

**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 <b>7921</b>	2. AGENT NAME <b>Bevacizumab (rhuMAb VEGF)</b>	3. DATE <b>November 4, 2011</b>
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4. SPONSOR  
**Division of Cancer Treatment and Diagnosis, National Cancer Institute**

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>
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8a. PROTOCOL NUMBER (AE#) <b>RTOG-0825 (AE# 1301534)</b>	8b. AE GRADE: AE <b>Grade 3: Eye disorders: Optic neuropathy</b>
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9. PATIENT IDENTIFICATION <b>220</b>	10. AGE <b>70 years</b>	11. SEX <b>Male</b>
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12. PROTOCOL SPECIFIED  
**Cycle = 4 weeks**  
**Bevacizumab: 10 mg/kg of actual body weight IV over 30-90 minutes on Days 1 and 15**

13. TREATMENT RECEIVED AND DATES  
**The patient began the open label arm of the investigational therapy on August 23, 2011, and received the last dose of bevacizumab on September 20, 2011 (Cycle 2, Day 1).**

14. DESCRIPTION OF ADVERSE EVENT  
**The patient is a 70-year-old male with glioblastoma multiforme who experienced grade 3 optic neuropathy while on a phase 3 trial utilizing the investigational agent bevacizumab. The patient was diagnosed with gliosarcoma of the left temporal lobe in December 2009 (pathologic diagnosis), and is status post a left temporal craniotomy with a subtotal resection. Before starting the current arm of this protocol therapy he received radiation therapy concurrent with temzolomide and bevacizumab/placebo, followed by chemotherapy with bevicizumab/placebo and temzolomide. The patient's significant past medical history includes coronary artery disease status post left anterior descending artery stent placement in August 2009, asthma, cataract surgeries, and sensorineural hearing loss. On October 4, 2011 (Cycle 2, Day 15), the patient presented to the clinic and reported that 2 weeks prior the vision in his right eye had started to become cloudy and continued to worsen until that morning when he had no vision at all in that eye. The patient also reported hearing problems, imbalance, and slower processing. Upon examination, his left visual fields were intact; he was unable to see through pin holes on the right; he had a right afferent papillary defect (APD); and a pale right disc suggesting a chronic process. His protocol treatment was held and he was treated with 4 mg of dexamethasone. The following day, an MRI of the brain and orbits revealed abnormal enhancement and signal involving the right optic chiasm and proximal postchiasmatic right optic nerve, likely representing retrobulbar optic neuritis. It also showed interval progression of disease involving the posterior body of the corpus callosum. The MRI enhancement was concerning for treatment related (radiation and bevacizumab) optic neuropathy and was not thought to be related to tumor extension. On October 10, 2011, the patient reported no change in his eyesight. His blood pressure was 144/76 mmHG, his pulse was 82 bpm, and his oxygen saturation was 98%. His visual fields revealed no light perception in the right eye. His pupils were equal and reactive to light and accommodation but there was a right relative APD. Extraocular movements were intact without nystagmus. Fundi exam revealed right optic nerve atrophy. He was placed on supportive care and started on dexamethasone for symptom management. He was removed from the protocol on October 11, 2011. On October 13, 2011, the patient's wife reported that the patient's left eye was getting a little cloudy. Additional information has been requested from the investigational site. There is a reasonable possibility that the experience may have been caused by the drug.**

15. ACCRUAL AND IND EXPERIENCE  
**Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 35,232. There have been no other cases of optic neuropathy and 1 other cases of optic nerve disorder (grade 3, probably related) reported to the NCI through AdEERS as serious adverse events for bevacizumab, as summarized in the table below.**

16. ASSESSMENT

In this case, it is felt that both the radiation therapy and the bevacizumab possibly contributed to the event.

	Optic neuropathy
Bevacizumab	Possible
Glioblastoma multiforme	Unlikely
Radiation therapy	Possible

17. COMMENTS

Medications taken at the time of the event included Dulcolax<sup>®</sup>, Tylenol<sup>®</sup>, Zyrtec<sup>®</sup>, Plavix<sup>®</sup>, Toprol XL<sup>®</sup>, Flonase<sup>®</sup>, and Zocor<sup>®</sup>.

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(c): 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.**