Phase 1b Study of Vactosertib in Combination with FOLFOX in Patients with Metastatic Pancreatic Ductal Adenocarcinoma who have Failed First-Line Gemcitabine/*nab*-Paclitaxel

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Introduction

- Pancreatic ductal adenocarcinoma (PDAC) remains one of the most aggressive malignancies and the leading cause of cancer-related death in the world, although recent advances in chemotherapies for metastatic PDAC provide better clinical outcomes.
- TGF-β is strongly involved in the tumor microenvironment of PDAC, and dysregulation of TGF-β signaling is a frequent molecular disturbance in PDAC progression and metastasis.
- Vactosertib is an orally bioavailable TGF-β signaling inhibitor that targets the TGF-β type I receptor kinase. In preclinical studies, vactosertib in combination with FOLFOX improves pancreatic cancer survival by suppressing cell migration, invasion, and epithelial-mesenchymal transition (EMT), highlighting a potential clinical application of this approach for PDAC patients.
- Based on this preclinical study, we develop a phase 1b study to determine the recommended phase 2 dose (RP2D) and to evaluate the safety of vactosertib in combination with FOLFOX in patients with metastatic PDAC who have failed first-line gemcitabine with *nab*-paclitaxel.

Preclinical study

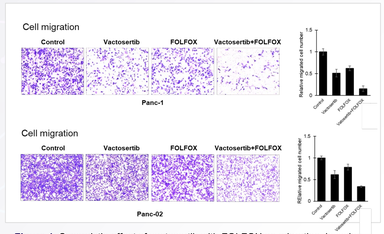


Figure 1. Synergistic effect of vactosertib with FOLFOX on migration, invasion, and EMT of pancreatic cancer cells (Panc-1 & Panc-02).

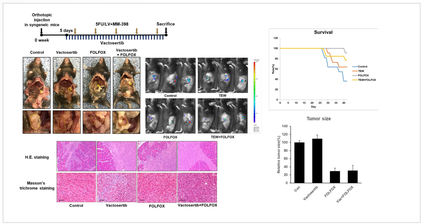


Figure 2. Survival improvement in response to combination treatment of vactosertib with FOLFOX

Study Scheme

Dose Escalation

Vactosertib: dose escalation
FOLFOX: fixed dose

DL 1
Vactosertib 200 mg BID
5 day on/2 day off

DL 0
Vactosertib 100 mg BID
5 day on/2 day off

DL -1
Vactosertib 50 mg BID
5 day on/2 day off

+ FOLFOX
Day1/14-day schedule

Dose Expansion

Back-fill DL 1 Cohort
Vactosertib 200 mg BID
or
Back-fill DL 0 Cohort
Vactosertib 100 mg BID

Dose Escalation (3+3 design)

a	Vactosertib	FOLFOX D1-14 q2wks
Dose level -1	**50 mg bid**	**100%**
Dose level 0	**100 mg bid**	**100%**
Dose level 1	**200 mg bid**	**100%**

Purpose

Primary Endpoint

- To determine RP2D and to evaluate the safety of vactosertib with FOLFOX

Secondary Endpoints

- Progression-free survival (PFS)
- Objective response rate (ORR)
- Disease-control rate (DCR)
- Overall survival (OS)

Exploratory Endpoint

- PK, PD & biomarkers analysis

Inclusion & Exclusion Criteria

Inclusion

- Histologically confirmed pancreatic adenocarcinoma
- Failed to gemcitabine-based chemotherapy for advanced pancreatic cancer
- Measurable or evaluable lesion by RECIST ver.1
- ECOG 0-1
- Life expectancy of ≥ 12 weeks
- Adequate normal organ and marrow function
- Written informed consent

Exclusion

- Patients received other chemotherapy within 14days prior to administration of IP
- Current or prior use of immunosuppressive medication
- Major surgical procedure within 28 days
- Uncontrolled intercurrent illness, or active infection
- History of another primary malignancy
- History of leptomeningeal carcinomatosis, brain metastasis or spinal cord compression

Treatment

- In the dose escalation part (phase 1b), different dose levels of vactosertib (50 mg bid, 100 mg bid, and 200 mg bid) for escalation were tested, starting with dose level 0 (DL 0, 100 mg bid) with 3 to 6 subjects recruited in each cohort. DL -1 was only planned to test when DL 0 was unacceptable.
- In the dose expansion part, an additional backfill cohort was planned to open for determination of the final RP2D.
- Patients in each cohort were planned to receive vactosertib 50-200 mg orally twice per day 1-5 & day 8-12 with oxaliplatin 85 mg/m^2 on day 1, LV 200mg/m^2 IV on day 1, 5FU 200mg/m^2 bolus on day 1 and continuous 5-FU 2400mg/m^2 infusion over 48 hours every 2 weeks.

Results

Toxicities

- A total of 16 patients were enrolled, 3 in DL 0, 4 in DL 1 and 9 in DL 1 backfill cohort.
- No dose limiting toxicities (DLTs) were observed and the RP2D was established as vactosertib 200 mg orally twice per day 1-5 & day 8-12 with FOLFOX.
- The vactosertib related adverse events (AEs) of any grade included fatigue, nausea, vomiting and anorexia.

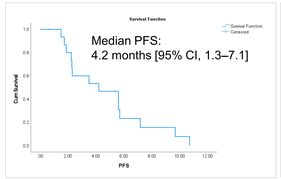
Efficacy

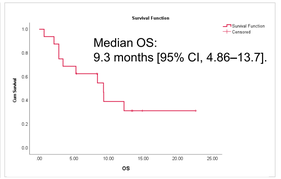
- **Tumor response**

Three of 13 patients (23.1%) had partial response and 5 (38.5%) stable disease as best response, with clinical benefit rate of 61.5 % in DL 1, while there were no PR or SD in DL 0.

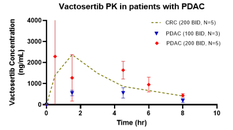
	DL0 (Vactosertib 100mg bid) (N=3)	DL1 + backfill cohort (Vactosertib 200 mg bid) (N=13)	Total
CR	0	0	0
PR	0	3 (23.1%)	3 (18.9%)
SD	0	5 (38.5%)	5 (31.3%)
PD	3	5 (38.5%)	8 (50.0%)

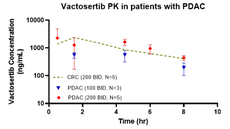
- **Survival**





Vactosertib PK Analysis





- Vactosertib PK was examined in patients with PDAC after combined treatment with FOLFOX
- PK samples were collected at pre-dose, 1.5, 4.5, and 8 hours

PK parameter	Vactosertib (+FOXFOX) in Patients with PDAC		Vactosertib (+Pembro) in Patients with CRC
	100 mg BID (n=3)	200 mg BID (n=5)	200 mg BID (n=5)
C_{max} (ng/mL)[1]	635 (27)	2062 (45)	2240 (42)[1]
AUC_{0-8hr} (hr*ng/mL)[1]	3328 (28)	8955 (33)	8998 (22)[1]
T_{max} (hr)[#]	4.5 (1.5-4.5)	4.5 (0.5-4.5)	1.5 (1.5-3)[#]

[1], geometric mean (CV%)
[#], median (min-max)

- Compared to 100 mg BID cohort, overall exposure after 200 mg BID vactosertib administration was increased in a dose-dependent manner
- When compared to previous study in CRC patients (vactosertib + pembrolizumab), overall exposure of 200 mg vactosertib was comparable in patients with PDAC (vactosertib + FOLFOX)

Conclusion

- **In the phase Ib, we demonstrated the feasibility and safety of adding vactosertib to FOLFOX in 2nd line setting (RP2D = vactosertib 200mg bid), which needs to be further investigated.**
- **The stud drugs were kindly provided from MedPacto (vactosertib) and Boryung (oxaliplatin).**
- **This study was prospectively registered on ClinicalTrials.gov, NCT03666832.**

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