



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_CA200708001635_F2

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) LB | 1a. COUNTRY CANADA | 2. DATE OF BIRTH | | | 2a. AGE | 3. SEX | 3a. WEIGHT | 4-6 REACTION ONSET | | | 8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION |
| | | Day 07 | Month JAN | Year 1960 | 47 Years | Female | 50.00 kg | Day 20 | Month JUL | 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: medical significance AML [Myeloid leukaemia] myelodysplastic syndrome [Myelodysplastic syndrome] | | | | | | | | | | <input checked="" type="checkbox"/> PATIENT DIED Date: 22-OCT-2007 | |
| Case Description: This clinical trial case (H3E-CA-JMHU) concerns a 47-year-old female of unknown origin. | | | | | | | | | | <input type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION | |
| The patient's medical history included grade 3 esophagitis and grade 3 dehydration requiring a prior hospitalization (see linked case), pancreatitis, gastroesophageal reflux disease, and an 10 pack year smoking history which (continue) | | | | | | | | | | <input type="checkbox"/> INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY | |
| | | | | | | | | | | <input type="checkbox"/> LIFE THREATENING | |

II. SUSPECT DRUG(S) INFORMATION

(Continued on Additional Information Page)

| | | |
|---|--|--|
| 14. SUSPECT DRUG(S) (include generic name) #1 PEMETREXED (PEMETREXED) Vial #2 *CISPLATIN(*CISPLATIN)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) #1 765 mg, UNK #2 38.25 mg, other | 16. ROUTE(S) OF ADMINISTRATION #1 Intravenous #2 Intravenous | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> NA |
| 17. INDICATION(S) FOR USE #1 non small cell lung cancer(Non-small cell lung cancer) #2 non-small cell(Non-small cell lung cancer) | | |
| 18. THERAPY DATES(from/to) #1 20-DEC-2006 00:00 / 20-DEC-2006 00:00 #2 20-DEC-2006 00:00 / 22-DEC-2006 00:00 | 19. THERAPY DURATION #1 1 day #2 3 days 0 hrs | |

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 CODEINE (CODEINE) ; 07-DEC-2006 00:00 / Ongoing #2 FENTANYL (FENTANYL) ; 18-JAN-2007 00:00 / Ongoing #3 FOLIC ACID (FOLIC ACID) ; 13-DEC-2006 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 | Medical Condition | Pancreatitis |
| Unknown | Medical Condition | Gastroesophageal reflux disease |

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 CA200708001635 | 25b. NAME AND ADDRESS OF REPORTER NAME AND ADDRESS WITHHELD. |
| 24c. DATE RECEIVED BY MANUFACTURER 23-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 28-NOV-2007 | 25a. REPORT TYPE <input type="checkbox"/> INITIAL <input checked="" type="checkbox"/> FOLLOWUP 2 | |

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

stopped seven years ago. Concomitant medications included folic acid, vitamin B12, codeine and fentanyl.

On 20-Dec-2006, the patient first received pemetrexed disodium (Alimta) 765 mg intravenously (IV) on day 1 and cisplatin 38.25 mg IV on days 1 through 3, for the treatment of non-small cell lung cancer. On 10-Jan-2007, cycle 2, the patient received pemetrexed 765 mg IV on day 1 and cisplatin 38.25mg IV on days 1 through 3. On 22-Mar-2007, cycle 3, the patient received pemetrexed 730 mg IV and cisplatin 110 mg IV, and on 12-Apr-2007, cycle 4, pemetrexed 730 mg IV and Cisplatin 110 mg IV. The patient also received concurrent thoracic radiation therapy (66Gy/33tx). Pemetrexed, cisplatin, and radiation treatment completed on 12-Apr-2007. On 08-May-2007, the patient received a whole body bone scan with normal results. The patient returned to the clinic on 30-May-2007 for a follow-up visit. Blood work from that day demonstrated hemoglobin 89, platelets 56, leukocytes 2.1, and absolute neutrophils 1.7. On 26-Jun-2007, the patient was referred to a hematologist. On 17-Jul-2007, the patient saw the hematologist and had a bone marrow biopsy the same day. Blood work from 17-Jul-2007 demonstrated hemoglobin 81, platelets 144, leukocytes 1.2, and absolute neutrophils 0.8. The bone biopsy showed was 0.8 cm, and showed a significantly hypercellular bone marrow for age. The megakaryocytes were significantly increased with large dysplastic forms. Active granulopoiesis and erythropoiesis. No overt fibrotic changes. No large clusters of blasts. No infiltrates by solid tumor cells. A population of blasts was present on this flow cytometric sample seen on the CD45 versus scatter histogram. The blasts present at ~4% of all cells in this sample. The blasts express CD13/33/34/HLA-DR/MPO. CD7 was positive and other B and T cell markers were negative. This flow cytometric pattern was consistent with a small population of blasts demonstrating myeloid phenotype. On 17-Jul-2007, bone marrow results were: Myelomonocytic Associated Markers: C11b 0.11, CD13 0.82, CD15 0.22, CD33 0.76, CD34 0.47, CD56 0.03, CD65 0.15, CD117 equivocal, HLA-DR 0.77, CD33+CD34+ 0.41. Lymphoid Markers: CD2 0.05, CD3 0.06, CD4 0.03, CD7 0.60, CD10 0.08, CD19 0.04. Intracellular Markers: TdT <0.01, MPO 0.22, CyCD3 0.01, CyCD79a 0.01. Interpretation: Normal female karyotype. Twenty metaphase cells were analyzed. No abnormalities were detected at the level of resolution achieved. On 20-Jul-2007, seven months after first receiving pemetrexed, cisplatin, and radiation treatment and three months after last receiving pemetrexed, cisplatin and radiation, preliminary biopsy results showed myelodysplastic syndrome (MDS) with 3-4% blastocytes. The patient had been closely monitored receiving multiple blood draws and transfusions. Brain magnetic resonance imaging (MRI) on 26-Jul-2007 showed an abnormal marrow signal within the skull, central skull base, and upper cervical spine, thought to be reflective of marrow reactivation in light of recent normal bone scan. There was no evidence of parenchymal or extraaxial metastases. Laboratory data from 30-Jul-2007 included hemoglobin 77, platelets 102, leukocytes 1.3, and absolute neutrophils 0.8. Additional laboratory results are available in the source documents. On 30-Aug-2007, blood and bone marrow results were: Diagnosis: Acute Myeloid Leukemia. >20% of circulation white cells are CD34+ myeloid blasts that positive for CD11b/13/33/117/HLA-DR/7/cyMPO with aberrant expression of T-cell marker CD7. Acute Leukemia Results: Myelomonocytic Associated Markers: CD11b 0.64, CD13 0.94, CD15 0.26, CD33 0.93, CD34 0.62, CD56 0.02, CD65 0.07, CD117 ~0.57 (dim), HLA-DR 0.74, CD33+CD34+ 0.59. Lymphoid Markers CD2 0.01, CD3 <0.01, CD4 <0.01, CD7 0.74, CD10 0.05, CD19 0.02. Intracellular Markers TdT 0.01, MPO 0.15, CyCD3 0.01, CyCD79a 0.01. The patient continued to be monitored by a radiation and medical oncologist as well as a medical hematologist. The event of myelodysplastic syndrome was ongoing. Consolidation therapy had previously been completed. On 22-Oct-2007, the patient expired due to acute myeloid leukemia. The investigator noted that there was no clear evidence of progression prior to her death, that he was aware of. The data showed continued objective response up until her death.

In the opinion of the investigator, the event of myelodysplastic syndrome was considered possibly related to pemetrexed, cisplatin, and radiation therapy. The investigator stated that the event was not immediately life threatening, but had a poor long term prognosis. MDS is typically caused by chemotherapy, but generally occurs years after treatment. It is felt in this case that the condition was likely preexisting and undetectable, but that the therapy was instrumental in revealing it or hastening its course. The fatal acute myeloid leukemia was not related to study therapy (verbatim as reported, clarification to be requested). The events were unrelated to protocol procedures.

This case is linked to case CA200702000405.

Update 08-Aug-2007: Additional information received 07-Aug-2007. Processed on 08-Aug-2007 at the same time that the initial case was entered.

Update 30-Aug-2007: Upon review, edit made: changed unexpected origin to unknown origin in the initial sentence of narrative.

Update 13-Sep-2007: Information received on 07-Sep-2007. Added all bone biopsy and bone marrow results from 17-Jul-2007 and 30-Aug-2007, added dosing of pemetrexed and cisplatin for all 4 cycles, added concomitant medications of folic acid and vitamin B12, added medical history of smoking, pancreatitis, and gastroesophageal reflux disease, updated narrative and PSUR comment.

Update 27-Nov-2007: Information received on 23-Nov-2007 added fatal event of acute myelogenous leukemia, and updated narrative and PSUR comment.

Update 28-Nov-2007: Upon Lilly Physician review, upgraded as determined causality for the event of AML from no to yes for pemetrexed, cisplatin, and radiation.

Lilly Analysis Statement: Agree with the investigator's remarks that the myelodysplastic state is possibly related to therapy but more likely related to an underlying undiagnosed condition given the diagnosis was made so shortly after the therapy was completed.

Analysis Statement Addendum (28-Nov-2007): Follow-up provides information that the myelodysplastic syndrome subsequently progressed to acute myeloid leukemia and the patient died approximately 10 months after the initiation of pemetrexed, cisplatin, and radiation therapy for non-small lung cancer. The investigator believed that the myelodysplastic syndrome was possibly related to pemetrexed, cisplatin and radiation therapy. The Sponsor believes that a relationship between acute myeloid leukemia and pemetrexed, cisplatin and radiation therapy cannot be excluded. There have been no prior reports of myelodysplastic syndrome or acute myeloid leukemia associated with pemetrexed. Although myelodysplastic syndrome and leukemia has been reported in patients who had previously received cisplatin with or without radiation therapy, the latency period between treatment and these events is

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued
generally longer than noted in this case.

13. Lab Data

| # | Date | Test / Assessment / Notes | Results | Normal High / Low |
|----|-------------|---|-----------|-------------------|
| 1 | 20-JUL-2007 | Biopsy bone marrow biopsy confirmed myelodysplastic syndrome | | |
| 2 | 26-JUL-2007 | Nuclear magnetic resonance imaging Magnetic resonance imaging (MRI) on the brain reported abnormal marrow signal within the skull, central skull base, and upper cervical spine, thought to be reflective of marrow reactivation in light of recent normal bone scan. There was no evidence of parenchymal or extraaxial metastases. | | |
| 3 | 20-DEC-2006 | Haemoglobin Within Normal Limits | 129 | 160 120 |
| 4 | 30-MAY-2007 | Haemoglobin Low | 89 | 160 120 |
| 5 | 17-JUL-2007 | Haemoglobin Low | 81 | 160 120 |
| 6 | 30-JUL-2007 | Haemoglobin Low | 77 | 160 120 |
| 7 | 20-DEC-2006 | Platelet count Within Normal Limits | 199 | 400 150 |
| 8 | 30-MAY-2007 | Platelet count Low | 56 | 400 150 |
| 9 | 17-JUL-2007 | Platelet count Low | 144 | 400 150 |
| 10 | 30-JUL-2007 | Platelet count Low | 102 | 400 150 |
| 11 | 20-DEC-2006 | White blood cell count Within Normal Limits | 4.1 | 11.0 4.0 |
| 12 | 30-MAY-2007 | White blood cell count Low | 2.1 | 11.0 4.0 |
| 13 | 17-JUL-2002 | White blood cell count Low | 1.2 | 11.0 4.0 |
| 14 | 30-JUL-2007 | White blood cell count Low | 1.3 | 11.0 4.0 |
| 15 | 20-DEC-2006 | Neutrophil count Within Normal Limits | 3.4 | 7.5 2.0 |
| 16 | 30-MAY-2007 | Neutrophil count Low | 1.7 | 7.5 2.0 |
| 17 | 17-JUL-2007 | Neutrophil count Low | 0.8 | 7.5 2.0 |
| 18 | 30-JUL-2007 | Neutrophil count Low | 0.8 | 7.5 2.0 |
| 19 | 17-JUL-2007 | Biopsy | See below | |

Bone: 0.8 cm. A significantly hypercellular bone marrow for age. The megakaryocytes were significantly increased with large dysplastic forms. Active granulopoiesis and erythropoiesis. No overt fibrotic changes. No large clusters of blasts. No infiltrates by solid tumor cells. A population of blasts was present on this flow cytometric sample seen on the CD45 versus scatter histogram. The blasts

ADDITIONAL INFORMATION

13. Lab Data

| # | Date | Test / Assessment / Notes | Results | Normal High / Low |
|---|------|---|---------|-------------------|
| | | present at ~4% of all cells in this sample. The blasts express CD13/33/34/HLA-DR/MPO. CD7 was positive and other B and T cell markers were negative. This flow cytometric pattern was consistent with a small population of blasts demonstrating myeloid phenotype. | | |

13. Relevant Tests

08-May-2007 Bone imaging. Results: Normal study. No evidence of bony metastases.

17-Jul-2007: Bone Marrow Results: Myelomonocytic Associated Markers: C11b 0.11, CD13 0.82, CD15 0.22, CD33 0.76, CD34 0.47, CD56 0.03, CD65 0.15, CD117 equivocal, HLA-DR 0.77, CD33+CD34+ 0.41. Lymphoid Markers: CD2 0.05, CD3 0.06, CD4 0.03, CD7 0.60, CD10 0.08, CD19 0.04. Intracellular Markers: TdT <0.01, MPO 0.22, CyCD3 0.01, CyCD79a 0.01. Interpretation: Normal female karyotype. Twenty metaphase cells were analyzed. No abnormalities were detected at the level of resolution achieved.

30-Aug-2007: Blood and Bone Marrow Report: Diagnosis: Acute Myeloid Leukemia. >20% of circulation white cells are CD34+ myeloid blasts that positive for CD11b/13/33/117/HLA-DR/7/cyMPO with aberrant expression of T-cell marker CD7. Acute Leukemia Results: Myelomonocytic Associated Markers: CD11b 0.64, CD13 0.94, CD15 0.26, CD33 0.93, CD34 0.62, CD56 0.02, CD65 0.07, CD117 ~0.57 (dim), HLA-DR 0.74, CD33+CD34+ 0.59. Lymphoid Markers CD2 0.01, CD3 <0.01, CD4 <0.01, CD7 0.74, CD10 0.05, CD19 0.02. Intracellular Markers TdT 0.01, MPO 0.15, CyCD3 0.01, CyCD79a 0.01.

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 #2 | 765 mg, UNK; Intravenous | | 10-JAN-2007 00:00 / 10-JAN-2007 00:00; 1 day |
| #1 PEMETREXED (PEMETREXED) Vial; Regimen #3 | 730 mg, UNK; Intravenous | | 22-MAR-2007 00:00 / Unknown; Unknown |
| #1 PEMETREXED (PEMETREXED) Vial; Regimen #4 | 730 mg, UNK; Intravenous | | 12-APR-2007 00:00 / 12-APR-2007 00:00; 1 day |
| #2 *CISPLATIN (CISPLATIN) Unknown; Regimen #2 | 38.25 mg, other; Intravenous | | 10-JAN-2007 00:00 / 12-JAN-2007 00:00; 3 days 0 hrs |
| #2 *CISPLATIN (CISPLATIN) Unknown; Regimen #3 | 110 mg, other; Intravenous | | 22-MAR-2007 00:00 / Unknown; Unknown |
| #2 *CISPLATIN (CISPLATIN) Unknown; Regimen #4 | 110 mg, other; Intravenous | | 12-APR-2007 00:00 / 12-APR-2007 00:00; 1 day |
| #3 *RADIATION (RADIATION) Unknown; Regimen #1 | 66 UNK, UNK; Unknown | non-small(Non-small cell lung cancer) | 20-DEC-2006 00:00 / 12-APR-2007 00:00; 114 days |

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

#4 VITAMIN B12 (CYANOCOBALAMIN) ; 13-DEC-2006 00:00 / Ongoing

23. OTHER RELEVANT HISTORY continued

| From/To Dates | Type of History / Notes | Description |
|---------------|-------------------------|-------------|
|---------------|-------------------------|-------------|

ADDITIONAL INFORMATION**23. OTHER RELEVANT HISTORY continued**

| From/To Dates | Type of History / Notes | Description |
|----------------------------|---|---------------|
| Unknown to 2000 | Medical Condition 10 pack a year smoking history | Ex-smoker; |
| 30-JAN-2007 to Unknown | Medical Condition Grade 3 | Oesophagitis; |
| 30-JAN-2007 to 20-FEB-2007 | Medical Condition Grade 3 | Dehydration; |