For **Protocol Amendment 7** to: RTOG 0837, Randomized, Phase II, Double-Blind, Placebo-Controlled Trial of Conventional Chemoradiation and Adjuvant Temozolomide Plus Cediranib Versus Conventional Chemoradiation and Adjuvant Temozolomide Plus Placebo in Patients With Newly Diagnosed Glioblastoma

NCI/Local Protocol #: RTOG 0837

NCI Protocol Version Date: November 13, 2014 (Broadcast December 15, 2014)

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cover pages</td>
<td>This amendment was added to the document history table. Contact information was updated for Dr. Aldape.</td>
</tr>
<tr>
<td>Global</td>
<td>Due to the transition to the National Clinical Trials Network (NCTN), &quot;Radiation Therapy Oncology Group&quot;, &quot;RTOG Headquarters&quot;, and &quot;RTOG&quot; were replaced with &quot;NRG Oncology&quot; or deleted, as appropriate, throughout the protocol. ACRIN was replaced with ECOG-ACRIN as appropriate throughout the protocol. In the footer, page numbering was updated to current NRG Oncology standard and a version date was added.</td>
</tr>
<tr>
<td>7.2.2.2</td>
<td>In the second paragraph, 6 months was corrected to 12 months for consistency with the rest of the protocol.</td>
</tr>
<tr>
<td>10.2.5</td>
<td>The address for Dr. Aldape was grayed out in light of his move (see cover page). No further tissue submissions are expected to be sent in conjunction with Step 1 registration, so the address was not updated in this section.</td>
</tr>
<tr>
<td>10.3.1</td>
<td>In the second sentence, the process for requesting a return was updated.</td>
</tr>
<tr>
<td>Appendix I (Sample Informed Consent)/Will my medical information be kept private?</td>
<td>&quot;RTOG Headquarters&quot; and &quot;The Radiation Therapy Oncology Group (RTOG)&quot; were replaced with &quot;NRG Oncology&quot; and &quot;The American College of Radiology Imaging Network (ACRIN)&quot; was replaced with &quot;ECOG-ACRIN Cancer Research Group.&quot;</td>
</tr>
<tr>
<td>Appendices VII, VIII, IX (Specimen Collection)</td>
<td>The information in these appendices were removed and replaced with reference to the NRG Oncology/RTOG wesbite.</td>
</tr>
</tbody>
</table>
For **Protocol** Update to: RTOG 0837, Randomized, Phase II, Double-Blind, Placebo-Controlled Trial of Conventional Chemoradiation and Adjuvant Temozolomide Plus Cediranib Versus Conventional Chemoradiation and Adjuvant Temozolomide Plus Placebo in Patients With Newly Diagnosed Glioblastoma

NCI/Local Protocol #: RTOG 0837

NCI Protocol Version Date: February 14, 2012
Update Date: May 1, 2014 (Broadcast May 1, 2014)

<table>
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<tr>
<th>Section</th>
<th>Change</th>
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<tbody>
<tr>
<td>Cover pages</td>
<td>This update was added to the document history table. Peixin Zhang has replaced Minhee Won as the Statistician.</td>
</tr>
<tr>
<td>Global</td>
<td>As required by CTEP, references to the “Adverse Event Reporting System (AdEERS)” have been changed to “CTEP Adverse Event Reporting System (CTEP-AERS)” throughout the protocol.</td>
</tr>
<tr>
<td>Informed Consent</td>
<td>No changes</td>
</tr>
</tbody>
</table>
SUMMARY OF CHANGES
Update: July 5, 2012
(Broadcast: July 5, 2012)

RTOG 0837, “Randomized, Phase II, Double-Blind, Placebo-Controlled Trial of Conventional Chemoradiation and Adjuvant Temozolomide Plus Cediranib Versus Conventional Chemoradiation and Adjuvant Temozolomide Plus Placebo in Patients With Newly Diagnosed Glioblastoma”

Study Chair: Tracy Batchelor, MD; 617-724-8770; tbatchelor@partners.org

RTOG 0837 was updated as follows:

Section 7.1: In the 1st paragraph, it was clarified that code breaks are permissible for patients eligible for another clinical trial or salvage treatment. For clarity, the last sentence was deleted and combined with the first sentence.

The post-treatment collection time point for serum, plasma, and urine was clarified to be after all chemotherapy completion. Changes were made to the following sections:
- Section 10.3.3: 1st bullet
- Section 10.4: Serum, plasma, and urine rows
- Appendix I (Sample Consent), Consent Form for Use of Tissue, Blood, and Urine: 3rd paragraph/2nd sentence and 4th paragraph/2nd sentence
- Appendix II (Study Parameters): Follow-Up column

Section 7.3.7.1: In the last sentence, the cross reference was corrected to Section 7.5.4.

Section 7.5.1: The Definition of Dose-Limiting Toxicity section was deleted because it was included in error as an inadvertent cut and paste from an earlier-phase study. Subsequent sections and cross references were appropriately renumbered.

Appendix II
- CBC w/ diff: The “≤ 7 d prior to treatment start” time point was corrected to “≤ 72 hrs” for consistency with instructions in Section 7.2.3.2
- UPC and Urine Dipstick or equivalent: All collection time points post-registration were removed and added to Urine Dipstick or equivalent. Per Section 7.5.5, dose modifications during treatment are based on urine dipstick or equivalent routine laboratory analysis and not UPC levels.
RTOG 0837, “Randomized, Phase II, Double-Blind, Placebo-Controlled Trial of Conventional Chemoradiation and Adjuvant Temozolomide Plus Cediranib Versus Conventional Chemoradiation and Adjuvant Temozolomide Plus Placebo in Patients With Newly Diagnosed Glioblastoma”

Study Chair: Tracy Batchelor, MD; 617-724-8770; tbatchelor@partners.org

In response to a request for amendment (RA) for cediranib from CTEP, RTOG 0837 was amended as follows:

Title Pages: The document history table was updated to include Amendment 6, Version Date February 14, 2012.

Section 7.3.6: CAEPR Version 2.10 (January 13, 2011) was replaced by CAEPR Version 2.11 (November 10, 2011).

There is no new or modified risk information for cediranib. However, as part of the new NCI adverse events reporting guidelines (effective July 26, 2011), the Comprehensive Adverse Events and Potential Risks (CAEPR) list for cediranib, which previously included the Agent Specific Adverse Events List (ASAEL) (version 2.10), now includes the Specific Protocol Exceptions to Expedited Reporting (SPEER) list (version 2.11). The SPEER was developed to facilitate expedited adverse event (AE) reporting to the Food and Drug Administration (FDA) in compliance with 21 CFR 312. AEs listed on the SPEER should be reported expeditiously by investigators to the NCI only if they exceed the grade of the event listed in parentheses after the event. CTEP expects that including the SPEER in protocols will reduce the clinical sites’ expedited reporting burden by decreasing the number of reports needed for serious AEs that are common and expected for the agent(s) used in a trial.

The risk profile for cediranib in the informed consent (Appendix II) remains unchanged and consistent with CAEPR Version 2.11.

Other Changes
Based upon the analysis of the first 85 patients entered, the rate of patients not being randomized due to disease progression (2), patient refusal (10), physician preference (5), insufficient tissue (3), or other reasons (17) was very much underestimated (44% vs. originally projected 12%), while the rate of ineligibility determined post randomization remained the same. Therefore, a higher nonrandomized rate of 44% was adopted to recalculate the targeted sample size for the study. With a rate a total of 47% patients who are either not randomized (44%) or found ineligible post randomization (3%), 283 patients would have to be entered in order to have 150 eligible and randomized patients. The total sample size therefore amended from 177 patients pre randomization to 283. Related changes were made to the following sections:

- **Schema Page, Required Sample Size**
- **Section 13.2.1**: The 4th-to-last sentence was revised and the last 3 sentences were added.
- **Section 13.6, Projected Distribution of Gender and Minorities Table**
- **Appendix I (sample consent), How many people will take part in the study?**

Eligibility Checklist, Step 2/question 13: The first sub-question response was corrected to “N.”

Section 3.1.2: A web link for tissue submission timelines was added as a timing aid to sites.

Section 3.1.13: The criterion was corrected to indicate that systolic AND diastolic pressure are required. Corresponding changes were made to the Eligibility Checklist.
Section 5.2, 2nd-to-last bullet: The time period for obtaining MGMT test results was added as a timing aid to sites.

Section 7.2.2.2: The 1st sentence was revised and the 2nd and 3rd sentences were added to explain the intent that cediranib/placebo can be extended for up to 49 days if radiation is delayed and to provide guidelines for this administration.

Section 7.5.5, table
- For mild to moderate hypertension, the last 3 bullets were corrected/modified for clarity as follows:
  - Bullet 7: 15 mg was added
  - Bullet 8 (original): Deleted
  - Bullet 8 (final; formerly Bullet 9): “2 dose reductions” was corrected to “1 dose reduction”
- For severe hypertension, the last 4 bullets were corrected/modified for clarity as follows:
  - Bullet 5: 15 mg was added
  - Bullets 6 and 7 (original): Deleted
  - Bullet 6 (final; formerly Bullet 8): “2 dose reductions” was corrected to “1 dose reduction”

Section 10.2.5: As a timing aid to sites, “to start protocol treatment more than 3 weeks but within 6 weeks after surgery” and a web link for tissue submission timelines were added.

Section 11.3: The following sentence was bolded for emphasis: “The primary measure of response will be by Macdonald criteria (Macdonald 1990).”

Appendix I (sample consent)
- Will my medical information be kept private?”
  - The last bullet was added because it was inadvertently omitted; ACRIN will collect images for central review for all patients.
  - 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
- Blood and Tissue Consent, last 4 pages: The last 4 pages were deleted because they refer to the ACRIN 6689 sub-study and were inadvertently not deleted in Amendment 5, which removed ACRIN 6689.

Appendix II (study parameter table): Time points were added for assessment of vital signs during treatment and of blood pressure pre-treatment and during treatment. This information was inadvertently omitted. The * footnote was moved from the last page of the table to the second-to-last page of the table to be closer to the text to which it refers.
SUMMARY OF CHANGES
Amendment 5, Version Date: October 18, 2011
(Broadcast October 26, 2011)

RTOG 0837, “Randomized, Phase II, Double-Blind, Placebo-Controlled Trial of Conventional Chemoradiation and Adjuvant Temozolomide Plus Cediranib Versus Conventional Chemoradiation and Adjuvant Temozolomide Plus Placebo in Patients With Newly Diagnosed Glioblastoma”

Study Chair: Tracy Batchelor, MD; 617-724-8770; tbatchelor@partners.org

RTOG 0837 was amended as follows:

Title page: The statement “not responsible for patient care” was added for Dr. Hossain. A second title page was added to better accommodate the Document History Table.

Eligibility Checklist, Eligibility Checklist, Step 1/question 6 (verifying physician) and Step 2/question 4 (verifying physician): “Investigator’s” was corrected from “sites” and Section 7.3.9.1 was corrected from 7.3.9.2.

Section 3.1.4 was amended to indicate that the Mini Mental Status Exam (MMSE) is no longer required as part of the neurological examination. The MMSE is not a validated metric to track mental status in brain tumor patients, is heavily dependent on preserved language function, and there can be interobserver variability in administering this assessment. This change also was made in Appendix II.

Section 3.1.13: Systolic blood pressure was corrected to ≤140, for consistency with other sections of the protocol. This change also was made in the Eligibility Checklist.

Section 3.2.6.12: The statement, “note, however, that laboratory tests for liver function and coagulation parameters are not required for entry into this protocol,” was deleted because it is inaccurate. This change also was made in the Eligibility Checklist.

Section 6.0: The last statement was added to clarify the beginning of protocol treatment.

Section 5.1.1.1: The 2nd sentence was added to instruct sites that regulatory documents may be e-mailed (vs. faxed) to CTSU.

Section 7.2.2.5: The absolute neutrophil count and the platelet count were amended to correct error and inconsistency in the protocol. The intent is to resume treatment with temozolomide (with concomitant radiation) once the platelet count increases to ≥ 75,000 and the absolute neutrophil count increases to ≥ 1,000 (consistent with thresholds used RTOG 0825), and the protocol has been amended to reflect this.

Section 7.5.4: In the 2nd row under “Observation,” item 2 was deleted. This is a correction, as it was not intended to hold cediranib for non-hematological AEs (attributed to cediranib) < grade 3 or for hematological AEs (attributed to cediranib) < grade 4.

Section 10.2.5: The phone and fax numbers for Dr. Aldape were updated.

Section 10.3.3: In the 3rd bulleted item, the storage temperature was amended from 20°C to 80°C to be consistent with current RTOG Biospecimen Resource standard text.

Section 10.3.5 and Appendices VII, VIII, and IX: The street address was updated for the RTOG Biospecimen Resource.
Section 10.4: In the 1st row and last column under “Strongly Encouraged for Tissue Banking and Translational Research,” “overnight mail” was corrected to “overnight carrier.”

Section 11.3: The entire section was updated to reflect scoring by Macdonald criteria.

Appendix I (sample consent)
- Under “Before you begin the study,” ECHO/MUGA was added as the last bullet for consistency with Section 4.1 of the protocol.
- Under “Risks and side effects related to the radiation…likely,” “difficulty with concentration” was added for consistency with radiation risk profiles in more recent RTOG CNS protocol sample consents.
- Under “What are my rights if I take part in this study?,” the 3rd paragraph was amended to reflect that the study is monitored by the Data Monitoring Committee (vs. the Data Safety Monitoring Board).
- Under “About Using Tissue for Research,” the title of and web address for NCI’s information sheet was updated.

Appendix II
- The first column was titled “Assessments” to update the protocol to RTOG standard text.
- Under “Assessments,” “Urinalysis” was amended to “UPC” to be consistent with Section 3.1.11.3.
- Under “During Cediranib/Placebo + TMZ (Wks 11+),” instructions were added for the CD4 count.

The ACRIN 6689 sub-study was deleted from the protocol, as follows:

Title page: Reference to the ACRIN 6689 collaborative trial has been deleted. The listing of ACRIN investigators has been deleted.

Index: Reference to ACRIN 6689 and all associated Appendices (X through XII) has been deleted.

ACRIN 6689 Schema: Has been deleted, as well as reference to the ACRIN Schema on the prior page below the RTOG Schema.

Eligibility Checklist—Step 1: Reference to certification of MR and PET scanners for ACRIN 6689 advanced-imaging sites has been deleted.

Eligibility Checklist—Step 2: Item #41 has been deleted (page 3 of 5) and Item #21 (page 5 of 5) has been deleted; subsequent numbering has been updated.

Section 1.9: Has been deleted.

Section 2.3: Has been deleted.

Section 3.0: Contents describing ACRIN 6689 that appeared below the NOTE has been deleted.

Section 3.2.15: Has been deleted.

Section 5.1.4: Has been deleted.

Section 6.11: Has been deleted.

Section 6.12: Has been deleted.

Section 7.9: The NOTE related to ACRIN 6689 has been deleted.
Section 7.10: Has been deleted.

Section 10.8: Has been deleted.

Section 11.5: The NOTE related to ACRIN 6689 has been deleted.

Section 11.6: Has been deleted.

Section 12.3: Has been revised to reflect the deletion of the ACRIN 6689 component and to reduce redundant language.

Section 12.4: Has been deleted.

Section 13.1: The NOTE related to ACRIN 6689 has been deleted.

Section 13.7: Has been deleted.

REFERENCES: Citations related to the ACRIN 6689 content has been deleted.

The following changes were made to the sample consents (Appendix I and Appendix I Continued):

- Under “Will my medical information be kept private?”, in the 2nd paragraph, 4th bullet, reference to the ACRIN 6689 advanced imaging component has been deleted.
- Appendix I Continued, which provided the combined RTOG 0837/ACRIN 6689 informed consent form template, has been deleted.

Appendix II: Reference to the ACRIN 6689 advanced imaging component has been deleted from the main study parameter table, and the entire study table for the ACRIN 6689 component.

Appendix X: Has been deleted.

Appendix XI: Has been deleted.

Appendix XII: Has been deleted.
In response to a request for a rapid protocol amendment from CTEP, RTOG 0837/ACRIN 6689 was amended to reflect changes to the Comprehensive Adverse Events and Potential Risks List (CAEPR) for cediranib. Changes were made to the following sections:

**Section 7.3.6**
CAEPR Version 2.9 (February 19, 2010) was replaced by CAEPR Version 2.10 (January 13, 2011).

- **Added New Risk:**
  - Also Reported on Cediranib Trials But With the Relationship to Cediranib Still Undetermined: Bruising; CPK increased; Cardiac arrest; Cholesterol high; Cognitive disturbance; Colonic perforation; Depressed level of consciousness; Dysphasia; Ear and labyrinth disorders - Other (viral labyrinthitis); Fracture; Gallbladder obstruction; Gastric ulcer; Gastrointestinal disorders - Other (abdominal abscess); Heart failure; Hepatobiliary disorders - Other ( bile duct obstruction); Hepatobiliary disorders - Other (jaundice cholestatic); Hypercalcemia; Ileal perforation; Injury, poisoning and procedural complications - Other (tracheostomy malfunction); Investigations – Other (elevated LDH); Lipase increased; Memory impairment; Nervous system disorders - Other (spinal cord compression); Pain; Rectal pain; Renal and urinary disorders - Other (nephrotic syndrome); Skin ulceration; Suicide attempt; Urinary retention

- **Increase in Risk Attribution:**
  - Changed to Less Likely from Reported But Undetermined: Hypophosphatemia; Seizure; Thromboembolic event

- **Decrease in Risk Attribution:**
  - Changed to Reported But Undetermined from Less Likely: Neutrophil count decreased; Platelet count decreased

- **Provided Further Clarification:**
  - Allergic reaction is now reported as Anaphylaxis.
  - Gum infection, Lung infection, Sepsis, Skin infection, Soft tissue infection, and Urinary tract infection are now all reported as Infection, and the following footnote added: “Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC."

- **Modified Agent Specific Adverse Events List (ASAEL) Reporting Requirements:**
  - **Added:** Alanine aminotransferase increased; Aspartate aminotransferase increased; Hypophosphatemia; Thromboembolic event

- **Deleted:**
Also Reported on Cediranib Trials But With the Relationship to Cediranib Still Undetermined: Endocrine disorders - Other (thyrotoxicosis); Hematoma; Investigations – Other (decreased thyroxine); Ischemia cerebrovascular; Leukocytosis; Vertigo

Appendix I/Sample Consent, Risks associated with cediranib
The risk profile was updated to reflect the revised CAEPR. Specific changes are as follows:

- **Increase in Risk Attribution:**
  - Changed to Less Likely from Reported But Undetermined: Convulsion or seizure; Decreased blood level of phosphate; Formation of a blood clot that plugs the blood vessel, blood clots may break loose and travel to another place, such as the lung

- **Decrease in Risk Attribution:**
  - Changed to Reported But Undetermined from Less Likely (i.e., Removed From the Risk Profile): Decreased number of a type of blood cell that helps to clot blood (platelet); Decreased number of a type of white blood cell (neutrophil/granulocyte)

*Administrative/Editorial Changes*

**Global:** All weblinks and related descriptions to sub-pages of the RTOG website were updated.

**Cover Pages:** The email address for Meihua Wang was updated. A document history table was added per current RTOG standard.

**Eligibility Checklist, Step 2, page 5 of 5, question 22:** This question was added for logistical purposes.

**Sections 3.1.15 and 3.2.10:** It was clarified that these criteria need to occur prior to Step 1 registration. Corresponding changes were made to the Eligibility Checklist and Appendix II.

**Section 3.1.6:** “1st step registration” was changed to “step 1 registration” for consistency with terminology throughout this section.

**Sections 3.1.4, 3.1.5, 3.1.7, 3.1.8, 3.1.10, 3.1.11.1, 3.1.11.2, 3.1.11.3, 3.1.12.1, 3.1.12.2, 3.1.13, 3.1.14, 3.1.17, 3.2.6.3, 3.2.6.4, 3.2.6.9, 3.2.6.10, and 3.2.6.11:** It was clarified that these criteria need to occur prior to Step 2 registration. Corresponding changes were made to the Eligibility Checklist and Appendix II.

**Section 7.3.9:** The last line of the 2nd paragraph was revised per current shipping policy, in accordance with the newly added Eligibility Checklist question 22 (described above).

**Section 7.5.4:** In the 3rd row, 10 mg was corrected to 15 mg, for consistency with Section 7.5.3.

**Section 10.2.6:** The section was rewritten to reflect that Dr. Aldape will inform the site when his review is complete, rather than informing the site that the patient can register.

**Section 10.3.1:** The 2nd sentence was clarified to indicate that the Biospecimen Resource will bank and/or punch tissue for consenting patients.

**Section 10.4:** Per current RTOG standard: In the first column, the description of serum, plasma, DNA, and urine was updated; in the second column for DNA, a clarifying note was added to indicate that collection may occur at any point if the pretreatment time point is missed.
Section 10.4 and Appendix VIII: The number of vials for serum and plasma was changed from "up to 10 to "5 to 10" and the number of vials for whole blood was changed from "up to 5" to "3 to 5" per current RTOG process.

Appendix I/Sample Consent
- During the Study/"If you are in group 1..." and "If you are in group 2...:" In the 3rd paragraph, 2nd sentence, "5 days per week" was corrected to "days 1 through 5"
- Risks associated with cediranib: In the first bullet under Rare but Serious, "decreased" was corrected to "decrease."
- About Using Tissue for Research: In the last 2 lines of the 2nd paragraph, the weblink was updated to the current NCI weblink and the title of the information sheet was updated.
SUMMARY OF CHANGES
Amendment 3, Version Date: January 26, 2011
(Broadcast March 23, 2011)

RTOG 0837/ACRIN 6689, “Randomized, Phase II, Double-Blind, Placebo-Controlled Trial of Conventional Chemoradiation and Adjuvant Temozolomide Plus Cediranib Versus Conventional Chemoradiation and Adjuvant Temozolomide Plus Placebo in Patients With Newly Diagnosed Glioblastoma”

Study Chair: Tracy Batchelor, MD; 617-724-8770; tbatchelor@partners.org

RTOG 0837/ACRIN 6689 was amended to introduce the CAEPRs-related language provided by NCI CTEP for inclusion in the protocol amendment; to make three of the advanced imaging scans optional for the ACRIN 6689 component of the trial; and to specify the standard-of-care imaging scans to be submitted to the ACRIN core lab for the RTOG central reader study related to its primary endpoint. Changes were made to the following sections:

Cover Page
Dr. David Mankoff was added as an ACRIN Co-Principal Investigator/PET for the trial

Version date has been updated to January 26, 2011; “Amendments 1–3” has been amended

ACRIN 6689 Schema
Each imaging time point has been updated with a descriptor to identify it as “MANDATORY” or “OPTIONAL” for the advanced imaging component of the trial

Eligibility and Sample Size information below the Schema page have been revised to further discuss the mandatory/optional status of advanced imaging

Eligibility Checklist Step 2 (page 3 of 5)
Item #44 has been revised

Eligibility Checklist Step 2 (page 5 of 5)
Item #21 has been revised

Section 1.9.3
1st paragraph, 1st sentence: a comma has been deleted

Section 3.0
Has been revised to describe the mandatory/optional status of the advanced imaging scans

Section 5.1.4
2nd paragraph, 4th sentence: reference to Appendix IX has been deleted

Section 6.11
Has been revised to reflect the mandatory/optional status of the advanced imaging scans

Section 6.12
A capital “I” has been added to the header for consistency

Section 7.10.2
An additional line item has been introduced to definitions for Serious Adverse Events to conform to the NCI template

Section 7.10.6.2
A paragraph related to the use of the gadolinium contrast agent has been introduced in response to a recent FDA request

Section 7.10.6.3
Has been extensively revised to introduce the CAEPRs description for 3'-deoxy-3'-[F-18]fluorothymidine, version 1.0, dated July 1, 2010

**Section 7.10.6.4**
Has been extensively revised to introduce FDA-requested revisions to the discussion of the FLT PET agent and radiation exposure

**Section 11.2.2**
Introduces that Section 12.3 now contains a list of standard MRI exams to be submitted to the ACRIN core laboratory

**Section 11.6**
Sections 11.6.1 and 11.6.2.7 have been revised to reflect the mandatory/optional status of the advanced imaging scans

Sections 11.6.5.1 and 11.6.5.2 have been revised to direct readers to Appendix XI for details

Section 11.6.6, 2nd paragraph, 4th sentence parenthetical has been revised to direct readers to Appendix XII for imaging submission details

Section 11.6.7 has been revised to accommodate the mandatory versus optional imaging scans

**Section 12.3**
Has been extensively revised to introduce a table describing the standard image scan cases to be submitted to the ACRIN core laboratory and instructions for submission

**Section 12.4**
Has been revised to direct readers to Appendix XII for imaging submission details

**Section 13.7.4**
Has been revised to describe mandatory versus optional imaging for the advanced imaging component of the trial

**Section 13.7.5.2.5**
Has been revised to specify that the endpoint assessment will focus on the mandatory imaging scans only

**Appendix I/Sample Consent, Consent Form for ACRIN 6689: Advanced Imaging Sub-Study**
“APPENDIX I CONT”, which contains an informed consent form template for use at sites conducting the ACRIN 6689 sub-study of the trial, has been updated to:

- Reflect the mandatory/optional status of advanced imaging scans (throughout)
- Clarify that both blood collection (before MRI) and blood sampling (during PET) will be conducted
- Move a parenthetical under “About Advanced Imaging in the Study” that describes the length of the MRI examinations
- Introduce a location for potential participants to agree or decline to participate in the optional MRI scans for the advanced imaging component of the trial (see under Imaging Study Plan)
- Introduce Risks and Side Effects related to the [18F]FLT agent, its administration, and the PET/CT scan as provided by CTEP with the CAEPRs table;
  - Note: The following differ from the exact copy supplied by CTEP for the informed consent—
    - The headers have been revised to adhere to RTOG standard language;
    - The side effects for the IV injection have been delineated by “Likely” to “Rare” per standardized practice;
    - A descriptive paragraph for more information about PET scans available on ACRIN’s web site has been included;
    - Language for the FLT PET scan has been supplied by Dr. Mankoff to accommodate the specific risks for this trial;
    - Additional language for the radiation exposure risk has been added to conform to recent FDA request.
- Under “What other choices do I have if I do not take part in this study?”—“and standard-of-care imaging only” has been deleted
Appendix II: Study Parameter Table
The ACRIN 6689 MR and Dynamic PET Study Time Table and Study Procedures Table have been revised to include the mandatory or optional status of each advanced imaging scan time point

Appendix XII: MRI and PET Image Submission
Reference to Appendix IX has been deleted and language describing the mandatory.optional status of the advanced imaging scans has been introduced

Attachment A
Has been added
RTOG 0837/ACRIN 6689, "Randomized, Phase II, Double-Blind, Placebo-Controlled Trial of Conventional Chemoradiation and Adjuvant Temozolomide Plus Cediranib Versus Conventional Chemoradiation and Adjuvant Temozolomide Plus Placebo in Patients With Newly Diagnosed Glioblastoma"

Study Chair: Tracy Batchelor, MD; 617-724-8770; tbatchelor@partners.org

RTOG 0837/ACRIN 6689 was updated as follows:

Other Changes

Eligibility Checklist, Step 1: Question 19 was added to correspond with the tissue submission clarifications that were made in Amendment 2.

Appendix I/Sample Consent, Risks and side effects related to cediranib, last sentence: The sentence, "Cediranib in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent," because it was included in duplicate.
SUMMARY OF CHANGES
Amendment 2, Version Date: August 26, 2010
(Broadcast September 14, 2010)

RTOG 0837/ACRIN 6689, "Randomized, Phase II, Double-Blind, Placebo-Controlled Trial of Conventional Chemoradiation and Adjuvant Temozolomide Plus Cediranib Versus Conventional Chemoradiation and Adjuvant Temozolomide Plus Placebo in Patients With Newly Diagnosed Glioblastoma"

Study Chair: Tracy Batchelor, MD; 617-724-8770; tbatchelor@partners.org

RTOG 0837/ACRIN 6689 was amended as follows:

RTOG 0837

To allow adequate time for tissue processing before randomization and treatment start, the outer limit for treatment start was extended from 5 to 6 weeks post-surgery. Changes were made to the following sections:

- Section 3.1.2, 4th bullet
- Section 6.0, 3rd sentence
- Section 7.0, 2nd sentence
- Section 7.2.1, 2nd paragraph, 1st sentence

Per current RTOG Biospecimen Resource standard, buffy coat collection was changed to whole blood collection. In addition, collection instructions for all specimens were updated. Changes were made to the following sections:

- Section 10.3.3
- Section 10.4
- Appendix II/Study Parameter Table
- Appendix VII/RTOG Frozen Tissue Kit Instructions
- Appendix VIII/RTOG Blood Collection Kit Instructions
- Appendix IX/RTOG Urine Collection Kit Instructions

Other Changes

Section 3.1.2, 4th bullet: The timing of tissue submission was clarified.

Section 3.1.13: mg Hg was corrected to mm Hg. Corresponding changes were made to the Eligibility Checklist.

Section 10.2.5, 5th bullet: The timing of tissue submission was corrected from 21 to 28 days following surgery for consistency with Section 3.1.2.
Section 10.5: Reimbursement information was updated to current RTOG standard.

Appendix I/Sample Consent, Why is this study being done: The last paragraph was added to due availability of data in a study of cediranib in patients with recurrent glioblastoma.

Appendix II/Study Parameter Table: The timeframes were deleted for height assessment during treatment because they were included in error.

ACRIN 6689 ADVANCED IMAGING STUDY

ACRIN 6689 was amended to correct the amount of blood to be collected prior to the MRIs in the ACRIN component, to provide a "unified" Informed Consent Template with treatment and imaging content inclusive, to explain the intent of the blood sampling during the FLT PET component, and to introduce the ACRIN Biomarker Process Manual. Changes were made to the following sections:

Throughout

Improved consistency in the use and presentation of "[^18F]FLT" appears throughout the document. (For examples, see Sections 1.9.3, 5.1.4, and 11.6.)

Section 6.11.2

1st paragraph, 2nd bullet: "MRI" has been added to clarify

Section 7.10.6.3

3rd paragraph, 1st sentence: A description of the monitoring of vital signs has been added in relation to the[^18F]FLT IND agent

Section 10.8

Header: "Collection and Blood" has been added

Section 10.8.1, 2nd sentence: "A single vial of blood" is now "Two vials of blood" for "(less than 20 mL)" instead of "(less than 1 mL)" for the pre-MRI blood collection

Section 10.8.1, new-final sentence: "See the Biomarker Process Manual posted to www.acrin.org/6689_imagingmaterials.aspx," has been added

Section 10.8.2, 1st paragraph, new-1st and 2nd sentences: "This study will use blood samples taken during[^18F]FLT PET scans to obtain FLT blood clearance function and to calibrate and correct an image-based blood clearance curve based on the level of FLT in venous blood close to the end of the study when there are no arterial-venous differences."
This is needed for kinetic analysis and modeling. Metabolites also may be evaluated." has been added

Section 10.8.2, 1st paragraph, now-5th sentence: "centrally" has been added

Section 10.8.2, 2nd paragraph, NOTE, new-2nd sentence: "Note that for [$^{18}$F]FLT PET, two IV lines are needed, as it is not feasible to perform blood sampling and [$^{18}$F]FLT infusion through the same catheter." has been added

**Section 11.6**

Section 11.6.1, header: "and Overview" has been added

Section 11.6.1, 2nd paragraph under NOTE, 1st sentence: "sampling" has been replaced with "collection (two vials, less than 20 mL)" and "collected" has been replaced with "drawn"

Section 11.6.1, 2nd paragraph under NOTE, new-2nd and 3rd sentences: "The blood collection will be submitted to an ACRIN-certified laboratory for analysis of circulating biomarkers. See the Biomarker Process Manual posted to www.acrin.6689_imagingmaterials.aspx." has been added

Section 11.6.1, 2nd paragraph under NOTE, now-4th sentence: "for the pre-MR blood collection" has been added

Section 11.6.2, header: "and Overview" has been added

Section 11.6.2.7, 1st paragraph, 2nd bullet: "MRI" has been added to clarify

Section 11.6.5, new-1st and 2nd sentences: "In this study, we will use blood samples taken during the [$^{18}$F]FLT PET scans to determine the FLT blood clearance function and perform kinetic analysis for subsequent modeling. Metabolites also may be evaluated."

**Section 13.7.2**

Section 13.7.2.2: "T2" has been corrected to "T3"

Section 13.7.2.3: "T2" has been corrected to "T3"

**Appendix I/Sample Consent, Consent Form for ACRIN 6689: Advanced Imaging Sub-Study**

The description of the ACRIN 6689 Advanced Imaging Sub-Study presented as an add-on to the RTOG consent has been deleted; the sentence relating to specific sign-off for the ACRIN imaging sub-study "If I qualify, my signature below indicates that I choose to participate in the advanced MR and PET imaging studies that are being done for
research as a part of this study (RTOG 0837/ACRIN 6689)." has been deleted

"APPENDIX I CONT" has been added, followed by an informed consent template comprising RTOG therapeutic and ACRIN imaging elements as a single consent form for use at advanced imaging sites

**Appendix II: Study Parameter Table**

An ACRIN 6689 MR and Dynamic PET Study Procedures Table has been introduced
SUMMARY OF CHANGES
Amendment 1, Version Date: April 5, 2010
Broadcast April 27, 2010

RTOG 0837/ACRIN 6689, "Randomized, Phase II, Double-Blind, Placebo-Controlled Trial of Conventional Chemoradiation and Adjuvant Temozolomide Plus Cediranib Versus Conventional Chemoradiation and Adjuvant Temozolomide Plus Placebo in Patients With Newly Diagnosed Glioblastoma"

Study Chair: Tracy Batchelor, MD; 617-724-8770; tbatchelor@partners.org

In response to a request for a rapid protocol amendment from CTEP, RTOG 0837/ACRIN 6689 was amended to reflect changes to the Comprehensive Adverse Events and Potential Risks List (CAEPR) for cediranib. Changes were made to the following sections:

Section 7.3.6

CAEPR Version 2.8 (September 25, 2008) was replaced by CAEPR Version 2.9 (February 19, 2010). Specific changes are as follows and utilize CTCAE version 4.0 language unless otherwise noted:

- **Added New Risk:**
  - Less Likely: Investigations - Other (increased blood erythropoietin)
  - Reported on cediranib trials but with the relationship to cediranib still undetermined: Leukocytosis; Acute coronary syndrome; Chest pain - cardiac; Tinnitus; Vertigo; Endocrine disorders - Other (thyrotoxicosis); Abdominal distension; Colitis; Enterocolitis; Esophagitis; Gastric perforation; Rectal hemorrhage; Allergic reaction; Gum infection; Skin infection; Urinary tract infection; Cardiac troponin T increased; Hypertriglyceridemia; Chest wall pain; Muscle weakness lower limb; Lethargy; Somnolence; Transient ischemic attacks; Hematuria; Irregular menstruation; Bronchopulmonary hemorrhage; Pneumonitis; Pneumothorax; Pruritus

- **Increase in Risk Attribution:**
  - Changed to Less Likely from Reported but Undetermined: Hyperthyroidism; Neutrophil count decreased; Platelet count decreased

- **Decrease in Risk Attribution:**
  - Changed to Less Likely from Likely: Anorexia; Voice alteration
• Changed to Reported but Undetermined from Less Likely; Fever; Arthralgia; Back pain; Myalgia; Dry skin

• Provided further clarification:
  • Mucositis/stomatitis (functional/symptomatic) - Select (*CTCAE version 3.0 language*) is now reported as the following individual events: Anal mucositis, Mucositis oral, Rectal mucositis, Small intestinal mucositis, Laryngeal mucositis, Pharyngeal mucositis, and Tracheal mucositis.
  • Mucositis/stomatitis (clinical exam): oral cavity (*verbatim from source documents*), which was previously under Reported but Undetermined, is now reported as part of Mucositis oral under Less Likely.

• Deleted risk (*verbatim from source documents*):
  • Reported on cediranib trials but with the relationship to cediranib still undetermined: speech impairment (aphasia)

Appendix I/Sample Consent, Risks associated with cediranib
The risk profile was updated to reflect the revised CAEPR. Specific changes are as follows:

• Added New Risk:
  • Less Likely: Increased levels of a substance involved in the production of red blood cells

• Increase in Risk Attribution:
  • Changed to Less Likely from Reported but Undetermined: Abnormally high level of thyroid gland hormone; Decreased number of a type of white blood cell (neutrophil/granulocyte); Decreased number of a type of blood cell that help to clot blood (platelet)

• Decrease in Risk Attribution:
  • Changed to Less Likely from Likely: Loss of appetite; Voice change

Please note that CTEP provided a Risk Profile for the first time for cediranib. All terminology was changed to be consistent with CTEP’s profile.
RTOG 0837/ACRIN 6689, "Randomized, Phase II, Double-Blind, Placebo-Controlled Trial of Conventional Chemoradiation and Adjuvant Temozolomide Plus Cediranib Versus Conventional Chemoradiation and Adjuvant Temozolomide Plus Placebo in Patients With Newly Diagnosed Glioblastoma"

Study Chair: Tracy Batchelor, MD; 617-724-8770; tbatchelor@partners.org

RTOG 0837/ACRIN 6689 has updated as follows:

Section 7.1, 3rd paragraph: RTOG business hours were updated.

Sections 12.1 and 12.2: "SECTION 12.3 FOR ALL IMAGING SUBMISSION" was added for clarity.