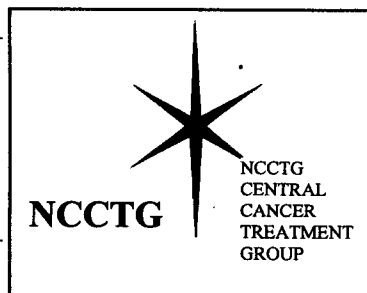

Operations Office

Telephone (507) 266-3853



Date: June 27, 2003

To: NCCTG Primary Clinical Research Associates

From: Linda S. Long

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_2001000102_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 Linda S. Long at 507-266-3853.

lsl
enclosure

MED WATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

OSI Pharmaceuticals
For use by user-facilities,
distributors and manufacturers for
MANDATORY reporting

FDA Form 3549e Approved 09/25/95 (Changes)

Mfr report # 2001000102
UR/Dist report #
FDA Use Only

Page 1 of 4

Patient information			
1. Patient identifier SC	2. Age at time of event: or <u>60 Years</u> Date of birth: <u>03/07/1941</u>	3. Sex <input type="checkbox"/> female <input checked="" type="checkbox"/> male	4. Weight <u>Unk</u> lbs or <u>Unk</u> kgs

B. Adverse event or product problem	
1. <input checked="" type="checkbox"/> Adverse event and/or	<input type="checkbox"/> Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)	<input type="checkbox"/> disability
<input checked="" type="checkbox"/> death <u>05/07/01</u> (month/day/yr)	<input type="checkbox"/> congenital anomaly
<input type="checkbox"/> life-threatening	<input type="checkbox"/> required intervention to prevent permanent impairment/damage
<input checked="" type="checkbox"/> hospitalization - initial or prolonged	<input type="checkbox"/> other: _____

3. Date of event (month/day/yr) <u>05/02/01</u>	4. Date of this report (month/day/yr) <u>06/09/03</u>
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5. Describe event or problem

RESPIRATORY FAILURE (Hypoxic Respiratory Failure), RENAL FAILURE ACUTE (Acute Renal Failure), PNEUMONIA NOS (Pneumonia), NEUTROPENIA (Neutropenia)

This 60-year-old male patient was enrolled in study OSI-774-154, A Phase 1b Trial to Determine the Safety, Tolerance and Preliminary Antineoplastic Activity of Gemcitabine/Cisplatin Administered in Combination with Escalating Oral Doses of OSI-774 to Patient Cohorts with Newly Diagnosed/Previously Untreated or Minimally Treated, Potentially Responsive Malignancies. The patient was diagnosed with recurrent carcinoma of the right tonsil diagnosed in 1999 and has metastases to the lung. The patient was initially treated with radiation therapy (8840 cGy) in 1999 followed by paclitaxel and carboplatin ending Mar-2000, paclitaxel ending Jun-2000, 5-FU, paclitaxel and gemcitabine ending Jan-2001 and radiation therapy to the right neck (7100 cGy) ending Jan-2001.

The patient's disease progressed and as a result, he was considered for entry into _____

6. Relevant tests/laboratory data, including dates

CXR revealed bibasilar infiltrates.

All culture results were negative.

See next Page

Cont. _____

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

Concurrent Disease:
GERD
HYPOKALEMIA

C. Suspect medications	
1. Name (give labeled strength & mfr/labeler, if known)	Cont. ...
#1 Erlotinib HCl (Tablets)	
#2 Gemcitabine (Solution)	

2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration from/to (or best estimate))
#1 100 mg (QD), Oral	#1 05/01/01 - 05/02/01
#2 1700 mg (Days 1, 8, 15 Q 28)	#2 05/01/01 - 05/01/01

4. Diagnosis for use (indication)	5. Event abated after use stopped or dose reduced
#1 POTENTIALLY RESPONSIVE MALIGNANCIES	#1 <input type="checkbox"/> yes <input checked="" type="checkbox"/> no <input type="checkbox"/> doesn't apply
#2 POTENTIAL RESPONSIVE MALIGNANCIES	#2 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply

6. Lot # (if known)	7. Exp. date (if known)	8. Event reappeared after reintroduction
#1 101-0210	#1 Unk	#1 <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> doesn't apply
#2 Unk	#2 Unk	#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) OMEPRAZOLE
- 2) FAMOTIDINE
- 3) POTASSIUM

G. All manufacturers	
1. Contact office - name/address (& mfring site for devices)	2. Phone number

OSI Pharmaceuticals
Boulder Safety
2860 Wilderness Place
Boulder, CO 80301
USA
(Informing Unit)

303-444-5893

4. Date received by manufacturer (month/day/yr) <u>05/30/03</u>	5. (A)NDA # IND # <u>53,728</u> PLA # _____ pre-1938 <input type="checkbox"/> yes OTC product <input type="checkbox"/> yes	3. Report source (check all that apply)
6. If IND, protocol # <u>OSI-774-154</u>		<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: _____

7. Type of report (check all that apply)

5-day 15-day
 10-day periodic
 Initial follow-up # 2

8. Adverse event term(s)

- 1) HYPOXIC RESPIRATORY FAILURE (Respiratory failure (excl neonatal))
- 2) ACUTE RENAL FAILURE (Renal failure acute)
- 3) PNEUMONIA (Pneumonia)

9. Mfr. report number
2001000102

E. Initial reporter	
1. Name & address	phone # <u>773 702 4400</u>
Dr. Mark Ratain University of Chicago 5841 South Maryland Avenue MC 2115 Chicago, IL 60637-1470 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.5 Describe event or problem (Cont...)

this phase 1b trial. His performance status at baseline was 80% by the Karnofsky scale. Protocol therapy consisting of erlotinib 100 mg PO QD, gemcitabine 1700 mg IV Days 1, 8 and 15 Q 28 days and cisplatin 170 mg IV every 28 days was commenced on 01-May-2001 at which time the patient was afebrile. The patient had no significant past medical history. Concomitant medications at the time of the event included omeprazole (20 mg PO QD since Dec-2000) and famotidine (20 mg PO QD since Jan-2001).

On study Day 3 (03-May-2001) the patient presented to his local emergency room with fever, hypotension, tachycardia, and dyspnea. Hematologic and serum chemistry evaluations revealed leukopenia/neutropenia (WBC 0.1 x 10⁹/L; ANC < 0.06 decreased from 3.6 at screening) and rising creatinine (1.5 mg/dL, increased from 0.9 mg/dL at screening). The patient was admitted to the ICU. Other lab results on admission were pH of 7.24, PCO₂ of 43, PO₂ of 53 and oxygen saturation of 89% on 15 liters of oxygen. The patient was placed on dopamine. Cultures were obtained, and antibiotic therapy with vancomycin and imipenem for the treatment of suspected sepsis was initiated. Chest radiography revealed bibasilar infiltrates. All culture results were negative. Protocol therapy was held starting 03-May-2001.

The patient's condition rapidly deteriorated, with worsening respiratory failure and progressive renal failure (creatinine 4.3 on 06-May-2001). Bronchoscopy was not performed. Five days after admission the patient was placed on "comfort care only" and filgrastim was started to improve the neutropenia. On 07-May-2001 the patient was placed on palliative care and continued to deteriorate until he expired in the evening of 07-May-2001. The cause of death was reported as septic shock with pneumonia secondary to neutropenia. The patient's acute renal failure was felt to be related to septic shock and pneumonia, a likely consequence of neutropenia and the patient's history of right lung lobectomy.

The patient's primary physician reported that the patient's terminal event occurred too rapidly to be attributed to the agents administered under the protocol. He stated that he strongly considered that an unsuspected infection led to the patient's presumed sepsis and sequent death.

The investigator assessed the patient's respiratory failure, acute renal failure and pneumonia as remotely related to erlotinib and possibly related to chemotherapy with cisplatin and gemcitabine and assessed the neutropenia as remotely related to erlotinib and definitely related to cisplatin and gemcitabine administration.

Follow-up Information received 31-Jan-2002: Follow-up indicated that the patient died on 07-May-2001. The cause of death reported as septic shock with pneumonia secondary to neutropenia. The acute renal failure is therefore related to septic shock and pneumonia, a likely consequence of neutropenia and the patient's history of right lung lobectomy. Febrile neutropenia was changed to neutropenia and pneumonia was added as an event term. The patient was treated with intravenous antibiotics and oxygen. filgrastim therapy for neutropenia was initiated without response. He was placed on palliative care and his condition continued to worsen until his death. In the opinion of the investigator the pneumonia is possibly due to study drug. The patient's primary physician reported that the patient's terminal event occurred too rapidly to be attributed to the agents administered under the protocol. He stated that he strongly considered that an unsuspected infection led to the patient's presumed sepsis and subsequent death.

Follow-up Information received 30-May-2003: The investigator assessed the patient's respiratory failure, acute renal failure and pneumonia as remotely related to erlotinib and possibly related to chemotherapy with cisplatin and gemcitabine and assessed the neutropenia as remotely related to erlotinib and definitely related to cisplatin and gemcitabine administration.

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

Lab Result :

Test name	Test date	Test result	Normal value
BUN	05/02/01	33	
Creatinine (Serum)	05/02/01	1.5	
	05/06/01	4.6	
HCT	05/02/01	33 %	
	05/02/01	12	
Neutrophils	05/06/01	<0.06	1.1-6.7
Calc Sat	05/03/01	89 %	
pCO ₂	05/03/01	43	
pH (Serum)	05/03/01	7.24	
PLT	05/02/01	150,000	
pO ₂	05/03/01	53	
Potassium	05/02/01	3.8	
Sodium	05/02/01	126	

C. Suspect medication (Cont...)

Seq No. : 1
C.1 Suspect medication : Erlotinib HCl (Tablets)
C.5 Dechallenge : 2) Negative
 : 3) Negative
 : 4) Negative

C.8 Rechallenge : 2) Not Applicable
 : 3) Not Applicable
 : 4) Not Applicable

Seq No. : 2
C.1 Suspect medication : Gemcitabine (Solution)
C.2 Dose, frequency & route used : 1) 1700 mg (Days 1, 8, 15 Q 28 Days), Intravenous
Approval information
IND # :
C.5 Dechallenge
C.8 Rechallenge

Seq No. : 3
C.1 Suspect medication : Cisplatin (Solution)
C.2 Dose, frequency & route used : 1) 170 mg (Day 1 Q 28 Days), Intravenous
Approval information
IND # :
C.5 Dechallenge
C.8 Rechallenge

G All manufacturers

Adverse event term(s)

- 3) PNEUMONIA (Pneumonia NOS)
- 4) NEUTROPENIA (Neutropenia)