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**SUBJECT:** BAY 43-9006 Tosylate (BAY 54-9085; Sorafenib Tosylate) and CCI-779 (temsirolimus, Torisel<sup>®</sup>) NCI IND Safety Report, AE# 1416121 *L. Austin Doyle MD*

**TO:** Investigators Using Sorafenib (NSC 724772) and CCI-779 (temsirolimus, Torisel<sup>®</sup>) (NSC 683864)

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 agents sorafenib and CCI-779.

The following must be completed by all investigators using sorafenib under NCI IND 69896 and CCI-779 under NCI IND 61010

- 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 INDs 69896 and IND 61010, 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 and CCI-779, there does not appear to be a change in the risk-benefit ratio for sorafenib and CCI-779 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 74-year-old female with metastatic melanoma experienced grade 5 pancreatitis while on a phase 2 trial utilizing the investigational agent sorafenib in combination with CCI-779.

**ADVERSE EVENTS ASSESSMENT**

IND 69896	61010	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: <b>Gr. 5: Pancreatitis</b>
NSC 724772	683864	
<b>BAY 43-9006 tosylate (BAY 54-9085; sorafenib tosylate)</b>	<b>CCI-779 (temsirolimus; Torisel®)</b>	
AE: 1416121	Protocol: <b>S0438</b>	

The patient was a 74-year-old female with metastatic melanoma who died from pancreatitis while on a phase 2 trial utilizing the investigational agents sorafenib and CCI-779. She began the first course of treatment on October 14, 2009, receiving sorafenib 200 mg PO BID and CCI-779 25 mg IV over 30 minutes on Days 1, 8, 15, and 22, every 28 days. She received her last dose of sorafenib on January 24, 2010 (Cycle 4, Day 24) and her last dose of CCI-779 on January 13, 2010 (Cycle 4, Day 13).

The patient was diagnosed with metastatic melanoma in June 2008 and was status post lymph node resection, melanoma resection, and multiple-agent systemic chemotherapy. The patient began the investigational therapy on October 14, 2009.

On January 24, 2010 (Cycle 4, Day 24), the patient presented to the emergency room via ambulance after having been found by her family. She had been suffering from nausea for 2 weeks and had had 2 days of altered mental status and constant abdominal pain that was described as being located in the right, left, and lower abdomen, periumbilical area, and pelvic area. The patient had also had episodes of diarrhea and had been on antibiotics for treatment of a urinary tract infection approximately one month ago. Laboratory results showed: amylase 173 IU/L (reference range: 30-110 IU/L), lipase was 2111 IU/L (reference range: 114-286 IU/L), WBC 14.1 k/mm<sup>3</sup> (reference range: 4.8-10.8 k/mm<sup>3</sup>), BUN 38 mg/dL (reference range: 7-18 mg/dL), creatinine 2.0 mg/dL (reference range: 0.6-1.3 mg/dL), and total CK was 357 (reference range: 21-215). A CT scan of the abdomen and pelvis revealed multiple pulmonary nodules consistent with metastatic disease, multiple solid liver lesions suspicious for metastatic disease, ascites, inflammation with a nodular component in the omentum/mesentery suspicious for malignant involvement, and an unremarkable pancreas. It was felt that her pancreatitis was possibly related to the study medications. On January 25, 2010, the laboratory results showed: amylase 547 IU/L, lipase 5671 IU/L, WBC 17.1 k/mm<sup>3</sup>, BUN 39 mg/dL, and creatinine 2.6 mg/dL. The patient expired on January 25, 2010, and no autopsy was performed.

The patient's past medical/surgical history is significant for hypertension, lung cancer, prior history of smoking, and cholecystectomy. Medications taken at the time of the event included amlodipine, hydrochlorothiazide, Cozaar®, and aspirin.

There have been 25 other cases of pancreatitis reported to the NCI as serious adverse events through AdEERS under the sorafenib NSC and/or IND. There have been 2 other cases of pancreatitis reported to the NCI as serious adverse events through AdEERS under the CCI-779 NSC and/or IND. The findings are summarized in the table below:

Adverse Event	Grade	Attribution
<b>Sorafenib (NSC 724772)</b>		
Pancreatitis (n=25)	4	1 Possible
	3	1 Unrelated, 4 Unlikely, 1 Possible, 1 Probable, 1 Definite
	2	1 Unlikely, 10 Possible, 2 Probable, 2 Definite
	1	1 Possible
<b>CCI-779 (NSC 683864)</b>		
Pancreatitis (n=2)	2	1 Definite
	1	1 Unlikely

A total of 6287 patients have been enrolled in NCI-sponsored clinical trials under the sorafenib IND and/or NSC, and a total of 2186 patients have been enrolled under the CCI-779 IND and/or NSC.

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

	<b>Pancreatitis</b>
<b>Sorafenib</b>	Possible
<b>CCI-779</b>	Possible
<b>Melanoma</b>	Possible
<b>Dehydration</b>	Unlikely

Date: 10/22/10

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

Date: 8/31/10

Signature: L. Austin Doyle MD  
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(IDB Monitor for CCI-779)

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

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