



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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_IN200701006175

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)	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
Unk	INDIA	Day	Month	Year	55 Years	Male	65.00 kg	Day	Month	Year	
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) hydropneumothorax [Hydropneumothorax] Haemoptysis [Haemoptysis]										<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 type="checkbox"/> LIFE THREATENING	
Case Description: This Lilly-sponsored, corporate registration clinical trial case (H3E-MC-JMHO EUDRACT # 2006-001173-14) concerns a 55 years old Asian male The patient's medical history did not include any relevant or concurrent conditions. (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) #1 895 mg, once in 3 weeks #2 792.5 mg, once in 3 weeks	16. ROUTE(S) OF ADMINISTRATION #1 Intravenous #2 Intravenous	
17. INDICATION(S) FOR USE #1 Small cell lung cancer extensive stage(Small cell lung (continue)) #2 Small cell lung cancer extensive stage(Small cell lung (continue))		21. DID REACTION REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA Unknown
18. THERAPY DATES(from/to) #1 15-JAN-2007 00:00 / 10-APR-2007 00:00 #2 15-JAN-2007 00:00 / Unknown	19. THERAPY DURATION #1 86 days #2 Unknown	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) #1 FOLIC ACID (FOLIC ACID) Unknown ; 08-JAN-2007 00:00 / Ongoing #2 VITAMIN B12 (CYANOCOBALAMIN) Unknown ; 08-JAN-2007 00:00 / Ongoing #3 DEXAMETHASONE (DEXAMETHASONE) Unknown ; 08-JAN-2007 00:00 / Ongoing	
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.) From/To Dates Type of History / Notes Description Unknown	

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. IN200701006175		
24c. DATE RECEIVED BY MANUFACTURER 14-AUG-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 14-DEC-2007	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP:	

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

The patient was taking concomitant medication in the form of supplementation therapy: folic acid, vitamin B12 and dexamethasone which all started on 08-Jan-2007 and were continuing.

On 15-Jan-2007, the patient first received pemetrexed (Alimta) 895mg once in every three weeks (day not specified) and carboplatin 792.5mg once in every three weeks (day not specified) for the treatment of small cell lung cancer extensive stage. On 27-Jan-2007, 13 days after receiving the last doses of pemetrexed and carboplatin (the patient had received one cycle with pemetrexed and carboplatin), the patient experienced dyspnoea and haemoptysis and reported to the study co-ordinator. On examination the physician found air entry decreased on the right side of the chest. Haematology and urine samples were within normal limits. X-ray chest revealed hydropneumothorax. Hydropneumothorax was the overall diagnosis. It was stated in follow up (14-Aug-2007) that the haemoptysis was a symptom of the disease and the dyspnoea was a symptom of hydropneumothorax. Haemoptysis was still considered serious for hospitalisation. Pleural tapping was done which revealed pus collection. Pus samples were sent for culture and sensitivity test. The pus culture reveals no growth after 48 hours incubation. The patient was admitted to the hospital on 30-Jan-2007 for an ICD (intrathoracic drainage) procedure and 950 ml of fluid was drained, and dyspnoea improved considerably. He received as corrective treatment on 30-Jan-2007, promethazine hydrochloride, cefuroxime axetil, vitamin B complex, cefatazidime, tramadol, ketorolac and theophylline. Laboratory investigations performed on the 30-Jan-2007 included: haemoglobin (Hb) was 9.2gm% (normal value 14-16), platelets 3.36 (reported as 336000cmm) (normal value 2.5-5 lakhs), bleeding time 1min 30secs (normal value 1-6-min), clotting time 6mins (normal value 2-8-min), prothrombin time 17secs (controlled) and white blood cell count (WBC) (to be clarified) N-7000, M-48, L-5, E-1 (normal value 5-10 Lakhs). Corrective treatments given for the events were: ethamsalate and tramadol. The patient received the second dose of pemetrexed (895 mg)/carboplatin (757 mg) on 05-Feb-2007 while hospitalised. On 07-Feb-2007, another 20 ml of fluid was drained by ICD and the patient's dyspnoea had improved considerably. On examination, bilateral air entry into the lungs was equal. On 08-Feb-2007 another x-ray was performed (results unknown). On 09-Feb-2007 the surgical oncologist changed the position of the ICD. On 10-Feb-2007 another 200ml of fluid was drained, on 11-Feb-2007 160ml, on 12-Feb-2007 220ml was drained. The pus culture sensitivity report, received on 14-Feb-2007, was as follows: gentamycin, amikacin, netilmicin, ciprofloxacin, piperacillin-tazobactam, tobramycin and ceftazidime sensitive; aztreonam and piperacillin resistant. The patient's medications were revised on 15-Feb-2007 as follows: piperacillin plus tazobactam, tramadol and ketorolac tablets. On 16-Feb-2007 ICD drainage was repeated and 60ml was drained. The ICD was removed on the evening of 16-Feb-2007; the patient was relieved of dyspnoea. The patient recovered from the haemoptysis on 17-Feb-2007. As per the investigator the dyspnoea was due to the disease itself and not due to the study drug or protocol procedures. The outcome of the hydropneumothorax was not reported. The patient was discontinued from the study on 10-Apr-2007 due to disease progression. He had received a total of four cycles of chemotherapy.

The investigator stated that the haemoptysis was not related to the study drugs or protocol procedure. An opinion of relatedness for the hydropneumothorax to study drugs and protocol procedure was not provided.

Update 10-Feb-2007: additional information received on 07-Feb-2007 from the investigator: added second cycle of chemotherapy, added ICD on 07-Feb-2007 and confirmed that dyspnoea improving, added exam for bilateral air entry, updated narrative.

Update 01-Mar-2007: additional information received on 12-Feb-2007 and 19-Feb-2007 and entered together: add lab data (x-ray on 08-Feb-2007 & pus culture on 14-Feb-2007), additional corrective treatment, hosp discharge date, end date for dyspnoea, changed protocol procedure relatedness for dyspnoea from unknown to no; updated narrative & PSUR comment

Edits: 01-Mar-2007: Due to system error (study code deleted) had to recode study drugs & reassign listedness.

Update 20-Aug-2007: additional information received on 14-Aug-2007, no new information added. Case closed.

Update 12-Dec-2007: Additional information received from the investigator on 14-Aug-2007 and 28-Nov-2007: Deleted event of dyspnoea, added event of hydropneumothorax, changed doses of carboplatin, changed action taken with study drugs to discontinued and added stop date for study drugs and stop date for study, added relatedness for haemoptysis, added stop date for haemoptysis and hospitalisation discharge date, number of cycles completed, changed start date for haemoptysis, added corrective treatment and added doses to corrective treatment, changed action taken for cefuroxime axetil to discontinued. Corrected previous follow up date from 14-Feb-2007 to 14-Aug-2007. Updated relevant fields, narrative and PSUR comment.

Lilly Analysis Statement: 14-Dec-2007: This clinical trial case relates to an unexpected event of hydropneumothorax in a patient on combined chemotherapy. Hydropneumothorax is usually due to a procedure related complication (e.g post pleural aspiration), following trauma or due to gas-producing organisms. The causative role of suspect drugs Pemetrexed and Carboplatin is dubious, given the limited information and the presence of a progressive malignancy. Investigator's opinion and f/u is requested. The event is however not related to protocol procedures.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		Physical examination		
		On examination air entry decreased on the right side of the chest		
2		X-ray		
		X-ray chest revealed hydropneumothorax		

ADDITIONAL INFORMATION**13. Lab Data**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
3	30-JAN-2007	Haemoglobin Low	9.2 gm%	16 14
4	30-JAN-2007	Platelet count Within Normal Limits	3.36 lakhs	5 2.5
5	30-JAN-2007	Bleeding time Within Normal Limits 1min 30secs		6 1
6	30-JAN-2007	Coagulation time Within Normal Limits	6 mins	8 2
7	30-JAN-2007	Prothrombin time controlled	17 secs	
8	19-FEB-2007	Bacterial culture Pus Culture Sensitivity Report: Gentamycin - sensitive Amikacin - sensitive Netilmicin - sensitive Ciprofloxacin - sensitive Pipero-tazo - sensitive Aztreanom - resistant Tobramycin - sensitive Piperacillin - resistant Ceftazidime - sensitive		
9	08-FEB-2007	X-ray Result not provided		

13. Relevant Tests

On an unknown date - unspecified tests of haematology and urine samples were with in normal limits

Pleural tapping was done which revealed pus collection. Pus samples were sent for culture and sensitivity test pus culture revealed no growth after 48 hours incubation

White blood cell count (WBC) reported as N-7000, M-48, L-5, E-1, 5-10 Lakhs.

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	895 mg, once in 3 weeks; Intravenous	Small cell lung cancer extensive stage(Small cell lung cancer extensive stage)	15-JAN-2007 00:00 / 10-APR-2007 00:00; 86 days
#2 *CARBOPLATIN (CARBOPLATIN) Unknown; Regimen #1	792.5 mg, once in 3 weeks; Intravenous	Small cell lung cancer extensive stage(Small cell lung cancer extensive stage)	15-JAN-2007 00:00 / Unknown; Unknown
#2 *CARBOPLATIN (CARBOPLATIN) Unknown; Regimen #2	757 mg, once in 3 weeks; Intravenous		05-FEB-2007 00:00 / 10-APR-2007 00:00; 65 days