



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: March 13, 2009

To: NCCTG Primary Clinical Research Associates

From: Lynn Flickinger
Protocol Development Coordinator

Re: N0735, Phase II Trial of Albumin-Bound Paclitaxel in Combination with Gemcitabine and Bevacizumab in Patients with Metastatic Breast Cancer

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_1809808_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 Lynn Flickinger at Flickinger.lynn@mayo.edu or 507-538-7034.

LF/kjm
enclosure



DATE: December 19, 2008
FROM: Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: Bevacizumab (rhuMAb VEGF) IND Safety Report, AE# **1809808**
TO: Investigators Using Bevacizumab (rhuMAb VEGF), 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.

CTEP's evaluation of this IND Safety Report in light of previous experience with bevacizumab does not require a change in the clinical protocols for this agent at this time. The risk benefit ratio has not been altered based on CTEP's assessment.

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 68-year-old male with metastatic carcinoid tumor experienced a **grade 2 bilateral lower extremity rash, grade 3 bilateral thigh pain, and grade 3 lethargy** while on a phase 3 trial utilizing the investigational agent bevacizumab in combination with octreotide.

ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 Bevacizumab (rhuMab VEGF) AE: 1809808	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Event: Gr. 3: Pain: Extremity-limb (myalgia) Gr. 2: Rash/desquamation Gr. 3: Lethargy Protocol: S0518
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The patient is a 68-year-old male with carcinoid tumor metastatic to the retroperitoneal and periaortic lymph nodes, right lung base, left kidney, and bone, who experienced a bilateral lower extremity rash, bilateral thigh pain, and lethargy while on a phase 3 trial using the investigational agent bevacizumab in combination with octreotide. The patient was to receive bevacizumab 15 mg/kg IV over 30-90 minutes, and octreotide LAR depot 20 mg IM, on Day 1, every 21 days, but received his first and only course of treatment on September 5, 2008 (Cycle 1, Day 1).

The patient was diagnosed with well-differentiated neuroendocrine cancer of the cecum in January 2003 with metastases at that time to the retroperitoneal lymph nodes, right lung base, left kidney, and bone. He is status post exploratory laparotomy, kyphoplasty of T8-9 vertebral bodies in May 2003, radiation therapy, and a transsphenoidal resection of a suprasellar clival mass in May 2008. For management of his carcinoid syndrome, he received octreotide LAR every 4 weeks and Zometa® for bony metastasis. The patient began the investigational therapy on September 5, 2008. Zometa was switched to Fosamax on September 8, 2008.

On September 11, 2008 (Cycle 1, Day 7), the patient had difficulty staying awake and was too weak to call for help. He was transported to the emergency room by ambulance with extreme somnolence. Upon examination, he had a fever of 102.4°F, blood pressure of 100/58 mmHg, and his oxygen saturation on room air was 93% to 96%. He had a dark, violaceous skin rash on the inner thighs bilaterally as well as smaller areas of involvement in the lower legs. He also reported pain in the anterior thighs especially when rising from a sitting position or climbing stairs. These symptoms started several days after receiving the investigational treatment. Of note: two years previously he also noted rash after Fosamax, but that was a typical maculopapular, erythematous reaction, different from the presentation this time. Laboratory findings included a WBC of 10.6×10^9 (reference range: $5-10 \times 10^9$), hemoglobin 12.1 g/dL (reference range: 14-18 g/dL), platelet count 221×10^9 (reference range: $150-400 \times 10^9$), total bilirubin 1.9 mg/dL (reference range: 0.3-1.0 mg/dL) with a direct bilirubin of 0.4 mg/dL (reference range: 0.1-0.3 mg/dL), (the patient has history of Gilbert syndrome) and normal liver function tests. Blood and urine cultures were obtained; he was given hydration and one dose of Zosyn®, and then admitted for further evaluation. A head CT scan on the same day was unremarkable. An MRI on September 13, 2008, showed skull base mass with intracranial extension that was not changed from baseline, and no evidence of brain parenchymal metastasis or acute infarct; there were a few white matter signal abnormalities which could be due to small-vessel ischemia or age-related changes, as well as a small focus of very low signal on the susceptibility-weighted images within the left anterior aspect of the pons, most likely representing an area of microhemorrhage. In retrospect, these changes appeared consistent with an MRI five months previously.

On September 12, 2008, his lightheadedness had improved, and he was afebrile. He underwent a skin biopsy of his lower extremity rash which revealed superficial and deep perivascular dermatitis, compatible with a dermal hypersensitivity reaction, most likely due to a medication. The microscopic examination showed hyperorthokeratosis, a superficial and deep predominantly perivascular infiltrate of lymphocytes, histiocytes, neutrophils, and scattered eosinophils that were present in the dermis and extended to the biopsy base, and no evidence of leukocytoclastic vasculitis. Bacterial and fungal stains showed scattered gram positive cocci in the stratum corneum and a rare budding yeast form in the stratum corneum with a possible rare hyphal or pseudohyphal fungal element present. On September 13, 2008, he

was alert and oriented, afebrile, and his blood and urine cultures were negative. He remained stable and was discharged later that day.

On September 23, 2008 (Cycle 1, Day 19), the patient presented to the clinic for follow-up and reported continued lower extremity aches and weakness, although the pain was controlled with one Vicodin® per day. The lesions on his lower legs were ruddier in appearance and much smaller. He was removed from the protocol. Fosamax was also stopped since the hospitalization. He returned to the clinic on September 26, 2008, for continued follow-up. He reported feeling improved with less thigh pain. His violaceous lesions had continued to decrease.

The patient's past medical history is significant for hypertension, liver cirrhosis of unknown etiology with compensated liver function, and Baker's cyst removal (1998). Medications taken at the time of the event included clonazepam, famotidine, Fosamax®, furosemide, hydrocortisone, levothyroxine, and octreotide.

There have been 24 other incidences of rash/desquamation and 10 other incidences of extremity pain previously reported to the NCI as serious adverse events through AdEERS under the bevacizumab NSC, which are summarized in the table below.

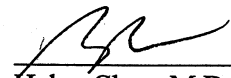
Adverse Event	N	Grade	Attribution
Rash/desquamation	24	3 2	1 Definite, 1 Probable, 5 Possible, 3 Unlikely, 1 Unrelated 2 Probable, 5 Possible, 3 Unlikely, 3 Unrelated
Pain: Extremity	10	4 3 2	1 Unrelated 1 Probable, 1 Unlikely, 4 Unrelated 3 Unlikely
Lethargy	319	2-4	6 Definite, 24 Probable, 179 Possible, 72 Unlikely, 38 Unrelated

There have been 18,137 patients enrolled in NCI-sponsored clinical trials under this NSC.

In this case, it is believed that the skin reaction is probably related to bevacizumab and possibly related to Fosamax. The etiology of mental status change (lethargy) is unclear but a probable relationship to bevacizumab cannot be ruled out.

	Rash/desquamation	Lethargy	Pain: Extremity (myalgia)
Bevacizumab	Probable	Possible	Probable
Octreotide acetate	unrelated	Unrelated	unrelated
Fosamax®	Possible	Unlikely	Possible
Carcinoid tumor	Unrelated	Unrelated	Unrelated
Skin reaction	N/A	Possible	Possible

Date: 12/18/08

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

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

cc: Murielle Mueller
 Drug Safety: onc_drug_safety@gene.com
 Genentech, Incorporated