



National Institutes of Health  
National Cancer Institute  
Bethesda, Maryland 20892

**DATE:** October 22, 2009

**FROM:** Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI  
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**SUBJECT:** Bevacizumab (rhuMab VEGF) and Sunitinib Malate (SU011248 L-malate; Sutent®) NCI  
IND Safety Report, AE# 1613977, 1312527, 1474081, and 1395393

**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.

**AE# 1613977 (Patient 1)**

A 69-year-old male with renal cell carcinoma experienced grade 1 thrombotic microangiopathy while on a phase 1 study using the investigational agents bevacizumab and sunitinib.

**AE# 1312527 and 1474081 (Patient 2)**

A 57-year old female with renal cell carcinoma experienced grade 1 thrombotic microangiopathy while on a phase 1 study using the investigational agents bevacizumab and sunitinib.

**AE # 1395393 (Patient 3)**

A 60-year-old male with renal cell carcinoma experienced grade 1 thrombotic microangiopathy while on a phase 1 study using the investigational agents bevacizumab and sunitinib.

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**ADVERSE EVENTS ASSESSMENT**

IND 74019 NSC 736511 Sunitinib malate (SU011248 L-malate; Sutent®)	7921 704865 Bevacizumab (rhuMAb VEGF)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Event: <b>Gr. 1: Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS])</b>
AE: 1613977, 1312527, 1474081, and 1395393		Protocol: 7537

Three cases of thrombotic microangiopathy have been reported to NCI as serious adverse events under INDs 74019 and 7921 on protocol 7537 "A Phase 1 study of Bevacizumab in Combination with SU011248." These cases are summarized below.

**AE # 1613977 (Patient 1):** The patient is a 69-year-old male with renal cell carcinoma who experienced thrombotic microangiopathy while on a phase 1 study using the investigational agents bevacizumab and sunitinib. He began the first course of the investigational therapy on May 1, 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. He received his last dose of bevacizumab on May 15, 2009 (Cycle 1, Day 15) and his last dose of sunitinib on July 9, 2009 (Cycle 2, Day 28).

The patient was diagnosed with Fuhrman nuclear grade 3/4 papillary type renal cell carcinoma and is status post left radical nephrectomy in November 2007. He developed recurrent disease in February 2009, with two nodules in the left nephrectomy bed. He began the investigational treatment on May 1, 2009.

On May 15, 2009, the investigator informed that patient that he would no longer be eligible to participate in the trial because other patients with renal cancer on the same trial, had developed thrombotic microangiopathy and there was concern that the combination of sunitinib plus bevacizumab were causally related to this toxicity. The investigator offered the patient the option to continue treatment with single agent sunitinib. While receiving single agent sunitinib, on July 10, 2009, almost 2 months later, the patient developed evidence of thrombotic microangiopathy. It is impossible to know if the patient would have developed this adverse event if he had only received single agent sunitinib from day 1; however, it is appropriate to speculate that the combination of drugs contributed to the later manifestation of thrombotic microangiopathy.

On July 10, 2009, his blood pressure was elevated at 190/111 mmHg, but he was otherwise clinically well. His laboratory report was suggestive of thrombotic microangiopathy (see table below). Sunitinib was held and his anti-hypertensive medications were adjusted. On July 24, the laboratory findings, including haptoglobin and platelet counts, were improved. His blood pressure was still 150/100 mmHg, and sunitinib was to be held again and the patient was to return to the clinical in the following week.

The patient's past medical/surgical history is significant for hypertension, type 2 diabetes mellitus with diabetic neuropathy, hernia repair, appendectomy, and tonsillectomy. Medications taken at the time of the event included metformin, ramipril, and amlodipine.

Pertinent laboratory values:

	5/1/09 Baseline	5/15/09 C1, D15 Last dose Bevacizumab	6/12/09 C2, D1	7/10/09 C2, D29 Treatment held	7/24/09 C2, D43
WBC (reference range: 3.70-11.0 K/ $\mu$ L)	7.27	4.52	4.56	4.01	5.35

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**AE#s 1613977, 1312527,  
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	5/1/09 Baseline	5/15/09 C1, D15	6/12/09 C2, D1	7/10/09 C2, D29	7/24/09 C2, D43
Hemoglobin (reference range: 13-17g/dL)	15.2	16.7	16.4	16.6	17.0
Hematocrit (reference range: 39-51%)	43.2	48.7	48.8	47.8	49.4
Platelets (reference range: 150-400 K/ $\mu$ L)	158	125	121	72	136
Reticulocyte count %	0.9	2.0	0.6	2.2	*
Red cell morphology	Unremarkable	Unremarkable	Anisocytosis	Slight polychromasia, anisocytosis	Anisocytosis
Haptoglobin (reference range: 37-246 mg/dL)	118	96	129	<20	161
LDH (reference range: 100-220 U/L)	*	*	*	324	218
BUN (reference range: 10-25 mg/dL)	*	*	*	19	24
Creatinine (reference range: 0.7-1.4 mg/dL)	*	*	*	1.56	1.45
Urine protein (reference range: Neg.)	Neg.	Neg.	Neg.	100	*
Conj. bilirubin (reference range: 0.0-0.4 mg/dL)	0.1	0.2	0.2	0.4	0.2
T. bilirubin (reference range: 0.0-1.5 mg/dL)	0.4-0.5	0.7	0.8	1.2	0.7

\*= not done/provided

**AE #s 1312527 and 1474081 (Patient 2):** The patient is a 57-year-old female with renal cell carcinoma who experienced thrombotic microangiopathy while on a phase 1 study using the investigational agents bevacizumab and sunitinib. She began the first course of the investigational therapy on December 15, 2008, 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 May 6, 2009 (Cycle 4, Day 15), and her last dose of sunitinib on June 29, 2009 (Cycle 5, Day 27).

The patient was diagnosed with Fuhrman nuclear grade 3 renal cell carcinoma with vascular invasion in November 2008, and is status post left nephrectomy. She began the investigational treatment on December 15, 2008.

On May 20, 2009 (Cycle 4, Day 29), the patient presented to the clinic for follow-up, and her laboratory results from May 6, 2009, showed evidence of hemolysis and thrombocytopenia; urine analysis was not performed. Her blood pressure was 148/91 mmHg. Although she was clinically well, both bevacizumab and sunitinib were held (bevacizumab was discontinued permanently), and the patient was scheduled for further laboratory work-up of the thrombotic microangiopathy. By June 3, 2009, her platelets, haptoglobin, and lactate dehydrogenase (LDH) had improved; her blood pressure was 123/76 mmHg. The patient resumed sunitinib monotherapy off study and restarted sunitinib that day.

At a follow-up visit on July 1, 2009, the patient again had laboratory evidence of thrombotic microangiopathy. She had stopped her sunitinib 2 days prior due to hypertension. Her other complaints were of periorbital swelling, constipation, diarrhea, fatigue and nausea. Arrangements were made for further laboratory testing and imaging and her medications were adjusted.

The patient's past medical/surgical history is significant for tonsillectomy. Medications taken at the time of the event included Ativan<sup>®</sup>, metoclopramide, and Zofran<sup>®</sup>.

Pertinent laboratory values:

	12/15/08 Baseline	4/8/09 C3, D29	4/22/09 C4, D1	5/20/09 C4, D29	6/3/09 C5, D1	7/1/09 Off-Study
<b>Treatment</b>	Combination			Both drugs held	Sunitinib resumed	Off study
Conj. bilirubin (reference range: 0.0-0.4 mg/dL)	0.1	*	*	*	0.1	0.1
T. bilirubin (reference range: 0.0-1.5 mg/dL)	0.2	0.6	0.4	0.7	0.5	0.7
BUN (reference range: 8-25 mg/dL)	20	16	*	13	15	16
Creatinine (reference range: 0.7-1.4 mg/dL)	0.94	1.10	*	1.13	1.17	1.27
WBC (reference range: 3.70-11.0 K/ $\mu$ L)	7.72	4.95	4.81	4.59	3.87	*

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<b>Hemoglobin</b> (reference range: 11.5-15.5 g/dL)	11.7	15.1	11.8	11.5	9.8	9.3
<b>Hematocrit</b> (reference range: 36-46%)	35.6	42.5	35.8	32.8	30	27
<b>Platelets</b> (reference range: 150-400 K/ $\mu$ L)	490	71	174	59	161	51
<b>Red cell morphology</b>	Unremarkable	Anisocytosis	Anisocytosis	Unremarkable	Slight polychromasia, anisocytosis, occasional RBC fragments	Anisocytosis
<b>Haptoglobin</b> (reference range: 37-246 mg/dL)	389	78	91	<20	38	<20
<b>LDH</b> (reference range: 100-220 U/L)	324	363	212	353	203	374

\*= not done/provided

**AE # 1395393 (Patient 3):** The patient is a 60-year-old male with metastatic renal cell carcinoma who experienced thrombotic microangiopathy while on a phase 1 study using the investigational agents bevacizumab and sunitinib. He began the first course of the investigational therapy on February 17, 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. He received his last dose of bevacizumab on April 13, 2009 (Cycle 2, Day 15), and his last dose of sunitinib on April 26, 2009 (Cycle 2, Day 28).

The patient was diagnosed with renal cell carcinoma in July 2000 and is status post left radical nephrectomy and left adrenalectomy (2000), right distal femoral resection (2001) and right adrenalectomy (2004). He began the investigational therapy on February 17, 2009.

On April 27, 2009 (Cycle 2, Day 29), the patient presented for a clinic visit when he was found to have a blood pressure of 163/101 mmHg, low haptoglobin, thrombocytopenia, and anemia as shown in the table below. He was asymptomatic. Treatment was held, he was later removed from the study therapy. At a clinic visit on May 11, 2009, the platelet count and haptoglobin returned to the normal range. A decision was made to resume single agent sunitinib off study. Follow-up laboratory studies on June 8, 2009, again showed a decrease in haptoglobin and platelet count

The patient's past medical/surgical history is significant for hypertension, esophageal reflux, and asthma. Medications taken at the time of the event include amlodipine, hydrocortisone, esomeprazole, and Advair Diskus<sup>®</sup>.

Pertinent laboratory values:

	2/16/09 Baseline	4/27/09 C2, D29 Both agents held	5/11/09 Sunitinib resumed	6/8/09
<b>WBC</b> (reference range: 3.0-11.0 K/ $\mu$ L)	*	4.43	5.49	3.86
<b>Hemoglobin</b> (reference range: 13-17 g/dL)	*	12.7	12.4	13.3
<b>Hematocrit</b> (reference range: 39-51%)	*	36.4	38	38.7
<b>Platelets</b> (reference range: 150-400 K/ $\mu$ L)	273	76	256	102
<b>Red cell morphology</b>	*	Anisocytosis Occasional RBC fragments	*	*
<b>Haptoglobin</b> (reference range: 37-246 mg/dL)	209	<20	53	<20
<b>LDH</b> (reference range: 100-220 U/L)	176	306	221	293
<b>UPC ratio</b>		0.17	0.21	0.22
<b>Conj. bilirubin</b> (reference range: 0.0-0.4 mg/dL)	*	0.2	0.1	0.2
<b>T. bilirubin</b> (reference range: 0.0-1.5 mg/dL)	*	0.9	0.3	0.7
<b>BUN</b> (reference range: 10-25 mg/dL)	*	25	23	21
<b>Creatinine</b> (reference range: 0.7-1.4 mg/dL)	*	1.29	1.28	1.36

\*= not done/provided

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There has been 1 other case of thrombotic microangiopathy reported to the NCI as a serious adverse event through AdeERS under the sunitinib NSC and/or IND and 7 other cases of thrombotic microangiopathy reported to the NCI as serious adverse events through AdeERS under the bevacizumab NSC and/or IND as summarized in the table below:


Adverse Event	Grade	Attribution
<b>Sunitinib (NSC 736511)</b>		
Thrombotic microangiopathy (n=1) (Sunitinib was used as single agent in a patient with pancreatic cancer)	3	1 Possible
<b>Bevacizumab (NSC 704865)</b>		
Thrombotic microangiopathy (n=7) (In 6 of the 7 cases, bevacizumab was administered in combination with gemcitabine in patients with pancreatic cancer; in one case, bevacizumab was given in combination with docetaxel in a patient with prostate cancer)	4 3	2 Possible, 1 Unlikely, 1 Unrelated 2 Possible, 1 Unlikely

To date, a total of 22,993 patients have been enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC, and 1,975 patients have been enrolled in NCI-sponsored clinical trials under the sunitinib and/or NSC.

In this case, it is thought that a probable causal relationship between the event and both sunitinib and bevacizumab therapy exists.

	Thrombotic microangiopathy
<b>Sunitinib</b>	Probable
<b>Bevacizumab</b>	Probable
<b>Renal cell carcinoma</b>	Unrelated
<b>Combination of sunitinib and bevacizumab in patient with renal cell carcinoma</b>	Probable

Date: 10/29/09

Signature:   
 Helen Chen, M.D.  
 (IDB Monitor for bevacizumab)

Date: 10/29/05

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

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

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