

1316 **A NOVEL CLASS OF T CELL-ACTIVATING ANTIBODY THAT SELECTIVELY TARGETS THE TCR B CHAIN TO PROMOTE ANTITUMOR ACTIVITY THROUGH ACTIVATION AND EXPANSION OF A NOVEL, POLYCLONAL EFFECTOR MEMORY T CELL SUBSET**

¹Andy Bayliffe*, ¹Zhen Su, ²John Wherry, ¹Jonathan Hsu, ¹Madan Katraggada, ¹Jacques Moisan, ¹Gurkan Guntas, ¹Karunya Srinivasan, ¹Jessica Lowry, ³Rajesh Chopra, ¹Roya Servattalab, ¹Wei Huang, ¹Jian Tang. ¹Marengo Therapeutics, Cambridge, MA, USA; ²University of Pennsylvania, Philadelphia, PA, USA; ³Apple Tree Partners, London, UK

Background Limitations with agents that enhance endogenous T cell responses to cancer, particularly in solid tumors, supports the study of alternative approaches. Directly targeting the variable (V) regions of the T cell receptor (TCR) is a novel approach to inducing T cell activation. STAR0602 is a bispecific antibody-fusion molecule that selectively activates and expands a subset of human $\alpha\beta$ T cells expressing the germline-encoded Vb6 and Vb10 TCRs that are enriched in tumor infiltrating lymphocytes. STAR0602 simultaneously engages a novel, non-clonal mode of TCR activation with cytokine co-stimulation.

Methods The effects of STAR0602 on activation and expansion of primary human T cells was assessed *in vitro* by flow cytometry, homogeneous time-resolved fluorescence, TCRseq, and NanoString. A murine surrogate (mSTAR0602) was tested in murine syngeneic tumor models with tumor re-challenge and cellular depletion studies to assess potential for long-term protection and cell-specific activities, respectively. EMT6 tumors were excised for IHC staining and phenotyping of tumor-infiltrating lymphocytes (TILs) using flow cytometry and scRNAseq/TCRseq.

Results *In vitro*, STAR0602 induced TCR signalling and IL-2R pathway activation in human T cells that preceded expansion of Vb6/Vb10 T cell subsets to 80-90% of the T cell compartment. Compared to controls, 80-90% of STAR0602-stimulated human T cells adopted a novel, activated central memory (T_{CM}) phenotype. In multiple syngeneic murine tumor models, mSTAR0602 monotherapy eradicated tumors, or led to substantial regressions (60-70% tumor growth inhibition) with long-term protection from tumor rechallenge. *In vivo* anti-tumor activity was dependent on the accumulation of Vb T cell subsets, and analysis of TILs showed expanded Vb T cells were almost exclusively polyclonal effector memory T cells (T_{EM}) or T_{CM} cells with minimal exhausted T cells or Tregs and were associated with a novel gene signature with upregulation of memory and effector programs, and downregulation of exhaustion pathways.

Conclusions STAR0602 is a first-in-class bi-specific fusion molecule that selectively binds and activates subsets of the germline TCR repertoire. *In vitro*, STAR0602 promotes a novel T cell phenotype with hallmarks of both effector and central memory cells, and *in vivo* mSTAR0602 demonstrates potent and durable single-agent anti-tumor activity in several solid tumor models that is dependent on expanded Vb T cells. The modulation of the tumor microenvironment (TME), striking increase in TCR diversity, and functional immune memory observed in murine models suggests that STAR0602 could remodel the adaptive immune response to solid tumors that are refractory to checkpoint inhibitor therapy, and thus represents a novel therapeutic strategy for patients.

<http://dx.doi.org/10.1136/jitc-2022-SITC2022.1316>