2 STUDY SYNOPSIS

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

Title of Study:

An Open-Label Study to Characterize the Pharmacokinetic Parameters of Erlotinib (Tarceva®, OSI-774) in Cancer Patients with Advanced Solid Tumors with Adequate and Moderately Impaired Hepatic Function

Investigators:

Patients were enrolled at 5 of 6 initiated centers: [redacted] (Dr [redacted]), [redacted] (Dr [redacted]), [redacted] (Dr [redacted]), [redacted] (Dr [redacted]), and the [redacted] (Dr [redacted]). Complete addresses are provided in **Appendix 16.1.4**.

Publication (reference):

O'Bryant C, Eckhardt S, Hariharan S, Leong S, Belani C, Ramanathan R et al. An open-label study to characterize the pharmacokinetic (PK) parameters of erlotinib in patients with advanced solid tumors with adequate or moderately impaired hepatic function. Eur J Cancer Suppl 2006; 4(12):126-7 [Abstract 412].

Studied Period:	Phase of Development: 1
Date first patient started therapy: 22 AUG 2005 Date last patient registered: 04 APR 2007 Database lock: 25 JUN 2007	

Objectives:

The primary objective of this study was to compare the pharmacokinetic parameters of a single oral 150 mg dose of erlotinib in cancer patients with moderate hepatic impairment with the same dose in cancer patients with adequate hepatic function.

The secondary objectives of this study were to evaluate the safety of a single oral 150 mg dose of erlotinib in cancer patients with moderate hepatic impairment and to evaluate erlotinib protein binding in cancer patients with moderate hepatic impairment.

Methodology:

This was a multicenter, open-label, 2-arm study comparing pharmacokinetic parameters of erlotinib in cancer patients with adequate hepatic function with cancer patients with moderate hepatic impairment. Patients received a single 150 mg dose of erlotinib on Day 1 followed by 96 hours of plasma sampling, during which time no drug was given, for pharmacokinetic and protein-binding studies.

Starting on Day 5, patients could elect to continue receiving daily erlotinib in the maintenance phase of the study.

Number of Patients (planned/analyzed):

Planned: 42; 21 evaluable cancer patients with moderate hepatic impairment and 21 evaluable cancer patients with adequate hepatic function.

Analyzed: 39 enrolled, 36 evaluable: 15 evaluable cancer patients with moderate hepatic impairment and 21 evaluable cancer patients with adequate hepatic function.

Diagnosis and Main Criteria for Inclusion:

Patients were nonsmokers, 18 years of age or older, with histologically confirmed, advanced solid tumors, an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, a predicted life expectancy of at least 12 weeks, and adequate hematopoietic and renal function. Patients were required to have either adequate hepatic function (total bilirubin ≤ upper limit of normal [ULN] and ALT/AST ≤ 1.5 x ULN) or moderate hepatic impairment (Child-Pugh Score of 7 – 9 points). All patients enrolled in the study provided written informed consent.

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

Tarceva® (erlotinib) 150 mg and 100 mg tablets; administered orally

Lot numbers: [redacted] and [redacted] (150 mg); [redacted] (100 mg)

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

None

Duration of Treatment:

Patients received a single 150 mg dose of erlotinib on Day 1. Following final plasma sample collection on Day 5, patients could enter the maintenance phase of the study and elect to continue erlotinib therapy until disease progression or unacceptable toxicity.

Criteria for Evaluation:

Pharmacokinetics

Plasma samples were analyzed for total erlotinib and its metabolites OSI-420/413. Pharmacokinetic parameters were calculated for total erlotinib for each patient following the Day 1 dose using noncompartmental methods. Parameters included C_{max}, AUC_{0-t}, AUC_{0-inf}, percent of AUC extrapolated, T_{max}, $T_{1/2\lambda z}$, Cl/F, and Vz/F.

To assess the influence of moderate hepatic dysfunction on erlotinib plasma protein binding, the percent of erlotinib bound to plasma proteins was determined by an ultracentrifugation method.

Safety

Frequency of adverse events and changes in biochemistry laboratory parameters were analyzed.

Statistical Methods:

The sample size of 21 evaluable cancer patients with moderate hepatic impairment and 21 evaluable cancer patients with adequate hepatic function was calculated based on the AUC_{0-24} and C_{max} pharmacokinetic data from Study A248-004 (single-agent erlotinib, phase 1 dose escalation in cancer patients). A sample size of 21 patients per cohort would allow the estimation of the ratio of geometric means with 90% confidence intervals of ± 35%. However, due to a limited number of patients available who met the criteria for moderate hepatic impairment, the study was stopped with 15 evaluable hepatic-impaired patients enrolled.

Pharmacokinetic parameter estimates were summarized using descriptive statistics: median, minimum, and maximum. In addition, geometric means were calculated for AUC_{0-t}, AUC_{0-inf}, and C_{max}. Patients were evaluable if sufficient data were available to adequately characterize AUC_{0-t} and C_{max}.

For the assessment of a pharmacokinetic effect due to hepatic impairment following the 150 mg dose, 90% confidence intervals for the ratio of geometric means of moderate versus adequate hepatic function of AUC_{0-t} and C_{max} were calculated.

To evaluate the safety of erlotinib in cancer patients with moderate hepatic impairment, adverse events were displayed as patients with adequate hepatic function versus patients with moderate hepatic impairment.

Summary and Conclusions:

Patient Characteristics:

Thirty-six patients received at least 1 dose of erlotinib in the following cohorts: hepatic impaired, 15 patients; adequate hepatic function, 21 patients. Over two-thirds of the patients enrolled in the study were males (69%), and all but 5 patients (87%) were white. Over half of the patients were 40 – 64 years old, with a median age of 57 years (range 31 – 85).

There were notable differences between the 2 cohorts. There was a higher percentage of males, more patients who were black, younger patients, and patients with poorer performance status in the cohort of hepatic impaired patients compared with the patients in the adequate hepatic function cohort. Patients in the hepatic-impaired cohort weighed

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more than patients in the adequate hepatic function cohort.

Summary of Pharmacokinetics:

Although the study was stopped with 15 evaluable hepatic-impaired patients, the 90% confidence intervals for erlotinib C_{max} and AUC_{0-t} were no more than ± 33%, which was determined to be acceptable for the assessment of the primary endpoint.

The pharmacokinetics of erlotinib appeared to be similar in cancer patients with adequate and moderately impaired hepatic function. Following oral administration of erlotinib, plasma concentrations of erlotinib peaked at a median T_{max} of 2 hours in patients with adequate hepatic function and at 6 hours in patients with moderate hepatic impairment. However, T_{max} was highly variable in both cohorts and was not statistically significantly different ($P = 0.0631$). The median plasma C_{max} of erlotinib was 1.09 (90% CI: 0.980, 1.21) and 0.828 µg/mL (90% CI: 0.608, 1.06) in patients with adequate and moderately impaired hepatic function, respectively. The corresponding median AUC_{0-t} values were 29.3 (90% CI: 25.7, 33.4) versus 30.5 µg•hr/mL (90% CI: 19.9, 36.7). Median C_{max} of erlotinib was statistically significantly lower in moderately hepatic-impaired patients (90% CI for geometric mean ratio of impaired/adequate: 57.3, 95.6). However, this is consistent with the delayed T_{max} in this cohort of patients. Thus, moderate hepatic impairment did not result in a significant increase in erlotinib exposure. The pharmacokinetics of the metabolite OSI-420 were also similar in patients with adequate and moderately impaired hepatic function. The median plasma AAG concentrations and the median percent plasma protein binding of erlotinib appeared to be unaffected by moderate hepatic impairment. Based on the pharmacokinetic data from this study, erlotinib dose reductions are not required in moderately hepatic-impaired patients.

Summary of Safety:

Thirty-six patients received study drug and were included in the safety population. All but 1 patient experienced at least 1 adverse event during the study.

In general, the patients in the hepatic-impaired cohort had more baseline signs and symptoms, which were also higher in severity grade than those reported by the patients in the adequate hepatic function cohort.

The patients in the hepatic-impaired cohort had more severe adverse events (hepatic-impaired 40% vs adequate hepatic function 14%) and more serious adverse events (hepatic-impaired 73% vs adequate hepatic function 33%) than the patients in the adequate hepatic function cohort. The percentage of patients with at least 1 erlotinib-related adverse event was 67% in the hepatic-impaired cohort versus 86% in the adequate hepatic function cohort. The most frequent erlotinib-related adverse events in the hepatic-impaired cohort were dermatitis acneform and diarrhea (4 patients each, 27%), rash, vomiting, and fatigue (3 patients each, 20%). The most frequent erlotinib-related adverse events among patients with adequate hepatic function were diarrhea and nausea (10 patients each, 48%), fatigue (9 patients, 43%), anorexia (7 patients, 33%), and rash (6 patients, 29%). The percentage of grade 3 and 4 adverse events that were considered to be related to erlotinib was similar in both cohorts (hepatic impaired, 20%; adequate hepatic function, 19%).

In both cohorts, most of the adverse events were mild to moderate in severity. The hepatic-impaired cohort had a higher incidence of severe adverse events regardless of causality. Two patients in the hepatic-impaired cohort had severe diarrhea; no other single type of adverse event was severe in more than 1 patient with impaired hepatic function Among patients with adequate hepatic function, 2 had severe dermatitis acneform; no other single type of adverse event was severe in more than 1 patient with adequate hepatic function.

Nine patients died on treatment or within 30 days of their last dose, all of whom were from the hepatic-impaired cohort. Seven of these deaths were due to progressive disease, 1 was due to hepatorenal syndrome, and 1 was due to worsening liver failure. All deaths were considered to be unrelated to erlotinib therapy as assessed by the investigator. Seven patients, 5 of whom were in the hepatic-impaired cohort discontinued due to adverse events. Only 2 patients, 1 patient in each cohort, discontinued due to erlotinib-related events (1 patient with diarrhea; 1 patient with liver failure).

The most frequent serious adverse events in the hepatic-impaired cohort were small intestinal obstruction, peripheral edema, and hepatic failure (2 patients each, 13%), compared with the adequate hepatic function cohort, which were

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vomiting and nausea (2 patients each, 10%).

No patient in the adequate hepatic function cohort experienced a grade 3 or 4 blood chemistry laboratory value. In the hepatic-impaired cohort, 7 (47%) patients experienced a grade 3 or 4 blood chemistry laboratory value (ALT, AST, bilirubin, alkaline phosphatase, and albumin); 5 of these patients had no change in grade from baseline.

Considering the inherent differences in the 2 cohorts at baseline, the safety of erlotinib in cancer patients with moderate hepatic impairment appears comparable to that in patients with adequate hepatic function. There was no evidence of increased toxicity of erlotinib in patients with moderate hepatic impairment.

Conclusion:

The pharmacokinetic and safety profiles of erlotinib in moderately hepatic-impaired patients were similar to patients with adequate hepatic function. Based on the pharmacokinetic data from this study, erlotinib dose reductions are not required in moderately hepatic-impaired patients. Subsequent dose adjustment should be guided by patients' tolerability.

Date of the Report: 20 AUG 2007