



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: October 12, 2007

To: NCCTG Primary Clinical Research Associates

From: Janis Wobschall
Protocol Development Coordinator

Re: N0626, Phase II Randomized Study Pemetrexed With Sorafenib versus Pemetrexed Alone as Second-line Therapy in Patients With Advanced Non-Small Cell Lung 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 ALIMTA at a non-NCCTG institution. You may have also received this communication directly from the drug manufacturer.

AE_DE_031212518

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/dkf
enclosure

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last) A.D.	1a. COUNTRY GERMANY	2. DATE OF BIRTH			2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day 08	Month AUG	Year 1934	69 Years	Male	79.20 kg	Day	Month	Year 2003	
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Pancytopenia [Pancytopenia] PETECHIA LOWER LEG [Petechiae] PAIN [Pain] NAUSEA [Nausea]										<input checked="" type="checkbox"/> PATIENT DIED Date: 09-DEC-2003	
Case Description: THIS CLINICAL TRIAL CASE CONCERNS A 69 YEARS OLD CAUCASIAN MALE PATIENT.										<input checked="" type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION	
RELEVANT HISTORY INCLUDED PLEURAL MESOTHELIOMA FIRST DIAGNOSED ON 29-AUG-2003 WITH NO LIVER-METASTASES. (continue)										<input type="checkbox"/> INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY	
										<input checked="" type="checkbox"/> LIFE THREATENING	

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name) #1 PEMETREXED (PEMETREXED) Vial #2 *CARBOPLATIN(*CARBOPLATIN)Unknown		20. DID REACTION ABATE AFTER STOPPING DRUG? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA Unknown
15. DAILY DOSE(S) #1 1000 mg, unknown #2 480 mg, unknown	16. ROUTE(S) OF ADMINISTRATION #1 Intravenous #2 Intravenous	
17. INDICATION(S) FOR USE #1 pleural mesothelioma(Pleural mesothelioma) #2 pleural mesothelioma(Pleural mesothelioma)		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 29-OCT-2003 00:00 / Unknown #2 29-OCT-2003 00:00 / 20-NOV-2003 00:00	19. THERAPY DURATION #1 Unknown #2 23 days	

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) #1 IBUHEXAL (IBUPROFEN) ; Unknown / 25-Nov-2003 00:00 #2 NEXIUM (ESOMEPRAZOLE) ; Unknown / 24-Nov-2003 00:00 #3 DUROGESIC (FENTANYL) ; 27-Oct-2003 00:00 / 08-Dec-2003 00:00		
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.) From/To Dates Type of History / Notes Description Unknown to Ongoing Medical Condition THE PATIENT HAS A HISTORY OF PLEURAL MESOTHELIOMA FIRST DIAGNOSED ON 29-AUG-2003.		

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER Eli Lilly & Company Lilly Corporate Center, Global Product Safety, Indianapolis, IN 46285 UNITED STATES		26. REMARKS
	24b. MFR CONTROL NO. DE_031212518	25b. NAME AND ADDRESS OF REPORTER NAME AND ADDRESS WITHHELD.
24c. DATE RECEIVED BY MANUFACTURER 20-SEP-2007	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 05-OCT-2007	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:	

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

HIS KARNOFSKY PERFORMANCE SCORE WAS 80 AT STUDY ENTRY ON 24-OCT-2003. BASELINE LABS DRAWN ON 23-OCT-2003 INCLUDED A HEMOGLOBIN LEVEL OF 14.3, LEUKOCYTE COUNT OF 10.75, NEUTROPHILS WERE 8.07 AND PLATELET COUNT WAS 457. CONCOMITANT MEDICATIONS INCLUDED IBUPROFEN (IBUHEXAL), ESOPEPRAZOL (NEXIUM), TRANSDERMAL FENTANYL (DUROGESIC) AND FOLIC ACID, VITAMIN B12 AND DEXAMETHASONE.

THE PATIENT RECEIVED STUDY MEDICATION LY231514 (ALIMTA) 1000 MG AND CARBOPLATIN 635 MG INTRAVENOUSLY (IV) BEGINNING ON 29-OCT-2003 FOR THE TREATMENT OF PLEURAL MESOTHELIOMA-SARCOMATOID. LAB VALUE DRAWN ON THE 05-NOV-2003 AND 12-NOV-2003 FOUND HEMOGLOBIN 12/10.7 (RESPECTIVELY), LEUKOCYTE COUNT OF 2.3/1.6, AND A PLATELET COUNT OF 225/51. THE PATIENT WAS CHEMONAIVE PRIOR TO THIS TREATMENT. THE LAST APPLICATION OF CHEMOTHERAPY WAS ON 19-NOV-2003 AND CARBOPLATIN WAS NOTED TO BE DECREASED TO 480 MG IV. ON 19-NOV-2003, HE EXPERIENCED PAIN (CTC GRADE 3) AND NAUSEA (CTC GRADE 2). LABORATORY VALUES FROM THE 25-NOV-2003 INCLUDED A HEMOGLOBIN OF 9.2, LEUKOCYTE COUNT OF 4.77, NEUTROPHILS 4.2 AND PLATELET COUNT OF 357. SINCE 01-DEC-2003, HE HAD PANCYTOPENIA AND ON AN UNKNOWN TIME PETECHIA ON THE LOWER LEGS. THE EVENTS WERE TREATED WITH FENTANYL, DEXAMETHASONE, METRONIDAZOL, CEFTRIAXONE. THE EVENTS PAIN AND NAUSEA ABATED ON 09-DEC-2003, BUT PANCYTOPENIA HAD NOT AS LABS ON 08-DEC-2003 NOTED A HEMOGLOBIN OF 8.1, LEUKOCYTE COUNT OF 0.16, NEUTROPHILS COUNT OF 0.03, AND PLATELET COUNT OF 19. IT WAS NOT PROVIDED IF STUDY MEDICATION LY231514 WAS CONTINUED, BUT CONCOMITANT STUDY MEDICATION CARBOPLATIN WAS DISCONTINUED ON 08-DEC-2003. ON 09-DEC-2003, LESS THAN A MONTH AFTER THE LAST DOSE OF CHEMOTHERAPY, THE PATIENT WAS REPORTED TO HAVE DIED DUE TO STUDY DRUG TOXICITY, MORE SPECIFICALLY, PANCYTOPENIA. IT WAS NOT PROVIDED IF AN AUTOPSY WAS PERFORMED.

THE INVESTIGATOR DID NOT SEE A RELATIONSHIP BETWEEN STUDY MEDICATION LY231514/CARBOPLATIN/PROTOCOL PROCEDURES FOR PAIN AND NAUSEA. PANCYTOPENIA AND PETECHIA WERE THOUGHT TO HAVE A CAUSAL RELATIONSHIP FOR BOTH LY231514 AS CARBOPLATIN WAS INTENSIFIED BY LY231514. NO RELATIONSHIP TO PROTOCOL PROCEDURES WAS PROVIDED FOR THESE EVENTS.

UPDATE ON 8-DEC-03: CHANGED START DATE PEMETR, TO 29-OCT, CLIN. EVENTS (UPGRADE RELATIONSHIP AGRANULOC, THROMBOP., PETECHIA FOR PEMETREXED
F/U 10-DEC-2003: ADDITIONAL INFORMATION RECEIVED FROM INVESTIGATOR. ADDED END DATE OF CONC.MED., ADDED END DATE OF CARBOPLATIN, ADDED END DATE OF EVENTS 1,2,4,5. ADDED LAB VALUES, AMEND SERIOUS CRITERIA AND CIB EXPECTEDNESS

UPDATE 21-SEP-2007: ADDITIONAL INFORMATION RECEIVED FROM DATA RECONCILIATION AND DATA MANAGEMENT ON 20-SEP-2007. INSERTED LABORATORY TESTS AND RESULTS, CODED FATAL EVENT OF PANCYTOPENIA AND DELETED EVENTS AGRANULOCYTOSIS AND THROMBOCYTOPENIA. NARRATIVE AND PSUR UPDATED.

Lilly Analysis Statement: 05-Oct-2007: This clinical trial case relates to death of a patient while on treatment with pemetrexed and carboplatin for pleural mesothelioma. The suggested cause of death is drug toxicity leading to pancytopenia. Although pancytopenia is an expected event with the cytotoxic study drugs, and their role in causing the event cannot be dismissed, it is difficult to relate the event to cause of death given that the patient has an underlying poor prognosis malignancy. No autopsy results or state of malignancy was known and hence study drug toxicity leading to pancytopenia with eventual fatality can only be presumed. The event is not related to protocol procedures.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	23-OCT-2003	Haemoglobin Within Normal Limits	14.3 g/dl	
2	01-DEC-2003	Haemoglobin Low	8.8 g/dl	18 15
3	23-OCT-2003	White blood cell count High	10750 CELLS/mm3	
4	01-DEC-2003	White blood cell count Low	200 CELLS/mm3	
5	02-DEC-2003	White blood cell count Low	180 CELLS/mm3	10000 4000
6	23-OCT-2003	Platelet count High	457000 CELLS/mm3	
7	18-NOV-2003	Platelet count High	571000 CELLS/mm3	
8	29-NOV-2003	Platelet count Low	125000 CELLS/mm3	
9	01-DEC-2003	Platelet count	28000 CELLS/mm3	

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
10	02-DEC-2003	Platelet count Low	10000 CELLS/mm3	400000 150000
11	01-DEC-2003	Haematocrit Low	26.2 %	50 42
12	01-DEC-2003	White blood cell count Low	3070 CELLS/mm3	6000 4200
13	01-DEC-2003	Neutrophil count Low	0 %	75 37
14	01-DEC-2003	Lymphocyte count High	90 %	50 15
15	01-DEC-2003	Neutrophil count Low	0 CELLS/mm3	7500 2000
16	23-OCT-2003	Blood creatinine Within Normal Limits	0.8 mg/dl	
17	21-NOV-2003	Blood creatinine High	2.1 mg/dl	
18	25-NOV-2003	Blood creatinine High	3.1 mg/dl	
19	01-DEC-2003	Blood creatinine High	1.2 mg/dl	1.1 0.2
20	23-OCT-2003	Gamma-glutamyltransferase High	78 U/liter	
21	01-DEC-2003	Gamma-glutamyltransferase High	254 U/liter	66
22		Gamma-glutamyltransferase		
23	23-OCT-2003	Blood alkaline phosphatase Within Normal Limits	119 U/liter	
24	02-DEC-2003	Blood alkaline phosphatase High	185 U/liter	129 40
25	23-OCT-2003	Blood bilirubin Within Normal Limits	0.6 mg/dl	
26	01-DEC-2003	Blood bilirubin High	1.5 mg/dl	1
27	23-OCT-2003	Blood cholinesterase Low	3584 U/liter	
28	01-DEC-2003	Blood cholinesterase Low	2671 U/liter	12920 5320
29	23-OCT-2003	Blood lactate dehydrogenase Within Normal Limits	190 U/liter	
30	01-DEC-2003	Blood lactate dehydrogenase High	250 U/liter	225 135
31	01-DEC-2003	Aspartate aminotransferase Within Normal Limits	27 U/liter	50 10
32	01-DEC-2003	Alanine aminotransferase Within Normal Limits	30 U/liter	50 10
33	29-NOV-2003	C-reactive protein High	190.4 mg/liter	5
34	03-DEC-2003	Haemoglobin	10.0 g/dl	
35	04-DEC-2003	Haemoglobin	8.8 g/dl	

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
36	05-DEC-2003	Haemoglobin	9.0 g/dl	
37	06-DEC-2003	Haemoglobin	9.7 g/dl	
38	07-DEC-2003	Haemoglobin	9.4 g/dl	
39	05-NOV-2003	Haemoglobin	12 g/dl	
40	08-DEC-2003	Haemoglobin	8.1 g/dl	
41	03-DEC-2003	White blood cell count	110 CELLS/mm3	
42	04-DEC-2003	White blood cell count	220 CELLS/mm3	
43	05-DEC-2003	White blood cell count	180 CELLS/mm3	
44	06-DEC-2003	White blood cell count	260 CELLS/mm3	
45	07-DEC-2003	White blood cell count	260 CELLS/mm3	
46	08-DEC-2003	White blood cell count	160 CELLS/mm3	
47	03-DEC-2003	Platelet count	6000 CELLS/mm3	
48	04-DEC-2003	Platelet count	35000 CELLS/mm3	
49	05-DEC-2003	Platelet count	21000 CELLS/mm3	
50	06-DEC-2003	Platelet count	8000 CELLS/mm3	
51	07-DEC-2003	Platelet count	5000 CELLS/mm3	
52	08-DEC-2003	Platelet count	19000 CELLS/mm3	
53	03-DEC-2003	Neutrophil count	0 %	
54	04-DEC-2003	Neutrophil count	0 %	
55	05-DEC-2003	Neutrophil count	6 %	
56	06-DEC-2003	Neutrophil count	4 %	
57	07-DEC-2003	Neutrophil count	12 %	
58	08-DEC-2003	Neutrophil count	19 %	
59	23-OCT-2003	Neutrophil count	8.07 %	
60	12-NOV-2003	Haemoglobin	10.7 g/dl	
61	05-NOV-2003	White blood cell count	2300 CELLS/mm3	

ADDITIONAL INFORMATION**13. Lab Data**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
62	05-NOV-2003	Platelet count	225000 CELLS/mm3	
63	12-NOV-2003	White blood cell count	1600 CELLS/mm3	
64	12-NOV-2003	Neutrophil count	59 %	
65	12-NOV-2003	Platelet count	51000 CELLS/mm3	
66	18-NOV-2003	Haemoglobin	10.4 g/dl	
67	18-NOV-2003	White blood cell count	2930 CELLS/mm3	
68	18-NOV-2003	Neutrophil count	1.56 %	
69	25-NOV-2003	Haemoglobin	9.2 g/dl	
70	25-NOV-2003	Neutrophil count	4.2 %	
71	25-NOV-2003	White blood cell count	4770 CELLS/mm3	
72	25-NOV-2003	Platelet count	357000 CELLS/mm3	

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

#4 DUROGESIC (FENTANYL) ; Unknown / 25-Oct-2003 00:00

#5 LAFOL (FOLIC ACID) ; 24-OCT-2003 00:00 / 08-DEC-2003 00:00

#6 DEXAMETHASONE (DEXAMETHASONE) ; 28-Oct-2003 00:00 / 08-Dec-2003 00:00

#7 VITAMIN B12 (VITAMIN B12) ; 24-OCT-2003 00:00 / 24-OCT-2003 00:00