OPTIMIZE-1, an open-label phase 1b/2 study assessing the safety and efficacy of mitazalimab in combination with chemotherapy in patients with metastatic pancreatic ductal adenocarcinoma

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Mitazalimab, a CD40 agonist with best-in-class profile

- Mitazalimab is a **FcγR crosslinking dependent CD40 agonistic** antibody (IgG1) with a tumor-directed immune activation
- Mitazalimab binds with **high affinity** to a unique binding epitope on the CD40 receptor allowing for high efficacy and potency
- Mitazalimab has the potential for **superior clinical activity**, since mitazalimab is the only FcγR-dependent CD40 agonist with tumor-directed activity that can be dosed >1 mg/kg

Mode of Action

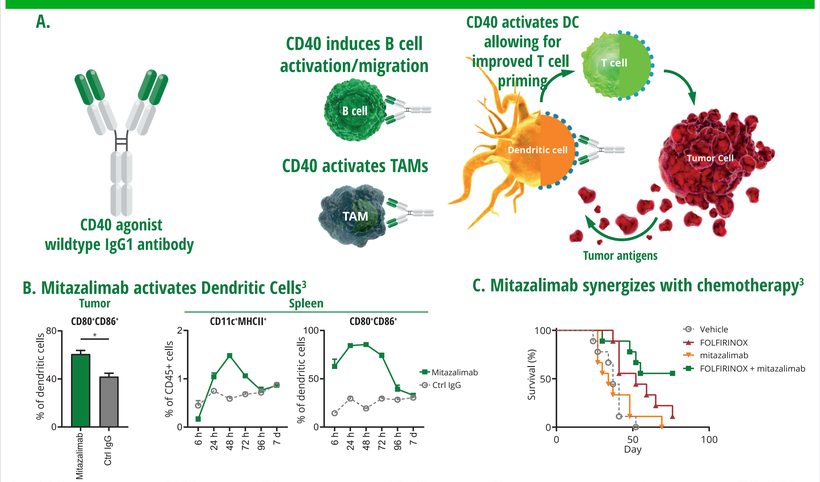


Figure 1. A. Mitazalimab mode of action. **B.** MB49 tumor-bearing hCD40tg mice received one dose of 100 µg Mitazalimab i.p. and 24 h later, tumors were collected and activation of dendritic cells ($CD11c^+$ $MHCII^+$) assessed by determining the frequency of $CD80^+$ $CD86^+$ cells. Alternatively, hCD40tg mice received one dose of 100 µg Mitazalimab i.p. and spleens were collected at the indicated time points following treatment. **C.** MB49 tumor-bearing hCD40tg mice received treatment with FOLFIRINOX (oxaliplatin, irinotecan, folinic acid and 5-fluorouracil) on days 7-8, 14-15 and 21-22, and/or 100 µg mitazalimab on days 10, 17 and 24.

Mitazalimab has shown clinical activity and a manageable safety profile in Phase 1 studies

NCT02829099 (2016-2021): Mitazalimab monotherapy, **95 patients**[4]:

Safety:
- Safe and tolerable up to 1200 µg/kg i.v.
- Most drug-related adverse events grade 1-2

Responses:
- 1 patient with partial response
- 10 patients with stable disease

Mitazalimab Proof of Mechanism

- Administration of 600-1200 µg/kg induced cytokine profiles consistent with T cell (IFN-γ, TNF-α), B cell (IL-6, IL-12) and macrophage (MCP-1, IL-8) activation
- Circulating B cell frequencies decrease in the first 24h, while showing an activated phenpotype with increased CD80 and HLA-DR expression
- Analysis of RNA seq data has shown dose-dependent changes in gene signatures related to CD40 biology, including IFN-γ signaling and upregulation of PD-L1

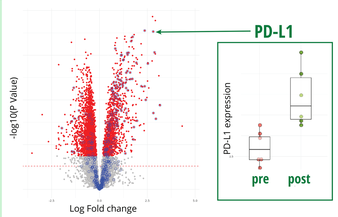


Figure 2. Left, volcano plot of genome wide RNA expression changes before and after mitazalimab administration. Right, detailed changes in the expression of PD-L1 in response to mitazalimab treatment

Mitazalimab, a human CD40 agonistic antibody developed for cancer immunotherapy

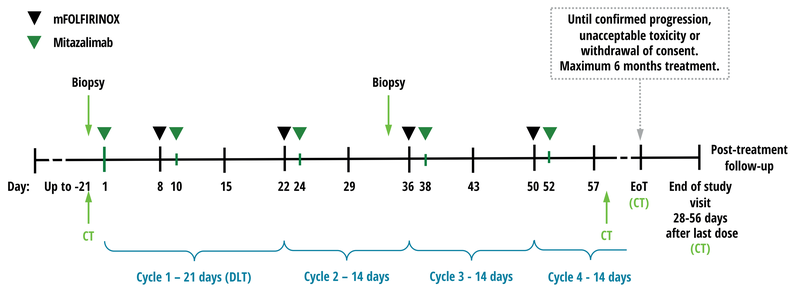
- Targeting CD40 kickstarts the cancer-immunity cycle priming and activating tumor-specific T cells[1,2].
- Pancreatic ductal adenocarcinoma (PDAC) is defined by a desmoplastic tumor stroma that hosts immune-suppressive macrophages.
- CD40 agonists promote degradation of the tumor stroma by myeloid cells, improving the influx of T cells and chemotherapeutic agents into the tumor[1].

OPTIMIZE-1 study design

OPTIMIZE-1 (NCT04888312) is a phase 1b/2, open-label, multicenter study designed to evaluate safety, tolerability, and efficacy of mitazalimab in combination with chemotherapy (mFOLFIRINOX) in adults diagnosed with previously untreated metastatic PDAC.

Mitazalimab and mFOLFIRINOX will be administered by intravenous infusions following a 14-day cycle schedule where mitazalimab will be administered 2 days after mFOLFIRINOX, except for the first cycle of 21 days where mitazalimab will be administered on Day 1 and 10 and mFOLFIRINOX infusion will start on Day 8.

Dosing regimen

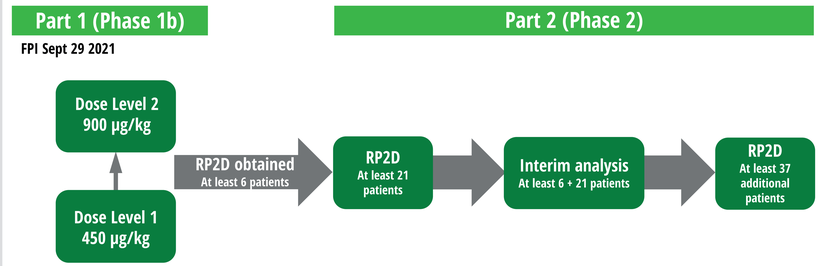


CT (Computed Tomography) EoT (End of Treatment Visit)

Mitazalimab will be administered before mFOLFIRINOX in the first cycle, to allow for **optimal macrophage activation**, sensitizing the tumor to mFOLFIRINOX.

Mitazalimab is **well tolerated**, allowing for:
- **High doses** that potentially have improved efficacy
- **Combination** with the more effective chemotherapy mFOLFIRINOX
- More **frequent dosing** (Q2W, 2 days following chemotherapy)

OPTIMIZE-1 study overview



RP2D (recommended phase 2 dose)
FPI (first patient in)

Study Objectives

Phase 1b

Primary objective: To determine the recommended Phase 2 dose. Assesment of clinical activity (overall response rate (ORR), disease control rate and time to next anti-cancer therapy) and survival outcome will be secondary objectives.

Phase 2

Primary objective: To assess the clinical activity of mitazalimab in combination with chemotherapy as determined by ORR.

Secondary objectives include survival outcomes, Best Overall Response (BOR), Duration of response (DoR), Duration of SD, Disease control rate, and time to next anti-cancer therapy

Key Eligibility Criteria

Inclusion:
- Diagnosis of previously PDAC with metastasis
- ECOG status of 0 or 1
- No previous chemotherapy for PDAC
- No prior abdominal radiotherapy
- Life expectancy ≥ 3 months
- Acceptable hematologic and clinical laboratory chemistry values

Exclusion:
- Other types of non-ductal tumor of the pancreas
- Known CNS metastases or carcinomatous meningitis
- Has other current cancer or history of cancer in the prior 3 years
- Receipt of attenuated vaccine within 28 days before the first dose of study treatment

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- **The study investigators and members of the clinical study team.**

References

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