with stabilization of previous progressive disease. Our results demonstrate that BAY 43-9006 administered at dose levels >200 mg bid inhibits PMA-stimulated ERK phosphorylation in treated patients and indicates that PBLs are suitable surrogate tissues for biomarker studies in future trials.

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Results of a phase I trial of the humanized anti epidermal growth factor receptor (EGFr) monoclonal antibody emd 72000 in patients with EGFr expressing solid tumors

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The epidermal growth factor receptor has been identified as an important target for anticancer therapy. EMD 72000 is a humanized monoclonal antibody that binds selectively to the EGFr and inhibits ligand mediated activation.
Study objective: To determine the maximum tolerated dose (MTD), dose-limiting toxicities (DLT) and the pharmacokinetic profile of EMD 72000.
Methods: Patients (pts) had to have EGFr-positive (confirmed by immunohistochemistry) tumors, measurable disease, refractory to standard chemotherapy (CTx). EMD 72000 was administered once a week as 1 h infusion without any routine premedication. The initial dose level (DL) of 400 mg (absolute dose)/week was escalated in 400 mg steps in cohorts of 3 patients until DLT was reached.
Results: 22 pts received EMD 72000 on 5 different DLs. Pts characteristics: Male 11/female 11; median age 58 years (range 29-71); median PS 90% (range 70-100%), primary tumors: upper oesophagus 2 pts, colorectal 11 pts, head and neck 4 pts, others 5 pts. The median number of prior CTx regimens was 3 (range 1-4) and all pts had progressive disease. The MTD was exceeded at DL5 (2000 mg of EMD 72000/week); DLTs were NCI-CTC grade 3 headache and fever after the first infusion. All 3 patients continued therapy with EMD 72000 at a reduced dose (1600 mg/week). Acneiforme skin reactions were mild with NCI-CTC grade 1 in 9 pts (41%) and grade 2 in 4 pts (18%). No other related adverse events especially no severe diarrhea and alterations in transaminases were seen. All pts are evaluable for tumor response: 5 out of 22 pts had a partial remission and 4 pts had stable disease. Responding pts have been treated for up to 25+ weeks without severe cumulative toxicities. Pharmacokinetic analysis showed a dose proportional increase of EMD 72000 in terms of Cmax and AUC, indicating that EMD 72000 exhibits predictable pharmacokinetics at the investigated dose range.
Conclusions: The MTD of a weekly schedule of EMD 72000 is 1600 mg per week with severe headache and fever being dose-limiting at higher doses. Objective remissions have been observed with EMD 72000 as single agent therapy.

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Thalidomide modulation of Irinotecan; an NF-kB dependent effect?

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Irinotecan (I) and thalidomide (T) in combination result in considerable antitumor activity in patients (pts) with colorectal cancer and attenuated toxicity. Preclinical evidence suggests T inhibits activation of the transcription factor NFkB, and decreases tumor resistance to I by inhibition of NFkB nuclear localization. We hypothesized that the mechanism for the favorable interactions of these agents is inhibition of NFkB activation. To test this hypothesis, we performed a phase I trial of I in combination with T. I, 125 mg/m^2 IV on days 1 and 8, every 3 weeks was administered in combination with daily oral T to pts with solid malignancies. To evaluate potential pharmacokinetic (PK) and biological interactions, T was started on day 3 of the first cycle. Plasma, serum and peripheral blood mononuclear cells (PBMC) lysates were obtained during days 1-3, 12-14 and 22-24, for evaluation of I and T Pks, as well as serum TNF alpha, bFGF and PBMC NFkB nuclear-localization (Trans-AM Active Motif ELISA). The starting T dose was 400 mg/day in a 10 pts cohort. De-escalation to 200 mg was planned in a second cohort of 10 pts if NFkB activation was inhibited in 80% of pts at 400 mg, for dose-effect evaluation. 33 cycles of the combination were given to the first 10 pts. Somnolence, nausea/vomiting and mild peripheral neuropathy were the most frequent side effects. No episodes of grade 3/4 diarrhea or myelosuppression occurred. 1 patient experienced a pulmonary embolism but was able to continue treatment while on oral anticoagulants. No differences in I Pks for the combination as compared to single agent were detected (SN-38+SN38G/I AUC metabolic ratio d1, 0.18±0.09; d22, 0.17±0.05). Although no changes in serum TNF or bFGF levels were detected on the first 4 pts, NFkB expression normalized to control increased after I alone (d1 baseline, 0.079±0.035mg; 48 h, 0.118±0.06 mg) (mean percentage increase, 44), but decreased after exposure to combined I/T (d22 baseline, 0.087±0.048 mg; 48 h, 0.06±0.024 mg) (mean decrease, 25%). Antitumor activity was observed in various refractory malignancies, including non-small cell lung, carcinoid, colorectal and thyroid carcinoma. In summary, T appears to improve the tolerability of I without interfering with its disposition and metabolism. Initial results suggest that I induces NFkB activation and that 400 mg of T daily can inhibit this activation. Data on additional patients receiving lower doses (200 mg) of T will be presented.

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Phase I, pharmacokinetic (PK), and biological studies of the epidermal growth factor receptor-tyrosine kinase (EGFR-TK) inhibitor OSI-774 (Erlotinib or Tarceva) in combination with docetaxel

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OSI-774, an oral quinazoline with potent and selective inhibitory effects on EGFR-TK, has demonstrated impressive activity in non-small cell lung carcinoma, and head/neck cancers in early clinical trials. This study was undertaken to evaluate the feasibility of administering OSI-774 with docetaxel, the propensity for PK interactions, and pertinent pharmacodynamic effects, in patients with advanced solid malignancies. From April 2001 to June 2002, 24 patients have received 84 total courses of OSI-774 (mg/day)/docetaxel (mg/m^2 every 3 weeks iv) at the: 100/60, 100/75, 125/75 and, 150/75 dose levels. Since docetaxel is begun 3 days before OSI-774 in course 1, docetaxel and OSI-774 PKs are being assessed alone (course 1) and in combination (course 2) to identify drug-drug interactions. To determine the effects of treatment on EGFR-TK phosphorylation, serial skin and tumor biopsies are being performed in selected patients. 150/75 and 125/75 dose levels were poorly tolerated due to a relatively high incidence of febrile neutropenia. Thus far, 100/75 dose level has been reasonably well tolerated in 11 patients and 100/75 appears to be the recommended dose for subsequent trials. The principal dose-limiting event has been fever associated with neutropenia. Anti-tumor activity observed includes a complete response (nasopharyngeal carcinoma), a minor response (non small cell lung cancer), and stable disease for 4-7+ months (bladder, ovary, stomach, skin, and non-small cell lung cancer). Paired analyses of docetaxel clearance values with and without OSI-774 indicates that OSI-774 does not significantly affect docetaxel clearance ($p = 0.67$, paired t-test). Pharmacodynamic studies assessing drug effects on EGFR-TK phosphorylation in normal skin (5 patients) and tumors (2 patients) have also been performed. Accrual of additional new patients is ongoing at the 100/75 dose level. In summary, the maximum tolerated and recommended dose of OSI-774 is projected to be 100 mg daily in combination with docetaxel 75 mg every 3 weeks for patients previously treated with chemotherapy. This study provides preliminary evidence of anti-tumor activity of this combination in head and neck, NSCLC, ovarian, and some other epithelial cancers. Subsequent phase II studies should be considered to evaluate the efficacy of this combination, especially in NSCLC where both OSI-774 and docetaxel have previously demonstrated activity.

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A clinical phase I and biomarker study of the Raf kinase inhibitor BAY 43-9006: preliminary evidence of activity in patients with advanced solid tumors

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Raf is a protein kinase that acts downstream of Ras, and is thus a significant contributor to the malignant phenotype driven by activated Ras signaling. BAY 43-9006 is a novel potent, orally active inhibitor of Raf and the first compound in this class to enter clinical trials. The primary objectives of the present study are to: define dose limiting toxicities (DLTs) and maximum

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