Abstract 263P: A Phase 1b Dose Escalation Trial of Gemcitabine and Nab-Paclitaxel in Combination with Lixumistat in Patients with Advanced Pancreatic Cancer (COMBAT-PC)

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Background

- Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal cancer with poor survival.[1]
- PDAC cells rely on oxidative phosphorylation (OXPHOS) for survival and resistance. Lixumistat (IM156), a small-molecule biguanide, inhibits the first step of OXPHOS.[2]
- A phase 1 trial in unselected patients with refractory advanced tumors showed that IM156 is safe at 800 mg QD; common side effects were nausea (68%), diarrhea (46%), and emesis (41%). Stable disease occurred in 32% of patients.[3]

Methods

- COMBAT-PC is a single-center Phase 1b trial (NCT05497778) at MD Anderson Cancer Center, enrolling treatment-naïve metastatic PDAC patients to assess the safety and tolerability of lixumistat with Gem (1000 mg/m² IV) + NP (125 mg/m² IV) on Days 1, 8, and 15 of a 28-day cycle. .
- Consenting, adults with metastatic PDAC, measurable disease (RECIST 1.1), ECOG 0–1, and adequate organ function are eligible. Exclusions include those on biguanides, CYP2D6-sensitive drugs, or with uncontrolled conditions.
- Objectives:
  - *Primary*: Assess safety and tolerability via adverse event frequency/severity.
  - *Exploratory Efficacy*: Measure disease control (CR, PR, SD), ORR, PFS, and OS.
- The trial employed a Bayesian Optimal Interval (BOIN) design (Fig. 1).

Fig 1: Study design

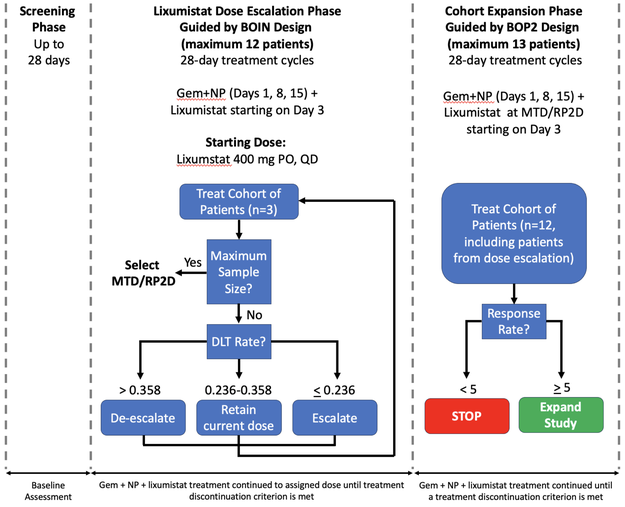


Fig 2a: Swimmer plot for patients treated at 400mg

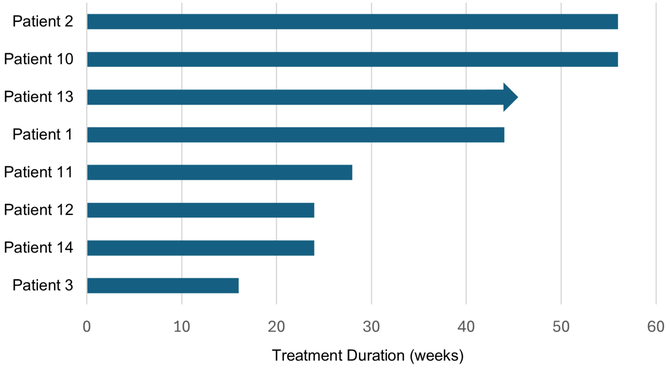


Fig 2b: Waterfall plot for patients treated at 400mg

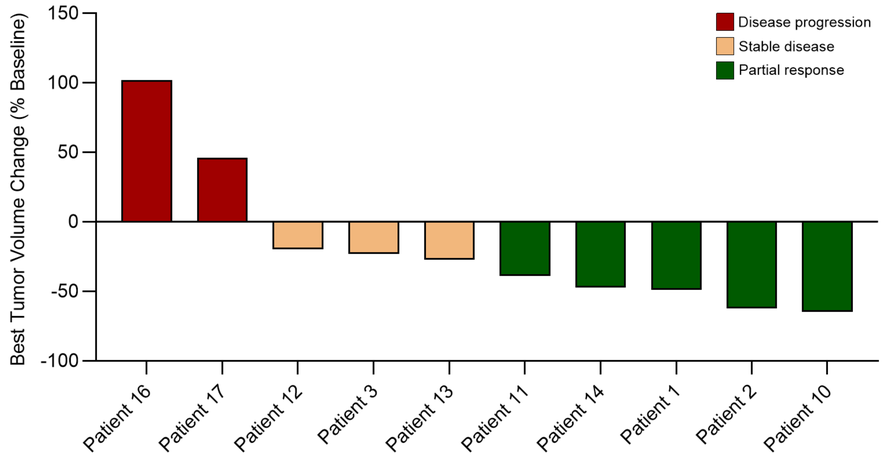
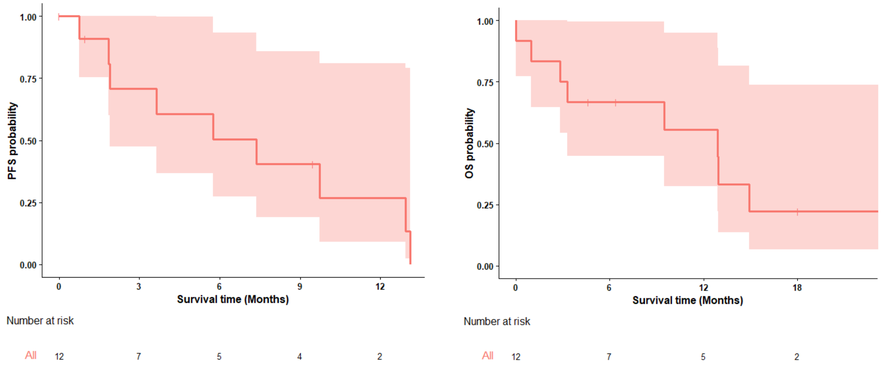


Fig 3. PFS (3a) and OS (3b) plots for patients treated at 400mg



Results

- Between Nov 2022 and Dec 2024, 19 patients enrolled. Median age was 68 (50–77) years; 63% were female.
- Fourteen patients received lixumistat 400 mg QD, five 800 mg.
- No grade 4–5 toxicities were seen. Two DLTs occurred at 800 mg (Gr 3 diarrhea, fatigue); none at 400 mg. Common lixumistat-related AEs were Gr 1/2 nausea/vomiting, rash, fatigue, and diarrhea. Due to toxicity at 800 mg, 400 mg QD was selected as recommended phase 2 dose (RP2D).
- At 12.9-month median follow-up, four patients died. Among 10 evaluable patients treated at RP2D, PR rate was 50%, and DCR rate was 80%. (Fig 2a and 2b).
- Median PFS was 7.4 months and median OS was 18 months (Fig 3a and 3b).

Conclusion

- Lixumistat at 400 mg daily with gemcitabine and nab-paclitaxel was safe and showed promising activity in advanced PDAC
- The trial is ongoing, and further evaluation in larger studies is warranted.

References

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3. Janku F, Beom SH, Moon YW, et al. First-in-human study of IM156, a novel potent biguanide oxidative phosphorylation (OXPHOS) inhibitor, in patients with advanced solid tumors. Invest New Drugs 2022;40(5):1001-1010.

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