



DATE: OCT 04 2010

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

SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# 1544184

TO: Investigators Using Bevacizumab (NSC 704865)

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 agent bevacizumab.

The following must be completed by all investigators using bevacizumab under NCI INDs 7921 and 11460.

- 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 and 11460 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, there does not appear to be a change in the risk-benefit ratio for bevacizumab 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 NSC, and the total number of patients enrolled in trials under these INDs and/or NSC.

A 61-year-old male with adenocarcinoma of the rectum experienced cardiac arrest, a grade 4 small bowel obstruction, grade 4 hyponatremia, and grade 4 hypokalemia while on a phase 2 study using the investigational agent bevacizumab in combination with radiation therapy, capecitabine, oxaliplatin, leucovorin, and 5-FU.

ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 Bevacizumab (rhuMAb VEGF) AE: 1544184	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: Gr. 5: Cardiac general: Cardiac arrest Gr. 4: Obstruction, GI: Small bowel NOS Gr. 4: Sodium, serum-low (hyponatremia) Gr. 4: Hypokalemia Protocol: E3204
--	---

The patient was a 61-year-old male with rectal adenocarcinoma who died after developing an ileus, a small bowel obstruction, hypothermia, DIC, and hyponatremia, and while on a phase 2 study using the investigational agent bevacizumab in combination with radiation therapy (RT), capecitabine, oxaliplatin, leucovorin, and 5-FU. He began his first course of treatment on January 20, 2010, with pre-operative chemotherapy receiving bevacizumab 5 mg/kg IV over 30-90 minutes every other week on Days 1, 15, and 29 during RT, capecitabine 825 mg/m² PO every 12 hours 5 days per week starting on Day -1 to RT, oxaliplatin 50 mg/m² IV over 2 hours every week on Days 1, 8, 15, 22, and 29 during RT, and RT 50.4 Gy at 1.8 Gy/fraction 5 days per week for 5.5 weeks. He was then to have surgery followed by post-operative chemotherapy (Cycle= 2 weeks) consisting of bevacizumab 5 mg/kg IV over 30-90 minutes on Day 1 for a total of 12 cycles, leucovorin 400 mg/m² IV over 2 hours on Day 1, and 5-FU 400 mg/m² IVP on Day 1 followed by 2.4 gm/m² IV continuous infusion over 46 hours on Day 1 for a total of 12 cycles, and oxaliplatin 85 mg/m² IV over 2 hours on Day 1, for a total of 9 cycles. He received his last dose of bevacizumab on February 3, 2010 (Cycle 1, Day 15), his last dose of oxaliplatin on February 10, 2010 (Cycle 1, Day 22), the last dose of capecitabine on February 17, 2010, (Cycle 1, Day 29), and the last radiation therapy on February 16, 2010, (Cycle 1, Day 28).

The patient was diagnosed with rectal adenocarcinoma in November 2009. He began the investigational therapy on January 20, 2010.

On February 17, 2010 (Cycle 1, Day 29), the patient presented to the clinic with chronic, non-bloody diarrhea for several weeks as well as one week history of nausea and vomiting after the initiation of the investigational treatment. His sodium was 125 mmol/L (reference range: 136-145 mmol/L), and his potassium was 2.7 mmol/L (reference range: 3.6-5.1 mmol/L). All study treatment was held. He was started on Zofran[®], given IV fluids with potassium chloride, and sent home. The patient was instructed to follow-up at the clinic in 2 days, but did not show up due to persistent symptoms. He was advised to go to the emergency room (ER) for further evaluation.

On February 23, 2010 (Cycle 1, Day 35), the patient was admitted to the hospital for abdominal cramps, persistent non-bloody emesis, watery diarrhea, weakness, and poor appetite. His temperature was 95°F, BP 111/64 mm Hg, and pulse 93 bpm. He had dry mucous membranes, hyperactive bowel sounds, and a distended abdomen that was nontender without rebound or guarding. His sodium was 119 mmol/L, potassium 3.0 mmol/L, chloride 66 mmol/L (reference range: 99-111 mmol/L), bicarbonate 37.0 (reference range: 22-32 mmol/L), BUN 63 mg/dL (reference range: 8-23 mg/dL), creatinine 1.3 mg/dL (reference range: 0.5-1.2 mg/dL), glucose 160 mg/dL (reference range: 70-110 mg/dL, total bilirubin 1.1 mg/dL (reference range: 0.3-1.2 mg/dL), alkaline phosphatase 107 IU/L (reference range: 32-103 IU/L), unremarkable ALT and AST, hemoglobin (Hgb) 12.4 g/dL (reference range: 14-18 g/dL), hematocrit (Hct) 34.1% (reference range: 40-52%), and unremarkable WBC and platelets. He was given IV fluids and kept on Zofran[®]. On February 24, 2010, the laboratory findings were improved with sodium 123

mmol/L, potassium 3.2 mmol/L, chloride 78 mmol/L, bicarbonate 37.0 mmol/L, BUN 44 mg/dL, and creatinine 1.0 mg/dL. It was felt that his hyponatremia could be secondary to vomiting and diarrhea but superimposing SIADH could not be ruled out. IV fluids were continued with the option of instituting water restriction if clinically warranted.

On February 25, 2010 (Cycle 1, Day 37), the patient developed abdominal distention with tympanitic sounds and mild diffuse tenderness. An abdominal CT scan revealed a distended stomach, dilated partially fluid-filled and air-filled loops of small bowel, and a transition zone from dilated small bowel to collapsed small bowel that was suggestive of a high-grade small bowel obstruction. The scan also revealed free intraperitoneal air along with air within the anterior abdominal wall and right rectus abdominus muscle. A nasogastric tube was inserted. On February 27, 2010, the patient's sodium was 132, potassium 2.0 mmol/L, chloride 99 mmol/L, bicarbonate 29 mmol/L, BUN 12 mg/dL, creatinine 0.6 mg/dL, glucose 130 mg/dL, WBC 5.8 K/cmm (reference range: 4-11 K/cmm), Hgb 9.8 g/dL, Hct 28.3%, platelet 187 K/cmm. Volume repletion was continued, and electrolytes were repleted, notably potassium which was aggressively administered by mouth and IV. He initially reported feeling much better, but overnight he developed a cardiac arrest. Resuscitative measures were initiated. He quickly gained pulse but remained unresponsive. He was placed on mechanical ventilation, and transferred to the MICU. He started to have acidosis and DIC, and had significant blood loss upon emergent femoral vein cannulation but thrombostasis was eventually achieved. The patient remained unresponsive to any stimuli, acidotic, and on vasopressors. He became pulseless again and expired that day after resuscitative measures failed.

The patient's past medical and surgical history was significant for fuchs heterochromic iridocyclitis, senile nuclear cataract, arthralgia, male erectile disorder, rash/dermatitis, chlamydia, viral warts, hepatitis, gonorrhea, hypertension, onychomycosis, and seizure disorder. He had a 40 pack-year smoking history, and a history of IV drug and alcohol abuse. Medications taken at the time of the event included simethicone, psyllium, atropine/diphenoxylate, brimonidine, diphenhydramine, dorzolamide/timolol, ondansetron, thiamine, phenytoin, hydrocodone/acetaminophen, hydrocortisone/pramoxine foam, megestrol acetate, morphine, omeprazole, multivitamin, prednisolone, prochlorperazine, and topical medications: silver sulfadiazine, hydrophilic ointment, and moisturizing lotion.

There have been 30 other cases of cardiac arrest/cardiopulmonary arrest, 142 other cases of hypokalemia, 198 other cases of hyponatremia, and 137 other cases of small bowel obstruction reported to the NCI through AdEERS as serious adverse events under the bevacizumab NSC and/or IND as shown in the table below.

Adverse Event	Grade	Attribution
Cardiac arrest/cardiopulmonary arrest (n=30)	5	10 Possible, 5 Unlikely
	4	8 Possible, 6 Unlikely, 1 Unrelated
Hypokalemia (n=142)	4	1 Probable, 3 Possible, 12 Unlikely, 8 Unrelated
	3	7 Probable, 23 Possible, 40 Unlikely, 28 Unrelated
	1	6 Possible, 7 Unlikely, 5 Unrelated
Hyponatremia (n=198)	4	1 Probable, 10 Possible, 15 Unlikely, 15 Unrelated
	3	4 Probable, 42 Possible, 64 Unlikely, 28 Unrelated
	1	1 Probable, 2 Possible, 8 Unlikely, 8 Unrelated
Small bowel obstruction (n=137)	5	1 Possible
	4	3 Possible, 7 Unlikely, 4 Unrelated
	3	1 Probable, 22 Possible, 43 Unlikely, 49 Unrelated
	2	3 Unlikely, 4 Unrelated

There have been 28,700 patients enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC.

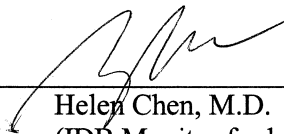
In this case, a probable causal relationship between the events and bevacizumab cannot be excluded.

	Cardiac arrest	Small bowel obstruction	Hypokalemia	Hyponatremia
Bevacizumab	Possible	Possible	Unlikely	Unlikely
Capecitabine	Possible	Possible	Unlikely	Unlikely
Oxaliplatin	Possible	Possible	Unlikely	Unlikely e
Radiation	Possible	Probable	Unlikely	Unlikely
Rectal Adenocarcinoma	Possible	Probable	Unlikely	Possible
Dehydration	Unrelated	Unrelated	Probable	Definite
Bowel obstruction	Possible	N/A	Probable	Probable

Date:

10/5/10

Signature:



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

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

cc: Arther Cannon
Safety Contact: onc_drug.safety@gene.com
Genentech, Inc.