p53-mutated human colon adenocarcinoma cell line SW480 (proliferation, clonogenicity, cell cycle, different schedulings) and *in vivo* with the combination of EPO906 and a minimally fractionated treatment schedule of IR (4×3Gy) in an nude mice xenograft tumor model.
Results: The paclitaxel-refractory colon cancer cell line SW480 was sensitive to treatment with subnanomolar concentrations of EP0906. Combined treatment with EPO906 followed by clinically relevant doses of IR (2 and 5 Gy) further resulted in a supraadditive cytotoxic effect in the low dose range (0.1 nM EPO906). Cell cycle analysis revealed a G2/M-related mechanism of radiosensitization by EPO906. Based on the supraadditive *in vitro* effects in this radioresistant cell line, combined treatment with EPO906 and fractionated irradiation was tested *in vivo* against nude mice tumor xenografts. Combined treatment resulted in an at least additive tumor growth delay.
Conclusions: EPO906 retains full activity in multidrug-resistant human colon cancer cell line *in vitro* and *in vivo* alone and in combination with IR. Thus Epothilone might be a promising alternative in Paclitaxel-resistant, PgP-overexpressing tumors for a combined treatment regimen using IR and microtubule inhibitors.

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New synthetic Epothilone Derivative ZK-EPO inhibits tumors generally resistant to chemotherapy

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Based on a broad fully synthetic drug optimization program with more than 350 synthesized Epothilone analogs, we have developed ZK-EPO, a new derivative with outstanding preclinical efficacy.
In contrast to other tubulin targeting drugs (i.e. paclitaxel), ZK-EPO is rapidly taken up by the tumor cells and preferentially accumulates in the cell nucleus.
ZK-EPO inhibits the growth of a wide range of different human cancer cell lines, and, unlike paclitaxel, also suppresses the growth of cell lines that over-express P-glycoprotein at sub-nanomolar concentrations. We have shown that this epothilone is not recognized by cellular efflux mechanisms. Dose response studies with *in vivo* xenograft cancer models either sensitive or intrinsically resistant to paclitaxel demonstrated strong antiproliferative activity and a large therapeutic window of ZK-EPO.
To identify further indications for clinical development we have tested ZK-EPO in a broad range of tumor models. Beside to the classical indications for tubulin stabilizing drugs as breast, ovarian, and lung cancer, we have observed strong antiproliferative activity in pancreatic and colorectal cancer, as well as in melanomas.
In pancreatic cancer models, ZK-EPO has clearly demonstrated antitumor activity that is superior to Gemcitabine in all five tumors evaluated in this study (four cell lines and one clinically derived tumor). Against paclitaxel- or dacarbacine-resistant human melanoma models, ZK-EPO produced strong antiproliferative activity: *i.e.* SK-Mel-28 and A375.
This broad preclinical activity spectrum provides strong evidence, that the novel epothilone analog ZK-EPO may have antitumor efficacy in a variety of rather chemoresistant cancer indications and recommends an extended evaluation of this compound in clinical trials.
The potential of the new derivative is currently being investigated in patients with different solid tumors.

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Comparative pharmacokinetic (PK) study of a cremophor-free, protein stabilized, nanoparticle formulation (ABI-007) and a cremophor-based formulation of paclitaxel (P) in patients with advanced solid tumors

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Background: Abraxane™ (ABI-007 or ABX), a novel, albumin-bound nanoparticle P, was developed to eliminate solvents from the 1st-generation formulation of P (Taxol® or TAX). The absence of Cremophor-EL (CrEL) and alcohol allowed ABX to be administered with a shorter infusion (30 minutes) using standard IV tubing without steroid and antihistamine premedication. A phase 3 trial of ABX vs TAX in patients with metastatic breast cancer demonstrated superior antitumor activity for ABX as measured by response rate and time to disease progression (O'Shaughnessy, SABCS 2003). The present study compared the PK of P following administration of ABX and TAX at the doses and schedules used in the phase 3 trial.
Patients and Methods: Patients with advanced solid tumors were randomly assigned to receive either ABX 260 mg/m^2 (n=14) or TAX 175 mg/m^2 (n=12), both IV q3w. Whole blood samples (12 scheduled for ABX; 13 for TAX) from the first dose cycle were analyzed using a validated LC-MS/MS method (lower limit of quantitation: 5 ng/mL). Noncompartmental PK parameters were estimated using WinNonlin 4.1 (Pharsight, Cary NC).
Results: For both ABX and TAX, P displayed multiphasic disposition. AUC_{inf}, λ_z, and $T_{1/2}$ were similar for ABX and TAX (see Table). Plasma clearances and volumes of distribution were clinically different and reached statistical significance for CL and V_z. Differences in T_{max}, C_{max}, and dose adjusted C_{max} were attributed to differences in dose and duration of administration. When analyzed with data from other clinical trials, ABX AUCs were linear with respect to dose from 80 to 300 mg/m^2. The observed parameters were similar to those reported for TAX and to previous clinical trials for ABX.
Conclusion: Nonlinear pharmacokinetics of TAX have been attributed to the formation of CrEL micelles which sequester P in the intravascular compartment. This study suggests that CrEL micelles also decrease P clearance by prolonging circulation in the intravascular space. In animals bearing the MX-1 mammary tumor, ABX resulted in 30–40% higher intratumor P concentrations compared to equal doses of TAX. This difference may be due to in part to sequestration of P by CrEL micelles which reduced the bioavailability of TAX compared to ABX. In addition, the use of albumin as the delivery vehicle may enhance plasma clearance and drug transport into tumors by taking advantage of albumin receptor (gp60)-mediated transcytosis across endothelial cells (Desai, SABCS 2003).

Parameter	Abraxane (260 mg/m^2 IV over 30 minutes) Mean (%CV)		Taxol (175 mg/m^2 IV over 3 hours) Mean (%CV)		p-value
CL (L/h•m^2)	21.13	(43.8)	14.76	(31.8)	0.048
Vd_{ss} (L/m^2)	230.7	(54.3)	156.3	(43.2)	0.211
V_z (L/m^2)	663.8	(48.1)	433.4	(31.1)	0.040
AUC_{inf} (ng•h/mL)	14,788.6	(45.3)	12,602.7	(21.0)	0.524
Dose adjusted AUC_{inf} (ng•h/mL)	56.84	(46.3)	71.90	(21.1)	0.049
C_{max} (ng/mL)	22,968.6	(112.5)	3,543.3	(57.2)	< 0.001
Dose adjusted C_{max} (ng/mL)	88.69	(114.2)	20.14	(55.8)	< 0.001
T_{max} (h)	0.36	(45.2)	2.65	(27.6)	< 0.001
λ_z (h^{-1})	0.033	(16.9)	0.034	(13.0)	0.477
$T_{1/2}$ (h)	21.6	(17.2)	20.5	(14.6)	0.479
$AUC_{\%extrap}$ (%)	2.8	(41.3)	2.8	(52.6)	0.983

DNA-interactive agents

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Clofarabine administered weekly to adult patients with advanced solid tumors in a phase I dose-finding study

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Background: Clofarabine, a next-generation nucleoside analogue that inhibits DNA synthesis, has demonstrated activity in acute leukemia in Phase I & II trials. The agent has also shown potent cytotoxic activity in a wide range of solid tumor cell lines and therapeutic activity in murine tumor models.
Methods: A Phase I dose-finding study is ongoing to determine the maximum tolerated dose (MTD) of clofarabine in patients with advanced solid tumors. To avoid myelosuppression observed with the daily × 5 administration used for hematologic malignancies but yet to achieve high plasma concentrations, clofarabine is administered IV on days 1, 8, and 15 of a 28-day cycle. Patients are treated with escalating doses starting at 4 mg/m^2 until MTD is determined.
Results: Preliminary data are available for 32 patients, 17 males and 15 females with a median age of 66 years (range 48 to 78). The patients were treated in 8 cohorts; 3 each at 4, 6, 10, 14, and 27.5 mg/m^2, 5 at 18 mg/m^2, 8 at 22 mg/m^2, and 4 at 34 mg/m^2. Tumor types include lung (7), colorectal (7), pancreas (3), prostate (3), SCC larynx (2), transitional cell bladder (2), cholangiocarcinoma (2) and one each of melanoma, ovarian, gallbladder, SCC esophagus, SCCHN, and leiomysarcoma. All patients received at least one cycle of therapy, 8 pts completed ⩾3 cycles of treatment with 5 pts completing 4 cycles. Adverse events occurring in >30% of patients include fatigue, nausea, vomiting, weakness, anorexia, and dyspnea. Available hematologic data on 30 patients indicate 4 (13%) experienced transient grade 3 or 4 neutropenia; no febrile neutropenia was observed. Twenty-six of 30 patients (87%) experienced grade 3 lymphopenia; however 18 (60%)