



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_1396114

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: December 3, 2007

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

SUBJECT: BAY 43-9006 Tosylate (BAY 54-9085; sorafenib tosylate) and OSI-774 (erlotinib; Tarceva[®]) NCI IND Safety Report, AE# 1396114

TO: Investigators Using CTEP-supplied Investigational BAY 43-9006 Tosylate (NSC 724772) and OSI-774 (NSC 718781)

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 agents BAY 43-9006 tosylate and OSI-774.

The following must be completed by all investigators using BAY 43-9006 tosylate under NCI IND 69896 and OSI-774 under NCI IND 63383:

- 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 INDs 69896 and 63383, 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 and OSI-774, there does not appear to be a change in the risk-benefit ratio for BAY 43-9006 tosylate and OSI-774 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 Assessments describe the adverse event (synopsis provided below), relevant previous experience under these INDs and/or NSCs, and the total number of patients enrolled in trials under these INDs and/or NSCs.

A 48-year-old male with recurrent glioblastoma multiforme developed a perforated colon while on a phase 2 trial utilizing the investigational agents BAY 43-9006 tosylate in combination with OSI-774.

ADVERSE EVENTS ASSESSMENT

IND 69896	63383	ADVERSE EXPERIENCE REPORT NO. 23 IND Safety Report: Initial Event: Gr. 3: Perforation, GI: Colon
NSC 724772	718781	
BAY 43-9006 tosylate (BAY 54-9085, sorafenib tosylate)	OSI-774 (erlotinib, Tarceva®)	
AE: 1396114	Protocol: NABTT-0502	

The patient is a 48-year-old male with recurrent glioblastoma multiforme (GBM) who developed a perforated colon while receiving treatment on a phase 2 trial utilizing the investigational agents BAY 43-9006 tosylate and OSI-774. He began his first course of treatment on April 12, 2007, receiving BAY 43-9006 tosylate 400 mg PO twice daily and OSI-774 150 mg PO once daily on Days 1-28, every 28 days. He received the last dose of BAY 43-9006 tosylate and the last dose of OSI-774 on April 25, 2007 (Cycle 1, Day 14).

The patient was initially diagnosed with left temporal GBM in June 2006 and is status post surgical resection, vaccine therapy, radiation plus low-dose temozolomide, and a second surgical resection in December 2006. The patient started the investigational therapy on April 12, 2007.

On April 25, 2007 (Cycle 1, Day 14), the patient presented to the clinic for a scheduled follow-up visit with a several-day history of poor oral intake, decreased urine output, and progressive weakness. According to his caregiver, he also had a 3- to 4-week history of generalized abdominal pain without a change in bowel movements, and lower extremity edema. He denied nausea, vomiting, or fevers. Upon examination he appeared cushingoid and pale, he was afebrile, his blood pressure was 130/80 mmHg, and his heart rate was 103 bpm, regular, without murmurs. His lung sounds were decreased bilaterally with dullness in the right lower base and crackles in the mid lung field, his abdomen was tender bilaterally, he had 2+ lower extremity edema, and a generalized non pruritic rash. A foley catheter was placed with 140 cc of dark urine return. He was admitted to the hospital for dyspnea and dehydration. His admission chest X-ray was significant for large amounts of free air under both hemidiaphragms and his chest CT scan was significant for extensive intraperitoneal free air with colonic pneumatosis.

On April 26, 2007, the patient was seen for a colorectal consult, secondary to his CT scan findings and increasing abdominal pain and distention since admission, which had become associated with nausea and bilious emesis. He underwent an emergency exploratory laparotomy on the same day and was found to have a necrotic distal sigmoid colon just above the rectosigmoid junction. There was a perforation in the lateral wall of the sigmoid colon at that level, with pre-perforation of fecal contents in the pelvis. He underwent resection of sigmoid colon with oversewing of rectal stump, and a descending colostomy. He tolerated the procedure well without any intraoperative complications. By April 29, 2007, the patient was started on clear liquids and by May 1, 2007, soft foods were introduced.

The remainder of his hospitalization was notable for extensive deep vein thromboses on the left leg found on bilateral leg venous duplex studies done on May 3, 2007. He was started on anticoagulation with heparin, his legs were elevated, and he was observed for signs of bleeding.

On May 5, 2007, he was transferred to a skilled nursing facility in stable condition. On May 8, 2007, the patient became febrile, had labored breathing, and was unable to tolerate oral intake. Hospice was consulted and his status was changed to "do not resuscitate." Later that day the patient expired. No autopsy was performed.

The patient's past medical/surgical history is significant for right inguinal hernia repair, GERD, and inflammatory bowel disease. Medications taken at the time of the initial event included Provigil®, Keppra®, K-Dur®, dexamethasone, Lasix®, ondansetron, loperamide, and quinine.

There have been 19 other cases of GI perforation in patients treated with BAY 43-9006 tosylate, and 4 other case of GI perforation in patients treated with OSI-774 reported to the NCI as serious adverse events through AdEERS under the BAY 43-9006 tosylate NSC and the OSI-774 NSC which are summarized in the following table:

Adverse Event	Grade	Attribution
BAY 43-9006 tosylate (NSC 724772)		
Perforation, GI (n=19)	4	1 Probable, 2 Possible
	3	1 Probable, 13 Possible, 2 Unlikely
OSI-774 (NSC 718781)		
Perforation, GI (n=9)	5	1 Possible, 1 Unrelated
	4	3 Possible, 3 Unlikely
	3	1 Unlikely

A total of 3,247 patients have been enrolled in NCI-sponsored clinical trials under the BAY 43-9006 tosylate IND and/or NSC and a total of 2396 patients have been enrolled in under the OSI-774 IND and/or NSC.

In this case, it is felt that a probable causal relationship exists between the event and BAY 43-9006 tosylate and a possible relationship between the event and the OSI-774 cannot be excluded.

	GI perforation: Colon
BAY 43-9006 tosylate	Probable
OSI-774	Possible
Glioblastoma multiforme	Unrelated
Decadron	Definite
Long term steroid use	Definite
History of diverticulitis/inflammatory bowel disease	Possible

Date: 12/20/07

Signature: John Wright M.D.
 John Wright, M.D., Ph.D.
 (IDB Monitor for BAY 43-9006 Tosylate)

Date: 12/31/07

Signature: Janet Dancey
 Janet Dancey, M.D.
 (IDB Monitor for OSI-774)

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

cc: Jeffrey Humphrey, M.D
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