



DATE: JAN 10 2011
FROM: Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# 1470711
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 13-year-old female with pilocytic astrocytoma experienced grade 3 avascular osteonecrosis while on a phase 2 study using the investigational agent bevacizumab in combination with irinotecan.

ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 Bevacizumab (rhuMAb VEGF)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: Gr. 3: Osteonecrosis (avascular necrosis)
AE: 1470711	Protocol: PBTC-022

The patient is a 13-year-old female with pilocytic astrocytoma who experienced avascular osteonecrosis while on a phase 2 study using the investigational agent bevacizumab in combination with irinotecan. She began her first course of treatment on February 9, 2009, receiving bevacizumab 10 mg/kg IV over 30-90 minutes on Days 1 and 15, and irinotecan 125-150 mg/m² IV over 90 minutes every 2 weeks starting on Day 15, every 4 weeks. She received her last dose of bevacizumab on October 4, 2010 (Cycle 18, Day 1), and her last dose of irinotecan on August 2, 2010 (Cycle 15, Day 22).

The patient was diagnosed with pilocytic astrocytoma in April 2002, and is status post tumor biopsy and ventriculoperitoneal shunt placement in April 2002, subtotal resection in April 2004, and multiple agents systemic chemotherapy in February 2003, July 2005, and November 2008. She began the investigational therapy on February 9, 2009.

In mid-September 2010, the patient started complaining of left wrist pain, and an X-ray of the wrist was read as normal. On September 20, 2010 (Cycle 17, Day 15), the patient presented to the clinic with mild swelling of the left wrist, tenderness of the left anterior aspect of the wrist, with limited range of motion, and the inability to make a fist. The same day, her dosage of bevacizumab was held. An orthopedist noted that the patient had pain with hyperextension of the wrist, while all motor functions were normal. A repeat X-ray of the left wrist showed no evidence of fracture or dislocation; however, osteopenia was identified. The orthopedist was unclear as to the etiology of her symptoms and recommended consultation with a rheumatologist if her symptoms did not improve.

On October 4, 2010 (Cycle 18, Day 1), the patient returned to the clinic and reported that the pain had improved, although she continued to experience some discomfort. On October 12, 2010 (Cycle 18, Day 9), an MRI of the left wrist revealed diffuse bone marrow edema and mild fragmentation with collapse of the lunate, which were findings consistent with a diagnosis of Kienbock malacia (avascular necrosis of the lunate). It was decided that the patient's bevacizumab would be discontinued indefinitely; therefore, she was removed from the study, and a consultation with a hand surgeon was scheduled.

On October 21, 2010, the hand surgeon noted that the patient's wrist showed global tenderness and mild swelling, especially at the dorsal portion of the wrist overlying the lunate, which resulted in limited motion in the flexion and extension arc. An MRI of the lumbar spine showed no evidence of bone density measurement below the expected range for the patient's age. The orthopedist agreed with the original diagnosis of left wrist Kienbock disease. The treatment plan was to immobilize the patient's wrist with an Exos fracture brace, to be worn full-time, and to monitor the patient closely over time. She was scheduled to return to the clinic in 6 weeks for reassessment.

The patient's past medical and surgical history is significant for blindness, diabetes, tumor biopsy, ventriculoperitoneal shunt placement, and subtotal resection. The medication taken at the time of the event was Cozaar®.

There have been 15 other cases of osteonecrosis reported to the NCI through AdEERS as serious adverse events under the bevacizumab NSC and/or IND as shown in the table below.

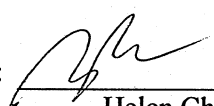
Adverse Event	Grade	Attribution
Osteonecrosis (n=15)	4	1 Possible, 1 Probable
	3	1 Unrelated, 3 Possible
	2	1 Unrelated, 1 Unlikely, 5 Possible, 1 Probable
	1	1 Probable

There have been 30,255 patients enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC.

In this case, a possible causal relationship exists between the event and bevacizumab.

	Osteonecrosis
<u>Bevacizumab</u>	Possible
<u>Irinotecan</u>	Unrelated
<u>Pilocytic astrocytoma</u>	Unrelated

Date: 1/5/11

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

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

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 Safety Contact: onc_drug.safety@gene.com
 Genentech, Inc.