

## IND SAFETY REPORT: INITIAL WRITTEN REPORT

To: *Division of Biologic Oncology Products, Center for Drug Evaluation and Research, FDA*  
*Division of Drug Oncology Products, Center for Drug Evaluation and Research, FDA*

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1. IND NUMBER  
7921  
61010

2. AGENT NAME  
Bevacizumab (rhuMab VEGF)  
CCI-779 (tamsirolimus, Torisel™)

3. DATE  
April 14, 2010

4. SPONSOR  
Division of Cancer Treatment and Diagnosis, National Cancer Institute

5. REPORTER'S NAME, TITLE, AND INSTITUTION  
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8a. PROTOCOL NUMBER (AE #)  
8233 (AE# 1220746)

8b. AE GRADE: AE  
Grade 4: Renal failure

9. PATIENT IDENTIFICATION  
ph1525

10. AGE  
65

11. SEX  
Male

12. DESCRIPTION OF ADVERSE EVENT

The patient was a 65-year-old male with hepatocellular carcinoma who experienced grade 4 renal failure while on a phase 2 trial utilizing the investigational agents bevacizumab and tamsirolimus. He began the investigational therapy on March 24, 2010, and received only one dose of bevacizumab and tamsirolimus. On March 31, 2010 (Cycle 1, Day 8), the patient presented to the ER with severe nausea without vomiting or diarrhea, diffuse abdominal pain and distension, dizziness, anuria for 2 days, hypotension, and tachycardia. His creatinine was 1.6 mg/dL (reference range: 0.5-1.7 mg/dL) from a baseline value of 0.5 mg/dL and BUN 27 mg/dL (reference range: 8-25 mg/dL). Physical examination revealed tenderness in the midepigastrium with guarding. A CT scan of the abdomen and pelvis showed interval development of increased ascites, thickening of the terminal ileum, non obstructing left renal calculus, and no evidence of hydronephrosis. Following a diagnostic paracentesis in the ER, the patient developed worsening peritonitis, acute renal failure, and metabolic acidosis. He was started on IV fluids, antiemetics, and morphine. On April 1, 2010 (Cycle 1, Day 9), the patient underwent a diagnostic laparoscopy and liver biopsy at which time he was found to have metastatic disease. The patient developed respiratory failure and he was placed on mechanical ventilation. His creatinine increased to 3.39 mg/dL and his BUN to 48 mg/dL. He started dialysis the next day; however, in view of his poor prognosis, it was decided he would no longer be dialyzed. After discussions about the patient's prognosis with his family, he was made DNR, and palliative care was consulted. The patient was discontinued from the ventilator, and he died on April 3, 2010. 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 March 24, 2010, and received only one dose of bevacizumab and tamsirolimus.

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using tamsirolimus=1,970; and bevacizumab=25,522. There have been 20 other cases of renal failure reported to the NCI through AdEERS as serious adverse events for tamsirolimus. Renal failure 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).

**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.**

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