



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_1274544_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: June 26, 2008

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

SUBJECT: BAY 43-9006 Tosylate (BAY 54-9085; Sorafenib Tosylate) and Sunitinib Malate (SU011248 L-malate; Sutent®) NCI IND Safety Report, AE# 1274544

TO: Investigators Using Sorafenib (NSC 724772) and Sunitinib (NSC 736511)

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 sorafenib and sunitinib.

The following must be completed by all investigators using sorafenib under NCI IND 69896 and sunitinib under NCI IND 74019:

- 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 74019, 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 sorafenib and sunitinib, there does not appear to be a change in the risk-benefit ratio for sorafenib and sunitinib 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 these INDs and/or NSCs, and the total number of patients enrolled in trials under these INDs and/or NSCs.

A 69-year-old male with renal cell carcinoma developed a grade 4 gastrointestinal hemorrhage while on a phase 3 trial comparing the investigational agents sorafenib (or placebo) to sunitinib (or placebo), following a radical or partial nephrectomy.

ADVERSE EVENTS ASSESSMENT

IND 69896 NSC 724772 BAY 43-9006 tosylate (BAY 54- 9085; sorafenib tosylate) AE: 1274544	74019 736511 Sunitinib malate (SU011248 L- malate; Sutent®)	ADVERSE EXPERIENCE REPORT NO. 19 IND Safety Report: # 1 Event: Gr. 4: Hemorrhage, GI: Stomach Protocol: E2805
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The patient is a 69-year-old male with renal cell carcinoma who experienced a gastrointestinal hemorrhage while on a phase 3 trial comparing adjuvant sorafenib (or placebo) to sunitinib (or placebo) following a radical or partial nephrectomy. He began his first course of treatment on December 10, 2007, and was to receive sorafenib or placebo 400 mg PO twice daily for six weeks and sunitinib or placebo 50 mg PO daily for four weeks followed by rest for two weeks for nine cycles. He received his last dose of sorafenib or placebo and the last dose of sunitinib or placebo on May 30, 2008 (Cycle 4, Day 33).

The patient was initially diagnosed with renal cell carcinoma in November 2007 and is status post right radical nephrectomy on November 15, 2007. The patient began the investigational treatment on December 10, 2007.

On May 31, 2008 (Cycle 4, Day 34), the patient presented to the emergency room with increasing fatigue and facial edema. He reported a chronic non-productive cough without dyspnea. His physical examination was remarkable for a blood pressure of 149/65 mmHg and stools positive for occult blood. Significant laboratory findings included a hemoglobin level of 8.0 g/dL (reference range: 13.0-17.5 g/dL). He was admitted to the hospital for severe anemia and gastrointestinal bleeding. Of note is the patient's history of a benign stomach ulceration for which he was hospitalized in April 2008. He underwent an EGD during which active bleeding within the gastric cardia was cauterized. A biopsy of the gastric cardia was taken with results showing a mild, chronic superficial gastritis with negative results for *Helicobacter pylori*, ulceration, or malignancy. He was transfused with 2 units of packed red blood cells and was removed from the protocol as a result of this repeat episode. It was felt that while the investigational therapy did not cause the patient's gastrointestinal bleeding, it might be preventing the healing of the ulceration. On June 1, 2008, his hemoglobin was 10.8 g/dL, and an abdominal ultrasound showed no left kidney abnormality and no evidence of metastatic disease to the liver. He also had a normal liver/spleen scan on June 2, 2008. He remained stable throughout the remainder of his hospital stay without further melena or hematochezia. His hemoglobin was 10.2 g/dL on June 3, 2008, and he was discharged later that day.

On June 11, 2008, the patient presented to the clinic for follow-up with no complaints and a Karnofsky Performance Status of 100%. His vital signs and physical exam were unremarkable, and his hemoglobin was 12.0 g/dL.

The patient's past medical/surgical history is significant for questionable diabetes (the patient denies having diabetes and has a normal glycosylated hemoglobin, but there is laboratory evidence of hyperglycemia and diabetes documented in his medical record), hypertension, anemia, chronic cough, and left knee arthroscopic surgery. Medications taken at the time of the event included lisinopril, Protonix®, amlodipine, hydrochlorothiazide, and Claritin®.

There have been 47 other occurrences of gastrointestinal hemorrhage (5 of which were stomach hemorrhages) reported to the NCI as serious adverse events through AdEERS under the sorafenib IND and/or NSC, and 13 other occurrences of gastrointestinal hemorrhage (2 of which were stomach hemorrhages) reported to the NCI as serious adverse events through AdEERS under the sunitinib IND and/or NSC, which are summarized in the following table:

Adverse Event	Grade	Attribution
Sorafenib (NSC 724772)		
Hemorrhage, GI (n=47)	5	1 Unlikely
	4	2 Possible, 2 Unlikely
	3	18 Possible, 9 unlikely, 5 Unrelated
	2	5 Possible, 3 Unlikely, 1 Unrelated
	1	1 Unrelated
Sunitinib (NSC 736511)		
Hemorrhage, GI (n=13)	3	6 Possible, 1 Unlikely, 2 Unrelated
	2	4 Possible

A total of 4107 patients have been enrolled in NCI-sponsored clinical trials under the sorafenib IND and/or NSC and a total of 1098 patients have been enrolled under the sunitinib IND and/or NSC.

In this case, it is felt that a possible causal relationship between the event and sorafenib or sunitinib therapy cannot be excluded.

	Hemorrhage, GI
Sorafenib/Placebo	Possible
Sunitinib/Placebo	Possible
Renal cell carcinoma	Unrelated

Date: 7/3/08

Signature: John Wright M.D.
John Wright, M.D., Ph.D.
(IDB Monitor Sorafenib)

Date: 06.27.08

Signature: S. Percy Ivy
S. Percy Ivy, M.D.
(IDB Monitor for Sunitinib)

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

cc: Jeffrey Humphrey, M.D.
Diane M. Plateis, Pharm D.
Bayer Pharmaceuticals Corporation

Todd J. Yancey, M.D.
Onyx Pharmaceuticals Incorporated

Subramanian Hariharan, M.D., FACP
Alissa Levner
ADVEXP@pfizer.com
Pfizer Incorporated