

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 2, 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 #)
CALGB-40603 (AE # 1335267)

8b. AE GRADE: AE
**Grade 3: Nervous system disorder: Unresponsiveness
Grade 3: Nervous system disorder: T2 periventricular enhancement (small and scattered)**

9. PATIENT IDENTIFICATION
123633

10. AGE
74 yrs

11. SEX
Female

12. DESCRIPTION OF ADVERSE EVENT

The patient is a 74-year-old female with invasive breast cancer who experienced grade 3 unresponsiveness and grade 3 small and scattered T2 periventricular enhancement while on a phase 2 trial utilizing the investigational agent bevacizumab in combination with doxorubicin, cyclophosphamide, and paclitaxel. She began the first dose of the investigational therapy on December 8, 2010, and received the last dose of bevacizumab on March 16, 2011 (Week 15, Day 1), the last doses of doxorubicin and cyclophosphamide on March 31, 2011 (Week 17, Day 1), and the last dose of paclitaxel on February 23, 2011 (Week 11, Day 1). On February 2, 2011 (Week 9, Day 1), the patient presented for her scheduled investigational treatment and complained of confusion, fatigue, and numbness/burning of her hands and feet. A MRI of the brain showed multiple small scattered foci of T2 prolongation of the subcortical and periventricular white matter, which presumably were due to chronic microangiopathic white matter ischemic changes. Bevacizumab was held. She subsequently continued on the investigational therapy. On March 23, 2011 (Week 16, Day 1), the patient had a sudden onset of unresponsiveness and hypotension while being hospitalized for fatigue. A CT scan of the brain showed no acute process. Her blood pressure increased to 130/100 mmHg and her sensorium gradually returned to baseline. She was discharged on March 27, 2011. On March 31, 2011 (Week 17, Day 1), the patient, who was assessed earlier that day prior to a planned hospitalization for the investigational therapy, experienced depressed level of consciousness which lasted for 8-12 hours. Bevacizumab was again held. She recovered gradually with no residual sequelae, and was discharged on April 1, 2011. 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 = 19 weeks**

Bevacizumab: 10 mg/kg IV over 30-90 minutes on Day 1 of Weeks 1, 3, 5, 7, 9, 11, 13, 15, and 17

14. DATES OF TREATMENT **The patient began the investigational therapy on December 8, 2010, and received the last dose of bevacizumab on March 16, 2011 (Week 15, Day 1).**

15. ACCRUAL AND IND EXPERIENCE **Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 32,949. There have been no other cases of unresponsiveness, 1 other case of small and scattered T2 periventricular enhancement, and 23 other cases of depressed level of consciousness reported to the NCI as serious adverse events through AdEERS for bevacizumab.**

16. COMMENTS **The following was also administered:**

Doxorubicin: 60 mg/m² IV over 5-10 minutes on Day 1 of Weeks 13, 15, 17, and 19

Cyclophosphamide: 600 mg/m² IV over 5-30 minutes on Day 1 of Weeks 13, 15, 17, and 19

Paclitaxel: 80 mg/m² IV over 1 hour on Day 1 of Weeks 1-12

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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