



DATE: MAY 24 2011

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

SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# 1250501

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 75-year-old female with glioblastoma multiforme experienced grade 4 abdominal pain and subsequently expired while on a phase 3 trial utilizing the investigational agent bevacizumab/placebo in combination with temozolomide and radiation therapy.

ADVERSE EVENTS ASSESSMENT

IND 7921	ADVERSE EXPERIENCE REPORT NO.
NSC 704865	IND Safety Report: # 1
Bevacizumab (rhuMAB VEGF)	Event: Gr. 5: Death NOS Gr. 4: Abdominal pain
AE: 1250501	Protocol: RTOG-0825

The patient was a 75-year-old female with glioblastoma multiforme (GBM) who experienced abdominal pain and subsequently expired while on a phase 3 trial utilizing the investigational agent bevacizumab/placebo in combination with temozolomide and concurrent radiation. She began her first course of treatment on February 7, 2011, receiving bevacizumab/placebo 10 mg/kg of actual body weight IV over 30-90 minutes on Day 1 of Weeks 4 and 6, radiation therapy 60 Gy over 6 weeks (delivered in 2 Gy fractions on Days 1-5 every week), and temozolomide 75 mg/m² PO daily (concurrent treatment course = 6 weeks); bevacizumab/placebo 10 mg/kg of actual body weight IV over 30-90 minutes at the beginning of week 2 (Cycle = 4 weeks); and bevacizumab/placebo 10 mg/kg of actual body weight IV over 30-90 minutes on Days 1 and 15, and temozolomide 150-200 mg/m² PO on Days 1-5 for a maximum of 12 cycles (Cycle = 4 weeks). The patient received the last dose of bevacizumab/placebo on March 1, 2011 (Cycle 1, Day 23), and the last dose of temozolomide on March 14, 2011 (Cycle 1, Day 36), and the last dose of radiation therapy on March 21, 2011 (Cycle 1, Day 43).

The patient was diagnosed with glioblastoma multiforme in January 2011. She was status post craniotomy with gross total resection of the brain tumor on January 4, 2011. The pathology report revealed glioblastoma multiforme. The patient began the investigational therapy on February 7, 2011.

On March 15, 2011 (Cycle 1, Day 37), the patient presented to the clinic with profound weakness. The patient reported that she had been experiencing progressive weakness for the past 2 weeks which had become more severe in the past week. She was admitted to the hospital, where she developed abdominal pain, fatigue, bilateral deep vein thrombosis, agitation, delirium, and encephalopathy. Her vital signs were significant for a blood pressure of 104/72 mmHg, an oxygen saturation of 97% on room air, a respiratory rate of 18 breaths per minute, and a temperature of 97.4⁰F. Her laboratory findings were significant for a white blood cell (WBC) of 2.2 K/ μ L (reference range: 4.0-10.0 K/ μ L), a red blood cell (RBC) of 3.87 M/ μ L (reference range: 4.20-5.40 M/ μ L), a hemoglobin of 11.9 g/dL (reference range: 12.0-16.0 g/dL), and a hematocrit of 33.9 % (reference range: 37.0-47.0 %). A CT scan of the abdomen and pelvis revealed no acute abnormalities. A brain MRI revealed a lobe lesion which was decreased in size compared to a previous scan, a lobulated enhancement present in the wall of the lesion consistent with residual neoplasm, and mild cerebral and cerebellar atrophy. The neurology evaluation revealed an abnormal EEG, but the finding was consistent with a seizure. After several days of hospitalization and difficulty controlling and locating the pain, the patient and her family member decided that the patient did not want to pursue any further aggressive therapy. The patient was discharged from the hospital on March 26, 2011 and due to the severity of her pain, she was transferred to an inpatient hospice facility for comfort care with pain management. The patient expired in hospice care on March 28, 2011.

The patient's past medical/surgical history was significant for parathyroid surgery for hypercalcemia, hysterectomy, parathyroidectomy, lichen sclerosis, osteoporosis, hyperlipidemia, hypercholesterolemia, reflux esophagitis, and hyperglycemia. Medications taken at the time of the events included Prilosec[®], simvastatin, Keppra[®], Seroquel[®], calcium and vitamin D.

There have been 55 other cases of sudden death, and 166 other cases of death NOS reported to NCI as serious adverse events through AdEERS under the bevacizumab NSC and/or IND. Abdominal pain is an expected event for bevacizumab.

Adverse Event	Grade	Attribution
Sudden death (n = 55)	5	6 Unrelated, 10 Unlikely, 36 Possible, 3 Probable
Death NOS (n = 166)	5	61 Unrelated, 70 Unlikely, 34 Possible, 1 Probable

There have been 32,741 patients enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC.

In this case, a possible relationship exists between the events and the investigational agent bevacizumab.

	Death NOS	Abdominal pain
Bevacizumab/placebo	Possible	Possible
Temozolomide	Possible	Possible
Glioblastoma multiforme	Unlikely	Possible
Radiation therapy CNS	Possible	Possible

Date: 5/19/11

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.