



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: October 10, 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_1757003_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/kjm
enclosure



DATE: September 5, 2008

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# **1757003**

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 35-year-old male with melanoma metastatic to the mediastinum and pulmonary parenchyma experienced a grade 4 elevated lipase level, grade 3 elevated amylase level, grade 3 abdominal pain, and grade 2 pancreatitis while on a phase 3 trial utilizing the investigational agent BAY 43-9006 tosylate or placebo in combination with paclitaxel and carboplatin.

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ADVERSE EVENTS ASSESSMENT

IND 69896 NSC 724772 BAY 43-9006 tosylate (BAY 54-9085; sorafenib tosylate)	ADVERSE EXPERIENCE REPORT NO. 33 IND Safety Report: #1 Event: Gr. 4: Lipase Gr. 3: Amylase Gr. 3: Pain: Abdomen NOS Gr. 2: Pancreatitis
AE: 1757003	Protocol: E2603

The patient is a 35-year-old male with melanoma metastatic to the mediastinum and pulmonary parenchyma who experienced increased lipase and amylase levels, abdominal pain, and pancreatitis while on a phase 3 trial utilizing the investigational agent sorafenib or placebo in combination with paclitaxel and carboplatin. He began his first course of treatment on June 27, 2007, receiving sorafenib 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 minutes on Day 1, every 21 days, for Cycles 1-4. He received the last dose of sorafenib or placebo on June 29, 2007 (Cycle 1, Day 3), and the last doses of paclitaxel and carboplatin on June 27, 2007 (Cycle 1, Day 1).

The patient was initially diagnosed with malignant melanoma in August 2002, and is status post wide area excision and sentinel node biopsy, completion node dissection for a primary melanoma of the posterior trunk, and chemotherapy with high-dose interferon. He began the investigational therapy on June 27, 2007.

On June 30, 2007 (Cycle 1, Day 4), the patient presented to the emergency room reporting a 2-day history of severe upper abdominal pain after starting sorafenib. He denied nausea, vomiting, fever, chills, dizziness, or recent acute illness, but did report having a syncopal episode on his way to the hospital. Significant physical exam findings included minimal abdominal tenderness involving the epigastric and both upper quadrants without rebound tenderness. Significant laboratory findings included an amylase level of 377 U/L (reference range: 30-110 U/L) and a lipase level of 5,672 U/L (reference range: 23-300 U/L), normal liver enzymes, BUN, and creatinine levels, and mildly decreased sodium and chloride levels. A CT scan was suggestive of an active inflammatory process. He was admitted for further evaluation and treatment, and was treated with intravenous fluids, pain medication, and made n.p.o. (nothing by mouth). Sorafenib was discontinued, and the patient was removed from the protocol. The following day, his pain was improved, and he was discharged home on a liberal bland diet.

On July 23, 2007, he returned to the clinic for follow-up, having been treated with carboplatin and paclitaxel since his discharge. His abdomen was soft and non-tender, and his lipase, amylase, sodium, and chloride levels were normal. He was continued on the chemotherapy regimen.

The patient's past medical/surgical history is significant for hypertension, hyperlipidemia, GERD, tonsillectomy, adenoidectomy, molar tooth extraction, and seasonal allergies. Medications taken at the time of the event included Accupril[®], Fioricet[®], Zocor[®], ranitidine, Compazine[®], and Claritin[®].

There have been 32 other cases of increased lipase, 8 other cases of increased amylase, 131 other cases of abdominal pain, and 15 other cases of pancreatitis reported to the NCI as serious adverse events through AdEERS under the BAY 43-9006 tosylate NSC, as shown in the table below:

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Adverse Event	Grade	Attribution
Lipase (n = 32)	4 3 2	10 Probable, 8 Possible, 1 Unlikely 6 Probable, 4 Possible 3 Probable
Amylase (n = 8)	4 3 2	1 Possible 2 Probable, 3 Possible 2 Possible
Pain: Abdomen NOS (n = 131)	4 3 2 1	5 Possible, 2 Unlikely, 1 Unrelated 4 Probable, 24 Possible, 41 Unlikely, 17 Unrelated 21 Possible, 9 Unlikely, 6 Unrelated 1 unrelated
Pancreatitis (n = 15)	4 3 2	1 Possible 2 Definite, 1 Unlikely 3 Probable, 8 Possible

A total of 4,326 patients have been enrolled in NCI-sponsored clinical trials under the BAY 43-9006 tosylate NSC.

In this case, it is believed that a probable causal relationship between the events and BAY 43-9006 tosylate or placebo exists.

	Lipase	Amylase	Pain: Abdomen NOS	Pancreatitis
BAY 43-9006 or placebo	Probable	Probable	Probable	Probable
Carboplatin	Possible	Possible	Possible	Possible
Paclitaxel	Possible	Possible	Possible	Possible
Melanoma	Unlikely	Unlikely	Unlikely	Unlikely

Date: 10/2/08

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: Diane M. Plateis, PharmD
 Bayer Healthcare Pharmaceuticals, Inc.

Todd J. Yancey, MD
 Onyx Pharmaceuticals, Inc.

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