

**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 1, 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 (1329128)**9. PATIENT IDENTIFICATION  
**51244**10. AGE  
**66**11. SEX  
**Female**

## 12. DESCRIPTION OF ADVERSE EVENT

The patient was a 66-year-old female with invasive breast cancer who developed grade 4 pneumonitis and subsequently expired from hemorrhage in the lungs while on a phase 3 study utilizing the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, and paclitaxel. She began her first course of the investigational therapy on October 27, 2008, and received the last dose of bevacizumab/placebo on December 22, 2008, (Cycle 5, Day 1). On January 2, 2009 (Cycle 5, Day 12), the patient presented to the emergency room complaining fever (101.8° F), dyspnea, and excessive sneezing with epistaxis when she blew her nose. A chest X-ray and CT scan of the chest showed changes suggestive of bilateral atypical pneumonitis, possibly a drug reaction. The patient was admitted to the hospital and started on oxygen and broad spectrum antibiotics. Her hemoglobin was 8.3 g/dL (reference range: 12.0-16.0 g/dL) and she received 2 units of PRBC. A repeat CT scan of the chest on January 12, 2009, showed a worsened appearance of the lungs with extensive widespread interstitial pulmonary edema superimposed on a background of pulmonary emphysema. The patient developed respiratory distress and was placed on mechanical ventilation from which she was unable to be weaned. On January 20, 2009, a lung biopsy revealed areas of bronchiolitis obliterans with organizing pneumonia and some areas of alveolar hemorrhage. Having been on the ventilator for more than 3 weeks, the family in accordance with the patient's living will decided on comfort care and withdrew the ventilator. The patient expired on February 14, 2009. No autopsy was performed. Additional information has been requested from the site. There is a reasonable possibility that the experience may have been caused by the drug.

13. DOSE, ROUTE, AND SCHEDULE **Cycles 1-4: Bevacizumab/Placebo 10 mg/kg IV over 30-90 minutes on Day 1 (Cycle=14 days); Cycles 5-8: Bevacizumab/Placebo 15 mg/kg IV over 30-90 minutes on Day 1 (Cycle = 21 days)**14. DATES OF TREATMENT **The patient started the investigational therapy on October 27, 2008, and received the last dose of bevacizumab/placebo on December 22, 2008 (Cycle 5, Day 1).**15. ACCRUAL AND IND EXPERIENCE **Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 20,524. There have been 7 other incidences of pulmonary hemorrhage in the lungs and 10 other incidences of pneumonitis reported to the NCI through AdEERS as serious adverse events for 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 December 8, 2008. Pegfilgrastim: 6 mg SQ on Day 2; Last administered on December 9, 2008. Cycles 5-8: Paclitaxel: 80 mg/m<sup>2</sup> IV over 1 hour on Days 1, 8, and 15; Last administered on December 29, 2008.****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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