2 STUDY SYNOPSIS

Name of Company:	Name of Finished Product:	Name of Active Ingredient:
OSI Pharmaceuticals, Inc.	Tarceva®	Erlotinib

Title of Study:

A Phase 2 Randomized Study of Tarceva® (Erlotinib) as a Single Agent or Intercalated with Combination Chemotherapy in Patients with Newly Diagnosed Advanced Non-Small Cell Lung Cancer Who Have Tumors with EGFR Protein Overexpression and/or Increased EGFR Gene Copy Numbers

Investigators:

Patients were enrolled at 34 investigational sites under the direction of the Principal Investigator, [redacted], at the [redacted].

Publication (reference):

1. Kabbinavar F, Ross H, Martins R, et al. Erlotinib (E) as a single agent or intercalated with carboplatin and paclitaxel (ECP) in an EGFR biomarker-selected, previously untreated NSCLC population. J Thorac Oncol 2007; 2(8) (Supplement 4):S394 [Abstract 345].
2. Hirsch FR, Dziadziuszko R, Camidge DR, Kabbinavar F, Richardson K, Wacker B, et al. Biomarker Status Correlates with Clinical Benefit: Phase 2 Study of Single-agent Erlotinib (E) or E Intercalated with Carboplatin and Paclitaxel (ECP) in an EGFR Biomarker-selected NSCLC Population. J Thorac Oncol 2008; 3[11 Suppl 4], S267.
3. Camidge DR, Kabbinavar F, Martins R, Schnell F, Witta S, Eisen T, et al. EGFR biomarker-selected randomized phase II study of erlotinib (E) or intercalated E with carboplatin/paclitaxel (C/P) in chemo-naive advanced NSCLC- Chicago Multidisciplinary Symposium in Thoracic Oncology. J Thorac Oncol 2008; 3[11 Suppl 4], S268.
4. Hirsch FR. Randomized phase II study of erlotinib (E) or intercalated E with carboplatin/paclitaxel (CP) in chemotherapy-naive advanced NSCLC: Correlation of biomarker status and clinical benefit. J Clin Oncol 2009; 27[15S], 413s.

Studied Period:	Phase of Development: 2
Date first patient treated: 28 March 2006 Date of database lock: 20 March 2009	

Objectives:

The primary objective of this study was to evaluate in parallel the efficacy of 2 different erlotinib containing regimens as first-line therapy measured as the percentage of patients who have not progressed at 6 months among stage IIIB/IV NSCLC patients selected on the basis of EGFR protein overexpression and/or increased EGFR gene copy number.

The secondary objectives of this study were to select the better of these 2 regimens for testing in future studies; to obtain estimates of PFS, overall survival, and tumor response for planning future studies; to explore potential correlations between clinical outcome and biomarkers of interest, including EGFR protein overexpression and/or increased EGFR gene copy number in this population; and to evaluate in parallel the safety of these regimens in this population.

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Methodology:

This was a multicenter, open-label, 2-arm, randomized, phase 2 study of single-agent erlotinib and erlotinib intercalated with carboplatin and paclitaxel chemotherapy in patients with newly diagnosed, advanced (stage IIIB or stage IV) NSCLC.

At the time of screening, tumor tissue was tested for EGFR expression by IHC and for EGFR amplification by FISH. Patients in which at least 1 of these 2 tests was considered positive were eligible for enrollment and were randomized to 1 of 2 treatment arms. The 2 treatment arms were:

- Arm A: Single-agent erlotinib until progression, refusal, toxicity, or death;
- Arm B: Four cycles of chemotherapy intercalated with erlotinib. Patients received carboplatin and paclitaxel on Day 1 of each cycle. Erlotinib was administered from Day 2 to Day 15 of each cycle. After the 4 cycles of chemotherapy were completed, erlotinib was administered daily as a single agent until progression, refusal, toxicity, or death.

Patients were evaluated for safety at designated time points. All adverse events spontaneously reported, elicited, or observed by the investigators were recorded.

Radiological evaluations to assess the patient for response and disease progression were performed at designated time points.

Number of Patients (planned/analyzed):

Planned: 140; actual 143; 72 (Treatment Arm A), 71 (Treatment Arm B)

Analyzed: Efficacy and Safety population = 137; 69 (Treatment Arm A), 68 (Treatment Arm B)

Diagnosis and Main Criteria for Inclusion:

The main inclusion criteria were histologically or cytologically documented advanced (stage IIIB or IV) NSCLC; at least 1 of the 2 EGFR tests (IHC or FISH) must have been positive; radiologically measurable or evaluable disease; adequate hematopoietic, hepatic, and renal function; and accessibility for repeat dosing and follow-up.

The main exclusion criteria were: prior or concurrent anticancer therapy (surgery, radiation, chemotherapy, or molecularly-targeted therapy) for advanced NSCLC, with the exception of surgical resection of an isolated brain metastasis and palliative radiation therapy; other malignancies; uncontrolled brain metastases; gastrointestinal abnormalities; ocular inflammatory or infectious conditions; peripheral neuropathy ≥ grade 2; significant cardiac disease (including uncontrolled high blood pressure, unstable angina, congestive heart failure, myocardial infarction within the 3 months prior to randomization or serious cardiac arrhythmia requiring medication); and active infection or serious underlying medical condition.

Test Product, Dose and Mode of Administration, Batch Numbers:

Erlotinib, 150 mg, 100 mg, and 25 mg oral tablets

Lot numbers US: 150 mg (lot [redacted]), 150 mg (lot [redacted]), 100 mg (lot [redacted]), 100 mg (lot [redacted]), 100 mg (lot [redacted]), 25 mg (lot [redacted]), 25 mg (lot [redacted])

Lot numbers UK: 150 mg (lot [redacted]), 100 mg (lot [redacted]), 25 mg (lot [redacted])

Reference Therapy, Dose and Mode of Administration, Batch Numbers:

Paclitaxel, 200 mg/m^2 via a 3-hour infusion Day 1 every 21 days

Carboplatin AUC 6, IV on Day 1 every 21 days

Lot numbers: Not applicable; commercial supply of paclitaxel and carboplatin were used by investigational sites.

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Duration of Treatment:

In the single-agent erlotinib arm (Arm A), patients received daily erlotinib until disease progression was documented radiographically, the patient had symptomatic progression, the patient experienced intolerable toxicity to study drug, the patient refused additional therapy, or until death occurred.

In the erlotinib + chemotherapy arm (Arm B), erlotinib was intercalated with 4 cycles of chemotherapy, which were given according to current standards. After the 4 cycles of chemotherapy were completed, erlotinib was administered daily as a single agent until disease progression was documented radiographically, the patient had symptomatic progression, the patient experienced intolerable toxicity, the patient refused additional therapy, or until death occurred.

Criteria for Evaluation:

Safety

All patients who received at least 1 dose of study drug (chemotherapy or erlotinib) were considered evaluable for all safety analyses.

Efficacy

All patients who received any study therapy (chemotherapy or erlotinib) were included in the efficacy analyses of PFS and overall survival. Patients were classified by PFS status at 6 months. Six-month PFS rates were calculated for each treatment arm, with corresponding 95% confidence intervals. In addition, Kaplan-Meier estimates of PFS and overall survival were constructed for each treatment arm.

Statistical Methods:

The primary statistical objectives of this randomized, phase 2 study was to assess, in parallel, the efficacy of 2 erlotinib-containing regimens in first-line NSCLC patients with EGFR protein overexpression and/or increased *EGFR* gene copy numbers, and to determine the best of these 2 regimens for testing in future studies. The statistical analysis plan did not include formal comparisons between the 2 treatment arms. The treatment with the best 6-month PFS rate was selected as the principal determinant of superiority, unless other considerations such as treatment differences in overall survival or toxicities were compelling.

Summary and Conclusions:

Summary of Efficacy:

The demographic and baseline characteristics of patients in the erlotinib and CP + erlotinib arms were similar, with the exception of a greater proportion of females in the erlotinib arm compared with the CP + erlotinib arm (61% vs 44%, respectively) and a greater percentage of current smokers in the erlotinib arm (35%) compared with the CP + erlotinib arm (23%). Although the majority of patients were Caucasian, there was representation across a range of ethnic populations. Most patients had stage IV NSCLC and had adenocarcinoma histology. Overall 11% of patients had tumors carrying an EGFR activating mutation, with the majority of these consisting of exon 19 deletions. In addition, 20% of patients had tumors with activating mutations in the KRAS gene.

The 6-month progression-free survival (PFS) rate in the erlotinib arm was 30.7% and was 26.4% in the CP + erlotinib arm. Median PFS in the erlotinib arm was 2.69 months and was 4.57 months in the CP + erlotinib arm with the Kaplan-Meier PFS curves crossing each other after 5 – 6 months. The 6-month PFS rate for the sensitivity analysis was 39.0 % for the erlotinib arm and 19.1% for the CP + erlotinib arm.

In the erlotinib arm, the 6-month PFS rate was higher for females, in never smokers and former smokers compared with current smokers, for adenocarcinoma histology, in the presence of RASH during therapy, and for tumors with EGFR FISH positivity, EGFR activating mutation, or KRAS wild-type genotype. Similar differences were observed in the CP + erlotinib arm, except that neither the presence of RASH nor increased EGFR gene copy number correlated with the 6-month PFS rate in this treatment arm. The influence of EGFR activating mutation on the 6-month PFS rate was of lesser magnitude in the

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CP + erlotinib arm.

The 12-month overall survival rate in the erlotinib arm was 58.6% and was 46.4% in the CP + erlotinib arm. In contrast to its absence of influence on 6-month PFS rate, the presence of RASH was associated with an improved OS rate at 12 months. The disease control rate (DCR) was 46.4% in the erlotinib arm and 71.6% in the CP + erlotinib arm.

Summary of Safety:

The safety results of this study are consistent with those reported in previous studies of erlotinib monotherapy and erlotinib given in combination with chemotherapy.

The most common adverse events associated with erlotinib are rash, diarrhea, and, to a lesser extent, fatigue and nausea. These events are generally of mild or moderate severity. The addition of chemotherapy does not appear to exacerbate the erlotinib toxicities, nor does coadministration of erlotinib appear to exacerbate the adverse events known to be associated with chemotherapy, which include nausea, vomiting, alopecia, fatigue, weight decrease, and anorexia.

The abnormal laboratory values observed in the erlotinib arm were consistent with those observed in other clinical studies of erlotinib monotherapy, with no notable hematological toxicity. Patients in the CP + erlotinib arm experience the known hematological toxicity associated with chemotherapy.

Conclusions:

Although a direct comparison of the respective efficacies of the erlotinib and CP + erlotinib regimens was not a component of the analysis plan for this study, one objective was to determine a superior regimen for subsequent evaluation. This assessment incorporated the composite determinations of efficacy and safety. In both treatment arms, no unexpected toxicities were revealed in comparison with previous studies with these agents administered individually or in combination, and the relative safety profiles of the erlotinib and intercalated CP + erlotinib regimens has not been a significant determinant for identifying a superior regimen. Although supported by pre-clinical studies with erlotinib in cell culture and analogous pre-clinical studies with other tyrosine kinase inhibitors combined with cytotoxic agents, as well as preliminary phase 1 studies, intercalated therapy of erlotinib and cytotoxic chemotherapy was not clearly superior to erlotinib alone. The added value of sequentially administered erlotinib with CP over CP alone was not evaluated in this study.

This study demonstrated the feasibility and value of biomarker evaluation to select patients who might derive particular benefit from signaling-based therapies. Consistent with findings in second-line advanced NSCLC and in maintenance therapy for first-line advanced NSCLC (SATURN), the evaluation tumor samples for EGFR mutation identifies patients who are able to derive particular benefit from erlotinib monotherapy. The predictive value of the mutation appeared to be dependent on the treatment, as it was of a lesser magnitude for patients who received the CP + erlotinib regimen.

In summary, erlotinib therapy is feasible and well tolerated in patients with newly diagnosed advanced NSCLC with EGFR expression, and in this setting erlotinib has a composite efficacy and safety profile superior to intercalated CP + erlotinib. This study provides further definition of patient populations that may derive particular benefit from erlotinib and intercalated CP + erlotinib therapy.

Date of the Report: 20 MAY 2010