

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 November 23, 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# 1852653)	8b. AE GRADE: AE Grade 5: Infection: Skin (cellulitis)	
9. PATIENT IDENTIFICATION 53651	10. AGE 44 years	11. SEX Female
12. DESCRIPTION OF ADVERSE EVENT The patient was a 44-year-old female with invasive breast carcinoma who expired from a skin infection while on a phase 3 trial utilizing the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, and paclitaxel. The patient had not received paclitaxel. She began her first course of treatment on March 16, 2010, and received the last doses of bevacizumab/placebo, doxorubicin and cyclophosphamide on June 9 (Cycle 4, Day 1). On June 15, 2010 (Cycle 4, Day 7), the patient presented to the clinic with a fever of 103.1°F and left groin pain. She had a tender small white head in the folds of her left groin, and her ANC was 0 (reference range: > 1500 cells/mm³). The patient was treated with vancomycin and IVF, and was sent to the hospital for urgent admission. A CT scan of the pelvis was suspicious for subcutaneous edema and emphysema without a clear abscess. She was found to have necrotizing fasciitis. She was started on clindamycin, daptomycin, and Azactam®. On June 18, 2010, the patient underwent wound debridement, which was well tolerated. On July 16, 2010, her blood cultures were positive for <i>Pseudomonas</i>. On July 19, 2010, the patient underwent another wound debridement, irrigation and skin grafting. The next day, she was removed from the protocol. On August 9, 2010, she went into septic shock in the ICU. The patient remained hemodynamically unstable despite increasing fluid and pressors. The following day, she went into asystole 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 = 21 days (Cycles 1-8) 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 16, 2010, and received last dose of bevacizumab/placebo on June 9, 2010 (Cycle 4, Day 1).		
15. ACCRUAL AND IND EXPERIENCE Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 30,180. Infections are known events for bevacizumab.		
16. COMMENTS The following were also administered: Cycles 1-4: Doxorubicin: 60 mg/m² IVP on Day 1, cyclophosphamide: 600 mg/m² IV over 20-30 minutes on Day 1 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.		