



# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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**Date:** July 14, 2006

**To:** NCCTG Primary Clinical Research Associates

**From:** Lori Bratvold  
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 Sorafenib (BAY43-9006) 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\_1041096

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 Lori Bratvold at 507/266-3549.

LB/dg  
enclosure



**DATE:** June 16, 2006

**FROM:** John Wright, M.D., Ph.D., Investigational Drug Branch, CTEP, DCTD, NCI

**SUBJECT:** BAY 43-9006 tosylate (BAY 54-9085; sorafenib tosylate) IND Safety Report, AE# 1041096

**TO:** Investigators Using BAY 43-9006 Tosylate, IND 69896

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 agent BAY 43-9006 tosylate (IND 69896).

The following must be completed by all investigators using BAY 43-9006 tosylate under NCI IND 69896:

- 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.

Please note that for Cooperative Group studies, the Cooperative Group Operations Office will provide instructions for IRB submissions, any patient notifications, etc.

CTEP's evaluation of this IND Safety Report in light of previous experience with BAY 43-9006 tosylate does not require a change in the clinical protocols for this agent at this time.

Please continue to report events according to the adverse event reporting guidelines in your protocol(s).

The Adverse Events Assessment that describes the following adverse events, previous experience under this IND, and the total number of patients enrolled in trials under this IND is attached:

A 49-year-old female with cholangiocarcinoma experienced grade 4 hypertension and associated toxicities consistent with grade 3 reversible posterior leucoencephalopathy syndrome while on a phase 2 trial using the investigational agent BAY 43-9006 tosylate.

**CONFIDENTIAL**

1 of 1

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**ADVERSE EVENTS ASSESSMENT**

IND 69896	ADVERSE EXPERIENCE REPORT NO. 13
NSC 724772	IND Safety Report: Initial
Bay 43-9006 tosylate (Bay 54-9085; sorafenib tosylate)	Event: Gr: 4 Hypertension Gr: 3 Syndromes – Other (Reversible Posterior Leucoencephalopathy Syndrome)
AE: 1041096	Protocol: S0514

The patient is a 49-year-old female with cholangiocarcinoma who developed hypertension and associated toxicities consistent with reversible posterior leucoencephalopathy syndrome (RPLS) while on a phase 2 trial using the investigational agent Bay 43-9006 tosylate. She began her first course of treatment on January 12, 2006, receiving Bay 43-9006 400 mg orally, twice daily (Cycle = 28 days). She received the last dose of Bay 43-9006 on May 24, 2006 (Cycle 5, Day 21).

The patient was initially diagnosed with metastatic cholangiocarcinoma in July 2004 and was status post multiple abdominal surgeries. She began the investigational therapy on January 12, 2006, and received the last dose of Bay 43-9006 on May 24, 2006 (Cycle 5, Day 21). The patient was most recently hospitalized in April 2006 for abdominal pain attributed due to a bowel obstruction following a Whipple procedure. Her hospital course was complicated by sepsis due to an intrahepatic abscess and a *vancomycin-resistant enterococci* infection of an abdominal drain treated effectively with aggressive antibiotic therapy. On May 24, 2006, following her Cycle 5, Day 21 dose of the investigational agent, the patient experienced a severe headache followed by an episode of vision loss with a bright flash of light, upper extremity jerking movement, and loss of consciousness. She was transported to the emergency department for a presumed seizure and admitted with a diagnosis of hypertensive crisis (BP 188/103 mmHg). The patient's blood pressure was treated with IV hydralazine and oral labetalol and a neurology consult was obtained. An MRI of the brain revealed posterior parietal and occipital subcortical edema consistent with posterior reversible leucoencephalopathy syndrome. A lumbar puncture was attempted to rule out leptomenigeal disease but was unsuccessful. A renal ultrasound was normal with no evidence of renal artery stenosis. The patient's condition improved and she was discharged from the hospital on May 27, 2006, with oral medication to control her blood pressure. She was discontinued from protocol participation and will be followed closely by her attending physician.

The patient's past medical history is significant for gastric outlet syndrome and grade 1 hypertension noted since initiating the investigational therapy. Medications taken at the time of the event included Micro-K®, Nexium®, MS contin®, morphine sulphate, Colace®, Phenergan®, and magnesium sulphate.

There have been 8 other incidences of hypertension and no other incidences of reversible posterior leucoencephalopathy syndrome reported to the NCI as serious adverse events under this IND. The attributions are summarized in the following table:

Adverse Event	Grade	Attribution
Hypertension (n=8)	4	1 Probable
	3	1 Definite, 3 Probable
	2	3 Possible
Reversible Posterior Leucoencephalopathy Syndrome (n=0)	-	-

In this case, it is felt that a possible relationship between the hypertension, reversible posterior leucoencephalopathy syndrome, and 43-9006 tosylate cannot be excluded. There have been 1066 patients enrolled in NCI sponsored clinical trials under this IND.

	<b>Hypertension</b>	<b>Reversible Posterior Leucoencephalopathy Syndrome</b>
<b>Bay 43-9006 tosylate</b>	Possible	Possible

Cholangiocarcinoma

Unlikely

Unlikely

Date: 6/30/06

Signature:

John Wright M.D.  
John J. Wright, M.D., Ph.D.  
(IDB Monitor for Bay 43-9006 tosylate)

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

cc: Jeffrey Humphrey, M.D.  
Karen Wilson  
Bayer Pharmaceuticals Corporation

Fabio Benedetti, M.D.  
Onyx Pharmaceuticals, Inc.