



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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.

266802_F2_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 or 507-538-7034.

LF/kjm
enclosure

Genentech

IN BUSINESS FOR LIFE

Date: 20 October 2008

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

⇒ APLB

dc

AG

RE: IND Safety Report/Expedited Case Safety Report

Investigational Product(s): **Bevacizumab**

GNE MCN: **266802 Follow-Up #2** 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

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Mfr Report #	266802
UF/Importer Report #	
FDA Use Only	

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event: 55 Years or Date of Birth:	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight 121.0 lbs or 54.9 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)

<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) 08/20/2008	4. Date of This Report (mm/dd/yyyy) 10/15/2008
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5. Describe Event or Problem
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)
congestive heart failure with elevated troponin [CARDIAC FAILURE CONGESTIVE]

Case Description:
IND SAFETY REPORT

This case, manufacturer control number 266802, is a report from United States referring to a 55 year-old female subject (ID # _____). An Investigator reported this case from study AVF3744G, A phase II Non-small cell lung cancer/squamous cell study

Past medical treatments included paclitaxel and carboplatin. Medical history included chronic obstructive pulmonary disease. Concomitant medications included acetaminophen, hydrocodone continued in additional info section...

6. Relevant Tests/Laboratory Data, Including Dates

- #1 08/22/2008 BLOOD CREATINE PHOS (continued)
- #2 08/22/2008 CARDIAC ENZYMES (continued)
- #3 08/23/2008 ECHOCARDIOGRAM (continued)
- #4 08/20/2008 ELECTROCARDIOGRAM (continued)
- #5 08/25/2008 INVESTIGATION (continued)
- #6 08/20/2008 TROPONIN I (continued)

continued in additional info section...

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

- #1 Negative Med Cond, SMOKER
- #2 Negative Med Cond, DRUG ABUSE
- #3 Historical Condition, (Continued)

continued in additional info section...

C. SUSPECT PRODUCT(S)

1. Name (Give labeled strength & mfr/labeler)

#1. Avastin (BEVACIZUMAB) Powder and solvent for solution (Continued)

#2.

2. Dose, Frequency & Route Used	3. Therapy Dates (if unknown, give duration) from/to (or best estimate)
#1. 880 mg, Q3W, Intravenous	#1. 01/09/2008 to UNK
#2.	#2.

4. Diagnosis for Use (Indication)	5. Event Abated After Use Stopped or Dose Reduced?
#1. NSCLC (NSCLC)	#1. <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Doesn't Apply
#2.	#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply
6. Lot #	7. Exp. Date
#1. 703976	#1.
#2.	#2.
9. NDC# or Unique ID	
#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	

10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

#1. VICODIN (ACETAMINOPHEN, HYDROCODONE BITARTRATE) continued in additional info section...

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 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: _____	

4. Date Received by Manufacturer (mm/dd/yyyy) 10/07/2008	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 # AVF3744G	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 #2

9. Manufacturer Report Number 266802	8. Adverse Event Term(s) CARDIAC FAILURE CONGESTIVE
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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
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Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

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

bitartrate, fluticasone propionate, salmeterol xinafoate, oxycodone hydrochloride, and tiotropium bromide. Allergies reported included drug hypersensitivity to codeine, sulfa, and methocarbamol.

On 09-JAN-2008, the subject received bevacizumab (880 mg, Q3W, Intravenous). The lot number was #703976. The last dose prior to the event was administered on 06-AUG-2008.

On an unknown date, the subject presented with weakness and shortness of breath. On 20-AUG-2008, the subject hospitalized with troponin leak (TROPONIN INCREASED). Relevant laboratory tests included troponin I of 1.125. On 21-AUG-2008, troponin I was 0.450. EKG revealed a sinus bradycardia left axis deviation poor R progression anterior lead, no ectopy or arrhythmia. Chest x-ray was negative. The treatment for the event included sodium chloride. Treatment with Bevacizumab was held.

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

The Investigator assessed the event troponin increased as related to Bevacizumab. No other possible etiological factors were reported.

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

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

ADDITIONAL INFORMATION RECEIVED ON 28-AUG-2008:

On 22-AUG-2008, relevant laboratory tests included elevated CK 201 U/L (normal range 30-135), CKMB 8.8 ng/mL (normal range 0.1-3.2), troponin I ES 2.54 ng/mL (normal range 0.0-0.034). Relevant diagnostic tests included the following: echocardiogram done on 23-AUG-2008 that revealed an estimated ejection fraction 25-30%, moderate global hypokinesis of the left ventricle, and the mid-inferior, apical anterior, apical inferior, and apical wall segments were hypokinetic and a cardiac catheterization done on 25-AUG-2008 that revealed findings of normal coronaries with severely depressed left ventricular systolic function (LV ejection fraction 34%) probably secondary to chemotherapy.

No further information is available.

ADDITIONAL INFORMATION RECEIVED ON 07-OCT-2008:

This case no longer qualifies for expedited reporting.

Event term was amended from TROPONIN INCREASED to CONGESTIVE HEART FAILURE.

Treatment included enoxaparin sodium, simvastatin, and pantoprazole.

On 26-AUG-2008, the event was resolved and the subject was discharged from the hospital.

The Investigator assessed the event CONGESTIVE HEART FAILURE as related to Bevacizumab. No other possible etiological factors were reported.

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

PREVIOUSLY FILED IND SAFETY REPORTS OF SIMILAR EVENTS

Genentech has not filed previous IND safety reports of troponin leak or IND safety reports of similar events for subjects receiving bevacizumab.

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 troponin leak.

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

Pharmacovigilance:

MEDWATCH

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Congestive cardiac failure is listed and labeled per the bevacizumab IB and USPI. The patient's underlying cancer, concomitant medications, and chronic obstructive pulmonary disease are possible confounding factors. The event occurred 15 days after the last bevacizumab administration suggesting a causal association cannot be excluded.

B6. LABORATORY DATA

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	08/22/2008	BLOOD CREATINE PHOSPHOKINASE INCREASED	201 U/L	135 30
2	08/22/2008	CARDIAC ENZYMES	8.8 ng/mL	3.2 0.1
3	08/23/2008	ECHOCARDIOGRAM revealed an estimated ejection fraction 25-30%, moderate global hypokinesis of the left ventricle, and the mid-inferior, apical anterior, apical inferior, and apical wall segments were hypokinetic	see notes	
4	08/20/2008	ELECTROCARDIOGRAM sinuse bradycardia lt axis deviation poor r progression anterior lead no ectopy or arrythmia.	see notes	
5	08/25/2008	INVESTIGATION cardiac catheterization revealed an estimated ejection fraction 25-30%, moderate global hypokinesis of the left ventricle, and the mid-inferior, apical anterior, apical inferior, and apical wall segments were hypokinetic	see notes	
6	08/20/2008	TROPONIN I	1.125 ng/mL	0.034 0.0
7	08/21/2008	TROPONIN I	0.45 ng/mL	0.034 0.0
8	08/22/2008	TROPONIN I	2.54 ng/mL	0.034 0.0
9	08/20/2008	X-RAY Negative no infiltrates, no pneumothorax, no hemothorax, no masses, no cardiomegaly, no CHF, no effusion, no free air.	see notes	
10	08/22/2008	TROPONIN T Elevated	0.18 ng/mL	<0.01

B7. OTHER RELEVANT HISTORY

#	Start/Stop Date	Condition Type / Condition	Notes
3		Historical Condition CHRONIC OBSTRUCTIVE PULMONARY DISEASE	
4		Historical Drug PACLITAXEL; Drug Indication: DRUG USE FOR UNKNOWN INDICATION	
5		Historical Drug CARBOPLATIN; Drug Indication: DRUG USE FOR UNKNOWN INDICATION	

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6 Allergy Codeine and Methocarbamol.
DRUG HYPERSENSITIVITY

7 Allergy
DRUG HYPERSENSITIVITY

C1. NAME (Continued)

Suspect Medication #1: Avastin(BEVACIZUMAB) Powder and solvent for solution for infusion, 100mg

C10. CONCOMITANT MEDICAL PRODUCTS (Continued)

#2. ADVAIR DISKUS (FLUTICASONE PROPIONATE, SALMETEROL XINAFOATE)

#3. OXYCONTIN (OXYCODONE HYDROCHLORIDE)

#4. SPIRIVA (TIOTROPIUM BROMIDE)

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY UNITED STATES	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	55 Years	Female	54.88 kg	Day Month Year 20 AUG 2008	<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) congestive heart failure with elevated troponin [CARDIAC FAILURE CONGESTIVE] Case Description: IND SAFETY REPORT This case, manufacturer control number 266802, is a report from United States referring to a 55 year-old female subject (ID #). An Investigator reported this case from study AVF3744G, A phase II Non-small cell lung cancer/squamous cell study							
(Continued on Additional Information Page)							

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name) #1) Avastin (BEVACIZUMAB) Powder and solvent for solution for infusion, 100 mg {Lot # 703976}		20. DID REACTION ABATE AFTER STOPPING DRUG? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> NA
15. DAILY DOSE(S) #1) 880 mg, Q3W	18. ROUTE(S) OF ADMINISTRATION #1) Intravenous	
17. INDICATION(S) FOR USE #1) NSCLC (NSCLC)		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) 09-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) VICODIN (ACETAMINOPHEN, HYDROCODONE BITARTRATE) ; Unknown #2) ADVAIR DISKUS (FLUTICASONE PROPIONATE, SALMETEROL XINAFOATE) ; Unknown #3) OXYCONTIN (OXYCODONE HYDROCHLORIDE) ; Unknown #4) SPIRIVA (TIOTROPIUM BROMIDE) ; 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	Negative Med Cond	SMOKER (SMOKER)
Unknown	Negative Med Cond	DRUG ABUSE (DRUG ABUSE)

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. 266802	
24c. DATE RECEIVED BY MANUFACTURER 07-OCT-2008	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 15-OCT-2008	25a. REPORT TYPE <input type="checkbox"/> INITIAL <input checked="" type="checkbox"/> FOLLOWUP: 2	

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

Past medical treatments included paclitaxel and carboplatin. Medical history included chronic obstructive pulmonary disease. Concomitant medications included acetaminophen, hydrocodone bitartrate, fluticasone propionate, salmeterol xinafoate, oxycodone hydrochloride, and tiotropium bromide. Allergies reported included drug hypersensitivity to codeine, sulfa, and methocarbamol.

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Pharmacovigilance: Congestive cardiac failure is listed and labeled per the bevacizumab IB and USPI. The patient's underlying cancer, concomitant medications, and chronic obstructive pulmonary disease are possible confounding factors. The event occurred 15 days after the last bevacizumab administration suggesting a causal association cannot be excluded.

ADDITIONAL INFORMATION**13. Lab Data**

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3	23-AUG-2008	ECHOCARDIOGRAM	see notes	
		revealed an estimated ejection fraction 25-30%, moderate global hypokinesis of the left ventricle, and the mid-inferior, apical anterior, apical inferior, and apical wall segments were hypokinetic		
4	20-AUG-2008	ELECTROCARDIOGRAM	see notes	
		sinuse bradycardia lt axis deviation poor r progression anterior lead no ectopy or arrhythmia.		
5	25-AUG-2008	INVESTIGATION	see notes	
		cardiac catheterization revealed an estimated ejection fraction 25-30%, moderate global hypokinesis of the left ventricle, and the mid-inferior, apical anterior, apical inferior, and apical wall segments were hypokinetic		
6	20-AUG-2008	TROPONIN I	1.125 ng/mL	0.034 0.0
7	21-AUG-2008	TROPONIN I	0.45 ng/mL	0.034 0.0
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9	20-AUG-2008	X-RAY Negative no infiltrates, no pneumothorax, no hemothorax, no masses, no cardiomegaly, no CHF, no effusion, no free air.	see notes	
10	22-AUG-2008	TROPONIN T Elevated	0.18 ng/mL	<0.01

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Historical Condition	COPD (CHRONIC OBSTRUCTIVE PULMONARY DISEASE);
Unknown	Historical Drug	(PACLITAXEL); Drug Indication: DRUG USE FOR UNKNOWN INDICATION (DRUG USE FOR UNKNOWN INDICATION), Drug Reaction: ()
Unknown	Historical Drug	(CARBOPLATIN); Drug Indication: DRUG USE FOR UNKNOWN INDICATION (DRUG USE FOR UNKNOWN INDICATION), Drug Reaction: ()
Unknown	Allergy Codeine and Methocarbamol.	DRUG ALLERGY (DRUG HYPERSENSITIVITY);
Unknown	Allergy	SULFONAMIDE ALLERGY (DRUG HYPERSENSITIVITY);