



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: November 30, 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_US200707001194

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

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| SUSPECT ADVERSE REACTION REPORT | |
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| | |

I. REACTION INFORMATION

| 1. PATIENT INITIALS <small>(First, last)</small> | 1a. COUNTRY | 2. DATE OF BIRTH | | | 2a. AGE | 3. SEX | 3a. WEIGHT | 4-6 REACTION ONSET | | | 8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION |
|---|---------------|------------------|-------|------|-------------|--------|-------------|--------------------|-------|------|---|
| [REDACTED] | UNITED STATES | Day | Month | Year | 72 Years | Female | 50.79 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) Unresponsiveness [Unresponsive to stimuli] Encephalopathy [Encephalopathy] Dehydration/hypokalemia [Dehydration] Pancytopenia (afebrile) [Pancytopenia] Thrombocytopenia [Thrombocytopenia] Leukopenia [Leukopenia] Febrile neutropenia [Febrile neutropenia] | | | | | | | | | | | <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 clinical trial case (H3E-MC-JMHO, EUDRACT #2006-001173-14) concerned a 72-year-old Caucasian female. (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 checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA |
| 15. DAILY DOSE(S) #1 715 mg, other #2 5 D/F, other | 16. ROUTE(S) OF ADMINISTRATION #1 Intravenous #2 Intravenous | |
| 17. INDICATION(S) FOR USE #1 small cell(Small cell lung cancer extensive stage) #2 small cell(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 19-JUN-2007 00:00 / 19-JUN-2007 00:00 #2 19-JUN-2007 00:00 / 19-JUN-2007 00:00 | 19. THERAPY DURATION #1 1 day #2 1 day | |

III. CONCOMITANT DRUG(S) AND HISTORY (Continued on Additional Information Page)

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|--|-------------------------|-----------------------------------|---------------|-------------------------|-------------|---------|-------------------|-----------------------------------|---------|--------------------|---------------------|
| 22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) #1 FOLIC ACID (FOLIC ACID) ; 14-JUN-2007 00:00 / 30-JUN-2007 00:00 #2 VITAMIN B12 (CYANOCOBALAMIN) ; 15-JUN-2007 00:00 / 15-JUN-2007 00:00 #3 DEXAMETHASONE (DEXAMETHASONE) ; 18-JUN-2007 00:00 / 20-JUN-2007 00:00 | | | | | | | | | | | |
| 23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.) <table style="width:100%; border: none;"> <tr> <td style="width:33%; border: none;">From/To Dates</td> <td style="width:33%; border: none;">Type of History / Notes</td> <td style="width:33%; border: none;">Description</td> </tr> <tr> <td style="border: none;">Unknown</td> <td style="border: none;">Medical Condition</td> <td style="border: none;">Small cell lung cancer metastatic</td> </tr> <tr> <td style="border: none;">Unknown</td> <td style="border: none;">Hepatic Impairment</td> <td style="border: none;">Metastases to liver</td> </tr> </table> | | | From/To Dates | Type of History / Notes | Description | Unknown | Medical Condition | Small cell lung cancer metastatic | Unknown | Hepatic Impairment | Metastases to liver |
| From/To Dates | Type of History / Notes | Description | | | | | | | | | |
| Unknown | Medical Condition | Small cell lung cancer metastatic | | | | | | | | | |
| Unknown | Hepatic Impairment | Metastases to liver | | | | | | | | | |

IV. MANUFACTURER INFORMATION

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| 24a. NAME AND ADDRESS OF MANUFACTURER Eli Lilly & Company Lilly Corporate Center, Global Product Safety, Indianapolis, IN 46285 UNITED STATES | | 26. REMARKS [REDACTED] |
| | 24b. MFR CONTROL NO. US200707001194 | |
| 24c. DATE RECEIVED BY MANUFACTURER 07-NOV-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 09-NOV-2007 | 25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP | |

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

Medical history included small cell lung cancer with extensive liver metastases and back surgery on 04Apr06. She received multiple concomitant medications including folic acid, vitamin B12 and dexamethasone.

The patient first and last received pemetrexed disodium (Alimta) 715 mg intravenously (IV) in combination with carboplatin 5 AUC every 21 days beginning on 19Jun07 for the treatment extensive disease small cell lung cancer. On 30Jun07, 12 days after last receiving study therapy, she was admitted to the hospital due to unresponsiveness, encephalopathy, dehydration, hypokalemia, pancytopenia (afebrile), thrombocytopenia, leukopenia, and febrile neutropenia. Laboratory results included white blood cell (WBC) count 0.9, hemoglobin 10.8, platelet count 38, international normalized ratio (INR) 1.19, partial thromboplastin time (PTT) 30.4 seconds, and prothrombin time (PT) 15.7 seconds. Pan cultures were performed (results not provided). Treatment included IV hydration, potassium and magnesium replacement, broad spectrum antibiotics, and filgrastim. She continued to be extremely debilitated. She responded to verbal stimuli, but was only oriented to self. Potassium levels continued to be extremely low despite potassium replacement at 2.5 meQ/L (potassium level not provided). Additional treatment included a platelet transfusion on 02Jul07. Potassium level on 06Jul07 was 3.7. On 06Jul07, the events resolved. On 24Jul07, she was removed from protocol. She last received study therapy on 19Jun07.

In the opinion of the study investigator, the events of unresponsiveness, encephalopathy, dehydration/hypokalemia, pancytopenia (afebrile), thrombocytopenia, leukopenia, and febrile neutropenia were possibly related to study therapy. All the events were unrelated to protocol procedures.

Update 12Jul07: Information received 09Jul07. Added patient demographics, updated study status, added patient outcome, resolution date, and relatedness to study therapy. Updated narrative and PSUR comments. Upon review, added lab to database field.

Update 26Jul07: Additional information received on 24Jul07. Added patient initials. Added laboratory results including WBC, hemoglobin, platelet count, INR, potassium, PTT and PT. Updated the narrative and PSUR comment.

Update 08Nov07: Information received on 07Nov07. Added events of unresponsiveness, encephalopathy, thrombocytopenia, leukopenia, and febrile neutropenia; added stop date for study therapies and amended action taken from no change to drug discontinued; added stop dates for concomitant medications of folic acid and dexamethasone and amended action taken from no change to drug previously discontinued; updated narrative and PSUR comment.

Lilly Analysis Statement: Pancytopenia and dehydration are likely to be related to study treatment, listed events.

Update 09-NOV-2007: The added events of unresponsiveness, encephalopathy, thrombocytopenia, leukopenia and febrile neutropenia are also likely related to study treatment.

13. Lab Data

| # | Date | Test / Assessment / Notes | Results | Normal High / Low |
|---|-------------|--|--|-------------------|
| 1 | 2007 | Bacterial culture | pancultures completed; results not provided | |
| 2 | 30-JUN-2007 | White blood cell count Low | 0.9 | 11.0 4.5 |
| 3 | 30-JUN-2007 | Haemoglobin Low | 10.8 g/dL | 16.3 11.7 |
| 4 | 30-JUN-2007 | Platelet count Low | 38 | 400 150 |
| 5 | 30-JUN-2007 | International normalised ratio High | 1.19 | 1.14 0.86 |
| 6 | 30-JUN-2007 | Activated partial thromboplastin time High | 30.4 seconds | 35.1 23.7 |
| 7 | 30-JUN-2007 | Prothrombin time High | 15.7 seconds | 15.3 12.4 |
| 8 | 30-JUN-2007 | Blood potassium Within Normal Limits | 3.7 meQ/L | 5.4 3.7 |

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

#4 LORTAB (HYDROCODONE BITARTRATE, PARACETAMOL) ; 05-APR-2006 00:00 / Ongoing

#5 NICOTINE (NICOTINE) ; 30-MAY-2007 00:00 / Ongoing

ADDITIONAL INFORMATION

23. OTHER RELEVANT HISTORY continued

| From/To Dates | Type of History / Notes | Description |
|------------------------|-------------------------|-------------|
| 04-APR-2006 to Unknown | Procedure Back | Surgery; |