For **Protocol** Update to: RTOG 1122, Phase II Double-Blinded Placebo-Controlled Study of Bevacizumab With or Without AMG 386 in Patients With Recurrent Glioblastoma or Gliosarcoma

NCI/Local Protocol #: RTOG 1122

NCI Protocol Version Date: February 26, 2013; Update Date: March 13, 2013 (Broadcast March 13, 2013)

Section	Change
Section 7.2.2	The cross-reference to Section 7.4.26 was corrected to 7.4.16.
Section 7.4.16	To avoid confusion: ▪ The 3rd sentence was greyed and indication of the Cohort 1 closure was added, as this text was applicable only to Cohort 1. ▪ The 3rd column of the table was greyed and indication that this information is not applicable to Cohort 2 was added.

For **Protocol** Amendment # 2 to: RTOG 1122, Phase II Double-Blinded Placebo-Controlled Study of Bevacizumab With or Without AMG 386 in Patients With Recurrent Glioblastoma or Gliosarcoma

NCI/Local Protocol #: RTOG 1122

NCI Protocol Version Date: February 26, 2013 (Broadcast March 13, 2013)

Section	Change
Cover pages	The document history table was updated to include Amendment 2. Minhee Won has replaced Meihua Wang as the statistician.
Eligibility Checklist q 46 and 3.2.13, last bullet	In response to a CTEP Request for Amendment, patients with a history of venous or arterial thromboembolism within 12 months prior to registration have been excluded. This change was made to make the protocol compliant with the current standard AMG 386 protocol template and is not related to new toxicities.
Eligibility Checklist q 7, 8, 13, 16	Spacing was corrected
Eligibility Checklist q 20	“for” was added
Schema, 7.2.1, 7.2.2., 7.9.1, 7.9.2, 11.3.1	The protocol was amended to reflect the closure of Cohort 1 and the opening of Cohort 2.
5.1.3	In the first sentence, “also” was added for clarity.

Section	Change

7.4.18	In response to a CTEP Request for Amendment, the CAEPR for AMG 386 (Version 2.2, November 16, 2012) was revised as follows:
	• <u>Added New Risk:</u>
	  • <u>Less Likely:</u> Blurred vision
	  • <u>Also Reported on Trebananib Trials But With the Relationship to Trebananib Still Undetermined:</u> Abdominal distension; Alopecia; Anemia; Arthralgia; Back pain; Chills; Constipation; Cough; Dehydration; Dizziness; Dry skin; Dysgeusia; Dysphasia; Dyspnea; Epistaxis; Eye disorders – Other (eye edema); Fever; Flatulence; Flushing; Gastrointestinal obstruction; Generalized muscle weakness; Headache; Hypertension; Hypomagnesemia; Hypophosphatemia; Hypotension; Insomnia; Mucositis oral; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Myalgia; Nail discoloration; Nail loss; Non-cardiac chest pain; Palmar-plantar erythrodysesthesia syndrome; Platelet count decreased; Pruritus; Rash acneiform; Rash maculo-papular; Respiratory, thoracic and mediastinal disorders - Other (runny nose); Sepsis; Watering eyes; Weight gain; Weight loss; White blood cell decreased
	• <u>Provided Further Clarification:</u>
	  • The following footnote was added to Gastrointestinal obstruction, "Gastrointestinal obstruction may include: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Obstruction gastric, Rectal obstruction, or Small intestinal obstruction and other sites under the GASTROINTESTINAL DISORDERS SOC."

7.6.2	"l" was corrected to "L" for consistency
7.8	In the last paragraph, contact information was updated.
7.8.2	Per current RTOG standard, "including a male patient's impregnation of his partner" was added after "any pregnancy." The last sentence was deleted because it is no longer accurate.
7.8.3	Per current RTOG standard, information on secondary and second malignancy was added.
7.9.1, 7.9.2	The "NOTE" in the AE reporting tables was deleted because it is no longer accurate.
10.6.3	"Whole blood" was added before DNA for clarity.
10.6.4, Appendix IV	"Campus Box" was updated to "UCSF Box"

For **Protocol Consent** Amendment #2 to: RTOG 1122, Phase II Double-Blinded Placebo-Controlled Study of Bevacizumab With or Without AMG 386 in Patients With Recurrent Glioblastoma or Gliosarcoma

NCI/Local Protocol #: RTOG 1122

NCI Protocol Version Date: February 26, 2013 (March 13, 2013)

Section	Change
Front page	A version date was added.
Risks and side effects related to the AMG 386	The risk profile for AMG 386 was amended to be consistent with the revised CAEPR as follows: • Added New Risk: • Less Likely: Blurred vision Per CTEP, although there is modified risk information for AMG 386, the added risk is extremely similar to risks that were already included in the previous version of the CAEPR and would have been communicated to patients in the informed consent document (ICD). In this case, blurred vision is more specific information associated with the previously identified eye disorder, retinal vascular thrombosis, which may result in permanent impairment of vision. When changes such as these are made to the ICD (i.e., changes as to how risk information is presented and/or additional clarifying information), it is not necessary to suspend enrollment of new subjects until a revised ICD is reviewed and approved by the IRB. For this requested amendment, patient enrollment may continue before the IRB reviews and approves such changes to the informed consent; however, changes to the ICDs cannot be implemented until they are approved by the IRB. PLEASE NOTE: The potential risks listed in the CAEPR whose relationship to AMG-386 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.
How many people will take part in the study? What will happen if I take part in this research study? During the study Study Plan About Using Tissue and Blood for Research	The consent was amended to reflect the closure of Cohort 1 and the opening of Cohort 2.

For **Protocol** Amendment #1 to: RTOG 1122, Phase II Double-Blinded Placebo-Controlled Study of Bevacizumab with or without AMG 386 in Patients With Recurrent Glioblastoma or Gliosarcoma

NCI/Local Protocol #: RTOG 1122

NCI Protocol Version Date: October 25, 2012 (Broadcast November 8, 2012)

Section	Change
Global	To comply with CTEP's new formatting/document requirements, the protocol was reformatted and the sample consent was removed from the appendices. The appendices were appropriately renumbered. The informed consent continues to be available via MS Word on the protocol documents section of the main protocol page.
Cover pages	The document history table was updated to include Amendment 1. The participating sites list was updated to include Canadian sites.
Schema	For clarity, the ** footnote was expanded and was moved to under the Control Arm.
3.2.8	For accuracy, "No" was deleted before "prior."
5.0 5.1.3	Canadian institutions were added.
5.1.1-2	Regulatory Pre-Registration Requirements were adjusted to reflect enrollment via OPEN registration.
5.2	Registration logistics were amended for OPEN enrollment. All enrollment will now occur via OPEN.
7.3.4	For logistical purposes, the 4th sentence in the 2nd paragraph was added to provide a window of 3 days..
7.4.9	The agent preparation guidelines were revised at the request of CTEP and Amgen (manufacture of AMG 386) as follows: 1 hour time window from removal from the refrigerator until reconstitution of the drug was extended to 3 hours at room temperature; The dilution of the final IV solution in 50 mL and 100 mL NS was replaced with dilution to a final concentration of 1.2 mg/mL – 30 mg/mL; and Use of vial adaptors is permitted but site must use a 0.2 μm PES in-line filter during IV administration of AMG386.
7.4.16	The 2nd sentence was added to clarify that does is to be determined via the referenced table versus an exact weight calculation. For logistical purposes, the 4th to last sentence was added to provide a window of 3 days.
7.6.2	The guidelines concerning for Venous thromboembolic event Grade 3 or pulmonary embolism without vascular compromise or asymptomatic Grade 4 were corrected. For Hypertension Grade 1, "and" was corrected to "and/or". Hypertension Grade 2 was corrected to Hypertension Grade 2 or 3.
10.2.2	The paraffin block requirement was removed, as it is not mandatory for submission for central review. Subsequent sections were renumbered
10.2.3	P4 submission logistics was clarified.
10.3	It was clarified that tissue banking for future research is an option for all patients, not just those in Cohort 2. Archival tissue was clarified as consisting of slides and/or block. Reference to Section 10.6.3 was added.

Section	Change
10.4	"Cohort 1 or Cross-Over" was changed to "Cohort 1 and Cross-Over Patients" for clarity, and it was clarified that serum collection for PK analysis is mandatory for these patients. "Bevacizumab" was corrected to "open-label AMG 386 in combination with bevacizumab." Reference to Appendix V for kit requests from Covance was added.
10.5	"Cohort 1 or Cross-Over" was changed to "Cohort 1 and Cross-Over Patients" for clarity, and it was clarified that serum collection for antibody analysis is mandatory for these patients. Reference to Appendix V for kit requests from Covance was added.
10.6	It was clarified that blood banking for future research is an option for all patients, not just those in Cohort 2.
10.6.3	The first table was rewritten to incorporate changes made to Sections 10.2-10.6 as detailed above. The heading of the second table was rewritten for clarity.
Appendix I Appendix VIIA	For logistical purposes, a window of 3 days prior to drug administration was added to during treatment assessments. It was clarified that banking for future research is an option for all patients (Appendix I) and all cross-over patients (Appendix II).
Appendix V	Contact information for kit acquisition was updated.

For **Protocol Consent** Amendment #1 to: RTOG 1122, Phase II Double-Blinded Placebo-Controlled Study of Bevacizumab with or without AMG 386 in Patients With Recurrent Glioblastoma or Gliosarcoma

NCI/Local Protocol #: RTOG 1122

NCI Protocol Version Date: October 25, 2012 (Broadcast November 8, 2012)

Section	Change
Why is this study being done?	For clarity, the sentence "It is hoped that AMG 386 will kill tumor cells and that it may also block blood vessels that supply the tumor in your brain with nutrients and oxygen" was moved from the 2nd-to-last sentence of the 2nd paragraph to the last sentence of the 1st paragraph. For clarity, in the last sentence, "used" was changed to "evaluated."
Before you begin the study	In the 7th bullet, the first "CT" was corrected to "MRI"
During the study	In the last paragraph, AMG 486 was corrected to AMG 386.
About Using Tissue for Research	In the third paragraph, it was clarified that banking is an option for any patient, not just those on cohort 2.

SUMMARY OF CHANGES
Update: June 4, 2012
(Broadcast June 4, 2012)

RTOG 1122, Phase II Double-Blinded Placebo-Controlled Study of Bevacizumab With or Without AMG 386 in Patients With Recurrent Glioblastoma or Gliosarcoma

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RTOG 1122 was updated as follows:

For database needs, **Eligibility Checklist** questions 18 and 25 were re-worded.

Logistics for AMG 386 PK and antibody collection were clarified and corrected. Changes were made to the following places:

- **Section 2.2.7**: Plasma was corrected to serum, as outlined in Section 10.
- **Section 5.1.1**: A note was added referring sites to Appendix VI.
- **Sections 10.4 and 10.5**, 2nd sentences: Blood was corrected to serum.
- **Section 10.5**: Cycle 1 was added before Day 1.
- **Section 10.6.3**, table, Specimens for Pharmacokinetic Analysis and AMG 386 Antibodies section:
    - A page break was added to further differentiate from specimens to be submitted to the RTOG Biospecimen Resource.
    - Reference to Appendix VI and IRB approval were added.
    - Serum for antibody analysis row: Cycle 1 was added before Day 1.
- **Section 10.6.4**: Amgen was corrected to Covance.
- **Appendix I** (sample consent), During the Study, last paragraph:
    - 2nd sentence: "for these purposes" was deleted.
    - 1st bullet: Cycle 2 was corrected to Cycle 1; "and after" was deleted; "(AMG 386 and AMG 386 antibodies)" was deleted.
    - 2nd bullet: Day 1 was corrected to Day 1 and 8; "(AMG 386)" was deleted.
    - 3rd bullet: "(AMG 386 antibodies)" was deleted.
- **Appendix II**, Blood for AMG 386 antibodies row: Collection at Cycle 1, Day 1 was added for consistency with other sections of the protocol.
- **Appendix VI**: The entire appendix was revised to more clearly describe details for kit acquisition and specimen collection.

References: In-text references and corresponding citations were corrected as needed for accuracy and were styled per current RTOG standard.

Section 5.0: A statement was added that the protocol is open to US institutions only.

Section 7.4.9: The weblink was added for accessing the Online Agent Order Process (OAOP) and training manual.

Section 12.0: The location of the Specimen Transmittal Form on the RTOG website was corrected.