Background Checkpoint inhibitors (CPIs) have revolutionized treatment for Merkel cell carcinoma (MCC) patients. However, about 50% of patients fail to respond, or relapse, necessitating alternative therapies. More than 80% of MCC cases are driven by oncoproteins derived from Merkel cell polyomavirus (MCPyV), which represents an ideal target for T cell immunotherapy. We hypothesize that resistance to CPI therapy could be overcome by transferring MCPyV-specific T cell receptor-engineered T (TCR-T) cells to patients.

Methods We isolated a highly avid TCR specific to a human leukocyte antigen (HLA)-A*02:01-restricted MCPyV epitope from pooled healthy-donor peripheral blood mononuclear cells. Five CPI-refractory HLA-A*02:01+ patients with advanced MCPyV+ MCC received autologous T cells lentivirally transduced with the anti-MCPyV TCR. Clinical responses were monitored by computed tomography and positron emission tomography scans. Tumor biopsies were collected before and after T cell infusions and subjected to single-cell RNA-sequencing (scRNA-seq) and immunohistochemistry (IHC) to characterize infiltrating T cells and tumor cells.

Results One of the five patients had 11 of 12 detectable lesions regress representing a partial response (PR). Both scRNA-seq and IHC demonstrated that the TCR-T cells infiltrated the remaining lesion. TCR-T cells highly expressed T cell activation- and exhaustion-associated genes. Multiple intratumoral TCR-T cells shared the same endogenous TCR clonotypes, indicating clonal expansion. However, in the escape lesion from the PR patient and in lesions from the four non-responding patients, IHC showed that tumor cells lacked class-I HLA expression. Whole exome sequencing found an intact HLA-A*02:01 locus in all five patients. scRNA-seq detected HLA downregulation in three tumor cell clusters in the escape lesion biopsy. The most HLA-downregulated tumor cell cluster upregulated genes that are associated with histone methylation, suggesting that epigenetic changes could underly the immune evasion from TCR-T cells.

Conclusions MCPyV-specific TCR-T cells showed anti-tumor activity in a CPI-refractory MCC patient. Primary and acquired treatment resistance correlated with downregulated class-I HLA expression across five patients. Our results demonstrate that this TCR-T cell strategy is a promising novel therapy for patients with advanced, CPI-refractory MCC. These data also reveal immune evasion mechanisms that could be counteracted by pharmacological upregulation of class-I HLA. We are currently testing this hypothesis in a clinical trial by combining interferon gamma treatment with TCR-T cells.

Trial Registration NCT03747484

Ethics Approval The protocol was reviewed and approved by the United States Food and Drug Administration and the Institutional Review Board at the Fred Hutchinson Cancer Center. A written informed consent was obtained from all study participants before enrollment.