Background Renal cell carcinoma (RCC) is an immunologically paradoxical tumor. Despite high T cell infiltration, increased CD8+ T cells are not associated with response to programmed death 1 (PD-1) blockade. Through single-cell transcriptomic analysis, we previously identified a population of SLAMF7+ CD8+ exhausted T cells that was associated with resistance to nivolumab monotherapy in the HCRN GU16-260 trial (Braun, ASCO, 2023). In the present study, we generated a gene expression signature (GES) to capture the proportion of this SLAMF7+ T cell population and investigated the association of this GES with clinical outcomes in an external RCC cohort, CheckMate-025.

Methods For each gene in our bulk RNA sequencing (RNA-seq) expression matrix, we determined the Spearman correlation between the gene’s normalized expression level and the proportion of SLAMF7+ CD8+ T cells in patients with matched single cell (scRNA-seq) and bulk RNA-seq data (n = 7). Following z-scoring of all genes, we calculated the average expression of the twenty genes with the highest Spearman correlation coefficient to generate a GES score for all samples without matched scRNA-seq data in the HCRN GU16-260 cohort (n = 85). Both correlation and GES scoring included samples of clear cell and non-clear cell histology. GES scoring was repeated separately for patients receiving anti-PD1 monotherapy (nivolumab; n = 172) or mTOR inhibitor (everolimus; n = 109) monotherapy in the CheckMate-025 cohort.

Results Patients with progressive disease (PD) had higher GES scores than those with complete/partial response (CR/PR) in both HCRN GU16-260 (p=0.027) and the nivolumab arm of the CheckMate-025 (p=0.0058) cohort. Similarly, high (≥ median) scores were associated with worse progression free survival (PFS) (HCRN p=0.045, HR [95% CI] =1.72 [1.02–2.9]; CheckMate-025 nivolumab p=0.03, HR [95% CI] =1.62 [1.07–2.46]) in these cohorts. The same patterns were observed in clear cell and non-clear cell subsets of the HCRN GU16-260 cohort. Conversely, for the everolimus arm of CheckMate-025, there were no differences in scores between PD and CR/PR groups (p=0.4) or association with PFS (p=0.81, HR [95% CI] = 1.06 [0.65–1.74]).

Conclusions We present a GES characteristic of SLAMF7+ CD8+ exhausted T cells that is associated with worse clinical outcomes in patients receiving anti-PD1 monotherapy, but not in patients receiving mTOR inhibitor monotherapy. Future work will aim to validate our findings in additional external RCC cohorts, examine the applicability of our findings to additional cancer types, and experimentally interrogate the impact of SLAMF7 signaling on CD8+ T cell function.