A phase I trial of emavusertib (CA-4948) in combination with FOLFOX/ PD-1 inhibitor +/- trastuzumab as first-line treatment for untreated unresectable gastric and esophageal cancer.

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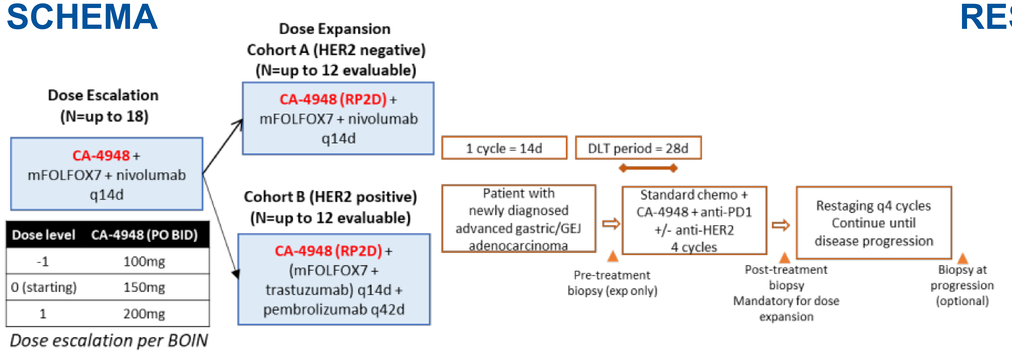
BACKGROUND

- Interleukin-1 Receptor Associated Kinase -4 (IRAK4) drives pro-survival NF-kB signaling in GI malignancies.
- In preclinical animal models, the oral IRAK4 inhibitor emavusertib (CA-4948) augments the efficacy of cytotoxic chemotherapy by suppressing cell intrinsic survival mechanisms and sensitizes tumors to immune checkpoint blockade.
- Emavusertib prolongs survival when combined with cytotoxic chemotherapy as well as reduces desmoplasia in preclincal models of GI malignancies.
- In advanced gastroesophageal adenocarcinoma, standard of care FOLFOX/anti-PD-1 and FOLFOX/anti-PD-1/anti-Her2 therapies yield ORR of approx 60% and 72%, respectively, with CR rates of 12-14%.

METHODS

- This is a single-institution, Phase I, dose escalation/ expansion clinical trial of emavusertib in combination with FOLFOX/ PD-1 inhibitor (with or without trastuzumab) as first-line therapy for metastatic or unresectable gastroesophageal cancers (NCT05187182).
- Key inclusion/exclusion criteria are newly diagnosed untreated unresectable or metastatic esophageal, gastroesophageal junction (GEJ) or gastric adenocarcinoma or squamous cell carcinoma, ECOG 0-1, 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 FOLFOX/ PD-1 inhibitor +/- trastuzumab.
- Emavusertib is given daily at escalating doses DL0 (150mg p.o. BID) or DL1 (200mg p.o. BID) with FOLFOX (5FU CIVI 2400mg/m^2, LV 400mg/m^2, oxaliplatin 85mg/m^2) i.v. every 2 weeks with nivolumab or pembrolizumab. Her2+ patients are given trastuzumab 4mg/kg every 14 days.
- Dose escalation is according to the BOIN design to determine the RP2D of emavusertib in the combination.
- Toxicities are graded according to CTCAE v5.0. Response is evaluated according to RECIST v1.1 criteria.

SCHEMA



RESULTS

- At data cutoff (31 December 2025), 19 patients were enrolled (16 patients evaluable).
- There were no DLTs.

Table 1: Enrollment	N (19)
Escalation	7
Expansion Cohort A (Her2 neg)	8
Expansion Cohort B (Her2 pos)	4

Table 2: Baseline Characteristics	All patients (N=19)
Median age (range)	62 (38-76)
Male: female	14:5
Adenocarcinoma	19
Squamous cell carcinoma	0
Esophageal	6
GEJ	7
Gastric	6

Table 3: G2-4 TRAE attributed to CA-4948	G2	G3	G4
Neutropenia	5	3	2
Lymphopenia	3	2	0
Anemia	3	0	0
Thrombocytopenia	2	0	0
Hypophosphatemia	0	2	0
Diarrhea	1	1	0
CPK elevation	0	0	0
Increased AST	0	0	0
Increased ALT	0	0	0

RESULTS

Figure 1: RECIST Best Response of Target Lesions

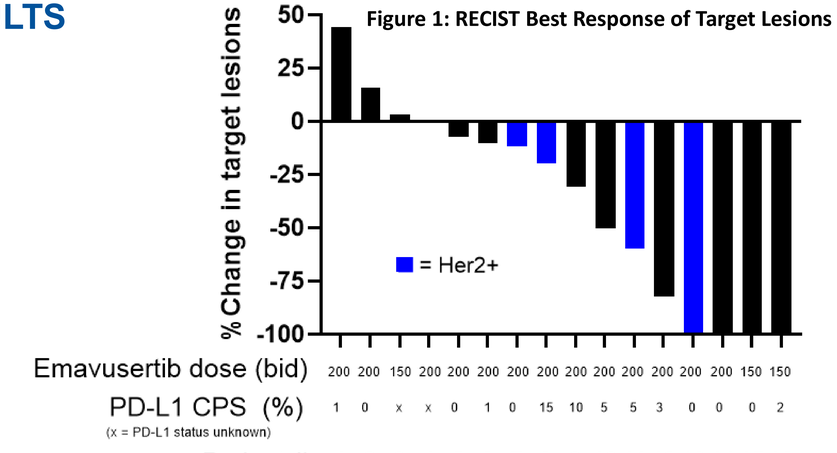
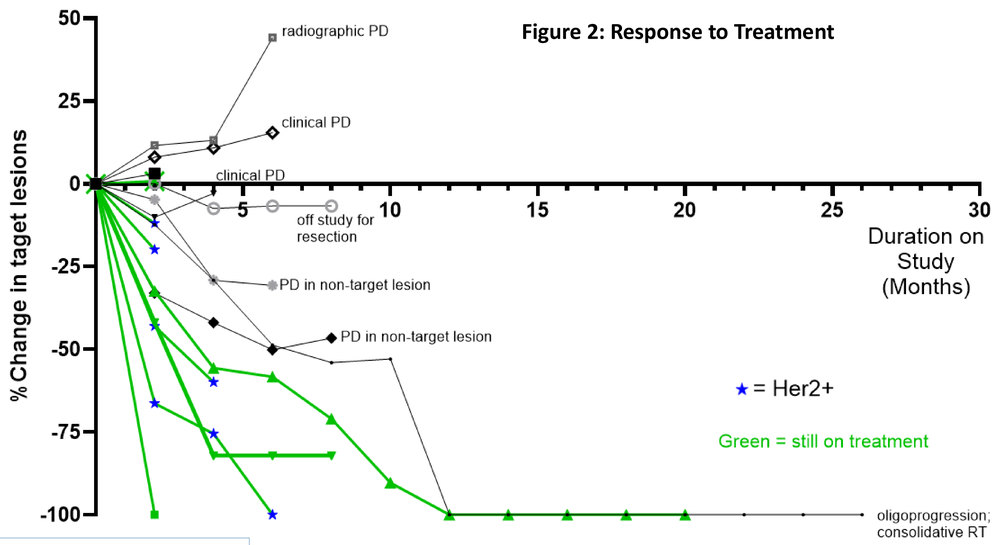


Figure 2: Response to Treatment



CONCLUSIONS

At this early stage of the study, emavusertib in combination with FOLFOX/ anti-PD1 +/- trastuzumab as first-line therapy for metastatic or unresectable gastroesophageal cancers has a manageable toxicity profile and shows encouraging preliminary results compared to standard of care regimens (ORR 50%, CR 25%). Enrollment in dose expansion arms at emavusertib 200mg BID (Her2 positive and negative) is ongoing.

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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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