



**DATE:** August 3, 2010  
**FROM:** Kevin Conlon, M.D., Investigational Drug Branch, CTEP, DCTD, NCI *Kevin Conlon*  
**SUBJECT:** Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# 1900497  
**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 66-year-old male with transitional cell carcinoma of the urothelial tract metastatic to the lungs expired while on a phase 3 trial utilizing the investigational agent bevacizumab/placebo in combination with cisplatin and gemcitabine.

## ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 <b>Bevacizumab (rhuMAb VEGF)</b> AE: 1900497	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: <b>Gr. 5: Death not associated with CTCAE term: Death NOS</b> Protocol: <b>CALGB-90601</b>
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The patient was a 66-year-old male with transitional cell carcinoma of the urothelial tract with metastases to the lungs who expired while on a phase 3 study utilizing the investigational agent bevacizumab/placebo in combination with cisplatin and gemcitabine. He began the first course of treatment on December 23, 2009, receiving bevacizumab/placebo 15 mg/kg IV over 30-90 minutes on Day 1, cisplatin 70 mg/m<sup>2</sup> IV over 1 hour on Day 1, and gemcitabine 1000 mg/m<sup>2</sup> IV over 30 minutes on Days 1 and 8, every 21 days for Cycles 1-6. Cycles 7+ would have included only bevacizumab/placebo 15 mg/kg IV over 30-90 minutes on Day 1. The patient received his last doses of bevacizumab/placebo and cisplatin on December 23, 2009 (Cycle 1, Day 1) and his last dose of gemcitabine on December 30, 2009 (Cycle 1, Day 8).

The patient was diagnosed with transitional cell carcinoma of the urothelial tract on October 2009 and was status post transurethral resection of the bladder tumor. He began the investigational therapy on December 23, 2009.

The patient was hospitalized on January 11, 2010 (Cycle 1, Day 20) for ischemic stroke, pulmonary emboli, and pleural effusion. He was treated with Lovenox<sup>®</sup>, and had a therapeutic thoracentesis done, which was positive for malignancy. He was removed from the protocol. By January 15, 2010, his condition had improved, and he was discharged home.

On January 25, 2010, he presented to the emergency room with a new-onset seizure-like activity and dyspnea on exertion (which began before the seizures). His physical examination was significant for speech difficulty, rhonchi in both lungs, and an oxygen saturation of 95% on room air. The CT scan of the head showed no intracranial hemorrhage or new infarcts. The CT scan of the chest showed multiple bilateral pulmonary emboli and progression of a large left pleural effusion. The chest X-ray showed worsening left pleural effusion with atelectasis and multiple nodules in the right lung. His white blood cell count was 32.4 K/ $\mu$ L (reference range: 4.5-11.0 K/ $\mu$ L), which raised the question of occult infection. However, the blood and urine cultures were negative. The possibilities of alcohol withdrawal, infection, brain metastasis, and cerebrovascular accident were considered. The patient was admitted, and started on 2 liters of oxygen, Keppra<sup>®</sup>, Ativan<sup>®</sup>, thiamine, folate, cefepime, Unasyn<sup>®</sup>, vancomycin, and later, fosphenytoin. Lovenox<sup>®</sup> was changed to a heparin drip.

On January 26, 2010, the neurologist recommended a 2-day telemetry electroencephalogram which revealed status epilepticus. On January 27, 2010, the follow-up chest X-ray showed a totally opacified left chest with concerns for mass effect and mediastinal shift to the right, compromising the aerated right lung. The thoracic surgery unit was consulted and a chest tube was inserted which drained a large amount of serosanguinous fluid.

On January 28, 2010, the patient's family decided that he should be transitioned to comfort care, and the chest tube was removed. Unfortunately, a chest X-ray performed after removal showed that his left pleural effusion had reaccumulated. On January 29, 2010, he was discharged home with hospice services in stable condition. In accordance with comfort care measures, anticoagulation was discontinued as were antibiotics. On February 4, 2010, the patient became restless and dyspneic. He was made comfortable with Haldol<sup>®</sup>, Roxanol<sup>®</sup>, and atropine, and he expired that day.

The patient's past medical and surgical history is significant for bladder carcinoma, CVA in 2006, hypertension, back surgery, 35 pack-year smoking history, and alcohol abuse (12 beers daily). Medications taken at the time of the event consisted of Colace®, Lopressor®, oxycodone, Compazine®, Lovenox®, dexamethasone, and aprepitant.

There have been 73 other cases of death NOS and 56 other cases of sudden death reported to the NCI as serious adverse events through AdEERS under the bevacizumab NSC and/or IND as summarized in the table below.


Adverse Event	Grade	Attribution
Death NOS (n=73)	5	23 Possible, 36 Unlikely, 14 Unrelated
Sudden Death (n=56)	5	3 Probable, 34 Possible, 13 Unlikely, 6 Unrelated

There have been 28,378 patients enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC.

In this case, a possible causal relationship exists between bevacizumab and the patient's death.

	Death NOS
<b>Bevacizumab/placebo</b>	Possible
<b>Cisplatin</b>	Possible
<b>Gemcitabine</b>	Possible
<b>Transitional cell carcinoma of the urothelial tract</b>	Possible
<b>Previously reported cerebrovascular ischemia</b>	Possible

Date: 3 August 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.