NOVEL DIGITAL IMAGE APPROACH OF MULTIPLEX IMMUNOFUORESCENCE BASED PD-L1 EXPRESSION ENABLES THE STRATIFICATION OF ADVANCED NSCLC PATIENTS TREATED WITH DURVALUMAB

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Background: Pathologist-based scoring of PD-L1 expression on tumor cells using IHC has shown clinical utility in predicting favorable overall survival in advanced non-small cell lung cancer (NSCLC). Patients treated with anti-PD-(L)1 therapies including durvalumab, were stained by mIF panel containing PD-L1. Similarly to IHC PD-L1 QCS, mIF PD-L1 QCS consists of two deep-learning models, first to segment epithelium regions and second to detect membrane, cytoplasm and nuclei of each epithelium cell, transferring for the second model annotations from IHC to mIF domain. The mIF images are normalized based on batch statistics prior to image analysis. PD-L1 expression is measured for each epithelium cell as the average of the PD-L1 signal in the segmented membrane. Cells with expression higher than an expression threshold (TPD-L1) are considered positive. A slide is considered QCS-positive if it comprises a greater percentage of PD-L1 positive cells (QCS-score) than a cutoff value (CoV).

Methods: Pre-treatment tumor samples from advanced NSCLC patients enrolled in durvalumab nonrandomized phase 1/2 trial (CP1108/NCT01693562), were stained by mIF panel containing PD-L1. Similarly to IHC PD-L1 QCS, mIF PD-L1 QCS consists of two deep-learning models, first to segment epithelium regions and second to detect membrane, cytoplasm and nuclei of each epithelium cell, transferring for the second model annotations from IHC to mIF domain. The mIF images are normalized based on batch statistics prior to image analysis. PD-L1 expression is measured for each epithelium cell as the average of the PD-L1 signal in the segmented membrane. Cells with expression higher than an expression threshold (TPD-L1) are considered positive. A slide is considered QCS-positive if it comprises a greater percentage of PD-L1 positive cells (QCS-score) than a cutoff value (CoV).

Results: The QCS-scores are computed on 119 NSCLC patients treated with durvalumab. As a first proof of concept that QCS-scoring can replicate tumor proportion scoring (TPS), we optimize TPD-L1 as to maximize the correlation between QCS and TPS scores (figure 1). Second, we estimate for different combinations of (TPD-L1, CoV) the log rank p-value associated with the stratification between patients with low and high QCS scores. A subregion of the parameter space was identified for which the stratification is significant (p<0.01) with respect to prevalence and log-rank test p-value. We here present the extension of QCS to mIF measured by multiplex immunofluorescence (mIF) to evaluate its ability to optimize patient stratification.

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Conclusions: The extension of QCS to mIF imaging provides opportunities to evaluate continuous PD-L1 expression of single tumor cells in relation to spatial distribution of other cells (e.g. PD1+ CD8+ T cells) and identify predictive biomarkers of tumor-immune cell interactions of anti-PD-(L)1 therapies.

Trial Registration: CP1108/NCT01693562

REFERENCES:

Abstract 579 Figure 1: Correlation to pathologist-based TPS score Top: Lineplots of Pearson and Spearman correlations as well as of Lin correlation coefficient between the pathologist-based TPS scores and the QCS-based scores, computed for increasing expression threshold values (TPD-L1). The QCS shows maximum Pearson (0.856), Spearman (0.866) and Lin (0.856) correlations to the manual TPS score for TPD-L1 ≥ 10. Bottom: QCS scores within the negative and positive patient subgroups as per pathologist assessment of IHC PD-L1 TPS.

Abstract 579 Figure 2: OS patient stratification Log rank p-values for OS stratification obtained by spanning the parameter space associated to the QCS, the higher CoV the lower the prevalence of the positive patient subgroup. Top right: Kaplan Meier (KM) curves obtained with manual IHC PD-L1 TPS score at 25% cutoff
(dashed line) and with median split for the QCS expression cut-off (TPD-L1=10) maximizing the correlation to TPS (full line). Bottom: KM curves of the QCS-based stratification as to minimize the p-value (TPD-L1=37) for a minimum prevalence of 50% (left) and as to maximize the prevalence (TPD-L1=18) (right).