

## IND SAFETY REPORT: INITIAL WRITTEN REPORT

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

**FAX: 301-796-9845**  
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1. IND NUMBER <b>7921</b> <b>61010</b>	2. AGENT NAME <b>Bevacizumab (rhuMab VEGF)</b> <b>CCI-779 (temsirolimus, Torisel)</b>	3. DATE <b>May 19, 2009</b>
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4. SPONSOR  
**Division of Cancer Treatment and Diagnosis, National Cancer Institute**

5. REPORTER=S NAME, TITLE, AND INSTITUTION <b>Helen Chen, MD-Associate Branch Chief for Investigational Therapeutics 3, CTEP, DCTD, NCI</b>  <b>L. Austin Doyle, M.D., Senior Investigator for Investigational Therapeutics 2, Investigational Drug Branch, CTEP, DCTD, NCI</b>	6. PHONE NUMBER <b>301-496-1196</b>  7. FAX NUMBER <b>301-402-0428</b>
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8. PROTOCOL NUMBER (AE #)  
**E1505 (AE # 1718620)**

9. PATIENT IDENTIFICATION <b>094-0229G-005</b>	10. AGE <b>79</b>	11. SEX <b>Female</b>
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12. DESCRIPTION OF ADVERSE EVENT  
**The subject is a 79-year-old female with endometrioid endometrial adenocarcinoma of the uterus, who suddenly expired while on a phase 2 study utilizing the investigational agents bevacizumab and temsirolimus. She began her first course of treatment on January 22, 2009, and received her last doses of bevacizumab and temsirolimus on April 30, 2009 (Cycle 3, Day 21). On May 3, 2009, the patient presented to the emergency room (ER) with the complaint of headache, right blurred vision, right jaw pain, and sudden onset of bilateral temporal pain. The pain symptoms subsided after she was treated with Tylenol. The subject noticed a "veil" covering her right eye half an hour after the onset of temporal headache, which resolved 2 to 3 hours later. She denied any associated symptoms. A CT of the head revealed small vessel ischemic changes but no intracranial hemorrhage. She was subsequently admitted to the hospital and treated with heparin. On May 7, 2009, the patient was awake, anxious and preparing for discharge. The investigational agents scheduled for the day were withheld. At about 11:00 am, she was found unresponsive on the floor of the hospital room. She was resuscitated, but her ECG showed marked ST abnormality with possible anterior subendocardial injury. An echocardiogram done revealed a large pericardial effusion, consistent with cardiac tamponade with 10 to 15% ejection fraction. Minutes after the transthoracic echocardiogram was performed she suffered another cardiac arrest, and CPR was started. However, the patient's family ended the resuscitation efforts. The patient's family declined an autopsy. 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 = 4 weeks**  
**Bevacizumab 10 mg/kg IV over 30-90 minutes on Days 1 and 15;**  
**Temsirolimus 25 mg IV over 30 minutes on Days 1, 8, 15 and 22.**

14. DATES OF TREATMENT **The patient started the investigational therapy on January 22, 2009, and received the last doses of bevacizumab and temsirolimus on April 30, 2009 (Cycle 3, Day 21).**

15. ACCRUAL AND IND EXPERIENCE: **Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 21,385; and temsirolimus = 1,596. There have been 4 other cases of sudden death and 12 cases of death NOS reported to the NCI through AdEERS as serious adverse events for bevacizumab, and there have been no other cases of sudden death and 3 cases of death NOS reported to the NCI through AdEERS as serious adverse events for temsirolimus.**

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 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.**