



DATE: OCT 04 2011

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

SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# 1037258

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 43-year-old female with metastatic invasive breast cancer experienced a grade 4 infection (perirectal abscess) while on a phase 3 trial utilizing the investigational agent bevacizumab in combination with nab-paclitaxel.

ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 Bevacizumab (rhuMAb VEGF)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Event: Gr. 4: Infection: Perirectal abscess
AE: 1037258	Protocol: CALGB-40502

The patient is a 43-year-old female with metastatic invasive breast cancer who experienced a perirectal abscess while on a phase 3 trial utilizing the investigational agent bevacizumab in combination with nab-paclitaxel. The planned protocol therapy the patient was assigned to is as follows:

Cycle = 28 Days

Bevacizumab: 10 mg/kg IV over 30-90 min on Days 1 and 15

Nab-paclitaxel: 150 mg/m² IV over 30 minutes on Days 1, 8 and 15

The patient was diagnosed with invasive breast cancer in April 2005, and is status post a left lumpectomy, radiation therapy, adjuvant chemotherapy, and hormonal therapy. In December 2010, the patient had a local recurrence and underwent bilateral mastectomies. Staging evaluations revealed metastases to distant lymph nodes and bone. She began the first course of investigational treatment on March 28, 2011, and received her last doses of bevacizumab and nab-paclitaxel on July 21, 2011 (Cycle 5, Day 1).

On July 27, 2011 (Cycle 5, Day 7), the patient presented to the emergency room with a 7-day history of progressive right gluteal pain and swelling. She was admitted to the hospital for an abscess of the right buttock that extended to the perineum. She was started on vancomycin and analgesics. Her WBC was 15.2 K/mm³ (reference range 3.8-9.8 K/mm³), her hemoglobin was 11.2 g/dL (reference range 12.1-15.1 g/dL), and her hematocrit was 33.5% (reference range 36.1-44.3%). A CT scan of the abdomen and pelvis showed a moderate amount of cellulitis involving the right buttock, perineum, labia, and right groin. Later that day, she was taken to surgery and underwent an incision and drainage of the perineal abscess with debridement of the abscess cavity and necrotic tissue over an area of 60 cm² (12 x 5cm), with some debridement of necrotic tissue down to the level of the subcutaneous fat. Penrose drains were placed to facilitate drainage, and she was sent to the recovery room in stable condition. A culture of the abscess fluid grew mixed aerobic and anaerobic organisms with many Actinomyces. The patient received additional antibiotics. The remainder of her hospital course was uncomplicated, and she was discharged home in stable condition on August 3, 2011. Her planned home antibiotic therapy included IV infusions of ertapenem for 1 month followed by Augmentin[®] for 6-12 months.

By August 25, 2011, 3 of 4 sinus tracts were completely closed with only one remaining unhealed area located in the inferior portion of her right buttock near the vulva. On September 22, 2011, at a follow-up visit, it was noted that her right groin wound was still not completely healed.

The patient's past medical and surgical history is significant for a hysterectomy, an internal jugular thrombosis resulting in facial swelling from disruption of facial venous drainage, and obesity. Medications taken at the time of the event included aspirin.

Infection is an expected adverse event for bevacizumab but is being reported because this event is unusually severe.

There have been 34,421 patients enrolled in NCI-sponsored clinical trials under the bevacizumab IND

and/or NSC.

In this case, it is felt that a possible causal relationship exists between the event and the investigational therapy.

	Infection (perirectal abscess)
Bevacizumab	Possible
Nab-paclitaxel	Possible
Invasive breast carcinoma	Unlikely

Date:

9/26/11

Signature:



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

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

cc: Arthur Cannon
Gilbert Jirau-Lucca
Safety Contact: onc_drug.safety@gene.com
Genentech, Inc.