



DATE: June 2, 2009

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

SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# **1881593**

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 62-year-old female with stage IV invasive breast carcinoma experienced **grade 3 renal failure** requiring hemodialysis while on a phase 3 trial utilizing the investigational agent bevacizumab in combination with letrozole.

ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 Bevacizumab (rhuMab VEGF) AE: 1881593	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Event: Gr. 3: Renal failure Protocol: CALGB-40503
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The patient was a 62-year-old female with Stage IV invasive breast carcinoma with metastases to the lungs and bone who experienced hyperkalemia, elevated creatinine, and renal failure while on a phase 3 trial using the investigational agent bevacizumab/placebo in combination with letrozole or tamoxifen. The patient began her first course of treatment on December 5, 2008, receiving bevacizumab/placebo 15 mg/kg IV piggyback over 30-90 minutes on Day 1 and letrozole 2.5 mg PO every day, every 3 weeks. The patient received her first and last dose of bevacizumab/placebo on December 5, 2008 (Cycle 1, Day 1) and the last dose of letrozole on December 16, 2008 (Cycle 1, Day 12).

The patient was diagnosed with invasive breast carcinoma (ER, PR positive) in October 2008, and is status post radiation therapy in December 2008. The patient began the investigational agent on December 5, 2008.

On the night of December 9, 2008 (Cycle 1, Day 5), the patient was brought to the emergency room (ER) because of mental status changes with slight disorientation, drowsiness and slurred speech. The family thought the mental status change was due to her fentanyl patch and had it removed earlier that day. She also complained of abdominal pain which resolved after having a bowel movement in the ER, vomiting for 1.5 weeks which resolved 4 days prior, intermittent, and non-radiating mid-chest pressure on the way to the ER. Significant findings on examination were a blood pressure (BP) of 72/47 mmHg, oxygen saturation 92% on 4 liters of oxygen via nasal cannula, dry mucosal membranes, and reproducible chest pain. Urinalysis revealed a urine protein of 100 mg/dL (reference range: negative-trace mg/dL), without evidence of hemoglobinuria. Urine cultures later revealed gram negative bacillus. A chest X-ray showed bilateral pleural effusions and bilateral infiltrates; a head CT scan showed no acute changes. Her CBC showed mild anemia and normal white cell and platelet counts. Her BUN was 31 (reference range: 6-24 mg/dL), creatinine 1.74 mg/dL (reference range: 0.49-1.11 mg/dL), and potassium 5.2 mmol/L (reference range: 3.5-5.1 mmol/L). The patient was admitted for dehydration and acute renal insufficiency and started on IV fluids and vancomycin (with Levaquin[®] later added). By the time she was evaluated by a neurologist that day, her mental status had improved significantly and her BP was 111/71 mmHg; it was thought that the changes had been the result of dehydration/hypotension and infection.

On December 11, 2008, the patient's creatinine had risen to 3.2 mg/dL, her potassium was 5.6 mmol/L, and her urine output was 10 mL/24 hr. A renal ultrasound showed no evidence of obstruction. An MRI of the brain showed atrophy out of proportion for the patient's age and numerous periventricular white matter lesions with increased signal involving the inferior surface of the corpus callosum, suggesting possible demyelinating disease such as multiple sclerosis, neurovascular Lyme disease, vasculitides, or extensive small vessel disease. An echocardiogram showed normal left ventricular function.

On December 12, 2008, the patient became mildly dyspneic, with rhonchi, decreased breath sounds, moderate jugular venous distension, and 1+ pitting edema. The chest X-ray revealed worsening pleural effusions. Repeat urine analysis showed a urine protein-creatinine ratio of 6.67, urine protein of >300 mg/dL, and urine RBC of >50; a 24-hour urine protein was not available. With worsening oliguria, hyperkalemia (7.1 mmol/L), and the development of acidosis, hemodialysis was initiated to be undertaken 3 times weekly. On December 15, 2008 (Cycle 1, Day 11), her dyspnea worsened, and she was placed in ICU on BiPAP. An arterial blood gas revealed respiratory acidosis. A chest X-ray showed pulmonary vascular congestion with increased prominence of the bilateral pleural effusions. A V/Q scan was low probability for pulmonary embolism. A thoracentesis removed 1 liter of straw-colored fluid, after which the patient's breathing improved. She was taken off BiPAP and put on a nasal cannula. She was removed from the protocol on December 22, 2008. The patient's hyperkalemia and renal function gradually improved, and by December 30, 2008, both had resolved. Video-

assisted thoracic surgery (VATS) with pleurodesis was performed first on the left, and subsequently on the right; however, the patient really did not regain her performance status and had progressive deterioration in her pulmonary function. The patient and her family declined any further treatment, and she was discharged to inpatient hospice care on January 9, 2009. She expired that same day.

Pertinent laboratory values are shown below:

	11/22/08 Baseline	12/10/09 C1, D 5	12/11/09 C1, D 6	12/12/09 C1, D 7	12/13/09 C1, D 8	12/18/09 C1, D13	12/31/08	1/6/09
BUN (reference range: 6-19 mg/dL)	15	31	40	47 52	32	37	16	13
Creatinine (reference range: 0.5-1.0 mg/dL)	0.71	1.74	3.20	4.38 4.99	3.91	4.69	0.97	0.82
Urine protein (reference range: neg- trace mg/dL)	negative	100 12/9/09	*	*	>300	*	*	*
Sodium (reference range: 136-145 mmol/L)	135	138	134	131 127	133	137	138	137
CO2 (reference range: 21-30 mmol/L)	22.4	23.1	21.8	18.5 17.9	25.9	32.4	33.4	35.7
Anion gap (reference range: 7-16)	13	13	9	12 14	9	9	7	7
Potassium (reference range: 4.0-5.5 mmol/L)	4.9	5.2	5.6	7.1 6.6	5.1	4.5	3.7	3.3
Chloride (reference range: 100-110 mmol/L)	100	102	103	101 95	98	96	98	94
BNP (reference range: 0-100 pg/mL)	*	*	189	*	*	*	*	*

*not provided

The patient's past medical/surgical history was significant for diabetes mellitus, an ill-defined neurological disorder labeled as multiple sclerosis or Lyme disease, chronic left lower extremity weakness, hypertension, and hyperlipidemia; she had been wheelchair-bound for 10 years. Medications taken at the time of the event included fentanyl patches, metformin, glipizide, lisinopril, hydrocodone, metoclopramide, and Niaspan®.

Renal insufficiency is known to be associated with bevacizumab, and this case is unusually serious and of early onset.

There have been 21,351 patients enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC.

Renal failure	
Bevacizumab/placebo	Possible
Letrozole	Unlikely
Invasive breast carcinoma	Unlikely
Dehydration	Possible

Date: 6/3/09

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

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

cc: Jessica Connor
Drug Safety: onc_drug_safety@gene.com
Genentech, Inc.