Identifying predictive biomarkers for long-term response on immunotherapy in NSCLC

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RESULTS

Clinicopathologic characteristics at baseline in the NSCLC patients under study

CONCLUSIONS and PERSPECTIVES

Comparison of clinicopathologic characteristics of NR versus LTR NSCLC patients collected before ICI showed no significant differences. In contrast, RNAseq analysis of primary lung tumor biopsies showed that 274 genes were significantly differentially expressed between both groups (Log2 fold change). To characterize how this impacted the use of specific metabolic processes, we performed gene ontology analysis. We found a specific downregulation of several UGT and AKR family members, involved in glutathione synthesis and detoxification respectively. We further confirmed their upregulation in lung tumor tissue from a TCGA-derived lung adenocarcinoma cohort. Finally, Kaplan-Meier analysis showed a prognostic value for low expression of two genes, indicative for their potential to be used as predictive biomarkers for ICI.

For further elucidation of the impact of downregulated UGT and AKR gene expression in lung tumors on response to immunotherapy, we plan to perform DNAseq analysis using a large capture-based panel to investigate specific mutations next to tumor mutational burden. Moreover we plan to include more patients via a prospective study.

Volcano plots: 274 differentially expressed (DE) genes. 

Volcano plot displaying DE genes when adjusted p-value < 0.05 and |Log2FC| > 2.

Red dots indicate genes upregulated in Long-term Responders (LTR) (n=3) compared to Non-Responders (NR) (n=4).

Volcano plot displaying DE genes when adjusted p-value < 0.05 and |Log2FC| > 2.

Top 5 results of GO analysis on downregulated DE genes

q-value cut-off < 0.25 indicates processes as significantly affected in LTR compared to NR.

Network plot shows top 5 downregulated Metabolic Biological Processes analyzed via GO analysis

Kaplan Meier plots identify two genes with a prognostic impact in stage III and IV LUAD patients

Gene expression cut-off was calculated via selected rank statistics using the survminer package in R. P-value was calculated using a log-rank test.

Volcano plot on DE genes linked to GO analysis

Heatmap of DE genes linked to GO analysis

Conclusions and perspectives

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Data availability

All data are available in the supplementary file.

COI: None with regards to this study

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RATIONAL

Although immunoecheckpointinhibitors (ICI) became standard of care in NSCLC stage IV, either alone or in combination with chemotherapy, responses are heterogeneous. Currently, the PD-L1 tumor proportional score is an approved predictive biomarker for ICI yet both long-term responders as non-responders have been observed within the PD-L1+ group. Due to the complex interactions between tumor cells, the tumor microenvironment and host immunity, a multidimensional profile should be developed to integrate complementary predictive biomarkers for ICI.

STUDY DESIGN

In the present retrospective single-center study, we compared clinicopathologic and bulk RNAseq data from the following two PD-L1+ (> 50%) NSCLC cohorts:

1) non-responders with complete lack of response (NR, N=4)
2) long-term responders with complete and maintained metabolic remission after immunotherapy cessation (LTR, N=3)

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