

IND SAFETY REPORT: INITIAL WRITTEN REPORT

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

FAX: 301-796-9845

1. IND NUMBER
69896

2. AGENT NAME
BAY 43-9006 tosylate (sorafenib tosylate)

3. DATE
December 6, 2010

4. SPONSOR
Division of Cancer Treatment and Diagnosis, National Cancer Institute

5. REPORTER'S NAME, TITLE, AND INSTITUTION
John Wright, MD, PhD-Associate Branch Chief for Investigational Therapeutics 2, Investigational Drug Branch, CTEP, DCTD, NCI

6. PHONE NUMBER
301-496-1196

7. FAX NUMBER
301-402-0428

8a. PROTOCOL NUMBER (AE #)
CALGB-80802 (AE# 1546556)

8b. AE GRADE: AE
Grade 5: Sepsis

9. PATIENT IDENTIFICATION
121520

10. AGE
79

11. SEX
Male

12. DESCRIPTION OF ADVERSE EVENT

The patient was a 79-year-old male with unresectable hepatocellular carcinoma who experienced grade 5 sepsis while on a phase 3 study utilizing the investigational agent sorafenib tosylate in combination with doxorubicin. He began the investigational therapy on July 8, 2010, and received his last dose of sorafenib tosylate on October 19, 2010 (Cycle 5, Day 7) and the last dose of doxorubicin on October 13 (Cycle 5, Day 1). On October 20, 2010, the patient presented to the emergency room with 24-hour history of lassitude and 1- to 2-hour period of profound lethargy, shaking chills, and rigors. His laboratory tests revealed: white blood cell count (WBC): 0.7 K/mcL (reference range: 3.5-11.0 mcL); absolute neutrophil count (ANC) 0.51 K/ mcL (reference range: 1.9-8.0 mcL). The patient was hypotensive (blood pressure 90/50 mmHg) and tachycardic (pulse 145 beats/minute). He was given intravenous fluids and antibiotics for presumed neutropenic sepsis and admitted to the intensive care unit. During his hospitalization, the patient was poorly responsive and barely oriented. He was started on Levophed® and then vasopressin at maximum doses, but his hypotension did not improve. The patient was anuric, and his urinalysis was positive for nitrites; it was felt that he had acute kidney injury due to acute tubular necrosis from severe septic shock. He was progressively dyspneic and hypoxic, which was treated with continuous positive airway pressure. The patient was treated and managed short of being given life support due to his previous request to be DNR. He developed progressive hypotension and then went into asystole. The patient died the day of admission. Two days later, it was revealed that his blood culture was positive for *Escherichia coli*. 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 = 21 Days (Cycles 1-6) sorafenib tosylate: 400 mg PO twice daily
Cycles 7+: sorafenib tosylate: 400 mg PO twice daily

14. DATES OF TREATMENT

The patient began the investigational therapy on July 8, 2010, and received his last dose of sorafenib tosylate on October 19, 2010 (Cycle 5, Day 7).

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using; sorafenib tosylate = 6,533. There have been 49 other cases of sepsis/blood infection reported to the NCI through AdEERS as serious adverse events for sorafenib tosylate.

16. COMMENTS

The following was also administered on this protocol:
Cycle = 21 Days (Cycles 1-6) Doxorubicin: 60 mg/m² IV on Day 1

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.

0002