

## IND SAFETY REPORT: INITIAL WRITTEN REPORT

<b>TO: Division of Biologic Oncology Products, Center for Drug Evaluation and Research, FDA</b>		<b>FAX: 301-796-9849</b>	
1. IND NUMBER <b>7921</b>	2. AGENT NAME <b>Bevacizumab (rhuMAb VEGF)</b>	3. DATE <b>April 26, 2011</b>	
4. SPONSOR <b>Division of Cancer Treatment and Diagnosis, National Cancer Institute</b>			
5. REPORTER'S NAME, TITLE, AND INSTITUTION <b>Helen Chen, MD-Associate Branch Chief for Investigational Therapeutics 3, Investigational Drug Branch, CTEP, DCTD, NCI</b>		6. PHONE NUMBER <b>301-496-1196</b>	
		7. FAX NUMBER <b>301-402-0428</b>	
8a. PROTOCOL NUMBER (AE#) <b>RTOG-0825 (AE# 1761191)</b>	8b. AE GRADE: AE <b>Grade 5: Respiratory failure</b>		
9. PATIENT IDENTIFICATION <b>0731</b>	10. AGE <b>60 years</b>	11. SEX <b>Male</b>	
12. DESCRIPTION OF ADVERSE EVENT <b>The patient was a 60-year-old male with glioblastoma multiforme who died while on a phase 3 trial utilizing the investigational agent bevacizumab/placebo in combination with temozolomide and radiation therapy. He began his first course of treatment on December 27, 2010, and received the last doses of bevacizumab/placebo and radiation treatment on February 15, 2011 (Cycle 1, Day 51), and the last dose of temozolomide on January 23, 2011 (Cycle 1, Day 28). The patient was hospitalized and treated with antibiotics for the right upper lobe pneumonia from January 23-28, 2011. On February 20, 2011 (Cycle 1, Day 56), the patient presented to the emergency room with new onset of severe abdominal pain and five-day-history of progressively worsened shortness of breath. He was found to have segmental colitis by abdominal CT scan with normal white blood cell count. His respiratory status deteriorated overnight; the arterial blood gases test showed evidence of respiratory failure. A chest CT scan revealed bilateral multifocal pneumonia and development of right pleural diffusion, but no evidence of pulmonary thromboemboli. The respiratory failure was considered to be secondary to the bilateral pneumonia. The patient also had tachycardia and confusion. He expired on the February 21, 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.</b>			
13. DOSE, ROUTE, AND SCHEDULE <b>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</b>			
14. DATES OF TREATMENT <b>The patient began the investigational therapy on December 27, 2010, receiving the last doses of bevacizumab and radiation treatment on February 15, 2011 (Cycle 1, Day 51), and the last dose of temozolomide on January 23, 2011 (Cycle 1, Day 28).</b>			
15. ACCRUAL AND IND EXPERIENCE <b>Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 32,525. There have been 28 other cases of respiratory failure reported to the NCI through AdEERS as serious adverse events for bevacizumab.</b>			
16. COMMENTS <b>Cycle = 6 weeks: Temozolomide: 75 mg/m<sup>2</sup> PO daily and radiation therapy 60 Grays over 6 weeks (delivered in 2 Gray fractions on Days 1-5 every week) Cycle = 4 weeks: (maximum of 12 cycles): Temozolomide: 150-200 mg/m<sup>2</sup> PO on Days 1-5</b>			
<b>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).</b>			
<b>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.</b>			

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