PRECLINICAL EVALUATION OF STAR0602, A NOVEL, FIRST-IN-CLASS ANTI-TCR VB TARGETED BISPECIFIC ANTIBODY WITH POTENT ANTI-TUMOR ACTIVITY FOR PD-1 REFRACTORY SOLID TUMORS

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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.