



DATE: MAY 18 2011

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

SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# 1706673

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 67-year-old male with glioblastoma multiforme (GBM) suddenly died while on a phase 3 trial utilizing the investigational agent bevacizumab/placebo in combination with temozolomide and radiation therapy.

ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 Bevacizumab (rhuMAb VEGF)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: Gr. 5: Sudden Death
AE: 1706673	Protocol: RTOG-0825

The patient was a 67-year-old male with glioblastoma multiforme (GBM) who suddenly died while on a phase 3 trial utilizing the investigational agent bevacizumab/placebo in combination with temozolomide and radiation. He began his first course of treatment on December 14, 2010, 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 January 4, 2011 (Cycle 1, Day 22), temozolomide on January 17, 2011 (Cycle 1, Day35), and radiation therapy on January 14, 2011 (concurrent treatment course).

The patient was diagnosed with right parietal glioblastoma multiforme in November 2010, and was status post tumor resection and a craniotomy in December 2010. The patient began the investigational therapy on December 14, 2010.

At baseline, the patient was cardiovascularly stable, but had a previous history of paroxysmal atrial fibrillation, well controlled in sinus rhythm with Rythmol[®] and Toprol[®]. He had not been on Coumadin[®] or had any recurrence of atrial fibrillation. On January 10, 2011 (Cycle 1, Day 27), per study protocol, the patient had a follow-up MRI of the brain which showed a cystic lesion that was in the right occipital lobe and approximately the same size compared with a MRI performed on December 6, 2010, but perhaps had more enhancement and some increased nodularity. There was persistent mass effect, but no new or larger lesions. The patient stated that he did not have a definite headache, though he had a minimal generalized stuffiness/pressure and stable energy level. On January 11, 2011, his vital signs were significant for a heart rate of 126 bt/min, a blood pressure of 129/70 mmHg, an oxygen saturation of 94% on room air and a temperature of 98.10⁰F. On January 17, 2011, the radiation oncologist noted that the patient complained of increased shortness of breath and fatigue for the last few days. A chest x-ray revealed mild atelectasis. His skin was without erythema, heart rate was 112-115 bt/min and irregular, blood pressure was 110/70 mmHg, and his oxygen saturation of 94-95% on room air. The patient died at home on the same day, January 17, 2011. As per patient's wife, the patient had a "massive heart attack" and but this was not documented or verified.

The patient's past medical/surgical history was significant for chronic obstructive pulmonary disease, asthma, hyperlipidemia, hypertension, hypothyroidism, ex-smoker, paroxysmal atrial fibrillation, and removal of a cyst from the arm. Medications taken at the time of the event included Bactrim[®], Advair Diskus[®], Compazine[®], albuterol, Spiriva HandiHaler[®], Rythmol[®], Synthroid[®], Keppra[®] and Colace[®].

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.

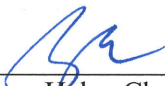
Adverse Event	Grade	Attribution
Sudden death (n=55)	5	6 Unrelated, 10 Unlikely, 36 Possible, 3 Probable
Death NOS (n=166)	5	61 Unrelated, 70 Unlikely, 34 Possible, 1 Probable

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 event and the investigational agent.

	Sudden Death
Bevacizumab/placebo	Possible
Temozolomide	Possible
Radiation	Unlikely
Glioblastoma multiforme	Possible
Possible arrhythmia	Probable

Date: 5/16/11

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.