



DATE: December 24, 2008 *L. Austin Doyle*

FROM: Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
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SUBJECT: Bevacizumab (rhuMab VEGF) and CCI-779 (temsirolimus, Torisel®) NCI IND Safety Report, AE# **1803957**

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 54-year-old female with endometrial adenocarcinoma experienced grade 4 hypomagnesemia 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.
NSC 704865	683864	IND Safety Report: #1
Bevacizumab (rhuMAb VEGF)	CCI-779 (temsirolimus, Torisel®)	Gr. 4: Hypomagnesemia
AE: 1803957		Protocol: GOG-0229G

The patient is a 54-year-old female with endometrioid endometrial adenocarcinoma who developed hypomagnesemia while on a phase 2 trial utilizing the investigational agents bevacizumab and temsirolimus. She began the first course of the investigational therapy on November 4, 2008, receiving bevacizumab 10 mg/kg IV over 30-90 minutes on Days 1 and 15, and temsirolimus 25 mg IV over 30-90 minutes on Days 1, 8, 15, and 22, every 28 days. The patient received her first and last dose of bevacizumab on November 4, 2008 (Cycle 1, Day 1), and the last dose of temsirolimus on November 11, 2008 (Cycle 1, Day 8).

The patient was initially diagnosed with endometrioid adenocarcinoma in January 2005, and is status post staging surgery, radiation therapy, and multiple-agent systemic chemotherapy. She began the investigational therapy on September 11, 2008.

On November 11, 2008, the patient presented to the clinic to receive Cycle 1, Day 8 investigational treatment with temsirolimus. She reported symptoms of weakness, fatigue, and mild nausea. Her magnesium level drawn that day was 0.5 mg/dL (reference range: 1.5-2.4 mg/dL). Her baseline level drawn on October 24, 2008, was 1.8 mg/dL. On the following day, she received 4 grams of IV magnesium sulphate. Later that day, her magnesium level recovered to 1.9 mg/dL. She was continued on protocol treatment as scheduled.

The patient's past medical/surgical history is significant for anemia, pulmonary embolism, and a right breast cyst (benign) removal in 2000. Medications taken at the time of the event included tramadol, Advil®, dicyclomine, oxycodone, morphine, and Coumadin®.

There have been no other cases of hypomagnesemia reported to the NCI as serious adverse events through AdEERS under the temsirolimus NSC and 32 other cases of hypomagnesemia reported to the NCI as serious adverse events through AdEERS under the bevacizumab NSC as summarized in the table below.

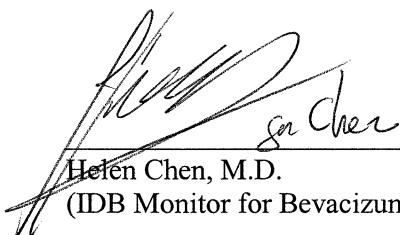
Adverse Event	Grade	Attribution
Bevacizumab		
Hypomagnesemia (n=32)	4	5 Unrelated, 1 Unlikely
	3	1 Probably, 1 Possible, 4 Unlikely, 1 Unrelated
	2	9 Unlikely, 3 Unrelated
	1	5 Unlikely, 2 Unrelated

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

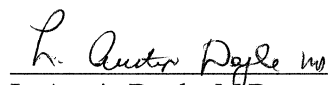
In this case, it is felt that a possible causal relationship exists between the event and the investigational agents.

	Hypomagnesemia
Bevacizumab (rhuMab VEGF)	Possible
CCI-779 (temsirolimus, Torisel[®])	Possible
Endometrioid endometrial adenocarcinoma	Unlikely

Date: 12/31/08

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

Date: 12/31/08

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

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

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