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) region segmentation model is applied which was enriched with additional training data; expanding previous learning (DL) region segmentation model is applied which was optimized 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).3,4 A second DL model segments individual tumor cells and their membranes. By applying color deconvolution, the resulting Optical Density (OD) provides a continuous measurement 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 their membranes. By applying color deconvolution, the resulting Optical Density (OD) provides a continuous measurement 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).3,4

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.

Trial Registration NCT01693562, NCT02453282

REFERENCES

Ethics Approval Clinical studies NCT01693562 and NCT02453282, from which data in this report were obtained, were carried out in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocols, amendments, and participant informed consent documents were approved by the appropriate institutional review boards.