Efficacy and Safety of mitazalimab in combination with mFOLFIRINOX in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC): an interim analysis of the OPTIMIZE-1 phase 1b/2 study

Abstract 4139

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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:** mitazalimab is the only FcγR-dependent CD40 agonist with tumor-directed activity that can be dosed at 1 mg/kg

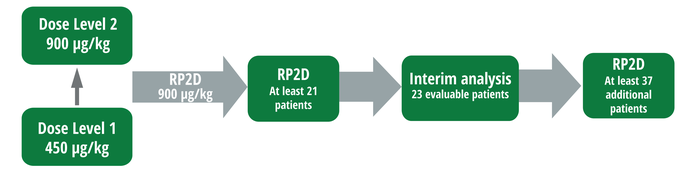
Mitazalimab in pancreatic cancer

- Targeting CD40 with mitazalimab kickstarts the cancer-immunity cycle, priming and activating tumor-specific T cells[1,2].
- Pancreatic ductal adenocarcinoma (PDAC) is characterized by a desmoplastic tumor stroma that creates a mechanical barrier that limits exposure to chemotherapy, hosts immune-suppressive macrophages and leads to poor immune infiltration[1].
- CD40 agonists promote degradation of the tumor stroma by myeloid cells, improving the influx of T cells and sensitivity to chemotherapeutic agents[1].

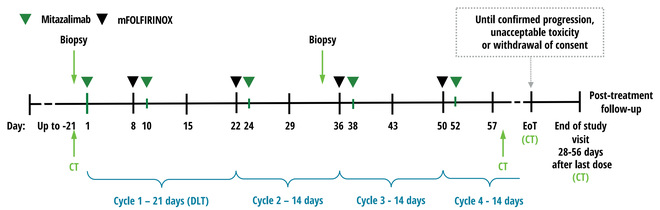
OPTIMIZE-1 study overview

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

Study design



Dosing Regimen



Study Objectives

Phase 1b

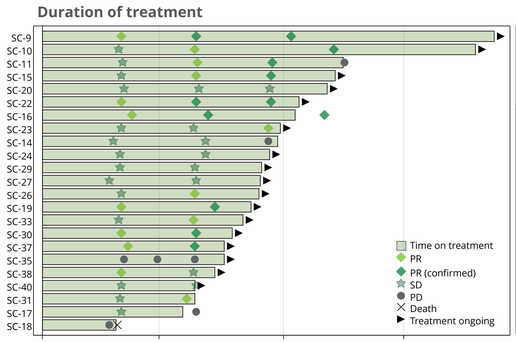
Primary objective: To determine the recommended Phase 2 dose (RP2D). Secondary objectives include: Assesment of clinical activity (ORR), and survival outcome.

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, duration of response, disease control rate, time to next anti-cancer therapy, safety and PK analysis. PD biomarkers will be analyzed as exploratory endpoints.

At the interim analysis mitazalimab in combination with mFOLFIRINOX demonstrated encouraging clinical activity and manageable safety in patients with previously untreated metastatic pancreatic ductal adenocarcinoma

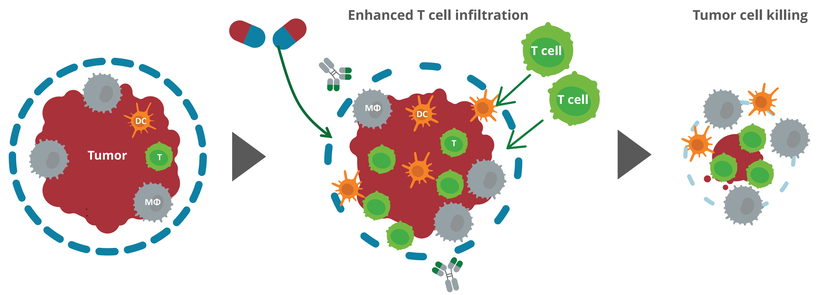


	Mitazalimab + mFOLFIRINOX 900 µg/kg N=23
Best Overall Response n (%)	
CR	0
PR	**12 (52.2)**
SD	9 (39.1)
PD	2 (8.7)
ORR n (%)	**12 (52.2%)**
Disease Control Rate n (%)	21 (91.3%)

- At cutoff (December 8, 2022), 23 patients treated with mFOLFIRINOX + 900 µg/kg mitazalimab had received at least 2 cycles and were evaluable for futility (efficacy) analysis.
- Median follow up was approximately six months.
- Mitazalimab + mFOLFIRINOX is a feasible regimen with a manageable safety profile.
- Mitazalimab administered at 900 µg/kg in combination with mFOLFIRINOX shows encouraging antitumor activity in mPDAC, supporting continued development.
- With an ORR of 52.2%, the OPTIMIZE-1 study passes futility and continues to full accrual.

Mode of Action

1. Mitazalimab activates macrophages (MΦ)
   - Stromal degradation
2. Enhanced chemotherapy sensitivity
   - Tumor cell death, releasing antigens picked up by DCs
3. Mitazalimab activates Dentritic Cells
   - Enhanced priming of tumor-specific T cells



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Patient Baseline Characteristics

	Safety set 450 µg/kg N=5	Safety set 900 µg/kg N=38	Efficacy set 900 µg/kg N=23
Age group n (%)			
65 or above	3 (60.0)	18 (47.4)	11 (47.8)
Below 65	2 (40.0)	20 (52.6)	12 (52.2)
Gender n (%)			
Female	2 (40.0)	23 (60.5)	14 (60.9)
Male	3 (60.0)	15 (39.5)	9 (39.1)
Time from diagnosis to treatment start, median (range)	21 (13-97)	31 (11-77)	27 (11-66)
ECOG performance status n (%)			
Grade 0	3 (60.0)	21 (55.3)	16 (69.6)
Grade 1	2 (40.0)	17 (44.7)	7 (30.4)
Presence of liver metastasis n (%)			
Yes	5 (100)	29 (76.3)	18 (78.3)
No	0 (0.0)	9 (23.7)	5 (22.7)
Modified Glasgow Prognostic Score[3]			
0	2 (40.0)	20 (52.6)	11 (47.8)
1	3 (60.0)	17 (44.7)	12 (52.2)
2	0 (0.0)	1 (2.6)	0 (0.0)
Received prior surgery n (%)			
Yes	1 (20.0)	1 (2.6)	1 (4.3)
No	4 (80.0)	37 (97.4)	22 (95.7)
CA19-9 at baseline n(%)			
<100	1 (20.0)	8 (21.1)	5 (21.7)
100-1000	0 (0.0)	7 (18.4)	5 (21.7)
>1000	4 (80.0)	17 (44.7)	11 (47.8)
Unknown	0 (0.0)	6 (15.8)	2 (8.7)
Neutrophil/Lymphocyte ratio			
< 5	4 (80.0)	33 (86.8)	19 (82.6)
≥ 5	1 (20.0)	5 (13.2)	4 (17.4)

Key Eligibility Criteria

Inclusion:
- Diagnosis of metastatic PDAC
- 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

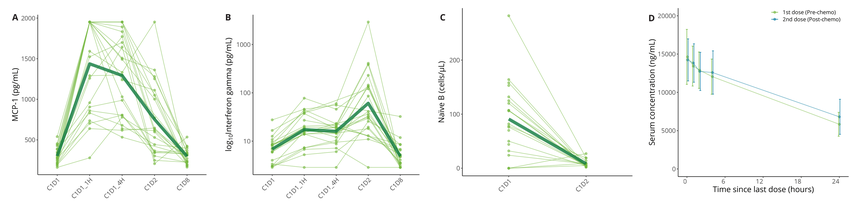
Exclusion:
- Other types of non-ductal pancreatic tumor
- Known CNS metastases or carcinomatous meningitis
- Has other current cancer or history of cancer in the prior 3 years

Safety

Patients with Grade ≥3 AEs (any causality) n (%)	900 µg/kg N=38
Grade ≥3 AEs occurring in ≥5% patients:	**26 (68.4)**
Neutropenia	7 (18.4)
Fatigue	5 (13.2)
Thrombocytopenia	4 (10.5)
Hypokalemia	4 (10.5)
Anemia	3 (7.9)
Diarrhea	3 (7.9)
Vomiting	2 (5.3)
Pneumonia	2 (5.3)

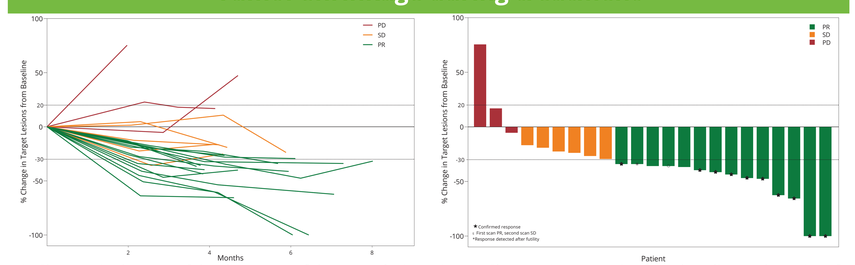
- At cutoff, 43 patients were treated with mFOLFIRINOX and 450 µg/kg (N=5) or 900 µg/kg (N=38) mitazalimab and evaluated for safety
- Mitazalimab + mFOLFIRINOX has a manageable safety profile
- The overall safety profile is consistent with mFOLFIRINOX chemotherapy
- No new safety signals or evidence of additive toxicity
- 6 patients (15.8%) experienced mitazalimab related grade >3 AEs
- 5 patients presented TEAEs that lead to discontinuation of study treatment: Pneumonia, gastric obstruction, neuropathy, bacteremia, and altered general condition

Biomarkers in peripheral blood confirm mitazalimab's mode of action



(A-B) Transient increases in serum MCP-1 and IFN-γ after mitazalimab administration. (C) Circulating *naïve* B cells decrease after the first mizalimab dose administration; (D) Serum concentration of mitazalimab within 24 hours after dose administration; PK profiles were not altered after mFOLFIRINOX. N=23

Tumor shrinkage during treatment



(A) Changes in the sum of the diameters of the target lesions (%); (B) Changes in tumor size from baseline at the point of best tumor reduction. In two PR patients, all target lesions were resolved, but non-target lesions were still present. N=23

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