Ciclopirox (CPX) is an antifungal agent contained in several FDA-approved topical drug products. CPX possesses antitumor activity in a number of in vitro and in vivo preclinical models, however, its clinical utility is limited due to low oral bioavailability, 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 Notch signaling pathways. A study CPX-POM-001 (NCT03348314) is ongoing at USC multichem, 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 (RPD) 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 glucuronidase are being characterized in both plasma and urine. Urine B-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 signaling pathways. Enrollment began in January 2018 at a starting IV CPX-POM dose of 30 mg/m². Doses are currently being escalated in 100% increments until a 2xR is encountered, at which point that cohort and all subsequent cohorts will follow a classical “3 + 3” dose escalation design.

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 U.S. sites (NCT03348314). 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

Ciclopirox Prodrug

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 ciclopirox glucuronidase following IV and multiple dose administration
- Identify preliminary anti-tumor activity of CPX-POM
- Determine urine B-glucuronidase activity in patients

Exploratory Objectives:
- Characterize the pharmacologic effects of CPX-POM on circulating biomarkers of Wnt and Notch 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 ≥2 ± ≤3 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, unacceptable toxicity occurs, or another withdrawal criterion applies
- Initial starting dose 30 mg/m²

Dose Escalation

Accelerated Dose Escalation (Single-Patient Cohorts):
- No ≥ 2 DLTs in 3 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 RPD

Intra-patient dose escalation is not allowed

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 period after the first (Day 1) and fifth (Day 5) doses of CPX-POM during the Phase 1 cohort
- Plasma and urine CPX-POM, CPX and ciclopirox glucuronidase determined by LC-MS/MS
- Non-parametric pharmacokinetic data analysis using Phoenix Wilkinson® 8.0 (Certara LP, Princeton, NJ)
- Urine B-glucuronidase activity determined by enzyme-linked immunosassay (ELISA) in 0-12 and 12-24 hour complete urine samples collected on Days 1-2 and 5-6

Pharmacodynamics:
- UGE, 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 defined by total bilirubin ≤ 1.5 x ULN, AST, and/or ALT ≤ 5 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 ≥ 100,000/mm3, and WBC ≥ 3,000/mm3
- 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 points
- 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

Abstract #

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Poster Board #

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