

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
79212. AGENT NAME
Bevacizumab (rhuMab VEGF)3. DATE
May 8, 20094. SPONSOR
Division of Cancer Treatment and Diagnosis, National Cancer Institute5. REPORTER'S NAME, TITLE, AND INSTITUTION
Helen Chen, MD-Associate Branch Chief for Investigational Therapeutics 3, Investigational Drug Branch, CTEP, DCTD, NCI6. PHONE NUMBER
301-496-11967. FAX NUMBER
301-402-04288. PROTOCOL NUMBER (AE #)
E5103 (1833568)9. PATIENT IDENTIFICATION
5092210. AGE
6111. SEX
Female

12. DESCRIPTION OF ADVERSE EVENT

The patient is a 61-year-old female with invasive breast cancer who developed grade 3 leukoencephalopathy and seizure, and grade 2 elevated creatinine while on a phase 3 study utilizing the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, and paclitaxel. She began her first course of the investigational therapy on September 8, 2008, and received the last dose of bevacizumab/placebo on February 4, 2009, (Cycle 9, Day 1), the last doses of doxorubicin and cyclophosphamide on October 21, 2008 (Cycle 4, Day 1), the last dose of pegfilgrastim on October 22, 2008 (Cycle 4, Day 2), and the last dose of paclitaxel on January 27, 2009 (Cycle 8, Day 15). On February 18, 2009 (Cycle 9, Day 15), the patient presented to the emergency room (ER) with complaints of difficulty awakening in the morning, urinary incontinence, and drooling. While on the way to the ER, the patient was observed to have a tonic-clonic seizure. She was febrile with a blood pressure of 236/104 mmHg. The patient was started on empirical IV antibiotics, acyclovir, and Dilantin[®]. She was admitted to the hospital for seizures and change in mental status which was thought to be due to posterior reversible encephalopathy syndrome (PRES), likely related to bevacizumab and acute hypertension. A CT scan of the brain showed some low density change on the posterior right with questionable white matter changes. The MRI with and without contrast revealed extensive subcortical white matter abnormalities considered to be caused by PRES. The patient later developed elevated creatinine which was attributed to IV antibiotics administered during hospitalization. The patient's condition improved and she was discharged home on February 26, 2009. 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 Cycles 1-4, Cycle = 14 days: Bevacizumab/Placebo 10 mg/kg IV over 30-90 minutes on Day 1; Cycles 5-8, Cycle = 21 days: Bevacizumab/Placebo 15 mg/kg IV over 30-90 minutes on Day 1; Cycle 9-18, Cycle = 21 days: Bevacizumab/Placebo 15 mg/kg IV over 30-90 minutes on Day 1 with concurrent hormonal therapy

14. DATES OF TREATMENT The patient started the investigational therapy on September 8, 2008, and received the last dose of bevacizumab/placebo on February 4, 2009 (Cycle 9, Day 1).

15. ACCRUAL AND IND EXPERIENCE Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 21,331. There have been 5 other incidences of leukoencephalopathy, 46 other incidences of seizure, and 73 other incidences of creatinine reported to the NCI through AdEERS as serious adverse events for bevacizumab.

16. COMMENTS The following was also administered: Cycles 1-4: Doxorubicin: 60 mg/m² IV on Day 1, Cyclophosphamide: 600 mg/m² IV over 20-30 min on Day 1; Last administered on October 21, 2008 (Cycle 4, Day 1). Pegfilgrastim: 6 mg SQ on Day 2; Last administered on October 22, 2008 (Cycle 4, Day 2). Cycles 5-8: Paclitaxel: 80 mg/m² IV over 1 hour on Days 1, 8, and 15; Last administered on January 27, 2009 (Cycle 8, Day 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.**

0002