



DATE: May 8, 2009

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SUBJECT: Bevacizumab (rhMab VEGF) and Oxaliplatin (Eloxatin®) NCI IND Safety Report, AE# 1201753

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 53-year-old male with adenocarcinoma of the rectum experienced **grade 4 allergic reaction/hypersensitivity** while on a phase 3 study using the investigational agents oxaliplatin and bevacizumab in combination with leucovorin and 5-fluorouracil.

ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 Bevacizumab (rhuMAb VEGF) AE: 1201753	57004 266046 Oxaliplatin (Eloxatin®)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: Gr. 4: Allergic reaction/ hypersensitivity Protocol: E5204
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The patient is a 53-year-old male with adenocarcinoma of the rectum who experienced an allergic reaction (angioedema) while on a phase 3 study using the investigational agents oxaliplatin and bevacizumab in combination with leucovorin and 5-fluorouracil (5-FU). He began his first course of treatment on January 13, 2009, 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 CIV over 46 hours immediately following the 5-FU bolus on Days 1 and 2, every 2 weeks for a total of 12 cycles. The patient received his first and last dose of bevacizumab, oxaliplatin, 5-FU, and leucovorin on January 13, 2009 (Cycle 1, Day 1).

The patient was diagnosed with adenocarcinoma of the rectum in July 2008, and is status post colectomy, neo-adjuvant chemotherapy, and radiation therapy. He began the investigational therapy on January 13, 2009.

In the early morning of January 14, 2009 (Cycle 1, Day 2), the patient's wife called 911 after the patient awoke with a swollen tongue, dyspnea, and drooling. In the emergency room, he presented with angioedema and upper airway obstruction. The patient's wife reported that he experienced 3 or 4 bouts of vomiting immediately upon returning home after his first infusion, but later went to bed and slept well until he woke up. He had had no similar events in the past per his wife. The patient was awake and alert, but he was in significant distress, indicating that he could only breathe through his right nostril. Of note, his oxygen saturation was 97% on room air. On examination, his tongue was so large that it completely filled his oropharynx anteriorly, and he could not stick it out of his mouth. His neck was noted to be very tight when palpated. His left nostril was partially occluded because of a nose deviation to the left from a previous injury. His lungs were clear, but he was in significant respiratory distress and very anxious. The 5-FU continuous infusion pump was disconnected, and he was given epinephrine 0.3 mg subcutaneously, Benadryl® and Solu-Medrol® without any relief of his swelling. It was felt that the patient needed to be prophylactically intubated since his airway was significantly compromised. With his agreement, he was premedicated with phenylephrine and viscous lidocaine and was successfully nasotracheally intubated with a fiberoptic scope. He was admitted to the ICU and continued to receive steroids and Benadryl®; the lisinopril that he had been taking for years was discontinued. The swelling went down promptly, and the patient was able to be extubated and observed for 24 hours. He experienced hypertension throughout the hospital stay for which he was treated with Norvasc® 2 mg daily. He was discharged on January 17, 2009 and was not re-challenged with the investigational agents.

The patient's past medical history is significant for hypertension, prior alcohol abuse, diabetes, hypercholesterolemia, adenomatous polyps, mediport placement, left arm fracture repair with plate, and tobacco abuse. Medications taken at the time of the event include hydrochlorothiazide, lisinopril, atenolol, aspirin, and Viagra®.

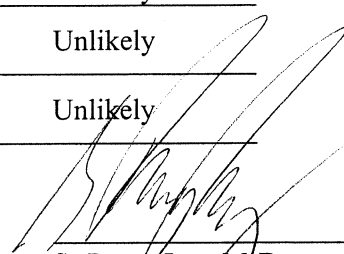
Allergic reactions are expected events for both oxaliplatin and bevacizumab.

A total of 20,509 patients have been enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC, and a total of 20,134 patients have been enrolled in NCI-sponsored clinical trials under the oxaliplatin IND and/or NSC.

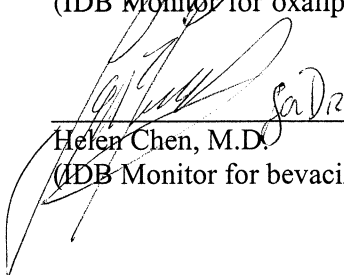
In this case, it is felt that a possible causal relationship exists between bevacizumab and the event, and that a probable causal relationship exists between oxaliplatin and the event.

	Allergic reaction/ hypersensitivity
Bevacizumab	Possible
Oxaliplatin	Probable
5-FU	Unlikely
Leucovorin	Unlikely
Possible allergic reaction to Lisinopril	Unlikely
Adenocarcinoma of the rectum	Unlikely

Date: 05.11.09

Signature: 
S. Percy Ivy, M.D.
(IDB Monitor for oxaliplatin)

Date: 5/11/09
AE for HC

Signature:  *Dr. Helen Chen*
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(IDB Monitor for bevacizumab)

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

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