Phase I trial of CA-4948, an IRAK4 inhibitor, in combination with FOLFOX/PD-1 inhibitor +/- trastuzumab for untreated unresectable gastric and esophageal cancer

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Background & Rationale

Activated NFκB is linked to aggressive phenotype, poor survival, and resistance to chemotherapy in multiple GI cancers including gastroesophageal cancer (GEC).

Preclinical studies established that:
1) Genotoxic stress incurred by chemotherapy induces TLR9, which signals through IRAK4 to drive pro-survival NFκB signaling
2) The survival mechanism through IRAK4 is independent of cancer types and mutational profiles based on colorectal and pancreatic cancer models
3) IRAK4 inhibition reduces tumor desmoplasia and revitalizes intratumoral T cells, setting the stage for successful combination with immune checkpoint inhibitors in a highly aggressive autochthonous pancreatic cancer mouse model.

These data provide strong rationale to add CA-4948 to systemic therapy for advanced GI cancers, where chemotherapy resistance is inevitable and benefit of PD-1 inhibitors is limited to a small population.

CA-4948 is a novel, first-in-class reversible IRAK4 inhibitor. In a phase I trial, patients with relapsed/refractory hematologic malignancies tolerated CA-4948 monotherapy well with mild fatigue, neutropenia, and nausea as the most common adverse events. Recommended phase 2 dose (RP2D) was determined as 300 mg orally twice daily.

We hypothesize that inhibition of IRAK4 with CA-4948 will potentiate the effect of immune checkpoint inhibitor while deepening the efficacy of cytotoxic chemotherapy in GEC.

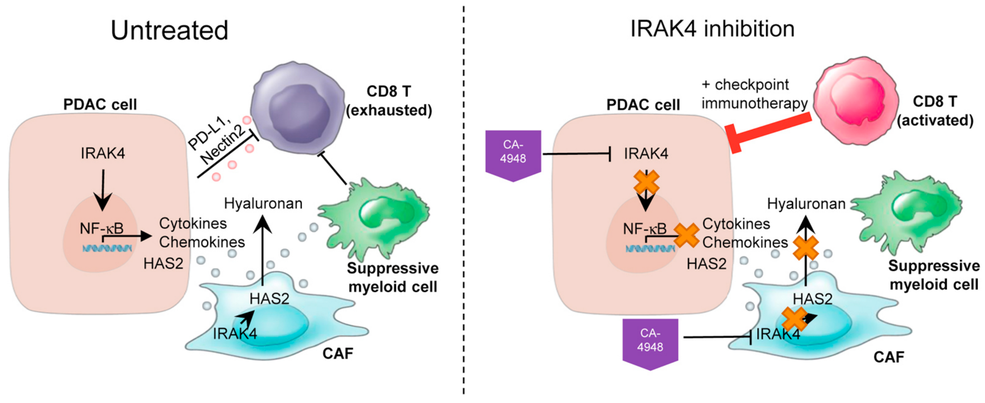


Fig. 1 Proposed mechanism of IRAK4 inhibition in pancreatic ductal adenocarcinoma (PDAC). Inhibition of IRAK4 abrogates NFκB activity in PDAC cells and CAFs. This in turn reduces production of immunosuppressive factors, immune checkpoint ligands, and hyaluronan synthetase 2. This relieves immunosuppression surrounding PDAC tumors, which improves response to immune checkpoint blockade in models of GI cancers.

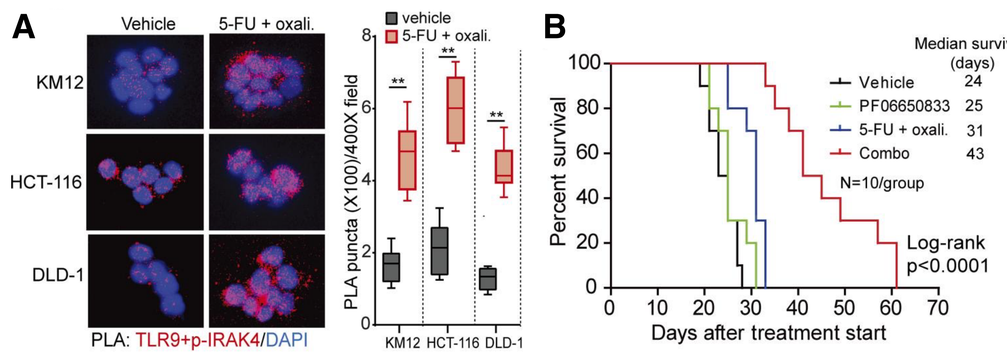


Fig. 2 IRAK4 inhibition potentiates chemotherapy effect in preclinical colorectal cancer models. A) Chemotherapy led to increased TLR9/p-IRAK4 interaction. B) Xenograft survival when treated with FOLFOX with or without IRAK4 inhibitor (PF06650833)

Treatment Plan

Dose Escalation
(n = up to 18)

CA-4948 + FOLFOX + nivolumab q14d

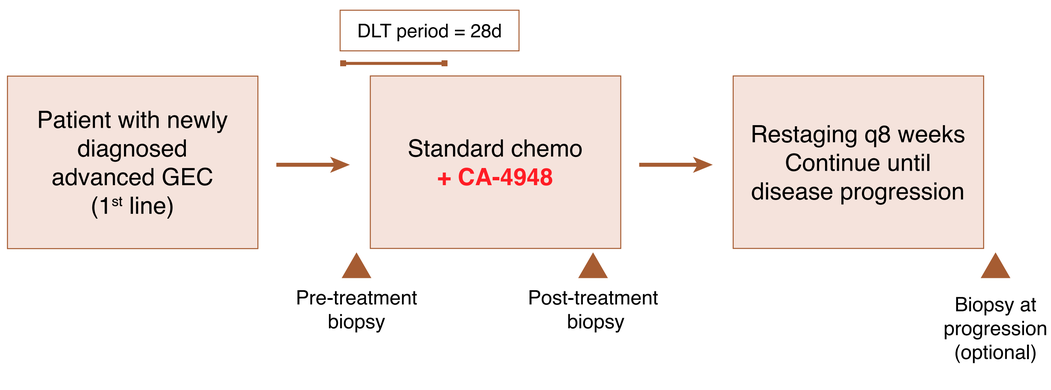
Dose Expansion
Cohort A (HER2-)
(n = up to 12 evaluable)

CA-4948 (RP2D) + FOLFOX + nivolumab q14d

Cohort B (HER2+)
(n = up to 12 including safety lead-in)

CA-4948 (RP2D)+ FOLFOX q14d + pembrolizumab + trastuzumab q21d

Dose level	CA-4948 (PO BID)
-1	150 mg
0 (starting)	200 mg
1	250 mg
2	300 mg



Study Population and Key Eligibility

Inclusion Criteria

- Advanced adenocarcinoma or squamous cell carcinoma of the stomach, GE junction, or esophagus
- No prior systemic therapy
- ECOG 0-1
- Measurable disease by RECIST 1.1

Exclusion Criteria

- Interstitial lung disease
- Inability to take oral medications
- Autoimmune disease requiring systemic immunosuppressive medication

Dose escalation will follow a Bayesian optimal interval (BOIN) design with a targeted 30% dose-limiting toxicity (DLT) rate, and up to 12 patients can be enrolled for each cohort.

Study Objectives & Endpoints

Primary Endpoint
Safety and RP2D of CA-4948 + FOLFOX/PD-1 inhibitor +/- trastuzumab

Secondary Endpoints
DCR, ORR, PFS/OS

Exploratory Endpoints
p-IRAK4, p-NFκB, and p-ERK IHC staining in pre- and post-treatment biopsies
Serum chemokine and cytokine expression before and after treatment
PK indices in the Expansion Cohorts
Proportion of samples with PDX/PDO generation and model response to treatment

Enrollment Status

Active, not yet recruiting. Please contact haeseongpark@wustl.edu for inquiries.
ClinicalTrials.gov Identifier: NCT05187182

References

1. Somani, et al. Gastroenterology 2022 2. Zhang, et al. Clin Cancer Res 2017 3. Nowakowski et al., ASH Annual Meeting 2020