Background
Despite recent advancements with immune checkpoint inhibitors (e.g., anti-PD1 inhibitors) many cancer patients develop treatment resistance, which supports the study of alternative approaches to induce potent and safe anti-tumor T cell responses. STAR0602 is a bifunctional antibody-fusion molecule that selectively activates and expands a sub-set of human αβ T cells expressing variable (V)b6 and b10 regions of the T cell receptor (TCR). STAR0602 simultaneously engages a novel, non-clonal mode of TCR activation with cytokine co-stimulation.

Methods
The prevalence of STAR0602-targeted Vb T cells in tumor-infiltrating lymphocytes (TILs) from human tumor tissues was investigated by flow cytometry and by interrogating TIL TCRseq data from a large cancer database. The effects of STAR0602 on T cells from healthy donors and cancer patients were assessed in vitro by flow cytometry and NanoString. Using high tumor mutational burden (TMB) and anti-PD1-insensitive murine and human models, we investigated anti-tumor activity, mechanism of action, and an enrichment strategy for patient trials. Finally, the pharmacokinetics (PK) and pharmacodynamics (PD) of IV STAR0602 were investigated in Cynomolgus monkeys.

Results
Presence of STAR0602-targeted Vb T cells were confirmed in tissue from a range of human tumors, and present as 10-12% of TILs. Stimulation of T cells with STAR0602 resulted in potent expansion with ~80% adopting a novel memory phenotype, and significant boosting of antigen-specific T cells. In human autologous tumor organoid models, STAR0602 induced potent expansion of TILs and killing of tumors, including several PD1 refractory tumors. Dose-related anti-tumor activity (100% cure rate with a murine surrogate (mSTAR0602)) in EMT6-bearing mice correlated with expansion of memory Vb CD8+ T cells. In Cynomolgus monkeys, IV STAR0602 induced robust expansion of Vb CD8+ T cells in blood, with limited cytokine release or expansion of Treg. These data were used to build a PK/PD model to simulate human pharmacology and design a first-in-human trial with an enriched patient population.

Conclusions
STAR0602 is a first-in-class T cell activator that targets subsets of the germline TCR repertoire that are enriched in TILs. STAR0602 potently expands both naive and antigen-specific human T cells. In PD1 refractory human and murine tumor models with a high TMB, STAR0602 and mSTAR0602 induce potent anti-tumor activity as monotherapy, mediated by selective expansion of Vb CD8+ memory T cells. This pharmacology was translated into monkeys with IV dosed STAR0602 and supports the design of a novel Phase 1/2 precision-oncology trial with STAR0602 planned to commence in 2022.