Pelareorep combined with atezolizumab and chemotherapy shows immune conversion activity in advanced pancreatic cancer: biomarker results of cohort 1 of the phase I/II GOBLET trial

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Introduction & Background

Pancreatic cancer features a profoundly immunosuppressive microenvironment and no approved immunotherapy to date. **Pelareorep** is a naturally occurring **reovirus** isolate that preferentially replicates in RAS upregulated tumor cells. In cohort 1 of the phase I/II GOBLET trial (NCT07280377), patients with **metastatic pancreatic cancer** were enrolled to receive first line (**1L**) **pelareorep** combined with **atezolizumab** and **gemcitabine/nab-paclitaxel** (Fig. 1A+B) yielding a previously reported confirmed objective response rate (**ORR**) of **54%** (7/13) and disease control rate (DCR) of 85% (11/13). While ORR did not directly translate to survival (Fig. 1C+D), individual patients showed exceptional responses. Of note, response trajectories revealed three clinically relevant classes: *Non-Responders (NR)*, *Transient Responders (TR)*, and *Durable Responders (DR)* (Fig. 1E).

In this biomarker study, we analyzed the association between clinical response and serum proteomics to identify therapy-induced immune processes, differential dynamics and a potentially predictive biomarker signature for upcoming trials.

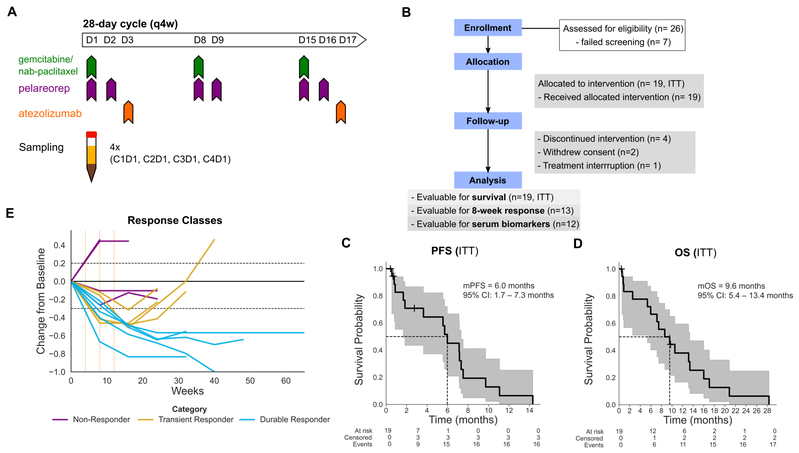

Figure 1. Trial design, recruitment and clinical data. (A) Treatment plan and dates of serum sample acquisition. **(B)** CONSORT diagram. **(C+D)** Kaplan-Meier curves for **(C)** PFS and **(D)** OS of the intention-to-treat population (mPFS: 6.0 months, mOS: 9.6 months). **(E)** Spider plots of tumor volume change showing distinct patient trajectories (NR, TR, DR).

Methods

Routine **serum markers** and 172 **circulating proteins** quantified via **proximity extension assay** (PEA; Olink®: *immuno-oncology panel & immune-response panel*) at baseline (week 0), C2D1 (week 4) and C3D1 (week 8) were integrated with selected **T cell receptor (TCR) sequencing** and clinical outcomes. Longitudinal data were analyzed using correlation, linear mixed effects models (LMM) and hierarchical clustering. (FDR-correction: Benjamini-Hochberg, alpha: 0.05)

Serum Proteome Dynamics Under Therapy

Differentially quantified proteins (n=38) displayed two dynamical patterns reflecting a **tumor/stroma and immune-related signature**, respectively (Fig. 2A), with opposing association to tumor dynamics (Fig. 2B). Unsurprisingly, overall immune dynamics spike early (week 4), then subside (Fig. 2C).

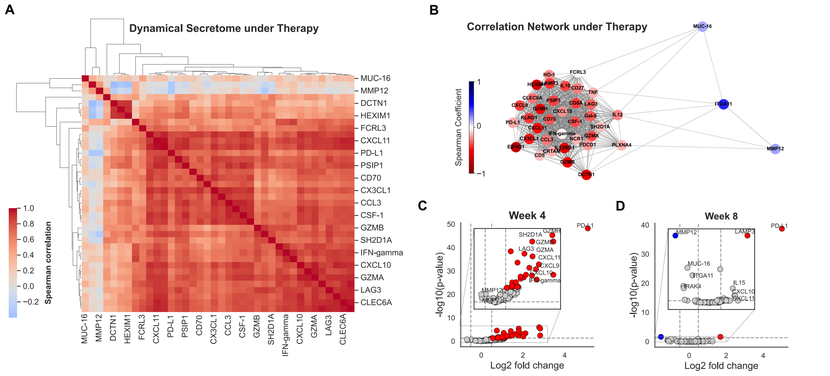

Figure 2. Correlation matrix and network analysis of serum proteomics under therapy. (A) Spearman correlation with hierarchical clustering of differentially quantified serum proteins (n=38). **(B)** Network analysis with edge weights representing Spearman coefficients (rho > 0.7) and node colors representing the correlation of each analyte across samples with tumor volume change at week 8 (blue: increase, red: decrease). **(C+D)** Volcano plot of differential serum proteins at week 4 (C2D1) and week 8 (C3D1), respectively (left: decrease, right: increase) (thresholds: p<0.05, LFC >0.5).

Therapy-Induced Immune Phenotypes

A biology-informed subset of differential serum proteins (n=13/38) assumingly associated with oncolytic-response suggests a binary **hot/cold immune response phenotype** that is not present at baseline.

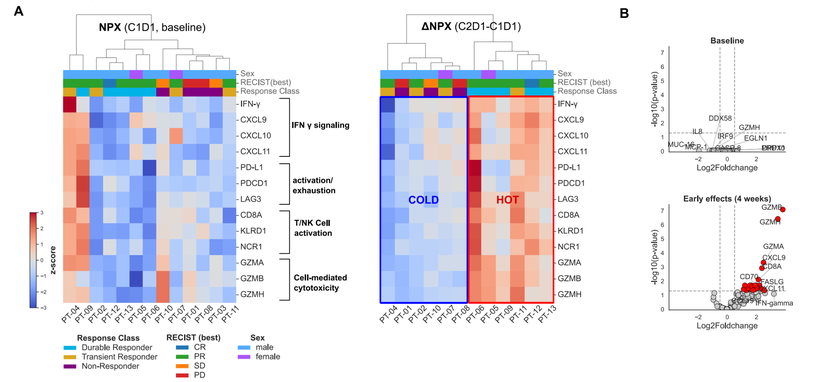

Figure 3. Oncolytic-associated differential serum proteins suggests two immune response phenotypes. (A) Unsupervised clustering for NPX (normalized protein expression, log2) change at week 4, but not baseline, reveals a distinct two-class pattern. **(B)** Volcano plots for ‚hot' (red) *versus* ‚cold' (blue) highlight the phenotypes as being response and not baseline characteristics. (thresholds: p<0.05, LFC >0.5)

Exploratory Biomarker Evaluation

The 'hot' response phenotype associates with a ~ 2 months improved PFS (Fig. 3A) and beyond its biology-informed signature definition shows a separation for both tested panels with regard to week 4 protein variation (Fig. 3B). A weighted signature derived immune score strongly **correlates with PFS** (Fig. 3C+D) and is **associated with TIL expansion** (Fig. 3E).

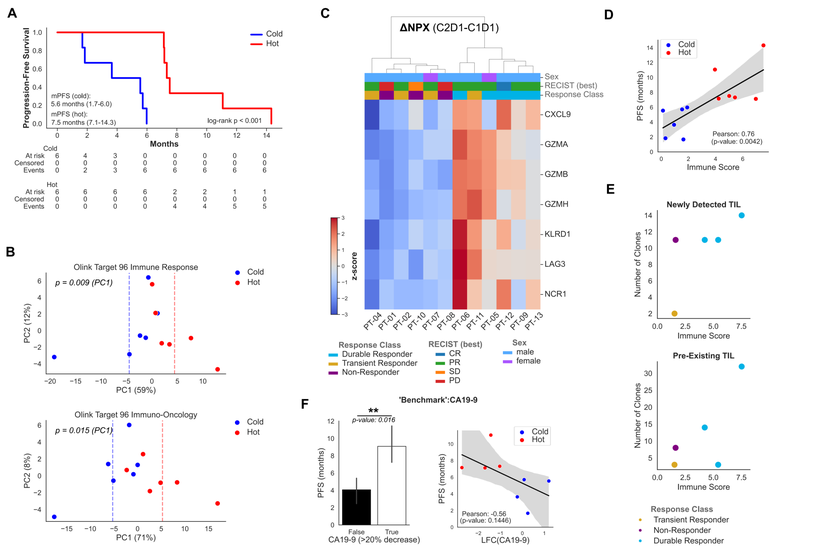

Figure 4. Immune scoring and biomarker evaluation. (A) Kaplan-Meier curve comparison by class: mPFS(cold) 5.6 months, mPFS(hot) 7.5 months *(log-rank p < 0.001)*, mean ΔRMST: 1.91 months *(p < 0.001)*. **(B)** Principal Compenent Analysis of the two panels for ΔNPX at week 4 (Mann-Whitney-U: p = 0.009/0.015, Permutation test: p = 0.008/0.012). **(C)** Clustermap (ΔNPX at week 4) of the penalized logistic regression derived protein signature from all differentially measured proteins at week 4. **(D)** The signature-derived immune score shows a strong correlation with PFS (Pearson: rho 0.76, p-value <0.005) and is robust with respect to leave-one-out statistics (rho min: 0.65, rho max: 0.83). **(E)** Expansion of tumor-infiltrating lymphocytes (TIL) clones derived from TCR sequencing. **(F)** CA19-9 shows categorical prognostic qualitiy for a decrease of at least 20% (Mann-Whitney-U: p-value 0.016), and moderate though not significant correlation with PFS (rho: -0.56, p-value: 0.14).

Conclusions

- An early immune-response serum protein signature after 4 weeks of treatment, but not baseline suggests a **hot/cold immune context**.
- A **signature-derived score** links a 'hot' immune phenotype to improved outcome and **strongly correlates with progression-free survival**
- The signature provides a **plausible mechanism** of action and **potentially helps stratify** patients who benefit from oncolytic therapy upon validation.

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