



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: April 4, 2008

To: NCCTG Primary Clinical Research Associates

From: Alicia Elsing
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_IN200708002424_F1

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 Alicia Elsing at elsing.alicia@mayo.edu or 507-538-3893.

AE/dkf
enclosure

SUSPECT ADVERSE REACTION REPORT												

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last) Unk	1a. COUNTRY INDIA	2. DATE OF BIRTH			2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day 12	Month JUN	Year 1957	50 Years	Male	66.00 kg	Day 09	Month AUG	Year 2007	
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Acute left ventricular Failure with cardiogenic shock [Acute left ventricular failure] acute respiratory distress [Acute respiratory distress syndrome]										<input checked="" type="checkbox"/> PATIENT DIED Date: 09-AUG-2007 <input type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION <input type="checkbox"/> INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY <input checked="" type="checkbox"/> LIFE THREATENING	
Case Description: This clinical trial case (H3E-MC-JMHO; EudraCT number 2006-001173-14) concerns a 50-year old male patient of Asian origin.											
Patient had no medical history of co-morbid cardiac condition. The patient had reported to the site on 28-Jul-2007 with cough and haemoptysis and was admitted. (continue)											

II. SUSPECT DRUG(S) INFORMATION

(Continued on Additional Information Page)

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) #1 800 mg #2 715 mg, unknown	16. ROUTE(S) OF ADMINISTRATION #1 Intravenous #2 Intravenous		
17. INDICATION(S) FOR USE #1 extensive stage small cell lung cancer(Small cell lung (continue) #2 non small cell lung cancer metastatic(Non-small cell lu (continue)		21. DID REACTION REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA	
18. THERAPY DATES(from/to) #1 06-AUG-2007 00:00 / Unknown #2 06-AUG-2007 00:00 / Unknown		19. THERAPY DURATION #1 Unknown #2 Unknown	

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 RICONIA (MINERALS NOS, VITAMINS NOS) ; 28-JUL-2007 00:00 / Unknown #2 PANTOPRAZOLE (PANTOPRAZOLE) ; 28-JUL-2007 00:00 / Unknown #3 HEXIDIN (CHLORHEXIDINE GLUCONATE) ; Unknown		
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)		
From/To Dates	Type of History / Notes	Description
JUL-2007 to Unknown	Medical Condition	Small cell lung cancer metastatic
	small cell lung cancer with extensive liver metastases.	
Unknown	Hepatic Impairment	Metastases to liver
	Extensive liver metastases	

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. IN200708002424	25b. NAME AND ADDRESS OF REPORTER NAME AND ADDRESS WITHHELD.
24c. DATE RECEIVED BY MANUFACTURER 05-MAR-2008	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 07-MAR-2008	25a. REPORT TYPE <input type="checkbox"/> INITIAL <input checked="" type="checkbox"/> FOLLOWUP: 1	

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

The patient was diagnosed to have small cell lung cancer with extensive liver metastases. Laboratory tests on 04-Aug-2007: serum Na 111 meq/L and 130 meq/L (normal 136-145), serum K 4.6 meq/L (3.5-5.2). Concomitant medications of the patient included: flupentixol decanoate as antidepressant, ipratropium bromide/salbutamol nebulization, vitamin K for raised prothrombin time and activated partial thromboplastin time, diclofenac sodium for pain, diazepam for insomnia, amoxicillin sodium/clavulanate potassium, metronidazole and amikacin for antibiotic treatment, haloperidol and lorazepam as sedative therapy, lactulose/galactose/lactose as laxative, tranexamic acid for coagulation, allopurinol for hyperuricemia, ursodeoxycholic acid as hepatoprotective, theophylline for bronchodilatation, metoclopramide hydrochloride as antiemetic therapy, pantoprazole for gastritis prophylaxis, sorbilene (enzyme and carminative) as hepatoprotective, minerals and vitamins, chlorhexidine mouthwash. The patient was receiving supplemental therapy with folic acid, vitamin B12 and dexamethasone.

On 06-Aug-2007 the patient first received pemetrexed (Alimta) 880mg intravenously (IV) and carboplatin 715mg IV for the treatment of small cell lung cancer with extensive liver metastases. This was also the only dose of the study drugs administered to the patient. In the first week of Aug-2007 the patient showed symptoms of hyponatraemia and upper respiratory tract infection. On an unknown date within two days of receiving the study drugs the patient developed decompensatory liver disease. Laboratory tests on 08-Aug-07: prothrombin time 34 seconds (normal 12), partial thromboplastin time 92 seconds (normal 31). On 09-Aug-2007 at 09:30 hours the patient developed severe respiratory distress and drowsiness. On follow-up, acute respiratory distress has been captured as an event with serious criteria life threatening. He was immediately treated with moist oxygen inhalation, hydrocortisone hydrogen succinate, furosemide, unspecified nebulization and dexamethasone. However, the condition of the patient kept deteriorating and the patient developed tachycardia and hypotension around 10:30 hours. Dobutamine infusion was started to control the condition of the patient. The outcome of the acute respiratory distress was unknown (follow-up sought). The patient developed signs of acute left ventricular failure with cardiogenic shock around 12:30 hours. The patient could not be revived and expired at 14:10 hours. The cause of death has been recorded as acute ventricular failure. It was unknown if an autopsy was performed. Further information has been requested.

As per the investigator since the patient had no pre-existing cardiac co morbid condition and the acute left ventricular failure with cardiogenic shock developed within 72 hours of study drug administration, the event was related to the study drugs but not to the protocol procedures. In the opinion of the investigator, the event of acute respiratory distress was related to the study drugs because the event developed within 72 hours of study drug administration and progressed to cardiac failure. The event of acute respiratory distress was not considered related to protocol procedures.

Update 10-Nov-2007: Data reconciliation notification received on 06-Nov-2007: added investigator number.

Update 24-Nov-2007: no new information received from the study investigator.

Update 06-Mar-2008: Additional information received from the study investigator on 05-Mar-2008: Added new life threatening related event of acute respiratory distress. Relevant fields and narrative updated accordingly.

Lilly Analysis Statement: Patient with aggressive metastatic SCL cancer and recent haemoptysis developing decompensatory liver disease with coagulation disorders within two days after the first study drugs experienced on day 4 cycle 1 severe respiratory distress and did not respond to corrective therapy including oxygen, IV steroids and diuretics. One hour later, due to hypotension and tachycardia, the patient received Dobutamine without results, developed acute left failure signs leading to death from cardiogenic shock. It was unknown if he experienced non exteriorised haemoptysis. Cardiogenic shock has been reported in clinical trials in patients receiving pemetrexed in combination with other platinum agents but unlisted in association with carboplatin. Events Causal relationship to the study drugs in absence of known cardiac comorbidity could not be ruled out. Additional information such as clinical details and electrocardiogram results may help to identify the initial disorder such as cardiac rhythm or ischemic myocardial disorders. Autopsy information if performed should be of value.

07-Mar-2008: With the additional and updated information available: New listed event for pemetrexed (Ref: CIB) and unlisted event for carboplatin (Ref: Micromedex) acute respiratory distress was reported. Causal relationship to the study drugs for both events could not be ruled out. The event is however not related to protocol procedures.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	04-AUG-2007	Blood sodium Low	111 Meq/L	145 136
2	04-AUG-2007	Blood sodium Low	130 Meq/L	145 136
3	04-AUG-2007	Blood potassium Within Normal Limits	4.6 Meq/L	5.2 3.6
4	08-AUG-2007	Prothrombin time High	34 sec	12
5	08-AUG-2007	Activated partial thromboplastin time High	92 sec	31

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 PEMETREXED (PEMETREXED) Vial; Regimen #1	800 mg; Intravenous	extensive stage small cell lung cancer(Small cell lung cancer extensive stage)	06-AUG-2007 00:00 / Unknown; Unknown
#2 *CARBOPLATIN (CARBOPLATIN) Unknown; Regimen #1	715 mg, unknown; Intravenous	non small cell lung cancer metastatic(Non-small cell lung cancer metastatic)	06-AUG-2007 00:00 / Unknown; Unknown

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

#4 REGLAN (METOCLOPRAMIDE HYDROCHLORIDE) ; 28-JUL-2007 00:00 / Unknown

#5 THEOPHYLLINE (THEOPHYLLINE) ; 28-JUL-2007 00:00 / Unknown

#6 UDILIV (URSODEOXYCHOLIC ACID) ; 01-AUG-2007 00:00 / Unknown

#7 ZYLORIC (ALLOPURINOL) ; 01-AUG-2007 00:00 / Unknown

#8 ATIVAN (LORAZEPAM) ; 01-AUG-2007 00:00 / Unknown

#9 TRANEXAMIC ACID (TRANEXAMIC ACID) ; 01-AUG-2007 00:00 / Unknown

#10 DUPHALAC (GALACTOSE, LACTOSE, LACTULOSE) ; 01-AUG-2007 00:00 / Unknown

#11 SERENACE (HALOPERIDOL) ; 06-AUG-2007 00:00 / 09-AUG-2007 00:00

#12 AUGMENTIN /SCH/ (AMOXICILLIN SODIUM, CLAVULANATE POTASSIUM) ; 04-AUG-2007 00:00 /
08-AUG-2007 00:00

#13 AMIKACIN (AMIKACIN) ; 04-AUG-2007 00:00 / 08-AUG-2007 00:00

#14 METROGYL (METRONIDAZOLE) ; 04-AUG-2007 00:00 / 08-AUG-2007 00:00

#15 VITAMIN K (PHYTOMENADIONE) ; 08-AUG-2007 00:00 / Unknown

#16 DUOLIN (IPRATROPIUM BROMIDE, SALBUTAMOL) ; 04-AUG-2007 00:00 / Unknown

#17 FLUANXOL (FLUPENTIXOL DECANOATE) ; 04-AUG-2007 00:00 / Unknown

#18 VOVERAN (DICLOFENAC SODIUM) ; 28-JUL-2007 00:00 / 31-JUL-2007 00:00

#19 CALMPOSE (DIAZEPAM) ; 28-JUL-2007 00:00 / 31-JUL-2007 00:00

#20 FOLIC ACID (FOLIC ACID) ; 01-AUG-2007 00:00 / Unknown

#21 VITAMIN B12 (CYANOCOBALAMIN) ; 31-JUL-2007 00:00 / 31-JUL-2007 00:00

#22 DEXAMETHASONE (DEXAMETHASONE) ; 05-AUG-2007 00:00 / 07-AUG-2007 00:00

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
AUG-2007 to Unknown	Medical Condition	Hyponatraemia;

ADDITIONAL INFORMATION

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
AUG-2007 to Unknown	Medical Condition	Upper respiratory tract infection;