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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

	train (n=57)	validation (n=19)	p-value
Adenocarcinoma (%)	46 (81%)	17 (89%)	**0.5**
DCB (%)	32 (56%)	10 (56%)	**0.8**
Female (%)	19 (33%)	8 (42%)	**0.58**
Age (mean±SD)	68.39 (±12)	68.23 (±13)	**0.96**
Pack years (mean±SD)	47.5 (±29.7)	43.4 (±31.6)	**0.61**
ECOG≥2 (%)	12 (21%)	2 (10.5%)	**0.5**
PD-L1 score (mean±SD)	65.1 (±21.8)	62 (±21.8)	**0.59**

Patient characteristics of training and validation sets

- Baseline pts characteristics were similar between the training and validation sets, including age, gender, histology, ECOG PD-L1 score and DCB rate.
- The DL area segmentation model reached an accuracy of 81%-92% and the cell classification model reached an accuracy of 88%-96%, compared to pathologists' annotations.

Predicted

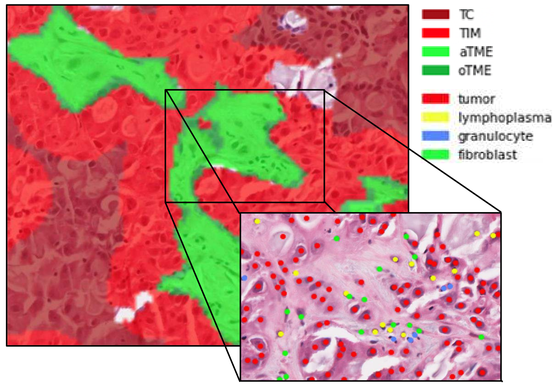
Reference	tumor	stroma	necrosis	other
tumor	90%	8%	2%	0%
stroma	6%	92%	1%	1%
necrosis	4%	8%	88%	0%
other	2%	16%	1%	81%

Accuracy of the area segmentations model

Predicted

Reference	tumor	fibroblast	lymphoplasma	granulocyte
tumor	96%	1%	2%	0%
fibroblast	6%	88%	6%	0%
lymphoplasma	1%	1%	96%	1%
granulocyte	1%	1%	8%	90%

Accuracy of the cell classification model



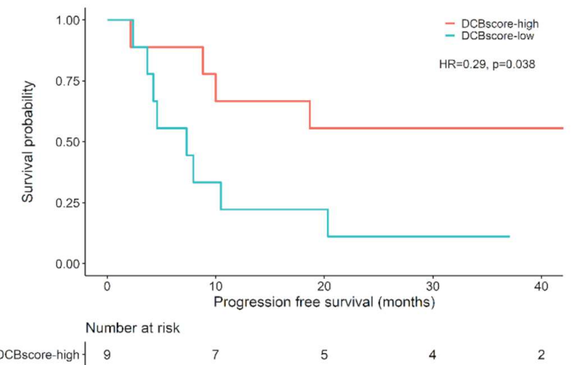
Visualization of the cell and area classifications models

***TIM=Tumor invasive margin - 40um wide region internal to the tumor-stroma border**

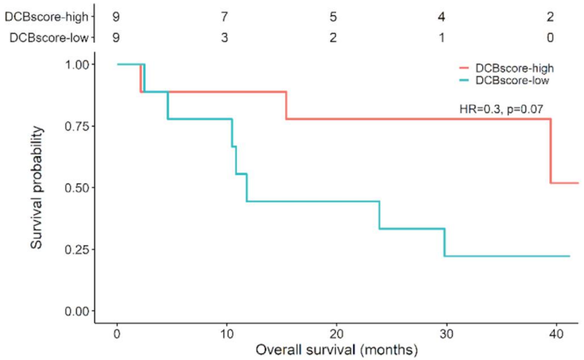
***TC=Tumor center – the area internal to the tumor invasive margin**

***aTME=Adjacent TME - 40um wide region external to the tumor-stroma border**

***oTME=Outer TME - the area outside the adjacent TME**



KM analysis of the PFS of positive vs. negative patients in the validation set



KM analysis of the OS of positive vs. negative patients in the validation set

- 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=0.3, 95% CI 0.076-1.19; 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).

CONCLUSIONS

- DL models that analyze the TME from H&E WSI 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.

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