




DATE: May 24, 2010

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SUBJECT: Bevacizumab (rhuMab VEGF) and CCI-779 (temsirolimus, Torisel®) NCI IND Safety Report, AE# 1448075

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 NSCs, and the total number of patients enrolled in trials under these INDs and/or NSCs.

A 69-year-old female with recurrent endometrioid endometrial adenocarcinoma experienced a grade 4 cognitive disturbance while on a phase 2 trial utilizing the investigational agents bevacizumab and temsirolimus.

ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 Bevacizumab (rhuMAb VEGF) AE: 1448075	61010 683864 CCI-779 (temsirolimus, Torisel[®])	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 <p style="text-align: center;">Gr. 4: Cognitive Disturbance</p> Protocol: GOG-0229G
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The patient is a 69-year-old female with recurrent endometrial cancer who experienced a cognitive disturbance while on a phase 2 trial utilizing the investigational agents temsirolimus and bevacizumab. She began the first course of the investigational therapy on December 3, 2008, receiving temsirolimus 25 mg IV over 30 minutes on Days 1, 8, 15, and 22, and bevacizumab 10 mg/kg IV over 30-90 minutes on Days 1 and 15, every 4 weeks. She received her last doses of both temsirolimus and bevacizumab on September 1, 2009 (Cycle 10, Day 1).

The patient was diagnosed in November 2008, with recurrent endometrial carcinoma, and is status post left ureteral mass resection with psoas hitch procedure and re-implantation of the left ureter. She began the investigational therapy on December 3, 2008.

She presented at the clinic for a routine CT scan of the chest on August 28, 2009 (Cycle 9, Day 25), which showed no evidence of metastatic disease in the chest, no new lesions, and no evidence of progressive disease. Her original mass of 3.8 cm went down to 2.5 cm. On another clinic visit on August 31, 2009 (Cycle 9, Day 28), she presented with fever, pelvic pain, and fatigue. Her vital signs were as follows: BP of 126/68 mmHg, pulse of 64 beats/minute, respiratory rate of 12 breaths/minute, and temperature of 99°F. Her physical examination revealed no gross abnormalities. Her hematology panel was significant for a low platelet count of 93 K/mm³ (reference range: 140-440 K/mm³). She was allowed to proceed to Cycle 10, and received the Cycle 10, Day 1 doses of both temsirolimus and bevacizumab on September 1, 2009. However, the patient requested that subsequent doses of both drugs be withheld. On a follow-up clinic visit on September 25, 2009 (Cycle 10, Day 25), she was found to be completely non-functional, unable to communicate, non-ambulatory, and needing total care. Although it was noted not to be due to toxicity, she was removed from the study due to failure to thrive. The patient and her family elected to receive hospice care.

Her past medical/surgical history is significant for hypertension, diabetes, and prior chemotherapy with Adriamycin[®], cisplatin, and Taxol[®] for seven cycles from February 2008 to July 2008.

There have been 12 other cases of cognitive disturbance reported to the NCI as serious adverse events through ADEERS under the bevacizumab NSC and/or IND and 1 other case of cognitive disturbance reported to the NCI as a serious adverse event through ADEERS under the temsirolimus NSC and/or IND, as summarized in the table below.


Adverse Event	Grade	Attribution
Bevacizumab		
Cognitive Disturbance (n=12)	4	3 Unrelated, 2 Unlikely
	3	1 Unrelated, 2 Unlikely, 1 Possible
	2	1 Unlikely, 1 Possible, 1 Probable
Temsirolimus		
Cognitive Disturbance (n=1)	2	1 Unlikely

To date, a total of 26,724 patients have been enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC and 2016 patients have been enrolled in NCI-sponsored clinical trials under the temsirolimus IND and/or NSC.

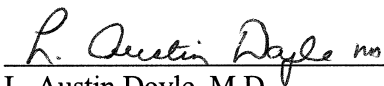
In this case, it is felt that a possible causal relationship between the event and the investigational agents cannot be excluded.

	Cognitive Disturbance
Bevacizumab (rhuMAB VEGF)	Possible
CCI-779 (temsirolimus, Torisel®)	Possible
Endometrioid Endometrial Carcinoma	Unrelated

Date: 5/24/10

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

Date: 5/26/10

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

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

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