

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
March 26, 2009

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, CTEP, DCTD, NCI

6. PHONE NUMBER
301-496-1196

7. FAX NUMBER
301-402-0428

8. PROTOCOL NUMBER (AE #)
E5103 (AE # 1987521)

9. PATIENT IDENTIFICATION
51215

10. AGE
49

11. SEX
Female

12. DESCRIPTION OF ADVERSE EVENT

The patient is a 49-year-old female with invasive breast carcinoma who developed a grade 4 cardiac troponin I level and cardiac ischemia/infarction 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 October 23, 2008, and received the last dose of bevacizumab/placebo on February 26, 2009 (Cycle 8, Day 1). On March 16, 2009 (Cycle 8, Day 19), the patient presented to the ER after being awakened by left-sided radiating chest pain. An ECG showed ST depressions in the anterior leads. Cardiac enzyme results were abnormal. The highest cardiac enzyme levels reached were: troponin I level was 92.9 ng/mL (reference range: >1.5 ng/mL indicative of myocardial infarction), total CK was 1190 unit/L (reference range: 21-215 unit/L), and CPK-MB was 165.6 ng/mL (reference range 0.0-3.6 ng/mL). The patient was started on anticoagulant therapy and beta-blockers. A cardiac catheterization was performed which showed a total blockage in the right coronary artery and a stent was placed. The patient was discharged on March 18, 2009 (Cycle 8, Day 21). 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 10 mg/kg IV over 30-90 minutes on Day 1 (Cycles 1-4);
Bevacizumab/Placebo 15 mg/kg IV over 30-90 minutes on Day 1 (Cycles 5-8)

14. DATES OF TREATMENT **The patient started the investigational therapy on October 23, 2008, and received the last dose of bevacizumab/placebo on February 26, 2009 (Cycle 8, Day 1).**

15. ACCRUAL AND IND EXPERIENCE **Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 19819. There have been 21 other incidences of cardiac troponin I and 87 other incidences of cardiac ischemia/infarction 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
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.