



DATE: August 12, 2009

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

SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE # **1687519**

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 or 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 53-year-old male with metastatic carcinoid tumor experienced a grade 4 CNS hemorrhage and subsequently expired from disease progression while on a phase 3 study utilizing the investigational agent bevacizumab in combination with depot octreotide.

0003

ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 Bevacizumab (rhuMAB VEGF)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Event: Gr. 5: Death no associated with CTCAE term: Disease Progression Gr. 4: Hemorrhage: CNS Protocol: S0518
AE: 1687519	

The patient was a 53-year-old male with metastatic carcinoid tumor who experienced a CNS hemorrhage and subsequently expired several days later from disease progression while on a phase 3 study utilizing the investigational agent bevacizumab in combination with depot octreotide. He began his first course of treatment on March 10, 2009, receiving bevacizumab 15 mg/kg IV over 30-90 minutes on Day 1, short-acting octreotide 100 mcg SQ on Day 1, Cycle 1 only, and octreotide LAR depot 20 mg IM on Day 1, every 21 days. He received his first and only dose of bevacizumab on March 11, 2009 (Cycle 1, Day 2), and octreotide on March 10, 2009 (Cycle 1, Day 1).

The patient was diagnosed with a carcinoid tumor in August 1999 and was status post octreotide treatment (1999 to present) and liver resection. He had metastases to the bone, liver, and lungs; mediastinal, retroperitoneal, and pelvic lymphadenopathy; and subcutaneous nodules. A CT scan of the abdomen on March 4, 2009, revealed hepatic metastases with lymphadenopathy and ascites, and a chest CT scan revealed pulmonary parenchymal nodules with adenopathy and subcutaneous nodules. He began the investigational therapy on March 10, 2009, receiving only octreotide that day; bevacizumab was delayed one day for insurance reasons.

On March 29, 2009 (Cycle 1, Day 20), the patient presented to the emergency room (ER) with complaints of nausea, vomiting, headache, dizziness, confusion, change in mental status, poor appetite, dysphagia, weight loss, and ataxia. The patient was admitted to the intensive care unit (ICU) hemodynamically stable after a CT scan of the head revealed a right tentorial subdural hematoma as well as an acute bleed in the right inferior cerebellum and a slight mass effect on the fourth ventricle. Of note, the patient had a history of a traumatic brain injury in 2004, and had had some elements of occasional memory difficulties and mild dementia since then. His international normalized ratio (INR) was 4.7 (reference range: 0.9-1.1). The cerebellar bleed was thought to be secondary to his Coumadin[®]. Hence aspirin, Coumadin[®], Plavix[®], and Avastin[®] were discontinued, and on March 30, 2009, the patient received vitamin K, two units of fresh frozen plasma, and activated Factor VII. He was evaluated by a neurologist, and it was decided that the patient's INR should be maintained below 1.3, and the patient managed conservatively with a repeat CT scan within 6 hours of the previous CT scan (the results of which showed little change). His prothrombin time (PT), partial thromboplastin time (PTT), and INR were regularly and strictly monitored. The patient was started on tube feedings and antibiotics for possible aspiration pneumonia. He was also started on Lasix[®] for lower extremity edema. A Doppler[®] ultrasound of the lower extremities revealed no deep vein thrombosis; and an echocardiogram revealed an ejection fraction of 70% with normal left ventricular systolic function, mild to moderately reduced right ventricular systolic function, moderate aortic regurgitation, and mild mitral regurgitation. He was eventually transferred out of the ICU, though his mental status had not changed.

A repeat CT scan of the head on April 4, 2009 (Cycle 1, Day 26), revealed no changes from the previous scans. The possibility of sepsis was considered when the patient's white count began to rise. Blood and urine cultures were negative, while MRSA was isolated from the patient's nares. The family requested that the patient be placed under comfort measures; and he underwent a hospice consultation. The patient's clinical condition continued to worsen with decline of his neurological status, and on April 10, 2009 (Cycle 1, Day 32), the patient died.

The patient's past medical and surgical history is significant for head trauma in 2004, tricuspid valve replacement with a mechanical valve in 2004, paroxysmal atrial fibrillation/flutter status post cardioversion, depression, liver resection, benign prostatic hyperplasia, and valvular dysfunction in January 2009. There are multiple cancers on his mother's side of the family; further details are unknown. Medications taken at the time of the event included spironolactone, Zofran[®], Coumadin[®], Effexor[®], aspirin, terazosin, Lasix[®], potassium chloride, Zolof[®], digoxin, Nexium[®], and OxyContin[®].

There have been 244 deaths due to progressive disease and 65 cases of death NOS reported to the NCI as serious adverse events through AdEERS under the bevacizumab NSC and/or IND. CNS hemorrhage is a known event for bevacizumab.

Event	Grade	Attribution
Death: Progressive disease (n=244)	5	105 Unrelated, 129 Unlikely, 10 Possible
Death NOS (n=65)	5	12 Unrelated, 36 Unlikely, 17 Possible

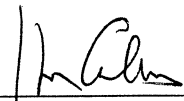
There have been 22,929 patients enrolled in NCI-sponsored clinical trials under this IND and/or NSC.

In this case, it is thought that a probable relationship between bevacizumab and CNS hemorrhage exists and that a possible relationship between bevacizumab and the patient's death could not be excluded.

	CNS Hemorrhage	Death
Bevacizumab	Probable	Possible
Octreotide acetate	Unlikely	Unrelated
Carcinoid tumor	Unlikely	Definite
Coumadin	Probable	Unlikely

Date: 12 August 2009

Signature: _____


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

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

cc: Jessica Conner
 Drug Safety: onc_drug.safety@gene.com
 Genentech, Incorporated