



# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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**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\_232048\_F4**

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

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

**MEDWATCH**  
3500A Facsimile

Mfr Report #	232048
UF/Importer Report #	
FDA Use Only	

A. PATIENT INFORMATION			
1. Patient Identifier	2. Age at Time of Event: 73 Years or Date of Birth:	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 191.2 lbs or 86.7 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 type="checkbox"/> Death: _____ (mm/dd/yyyy)		<input checked="" type="checkbox"/> Disability or Permanent Damage	
<input checked="" 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) 10/10/2006		4. Date of This Report (mm/dd/yyyy) 09/30/2008	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) encephalopathy due to chemo drug [TOXIC ENCEPHALOPATHY]			
Case Description: IND SAFETY REPORT			
This case, manufacturer control number 232048, is a report from the United States referring to a 73-year-old male subject. An investigator reported this case from a Genentech-sponsored study OSI3364g, a phase III, multicenter, placebo-controlled, double-blind, randomized clinical trial to evaluate the efficacy of Avastin (bevacizumab) in combination with Tarceva (erlotinib) 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 10/11/2006 X-RAY (Continued)			
#2 10/11/2006 WHITE BLOOD CELL CO (continued)			
#3 10/11/2006 HAEMOGLOBIN 9.0			
#4 10/11/2006 BLOOD GLUCOSE 129			
#5 10/11/2006 BLOOD UREA 20			
#6 10/11/2006 BLOOD CREATININE 0.9 continued in additional info section...			
7. Other Relevant History, including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) Race: Caucasian			
#1 Current Condition, (Continued)			
#2 Historical Condition, APPENDICECTOMY			
#3 Historical Condition, FOOT OPERATION continued in additional info section...			

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler)			
#1. BEVACIZUMAB OR PLACEBO (Code Not Broken) (Continued)			
#2. Erlotinib (ERLOTINIB) Tablet			
2. Dose, Frequency & Route Used		3. Therapy Dates (if unknown, give duration) from/to (or best estimate)	
#1. 1335 mg, Q3W, Intravenous		#1. 06/28/2006 to 09/20/2006	
#2. 150 mg, qd, Oral		#2. 06/28/2006 to 10/10/2006	
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced?	
#1. NON-SMALL CELL (Continued)		#1. <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
#2. NON-SMALL CELL (Continued)		#2. <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
6. Lot #	7. Exp. Date	8. Event Reappeared After Reintroduction?	
#1. 1(Continued)	#1.	#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2. 103734	#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. MEGACE (MEGESTROL ACETATE)			
#2. DUONEB (ALBUTEROL, ALBUTEROL SULFATE, continued in additional info section...			
G. ALL MANUFACTURERS			
1. Contact Office - Name/Address (and Manufacturing Site for Devices)		2. Phone Number	
Genentech, Inc. James Nickas Pharm.D. 1 DNA Way South San Francisco, CA 94080 UNITED STATES		6502255591	
4. Date Received by Manufacturer (mm/dd/yyyy) 09/26/2008		3. Report Source (Check all that apply)	
6. If IND, Give Protocol # OSI3364G		<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)		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	
<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 #4			
9. Manufacturer Report Number 232048		8. Adverse Event Term(s) TOXIC ENCEPHALOPATHY	
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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**ADDITIONAL INFORMATION****B5. EVENT DESCRIPTION (Continued)**

Past medical history included appendectomy, bilateral foot surgery, left knee replacement and tobacco use. Concurrent conditions included chronic obstructive pulmonary disease. Concomitant medications included megestrol, albuterol/ipratropium, acetaminophen, oxycodone, carisoprodol and pantoprazole. The subject had no known drug allergies.

On 28-JUN-2006, the subject initiated therapy with bevacizumab or placebo (1335 mg, Q3W, Intravenous) and erlotinib (100 mg, qd, Oral). The last dose of bevacizumab or placebo administered prior to the event onset was on 20-SEP-2006 and the last dose of erlotinib administered prior to the event onset was on 10-OCT-2006. The lot numbers of bevacizumab or placebo were 15879, 16147 and 15878. The lot number of erlotinib was 103734.

On 10-OCT-2006, the subject presented with generalized weakness and loss of motor strength and was admitted to the hospital. It was reported that he woke up in the morning and was unable to move and get up. Vital signs included temperature 34.1 degrees Celsius, P 124, RR 18 and BP 102/67. Neurological assessment showed the subject was alert, moving all 4 extremities and was non-focal except for some mild diffuse weakness. Motor strength in the upper extremity was 4/5 bilaterally and lower extremity was 3/5 to 4/5 bilaterally.

Chest x-ray showed some mild perihilar fullness compared to previous x-ray with no acute cardiopulmonary disease. CT of the thorax without contrast showed 2.3 x 1.9 cm right upper lobe pulmonary nodule with two adjacent subcentimeter nodules; additional 14 mm left apical nodule; severe emphysema and no definite pathologic lymphadenopathy. X-ray of the ribs revealed a 2.2 cm nodular opacity within the upper lobe, was unchanged in size compared to prior study and probable left eighth and ninth rib fractures. CT of the head/brain with and without contrast showed mild atrophy, but otherwise, a negative CT. Laboratory tests included WBC 6.0, Hgb 0.9 (as reported - awaiting confirmation), glu 129, BUN 20, creat 0.9, Na 137, K 3.7, normal liver function tests and CPK 54.

On an unspecified date, the subject was seen by Neurology who believed that the encephalopathy was related to chemotherapy drug. The subject also developed a fever and was found to have *C. difficile* colitis and received unspecified medications. Laboratory tests included blood and urine cultures which revealed no growth. On an unspecified date, the subject experienced an episode of paroxysmal tachycardia. A 2-D echocardiogram showed ejection fraction of 60% trivial tricuspid regurgitation and diastolic dysfunction. Treatment with unspecified beta and calcium channel blockers were given with improvement. The subject also had an x-ray for some left upper arm swelling which showed osteoporosis and degenerative joint disease. Treatment with bevacizumab or placebo and erlotinib were discontinued.

On 27-OCT-2006, the subject was transferred to a skilled nursing facility. Laboratory tests included WBC 5.3, Hgb 11.1, plt 334, BUN 14 and creat 0.9.

The Investigator assessed the event encephalopathy to be related to bevacizumab or placebo and erlotinib. No other suspected causes were identified.

No further information was available.

**ADDITIONAL INFORMATION RECEIVED 08-MAY-2007**

The previously reported laboratory result from 11-OCT-2006 of Hgb 0.9 has been corrected to Hgb 9.0.

The subject's past medical history was negative for liver disease, kidney disease and metabolic diseases. The subject did not have intracranial hypertension.

The encephalopathy was reported as life threatening.

A baseline tumor assessment from a CT scan performed on 22-JUN-2006, prior to therapy with erlotinib, showed multiple nodules: 1.7 cm left apical, lobulated 1.5 cm posterior segment right upper lobe and a 1.7x 1.2 cm central anterior segment right upper lobe abutting the superior vena cava. Given the intense activity on the most recent PET scan, neoplasm is a concern particularly in the left apical nodule. Interval appearance of a new 1.3 x 0.9 cm lateral segment right middle lobe nodule, and hazy right lower lobe superior segment opacity. Given the rapid appearance since January 2006, infectious granulomatous disease seems most likely. On 29-SEP-2006, a CT scan showed spiculated lesion in the medial right upper lobe, 1.5 cm mildly spiculated lesion, left apex, multilobulated noncalcified density is seen in the posterior right upper lobe. Small subcentimeter nodular density is in the basilar left lower lobe and the peripheral/posterolateral right upper lobe, findings may represent metastatic disease. Extensive emphysematous

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changes of the mid to upper lung fields. Atherosclerotic change of the abdominal aorta.

The reporter reported that progressive disease, brain metastasis or central nervous system metastases were not related to the event.

The Investigator assessed the event encephalopathy to be related to bevacizumab or placebo and erlotinib. No other suspected causes were identified.

No further information was reported.

No further follow up is expected.

**ADDITIONAL INFORMATION RECEIVED ON 29-AUG-2007**

It was clarified that both bevacizumab or placebo and erlotinib were held in response to the event.

No additional information was provided.

**31-AUG-2007: AFTER FURTHER REVIEW OF THE REPORT, ADDITIONAL CLARIFICATION IS REQUIRED:**

On 27-OCT-2006, the event resolved.

**25-AUG-2008: AFTER FURTHER REVIEW OF THE REPORT, ADDITIONAL CLARIFICATION IS REQUIRED:**

The event term was amended from encephalopathy to toxic encephalopathy.

The assessment of the event remained unchanged.

No further information was provided.

**26-SEP-2008: AFTER FURTHER REVIEW OF THE REPORT, ADDITIONAL CLARIFICATION IS REQUIRED:**

The dose for Erlotinib should have been 150 mg.

No further information was provided.

**PREVIOUSLY FILED IND SAFETY REPORTS OF SIMILAR EVENTS**

Genentech has not filed previous IND safety reports of encephalopathy for subjects receiving erlotinib.

**SPONSOR ASSESSMENT**

Based on review of available data, the Sponsor cannot establish or exclude the possibility of a cause-and-effect relationship between administration of erlotinib and the occurrence of encephalopathy. At this time, the Sponsor does not believe that changes to the conduct of this clinical trial are warranted.

**Pharmacovigilance:**

Encephalopathy is listed per the bevacizumab IB, unlabeled per the Avastin USPI, and unlisted per the erlotinib IB.

**B6. LABORATORY DATA**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	10/11/2006	X-RAY  of the chest showed some perihilar fullness compared to previous x-ray.		
2	10/11/2006	WHITE BLOOD CELL COUNT	6.0	
7	10/11/2006	BLOOD SODIUM	137	

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8	10/11/2006	BLOOD POTASSIUM	3.7
9	10/11/2006	LIVER FUNCTION TEST Normal	
10	10/11/2006	LABORATORY TEST  CPK	54
11	10/13/2006	COMPUTERISED TOMOGRAM  of the thorax without contrast showed 2.3 x 1.9 cm right upper lobe pulmonary nodule with two adjacent subcentimeter nodules, additional 14 mm left apical nodule, severe emphysema and no definite pathologic lymphadenopathy.	
12	10/13/2006	X-RAY  of the ribs showed a 2.2 cm nodular opacity within the upper lobe, unchanged in size compared to prior study and probable left eight and ninth rib fractures.	
13	10/12/2006	COMPUTERISED TOMOGRAM  of the head/brain with and without contrast showed mild atrophy, otherwise, a negative CT.	
14	10/11/2006	X-RAY  of the chest showed no acute cardiopulmonary disease	
15	10/27/2006	X-RAY  of the left hand showed osteoporosis, moderate degenerative joint disease changes in the fingers and thumb, severe degenerative joint disease changes in the thumb carpometacarpal joint and no fractures were identified.	
16		BLOOD CULTURE  showed no growth	
17		CULTURE URINE  showed no growth	
18		ECHOCARDIOGRAM  2-D, showed ejection fraction of 60% trivial tricuspid regurgitation and diastolic dysfunction.	
19	10/27/2006	WHITE BLOOD CELL COUNT	5.3
20	10/27/2006	HAEMOGLOBIN	11.1
21	10/27/2006	PLATELET COUNT	334
22	10/27/2006	BLOOD UREA	14
23	10/27/2006	BLOOD CREATININE	0.9
24	06/22/2006	COMPUTERISED TOMOGRAM	

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**PRE-ERLOTINIB ASSESSMENT**

multiple nodules: 1.7 cm left apical, lobulated 1.5 cm posterior segment right upper lobe and a 1.7x 1.2 cm central anterior segment right upper lobe abutting the superior vena cava. Given the intense activity on the most recent pet scan, neoplasm is a concern particularly in the left apical nodule. Interval appearance of a new 1.3 x 0.9 cm lateral segment right middle lobe nodule, and hazy right lower lobe superior segment opacity. Given the rapid appearance since January 2006, infectious granulomatous disease seems most likely

25 09/29/2006 COMPUTERISED TOMOGRAM

spiculated lesion in the medial right upper lobe, 1.5 CM mildly spiculated lesion, left Apex. multilobulated noncalcified density is seen in the posterior right upper lobe. Small subcentimeter nodular density is in the basilar left lower lobe and the peripheral/posterolateral right upper lobe, findings may represent metastatic disease. Extensive emphysematous changes of the mid to upper lung fields. Atherosclerotic change of the abdominal aorta.

**B7. OTHER RELEVANT HISTORY**

#	Start/Stop Date	Condition Type / Condition	Notes
1		Current Condition CHRONIC OBSTRUCTIVE PULMONARY DISEASE	
4		Historical Condition KNEE ARTHROPLASTY	
5		Historical Condition TOBACCO USER	
6		Negative Med Cond LIVER DISORDER	
7		Negative Med Cond RENAL DISORDER	
8		Negative Med Cond METABOLIC DISORDER	
9		Negative Med Cond INTRACRANIAL PRESSURE INCREASED	

**C1. NAME (Continued)**

Suspect Medication #1: BEVACIZUMAB OR PLACEBO(Code Not Broken) 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)

**C6. LOT# (Continued)**

Suspect Medication #1: 15879, 16147, 15878

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

IPRATROPIUM BROMIDE)

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- #3. PERCOCET (ACETAMINOPHEN, OXYCODONE HYDROCHLORIDE)
- #4. PROTONIX (PANTOPRAZOLE)
- #5. CARISOPRODOL (CARISOPRODOL)

<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>73 Years</b>	3. SEX <b>Male</b>	3a. WEIGHT <b>86.71 kg</b>	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION  <input type="checkbox"/> PATIENT DIED <input checked="" type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION  <input checked="" type="checkbox"/> INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY  <input checked="" 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>encephalopathy due to chemo drug [TOXIC ENCEPHALOPATHY]</b>  Case Description: IND SAFETY REPORT  This case, manufacturer control number 232048, is a report from the United States referring to a 73-year-old male subject.  <div style="text-align: right;">(Continued on Additional Information Page)</div>											

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

14. SUSPECT DRUG(S) (include generic name) #1 ) BEVACIZUMAB OR PLACEBO (Code not broken) Powder and solvent for solution for infusion, 100 mg {Lot # #2 ) Erlotinib (ERLOTINIB) Tablet {Lot # 103734} <div style="text-align: right;">(Continued on Additional Information Page)</div>		20. DID REACTION ABATE AFTER STOPPING DRUG?  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA
15. DAILY DOSE(S) #1 ) 1335 mg, Q3W #2 ) 150 mg, qd	16. ROUTE(S) OF ADMINISTRATION #1 ) Intravenous #2 ) Oral	
17. INDICATION(S) FOR USE #1 ) NON-SMALL CELL LUNG CANCER ( #2 ) NON-SMALL CELL LUNG CANCER ( <div style="text-align: right;">(Continued on Additional Information Page)</div>		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 ) 28-JUN-2006 / 20-SEP-2006 #2 ) 28-JUN-2006 / 10-OCT-2006	19. THERAPY DURATION #1 ) 85 days #2 ) 105 days	

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

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) #1 ) MEGACE (MEGESTROL ACETATE) ; Unknown #2 ) DUONEB (ALBUTEROL, ALBUTEROL SULFATE, IPRATROPIUM BROMIDE) ; Unknown #3 ) PERCOCET (ACETAMINOPHEN, OXYCODONE HYDROCHLORIDE) ; Unknown #4 ) PROTONIX (PANTOPRAZOLE) ; Unknown #5 ) CARISOPRODOL (CARISOPRODOL) ; Unknown		
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	COPD (CHRONIC OBSTRUCTIVE PULMONARY DISEASE)
Unknown	Historical Condition	APPENDECTOMY (APPENDICECTOMY)

**IV. MANUFACTURER INFORMATION**

24a. NAME AND ADDRESS OF MANUFACTURER Genentech, Inc. James Nickas 1 DNA Way South San Francisco, CA 94080 UNITED STATES Phone: 6502255591		26. REMARKS
24b. MFR CONTROL NO. <b>232048</b>		
24c. DATE RECEIVED BY MANUFACTURER <b>26-SEP-2008</b>	24d. REPORT SOURCE <input checked="" type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input checked="" type="checkbox"/> HEALTH PROFESSIONAL <input type="checkbox"/> OTHER:	25b. NAME AND ADDRESS OF REPORTER
DATE OF THIS REPORT <b>30-SEP-2008</b>	25a. REPORT TYPE <input type="checkbox"/> INITIAL <input checked="" type="checkbox"/> FOLLOWUP: 3	

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

An investigator reported this case from a Genentech-sponsored study OSI3364g, a phase III, multicenter, placebo-controlled, double-blind, randomized clinical trial to evaluate the efficacy of Avastin (bevacizumab) in combination with Tarceva (erlotinib) compared with Tarceva alone for treatment of advanced non-small cell lung cancer (NSCLC) after failure of standard first-line chemotherapy.

Past medical history included appendectomy, bilateral foot surgery, left knee replacement and tobacco use. Concurrent conditions included chronic obstructive pulmonary disease. Concomitant medications included megestrol, albuterol/ipratropium, acetaminophen, oxycodone, carisoprodol and pantoprazole. The subject had no known drug allergies.

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On 10-OCT-2006, the subject presented with generalized weakness and loss of motor strength and was admitted to the hospital. It was reported that he woke up in the morning and was unable to move and get up. Vital signs included temperature 34.1 degrees Celsius, P 124, RR 18 and BP 102/67. Neurological assessment showed the subject was alert, moving all 4 extremities and was non-focal except for some mild diffuse weakness. Motor strength in the upper extremity was 4/5 bilaterally and lower extremity was 3/5 to 4/5 bilaterally.

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On an unspecified date, the subject was seen by Neurology who believed that the encephalopathy was related to chemotherapy drug. The subject also developed a fever and was found to have *C. difficile* colitis and received unspecified medications. Laboratory tests included blood and urine cultures which revealed no growth. On an unspecified date, the subject experienced an episode of paroxysmal tachycardia. A 2-D echocardiogram showed ejection fraction of 60% trivial tricuspid regurgitation and diastolic dysfunction. Treatment with unspecified beta and calcium channel blockers were given with improvement. The subject also had an x-ray for some left upper arm swelling which showed osteoporosis and degenerative joint disease. Treatment with bevacizumab or placebo and erlotinib were discontinued.

On 27-OCT-2006, the subject was transferred to a skilled nursing facility. Laboratory tests included WBC 5.3, Hgb 11.1, plt 334, BUN 14 and creat 0.9.

The Investigator assessed the event encephalopathy to be related to bevacizumab or placebo and erlotinib. No other suspected causes were identified.

No further information was available.

**ADDITIONAL INFORMATION RECEIVED 08-MAY-2007**

The previously reported laboratory result from 11-OCT-2006 of Hgb 0.9 has been corrected to Hgb 9.0.

The subject's past medical history was negative for liver disease, kidney disease and metabolic diseases. The subject did not have intracranial hypertension.

The encephalopathy was reported as life threatening.

A baseline tumor assessment from a CT scan performed on 22-JUN-2006, prior to therapy with erlotinib, showed multiple nodules: 1.7 cm left apical, lobulated 1.5 cm posterior segment right upper lobe and a 1.7x 1.2 cm central anterior segment right upper lobe abutting the superior vena cava. Given the intense activity on the most recent PET scan, neoplasm is a concern particularly in the left apical nodule. Interval appearance of a new 1.3 x 0.9 cm lateral segment right middle lobe nodule, and hazy right lower lobe superior segment opacity. Given the rapid appearance since January 2006, infectious granulomatous disease seems most likely. On 29-SEP-2006, a CT scan showed spiculated lesion in the medial right upper lobe, 1.5 cm mildly spiculated lesion, left apex, multilobulated noncalcified density is seen in the posterior right upper lobe. Small subcentimeter nodular density is in the basilar left lower lobe and the peripheral/posterolateral right upper lobe, findings may represent metastatic disease. Extensive emphysematous changes of the mid to upper lung fields. Atherosclerotic change of the abdominal aorta.

The reporter reported that progressive disease, brain metastasis or central nervous system metastases were not related to the event.

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

The Investigator assessed the event encephalopathy to be related to bevacizumab or placebo and erlotinib. No other suspected causes were identified.

No further information was reported.

No further follow up is expected.

**ADDITIONAL INFORMATION RECEIVED ON 29-AUG-2007**

It was clarified that both bevacizumab or placebo and erlotinib were held in response to the event.

No additional information was provided.

**31-AUG-2007: AFTER FURTHER REVIEW OF THE REPORT, ADDITIONAL CLARIFICATION IS REQUIRED:**

On 27-OCT-2006, the event resolved.

**25-AUG-2008: AFTER FURTHER REVIEW OF THE REPORT, ADDITIONAL CLARIFICATION IS REQUIRED:**

The event term was amended from encephalopathy to toxic encephalopathy.

The assessment of the event remained unchanged.

No further information was provided.

**26-SEP-2008: AFTER FURTHER REVIEW OF THE REPORT, ADDITIONAL CLARIFICATION IS REQUIRED:**

The dose for Erlotinib should have been 150 mg.

No further information was provided.

**PREVIOUSLY FILED IND SAFETY REPORTS OF SIMILAR EVENTS**

Genentech has not filed previous IND safety reports of encephalopathy for subjects receiving erlotinib.

**SPONSOR ASSESSMENT**

Based on review of available data, the Sponsor cannot establish or exclude the possibility of a cause-and-effect relationship between administration of erlotinib and the occurrence of encephalopathy. At this time, the Sponsor does not believe that changes to the conduct of this clinical trial are warranted.

Pharmacovigilance: Encephalopathy is listed per the bevacizumab IB, unlabeled per the Avastin USPI, and unlisted per the erlotinib IB.

**13. Lab Data**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	11-OCT-2006	X-RAY  of the chest showed some perihilar fullness compared to previous x-ray.		
2	11-OCT-2006	WHITE BLOOD CELL COUNT	6.0	
3	11-OCT-2006	HAEMOGLOBIN	9.0	
4	11-OCT-2006	BLOOD GLUCOSE	129	
5	11-OCT-2006	BLOOD UREA	20	
6	11-OCT-2006	BLOOD CREATININE	0.9	
7	11-OCT-2006	BLOOD SODIUM	137	

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**ADDITIONAL INFORMATION**


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**13. Lab Data**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
8	11-OCT-2006	BLOOD POTASSIUM	3.7	
9	11-OCT-2006	LIVER FUNCTION TEST Normal		
10	11-OCT-2006	LABORATORY TEST  CPK	54	
11	13-OCT-2006	COMPUTERISED TOMOGRAM  of the thorax without contrast showed 2.3 x 1.9 cm right upper lobe pulmonary nodule with two adjacent subcentimeter nodules, additional 14 mm left apical nodule, severe emphysema and no definite pathologic lymphadenopathy.		
12	13-OCT-2006	X-RAY  of the ribs showed a 2.2 cm nodular opacity within the upper lobe, unchanged in size compared to prior study and probable left eight and ninth rib fractures.		
13	12-OCT-2006	COMPUTERISED TOMOGRAM  of the head/brain with and without contrast showed mild atrophy, otherwise, a negative CT.		
14	11-OCT-2006	X-RAY  of the chest showed no acute cardiopulmonary disease		
15	27-OCT-2006	X-RAY  of the left hand showed osteoporosis, moderate degenerative joint disease changes in the fingers and thumb, severe degenerative joint disease changes in the thumb carpometacarpal joint and no fractures were identified.		
16		BLOOD CULTURE  showed no growth		
17		CULTURE URINE  showed no growth		
18		ECHOCARDIOGRAM  2-D, showed ejection fraction of 60% trivial tricuspid regurgitation and diastolic dysfunction.		
19	27-OCT-2006	WHITE BLOOD CELL COUNT	5.3	
20	27-OCT-2006	HAEMOGLOBIN	11.1	
21	27-OCT-2006	PLATELET COUNT	334	
22	27-OCT-2006	BLOOD UREA	14	

**ADDITIONAL INFORMATION****13. Lab Data**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
23	27-OCT-2006	BLOOD CREATININE	0.9	
24	22-JUN-2006	COMPUTERISED TOMOGRAM		

**PRE-ERLOTINIB ASSESSMENT**

multiple nodules: 1.7 cm left apical, lobulated 1.5 cm posterior segment right upper lobe and a 1.7x 1.2 cm central anterior segment right upper lobe abutting the superior vena cava. Given the intense activity on the most recent pet scan, neoplasm is a concern particularly in the left apical nodule. Interval appearance of a new 1.3 x 0.9 cm lateral segment right middle lobe nodule, and hazy right lower lobe superior segment opacity. Given the rapid appearance since January 2006, infectious granulomatous disease seems most likely

25 29-SEP-2006 COMPUTERISED TOMOGRAM

spiculated lesion in the medial right upper lobe, 1.5 CM mildly spiculated lesion, left Apex. multilobulated noncalcified density is seen in the posterior right upper lobe. Small subcentimeter nodular density is in the basilar left lower lobe and the peripheral/posterolateral right upper lobe, findings may represent metastatic disease. Extensive emphysematous changes of the mid to upper lung fields. Atherosclerotic change of the abdominal aorta.

**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 (Code not broken) Powder and solvent for solution for infusion, 100 mg {Lot # 15879, 16147, 15878}; Regimen #1	1335 mg, Q3W; Intravenous	NON-SMALL CELL LUNG CANCER (NON SMALL CELL LUNG CANCER)	28-JUN-2006 / 20-SEP-2006; 85 days
#2 ) Erlotinib (ERLOTINIB) Tablet {Lot # 103734}; Regimen #1	150 mg, qd; Oral	NON-SMALL CELL LUNG CANCER (NON SMALL CELL LUNG CANCER)	28-JUN-2006 / 10-OCT-2006; 105 days

**23. OTHER RELEVANT HISTORY continued**

From/To Dates	Type of History / Notes	Description
Unknown	Historical Condition	FOOT SURGERY (FOOT OPERATION);
Unknown	Historical Condition	TOTAL KNEE REPLACEMENT (KNEE ARTHROPLASTY);
Unknown	Historical Condition	TOBACCO USER (TOBACCO USER);
Unknown	Negative Med Cond	LIVER DISORDER (LIVER DISORDER);
Unknown	Negative Med Cond	KIDNEY DISORDER (RENAL DISORDER);
Unknown	Negative Med Cond	METABOLIC DISORDER (METABOLIC DISORDER);
Unknown	Negative Med Cond	INTRACRANIAL HYPERTENSION (INTRACRANIAL PRESSURE INCREASED);