



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: March 28, 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_DE200802002043_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

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

This patient was enrolled in a randomized phase II study of pemetrexed (Alimta) in combination with cisplatin or carboplatin in the first line therapy of advanced non-small cell lung cancer (NSCLC). On 13-Nov-2007, the patient first received study pemetrexed (950 unit unspecified, route and frequency unspecified) and carboplatin (700 units unspecified, route and frequency unspecified) for the treatment of NSCLC. The last dose of both pemetrexed and carboplatin was received on 18-Jan-2008. On 07-Feb-2008, 21 days after the last dose of pemetrexed and carboplatin, the patient was hospitalized for the fifth cycle scan as planned. A computerized tomography (CT) on 07-Feb-2008 as planned, showed a new cavitation in the right upper lobe that was suspect for a aspergilloma (reported as suspicion of pulmonary cavity of the right upper lobe (pulmonary cavitation), serious for prolonging hospitalization (to be confirmed). The CT also revealed the primary pulmonal tumor on the right side showing back formation and a new alteration on the left sided lower area of the lung. A bronchoscopy was planned to confirm diagnosis (results have been requested). Laboratory data on 07-Feb-2008 included c-reactive protein: 6.0 mg/l (normal range: 0.0-10.0), HST (to be confirmed (TBC)): 62 mg/dl (normal range: 0-50), creatine urine (CREA-S): 0.98 mg/dl (normal range: 0.00-1.25), blood sodium: 140 mmol/l (normal range: 135-145), blood potassium: 3.8 mmol/l (normal range: 3.5-5.1), blood calcium: 2.00 mmol/l (normal range: 2.10-2.60), blood lactate dehydrogenase (LDH): 622 U/l (normal range: 0-225), aspartate aminotransferase (GOT): 31 U/l (normal range: 0-50), alanine aminotransferase (GPT): 87 U/l (normal range: 0-50), gamma-glutamyltransferase (GGT): 46 U/l (normal range: 0-66), blood alkaline phosphatase: 82 U/l (normal range: 0-129), bilirubin: 0.4 mg/dl (normal range: 0.0-1.3), protein-S: 5.8 g/dl (normal range: 5.5-8.0), glucose urine: 109 mg/dl (normal range 75-115) and the following flagged results with no normal ranges provided, white blood cells: 8.23 x10E9/uL, neutrophils: 4.81 x10E9/uL (58.5%), lymphocyte: 2.16 x10E9/uL (26.2%), monocytes: 1.12 x10E9/uL (13.6%), basophils: 0.12 x10E9/uL (1.5%) and platelet count: 119 x10E8/uL (flagged as thrombocytopenia). Laboratory data from 18-Feb-2008 included HST (TBC): 49 mg/dl (0-50), creatine urine: 1.25 mg/dl (0.00-1.25), blood sodium: 142 mmol/l (135-145), blood potassium: 4.3 mmol/l (3.5-5.1), blood calcium: 1.63 mmol/l (2.10-2.60), blood lactate dehydrogenase: 535 U/l (0-225), aspartate aminotransferase: 37 U/l (0-50), alanine aminotransferase: 57 U/l (0-50), gamma-glutamyltransferase: 41 U/l (0-66), alkaline phosphatase: 120 U/l (0-129), bilirubin: 1.1 mg/dl (0.0-1.3), c-reactive protein: 200.9 mg/l (0.0-10.0), blood calcium: 1.60 mmol/l (2.10-2.60). No values were flagged from blood tests on 21-Feb-2008. Laboratory data from 23-Feb-2008 included HST (TBC): 56 mg/dl (0-50), creatine urine: 1.63 mg/dl (0.00-1.25), blood sodium: 143 mmol/l (135-145), blood potassium: 3.0 mmol/l (3.5-5.1), blood calcium: 1.37 mmol/l (2.10-2.60). Laboratory values from 25-Feb-2008 included HST (TBC): 51 mg/dl (0-50), creatine urine: 1.39 mg/dl (0.00-1.25), blood sodium: 143 mmol/l (135-145), blood potassium: 3.0 mmol/l (3.5-5.1), blood calcium: 1.38 mmol/l (2.10-2.60), blood lactate dehydrogenase: 786 U/l (0-225), aspartate aminotransferase: 29 U/l (0-50), alanine aminotransferase: 31 U/l (0-50), gamma-glutamyltransferase: 32 U/l (0-66), alkaline phosphatase: 109 U/l (0-129), bilirubin: 1.1 mg/dl (0.0-1.3). Anaemia was flagged in blood tests from 25-Feb-2008, low results included red blood cell count: 2.79 x10E8/mcl, hemoglobin: 8.0 g/dl, hematocrit: 25.4 % and mean cell hemoglobin concentration: 31.5 g/dl, no normal ranges were included. Laboratory data from 28-Feb-2008 included HST (TBC): 42 mg/dl (0-50), creatine urine: 0.91 mg/dl (0.00-1.25), blood sodium: 141 mmol/l (135-145), blood potassium: 3.0 mmol/l (3.5-5.1), blood calcium: 1.64 mmol/l (2.10-2.60). Corrective treatment medication was not reported. The outcome of the event was unknown. Planned chemotherapy was delayed until an unspecified date. It was unknown if the event resulted in permanent discontinuation of the study drug.

In the opinion of the study investigator, the pulmonary cavitation was related to pemetrexed and carboplatin but not to protocol procedures.

Initial and follow-up (email from investigator on 11-Feb-2008) processed at the same time.

Update 11-Mar-2008: Additional information received from the investigator on 29-Feb-2008: Added relevant laboratory data from 18-Feb-2008, 23-Feb-2008, 25-Feb-2008 and 28-Feb-2008. Relevant fields and narrative updated accordingly.

Lilly Analysis Statement: This patient developed right upper lobe cavitation after receiving 4 cycles of study drug. The investigator believes the cavitation is possibly related to study drugs. Lung cavitation is not listed as a serious adverse event in Investigator's Brochure; however, serious events that might lead to lung cavitation (lung abscess, aspiration, Aspergilliosis) have been described. Further information concerning results of diagnostic studies has been requested.

12-Mar-2008: No change in analysis statement. Awaiting F/u

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	07-FEB-2008	Computerised tomogram Result: Aspergilloma Revealed primary tumor pulmonal on the right side shows back formation, new focus on the upper lobe of lung, new alteration on the left sided lower area of lung.		
2	07-FEB-2008	C-reactive protein Within Normal Limits	<6.0 mg/l	10.0 0.0
3	07-FEB-2008	Creatine urine Within Normal Limits CREA-S (spot test)	0.98 mg/dl	1.25 0.0

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
4	07-FEB-2008	Blood sodium Within Normal Limits	140 mmol/l	145 135
5	07-FEB-2008	Blood potassium Within Normal Limits	3.8 mmol/l	5.1 3.5
6	07-FEB-2008	Blood calcium Low	2.00 mmol/l	2.60 2.10
7	07-FEB-2008	Blood lactate dehydrogenase High	622 U/l	225 0
8	07-FEB-2008	Aspartate aminotransferase Within Normal Limits	31 U/l	50 0
9	07-FEB-2008	Alanine aminotransferase High	87 U/l	50 0
10	07-FEB-2008	Gamma-glutamyltransferase Within Normal Limits	46 U/l	66 0
11	07-FEB-2008	Blood alkaline phosphatase Within Normal Limits	82 U/l	129 0
12	07-FEB-2008	Blood bilirubin Within Normal Limits	0.4 mg/dl	1.3 0.0
13	07-FEB-2008	Protein S Within Normal Limits	5.8 g/dl	8.0 5.5
14	07-FEB-2008	Glucose urine Within Normal Limits	109 mg/dl	115 75
15	07-FEB-2008	White blood cell count	8.23 x10E9/ul	
16	07-FEB-2008	Neutrophil count 58.5 %	4.81 x10E9/ul	
17	07-FEB-2008	Lymphocyte count 26.2%	2.16 x10E9/ul	
18	07-FEB-2008	Monocyte count 13.6%	1.12 x10E9/ul	
19	07-FEB-2008	Basophil count 1.5%	0.12 x10E9/ul	
20	07-FEB-2008	Platelet count	119 x10E8/ul	
21	18-FEB-2008	Creatine urine Within Normal Limits CREA-S (spot test)	1.25 mg/dl	1.25 0.00
22	18-FEB-2008	Blood sodium Within Normal Limits	142 mmol/l	145 135
23	18-FEB-2008	Blood potassium Within Normal Limits	4.3 mmol/l	5.1 3.5
24	18-FEB-2008	Blood calcium Low	1.63 mmol/l	2.60 2.10
25	18-FEB-2008	Blood lactate dehydrogenase High	535 U/l	225 0

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
LDH				
26	18-FEB-2008	Aspartate aminotransferase Within Normal Limits GOT	37 U/l	50 0
27	18-FEB-2008	Alanine aminotransferase High GPT	57 U/l	50 0
28	18-FEB-2008	Gamma-glutamyltransferase Within Normal Limits GGT	41 U/l	66 0
29	18-FEB-2008	Blood alkaline phosphatase Within Normal Limits AP	120 U/l	129 0
30	18-FEB-2008	Blood bilirubin Low	1.1 mg/dl	1.3 0.0
31	18-FEB-2008	C-reactive protein High	200.9 mg/l	10.0 0.0
32	18-FEB-2008	Blood calcium Low	1.60 mmol/l	2.6 2.10
33	23-FEB-2008	Creatine urine High CREA-S	1.63 mg/dl	1.25 0.00
34	23-FEB-2008	Blood sodium Within Normal Limits	143 mmol/l	145 135
35	23-FEB-2008	Blood potassium Low	3.0 mmol/l	5.1 3.5
36	23-FEB-2008	Blood calcium Low	1.37 mmol/l	2.6 2.10
37	25-FEB-2008	Creatine urine High CREA-S	1.39 mg/dl	1.25 0.00
38	25-FEB-2008	Blood sodium Within Normal Limits	143 mmol/l	145 135
39	25-FEB-2008	Blood potassium Low	3.0 mmol/l	5.1 3.5
40	25-FEB-2008	Blood calcium Low	1.38 mmol/l	2.6 2.1
41	25-FEB-2008	Blood lactate dehydrogenase High	786 U/l	225 0
42	25-FEB-2008	Aspartate aminotransferase Within Normal Limits	29 U/l	50 0
43	25-FEB-2008	Alanine aminotransferase Within Normal Limits	31 U/l	50 0
44	25-FEB-2008	Gamma-glutamyltransferase Within Normal Limits	32 U/l	66 0
45	25-FEB-2008	Blood alkaline phosphatase Within Normal Limits	109 U/l	129 0

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
46	25-FEB-2008	Blood bilirubin Within Normal Limits	1.1 mg/dl	1.3 0.0
47	25-FEB-2008	Red blood cell count Low	2.79 x10E8/ul	
48	25-FEB-2008	Haemoglobin Low	8.0 g/dl	
49	25-FEB-2008	Haematocrit Low	25.4 %	
50	25-FEB-2008	Mean cell haemoglobin concentration Low	31.5 g/dl	
51	28-FEB-2008	Creatine urine Within Normal Limits CREA-S	0.91 mg/dl	1.25 0.00
52	28-FEB-2008	Blood sodium Within Normal Limits	141 mmol/l	145 135
53	28-FEB-2008	Blood potassium Low	3.0 mmol/l	5.1 3.5
54	28-FEB-2008	Blood calcium Low	1.64 mmol/l	2.60 2.10

13. Relevant Tests

18-Feb-2008-HST: 49 mg/dl (0-50)

No flagged values for bloods on 21-Feb-2008.

23-Feb-2008-HST: 56 mg/dl (0-50)

25-Feb-2008-HST: 51 mg/dl (0-50), RBC flag: anaemia

28-Feb-2008-HST: 42 mg/dl (0-50)

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

#4 BISOPROLOL (BISOPROLOL) ; 05-DEC-2007 00:00 / Ongoing

#5 DIGOXIN (DIGOXIN) ; 05-DEC-2007 00:00 / Ongoing

#6 PHENPROCOUMON (PHENPROCOUMON) ; 05-DEC-2007 00:00 / Ongoing