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