

**INITIAL IND SAFETY REPORT: INITIAL WRITEN 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  
**December 24, 2008**

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, CTEP, DCTD, NCI**

6. PHONE NUMBER  
**301-496-1196**

7. FAX NUMBER  
**301-402-0428**

8. PROTOCOL NUMBER (AE #)  
**CALGB-40503 (AE # 1881593)**

9. PATIENT IDENTIFICATION  
**113795**

10. AGE  
**62**

11. SEX  
**Female**

12. DESCRIPTION OF ADVERSE EVENT

The patient is a 62-year-old female with invasive breast carcinoma who experienced grade 4 hyperkalemia, grade 3 creatinine, and grade 3 renal failure while on a phase 3 study using the investigational agent bevacizumab in combination with letrozole. She began the first course of treatment on December 5, 2008, and received the only dose of bevicizumab on December 5, 2008 (Cycle 1, Day 1) and the last dose of letrozole on December 16, 2008 (Cycle 1, Day 12). On the evening of December 9, 2008 (Cycle 1, Day 5), the patient was brought to the emergency room by her daughter complaining of mental confusion, shortness of breath, hypoxia, extreme fatigue, and weakness. Upon examination, she was dehydrated, her blood pressure was 72/47 mmHg, oxygen saturation was 92%, proteinuria was 100 mg/dL (reference range 0 mg/dL), blood creatinine was 1.74 mg/dL (reference range 0.5-1.7 mg/dL) and potassium was 5.2 mmol/L (reference range 3.5-5.1 mmol/L). She was hydrated and started on vancomycin IV after blood cultures tested positive. A chest x-ray revealed bilateral pneumonia with or without CHF, and she was started on levofloxacin. She was admitted to the hospital and on December 11, 2008; her creatinine was 4.38 mg/dL, her potassium was 5.6 mmol/L, and her urine output was 10 mL/24 hr. It was thought that the patient was in acute renal failure related to volume depletion and hypotension. An MRI of the brain showed atrophy out of proportion for the patient's age and numerous per ventricular white matter lesions with increased signal, suggesting possible multiple sclerosis. On December 12, 2008, her creatinine was 4.38 mg/dL and potassium was 7.1 mmol/L, and hemodiaylsis was started. The patient showed some improvement. There were still no urine output and she still had difficulty in breathing with clear lung fields. On December 15, 2008, the patient was extremely dyspneic and was transferred to the ICU on Bipap. Chest x-rays showed pulmonary vascular congestion with increased prominence of plural effusion. Thoracentesis was performed and 1 L of fluid was removed. There was no sign of recovery of renal function but her breathing was improved. As of December 17, 2008, the patient was still in the ICU and her medical situation was unresolved. Her creatinine was 3.79 mg/dL and her BUN/creatinine ratio was 6.3 (reference range 7.0-25.0). Additional information has been requested from the investigative 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  
Endocrine therapy-Letrozole 2.5 mg or Tamoxifen 20mg PO QD

14. DATES OF TREATMENT

The patient received the first dose of bevacizumab/placebo on December 5, 2008.

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 18,356. There have 59 other incidences of creatinine, 17 other incidences of hyperkalemia and 44 other incidences of renal failure reported to the NCI through AdEERS as serious adverse events for bevacizumab.

16. COMMENTS

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.**