



# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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**Date:** March 27, 2009

**To:** NCCTG Primary Clinical Research Associates

**From:** Janis Wobschall  
Protocol Development Coordinator

**Re:** N0776, Phase II Trial of Avastin® in Combination with Sorafenib in Recurrent Glioblastoma Multiforme

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\_265652\_F3**

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 Janis Wobschall at [wobschall.janis@mayo.edu](mailto:wobschall.janis@mayo.edu) or 507-284-4852.

JW/kjm  
enclosure

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

**MEDWATCH**  
3500A Facsimile

Page 1 of 7

Mfr Report #	265652
UF/Importer Report #	
FDA Use Only	

A. PATIENT INFORMATION			
1. Patient Identifier	2. Age at Time of Event: 65 Years or Date of Birth:	3. Sex <input type="checkbox"/> Female <input checked="" type="checkbox"/> Male	4. Weight 224.0 lbs or 101.6 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 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) 08/01/2008		4. Date of This Report (mm/dd/yyyy) 11/17/2008	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) blurred vision [VISION BLURRED]			
Case Description: IND SAFETY REPORT			
This case, manufacturer control number 265652, is a report from the United States referring to a 65 year-old male subject (ID# ). An Investigator reported this case from a Genentech sponsored 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 or metastatic non-squamous non-small cell lung cancer (NSCLC).			
continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates #1 06/13/2008 INVESTIGATION (continued) #2 07/28/2008 NUCLEAR MAGNETIC RE (continued) #3 06/13/2008 VISUAL ACUITY TESTS (continued)			
7. Other Relevant History, Including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) Race: Caucasian #1 Historical Condition, NEPHROLITHIASIS #2 Historical Condition, HEADACHE (rarely) #3 Historical Condition, RENAL CYST continued in additional info section...			

C. SUSPECT PRODUCT(S)			
1. Name (Give labeled strength & mfr/labeler)			
#1. ERLOTINIB OR PLACEBO (Erlotinib) Tablet			
#2. Avastin (BEVACIZUMAB) Powder and solvent for solution (Continued)			
2. Dose, Frequency & Route Used		3. Therapy Dates (if unknown, give duration) from/to (or best estimate)	
#1. 150 mg, qd, Oral		#1. 01/05/2008 to 07/31/2008	
#2. 1636 mg, Q3W, Intravenous		#2. 09/28/2007 to 07/11/2008	
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced?	
#1. nsclc (NSCLC)		#1. <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
#2. nsclc (NSCLC)		#2. <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
6. Lot #	7. Exp. Date	8. Event Reappeared After Reintroduction?	
#1. 2006777	#1.	#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2. 701872	#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. LIPITOR (ATORVASTATIN CALCIUM)			
#2. LOTREL (AMLODIPINE BESYLATE, BENAZEPRIL) 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) 11/12/2008		3. Report Source (Check all that apply)	
6. If IND, Give Protocol # AVF3671G-B		<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 #	
<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 #3		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	
9. Manufacturer Report Number 265652		8. Adverse Event Term(s) VISION BLURRED	

E. INITIAL REPORTER			
1. Name and Address		Phone #	
2. Health Professional?	3. Occupation	4. Initial Reporter Also Sent Report to FDA	
<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		<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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C. SUSPECT PRODUCT(S)	
1. Name (Give labeled strength & mfr/labeler)	
#3. PARAPLATIN (CARBOPLATIN)	
#4. TAXOL (PACLITAXEL)	
2. Dose, Frequency & Route Used	3. Therapy Dates (if unknown, give duration from/to (or best estimate))
#3. UNK	#3. 09/28/2007 to 11/30/2007
#4. UNK	#4. 09/28/2007 to 11/30/2007
4. Diagnosis for Use (Indication)	5. Event Abated After Use Stopped or Dose Reduced?
#3. nsclc (NSCLC)	#3. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply
#4. nsclc (NSCLC)	#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)	

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

The subject's medical history was significant for renal stones, rare headaches and migraines, renal cysts, hepatic cysts, and sacroiliitis. The subject denied any diabetic history. In 1991, the subject quit smoking. The subject denied alcohol use. On 24-JUL-2007, the subject was diagnosed with non-small cell lung cancer with metastases to the bone and brain. On 06-AUG-2007, during pre-screening and prior to study treatment, the subject denied any symptoms of blurred vision or eye pain. On 12-AUG-2007, following treatment with radiation for cerebral metastases and prior to receiving treatment with bevacizumab and erlotinib or placebo, the subject reported intermittently mild blurred vision. The subject was told by his radio-oncologist that this was not related to radiation therapy. On approximately 01-MAR-2008, the subject was diagnosed with glaucoma. Concurrent conditions included hypertension, depression, arthritis, hypercholesterolemia, neurofibromatosis, pain, (unspecified) gastrointestinal disorder, (unspecified) prostatic disorder, glaucoma, and deep vein thrombosis in the right leg. The subject reported a peri-oral facial rash thought to be related to erlotinib. The subject also reported symptoms of prostate hypertrophy, but denied any pulmonary symptoms. Concomitant medications include atorvastatin calcium, amlodipine besylate/ benazepril hydrochloride, ibuprofen, acetaminophen/hydrocodone bitartrate, glucosamine, chondroitin sulfate, hydrochlorothiazide/ triamterene, pantoprazole, senna, tamsulosin hydrochloride, oxycodone hydrochloride, dexamethasone, latanoprost, enoxaparin sodium, (unspecified) antiglaucoma agent, bimatoprost, citalopram, lorazepam, and warfarin sodium. The subject had seasonal allergies. The subject denied any drug hypersensitivities.

The subject is enrolled in the post-chemotherapy phase of trial AVF3671g and on 28-SEP-2007 received an (unspecified) antineoplastic agent (dose, frequency, and route not reported). The last dose of unspecified antineoplastic agent administered prior to the event was on 30-NOV-2008. On 28-SEP-2007, the subject received bevacizumab (1636 mg, Q3W, Intravenous). The bevacizumab lot number was reported as 701872. On 05-JAN-2008, the subject began treatment with erlotinib or placebo (150 mg, qd, Oral). The erlotinib or placebo lot number was reported as 2006777. The last dose of bevacizumab administered prior to the event was on 11-JUL-2008. The last dose of erlotinib or placebo administered prior to the event was on 31-JUL-2008.

On 30-MAY-2008, the subject experienced blurred vision in the left eye and the condition was continuously monitored. The right eye was reportedly "still good."

On an unspecified date, the subject was seen by psychology and psychosomatic symptoms were ruled out. The subject reported seeing "white areas" and "as if there was a screen" in his visual area.

On 13-JUN-2008, the subject was seen by a neuro-ophthalmologist. The subject's visual acuity was (20/25) on the right and (20/30) on the left. On Ishihara testing, the subject correctly responded to (7/15) color test plates presented to the right eye and "(?)2/15" color test plates presented to the left eye. On examination, the pupils reactions were questionable for "deafferent reaction on the or left." The lids, orbits, and ocular motility were normal in both eyes. On slit lamp examination, the conjunctiva, cornea, anterior chamber, iris, and lens revealed mild lenticular changes of early cataract formation in both eyes. The treating neuro-ophthalmologist diagnosed the patient with bilateral optic neuropathy; however, noted the radiation dose may not have been high enough to account for the subject's visual disturbance.

On 28-JUL-2008, MRI of the orbits were reportedly normal.

At the time of the report, no eye exam information was available.

On 01-AUG-2008, the subject's blurred vision assessed as grade IV had deteriorated and became disabling (BLURRED VISION). The subject reportedly was no longer able to drive or distinguish faces. At the time of the report, the Investigator and consulting ophthalmologist did not know the underlying etiology and on 01-AUG-2008, decided to remove the subject from the study. The subject did not receive any treatment for the event.

On 04-AUG-2008, the subject was unblinded and received active drug.

At the time of the report, the event remained ongoing.

The investigator assessed the event of blurred vision as related to erlotinib and bevacizumab. The investigator did not provide a causality assessment for the event in relation to the unspecified antineoplastic agent. In the reporter's opinion, other possible etiological factors included the disease under study.

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

Additional information has been requested. If received, the case will be updated accordingly.

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**ADDITIONAL INFORMATION WAS RECEIVED ON 07-AUG-2008:**

The last dose of unspecified antineoplastic agent administered prior to the event was confirmed to be administered on 30-NOV-2007 (previously reported as "2008"). The reporter confirmed that the event blurred vision was a pre-existing condition which worsened following the administration of Bevacizumab and that bilateral optic neuropathy was not considered a causative agent. The etiology of the event blurred vision remained unknown at the time of this report.

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 28-AUG-2008:**

Concomitant medications included lycopene/pygeum africanum extract/saw palmetto/stinging nettle and acetaminophen/hydrocodone bitartrate.

Additional information has been requested. If received, the case will be updated accordingly.

**ADDITIONAL INFORMATION WAS RECEIVED ON 12-NOV-2008:**

On 17-SEP-2008, the subject was seen by a neuro-ophthalmologist, the Physician reported that the subject was having a very hard time getting around, and was only able to make out shadows and large objects. The subject denied any other associated symptoms at that time, including double vision, flashes of light, and floaters. The subject reported occasional headaches, which were not considered out of the ordinary, and stated that his vision has rapidly and progressively declined over the last several months. The Physician completed a neuro-ophthalmologic evaluation and reported "his visual acuity was found to be significantly reduced, his color vision was grossly intact, and his visual field was found to be significantly restricted. Both his optic nerves appear severely atrophied with pallor and excavation. Based on the patient's historical information and the findings from this examination, there may be multiple etiologies of his optic nerve atrophy." Other etiological factor reported by the Physician included cancer-associated retinopathy and/or radiation-associated atrophy. The Physician reported, not one diagnosis could be completely confirmed given the multi-factorial factors including the risk of radiation-associated atrophy, his newly diagnosed low-tension glaucoma, and his chemotherapeutic agents, all of which could play a factor into causing optic nerve atrophy.

Previously reported "(unspecified) antineoplastic agent" was amended to Carboplatin (dose, frequency and route not reported) and Paclitaxel (dose, frequency and route not reported).

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

**ADDITIONAL INFORMATION IS BEING REQUESTED. IF RECEIVED, THE CASE WILL BE UPDATED ACCORDINGLY.**

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

Genentech has previously filed the following IND safety report of similar events from studies of erlotinib.

Manufacturer Control Number	ISR Primary Event Term	Date Submitted
104877	UVEITIS	22-NOV-2002

Genentech has not filed previous IND safety reports of blurred vision for subjects receiving bevacizumab.

**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/ or bevacizumab and the occurrence of blurred vision.

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

**B6. LABORATORY DATA**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	06/13/2008	INVESTIGATION	see notes	

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Isihara testing  
7/15 color test plates to the right eye

"(?)2/15" color test plates to the left eye

2	07/28/2008	NUCLEAR MAGNETIC RESONANCE IMAGING Normal MRI of orbits	see notes
---	------------	--	-----------

3	06/13/2008	VISUAL ACUITY TESTS  20/25 on the right 20/30 on the left correctable	see notes
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**B7. OTHER RELEVANT HISTORY**

#	Start/Stop Date	Condition Type / Condition	Notes
---	-----------------	----------------------------	-------

4		Historical Condition HEPATIC CYST	
---	--	--------------------------------------	--

5		Historical Condition SACROILIITIS	
---	--	--------------------------------------	--

6		Current Condition HYPERTENSION	
---	--	-----------------------------------	--

7		Current Condition DEPRESSION	
---	--	---------------------------------	--

8		Current Condition ARTHRITIS	
---	--	--------------------------------	--

9		Current Condition HYPERCHOLESTEROLAEM IA	
---	--	--	--

10		Current Condition NEUROFIBROMATOSIS	
----	--	--	--

11	UNK --/1991	Historical Condition TOBACCO USER	
----	----------------	--------------------------------------	--

12		Allergy SEASONAL ALLERGY	
----	--	-----------------------------	--

13		Current Condition PAIN	
----	--	---------------------------	--

14		Current Condition GASTROINTESTINAL DISORDER	
----	--	---	--

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15		Current Condition PROSTATIC DISORDER	
16	03/01/2008 UNK	Current Condition GLAUCOMA	
17		Current Condition DEEP VEIN THROMBOSIS	right leg
18	08/12/2007 UNK	Historical Condition VISION BLURRED	assessed as mild
19	08/--/2007 UNK	Procedure RADIOTHERAPY	14 days of whole brain radiation for cerebral metastases
20		Negative Med Cond DRUG HYPERSENSITIVITY	
21		Historical Condition MIGRAINE	rarely
22		Negative Med Cond DIABETES MELLITUS	
23		Negative Med Cond ALCOHOL USE	
24		Current Condition BENIGN PROSTATIC HYPERPLASIA	
25		Current Condition RASH	believed to be related to erlotinib
26		Negative Med Cond LUNG DISORDER	denied pulmonary symptoms
27		Current Condition OPTIC ATROPHY	

## C1. NAME (Continued)

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

## C10. CONCOMITANT MEDICAL PRODUCTS (Continued)

HYDROCHLORIDE) --/2004 to UNK

#3. MOTRIN (IBUPROFEN) 06/--/2007 to UNK

#4. VICODIN ES (ACETAMINOPHEN, HYDROCODONE BITARTRATE) 08/--/2007 to UNK

#5. VICODIN ES (ACETAMINOPHEN, HYDROCODONE BITARTRATE) 08/--/2007 to UNK

#6. GLUCOSAMINE (GLUCOSAMINE) --/1994 to UNK

#7. CHONDROITIN (CHONDROITIN SULFATE) --/1994 to UNK

#8. DYAZIDE (HYDROCHLOROTHIAZIDE, TRIAMTERENE) --/2002 to UNK

#9. PROTONIX (PANTOPRAZOLE) 02/--/2008 to UNK

#10. SENNA (SENNALAX) 02/--/2008 to UNK

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- #11. FLOMAX (TAMSULOSIN HYDROCHLORIDE) 02/--/2008 to UNK
- #12. OXYCONTIN (OXYCODONE HYDROCHLORIDE)
- #13. DEXAMETHASONE (DEXAMETHASONE)
- #14. DEXAMETHASONE (DEXAMETHASONE) 11/--/2008 to UNK
- #15. XALATAN (LATANOPROST) 02/--/2008 to UNK
- #16. LOVENOX (ENOXAPARIN SODIUM)
- #17. GLAUCOMA EYE DROPS (UNK INGREDIENTS) (ANTIGLAUCOMA AGENT NOS)
- #18. LUMIGAN (BIMATOPROST) 06/--/2008 to UNK
- #19. CELEXA (CITALOPRAM) 06/--/2008 to UNK
- #20. ATIVAN (LORAZEPAM)
- #21. COUMADIN (WARFARIN SODIUM)
- #22. VICODIN (ACETAMINOPHEN, HYDROCODONE BITARTRATE)
- #23. PROSTATE SUPPORT (LYCOPENE, PYGEUM AFRICANUM EXTRACT, SAW PALMETTO, STINGING NETTLE) 05/--/2008 to UNK

<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	3. SEX	3a. WEIGHT	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION  <input type="checkbox"/> PATIENT DIED  <input type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION  <input checked="" type="checkbox"/> INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY  <input type="checkbox"/> LIFE THREATENING
		Day	Month	Year	65 Years	Male	101.59 kg	Day	Month	Year	
							01	AUG	2008		

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

Case Description: **IND SAFETY REPORT**

This case, manufacturer control number 265652, is a report from the United States referring to a 65 year-old male subject (ID# ).

(Continued on Additional Information Page)

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

14. SUSPECT DRUG(S) (include generic name) #1 ) ERLOTINIB OR PLACEBO (Erlotinib) Tablet {Lot # 2006777} #2 ) Avastin (BEVACIZUMAB) Powder and solvent for solution for infusion, (Continued on Additional Information Page)		20. DID REACTION ABATE AFTER STOPPING DRUG?  <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> NA
15. DAILY DOSE(S) #1 ) 150 mg, qd #2 ) 1636 mg, Q3W	16. ROUTE(S) OF ADMINISTRATION #1 ) Oral #2 ) Intravenous	
17. INDICATION(S) FOR USE #1 ) nslc (NSCLC) #2 ) nslc (NSCLC)		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 ) 05-JAN-2008 / 31-JUL-2008 #2 ) 28-SEP-2007 / 11-JUL-2008	19. THERAPY DURATION #1 ) 209 days #2 ) 288 days	

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

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) #1 ) LIPITOR (ATORVASTATIN CALCIUM) ; Unknown #2 ) LOTREL (AMLODIPINE BESYLATE, BENAZEPRIL HYDROCHLORIDE) ; 2004 / Unknown #3 ) MOTRIN (IBUPROFEN) ; JUN-2007 / Unknown #4 ) VICODIN ES (ACETAMINOPHEN, HYDROCODONE BITARTRATE) ; AUG-2007 / Unknown #5 ) GLUCOSAMINE (GLUCOSAMINE) ; 1994 / Unknown #6 ) CHONDROITIN (CHONDROITIN SULFATE) ; 1994 / Unknown <span style="float: right;">(Continued on Additional Information Page)</span>		
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)		
From/To Dates	Type of History / Notes	Description
Unknown	Historical Condition	RENAL STONE (NEPHROLITHIASIS)
Unknown	Historical Condition	HEADACHE (HEADACHE)
	rarely	

**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>265652</b>	25b. NAME AND ADDRESS OF REPORTER
24c. DATE RECEIVED BY MANUFACTURER <b>12-NOV-2008</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>17-NOV-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 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 or metastatic non-squamous non-small cell lung cancer (NSCLC).

The subject's medical history was significant for renal stones, rare headaches and migraines, renal cysts, hepatic cysts, and sacroiliitis. The subject denied any diabetic history. In 1991, the subject quit smoking. The subject denied alcohol use. On 24-JUL-2007, the subject was diagnosed with non-small cell lung cancer with metastases to the bone and brain. On 06-AUG-2007, during pre-screening and prior to study treatment, the subject denied any symptoms of blurred vision or eye pain. On 12-AUG-2007, following treatment with radiation for cerebral metastases and prior to receiving treatment with bevacizumab and erlotinib or placebo, the subject reported intermittently mild blurred vision. The subject was told by his radio-oncologist that this was not related to radiation therapy. On approximately 01-MAR-2008, the subject was diagnosed with glaucoma. Concurrent conditions included hypertension, depression, arthritis, hypercholesterolemia, neurofibromatosis, pain, (unspecified) gastrointestinal disorder, (unspecified) prostatic disorder, glaucoma, and deep vein thrombosis in the right leg. The subject reported a peri-oral facial rash thought to be related to erlotinib. The subject also reported symptoms of prostate hypertrophy, but denied any pulmonary symptoms. Concomitant medications include atorvastatin calcium, amlodipine besylate/ benazepril hydrochloride, ibuprofen, acetaminophen/hydrocodone bitartrate, glucosamine, chondroitin sulfate, hydrochlorothiazide/ triamterene, pantoprazole, senna, tamsulosin hydrochloride, oxycodone hydrochloride, dexamethasone, latanoprost, enoxaparin sodium, (unspecified) antiglaucoma agent, bimatoprost, citalopram, lorazepam, and warfarin sodium. The subject had seasonal allergies. The subject denied any drug hypersensitivities.

The subject is enrolled in the post-chemotherapy phase of trial AVF3671g and on 28-SEP-2007 received an (unspecified) antineoplastic agent (dose, frequency, and route not reported). The last dose of unspecified antineoplastic agent administered prior to the event was on 30-NOV-2008. On 28-SEP-2007, the subject received bevacizumab (1636 mg, Q3W, Intravenous). The bevacizumab lot number was reported as 701872. On 05-JAN-2008, the subject began treatment with erlotinib or placebo (150 mg, qd, Oral). The erlotinib or placebo lot number was reported as 2006777. The last dose of bevacizumab administered prior to the event was on 11-JUL-2008. The last dose of erlotinib or placebo administered prior to the event was on 31-JUL-2008.

On 30-MAY-2008, the subject experienced blurred vision in the left eye and the condition was continuously monitored. The right eye was reportedly "still good."

On an unspecified date, the subject was seen by psychology and psychosomatic symptoms were ruled out. The subject reported seeing "white areas" and "as if there was a screen" in his visual area.

On 13-JUN-2008, the subject was seen by a neuro-ophthalmologist. The subject's visual acuity was (20/25) on the right and (20/30) on the left. On Ishihara testing, the subject correctly responded to (7/15) color test plates presented to the right eye and "(?)2/15" color test plates presented to the left eye. On examination, the pupils reactions were questionable for "deafferent reaction on the or left." The lids, orbits, and ocular motility were normal in both eyes. On slit lamp examination, the conjunctiva, cornea, anterior chamber, iris, and lens revealed mild lenticular changes of early cataract formation in both eyes. The treating neuro-ophthalmologist diagnosed the patient with bilateral optic neuropathy; however, noted the radiation dose may not have been high enough to account for the subject's visual disturbance.

On 28-JUL-2008, MRI of the orbits were reportedly normal.

At the time of the report, no eye exam information was available.

On 01-AUG-2008, the subject's blurred vision assessed as grade IV had deteriorated and became disabling (BLURRED VISION). The subject reportedly was no longer able to drive or distinguish faces. At the time of the report, the Investigator and consulting ophthalmologist did not know the underlying etiology and on 01-AUG-2008, decided to remove the subject from the study. The subject did not receive any treatment for the event.

On 04-AUG-2008, the subject was unblinded and received active drug.

At the time of the report, the event remained ongoing.

The investigator assessed the event of blurred vision as related to erlotinib and bevacizumab. The investigator did not provide a causality assessment for the event in relation to the unspecified antineoplastic agent. In the reporter's opinion, other possible etiological factors included the disease under study.

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

Additional information has been requested. If received, the case will be updated accordingly.

ADDITIONAL INFORMATION WAS RECEIVED ON 07-AUG-2008:

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

The last dose of unspecified antineoplastic agent administered prior to the event was confirmed to be administered on 30-NOV-2007 (previously reported as "2008"). The reporter confirmed that the event blurred vision was a pre-existing condition which worsened following the administration of Bevacizumab and that bilateral optic neuropathy was not considered a causative agent. The etiology of the event blurred vision remained unknown at the time of this report.

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 28-AUG-2008:**

Concomitant medications included lycopene/pygeum africanum extract/saw palmetto/stinging nettle and acetaminophen/hydrocodone bitartrate.

Additional information has been requested. If received, the case will be updated accordingly.

**ADDITIONAL INFORMATION WAS RECEIVED ON 12-NOV-2008:**

On 17-SEP-2008, the subject was seen by a neuro-ophthalmologist, the Physician reported that the subject was having a very hard time getting around, and was only able to make out shadows and large objects. The subject denied any other associated symptoms at that time, including double vision, flashes of light, and floaters. The subject reported occasional headaches, which were not considered out of the ordinary, and stated that his vision has rapidly and progressively declined over the last several months. The Physician completed a neuro-ophthalmologic evaluation and reported "his visual acuity was found to be significantly reduced, his color vision was grossly intact, and his visual field was found to be significantly restricted. Both his optic nerves appear severely atrophied with pallor and excavation. Based on the patient's historical information and the findings from this examination, there may be multiple etiologies of his optic nerve atrophy." Other etiological factor reported by the Physician included cancer-associated retinopathy and/or radiation-associated atrophy. The Physician reported, not one diagnosis could be completely confirmed given the multi-factorial factors including the risk of radiation-associated atrophy, his newly diagnosed low-tension glaucoma, and his chemotherapeutic agents, all of which could play a factor into causing optic nerve atrophy.

Previously reported "(unspecified) antineoplastic agent" was amended to Carboplatin (dose, frequency and route not reported) and Paclitaxel (dose, frequency and route not reported).

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

ADDITIONAL INFORMATION IS BEING REQUESTED. IF RECEIVED, THE CASE WILL BE UPDATED ACCORDINGLY.

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

Genentech has previously filed the following IND safety report of similar events from studies of erlotinib.

Manufacturer Control Number	ISR Primary Event Term	Date Submitted
104877	UVEITIS	22-NOV-2002

Genentech has not filed previous IND safety reports of blurred vision for subjects receiving bevacizumab.

**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/ or bevacizumab and the occurrence of blurred vision.

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

**13. Lab Data**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	13-JUN-2008	INVESTIGATION  Isihara testing 7/15 color test plates to the right eye  "(?)2/15" color test plates to the left eye	see notes	
2	28-JUL-2008	NUCLEAR MAGNETIC RESONANCE IMAGING Normal	see notes	

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

#	Date	Test / Assessment / Notes	Results	Normal High / Low
		MRI of orbits		
3	13-JUN-2008	VISUAL ACUITY TESTS	see notes	
		20/25 on the right 20/30 on the left correctable		

**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 ) Avastin (BEVACIZUMAB) Powder and solvent for solution for infusion, 100 mg {Lot # 701872}; Regimen #1	1636 mg, Q3W; Intravenous	nsclc (NSCLC)	28-SEP-2007 / 11-JUL-2008; 288 days
#3 ) PARAPLATIN (CARBOPLATIN); Regimen #1	UNK; Unknown	nsclc (NSCLC)	28-SEP-2007 / 30-NOV-2007; 64 days
#4 ) TAXOL (PACLITAXEL); Regimen #1	UNK; Unknown	nsclc (NSCLC)	28-SEP-2007 / 30-NOV-2007; 64 days

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

- #7 ) DYAZIDE (HYDROCHLOROTHIAZIDE, TRIAMTERENE) ; 2002 / Unknown
- #8 ) PROTONIX (PANTOPRAZOLE) ; FEB-2008 / Unknown
- #9 ) SENNA (SENNALAX) ; FEB-2008 / Unknown
- #10 ) FLOMAX (TAMSULOSIN HYDROCHLORIDE) ; FEB-2008 / Unknown
- #11 ) OXYCONTIN (OXYCODONE HYDROCHLORIDE) ; Unknown
- #12 ) DEXAMETHASONE (DEXAMETHASONE) ; Unknown
- #13 ) XALATAN (LATANOPROST) ; FEB-2008 / Unknown
- #14 ) LOVENOX (ENOXAPARIN SODIUM) ; Unknown
- #15 ) GLAUCOMA EYE DROPS (UNK INGREDIENTS) (ANTIGLAUCOMA AGENT NOS) ; Unknown
- #16 ) LUMIGAN (BIMATOPROST) ; JUN-2008 / Unknown
- #17 ) CELEXA (CITALOPRAM) ; JUN-2008 / Unknown
- #18 ) ATIVAN (LORAZEPAM) ; Unknown
- #19 ) COUMADIN (WARFARIN SODIUM) ; Unknown
- #20 ) VICODIN (ACETAMINOPHEN, HYDROCODONE BITARTRATE) ; Unknown
- #21 ) PROSTATE SUPPORT (LYCOPENE, PYGEUM AFRICANUM EXTRACT, SAW PALMETTO, STINGING NETTLE) ; MAY-2008 / Unknown

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**ADDITIONAL INFORMATION**
**23. OTHER RELEVANT HISTORY continued**

From/To Dates	Type of History / Notes	Description
Unknown	Historical Condition	RENAL CYST (RENAL CYST);
Unknown	Historical Condition	HEPATIC CYST (HEPATIC CYST);
Unknown	Historical Condition	SACROILIITIS (SACROILIITIS);
Unknown	Current Condition	HYPERTENSION (HYPERTENSION);
Unknown	Current Condition	DEPRESSION (DEPRESSION);
Unknown	Current Condition	ARTHRITIS (ARTHRITIS);
Unknown	Current Condition	HYPERCHOLESTEROLEMIA (HYPERCHOLESTEROLAEMIA);
Unknown	Current Condition	NEUROFIBROMATOSIS (NEUROFIBROMATOSIS);
Unknown to 1991	Historical Condition	TOBACCO USER (TOBACCO USER);
Unknown	Allergy	SEASONAL ALLERGY (SEASONAL ALLERGY);
Unknown	Current Condition	PAIN (PAIN);
Unknown	Current Condition	GASTROINTESTINAL DISORDER (GASTROINTESTINAL DISORDER);
Unknown	Current Condition	PROSTATIC DISORDER (PROSTATIC DISORDER);
01-MAR-2008 to Unknown	Current Condition	GLAUCOMA (GLAUCOMA);
Unknown	Current Condition right leg	DVT (DEEP VEIN THROMBOSIS);
12-AUG-2007 to Unknown	Historical Condition assessed as mild	BLURRED VISION (VISION BLURRED);
AUG-2007 to Unknown	Procedure 14 days of whole brain radiation for cerebral metastases	RADIATION THERAPY (RADIOTHERAPY);
Unknown	Negative Med Cond	DRUG HYPERSENSITIVITY (DRUG HYPERSENSITIVITY);
Unknown	Historical Condition rarely	MIGRAINE (MIGRAINE);
Unknown	Negative Med Cond	DIABETES (DIABETES MELLITUS);
Unknown	Negative Med Cond	ALCOHOL USE (ALCOHOL USE);
Unknown	Current Condition	PROSTATIC HYPERTROPHY (BENIGN PROSTATIC HYPERPLASIA);
Unknown	Current Condition believed to be related to erlotinib	RASH FACE (RASH);
Unknown	Negative Med Cond denied pulmonary symptoms	PULMONARY DISORDER (LUNG DISORDER);
Unknown	Current Condition	ATROPHY OPTIC NERVE (OPTIC ATROPHY);