the 17-AAG ratio. Utilizing recombinant human cytochrome P450 3A4 and 3A5 preparations, we found 17-AAG to be a substrate for both CYP3A4 and CYP3A5 with a similar rate of transformation. Therefore, we proceeded with CYP3A5 genotyping (n=13) and found 2/13 patients carried the *3 polymorphism and 0/13 patients carried the *6 polymorphism. At the time of the meeting we will update the PK analysis on the remaining patients and include CYP3A5 and NQO1 genotype correlation. (Supported by CA69912, CA15083, and RR00585)

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Combination therapy with ZD1839 ('Iressa') and docetaxel in patients with advanced or metastatic non-small-cell lung cancer (nsclc): preliminary safety results of an open-label, pilot trial

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Patients (pts) with advanced non-small-cell lung cancer (NSCLC) continue to have a poor prognosis with conventional therapy. ZD1839 ('Iressa') is an orally active, selective epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), which has antitumor activity and is generally well tolerated as monotherapy in pretreated pts with advanced NSCLC. ZD1839 has shown additive/synergistic activity with a range of chemotherapy agents in preclinical studies. In this study, we investigated the combination of ZD1839 with docetaxel, an agent established as a second-line therapy for advanced NSCLC. The primary trial objective was to assess the safety of ZD1839 (250 or 500 mg) once daily, in combination with docetaxel in pts with advanced or metastatic, untreated or pretreated NSCLC. Oral ZD1839 treatment started on day 2 of the first cycle of the standard chemotherapy regimen of docetaxel (75 mg/m^2 iv), which started on day 1. Further cycles of docetaxel were administered every 3 weeks concurrently with ZD1839 for up to 6 cycles in total. To date, 18 pts have been enrolled - median (range) age: 59 (40-73) years; M/F: 13/5; performance status 0/1: 4/14; disease stage IIIB/IV: 3/15. Adverse event (AE) data are available for 12 pts (6 pts at each ZD1839 dose level). At 250 mg/day ZD1839, no dose-limiting toxicities (DLTs) were observed. AEs considered to be ZD1839-related included G1/2 skin rash (4 pts) and G1 diarrhea (1 pt), and AEs considered to be docetaxel-related included leucopenia (G1/2, 2 pts; G3, 4 pts), neutropenia (G1, 1 pt; G3/4, 5 pts), fatigue (G2, 4 pts), mucositis/stomatitis (G1, 4 pts), and nausea (G1/2, 3 pts). In the 500 mg/day group, 2 pts had DLT: G3 diarrhea lasting over 4 days (1 pt) and G3 skin rash (1 pt). At this dose, the most common ZD1839-related AEs were diarrhea (G1/2, 3 pts; G3, 3 pts) and skin rash (G1/2, 3 pts; G3, 1 pt), and docetaxel-related AEs included leucopenia (G2, 2 pts; G3/4, 4 pts), neutropenia (G2, 1 pt; G3/4, 5 pts of whom 3 had febrile neutropenia with no proven sepsis), and mucositis/stomatitis (G1/2, 4 pts; G3, 1 pt). Pharmacokinetic data and antitumor activity will be presented. In conclusion, the combination of ZD1839 and docetaxel for the treatment of pts with advanced NSCLC did not cause any unpredictable toxicity. No DLT has been observed to date at the recommended monotherapy doses of 250 mg ZD1839 and 75 mg/m^2 docetaxel. 'Iressa' is a trademark of the AstraZeneca group of companies

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A Phase I study of weekly BMS-214662, a novel farnesyl:protein transferase inhibitor, combined with weekly paclitaxel

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BMS-214662 is a novel farnesyl:protein transferase (FPT) inhibitor (FTI) undergoing phase I and II testing. Preclinical testing has revealed potent and specific inhibition of FPT at nanomolar concentrations with growth inhibitory effects against many tumor types independent of ras status. Preclinical studies have demonstrated a significant, sequence-specific synergy between anti-microtubular agents, such as paclitaxel, and FTIs. We are conducting a phase I dose escalation study of weekly paclitaxel (80 mg/m^2 over 1 hour) and BMS-214662 (escalating doses over 1 hour) administered 30 minutes after paclitaxel. Nineteen patients, with advanced solid tumors, have been entered at 6 dose levels of BMS-214662; level 0 (80 mg/m^2/week, 3 pts), level 1 (120 mg/m^2, 3 pts), level 2 (160 mg/m^2, 3 pts), level 3 (200 mg/m^2, 4 pts), level 4 (225 mg/m^2, 3 pts), and level 5 (245 mg/m^2, 3 pts). Commonly observed toxicities have been grade 1 nausea, diarrhea and fatigue. Two of three patients at level 5 had rapid onset (day 2 of course 1) of culture positive, grade 4 febrile neutropenia, which resolved with supportive measures. Evidence of clinical response (measurable or evaluable) has been observed at multiple dose levels in patients with laryngeal, prostate, and ovarian cancer and in a patient with sarcoma. Paclitaxel pharmacokinetics have not significantly varied with increasing doses of BMS-214662. Preliminary assessment of FPT activity in peripheral mononuclear cells and BMS-214662 pharmacokinetics has observed a correlation between degree of FPT inhibition and drug concentrations. Further enrollment is ongoing with patients receiving BMS-214662 as a 24-hour infusion rather than a 1-hour infusion. In preclinical models, 24-hour infusions of BMS-214662, compared to bolus infusions, increase this compound's therapeutic index, both when used as a single agent or in combination with paclitaxel.

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Final results of a phase I study of the Raf-1 kinase inhibitor bay 43-9006 in patients with advanced refractory solid tumours

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Introduction: Raf-1 is a protein kinase that exerts its effects downstream of Ras in the mitogen-activated protein kinase pathway and is thus likely to be crucial in the development of a malignant phenotype. BAY 43-9006 is a selective inhibitor of Raf-1 and the first compound of its class to enter clinical trials. Final results of a phase I study designed to determine the maximal tolerated dose (MTD), toxicity profile, pharmacokinetics and antitumour activity of BAY 43-9006 in patients(pts) with refractory solid tumors are presented.
Patients and methods: BAY 43-9006 was administered orally in escalating doses to eligible pts during the first 28 days of a 35-day cycle. 37 pts were entered in 8 cohorts (50mg twice weekly - 3 pts, 50mg every other day - 6 pts, 50mg daily - 4 pts, 100mg daily - 4 pts, 100mg BID - 3 pts, 200mg BID - 6 pts, 400mg BID - 3 pts, 600mg BID - 7 pts). PS 0-2, median age 52 (range, 33-70), 46% male. Primary tumor types: ovary/abdominopelvic (13 pts), colon (14 pts), pancreas (3 pts), renal (2pts), other (5 pts). Cohort 7 has recently been expanded by 5 pts (CRC - 4, ovary - 1).
Results: MTD has been reached. A total of 101 cycles have been given and 28 pts are off study (adverse event (AE) - 6, progression or death - 21, other - 1). Most drug-related AEs were mild (grade 1-2) and consisted of dermatologic (31), dyspepsia (7), flatulence (8), diarrhea (7), nausea (5), anorexia (5), fatigue (9), pain (5), neurological (6), alopecia (3), insomnia (2). Grade 3 biochemical abnormalities included hyponatremia (10), ALP (8), lymphocytes (8), bilirubin (5), AST/ALT (5), others (8). In cohort 8, one pt had grade 3 hand-foot syndrome (HFS). This cohort was expanded by 4 pts, with 2 pts getting HFS. Analysis of D1 PK samples resulted in Cmax values of 0.60 $\pm$ 0.20, 0.66 $\pm$ 0.37, 0.49 $\pm$ 0.24, 0.86 $\pm$ 0.32, and 1.28 $\pm$ 0.19 mg/L, AUC (0-24) values of 8.72 $\pm$ 2.52, 10.97 $\pm$ 6.61, 7.0 $\pm$ 2.9, 10.7 $\pm$ 4.4 and 18.7 $\pm$ 6.8 hr mg/L, and a terminal half-life of 27.7 $\pm$ 4.3, 27.9 $\pm$ 6.2, 21.5 $\pm$ 1.7, 24.8 $\pm$ 1.4 and 38.6 $\pm$ 6.5 hours for cohorts 1 to 5. To date, 3 pts have had tumour shrinkage of at least 20%.
Conclusions: DLT has been reached at 600mg BID. Future phase II studies are planned and should use the RPTD of 400mg BID.

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A Phase I trial assessing the pharmacokinetics and tolerability of ZD1839 ('Iressa') in hepatically impaired patients with solid tumours

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ZD1839 ('Iressa'), an orally active, selective epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), has shown antitumour activity and good tolerability in patients (pts) with a range of tumours. Hepatic dysfunction as a result of liver metastases is common in pts with solid tumours;

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