

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
January 25, 2011

4. SPONSOR
Division of Cancer Treatment and Diagnosis, National Cancer Institute

5. REPORTER'S NAME, TITLE, AND INSTITUTION
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Investigational Drug Branch, CTEP, DCTD, NCI

6. PHONE NUMBER
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301-402-0428

8a. PROTOCOL NUMBER (AE #)
E5103 (AE# 1483749)

8b. AE GRADE: AE
Grade 4: Pneumonitis/pulmonary infiltrates

9. PATIENT IDENTIFICATION
54353

10. AGE
66 years

11. SEX
Female

12. DESCRIPTION OF ADVERSE EVENT

The patient is a 66-year-old female with invasive breast carcinoma who experienced pneumonitis/pulmonary infiltrates 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 August 18, 2010, and received the last dose of bevacizumab/placebo on December 3, 2010 (Cycle 6, Day 3), the last doses of doxorubicin, pegfilgrastim, and cyclophosphamide on October 20, 2010 (Cycle 4, Day 7), and the last dose of paclitaxel on December 8, 2010 (Cycle 6, Day 8). On December 14, 2010 (Cycle 6, Day 14), the patient presented to the emergency room with a 2-3 day history of shortness of breath, high temperature, dry cough, and sore throat and was admitted to the hospital. On December 14, 2010, a chest X-ray revealed interval development of vague bibasilar opacities which may represent developing pneumonia. On December 15, 2011, a chest CT scan revealed fibrotic changes of the upper lungs bilaterally, patchy areas of both groundglass and more consolidative opacities, which could represent multifocal pneumonia, cryptogenic organizing pneumonia, and/or sarcoidosis. Despite antibiotics, the patient worsened and was transferred to the intensive care unit (ICU) with acute respiratory failure which required intubation. The patient underwent a bronchoscopy and all cultures were negative. She was started on steroids, with quick improvement in her respiratory status, and she was extubated 2 days after starting the steroids. The patient had a slow recovery in the ICU, and then was transferred to the respiratory unit, where she required a few days on BiPAP, CPAP, and face mask oxygen. The patient developed bilateral pleural effusions while in the ICU. Bronchoscopy cytology showed some atypical cells suggestive of adenocarcinoma but ultimately, it was difficult to judge these cells in the setting of acute respiratory failure and intubation. The patient gradually improved, and she was discharged on January 6, 2011, to a rehabilitation facility. Additional information has been requested from the investigational site. The possible cause in this case is chemotherapy, but relatedness to bevacizumab cannot be excluded.

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 August 18, 2010, and received the last dose of pegfilgrastim on December 3, 2010 (Cycle 6, Day 3).

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 30,893. There have been 191 other cases of pneumonitis/pulmonary infiltrates 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/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.