Results: All 23 pts enrolled by 15-Apr-08 received ⩾1 dose of MLN8237, with a median of 2 cycles (range, 1−11+), and 9 (39%) pts were still on study. No DLTs were observed for 5−80 mg. At 80 mg 2 pts experienced G1−2 neutropenia on days 8 or 15. At 150 mg, 3 of 6 pts had DLTs: (a) prolonged G3−4 neutropenia requiring delay of cycle 2 at a reduced dose of 80 mg; (b) G3 mucositis/oral candidiasis requiring hospitalization and dose reduction to 80 mg for cycle 2; (c) G3 somnolence with concurrent initiation of a long-acting opiate and confusion/agitation on day 2 (MLN8237 was discontinued). Alopecia was seen in 1 pt at 80 mg and 2 pts at 150 mg. MLN8237 was rapidly absorbed (mean T_{max}, 1−4 h). Mean $AUC_{0-24\,h}$ and C_{max} increased with dose. At 150 mg, mean steady-state C_{max} was 4.6 μM and mean steady-state $C_{24\,h}$ was ⩾1 μM, the estimated efficacious exposure in preclinical models. Day 7 concentrations were ⩾1 μM for ⩾12 h in 1 of 3 pts at 80 mg (C_{max}, ~4 μM) and 4 of 6 pts at 150 mg (C_{max}, ~5 μM). Mean $t_{1/2}$ was 30−40 h for 5 to 80 mg, and 15 h at 150 mg. One pt had preliminary evidence of antitumor activity after 2 cycles (cycle 1, 150 mg; cycle 2, 80 mg) in platinum-refractory, radiation-resistant, metastatic ovarian cancer. 4 pts received 6−13+ cycles. Effects of MLN8237 in serial skin biopsies will be presented to support proof-of-mechanism.
Conclusions: Dosing with MLN8237 for 7 days in 21-day cycles was well-tolerated. Anti-proliferative clinical effects of MLN8237 were first noted at 80 mg and DLTs were seen at 150 mg. Clinically significant benzodiazepine-like side effects were not observed, except when MLN8237 was administered with long-acting opiates. Planned dose groups include 110 mg QD and 70–100 mg twice daily. Lower doses over 14−21 days will be evaluated.

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Phase I and pharmacokinetic study of MLN8054, a selective inhibitor of Aurora A kinase

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Background: MLN8054 is a selective small-molecule inhibitor of Aurora A kinase. This phase I clinical trial examined the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of MLN8054.
Materials and Methods: MLN8054 was given orally for 7−21 consecutive days followed by 14 days break (21−35 day cycles). Cohorts of 3−6 patients (pts) with advanced solid tumors at 3 centers in the US were enrolled in escalating cohorts until dose-limiting toxicity (DLT) was seen in ⩾2 of 6 pts. Serial blood samples were collected to estimate PK. The PD effects of MLN8054 on Aurora A kinase were inferred from accumulation of mitotic cells in basal epithelium in 2−3 mm skin biopsies obtained before and after dosing.
Results: 61 pts were treated (38 men, 23 women, median age 60). Tumor types included gastrointestinal (30), lung (9), genitourinary (8), sarcoma (8), breast (3), and other (3). Dose levels evaluated were 5, 10, 20, 30 and 40 mg/day in single daily doses (QD) for 7 days; 25, 35, 45 and 55 mg/day in four divided doses (QID) for 7 days; and 55, 60, 70 and 80 mg/day in QID doses for 7−21 days plus methylphenidate (MP) 5−10 mg with daytime doses to reduce somnolence. Pts received a median of 2 cycles (range, 1−14). Maximum tolerated doses were 30 mg/day for QD dosing, 45 mg/day for QID dosing, and 60 mg/day for QID dosing plus MP. Reversible Grade 3 benzodiazepine-like effects, especially somnolence, were the DLTs in all dosing permutations, usually starting in the first week of dosing. No dose studied was associated with significant myelosuppression or mucositis. MLN8054 was rapidly absorbed and exposure was dose-proportional. Terminal half-life was 30−40 hours. Skin biopsies were evaluable both pre- and post-treatment in 52 pts. Accumulation of mitotic cells was observed within 24 hours after either the first or last daily dose; the level of this effect varied by pt. While no RECIST responses were seen, 3 pts had stable disease for more than 6 cycles.
Conclusions: MLN8054 dosing for up to 21 days of a 35-day cycle was feasible. Despite divided daily dosing and MP, reversible benzodiazepine-like effects, especially somnolence, continued to be dose-limiting. PD studies suggested that Aurora A was inhibited in the skin of some pts. Studies of MLN8237, a second-generation Aurora A kinase inhibitor, are ongoing.

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Preliminary results of a Phase I accelerated dose-escalation, pharmacokinetic and pharmacodynamic study of PF-03814735, an oral Aurora kinase A and B inhibitor, in patients with advanced solid tumors

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Background: Aurora kinases are a family of kinases that are key regulators of mitosis and cytokinesis, and have been associated with carcinogenesis. Aurora kinase A is commonly amplified in solid tumors and has been established as an oncogene. Aurora B over-expression in tumors leads to defects in mitosis and is associated with increased invasiveness. PF-03814735 is a novel oral ATP-competitive, reversible inhibitor of Aurora A and B kinases with a broad spectrum of preclinical antitumor activity.
Material and Methods: This is an ongoing dose-escalation study to identify the Maximum Tolerated Dose (MTD) and Recommended Phase II Dose, to assess the pharmacokinetics (PK), and to obtain proof-of-mechanism (by assessment of pH3 inhibition in tumor biopsies and FDG-PET) with PF-03814735 administered daily for 5 or 10 consecutive days q3w.
Results: In the 5-day schedule, 25 patients received a median of 2 cycles (1−8) across 7 dose levels from 5–100 mg/day. The most common primary diagnoses in this cohort were non-small cell lung cancer, colorectal cancer and malignant melanoma. Dose-limiting febrile neutropenia was observed in 2/7 patients treated at 100 mg/day. The most commonly observed treatment-related adverse events were mild to moderate diarrhea (44%), vomiting, anorexia, fatigue, (25% each) and nausea (20%). MTD expansion for safety and pharmacodynamics is currently ongoing. No objective response has been observed so far. Serum exposure of PF-03814735 (Cmax and AUC) increased in a dose-proportional manner at all dose levels tested, indicating a linear PK at least up to 100 mg/day. After a single dose, the total clearance of PF-03814735 is 1.25±0.39 L/h and the median t1/2 was 20.2 h. Dose escalation on the 10-day treatment schedule is ongoing. Three patients have been treated at 40 mg/day, and 2 patients have been treated at the next dose level (50 mg/day).
Conclusions: For the 5-day treatment schedule, the MTD was defined as 80 mg/day. The effects of PF-03814735 on tumor metabolism and pH3 levels are currently being evaluated. The 10 day schedule is open for accrual, and results will be reported.

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Phase 1 trial of SNS-314, a novel selective inhibitor of Aurora kinases A, B, and C, in advanced solid tumor patients

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Background: The Aurora Kinases are a family of serine/threonine kinases (Aurora kinases (AK) A, B, and C) that play a key role in orderly progression through mitosis and have been implicated in a wide range of human tumors. Elevated expression levels of AKs have been detected in a high percentage of melanoma, colon, breast, ovarian, gastric, and pancreatic tumors, and in a subset of these tumors the AURKA locus (20q13) is amplified. SNS-314, a novel aminothiazole-derived urea, is a selective inhibitor of AKs A, B, and C with IC50 values in the low nanomolar range.
Methods: The trial is a standard 3+3 phase 1 dose escalation study design. Patients (pts) with advanced solid tumors were treated with SNS-314 given as a three hour IV infusion once weekly X 3 (28 day cycle). Primary endpoints of the study are: safety, tolerability, and DLT assessment. Secondary endpoints of the study include: pharmacokinetic (PK) evaluation on Days 1 and 15 and pharmacodynamic (PD) evaluation. PD evaluation assesses histone H3 phosphorylation (pHH3) in cells obtained by punch skin biopsies.
Results: A total of 19 pts (10M/9F) have been enrolled into 5 cohorts: median age = 59 (range 38−66). The initial dose was 30 mg/m^2 with subsequent dose escalation doubling until first observation of clinically significant ⩾Grade 2 related toxicity then according to a modified Fibonacci schema. No dose limiting hematological or non-hematological toxicities

(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.

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

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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.

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

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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.

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

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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.