with T_{max} ranging between 1 and 4 hours. The harmonic mean terminal half-life was 30 to 40 hours. AUC and C_{max} were roughly dose-proportional. The peak-to-trough ratios (C_{max}/C_{min}) were approximately 5 for once daily dosing. PK model-based simulations predicted that the mean C_{max}/C_{min} could be reduced from ~5 for once daily dosing to ~1.5 for divided daily dosing (four times a day, with the largest dose at night). A dose of 30 mg once daily for 7 days was the first maximum tolerated dose (MTD) because of dose-limiting somnolence. By implementing divided daily dosing, dose escalation was able to proceed to a maximum of 80 mg for 14 consecutive days and steady-state concentrations were achieved above 2 uM, the optimal efficacious exposure level predicted in preclinical studies. Nevertheless, somnolence remained the dose-limiting toxicity (DLT). Near real-time PK data allowed confirmation of simulations at each decision step.
Conclusions: PK modeling and simulations allowed implementation of successful dosing strategies to reduce C_{max} and increase steady-state concentrations. Still, dose-limiting CNS adverse effects were not fully mitigated and safe doses causing anti-proliferative effects were not observed. MLN8054 has been replaced in clinical trials by MLN8237, a more potent second-generation Aurora A kinase inhibitor anticipated to have less CNS adverse effects.

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Phase I trial of ixabepilone administered as a 24-hour infusion in patients with advanced solid malignancies: updated safety profile and maximum tolerated dose

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Background: Ixabepilone is the first epothilone approved for use in the US as a single agent in metastatic breast cancer (MBC) resistant to anthracyclines, taxanes and capecitabine or in combination with capecitabine in MBC resistant to anthracyclines and taxanes. This study was designed to investigate the safety, tolerability and pharmacokinetics (PK) of Cremophor free ixabepilone given as a 24 h infusion. Here we report an update of the safety profile and the maximum tolerated dose (MTD).
Methods: Eligible patients (pts) had normal renal and hepatic function and may have received up to 3 prior chemotherapy regimens in metastatic setting. Cremophor free ixabepilone was administered as a 24 h infusion Q 3 weeks (cycle). Study utilized a "3+3" dose escalation design, with the MTD determined by evaluating dose-limiting toxicities (DLTs) during cycle 1.
Results: Thirty-three pts (median age: 60, range 39–79; male/female: 19/14) enrolled in 6 cohorts (dose range: 10−45 mg/m^2) received a total of 106 cycles of ixabepilone. Tumor types: non-small cell lung (NSCLC, 10 pts), gastrointestinal (5 pts), gynecologic (2 pts), breast (4 pts), prostate (3 pts) and other cancers (9 pts).
The MTD was 40 mg/m^2. One pt had DLT of febrile neutropenia at 40 mg/m^2 and died with hepato-renal syndrome due to liver metastasis. At 45 mg/m^2 2 pts had DLTs (gr 4 neutropenia). No additional DLTs were observed in the expanded 40 mg/m^2 dose level. Twenty-two pts discontinued treatment due to disease progression, 5 due to study drug toxicity and 1 due to ixabepilone related sensory neuropathy (gr 2, after 6 cycles). Grade 3/4 neutropenia, thrombocytopenia and febrile neutropenia were 44%, 19% and 6%, respectively. Two pts experienced gr 3 fatigue; 1 gr 3/4 event was reported for dehydration, pulmonary embolism, deep vein thrombosis, epistaxis, and esophagitis. Thirty-one pts were evaluable for PK. At 40 mg/m^2 (n = 8), the peak concentration of ixabepilone was about 1/4 of that observed in pts treated with 40 mg/m^2 over 3 h and geometric mean of the area under the concentration-time curve from time zero to infinity was similar. No responses were observed. One pt with NSCLC at 20 mg/m^2 had stable disease for 15 cycles. Two additional pts with NSCLC and MBC had stable disease for 8 cycles.
Conclusions: Cremophor free ixabepilone administered over 24 h was well tolerated and neuropathy was uncommon. The MTD and recommended phase II dose is 40 mg/m^2 Q 3 weeks.

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Phase I study of E7389/Gemcitabine combination in patients with advanced solid tumours

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Background: E7389 (E) is a synthetic analogue of halichondrin B, an investigational tubulin-based antimitotic drug. Gemcitabine (G) is a nucleoside analogue clinically active in several human tumours These 2 drugs exhibited synergistic cytotoxic effects against the H522 non-small cell lung cancer (NSCLC) xenografts.
Methods: A phase I/pharmacokinetic clinical study of these 2 drugs in combination was initiated in patients with advanced solid tumours. Two prior chemotherapy regimens for metastatic disease are allowed. Patient characteristics: male 7/female 8; median age 53 (range 28−76); performance status 0 (n = 1), 1 (n = 9), and 2 (n = 5); prior therapy: chemotherapy 15, radiotherapy 7; tumour types: gynecologic 5, NSCLC 2, colorectal cancer 2, head and neck cancer 2, miscellaneous 4. Cohort 1: E/G given days 1, 8, 15 q28 days. Due to DLT, regimen changed in cohort 2 with E/G given days 1, 8 q21 days.
Results: Cycles (C) given: median 2, range 1−8, total 35.

Hematologic toxicities (HT)

CT	N	Dose E/G mg/m^2	WBC N*	PMN N*	Platelet N*	C1 HT ⩾Grade 3, related (n)	DLT
1	6	0.7/800	3.7 (1.8−7.9)	1.8 (1.0−6.4)	117 (19−159)	Lymphopenia (1), leukopenia (2), thrombo-cytopenia (2)	N = 2 Inability to administer C1D15 dose
2	3	0.7/800	3.6 (3.3−4.8)	2.0 (1.9−2.1)	127 (122−236)	None	0
3	3	0.7/1000	3.0 (2.0−3.0)	1.0 (0.9−1.4)	126 (107−130)	Neutropenia (1)	0
4	3	1.0/1000	1.8 (1.3−3.2)	0.9 (0.8−2.1)	66 (64−150)	Hemoglobin (1), leukopenia (2), neutropenia (2)	0

* N: 10^9/L median, (range).

No significant non-hematologic toxicity has been observed, to date. Seven of 11 patients had stable disease, at least after 2 cycles of E/G. Three of the longest durations of stable disease were 15, 16, and 31 weeks, respectively. We are continuing to accrue patients onto the study.
Conclusions: This chemotherapy regimen at the q21 day schedule seems to be well tolerated.

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A phase I trial of GMX1777: an inhibitor of nicotinamide phosphoribosyl transferase (NAMPRT)

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Background: GMX1777 is a soluble pro-drug which converts in serum to GMX1778, recently established to be a small molecule inhibitor of the rate-limiting enzyme in the NAD+ salvage pathway. The aims of this first-in-man study were to define a dose of GMX1777 for Phase II studies, characterize the safety of 24-hour infusions of GMX1777, and determine the pharmacokinetic (PK) parameters of both GMX1777 and GMX1778.
Material and Methods: GMX1777 was administered at ascending doses as a 24 hour infusion every 21 days to cohorts of patients with advanced malignancies with no standard therapy options. Single patient cohorts were utilized until a toxicity >Grade (Gr) 1 was observed during cycle 1; then a standard 3+3 dose escalation schema was utilized to enroll patients in subsequent cohorts. During Cycle 1, PK samples were drawn at regular intervals before, during and after the 24 hour infusion.
Results: Twelve patients received doses of 60, 120, 160 or 200 mg/m^2 over 24 hours. Thirty-five doses have been administered. There were no toxicities >Gr 1 in the single patient enrolled at 60 mg/m^2 during cycle 1; however Gr 2 toxicities were observed at 120 mg/m^2 and the cohort was expanded to 3. Preliminary data indicate that adverse events of all grades with >25% incidence overall were diarrhea (92%), nausea (83%), vomiting (67%), fatigue (58%) insomnia (42%), thrombocytopenia (42%), pruritus (42%), anemia (33%), anorexia (33%), neuropathy (33%), and rash (33%). Gr 3 and 4 events were single events of Gr 3 diarrhea at 60 mg/m^2; Gr 3 infusion site infection and dehydration at 120 mg/m^2; Gr 3 alk

phos increase, hypokalemia, extremity pain, renal failure, urinary retention, pruritus, Gr 4 rash and purpura, and Gr 5 cerebrovascular accident at 160 mg/m^2; Gr 3 melena, Gr 4 GI hemorrhage and thrombocytopenia at 200 mg/m^2. The Gr 4 thrombocytopenia was a DLT. Rash developing in 3 patients after several cycles at 160 mg/m^2 has led to an ongoing evaluation of 140 mg/m^2. Three patients have had stable disease for >3 months. Preliminary PK data document rapid conversion of GMX1777 to GMX1778 at all dose levels tested to date, and that exposure increases in a more than dose-proportional manner.
Conclusions: GMX1777 can be administered as a 24 hour infusion with a tolerable safety profile. The dose-limiting toxicities of thrombocytopenia and skin rash may be modified by the use of alternative schedules.

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A phase I safety and pharmacokinetic (PK) study of 3 and 6 hours (h) intravenously administered belinostat (PXD101) plus carboplatin (C) and paclitaxel (P) in patients (pts) with advanced solid tumours

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Background: Belinostat (Bel), an HDAC inhibitor of the hydroxamate class, has been well tolerated as a 30-min intravenous (iv) infusion in >100 pts treated at the MTD, 1000 mg/m^2/day, days 1−5 q3 weeks. The main toxicity has been manageable nausea/vomiting. Prolonged exposure of tumor cell lines to Bel leads to improved cell kill in vitro, which was the rationale to prolong the daily exposure time in the clinic. The purpose of this study is to examine PK and safety of prolonged exposure of Bel.
Methods: The MTD for 30-min infusion of Bel (1000 mg/m^2/day, days 1−5 q3 weeks) in combination with C (AUC 5) and P (175 mg/m^2(delivered on day 3 has been determined (Sinha et al ASCO 2007). Based on a PK model derived from 30-min Bel infusion data, the present study included cohorts of 3−6 pts receiving C and P together with Bel administered as a 3 or 6 h iv infusion. Assessments included safety evaluations (NCI-CTCAE) and standard PK determinations. Acetylation status of histones H3 and H4 was assessed by Western blotting of extracted histones from peripheral blood mononuclear cells.
Results: The Bel PK model (V1 = 0.015 ml/m^2; K21 = 2.082096 h-1; K31 = 0.158794 h-1; a = 5.6 h-1; b = 1.21 h-1; g = 0.156 h-1) predicted that extension of the infusion time to 3 or 6 h would lead to biologic effective plasma concentrations (~1 mM) for ~5−7.5 h without accumulation of Bel. Seven pts were treated, 4 in the 3-h cohort (1 not evaluable due to early withdrawal) and 3 in the 6-h cohort. No major increase in clinical toxicity was seen as compared to pts treated with 30-min infusions, and no DLTs were observed. Initial PK data for the 3-h cohort confirm the simulation model with Bel concentrations remaining above biological active concentrations for 5.4 h. Further PK (including 6-h cohort) and clinical data will be presented at the meeting.
Conclusion: The combination of Bel with an infusion time of 3 or 6 h, with C and P was well tolerated, and the prolonged infusion of Bel resulted in an increased time above a biological effective plasma concentration as compared to 30-min infusion.

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A phase I clinical trial of belinostat (PXD101) in combination with doxorubicin (BelDox) in advanced solid tumours, including soft tissue sarcomas (STS)

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Background: Belinostat (Bel) is a hydroxamate HDAC inhibitor with broad spectrum activity in vitro and in vivo and synergy in combination with doxorubicin (Dox). In Phase I studies in patients (pts) Bel is well-tolerated at a dose of 1000 mg/m^2 IV daily x 5, q 21 days. This study will determine the maximum tolerated dose (MTD), safety and pharmacokinetics (PK) of Bel plus doxorubicin (BelDox) in advanced solid tumours.
Materials and Methods: Sequential cohorts of 3−6 pts are planned to receive Bel at doses of 600, 800 and 1000 mg/m^2 daily x 5 plus Dox day 5, initially 50 mg/m^2 then 75 mg/m^2, q21. PK studies, ECG monitoring for QTc prolongation, assessment of toxicity by CTCAEv3 and tumor imaging evaluated by RECIST was performed in all pts.
Results: 15 pts so far have been treated at 3 dose levels: 600/50, 600/75, 800/75 mg/m^2 of BelDox. 8 pts had received 0–1 previous treatment regimens and 7 pts had received 2–4 regimens. Median age was 63 years (range 49–70) and the m:f ratio was 1.5: 1. The median number of cycles was 4.5 (range:1–7 cycles). Grade 3/4 adverse events (AE) included neutropenia in 5 pts, neutropenic fever in 2 pts, fatigue in 2 pts, and diarrhea, hand-foot syndrome, gram neg. bacteriemia and anemia in one pt each. The most common AE's were neutropenia, fatigue and nausea. Grade 4 neutropenia in cycle 1 was observed in 4 out of 11 pts in the 75 mg/m^2 Dox cohorts, and 3 of these pts had more than 2 prior regimens. There was one dose limiting toxicity (DLT) at the 600/75 cohort in a heavily pre-treated pt and 3 DLTs at 800/75. 3 out of 4 pts with DLT were heavily pretreated with other diagnoses rather than STS (i.e. pancreatic, renal and esophagus cancers). Currently, pts with no or limited previous treatment are being enrolled at 800/75. To date, the best clinical response observed has been partial response in cervical cancer. Mean values±SD for $t\frac{1}{2}$, AUClast and Cmax for Bel Day 4 were in cohort 600/50 (n = 2): 1.2±0.1 hr, 11±2 hr μg/ml and 22±5 μg/ml; cohort 600/75(n = 6): 1.1±0.4 hr, 12±3 hr μg/ml, 20±8 μg/ml and cohort 800/75 (n = 3) 1.4±2.6 hr, 12±4 hr μg/ml, 20±10 μg/ml, respectively. Bel PK results for Day 5 was similar to Day 4.
Conclusion: Tolerance of BelDox was influenced by prior treatment. The regimen was best tolerated in patients with no or limited pre-treatment. Safety evaluation is ongoing In this population and a further escalation is planned.

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Phase I dose escalation and pharmacokinetic study of oral enzastaurin in Japanese patients with advanced solid tumour

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Background: Enzastaurin (ENZ) targets the protein kinase C and phosphoinositide 3-kinase /AKT pathways to inhibit tumor cell proliferation, induce tumor cell apoptosis, and suppress tumor-induced angiogenesis. A phase I study was conducted in Japan to evaluate the tolerability of ENZ and pharmacokinetic (PK) profile in patients (pts) with advanced solid tumor, and determine the recommended dose (RD) of ENZ for the phase II study.
Material and Methods: Eligible pts had incurable solid tumors, a PS of 0−2, and adequate organ function. Pts received ENZ once daily until disease progression (PD) or unacceptable toxicity occurred (1 cycle = 28 days). A six patient cohort for each dose level was used with a starting dose of 250 mg daily. The level was escalated in a stepwise manner based on the incidence of Dose Limiting Toxicities (DLTs). DLT was defined as any of the following: grade (G) 3, 4 or 5 non-hematologic toxicity, G4 neutropenia or thrombocytopenia, febral neutropenia, G2 QTc prolongation lasting at least 1 week, or dose omission lasting at least 8 days in Cycle 1. Maximum tolerated dose (MTD) was defined as the lowest dose level where the incidence of DLTs was 33% or higher.
Results: 23 pts (7 pts: 250 mg, 6 pts: 375 mg, 6 pts: 500 mg, 4 pts: 750 mg) with median age of 55.0 years were enrolled and received ENZ. The major tumor types were non-small-cell lung cancer (n = 5) and breast cancer (n = 3).
Of the 23 pts, 4 pts discontinued the study for PD in Cycle 1 and 19 pts were evaluable for DLT (5: 250 mg, 6: 375 mg, 5: 500 mg, 3: 750 mg). No DLT was reported at doses of 500 mg or less, while 2 DLTs (G2 QTc prolongation) were observed at 750 mg. Based on these results, 750 mg ENZ was determined as the MTD and 500 mg as the RD for the phase II study.
The most common toxicities in the treated pts were chromaturia (n = 15) and somnolence (n = 9), which were all G1. The incidence of somnolence increased dose-dependently, however, no exacerbation was observed when the treatment was continued. The only G3 toxicity was lymphocytopenia (n = 1). 3 pts (375 mg: 1, 750 mg: 2) required dose omission for G2 QTc prolongation. These pts showed signs of recovery from the event during dose omission while the events occurred again after receiving ENZ.
Multiple daily doses of 500 mg achieved the target plasma concentration (1400 nmol/L); the predicted average drug concentration of ENZ and its active metabolites at steady-state ranged from 1680 to 5040 nmol/L.
Although none of the 23 pts achieved CR or PR in accordance with RECIST criteria, 9 pts (1: 250 mg, 4: 375 mg, 3: 500 mg, 1: 750 mg) achieved SD. A mesothelioma pt showed radiographical improvement.
Conclusions: Treatment with a daily dose of ENZ up to 500 mg was well tolerated in Japanese pts. Based on the incidence of DLTs (2 pts: G2 QT prolongation) the RD of ENZ for the phase II study was determined as 500 mg/day for a 28-day-cycle. PK results support 500 mg as the RD to achieve the target plasma concentration of ENZ and its metabolites.