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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Poster # 3453

Rationale

- CAR-T cells have demonstrated compelling clinical efficacy in hematologic malignancies
- Compromised T cell function, expansion, and persistence can limit CAR-T cells from reaching their full curative potential
- Combining CAR-T cells with consistent cytokine support, such as with the master regulator IL-2, may boost their clinical utility
- While short-term IL-2 support can be used with cell therapies to promote expansion, prolonged use is impossible due to severe toxicities such as capillary leak syndrome

SYNCAR-001 and STK-009 design

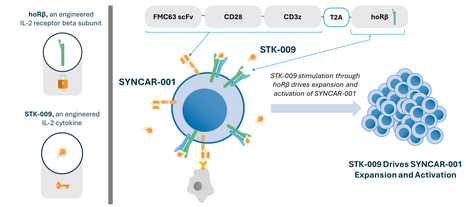
- **SYNCAR-001 + STK-009 is a combination therapy incorporating two components:**

a) An autologous CD19 CAR-T cell engineered with a mutated IL-2 receptor (SYNCAR-001)

b) An engineered IL-2 ligand (STK-009) that only binds through the mutated IL-2 receptor

- STK-009 may enhance CAR-T cell expansion, persistence, cytotoxic activity, and tumor infiltration

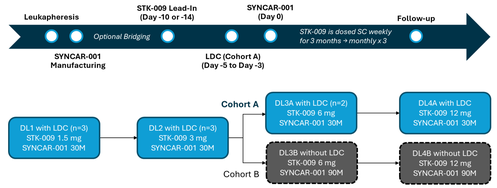
SYNCAR-001 + STK-009 mechanism of action[1–3]



Study design

- STK-009-101 (NCT05665062) is a first-in-human, dose-finding study of SYNCAR-001 + STK-009 in patients with relapsed/refractory (R/R), histologically confirmed B cell malignancies
- **Primary endpoint:** Identify dose-limiting toxicities (DLTs) and establish the recommended phase 2 dose (RP2D)
- **Secondary endpoints:** Cellular kinetics, immunogenicity, and efficacy

STK-009-101 study design



The study follows a standard 3 +3 design. STK-009 is administered SC once weekly for 12 doses followed by once monthly for three doses; a safety lead-in dose of STK-009 will be administered either 10 or 14 days prior to SYNCAR-001. **Cohort A:** STK-009 administered in escalating doses of 1.5, 3, 6, and 12 mg with a fixed dose of SYNCAR-001 (30M cells IV) following a cy/flu LDC regimen. **Cohort B:** STK-009 administered in escalating doses of 6 and 12 mg with a fixed dose of SYNCAR-001 (90M cells IV) without prior LDC.
IV, intravenous; LDC, lymphodepleting chemotherapy; SC, subcutaneously.

Results

Patient demographics

- **As of November 2024, 8 patients have been enrolled into Cohort A and received SYNCAR-001 + STK-009**
- All 4 CLL patients had features of poor prognosis including mutant TP53 (2/4), unmutated IGHV (3/4), del 17p (3/4), ≥3 chromosomal aberrations (2/4) and progression following BTKi and venetoclax (4/4)

Table 1: Baseline characteristics

Patient	1	2	3	4	5	6	7	8
Dose Level	DL1	DL1	DL2	DL3	DL1	DL2	DL2	DL3
Histology	CLL	CLL	CLL	CLL	MZL	MZL	FL → DLBCL	MCL
Age, years (sex)	59 (M)	67 (M)	70 (M)	67 (M)	56 (M)	64 (M)	61 (F)	65 (M)
Prior lines	5	5	6	5	4	2	3	4
SPD (mm^2) post-bridging	5300	1860	2160	9090	860	530	Not measurable	6260
LDH at Day 0 (IU/L)	996	501	705	341	158	202	357	140

CLL, chronic lymphocytic leukemia; DL, dose level; DLBCL, diffuse large B-cell lymphoma; Dx, diagnosis; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; LDH, lactate dehydrogenase; SPD, sum of the product of diameters.

Safety

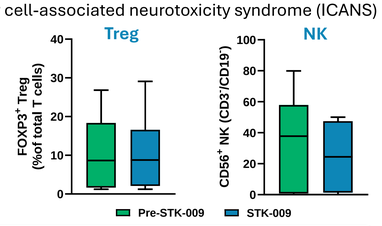
- **SYNCAR-001 + STK-009 was well tolerated with no DLTs observed**

Table 2: Adverse events

Study ID	1	2	3	4	5	6	7	8
Dose Level	DL1	DL1	DL2	DL3	DL1	DL2	DL2	DL3
Histology	CLL	CLL	CLL	CLL	MZL	MZL	FL → DLBCL	MCL
CRS	--	Grade 2	--	Grade 2	--	--	Grade 2	Grade 1
ICANS	--	--	--	--	--	--	Grade 1	--
STK-009 held	--	Yes	--	Yes	--	--	Yes	Yes
Tocilizumab received	--	Yes	--	Yes	--	--	Yes	Yes

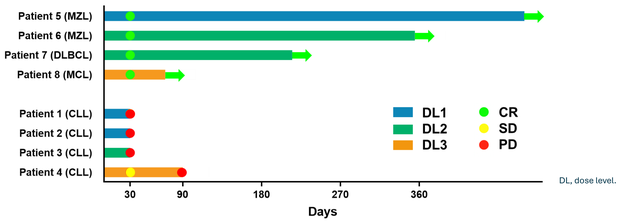
CLL, chronic lymphocytic leukemia; CRS, cytokine release syndrome; D, day; DL, dose level; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; ICANS, immune effector cell-associated neurotoxicity syndrome (ICANS); MCL, mantle cell lymphoma; MZL, marginal zone lymphoma.

- No IL-2-related toxicities were observed
- The majority of adverse events (AEs) were Grade 1 or 2; the most common AEs were cytopenias expected to occur with the lymphodepletion regimen
- Limited, mild–moderate cytokine release syndrome (CRS) was observed in 4 patients; immune effector cell-associated neurotoxicity syndrome (ICANS) was observed in 1 patient
- **No increase in natural killer (NK) cells or regulatory T (Treg) cells were observed with STK-009 treatment, suggesting native lymphocytes are not stimulated by STK-009**



Efficacy

Duration of best objective responses

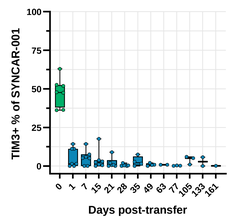


- **Best objective response (BOR) was complete response (CR) in 4 patients; 1 patient experienced stable disease (SD)**
- All 4 patients with non-Hodgkin lymphoma (NHL) exhibited a response and remain in durable CRs; the longest duration of CR is beyond 480 days

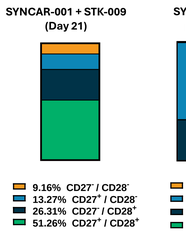
Translational data

- **STK-009 induced and maintained a SYNCAR-001 phenotype of more than 90% non-exhausted (TIM3-) and non-senescent ($CD27^+/CD28^+$) SYNCAR-001 cells, with a low proportion of senescent T cells ($CD27+/CD28^-$) present**
- STK-009 also sustained 25–50% central memory T cells

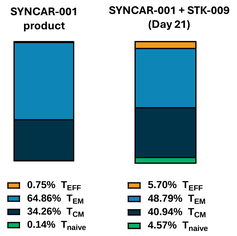
T cell exhaustion (TIM3)



Senescence

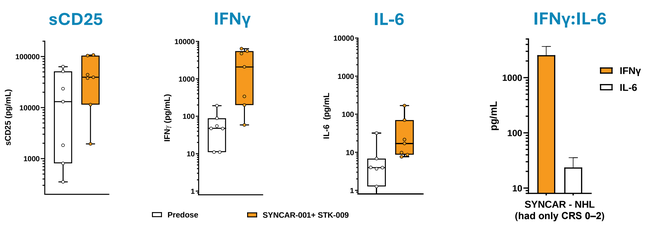


T cell subtypes



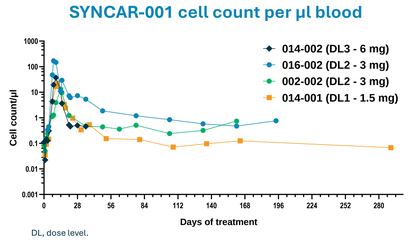
Mean of all patients presented; CLL plus NHL (n=8).
T_{naive}, naive T cells ($CD45RO^-/CCR7^+$); T_{CM}, central memory T cells ($CD45RO^+/CCR7^+$); T_{EM}, effector memory T cells($CD45RO^+/CCR7^-$); T_{EFF}, effector T cells ($CD45RO^-/CCR7^-$).

- **STK-009 preferentially induced CAR-T activation markers such as IFNγ and sCD25 with limited elevation of IL-6, yielding a favorable IFNγ:IL-6 ratio**



CRS, cytokine release syndrome; IFNγ, interferon gamma; IL-6, interleukin-6; NHL, non-Hodgkin lymphoma; sCD25, soluble interleukin 2 receptor α.

SYNCAR-001 cell count per µl blood



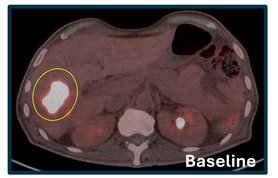
DL, dose level.

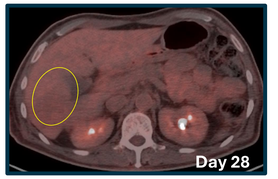
- **STK-009 mediated SYNCAR-001 expansion and persistence**

Case study 1: Patient 8

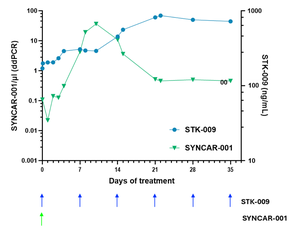
- **Patient with mantle cell lymphoma (MCL) and high disease burden**
- **Metabolic CR with 86% tumor regression at Day 28; response and treatment ongoing**
- **SYNCAR-001 expansion correlated with target-mediated clearance of STK-009**
- **Significant induction of IFNγ without induction of IL-6; sCD25 correlated with expanding SYNCAR-001**

Complete response observed after 28 days on therapy





SYNCAR-001 and STK-009 levels

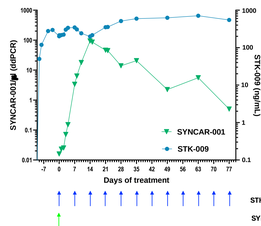


IFNγ, interferon gamma; IL-6, interleukin-6; NHL, non-Hodgkin lymphoma; sCD25, soluble interleukin 2 receptor α.

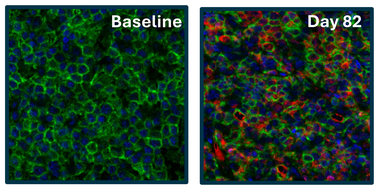
Case study 2: Patient 4

- **Patient with chronic lymphocytic leukemia (CLL) and high disease burden**
- **BOR of SD with 40% tumor regression at Day 28**
- **Progressive disease (PD) observed at Day 82**
- **Significant CAR-T expansion even despite high disease burden**
- **B cell aplasia observed until PD**
- **Day 82 biopsy showed strong infiltration of CAR-T cells into the tumor**

SYNCAR-001 and STK-009 levels



SYNCAR-001 tumor infiltration in CLL



Conclusions

- Favorable safety and efficacy signals were observed for STK-009 + SYNCAR-001 in patients with a fixed, low dose of 30M SYNCAR-001 cells
- No CRS or ICANS > Grade 2, no signs of IL-2 (STK-009) mediated toxicity on endogenous T cells; all 4 patients with NHL are in ongoing durable CRs, with the longest extending beyond 480 days
- Minimal exhaustion and senescence of SYNCAR-001 cells was observed up to 160+ days, and a central memory phenotype was sustained
- STK-009 is able to drive activation, expansion and persistence of SYNCAR-001 cells, and maintains SYNCAR-001 long-term memory
- Next steps: Treatment of non-lymphodepleted patients in heme and non-renal systemic lupus erythematosus/lupus nephritis studies

Poster presented at the 66th American Society for Hematology Annual Meeting, San Diego, December 7–10, 2024. For more information, please contact: nrizvi@synthekine.com.
The study was funded by Synthekine. Medical writing support was provided by Bioscript Group Ltd, Macclesfield, UK.

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