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ORIGINAL ARTICLE

# Phase I and pharmacokinetic study of erlotinib (OSI-774) in combination with docetaxel in squamous cell carcinoma of the head and neck (SSCHN)

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**Abstract**
*Purpose* This phase I study determined the maximal-tolerated dose, dose-limiting toxicities, pharmacokinetics, and recommended dose of erlotinib with docetaxel.
*Patients and methods* Twenty-eight patients with head and neck cancer were enrolled. Patients were orally given erlotinib (50 mg) daily plus 35 mg/m$^2$ of docetaxel intravenously weekly × 3 every 4 weeks. Dose escalation of erlotinib was in 50-mg increments until toxicity. Pharmacokinetics were studied with LC–MS/MS, standard, and population pharmacokinetic methods.
*Results* Ninety-five courses were successfully given (median 3, range 1–6). The most frequent side effects were diarrhea, fatigue, skin rash, anemia, and hypoalbuminemia. Dose de-escalation for both erlotinib and docetaxel was due to skin rash, neutropenia and/or severe infection with docetaxel to 25 mg/m$^2$ and erlotinib to starting dose of 50 mg and re-escalation of docetaxel to 35 mg/m$^2$. Responses were observed in 4/26 evaluable patients (100 mg erlotinib). In 24 patients, the mean Cmax and AUC erlotinib values increased with dose and following cumulative dosing (days 7 and 8 vs. day1, $p < 0.05$). The CL/F (~7 L/h), V/F (~140 L), and t1/2 (~20 h) for erlotinib were similar to the reported. The mean AUC ratio of metabolite OSI-420 to erlotinib following repetitive dosing at 100 mg (+ or − docetaxel) showed a ~50% increase ($p < 0.02$), possibly suggesting self-enzyme induction. Population pharmacokinetic studies showed no significant covariate affecting erlotinib pharmacokinetics.
*Conclusions* The combination of erlotinib and docetaxel was associated with significant toxicity, which limited the amount of administered erlotinib. Dosing for phase II trials was docetaxel 35 mg/m$^2$ and erlotinib 50 mg. The reason for excessive toxicity is not clear, but not due to change in pharmacokinetics.

**Keywords** Erlotinib · Squamous cell carcinoma of the head and neck · OSI-774 · Phase I

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## Introduction

The epidermal growth factor receptor (EGFR) and its ligands EGF and TGF-alpha are involved in several cellular processes associated with malignancy including proliferation, adhesion, invasion, survival, and angiogenesis [1]. The rationale for targeting EGFR in the treatment of squamous cell cancer of the head and neck (SCCHN) is based on the observation that overexpression of EGFR leads to malignant transformation in vitro, and expression of EGFR is increased in 80–100% of SCCHNs [2, 3]. Additionally, several studies have demonstrated a relationship between degree of EGFR expression, advanced stage and prognosis, and chemosensitivity in patients with head and neck cancer [4–7]. Evidence of antitumor activity of the monoclonal antibody C225 directed against the

EGFR receptor in patients with advanced head and neck cancer supports this concept [8, 9].

Erlotinib (OSI-774; Tarceva, OSI Pharmaceuticals) is an orally active, potent, and selective inhibitor of the EGFR tyrosine kinase [10, 11]. Erlotinib inhibits EGFR-dependent proliferation of cells at submicromolar concentrations and blocks cell-cycle progression in the $G_1$ phase. Phase I studies of erlotinib established the MTD (maximal-tolerated dose) of 150 mg by mouth daily with the major toxicity being a diffuse rash and diarrhea [12]. A phase II study of erlotinib in patients with advanced head and neck cancer showed an objective response rate of 4.3% with stabilization of disease in an additional 38% of patients, suggesting a possible role for this drug in treatment of these patients [13].

One possible approach supported by both in vitro studies and clinical investigation is to combine EFGR inhibition and chemotherapy [11]. In a randomized, double-blind study comparing cisplatin alone with cisplatin in combination with cetuximab in recurrent SCCHN, tumor response was significantly higher with combination therapy [14]. In order to further evaluate whether erlotinib and chemotherapy can be used in head and neck cancer, we initiated a NCI-sponsored phase I trial with weekly docetaxel and daily erlotinib. Weekly docetaxel was chosen due to its known activity as a single agent and the possibility that this might increase dose intensity while maintaining drug effectiveness and reducing toxicity [15–18]. In addition, in breast cancer cell lines, a EGFR tyrosine kinase inhibitor when combined with a taxane overcame drug resistance of the cells [19].

The goals of the study were to determine the dose-limiting toxicity and MTD of the combination of erlotinib and docetaxel in previously treated patients with advanced and/or metastatic head and neck cancer. In addition, we determined the pharmacokinetics of erlotinib and its metabolite OSI-420 when combined with docetaxel.

## Patients and methods

### Patient eligibility

Patients eligible for this trial had pathologically confirmed recurrent or metastatic squamous cell carcinoma of the head and neck or locally advanced disease not felt curable by radiation and surgery; bidimensionally measurable disease; ECOG performance status of 0–2; age $\geq$ 18; peripheral neuropathy $\leq$ grade 2; neutrophil counts $\geq$ 1,500/μL, platelets $\geq$ 100,000 μL, normal creatinine; SGPT and SGOT $\leq$ 2μl. Patients were allowed one chemotherapy in adjuvant or neoadjuvant setting and one chemotherapy for metastatic disease. Patients were excluded if they had been treated with an EGFR inhibitor; had known brain metastases; or were pregnant or lactating. An amendment was added during the trial due to pulmonary complications, so that patients with significant pulmonary disease as defined by oxygen saturation of $\leq$90% or $CO_2 \geq$ 50 mm were not eligible. The study protocol was approved by both the National Cancer Institute and the Ohio State University Institutional Review Board, and written informed consent was obtained according to institutional and federal guidelines prior to treatment.

### Dosage and drug administration

Patients were treated on an outpatient basis with a starting dose of erlotinib of 50 mg by mouth per day on day 1 and then begun on docetaxel 35 mg/m$^2$ intravenously weekly on day 8, 15, and 22. The dose of weekly docetaxel was based on the recommended phase II dose in solid tumors [18]. Each course would consist of 28 days of erlotinib and 3 weekly doses of docetaxel. Erlotinib was to be escalated by 50 mg with a fixed dose of docetaxel until dose-limiting toxicity was reached. However, unexpected toxicity required dose de-escalation of docetaxel to 25 mg/m$^2$ with re-escalation by 5 mg/m$^2$. Additionally, erlotinib after an initial increase to 100 mg per day was reduced back to 50 mg per day due to side effects. Levels are noted in Table 1. Patients remained on study unless significant toxicity or disease progression occurred. Erlotinib and reference standards CP-396,059 and 0SI-420 for analysis were supplied by OSI Pharmaceuticals (Melville, NY).

### Toxicity and response assessment

Toxicity was assessed weekly using the National Cancer Institute Common Toxicity Criteria, version 2. DLT was defined as grade 4 myelosuppression or grade 3 or greater non-hematological toxicity or grade $\geq$3 nausea, vomiting or diarrhea despite maximal supportive treatment. Response was determined by physical examination and radiographic studies every 8 weeks while patients were on study using the RECIST criteria [20].

## Drug assay and pharmacokinetic analysis

### Plasma sampling

Serial plasma samples were collected for pharmacokinetics at the following time points. For day 1, at both dose levels of 50 and 100 mg: 0 (pre-dose), 1, 2, 4, 5, 6, 8, 12, 24 h erlotinib (OSI-774); for day 8, at both dose levels of 50 and 100 mg: 0 (pre-dose), 0.5, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, 12, 24 h after start of docetaxel infusion (erlotinib + docetaxel). In a

**Table 1** Dosing scheme of docetaxel and erlotinib in patients with squamous cell carcinoma of the head and neck

| Dose level | Docetaxel(mg/m$^2$)/ erlotinib (mg) | No. of patients | Median cycles per patient (range) | Total cycles | Dose intensity doc/erlotinib (%) | Patients requiring dose reductions/total dose reductions docetaxel:erlotinib | DLT |
|---|---|---|---|---|---|---|---|
| 1 | 35/50 | 3 | 4 (3–6) | 12 | 97.2/99.1 | 1/1:1/1 | No |
| 2 | 35/100 | 3 | 6 (2–6) | 14 | 96.0/77.3 | 2/2:2/3 | Yes |
| 2B | 25/100 | 6 | 3.5 (2–6) | 23 | 91.9/80.6 | 3/3:4/8 | Yes |
| 2C | 25/50 | 7 | 3 (1–6) | 24 | 84.7/91.5 | 4/4:3/3 | No |
| 3 | 30/50 | 6 | 2.5 (1–6) | 14 | 100.0/100.0 | 0:0 | No |
| 4 | 35/50 | 3 | 2 (2–4) | 8 | 100.0/100.0 | 0:0 | No |
| Total | | 28 | 3 (1–6) | 95 | 93.2/86.7 | 10/10:10/15 | |

subsequent amendment, at day 7 (erlotinib only) at dose level of 50 mg, additional blood samples were drawn at: 0 (pre-dose), 0.5, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, 12, 24 h to examine any potential alteration of pharmacokinetics due to sequential dosing.

## Quantification of erlotinib and its metabolite OSI-420 in patients plasma

Plasma levels of erlotinib and the active metabolite OSI-420 were analyzed by a LC–MS/MS (modified from the unpublished method of OSI Pharmaceutical Inc). The internal standard CP-396,059 was used for the assay. The specific conditions and procedures are described later.

### *Mass spectrometry*

A Perkin-Elmer Sciex API 300 triple-quadrupole mass spectrometer (Thornhill, Ontario, Canada) coupled to a Shimadzu HPLC system (Shimadzu, Columbia, MD) was used.

The mass spectrometer was operated using an electrospray ionization (ESI) with an ionspray voltage of +5,000 V. The multiple-reaction-monitoring (MRM) mode analysis was used with nitrogen as the collision gas. The curtain gas (nitrogen) flow and the ionspray flow were set at 0.6 and 0.9 L/min, respectively. The pressure in the collision cell was set at 0.29 Pa. The orifice voltage and ring voltage was set to +15 and +300 V, respectively. A dwell time of 500 ms and a pause time of 5 ms between scan were typically used to monitor the following precursor/product ion pairs: 394.3/278.0 for OSI-774, 380.0/278.0 for OSI-420, and 408.4/292.0 for CP-396059. The mass spectrometer was tuned by injection of a fresh standard solution of OSI-774 at 10 ng/mL in the HPLC mobile phase as described previously.

### Sample preparation and assay procedure

Human plasma, 0.2 mL each, spiked with various amounts of erlotinib and OSI-420 standards was added to 16 × 100 mm screw-cap tubes. A 750-μL aliquot of the internal standard solution (30 ng/mL) was added into tubes. After vortexing for 5 s, 4 mL of t-butyl methyl ether was added into tubes. The mixture was shaken at high speed for 15 min and then centrifuged at 3000 g for 5 min. The organic layer was transferred to a clean 13 × 100 mm culture tube and evaporated to dryness under a stream of nitrogen. The residue was reconstituted with 200 μL of the mobile phase, and the solution was transferred into injection vials and capped. A 50-μL aliquot was injected into a LC/MS system for analysis.

### Chromatographic conditions

An isocratic elution system was used in the determination of erlotinib and OSI-420 concentrations in human plasma. The mobile phase used consisted of 70% methanol and 30% of 10 mM ammonium formate in water (pH = 4.80). The mobile phase was delivered at a flow rate of 0.2 mL/min to a Thermo Beta Basic C8 5-μm column (50 cm × 2.1 mm; Thermo Hypersil-Keystone, Bellefonte, PA), which was coupled to a 2-μm pre-column filter (Thermo Hypersil-Keystone, Bellefonte, PA). The total run time was 5 min. The LC eluate was introduced into the API source at 10 μL/min after a 95:5 (LC/MS) split.

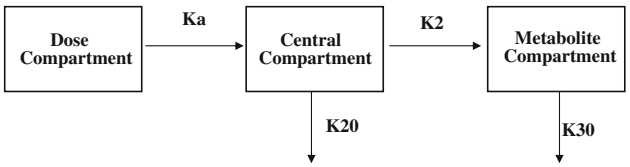
### Data analysis

All of the plasma concentration–time data were analyzed by WinNonlin computer software (Pharsight, Mountain View, CA), using both non-compartment and compartment methods. For more detailed population pharmacokinetic data analysis, the non-linear mixed-effect modeling (NONMEM) computer software (Version VI, GloboMax, Hanover, MD) was used. This method entails the incorporation of patient covariates screening to build a covariate-based model for dose optimization. Pharmacokinetic (PK) modeling was done for both parent compound and metabolite to investigate the possible mechanism for metabolite accumulation. Statistics were performed using appropriate paired and unpaired *t* test with standard methods.

Pharmacokinetics analysis using NONMEM

Population pharmacokinetic approach was used to analyze plasma concentrations of erlotinib and OSI-420 on all patients enrolled in the pharmacokinetic studies using NONMEM. Exploratory data analysis was undertaken to examine the basic structure of the concentration–time profile and to identify any outliers. A one-compartment model linking to a metabolite compartment model (shown below) with a first-order input was used for evaluation on the basis of parameter estimates, residual variability, objective function value, and goodness-of-fit.

*Model*




The appropriate structural model was used for covariate analysis that was performed on the pharmacokinetic parameters by adding the covariates incrementally. Covariates tested were age, weight, dose, body mass index, gender, total bilirubin, and creatinine clearance. CLcr values were calculated using the Cockroft–Gault formula. Any calculated CLcr values that was above 140 mL/min was fixed to 140 mL/min.

A reduction of objective function value of 6.63 was considered significant ($p = 0.01$) for the covariate assuming that the change in objective function values follows a chi-square distribution. The first-order conditional estimation method with interaction (FOCE-INT) was employed for all model runs.

## Results

Twenty-eight patients participated in this study with all patients evaluable for toxicity. The demographics are shown in Table 2. Nineteen patients were men with nine women and a median age of 58. Twenty of the 28 patients had a good performance status of 0–1, and nineteen patients were chemotherapy naive. Locoregional recurrence was present in eight patients, seven patients had metastatic disease, and 13 patients had both.

Toxicity

Ninety-five courses were given with a median of three courses per patient (range 1–6). The most frequent side effects (Table 3) seen in all dose levels were diarrhea, fatigue, skin rash, anemia, and hypoalbuminemia. A mild peripheral sensory neuropathy was also seen in several patients. One episode of progressive dyspnea with X-ray changes prompted a change in eligibility requirements excluding patients with significant pulmonary disease.

**Table 2** Patient characteristics

| | |
|---|---|
| Age (median) | 58 |
| Range | 34–78 |
| Sex | |
| M | 19 |
| F | 9 |
| Performance | |
| 0 | 4 |
| 1 | 16 |
| 2 | 8 |
| Disease | |
| Local regional recurrence | 8 |
| Metastatic | 7 |
| Both | 13 |
| Prior therapy | |
| Surgery alone | 1 |
| Surgery and radiation | 16 |
| Surgery, radiation and chemotherapy | 11 |

Dose escalation was limited due to several significant toxicities, which occurred during the first several therapy courses. A patient treated at the second dose level with docetaxel 35 mg/m$^2$ and erlotinib 100 mg died suddenly of an infection associated with mild neutropenia and a second patient at this level had a grade 3 rash requiring dose reduction. Based on the recommendations of the NCI, the dose of docetaxel was decreased to 25 mg/m$^2$ with erlotinib 100 mg, but significant toxicity again occurred. At this dose level, there were two potential dose-limiting toxicities with grade 3 rash and grade 3 acute renal failure, and for the next level, the erlotinib was reduced to 50 mg per day. Subsequent patients were then treated with erlotinib at 50 mg per day with docetaxel at 30 mg/m$^2$ with return to the original starting dose of docetaxel 35 mg/m$^2$ and erlotinib 50 mg. This dose level was established as the dose recommended for further clinical trials of this combination.

Responses

There were four partial responses in 26 evaluable patients. All responses were of short duration and were seen when erlotinib was given at 100 mg per day. Two of three patients received docetaxel 35 mg/m$^2$ and two of five patients received docetaxel 25 mg/m$^2$. Of the six patients treated at the recommended phase II dose of erlotinib

**Table 3** Summary of most frequent (>25%) adverse events by dose level (values are numbers of patients)

| Dose level | 1 | | 2 | | 2B | | 2C | | 3 | | 4 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Docetaxel (mg/m2)/erlotinib (mg) | 35/50 | | 35/100 | | 25/100 | | 25/50 | | 30/50 | | 35/50 | |
| Number of patients | $n = 3$ | | $n = 3$ | | $n = 6$ | | $n = 7$ | | $n = 6$ | | $n = 3$ | |
| Adverse event type | Any | Grade 3/4 | Any | Grade 3/4 | Any | Grade 3/4 | Any | Grade 3/4 | Any | Grade 3/4 | Any | Grade 3/4 |
| Alopecia | 0 | 0 | 0 | 0 | 1 | 0 | 3 | 0 | 0 | 0 | 1 | 0 |
| Anorexia | 2 | 0 | 1 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Cough | 2 | 1 | 1 | 0 | 2 | 0 | 4 | 0 | 1 | 0 | 0 | 0 |
| Dehydration | 0 | 0 | 2 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Diarrhea | 3 | 0 | 3 | 0 | 5 | 0 | 2 | 1 | 1 | 0 | 2 | 0 |
| Dry skin | 3 | 0 | 2 | 0 | 5 | 0 | 5 | 0 | 1 | 0 | 0 | 0 |
| Dyspnea | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |
| Edema | 2 | 0 | 2 | 0 | 3 | 0 | 3 | 0 | 1 | 0 | 0 | 0 |
| Fatigue (lethargy, malaise, asthenia) | 3 | 1 | 3 | 1 | 5 | 1 | 4 | 2 | 2 | 1 | 3 | 2 |
| Headache | 1 | 0 | 0 | 0 | 4 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Hemoglobin | 2 | 0 | 3 | 0 | 6 | 1 | 6 | 1 | 4 | 0 | 2 | 0 |
| Hyperglycemia | 0 | 0 | 0 | 0 | 2 | 0 | 5 | 0 | 1 | 0 | 0 | 0 |
| Hypoalbuminemia | 3 | 0 | 3 | 1 | 6 | 1 | 5 | 0 | 1 | 0 | 0 | 0 |
| Hypocalcemia | 1 | 0 | 0 | 0 | 2 | 0 | 4 | 0 | 1 | 0 | 0 | 0 |
| Hyponatremia | 1 | 1 | 2 | 1 | 2 | 1 | 3 | 0 | 1 | 0 | 0 | 0 |
| Hypotension | 2 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Keratitis | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Leukocytes (total WBC) | 1 | 0 | 2 | 1 | 2 | 0 | 1 | 0 | 1 | 1 | 1 | 0 |
| Lymphopenia | 3 | 3 | 3 | 3 | 2 | 2 | 5 | 3 | 3 | 3 | 0 | 0 |
| Mouth dryness | 2 | 0 | 1 | 0 | 2 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Myalgia (muscle pain) | 1 | 0 | 1 | 0 | 2 | 0 | 2 | 0 | 1 | 0 | 1 | 0 |
| Nausea | 3 | 0 | 2 | 0 | 2 | 0 | 3 | 1 | 2 | 0 | 1 | 0 |
| Neuropathy-sensory | 2 | 0 | 1 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Pruritus | 2 | 0 | 2 | 0 | 3 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| Rash/desquamation | 1 | 0 | 3 | 1 | 4 | 1 | 5 | 0 | 2 | 0 | 2 | 0 |

50 mg and docetaxel 35 mg/m$^2$, three patients had stable disease and three patients showed disease progression.

## Pharmacokinetics of erlotinib and metabolite

A composite set of representative plasma concentration–time profiles of erlotinib (OSI-774) and its active metabolite OSI-420 following treatment on day 1 and day 8 is shown in Fig. 1. As shown, plasma concentrations peaked rapidly at approximately 3–4 h post-dose. This followed a mono-exponential decline with time. Plasma concentration–time profiles of erlotinib can be fitted well with a one-compartment model with first-order absorption and first-order elimination using WinNonlin software.

The relevant pharmacokinetic parameters of the parent drug and metabolite were computed from 24 patients, who have drug concentration records from each dose levels at day 1 ($n = 16$), day 7 (n = 8), and day 8 ($n = 9$), and the results are shown in Tables 4a and b. As shown, mean plasma Cmax and AUC values were proportional to doses between 50 and 100 mg, indicating dose-independent kinetics of erlotinib (Table 4a). The CL/F (~8 L/h), V/F (150-170 L), and t1/2 (15–19 h) for erlotinib were similar to literature reports with single agent. Erlotinib plasma concentrations appeared to have reached a steady state following once a day oral administration of erlotinib for 7–8 days as indicated by similar exposure level between days 7 and 8. There was drug accumulation following repetitive dosing, as evidenced by higher Cmax and AUC values on day 7 and day 8 relative to day 1 on the 50- and 100-mg dose ($p < 0.05$ paired or non-paired $t$ test).

The mean ratio for both AUC and Cmax values for the major metabolite, OSI-420, and erlotinib was approximately 1/10, suggesting approximately 10% of the drug was converted to the metabolite. Initially, we have found that the mean ratio of Cmax and AUC values of the metabolite to the parent drug after docetaxel administration showed statistically higher values (at least 50% increase,

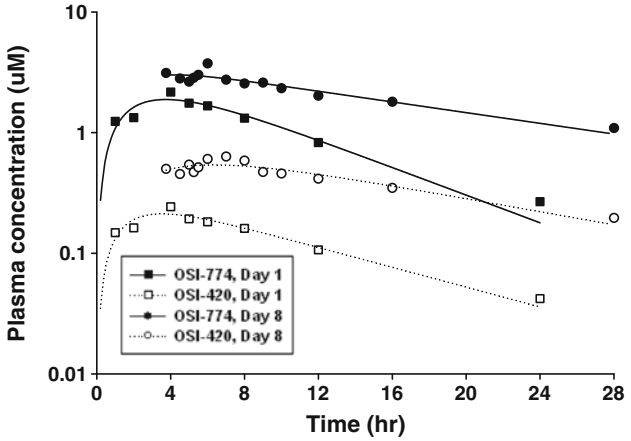



**Fig. 1** A set of representative plasma concentration–time profiles of erlotinib (OSI-774) and OSI-420 on day 1 and day 8 at 100-mg dose

$p < 0.05$) [21]. These changes might be caused by docetaxel or repetitive dosing of erlotinib itself. In order to sort out these effects, in the subsequent amendment, we performed pharmacokinetics of erlotinib and OSI-420 in six additional patients on day 7. Again, there was a trend of drug accumulation due to repetitive dosing. The mean AUC metabolite to drug ratio, however, did not show a significant increase, when comparing with the data on day 1, using unpaired $t$ test of all evaluated patients; however, there was a significant increase between day 1 and day 7 and between day 1 and day 8 ($p < 0.05$) using paired $t$ test. Similarly, comparing the same between day 7 and day 8, there was no statistical difference. On the other hand, there is a consistent higher AUC metabolite to drug ratio between day 1 and the expanded day 8 ($n = 14$) data, supporting that repetitive dosing of erlotinib induces its metabolism to OSI- 420.

## Population PK analysis

Using population pharmacokinetic analysis, the renal clearance, CL/F was found to be 5.82 L/h, which was similar to that from the compartment analysis and from the

**Table 4** Relevant pharmacokinetic parameters

| Day | Erlotinib dose level | Tmax (h) | Cmax (μM) | $AUC_{0-24\ h}$ (μM *h) | $AUC_{o-\infty}$ (μM*h) | V/F L (L) | CL/F (L/h) | $t_{1/2\ h}$ (range) |
|---|---|---|---|---|---|---|---|---|
| a. Erlotinib in patients | | | | | | | | |
| 1 | 50 mg ($N = 16$) | 4.0 (1.0–8.0) | 1.17 ± 0.61 | 12.49 ± 6.38 | 18.37 ± 8.34 | 147 ± 73 | 8.59 ± 4.52 | 14.76 ± 11.57 (4.1–42) |
| 1 | 100 mg ($N = 9$) | 2.0 (1.0–8.0) | 1.82 ± 0.60 | 21.89 ± 6.41 | 37.21 ± 14.64 | 174 ± 79 | 8.10 ± 3.89 | 18.82 ± 15.09 (6.0–48.) |
| 7 | 50 mg ($N = 8$) | 2.3 (0.5–8.0) | 1.84 ± 0.62 | 24.91 ± 9.33 | NA | NA | NA | NA |
| 8 | 50 mg ($N = 14$) | 1.5 (0.0–6.0) | 1.64 ± 0.68 | 20.48 ± 11.50 | NA | NA | NA | NA |
| 8 | 100 mg ($N = 9$) | 3.0 (0.0–24.0) | 2.78 ± 1.22 | 45.51 ± 23.69 | NA | NA | NA | NA |

| Day | Erlotinib dose l level | Tmax (h) | Cmax (μM) | $AUC_{0-24\ h}$ (μM *h) | $Cmax_{OSI-420}$/ $Cmax_{-erlotinib}$ | $AUC_{OSI-420}$/ $AUC_{erlotinib}$ |
|---|---|---|---|---|---|---|
| b. OSI-420 in patients | | | | | | |
| 1 | 50 mg ($N = 16$) | 4.5 (1.0–8.0) | 0.126 ± 0.075 | 1.182 ± 0.604 | 0.107 ± 0.037 | 0.0920 ± 0.0297 |
| 1 | 100 mg ($N = 9$) | 4.0 (1.0–8.0) | 0.177 ± 0.068 | 2.202 ± 0.742 | 0.098 ± 0.019 | 0.0982 ± 0.0217 |
| 7 | 50 mg ($N = 8$) | 3.0 (0.5–8.0) | 0.177 ± 0.072 | 2.735 ± 1.198 | 0.094 ± 0.023 | 0.1055 ± 0.0364 |
| 8 | 50 mg ($N = 14$) | 1.8 (0.5–24.0) | 0.187 ± 0.093 | 2.247 ± 1.353 | 0.113 ± 0.031 | 0.1084 ± 0.0308 |
| 8 | 100 mg ($N = 9$) | 24.0 (3.0–24.0) | 0.425 ± 0.275 | 7.23 ± 5.11 | 0.141 ± 0.050* | 0.1423 ± 0.0431* |

Tmax data are expressed as median (range), and data of all other parameters are presented as mean ± SD

*NA* not applicable

* Significant compared to day 1 at the same dose at $p < 0.05$ using paired $t$ test

**Table 5** Population pharmacokinetic parameter estimates of erlotinib and OSI-420 from model for both parent drug and metabolite

| Model Parameters | Estimate | SE | RSE (%) |
|---|---|---|---|
| Oral absorption rate, Ka ($h^{-1}$) | 1.04 (FIX) | NA | NA |
| Erlotinib elimination rate, K20 ($h^{-1}$) | 0.0321 | 0.0151 | 47.0 |
| OSI-420 production rate, K23 ($h^{-1}$) | 0.00187 | 0.000678 | 36.3 |
| Erlotinib oral clearance, CL/F (L/h) | 5.82 | 1.35 | 23.2 |
| OSI-420 Elimination Rate, K30 ($h^{-1}$) | 3.01 | 0.979 | 32.5 |
| Between-subject variability, Ka | 2.86 | 1.27 | 44.4 |
| | CV = 406% | | |
| Between-subject variability, K20 | 0.551 | 0.432 | 78.4 |
| | CV = 85.7% | | |
| Between-subject variability, K23 | 0.144 | 0.212 | 147 |
| | CV = 39.4% | | |
| Between-subject variability, CL/F | 0.216 | 0.113 | 52.3 |
| | CV = 49.1% | | |
| Between-subject variability, K30 | 0.0945 | 0.201 | 213 |
| | CV = 31.5% | | |
| OSI-774 Residual variability, proportional | 0.161 | 0.0153 | 9.5 |
| | CV = 40.1% | | |
| OSI-420 Residual variability, proportional | 0.164 | 0.0190 | 11.6 |
| | CV = 40.5% | | |

For exponential between-subject variability: $CV = [\exp(\text{variance}) - 1]^{1/2} \times 100$

For proportional residual variability: $CV = (\text{variance})^{1/2} \times 100$

Residual standard error (RSE) = SE/estimate × 100

literature report. Significant variability was found in some pharmacokinetic parameters. Among the tested covariates, none was found to affect erlotinib and OSI-420 pharmacokinetic parameters, based on the objective function criteria. The typical population pharmacokinetic parameter estimates and their 90% confidence interval (90% CI), obtained from the final erlotinib model, are presented in Table 5.

## Discussion

This phase I study evaluated the toxicity and pharmacokinetics of the combination of the active single-agent docetaxel and the reversible tyrosine kinase inhibitor of the EGFR receptor erlotinib in patients with SCCHN. Utilizing the weekly docetaxel with daily erlotinib, we encountered significant toxicity that limited our ability to combine these two drugs at optimal doses. Patients did not tolerate erlotinib in doses greater than 50 mg per day. Toxicities seen included those common to erlotinib when used as a single agent but also included idiosyncratic reactions including an infectious death and acute renal failure. The dose of erlotinib, which appears tolerable, was markedly lower than the phase II dose of this drug used as a single agent. Moreover, although the number of patients treated was small, responses were only seen with erlotinib at 100 mg per day when combined with docetaxel.

Our population pharmacokinetic analysis did not find any of the tested covariates, including age, weight, dose, body mass index, gender, total bilirubin, and creatinine clearance affecting the pharmacokinetic parameters of erlotinib or OSI-420. There appears to be a trend of drug accumulation and increase of drug metabolism to OSI-420 on repetitive dosing, but this change of metabolism is probably not due to combination with docetaxel. Though toxicity does not appear to be due to drug interaction, we did not evaluate the effect of erlotinib on docetaxel kinetics.

The difficulty in combining erlotinib with docetaxel in optimum dosing has been noted before. In a phase I study using daily erlotinib and every 3 weeks docetaxel, recommended phase II doses were 60–70 mg/m$^2$ of docetaxel and 100 mg of erlotinib orally daily [22] or 200 mg for days 2–16 every 3 weeks [23]. Toxicity-limiting dosage included febrile neutropenia. The explanation for the toxicity was not due to significant pharmacokinetic interactions.

An additional phase I study of patients with solid tumor with no prior taxane exposure used full-dose erlotinib at 150 mg by mouth daily and escalating doses of docetaxel from 20 to 35 mg/m$^2$ given weekly [24]. Ten patients tolerated the first course with docetaxel at 35 mg/m$^2$; however, patients who received repetitive doses of this amount developed significant diarrhea, mucositis, and neutropenia. This observation of cumulative toxicity in patients was similar to ours and led to recommending docetaxel 30 mg/m$^2$ and erlotinib 150 mg for phase II trials.

The original intent of this study was to establish that docetaxel and erlotinib could be given safely together in

doses thought to have a synergistic antitumor effect. From prior studies, the dose necessary to inhibit EGFR was 100 mg or greater, a dose we could not maintain with higher doses of docetaxel in our patient population. There is no explanation for the difference in our ability to combine the two drugs when compared to previous phase I trials other than the difference in patient populations. Although we did see responses in our patients, the durations were short and there were no responses with docetaxel at 35 mg/m$^2$ with erlotinib at 50 mg. Thus, we cannot recommend a further trial of this schedule and combination in SCCHN.

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**Conflict of interest** The authors have no significant conflict of interest.

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