ROGEL CANCER CENTER
MICHIGAN MEDICINE

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A Multi-Center Randomized Phase IB/II Study of Gemcitabine and Cisplatin With or Without CPI-613 as First-Line Therapy for Patients with Advanced Unresectable Biliary Tract Cancer: BilT-04

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BACKGROUND

Biliary Tract Cancer Overview

- Biliary tract cancers (BTCs) are comprised of intra- and extra-hepatic (peri-hilar and distal) cholangiocarcinomas, and gallbladder cancer.
- The incidence of BTCs is rising globally and in the US (Razumilava, Gores et al 2013).
- Advanced BTCs are aggressive tumors with median overall survival (OS) less than 12 months and 5-year OS rate of less than 5% (Valle, Wassan et al 2011; Sahai, Catalano et al 2018).
- In the phase III ABC-02 trial, patients with untreated advanced BTCs on the gemcitabine and cisplatin arm demonstrated an objective response rate of 26.1% and improvement in OS (11.7 versus 8.1 months; hazard ratio (HR), 0.64; 95% CI, 0.52 to 0.80; p<0.001) as compared to the gemcitabine alone arm (Valle, Wassan et al 2011).

CPI-613

- Devimistat (CPI-613®) is a stable analog of normally transient, acylated catalytic intermediates of lipoic acid (lipoate), an essential co-factor for 2 enzyme complexes, pyruvate dehydrogenase (PDH) and α-ketoglutarate dehydrogenase (KGDH) central to the tricarboxylic acid (TCA) cycle (Zachar, Marecek et al. 2011).
- Cancer cells take up CPI-613 preferentially, apparently through upregulated vitamin and fatty acid transporters which limits the toxicity to normal cells (Stuart, Schauble et al. 2014).
- CPI-613 selectively inactivates PDH and KGDH (Figure 1), thereby collapsing mitochondrial metabolism of the tumor cells which, in turn, leads to redundant activation of apoptotic and necrotic cell death pathways (Zachar, Marecek et al. 2011).

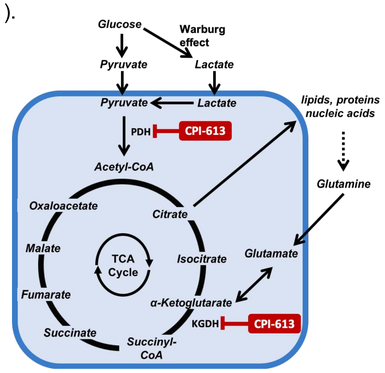
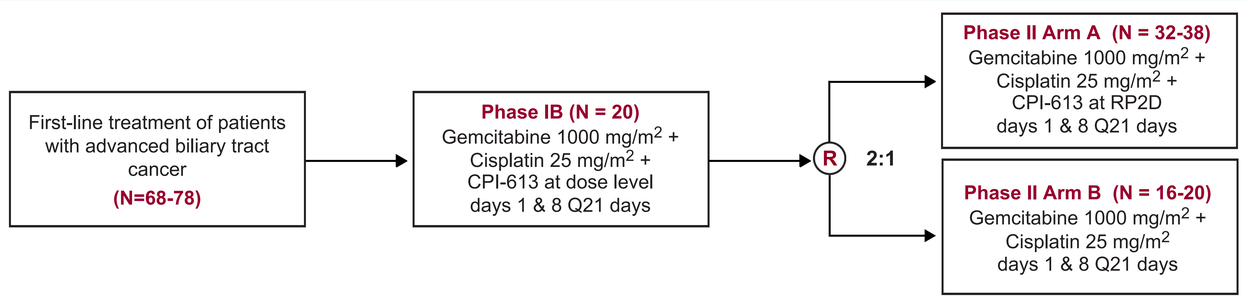


Figure 1. CPI-613 inhibits PDH and KGDH in the Tricarboxylic Acid (TCA) cycle

STUDY DESIGN

Figure 1. Study Schema



Phase IB Dose Levels

Dose Level	CPI-613	Gemcitabine	Cisplatin
3	2000 mg/m^2	1000 mg/m^2	25 mg/m^2
2	1500 mg/m^2	1000 mg/m^2	25 mg/m^2
1*	1000 mg/m^2	1000 mg/m^2	25 mg/m^2
-1	500 mg/m^2	800 mg/m^2	25 mg/m^2

**starting dose level*

Statistical Design

- **Phase IB:** Time to Event - Continual Reassessment Methodology (TiTE-CRM) with expected DLT rate <35% (DLT period days 1-22)
- **Phase II:** Randomized (2:1) two-arm design. The alternative hypothesis is best ORR rate of 43% with a historical null hypothesis of 25% based on the ABC-02 trial but will be adjusted based on the control arm. Type 1 error of 5% (one-sided) and power of >80%.

STUDY OBJECTIVES

Primary

- Phase IB - Determine the maximum tolerated dose/ recommended phase 2 dose (RP2D) for gemcitabine, cisplatin and CPI-613
- Phase II - Determine the overall response rate in patients with advanced BTC treated with gemcitabine, cisplatin and CPI-613

Secondary

- Evaluate clinical efficacy by assessment of median OS, PFS of patients with advanced BTC
- Evaluate the safety of CPI-613 in combination with gemcitabine and cisplatin in this patient population

Exploratory

- Explore molecular markers of response and resistance through serial biopsies and blood
  - Immunohistochemical staining for PDK, PDH, KGDH, SOD2 and CD79a
  - Genomic and transcriptomic (RNAseq) analysis for tumor biology at baseline and progression, if available tissue
  - Blood collection, including serum, plasma for future biomarker analysis, including ctDNA

ELIGIBILITY CRITERIA

- Advanced or metastatic BTC with no prior systemic therapy.
- Prior adjuvant therapy permitted provided it was completed more than 6 months from enrollment
- Radiographically measurable disease per RECIST1.1
- May have undergone surgery, radiation or liver directed therapy
- ECOG PS 0-1
- No prior history of brain metastasis (unless treated, asymptomatic and stable for at least 3 months), or organ transplantation
- Must not have prolonged QTcF interval >480 msec
- Adequate organ function
  - ANC ≥1500/mm³
  - Platelets ≥100,000/mm³
  - Hemoglobin ≥9 g/dL
  - Albumin ≥3 g/dL
  - AST/ALT ≤3 x ULN (≤5 x ULN if liver metastasis)
  - Creatinine ≤1.5 x ULN
  - CrCl ≥ 50 mL/min
  - INR ≤1.5 x ULN
  - Total bilirubin ≤1.5 x ULN
- No active second malignancy. If prior malignancy, then treatment must have completed > 1 year from registration and free of recurrence/progression.

SITES & ENROLLMENT

- The trial is open or due to open at the following sites:
  - University of Michigan (lead site)
  - University of Washington
  - University of Texas Southwestern
  - Northwestern University
  - University of Wisconsin
  - University Hospital Cleveland
  - University of Arizona
  - Vanderbilt University
  - Atlantic Health
- 10 out of 20 patients have been enrolled to date in Phase IB
- No dose-limiting toxicity (DLT) at CPI-613 1000 mg/m^2 and 1500 mg/m^2. One patient had DLT at CPI-613 2000 mg/m^2 dose level due to grade 2 renal dysfunction
- Enrollment is expected to complete in Q2 2022

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Disclosures

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