OPTIMIZE-1 primary analysis: Safety, efficacy and biomarker results of a phase 1b/2 study combining CD40 agonist mitazalimab with mFOLFIRINOX in previously untreated metastatic pancreatic ductal adenocarcinoma (mPDAC)

Abstract 4133

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

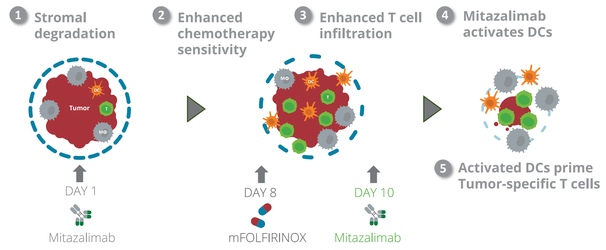
- Mitazalimab is a **FcγR crosslinking dependent CD40 agonistic** antibody (IgG1) with a tumor-directed immune activation
- Mitazalimab binds with **high affinity** to a unique binding epitope on the CD40 receptor allowing for high efficacy and potency
- Mitazalimab has the **potential for superior clinical activity:** mitazalimab is the only FcγR-dependent CD40 agonist with tumor-directed activity that can be dosed at 0.9 mg/kg

Mitazalimab in pancreatic cancer

DAY 1 Lead-in
Mitazalimab activates macrophages for stromal degradation.

DAY 8 Chemotherapy
mFOLFIRINOX induces tumor cell death, releasing antigens that are presented to the immune system

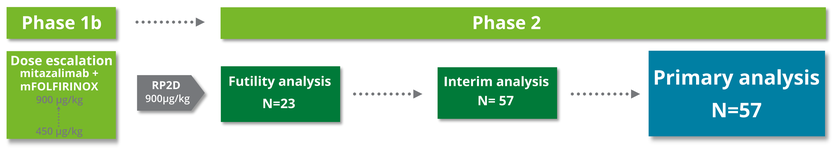
DAY 10 Mitazalimab primes for immunity
Enhanced priming of tumor-specific T cells via activation of dendritic cells (DCs).



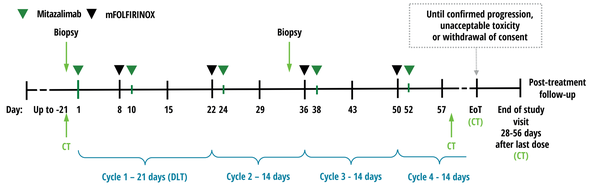
OPTIMIZE-1 study overview

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.

Key eligibility criteria include: Histologically confirmed diagnosis of metastatic PDAC, ECOG 0-1, No prior chemotherapy for PDAC



Dosing Regimen



Objectives and Endpoints

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.

Primary endpoint: ORR compared to historical FOLFIRINOX (30%)

Primary endpoint was met: Confirmed ORR 40.4% (unconfirmed ORR 50.9%)

Mitazalimab + mFOLFIRINOX demonstrated promising durability of response (median DoR 12.5 months) and overall survival (mOS 14.3 months

These encouraging results support continued development in a confirmatory trial

Patient Baseline Characteristics

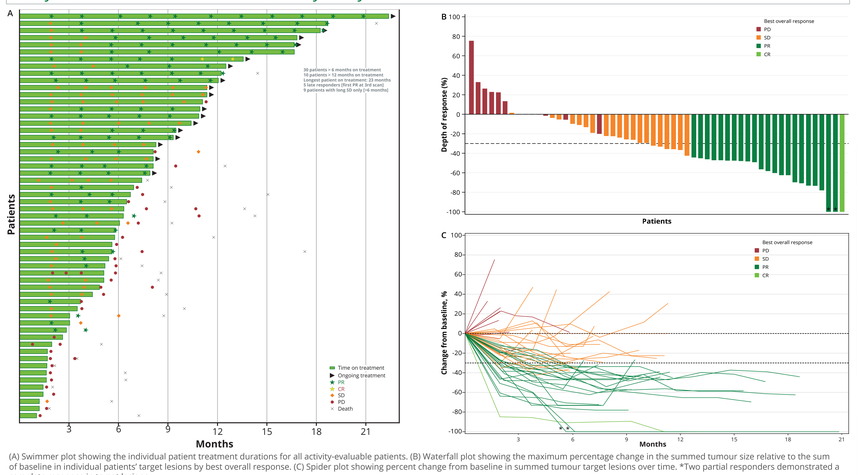
	Safety set 450 µg/kg N=5	Safety set 900 µg/kg N=65	Efficacy Set 900 µg/kg N=57
Age, years			
Under 65	2 (40.0)	38 (58.5)	35 (61.4%)
65 or above	3 (60.0)	27 (41.5)	22 (38.6%)
Gender			
Female	3 (60.0)	38 (58.5)	33 (57.9%)
Male	2 (40.0)	27 (41.5)	24 (42.1%)
Days from diagnosis to treatment start; median (IQR)	21 (20-33)	29 (21–35)	30 (21.8-35%)
ECOG performance status			
Grade 0	3 (60.0)	35 (53.8)	31 (54.4%)
Grade 1	2 (40.0)	30 (46.2)	26 (45.6%)
CA19-9 at baseline (n)	5	56	48
<100	1 (20.0)	8 (14.3)	8 (16.7%)
100-1000	0 (0.0)	13 (23.2)	13 (27.1%)
>1000	4 (80.0)	35 (62.5)	27 (56.3%)
Neutrophil/lymphocyte ratio (n)	5	64	56
<5	5 (100.0)	52 (81.3)	46 (82.1%)
>5	0 (0.0)	12 (18.8)	10 (17.9%)

	Safety set 450 µg/kg N=5	Safety set 900 µg/kg N=65	Efficacy Set 900 µg/kg N=57
Prior surgery			
Yes	1 (20.0)	2 (3.1)	2 (3.5%)
No	4 (80.0)	63 (96.9)	55 (96.5%)
Primary tumour location (n)	4	63	55
Head	0 (0.0)	29 (46.0)	25 (45.5%)
Body	1 (25.0)	22 (34.9)	21 (38.2%)
Tail	3 (75.0)	12 (19.0)	9 (16.4%)
Number of target lesions			
1	0 (0.0)	12 (18.5)	12 (17.1%)
2	2 (40.0)	19 (29.2)	21 (30.0%)
3 or more	3 (60.0)	34 (52.3)	37 (52.9%)
Sites of metastatic disease			
Liver	5 (100.0)	55 (78.6%)	42 (73.7%)
Lung	1 (20.0)	12 (17.1%)	9 (15.8%)
Peritoneal	1 (20.0)	10 (14.3%)	9 (15.8%)
Lymph Node	2 (40.0)	14 (20.0%)	10 (17.5%)
Other	2 (40.0)	20 (28.6%)	16 (28.1%)

Primary Endpoint

Overall response	**Efficacy Evaluable (n=57)**
ORR, n, % (90% CI)	29, 50.9% (39.3-62.4)
ORR (confirmed), n, % (90% CI)	23, 40.4% (29.4-52.1)
Best Overall Response (confirmed) n (%)	
Complete Response	1 (1.8%)
Partial Response	22 (38.6%)
Stable Disease	22 (38.6%)
Progressive Disease	12 (26.3%)
Disease Control Rate	45 (78.9%)

At cutoff (November 14, 2023), 57 patients treated with mFOLFIRINOX + 900 µg/kg mitazalimab had received ≥2 cycles and were evaluable for efficacy analysis.



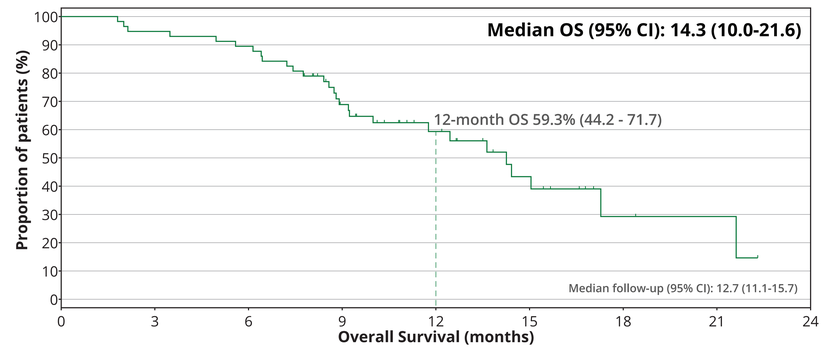
(A) Swimmer plot showing the individual patient treatment durations for all activity-evaluable patients. (B) Waterfall plot showing the maximum percentage change in the summed tumour size relative to the sum of baseline in individual patients' target lesions by best overall response. (C) Spider plot showing percent change from baseline in summed tumour target lesions over time. *Two partial responders demonstrated a complete response in target lesions

Safety

- At cutoff, 70 patients were treated with mFOLFIRINOX and 450 µg/kg (N=5) or 900 µg/kg (N=65) 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
- Eleven patients (15.7%) experienced mitazalimab related grade >3 AEs
- Four (5.7%) patients discontinued study treatment due to TEAEs, one with fatigue, chest pain, and headache, one with general deterioration in physical health, one with pneumonia, and one with an IRR (pruritus)

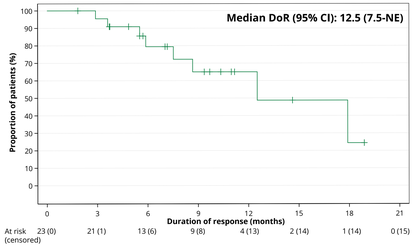
Patients with Grade ≥3 AEs (any causality) n (%)	**N=70**
Any Grade ≥3 AEs	**55 (78.6)**
Occurring in ≥5% patients:	
Neutropenia	18 (25.7)
Hypokalaemia	11 (15.7)
Anaemia	8 (11.4)
Thrombocytopenia	8 (11.4)
Fatigue	7 (10.0)
Diarrhoea	6 (8.6)
Neuropathy peripheral	6 (8.6)
Nausea	4 (5.7)
Asthenia	4 (5.7)

Overall Survival



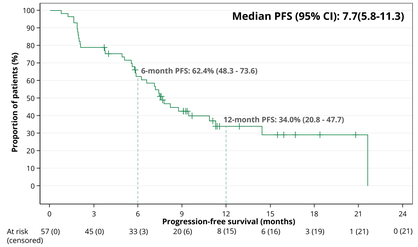
At risk (censored)	57 (0)	54 (0)	51 (0)	33 (7)	19 (17)	10 (22)	3 (27)	2 (28)	0 (29)

Duration of Response



At risk (censored)	23 (0)	21 (1)	13 (6)	9 (8)	4 (13)	2 (14)	1 (14)	0 (15)

Progression Free Survival



At risk (censored)	57 (0)	45 (0)	33 (3)	20 (6)	8 (15)	6 (16)	3 (19)	1 (21)	0 (21)

KRAS mutation subgroup analysis

n(%(95%CI))	KRAS[a] G12D (n=20)	KRAS G12V (n=21)	KRAS G12R (n=5)	Efficacy Evaluable (n=57)
ORR (confirmed)	5* (25 (10.4 - 45.6))	13 (61.9 (41.7 - 79.4))	3 (60 (18.9 – 92.4))	23* (40.4(29.4 - 52.1))
Median DoR, mo	NE	12.5 (7.5-NE)	NE	12.5(7.5-NE)
Median PFS, mo	5.7 (1.9 - 8.2)	10.8 (6.2- NE)	7.8 (5.7- NE)	7.7 (5.8 - 11.3)
6 mo PFS, %	45 (23.1 - 64.7)	76.2 (51.9 - 89.3)	80 (20.4 - 96.9)	62.4 (48.3 - 73.6)
Median OS, mo	9.2 (6.4- NE)	14.4 (11.8- NE)	15 (6.1- NE)	14.3 (10 - 21.6)
12 mo OS, %	39 (16.9 - 60.8)	69.3 (43.2 - 85.2)	60(12.6 - 88.2)	59.3 (44.2 - 71.7)

*1 CR- [a]KRAS mutations not detected in 11pts- NE=Not Estimable

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