




DATE: APR 13 2011

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

SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# **1574705**

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 54-year-old female with invasive breast carcinoma experienced grade 3 arterial thrombus (brachial) while on a phase 3 study using the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, and paclitaxel.

ADVERSE EVENTS ASSESSMENT

IND 7921	ADVERSE EXPERIENCE REPORT NO.
NSC 704865	IND Safety Report: # 1
Bevacizumab (rhuMAb VEGF)	Event: Gr. 3: Arterial thrombus (brachial)
AE: 1574705	Protocol: E5103

The patient is a 54-year-old female with invasive breast carcinoma who experienced a brachial artery thrombus while on a phase 3 study using the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, and paclitaxel. She began her first course of treatment on September 25, 2009, receiving bevacizumab/placebo 15 mg/kg IV over 30-90 minutes on Day 1 for Cycle 1-18, doxorubicin 60 mg/m² IVP and cyclophosphamide 600 mg/m² IV over 20-30 minutes on Day 1 for Cycles 1-4, and paclitaxel 80 mg/m² IV over 1 hour on Days 1, 8, and 15 for Cycle 5-8, every 21 days. She received the last dose of bevacizumab/placebo on September 17, 2010 (Cycle 18, Day 1), the last doses of doxorubicin and cyclophosphamide on November 27, 2009 (Cycle 4, Day 1), and the last dose of paclitaxel on March 5, 2010 (Cycle 8, Day 15).

The patient was diagnosed with invasive breast carcinoma in May 2009. She began the investigational therapy on September 25, 2009.

On January 6, 2011 (Cycle 18, Day 111), the patient started to feel some discomfort, pain, and tingling in her right hand. Her right upper extremity arterial system was evaluated by arterial doppler study on January 10, 2011, which revealed that there was evidence of an arterial occlusion approximately 2.5 cm in length in the proximal right brachial artery or distal axillary artery. The arterial perfusion in the distal right arm appeared to be significantly reduced due to this singular lesion. No significant atherosclerotic disease or stenosis was observed in the visualized areas of the arterial tree in the right arm, and there was no definitive evidence of aneurysmal disease where accessible to study. The echogenicity in this area of occlusion suggested a thrombus or an embolus and there was no evidence of a "halo sign" to suggest vasculitis. The differential diagnosis included a possible embolus from either a cardiac source, the aortic arch, or the most proximal subclavian artery proximal to the current level of the study possible with ultrasound. On January 11, 2011, the patient was admitted to the hospital. The coagulation tests revealed that her PT and PTT were within normal range, but her D-dimer was significantly elevated at 9.32 µg/ml (reference range: 0-0.56 µg/ml). The patient was initiated on anticoagulation with Lovenox[®] and Coumadin[®]. It was felt that the arterial occlusion was due to a clot, which might be related to the previous presence of a catheter associated with the patient's PowerPort. The patient was discharged in stable condition on the second day of the admission.

During a follow-up visit on January 14, 2011, the patient's paresthesia was improving. The hypercoagulable workup revealed negative prothrombin gene mutation. Lovenox[®] and Coumadin[®] were continued.

The patient's past medical and surgical history is significant for diminished left ventricular ejection fraction, herpes zoster, ovarian cyst and tonsillectomy. Medications taken at the time of the event are not provided from the site.

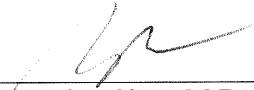
Arterial thrombus is an expected event for bevacizumab.

There have been 31,666 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 events and the investigational agent bevacizumab.

	Arterial thrombus
Bevacizumab/placebo	Possible
Portacath	Probable
Invasive breast carcinoma	Unlikely

Date: 4/8/11

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

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

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Genentech, Inc.