

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 January 7, 2010
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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
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8a. PROTOCOL NUMBER (AE #) 8233 (AE# 1075201)	8b. AE GRADE: AE Grade 4: Gastrointestinal: Duodenal-aortic fistula Grade 4: Duodenal perforation
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9. PATIENT IDENTIFICATION PH1650	10. AGE 59 years	11. SEX Female
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12. DESCRIPTION OF ADVERSE EVENT
The patient is a 59 year-old female with metastatic endometroid endometrial adenocarcinoma who experienced a grade 4 duodenal-aortic fistula and grade 4 duodenal perforation while on a phase 2 trial utilizing the investigational agents bevacizumab and tamsirolimus. She began the investigational therapy on October 1, 2010, and received the last doses of bevacizumab and tamsirolimus on October 29, 2010 (Cycle 2, Day 1). On November 1, 2010 (Cycle 2, Day 4), the patient, who was on Coumadin® for IVC thrombosis, presented to the ER with complaints of diffuse abdominal pain, nausea, and bright red emesis. She was pale, had dry mucous membranes, and generalized epigastric tenderness. The patient's hemoglobin was 11.7 g/dL (reference range: 12 – 16 g/dL), her PT was 38.7 seconds (reference range: 11-12.5 seconds), her APTT was 75 seconds (reference range 30-40 seconds), and her INR was 4.04 (reference range 1.5-2.0). She was started on IV fluids, Protonix®, Zofran®, and Dilaudid®, and was admitted for close observation. An upper GI endoscopy the next day, showed evidence of bleeding from the second portion of the duodenum. The patient successfully underwent coil and Gelfoam™ embolization of the gastroduodenal artery that day. On November 4, 2010 (Cycle 2, Day 7), a CT scan of the abdomen and pelvis revealed a 4-cm centrally necrotic mass in the retroperitoneum with evidence of invasion into the third portion of the duodenum with duodenal outlet obstruction and malignant duodenal perforation, which was concerning for an increased risk for aortoduodenal fistula and massive bleeding. The following day, she underwent an endovascular grafting of the distal abdominal aortic injury and placement of a percutaneous venting gastrostomy tube. On November 8, 2010 (Cycle 2, Day 11), the patient developed bright red bleeding from her gastrostomy tube, with a drop in her blood pressure. Her INR was 3.6. An angiogram of the abdominal aorta demonstrated a persistent aorto-enteric fistula arising from the inferior margin of the previously placed lower abdominal aortic endograft anteriorly and on the right side. Additional multiple endovascular grafts were again placed and successful hemostasis was obtained. The patient was started on IV vitamin K and received 4 units of packed red blood cells over the course of 24 hours due to a hemoglobin of 9.4 g/dL on November 9, 2010. On November 11, 2010 (Cycle 2, Day 14), the patient's hemoglobin improved to 11.2 g/dL and she was discharged to hospice on TPN at the family's request. On November 12, 2010, she was removed from the protocol. Additional information has been requested from the investigational site. There is a reasonable possibility that the experience may have been caused by the drugs.

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 October 1, 2010, and received the last doses of bevacizumab and tamsirolimus on October 29, 2010 (Cycle 2, Day 1).

15. ACCRUAL AND IND EXPERIENCE
Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab=30,255; and tamsirolimus=2,429. There has been 1 other case of duodenal fistula reported to the NCI through AdEERS as serious adverse events for bevacizumab, and no other cases of duodenal fistula reported to the NCI through AdEERS as serious adverse events for tamsirolimus. There have been 134 other cases of gastrointestinal fistulas reported to the NCI through AdEERS as serious adverse events for bevacizumab, and 12 other cases of gastrointestinal fistulas reported to the NCI through AdEERS as serious adverse events for tamsirolimus. Duodenal perforations are expected events for bevacizumab and tamsirolimus.

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.