

**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  
**March 4, 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, CTEP, DCTD, NCI**

6. PHONE NUMBER  
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**301-402-0428**

8. PROTOCOL NUMBER (AE #)  
**RTOG-0825 (AE # 1366672)**

9. PATIENT IDENTIFICATION  
**50**

10. AGE  
**57**

11. SEX  
**Male**

12. DESCRIPTION OF ADVERSE EVENT

The patient was a 57-year-old male with glioblastoma multiforme who expired while on a phase 3 trial utilizing the investigational agent bevacizumab/placebo in combination with temozolomide and concurrent chemoradiation therapy. He began the first course of the investigational therapy on September 28, 2009, and received the last dose of bevacizumab/placebo on January 20, 2010 (Cycle 3, Day 16), the last dose of temozolomide on January 10, 2010 (Cycle 3, Day 6), and the last dose of radiation on October 15, 2009 (Cycle 1, Day 18). On October 27, 2009, bevacizumab/placebo was held for a platelet count of  $20 \times 10^9/L$  (reference range:  $150-450 \times 10^9/L$ ) and resumed on November 10, 2009 when the platelet count recovered to  $131 \times 10^9/L$ . On November 10, 2009, an MRI of the brain showed a smaller left temporal lobe resection cavity than on the previous study in September 2009, two peripheral lesions which were unchanged, no significant mass effect, and evidence of possible radiation-associated microangiopathy. On December 8, 2009, bevacizumab/placebo was again held for 2 weeks due to confusion which did not improve with Decadron<sup>®</sup>. He was started on Haldol<sup>®</sup> with much improvement. On December 14, 2009, a repeat MRI of the brain showed a slightly larger left lobe resection cavity with stable peripheral enhancement, no significant mass effect, and stable radiation-associated microangiopathy. On February 1, 2010, during a clinic visit, the patient was very confused and clinically deteriorating. He was removed from the protocol and referred to hospice care. On February 10, 2010, the patient expired. 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 = 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 September 28, 2009, and received the last dose of bevacizumab/placebo on January 20, 2010 (Cycle 3, Day 16).

15. ACCRUAL AND IND EXPERIENCE Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 25,462. There have been 49 other cases of sudden death and 68 other cases of death NOS 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.**