Background Chimeric antigen receptor (CAR) T-cell therapy has shown clinical efficacy in hematologic cancers, but success is limited in solid tumors due to a lack of tumor-specific targets that distinguish cancer from normal cells and an immunosuppressive tumor microenvironment. Integrating synthetic biology and comprehensive molecular profiling of tumors may provide active and tolerable approaches to CAR T-cell therapy in patients with solid tumors.

Human leukocyte antigen (HLA) loss of heterozygosity (LOH) in tumors offers a definitive tumor vs normal discriminator target for CAR T-cell therapy. The Tmod platform is a modular logic-gated CAR T system comprising different versions including a carcinoembryonic antigen (CEA)- or mesothelin (MSLN)-targeting CAR activator and a separate blocker receptor targeting HLA-A*02 or other HLA alleles to protect normal cells. Compared with existing immunohistochemistry (IHC) tests, Tempus xT-Onco is a standard-of-care next-generation sequencing (NGS) assay that detects somatic alterations including HLA LOH and generates whole transcriptome RNA data (eg, CEA or MSLN expression) and a tumor immune infiltration profile, which can effectively identify patients appropriate for Tmod CAR T-cell therapy.

Methods HLA LOH in solid tumors was assessed with paired germine and somatic DNA sequencing. Common driver mutations, microsatellite instability status, and tumor mutational burden were examined in HLA-A LOH or HLA-A intact cohorts. Tumor expression of CEA and MSLN was evaluated via RNA sequencing and compared with immunohistochemistry (IHC) results.

Results A total of 21,053 tumor samples in the Tempus database were compared with their matched-normal samples. HLA-A LOH was detected in 16% of 10,867 advanced solid tumors (table 1) and similar LOH frequencies were observed among common HLA-A alleles. Clinical factors and molecular biomarkers were similar between HLA-A LOH and HLA-A intact cohorts. High CEA expression was seen in IHC-positive patients.

Conclusions The frequency of HLA-A LOH in solid tumors in the Tempus database is similar to that reported in the Cancer Genome Atlas. Tempus xT-Onco reliably detects HLA LOH and quantifies CEA and MSLN expression. Based on these data, patients with solid tumors are now being prospectively screened for HLA LOH using xT-Onco in an ongoing tissue banking study (BASECAMP-1, NCT04981119), preparing for future interventional protocols.

REFERENCES

Abstract 77 Table 1: Solid tumor samples (n) and HLA-A LOH frequency (%)