



**DATE:** 5/10/11

**FROM:** Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI  
L. Austin Doyle, M.D., Investigational Drug Branch, CTEP, DCTD, NCI

**SUBJECT:** Bevacizumab (rhuMAb VEGF) and CCI-779 (temsirolimus, Torisel®) NCI IND Safety Report, AE# 1345682

**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 this letter to your Institutional Review Board (IRB) of record according to your 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 61-year-old female with stage III primary peritoneal cancer experienced grade 3 anal fissure while on a phase 2 trial utilizing the investigational agents bevacizumab and temsirolimus.

## ADVERSE EVENTS ASSESSMENT

IND	7921	61010	ADVERSE EXPERIENCE REPORT NO.
NSC	704865	683864	IND Safety Report: #1
Bevacizumab (rhuMab VEGF)	CCI-779 (tensirolimus, Torisel™)		Gr. 3: Anal fissure
AE:	1345682		Protocol: 8233

The patient is a 61-year-old female with primary peritoneal cancer who experienced an anal fissure while on a phase 2 trial utilizing the investigational agents bevacizumab and tensirolimus. She began her first course of the investigational therapy on January 28, 2011, receiving bevacizumab 10 mg/kg IV over 30-90 minutes on Days 1 and 15 and tensirolimus 25 mg IV on Days 1, 8, 15, and 22, every 28 days. She received her last dose of bevacizumab on February 25, 2011 (Cycle 2, Day 1), and the last dose of tensirolimus on March 18, 2011 (Cycle 2, Day 22).

The patient was diagnosed with stage III primary peritoneal cancer in February 2010. She is status post multiple-agent systemic chemotherapy, single-agent systemic chemotherapy, and debulking surgery in May 2010. The surgery included a right hemicolectomy as well as a sigmoid colectomy with colorectal anastomosis and ileal transverse colon anastomosis. In the immediate aftermath of the procedure, the patient developed chronic, constant, and ongoing perianal pain associated with bowel movements; she also reported erratic bowel movements and chronic constipation. She began the investigational therapy on January 28, 2011.

The patient was seen in the outpatient clinic on March 11, 2011 (Cycle 2, Day 15) and noted to have significant perianal pain as well as significant diarrhea associated with oral intake and antibiotic use; an examination revealed a thrombosed and indurated external hemorrhoid. On March 15, 2011 (Cycle 2, Day 19), the patient underwent an examination under anesthesia, and a hard ulceration proximal to the lesion was found on the right anal canal wall; the hemorrhoid with anal skin tag was excised and the tag was found to be pathologically non-significant. The pain became severe and persistent after the procedure. During a follow-up evaluation, the patient revealed that she had been experiencing deep anal pain for months in duration, which was most often confined to the time of her bowel movements. The pain was not controllable with significant narcotics. On March 23, 2011 (Cycle 2, Day 27), the patient was admitted to the hospital for severe anal pain secondary to an anal fissure. She had a surgical evaluation on March 28, 2011. It revealed that the patient had an approximately 3 cm longitudinal by 2 cm cross-sectional ulceration extending from the dentate line to the level of the external anal skin; the margins of this fissure and ulceration were heaped up with a significant amount of sclerotic tissue, and the underlying internal sphincter musculature was exposed. Debridement and lateral internal anal sphincterotomy were performed. Pathological examination on the anal fissure revealed benign squamous covered anal tissue with mild squamous hyperplasia and underlying scarring, inflammation, and inflamed granulation consistent with a fissure; no evidence of malignancy. During the hospitalization, the patient was also treated with analgesics and antibiotics. The pain was improved and she was discharged on April 1, 2011.

During a follow-up visit on April 15, 2011, the patient was feeling much better and her anal pain was markedly improved.

The patient's past medical/surgical history is significant for hypothyroidism, total abdominal hysterectomy and bilateral salpingo-oophorectomy for benign disease in 1994, right chest Port-A-Cath placement, and G-tube placement. Medications taken at the time of the event included levothyroxine, Dilaudid®, and Duragesic® patch.

There have been 12 other cases of anal fissure reported to the NCI through AdEERS as a serious adverse event for bevacizumab, and 2 other cases of anal fissure reported to the NCI through AdEERS as serious adverse events for temsirolimus.

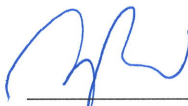
Adverse Event	Grade	Attribution
<b>Bevacizumab</b>		
Anal fissure (n=12)	3	3 Possible, 1 Probable
	2	1 Unrelated, 6 Possible
	1	1 Possible
<b>Temsirolimus</b>		
Anal fissure (n=2)	2	2 Possible

To date, a total of 32,122 patients have been enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC, and 2,649 patients have been enrolled in NCI-sponsored clinical trials under the temsirolimus IND and/or NSC.

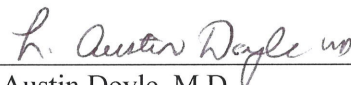
In this case, it is felt that a possible causal relationship exists between the event and the investigational agents bevacizumab and temsirolimus.

	<b>Anal fissure</b>
<b>Bevacizumab</b>	Possible
<b>Temsirolimus</b>	Possible
<b>Primary peritoneal cancer</b>	Possible

Date: 5/6/11

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

Date: 5/10/11

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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