Background Immune checkpoint inhibitors (ICIs) targeting PD-1 or its ligand PD-L1 have shown clinical activity in patients with metastatic non-small cell lung cancer (mNSCLC). However, only subgroups of mNSCLC patients respond to ICI, while their robust and accurate identification using PD-L1 as a biomarker remains challenging. Typically, PD-L1 expression is assessed by pathologist scoring of immunohistochemically (IHC) stained tissue, e.g. using the tumor proportion score (TPS). However, this manual process is subjective and semi-quantitative. To this end, we aim to develop robust quantitative continuous scoring of PD-L1 expression via IHC (PD-L1 QCS), relying on digitized image analysis, with the aim of improving robustness of patient selection.

Methods QCS of PD-L1 (Ventana SP263) on digitized whole slide images (WSI) is approached by segmenting the tumor epithelium within a given region of interest. Here, a deep learning (DL) model segment individual tumor cells and their membranes. By applying color deconvolution, the resulting Optical Density (OD) provides a continuous measure of PD-L1 intensity on each cell membrane. The percentage of positive cells is derived by thresholding the OD, whereas the specific cut-point for stratification was obtained by optimizing on an exploratory cohort (samples from 163 mNSCLC patients treated with anti-PD-L1; NCT01693562) and validated for its robustness using an independent cohort (samples from 252 patients treated with anti-PD-L1; NCT02453282), for which IHC staining and WSI scanning were completed at a contract research organization (CRO).1,2 A second DL model segments individual tumor cells and their membranes. By applying color deconvolution, the resulting OD provides a continuous measure of PD-L1 intensity on each cell membrane. The percentage of positive cells is derived by thresholding the OD, whereas the specific cut-point for stratification was obtained by optimizing on an exploratory cohort (samples from 163 mNSCLC patients treated with anti-PD-L1; NCT01693562) and validated for its robustness using an independent cohort (samples from 252 patients treated with anti-PD-L1; NCT02453282), for which IHC staining and WSI scanning were completed at a contract research organization (CRO).1,2

Results On the exploratory cohort, pathologist TPS correlated favorably against PD-L1 QCS (Spearman R=0.86), confirming the validity of image analysis. PD-L1 QCS yielded a group of responders to anti-PD-L1 treatment with a significantly increased median overall survival (mOS) by 9.2 months (log-rank p=0.0017, HR=0.54, prevalence=46%). On the independent validation cohort, this finding was confirmed with an mOS increase of 9.9 months (log-rank p=0.0001, HR=0.55, prevalence=40%), although IHC for the second cohort was completed in a different laboratory and slides digitized with a different scanner.

Conclusions We describe a computational pathology approach for precise quantification of PD-L1 expression and selection of mNSCLC patients for anti-PD-L1 treatment using the Ventana SP263 assay. Importantly, we successfully validated the performance of our PD-L1 QCS solution in two independent clinical trial datasets, which were processed by different CROs using different scanners revealing broad applicability and thereby underscoring the potential of PD-L1 QCS to transform pathology.

Trials Registration NCT01693562, NCT02453282