



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_1447378

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 9, 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# 1447378
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 72-year-old female with acute lymphoblastic leukemia experienced a grade 5 CNS hemorrhage while on a phase I trial utilizing the investigational agent BAY 43-9006 tosylate.

ADVERSE EVENTS ASSESSMENT

IND 69896 NSC 724772 BAY 43-9006 tosylate (Bay 54-9085; sorafenib tosylate)	ADVERSE EXPERIENCE REPORT NO. 16 IND Safety Report: Initial Event: Gr. 5: Hemorrhage, CNS
AE: 1447378	Protocol: 6745

The patient was a 72-year-old female with acute lymphoblastic leukemia (ALL) who experienced a CNS hemorrhage and subsequently died while on a phase I trial utilizing the investigational agent BAY 43-9006 tosylate. She began her first course of treatment on August 30, 2006, receiving BAY 43-9006 tosylate 400 mg PO twice daily on Days 1-21, every 28 days. She received her last dose of BAY 43-9006 tosylate on November 13, 2006 (Cycle 3, Day 15).

The patient was initially diagnosed with pre-B cell ALL in October 2004 and was status post multiple systemic chemotherapy regimens. She began the investigational therapy on August 30, 2006 and tolerated therapy well with complaints of some fatigue and intermittent diarrhea alternating with constipation. She began Cycle 3 on October 30, 2006, after having a good response to the first two cycles of treatment. On November 14, 2006, the patient fell in her bathroom sustaining a severe head injury and was taken to the trauma center. According to the patient's husband, she was initially responsive but slowly drifted into an unresponsive state. When she arrived at the trauma center, she was comatose with decerebrate posturing. Her pupils were fixed and dilated. There was no abnormal drainage from her nose, mouth, or ears, and there was no obvious evidence of facial fractures. Upon examination of the rest of her body, there were no obvious external injuries or deformities found. She was intubated, and a STAT head CT scan showed a very large, left-sided subdural hematoma associated with a significant midline shift, compression of the brainstem, and intraventricular and subarachnoid hemorrhage. No skull fractures were found. A CT scan of the chest, cervical spine, abdomen, and pelvis showed no evidence of acute injuries. Admission laboratory values were remarkable for a white blood cell count of $12.4 \times 10^3/\mu\text{L}$ (reference range: $3.7-10.3 \times 10^3/\mu\text{L}$) and a platelet count of $12 \times 10^3/\mu\text{L}$ (reference range: $140-440 \times 10^3/\mu\text{L}$). She was transferred to the critical care unit for continued management and was maintained on mechanical ventilation. Emergency surgery was not considered due the severity of her intracranial injuries and leukemia, and the decision was made after discussion with family members to proceed with comfort care only. She expired later that day.

The patient's past medical/surgical history is significant for L-asparaginase induced hepatitis (resolved), L3-L4 and L4-L5 laminectomy, mitral valve prolapse, gastroesophageal reflux disease, sensory neuropathy secondary to vincristine, and significant sulfa allergy, including Lasix[®]. Medications taken at the time of the event included allopurinol, voriconazole, ursodiol, Protonix[®], and Valtrex[®].

There have been six other occurrences of CNS hemorrhage reported to the NCI as serious adverse events through AdEERS under the BAY 43-9006 tosylate NSC, which are summarized in the following table:

Adverse Event	Grade	Attribution
CNS hemorrhage (n=6)	5	1 Unlikely
	4	1 Possible, 2 Unlikely
	3	1 Possible
	2	1 Possible

A total of 1,948 patients have been enrolled in NCI-sponsored clinical trials under NSC 724772.

In this case, it is felt that a possible causal relationship between the event and BAY 43-9006 tosylate therapy cannot be excluded.

	CNS Hemorrhage
BAY 43-9006 tosylate	Possible
Acute lymphoblastic leukemia	Possible
Fall	Possible
Thrombocytopenia	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 Incorporated