CT125:A Phase 1 Study to Evaluate the Safety and Tolerability of a Combination Autologous CD19 CAR T Cell Therapy (SYNCAR-001) and Orthogonal IL-2 (STK-009) in Subjects With Relapsed or Refractory CD19 expressing Hematologic Malignancies

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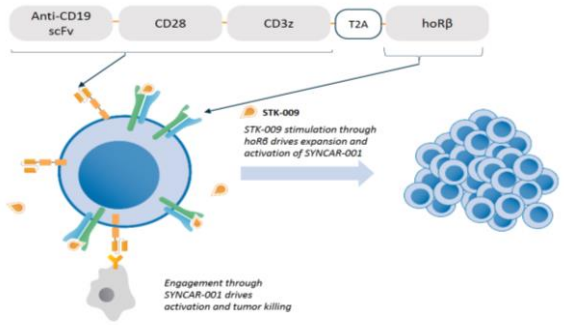
BACKGROUND

- Chimeric antigen receptor T cell therapy (CAR T) has demonstrated remarkable clinical efficacy in hematological malignancies.
- However, compromised T cell effector function, proliferation, and persistence can limit CAR T from reaching their full curative potential.
- Insufficient cytokine support for the CAR T cells is a fundamental limitation of CD19 CAR T cell therapies.
- SYNCAR-001 + STK-009 is a combination therapy incorporating 2 components: (1) an engineered IL-2 ligand (STK-009) and (2) a CD19 CAR T cell expressing a complementarily engineered IL-2Rβ (SYNCAR-001)
- SYNCAR-001 is a CD19-directed CAR T cell with a CD28 costimulatory domain and a CD3ζ activation domain which also bicistronically co-expresses an engineered human orthogonal IL-2Rβ (hoRb) as a separate surface bound protein.
- STK-009 is a half life extended hoIL-2 mutein that selectively signals through the hoRb expressed on SYNCAR-001 facilitating CAR T cell-specific expansion and persistence.

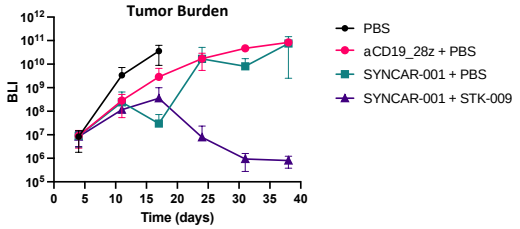
SYNCAR-001 Construct & Mechanism of Action



Pre-Clinical Rationale

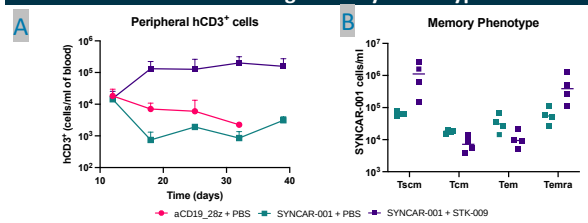
- In mouse models of refractory lymphoma, STK-009 treatment led to in-vivo expansion and activation of SYNCAR-001 cells with a maintenance of stem cell memory and effector T cell phenotypes.
- When added to SYNCAR-001, STK-009 increased complete response rate and durable responses in a dose dependent manner.
- In non-human primate studies, STK-009 alone demonstrated no significant biological activity in IL-2 sensitive populations (T cells or NK cells) and was tolerable without toxicity.

Figure 1: SYNCAR-001 + STK-009 Outperforms CD19_28z CAR T Cells In a Stress Test Mouse Model of Lymphoma



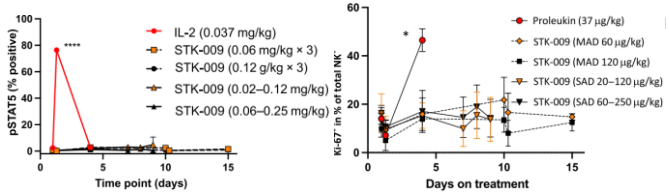
- Equivalent suboptimal doses of conventional αCD19_28z or SYNCAR-001 -/+ STK-009 were administered to mice bearing disseminated Raji lymphoma. CRs only obtained in mice receiving SYNCAR-001 + weekly doses of STK-009

Figure 2: STK-009 Expands and Maintains SYNCAR-001 While Maintaining Memory Phenotypes



- STK-009 treated mice (1 µg/week) exhibited more than a 10-fold increase of CAR T cells compared to control mice demonstrating that STK-009 is capable of selective in vivo expansion of SYNCAR T cells (A)
- In vivo expanded SYNCAR T cells were highly biased toward either CD45RA+ CCR7+ T cells (T_{SCM}) or CD45RA+ CCR7− T cells [effector T cells (T_{eff}/T_{EMRA})], representing long-term memory T cells and short-lived cytotoxic Teff, respectively (Day 25) (B)

Figure 3: STK-009 Safety In Non-Human Primates

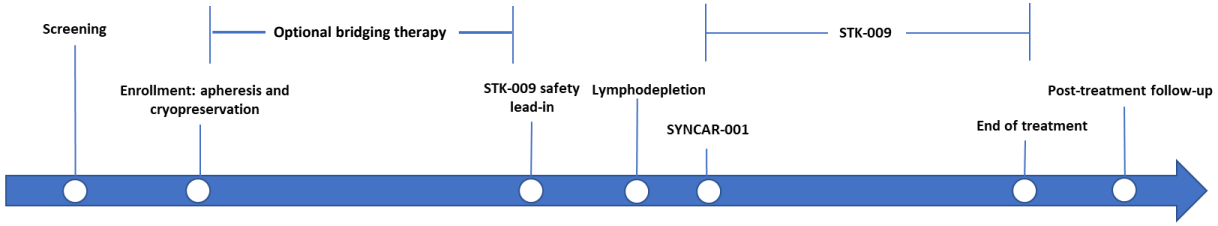


- WT hIL-2 induced phosphorylation of signal transducer and activator of transcription 5 (pSTAT5) in peripheral blood–derived IL-2Rα+ CD4+ T cells, whereas STK-009 did not
- STK-009 also did not activate cell populations correlated with IL-2–mediated toxicity including NK cells

STK-009-101 FIH STUDY

- This is a first-in-human, open-label, dose escalation study of combination SYNCAR-001 + STK-009 in adults with relapsed or refractory (r/r) CD19+ hematologic malignancies.
- The objectives of this study are to evaluate the safety, preliminary efficacy, pharmacokinetics, immunogenicity, and pharmacodynamics of SYNCAR-001 + STK-009.
- Dose escalation follows a standard 3+3 design with STK-009 being escalated while SYNCAR-001 is held at a single fixed dose.
- A dose extension will enroll a cohort of patients treated at a selected dose level and indication based on dose escalation findings.
- SYNCAR-001 is dosed intravenously (IV) once at Day 0 and STK-009 is dosed subcutaneously (SC) over the course of the study.

Study Design



Key eligibility criteria

- Age ≥18 years
- Histologically confirmed B cell malignancy (CLL/SLL, DLBCL, FL, MZL, MCL)
- CAR-T naive
- Measurable disease at enrollment
- Relapsed/refractory disease
- ECOG PS 0-2
- Adequate organ function

Study treatment

- A safety lead-in dose of STK-009 will be administered prior to lymphodepletion.
- Lymphodepletion (Day -5 to -3): Cyclophosphamide 300 mg/m^2/day and fludarabine 30 mg/m^2/day, administered ×3 days.
- SYNCAR-001 treatment (Day 0) consists of a single intravenous infusion
- After SYNCAR-001 initiation, STK-009 is dosed SC weekly for 12 weeks and then monthly for 3 months

Key end points

- **Primary**: Incidence of DLTs and safety to determine a recommended dose
- **Secondary**: Cellular kinetics, immunogenicity, ORR, DOR, PFS, OS

Study Information

- Recruitment for STK-009-101 dose escalation has been initiated.
- The trial is registered with Clinicaltrials.gov, NCT05665062

References

1. Aspuria et al., Sci. Transl. Med. 2021 Dec 22; 13 (625)