pts but one have had elevations in glucose (gr 1-2, 31 crs; gr 3-4, 5 crs) that are felt to be related to dexamethasone. No hematologic or dose-limiting toxicity has been encountered. Although there have been no partial or complete responses, 3/15 evaluable pts have maintained stable disease for 2, 4, and 10 crs. One pt with melanoma refractory to biochemotherapy has had a decrease in the size and number of pulmonary metastases. Preliminary PK analysis shows no evidence of drug accumulation with chronic dosing. These results indicate that PI-88 administered SQ on this schedule is well-tolerated, achieves plasma concentrations capable of biologic activity, and demonstrates antitumor activity. Updated biologic correlate analysis will be presented. Dose escalation will continue until identification of an MTD, after which phase II studies in melanoma with biological as well as clinical endpoints are planned.

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Role of Id proteins in tumor angiogenesis

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Pathological angiogenesis is a hallmark of cancer. The helix-loop-helix Id proteins (Inhibitor of differentiation/DNA binding) are essential for angiogenesis of tumors. Blood vessels in Id knockout (Id1-/-; Id3+/-) mice lack the ability to branch and sprout to support growth or metastasis of tumors, and any tumor growth present show defective vascularization and extensive necrosis. To examine the molecular mechanisms by which Id exerts its effects on angiogenesis we used PTEN+/- mice that are genetically predisposed to lymphoma formation. Gene expression patterns of lymphomas derived from PTEN+/- Id wild type mice and from PTEN+/-, Id1-/-Id3+/- mutant mice were compared by using high-density DNA arrays. Comprehensive data analysis (including error model building, cis-regulatory element analysis) unraveled markers that are differentially regulated in the absence of Id expression. We identified both novel genes and genes known to be previously involved in the process of angiogenesis. Array data was validated by independent methods such as RT-PCR and Northern blotting. To demonstrate that the differentially expressed transcripts were derived from the endothelium of the blood vessels and not from contaminating tumor cells in situ hybridization or immunohistochemistry on Id wild type and Id mutant tumor tissues was performed. Functional assays to determine *in vivo* roles of these candidate genes in angiogenesis are underway.

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Preclinical evaluation of the tyrosine kinase inhibitor SU11248 for the treatment of breast cancer

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SU11248 is a potent inhibitor of the receptor tyrosine kinases Flk-1/KDR, PDGFR and Kit, all of which are expressed in human breast cancer and/or its supporting tissues. Angiogenesis is believed to play an important role in breast cancer, as microvessel density and elevated plasma VEGF levels have been reported as negative prognostic indicators. Additionally, we have demonstrated PDGFRb expression and phosphorylation in a majority of human breast cancer specimens by western analysis. Immunohistochemical analyses demonstrated the presence of PDGFRa, KDR, and their ligands in human breast cancer tumor samples as well. To support the potential use of SU11248 in breast cancer treatment, we are evaluating it as a monotherapy and in combination with other agents in preclinical models. In a transgenic model of mutant Ras-driven breast cancer (MMTV-Ha-Ras), SU11248 was administered orally to mice with established mammary tumors. Daily treatment of 40 mg/kg for 20 days resulted in tumor regression. In the MX-1 human breast cancer xenograft model in athymic mice bearing established subcutaneous tumors at the start of therapy, 40 mg/kg/day of SU11248 treatment resulted in significant tumor inhibition (52% inhibition, p = 0.02) as compared to controls. SU11248 and docetaxel (Taxotere®), an anti-mitotic microtubule inhibitor, have both been shown to prolong survival in murine breast cancer models. Therefore, combination therapy of these two agents is of interest in examining efficacy for the treatment of breast cancer. In the MX-1 model, a 3-arm dose-response study was performed in mice treated with SU11248 (40 mg/kg/day), docetaxel (10 mg/kg once per week for 3 weeks), or their combination, yielding 53% (p = 0.02), 73% (p = 0.0007), and 89% ($p < 0.0001$) inhibition of tumor volume, respectively, after 20 days of dosing. The combination therapy resulted in enhanced *in vivo* anti-tumor activity as compared to each treatment alone. The combination of SU11248 and docetaxel was well-tolerated. Additional combination studies with SU11248 are currently in progress. SU11248 is currently in Phase I clinical trials in patients with advanced cancers.

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Defining the biologically active dose for PTK787/ZK222584 (ptk/zk), a vascular endothelial growth factor (VEGF) receptor inhibitor, based on the assessment of two biomarkers [dynamic contrast enhanced magnetic resonance imaging (DCE-MRI), plasma VEGF] in two phase I studies

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PTK/ZK is an orally active inhibitor of the VEGF receptor tyrosine kinases (flt-1/KDR), inhibiting VEGF-induced angiogenesis. Selecting the target dose may be difficult as the biologically active dose is likely to be lower than the maximum tolerated dose. Two biomarkers, DCE-MRI and plasma VEGF, were evaluated to identify the biologically active dose. PTK/ZK treated patients received a continuous daily dose of 50, 150, 300, 500, 750, 1000, 1200, 1500, or 2000 mg until progressive disease or intolerable toxicity. Pharmacokinetic (PK) samples were taken at predose, and days 1, 15, and 28. DCE-MRI was performed at baseline, day 2 (d2) and end of cycle 1 (ec1). The contrast enhancement for tumor was assessed by calculating the bi-directional transfer constant (ki) and expressed as a percentage (%) of baseline. Plasma VEGF was sampled at predose, 10 hrs, days 8, 15, 15 + 10 hrs, 22, and 28. Two Phase I studies (n=76), provided 22 evaluable patients with colorectal cancer and liver metastasis for DCE-MRI analysis, and 63 evaluable patients with advanced cancers for plasma VEGF and PK analysis. Using SWOG criteria, non-progressive disease was defined as >= 2 months stable disease. PTK/ZK was rapidly absorbed with T_{max} of 1 to 2.5 hours. At steady-state (day 15), the exposure (AUC) reduced by 30%. Dose proportionalilty was observed up to 1000 mg. The $t_{1/2}$ was 3-6 hours. No dose-limiting toxicity was observed up to 2000 mg. A significant relationship exists between the reduction in % of baseline ki and dose (d2:p=0.01; ec1: p=0.0003), AUC (d2:p<0.0001; ec1:p=0.003), C_{min} (d2:p=0.0003; ec1:p<0.0001), and liver disease size at end of cycle 2 (d2:p=0.004; ec1:p=0.0001). Non-progressors had significantly greater reduction in mean ki (d2: p=0.004; ec1: p=0.006). A 50-60% reduction in ki was associated with non-progressive disease, and exposure-response modelling suggests a target exposure of 114 hr·μM. Accounting for PK variability, a dose with the lower limit of exposure at 114 hr·μM should be the optimal dose, and thus 1200 mg/day is recommended as the biologically active dose. Supporting the selected dose is the dose-dependent rise in VEGF for non-progressors; these patients who received >= 1000 mg achieved up to 5 fold rise in VEGF. The rise in VEGF would be consistent with an increased expression of VEGF by tumor cells in response to hypoxia induced by the reduction in tumor vascular permeability and vascularization with PTK/ZK treatment.

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First dose in man phase I study of the anti-metastatic uPA inhibitor WX-UK1

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The plasminogen activation system with its key components urokinase-type plasminogen activator (uPA), the cell surface receptor uPAR and the inhibitor PAI-1, plays an important role in cancer cell invasion and metastasis. Inhibition of this system results in reduction of primary tumor growth and metastasis and is therefore an attractive target for therapeutic intervention. WX-UK1 is a synthetic inhibitor of uPA and the first representative of this substance class in clinical development. In this first dose in man, double-blind, randomized, three-way cross-over, placebo-controlled, phase I study pharmacokinetics, pharmacodynamics and safety and tolerability was investigated. Six escalating i.v. doses of WX-UK1 were administered in the range of 0.01-0.3 mg/kg and each dose was given to six healthy, male vol-