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Ixabepilone, a novel tubulin interacting agent, given every other week in combination with irinotecan in patients with advanced malignancies: a phase i and pharmacokinetic study

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Background: Ixabepilone, a semisynthetic novel derivative of Epothilone B, is active against paclitaxel resistant and sensitive tumors. Myelosuppression and neuropathy were dose limiting in single agent phase **I**. This combination phase **I** study aims to establish the Maximal Tolerated Dose (MTD) of Ixabepilone with Irinotecan, characterize dose limiting toxicities (DLTs), the safety profile of the combination and describe antitumor activity.
Methods: Ixabepilone and Irinotecan were given intravenously, on days 1 and 15 of a 28-day cycle, to patients (pts) with advanced solid tumors previously treated with up to 3 prior chemotherapy regimens. Plasma levels of both drugs were measured on the first course.
Results: Thirty pts (median age: 52, ranging 26–71; male/female: 17/13; PS: 0–1) including 29 pts evaluable for toxicity received a total of 116 cycles of Ixabepilone/Irinotecan. Tumor types consisted of lung (7 pts), gynecological (6 pts) gastrointestinal (8 pts), breast (2 pts), and others (7 pts) cancers. Median number of prior chemotherapy regimens was 2.

Dose level	Ixabepilone (mg/m^2)	Irinotecan (mg/m^2)	# patients	DLTs
0*	20	120	6	1/6 Gr3 Neutropenia
1	15	150	3	0/6
2	15	180	6	1/6 Febrile neutropenia
3	20	180	3	0/6
4	25	180	6	1/6 Febrile neutropenia
5	30	180	6	1/6 Gr3 Diarrhea

* 1 patient had G2 neutropenia at D14 which would be a DLT before the protocol was amended to allow dose escalation with up to grade 2 ANC at Day 15.

While a protocol defined MTD has not been reached, dose level (DL) 3 (Ixabepilone 20mg/irinotecan 180mg) is being expanded as a potential recommended phase **II** dose based on cumulative neuropathy at higher doses (Gr 3 neuropathy: 1 pt at DL 3, 3 pts at DL 4 and 2 pts at DL5). The combination has antitumour activity with 4 partial responses in pts with non-small cell lung cancer (2), small-cell lung cancer (1), and carcinoma of unknown primary (1).
Conclusion: Ixabepilone 20 mg irinotecan 180 mg on days 1 and 15 of a 28-day cycle is the potential recommend dose. Final assessment will be presented at the meeting.

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Phase I study of a new Halichondrin B analog, E7389, administered by 1-hour IV infusion every 21 days

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E7389 is a synthetic analog of the biologically active portion of Halichondrin B and is currently in clinical studies. It is a novel tubulin-binding agent that inhibits tubulin polymerization into functional microtubules. This Phase **I** study was designed to determine the MTD, safety and pharmacokinetics (PK) using a 1-hour IV infusion on Day One of a 21 day-cycle.
13 patients (pts) with advanced solid tumors were enrolled at 2 centers. Median age was 61 (30–72). All patients were PS 0/1. Tumor types were lung adenocarcinoma (3), renal cell (3), gall bladder (1), bladder (1), sarcoma (1), pancreas (1), NSCLC (1), endometrial (1), prostate (1). Prior treatments included at most two prior chemotherapies. Doses ranged from 0.25 to 4 mg/m2.
Three out of 3 pts developed DLT at 4 mg/m2. All had febrile neutropenia, accompanied by grade (Gr.) 2 mucositis in one. The first pt. at the next lower dose (2.8) experienced febrile neutropenia. A Gr. 3 neutropenia attributed to extensive prior radiation occurred in every cycle (6) in one pt. treated at 1 mg/m2. The other drug-related toxicities reported were Gr. 1/2 and included anorexia, fatigue, nausea, anemia and thrombocytopenia (Gr. 1), increased alkaline phosphatase, increased ALT and hyperkalemia. The median number of cycles received was 2 (1–6). No response has yet been observed but 4 pts. had SD for 4 cycles or more. Enrollment is continuing.
Preliminary pharmacokinetics (N=10) were best described by a two-compartment model, in which there was rapid distribution, slow clearance, and prolonged elimination with a small fraction (5–12%) excreted unchanged into the urine. Average V_{ss}, CL, and MRT ranged from 53.2 to 218.5 L, 1.4 to 4.4 L/hr, 28.1 to 50.1 hours at the dose levels observed. The C_{max} and AUC increased in a dose-dependent manner between 0.25 and 1 mg/m^2. Higher dose levels are being studied. The ratios of C_{max} to $C_{trough,96hr}$ ranging from 0.33% to 1.5% as well as the calculated accumulation factor of 1 for all 10 subjects indicated that despite the prolonged elimination phase, repeated dosing is unlikely to cause drug accumulation with the regimen studied.
Updated information will be provided at the meeting. Phase **II** studies will be started upon completion of Phase **I**.

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A Phase 1 study of Epothilone B analog BMS-247550 in combination with carboplatin in recurrent and/or refractory solid tumors

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Background: BMS-247550 is a semi-synthetic analog of the natural product epothilone B. BMS 247550 belongs to a novel class of non-taxane microtubule stabilizing agents obtained from the fermentation of a cellulose-degrading myxobacterium, *Sorangium cellulosum*.
Material and methods: BMS-247550 is administered by a 1-hour infusion on days 1, 8 and 15 of each 28 day cycle. Subjects received pretreatment with diphenhydramine, ranitidine and dexamethasone prior to each infusion. The starting BMS-247550 dose was 10 mg/m^2 with planned dose escalation in successive cohorts of 3–6 subjects. Carboplatin was administered on day 1 to achieve an AUC=6. Enrollment at the maximum tolerated dose (MTD) was expanded to allow collection of tumor biopsies in at least ten subjects to determine pretreatment expression of survivin.
Results: A total of 26 subjects have been enrolled onto this study. The maximum administered dose was 15 mg/m^2 of BMS-247550 in combination with carboplatin AUC=6. At this dose level two of five subjects experience dose-limiting hematologic toxicity, which halted dose-escalation. Enrollment was then started at a dose of BMS-247550 12.5 mg/m^2, which ultimately proved to be the maximum tolerated dose. Tumor biopsies were obtained in at least ten subjects at this dose level. The survivin protein levels ranged between 1.7 to 34.5 ng/mg of protein, as determined by an ELISA. In 5 of the 10 samples, where both protein and mRNA transcript levels (by QPCR) of survivin were determined, survivin/histone H3 mRNA copy ratio ranged between 0.01 to 0.52, which in each sample did not correlate with the survivin protein level.
Conclusions: The MTD of this regimen is 12.5 mg/m^2 of BMS247550 weekly $\times$ 3 in combination with Carboplatin AUC=6 when administered every 28 days.
This study was partially supported by Bristol-Myers Squibb and CTEP/NCI.

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Multidrug-resistant tumors treated with Epothilone B in combination with clinically relevant doses of ionizing radiation

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Background: Treatment with ionizing radiation (IR) in combination with microtubule inhibitors like taxanes represents a favourable radiochemotherapeutical approach against various tumor entities. However treatment with taxanes is often limited by taxane-related toxicities and furthermore taxanes are less effective in tumors overexpressing the P-glycoprotein efflux pump. EPO906, a novel microtubule inhibitor, retains full activity in multidrug-resistant tumor cells. Here we have investigated combined treatment of EPO906 with IR in vitro and in vivo against human, treatment-resistant adenocarcinoma cells.
Material and Methods: The effect of the combined treatment with IR and Epothilone B (EPO906, Novartis Oncology) or Paclitaxel was tested *in vitro* with the multi-drug-resistant (P-glycoprotein (PgP)-overexpressing) and

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%)