

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 6, 2011

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
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301-402-0428

8a. PROTOCOL NUMBER (AE #)
GOG-0240 (AE# 1874144)

8b. AE GRADE: AE
Grade 5: Necrotizing fasciitis

9. PATIENT IDENTIFICATION
034-0240-009

10. AGE
56 yrs

11. SEX
Female

12. DESCRIPTION OF ADVERSE EVENT
The patient was a 56-year-old female with stage III cervical carcinoma who expired from necrotizing fasciitis while on a phase 3 trial utilizing the investigational agent bevacizumab in combination with paclitaxel and topotecan. She began the first course of the investigational therapy on June 14, 2011 and received the last doses of bevacizumab and paclitaxel on August 3, 2011 (Cycle 3, Day 1), and the last dose of topotecan on August 5, 2011 (Cycle 3, Day 3). The patient had a history of chronic right lower extremity lymphedema. On August 14, 2011 (Cycle 3, Day 12), the patient was found barely responsive on the floor and taken to the emergency room. She had a right lower extremity pain, which had gotten progressively worse over the last 24 hours. She was lethargic, hypotensive (blood pressure: 73/19 mmHg), and tachycardic (HR: 126 beats/min). A physical exam revealed severe swelling and ecchymoses of the right lower leg, which was exquisitely tender. Her femoral pulse was palpable, but her dorsalis pedis pulse and posterior tibial pulse were non-palpable and not detectable with Doppler. The patient was started on fluid resuscitation, empiric antibiotics, and norepinephrine for blood pressure support. The laboratory test showed a pH of 7.31 (reference range: 7.35-7.45), CPK of 2600 (reference range: 30-135 units/L), WBC count of 2.3 (reference range: 5-10 x 10⁹/L), ANC of 0.5 (reference range: 2.5-8 x 10⁹/L), BUN of 39 (reference range: 10-20 mg/dL), and creatinine of 3.0 (reference range: 0.5-1.1 mg/dL). A non-contrast CT scan of the tibia and fibula revealed extensive edema of the entire right lower extremity, but no focal fluid or gas collections. No evidence for deep venous thrombosis was found by right lower extremity ultrasound. The patient was transferred to the ICU for sepsis shock. Her condition progressively deteriorated and she died later that day. On August 15, 2011, blood cultures were positive for gram-positive cocci in pairs and chains. The leading diagnosis was necrotizing fasciitis. 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 = 21 days:
Bevacizumab: 15 mg/kg IV over 30-90 minutes on Day 1**

14. DATES OF TREATMENT
The patient began the investigational therapy on June 14, 2011, and received the last dose of bevacizumab on August 3, 2011 (Cycle 3, Day 1).

15. ACCRUAL AND IND EXPERIENCE
Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 34,327. There have been 8 other cases of necrotizing fasciitis reported to the NCI as serious adverse events through AdEERS for bevacizumab.

16. COMMENTS **Also administered on this protocol: Paclitaxel: 175 mg/m² IV over 3 hours on Day 1; Topotecan: 0.75 mg/m² IV over 30 min on Days 1-3**

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.