Phase IB Results of a Multi-Center Randomized Phase IB/II Study of Gemcitabine and Cisplatin With or Without CPI-613 (Devimistat) as First-Line Therapy for Patients with Advanced Biliary Tract Cancer (BilT-04)

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ROGEL CANCER CENTER
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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; p<0.001) as compared to the gemcitabine (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).
- CPI-613 inactivates PDH and KGDH preferentially in the cancer cells, thereby collapsing mitochondrial metabolism which leads to redundant activation of apoptotic and necrotic cell death pathways (Zachar, Marecek *et al*. 2011).

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

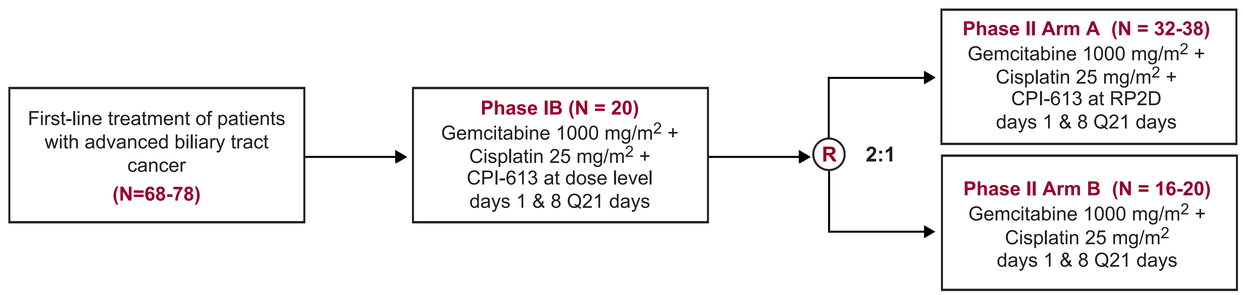
- Evaluate clinical efficacy by assessment of median OS, PFS of patients with advanced BTC
- Evaluate the safety of CPI-613 in combination with gemcitabine and cisplatin in this patient population

Exploratory

- Explore molecular markers of response and resistance through tissue and blood

STUDY DESIGN

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%.

RESULTS

Patient Characteristics		
Patients, N (%)	Evaluable	20 (100)
	Still on-treatment	7 (35)
Sex, N (%)	Female	9 (45)
ECOG PS, N (%)	0	11 (55)
	1	9 (45)
Age, years	Median (range)	65 (43-75)
Race, N (%)	Caucasian	17 (85)
	Asian	1 (5)
	Not reported	2 (10)
Ethnicity, N (%)	Hispanic	2 (10)
	Non-Hispanic	18 (90)
Sub-type, N (%)	Intrahepatic	9 (45)
	Hilar	5 (25)
	Distal	2 (10)
	Gallbladder	3 (15)
	Not reported	1 (5)
Stage, N (%)	Locally Advanced	5 (25)
	Metastatic	15 (75)

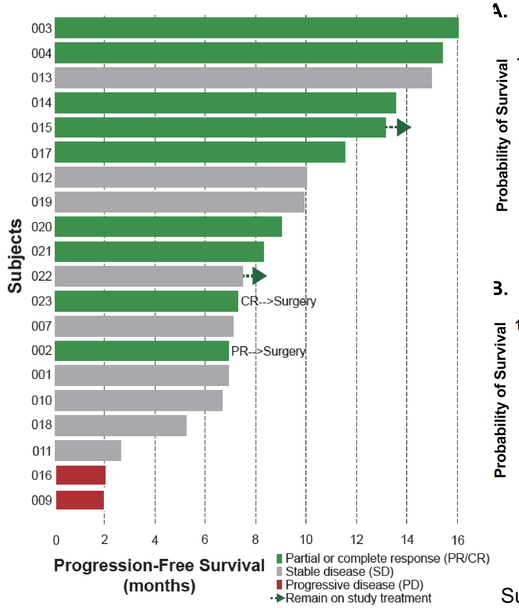


Figure 1. Phase IB Swimmer's Plot

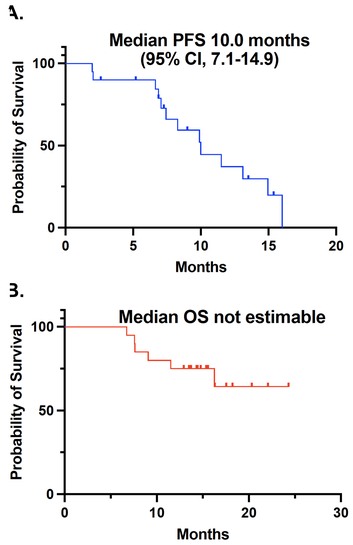


Figure 2. **A.** Progression-free Survival and **B.** Overall Survival of patients on Phase IB.

RESULTS

- No dose-limiting toxicity (DLT) observed at CPI-613 500 mg/m^2 (n=1), 1000 mg/m^2 (n=1) and 1500 mg/m^2 (n=2) dose levels. At 2000 mg/m^2 (n=16), **one patient had DLT with grade 2 renal dysfunction**.
- In Phase IB, the **objective response rate is 45%** (1 complete response and 8 partial responses).
- **Median progression-free survival is 10.0 months (95% CI, 7.1 - 14.9)** with 2 patients still on treatment.
- **Overall survival is not yet estimable** with 14 (70%) patients still alive on the Phase 1B. The median follow-up time was 15.6 months using the reverse censoring method.
- **Treatment-related SAEs were reported in 4 (20%) patients** and included grade 3 febrile neutropenia (2; 10%) and infection (2; 10%).

CONCLUSIONS

- RP2D was determined to be CPI-613 2000 mg/m^2, gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2.
- This **combination was well-tolerated** and initial efficacy observations in this Phase IB trial suggest that **CPI-613 in combination with gemcitabine and cisplatin may be active in this malignancy**.
- 63 out of 78 patients have been enrolled to date, and Phase II enrollment is expected to complete in Q4 2022.
- The trial is now **open to accrual** at the following 10 sites:
  - University of Michigan (lead site)
  - University of Washington
  - University of Texas Southwestern
  - Northwestern University
  - University Hospital Cleveland
  - Atlantic Health
  - Vanderbilt University
  - University of Wisconsin
  - University of Arizona
  - Allegheny Health

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Grant Support

NCT04203160 supported by Rafael Pharmaceuticals & University of Michigan Rogel Cancer Center.

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