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PREDICTING RESPONSE TO IMMUNE CHECKPOINT INHIBITORS (ICI) IN NON-SMALL-CELL LUNG CANCER (NSCLC) BY COMBINING SPATIAL ANALYSIS OF CELLS AND RNA SEQUENCING DATA FROM BIOPSIES USING DEEP LEARNING (DL)

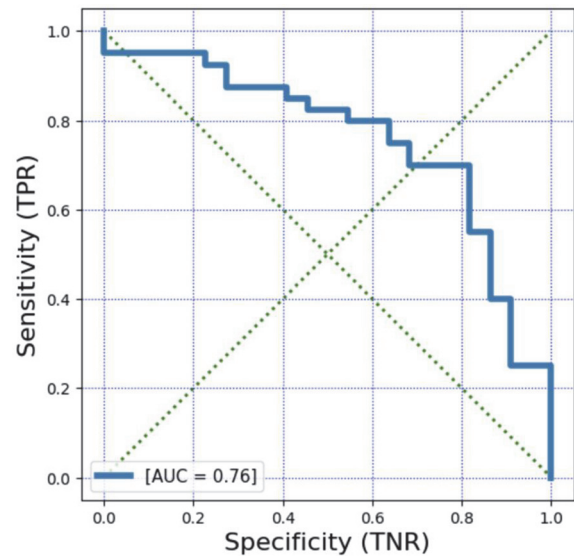
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Background ICI have transformed treatment of metastatic NSCLC, however, only a small proportion of patients respond. Spatial biology plays a significant role in further understanding the complexities of the tumor microenvironment and drivers of response to ICI. Here, we utilized DL to analyze whole slide images (WSI) of sequential biopsies stained for H&E and five IHC stains and combined it with RNA sequencing data to identify features associated with response to ICI.

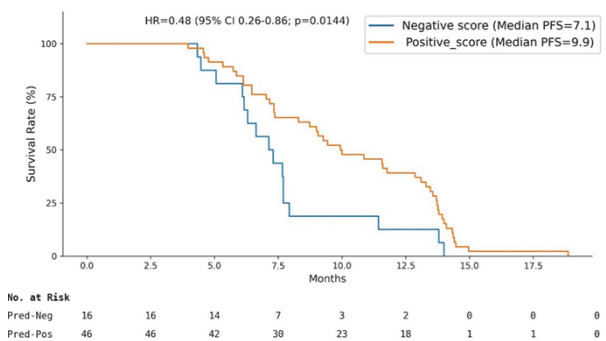
Methods 103 NSCLC patients treated with second line ICI were procured. For each patient, a total of 12 WSI from pre- and post-treatment biopsies, sequentially stained for H&E, CD3, CD8, CD163, CD137 and PD-L1 IHC were analyzed. RNA sequencing data of pre-treatment biopsies from 81 patients were also analyzed. Endpoints included overall response rate (ORR) and progression-free survival (PFS). DL models were trained to classify tumor cells, lymphocytes, fibroblasts, and tumor versus stromal areas from H&E, and positivity of IHC markers per cell. Based on biological hypotheses, 362 spatial and 72 RNA features were pre-defined and calculated for each patient. Univariate analysis identified features associated with clinical outcomes and the best performing features were selected to generate a binary classifier for response prediction. Cross-validation was performed.

Results Multiple spatial and RNA features were significantly correlated with ORR and PFS. Responders had greater density of CD3 in the invasive margin and closer proximity between PD-L1+ tumor cells and CD8+ cells in pre-treatment biopsies compared to non-responders ($p < 0.01$). Gene set enrichment analysis identified upregulation of hallmark TNF-alpha signaling and IFN gamma response genes in responders to ICI pre-treatment ($p < 0.0001$). When comparing pre- and post-treatment biopsies, responders had greater increases in density of CD8+ cells in the tumor microenvironment following ICI ($p = 0.02$). The resulting classifier combined 7 spatial and 3 RNA features and reached an AUC=0.76 when correlated with ORR (figure 1). 62 patients with both RNA and spatial features were classified as positive ($n=46$) or negative ($n=16$). In a Kaplan-Meier (KM) analysis, PFS was significantly longer in positive-scored compared to negative-scored patients (HR=0.48, 95% CI 0.26-0.86, $p < 0.02$) (figure 2).

Conclusions DL for spatial analysis of cells combined with pathway modulation, as measured by RNA sequencing can elucidate unique tumor contexture relevant for response to ICI in NSCLC.



Abstract 1289 Figure 1 AUC and ROC curve of the predictive binary classifier



Abstract 1289 Figure 2 KM analysis of PFS in patients with positive vs. negative prediction score

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