



DATE: January 30, 2009

FROM: John Wright, M.D., Ph.D., Senior Investigator, CTEP, DCTD, NCI
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SUBJECT: BAY 43-9006 Tosylate (BAY 54-9085; Sorafenib Tosylate) and Sunitinib Malate (SU011248 L-malate; Sutent®) NCI IND Safety Report, AE# 1434562

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 73-year-old male with renal cell carcinoma developed a pulmonary embolism while on a phase 3 trial comparing the investigational agents sorafenib (or placebo) in combination with sunitinib (or placebo).

ADVERSE EVENTS ASSESSMENT

| | | |
|---|--|--|
| IND 69896 | 74019 | ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: Gr. 4: Thrombosis/thrombus/emboli |
| NSC 724772 | 736511 | |
| BAY 43-9006 tosylate (BAY 54-9085; sorafenib tosylate) | Sunitinib malate (SU011248 L-malate; Sutent®) | Protocol: E2805 |
| AE: 1434562 | | |

The patient is a 73-year-old male with renal cell carcinoma who experienced a pulmonary embolism 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 28, 2007, and depending on the arm of the study, was to receive either sorafenib 400 mg PO twice daily for six weeks with placebo for sunitinib 50 mg PO daily for four weeks followed by rest for two weeks; sunitinib 50 mg PO daily for four weeks followed by rest for two weeks with placebo for sorafenib 400 mg PO twice daily for six weeks; or placebo for sorafenib 400 mg PO twice daily for six weeks with placebo for sunitinib 50 mg PO daily for four weeks followed by rest for two weeks, all for nine cycles, every 42 days. He received his last dose of the investigational agents on May 22, 2008 (Cycle 4, Day 22).

The patient was initially diagnosed with renal cell carcinoma in November 2007, and is status post right radical nephrectomy on October 18, 2007. The patient began investigational treatment on December 28, 2007.

On May 23, 2008 (Cycle 4, Day 23), the patient presented to the emergency room complaining of shortness of breath and right pleuritic chest pain. Significant findings on examination at the time were pulse of 104 bpm, oxygen saturation of 98% on room air, respiratory rate of 22, and decreased breath sounds at bilateral bases. His CBC revealed mild anemia, and his cardiac markers were within normal limits. His PT was 14.5 seconds (reference range: 11.0-15.0 seconds), INR 1.18, and APTT 88.0 seconds (reference range: 23.0-35.0 seconds). A CT scan of the chest was positive for pulmonary embolism with extensive thrombus (of the saddle variant) filling the distal right pulmonary artery extending into the adjacent first, second and smaller subsegmental branches in the right lower chest; and smaller thrombi within first order and smaller adjacent segmental branches in the left lower chest; and suggestive evidence of atelectasis, although a small infiltrate at the right base could not be excluded. The patient was started on heparin drip, and his symptoms began to improve. The investigational agents were held. The patient was seen by several consultants on May 24, 2008, and a hypercoagulable work-up was initiated. Physical examination at this time was notable for lack of lower extremity edema and negative Homan's sign. The patient underwent venous Doppler ultrasound on both lower extremities, and there was no evidence of deep vein thrombosis. The patient was switched to Lovenox® and Coumadin®, and on May 29, 2008, he was discharged home on 5 mg of Coumadin®.

On May 30, 2008, the patient was readmitted to the hospital complaining of severe nausea, vomiting, and diarrhea. He received Zofran® for his vomiting and Imodium® for his diarrhea, and was discharged on June 1, 2008, with instructions to follow-up with his physician for Coumadin® management.

The patient's past medical/surgical history is significant for benign prostatic hypertrophy and hernia repairs. Medications taken at the time of the event included Tylenol® with codeine.

There have been 94 other cases of thrombosis/thrombus/embolism and 11 cases of thrombosis/embolism (vascular access-related) reported to the NCI as serious adverse events through AdEERS under the sorafenib NSC and/or IND. There have been 21 other cases of thrombosis/thrombus/embolism and no cases of vascular access-related thrombosis/embolism reported to the NCI as serious adverse events through AdEERS under the sunitinib NSC and/or IND. The findings are summarized in the following table:

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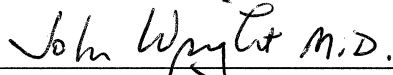
| Adverse Event | Grade | Attribution |
|--|-------|---|
| Sorafenib (NSC 724772) | | |
| Thrombosis/thrombus/embolism (n=94) | 5 | 1 Possible, 1 Unrelated |
| | 4 | 30 Possible, 21 Unlikely, 6 Unrelated |
| | 3 | 1 Probable, 13 Possible, 11 Unlikely, 7 Unrelated |
| | 2 | 3 Possible |
| Thrombosis/embolism (vascular access-related) (n=11) | 4 | 3 Possible, 2 Unlikely |
| | 3 | 1 Probable, 2 Possible, 1 Unlikely, 1 Unrelated |
| | 2 | 1 Possible |
| Sunitinib (NSC 736511) | | |
| Thrombosis (n=21) | 5 | 1 Possible |
| | 4 | 6 Possible, 1 Unlikely, 4 Unrelated |
| | 3 | 1 Probable, 5 Possible, 2 Unlikely |
| | 2 | 1 Possible |

A total of 4777 patients have been enrolled in NCI-sponsored clinical trials under the sorafenib IND and/or NSC, and a total of 1598 patients have been enrolled under the sunitinib IND and/or NSC.

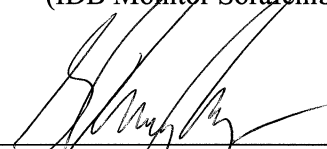
In this case, it is felt that a causal relationship between the event and sorafenib or sunitinib therapy probably exists.

| | Pulmonary embolism |
|-----------------------------|---------------------------|
| Sorafenib | Probable |
| Sunitinib | Probable |
| Renal cell carcinoma | Possible |

Date: 2/15/09

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

Date: 02.18.09

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

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

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