

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, 2010

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, Investigational Drug Branch, CTEP, DCTD, NCI

6. PHONE NUMBER
301-496-1196

7. FAX NUMBER
301-402-0428

8. PROTOCOL NUMBER (AE #)
E3204 (AE # 1544184)

9. PATIENT IDENTIFICATION
32040

10. AGE
61

11. SEX
Male

12. DESCRIPTION OF ADVERSE EVENT

The patient was a 61-year-old male with adenocarcinoma of the rectum who experienced grade 5 ileus, grade 4 small bowel obstruction, grade 4 hypothermia, grade 4 DIC, and grade 4 hyponatremia while on a phase 2 trial utilizing the investigational agent bevacizumab in combination with radiotherapy, capecitabine, and oxaliplatin. He began the first course of the investigational therapy on January 20, 2010, and received the last doses of bevacizumab and oxaliplatin on February 3, 2010 (Cycle 1, Day 15), and the last dose of capecitabine on February 17, 2010 (Cycle 1, Day 29). On February 17, 2010 (Cycle 1, Day 29), the patient presented to the clinic with complaints of nausea, vomiting, and diarrhea. His sodium was 125 mmol/L (reference range: 136-145 mmol/L). The investigational agent treatment was held, and he was given IV normal saline. He was instructed to follow-up at the clinic in two days, but did not show up for this appointment. He returned to the clinic on February 23, 2010 (Cycle 1, Day 35), with a sodium of 119 mmol/L, and he was sent to the ER. He was admitted, and started on IV fluids and Zofran[®]. On February 25, 2010, the patient developed abdominal distention with tympanitic sounds. An abdominal CT scan revealed small bowel obstruction, and a nasogastric tube was inserted. He also had the symptoms of anemia, thrombocytopenia, DIC, acidosis, and hypothermia. On February 27, 2010, he was transferred to the MICU, where his condition deteriorated, and he expired on February 28, 2010. 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 **Cycle = 5.5 weeks**

Bevacizumab: 5 mg/kg IV over 30-90 minutes every other week on Days 1, 15, 29 during radiotherapy.

14. DATES OF TREATMENT **The patient began the investigational therapy on January 20, 2010, and received the last dose of bevacizumab on February 3, 2010 (Cycle 1, Day 15).**

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 25,513. There have been 87 other cases of ileus, 122 other cases small bowel obstruction, no other cases of hypothermia, 6 other cases of DIC, and 164 other cases of hyponatremia reported to the NCI as serious adverse events through AdEERS for bevacizumab.

16. COMMENTS **The following was also administered:**

Cycle = 5.5 weeks

Radiotherapy: 50.4 Gy at 1.8 Gy per fraction 5 days per week × 5.5 weeks

Capecitabine: 825 mg/m² PO every 12 hours 5 days per week starting on Day -1 to radiotherapy

Oxaliplatin: 50 mg/m² IV over 2 hours every week on Days 1, 8, 15, 22, 29 during radiotherapy

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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