

NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: March 28, 2008

To: NCCTG Primary Clinical Research Associates

From: Janis Wobschall
Protocol Development Coordinator

Re: N0572, A Phase I/II Study of Sorafenib and CCI-779 in Patients with Recurrent Glioblastoma

The purpose of this memorandum is to provide investigators with a recent report of an adverse event that has occurred in association with BAY 43-9006 for a study where the Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI) is distributing this agent. You may have also received this communication directly from DCTD.

AE_1829917

Please note that all risks currently cited in the NCCTG consent form cannot be omitted; it is at the discretion of your local IRB as to whether they wish to add risks based on the enclosed information. If a determination has been made by the NCCTG Research Base that a protocol amendment is necessary, you will receive the NCI-approved protocol addendum at a later date; for purposes of cross-reference, this communication will cite the adverse event noted above.

Please submit this adverse event to your Institutional Review Board.

If you have any questions concerning this communication, please contact Janis Wobschall at wobschall.janis@mayo.edu or 507/284-4852.

JW/df
enclosure



DATE: February 29, 2008

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

SUBJECT: BAY 43-9006 Tosylate (BAY 54-9085; Sorafenib Tosylate) and Sunitinib Malate (SU011248 L-malate; Sutent[®]) NCI IND Safety Report, AE# 1829917

TO: Investigators Using CTEP-supplied Investigational Sorafenib (NSC 724772) and Sunitinib (NSC 736511)

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 sunitinib.

The following must be completed by all investigators using sorafenib under NCI IND 69896 and sunitinib under NCI IND 74019:

- 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 74019, 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 sunitinib, there does not appear to be a change in the risk-benefit ratio for sorafenib and sunitinib 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 male with renal cell carcinoma developed renal failure while on a phase 3 trial comparing the investigational agents sorafenib (or placebo) to sunitinib (or placebo), following a radical or partial nephrectomy.

ADVERSE EVENTS ASSESSMENT

IND 69896	74019	ADVERSE EXPERIENCE REPORT NO. #26 IND Safety Report: Initial Event: Gr. 3: Renal failure Protocol: E2805
NSC 724772	736511	
BAY 43-9006	Sunitinib malate	
tosylate (BAY 54-9085; sorafenib tosylate	(SU011248 L-malate; Sutent®)	
AE: 1829917		

The patient is a 74-year-old male with stage III renal cell carcinoma who experienced renal failure while on a phase 3 trial comparing adjuvant sorafenib (or placebo) to sunitinib (or placebo) following a radical or partial nephrectomy. He began his first course of treatment on October 18, 2007, and was to receive sorafenib or placebo 400 mg PO twice daily for six weeks and sunitinib or placebo 50 mg PO daily for four weeks followed by rest for two weeks for nine cycles. He received his last dose of sorafenib or placebo and the last dose of sunitinib or placebo on November 12, 2007 (Cycle 1, Day 26).

The patient was initially diagnosed with stage III renal cell carcinoma with a partial (5%) sarcomatoid differentiation in August 2007 and is status post left radical nephrectomy on August 7, 2007. The patient began investigational treatment on October 18, 2007. Shortly after initiation of treatment, the patient developed diarrhea and mouth sores. On November 7, 2007, he was found to have oral herpes simplex virus type 1, which led to herpetic stomatitis.

On November 15, 2007 the patient presented to the emergency room with a 5-day history of worsening diarrhea, anorexia, oral lesions, progressive malaise and intermittent confusion. Upon examination he was alert, afebrile, his blood pressure was 93/60 mmHg, his chest was clear to auscultation anteriorly, and he had a regular heart rate ranging from 60 to 90 bpm. His upper extremities were notable for significant excoriations and psoriasiform plaques. Laboratory results were remarkable for creatinine of 7.1 mg/dL (reference range: 0.4-1.5 mg/dL), BUN of 77 (reference range: 5-25 mg/dL), and CO₂ of 17 mmol/L (reference range: 23-31 mmol/L). The patient's baseline creatinine post nephrectomy ranged from 1.6 to 2.04 mg/dL. Dipstick urine test revealed 3+ hemoglobin and 2+ protein. He was rehydrated and admitted to the hospital for acute renal failure, anion gap acidosis, and mental status changes. Of note is the patient's recent intake of up to nine ibuprofen tablets per day and loperamide for symptoms of pain and diarrhea. He was treated with aggressive IV hydration with a bicarbonate solution, acyclovir, and empiric levofloxacin. On November 16, 2007, the patient had a renal ultrasound which showed no evidence of hydronephrosis. A chest, abdomen, and pelvis CT scan without contrast revealed a small hypodense lesion in the right kidney which likely represented a cyst, distended gallbladder, and prostatomegaly. His urine culture was negative for bacteria or yeast. His antihypertensive medications were held. Throughout the course of his hospitalization, the patient's condition improved significantly and by November 21, 2007, his creatinine was 1.5 mg/dL and he was discharged home. He was removed from protocol treatment on November 28, 2007.

The patient's past medical/surgical history is significant hypertension, atherosclerotic triple vessel coronary artery disease status post multiple cardiac catheterizations with angioplasty, and right carotid endarterectomy. Medications were taken at the time of the event included Crestor®, Atacand HCT®, Tenormin®, isosorbide mononitrate, nitroglycerine, aspirin, paroxetine, fish oil, flax seed, ibuprofen, loperamide, topical Clobex®, CoQ10, and Pulmicort®.

There have been 18 other occurrences of renal failure reported to the NCI as serious adverse events through AdEERS under the sorafenib IND and/or NSC, and 7 other occurrences of renal failure reported to the NCI as serious adverse events through AdEERS under the sunitinib IND and/or NSC, which are summarized in the following table:

Adverse Event	Grade	Attribution
Sorafenib (NSC 724772)		
Renal failure (n=18)	5	1 Unlikely
	4	1 Possible, 3 Unlikely
	3	1 Probable, 3 Possible, 6 unlikely, 2 Unrelated
	1	1 Unlikely
Sunitinib (NSC 736511)		
Renal failure (n=7)	5	1 Possible
	4	1 unlikely, 1 Unrelated
	3	1 Probable, 1 Possible, 2 Unlikely

A total of 3466 patients have been enrolled in NCI-sponsored clinical trials under the sorafenib IND and/or NSC and a total of 740 patients have been enrolled under the sunitinib IND and/or NSC.

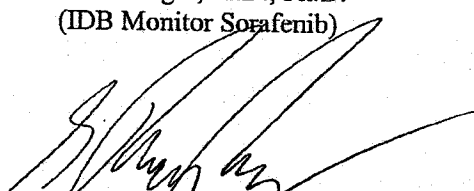
In this case, it is felt that a causal relationship between the event and sorafenib or sunitinib therapy cannot be excluded.

	Renal failure
Sorafenib	Possible
Sunitinib	Possible
Renal cell carcinoma	Unrelated
Ibuprofen	Probable
Loperamide	Unrelated
Severe diarrhea with acidosis and dehydration	Probable

Date: 3/13/08

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

Date: 03.13.08

Signature: 
 S. Percy Ivy, M.D.
 (IDB Monitor for Sunitinib)

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

cc: Jeffrey Humphrey, M.D.
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