

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 69896	2. AGENT NAME Bevacizumab (rhuMab VEGF) BAY 43-9006 tosylate (BAY 54-9085; sorafenib tosylate)	3. DATE March 18, 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 John Wright, MD, PhD-Senior Investigator for Investigational Therapeutics 1, Investigational Drug Branch, CTEP, DCTD, NCI	6. PHONE NUMBER 301-496-1196
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8. PROTOCOL NUMBER (AE #)
E2804 (AE# 1706912)

9. PATIENT IDENTIFICATION 28187	10. AGE 45	11. SEX Female
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12. DESCRIPTION OF ADVERSE EVENT
The patient was a 45-year-old female with clear cell renal cell adenocarcinoma who experienced grade 4 reversible posterior leukoencephalopathy syndrome (RPLS), grade 4 hypertension, and subsequently expired due to disease progression while on a phase 2 trial utilizing the investigational agents bevacizumab and sorafenib tosylate. She began the investigational therapy on August 7, 2009, and received her last dose of bevacizumab on September 8, 2009 (Cycle 2, Day 1), and her last dose of sorafenib tosylate on September 1, 2009 (Cycle 1, Day 26). The patient had a seizure at home on September 10, 2009, and was rushed to the emergency room. She was unresponsive to verbal and tactile stimuli. She was started on Dilantin® but had another seizure shortly after being admitted to the ICU; her blood pressure was 144/113 mmHg. It was felt that the cause of the seizure was RPLS. The patient had a history of hypertension and depression, and she had respiratory failure which required ventilator support while she was in the hospital. According to the discharge summary, the patient failed to thrive and continued to deteriorate. She was given comfort care and expired on October 7, 2009. 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
Bevacizumab: 5 mg/kg IV over 30-90 minutes on Days 1 and 15
Sorafenib tosylate: 200 mg PO twice a day on Days 1-5, 8-12, 15-19, and 22-26

14. DATES OF TREATMENT
The patient began the investigational therapy on August 7, 2009, and received her last dose of bevacizumab on September 8, 2009 (Cycle 2, Day 1), and her last dose of sorafenib tosylate on September 1, 2009 (Cycle 1, Day 26).

15. ACCRUAL AND IND EXPERIENCE
Number of patients enrolled in NCI-sponsored clinical trials using sorafenib tosylate = 5912; and bevacizumab= 25,481. There have been no other case of RPLS, 4 other cases of encephalopathy, 1 other case of leukoencephalopathy and 252 cases of disease progression reported to the NCI through AdEERS as serious adverse events for sorafenib; and 19 other cases of RPLS, 22 other cases of encephalopathy, 5 other cases of leukoencephalopathy and 270 cases of disease progression reported to the NCI through AdEERS as serious adverse events for bevacizumab. Hypertension is an expected event for both agents.

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.