamycin to inhibit metastatic potential, tumor growth, VEGF-mediated angiogenesis.<sup>15</sup> Del Bufalo et al demonstrated the ability of the mTOR inhibitor temsirolimus to inhibit VEGF production and in vitro/in vivo endothelial cell proliferation and vessel formation in breast cancer cell lines.<sup>16</sup> RAD001 appears to have a similar impact on angiogenesis, with an inhibition of endothelial cell proliferation and blood vessel density in melanoma tumor model systems.

### **1.3 Combining mTOR Inhibitors to the Chemoradiation Platform in GBM**

In addition to having independent activity in GBM cell lines,<sup>17-19</sup> mTOR inhibitors have also demonstrated the capacity to enhance response to both radiation and chemotherapy, the therapeutic backbone in the management of newly diagnosed GBM.

#### **1.3.1 mTOR Inhibition and Radiation Response**

Several investigators have identified the capacity of mTOR inhibitors to modulate radiation response. As stated above, the PI3K/Akt/mTOR pathway appears to portend a resistant phenotype in GBM patients.<sup>4</sup> In preclinical models, targeting this pathway by inhibiting both PI3K<sup>20</sup> and Akt<sup>21</sup> has been shown to augment radiation response in GBM. Similarly, targeting mTOR directly has also demonstrated radiosensitization in a variety of tumor cell lines, including, GBM<sup>17</sup>, prostate,<sup>22</sup> and breast cancer<sup>23</sup>. Interestingly, Eshleman et al demonstrated that the mTOR inhibitor rapamycin did not seem to enhance radiosensitivity in GBM lines in vitro, but showed striking radiosensitization in vivo using a xenograft model, suggesting a role in tumor microenvironment.<sup>17</sup> This hypothesis was further strengthened by Shinohara et al<sup>24</sup> and Manegold et al<sup>25</sup>, both demonstrating enhanced radiation damage to tumor vasculature with mTOR inhibition.

#### **1.3.2 mTOR Inhibition Combined With Cytotoxics**

In addition to radiation, mTOR inhibitors have also demonstrated the ability to sensitize cells to a variety of chemotherapies. Beuvink et al demonstrated the capacity of the mTOR inhibitor RAD001 to sensitize tumor cells to cisplatin by inhibiting p53-induced p21 expression.<sup>26</sup> Specific to GBM, the mTOR inhibitor rapamycin enhanced nitrosurea cytotoxicity in U251 cells, also attributed to attenuating p21 expression.<sup>27</sup> In addition, using a U87 xenograft and orthotopic mouse model, RAD001 demonstrated synergistic antitumor activity when combined with temozolomide. (RAD001 Investigator's Brochure).

### **1.4 RAD001 (everolimus)**

RAD001 (everolimus) is a novel oral derivative of the mTOR inhibitor rapamycin. RAD001 has been in clinical development since 1996 as an immunosuppressant in solid organ transplantation and has obtained marketing authorization (Certican®) for prophylaxis of rejection in renal and cardiac transplantation in a number of countries, including the majority of the European Union. RAD001 has been in development for patients with various malignancies since 2002. Clinical interest in RAD001 has been stimulated by its demonstrated activity in patients with advanced renal cell carcinoma, which lead to a recent FDA approval.

RAD001 is being investigated as an anticancer agent based on its potential to act both directly on the tumor cells by inhibiting tumor cell growth and proliferation and indirectly by inhibiting angiogenesis leading to reduced tumor vascularity (via potent inhibition of tumor cell HIF-1 activity, VEGF production and VEGF-induced proliferation of endothelial cells). The role of angiogenesis in the maintenance of solid tumor growth is well established, and the mTOR pathway has been implicated in the regulation of tumor production of pro-angiogenic factors as well as modulation of VEGFR signaling in endothelial cells. At weekly and daily schedules and at various doses explored, RAD001 is generally well tolerated. The most frequent adverse events (rash, mucositis, fatigue and headache) associated with RAD001 therapy are manageable. Non-infectious pneumonitis has been reported with mTOR inhibitors but is commonly low-grade and reversible.

#### 1.4.1 Preclinical Studies

Pre-clinical investigations have demonstrated that RAD001 is a potent inhibitor of the proliferation of a range of human tumor cell lines in-vitro with IC50s ranging from sub/low nM to  $\mu$ M concentrations, concentrations capable of being reached in patients at the doses used in clinical trials. RAD001 was shown to have activity in human tumor cell lines originating from lung, breast, prostate, colon, kidney, melanoma and glioblastoma. RAD001 was also shown to have activity in human pancreatic neuroendocrine cells, where induction of apoptosis was reported,<sup>28</sup> as well as in acute myeloid leukemia cells,<sup>29</sup> adult T-cell leukemia cells,<sup>30</sup> diffuse large B cell lymphoma cells (DLBCL),<sup>31</sup> pancreatic tumor cells,<sup>32</sup> ovarian cancer cells<sup>33,34</sup> and hepatocellular carcinoma cells.<sup>35</sup>

As a single agent, RAD001 inhibited proliferation in three mantle cell lymphoma cell lines (Jeko1, SP49 and NCEB1) approximately 40–65% compared to control cells. This was associated with G1 cell-cycle arrest and reduced phosphorylation of the mTOR downstream target, 4E-BP1.<sup>36</sup> In a clonogenic assay using cells derived from 81 patient-derived tumor xenografts never cultured *in vitro* (11 human tumor types with 3 to 24 tumors each: bladder, colon, gastric, NSCLC [adeno, squamous epithelium and large cell], SCLC, breast, ovary, pancreatic, renal, melanoma, and pleural mesothelioma), RAD001 inhibited colony formation in a concentration dependent manner. In addition, normal hematopoietic stem cells were insensitive to RAD001, with an IC50 about 15 fold higher than the tumor lines. RAD001 also inhibits the proliferation of human umbilical vein endothelial cells (HUVECS), with particular potency against VEGF-induced proliferation. The inhibition of endothelial proliferation and anti-angiogenic activity of RAD001 was confirmed *in vivo*, as RAD001 selectively inhibited VEGF-dependent angiogenic response. Mice with primary and metastatic tumors treated with RAD001 showed a significant reduction in blood vessel density when compared to controls at well-tolerated doses. Additionally, activity in a VEGF-impregnated s.c. implant model of angiogenesis and reduced vascularity (vessel density) of RAD001-treated tumors (murine melanoma) provided evidence of *in vivo* effects of angiogenesis. RAD001 also inhibits tumor growth *in-vivo* in xenografted, syngeneic and orthotopic animal models, residing longer in tumor tissue than in plasma and demonstrating high tumor penetration in a rat pancreatic tumor model. These effects occurred within the dose range of 2.5 to 10 mg/kg p.o. daily. Typically, the antitumor activity of RAD001 monotherapy was that of reduction of tumor growth rates rather than producing regressions or stable disease.

RAD001, administered p.o., was a potent inhibitor of tumor growth and well tolerated in:

- Subcutaneous mouse xenograft model, established from a variety of tumor cell lines of diverse histotypes (NSCLC, pancreatic, colon, melanoma, epidermoid), including a Pgp170 overexpressing multi-drug resistant tumor line;
- A series of low-passage tumor xenografts established directly from human tumor material, maintained only *in vivo* and considered highly predictive of therapeutic outcome in patients. These included breast (5 lines), colorectal (9 lines), gastric (3 lines), lung (22 lines including adenocarcinomas, epidermoid cell, large cell and small cell histotypes), melanoma (6 lines), ovarian (4 lines), pancreatic (3 lines) and renal (6 lines); and
- Two syngeneic models (CA20948 rat pancreatic, B16/Bl6 mouse orthotopic melanoma)

Taken together, these data indicate the broad anti-proliferative potential of RAD001. It is not clear which molecular determinants predict responsiveness of tumor cells to RAD001.

Molecular analysis has revealed that relative sensitivity to RAD001 in vitro correlates with the degree of phosphorylation (activation) of the AKT/PKB protein kinase and the S6 ribosomal protein. PTEN status alone may not be predictive of RAD001 relative in vitro sensitivity. However in some cases (i.e., GBM) there is also a correlation with PTEN status. In preclinical models, the administration of RAD001 is associated with reduction of protein phosphorylation in target proteins downstream of mTOR, notably phosphorylated S6 (pS6) and p4E-BP1, and occasionally with an increase in phosphorylation AKT (pAKT).

#### 1.4.2 Preclinical Safety

In safety pharmacology studies, RAD001 was devoid of relevant effects on vital functions including the cardiovascular, respiratory and nervous systems. RAD001 had no influence on QT interval prolongation. Furthermore, RAD001 showed no antigenic potential. Although RAD001 passes the blood-brain barrier, there was no indication of relevant changes in the behavior of

rodents, even after single oral doses up to 2000mg/kg or after repeated administration at up to 40 mg/kg/day. Based on these findings, the potential of RAD001 to affect vital functions in patients is considered to be low.

RAD001 is considered to have no genotoxicity or carcinogenicity potential. All significant adverse events observed in preclinical toxicology studies with RAD001 in mice, rats, monkeys and minipigs were consistent with its anticipated pharmacologic action as an antiproliferative and immunosuppressant and at least in part reversible after a 2- or 4-week recovery period with the exception of the changes in male reproductive organs, most notably testes. Ocular effects (lenticular disorders) observed in rats were not observed in any other species and are considered to be a species-specific disorder.

#### 1.4.3 Clinical Experience

RAD001 has been in clinical development since 1996 as an immunosuppressant in solid organ transplantation and was approved in Europe in 2003 under the trade name Certican®, for the prevention of organ rejection in patients with renal and cardiac transplantation. Additional nononcologic indications currently being explored are wet age-related macular degeneration (AMD) and autosomal dominant polycystic kidney disease (ADPKD). Clinical experience of RAD001 in the transplant indication is summarized in a separate Investigator's Brochure.

In oncology, RAD001 has been in clinical development since 2002 for patients with various hematologic and non-hematologic malignancies as a single agent or in combination with antitumor agents. Please note that safety pharmacology and toxicology studies as well as some human pharmacology studies which have been conducted in support of the transplant indication, are described in the oncology Investigator's Brochure due to the relevance of these data for the oncology indication. Malignancies that are currently being evaluated in Novartis-sponsored studies include the following: metastatic renal cell carcinoma (mRCC), breast cancer, gastroenteropancreatic neuroendocrine tumors (GEP-NET), mantle cell lymphoma and diffuse large B cell lymphoma (DLBCL), hepatocellular cancer (HCC), gastric cancer, and lung cancer. In addition, treatment of patients with tuberous sclerosis complex (TSC)-associated subependymal giant cell astrocytoma (SEGA) and angiomyolymphoma is also being evaluated.

RAD001 has been evaluated as a single agent and in combination with other antitumor agents, including cytotoxic chemotherapeutic agents, targeted therapies, antibodies, and hormonal agents. Approximately 7090 cancer patients have been treated with RAD001 as of 31-Aug-2009; 3275 patients in Novartis-sponsored clinical trials, 615 patients in the single patient use IND program for renal cell cancer, and 3200 in investigator-sponsored studies.

RAD001 5 mg and 10 mg tablets were recently approved under the trade name Afinitor® for patients with advanced renal cell carcinoma in the United States, European Union, and several other countries and is undergoing registration in other regions worldwide. Phase I dose escalating studies, exploratory phase I/II studies with RAD001 as single agent or in combination with other anticancer agents, phase II/III studies of RAD001 in indications, and phase III double-blind studies are contributing to the extensive database. Approximately 7090 cancer patients have been treated with RAD001 as of 31-Aug-2009:

- 3275 patients in Novartis-sponsored clinical trials
- 615 patients in the single patients use IND program for renal cell cancer
- 3200 in investigator-sponsored studies.

In addition, healthy volunteer subjects have participated in the clinical pharmacology studies.

As of 31-Aug-2009, there are a total of 8 phase III trials ongoing in the indications mRCC (1), advanced GEP-NET (2), breast cancer (1), TSC (2), DLBCL (1), and gastric cancer (1). Three additional phase III trials in the indications breast cancer (2) and HCC (1) will be starting in 2010.

Six new Novartis sponsored studies with RAD001 are planned to open for recruitment by 31-Aug-2010:

- Phase I [X2102] involving volunteer subjects with hepatic insufficiency
- Phase I [L2101] involving mRCC patients in China
- Phase II [L2202] involving mRCC

- Phase III [J2301] involving HER2+ breast cancer patients
- Phase III [W2301] involving HER2/neu breast cancer patients
- Phase III [O2301] involving hepatocellular carcinoma patients

Recent approvals of RAD001 (Afinitor®) were based upon a phase III, international, multicenter randomized, double-blind, placebo-controlled study [C2240] in patients with mRCC whose disease had progressed despite prior treatment with VEGFR-TKI (vascular endothelial growth factor receptor tyrosine kinase inhibitor) therapy. Progression-free survival assessed via a blinded, independent central review was the primary endpoint. Secondary endpoints included safety and objective tumor response

In the pivotal phase III study [C2240], which included patients with advanced renal cell carcinoma, the most common adverse reactions (incidence ≥10%) were stomatitis, rash, fatigue, asthenia, diarrhea, anorexia, nausea, mucosal inflammation, vomiting, pneumonitis, cough, peripheral edema, infections, dry skin, epistaxis, pruritus, and dyspnea. The most common grade 3/4 adverse reactions (incidence ≥2%) were infections, stomatitis, fatigue, and pneumonitis. Non-infectious pneumonitis is a class effect of rapamycin derivatives, including RAD001; some of these cases have been severe and, on rare occasions, fatal outcomes have been observed. RAD001 has immunosuppressive properties and may predispose patients to bacterial, fungal, viral, or protozoan infections, including infections with opportunistic pathogens. Localized and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections, such as aspergillosis or candidiasis and viral infections including reactivation of hepatitis B virus, have been described in patients taking RAD001. Some of these infections have been severe (e.g., leading to respiratory or hepatic failure) and occasionally have had a fatal outcome.

The most common laboratory abnormalities ≥50% were anemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia, and increased creatinine. The most common grade 3/4 laboratory abnormalities (incidence ≥2%) were lymphopenia, hyperglycemia, anemia, hypophosphatemia, and hypercholesterolemia. Deaths due to acute respiratory failure (0.7%), infection (0.7%), and acute renal failure (0.4%) were observed on the RAD001 arm. The rates of treatment-emergent adverse reactions resulting in permanent discontinuation were 7% and 0% for the RAD001 and placebo treatment groups, respectively. Overall, safety data available from completed, controlled and uncontrolled studies are consistent with the aforementioned findings of the phase III trial. RAD001 is generally well tolerated at weekly and daily dose schedules. The safety profile is characterized by manageable adverse events. These events are generally reversible and non-cumulative.

Further detailed information regarding RAD001 clinical development, safety, and efficacy is provided in the Investigator's Brochure.

#### **1.4.3.1 *Combination of RAD001 and temozolomide in GBM***

The NCI Canada Clinical Trials Group has recently completed investigating the safety and toxicity profile of daily RAD001 combined with adjuvant temozolomide in newly diagnosed GBM (PI: Dr. Warren Mason). This phase I study determined the daily dose of RAD001 at 10 mg/day was safe and tolerable when combined with adjuvant temozolomide. Based on these findings, a dose of RAD001 at 10 mg/day will be combined with temozolomide in the adjuvant setting (150-200 mg/m<sup>2</sup> days 1-5 every 28 days) in both the phase I and phase II components of this trial.

### **1.5 Correlative Studies**

Correlative studies will be performed in an attempt to provide data to help identify specific patients who may receive benefit from RAD001. Submission of tissue is **required** for the Phase II portion of this study to accomplish these goals. Specifically, studies will evaluate pretreatment tissue for MGMT methylation status, which is an important prognostic factor in GBM, and proteins that play a role in the mTOR pathway. This will include activated Akt (phospho-Akt), which as described above, is a poor prognostic factor in GBM and plays a contributory role in activating the mTOR pathway. In addition, activated mTOR (phospho-mTOR), the primary target of RAD001, will be similarly evaluated. Clinical outcomes of patients on this trial expressing activated forms these proteins will be compared to similar patients on the control arm of the recently completed RTOG 0525. These patients represent a matched cohort (i.e., demonstrate activation of Akt and/or mTOR) that has undergone therapy consisting of temozolomide and radiation for newly

diagnosed GBM without RAD001 as in initial attempt in identifying specific molecular characteristics that may predict response to this regimen.

## **1.6 Potential Trends in Glioblastoma Survivorship**

Historically, clinical outcomes for glioblastoma patients have been relatively consistent. However in recent years, it appears as though this landscape may be changing. A median survival of 14.6 months with the addition of temozolomide, as demonstrated by the EORTC,<sup>2</sup> has served as the clinical benchmark for newly diagnosed glioblastoma patients and was therefore used to test the efficacy of single-arm phase II trials incorporating novel agents to this regimen. The NABTT CNS Consortium recently presented interesting data challenging the application of these EORTC results to current patient populations in the United States.<sup>42</sup> In this report, the results of three single-arm phase II studies were presented with median survival ranging from 18.3 months to 21.9 months, all of these representing a statistically significant improvement in outcome when compared to published EORTC data. Authors contend these findings may not be related to a specifically effective agent and actually may represent the current clinical benchmark in the United States using a standard temozolomide/radiation regimen. Although still unclear, with the potential for a different survivorship for glioblastoma patients in the United States (which may be continuing to change with the emergence of novel agents), rather than a single-arm phase II study, we propose to randomize patients 1:1 (for the experimental and control arm, respectively) to establish and confirm the baseline survival in the current glioblastoma patient population. We believe such an approach will provide important direction in interpreting the results of this study by limiting the potential for proceeding with a large-scale phase III effort based on false-positive results.

## **1.7 Summary**

In summary, overall prognosis of GBM patients remains poor. Although clinical gains have recently been achieved, these have been modest, with a majority of patients succumbing to disease progression within 2 years. New agents need to be identified which can be integrated into and enhance the cytotoxic effects of the current treatment regimen to achieve further clinical gains in this disease. mTOR, which serves as a regulatory hub for both potent pro-survival pathways and tumor angiogenesis, represents a promising target in GBM. Preclinical studies demonstrate independent activity of mTOR inhibitors in GBM cell lines, and most importantly, their strong potential to enhance cytotoxic effects of both radiation and chemotherapy. Favorable early clinical experience with RAD001 coupled with preclinical findings provide the rationale for this proposed Phase I/II trial designed to define the toxicity profile and efficacy of adding the mTOR inhibitor RAD001 into the current chemoradiation platform for newly diagnosed GBM patients.

## **2.0 OBJECTIVES**

### **2.1 Phase I**

- 2.1.1 Primary Objective:** To define the maximum tolerated dose of RAD001 (up to established dose of 10 mg/day) when combined with concurrent radiation and temozolomide in newly diagnosed GBM.
- 2.1.2 Secondary Objective:** To characterize the safety profile of RAD001 in combination with radiation and temozolomide.

### **2.2 Phase II**

#### **2.2.1 Primary Objective**

To determine the efficacy of RAD001 in combination with radiation and temozolomide followed by RAD001 in combination with temozolomide in patients with newly diagnosed GBM as measured by progression-free survival .

#### **2.2.2 Secondary Objectives**

- 2.2.2.1** To determine overall survival in newly diagnosed GBM treated with the study regimen.
- 2.2.2.2** To further evaluate the safety profile of RAD001 in combination with radiation and temozolomide in this patient population.
- 2.2.2.3** To determine if activation of the Akt/mTOR axis predicts response to RAD001 therapy.
- 2.2.2.4** To determine if there is an association between tumor MGMT gene methylation status and response to RAD001

### **3.0 PATIENT SELECTION**

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

#### **3.1 Conditions for Patient Eligibility**

- 3.1.1** Histologically proven diagnosis of glioblastoma (WHO grade IV) **confirmed by central pathology review prior to Step 2 registration.** Since gliosarcoma is a variant of glioblastoma, gliosarcoma is also an eligible diagnosis.
- 3.1.2** Tumor tissue available for correlative studies (Required ONLY in phase II portion, as described below and in Section 10).
- Patients must have at least 1 block of tissue; if a block cannot be submitted, *two* tissue specimens punched with a skin punch (2 mm diameter) from the tissue block containing the tumor may be submitted (see Section 10).
  - Diagnosis must be made by surgical excision, either partial or complete. Stereotactic biopsy or CUSA (Cavitron ultrasonic aspirator)-derived tissue is not allowed for patients on Phase I or Phase II, as it will not provide sufficient tissue for MGMT analysis.
- 3.1.3** The tumor must have a supratentorial component
- 3.1.4** Patients must have recovered from the effects of surgery, postoperative infection, and other complications.
- 3.1.5** A diagnostic contrast-enhanced MRI or CT scan (if MRI is not available due to non-compatible devices) of the brain must be performed preoperatively and postoperatively. The postoperative scan must be done within 28 days prior to step 2 registration, preferably within 96 hours of surgery. Preoperative and postoperative scans must be the same type.
- 3.1.5.1** Patients unable to undergo MR imaging because of non-compatible devices can be enrolled, provided pre- and post-operative contrast enhanced CT scans are obtained and are of sufficient quality.
- 3.1.6** History/physical examination within 14 days prior to step 2 registration
- 3.1.7** Neurologic examination within 14 days prior to step 2 registration
- 3.1.8** Documentation of steroid doses within 14 days prior to step 2 registration
- 3.1.9** Karnofsky performance status  $\geq 70$
- 3.1.10** Age  $\geq 18$  years
- 3.1.11** CBC/differential obtained within 14 days prior to step 2 registration, with adequate bone marrow function defined as follows:
- 3.1.11.1** Absolute neutrophil count (ANC)  $\geq 1,800$  cells/mm<sup>3</sup>;
- 3.1.11.2** Platelets  $\geq 100,000$  cells/mm<sup>3</sup>;
- 3.1.11.3** Hemoglobin  $\geq 10.0$  g/dl (Note: The use of transfusion or other intervention to achieve Hgb  $\geq 10.0$  g/dl is acceptable.)
- 3.1.12** INR and PTT  $\leq 1.5$ .
- 3.1.12.1** Anticoagulation is allowed if target INR  $\leq 1.5$  on a stable dose of warfarin or on a stable dose of LMW heparin for  $> 2$  weeks at the time of enrollment.
- 3.1.13** Adequate renal function, as defined below:
- 3.1.13.1** BUN  $\leq 30$  mg/dl within 14 days prior to step 2 registration
- 3.1.13.2** Serum creatinine  $\leq 1.5$  x ULN within 14 days prior to step 2 registration
- 3.1.14** Adequate hepatic function, as defined below:
- 3.1.14.1** Bilirubin  $\leq 1.5$  x normal range within 14 days prior to step 2 registration
- 3.1.14.2** ALT  $\leq 2.5$  x normal range within 14 days prior to step 2 registration
- 3.1.14.3** AST  $\leq 2.5$  x normal range within 14 days prior to step 2 registration
- 3.1.15** Fasting serum cholesterol  $\leq 300$  mg/dL OR  $\leq 7.75$  mmol/L AND fasting triglycerides  $\leq 2.5$  x ULN. **NOTE:** If one or both of these thresholds are exceeded, the patient can only be included after initiation of appropriate lipid lowering medication.
- 3.1.16** For females of child-bearing potential, negative serum pregnancy test within 14 days prior to step 2 registration
- 3.1.17** Women of childbearing potential and male participants must practice adequate contraception
- 3.1.18** Patient must provide study-specific informed consent prior to registration

#### **3.2 Conditions for Patient Ineligibility**

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



- 3.2.2 Recurrent or multifocal malignant glioma
- 3.2.3 Metastases detected below the tentorium or beyond the cranial vault
- 3.2.4 Prior use of Gliadel wafers or any other intratumoral or intracavitary treatment
- 3.2.5 Prior radiotherapy to the head or neck (except for T1 glottic cancer), resulting in overlap of radiation therapy fields
- 3.2.6 Prior chemotherapy or radiosensitizers for cancer of the head and neck region; note that prior chemotherapy for a different cancer is allowable, except prior temozolomide or RAD001.
- 3.2.7 Prior radiation therapy or chemotherapy for glioblastoma
- 3.2.8 Severe, active co-morbidity, defined as follows:
  - 3.2.8.1 Symptomatic congestive heart failure of New York heart Association Class III or IV
  - 3.2.8.2 Unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction within the last 6 months, serious uncontrolled cardiac arrhythmia or any other clinically significant cardiac disease
  - 3.2.8.3 Severely impaired lung function as defined as spirometry and DLCO that is 50% of the normal predicted value and/or O<sub>2</sub> saturation that is 88% or less at rest on room air
  - 3.2.8.4 Uncontrolled diabetes as defined by fasting serum glucose >1.5 x ULN
  - 3.2.8.5 Active (acute or chronic) or uncontrolled severe infections requiring intravenous antibiotics
  - 3.2.8.6 Liver disease such as cirrhosis, chronic active hepatitis or chronic persistent hepatitis
  - 3.2.8.7 Acquired immune deficiency syndrome (AIDS) based upon current CDC definition or known HIV seropositivity; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with HIV/AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive.
  - 3.2.8.8 Active connective tissue disorders, such as lupus or scleroderma, that in the opinion of the treating physician may put the patient at high risk for radiation toxicity
  - 3.2.8.9 Other major medical illnesses or psychiatric impairments that in the investigator's opinion will prevent administration or completion of protocol therapy
- 3.2.9 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
- 3.2.10 Women who are breast feeding, due to possible adverse effects on the infant
- 3.2.11 Prior allergic reaction to temozolomide
- 3.2.12 Patients who have received prior treatment with an mTOR inhibitor (e.g., sirolimus, temsirolimus, everolimus) or with a known hypersensitivity to these agents or to their excipients
- 3.2.13 Treatment on any other therapeutic clinical protocol
- 3.2.14 Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of RAD001 (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)
- 3.2.15 Concurrent use of enzyme-inducing anti-epileptic drugs (EIAEDs) (See Appendix V)
  - 3.2.15.1 Patients previously receiving these agents must have discontinued their use at least 14 days prior to step 2 registration
- 3.2.16 History of deep vein thrombosis or pulmonary embolism.

#### **4.0 PRETREATMENT EVALUATIONS/MANAGEMENT**

- 4.1 Fasting glucose (See Section 9.6 for supportive care details)

#### **5.0 REGISTRATION PROCEDURES**

##### **5.1 Pre-Registration Requirements for IMRT Treatment Approach**

- 5.1.1 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 The institution or investigator must complete a new IMRT facility questionnaire 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.

## **5.2 Pre-Registration Requirements for 3DCRT Treatment Approach**

- 5.2.2 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.

- 5.2.3 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.

## **5.3 Regulatory Pre-Registration Requirements**

- 5.3.1 **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](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 and native language versions\*)  
\*Note: Institutions must provide certification of consent translation to RTOG Headquarters
- IRB/REB assurance number

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

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.

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

**NOT APPLICABLE: This study is open to North American sites only.**

5.3.4 **Pre-Registration Requirements for the Initial Shipment of RAD001**

5.3.4.1 **U.S. and Canadian Institutions:**

All pre-registration requirements must be met before registering the first case. Institutions must electronically complete (versus hand write) a Study Agent Shipment Form (SASF) available on the RTOG web site, [www.rtog.org](http://www.rtog.org) (next to the protocol). U.S. and Canadian institutions must fax the SASF to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified.

5.3.4.2 **Non-Canadian International Institutions:**

**NOT APPLICABLE: This study is open to North American sites only.**

## **5.4 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](http://www.rtog.org/members/webreg.html) (bottom right corner of the screen), and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

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

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. 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](mailto: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**

**Note: Intensity Modulated RT (IMRT) Is Allowed**

**Radiation therapy must begin  $\leq$  5 weeks after surgery**

**The modality chosen at registration MUST be used for the entire course of treatment**

### **6.1 Dose Specifications**

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

### **6.2 Technical Factors**

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

### **6.3 Localization, Simulation, and Immobilization**

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

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

### **6.4 Treatment Planning/Target Volumes**

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

#### **6.4.1 Initial Target Volume**

Target volumes will be based upon postoperative-enhanced MRI. Preoperative imaging should be used for correlation and improved identification. Two planning target volumes (PTV) will be defined, as outlined below. The initial gross tumor volume (GTV1) will be defined by either the T2 or the FLAIR abnormality on the post-operative MRI scan. This must also include all postoperative-enhanced MRI enhancement, and the surgical cavity. The initial clinical target volume (CTV1) will be the GTV plus a margin of 2 cm. If no surrounding edema is present, the initial planning target volume (PTV1) should include the contrast-enhancing lesion (and should include the surgical resection cavity) plus a 2.5-cm margin. The CTV1 margin may be reduced to 0.5 cm around natural barriers to tumor growth such as the skull, ventricles, falx, etc, and also to allow sparing of the optic nerve/chiasm, if necessary. The initial planning target volume (PTV1) is an additional margin of 3 to 5 mm, depending upon localization method and reproducibility, at each center. PTV margins account for variations in set-up and reproducibility. Reducing PTV margins to modify organ at risk (OAR) dose(s) is not generally permissible. However, OAR must be defined, along with a planning risk volume (PRV) for each OAR. Each PRV will be its OAR plus 3 mm. In the event that an OAR is in immediate proximity to a PTV such that dose to the OAR cannot be constrained within protocol limits, a second PTV (PTV<sub>overlap</sub>), defined as the overlap between the PTV1 and the particular PRV of concern, may be created. Dose to the PTV<sub>overlap</sub> 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) is an additional margin of 3 to 5 mm, depending upon localization method and reproducibility, at each center. PTV margins account for variations in set-up and reproducibility. Reducing PTV margins to modify organ at risk (OAR) dose(s) is not generally permissible. However, OAR must be defined, along with a planning risk volume (PRV) for each OAR. Each PRV will be its OAR plus 3 mm. In the event that an OAR is in immediate proximity to a PTV such that dose to the OAR cannot be constrained within protocol limits, a second PTV (PTV<sub>overlap</sub>), defined as the overlap between the PTV2 and the particular PRV of concern, may be created (the overlap is the intersection between the PTV1 and the PRV). Dose to the PTV<sub>overlap</sub> must be as close as permissible to 14 Gy while not exceeding the OAR dose limit.

#### **6.4.3 Dose Guidelines**

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

Isodose distributions for the initial target volume (PTV1) and the conedown target volume (PTV2) are required on all patients. A composite plan is required showing the respective target volumes. The inhomogeneity within the target volume shall be kept to  $\pm 10\%$  of the prescribed dose.

The minimum dose to the target volume should be kept within 10% of the dose at the center of the volume. Doses are specified such that at least 95% of the PTV shall receive 100% of the prescribed dose; DVHs are encouraged to make this selection.

## **6.5 Critical Structures**

In addition to the above defined GTVs, CTVs and PTVs the lenses of both eyes, both retinæ, 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.

<b>Critical Structure</b>	<b>Maximum Dose</b>
Lenses	7 Gy
Retinæ	50 Gy
Optic Nerves	55 Gy
Optic Chiasm	56 Gy
Brainstem	60 Gy

## **6.6 Compliance Criteria**

- 6.6.1** For all patients, as mentioned above, two PTV prescriptions, PTV1 and PTV2 will be used and the prescription isodose (46 Gy for PTV1 and 60 Gy for PTV2) must cover >95% of the PTV volume; therefore, the total dose in the PTV2 volume will be 60 Gy. The allowable dose within PTV1 (target dose 46 Gy) must be between 41.4 Gy (90% of 46 Gy) and 50.6 Gy (110% of 46 Gy). The allowable dose within PTV2 (target dose 60 Gy) must be between 54 Gy (90% of 60 Gy) and 66 Gy (110% of 60 Gy). If the minimum dose falls below and/or the maximum dose falls above these parameters, an unacceptable deviation will be assigned.
- 6.6.2** 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.

## **6.7 R.T. Quality Assurance Reviews**

In concert with other assigned radiation oncologist(s), the Radiation Oncology Co-Chair, Prakash Chinnaiyan, MD, will perform an RT Quality Assurance Review. These reviews will be ongoing. The final cases will be reviewed within 6 months after this study has reached the target accrual.

## **6.8 Radiation Therapy Adverse Events**

### **6.8.1 Acute**

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

### **6.8.2 Early Delayed**

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

### 6.8.3 Late Delayed

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

## 6.9 Radiation Therapy Adverse Event Reporting

See Section 7.10

## 7.0 DRUG THERAPY

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

**Drug therapy must begin  $\leq$ 5 weeks after surgery.**

### 7.1 Phase 1

RAD001 Dose Levels During Radiation Therapy:

ARM 1: RAD001 2.5 mg/day

ARM 2: RAD001 5 mg/day

ARM 3: RAD001 10 mg/day

Concurrent RAD001 During Radiation Therapy:

RAD001 orally per assigned Treatment Arm, daily during radiation therapy; one hour prior to radiation and in the morning on weekends on days 1-42.

Concurrent Temozolomide During Radiation Therapy:

Temozolomide 75 mg/m<sup>2</sup>/day orally daily during radiation therapy; one hour prior to radiation and in the morning on weekends on days 1-42. Dose should be rounded to the nearest 5 mg.

28-Day Break

Post-Radiation RAD001:

RAD001 10 mg orally daily on days 1-28 of each cycle, for up to 12 cycles, starting 28 days after the completion of radiation therapy (Cycle = 28 days).

Post-Radiation Temozolomide:

Temozolomide 150 mg/m<sup>2</sup>/day – 200 mg/m<sup>2</sup>/day orally daily on days 1-5 of each cycle, starting 28 days after the completion of radiation therapy for up to 12 cycles (Cycle = 28 days). Dose should be rounded to the nearest 5 mg.

Cycle 1: Patients will receive temozolomide 150 mg/m<sup>2</sup>/day.

Cycles 2+: Patients will receive temozolomide 200 mg/m<sup>2</sup>/day, assuming no grade 2 or higher hematologic toxicity at the initial dose (See Section 7.8.4.2 for details).

### 7.2 Phase II

Patients will be randomized to one of two treatment arms:

#### **Arm 1 (No RAD001):**

Concurrent Temozolomide During Radiation Therapy:

Temozolomide 75 mg/m<sup>2</sup>/day orally daily during radiation therapy; one hour prior to radiation and in the morning on weekends on days 1-42. Dose should be rounded to the nearest 5 mg.

28-Day Break

Post-Radiation Temozolomide:

Temozolomide 150 mg/m<sup>2</sup>/day – 200 mg/m<sup>2</sup>/day orally daily on days 1-5 of each cycle, starting 28 days after the completion of radiation therapy for up to 12 cycles (Cycle = 28 days). Dose should be rounded to the nearest 5 mg.

Cycle 1: Patients will receive temozolomide 150 mg/m<sup>2</sup>/day.

Cycles 2+: Patients will receive temozolomide 200 mg/m<sup>2</sup>/day, assuming no grade 2 or higher hematologic toxicity at the initial dose (See Section 7.8.4.2 for details).

## **Arm 2:**

### **Concurrent RAD001 During Radiation Therapy:**

RAD001 (Phase I MTD) orally daily during radiation therapy; one hour prior to radiation and in the morning on weekends on days 1-42.

### **Concurrent Temozolomide During Radiation Therapy:**

Temozolomide 75 mg/m<sup>2</sup>/day orally daily during radiation therapy; one hour prior to radiation and in the morning on weekends on days 1-42.

### **28-Day Break**

### **Post-Radiation RAD001:**

RAD001 10 mg orally daily on days 1-28 of each cycle, for up to 12 cycles, starting 28 days after the completion of radiation therapy (Cycle = 28 days).

### **Post-Radiation Temozolomide:**

Temozolomide 150 mg/m<sup>2</sup>/day – 200 mg/m<sup>2</sup>/day orally daily on days 1-5 of each cycle, starting 28 days after the completion of radiation therapy for up to 12 cycles (Cycle = 28 days). Dose should be rounded to the nearest 5 mg.

Cycle 1: Patients will receive temozolomide 150 mg/m<sup>2</sup>/day.

Cycles 2+: Patients will receive temozolomide 200 mg/m<sup>2</sup>/day, assuming no grade 2 or higher hematologic toxicity at the initial dose (See Section 7.8.4.2 for details).

## **7.3 RAD001 and Temozolomide Administration Guidelines**

### **7.3.1 General**

**7.3.1.1** RAD001 will be administered simultaneously with temozolomide in both the concurrent and adjuvant settings for patients enrolled in the Phase I (Arms 1-3) and Phase II (Arm 2) portions of the trial. Patients randomized to Arm 1 of the Phase II portion of the trial will receive standard therapy consisting of temozolomide and radiation (no RAD001), as described in Section 7.2, using the same guidelines described below.

**7.3.1.2** Patients will be instructed to take RAD001 and temozolomide in both the concurrent and adjuvant setting in a fasting state<sup>41</sup> 1 hour before and 1 hour after administration. Water is allowed during the fasting period.

**7.3.1.3** Patients should be told to swallow the whole capsules/tablets in rapid succession without chewing them.

**7.3.1.4** If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. Use of prophylactic antiemetics is strongly encouraged. (See Section 9.1)

### **7.3.2 During Radiation**

**7.3.2.1** Both RAD001 and temozolomide will be taken 1 hour prior to radiation during weekdays (Monday through Friday) and in the morning on weekends (Saturday and Sunday) for a maximum of 49 days.

**7.3.2.2** On weekdays in which no radiation is received (i.e., holidays) patients will be instructed to continue with their daily administration of RAD001 and temozolomide. They will continue taking RAD001 and temozolomide daily until the completion of radiation, or until the maximum of 49 daily treatments has been reached.

### **7.3.3 Post-Radiation**

The start of the first cycle of adjuvant RAD001 and temozolomide should be started 28 days (± 3 days) following completion of radiation. The start of all subsequent cycles (2-12) will be scheduled every 4 weeks (28 days) ± 3 days after the first daily dose of the preceding cycle.

## **7.4 RAD001 (everolimus) Agent Information**

**7.4.1** Chemical name: (1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-

methylethyl}-19,30 dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.04,9]hexatriaconta-16,24, 26,28-tetraene-2,3,10,14,20-pentaone

7.4.2 Chemical Abstracts registry number: 159351-69-6

7.4.3 International non-proprietary name: everolimus

7.4.4 Molecular formula: C53H83NO14

7.4.5 Molecular weight: 958.2

7.4.6 Physical form: White to faintly yellow powder. RAD001 stabilized with butylated hydroxytoluene (BHT) is amorphous, and contains 0.2% BHT as an antioxidant.

7.4.7 Chirality: The drug substance, RAD001, contains 15 asymmetric carbon atoms and 4 substituted double bonds. The configuration of the asymmetric carbon atoms and the double bonds are guaranteed by the microbial origin of rapamycin, the starting material of the synthesis, and by the X-ray analysis performed on crystalline RAD001. The configuration at carbon 40 is not changed by the chemical derivatization that converts rapamycin into RAD001.

7.4.8 Formulation: All formulations are based on a RAD001 solid dispersion intermediate that was selected on the basis of the chemical stability of the active ingredient and properties allowing for a good *in vivo* performance.

7.4.9 Dosage forms: Tablets: 2.5 mg, 5 mg and 10 mg. The tablets are supplied as 10 tablets per blister pack, 16 blister packs per box.

7.4.10 Composition/excipients: Tablets: butylhydroxytoluene/butylated hydroxytoluene (BHT), magnesium stearate, lactose monohydrate, hypromellose/hydroxypropyl methylcellulose, crospovidone, lactose anhydrous  
The excipients comply with the requirements of the applicable compendial monographs (Ph. Eur., USP/NF).

7.4.11 Stability: Current stability data permit a shelf life of either 36 months (for 5 mg tablet variants based on solid dispersion dried by evaporation/drying oven) or 24 months (for 2.5 mg, 5 mg and 10 mg tablet variants based on solid dispersion dried by paddle dryer), assuming correct storage below 30°C in the original double sided aluminum blister and protected from light and moisture.

7.4.12 Adverse events

Adverse events most frequently observed with RAD001 are rash, stomatitis/oral mucositis, fatigue, headache, anorexia, nausea, vomiting, diarrhea. Infections have not been notably frequent or severe. Non-infectious pneumonitis has also been observed. The majority of these AEs have been of mild to moderate severity (CTC grade 1-2). Overall, the most frequently observed laboratory abnormalities include reduced blood counts, hyperlipidemia mostly reported as hypercholesterolemia and/or hypertriglyceridemia.

The principal dose-limiting toxicity in phase 1 trials has been Grade 3 stomatitis. Hyperlipidemia was reported as a serious adverse reaction. It is a recognized side effect of rapamycins. Hyperglycemia was reported as a serious adverse reaction.

Pneumonitis is a recognized adverse effect of rapamycins (sirolimus, temsirolimus, and everolimus). Numerous case reports in the literature suggest that rapamycin-associated pneumonitis is relatively unaggressive, limited in extent, and reversible upon drug discontinuation. The term 'pneumonitis' is used here to describe non-infectious, nonmalignant infiltration in the lungs, which is evident radiologically. More precise diagnosis should follow histocytological examination following lung biopsy, generally during bronchoscopy which may or may not be symptomatic.

In oncology studies with RAD001, severe pneumonitis suspected as drug-related has been reported as a serious adverse event on 13 occasions and additionally in the following associated preferred terms including acute respiratory distress syndrome (n=2), alveolitis (n=1) and allergic alveolitis (n=1), interstitial lung disease (n=10), lung infiltration (n=23), cryptogenic organizing pneumonia, lung consolidation, pulmonary alveolar hemorrhage, pulmonary toxicity and pulmonary fibrosis (n=1, each). One fatal case of drug-related pneumonitis was reported for a patient with metastatic infiltrating ductal carcinoma of the breast treated with 10 mg/day, which developed approximately two months after starting RAD001. Cytology for both the pleural and pericardial fluids were



positive for malignancy. The death was considered possibly related to the underlying late stage tumor and study drug.

Additionally, one patient treated with 10 mg/day died due to severe acute respiratory distress syndrome and septic shock. Thoracic CT scan demonstrated condensation in the majority of the left lower lobe and frosted glass appearance in the left upper lobe, lingula, and right lung. Along with the cases of non-infectious pneumonitis, serious opportunistic infections have also been reported in cancer patients treated with RAD001: mycobacterium, aspergillus, and fatal candidal sepsis, and fatal *Pneumocystis carinii* in particular. Because RAD001, as other rapamycins, inhibits proliferation of activated lymphocytes and reduces neutrophil counts, treatment with RAD001 must be considered as predisposing patients to the risk of infection. This risk will be higher in patients severely immunocompromised because of their underlying disease and/or co-medications. Outcome may be fatal in case of serious infections.

Discrete, reversible changes in liver enzymes have been found to occur in numerous patients during treatment with RAD001 in oncology clinical studies, and in a study in rheumatoid arthritis. In oncology studies, these changes may be evident only in patients without severe underlying morbidity. The increase in transaminases (AST and ALT) generally appears after 4 weeks of treatment. In all but a few cases it does not exceed Grade 1 ( $\leq 2.5 \times \text{ULN}$ ).

Similarly, mild increases in alkaline phosphatases can coexist. Spontaneous corrections or intermittent correction with continued treatment can occur. Serum bilirubin is not increased. In studies of patients with advanced cancers, clinically relevant changes in liver enzymes have been invariably associated with the presence of liver metastases and/or progression of the underlying cancer.

Renal failure has been reported in five suspected cases to date. One patient with no alternative explanation made a complete recovery following study drug adjustment and no treatment/therapy for the event. The rest of the patients had concurrent morbidities, which might have contributed to the reported events.

Hypophosphatemia, hypomagnesemia, hyponatremia and hypocalcemia have been reported as serious adverse reactions.

#### 7.4.13

##### Supply

The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption.

The Study Agent Shipment Form [SASF; available on the RTOG web site, [www.rtog.org](http://www.rtog.org) (next to the protocol)] for U.S. and Canadian sites must be submitted to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. **Note: International sites must receive written approval of submitted LOI Forms from RTOG Headquarters prior to submitting documents to local ethics committee for approval. See [http://www.rtog.org/pdf\\_forms.html?members/forms=Intl\\_LOI\\_Form.doc](http://www.rtog.org/pdf_forms.html?members/forms=Intl_LOI_Form.doc). Approved international institutions must submit the Study Agent Shipment Form and documentation of IRB approval to RTOG Headquarters (Fax 215-574-0300).** This must be done prior to registration of the institution's first case. The drug supply will not be shipped by Biologics, Inc. until the patient has been registered. Biologics, Inc. generally ships drug Mondays through Thursdays. Canadian and international shipments may require additional time. RTOG will notify Biologics, Inc. to initiate each of these shipments after registration of the patient. Drug shipments may not be immediate if the protocol includes a delay in the initial dosing. Drug will be delivered in time for the patient's first dose. **Please contact the drug distributor listed in the protocol directly for shipment tracking information and anticipated delivery dates or if a shipment has not been received by the expected date.**

**Unused supplies at the sites will be returned directly to Biologics, Inc.** Additional questions about supply and delivery should be directed to:

**Biologics, Inc.**  
**120 Weston Oaks Ct**  
**Cary, NC 27513**  
**Phone: 800-693-4906**  
**Fax: 919-256-0794**  
[clinicaltrials@biologicstoday.com](mailto:clinicaltrials@biologicstoday.com) or [KBuer@biologicstoday.com](mailto:KBuer@biologicstoday.com)

**7.4.13.2 Accountability**

Drug accountability records must be maintained at all sites according to good clinical practices and NCI guidelines.

**7.4.14 Investigator Brochure**

To obtain the investigator brochure, contact:

Amy Bartalotta  
Sr. Clinical Research Scientist  
Novartis Pharmaceuticals Corporation  
US Medical Affairs  
USEH432/3530A  
One Health Plaza  
East Hanover, NJ 07936-1080  
Phone: 862-778-7031  
Email : [amy.bartalotta@novartis.com](mailto:amy.bartalotta@novartis.com)

**7.5 Temozolomide Agent Information** (Temodar, Temodal)

Please refer to the package insert for comprehensive information.

**7.5.1 Formulation**

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

**7.5.2 Mode of Action**

Alkylating agent of imidazotetrazinone class.

**7.5.3 Storage and Stability**

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

**7.5.4 Pharmacokinetics**

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

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

**7.5.5 Metabolism and Elimination**

Temozolomide is spontaneously hydrolyzed at physiologic pH to the active species, 3-methyl-(triazene-1-yl)imidazole-4-carboxamide (MTIC) and to temozolomide acid metabolite. MTIC is further hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC), which is known to be an intermediate in purine and nucleic acid biosynthesis and to methylhydrazine, which is believed to be the active alkylating species. Cytochrome P450 enzymes play only a minor role in the metabolism of temozolomide and MTIC. Relative to the AUC of temozolomide, the exposure to MTIC and AIC is 2.4% and 23%, respectively. About 38% of the administered temozolomide

total radioactive dose is recovered over 7 days; 37.7% in urine and 0.8% in feces. The majority of the recovery of radioactivity in urine is as unchanged temozolomide (5.6%), AIC (12%), temozolomide acid metabolite (2.3%), and unidentified polar metabolites(s) (17%). Overall clearance of temozolomide is about 5.5 L/hr/m<sup>2</sup>.

## 7.5.6 Special Populations

**7.5.6.1** Creatinine Clearance: Population pharmacokinetic analysis indicates that creatinine clearance over the range of 36-130 mL/min/m<sup>2</sup> has no effect on the clearance of temozolomide after oral administration. The pharmacokinetics of temozolomide have not been studied in patients with severely impaired renal function (CL<sub>Cr</sub> < 36 mL/min/m<sup>2</sup>).

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

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

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

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

## 7.5.7 Drug-Drug Interactions

In a multiple dose study, administration of temozolomide with ranitidine did not change the C<sub>max</sub> or AUC values for temozolomide or MTIC. Population analysis indicates that administration of valproic acid decreases the clearance of temozolomide by about 5%. The clinical implication of this effect is not known. Population analysis failed to demonstrate any influence of co-administered dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H<sub>2</sub>-receptor antagonists, or phenobarbital on the clearance of orally administered temozolomide.

## 7.5.8 Adverse Events

Hematologic: Thrombocytopenia, leukopenia, myelodysplastic syndrome

Gastrointestinal: Nausea, vomiting, anorexia

Hepatic: Elevated liver enzymes (reversible)

Skin: Rash

Neurologic: Convulsions, weakness on one side of the body, abnormal coordination, paralysis

Other: Constipation, diarrhea, stomatitis, fatigue, decreased performance status, headache

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

## 7.5.10 Contraindications

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

## 7.5.11 Pregnancy Category D

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

Treatment of a man with temozolomide may increase the risk of birth defects if he causes a woman to become pregnant while he is taking temozolomide. Men treated with temozolomide may have difficulty causing a woman to become pregnant after their treatment is completed. Men receiving temozolomide should be directed to use effective contraception while they are being treated. There is insufficient data to know what the risk of subsequent problems with

fertility will be. Similarly, women who are treated with temozolomide may have difficulty becoming pregnant in the future and may at be at increased risk of having children with birth defects. There is insufficient evidence to determine what the risk of these complications will be.

**7.5.12** Supply

Commercially available.

**7.5.12.1** **Non-Canadian International Institutions**

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

**7.6** **Dose Escalation and Definition of Maximum Tolerated Dose (MTD) (Phase I)**

**7.6.1** The first cohort of patients in the phase I portion will begin at a RAD001 dose of 2.5 mg/day. Dose will escalate at dose levels described in Section 7.1.1 and according to the rules described in Section 13 and below. Dose-limiting toxicities (DLTs) will be determined based on toxicities observed during the first 8 weeks of treatment.

**7.6.2** With standard therapy, consisting of concurrent temozolomide and radiation, we expect 1 out of 6 patients to experience a DLT. Therefore, the target DLT rate for this study is  $\leq 33\%$ . Dose escalation will continue (or MTD will be defined if at the final dose level) as long the dose produces DLTs in  $\leq 2$  out of 6 patients. The DLT rate chosen is slightly higher than the more conventional  $< 2/6$  patients due to the relatively high frequency of expected toxicities during treatment with radiation therapy and temozolomide. The following rules apply:

<b>Number of patients with DLT</b>	<b>Rule</b>
0/3 DLT	Escalate
1/3 or 2/3	Increase evaluable cohort to 6 patients
3/3	MTD has been surpassed and the dose should be decreased to the next lower level

If the cohort size is increased to 6 patients, the following rules apply:

<b>Number of patients with DLT</b>	<b>Rule</b>
1/6 or 2/6 DLT	Escalate
$\geq 3/6$ DLT	MTD has been surpassed

**7.6.3** If 3 or more patients experience DLT in a cohort, the maximum-administered dose has been determined and dosing for any remaining patients within that cohort will be reduced by one dose level.

**7.7** **Definition of Dose-Limiting Toxicity (DLT)**

Toxicities will be graded according to the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4. If multiple toxicities are seen, the presence of DLT should be based on the most severe toxicity experienced. DLT will be defined as any of the following events occurring during the first 8 weeks of treatment with RAD001 and temozolomide and attributable to the study drugs:

- Any grade 3 or 4 thrombocytopenia, grade 4 anemia, or grade 4 neutropenia lasting more than 7 days.
- Any febrile neutropenia.
- Any non-hematologic grade 3 or greater toxicity, excluding alopecia, despite maximal medical therapy
  - Non-hematologic toxicities such as rash, nausea, vomiting, diarrhea, mucositis, hypophosphatemia, and hypertension will only be considered DLTs if they remain grade 3 or greater despite maximal medical therapy (See Section 9.0 for information related to supportive therapy).
  - Second occurrence of thromboembolism: Patients who develop deep vein thrombosis (DVT) or pulmonary embolism (PE) may receive anticoagulation and resume therapy

once clinically stable. Because DVT and PE are common complications among GBM and gliosarcoma patients, the first DVT and PE will not be considered a DLT (See Section 9.1). Recurrent DVT or PE on therapy will be considered a DLT.

- Any grade 4 radiation-induced skin changes.
- Failure to recover from toxicities to be eligible for re-treatment with RAD001 and temozolomide within 14 days of the last dose of either drug.
- Any episode of non-infectious pneumonitis grade 2, 3, or 4 of any duration (please refer to Section 7.8.2.1)

**7.8 Dose Modifications**

**7.8.1 General Considerations**

In general, if toxicity occurs that is attributed to only one of the agents, only that agent should be dose reduced, while the dose of the other agent can be maintained at the same level. This excludes hematologic toxicities; dose modifications specific to hematologic toxicities can be found in Section 7.8.3 (concurrent phase) and Section 7.8.4 (adjuvant phase). Dose modifications specific to RAD001 toxicity, including stomatitis, hyperlipidemia, and non-infectious pneumonitis are described in Section 7.8.2.

**NOTE:** Grade 2 non-infectious pneumonitis is defined as a DLT (Section 7.8.2.1).

**7.8.2 RAD001-Suspected Adverse Events**

If adverse events persist, treatment should be delayed for up to 2 consecutive weeks. If, after 2 weeks of delay, all adverse events have still not resolved, then any further treatment with RAD001 should be discontinued. However, if the patient has benefited from therapy and it is felt that it would be in the best interest of patient to continue therapy, continuing is permissible following discussion and agreement with the Principal Investigator.

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value suspected to be related to RAD001 must be followed at least weekly until the adverse event or abnormal laboratory resolves or returns to grade 1.

Table 7-1 provides general recommendations for the management of patients with suspected drug toxicities while on treatment with RAD001.

**TABLE 7-1: Dose Modifications for RAD001-Associated Adverse Events**

<b>Grade 3</b> (except hyperlipidemia* & non-infectious pneumonitis**)	Interrupt RAD001 until recovery to grade ≤1. Then reintroduce RAD001 at the lower dose level
<b>Grade 4</b>	Discontinue RAD001
Any hematological or non-hematological toxicity requiring interruption for ≥ 2 weeks	Discontinue RAD001

\*Grade 3 hyperlipidemia (hypercholesterolemia and/or hypertriglyceridemia should be managed using medical therapies (see Section 9)

\*\*Refer to Table 7-2

**7.8.2.1 Management of non-infectious pneumonitis**

Non-infectious pneumonitis is a class effect of rapamycin derivatives. Cases of non-infectious pneumonitis (including interstitial lung disease) have also been described in patients taking RAD001. Some of these have been severe, and on rare occasions, a fatal outcome was observed.

A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnea, and in whom infectious, neoplastic and other non-medicinal causes have been excluded by means of appropriate investigations. Patients should be advised to report promptly any new or worsening respiratory symptoms.

Both asymptomatic radiological changes (grade 1) and symptomatic non-infectious pneumonitis (grade 2 = not interfering with activities of daily living or grade 3 = interfering with activities of daily living and oxygen indicated) have been noted in patients receiving RAD001 therapy. In order to monitor for asymptomatic (grade 1) pulmonary infiltrates, a chest X-ray is required if a CT scan of chest is not used for bi-monthly disease evaluations. Additional chest CT scans may be performed, when clinically necessary. If noninfectious pneumonitis develops, a consultation with a pulmonologist should be considered. If the patient develops grade 3 pneumonitis, treatment with RAD001 should be interrupted and the patient should be treated as medically indicated (short course corticosteroids, oxygen, etc).

**TABLE 7-2: Management of Non-Infectious Pneumonitis**

<b>Worst Grade</b>	<b>Required Investigations</b>	<b>Management</b>	<b>RAD001 Dose Adjustment</b>
Grade 1	CT scan with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O <sub>2</sub> saturation at rest. Repeat chest CT scan every 2 Cycles until return to baseline.	No specific therapy required	Administer 100% of RAD001 dose.
Grade 2*	CT scan with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O <sub>2</sub> saturation at rest. Repeat each subsequent Cycle until return to baseline.	Symptomatic only. Corticosteroids for troublesome cough.	Reduce RAD001 dose until recovery to ≤ Grade 1. RAD001 may also be interrupted if symptoms are troublesome. Patients will be withdrawn from the study if they fail to recover to ≤ Grade 1 within 2 weeks.
Grade 3*	CT scan with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O <sub>2</sub> saturation at rest. Repeat each subsequent Cycle until return to baseline.	Corticosteroids if infective origin ruled out. Taper as medically indicated.	Hold treatment until recovery to ≤ Grade 1. May restart protocol treatment within 2 weeks at a reduced dose (by one level) if evidence of clinical benefit.
Grade 4*	CT scan with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O <sub>2</sub> saturation at rest.	Corticosteroids if infective origin ruled out. Taper as medically indicated.	Discontinue treatment.

\* Bronchoscopy with biopsy and/or bronchoalveolar lavage recommended

### **7.8.3 Dose Modifications During Concurrent Phase (During Radiation)**

#### **7.8.3.1 Temozolomide Dose Modifications**

No dose reduction will be made, however the drug may be held or discontinued depending on the toxicity experienced, as described in Section 7.8.3.3.

#### **7.8.3.2 RAD001 Dose Modifications**

Dose reductions during the concurrent phase are defined below.

One dose reduction is allowed during the concurrent phase.

<b>Dose Level</b>	<b>RAD001 Dose</b>
1	2.5 mg daily
2	5 mg daily
3	10 mg daily

### 7.8.3.3 Delay or Discontinuation of Concurrent Therapy

Delay or discontinuation of concurrent therapy will be decided weekly according to hematologic and non-hematologic adverse events, as specified below.

If the administration of concurrent therapy has to be interrupted, the radiotherapy will proceed normally. Missed doses of either temozolomide or RAD001 will not be made up at the end of radiotherapy. The total number of days and total dose of each drug will be recorded on the Treatment Summary Form (TF).

If any patient requires treatment to be held for more than 2 consecutive weeks because of ongoing toxicity, the investigator and the Principal Investigator will assess if the patient should remain in the study.

In case of hematologic adverse events as defined above, a complete blood count should be performed at least twice weekly.

In case of non-hematologic adverse events, the patient should be assessed at least weekly with relevant laboratory test(s).

If the duration of radiotherapy exceeds 7 weeks, then concurrent treatment with temozolomide and RAD001 should be stopped after 49 days of temozolomide and RAD001 treatment.

If radiotherapy has to be temporarily interrupted for technical or medical reasons unrelated to the temozolomide and/or RAD001 administration, then treatment with daily temozolomide and RAD001 should continue. If radiotherapy has to be permanently interrupted then treatment with daily temozolomide and RAD001 should stop.

### 7.8.3.4 Dose Reductions (During Radiation)

**Refer to Section 7.8.2 for dose modifications for RAD001 specific toxicities (including stomatitis, hyperlipidemia, and grade 2-4 non-infectious pneumonitis).** If only these toxicities are experienced, only Section 7.8.2 rules apply. If a patient experiences toxicities in addition to RAD001-specific toxicities, dose modifications will be based on the most severe toxicity.

Only one dose reduction of RAD001 will be allowed during the concurrent phase. If toxicities persist despite RAD001 dose reduction, RAD001 will be stopped during the remainder of the concurrent phase.

1) If any one or more of the below are observed, then treatment with concurrent temozolomide AND RAD001 should be **STOPPED**.

- **ANC < 0.5 x 10<sup>9</sup>/L (Grade 4)**
- **Platelet count < 25 x 10<sup>9</sup>/L (Grade 4)**
- **Grade 4 non-hematologic AE** (except alopecia, nausea and vomiting, unless the patient has failed maximal anti-emetic therapy, and fatigue).
- **Febrile neutropenia**

2) If one of the following is observed:

- **ANC ≥ 0.5 to < 1.0 x 10<sup>9</sup>/L (Grade 3)**
- **Platelet count ≥ 25 to < 50 x 10<sup>9</sup>/L (Grade 3)**

*then* treatment with RAD001 should be **STOPPED** and temozolomide will be **WITHHELD** until all of the following conditions are met:

- **ANC ≥ 1.0 x 10<sup>9</sup>/L**
- **Platelet count ≥ 75 x 10<sup>9</sup>/L**

As soon as all of the above conditions are met, the administration of temozolomide will resume at the same dose level (75 mg/m<sup>2</sup>/day).

- 3) If one of the following is observed:
- **Grade 3 non-hematologic AE** (except alopecia, nausea and vomiting (unless failed maximal anti-emetic therapy), and fatigue).
  - **Platelet count  $\geq 50$  to  $< 75 \times 10^9/L$  (Grade 2)**

then treatment with RAD001 and temozolomide will be **WITHHELD** until all of the following conditions are met:

- ANC  $\geq 1.0 \times 10^9/L$
- Platelet count  $\geq 75 \times 10^9/L$
- Grade  $\leq 1$  non-hematologic AE (except alopecia, nausea and vomiting (unless failed maximal anti-emetic therapy), and fatigue).

As soon as all of the above conditions are met, the administration of temozolomide will resume at the same dose level ( $75 \text{ mg/m}^2/\text{day}$ ) and RAD001 may resume with a dose level reduction (as described in Section 7.8.3.2).

#### **7.8.4 Dosing Modifications During Adjuvant Phase (Post-Radiation)**

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

##### **7.8.4.1** RAD001 Dose Modifications

RAD001 will be started at 10 mg/day. If it is felt by the treating physician that the patient will likely not tolerate this starting dose of RAD001, a dose reduction will be considered by the Principal Investigator.

RAD001 dose modifications are described below.

Two dose reductions are permitted. For patients who would require dose reductions to a RAD001 dose level  $< 2.5 \text{ mg/day}$ , RAD001 will be stopped.

<b>RAD001 Dose Level</b>	<b>Dose (mg/day)</b>	<b>Remarks</b>
-2	2.5	Reduction if prior adverse event
-1	5	Reduction if prior adverse event
0	10	Starting dose cycle 1 (adjuvant)

##### **7.8.4.2** Temozolomide Dose Modifications

Temozolomide dose modifications are as described below.

For patients who would require dose reductions to a temozolomide dose level  $< 100 \text{ mg/m}^2/\text{day}$ , temozolomide will be stopped.



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

*First cycle*

Temozolomide will be started at a dose of 150 mg/m<sup>2</sup>/day.

*Second cycle*

If, *during* the first cycle, all non-hematologic adverse event observed were grade ≤ 2 (except alopecia, nausea and vomiting, unless the patient has failed maximal anti-emetic therapy) **and** platelets ≥ 100 x 10<sup>9</sup>/L and ANC ≥ 1.5 x 10<sup>9</sup>/L, then the temozolomide dose can be escalated to dose level 1 and this dose should be used as the starting dose for subsequent cycles.

If treatment has to be delayed because of *ongoing* non-hematologic adverse events of grade ≥ 2, then no escalation of temozolomide is possible and the Delay and Dose Reduction rules apply (as described below). If the dose was not escalated at cycle 2, then the temozolomide dose should not be escalated in further cycles (3-12).

If treatment has to be delayed because of ongoing hematologic adverse events, the Delay and Dose Reduction rules apply (as described below).

#### 7.8.4.3 Delay

**Treatment may begin on day 1 of each cycle (within the prior 72 hours) if:**

- ANC ≥ 1.5 x 10<sup>9</sup>/L
- platelet count ≥ 100 x 10<sup>9</sup>/L
- all grade 3 or 4 non-hematologic adverse events (except alopecia, nausea, and vomiting, unless the patient has failed maximal anti-emetic therapy) must have resolved to grade ≤ 1.

If adverse events persist, treatment should be delayed for up to 2 consecutive weeks in patients receiving RAD001 (up to 4 consecutive weeks for patients receiving temozolomide alone). If all AEs have not resolved to acceptable levels, the investigator and the Principal Investigator will assess if the patient should remain in the study if the patient has benefited from therapy.

#### 7.8.4.4 Dose reductions (Post-radiation)

**Refer to Section 7.8.2 for dose modifications for RAD001 specific toxicities (including stomatitis, hyperlipidemia, and Grade 2-4 non-infectious pneumonitis).** If only these toxicities are experienced, only Section 7.8.2 rules apply. If a patient experiences toxicities in addition to RAD001 specific toxicities, dose modifications will be based on the most severe toxicity.

**1) If hematologic or non-hematologic adverse events observed was grade 4 (except alopecia, nausea and vomiting, unless the patient has failed maximal antiemetic therapy) or if any febrile neutropenia was observed, then both adjuvant temozolomide and**

**RAD001 treatment should be stopped.**

**2) If ANC <1.0 x 10<sup>9</sup>/L (Grade 3) OR platelets < 50 x 10<sup>9</sup>/L (Grade 3):**

*then* treatment with RAD001 and temozolomide will be **WITHHELD** until all of the following conditions are met:

- ANC ≥ 1.5 x 10<sup>9</sup>/L
- Platelet count ≥ 100 x 10<sup>9</sup>/L

As soon as all of the above conditions are met, the **administration of temozolomide and RAD001 may resume with one dose level reduction** (as described in Section 7.8.4).

**3) If a Grade 3 non-hematologic AE** (except alopecia, nausea and vomiting (unless failed maximal anti-emetic therapy), and fatigue is observed:

*then* treatment with RAD001 and temozolomide will be **WITHHELD** until they have resolved to Grade ≤ 1 .

As soon as all of the above conditions are met, adjuvant therapy may continue with a dose level reduction in **EITHER** temozolomide **OR** RAD001, depending on which agent is likely contributing towards the observed toxicity. Dose reductions for **BOTH** temozolomide and RAD001 is allowed at the discretion of the investigator if it is unclear which agent is causing the observed toxicity.

If any of the same non-hematologic grade 3 adverse events recurs (except alopecia, nausea and vomiting (unless the patient has failed maximal anti-emetic therapy) after reduction for that adverse event, then both RAD001 and temozolomide will be stopped.

No dose escalation of adjuvant temozolomide is allowed after cycle 2. 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.

## **7.9 Modality Review**

The Medical Oncology Co-Chair, Patrick Wen, 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.

Dr. Wen will perform a Quality Assurance Review after complete data for the first 20 cases enrolled has been received at RTOG Headquarters. Dr. Wen 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.

## **7.10 Adverse Events**

This study will utilize the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for grading all adverse events. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (<http://ctep.cancer.gov>).

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

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

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

#### **7.10.1 Adverse Events (AEs)**

**Definition of an AE:** Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: 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 7.7 also must be reported via AdEERS.**

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

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

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

- **Phase 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. In addition, to ensure patient safety each pregnancy must also be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

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

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

**All supporting source documentation indicated as being provided in the Additional Information Section of the AdEERS Report must be properly labeled with the study/case numbers and the date of the event and must be faxed to both the NCI at 301-230-0159**

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

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

**7.10.3 Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)**

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

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

## 7.11 AdEERS Expedited Reporting Requirements

### Phase I Component

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

### Phase 1 Trial: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days<sup>1</sup> of the Last Dose of the Agent [RAD001]

Phase 1 Trials								
	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5 <sup>2</sup>
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	without Hospitalization	Expected with Hospitalization	without Hospitalization	Unexpected and Expected
<b>Unrelated Unlikely</b>	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days
<b>Possible Probable Definite</b>	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
<sup>1</sup> Adverse events with attribution of possible, probable, or definite that occur <u>greater</u> than 30 days after the last dose of treatment require reporting as follows: AdEERS 24-hour notification followed by complete report within 5 calendar days for: <ul style="list-style-type: none"> <li>• Grade 3 unexpected events with hospitalization or prolongation of hospitalization</li> <li>• Grade 4 unexpected events</li> <li>• Grade 5 expected events and unexpected events</li> </ul> <sup>2</sup> Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.								
<b>Please see exceptions below under section entitled “Additional Instructions or Exceptions.”</b>								
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 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - “10 calendar days” - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

### Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 1 Trials:

None

### Phase 2 Component

CTEP defines expedited AE reporting requirements for phase 2 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 Trial: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days<sup>1</sup> of the Last Dose of the Agent [RAD001] in this Study**

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

<sup>1</sup> Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment 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

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

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

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

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

**Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 Trials:**

None

**8.0 SURGERY**

Not applicable to this study.

**9.0 OTHER 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 Permitted Supportive Therapy**

**9.1.1** Antiemetics: Use of prophylactic antiemetics is at the discretion of the treating physician but is strongly encouraged. For example, a 5-HT3-antagonist during the first cycle of therapy may be administered 30-60 minutes before the RAD001/temozolomide combination.

**9.1.2** Anticoagulants: Oral anticoagulants such as warfarin are CYP2C9 substrates and, as such, no interaction with RAD001 is expected. However, drug-drug interaction studies between macrolide antibiotics and warfarin have produced mixed outcomes and the disparity in these findings has led to the conclusion that multiple factors may alter the clearance of warfarin. The coadministration of RAD001 and oral anticoagulants is possible but should be subject to verification of coagulation (INR) once steady state is reached (after 1 week's treatment).

Patients who develop deep vein thrombosis (DVT) or pulmonary embolism (PE) may receive anticoagulation and resume therapy once clinically stable.

**9.1.3** Corticosteroids: See Section 7.8.2.1 for use for non-infectious pneumonitis.

**NOTE**: See Sections 9.3 through 9.5 for complete guidelines concerning permitted and non-permitted agents in the following categories:

- CYP3A4 inhibitors: See Section 9.3
- *Pneumocystis jiroveci* pneumonitis/*Pneumocystis carinii* pneumonitis (PJP/PCP) prophylaxis: See Section 9.4
- Stomatitis/oral mucositis/mouth ulcers: See Section 9.5
- Hyperglycemia: See Section 9.6
- Hyperlipidemia: See Section 9.7

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

**9.2.1** RAD001 may affect the response to vaccinations, making the response to the vaccination less effective. Live vaccines should be avoided while a patient is treated with RAD001.

**NOTE**: See Sections 9.3 through 9.5 for complete guidelines concerning permitted and non-permitted agents in the following categories::

- CYP3A4 inhibitors: See Section 9.3
- *Pneumocystis jiroveci* pneumonitis/*Pneumocystis carinii* pneumonitis (PJP/PCP) prophylaxis: See Section 9.4
- Stomatitis/oral mucositis/mouth ulcers: See Section 9.5
- Hyperglycemia: See Section 9.6
- Hyperlipidemia: See Section 9.7

## **9.3 CYP3A4 Inhibitors**

**9.3.1** Antifungal agents must be avoided unless a fungal infection is diagnosed. In particular, systemic imidazole antifungal agents (e.g. ketoconazole and itraconazole, which are strong CYP3A4 inhibitors) should be avoided in all patients due to their strong inhibition of RAD001 metabolism, thereby leading to higher RAD001 exposures. Therefore, topical antifungal agents are preferred if an infection is diagnosed. Similarly, antiviral agents such as acyclovir should be avoided unless a viral infection is diagnosed.

**9.3.2** Concurrent administration of RAD001 with other strong CYP3A4 inhibitors (such as ritonavir) and inducers (such as rifampin, rifabutin) should be avoided. If there is no alternative treatment available, patients should be closely monitored for potential toxicities.

**9.3.3** Concurrent administration of RAD001 and moderate CYP3A4 inhibitors (such as erythromycin, fluconazole, calcium channel blockers, benzodiazepines) and moderate CYP3A4 inducers (e.g. carbamazepine, phenobarbital, phenytoin) should also be avoided if possible, or used subject to caution (e.g. increased frequency of safety monitoring, temporary interruption of RAD001).

**9.3.4** Competitive inhibition could occur when RAD001 is combined with drugs that are also CYP3A4 substrates. Therefore caution should be exercised in such cases.

**9.3.5** Patients should avoid Seville oranges and star fruit, as well as the juice of these fruits, which are potent CYP3A4 inhibitors.

**9.3.6** A comprehensive list of cytochrome P450 isoenzymes and CYP3A4 inhibitors, inducers, and substrates can be found in Appendix VII and at <http://medicine.iupui.edu/flockhart>. This website is continually revised and may be checked frequently for updates.

## **9.4 Management of *Pneumocystis Jiroveci* Pneumonitis/*Pneumocystis Carinii* Pneumonitis (PJP/PCP) Prophylaxis**



Both corticosteroid therapy and continuous temozolomide therapy induce lymphocytopenia. Patients receiving any of these drugs or both concomitantly are at an increased risk for opportunistic infections. Therefore, prophylaxis against *Pneumocystis Jiroveci* Pneumonitis (PJP) is recommended for all patients receiving temozolomide during radiotherapy. Due to the potential of augmenting neutropenia associated with the temozolomide and RAD001 combination, use of trimethoprim-sulfamethoxazole (Bactrim) as PJP prophylaxis is discouraged. Alternate agents, including pentamidine inhalations (300 mg via aerosol monthly), are recommended.

- Prophylaxis is recommended to continue for the duration of radiotherapy, regardless of the lymphocyte count.
- After completion of the chemoradiation, patients with a lymphocyte count <500/mm<sup>3</sup> should have CD4 quantification.
- If the CD4 is <200, then prophylaxis is recommended to continue and the CD4 should be quantified on a monthly basis.
- If the lymphocyte count is ≥ 500 or the CD4 is >200, then prophylaxis can be stopped.

### **9.5 Management of RAD001-Associated Stomatitis/Oral Mucositis/Mouth Ulcers**

Stomatitis/oral mucositis/mouth ulcers due to RAD001 should be treated using local supportive care as follows:

- For mild toxicity (grade 1), use conservative measures such as non-alcoholic mouth wash or salt water (0.9%) mouth wash several times a day until resolution.
- For more severe toxicity (grade 2 in which case patients have pain but are able to maintain adequate oral alimentation, or grade 3 in which case patients cannot maintain adequate oral alimentation), the suggested treatments are topical analgesic mouth treatments (i.e., local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase).
- Agents containing hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.
- Antifungal agents must be avoided unless a fungal infection is diagnosed. In particular, systemic imidazole antifungal agents (ketoconazole, fluconazole, itraconazole, etc.) should be avoided in all patients due to their strong inhibition of RAD001 metabolism, thereby leading to higher RAD001 exposures. Therefore, topical antifungal agents are preferred if an infection is diagnosed. Similarly, antiviral agents such as acyclovir should be avoided unless a viral infection is diagnosed.

### **9.6 Management of Hyperglycemia**

Hyperglycemia has been observed in patients receiving RAD001 therapy. In many cases, the affected patients had an abnormal fasting glucose at baseline. Based on this finding, it is suggested that optimal glucose control should be achieved before starting a patient on RAD001 and should be monitored during RAD001 therapy. The method used to normalize glucose control may include oral hypoglycemics or insulin. The precise method will be left at the discretion of the investigator.

### **9.7 Management of RAD001-Associated Hyperlipidemia**

Hyperlipidemia has been reported as a serious adverse reaction to RAD001. It is a recognized side effect of rapamycins. Use of lipid-lowering drugs should be associated with dietary recommendations.

Grade 2 hypercholesterolemia (> 300 mg/dL or 7.75 mmol/L) or grade 2 hypertriglyceridemia (>2.5 x ULN) should be treated with a 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase inhibitor (e.g., atorvastatin, pravastatin) or appropriate lipid-lowering medication, in addition to diet.

HMG-CoA reductase inhibitors are associated with an increased risk of a rare but serious skeletal muscle toxicity manifested by rhabdomyolysis, markedly elevated creatine kinase (CPK) levels and myoglobinuria, acute renal failure and sometimes death. This risk is significantly increased when HMG-CoA reductase inhibitors are combined with fibrates. The risk versus benefit of using this therapy should be determined for individual patients based on their risk of cardiovascular complications of hyperlipidemia.



## **9.8 Other Management Instructions**

- 9.8.1** Grapefruit and grapefruit juice affect cytochrome P450 and P-glycoprotein activity and should therefore be avoided.

## **10.0 TISSUE/SPECIMEN SUBMISSION**

**NOTE: All patients must be offered the opportunity to participate in the tissue banking component of the study. Patients enrolling in phase I of the protocol must be offered the opportunity to participate in the correlative component of the study. (Mandatory for patients enrolling in phase II).**

If the patient consents to participate in these study components, the site is required to submit the patient's specimens as specified below. Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

### **10.1 Tissue/Specimen Submission**

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

In this study, tissue will be submitted to the RTOG Biospecimen Resource for the following purposes:

- Central review of pathology (**mandatory** for eligibility for patients enrolling on phase I and II);
- Correlative studies involving tissue to evaluate MGMT methylation status and p-AKT/mTOR-specific molecular markers, as described in Section 1.5 (**strongly encouraged** for patients enrolling on phase I; **mandatory** for patients enrolling on phase II); and
- Banking of remaining tissue received from submission of tissue for central pathology review and correlative studies (**strongly encouraged** for patients enrolling on phase I and II).
- Banking of frozen tissue, plasma, and urine (**strongly encouraged** for patients enrolling on phase I and II).

### **10.2 Tissue Submission for Central Review for Eligibility (Mandatory for all patients PRIOR to Step 2 registration)**

The following material must be provided to the RTOG Biospecimen Resource for Central Review:

- 10.2.1** One to two H & E stained slides from biopsy or surgical specimen.
- 10.2.2** A Pathology Report documenting that the submitted block, core, or slides contain tumor; the report must include the RTOG protocol number and 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 stating that the tissue is being submitted for Central Review. The Form must include the RTOG protocol number and the patient's initials.
- 10.2.4** Central Review will be performed for every case by Aryn Rojiani, MD, PhD; in general, Dr. Rojiani expects to be able to complete the review within 3 business days of submission receipt.
- 10.2.5** **Submit tissue for central pathology review by overnight courier to:**

**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](mailto:RTOG@ucsf.edu)**

Prepaid overnight Federal Express labels can be requested from the RTOG Biospecimen Resource ([rtog@ucsf.edu](mailto:rtog@ucsf.edu)) for shipment from U.S. sites.

**10.3 Specimen Submission for Correlative Studies Involving MGMT Methylation Status and p-AKT/p-mTOR Axis (Strongly encouraged for patients enrolling on Phase I; mandatory for patients enrolling on Phase 2)**

**10.3.2** Where possible, every effort should be made to obtain a paraffin block containing a sample of tumor tissue measuring approximately 1 cubic centimeter. If a block cannot be submitted, sites can submit *two* tissue specimens punched with a punch tool (2 mm diameter) from the tissue block containing the tumor and submitted in a plastic tube labeled with the surgical pathology number. A kit with the punch, tube, and instructions for obtaining a punch biopsy can be obtained from the RTOG Biospecimen Resource free of charge. (See Appendix VI for detailed collection instructions). Please ensure the entire tissue punch contains tumor. Following analysis, the remaining portion of the block or unused slides will be 1) retained at the RTOG Biospecimen Resource for future banking for consenting patients or 2) returned to the submitting institution for non-consenting patients.

**10.3.3 Submit tissue for per Section 10.6.**

**10.4 Specimen Collection for Banking [For patients who have consented to participate in this component of the study (See Tissue Consent of Appendix I)] (Strongly Encouraged for all patients).**

**See Appendix VI for detailed biospecimen collection and preparation instructions, including information pertaining to collection kits. Kits can be requested from the Biospecimen Resource by email. ([rtog@ucsf.edu](mailto:rtog@ucsf.edu)). Note:** Kits include a pre-paid overnight courier label for shipping of Frozen samples.

**10.4.1 Frozen Tissue**

When available, frozen tissue should be sent on dry ice to the RTOG Biospecimen Resource.

**10.4.2 Tissue Blocks (Collected and shipped per Sections 10.1-10.3)**

Remaining tissue of consenting patients will be retained at the RTOG Biospecimen resource.

**10.4.3 Plasma**

Plasma will be collected at the following times:

- Pretreatment
- Prior to the first and third cycle of adjuvant treatment

Plasma must be stored frozen at -80° C and shipped on dry ice.

**10.4.4 Urine**

Urine will be collected at the following times:

- Pretreatment
- Prior to the first and third cycle of adjuvant treatment

Urine must be stored frozen and shipped on dry ice.

**10.5 Storage Conditions**

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

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

**-OR:**

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

**- OR:**

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

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

**10.6 Shipment Address for Correlative Studies and Banking (See Section 10.2.5 for shipment information for central pathology review)**

**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

### 10.7 Summary of Specimen Submission Details

Specimen	Taken When	Submitted As	Shipping
<b>REQUIRED for Central Pathology Review (all patients)</b>			
1-2 H & E slides	From pre-study open biopsy or surgical resection	Slides	Shipped ambient by overnight courier to RTOG Biospecimen Resource prior to Step 2 registration
<b>STRONGLY ENCOURAGED for Correlative Studies (phase I patients) REQUIRED for Correlative Studies (phase II patients)</b>			
Paraffin block or <i>two</i> tissue specimen punches	From pre-study open biopsy or surgical resection	Paraffin-embedded block	Mailed ambient to RTOG Biospecimen Resource prior to Step 2 registration
<b>STRONGLY ENCOURAGED for Tissue Banking</b>			
Frozen tissue	From pre-study open biopsy or surgical resection	Snap freeze tissue samples in liquid nitrogen. <i>(If no liquid nitrogen is available, freeze on dry ice.)</i> Store at minimum -80° C	Shipped frozen on dry ice to RTOG Biospecimen Resource via overnight courier post Step 2 registration (Monday-Wednesday)
Plasma	Pretreatment and prior to the first and third cycle of adjuvant treatment	Aliquot a minimum of 0.5ml plasma into each of the 1ml cryovials. (up to 10) Store at minimum -80° C	Shipped frozen on dry ice to RTOG Biospecimen Resource via overnight courier (Monday-Wednesday)
Urine	Pretreatment and prior to the first and third cycle of adjuvant treatment	10-20 mL urine aliquotted into two 15 ml polypropylene tubes. Store frozen.	Shipped frozen on dry ice to RTOG Biospecimen Resource via overnight courier (Monday-Wednesday)

### 10.8 Reimbursement

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

received, RTOG Clinical Trials Administration will authorize payment according to the schedule posted with the Reimbursement and Case Credit Schedule found on the RTOG web site ([http://www.rtog.org/pdf\\_document/RTOG\\_STUDY\\_LIST.pdf](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.

## **10.9 Confidentiality/Storage**

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

**10.9.1** 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.

**10.9.2** 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 correlative 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 and/or destroyed.

## **11.0 PATIENT ASSESSMENTS**

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

**11.1.1 Assessment of non-infectious pneumonitis:** See Section 7.8.2.1.

### **11.2 Measurement of Response**

The primary measure of response will be by serial measures of the product of the two largest cross-sectional diameters. 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.info.nih.gov/guidelines/recist.html> for further details.

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

Partial Response (PR): Decrease of >50% in the product of two diameters. **The steroid dose at the time of the scan evaluation should be no greater than the maximum dose used in the first 8 weeks from initiation of therapy.** PR will be coded only if confirmed by a second CT/MR scan performed a minimum of 4 weeks after the initial scan.

Minor Response (MR): Decrease in diameter products of <50%. **The steroid dose at the time of the scan evaluation should be no greater than the maximum dose used in the first 8 weeks from initiation of therapy.** This will not need a confirmatory scan.

Stable Disease (SD): Does not qualify for CR, PR, MR, or P. This will not need a confirmatory scan.

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, OR appearance of a new lesion/site, OR clear clinical worsening or failure to return for evaluation due to death or deteriorating condition (unless clearly unrelated to this cancer). 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 RT.

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

- Progression of disease;

- Unacceptable toxicity to the patient (at the discretion of the treating physician)- Reasons for removal must be clearly document on the appropriate case report form/flowsheet, and RTOG Headquarters Data Management must be notified;
- A delay in protocol treatment, as specified in Sections 7.0.
- 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.

## **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**

<b><u>Item</u></b>	<b><u>Due</u></b>
Demographic Form <b>(A5)</b>	Within 2 weeks of registration
Initial Evaluation Form <b>(I1)</b>	Within 2 weeks of registration
Pathology Report <b>(P1)</b>	Within 2 weeks of registration
Specimen Transmittal Form <b>(ST)</b>	Within 4 weeks of Step 1 registration
Central Pathology Review Form <b>(P4)</b>	Within 4 weeks of Step 1 registration
Treatment Form <b>(TF)</b>	Within 3 weeks of the end of concurrent treatment then monthly for each 28-day cycle
Follow-up Form <b>(F1)</b>	At the conclusion of protocol therapy; then q 3 months x 1 year; then every 4 months x 1 year; then q 6 months. Also at progression/relapse and at death

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

<b><u>Item</u></b>	<b><u>Due</u></b>
<b>Preliminary Dosimetry Information (DD)</b> †Digital Data Submission – <u>Treatment Plan</u> submitted to ITC via SFTP account exported from treatment planning machine by Physicist Digital data submission includes the following: <ul style="list-style-type: none"><li>• CT data, critical normal structures, all GTV, CTV, and PTV contours</li><li>• Digital beam geometry for initial and boost beam sets</li><li>• Doses for initial and boost sets of concurrently treated beams</li><li>• Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan</li></ul>	Within 1 week of RT start

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](mailto:itc@wustl.edu)) after digital data is submitted. The e-mail must include study and case numbers or, if the data is phantom, “dry run” or “benchmark”.**

**Final Dosimetry Information**

Within 1 week of RT end

Radiotherapy Form (T1)

Daily Treatment Record (T5) [copy to HQ and ITC]

Modified digital patient data as required through consultation with Image-Guided Therapy QA Center

†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](mailto:itc@wustl.edu)

For media submission: Please contact the ITC about acceptable media types and formats.

Hardcopies accompanying digital data should be sent by mail or Federal Express and should be addressed to:

**Image-Guided Therapy Center (ITC)**

**ATTN: Roxana Haynes**

**4511 Forest Park, Suite 200**

**St. Louis, MO 63108**

**314-747-5415**

**FAX 314-747-5423**

## **13.0 STATISTICAL CONSIDERATIONS**

### **13.1 Study Endpoints**

#### **13.1.1 Study Endpoints for Phase I Component**

##### **13.1.1.1 Primary Endpoint**

Dose-limiting toxicity (DLT), as defined as any of the following events occurring during the first 8 weeks of treatment with RAD001 and temozolomide and attributable to the study drugs:

- Any grade 3 or 4 thrombocytopenia, grade 4 anemia, or grade 4 neutropenia lasting more than 7 days.
- Any non-hematologic grade 3 or greater toxicity, excluding alopecia, despite maximal medical therapy.
- Any grade 4 radiation-induced skin changes.
- Failure to recover from toxicities to be eligible for re-treatment with RAD001 and temozolomide within 14 days of the last dose of either drug.
- Any episode of non-infectious pneumonitis grade 2, 3, or 4 of any duration.

##### **13.1.1.2 Secondary Endpoint**

Treatment-related toxicity, measured by the CTCAE version 4.0.

#### **13.1.2 Study Endpoints for Phase II Component**

##### **13.1.2.1 Primary Endpoint**

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

##### **13.1.2.2 Secondary Endpoints**

**13.1.2.2.1** Overall survival, defined as the interval from randomization to death due to any cause;

**13.1.2.2.2** Treatment-related toxicity, measured by the CTCAE version 4.0.

## **13.2 Sample Size and Power Justification**

### **13.2.1 Phase I Component**

The objective of the phase I portion of this study is to determine the maximum tolerated dose (MTD) of RAD001 when combined with concurrent radiation therapy and temozolomide. Three dose levels are specified for testing, and the starting dose is the lowest dose level. For each dose level, 7 patients will be accrued to assure that there will be 6 patients eligible for treatment adverse event evaluation. A patient registered to the study who is found retrospectively not to meet the study eligibility criteria in Section 3 or who does not receive any RAD001 will be excluded from evaluation of treatment adverse events. Patient accrual will be suspended until there is sufficient information collected to make a decision relative to dose escalation. A dose level for RAD001 will be considered acceptable if no patient of the first 3 eligible patients or no more than 2 patients of the 6 eligible patients experience a DLT. Should all 7 patients be analyzable for adverse events, only the first 6 will be considered in the determination of DLTs. If the current level is considered acceptable, then dose escalation will occur and the protocol will be reopened. Otherwise, the preceding acceptable dose level will be declared the MTD. There will be a maximum of 2 dose level escalations in this study. The RTOG Data Safety Monitoring Board (DSMB) will evaluate each cohort prior to dose escalation. If, at any time, a grade 5 adverse event is observed, then accrual will be suspended and the study chairs will review the event. **If the study chairs determine that the grade 5 toxicity is treatment related, the Executive Steering Committee will be notified; this committee will determine whether the dose level should be closed.** The maximum sample size for the phase I component of the study will be 21 patients.

### **13.2.2 Phase II Component**

**13.2.2.1** The primary objective of the phase II portion of this study is to determine whether RAD001 in combination with radiation therapy plus temozolomide followed by adjuvant temozolomide improves progression-free survival in newly diagnosed GBM patients. Concurrent chemoradiation and standard temozolomide dose maintenance, serving as the control arm in the ongoing phase III study RTOG 0525, will continue to serve as the control arm in the current study design. Assuming an exponential survival with a median progression-free survival of 6.7 months for the control arm, the alternative hypothesis is that there will be 43% improvement in median progression-free survival for the experimental arm, corresponding to a median survival time of 9.6 months. This survival improvement also corresponds to a 30% relative reduction in hazard rate from 0.1035(control arm) to 0.0722 (experimental arm) per month, which is equivalent to a



hazard ratio of 0.70 between the experimental arm and the control arm. The study will be a randomized phase II screening trial as proposed by Rubinstein et al.<sup>43</sup> The randomization of experimental and standard arms is set as 1:1. A total of **134** events (death or progression) are required to detect the 43% increase in median progression-free survival with 85% power at the 1-sided 0.15 significance level. A total of **180** analyzable patients accrued over 12 months are required. Guarding against up to 20% patients not eligible for the following randomization due to insufficient tissue, progression, death, or other reasons, the final targeted accrual for this study component will be **225** cases. Up to 20% loss of patients refers to patients lost between step 1 and step 2 registrations and before randomization.

### 13.2.2.2

#### Association of MGMT Status and Survival: Power Justifications

A retrospective analysis of EORTC 26981/22981\_NCIC CE.3 in GBM showed that patients with methylated MGMT promoter had significantly improved survival compared with patients with unmethylated MGMT promoter (HR = 2.5); this effect was also seen when the comparison was done by treatment arm.<sup>44</sup> Endpoints for the correlative studies of the current trial will be overall survival and progression-free survival. Endpoints will be measured within each treatment arm, as well as for 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. Tissue submission for the MGMT analysis is mandatory in this study component; 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.

When the proposed analysis is performed, we expect approximately **55, 65, and 120** deaths with MGMT methylated/unmethylated status on the experimental arm, the control arm, and combined arms, respectively, if the study results show a positive treatment effect. 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 the MGMT methylated and unmethylated groups, as well as hazard ratio detections with 80% power. As seen below, in the comparisons of the experimental arm, standard arm, and combined arms, there will be approximately 80% or greater statistical power to detect a hazard ratio of 2.23, 2.09, and 1.72 or greater between the MGMT unmethylated and methylated 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 in Methylated and Unmethylated Groups	Number of Events in Methylated and Unmethylated Groups	Statistical Power for HR of				80% Power HR Detection
				2.0	2.25	2.5	3	
Experimental arm	90	81	55	67%	80%	89%	96%	2.23
Standard arm	90	81	65	74%	86%	93%	98%	2.09
Whole study	180	172	120	94%	98%	99%	99%	1.72

### 13.2.2.3

#### Power Justifications for pAKT/mTOR-Positive Subset

Based on the literature, the incidences of p-AKT-positive<sup>4</sup> and p-mTOR-positive<sup>45</sup> tumors are 66% and 75%, respectively. Both studies suggest that these pathways are associated with poor prognosis. One of the secondary objectives of this study is to determine

whether the survival advantage of the experimental arm also exists in the p-AKT/p-mTOR-positive subset. Assuming a median survival time of 12 months for patients with p-AKT/p-mTOR-positive tumors in the control arm, the null hypothesis is that the median survival time in both experimental and control arms in these subsets is 12 months; the alternative hypothesis is that there will be a 54% increase to 18.5 months in median survival time for the experimental arm, corresponding to a hazard ratio of 0.65 between the experimental arm and control arm in these subsets.

According to the above incidences of p-AKT/p-mTOR-positivity, there will be 120 cases (60 in each arm) and 134 cases (67 in each arm) in the p-AKT-positive and p-mTOR-positive subsets, respectively. When the proposed subset analyses are performed at the time of the initial report of the primary endpoint, we expect approximately at least 87 deaths and 100 deaths in the two subsets, respectively, under the alternative hypothesis. Correspondingly, there will be 76% and 78% power, respectively, to detect the hypothesized survival benefit at the one-sided significance level of 0.1. If all patients in the corresponding subset die, the statistical power to detect the hypothesized difference increases to 85% and 88% at the one-sided significance level of 0.1, respectively.

#### **13.2.4 Phase I/II Components**

The maximum sample size is 21 patients for the phase I component and 225 patients for the phase II component; therefore, the maximum sample size for this phase I/II study is **246 patients**.

#### **13.3 Patient Accrual**

Based on the monthly accrual for prior RTOG GBM phase I/II studies, this study is projected to accrue 2 and 15 cases per month for the phase I and II components, respectively. For the phase I component, the study will be suspended when 7 patients enter the tested dose level. Patient accrual will not reopen until there is sufficient information collected to make a decision relative to dose escalation.

For the phase II component, no accrual is expected during the first 2 months of trial activation as institutions obtain IRB approval; a total accrual of 20 patients is expected during the next 4 months; and thereafter monthly accrual is expected to reach 15 patients per month. Therefore, the target accrual should be completed within 20 months of study activation. If the average monthly accrual rate (excluding the first 6 months) is less than 7.5 patients, the study will be re-evaluated with respect to feasibility.

#### **13.4 Stratification and Randomization**

The randomization will occur in a 1:1 ratio between the experimental arm and control arm. The RTOG has previously performed a recursive partitioning analysis (RPA) 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.<sup>46</sup> 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 KPS 70-100 and partially or total resected with no worse than minor neurofunction impairment), or class V (age ≥ 50 and KPS 70-100 and underwent prior partial or total tumor resection with worse than minor neurofunction impairment; **OR** age ≥ 50 and KPS 70-100 and underwent prior tumor biopsy only; **OR** age ≥ 50 and KPS <70). Patients will be randomized in a permuted block design using the method of described by Zelen.<sup>47</sup>

#### **13.5 Analyses Plans**

##### **13.5.1 Statistical Methods**

Overall and progression-free survival rates will be estimated using the Kaplan-Meier method,<sup>48</sup> and differences between the experimental and control arms will be tested using the log rank test.<sup>49</sup> 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<sup>50</sup> for overall and progression-free survival will be performed to assess the treatment effect adjusting patient-specific risk factors.

The covariates to be evaluated for the multivariate models are: treatment assignment, MGMT methylation status, p-AKT/p-mTOR status, RPA risk class, and other prognostic factors. The interactions of treatment with methylation status and p-AKT/p-mTOR status will also be evaluated and included in the model selection process. 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, use the 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. In the univariate analysis, the log rank test will be used to test for overall and progression-free survival differences between the two groups (methylated vs. unmethylated) in experimental arm, control arm, and the study as a whole. For the p-AKT/p-mTOR-positive subsets, the difference between the experimental arm and control arm will also be tested using the log rank test.

### **13.5.2 Interim Analysis**

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

- the patient accrual rate with a projected accrual completion date;
- accrual by institution;
- the pretreatment characteristics of accrued patients including MGMT methylation, p-AKT, and p-mTOR status (if applicable);
- the frequency and severity of toxicities; and
- the results of any completed study chair modality reviews.

The statistician will report any problems identified to the study chairs; the RTOG CNS Committee Chair; and the RTOG DSMB, the monitoring board responsible for overseeing phase I and II trials.

For the phase I component, the RTOG DSMB will review each cohort prior to the next dose escalation. The responsible statistician may recommend dose escalation if no patient of the first 3 eligible patients or no more than 2 patients of the 6 eligible patients experience a DLT. The significant toxicity and/or DLT observed will be included in the report to the DSMB, in addition to those toxicities listed above for inclusion in regular interim analysis reports. The accrual and treatment compliance rates are also considered in making such a recommendation. The DSMB will then make a recommendation about the trial to the RTOG Group Chair.

### **13.5.3 Analysis for Reporting the Initial Treatment Results**

For the phase I component, the analysis to report the MTD will be undertaken when sufficient toxicity information has been collected, the DLTs have been determined for every patient, and there are no any dose escalations.

For the phase II component, the final analysis will be performed on an intent-to-treat basis, such that all eligible cases on the study will be included in the arm to which they were randomized regardless of what treatment the patients actually received. The analysis to report the final results of treatment comparison between the experimental arm and the control arm will be undertaken when 134 events (death or progression) have been reported. A one-sided log-rank test at the 0.15 significance level will be performed to test the difference in progression-free survival 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 progression-free survival 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 13.5.2) and treatment compliance with respect to radiation and chemotherapy will also be included in the final report.

### **13.5.4 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, we address this issue here; both men and women of all races and ethnic groups are eligible for this study. The following table lists the projected accrual for each racial and ethnic group based upon previous RTOG GBM trials.

**Projected Distribution of Gender and Minorities**

	<b>Gender</b>		
<b>Ethnic Category</b>	<b>Females</b>	<b>Males</b>	<b>Total</b>
Hispanic or Latino	2	19	21
Not Hispanic or Latino	93	132	225
<b>Ethnic Category: Total of all subjects</b>	<b>95</b>	<b>151</b>	<b>246</b>
	<b>Gender</b>		
<b>Racial Category</b>	<b>Females</b>	<b>Males</b>	<b>Total</b>
American Indian or Alaskan Native	1	5	6
Asian	0	2	2
Black or African American	1	3	4
Native Hawaiian or other Pacific Islander	0	1	1
White	93	140	233
<b>Racial Category: Total of all subjects</b>	<b>95</b>	<b>151</b>	<b>246</b>

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## APPENDIX I

### RTOG 0913

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

### RTOG 0913

#### **PHASE I/II TRIAL OF CONCURRENT RAD001 (EVEROLIMUS) WITH TEMOZOLOMIDE/RADIATION FOLLOWED BY ADJUVANT RAD001/TEMOZOLOMIDE IN 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 glioblastoma brain tumor, for which you have not yet received treatment other than surgery to biopsy or remove your tumor (meaning your tumor is “newly diagnosed”).

#### **Why is this study being done?**

The purpose of this study is to find out what effects (good and bad) radiation therapy combined with temozolomide and RAD001 (everolimus) have on you and your brain tumor.

RAD001 (everolimus) is a targeted anti-cancer therapy that has been approved by the FDA for treating advanced renal cell carcinoma. Laboratory studies suggest RAD001 may target specific pathways important for glioblastoma growth and treatment resistance. RAD001 has not been approved by the FDA for treatment of glioblastoma or other brain tumors.

Temozolomide is a chemotherapy agent approved by the FDA for treating glioblastomas and other brain tumors.

The standard treatment for glioblastoma is a combination of surgery, radiation therapy, and temozolomide. However, this treatment is not considered curative. This research is being done to see if adding RAD001 to standard therapy will improve the treatment of newly diagnosed glioblastoma patients by improving survival or delaying the growth of the cancer..

Depending on when you are enrolling in this study, you are being asked to participate in either the study’s phase I or phase II part. The purpose of the phase I (first part) of this study is to determine the safety and tolerability of RAD001 when combined with temozolomide and radiation. This part will be followed by the phase II (second part) of the study. The purpose of



the phase II part of this study is to determine how well RAD001 works when combined with temozolomide and radiation.

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

At the beginning of the study, 7 participants will be treated with a low dose of RAD001. If this dose does not cause bad side effects, it will slowly be made higher as new participants take part in the study. A maximum of 21 participants will take part in the first part of the study (phase I), and 225 participants will take part in the second part of the study (phase II).

### **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 neurologic examination
- MRI (with gadolinium) or CT (with contrast) scan
- Blood tests

#### **During the study ...**

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. If the tumor is not a glioblastoma, you will not be able to continue to participate on this study.

If you are entered into the phase II portion of this study, in addition to your tumor being analyzed to confirm that it is a glioblastoma, your tumor will also be analyzed to see whether it contains certain molecular genes (MGMT, Akt, and mTOR). Determining the presence of these genes will help the study doctors determine whether RAD001 plus temozolomide and radiation works differently in participants with this profile. If there is not enough tumor tissue present to perform the molecular analyses, you will not be able to continue on the study.

If all 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.

- MRI or CT scan
- Blood work for blood counts as well as kidney and liver function

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

- Physical and neurologic examination

You will need these tests and procedures that are either being tested in this study or being done to see how the study is affecting your body.

- Blood work for cholesterol levels and fasting glucose levels

MRI/CT scans, blood work, and documentation of side effects will be repeated throughout the study so that the study doctor can monitor you. 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.

### Phase I

If you are enrolled in Phase I of the study, you will receive outpatient treatment with radiation therapy, temozolomide, and RAD001 as follows:

- Radiation Treatments: These treatments will be given once per day, 5 days per week (Monday-Friday) for 30 treatments over 6 weeks.
- Temozolomide: You will take oral temozolomide every day (7 days a week) while you are receiving radiation treatment. Beginning 28 days after your last radiation treatment, you will take temozolomide for 5 days every 28 days for up to 12 cycles (1 cycle = 28 days).
- RAD001: You will take oral RAD001 every day (7 days a week) while you are receiving radiation treatment. Beginning 28 days after your last radiation treatment, you will take RAD001 every day for up to 12 cycles (1 cycle = 28 days).

### Phase II

If you are enrolled in Phase II the study, you will be “randomized” into one of two study groups. 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 an equal chance of being placed in either group.

#### **Group 1 (Arm 1)**

- Radiation Treatments: These treatments will be given once per day, 5 days per week (Monday-Friday) for 30 treatments over 6 weeks.
- Temozolomide: You will take oral temozolomide every day (7 days a week) while you are receiving radiation treatment. Beginning 28 days after your last radiation treatment, you will take temozolomide for 5 days every 28 days for up to 12 cycles (1 cycle = 28 days).

#### **Group 2 (Arm 2)**

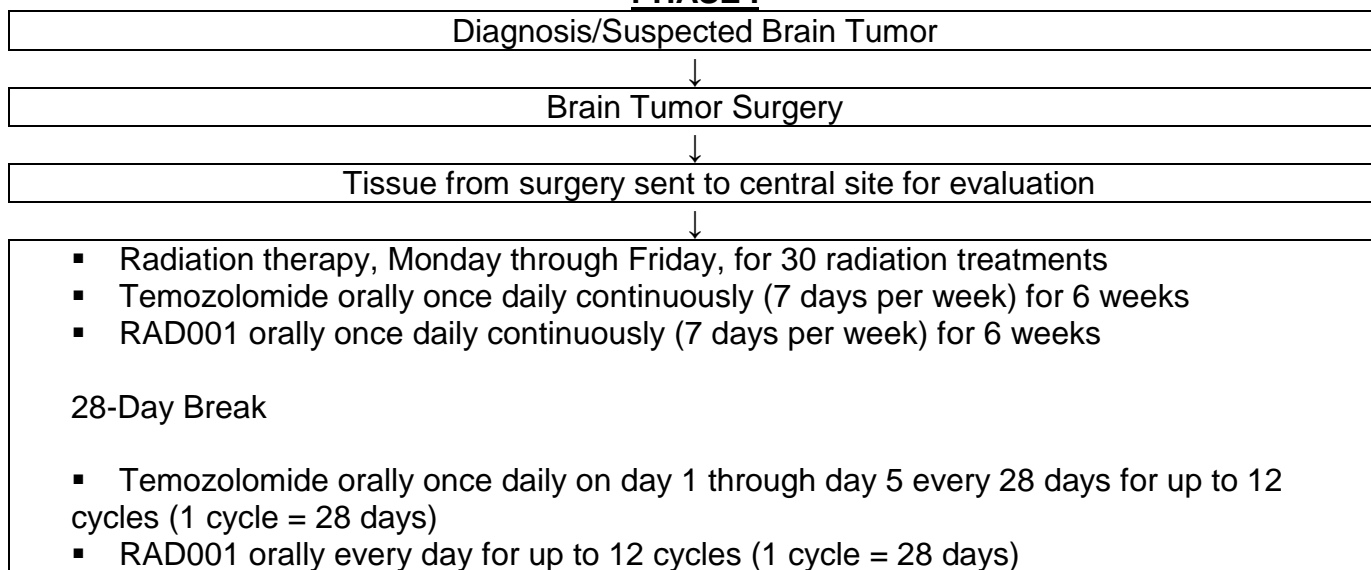
- Radiation Treatments: These treatments will be given once per day, 5 days per week (Monday-Friday) for 30 treatments over 6 weeks.
- Temozolomide: You will take oral temozolomide every day (7 days a week) while you are receiving radiation treatment. Beginning 28 days after your last radiation treatment, you will take temozolomide for 5 days every 28 days for up to 12 cycles (1 cycle = 28 days).
- RAD001: You will take oral RAD001 every day (7 days a week) while you are receiving radiation treatment. Beginning 28 days after your last radiation treatment, you will take

RAD001 every day for up to 12 cycles (1 cycle = 28 days). You will receive RAD001 at the maximum tolerated dose from the Phase I portion.

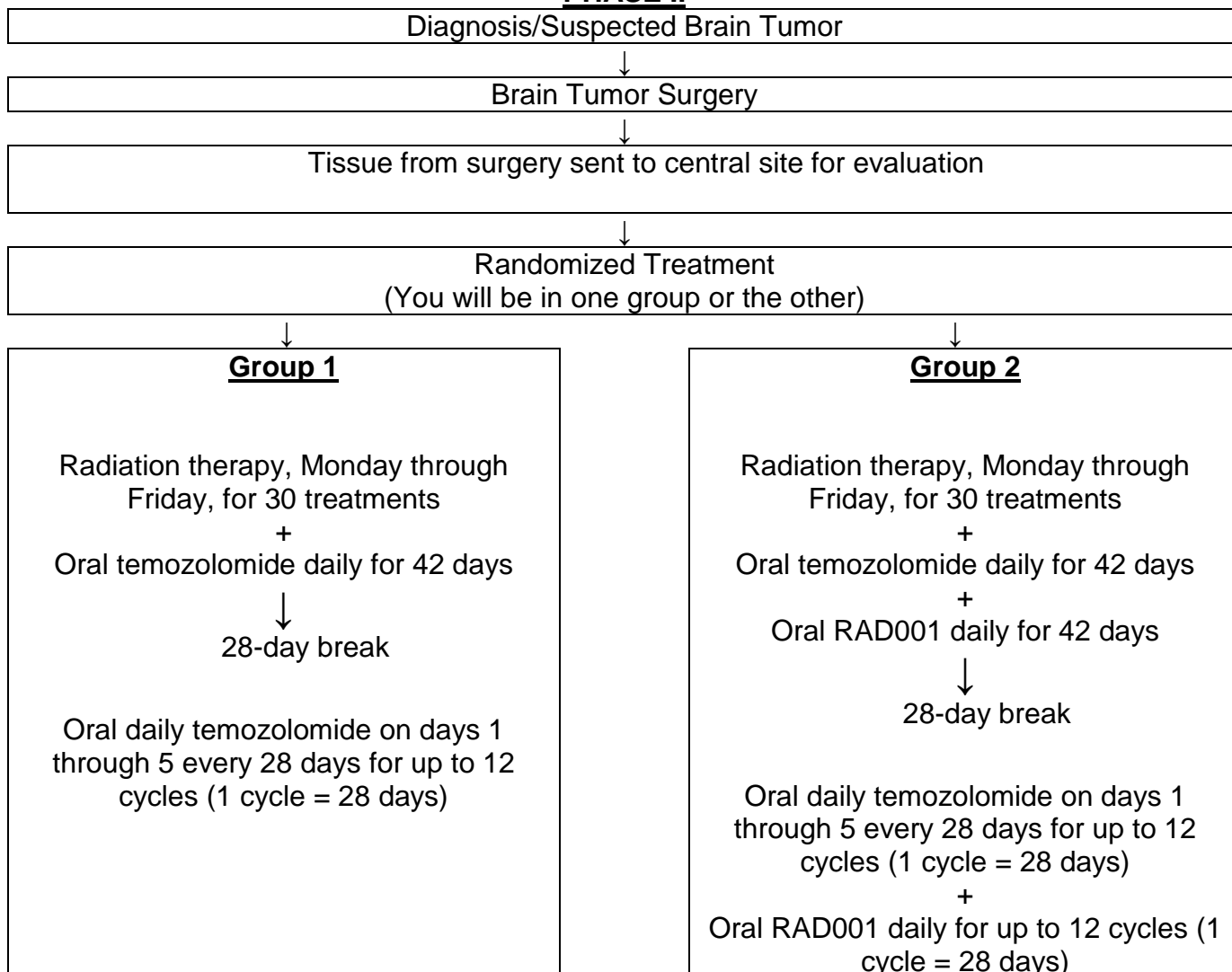
### **Study Plan**

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.

## PHASE I



## PHASE II



### **When I am finished treatment with radiation, temozolomide, and RAD001...**

You will be followed at regular check-ups, including MRI or CT scans, every 3 months for the first year after treatment, every 4 months for the next year, then every 6 months thereafter.

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

You will receive radiation therapy plus drug therapy with temozolomide and RAD001 for 6 weeks. 28 days after you are finished taking the drugs and radiation therapy, the study doctor will ask you to visit the office for a follow-up exam. You will then take temozolomide and RAD001 for up to 12 months; you will be asked to return to the office monthly during that time. You will then be asked to return to the office for a follow-up exam every 3 months for the first year after treatment, every 4 months for the next year, and every 6 months thereafter.

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

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so he/she can evaluate any risks from the radiation therapy, temozolomide, and RAD001. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

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

### **What side effects or risks can I expect from being in the study?**

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, researchers don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the radiation therapy, temozolomide, and RAD001. 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 therapy include those that are:**

#### **Likely**

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

#### **Less Likely**

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

**Rare but Serious**

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

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

**Likely**

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

**Less Likely**

- Decrease in blood counts that may cause infection, bleeding, and bruising
- Diarrhea
- Fever
- Sores in your mouth
- Rash
- Elevated liver enzymes (reversible)
- Swelling in your arms and legs
- Memory loss
- Confusion
- Itchiness
- Increased need to urinate
- Weakness
- Back pain
- Dizziness
- Tingling/burning in your arms and legs
- Anxiety
- Depression

- Stomach pain
- Blurred vision

### **Rare but Serious**

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

**Risks and side effects related to RAD001 include those that are:**

### **Likely**

- Rash
- Sores in your mouth
- Fatigue, tiredness
- Headache
- Loss of appetite
- Nausea
- Vomiting
- Diarrhea
- Dry skin
- Itching
- Cough
- Swelling of your feet and legs
- Shortness of breath
- Nose bleeds
- Anemia (decrease in red blood cells which may cause tiredness)
- High blood cholesterol level
- High blood level of a form of fat called triglyceride

### **Less Likely**

- Decrease in blood counts that may cause infection, bleeding, and bruising
- Elevated liver enzymes (reversible)
- Mild or moderate pneumonitis (inflammation of the lungs)
- High blood sugar level
- Lowering in levels of some electrolytes

### **Rare but Serious**

- Toxicity to kidneys
- Severe pneumonitis (inflammation of the lungs)

### **Other**

RAD001 may react with other medications or beverages (such as grapefruit juice). You should talk with your study doctor before taking any new prescription or any over-the-counter medications or supplements.

### **Reproductive Risks**

You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breast feed a baby while on this study. 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 treatment has been completed. There is not enough information about temozolomide in men and women of childbearing age who subsequently try to have children to know how likely problems will be.

For more information about risks and side effects, ask your study doctor.

### **Are there benefits to taking part in the study?**

Taking part in this study may or may not make your health better. While researchers hope the addition of RAD001 to the established treatment will be more effective against your glioblastoma compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help researchers learn more about the use of temozolomide, RAD001, and radiation therapy as a treatment for brain tumors. This information could help future patients with cancer.

### **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. This might include radiation therapy plus temozolomide, which is the standard treatment for newly diagnosed glioblastoma
- Taking part in another study
- Having surgery alone or surgery in combination with radiation therapy and/or other drugs
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your study doctor about your choices before you decide if you will take part in this study.

### **Will my medical information be kept private?**

Data are housed at RTOG Headquarters in a password-protected database. We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if



required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

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

- The Radiation Therapy Oncology Group
- Local institutional review board
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- The pharmaceutical collaborator

### **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.

Temozolomide is commercially available.

Biologics, Inc., a subsidiary of Novartis, will provide the study agent, RAD001 free of charge to you while you are participating in this study. However, you or your health plan may need to pay for costs of the supplies and personnel who give you the drug.

Even though it probably won't happen, it is possible that the manufacturer may not continue to provide the RAD001 to Biologics, Inc., for some reason. If this would occur, other possible options are:

- You might be able to get the RAD001 from the manufacturer or your pharmacy but you or your insurance company may have to pay for it.
- If there is no RAD001 available at all, no one will be able to get more, and the study would close.

If a problem with getting RAD001 occurs, your study doctor will talk to you about these options.

You will not be paid for taking part in this study.

**For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at**

**<http://cancer.gov/clinicaltrials/understanding/insurance-coverage>. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.**

**Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.**

### **What happens if I am injured because I took part in this study?**

It is important that you tell your study doctor, \_\_\_\_\_ *[investigator's name(s)]*, if you feel that you have been injured because of taking part in this study. You can tell the study doctor in person or call him/her at \_\_\_\_\_ *[telephone number]*.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

**What are my rights if I take part in this study?**

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

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.]

**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 research. Below, please mark your choice.**

### *Consent Form for Use of Tissue, Blood, and Urine for Research*

#### **About Using Tissue, Blood, and Urine for Research**

You have had surgery to see if you have cancer. Your doctor has removed some tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care. We plan to evaluate the block of tumor tissue to confirm that the tumor is a glioblastoma and to use the tissue to evaluate the genetic (molecular) profile. These studies are essential components of the clinical trial and therefore permission to use the tissue block for this purpose is mandatory.

We would like to keep some of the tissue that is left over for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How is Tissue Used for Research" to learn more about tissue research. This information sheet is available to all at the following web site: [http://www.rtog.org/tissue%20for%20research\\_patient.pdf](http://www.rtog.org/tissue%20for%20research_patient.pdf)

As a result of your participation in the trial, you will also have blood tests performed. We would like to collect for future research about three tablespoons of blood at the following times that these blood tests are performed: before you start treatment; 4 weeks after you finish radiation; and 12 weeks after you finish radiation.

In addition, we would also like to collect some of your urine for future research. We would collect your urine at the following times: before you start treatment; 4 weeks after you finish radiation; and 12 weeks after you finish radiation.

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, blood, and urine 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 and collect the blood and urine 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. Then any tissue that remains will no longer be used for research and will be returned to the institution that submitted it.

In the future, people who do research may need to know more about your health. While the (doctor/institution) may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue, blood, and urine is used for genetic research (about diseases that are passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records.

Your tissue will be used only for research and will not be sold. The research done with your tissue, blood, and urine may help to develop new treatments for cancer and other diseases 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 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**

	Pre-Study Entry		During Radiation	BREAK				Adjuvant (Post-Radiation)		After Therapy Completion
	≤28 d	≤14 d prior to step 2 registration	Weekly (Weeks 1-6)	Wk 7	Wk 8	Wk 9	Wk 10	Prior to cycles 1, 3, 5, 7, 9, 11	Prior to cycles 2, 4, 6, 8, 10, 12	q3 mo for 1 yr, then q4 mo for 1 yr, then q6 mo
Informed consent	X									
Tissue evaluation for histology	X									
Tissue for MGMT and p-AKT/p-mTOR analysis (Phase II: mandatory; Phase I: for consenting pts)	X									
Tissue for banking (for consenting pts)	X									
Plasma for banking (for consenting pts)	X							Prior to cycles 1 and 3 only		X
Urine for banking (for consenting pts)	X							Prior to cycles 1 and 3 only		
History/physical		X						X	X	X
Neurologic exam		X						X	X	
MRI/CT	X							X		X
Performance status		X						X	X	
CBC w/ diff & ANC		X	X	X	X			X	X	
Prothrombin time		X	X	X	X			X	X	
BUN		X	X	X	X			X	X	
Serum creatinine		X	X	X	X			X	X	
Bilirubin		X	X	X	X			X	X	
ALT/AST		X	X	X	X			X	X	
Fasting glucose		X	X	X	X			X	X	
Fasting serum cholesterol/triglycerides*		X	X	X	X			X	X	

\*See Sections 3.1 and 4.1 for details.

**APPENDIX II (CONT'D)**

	Pre-Study Entry		During Radiation	BREAK				Adjuvant (Post-Radiation)		After Therapy Completion
	≤28 d	≤14 d prior to step 2 registration	Weekly (Weeks 1-6)	Wk 7	Wk 8	Wk 9	Wk 10	Prior to cycles 1, 3, 5, 7, 9, 11	Prior to cycles 2, 4, 6, 8, 10, 12	q3 mo for 1 yr, then q4 mo for 1 yr, then q6 mo
CD4 count (if lymphocyte count < 500 mm <sup>3</sup> )		X	X	X	X			X	X	
Serum pregnancy test (if applicable)		X								
Tumor response evaluation								X		
Adverse event evaluation			X	X	X			X	X	

\*See Sections 3.1 and 4.1 for details.

### APPENDIX III

#### KARNOFSKY PERFORMANCE SCALE

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



## APPENDIX IV

### 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

### EIAEDS AND NON-EIAEDS

#### **EIAEDs:**

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

#### **Non-EIAEDs:**

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

## APPENDIX VI

### APPENDICES FOR RTOG BIOSPECIMEN COLLECTION

RTOG FFPE SPECIMEN PLUG KIT INSTRUCTIONS  
RTOG FROZEN TISSUE KIT INSTRUCTIONS  
RTOG BLOOD COLLECTION KIT INSTRUCTIONS  
RTOG URINE COLLECTION KIT INSTRUCTIONS

#### **Shipping Instructions:**

**US Postal Service Mailing Address: For FFPE or 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 or Trackable Specimens**

RTOG Biospecimen Resource  
University of California San Francisco  
1657 Scott Street, Room 223,  
San Francisco, CA 94115

- ❑ Include all RTOG paperwork in pocket of biohazard bag.
- ❑ Check that the STF has the consent boxes checked off.
- ❑ Check that all samples are labeled with RTOG study and case number, and include date of collection as well as collection time point.
  
- ❑ **FFPE Specimens:**
  - Slides should be shipped in a plastic slide holder/ slide box. Place a small wad of padding in top of container. If you can hear the slides shaking they are likely to break during shipping.
  - FFPE Blocks can be wrapped with paper towel, or placed in a cardboard box with padding. Do not wrap blocks with bubble wrap. Place padding in top of container so that if you shake the container the blocks are not shaking. If you can hear them shaking they are likely to break during shipping.
  - Slides, Blocks or Plugs can be shipped ambient or with a cold pack either by USPS to the USPS address (94143) or by Courier to the Street Address (94115). Do NOT ship on Dry Ice.
  
- ❑ **Frozen Specimens:**
  - Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified.
  - Place specimens and absorbent shipping material in Styrofoam cooler filled with dry ice (at least 7 lbs). There should be plenty of dry ice under and above the specimens. If the volume of specimens is greater than the volume of dry ice then ship in a larger Styrofoam box, or two separate boxes. Any Styrofoam box can be used, as long as it is big enough.
  - Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
  - Send frozen specimens via overnight courier to the address above. Specimens should only be shipped Monday through Wednesday (Monday-Tuesday for Canada) to prevent thawing due to delivery delays. Saturday or holiday deliveries cannot be accepted. Samples can be stored frozen at -80C until ready to ship.
  
- ❑ **For Questions regarding collection/shipping please contact the RTOG Biospecimen Resource by email at: [RTOG@ucsf.edu](mailto:RTOG@ucsf.edu) or (415)-476-7864 or fax (415)-476-5271**

## **RTOG FFPE SPECIMEN PLUG KIT INSTRUCTIONS**

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



### **Step 1**

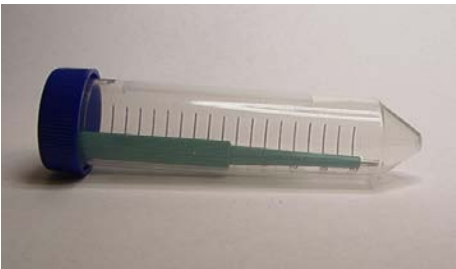
If the block is stored cold, allow it to equilibrate for 30 minutes at room temperature. Place the punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate the plug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



### **Step 2**

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

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



### **Step 3**

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

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

\*NOTE: If your facility is uncomfortable obtaining the plug but wants to retain the tissue block, please send the entire block to the RTOG Biospecimen Resource and we will sample a plug from the block and return the remaining block to your facility. Please indicate on the submission form the request to perform the plug procedure and return of the block.

Ship: Specimen plug kit, specimen in punch tool, and all paperwork to the address below:

- For Questions regarding collection/shipping or to order an FFPE Specimen Plug Kit, please contact the RTOG Biospecimen Resource by email at: [RTOG@ucsf.edu](mailto:RTOG@ucsf.edu) or call 415-476-RTOG(7864) /FAX 476-5271;

**US Postal Service Mailing Address: For FFPE or Non-frozen Specimens Only**  
**RTOG Biospecimen Resource at UCSF**  
**Campus Box 1800**  
**1657 Scott Street, Room 223**  
**San Francisco, CA 94143-1800**

**Courier Address (FedEx, UPS, etc.): For Trackable FFPE shipments**  
**RTOG Biospecimen Resource at UCSF**  
**1657 Scott Street, Room 223**  
**San Francisco, CA 94115**

## **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 liq. 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: by Email [RTOG@ucsf.edu](mailto:RTOG@ucsf.edu) or call (415)476-7864

**Courier Address (FedEx, UPS, etc.): For all frozen specimens**

**RTOG Biospecimen Resource at UCSF  
1657 Scott Street, Room 223,  
San Francisco, CA 94115  
Contact Phone 415.476.7864**

## RTOG BLOOD COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of plasma as specified in protocol

### Kit contents:

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

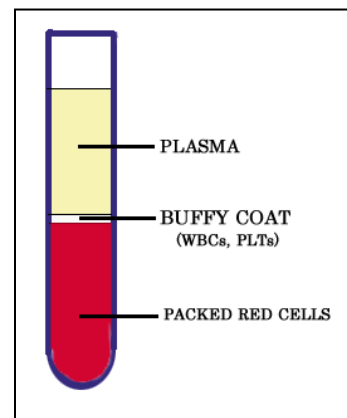
### Preparation and Processing of Plasma

#### A) Plasma: 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 -70 to -90°C 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.**

### 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 liq. 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.

## RTOG BLOOD COLLECTION KIT INSTRUCTIONS

- ❑ 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 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.*
- ❑ For questions regarding collection, shipping or to order a Blood Collection Kit, please Email [RTOG@ucsf.edu](mailto:RTOG@ucsf.edu) or call (415)476-7864 or fax (415) 476-5271

**Shipping Address :    **FedEx/UPS/Courier address (For all frozen samples)****

**RTOG Biospecimen Resource at UCSF  
1657 Scott Street, Room 223  
San Francisco, CA 94115  
Contact Phone 415.476.7864**

## 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.
- ❑ Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
- ❑ 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 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 ordering, collection, or shipping a Urine Collection Kit, please Email [RTOG@ucsf.edu](mailto:RTOG@ucsf.edu) or call (415) 476-7864 or fax (415) 476-5271

**Shipping Address :** **FedEx/UPS/Courier address** (For all frozen samples)

**RTOG Biospecimen Resource at UCSF  
1657 Scott Street, Room 223  
San Francisco, CA 94115**

**Contact Phone 415.476.7864**



## APPENDIX VII

### EXAMPLES OF CLINICALLY RELEVANT DRUG INTERACTION: SUBSTRATES, INDUCERS AND INHIBITORS OF ISOENZYME CYP3A.

<b>Substrates (competitive inhibition)</b>	
Antibiotics <sup>1</sup> : clarithromycin* erythromycin telithromycin* Anti-arrhythmics* quinidine Benzodiazepines: alprazolam diazepam midazolam triazolam Immune Modulators: cyclosporine tacrolimus (FK506) HIV Protease Inhibitors: indinavir* ritonavir* saquinavir* Prokinetic: cisapride Antihistamines: astemizole chlorpheniramine	Calcium Channel Blockers: amlodipine diltiazem felodipine nifedipine nisoldipine nitrendipine verapamil HMG CoA Reductase Inhibitors <sup>2</sup> : atorvastatin cerivastatin lovastatin simvastatin Miscellaneous: aprepitant buspirone haloperidol methadone pimozide quinine sildenafil tamoxifen trazodone vincristine
<b>Inducers</b>	
Carbamazepine Phenobarbital Phenytoin* Rifabutin*	Rifampin* St John's wort Troglitazone
<b>Inhibitors</b>	
Amiodarone Cimetidine Clarithromycin Delavirdine Diltiazem Erythromycin Fluvoxamine* Grapefruit juice Sevilla orange	Indinavir Itraconazole* Ketoconazole* Voriconazole* Posaconazole* Mibefradil Nefazodone* Nelfinavir* Troleandomycin Verapamil

Based on: Ingelman-Sundberg M, Human drug metabolizing cytochrome P450 enzymes: properties and polymorphisms, Naunyn Schmiedebergs Arch Pharmacol. 2004 Jan;369(1):89-104. and [<http://www.medicine.iupui.edu/flockhart/clinlist.htm> as of July 13, 2006]

\*asterisk denotes strong inhibition/ induction

Please note:

- strong inhibitor implies that it can cause  $\geq 5$ -fold increase in AUC or  $\geq 80\%$  decrease in clearance of sensitive CYP substrates
- moderate inhibitor implies that it can cause 2 to 5-fold increase in AUC values or 50-80% decrease in clearance of sensitive CYP substrates.  
(Distinction is not always categorical as interaction can vary according to conditions.)

1. Macrolide antibiotics: Azithromycin is not a CYP3A substrate. It may therefore be employed where antibiotherapy with a macrolide is desirable in a patient being treated with RAD001.
2. Statins: Atorvastatin and pravastatin may be associated with RAD001, since a PK interaction study has shown that there is no relevant PK interaction.