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.

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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.

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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