For **Protocol** Amendment #12 to: RTOG 0929, A Randomized Phase I/II Study of ABT-888 in Combination With Temozolomide in Recurrent (Temozolomide Resistant) Glioblastoma

NCI/Local Protocol #: RTOG 0929

NCI Protocol Version Date: June 3, 2016

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cover pages</td>
<td>• Contact information for Dr. Gilbert was updated.</td>
</tr>
<tr>
<td></td>
<td>• The street address for the Supporting Statistician was amended.</td>
</tr>
<tr>
<td></td>
<td>• This amendment was added to the Document History table.</td>
</tr>
<tr>
<td>Section 7.3.1</td>
<td>In response to a CTEP Request for Amendment, the CAEPR for ABT-888 (Version 2.3, March 4, 2016) was revised as follows:</td>
</tr>
<tr>
<td></td>
<td>• The SPEER grades have been updated.</td>
</tr>
<tr>
<td></td>
<td><strong>Added New Risk:</strong></td>
</tr>
<tr>
<td></td>
<td>• <strong>Reported But With Insufficient Evidence for Attribution:</strong></td>
</tr>
<tr>
<td></td>
<td>Agitation; Alanine aminotransferase increased; Appendicitis; Arthritis; Aspites; Aspartate aminotransferase increased; Blood and lymphatic</td>
</tr>
<tr>
<td></td>
<td>system disorders - Other (bone marrow failure); Blood and lymphatic system disorders - Other (pancytopenia); Cardiac disorders - Other</td>
</tr>
<tr>
<td></td>
<td>(Takotsubo cardiomyopathy); Cardiac troponin I increased; Catheter related infection; Cognitive disturbance; Colonic obstruction; Dental</td>
</tr>
<tr>
<td></td>
<td>caries; Dermatitis radiation; Duodenal ulcer; Dysarthria; Esophagitis; Extrapyramidal disorder; Flu like symptoms; Flushing; Gastritis;</td>
</tr>
<tr>
<td></td>
<td>Heart failure; Hepatobiliary disorders - Other (cirrhosis); Hypertension; Infections and infestations - Other (peritonsillar abcess);</td>
</tr>
<tr>
<td></td>
<td>Infections and infestations - Other (shingles); Injury, poisoning and procedural complications - Other (radiation proctitis); Intracranial</td>
</tr>
<tr>
<td></td>
<td>hemorrhage; Lipase increased; Lung infection; Malaise; Memory impairment; Movements involuntary; Mucosal infection; Myelodysplastic</td>
</tr>
<tr>
<td></td>
<td>syndrome; Nasal congestion; Neck pain; Obstruction gastric; Palpitations; Peripheral motor neuropathy; Pneumonitis; Presyncope; Proteinuria;</td>
</tr>
<tr>
<td></td>
<td>Psychiatric disorders - Other (emotional instability); Rash acneiform; Rectal hemorrhage; Rectal pain; Renal and urinary disorders - Other</td>
</tr>
<tr>
<td></td>
<td>(dysuria); Restlessness; Reversible posterior leukoencephalopathy syndrome; Sepsis; Sinus bradycardia; Sinus tachycardia; Skin and subcutaneous</td>
</tr>
<tr>
<td></td>
<td>tissue disorders - Other (nail bed changes); Stroke; Treatment related secondary malignancy; Tremor; Tumor pain; Urinary tract infection</td>
</tr>
<tr>
<td></td>
<td>• <strong>Decrease in Risk Attribution:</strong></td>
</tr>
<tr>
<td></td>
<td>• Changed to Less Likely from Likely: Neutrophil count decreased</td>
</tr>
<tr>
<td></td>
<td>• <strong>Provided Further Clarification:</strong></td>
</tr>
<tr>
<td></td>
<td>• Gastrointestinal disorders - Other (mouth ulceration) (under Reported But With Insufficient Evidence for Attribution) is now reported as</td>
</tr>
<tr>
<td></td>
<td>Mucositis oral (under Reported But With Insufficient Evidence for Attribution).</td>
</tr>
<tr>
<td>12.0</td>
<td>The street address for data submission was updated.</td>
</tr>
</tbody>
</table>
For **Protocol Consent** Amendment #12 to: RTOG 0929, A Randomized Phase I/II Study of ABT-888 in Combination With Temozolomide in Recurrent (Temozolomide Resistant) Glioblastoma

NCI/Local Protocol #: RTOG 0929

NCI Protocol Version Date: June 3, 2016

<table>
<thead>
<tr>
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<th>Change</th>
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</thead>
<tbody>
<tr>
<td>First page</td>
<td>The version date was updated.</td>
</tr>
<tr>
<td>What side effects or risks can I expect from being in this study?</td>
<td>At CTEP’s request, the text immediately under the heading was amended to be consistent with CTEP’s current standard text.</td>
</tr>
<tr>
<td>Risks and side effects related to ABT-888</td>
<td>The version date for the risk profile for ABT-888 was updated to be consistent with the revised CAEPR. No changes were made to the risk profile content.</td>
</tr>
<tr>
<td>Risks and side effects related to temozolomide</td>
<td>The risk profile for temozolomide was updated to CTEP’s May 20, 2015, version of this table. The risks are comparable to the package insert. There is no change to the overall safety and risk-benefit profile.</td>
</tr>
<tr>
<td>About Using Tissue for Research</td>
<td>The last three lines of the second paragraph were deleted because the NCI tissue information sheet is no longer available on the cancer.gov website.</td>
</tr>
</tbody>
</table>
For **Protocol** Amendment #11 to: RTOG 0929, A Randomized Phase I/II Study of ABT-888 in Combination with Temozolomide in Recurrent (Temozolomide Resistant) Glioblastoma.

NCI/Local Protocol #: RTOG 0929

NCI Protocol Version Date: February 21, 2014 (Broadcast March 6, 2014)

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cover pages</td>
<td>The document history table was updated to include Amendment 11. In preparation for the transition to the National Clinical Trials Network (NCTN), the title pages were revised to include our new organization name, NRG Oncology.</td>
</tr>
<tr>
<td>7.4.8</td>
<td>At CTEP’s request, this section was added to address rare hepatic failure associated with temozolomide.</td>
</tr>
<tr>
<td>7.7-7.8</td>
<td>The Adverse Event sections were updated per current RTOG standard. References to the “Adverse Event Expedited Reporting System (AdEERS)” have been changed to “CTEP Adverse Event Reporting System (CTEP-AERS)” throughout.</td>
</tr>
<tr>
<td>Appendix I, Assessments During Treatment</td>
<td>At CTEP’s request, liver function tests were added at the end of the last temozolomide treatment cycle to address rare hepatic failure associated with temozolomide.</td>
</tr>
</tbody>
</table>
For Protocol Update 7/24/13 to: RTOG 0929, A Randomized Phase I/II Study of ABT-888 in Combination With Temozolomide in Recurrent (Temozolomide Resistant) Glioblastoma

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cover pages</td>
<td>The document history table was updated to include the update.</td>
</tr>
<tr>
<td></td>
<td>Minhee Won’s email address was corrected.</td>
</tr>
<tr>
<td>Section 7.5.2</td>
<td>Under “Dose reductions”:</td>
</tr>
<tr>
<td></td>
<td>“if platelets &lt; 100 x 10^9/L and ANC &lt; 1 x 10^9/L” was corrected to “if platelets &lt; 100 x 10^9/L or ANC &lt; 1 x 10^9/L”; in Amendment 10, it was inadvertently changed to “and”.</td>
</tr>
</tbody>
</table>
For Protocol Amendment #10 to: RTOG 0929, A Randomized Phase I/II Study of ABT-888 in Combination With Temozolomide in Recurrent (Temozolomide Resistant) Glioblastoma

NCI/Local Protocol #: RTOG 0929

NCI Protocol Version Date: July 19, 2013 (Broadcast July 24, 2013)

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>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.</td>
</tr>
<tr>
<td>Cover Pages</td>
<td>The document history table was updated to include Amendment 10. Minhee Won has replaced Meihua Wang as the statistician. The protocol agents table and participating sites list were added per current RTOG standard.</td>
</tr>
<tr>
<td>Schema</td>
<td>The schema was updated to reflect the closure of the phase I component, the opening of the phase II component, and the subsequent closure of the bevacizumab-failure group within the phase II component.</td>
</tr>
<tr>
<td>Sections 1.1.1-1.2</td>
<td>Numbering was corrected.</td>
</tr>
<tr>
<td>Section 5.2</td>
<td>Contact information was updated in event of RTOG web registration problems.</td>
</tr>
<tr>
<td>Section 7.3</td>
<td>Reference to the investigator brochure for complete toxicity information was added per current RTOG standard.</td>
</tr>
<tr>
<td>Section 7.3.1</td>
<td>The CAEPR for ABT-888 was updated at CTEP’s request. As broadcast to RTOG sites on 6/13/13, CTEP issued a condensed risk profile and accompanying CAEPR (version 2.2) for ABT-888. The risk profile format for ABT-888 was changed to the new condensed risk profile format, and the version number of the accompanying CAEPR was upgraded from version 2.1 to version 2.2. There were NO changes to the risk information on the CAEPR.</td>
</tr>
<tr>
<td>Section 7.4</td>
<td>“Comprehensive information” was clarified as “detailed pharmacologic and safety information” to be consistent with current RTOG standard.</td>
</tr>
<tr>
<td>Section</td>
<td>Change</td>
</tr>
<tr>
<td>---------</td>
<td>--------</td>
</tr>
</tbody>
</table>
| Section 7.4.1 | “Sodium lautyl” was corrected to “sodium lauryl”.
| Section 7.5.2 | Under “Dose reductions”:
| | “If any non-hematologic AE observed was grade > 2… or if platelets < 50 x 10⁹/L or ANC < 1 x 10⁹/L” was corrected to
| | “If any non-hematologic AE observed was grade > 2… and/or if platelets < 100 x 10⁹/L and ANC < 1 x 10⁹/L” |
| Section 7.5.3 | In the table, a note was added for lymphopenia for clarity. Consideration for pneumocystis, herpes zoster, and thrush prophylaxis was also added.
| Sections 7.7-7.8 | The Adverse Events and AdEERs Reporting Requirements sections were updated to current RTOG standard.
| Section 9.1.9 | “Pneumocystis and herpes viral prophylaxis” was changed to “Pneumocystis, herpes zoster, and thrush prophylaxis” to be consistent with the added note to Section 7.5.3.
| Sections 10.2.1, 10.6, Appendix I | Specimen submission instructions were updated to current RTOG standard.
| Section 11.2 | Numbering was corrected.

For **Protocol Consent** Amendment #10 to: RTOG 0929, A Randomized Phase I/II Study of ABT-888 in Combination With Temozolomide in Recurrent (Temozolomide Resistant) Glioblastoma

NCI/Local Protocol #: RTOG 0929

NCI Protocol Version Date: July 19, 2013 (Broadcast July 24, 2013)

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
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</thead>
<tbody>
<tr>
<td>Front page</td>
<td>A version date was added.</td>
</tr>
<tr>
<td>Section</td>
<td>Change</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Risks and side effects related to ABT-888</td>
<td>The risk profile for ABT-888 was updated at CTEP’s request.</td>
</tr>
<tr>
<td></td>
<td>As broadcast to RTOG sites on 6/13/13, CTEP issued a condensed risk profile and accompanying CAEPR (version 2.2) for ABT-888. The risk profile format for ABT-888 was changed to the new condensed risk profile format, and the version number of the accompanying CAEPR was upgraded from version 2.1 to version 2.2. There were <strong>NO</strong> changes to the risk information on the CAEPR.</td>
</tr>
<tr>
<td>Risks and side effects related to temozolomide</td>
<td>The risk profile for temozolomide was updated to incorporate CTEP’s recently developed side effect profile for this agent. The risks are comparable to the package insert.</td>
</tr>
<tr>
<td>For more information on clinical trials and insurance coverage</td>
<td>This information was deleted because it is no longer available.</td>
</tr>
<tr>
<td><strong>Consent Form for Use of Tissue, Blood, and Urine for Research:</strong></td>
<td>Risks associated with central databases were added per current RTOG standard.</td>
</tr>
<tr>
<td><strong>Risks, 2nd-5th paragraphs</strong></td>
<td></td>
</tr>
</tbody>
</table>
SUMMARY OF CHANGES
Amendment 9: August 24, 2012
(Broadcast: August 30, 2012)

RTOG 0929, "A Randomized Phase I/II Study of ABT-888 in Combination With Temozolomide in Recurrent (Temozolomide Resistant) Glioblastoma"

Study Chair: H. Ian Robins MD, PhD; 608-263-1416; hirobins@wisc.edu

RTOG 0929 was amended due to the following:

Background
Recently, six cases of seizure, regardless of relatedness, have been observed in patients enrolled in clinical studies utilizing the investigational agent veliparib. These serious adverse events were submitted via the Adverse Event Expedited Report System (AdEERS), and the following are brief summaries of each patient.

- Case 1 (Patient ID: 7968-001-003): The subject is 75-year-old Caucasian male with acute myeloid leukemia, who experienced grade 3 seizure while participating in a phase 1 study utilizing the investigational agent veliparib in combination with topotecan and carboplatin. The patient was found to have a subdural hematoma and this was assessed to be the cause of the seizure.
- Case 2 (Patient ID: 2-8-69): The subject is a 63-year-old African American female with olfactory neuroblastoma, who experienced grade 2 seizures while participating in a phase 1 study utilizing the investigational agent veliparib in combination with carboplatin and paclitaxel. The patient had evidence of tumor recurrence apparent from a CT of the head. The event of seizure was assessed as unlikely related to veliparib.
- Case 3 (Patient ID: 1-8-54): The subject is a 67-year-old Caucasian female with ovarian cancer, who experienced grade 2 seizure on cycle 1 day 13, while participating in a phase 1 study utilizing the investigational agent veliparib. The patient was receiving veliparib 400 mg BID. Additionally, the patient was hypoxic from pleural effusion and improved on oxygen. This event was assessed as possibly related to veliparib.
- Case 4 (Patient ID: ABT-008): The subject was a 48-year-old Caucasian female with breast cancer who experienced grade 4 seizure, and subsequently expired approximately 3 months after the last dose of veliparib. She participated in a phase 1 study utilizing the investigational agent veliparib in combination with carboplatin. The patient had disease progression in the CNS and was taken off the study. The event of seizure was assessed as not related to veliparib.
- Case 5 (Patient ID: ABT-039): The subject is a 68-year-old Caucasian female with breast cancer who experienced grade 2 seizure while participating in a phase 1 study utilizing the investigational agent veliparib in combination with carboplatin. The patient had a craniotomy for CNS metastases resection at the time of diagnosis. She was started on the study three months later. The patient had an episode of grade 2 seizure on cycle 3, day 6. At the time of the event, the subject was taking a dose of 200 mg of veliparib. She was retreated at a lower dose of 150 mg BID of veliparib. This event was assessed as possibly related to veliparib.
- Case 6 (Patient ID: 1-9-72): The subject is a 46-year-old African American female with fallopian tube carcinoma, who experienced grade 2 seizure on cycle 1, day 5 of the study while participating in a phase 1 study utilizing the investigational agent veliparib. The patient was removed from the study, and this event was assessed as possibly related to veliparib.

Thirty-five patients have been treated at 400 mg BID both in a single agent phase I and a phase II ovarian cancer trial and no additional seizures have been seen. In laboratory toxicity studies performed by Abbott, seizure was seen in animals in high doses. At present, there are not enough data to state conclusively whether veliparib is associated with an increase in the incidence of seizures.
Protocol changes were made at the request of CTEP as outlined below:

1) **Specific protocol revisions to address Risk Mitigation Plan**
   *Section 3.1.12* was added to require patients with a history of seizure or new onset of seizures to be clinically controlled with no seizures for at least 14 days prior to registration. Corresponding changes were made to **Eligibility Checklist Question 15/page 2 of 4**. All sections and questions were appropriately renumbered.

2) **Revision of the protocol CAEPR:**
   *Section 7.3.1:* ABT-888 CAEPR Version 2.0 (October 28, 2011) was replaced by CAEPR Version 2.1 (August 9, 2012). Specific changes are:
   - **Added New Risk:**
     - Rare But Serious: Seizure
   - **Increase in Risk Attribution:**
     - Changed to Less Likely from Reported But Undetermined: Hypophosphatemia
     - Changed to Rare But Serious from Reported But Undetermined: Thromboembolic event
   - **Modified Specific Protocol Exceptions to Expedited Reporting (SPEAR) reporting requirements:**
     - Added: Hypophosphatemia

3) **Revision of the Informed Consent:**
   *Appendix I, Informed Consent:* The risk profile for ABT-888 was replaced with CTEP's revised risk profile corresponding with the updated CAEPR. Specific risk changes are:
   - **Added New Risk:**
     - Rare But Serious: Convulsion or seizure
   - **Increase in Risk Attribution:**
     - Changed to Less Likely from Reported But Undetermined: Decreased blood level of phosphate
     - Changed to Rare But Serious from Reported But Undetermined: Formation of a blood clot that plugs the blood vessel; blood clots may break loose and travel to another place, such as the lung

   **PLEASE NOTE:** The potential risks listed in the CAEPR whose relationship to veliparib is still undetermined are not required by CTEP to be described in the ICD; however, they may be communicated to patients according to local IRB requirements.

   **In addition to CTEP's requested changes, the following other changes were made:**

   **Cover Page:** Formatting was adjusted to allow document history table to appear on one page.

   Due to timing logistics for patients with a recent resection, the protocol was modified to require a stable or decreasing dose of steroids at least 5 days prior to scanning only for patients without a recent resection. Changes were made to the following sections:
   - **Eligibility Checklist, question 5, page of 1 of 4:** statement added
   - **Section 3.1.4:** statement added
   - **Section 3.1.4.2:** statement added
   - **Section 3.1.4.4:** criterion deleted
   - **Section 11.2.1.2:** statement added
Eligibility Checklist, question 14, page 1 of 4:

- “or another modality approved by the disease chair” was removed because it was included in error. This eligibility checklist question is intended to directly reflect Section 3.1.11.
- Perfusion MRI was added due to the addition in Section 3.1.11 (see below).

Section 3.1.11: Perfusion MRI was added.

Section 7.5, 1st paragraph: A window of +/-3 days was added for the cycle start date.

Section 7.5.2.4 and Section 7.5.2.5.1/last 2 tables: The window for obtaining laboratory values was changed from 72 to 48 hours.
SUMMARY OF CHANGES
Amendment 8: July 24, 2012
(Broadcast: August 30, 2012)

RTOG 0929, “A Randomized Phase I/II Study of ABT-888 in Combination With Temozolomide in Recurrent (Temozolomide Resistant) Glioblastoma”

Study Chair: H. Ian Robins MD, PhD; 608-263-1416; hirobins@wisc.edu

RTOG 0929 was amended as follows:

The phase I portion of RTOG 0929 recently established an MTD of 75 mg/m² for temozolomide and 40 mg BID for ABT-888 (ie, dose level 3 from phase I). The phase II portion of this study opened on 3/6/12, with Arm 1 administered at those doses. The following sections of the protocol were amended to reflect this information:

- Schema, Phase II, Arm 1
  - Section 7.2.1: The Note was added.
  - Section 7.3: In the Phase II Arm 1 shipment table, information for the ABT-888 20 mg BID dose was deleted
  - Section 7.5.2.1: The Note was added; the heading for the dose adjustment table for temozolomide 75 mg/m² was modified; and the dose adjustment table for temozolomide 60 mg/m² was deleted.
  - Section 7.6.2.1: “60 or” was deleted
  - Appendix IA/Sample Consent:
    - Why is this study being done: The Note was added.
    - During the study: The Note was added.

Other Changes

- Section 3.1.4.3: “2 adjuvant cycles” was modified to “2 consecutive adjuvant cycles” for clarity. Related changes were made to the Patient Population description on the Schema Page and to the Eligibility Checklist.
- Section 3.2.4.10: “(with the exception of craniotomy” was added for clarity.
- Section 7.2.2.2: (“first does given on D1 AM)” was added for clarity.
- Section 7.3: In the Phase II, Arm 1 shipment table, information for the ABT-888 20 mg BID dose was deleted because it was included in error.
- Section 7.5.2.1: The note stating “A complete blood count must be performed on days 14, 21 and 28 (± 48 hours) after the first daily dose of each treatment cycle” was deleted because it was included in error and is contradictory to the correct guideline specified in Appendix II.
- Section 7.5.2.5.1, 1st sentence:
  - “and/or” was replaced by “or” in both places to more clearly reflect that dose should be reduced if any of the preceding AEs occur.
  - For increased accuracy; “by one dose level” was replaced by “per the guidelines in the table below (worst treatment-related hematologic AE during the previous cycle),” because doses may be reduced by more than one dose level.
- 7.5.3, Table: 1st row, 1st column: “5-day schedule” was added for clarity and consistency with other parts of the table.
RTOG 0929, "A Randomized Phase I/II Study of ABT-888 in Combination With Temozolomide in Recurrent (Temozolomide Resistant) Glioblastoma"

Study Chair: H. Ian Robins MD, PhD; 608-263-1416; hirobins@wisc.edu

Eligibility Checklist question 5: "(or decreasing)" was added to correspond with changes made to Section 3.1.4.4 in Amendment 6.
SUMMARY OF CHANGES
Amendment 7: January 12, 2012
(Broadcast: January 25, 2012)

RTOG 0929, "A Randomized Phase I/II Study of ABT-888 in Combination With Temozolomide in Recurrent (Temozolomide Resistant) Glioblastoma"

Study Chair: H. Ian Robins MD, PhD; 608-263-1416; hirobins@wisc.edu

Section 3.1.4.2: It was clarified that the post-surgery scan should (versus must) be within 96 hours following surgery. Related changes were made to Eligibility Checklist questions 5 and 13 and to the MRI assessment row of Appendix II.

Appendix II, Study Parameter Table: In the MRI assessment row: It was clarified that the MRI must be performed ≤28 d prior to registration for recent resection OR < 14 days for no resection. An asterisk was added to refer sites to Section 3.1 for further details.
In response to a CTEP Request for Amendment (RA), RTOG 0929 was revised to reflect changes to the Comprehensive Adverse Events and Potential Risks List (CAEPR) for Velibarib (ABT-888). Changes were made to the following sections:

Section 7.3.1: CAEPR Version 1.4 (December 8, 2010) was replaced by CAEPR Version 2.0 (October 26, 2011). Specific changes are as follows:

- This CAEPR version includes frequency data. The previous version did not have the categories for Likely, Less Likely or Rare but Serious.

- The Agent Specific Adverse Event List (ASAEL) is now termed the Specific Protocol Exceptions to Expedited Reporting (SPEER) and includes grades for adverse events found on the SPEER that are used to determine if expedited reporting is required.

- Added New Risk:
  - Also Reported on ABT-888 Trials But With the Relationship to ABT-888 Still Undetermined: Alkaline phosphatase increased; Anxiety; Ataxia; Back pain; Blood bilirubin increased; Blurred vision; Bone pain; Bruising; Colitis; Confusion; Cough; Creatinine increased; Depressed level of consciousness; Depression; Dry mouth; Dysphagia; Edema limbs; Electrocardiogram QT corrected interval prolonged; Enterocolitis; Epistaxis; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (mouth ulceration); Generalized muscle weakness; Hematuria; Hepatic failure; Hot flashes; Hyperhidrosis; Hypertremia; Hypoaluminemia; Hypocalcemia; Hypomagnesemia; Hyponatremia; Hypotension; Hypoxia; Insomnia; Left ventricular systolic dysfunction; Lethargy; Lymph gland infection; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Myalgia; Non-cardiac chest pain; Pain in extremity; Palmar-plantar erythrodysesthesia syndrome; Paresthesia; Peripheral sensory neuropathy; Pharyngolaryngeal pain; Pleural effusion; Psychosis; Respiratory failure; Skin infection; Small intestinal obstruction; Syncope; Upper respiratory infection; Vascular disorders - Other (brainstem infarction); Vertigo

- Increase in Risk Attribution:
  - Changed to Less Likely from Reported But Undetermined: Febrile neutropenia

- Decrease in Risk Attribution:
  - Changed to Reported But Undetermined from Possible: Alopecia; Chills; Fever; Mucositis oral; Pruritus; Purpura

- Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:
  - Added: Constipation; Dysgeusia; Febrile neutropenia; Weight loss

Appendix I, Informed Consent: The risk profile was updated to reflect the CAEPR as follows:
• **Increase in Risk Attribution:**
  - **Changed to Less Likely from Reported But Undetermined:** Fever associated with dangerously low levels of a type of white blood cell (neutrophils)

• **Decrease in Risk Attribution:**
  - **Changed to Reported But Undetermined from Possible (i.e., removed from the Risk Profile):** Hair loss; Chills; Fever; Irritation or sores in the lining of the mouth; Itching; Area of bleeding within the skin causing a reddish purple discoloration

**Other Changes**

**Sections 3.1.11, 3.11.1, and 3.11.2:** These sections were removed and were incorporated into **Sections 3.1.4, 3.1.4.1, and 3.1.4.2** for clarity, and the timeline for the post-operative scan was changed from within 14 days prior to registration to within 28 days prior to registration for feasibility purposes. All sections were appropriately renumbered. Related changes were made to **Eligibility Checklist** questions 5 and 13 and to the MRI assessment row of **Appendix II.**

**Section 3.1.4.4:** “(or decreasing)” was added for clarity and accuracy.

**Section 10.3 and Appendix IV, FFPE Specimen Plug Kit Instructions:** The mailing address was updated for the RTOG Biospecimen Resource.

**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, Study Parameter Table:** A 24-48 hour timeframe was added for the history/physical assessment occurring every 28 days during treatment.
SUMMARY OF CHANGES
Amendment 5: August 31, 2011
(Broadcast: September 8, 2011)

RTOG 0929, "A Randomized Phase I/II Study of ABT-888 In Combination With Temozolomide in Recurrent (Temozolomide Resistant) Glioblastoma"

Study Chair: H. Ian Robins MD, PhD; 608-263-1416; hirobins@wisc.edu

RTOG 0929 was amended as follows:

Appendix I/Sample Consent

Risks and side effects related to ABT-888: The additional ABT-888 risk information supplied by Abbott Laboratories was amended as follows:

Added under “possible” risks
- Decreased glucose (sugar) in the blood
- Infection of the urinary tract
- Pain or problems with movement caused by nerve damage
- Fast heartbeat
- Difficulty breathing
- Difficulty falling asleep and/or staying asleep
- Dry mouth
- Fluid in the area around the lungs (pleural effusion)
- Hot flush
- Problem with the gland that makes saliva
- Blockage of the small intestine
- Sinus infection
- Feeling sad
- Cough
- Bloody nose
- Increased potassium (a substance in the blood important for multiple body functions)

Modified under “possible” risks
- “Decreased blood electrolytes” changed to “Changes in blood electrolytes"
- “Increases in liver enzymes (substances produced by the liver used to measure liver function)” changed to “Increases in liver enzymes (ALT and AST: substances produced by the liver used to measure liver function) and alkaline phosphatase (an indicator of liver injury in the blood"
- “Swelling of the legs, feet or ankles” changed to “Swelling of the legs, hands, or other parts of the body because of fluid retention”

Deleted under “possible” risks
- Back pain

Modified under “ABT-888 and Temozolomide”
- Entire section was replaced with updated text

Risks and side effects related to temozolomide:

Deleted under “less likely”/last bullet
- “(if anti-nausea drugs are used),” because it was included in error
SUMMARY OF CHANGES
Amendment 1: October 6, 2010
(Broadcast: October 12, 2010)

RTOG 0929, "A Randomized Phase I/II Study of ABT-888 In Combination With Temozolomide in Recurrent (Temozolomide Resistant) Glioblastoma"

Study Chair: H. Ian Robins MD, PhD; 608-263-1416; hirobins@wisc.edu

RTOG 0929 was amended as follows:

Cover Page: The IND number for ABT-888 was added for clarity.

Section 2.1.1 and 13.2.1: "previously treated with temozolomide" was corrected to "previously treated or not treated with temozolomide."

Sections 7.3.2 and 7.3.3: At the request of CTEP, these sections were revised to add the availability of a new packaging size of ABT-888; in addition to the previously available containers of 16 capsules per bottle, capsules are now available in containers of 64 capsules per bottle.

Section 9.1.9: This section was added for provisions for Pneumocystis and herpes virus prophylaxis.

Section 10.4: Reimbursement information was updated to current RTOG standard.

The following sections were updated to current RTOG Biospecimen Resource standard:

- **Sections 10.2.1 and 10.6:** "skin punch" was changed to "punch tool," and reference to Appendix IV was added. (Section 10.2.1 numbering was also corrected from 10.21)
- **Appendix IV** was added

Section 12.1: The P2 was removed because it was included in error.
SUMMARY OF CHANGES
Amendment 2: January 26, 2011
(Broadcast: February 8, 2011)

RTOG 0929, “A Randomized Phase I/II Study of ABT-888 In Combination With Temozolomide in Recurrent (Temozolomide Resistant) Glioblastoma”

Study Chair: H. Ian Robins MD, PhD; 608-263-1416; hirobins@wisc.edu

In response to a CTEP Request for Rapid Amendment (RRA), RTOG 0929 was revised to reflect changes to the Comprehensive Adverse Events and Potential Risks List (CAEPR) for ABT-888. Changes were made to the following sections:

Section 7.3.1: ABT-888 CAEPR Version 1.4 (January 8, 2010) was replaced by CAEPR Version 1.4 (December 8, 2010). Specific changes are as follows:

- **Added New Risk:**
  - Possible: Abdominal pain; Alopecia; Chills; Constipation; Dysgeusia; Headache; Mucositis oral; Pruritus; Purpura
  - Also Reported on Veliparib Trials But With the Relationship to Veliparib Still Undetermined: Abdominal distension; Arthralgia; Dry skin; Dyspepsia; Dyspnea; Hyperglycemia; Hypokalemia; Hypophosphatemia; Pain; Thromboembolic event

- **Increase in Risk Attribution:**
  - Changed to Possible from Reported But Undetermined: Dizziness; Fever

- **Decrease in Risk Attribution:**
  - Changed to Reported But Undetermined from Possible: Febrile neutropenia

- **Modified Agent Specific Adverse Events List (ASAEL) Reporting Requirements:**
  - Added: Anorexia; Diarrhea; Headache

- **Provided Further Clarification:**
  - The following footnote has been added to thromboembolic event, “Thromboembolic events, including deep vein thrombosis and pulmonary embolism, have been observed at a higher frequency compared to control arm when administered in combination with temozolomide.”
  - Animal data has been deleted.

Appendix I, Informed Consent: The risk profile for ABT-888 was replaced with CTEP’s revised risk profile corresponding with the updated CAEPR. Specific risk changes are as follows:

- **Added New Risk:**
  - Possible: Area of bleeding within the skin causing a reddish purple discoloration; Belly pain; Chills; Constipation; Hair loss; Headache or head pain; Irritation or sores in the lining of the mouth; Itching; Taste changes

- **Increase in Risk Attribution:**
  - Changed to Possible from Reported But Undetermined: Dizziness (or sensation of lightheadedness, unsteadiness or giddiness); Fever

- **Decrease in Risk Attribution:**
• Changed to Reported But Undetermined from Possible (i.e., Removed From the Risk Profile): Fever associated with dangerously low levels of a type of white blood cell (neutrophils)
SUMMARY OF CHANGES
Amendment 3: April 14, 2011
(Broadcast: May 2, 2011)

RTOG 0929, "A Randomized Phase I/II Study of ABT-888 In Combination With Temozolomide in Recurrent (Temozolomide Resistant) Glioblastoma"

Study Chair: H. Ian Robins MD, PhD; 608-263-1416; hirobins@wisc.edu

RTOG 0929 was amended as follows:

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

Section 3.1.13: The sentence "Use of modalities not listed above to confirm disease progression are acceptable with approval of the study chair" was removed because it had been inserted in error.

Section 3.2.4.2: The baseline EKG requirement was removed because it was not deemed necessary for a study involving only ABT-888 and temozolomide. An EKG ordinarily would not be standard of care for such patients. All subsequent subsections were appropriately renumbered.

Sections 5.1.1, 5.1.2, and 7.3.3: The option was added to email regulatory documents to the CTSU.

Sections 7.2.2.1 and 7.2.2.2: The section numbering was corrected.

Sections 7.3.2 and 7.3.3: ABT-888 packaging, supply, and distribution information was updated.

Appendix I/Sample Consent/Risks and side effects related to ABT-888
- For clarity, the statement "To correspond with CTEP-issued cediranib CAEPR Version 2.10, January 13, 2011" was added above the "possible" risks
- A section was added to provide additional ABT-888 risk information supplied by Abbott Laboratories
SUMMARY OF CHANGES
Amendment 4: April 22, 2011
(Broadcast: May 2, 2011)

RTOG 0929, “A Randomized Phase I/II Study of ABT-888 In Combination With Temozolomide in Recurrent (Temozolomide Resistant) Glioblastoma”

Study Chair: H. Ian Robins MD, PhD; 608-263-1416; hirobins@wisc.edu

RTOG 0929 was amended as follows:

Cover Page: The email address for Meihua Wang was updated.

Sections 7.3.3: The tables added in Amendment 3 concerning bottle dispensation were updated.

Appendix I/Sample Consent/Risks and side effects related to ABT-888: The section added in Amendment 3 to provide additional ABT-888 risk information supplied by Abbott Laboratories was updated.
SUMMARY OF CHANGES
Updated: May 11, 2011
(Broadcast: May 11, 2011)

RTOG 0929, "A Randomized Phase I/II Study of ABT-888 In Combination With Temozolomide in Recurrent (Temozolomide Resistant) Glioblastoma"

Study Chair: H. Ian Robins MD, PhD; 608-263-1416; hirobins@wisc.edu

RTOG 0929 was updated as follows:

Appendix I/Sample Consent/Risks and side effects related to ABT-888: In the statement “To correspond with CTEP-issued cediranib CAEPR Version 2.10, January 13, 2011”, “cediranib” has been replaced with “veliparib” and the CAEPER Version number and date has been replaced with “Version 1.4, December 8, 2010”.

Note: This is a correction of a revision to the sample consent broadcast as part of Amendment #3 on May 2, 2011 (Version Date April 14, 2011). No other changes have been made to the protocol or sample consent.