



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: July 11, 2008

To: NCCTG Primary Clinical Research Associates

From: Alicia Elsing

Re: N0626, Phase II Randomized Study Pemetrexed With Sorafenib versus Pemetrexed Alone as Second-line Therapy in Patients With Advanced Non-Small Cell Lung Cancer

The purpose of this memorandum is to provide investigators with a recent report of an adverse event that has occurred in association with BAY43-9006 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_1838547_F1

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 Alicia Elsing at elsing.alicia@mayo.edu or call 507/538-3893.

AE/df
enclosure



DATE: July 8, 2008 (JW) 7/23/08

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# 1838547

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 tosylate, there does not appear to be a change in the risk-benefit ratio for BAY 43-9006 tosylate 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 58-year-old male with metastatic colorectal cancer experienced a grade 4 gastrointestinal fistula and a grade 3 bowel obstruction while on a phase 1/2 trial utilizing the investigational agent BAY 43-9006 tosylate in combination with cetuximab and irinotecan.

ADVERSE EVENTS ASSESSMENT

IND 69896	ADVERSE EXPERIENCE REPORT NO. 30
NSC 724772	IND Safety Report: #1
BAY 43-9006 tosylate (BAY 54-9085; sorafenib tosylate)	Event: Gr. 4: Fistula, GI: Small bowel Gr. 3: Obstruction, GI: Small bowel
AE: 1838547	Protocol: 6996

The patient is a 58-year-old male with metastatic colorectal cancer who experienced a small bowel fistula and small bowel obstruction while on a phase 1/2 trial utilizing the investigational agent BAY 43-9006 tosylate in combination with cetuximab and irinotecan. He began his first course of treatment on March 25, 2008, receiving for Cycle 1: BAY 43-9006 tosylate 200 mg PO daily; cetuximab 400 mg/m² IV over 2 hours on Day 1; cetuximab 250 mg/m² over 1 hour weekly, starting on Day 8; and irinotecan 100 mg/m² over 90 minutes on days 15 and 22 for 35 days. Beginning with Cycle 2 and continuing every 21 days, he was to receive BAY 43-9006 200 mg PO daily, cetuximab 250 mg/m² over 1 hour weekly, starting on Day 1, and irinotecan 100 mg/m² over 90 minutes on days 1 and 8. He received his last dose of BAY 43-9006 tosylate on May 5, 2008 (Cycle 2, Day 7) and his last doses of cetuximab and irinotecan on April 29, 2008.

The patient was initially diagnosed with adenocarcinoma in December 2003 and is status post sigmoid colectomy, radiation, and multiple agent chemotherapy regimens. In November 2007, he developed recurrent disease in the left pelvic area and underwent multiple surgeries including N-Block resection of the retroperitoneal recurrent tumor, small bowel resection, retroperitoneal resection and multiple biopsies. He also had irrigation and debridement of an infection of the left thigh, and drainage of a hematoma. A PET/CT scan of February 20, 2008 showed liver metastases. He began the investigational therapy on March 25, 2008.

On May 6, 2008 (Cycle 2, Day 8), the patient presented to the clinic with an overnight history of vomiting up to 12 times. He was known to have a left lower quadrant infiltrative mass and a left-sided external abdominal wall abscess, which had developed over the previous few days. Upon examination, he was afebrile, his abdomen was tender to palpation, and he had a 3 cm × 3 cm abscess on the left side of his abdomen with some skin irritation and mild fluctuance. He had an unremarkable white blood cell count. An abdominal X-ray revealed a partial small bowel obstruction, which was thought to be mechanical due to the left lower quadrant mass. Wound cultures of the abdominal wall abscess grew only rare gram-positive cocci. He received fluids, anti-nausea medication, and Bactrim[®], and was admitted to the hospital for bowel rest. He was discharged the following day after having no further episodes of vomiting, with an appointment for a surgical evaluation of his abdominal abscess.

On May 8, 2008 (Cycle 2, Day 10), he presented to the outpatient surgical center with hypotension, tachycardia, and fever. He was transferred to the emergency room and admitted to the intensive care unit for management of sepsis syndrome. While in the emergency room his blood pressure ranged from 141/70 mmHg to 91/47 mmHg, his pulse ranged from 96 to 132, and his white blood cell count (WBC) was 11.6 × 10⁹/L (reference range: 4.0-11.1 × 10⁹/L). A CT scan of the abdomen revealed two small perforations, one of which was an enterocutaneous fistula. The patient was determined to be a poor surgical risk, and he was treated with levofloxacin and metronidazole. An ostomy bag was placed over his abdominal wound and the output monitored. By the time of his discharge on May 11, 2008, his abdominal wound output was greater than 3 liters daily, he was afebrile, his white blood cell count had normalized, and his blood cultures were negative. He was instructed to drink large amounts of fluids to offset the fluid loss from his fistula, and he was removed from the protocol.

On May 12, 2008, the patient presented to the clinic for follow-up. He reported feeling somewhat improved and that his previous day's fistula drainage was 300 cc. He denied fevers, nausea, shortness of breath, pain, or extremity edema, and his vital signs were stable. By the time of his follow-up

appointment on June 3, 2008, he was much improved and there was no output from his fistula which appeared to have healed spontaneously.

The patient's past medical/surgical history is significant for hypertension, cardiomegaly since 1998 (viral in etiology), lung abscess, renal stone, right ureteral stricture, and hernia repair. Medications taken at the time of the event included Lunesta®, Zofran®, Benicar®, Imodium®, Megace®, and Advil®.

There have been 6 other cases of gastrointestinal fistula and 40 other cases of gastrointestinal obstruction reported to the NCI as serious adverse events through AdEERS under the BAY 43-9006 tosylate NSC, as shown in the table below:

Adverse Event	Grade	Attribution
Fistula, GI: Small bowel (n=6)	3	1 Possible, 1 Unlikely
	2	2 Possible
	1	1 Unlikely, 1 Unrelated
Obstruction, GI: Small bowel (n=40)	5	2 Unlikely
	3	5 Possible, 18 Unlikely, 11 Unrelated
	2	4 Unlikely

A total of 4,107 patients have been enrolled in NCI-sponsored clinical trials under the BAY 43-9006 tosylate NSC.

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

	Fistula, GI: Small bowel	Obstruction, GI: Small bowel
BAY 43-9006 tosylate or placebo	Possible	Possible
Cetuximab	Unlikely	Unlikely
Irinotecan	Unlikely	Possible
Colorectal Cancer	Probable	Probable

Date: 7/23/08

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, MD
 Diane M. Plateis, PharmD
 Bayer Pharmaceuticals Corporation

Todd J. Yancey, MD
 Onyx Pharmaceuticals, Inc.