



DATE: January 2, 2009

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

SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE #1729567

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 IND 7921 or 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 this IND and/or NSC, and the total number of patients enrolled in trials under this IND and/or NSC.

A 41-year-old female with invasive breast carcinoma experienced **grade 4 pulmonary artery and right atrial thrombi** while on a double-blind phase 3 study utilizing the investigational agent bevacizumab/placebo in combination with paclitaxel, doxorubicin and cyclophosphamide.

ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 Bevacizumab (rhuMab VEGF)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Event: Gr. 4: Thrombosis (pulmonary arteries and right atrium)
AE: 1729567	Protocol: E5103

The patient is a 41-year-old female with invasive breast carcinoma who experienced pulmonary and right atrial thrombi while on a double-blind phase 3 study utilizing the investigational agent bevacizumab/placebo in combination with paclitaxel, doxorubicin and cyclophosphamide. She began the first course of treatment on June 9, 2008, receiving bevacizumab/placebo 10 mg/kg IV over 30-90 minutes on Day 1, doxorubicin 60 mg/m² IVP over 20-30 minutes on Day 1, and cyclophosphamide 600 mg/m² IV over 20-30 minutes on Day 1, filgrastim 5 mcg/kg SQ on Days 2-11 or pegfilgrastim 6 mg SQ on Day 2. After 4 cycles, she was to receive bevacizumab 15 mg/kg IV over 30-90 minutes on Day 1, and paclitaxel 80 mg/m² IV over 1 hour on Days 1, 8, and 15, very 21 days for Cycles 5-8. The patient received her last dose of bevacizumab/placebo on September 15, 2008 (Cycle 7, Day 1). She received her last doses of paclitaxel on September 8, 2008 (Cycle 6, Day 8), cyclophosphamide and doxorubicin on July 21, 2008 (Cycle 4, Day 1), and filgrastim on July 22, 2008, (Cycle 4, Day 2).

The patient was diagnosed with invasive mammary ductal carcinoma (T3, N1, M0) in April 2008 and is status post bilateral mastectomy and right axillary lymph node dissection. The patient received her first dose of investigational therapy on June 9, 2008. On September 8, 2008 (Cycle 6, Day 8), the patient's paclitaxel dose was reduced by 20% due to Grade 2 neuropathy.

On September 24, 2008 (Cycle 6, Day 10), the patient presented to the emergency room with shortness of breath, which was worse in the evening when lying down, as well as increasing lower extremity weakness, fatigue and confusion. She reported that these symptoms had been getting worse over the past 3 weeks. On the morning before admission, the patient apparently suffered a syncopal event after standing up in bathroom and feeling light-headed. Upon arrival to the ER, the patient's blood pressure was 128/82 mmHg. By the time she was transported to the cardiac intensive care unit, her blood pressure was 92/58 mmHg and respiration was 27. On examination, the patient was alert but confused, had distant heart sounds, an intact Port-A-Cath[®], negative peripheral edema but mild tenderness of her posterior calves bilaterally. The laboratory results were significant for a WBC of 17,700 K/ μ L (reference range: 4.5-11 K/ μ L), a myoglobin level of 239 ng/mL (reference range: 0-120 ng/mL), and a troponin level of 0.07 ng/mL (reference range: 0.00-0.04 ng/mL). A urine culture was drawn that was later positive for *Klebsiella pneumoniae*. A chest x-ray showed no acute process, and a CT chest angiogram revealed extensive pulmonary emboli involving the main pulmonary arteries through the arterial supply to all visualized lobes. In addition, an echocardiogram showed a mobile 5.3 \times 1.0 cm right atrial thrombus that was prolapsed through the tricuspid valve into the right ventricle (RV). The RV was moderately dilated and its free wall was hypokinetic. Her right ventricular systolic pressure was 62 mmHg, and she had severe pulmonary hypertension. Left ventricular function was unremarkable. A bilateral lower extremity Doppler ultrasound was negative for deep vein thrombosis. The patient was started on IV heparin, antibiotics, and IV hydration.

Due to the increased risk of mortality associated with it, surgical intervention for the atrial thrombus was bypassed, and thrombolytic therapy was implemented on September 24, 2008 to reduce the thrombus burden. While in the cardiac intensive care unit, the patient received 2 hours of t-PA which was followed by heparin then Coumadin[®]. The patient was unblinded, discovered to be receiving bevacizumab, and was removed from protocol on September 26, 2008. The patient's symptoms improved. A metastatic workup was negative. A subsequent echocardiogram was negative for atrial thrombus (it had presumably

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embolized).

On October 3, 2008, the patient was transferred to a rehabilitation unit to strengthen her mobility and self-care skills. Her labs showed a prothrombin time of 25.6 seconds, and her APTT was 61 seconds. She continued Coumadin[®] therapy and was placed on Lovenox[®] until October 8, 2008. The patient was discharged to home on October 11, 2008.

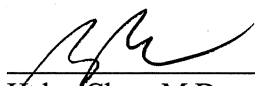
The patient's past medical and surgical history is significant for tobacco abuse of half a pack a day for 15 years, post-traumatic stress disorder (PTSD), migraines, irritable bowel syndrome, GERD, brain cyst, kidney stones, splenectomy, hysterectomy, 2 hernia repairs, tonsillectomy and adenoidectomy. Medications taken at the time of the event included Wellbutrin[®], Klonopin[®], Flexeril[®], Lexapro[®], Ativan[®], cyproheptadine, and morphine, Protonix[®], Zofran[®], Inderal[®], Seroquel[®], and Ambien[®].

Thrombosis/thrombus/embolism is known to be associated with chemotherapy combined with bevacizumab, however, the presentation in this case was unusually severe. There have been 18,356 patients enrolled in NCI-sponsored clinical trials under this NSC.

In this case, it is felt that a probable causal relationship exists between bevacizumab/paclitaxel and the thrombosis/thrombus/embolism.

Thrombosis/thrombus/embolism	
Bevacizumab	Possible
Cyclophosphamide	Unlikely
Doxorubicin	Unlikely
Filgrastim	Unlikely
Paclitaxel	Possible
Invasive breast carcinoma	Unlikely

Date: 1/2/09

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

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

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Genentech, Incorporated