



DATE: MAY 11 2011

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SUBJECT: Bevacizumab (rhuMab VEGF) and CCI-779 (temsirolimus, Torisel®) NCI IND Safety Report, AE# 1792675

TO: Investigators Using Bevacizumab (NSC 704865) and Temsirolimus (NSC 683864)

R. 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 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 71-year-old male with clear cell renal cell adenocarcinoma experienced grade 3 left ventricular systolic dysfunction 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	CCI-779	Gr. 3: Left ventricular systolic
(rhuMab VEGF)	(temsirolimus,	dysfunction
	Torisel™)	
AE: 1792675		Protocol: E2804

The patient is a 71-year-old male with clear cell renal cell adenocarcinoma who experienced left ventricular systolic dysfunction while on a phase 2 trial utilizing the investigational agents bevacizumab and temsirolimus in combination with sorafenib. The patient was not enrolled on an arm that contained sorafenib. The patient began his first course of the investigational therapy on June 15, 2010, receiving bevacizumab 10 mg/kg IV over 30-90 min on Days 1 and 15, and temsirolimus 25 mg IV over 30 min on Days 1, 8, 15, and 22, every 28 days. He received his last doses of bevacizumab and temsirolimus on March 25, 2011 (Cycle 10, Day 15).

The patient was diagnosed with clear cell renal cell adenocarcinoma in April 2010 and is status post right nephrectomy and a cholecystectomy (April 23, 2010). He began the investigational therapy on June 15, 2010.

On March 30, 2011, the patient, who has a past medical history of chronic kidney disease, had a follow-up and was found to have hyperkalemia with a potassium level of 6.5 mEq/L (reference range: 3.5-5 mEq/L). He was admitted to the intensive care unit due to severe hyperkalemia and risk of lethal arrhythmias. On arrival, he was afebrile, his vital signs were stable, his chest x-rays was clear; however, his BNP was elevated at greater than 2000 pg/mL (reference range: 0-100 pg/mL), his ejection fraction (EF) was 30-35 % and creatinine of 2.3 mg/dL (reference range: 0.5-1.7 mg/dL), increased from a baseline creatinine of 1.8 mg/ dL. The patient's potassium remained elevated and he was given Kayexalate® with Lasix® 80 mg IV and insulin with D50, which decreased the potassium to 6.0 mEq/L. An ECG on March 31, 2011, revealed a sinus rhythm with frequent ventricular premature complexes, possible left atrial enlargement, and right bundle branch block. Initially, the patient did not respond to treatment. At that time, a cardiology examination was performed, and no further acute cardiac intervention was recommended. His diabetes was managed with glipizide 1 tablet PO daily. The patient was discharged in stable condition on April 3, 2011.

The patient's past medical/surgical history is significant for type 2 diabetes mellitus, hypertension, hyperlipidemia, chronic kidney disease stage III, anemia and coronary artery disease status post coronary artery bypass graft (CABG). Medications taken at the time of the event included Tylenol®, aspirin, Pepcid®, glucagon, hydralazine, ondansetron, Zocor® and Prograf®.

There have been 18 other cases of left ventricular systolic dysfunction reported to the NCI as serious adverse events through AdEERS under the temsirolimus NSC and/or IND as summarized in the table below. Left ventricular systolic dysfunction is an expected event for bevacizumab.

Adverse Event	Grade	Attribution
<i>Temsirolimus</i>		
Left ventricular systolic dysfunction (n=16)	4	1 Unrelated
	3	5 Unrelated, 5 Unlikely, 4 Possible
	2	1 Unlikely

To date, a total of 32,741 patients have been enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC, and 2,658 patients have been enrolled in NCI-sponsored clinical trials under the temsirolimus IND and/or NSC.

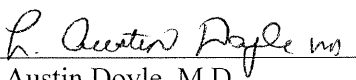
In this case, it is felt that a possible causal relationship exists between the event and both investigational agents.

	Left ventricular systolic dysfunction
Bevacizumab	Possible
Temsirolimus	Possible
Renal cell carcinoma	Unlikely

Date: 5/6/11

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

Date: 5/6/11

Signature: 
L. Austin Doyle, M.D.
(IDB Monitor for temsirolimus)

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

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