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Effects of Indoximod Plus Gemcitabine/Nab-paclitaxel on the Tumor Microenvironment of Patients With Metastatic Pancreatic Cancer

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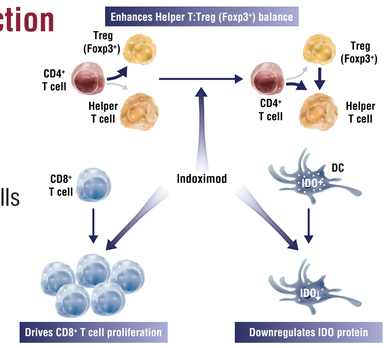
INTRODUCTION

- The indoleamine 2,3-dioxygenase (IDO) pathway mediates immunosuppressive effects through the metabolism of tryptophan (Trp) into kynurenine (Kyn), triggering downstream signaling through the Trp sensors GCN2 and mTOR as well as through the aryl hydrocarbon receptor (AhR), which senses Kyn[1-4]
- Indoximod is an orally administered, small-molecule IDO pathway inhibitor that reverses the immunosuppressive effects of low Trp and high Kyn that result from IDO activity[5]
- The combination of gemcitabine and nab-paclitaxel is a current standard of care (SOC) for metastatic pancreatic cancer, providing a moderate improvement in overall survival vs. gemcitabine alone (8.5 vs. 6.7 months)[6]
- Preclinical models have demonstrated synergy between indoximod and chemotherapy[7]

Indoximod Mechanism of Action

- Indoximod has immunostimulatory effects involving 4 main cell types:
  - Reverses the effects of low Trp by increasing proliferation of effector ($CD8^+$) T cells
  - Directly reprograms T regulatory cells (Treg) into helper T cells
  - Downregulates IDO expression in dendritic cells (DCs)



OBJECTIVES

- To define the effect of indoximod + gemcitabine/nab-paclitaxel on the tumor microenvironment of patients with metastatic pancreatic cancer
- To examine pharmacodynamic effects of indoximod related to its MOA

METHODS

Phase 2 Single-Arm, Open-Label Study (NCT02077881)

Treatment-naïve patients with metastatic pancreatic cancer → **Indoximod 1200 mg orally BID + SOC (Gemcitabine 1000 mg/m² + nab-paclitaxel 125 mg/m² IV)** *Days 1, 8 and 15 of 4-wk cycles*

- Cross-sectional imaging performed every 2 cycles per protocol; response determined by local radiologist review per standard RECIST criteria, v1.1
- Treatment continued until disease progression or significant toxicity

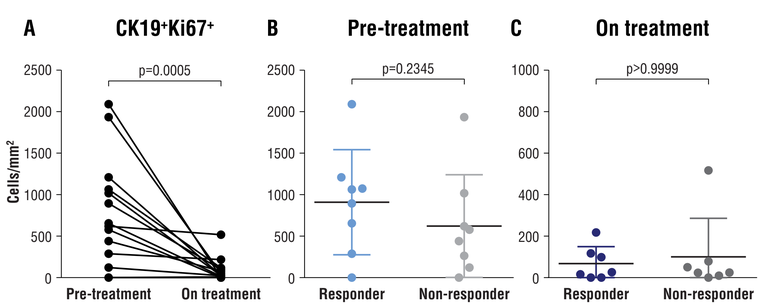
Tumor response defined as complete response and partial response by site report according to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, version 1.1. Efficacy was assessed in patients who received ≥1 dose of study medication and had ≥1 post-baseline response evaluation (efficacy evaluable population).

- RNA-seq analysis and immunohistochemistry (IHC) performed on tumor biopsies

RESULTS

- Tumor biopsies from 16 patients (a subset of a larger Phase 2 study population treated with indoximod + SOC) were analyzed

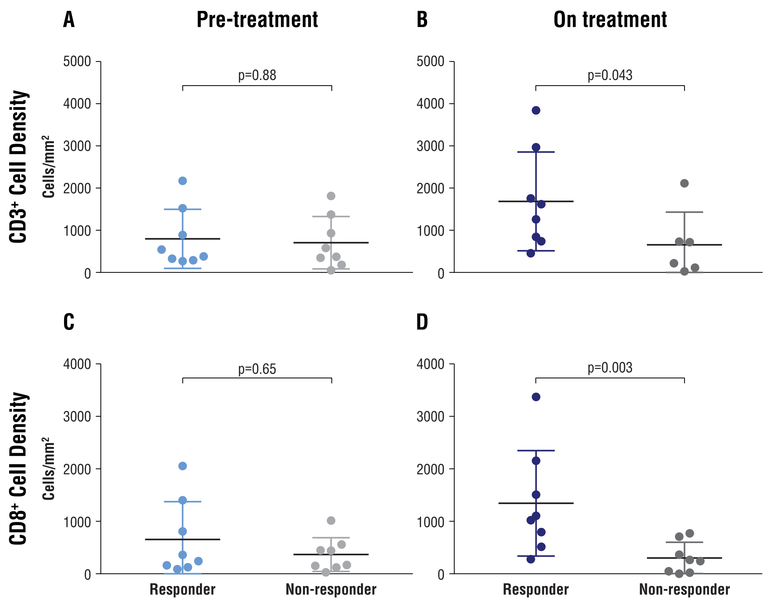
Changes in the Tumor Microenvironment



Paired analysis of $CK19^+$ (tumor marker) $Ki67^+$ (proliferation marker) cells in tumor tissue seen at pre- vs. on treatment (A), as well as $CK19^+Ki67^+$ cell density in pre- (B) and on-treatment (C) biopsies of responders and non-responders using IHC staining. Wilcoxon test used for statistical analysis of (A), and Mann-Whitney tests for (B) and (C).

- Tumor cells ($CK19^+$ cells) entered a non-proliferative state after treatment with indoximod + SOC
- This reduced tumor cell proliferation was not associated with clinical response

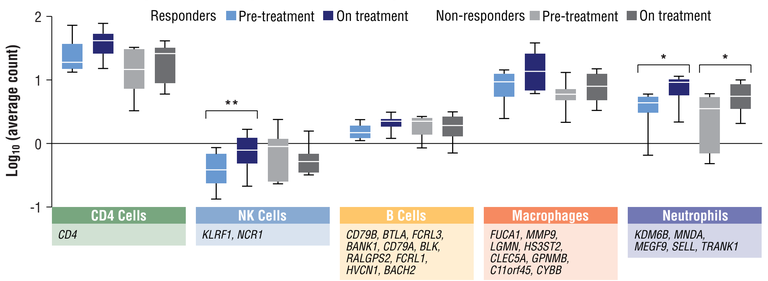
Indoximod + SOC Associated With Intra-tumoral $CD3^+$ and $CD8^+$ Infiltration in Responders



$CD3^+$ (A, B) and $CD8^+$ (C, D) density in pre-treatment and on-treatment tumor biopsies of responders and non-responders using IHC staining. Mann-Whitney tests used for statistical analyses.

Changes in Immune Cell Populations

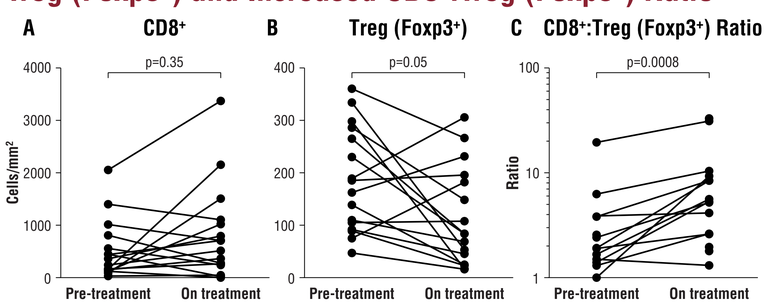
Per RNA-seq Gene Signature Analysis



Significance indicated as *p<0.05; **p<0.01, determined by paired *t*-test. Expression scores calculated as geometric mean of FPKM values of genes.

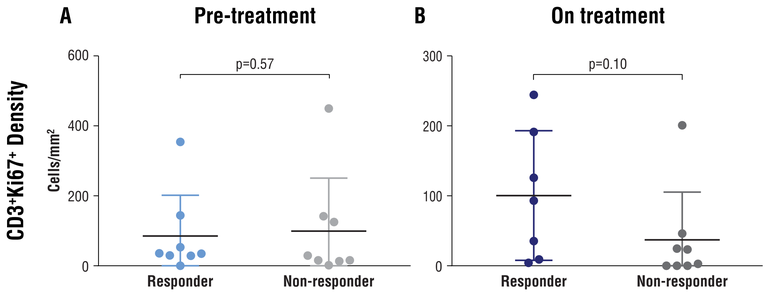
- Upon treatment, there were significant increases in gene expression associated with
  - Natural killer (NK) cells and neutrophils in responding patients
  - Neutrophils in non-responding patients

Indoximod + SOC Associated With Downregulation of Treg ($Foxp3^+$) and Increased $CD8^+$:Treg ($Foxp3^+$) Ratio



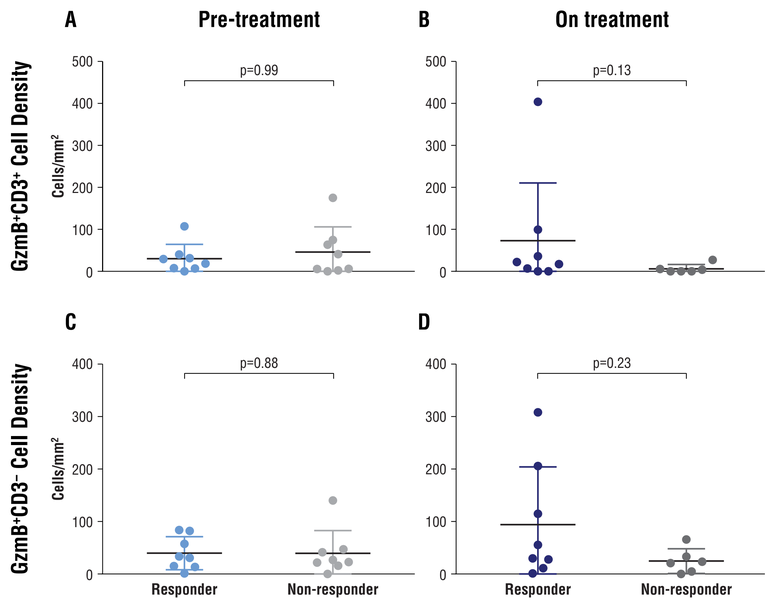
Paired analysis of $CD8^+$ (A) and $Foxp3^+$ (B) cell infiltrates into tumor tissue at pre- vs. on treatment; paired analysis of ratio of $CD8^+$ to $Foxp3^+$ cells (C) in pre- vs. on-treatment biopsies using IHC staining. Wilcoxon tests used for statistical analyses.

Indoximod + SOC Associated with Trend Toward Increased $CD3^+Ki67^+$ T Cell Proliferation in Responders



$CD3^+Ki67^+$ in pre- (A) and on-treatment (B) tumor biopsies of responders and non-responders using IHC staining. Mann-Whitney tests used for statistical analyses.

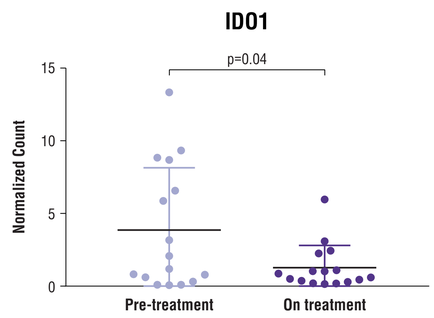
GzmB Expression in $CD3^+$ and $CD3^-$ Cells



$GzmB^+CD3^+$ and $GzmB^+CD3^-$ density in pre- and on-treatment tumor biopsies of responders and non-responders using IHC staining. Mann-Whitney tests used for statistical analyses.

Indoximod + SOC Associated with Downregulation of IDO1 Expression in the Tumor Microenvironment

Per RNA-seq Gene Signature



Paired *t*-test used for statistical analyses.

CONCLUSIONS

- Responders to treatment with indoximod + SOC were observed to have changes in the tumor microenvironment, consistent with the proposed MOA for indoximod
- In responding patients, the addition of indoximod to SOC was associated with multiple anti-tumor and pro-inflammatory effects on the tumor microenvironment, including:
  - Density and activity of intra-tumoral T cells
  - Density of innate immune cells (NK cells, neutrophils)
- Treatment also significantly downregulated the Treg ($Foxp3^+$) population and IDO1 expression in the tumor microenvironment
- Treatment with indoximod + SOC was associated with an increase in both innate and adaptive immune responses in the tumor microenvironment of patients with metastatic pancreatic cancer

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