Methods: This study is a multi-center, placebo-controlled, Phase II randomized discontinuation study in patients with advanced refractory progressive solid tumors which included advanced sarcoma patients. Initially, all patients received oral BAY at 400 mg twice-daily for12-weeks. At the end of this 12-week induction phase, antitumor responses were assessed. Patients whose target lesion tumor burden showed growth greater than 25%(progressive disease, PD) during the induction phase were discontinued from the study. Patients whose tumor demonstrated target lesion tumor burden shrinkage greater than 25% (responders) were not randomized and continued BAY in an open label phase, until disease progression or toxicity. Patients with tumor target lesion measurements that remained within 25% of the baseline pretreatment measurements (stable disease, SD) were randomized to receive either BAY, 400 mg every 12 hours, or matching placebo.
Results: To date 27 advanced sarcoma patients with different histologies have been enrolled of which 23 pts were evaluable for response. The median age was 56 years (range of 24y to 79y), ECOG performance status 0 (38%) and 1 (63%) and all (100%) had at least one prior systemic therapy. Seven pts discontinued study drug earlier than the 12-week assessment and 16 pts have been treated with BAY up to the 12-week assessment point. Investigator's assessment of response at the 12 week assessment point demonstrated 3 responders (continued on BAY), 5 SD (randomized to either BAY versus placebo) and 8 PD (off study) at the 12 week assessment point. Responder's histologies were 2 gastrointestinal stromal tumors (refractory to imatinib mesylate) and 1 synovial sarcoma. The most frequent drug-related toxicities included hand-foot skin reaction, rash/desquamation, anorexia, diarrhea, hypertension and fatigue.
Conclusion: While the study is still ongoing and the randomized portion of the study is yet to be analyzed, these preliminary data suggest that BAY may have potential anti-tumor activity in advanced sarcoma. Further clinical study in this setting is warranted.

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Preclinical antitumor activity of second generation analogs of SDX-101

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Introduction: SDX-101 is an anti-neoplastic drug with a novel mechanism of action currently in Phase II clinical trials in leukemia. SDX-101 exerts its anti-neoplastic activity by inhibiting the activity of the beta-catenin pathway, via its interaction with the PPAR-RXR/beta-catenin nuclear complex.
Aim: The aim of this project was to synthesize and assess the cytotoxic activity and the mechanism of action of a series of SDX-101 analogs created by structural modification at various positions on the parent molecule.
Results: The SDX-101 analogs were screened in cell-based cytotoxicity assays and functional assays for beta-catenin inhibition. Three lead compounds have been identified: compound # 2, compound #5 and compound #8. As is the case with SDX-101, these compounds displayed selective cytotoxic activity for malignant cells when compared to the normal cells. The IC50 observed in LNCaP prostate cancer cell line ranged from 13±3 μM (#5) to 39±13 μM (#2). Compound #5 displayed an IC50 of 48±1 μM and 28±3 μM in the prostate cancer cell lines DU-145 and PC-3 and an IC50 of 16±2 μM and 8±3 μM in the colon cancer cell lines SW-480 and HCT-116. The IC50 values obtained with each of the analogs in these prostate cancer cells were markedly lower than those of SDX-101 (range 122–505 μM). Beta-catenin inhibitory activity of these leads was confirmed by reporter-promoter assays as well as by measuring mRNA and protein levels of beta-catenin-regulated genes such as cyclin D1 in cancer cell lines. The analogs were also potent in inhibiting tumor growth of Daudi xenografts in SCID mice. Following treatment with 125–250 mg/kg/d oral dose for four weeks, the mean tumor volumes for vehicle, #5, #8, and #2, were 1543 mm3, 946 mm3, 1078 mm3 and 825 mm3, respectively ($p<0.07$ each analog vs vehicle). The tumor volumes of SDX-101(400 mg/kd/d) and chlorambucil (2 mg/kg/d) treated mice were 1157 mm3 and 864 mm3 respectively. Time for the tumors to reach eight times (8X) the initial volume (100 mm3) was markedly delayed with all SDX-101 analogs: the controls reached 8X volume in approximately 9 days compared to approximately 21 days for the analogs. The treatment was well tolerated with no mortalities and no significant body weight loss.
Conclusions: Orally effective and well tolerated SDX-101 analogs have been identified with potent anti-neoplastic activity and similar mechanism of action.

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Sulindac sulfide modulates beta-catenin dependent expression of the metastasis-associated gene S100A4/mts1

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Background: This study was designed to identify the impact of pathway modulators on the newly identified target gene of the beta-catenin/TCF pathway, the metastasis-associated gene S100A4/mts-1/metastasin.
Material and Methods: Gene knock-out technology was coupled to cDNA array analysis of the colon carcinoma cell line HCT116 (heterozygous for D45; wt/m) and a derived wt/-knock-out strain. Target gene confirmation was pursued using additional knock-out cell strains (wt/−; −/m) and a naturally nullosomic tumor cell line NCI-H28 investigating both mRNA and protein levels. Wild type and/or D45-beta-catenin-transduced clones of knock-out strains and NCI-H28 were created to prove the impact of D45-mutation on target gene expression and migration. The beta-catenin/TCF-pathway was analyzed by gel shift and reporter assays with several target gene promoter variants. In order to analyze the dependency of S100A4 expression on the beta-catenin/TCF-pathway, the modulators LiCl, known as inhibitor of the glycogen synthase kinase 3b, and sulindac sulfide, known to target the nuclear accumulation of beta-catenin, were employed.
Results: S100A4, which is associated with the metastatic phenotype, was dramatically down-regulated in wt/-knock-out strains compared with HCT116 cells and −/m knock-out strains. S100A4 expression positively correlated with the in vitro invasive phenotype. In NCI-H28/D45 cells, S100A4 levels were increased up to 70-fold, correlating with enhanced migration behavior. S100A4 promoter activity of deletion variants was dependent on beta-catenin availability and TCF-4 binding site presence. Treatment with the pathway activator LiCl led to induction of S100A4 expression in HCT116 cells and in the knock out strains analyzed. Treatment with the pathway inhibitor sulindac, however, clearly reduced the expression levels of S100A4 in these cell lines. Moreover, sulindac-treated cells showed reduced migration behavior compared with the non-treated controls.
Conclusion: S100A4 is a target gene of the beta-catenin/TCF-pathway. Mutant D45-beta-catenin allele acts in a dominant fashion to activate S100A4 expression. Modulators of beta-catenin signaling may offer potential as antimetastatic agents by interdicting S100A4 expression.

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A phase II trial to assess the efficacy and safety of Gefitinib (IressaTM) in patients with metastatic hormone refractory prostate cancer (HRPC) who progressed on treatment with a luteinising hormone releasing hormone analogue (or post orchiectomy) plus an antiandrogen

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EGFR is overexpressed in HRPC. Gefitinib enhances antiproliferative effect of antiandrogen bicalutamide when coadministered to moderately androgen-independent prostate tumour xenografts. This is a phase II trial aimed to assess activity and safety of gefitinib in patients with metastatic HRPC who progressed to an LHRH analogue plus antiandrogen. Patients received gefitinib 250 mg daily and antiandrogen plus LHRH analogue for 2 months or until disease progression (PD). Patients with PD stopped antiandrogen therapy and continued gefitinib with LHRH analogue. Thirty-four patients have been planned for the study. Global health status, pain score and quality of life (QoL) have been assessed at baseline and every 2 months by visual analogue scale, McGill-Melzack and EORTC QLC-30 questionnaires. Patients who had no surgery underwent a prostate biopsy to study EGFR and HER2 expression. Serum HER2 and EGFR extracellular domain (ECD) were evaluated every 2 months. EGFR and HER2 ECD were assayed by ELISA method. A cut-off of 15 ng/ml was used for HER2 ECD. A reference range for HER1 was determined on 30 healthy subjects sera (45.7–71.3 ng/ml). From April 2003 to May 2004 18 patients have been enrolled. Baseline data are available for all cases, 16 cases are evaluable for safety and 11 for efficacy. The median age was 65 years (range 56–78). WHO performance status was 0 in 13 and 1 in 3 patients. Seven patients received no prior surgery. Median basal PSA was 35.9 ng/ml (8.2–463.0). Median duration of treatment with gefitinib was 98 days (5–369). A PSA levels drop (>25%) respect to baseline was observed in 2 patients, and PSA stabilization in 1 case. Median time to progression