




DATE: March 29, 2010

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SUBJECT: Bevacizumab (rhuMab VEGF) and Sunitinib Malate (SU011248 L-malate; Sutent®) NCI
IND Safety Report, AE# **1329500**

TO: Investigators Using Bevacizumab (NSC 704865) 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 bevacizumab and sunitinib.

The following must be completed by all investigators using bevacizumab under NCI INDs 7921 and 11460 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 7921, 11460, 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 bevacizumab and sunitinib, there does not appear to be a change in the risk-benefit ratio for bevacizumab 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 36-year-old female with metastatic adrenal carcinoma experienced a grade 4 myocardial infarction, grade 4 pulmonary thrombosis, grade 4 hypotension, grade 4 platelets and grade 3 neutropenia, and subsequently expired while on a phase 1 study using the investigational agents bevacizumab and sunitinib.

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ADVERSE EVENTS ASSESSMENT

IND 74019	7921	ADVERSE EXPERIENCE REPORT NO.
NSC 736511	704865	IND Safety Report: #1
Sunitinib Malate (SU011248 L- malate; Sutent®)	Bevacizumab (rhuMAb VEGF)	Event: Gr. 5: Death NOS Gr. 4: Myocardial infarction Gr. 4: Pulmonary thrombosis Gr. 4: Hypotension Gr. 4: Platelets Gr. 3: Neutropenia
AE: 1329500		Protocol: 7537

The patient was a 36-year-old female with metastatic adrenal cortical carcinoma who experienced a myocardial infarction with cardiogenic shock, pulmonary thrombosis, pancytopenia, and subsequently expired while on a phase I study using the investigational agents bevacizumab and sunitinib. She began the first course of the investigational therapy on October 30, 2009, receiving bevacizumab 5 mg/kg IV over 30-90 minutes on Days 1, 15, and 29, and sunitinib 37.5 mg PO once daily on Days 1-28, every 42 days. She received her last dose of bevacizumab on November 13, 2009 (Cycle 1, Day 15), and the last dose of sunitinib on November 21, 2009 (Cycle 1, Day 23).

The patient was diagnosed with adrenal cortical carcinoma in May 2009 and was status post right adrenalectomy. She developed metastatic disease in the abdomen in October 2009. She began the above protocol therapy on October 30, 2009.

The patient had a history of benign secondary hypertension which was controlled at baseline but worsened after the protocol therapy. She was seen in the clinic on November 13, 2009 (Cycle 1, Day 15), when physical examination showed a BP of 144/105 mmHg, a pulse of 97 bpm, and no lower extremity edema. Her platelet count was 106 k/μL (reference range: 150-400 k/μL) and WBC was 1.59 k/μL (reference range: 3.7-11 k/μL) with ANC of 1.32 k/μL (reference range: 1.45-7.5 k/μL). Since several changes had been made to her antihypertensive drug regimen the day before, no additional adjustment was made at this visit. She received the Cycle 1, Day 15 dose of bevacizumab, and sunitinib was continued.

The patient presented to the emergency department (ED) on November 20, 2009 (Cycle 1, Day 22), with bilateral lower extremity edema. Laboratory tests showed that her hemoglobin (Hb) was 9.1 g/dL (reference range: 11.5-15.5 g/dL), and platelets were 33 k/μL. She was given Lasix® and discharged home. On November 22, 2009 (Cycle 1, Day 24), she was transported to the ED via EMS presenting with persistent severe midsternal and left sided chest pain, ST elevations on ECG, and severe hypotension. She was given aspirin by EMS en route to the hospital. At the ED, vital signs included a BP of 69/48 mmHg, pulse of 94 bpm, and an oxygen saturation of 97% at room air. She appeared acutely ill, had a flat affect, and was sleepy but arousable. She also had icteric conjunctiva, a mildly distended nontender abdomen, and lower extremity non-pitting edema. Vasopressors, heparin, and Plavix® were started. Her laboratory values showed an elevated troponin of 8.96 ng/mL (reference range: 0-0.1 ng/mL). Emergency cardiac catheterization revealed normal coronary arteries, and an echocardiogram showed severe left ventricular (LV) hypertrophy, mild-moderate LV global hypokinesia with an ejection fraction (EF) of 40%, moderate right ventricular (RV) hypokinesia, and a small pericardial effusion without tamponade. Due to her continued hypotension and low output, an intraaortic balloon pump was placed and she was transferred to the cardiac ICU. She subsequently developed hypoxemia which required intubation. She had multi-organ failure including renal failure and elevation of the liver enzymes, presumably due to cardiogenic shock. She was also found to have pancytopenia, with WBC of 0.51 k/μL, Hb of 6.7 g/dL and platelet count of 11 k/μL on November 22, 2009. A repeat echocardiogram on November 23, 2009, revealed normal LV size and mild global dysfunction with an ejection fraction of 45%, normal RV size and systolic function, mild pulmonary hypertension, and moderate circumferential pericardial effusion without tamponade. Despite multiple therapies, her prognosis was poor.

On November 24, 2009 (Cycle 1, Day 26), the patient went into asystole and despite extensive resuscitative efforts, she expired. An autopsy was performed, and revealed acute myocardial infarction with extensive myocardium necrosis involving the basal interventricular septum and left lateral ventricular wall from base to apex, but there was no luminal narrowing of the coronary arteries; there was also epicardial ecchymoses and pericardial effusion. Additional findings included: a pulmonary thrombus in the right lobe segmental artery; liver steatosis and centrilobular congestion and necrosis; and bone marrow hypoplasia with decreased granulocytes and megakaryocytes.

The patient's past medical and surgical history is significant for Cushing's syndrome, hypertension, and right adrenalectomy. Her family history is significant for hypertension in her mother, sister and maternal grandmother. Medications taken at the time of the event included amlodipine, spironolactone, Roxicet®, potassium chloride, risperidone, aspirin, docusate sodium and labetalol.

Myocardial infarction and thrombosis are known side effects associated with bevacizumab therapy. Neutropenia and thrombocytopenia are known adverse events associated with sunitinib. In this case, it is felt that myocardial infarction and pulmonary embolism were possibly related to the combination of bevacizumab and sunitinib, and pancytopenia was possibly related to sunitinib. The cause of death was likely to be multifactorial, and attributable to the protocol therapy, myocardial infarction, pulmonary embolism, cardiogenic shock and multiorgan failure.

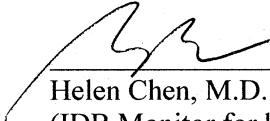
There have been 10 other cases of myocardial infarction, and 24 other cases of thrombosis, reported to the NCI through AdEERS as serious adverse events for the sunitinib NSC and/or IND as shown in the table below.

Sunitinib (NSC 736511)		
Myocardial infarction (n=10)	5	1 Unlikely, 1 Unrelated
	4	1 Unlikely, 4 Possible
	3	1 Unrelated, 2 Possible
Thrombosis/thrombus/embolism (n=24)	5	1 Possible
	4	4 Unrelated, 1 Unlikely, 7 Possible, 1 Probable
	3	1 Unlikely, 7 Possible
	2	2 Possible


To date, a total of 25,513 patients have been enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC, and 2,332 patients have been enrolled in NCI-sponsored clinical trials under the sunitinib IND and/or NSC.

	Death	Myocardial infarction	Pulmonary thrombus	Neutropenia	Platelets
Bevacizumab	Possible	Possible	Possible	Unlikely	Unlikely
Sunitinib	Possible	Possible	Possible	Possible	Possible
Adrenal carcinoma	Unlikely	Unlikely	Possible	Unlikely	Unlikely
Hypertension	NA	Possible	NA	NA	NA

Date: 3/25/2010

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

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