

IND SAFETY REPORT: FOLLOW-UP #1TO: *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 15, 2011
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# 1712748)	8b. AE GRADE: AE Grade 4: Platelets	
9. PATIENT IDENTIFICATION 481	10. AGE 47 yrs	11. SEX Female
12. DESCRIPTION OF ADVERSE EVENT The patient is a 47-year-old female with glioblastoma multiforme who experienced grade 4 thrombocytopenia while on a phase 3 trial utilizing the investigational agent bevacizumab/placebo in combination with temozolomide and concurrent chemoradiation therapy. She began the first course of the investigational therapy on July 15, 2010, and received her last doses of bevacizumab and temozolomide on August 9, 2010 (Cycle 1, Day 26), and the last dose of radiation on August 17, 2010 (Cycle 1, Day 34). On August 10, 2010 (Cycle 1, Day 27), the patient presented to the clinic for a routine visit and complained of fatigue. She reported starting her menstrual cycle the day before. Her platelet count was 13 k/mm ³ (reference range: 130-450 k/mm ³) from a value of 121 k/mm ³ on August 3, 2010. The patient was instructed to go to the ER where her platelet count was 11 k/mm ³ . The patient reported a 1-week history of bleeding from the gums and rectum, and increased bruising. She also reported a heavier vaginal bleeding during her menses. The patient was admitted to the hospital and transfused with 1 unit of platelets. On August 11, 2010, a repeat CBC showed increased platelet count of 81 k/mm ³ (reference range: 150-450 k/mm ³). A CT scan of the brain showed stable postsurgical changes and no evidence of an acute intracranial hemorrhage or mass. Temozolomide was held. On August 12, 2010 (Cycle 1, Day 29), the patient was discharged home. A follow-up CBC the next day showed a platelet count of 48 k/mm ³ . She was readmitted to the hospital on August 18, 2010 (Cycle 1, Day 35), for a platelet count of 11 k/mm ³ , WBC of 0.7 k/mm ³ (reference range: 4.0-11.0 k/mm ³), and hemoglobin of 10 g/dL (reference range: 11.5-16.0 g/dL). The patient was removed from the protocol on August 26, 2010. She remains hospitalized as of August 27, 2010. Additional information has been requested from the site. It is felt that the aplastic anemia is a result of long term use of Tegrato [®] aggravated by temozolomide. There is also a reasonable possibility that the experience may have been caused by bevacizumab.		
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 July 15, 2010, and received the last dose of bevacizumab/placebo on August 9, 2010 (Cycle 1, Day 26).		
15. ACCRUAL AND IND EXPERIENCE Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 28,686. There have been 253 other cases of thrombocytopenia 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 ² PO daily; and Cycle = 4 weeks (Max = 12 cycles): Temozolomide: 150-200 mg/m ² PO on Days 1-5		
FOLLOW-UP: BASED UPON FURTHER INVESTIGATION, THE SENIOR INVESTIGATOR HAS DECIDED THAT THIS ADVERSE EVENT IS UNRELATED TO THE INVESTIGATIONAL AGENT/THERAPY.		