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A phase I study of oral panobinostat (LBH589) in Japanese patients with advanced solid tumours

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Background: Histone deacetylases act on chromatin and on transcription factors to modulate the expression of genes such as the tumor suppressor p53, and Rb. Panobinostat (LBH589) is a pan-deacetylase (pan-DAC) inhibitor belonging to a structurally novel cinnamic hydroxamic acid class of compounds. DAC inhibitors have been shown to have activity against various tumor types by inhibiting proliferation and inducing apoptosis both in vitro and in vivo. They have also been shown to have anti-angiogenic activity.
Methods: This study is a single-arm, dose-escalation Phase I study designed to characterize the safety, tolerability, biologic activity, and pharmacokinetic profile of oral panobinostat given as a single agent to adult Japanese patients with advanced solid tumors or CTCL. Eligibility criteria were standard; in particular, patients were required to have normal hematological parameters (incl. plt) at entry. Three dose levels were investigated: 10 mg, 15 mg, and 20 mg given three times each week (Monday/Wednesday/Friday) without planning interruptions in treatment. Dose escalation was capped at 20 mg/day. Adverse events were reported using the CTCAE Version 3.0.
Results: Fourteen patients were enrolled as follows: 3 pts (10 mg), 4 pts (15 mg), 7 pts (20 mg). One patient enrolled to the 20 mg dose did not receive study drug due to a disqualifying baseline laboratory abnormality. Reviewing the data from the first cycle of treatment. Grade 3 or 4 toxicity was not observed in any patient treated at the 10 mg dose. Two of 4 patients treated at 15 mg experienced grade 3 thrombocytopenia. Two of 6 patients treated at 20 mg experienced grade 3 thrombocytopenia and one patient at this dose experienced grade3 neutropenia. Although grade 3 thrombocytopenia and neutropenia did occur, no dose-limiting toxicities were observed and all toxicities were reversible following dose interruption. PK samples were obtained in all patients after the first dose (day1) and at steady state (day15). PK parameters were evaluated by non-compartmental analysis.
Conclusion: Panobinostat is well-tolerated at a dose as high as 20 mg PO given each Monday, Wednesday and Friday in Japanese patients with advanced solid tumors.

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Phase I dose escalation study of NK012, polymer micelle of irinotecan metabolite SN-38, in patients with advanced cancer

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Background: NK012 is a new formulation of drug delivery system for SN-38 which is an active metabolite of irinotecan. SN-38 is conjugated with micellar nanoparticles. Preclinical studies suggested that NK012 had a higher antitumor activity with a lower incidence of diarrhea as compared with irinotecan. Aims of this study were to determine pharmacokinetics, toxicity profile and recommended dose (RD) for phase II study.
Methods: Patients suffering from advanced cancer were intravenously administered with NK012 in 30 min, every 3 weeks. Starting dose was 2 mg/m^2 as SN-38 equivalent, and it was escalated with by the accelerated titration method and modified Fibonacci method.
Results: Twenty four patients having cancers of the colorectum (n = 12), lung (n = 5), pancreas (n = 4) or esophagus (n = 3) have recieved the following fixed doses: 2 mg/m^2 (n = 1); 4 mg/m^2 (n = 1); 8 mg/m^2 (n = 1); 12 mg/m^2 (n = 3); 16 mg/m^2 (n = 3); 20 mg/m^2 (n = 3); 24 mg/m^2 (n = 3); 28 mg/m^2 (n = 9). Predominant hematological toxicity was neutropenia. Non-hematological toxicities including diarrhea were mostly grade 1 or 2 in course 1. DLT (grade 3 febrile neutropenia, grade 4 neutropenia) occurred at 28 mg/m^2 for the first time in course one. Partial response has been confirmed in a patient with esophageal cancer. Stable disease was observed in 11 patients. Polymer-bound SN-38 and polymer-unbound SN-38 were slowly eliminated from plasma, with terminal phase half-lives of approximately 120 hr and 240 hr, respectively. The systemic exposure to both polymer-bound and unbound SN-38 increased with escalation of the dose.
Conclusions: Phase I study is ongoing at a dose of 28 mg/m^2. MTD will become 28 mg/m^2. RD may become equal to or less than 28 mg/m^2. DLT seems to be a neutropenia. A 30 min infusion of NK012 once every 3 weeks was well tolerated and may be feasible for phase II study.

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ANG1005, an Angiopep-2/paclitaxel conjugate: the first clinical trial in patients with advanced cancer and brain metastases: Preliminary safety and tolerability data

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Background: Treatment options for patients with metastatic brain cancer are limited and often focus on relief of symptoms. The main obstacle to treatment is the blood–brain barrier (BBB) which prevents most drugs from reaching tumor cells in the brain. Angiopep-2 is a 19 amino acid peptide shown in animal models to cross the BBB using a physiological approach through transcytosis via low-density lipoprotein receptor-related protein (LRP) expressed on the surface of the BBB. ANG1005 is a new chemical entity that combines 1 molecule of Angiopep-2 with 3 molecules of paclitaxel. Preclinical studies demonstrate the brain's uptake of ANG1005 to be ~100 times greater than paclitaxel and ~10 times greater than temozolomide. Once in the brain compartment, ANG1005 again uses LRP, which is upregulated on metastatic brain cancer cells, to enter tumor cells where the molecule is cleaved releasing paclitaxel to exert its antimitotic effects. A Phase I clinical trial was initiated in Oct 2007 to explore the maximum tolerated dose and obtain data on safety, tolerability and preliminary evidence of efficacy of ANG1005 in patients with advanced solid tumors and brain metastases.
Material and Methods: A multicenter, open-label, dose escalation study of ANG1005 is being conducted in the US with sequential dose cohorts ranging from 30–558 mg/m^2. ANG1005 is administered IV over 1 hour every 21 days. Study participants include adult patients with measureable disease and an ECOG performance status $\leqslant$ 2 who are ineligible for standard treatment options.
Results: As of May 22, 16 patients (median age, 54 years; 56% female) with advanced solid tumors (breast cancer, n = 5; melanoma, n = 4; hepatocellular carcinoma, n = 2; other, n = 5) and/or brain metastases (n = 10) have received ANG1005. Safety and tolerability were demonstrated up to doses of 300 mg/m^2 and escalation is ongoing as planned. No patient has discontinued from the study due to drug-related AEs. Anemia, neutropenia and leucopenia, all Grade II in severity and established paclitaxel-related effects, were observed in the study to the present time.
Conclusion: To date, the safety and tolerability profile of ANG1005 has been excellent in patients with advanced solid tumors and brain metastases. Angiopep conjugates may represent a potentially safe and effective way to treat currently unmanageable CNS diseases; ANG1005 is the first of many compounds to be tested as a means of overcoming restrictions to treatments due to the BBB.

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ANG1005: Preliminary clinical safety and tolerability in patients with recurrent malignant glioma

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Background: The blood–brain barrier (BBB) complicates the clinical treatment of most CNS diseases, including malignant glioma. Angiopep-2 is a 19 amino acid peptide shown in animal models to cross the BBB using a physiological approach through transcytosis by binding to low-density lipoprotein receptor-related protein (LRP) expressed on the surface of the BBB. ANG1005 is a new chemical entity (NCE) that combines one molecule of Angiopep-2 with three molecules of paclitaxel. Preclinical studies demonstrate the brain's uptake of ANG1005 to be ~100 times greater than paclitaxel and ~10 times greater than temozolomide. Because LRP is upregulated on malignant glioma cells, once in the brain

compartment, ANG1005 uses the same receptor-mediated mechanism described above to enter tumor cells where cleavage of ANG1005 occurs, releasing paclitaxel to perform its antimitotic functions. A Phase I clinical trial was initiated in October 2007 to explore the maximum tolerated dose and obtain data on safety, tolerability and preliminary evidence of efficacy of ANG1005 in patients with recurrent malignant glioma.
Material and Methods: A multicenter, open-label, dose escalation study of ANG1005 is being conducted in the United States with sequential dose cohorts ranging from 30–558 mg/m^2. ANG1005 is administered IV over 1 hour every 21 days. Study participants include adult patients with measureable disease and an ECOG performance status $\leqslant$ 2 who are ineligible for standard treatment options.
Results: As of May 26, 7 patients with recurrent malignant glioma have received ANG1005 (4 patients with glioblastoma multiforme, 1 with anaplastic astrocytoma, and 2 with anaplastic oligodendrocytoma). No patient has discontinued from the study due to study drug-related adverse events. The presently enrolling dose is 50 mg/m^2 and escalation is ongoing.
Conclusion: To date, treatment options for patients with recurrent malignant glioma are limited and prognosis is bleak because of the brain's highly evolved physiological structure. Angiopep conjugates may provide a potentially safe and effective way to treat this and other currently unmanageable CNS diseases. ANG1005 is the first of a list of compounds to be tested in this regard.

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Effects of food on the single-dose pharmacokinetics of oral MP-470 capsules

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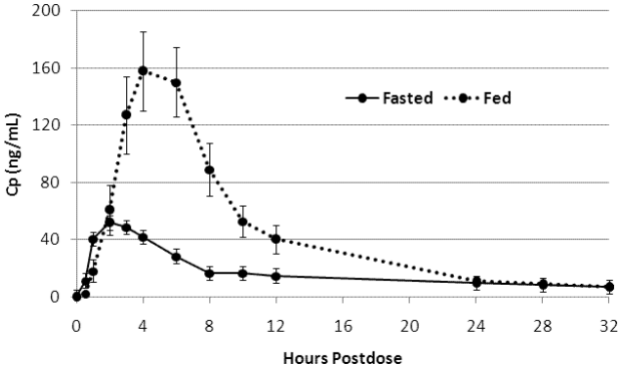
Background: MP-470 (MP) is a multi-targeted tyrosine kinase inhibitor which hits a number of validated tumor targets. MP also sensitizes cancer cells to DNA damaging agents and to radiation therapy, presumably through the suppression of Rad51, a key component to the cellular repair machinery in response to DNA double-strand breaks. The HCl salt of MP (MP-HCl) is orally bioavailable and under clinical investigation as single-agent therapy and in combination with standard anticancer agents. Data presented here describe the effect of food on the pharmacokinetics of MP.
Material and Methods: Sixteen healthy volunteer subjects were enrolled into a randomized, 2-period crossover study at MDS Pharma Services (Lincoln, Nebraska, USA). Each subject was to receive a single 700-mg dose of MP on D1 in each of two study periods separated by 7 days rest. Doses were given as seven 100-mg capsules each containing 108.1 mg of MP-HCl. Procedures common to both study periods included admission to the study center the evening before dosing, fasting overnight, swallowing the MP dose with 240 mL water in the morning, and refraining from eating food until 4 hours after dosing. A high-fat, high-calorie breakfast preceded dosing in one of the two study periods. Study period sequence (fed-fasted or fasted-fed) was determined by a randomization schedule stratified by gender. PK blood samples collected predose and at 12 time points up to 32 hours postdose were assayed for MP by Ricerca Biosciences (Concord, Ohio, USA).



Average (±SE) MP-470 plasma concentrations.

Results: Demographic characteristics are 8M/8F; median age 27 years (range 20−43); and median body mass 27.3 kg/m^2 (range 19.9–31.6). All 16 subjects received MP in Period 1, and 15/16 (94%) in Period 2 (1 subject withdrew for personal reasons, and a second subject did not complete scheduled PK blood draws). The only Gr-2 or greater adverse event was Gr-2 headache reported by 2 subjects (13%). There was a pronounced effect of food on the PK of MP with higher exposure following the high-fat, high-calorie breakfast compared to the fasted state (average C_{max} was 196 versus 61 ng/mL [CV 58% and 56%] and average $AUC_{0-\infty}$ was 1541 versus 740 ng·hr/mL [CV 61% and 62%] in the fed and fasted states, respectively). T_{max} was later with food (average 4.8 versus 2.6 hr).
Conclusions: Systemic exposure to MP assessed by C_{max} and $AUC_{0-\infty}$ is increased 3-fold and 2-fold, respectively, following food consumption compared to fasting. Variability of these PK parameters does not appear to be affected.

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Pharmacokinetics (PK) of EZN-2208, a novel anticancer agent, in patients (pts) with advanced malignancies: a phase I dose-escalation study

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Background: EZN-2208 is a water-soluble, polyethylene glycol (PEG) conjugate of SN38 that is active in a broad spectrum of preclinical models, including an *in vivo* CPT-11-resistant tumor model. EZN-2208 accumulates in tumors, where it releases SN38.
Methods: Pts with advanced solid tumors were enrolled to determine the safety, tolerability, PK, maximum tolerated dose, recommended dose, and preliminary evidence of antitumor activity of EZN-2208 administered as a 1-h IV infusion, weekly x 3 per 4-week cycle, in a 3+3 escalating-dose design. Dose escalation was based on drug-related toxicities during the first cycle. PK samples were obtained after the first and third doses. Plasma concentrations of EZN-2208, SN38, and SN38G were determined by HPLC using fluorescence detection. PK parameters were estimated using a noncompartmental model analysis.
Results: 12 pts (7 females; median age = 61 y [39−85]) were treated at doses of 1 (3 pts), 2 (3 pts), 3.3 (3 pts), and 5 (3 pts) mg/m^2. 11 pts had received multiple prior therapies (median prior regimens = 3; range = 1–8). Tumor types included colorectal cancer (CRC) (5 pts); melanoma (1 pt); and anal, breast, esophageal (E), gastric, ovarian, and pancreatic cancer (1 pt each). Pts have received 1 to 7 treatment cycles. The most common adverse events (AEs) were nausea (6 pts); diarrhea and fatigue (4 pts each); and constipation, vomiting, and anorexia (3 pts each). Most AEs were Grade 1 or 2. No dose-limiting toxicities have been observed to date. Stable disease was observed in 1 pt with E cancer (120 days) and 3 pts with CRC (57, 57, and 216+ days). Plasma PK for the first 3 cohorts (9 pts) is provided in the table.
Conclusions: EZN-2208 was well tolerated. Qualitative assessment shows the AUCs of EZN-2208 increased proportionally with increasing dose. The SN38 t1/2 was independent of dose. There was no accumulation of EZN-2208 or SN38 after weekly dosing for 3 of 4 weeks. Dose escalation is ongoing; updated clinical and PK data will be presented.

PK Parameters After First Dose of First Cycle

	EZN-2208[b]			SN38[b]		
Dose[a] (mg/m^2)	Cmax[a] (μg/mL)	AUC(0-inf)[a] (h·μg/mL)	Terminal t/12 (h)	Cmax (ng/mL)	AUC(0-t)[c] (h·ng/mL)	Terminal t/12 (h)
1	14.9±1.8	459.8±37.5	53.3±30.5	57.3±13.3	1388±293	26.5±4.6
2	29.8±6.4	919.9±174.9	32.9±6.7	11.7±7.7	228±77	24.2±2.9
3.3	40.1±24.5	1140.3±739.5	21.3±4.9	11.5±7.0	227±179	27.3±3.3

[a]SN38 equivalents; [b]Mean±standard deviation; [c]AUC(0−t), t is time of last measurable concentration.

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A phase I dose-escalation study of TAS-102, a novel oral functional antitumor nucleoside, administered twice daily to Japanese patients (pts) with advanced solid tumors

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Background: TAS-102 consists of trifluorothymidine (FTD) and an inhibitor of thymidine phosphorylase (TPI). FTD is an inhibitor of thymidylate