Evaluating the relative treatment efficacy of CD40 agonist mitazalimab in combination with mFOLFIRINOX in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) using unanchored indirect treatment comparisons (ITCs)

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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 m (modified) FOLFIRINOX in adults diagnosed with previously untreated metastatic pancreatic ductal adenocarcinoma (mPDAC). This reported analysis utilized the 18-month follow-up data (data cutoff: May 24, 2024; Geboes *et al*, SITC 2024).

Key OPTIMIZE-1 results (efficacy set, n=57)

Primary endpoint:

› Confirmed Objective Response Rate (ORR): 42.1% (RECIST 1.1)

Secondary endpoints:

› Median Overall survival (OS): 14.9 months
› Median Progression Free Survival (PFS): 7.7 months
› Median Duration of response (DoR): 12.6 months
› Safety Profile: consistent with mFOLFIRINOX chemotherapy. No new safety signals or evidence of additive toxicity

Objectives

To compare ORR, PFS and OS for mitazalimab + mFOLFIRINOX vs FOLFIRINOX (FFX), mFOLFIRINOX (mFFX) or NALIRIFOX (NFX) utilizing Indirect Treatment Comparison (ITC) methods

Methodology

Data sources: A systematic literature review was conducted to identify relevant published evidence from randomized Phase 2/3 trials on the efficacy and safety of FOLFIRINOX, mFOLFIRINOX or NALIRIFOX in previously untreated mPDAC.

TRIAL	PHASE	N	TREATMENT	AUTHOR / YEAR
ACCORD 11- PRODIGE4	2/3	171	FOLFIRINOX	Conroy, 2011
SWOG S1313	1/2	56	mFOLFIRINOX	Ramanathan, 2019
AVENGER500	3	262	FOLFIRINOX	Philipp, 2022
PANOPTIMOX - PRODIGE 35	2	91	FOLFIRINOX	Dahan, 2021
NAPOLI-3	3	383	NALIRIFOX	Wainberg, 2023

Approaches used to implement unanchored ITC:

› **Matching-Adjusted Indirect Comparison (MAIC):** adjusts for observed heterogeneity of potential effect modifiers across the study populations utilising propensity score weighting methods
› **Simulated Treatment Comparison (STC):** adjusts for observed heterogeneity of potential prognostic factors and effect modifiers across the study populations utilising regression methods. Among standard parametric distributions that were considered for OS and PFS, the goodness-of-fit and the clinical plausibility were used to identify the best fitting distribution for each outcome
› **Adjustment variables:** Age, gender, the presence of a liver metastasis and the WHO/ECOG performance status were adjusted for in the STC and the MAIC as they were considered as potential effect modifiers or prognostic factors based clinical opinion, literature review and statistical assessment. CA19-9 was included in the list of adjustment variables in a sensitivity analysis with no major changes in the results. Only the basecase analysis results are presented in this poster

Indirect comparisons Performed:

5 individual pairwise comparisons of OPTIMIZE-1 vs. each trial:

› **FOLFIRINOX-based:** ACCORD 11-PRODIGE 4, SWOG S1313, AVENGER500, PANOPTIMOX-PRODIGE 35
› **NALIRIFOX-based:** NAPOLI-3

Pooled comparisons:

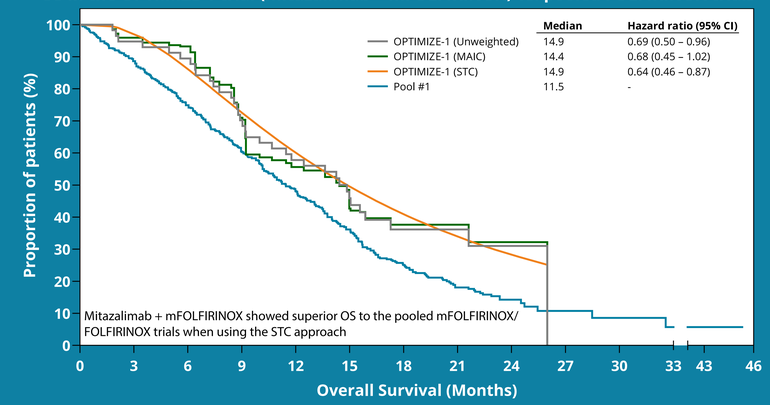
› **Pool #1:** OPTIMIZE-1 vs. all **FOUR** trials with FOLFIRINOX
› **Pool #2:** OPTIMIZE-1 vs. all **FIVE** trials with FOLFIRINOX / NALIRIFOX

Summary and Conclusions:

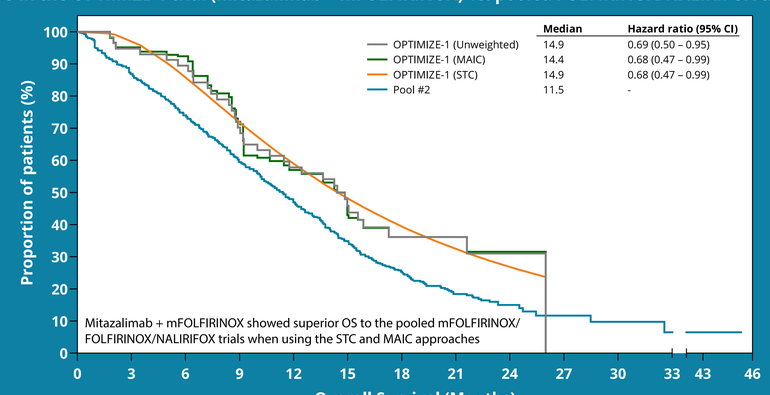
Literature based ITCs show a significantly better OS of mitazalimab + mFOLFIRINOX versus the current available therapies in patients with mPDAC

› In the STC analysis, mitazalimab + mFOLFIRINOX showed a significantly higher OS versus Pool #1 and #2, corresponding to an improvement in median OS by 3.4 and 3.3 months respectively.
› OS HRs of study-level pairwise comparisons ranged from 0.57 (95% CI: 0.39 – 0.80) to 0.85 (95% CI: 0.53 – 1.39) with only one non-significant comparison. MAICs showed similar trends.
› Results will need to be confirmed in a randomized Phase 3 trial of mitazalimab in combination with mFOLFIRINOX in mPDAC

OS in the OPTIMIZE-1 trial (mitazalimab + mFOLFIRINOX) vs. pooled FOLFIRINOX trials



OS in the OPTIMIZE-1 trial (mitazalimab + mFOLFIRINOX) vs. pooled FOLFIRINOX/NALIRIFOX trials

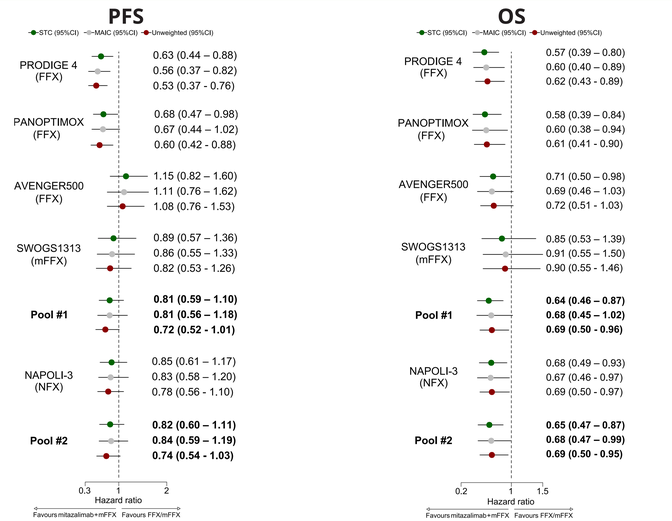


Baseline Characteristics

		Difference with respect to OPTIMIZE-1 trial (p-value)				
	OPTIMIZE-1 (N= 57)	ACCORD 11/ PRODIGE 4 (N= 171)	PANOPTIMOX-PRODIGE (N= 91)	SWOG S1313 (N= 56)	AVENGER500 (N= 262)	NAPOLI 3 (N= 383)
Age (Median)	62	1 (0.940)	**-2.6 (0.004)**	1 (0.940)	-1 (0.103)	**-2 (0.013)**
Gender - Female, n (%)	33 (57.9)	**19.9 (0.013)**	**19.4 (0.032)**	13.3 (0.222)	**19.0 (0.013)**	11.2 (0.152)
Liver metastasis, n (%)	42 (73.7)	**-13.5 (0.029)**	-8.7 (0.288)	-6.7 (0.536)	-2.3 (0.848)	-6.5 (0.342)
ECOG/WHO - PS 0, n (%)	31 (54.4)	**17.0 (0.036)**	14.8 (0.111)	-1.0 (1.000)	6.3 (0.474)	**12.6 (0.099)**
ECOG/WHO - PS 1, n (%)	26 (45.6)	**-16.4 (0.044)**	-14.8 (0.111)	1.0 (1.000)	-6.3 (0.474)	-12.3 (0.107)
Biliary stent, n (%)	5 (8.8)	-7.0 (0.271)	-9.9 (0.158)	NS	NS	NS
Disease status - Metastatic (Stage IV), n (%)	56 (98.2)	-1.8 (0.250)	-1.8 (0.385)	-1.8 (1.000)	-1.8 (0.179)	-1.8 (0.130)
Disease status - Locally advanced, n (%)	1 (1.8)	1.8 (0.250)	1.8 (0.385)	1.8 (1.000)	1.8 (0.179)	1.8 (0.130)
CA 19-9 - Normal, n (%)	11 (19.3)	5.3 (0.458)	NS	1.4 (1.000)	NS	NS
CA 19-9 - <59xULN, n (%)	22 (38.6)	-3.5 (0.756)	NS	**-43.5 (<0.001)**	NS	**22.9 (<0.001)**
CA 19-9 - ≥59 x ULN, n (%)	24 (42.1)	2.3 (0.876)	NS	**42.1 (<0.001)**	0.5 (1.000)	**-41.7 (<0.001)**
Primary Tumor Location - Head, n (%)	25 (45.5)	4.7 (0.640)	NS	15.3 (0.135)	NS	5.5 (0.519)
Primary Tumor Location - Body, n (%)	21 (38.2)	5.8 (0.514)	NS	8.3 (0.462)	NS	NS
Primary Tumor Location - Tail, n (%)	9 (16.4)	-10.5 (0.150)	NS	-11.0 (0.231)	NS	NS
Primary Tumor Location, -Multicentric n(%)	30 (54.5)	**49.1 (<0.001)**	NS	**52.6 (<0.001)**	NS	-9.0 (0.250)
Prior Surgery, n (%)	2 (3.5)	NS	**-13.0 (0.032)**	-0.1 (1.000)	NS	-1.2 (1.000)

There were statistically significant differences between trial populations, especially on characteristics included as adjustment variables (age, gender, liver metastasis, WHO/ECOG performance status at baseline, and CA19-9) in the unanchored STC and MAIC. Significant differences are represented in **bold**. Level of significance is 10%; NS: Not specified.

Adjusted OS and PFS ITC comparisons for individual trials



The results of this unanchored indirect treatment comparison indicate an improvement of the OS in favor of mitazalimab in patients with mPDAC compared to (m)FOLFIRINOX/NALIRIFOX.

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