



# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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**Date:** June 15, 2007

**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\_1117502**

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](mailto:wobschall.janis@mayo.edu) or 507/284-4852.

JW/df  
enclosure



National Institutes of Health  
National Cancer Institute  
Bethesda, Maryland 20892

**DATE:** June 11, 2007

**FROM:** John J. 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<sup>®</sup>) NCI IND Safety Report, AE# 1117502

**TO:** Investigators Using CTEP-supplied Investigational BAY 43-9006 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 BAY 43-9006 tosylate and sunitinib malate.

The following must be completed by all investigators using BAY 43-9006 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 BAY 43-9006 tosylate and sunitinib malate, there does not appear to be a change in the risk-benefit ratio for BAY 43-9006 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 31-year-old male with stage III papillary renal cell carcinoma developed grade 3 left ventricular systolic dysfunction (dilated cardiomyopathy with decreased ventricular ejection fraction) while on a phase 3 trial comparing the investigational agents BAY 43-9006 tosylate (or placebo) to sunitinib malate (or placebo), following a radical or partial nephrectomy. Of note, the patient's therapy has not been unblinded.

**ADVERSE EVENTS ASSESSMENT**

IND 69896	74019	ADVERSE EXPERIENCE REPORT NO. 20
NSC 724772	736511	IND Safety Report: Initial
BAY 43-9006 Tosylate (BAY 54-9085, Sorafenib Tosylate)	Sunitinib malate (SU011248 L- malate; Sutent®)	Event: Gr. 3: Left ventricular systolic dysfunction
AE: 1117502		Protocol: E2805

The patient is a 31-year-old male with stage III renal cell carcinoma who experienced left ventricular systolic dysfunction while on a phase 3 trial comparing the investigational agents BAY 43-9006 tosylate (or placebo) to sunitinib malate (or placebo), following a radical or partial nephrectomy. He began his first course of treatment on January 12, 2007, receiving BAY 43-9006 tosylate or placebo 400 mg PO twice daily for 6 weeks and sunitinib malate or placebo 50 mg PO daily for 4 weeks followed by a 2-week rest, every 6 weeks for nine cycles. The patient received his last dose of BAY 43-9006 tosylate or placebo on April 2, 2007 (Cycle 2, Day 39) and the last dose of sunitinib malate or placebo on March 15, 2007 (Cycle 2, Day 21).

The patient was initially diagnosed with renal cell carcinoma secondary to hereditary leiomyomatosis in October 2006 and is status post left radical nephrectomy on October 27, 2006. He began the investigational therapy on January 12, 2007, and completed the first cycle of treatment with no reported events. He began Cycle 2 on February 23, 2007 as scheduled. On March 16, 2007 (Cycle 2, Day 22), the patient experienced hand foot syndrome and temporarily stopped taking the investigational medications. He resumed treatment with BAY 43-9006 or placebo on March 27, 2007 (Cycle 2, Day 33), but not sunitinib or placebo, after his hands returned to normal. The patient developed some dyspnea on exertion during this time he was receiving treatment although he did not have paroxysmal nocturnal dyspnea, orthopnea, lower extremity edema or other signs/symptoms of congestive heart failure. A MUGA scan was obtained on March 30, 2007 (Cycle 2, Day 36), that was concerning for a left ventricular ejection fraction (LVEF) of 38.8% (reference range: >50%), which was significantly decreased from his baseline LVEF of 52.9% on January 6, 2007. The scan and a subsequent echocardiogram also showed development of a mild dilated cardiomyopathy with dilation of the left ventricle and hypokinesis of the septum. Of note is the patient's history of Wolf-Parkinson-White Syndrome for which he underwent surgical ablation in 1990 and has not had tachycardiac symptoms since that time. His protocol therapy was put on hold on April 2, 2007.

An echocardiogram was performed on April 9, 2007, which indicated mild global cardiomyopathy with a LVEF of approximately 40%. He had no symptoms of congestive heart failure. Upon physical examination, his blood pressure was 122/84 mmHg, his pulse was 88 bpm with a regular rhythm, normal femoral and tibial pulses were present, and there was no lower extremity edema noted. Upon auscultation, a II/VI holosystolic heart murmur was heard at the left sternal border, normal S1 and S2 sounds were present, no S3 or S4 gallop was heard, and his lungs were clear. He was started on lisinopril and Coreg®. Protocol treatment will remain on hold for 4 weeks at which time treatment will be restarted pending a cardiac reevaluation. The patient's treatment has not been unblinded.

The patient's past medical/surgical history is significant for Wolf-Parkinson-White Syndrome status post surgical ablation in 1990, hereditary leiomyomatosis associated with papillary renal cell cancer that was diagnosed by the genetics group after his cancer diagnosis, and arthroscopic left knee surgery. The patient's father died from renal cancer as well. No other concomitant medications were being taken by the patient at the time of this cardiac event.

There have been 11 other cases of left ventricular systolic dysfunction reported to the NCI as serious adverse events through AdEERS under the BAY 43-9006 tosylate NSC and two other cases of left

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**AE #1117502**

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ventricular systolic dysfunction reported to the NCI as serious adverse events through AdEERS under the sunitinib malate NSC, which are summarized in the following table:

Adverse Event	Grade	Attribution
<b>BAY 43-9006 tosylate (NSC 724772)</b>		
Left ventricular systolic dysfunction (n=11)	4	1 Unlikely
	3	5 Possible, 5 Unlikely
<b>Sunitinib malate (NSC 736511)</b>		
Left ventricular systolic dysfunction (n=2)	3	1 Possible
	2	.1 Probable

A total of 2,544 patients have been enrolled in NCI-sponsored clinical trials under the BAY 43-9006 NSC, and a total of 164 patients have been enrolled in NCI-sponsored clinical trials under the sunitinib NSC and IND.

In this case, it is felt that a probable causal relationship between the event and the investigational therapy exists. Since the patient has not been unblinded, it is unknown whether the patient received BAY 43-9006 or sunitinib malate or placebo.

	Left ventricular systolic dysfunction
<u>BAY 43-9006 tosylate or placebo</u>	Probable
<u>Sunitinib malate or placebo</u>	Probable
<u>Renal cell carcinoma</u>	Unlikely

Date: 6/10/07

Signature: John Wright M.D.  
John Wright, M.D., Ph.D.  
(IDB Monitor for BAY 43-9006 tosylate)

Date: 06.11.07

Signature: S. Percy Ivy M.D.  
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.  
Karen Wilson  
Bayer Pharmaceuticals Corporation

Todd J. Yancey, M.D.  
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