



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: October 31, 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 industry report of an adverse event that has occurred in association with Bevacizumab at a non-NCCTG institution. You may have also received this communication directly from the drug manufacturer.

AE_265846_F2

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

For use by user-facilities,
importers, distributors and manufacturers
for MANDATORY reporting

MEDWATCH
3500A Facsimile

Mfr Report #	265846
UF/Importer Report #	
FDA Use Only	

A. PATIENT INFORMATION			
1. Patient Identifier	2. Age at Time of Event: 48 Years or Date of Birth:	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight 121.3 lbs or 55.0 kgs
In confidence			
B. ADVERSE EVENT OR PRODUCT PROBLEM			
1. <input checked="" type="checkbox"/> Adverse Event and/or <input type="checkbox"/> Product Problem (e.g., defects/malfunctions)			
2. Outcomes Attributed to Adverse Event (Check all that apply)			
<input type="checkbox"/> Death: _____ (mm/dd/yyyy)		<input type="checkbox"/> Disability or Permanent Damage	
<input type="checkbox"/> Life-threatening		<input type="checkbox"/> Congenital Anomaly/Birth Defect	
<input checked="" type="checkbox"/> Hospitalization - initial or prolonged		<input checked="" type="checkbox"/> Other Serious (Important Medical Events)	
<input type="checkbox"/> Required Intervention to Prevent Permanent Impairment/Damage (Devices)			
3. Date of Event (mm/dd/yyyy) 08/01/2008		4. Date of This Report (mm/dd/yyyy) 09/18/2008	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) right thigh fasciitis [FASCIITIS]			
Case Description: IND SAFETY REPORT			
This case, manufacturer control number 265846, is a report from PHILIPPINES referring to a 48 year-old female subject (ID# _____). An Investigator reported this case from study AVF3693G, A phase III, multicenter, randomized, placebo-controlled trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy regimens in subjects with previously treated metastatic breast cancer.			
On 23-MAY-2008, the subject received BEVACIZUMAB OR PLACEBO (922.5 mg, Q3W, Intravenous) and VINOURELBINE continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates #1 CULTURE Negative (Continued)			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) Race: Asian #1 04/-/2008 to UNK Procedure, (Continued) #2 06/-/2008 to UNK Procedure, (Continued) #3 Procedure, RADIOTHERAPY (Continued) #4 Negative Med Cond, DIABETES MELLITUS			

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeled)			
#1. BEVACIZUMAB OR PLACEBO (Bevacizumab) (Continued)			
#2. VINOURELBINE (VINOURELBINE)			
2. Dose, Frequency & Route Used		3. Therapy Dates (if unknown, give duration) from/to (or best estimate)	
#1. 922.5 mg, Q3W, Intravenous		#1. 05/23/2008 to UNK	
#2. 48.9 mg, 1/Week, Intravenous		#2. 05/23/2008 to UNK	
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced?	
#1. metastatic breast (Continued)		#1. <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
#2. METASTATIC (Continued)		#2. <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
6. Lot #	7. Exp. Date		8. Event Reappeared After Reintroduction?
#1. 9(Continued)	#1.		
#2.	#2.		#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply
9. NDC# or Unique ID			
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)			
#1. CEFUROXIME (CEFUROXIME)			
#2. FUROSEMIDE (FUROSEMIDE)			
continued in additional info section...			
G. ALL MANUFACTURERS			
1. Contact Office - Name/Address (and Manufacturing Site for Devices)		2. Phone Number	
Genentech, Inc. James Nickas Pharm.D. 1 DNA Way South San Francisco, CA 94080 UNITED STATES		6502255591	
4. Date Received by Manufacturer (mm/dd/yyyy) 09/10/2008		5. (A)NDA # IND # BB 7023 STN # PMA/ 510(k) # Combination Product <input type="checkbox"/> Yes Pre-1938 <input type="checkbox"/> Yes OTC Product <input type="checkbox"/> Yes	
6. If IND, Give Protocol # AVF3693G		3. Report Source (Check all that apply) <input checked="" type="checkbox"/> Foreign PHL <input checked="" type="checkbox"/> Study <input type="checkbox"/> Literature <input type="checkbox"/> Consumer <input checked="" type="checkbox"/> Health Professional <input type="checkbox"/> User Facility <input type="checkbox"/> Company Representative <input type="checkbox"/> Distributor <input type="checkbox"/> Other:	
7. Type of Report (Check all that apply) <input type="checkbox"/> 5-day <input type="checkbox"/> 30-day <input type="checkbox"/> 7-day <input type="checkbox"/> Periodic <input type="checkbox"/> 10-day <input type="checkbox"/> Initial <input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up #2			
9. Manufacturer Report Number 265846		8. Adverse Event Term(s) FASCIITIS	
E. INITIAL REPORTER			
1. Name and Address		Phone #	
2. Health Professional?		3. Occupation	
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
4. Initial Reporter Also Sent Report to FDA			
<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Unk			

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

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ADDITIONAL INFORMATION**B5. EVENT DESCRIPTION (Continued)**

(48.9 unit, route and frequency not reported). The lot numbers for Bevacizumab or placebo were reported as 913594, 913598, 905059, 905073, and 913604. The most recent doses of Bevacizumab or placebo and Vinorelbine were administered on 21-JUL-2008.

On 28-JUL-2008, cycle 2 week 2 dosing was deferred due to low ANC (0.385, unit not reported). On 01-AUG-2008, the subject developed right thigh fasciitis (FASCIITIS) and subcutaneous infection and was admitted to the hospital on 2-AUG-2008. No relevant laboratory or diagnostic tests were provided. Treatment included clindamycin and ciprofloxacin. On 2-AUG-2008, the subject underwent debridement of right thigh fasciitis and removal of port-a-cath. No abscess was seen and subject was continued on unspecified "meds." No additional details regarding the clinical course were provided. On 4-AUG-2008, it was reported that chemotherapy was deferred until 11-AUG-2008 if the wound healed.

On 7-AUG-2008, the subject was unblinded and found to be on bevacizumab.

At the time of this report, the event outcome was unknown.

The investigator assessed the event FASCIITIS as related to BEVACIZUMAB OR PLACEBO. In the reporter's opinion, other possible etiological factors included protocol-specified chemotherapy.

This report contains case details known at the time of the submission.

Additional information is being requested. If received, case will be updated accordingly.

ADDITIONAL INFORMATION RECEIVED ON 19-AUG-2008:

Concomitant medication included cefuroxime, furosemide, iberet, calcium carbonate, and gabapentin.

On 11-AUG-2008, the event resolved.

Physical examination done which showed fullness of the neck and cervical lymphadenopathy. On the right thigh, an open wound with mesenteric tissue with some bleeding was observed.

Treatment with bevacizumab was discontinued.

No further information was available.

ADDITIONAL INFORMATION RECEIVED ON 10-SEP-2008

The subject's past medical history included port-a-cath insertion to the chest in APR-2008, which was reported to have been used several times before it was noted to have been blocked. In JUN-2008, a second port-a-cath was then placed at the femoral vessel of the right thigh. It was reported that a site of insertion of the second port-a-cath was chosen due to the fact that the subject had a history of radiation therapy to the chest and supraclavicular region and due to the damage caused by radiation therapy, the vessels in the chest were not suitable. The subject received radiation therapy from 26-OCT-2004 through 07-DEC-2004 to the left chest wall and from 31-JAN-2008 to 06-MAR-2008 to the supraclavicular regions. It was reported that the subject did not have a history of diabetes or any other medical condition that would predispose her to infection.

On 23-MAY-2008, the subject began treatment with VINOELBINE (48.9 mg, weekly for 3 weeks, Intravenous).

On 23-JUN-2008, that the subject received cycle 2, week 1 of treatment and no edema was noted to the right thigh.

On 01-JUL-2008, the subject received cycle 2, week 2 of treatment and edema was noted to the right thigh at the site of port-a-cath insertion (approximately 1 inch in diameter). No redness, pain, or warmth was noted.

On 11-JUL-2008, the subject received cycle 2, week 3 of treatment and the edema had resolved. Per report, no other problem was observed with the port-a-cath prior to event onset.

On 21-JUL-2008, it was reported that no edema was noted by the investigator and the subject received cycle 3, week 1 of treatment.

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On 07-AUG-2008, the subject was hospitalized and removal of port-a-cath to the right thigh and debridement of right thigh fasciitis (FASCIITIS) were performed. A new port-a-cath was placed to the left lower abdomen due to the fact that the subject had no other available veins. Per report, there was no trauma noted at the site of necrotizing fasciitis and it was clarified that upon exam of the right thigh, an open wound with necrotic tissue (previously reported as mesenteric tissue) with some bleeding was observed. It was reported that the diagnosis of fasciitis was a clinical diagnosis made by the investigator. Relevant laboratory tests included an unspecified culture which was negative.

On 09-AUG-2008, the subject was discharged.

On 11-AUG-2008, it was reported that the wound was still not healing and was now gaping.

On an unspecified date, the subject was discontinued from the study due to grade 3 wound dehiscence and grade 3 fasciitis.

On 06-SEP-2008, the subject died due to multiorgan failure (refer to MCN 267831). At the time of death the event of fasciitis remained ongoing.

This report contains case details known at the time of the submission.

Additional information is being requested. If received, case will be updated accordingly.

PREVIOUSLY FILED IND SAFETY REPORTS OF SIMILAR EVENTS

Genentech has previously filed the following IND safety reports of similar events from studies of Bevacizumab.

Manufacturer Control Number	ISR Primary Event Term	~Date Submitted
263914	NECROTISING FASCIITIS	~7-JUL-2008 (Initial)
263914	NECROTISING FASCIITIS	~17-JUL-2008 (FU#1)

SPONSOR ASSESSMENT

Based on review of available data, no compelling evidence of a cause-and-effect relationship between administration of Bevacizumab and the occurrence of fasciitis can be identified.

At this time, the Sponsor does not believe changes to the conduct of this clinical trial are warranted.

B6. LABORATORY DATA

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		CULTURE Negative type of culture not reported		

B7. OTHER RELEVANT HISTORY

#	Start/Stop Date	Condition Type / Condition	Notes
1	04-/2008 UNK	Procedure CENTRAL VENOUS CATHETERISATION	chest
2	06-/2008 UNK	Procedure CENTRAL VENOUS CATHETERISATION	right thigh
3		Procedure RADIOTHERAPY	to chest and supraclavicular region

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C1. NAME (Continued)

Suspect Medication #1: BEVACIZUMAB OR PLACEBO(Bevacizumab) Powder and solvent for solution for infusion, 100mg

C4. DIAGNOSIS FOR USE (Continued)

#1:metastatic breast cancer (METASTATIC BREAST CANCER)

#2:METASTATIC BREAST CANCER (METASTATIC BREAST CANCER)

C6. LOT# (Continued)

Suspect Medication #1: 913594, 913598, 905059, 905073

C10. CONCOMITANT MEDICAL PRODUCTS (Continued)

#3. IBERET (ASCORBIC ACID, FERROUS SULFATE, SODIUM ASCORBATE, VITAMIN B NOS) --/--/2004 to ongoing

#4. CALCIUM CARBONATE (CALCIUM CARBONATE) --/--/2004 to ongoing

#5. NEURONTIN (GABAPENTIN) ongoing

ADDITIONAL INFORMATION**7+13. DESCRIBE REACTION(S) continued**

An Investigator reported this case from study AVF3693G, A phase III, multicenter, randomized, placebo-controlled trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy regimens in subjects with previously treated metastatic breast cancer.

On 23-MAY-2008, the subject received BEVACIZUMAB OR PLACEBO (922.5 mg, Q3W, Intravenous) and VINOELBINE (48.9 unit, route and frequency not reported). The lot numbers for Bevacizumab or placebo were reported as 913594, 913598, 905059, 905073, and 913604. The most recent doses of Bevacizumab or placebo and Vinorelbine were administered on 21-JUL-2008.

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ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

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SPONSOR ASSESSMENT

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At this time, the Sponsor does not believe changes to the conduct of this clinical trial are warranted.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		CULTURE Negative type of culture not reported		

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) BEVACIZUMAB OR PLACEBO (Bevacizumab) Powder and solvent for solution for infusion, 100 mg {Lot # 913594, 913598, 905059, 905073}; Regimen #1	922.5 mg, Q3W; Intravenous	metastatic breast cancer (METASTATIC BREAST CANCER)	23-MAY-2008 / Unknown; Unknown
#2) VINORELBINE (VINORELBINE); Regimen #1	48.9 mg, 1/Week; Intravenous	METASTATIC BREAST CANCER (METASTATIC BREAST CANCER)	23-MAY-2008 / Unknown; Unknown

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued

#3) IBERET (ASCORBIC ACID, FERROUS SULFATE, SODIUM ASCORBATE, VITAMIN B NOS) ; 2004 / Ongoing

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Procedure	RADIATION THERAPY (RADIOTHERAPY); to chest and supraclavicular region

ADDITIONAL INFORMATION

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Negative Med Cond	DIABETES (DIABETES MELLITUS);