



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: December 21, 2007

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

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 CHINA	2. DATE OF BIRTH			2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day 25	Month APR	Year 1950	57 Years	Male	70.00 kg	Day 14	Month NOV	Year 2007	
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]										<input type="checkbox"/> PATIENT DIED	
Case Description: This Lilly sponsored clinical trial case (H3E MC-JMHO, Eudract 2006-001173-14) concerns a 57-year old Chinese male.										<input checked="" type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION	
Relevant medical history included small cell lung cancer. (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 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 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, allergics, pregnancy with last month of period, etc.)		
From/To Dates Unknown	Type of History / Notes Medical Condition	Description 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. CN200711005186	25b. NAME AND ADDRESS OF REPORTER NAME AND ADDRESS WITHHELD.
24c. DATE RECEIVED BY MANUFACTURER 05-DEC-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 11-DEC-2007	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP	

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/m²) intravenously Day 1 of a 21 days cycle and carboplatin (5 AU, Day 1 of a 21 Day cycle) for the treatment of extended disease small cell lung cancer with vertebrae bone metastases. On the 14-Nov-2007, 24 days after 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. It was reported that the vertebrae was found to be compressed. No corrective treatment for this event was provided. It was reported that the patient would be assessed by a surgeon to establish if he required surgery. On 26-Nov-2007, 36 days after the last dose of pemetrexed and carboplatin, the patient experienced diarrhoea and mucositis (rectum). 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. 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. At the time of this report the patient had not recovered from any of the events. It was unknown whether the patient received the next cycle of the study drugs pemetrexed and carboplatin. At the time of this report it was not known if the patient had been discharged. Further information has been requested, if any information is received the case will be updated accordingly.

In the opinion of the study investigator the event of paralysis of the lower limbs was not related to the study drugs pemetrexed and carboplatin and not related to the protocol procedures. 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 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.

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.

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
4	28-NOV-2007	Neutrophil count Within Normal Limits		

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

#4 PAMIDRONATE DISODIUM (PAMIDRONATE DISODIUM) ; Unknown