DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

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FROM: Kevin Conlon, M.D., Senior Investigator, Investigational Drug Branch, CTEP, DCTD, NCI

SUBJECT: Bevacizumab (rhuMab VEGF) NCI IND Safety Report, AE# **1836781**

TO: Investigators Using Bevacizumab (rhuMab VEGF) 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 this IND and/or NSC, and the total number of patients enrolled in trials under this IND and/or NSC.

> A 54-year-old female with fallopian tube carcinoma experienced grade 3 left hydronephrosis and grade 3 kidney hemorrhage while on a phase 3 trial using the investigational agent bevacizumab/placebo in combination with paclitaxel and carboplatin.

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ADVERSE EVENTS ASSESSMENT

IND **7921** NSC **704865** **Bevacizumab (rhuMAb VEGF)**	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: **#1** Event: **Gr. 3: Renal/Genitourinary – Other (Left Hydronephrosis)** **Gr. 3: Hemorrhage, GU: Kidney**
AE: **1836781**	Protocol: **GOG-0218**

The patient is a 54-year-old female with fallopian tube carcinoma who experienced left hydronephrosis and kidney hemorrhage while on a phase 3 trial using the investigational agent bevacizumab/placebo in combination with paclitaxel and carboplatin. The patient began her first course of treatment on December 8, 2008, receiving bevacizumab/placebo 15 mg/kg IV on Day 1 of Cycles 2-6, paclitaxel 175 mg/m^2 IV over 3 hours on Day 1 of Cycles 1-6, and carboplatin AUC 6 IV over 30 minutes on Day 1 of Cycles 1-6 (1 cycle = 21 days). The patient received her last dose of bevacizumab/placebo, paclitaxel, and carboplatin on March 25, 2009 (Cycle 5, Day 1).

The patient was diagnosed with fallopian tube carcinoma in November of 2008 and is status post debulking surgery. She began the investigational therapy on December 8, 2008.

The patient presented to the emergency room on March 27, 2009 (Cycle 5, Day 3), complaining of hematuria and left lower quadrant pain. She had been experiencing urinary urgency along with chest and epigastric discomfort since the previous night. The discomfort gradually became worse and was accompanied by nausea, vomiting and hematuria. She denied any fever or chills. A physical examination was unremarkable and her vital signs were as follows: blood pressure 125/60 mm/Hg, pulse 85 beats per minute, temperature 98.4^0 F, and respiratory rate of 18 per minute. The patient was admitted to the hospital for further evaluation. A CT scan of the abdomen and pelvis with contrast showed a mild enlargement of the left kidney with perinephric and periureteral stranding with mild dilatation of the mid ureters. A CT scan of the abdomen and pelvis without contrast revealed a mildly enlarged left kidney with a hyperdense pelvis and proximal aspect of the ureter. The scan also showed mild hydronephrosis with no evidence of an obstructive stone. The patient's urinalysis revealed the presence of red blood cells (RBCs), white blood cells, protein, ketones and trace bacteria. Her blood tests showed: glucose 142 mg/dL (reference range: 70-110 mg/dL), serum glutamic oxaloacetic transaminase (SGOT) 74 U/L (reference range: 15-37 U/L), serum glutamate pyruvate transaminase (SGPT) 60 U/L (reference range: $\leq$ 31 U/L), total bilirubin 1.6 mg/dL (reference range: 0.0-1.0 mg/dL), alkaline phosphatase 109 U/L (reference range: 35-104 U/L), sodium 134 mmol/L (reference range: 136-145 mmol/L) and potassium 3.4 mmol/L (reference range 3.5-5.1 mmol/L). On March 28, 2009, her laboratory values were: RBC 2.18×10^6/uL (reference range: 4.2-5.5×10^6/uL), hemoglobin (Hb) 8.8 g/dL (reference range: 12.0-16.0 g/dL), hematocrit 27.1% (reference range 37-47%), and platelets 74×10^3/uL (reference range: 150-450×10^3/uL). The patient received two units of packed red blood cells. Although the patient reported feeling better the next day, she was given another two units of packed red blood cells as her repeat blood tests showed Hb 7.9 g/dL, hematocrit 24.6%, and platelets 52×10^3/uL.

On March 30, 2009 (Cycle 5, Day 6), a cystoscopy showed bilateral renal bleeding. A 2.5 cm neovascularity on the posterior wall of the bladder was biopsied and found to be benign. A bladder washing was performed and 140 cc of cloudy, blood fluid was sent to pathology, where it was found to be negative for malignant cells. A left renal barbotage was also performed; 12.5 cc of cloudy, blood fluid was collected and was found to be positive for reactive urothelial cells. Fifteen cc of cloudy, bloody fluid was collected from a right renal barbotage and was found to be negative for malignancy. On March 31, 2009, the patient's laboratory results showed: Hb 10.5 g/dL, hematocrit 32%, and platelets 69×10^3/uL for which she patient received one unit of leukoreduced platelets. During her hospital stay, the patient's hematuria continued to resolve and she was discharged on April 1, 2009.

The patient's past medical/surgical history is significant for urinary tract infections and hysterectomy. Medications taken at the time of the event included G-CSF, erythropoietin, and Xanax®.

There have been 3 other cases of kidney hemorrhage and 1 other case of hydronephrosis reported to the NCI as serious adverse events through AdEERS under the bevacizumab NSC and/or IND as shown in the table below.

Adverse Event	Grade	Attribution
Hydronephrosis (n=1)	3	1 Unrelated
Renal hemorrhage (n=3)	3 1	1 Unlikely, 1 Possible 1 Unlikely

There have been 22,954 patients enrolled in NCI-sponsored clinical trials under this IND and/or NSC.

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

	Left hydronephrosis	Kidney hemorrhage
Bevacizumab	Possible	Possible
Carboplatin	Possible	Possible
Paclitaxel	Possible	Possible
Fallopian tube carcinoma	Possible	Possible

Date: 10 August 2009

Signature: Kevin Conlon

Kevin Conlon, M.D.
(IDB Monitor for Bevacizumab)

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

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Genentech, Inc.