(DLT) or grade 3 or higher related adverse events have been observed to date. Pharmacokinetic estimates over the doses administered reveal dose linear increases in AUC of the plasma concentration versus time curves, a moderate to low clearance, and a terminal half-life of 7 hours. Pharmacokinetic parameters were similar after the first and third-weekly dose administrations, indicating no change in SNS-314 disposition following repeated administration. At all dose levels concentration vs. time profiles showed spikes in plasma concentrations or a flat terminal phase suggesting possible entero-hepatic recirculation of SNS-314. Inhibition of pHH3 induced by SNS-314 was observed in skin biopsies of patients treated at doses of 240 mg/m^2 and greater.
Conclusions: SNS-314 is a novel inhibitor of AKs A, B, and C. At the 240 mg/m^2 dose level we observe inhibition of Histone -H3 phosphorylation and serum SNS-314 levels exceeded preclinical target inhibitory levels. PD assessment of drug-mediated target modulation is ongoing. The compound has been well tolerated with no observed DLTs. Enrollment and dose escalation continues.

284 POSTER

ENMD-2076 exerts antiangiogenic and antiproliferative activity against human colorectal cancer (CRC) xenograft models

J.J. Tentler[1], E.L.B. Pierce[2], N.J. Serkova[2], T.M. Pitts[1], M.R. Bray[3], G.C. Fletcher[3], S.G. Eckhardt[1]. *[1]University of Colorado Cancer Center, Division of Medical Oncology, Aurora, CO, USA; [2]University of Colorado, Department of Anesthesiology, Aurora, CO, USA; [3]EntreMed Inc, Research Department, Toronto, Ontario, Canada*

Background: ENMD-2076 is a novel, small molecule kinase inhibitor with activity against Aurora kinase A as well as multiple tyrosine kinases linked to cancer, including VEGFR2, cKit and PDGFR-alpha. As a result, ENMD-2076 exerts its effects through multiple mechanisms of action, including antiproliferative activity and the inhibition of angiogenesis. The goal of the current study was to test the efficacy and potential toxicity of ENMD-2076 in a mouse xenograft model of CRC.
Methods and Results: Athymic nude mice were injected subcutaneously in the left flank with 2×10^6 HT29 CRC cells. When tumors reached a volume of 100 mm^3, mice were randomized into three groups: (1) vehicle, (2) ENMD-2076 (100 mg/kg), or (3) ENMD-2076 (200 mg/kg); n = 5 per group. Vehicle or drug was administered p.o., q.d, for 28 days by oral gavage. ENMD-2076 was well-tolerated, with no apparent toxicity and no significant weight loss over the course of the study, at either dose. Tumor volume measurements, taken every 3 days, revealed initial stasis in tumor growth in mice treated with either dose of ENMD-2076 and tumor regression at the 200 mg/kg dose beginning on day 18 and continuing to the end of the study. Tumors in the mice treated with the 200 mg/kg dose also displayed significant blanching, indicating a loss of tumor vascularity. To further quantify the effects of ENMD-2076 on tumor angiogenesis, gadolinium (Gd) based dynamic-contrast enhanced magnetic resonance imaging (DCE-MRI) was performed. Three animals per group underwent DCE-MRI scans at baseline and days 7 and 28 after the initiation of treatment. The initial area under the Gd-curve (IAUC) of the tumor, calculated for the first 90 seconds post Gd injection, were significantly lower versus control for both the 100 and 200 mg/kg treatment groups on day 28 ($p < 0.05$) indicating decreased vascular perfusion. Finally, at study end, the tumors were resected and histologically examined. Tumors from the mice treated with 200 mg/kg ENMD-2076 showed significant areas of necrosis compared to controls. IHC analysis for Ki-67 demonstrated a dramatic decrease in the number of proliferating cells in the tumors from mice treated with 200 mg/kg ENMD-2076 compared to vehicle controls.
Conclusions: The results of this study indicate that ENMD-2076 has antitumor effects on an HT29 CRC xenograft model. We observed tumor stasis and regression in mice treated with 200 mg/kg ENMD-2076. DCE-MRI and post-study histological examination suggests that these antitumor effects are exerted through a combination of antiangiogenic and antiproliferative actions. These preclinical studies provide evidence that ENMD-2076 may be an effective therapy option for clinical treatment of CRC.

285 POSTER

MLN8237, an oral selective Aurora A kinase inhibitor: initial results of dose-finding pharmacokinetic-pharmacodynamic phase I study

J. Tabernero Caturla[1], A. Cervantes[2], E. Elez[1], T. Macarulla[1], S. Roselló[2], E. Rodríguez-Braun[2], B. Stringer[3], V. Shinde[3], H. Danaee[4], O. Eton[5]. *[1]Hospital Universitario Vall d'Hebron, Medical Oncology, Barcelona, Spain; [2]Hosp. Clínico Universitario de Valencia, Hematology and Medical Oncology, Valencia, Spain; [3]Millennium Pharmaceuticals Inc., Molecular Technologies, Cambridge, MA, USA; [4]Millennium Pharmaceuticals Inc., Molecular Medicine, Cambridge, MA, USA; [5]Millennium Pharmaceuticals Inc., Oncology Clinical Research, Cambridge, MA, USA*

Background: Modification of the Aurora A kinase inhibitor, MLN8054, by adding a methoxy group to either end of the molecule resulted in a more potent derivative, MLN8237, which was also less likely to cause benzodiazepine-like effects in animal studies. This phase I clinical trial is examining the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of MLN8237.
Materials and Methods: Patients (pts) with advanced solid tumors received MLN8237 orally once daily (QD) for 7 days in 21-day cycles. Serial blood samples were collected to estimate PK. Tumor and skin biopsies were obtained before and on-dosing to assess accumulation of mitotic cells, from which Aurora A kinase inhibition was inferred. Doses were to be increased successively in cohorts of 3 pts until dose-limiting toxicity (DLT) was observed in $\geqslant$2 of 6 pts.
Results: Of the 9 pts enrolled and treated with MLN8237 as of 15-Apr-08, 4 (44%) were still on study, with a median of 2 cycles (range, 2−4+) of treatment. There were no DLTs in the first three dose cohorts of 5, 80, and 150 mg QD. Notable toxicity at 80 mg QD included grade (G) 2 alopecia in 2 pts; G1 mucositis in 1; and G2 somnolence in 2 (1 was on long-acting opiate). Notable toxicity at 150 mg QD included transient neutropenia G4 (1 pt) and G2 (2 pts); G2 alopecia in 2 pts after cycle 1; and G2 somnolence in 1 pt taking long-acting opiates. To reduce somnolence related to peak exposures, twice-daily dosing will be evaluated at the higher dose levels. Preliminary PK data show attainment of nM concentrations shown to be effective in preclinical models with a dose-proportional profile. The complete PK data will be presented at the meeting. Preliminary tumor and skin PD analysis show accumulation of mitotic cells after dosing. The complete PD results will be presented.
Conclusions: Dosing with MLN8237 for 7 days in 21-day cycles resulted in evidence of antimitotic-related toxicity (alopecia, mucositis, and neutropenia) at 80 mg QD and 150 mg QD. To date there have been no DLTs at doses up to 150 mg QD. Dose escalation continues.

286 POSTER

Pediatric Preclinical Testing Program (PPTP) stage 2 testing of the Aurora A kinase inhibitor MLN8237

M.A. Smith[1], P.J. Houghton[2], C.L. Morton[2], J.M. Maris[3], J. Courtright[3], H. Carol[4], R.B. Lock[4], Y. Yang[5], M.G. Manfredi[5]. *[1]National Cancer Institute, Cancer Therapy Evaluation Program, Bethesda, USA; [2]St. Jude Children's Research Hospital, Dept of Molecular Pharmacology, Memphis, USA; [3]Children's Hospital of Philadelphia, Pediatric Oncology, Philadelphia, USA; [4]Children's Cancer Institute Australia, Leukaemia Biology Program, Randwick, NSW, Australia; [5]Millennium Pharmaceuticals, Dept of Oncology, Cambridge, USA*

Background: MLN8237 is a small molecule inhibitor of Aurora A kinase that is in adult phase 1 testing. Aurora A kinase plays a pivotal role in centrosome maturation and spindle formation during mitosis. MLN8237 demonstrated activity in preclinical models of adult cancers, and previous PPTP testing identified broad in vivo activity for MLN8237 when tested at its MTD against neuroblastoma and acute lymphoblastic leukemia (ALL) xenografts.
Methods: MLN8237 was tested against selected responsive lines from the PPTP in vivo panels at doses of 20, 10, 5, and 2.5 mg/kg administered orally twice daily $\times$5 days repeated weekly and against 2 additional neuroblastoma models at 20 mg/kg. Treatment duration was 6 weeks for solid tumor xenografts and 3 weeks for ALL xenografts, with a total treatment/observation period of 6 weeks for all xenografts. Three measures of antitumor activity were used: (1) an objective response measure modeled after the clinical setting; (2) a treated to control (T/C) tumor volume measure; and (3) a time to event (4-fold increase in tumor volume) measure based on the median event-free survival (EFS) of treated and control animals for each xenograft. Pharmacodynamic (PD) studies were performed on selected neuroblastoma lines to evaluate the effect of MLN8237 on mitotic index (determined by %MPM2), with %pHistH3 positive cells determined to support Aurora A rather than Aurora B kinase inhibition.