



DATE: DEC 06 2010 *L. Austin Doyle ms*

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SUBJECT: Bevacizumab (rhuMAb VEGF) and CCI-779 (tamsirolimus, Torisel™) NCI IND Safety Report, AE#1981052

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 63-year-old male with renal cell adenocarcinoma experienced a grade 3 abdominal abscess and grade 3 opportunistic infection while on a phase 2 trial utilizing the investigational agents bevacizumab and CCI-779 in combination with sorafenib; however, the patient was on an arm that did not include sorafenib.

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. 3: Infection: Abdomen NOS Gr. 3: Opportunistic infection
AE: 1981052		Protocol: E2804

The patient is a 63-year-old male with renal cell adenocarcinoma who developed an abdominal abscess with an opportunistic infection, while on a phase 2 trial utilizing the investigational agents bevacizumab and temsirolimus. The patient began his first course of the investigational therapy on January 12, 2010, receiving bevacizumab 10 mg/kg IV over 30-90 minutes on Days 1 and 15, and temsirolimus 25 mg IV over 30 minutes on Days 1, 8, 15, and 22, every 28 days. He received his last dose of bevacizumab on May 4, 2010.(Cycle 5, Day 1), and his last dose of temsirolimus on May 11, 2010 (Cycle 5, Day 8).

The patient was diagnosed with renal cell carcinoma in April 2009, and is status post right nephrectomy in April 2009. He began the investigational therapy on January 12, 2010.

On May 14, 2010 (Cycle 5, Day 11), the patient presented to the clinic with acute abdominal pain, dehydration, anorexia, and weight loss. He was febrile with a temperature of 39.1°C. His white blood cell (WBC) count was normal; however, he had bandemia and his C-reactive protein (CRP) was elevated at 12.6 mg/dL (reference range: 0-1 mg/dL). A CT scan of the abdomen and pelvis revealed a phlegmon and abscess between the stomach and pancreas. Specimens for blood and urine cultures were ultimately negative. The patient was admitted and started on IV fluids and Zosyn®.

On May 15, 2010 (Cycle 5, Day 12), the patient remained persistently febrile, and as a result, Zosyn® was changed to imipenem. His Upper GI series showed normal findings. On May 18, 2010 (Cycle 5, Day 15), an aspiration of his abdominal fluid yielded 2 mL of muddy brown fluid; however, an attempt to place a drainage catheter was unsuccessful. A culture of the abdominal fluid revealed moderate gram-negative *Staphylococcus* and presumptive *Rhizobium radiobacter*. His blood cultures remained negative.

On May 19, 2010 (Cycle 5, Day 16), a second attempt to place a drainage tube was unsuccessful, due to the patient's diffuse paralytic ileus and distended large and small bowels. His laboratory results revealed a WBC count of 10.9 x 10⁹/L (reference range: 3.8 – 9.8 x 10⁹/L). By May 26, 2010 (Cycle 5, Day 23), the patient continued to be febrile with abdominal pain and an elevated WBC count despite being treated with various antibiotics. His family requested that he be transferred to another hospital for continuation of care. On June 2, 2010, the patient was removed from the study.

On June 10, 2010, following a two-week hospital course at the second hospital, during which the patient underwent a CT-guided biopsy of the intra-abdominal lesion, insertion of bilateral chest tubes for pleural effusion, and institution of total parenteral nutrition, he was transferred back to the first hospital. Although the biopsy showed no malignancy, an additional sample specimen for further evaluation could not be obtained.

On June 14, 2010, a CT scan of the abdomen showed progression of the abdominal mass. It was felt that he might have a tumor versus an abscess. His WBC count had increased to 23.6 x 10⁹/L. On June 16, 2010, the patient underwent a fine needle aspiration of the intra- abdominal lesion which yielded non-diagnostic findings. On June 19, 2010, following a hospital course during which the patient remained mostly afebrile, had negative blood and pleural fluid cultures, had stable breathing, and stable urinary and bowel functions, the patient was discharged on antibiotics and without the chest tube. Although the cause of the patient's abdominal infection remained unclear, and an adequate biopsy of the abdominal lesion was never obtained, there was a concern for progressive metastatic renal cancer within the abdomen.

On September 13, 2010, the patient was seen at the clinic, where he reported that he had been doing well for the last 3 months. He denied abdominal pain, showed no signs of weight loss, and although his breathing appeared stable, he reported having chronic dyspnea on exertion, which was related to his COPD. A CT scan of the chest, abdomen, and pelvis of August 2010 showed progression of the metastatic cancer involving hilar lymph nodes and parenchymal tumors. On the abdomen and pelvis, it appeared that the intra-abdominal finding had organized more clearly into a pseudo cyst. There was no evidence of progressive tumor. The patient was scheduled to return in two months for observation and follow-up CT scans.

The patient's past medical/surgical history is significant for chronic obstructive pulmonary disease (COPD), osteoporosis vs. osteopenia, hypertension, hypoalbuminemia, anemia, degenerative joint disease, cerebrovascular accident, diastolic congestive heart failure, peripheral arterial disease, erectile dysfunction, right nephrectomy, umbilical hernia repair, wedge resection of the left upper lobe nodule, arthroscopic surgery of the knees and left elbow, port placement (December 15, 2009), and exploratory laparotomy following a motor vehicle accident at the age of 12. He has a 50 pack-year smoking history, and a history of alcohol abuse. Medications taken at the time of the event included Norvasc®, Spiriva®, alendronate, Compazine®, aspirin, Toprol®, Diovan®, Lasix®, omeprazole, and topical betamethasone.

Infections are known events for bevacizumab. There have been 19 other cases of opportunistic infection and reported to the NCI as serious adverse events through AdEERS under the bevacizumab NSC and/or IND. Both infections and opportunistic infections are known events for temsirolimus.


Adverse Event	Grade	Attribution
Bevacizumab		
Opportunistic infection (n = 19)	5	1 Probable
	4	1 Unlikely
	3	2 Unrelated, 10 Unlikely, 2 Possible, 1 Probable
	2	1 Unrelated, 1 Possible

To date, a total of 30,065 patients have been enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC, and 2,277 patients have been enrolled in NCI-sponsored clinical trials under the temsirolimus IND and/or NSC.

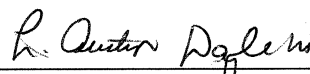
In this case, it is felt that a possible relationship exists between the abdominal abscess and bevacizumab, and that a possible relationship exists between abdominal abscess, opportunistic infection and temsirolimus.

	Abdominal abscess	Opportunistic infection
Bevacizumab	Possible	Unlikely
Temsirolimus	Possible	Possible
Renal cell carcinoma	Unlikely	Unrelated
Rhizobium radiobacter	Definite	N/A

Date: 11/22/10

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

Date: 12/3/10

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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