2 STUDY SYNOPSIS

<table>
<thead>
<tr>
<th>Name of Company:</th>
<th>OSI Pharmaceuticals, Inc.</th>
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<tbody>
<tr>
<td>Name of Finished Product:</td>
<td>Tarceva®</td>
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<tr>
<td>Name of Active Ingredient:</td>
<td>Erlotinib</td>
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**Title of Study:**
A Phase II, Open-label, Intrapatient Dose-escalation Study of Erlotinib in Patients with Advanced Non-Small Cell Lung Cancer who Have Failed Prior Chemotherapy

**Investigators:**
The study was conducted at 2 centers under the direction of 2 Principal Investigators: Dr. at USA and , at , The Netherlands. A list of the investigators, their affiliations, qualifications (CVs), and other important study personnel is provided in Appendix 16.1.4.

**Publication (reference):**

**Studied Period:**
Date first patient started therapy: 05 NOV 2003
Date last patient completed: 1 patient continuing
Database lock: 14 MAR 2007

**Phase of Development:** 2

**Objectives:**
The primary objective of this study was to determine the feasibility of intrapatient dose escalation of erlotinib to induce a characteristic, target rash and evaluate the effect on objective response rate in patients with advanced non-small cell lung cancer (NSCLC).

The secondary objectives were to determine the feasibility of correlating objective response rate and duration of response to grade of rash; explore the efficacy of a standardized treatment on erlotinib-associated rash; explore potential correlations of EGFR expression and/or activity in tumor tissue, skin biopsies, hair follicles (in Versions 1 and 2 of the protocol), and sebum and serum (proteomics and metabolomics) to rash and/or response.

**Methodology:**
This was a 2-center, open-label, phase 2 study to determine the feasibility of using intrapatient dose
escalation to induce a characteristic, target rash and to evaluate the effect on objective response rate in patients with advanced NSCLC.

A minimum of 15 patients were to be enrolled at a starting dose of erlotinib 150 mg given daily as oral single-agent therapy. The dose was escalated to 200 mg/day after 3 weeks provided that rash, if any, was tolerable and there was no nonrash dose-limiting toxicity (DLT). Subsequent dose escalation could continue in 25 mg/day increments every 2 weeks until either intolerable rash despite maximal intervention or other DLT occurred. Tumor assessments were done every 6 – 8 weeks to determine response (Response Evaluation Criteria in Solid Tumors [RECIST]). Confirmation assessments were done on all responders ≥ 4 weeks after the initial response assessment. Additional patients were enrolled if dose escalation was feasible for more than 5 patients (feasibility was defined as the development of a characteristic, target rash without unmanageable, nonrash DLT) (optimal, 2-stage Simon design).

A DLT was any toxicity that was considered related to study drug and that occurred in the first 3 weeks after initial dosing or in any subsequent 2-week treatment period after an increase in dose level. A DLT was defined as follows:

Nonhematologic:
- Intolerable rash despite maximal intervention;
- Grade 3 or 4 toxicity (excluding isolated nonclinically relevant biochemical changes, or unpremedicated or inadequately treated nausea and/or vomiting or diarrhea);
- Grade 3 aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) for ≥ 7 days or grade 4 AST and/or ALT;
- Any unacceptable toxicity (> grade 2) that did not resolve in 14 days.

Hematologic:
- Absolute neutrophil count (ANC) < 0.5 x 10^9/L for > 5 days;
- Febrile neutropenia ≥ grade 3 (ANC < 1.0 x 10^9/L and fever ≥ 38.5°C);
- Grade 3 or 4 clinically or microbiologically documented infection with grade 3 or 4 ANC (< 1.0 x 10^9/L);
- Platelets < 25 x 10^9/L or thrombocytopenic bleeding requiring transfusion.

Number of Patients (Planned/Analyzed):
- Planned: 50
- Analyzed: 42

Diagnosis and Main Criteria for Inclusion:
Patients had to be 18 years or older with histologically confirmed stage IIIB/IV NSCLC who had been treated with at least 1 chemotherapy regimen for advanced, metastatic NSCLC, with an ECOG performance status of 0 or 1, with a predicted life expectancy of ≥ 12 weeks, and with adequate hematopoietic, hepatic, and renal function.

Study Drug, Dose and Mode of Administration, Batch Numbers:
Erlotinib was supplied in bottles containing either 25, 100, or 150 mg tablets. The dispensed amount was sufficient to allow for 4 weeks (28 days) of consecutive once daily dosing and to provide for additional days of dosing, if necessary. Erlotinib was administered on an outpatient basis. The starting oral daily dose was 150 mg.

Lot numbers: 25 mg, lot numbers [redacted] and [redacted]; 100 mg, lot numbers [redacted] and [redacted]; 150 mg, lot numbers [redacted] and [redacted].
Name of Company: OSI Pharmaceuticals, Inc.
Name of Finished Product: Tarceva®
Name of Active Ingredient: Erlotinib

Combination Chemotherapy, Dose and Mode of Administration, Batch Numbers:
None

Duration of Treatment:
Patients were treated until clinically or radiographically documented progressive disease (PD), intolerable toxicity, DLT that did not resolve in 14 days, or death. If a patient experienced a DLT during treatment, yet at the same time, the investigator’s opinion was that the patient may have benefitted from continued therapy and the patient wished to continue, a dose reduction to the next-lower dose level could be considered for this patient’s subsequent courses.

Criteria for Evaluation:
Efficacy:
All patients who received at least 1 dose of erlotinib were considered evaluable for all efficacy analyses. The primary efficacy endpoint was feasibility of intrapatient dose escalation of erlotinib. If an individual patient developed a target rash (tolerable rash with intervention) without other unmanageable, nonrash DLTs, the dose-escalation strategy was considered feasible for that patient. The effect of development of a target rash on objective response rate was evaluated. Objective response was assessed according to RECIST.

Progression-free survival (PFS) was not specified in the protocol as a secondary endpoint; however, it was included in the efficacy analysis. Sufficient data to assess PFS were collected as part of the assessment of objective response and duration of response.

Safety:
All patients who received at least 1 dose of erlotinib were included in the safety evaluations, which included adverse events, assessments of laboratory parameters, physical examinations, and symptom evaluation to determine the safety and tolerability of erlotinib therapy.

Pharmacokinetics:
All patients who had sufficient plasma pharmacokinetic samples to calculate pharmacokinetic parameters at 1 or more dose levels were included in the statistical analyses of pharmacokinetic parameters. Plasma pharmacokinetic samples were obtained at baseline prior to erlotinib administration for all patients. In the original protocol, samples for pharmacokinetic assessment were to be collected 14 days after the 200 mg/day and subsequently escalated doses but the second protocol amendment added plasma sampling following 14 days of administration of the 150 mg/day starting dose.

Correlative Studies:
EGFR, p-EGFR, p-ERK, and other molecular markers linked to the EGFR signal transduction pathway were to be assessed from paraffin-embedded tumor tissue when available to identify potential markers associated with erlotinib response.

Erlotinib-associated rash was evaluated in patients using specified grading criteria and photographic documentation in conjunction with histological review of skin biopsies. The impact of rash on health-related quality of life was evaluated using a patient Dermatology Life Quality Index questionnaire.

Serum proteomic and/or metabonomic assessments (serum amyloid [SAA]) and sebum production/cytokine assessments were performed on patients to evaluate changes associated with erlotinib therapy.

For protocol versions prior to Version 3 (22 November 2004), hair follicles were evaluated for changes in expression of EGFR and p-ERK following erlotinib administration (first 27 patients).

Skin sebum production was quantified and changes in sebum cytokine production were evaluated to assess changes associated with erlotinib therapy.
**Statistical Methods:**

**Efficacy:**

Planned Sample Size:

Based on results from a completed phase 2 study in NSCLC, approximately 30% of patients who received 150 mg/day of erlotinib developed NCI CTC grade 2 or grade 3 rash. The strategy of intrapatient dose escalation was considered a success if at least 50% of the patients in this study satisfied the definition of feasibility. Therefore, the null hypothesis for this study was that the feasibility rate was $\leq 30\%$, and the alternative hypothesis was that the feasibility rate was $\geq 50\%$.

An optimal, 2-stage, Simon design for testing these hypotheses (with 0.05 probability of accepting the dose-escalation strategy if the null hypothesis was true and 0.80 probability of rejecting the strategy if the alternative hypothesis was true) was followed as described below.

Fifteen patients were to be enrolled in the first stage; the study was to be terminated and the dose-escalation strategy was to be declared not feasible if $\leq 5$ patients satisfied the definition of feasibility. If dose escalation was feasible for more than 5 patients, the study was to continue to the second stage and an additional 31 patients were to be enrolled, for a total sample size of 46 patients. To account for unevaluable patients, a total of 50 patients were to be enrolled. If dose escalation was feasible for more than 18 of the 46 patients, then the strategy was to be declared feasible. This study design had a 0.72 probability of early termination if the null hypothesis was true.

Actual Sample Size:

During the first stage, $> 5$ patients satisfied the definition of feasibility so the study continued to the second stage in which 31 more evaluable patients were to be enrolled. Following consultation between OSI and investigators, the decision was made to halt further enrollment into the study after 30 November 2005. Recruitment had reached 42 patients at that time. The rationale for this decision was that the primary objective of this exploratory study had essentially been achieved and it was unlikely that enrollment of the outstanding 8 patients would add substantially to the results of the trial. The protocol was written prior to publication of data that described the potential importance of pharmacogenetic factors such as EGFR copy number or mutational status. Further study of the relationship of rash with efficacy would need to consider these factors.

**Safety:**

The primary safety analyses were conducted on the following parameters.

All patients who received at least 1 dose of erlotinib were considered evaluable for all safety analyses. Descriptive statistics were used to summarize safety data. Adverse events were coded by body system using the Medical Dictionary for Regulatory Activities (MedDRA®) and summary tables for all adverse events were generated. Incidence rates were summarized for each preferred term and organ-class system. Additional summary tables were generated for the following population subsets: patients with serious adverse events, patients with erlotinib-related adverse events, patient deaths, and patients who discontinued due to adverse events. Depending on the doses achieved in this study, adverse events were summarized by dose level. Severity and duration and outcome of events were also recorded.

**Pharmacokinetics:**

The primary pharmacokinetic analyses were conducted on the plasma concentration versus time data obtained following the Day 14 administration of each dose level of erlotinib. Patients may have had 2 or more dose levels at which they had measured pharmacokinetic concentrations. Pharmacokinetic analysis output for erlotinib and its metabolite, OSI-420 included $C_{\text{max}}$, $T_{\text{max}}$, $AUC_{0-24}$, and $C_{24}$. Pharmacokinetic parameter estimates were summarized for each dose level using descriptive statistics: N, median, minimum, and maximum. Geometric means were also calculated for $AUC_{0-24}$ and $C_{\text{max}}$ for each dose.
Summary and Conclusions:

Patient Characteristics:
All 42 patients are included in the demographic data set. More males (67%) than females (33%) were enrolled in the study. All but 8 patients (81%) were White, and the median age was 63 years (range 41 to 78) with a quarter aged 70 years or greater. Most patients (71%) had a baseline ECOG PS of 1; 1 patient had a PS of 2. Approximately 80% of the patients were former smokers, 2 patients had never smoked, and 5 patients continued to smoke while on the study. The median time from initial diagnosis was 12.9 months (range 4.1 to 85.7) and the median time from the most recent progression was 1.3 months (range 0.2 to 10.5).

Over half of the patients enrolled in the study had adenocarcinoma (55%) and a quarter had squamous cell carcinoma (26%). Most patients had stage IV disease at time of diagnosis (57%) or stage IIIA/B disease (38%). Two patients had stage II disease at time of diagnosis but had locally advanced or metastatic disease at time of study entry.

Summary of Efficacy:

A target rash (defined as a tolerable rash with intervention with minocycline) was achieved in over one-half (57%) of the patients, which met the predefined definition of feasible. The first intervention with minocycline occurred at the starting dose of 150 mg/day for 19 of the 24 patients with a feasible target rash. For most of these patients (n = 21), however, the dose was escalated after the target rash occurred. Approximately one-third of the patients (17 of 42) developed no rash (1 patient) or a tolerable rash (16 patients) that did not require minocycline intervention even though the erlotinib dose was escalated.

There were no complete responses during the study; 5 patients (12%) had a partial response and stable disease occurred in 19 (45%) patients. All 5 PRs occurred in patients who developed target rash (5/24, 21%). No responses where observed in patients were target rash was not feasible. Among the 24 patients who had disease control (CR + PR + SD), 15 (63%) developed target rash. Nine of the 18 patients (50%) who did not experience a target rash had disease control. Among the 42 patients enrolled in the study, the median PFS was 2.3 months (95% CI: 1.61 to 4.14). The median PFS for the 24 patients who developed a feasible target rash was 3.5 months (95% CI: 1.61 to 6.97); the median PFS for the 18 patients who did not experience target rash was 1.9 months (P = 0.051).

The most common characterization of the rash was as acneiform with pustules, erythema, papules, and pruritus. Skin biopsies from patients with target rash were notable for altered differentiation to various follicular epithelial structures in the skin, including biopsies of clinically unaffected areas of skin. Damage was most frequently observed in hair follicles, epidermis, and sebaceous glands, with less consistent effects seen in eccrine (sweat) glands. Abnormal epidermal thickening was common, suggesting altered keratinocyte differentiation (condensed nuclei and vacuolization) in spinous epidermis and by compact orthokeratosis in the stratum corneum. No vasculitis was observed. Inflammatory skin lesions displayed these ‘background’ alterations in skin structure in conjunction with primarily mononuclear leukocyte infiltration in either interfollicular dermis, around pilosebaceous structures, or both.

There was no correlation between tumor EGFR status at baseline and the feasibility of achieving target rash, response rate, disease control, or progression-free survival. There were no trends in changes in SAA concentrations following 3 weeks of treatment with erlotinib. Although only 4 patients who were responders had baseline SAA values, that small group of patients had notably lower median SAA values at baseline, while non responders and patients who had disease control had notably higher median baseline SAA levels at baseline. The small sample size and broad range of values made interpretation of the sebum and cytokine data inconclusive.

The analysis of hair follicles showed a larger proportion of patients for whom target rash was feasible had
p-EGFR/EGFR protein activity decrease ≥ 10% from baseline at 1 to 2 hours following initiation of erlotinib (approximate T_{max}) when compared with patients for whom target rash was not feasible. Although this difference persisted, it was less notable at 14 days. The reverse was observed with protein activity decreases in p-ERK/ERK, where there was a smaller proportion of patients for whom target rash was feasible who had p-ERK/ERK protein decrease ≥ 10% from baseline.

The largest effect on dermatology quality of life was observed after the first treatment period, ie, after 3 weeks of erlotinib 150 mg, for all domains except “treatment,” in which the target rash first started at Treatment Periods 2 and 3. The largest mean change from baseline was in the “symptoms and feelings” domain in treatment period, possibly because it was during this period that patients experienced rash for the first time. There was less of an effect on daily activities, leisure, work, and personal relationships, but the trend was generally the same, ie, increase in Treatment Period 1 and then decrease.

Pharmacokinetic analyses showed no significant correlations between erlotinib exposure and patient baseline parameters with the exception of the maximum erlotinib dose, nor were there any significant differences in exposure based on patient gender, age, race, performance status, tumor histology, best response to prior therapy, discontinuations due to adverse events, or overall best response to treatment in this study.

Summary of Safety:

All 42 patients who received study treatment are included in the safety population. Thirty-eight patients (60%) were escalated above the 150 mg/day dose approved in the Tarceva® package insert for NSCLC. The most common final dose was 200 mg/day (15 patients), followed by 150 mg/day (6 patients), 225 mg/day (5 patients), and 10 patients had a final dose > 250 mg/day, including 1 patient who was escalated to 475 mg/day and stayed at that dose for 6 weeks. The median dose was 200 mg/day and the median duration of exposure was 9 weeks (range 3 to 115).

The most frequent adverse events were diarrhea (79%), nausea (64%), and fatigue (62%). Because the occurrence of rash was captured as an efficacy endpoint in this study, rash was not reported as an adverse event; however, 57% of patients had other nonrash skin, hair, or nail toxicity. Rash occurred in 98% of patients. The most frequent treatment-related adverse events were diarrhea (79%) and nausea (52%). The incidence of diarrhea, nausea, fatigue, and anorexia was generally greater in the higher dose levels with increasing frequencies of grade 2 events. The incidence and severity of adverse events were similar among patients for whom target rash was feasible compared with patients for whom it was not.

All 8 patients who died on study or within 30 days of last treatment died due to progressive disease. Seventeen patients (40%) experienced a serious adverse event. The most common serious adverse events were pulmonary embolism (4 patients) and pneumonia (4 patients). Four patients (10%) experienced a serious adverse event that was considered by the investigator to be treatment-related: coagulopathy, headache, acute prerenal failure, and pulmonary embolism. Eleven patients experienced 17 DLTs, including 5 patients with DLTs of intolerable rash and 3 patients with DLTs of fatigue. Three patients discontinued due to adverse events: pseudomona lung infection, progressive pain, and nausea and anorexia.

There were no notable changes in hematologic or blood chemistry laboratory parameters.

Conclusions:

Escalation to target rash was shown to be feasible in this patient population, although the hypothesis that an intrapatient dose escalation strategy would increase the objective response rate was not answered due to the small number of objective responses. Although dose escalation occurred in 90% of patients, only 5 patients
(12%) first experienced a manageable target rash at a dose greater than 150 mg/day (the starting dose), possibly suggesting dose escalation was not important in achieving the target rash. It remains unknown, if keeping patients at the initial dose of 150 mg/day if they developed target rash manageable with minocycline intervention might have resulted in less disease control. The strategy of erlotinib dose escalation to induce target rash as a means to improve outcome could not be fully validated in this study. Dose escalation was conservative, disease progression was rapid, and imbalances were apparent between patients in the manageable target rash feasible/not feasible groups.

Date of the Report: 24 AUG 2009