




DATE: MAY 25 2011

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#
1807371

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 this letter to your Institutional Review Board (IRB) of record according to your policies and procedures.
- File a copy of this letter 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 68-year-old male with metastatic hepatocellular carcinoma experienced grade 5 cardiac arrest while on a phase 3 study utilizing the investigational agent sorafenib in combination with doxorubicin.

ADVERSE EVENTS ASSESSMENT

IND 69896 NSC 724772 Sorafenib (BAY 43-9006)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Event: Gr. 5: Cardiac arrest
AE: 1807371	Protocol: CALGB-80802

The patient was a 68-year-old male with metastatic hepatocellular carcinoma who expired from cardiac arrest while on a phase 3 trial utilizing the investigational agent sorafenib in combination with doxorubicin. He began his first course of the investigational treatment on January 28, 2011, receiving sorafenib 400 mg PO twice daily, every 21 days and doxorubicin 60 mg/m² IV on day 1 for Cycles 1-6, every 21 days. He received his last dose of sorafenib on February 7, 2011 (Cycle 1, Day 11). The patient received his first and only dose of doxorubicin on January 28, 2011 (Cycle 1, Day 1).

The patient was diagnosed with metastatic hepatocellular carcinoma in August 2008 and is status post radiation therapy. On January 21, 2011, a CT scan of the abdomen and pelvis revealed a right hepatic mass which was slightly decreased in size but consistent with recurrent hepatocellular carcinoma, a new right pulmonary nodule, a left upper lobe nodule which was slightly increased in size, an unchanged right lower lobe bronchiectasis, an unchanged right portal vein thrombosis, and an unchanged 3.2 cm abdominal aortic aneurysm, compared to previous scans. On January 28, 2011 (Cycle 1, Day 1), a MUGA rest study was normal and he began the investigational therapy that day.

On February 3, 2011 (Cycle 1, Day 7), the patient called the clinic to report soreness of the scalp and a sore throat. He denied having sore mouth and pain or redness of his hands and feet. He was started on minocycline. On February 7, 2011 (Cycle 1, Day 11), EMS was called to the patient's home with reports of him being lethargic. He was transported to the local emergency room (ER) in cardiac arrest. The patient was started on cardiopulmonary resuscitation (CPR), IV fluids, and oxygen while enroute to the ER. He also received Narcan[®], epinephrine, atropine, and D50 for a blood sugar level of 33 mg/dL (reference range: 65-120 mg/dL).

On arrival at the ER at 2:55 PM, the patient had shallow respirations at a rate of 16 breaths per minute, a blood pressure of 115/21 mmHg, and a heart rate of 156 bpm. An ECG showed atrial fibrillation with rapid ventricular response and right bundle branch block. His chest X-ray revealed bilateral diffuse infiltrates which were greater in the right lung than in the left, and a questionable emphysematous pyelonephritis. His blood sugar increased to 221 mg/dL. A nasogastric tube was inserted, dopamine drip was started, and he was intubated and placed on mechanical ventilation with an oxygen saturation of 100%. However, his arterial blood gases results included a pH of 6.94 (reference range: 7.35-7.45), a pCO₂ of 22 mmHg (reference range: 32-45 mmHg), a pO₂ of 452 mmHg (reference range: 70-100 mmHg), and a bicarbonate of 5 mmol/L (reference range: 21-28 mmol/L).

At 3:30 PM that day, the patient's blood pressure increased to 151/110 mmHg and his respiration was 13 breaths per minute. CPR was reinitiated. Despite resuscitative measures, the patient's condition continued to deteriorate and he expired at 3:59 PM that day. An autopsy was not performed. On February 9, 2011, the site was notified by the patient's wife of his death.

The patient's past medical/surgical history was significant for hyperlipidemia, cirrhosis, hepatitis C, gastroesophageal reflux, tuberculosis in 1997, pneumothorax, and cigarette smoking (quitting 4 years ago). Medications taken at the time of the event included amlodipine, omeprazole, entecavir, prochlorperazine, and Zofran[®].

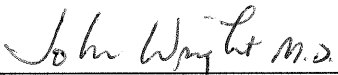
There have been 6 other cases of cardiac arrest (grade 4; 2 possibly related, 3 unlikely related, and 1 unrelated) reported to the NCI as serious adverse events through AdEERS under the sorafenib NSC and/or IND.

To date, a total of 6665 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 the investigational agent sorafenib.

	Cardiac arrest
Sorafenib	Possible
Doxorubicin hydrochloride	Possible
Hepatocellular carcinoma	Possible
Amlodipine	Possible
Entecavir	Possible
Smoking history	Possible
Hyperlipidemia	Possible
Hypoglycemia	Possible
Cirrhosis	Possible

Date: 5/23/11

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

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

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