



DATE: SEP 08 2010

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SUBJECT: Bevacizumab (rhuMAb VEGF) and CCI-779 (temsirolimus, Torisel™) NCI IND Safety Report, AE#1670473

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 75-year-old female with ovarian cancer experienced grade 3 dehydration, grade 3 hypophosphatemia, and grade 3 hypokalemia while on a phase 2 trial utilizing the investigational agents bevacizumab and CCI-779.

**ADVERSE EVENTS ASSESSMENT**

IND 7921	61010	ADVERSE EXPERIENCE REPORT NO.
NSC 704865	683864	IND Safety Report: #1
Bevacizumab (rhuMab VEGF)	CCI-779 (temsirolimus, Torisel™)	Gr. 3: Dehydration Gr. 3: Phosphate, serum-low (hypophosphatemia) Gr. 3: Potassium, serum-low (hypokalemia)
AE: 1670473		Protocol: 8233

The patient is a 75-year-old female with ovarian cancer who experienced dehydration, hypophosphatemia, and hypokalemia while on a phase 2 trial utilizing the investigational agents bevacizumab and CCI-779. The patient began her first course of the investigational therapy on March 1, 2010, receiving bevacizumab 10 mg/kg IV over 30-90 minutes on Days 1 and 15, and CCI-779 25 mg IV on Days 1, 8, 15, and 22, every 28 days. She received her last dose of bevacizumab on April 26, 2010 (Cycle 2, Day 15), and her last dose of CCI-779 on May 3, 2010 (Cycle 2, Day 22).

The patient was diagnosed with ovarian cancer in September 2007, and is status post total abdominal hysterectomy with bilateral salpingo-oophorectomy in 2007 and multiple agents' systemic chemotherapy from October 2007 to January 2008. She began the investigational therapy on March 1, 2010.

On March 29, 2010, the patient presented to the clinic with a 4-day history of anorexia, malaise, migratory arthralgias, dizziness, and oral mucositis. She denied any history of nausea, vomiting, and fever, but admitted to having chills. The patient appeared pale, fatigued, and tachycardic with a pulse rate of 112 bpm. She also had dry mucous membranes and an oral mucosa with aphthous ulcers. Her potassium was 2.7 mmol/L (reference range: 3.6-5.1 mmol/L), and her phosphorus was 1.5 mg/dL (reference range: 2.5-4.6 mg/dL). The patient was admitted to the hospital and started on IV fluids with potassium supplements, and IV acyclovir and benzocaine for her aphthous ulcers.

On March 30, 2010, the patient's potassium increased to 3.5 mmol/L and her phosphorus rose to 1.7 mg/dL. She was started on magnesium and phosphate supplements. The IV acyclovir was discontinued. On March 31, 2010, the patient was able to ambulate without difficulty, and her mouth sores seemed to be getting better. On April 1, 2010, the patient's condition continued to improve, and she was discharged home in a stable condition. On April 12, 2010 (Cycle 2, Day 1), the patient resumed therapy with the investigational agents; however, the RECIST Measurement Form of April 28, 2010 revealed disease progression. On May 3, 2010 (Cycle 2, Day 22), the patient presented for a follow-up visit without any new complaints, and she was removed from the protocol because of disease progression after completing the last treatment of Cycle 2.

The patient's past medical/surgical history is significant for hypertension, lymphedema, neuropathy, arthritis, left rotator cuff repair in 1994, facelift in 2001, and a hysterectomy in 2007. Medications taken at the time of the event included simvastatin, hydrochlorothiazide, diclofenac PRN (Could Not Find), acetaminophen-hydrocodone, and Actonel®.

There have been 580 other cases of dehydration, 54 other cases of hypophosphatemia, and 137 other cases of hypokalemia reported to the NCI as serious adverse events through AdEERS under the bevacizumab NSC and/or IND as summarized in the table below. Hypophosphatemia and hypokalemia are expected events for CCI-779. There have been 75 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:

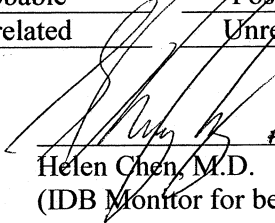
Adverse Event	Grade	Attribution
<b>Bevacizumab</b>		
Dehydration (n=580)	5	1 Unlikely
	4	8 Unlikely, 4 Possible, 1 Probable
	3	112 Unrelated, 217 Unlikely, 132 Possible, 24 Probable, 2 Definite, 3 No attribution
	2	20 Unrelated, 26 Unlikely, 24 Possible, 6 Probable, 1 Definite
	1	1 Unrelated, 1 Unlikely
Hypophosphatemia (n=54)	4	2 Unrelated, 1 Unlikely, 2 Possible
	3	5 Unrelated, 18 Unlikely, 6 Possible, 2 Probable, 1 Definite
	2	3 Unrelated, 9 Unlikely, 5 Possible
Hypokalemia (n=137)	4	8 Unrelated, 11 Unlikely, 3 Possible, 1 Probable
	3	27 Unrelated, 39 Unlikely, 22 Possible, 8 Probable, 2 No attribution
	1	5 Unrelated, 7 Unlikely, 6 Possible
<b>CCI-779</b>		
Dehydration (n=75)	4	1 Unrelated, 1 Possible
	3	11 Unrelated, 29 Unlikely, 7 Possible, 6 Probable, 1 Definite
	2	3 Unrelated, 11 Unlikely, 4 Possible, 1 Probable

To date, a total of 28,686 patients have been enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC, and 2,186 patients have been enrolled in NCI-sponsored clinical trials under the CCI-779 IND and/or NSC.

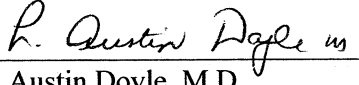
In this case, it is felt that a probable or possible relationship exists between the dehydration, bevacizumab, and CCI-779; hypophosphatemia is probably related to CCI-779 but unrelated to bevacizumab; and hypokalemia is possibly related to CCI-779 but unrelated to bevacizumab.

	Dehydration	Hypophosphatemia	Hypokalemia
<b>Bevacizumab</b>	Possible	Unrelated	Unrelated
<b>CCI-779</b>	Possible	Probable	Possible
<b>Ovarian cancer</b>	Unrelated	Unrelated	Unrelated

Date: 09.07.10

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

Date: 9/7/10

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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