



# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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**Date:** April 10, 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 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.

**252250\_10Apr2009**

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](mailto:Flickinger.lynn@mayo.edu) or 507-538-7034.

LF/kjm  
enclosure

# Genentech

IN BUSINESS FOR LIFE

Date: 5 November 2008

Evanthia Galanis, MD  
Mayo Clinic College of Medicine  
200 First Street SW  
Rochester, MN 55905

**RE: IND Safety Report/Expedited Case Safety Report**

Investigational Product(s): Bevacizumab

GNE MCN: **252250 Initial** Other Reference Number(s):

Dear Dr. Galanis,

Attached is a case summary of a serious and unexpected adverse drug reaction that occurred in a subject exposed to bevacizumab. Good Clinical Practice regulations require that you promptly submit a copy of this IND safety report/expedited case safety report to your Institutional Review Board or Independent Ethics Committee. File a copy of this IND safety report/expedited case safety report in your protocol file so that it is available for review during a Sponsor monitoring visit and/or regulatory audit.

In the European Economic Area (EEA) Genentech, Inc. or its designee will directly inform the Institutional Review Boards/Ethics Committees, as appropriate.

This IND safety report/expedited case safety report must be filed with your Investigator Brochure (IB) for information only. This IND safety report/expedited case safety report is not considered an addendum to your safety reference document.

Although this adverse event has been documented and reported to the appropriate Regulatory agencies, the report does not necessarily reflect a conclusion by Genentech or the Regulatory agencies that bevacizumab contributed to the adverse event.

If questions arise, please contact the undersigned.

Sincerely,



Eric Hedrick  
Medical Monitor  
AVF4271s  
AVF4430S

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

Mfr Report #	252250
UF/Importer Report #	
FDA Use Only	

**MEDWATCH**  
3500A Facsimile

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A. PATIENT INFORMATION			
1. Patient Identifier  In confidence	2. Age at Time of Event: 79 Years or Date of Birth:	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight 119.0 lbs or 54.0 kgs
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 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) 11/30/2007		4. Date of This Report (mm/dd/yyyy) 11/05/2008	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) T 8 compression fracture [SPINAL COMPRESSION FRACTURE]			
Case Description: This case, manufacturer control number 252250, is a report from the UNITED STATES referring to a 79-year-old female subject (ID# _____). An investigator reported this case from a Genentech-sponsored study AVF3694g (Eudract number 2006-000378-61), a multicenter, phase III, randomized placebo-controlled trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy regimens in subjects with previously untreated metastatic breast cancer.			
No past medical history, concomitant medications, allergies, or concurrent conditions were reported. continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates #1 11/30/2007 NUCLEAR MAGNETIC RE (continued) #2 12/01/2007 X-RAY (Continued)			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) Race: Caucasian #1 07/--/1996 to UNK Procedure, (Continued) #2 Historical Condition, OSTEOPOROSIS #3 Historical Condition, OSTEOPENIA continued in additional info section...			

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler)			
#1. BEVACIZUMAB OR PLACEBO (Bevacizumab) (Continued)			
#2. XELODA (CAPECITABINE)			
2. Dose, Frequency & Route Used		3. Therapy Dates (if unknown, give duration) from/to (or best estimate)	
#1. 880 mg, Q3W, Intravenous		#1. 05/08/2007 to UNK	
#2. 1300 mg, bid		#2. 05/08/2007 to UNK	
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced?	
#1. Metastatic breast (Continued)		#1. <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
#2. Metastatic breast (Continued)		#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
6. Lot #	7. Exp. Date	8. Event Reappeared After Reintroduction?	
#1. 22460, 22455	#1.	#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2.	#2.	#2. <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)			
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 650225591	
4. Date Received by Manufacturer (mm/dd/yyyy) 10/28/2008		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 # AVF3694G-B		3. Report Source (Check all that apply) <input type="checkbox"/> Foreign <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 checked="" type="checkbox"/> Initial <input checked="" type="checkbox"/> 15-day <input type="checkbox"/> Follow-up # _____		8. Adverse Event Term(s) SPINAL COMPRESSION FRACTURE	
9. Manufacturer Report Number 252250			
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.

**MEDWATCH**

3500A Facsimile (Back) (Continued)

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Mfr Report #	252250
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**ADDITIONAL INFORMATION****B5. EVENT DESCRIPTION (Continued)**

On 08-MAY-2007, the subject started treatment with BEVACIZUMAB OR PLACEBO (880 mg, Q3W, IV) and CAPECITABINE (1300 mg, bid, route not reported). The lot numbers for BEVACIZUMAB OR PLACEBO were reported as 22460 and 22455. The last dose of BEVACIZUMAB OR PLACEBO prior to the onset of the event was administered on 02-NOV-2007. The last dose of CAPECITABINE prior to the onset of the event was administered on 21-NOV-2007.

On 30-NOV-2007, the subject was hospitalized with compression fracture at T9 (COMPRESSION FRACTURE). Relevant laboratory tests included an MRI however results were not reported. Treatment for the event included a kyphoplasty. BEVACIZUMAB OR PLACEBO was held due to surgery. Action taken with CAPECITABINE was not reported.

On 02-DEC-2007, the subject recovered.

The Investigator assessed the event of COMPRESSION FRACTURE as not related to BEVACIZUMAB OR PLACEBO. In the reporter's opinion, other possible etiological factors included the disease under study.

Additional information has been requested.

**ADDITIONAL INFORMATION RECEIVED ON 17-JAN-2008:**

The subject's past medical history included OSTEOPOROSIS, OSTEOPENIA, COMPRESSION FRACTURE, and VITAMIN D DEFICIENCY.

The subject with severe osteoporosis and multiple compression fractures, was admitted for intractable pain and kyphoplasty. On 30-NOV-2007, MRI of the lower spine showed mild central canal narrowing at the L2-L3 and L3-L4 levels, moderate to severe central canal narrowing at the L4-L5 level, and moderate central canal narrowing at the L5-S1 level. Osteoporotic compression fractures were seen at the inferior aspect of T7, mid-T8, with an old kyphoplasty of T9. Findings in the thoracic spine were more compatible with osteoporotic compression fractures than metastatic disease. The subject underwent kyphoplasty of T7-T8 area with complete resolution of her pain. Further treatment included ACETAMINOPHEN/HYDROCODONE BITARTRATE and CYCLOBENZAPRINE HYDROCHLORIDE. On 01-DEC-2007, x-rays of the thoracic spine demonstrated kyphoplasty at three successive levels.

On 02-DEC-2008, the subject was discharged. CAPECITABINE resumption was planned for the 03-DEC-2007, with BEVACIZUMAB OR PLACEBO to be held for another three weeks.

No further information was expected.

**ADDITIONAL INFORMATION RECEIVED ON 28-OCT-2008:**

This case now qualifies for expedited reporting.

The event term was amended from COMPRESSION FRACTURE to COMPRESSION FRACTURE OF THE SPINE.

On 04-NOV-2008, the subject was unblinded and was found to be on active drug (Bevacizumab).

The Investigator assessed the event of COMPRESSION FRACTURE OF THE SPINE as related to Bevacizumab.

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

No further information was provided.

**ANALYSIS OF SIMILAR EVENTS**

Genentech has not filed previous IND safety reports of compression fracture of the spine or IND safety reports of similar events for subjects receiving bevacizumab.

Based on review of available data, the Sponsor cannot establish or exclude the possibility of a cause-and-effect relationship between administration of bevacizumab and the occurrence of compression fracture of the spine. The subject's history of osteoporosis, osteopenia, compression fracture and vitamin D deficiency are confounding factors.

**MEDWATCH**

3500A Facsimile (Back) (Continued)

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

**B6. LABORATORY DATA**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	11/30/2007	NUCLEAR MAGNETIC RESONANCE IMAGING		
MRI of the lower spine showed mild central canal narrowing at the L2-L3 and L3-L4 levels, moderate to severe central canal narrowing at the L4-L5 level, and moderate central canal narrowing at the L5-S1 level. Osteoporotic compression fractures were seen at the inferior aspect of T7, mid-T8, with an old kyphoplasty of T9. Findings in the thoracic spine were more compatible with osteoporotic compression fractures than metastatic disease.				
2	12/01/2007	X-RAY		
X-rays of the thoracic spine demonstrated kyphoplasty at three successive levels.				

**B7. OTHER RELEVANT HISTORY**

#	Start/Stop Date	Condition Type / Condition	Notes
1	07-/1996 UNK	Procedure HIP ARTHROPLASTY	right total hip replacement
4		Historical Condition COMPRESSION FRACTURE	T8
5	08-/2007 UNK	Procedure SURGERY	kyphoplasty
6		Historical Condition VITAMIN D DEFICIENCY	with need for replacement

**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)

<b>SUSPECT ADVERSE REACTION REPORT</b>	

**I. REACTION INFORMATION**

1. PATIENT INITIALS (first, last)	1a. COUNTRY <b>UNITED STATES</b>	2. DATE OF BIRTH			2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day	Month	Year	<b>79 Years</b>	<b>Female</b>	<b>53.97 kg</b>	Day	Month	Year	
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) <b>T 8 compression fracture [SPINAL COMPRESSION FRACTURE]</b>											<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
Case Description: This case, manufacturer control number 252250, is a report from the UNITED STATES referring to a 79-year-old female subject (ID# ). An investigator reported this case from a Genentech-sponsored study AVF3694g (Eudract number 2006-000378-61), a multicenter, phase III, randomized placebo-controlled trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy regimens in subjects with previously untreated metastatic breast cancer.											
(Continued on Additional Information Page)											

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

14. SUSPECT DRUG(S) (include generic name)		20. DID REACTION ABATE AFTER STOPPING DRUG?
#1 ) BEVACIZUMAB OR PLACEBO (Bevacizumab) Powder and solvent for solution for infusion, 100 mg (Lot # #2 ) XELODA (CAPECITABINE)		
15. DAILY DOSE(S)		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA
#1 ) 880 mg, Q3W #2 ) 1300 mg, bid		
16. ROUTE(S) OF ADMINISTRATION		21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
#1 ) Intravenous #2 ) Unknown		
17. INDICATION(S) FOR USE		<input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> NA
#1 ) Metastatic breast cancer (METASTAT #2 ) Metastatic breast cancer (METASTATIC BREAST CANCER)		
18. THERAPY DATES(from/to)		<input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> NA
#1 ) 08-MAY-2007 / Unknown #2 ) 08-MAY-2007 / 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
JUL-1996 to Unknown	Procedure	TOTAL HIP REPLACEMENT (HIP ARTHROPLASTY)
Unknown	right total hip replacement	
	Historical Condition	OSTEOPOROSIS (OSTEOPOROSIS)

**IV. MANUFACTURER INFORMATION**

24a. NAME AND ADDRESS OF MANUFACTURER		28. REMARKS
Genentech, Inc. James Nickas 1 DNA Way South San Francisco, CA 94080 UNITED STATES Phone: 6502255591		
24b. MFR CONTROL NO.		25b. NAME AND ADDRESS OF REPORTER
<b>252250</b>		
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE	
<b>28-OCT-2008</b>	<input checked="" type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input checked="" type="checkbox"/> HEALTH PROFESSIONAL <input type="checkbox"/> OTHER:	
DATE OF THIS REPORT	25a. REPORT TYPE	
<b>05-NOV-2008</b>	<input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:	

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

No past medical history, concomitant medications, allergies, or concurrent conditions were reported.

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

**ADDITIONAL INFORMATION**

**13. Lab Data**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	30-NOV-2007	NUCLEAR MAGNETIC RESONANCE IMAGING		
<p>MRI of the lower spine showed mild central canal narrowing at the L2-L3 and L3-L4 levels, moderate to severe central canal narrowing at the L4-L5 level, and moderate central canal narrowing at the L5-S1 level. Osteoporotic compression fractures were seen at the inferior aspect of T7, mid-T8, with an old kyphoplasty of T9. Findings in the thoracic spine were more compatible with osteoporotic compression fractures than metastatic disease.</p>				
2	01-DEC-2007	X-RAY		
<p>X-rays of the thoracic spine demonstrated kyphoplasty at three successive levels.</p>				

**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 # 22460, 22455}; Regimen #1	880 mg, Q3W; Intravenous	Metastatic breast cancer (METASTATIC BREAST CANCER)	08-MAY-2007 / Unknown; Unknown

**23. OTHER RELEVANT HISTORY continued**

From/To Dates	Type of History / Notes	Description
Unknown	Historical Condition	OSTEOPENIA (OSTEOPENIA);
Unknown	Historical Condition T8	COMPRESSION FRACTURE (COMPRESSION FRACTURE);
AUG-2007 to Unknown	Procedure kyphoplasty	SURGERY (SURGERY);
Unknown	Historical Condition with need for replacement	VITAMIN D DEFICIENCY (VITAMIN D DEFICIENCY);