Background Small cell lung cancer (SCLC) is generally known to exclude immune cells and durable responses to immunotherapies are rare. Only very few biomarkers to inform immuno-oncology (IO) treatments are established in clinical practice thus far. Recently, four major SCLC subtypes (SCLC-A, SCLC-N, SCLC-P and SCLC-I) were described. Whereas the first three are characterized by activation of specific transcription factors, the SCLC-I (inflamed) subtype is characterized by an inflamed gene signature, high expression of MHC class I (MHC-I) antigen presentation and shows the greatest benefit from addition of immunotherapy to chemotherapy treatment [1,2]. Importantly, MHC-I is epigenetically silenced in the vast majority of SCLC and the presence of MHC-I could serve as a biomarker for the identification of SCLC-I cases. [2]. Here, we aimed to assess the biology of MHC-I high SCLC cases to investigate its role as a biomarker to inform cancer immunotherapies.

Methods We combined the power of artificial intelligence (AI)-driven computational pathology with multiplex immunofluorescence (mIF) to gain critical insight into the tumor microenvironment (TME) of SCLC. 125 SCLC formalin-fixed, paraffin-embedded tissue samples were stained with a mIF panel consisting of six markers: PanCK, CD8, CD68, PD-1, PD-L1, and Ki67. We assessed the phenotype and spatial location of each cell in the pathologist-annotated tumor center and within the AI-segmented stroma and tumor epithelium. Pathologists classified immunohistochemically stained MHC-I slides from the same tissue blocks as MHC-I high, medium, or low according to their H-scores (low: ≤30; medium: 31–139; high: ≥140). TME characteristics between those groups were compared.

Results In all measured regions, we found higher densities of CD8+ and particularly PD-1/CD8 double positive T-cells in the MHC-I high group. Moreover, we observed the highest proportion of PD-1 positivity among cytotoxic T-cells in the tumor epithelium of MHC-I high samples, which also showed a high density of PD-L1+ tumor cells. Average distance of PD-1+ T-cells to their nearest tumor cell was lowest in the MHC-I high group. Moreover, we observed the highest proportion of PD-1+ T-cells to their nearest tumor cell was lowest in the MHC-I high group. In the same group, an average of 19.3% a high density of PD-L1+ tumor cells. Average distance of PD-1+ T-cells to their nearest tumor cell was lowest in the MHC-I high group. Moreover, we observed the highest proportion of PD-1+ T-cells to their nearest tumor cell was lowest in the MHC-I high group. In the same group, an average of 19.3% of tumor cells in the epithelium had at least one PD-1+ T-cell within a 50 μm radius, while in the MHC-I low group this average was only 8.9%.

Conclusions We utilized cutting-edge computational pathology to establish MHC-I as orchestrator of the composition and spatial arrangement of an inflamed SCLC TME. Beyond that, our findings corroborate the role of MHC-I as a potential biomarker for inflamed SCLC cases, which benefit most from cancer immunotherapies.

REFERENCES