

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
September 16, 2010

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
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301-402-0428

8a. PROTOCOL NUMBER (AE #)
CALGB-90601 (AE # 1448848)

8b. AE GRADE: AE
Grade 4: Perforation, GI: Small bowel NOS

9. PATIENT IDENTIFICATION
118647

10. AGE
64 yrs

11. SEX
Male

12. DESCRIPTION OF ADVERSE EVENT

The patient was a 64-year-old male with transitional cell carcinoma of the urothelial tract who experienced grade 4 bowel perforation, and subsequently died while on a phase 3 trial utilizing the investigational agent bevacizumab/placebo in combination with cisplatin and gemcitabine. He began the first course of the investigational therapy on December 23, 2009, and received his last dose of bevacizumab/placebo on June 25, 2010 (Cycle 7, Day 2), and the last doses of cisplatin and gemcitabine on June 4, 2010 (Cycle 6, Day 2). On July 6, 2010 (Cycle 7, Day 13), the patient presented to the clinic with a series of complaints including constipation, intermittent lower abdominal pain, chronic back pain, and decreased urine output. The patient reported having a small bowel movement the previous night, which was his first bowel movement in a week. He also reported that for 3-4 days he had felt nauseous with a daily episode of non-bloody, non-bilious emesis. He appeared lethargic and unsteady. His vital signs were as follows: blood pressure 132/70, heart rate 70 bpm, respiratory rate 16 bpm, and temperature 98.2°F. His abdomen was soft, non-tender, and non-distended, with hypoactive bowel sounds. Laboratory results revealed that his white blood cell count was elevated at $38.2 \times 10^9/L$ (reference range: $3.7-9.7 \times 10^9/L$). The patient was given IV fluids and was admitted to the intensive care unit for acute kidney injury. On July 7, 2010 (Cycle 7, Day 14), the patient's blood cultures revealed gram negative rods, and he was started on antibiotics. On July 8, 2010 (Cycle 7, Day 15), his condition continued to deteriorate and palliative care was given. On July 9, 2010 (Cycle 7, Day 16), the patient expired. Autopsy report findings revealed acute serositis, peritonitis, and bowel perforation. The immediate cause of death was listed as acute renal failure and sepsis. Additional information has been requested from the site. 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 1 for Cycles 1-7+

14. DATES OF TREATMENT

The patient started the investigational therapy on December 23, 2009, and received the last dose of bevacizumab on June 25, 2010 (Cycle 7, Day 2).

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 28,700. Bowel perforation is an expected event for bevacizumab.

16. COMMENTS Also administered on this protocol:

Cisplatin 70 mg/m² IV over 1 hour on Day 1 and Gemcitabine 1000 mg/m² IV over 30 minutes on Days 1 and 8 for Cycles 1-6.

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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