



DATE: May 5, 2010

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

SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# **1206408**

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 42-year-old female with invasive breast carcinoma experienced grade 4 confusion while on a phase 3 study using the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, filgrastim or pegfilgrastim, and paclitaxel.

ADVERSE EVENTS ASSESSMENT

IND 7921	ADVERSE EXPERIENCE REPORT NO.
NSC 704865	IND Safety Report: # 1
Bevacizumab (rhuMAb VEGF)	Event: Gr. 4: Confusion
AE: 1206408	Protocol: E5103

The patient is a 42-year-old female with invasive breast carcinoma who experienced confusion while on a phase 3 study using the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, filgrastim or pegfilgrastim, and paclitaxel. She began her first course of treatment on March 31, 2009, receiving bevacizumab/placebo 10 mg/kg IV over 30-90 minutes on Day 1, doxorubicin 60 mg/m² IVP on Day 1, cyclophosphamide 600 mg/m² IV over 20-30 minutes on Day 1, and filgrastim 5 mcg/kg SQ on Days 2-11 or pegfilgrastim 6 mg SQ on Day 2, every 14 days for Cycles 1-4. During Cycles 5-8, she received bevacizumab/placebo 15 mg/kg IV over 30-90 minutes on Day 1 and paclitaxel 80 mg/m² IV over 1 hour on Days 1, 8, and 15, every 21 days. She received the last dose of bevacizumab/placebo on July 31, 2009 (Cycle 8, Day 1), and the last dose of paclitaxel on August 11, 2009 (Cycle 8, Day 12).

The patient was diagnosed with invasive breast carcinoma in December 2008 and is status post bilateral mastectomies with sentinel node biopsy and axillary dissection in February 2009. She began the investigational agent on March 31, 2009.

On August 23, 2009, the patient presented to the emergency department with a 1-day history of shortness of breath, weakness, and confusion. Her oxygen saturation was 90% on 6 liters of oxygen, and she was tachycardic. A CT angiogram of the lungs revealed extensive bilateral pulmonary emboli and bilateral lower lobe infarcts. A CT scan of the head did not show any obvious bleed or mass effect. She was admitted to the ICU and started on IV fluids, heparin drip, and Zofran[®].

On August 24, 2009, an MRI of the brain revealed multiple small acute infarcts which were consistent with an embolic shower, the largest being in the left parietal periventricular region extending adjacent to the atrium of the left lateral ventricle. There was also the involvement of both occipital lobes and the right frontal lobe, with no mass effect or enhancement. An echocardiogram revealed a large thrombus in the right ventricle with right heart chamber enlargements, marked hypokinesis of the right ventricle, and moderate pulmonary hypertension. A follow-up bubble study was positive for a patent foramen ovale (PFO) with right-to-left shunting at rest. A Doppler[®] ultrasound of the lower extremities was negative for deep vein thrombosis (DVT). However, the Doppler[®] scan of the right upper extremity revealed a short segmental non-occlusive thrombus in the cephalic vein in the mid to distal arm representing a superficial thrombus but no DVT. A cardiologist felt that the patient was a poor candidate for PFO closure and suggested keeping the patient on chronic anticoagulation therapy. It was felt that the confusion was secondary to paradoxical emboli through the patent foramen ovale coincidental with her pulmonary emboli.

A follow up CT scan of the head performed on August 29, 2009 was unremarkable, and a repeat venous Doppler[®] ultrasound of the right upper extremity showed no evidence of superficial or deep thrombus. The anticoagulation therapy (Warfarin) was continued at the time of discharge with plans for prolonged therapy. The patient's general condition improved during her hospitalization, but she still experienced balance problems and required assistance for many regular daily activities. She was discharged on September 1, 2009, to be followed up at the clinic on September 4, 2009.

The patient's past medical and surgical history is significant for a tubal ligation in 1999. Medications

taken at the time of the event included Tylenol® and Benicar®.

There have been 128 other cases of confusion reported to the NCI through AdEERS as serious adverse events under the bevacizumab NSC and/or IND as shown in the table below:

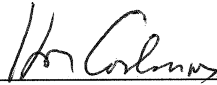
Adverse Event	Grade	Attribution
Confusion (n=128)	4	8 Unrelated, 13 Unlikely, 3 Possible, 1 Probable
	3	23 Unrelated, 26 Unlikely, 13 Possible, 1 Probable, 1 Definite
	2	8 Unrelated, 12 Unlikely, 14 Possible, 1 Probable
	1	1 Unrelated, 2 Unlikely, 1 Possible

There have been 25,910 patients enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC.

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

	Confusion
Bevacizumab	Possible
Paclitaxel	Possible
Invasive breast carcinoma	Unlikely
Paradoxical emboli/stroke	Definite
Pulmonary emboli	Unrelated

Date: 4 May 2010

Signature: 
 Kevin Conlon, M.D.
 (IDB Monitor for bevacizumab)

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

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 Genentech, Inc.