

**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  
**May 7, 2009**

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, CTEP, DCTD, NCI**6. PHONE NUMBER  
**301-496-1196**7. FAX NUMBER  
**301-402-0428**8. PROTOCOL NUMBER (AE #)  
**E5103 (AE # 1419144)**9. PATIENT IDENTIFICATION  
**51576**10. AGE  
**58**11. SEX  
**Female**

12. DESCRIPTION OF ADVERSE EVENT

The patient is a 58-year-old female with invasive breast carcinoma who developed a grade 4 pulmonary embolism and a grade 3 rectal infection while on a phase 3 study using the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, and paclitaxel. She began her first course of treatment on December 18, 2008, and received the last dose of bevacizumab/placebo on February 4, 2009 (Cycle 4, Day 1). Bevacizumab was held after this date due to decreased left ventricular ejection fraction and wound healing issues. On April 4, 2009 (Cycle 6, Day 11), the patient arrived to the emergency room with complaints of increased shortness of breath over the past few days. Upon arrival, her oxygen saturation was 87%. A CT scan of the chest showed an extensive bilateral pulmonary embolism as well as a saddle embolism. A venous duplex scan of the bilateral lower extremities showed evidence of a deep vein thrombus in the right superficial femoral and popliteal vein. The patient also complained of having pressure in the rectal area over the past 2-3 days. When examined, she was found to have a perirectal abscess with purulent drainage. The patient was admitted to the hospital and started on anticoagulant and antibiotic therapy. The patient remained hospitalized as of April 13, 2009 (Cycle 6, Day 20). Additional information has been requested. Due to bevacizumab's long half life, there is a reasonable possibility that the experience may have been caused by the drug.

13. DOSE, ROUTE, AND SCHEDULE

Bevacizumab/Placebo 10 mg/kg IV over 30-90 minutes on Day 1 (Cycles 1-4); Cycle = 14 days  
Bevacizumab/Placebo 15 mg/kg IV over 30-90 minutes on Day 1 (Cycles 5-8); Cycle = 21 days

14. DATES OF TREATMENT The patient started the investigational therapy on December 18, 2008, and received the last dose of bevacizumab/placebo on February 4, 2009 (Cycle 4, Day 7).

15. ACCRUAL AND IND EXPERIENCE Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 21331. These adverse events are known to be associated with the investigational agent, bevacizumab.

16. COMMENTS The following was also administered:

Cycles 1-4: doxorubicin: 60 mg/m<sup>2</sup> IVP on Day 1, cyclophosphamide: 600 mg/m<sup>2</sup> IV over 20-30 min on Day 1 (last administered on February 4, 2009 [Cycle 4, Day 1]), and filgrastim 5 mcg/kg SQ on days 2-11 OR pegfilgrastim: 6 mg SQ on Day 2 (pegfilgrastim last administered on February 5, 2009 [Cycle 4, Day 2]).  
Cycles 5-8: paclitaxel: 80 mg/m<sup>2</sup> IV over 1 hour on Days 1, 8, and 15; (last administered on April 1, 2009 [Cycle 6, Day 8]).

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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