



# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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**Date:** January 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\_CN200711005186\_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](mailto:elsing.alicia@mayo.edu) or 507-538-3893.

AE/dkf  
enclosure

<b>SUSPECT ADVERSE REACTION REPORT</b>	

**I. REACTION INFORMATION**

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day	Month	Year				Day	Month	Year	
Unk	CHINA	25	APR	1950	57 Years	Male	70.00 kg	14	NOV	2007	<input type="checkbox"/> PATIENT DIED <input checked="" type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION <input 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)  
 diarrhoea [Diarrhoea]  
 mucositis (rectum) [Proctitis]  
 infection with normal ANC [Infection]  
 paralysis of lower limbs [Diplegia]

Case Description: This Lilly sponsored clinical trial case (H3E MC-JMHO, EudraCT number 2006-001173-14) concerns a 57-year old Chinese male.

Relevant medical history included small cell lung cancer. (continue)

**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 checked="" type="checkbox"/> NA
15. DAILY DOSE(S) #1 500 mg/m2, day 1 of 21 day cycle #2 AUC Day 1 of 21 day cycle	16. ROUTE(S) OF ADMINISTRATION #1 Intravenous #2 Intravenous	
17. INDICATION(S) FOR USE #1 small cell lung cancer(Small cell lung cancer extensive stage) #2 small cell lung cancer(Small cell lung cancer extensive stage)		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 22-OCT-2007 00:00 / Unknown #2 22-OCT-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 FOLIC ACID (FOLIC ACID) ; Unknown #2 VITAMIN B12 (CYANOCOBALAMIN) ; Unknown #3 DEXAMETHASONE (DEXAMETHASONE) ; 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	Medical Condition	Small cell lung cancer extensive stage
Unknown	Medical Condition	Metastases to bone

**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. <b>CN200711005186</b>		
24c. DATE RECEIVED BY MANUFACTURER 12-DEC-2007	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 NAME AND ADDRESS WITHHELD.
DATE OF THIS REPORT 17-DEC-2007	25a. REPORT TYPE <input type="checkbox"/> INITIAL <input checked="" type="checkbox"/> FOLLOWUP: 1	

## ADDITIONAL INFORMATION

## 7+13. DESCRIBE REACTION(S) continued

Concomitant medications included pamidronate disodium which for the treatment of the bone metastasis. Supplementary treatments as per protocol requirements included folic acid, cyanocobalamin (vitamin B12) and dexamethasone.

The patient was enrolled in a randomized phase III trial study of pemetrexed (Alimta) and carboplatin versus etoposide and carboplatin in extensive-stage small cell lung cancer. On the 22-Oct-2007 the patient first received study drug pemetrexed (500 mg/m<sup>2</sup>) intravenously Day 1 of a 21 days cycle and carboplatin (5 AUC, Day 1 of a 21 Day cycle) for the treatment of extended disease small cell lung cancer with vertebrae bone metastases. On an unknown date after the first cycle of study drugs, the patient experienced waist pain worsened and right lower limb weakness. It was not confirmed if waist pain worsened and right lower limb weakness were reported as serious adverse events by the investigator and no other information was provided about these events. The patient received the last dose of study drugs before the events on 12-Nov-2007. On the 14-Nov-2007, three days after the last dose of pemetrexed and carboplatin, the patient experienced paralysis of the lower limbs. The serious criteria reported for paralysis of the lower limbs was hospitalisation. A magnetic resonance imaging (MRI) on 14-Nov-2007 revealed compression fracture in L2 and the orthopaedist suggested that based on the patient's condition the patient did not receive any surgery. Corrective treatment included physical support on waist. After the paralysis of lower limbs, the patient experienced urination disorder and decubitus (5cm x 7cm). It was not confirmed if urination disorder and decubitus were reported as serious adverse events by the investigator. Urethral catheter and physical cleaning was given as corrective treatment. The patient condition was stable. On 26-Nov-2007, 15 days after the last dose of pemetrexed and carboplatin, the patient experienced diarrhoea and mucositis (rectum) both were not caused by the infection. On 28-Nov-2007, 38 days after the last dose of pemetrexed and carboplatin, the patient experienced infection with normal absolute neutrophil count (ANC). All, diarrhoea, mucositis and infection with normal ANC, prolonged hospitalisation and were considered life-threatening by the investigator. The site of infection was unknown and the patient experienced fever which was considered a symptom of the infection. Relevant laboratory results on 30-Nov-2007 were potassium 2.9 mmol/L (3.5 - 5.5) and total protein (TP) 52 g/L (61 - 85) and on 02-Dec-2007 haemoglobin (Hb) 73 g/L (110-160). Corrective treatment for the events was smecta, vancomycin, loperamide, omeprazole and berberine. The patient was recovering from the events diarrhoea and mucositis (rectum) but had not recovered from the paralysis of the lower limbs and the infection. It was not reported if the patient had been discharged from hospital. The study drugs pemetrexed and carboplatin were discontinued on an unspecified date.

The study investigator reported that the paralysis of the lower limbs was clearly due to disease progression. The investigator considered diarrhoea, mucositis (rectum) and infection with normal ANC to be related to pemetrexed and carboplatin and not related to protocol procedures.

Update 10-Dec-2007: Additional information received on 05-Dec-2007. Amended the patient's date of birth. Added new events of diarrhoea, mucositis (rectum) and infection with normal ANC. Added corrective treatments and laboratory results.

Update 10-Dec-2007: Upon internal quality review, listedness for proctitis and pemetrexed changed from listed to unlisted.

Update 11-Dec-2007: Additional information received on 07-Dec-2007 and 11-Dec-2007. Added MRI results, events on first cycle, events of urination disorder and decubitus, investigator number, details about surgery and last dose of study drugs prior to events. Narrative and PSUR updated.

Update 14-Dec-2007: Additional information received from the study investigator on 12-Dec-2007. The event outcomes for diarrhoea and mucositis were changed from not recovered to recovering. Confirmed diarrhoea and mucositis were not caused by the infection. The action taken for the study drug was changed from ongoing to discontinued. The corresponding fields, narrative and PSUR comment were updated.

Lilly Analysis Statement: 10-Dec-2007: This clinical trial case relates to listed events of infection, diarrhoea and diplegia and proctitis, with only the proctitis being an unexpected event. Mucosal inflammation in general is listed for the combined treatment. Since the chemotherapy was combined and mucositis is known in general, the role of the suspect drugs in causing the event cannot be ruled out. None of the events are however related to protocol procedures.

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17-Dec-2007: With the additional and updated information available, unchanged statement regarding relatedness: The role of the suspect drugs in causing the event cannot be ruled out. None of the events are however related to protocol procedures.

## 13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	02-DEC-2007	Haemoglobin Low	73 g/L	160 110
2	30-NOV-2007	Blood potassium Low	2.9 mmol/L	5.5 3.5
3	30-NOV-2007	Protein total Low	52 g/L	85 61

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

#	Date	Test / Assessment / Notes	Results	Normal High / Low
4	28-NOV-2007	Neutrophil count Within Normal Limits		
5	14-NOV-2007	Nuclear magnetic resonance imaging  compression fracture on L2		

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

#4 PAMIDRONATE DISODIUM (PAMIDRONATE DISODIUM) ; Unknown