liver dysfunction was reported by 1 pt each. Two (4.8%) pts, both with thyroid carcinoma, achieved a partial response, and 11 pts (26.2%) had stable disease, with a median duration time of 5.6 months (range: 2.7–9.0 months).
Conclusions: In this safety study, the addition of enzastaurin to standard pemetrexed infusion did not result in additional pemetrexed-related toxicities. Thus, it appears that enzastaurin can be safely combined with pemetrexed. In addition, the antitumor responses observed suggest that this combination should be further evaluated for antitumor activity.

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Safety of Volociximab as a monotherapy and in combination with chemotherapy the result of three phase II studies

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Background: Volociximab is a novel high-affinity chimeric (82% human/18% murine) IgG4 monoclonal antibody that specifically binds $\alpha5\beta1$ integrin. Volociximab is being developed as an anti-angiogenic agent targeting $\alpha5\beta1$ integrin for the treatment of solid tumors. The mechanism of action of volociximab is distinct from that of other anti-angiogenic agents because it acts downstream and is independent of the growth factors that stimulate angiogenesis, such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF).
Methods: A total of 100 patients (pts) have been treated with volociximab, 10 mg/kg IV every 2 weeks in 3 different multicenter, open label, single cohort phase II studies. Forty pts with refractory or relapsed metastatic renal cell carcinoma (RCC) received volociximab as a single agent until disease progression, forty pts with metastatic melanoma received volociximab with DTIC, 1 g/m^2 monthly, twenty pts with metastatic adenocarcinoma of the pancreas (MPC) received volociximab every 2 weeks with gemcitabine (Gem), 1 g/m^2 q3w. Pts were evaluated for safety and efficacy every 8 weeks or until disease progression using RECIST criteria. An independent data safety monitoring board was utilized to review safety data.
Results: A total of 100 pts were evaluated for safety using (NCI-CTC). Ninety-eight pts (98%) reported at least one AE; 26 pts (26%) had grade 1 and 39 pts (39%) had grade 2. Twenty-five pts (25%) had grade 3 AEs and eight pts (8%) had grade 4 AE's. The total number of pts who had grade 3 or 4 AEs considered possibly or probably related to volociximab were 11 pts (11%) and 3 pts (3%), respectively. Twenty-nine pts (29%) had an SAE which in 11 pts (11%) were considered to be possibly related to volociximab. The most common all-grade AEs for RCC were fatigue in 25 pts (62.5%) and nausea in 13 pts (32.5%) of which none were grade 3 or 4. In the melanoma study nausea was observed in 20 pts (50%) and fatigue in 17 pts (42.5%); none were grade 3 or 4. In MPC, nausea was reported in 13 pts (65%), vomiting in 12 pts (60%) and constipation in 10 pts (50%). All AEs were grade 1 and 2 except 1 pt (5%) had grade 3 vomiting.
Conclusion: Volociximab is well tolerated as a single agent and in combination with chemotherapy. Side effects seen in melanoma and MPC are similar to those expected from Gem and DTIC. Volociximab is currently being evaluated at 15 mg/kg qw in ongoing trials in RCC, MPC and Melanoma.

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Functional biomarkers to select dose and predict tumor response to anti-VEGF drugs

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For efficient drug development, biomarkers are needed to aid selection of optimal dose and schedule, to select patients and to predict tumor response to treatment. Biomarkers may be molecular or, alternatively, functional parameters that are altered as a consequence of the action of a drug on its molecular target. For the development of anti-angiogenic drugs, direct molecular markers have proven difficult because of the low expression of the target within the tumor mass and limitations for repeated tumor tissue sampling. Functional parameters that can be measured easily and repeatedly before and during drug treatment would overcome these difficulties.
We have evaluated several physiological and tumor-related functional parameters in an orthotopic breast cancer model (BN472) in rats using, PTK787/ZK222584*, a VEGF receptor tyrosine kinase inhibitor currently in phase III clinical trials for cancer. Blood pressure (BP), heart rate (HR), body temperature (BT) and interstitial tumor pressure (IFP) were measured in conscious freely moving rats by telemetry.
PTK787/ZK induced dose-dependent and significant decreases in HR, BT and IFP and increases in BP. The changes in all of these parameters occurred in the same dose range (12.5−100 mg/kg p.o.) but the duration of the responses varied. Responses in BT and HR were more transient than for BP. IFP remained changed over a longer period after a single dose, was further reduced after repeated dosing and after several doses, remained continuously lowered. Effects on BP, HR and BT probably reflect effects of VEGF inhibition on normal physiological mechanisms, whereas the effects on IFP reflect changes in the tumor vasculature. All parameters might be useful for selection of effective doses for complete inhibition of VEGF activated pathways, whereas IFP may be useful to select the dose needed to impact tumor growth. Since the acute response in IFP after acute dosing correlated with effects on tumor size after chronic dosing, IFP may also be a parameter that could predict tumor response to treatment.
In conclusion, our data demonstrate that functional biomarkers may be used to assess effects of VEGF inhibition on normal physiological mechanisms (on target side effects) or effects on tumor growth. Some of these parameters may also be useful to predict anti-angiogenic and anti-tumor response.
*PTK787/ZK222584 is jointly developed by Novartis and Schering AG.

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Membrane-type I matrix metalloproteinase is tyrosine phosphorylated on its cytoplasmic domain: role in in vitro angiogenesis

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Background: Membrane-type 1 matrix metalloproteinase (MT1-MMP) is a transmembrane matrix metalloproteinase (MMP) that plays an important role in both tumor cell migration and angiogenesis. In addition to its matrix-degrading activity, the cytoplasmic domain of MT1-MMP has been suggested to be important for both processes although the mechanisms involved remain poorly understood.
Methods: COS-7 cells were transfected with MT1-MMP cDNA constructs and phosphorylation studies were performed using immunoprecipitation techniques and two-dimensional gel electrophoresis. We have also produced a phosphospecific antibody against MT1-MMP. *In vitro* angiogenesis was performed in human umbilical vein endothelial cells (HUVEC) and bovine aortic endothelial cells (BAEC), by measuring morphogenic differentiation into capillary-like structures on Matrigel® and cell migration in Boyden® chambers.
Results: In this study, we show for the first time that MT1-MMP is tyrosine phosphorylated on its cytoplasmic domain, and that this phosphorylation requires the kinase Src. MT1-MMP tyrosine phosphorylation is induced by stimulation of endothelial cells with the proangiogenic factor sphingosine-1-phosphate (S1P), and is important for *in vitro* angiogenesis since a MT1-MMP mutant lacking the phosphorylated tyrosine residue failed to promote endothelial cell migration and their morphogenic differentiation into capillary-like structures.
Conclusion: Given that pharmacological inhibition of MMP catalytic activities has been shown to induce several undesirable side-effects, these findings suggest that the inhibition of MT1-MMP tyrosine phosphorylation may represent an unexpected alternative strategy for antiangiogenic drug development.

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Matrix metalloproteinase-2 (MMP-2) and -9 (MMP-9) and their tissue inhibitors (TIMP-1 and TIMP-2) in differential diagnosis between low malignant potential (LMP) and malignant ovarian tumors

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Background: Ovarian tumors of low malignant potential (LMP), also called borderline ovarian tumors, account for about 10% to 15% of all epithelial ovarian malignancies. The most important criterion for LMP ovarian tumor is the lack of invasion. The overall survival of patients with a LMP tumor is significantly better compared to those with a malignant ovarian tumor. Preoperative differential diagnosis between LMP and malignant ovarian tumors is often difficult. At least in advanced ovarian cancer,