Predicting response to pembrolizumab in Non-Small-Cell Lung Cancer 
Using Spatial Analysis of Biopsy Images by Deep Learning

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**INTRODUCTION**  
- While immune checkpoint inhibitors (ICIs) have transformed the therapeutic landscape in advanced Non-Small-Cell Lung Cancer (NSCLC), only a small proportion of patients (pts) derive durable clinical benefit (DCB) from treatment with ICIs.  
- Programmed death ligand 1 (PD-L1) score is the only approved biomarker to select NSCLC pts for treatment with single-agent ICI; however, its predictive value is limited.  
- The spatial arrangement of immune cells in the tumor microenvironment (TME) has emerged 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 NSCLC pts treated with pembrolizumab.

**METHODS**  
- NSCLC pts (n=76) treated with single-agent 1st line pembrolizumab in four medical centers were identified.  
- 57 pts were used for training; 19 pts were used for validation.  
- Pre-treatment H&E whole slide images (WSI) were analyzed using two DL models trained on pathologists’ annotations to identify and classify tumor, immune and fibroblast cells, as well as tumor, necrotic and stromal areas; 72 spatial features were calculated.  
- We used 1-year progression-free survival (PFS) to determine DCB and correlated it with the spatial features to train a binary classifier to identify pts with DCB.  
- The classifier was then applied to the validation set and differences in DCB, PFS and OS between pts with positive and negative scores were assessed.

**RESULTS**  
- Baseline pts characteristics were similar between the training and validation sets including age, gender, histology, ECOG PD-L1 score and DCB rate.  
- The spatial arrangement of immune cells in the tumor microenvironment (TME) has emerged as a potential biomarker for ICI efficacy in NSCLC.

**CONCLUSIONS**  
- DL models that analyze the TME from H&E WSI images can identify NSCLC pts with DCB on pembrolizumab.  
- Identifying NSCLC pts who are exceptionally sensitive to ICI as monotherapy may improve clinical decision making and spare pts the unnecessary adverse effects associated with the addition chemotherapy or another IO agent.

**REFERENCES**  
- The resulting classifier included three different features related to the arrangement of immune cells and tumor cells and to the necrotic area, and the median value was used to determine positive or negative score for pts in the validation set.  
- In a Kaplan-Meier (KM) analysis, PFS was significantly higher in pts with a positive score compared to pts with a negative score (HR=0.29, 95% CI 0.087-1; p<0.05). Positive pts had a significantly higher median PFS (NR vs. 7.33 months; p=0.05) and 1-year PFS (67% vs. 22%; p=0.05) than negative pts.  
- Pts with positive score had a trend for a higher OS than pts with negative score (HR=0.39, 95% CI 0.076-2; p=0.07) as well as a higher median OS (NR vs. 11.8 months; p=0.07) and 1-year OS (89% vs. 44%; p=0.07).  
- The spatial arrangement of immune cells in the tumor microenvironment (TME) has emerged as a potential biomarker for ICI efficacy in NSCLC.