



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: March 2, 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_1333296

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: January 19, 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) IND Safety Report, AE #1333296

TO: Investigators Using CTEP-supplied Investigational 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.

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/or NSC, and the total number of patients enrolled in trials under this IND and/or NSC is attached:

A 57-year-old male with stage IV malignant melanoma metastatic to the adrenal glands and mediastinal region experienced grade 4 hypertension, grade 4 intracranial hemorrhage, and grade 3 somnolence while on a phase 3 trial utilizing the investigational agent BAY 43-9006 or placebo in combination with paclitaxel and carboplatin.

ADVERSE EVENTS ASSESSMENT

IND 69896 NSC 724772 BAY 43-9006 tosylate (BAY 54-9085; sorafenib tosylate)	ADVERSE EXPERIENCE REPORT NO. 14 IND Safety Report: Initial Event: Gr. 4: CNS Hemorrhage Gr. 4: Hypertension Gr. 3: Somnolence, depressed level of consciousness
AE: 1333296	Protocol: E2603

The patient is a 57-year-old male with stage IV malignant melanoma metastatic to the adrenal glands and mediastinal region who experienced somnolence, hypertension, and intracranial hemorrhage 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 November 28, 2006, receiving BAY 43-9006 400 mg PO twice daily or placebo 2 tablets twice daily on Days 2-19, paclitaxel 225 mg/m² IV over 3 hours on Day 1, and carboplatin AUC 6 IV over 30 min on Day 1, every 21 days for Cycles 1-4. He received his only doses of paclitaxel and carboplatin on November 28, 2006 (Cycle 1, Day 1) and the last dose of BAY 43-9006 or placebo on November 30, 2006 (Cycle 1, Day 3).

The patient was initially diagnosed with malignant melanoma of the right posterior arm in October 2000 and is status post excision, interferon therapy, and excision of a right posterior neck mass in August 2006. The patient was diagnosed with metastatic disease in October 2006. A follow-up scan on November 14, 2006 demonstrated extensive adenopathy around the vena cava and adrenal gland, along with suggestive involvement of the renal vein and a clot in the vena cava inferior, which was apparently asymptomatic and treated with Coumadin[®] since November 20, 2006. The patient's adrenal function was found to be normal.

The patient began the investigational therapy on November 28, 2006. On December 1, 2006, the patient's spouse called the clinic to report that he was hypertensive with a blood pressure of 168/102 mmHg and a follow-up of 190/129 mmHg. Of note, the patient had been taking Diovan[®] and hydrochlorothiazide, but had stopped them prior to the initiation of protocol treatment. He was instructed to take one dose of Diovan[®], with no apparent effect. He was found obtunded at home and taken to the ER, where his blood pressure was 220/120 mmHg. No falls or other injuries were reported. A CT scan of the head demonstrated two focal intracerebral hemorrhages: one in the right temporal lobe, measuring 2.15 cm, with a small focus of adjacent vasogenic edema; and second focus in the right parietal convexity, approximately a centimeter in size, with slight adjacent subarachnoid blood and edema. These findings were new compared to a baseline MRI of the brain, which was unremarkable and showed no evidence of metastases. The patient was treated with a Cardene[®] drip, and reversion of his anticoagulation therapy, with vitamin K and fresh frozen plasma infusions. A neurosurgical evaluation revealed a left facial droop and left-sided hemiparesis, as well as deviation of his eyes to the right and left homonymous hemianopsia. His pupils were round, equal, and reactive to light and accommodation. His tongue and palate were midline. The patient was able to follow complex commands bilaterally and briskly on the right side. It was felt that the patient was not a surgical candidate and was admitted to the intensive care unit for further evaluation and stroke care. His coagulation values at admission were remarkable for a prothrombin time of 22.3 seconds (reference range: 12.4-15.3 seconds), activated partial thromboplastin time of 41.9 seconds (reference range: 23.7-35.1 seconds), INR of 1.91 (reference range: 0.86-1.14). A complete blood count and chemistry panel were within the normal limits. A neurological consultation revealed an obtunded, confused and acutely disoriented patient who appeared to be blind. His face was symmetric, his tone, bulk, and strength were normal. Reflexes were symmetrical and normal with bilateral downgoing plantars. There was a sensitivity extinction of the left half of the body. A fundoscopic exam had a normal appearance, but was limited due to the patient's lack of cooperation. During his examination, he experienced focal seizures of the right arm with right nystagmus and then

evidence of tonic posturing of the right arm. The seizure persisted for over 8 minutes, and Ativan® had to be administered. It was presumed to be secondary to the intracerebral hemorrhage. Treatment with fosphenytoin and Decadron® was initiated. An MRI of the brain confirmed the acute parenchymal hemorrhage involving the right temporal and parietal cortex with evolution to mass-effect placed on the right temporal ventricle and generalized severe cerebral edema involving the right cerebral cortex. The patient was removed from the protocol on December 4, 2006.

Over the next few days, the patient slowly recovered. A surgical consultation regarding possible vena cava filter insertion recommended that the patient undergo a venacavogram to show the exact location of the thrombus. The evaluation was performed on December 8, 2006 and revealed completely occluded inferior vena cava (IVC) and patent azygos system. The portion of the upper IVC below the right atrium was too small for safe placement of a filter. The right common femoral venogram showed no visualization of the iliac vein or the IVC. It was felt that anticoagulation was contradicted for him, but he was in condition to be transferred to a rehabilitation unit on December 9, 2006. He was discharged on December 15, 2006 to continue with home rehabilitation. Per his spouse, he had lost the vision of his left eye and had expressive aphasia. He was ambulatory, but unable to carry out any work activities. It is unknown at this time whether the patient received BAY 43-9006 tosylate or placebo.

The patient's past medical history is significant for hypertension, hypertriglyceridemia, anemia, thrombotic disorder, diabetes mellitus, renal impairment, anxiety, recurrent hiatal hernia, asymptomatic gallstones, chronic back pain, and gastroesophageal reflux disease. His past surgical history is remarkable for right inguinal hernia repair and excision of mass in the right arm in 2000 and in the area behind his ear in 2006, both biopsies proved to be melanoma. The patient is a pipe smoker and was a heavy alcohol drinker for many years. Medications taken at the time of the event included Coumadin®, Dilaudid®, Diovan®, Tricor®, Prozac®, Protonix®, and Zetia®.

There have been six other incidences of CNS hemorrhage, six other incidences of somnolence, and 16 other incidences of hypertension 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
CNS hemorrhage (n= 6)	5	1 Unlikely
	4	1 Possible, 2 Unlikely
	3	1 Possible
	2	1 Possible
Somnolence (n= 6)	3	4 Unlikely, 2 Unrelated
Hypertension (n=16)	4	1 Definite, 1 Probable, 1 Possible
	3	1 Definite, 4 Probable, 4 Possible
	2	4 Possible

A total of 1993 patients have been enrolled in NCI-sponsored clinical trials under the BAY 43-9006 tosylate NSC.

In this case, it is felt that the hypertension is probably related to BAY 43-9006 tosylate or placebo administration, and that a possible causal relationship between the other events and BAY 43-9006 tosylate or placebo therapy cannot be excluded.

	Hemorrhage, CNS	Hypertension	Somnolence
BAY 43-9006 tosylate or placebo	Possible	Probable	Possible
Carboplatin	Possible	Unlikely	Unlikely
Paclitaxel	Possible	Unlikely	Unlikely
Melanoma	Probable	Unlikely	Possible
Coumadin [®]	Possible	Unlikely	Unlikely
Dilaudid [®]	Unlikely	Unlikely	Unlikely
Diovan [®]	Unlikely	Unlikely	Unlikely
Tricor [®]	Unlikely	Unlikely	Unlikely
Zetia [®]	Unlikely	Unlikely	Unlikely
Hemorrhage	N/A	Unlikely	Possible

Date: 2/18/07

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.