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SUBJECT: OSI-774 (erlotinib; Tarceva®) and BAY 43-9006 tosylate (BAY 54-9085; sorafenib tosylate) NCI IND Safety Report, AE# **1688406**

TO: Investigators using erlotinib and sorafenib (NSC 718781 and 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 these investigational agents. Please find attached a copy of an IND Safety Report recently submitted to the FDA for the CTEP-sponsored investigational agents erlotinib and sorafenib.

The following must be completed by all investigators using erlotinib under NCI IND 63383 and 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 INDs 63383 and 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 erlotinib and sorafenib, there does not appear to be a change in the risk-benefit ratio for erlotinib and 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 these INDs and/or NSCs.

A 56-year-old female with metastatic adenocarcinoma of the gallbladder experienced gastrointestinal perforation and died while on a phase 2 study utilizing the investigational agents erlotinib and sorafenib.

ADVERSE EVENTS ASSESSMENT

IND 63383 NSC 718781 OSI-774 (erlotinib, Tarceva®) AE: 1688406	69896 724772 Sorafenib BAY 43-9006 tosylate (BAY 54-9085; sorafenib tosylate)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: Gr. 5: Gastrointestinal perforation Protocol: S0941
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The patient was a 56-year-old female with metastatic adenocarcinoma of the gallbladder who experienced gastrointestinal (GI) perforation and died while on a phase 2 study utilizing the investigational agents erlotinib and sorafenib. The planned protocol therapy the patient was assigned was as follows:

Cycle = 28 days:
 Sorafenib: 400 mg PO BID
 Erlotinib: 100 mg PO QD

The patient was diagnosed with metastatic adenocarcinoma of the gallbladder in February 2011, and had received no prior therapy. Baseline CT scans on March 17, 2011, showed diffuse hepatic metastases, focal biliary dilatation with intrahepatic dilatation, a new area of low-attenuation in the spleen which likely represented a splenic infarct, and a low attenuation mass in the left adrenal gland. She began the investigational therapy on March 31, 2011. The patient received the last dose of erlotinib on April 10, 2011 (Cycle 1, Day 11), and the last dose of sorafenib on April 11, 2011 (Cycle 1, Day 12).

Of note, on March 23, 2011 (prior to study therapy), the patient was hospitalized for abdominal pain, nausea, vomiting, and chest pain. An abdominal and chest X-ray showed a relative diffuse and extensive bilateral pulmonary interstitial infiltrate which seemed progressive, no obstructive bowel gas pattern, and no free intraperitoneal air. She had a diffusely tender abdomen with increased tenderness in the left upper quadrant. The patient had an AST of 116 IU/L (reference range: 15-41 IU/L), an ALT of 225 IU/L (reference range: 10-54 IU/L), an alkaline phosphatase of 428 units/L (reference range: 27-120 units/L), and troponin of 5.90 ng/mL (reference range: < 0.03 ng/mL). Also of note, the patient had a cardiac catheterization in February 2011 that was normal with an ejection fraction of 70%. The cardiologist felt that based on the recent cardiac catheterization, the elevated troponin was a false positive and less likely a coronary spasm. The gastroenterologist's impression was that the patient's abdominal pain was multifactorial, related to her multiple intraabdominal metastatic disease, splenic infarcts, and possible gastroparesis due to pain medication. Gastritis or underlying peptic ulcer disease and empirical treatment with a proton pump inhibitor was recommended. Esophagogastroduodenoscopy was not done as it was thought it would not change management except if the patient developed signs of bleeding. The patient's condition improved and she was discharged home on March 28, 2011.

At a follow-up visit on April 11, 2011 (Cycle 1, Day 12), the patient presented to the clinic with a 2-day history of abdominal pain and black stools. She also reported taking Decadron®, which she had started during her recent hospitalization. The patient was found to have scleral icterus and a diffusely tender abdomen with minimal rebound. Laboratory results showed hemoglobin of 11.1 g/dL (reference range: 12.0-16.0 g/dL), AST of 95 IU/L, ALT of 220 IU/L, and alkaline phosphatase of 593 units/L. Erlotinib was held, and an abdominal X-ray was ordered. The doses of Decadron® and Ativan® were reduced.

On April 12, 2011, the treating physician was notified of the abdominal X-ray result which revealed a tiny amount of pneumoperitoneum. The patient was instructed to go to the emergency room for the perforated viscus, and she presented to the emergency room with reports of drenching sweats, nausea, and two episodes of black stools per day over the past 4 days. She had a blood pressure of 112/94 mmHg, a heart rate of 90 bpm, and an oxygen saturation of 93% on 3 liters of oxygen (of note, the patient had a history of emphysema and used 2 liters of oxygen at home). The patient appeared very sleepy but opened her

eyes to questions, had a deep breathing pattern, pinpoint pupils, and was in no apparent distress. Her abdomen was soft, with multiple masses, and there was increasing tenderness in the right upper quadrant. She had a hemoglobin of 10.4 g/dL.

An abdominal X-ray that day showed free air under the diaphragm which was similar to results seen the previous day. She was started on IV fluids and admitted to the hospital. A surgical consult was placed, and after assessment, it was felt that the patient was not a good candidate for surgery and that her prognosis was very dismal. After discussions with the patient's husband, the goal of care was changed to palliative and comfort care measures. She was continued on Zofran[®], Dilaudid[®], and Decadron[®], and was started on Compazine[®] as needed. No CT scans were performed.

On April 13, 2011, the patient was restless, confused, and tachycardic. She was given Haldol[®] and was initiated on a patient controlled analgesia (PCA) with morphine. The patient's condition deteriorated and she expired that day.

The patient's past medical/surgical history was significant for transient ischemic attack with expressive aphasia (September 2010), hypertension, migraine, constipation, non ST-segment elevation myocardial infarction (February 2011), urinary tract infection, tonsillectomy, laparoscopic cholecystectomy, dilation and curettage, and cigarette smoking. Medications taken at the time of the event included Aspirin[®], Zofran[®], Neurontin[®], Fentanyl[®], Colace[®], Decadron[®], metoprolol, albuterol, Ativan[®], and Dilaudid[®].

There have been 10 other cases of GI perforation reported to the NCI as serious adverse events through AdEERS under the erlotinib NSC and/or IND, and 30 other cases of GI perforation reported to the NCI as serious adverse events through AdEERS under the sorafenib NSC and/or IND.


Adverse Event	Grade	Attribution
Erlotinib		
GI perforation (n=10)	5	1 Possible, 1Unlikely, 1Unrelated
	4	3 Possible, 1 Unlikely
	3	1 Possible, 2 Unlikely,
Sorafenib		
GI perforation (n=30)	4	2 Probable, 1 Unlikely,
	3	1 Definite, 3 Probable, 20 Possible, 2 Unlikely
	2	1 Possible

To date, a total of 3, 527 patients have been enrolled in NCI-sponsored clinical trials under the erlotinib IND and/or NSC, and a total of 6, 694 patients have been enrolled in NCI-sponsored clinical trials under the sorafenib IND and/or NSC.

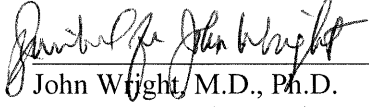
In this case, it is felt that a possible causal relationship exists between the event and the investigational agents.

	Gastrointestinal perforation
Erlotinib	Possible
Sorafenib	Possible
Gall bladder carcinoma	Definite
Decadron[®]	Probable

Date: 6/1/11

Signature: 
Helen Chen, M.D.
(IDB Monitor for erlotinib)

Date: 6/3/11

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

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

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