

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 21, 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 #) CALGB-90601 (AE # 1357433)	8b. AE GRADE: AE Grade 4: Pericardial tamponade	
9. PATIENT IDENTIFICATION 122341	10. AGE 50 yrs	11. SEX Male
12. DESCRIPTION OF ADVERSE EVENT The patient was a 50-year-old male with transitional cell carcinoma of the urothelial tract who experienced grade 4 cardiac tamponade while on a phase 3 trial utilizing the investigational agent bevacizumab/placebo in combination with cisplatin and gemcitabine. He began the first dose of the investigational therapy on September 9, 2010, and received the last dose of bevacizumab/placebo on March 3, 2011 (Cycle 9, Day 1), the last dose of cisplatin on December 30, 2010 (Cycle 6, Day 1), and the last dose of gemcitabine on January 6, 2011 (Cycle 6, Day 8). On March 17, 2011 (Cycle 9, Day 15), a routine re-staging CT scan of the chest/abdomen/pelvis revealed an interval increase in pericardial effusion and interval development of a small right effusion as compared to that of January 13, 2011. On March 18, 2011 (Cycle 9, Day 16), the patient presented to intervention radiology for the evaluation of his pericardial effusion. He developed diaphoresis, agitation, hypotension with a BP in the 50s/30s mmHg, and became unresponsive. A rapid response/code was called. The patient received bolus IV fluids and Narcan[®]; however, his heart rate became irregular, his oxygen saturation dropped to approximately 87%, and he had several witnessed seizures. He underwent an emergency ultrasound guided pericardiocentesis with pericardial drain which yielded 1 liter of bloody fluid. The patient's BP increased to 110/70 mmHg, his heart rate returned to normal sinus rhythm, his oxygen saturation was 100%, and he regained his baseline mental status. He was admitted to telemetry. The pericardial fluid cytopathology revealed malignant cells which were consistent with his urothelial carcinoma. The patient was taken off the study that day. On March 21, 2011, a transthoracic echocardiogram showed a small pericardial effusion, and he was discharged that day. On April 4, 2011, the patient developed shortness of breath during radiation therapy. He presented to the local ER and was admitted. The following day, the patient went into pulseless electrical activity (PEA), and he expired after 30 minutes of advanced cardiac life support (ACLS). 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 = 21 days Bevacizumab/placebo 15 mg/kg IV over 30-90 minutes on Day 1		
14. DATES OF TREATMENT The patient began the investigational therapy on September 9, 2010, and received the last dose of bevacizumab/placebo on March 3, 2011 (Cycle 9, Day 1).		
15. ACCRUAL AND IND EXPERIENCE Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 32,381. There have been no other cases of pericardial tamponade and 18 other cases of pericardial effusion reported to the NCI as serious adverse events through AdEERS for bevacizumab.		
16. COMMENTS The following was also administered: Cisplatin 70 mg/m² IV on Day 1 and Gemcitabine 1000 mg/m² IV over 30 minutes on Days 1 and 8 for Cycles 1-6. 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.		