



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: May 11, 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 Sorafenib 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_1893074

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: April 11, 2007 (JW)

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

SUBJECT: BAY 43-9006 Tosylate (BAY 54-9085; Sorafenib Tosylate) NCI IND Safety Report, AE# 1893074

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 49-year-old female with malignant peripheral nerve sheath tumor metastatic to the lungs, mediastinum and intra-abdominal nodes experienced vomiting and developed a perforated ileum while on a phase 2 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) AE: 1893074	ADVERSE EXPERIENCE REPORT NO. <input type="checkbox"/> IND Safety Report: Initial Event: Gr. 3: Perforation, GI: Ileum Gr. 3: Vomiting Protocol: 7060
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The patient is a 49-year-old female with malignant peripheral nerve sheath tumor metastatic to the lungs, mediastinum and intra-abdominal nodes who experienced vomiting and developed a perforated ileum while on a phase 2 trial utilizing the investigational agent BAY 43-9006 tosylate. She began her first course of treatment on December 20, 2006, receiving BAY 43-9006 tosylate 400 mg PO twice daily on Days 1-28, every 28 days. She received her last dose of BAY 43-9006 tosylate on December 29, 2006 (Cycle 1, Day 10).

The patient was initially diagnosed with neurofibromatosis in 1974 and malignant peripheral nerve sheath tumor in June 2001 and is status post surgery (2001 and 2002), multiple agent systemic chemotherapy, and radiation therapy. Prior to beginning the investigational therapy, she experienced nausea and diarrhea, which was felt to be secondary to gastroenteritis. The patient began treatment with BAY 43-9006 tosylate on December 20, 2006. She developed nausea beginning around December 25, 2006 (Cycle 1, Day 6), and several days later started vomiting. Her treatment was discontinued on December 29, 2006 (Cycle 1, Day 10, after her morning dose) due to her gastrointestinal symptoms. Initially, her symptoms were felt to be related to her expanding retroperitoneal tumor. On December 31, 2006 (Cycle 1, Day 12), she developed severe abdominal pain, which led to her admission to a local hospital on January 1, 2007. Her admission chest X-ray (compared to a CT scan performed on December 27, 2006) revealed a pneumoperitoneum beneath the right hemidiaphragm. Upon examination, she was found to be awake, alert, and afebrile. The patient had a distended abdomen with hypoactive bowel sounds, right lower extremity lymphedema, clear lungs bilaterally, and good urine output. A CT scan of the abdomen showed an extensive right retroperitoneal sarcoma invading the ascending colon just proximal to the cecum, causing obstruction with associated ureteral obstruction and right iliac venous obstruction. She was treated with morphine and antibiotics. A nasogastric tube was placed with dramatic relief of her abdominal discomfort.

On January 2, 2007 (Cycle 1, Day 14), the patient was transferred to a larger facility for further evaluation and treatment. She underwent an exploratory laparotomy and a diverting ileostomy on January 3, 2007 (Cycle 1, Day 15). A repeat abdominal CT scan on January 11, 2007 (Cycle 1, Day 23) revealed a small localized fluid collection in the left peritoneum, small amounts of fluid in the small bowel mesentery, a slightly more necrotic appearing mass in the right side of the abdomen extending into the pelvis, and right kidney hydronephrosis. She underwent a CT guided abdominal fluid aspiration on January 12, 2007 (Cycle 1, Day 24) with negative culture results. Post-operatively, her progress was complicated by peritonitis and dehiscence of her surgical wound requiring vacuum assisted closure dressing applications. The patient's condition slowly improved, and on January 22, 2007, she was discharged in stable condition to a rehabilitation facility.

The patient's past medical/surgical history is significant for neurofibromatosis, total abdominal hysterectomy, two cesarean sections, gastroenteritis, and lymphedema. Medications taken at the time of the event included Celexa®, Neurontin®, Ativan®, and MSIR®.

There have been 12 other occurrences of GI perforation and 55 other occurrences of vomiting in patients treated with BAY 43-9006 tosylate reported to the NCI as serious adverse events under this NSC, which are summarized in the following table:

Adverse Event	Grade	Attribution
GI Perforation: (n=12)	4	2 Possible
	3	9 Possible, 1 Unlikely
Vomiting: (n=55)	3	1 Definite, 1 Probable, 22 Possible, 2 Unlikely, 5 Unrelated
	2	3 Probable, 13 Possible, 4 Unlikely, 1 Unrelated
	1	1 Probable, 2 Possible

A total of 2,006 patients have been enrolled in NCI-sponsored clinical trials under NSC 724772.

	GI Perforation: Ileum	Vomiting
BAY 43-9006 tosylate	Possible	Possible
Malignant peripheral nerve sheath tumor	Probable	Possible
Pneumoperitoneum	Possible	Probable
Pain	Unlikely	Possible

Date: 4/11/07

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