INTRODUCTION

Agonists of the TNF receptor superfamily member CD40 in combination with chemotherapy show promise for the treatment of metastatic pancreatic ductal adenocarcinoma (mPDAC). CD40 agonists license/deduct dendritic cells for T cell priming and drive tumor stromal depletion via macrophage activation1-3. Further, the sequence of CD40 agonist and chemotherapy administration is a crucial determinant of efficacy4-6. In pre-clinical models, administration of a CD40 agonist prior to chemotherapy drives depletion of fibrosis in PDAC tumors and enhances chemotherapy efficacy7. Additionally, pre-treatment systemic inflammation may drive poor outcomes to CD40 agonist-based therapy8. 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 immune pharmacodynamics from the first 23 patients being treated with mitazalimab followed by mFOLFIRINOX.

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.

Mitazalim 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 Dunn’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). Pearson's correlation was used.

INTERPRETATION

Mitazalim triggered an expected immune response characterized by transient cytokine (IL-6, IL-8, IP-10, MCP-1, MIP1β and IFNγ) release and B cell margination. 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

- Mitazalim 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.

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