



# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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**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\_273064**

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

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

**MEDWATCH**  
3500A Facsimile

Mfr Report #	273064
UF/Importer Report #	
FDA Use Only	

A. PATIENT INFORMATION			
1. Patient Identifier	2. Age at Time of Event: 78 Years or Date of Birth:	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 152.6 lbs or 69.2 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 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) 12/04/2008		4. Date of This Report (mm/dd/yyyy) 12/18/2008	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) cardiac bundle block branch, axis deviation, bradycardia, cardiac disease [BUNDLE BRANCH BLOCK]  Case Description: IND SAFETY REPORT  This case, manufacturer control number 273064, is a report from UNITED STATES referring to a 78-year-old Male subject (ID # _____). An Investigator reported this case from Genentech-sponsored study AVF3671G-B, a randomized, double-blind, placebo-controlled, phase IIIb trial comparing bevacizumab therapy with or without erlotinib after completion of chemotherapy with bevacizumab for the first-line treatment of locally advanced or metastatic non-squamous non-small cell lung cancer. continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates #1 12/03/2008 ELECTROCARDIOGRAM (continued)			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) Race: Caucasian			

C. SUSPECT PRODUCT(S)	
1. Name (Give labeled strength & mfr/labeler)	
#1. ERLOTINIB OR PLACEBO (Code Not Broken) Tablet	
#2. Avastin (BEVACIZUMAB) Powder and solvent for solution (Continued)	
2. Dose, Frequency & Route Used	3. Therapy Dates (if unknown, give duration) from/to (or best estimate)
#1. 100 mg, qd, Oral	#1. 03/06/2008 to Ongoing
#2. UNK, Intravenous	#2. UNK to 06/26/2008
4. Diagnosis for Use (Indication)	5. Event Abated After Use Stopped or Dose Reduced? Doesn't Apply
#1. nsclc (NSCLC)	#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply
#2. nsclc (NSCLC)	#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply
6. Lot #	7. Exp. Date
#1. 3005709	#1. _____
#2. 701872	#2. 07/--/2009
9. NDC# or Unique ID	
8. Event Reappeared After Reintroduction? Doesn't Apply	
#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	
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)	

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) 12/10/2008	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 # AVF3671G-B	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 273064	8. Adverse Event Term(s) BUNDLE BRANCH BLOCK

E. INITIAL REPORTER		
1. Name and Address		Phone #
2. Health Professional?	3. Occupation	4. Initial Reporter Also Sent Report to FDA
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		<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 #	273064
UF/Importer Report #	
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**ADDITIONAL INFORMATION****B5. EVENT DESCRIPTION (Continued)**

On 06-MAR-2008, the subject received erlotinib or placebo (100 mg, qd, Oral). On an unspecified date, the subject received bevacizumab (dose not reported, Q3W, Intravenous). Bevacizumab was discontinued on 26-JUN-2008 due to a decrease in ejection fraction. The lot number for bevacizumab was reported as 701872. The last dose of erlotinib or placebo prior to the event was administered on 04-DEC-2008. The lot number for erlotinib or placebo was reported as 3005709.

In the past few weeks, the patient had 4 syncopal episodes. It was reported that the suspected cause was a bundle branch block and axis deviation which was considered to be a cardiac conduction system disease with bradycardia. On 03-DEC-2008, a cardiac rhythm strip revealed a 2:1 AV block with bradycardia. On 04-DEC-2008, the subject experienced "cardiac bundle block branch, axis deviation, bradycardia, cardiac disease" (BUNDLE BRANCH BLOCK). The subject was hospitalized the same day. Action taken with bevacizumab was not applicable. No action was taken with erlotinib or placebo. Treatment for the event included an unspecified procedure/ surgery.

The subject recovered on 05-DEC-2008.

The Investigator assessed the event of BUNDLE BRANCH BLOCK as not related to ERLOTINIB OR PLACEBO and related to bevacizumab. In the reporter's opinion, other possible etiological factors included an unspecified concurrent illness.

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

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

**ANALYSIS OF SIMILAR EVENTS**

Genentech has not previously filed IND safety reports of similar events of bundle branch block from studies of bevacizumab.~

**Sponsor Assessment**

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 bundle branch block.

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	12/03/2008	ELECTROCARDIOGRAM	SEE NOTES	
		2:1 AV BLOCK WITH BRADYCARDIA		

**C1. NAME (Continued)**

Suspect Medication #2: Avastin(BEVACIZUMAB) Powder and solvent for solution for infusion, 100mg

<b>SUSPECT ADVERSE REACTION REPORT</b>	

**I. REACTION INFORMATION**

1. PATIENT INITIALS (first, last)	1a. COUNTRY <b>UNITED STATES</b>	2. DATE OF BIRTH			2a. AGE <b>78 Years</b>	3. SEX <b>Male</b>	3a. WEIGHT <b>69.20 kg</b>	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day	Month	Year			Day	Month	Year		
										<input type="checkbox"/> PATIENT DIED	
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) <b>cardiac bundle block branch, axis deviation, bradycardia, cardiac disease [BUNDLE BRANCH BLOCK]</b>  Case Description: <b>IND SAFETY REPORT</b>  This case, manufacturer control number 273064, is a report from UNITED STATES referring to a 78-year-old Male subject (ID # ).										<input checked="" type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION	
										<input type="checkbox"/> INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY	
(Continued on Additional Information Page)										<input type="checkbox"/> LIFE THREATENING	

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

14. SUSPECT DRUG(S) (include generic name)		20. DID REACTION ABATE AFTER STOPPING DRUG?
#1 ) ERLOTINIB OR PLACEBO (Code not broken) Tablet {Lot # 3005709} #2 ) Avastin (BEVACIZUMAB) Powder and solvent for solution for infusion, 100 mg {Lot # 701872; Exp.Dt. JUL-2009}		
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	<input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> NA
#1 ) 100 mg, qd #2 ) UNK	#1 ) Oral #2 ) Intravenous	
17. INDICATION(S) FOR USE		21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
#1 ) nslc (NSCLC) #2 ) nslc (NSCLC)		
18. THERAPY DATES(from/to)	19. THERAPY DURATION	<input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> NA
#1 ) 06-MAR-2008 / Ongoing #2 ) Unknown / 26-JUN-2008	#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.) <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 20%;">From/To Dates</th> <th style="width: 40%;">Type of History / Notes</th> <th style="width: 40%;">Description</th> </tr> <tr> <td>Unknown</td> <td></td> <td></td> </tr> </table>	From/To Dates	Type of History / Notes	Description	Unknown		
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>273064</b>	25b. NAME AND ADDRESS OF REPORTER
24c. DATE RECEIVED BY MANUFACTURER <b>10-DEC-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>18-DEC-2008</b>	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:

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

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2:1 AV BLOCK WITH BRADYCARDIA				