2 STUDY SYNOPSIS

Name of Company: OSI Pharmaceuticals, Inc.

Name of Finished Product: Tarceva™ (OSI-774)

Name of Active Ingredient: Erlotinib

Title of Study:
A Phase Ib Multicenter Trial to Determine the Safety, Tolerance and Preliminary Antineoplastic Activity of Gemcitabine Administered in Combination with Escalating Oral Doses of OSI-774 to Patient Cohorts with Recently Diagnosed, Gemcitabine-Naïve, Advanced, Pancreatic Carcinoma or Other Potentially Responsive Malignancies

Investigators:
The study was conducted at 3 centers under the direction of the following Principal Investigators: [Name Redacted], MD at [Location Redacted]; [Name Redacted], MD at [Location Redacted]; and [Name Redacted], MD at [Location Redacted].

Publications (reference):

Studied Period:
Date first patient started therapy: 23 JUL 2001
Date last patient started therapy: 27 OCT 2003
Data cut-off: 22 APR 2004

Objectives:
The primary study objectives were to determine the safety, tolerability, pharmacokinetic interactions, and maximum tolerated dose (MTD) of daily oral administration of erlotinib (100 or 150 mg) in combination with gemcitabine (1000 mg/m² administered intravenously [IV] over 30 minutes, weekly x 7, with 1 week off, followed by repeated cycles of weekly x 3 with 1 week off) in patients with recently diagnosed, gemcitabine-naïve, carcinoma of the pancreas (or another potentially responsive untreated or minimally pretreated malignancy) that was locally advanced, metastatic, or otherwise inoperable.
The secondary objectives were to evaluate the preliminary antineoplastic activity of daily oral doses of erlotinib administered in combination with gemcitabine, as measured by objective antitumor response rate, duration of any objective antitumor responses, time to disease progression, and duration of overall survival.
Amendment #3 of the protocol added to the primary objective that patients prior to study entry had to be untreated or minimally pretreated.

Methodology:
A minimum of 3 patients were planned for treatment at each dose level and were evaluated throughout the study for evidence of acute and delayed toxicities. Interrupting or reducing the dose of either study agent without effecting a change in dosing of the other agent was allowed in order to manage therapy-related toxicities.
On study Day 1 of Cycle 1, patients received gemcitabine IV, and on study Day 3 patients began once daily oral dosing with erlotinib. Evaluation of the PK interactions of gemcitabine and erlotinib were conducted on plasma samples collected from all patients during Cycle 1. For safety, patients were closely monitored for the occurrence of adverse events, as well as for changes in clinical status, vital signs, and laboratory data.
If Cycle 1 was tolerated, further cycles could be administered. After completing Cycle 1 (and every 2 cycles thereafter), tumor response was assessed. Patients who achieved stable disease (SD) or an objective response could continue at the same dose previously administered, if tolerated. The total number of chemotherapy cycles administered was consistent with accepted standards of care and the product labeling. Erlotinib could be continued until disease progression (PD) or unacceptable toxicity occurred.

All patients in a cohort had to have demonstrated acceptable tolerance before escalation to the next erlotinib dose could occur. Up to 2 dosage cohorts of erlotinib were to be investigated (100 or 150 mg/day), with the potential to evaluate an intermediate dose (125 mg/day) in order to more fully characterize the identified MTD. Dose escalation was to stop either at a maximum dose of 150 mg/day of erlotinib given in combination with gemcitabine, or when a DLT had been observed in ≥ one third of the patients treated at any dosage level.

In such cases, further participation in this study was discontinued, except for defined end-of-study and follow-up evaluations. Patients with a DLT who also had documented SD or an objective response with respect to their underlying malignancy, or patients that had not yet completed one 8-week dosing cycle, could continue to be treated, at the discretion of the Investigator, after consultation with the medical monitor.

Follow-up continued for approximately 1 month or longer post-therapy if any erlotinib-related toxicity had not resolved by that time.

Number of Patients (planned/analyzed):
The initial enrollment was planned for up to 30 patients, and a total of 26 were enrolled. With the third protocol amendment, no further patients were accrued to the initial Treatment Group I (Cohort 1, n = 9). In protocol amendment #3, Treatment Group II, with a planned enrollment of up to 36 patients, was then added and was composed solely of patients previously untreated or minimally pretreated (0 to 1 prior chemotherapy regimes). This portion of the study also was planned to investigate 2 erlotinib dosages of 100 and 150 mg/day, and potentially an intermediate dose of 125 mg/day, in combination with gemcitabine at 1000 mg/m². Within this group it was further specified that up to 18 patients with pancreatic carcinoma could be entered at the identified MTD. Two patient cohorts were treated in this second treatment group (Cohort 2, n = 3; and Cohort 3, n = 14). Throughout the entire study, the doses evaluated were (gemcitabine mg/m²/erlotinib mg/day): Cohort 1 = 1000/100, Cohort 2 = 1000/100 (post-amendment #3), and Cohort 3 = 1000/150 (post-amendment #3).

Diagnosis and Main Criteria for Inclusion:
Patients at least 18 years of age who had a recurrent, locally advanced, and/or metastatic malignancy that was not amenable to surgical resection, were eligible for the study. Disease had to be documented, measurable, or evaluable and considered potentially responsive to gemcitabine therapy. Other inclusion criteria included Karnofsky performance status (KPS) ≥ 70%, and evidence of adequate hematological, hepatic, and renal function. Clinically significant cardiac, gastrointestinal (GI), or ophthalmologic abnormalities, uncontrolled infection, or any other life-threatening illness were not allowed. Patients who had previous therapy with agents targeting the epidermal growth factor receptor (EGFR) or having EGFR-specific tyrosine kinase activity were not eligible.

After implementation of the third protocol amendment, patients with > 1 prior chemotherapy regimen were not eligible; patients could not have evidence or suspicion of bone metastases; the KPS criteria was changed from ≥ 70% to ≥ 80%; patients could not have a baseline serum albumin level of < the lower limit of normal (LLN) for the institution (< 2.5 g/dL prior to Amendment #3); or a baseline AST or ALT of > 1.5 x the upper limit of normal (ULN) for the institution (≥ 2 x ULN prior to Amendment #3).
Erlotinib (Tarceva™, OSI-774)  
Study OSI-774-155  
Clinical Study Report, OSI-774-155, Final, Version 1

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| Name of Finished Product: | |
|--------------------------| |
| Tarceva™ (OSI-774) | |

| Name of Active Ingredient: | |
|---------------------------| |
| Erlotinib | |

**Study Drug, Dose and Mode of Administration, Batch Numbers:**

Erlotinib tablets (manufactured by [removed for privacy] and [removed for privacy]) were available in 25 mg, 100 mg, and 150 mg strengths. The 25 mg tablets were available but not used in this study.

Erlotinib was administered orally once a day beginning on Day 3 of Cycle 1 and continued daily without interruption.

Lot numbers (100 mg material): 100 mg (100-123456), 150 mg (150-67890112)
Lot numbers (150 mg material): 100 mg (150-67890111), 150 mg (150-67890112)

**Combination Chemotherapy, Dose and Mode of Administration:**

Gemcitabine (Gemzar®, Eli Lilly and Company) at a dose of 1000 mg/m² was administered IV over 30 minutes, weekly x 7, with 1 week off, followed by repeated cycles of weekly x 3 with 1 week off. Patients were premedicated with standard antiemetics and dexamethasone as indicated to prevent chemotherapy-associated side effects.

Gemcitabine was commercially available and was not supplied by OSI during the study. It was not modified in any way from its commercial state.

**Duration of Treatment:**

At the completion of the first cycle of the study (1 cycle of gemcitabine therapy, approximately 8 weeks of erlotinib therapy), patients with evidence of SD, or an objective, minor, partial, or complete response with respect to their underlying malignancy, could continue to be treated at the discretion of the principal Investigator, following discussion with the medical monitor. The standard number of cycles of gemcitabine could be administered, as indicated, depending upon tumor type. Erlotinib could continue to be administered until the occurrence of unacceptable toxicity or, documented PD, whichever took place first.

**Criteria for Evaluation:**

**Primary Objective: Safety, MTD, PK**

Patients were evaluated for safety and tolerability at designated time points after initiation of therapy. The NCI CTC, Version 2.0, were used to grade adverse events and clinical laboratory results.

Samples for determination of study drug plasma concentrations were obtained during Cycle 1. Effective with the first protocol amendment, samples were also collected in Cycle 1 for analysis of alpha-1 acid glycoprotein (AAG).

**Secondary Objectives: Antitumor Activity**

Response assessment was according to Response Evaluation Criteria in Solid Tumors (RECIST).

Tumor Markers (as appropriate, depending upon tumor type) were assessed at baseline, Week 5 of Cycle 1, prior to the start of each subsequent gemcitabine cycle, at the end of the last cycle (or upon early termination), and as clinically indicated.

**Statistical Methods:**

Analysis of safety and antitumor activity was based on all 26 patients. Descriptive statistical representation of the data includes summaries of demographics and other baseline patient characteristics. Summary statistics include sample sizes, medians, and ranges, where appropriate, for continuous variables. Frequencies and percents are provided for categorical variables.

**Primary Safety Endpoints:**

The safety analysis was based on rates of adverse events, serious adverse events, deaths, adverse events resulting in discontinuation, and DLTs. Safety was assessed by monitoring the incidence, seriousness, severity, and relationship of adverse events, changes in laboratory results, and use of concomitant medications.

The MTD was defined as the dose level preceding that which produced DLTs during Cycle 1 in > one third of the patients in a dose cohort (ie, > 1 of 3 in a 3-patient cohort or > 2 of 6 in a 6-patient cohort).
Pharmacokinetics:

Plasma from blood samples taken at each of the specified timepoints was analyzed to assess plasma exposure and to correlate erlotinib, metabolites OSI-420/413, and gemcitabine drug levels with selected patient variables, laboratory parameters, and adverse events.

Antitumor Activity Endpoints:

RECIST were used to evaluate the antitumor activity of the combination. Clinical and radiological assessments were to be repeated at least 4 weeks after first documentation to confirm a complete response (CR) or partial response (PR). SD criteria had to be met 1 or more times, at least 4 weeks after study entry. Best overall response was defined as the patient’s best response recorded from the first date of dosing until PD or recurrence. Response duration, time to progression (TTP), and survival were calculated to the last date of patient contact, last known date alive or last follow-up date.

Results:

The following dose cohorts were evaluated (gemcitabine mg/m² / erlotinib mg/day): Cohort 1 = 1000/100 (n = 9), Cohort 2 = 1000/100 (n = 3, post-amendment #3), and Cohort 3 = 1000/150 (n = 14, post-amendment #3).

Patient Characteristics:

A total of 26 patients were enrolled and treated. There were 13 males and 13 females, with a median age of 63 (range 29 to 82). All but 2 patients were Caucasian. At study entry, patients had KPS reported at 100% (7 patients), 90% (8 patients), and 80% (11 patients). Per the protocol, the primary diagnosis in the majority of patients (15 of 26 patients) was pancreatic carcinoma; in addition there were 2 patients with breast carcinoma, 2 patients with non-small cell lung carcinoma, and single cases of bladder, colon, gastric, prostate, renal, thyroid, and cholangiocarcinoma. Half of the patients had undergone a previous surgical resection or partial resection procedure. Nine patients received prior chemotherapy, 5 of which had received only 1 prior regimen, and 1 patient each had received 2, 3, 4 and 8 prior regimens. Five patients received prior radiotherapy. Four patients received prior hormonal or immunotherapy. Some patients had received more than 1 type of prior therapy. Nine patients entered the study with no prior treatment (excluding biopsy procedures).

Summary of Safety:

The majority of patients, 19 patients, received erlotinib and gemcitabine throughout the 8 weeks of Cycle 1, or longer. The median number of cumulative days of erlotinib exposure was 44 days, 140 days, and 113 days, in Cohort 1, 2, and 3, respectively. Only 1 patient required reduction of erlotinib (150 mg) while 18 required reduction in gemcitabine, the majority (12 patients) in Cohort 3. Three patients developed DLTs, all in Cohort 1 (erlotinib 100 mg/day gemcitabine 1000 mg/m²), and all due to transaminase elevations. Elevated transaminases (ie. AST, ALT) were frequently reported treatment-related adverse events. Hematological laboratory results frequently reported as adverse events included anemia, neutropenia, and leukopenia. The most common nonhematological adverse events related to erlotinib therapy were fatigue, rash, diarrhea, nausea, dry skin, and peripheral edema.

Five patients died within 30 days of the last dose of erlotinib, and all of these deaths involved progression of the patients’ respective underlying malignancies, however, possible pulmonary toxicity contributed in 1 patient in Cohort 3. Not including 1 serious adverse event of PD resulting in death, 15 patients experienced 1 or more other serious adverse events. Serious adverse events considered related to erlotinib occurred in 3 patients and included acute respiratory distress syndrome, dehydration, hypotension, and gastrointestinal hemorrhage.

Summary of Pharmacokinetics:

There were no significant effects of gemcitabine on the pharmacokinetics of erlotinib nor were there significant effects of erlotinib on the pharmacokinetics of gemcitabine. The type of tumor (pancreatic versus non-pancreatic) had no significant effect on the pharmacokinetics of erlotinib. The pharmacokinetics report is in Appendix 16.1.13.
### Summary of Antitumor Activity:

Two patients in Cohort 3 achieved PRs lasting 1.9 weeks in 1 patient, and 31.1 weeks in the other patient. The time to progression was 17.1 weeks for 1 patient, and 47 weeks for the other patient. One patient survived for 5.9 months, and the other patient survived for 12.8 months. Stable disease was observed across all cohorts in a total of 12 patients.

### Conclusions:

Based on the safety and tolerability results of this study, the dose administered to Cohort 3 (erlotinib 150 mg/day and gemcitabine 1000 mg/m\(^2\)) was tolerated in the untreated and minimally pretreated patients in this study.

Due to the Phase Ib nature of the study, it is not possible to evaluate the relative contribution of erlotinib to the antitumor activity seen with the active chemotherapeutic agent, gemcitabine.

**Date of the Report:** 20 JAN 2005