

IND SAFETY REPORT: INITIAL WRITTEN REPORT

: 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 April 21, 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 301-496-1196	
		7. FAX NUMBER 301-402-0428	
8a. PROTOCOL NUMBER (AE#) RTOG-0825 (AE# 1250501)	8b. AE GRADE: AE Grade 5: Death NOS		
9. PATIENT IDENTIFICATION 800	10. AGE 75 years	11. SEX Female	
12. DESCRIPTION OF ADVERSE EVENT The patient was a 75-year-old female with glioblastoma multiforme who died while on a phase 3 trial utilizing the investigational agent bevacizumab/placebo in combination with temozolomide and radiation. She began her first course of treatment on February 7, 2011, and received the last dose of bevacizumab/placebo on March 1, 2011 (Cycle 1, Day 23), the last dose of temozolomide on March 14, 2011 (Cycle 1, Day 36), and the last dose of radiation treatment on March 21, 2011 (Cycle 1, Day 43). On March 15, 2011, the patient presented to the clinic with profound weakness and was admitted to the hospital where she developed an abdominal pain, fatigue, bilateral deep vein thrombosis, agitation, delirium, and encephalopathy. The neurology evaluation revealed an abnormal EEG, but the finding was consistent with a seizure. After several days of hospitalization and difficulty controlling and locating the pain, the patient and her family member decided that the patient did not want to pursue any further aggressive therapy. The patient was discharged from the hospital on March 26, 2011 and due to the severity of her pain, she was transferred to an inpatient hospice for comfort care with pain management. The patient expired in hospice care on March 28, 2011. 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 the beginning of Week 2 Cycle = 4 weeks (maximum of 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 February 7, 2011, receiving the last dose of bevacizumab on March 1, 2011 (Cycle 1, Day 23), and the last dose of temozolomide on March 14, 2011 (Cycle 1, Day 36), and the last dose of radiation treatment on March 21, 2011 (Cycle 1, Day 43).			
15. ACCRUAL AND IND EXPERIENCE Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 32,381. There have been 58 other cases of sudden death and 164 other cases of death NOS reported to the NCI through AdEERS as serious adverse events for bevacizumab.			
16. COMMENTS Cycle = 6 weeks: Temozolomide 75 mg/m ² PO daily and Radiation therapy 60 Grays (delivered in 2 Gray fractions on Days 1-5 every week) Cycle = 4 weeks: (maximum of 12 cycles): Temozolomide 150-200 mg/m ² 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). <u>DISCLAIMER per 21 CFR 312.32(e):</u> 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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