For **Protocol** Update 5/10/13 to: RTOG 0913, Phase I/II Trial of Concurrent RAD001 (Everolimus) With Temozolomide/Radiation Followed by Adjuvant RAD001/Temozolomide in Newly Diagnosed Glioblastoma

Section	Change
Cover pages	The document history table was updated to include the update.
Sections 3.1.12 and 3.1.13	Formatting was corrected.

For **Protocol** Amendment #3 to: RTOG 0913, Phase I/II Trial of Concurrent RAD001 (Everolimus) With Temozolomide/Radiation Followed by Adjuvant RAD001/Temozolomide in Newly Diagnosed Glioblastoma

NCI/Local Protocol #: RTOG 0913

NCI Protocol Version Date: May 1, 2013 (Broadcast May 9, 2013)

Section	Change
Cover pages	The document history table was updated to include Amendment 3.
Eligibility checklist	A clarifying note was added concerning the RPA field to the end of the checklist.
Sections 1.5, 10.1, 10.4, and 10.7; Appendix I, Specimen Submission at Recurrence	Optional tumor tissue and blood collection at recurrence was added. Whole genome sequencing for patients consenting to specimen banking collected in the newly diagnosed setting and at recurrence was added. The technological advancements in genome sequencing have provided an unprecedented insight into the specific genetic mutations involved in driving the aggressive nature of glioblastoma. We hope that gaining this level of understanding into the biology of these tumors will help identify specific genetic mutations that may predict a patient likely to respond favorably to the described therapy, therefore, representing an important step towards offering personalized therapy to glioblastoma patients. Additionally, the proposed studies will allow for the prospective evaluation of specific genetic events leading towards treatment resistance, which we hope will provide meaningful direction in developing novel therapeutic strategies in this patient population, which are currently limited.
3.1.12 and Eligibility checklist Step 2 question 14.	Wording for PT/INR requirements was modified to be consistent with other RTOG glioblastoma protocols.
4.0	Pre-treatment fasting glucose was modified to be needed only for Arm 2 patients (patients randomized to RAD001).
7.4.12	A note to consult the RAD001 investigator brochure for comprehensive pharmacologic and safety information was added per current RTOG standard.
7.4.13	Directions for handling expired or unused drug supplies were modified, because it was stated in error that unused drug was to be returned to Biologics, Inc..
10.2.1 10.3.2 10.7 Appendix V	Specimen collection instructions were updated.

Section	Change
Appendix I, Assessments During Treatment	Fasting glucose and fasting serum cholesterol/ triglycerides were modified to be needed only for Arm 2 patients (patients randomized to RAD001).

For **Protocol Consent** Amendment #3 to: RTOG 0913, Phase I/II Trial of Concurrent RAD001 (Everolimus) With Temozolomide/Radiation Followed by Adjuvant RAD001/Temozolomide in Newly Diagnosed Glioblastoma

NCI/Local Protocol #: RTOG 0913

NCI Protocol Version Date: May 1, 2013 (Broadcast May 7, 2013)

Section	Change
What will happen if I take part in this research study? /During the study	For clarity, in the last sentence of the 2nd paragraph "continue" was changed to "enroll to receive treatment."
What will happen if I take part in this research study? /During the study	Blood work for cholesterol and fasting glucose levels were modified to be needed only for patients randomized to RAD001.
Reproductive Risks	A statement at the end of the 2nd paragraph was added regarding patients becoming pregnant while receiving treatment on study.
Will my medical information be kept private	"The pharmaceutical collaborator" was replaced with "Novartis, the manufacture of RAD001."
For more information on clinical trials and insurance coverage	This information was deleted because it is no longer available.

Section	Change
<u>Consent Form for Use of Tissue, Blood, and Urine for Research</u>: About Using Tissue, Blood, and Urine for Research, 5th paragraph Risks, 2nd-5th paragraphs	Optional tumor tissue and blood collection at recurrence was added. Whole genome sequencing for patients consenting to specimen banking collected in the newly diagnosed setting and at recurrence was added. The technological advancements in genome sequencing have provided an unprecedented insight into the specific genetic mutations involved in driving the aggressive nature of glioblastoma. We hope that gaining this level of understanding into the biology of these tumors will help identify specific genetic mutations that may predict a patient likely to respond favorably to the described therapy, therefore, representing an important step towards offering personalized therapy to glioblastoma patients. Additionally, the proposed studies will allow for the prospective evaluation of specific genetic events leading towards treatment resistance, which we hope will provide meaningful direction in developing novel therapeutic strategies in this patient population, which are currently limited.

For **Protocol** Amendment #2 to: RTOG 0913, Phase I/II Trial of Concurrent RAD001 (Everolimus) With Temozolomide/Radiation Followed by Adjuvant RAD001/Temozolomide in Newly Diagnosed Glioblastoma

NCI/Local Protocol #: RTOG 0913

NCI Protocol Version Date: December 20, 2012 (Broadcast December 21, 2012)

Section	Change
Global	To comply with CTEP's new formatting/document requirements, the protocol was reformatted and the sample consent was removed from the appendices. The appendices were appropriately renumbered. The informed consent continues to be available via MS Word on the protocol documents section of the main protocol page.
Cover pages	The document history table was updated to include Amendment 2. Stephanie Pugh has replaced Meihua Wang as senior statistician. The protocol agents table and participating sites list were added per current RTOG standard.
Schema page 7.1, 7.2, 7.8.3 dose modification table	The protocol was amended to reflect the closure of the phase I component, the establishment of the MTD from phase I, and the opening of the phase II component.
5.3-5.3.2	Information was added on translations for Canadian institutions per current RTOG standard.
5.4	Contact information in event of RTOG web registration inaccessibility was updated.
7.4.14	Contact information was updated.
7.5.12.1	Instructions for non-Canadian international institutions were deleted because the protocol is not open to enrollment outside of North America.
7.7	In the last bullet, the spelling of pseudoprogression was corrected.
7.8.2	Grade 3 hyperlipidemia was corrected to Grade 2 or 3 hyperlipidemia

Section	Change
7.8.2 7.8.3	The statement, "Supportive documentation of the result of the discussion between the site investigator and the Principal Investigator I must be mailed to RTOG Data Management (1818 Market Street; Suite 1600; Philadelphia, PA 19103), and the delay should be clearly documented on the treatment form (TF) for that reporting period," was added due to RTOG documentation needs.
7.10, 7.10.2, 7.11	Adverse Events reporting instructions and related tables were updated to current RTOG/FDA standards.
9.7	Grade 3 hypercholesterolemia was corrected to Grade 2 or 3 hypercholesterolemia Grade 3 hypertriglyceridemia was corrected to Grade 2 or 3 hypertriglyceridemia.
10.5	(STF) was added after Specimen Transmittal Form for clarity.
10.6	Contact information was updated
12.1	The time points for the TF form was changed from within 2 weeks from the end of concurrent treatment to within 3 weeks.
Appendix I	In order to comply with CTEP's new table formatting guidelines, the study parameter table was divided into three tables, one each for assessments pre-treatment, during treatment, and after therapy completion.

For **Protocol Consent** Amendment #2 to: RTOG 0913, Phase I/II Trial of Concurrent RAD001 (Everolimus) With Temozolomide/Radiation Followed by Adjuvant RAD001/Temozolomide in Newly Diagnosed Glioblastoma

NCI/Local Protocol #: RTOG 0913

NCI Protocol Version Date: December 20, 2012 (Broadcast December 21, 2012)

Section	Change
Front page	A version date was added.

Section	Change
Why is this study being done? How many people will take part in the study? What will happen if I take part in this research study?	The consent was amended to reflect the closure of the phase I component and the opening of the phase II component.

SUMMARY OF CHANGES
Amendment 1, January 13, 2012
(Broadcast January 25, 2012)

RTOG 0913, "Phase I/II Trial of Concurrent RAD001 (Everolimus) with Temozolomide/Radiation Followed By Adjuvant RAD001/Temozolomide in Newly Diagnosed Glioblastoma"

Study Chair: Prakash Chinnaiyan, MD; 813-745-3425; Prakash.Chinnaiyan@moffitt.org

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RTOG 0913 was amended as follows:

Global: Web links to the RTOG web site were updated along with related text.

Cover Page: Email addresses were updated for Dr. Rojiani and Dr. Wang.

Section 3.1.2: The last bullet was corrected to remove the reference to the Phase I portion of the trial.

Section 3.1.12: "INR and PTT" was corrected to "PT/INR". Corresponding changes were made to **the Eligibility Checklist** and **Appendix II**.

Section 5.3.1: The text was updated per current process.

Section 7.4.9: The section was updated to reflect current drug supply.
(**NOTE**: This update was intended for inclusion in the 4/1/11 update of this protocol; it was included in the tracked protocol version and summary of changes that were posted on the RTOG web site but was inadvertently not transferred to the final posted protocol.)

Section 7.4.9: The text was updated per current process.

Section 7.7: The last bullet was added to provide details for pseudoprogression.

Section 7.8.2.1: In the third paragraph, it was clarified that testing is required if a patient develops non-specific respiratory signs and symptoms.

Section 10.2.5, Section 10.6, and Appendix VI: The street address was updated for the RTOG Biospecimen Resource.

Section 11.2: The trial was updated to utilize the criteria recently proposed by the Response Assessment in Neuro- Oncology (RANO) working group. The RANO Criteria updates its established predecessor, the modified Macdonald Criteria. References were renumbered accordingly.

Appendix I (Informed Consent):

- **"Will my medical information be kept private?**": The last paragraph was added to comply with FDA requirement for new element of consent as found in 21 CFR 50.25(c).
- **"Where can I get more information?":** The NCI TTY number is no longer in service and has been removed.

Appendix II: Collection of plasma for banking was deleted after therapy completion because it was included in error.

SUMMARY OF CHANGES
Update: April 1, 2011
(Broadcast April 1, 2011)

RTOG 0913, "Phase I/II Trial of Concurrent RAD001 (Everolimus) with Temozolomide/Radiation Followed By Adjuvant RAD001/Temozolomide in Newly Diagnosed Glioblastoma"

Study Chair: Prakash Chinnaiyan, MD; 813-745-3425; Prakash.Chinnaiyan@moffitt.org

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RTOG 0913 was updated as follows:

Section 7.4.9: The section was updated to reflect current drug supply.

SUMMARY OF CHANGES
Update: October 28, 2010
(Broadcast October 28, 2010)

RTOG 0913, "Phase I/II Trial of Concurrent RAD001 (Everolimus) with Temozolomide/Radiation Followed By Adjuvant RAD001/Temozolomide in Newly Diagnosed Glioblastoma"

Study Chair: Prakash Chinnaiyan, MD; 813-745-3425; Prakash.Chinnaiyan@moffitt.org

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RTOG 0913 was updated as follows:

Global: The protocol was reformatted to current RTOG standard.