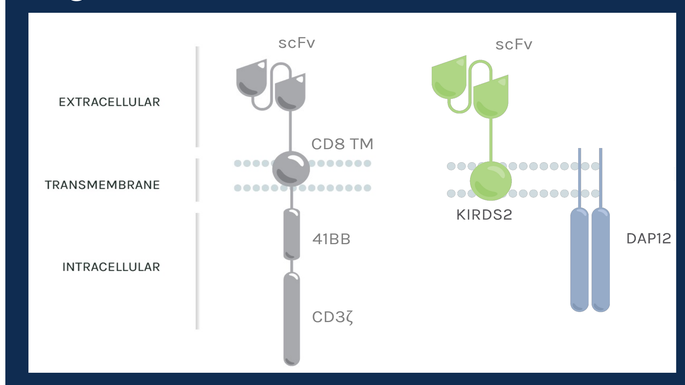
Abstract #TPS5630: SynKIR-CAR T cell Advanced Research (STAR)-101 Phase 1 clinical trial for patients with advanced mesothelin-expressing ovarian cancer, mesothelioma, or cholangiocarcinoma

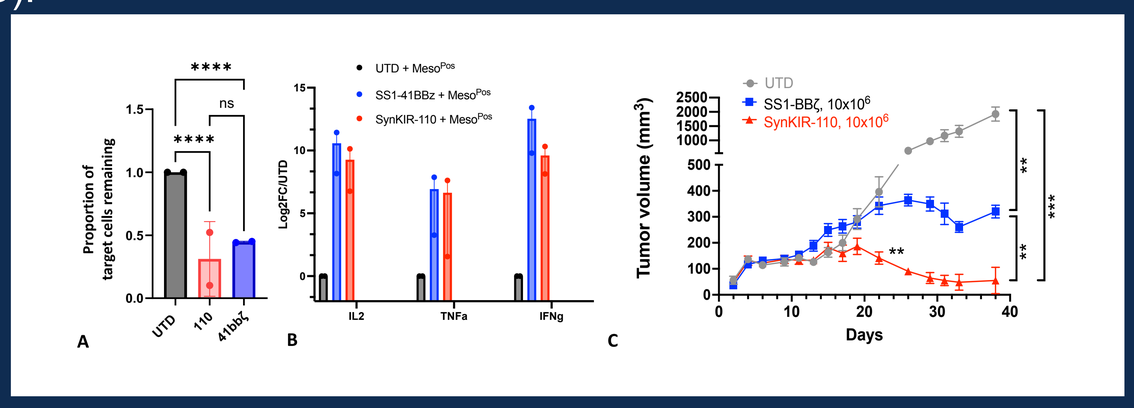
Authors: Janos L. Tanyi[1], Andrew R. Haas[1], Mark A. O'Hara[1], Mehmet Altan[2], Zhubin J. Gahvari[3], Raed Al-Rajabi[4], Donald L. Siegel[5], Daniel H. Sterman[6], Michael C. Milone[5], Susan K. Howard[7], Emily A. Winters[7], Andrea Campanile[7], Jun Xu[7] and Laura A Johnson[7]

Chimeric antigen receptor (CAR) T cells have been transformative in treating hematologic malignancies; however, they have not had the same impact in solid tumors. Previously, second generation CAR T targeting mesothelin with the SS1P scFv have been shown clinically to be safe, and demonstrated *early signs of tumor reduction in patients*, however those results were short lived, and lacked clinical benefit[1-3]. *CAR T failure in solid tumors has been largely attributed to lack of functional persistence and T cell* ***exhaustion.***

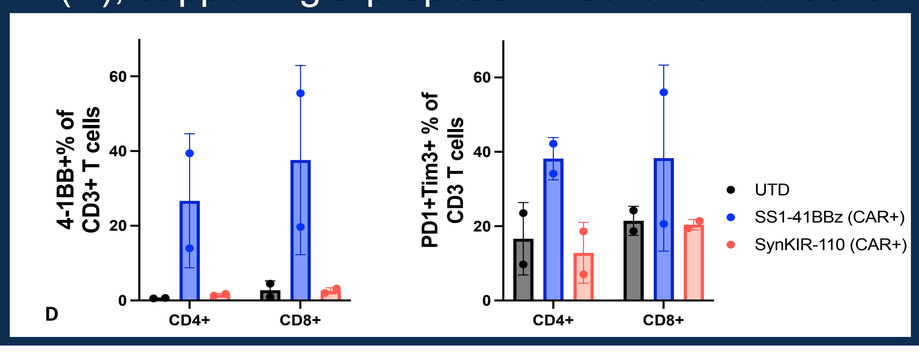
To reduce the exhaustion observed in CD3-based CAR T, we have generated a novel natural killer cell-based multi-chain *(KIR) signaling system that functions as a natural switch*, turning the T cell on only when and if the tumor target is engaged, *resting* when target is eliminated or released[4].



In vitro these SS1-KIR-CAR T cells (SynKIR-110) function the same as 2nd generation CD3-based single-chain CAR T, showing similar target lysis (A) and cytokine production (B) upon exposure to mesothelin-expressing tumors[5]. However, in *CAR-resistant mesothelioma mouse xenograft models,* ***SynKIR-110 markedly outperformed CD3-based CAR T,*** eliminating tumors where single-chain CAR T had minimal impact, in the absence of toxicity[6] (C).



At rest, SynKIR-110 T cells exhibit a *less-exhausted phenotype* ((PD1+Tim3+) with *less tonic signaling* (4-1BB) than single-chain CAR T[5] (D), supporting a proposed mechanism of action.



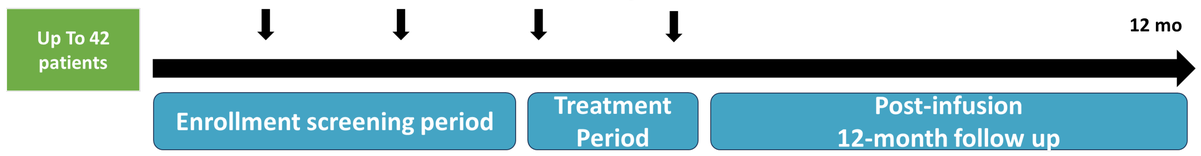
Background

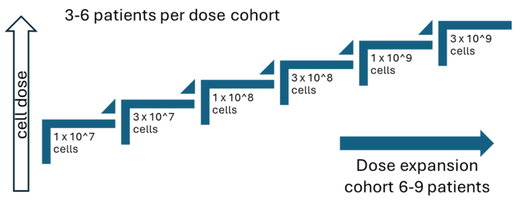
This is a Phase 1, FIH, multicenter, open-label, dose-escalation pilot study of a single IV gravity drip infusion of SynKIR-110 in subjects with advanced, mesothelin-expressing tumors (ovarian cancer, primary peritoneal cancer, fallopian tube cancer, cholangiocarcinoma, or mesothelioma). Up to 6 cohorts of 3 to 6 subjects per cohort will be assessed to determine the safety and feasibility of treatment with SynKIR-110. Doses will be escalated following a standard 3 + 3 design until either an MTD or MFD is reached. An additional 6 to 9 subjects will be treated at the MTD/MFD to further assess safety and potential activity of SynKIR-110. Up to 42 subjects will be assessed to determine the safety and feasibility of treatment with SynKIR-110.

Methods

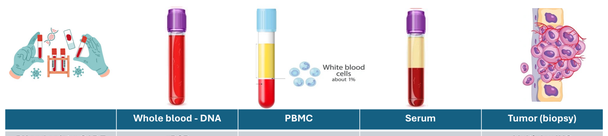
Patients with advanced ovarian cancer, mesothelioma or cholangiocarcinoma with ECOG 0-1, (m)RECIST-measurable disease, on <10 mg/d corticosteroid and having received at least 1 prior therapy, will receive an intravenous bolus of autologous, SynKIR-110 gene-modified T cells targeted to mesothelin on tumors, following a non-myeloablative lymphodepletion to enhance T cell engraftment and anti-tumor function.

Primary objectives include assessing safety and feasibility, with endpoints such as the incidence of treatment-emergent adverse events (TEAEs) and feasibility metrics. Secondary objectives aim to determine the maximum tolerated dose (MTD) or maximum feasible dose (MFD) and recommend a Phase 2 dose. Exploratory objectives include evaluations of best overall response (BOR) by iRECIST or mRECIST, overall survival, and SynKIR-110 persistence, phenotype, and immune impact. Biomarker data on pre-treatment tumor samples will be analyzed for potential correlates, for potential future patient selection markers.





STAR-101 Clinical Biomarkers



	Whole blood - DNA	PBMC	Serum	Tumor (biopsy)
PK and safety: CAR T Persistence	qPCR			Multiplex IHC
Exploratory: CAR T Phenotype	TCR sequencing	Flow cytometry		Multiplex IHC
PD: CAR T/tumor function			Cytokines by luminex	Multiplex IHC RNAseq/nanostring
PD: tumor response			Tumor specific antigens – ELISA (e.g., CA-125) ct/cfDNA (plasma)	Imaging (PET/CT or MRI)
Clinical Safety (Regulatory)	CAR T oncogenicity: clonality, insertion site analysis	RCL (replication competent lentivirus)	Immunogenicity (anti-CAR antibodies)	

Cohort 2 has been completed without DLT. Enrollment to cohort 3 began in April 2025. Clinical trial registry number NCT05568680

References and Acknowledgements

Author affiliations: *1. University of Pennsylvania Abramson Cancer Center, Philadelphia PA; 2. Thoracic/Head and Neck Medical Oncology, MD Anderson Cancer Center, Houston TX; 3. University of Wisconsin Carbone Cancer Center, Madison WI; 4. University of Kansas Cancer Center, Kansas City KS; 5. Department of Pathology & Laboratory Medicine and Center for Cellular Immunotherapies, University of Pennsylvania, Philadelphia PA; 6. New York University Perlmutter Cancer Center, New York NY; 7. Verismo Therapeutics, Philadelphia PA.*

References*: 1. Beatty GL et al. Cancer Immunol Res. 2014 Feb;2(2):112-20. 2. Haas AR et al. Mol Ther. 2019 Nov 6;27(11):1919-1929. 3. Beatty GL et al. Gastroenterology. 2018 Jul;155(1):29-32. 4. Wang E et al. Cancer Immunol Res. 2015 Jul;3(7):815-26. 5. Yucel N et al., Poster presentation at American Assoc of Immunol, 2025. 6. Xu J et al., Poster presentation at Society for Immunotherapy of Cancer, 2023.*

Trial contact information*: physicianconnect@verismotherapeutics.com*