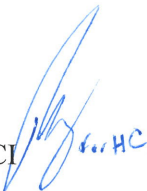




**DATE:** AUG 10 2011

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

**SUBJECT:** Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# **1268758**

**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 this letter 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 65-year-old female with invasive breast carcinoma experienced grade 4 cardiac arrest, grade 3 torsades de pointes, grade 3 sinus tachycardia, and grade 3 sinus bradycardia while on a phase 3 study using the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, filgrastim or pegfilgrastim, and paclitaxel.

## ADVERSE EVENTS ASSESSMENT

IND <b>7921</b> NSC <b>704865</b> <b>Bevacizumab</b> <b>(rhuMAb VEGF)</b>	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # <b>1</b> Event: <b>Gr. 4:   Cardiopulmonary arrest, cause unknown (non-fatal)</b> <b>Gr. 3:   Ventricular arrhythmia: Torsades de pointes</b> <b>Gr. 3:   Supraventricular and nodal arrhythmia: Sinus tachycardia</b> <b>Gr. 3:   Supraventricular and nodal arrhythmia: Sinus bradycardia</b>
AE: <b>1268758</b>	Protocol: <b>E5103</b>

The patient is a 65-year-old female with invasive breast carcinoma who experienced cardiac arrest, torsades de pointes, sinus tachycardia, and sinus bradycardia while on a phase 3 trial utilizing the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, filgrastim or pegfilgrastim, and paclitaxel. The planned protocol therapy the patient was assigned to is as follows:

Cycle = 14 days (Cycles 1-4)  
 Bevacizumab/Placebo: 10 mg/kg IV over 30-90 minutes on Day 1  
 Doxorubicin: 60 mg/m<sup>2</sup> IVP on Day 1  
 Cyclophosphamide: 600 mg/m<sup>2</sup> 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

Cycle = 21 days (Cycle 5-8)  
 Bevacizumab/Placebo: 15 mg/kg IV over 30-90 minutes on Day 1  
 Paclitaxel: 80 mg/m<sup>2</sup> IV over 1 hour on Days 1, 8, and 15

The patient was diagnosed with invasive breast carcinoma in December 2010, and is status post surgery. She began the investigational therapy on March 4, 2011, and received the last dose of bevacizumab/placebo on June 10, 2011 (Cycle 6, Day 1), the last doses of doxorubicin and cyclophosphamide on April 29, 2011 (Cycle 5, Day 1), the last dose of pegfilgrastim on April 30, 2011 (Cycle 5, Day 2), and the last dose of paclitaxel on June 17, 2011 (Cycle 6, Day 8).

On June 17, 2011 (Cycle 6, Day 8), the patient presented to the clinic for treatment, which was well tolerated. She had a blood pressure of 110/80 mmHg and a pulse of 60 bpm. She complained of ongoing neuropathy of her feet up to her knees, which she was treating with vitamins B6 and B12. On June 18, 2011, the patient complained of dizziness without chest pain or palpitations, and 15 minutes later, while sitting at a table at home, the patient became unresponsive. The EMS arrived, administered defibrillation once in field, and transported the patient to the ER. Upon arrival, an ECG revealed that she was in atrial fibrillation with a rate of 150 bpm with right bundle block branch, had agonal respirations, and remained unresponsive. Her vital signs in the ER were blood pressure 127/75 mmHg, pulse rate 88 bpm, and respiratory rate 20 breaths per minute. She was intubated, continued on IV therapy, and admitted to the CICU, where she was placed on a hypothermia protocol. The patient's ECG rhythm strips showed marked QT interval prolongation, sinus bradycardia, and pause-dependent torsades de pointes. The echocardiogram (ECHO) showed moderately reduced global systolic function of the left ventricle, appearing to show more severe hypokinesis of the base wall segments, while the right ventricle also showed moderately reduced global systolic function with mild dilatation, compared to an ECHO on May

5, 2011 (Cycle 5, Day 7), which revealed a normal left ventricular size and systolic function. Laboratory results revealed that her B-type natriuretic peptide level was 554 pg/mL (reference range: 0-100 pg/mL).

On June 19, 2011 (Cycle 6, Day 10), the patient's ECHO revealed mildly increased left ventricular wall thickness, severely reduced left ventricular ejection fraction (LVEF), estimated at 20-30%. There was also severely reduced global systolic function of the right ventricle, with mild dilatation. Laboratory analysis of her cardiac enzyme levels showed a creatinine kinase level of (CK) 247 U/L (reference range: 30-135 U/L), a CK-MB level of 6.6 ng/mL (reference range: 0.0-5.0 ng/mL), and a troponin level of 0.47 ng/mL (0.00-1.50 ng/mL). On June 20, 2011 (Cycle 6, Day 11), the patient completed the rewarming protocol.

On June 21, 2011 (Cycle 6, Day 12), the patient was extubated; her ECHO showed left ventricular dilatation, moderately reduced left ventricular EF estimated at 30-40%, and a hypokinetic inferior wall. She was emergently unblinded and was found to have received bevacizumab. On June 23, 2011, the patient underwent left heart catheterization. The left main coronary artery appeared normal, the left anterior descending (LAD) artery had a 50-70% lesion at its take-off, and the remainder of the vessel did not demonstrate significant obstruction. The circumflex appeared as a moderate-sized vessel without significant obstructive disease. The right coronary artery was dominant, giving off a PDA of posterolateral branches. A nonselective injection of the graft showed a very small atretic vessel which did not reach the heart. On July 1, 2011, the patient underwent insertion of an implantable cardioverter defibrillator (ICD) in her chest; she had a stable sinus rhythm. By July 5, 2011, the patient's condition had improved, and she was discharged to rehabilitation. She was to be re-evaluated for continued treatment with the investigational therapy.

The patient's past medical/surgical history is significant for hypertension, heart disease, coronary artery disease, hypercholesterolemia, hyperlipidemia, electrolyte imbalance, bypass surgery (2005) with left internal mammary artery (LIMA) to the LAD, and appendectomy. Medications taken at the time of the event included Toprol<sup>®</sup>, Lipitor<sup>®</sup>, Nexium<sup>®</sup>, lisinopril, folic acid, vitamins B6 and B12, and aspirin.

There have been 9 other cases of cardiopulmonary arrest, unknown cause (non-fatal) reported to the NCI through AdEERS as serious adverse events under the bevacizumab NSC and/or INDs as shown in the table below:

Adverse Event	Grade	Attribution
Cardiopulmonary arrest, cause unknown/non-fatal (n=9)	4	1 Unrelated, 4 Unlikely, 4 Possible

Cardiac arrhythmia is an expected event but is being reported because it is serious.

There have been 34,045 patients enrolled in NCI-sponsored clinical trials under the bevacizumab INDs and/or NSC.

In this case, a possible causal relationship between cardiac arrhythmia and bevacizumab cannot be excluded. LVEF dysfunction could be due to the acute arrhythmia or global cardiomyopathy.

	<b>Non-fatal Cardiac arrest</b>	<b>Torsades de pointes</b>	<b>Sinus tachycardia</b>	<b>Sinus bradycardia</b>
<b>Bevacizumab</b>	Possible	Possible	Possible	Possible
<b>Cyclophosphamide</b>	Unlikely	Unlikely	Unlikely	Unlikely
<b>Doxorubicin</b>	Possible	Possible	Possible	Possible
	Unlikely	Unlikely	Unlikely	Unlikely
<b>Paclitaxel</b>				
<b>Pegfilgrastim</b>	Unlikely	Unlikely	Unlikely	Unlikely
<b>Invasive breast carcinoma</b>	Unrelated	Unrelated	Unrelated	Unrelated
<b>History of bypass surgery for coronary artery disease in 2005</b>	Possible	Possible	Possible	Possible

Date: 08.09.2011

Signature: 

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

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

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