

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
June 20, 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 #)
CALGB-40502 (AE# 1471652)

8b. AE GRADE: AE
Grade 5: Multi-organ failure

9. PATIENT IDENTIFICATION
120670

10. AGE
75 yrs

11. SEX
Female

12. DESCRIPTION OF ADVERSE EVENT

The patient was a 75-year-old female with metastatic invasive breast carcinoma who expired while on a phase 3 trial utilizing the investigational agent bevacizumab in combination with paclitaxel. She began the first course of the investigational therapy on May 11, 2010 and received the last dose of bevacizumab on April 12, 2011 (Cycle 13, Day 1) and the last dose of paclitaxel on April 19, 2011 (Cycle 13, Day 8). On April 26, 2011, the patient, who had metastases to the bone, subcutaneous tissue, chest wall, and contra lateral (left) breast, presented to the clinic for her Cycle 13, Day 15 therapy. Her treatment was held for signs of a right chest central line infection and blood cultures confirmed *Staphylococcus aureus*. She was admitted to the hospital the following day for a left pleural effusion, lower extremity edema, shortness of breath, and to rule-out sepsis. She was treated with antibiotics and discharged on May 4, 2011 in stable condition. On May 10, 2011, she was re-admitted to the hospital for increasing abdominal ascites. On May 11, 2011, an abdominal paracentesis yielded 4 liters of fluid and no malignant cells were found by cytology. The patient went into respiratory/cardiac arrest and was resuscitated. An abdominal ultrasound on that day revealed ascites, cirrhotic liver, and a prominent splenic vein. On May 12, 2011, an abdominal CT scan showed a large right lower quadrant hematoma, ascites, bilateral pleural effusions, and extensive bibasilar atelectasis. The patient's status was changed to comfort measures only and the patient expired later that day. The death certificate attributed the cause of death to shock and acute intra-abdominal hemorrhage. 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 = 28 Days
Bevacizumab: 10 mg/kg IV over 30-90 minutes on Days 1 and 15.**

14. DATES OF TREATMENT

The patient began the investigational therapy on May 11, 2010, and received the last dose of bevacizumab on April 12, 2011 (Cycle 13, Day 1).

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 33,125. There have been 14 other cases of multi-organ failure reported to the NCI as serious adverse events through AdEERS for bevacizumab.

16. COMMENTS **Also administered on this protocol: Paclitaxel: 90 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.**