



# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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**Date:** October 19, 2007  
**To:** NCCTG Primary Clinical Research Associates  
**From:** Lori Bratvold  
Protocol Development Coordinator  
**Re:** N0177, A Phase I/II Study of OSI-774 and Temozolomide in Combination with Radiation Therapy in Glioblastoma Multiforme

The purpose of this memorandum is to provide investigators with a recent report of an adverse event that has occurred in association with OSI-774 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\_248756\_F1**

Please note that all risks currently cited in the NCCTG consent form can not 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/df  
enclosure

**MEDWATCH**  
3500A Facsimile

**Genentech, Inc.**  
For use by user-facilities,  
importers, distributors and manufacturers  
for MANDATORY reporting

Mfr Report #	248756
UF/Importer Report #	
FDA Use Only	

<b>A. PATIENT INFORMATION</b>			
1. Patient Identifier	2. Age at Time of Event: 57 Years or Date of Birth:	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 167.0 lbs or 75.7 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 checked="" type="checkbox"/> Death 10/01/2007 (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) 10/01/2007		4. Date of This Report (mm/dd/yyyy) 10/18/2007	
5. Describe Event or Problem Event Verbatim (PREFERRED TERM) (Related symptoms if any separated by commas) death[DEATH]			
Case Description: IND SAFETY REPORT			
This case, manufacturer control number 248756, is a report from the UNITED STATES referring to a 57 Year-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, recurrent, or metastatic non-small cell lung.			
The subject is enrolled in the post-chemotherapy phase of trial AVF3671g and began treatment with bevacizumab (1200 mg, Q3W, Intravenous) on 08-NOV-2006. The lot number was N38279. continued in additional info section...			
6. Relevant Tests/Laboratory Data, including Dates NI			
7. Other Relevant History, including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) #1 10/--/2006, Current Condition, PAIN (continued) #2 10/--/2006 to UNK, Current Condition, INSOMNIA #3 UNK, Current Condition, BACK PAIN #4 04/--/2006 to UNK Current Condition, (continued) #5 UNK, Current Condition, MASS (continued)			

<b>C. SUSPECT PRODUCT(S)</b>			
1. Name (Give labeled strength & mfr/labeler)			
#1. ERLOTINIB OR PLACEBO(Erlotinib) 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. 02/01/2007, duration UNK	
#2. 1200 mg, Q3W, Intravenous		#2. 11/08/2006, duration UNK	
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced?	
#1. non-small cell lung (continued)		#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2. non small cell lung (continued)		#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
6. Lot #		7. Exp. Date	
#1. 2004739		#1. UNK	
#2. N38279		#2. UNK	
9. NDC# or Unique ID			
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event) FENTANYL PATCH (FENTANYL CITRATE) 10/27/2006 to ongoing 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) 10/02/2007		5. (A)NDA # IND # US 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 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 #1			
9. Manufacturer Report Number 248756		8. Adverse Event Term(s) DEATH	
<b>E. INITIAL REPORTER</b>			
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)

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Mfr Report #	248756
UF/Importer Report #	
	FDA Use Only

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

On 01-FEB-2007, the subject began treatment with erlotinib or placebo (150 mg, qd, Oral). The lot number was 2004739. The last dose of bevacizumab prior to the event was administered on 19-SEP-2007. The last dose of erlotinib or placebo prior to the event was unknown.

On 01-OCT-2007, the subject was found dead (DEATH) at home. No relevant laboratory data was reported, it was unknown if an autopsy was preformed. There was no treatment for the event. The action taken with bevacizumab and erlotinib or placebo was not applicable.

On 4-OCT-2007, the subject was unblinded to erlotinib.

The Investigator assessed the event death as related to erlotinib and bevacizumab. There were no other suspected causes of the event.

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

Additional information has been requested.

**ADDITIONAL INFORMATION RECEIVED 12-OCT-07**

Concurrent conditions present at the time of the event included pain, insomnia, back pain, erectile dysfunction and a oropharynx mass on the floor of the mouth measuring 2.5 cm. Concomitant medications included fentanyl citrate, acetaminophen, hydrocodone bitartrate, tadalafil, acetaminophen, multivitamins nos, chondroitin sulfate, glucosamine, cholecalciferol, docosahexaenoic acid, eicosapentaenoic acid and polyethylene glycol.

Additional information has been requested.

**CASE CORRECTION MADE ON 18-OCT-2007:**

Upon Further case review of the ICSR, it was determined that the initial report did not include the "analysis of similar events". The Analysis has been included below.

**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
218003----	DEATH 4-Oct-05	
236761	DEATH	23-FEB-2007
236761	DEATH FU #1	28-FEB-2007
242285	DEATH	12-JUN-2007
242285	DEATH FU #1	2-JUL-2007
247765	DEATH	24-SEP-2007
247765	DEATH FU #1	15-OCT-2007
248750	DEATH	10-OCT-2007
248756	DEATH	11-OCT-2007

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.

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 7-MAY-2002	
102517	DEATH	23-MAY-2002
102517	DEATH FU #1	04-JUN-2002
104866	SUDDEN DEATH	22-NOV-2002
105566	DEATH	13-JAN-2003

**MEDWATCH**

3500A Facsimile (Back) (continued)

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200156	DEATH	13MAR2003
206723	DEATH	2-JUN-2004
207505	DEATH	09-JUL-2004
207505	DEATH FU #1	09-SEP-2004
207505	DEATH FU #2	22-AUG-2005
207952	DEATH	29-JUL-2004
207952	DEATH FU #1	31-AUG-2004
207952	DEATH FU #2	09-SEP-2004
207952	DEATH FU #3	17-MAY-2007
218003	DEATH	04-OCT-2005
247765	DEATH	24-SEP-2007
247765	DEATH FU#1	15-OCT-2007
248756	DEATH	11-OCT-2007

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.

## Pharmacovigilance:

DEATH is unlabeled in the USPI and unexpected in the IB for BEVACIZUMAB, and unexpected in the IB for ERLOTINIB. A report of death occurring after initiating bevacizumab therapy with unblinded erlotinib administered for non-small cell lung cancer in a 57 Year-old Male subject from the UNITED STATES participating in a study. The event is assessed as related to both drugs. Confounding factors include the possibility of progression of underlying condition.

## B7. OTHER RELEVANT HISTORY

#	Start/Stop Date	Condition Type / Condition	Notes
1	10/--/2006 UNK	Current Condition PAIN	left flank pain
4	04/--/2006 UNK	Current Condition ERECTION DYSFUNCTION	
5	UNK	Current Condition MASS	2.5 cm, oropharynx mass floor of mouth.

## C1. Name (Continued)

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

## C4. Diagnosis for use (Continued.)

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

## C10. CONCOMITANT MEDICAL PRODUCTS

VICODIN (ACETAMINOPHEN, HYDROCODONE BITARTRATE) 10/16/2006 to ongoing  
CIALIS (TADALAFIL) UNK to ongoing  
TYLENOL (ACETAMINOPHEN) 10/16/2006 to ongoing  
MULTI-VITAMIN SUPPLEMENT (MULTIVITAMINS NOS) UNK to ongoing  
GLUCOSAMINE/CHONDROITIN (CHONDROITIN SULFATE, GLUCOSAMINE) UNK to ongoing  
VITAMIN D (CHOLECALCIFEROL) UNK to ongoing  
OMEGA 3 (DOCOSAHEXAENOIC ACID, EICOSAPENTAENOIC ACID) UNK to ongoing  
MIRALAX (POLYETHYLENE GLYCOL) 11/06/2006 to ongoing

<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>57</b> Years	3. SEX <b>Male</b>	3a. WEIGHT <b>75.74</b> kg	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day	Month	Year			Day	Month	Year		
							<b>01</b>	<b>OCT</b>	<b>2007</b>		

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)  
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)  
**death [DEATH]**

Case Description: **IND SAFETY REPORT**

This case, manufacturer control number 248756, is a report from the UNITED STATES referring to a 57 Year-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, recurrent, or metastatic non-small cell lung. (continue)

PATIENT DIED  
Date: 01-OCT-2007  
  
 INVOLVED OR PROLONGED INPATIENT HOSPITALISATION  
  
 INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY  
  
 LIFE THREATENING

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

(Continued on Additional Information Page)

14. SUSPECT DRUG(S) (include generic name) #1 <b>ERLOTINIB OR PLACEBO (Erlotinib) Tablet (Lot # 2004739)</b> #2 <b>Bevacizumab (BEVACIZUMAB) Powder and solvent for (continue)</b>		20. DID REACTION ABATE AFTER STOPPING DRUG?  <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> NA
15. DAILY DOSE(S) #1 <b>150 mg, qd</b> #2 <b>1200 mg, Q3W</b>	16. ROUTE(S) OF ADMINISTRATION #1 <b>Oral</b> #2 <b>Intravenous</b>	
17. INDICATION(S) FOR USE #1 <b>non-small cell lung cancer(NON-SMALL CELL LUNG CANCER)</b> #2 <b>non small cell lung cancer(NON SMALL CELL LUNG CANCER)</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) #1 <b>01-FEB-2007 00:00 / Unknown</b> #2 <b>08-NOV-2006 00:00 / Unknown</b>	19. THERAPY DURATION #1 <b>Unknown</b> #2 <b>Unknown</b>	

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

(Continued on Additional Information Page)

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) #1 <b>FENTANYL PATCH (FENTANYL CITRATE) ; 27-OCT-2006 00:00 / Ongoing</b> #2 <b>VICODIN (ACETAMINOPHEN, HYDROCODONE BITARTRATE) ; 16-OCT-2006 00:00 / Ongoing</b> #3 <b>CIALIS (TADALAFIL) ; Ongoing</b>		
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)		
From/To Dates	Type of History / Notes	Description
OCT-2006 to Unknown	Current Condition left flank pain	PAIN
OCT-2006 to Unknown	Current Condition	INSOMNIA

**IV. MANUFACTURER INFORMATION**

24a. NAME AND ADDRESS OF MANUFACTURER <b>Genentech, Inc. James Nickas 1 DNA Way South San Francisco, CA 94080 UNITED STATES 6502255591</b>		26. REMARKS
	24b. MFR CONTROL NO. <b>248756</b>	25b. NAME AND ADDRESS OF REPORTER
24c. DATE RECEIVED BY MANUFACTURER <b>02-OCT-2007</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-OCT-2007</b>	25a. REPORT TYPE <input type="checkbox"/> INITIAL <input checked="" type="checkbox"/> FOLLOWUP: 1	

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

The subject is enrolled in the post-chemotherapy phase of trial AVF3671g and began treatment with bevacizumab (1200 mg, Q3W, Intravenous) on 08-NOV-2006. The lot number was N38279. On 01-FEB-2007, the subject began treatment with erlotinib or placebo (150 mg, qd, Oral). The lot number was 2004739. The last dose of bevacizumab prior to the event was administered on 19-SEP-2007. The last dose of erlotinib or placebo prior to the event was unknown.

On 01-OCT-2007, the subject was found dead (DEATH) at home. No relevant laboratory data was reported, it was unknown if an autopsy was preformed. There was no treatment for the event. The action taken with bevacizumab and erlotinib or placebo was not applicable.

On 4-OCT-2007, the subject was unblinded to erlotinib.

The Investigator assessed the event death as related to erlotinib and bevacizumab. There were no other suspected causes of the event.

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

Additional information has been requested.

**ADDITIONAL INFORMATION RECEIVED 12-OCT-07**

Concurrent conditions present at the time of the event included pain, insomnia, back pain, erectile dysfunction and a oropharynx mass on the floor of the mouth measuring 2.5 cm. Concomitant medications included fentanyl citrate, acetaminophen, hydrocodone bitartrate, tadalafil, acetaminophen, multivitamins nos, chondroitin sulfate, glucosamine, cholecalciferol, docosahexaenoic acid, eicosapentaenoic acid and polyethylene glycol.

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236761	DEATH		23-FEB-2007
236761	DEATH	FU #1	28-FEB-2007
242285	DEATH		12-JUn-2007
242285	DEATH	FU #1	2-JUL-2007
247765	DEATH		24-SEP-2007
247765	DEATH	FU #1	15-OCT-2007
248750	DEATH		10-OCT-2007
248756	DEATH		11-OCT-2007

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.

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	7-MAY-2002	
102517	DEATH		23-MAY-2002
102517	DEATH	FU #1	04-JUN-2002
104866	SUDDEN DEATH		22-NOV-2002
105566	DEATH		13-JAN-2003
200156	DEATH		13MAR2003
206723	DEATH		2-JUN-2004
207505	DEATH		09-JUL-2004
207505	DEATH	FU #1	09-SEP-2004
207505	DEATH	FU #2	22-AUG-2005

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

207952	DEATH	29-JUL-2004
207952	DEATH FU #1	31-AUG-2004
207952	DEATH FU #2	09-SEP-2004
207952	DEATH FU #3	17-MAY-2007
218003	DEATH	04-OCT-2005
247765	DEATH	24-SEP-2007
247765	DEATH FU#1	15-OCT-2007
248756	DEATH	11-OCT-2007

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.

Pharmacovigilance: DEATH is unlabeled in the USPI and unexpected in the IB for BEVACIZUMAB, and unexpected in the IB for ERLOTINIB. A report of death occurring after initiating bevacizumab therapy with unblinded erlotinib administered for non-small cell lung cancer in a 57 Year-old Male subject from the UNITED STATES participating in a study. The event is assessed as related to both drugs. Confounding factors include the possibility of progression of underlying condition.

**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 (Erlotinib) Tablet {Lot # 2004739}; Regimen #1	150 mg, qd; Oral	non-small cell lung cancer(NON-SMALL CELL LUNG CANCER)	01-FEB-2007 00:00 / Unknown; Unknown
#2 Bevacizumab (BEVACIZUMAB) Powder and solvent for solution for infusion, 100 mg {Lot # N38279}; Regimen #1	1200 mg, Q3W; Intravenous	non small cell lung cancer(NON SMALL CELL LUNG CANCER)	08-NOV-2006 00:00 / Unknown; Unknown

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

#4 TYLENOL (ACETAMINOPHEN) ; 16-OCT-2006 00:00 / Ongoing

#5 MULTI-VITAMIN SUPPLEMENT (MULTIVITAMINS NOS) ; Ongoing

#6 GLUCOSAMINE/CHONDROITIN (CHONDROITIN SULFATE, GLUCOSAMINE) ; Ongoing

#7 VITAMIN D (CHOLECALCIFEROL) ; Ongoing

#8 OMEGA 3 (DOCOSAHEXAENOIC ACID, EICOSAPENTAENOIC ACID) ; Ongoing

#9 MIRALAX (POLYETHYLENE GLYCOL) ; 06-NOV-2006 00:00 / Ongoing

**23. OTHER RELEVANT HISTORY continued**

From/To Dates	Type of History / Notes	Description
Unknown	Current Condition	BACK PAIN;
APR-2006 to Unknown	Current Condition	ERECTILE DYSFUNCTION;
Unknown	Current Condition	MASS; 2.5 cm, oropharynx mass floor of mouth.