



# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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**Date:** April 10, 2009

**To:** NCCTG Primary Clinical Research Associates

**From:** Alicia Elsing  
Protocol Development Coordinator

**Re:** N0821, A Phase II First-Line Study of a Combination of Pemetrexed, Carboplatin and Bevacizumab in Advanced Nonsquamous NSCLC Evaluating Efficacy and Tolerability in Elderly Patients (Age  $\geq$ 70 yrs) with Good Performance Status (PS  $<$ 2)

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.

**272529\_F1\_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 Alicia Elsing at [Elsing.alicia@mayo.edu](mailto:Elsing.alicia@mayo.edu) or 507-538-3893.

AE/kjm  
enclosure

# Genentech

IN BUSINESS FOR LIFE

Date: 23 December 2008

Evanthia Galanis, MD.  
Mayo Clinic  
200 First Street SW  
Rochester, MN 55905

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

Investigational Product(s): **Bevacizumab**

GNE MCN: **272529 Follow-Up #1** 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



CC: AVF4271s

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

**MEDWATCH**  
3500A Facsimile

Mfr Report #	272529
UF/Importer Report #	
FDA Use Only	

A. PATIENT INFORMATION			
1. Patient Identifier	2. Age at Time of Event: 51 Years or Date of Birth:	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight _____ lbs or _____ 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: _____		<input type="checkbox"/> Disability or Permanent Damage	
<input checked="" 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) 11/26/2008		4. Date of This Report (mm/dd/yyyy) 12/23/2008	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) acute stomach ulcer, complicated gastric bleeding [GASTRIC ULCER]			
Case Description: IND SAFETY REPORT			
This case, manufacturer control number 272529, is a report from Russian Federation referring to a 51 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 18-MAR-2008, the subject received bevacizumab or placebo, continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates #1 11/26/2008 ENDOSCOPY UPPER GAS (continued)			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)			

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler) #1. BEVACIZUMAB OR PLACEBO (Bevacizumab) (Continued) #2.			
2. Dose, Frequency & Route Used #1. 1215 mg, Q3W, Intravenous #2.		3. Therapy Dates (if unknown, give duration) from/to (or best estimate) #1. 03/18/2008 to UNK #2.	
4. Diagnosis for Use (Indication) #1. metastatic breast (Continued) #2.		5. Event Abated After Use Stopped or Dose Reduced? #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 type="checkbox"/> Doesn't Apply	
6. Lot # #1. 9(Continued) #2.	7. Exp. Date #1. #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 type="checkbox"/> Doesn't Apply	
9. NDC# or Unique ID			
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event) #1. DOCETAXEL (DOCETAXEL) 03/18/2008 to 09/23/2008			
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	
4. Date Received by Manufacturer(mm/dd/yyyy) 12/16/2008		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 RUS <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 #1 _____		8. Adverse Event Term(s) GASTRIC ULCER	
9. Manufacturer Report Number 272529			
E. INITIAL REPORTER			
1. Name and Address		Phone #	
2. Health Professional? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	3. Occupation	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 #	272529
UF/Importer Report #	
	FDA Use Only

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

(1215 mg, Q3W, Intravenous) and Docetaxel, (144 mg, frequency and route not reported),. The lot number of bevacizumab was 910162; 910232. The last dose of bevacizumab prior to the event was administered on 06-NOV-2008. The last dose of docetaxel prior to the event was administered on 23-SEP-2008.

On 26-NOV-2008, the subject experienced life threatening, grade 3, acute ulcer of gastric, complicated gastric bleeding (GASTRIC ULCER) and was subsequently hospitalized. Relevant diagnostic evaluations included esophagogastroscopy which revealed acute ulcer of gastric, complicated gastric bleeding. Treatment included unspecified medication. Action with study medication was not reported.

At the time of the report, the event remained ongoing.

On 02-DEC-2008, the subject was unblinded and found to be on bevacizumab.

The Investigator assessed the event gastric ulcer as related to bevacizumab. In the reporter's opinion, no other possible etiological factors were included.

Additional information requested. If available, the case will updated accordingly.

ON 04-DEC-2008: AFTER FURTHER REVIEW OF THE REPORT, ADDITIONAL CLARIFICATION IS REQUIRED.

The subject's initials were updated to UNKNOWN and the date of esophagogastroscopy was updated to 26-NOV-2008 in the safety database. Docetaxel was updated from suspect medication to concomitant medication.

**ADDITIONAL INFORMATION RECEIVED 16-DEC-2008**

The event term was updated to stomach ulcer (Gastric Ulcer) and the grade of the event was updated to grade 4.

There was no action taken with bevacizumab in regard to the event.

On 24-NOV-2008 the subject was hospitalized to chemotherapy department for planned examinations. On 26-NOV-2008 the subject was transferred to the intensive care unit for treatment of this event.

On 12-DEC-2008, the subject died and the event resolved.

The investigator assessed the event as related to bevacizumab.

Additional information has been requested, if received the case will be updated accordingly.

**ANALYSIS OF SIMILAR EVENTS**

Genentech has not filed previous IND safety reports of GASTRIC ULCER, ULCER GASTRIC or IND safety reports of similar events for subjects receiving bevacizumab.

**SPONSOR ASSESSMENT**

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 GASTRIC ULCER, ULCER GASTRIC.

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

**B6. LABORATORY DATA**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	11/26/2008	ENDOSCOPY UPPER GASTROINTESTINAL TRACT	SEE NOTES	
		ACUTE ULCER OF GASTRIC, COMPLICATED GASTRIC BLEEDING		

**MEDWATCH**

3500A Facsimile (Back) (Continued)

Mfr Report #	272529
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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)

C6. LOT# (Continued)

Suspect Medication #1: 910162; 910232



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

On 18-MAR-2008, the subject received bevacizumab or placebo, (1215 mg, Q3W, Intravenous) and Docetaxel, (144 mg, frequency and route not reported). The lot number of bevacizumab was 910162; 910232. The last dose of bevacizumab prior to the event was administered on 06-NOV-2008. The last dose of docetaxel prior to the event was administered on 23-SEP-2008.

On 26-NOV-2008, the subject experienced life threatening, grade 3, acute ulcer of gastric, complicated gastric bleeding (GASTRIC ULCER) and was subsequently hospitalized. Relevant diagnostic evaluations included esophagogastroscopy which revealed acute ulcer of gastric, complicated gastric bleeding. Treatment included unspecified medication. Action with study medication was not reported.

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**ANALYSIS OF SIMILAR EVENTS**

Genentech has not filed previous IND safety reports of GASTRIC ULCER, ULCER GASTRIC or IND safety reports of similar events for subjects receiving bevacizumab.

**SPONSOR ASSESSMENT**

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 GASTRIC ULCER, ULCER GASTRIC.

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

**13. Lab Data**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	26-NOV-2008	ENDOSCOPY UPPER GASTROINTESTINAL TRACT	SEE NOTES	
		ACUTE ULCER OF GASTRIC, COMPLICATED GASTRIC BLEEDING		

**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
#1 ) BEVACIZUMAB OR PLACEBO (Bevacizumab) Powder and solvent for solution for infusion, 100 mg {Lot # 910162; 910232}; Regimen #1	1215 mg, Q3W; Intravenous	metastatic breast cancer (METASTATIC BREAST CANCER)	18-MAR-2008 / Unknown; Unknown