we developed a score quantifying the evidence for sequence differences at the single nucleotide level. The score is based on read coverage and sequence quality and allows us to rank variants based on their support by the read data. We classified SNVs in loss of heterozygosity (LOH), substitution and gain of heterozygosity (GOH).
Results: Using the LOH and GOH classification of SNVs we were able to identify copy-number neutral chromosomal loss of heterozygosity, complete and partial quantitative chromosome losses, focal amplifications and deletions, as well as a range of other alterations in the genome. More fine scale analysis has identified sequence mutations in a number of genes that may help explain the development and progression of the disease. Most informative were missense mutations in LOH regions, which supplied a set of novel candidate tumor suppressor genes in ovarian cancer. Additional RNA-Seq data using polyA+ RNA derived from the tumor sample provides confirmation of many of the observed genomic alterations and allele specific expression.
Conclusions: Deep-sequencing of a paired tumor and germline DNA sample from the same patient has the potential to be a valuable tool for the discovery of novel ovarian cancer mechanisms, potential molecular targets and cancer therapeutics.

Anthracyclines, antimetabolites, antimicrotubules, topoisomerase inhibitor

570 POSTER

Phase 1 study of XMT-1001, a novel water soluble camptothecin conjugate, given as an IV infusion every 3 weeks to patients with advanced solid tumors

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Background: XMT-1001 is a water soluble macromolecular conjugate of camptothecin (CPT). In this novel CPT prodrug, CPT is conjugated with a 70 kDa biodegradable hydrophilic polyacetal, poly (1-hydroxymethylethylene hydroxymethylformal). XMT-1001 has an improved therapeutic window compared with irinotecan in human tumor xenograft models, providing a compelling rationale for its clinical development.
Methods: This is a dose escalation study of XMT-1001 given as an IV infusion once every 3 weeks. The objectives are to determine the maximum tolerated dose (MTD) and assess safety as well as pharmacokinetics (PK) of XMT-1001. Three patients (pts) are entered at each dose level, with expansion to 6 pts in the event of dose limiting toxicity. Analyses of plasma and urine are performed for XMT-1001 (conjugated CPT), two major drug release products, and for unconjugated (free) CPT.
Results: To date, 63 pts have received 186 cycles of XMT-1001 at dose levels from 1.0 to 151 mg CPT equivalents (eq)/m^2. Two pts had Grade (Gr) 3 infusion reactions related to study drug. After the introduction of clinical trial material with an improved formulation, no infusion reactions suggestive of hypersensitivity have occurred (42 pts, 124 cycles). No hemorrhagic cystitis or $\geqslant$Gr 2 diarrhea related to study drug was noted at any dose of study drug. Dose limiting toxicities (DLTs) were febrile neutropenia and Gr 4 neutropenia >5 days in two of six patients dosed at 151 mg CPT eq/m^2. The MTD is initially defined as 113 mg CPT eq/m^2 and is being confirmed. A partial response (PR) was observed in a patient with small cell lung carcinoma (SCLC) at the 151 mg CPT eq/m^2 dose level. Tumor shrinkage also was observed in a patient with colorectal carcinoma dosed at 15.4 mg CPT eq./m^2 and CEA declines occurred in a patient with colorectal cancer dosed at 113 mg CPT eq/m^2. Stable disease (SD) was noted in 17 of 60 evaluable pts with prolonged SD ($\geqslant$12 weeks) in 9 patients. Dose proportional increases in C_{max} and exposure to XMT-1001 and its release products were observed and levels of free CPT recovered in urine were low.
Conclusions: 1. The MTD for XMT-1001 was initially defined; DLTs were Gr 4 neutropenia and febrile neutropenia. 2. No drug related $\geqslant$ Gr 2 diarrhea and no hematuria were noted. 3. Anti-tumor activity was observed; a patient with SCLC had a PR; CEA declines and tumor shrinkage were documented in two pts and prolonged SD ($\geqslant$12 weeks) was noted in nine pts. 4. XMT-1001 and its release products have a favorable PK profile.

571 POSTER

TLC388, a novel topoisomerase-1 inhibitor with anti-hypoxia inducible factor-1 alpha activity: a phase I and pharmacokinetic study in patients with advanced solid malignancies

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Purpose: To assess the feasibility of administering TLC388, a novel derivative of topotecan with a unique modification in the lactone ring resulting in a more potent inhibition of topoisomerase I with anti-HIF1 alpha activity.
Patients and Methods: Patients with chemotherapy-refractory advanced solid malignancies were treated with escalating doses of TLC388 as a 30-minute intravenous infusion weekly X 3, repeated every 28 days. Plasma and urine sampling were performed to characterize the pharmacokinetics of TLC388.
Results: Forty-two patients (M:F = 24:18, median age 63, range 33−80) with advanced solid malignancies (prostate 7, colorectal 5, pancreas 3, esophageal 3, kidney 3, others 20) received 83 courses (range 1−7) of TLC388 at 9 dose levels ranging from 1.5 to 40 mg/m^2/d. Anemia was the most frequently reported hematological toxicity (37.5%). Leukopenia and neutropenia were reported in <20% of patients. Two DLT grade 4 hyponatremia cases and one grade 4 thrombocytopenia were observed at the level of 40 mg/m^2. To date, 15 out of 25 evaluable patients (60%) have stable disease (SD) as best response by RECIST. Prolonged stable disease was noted in 6 patients (7+ months in one patient with chromophobe renal cell carcinoma; 6 months in sorafenib-refractory hepatocellular carcinoma, docetaxel-refractory prostate cancer, and thymoma, one each; and 5 months in anal and cholangiocarcinoma, one each). Prolonged dosing does not lead to cumulative toxicity in patients. Pharmacokinetics of TLC388 was dose-independent; mean (SD) values for the volume of distribution at steady-state and plasma clearance were 845 (986) L/m^2 for S,R-TLC388 and 1102 (1481) L/m^2 for S,S-TLC388, and 2265 (2434) L/h-m^2 for S,R-TLC388 and 2914 (3233) L/h-m^2 for S,S-TLC388, respectively. The half-life values averaged 0.57 (1.18) hours for S,R-TLC388 and 0.65 (1.25) hours for S,S-TLC388.
Conclusion: TLC388 is safe as a weekly infusion up to 35 mg/m^2/d. The DLT of grade 4 hyponatremia at 40 mg/m^2/d is possibly drug-related and being investigated. Based on preliminary clinical efficacy, further disease-directed trials of TLC388 are planned.

572 POSTER

Berubicin, a topoisomerase II poison with high CNS uptake, inhibits cell growth and induces apoptosis in diffuse large B-cell lymphomas

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Background: Diffuse large B-cell lymphoma (DLBCL) is an aggressive form of lymphoma that frequently metastasizes to the central nervous system (CNS). Current clinically used drugs for DLBCL often fail to overcome drug resistance in relapsed and refractory DLBCL, especially in CNS DLBCL. Doxorubicin (DOX), an anthracycline, is an important component of the CHOP treatment regimen. We have designed a novel class of anthracyclines with high CNS uptake and an improved molecular targeting spectrum. Berubicin (BRN), the lead drug of this class, is being clinically evaluated in brain tumor patients. It has been shown that BRN is a topoisomerase II poison and a potent inhibitor of hypoxia induced factor-1α (HIF-1α) transcriptional activity.
Materials and Methods: Because of its high CNS uptake, we tested the effects of BRN in DLBCL cell lines. In our studies, two human large cell lymphoma cell lines, DB and Toledo, were treated with BRN and compared with DOX. We analyzed the effects of these compounds on cell proliferation, apoptosis, and the cell cycle using MTS assays and flow cytometry.
Results: BRN potently inhibited the growth of both cell lines in a dose-dependent manner, with IC_{50} values of 12.4 nM for the DB cell line and 3.3 nM for the Toledo cell line. BRN was more potent in both cell lines than DOX (IC_{50s} for DOX, 31.1 nM and 10.0 nM, respectively). BRN also potently induced apoptosis and G2/M cell cycle arrest in the DB and Toledo DLBCL cell lines in a dose-dependent manner.
Conclusions: BRN showed more potent activity against DLBCL cell lines than DOX. These results are promising and consistent with BRN's

mechanistic profile, which is different from that of DOX: BRN is a more potent topoisomerase II inhibitor that blocks the transcriptional activity of HIF-1a and circumvents ABC transporter-mediated efflux. Our data indicate that BRN is a potentially useful agent against diffuse large B cell lymphoma. Most importantly, its unique high CNS uptake makes BRN a good candidate for clinical evaluation in patients with diffuse large B cell lymphomas in CNS.

573 POSTER

Eribulin and cytochrome P450 effectors: *in vitro* studies and population pharmacokinetic–pharmacodynamic analysis

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Background: Eribulin belongs to the halichondrin class of antineoplastic agents and inhibits microtubule dynamics by suppressing microtubule growth without affecting shortening. Eribulin also sequesters tubulin into non-functional aggregates. The cytochrome p450 isoform, CYP3A4, has been shown to be the major enzyme responsible for eribulin metabolism in the liver. Here we report the results of *in vitro* studies and clinical population PK analysis of the effects of CYP P450 inhibitors and inducers on eribulin exposure as well as the effect of eribulin on co-administered drugs metabolized via CYP3A4 pathway.
Methods: The *in vitro* analysis utilized cultured primary human hepatocytes, isolated human liver microsomes, and cDNA-expressed recombinant CYP3A4 protein. Eribulin mesylate treatments of concentrations up to 10 μmol/L and exposure times ranging from 15 minutes to 3 days were used. Enzyme activity was measured by the specific CYP3A4-mediated hydroxylation of metabolites. Protein expression was determined immunocytochemically, and the nature of CYP3A4 inhibition by eribulin was determined by nifedipine dehydration. The population PK model was developed based on robust PK data collected from 7 phase I studies and sparse PK data collected from a phase II study. The model was constructed and evaluated from a final database consisting of 2729 observations from a total of 269 subjects. The effects of CYP3A4 inhibitors and inducers on eribulin clearance were tested as covariates in the population PK model.
Results: Eribulin inhibited CYP3A4 activity with an apparent inhibition constant (K_i) value ranging from 3 to 30 μmol/L (2190–21900 ng/mL, calculated as eribulin free base); this inhibition was shown to be reversible and competitive. In human hepatocytes, eribulin displayed minimal inhibition of carbamazepine, diazepam, paclitaxel, tamoxifen, midazolam, and terfenadine metabolism, at concentrations up to 10 μmol/L (7300 ng/mL). *In vitro* results were confirmed by population PK analyses that demonstrated co-administration of certain CYP3A4 inducers and inhibitors had no significant effect on eribulin clearance and exposure in clinical studies.
Conclusions: Eribulin, at clinically relevant concentrations (i.e. $\leqslant$700 ng/mL), has no effect on CYP3A4 expression, induction, enzyme activity or the processing of compounds metabolized by CYP3A4 *in vitro*. Clinical findings have confirmed that eribulin can be co-administered with drugs metabolized by CYP3A4.

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Eribulin mesylate pharmacokinetics in patients with solid tumors receiving repeated oral ketoconazole (KET)

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Background: Eribulin mesylate is a non-taxane microtubule dynamics inhibitor with a novel mechanism of action in development for the treatment of metastatic breast cancer, and other solid tumors. This study investigated the effects of ketaconazole (KET), a CYP3A4 inhibitor, on eribulin pharmacokinetics (PK).
Methods: In this phase I, randomized, open-label, 2-way crossover study, 12 patients with solid tumors were assigned to one of two groups. Group 1 (n = 6) received 1.4 mg/m^2 eribulin mesylate as a 2−5 min IV injection on day 1, 0.7 mg/m^2 eribulin mesylate IV + 200 mg oral KET on day 15, and 200 mg oral KET on day 16. Group 2 (n = 6) received 0.7 mg/m^2 eribulin mesylate IV + 200 mg oral KET on day 1, 200 mg oral KET on day 2, and 1.4 mg/m^2 eribulin mesylate IV on day 15. Plasma samples for PK analysis were collected over 144 hours post dose on days 1 and 15 of cycle 1. Log-transformed, dose normalized AUC and C_{max} values were analyzed using analysis of variance. Comparisons were made between eribulin alone and eribulin + KET treatment groups for AUC_∞ and C_{max}. Safety was also assessed.
Results: The C_{max} for eribulin + KET was not statistically different from that for eribulin alone (ratio of geometric least square means: 0.97, 90% CI 0.83, 1.12). Eribulin exposure (AUC_∞) following administration alone was statistically not different from that of eribulin + KET (ratio of geometric least square means: 0.95, 90% CI 0.80, 1.12). KET had no apparent effect on eribulin clearance (CL) or elimination half-life ($T_{1/2}$). CL (mean, [SD]) was 3.10 (1.903) for eribulin and 3.37 (2.507) L/hr for eribulin+KET. $T_{1/2}$ was 45.6 (13.62) vs 40.5 (7.69) hr, respectively. The most frequent treatment-related adverse events (AEs) reported for eribulin were nausea, fatigue and neutropenia, each occurring in 4 patients. For eribulin + KET, the most frequent AEs were nausea (n = 3) and fatigue (n = 3). Low numbers preclude the drawing of conclusions from comparisons across treatment groups, although the incidence and severity of AEs were broadly similar. There were no deaths, life threatening serious AEs or serious AEs reported as treatment related.
Conclusions: Co-administration of KET had no statistically significant effect on single dose exposure to eribulin. Eribulin was generally safe and well tolerated.

575 POSTER

ALB 109564(a), a novel tubulin inhibitor: phase 1 trial in patients with solid tumours

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Background: ALB 109564(a) [ALB] is a novel antimitotic agent which functions as a tubulin inhibitor, interfering with microtubule polymerization resulting in metaphase arrest. ALB showed significantly greater activity compared to vinorelbine in a number of xenograft models (NSCLC [H460], SCLC [H69], colon [Colo205] and prostate [PC3]); these data demonstrate that ALB has a preclinical profile that is superior to that of this established vinca alkaloid anti-cancer agent and warranted clinical development.
Methods: This study sought to determine the maximum tolerated dose based upon first cycle toxicity in 3−6 patients at each dose level, as well as to evaluate the pharmacokinetics of ALB when administered intravenously once every three weeks. The starting dose was 1.2 mg/m^2, and dose escalation by cohort proceeded according to a modified Fibonacci scheme.
Results: 35 patients have been administered ALB across 10 dose levels (1.2 to 22.5 mg/m^2). No dose-limiting toxicities have been observed. Adverse events reported to be at least possibly related to study drug were constipation (n = 12), fatigue (n = 5), anemia (n = 3), diarrhea (n = 3) blurred vision (n = 2), paresthesia (n = 2), peripheral neuropathy (n = 2), and neutropenia (n = 1). With the exception of neutropenia (grade 3), all adverse events were either grade 1 or 2. The mean half-life of ALB is 18.54±8.28 hours, which is comparable to that of approved vinca alkaloids. Of 28 patients evaluable for clinical activity, one alveolar soft part sarcoma (ASPS) patient, who had marked progression prior to enrollment, has received 26 cycles of study drug with stable disease. An additional seven patients have had stable disease after two or more cycles; one anal carcinoma (13 cycles), one pancreatic carcinoma (7 cycles), two colon carcinomas (4 and 2 cycles), one NSCLC (4 cycles), one leiomyosarcoma (3 cycles), and one neuroendocrine tumor (2 cycles).
Conclusions: ALB is well tolerated, with a favorable pharmacokinetic profile, and has shown preliminary activity in disease types not typically treated with vinca alkaloids. Further trials in soft tissue sarcoma are in development.