Interim pharmacodynamic analyses of mitazalimab in combination with mFOLFIRINOX in first-line mPDAC identify CD4 effector T cells as a correlate of treatment outcomes

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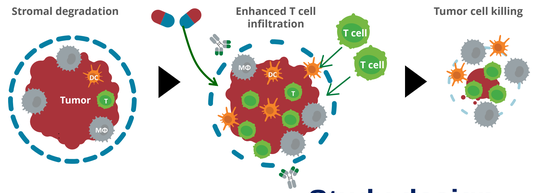
INTRODUCTION

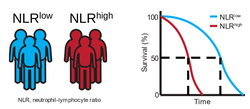
Agonists of the TNF receptor superfamily member CD40 in combination with chemotherapy show promise for the treatment of metastatic pancreatic ductal adenocarcinoma (mPDAC)[1,2]. CD40 agonists 'license' dendritic cells for T cell priming and drive tumor stromal depletion via macrophage activation[1,3-4]. Further, the sequence of CD40 agonist and chemotherapy administration is a crucial determinant of efficacy[3,4]. In pre-clinical models, administration of a CD40 agonist prior to chemotherapy drives depletion of fibrosis in PDAC tumors and enhances chemotherapy efficacy[3]. Additionally, pre-treatment systemic inflammation may drive poor outcomes to CD40 agonist based-therapy[5]. However, the efficacy, safety, immune pharmacodynamics and determinants of response of a CD40 agonist followed by chemotherapy in humans remains ill-defined. To address these questions, Optimize-1, a Phase II Clinical Trial, was initiated studying the CD40 agonist mitazalimab (mita) in combination with mFOLFIRINOX (mFFX) as first-line treatment for patients with mPDAC. Here we report interim immune pharmacodynamics from the first 23 patients being treated with mitazalimab followed by mFOLFIRINOX.

BACKGROUND

CD40 agonist mechanism of action

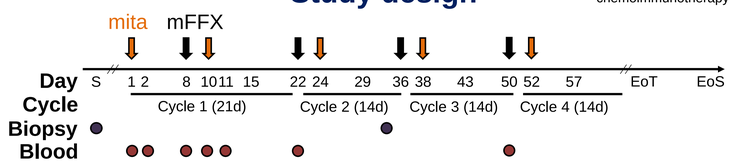


Determinants of outcomes to CD40 agonist therapy[5]



Systemic inflammation associates with poor outcomes to CD40 chemoimmunotherapy

Study design



Endpoints:

- Tumor response by RECIST v1.1
- Peripheral blood analyzed for cytokines, chemokines and leukocyte subsets
- Pre-treatment neutrophil-to-lymphocyte ratio calculated from clinical blood counts

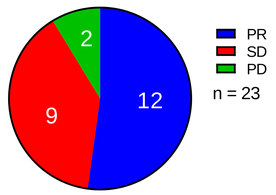
Patient demographics and baseline characteristics

Characteristic	(n = 23)
Age	
Median	64
Range	43 - 77
Sex - no (%)	
Male	14 (61)
Female	9 (39)
Race or ethnic group - no (%)	
White	17 (74)
Black	0 (0)
Asian	0 (0)
Hispanic	0 (0)
Not reported	6 (26)

Characteristic (cont.)	(n = 23)
ECOG performance status - no (%)	
0	16 (70)
1	7 (30)
Albumin (g/dL)	
Median	4.1
Range	3.7 - 4.5
CRP (mg/L)	
Median	12.6
Range	0.5 - 117
CA19-9 (U/mL)	
Median	1672
Range	26 - 54588

Response rate

Best Overall Response[6]	n (%)
Complete response (CR)	0
Partial response (PR)	12 (52.2)
Stable disease (SD)	9 (39.1)
Progressive disease (PD)	2 (8.7)
Not evaluable (NE)	0
Overall response rate (ORR)	12 (52.2)
Disease control rate (DCR)	21 (91.3)



RESULTS

Mitazalimab drives transient cytokine release

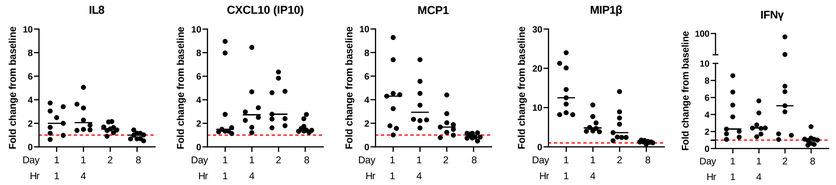


Figure 1. Cytokines were measured in serum at the times indicated after treatment with mitazalimab (mita). Fold change relative to pre-treatment cytokine levels are shown. Dotted red line indicates baseline which equals 1.

Mitazalimab impacts B cells and dendritic cells

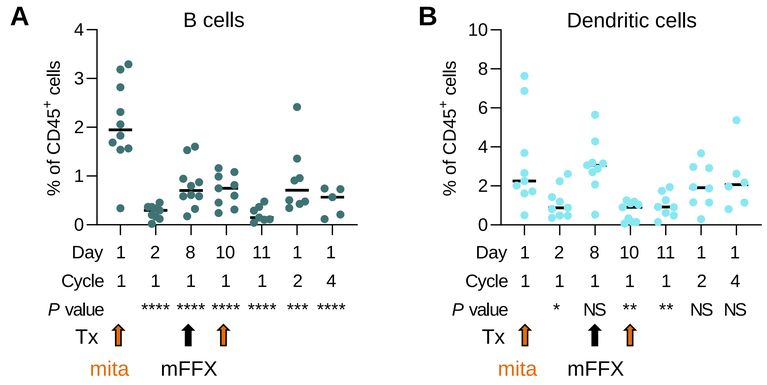


Figure 2. (A) Peripheral blood B cell frequencies over time. **(B)** Peripheral blood dendritic cell frequencies over time. One-way ANOVA with Dunnett's multiple comparisons testing was performed with all comparisons to cycle 1, day 1. Orange arrows denote mitazalimab (mita) administration. Black arrows denote mFOLFIRINOX (mFFX) administration. *, p < 0.05; **, p < 0.01; ***, p < 0.001; ****, p < 0.0001.

Chemotherapy impacts monocytes and Ki67+CD4+ T cells

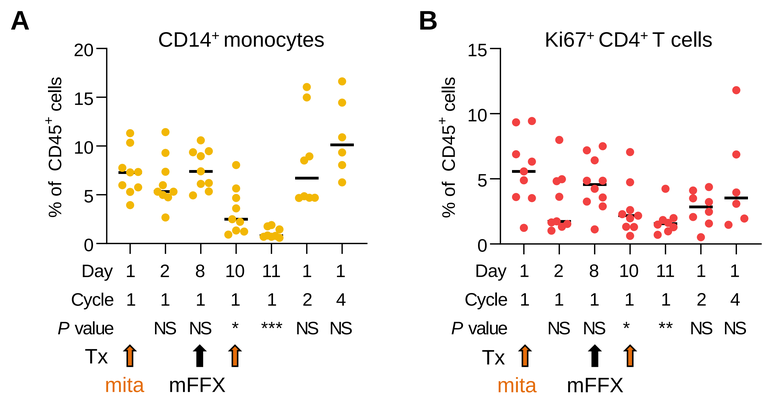


Figure 3. (A) Peripheral blood monocyte frequencies over time. **(B)** Peripheral blood proliferating (Ki67+) CD4+ T cell frequencies over time. One-way ANOVA with Dunnett's multiple comparisons testing was performed with all comparisons to cycle 1, day 1. Orange arrows denote mitazalimab (mita) administration. Black arrows denote mFOLFIRINOX (mFFX) administration. *, p < 0.05; **, p < 0.01; ***, p < 0.001.

RESULTS (cont.)

Tumor response associates with expansion of effector CD4 T cells at day 8 after mitazalimab

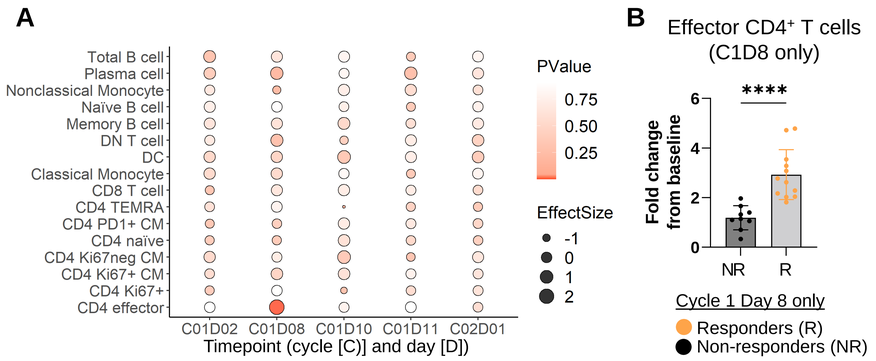


Figure 4. (A). Dotplot showing p value (unpaired Mann Whitney U test) and effect size (Cohens D) comparing change in frequency for each cell type from baseline to the indicated timepoint between responders (PR or CR) and non-responders (SD or PD). Dot size indicates effect size (smaller indicates higher in non-responders, larger indicates higher in responders). **(B)** Quantification of fold change in effector CD4+ T cells between responders (R) and non-responders (NR). Mann-Whitney U test was used. Unadjusted p values: *, p < 0.05; ***, p < 0.001; ****, p < 0.0001.

Tumor response does not correlate with NLR

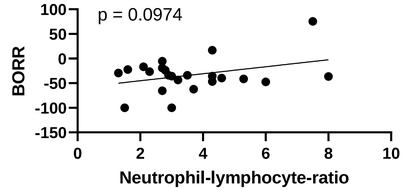


Figure 5. Correlation plot comparing best overall response rate (BORR) to neutrophil lymphocyte ratio (NLR). Pearsons correlation was used.

INTERPRETATION

Mitazalimab triggered an expected immune response characterized by transient cytokine (IL-8, IP-10, MCP-1, MIP1β and IFNγ) release and B cell marginization. Chemotherapy impacted monocytes and proliferating CD4+ T cells. Tumor response was associated with an expansion in the frequency of effector CD4 T cells at day 8 after receiving mitazalimab but did not correlate with neutrophil-to-lymphocyte ratio.

CONCLUSIONS

- Mitazalimab and mFOLFIRINOX induce distinct immune responses in mPDAC patients.
- Interim findings highlight CD4 effector T cells as a potential determinant of treatment outcomes.
- Sequential administration of CD40 agonist and then chemotherapy regimen may enhance anti-tumor immunity in mPDAC.

FUTURE DIRECTIONS

- Further investigation required to delineate the precise role of CD4 effector T cell to tumor responses.
- Analysis of the full study cohort and longer-term follow-up to validate these findings.

ACKNOWLEDGEMENTS

M.M.W is a Damon Runyon Physician Scientist supported (in part) by the Damon Runyon Research Foundation (PST-34-21). Additional funding provided by Alligator Bioscience AB. The authors acknowledge and thank all patients who participated in the study.

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