



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: October 3, 2008

To: NCCTG Primary Clinical Research Associates

From: Sara Braun

Re: N0775, A Randomized Phase II Trial of Temozolomide (TMZ) and Avastin® or ABI-007/Carboplatin (CBDCA) and Avastin® in Patients with Unresectable Stage IV Malignant Melanoma

The purpose of this memorandum is to provide investigators with a recent report of an adverse event that has occurred in association with bevacizumab for a study where the Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI) is distributing this agent. You may have also received this communication directly from DCTD.

AE_1226348_F1

Please note that all risks currently cited in the NCCTG consent form cannot be omitted; it is at the discretion of your local IRB as to whether they wish to add risks based on the enclosed information. If a determination has been made by the NCCTG Research Base that a protocol amendment is necessary, you will receive the NCI-approved protocol addendum at a later date; for purposes of cross-reference, this communication will cite the adverse event noted above.

Please submit this adverse event to your Institutional Review Board.

If you have any questions concerning this communication, please contact Sara Braun at braun.sara@mayo.edu or 507-538-8226.

SB/kjm
enclosure



DATE: September 5, 2008
FROM: Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE # 1226348
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 IND 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 this NSC, and the total number of patients enrolled in trials under this NSC:

A 72-year-old male with advanced stage diffuse large B-cell lymphoma experienced **sudden death** while on a phase 2 study utilizing the investigational agent bevacizumab in combination with cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab.

ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 Bevacizumab (rhuMAb VEGF)	ADVERSE EXPERIENCE REPORT NO. 30 IND Safety Report: #1 Event: Gr. 5: Death not associated with CTCAE term: Sudden Death
AE: 1226348	Protocol: S0515

The patient was a 72-year-old male with advanced stage diffuse large B-cell lymphoma, who experienced sudden death while on a phase 2 trial using the investigational agent bevacizumab in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) and rituximab. The patient began his first course of treatment on June 26, 2008, receiving bevacizumab 15 mg/kg IV over 30-90 minutes on Day 1, cyclophosphamide 750 mg/m² IV over 15 min on Day 1, doxorubicin 50 mg/m² slow IV infusion on day 1, vincristine 1.4 mg/m² (maximum 2 mg) slow IV infusion on Day 1, prednisone 100 mg PO on Days 1-5, and rituximab 375 mg/m² slow IV infusion on Day 1, every 21 days. The patient received his last dose of bevacizumab and chemotherapy on July 17, 2008 (Cycle 2, Day 1), with the exception of prednisone for which he received his last dose on July 21, 2008 (Cycle 2, Day 5).

The patient was diagnosed with testicular large B-cell lymphoma with metastases to the lymph nodes in May 2008, and was status post left radical orchiectomy in May 2008. The patient began the investigational therapy on June 26, 2008. The first course was complicated with pancreatitis, a bowel obstruction, nausea and vomiting. The patient recovered and received the 2nd cycle of treatment.

On July 28, 2008 (Cycle 2, Day 12), the patient presented to the hospital complaining of rectal pain due to external hemorrhoids and two anal fissures measuring 4 mm x 2 mm. He was prescribed topical lidocaine jelly and sitz baths. His laboratory results at the time of admission normal WBC and platelet counts, a hemoglobin of 8.4 g/dL (reference range: 14-18 g/dL), BUN of 26 mg/dL (reference range: 10-20 mg/dL), and creatinine of 1.8 mg/dL (reference range: 0.6-1.2 mg/dL).

On July 29, 2008, the patient was scheduled for discharge, but his oxygen saturation began to drop. He was placed on subcutaneous Lovenox[®] and sent for a V/Q scan to rule out pulmonary embolism. While returning to his room after the scan, he became cyanotic and hypoxic even though he was on 6 L/min supplemental oxygen by nasal cannula. The rapid response team was called and a full code was initiated. Despite all efforts the patient failed to respond to CPR, and he expired that same day. Because the results from the V/Q scan showed a low probability of pulmonary embolism, it was thought that the cyanosis, hypoxia and sudden death were cardiac in nature. Of note, the patient had had a cardiac catheterization in the year 2000 (results are unavailable per site), and he had a history of hypertension, hypercholesterolemia and diabetes. An echocardiogram on July 1, 2008, revealed normal left ventricular wall motion with an ejection fraction of 55-60%. An autopsy was not performed. The death certificate states the cause of death is a probable myocardial infarction with cardiopulmonary arrest.

The patient's past medical history is significant for tobacco use (3 cigarettes daily), type 2 diabetes, hypercholesterolemia, hypertension, peripheral vascular disease, GERD, degenerative joint disease, and mild depression. Surgical history is significant for vasectomy in 1963, left inguinal hernia repair in 1965, cardiac catheterization in 2000, multiple knee surgeries with total knee replacement in 2002, hemorrhoidectomy, bilateral cataract surgery in 2007 and 2008, peripheral vascular surgery in 2008, shoulder repair, and esophageal dilatation. Family history was significant for a mother with a cerebrovascular accident (CVA), father with congestive heart failure, and a sister with breast cancer. Medications taken at the time of the event included allopurinol, amitriptyline HCl, atenolol, Avandia[®], diphenhydramine, ferrous sulfate, Flonase[®], Glucotrol XL[®], Lantus[®], Lasix[®], Levaquin[®], lisonopril, Lopid[®], Micardis[®], Mobic[®], MSIR, Oxycodone[®], Pegfilgrastim[®], Plendil[®], Prilosec[®], Tekturna[®], Tylenol[®], Zantac[®], and Zofran[®].

There have been 39 other cases of sudden death, and 44 other cases of death NOS previously reported to the NCI as serious adverse events through AdEERS under the bevacizumab IND.


Adverse Event	Grade	N
Sudden death	5	39
Death NOS	5	44

There have been 17,005 patients enrolled in NCI-sponsored clinical trials under this NSC.

In this case, the exact cause of death cannot be confirmed, but given the patient's history of peripheral vascular disease and the risk factors for ischemia heart disease, a cardiac event is mostly likely. Therefore the death is most likely due to the underlying cardiovascular conditions but bevacizumab as an exacerbating factor cannot be ruled out.

	Sudden Death
<u>Bevacizumab</u>	Possible
<u>Cyclophosphamide</u>	Unrelated
<u>Doxorubicin</u>	Unrelated
<u>Vincristine</u>	Unrelated
<u>Prednisone</u>	Unrelated
<u>Rituximab</u>	Unrelated
<u>Diffuse large B-cell lymphoma</u>	Unrelated
<u>Possible cardiac ischemic event</u>	Possible

Date: 9/5/08

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

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

cc: Murielle Mueller
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 Genentech, Incorporated