



DATE: April 8, 2009

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SUBJECT: Bevacizumab (rhuMAb VEGF) and CCI-779 (temsirolimus, Torisel®) NCI IND Safety Report, AE# 1034535

TO: Investigators Using Bevacizumab (NSC 704865) and Temsirolimus (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 temsirolimus.

The following must be completed by all investigators using bevacizumab under NCI INDs 7921 and 11460 and temsirolimus 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 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 temsirolimus, there does not appear to be a change in the risk-benefit ratio for bevacizumab and temsirolimus 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 NSC's, and the total number of patients enrolled in trials under these INDs and/or NSC's.

A 61-year-old male with metastatic renal cell carcinoma experienced grade 3 dehydration while on a phase 2 study using the investigational agent bevacizumab in combination with temsirolimus.

ADVERSE EVENTS ASSESSMENT

IND 7921	61010	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Gr. 3: Dehydration
NSC 704865	683864	
Bevacizumab (rhuMab VEGF)	CCI-779 (temsirolimus, Torisel®)	
AE: 1034535	Protocol: E2804	

The patient is a 61-year-old male with renal cell carcinoma metastatic to the third right rib and lymph nodes who experienced dehydration while on a phase 2 trial utilizing the investigational agents bevacizumab and temsirolimus. He began the first course of the investigational therapy on December 15, 2008, receiving bevacizumab 10 mg/kg IV over 30-90 minutes on Days 1 and 15, and temsirolimus 25 mg IV over 30 minutes on Days 1, 8, 15, and 22, every 28 days. The patient received his last doses of bevacizumab and temsirolimus on December 31, 2008 (Cycle 1, Day 17).

The patient was initially diagnosed with metastatic clear cell renal carcinoma in September 2008 and is status post palliative radiation therapy to right rib (September 25, 2008-October 15, 2008) and robotic assisted laparoscopic left renal exploration with percutaneous left renal biopsy (November 10, 2008). He began the investigational therapy on December 15, 2008. Cycle 1, Day 15 treatment was delayed 2 days due to symptoms of nausea and mood alteration.

On January 5, 2009 (Cycle 1, Day 22), the patient presented to the clinic for his scheduled treatment and reported a history of progressively worsening watery diarrhea up to 12 times per day, and not having eaten solid food for 3 days. He denied bloody stools or fever. His treatment was held, he was given IV hydration and antiemetics, instructed in the use of Imodium®, and given a prescription for Lomotil®. He returned to the clinic the next day for follow-up. On examination, he was afebrile, his blood pressure was 138/86 mmHg, his pulse was 69 bpm, his lungs were clear to auscultation bilaterally, and his weight had decreased by 7 pounds since the previous week. He reported fatigue, continued diarrhea, although less frequent since using Lomotil®, and nausea controlled by Compazine®.

The patient was admitted to the hospital for evaluation and observation. At the time of admission he reported feeling very dry and thirsty, and less frequent bowel movements. Admission laboratory findings included normal BUN, creatinine, and electrolyte levels, and increased glucose, albumin, and alkaline phosphatase levels. Stool and urine cultures were negative. He was given intravenous hydration, antidiarrheals, and potassium supplementation. By January 8, 2009, he was feeling significantly improved and was discharged that day.

The patient's past medical/surgical history is significant for diabetes, coronary artery disease status post LAD stent in 2004, hypertension, hypercholesterolemia, iron deficiency anemia, depression, lumbar disc disease, tobacco abuse, colon polyps, and diverticulosis. Medications taken at the time of the event included prochlorperazine, ferrous sulfate, vitamin C, Zocor®, atenolol, Glucotrol®, aspirin, Bactrim®, Metamucil®, citalopram hydrobromide, hydrocortisone suppositories, senna, and nitroglycerin.

There have been 54 other cases of dehydration reported to the NCI as serious adverse events through AdEERS under the temsirolimus NSC and/or IND as summarized in the table below.

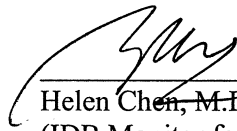
Adverse Event	Grade	Attribution
<i>CCI-779</i>		
Dehydration (n=54)	4	1 Possible, 1 Unrelated
	3	1 Probable, 7 Possible, 21 Unlikely, 10 Unrelated
	2	1 Possible, 10 Unlikely, 2 Unrelated

To date, a total of 19,819 patients have been enrolled in NCI-sponsored clinical trials under the bevacizumab NSC and/or IND, and 1,546 patients have been enrolled in NCI-sponsored clinical trials under the temsirolimus NSC and/or IND.

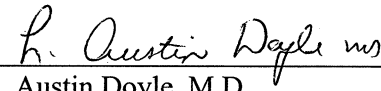
In this case, it is felt that a probable causal relationship exists between the event and CCI-779 and that an unlikely relationship exists between the event and bevacizumab.

	Dehydration
Bevacizumab (rhuMAb VEGF)	Unlikely
CCI-779 (temsirolimus, Torisel®)	Probable
Renal cell carcinoma, clear cell adenocarcinoma	Unlikely

Date: 4/8/09

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

Date: 4/8/09

Signature: 
L. Austin Doyle, M.D.
(IDB Monitor for Temsirolimus)

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

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