



# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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**Date:** June 27, 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\_1057624\_F1**

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



**DATE:** May 8, 2008

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

**SUBJECT:** BAY 43-9006 Tosylate (BAY 54-9085; Sorafenib Tosylate) NCI IND Safety Report, AE# **1057624**

**TO:** Investigators Using BAY 43-9006 Tosylate (NSC 724772)

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.

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.

If your study is not covered under IND 69896, 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, there does not appear to be a change in the risk-benefit ratio for BAY 43-9006 tosylate 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 73-year-old male with recurrent melanoma metastatic to the abdomen died suddenly while on a phase 3 trial utilizing the investigational agent BAY 43-9006 tosylate or placebo in combination with paclitaxel and carboplatin.

## ADVERSE EVENTS ASSESSMENT

IND <b>69896</b> NSC <b>724772</b> <b>BAY 43-9006 tosylate (BAY 54-9085; sorafenib tosylate)</b> AE: <b>1057624</b>	ADVERSE EXPERIENCE REPORT NO. <b>27</b> IND Safety Report: <b>#1</b> Event: <b>Gr. 5: Sudden Death</b>  Protocol: <b>E2603</b>
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The patient was a 73-year-old male with recurrent melanoma metastatic to the abdomen who died suddenly while on a phase 3 trial utilizing the investigational agent BAY 43-9006 tosylate or placebo in combination with paclitaxel and carboplatin. He began his first course of treatment on January 28, 2008, receiving BAY 43-9006 tosylate 400 mg PO twice daily or placebo 2 tablets twice daily on Days 2-19, paclitaxel 225 mg/m<sup>2</sup> IV over 3 hours on Day 1, and carboplatin AUC 6 IV over 30 minutes on Day 1, every 21 days, for Cycles 1-4. He received the last dose of BAY 43-9006 tosylate or placebo on March 4, 2008 (Cycle 2, Day 16), and the last doses of paclitaxel and carboplatin on February 18, 2008 (Cycle 2, Day 1).

The patient was initially diagnosed with malignant melanoma of the right deltoid in October 1987 and is status post surgical excision. In November 2007, he noticed abdominal swelling, and a CT scan revealed ascites. Abdominal metastasis was diagnosed by needle biopsy in December 2007. The patient had a large amount of ascites and a moderate-sized pleural effusion present at baseline. He began the investigational therapy on January 28, 2008 and tolerated the first cycle well except for body aches and fatigue. Of note, the patient lost 25 pounds in 1 week due to diuresis.

On February 18, 2008 (Cycle 2, Day 1), the patient had not required paracentesis in 4 weeks, and his ECOG performance status was 1. Upon physical examination, his blood pressure was 106/65 mmHg, his pulse was 102 bpm, he was afebrile, and his oxygen saturation on room air was 96%. It was noted that the lungs were clear to auscultation except for decreased sounds at the left base; his abdomen was less distended; he had normal bowel sounds and resolution of bilateral lower extremity edema.

On March 4, 2008 (Cycle 2, Day 16), the patient's family reported that the patient had gone to the lavatory when they heard him fall and then found him unresponsive. Emergency medical services were called, and CPR was initiated. When the paramedics arrived, the patient had shallow respirations, less than 4 per minute, and his carotid pulse was absent. An ECG showed an agonal rhythm at approximately 28 bpm. The patient was intubated, and CPR was continued. En route to the hospital, the patient began to have spontaneous respirations (approximately 6 per minute); however, upon arrival at the emergency room, the patient was pulseless, and despite continued CPR, the patient was unable to be revived. According to the patient's family, the patient had not reported chest pain, back pain, shortness of breath, or headache prior to the event. He did report feeling somewhat washed out. No autopsy was performed.

The patient's past medical history is significant for aortic sclerosis, hypertension, diabetes mellitus, gastroesophageal reflux disease, benign prostatic hyperplasia, gout, osteoarthritis, alcohol use (2-3 glasses of wine daily), and tobacco use (for 15 years, quit 30 years ago). Medications taken at the time of the event included Flomax<sup>®</sup>, Cipro<sup>®</sup>, Avodart<sup>®</sup>, Lortab<sup>®</sup>, Zofran<sup>®</sup>, Compazine<sup>®</sup>, Glipizide<sup>®</sup>, Nexium<sup>®</sup>, Decadron<sup>®</sup>, aspirin, and Lozol<sup>®</sup>.

There have been 13 other cases of sudden death reported to the NCI as serious adverse events through AdEERS under the BAY 43-9006 tosylate NSC, as shown in the table below:

Adverse Event	Attribution
Sudden death (n=13)	3 Possible, 9 Unlikely, 1 Unrelated

A total of 4,080 patients have been enrolled in NCI-sponsored clinical trials under the BAY 43-9006 tosylate NSC.

In this case, it is felt that a probable causal relationship between the event and BAY 43-9006 tosylate or placebo administration exists.

	<b>Sudden Death</b>
<b>BAY 43-9006 tosylate or placebo</b>	Probable
<b>Carboplatin</b>	Possible
<b>Paclitaxel</b>	Possible
<b>Melanoma</b>	Possible

Date: 6/12/08

Signature: John Wright  
John 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, MD  
Diane M. Plateis, PharmD  
Bayer Pharmaceuticals Corporation

Todd J. Yancey, MD  
Onyx Pharmaceuticals, Inc.