

## IND SAFETY REPORT: INITIAL WRITTEN REPORT

**TO: Division of Oncology Products 2, Center for Drug Evaluation and Research, FDA**

**FAX: 301-796-9849**

1. IND NUMBER <b>113916</b>	2. AGENT NAME <b>Bevacizumab (rhuMab VEGF)</b>	3. DATE <b>December 12, 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. EMAIL ADDRESS <b>ctepsupportae@tech-res.com</b>
8a. PROTOCOL NUMBER (AE#) <b>E1305 (AE# 1455510)</b>	8b. AE GRADE: AE <b>Grade 5: Bronchopulmonary hemorrhage</b>	
9. PATIENT IDENTIFICATION <b>13148</b>	10. AGE <b>58 years</b>	11. SEX <b>Male</b>
12. PROTOCOL SPECIFIED <b>Cycle = 21 days</b> <b>Bevacizumab: 15 mg/kg IV over 30-90 minutes on Day 1</b> <b>Docetaxel: 75 mg/m<sup>2</sup> IV over 1 hour on Day 1</b> <b>Cisplatin: 75 mg/m<sup>2</sup> IV over 1-2 hours on Day 1</b>		
13. TREATMENT RECEIVED AND DATES <b>The patient began the investigational therapy on November 2, 2011, and received the last doses of bevacizumab, docetaxel, and cisplatin on November 23, 2011 (Cycle 2, Day 1).</b>		
14. DESCRIPTION OF ADVERSE EVENT <b>The patient was a 58-year-old male with head and neck squamous cell carcinoma who expired from a bronchopulmonary hemorrhage while on a phase 3 trial utilizing the investigational agent bevacizumab in combination with docetaxel and cisplatin. Of note, the patient had a pre-existing cavitation of the tumor site causing a fistulous tract at the time of the event. On November 28, 2011 (Cycle 2, Day 6), he presented to the radiology unit for a PEG tube insertion, and was noted to have tachycardia and sent to the ER. In the ER, the patient had a pulse of 160 beats per minute for which he was given adenosine with no improvement. He also received IV Cardizem<sup>®</sup>, and was admitted for monitoring. His ECG was normal. On December 2, 2011 (Cycle 2, Day 10), the patient had a coughing spell while being prepared for discharge from the hospital. He initially coughed out clear sputum, but developed hemoptysis and gagged up fresh blood with sponge-sized gelatinous blood clots thereafter. The rapid response team was notified; the patient coded and died later that day. 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>		
15. ACCRUAL AND IND EXPERIENCE <b>Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 35,453. Bronchopulmonary hemorrhage is an expected event for bevacizumab; however, this event is being reported because it is a rare event with increased severity.</b>		
16. ASSESSMENT <b>In this case, a probable relationship exists between the event and bevacizumab.</b>		
_____	_____	_____
<b>Bevacizumab</b>	<b>Bronchopulmonary hemorrhage</b>	<b>Probable</b>
_____	_____	_____
<b>Cisplatin</b>	<b>Unrelated</b>	<b>Unrelated</b>
_____	_____	_____
<b>Docetaxel</b>	<b>Unrelated</b>	<b>Unrelated</b>
_____	_____	_____
<b>Head and neck squamous cell carcinoma</b>	<b>Possible</b>	<b>Possible</b>
_____	_____	_____
<b>Cavitation of tumor site, causing a fistula tract</b>	<b>Probable</b>	<b>Probable</b>
17. COMMENTS <b>Medications taken at the time of the event are not available at this time.</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>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>		