



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: April 4, 2008

To: NCCTG Primary Clinical Research Associates

From: Janis Wobschall
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_257362

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 or 507-284-4852.

JW/df
enclosure

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

MEDWATCH
3500A Facsimile

Mfr Report #	257362
UF/Importer Report #	
FDA Use Only	

A. PATIENT INFORMATION			
1. Patient Identifier	2. Age at Time of Event: 75 Years or Date of Birth:	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight 124.4 lbs or 56.4 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 03/05/2008 (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) 03/05/2008		4. Date of This Report (mm/dd/yyyy) 03/13/2008	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) unexplained death[DEATH]			
Case Description: IND SAFETY REPORT			
This case, manufacturer control number 257362, is a study report from the United States referring to a 75 Year-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, recurrent, or metastatic non-small cell lung cancer.			
On 26-NOV-2007, the subject initiated treatment with Bevacizumab (15 mg/kg, Q3W, Intravenous). The lot number of 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 11/26/2007 to 01/28/2008, Historical Drug, CARBOPLATIN; Drug Indication: NON-SMALL CELL LUNG CANCER #2 11/26/2007 to 01/28/2008, Historical Drug, TAXOL; Drug Indication: NON-SMALL CELL LUNG CANCER			

C. SUSPECT PRODUCT(S)			
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. 02/12/2008, duration UNK	
#2. 15 mg/kg, Q3W, Intravenous		#2. 11/26/2007, 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. 2006058		#1. UNK	
#2. Not reported		#2. UNK	
9. NDC# or Unique ID			
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event) NI			
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) 03/07/2008		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 # AVF3871G-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 checked="" type="checkbox"/> Initial <input checked="" type="checkbox"/> 15-day <input type="checkbox"/> Follow-up #		8. Adverse Event Term(s) DEATH	
9. Manufacturer Report Number 257362			
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)

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Mfr Report#	257362
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ADDITIONAL INFORMATION**B5. EVENT DESCRIPTION (Continued)**

the Bevacizumab was not reported. From 26-NOV-2007 through 28-JAN-2008, the subject was in the open phase of the study and received concomitant chemotherapy with Carboplatin (6 AUC, Intravenous, Q21 days) and Paclitaxel (200 mg/m², Intravenous, Q21 days) for four cycles. On the fourth cycle, the dose of Carboplatin was reduced to 5AUC and the Paclitaxel was reduced to 150 mg/m².

On 12-FEB-2008, the subject entered the blinded phase of the study and initiated treatment with Erlotinib or Placebo (150 mg, qd, Oral). The lot number for the Erlotinib or Placebo was 2006058. The last dose of Bevacizumab, prior to onset of the event was administered on 21-FEB-2008 and the last dose of Erlotinib or Placebo was administered on an unknown date in MAR-2008. On 10-MAR-2008, the subject was unblinded and found to be on Erlotinib.

On 05-MAR-2008, the subject was found dead in her home. The cause of the subject's death was unknown and an autopsy was not performed. No relevant laboratory tests were reported and no treatment was provided. The action taken with Erlotinib and Bevacizumab was not applicable.

The Investigator assessed the event Death Unexplained as related to Erlotinib and Bevacizumab. No other possible etiological factors were reported.

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

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 and erlotinib.

Manufacturer Control Number	ISR Primary Event Term	Date Submitted
102407	DEATH	07-May-2002
102517	DEATH	23-May-2002
105566	DEATH	13-Jan-2003
200156	DEATH	13-Mar-2003
206723	DEATH	02-Jun-2004
207505	DEATH	09-Jul-2004
207952	DEATH	29-Jul-2004
218003	DEATH	04-Oct-2005
236761	DEATH	23-Feb-2007
242285	DEATH	12-Jun-2007
247765	DEATH	24-Sep-2007
249106	DEATH	16-Oct-2007
250243	DEATH	01-Nov-2007
255141	DEATH	07-Feb-2008

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 erlotinib and the occurrence of death can be identified.

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

Pharmacovigilance:

Death unexplained is not listed in the Erlotinib IB, not listed in the Bevacizumab IB and not labelled per the Avastin USPI. The event occurred approximately 4 months after initiating Bevacizumab and 3 weeks after initiating Erlotinib/Placebo. The cause and effect relationship cannot be determined with the information currently available with cause of death undetermined.

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)

MEDWATCH

3500A Facsimile (Back) (continued)

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

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY UNITED STATES	2. DATE OF BIRTH			2a. AGE 75 Years	3. SEX Female	3a. WEIGHT 56.40 kg	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day	Month	Year			Day	Month	Year		
										<input checked="" type="checkbox"/> PATIENT DIED Date: 05-MAR-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 test/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) unexplained death [DEATH] Case Description: IND SAFETY REPORT This case, manufacturer control number 257362, is a study report from the United States referring to a 75 Year-old Female subject (ID#). (continue)											

II. SUSPECT DRUG(S) INFORMATION

(Continued on Additional Information Page)

14. SUSPECT DRUG(S) (include generic name)		20. DID REACTION ABATE AFTER STOPPING DRUG?
#1 ERLOTINIB OR PLACEBO (Erlotinib) Tablet {Lot # 2006058} #2 Bevacizumab (BEVACIZUMAB) Powder and solvent for (continue)		
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	#1 Oral	
#2 15 mg/kg, Q3W	#2 Intravenous	
17. INDICATION(S) FOR USE		21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
#1 non small cell lung cancer(NON SMALL CELL LUNG CANCER) #2 non small cell lung cancer(NON SMALL CELL LUNG CANCER)		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	<input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> NA
#1 12-FEB-2008 00:00 / Unknown	#1 Unknown	
#2 26-NOV-2007 00:00 / Unknown	#2 Unknown	

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)									
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.) <table style="width:100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left;">From/to Dates</th> <th style="text-align: left;">Type of History /Notes</th> <th style="text-align: left;">Description</th> </tr> </thead> <tbody> <tr> <td>26-NOV-2007 to 28-JAN-2008</td> <td>Historical Drug</td> <td>(continue)</td> </tr> <tr> <td>26-NOV-2007 to 28-JAN-2008</td> <td>Historical Drug</td> <td>(continue)</td> </tr> </tbody> </table>	From/to Dates	Type of History /Notes	Description	26-NOV-2007 to 28-JAN-2008	Historical Drug	(continue)	26-NOV-2007 to 28-JAN-2008	Historical Drug	(continue)
From/to Dates	Type of History /Notes	Description							
26-NOV-2007 to 28-JAN-2008	Historical Drug	(continue)							
26-NOV-2007 to 28-JAN-2008	Historical Drug	(continue)							

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER Genentech, Inc. James Nickas 1 DNA Way South San Francisco, CA 94080 UNITED STATES 6502255591	26. REMARKS
24b. MFR CONTROL NO. 257362	25b. NAME AND ADDRESS OF REPORTER
24c. DATE RECEIVED BY MANUFACTURER 07-MAR-2008	
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 13-MAR-2008	25a. REPORT TYPE <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, 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 cancer.

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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
#1 ERLOTINIB OR PLACEBO (Erlotinib) Tablet (Lot # 2006058); Regimen #1	150 mg, qd; Oral	non small cell lung cancer(NON SMALL CELL LUNG CANCER)	12-FEB-2008 00:00 / Unknown; Unknown

ADDITIONAL INFORMATION**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 # Not reported); Regimen #1	15 mg/kg, Q3W; Intravenous	non small cell lung cancer(NON SMALL CELL LUNG CANCER)	26-NOV-2007 00:00 / Unknown; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
26-NOV-2007 to 28-JAN-2008	Historical Drug	CARBOPLATIN; Drug Indication: NON-SMALL CELL LUNG CANCER
26-NOV-2007 to 28-JAN-2008	Historical Drug	TAXOL; Drug Indication: NON-SMALL CELL LUNG CANCER