A predictive signature for response to immunotherapy in non-small cell lung cancer based on plasma proteomics and clinical parameters

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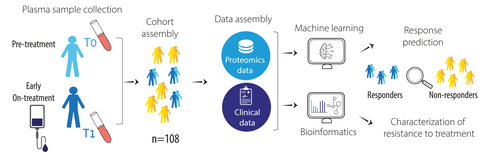
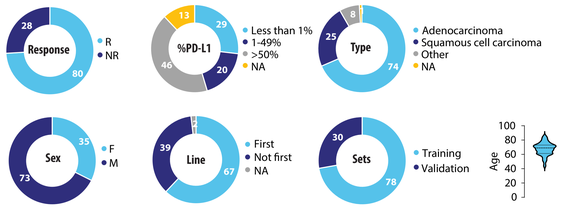
1 Background

Immune checkpoint inhibitor (ICI)-based treatment has revolutionized the cancer therapy landscape, displaying durable response in patients with advanced stage disease. However, only a small fraction of patients responds to this treatment. It is therefore critical to identify reliable biomarkers for response and understand the mechanisms underlying resistance. Here we examined host-mediated effects occurring in response to ICI treatment and their contribution to therapy resistance in stage IV non-small cell lung cancer (NSCLC) patients.



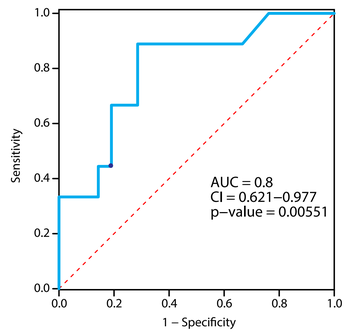
Plasma samples were obtained at baseline and early-on treatment from NSCLC patients as part of an ongoing multi-center clinical trial (NCT04056247), along with comprehensive clinical data. Proteomic profiling of plasma samples was performed using proximity-extension assay (PEA) technology. The data were analyzed to identify biomarkers for response to ICI-based treatment, as well as to gain insights into mechanisms of resistance to treament

2 Cohort overview

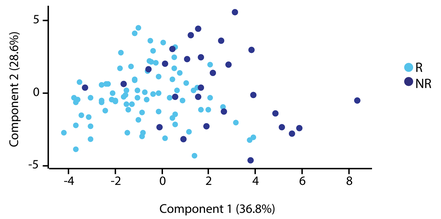


Overall, 108 subjects participated in the study, of whom 80 were responders and 28 were non-responders (based on RECIST evaluation at 3 months). Basic clinical features are presented in the figure (Response groups; %PD-L1 staining; NSCLC histology type; Sex; Line of treatment; Age). For the machine learning analysis the cohort was divided into a training set (n=78) and an independent validation set (n=30).

3 Response prediction

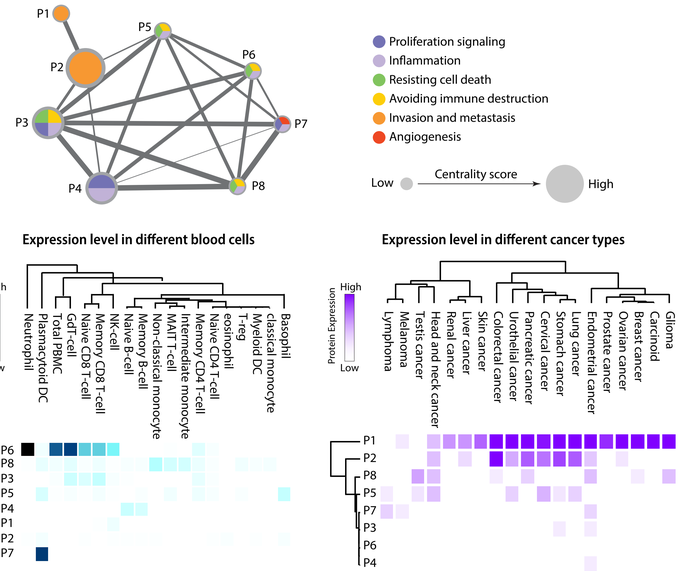


A signature comprised of 8 proteins and 2 clinical parameters was found to predict outcome for ICI treatment. The validation set displayed an area under the curve (AUC) of the receiver operating characteristics (ROC) curve of 0.8. The blue dot in the ROC curve indicates the point at which the specificity and the negative predictive value are 0.81 and 0.77, respectively.



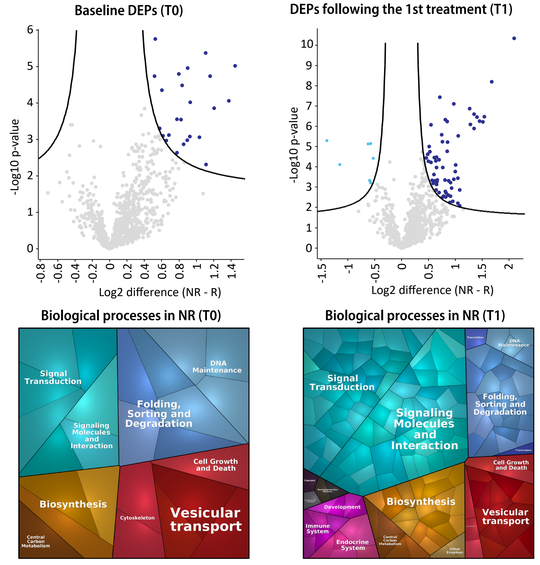
The predictive signature segregates between responders and non-responders based on unsupervised analysis (principal component analysis).

4 Characterization of resistance to treatment: Biological insights from the predictive signature



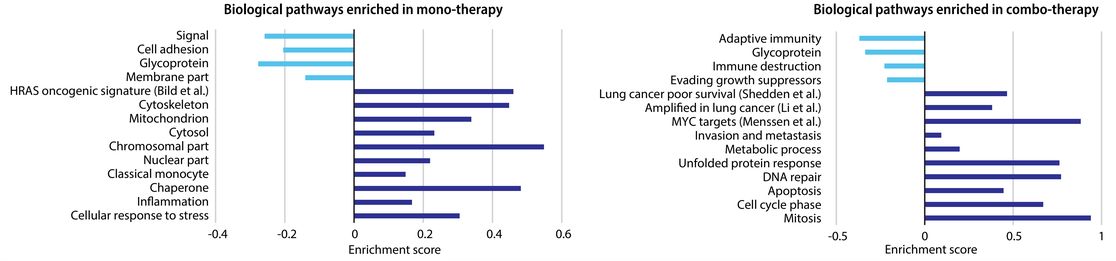
All 8 proteins that comprise the predictive signature are interconnected, as observed in the network above. Two proteins (P1 and P2) are related exclusively to invasion and metastasis, while the rest are involved in inflammation and other tumor-related processes. High expression levels of P1 and P2 are found in multiple cancer types, including NSCLC. The other proteins are likely to originate from neutrophils (P6), plasmacytoid dendritic cells (P7), T-cells (P8 and P3) and B-cells (P4). Expression levels in blood cells and tumor tissues are based on Human Protein Atlas (HPA). Protein names are not disclosed due to IP issues.

5 Characterization of resistance to treatment: Differentially Expressed Proteins (DEPs)



Proteins found at significantly different levels in responders and non-responders are termed differentially expressed proteins (DEPs). Bioinformatics analysis showed a larger number of DEPs at on-treatment (T1) timepoint in comparison to baseline (T0) based on student's t-test (FDR < 0.1; S0=0.1). Dark blue- DEPs higher in non-responders. Light blue- DEPs higher in responders. Proteomaps functional analysis showed that T1 DEPs that were higher in non-responders (NR) are mainly involved in signaling and signal transduction related processes, as well as immune-system processes and protein folding.

6 Characterization of resistance to treatment: Functional differences between mono- and combo- therapies



Comparison between significantly enriched biological pathways in mono- and combo- tharapy groups reveals that many processes are modality- unique. The analysis is based on 1D-enrichment analysis (FDR < 0.1). The enrichment score is between -1 and 1. A positive enrichment score designates enrichment in non-reponders. A negative enrichment score indicates enrichment in responders. Dark blue- biological processes enriched in non-responders. Light blue- biological processes enriched in responders.

7 Take-home messages

- We identified a predictive signature for response to ICI based on clinical parameters and plasma proteins. The proteins that comprise the signature are derived either from the tumor or the host's blood cells.
- Plasma proteome changes occur following treatment, suggesting host reponse to ICI treatment.
- Analysis of differentially expressed proteins in patients receiving mono- and combo- therapy modalities suggests therapy-specific mechanisms of resistance.
- Our study demonstrates the potential clinical utility of analyzing proteomic changes in the plasma during ICI therapy, specifically for the discovery of novel predictive biomarkers for response in NSCLC patients.

The study was sponsored by OncoHost LTD.
YS is a co-founder of OncoHost and also serves as a consultant.

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Abstract Number: 300
e-Poster 74P