



DATE: June 4, 2009

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

SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# **1987521** *h. al. in*

TO: Investigators Using Bevacizumab (rhuMAb VEGF), 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 IND 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 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 this IND and/or NSC, and the total number of patients enrolled in trials under this IND and/or NSC.

The patient is a 49-year-old female with invasive breast carcinoma who developed a **grade 4 elevated cardiac troponin I, a grade 4 elevated CPK level, and grade 4 cardiac ischemia/infarction** 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 NSC 704865 Bevacizumab (rhuMAb VEGF)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Event: Gr. 4: Cardiac troponin I Gr. 4: Cardiac ischemia/infarction Gr. 4: CPK Protocol: E5103
AE: 1987521	

The patient is a 49-year-old female with invasive breast carcinoma who developed an elevated cardiac troponin I level, elevated creatine phosphokinase (CPK) level, and cardiac ischemia/infarction while on a double-blind phase 3 study utilizing the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, and paclitaxel. She began her first course of treatment on October 23, 2008, receiving 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 for Cycles 1-4. After 4 cycles, the patient received 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, every 21 days for Cycles 5-8. The patient received her last dose of bevacizumab/placebo on February 26, 2009 (Cycle 8, Day 1). She received her last doses of cyclophosphamide and doxorubicin on December 4, 2008 (Cycle 4, Day 1), pegfilgrastim on December 5, 2008 (Cycle 4, Day 2), and paclitaxel on March 5, 2009 (Cycle 8, Day 8).

The patient was diagnosed with invasive ductal carcinoma (T2, N0, M0; ER, PR positive; HER-2 negative) of the left breast on August 11, 2008, and is status post bilateral mastectomy. She began the investigational study on October 23, 2008.

On March 16, 2009 (Cycle 8, Day 19), the patient presented to the ER after being awakened by chest pain. Of note, the patient had previously been hospitalized from March 9 to March 13, 2008, for chest pains and left arm pains deemed secondary to breast cancer and left arm neuropathy. A MUGA scan on March 13, 2009, revealed an ejection fraction of 66.9% and a normal study. The patient now described her current chest pain as left-sided, radiating to the left shoulder, neck, throat, and left arm, with 10/10 intensity and duration of over 1 hour. The patient was given morphine and sublingual nitroglycerin. Patient continued to experience pain although now at a 6/10 intensity, as well as left hand tingling, dyspnea, and diaphoresis. Vital signs upon admission were as follows: blood pressure 136/72 mmHg, pulse 71, respiratory rate 20, and the patient was afebrile. She was in moderate distress secondary to pain, but her examination was unremarkable. Her CPK was 25 U/L (reference range 21-215 U/L), CPK-MB 25 ng/mL (reference range: 0.0-3.6 ng/mL), and troponin I 2.9 ng/mL (reference range: 0.0-0.1 ng/mL, >1.5 ng/mL indicative of myocardial infarction). Her urine drug screen tested positive for opiates and cannabinoids. An ECG showed sinus arrhythmia with ST-T depressions in the anterior leads. She was diagnosed with a non-Q-wave myocardial infarction and started on metoprolol, aspirin, nitroglycerin, and a heparin drip.

The patient was evaluated by a cardiologist who added Integrillin[®] to her regimen. A cardiac catheterization was performed that day which showed a 100% blockage in the mid right coronary artery (RCA), and a bare metal stent was placed resulting in 0% residual stenosis. The catheterization also revealed an ejection fraction of 45%, and mild diaphragmatic and posterobasal hypokinesis. Post-catheterization, the patient was placed on Plavix[®], and a statin drug was added to her medication regimen. On March 17, 2008, the patient's cardiac enzymes began to trend downward. Her cardiac enzymes reached a maximum of: troponin I 92.9 ng/mL, total CPK 1190 U/L, and CPK-MB 165.6 ng/mL. She also had an elevated AST of 184 U/L (reference range: 10-36 U/L) which decreased to 65 U/L the next day. On March 18, 2009 (Cycle 8, Day 21), the patient was treated for a potassium level of 3.2 mmol/L (reference range: 3.5-5.1 mmol/L) and subsequently discharged home.

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	3/9/09 C8, D12	3/16/09 C8, D19	3/17/09 C8, D20	3/18/09 C8, D21	3/19/09 C8, D22
Troponin I (reference range: 0.0-0.1 ng/mL; 0.1-1.5 ng/mL potential for myocardial damage; >1.5 ng/mL indicative of MI)	*	2.9 13.1 77.0	92.9 73.2	*	32
CPK (reference range: 21-215 U/L)	49	25 626 1190	980 514	176	3.91
CPK-MB (reference range: 0.0-3.6 ng/mL)	*	1.1 102.8 165.6	111.6 47.6	*	>300

*not provided

The patient's past medical and surgical history is significant for hypertension, peptic ulcer disease, failure to thrive as an adult, tobacco abuse, substance abuse, fibroids and hysterectomy. Her family history includes breast cancer (maternal aunt, cousin, and sister who died at age 58). Medications taken at the time of the event included hydrochlorothiazide, Toprol-XL[®], Ambien[®], Megace[®], Ativan[®], Compazine[®], Celexa[®], Percocet[®], gabapentin, Protonix[®], and magnesium oxide.

Cardiac troponin I and cardiac ischemia/infarction are known to be associated with bevacizumab. There have been 4 cases of CPK (grade 3: 1 unrelated, 1 unlikely and grade 4: 2 unrelated) previously reported to the NCI as serious adverse events through AdEERS under the bevacizumab NSC and/or IND.

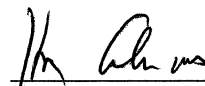
There have been 21,395 patients enrolled in NCI-sponsored clinical trials under this IND and/or NSC.

In this case, it is felt that a causal relationship between bevacizumab and the events could not be excluded.

	Cardiac troponin I	Cardiac ischemia/infarction	CPK
Bevacizumab	Possible	Possible	Possible
Cyclophosphamide	Unlikely	Unlikely	Unlikely
Doxorubicin	Possible	Possible	Unlikely
Paclitaxel	Unrelated	Unrelated	Unrelated
Pegfilgrastim	Unrelated	Unrelated	Unrelated
Invasive breast carcinoma	Unrelated	Unrelated	Unrelated
Hypertension	Possible	Possible	Possible

Date: 8 JUNE 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, Incorporated

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