

**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  
**August 30, 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  
**301-496-1196**7. FAX NUMBER  
**301-402-0428**8a. PROTOCOL NUMBER (AE #)  
**E5103 (AE# 1645650)**8b. AE GRADE: AE  
**Grade 5: Infection: Bladder (urinary)**9. PATIENT IDENTIFICATION  
**53523**10. AGE  
**66 years**11. SEX  
**Female**

## 12. DESCRIPTION OF ADVERSE EVENT

The patient was a 66-year-old female with invasive breast cancer who died from a bladder infection while on a phase 3 trial utilizing the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, pegfilgrastim, and paclitaxel. She began her first course of treatment on February 4, 2010, and received the last dose of bevacizumab/placebo on June 17, 2010 (Cycle 8, Day 1), the last doses of doxorubicin and cyclophosphamide on March 25, 2010 (Cycle 4, Day 1), the last dose of pegfilgrastim on March 26, 2010 (Cycle 4, Day 2), and the last dose of paclitaxel on June 24, 2010 (Cycle 8, Day 8). On June 24, 2010 (Cycle 8, Day 8), the patient presented to the clinic for evaluation prior to investigational therapy with complaints of fatigue and urinary frequency, for which she had been on Ditropan<sup>®</sup>. She was lethargic, hypotensive with a BP of 58/40 mmHg, and hypoxic with an oxygen saturation of 89-90%, after receiving paclitaxel. The patient was started on oxygen and IV fluids. She was transferred to the ER, at which time she complained of shortness of breath, and her BP was 87/43 mmHg. The patient's urinalysis was indicative of a urinary tract infection. She was started on dopamine infusion, Maxipime<sup>®</sup>, and vancomycin. The patient was transferred to the ICU, and started on Levophed<sup>®</sup> and Levonox<sup>®</sup>. She was initially placed on BiPAP, but was later intubated, and placed on mechanical ventilation. The following day, she was started on Cubicin<sup>®</sup>, meropenem, and micafungin. On June 26, 2010 (Cycle 8, Day 10), the patient developed fever with a temperature of 101°F, was placed on Levaquin<sup>®</sup> and Zovirax<sup>®</sup>. Her urine culture was positive for *Klebsiella oxytoca*. On July 23, 2010, the patient was extubated, but required reintubation, and was later extubated, and placed on a BiPAP on July 23, 2010. On July 27, 2010, the patient was transferred to a rehabilitative hospital, where she had to be emergently intubated, and continued on antibiotics. On July 28, 2010, the patient went into ventricular tachycardia/ventricular fibrillation. Resuscitative measures were unsuccessful, and she expired that day. 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 = 14 days (Cycles 1-4)  
Bevacizumab/Placebo 10 mg/kg IV over 30-90 minutes on Day 1  
Cycle = 21 days (Cycles 5-8)  
Bevacizumab/Placebo 15 mg/kg IV over 30-90 minutes on Day 1

## 14. DATES OF TREATMENT

The patient began the investigational therapy on February 4, 2010, and received last dose of bevacizumab on June 17, 2010 (Cycle 8, Day 1).

## 15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab =28650. Infections are known events for bevacizumab.

## 16. COMMENTS The following were also administered:

Cycles 1-4: Doxorubicin: 60 mg/m<sup>2</sup> IVP on Day 1, cyclophosphamide: 600 mg/m<sup>2</sup> IV over 20-30 minutes on Day 1, pegfilgrastim: 6 mg on Day 2  
Cycles 5-8: Paclitaxel: 80 mg/m<sup>2</sup> 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.**