



DATE: APR 05 2011

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

SUBJECT: Sunitinib Malate (SU011248 L-malate; Sutent[®]) NCI IND Safety Report, AE# 1423773

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 this letter to your Institutional Review Board (IRB) of record according to your policies and procedures.
- File a copy of this letter 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 61-year-old female with leiomyosarcoma of the uterus experienced grade 4 myelodysplastic syndrome after completing a phase 2 trial utilizing the investigational agent sunitinib malate.

ADVERSE EVENTS ASSESSMENT

IND 74019 NSC 736511 Sunitinib malate (SU011248 L-malate; Sutent®)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Event: Gr. 4: Secondary Malignancy – possibly related to cancer treatment – (Myelodysplastic Syndrome [MDS])
AE: 1423773	Protocol: GOG-0231C

The patient is a 61-year-old female with stage IV leiomyosarcoma of the uterus who developed myelodysplastic syndrome after completing a phase 2 trial utilizing the investigational agent sunitinib malate. She began the first course of treatment on March 19, 2007, receiving sunitinib malate 50 mg orally daily for 4 weeks, resting for 2 weeks in between, then continuous, every 6 weeks. She received her last dose of sunitinib malate on July 10, 2007 (Cycle 3, Day 37).

The patient was diagnosed with leiomyosarcoma of the uterus in July 2006, and is status post total abdominal hysterectomy with bilateral salpingo-oophorectomy, chemotherapy, and intravaginal brachytherapy. The patient received sunitinib without response and was removed from the protocol on August 3, 2007. This was followed by trabectedin from August 2007 to March 2009 with a near complete response, but was discontinued at that time due to pancytopenia. The patient began the investigational therapy with sunitinib malate on March 19, 2007.

On December 27, 2010, the patient was evaluated for intermittent nose-bleeds and night sweats, increasing fatigue, and a low-grade fever of 1-month duration. She had a white blood cell count (WBC) of $5.2 \times 10^9/L$ (reference range: $4.4-11.3 \times 10^9/L$), red blood cell count (RBC) on $2.37 \times 10^{12}/L$ (reference range: $4.00-5.20 \times 10^{12}/L$), hemoglobin (Hgb) of 6.4 g/dL (reference range: 12.0-16.0 g/dL), and a platelet count of $9 \times 10^9/L$ (reference range: $150-450 \times 10^9/L$). The patient was admitted to the hospital for further evaluation, and was transfused with 4 units of platelets and 2 units of packed red blood cells (PRBC) within a 24-hour period. On December 28, 2010, the pathology report of a bone marrow biopsy earlier that day showed trilineage myelodysplasia which was thought to be likely related to her previous treatment with trabectedin. She was transferred to the bone marrow transplant unit for further management. A CT scan of the chest, abdomen, and pelvis showed colonic diverticula without evidence of acute inflammation and no evidence of recurrent neoplastic or metastatic disease. After a lengthy discussion with the patient and her husband, they agreed to her participation in another study. She was discharged home that day with plans for follow-up.

On January 1, 2011, the patient presented to the emergency room reporting intermittent fevers. She had a WBC of $3.0 \times 10^9/L$, RBC of $3.01 \times 10^{12}/L$, Hgb of 8.5 g/dL, and platelet count of $14 \times 10^9/L$. The patient was readmitted to the hospital for neutropenic fever and myelodysplastic syndrome. She was started on vancomycin, azithromycin, Zosyn®, and prophylaxis for viral and fungal infection after obtaining blood cultures. A chest X-ray the next day was suggestive of right upper lobe pneumonia. On January 4, 2011, the patient received 5 units of platelets after pre-medication with Tylenol®, Benadryl®, and hydrocortisone. The patient had several transfusions and transfusion related reactions during the hospitalization course. Blood cultures showed no growth. On January 16, 2011, the patient's platelet count improved to $26 \times 10^9/L$ and her RBC to $3.88 \times 10^{12}/L$. Though her WBC was $1.6 \times 10^9/L$, she remained afebrile. The patient was discharged home later that day in stable condition.

The patient's past medical and surgical history is significant for hypertension. Medications taken at the time of the event included Lopressor.

There has been one other case of secondary malignancy (grade 3, probably related) reported to the NCI as a serious adverse event through AdEERS under the sunitinib malate NSC and/or IND.

There have been 2864 patients enrolled in NCI-sponsored clinical trials under the sunitinib malate IND and/or NSC.

In this case, it is thought that a possible relationship exists between the adverse event and the investigational therapy sunitinib malate.

	Myelodysplastic Syndrome
Sunitinib malate	Possible
Gemcitabine	Possible
Taxotere	Possible
Trabectedin	Possible
Leiomyosarcoma of the uterus	Unrelated

Date: 3/31/2011

Signature:



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

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

cc: Jocelyn Ulrich, R.Ph.
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