



DATE: June 23, 2010

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SUBJECT: Bevacizumab (rhuMAb VEGF) and CCI-779 (tamsirolimus, Torisel[®]) NCI IND Safety Report, AE# **1249518**

TO: Investigators Using Bevacizumab (NSC 704865) and Tamsirolimus (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 tamsirolimus.

The following must be completed by all investigators using bevacizumab under NCI INDs 7921 and 11460; and tamsirolimus 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 tamsirolimus, there does not appear to be a change in the risk-benefit ratio for bevacizumab and tamsirolimus 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 58-year-old female with neuroendocrine carcinoma of the pancreas metastatic to the liver experienced grade 3 congestive heart failure (CHF) and grade 3 pneumonitis while on a phase 2 trial utilizing the investigational agents bevacizumab and tamsirolimus.

ADVERSE EVENTS ASSESSMENT

IND 7921	61010	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1
NSC 704865	683864	
Bevacizumab (rhuMab VEGF)	CCI-779 (temsirolimus, Torisel™)	Gr. 3: Congestive heart failure
AE: 1249518		Gr. 3: Pneumonitis/pulmonary infiltrates
		Protocol: 8233

The patient is a 58-year-old female with neuroendocrine carcinoma of the pancreas metastatic to the liver, who experienced a congestive heart failure (CHF) exacerbation and pneumonitis while on a phase 2 trial utilizing the investigational agents bevacizumab and temsirolimus. The patient began her first course of the investigational therapy on December 22, 2009, receiving bevacizumab 10 mg/kg IV over 30-90 minutes on Days 1 and 15, and temsirolimus 25 mg IV on Days 1, 8, 15, and 22, every 28 days. She received her last dose of bevacizumab on March 16, 2010 (Cycle 4, Day 1), and her last dose of temsirolimus on March 23, 2010 (Cycle 4, Day 8).

The patient was diagnosed with neuroendocrine carcinoma of the pancreas in October 2009. She began the investigational therapy on December 22, 2009.

On March 30, 2010 (Cycle 1, Day 15), the patient, who had a prior history of diastolic heart failure with an ejection fraction (EF) of 55% in December 2009, presented to the emergency room (ER) with a 1-week history of intermittent dyspnea, productive cough with greenish sputum, and wheezing. She was anxious and dyspneic in the ER with an oxygen saturation of 91% on 6L of oxygen via nasal cannula, bilateral rales in the lung bases, and rhonchi. Her blood pressure was 147/107 mmHg and heart rate was 87 bpm. The patient showed mild improvement after receiving nebulizer treatments and oxygen via non-rebreather mask; however, after returning from the CT scan, she desaturated to 83% oxygen saturation on 15L oxygen with lungs exhibiting diffuse bilateral rhonchi. She was intubated, placed on mechanical ventilation for respiratory failure, and admitted to the ICU. The chest CT scan revealed bilateral patchy infiltrates and pleural effusions. On March 31, 2010, an echocardiogram showed a mildly decreased left ventricular (LV) EF of 45-50%, a mildly increased LV cavity size, and moderate mitral valve regurgitation. Her condition improved, and she was discharged home on April 2, 2010.

On April 6, 2010 (Cycle 1, Day 22), the patient presented to the infusion center for treatment, and after receiving a liter of IV fluid, she suddenly developed dyspnea, tachypnea, chest pain, and 2 + pitting edema of the lower extremities. She became hypoxic, and was treated with steroids and albuterol without success. The patient was transferred to the ER. Her BNP was 3135 pg/mL (reference range: <100 pg/mL). A chest X-ray showed increased edema-like opacities and small bilateral pleural effusions. The patient was readmitted to the hospital with CHF and given Lasix®. A repeat chest X-ray later that evening showed a partial clearing of the pulmonary edema pattern. She responded well to diuresis and within 48 hours of her hospital stay, she was back to her baseline. Her antihypertensive medication was slowly resumed. On April 8, 2010, the patient was discharged home in stable condition.

On April 13, 2009 (Cycle 1, Day 29), a restaging CT scan of the chest showed interval near-complete clearing of bilateral air space opacities as compared to the report of March 30, 2010, with a small amount of residual ground-glass density and centrilobular nodularity in the lower lobes and left upper lobe. Several nodules in both lungs were felt to be post-infectious in nature. There was also interval near-complete resolution of bilateral pleural effusions, with trace residual left-sided pleural effusion. The patient continued to have dyspnea and a non-productive cough, but her examination was unremarkable. It was felt that the CHF had resolved. Bevacizumab was discontinued, and the patient continued on temsirolimus. An echocardiogram on April 20, 2010, showed a moderate increase in the LV cavity size,

an EF of 40-45%, impaired relaxation pattern of LV diastolic filling, and moderate to severe mitral valve regurgitation. The chest X-ray that day revealed clear lungs and was otherwise unremarkable.

The patient's past medical/surgical history is significant for diastolic heart failure (in December 2009), hypertension, depression, hyperbilirubinemia, a remote smoking history, port placement, and hysterectomy. Medications taken at the time of the event included Nexium®, fluoxetine, lisinopril, metoprolol, potassium chloride, Imodium®, doxycycline, Restasis®, compounded hormone replacement capsules (estradiol, progesterone, testosterone, and DHEA), Finacea®, Tums®, and ibuprofen.

There have been 169 other cases of pneumonitis reported to the NCI as serious adverse events through AdEERS under the bevacizumab NSC and/or IND and 13 other cases of left ventricular systolic dysfunction (LVSD) and 4 other cases of heart failure reported to the NCI as serious adverse events through AdEERS under the temsirolimus NSC and/or IND as summarized in the table below. Pneumonitis is a known event for temsirolimus; left ventricular systolic dysfunction and heart failure are known events for bevacizumab.

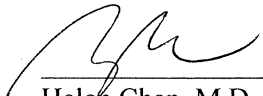
Adverse Event	Grade	Attribution
Bevacizumab		
Pneumonitis (n=169)	5	11 Unlikely, 3 Possible
	4	14 Unlikely, 8 Possible, 2 Probable
	3	15 Unrelated, 43 Unlikely, 47 Possible, 4 Probable, 1 Definite
	2	5 Unrelated, 7 Unlikely, 4 Possible, 1 Probable
	1	1 Unrelated, 1 Possible
Temsirolimus		
LVSD (n=13)	3	4 Unrelated, 3 Unlikely, 5 Possible
	2	1 Possible
Heart failure (n=4)	3	1 Unlikely, 3 Possible

To date, a total of 26,942 patients have been enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC, and 2,071 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 the study agents.

	Pneumonitis	Congestive heart failure
Bevacizumab	Unlikely	Possible
Temsirolimus	Possible	Unlikely
Carcinoid tumor	Unlikely	Unlikely
Prior history of diastolic dysfunction	Unlikely	Possible

Date: 6/24/10

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

Date: 6/29/10

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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