A phase I trial of emavusertib (CA-4948) in combination with gemcitabine and nab-paclitaxel in metastatic or unresectable pancreatic ductal adenocarcinoma (PDAC).

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BACKGROUND

- Interleukin-1 Receptor Associated Kinase -4 (IRAK4) drives pro-survival NF-kB signaling in PDAC.
- In preclinical animal models, the oral IRAK4 inhibitor emavusertib (CA-4948) augments the efficacy of cytotoxic chemotherapy by suppressing cell intrinsic survival mechanisms and prolongs survival when combined with gemcitabine (G)/nab-paclitaxel (nP) as well as reduces desmoplasia in preclincal models.

METHODS

- This is a multi-institution, Phase I, dose escalation/ expansion clinical trial of emavusertib in combination with G/nP as second-line therapy for metastatic or unresectable PDAC (NCI 10522, NCT05685602).
- Key inclusion/exclusion criteria are progression on 5FU-based therapy for unresectable or metastatic PDAC, ECOG 0-2, adequate end organ function, no history of rhabdomyolysis or elevated CPK.
- The primary objectives of this study are to determine the dose-limiting toxicities and the Recommended Phase 2 Dose (RP2D) of emavusertib in combination with G/nP.
- Emavusertib is given daily at escalating doses of DL0 (150 mg p.o. BID), DL1 (200 mg BID), and DL2 (250 mg BID) with G (1000mg/m^2 i.v.) and nP (125mg/m^2 i.v.) on Days 1 and 8 of every 21-day cycle. DL3 (emavusertib 200 mg BID) and DL4 (emavusertib 250 mg BID) are given with G/nP on Days 1, 8, and 15 of every 28-day cycle.
- Dose escalation is according to the BOIN design to determine the MTD of emavusertib in combination with G/nP.
- Toxicities are graded according to CTCAE v5.0. Response was evaluated according to RECIST v1.1 criteria.

SCHEMA

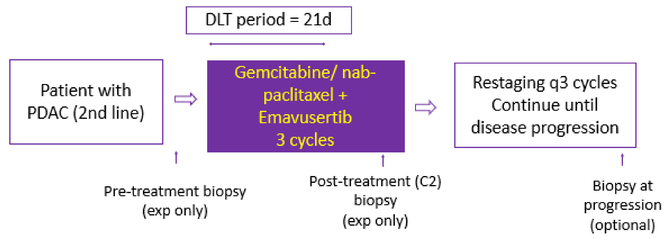
Part A. Dose Escalation (N=up to 25)

Emavusertib + gemcitabine/nab-paclitaxel (D1, 8 q21d)

Dose level	Emavusertib (PO BID)
-1	100mg
0 (starting)	150mg
1	200mg
2	250mg
3	MTD (-)1 level
4	MTD

*For Dose Levels 3 and 4, gem/nab-paclitaxel will be given D1, 8, 15 q28d

Part B. Dose Confirmation/Expansion (N=up to 18)



RESULTS

- At data cutoff (13 September 2025), 19 patients were enrolled (Table 1).
- The study has currently completed enrollment in DL3.

Table 1: Baseline Characteristics

Age, median (range), years	62 (40-80)
Sex	
Male	13
Female	6
ECOG	
0	9
1	10
Race	
Caucasian	13
African American	2
Asian	2
Hispanic	2
Stage	
Locally Advanced	7
Metastatic	12

Table 2: Treatment Related Adverse Events (Grade 3 and 4 only)

AE	DL0 (N=4)	DL1 (N=6)	DL2 (N=3)	DL3 (N=6)	Total % (N=19)
	Grade 3	Grade 3	Grade 3	Grade 3	
Neutropenia	1	4	2	4	58%
Pancytopenia	1*	0	0	0	5%
Sepsis	1*	0	0	0	5%
Anemia	2	1	0	0	16%
Diarrhea	0	0	0	1	5%
Thrombocytopenia	0	0	0	1	5%
Hypokalemia	0	0	1	0	5%
Elevated Alk. Phos.	0	0	1	0	5%
Elevated ALT	1	0	0	0	5%
Elevated CPK	0	1	0	0	5%
Supraventricular tachycardia	0	1	0	0	5%

* Grade 4 events

Table 3: Best Overall Response

Response	N
PD	7
SD	4
PR	3

- 14 of 19 patients have undergone at least one post-baseline imaging assessment.
- Disease control rate (DCR) is 50%.
- Median duration on treatment is 2.1 months at the present time.

CONCLUSIONS

At this early stage of the study, emavusertib in combination with G and nP as second-line therapy for metastatic or unresectable PDAC has a manageable toxicity profile and shows encouraging preliminary results. Escalation to DL4 is ongoing, which will be followed by dose expansion at the Recommended Phase 2 Dose (RP2D).

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- Patrick M Grierson and Kian-Huat Lim have a financial conflict of interest with Aclaris Therapeutics for an investigational agent used in pancreatic cancer, however the present work is not directly related to the stated financial conflict of interest.

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