Predicting Response to Pembrolizumab in Non-Small-Cell Lung Cancer by Analyzing the Spatial Arrangement of Tumor-Infiltrating Lymphocytes (TILs) Using Deep Learning

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INTRODUCTION

- Only a small proportion of Non-Small-Cell-Lung-Cancer (NSCLC) patients derive durable benefit from treatment with immune checkpoint inhibitors (ICI)
- PD-L1 score is the only approved biomarker to select NSCLC patients for treatment with single-agent ICI, however, its predictive value is limited
- The spatial arrangement of immune cells in the tumor microenvironment (TME), emerges as a potential biomarker for ICI efficacy in NSCLC
- We utilized deep-learning (DL) models to extract TME features from digitized H&E slides and evaluated their predictive role in patients with NSCLC treated with Pembrolizumab

METHODS

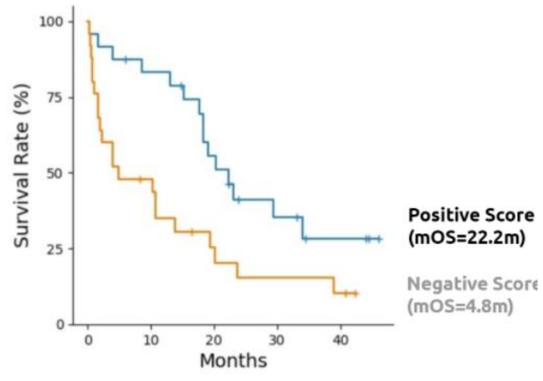
- NSCLC patients (n=92) treated with single-agent 1st line pembrolizumab in two medical centers were identified
- 49 patients from one center were used for training, and 43 patients from another center were used for validation
- Pre-treatment H&E whole slide images were analyzed using a deep-learning model to identify and classify tumor cells, TILs, tumor and stromal areas, and spatial features were calculated
- We used 1-year overall survival (OS) to determine durable clinical benefit; spatial and clinical features were combined to train a binary classifier that identifies patients with a favorable clinical outcome
- The classifier was then applied to the validation set and differences in OS between patients with positive and negative scores were assessed

RESULTS

- The trained classifier combined three spatial features, such as the average proximity between tumor cells and TILs, as well as three clinical features
- Median score was used to determine positive or negative patients
- In a cross-validation on the training set, patients with positive score had a significantly higher median OS (mOS) than patients with negative score (HR=0.43, 95% CI 0.22-0.83;p=0.01)
- The classifier was then applied to the validation set, dividing patients to either positive (n=18) or negative (n=25) scores
- Baseline patient characteristics and PD-L1 score were similar between the positive and negative groups.
- In a Kaplan-Meier (KM) analysis, OS was significantly higher in patients with a positive score compared to patients with a negative score (HR=0.35, 95% CI 0.13-0.98; p<0.05).
- **Positive patients had a significantly higher median OS (NR vs.17.8m, p<0.05) and 2-year OS (70.8% vs. 33%, p=0.02) than negative patients.**

KM analysis of the training set

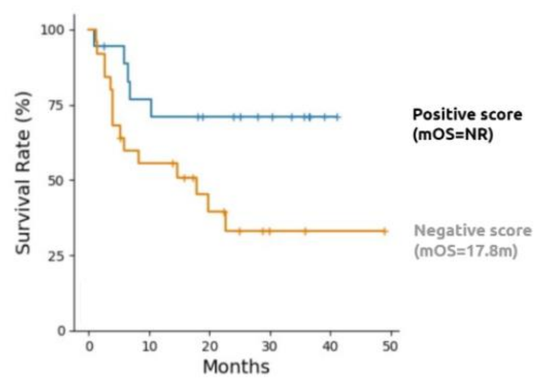
HR=0.43 (95% CI 0.22-0.83; p=0.01)



No. at Risk						
Positive Score	24	19	12	6	3	0
Negative Score	25	11	5	3	2	0

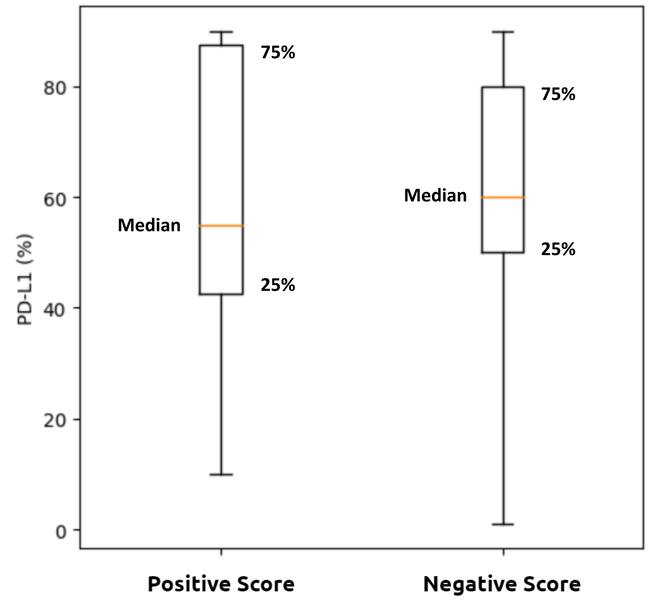
KM analysis of the validation set

HR=0.35 (95% CI 0.13-0.98; p<0.05)



No. at Risk						
Positive score	18	13	10	7	1	0
Negative Score	25	13	7	2	1	0

RESULTS (Continued)



- PD-L1 scores were similar between patients with positive and negative DL-based spatial scores (p=0.9)

CONCLUSIONS

- Deep-learning models that analyze the TME from H&E whole-slide images can identify NSCLC patients with durable benefit on Pembrolizumab.
- Identifying NSCLC patients who are exceptionally sensitive to anti-PD-1 therapy as monotherapy may improve clinical decision making and spare patients the unnecessary adverse effects associated with the addition chemotherapy or another IO agent.

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