



# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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**Date:** October 17, 2008

**To:** NCCTG Primary Clinical Research Associates

**From:** Janis Wobschall

**Re:** N0776, Phase II Trial of Avastin® in Combination with Sorafenib in Recurrent Glioblastoma Multiforme

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\_266802**

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 Janis Wobschall at [wobschall.janis@mayo.edu](mailto:wobschall.janis@mayo.edu) or 507-284-4852.

JW/kjm  
enclosure

# Genentech

IN BUSINESS FOR LIFE

Date: 3 September 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: **266802 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

**MEDWATCH**  
3500A Facsimile

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

<b>A. PATIENT INFORMATION</b>			
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
In confidence			
<b>B. ADVERSE EVENT OR PRODUCT PROBLEM</b>			
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) 08/20/2008		4. Date of This Report (mm/dd/yyyy) 08/29/2008	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) troponin leak [TROPONIN INCREASED]			
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 bitartrate, fluticasone propionate, salmeterol xinafoate, continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates #1 08/20/2008 ELECTROCARDIOGRAM (continued) #2 08/20/2008 TROPONIN I (continued) #3 08/21/2008 TROPONIN I (continued) #4 08/20/2008 X-RAY see notes (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 Negative Med Cond, SMOKER #2 Negative Med Cond, DRUG ABUSE #3 Historical Condition, (Continued) continued in additional info section...			

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

<b>C. SUSPECT PRODUCT(S)</b>			
1. Name (Give labeled strength & mfr/labeler) #1. Avastin (BEVACIZUMAB) Powder and solvent for solution (Continued) #2.			
2. Dose, Frequency & Route Used #1. 880 mg, Q3W, Intravenous #2.		3. Therapy Dates (if unknown, give duration) from/to (or best estimate) #1. 01/09/2008 to UNK #2.	
4. Diagnosis for Use (Indication) #1. NSCLC (NSCLC) #2.		5. Event Abated After Use Stopped or Dose Reduced? #1. <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Doesn't Apply #2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
6. Lot # #1. 703976 #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. VICODIN (ACETAMINOPHEN, HYDROCODONE BITARTRATE) continued in additional info section...			
<b>G. ALL MANUFACTURERS</b>			
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) 08/22/2008		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		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 #			
9. Manufacturer Report Number 266802		8. Adverse Event Term(s) TROPONIN INCREASED	
<b>E. INITIAL REPORTER</b>			
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

**MEDWATCH**

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Mfr Report #	266802
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**ADDITIONAL INFORMATION****B5. EVENT DESCRIPTION (Continued)**

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.

**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.

**B6. LABORATORY DATA**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	08/20/2008	ELECTROCARDIOGRAM  sinuse bradycardia lt axis deviation poor r progression anterior lead no ectopy or arrhythmia.	see notes	
2	08/20/2008	TROPONIN I	1.125 ng/mL	0.034 0.0
3	08/21/2008	TROPONIN I	0.45 ng/mL	0.034 0.0
4	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	

**B7. OTHER RELEVANT HISTORY**

#	Start/Stop Date	Condition Type / Condition	Notes
3		Historical Condition CHRONIC OBSTRUCTIVE PULMONARY DISEASE	

**MEDWATCH**

3500A Facsimile (Back) (Continued)

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Mfr Report #	266802
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4	Historical Drug PACLITAXEL; Drug Indication: DRUG USE FOR UNKNOWN INDICATION
5	Historical Drug CARBOPLATIN; Drug Indication: DRUG USE FOR UNKNOWN INDICATION
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)

<b>SUSPECT ADVERSE REACTION REPORT</b>	

**I. REACTION INFORMATION**

1. PATIENT INITIALS (first, last)	1a. COUNTRY <b>UNITED STATES</b>	2. DATE OF BIRTH Day Month Year	2a. AGE <b>55 Years</b>	3. SEX <b>Female</b>	3a. WEIGHT <b>54.88 kg</b>	4-6 REACTION ONSET Day Month Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) <b>troponin leak [TROPONIN INCREASED]</b>  Case Description: <b>IND SAFETY REPORT</b>  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.							<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
(Continued on Additional Information Page)							

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

14. SUSPECT DRUG(S) (include generic name) <b>#1 ) Avastin (BEVACIZUMAB) Powder and solvent for solution for infusion, 100 mg {Lot # 703976}</b>	20. DID REACTION ABATE AFTER STOPPING DRUG?  <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> NA
15. DAILY DOSE(S) <b>#1 ) 880 mg, Q3W</b>	16. ROUTE(S) OF ADMINISTRATION <b>#1 ) Intravenous</b>
17. INDICATION(S) FOR USE <b>#1 ) NSCLC (NSCLC)</b>	21. DID REACTION REAPPEAR AFTER REINTRODUCTION?  <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> NA
18. THERAPY DATES(from/to) <b>#1 ) 09-JAN-2008 / Unknown</b>	19. THERAPY DURATION <b>#1 ) Unknown</b>

**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 <b>Genentech, Inc. James Nickas 1 DNA Way South San Francisco, CA 94080 UNITED STATES Phone: 6502255591</b>	26. REMARKS
24b. MFR CONTROL NO. <b>266802</b>	25b. NAME AND ADDRESS OF REPORTER
24c. DATE RECEIVED BY MANUFACTURER <b>22-AUG-2008</b>	
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 <b>29-AUG-2008</b>	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:

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

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.

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.

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**13. Lab Data**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
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2	20-AUG-2008	TROPONIN I	1.125 ng/mL	0.034 0.0
3	21-AUG-2008	TROPONIN I	0.45 ng/mL	0.034 0.0
4	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	

**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

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**ADDITIONAL INFORMATION**

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**23. OTHER RELEVANT HISTORY continued**

From/To Dates	Type of History / Notes	Description
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Reaction: ()

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**ADDITIONAL INFORMATION**

**23. OTHER RELEVANT HISTORY continued**

From/To Dates	Type of History / Notes	Description
Unknown	Allergy	SULFONAMIDE ALLERGY (DRUG HYPERSENSITIVITY);