



# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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**Date:** April 3, 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.

### **263520\_F3\_03Apr2009**

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: 22 October 2008

Axel Grothey, MD  
Mayo Clinic  
200 First Street S.W.  
Rochester, MN 55905

→ APLB  
LL  
AG

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

Investigational Product(s): **Bevacizumab**

GNE MCN: **263520 Follow-Up #3** Other Reference Number(s):

Dear Dr. Grothey,

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  
AVF3918s AVF3870s

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

**MEDWATCH**  
3500A Facsimile

Mfr Report #	263520
UF/Importer Report #	
FDA Use Only	

**A. PATIENT INFORMATION**

1. Patient Identifier	2. Age at Time of Event: <b>58 Years</b> or Date of Birth:	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight <b>123.5</b> lbs or <b>56.0</b> kgs
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In confidence

**B. ADVERSE EVENT OR PRODUCT PROBLEM**

1.  Adverse Event and/or  Product Problem (e.g., defects/malfunctions)

2. Outcomes Attributed to Adverse Event (Check all that apply)

Death: 06/21/2008 (mm/dd/yyyy)  Disability or Permanent Damage

Life-threatening  Congenital Anomaly/Birth Defect

Hospitalization - initial or prolonged  Other Serious (Important Medical Events)

Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event (mm/dd/yyyy) 06/17/2008      4. Date of This Report (mm/dd/yyyy) 10/22/2008

5. Describe Event or Problem  
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)  
**gastrointestinal perforation [GASTROINTESTINAL PERFORATION]**

Case Description:  
**IND SAFETY REPORT**

This case, manufacturer control number 263520, is a report from SOUTH AFRICA referring to a 58-year-old Female subject (ID # ). An Investigator reported this case from Genentech-sponsored 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.

continued in additional info section...

6. Relevant Tests/Laboratory Data, Including Dates  
**#1 06/20/2008 COMPUTERISED TOMOGR (continued)**

7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)  
Race: Other

**C. SUSPECT PRODUCT(S)**

1. Name (Give labeled strength & mfr/labeler)  
**#1. BEVACIZUMAB OR PLACEBO (Bevacizumab) (Continued)**  
#2.

2. Dose, Frequency & Route Used      3. Therapy Dates (if unknown, give duration from/to (or best estimate))  
**#1. 840 mg, Q3W, Intravenous**      **#1. 01/03/2008 to UNK**  
#2.      #2.

4. Diagnosis for Use (Indication)      5. Event Abated After Use Stopped or Dose Reduced?  
**#1. metastatic breast (Continued)**      #1.  Yes  No  Doesn't Apply  
#2.      #2.  Yes  No  Doesn't Apply

6. Lot #      7. Exp. Date  
**#1. 9(Continued)**      #1.  
#2.      #2.

8. Event Reappeared After Reintroduction?  
#1.  Yes  No  Doesn't Apply  
#2.  Yes  No  Doesn't Apply

9. NDC# or Unique ID

10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)  
**#1. XELODA (CAPECITABINE) 01/03/2008 to UNK**

**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)  
 Foreign ZAF  
 Study  
 Literature  
 Consumer  
 Health Professional  
 User Facility  
 Company Representative  
 Distributor  
 Other:

4. Date Received by Manufacturer (mm/dd/yyyy)  
**10/14/2008**

5. (A)NDA #  
IND # **BB 7023**  
STN #  
PMA/510(k) #  
Combination Product  Yes  
Pre-1938  Yes  
OTC Product  Yes

6. If IND, Give Protocol #  
**AVF3693G**

7. Type of Report (Check all that apply)  
 5-day  30-day  
 7-day  Periodic  
 10-day  Initial  
 15-day  Follow-up #3

9. Manufacturer Report Number  
**263520**

8. Adverse Event Term(s)  
**GASTROINTESTINAL PERFORATION**

**E. INITIAL REPORTER**

1. Name and Address      Phone #

2. Health Professional?      3. Occupation      4. Initial Reporter Also Sent Report to FDA  
 Yes  No       Yes  No  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 #	263520
UF/Importer Report #	
	FDA Use Only

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

On 03-JAN-2008, the subject received BEVACIZUMAB OR PLACEBO (840 mg, Q3W, Intravenous). Concomitant chemotherapy included capecitabine. The last dose of capecitabine administered prior to the event was 16-APR-2008. The last dose of bevacizumab or placebo administered prior to the event was 28-May-2008. The lot number for bevacizumab or placebo was reported as 912202 and 912207.

On 21-JUN-2008, the subject experienced unexplained death (DEATH UNEXPLAINED). No relevant laboratory tests were reported. Treatment was not reported and action taken with bevacizumab or placebo was not applicable.

It was unknown as to whether an autopsy was performed.

The Investigator did not provide a causality assessment of the event DEATH UNEXPLAINED in relation to BEVACIZUMAB OR PLACEBO. No other etiological factors were reported.

On 30-JUN-2008, the subject was unblinded and found to be on bevacizumab.

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

Additional follow-up is being requested. If received, the case will be updated accordingly.

**ADDITIONAL INFORMATION RECEIVED ON 22-JUL-2008:**

It was reported that the subject may have experienced a gastrointestinal perforation based on the investigator's conversation with the subject's sister.

At the time of this report, the investigator was awaiting receipt of additional information regarding the event.

Additional follow-up is being requested. If received, the case will be updated accordingly.

**ADDITIONAL INFORMATION RECEIVED ON 25-AUG-2008:**

The event term was amended to gastrointestinal perforation. This case no longer qualifies as an expedited report.

On 20-JUN-2008, a CT scan of the abdomen was done which revealed perforated bowel.

On 21-JUN-2008, the subject died due to septic shock. The surgeon confirmed no evidence of intra-abdominal metastatic disease. Single perforation was noted in the small bowel +/- 10cm proximal to the ileo-cecal junction.

The investigator assessed the event of gastrointestinal perforation as related to bevacizumab. No other etiological factors were reported.

No further information was available.

**14-OCT-2008: AFTER FURTHER REVIEW OF THE CASE ADDITIONAL CLARIFICATION IS REQUIRED.**

The statement, previously entered as "On 21-JUN-2008, the subject experienced unexplained death (DEATH UNEXPLAINED)," should read: "On 17-JUN-2008, the subject experienced unexplained death (DEATH UNEXPLAINED)."

No further information was available.

**PREVIOUSLY FILED IND SAFETY REPORTS OF SIMILAR EVENTS**

Genentech has previously filed IND safety reports of similar events of death unexplained from studies of BEVACIZUMAB.

Manufacturer control number~ISR Primary event term~~~Date submitted

218003~unexplained death~4-Oct-05

249106~unexplained death~16-Oct-07

255141~unexplained death~7-Feb-08

**MEDWATCH**

3500A Facsimile (Back) (Continued)

Mfr Report #	263520
UF/Importer Report #	
FDA Use Only	

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257362~unexplained death~14-Mar-08  
 258964~death cause unknown~16-Apr-08  
 257362~unexplained death~8-May-08

Based on review of available data, the Sponsors cannot establish or exclude the possibility of a cause-and-effect relationship between administration of BEVACIZUMAB and the occurrence of death unexplained.

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

**Pharmacovigilance:**

DEATH is unlabeled and unexpected per bevacizumab USPI and IB, respectively. Additional information including past medical history, concurrent illness, concomitantly administered medications and autopsy report, if performed, would be helpful in providing a clinically meaningful assessment of causality. Confounders include the underlying cancer complicated with gastrointestinal perforation which is a labeled event.

The event term was amended to GASTROINTESTINAL PERFORATION which is labeled and expected per the Avastin USPI and IB respectively. The concomitant treatment with Capecitabine is a possible contributing factor. This case no longer qualifies as an expedited report.

**B6. LABORATORY DATA**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	06/20/2008	COMPUTERISED TOMOGRAPHY  perforated bowel	see notes	

**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)

**C6. LOT# (Continued)**

Suspect Medication #1: 912202, 912207

<b>SUSPECT ADVERSE REACTION REPORT</b>	

**I. REACTION INFORMATION**

1. PATIENT INITIALS (first, last)	1a. COUNTRY <b>SOUTH AFRICA</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	58 Years	Female	56.00 kg	Day	Month	Year	
								17	JUN	2008	
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) <b>gastrointestinal perforation [GASTROINTESTINAL PERFORATION]</b>											<input checked="" type="checkbox"/> PATIENT DIED Date: 21-JUN-2008  <input type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION  <input type="checkbox"/> INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY  <input type="checkbox"/> LIFE THREATENING
Case Description: <b>IND SAFETY REPORT</b>											
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(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 # (Continued on Additional Information Page)		20. DID REACTION ABATE AFTER STOPPING DRUG?  <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> NA
15. DAILY DOSE(S) #1 ) 840 mg, Q3W	16. ROUTE(S) OF ADMINISTRATION #1 ) Intravenous	
17. INDICATION(S) FOR USE #1 ) metastatic breast cancer (METASTATI (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 ) 03-JAN-2008 / Unknown	19. THERAPY DURATION #1 ) Unknown	

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

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) #1 ) XELODA (CAPECITABINE) ; 03-JAN-2008 / Unknown		
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>263520</b>	
24c. DATE RECEIVED BY MANUFACTURER <b>14-OCT-2008</b>	24d. REPORT SOURCE <input checked="" type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input checked="" type="checkbox"/> HEALTH PROFESSIONAL <input type="checkbox"/> OTHER:	25b. NAME AND ADDRESS OF REPORTER
DATE OF THIS REPORT <b>22-OCT-2008</b>	25a. REPORT TYPE <input type="checkbox"/> INITIAL <input checked="" type="checkbox"/> FOLLOWUP: 3	

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

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255141~unexplained death~7-Feb-08  
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258964~death cause unknown~16-Apr-08  
257362~unexplained death~8-May-08

Based on review of available data, the Sponsors cannot establish or exclude the possibility of a cause-and-effect relationship between administration of BEVACIZUMAB and the occurrence of death unexplained.

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

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Pharmacovigilance: DEATH is unlabeled and unexpected per bevacizumab USPI and IB, respectively. Additional information including past medical history, concurrent illness, concomitantly administered medications and autopsy report, if performed, would be helpful in providing a clinically meaningful assessment of causality. Confounders include the underlying cancer complicated with gastrointestinal perforation which is a labeled event.

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**13. Lab Data**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	20-JUN-2008	COMPUTERISED TOMOGRAM	see notes	
		perforated bowel		

**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 # 912202, 912207}; Regimen #1	840 mg, Q3W; Intravenous	metastatic breast cancer (METASTATIC BREAST CANCER)	03-JAN-2008 / Unknown; Unknown