#4144: Comprehensive Molecular Mapping of Pancreatic Ductal Adenocarcinoma Relates *XPO1* mRNA Expression Levels to Potential Clinical Targets

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Background

- Encouraging pre-clinical efficacy using inhibitors targeting Exportin-1 (*XPO1*) - a master regulator of tumor suppressor protein export - has been reported in pancreatic ductal adenocarcinoma (PDAC) and clinical trials are currently ongoing.
- Limited data is available regarding expression and function of *XPO1* in PDAC.
- Thus, we investigated *XPO1* mRNA expression and its clinical and immune correlates in PDAC.

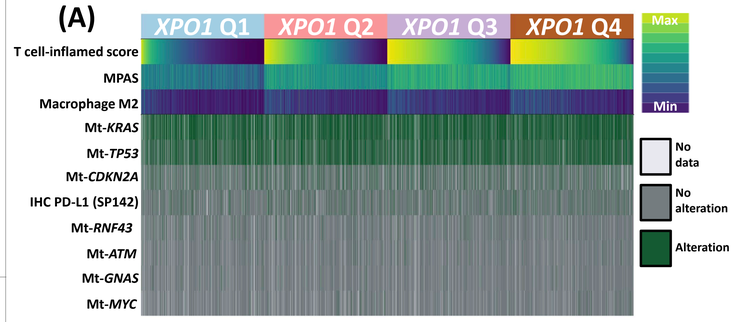
Methods

- 5,488 PDAC tumors were tested at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing of DNA (592-gene or whole exome) and RNA (whole transcriptome).
- High tumor mutational burden (TMB-H) was defined as ≥10 mutations/MB.
- The cohort was stratified in quartiles according to *XPO1* mRNA expression.
- Immune cell fraction was calculated by QuantiSeq (Finotello 2019, Genome Medicine).
- Gene expression profiles were analyzed for transcriptomic signatures predictive of response to immune checkpoint inhibitors (T cell-inflamed score [Bao, 2020]) and MAPK pathway activation (MPAS)).
- The Mann-Whitney U and χ^2 tests were applied as appropriate, with P-values adjusted for multiple comparisons.
- Real-world overall survival (OS) data was obtained from insurance claims and Kaplan-Meier estimates were calculated for molecularly defined subpopulations of patients.

Any questions? Contact me: andreas.seeber@tirol-kliniken.at

Results

1. Genomic landscape and biomarkers



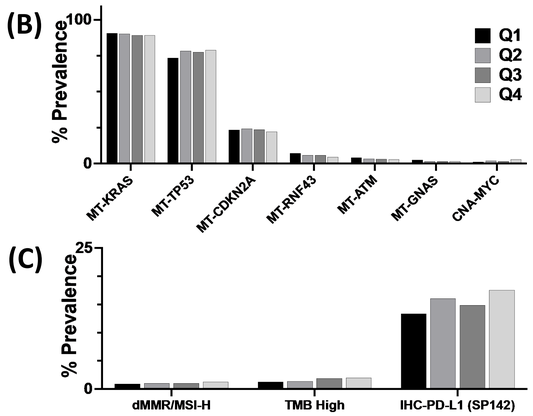


Figure 1: (A) Oncoprint of genomic alterations, immune cell infiltrate, and transcriptomic signatures (immunotherapy response (T cell-inflamed) and MAPK pathway activation (MPAS)). Prevalence of **(B)** genomic alteration and **(C)** immune biomarkers.

2. Transcriptomic signatures and immune landscape

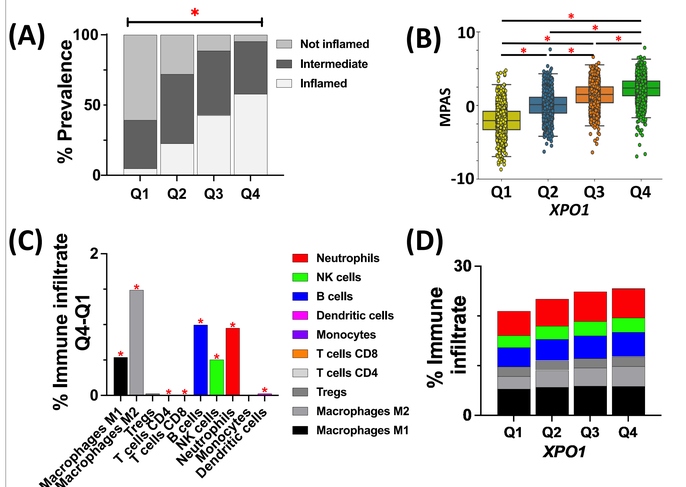


Figure 2: **(A)** Prevalence of T cell-inflamed tumors (predictive of response to immunotherapy). **(B)** MPAS score, a transcriptomic signature representative of MAPK pathway activation. **(C,D)** Quantification of tumor immune infiltrate, derived via QuantiSeq (asterisks indicate statistical significance, $p < 0.05$).

3. Outcomes data

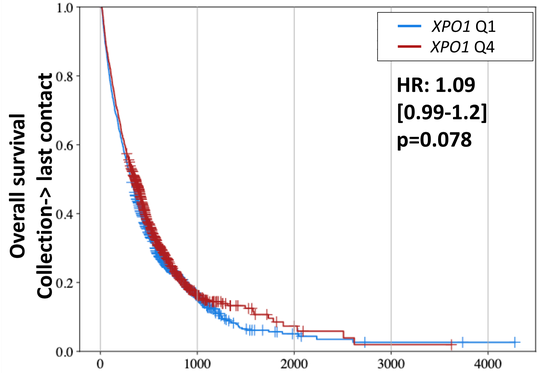


Figure 3: Outcomes data for pancreatic tumors segmented by *XPO1* expression.

Study Highlights

- There were no significant alterations in the genomic landscape between high and low *XPO1* expression.
- Tumors with high expression of *XPO1* tended to be more T cell-inflamed, had activation of the MAPK pathway and had an increase in M2 macrophage infiltrate.

Conclusions

- This is the first study comprehensively mapping *XPO1* mRNA expression and immune-correlates in PDAC.
- We found that high *XPO1* is linked to increased immune cell infiltration and more T cell-inflamed tumors.
- Our data provides a potential rationale to combine immune checkpoint therapy (+/- XPO1 inhibitors) in *XPO1*^{H} PDACs.