



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: December 14, 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_IN200704005797_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 42 Years	3. SEX Male	3a. WEIGHT 32.00 kg	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day 15	Month DEC	Year 1964				Day 23	Month APR	Year 2007	
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim (PREFERRED TERM) (Related symptoms if any separated by commas) Other Serious Criteria: Med significant Cardio-respiratory arrest [Cardio-respiratory arrest] cardiac arrest [Cardiac arrest] Acute lung injury [Lung injury] Endobronchial obstruction due to mucus plugs [Bronchial secretion retention] Atrial fibrillation [Atrial fibrillation]										<input checked="" type="checkbox"/> PATIENT DIED Date: 12-MAY-2007	
Case Description: This clinical trial case (H3E-MC-JMHO, Eudract No: 2006-001173-14), concerns a 42 year old Asian male patient. (continue)										<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	

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
15. DAILY DOSE(S) #1 595 mg, once every 21 days #2 488 mg, once every 21 days	16. ROUTE(S) OF ADMINISTRATION #1 Intravenous #2 Intravenous	
17. INDICATION(S) FOR USE #1 (Small cell lung cancer stage unspecified) #2 small cell lung cancer(Small cell lung cancer stage unspecified)		21. DID REACTION REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA
18. THERAPY DATES(IronTo) #1 21-APR-2007 00:00 / 21-APR-2007 00:00 #2 21-APR-2007 00:00 / 21-APR-2007 00:00	19. THERAPY DURATION #1 1 day #2 1 day	

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) ; 17-APR-2007 00:00 / 24-APR-2007 00:00 #2 VITAMIN B12 (CYANOCOBALAMIN) ; 19-APR-2007 00:00 / Unknown #3 DEXAMETHASONE (DEXAMETHASONE) ; 20-APR-2007 00:00 / 22-APR-2007 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		Small cell lung cancer extensive stage
Unknown	with extensive mediastinal and retroperitoneal lymphadenopathy	Hepatic Impairment
	liver metastasis	Metastases to liver

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER Lilly Deutschland GmbH Safety Dept. , Saalburgstraße 153 Bad Homburg, 61350 GERMANY		26. REMARKS
24b. MFR CONTROL NO. IN200704005797		
24c. DATE RECEIVED BY MANUFACTURER 24-APR-2007		25b. NAME AND ADDRESS OF REPORTER NAME AND ADDRESS WITHHELD.
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-DEC-2007		
25a. REPORT TYPE <input type="checkbox"/> INITIAL <input checked="" type="checkbox"/> FOLLOWUP: 1		

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

The medical history of the patient included: small cell lung cancer with extensive mediastinal and retroperitoneal lymphadenopathy and liver metastasis. Concomitant medications were provided as follows: lorazepam, granisetron hydrochloride, metoclopramide hydrochloride, ranitidine hydrochloride, benzydamine hydrochloride for prophylaxis against chemotherapy induced nausea and vomiting, pantoprazole for prophylaxis against drug induced gastritis, ondansetron for anti-emetic therapy, beclomethason dipropionate clotrimazol for oral hygiene, allopurinol and disodium hydrogen citrate (Cital syrup) for tumour lysis prophylaxis. The patient was also taking the following supplemental medications as per protocol: folic acid, vitamin B12 and dexamethasone.

The patient was first admitted to hospital on 09-Apr-2007 after consenting for the study for performing the screening investigations followed by administration of cycle 1 of chemotherapy. On 21-Apr-2007, the patient first received pemetrexed (Alimta) 595 mg (cycle 1) and carboplatin 488 mg, both intravenously (IV) once every 21 days for the treatment of small cell lung cancer (SCLC). The patient received the last dose of study drugs pemetrexed and carboplatin on 21-Apr-2007. On 23-Apr-2007, three days after last dose of study drugs, the patient experienced worsening of dyspnoea and developed irregular tachycardia and clinical signs of left lung consolidation. The events were serious due to prolongation of existing hospitalisation. The patient was moved to intensive care unit (ICU) for management. In ICU, an electrocardiograph performed on unknown date showed atrial fibrillation which was restored to sinus rhythm by injections of amiodarone (600 mg) IV over 24 hours. On 23-Apr-2007, an x-ray confirmed that the patient had developed left lobar consolidation with opaque left hemithorax. A pleural effusion of significant proportion was ruled out by a bedside ultrasound. The patient had recovered from atrial fibrillation by 24-Apr-2007. The following laboratory tests were performed on 24-Apr-2007: troponin T was negative, white blood cell (WBC) count was 38,900 cells per cmm (cmm) (normal range 4000-11000 ccm). Haemoglobin (Hb), platelet count and serum creatinine did not show any clinically significant alterations. The patient was also treated with non-invasive ventilation, piperacillin, azobactam, amikacin, fluconazole, clexane, dexamethasone and supportive care in ICU. At the time of the initial report the working diagnosis was an acute lung injury, possibly due to an infective consolidation or study drug or pulmonary embolism. On an unconfirmed date, a computerised tomography (CT) scan ruled out metastasis, but the working diagnosis was endobronchial mucus/infective plugs. A CT scan was performed on 25-Apr-2007 (to be confirmed if this refers to the same occasion), which showed confluent hypotense enhancing mass encasing the mediastinal structure suggestive of lymph node mass. This CT scan showed no significant change in size and extent as compared to the previous CT Scan. The CT Scan also showed that the left main bronchus was significantly narrowed with segmental and subsegmental lung consolidation and volume loss, causing mediastinal shift. The liver metastasis were unchanged, but bilateral small pleural effusions had increased. A bronchoscopy was performed on 26-Apr-2007 which revealed an ulcerative inflammatory response. Therapeutically many mucus plugs were removed while performing bronchoscopy. By the afternoon of 26-Apr-2007, the patient's condition had improved. His respiratory rate and pulse rate decreased and his consciousness improved. The patient was extubated on 27-Apr-2007 and at the time of the follow up report on 27-Apr-2007 was breathing on his own. The diagnosis was acute lung injury secondary to infective pathology and endobronchial obstruction due to mucus plugs. On an unknown date a urine culture showed sensitivity to imipenem and hecopenem, E. Coli isolated. By 28-Apr-2007 the patient was doing fairly well on supplemental oxygen by nasal mask. However, on 30-Apr-2007 the patient developed tachypnoea, hyperapnea and signs of left lung collapse. The patient was intubated again and he was put on ventilator. On 01-May-2007 his saturation and hemodynamics were satisfactory. A tracheostomy was performed on 01-May-2007 and connected to BIPAP (abbreviation to be confirmed). The patient was doing well after the tracheostomy, however he had an episode of hypokalemia (potassium was 2.9 mEq) at 10 pm on 02-May-2007. On the morning of 03-May-2007, the patient had an episode of bradycardia, followed by asystolic arrest. The patient was administered cardiopulmonary resuscitation and two shocks. He also had an episode of ventricular fibrillation on the monitor. After administration of noradrenaline and amiodarone, the patient had an organised rhythm. The diagnosis at the time of follow up on 04-May-2007 was most probably cardiac arrest due to electrolyte imbalance and sepsis. The patient was being treated with IV antibiotic injection of enoxaparin sodium, injection of amikacin, imipenem-cilastatin (Cilanem), dexamethasone, allopurinol, amiodarone and supportive care in ICU. On 05-May-2007, the patient discontinued study drugs. Despite treatment the patient's respiratory problems persisted due to the non-resolving collapse condition of the left lower lobe and the patient expired on 12-May-2007. The cause of death was cardio-respiratory arrest with underlying extensive distress. An autopsy was not performed.

The cardio-respiratory arrest occurred following the acute lung injury, persistent ventilatory problems and non-resolving collapse consolidation of the left lower lobe. The investigator felt that the cardio-respiratory arrest on 12-May-2007 may have been due to the study drugs, but not due to protocol procedures. No causality opinion was provided for the cardiac arrest on 03-May-2007, although the investigator considered it due to electrolyte imbalance and sepsis. The investigator stated that acute lung injury could probably be due to infective pathology and/or pemetrexed, but not to carboplatin or protocol procedures. As per the investigator the reasons for atrial fibrillation could be multifactorial one of which includes exposure to pemetrexed, however no assessment for carboplatin and protocol procedures was provided. No opinion of relatedness was provided for endobronchial obstruction due to mucus plugs.

Update 03-May-2007: Additional information received from investigator on 27-Apr-2007, 01-May-2007 and 03-May-2007 (added at the same time): Added atrial fibrillation as event, added relatedness for atrial fibrillation. Changed the event of lung consolidation to two separate events following diagnosis: acute lung injury secondary to infective pathology and endobronchial obstruction due to mucus plugs. Updated relatedness as applicable. Added further lab results (CT scan, bronchoscopy, urine culture) and course of events from 25-Apr-2007 to 01-May-2007. Updated narrative and PSUR comment.

Update 10-May-2007: Additional information received from the investigator on 04-May-2007: Added stop dates for conc meds ondansetron and dexamethasone, added further course of events after 01-May-2007, including potassium lab results. Checked medically significant for bronchial obstruction event. Changed as determined protocol procedure relatedness for all events to no. Updated narrative and PSUR comment.

Update 22-May-2007: Additional information received from investigator on 17-May-2007: Changed as reported event term to acute lung injury; changed outcome for event acute lung injury from not recovered to fatal; added date & cause of death; changed study

ADDITIONAL INFORMATION**13. Lab Data**

#	Date	Test / Assessment / Notes	Results	Normal High / Low
8		Creatinine renal clearance Within Normal Limits creatinine serum No clinically significant alteration		
9		Computerised tomogram Abnormal Metastasis was ruled out by CT scan, working diagnosis was endobronchial mucus/infective plugs.		
10	25-APR-2007	Computerised tomogram Abnormal Showed confluent hypotense enhancing mass encasing the mediastinal structure suggestive of lymph node mass. The CT scan showed no significant change in size and extent as compared to the previous CT Scan. The CT Scan also showed that the left main bronchus was significantly narrowed with segmental and subsegmental lung consolidation and volume loss, causing mediastinal shift. The liver metastasis were unchanged, but bilateral small pleural effusions had increased.		
11	26-APR-2007	Bronchoscopy Abnormal Ulcerative inflammatory response. Therapeutically, many mucus plugs were removed while performing bronchoscopy.		
12		Bacterial culture Abnormal Showed sensitivity to Imipenen and Hecopenen, E. Coli isolated.		
13	02-MAY-2007	Blood potassium Low at 10pm	2.9 mEq	

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

#4 ATIVAN (LORAZEPAM) ; 22-APR-2007 00:00 / 23-APR-2007 00:00

#5 GRANISETRON HYDROCHLORIDE (GRANISETRON HYDROCHLORIDE) ; 22-APR-2007 00:00 / 23-APR-2007 00:00

#6 PERINORM (METOCLOPRAMIDE HYDROCHLORIDE) ; 22-APR-2007 00:00 / 23-APR-2007 00:00

#7 RANTAC (RANITIDINE HYDROCHLORIDE) ; 22-APR-2007 00:00 / 23-APR-2007 00:00

#8 TANTUM (BENZYLAMINE HYDROCHLORIDE) ; 22-APR-2007 00:00 / 23-APR-2007 00:00

#9 PANTOPRAZOLE (PANTOPRAZOLE) ; 24-APR-2007 00:00 / Ongoing

#10 ONDANSETRON (ONDANSETRON) ; 24-APR-2007 00:00 / 25-APR-2007 00:00

#11 CANDID B (BECLOMETASONE DIPROPIONATE, CLOTRIMAZOLE) ; 24-APR-2007 00:00 / Ongoing

#12 ALLOPURINOL (ALLOPURINOL) ; 24-APR-2007 00:00 / Ongoing

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

drug relatedness for acute lung injury from not reported to yes; updated narrative accordingly.

Update 24-May-2007: Following physician review on 24-May-2007 amended as determined relatedness for event endobronchial obstruction due to mucus plugs to pemetrexed & carboplatin to no (previously not reported) and amended as determined causality for event atrial fibrillation to carboplatin to yes (previously not reported).

Update 24-May-2007: Following case review on 24-May-2007: added cardio-respiratory arrest as new event with fatal outcome; changed event coding for event acute lung injury, reassigned listedness; removed fatal criteria & changed outcome from fatal to not recovered.

Update 22-Oct-2007: Additional information received from the site on 17-Oct-2007. Added stop dates for study drugs, start and stop dates for concomitant and treatment medications, autopsy not performed. Narrative, PSUR and corresponding fields updated accordingly.

Update 29-Oct-2007: Dose units deleted for folic acid and vitamin B12 to allow reporting.

Update 03-Dec-2007: Upon post-data quality check from the affiliate of the initial information received on 24-Apr-2007 the following changes were made: Stop date of both study drugs changed. Stop date of folic acid changed. Stop dates of pantoprazole, beclometason/clotrimazol and allopurinol reported as 12-Dec-2007 (date of death), therefore coded as ongoing. Narrative and PSUR updated

Edit 03-Dec-2007: Upon review of previously received information, causality for lung injury and protocol procedures changed from unknown to no in relevant field. Causality for lung injury and carboplatin changed from yes to no in narrative. Added life-threatening event of cardiac arrest on 03-May-2007. Date of fatal cardio-respiratory arrest event changed from 03-May-2007 to 12-May-2007.

Lilly Analysis Statement: This case of a man receiving pemetrexed and carboplatin for SCLC who developed lung consolidation. This is unlisted against the carboplatin and pemetrexed ClB. Carboplatin is not associated with lung damage, but is associated with infection. Pemetrexed is associated with pneumonitis, pulmonary embolus and pulmonary haemorrhage. In this case, in the presence of extensive thoracic malignancy, and the administration of chemotherapy the patient is at high risk of lung infection, which is probably what this is in view of the raised white blood count and the treatment administered. The event is possibly related to the carboplatin and pemetrexed.

22-Oct-2007: No change in analysis statement.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		Electrocardiogram Abnormal Atrial fibrillation which has now been restored to sinus rhythm	Atrial fibrillation	
2	23-APR-2007	X-ray Abnormal Chest x-ray = opaque left hemithorax, confirmed diagnosis of left lobular consolidation of lung		
3	24-APR-2007	Troponin Troponin T	negative	
4	24-APR-2007	White blood cell count High	38,900 cmm	11000 4000
5		Ultrasound scan Within Normal Limits Pleural effusion of significant proportion was ruled out by bedside ultrasound		
6		Haemoglobin Within Normal Limits No clinically significant alteration		
7		Platelet count Within Normal Limits No clinically significant alteration		