

**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 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 #)  
**RTOG-0825 (AE# 1226745)**8b. AE GRADE: AE  
**Grade 5: Encephalopathy  
Grade 3: Seizure**9. PATIENT IDENTIFICATION  
**420**10. AGE  
**47 yrs**11. SEX  
**Female**

## 12. DESCRIPTION OF ADVERSE EVENT

The patient was a 47-year-old female with glioblastoma multiforme who experienced grade 5 encephalopathy and a grade 3 seizure while on a phase 3 trial utilizing the investigational agent bevacizumab/placebo in combination with temozolomide and concurrent radiation therapy. She began the first course of the investigational therapy on June 2, 2010, and received her last dose of bevacizumab on July 27, 2010 (Cycle 2, Day 1), and the last doses of temozolomide and radiation on July 14, 2010 (Cycle 1, Day 42). On August 2, 2010 (Cycle 2, Day 7), the patient suffered a seizure at home. She was transported to the emergency room where she experienced another seizure associated with an altered mental status. The patient's sodium was 125 mEq/L (reference range: 136-145 mEq/L). She was started on IV hypertonic saline and Keppra<sup>®</sup>, which improved her mental status. The patient was later switched to oral sodium tablets and admitted to the IMCU with neuro-checks every 4 hours. She was treated with Decadron<sup>®</sup>, fluconazole, Zosyn<sup>®</sup>, and Lovenox<sup>®</sup>. On August 3, 2010 (Cycle 2, Day 8), an MRI of the brain showed a new small area of restricted diffusion in the right insular cortex without associated contrast enhancement or hemorrhage, which was thought to be representative of seizure-related changes versus an area of infarction. On August 7, 2010 (Cycle 2, Day 12), the findings of a CT scan of the head included a generalized lucent appearance to the right temporal lobe which appeared new as compared to the examination of August 3, 2010. Based on the recent MRI, an evolving acute infarct was of concern. A repeat MRI of the brain the next day showed significant interval increase in the area of parenchymal hyperintensity and restricted diffusion involving the right insular cortex, both medial temporal lobes, the cingulate gyri, and the left insular cortex, changes that were felt to be highly representative of encephalitis, especially herpes encephalitis. The patient was started on acyclovir. Her sodium improved to 134 mEq/L on August 10, 2010. She was later discharged to hospice where she died 2 days later. 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 = 6 weeks: Bevacizumab/placebo: 10 mg/kg of actual body weight IV over 30-90 minutes on Day 1 of Weeks 4 and 6; Cycle = 4 weeks: Bevacizumab/placebo: 10 mg/kg of actual body weight IV over 30-90 minutes at beginning of Week 2; and Cycle = 4 weeks (Max = 12 cycles): Bevacizumab/placebo: 10 mg/kg of actual body weight IV over 30-90 minutes on Days 1 and 15.

## 14. DATES OF TREATMENT

The patient began the investigational therapy on June 2, 2010, and received the last dose of bevacizumab/placebo on July 27, 2010 (Cycle 2, Day 1).

## 15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 28, 734. There have been 25 other cases of encephalopathy, 7 other cases of leukoencephalopathy, 23 other cases of reversible posterior leukoencephalopathy syndrome, and 80 other cases of seizure reported to the NCI as serious adverse events through AdEERS for bevacizumab.

16. COMMENTS The following was also administered: Cycle = 6 weeks: RT 60 Gy over 6 weeks (delivered in 2 Gy fractions on Days 1-5 every week) and Temozolomide: 75 mg/m<sup>2</sup> PO daily; and Cycle = 4 weeks (Max = 12 cycles): Temozolomide: 150-200 mg/m<sup>2</sup> PO on Days 1-5.

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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