



DATE: August 31, 2009

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

SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE # **1333814**

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 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 these INDs and/or NSC, and the total number of patients enrolled in trials under these INDs and/or NSC.

A 32-year-old female with invasive breast carcinoma developed grade 4 cardiopulmonary arrest, cause unknown, while on a double-blind phase 3 study utilizing the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, paclitaxel, and pegfilgrastim.

ADVERSE EVENTS ASSESSMENT

IND 7921	ADVERSE EXPERIENCE REPORT NO.
NSC 704865	IND Safety Report: # 1
Bevacizumab (rhuMAb VEGF)	Event: Gr. 4: Cardiopulmonary arrest, cause unknown (non-fatal)
AE: 1333814	Protocol: E5103

The patient is a 32-year-old female with invasive breast carcinoma who experienced cardiopulmonary arrest while on a double-blind phase 3 study utilizing the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, paclitaxel, and pegfilgrastim. She began her first course of treatment on April 3, 2009. She was to receive bevacizumab/placebo 10 mg/kg IV over 30-90 minutes on Day 1, doxorubicin 60 mg/m² IVP on Day 1, cyclophosphamide 600 mg/m² IV over 20-30 minutes on Day 1, and pegfilgrastim 6 mg SQ on Day 2, every 14 days on Cycles 1-4. On Cycles 5-8 she was to receive bevacizumab/placebo 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, every 21 days. She received her first and last dose of bevacizumab, cyclophosphamide, doxorubicin, and pegfilgrastim on April 3, 2009 (Cycle 1, Day 1). She never received paclitaxel.

The patient was diagnosed with biopsy proven right ductal invasive breast carcinoma in November 2008 and is status post axillary dissection and partial mastectomy. She began the investigational agent on April 3, 2009.

On April 17, 2009 (Cycle 1, Day 15), the patient presented to the clinic to start her second cycle of investigational therapy. She was to have taken Emend[®] as premedication for nausea, but there is some question as to whether this was taken. Following introduction of normal saline (50 ml/hr) into her venous port, the patient complained of feeling faint, leaned back in the chair, and at that point lost consciousness. There was a brief period of posturing/seizure activity. She was pulseless with the cardiac monitor/ECG showing asystole. The patient reportedly underwent life-saving efforts for seven to ten minutes and was resuscitated with CPR. She did not receive any medication during the code. Following her resuscitation, the cardiac monitor showed an atrial fibrillation with rapid ventricular heart rate in the 160s. It is noted that her ECG at 10:48 AM prior to the event revealed rapid atrial fibrillation at 156 bpm with diffuse ST depressions in the inferior and anterolateral leads. The patient also described a prior history of palpitations at the age of 20 for which she wore a Holter monitor which revealed no abnormalities despite many episodes of palpitations. The etiology of these prior events remained undetermined (it was thought possibly due to various medications); her symptoms were never treated and never associated with loss of consciousness. Within an hour of her cardiac arrest, the patient was transferred to the emergency department (ED) for further evaluation and treatment. When seen in the ER, the patient complained of chest pain, was alert and appropriate with vital signs as follows: pulse 102 bpm, respiration rate 20 breaths per minute, blood pressure 104/59 mmHg, and oxygen saturation 97% on room air. Her cardiac examination revealed normal rate, rhythm, heart sounds and distal pulses; lungs were unremarkable. The ED ECG at 11:45 AM revealed sinus tachycardia at a rate of 103 bpm. The patient could not recall any of her symptoms during the event. She was, however, alert and responsive prior to being admitted to the ICU for observation and additional cardiac testing.

A transthoracic echocardiogram performed that afternoon revealed normal left and right ventricular function and size with a left ventricular ejection fraction of 51%. There were no significant valvular abnormalities. CT scans of the head and pelvis and a CT angiogram of chest were unremarkable. There were no events recorded on telemetry overnight. A cardiac MRI performed on April 19, 2009, revealed no structural findings suggestive of right ventricular cardiomyopathy. There was no delayed enhancement indicative of myocardial scarring, chamber sizes were normal, left and right ventricular

systolic function was normal (LVEF 56%; RVEF 61%), and there was no gross valvular regurgitation. The electrophysiology (EP) cardiologist involved in her care determined that since the heart was structurally normal and no events were captured on telemetry, the benefit of performing an EP study was marginal. Her condition stabilized without further intervention, and she was discharged in good condition on April 20, 2009, with instructions to followed-up with the general cardiologist and the EP cardiologist in three to four weeks. She decided to receive her second cycle of chemotherapy and was to call for an appointment within the week.

The patient's past medical and surgical history is significant for renal calculus status post cystoscopy in May 2002, herpes, cesarean section in March 2007, breast augmentation in June 2007, and partial mastectomy in January 2009. Her family history is significant for lung cancer and pancreatic cancer, and her maternal grandmother had breast cancer. Medications taken at the time of the event include Emend[®], moxifloxacin, lidocaine-prilocaine topical cream, ondansetron, promethazine, a "de-tox pill", and Ambrotose[®] (multivitamin and anti-oxidant).

There have been 6 other cases of non-fatal cardiopulmonary arrest reported to the NCI through AdEERS as serious adverse events under the bevacizumab NSC and/or IND as shown in the table below.


Adverse Event	Grade	Attribution
Cardiopulmonary arrest, cause unknown (n=6)	4	3 Possible, 2 Unlikely, 1 Unrelated

There have been 22,983 patients enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC.

In this case, a causal relationship between the event and bevacizumab cannot be excluded.

	Cardiopulmonary arrest
<u>Bevacizumab (rhuMAb VEGF)</u>	Possible
<u>Cyclophosphamide</u>	Unrelated
<u>Doxorubicin hydrochloride</u>	Unrelated
<u>Pegfilgrastim (Neulasta)</u>	Unrelated
<u>Invasive breast carcinoma</u>	Unrelated
<u>Phena-S Liquid</u>	Possible

Date: 31 August 2009

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.