

## 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 13, 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 #)  
E5103 (AE# 1727423)

8b. AE GRADE: AE  
Grade 4: Pneumonitis/pulmonary infiltrates  
Grade 4: Adult respiratory distress syndrome

9. PATIENT IDENTIFICATION  
54891

10. AGE  
59 years

11. SEX  
Female

12. DESCRIPTION OF ADVERSE EVENT  
The patient is a 59-year-old female with invasive breast carcinoma who experienced grade 4 pneumonitis/pulmonary infiltrates and grade 4 adult respiratory distress syndrome 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 February 3, 2011, and received the last dose of bevacizumab/placebo on February 17, 2011 (Cycle 2, Day 1), the last doses of doxorubicin and cyclophosphamide on March 17, 2011 (Cycle 4, Day 1), the last dose of pegfilgrastim on March 18, 2011 (Cycle 4, Day 2), and the last dose of paclitaxel on April 12, 2011 (Cycle 5, Day 8). On April 16, 2011, the patient's family members found her unarousable and with periods of apnea. She was intubated on the field as she was significantly hypoxic. Upon arrival to the emergency room she was not ventilating well, and required Ambu<sup>®</sup> bag ventilation with PEEP of 10-cm water by 2 respiratory therapists. A chest X-ray showed diffuse alveolar infiltrates with vascular congestion. The patient was hypotensive and was admitted to the intensive care unit. She was started on IV antibiotics. On April 19, 2011, the patient was critically ill. Her acute respiratory failure had no significant improvement in the ventilator settings. Adult respiratory distress syndrome was of unknown etiology. Blood and sputum cultures were negative, and she continued to receive broad spectrum antibiotics and was started on steroids and solumedrol 40 mg IV every 8 hours. 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 February 3, 2011, and received the last dose of bevacizumab/placebo on February 17, 2011 (Cycle 2, Day 1).

15. ACCRUAL AND IND EXPERIENCE  
Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 32,900. There have been 196 other cases of pneumonitis/pulmonary infiltrates and 19 other cases of adult respiratory distress syndrome reported to the NCI through AdEERS as serious adverse events for bevacizumab.

16. COMMENTS The following were also administered:  
Cycle = 14 days (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 minutes on Day 1, filgrastim: 5 mcg/kg SQ on Days 2-11, or pegfilgrastim: 6 mg SQ on Day 2.  
Cycle = 21 days (Cycles 5-8): Paclitaxel: 80 mg/m<sup>2</sup> 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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