
Operations Office

Telephone (507) 266-3549



Date: January 2, 2004

To: NCCTG Primary Clinical Research Associates

From: Lori Kelly

Re: N0177, Pilot and Phase II Trial of OSI-774 and Radiation in Glioblastoma Multiforme Patients

The purpose of this memorandum is to provide investigators with a recent report of an adverse event that has occurred in association with OSI-774 for a study where the Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI) is distributing this agent. You may have also received this communication directly from DCTD.

AE_2003001523_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 Lori Kelly at 507-266-3549.

lk
enclosure

MED WATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Mfr report # 2003001523
UF/Dist report #
FDA Use Only

A. Patient information

1. Patient identifier L-S In confidence	2. Age at time of event: 60 Years Date of birth: 11/25/1942	3. Sex <input type="checkbox"/> female <input checked="" type="checkbox"/> male	4. Weight ____ lbs or 104.1 kgs
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B. Adverse event or product problem

1. Adverse event and/or Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)

<input type="checkbox"/> death (____/____/____)	<input type="checkbox"/> disability
<input type="checkbox"/> life-threatening	<input type="checkbox"/> congenital anomaly
<input checked="" type="checkbox"/> hospitalization - initial or prolonged	<input type="checkbox"/> required intervention to prevent permanent impairment/damage
	<input checked="" type="checkbox"/> other: <u>Medica-Cont...</u>

3. Date of event (mo/day/yr) 08/05/03	4. Date of this report (mo/day/yr) 09/29/03
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5. Describe event or problem

OEDEMA NOS (Edema), LEUKOCYTOSIS (Leukocytosis), FATIGUE (Fatigue), ANOREXIA (Anorexia), LIVER FUNCTION TESTS NOS ABNORMAL (Elevated LDH, etc), ASPARTATE AMINOTRANSFERASE INCREASED (SGOT), ALANINE AMINOTRANSFERASE INCREASED (SGPT), HYPOTENSION NOS (Hypotension), HAEMATEMESIS (Coffee ground emesis)

This 60-year-old male patient was enrolled in OSI Protocol PA.3, a randomized, placebo-controlled study of erlotinib (Tarceva) plus gemcitabine in patients with locally advanced, unresectable, or metastatic pancreatic cancer. Protocol therapy with erlotinib/placebo 100 mg PO QD and gemcitabine 2144 mg IV weekly commenced on 30-Jan-2003.

The patient's medical history is significant for diabetes mellitus, hypertension and hypercholesterolemia. On 8-Nov-2002, prior to entering the study, the patient's LDH was 371 U/L. On 20-Jan-2003, at study baseline, the patient's ECOG performance score was 0, his weight was 211 pounds, and his laboratory values included an SGOT of 20

6. Relevant tests/laboratory data, including dates

Date not given: A chest x-ray showed the patient's port to be in place, and Doppler studies were negative for evidence of thrombosis.

19-Aug-2003: A CT scan was suggestive of progressive disease, with interval development of a small left pleural effusion, enlargement of a left hepatic lobe lesion, enlarging soft tissue densities in the left and right anterior abdomen, and

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Concurrent Disease:
HYPERTENSION
HYPERCHOLESTEROLEMIA
INSULIN RESISTANCE

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)	
#1 Erlotinib HCl (Tablets)	
#2 Gemcitabine (GEMCITABINE) (Injection for infusion) Cont...	
2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration) (from/to or best estimate)
#1 100 mg (QD), Oral	#1 01/30/03 - 08/13/03
#2 2140 mg (Q1W), Intravenous	#2 01/30/03 - 07/31/03
4. Diagnosis for use (indication)	
#1 PANCREATIC CANCER	
#2 PANCREATIC CANCER	
5. Event abated after use stopped or dose reduced	#1 <input type="checkbox"/> yes <input checked="" type="checkbox"/> no <input type="checkbox"/> doesn't apply
	#2 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply
6. Lot # (if known)	7. Exp. date (if known)
#1 Unk	#1 Unk
#2 Unk	#2 Unk
8. Event reappeared after reintroduction	
#1 <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> doesn't apply	
#2 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply	
9. NDC # - for product problems only (if known)	
10. Concomitant medical products and therapy dates (exclude treatment of event)	
1) METFORMIN 04/03/02 - Unk	
2) ATENOLOL	
3) GEMFIBROZIL 04/16/01 - Unk	
4) ATORVASTATIN	
5) ACETYLSALICYLIC	

G. All manufacturers

1. Contact office - name/address (& mfg site for devices)	2. Phone number
OSI Pharmaceuticals Boulder Safety 2860 Wilderness Place Boulder, CO 80301 USA (Informing Unit)	303-546-7600
3. Report source (check all that apply)	
<input type="checkbox"/> foreign	
<input checked="" type="checkbox"/> study	
<input type="checkbox"/> literature	
<input type="checkbox"/> consumer	
<input checked="" type="checkbox"/> health professional	
<input type="checkbox"/> user facility	
<input type="checkbox"/> company representative	
<input type="checkbox"/> distributor	
<input type="checkbox"/> other:	
4. Date received by manufacturer (mo/day/yr)	5. (A)NDA #
09/26/03	53,728
6. If IND, protocol #	IND #
PA. 3	PLA #
7. Type of report (check all that apply)	pre-1938 <input type="checkbox"/> yes
<input type="checkbox"/> 5-day <input checked="" type="checkbox"/> 15-day	OTC product <input type="checkbox"/> yes
<input type="checkbox"/> 10-day <input type="checkbox"/> periodic	
<input type="checkbox"/> Initial <input checked="" type="checkbox"/> follow-up # <u>2</u>	
8. Adverse event term(s)	
1) EDEMA (Oedema NOS)	
2) LEUKOCYTOSIS (Leukocytosis)	
3) COFFEE GROUND EMESIS (Haematemesis)	
4) HYPOTENSION	
9. Mfr. report number	
2003001523	

E. Initial reporter

1. Name & address	phone # 860-224-5660
Dr. Peter Byeff New Britain General Hospital 100 Grand Street New Britain, CT 06050 USA	

2. Health professional? <input checked="" type="checkbox"/> yes <input type="checkbox"/> no	3. Occupation Study Investigator	4. Initial reporter also sent report to FDA <input type="checkbox"/> yes <input checked="" type="checkbox"/> no <input type="checkbox"/> unk
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Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

B. Adverse event or product problem

B.2 Outcome attributed to adverse event (Cont...)

Other : Medically significant per investigator

B.5 Describe event or problem (Cont...)

U/L, an SGPT of 29 U/L, a serum albumin of 4.2 gm/dL, a total protein of 7.5 gm/dL, a total bilirubin of 0.2 mg/dL, a white blood cell count of 10.8 thou/uL, and an absolute neutrophil count of 7.6 thou/uL.

On 3-Jul-2003, the patient's laboratory values included an SGOT of 51 U/L, an SGPT of 66 U/L, a total bilirubin of less than 0.2 mg/dL, a serum albumin of 3.6 gm/dL and a total protein of 6.5 gm/dL, and on 17-Jul-2003, his laboratory values included an SGOT of 46 U/L, an SGPT of 49 U/L, a total bilirubin of 0.2 mg/dL, a serum albumin of 3.6 gm/dL and a total protein of 6.4 gm/dL.

On 5-Aug-2003, in Cycle 6 of therapy, the patient developed grade 3 fatigue and grade 2 anorexia.

On 7-Aug-2003, the patient was seen in clinic and was noted to also have developed grade 4 edema, with an 11-pound weight gain in the preceding week (weight not provided), edema of the hands, forearms, ankles and abdomen, an SGOT of 204 U/L, an SGPT of 166 U/L, a total bilirubin of 0.5 mg/dL, a serum albumin of 2.3 gm/dL, a total protein of 4.8 gm/dL, and a white blood cell count of 9.7 thou/uL.

On 11-Aug-2003, the patient's laboratory values included an SGOT of 258 U/L, an SGPT 184 U/L, a total bilirubin of 0.7 mg/dL, a serum albumin of 2.4 gm/dL, and a total protein of 4.9 gm/dL.

On 13-Aug-2003, the patient received the last dose of erlotinib/placebo. The last dose of gemcitabine was administered on 31-Jul-2003.

On 14-Aug-2003, the patient's anorexia resolved. On this date, the patient developed leukocytosis with a white blood cell count of 55.4 thou/uL, with a differential that included 69% lymphocytes, 12% bands, 1% eosinophils, 3% lymphocytes, 10% monocytes, 1% metamyelocytes, and 4% myelocytes. Also on this date, the patient was noted to have an elevated LDH of 1542 U/L, an SGOT of 131 U/L, an SGPT of 104 U/L, a total bilirubin of 0.6 mg/dL, a serum albumin of 2.3 gm/dL, and a total protein of 5.2 gm/dL.

On 15-Aug-2003, the patient was seen in clinic. His weight was 229 pounds. A physical exam revealed continuing grade 4 edema of the upper and lower extremities, and the decision was made to remove the patient from the study due to the events grade 4 edema and grade 3 leukocytosis.

On 19-Aug-2003, a CT scan was performed which was suggestive of progressive disease, with interval development of a small left pleural effusion, enlargement of a left hepatic lobe lesion, enlarging soft tissue densities in the left and right anterior abdomen, and thickening of the abdominal anterior wall musculature. Stable findings included a soft tissue density in the perinephric splenic bed, left adrenal enlargement, a pseudocyst in the pancreatic tail and a soft tissue density presumed to be a lymph node in the region of the gastrohepatic ligament. The patient's new left pleural effusion, with mild fullness of the infrahepatic inferior vena cava, edema within the subcutaneous fat and mild veiling of the abdominal and pelvic mesenteric fat were felt to be suggestive of right heart failure and/or hypoproteinemia. However, on 20-Aug-2003, a MUGA scan showed the patient's ejection fraction to be 67%.

On 21-Aug-2003, the patient was seen in clinic, and was noted to have 2+ edema of the upper and lower extremities. His weight on this date was 238 pounds. Laboratory values included a white blood cell count of 19.6 thou/uL, an LDH of 1174 U/L, an SGOT of 58 U/L, an SGPT of 53 U/L, a total bilirubin of 0.4 mg/dL, a serum albumin of 2.3 gm/dL, and a total protein of 5.0 gm/dL. Treatment of the event included furosemide.

On 28-Aug-2003, the patient returned for a clinic visit. He continued to complain of peripheral edema but had an 8-pound weight loss since the prior visit, to 230 pounds, and he stated that he was feeling better. Laboratory values from this visit included a total bilirubin of 0.3 mg/dL, a total protein of 5.8 gm/dL, a serum albumin of 2.6 gm/dL, an SGOT of 44 U/L, an SGPT of 36 U/L, and an alkaline phosphatase of 134 U/L.

Diagnostic testing related to these events also included a chest x-ray, which showed the patient's port to be in place, and Doppler studies, which were negative for evidence of emboli, both of which were performed on unspecified dates.

On 4-Sep-2003, the patient was seen in clinic. His weight was 225 pounds. Laboratory test results included a white blood cell count of 10.0 thou/uL, an LDH of 794 U/L, an SGOT of 62 U/L, an SGPT of 44 U/L, a total bilirubin of 0.3 mg/dL, a serum albumin of 2.4 gm/dL, and a total protein of 5.4 gm/dL.

On 8-Sep-2003, the patient's wife called the clinic because the patient had suffered an episode of hypotension with a blood pressure of 90/56 and a cold sweat and feeling of lethargy. The patient's wife was instructed to hold his furosemide, but to administer his potassium supplement as usual.

On 9-Sep-2003, the patient was again seen in clinic, and his weight was 233 pounds, which represented an 8-pound weight gain in the prior five days. He had 2+ bilateral lower extremity edema, 1+ left upper extremity edema and trace right upper extremity edema. Laboratory values included a white blood cell count of 10.9 thou/uL.

On 12-Sep-2003, the patient was admitted to his local hospital with orthostatic changes and dehydration. The patient complained of nausea, weakness, diaphoresis, and two episodes of coffee-ground emesis. Laboratory values on this date included a hemoglobin of 10.7 gm/dL, a hematocrit of 32%, a platelet count of 50 thou/uL, and a white blood cell count of 8.92 thou/uL.

On 13-Sep-2003, a chest x-ray revealed left lower lobe consolidation and a probable effusion. A CT scan showed a left pleural effusion and consolidation, an unchanged mass in the head of the pancreas, and likely no significant interval change in the patient's disease.

On 15-Sep-2003, an upper esophagogastroduodenoscopy with biopsy was performed due to the coffee ground emesis. Findings included mild erosions of the esophagus consistent with vomiting, multiple gastric erosions, primarily in the antral area, and multiple erosions in the duodenum, oozing blood. Treatment with a proton pump inhibitor was initiated. Physical assessment findings on this date included 3+ edema of the extremities. The patient was noted to be in acute renal failure, possibly related to acute tubular necrosis. Hemodialysis was considered but was not performed.

On 16-Sep-2003, the patient expired.

The investigator deemed these events to be medically significant adverse events, possibly related to study therapy. The patient's death was due to the underlying disease.

Follow-up received 2-Sep-2003: Prestudy LDH value was received.

Follow-up received 3-Sep-2003: 28-Aug-2003 lab values received.

Follow-up received 10-Sep-2003: Laboratory values and clinic notes from 4-Sep-2003 and 9-Sep-2003 received. Serial weights were added to the narrative.

Follow-up received 16-Sep-2003: Received email from study coordinator that patient was admitted to local hospital on 12-Sep-2003 due to dehydration and orthostasis, and expired on 16-Sep-2003. Awaiting further information.

Follow-up received 23-Sep-2003: Hospital records and diagnostic test reports received.

Follow-up received 26-Sep-2003: The patient did not undergo hemodialysis.

B.6 Relevant tests/laboratory data, including dates (Cont...)

thickening of the abdominal anterior wall musculature. Stable findings included a soft tissue density in the perinephric splenic bed, left adrenal enlargement, a pseudocyst in the pancreatic tail and a soft tissue density presumed to be a lymph node in the region of the gastrohepatic ligament. The patient's new left pleural effusion, with mild fullness of the infrahepatic inferior vena cava, edema within the subcutaneous fat and mild veiling of the abdominal and pelvic mesenteric fat were felt to be suggestive of right heart failure and/or hypoproteinemia.

20-Aug-2003: A MUGA scan showed the patient's ejection fraction to be 67%.

13-Sep-2003: A chest x-ray revealed left lower lobe consolidation and a probable effusion. A CT scan showed a left pleural effusion and consolidation, an unchanged mass in the head of the pancreas, and likely no significant interval change in the patient's disease.

15-Sep-2003: An upper esophagogastroduodenoscopy with biopsy was performed due to coffee ground emesis. Findings included mild erosions of the esophagus consistent with vomiting, multiple gastric erosions, primarily in the antral area, and multiple erosions in the duodenum, oozing blood.

Lab Result:

Test name	Test date	Test result	Normal value
Albumin	01/20/03	4.2 gm/dL	
	07/03/03	3.6 gm/dL	
	07/17/03	3.6 gm/dL	
	08/07/03	2.3 gm/dL	
	08/11/03	2.4 gm/dL	
	08/14/03	2.3 gm/dL	
	08/21/03	2.3 gm/dL	
	08/28/03	2.6 gm/dL	

	09/04/03	2.4 gm/dL
Alk Phos	08/28/03	134 U/L
	09/04/03	130 U/L
ANC	01/20/03	7.6 THOUS/MCL
	08/21/03	12.8 THOUS/MCL
	09/04/03	6.5 THOUS/MCL
	09/09/03	10.1 THOUS/MCL
	09/12/03	8.7
Bands	08/14/03	12 %
Bilirubin (Total)	01/20/03	0.2 mg/dL
	07/03/03	> 0.2 mg/dL
	07/17/03	0.2 mg/dL
	08/07/03	0.5 mg/dL
	08/11/03	0.7 mg/dL
	08/14/03	0.6 mg/dL
	08/21/03	0.4 mg/dL
	08/28/03	0.3 mg/dL
	09/04/03	0.3 mg/dL
BUN	07/03/03	20 mg/dL
	07/17/03	19 mg/dL
	08/07/03	59 mg/dL
	08/11/03	29 mg/dL
	08/14/03	24 mg/dL
Creatinine (Serum)	07/03/03	1.4 mg/dL
	07/17/03	1.6 mg/dL
	08/07/03	1.9 mg/dL
	08/11/03	1.3 mg/dL
	08/14/03	1.3 mg/dL
Eosinophils	08/14/03	1 %
HGB	09/12/03	10.7 gm/dL
INR	09/12/03	1.53
LDH	11/08/02	371 U/L
	08/14/03	1542 U/L
	08/21/03	1174 U/L
	09/04/03	794 U/L
Lymphocytes	08/14/03	3 %
Metamyelocytes	08/14/03	1 %
Monocytes	08/14/03	10 %
Myelocytes	08/14/03	4 %
PLT	09/12/03	50 THOUS/MCL
Protein (Total)	01/20/03	7.5 gm/dL
	07/03/03	6.5 gm/dL
	07/17/03	6.4 gm/dL
	08/07/03	4.8 gm/dL
	08/11/03	4.9 gm/dL
	08/14/03	5.2 gm/dL
	08/21/03	5.0 gm/dL
	08/28/03	5.8 gm/dL
	09/04/03	5.4 gm/dL
PT	09/12/03	14.3 sec
PTT	09/12/03	36 sec
RBC	09/12/03	3.29 MILL/MCL
SEGS	08/14/03	69 %
SGOT	01/20/03	20 U/L
	07/03/03	51 U/L
	07/17/03	46 U/L
	08/07/03	204 U/L
	08/11/03	184 U/L
	08/14/03	131 U/L
	08/21/03	58 U/L
	08/28/03	44 U/L
	09/04/03	62 U/L
SGPT	01/20/03	29 U/L
	07/03/03	66 U/L
	07/17/03	49 U/L
	08/07/03	166 U/L
	08/11/03	258 U/L
	08/14/03	104 U/L
	08/21/03	53 U/L
	08/28/03	36 U/L
	09/04/03	44 U/L
WBC	01/20/03	10.8 THOUS/MCL
	08/07/03	9.7 THOUS/MCL
	08/14/03	55.4 THOUS/MCL
	08/21/03	19.6 THOUS/MCL
	09/04/03	10.0 THOUS/MCL
	09/09/03	10.9 THOUS/MCL
	09/12/03	8.92 THOUS/MCL

C. Suspect medication (Cont...)

Seq No.	: 1
C.1 Suspect medication	: Erlotinib HCl (Tablets)
C.5 Dechallenge	: 2) Negative
	: 5) Not Applicable
	: 6) Not Applicable
	: 7) Not Applicable
	: 8) Not Applicable
	: 9) Not Applicable

Continuation Sheet for FDA-3500A Form

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C.8 Rechallenge

: 2) Not Applicable
: 5) Not Applicable
: 6) Not Applicable
: 7) Not Applicable
: 8) Not Applicable
: 9) Not Applicable

C10. Concomitant medical products

Seq No. : 5
Concomitant Medical Product : ACETYLSALICYLIC ACID
Therapy Dates : 1) 06/24/99 - Unk

Seq No. : 6
Concomitant Medical Product : ZOLEDRONIC ACID

Seq No. : 7
Concomitant Medical Product : WARFARIN SODIUM

Seq No. : 8
Concomitant Medical Product : POTASSIUM

G. All manufacturers

8. Adverse event term(s)

- 4) HYPOTENSION (Hypotension NOS)
- 5) FATIGUE (Fatigue)
- 6) ANOREXIA (Anorexia)
- 7) ELEVATED LDH ETC (Liver function tests NOS abnormal)
- 8) SGOT (Aspartate aminotransferase increased)
- 9) SGPT (Alanine aminotransferase increased)