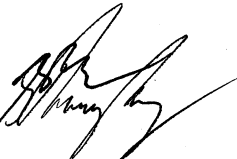




DATE: January 5, 2009

FROM: Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
S. Percy Ivy, M.D., Investigational Drug Branch, CTEP, DCTD, NCI 

SUBJECT: Bevacizumab (rhuMab VEGF) and Oxaliplatin (Eloxatin®) NCI IND Safety Report,
AE# **1118620**

TO: Investigators Using Bevacizumab (NSC 704865) and Oxaliplatin (NSC 266046).

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 oxaliplatin.

The following must be completed by all investigators using bevacizumab under NCI INDs 7921 and 11460 and oxaliplatin under NCI IND 57004:

- 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 57004, 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 oxaliplatin, there does not appear to be a change in the risk-benefit ratio for bevacizumab and oxaliplatin 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 61-year-old female with rectal cancer experienced **grade 4 left ventricular systolic dysfunction** while on a phase 3 study using the investigational agent bevacizumab in combination with oxaliplatin, leucovorin, and 5-fluorouracil.

ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 Bevacizumab (rhuMab VEGF)	57004 266046 Oxaliplatin (Eloxatin®)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: Gr. 4: Left ventricular systolic dysfunction (CHF)
AE: 1118620	Protocol: E5204	

The patient is a 61-year-old female with Stage III rectal cancer who experienced left ventricular systolic dysfunction (congestive heart failure) while on a phase 3 study using the investigational agent bevacizumab in combination with oxaliplatin, leucovorin and 5-fluorouracil (5-FU) following neoadjuvant chemoradiation and surgical resection. She began her first course of treatment on September 9, 2008, receiving bevacizumab 5 mg/kg IV over 30 to 90 minutes on Day 1, oxaliplatin 85 mg/m² IV over 2 hours on Day 1, leucovorin 400 mg/m² IV over 2 hours on Day 1 followed by 5-FU 400 mg/m² IV bolus on Day 1, and 5-FU 2.4 g/m² IV over 46 hours continuously immediately following the 5-FU bolus on Days 1 and 2, every 2 weeks for a total of 12 cycles. The patient received her last doses of bevacizumab, oxaliplatin, and leucovorin on September 23, 2008 (Cycle 2, Day 1), and the last dose of 5-FU on September 25, 2008 (Cycle 2, Day 3).

The patient was initially diagnosed with rectal cancer in February 2008, and is status post neoadjuvant chemoradiation and tumor resection. She began the investigational protocol therapy on September 9, 2008, with a blood pressure of 150/90 mmHg on Norvasc®. Cycle 1 was complicated by an episode of laryngospasm versus chest pain that yielded a negative work-up as well as dyspnea. Of note, Cycle 2 was initiated with a blood pressure of 130/90 mmHg.

On the night of September 25, 2008 (Cycle 2, Day 3), the patient was brought in to the emergency room by EMS after developing respiratory distress. She was given sublingual nitroglycerin and Lasix®, and placed on CPAP in the field for an oxygen saturation of 76% on room air. She had a heart rate of 143 bpm, blood pressure of 198/107 mmHg, respiratory rate of 23 and an oxygen saturation of 94% upon arrival to the ER, and with evidence of cyanosis, she was quickly intubated. Lung examination revealed bibasilar crackles. Pro-BNP was 9089 pg/mL (reference range: 0-100 pg/mL), troponin I was 0.06 ng/mL (reference range: 0.04-0.05 ng/mL), and CK was normal. Her WBC was normal, and blood cultures were negative. A chest X-ray showed pulmonary edema with a right pleural effusion. CT pulmonary angiography was negative for pulmonary embolism but showed bilateral pleural effusions with bibasilar atelectasis, bilateral groundglass opacities, and mild cardiomegaly suggestive of pulmonary edema. An echocardiogram on September 26, 2008, revealed a dilated cardiomyopathy with ejection fraction of 15%, severely reduced left ventricular (LV) systolic function, diffuse hypokinesis, severely increased LV size, mild LV hypertrophy, and severe mitral regurgitation. Also noted was a small pericardial effusion and bilateral pleural effusions. The patient was admitted to the ICU where she was evaluated by a cardiologist and maintained on diuretics, nitroglycerin, vasopressors, ace inhibitors, Digoxin®, and beta-blockers. She was removed from the protocol on this day.

The patient remained in sinus tachycardia, concomitantly developing metabolic acidosis, diarrhea, renal insufficiency, and fever. A repeat echocardiogram on October 3, 2008, revealed a mildly reduced LV systolic function, mildly increased LV size, trace mitral regurgitation and an ejection fraction of 40%. On October 5, 2008, the patient was extubated. An echocardiogram performed on October 7, 2008, revealed an ejection fraction of less than 20%, continued evidence of a dilated cardiomyopathy, and moderate to severe mitral regurgitation.

On October 10, 2008, the patient was outfitted with an external defibrillator life vest for 60 days due to her dilated cardiomyopathy; she had also had an episode of ventricular tachycardia some days prior. She

was very deconditioned and hypotonic, with difficulties swallowing. It was recommended that she undergo inpatient rehabilitation with an ultimate goal of returning home with home health care. She was seen in follow-up on November 4, 2008, appearing well and with an unremarkable physical exam. (She planned to see her cardiologist, as well, later that day.) It was recommended that she be evaluated by an ENT specialist for hoarseness resulting from the prolonged intubation. It was also determined that the patient would not receive any further treatment for her cancer but be monitored closely for signs of recurrence.

The patient's past medical history is significant for hypertension, anemia, and tobacco use. Her father died of colon cancer. Medications taken at the time of the event include Lasix[®], Norvasc[®], and Hemax[®].

There have been 115 other cases of left ventricular systolic dysfunction reported to the NCI through AdEERS as serious adverse events for bevacizumab, and 17 other cases of left ventricular dysfunction reported to the NCI through AdEERS under the oxaliplatin NSC as summarized in the table below.

Adverse Event	Grade	Attribution
<i>Bevacizumab</i>		
Left ventricular systolic dysfunction (n=115)	1-4	3 Definite, 13 Probable, 91 Possible, 6 Unlikely, 2 Unrelated
<i>Oxaliplatin</i>		
Left ventricular systolic dysfunction (n=17)	5	1 Definite
	3	8 Possible, 7 Unrelated
	2	1 Possible

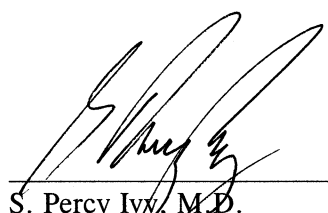
A total of 18,356 patients have been enrolled in NCI-sponsored clinical trials under the bevacizumab NSC, and a total of 19,168 patients have been enrolled in NCI-sponsored clinical trials under the oxaliplatin NSC.

In this case, it is felt that the adverse event is probably related to bevacizumab and unlikely related to oxaliplatin.

	Left ventricular systolic dysfunction
Bevacizumab	Probable
Oxaliplatin	Unlikely
5-Fluorouracil	Possible
Leucovorin calcium	Unrelated
Norvasc	Unrelated
Adenocarcinoma of the rectum	Unrelated


Date: 01.05.09

Signature: _____


S. Percy Ivy, M.D.
(IDB Monitor for Oxaliplatin)

Date: 1/5/09

Signature: _____


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

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

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