SUMMARY OF CHANGES
Amendment #3: August 2, 2010
(Broadcast: September 2, 2010)

RTOG 0825/ACRIN 6686, Phase III Double-Blind Placebo-Controlled Trial of Conventional Concurrent Chemoradiation and Adjuvant Temozolomide Plus Bevacizumab Versus Conventional Concurrent Chemoradiation and Adjuvant Temozolomide in Patients With Newly Diagnosed Glioblastoma

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In response to a CTEP Request for Amendment (RA) for protocols using bevacizumab (NSC 704865, IND 7921) RTOG 0825/ACRIN 6686 was amended as follows:

Section 7.6.12: Comprehensive Adverse Events and Potential Risks list (CAEPR) version 2.1 (May 4, 2010) has replaced CAEPR Version 1.2 (June 19, 2007). Specific changes are as follows: (NOTE: This CAEPR version includes frequency data. The previous version did not have the categories for Likely, Less Likely or Rare but Serious. The section below utilizes CTCAE version 4.0 language unless otherwise noted.)

Added New Risk:
- **Less Likely:** Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia); Hematuria
- **Rare But Serious:** Blood and lymphatic system disorders - Other (renal thrombotic microangiopathy)
- Reported on Bevacizumab Trials But with the Relationship to Bevacizumab Still Undetermined: Hepatic failure; Osteonecrosis of jaw

Increase in Risk Attribution:
- Changed to Less Likely from Reported But Undetermined: Infections and infestations - Other (peri-rectal abscess); Syncope

Decrease in Risk Attribution:
- Changed to Reported But Undetermined from Possible: Skin ulceration

Provided Further Clarification:
- Allergic reaction/hypersensitivity (CTCAE version 3.0 language) is now reported as Allergic reaction and Anaphylaxis.
- Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip) and Nasal cavity/paranasal sinus reactions (CTCAE version 3.0 language) is now reported as Respiratory, thoracic, and mediastinal disorders - Other (rhinitis).
- Ventricular fibrillation (CTCAE version 3.0 language) is now reported as Ventricular arrhythmia and Ventricular fibrillation.
- Cardiac ischemia/infarction (CTCAE version 3.0 language) is now reported as Acute coronary syndrome and Myocardial infarction.
- Rash/desquamation (CTCAE version 3.0 language) is now reported as Skin and subcutaneous tissue disorders - Other (rash).
- Leak (including anastomotic), GI: large bowel (CTCAE version 3.0 language) is now reported as Gastrointestinal anastomotic leak.
- Mucositis/stomatitis (functional/symptomatic) – Select (CTCAE version 3.0 language) is now only reported as Mucositis oral.
- The following footnotes were added to clarify those adverse events that were previously on the version 1.2 CAEPR under - Select terms (CTCAE version 3.0 language): #2 (Fistula, GI), #3 (Hemorrhage, GI), #4 (Perforation, GI), and #5 (Ulcer, GI).
• Infection with normal ANC or Grade 1 or 2 neutrophils – Select and Infection with normal ANC or Grade 1 or 2 neutrophils – Select (pelvis, peritoneal cavity, rectum, scrotum, skin, wound) (CTCAE version 3.0 language) is now reported as Infection and the following footnote (#6) added: “Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.”
• Rectal abscess/necrosis (verbatim from source documents) is now reported as Infections and infestations – Other (peri-rectal abscess).
• Dizziness (CTCAE version 3.0 language) is now reported as Dizziness and Vertigo.
• Neurology - Other: (Leukoencephalopathy syndrome including reversible posterior leukoencephalopathy syndrome [RPLS]) (CTCAE version 3.0 language) is now only reported as Reversible posterior leukoencephalopathy syndrome.
• Fistula, pulmonary/upper respiratory – Select (CTCAE version 3.0 language) is now reported as Bronchopleural fistula and Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula).
• Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis) (CTCAE version 3.0 language) is now reported as Hoarseness.
• Fistula, GU – Select (CTCAE version 3.0 language) is now reported as Urinary fistula and Vaginal fistula.
• Renal failure (CTCAE version 3.0 language) is now reported as Acute kidney injury, Renal and urinary disorders - Other (Nephrotic Syndrome), and Renal and urinary disorders - Other (renal failure).
• Cytokine release syndrome/acute infusion reaction (CTCAE version 3.0 language) is now reported as Infusion related reaction.
• Visceral arterial ischemia (non-myocardial) (CTCAE version 3.0 language) is now reported as Vascular disorders - Other (arterial thromboembolic event), and the following footnote (#8) added: “Arterial thromboembolic event includes visceral arterial ischemia, peripheral arterial ischemia, heart attack, and stroke”.
• The following footnote (#7) was added to Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia): “Metaphyseal dysplasia was observed in young patients who still have active epiphyseal growth plates”.
• Peripheral neuropathy (verbatim from source documents) is now reported as Peripheral motor neuropathy and Peripheral sensory neuropathy.

Modified Agent Specific Adverse Events List (ASALE) Reporting Requirements:
• Added: Pain; Wound dehiscence; Weight loss; Hematuria
• Deleted (CTCAE version 3.0 language): Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L); Rigors/chills; Hemorrhage, pulmonary/upper respiratory: lung

Deleted Risk:
• Possible (CTCAE version 3.0 language): Hypotension; Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L); Rigors/chills; Creatinine; Bronchospasm, wheezing
• Reported on Bevacizumab Trials But with the Relationship to Bevacizumab Still Undetermined (verbatim from source documents): Platelets; Cardiac arrest; Hypopigmentation; Hyperglycemia; Hypoglycemia; Hypomagnesemia; Cataract; Watery eye; Urinary frequency

Appendix I/Sample Consent, Risks associated with bevacizumab: The risk profile was updated to reflect the CAEPR.

Based upon the analysis of the first 360 patients entered, the rate of patients not being randomized due to ineligibility, insufficient tissue, progression, patient refusal, or other reasons, was very much underestimated (35% vs. originally projected 15%). So a slightly higher nonrandomized rate of 35% was adopted to recalculate the targeted sample size for the study. With that rate 942 patients would have to be entered in order to have 612 patients randomized.
The sample size was therefore revised from 720 to 942 patients. Related changes were made to the following sections:

- **Schema Pages**: required sample size updated
- **Section 1.8.3**: 1st sentence updated
- **Section 6.10.2**: 1st and last sentences updated
- **Section 11.7.1**: 1st sentence updated
- **Section 13.2.1**: Last three sentences added
- **Section 13.2.3**: Last sentence updated
- **Section 13.3**: Last paragraph added
- **Section 13.6**: Table 13.7 updated
- **Section 13.7.1**: 2nd-to-last sentence updated
- **Appendix I, How many people will take part in the study**: Updated

Time frame prior to step 2 registration was clarified in the following places, for consistency with the eligibility checklist:

- 3.1.4
- 3.1.5
- 3.1.7
- 3.1.10
- 3.1.11.1
- 3.1.12.1
- 3.1.12.2
- 3.1.13
- 3.1.13.1
- 3.1.14
- 3.1.17
- 3.2.6.3
- 3.2.6.4
- 3.2.6.9
- 3.2.6.11
- **Appendix I**: Pretreatment assessments, ≤ 14 d prior to step 2 registration and ≤ 1 wk prior to step 2 registration

Other Changes:

**Cover Pages**: Contact information was updated for Dr. Mehta, Dr. Aldape, and Dr. Brown.

**Study Participants**: NCCTG was added as an endorsing cooperative group via the endorsement plus option.

**Section 1.8**: Background details have been added explaining the rational for new Aims included to assess the MacDonald Criteria with Biomarker, Imaging Quality of Life Study (BIQSFP) funding.

**Section 2.4.3**: Three new BIQSFP-driven study Aims have been added.

**Section 3.1.6.1**: The timeframe for scanning was changed from “1 week prior to registration” to “10 days prior to the start of radiation therapy” for logistical reasons. Corresponding changes were made to the Eligibility Checklist.

**Section 3.1.11.3.1**: Instructions were added for calculating the UPC ratio for clarity.

**Sections 6.6.1-6.6.3**: Compliance criteria was revised and expanded for clarity and accuracy. Subsequent sections were appropriately renumbered.
Sections 7.1-7.1.2: Instructions for unblinding were expanded for clarity. RTOG business hours were corrected.

Section 7.4.1, last sentence: Adverse events was qualified as "treatment-related" adverse events for clarity.

Section 7.6.3, 2nd paragraph, 4th-to-last sentence: "week six of radiation" was deleted after "third dose" because it was included in error.

Section 7.6.3, 2nd-to-last paragraph, sentences 6, 7 and 10: Instructions for obtaining open-label bevacizumab were revised for clarity and accuracy.

Section 7.8.2.2, 2nd paragraph: In the first sentence, adverse events was qualified as "treatment-related" adverse events for clarity. The second-to-last sentence was rewritten and expanded for clarity.

Sections 10.3.3 and 10.5: Per current RTOG Biospecimen Resource standard, buffy coat collection was changed to whole blood collection.

Section 10.5: Instructions for serum, plasma and urine collection were revised and expanded per current RTOG Biospecimen Resource standard.

Section 10.6: Reimbursement information was revised per current RTOG standard.

Section 11.4, “NOTE” accompanying the heading: “Radiologist” was changed to “MD” for logistical reasons.

Sections 11.4.6-11.4.6.1: A definition of pseudo-progression was added for clarity.

Section 11.7: Details of the reader study design for BIQSFP component of the study assessment have been added.

Section 12.1
- The Adverse Event Form was deleted because it was included in error.
- The timing was corrected for the Treatment Summary Form.
- The timing was corrected for the Salvage Treatment Guideline Questionnaire

Section 12.3
- For clarity, the following statement was added underneath the header: “ATTENTION: Sites are to submit all cases to ACRIN for image archiving. This is not be confused with the ACRIN 6686 Advance Imaging Component.”
- For clarity, the following statement was added for each scan collection: “Each scan must be accompanied by an ITW MRI submission form”

Section 13.3: Ending parentheses added to first sentence due to inadvertent omission.

Section 13.7.2.3: Rationale descriptions, analytical criteria, and power calculations for the BIQSFP-driven Aims have been introduced.

References: New references in support of the BIQSFP-driven Aims have been introduced.

Appendix I/Consent Form for Use of Tissue, Blood, and Urine for Research: The web link was updated in the second paragraph.

Appendix I/Consent Form for ACRIN 6686: Advanced Imaging Sub-Study
- Under About Advanced Imaging Study, second paragraph: “the investigational” has been added.
Above the schema, three time points was corrected to four time points; the schema has been revised to show the four time points.

In second paragraph of the risks sections/gadolinium contrast agent: triple dose was corrected to double dose.

In third paragraph, effects/affects typo has been corrected.

Appendix II

- Urine protein row: UPC ratio was added next to urine protein for clarity
- CD4 count row: "if lymphocyte count <500 mm$^3$" was added to the first time point in the adjuvant phase because it was inadvertently omitted.

Appendix VII: Blood and urine collection instructions were updated to current RTOG Biospecimen Resource standard.