

# 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).

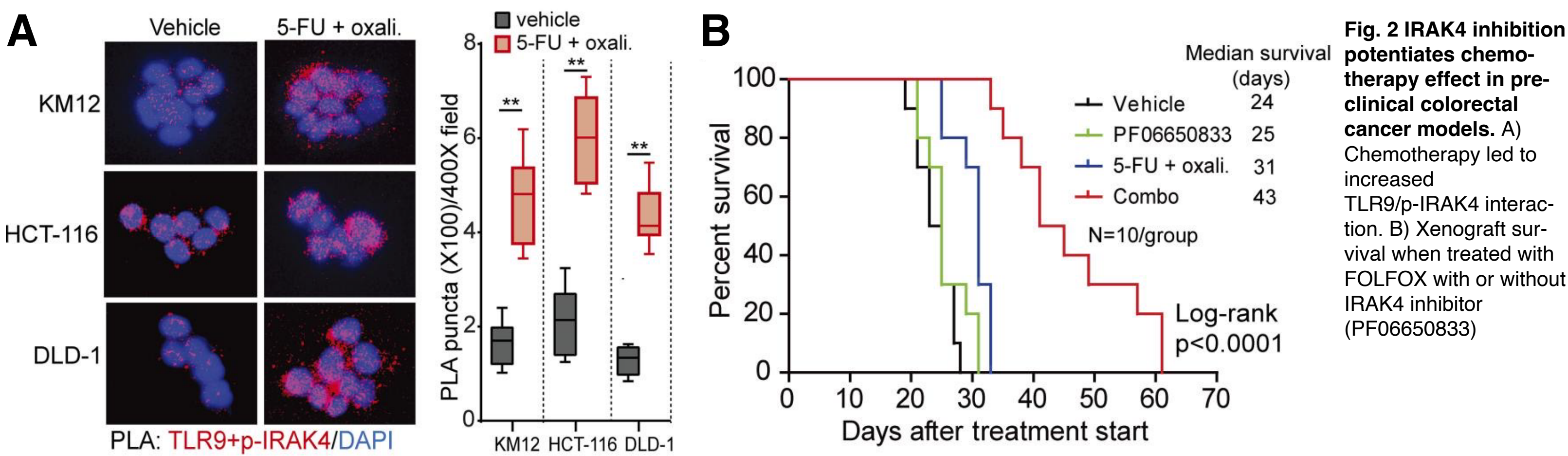
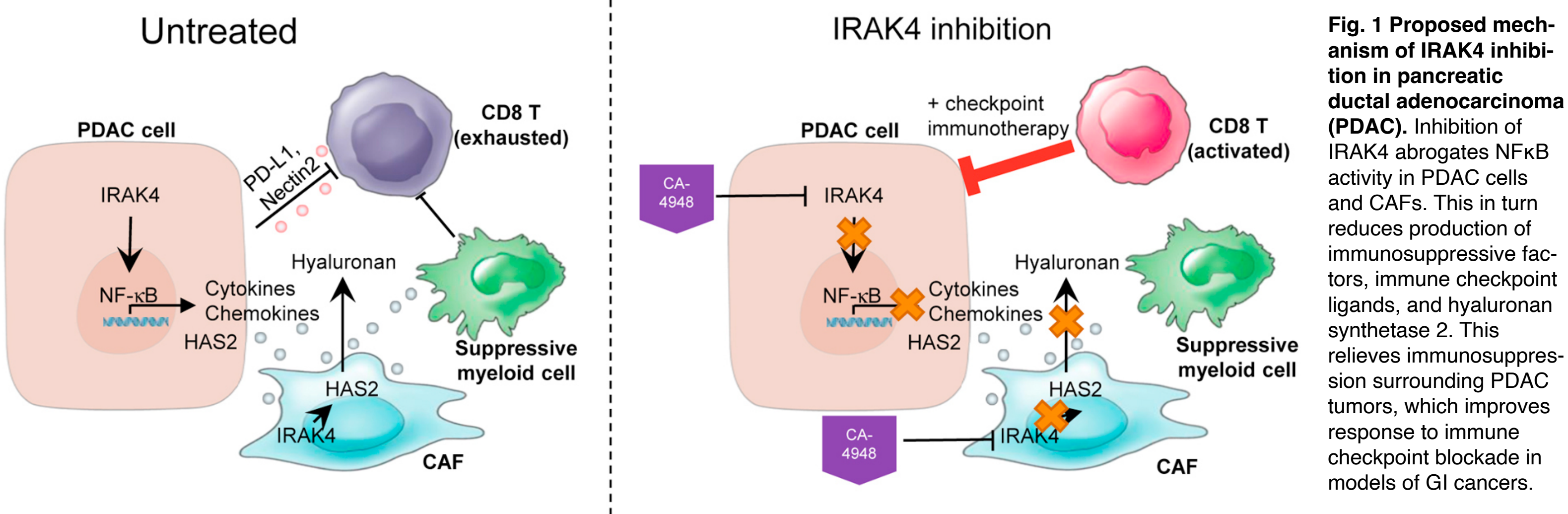
Preclinical studies established that:

- 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.

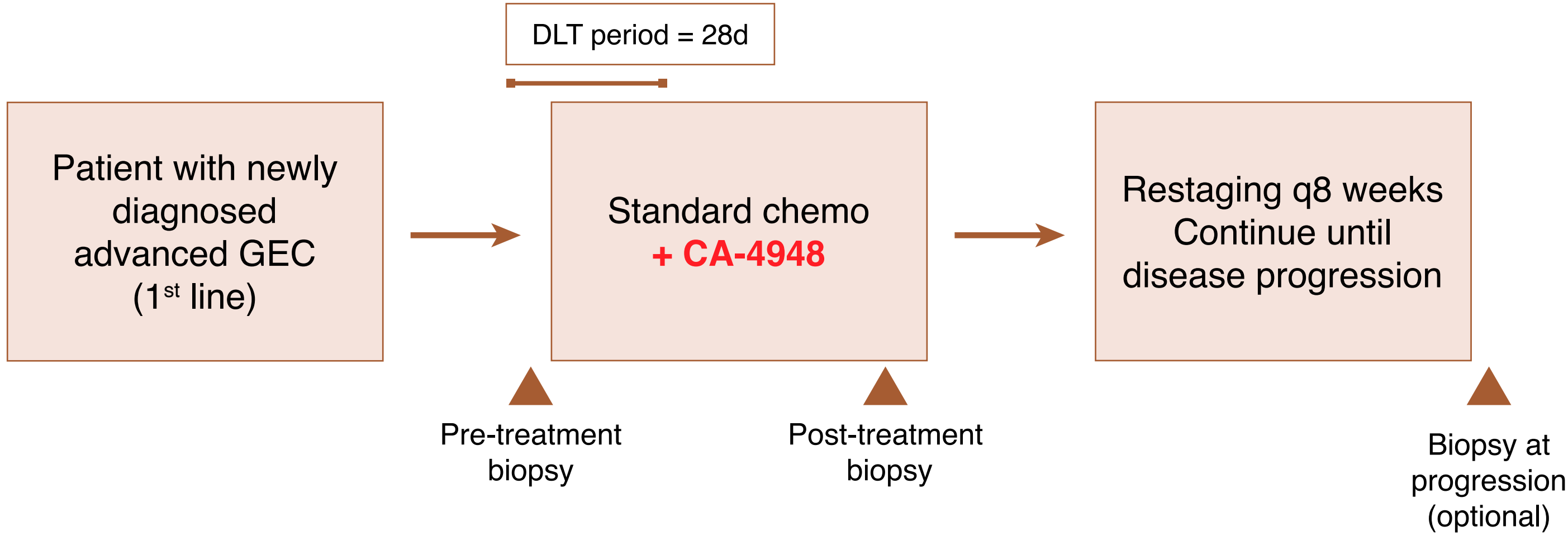
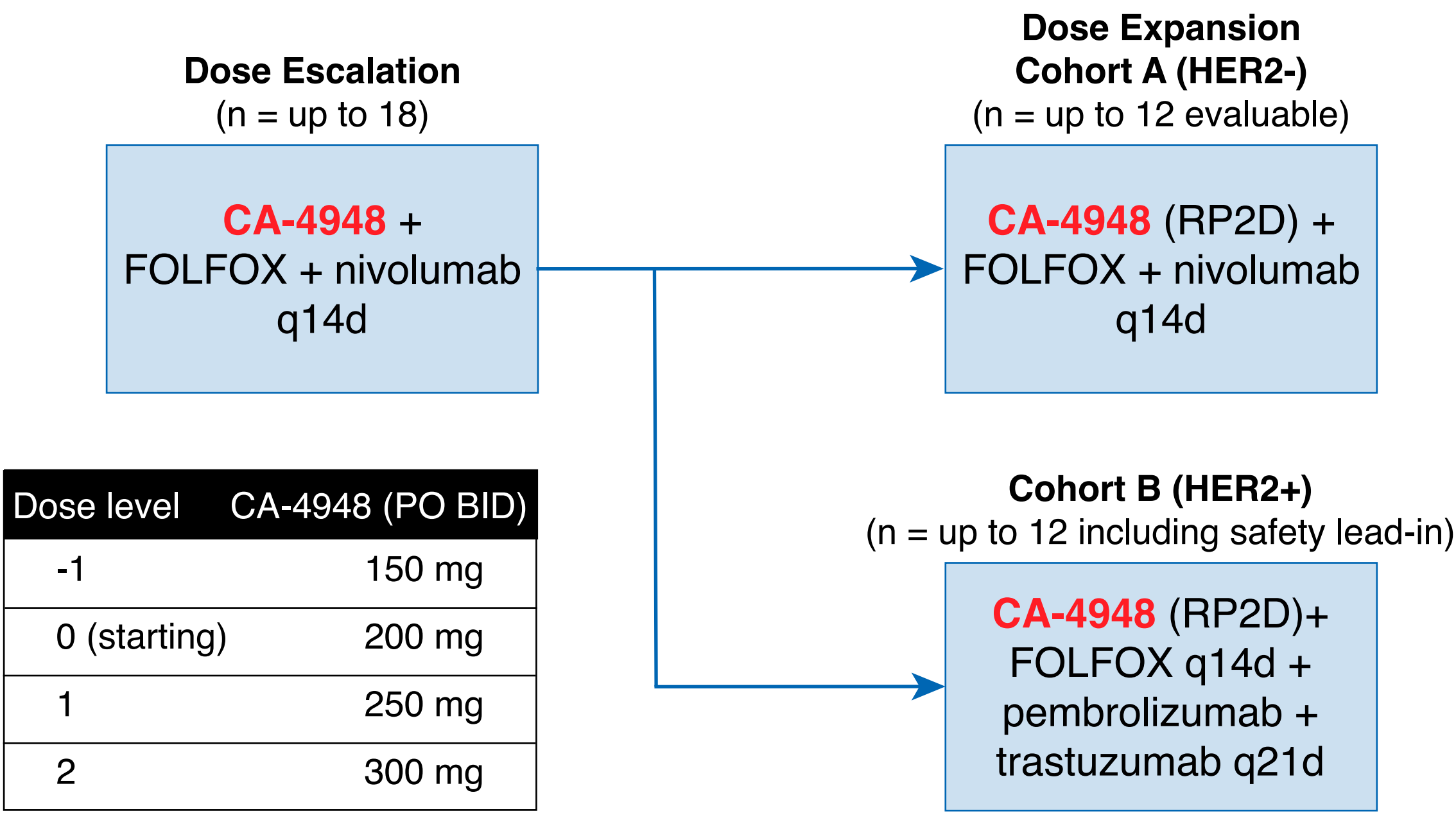
These data provide strong rationale to add CA-4948 to systemic therapy for advanced GI cancers, where chemotherapy resistance is inevitable and benefit of PD-1 inhibitors is limited to a small population.

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.



## Treatment Plan



## 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