



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: October 31, 2008

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 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_265033_F1

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 or 507-538-8226.

SB/kjm
enclosure

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

MEDWATCH
3500A Facsimile

Mfr Report #	265033
UF/Importer Report #	
FDA Use Only	

A. PATIENT INFORMATION			
1. Patient Identifier	2. Age at Time of Event: 67 Years or Date of Birth:	3. Sex <input type="checkbox"/> Female <input checked="" 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 checked="" type="checkbox"/> Death: 01/04/2008 (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) 12/26/2007		4. Date of This Report (mm/dd/yyyy) 09/17/2008	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) pneumonia [PNEUMONIA]			
Case Description: IND SAFETY REPORT			
This case, manufacturer control number 265033, is a report from GERMANY referring to a 67 Year-old Male subject (ID # _____). An Investigator reported this case from Genentech sponsored trial OSI3364G, A phase III, multicenter, placebo-controlled, double-blind, randomized clinical trial to evaluate the efficacy of bevacizumab in combination with tarceva compared with tarceva alone for treatment of advanced non-small cell lung cancer (NSCLC) after failure of standard first-line chemotherapy.			
continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates #1 INVESTIGATION (continued)			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) Race: Caucasian			

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler)			
#1. BEVACIZUMAB OR PLACEBO (Bevacizumab) (Continued)			
#2. Erlotinib (ERLOTINIB) Tablet, 150mg			
2. Dose, Frequency & Route Used		3. Therapy Dates (if unknown, give duration) from/to (or best estimate)	
#1. 1260 mg, Q3W, Intravenous		#1. 11/08/2007 to UNK	
#2. 150 mg, qd, Oral		#2. 11/08/2007 to UNK	
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced? (Doesn't Apply)	
#1. nsclc (NSCLC)		#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2. nsclc (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? (Doesn't Apply)	
#1. 4(Continued)	#1.	#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2. PT9498T29	#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. UNACID (AMPICILLIN SODIUM, SULBACTAM SODIUM) 12/04/2007 to 01/06/2008 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) 09/10/2008		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 # OSI3364G		3. Report Source (Check all that apply) <input checked="" type="checkbox"/> Foreign DEU <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 checked="" 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 # <u>1</u>		9. Manufacturer Report Number 265033	
8. Adverse Event Term(s) PNEUMONIA		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 08-NOV-2007, the subject began treatment with BEVACIZUMAB OR PLACEBO (1260 mg, Q3W, Intravenous) and ERLOTINIB (150 mg, qd, Oral). The lot numbers for BEVACIZUMAB OR PLACEBO was reported as 41559, 41565, and 41555. The lot number for Erlotinib was reported as PT9498T29. The last dose of BEVACIZUMAB OR PLACEBO prior to the onset of the event was administered on 09-NOV-2007. The last dose of Erlotinib prior to the onset of the event was administered on 29-NOV-2007.

On 26-DEC-2007, the subject was hospitalized with suspicion of hemiparesis (HEMIPARESIS). No relevant laboratory or diagnostic tests were reported. Treatment for the event was reported as unknown.

On 04-JAN-2008, the subject expired due to hemiparesis. It was unknown if an autopsy was performed. The action taken with Bevacizumab or placebo and Erlotinib was not applicable.

The Investigator assessed the event hemiparesis as related to Bevacizumab or Placebo and not related to Erlotinib. In the reporter's opinion, other possible etiological factors included the subject's disease under study.

On 29-JUL-2008, the subject was unblinded to Bevacizumab.

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

Additional follow up is being requested. If received, the case will be updated accordingly.

ADDITIONAL INFORMATION RECEIVED ON 10-SEP-2008

The primary event term was amended by the investigator from suspicion of hemiparesis to pneumonia and therefore this case no longer qualifies for expedited reporting.

Concomitant medications included ampicillin sodium, sulbactam sodium, "expectorantia", and "mucolytica".

On 26-DEC-2007, the subject was hospitalized with pneumonia (PNEUMONIA) and associated symptoms included increased dyspnea and muscle weakness to the left arm. On an unspecified date, an unspecified radiology test confirmed "pneumonia".

The investigator assessed the event pneumonia as related to bevacizumab or placebo and not related to erlotinib. In the reporter's opinion, other possible etiological factors included the subject's disease under study.

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

No further information is available.

PREVIOUSLY FILED IND SAFETY REPORTS OF SIMILAR EVENTS:

Genentech has not filed previous IND safety reports of hemiparesis for subjects receiving Bevacizumab.

SPONSOR ASSESSMENT

Based on review of available data, no compelling evidence of a cause-and effect-relationship between administration of Bevacizumab and the occurrence of hemiparesis can be identified.

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

Pharmacovigilance:

PNEUMONIA is labeled per the Avastin USPI and is expected per the IB. The underlying malignancy is a possible contributing factor.

B6. LABORATORY DATA

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		INVESTIGATION	see notes	
		"radiology test" confirmed pneumonia		

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C1. NAME (Continued)

Suspect Medication #1: BEVACIZUMAB OR PLACEBO(Bevacizumab) Powder and solvent for solution for infusion, 100mg

C6. LOT# (Continued)

Suspect Medication #1: 41559, 41565, 41555

C10. CONCOMITANT MEDICAL PRODUCTS (Continued)

#2. MEDICATION (UNK INGREDIENT) (GENERIC COMPONENT(S) NOT KNOWN) 12/04/2007 to 01/06/2008

#3. MEDICATION (UNK INGREDIENT) (GENERIC COMPONENT(S) NOT KNOWN) 12/04/2007 to 01/06/2008

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

An Investigator reported this case from Genentech sponsored trial OS13364G, A phase III, multicenter, placebo-controlled, double-blind, randomized clinical trial to evaluate the efficacy of bevacizumab in combination with tarceva compared with tarceva alone for treatment of advanced non-small cell lung cancer (NSCLC) after failure of standard first-line chemotherapy.

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SPONSOR ASSESSMENT

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

Pharmacovigilance: PNEUMONIA is labeled per the Avastin USPI and is expected per the IB. The underlying malignancy is a possible contributing factor.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		INVESTIGATION	see notes	
		"radiology test" confirmed pneumonia		

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
#1) BEVACIZUMAB OR PLACEBO (Bevacizumab) Powder and solvent for solution for infusion, 100 mg {Lot # 41559, 41565, 41555}; Regimen #1	1260 mg, Q3W; Intravenous	nscic (NSCLC)	08-NOV-2007 / Unknown; Unknown

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

#2) MEDICATION (UNK INGREDIENT) (GENERIC COMPONENT(S) NOT KNOWN) ; 04-DEC-2007 / 06-JAN-2008

#3) MEDICATION (UNK INGREDIENT) (GENERIC COMPONENT(S) NOT KNOWN) ; 04-DEC-2007 / 06-JAN-2008