



MAY 24 2011

**DATE:**

**FROM:** Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI 

**SUBJECT:** Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# 1761191

**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 this letter to your Institutional Review Board (IRB) of record according to your 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 60-year-old male with glioblastoma multiforme experienced colitis and respiratory failure and subsequently expired while on a phase 3 trial utilizing the investigational agent bevacizumab/ placebo in combination with temozolomide and radiation therapy.

## ADVERSE EVENTS ASSESSMENT

IND 7921	ADVERSE EXPERIENCE REPORT NO.
NSC 704865	IND Safety Report: # 1
Bevacizumab (rhuMAb VEGF)	Event: Gr. 5: Respiratory failure Gr. 3: Colitis
AE: 1761191	Protocol: RTOG-0825

The patient was a 60-year-old male with glioblastoma multiforme who experienced colitis and respiratory failure and subsequently expired while on a phase 3 trial utilizing the investigational agent bevacizumab/placebo in combination with temozolomide and radiation. He began his first course of treatment on December 27, 2010, receiving bevacizumab/placebo 10 mg/kg of actual body weight IV over 30-90 minutes on Day 1 of Weeks 4 and 6, radiation therapy 60 Gy over 6 weeks (delivered in 2 Gy fractions on Days 1-5 every week), and temozolomide 75 mg/m<sup>2</sup> PO daily (Concurrent treatment course = 6 weeks); bevacizumab/placebo 10 mg/kg of actual body weight IV over 30-90 minutes at beginning of week 2 (Cycle = 4 weeks); bevacizumab/placebo 10 mg/kg of actual body weight IV over 30-90 minutes on Days 1 and 15, and temozolomide 150-200 mg/m<sup>2</sup> PO on Days 1-5 for a maximum of 12 cycles (Cycle = 4 weeks). The patient received three doses of bevacizumab during Cycle 1 due to the delay of radiation treatment; and he received the last doses of bevacizumab/placebo and radiation therapy on February 15, 2011 (Cycle 1, Day 51), and the last dose of temozolomide on January 23, 2010 (Cycle 1, Day 28).

The patient was diagnosed with left parietal glioblastoma multiforme in October 2010, and was status post glioblastoma multiforme resection. He began the investigational therapy on December 27, 2010.

The patient was hospitalized and treated with antibiotics for the right upper lobe pneumonia from January 23-28, 2011. During the hospitalization, blood culture results were negative; respiratory system bacterial stain revealed 2+ Gram-positive cocci in pairs and in clusters, 2+ Gram-positive rods, and 1+ Gram-negative diplococci, but respiratory culture result showed normal respiratory flora. On January 26, 2011, a chest X-ray revealed partial or complete clearing of previous patchy infiltrative opacity in the right upper lung zone, no segmental or lobar collapse or consolidation, but a development of traces of bilateral pleural fluid at the posterior sulci. His condition improved and he was discharged on Levaquin<sup>®</sup>. On February 20, 2011 (Cycle 1, Day 56), the patient presented to the emergency room with new onset of severe abdominal pain and a 5-day-history of progressively worsening shortness of breath. His respiratory status deteriorated overnight; the arterial blood gas test showed evidence of respiratory failure with PO<sub>2</sub> of 68.1 mmHg (reference range: 80-100 mmHg) and PCO<sub>2</sub> of 27.4 mmHg (reference range: 35-45 mmHg). The patient was afebrile and his white blood cell count was normal, his blood pressure was 98/78 mmHg, his pulse rate was 126 beats/min, and his respiratory rate was 16 breaths/min. A chest CT scan revealed bilateral extensive perihilar airspace consolidations suggestive of multifocal pneumonia, moderately enlarged right pleural effusion, and compressive collapse of the right lower lobe, but no evidence of pulmonary thromboemboli. An abdominal CT scan showed wall thickening and edema involving the ascending colon, with pericolonic fat induration and free intraperitoneal fluid; the findings were compatible with segmental colitis. The patient also had significant tachycardia and confusion. He was started on broad-spectrum antibiotics for possible pneumonia. The laboratory tests revealed D-dimer of 1396 ng/mL (reference range: 0-257 ng/mL), BNP of 122 pg/mL (reference range: 1-100 pg/mL), troponin I of 0.08 ng/mL (reference range: 0-0.03 ng/mL), and myoglobin of 120 ng/mL (reference range: 0-69 ng/mL). The patient was diagnosed with acute hypoxemic respiratory failure, which was considered to be secondary to pneumonia, but congestive heart failure could not be excluded as a cause of the respiratory failure. The condition of the patient deteriorated, and he went into asystole; though he was intubated and resuscitated, the patient expired on February 21, 2011.

The patient's past medical/surgical history was significant for diabetes mellitus, hypertension,

pancytopenia, seizures, SIADH, and thrombocytopenia. Medications taken at the time of the events included Keppra®, Decadron®, clonazepam, Colace®, insulin, MiraLax®, and Pepcid®.

There have been 28 other cases of respiratory failure reported to NCI as a serious adverse event through AdEERS under the bevacizumab NSC and/or IND. Colitis is an expected event for bevacizumab.


Adverse Event	Grade	Attribution
Respiratory failure (n=28)	5	3 Unrelated, 5 Unlikely, 7 Possible
	4	5 Unrelated, 2 Unlikely, 3 Possible
	3	1 Unrelated, 2 Unlikely

There have been 32,525 patients enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC.

In this case, a possible relationship exists between the events and the investigational agent.

	Respiratory failure	Colitis
Bevacizumab /placebo	Possible	Possible
Temozolomide	Possible	Possible
Radiation	Possible	Unlikely
Glioblastoma multiforme	Unlikely	Unlikely

Date: 5/19/2011

Signature:   
 Helen Chen, M.D.  
 (IDB Monitor for bevacizumab)

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

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 Genentech, Inc.