



DATE: December 23, 2009

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

SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# 1279067

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 19-year-old male with Ewing sarcoma/peripheral primitive neuroectodermal tumor developed a **grade 3 esophageal stricture and grade 3 esophagitis** while on a phase 2 study using the investigational agent bevacizumab/placebo in combination with vincristine, topotecan and cyclophosphamide.

ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 Bevacizumab (rhuMab VEGF)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: Gr. 3: Stricture/stenosis, GI: Esophagus Gr. 3: Esophagitis
AE: 1279067	Protocol: AEWS0521

The patient is a 19-year-old male with Ewing sarcoma/peripheral primitive neuroectodermal tumor who developed an esophageal stricture while on a phase 2 study using the investigational agent bevacizumab/placebo in combination with vincristine, topotecan, and cyclophosphamide. He began his first course of treatment on July 1, 2008, receiving bevacizumab/placebo 15 mg/kg IV over 30-90 min on Day 1, vincristine 1.5 mg/m² IVP on Day 1 of each week of Cycles 1 and 2, topotecan 0.75 mg/m² IV over 30 min on Days 1-5, and cyclophosphamide 250 mg/m² IV over 60 min on Days 1-5, every 21 days. He received the last dose of bevacizumab on June 22, 2009 (Cycle 12, Day 1), the last doses of cyclophosphamide and topotecan on June 26, 2009 (Cycle 12, Day 5), and the last dose of vincristine on July 6, 2009 (Cycle 12, Day 15).

The patient, who has a history of Hodgkin's lymphoma in remission, was diagnosed with Ewing sarcoma in the right chest wall in February 2007 and is status post resection, chemotherapy, and radiation therapy in July 2007.

The patient began the investigational therapy on July 1, 2008. From November to December 2008 (during Cycles 5 and 6) the patient also received radiation therapy to the right chest wall, while the chemotherapy was continued. The radiotherapy was added as the tumor size had decreased by only 13% during the first 4 cycles of therapy and it was felt radiotherapy might help improve the tumor control. The patient developed dysphagia in February 2009, after the radiation therapy. On June 23, 2009 (Cycle 12, Day 2), a barium swallow showed a tubular narrowing of the esophagus at the level of T5-T6 likely secondary to radiation esophagitis and another focal narrowing in the distal esophagus about 2 cm above the gastroesophageal junction.

On July 15, 2009 (Cycle 12, Day 24), the patient presented to the emergency department (ED) with complaints of progressive hematemesis associated with epigastric abdominal pain. The esophagram was reviewed in the ED by specialists who determined that the stricture was about 2-3 cm long and approximately 5 mm wide and would require dilation. Dilation of the stricture was deferred, however, due to the patient's recent chemotherapy, pancytopenia, and the possible risk of infection, bleeding and perforation. It was felt that the etiology of the hematemesis included: diffuse esophagitis, gastritis, or mucositis from the chemotherapy, or a gastric or duodenal ulcer. The patient was given high-dose Nexium[®], platelets, and packed RBCs. Admission hemoglobin was 7.8 g/dL (reference range: 12.7-16.7 g/dL), hematocrit 22.3% (reference range: 36.7%-48.3%), platelets 50 K/mm³ (reference range: 154-345K/mm³) WBC 1.1 K/mm³ (reference range: 3.3-9.6 K/mm³). The patient had no further episodes of hematemesis the next day, and tolerated fluids and soft foods. He was discharged in stable condition on July 18, 2009 (Cycle 12, Day 27), with the plan for esophageal dilation as an outpatient when his counts improved and his mucosa had recovered.

In early August, the patient had another episode of hematemesis. An upper gastrointestinal endoscopy with biopsies was performed on August 12, 2009 (Cycle 12, Day 52). The proximal esophagus showed an intraepithelial acute inflammation with numerous microabscesses in the stratified squamous epithelium and multiple fragments of fibrinopurulent exudates. A special stain for fungi showed no organisms. The patient was placed on fluconazole for a presumptive diagnosis of esophageal candidiasis.

The patient's past medical/surgical history is significant for trisomy 21, an ASD/PDA repair as an infant, Hodgkin's lymphoma, and sleep apnea. Medications taken at the time of the event included Adderall[®], Lexapro[®], Zyrtec[®], Abilify[®], Septra[®], Nexium[®] and MiraLax[®].

There have been 3 other cases of esophageal stricture reported to the NCI as serious adverse events through AdEERS under the bevacizumab IND and/or NSC. The incidences are shown in the table below:


Adverse Event	Grade	Attribution
Esophageal stricture (n=3)	3	1 Unlikely, 1 Unrelated
	2	1 Possible

There have been 22,773 patients enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC.

In this case, the esophageal stricture developed approximately 6 months after the radiation and during the protocol therapy with bevacizumab and chemotherapy. It is felt that a possible relationship between bevacizumab in combination with radiation and the event exists.

	Stricture/stenosis, GI: Esophagus	Esophagitis
Bevacizumab	Probable	Probable
Cyclophosphamide	Possible	Possible
Topotecan	Possible	Possible
Vincristine	Possible	Possible
Ewing sarcoma	Unrelated	Unrelated
Radiation therapy	Definite	Definite

Date: 12/23/09

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.