

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
January 2, 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, CTEP, DCTD, NCI6. PHONE NUMBER
301-496-11967. FAX NUMBER
301-402-04288. PROTOCOL NUMBER (AE #)
E5103 (AE # 1324148)9. PATIENT IDENTIFICATION
5027110. AGE
5911. SEX
Female

12. DESCRIPTION OF ADVERSE EVENT

The patient was a 59-year-old female with invasive breast cancer who developed somnolence and died suddenly while on a phase 3 study using the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, and paclitaxel. She began her first course of treatment on April 28, 2008, and received the last dose of bevacizumab/placebo on September 30, 2008, (Cycle 8, Day 1). On December 27, 2008, the patient developed severe leg pain and shortness of breath. She went to bed and when her son checked on her she was difficult to arouse and later became unresponsive. She was taken to the hospital via ambulance, where she was aroused and reported that she could not breathe. She was admitted to ICU and died at approximately 2:00 am on December 29, 2008. The patient's husband was told her death was due to heart failure. The patient had a history of Grade 4 LVSD during cycle 7 and was under the care of a cardiologist. No autopsy was performed. Additional information has been requested. There is a reasonable possibility that the experience may have been caused by the drug.

13. DOSE, ROUTE, AND SCHEDULE **Cycle = 21 days**
Bevacizumab/Placebo 15 mg/kg IV over 30-90 minutes on Day 114. DATES OF TREATMENT **The patient started the investigational therapy on April 28, 2008, and received the last dose of bevacizumab/placebo on September 30, 2008 (Cycle 8, Day 1).**15. ACCRUAL AND IND EXPERIENCE **Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 18,356. There have been 41 other incidences of somnolence/depressed level of consciousness and 43 other incidences of sudden death 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 IVP on Day 1, cyclophosphamide: 600 mg/m² IV over 20-30 min on Day 1; Last administered on June 30, 2008.****Cycles 5-8: paclitaxel: 80 mg/m² IV over 1 hour on Days 1, 8, and 15; Last administered on October 13, 2008.****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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