

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**
December 10, 2010**4. SPONSOR**
Division of Cancer Treatment and Diagnosis, National Cancer Institute**5. REPORTER'S NAME, TITLE, AND INSTITUTION**
Kevin Conlon, MD-Senior Investigator 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# 1383388)**8b. AE GRADE: AE**
Grade 5: Left ventricular systolic dysfunction**9. PATIENT IDENTIFICATION**
53973**10. AGE**
58 years**11. SEX**
Female**12. DESCRIPTION OF ADVERSE EVENT**

The patient was a 58-year-old female with invasive breast carcinoma who died from left ventricular (LV) systolic dysfunction while on a phase 3 trial utilizing the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, filgrastim/pegfilgrastim, and paclitaxel. She began her first course of treatment on May 26, 2010, and received the last dose of bevacizumab/placebo and paclitaxel on September 29, 2010 (Cycle 8, Day 1), the last and only dose of filgrastim on September 2, 2010 (Cycle 7, Day 16), the last doses of doxorubicin and cyclophosphamide on July 7, 2010 (Cycle 4, Day 1), and the last dose of pegfilgrastim on July 8, 2010 (Cycle 4, Day 2). On October 6, 2010 (Cycle 8, Day 8), the patient presented to the clinic with a severe headache of several days, blurred vision, dyspnea, decreased oral intake, weakness, and was walking with a cane. Her blood pressure was 160/110 mmHg and heart rate 139 bpm. Her investigational treatment was held, she was removed from the protocol, and she was sent to the ER and admitted. The patient was started on IV fluids and oxygen, and a head CT scan was negative. A pulmonologist reviewed the patient's chest X-ray and CT angiogram, which revealed small pleural effusions and mild congestive changes with no obvious pulmonary embolism. It was felt that the etiology of the dyspnea and small pleural effusions were mostly likely due to congestive heart failure. Monitoring of the patient's B-type Natriuretic Peptide (BNP) levels was recommended, and IV fluids were held. On October 9, 2010, the patient underwent an echocardiogram which revealed that the LV wall thickness and chamber were normal in size with severely depressed systolic function, and estimated LV ejection fraction was 10-15%. Moderate mitral regurgitation, mild tricuspid regurgitation, and mild pulmonary hypertension (estimated right ventricular systolic pressure: 46 mmHg) were also found. The patient's discharge date from her October hospitalization is currently unknown. November 12, 2010, the patient again presented to the ER with severe hypotension, lethargy, weakness, and was unresponsive. A cardiologist noted her blood pressure was 40 per Doppler and heard distant heart sounds. Her skin was mottled and her temperature was approximately 93°F; she was in shock. She was given IV fluids, oxygen, and started on Levophed®. The patient subsequently went into cardiac arrest and expired. Additional information has been requested from the investigational site. There is a reasonable possibility that the experience may have been caused by the drug.

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 May 26, 2010, and received last dose of bevacizumab on September 29, 2010 (Cycle 8, Day 1).

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 30,180. Left ventricular systolic dysfunction is an expected event for bevacizumab.

16. COMMENTS The following were also administered:

Cycle = 14 days (Cycles 1-4): Doxorubicin: 60 mg/m² IVP on Day 1, cyclophosphamide: 600 mg/m² IV over 20-30 minutes on Day 1, filgrastim: 5 mcg/kg SQ on Days 2-11, pegfilgrastim: 6 mg SQ on Day 2.
Cycle = 21 days (Cycles 5-8): Paclitaxel: 80 mg/m² 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.

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