

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
April 27, 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# 1706673)

8b. AE GRADE: AE
Grade 5: Sudden death

9. PATIENT IDENTIFICATION
709

10. AGE
67 years

11. SEX
Male

12. DESCRIPTION OF ADVERSE EVENT

The patient was a 67-year-old male with glioblastoma multiforme who suddenly died while on a phase 3 trial utilizing the investigational agent bevacizumab/placebo in combination with temozolomide and radiation. He began his first course of treatment on December 14, 2010, and received the last dose of bevacizumab/placebo on January 4, 2011 (Cycle 1, Day 22), the last dose of temozolomide on January 17, 2011 (Cycle 1, Day 35) and the last dose of radiation treatment on January 14, 2011 (Cycle 1, Day 32). At baseline, the patient was cardiovascularly stable but had a previous history of paroxysmal atrial fibrillation. On January 10, 2011 (Cycle 1, Day 27), per study protocol, the patient had a follow-up MRI of the brain which showed a cystic lesion that was in the right occipital lobe and approximately the same size compared with MRI performed on December 6, 2010, but perhaps may have more enhancement and some increased nodularity. There was persistent mass effect but no new lesions or larger lesions. The patient received the radiation therapy on January 14, 2011. As per patient's wife, the patient had a massive heart attack and expired on January 17, 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 December 14, 2010, receiving the last dose of bevacizumab on January 4, 2011, 2011 (Cycle 1, Day 21), the last dose of temozolomide On January 17, 2011 (Cycle 1, Day 35), and the last dose of radiation treatment on January 14, 2011 (Cycle 1, Day 32).

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 32,526. 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/m² 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/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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