

## 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>August 26, 2009</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, CTEP, DCTD, NCI</b>		6. PHONE NUMBER <b>301-496-1196</b>
		7. FAX NUMBER <b>301-402-0428</b>
8. PROTOCOL NUMBER (AE #) <b>AEWS0521 (AE # 1279067)</b>		
9. PATIENT IDENTIFICATION <b>782007</b>	10. AGE <b>19</b>	11. SEX <b>Male</b>
12. DESCRIPTION OF ADVERSE EVENT <b>The patient is a 19-year-old male with trisomy 21, history of Hodgkins lymphoma, and Ewing sarcoma/peripheral primitive neuroectodermal tumor who developed a grade 3 esophageal stricture while on a phase 2 study using the investigational agent bevacizumab/placebo in combination with vincristine, topotecan and cyclophosphamide. He began his first course of treatment on July 1, 2008, and received the last dose of bevacizumab on June 22, 2009 (Cycle 12, Day 1), the last doses of cyclophosphamide and topotecan on June 26, 2009 (Cycle 12, Day 5), and the last dose of vincristine on July 6, 2009 (Cycle 12, Day 15). On July 15, 2009 (Cycle 12, Day 24), the patient, who is known to have an esophageal stricture from radiation therapy, was admitted to the hospital for the treatment of hematemesis and dysphagia due to esophageal strictures. On June 23, 2009, an esophagram had shown a moderate tubular narrowing of the esophagus at the level of T5-T6 with delayed passage of the barium, likely secondary to radiation esophagitis, as well as another mild to moderate focal narrowing 2 cm above the gastroesophageal junction in the distal esophagus. The patient was placed on total parenteral nutrition and received platelets and blood transfusions. On August 12, 2009, an EGD revealed white plaques and slight mucosal thickening with decreased vascular pattern. The proximal esophageal biopsies showed stratified squamous epithelium with a band-like infiltrate of neutrophils which formed numerous microabscesses within the squamous epithelium. There were also several fragments of fibrinopurulent exudates that were not associated with epithelium or stroma. The patient was started on fluconazole for a presumptive diagnosis of esophageal candidiasis, and he was kept on Nexium®. Additional information has been requested. There is a reasonable possibility that the experience may have been caused by the drug.</b>		
13. DOSE, ROUTE, AND SCHEDULE <b>Cycle = 21 days Bevacizumab 15 mg/kg IV over 30-90 min on Day 1</b>		
14. DATES OF TREATMENT <b>The patient started the investigational therapy on July 1, 2008, and received the last dose of bevacizumab on June 22, 2009 (Cycle 12, Day 1).</b>		
15. ACCRUAL AND IND EXPERIENCE <b>Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 22,983. There have been 3 cases of esophageal stricture reported to the NCI through AdEERS as serious adverse events for bevacizumab.</b>		
16. COMMENTS <b>The following was also administered: Vincristine: 1.5 mg/m<sup>2</sup> IVP on Day 1 of each week of Cycles 1 and 2 Topotecan: 0.75 mg/m<sup>2</sup> IV over 30 min on Days 1-5 Cyclophosphamide: 250 mg/m<sup>2</sup> IV over 60 min 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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