Background Surfaceome profiling of prostate cancer identified six transmembrane epithelial antigen of the prostate 1 (STEAP1) as a compelling prostate cancer-associated antigen. Adoptive transfer of chimeric antigen receptor (CAR) T cells has shown limited success in solid tumors, like prostate cancer due to the immunosuppressive tumor microenvironment (TME). Combining CAR T cell therapy with strategies that augment host immune responses and remodel immunologically “cold” TMEs may represent a promising treatment strategy for metastatic castration-resistant prostate cancer (mCRPC).

Methods We evaluated differences in the patterns of STEAP1 and prostate-specific membrane antigen (PSMA) expression using lethal mCRPC tissue microarrays. Second-generation STEAP1 CAR T cell therapy was developed and tested for its antitumor potency in various human prostate cancer disseminated mice models. We also generated a humanized STEAP1 knock-in (hSTEAP1-KI) mouse model and tested the potency and safety of murine STEAP1 CAR T cells. Systemic administration of a collagen binding domain-IL-12 (CBD-IL-12) fusion cytokine in combination with STEAP1 CAR T cells was assessed as a strategy to potentiate anti-tumor responses.

Results STEAP1 was found to be broadly expressed in ~87% of lethal mCRPC tissues compared to PSMA in 60%. CAR T cells targeting STEAP1 showed anti-tumor efficacy in various disseminated models tested with complete responses in the C4-2B model and substantial tumor growth inhibition in the 22Rv1 model with evidence of antigen loss in residual tumors. Mouse-in-mouse studies in hSTEAP1-KI mice bearing RM9-hSTEAP1 tumors treated with murine STEAP1 CAR T cell therapy showed preliminary safety without gross toxicity or architectural disruption and increased T cell infiltration at sites of systemic hSTEAP1 expression. Transient anti-tumor responses and a modest survival benefit were observed with progressive tumors demonstrating loss of STEAP1 expression. Concomitant treatment with STEAP1 CAR T cells and CBD-IL-12 showed enhanced anti-tumor effects by engaging host immune cells and increased epitope spreading.

Conclusions We generated STEAP1 CAR T cell therapy with promising potency in preclinical prostate cancer models and preliminary evidence of safety. We highlight antigen heterogeneity and escape as a major mechanism of resistance to effective STEAP1 CAR T cell therapy in prostate cancer. A strategy of combining CBD-IL-12 together with STEAP1 CAR T cell therapy enhances anti-tumor responses by remodeling the TME and engaging host immunity.

Ethics Approval All mouse studies were performed in accordance with protocols approved by the Fred Hutchinson Cancer Center Institutional Animal Care and Use Committee and regulations of Comparative Medicine.