




**DATE:** June 1, 2010

**FROM:** Kevin Conlon, M.D., Investigational Drug Branch, CTEP, DCTD, NCI 

**SUBJECT:** Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# 1901777

**TO:** Investigators Using Bevacizumab (NSC 704865)

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies conducted under a U.S. IND to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. Please find attached a copy of an IND Safety Report recently submitted to the FDA for the CTEP-sponsored investigational agent bevacizumab.

The following must be completed by all investigators using bevacizumab under NCI INDs 7921 and 11460.

- Send a copy of the IND Safety Report to your Institutional Review Board (IRB) according to your local IRB's policies and procedures.
- File a copy of the IND Safety Report in your protocol file.

If your study is not covered under INDs 7921 and 11460 it is strongly recommended that you follow the instructions above.

Please note that for Cooperative Group studies, the Cooperative Group Operations Office will provide instructions for IRB submissions, any patient notifications, etc.

Based on CTEP's assessment of the current information in light of previous experience with bevacizumab, there does not appear to be a change in the risk-benefit ratio for bevacizumab studies; therefore, CTEP is not requiring a protocol amendment at this time.

Please continue to report events according to the adverse event reporting guidelines in your protocol(s).

The attached Adverse Events Assessment describes the adverse event(s) (synopsis provided below), relevant previous experience under these INDs and/or NSC, and the total number of patients enrolled in trials under these INDs and/or NSC.

A 61-year-old male with squamous cell carcinoma of the lung experienced grade 4 cerebrovascular ischemia and died of significant hemoptysis while on a phase 3 trial utilizing the investigational agent bevacizumab in combination with cisplatin and docetaxel.

## ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 <b>Bevacizumab</b> <b>(rhuMAb VEGF)</b> AE: 1901777	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: <b>Gr. 5: Hemorrhage: Lung</b> <b>Gr. 4 CNS cerebrovascular ischemia</b> Protocol: <b>E1505</b>
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The patient was a 61-year-old male with squamous cell carcinoma of the lung who experienced cerebrovascular ischemia and died of significant hemoptysis while on a phase 3 study using the investigational agent bevacizumab/placebo in combination with docetaxel and cisplatin. He began his first course of treatment on December 2, 2009, receiving bevacizumab 15 mg/kg IV over 30-90 minutes on Day 1, docetaxel 75 mg/m<sup>2</sup>/day IV over 60 minutes on Day 1, and cisplatin 75 mg/m<sup>2</sup> IV over 60 minutes on Day 1. After 4 cycles, the patient was to receive bevacizumab 15 mg/kg IV over 30-90 minutes on Day 1 every 3 weeks, for up to 1 year. The patient received his last doses of bevacizumab, docetaxel, and cisplatin on December 2, 2009 (Cycle 1, Day 1).

The patient was diagnosed with non-small cell lung cancer in August 2009 and was status post right upper and middle lobectomy. He began the investigational therapy on December 2, 2009.

On December 18, 2009 (Cycle 1, Day 17), the patient presented to the ER after experiencing hemoptysis, 0.5 to 1 cup of bright red blood, which occurred without associated prior symptoms. He expelled a total of 300 mL of blood both outside and within the hospital. The patient stated that he had had a fever of 102°F a week ago and was placed on Levaquin®. He denied chest pain, and his baseline shortness of breath had not worsened. On examination, he was not in respiratory distress, his BP was 142/80 mmHg, his temperature was 97.9° F, his pulse rate was 95 beats/minute and respiratory rate was 18 breaths/minute. Auscultation of his lungs revealed few coarse crackles but otherwise good air movement, other systems were unremarkable. Laboratory values were within normal limits.

The patient had been previously hospitalized for right lower lobar pneumonia from October 7-19, 2009. A CT scan of the chest done on October 7, 2009, showed a thick-walled cavitory lesion in the right apex, the same sight as a previous infiltrate seen on CT scan 2 weeks prior to that. A bronchoscopy was also carried out to evaluate the right lung cavity at that time, and it showed a normal right lower lobe with no signs of purulent secretions or blood; transbronchial biopsy revealed a high number of inflammatory cells but was negative for malignancy. The patient presented to the hospital on December 17, 2009, complaining of large volume hemoptysis prompting a CT scan which showed no pulmonary embolism, an unchanged cavitory lesion with no evident bronchiolar communication, and a mild right-sided pleural effusion. Since the cause of his bleeding had not been defined with the CT scan and his hemoptysis progressed to frank pulmonary hemorrhaging, the patient underwent a bronchoscopy. At bronchoscopy, no bleeding was observed from his bronchial stump, from the previously noted cavitory lesion, or any single source. During the procedure, the patient suffered a cardiac arrest and was resuscitated after significant effort. The continued bleeding was not considered a complication of the bronchoscopy. Because the source of his pulmonary hemorrhage had not been identified, the patient had a pulmonary angiogram which also did not identify the cause of his pulmonary hemorrhage. He eventually required a bronchial artery embolization to eventually halt his bleeding. Post these procedures, the patient remained intubated and required mechanical ventilation for respiratory support. Later, the patient was noted to exhibit jerking movements of his upper extremities that had not been noted the day prior to these events when he exhibited upper extremity weakness. A consulting neurologist felt the patient had suffered significant anoxic insult during his cardiac arrest, but also may have suffered a thrombotic stroke in proximity to all these adverse events. CT scan of the head without contrast showed no acute intracranial hemorrhage or mass effect; there was no acute infarct seen. An EEG was done on December 22, 2009

(Cycle 1, Day 21), which confirmed anoxic encephalopathy. He was removed from the study. An MRI was recommended but was not done. He was discharged to the hospice on December 31, 2009, and later died on January 6, 2010.

The patient's past medical and surgical history was significant for coronary heart disease, hypertension, anemia, and hyperlipidemia. Medications taken at the time of the event consisted of fish oil, aspirin, ibuprofen, glucosamine, melatonin, Zocor®, Toprol XL® and vitamin D.


Both pulmonary hemorrhage and cerebrovascular ischemia are expected adverse events for bevacizumab.

There have been 26,872 patients enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC.

In this case, a probable causal relationship between bevacizumab and pulmonary hemorrhage exists.

	<b>Pulmonary hemorrhage</b>	<b>Cerebrovascular ischemia</b>
<b>Bevacizumab</b>	Definite	Definite
<b>Cisplatin</b>	Unrelated	Unrelated
<b>Docetaxel</b>	Unrelated	Unrelated
<b>Squamous cell lung cancer</b>	Unrelated	Unrelated
<b>Aspirin</b>	Possible	Possible

Date: 2 June 2010

Signature:   
Kevin Conlon, M.D.  
(IDB Monitor for bevacizumab)

If this assessment is changed, we will notify your office.

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Genentech, Inc.