

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 December 1, 2009
4. SPONSOR Division of Cancer Treatment and Diagnosis, National Cancer Institute		
5. REPORTER'S NAME, TITLE, AND INSTITUTION Kevin Conlon, MD-Senior Investigator for Investigational Therapeutics 3, CTEP, DCTD, NCI		6. PHONE NUMBER 301-496-1196
		7. FAX NUMBER 301-402-0428
8. PROTOCOL NUMBER (AE #) E5103 (AE # 1206408)		
9. PATIENT IDENTIFICATION 52233	10. AGE 42	11. SEX Female
12. DESCRIPTION OF ADVERSE EVENT The patient is a 42-year-old female with invasive breast carcinoma who developed grade 4 confusion and grade 4 thrombosis/thrombus/embolism while on a phase 3 study using the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, filgrastim or pegfilgrastim and paclitaxel. She began her first course of treatment on March 31, 2009, and received the last dose of bevacizumab/placebo on July 31, 2009 (Cycle 8, Day 1). The last dose of other medications administered on this protocol is not available on the report. On August 23, 2009 (Cycle 8, Day 24), the patient was brought by her husband to the emergency department complaining of dyspnea, hypoxia and confusion. A CT scan of the lungs revealed extensive bilateral pulmonary emboli and bilateral lower lobe infarcts. A CT scan of the head did not show any obvious bleed or mass effect. On August 24, 2009, an MRI of the brain revealed multiple small acute infarcts suggesting the presence of emboli, the largest being in the left parietal periventricular region extending adjacent to the atrium of the left lateral ventricle. There was also involvement in both occipital lobes and right frontal region. An echocardiogram revealed a large right atrial and right ventricular thrombus partially extending into the inferior vena cava (IVC) with a patent foramen ovale. The patient was admitted to the intensive care unit and started on heparin and Coumadin®. An IVC filter was inserted and she was evaluated by the cardiologist who suggested keeping the patient on chronic anticoagulation therapy. On September 1, 2009, the patient was discharged. 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 Bevacizumab/Placebo 10 mg/kg IV over 30-90 minutes on Day 1 (Cycles 1-4); Cycle = 14 days Bevacizumab/Placebo 15 mg/kg IV over 30-90 minutes on Day 1 (Cycles 5-8); Cycle = 21 days		
14. DATES OF TREATMENT The patient started the investigational therapy on March 31, 2009, and received the last dose of bevacizumab/placebo on July 31, 2009 (Cycle 8, Day 1).		
15. ACCRUAL AND IND EXPERIENCE Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 23,774. There have been 118 other cases of confusion, reported to the NCI through ADEERS as serious adverse events for bevacizumab. The adverse event of thrombosis is known to be associated with the investigational agent, bevacizumab.		
16. COMMENTS The following are also included in the regimen: Cycles 1-4: doxorubicin: 60 mg/m² IVP on Day 1, cyclophosphamide: 600 mg/m² IV over 20-30 minutes on Day 1 and filgrastim 5 mcg/kg SQ on Days 2-11, or pegfilgrastim 6 mg SQ on Day 2. 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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