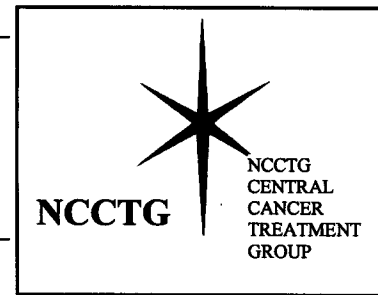


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**Operations Office**

Telephone (507) 266-3853

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**Date:** April 11, 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\_2002001895

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



1 DNA Way, MS 59  
South San Francisco, CA 94080  
Fax (650) 225-5862

13 February 2003

PEREZ, Edith, MD  
Mayo Clinic Jacksonville  
Division of Hematology/Oncology  
4500 San Pablo Road  
Jacksonville, FL 32224

RE: OSI Pharmaceuticals IND Safety Report MCN Number: 2002001895  
Genentech MCN Number: 105938  
Tarceva™ (erlotinib hydrochloride)

Dear Dr. Perez:

A sponsor conducting a study under an investigational new drug application (IND) is required to inform all participating investigators, in writing, of any IND study occurrence of a serious and unexpected adverse drug reaction (ADR). An unexpected ADR is an adverse event that is judged by either an investigator or the sponsor as having a reasonable suspected causal relationship to an investigational product, and that is not already identified as an ADR in the current product Investigator Brochure (IB) or in its amendments.

Attached is a case summary and analysis of similar events of a serious and unexpected ADR that occurred in a subject exposed to Tarceva while participating in a study conducted by the NCI-CTEP. Please review this case report and promptly submit this information to your Institutional Review Board or Independent Ethics Committee. Also, append this report to your Tarceva Investigator Brochure.

Although this adverse event has been documented and reported to the appropriate Regulatory agencies, this does not reflect a conclusion by Genentech or the Regulatory agencies that Tarceva contributed to the adverse event.

Genentech, Inc. intends the submission of this IND Safety Report to represent a safety amendment to the Tarceva Investigator Brochure.

If questions arise, please contact the undersigned.

Sincerely,

A handwritten signature in black ink, appearing to be "R Mass".

Robert Mass, MD  
Medical Monitor

Enclosure

# MED WATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

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

Page 1 of 2

FDA Facsimile Approval 09/25/95 (Classroom)

Mfr report # <b>2002001895</b>
UR/Dist report #
FDA Use Only

## A. Patient information

1. Patient identifier <b>002-007</b>	2. Age at time of event: <b>61 Years</b> Date of birth: <b>10/??/1941</b>	3. Sex <input type="checkbox"/> female <input checked="" type="checkbox"/> male	4. Weight ____ lbs or <b>86</b> kgs
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## 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 checked="" type="checkbox"/> death <b>12/08/02</b> (mo/day/yr) <input type="checkbox"/> life-threatening <input checked="" type="checkbox"/> hospitalization - initial or prolonged <input type="checkbox"/> disability <input type="checkbox"/> congenital anomaly <input type="checkbox"/> required intervention to prevent permanent impairment/damage <input type="checkbox"/> other: _____	
3. Date of event (mo/day/yr) <b>11/29/02</b>	4. Date of this report (mo/day/yr) <b>02/06/03</b>

5. Describe event or problem  
**SEPSIS NOS (Sepsis), RENAL FAILURE NOS (Renal Failure), OBSTRUCTIVE AIRWAYS DISORDER (Obstructed Airway)**

This 61-year-old male patient enrolled in protocol 5380, a phase I/II study of OSI-774 in combination with cisplatin in patients with recurrent or metastatic squamous cell cancer of the head and neck. The patient was diagnosed with laryngeal cancer metastatic to the lymph nodes and had received radiotherapy ending Jan-1999 and left radical neck cancer resection in Oct-1998. Sites of metastasis include the cervical lymph nodes and skin. Other medical history includes diabetes mellitus, hypertension and a possible myocardial infarction in the Spring of 2002. Protocol therapy consisted of erlotinib 150 mg po QD and cisplatin 75 mg/m<sup>2</sup> Q 21 Days commencing on 29-Aug-2002. The cisplatin dose was reduced to 56.25 mg/m<sup>2</sup> on 13-Nov-2002 due to grade 1 creatinine elevation.

On 13-Nov-2002, the patient presented for Cycle 4 of therapy and was experiencing stridor and voice change. Laryngoscopy on Cont...

6. Relevant tests/laboratory data, including dates Blood cultures drawn from the arterial line and peripheral vein, as well as cultures from the catheter tip were positive for Staphylococcus aureus.  See next Page  Cont...
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7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) Past Disease: <b>POSSIBLE MYOCARDIAL INFARCTION</b>  Concurrent Disease: <b>DIABETES MELLITUS</b> <b>HYPERTENSION</b>
--

## C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known) <b>#1 Erlotinib HCl (Tablets)</b>  <b>#2 Cisplatin (CISPLATIN) (Injection for infusion) Cont...</b>	3. Therapy dates (if unknown, give duration from/to (or best estimate)) <b>#1 08/29/02 - 11/15/02</b> <b>#2 08/29/02 - 11/13/02</b>
2. Dose, frequency & route used <b>#1 150 mg (QD), Oral</b> <b>#2 75 mg/m<sup>2</sup> (Q 3 weeks), Injection</b>	4. Diagnosis for use (indication) <b>#1 LARYNGEAL CANCER</b> <b>#2 LARYNGEAL CANCER</b>
6. Lot # (if known) <b>#1 Unk</b> <b>#2 Unk</b>	7. Exp. date (if known) <b>#1 Unk</b> <b>#2 Unk</b>
9. NDC # - for product problems only (if known)	

5. Event abated after use stopped or dose reduced <b>#1</b> <input type="checkbox"/> yes <input checked="" type="checkbox"/> no <input type="checkbox"/> doesn't apply <b>#2</b> <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply	8. Event reappeared after reintroduction <b>#1</b> <input type="checkbox"/> yes <input type="checkbox"/> no <input checked="" type="checkbox"/> doesn't apply <b>#2</b> <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> doesn't apply
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## G. All manufacturers

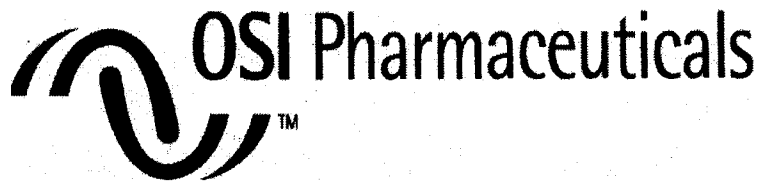
1. Contact office - name/address (& mfg site for devices) <b>OSI Pharmaceuticals</b> <b>Boulder Safety</b> <b>2860 Wilderness Place</b> <b>Boulder, CO 80301</b> <b>USA</b> <b>( Informing Unit )</b>	2. Phone number <b>303-444-5893</b>
4. Date received by manufacturer (mo/day/yr) <b>01/29/03</b>	5. (A)NDA # <b>53,728</b> IND # <b>5380</b> PLA # pre-1938 <input type="checkbox"/> yes OTC product <input type="checkbox"/> yes
6. If IND, protocol # <b>5380</b>	3. Report source (check all that apply) <input checked="" 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) <input type="checkbox"/> 5-day <input checked="" type="checkbox"/> 15-day <input type="checkbox"/> 10-day <input type="checkbox"/> periodic <input checked="" type="checkbox"/> Initial <input type="checkbox"/> follow-up # _____	8. Adverse event term(s) <b>1) SEPSIS (Sepsis NOS)</b> <b>2) RENAL FAILURE (Renal failure NOS)</b> <b>3) AIRWAY OBSTRUCTION (Obstructive airways disorder NOS)</b>
9. Mfr. report number <b>2002001895</b>	

## E. Initial reporter

1. Name & address <b>Dr. Lillian Siu</b> <b>Princess Margaret Hospital</b> <b>Dept. Medical Oncology</b> <b>610 University Avenue</b> <b>Toronto, Ontario M5G 2M9</b> <b>CANADA</b>	phone # <b>416 946 4501</b>
2. Health professional? <input checked="" type="checkbox"/> yes <input type="checkbox"/> no	3. Occupation <b>Study Investigator</b>
4. Initial reporter also sent report to FDA <input type="checkbox"/> yes <input checked="" type="checkbox"/> no <input type="checkbox"/> unk	

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.





## Drug Safety Department

### **Tarceva™ (erlotinib HCl, OSI-774) Serious Adverse Event Report – 15 Day Investigator Notification**

7-February-2003

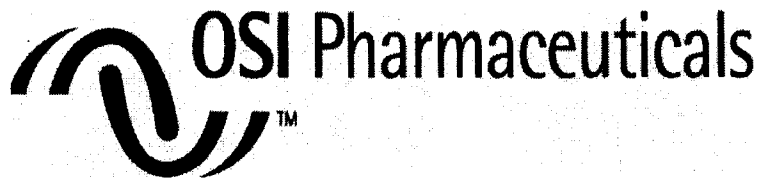
RE: **OSI MCN 2002001895** (NCI-CTEP AER 1843487), a report of **Infection without Neutropenia** from NCI-CTEP Sponsored Trial 5380, a phase I/II study of OSI-774 in combination with cisplatin in patients with recurrent or metastatic squamous cell cancer of the head and neck.

RE: **OSI MCN 2003000032** (NCI-CTEP AER 1898327), a report of **CNS Hemorrhage** from NCI-CTEP Sponsored Trial S0127, a phase II study utilizing OSI-774 (NSC-718781) (erlotinib HCl, Tarceva) to evaluate patients with unresectable or metastatic adenocarcinoma of the stomach and gastroesophageal junction.

Dear Investigator:

Attached please find two safety letters from the NCI-CTEP relating to reports submitted as 15-Day Alert Reports to local regulatory authorities and NCI-CTEP investigators regarding; 1) a patient who experienced a non-neutropenic infection and subsequent death considered probably related to erlotinib treated in NCI-CTEP sponsored study 5380 (OSI MCN 2002001895) and 2) a patient who experienced a stroke, considered possibly related to erlotinib and died while participating in NCI-CTEP sponsored study S0127 (OSI MCN 2003000032). Please include a copy of the letter as a supplement to the Investigator's Brochure for Tarceva™ (erlotinib HCl, OSI-774), and forward a copy to your Institutional Review Board/Ethics Committee as required by local regulations.

The events of infection without neutropenia and CNS hemorrhage are considered to be expected events according to the Tarceva™ (erlotinib HCl, OSI-774) Investigator's Brochure. After review of the clinical details and investigator's comments pertaining to this adverse event, and based upon the experience with erlotinib to date, the sponsor does not believe that changes to the conduct of this clinical trial are warranted. However, OSI Pharmaceuticals, Inc. intends the submission of this IND Safety Report on the events renal failure and sepsis to represent a safety amendment to the Tarceva™ (erlotinib HCl, OSI-774) Investigator's Brochure.



## Drug Safety Department

Please feel free to contact OSI Drug Safety Department with any questions or concerns you may have in this regard. We appreciate your continuing efforts and cooperation in the conduct of our clinical trials.

Sincerely,

A handwritten signature in black ink, appearing to read "Karsten Witt", is positioned above the typed name.

Karsten Witt, M.D.  
Sr. Medical Director  
Drug Safety and Clinical Development

" A safety report or other information submitted by a sponsor under this section (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the sponsor or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse experience. A sponsor need not admit, and may deny, that the drug caused or contributed to an adverse experience." [CFR 312.32]

Attached: Copy of NCI-CTEP Letter to Investigators for NCI AER 1843487 (OSI 2002001895)  
Copy of NCI-CTEP Letter to Investigators for NCI AER 1898327 (OSI 2003000032)

**ADVERSE EVENTS ASSESSMENT**

IND 63383 NSC 718781 OSI-774	ADVERSE EXPERIENCE REPORT NO. #3 IND Safety Report: Event: Gr. 5 Infection without neutropenia
AE 1843487	Protocol: 5380

The patient was a 61-year-old male with laryngeal cancer metastatic to the cervical lymph nodes and skin who developed respiratory failure secondary to cancer obstructing his airway, cardiac ischemia, renal failure, and infection without neutropenia and ultimately expired while on a phase 1/2 trial using the investigational agent OSI-774 in combination with cisplatin in patients with recurrent or metastatic squamous cell cancer of the head and neck. He began his first course of treatment on August 29, 2002 with intravenous (IV) doses of cisplatin 75 mg/m<sup>2</sup> on day 1 and OSI-774 150 mg orally (PO) every day for 28 days. He completed three courses of therapy and began cycle 4 on November 13, 2002 receiving the planned IV dose of cisplatin 56.25 mg/m<sup>2</sup> (previously dose reduced for grade 1 creatinine) and two doses of OSI-774 on this cycle.

When the patient presented for cycle 4 of therapy on November 13, 2002, he was experiencing increased stridor and voice change. He underwent a laryngoscopy that day, which revealed sluggish cords and swollen epiglottis. The investigator felt that stridor was due to airway obstruction possibly related to tumor or IND agent. OSI-774 was held on November 15, 2002. At this time, the patient refused medical intervention, and the symptoms worsened over the subsequent days. He was admitted to a local hospital on November 19, 2002 and then transferred to the intensive care unit (ICU) requiring intubation and ventilation. A tracheostomy was performed on November 20, 2002 with the findings of secretions and tumor. His airway was again obstructed (from a blood clot) on November 21, 2002, and a tracheotomy tube was reinserted. The course in the ICU was complicated by *Staphylococcus aureus* bacteremia, thought to be related to an infected portacath and *Klebsiella* in the sputum. Blood cultures drawn from arterial line and peripheral vein, as well as cultures from the catheter tip were positive for *Staphylococcus aureus*. The patient's creatinine level was elevated at the start of cycle 4 to 171 µmol/L, which resolved with IV hydration to 109 µmol/L. During the ICU admission, the patient subsequently developed acute renal failure, with a creatinine of 510 µmol/L on December 7, 2002. The absolute neutrophil count fell to a low of  $1.57 \times 10^9/L$  on November 24, 2002, and the platelet count fell to low of  $32 \times 10^9/L$  on November 20, 2002. PT and PTT were not elevated. His albumin level decreased to 16 g/L from a pretreatment level of 39 g/L. The patient also developed hyperbilirubinemia, with a bilirubin level of 177 µmol/L on December 2, 2002, and with normal transaminase levels throughout the course of therapy. The albumin dropped from 39 g/L pretreatment on November 12, 2002 to 16 g/L on December 6, 2002. The patient's ICU course was also complicated by cardiac ischemia/atrial fibrillation, anasarca, and bleeding from the tracheostomy site. Thrombocytopenia, hepatic dysfunction, cardiac ischemia/atrial fibrillation, and anasarca are thought to be related to sepsis. Bleeding from the tracheostomy site is thought to be related to the surgical procedure, sepsis, and thrombocytopenia. The decision was made on December 2, 2002 for no resuscitation and no dialysis. The patient died on December 8, 2002, and no autopsy was performed. The cause of death was reported to be respiratory failure due to sepsis and laryngeal carcinoma.

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His past medical history is significant for diabetes mellitus, hypertension, and a possible myocardial infarction in the Spring.

There have been no previous reports of stridor or airway edema/laryngeal edema under this IND, and this adverse event is likely related to laryngeal carcinoma. Renal failure is thought to be related to sepsis with possible contribution of cisplatin. Thrombocytopenia, hepatic dysfunction, cardiac ischemia/atrial fibrillation, anasarca, and hypoalbuminemia are thought to be related to *Staphylococcus aureus* septicemia. There have been seven other incidences of infection without neutropenia/unknown neutropenia, with an attribution of unrelated to the agent, reported to the NCI as serious adverse events under this IND. A possible causal relationship to the underlying laryngeal cancer may have contributed to this event; however, a possible attribution to the agent cannot be excluded. There have been 177 patients enrolled in NCI-sponsored clinical trials under this IND.

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**CONFIDENTIAL**

## ADVERSE EVENTS ASSESSMENT

IND 63383 NSC 718781 OSI-774	ADVERSE EXPERIENCE REPORT NO. 4 IND Safety Report: Event: Gr. 5: CNS cerebrovascular ischemia
AE 1898327	Protocol: S0127

The patient is a 68-year-old female with gastric cancer who apparently suffered a stroke while on a phase 2 trial using the investigational agent OSI-774 in unresectable or metastatic adenocarcinoma of the stomach and gastroesophageal junction. She began her first course of treatment on December 13, 2002 taking OSI-774 150 mg orally (PO) every day, with a cycle being 28 days.

During the patient's initial consultation on December 6, 2002, the patient's physical examination was unremarkable. The cardiovascular examination was within normal limits. The neurologic examination was symmetric. The patient's performance status was 100%. The endoscopy that was performed confirmed the malignant gastric mass, demonstrating an invasive adenocarcinoma. The pre-study computerized tomography (CT) scan of the abdomen and pelvis demonstrated multiple hepatic metastases. The baseline complete blood count with differential revealed a white blood cell count of  $14.9 \times 10^3/\mu\text{l}$  (upper limit of normal is  $10.0 \times 10^3/\mu\text{l}$ ), with values for hemoglobin and platelets falling within the normal range. The renal function studies and liver function studies were all within normal limits. The prothrombin time (PT) was slightly elevated at 15.6 seconds (upper limit of normal is 13.9 seconds).

The patient had only received 2 days of the study drug when she awoke on the morning of December 15, 2002, somewhat confused, and unable to move the right side of her body. There was associated pain/discomfort with this event. The clinical syndrome was consistent with a cerebral vascular event but no investigations were conducted. The patient's status continued to decline following this event, and she was placed in hospice care. The patient died on December 20, 2002. No autopsy was performed.

The patient's past medical history is significant for the underlying gastric cancer metastatic to the liver. Prior to enrollment on study there was no history or clinical evidence of brain metastases. The patient had no history nor known risk factors for cardiovascular or cerebral vascular disease other than age and malignancy. She had no prior surgical history. The patient's medications at the time of the event was Oxycontin.

There have been no other incidences of CNS cerebrovascular ischemia reported to the NCI as a serious adverse event under this IND. It should be noted that the absence of investigations in to the patient's

**CONFIDENTIAL**

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hemiparesis renders a diagnosis and attribution for this event difficult. It is possible that the patient hemorrhaged into an unsuspected brain metastasis. It is also possible that the patient experienced a cerebral vascular accident due to thrombosis/embolism as she is at risk of cerebral vascular disease (CVD) due to her age; however, she had no document history of CVD or risk factors. In addition, there is a known risk of both venous and arterial thrombosis and embolism with malignancy; however, a possible causal relationship between the investigational agent cannot be excluded. There have been 178 patients enrolled in NCI-sponsored clinical trials under this IND.

***CONFIDENTIAL***