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Dose and Schedule-Duration Escalation of the Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase (TK) Inhibitor CP-358, 774: A Phase I and Pharmacokinetic (PK) Study. *L.L. Siu, M. Hidalgo, J. Nemunaitis, J. Rizzo, J. Moczygemba, S.G. Eckhardt, A. Tolcher, L. Smith, L. Hammond, A. Blackburn, T. Tensfeldt, S. Silberman, D.D. Von Hoff, E.K. Rowinsky. Pfizer Inc., Groton, CT.*

CP-358, 774 is an oral quinazolin compound which disrupts cellular signal transduction and triggers apoptosis via direct inhibition of EGFR TK. At nanomolar concentrations, CP-358, 774 inhibits purified EGFR TK and reduces EGFR autophosphorylation in intact tumor cells, with a selectivity of >1000-fold over other human TKs. Based on continuous oral dosing studies using xenograft models, the projected target average plasma concentration (Cavg) for clinical efficacy is 500 ng/ml. This phase I study was designed to assess the feasibility of administering CP-358, 774 on prolonged oral dosing schedules and to determine if biologically relevant concentrations are sustainable. Pts on Leg 1 receive CP-358, 774 on 3 consecutive d per wk for 3 wks followed by 1 wk of rest. Pts on Leg 2 receive CP-358, 774 on d 1, then after a 2-d washout period, drug is given continuously for 3 wks followed by 1 wk of rest. To date, 27 pts with solid cancers (M/F 12:15, median age 56, median KPS 90%) have completed 61 courses on these schedules: 9 pts/23 courses on 3 dose levels in Leg 1 (25 mg/d, 50 mg/d and 100 mg/d), 18 pts/38 courses on 5 dose levels in Leg 2 (50 mg/d, 100 mg/d, 150 mg/d, 200 mg/d and 100 mg bid). Dose-limiting gr 4 diarrhea was encountered at the 200 mg/d level in Leg 2, and subsequent cohort expansion to 6 pts resulted in 2 pts with gr 4 and 4 pts with gr 1-2 diarrhea. An intermediate dose level of 150 mg/d was added with implementation of intensive loperamide therapy upon the first sign of diarrhea, and 2/3 pts had only gr 1 diarrhea. Accrual is ongoing at 200 mg/d or 100 mg bid with loperamide support for diarrhea. Gr 1-2 acneiform rashes limited to the upper body have been observed in 9 pts thus far in Leg 2, with histopathology of skin biopsies showing subepidermal neutrophilic infiltration and epidermal hyperproliferation. Other toxicities have been mild and include headache, nausea, fatigue, and transient rises in serum bilirubin and transaminases. Preliminary PK analysis reveals an approximate 2-fold range in inter-subject variability in exposure. Dose-related increases in exposure were observed; mean Cavg values following continuous daily dosing at the 50, 100 and 200 mg/d levels in Leg 2 were 432 (n=3), 973 (n=3) and 2120 (n=5) ng/ml, respectively. Dose-related accumulation in exposure was observed (AUC_{0-24} ratio d 24/d 1=1.2-4.8). The target Cavg of 500 ng/ml was achievable at doses≥100 mg/d on a well-tolerated schedule.

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Phase I Dose Escalation Study of Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase (TK) Inhibitor CP-358,774 in Patients with Advanced Solid Tumors. *D.D. Karp, S.L. Silberman, R. Csudae, F. Wirth, L. Gaynes, M. Posner, G. Bubley, H. Koon, M. Bergman, M. Huang, L.E. Schnipper. Beth Israel Deaconess Medical Center, Boston, MA; Pfizer Inc. Groton, CT.*

CP-358,774 is a novel oral anti-tumor agent that directly inhibits EGFR TK, a receptor that is over-expressed in many solid tumors. Pre-clinical studies reveal that CP-358,774 inhibits EGFR autophosphorylation and cell proliferation in human cell lines and mouse xenograft models. The objectives of this trial were to define the MTD, toxicity, and pharmacokinetics (PK) of weekly administration of CP-358,774. Escalating doses were administered orally once every week for 3 out of 4 weeks to cohorts of 3 pts per dose. Eighteen pts (median age 53.5yrs, 12:M/6:F, median Karnofsky performance status 80%) with advanced solid tumors (7 lung, 3 prostate, 3 colon, 3 head and neck, 1 breast, 1 renal, 1 liposarcoma) who had received a median of 2 (range 1–3) prior treatment regimens were treated at 5 doses (100, 220, 400, 800, 1,000 mg) for a maximum period of 24 weeks. No significant toxicities were observed at 100 and 200 mg. Toxicities observed in subsequent cohorts included fatigue, which was virtually universal but mild, Grade (Gr) 2 headache, Gr 1 mucositis, Gr 2 maculo-papular (acneiform) rash, Gr 2 nausea, and Gr 2 diarrhea. One pt on 1000mg developed Gr 3 diarrhea, thus 3 additional pts received 1000mg and 2/3 developed Gr 2 diarrhea. Pts continue to be accrued at the 1200 mg dose. Preliminary PK analysis reveals large intra- and inter- subject variability, although relatively dose proportional increases are seen when doses are escalated from 100 to 1000 mg weekly. AUC_{0-24} ranged from 21.3 µg.hr/ml to 116.0µg.hr/ml; Cavg from 0.9 µg/ml to 4.8 µg/ml; and Cmax from 1.5µg/ml to 7.1 µg/ml (all values measured at Day 1). The ratio of Day 8 to Day 1 AUC_{0-24} ranged from 0.66 to 1.21. Thus, CP-358,774 is a well tolerated oral agent when administered weekly in doses up to 1,000mg. The MTD has not been reached, and further dose escalation is continuing.

*1500

ZD1839, an Oral Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitor: First Phase 1, Pharmacokinetic (PK) Results in Patients. *Lisa Hammond, M. Ranson, D. Ferry, M. Kris, H. Kelly, J. Ochs, S. Averbuch, E. Rowinsky. Zeneca Pharmaceuticals, Wilmington, DE.*

ZD1839 is a potent and selective inhibitor of the EGFR-associated tyrosine kinase involved in signal transduction and mitogenic stimulation. The IC50 for ZD1839 enzyme inhibition of EGFR isolated from A431 vulval squamous carcinoma was 10.3-35.0ng/ml. In preclinical studies that served as the impetus for this study, prolonged daily oral dosing resulted in tumor growth inhibition and regression. This present study was designed to assess the feasibility of administering oral ZD1839 daily for 14 consecutive days to cancer patients with tumors that are known to commonly overexpress EGFR. At the first dose level (for PK data purposes only), patients received one dose of ZD1839 followed by a seven-day washout prior to consecutive ZD1839 daily dosing. To date, 27 patients (median age 51.5 years, range 28-68 years, median KPS 1) have received 38 courses at the following dose levels: 50, 100 150 and 225mg/day. Drug-related toxicities (all Grade 1) have included anemia, leukopenia, uveitis (n=1 patient), nausea, emesis, HA, dry mouth and skin (n=1 patient). PK parameters (mean) for single and multiple dosing iterations are:

Dose Level (mg)	N	C_{max} (ng/ml)	T_{max} (hr)	$T_{1/2}$ (hr)	AUC (ng*h/ml)
50 single D1	8	45	3.5	34	1301
50 multiple D14	6	113	3.7	39	4519
100 single D1	7	46	4.7	–	–
100 multiple D14	7	190	4.1	53	12784
150 single D1	7	128	3.6	–	–
150 multiple D14	4	273	3.5	–	–

These results indicate that potentially biological relevant concentrations of ZD1839 are achievable and feasible and that oral daily ZD1839 is well-tolerated at doses up to 225mg/day for 14 days.

*1501

Phase I Trial of Chimerized Anti-Epidermal Growth Factor Receptor (Anti-EGFr) Antibody in Combination with Either Once-Daily or Twice-Daily Irradiation for Locally Advanced Head and Neck Malignancies. *Mark P. Ezekiel, James A. Bonner, Francisco Robert, Ruby F. Meredith, Sharon A. Spencer, Albert F. LoBuglio, Harlan W. Waksal. ImClone Systems Incorporated, Somerville, NJ.*

Preclinical studies have revealed that combined treatment of anti-EGFr (C225) and irradiation results in radiosensitization in squamous cell carcinomas that overexpress epidermal growth factor receptor (Saleh et al, Proceedings Am Assoc Can Res, 37:612, 1996). Therefore, a phase I trial has undertaken to determine the tolerability of combined C225 and irradiation for patients with locally advanced (unresectable) head and neck malignancies. A standard dose escalation procedure was utilized with 3 patients entered at each increment of C225 given with 70 Gy (2.0 Gy given once-daily: 2 Gy q d) of radiation therapy with the final 3 patients receiving 76.8 Gy (given twice-daily: 1.2 Gy BID) with no increment in C225 dose. C225 was delivered as a loading dose of 100-500 mg/m^2 I.V. followed by weekly infusions of 100-250 mg/m^2 x 7. Sixteen patients were entered on the trial with the following primary sites: oropharynx (7), oral cavity (5), larynx (1), hypopharynx (3). Thirteen patients had stage IV disease and 3 had stage III disease. One patient was not evaluable for toxicity or response due to recent completion of treatment and another patient was not evaluable for response due to an anaphylactic reaction (grade 4) during the initial C225 treatment. The latter patient subsequently discontinued protocol therapy. Nine (56%) patients experienced irradiation-related grade ≥3 mucositis (one was grade 4) and five (31%) patients experienced C225 and/or irradiation related grade 3 skin toxicity (primarily related to a follicular rash). No C225 dose delays were required and in general, the skin toxicities recovered completely or to grade 1 or 2 during treatment or shortly thereafter. The irradiation-related toxicities were not exacerbated by adding C225 to radiation therapy. There was no increase in frequency or severity, nor was there any need for unexpected treatment medication or procedures, demonstrating that this combined therapy is both safe and well-tolerated. Of the 15 evaluable patients, 14 (93%) achieved complete responses based on physical and endoscopic examination. These results are highly encouraging when compared to published rates of complete response ranging from 20% to 50% in similar patients treated with irradiation alone.