SynKIR-CAR T Cell Advanced Research (STAR)-101 Phase 1 Clinical Trial for Patients with Advanced Mesothelin-expressing Mesothelioma, Ovarian Cancer, or Cholangiocarcinoma

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Objectives: Chimeric antigen receptor (CAR) T cells have transformed treatment of hematologic malignancies but have shown limited efficacy in solid tumors, due to T cell exhaustion and lack of functional persistence. Second-generation CD3-based CAR T cells targeting mesothelin have demonstrated safety and initial tumor reduction (1-3). SynKIR-110, a novel multichain natural-killer cell-signaling based CAR T therapy designed to overcome exhaustion via a natural on/off switch. In preclinical studies, SynKIR-110 outperforms second-generation CD3-based CAR T and eliminates tumors without observed toxicity in an established CAR T-cell-resistant mesothelioma xenograft mouse model (4-5). We have initiated a Phase 1 multicenter dose-escalation study (NCT05568680) to evaluate the safety, feasibility and preliminary efficacy of SynKIR-110 in patients with advanced mesothelin-expressing tumors, including mesothelioma, ovarian cancer, and cholangiocarcinoma.

Methods: This Phase 1 study is at multiple sites across the US. Subjects will receive non-myeloablative lymphodepletion (NMA-LD) with cyclophosphamide and fludarabine, followed by a single intravenous infusion of SynKIR-110. The study includes an enrollment screening period (which includes pre-leukapheresis safety/eligibility and leukapheresis visits), treatment period (NMA-LD followed by infusion of SynKIR-110), and a 12-month follow-up period. Up to six dose cohorts (3+3 design) of 3 to 6 subjects will be assessed. Primary objectives include safety and feasibility, with primary endpoints including the incidence of treatment-emergent adverse events and feasibility. Secondary objectives are to establish the maximum tolerated/feasible dose, with an expansion cohort to evaluated preliminary efficacy at the recommended phase 2 dose. Outcomes evaluated will include best overall response, survival, drug persistence, phenotype, immune impact, and correlation with tumor mesothelin levels, through exploratory biomarker analyses. Eligible subjects must have recurrent or relapsed epithelial pleural or peritoneal mesothelioma, ovarian cancer, or cholangiocarcinoma after at least one prior systemic therapy. Additional eligibility criteria include measurable disease by (m)RECIST, ECOG performance status of 0-1, and adequate organ and bone marrow function.

Results: As of May 2025, STAR-101 has completed enrollment of Cohorts 1-3 without observed dose-limiting toxicities (DLTs).

Conclusions: Based upon our preclinical studies, SynKIR-110 represents a promising approach to overcoming the limitations of CAR T cells in mesothelioma and other solid tumors.

References:

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