



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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_270965_F2

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

MEDWATCH
3500A Facsimile

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

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Mfr Report #	270965
UF/Importer Report #	
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A. PATIENT INFORMATION			
1. Patient Identifier	2. Age at Time of Event: <u>78 Years</u> or Date of Birth:	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight <u>130.4</u> lbs or <u>59.1</u> 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 checked="" type="checkbox"/> Death: <u>11/02/2008</u> (mm/dd/yyyy)		<input type="checkbox"/> Disability or Permanent Damage	
<input type="checkbox"/> Life-threatening		<input type="checkbox"/> Congenital Anomaly/Birth Defect	
<input 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) <u>11/02/2008</u>		4. Date of This Report (mm/dd/yyyy) <u>11/19/2008</u>	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) <u>progression of non small cell lung cancer [NON-SMALL CELL LUNG CANCER]</u>			
Case Description: IND SAFETY REPORT			
This case, manufacturer control number 270965, is a report from UNITED STATES referring to a 78 Years-old Male 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			
continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) Race: <u>Caucasian</u>			

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler)			
#1. <u>ERLOTINIB OR PLACEBO (Erlotinib) Tablet</u>			
#2. <u>Bevacizumab (BEVACIZUMAB) Powder and solvent for (Continued)</u>			
2. Dose, Frequency & Route Used		3. Therapy Dates (if unknown, give duration) from/to (or best estimate)	
#1. <u>150 mg, qd, Oral</u>		#1. <u>07/09/2008 to UNK</u>	
#2. <u>15 mg/kg, Q3W, Intravenous</u>		#2. <u>04/16/2008 to UNK</u>	
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced? (Check all that apply)	
#1. <u>nsclc (NSCLC)</u>		#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2. <u>nsclc (NSCLC)</u>		#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? (Check all that apply)	
#1. <u>2006154</u>	#1.	#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2. <u>703976</u>	#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)			
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 <u>6502255591</u>	
4. Date Received by Manufacturer (mm/dd/yyyy) <u>11/10/2008</u>		5. (A)NDA # IND # <u>BB 7023</u> 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 # <u>AVF3671G-B</u>		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 type="checkbox"/> Initial <input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up #2			
9. Manufacturer Report Number <u>270965</u>		8. Adverse Event Term(s) <u>NON-SMALL CELL LUNG CANCER</u>	
E. INITIAL REPORTER			
1. Name and Address		Phone #	
2. Health Professional?		3. Occupation	
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
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.

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C. SUSPECT PRODUCT(S)	
1. Name (Give labeled strength & mfr/labeler)	
#3. CARBOPLATIN (CARBOPLATIN)	
#4. PACLITAXEL (PACLITAXEL)	
2. Dose, Frequency & Route Used	3. Therapy Dates (if unknown, give duration from/to (or best estimate))
#3. UNK, Intravenous	#3. 04/16/2008 to UNK
#4. UNK, Intravenous	#4. 04/16/2008 to UNK
4. Diagnosis for Use (Indication)	5. Event Abated After Use Stopped or Dose Reduced?
#3. nslc (NSCLC)	#3. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply
#4. nslc (NSCLC)	#4. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply
6. Lot #	7. Exp. Date
#3.	#3.
#4.	#4.
9. NDC# or Unique ID	8. Event Reappeared After Reintroduction?
NA	#3. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply
	#4. <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)	

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

On 16-APR-2008, the subject received bevacizumab, (15 mg/kg, Q3W, Intravenous). On 16-APR-2008, the subject received concomitant chemotherapy which included carboplatin, (dose not reported, Q3W, Intravenous) and paclitaxel, (dose not reported, Q3W, Intravenous). On 09-JUL-2008, the subject received erlotinib or placebo, (150 mg, qd, Oral). The lot number of erlotinib was #2006154 and the lot number of bevacizumab was #703976. The last dose of carboplatin and paclitaxel prior to the event was administered on 18-JUN-2008. The last dose of bevacizumab prior to the event was administered on 12-SEP-2008. The last dose of erlotinib prior to the event was administered on 03-OCT-2008.

On 02-NOV-2008, the subject experienced grade 5, unexplained death (DEATH UNEXPLAINED). No relevant laboratory tests or diagnostic evaluations were included. Treatment for the event and action taken with study medication was not applicable.

Autopsy was reported as unknown.

On 07-NOV-2008, the subject was unblinded and found to be on Erlotinib.

The Investigator assessed the event of death unexplained as not related to erlotinib and bevacizumab. The investigator did not provide an assessment of the event of death unexplained to carboplatin or paclitaxel. In the reporter's opinion, other possible etiological factors included disease under study.

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

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

ADDITIONAL INFORMATION RECEIVED ON 10-NOV-2008:

This case no longer qualifies for expedited reporting.

The event term was amended from DEATH UNEXPLAINED to PROGRESSION OF NON SMALL CELL LUNG CANCER.

It was reported that the cause of death was progression of non-small cell lung cancer per death certificate.

The investigator assessed the event of PROGRESSION OF NON SMALL CELL LUNG CANCER as not related to bevacizumab and not related to erlotinib.

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

ANALYSIS OF SIMILAR EVENTS

Genentech has previously filed IND safety reports of similar events of DEATH from studies of Erlotinib.

Manufacturer control number~	ISR Primary event term~	Date submitted
247765~	death~	24-Sep-07
247765~	death~	15-Oct-07
255141~	unexplained death~	7-Feb-08
257362~	unexplained death~	14-Mar-08
257362~	unexplained death~	8-May-08

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

Manufacturer Control Number	ISR Primary Event Term	Date Submitted
236761	DEATH	23-FEB-2007
242285	DEATH	12-JUN-2007
250243	DEATH	01-NOV-2007

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 Erlotinib and the occurrence of DEATH.

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

Pharmacovigilance:

DEATH UNEXPLAINED is not expected in the IB and not labeled in the USPI of Avastin. The limited information currently available does not allow a meaningful causality assessment between the event and the drug administered.

FOLLOW-UP RECEIVED: PROGRESSION OF NON SMALL CELL LUNG CANCER is listed per the erlotinib IB, listed and labeled per the bevacizumab IB and USPI. The underlying non-small cell lung cancer is a confounding factor. The investigator assessed the event as not related to bevacizumab and not related to erlotinib. This case no longer requires a PV comment.

C1. NAME (Continued)

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

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

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

On 16-APR-2008, the subject received bevacizumab, (15 mg/kg, Q3W, Intravenous). On 16-APR-2008, the subject received concomitant chemotherapy which included carboplatin, (dose not reported, Q3W, Intravenous) and paclitaxel, (dose not reported, Q3W, Intravenous). On 09-JUL-2008, the subject received erlotinib or placebo, (150 mg, qd, Oral). The lot number of erlotinib was #2006154 and the lot number of bevacizumab was #703976. The last dose of carboplatin and paclitaxel prior to the event was administered on 18-JUN-2008. The last dose of bevacizumab prior to the event was administered on 12-SEP-2008. The last dose of erlotinib prior to the event was administered on 03-OCT-2008.

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The Investigator assessed the event of death unexplained as not related to erlotinib and bevacizumab. The investigator did not provide an assessment of the event of death unexplained to carboplatin or paclitaxel. In the reporter's opinion, other possible etiological factors included disease under study.

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

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

ADDITIONAL INFORMATION RECEIVED ON 10-NOV-2008:

This case no longer qualifies for expedited reporting.

The event term was amended from DEATH UNEXPLAINED to PROGRESSION OF NON SMALL CELL LUNG CANCER.

It was reported that the cause of death was progression of non-small cell lung cancer per death certificate.

The investigator assessed the event of PROGRESSION OF NON SMALL CELL LUNG CANCER as not related to bevacizumab and not related to erlotinib.

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

ANALYSIS OF SIMILAR EVENTS

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

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

Pharmacovigilance: DEATH UNEXPLAINED is not expected in the IB and not labeled in the USPI of Avastin. The limited information currently available does not allow a meaningful causality assessment between the event and the drug administered.

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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
#2) Bevacizumab (BEVACIZUMAB) Powder and solvent for solution for infusion, 100 mg {Lot # 703976}; Regimen #1	15 mg/kg, Q3W; Intravenous	nslc (NSCLC)	16-APR-2008 / Unknown; Unknown
#3) CARBOPLATIN (CARBOPLATIN) ; Regimen #1	UNK; Intravenous	nslc (NSCLC)	16-APR-2008 / Unknown; Unknown
#4) PACLITAXEL (PACLITAXEL) ; Regimen #1	UNK; Intravenous	nslc (NSCLC)	16-APR-2008 / Unknown; Unknown