CD40 agonist mitazalimab combined with mFOLFIRINOX in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC): Updated efficacy and correlative biomarkers from the OPTIMIZE-1 trial

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

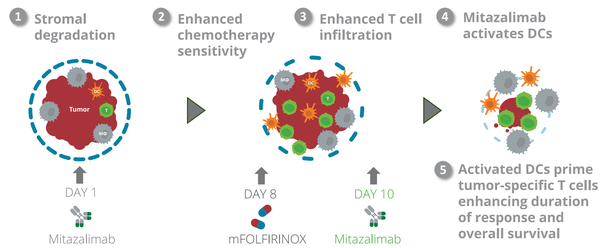
- Mitazalimab binds to a **unique epitope** on CD40 (domain 1), associated with strong, FcγR-conditional, agonistic activity
- Mitazalimab has a **wt IgG1 Fc**, providing the right balance of immune activation in the periphery and the TME
- The combination of **epitope** and **Fc-region** provides mitazalimab with a differentiated therapeutic window resulting in excellent tolerability and activity

Mitazalimab in pancreatic cancer

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

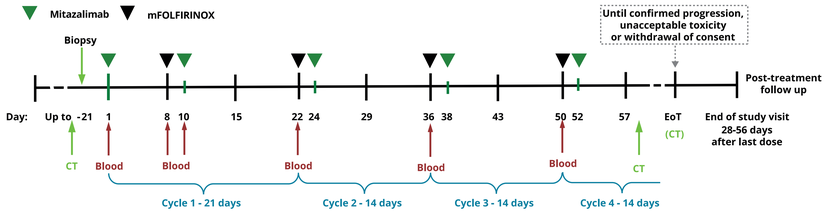
DAY 8 Chemotherapy
mFOLFIRINOX induces tumor cell death, releasing antigens that are presented to the immune system

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.



Endpoints and Eligibility Criteria

Primary endpoint:
- ORR vs. historical FOLFIRINOX (30%)

Key Secondary endpoints:
- Overall survival
- Progression Free Survival
- Duration of response
- Safety

Inclusion Criteria
- Diagnosis of metastatic PDAC
- ECOG status of 0 or 1
- No previous chemotherapy for PDAC

Exclusion Criteria
- Non-ductal pancreatic tumor
- Known CNS metastases

Patient Baseline Characteristics

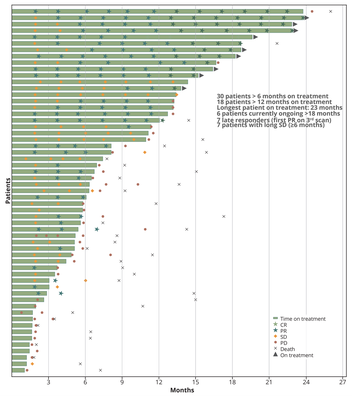
	N=57
Age, years	
Under 65	35 (61.4%)
65 or above	22 (38.6%)
Gender	
Female	33 (57.9%)
Male	24 (42.1%)
Days from diagnosis to treatment start; median (IQR)	30 (21.8 - 35%)
ECOG performance status	
Grade 0	31 (54.4%)
Grade 1	26 (45.6%)
CA19-9 at baseline (n)	48
<100	8 (16.7%)
100-1000	13 (27.1%)
>1000	27 (56.3%)
Neutrophil/lymphocyte ratio (n)	56
<5	46 (82.1%)
>5	10 (17.9%)

	N=57
Prior surgery	
Yes	2 (3.5%)
No	55 (96.5%)
Primary tumour location (n)	55
Head	25 (45.5%)
Body	21 (38.2%)
Tail	9 (16.4%)
Number of target lesions	
1	12 (17.1%)
2	21 (30.0%)
3 or more	37 (52.9%)
Sites of metastatic disease	
Liver	42 (73.7%)
Lung	9 (15.8%)
Peritoneal	9 (15.8%)
Lymph Node	10 (17.5%)
Other	16 (28.1%)

In this 18-month follow-up of the OPTIMIZE-1 study, mitazalimab + mFOLFIRINOX confirmed promising duration of response (median DoR 12.6 months) and improved overall survival (mOS 14.9 months)

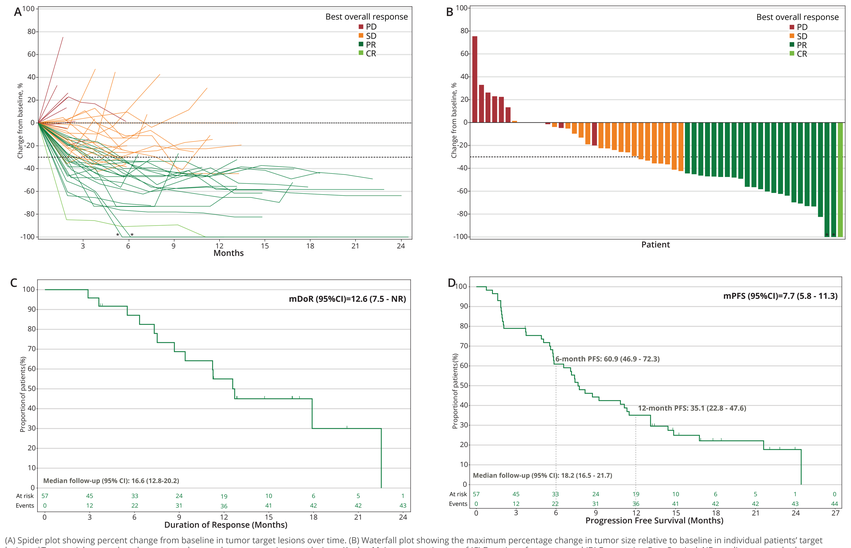
Classical tumor phenotype and on-treatment immune activation profiles (Cycle 1 Day 8) were associated with improved overall survival

These encouraging results from form the basis of a randomized Phase 3 trial of mitazalimab in combination with mFOLFIRINOX in mPDAC



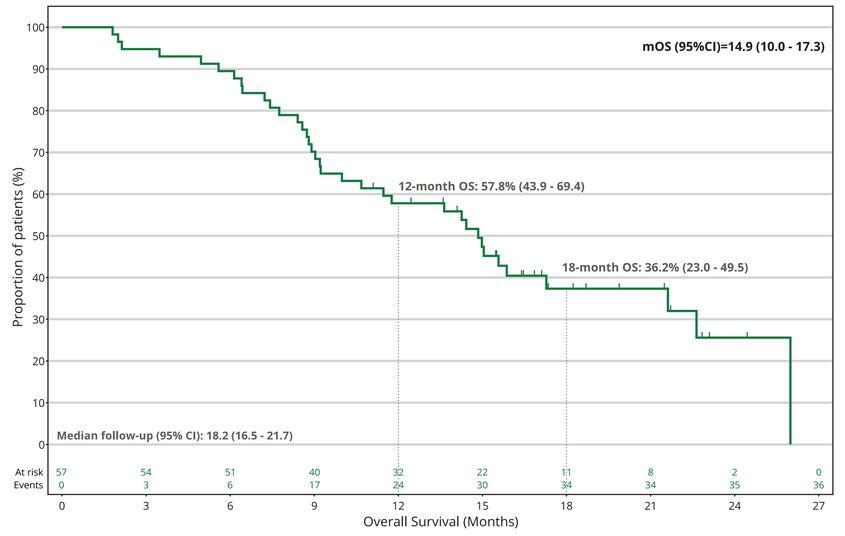
	N=57
Median follow-up, months	18.2
Best Overall Response, n (%)	
CR	1 (1.8%)
PR	23 (40.4%)
SD	21 (36.8%)
PD	12 (21.1%)
Disease Control Rate	45 (78.9%)
Objective response	
Number of patients with objective response (unconfirmed)	31
ORR (unconfirmed), % (90% CI)	54.4 (42.7 - 65.7)
Number of patients with objective response (confirmed)	24
ORR (confirmed), % (90% CI)	42.1(31.0 - 53.9)
Median DoR, months (95% CI)	12.6 (7.5 - NE)
Progression Free Survival	
Median PFS, months (95% CI)	7.7 (5.8 - 11.3)
6-month PFS rate, % (95% CI)	60.9(46.9 - 72.3)
12-month PFS rate, % (95% CI)	35.1 (22.8 - 47.6)
Overall Survival	
Median OS, months (95% CI)	14.9 (10.0 - 17.3)
12-month OS rate, % (95% CI)	57.8 (43.9 - 69.4)
18-month OS rate, % (95% CI)	36.2 (23.0 - 49.5)

At cutoff (May 15, 2024), 57 patients treated with mFOLFIRINOX + 900 µg/kg mitazalimab had received ≥2 cycles and were evaluable for efficacy analysis.



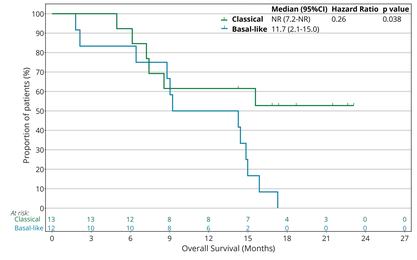
(A) Spider plot showing percent change from baseline in tumor target lesions over time. (B) Waterfall plot showing the maximum percentage change in tumor size relative to baseline in individual patients' target lesions. *Two partial responders demonstrated a complete response in target lesions. Kaplan Meier curve estimates of (C) Duration of response and (D) Progression Free Survival. NR: median not reached

Overall Survival

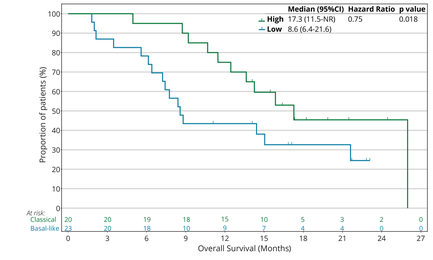


Biomarker Correlations with Overall survival

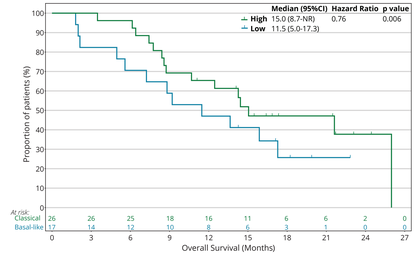
Basal/Classical Subtype (Baseline)



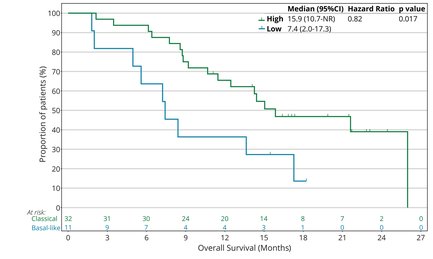
Plasmablasts (Cycle 1 Day 8)



CD54⁺ monocytes (Cycle 1 Day 8)



CD54⁺ mDCs (Cycle 1 Day 8)



Biomarkers associated with Overall Survival. (A) Molecular subtype as a prognostic factor in efficacy evaluable patients with available RNA-sequencing data at baseline (n=25). Patients were classified into "classical" and "basal-like" subtypes using the genesets published by Moffit et al and Zhou et al. A multivariate Cox proportional hazards (PH) model was fitted to estimate hazard ratios for associations between molecular subtype and all-cause mortality, while adjusting for KRAS G12 subtype. Efficacy evaluable patients stratified according to the foldchange of (B) percentage of plasmablasts from B cells, (C) CD54+ Monocytes from total monocytes, and (D) CD54+ mDC from total mDCs, at C1D8 from baseline. A univariate Cox proportional hazards (PH) model was fitted to estimate hazard ratios for associations between each population and OS. NR: median not reached

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