



DATE: SEP 27 2010

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SUBJECT: Bevacizumab (rhuMab VEGF) and CCI-779 (temsirolimus, Torisel®) NCI IND Safety Report, AE# 1746507

TO: Investigators Using Bevacizumab (NSC 704865) and CCI-779 (NSC 683864)

L. Austin Doyle MD

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, 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 or 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 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 67-year-old female with jejunal carcinoid tumor experienced grade 3 rectal bleeding 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 (tamsirolimus, Torisel™)	Gr. 3: Hemorrhage, GI: Rectum
AE: 1746507		Protocol: 8233

The patient is a 67-year-old female with jejunal carcinoid tumor who experienced rectal bleeding 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 January 27, 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 only dose of bevacizumab on January 27, 2010 (Cycle 1, Day 1), and her last dose of CCI-779 on April 7, 2010 (Cycle 3, Day 8).

The patient was diagnosed with jejunal carcinoid tumor in February 2002 and is status post tumor resection, pylorus-preserving Whipple procedure with duodenojejunostomy, hormonal therapy, radiation therapy in April, and multiple-agent systemic chemotherapy. She began the investigational therapy on January 27, 2010.

On January 28, 2010 (Cycle 1, Day 2), the patient, who had been on Coumadin® for DVT and mesenteric thrombosis, presented to the emergency department (ED) with an episode of bright red blood per rectum followed by dark, melanic stools 24 hours after starting the investigational treatment. A CT scan of the abdomen and pelvis revealed increased duodenal wall density at the site of small bowel anastomosis which was indeterminate but could represent gastrointestinal hemorrhage or ingested material. Her INR was 2.5 (reference range: 0.9-1.2) and her hemoglobin was 10.1 g/dL (reference range: 12.0-15.5 mg/dL). The patient's INR later dropped to 1.7 and her hemoglobin dropped to 7.3 g/dL. Coumadin® was held. She was admitted to the MICU, and given 2 units of Fresh Frozen Plasma (FFP) and vitamin K. Upper and lower gastrointestinal endoscopies did not reveal the site of the bleed. This GI bleed was attributed to bevacizumab and it was discontinued; however, she continued treatment with CCI-779. By February 1, 2010 (Cycle 1, Day 6), the patient's condition had improved, and her Coumadin® was restarted. Later that day, she was discharged home in a stable condition with instructions for outpatient follow-up.

On April 8, 2010 (Cycle 3, Day 9), the patient presented to the ED with another episode of bright red bleeding per rectum and maroon stools one day after receiving CCI-779. She had dry mucous membranes and was tachycardic with standing. There was no stool specimen present on which to perform a proper hemoccult test. Her hemoglobin was 8.1 mg/dL. The patient was admitted to the hospital and was transfused with 2 units of packed red blood cells (PRBC). An esophagogastroduodenoscopy (EGD) the next day showed prior pylorus-preserving Whipple with duodenojejunostomy but was otherwise normal; the bleeding site was not identified. On April 10, 2010, the patient reported feeling better, and her hemoglobin was now 10.5 mg/dL. She was discharged home in a stable condition that day with plans to follow-up with her oncologist.

On June 9, 2010, the patient was admitted for an acute lower extremity DVT, which necessitated an IVC filter placement on the following day. On June 16, 2010, she developed lower GI bleeding while on Coumadin®. The Coumadin® was held, and she was given FFP and vitamin K. Later that day, the patient received 2 units of PRBC. An EGD the next day revealed diffuse gastric erythema and friability, large amounts of blood and clot throughout the stomach and small bowel, and small vascular ectasias/angiectasias at the anastomosis which were treated with argon plasma coagulation (APC). She was stabilized in the ICU and had no further evidence of bleeding. On June 18, 2010, an angiogram revealed no active arterial lesion that could explain the bleeding; however, there were multiple collateral

varicosities around the duodenum due to the portal vein encasement by the tumor which could be the cause of the blood loss. She was started on propranolol and Protonix®. She was discharged on June 23, 2010, with plans to follow-up as an outpatient.

The patient's past medical/surgical history is significant for hypertension, possible type 2 diabetes mellitus, peptic ulcer disease, mesenteric vein thrombosis, lower extremity DVT, TIA, and patent foramen ovale. Medications taken at the time of the event included calcium, Centrum®, dexamethasone, Coumadin®, dicyclomine, fentanyl, prednisone, Protonix®, Tylenol®, vitamin C, vitamin E, octreotide, hydrochlorothiazide, lisinopril, and Celexa®.

There have been 4 other cases of rectal bleeding reported to the NCI as serious adverse events through AdEERS under the CCI-779 NSC and/or IND as summarized in the table below. Gastrointestinal hemorrhage is a known event for bevacizumab.

Adverse Event	Grade	Attribution
CCI-779		
Rectal bleeding (n=4)	3	1 Unrelated, 1 Unlikely, 1 Possible
	2	

To date, a total of 28,700 patients have been enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC, and 2213 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 possible causal relationship exists between the event and CCI-779 and that there is no relationship between the event and bevacizumab.

	Rectal bleed
Bevacizumab	Unrelated
CCI-779	Possible
Carcinoid tumor	Unlikely

Date: 9/2/10

Signature: _____

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

Date: 9/23/10

Signature: _____

L. Austin Doyle MD
L. Austin Doyle, M.D.
(IDB Monitor for CCI-779)

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

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