

## 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>July 21, 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>GOG-0252 (AE# 1258239)</b>	8b. AE GRADE: AE <b>Grade 4: Cerebellar syndrome Grade 4: Ataxia</b>	
9. PATIENT IDENTIFICATION <b>066-0252-025</b>	10. AGE <b>79 years</b>	11. SEX <b>Female</b>
12. DESCRIPTION OF ADVERSE EVENT <b>The patient is a 79-year-old female with ovarian epithelial cancer who experienced grade 4 cerebellar syndrome and grade 4 ataxia while on a phase 3 trial utilizing the investigational agent bevacizumab in combination with paclitaxel and carboplatin. She began her first course of treatment on November 4, 2010, and received the last dose of bevacizumab on June 16, 2011 (Cycle 11, Day 1), and the last doses of paclitaxel and carboplatin in March 2011 (dates not provided). On July 2, 2011 (Cycle 11, Day 17) the patient was seen in the ER with a 2-3 day history of tremors which decreased at rest, but prevented her from walking due to an unsteady gait. Her KUB, CT scan of the head, and CT scan of the abdomen/pelvis were all negative. Laboratory results showed no evidence of infarction, infection, obstruction, or tumor. Her cardiac markers, ECG, and electrolytes were also normal. On July 3, 2011 (Cycle 11, Day 18), the patient was transferred to another hospital and admitted for further evaluation of her symptoms. She also reported experiencing nystagmus and having previous episodes of nausea and vomiting, along with a decreased appetite. The neurology consultation determined that her history and examination were consistent with a cerebellar syndrome, more precisely truncal ataxia with severe ataxia of her gait. In addition to what appeared to be extraocular movement irregularity, there was concern for a paraneoplastic cerebellar degeneration of the type described in individuals with ovarian cancer. There was also concern for a metastasis to the cerebellum, vitamin deficiency, rare side effect of bevacizumab, and Parkinsonian tremors. The patient was started on IV fluids, her bevacizumab was held, and a paraneoplastic profile and additional blood tests were ordered. On July 5, 2011, the patient's brain MRI revealed minimal chronic patchy white matter changes and mild diffuse cerebral volume loss; however, there were no abnormal enhancement to represent metastatic disease specifically in the cerebellum. 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 = 3 weeks: Phase A (Cycles = 1-6): Bevacizumab: 15 mg/kg IV over 30-90 minutes on Day 1, beginning with cycle 2 Phase B: (Cycles 7-22): Bevacizumab: 15 mg/kg IV over 30-90 minutes on Day 1</b>		
14. DATES OF TREATMENT <b>The patient began the investigational therapy on November 4, 2010, and received the last dose of bevacizumab on June 16, 2011 (Cycle 11, Day 1), and the last doses of paclitaxel and carboplatin in March 2011(dates not provided).</b>		
15. ACCRUAL AND IND EXPERIENCE <b>Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 33,935. There have been 37 other cases of ataxia and no other cases of cerebellar syndrome reported to the NCI through AdEERS as serious adverse events for bevacizumab.</b>		
16. COMMENTS Also administered: <b>Phase A (Cycles = 1-6): Paclitaxel: 80 mg/m<sup>2</sup> IV over 1 hour on Days 1, 8, and 15. Carboplatin: AUC 6 IP on Day 1</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). 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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