



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: March 27, 2009

To: NCCTG Primary Clinical Research Associates

From: Lynn Flickinger
Protocol Development Coordinator

Re: N0735, Phase II Trial of Albumin-Bound Paclitaxel in Combination with Gemcitabine and Bevacizumab in Patients with Metastatic Breast Cancer

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_272175_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 Lynn Flickinger at Flickinger.lynn@mayo.edu or 507-538-7034.

LF/kjm
enclosure

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

MEDWATCH
3500A Facsimile

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Mfr Report #	272175
UF/Importer Report #	
FDA Use Only	

A. PATIENT INFORMATION			
1. Patient Identifier	2. Age at Time of Event: 59 Years or Date of Birth:	3. Sex <input checked="" type="checkbox"/> Female <input type="checkbox"/> Male	4. Weight 178.6 lbs or 81.0 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 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) 11/19/2008		4. Date of This Report (mm/dd/yyyy) 12/05/2008	
5. Describe Event or Problem Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) rectitis [PROCTITIS]			
Case Description: IND SAFETY REPORT			
This case, manufacturer control number 272175, is a study report from Canada referring to a 59 Year-old Female subject (Study ID # _____). An Investigator reported this case from study AVF3693G a phase III, multicenter, randomized, placebo-controlled trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy regimens in subjects with previously treated metastatic breast cancer sponsored by Genentech, Inc.			
On 20-JUN-2008, the subject initiated treatment with continued in additional info section...			
6. Relevant Tests/Laboratory Data, Including Dates			
#1 11/20/2008 COLONOSCOPY (continued)			
#2 11/21/2008 CULTURE STOOL (continued)			
#3 11/19/2008 HAEMOGLOBIN 106 g/L			
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.			
2. Dose, Frequency & Route Used		3. Therapy Dates (if unknown, give duration) from/to (or best estimate)	
#1. 811 mg, Q2W, Intravenous		#1. 06/20/2008 to UNK	
#2.		#2.	
4. Diagnosis for Use (Indication)		5. Event Abated After Use Stopped or Dose Reduced?	
#1. metastatic breast (Continued)		#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply	
#2.		#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply	
6. Lot #	7. Exp. Date		8. Event Reappeared After Reintroduction?
#1. 9(Continued)	#1.		#1. <input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Doesn't Apply
#2.	#2.		#2. <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Doesn't Apply
9. NDC# or Unique ID			
10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)			
#1. TAXOL (PACLITAXEL) 06/20/2008 to UNK			
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)		5. (A)NDA #	
11/27/2008		IND # BB 7023	
6. If IND, Give Protocol #		STN #	
AVF3693G		PMA/510(k) #	
7. Type of Report (Check all that apply)		Combination Product <input type="checkbox"/> Yes	
<input type="checkbox"/> 5-day <input type="checkbox"/> 30-day		Pre-1938 <input type="checkbox"/> Yes	
<input type="checkbox"/> 7-day <input type="checkbox"/> Periodic		OTC Product <input type="checkbox"/> Yes	
<input type="checkbox"/> 10-day <input type="checkbox"/> Initial			
<input checked="" type="checkbox"/> 15-day <input checked="" type="checkbox"/> Follow-up #1			
9. Manufacturer Report Number		8. Adverse Event Term(s)	
272175		PROCTITIS	
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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ADDITIONAL INFORMATION**B5. EVENT DESCRIPTION (Continued)**

Bevacizumab or Placebo (811mg, Q2W, Intravenous). The lot numbers of the Bevacizumab or placebo were 9112630 and 910630. Concomitant chemotherapy included Paclitaxel, (90mg/m², Route and Frequency not reported). The last dose of Bevacizumab or Placebo was administered on 14-NOV-2008.

Since 17-OCT-2008, the subject was reported to have had occasional diarrhea which was grade I at its worst with a maximum of 3 stools per day.

On 19-NOV-2008 the diarrhea increased to grade II with blood in the stool and the subject was admitted to the emergency room. On 19-NOV-2008, the subject had a hemoglobin of 106 g/L. On 20-NOV-2008, the subject had a colonoscopy that showed no active bleeding, but showed initis (inflammation of the anus). Treatment for the event included Metronidazole. No action was taken with Bevacizumab or Placebo.

On 20-NOV-2008, the subject was discharged from the hospital.

On 21-NOV-2008, the subject had a stool culture, the results of which were pending.

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

On 25-NOV-2008, the subject's treatment strategy was unblinded and the subject was found to be on Bevacizumab.

The Investigator assessed the event of inflammation of the anus as related to Bevacizumab. No other possible etiological factors were reported.

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 RECEIVED ON 27-NOV-2008:

The event term was amended to rectitis from initis. Therefore this case no longer qualifies as an IND safety report.

On 20-NOV-2008, the event resolved.

Stool cultures were found to be negative.

The Investigator assessed the event of rectitis as related to Bevacizumab. No other possible etiological factors were reported.

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

PREVIOUSLY FILED IND SAFETY REPORTS OF SIMILAR EVENTS

Genentech has not filed previous IND safety reports of inflammation of the anus or IND safety reports of similar events 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 inflammation of the anus can be identified. At this time, the sponsor does not believe changes to the conduct of the trial are warranted.

Pharmacovigilance:

PROCTITIS is not labeled per the Avastin USPI and is expected per the the IB. No confounding factors were reported.

B6. LABORATORY DATA

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	11/20/2008	COLONOSCOPY	see notes	
		Showned no active bleeding.		

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2 11/21/2008 CULTURE STOOL see notes
Negative

C1. NAME (Continued)

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

C4. DIAGNOSIS FOR USE (Continued)

#1:metastatic breast cancer (METASTATIC BREAST CANCER)

C6. LOT# (Continued)

Suspect Medication #1: 9112630, 910630

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

On 20-JUN-2008, the subject initiated treatment with Bevacizumab or Placebo (811mg, Q2W, Intravenous). The lot numbers of the Bevacizumab or placebo were 9112630 and 910630. Concomitant chemotherapy included Paclitaxel, (90mg/m², Route and Frequency not reported. The last dose of Bevacizumab or Placebo was administered on 14-NOV-2008.

Since 17-OCT-2008, the subject was reported to have had occasional diarrhea which was grade I at its worst with a maximum of 3 stools per day.

On 19-NOV-2008 the diarrhea increased to grade II with blood in the stool and the subject was admitted to the emergency room. On 19-NOV-2008, the subject had a hemoglobin of 106 g/L. On 20-NOV-2008, the subject had a colonoscopy that showed no active bleeding, but showed initis (inflammation of the anus). Treatment for the event included Metronidazole. No action was taken with Bevacizumab or Placebo.

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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 inflammation of the anus can be identified. At this time, the sponsor does not believe changes to the conduct of the trial are warranted.

Pharmacovigilance: PROCTITIS is not labeled per the Avastin USPI and is expected per the the IB. No confounding factors were reported.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	20-NOV-2008	COLONOSCOPY	see notes	
		Shown no active bleeding.		
2	21-NOV-2008	CULTURE STOOL	see notes	
		Negative		
3	19-NOV-2008	HAEMOGLOBIN	106 g/L	

ADDITIONAL INFORMATION**13. Lab Data**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
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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) BEVACIZUMAB OR PLACEBO (Bevacizumab) Powder and solvent for solution for infusion, 100 mg (Lot # 9112630, 910630); Regimen #1	811 mg, Q2W; Intravenous	metastatic breast cancer (METASTATIC BREAST CANCER)	20-JUN-2008 / Unknown; Unknown