



DATE: AUG 3 1 2010

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SUBJECT: Bevacizumab (rhuMab VEGF) and CCI-779 (temsirolimus, Torisel®) NCI IND Safety Report, AE#1367114

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 52-year-old male with carcinoid tumor developed a grade 3 anal ulcer while on a phase 2 trial utilizing the investigational agents bevacizumab and CCI-779.

ADVERSE EVENTS ASSESSMENT

IND 7921	61010	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Gr. 3: Ulcer, GI: Anus Protocol: 8233
NSC 704865	683864	
Bevacizumab (rhuMAb VEGF)	CCI-779 (tensirolimus, Torisel®)	
AE: 1367114		

The patient is a 52-year-old male with carcinoid tumors involving the liver and lung who developed an anal ulcer while on a phase 2 trial utilizing the investigational agents bevacizumab and CCI-779. The patient began his first course of the investigational therapy on February 12, 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. He received his last dose of bevacizumab on March 26, 2010 (Cycle 2, Day 15), and his last dose of CCI-779 on April 16, 2010 (Cycle 3, Day 8).

The patient was diagnosed with carcinoid tumor in January 2008 and is status post single-agent chemotherapy and hormonal therapy in 2008. The patient began the investigational therapy on February 12, 2010.

On April 23, 2010 (Cycle 3, Day 15), the patient, who had earlier complained of anal ulcer which necessitated holding of bevacizumab therapy on April 9, 2010 (Cycle 3, Day 1), presented to the hospital and was admitted for a 3-week history of constant rectal pain, one episode of hematochezia, and one-week history of an oral ulcer. His rectal examination by a surgeon revealed a posterior midline anal fissure with a hypertrophic anal papilla and sentinel tag which was exquisitely tender to palpation. His hemoglobin was normal, and his stool cultures were negative. The surgeon recommended a high-fiber diet, fiber supplements, increased water intake, sitz baths, and rectal applications of hydrocortisone cream. His aphthous ulcer was treated with Magic Mouthwash. He was discharged the next day.

During a surgical evaluation on April 30, 2010 (Cycle 3, Day 22), the patient reported continuing rectal pain, and his examination revealed the same posterior midline anal fissure. The recommendation was therapy with topical nitroglycerin, Colace®, and sitz baths. Later that day, CCI-779 was held based on the non-resolution of his anal fissure.

At a follow-up visit on May 7, 2010, the patient reported an improvement in his anal pains and the resolution of his mouth sores. CCI-779 was resumed, while bevacizumab continued to be held due to his anal fissure.

The patient's past medical/surgical history is significant for right hepatectomy in 2001 for hepatoma versus hepatocellular carcinoma, multiple duodenal ulcers, antrectomy for perforated gastric ulcer (2001), ankle surgery, hemorrhoids, hypertension, hyperlipidemia, endoscopy, colonoscopy, and lung biopsy. Medications taken at the time of the event included hydrochlorothiazide, Pepcid®, metoprolol, Norvasc®, Vytorin®, insulin, potassium, and simvastatin.

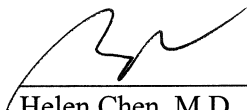
Gastrointestinal ulcers are known events for bevacizumab. There has been one other case of anal ulcer (grade 2, possible related) reported to the NCI as serious adverse events through AdEERS under the CCI-779 NSC and/or IND.

To date, a total of 28,649 patients have been enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC, and 2,152 patients have been enrolled in NCI-sponsored clinical trials under the CCI-779 IND and/or NSC.

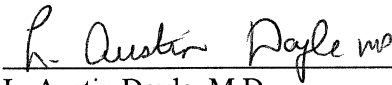
In this case, it is felt that a probable relationship exists between the event and bevacizumab, and a possible relationship exists between the event and CCI-779.

	<u>Anal ulcer</u>
<u>Bevacizumab</u>	<u>Probable</u>
<u>CCI-779</u>	<u>Possible</u>
<u>Carcinoid tumor</u>	<u>Unrelated</u>

Date: 8/24/10

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

Date: 8/31/10

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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