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

N. Schleucher[1], M. Tewes[1], O. Dirsch[1], K.W. Schmid[1], O. Rosen[2], S. Kovar[2], S. Seeber[1], A. Harstrick[2], U. Vanhoefer[1]. [1]*West German Cancer Center, Internal Medicine, Essen, Germany;* [2]*Merck KgaA, Darmstadt, Germany*

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?

M. Villalona-Calero[1], W. Duan[1], G. Otterson[1], B. Kleiber[1], K. Hindman[1], M. Shah[1], D. Young[1], W. Wu[2], J. Kuhn[2]. [1]*Ohio State University Comprehensive Cancer Center, Medicine, Columbus;* [2]*University of Texas Health Science center, School of Pharmacy, San Antonio, USA*

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

A. Mita[1], B. Forouzesh[1], M. Hidalgo[1], C. Takimoto[1], J. Norris[1], P. Nadler[2], D. Wood[2], A. Zitelli[2], J. Slack[2], E. Rowinsky[1]. [1]*Institute for Drug Development, San Antonio, Texas, USA;* [2]*OSI Pharmaceuticals, Melville, NY, USA*

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

D. Strumberg[1], D. Voliotis[2], J.G. Moeller[2], R.A. Hilger[1], H. Richly[1], C. Beling[1], M. Tewes[1], N. Schleucher[1], M.E. Scheulen[1], S. Seeber[1]. [1]*West German Cancer Center, Department of Internal Medicine and Medical Oncolog, Essen, Germany;* [2]*Bayer AG, Wuppertal, Germany*

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