Safety, Dose Tolerance, Pharmacokinetics and Pharmacodynamics Study of CPX-POM in Patients with Advanced Solid Tumors

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Abstract

Ciclopirox (CPX) is an antifungal agent contained in several FDA-approved topical drug products. CPX possesses anticancer activity in a number of *in vitro* and *in vivo* preclinical models, however, it's clinical utility is limited due to low oral bioavailabilty, gastrointestinal toxicity, and poor water solubility. Ciclopirox Prodrug (CPX-POM) selectively delivers its active metabolite, CPX, to the entire urinary tract following systemic administration. In a chemical carcinogen mouse model of bladder cancer, CPX-POM treatment resulted in significant decreases in bladder weight, a clear migration to lower stage tumors, dose-dependent reductions in Ki67 and PCNA staining, and inhibition of Notch-1 and Wnt signaling pathways. Study CPX-POM-001 (NCT03348514) is an ongoing US multicenter, Phase I, open-label, dose escalation study to evaluate dose-limiting toxicities (DLTs), define the maximum tolerated dose (MTD), and to determine the recommended Phase II dose (RP2D) of IV CPX-POM. Approximately 24 patients with any histologically- or cytologically-confirmed solid tumor type refractory to standard therapy, and also meet other standard Phase I eligibility criteria, will be enrolled in dose escalation cohorts. The MTD will be defined as the dose BELOW that dose which causes DLTs in ≥33% of patients. Safety and tolerability will be based on an assessment of adverse events, physical examinations, vital signs, electrocardiogram, clinical laboratory tests, ophthalmologic assessments, and concomitant medications. Single dose and steady-state pharmacokinetics of CPX-POM, CPX and ciclopirox glucuronide are being characterized in both plasma and urine. Urine ß-glucuronidase activity is also being determined. Single and multiple dose pharmacodynamics of CPX-POM are being characterized by measuring circulating biomarkers of Wnt and Notch cell signaling pathways. Enrollment began in January 2018 at a starting IV CPX-POM dose of 30 mg/m^2. Doses are currently being escalated in 100% increments until a ≥Grade 2 is encountered, at which point that cohort and all subsequent cohorts will follow a classical "3 + 3" dose escalation design.

Background & Significance

Bladder cancer is a devastating disease that currently ranks as the fourth most common cancer among men and the sixth most common among men and women combined. The American Cancer Society estimates that in 2018 alone, 81,190 new cases will be diagnosed in the U.S. and 17,240 will die of the disease. Bladder cancer is defined as two diseases, each with different treatment approaches and outcomes.

IV CPX-POM IND 132545 received FDA clearance to proceed with a first-in-human Phase 1 trial on 15 September 2017. The safety, dose tolerance, pharmacokinetics and pharmacodynamics of IV CPX-POM are currently being characterized in patients with advanced solid tumors at four US sites (NCT03348514). Development of a subcutaneous injectable formulation of CPX-POM is planned as a more convenient dosage form for self administration by bladder cancer patients.

Acknowledgements

CPX-POM is being developed for the treatment of non-muscle invasive and muscle invasive bladder cancer through a unique public-private partnership between CicloMed LLC, Kansas City, MO and the NCI Cancer Center at the University of Kansas. Preclinical proof of principle and IND-enabling studies were supported by CicloMed and The Institute for Advancing Medical Innovation at the University of Kansas Medical Center. This drug development program has and continues to utilize Lead Development and Optimization as well as Clinical Pharmacology shared resources supported by the National Cancer Institute Cancer Center Support Grant P30 CA168524.

Ciclopirox Prodrug

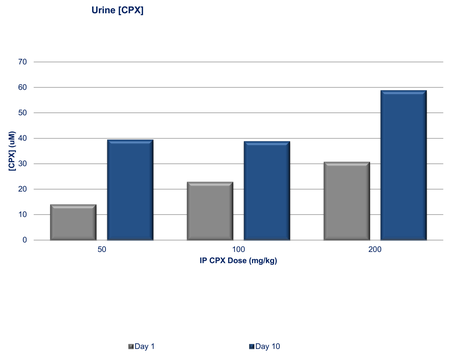

Figure 1. Systemic administration of Ciclopirox Prodrug (CPX-POM) results in selective delivery of the active metabolite, ciclopirox (CPX), to the entire urinary tract. CPX-POM is rapidly and completely metabolized via circulating phosphatases to CPX. CPX is excreted in urine and metabolized to the inactive glucuronide metabolite, which is also eliminated in urine. A portion of the inactive glucuronide metabolite is hydrolyzed in urine of bladder cancer patients to reactivate CPX due to high β-glucuronidase activity.

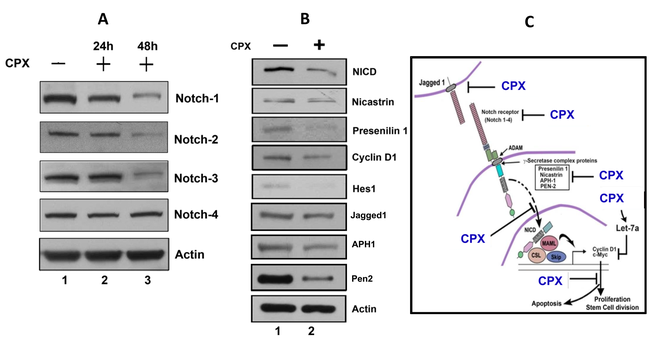

Figure 2. CPX inhibited gene expression for Wnt, Hedgehog and Notch cell signaling pathways in T24 and 253JBV cell lines. Protein expression levels for Notch 1, 2 and 3 isoforms were inhibited following exposure to CPX in T24 cells, whereas Notch 4 was not affected (A). CPX inhibited Notch 1 activation and Jagged 1, a ligand for the Notch 1 receptor (B). Additionally, CPX inhibited expression of secretase complex proteins including Presenelin 1, Nicastrin, APH-1, and PEN-2, resulting in decreased levels of cleaved NICD1 reflected in schematic C.

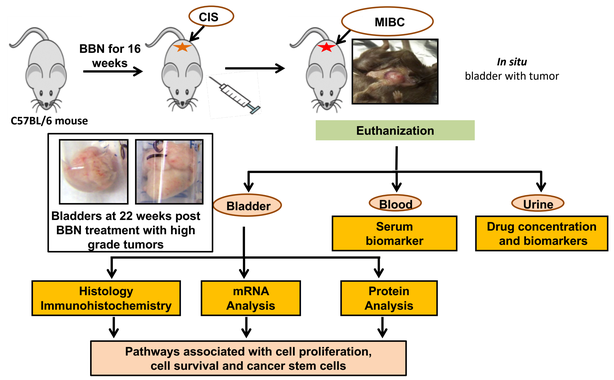

Figure 3. *In vivo* proof of principle was established employing the validated N-butyl-N-(4-hydroxybutyl)-nitrosamine (BBN) chemical carcinogen mouse model of bladder cancer. In C57Bl/6 mice, this model demonstrates Carcinoma *in situ* following exposure to BBN for 16 weeks via the drinking water. At 16 weeks, the carcinogen is removed and drug treatment initiated. Without treatment, Carcinoma *in situ* progresses to MIBC over 16-20 weeks. Over a once daily IP dose range of 25-200 mg/kg, significantly ($p < 0.05$) lower bladder weights were observed in CPX-POM treated mice compared to control animals. There was a moderate to strong correlation between CPX-POM treatment and pathologic outcome (Pearson's Chi-Square R^2=0.74) that did not reach statistical significance (p=0.12). Cell proliferation by Ki67 and PCNA staining was reduced in CPX-POM treated animals. Dose-dependent reductions in Notch 1, Presenelin 1, and Hey 1 in bladder cancer tissues were also observed in CPX-POM treated animals.

Study Objectives

Primary Objective:

❑ Evaluate dose limiting toxicities (DLTs) and the maximum tolerated dose (MTD) of CPX-POM administered IV and establish the CPX-POM dose recommended for further investigation

Secondary Objectives:

❑ Characterize plasma and urine pharmacokinetics (PK) of CPX-POM and its metabolites following single and multiple dose administration
❑ Identify preliminary anti-tumor activity of CPX-POM
❑ Determine urine β-glucuronidase activity in patients

Exploratory Objectives:

❑ Characterize the pharmacologic effects of CPX-POM on circulating biomarkers of Wnt and Notch cell signaling pathways
❑ Explore pharmacodynamic (PD) relationships between changes in circulating biomarkers and drug and/or metabolite exposure and other outcomes

Study Design

❑ First-in-human, Phase 1, multicenter, open-label, dose escalation study
❑ Approximately 24 patients will be enrolled in dose escalation cohorts to establish MTD. Expansion cohort(s) may be enrolled once MTD is reached
❑ Target patient population includes patients with any histologically- or cytologically-confirmed solid tumor type refractory to standard therapy
❑ Study schedule includes 14-day screening period, 21-day treatment cycle(s) and 28 ± 5 follow-up period
❑ CPX-POM administered IV over 10 minutes once daily on Days 1-5 of each treatment cycle
❑ Patients may receive additional cycles of CPX-POM until progression of disease, intolerable toxicity occurs, or another withdrawal criterion applies
❑ Initial starting dose 30 mg/m^2

Dose Escalation

Accelerated Dose Escalation (Single-Patient Cohorts)
❑ No ≥ Grade 2 Adverse Events
❑ Continue evaluation of single-patient dose cohorts
❑ Escalate doses by 100%

Transition from Accelerated to Standard Dose Escalation
❑ At least 1 ≥ Grade 2 Adverse Events not meeting definition of DLT results in expansion of current and subsequent dose cohorts to at least 3 patients
❑ One DLT – Expand current cohort up to 6 patients or until 2 DLTs are encountered

Standard Dose Escalation (N = 3 to 6 each)
❑ No DLT – Escalate by 25-50% to the next dose level
❑ One DLT in ≤ 3 patients – Expand cohort up to 6 patients
❑ One DLT in 6 patients – Escalate by 25-50% to next dose level
❑ > 1 DLT in ≤ 6 patients – MTD reached, stop dose escalation, possibly explore intermediate doses for the RP2D

❑Intra-patient dose escalation is not allowed

CicloMed

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Abstract # TPS2618

Poster Board # 433a

Study Endpoints

Safety:

❑ Adverse events, physical exam, vital signs, ECGs, clinical laboratory tests, ophthalmologic assessment, and concomitant medications
❑ MTD defined as the dose below that dose that causes DLTs in ≥ 33% of patients

Pharmacokinetics:

❑ Serial blood (plasma) samples and complete urine collected over 24-hour periods after the first (Day 1) and fifth (Day 5) doses of CPX-POM during Cycle 1
❑ Plasma and urine CPX-POM, CPX and CPX glucuronide concentrations determined by LC-MS/MS
❑ Non-parametric pharmacokinetic data analysis using Phoenix WINNONLIN® 8.0 (Certara LP, Princeton, NJ)
❑ Urine β-glucuronidase activity determined by enzyme-linked immunoassay (ELISA) in 0-12 and 12-24 hour complete urine samples collected on Days 1-2 and 5-6

Pharmacodynamics:

❑ VEGF, IL-6, and IL-8 concentrations measured by ELISA
❑ qRT-PCR to characterize gene expression of circulating biomarkers of Wnt and Notch signaling pathways in PBMCs

Major Inclusion Criteria

❑ Patients with any histologically- or cytologically-confirmed solid tumor type refractory to standard therapy
❑ May have received up to 4 prior lines of cytotoxic chemotherapy or immunotherapy for their metastatic disease
❑ Experienced progressive disease during, following or intolerant of the most recent treatment regimen
❑ Male or female aged ≥ 18 years
❑ ECOG performance status of 0 or 1
❑ Life expectancy of ≥ 3 months
❑ Adequate renal function defined as serum creatinine ≤ 1.5 x ULN or GFR ≥ 50 mL/min
❑ Adequate hepatic function as evidenced by total bilirubin ≤ 1.5 x ULN, AST, and/or ALT ≤ 3 x ULB or ≤ 5 x ULN if due to liver involvement by tumor
❑ Adequate bone marrow function as evidenced by hemoglobin ≥ 9.0 g/dL in the absence of transfusion within previous 72 hours, platelet count ≥ 100 x 10^9 cells/L, and ANC ≥ 1.5 x 10^{9}cells/L
❑ No significant ischemic heart disease or myocardial infarction within 6 months, adequate cardiac function defined by left ventricular ejection fraction > 50%, corrected QT interval < 470 msec
❑ Patient and partner agree to use adequate contraception

Major Exclusion Criteria

❑ History of risk factors for torsade de pointes
❑ Abnormal cardiac appearance/heart size
❑ Uncontrolled or severe intercurrent medical condition
❑ Underwent major surgery within 4 weeks before first CPX-POM dose
❑ If female, pregnant or breast feeding
❑ Evidence of serious infection including active Hepatitis A, B or C, or HIV infection
❑ Taking warfarin
❑ History of other malignancy treated with curative intent within previous 5 years with exception of adequately treated non-melanoma skin cancer or carcinoma in situ of the cervix
❑ Known allergy or hypersensitivity to components of CPX-POM

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