



**DATE:** December 24, 2008  
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**SUBJECT:** CCI-779 (Temsirolimus, Torisel®) and Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# 1205368  
**TO:** Investigators Using CCI-779 (NSC 683864) and Bevacizumab (NSC 704865)

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 temsirolimus and bevacizumab.

The following must be completed by all investigators using temsirolimus and bevacizumab under NCI INDs 61010, 7921 and 11460.

- 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 61010, 7921, or 11460, 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 temsirolimus and bevacizumab, there does not appear to be a change in the risk-benefit ratio for temsirolimus and bevacizumab 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 Adverse Events Assessment that describes the following adverse event(s), previous experience under these INDs and/or NSCs, and the total number of patients enrolled in trials under these INDs and/or NSCs is attached:

A 69-year-old female with metastatic renal cell carcinoma developed left ventricular systolic dysfunction (congestive heart failure) while on a phase 2 trial utilizing the investigational agents bevacizumab and temsirolimus.

## ADVERSE EVENTS ASSESSMENT

IND <b>61010</b> NSC <b>683864</b> <b>CCI-779</b> (tamsirolimus, Torisel®) AE: <b>1205368</b>	<b>7921</b> <b>704865</b> <b>Bevacizumab</b> (rhuMAb VEGF)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: <b>#1</b> Event: <b>Gr. 3: Left ventricular systolic dysfunction</b> Protocol: <b>E2804</b>
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The patient is a 69-year-old female with renal cell carcinoma metastatic to the lungs and retroperitoneum who developed left ventricular systolic dysfunction (congestive heart failure) while on a phase 2 trial utilizing the investigational agents bevacizumab and tamsirolimus. She began the first course of the investigational therapy on September 11, 2008, receiving bevacizumab 10 mg/kg IV over 30-90 minutes on Days 1 and 15, and tamsirolimus 25 mg IV over 30 minutes on Days 1, 8, 15, and 22, every 28 days. The patient received her last dose of bevacizumab on September 25, 2008 (Cycle 1, Day 15), and the last dose of tamsirolimus on October 16, 2008 (Cycle 2, Day 8).

The patient was initially diagnosed with clear cell renal cell carcinoma of the left kidney in July 2006, and is status post a left radical nephrectomy. Of note, a June 12, 2008, echocardiogram revealed mild left ventricular hypertrophy (LVH), a normal left ventricular ejection fraction of 60%, mildly impaired left ventricular diastolic function, mild mitral valve (MV) thickening with mitral regurgitation (MR), and mild aortic regurgitation (AR). The patient has a history of mild hypertension, mitral valve prolapse with left bundle branch block, and bradycardia. After a 2-year remission, an MRI of the kidney on July 16, 2008, showed a soft tissue mass in the nephrectomy bed on the left side measuring 3.6 × 3.9 cm. A CT scan of the chest on August 13, 2008, showed a mass in the nephrectomy bed and multiple bilateral pulmonary nodules. She began the investigational therapy on September 11, 2008.

On October 22, 2008 (Cycle 2, Day 14), the patient presented to the emergency room complaining of a headache, weakness, dyspnea, nausea, and vomiting. She reported that on October 16, 2008 (Cycle 2, Day 8), after receiving her investigational treatment, she developed a headache with generalized body aches, fatigue, weakness, sweat and chills, and had general flu-like symptoms that did not respond to acetaminophen or Benadryl®. Her symptoms, which were intermittent with waves of nausea and vomiting, progressed over the next 2 days. The patient, who appeared very anxious, had a temperature of 99.2° F; respiration 18 breaths per minute, pulse 94 bpm, blood pressure 165/104 mmHg, and an oxygen saturation of 93% on room air. On physical examination there were coarse bilateral breath sounds and slight hyper-resonance at the apices but no frank respiratory distress, no remarkable cardiac findings, a slightly protuberant abdomen, and a large bony induration overlying the location of her 12<sup>th</sup> rib. A CT chest angiogram revealed bilateral pleural effusions, right greater than left, stable subpleural and pulmonary nodules, scarring at bilateral lung apices, and areas of peripheral increased density in the right middle lobe representative of focal atelectasis. The patient was started on IV fluids, 2 litres of oxygen, treated for her symptoms, and admitted to the telemetry unit for observation.

On October 23, 2008 (Cycle 2, Day 15), the patient developed multifocal atrial tachycardia (MAT). An EKG revealed an anterolateral infarct, age undetermined, sinus tachycardia with a heart rate of 120 bpm, and a left bundle branch block. Her troponin I was 0.120 ng/mL (reference range: 0-0.060 ng/mL), CK-MB 4.20 ng/mL (reference range: 0.34-4 ng/mL), and her BNP was 1060 pg/mL (reference range: <100 pg/mL). On October 24, 2008, a 2D echocardiogram showed a mildly depressed left ventricular function with an estimated ejection fraction of less than 50%, a small pericardial effusion, pleural effusion, and a mild-moderately elevated pulmonary artery pressure. A repeat EKG showed atrial fibrillation with a rapid ventricular response. The cardiologist felt that the MAT and borderline troponin elevation were likely a result of increased stress, and that the patient probably had congestive heart failure. It was also felt that her cardiomyopathy developed following chemotherapy. The patient was kept on oxygen for her

dyspnea while being treated with Cardizem<sup>®</sup>, Lovenox<sup>®</sup>, and an increasing dose of beta-blockers for her atrial fibrillation. Solu-Medrol<sup>®</sup>, Lasix<sup>®</sup>, and antibiotics were added to her treatment regimen. The patient's condition gradually improved. Blood cultures were negative and urine cultures revealed mixed flora. On October 26, 2008 (Cycle 2, Day 18), her troponin decreased to 0.050 ng/mL and BNP to 998 pg/mL. Her CK-MB remained elevated at 6.0 ng/mL. A nuclear stress test done on October 27, 2008, revealed poor exercise tolerance, moderate size fixed anterior wall defect of moderate severity that appeared consistent with a prior myocardial infarction, moderately reduced left ventricular systolic function, and a high probability of hemodynamically significant coronary artery disease. On October 29, 2008 (Cycle 2, Day 21), she was discharged home in a stable condition.

On November 6, 2008, the patient was seen for follow-up and reported that she felt somewhat better; she was out of bed all day and capable of doing most of her usual activities including going up a flight of stairs. It was thought that the patient had recovered reasonably well from her past cardiac event. Restaging CT scans of the chest, abdomen and pelvis showed no major changes. The patient expressed her desire to withdraw from further participation in the study due to the lengthy travel involved, and she was taken off the protocol.

The patient's past medical/surgical history is significant for hypertension, COPD, sinus bradycardia, gastroesophageal reflux, left bundle branch block associated with mitral valve prolapse, mucositis, hematuria, hysterectomy for fibroids, and prior heavy tobacco usage (quit in 2006). Her family history is non-contributory. Medications taken at the time of the event included atenolol, Premarin<sup>®</sup>, tramadol, acetaminophen, Phenergan<sup>®</sup>, and Benadryl<sup>®</sup>.

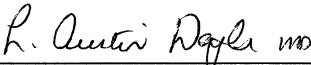
There have been 6 other cases (one grade 2: unlikely related and four grade 3: 1 unrelated, 2 unlikely, 1 possibly related) of left ventricular systolic dysfunction (congestive heart failure) reported to the NCI as a serious adverse event through ADEERS under the temsirolimus NSC and there have been 122 other cases of left ventricular systolic dysfunction reported to the NCI as serious adverse events through ADEERS under bevacizumab NSC respectively.

To date, a total of 1,416 patients have been enrolled in NCI-sponsored clinical trials under the temsirolimus NSC and 18,356 patients have been enrolled in NCI-sponsored clinical trials under the bevacizumab NSC.


In this case, it is felt that a possible relationship exists between the event and the investigational agents.

	<b>Left ventricular systolic dysfunction</b>
<b>CCI-779 (temsirolimus, Torisel)</b>	Possible
<b>Bevacizumab (rhuMAb VEGF)</b>	Possible
<b>Renal cell carcinoma, clear cell adenocarcinoma</b>	Unlikely
<b>IV hydration</b>	Unlikely

Date: 12/24/08

Signature:   
L. Austin Doyle, M.D.  
(IDB Monitor for CCI-779)

Date: 12/24/08

Signature:   
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(IDB Monitor for Bevacizumab)

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

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