

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 (temsirolimus, Torisel™)	3. DATE March 15, 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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8. PROTOCOL NUMBER (AE #)
E2804 (AE# 1671222)

9. PATIENT IDENTIFICATION 28204	10. AGE 74	11. SEX Female
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12. DESCRIPTION OF ADVERSE EVENT
The patient is a 74-year-old female with renal cell carcinoma who experienced grade 3 rectal pain and grade 3 anal fistula while on a phase 2 trial utilizing the investigational agents bevacizumab, temsirolimus and sorafenib. The patient was on a treatment arm that did not include sorafenib. She began the investigational therapy on September 18, 2009, and received her last dose of bevacizumab on December 30, 2009 (Cycle 4, Day 20), and the last dose of temsirolimus on January 13, 2010 (Cycle 5, Day 1). The patient, who had been removed from the protocol on February 9, 2010 (Cycle 5, Day 28), presented to the ER on February 24, 2010, with complaints of rectal pain and fecal incontinence with bloody diarrhea. She was admitted and had a surgical consultation. The rectal examination was significant for a deep anterior midline fissure/fistula with an opening about the size of the anus itself just below the anus, and it was leaking stool. It was felt not to be a rectovaginal fistula, but rather, an unusually complicated perineal fistula. Two topical antibiotics and daily sitz bath after bowel movements were recommended. She was discharged home on February 25, 2010. She was advised to follow-up with her primary oncologist the next week and the colorectal surgeon in four weeks. 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.
Temsirolimus: 25 mg IV over 30 minutes 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 September 18, 2009, and received the last dose of bevacizumab on December 30, 2009 (Cycle 4, Day 20), and the last dose of temsirolimus on January 13, 2010 (Cycle 5, Day 1)

15. ACCRUAL AND IND EXPERIENCE
Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 21,298, and for temsirolimus = 1,187. Anal fistula is a known event for bevacizumab. There have been 30 other cases of rectal pain reported to the NCI through AdEERS as serious adverse events for bevacizumab; and 7 other cases of rectal pain and 2 other cases of anal fistula reported to the NCI through AdEERS as serious adverse events for temsirolimus.

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 21CFR312.32(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.