

**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  
**July 7, 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  
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**301-402-0428**

8a. PROTOCOL NUMBER (AE #)  
**E1505 (AE# 1150431)**

8b. AE GRADE: AE  
**Grade 4: Hemorrhage, pulmonary/upper respiratory: Respiratory tract NOS**

9. PATIENT IDENTIFICATION  
**15866**

10. AGE  
**56 yrs**

11. SEX  
**Female**

12. DESCRIPTION OF ADVERSE EVENT

The patient is a 56-year-old female with non-small cell lung cancer who experienced grade 4 pulmonary hemorrhage while on a phase 3 trial utilizing the investigational agent bevacizumab in combination with gemcitabine and cisplatin. She began the first course of the investigational therapy on April 11, 2011, and received the last dose of bevacizumab on May 23, 2011 (Cycle 3, Day 1), the last dose of gemcitabine on June 20, 2011 (Cycle 4, Day 8), and the last dose cisplatin on June 13, 2011 (Cycle 4, Day 1). On June 13, 2011 (Cycle 4, Day 1), the patient presented to the clinic for the scheduled investigational treatment, and had a BP of 190/100 mmHg. Bevacizumab was held. On June 28, 2011 (Cycle 4, Day 16), the patient presented to the cardiologist office with complaints of dyspnea and associated diaphoresis which woke her up from sleep the previous night. She also reported fatigue and dyspnea on exertion in the past 5 days. Admission to the hospital was recommended. In the ER, the patient's oxygen saturation was 75% on room air, and she was placed on 4-6 liters of oxygen by nasal cannula. While in the ER, the patient had an episode of hemoptysis of about 25cc of bright red blood for which she was intubated, and admitted to the ICU. A chest X-ray showed bilateral patchy opacities which were concerning for aspiration, pneumonia, or hemorrhage. A CT scan of the chest revealed bilateral diffuse pulmonary hemorrhage. The patient's hemoglobin was 7.5 g/dL (reference range: 12-16 g/dL) as compared to a hemoglobin of 8.8 g/dL on June 20, 2011 (Cycle 4, Day 8), her platelet count was 16 K/mm<sup>3</sup> (reference range: 150-400 K/mm<sup>3</sup>), PT was 13.1 seconds (reference range: 11.0-12.5 seconds), PTT was 33 seconds (reference range: 60-70 seconds), and her INR was 1.01 (reference range: 1.5-2). She was transfused with 10 units of platelets and 2 units of packed red blood cells. The patient was started on vancomycin and Zosyn<sup>®</sup>. A gastric lavage later that day was negative for hematemesis. She remains hospitalized at this time. Of note, the patient has a history of hypertension, scleroderma, and Raynaud's phenomenon. 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 = 3 weeks

**Bevacizumab: 15 mg/kg IV over 30-90 minutes on Day 1 (Cycles 1-4);**

**Bevacizumab: 15 mg/kg IV over 30-90 minutes on Day 1 every 3 weeks, for up to 1 year (after 4 Cycles).**

14. DATES OF TREATMENT

**The patient began the investigational therapy on April 11, 2011, and received the last dose of bevacizumab on May 23, 2011 (Cycle 3, Day 1).**

15. ACCRUAL AND IND EXPERIENCE

**Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 33,172. Pulmonary hemorrhage is an expected adverse event for bevacizumab.**

16. COMMENTS Also administered on this protocol: Cycles 1-4

**Gemcitabine: 1200 mg/m<sup>2</sup>/day IV over 30 minutes on Days 1 and 8**

**Cisplatin: 75 mg/m<sup>2</sup> IV over 60 minutes on Day 1**

**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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