

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 8, 2010
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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, Investigational Drug Branch, CTEP, DCTD, NCI	6. PHONE NUMBER 301-496-1196
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8. PROTOCOL NUMBER (AE #)
E5103 (AE # 1295253)

9. PATIENT IDENTIFICATION 53401	10. AGE 63	11. SEX Female
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12. DESCRIPTION OF ADVERSE EVENT
The patient was a 63-year-old female with invasive breast carcinoma who experienced grade 5 colitis while on a phase 3 trial utilizing the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, and pegfilgrastim. She began the first course of the investigational therapy on September 18, 2009, and received the last doses of bevacizumab/placebo, doxorubicin, cyclophosphamide on November 6, 2009 (Cycle 4, Day 1), and the last dose of pegfilgrastim on November 7, 2009 (Cycle 4, Day 2). On November 13, 2009 (Cycle 4, Day 8), the patient presented to the ER after sustaining a fall. She was severely dehydrated, and had a fever of 100.7°F. She had a WBC of $0.2 \times 10^9/L$ (reference range: $5.0-10.0 \times 10^9/L$), and an ANC of $0.0 \times 10^9/L$ (reference range: $2.0-9.0 \times 10^9/L$). She was admitted, pan-cultured, and started on Fortaz® and vancomycin. On November 14, 2009 (Cycle 4, Day 9), the stool culture was positive for *Clostridium difficile*, and the patient was started on IV Flagyl®, fluconazole, and acyclovir. On November 18, 2009 (Cycle 4, Day 13), she was placed on total parenteral nutrition. By November 20, 2009 (Cycle 4, Day 15), the patient's condition had deteriorated as she became restless and confused. On November 22, 2009 (Cycle 4, Day 17), the patient, who was DNR, was found unresponsive and died. It was felt that the event was a treatment-related death, that the patient had more going on than the *C. difficile* colitis, and that she suffered some type of irreversible bowel complication such as ischemia, necrosis or a typhlitis type of process. 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
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 began the investigational therapy on September 18, 2009, and received the last dose of bevacizumab/placebo on November 6, 2009 (Cycle 4, Day 1).

15. ACCRUAL AND IND EXPERIENCE Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 25,462. Colitis is a known event 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 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.