



# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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**Date:** October 31, 2008

**To:** NCCTG Primary Clinical Research Associates

**From:** Janis Wobschall

**Re:** N0776, Phase II Trial of Avastin® in Combination with Sorafenib in Recurrent Glioblastoma Multiforme

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**

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 Janis Wobschall at [wobschall.janis@mayo.edu](mailto:wobschall.janis@mayo.edu) or 507-284-4852.

JW/kjm  
enclosure

**MEDWATCH**  
3500A Facsimile

**Genentech, Inc.**

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

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

Page 1 of 2

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) 08/13/2008	
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 VINORELBINE continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) Race: Asian			

C. SUSPECT PRODUCT(S)	
1. Name (Give labeled strength & mfr/labeler)	
#1. BEVACIZUMAB OR PLACEBO (Bevacizumab) (Continued)	
#2. VINORELBINE (VINORELBINE)	
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 unk, UNK	#2. 05/23/2008 to UNK
4. Diagnosis for Use (Indication)	5. Event Abated After Use Stopped or Dose Reduced? Doesn't Apply
#1. metastatic breast (Continued)	#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply
#2. METASTATIC (Continued)	#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply
6. Lot #	7. Exp. Date
#1. 9(Continued)	#1.
#2.	#2.
9. NDC# or Unique ID	
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)	

G. ALL MANUFACTURERS	
1. Contact Office - Name/Address (and Manufacturing Site for Devices) Genentech, Inc. James Nickas Pharm.D. 1 DNA Way South San Francisco, CA 94080 UNITED STATES	2. Phone Number 6502255591
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:	
4. Date Received by Manufacturer(mm/dd/yyyy) 08/05/2008	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	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 checked="" type="checkbox"/> Initial
	<input checked="" type="checkbox"/> 15-day <input type="checkbox"/> Follow-up #
9. Manufacturer Report Number 265846	8. Adverse Event Term(s) FASCIITIS

E. INITIAL REPORTER			
1. Name and Address		Phone #	
2. Health Professional?	3. Occupation	4. Initial Reporter Also Sent Report to FDA	
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		<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.

**MEDWATCH**

3500A Facsimile (Back) (Continued)

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

**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.

**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.

**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

<b>SUSPECT ADVERSE REACTION REPORT</b>	

**I. REACTION INFORMATION**

1. PATIENT INITIALS (first, last)	1a. COUNTRY <b>PHILIPPINES</b>	2. DATE OF BIRTH			2a. AGE <b>48</b> Years	3. SEX <b>Female</b>	3a. WEIGHT <b>55.00</b> kg	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day	Month	Year			Day	Month	Year		<input type="checkbox"/> PATIENT DIED <input checked="" type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION <input type="checkbox"/> INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY <input type="checkbox"/> LIFE THREATENING
							<b>01</b>	<b>AUG</b>	<b>2008</b>		

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)  
 Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)  
 Other Serious Criteria: Medically Significant  
**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# ).

(Continued on Additional Information Page)

**II. SUSPECT DRUG(S) INFORMATION**

14. SUSPECT DRUG(S) (include generic name) #1 ) BEVACIZUMAB OR PLACEBO (Bevacizumab) Powder and solvent for solution for infusion, 100 mg {Lot # #2 ) VINOURELBINE (VINOURELBINE) (Continued on Additional Information Page)		20. DID REACTION ABATE AFTER STOPPING DRUG?  <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA <span style="float: right;">Unknown</span>
15. DAILY DOSE(S) #1 ) 922.5 mg, Q3W #2 ) 48.9 unk, UNK	16. ROUTE(S) OF ADMINISTRATION #1 ) Intravenous #2 ) Unknown	
17. INDICATION(S) FOR USE #1 ) metastatic breast cancer (METASTATI #2 ) METASTATIC BREAST CANCER (M (Continued on Additional Information Page)		21. DID REACTION REAPPEAR AFTER REINTRODUCTION?  <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> NA
18. THERAPY DATES(from/to) #1 ) 23-MAY-2008 / Unknown #2 ) 23-MAY-2008 / Unknown	19. THERAPY DURATION #1 ) Unknown #2 ) Unknown	

**III. CONCOMITANT DRUG(S) AND HISTORY**

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)		
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)		
From/To Dates	Type of History / Notes	Description
Unknown		

**IV. MANUFACTURER INFORMATION**

24a. NAME AND ADDRESS OF MANUFACTURER Genentech, Inc. James Nickas 1 DNA Way South San Francisco, CA 94080 UNITED STATES Phone: 6502255591		26. REMARKS
	24b. MFR CONTROL NO. <b>265846</b>	25b. NAME AND ADDRESS OF REPORTER
24c. DATE RECEIVED BY MANUFACTURER <b>05-AUG-2008</b>	24d. REPORT SOURCE <input checked="" type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input checked="" type="checkbox"/> HEALTH PROFESSIONAL <input type="checkbox"/> OTHER:	
DATE OF THIS REPORT <b>13-AUG-2008</b>	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:	

(Continued on Additional Information Page)

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

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**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 unk, UNK; Unknown	METASTATIC BREAST CANCER (METASTATIC BREAST CANCER)	23-MAY-2008 / Unknown; Unknown

**25b. Name And Address of Reporters continued**

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**ADDITIONAL INFORMATION**

**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

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