BACKGROUND
Adoptive cell therapy with ex vivo expanded tumor infiltrating lymphocytes (TIL) offers a potentially curative treatment for cancer. However, the immunosuppressive tumor microenvironment limits the effectiveness of TIL therapy. To address this medical need, we used our Immune-CRISPRomics® Platform to perform a series of genome-wide CRISPR/Cas9 screens to identify targets enhancing the ability of T cells to infiltrate and kill solid tumors in an in vivo setting. These screens identified SOCS1 as a top target that restrains T cell anti-tumor immunity. Based on these findings, we developed KSQ-001, an engineered TIL (eTIL) therapy created via CRISPR/Cas9-mediated editing of SOCS1 for the treatment of solid tumors.

METHODS
Genome-wide CRISPR/Cas9 screens were conducted in in vitro primary human T cells and TIL cultures and in in vivo primary mouse OT1 and PMEL-TCR-Tg T cells in syngeneic tumor models. The efficacy of surrogate murine KSQ-001 (mKSQ-001), in which the SOCS1 gene is inactivated by CRISPR/Cas9 in OT1 or PMEL-TCR-Tg T cells, was evaluated in both the B16-Ova and CRC-gp100 syngeneic tumor models, with memory formation and efficacy evaluated both in the presence and absence of cyclophosphamide-mediated lymphodepletion. KSQ-001 was manufactured from human TIL using SOCS1-targeting sgRNAs selected for therapeutic use based on potency and selectivity, with KSQ-001 characterized for in vitro function and in vivo anti-tumor efficacy.

RESULTS
Upon adoptive transfer of a single dose into solid tumor-bearing hosts, mKSQ-001 was found to robustly enhance anti-tumor efficacy and eradicate tumors in 7/10 mice in the PD1-sensitive OT1/B16-Ova model and to drive responses in the PD-1 refractory PMEL/CRC-gp100 syngeneic tumor model. mKSQ-001 also showed a ten-fold increase in anti-tumor potency in vivo compared to unengineered T-cell product and established durable anti-tumor memory by persisting in the form of T central memory cells detectable at high frequency in the peripheral blood of complete responder mice. In the setting of lymphodepletion, mKSQ-001 also displayed heightened anti-tumor potency, accumulation, and memory formation in comparison to inactivation of PD-1. Importantly, human KSQ-001 displayed a transcriptional signature indicative of increased anti-tumor function, produced increased amounts of pro-inflammatory cytokines, exhibited a hypersensitivity to IL-12 signaling, and demonstrated increased anti-tumor function both in vitro and in vivo solid tumor models.

CONCLUSIONS
Based on insights from our Immune-CRISPRomics® platform and demonstrated efficacy across multiple preclinical tumor models, we have developed KSQ-001, a novel eTIL therapy. These preclinical data support clinical testing of KSQ-001 in a variety of solid tumor indications.

http://dx.doi.org/10.1136/jitc-2021-SITC2021.186