



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: March 27, 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.

AE_252250_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

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

MEDWATCH
3500A Facsimile

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

A. PATIENT INFORMATION			
1. Patient Identifier In confidence	2. Age at Time of Event: <u>79</u> Years or Date of Birth:	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight <u>119.0</u> lbs or <u>54.0</u> 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: _____ <input type="checkbox"/> Disability or Permanent Damage <input type="checkbox"/> Life-threatening (mm/dd/yyyy) <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) <u>11/30/2007</u>		4. Date of This Report (mm/dd/yyyy) <u>11/18/2008</u>	
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 <u>11/30/2007 NUCLEAR MAGNETIC RE (continued)</u> #2 <u>12/01/2007 X-RAY (Continued)</u>			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) Race: <u>Caucasian</u> #1 <u>07/--/1996 to UNK Procedure, (Continued)</u> #2 <u>Historical Condition, OSTEOPOROSIS</u> #3 <u>Historical Condition, OSTEOPENIA</u> continued in additional info section...			

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler)			
#1. <u>BEVACIZUMAB OR PLACEBO (Bevacizumab) (Continued)</u>			
#2. <u>XELODA (CAPECITABINE)</u>			
2. Dose, Frequency & Route Used		3. Therapy Dates (if unknown, give duration) from/to (or best estimate)	
#1. <u>880 mg, Q3W, Intravenous</u>		#1. <u>05/08/2007 to UNK</u>	
#2. <u>1300 mg, bid</u>		#2. <u>05/08/2007 to UNK</u>	
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced?	
#1. <u>Metastatic breast (Continued)</u>		#1. <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
#2. <u>Metastatic breast (Continued)</u>		#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
6. Lot #		7. Exp. Date	
#1. <u>22460, 22455</u>		#1. _____	
#2. _____		#2. _____	
8. Event Reappeared After Reintroduction?			
#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply			
#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)		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) <u>11/07/2008</u>		5. (A)NDA # _____ IND # <u>BB 7023</u> 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 # <u>AVF3694G-B</u>		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 type="checkbox"/> Initial <input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up # <u>1</u>		9. Manufacturer Report Number <u>252250</u>	
		8. Adverse Event Term(s) <u>SPINAL COMPRESSION FRACTURE</u>	
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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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.

ADDITIONAL INFORMATION RECEIVED ON 07-NOV-2008:

The Investigator amended the causality assessment of the event of compression fracture of the spine to not related to Bevacizumab. No other possible etiological factors were reported.

Due to the change in the causality assessment, this event no longer qualifies for expedited reporting.

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

MEDWATCH

3500A Facsimile (Back) (Continued)

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Mfr Report #	252250
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No further information was available.

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.

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)

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY UNITED STATES	2. DATE OF BIRTH			2a. AGE 79 Years	3. SEX Female	3a. WEIGHT 53.97 kg	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION <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
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) 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.											
(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) XELODA (CAPECITABINE) (Continued on Additional Information Page)		20. DID REACTION ABATE AFTER STOPPING DRUG? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA
15. DAILY DOSE(S) #1) 880 mg, Q3W #2) 1300 mg, bid	16. ROUTE(S) OF ADMINISTRATION #1) Intravenous #2) Unknown	
17. INDICATION(S) FOR USE #1) Metastatic breast cancer (METASTAT #2) Metastatic breast cancer (METASTATIC BREAST CANCER) (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) 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	Historical Condition	right total hip replacement OSTEOPOROSIS (OSTEOPOROSIS)

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. 252250	
24c. DATE RECEIVED BY MANUFACTURER 07-NOV-2008	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 18-NOV-2008	25a. REPORT TYPE <input type="checkbox"/> INITIAL <input checked="" type="checkbox"/> FOLLOWUP: 1	
		25b. NAME AND ADDRESS OF REPORTER

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

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

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.

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ANALYSIS OF SIMILAR EVENTS

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

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

13. Lab Data

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2	01-DEC-2007	X-RAY		
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X-rays of the thoracic spine demonstrated kyphoplasty at three successive levels.

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);

ADDITIONAL INFORMATION

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
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