Materials and Methods: Eligible patients (pts) had ECOG ⩽1, advanced or metastatic solid tumors, at least one target lesion by RECIST, and acceptable hematologic, liver and renal function. A modified accelerated titration design was used. TH-302 was administered intravenously over 30 minutes on Day 1, 8 and 15 of a 28-day cycle. CT scans were obtained after every 2 cycles. Detailed pharmacokinetic (PK) sampling was performed during Days 1 and 15. The objectives of this study were to determine the maximum tolerated dose and dose limiting toxicity (DLT) and to evaluate the safety, PK and preliminary efficacy of TH-302 in advanced solid tumors.
Results: Seventeen pts have enrolled to date at 3 sites. Median age: 65. ECOG 0/1 in 11/6 pts. Primary tumor: prostate (5), colorectal (4), NSCLC (2), SCLC (2), other (4). Pts received 1−8 cycles (median 2;1−22 doses) at 7.5–480 mg/m^2. Twelve pts have discontinued: progressive disease (PD; 9), PSA PD (1; SD by RECIST) and adverse event (AE; 2; unrelated to TH-302). No DLT has occurred to date. Grade 1 or 2 study drug-related AEs have been reported in 10 of 17 pts treated at doses up to 480 mg/m^2 including fatigue in 4 pts (2 grade 1 and 2 grade 2 at 30 and 480 mg/m^2) and grade 1 nausea in 3 pts (7.5, 7.5 and 120 mg/m^2). One pt treated at 7.5 mg/m^2 with pre-existing cyclic neutropenia had intermittent grade 2 neutropenia not considered due to TH-302. Six subjects developed worsening or new lymphopenia (4 grade 2, 3 grade 3) but none were reported as clinically significant. Four pts had worsening or new anemia (2 grade 1, 2 grade 2). Seven of 14 evaluable pts had a best response of stable disease, one of whom (NSCLC; dose level 7.5 mg/m^2) had PET metabolic response with 35% and 36% declines in maximum SUV following cycles 2 and 4. PK Cmax and AUC for TH-302 and Br-IPM increased linearly over the range of doses evaluated to date (7.5–240 mg/m^2) with no accumulation at Day 15. Half-life ranged from 0.5−1 h. The ratio of TH-302 to Br-IPM is higher than in rats or dogs but the Cmax and AUC for Br-IPM are similar to dogs at comparable doses.
Conclusions: TH-302 administered as a weekly dose is well tolerated to date. There is early evidence of clinical activity. Preclinical toxicology in rats and dogs predicted hematologic toxicity and xenograft studies predicted efficacy at doses over 100 mg/m^2. Dose escalation is continuing. Studies of TH-302 combined with other therapies are planned.

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A phase I dose escalation study of oral SB939 when administered thrice weekly (every other day) for 3 weeks in a 4-week cycle in patients with advanced solid malignancies

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Background: SB939 is a potent competitive inhibitor of Class 1 and 2 histone deacetylase (HDAC). This study was designed to assess the safety, maximum tolerated dose (MTD), dose limiting toxicity (DLT), pharmacokinetics, pharmacodynamics and preliminary efficacy of SB939 in patients with advanced solid malignancies.
Methods: SB939 was administered orally every other day 3 times a week for 3 consecutive weeks, in a 4-week cycle. Cohorts of patient were treated with escalating doses of SB939 starting from 10 mg; first cycle DLT were used in dose escalation decisions.
Results: Twenty patients (10 males, 10 females; mean age 55.6 yrs, range 41−74) were treated with the following dose levels: 10 mg, 20 mg, 40 mg and 80 mg with 3, 3, 8, and 6 patients in each cohort, respectively. DLTs were observed at the highest 2 dose levels (40 mg, n = 1 of 8 and 80 mg, n = 3 in 6). DLTs were grade 3 fatigue (1 patient at 40 mg and 80 mg each), asymptomatic QT prolongation (1 patient, at 80 mg) and troponin T elevation (1 patient, at 80 mg). Grade 3 anaemia and thrombocytopenia (1 patient each) were observed in the 80 mg cohort. Other adverse events included nausea (5 patients), vomiting (7 patients) and diarrhoea (3 patients). SB939 was rapidly absorbed reaching Tmax between 1−3 h after ingestion, and mean elimination half-life and oral clearance of SB939 were 8 hrs and 50.2 L/h respectively. Cmax and AUC (0-∞) were dose-proportionally increased over the range studied. There was no substantial accumulation of SB939 following repeated dosing. The mean plasma concentrations of SB939 were above its HDAC enzyme IC50 (T>IC50) for 12 and 24 h in 40 and 80 mg cohorts, respectively. Of the 13 patients evaluable for response, stable disease was seen in 1 patient with follicular thyroid carcinoma and 1 patient with hepatocellular carcinoma for 51 and 164 days, respectively.
Conclusion: SB939 has a manageable toxicity profile. The 80 mg dose was the highest dose tested in this study and was not tolerated by 3 out 6 patients. Patients are currently being enrolled at a 60 mg dose to further define the recommended phase II dose.

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A phase I, open-label, dose escalation study of the humanized monoclonal antibody (HuMAb) TRC093, an inhibitor of angiogenesis that binds to cleaved collagen, in patients with locally advanced or metastatic solid tumors

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Background: TRC093 is a HuMAb that binds cleaved collagen to inhibit angiogenesis and tumor growth. Preclinical studies confirm safety and antitumor activity of the agent in multiple solid tumors as monotherapy and in combination with cytotoxic and targeted agents. We performed a phase 1 trial to evaluate the safety and tolerability of TRC093 in patients with solid tumors.
Methods: Patients were required to have advanced refractory cancer, ECOG ⩽ 2, and adequate organ function including proteinuria and hematuria ⩽ 1+. TRC093 was administered by 90 minute IV infusion on days 1 and 15 of each 28-day cycle until progression. Cohorts of 3 patients were planned at doses of 0.5, 1.5, 5, 12 and 24 mg/kg.
Results: A total of 16 patients have been treated to date, 3 at each of the 0.5, 1.5, and 5 mg/kg dose levels, 6 at the 12 mg/kg and 1 at the 24 mg/kg dose levels without the development of dose-limiting toxicity. The 12 mg/kg dose level was expanded and considered the maximal feasible dose (rather than the top dose level of 24 mg/kg) due to limited drug supply. The most common adverse event (all grade 1 or 2) felt to be possibly drug-related was fatigue. Related grade 3 or 4 AEs and infusion reactions have not been observed. One patient with non-small-cell lung cancer treated at the 1.5 mg/kg dose, a patient with malignant hemangiopericytoma treated at the 5.0 mg/kg dose and a patient with metastatic cervical cancer treated at the 12.0 mg/kg dose had stable disease for 2 months, 6 months (ongoing) and 2 months respectively. In addition, one patient with granulosa cell carcinoma of the ovary with progressive disease had a mixed response in the liver after 2 months of treatment. Biomarker, immunogenicity and PK analyses are ongoing and will be presented.
Conclusion: TRC093 is well-tolerated when administered by 90 minute IV infusion every 2 weeks. Phase 1b and 2 trials based on preclinical studies will evaluate this novel agent in combination with other targeted and standard cytotoxic therapies.

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Dosing strategies for MLN8054, a selective Aurora A kinase inhibitor, based on pharmacokinetic modeling and simulations

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Background: MLN8054, an oral selective small-molecule inhibitor of Aurora A kinase, is being developed as an anti-mitotic agent for the treatment of cancer. MLN8054 binds to the $GABA_A$-alpha1 benzodiazepine receptors and causes CNS adverse effects, such as somnolence. A pharmacokinetic (PK) model was developed to simulate PK profiles in order to find a dosing regimen to reduce peak concentrations (C_{max}) thereby potentially minimizing CNS adverse effects, while maximizing steady-state concentrations to increase the likelihood of Aurora A kinase inhibition.
Materials and Methods: MLN8054 was evaluated in two Phase I trials in patients with advanced solid tumors. Serial blood samples were collected to measure plasma concentrations of MLN8054 using LC/MS/MS methods. PK parameters of MLN8054 were estimated using non-compartmental analyses. A two-compartment model was developed to characterize the PK of MLN8054 based on the PK data obtained from the first 10 patients enrolled. The model was then used to simulate PK profiles for testing various dosing regimens. WinNonlin® was applied to non-compartmental PK analyses and compartmental PK modeling/simulations.
Results: MLN8054 was evaluated for 7 to 21 days of dosing in 104 patients and 12 dose levels between 5 and 80 mg. The drug was rapidly absorbed

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