



# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

---

**Date:** January 16, 2009

**To:** NCCTG Primary Clinical Research Associates

**From:** Sara Braun

**Re:** N0775, A Randomized Phase II Trial of Temozolomide (TMZ) and Avastin® or ABI-007/Carboplatin (CBDCA) and Avastin® in Patients with Unresectable Stage IV Malignant Melanoma

The purpose of this memorandum is to provide investigators with a recent report of an adverse event that has occurred in association with Bevacizumab for a study where the Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI) is distributing this agent. You may have also received this communication directly from DCTD.

**AE\_270229**

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 Sara Braun at [braun.sara@mayo.edu](mailto:braun.sara@mayo.edu) or 507-538-8226.

SB/kjm  
enclosure



National Institutes of Health  
National Cancer Institute  
Bethesda, Maryland 20892

**DATE:** November 18, 2008

**FROM:** Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI 

**SUBJECT:** Bevacizumab (rhuMAb VEGF) Investigator Notification: **Death of Unknown Cause**  
Genentech Manufacturer Report # 270229

**TO:** Investigators using Bevacizumab (NSC 704865)

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies conducted under a U.S. IND to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. A MedWatch report and CIOMS form, which describe death of unknown cause in a patient participating in a Genentech-sponsored clinical trial utilizing the investigational agent bevacizumab and chemotherapy, was recently distributed to investigators.

The following must be completed by all investigators using bevacizumab under NCI INDs 7921 and 11460:

- Send a copy of this letter to your Institutional Review Board (IRB) according to your local IRB's policies and procedures.
- File a copy of this letter in your protocol file.

If your study is not covered under INDs 7921 or 11460, it is strongly recommended that you follow the instructions above.

Please note that for Cooperative Group studies, the Cooperative Group Operations Office will provide instructions for IRB submissions, any patient notifications, etc.

Based on CTEP's assessment of the current information in light of previous experience with bevacizumab, there does not appear to be a change in the risk-benefit ratio for bevacizumab studies; therefore, CTEP is not requiring a protocol amendment at this time.

Please continue to report events according to the adverse event reporting guidelines in your protocol(s).

The MedWatch Report and CIOMS Form that describe the following adverse event are attached:

A 56-year-old male died of unknown cause while on a phase 3b study utilizing the investigational agent bevacizumab in combination with carboplatin, paclitaxol without erlotinib. Listings of similar events are provided in the attached reports submitted by Genentech.

Attachments: MedWatch Report  
CIOMS Form

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

**MEDWATCH**  
3500A Facsimile

Mfr Report #	270229
UF/Importer Report #	
FDA Use Only	

A. PATIENT INFORMATION			
1. Patient Identifier	2. Age at Time of Event: 56 Years or Date of Birth:	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 121.3 lbs or 55.0 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: 10/13/2008 (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) 10/13/2008		4. Date of This Report (mm/dd/yyyy) 10/30/2008	
5. Describe Event or Problem Event Verbatim (PREFERRED TERM) (Related symptoms if any separated by commas) death of unknown cause [DEATH]			
Case Description: IND SAFETY REPORT			
This case, manufacturer control number 270229, is a report from Thailand referring to a 56 year-old male subject (# ). An Investigator reported this case from study AVF3671G-B. An investigator reported this case from a Genentech-sponsored study AVF3671g-O, 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, recurrent, or metastatic non-small cell lung			
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: Asian #1 Current Condition, HYPERTENSION #2 Current Condition, TUMOUR PAIN #3 Current Condition, ANOREXIA continued in additional info section...			

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler)			
#1. ERLOTINIB OR PLACEBO (PLACEBO)			
#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. 04/10/2008 to UNK	
#2. 825 mg, Q3W		#2. 01/16/2008 to UNK	
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced?	
#1. nslc (NSCLC)		#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2. nslc (NSCLC)		#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. 500521	#1.	#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2. B(Continued)	#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. HYDROCHLOROTHIAZIDE (HYDROCHLOROTHIAZIDE) --/--/2006 to ongoing 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) 10/22/2008		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 # AVF3671G-B		3. Report Source (Check all that apply) <input checked="" type="checkbox"/> Foreign THA <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 270229		8. Adverse Event Term(s) DEATH	
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.

**MEDWATCH**  
3500A Facsimile (Back) (Continued)

Page 2 of 4

Mfr Report #	270229
UF/Importer Report #	
	FDA Use Only

C. SUSPECT PRODUCT(S)	
1. Name (Give labeled strength & mfr/labeler)	
#3. PACLITAXEL (PACLITAXEL)	
#4. CARBOPLATIN (CARBOPLATIN)	
2. Dose, Frequency & Route Used	3. Therapy Dates (if unknown, give duration from/to (or best estimate))
#3. UNK, Intravenous	#3. 01/16/2008 to UNK
#4. UNK, Intravenous	#4. 01/16/2008 to UNK
4. Diagnosis for Use (Indication)	5. Event Abated After Use Stopped or Dose Reduced?
#3. non small cell lung (Continued)	#3. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply
#4. non small cell lung (Continued)	#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)	

**MEDWATCH**

3500A Facsimile (Back) (Continued)

Page 3 of 4

Mfr Report #	270229
UF/Importer Report #	
	FDA Use Only

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

Past medical history included heart disorder. Concurrent conditions hypertension, tumour pain, anorexia, constipation, blood cholesterol increased, and hypokalaemia. Concomitant medications included hydrochlorothiazide, senna, acetaminophen, codeine phosphate, tramadol hydrochloride, cyproheptadine hydrochloride, and ubenimex. No allergies were reported.

On 16-JAN-2008, the subject is enrolled in the post-chemotherapy phase of trial AVF3671g and began treatment with BEVACIZUMAB, (825mg, intravenous, Q3W). Concomitant chemotherapy included paclitaxol (dose not reported, IV, Q3W) and carboplatin (dose not reported, IV Q3W). On 10-APR-2008, the subject received erlotinib or placebo (150 mg, oral, QD). The lot number of bevacizumab was B3002 and B3220. The lot number of erlotinib or placebo was 500521. The last dose of paclitaxol and carboplatin prior to the event onset was 18-MAR-2008. The last dose of bevacizumab prior to the event was administered on 30-SEP-2008. The last dose of erlotinib or placebo prior to the event was administered on 13-OCT-2008.

On 13-OCT-2008, the subject died of an unknown cause (UNKNOWN CAUSE OF DEATH). No relevant laboratory tests or diagnostic evaluations were reported. Treatment and action taken with study medications was not applicable.

No autopsy was performed.

On 24-OCT-2008, the subject was unblinded and found to be on PLACEBO for erlotinib/placebo.

The Investigator assessed the event UNKNOWN CAUSE OF DEATH as not related to PLACEBO. The Investigator assessed the event UNKNOWN CAUSE OF DEATH as not related to bevacizumab. The investigator did not provide an assessment for the event of unknown cause of death to paclitaxol or carboplatin. In the reporter's opinion, other possible etiological factors included history of "heart problems".

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

Additional information has been requested. If received, this 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
102407~	Death of unknown cause~	7-May-02
105566~	death, cause unknown~	13-Jan-03
200156~	Death Unknown Cause~	13-Mar-03
206723~	Death unexplained~	2-Jun-04
207505~	Unexplained death~	9-Jul-04
207952~	Death unexplained~	9-Sep-04
218003~	Death unexplained~	17-May-07
247765~	death~	15-Oct-07
250243~	unexplained death~	7-Feb-08
255141~	unexplained death~	14-Mar-08
257362~	unexplained death~	8-May-08

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.

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

**ANALYSIS OF SIMILAR EVENTS**

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

**MEDWATCH**

3500A Facsimile (Back) (Continued)

Page 4 of 4

Mfr Report #	270229
UF/Importer Report #	
FDA Use Only	

Manufacturer control number~	ISR Primary event term~	Date submitted
236761~	death~	23-Feb-07
242285~	death~	12-Jun-07
247765~	death~	24-Sep-07
249106~	unexplained death~	16-Oct-07
250243~	death~	1-Nov-07
255141~	unexplained death~	7-Feb-08
257362~	unexplained death~	14-Mar-08
264926~	unexplained death~	25-Jul-08
268723~	death of unknown cause~	6-Oct-08

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 DEATH.

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

**B7. OTHER RELEVANT HISTORY**

#	Start/Stop Date	Condition Type / Condition	Notes
4		Current Condition CONSTIPATION	
5		Current Condition CARDIAC DISORDER	
6		Current Condition BLOOD CHOLESTEROL INCREASED	
7		Current Condition HYPOKALAEMIA	

**C1. NAME (Continued)**

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

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

#3:non small cell lung cancer (NON SMALL CELL LUNG CANCER)

#4:non small cell lung cancer (NON SMALL CELL LUNG CANCER)

**C6. LOT# (Continued)**

Suspect Medication #2: B3002, B3220

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

#2. SENOKOT (SENNA) 12/13/2007 to ongoing

#3. CODIGESIC (ACETAMINOPHEN, CODEINE PHOSPHATE) 12/13/2007 to 01/08/2008

#4. TRAMADOL (TRAMADOL HYDROCHLORIDE) 01/08/2008 to ongoing

#5. PERIACTIN (CYPROHEPTADINE HYDROCHLORIDE) 02/26/2008 to ongoing

#6. BESTATIN (UBENIMEX) 09/09/2008 to ongoing

#7. POTASSIUM CHLORIDE (POTASSIUM CHLORIDE) 09/30/2008 to 10/01/2008

0005

<b>SUSPECT ADVERSE REACTION REPORT</b>	

**I. REACTION INFORMATION**

1. PATIENT INITIALS (first, last)	1a. COUNTRY <b>THAILAND</b>	2. DATE OF BIRTH			2a. AGE <b>56 Years</b>	3. SEX <b>Male</b>	3a. WEIGHT <b>55.00 kg</b>	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day	Month	Year				Day	Month	Year	
								<b>13</b>	<b>OCT</b>	<b>2008</b>	<input checked="" type="checkbox"/> PATIENT DIED Date: 13-OCT-2008 <input 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) <b>death of unknown cause [DEATH]</b>											
Case Description: <b>IND SAFETY REPORT</b>  This case, manufacturer control number 270229, is a report from Thailand referring to a 56 year-old male subject (# ).											
(Continued on Additional Information Page)											

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

14. SUSPECT DRUG(S) (include generic name)		20. DID REACTION ABATE AFTER STOPPING DRUG?
#1 ) ERLOTINIB OR PLACEBO (PLACEBO) {Lot # 500521} #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 ) Unknown	
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 ) 10-APR-2008 / Unknown #2 ) 16-JAN-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 ) HYDROCHLOROTHIAZIDE (HYDROCHLOROTHIAZIDE) ; 2006 / Ongoing #2 ) SENOKOT (SENNA) ; 13-DEC-2007 / Ongoing #3 ) CODIGESIC (ACETAMINOPHEN, CODEINE PHOSPHATE) ; 13-DEC-2007 / 08-JAN-2008 #4 ) TRAMADOL (TRAMADOL HYDROCHLORIDE) ; 08-JAN-2008 / Ongoing #5 ) PERIACTIN (CYPROHEPTADINE HYDROCHLORIDE) ; 26-FEB-2008 / Ongoing #6 ) BESTATIN (UBENIMEX) ; 09-SEP-2008 / Ongoing		
(Continued on Additional Information Page)		
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)		
From/To Dates	Type of History / Notes	Description
Unknown	Current Condition	HYPERTENSION (HYPERTENSION)
Unknown	Current Condition	TUMOR PAIN (TUMOUR 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>270229</b>	
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE	
<b>22-OCT-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>30-OCT-2008</b>	<input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:	

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

An Investigator reported this case from study AVF3671G-B, An investigator reported this case from a Genentech-sponsored study AVF3671g-O, 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, recurrent, or metastatic non-small cell lung

Past medical history included heart disorder. Concurrent conditions hypertension, tumour pain, anorexia, constipation, blood cholesterol increased, and hypokalaemia. Concomitant medications included hydrochlorothiazide, senna, acetaminophen, codeine phosphate, tramadol hydrochloride, cyproheptadine hydrochloride, and ubenimex. No allergies were reported.

On 16-JAN-2008, the subject is enrolled in the post-chemotherapy phase of trial AVF3671g and began treatment with BEVACIZUMAB, (825mg, intravenous, Q3W). Concomitant chemotherapy included paclitaxol (dose not reported, IV, Q3W) and carboplatin (dose not reported, IV Q3W). On 10-APR-2008, the subject received erlotinib or placebo (150 mg, oral, QD). The lot number of bevacizumab was B3002 and B3220. The lot number of erlotinib or placebo was 500521. The last dose of paclitaxol and carboplatin prior to the event onset was 18-MAR-2008. The last dose of bevacizumab prior to the event was administered on 30-SEP-2008. The last dose of erlotinib or placebo prior to the event was administered on 13-OCT-2008.

On 13-OCT-2008, the subject died of an unknown cause (UNKNOWN CAUSE OF DEATH). No relevant laboratory tests or diagnostic evaluations were reported. Treatment and action taken with study medications was not applicable.

No autopsy was performed.

On 24-OCT-2008, the subject was unblinded and found to be on PLACEBO for erlotinib/placebo.

The Investigator assessed the event UNKNOWN CAUSE OF DEATH as not related to PLACEBO. The Investigator assessed the event UNKNOWN CAUSE OF DEATH as not related to bevacizumab. The investigator did not provide an assessment for the event of unknown cause of death to paclitaxol or carboplatin. In the reporter's opinion, other possible etiological factors included history of "heart problems".

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

Additional information has been requested. If received, this 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
102407~	Death of unknown cause~	7-May-02
105566~	death, cause unknown~	13-Jan-03
200156~	Death Unknown Cause~	13-Mar-03
206723~	Death unexplained~	2-Jun-04
207505~	Unexplained death~	9-Jul-04
207952~	Death unexplained~	9-Sep-04
218003~	Death unexplained~	17-May-07
247765~	death~	15-Oct-07
250243~	unexplained death~	7-Feb-08
255141~	unexplained death~	14-Mar-08
257362~	unexplained death~	8-May-08

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.

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

**ANALYSIS OF SIMILAR EVENTS**

Genentech has previously filed 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-07

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

242285~	death~	12-Jun-07
247765~	death~	24-Sep-07
249106~	unexplained death~	16-Oct-07
250243~	death~	1-Nov-07
255141~	unexplained death~	7-Feb-08
257362~	unexplained death~	14-Mar-08
264926~	unexplained death~	25-Jul-08
268723~	death of unknown cause~	6-Oct-08

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 DEATH.

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

**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 # B3002, B3220}; Regimen #1	825 mg, Q3W; Unknown	nsclc (NSCLC)	16-JAN-2008 / Unknown; Unknown
#3 ) PACLITAXEL (PACLITAXEL) ; Regimen #1	UNK; Intravenous	non small cell lung cancer (NON SMALL CELL LUNG CANCER)	16-JAN-2008 / Unknown; Unknown
#4 ) CARBOPLATIN (CARBOPLATIN) ; Regimen #1	UNK; Intravenous	non small cell lung cancer (NON SMALL CELL LUNG CANCER)	16-JAN-2008 / Unknown; Unknown

**22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued**

#7 ) POTASSIUM CHLORIDE (POTASSIUM CHLORIDE) ; 30-SEP-2008 / 01-OCT-2008

**23. OTHER RELEVANT HISTORY continued**

From/To Dates	Type of History / Notes	Description
Unknown	Current Condition	ANOREXIA (ANOREXIA);
Unknown	Current Condition	CONSTIPATION (CONSTIPATION);
Unknown	Current Condition	HEART DISORDER (CARDIAC DISORDER);
Unknown	Current Condition	HIGH CHOLESTEROL (BLOOD CHOLESTEROL INCREASED);
Unknown	Current Condition	HYPOKALEMIA (HYPOKALAEMIA);