



DATE: July 2, 2009 *Pamela J. Harris*
7/2/09

FROM: Pamela Harris, M.D., Senior Investigator, Investigational Drug Branch, CTEP, DCTD, NCI

SUBJECT: Sunitinib Malate (SU011248 L-malate; Sutent®) NCI IND Safety Report, AE# **1140081**

TO: Investigators Using Sunitinib Malate (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 agent sunitinib malate.

The following must be completed by all investigators using sunitinib malate 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 IND 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 sunitinib malate, there does not appear to be a change in the risk-benefit ratio for sunitinib malate 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 this IND and/or NSC, and the total number of patients enrolled in trials under this IND and/or NSC.

A 46-year-old female with stage IV non-small cell lung cancer expired from a bronchopulmonary hemorrhage while on a phase 2 study using the investigational agent sunitinib malate.

ADVERSE EVENTS ASSESSMENT

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|---|---|
| IND 74019 | ADVERSE EXPERIENCE REPORT NO. |
| NSC 736511 | IND Safety Report: #1 |
| Sunitinib malate (SU011248 L-malate; Sutent®) | Event: Gr. 5: Hemorrhage, Pulmonary/Upper Respiratory: Bronchopulmonary |
| AE: 1140081 | Protocol: CALGB-30704 |

The patient was a 46-year-old female with stage IV non-small cell lung cancer metastatic to the brain, adrenal gland, and mediastinum who expired from a bronchopulmonary hemorrhage while on a phase 2 trial utilizing the investigational agent sunitinib malate. She began the first course of treatment on November 19, 2008, receiving sunitinib malate 37.5 mg PO daily, every 21 days. She received her last dose of sunitinib malate on February 9, 2009 (Cycle 4, Day 12).

The patient was diagnosed with non-small cell lung cancer in June 2007, and is status post resection of a right parietal brain mass, radiation to the brain, and chemotherapy. She began the investigational therapy on November 19, 2008. A CT scan of the chest with contrast on December 26, 2008, showed a slight interval decrease in the right paratracheal lymphadenopathy which continued to moderately narrow the distal right main pulmonary artery and distal right upper lobe bronchus and bifurcation, and to severely narrow the right truncus anterior when compared to previous scans. It also revealed a stable, partially necrotic, spiculated mass in the apical segment of the right upper lobe, which was tethered to all right upper lobe pleural surfaces, broad-based on the posterior pleura and right major fissure (without chest wall invasion), and extended into the right hilum. An MRI of the brain with and without contrast the same day showed no evidence of recurrent metastatic lesions. On January 29, 2009, the patient began Cycle 4 with a sunitinib dose reduced to 25 mg due to grade 3 liver function test abnormalities which later resolved.

On February 10, 2009 (Cycle 4, Day 13), the patient called the treating physician to report one episode of coughing up a quarter-sized clot of blood. The patient was on a road trip with her brother, so she could not return to the clinic for evaluation. The treating physician advised the patient to stop the sunitinib and to go to the emergency room. Late that night, the treating physician received a call from a hospital emergency room reporting that patient passed away after having massive hemoptysis. She had progressed from respiratory distress to cardiopulmonary arrest, and was in asystole by the time EMS arrived. The patient was not able to be intubated due to the massive amount of blood in her airway. The patient's brother was present and requested that resuscitation efforts be stopped based on the patient's prior wishes.

The patient's past medical/surgical history is significant for tobacco abuse, periodontal disease, ankle fracture with subsequent development of a deep vein thrombosis, tubal ligation, and appendectomy. Family history is significant for a paternal grandmother with multiple myeloma, paternal grandfather with colon cancer, and maternal grandfather with multiple myeloma. Medications taken at the time of the event included Ativan®, Compazine®, Klonopin®, Neurontin®, nystatin, Prilosec OTC®, and Zolof®.

There have been no other cases of bronchopulmonary hemorrhage reported to the NCI as serious adverse events through AdEERS under the sunitinib malate NSC and/or IND.

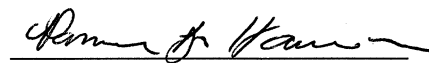
There have been 1833 patients enrolled in NCI-sponsored clinical trials under the sunitinib malate IND and/or NSC.

In this case, a possible relationship between the adverse event and sunitinib malate exists.

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| | Bronchopulmonary hemorrhage |
| Sunitinib malate | Possible |
| Non-small cell lung cancer NOS | Possible |

Date: July 2, 2009

Signature:



Pamela Harris, M.D.
(IDB Monitor for sunitinib malate)

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

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Pfizer, Inc.