

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 74019	2. AGENT NAME Bevacizumab (rhuMab VEGF) Sunitinib malate (SU011248 L-malate; Sutent®)	3. DATE December 7, 2009
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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 III, Investigational Drug Branch, CTEP, DCTD, NCI Pamela Harris, MD-Senior Investigator for Investigational Therapeutics I, Investigational Drug Branch, CTEP, DCTD, NCI	6. PHONE NUMBER 301-496-1196	7. FAX NUMBER 301-402-0428
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8. PROTOCOL NUMBER (AE #)
 7537 (AE # 1329500)

9. PATIENT IDENTIFICATION 046	10. AGE 36	11. SEX Female
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12. DESCRIPTION OF ADVERSE EVENT
 The patient was a 36-year-old female with metastatic adrenal carcinoma who developed grade 4 hypotension, grade 4 neutropenia, grade 3 pericardial effusion and grade 3 decreased platelets and subsequently expired from an undetermined cause while on a phase 1 study using the investigational agents bevacizumab and sunitinib. She began her first course of treatment on October 30, 2009, and received her last dose of bevacizumab on November 13, 2009 (Cycle 1, Day 15), and the last dose of sunitinib on November 21, 2009 (Cycle 1, Day 23). On November 20, 2009 (Cycle 1, Day 22), the patient's lab values included an absolute neutrophil count (ANC) of 1.32 K/ μ L (reference range: 1.45-7.50 K/ μ L) and a platelet count of 33 K/ μ L (reference range: 150-400 K/ μ L). On November 22, 2009 (Cycle 1, Day 24), the patient presented via EMS to the ER with persistent severe midsternal and left sided chest pain, ST elevations on ECG and a BP of 69/48 mmHg. She was intubated and started on vasopressors then urgently transferred to the cardiac cath lab where an intra-aortic balloon pump was placed. Findings included normal coronary arteries, severe left ventricular hypertrophy, a small pericardial effusion without tamponade and global mild left ventricular systolic dysfunction which was disproportionate to her hypotension. Her condition continued to deteriorate with mixed respiratory and metabolic acidosis, multi-organ system failure including cardiogenic and possible septic shock and respiratory failure. On November 24, 2009 (Cycle 1, Day 26), the patient coded and expired. Additional information has been requested from the investigative site. There is a reasonable possibility that the experience may have been caused by the drugs.

13. DOSE, ROUTE, AND SCHEDULE
 Cycle = 42 days, Bevacizumab: 5 mg/kg IV over 30 - 90 minutes on Days 1, 15, and 29
 Sunitinib: 37.5 mg PO once daily on Days 1-28

14. DATES OF TREATMENT
 The patient started the investigational therapy on October 30, 2009, and received her last dose of bevacizumab on November 13, 2009 (Cycle 1, Day 15), and sunitinib on November 21, 2009 (Cycle 1, Day 23).

15. ACCRUAL AND IND EXPERIENCE
 Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab = 23,777; and using sunitinib = 2,075. Neutropenia is a known event for bevacizumab and sunitinib. Hypotension is a known event for bevacizumab. Decreased platelets is a known event for sunitinib. There have been 67 other cases of death NOS for bevacizumab and 4 other cases for sunitinib, 13 other cases of hypotension for sunitinib, 13 other cases of non-malignant pericardial effusions for bevacizumab and 4 other cases for sunitinib, and 195 other cases of decreased platelets for bevacizumab reported to the NCI through AdEERS as serious adverse events 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.