



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: January 4, 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_1853625

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: November 30, 2007

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

SUBJECT: BAY 43-9006 Tosylate (BAY 54-9085; Sorafenib Tosylate) NCI IND Safety Report, AE# 1853625

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 there does not appear to be a change in the risk-benefit ratio for BAY 43-9006 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 60-year-old female with melanoma metastatic to the lungs, adrenal gland, small bowel, and brain experienced a brain hemorrhage and subsequently expired while receiving treatment 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 69896 NSC 724772 BAY 43-9006 tosylate (BAY 54-9085; sorafenib tosylate) AE: 1853625	ADVERSE EXPERIENCE REPORT NO. 22 IND Safety Report: Initial Event: Gr. 5: Hemorrhage, CNS Protocol: E2603
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The patient was a 60-year-old female with melanoma metastatic to the lungs, adrenal gland, small bowel, and brain who experienced a brain hemorrhage and subsequently expired while on a phase 3 trial utilizing the investigational agent BAY 43-9006 tosylate (or placebo) in combination with paclitaxel and carboplatin. She began her first course of treatment on August 14, 2007, receiving paclitaxel 225 mg/m² IV over 3 hours on Day 1, carboplatin AUC=6 IV over 30 min on Day 1, and BAY 43-9006 tosylate 400 mg PO or placebo twice daily on Days 2-19, every 21 days for four cycles. She received the last dose of paclitaxel and carboplatin on September 5, 2007 (Cycle 2, Day 1), and the last dose of BAY 43-9006 tosylate/placebo on September 23, 2007 (Cycle 2, Day 19).

The patient was initially diagnosed with malignant melanoma (primary left shoulder lesion) in March 2006 and was status post wide excision of left shoulder lesion and left cervical and axillary nodal dissection. She completed a year of high dose interferon alpha therapy in June of 2007. She subsequently developed lung and small bowel metastasis and underwent open laparotomy and small bowel resection in July 2007. She began the investigational therapy on August 14, 2007.

On September 25, 2007, she presented to the clinic for Cycle 3, at which time her treatment was held due to thrombocytopenia (platelet counts of 65×10^3 cells/ μ L, reference range: $156-369 \times 10^3$ cells/ μ L). Upon physical examination, her blood pressure was 140/100 mmHg, and was otherwise unremarkable. She had a chest, abdomen, and pelvic CT scan that day which revealed a significant decrease in pulmonary nodules, coronary artery disease, atherosclerotic disease of the aorta, no change in adrenal gland nodules, and scattered colonic diverticula.

On September 30, 2007, the patient presented to the emergency room at her local hospital with a severe headache and expressive aphasia. Two hemorrhagic lesions, one in the temporoparietal area, measuring approximately 3 cm \times 3 cm, with layering of blood, and one in the right occipital area were found on CT scan and the patient was transferred to a different facility for further management. Upon arrival at the emergency department after transfer, she reported some improvement in her expressive aphasia and denied any focal loss of sensation or weakness, changes in vision, neck stiffness, or chest pain. Her physical examination was remarkable for mild aphasia and blood pressure of 170/90 mmHg. An MR angiography of the brain without contrast showed focal hematomas, focal enhancing lesions both separate from and adjacent to hematoma suggesting metastatic disease as the source of hemorrhage, and blood fluid levels within hematomas. No evidence of aneurysm was found. Of note, an MRI of the brain with or without contrast done on August 6, 2007 was negative for brain metastasis. She received platelet transfusion empirically, secondary to her intermittent aspirin use and history of thrombocytopenia, and hydralazine and was admitted to the neurosurgical intensive care unit. She was removed from the protocol at that time. Because the patient was not considered to be a surgical candidate due to the severity of her condition, she was treated with high dose corticosteroids which were tapered prior to her discharge on October 12, 2007.

On October 13, 2007, the patient was readmitted to the hospital for severe headache. She was treated with high-dose steroids; however her condition deteriorated and she was changed to comfort measures only. She expired on October 15, 2007.

The patient's past medical history is significant for sleep apnea, urinary tract infection, smoking (1/2 pack per day for 50 years), arthritis, hypertension, and intermittent atrial fibrillation. Medications taken at the

time of the event include metoprolol, aspirin, potassium, Norvasc®, trazadone, spironolactone, Actonel®, terazosin, and Lopressor®.

There have been 10 other incidences of CNS hemorrhage reported to the NCI through AdEERS as serious adverse events under the BAY 43-9006 tosylate NSC, as shown in the table below:

Adverse Event	Grade	Attribution
Hemorrhage, CNS (n=10)	5	1 Possible, 1 Unlikely
	4	4 Possible, 2 Unlikely
	3	1 Possible
	2	1 Possible

A total of 3206 patients have been enrolled in NCI-sponsored clinical trials under the BAY 43-9006 tosylate IND and/or NSC.

In this case, it is felt that a relationship between the CNS hemorrhage and the BAY 43-9006 tosylate/placebo administration cannot be excluded.

	Hemorrhage, CNS
BAY 43-9006 tosylate or placebo	Possible
Carboplatin	Possible
Paclitaxel	Possible
Melanoma	Probable

Date: 12/20/07

Signature: John Wright M.D.
 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, M.D.
 Karen Wilson
 Bayer Pharmaceuticals Corporation

Todd J. Yancey, M.D.
 Onyx Pharmaceuticals, Inc.