

**IND SAFETY REPORT: INITIAL WRITTEN REPORT**

To: <i>Division of Biologic Oncology Products, Center for Drug Evaluation and Research, FDA</i>		FAX: 301-796-9849
Division of Drug Oncology Products, Center for Drug Evaluation and Research, FDA		FAX: 301-796-9845
1. IND NUMBER 7921 61010	2. AGENT NAME Bevacizumab (rhuMAb VEGF) CCI-779 (tamsirolimus, Torisel™)	3. DATE April 20, 2010
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 L. Austin Doyle, MD-Senior Investigator for Investigational Therapeutics 2, Investigational Drug Branch, CTEP, DCTD, NCI		6. PHONE NUMBER 301-496-1196
		7. FAX NUMBER 301-402-0428
8a. PROTOCOL NUMBER (AE #) 8233 (AE# 1249518)	8b. AE GRADE: AE Grade 4: Left ventricular systolic dysfunction Grade 3: Pneumonitis/pulmonary infiltrates	
9. PATIENT IDENTIFICATION PH1432	10. AGE 58	11. SEX Female
12. DESCRIPTION OF ADVERSE EVENT The patient is a 58-year-old female with carcinoid tumor of the pancreas who experienced grade 4 congestive heart failure (CHF) and grade 3 pneumonitis while on a phase 2 trial utilizing the investigational agents bevacizumab and tamsirolimus. She began the investigational therapy on December 22, 2009, and received the last dose of bevacizumab on March 16, 2010 (Cycle 4, Day 1), and the last dose of tamsirolimus on March 23, 2010 (Cycle 4, Day 8). On March 30, 2010 (Cycle 4, Day 15), the patient, who had a history of heart failure with an ejection fraction (EF) of 55% in December 2009, presented to the ER with a 1-week history of intermittent dyspnea, productive cough with greenish sputum, and wheezing. She was anxious and dyspneic with an oxygen saturation in the mid 80s on room air, and she had diffuse bilateral rhonchi on examination. A chest CT scan revealed bilateral patchy infiltrates and pleural effusions consistent with pneumonia. The patient showed mild improvement after receiving nebulizer treatments and oxygen; however, she later desaturated back to the mid 80s. She was intubated, placed on mechanical ventilation for respiratory failure, and admitted to the ICU. On March 31, 2010, an echocardiogram showed a mildly decreased left ventricular EF of 45-50%. Her condition improved and she was discharged home on April 2, 2010. On April 6, 2010 (Cycle 4, Day 22), the patient presented to the clinic to reinstate chemotherapy and after receiving a few liters of IV fluid, suddenly developed dyspnea, tachypnea, chest pain, and 2 + pitting edema of the lower extremities. The patient became hypoxic and was treated with steroids and albuterol without success. Her BNP was 3135 pg/mL (reference range: <100 pg/mL). A chest X-ray showed edema-like opacities and small bilateral pleural effusions. The patient was readmitted to the hospital with CHF and given Lasix®. She responded well to treatment and within 48 hours of her hospital stay was back to her baseline. On April 8, 2010, the patient was discharged home in stable condition. 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 = 28 Days Tamsirolimus: 25 mg IV on Days 1, 8, 15, and 22 Bevacizumab: 10 mg/kg IV over 30-90 minutes on Days 1 and 15		
14. DATES OF TREATMENT The patient began the investigational therapy on December 22, 2009, and received last dose of bevacizumab on March 16, 2010 (Cycle 4, Day 1) and the last dose of tamsirolimus on March 23, 2010. (Cycle 4, Day 8).		
15. ACCRUAL AND IND EXPERIENCE Number of patients enrolled in NCI-sponsored clinical trials using tamsirolimus = 1,971; and bevacizumab 25,571. There have been 10 other cases of left ventricular systolic dysfunction reported to the NCI through AdEERS as serious adverse events for tamsirolimus and 161 other cases of pneumonitis reported to the NCI through AdEERS as serious adverse events for bevacizumab. Pneumonitis is a known event for tamsirolimus and left ventricular systolic dysfunction is a known event for bevacizumab.		
16. COMMENTS 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). <u>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.</u>		

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