

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
June 30, 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# 1675188)

8b. AE GRADE: AE
Grade 3: Pneumonitis/pulmonary infiltrates

9. PATIENT IDENTIFICATION
54892

10. AGE
56 years

11. SEX
Female

12. DESCRIPTION OF ADVERSE EVENT

The patient is a 56-year-old female with invasive breast carcinoma who experienced grade 3 pneumonitis/pulmonary infiltrates while on a phase 3 trial utilizing the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, filgrastim or pegfilgrastim, and paclitaxel. She began her first course of treatment on February 3, 2011, and received the last dose of bevacizumab/placebo on May 12, 2011 (Cycle 7, 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 May 26, 2011 (Cycle 7, Day 15). On June 2, 2011, the patient presented to the clinic with a fever, neuropathy of her fingers and toes, a burning sensation in both feet when weight bearing, weakness, and fatigue. Her lung examination was negative. The study agents were held and urine culture/urinalysis was ordered. The patient was advised to go to the ER if her symptoms persisted. On June 5, 2011, the patient presented to the ER with a sore throat and a 3-day history of fever which had peaked at 102.9 °F, for which she had been treating with Tylenol®. Upon examination, her temperature was 101 °F, blood pressure was 124/76 mmHg, pulse rate was 137 bpm, and respiratory rate was 22 breaths per minute. Her oxygen saturation was 96% on room air. She was admitted to the hospital and started on IV fluids with IV antibiotics. On June 6, 2011, the patient's chest X-ray showed clear lungs without consolidation, mass, or infiltrate. There was no radiographic evidence for pneumonia or other acute cardiopulmonary disease. On June 7, 2011, a chest/thorax CT scan revealed diffuse increased interstitial markings more prominent in the upper lobes. There were diffuse areas of groundglass and frank opacity; small nodular densities were also present. A small right plural effusion was also present. These findings were most concerning for an infectious or inflammatory process. Pulmonary edema and hemorrhage were less likely, and a drug reaction was also considered. 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 May 12, 2011 (Cycle 7, 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 May 26, 2011 (Cycle 7, Day 15).

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 33,172. There have been 199 other cases of pneumonitis/pulmonary infiltrates reported to the NCI through AdEERS as serious adverse events for bevacizumab.

16. COMMENTS Also administered:

Cycle = 14 days (Cycles 1-4): Doxorubicin: 60 mg/m² IVP on Day 1; cyclophosphamide: 600 mg/m² 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/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.

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