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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