

IND SAFETY REPORT: INITIAL WRITTEN REPORT

TO: *Division of Biologic Oncology Products, Center for Drug Evaluation and Research, FDA*

FAX: 301-796-9849

1. IND NUMBER 7921	2. AGENT NAME Bevacizumab (rhuMab VEGF)	3. DATE July 8, 2011
4. SPONSOR Division of Cancer Treatment and Diagnosis, National Cancer Institute		
5. REPORTER'S NAME, TITLE, AND INSTITUTION Helen Chen, MD-Associate Branch Chief for Investigational Therapeutics 3, Investigational Drug Branch, CTEP, DCTD, NCI		6. PHONE NUMBER 301-496-1196
		7. FAX NUMBER 301-402-0428
8a. PROTOCOL NUMBER (AE #) E5103 (AE# 1268758)	8b. AE GRADE: AE Grade 4: Cardiac arrest	
9. PATIENT IDENTIFICATION 54983	10. AGE 65 years	11. SEX Female
12. DESCRIPTION OF ADVERSE EVENT <p>The patient is a 65-year-old female with invasive breast carcinoma who experienced grade 4 cardiac arrest while on a phase 3 trial utilizing the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, filgrastim or pegfilgrastim, and paclitaxel. She began her first course of treatment 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 18, 2011 (Cycle 6, Day 9), the patient became unresponsive while sitting at the table at home. The EMS staff arrived, administered defibrillation once in field, and transported the patient to the ER. Upon arrival, the patient was in afibrillation with 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 hypothermia protocol. The patient's ECG showed marked QT interval prolongation, sinus bradycardia, and pause-dependent torsades de pointe. 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. Laboratory results revealed 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 (EF) estimated at 20-30%, and severely reduced global systolic function of the left ventricle. There was also severely reduced global systolic function of right ventricle, with mild dilatation. Laboratory results showed his cardiac enzymes were creatinine kinase (CK) 247 U/L (reference range: 30-135 U/L), CK-MB of 6.6 ng/mL (reference range: 0.0-5.0 ng/mL), and 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, and was extubated. On June 21, 2011 (Cycle 6, Day 12), the patient's ECHO showed left ventricular dilatation, moderately reduced left ventricular EF estimated at 30-40%, and a hypokinetic inferior wall. The right ventricle was normal in size and function. The patient remains hospitalized for further evaluation. Of note, the patient has a past cardiac history; however, she was cleared by her cardiologist to initiate the study treatment. Additional information has been requested from the investigational site. There is a reasonable possibility that the experience may have been caused by the drug.</p>		
13. DOSE, ROUTE, AND SCHEDULE Cycle = 14 days (Cycles 1-4) Bevacizumab/Placebo: 10 mg/kg IV over 30-90 minutes on Day 1 Cycle = 21 days (Cycles 5-8) Bevacizumab/Placebo: 15 mg/kg IV over 30-90 minutes on Day 1		
14. DATES OF TREATMENT The patient 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).		
15. ACCRUAL AND IND EXPERIENCE Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 33,172. There have been 9 other cases of grade 4 cardiac arrest reported to the NCI through AdEERS as serious adverse events for bevacizumab.		
16. COMMENTS Also administered: Cycle = 14 days (Cycles 1-4): Doxorubicin: 60 mg/m ² IVP on Day 1; cyclophosphamide: 600 mg/m ² 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 (Cycles 5-8): Paclitaxel: 80 mg/m ² IV over 1 hour on Days 1, 8, and 15		
AT THIS TIME, NO OTHER INFORMATION IS AVAILABLE. IF UPON FURTHER INVESTIGATION RELEVANT INFORMATION BECOMES AVAILABLE, THEN A FOLLOW-UP REPORT WILL BE SUBMITTED IN ACCORDANCE WITH 21CFR 312.32(d) (2). DISCLAIMER per 21 CFR 312.32(e): THIS SAFETY REPORT DOES NOT NECESSARILY REFLECT A CONCLUSION OR ADMISSION BY THE CTEP IDB SENIOR INVESTIGATOR/SPONSOR THAT THE INVESTIGATIONAL AGENT/THERAPY CAUSED OR CONTRIBUTED TO THE ADVERSE EXPERIENCE BEING REPORTED.		