tolerated dose (MTD), determine the pharmacokinetic (PK) profile, and describe evidence of antitumor activity and inhibition of ERK1/2 phosphorylation in treated patients (pts). BAY 43-9006 was started at weekly doses and developed into continuous daily treatment at doses of 100, 200, 400, 600 and 800 mg bid. Sixty-two advanced stage cancer pts, most heavily pretreated, median age 54, PS 0-2 with refractory malignancies [28 colorectal (CRC), 11 hepatocellular (HCC), 4 breast, 2 non-small cell lung, and 17 others] received BAY 43-9006. At dose level (DL) 800 mg bid/ daily continuous, DLT was diarrhea CTC 3 in 2/6 pts. However, at DL 600 mg bid/ daily continuous, DLT changed toward skin toxicity (rash, PPE, facial erythema) CTC 3 in 3/14 pts. Other clinical toxicities included pancreatitis (CTC 3, n=1 at 100 mg bid /daily), anorexia, and fatigue, but these were not dose limiting. Preliminary evidence of antitumor activity was seen in one pt with HCC who achieved a sustained (47+ wks) partial remission (PR) after 20 wks of treatment at 400 mg bid. Furthermore, prolonged stabilization (> 3 months) of previous progressive disease was seen in 20 pts (32%). The median TTP was 9+ wks (range 2-46+ wks) in pts with CRC and 16.3+ wks (range 5-45+ wks) in pts with HCC. PK profiles (0-12h), obtained at start of treatment and steady state (after day 7), were AUC0-12h, ss = 73 mg*h/L, Cmax = 9.9 mg/L, and tmax = 1.75 h at 400 mg bid. In summary, BAY 43-9006 is a Raf inhibitor that is well-tolerated using continuous oral dosing. Toxicities were generally mild to moderate. DLT was diarrhea at DL 800 mg bid and skin toxicity at DL 600 mg bid. Preliminary antitumor activity was evident due to a confirmed partial remission in one pt and 32% of pts with prolonged tumor stabilization of previous progressive disease. Phase I combination studies with BAY 43-9006 are in progress and phase II studies are planned at the recommended dose of 400 mg bid continuous.

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Phase I, bioavailability, and pharmacokinetic study of oral dosage of CCI-779 administered to patients with advanced solid malignancies

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Background: CCI-779 exerts its cell cycle inhibitory effects by binding to FKBP-12 and blocking the activity of mTOR (mammalian target of rapamycin), that, in turn, results in inhibition of translation of key proteins involved in progression from G1 to S phase. In 2 previous phase 2 clinical studies, CCI-779 was administered intravenously weekly to patients with advanced renal cell carcinoma or advanced or metastatic breast cancer and was generally well tolerated and active. Because CCI-779 is a non-cytotoxic agent, the feasibility of oral administration of the drug was examined.
Objectives: To determine the safety/tolerability, maximum tolerated dose (MTD), pharmacokinetics (PK), and bioavailability of CCI-779 administered orally daily for 5 days every 2 weeks (daily × 5) in patients with advanced solid malignancies.
Design: Prior to the daily × 5 portion of the study, absolute bioavailability was assessed. Patients received a single dose of CCI-779 administered intravenously or orally, followed one week later by the other route. The IV dose was 20% of the planned oral dose. During the daily × 5 portion of the study, CCI-779 dose-escalation to the next level was based on the toxicities observed during the first 2-week course. The starting oral dose was 25 mg daily × 5. The dose was doubled for subsequent cohorts until grade 2 or higher drug-related toxicity was observed. At least 3 patients were evaluated at each dose level.
Results: To date, 24 patients (median age = 55 years, range = 25 to 83 years) have received 149 total courses of CCI-779 (median courses = 6, range = 1 to 21, at 25-, 50-, 75-, and 100-mg dose levels). At the 100-mg dose level, 2 of 6 patients experienced dose-limiting toxicity consisting of grade 3 stomatitis, grade 3 AST elevation, or grade 3 solar-plantar desquamative rash. Although several patients required treatment delays of 1 to 2 weeks at the 75-mg dose level, this is the recommended MTD. Preliminary evidence of anti-tumor activity of oral CCI-779 includes disease stabilization for 8 to 9+ months in patients with renal cell carcinoma, non-small-cell lung carcinoma, myxoid chondrosarcoma, mesothelioma, and leiomyosarcoma. Preliminary PK data indicate moderately rapid absorption, dose-related increases in exposure, and formation of sirolimus as a major metabolite.
Summary: The recommended oral dosage of CCI-779 is 75 mg/day administered daily for 5 days every 2 weeks.

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Phase I, pharmacokinetic (PK) and biologic study of OSI-774, a selective epidermal growth factor receptor (EGFR) tyrosine kinase (TK) inhibitor in combination with paclitaxel and carboplatin in patients with advanced solid malignancies

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OSI-774, an oral quinazoline which selectively inhibits EGFR-TK has demonstrated significant activity in multiple solid tumors, including non-small-cell lung cancer (NSCLC), ovarian and head/neck cancers in early Phase 2 studies. The preclinical synergism of therapeutics targeting EGFR with platinum- and/or taxane-based chemotherapy, the single agent activity of OSI-774 in taxane-sensitive malignancies, as well as nonoverlapping toxicities, provided the rationale for the evaluation of this regimen, in which minimally or untreated patients are receiving escalating doses of OSI-774 on an uninterrupted oral daily schedule with a fixed dose of paclitaxel 225 mg/m^2 IV and carboplatin AUC 6 IV every 3 weeks. Paclitaxel and carboplatin are administered 3 days before OSI-774 in course 1, permitting the assessment of paclitaxel/carboplatin PKs alone (course 1) and in combination with OSI-774 (course 2). EGFR-TK phosphorylation is being evaluated in serial biopsies of skin, buccal mucosa and tumor. Thus far, 15 patients (median age, 59 [range, 22-72]; 14 M:1 F; untreated [9]] have received 71 courses at OSI-774 dose levels of 100 mg daily (6 patients), 125 mg daily (4 patients) and 150 mg daily (5 patients) plus paclitaxel/carboplatin. The MTD is defined as the dose level below which greater than 1/3rd of patients experience dose-limiting toxicity (DLTs). Dose-limiting neutropenia and diarrhea have been observed in 2 of 6 patients receiving OSI-774 at 100 mg daily, while 2 patients receiving OSI-774 at 150 mg daily have had grade 3 rash as DLT and 1 patient has had febrile neutropenia. Peripheral neuropathy, fatigue, and diarrhea have also been observed. To date, antitumor activity includes 2 partial responses (NSCLC), and four minor responses (2 NSCLC, penile carcinoma, head/neck) with stable disease for 3-7+ months. P27 expression was increased in the skin of 1 patient following treatment. Other biological studies are being performed and will be reported. Paclitaxel and total platinum plasma PKs were unchanged between course 1 and 2. The recommended phase II dose of OSI-774 is 125 mg daily in combination with full doses of paclitaxel/carboplatin in this patient population.

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A phase I trial of 17-Allyl-Amino-Geldanamycin (17-AAG) in patients with advanced cancer

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17-allylamino-geldanamycin (17-AAG) is an anticancer agent that represents a class of drugs capable of binding and disrupting the function of Hsp90, leading to the depletion of multiple oncogenic client proteins involved in tumor cell proliferation and survival. We performed a phase I study to define the maximally tolerated dose (MTD), toxicity, pharmacokinetics, effect on surrogate markers, the dose limiting toxicity (DLT), and clinical activity of 17-AAG when given as a 90-minute infusion on days 1, 8, and 15 of a 28-day cycle in patients with advanced solid tumors. In addition, we are evaluating the relationship between 17-AAG pharmacokinetics and toxicity with known functional polymorphisms in Cytochrome P450 3A5 and NQO1. An accelerated titration design was used with one patient per cohort until grade 2 toxicity was achieved. In the first 20/21 patients treated, there were 10 male, 10 female (median age 60.5) who received a total of 42 courses (median 2) at doses of 15, 21, 29, 41, 57, 80, 112, 157, 220, 308, and 431 mg/m^2/dose. DLT in 2 patients (graded by NCI CTC and recorded as maximum grade per patient for all treatment cycles) was noted at the 431 mg/m^2/dose and included the following grade 3 toxicities: liver (bilirubin and AST), fatigue, nausea/vomiting, and anemia. The most common grade 1 and 2 toxicities were anorexia (3 grade 1, 4 grade 2); nausea (6 grade 1, 2 grade 2); anemia (4 grade 1, 3 grade 2), and diarrhea (8 grade 1, 3 grade 2). Pharmacokinetic (PK) analysis of plasma samples drawn on day 1 (n=9) revealed that the median clearance was 412 ml/min/m^2 (208-4,885). The Cmax increased linearly with dose and the t1/2 was 166 min ± 115 min. Formation of the active metabolite, 17-amino-geldanamycin (17-AG), was detected at all dose levels. The AUC for 17-AG was 85%(± 42%) of

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;