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Phase I and Pharmacologic Study of OSI-774, an Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor, in Patients With Advanced Solid Malignancies

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Purpose: **To assess the feasibility of administering OSI-774, to recommend a dose on a protracted, continuous daily schedule, to characterize its pharmacokinetic behavior, and to acquire preliminary evidence of anticancer activity.**

Patients and Methods: **Patients with advanced solid malignancies were treated with escalating doses of OSI-774 in three study parts (A to C) to evaluate progressively longer treatment intervals. Part A patients received OSI-774 25 to 100 mg once daily, for 3 days each week, for 3 weeks every 4 weeks. Part B patients received OSI-774 doses ranging from 50 to 200 mg given once daily for 3 weeks every 4 weeks to establish the maximum tolerated dose (MTD). In part C, patients received this MTD on a continuous, uninterrupted schedule. The pharmacokinetics of OSI-774 and its *O*-demethylated metabolite, OSI-420, were characterized.**

Results: **Forty patients received a total of 123 28-day courses of OSI-774. No severe toxicities precluded dose escalation of OSI-774 from 25 to 100 mg/d in part A. In part B, the incidence of severe diarrhea and/or cutaneous toxicity was unacceptably high at OSI-774 doses exceeding 150 mg/d. Uninterrupted, daily administration of OSI-774 150 mg/d represented the MTD on a protracted daily schedule. The pharmacokinetics of OSI-774 were dose independent; repetitive daily treatment did not result in drug accumulation (at 150 mg/d [average]: minimum steady-state plasma concentration, 1.20 ± 0.62 μg/mL; clearance rate, 6.33 ± 6.41 L/h; elimination half-life, 24.4 ± 14.6 hours; volume of distribution, 136. 4 ± 93.1 L; area under the plasma concentration-time curve for OSI-420 relative to OSI-774, 0.12 ± 0.12 μg/h/mL).**

Conclusion: **The recommended dose for disease-directed studies of OSI-774 administered orally on a daily, continuous, uninterrupted schedule is 150 mg/d. OSI-774 was well tolerated, and several patients with epidermoid malignancies demonstrated either antitumor activity or relatively long periods of stable disease. The precise contribution of OSI-774 to these effects is not known.**

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THE EPIDERMAL GROWTH factor receptor (EGFR), a type I receptor tyrosine kinase (TK) involved in the regulation of cellular differentiation and proliferation, is highly expressed by many types of human cancer and is a rational strategic target for anticancer therapeutic development.[1-3] The receptor is composed of three major domains: an extracellular ligand-binding domain, a transmembrane lipophilic segment, and a cytoplasmic protein TK domain.[1] After binding of epidermal growth factor (EGF), transforming growth factor alpha, and other activating ligands, the EGFR undergoes dimerization, which, in turn, activates the intrinsic protein TK via intermolecular autophosphorylation within its cytoplasmic domain. The tyrosine autophosphorylated region functions as a binding site for cytoplasmic messenger proteins, which thereby initiate a series of signals from the cytoplasm to the nucleus that culminate in DNA synthesis and cell division.[2]

The notion of targeting EGFR TK as a therapeutic strategy against cancer is supported by experimental evidence indicating that the dysregulation of the EGFR-mediated signal transduction pathways plays a role in tumorigenesis and cancer cell proliferation.[3] The clinical relevance of this strategy is further substantiated by the overexpression of EGFR in head and neck, breast, brain, lung, cervical, bladder, gastrointestinal, renal, and other epithelial malignancies and the evidence indicating that EGFR overexpression is a determinant of tumor aggressiveness.[3] EGFR activation can be inhibited by anti-EGFR antibodies, which block binding of endogenous ligands, as well as

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OSI-774 (OSI Pharmaceuticals, Uniondale, NY) was formerly known as CP-358,774 (Pfizer Global Research and Development, Groton, CT).

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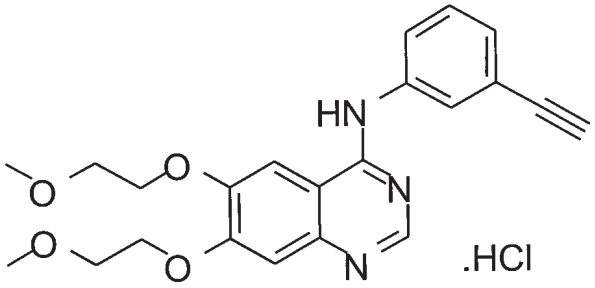

Fig 1. Structure of OSI-774.

small molecules, which results in the inhibition of downstream components of the EGFR pathway.[4] Because the activity and function of EGFR TK are necessary for receptor signaling, the development of specific small molecules that inhibit EGFR TK represents a logical therapeutic approach.[5,6]

Recently several classes of agents have been shown to be highly selective for EGFR TK and possess impressive preclinical activity against tumors that express EGFR.[5,6] Nanomolar concentrations of the quinazoline OSI-774 ([6,7-bis(2-methoxy-ethoxy)-quinazolin-4-yl]-[3-ethylphenyl]amine; OSI Pharmaceuticals, Uniondale, NY; formerly known as CP-358,774; Pfizer Pharmaceuticals, Inc, Groton, CT) (Fig 1) inhibit the activity of purified EGFR TK and EGFR autophosphorylation in intact tumor cells, with 50% inhibitory concentration values of 2 and 20 nmol/L, respectively.[6] OSI-774 is 1,000-fold more potent against EGFR TK than most other human kinases, including *c-src* and insulin receptor TK.[6] In studies of Fisher rat embryo fibroblasts, nanomolar concentrations of OSI-774 inhibited cell division induced by EGF, whereas 1,000-fold higher drug concentrations were required to block cell division stimulated by other growth factors. Nanomolar concentrations of OSI-774 also were demonstrated to inhibit growth of various EGFR-expressing cancers in vitro, which is associated with cell cycle arrest in G_1 and apoptosis.[6] In addition, treatment of mice that bear human HN5 head and neck carcinoma xenografts with OSI-774 profoundly inhibited tumor growth, with a 50% effective dose of 9.2 mg/kg/d.[7] In HN5 xenografts, OSI-774 inhibited intratumoral EGFR autophosphorylation with 50% effective doses of 9.2 and 9.9 mg/kg after intraperitoneal and oral administration, respectively. Maximum (90%) inhibition of EGFR autophosphorylation was evident 1 hour after administration of 100 mg/kg orally, EGFR autophosphorylation was reduced by 75% to 85% for at least 12 hours, and complete recovery was noted by 24 hours after treatment.[7]

Toxicology studies in both rodents and dogs revealed negligible toxicity after protracted daily administration of OSI-774 doses up to 15 mg/kg/d. At higher doses, emesis, gastric distention, and transient elevations in serum bilirubin occurred. Two of eight dogs treated with protracted daily OSI-774 doses in excess of 50 mg/kg/d developed edema, ulceration, and perforation of the cornea, and three developed azotemia. In preclinical pharmacology studies, OSI-774 was highly bioavailable (approximately 80%), and peak plasma concentrations were achieved within 2 hours after oral treatment. The agent also was demonstrated to be highly bound to plasma proteins (90% to 95%) and predominantly metabolized by the P450 microsomal isoenzyme CYP1C to an *O*-demethylated active metabolite (OSI-420). Dose-dependent pharmacokinetics were noted at OSI-774 doses that ranged from 2 to 50 mg/kg/d, but nonlinear pharmacokinetics were observed at higher doses.[8]

OSI-774 also was administered to healthy human volunteers before evaluations in cancer patients.[8] Administration of a wide range of single oral doses of OSI-774 (10 to 1,000 mg) resulted in mild to moderate toxicities, including headache and a mild, diffuse, erythematous rash at the highest dose. However, all patients treated continuously with OSI-774 400 mg/d, in two divided daily doses, developed a severe papulopustular dermatitis that involved the face, scalp, chest, back, and arms. As a result, treatment was discontinued in all patients after a maximum of nine doses. The rash resolved slowly thereafter. Other, less profound effects included diarrhea, mucositis, and transient elevation of hepatic transaminases. Pharmacokinetic studies revealed drug accumulation with protracted daily treatment, which was not predicted from single-dose studies.

The novel mechanism of action of OSI-774 as an EGFR TK inhibitor, and its impressive preclinical antitumor activity, served as the impetus for its clinical development. This phase I and pharmacokinetic study sought to evaluate the feasibility of oral OSI-774 administration on a protracted, continuous daily schedule to patients with advanced solid malignancies. The principal objectives of the study were to (1) determine the principal toxicities of OSI-774 administered on a protracted, continuous daily schedule, (2) determine the maximum tolerated dose (MTD) and recommend a dose for subsequent disease-specific evaluations, (3) characterize the pharmacokinetic behavior of OSI-774, and (4) seek preliminary evidence of antitumor activity.

PATIENTS AND METHODS

Eligibility

Patients with histologically documented advanced solid malignancies refractory to conventional therapy or for whom no effective therapy existed were candidates for this study. Eligibility criteria also included the following: (a) age 18 years or older; (b) Karnofsky performance status higher than 70% (capable of self-care); (c) life expectancy greater than 12 weeks; (d) no previous chemotherapy,

radiation therapy, or major surgical procedures within 4 weeks of entry onto the study; (e) adequate hematopoietic (absolute neutrophil count ≥ 1,500/μL, hemoglobin level ≥ 9.0 g/dL, and platelet count ≥ 100,000/μL), hepatic (total bilirubin concentration ≤ 1.5 mg/dL; AST and ALT levels ≤ two times the upper normal limit [≤ five times the upper normal limit for patients with liver metastases]), and renal (creatinine concentration ≤ 1.5 mg/dL or creatinine clearance ≥ 50 mL/min) functions; (f) no active infection or other coexisting medical problems of sufficient severity to limit compliance with the study; and (g) no malabsorption syndrome or any other disorder that would affect gastrointestinal absorption. All patients gave written informed consent in accordance with federal and institutional guidelines before treatment.

Drug Administration

OSI-774 was supplied by Pfizer Research Institute (Groton, CT) as 25-mg and 100-mg tablets. The agent was administered orally with at least 200 mL of water in the morning before breakfast. Subjects fasted for at least 2 hours before and 1 hour after treatment. The study was conducted in three parts in successive cohorts of new patients; the main objective was assessment of feasibility and toxicities, as well as determination of a recommended phase II dose of OSI-774 administered daily on a continuous, uninterrupted daily schedule.

In the first part of the study (part A), OSI-774 was administered daily for 3 days each week for 3 weeks. Courses were repeated every 4 weeks. The starting dose of OSI-774 was 25 mg, which was equivalent to one third of the toxic dose low of a single dose of the agent in healthy volunteers. At least three new patients each were treated successively with OSI-744 at dose levels of 25 mg/d, 50 mg/d, and 100 mg/d. In part B of the study, patients were treated with OSI-774 daily for 3 weeks every 4 weeks. In course 1 only, patients received a single dose of the agent on day 1, which was followed by a 2-day washout period for pharmacokinetic studies. Patients resumed treatment on day 4. The starting dose of OSI-744 in part B was to be 50 mg, provided that 100 mg was determined to be safe in part A. Dose escalation was to proceed in cohorts of at least three patients each in increments of 100%, spanning doses levels of 50 mg/d, 100 mg/d, and 200 mg/d. Thereafter, dose escalation was to be in increments of 200 mg/d in separate cohorts of new patients. Intermediate dose levels could be established to more precisely define the MTD. Once the MTD was established in part B, patients were treated with OSI-774 at this dose on a continuous, uninterrupted schedule (part C), and each 28-day period was considered one course of treatment. There was to be no further dose escalation in part C.

Successive cohorts of at least three patients were treated at each dose level in parts A, B, and C. If any patient experienced dose-limiting toxicity (DLT) during course 1, as many as three additional patients were treated. The MTD was defined as the highest dose level at which less than two of six new patients experienced DLT in course 1. DLT was defined as any grade 3 or 4 hematologic or nonhematologic toxicity, because the principal study objective was to evaluate the feasibility of protracted daily administration. Nausea, vomiting, and diarrhea of grade 3 severity were considered DLT, provided that patients had received optimal antiemetics and antidiarrheal premedication and management, and elevations of hepatic transaminases were a DLT if grade 3 toxicity lasted longer than 7 days. Toxicities were graded according to the National Cancer Institute common toxicity criteria (version 1.0). Patients who developed DLT could continue to receive treatment at a reduced dose-schedule level after recovery. Intraindividual escalation of the dose-schedule level was allowed, provided that the patient had completed at least two courses of treatment with either no or grade 1 toxicity, the patient did not experience disease progression, and the next higher dose level had previously been determined to be safe in accordance with the aforementioned criteria.

Pretreatment and Follow-Up Studies

Patient histories, including performance status, concomitant medications, physical examinations, and routine laboratory evaluations, were obtained before treatment and weekly thereafter. Routine laboratory evaluations included complete blood counts with differential, electrolytes, blood urea nitrogen, creatinine, glucose, total protein, albumin, calcium, phosphate, uric acid, alkaline phosphatase, total and direct bilirubin, AST, ALT, prothrombin and partial thromboplastin times, and urinalysis. ECGs, chest radiographs, and skin biopsies were performed before treatment and after the first course. Skin biopsies of affected areas also were performed in selected patients who developed cutaneous toxicity. For the routine skin biopsies, a 5-mm area of the back or underside of the upper arm was cleaned with an antiseptic and anesthetized with 2% lidocaine, and a 4-mm punch biopsy was obtained. The specimen was next embedded in an OCT gel (10.24% w/w polyvinylalcohol, 4.26% w/w polyethylenglycol, and 85.5% w/w non reactive ingredients), snap frozen in a methanol and dry ice bath, cut into 5-μm sections, and assessed for epidermal proliferation and histopathologic changes by a dermatopathologist.

Evaluations of measurable and assessable disease by appropriate radiologic studies, as well as an assessment of relevant tumor markers, were performed before treatment and after every other course. Patients were able to continue treatment in the absence of progressive disease. A complete response was scored if there was disappearance of all active disease on two measurements separated by a minimum period of 4 weeks, and a partial response required at least a 50% reduction in the sum of the products of the bidimensional measurements of all lesions documented by two measurements at least 4 weeks apart. A concurrent increase in the size of any lesion by 25% or more, or the appearance of new lesions, was considered disease progression.

Pharmacokinetic Sampling and Assay

To study the pharmacokinetic behavior of OSI-774 and its *O*-demethylated metabolite (OSI-420), blood was sampled during the first course in all patients. The sampling scheme differed in parts A, B, and C of the study. In part A, in which OSI-774 was administered daily for 3 days each week, blood was collected before treatment and at 2, 4, 6, 8, 12, and 24 hours after treatment on day 1; before treatment and 2, 4, 6, 8, and 12 hours after treatment on day 3; and before treatment on days 8 and 15. In part B, in which OSI-774 was administered daily for 3 weeks every 4 weeks, except in course 1, in which there was a 2-day washout period after the first dose, blood was collected before treatment and 2, 4, 6, 8, 12, 24, 36, and 48 hours after treatment on day 1; before treatment on days 4, 6, 11, and 18; and before treatment and 2, 4, 6, 8, 12, 24, 36, and 48 hours after treatment on the last treatment day (day 24). In part C, in which OSI-774 was administered daily on a continuous schedule, blood was sampled before treatment and 2, 4, 6, 8, 12, and 24 hours after treatment on day 1; before treatment on days 8, 15, and 22; and before treatment and 2, 4, 6, 8, 12, and 24 hours after treatment on day 28. The samples were centrifuged at 3,000 rpm for 15 minutes immediately after collection in a refrigerated centrifuge. Next, the plasma was transferred to a screw-capped polypropylene tube, which was frozen at −80°C.

Separation of the plasma samples for quantification of both OSI-774 and OSI-420 was accomplished by reverse-phase high-performance liquid chromatography (HPLC) after extraction in our laboratory. After

plasma samples were thawed to room temperature and vortexed, 100 μL of internal standard (OSI-597) solution was added to a 200-μL aliquot of sample in a 15-mL polypropylene extraction tube, and 5.0 mL of methyl *t*-butyl ether was added to each tube. The samples were then rotated for 10 minutes and centrifuged at 3,000 rpm for 5 minutes. The supernatant was transferred to a clean 5-mL polypropylene tube and evaporated to dryness under a gentle stream of nitrogen at room temperature.

The extracts were reconstituted with 200 μL of the mobile phase, filtered through an Alltech Microspin Nylon 66 microcentrifuge filter (Alltech Associates, Deerfield, IL), centrifuged at 6,000 rpm for 3 minutes, and transferred to glass microinserts; 75 μL were then injected into the HPLC system. The HPLC system was equipped with a Waters model no. 515 isocratic solvent delivery pump (Waters Corporation, Milford, PA), a Waters model no. 717 refrigerated autosampler, a Waters model no. 2487 dual wavelength absorbance detector, and a Waters Symmetry (4.9 mm $\times$ 150 mm, 5 μm) C_{18} column. The flow rate was 1.0 mL/min, and an aliquot of 75 μL was injected for sample analysis. Detection of the compounds of interest was at 345 nm, and the data were collected by use of the Waters Millennium chromatography data collection software. OSI-774, OSI-420, and the internal standard were separated on a Waters Symmetry (4.9 mm $\times$ 150 mm, 5 μm) C_{18} column. Samples were eluted isocratically at a flow rate of 1.0 mL/min with a mobile phase that consisted of acetonitrile and water (vol/vol, 30/70; pH 2.40). Under these conditions, the retention times for OSI-774, OSI-420, and the internal standard were 3.2, 2.1, and 5.0 minutes, respectively. Standard curves for OSI-774 and OSI-420 were prepared over a concentration range of 10.0 to 2,500 ng/mL by the addition of known amounts of OSI-774, OSI-420, and internal standard to appropriate volumes of human plasma. Plasma concentrations were determined by plotting the plasma OSI-774 and OSI-420 peak areas to that of the internal standard versus known concentrations. The lower limit of assay quantification, which was based on the extraction of 200-μL plasma samples, was 10 ng/mL for both OSI-774 and OSI-420. The performance of the assay was monitored using quality control (QC) samples at 20, 200, and 2,000 ng/mL. On each day of analysis, duplicate QC samples at each concentration were extracted and quantified along with patient samples. Each separate analysis was considered acceptable if two thirds of all QC samples were within 15% of the nominal concentration and at least one QC sample was acceptable at each concentration analyzed.

Pharmacokinetic Analysis

Individual plasma OSI-774 and OSI-420 concentration data from days 1 and 3 (part A), day 24 (part B), and day 28 (part C) were analyzed by noncompartmental methods analysis with the WINNonlin software program (Scientific Consultant, Apex, SC). The maximum plasma concentration (C_{max}) and the time to the maximum plasma concentration (T_{max}) were determined by inspection of the data. The area under the plasma concentration-time curve (AUC) from time 0 to 24 hours ($AUC_{0\text{-}24}$) was calculated by the linear trapezoidal rule. The AUC was extrapolated to infinity ($AUC_{0\text{-}\infty}$) by dividing the last measured concentration by the terminal rate constant (λ_z), which was determined from the log-linear fit of the terminal portion of the drug concentration-time curve. The oral clearance (Cl/F) was determined by dividing the dose by the AUC; the elimination half-life ($t_{1/2}$) was calculated by dividing 0.693 by λ_z; and the apparent volume of distribution was calculated by dividing CL/F by λ_z. The accumulation ratio was calculated as the ratio of $AUC_{0\text{-}24}$ during the dosing interval to the $AUC_{0\text{-}\infty}$ after the first dose. The plasma OSI-774 minimum steady-state concentration ($C_{ss,min}$) was equivalent to the average of the pretreatment drug concentrations from days 8 to 28. Intersubject variability in the pharmacokinetic parameter estimates was expressed in terms of the coefficient of variation percentage. The extent of conversion of OSI-774 to OSI-420 (metabolic ratio) was determined by dividing the $AUC_{0\text{-}24}$ of the metabolite by the $AUC_{0\text{-}24}$ AUC of the parent compound.

Pharmacokinetic parameters were characterized by use of descriptive statistics. The nonparametric statistical test for several unrelated (Kruskal-Wallis one-way analysis of variance [ANOVA]) or related (Wilcoxon matched-pairs signed-rank test) parameters was used to determine whether the pharmacokinetics of OSI-774 were dose or time dependent. Relationships between drug dose and indices that reflect drug exposure (C_{max}, AUC, and $C_{ss,min}$) were evaluated with the Kruskal-Wallis one-way ANOVA test. The extent of drug exposure as determined by C_{max}, AUC, and $C_{ss,min}$ was compared among patients with various grades of toxicity with the use of nonparametric statistical tests for two (Mann-Whitney *U* test) or several (Kruskal-Wallis one-way ANOVA) independent samples.

Immunohistochemistry

Paraffin-embedded tissues from tumor biopsies were sent to IMPATH (Los Angeles, CA) for evaluation of EGFR expression. Immunohistochemical studies on formalin-fixed paraffin-embedded specimens were performed by use of an indirect immunoperoxidase method. Slides were heated to 60°C, deparaffinized in xylene, rehydrated in graded alcohols, and rinsed with tap water. The tissues were then subjected to epitope retrieval by treatment with proteinase K (Dako, Carpinteria, CA) for 15 minutes at room temperature. After the slides were washed with phosphate-buffered saline (PBS) (Amresco, Solon, OH), endogenous peroxidase activity was blocked using peroxidase block (Dako Envision Plus System) for 5 minutes followed by three consecutive rinses with PBS. The sections were then incubated with one of two anti-EGFR antibodies including clone H1 (Dako) at a concentration of 5.81 μg/mL or clone 31G7 (Zymed, Inc, San Francisco, CA) at a concentration of 1.5 μg/mL. Murine immunoglobulin G_1 antibodies from Dako and Sigma Chemical Co (St Louis, MO) were used as negative reagent controls for the clone H1 and clone 31G7 anti-EGFR antibodies, respectively. All antibodies were diluted in primary antibody diluent (Research Genetics, Huntsville, AL). Slides were incubated for 30 minutes at room temperature, then washed three times in PBS. The sections were then incubated with labeled polymer (Dako Envision Plus System) for 30 minutes at room temperature and washed three times in PBS. The peroxidase reaction was visualized after the sections were incubated for 1 minute with 3,3-diaminobenzidine-tetrahydrochloride solution (Dako). The slides were then thoroughly washed with tap water, counterstained with a modified Harris hematoxylin (Fisher Scientific, Fairlawn, NJ), dipped in 0.25% acid alcohol, and treated with 0.2% ammonia. Subsequently, the sections were dehydrated through graded alcohols and treated with xylene, and finally coverslips were applied. EGFR expression was assessed by use of the following scoring procedure: 0, no staining; 1^+, weakly positive staining of tumor cells; 2^+, moderately positive staining of tumor cells; and 3^+, strong positive staining of tumor cells. Positive staining was scored if stain was visualized within the cytoplasm and/or the cytoplasmic rim. In addition, the intensity of staining and the percentage of tumor cell that stained positive for EGFR also were recorded.

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