



DATE: JUL 08 2011

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

SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# 1226625

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 this letter to your Institutional Review Board (IRB) of record according to your 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 57-year-old female with glioblastoma multiforme experienced grade 3 acute kidney injury while on a phase 3 trial utilizing the investigational agent bevacizumab/placebo in combination with temozolomide and radiation therapy.

ADVERSE EVENTS ASSESSMENT

IND 7921	ADVERSE EXPERIENCE REPORT NO.
NSC 704865	IND Safety Report: # 1
Bevacizumab (rhuMAb VEGF)	Event: Gr. 3: Acute kidney injury
AE: 1226625	Protocol: RTOG-0825

The patient is a 57-year-old female with glioblastoma multiforme who experienced acute kidney injury while on a phase 3 trial utilizing the investigational agent bevacizumab/placebo in combination with temozolomide and radiation. The planned protocol therapy the patient was assigned to is as follows:

Cycle = 6 weeks:

RT: 60 Gy over 6 wks (delivered in 2 Gy fractions on days 1-5 q wk)

Temozolomide: 75 mg/m² PO QD

Bevacizumab/Placebo: 10 mg/kg of actual body weight IV over 30-90 min on day 1 of wks 4 and 6

Cycle = 4 weeks:

Bevacizumab/placebo: 10 mg/kg of actual body weight IV over 30-90 min at beginning of week 2

Cycle = 4 weeks (Max = 12 cycles)

Temozolomide: 150-200 mg/m² PO on days 1-5

Bevacizumab/Placebo: 10 mg/kg of actual body weight IV over 30-90 min on days 1 and 15

The patient was diagnosed with glioblastoma multiforme in June 2010, and is status post glioblastoma resection. She began the investigational therapy on July 1, 2010. Her baseline creatinine was 0.94 mg/dL (reference range: 0.44-1.03 mg/dL) and urea nitrogen was 21 mg/dL (reference range: 8-20 mg/dL). She received the last dose of bevacizumab/placebo on April 7, 2011 (Cycle 7, Day 15), the last dose of temozolomide on March 29, 2011 (Cycle 7, Day 6), and the last dose of radiation treatment on August 13, 2010 (Cycle 1, Day 44). The study agents were then held after Cycle 7 treatment due to thrombocytopenia.

On May 5, 2011 (Cycle 7, Day 43), the patient presented to the hospital with elevated levels of creatinine (12.6 mg/dL) and urea nitrogen (63 mg/dL) and a two-week history of mild low back pain. She was admitted for renal failure. The patient had been treated with Cipro[®] for approximately two weeks for a sinus infection. She was afebrile. Her blood pressure was 122/61 mmHg. Her urine protein was negative. Her GFR was 3 mL/min/1.73 m² (reference range: >60 mL/min/1.73 m²). A renal ultrasound showed a possible 2.8 x 2.5 cm mass laterally in the left kidney, which could represent a renal neoplasm or more likely a column of Bertin, but no evidence of hydronephrosis. On May 6, 2011, a renal doppler ultrasound did not show evidence of artery stenosis. The patient was given high-dose steroids and placed on dialysis several times. On May 11, 2011, her urea nitrogen and creatinine were 32 mg/dL and 3.3 mg/dL, respectively; her urine protein remained negative. Her kidney function slowly improved. The dialysis was discontinued and the steroids were slowly tapered. At the time of discharge on May 19, 2011, her creatinine level had returned close to normal with creatinine level of 1.2 mg/dL and urea nitrogen level of 21 mg/dL; her GFR was 46 mL/min/1.73 m².

During a follow-up clinic visit on May 23, 2011, the patient still had back pain, but she was otherwise doing well. The levels of her creatinine and urea nitrogen were 1.07 mg/dL and 11 mg/dL, respectively, and her GFR was recovering to 56 mL/min/1.73 m². The study agents were still held due to her low platelet count.

The patient's past medical/surgical history is significant for hypertension and hypercholesterolemia. Medications taken at the time of the events included Cipro[®], clonazepam, estradiol, ibuprofen, Lipitor[®], lorazepam, Micardis[®], ondansetron, Prilosec[®], and trazodone.

Acute kidney injury is an expected event for bevacizumab.

There have been 33,125 patients enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC.

In this case, a possible relationship exists between the event and the investigational agent.

	Acute kidney injury
Bevacizumab/placebo	Possible
Temozolomide	Unrelated
Radiation	Unrelated
Glioblastoma multiforme	Unrelated

Date: 7/6/11

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

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

cc: Arthur Cannon
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Genentech, Inc.