20P Identifying novel biomarkers with deep proteomics profiling and survival analysis in NSCLC patients treated with anti-PD-1-blockade

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Background: Use of immune checkpoint inhibitors in cancer therapy has significantly improved response and survival rates of patients with various cancer types including NSCLC. However, only a fraction of patients experienced clinical benefit. Existing predictive biomarkers are suboptimal especially when outcomes such as progression free survival (PFS) or overall survival are applied. Hence, the use of novel tools in precision medicine such as state-of-the-art proteomics using data independent acquisition mass spectrometry (DIA-MS) could address some of these drawbacks.

Methods: Proteins from plasma samples were extracted and analyzed by capillary flow liquid chromatography coupled to DIA-MS. They were identified and quantified with Spectronaut™ (Biognosys). Univariate statistical approaches were used to identify significantly changing proteins based on patient response status and progression free survival associated with endo toxicity. Relationships between proteins identified as significant and common for both outcomes were analyzed further using publicly available bioinformatics tools.

Results: 125 plasma samples from advanced-stage NSCLC patients treated with anti-PD-1 (75 baseline and 50 after 8-weeks treatment) were analyzed and more than 850 proteins were quantified. Protein signatures associated with response to anti-PD-1 treatment were combined with signatures associated to PFS. In addition, proteomic signatures related to toxicity (irAEs) were also analyzed. This study identifies potential prognostic and predictive biomarkers that will require further validation and highlights possible protein networks associated with anti-tumor immune responses.

Conclusions: Deep proteomic profiling of plasma samples using DIA-MS in conjunction with clinical outcome enables a holistic and stringent analysis of potentially predictive circulating biomarkers. This analysis provides functional insights into the plasma proteome that enables deeper understanding and comprehensive integration of clinical data with outcome to PD-1 blockade.

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21P Predictive immunological markers of anti-PD-1/PD-L1 therapy efficacy in non-small cell lung cancer

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Background: Immune checkpoint inhibitors (ICI) have become a new standard of treatment of patients with advanced non-small cell lung cancer (aNSCLC), but 60% of patients are resistant to the therapy. The aim of this study was to investigate the prognostic value of immunological markers in patients with aNSCLC receiving anti-PD-1/PD-L1 antibody.

Methods: The study included 2 groups: group 1- 45 patients receiving ICI in monotherapy in 2 and subsequent lines, group 2- 30 patients receiving first-line chemotherapy. Group 1 was divided into subgroups: response to therapy $\geq$6 months (n=26) and progression <6 months (n=19). In both groups there was no history of autoimmune diseases. In group 1, the determination of HLA-DRB1, neopterin (NPT), beta2-microglobulin (B2-MG), autoantibodies, IL-6, IL-18 was carried out after 2 months of starting therapy, and in group 2 this was done before the start of the next cycle of a platinum-based doublet.

Results: In patients in group 2, no autoantibodies were detected, and the level of B2-MG and NPT was lower than in patients in group1 ($p < 0.0001$). In group 1, the level of B2-MG was lower in patients with a duration of response to ICI $\geq$6 months, than in patients with progression <6 months: median was 1.7 mg/L and 2.9 mg/L, respectively ($p < 0.0001$). Progression-free survival (PFS) was lower in patients receiving ICI with high level of B2-MG ($\geq$2.5 mg/L) than in patients with B2-MG <2.5 mg/L: 168 days and not reached, respectively ($p = 0.017$). The level of NPT was lower in patients with response $\geq$6 months than in those with disease progression <6 months: 8.6 nmol/L and 13.4 nmol/L, respectively ($p < 0.0001$). PFS was shorter in patients with NPT $\geq$12 nmol/L than in patients with NPT <12 nmol/L: 164 days and not reached, respectively ($p = 0.0007$). HLA-DRB1*03 and anti-TPO was associated with response $\geq$6 months ($p = 0.0156$ for each marker). HLA-DRB1*03 was associated with longer PFS compared with other allelic variants: not reached versus 224 days, respectively ($p = 0.028$). Higher levels of IL-6 and IL-18 were observed in patients receiving ICI with early progression than in patients with a response of $\geq$6 months and in patients in the comparison group ($p = 0.001$ and $p < 0.0001$, respectively).

Conclusions: Immunological markers allow prediction of response to ICI in patients with aNSCLC.

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22P Comprehensive statistical analysis of predictive markers to immune checkpoint inhibitors in patients with non-small cell lung cancer

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Background: Immune checkpoint inhibitors (ICI) improved survival of non-small cell lung cancer (NSCLC) patients. As not every patient will respond to this treatment, finding predictive markers is crucial. Differently used statistical tests can however mask the real impact of such markers; here, we applied advanced statistical approaches to identify markers of response to ICI.

Methods: Data were collected from 182 stage IV NSCLC patients treated either in first line (FL) or after first line (AFL) with ICI including 16 variables: age, sex, histology, smoker, use of metformin, steroids, antibiotics, non-steroidal anti-inflammatory drugs (NSAR), PD-L1 expression, treatment (ICI, ICI + Chemotherapy), BMI, lymphocytes, neutrophils, monocytes, basophils, eosinophils. Correlations were made with response to therapy at three months, immune adverse events (iAE) and on overall survival (OS). Cox Proportional Hazard regression, Logistic Regression, Wilcoxon test and Random Forest were used, as well as multiple testing correction with respect to influential observations and assumptions of the methods.

Results: In the AFL cohort, increased eosinophils, basophils and steroid treatment were associated to response at three months and increased basophils were associated with iAE, but, after p value adjustment, basophils were only predictive for response at three months. In the FL cohort, no variable was associated to response at three months or iAE in any model. For OS, increased lymphocyte counts, higher PD-L1 expression and a positive smoking status associated with improved survival in the AFL cohort, but significance was lost after adjustment. In the FL cohort, increased lymphocyte count and use of NSAR associated with improved survival but significance was lost after adjustment. After removing of influential observations, NSAR and lymphocytes turned to be significant even after adjustment.

Conclusions: This study underlines the importance of interpretation of data through comprehensive statistical analysis. These results might generate research hypothesis, regarding the role of basophils in patients with NSCLC treated with ICI and eventually play a role in patients' stratification for clinical studies.

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