thus we aimed to assess the effect of hepatic impairment on the pharmacokinetics (PK) and tolerability of once-daily oral ZD1839 (250 mg/day for 28 days). In this open-label, non-randomized Phase I trial, pts (n=41; 18 with normal liver function, 16 with moderate impairment and 7 with severe hepatic impairment) with refractory solid malignant tumours were given 2 oral doses of 250 mg ZD1839 on Day 1, followed by single daily doses of 250 mg ZD1839 on Days 2-28. Primary endpoint was the effect of hepatic impairment on Day-28 steady-state AUC ($AUC_{24}^{ss}$) of ZD1839. Hepatic impairment was scored by summing baseline NCI-CTC grade (1-4) for aspartate aminotransferase, alkaline phosphatase and total bilirubin. A score of 0-2 was classified as normal, 3-5 as moderate and 6-12 as severe liver impairment. Secondary endpoints included safety. Fourteen pts from the normal group, 13 from the moderately impaired group and 4 from the severely impaired group were evaluable for PK: preliminary analysis demonstrated no clinically significant differences between the normal pt group and moderately or severely impaired pts in $AUC_{24}^{ss}$ (gmean [range] 8900 [3300-26200], 9500 [2300-23300] and 6200 [4850-8850] ng.h/ml, respectively); and $C_{max}^{ss}$ (gmean [range] 466 [176-1230], 517 [138-1120] and 372 [264-428] ng.ml, respectively). All pts were evaluable for safety. In all 3 groups, ZD1839 had a good safety profile and drug-related grade 3/4 adverse events (AEs) were rare; there was no apparent increase in frequency or severity of AEs in pts with greater hepatic impairment. Two normal, 3 moderately impaired and 1 severely impaired pt(s) have received or are continuing to receive treatment for 6 months or longer. In conclusion, ZD1839 250 mg once daily in cancer pts with moderately and severely impaired hepatic function due to liver metastases achieves a systemic exposure and tolerability profile similar to those observed in pts with normal liver function, indicating no need for dosage adjustment. 'Iressa' is a trademark of the AstraZeneca group of companies

## 175

### A Phase I and pharmacokinetic study of the farnesyl transferase inhibitor, CP-609,754 in patients with advanced solid tumors

R. Lush[1], J. Mahany[1], M. Langevin[1], M. Bartkowski[2], D. Noe[2], K. Ferrante[2], D. Sullivan[1]. [1]*H. Lee Moffitt Cancer Center & Research Insitute, Experimental Therapeutics, Tampa;* [2]*Pfizer Globel Research & Development, New London, CT, USA*

CP- 609,754 is a potent, reversible, competitive inhibitor of human farnesyl transferase that blocks farneslyation of several proteins. Following sustained systemic exposure, CP-609,754 inhibits growth of mutant, H- and K-ras expressing tumors and produces regressions of a human bladder carcinoma xenograft in athymic mice. The objectives of this study were to establish the safety, tolerability, maximum tolerated dose and dose limiting toxicities of this agent given once daily (qd) or twice daily (bid) for 28 days (d). A total of 21 patients were enrolled (14 males and 7 females). Tumor types included colorectal 7, lung 4, sarcoma 3, urothelial/renal 2, GI/stromal 2, thyroid 1, hepatoma 1and pancreatic 1. The median age was 61 years (range 47-73). CP-609,754 doses were doubled starting at 20 mg to 1280 mg given qd or bid for 28 d (except 1280 mg, which was only given as 640 mg bid). The median number of cycles administered was 2 (range 0.5-8.5). Myelosuppression (grade <3; 11/21 pts), nausea (grade <2; 5/21 pts) and diarrhea (grade <3; 4/21 pts) were the most frequent treatment related AEs observed primarily at the highest dose levels. Reversible, but dose limiting, neurotoxicity (grade 3) was observed in 1 of 6 pts treated at the 640 mg bid dose. Preliminary PK analysis of steady-state bid dosing (d 15) yielded the parameter values listed below (the 1280 mg/d cohort are the mean values). These data suggest that the PK of CP-609,754 are dose proportional across the dose range studied.

| Dose (mg/d) | Number of Pts | AM Dose (fasting) | | | | PM Dose | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Cmax (ng/ml) | Cave (ng/ml) | Cmin (ng/ml) | $T_{1/2}$ (hr) | Cmax (ng/ml) | Cave (ng/ml) | Cmin (ng/ml) | $T_{1/2}$ (hr) |
| 20 | 1 | 27 | 6 | <LLOQ | 2.2 | 6 | 2 | 2 | NC |
| 40 | 1 | 17 | 5 | <LLOQ | 3.3 | 11 | 5 | 2 | 4.4 |
| 80 | 1 | 140 | 37 | 4 | 3.4 | 160 | 35 | 5 | 3.5 |
| 160 | 1 | 59 | 23 | 4 | 2.9 | 24 | 13 | 5 | 4.7 |
| 320 | 1 | 230 | 99 | 17 | 2.2 | 130 | 87 | 22 | NC |
| 640 | 1 | 600 | 188 | 14 | 2.1 | 920 | 433 | 35 | 1.4 |
| 1280 | 5 | 1110 | 304 | 46 | 3.1 | 656 | 290 | 109 | 3.0 |

NC: not calculated; LLOQ: lower limit of quantitation

Objective tumor responses were not observed, but 2 patients were on study with stable disease for more than 5 cycles including one who completed 12 cycles. In conclusion, CP-609,754 appears to be well tolerated at the dose levels tested and the MTD has not been reached.

## 176

### Gleevec therapy in c-KIT negative soft tissue sarcomas: a molecular rationale

D. Thomas[1], T.J. Giordano[1], R.S. Benjamin[2], B.L. Samuels[3], D.A. Priebat[4], S.S. Bacus[5], L.H. Baker[1]. [1]*University of Michigan Cancer Center, Pathology, Ann Arbor, USA;* [2]*M.D. Anderson Cancer Center., University of Texas, Melanoma/Sarcoma Medical Oncology;* [3]*Lutheran General Cancer Care Center, Park Ridge, IL, USA;* [4]*Washington Cancer Institute, Medical Oncology, Washington;* [5]*Ventana Medical Systems, Inc., Westmont, USA*

Imatinib mesylate (Gleevec) therapy has revolutionized the treatment of c-KIT positive soft tissue sarcomas (STS) such as GIST. The North American branch of the Connective Tissue Oncology Society is currently conducting a phase II trial of Gleevec in patients with advanced non-GIST STSs. Recently, a patient with advanced Malignant Fibrous Histiocytoma (MFH) responded dramatically to Gleevec therapy. Immunohistochemical analysis of the resected tumor demonstrated the absence of c-KIT and the presence of PDGFR a and its ligand PDGF-A. The phosphorylated form of AKT was also present. PDGFR a and b are membrane bound receptor tyrosine kinases (RTK), which are thought to be alternate targets for the RTK inhibitor, Gleevec. The genomic sequence for these RTKs share extensive homology with both c-KIT and c-ABL, especially in the region coding for the ligand-binding domain. PDGFR a and b, c-KIT and c-ABL are all strongly inhibited by Gleevec. AKT is a cytoplasmic serine/threonine kinase, which is a common target for RTK phosphorylation. It is involved in the regulation of cell survival. In order to further determine which patients would benefit from empirical Gleevec therapy, sections of a tissue microarray (TMA) with multiple cores from eight different STS subtypes (rhabdomyosarcoma (n=15), leiomyosarcoma (n=8), liposarcoma (n=10), angiosarcoma (n=8), MFH (n=16), GIST (n=5), synovial sarcoma (n=12), and fibrosarcoma (n=11)) were stained using routine immunohistochemical stains for PDGFR a and b, c-KIT and AKT. Sections were also stained with antibodies specific for the phosphorylated form of AKT. Analysis of the data indicates that although PDGFR a and b are ubiquitous in distribution amongst STS, c-KIT immunoreactivity was only observed in GISTs, synovial sarcomas and angiosarcomas. AKT immunoreactivity was observed in 68 of 85 STS (80%). The phosphorylated form of AKT was seen in 68%, ranging from 36% in fibrosarcomas to 87.5 % in MFH. These results suggest that adjuvant therapy with Gleevec is may be useful in c-KIT negative STSs, where activated forms of AKT is present. The results also provide a molecular rationale for the dramatic response seen in the c-KIT negative MFH patient undergoing therapy with Gleevec.

## 177

### ZD1839 ('Iressa') provides clinically significant antitumor activity and improves disease-related symptoms in pretreated patients with advanced non-small-cell lung cancer (NSCLC): results of two Phase II trials (IDEAL 1 and IDEAL 2)

J.-Y. Douillard[1], R. Natale[2], G. Giaccone[3], T. Lynch[4], K. Nakagawa[5], J. Brahmer[6], S. Averbuch[7], A. Kay[7]. [1]*CRLCC Rene Gauducheau, Saint Herblain, France;* [2]*Cedars-Sinai Comprehensive Cancer Center, Los Angeles, USA;* [3]*Academic Hospital Free University, Amsterdam, The Netherlands;* [4]*Massachusetts General Hospital Cancer Center, Boston, USA;* [5]*Kinki University School of Medicine, Osaka, Japan;* [6]*Johns Hopkins University Hospital, Baltimore, USA;* [7]*AstraZeneca, Wilmington, USA*

Phase III studies of treatment of locally advanced or metastatic non-small-cell lung cancer (NSCLC) with docetaxel, after failure of prior chemotherapy, gave objective response rates (RR) <7%, and demonstrated a small survival advantage for docetaxel over best supportive care (J Clin Oncol 2000;18:2095-103; 2354-62.). However, docetaxel treatment is associated with a high incidence of severe toxicity, particularly neutropenia, thus highlighting the need for better-tolerated second-line therapy. In two, large, double-blind Phase II trials we evaluated the efficacy and tolerability of 250 mg or 500 mg oral doses of ZD1839 ('Iressa'), a selective epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), in pretreated patients (pts) with advanced NSCLC. In IDEAL 1, pts (209) had received one or two prior chemotherapy regimens (at least one platinum based), whereas in IDEAL 2, pts (216) had received at least two prior chemotherapy regimens, containing platinum and docetaxel, either concurrently or separately. Pts in IDEAL 2 had to be symptomatic at trial entry (Functional Assessment of Cancer Therapy-Lung [FACT-L], Lung Cancer Subscale [LCS] score */=24); in IDEAL 1, 65% of pts were symptomatic at entry. The RRs were 18.4% and 11.8% for the 250 mg/day group and 19.0% and 8.8% for the 500