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DATE:

FROM: John Wright, M.D., Ph.D., Investigational Drug Branch, CTEP, DCTD, NCI 

SUBJECT: BAY 43-9006 tosylate (BAY 54-9085; sorafenib tosylate) NCI IND Safety Report, AE# 1546556

TO: Investigators Using Sorafenib (NSC 724772)

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies conducted under a U.S. IND to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. Please find attached a copy of an IND Safety Report recently submitted to the FDA for the CTEP-sponsored investigational agent sorafenib.

The following must be completed by all investigators using sorafenib under NCI IND 69896.

- Send a copy of the IND Safety Report to your Institutional Review Board (IRB) according to your local IRB's policies and procedures.
- File a copy of the IND Safety Report in your protocol file.

If your study is not covered under IND 69896, it is strongly recommended that you follow the instructions above.

Please note that for Cooperative Group studies, the Cooperative Group Operations Office will provide instructions for IRB submissions, any patient notifications, etc.

Based on CTEP's assessment of the current information in light of previous experience with sorafenib, there does not appear to be a change in the risk-benefit ratio for sorafenib studies; therefore, CTEP is not requiring a protocol amendment at this time.

Please continue to report events according to the adverse event reporting guidelines in your protocol(s).

The attached Adverse Events Assessment describes the adverse event(s) (synopsis provided below), relevant previous experience under these INDs and/or NSCs, and the total number of patients enrolled in trials under this IND and/or NSC.

A 79-year-old male with unresectable hepatocellular carcinoma experienced grade 5 sepsis while on a phase 3 study utilizing the investigational agent sorafenib in combination with doxorubicin.

ADVERSE EVENTS ASSESSMENT

IND 69896 NSC 724772 BAY 43-9006 tosylate (BAY 54-9085; sorafenib tosylate)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: Gr. 5: Sepsis
AE: 1546556	Protocol: CALGB-80802

The patient was a 79-year-old male with unresectable hepatocellular carcinoma who expired from sepsis while on a phase 3 study utilizing the investigational agent sorafenib in combination with doxorubicin. He began the investigational therapy on July 8, 2010, receiving doxorubicin 60 mg/m² IV on Day 1 of Cycles 1-6, and sorafenib 400 mg PO BID orally, every 21 days. He received his last dose of sorafenib on October 19, 2010 (Cycle 5, Day 7), and his last dose of doxorubicin on October 13, 2010 (Cycle 5, Day 1).

The patient was diagnosed with unresectable hepatocellular carcinoma in May 2010, and he did not receive other prior therapies. The patient began the investigational therapy on July 8, 2010.

On October 20, 2010, the patient presented to the emergency room with a 24-hour history of lassitude and 1- to 2-hour period of profound lethargy and shaking chills. His laboratory tests revealed a white blood cell count (WBC) of 0.7 K/mcL (reference range: 3.5-11.0 K/mcL) and an absolute neutrophil count (ANC) of 0.51 K/mcL (reference range: 1.9-8.0 K/mcL). The patient was hypotensive (blood pressure 90/50 mmHg) and tachycardic (pulse 145 beats/minute). The patient was also noted to be making very little urine and his urinalysis was positive for nitrites. 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 became anuric. It was felt that he had acute kidney injury due to acute tubular necrosis from severe sepsis/septic shock. He was progressively dyspneic and hypoxic, and he was treated with continuous positive airway pressure (CPAP). 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*.

The patient's past medical/surgical history was significant for superficial urothelial malignancies, diabetes, hypertension, post-polio syndrome with persistent weakness, cataracts, asthma, rotator cuff problems, obesity, chronic leg ulcers, right knee replacement, right hip arthrotomy, cholecystectomy, appendectomy, tonsillectomy, and cystoscopies. Medications taken at the time of the event included amlodipine, aspirin, calcium, Combivent[®] inhaler, Enablex[®], glipizide, lorazepam, Lyrica[®], multivitamins, mupirocin, Oxycontin[®], oxycodone, Prevacid[®], Compazine[®], Darvocet[®], Symbicort[®], and Zofran[®].

Sepsis/blood infection is a known event for sorafenib.

A total of 6,567 patients have been enrolled in NCI-sponsored clinical trials under the sorafenib IND and/or NSC.

In this case, it is felt that a possible causal relationship exists between the event and sorafenib therapy.

	Sepsis
Sorafenib	Possible
Doxorubicin	Definite
Diabetes	Possible
Urinary urgency and retention	Probable
Hepatocellular carcinoma	Unrelated

Date: 3/19/11

Signature: John Wright M.D.
John Wright, M.D., Ph.D.
(IDB Monitor for sorafenib)

If this assessment is changed, we will notify your office.

cc: Kimberly Boothe, Pharm D.
Bayer Healthcare Pharmaceuticals, Inc.

Joseph A. Leveque, M.D.
Onyx Pharmaceuticals, Inc.