

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
79212. AGENT NAME
Bevacizumab (rhuMab VEGF)3. DATE
May 7, 20104. SPONSOR
Division of Cancer Treatment and Diagnosis, National Cancer Institute5. REPORTER'S NAME, TITLE, AND INSTITUTION
Kevin Conlon, MD-Senior Investigator for Investigational Therapeutics 3, Investigational Drug Branch, CTEP, DCTD, NCI6. PHONE NUMBER
301-496-11967. FAX NUMBER
301-402-04288a. PROTOCOL NUMBER (AE #)
RTOG-0825 (AE# 1138043)8b. AE GRADE: AE
**Grade 4: Cerebral edema
Grade 4: Ventricular Tachycardia
Grade 3: Glucose serum-high (hyperglycemia)**9. PATIENT IDENTIFICATION
13510. AGE
67 years11. SEX
Female

12. DESCRIPTION OF ADVERSE EVENT

The patient was a 67-year-old female with brain cancer who experienced grade 4 cerebral edema, grade 4 ventricular tachycardia, and grade 3 hyperglycemia and subsequently died on March 21, 2010, while on a phase 3 trial utilizing the investigational agent bevacizumab/placebo. She began her first course of treatment on November 23, 2009 and based on our evaluation she received the last dose of bevacizumab/placebo on March 3, 2010 (Cycle 4, Day 1), the last dose of temozolomide on March 7, 2010 (Cycle 4, Day 5), and the last dose of radiation therapy on January 6, 2010 (Cycle 2, Day 13). On March 8, 2010 (Cycle 4, Day 6), the patient presented to the emergency room with complaints of poor appetite and constipation, without nausea or vomiting. Vitals signs were: blood pressure 100/77 Hg mm, heart rate 94 bpm, respiratory rate 20 bpm, and temperature 98.5° F. Her laboratory work revealed a glucose level of 393 mg/dL (reference range: 70-110 mg/dL). The patient received insulin to control her glucose level. She received intravenous fluids and oxygen therapy. On the same day, a brain CT scan revealed left sided edema with a possible ischemic infarction. On March 9, 2010 (Cycle 4, Day 7), the patient's glucose was 253 mg/dL. On March 11, 2010 (Cycle 4, Day 9), the patient's level of alertness changed and she developed a fever of 101.7° F. The patient was transferred to the intensive care unit at another hospital for further evaluation, with an initial diagnosis of left middle cerebral artery (MCA) ischemia and a cerebrovascular accident (CVA) with cerebral edema. Later, a CVA was ruled out and the diagnosis was changed to possible tumor progression and massive cerebral edema. The patient received aggressive treatment with intravenous steroids to reduce the brain edema. It was felt that her hyperglycemia was secondary to diabetes mellitus type 2 and treatment with steroids. On March 12, 2010, the patient experienced a cardiac arrest. On March 22, 2010 the clinical site was informed that the patient died on March 21, 2010. 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 1 = 6 weeks: Bevacizumab/Placebo: 10 mg/kg IV over 30-90 minutes on Day 1 of weeks 4 and 6
Cycle 2 = 4 weeks: Bevacizumab/Placebo: 10 mg/kg IV over 30-90 minutes at the beginning of week 2
Cycle 3+ = 4 weeks (maximum of 12 cycles): Bevacizumab/Placebo: 10 mg/kg IV over 30-90 minutes on Days 1 and 15

14. DATES OF TREATMENT

The patient began the investigational therapy on November 23, 2009, and received last dose of bevacizumab on March 3, 2010 (Cycle 4, Day 1), the last dose of temozolomide on March 7, 2010. (Cycle 4, Day 4), and the last dose of radiation therapy on January 16, 2010 (Cycle 2, Day 13).

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab =704,865. There has been 1 other case of cerebral edema, 6 cases of ventricular tachycardia, and 87 cases of hyperglycemia reported to the NCI through AdEERS as serious adverse events for bevacizumab.

16. COMMENTS

Cycle 1= 6 weeks: Temozolomide 75 mg/m² PO daily
Radiation therapy 60 Grays (delivered in 2 Gray fractions on Days 1-5 every week
Cycle 3+ = 4 weeks (maximum of 12 cycles): Temozolomide 150-200 mg/m² 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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