



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: January 18, 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_1303740

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: December 26, 2007

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# 1303740

TO: Investigators Using CTEP-supplied Investigational Sorafenib Tosylate (NSC 724772) and Sunitinib Malate (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 tosylate and sunitinib malate.

The following must be completed by all investigators using sorafenib tosylate under NCI IND 69896 and sunitinib malate 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 tosylate and sunitinib malate, there does not appear to be a change in the risk-benefit ratio for sorafenib tosylate and sunitinib malate 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 this IND and/or NSC, and the total number of patients enrolled in trials under this IND and/or NSC.

A 68-year-old female with renal cell carcinoma developed cerebrovascular ischemia while on a phase 3 trial comparing the investigational agents sorafenib tosylate (or placebo) to sunitinib malate (or placebo), following a radical or partial nephrectomy.

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ADVERSE EVENTS ASSESSMENT

IND 69896 NSC 724772 BAY 43-9006 tosylate (BAY 54-9085; sorafenib tosylate AE: 1303740	74019 736511 Sunitinib malate (SU011248 L-malate; Sutent®)	ADVERSE EXPERIENCE REPORT NO. 24 IND Safety Report: Initial Event: Gr. 4: CNS cerebrovascular ischemia Protocol: E2805
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The patient is a 67-year-old female with renal cell carcinoma who experienced cerebrovascular ischemia while on a phase 3 trial comparing adjuvant sorafenib tosylate to sunitinib malate to placebo following a radical or partial nephrectomy. She began her first course of treatment on June 1, 2007, receiving sorafenib tosylate or placebo 400 mg PO twice daily for 6 weeks for nine cycles and sunitinib malate or placebo 50 mg PO daily for 4 weeks followed by a 2-week rest for nine cycles. She received her last dose of sorafenib tosylate or placebo on October 8, 2007 (Cycle 3, Day 42) and the last dose of sunitinib malate or placebo on September 24, 2007 (Cycle 3, Day 28).

The patient was initially diagnosed with stage 3 renal cell carcinoma of the right kidney, sarcomatoid variant in March 2007 and is status post exploratory laparotomy and right nephrectomy. The patient began investigational treatment on June 1, 2007. Of note, the patient has a history of transient ischemic attack (TIA) in 2001 and hypertensive arteriosclerotic cardiovascular disease.

On October 10, 2007 the patient developed weakness on her left side, dizziness, and ataxia and contacted her primary care physician. Her investigational treatment had been on hold since the day before awaiting re-supply of study drug. The following day she was admitted to her local hospital for evaluation and treatment. Upon physical exam no gross neurological deficits were noted. Her blood pressure was 162/78 mmHg. A CT scan of the brain without contrast and a carotid Doppler study done on October 11, 2007 were unremarkable. An echocardiogram done on the following day revealed normal left ventricular function, trace mitral regurgitation, and mild tricuspid insufficiency. The patient was thought to have had a TIA. She had already been taking Plavix® since her first TIA in 2001 and was started on aspirin. She was discharged home on October 13, 2007.

On October 15, 2007, the patient called the clinic to report the event and continued symptoms. She had an MRI with and without contrast done on that day which revealed abnormal signal intensity in the left basal ganglia region consistent with an area of acute infarct and multiple areas within the periventricular white matter of both cerebral hemispheres consistent with chronic small vessel ischemic changes. There was no evidence of malignancy or metastasis. Her investigational therapy continued to be on hold. On October 24, 2007, she had a neurological evaluation and her condition was assessed as cerebral infarction secondary to thrombosis of cerebral arteries (left basal ganglia) related to her pre-existing hypertension. Plavix® and aspirin were discontinued and she was started on Aggrenox®. On November 2, 2007, the patient returned to the clinic for follow-up. Upon evaluation, her blood pressure was 119/70 mmHg, and she had no focal neurological deficits. The patient withdrew from study participation at that time.

The patient's past medical/surgical history is significant hypertension, hypercholesterolemia, arteriosclerotic cardiovascular disease, and one TIA. Medications taken at the time of the event included Diovan®, Plavix®, Cardizem®, and Zetia®.

There have been 13 other occurrences of cerebrovascular ischemia reported to the NCI as serious adverse events through AdEERS under the sorafenib tosylate IND and/or NSC, and 2 other occurrences

of cerebrovascular ischemia reported to the NCI as serious adverse events through AdEERS under the sunitinib malate IND and/or NSC, which are summarized in the following table:

Adverse Event	Grade	Attribution
Sorafenib tosylate (NSC 724772)		
Cerebrovascular ischemia (n=13)	4 3 2	5 Possible, 3 Unlikely 4 Possible 1 Probable
Sunitinib malate (NSC 736511)		
Cerebrovascular ischemia (n=2)	3	2 Possible

A total of 3233 patients have been enrolled in NCI-sponsored clinical trials under NSC 724772 and a total of 599 patients have been enrolled under NSC 736511.

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

	CNS cerebrovascular ischemia
Sorafenib tosylate	Possible
Sunitinib malate	Possible
Renal cell carcinoma	Possible
Cardizem®	Unlikely
Diovan®	Unlikely
Plavix®	Unlikely
Hypertension	Possible
Prior history of TIA	Possible

Date: 1/3/08

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

Date: 01.07.08

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

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

cc: Jeffrey Humphrey, M.D
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