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

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

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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.

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

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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.

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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)

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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

mg/day group, in IDEAL 1 and 2, respectively. In pts who were symptomatic at entry, a symptom improvement (SI) (*/=2 point increase, */=4 weeks) was observed in 40% and 37% of pts receiving 250 and 500 mg/day, respectively, in IDEAL 1, and in 43% and 34% of all pts, respectively, in IDEAL 2. A positive association was observed between SI and both radiologic response and survival in both trials. Overall, quality of life (QoL) was improved in 24% and 22% of pts receiving 250 and 500 mg/day, respectively, in IDEAL 1, and in 34% and 23% of pts, respectively, in IDEAL 2. Most drug-related adverse events (AEs) were mild grade 1/2 diarrhea and skin disorders. Drug-related AEs were more frequent in the higher dose group. Withdrawal due to drug-related AEs was 2% and 9% for pts receiving ZD1839 250 and 500 mg/day, respectively, in IDEAL 1, and 1% and 5%, respectively, in IDEAL 2. In conclusion, in pretreated pts with advanced NSCLC, oral ZD1839 250 mg/day resulted in clinically significant antitumor activity, had an acceptable tolerability profile and provided improvement in disease-related symptoms and QoL. 'Iressa' is a trademark of the AstraZeneca group of companies

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ABX-EGF, a fully human anti-epidermal growth factor receptor (EGFr) monoclonal antibody: phase II clinical trial in renal cell cancer (RCC)

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EGRr is a transmembrane glycoprotein that promotes cell growth in a variety ofnormal and transformed tissues. ABX-EGF is a high-affinity, fully human IgG2monoclonal antibody to EGFr generated in Xenomouse mice. Part 1 of a two-partphase 2 trial consisting of 8 weekly infusions of ABX-EGF was performed inpatients (pts) with RCC who failed or were unable to receive IL-2/IFN-alfa.Stable or responding pts were eligible for extended weekly treatment at theassigned dose for 8 additional months or until disease progression. In Part 1,88 pts received at least one dose of ABX-EGF at the following dose levels: 1.0mg/kg (22 pts), 1.5 mg/kg (22 pts), 2.0 mg/kg (23 pts), and 2.5 mg/kg (21 pts).Overexpression of EGFr was documented in 95% of pts enrolled. Eleven percent of the pts had received no prior biotherapy or chemotherapy, whereas 56% and 33%were more heavily-pretreated, having received 1?2 and at least 3 prior regimens,respectively. All pts have completed one 8-week cycle of ABX-EGF and areevaluable for response. Three pts (1 each at 1, 1.5 & 2.5 mg/kg) had partialresponses. Two patients (1 each at 1.0 & 2.5 mg/kg) had minor responses. Fiftypercent of pts had stable disease as their best response. A transient acneiformskin rash, which is a potential pharmacodynamic surrogate of EGFr blockade, wasobserved in 70%, 91%, 95% and 100% of pts treated with at least 3 doses ofABX-EGF at 1.0, 1.5, 2.0 and 2.5 mg/kg, respectively. Other >/= grade 2 adverseevents in over 2% of pts included asthenia, pain, abdominal pain, back pain,constipation, cough and dyspnea. An analysis of peak and trough serum ABX-EGFconcentrations indicates low intrapatient variability and consistent drugexposure in individual pts throughout the 8-week treatment period in all dosinggroups which is consistent with the lack of human anti-human antibody (HAHA)formation in pts tested to date. The inter-patient variability in ABX-EGFexposure was extremely low and trough concentrations at ABX-EGF doses of atleast 2 mg/kg consistently exceeded IC90 values determined for human tumorsxenograft models. The relationship between the incidence of skin rash and dosewas well described by a sigmoidal model, which predicted a 90% incidence of skinrash at an ABX-EGF dose of 1.5 mg/kg (ED90) in agreement with the results ofphase 1 studies. In conclusion, ABX-EGF is well tolerated and preliminaryevidence of antitumor activity was observed in heavily-pretreated RCC pts.

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Phase II study of OSI-774 in patients with metastatic colorectal cancer

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Epidermal Growth Factor Receptor overexpression is seen in upto 75% of colorectal cancers, and has been implicated in the development and propagation of the malignancy. OSI-774 is a potent epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) which is being evaluated in a phase II study to assess the activity in patients with metastatic colorectal cancer. Primary endpoints are response or disease stabilization, with a multinomial stopping rule and secondary endpoints are the assessment of molecular changes with therapy. The study is currently ongoing. Sixteen evaluable patients with metastatic colorectal cancer have been treated with OSI-774 at a dose of 150 mg PO daily continuously on a four weekly cycle. Paired biopsies of the tumors and skin have been obtained in 15 patients. Radiologic evaluation was done every 8 weeks and skin and tumor biopsies were performed prior to treatment and on day 8. Eleven (69%) were male and the median age was 59 years with a range from 43-76 years. Eight (50%) of patients had an ECOG status of 1 and 8 (50%) had an ECOG status of 0. Apart from adjuvant chemotherapy, patients had only received chemotherapy for metastatic disease with one line irinotecan/5FU in combination or sequentially. The most common sites of disease were liver in 13 (81%), lymph nodes in 10 (63%) and lung in 7 (44%). Thirteen patients were evaluable for efficacy and toxicity. There are 3 (23%) patients with stable disease (2 confirmed and one pending confirmation) who remain on study (5, 4 and 3 cycles to date). Ten patients have progressed. The two most common toxicities observed were diarrhea [grade 1: 4pts (31%), grade 2: 1pt (8%) grade 3: 1pt (8%)] and rash [grade 1: 4pts (31%), grade 2: 5pts (38%) grade 3: 1pt (8%)]. There were no grade 4 toxicities related to this drug. There were 4 grade 3 toxicities assessed to be possibly or probably related to this drug including diarrhea, rash, elevation in INR and elevation in ALP. Treating patients with flamazine cream and minocycline antibiotic improved rash from OSI-774 in 70% of patients with a grade 2 or greater rash. Conclusion: Patients are being evaluated and correlative studies are ongoing.

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The use of predicting factors and surrogate markers in breast cancer biopsies treated with targeted erbB tyrosine kinase inhibitor

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Over-expression of erbB receptors is associated with aggressive breast cancers. Therapeutic strategies targeting these oncoproteins are in clinical trials. One approach is the use of a monoclonal antibody to erbB2, Herceptin. Studies performed *in vitro* have attributed the therapeutic potential of Herceptin to enhance intracellular degradation resulting in a functional inhibition of erbB2. Another effective approach is the use of tyrosine kinase inhibitors (TKIs) that block the nucleotide-binding site of the erbB kinases, specifically erbB1 and erbB2. An alternative way to enhance degradation and inhibit activity of erbB proteins involves targeting the heat shock protein 90 (Hsp90) using benzoquinone ansamycins such as geldanamycin (GA). Hsp90 forms complexes with erbB2 proteins and stabilizes them. GA blocks ATP binding to Hsp90 resulting in poly-ubiquitination and destruction of the erbB2. However, GA's broad effect is of concern. In contrast, the TKI group of drugs is highly selective to erbB receptors blocking only the nucleotide-binding site of tyrosine kinase proteins. Consequent to blocking kinase activity, most downstream signaling pathways are inhibited leading to growth arrest. In this work, we used cancer tissue biopsies from patients before and after TKI treatment to understand the mechanism and the factors associated with response or non-response to TKI treatment. Breast cancer biopsies from patients, before and after TKI treatment, were immunostained for erbB1 and erbB2. Their phosphorylated forms and phosphorylated ERK (pERK) (a downstream signal) were used as a surrogate marker of response (antibodies were purchased from Cell Signaling and Ventana). Levels of staining were quantitated by microscope based image analysis. Patients with high levels of EGFR, HER-2 and pERK responded to TKI. Their response was confirmed by using surrogate biomarkers as