

North Central Cancer Treatment Group

N057K: Phase I/II Evaluation of Everolimus (RAD001), Radiation and Temozolomide (TMZ)
Followed by Adjuvant Temozolomide and Everolimus in Newly Diagnosed Glioblastoma

Addendum 1– October 17, 2008

Summary

- Entire protocol revised to change from Mayo Clinic Jacksonville (MCJ) to currently accepted Mayo Clinic Florida (MCF)
- New Phase I eligibility criteria has been added to Section 3.23.
- Section 14.0 and Section 17.0 have been revised for clarification.
- Section 15.0 and Consent Form revisions due to review of Temozolomide Investigator Brochure, dated December 18, 2007.
- Clarification has been made in Section 16.61 with regard to patient pre-registration accrual.
- Appendix VI has been separated into 3 separate documents that are now Appendix VI though Appendix VIII.
- Administrative/Editorial Corrections.

A replacement protocol is provided. Please replace the current copy with the one attached. Please keep this addendum with your protocol.

Title page Revised NCI version date and addition of Addendum 1

Protocol Resource Page

Page 2: NCCTG Member Nurse has been revised as follows:

~~Beverly L. Kowbel~~ **Wanda DeKrey**

NCCTG Member Nurse

Phone: ~~(306)766-2684~~ **(701)780-6520**

E-mail: ~~bev.kowbel@saskeancer.ca~~ wdekrey@altru.org

Title change has occurred for the 'Protocol document, consent form, regulatory issues' contacts.

Jacqueline Lafky's fax number has been revised.

Index

Page 3: The title for Appendix 1A has been revised to change Mayo Clinic Jacksonville (MCJ) to Mayo Clinic Florida (MCF). The entire protocol has been adjusted due to this change.

Appendix VI has been separated into three documents, now encompassing Appendix VI, VII, and VIII. The remainder of this section has been renumbered and the protocol references have been adjusted to this new numbering. Changes are as follows:

Appendix VI **FDG-PET and FDG-PET/CT Imaging parameters Manual (Phase I – MCR and MCF only)** and ~~MR imaging pulse sequence parameters~~

Appendix VII **FLT-PET/CT Imaging parameters (Phase II – MCR only)**

Appendix VIII **MRI pulse-sequence parameters**

Section 2.0**Goals**

Page 13: In Section 2.224, the second sentence has been revised for clarification as follows:
For ~~those~~ **MCR** patients in which both types of tissue are available.

Section 3.0**Patient Eligibility (PHASE I and II)**

Page 13: New eligibility criteria for Phase I has been added (Section 3.23) as follows and the remainder of the section has been renumbered accordingly:

3.23 (For Phase I patients only) Measurable disease $\geq 1\text{cm}^3$.

Page 14: Section 3.29a has been revised for clarification as follows:

3.29a Willingness to undergo 2 mandatory research PET or PET/CT scans.
(Sections 4.2 and 6.36)

PHASE I: All MCR and ~~MCJ~~ **MCF** patients.

PHASE II: MCR patients ~~only~~ **with measurable disease of $\geq 1\text{cm}^3$**

The first bullet point in Section 3.29b has been revised with current section references and has had text added for clarification, as follows:

Two mandatory research blood draws (Sections 6.33, 14.114, ~~14.124~~)

PHASE I: All MCR and ~~MCJ~~ **MCF** patients

PHASE II: MCR patients only **who are at MTD and undergo FLT PET**

Section 4.0**Test Schedule**

Page 16: In the first column of the test schedule table (Test and Procedures), Row 17, 18, and 19 have been revised for clarification as follows:

Mandatory Research blood draw, PHASE I – MCR and ~~MCJ~~ **MCF**. PHASE II – MCR only (see Section 14.02)

Optional Baseline Research blood draw, **all patients (see Section 14.0)**

Mandatory Research tissue collection, **all patients (see Section 17.3)**

The following has been added as Row 20 of the Test Schedule. The X¹⁵ has been placed in the “≤14 days prior to registration” column. Row 20 now reads:

Optional Research frozen tissue collection, MCR patients only (See Section 17.4)

Page 17: The first sentence in Footnote 9 has been revised for clarification as follows:
 PHASE II - MCR ONLY: The FLT PET/CT scans will be done only for those patients at the MTD **who have measurable disease of $\geq 1\text{cm}^3$.**

Footnote 11 has been revised for clarification as follows:
 Mandatory research blood: must be obtained 24 ± 2 hours after 1st dose of everolimus (Cycle 1, day 2) and must be drawn again just before 2nd dose of everolimus (Cycle 1, day 8, ~~and~~ **must** be done...

Footnote 14 has been revised for clarification and consistency as follows:
Tissue specimens must be shipped ≤ 30 days following registration. Submit within 30 days of registration.—See Section 17.3.

New Footnote 15 has been added as follows:
When requested by study chair and/or study pathologist. See Section 17.4

Section 6.0 **Registration Procedures**

Page 19: The title for this section has been revised for clarification as follows:
 Registration Procedures (**Applies to Phase I and II unless otherwise specified.**)

Page 20: The following has been added to Section 6.2 for clarification:
 Pre-Registration (Step 1) (**Applies to Phase I and II unless otherwise specified.**)
 6.21 (**Phase I only**) To pre-register a patient, call....

(Phase II only) To pre-register a patient, access the NCCTG web page at <https://ncctg.mayo.edu/training> and enter the remote registration/randomization application. The remote registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the NCCTG Registration Office at (507)-284-4130 between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for remote registration are available on the NCCTG web page and detail the process for completing and confirming patient pre-registration. Users should refer to the section titled “Pre-Registration Components” for details on how to pre-register a patient to a study. At the time of pre-registration the patient will receive an NCCTG patient identification number. This number is to be used when submitting tissue or blood samples (See Section 17.0). Patient pre-registration via the remote system can be confirmed in any of the following ways:

- **Contact the NCCTG Registration Office (507) 284-4130. If the**

patient was pre-registered, the Registration Office staff can access the information from the centralized database and confirm the pre-registration.

- **Refer to “Instructions for Remote Registration” in section “Finding/Displaying Information about A Registered Subject.”**

Because of large amount of added text, repagination from this point forward has occurred.

Section 6.23 has an editorial correction for the reference. The correct reference is Section 17.2.

Section 6.3 has added text for clarification as follows:

Registration (Step 2) (Applies to Phase I and II unless otherwise specified.)

Page 21:

Section 6.32 has added text for clarification as follows:

6.32 (Phase I only) To register a patient call...

(Phase II only) To register a patient, access the NCCTG web page at <https://ncctg.mayo.edu/training> and enter the remote registration/randomization application. The remote registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the NCCTG Registration Office at (507)-284-4130 between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for remote registration are available on the NCCTG web page and detail the process for completing and confirming patient registration. Users should refer to the section titled “Pre-Registration Components” for details on how to register a pre-registered patient to a study. Prior to initiation of protocol treatment, this process must be completed in its entirety and a NCCTG subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the remote system can be confirmed in any of the following ways:

- **Contact the NCCTG Registration Office (507)-284-4130. If the patient was fully registered, the Registration Office staff can access the information from the centralized database and confirm the registration.**
- **Refer to “Instructions for Remote Registration” in section “Finding/Displaying Information about A Registered Subject.”**

Section 6.33 has been revised for clarification as follows:

The Registration Office will automatically register patients separately to the mandatory **blood (Phase I – MCR and MCF only, Phase II - MCR only; see Section 3.29a and 14.2) and mandatory tissue (all patients, see Sections 3.29a and 17.3)** translational component of this study (see Sections 3.29a, 14.111, 14.121, and 17.3).

Section 6.34 has been revised for clarification as follows:

The Registration Office will register patients separately to the optional translational research component of this study (see Sections 14.112 and 14.312). The following will be recorded.

- Patient has/has not given permission to give ~~blood~~ **tissue** samples for the optional research testing. (*Applies to Phase I & II, MCR patients only - previously collected frozen, surgical tissue*)

In Section 6.36, the first two bullets have been revised for clarification as follows:

- 6.36 At the time of registration/randomization, the following will also be recorded:
- Patient has/has not given permission to **collect and keep** blood sample(s) for use in future research to learn about, prevent, or treat cancer.
 - Patient has/has not given permission to **collect and keep** blood sample(s) for use in future research to learn about, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Section 7.0

Page 23:

Protocol Treatment

Text in the third paragraph of Section 7.114 has been revised for clarification as follows:

Failure to administer >75% of everolimus/temozolomide **per cycle** or interruption of radiation for more than 5 days due to adverse events.

New Section 7.117 has been added as follows for clarification:

7.117 If a patient fails to complete cycle 1 for reasons other than toxicity, the patient will be regarded as unevaluable for determination of the MTD and will be replaced by an additional patient that will be treated at the current dose level; however, all toxicity information will be utilized in the analysis. For these instances, a specific notation will be made for review by the Cancer Center Clinical Research Administrative Subcommittee (CCCRAS).

Section 14.0

Pages 44-45:

Body Fluid Biospecimens

Sections 14.1 and 14.2 have been replaced/revised for clarity. These sections are now 14.1 through 14.3 (now pages 44-47), with the remainder of the section renumbered.

Page 47: Newly numbered Section 14.4 has been revised as follows for clarification:

14.411 Everolimus blood levels will be determined by LC-MSMS method following liquid extraction by Clinical Reference Laboratory (CRL; Lenexa, KS).). **Everolimus blood levels will be analyzed for all Phase I patients (Mayo Clinic Rochester [MCR] and Mayo Clinic Florida [MCF]) and for only MCR Phase II patients who are at MTD and undergo FLT PET. Two mL of whole blood will be collected approximately 24 hours after the 1st dose of everolimus (cycle 1, day 2) and before 2nd dose of everolimus (cycle 1, day 8).** Everolimus blood levels...

14.412 As part of ongoing NCCTG research, we will also collect plasma and buffy coat **from 10 mL whole blood prior to first dose of everolimus treatment (baseline)** for future studies...

Section 15.0 Drug Information

Page 50: Section 15.19d3 has been revised due to incorrect reference. The last sentence has been corrected as follows:

See section ~~9-2~~**9.6**

Section 15.19d7 has been revised due to incorrect reference. The last sentence is as follows:

See section ~~9-5~~**9.3**

In Section 15.2, the following text has been added at the beginning of the section for direction on where the investigator brochure can be found, as follows:

- **Investigator brochure available on NCCTG web site**

Page 51-53: An error in section numbering has been corrected. Starting after Section 15.26 (Drug interactions) and through the end of Section 15.0 numbering has been adjusted accordingly.

Page 51: The following text has been removed from Section 15.29b for clarity, as this section states that the investigator brochure is the reference to use, both at the beginning of Section 15.2 and the end of Section 15.29b:

~~15.27 Known potential adverse events: (Please see the temozolomide package insert for a comprehensive list of adverse events)~~

Page 52: Due to review of Temozolomide Investigator Brochure, dated December 18, 2007, the following paragraph has been added at the end of Section 15.27:

Due to review of temozolomide investigator brochure, dated December 18, 2007, the following potential adverse events have been added: fever, weakness, dizziness, anxiety, depression, memory loss, tingling or burning in arms or legs, convulsions, ataxia, paralysis, pain in abdomen, muscle or joint pain, edema, pruritus, severe skin reaction, allergic reaction, re-activation of hepatitis infection, dyspnea, cough, increased urinary urgency.

Section 16.0 **Statistical Considerations and Methodologies**

Page 59:

The first sentence in Section 16.51 has been modified for correction. Changes are as follows:

The study chair and study statistician will assess the adverse events profiles for each cohort of ~~three~~ **six** and make decisions...

In Section 16.61 the following text was added as a second sentence for clarification:

We anticipate pre-registering 129 patients to register/randomize a total of 117 patients necessary for the study design and allotted over accrual.

Section 17.0 **Pathology Considerations/Tissue Biospecimens**

Page 61:

In the first column, the second row has been revised for clarity as follows:

Formalin-fixed paraffin embedded (FFPE) tissue blocks/ with corresponding H&E (OR unstained slides with corresponding H&E)

In the first column, the last row of the table in 17.1 has been revised for clarification as follows:

Frozen tissue, if available (**MCR patients only**)

Page 63:

Section 17.31 has been separated into two sections, with the remainder of this section renumbered. The first sentence is the only text that remains in Section 17.31, with the following added text at the end of the paragraph for clarification:

A corresponding H&E slide for the block submitted must be provided to permit quality assessment (QA) of the tissue block. Once the QA is completed, all slides will be returned, unless specified otherwise in Section 17.29b.

Newly numbered Section 17.32 and Section 17.33 have been revised as follows for clarification:

17.31 The FFPE tissue block is preferred; however, if an institution is unable to provide a tissue block, ~~submit cut 14 (2 slides for H&E + 12 slides for correlative studies~~ **five micron sections and mount sections on charged glass slides** ~~charged and unstained glass slides cut at 5 microns~~. Sections should be cut with a new blade, using “fresh water” in the water bath to prevent carry over and/or contamination from previous cases for analysis of MGMT methylation status. Label the slides with NCCTG patient ID number, accession number, and order of sections. **(i.e., 1-14). H&E stain every 10th slide that is cut, starting with the first cut slide (i.e., slides labeled 1 and 11). These slides will be** ~~The first and last slide will be H&E stained and~~ reviewed centrally under the research base’s protocol for assessing tissue quality. The remaining slides will be processed as described in 17.5. For samples containing less than 7 square millimeters of tumor tissue, multiple sections should be mounted onto each slide to ensure that the

appropriate amount of tumor tissue is available. Ideally, each slide must have a minimum of 75% tumor tissue on the slide to be deemed adequate for study. Do not bake or place covers slips on the slides.

17.33 The following materials below are mandatory (unless indicated otherwise) and required for shipment:

- FFPE tissue block/~~slides~~ **with Corresponding H&E Slide (OR 12 Unstained Slides with 2 Corresponding H&E Slides)**
- NCCTG Tissue Specimen Submission Form
- Surgical Pathology Report
- Operative Report (optional)

Pages 64/65: The following text has been added to the first sentence only in Sections 17.53, 17.54, and 17.55 for clarification:

17.53 Gene expression profiling in patients with frozen tissue **will be performed in Dr. Sarkaria's laboratory.**

17.54 **Dr. Sarkaria's laboratory is** ~~We are~~ in the process of developing a custom gene expression array for use in paraffin...

17.55 At the completion of the study, any remaining/unused **frozen tissue will be returned to the Brain Spore Tissue Bank. Any remaining/unused paraffin-embedded** material will be stored **at the NCCTG Operations Office** for future research depending on the patient consent permission (see Section 6.36)...

Section 18.0 **Records and Data Collection Procedures**

Pages 66/67: Footnote 8 has been added with regards to the NCCTG Blood Specimen Submission form, and annotated in the '≤14 days after registration' column:

- 8. To be submitted within 7 days of specimen collection.**

Appendix 1A **Consent Form**

Page 3 of 11: Text has been revised for clarification in the "Calendar of Events" table. For Cycle 1, under Weeks 1 & 2, the following have been revised:

- PET scan of brain (**all Phase I patients and Phase II MCR patients with measurable disease**)

Page 6 of 11: Due to review of Temozolomide Investigator Brochure, dated December 18, 2007, the following revisions have occurred:

Likely risks of temozolomide (events occurring ~~greater~~ less than 20% of the time)

- Nausea (feeling sick to your stomach)
- Vomiting (throwing up)
- Decreased appetite
- Headache
- Constipation (**difficulty passing stools**)
- Fatigue
- Fever

Less Likely risks of temozolomide (events occurring ~~greater~~ less than or equal to 20% of the time)

- Fall in the white blood cell counts that leads to a higher risk of infection
- Fall in the platelet count leading to a higher risk of bleeding
- Fall in the red blood cell count leading to anemia (feeling tired and low energy)
- Diarrhea (**loose stools**)
- Sores in your mouth
- Rash
- Change in liver function tests (tests that show how the liver is working)
- Lack of interest in or ability to carry out daily activities
- Swelling in your arms and legs
- Memory loss
- Itchiness
- Increased need to urinate
- Weakness
- Dizziness
- Tingling/burning in your arms and legs
- Anxiety
- Depression
- Stomach/abdominal pain
- Muscle or joint pain
- Shortness of breath
- Cough

Rare but Serious **risks of temozolomide** (events occurring less than 2-3% of the time)

- Convulsions
- Weakness on one side of your body
- Abnormal coordination
- Paralysis (**inability to move arm or leg**)
- Myelodysplastic syndrome (problem with the bone marrow that causes decreased production of red cells, ~~white~~ **white** cells, or platelets that can sometimes turn into blood cancer)
- Severe skin reaction
- Allergic reaction
- **Re-activation of hepatitis infection (if you have previously been diagnosed with hepatitis, which is a type of infection in the liver)**

Page 8 of 11: In the question “What are the costs of taking part in this research study?”, the last sentence of the second paragraph has been removed, as it is clarified in forthcoming paragraphs of this question. The following sentence was removed:

~~You and/or your health plan may also have to pay for other drugs or treatment that are given to help control side effects as well as the cost of tests or exams to evaluate possible side effects.~~

Text has been revised in the fourth paragraph of the question “What are the costs of taking part in this research study?” for clarification as follows:

The drug temozolomide can be bought with a prescription. You and/or your health plan/**insurance company** will need to pay for ~~all costs associated with this treatment~~ **the drug temozolomide.**

Page 9 of 11: In the Section “Biological Samples for Research” text has been added to the first paragraph for clarification as follows:

This study ~~also~~ has **mandatory** laboratory tests that will be performed to study small samples of your blood and/or tissue. **A blood sample will be done by drawing some blood from a vein. The blood will be taken 1 day after your first dose of everolimus and right before your second dose of everolimus. You are going to have or may already have had a biopsy (or surgery) to see if you have cancer. Your doctor will remove some body tissue to do some tests. No additional biopsies will be done to get this tissue.**

In the third paragraph of the section “Biological Samples for Research” the word **research** has been added to the first sentence for clarity.

A new fourth paragraph has been added in the section “Biological Samples for Research” for clarification as follows:

Also as part of this study we would like to collect additional blood (about 1 tablespoon) to be kept for use in future research. If you consent to this, the blood will be drawn before you receive your first dose of everolimus.

Before the signature line in the section “Biological Samples for Research”, the following text has been revised:

(Insert the following statements for MCR only)

With your permission, we would also like to retrieve your frozen tumor tissue, if available from a previous surgery or biopsy, to use for research testing. ~~You can take part in the treatment portion of this study without taking part in these research laboratory tests.~~

The first set of signature lines in “Biological Samples for Research” has been removed because the blood samples are mandatory. An additional statement has been added before the signature line for clarification.

The first paragraph after the signature line in “Biological Samples for Research” has been revised for clarification. The words “some of” have been removed from the first sentence.

Page 10 of 11: The first two signature line under “Making Your Choice” have been reworded for clarity as follows:

1. ~~My~~ **I agree to provide** blood sample(s) to NCCTG which may be....
2. ~~My~~ **I agree to provide** blood sample(s) to NCCTG which may be....

Appendix 1B **Consent Form**

Page 6 of 11: Due to review of Temozolomide Investigator Brochure, dated December 18, 2007, the following revisions have occurred:

Likely risks of temozolomide (events occurring greater than 20% of the time)

- Nausea (feeling sick to your stomach)
- Vomiting (throwing up)
- Decreased appetite
- Headache
- Constipation (**difficulty passing stools**)
- Fatigue
- Fever

Less Likely **risks of temozolomide** (events occurring ~~greater~~ less than or equal to 20% of the time)

- Fall in the white blood cell counts that leads to a higher risk of infection
- Fall in the platelet count leading to a higher risk of bleeding
- Fall in the red blood cell count leading to anemia (feeling tired and low energy)
- Diarrhea (**loose stools**)
- Sores in your mouth
- Rash
- Change in liver function tests (tests that show how the liver is working)
- Lack of interest in or ability to carry out daily activities
- Swelling in your arms and legs
- Memory loss
- Itchiness
- Increased need to urinate
- Weakness
- Dizziness
- Tingling/burning in your arms and legs
- Anxiety
- Depression
- Stomach/abdominal pain
- Muscle or joint pain
- Shortness of breath
- Cough

Rare but Serious **risks of temozolomide** (events occurring less than 2-3% of the time)

- Convulsions
- Weakness on one side of your body
- Abnormal coordination
- Paralysis (**inability to move arm or leg**)
- Myelodysplastic syndrome (problem with the bone marrow that causes decreased production of red cells, ~~white~~ **white** cells, or platelets that can sometimes turn into blood cancer)
- Severe skin reaction
- Allergic reaction
- **Re-activation of hepatitis infection (if you have previously been diagnosed with hepatitis, which is a type of infection in the liver)**

Page 8 of 11: In the question “What are the costs of taking part in this research study?”, the last sentence of the second paragraph has been removed, as it is clarified in forthcoming paragraphs of this question. The following sentence was removed:

~~You and/or your health plan may also have to pay for other drugs or treatment that are given to help control side effects as well as the cost of tests or exams to evaluate possible side effects.~~

Text has been revised in the fourth paragraph of the question “What are the costs of taking part in this research study?” for clarification as follows:

The drug temozolomide can be bought with a prescription. You and/or your health plan/**insurance company** will need to pay for ~~all costs associated with this treatment~~ **the drug temozolomide.**

Page 9 of 11: In the Section “Biological Samples for Research” text has been added to the first paragraph for clarification as follows:

This study ~~also~~ has mandatory laboratory tests that will be performed to study small samples of your ~~blood and/or~~ tissue. **You are going to have or may already have had a biopsy (or surgery) to see if you have cancer. Your doctor will/did remove some body tissue to do tests. No additional biopsies will be done to get this tissue.**

In the Section “Biological Samples for Research” the second paragraph has been removed as follows because it does not apply to non MCR/MCF sites:

~~The following samples will be sent to laboratories associated with NCCTG and Novartis where the tests will be done:~~

- ~~• Blood tests for everolimus drug levels.~~

The third paragraph in the section “Biological Samples for Research”, the following text changes have occurred for clarity:

Also as part of this study we would like to collect additional blood (about 1 tablespoon) to be kept for use in future research. A blood sample will be done by drawing some blood from a vein. If you consent to this, the blood will be drawn before you receive your first dose of everolimus. You can take part in the treatment portion of this study without taking part in these research laboratory tests.

The blood signature line has been removed in the section “Biological Samples for Research” because it is being collected for storage only at this time and possible future testing. Permission for this blood sample is located under the section “Making your choice”.

The tissue signature line was removed because it is a mandatory sample which does not require a separate signature line.

The first sentence in the fourth paragraph in the section “Biological Samples for Research” has been revised for clarification as follows:

We would like to keep ~~some of~~ the blood **which is collected** and tissue...

Page 10 of 11: The first two signature line under “Making Your Choice” have been reworded for clarity as follows:

3. ~~My~~ **I agree to provide** blood sample(s) **to NCCTG which** may be....
4. ~~My~~ **I agree to provide** blood sample(s) **to NCCTG which** may be....

Pages 1/2 of 5: Revised formatting with additional shading and days added at end of.

Appendix XI **NCCTG Research Base Instructions for Biospecimen Processing in BAP Laboratory**

Page 1 of 1: Two new footnotes have been added below the summary table for clarification. Footnote 1 has been annotated in the first row, the second column (Volume...), and Footnote 2 has been annotated in the second row, the second column. The new footnotes are as follows:

¹**For Phase I, ALL MCR and MCF patients. For Phase II, only MCR patients who are at MTD and undergo FLT PET.**

²**All patients, both Phase I and Phase II.**

The last sentence in number 3 has been revised for clarification as follows:

Plasma and buffy coat samples will be stored **in BAP** at 80°C...