



# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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**Date:** April 10, 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.

**272778\_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 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 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: **272778 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.

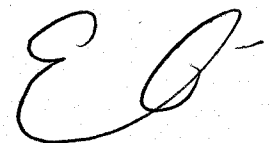
If questions arise, please contact the undersigned.

Sincerely,



Eric Hedrick  
Medical Monitor

CC: AVF4271s



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

Mfr Report #	272778
UF/Importer Report #	
FDA Use Only	

**MEDWATCH**  
3500A Facsimile

A. PATIENT INFORMATION			
1. Patient Identifier	2. Age at Time of Event: 48 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: _____ (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) 11/29/2008		4. Date of This Report (mm/dd/yyyy) 12/22/2008	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) obstructive hydrocephalus [HYDROCEPHALUS]			
Case Description: This case, manufacturer control number 272778, is a report from SINGAPORE referring to a 48 Years-old Female subject (ID# _____). An Investigator reported this case from 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			
No past medical history, concurrent illnesses, allergies or concomitant medications were reported.			
continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates #1 11/30/2008 CSF CULTURE (continued) #2 11/30/2008 CYTOLOGY (continued) #3 11/30/2008 LUMBAR PUNCTURE (continued)			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) Race: Asian #1 Negative Med Cond, TOBACCO USER #2 02/09/2008 to UNK, Current Condition, BACK PAIN #3 02/09/2008 to UNK, Current Condition, BACK PAIN #4 Procedure, RADIOTHERAPY			

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler)			
#1. ERLOTINIB OR PLACEBO (Code Not Broken) Tablet			
#2. Bevacizumab (BEVACIZUMAB) Powder and solvent for (Continued)			
2. Dose, Frequency & Route Used		3. Therapy Dates (if unknown, give duration) from/to (or best estimate)	
#1. 150 mg, qd, Oral		#1. 06/11/2008 to UNK	
#2. 825 mg, Q3W, Intravenous		#2. 03/20/2008 to UNK	
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced?	
#1. non-squamous cell (Continued)		#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2. non-squamous cell (Continued)		#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
6. Lot #	7. Exp. Date	8. Event Reappeared After Reintroduction?	
#1. 501056	#1.	#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2. B3228	#2.	#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
9. NDC# or Unique ID			
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)			
#1. OXYCODONE (OXYCODONE)			
#2. AMITRIPTYLINE (AMITRIPTYLINE) 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	
4. Date Received by Manufacturer(mm/dd/yyyy) 12/17/2008		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		3. Report Source (Check all that apply) <input checked="" type="checkbox"/> Foreign SGP <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 272778		8. Adverse Event Term(s) HYDROCEPHALUS	
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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**ADDITIONAL INFORMATION****B5. EVENT DESCRIPTION (Continued)**

On an unknown date, the subject began treatment with ERLOTINIB OR PLACEBO (dose, route and frequency not reported) and BEVACIZUMAB (dose, route and frequency not reported). The lot numbers for ERLOTINIB OR PLACEBO and BEVACIZUMAB were not reported. The last administration dates of ERLOTINIB OR PLACEBO and BEVACIZUMAB were not reported.

On an unreported date treatments with ERLOTINIB OR PLACEBO and BEVACIZUMAB were delayed due to persistent interscapular pain. The subject then received 5 days of radiotherapy (dates and location of radiotherapy not reported).

On 27-NOV-2008, the subject developed an intolerable headache (HEADACHE) unrelieved by pain killers. On 29-NOV-2008, the subject was hospitalized for a grade 4 headache. During hospitalization, the subject was treated with a stronger analgesic. On 30-NOV-2008 a lumbar puncture was performed, results were reported "to be followed up." No action was taken with ERLOTINIB OR PLACEBO and BEVACIZUMAB due to the event.

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

The Investigator assessed the event of HEADACHE as related to BEVACIZUMAB and not related to ERLOTINIB OR PLACEBO. In the reporter's opinion, other possible etiological factors included disease under study.

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

**ADDITIONAL INFORMATION RECEIVED ON 17-DEC-2008:**

This case now qualifies for expedited reporting because the event term was amended from headache to obstructive hydrocephalus.

It was reported that the subject did not have a history of tobacco use. On 09-FEB-2008, the subject began to experience pain to right lower back extending to right knee and pain to the left upper back. Concomitant medications included oxycodone, amitriptyline, codeine, hydroxyzine and zoledronic acid.

On 20-MAR-2008, the subject received Bevacizumab (825 mg, Q3W, Intravenous). On 11-JUN-2008, the subject received Erlotinib or placebo (150 mg, qd, Oral). The last dose of bevacizumab prior to the event was administered on 30-OCT-2008. The lot number for bevacizumab was reported as B3228. The last dose of erlotinib or placebo prior to the event was administered on 19-NOV-2008. The lot number for erlotinib or placebo was reported as 501056.

On 29-NOV-2008, the subject experienced obstructive hydrocephalus (OBSTRUCTIVE HYDROCEPHALUS) and was hospitalized the same day. Relevant laboratory tests performed on 30-NOV-2008 included a lumbar puncture which revealed no sign of infection or organisms, a CSF culture which revealed no bacterial growth and a CSF non-gynecologic cytology which was negative for malignant cells. On 03-DEC-2008, a right lumboperitoneal shunt insertion was performed.

The subject recovered on 06-DEC-2008 without complications and was discharged the same day.

The Investigator assessed the event of OBSTRUCTIVE HYDROCEPHALUS as not related to Erlotinib or placebo and related to Bevacizumab.

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

**Previously Filed IND Safety Reports Of Similar Events**

Genentech has previously filed the following IND safety reports of similar events from studies of bevacizumab .

Manufacturer Control Number	ISR Primary Event Term	Date Submitted
234306	HYDROCEPHALUS	08-JAN-2007
260365	HYDROCEPHALUS	13-MAY-2008

**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 hydrocephalus.

**MEDWATCH**

3500A Facsimile (Back) (Continued)

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

**B6. LABORATORY DATA**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	11/30/2008	CSF CULTURE  no bacterial growth	see notes	
2	11/30/2008	CYTOLOGY  CSF non-gynecologic cytology; negative for malignant cells	see notes	
3	11/30/2008	LUMBAR PUNCTURE  no sign of infection, no organisms seen	see notes	

**C1. NAME (Continued)**

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

**C4. DIAGNOSIS FOR USE (Continued)**

#1:non-squamous cell non-small cell lung cancer (NON-SQUAMOUS CELL NON-SMALL CELL LUNG CANCER)

#2:non-squamous cell non-small cell lung cancer (NON-SQUAMOUS CELL NON-SMALL CELL LUNG CANCER)

**C10. CONCOMITANT MEDICAL PRODUCTS (Continued)**

HYDROCHLORIDE)

#3. CODEINE (CODEINE)

#4. HYDROXYZINE (HYDROXYZINE HYDROCHLORIDE)

#5. ZOMETA (ZOLEDRONIC ACID)

<b>SUSPECT ADVERSE REACTION REPORT</b>	

**I. REACTION INFORMATION**

1. PATIENT INITIALS (first, last)	1a. COUNTRY <b>SINGAPORE</b>	2. DATE OF BIRTH			2a. AGE <b>48</b> Years	3. SEX <b>Female</b>	3a. WEIGHT <b>Unk</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>obstructive hydrocephalus [HYDROCEPHALUS]</b>  Case Description: This case, manufacturer control number 272778, is a report from SINGAPORE referring to a 48 Years-old Female subject (ID# ). An Investigator reported this case from 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										<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 # 501056) #2 ) Bevacizumab (BEVACIZUMAB) Powder and solvent for solution for (Continued on Additional Information Page)		
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	<input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> NA
#1 ) 150 mg, qd #2 ) 825 mg, Q3W	#1 ) Oral #2 ) Intravenous	
17. INDICATION(S) FOR USE		21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
#1 ) non-squamous cell non-small cell lung c #2 ) non-squamous cell non-small cell lung c (Continued on Additional Information Page)		
18. THERAPY DATES(from/to)	19. THERAPY DURATION	<input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> NA
#1 ) 11-JUN-2008 / Unknown #2 ) 20-MAR-2008 / Unknown	#1 ) Unknown #2 ) Unknown	

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

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)	
#1 ) OXYCODONE (OXYCODONE) ; Unknown #2 ) AMITRIPTYLINE (AMITRIPTYLINE HYDROCHLORIDE) ; Unknown #3 ) CODEINE (CODEINE) ; Unknown #4 ) HYDROXYZINE (HYDROXYZINE HYDROCHLORIDE) ; Unknown #5 ) ZOMETA (ZOLEDRONIC ACID) ; Unknown	
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)	
From/To Dates	Type of History / Notes
Unknown	Negative Med Cond
09-FEB-2008 to Unknown	Current Condition
	Description
	TOBACCO USER (TOBACCO USER)
	LOW BACK PAIN (BACK PAIN)

**IV. MANUFACTURER INFORMATION**

24a. NAME AND ADDRESS OF MANUFACTURER		26. REMARKS
Genentech, Inc. James Nickas 1 DNA Way South San Francisco, CA 94080 UNITED STATES Phone: 6502255591		
	24b. MFR CONTROL NO.	25b. NAME AND ADDRESS OF REPORTER
	<b>272778</b>	
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE	
<b>17-DEC-2008</b>	<input checked="" type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input checked="" type="checkbox"/> HEALTH PROFESSIONAL <input type="checkbox"/> OTHER:	
DATE OF THIS REPORT	25a. REPORT TYPE	
<b>22-DEC-2008</b>	<input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:	

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

No past medical history, concurrent illnesses, allergies or concomitant medications were reported.

On an unknown date, the subject began treatment with ERLOTINIB OR PLACEBO (dose, route and frequency not reported) and BEVACIZUMAB (dose, route and frequency not reported). The lot numbers for ERLOTINIB OR PLACEBO and BEVACIZUMAB were not reported. The last administration dates of ERLOTINIB OR PLACEBO and BEVACIZUMAB were not reported.

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

The Investigator assessed the event of HEADACHE as related to BEVACIZUMAB and not related to ERLOTINIB OR PLACEBO. In the reporter's opinion, other possible etiological factors included disease under study.

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

**ADDITIONAL INFORMATION RECEIVED ON 17-DEC-2008:**

This case now qualifies for expedited reporting because the event term was amended from headache to obstructive hydrocephalus.

It was reported that the subject did not have a history of tobacco use. On 09-FEB-2008, the subject began to experience pain to right lower back extending to right knee and pain to the left upper back. Concomitant medications included oxycodone, amitriptyline, codeine, hydroxyzine and zoledronic acid.

On 20-MAR-2008, the subject received Bevacizumab (825 mg, Q3W, Intravenous). On 11-JUN-2008, the subject received Erlotinib or placebo (150 mg, qd, Oral). The last dose of bevacizumab prior to the event was administered on 30-OCT-2008. The lot number for bevacizumab was reported as B3228. The last dose of erlotinib or placebo prior to the event was administered on 19-NOV-2008. The lot number for erlotinib or placebo was reported as 501056.

On 29-NOV-2008, the subject experienced obstructive hydrocephalus (OBSTRUCTIVE HYDROCEPHALUS) and was hospitalized the same day. Relevant laboratory tests performed on 30-NOV-2008 included a lumbar puncture which revealed no sign of infection or organisms, a CSF culture which revealed no bacterial growth and a CSF non-gynecologic cytology which was negative for malignant cells. On 03-DEC-2008, a right lumboperitoneal shunt insertion was performed.

The subject recovered on 06-DEC-2008 without complications and was discharged the same day.

The Investigator assessed the event of OBSTRUCTIVE HYDROCEPHALUS as not related to Erlotinib or placebo and related to Bevacizumab.

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260365	HYDROCEPHALUS	13-MAY-2008

**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 hydrocephalus.

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

**ADDITIONAL INFORMATION****13. Lab Data**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	30-NOV-2008	CSF CULTURE  no bacterial growth	see notes	
2	30-NOV-2008	CYTOLOGY  CSF non-gynecologic cytology; negative for malignant cells	see notes	
3	30-NOV-2008	LUMBAR PUNCTURE  no sign of infection, no organisms seen	see notes	

**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 ) ERLOTINIB OR PLACEBO (Code not broken) Tablet {Lot # 501056}; Regimen #1	150 mg, qd; Oral	non-squamous cell non-small cell lung cancer (NON-SQUAMOUS CELL NON-SMALL CELL LUNG CANCER)	11-JUN-2008 / Unknown; Unknown
#2 ) Bevacizumab (BEVACIZUMAB) Powder and solvent for solution for infusion, 100 mg {Lot # B3228}; Regimen #1	825 mg, Q3W; Intravenous	non-squamous cell non-small cell lung cancer (NON-SQUAMOUS CELL NON-SMALL CELL LUNG CANCER)	20-MAR-2008 / Unknown; Unknown

**23. OTHER RELEVANT HISTORY continued**

From/To Dates	Type of History / Notes	Description
09-FEB-2008 to Unknown	Current Condition	UPPER BACK PAIN (BACK PAIN);
Unknown	Procedure	RADIOTHERAPY (RADIOTHERAPY);