



DATE: SEP 02 2010

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SUBJECT: Bevacizumab (rhuMAb VEGF) and CCI-779 (tamsirolimus, Torisel™) NCI IND Safety Report, AE#1220746

L. Austin Doyle MD

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 65-year-old male with metastatic hepatocellular carcinoma experienced grade 4 renal failure and died of multi-organ failure 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	CCI-779	Gr. 5 Multi-organ failure
(rhuMab VEGF)	(temsirolimus, Torisel™)	Gr. 4: Renal failure
AE: 1220746		Protocol: 8233

The patient was a 65-year-old male with metastatic hepatocellular carcinoma who experienced renal failure while on a phase 2 trial utilizing the investigational agents bevacizumab and CCI-779. He began his first course of the investigational therapy on March 24, 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 only doses of bevacizumab and CCI-779 on March 24, 2010 (Cycle 1, Day 1).

The patient was diagnosed with hepatocellular carcinoma in January 2010 and was status post liver biopsy in January 2010. He began the investigational therapy on March 24, 2010.

On March 31, 2010 (Cycle 1, Day 8), the patient presented to the ER with severe nausea with-vomiting and diarrhea, diffuse abdominal pain and distension, dizziness, anuria for 2 days, hypotension (BP 93/56 mm Hg), and tachycardia. His serum creatinine was 1.6 mg/dL (reference range: 0.7-1.5 mg/dL) from a baseline value of 0.5 mg/dL, BUN was 27 mg/dL (reference range: 5-25 mg/dL). Physical examination revealed tenderness in the midepigastrium with guarding. A CT scan of the abdomen and pelvis showed interval development of increased ascites, thickening of the terminal ileum, non obstructing left renal calculus, and no evidence of hydronephrosis. It also revealed hepatic enlargement due to the infiltrative right hepatic tumor. Following a diagnostic paracentesis in the ER, the patient developed worsening abdominal pain, acute renal failure, and metabolic acidosis. He was started on IV fluids, antibiotics pending culture results, antiemetics, and pain medication. WBC was 15.4 K/ μ L (reference range: 3.9-10.7 K/ μ L) compared to the baseline of 8.7 K/ μ L on March 24, 2010, hemoglobin 13.5 g/dL (reference range: 14-18.1 g/dL) compared to 9.9 g/dL baseline, platelets 629 K/ μ L (reference range: 135-371 K/ μ L) compared to baseline of 320 K/ μ L, ANC 12.86 K/ μ L (reference range: 1.6-8.1 K/ μ L), and PT 13.8/INR 1.1.

On April 1, 2010 (Cycle 1, Day 9), the patient underwent an exploratory laparoscopy with a laparoscopic paracentesis and liver biopsy, at which time he was found to have metastatic disease but no other significant findings. ALT was 364 U/L (reference range 4-40 U/L) compared to 68 U/L on March 17, 2010, AST 1897 U/L (reference range 4-40 U/L), and LDH 5268 U/L (reference range: <226). His serum creatinine had increased to 3.39 mg/dL, and his BUN increased to 48 mg/dL, with hyperkalemia and anuria. He was started on dialysis. The patient also developed respiratory failure and was placed on mechanical ventilation with vasopressors. Urine-analysis revealed a urine protein of 4.2 g/L and urine creatinine of 1.2 (UPC ratio 3.5), compared to a UPC ratio of 0.18 at baseline. Data on 24-hour urine protein are not available.

On April 2, 2010 (Cycle 1, Day 10), the patient's condition continued to deteriorate. His serum creatinine was 2.23 mg/dL and BUN was 25 mg mg/dL. In view of the patient's poor prognosis, it was decided he would no longer be dialyzed. Following a palliative care consultation with the patient's family, it was decided that the patient would be extubated and designated as DNR. The patient died on April 3, 2010.

The patient's past medical was significant for diabetes mellitus, hypertension, rheumatoid arthritis requiring methotrexate, and prior alcohol and tobacco abuse. Medications taken at the time of the event included glyburide, metformin, Norvasc®, lisinopril, oxycodone, Reglan®, magnesium, and vitamin D.

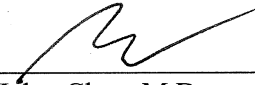
Renal failure is a known event for both bevacizumab and CCI-779. The deterioration of the hepatic and respiratory status is likely a result of renal failure and the underlying liver carcinoma.

To date, a total of 28,643 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.

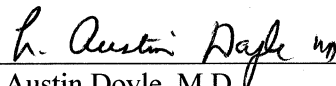
In this case, it is felt that a possible relationship exists between the event and the study agents.

	Renal failure	Multiorgan failure
Bevacizumab	Possible	Possible
CCI-779	Possible	Possible
Hepatocellular carcinoma	Possible	Possible
Progression of disease	Possible	Possible

Date: 9/1/10

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

Date: 9/2/10

Signature: 
L. Austin Doyle, M.D.
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If this assessment is changed, we will notify your office.

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