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FROM: Pamela J. Harris, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
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SUBJECT: Sunitinib Malate (SU011248 L-malate; Sutent[®]) and BAY 43-9006 Tosylate (BAY 54-9085; sorafenib tosylate), NCI IND Safety Report, AE# 1222406 (JW)

TO: Investigators Using Sunitinib Malate (SU011248 L-malate; Sutent[®]) (NSC 736511) and BAY 43-9006 Tosylate (BAY 54-9085; sorafenib 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 agents sunitinib and sorafenib.

The following must be completed by all investigators using sunitinib malate and sorafenib tosylate under NCI INDs 74019 and 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 INDs 74019 and 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 sunitinib and sorafenib, there does not appear to be a change in the risk-benefit ratio for sunitinib and sorafenib 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 Assessments describe 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 67-year-old male with clear cell renal cell carcinoma experienced a grade 4 pulmonary embolism while on a phase 3 trial utilizing the investigational agents sunitinib and sorafenib.

ADVERSE EVENTS ASSESSMENT

IND 69896 NSC 724772 BAY 43-9006 tosylate (BAY 54-9085; sorafenib tosylate) AE: 1222406	74019 736511 Sunitinib malate (SU011248 L-malate; Sutent®)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: Gr. 4: Thrombosis/thrombus/ embolism Protocol: E2805
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The patient is a 67-year-old male with stage III clear cell renal cell carcinoma who experienced a pulmonary embolism while on a phase 3 trial comparing adjuvant sorafenib (or placebo) to sunitinib (or placebo). He began his first course of treatment on April 13, 2009, and depending on the arm of the study, was scheduled to receive one of three treatments every 6 weeks, for a maximum of nine cycles: sorafenib 400 mg PO twice daily for 42 days with placebo for sunitinib; sunitinib 50 mg PO daily for 4 out of 6 weeks with placebo for sorafenib; or placebo for both sorafenib and sunitinib. The patient received his last doses of sorafenib (or placebo) and sunitinib (or placebo) on August 14, 2009 (Cycle 3, Day 39).

The patient was diagnosed with renal cell carcinoma in February 2009, and is status post left nephrectomy. He began the investigational therapy on April 13, 2009, but therapy was discontinued on May 12, 2009 (Cycle 1, Day 30), due to grade 4 ANC. His therapy was resumed on May 19, 2009, with a dose reduction, and he has remained at that level.

On August 14, 2009 (Cycle 3, Day 39), a routine CT scan of the chest demonstrated a small filling defect within the interlobar branch of the right pulmonary artery consistent with a small pulmonary embolus. At a follow-up clinic visit on August 18, 2009, the patient complained of mild fatigue only; his vital signs were: BP 152/80 mmHg; pulse 60 bpm; respiration 16 breaths per minute; and temperature 97.1°F. The patient had subsequent clinic visits that were unremarkable. A repeat CT scan of chest was done on December 18, 2009 (Cycle 6, Day 39), showing the same small filling defect within the right descending interlobar pulmonary artery, but smaller in size as compared to the August 2009 scan. A clinic evaluation on December 22, 2009 (Cycle 7, Day 1), was unremarkable. A venous Doppler® ultrasound of both lower extremities was negative; however, a D-dimer done on the same day was 1.1 µg/mL (reference: < 0.35 µg/mL). The patient was placed on Coumadin® on December 23, 2009. The investigational agent was not held, and the patient is currently on Cycle 7 of treatment which commenced on December 22, 2009.

Note that the August 14, 2009, CT scan was originally viewed as being unremarkable. It was when the December 18, 2009, scan came to light that the August scan was reviewed. It was noted in retrospect that a pulmonary embolus had in fact been present, and an addendum to that effect was added to the radiology report.

The patient's past medical/surgical history is significant for hypertension, gout, and proteinuria. Medications taken at the time of the event included Allegra®, allopurinol, aspirin, Diovan®, Flomax®, Lipitor®, and Norvasc®.

There have been 25 other cases of thrombosis/thrombus/embolism reported to the NCI as serious adverse events through AdEERS under the sunitinib NSC and/or IND. Thrombosis/thrombus/embolism is an expected adverse event for sorafenib. The findings are summarized in the following table:

Adverse Event	Grade	Attribution
Sunitinib (NSC 736511)		
Thrombosis/thrombus/embolism (n=25)	5	1 Possible
	4	4 Unrelated, 1 Unlikely, 7 Possible, 1 Probable
	3	2 Unlikely, 7 Possible
	2	2 Possible

A total of 2,322 patients have been enrolled under the sunitinib IND and/or NSC and a total of 5,910 patients have been enrolled in NCI-sponsored clinical trials under the sorafenib IND and/or NSC.

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

	Pulmonary embolism
Sorafenib/placebo	Probable
Sunitinib/placebo	Probable
Renal cell carcinoma	Possible

Date: 2/19/10

Signature: John Wright M.D.
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(IDB Monitor for sorafenib)

Date: 2/18/2010

Signature: Pamela J. Harris
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If this assessment is changed, we will notify your office.

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