



**DATE:** SEP 02 2010

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**SUBJECT:** Bevacizumab (rhuMab VEGF) and CCI-779 (temsirolimus, Torisel™) NCI IND Safety Report, AE#1561869  
*L. Austin Doyle MD*

**TO:** Investigators Using Bevacizumab (NSC 704865) and CCI-779 (NSC 683864)

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 CCI-779.

The following must be completed by all investigators using bevacizumab under NCI INDs 7921 and 11460 and CCI-779 under NCI IND 61010:

- 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/or 61010, 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 CCI-779, there does not appear to be a change in the risk-benefit ratio for bevacizumab and CCI-779 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 these INDs and/or NSCs, and the total number of patients enrolled in trials under these INDs and/or NSCs.

A 56-year-old male with renal cell adenocarcinoma experienced grade 3 dehydration and grade 3 dyspnea while on a phase 2 trial utilizing the investigational agents bevacizumab and CCI-779 in combination with sorafenib. The patient did not receive sorafenib.

**ADVERSE EVENTS ASSESSMENT**

IND 7921	61010	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1
NSC 704865	683864	
Bevacizumab (rhuMAb VEGF)	CCI-779 (tamsirolimus, Torisel™)	Gr. 3: Dehydration Gr. 3: Dyspnea (shortness of breath)
AE: 1561869		Protocol: E2804

The patient is a 56-year-old male with metastatic renal cell adenocarcinoma who experienced dehydration and dyspnea while on a phase 2 trial utilizing the investigational agents bevacizumab, CCI-779, and sorafenib. The patient began his first course of the investigational therapy on November 13, 2009, receiving bevacizumab 10 mg/kg IV over 30-90 minutes on Days 1 and 15, and CCI-779 25 mg IV over 30 minutes on Days 1, 8, 15, and 22, every 28 days. The patient was on an arm that did not include sorafenib. He received his last doses of bevacizumab and CCI-779 on February 19, 2010 (Cycle 4, Day 15).

The patient was initially diagnosed with renal cell adenocarcinoma in October 2008, and is status post right nephrectomy in 2008. He began the investigational therapy on November 13, 2009.

On February 25, 2010 (Cycle 4, Day 21), the patient presented to the emergency department with increased dyspnea and weakness for approximately 5-10 days, and a poor appetite. He had a blood pressure of 120/81 mmHg, pulse rate of 91 bpm, and respiratory rate of 16 bpm. His oxygen saturation was 97% on room air. Laboratory work revealed an elevated creatinine of 1.73 mg/dL (reference range: 0.50-1.30 mg/dL), blood urea nitrogen (BUN) of 31 mg/dL (reference range: 6-24 mg/dL), estimated glomerular filtration rate of (eGFR) of 41 mL/min (reference range: low: >= 60 mL/min), and hemoglobin (Hgb) of 12.7 gm/dL (reference range: 14.0-18.0 gm/dL). Both his cardiac evaluation and CT scan of the chest were negative, and no pulmonary emboli and signs of disease progression were seen. The patient was admitted for dehydration and started on IV fluids, after which he reported feeling better. After receiving some IV fluids, his creatinine decreased to 1.27 mg/dL, and BUN to 23 mg/dL.

On February 27, 2010 (Cycle 4, Day 23), the oncologist suggested that the CCI-779 could be the cause of the patient's symptoms, and recommended that the medication be held until his next clinic visit later in the week. He was discharged in good condition.

On March 3, 2010, the patient's creatinine was 1.64 mg/dL, BUN 25 mg/dL, and Hgb 13.2 mg/dL. A CT scan of the chest, abdomen, and pelvis showed no significant changes from the patient's pre-enrollment scans. There was a question as to whether some of the previously noted lesions might have resolved.

At a follow-up appointment on March 5, 2010, the patient complained of increased fatigue, decreased oral intake, slight weight loss, intermittent left-sided chest pains, dyspnea, and a cough; however, these symptoms had improved since his discharge from the hospital. Although the patient's disease seemed responsive to his investigational treatment and his cardiac work-up was negative, due to his recent cardiac symptoms it was felt that treatment with CCI-779 should be discontinued, while treatment with bevacizumab would continue. Following this decision, the plan was to monitor the patient through repeat scans and to make a re-assessment in two months. At the same time, a search for another clinic trial would be made. His follow-up clinic visit was in two weeks to evaluate his symptoms and to receive bevacizumab. On March 19, 2010, the patient stated that he felt better. His dyspnea had improved, and his chest pain resolved completely.

The patient's past medical/surgical history is significant for lung cancer right hilar mass biopsy, hypertension, 20 pack-year smoking history, hematuria, heartburn, tonsillectomy and adenoidectomy, bronchoscopy and lung biopsy, abdominal surgery, and right inguinal hernia repair. Medications taken at the time of the event included Toprol XL®, Hydrodiuril®, lisinopril, acetaminophen, Ativan®, and Compazine®.

Dyspnea is a known event for both bevacizumab and CCI-779. There have been 580 other cases of dehydration reported to the NCI as serious adverse events through AdEERS under the bevacizumab NSC and/or IND, and 70 other cases of dehydration reported to the NCI as serious adverse events through AdEERS under the CCI-779 NSC and/or IND as summarized in the table below.


Adverse Event	Grade	Attribution
<b>Bevacizumab</b>		
Dehydration (n=580)	5	1 Unlikely
	4	1 Probable, 4 Possible, 8 Unlikely
	3	2 Definite, 24 Probable, 132 Possible, 217 Unlikely, 112 Unrelated
	2	1 Definitely, 6 Probable, 24 Possible, 26 Unlikely, 20 Unrelated
	1	1 Unlikely, 1 Unrelated
<b>CCI-779</b>		
Dehydration (n=70)	4	1 Possible, 1 Unrelated
	3	1 Definite, 4 Probable, 5 Possible, 32 Unlikely, 11 Unrelated
	2	1 Probable, 1 Possible, 11 Unlikely, 2 Unrelated

To date, a total 28,612 patients have been enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC, and 2,147 patients have been enrolled in NCI-sponsored clinical trials under the CCI-779 IND and/or NSC.

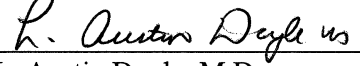
In this case, it is felt that a possible causal relationship exists between the event and CCI-779, but that an unlikely relationship exists between the event and bevacizumab.

	Dehydration	Dyspnea
<b>Bevacizumab</b>	Unlikely	Unlikely
<b>CCI-779</b>	Possible	Probable
<b>Renal cell carcinoma</b>	Unlikely	Unlikely

Date: 9/1/10

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

Date: 9/2/10

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

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

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