Clinical Trial in Progress: Evaluation of huCART19-IL18 Manufactured Using Synecta™ CDNP Technology to Improve CAR-T Yield and Consistency in Cohort D of an Ongoing Phase I Study (NCT04684563)

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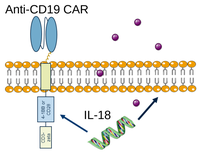
Background

Chimeric antigen receptor (CAR) T cells targeting CD19 have demonstrated substantial efficacy in B-cell malignancies, though durable responses remain limited in many patients. huCART19-IL18 is a fourth-generation, CD19-directed CAR T cell therapy engineered to secrete interleukin-18 (IL-18) to enhance antitumor activity by engaging both innate and adaptive immunity. In Cohorts A–C of the ongoing Phase I study (NCT04684563), huCART19-IL18 exhibited a manageable safety profile and encouraging antitumor activity in patients with relapsed or refractory non-Hodgkin lymphoma and chronic lymphocytic leukemia, as recently reported in *NEJM* (Svoboda et al., 2025; DOI: 10.1056/NEJMoa2408771). These cohorts employed a 3-day manufacturing protocol—significantly shorter than standard CAR T cell production timelines—which introduced challenges in consistently achieving target dose levels, particularly at higher planned dose cohorts.

Background

- Many patients receiving CD19 CAR treatment do not have long-term remission.
- A promising strategy is a fourth-generation "Armored CAR" to treat refractory disease.
- Armored with the capacity to secrete IL-18 and a humanized version of scFv.
- In addition, CAR T cells are manufactured in an expedited 3-day process, resulting in increased T cell stemness.



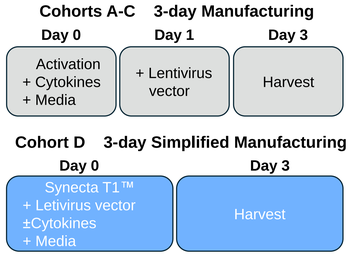
Data from cohorts A-C of the ongoing Phase I study have been recently published in NEJM. The expedited 3-day manufacturing process was successful at low dose levels, but higher dose levels showed an increase in manufacturing failures. To mitigate out-of-specification products, manufacturing started with high seeding densities (1.5 billion cells on average), resulting in high vector and reagent usage. Early de-beading process can raise the level of stress on T cells.

Manufacturing feasibility data by target dose levels

Dose Level (DL)	# Assigned to DL	# Infused at target DL	# Infused at non-target DL	# not infused	Total # of infused at this DL
DL 1 (3 x10^6)	3	3 (100%)	0	0	3
DL 2 (7 x10^6)	1	1 (100%)	0	0	4
DL 3 (3 x10^7)	7	5 (71%)	2	0	6
DL 4 (7 x10^7)	5	3 (60%)	1	1	5
DL 5 (3 x10^8)	6	2 (33%)	4	0	2

Study Objectives

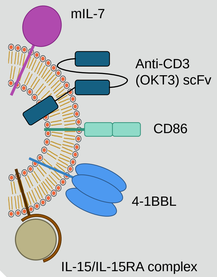
- Cohort D was initiated to evaluate a modified manufacturing process designed to improve cell expansion, transduction efficiency, and product consistency
- The new process incorporates Synecta™ Cell-Derived Nanoparticles (CDNPs), a reduced number of seeding cells (500 million), no de-beading, and Day 0 transduction



Synecta CDNPs are referenced in an FDA-reviewed Drug Master File

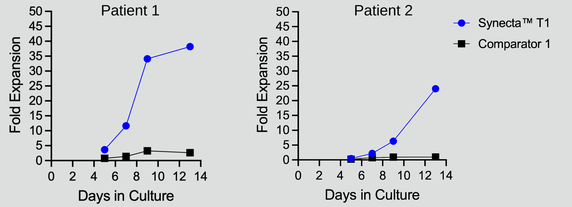
Primary	• To evaluate manufacturing feasibility using CDNPs with and without exogenous cytokines
Secondary	• Safety of huCART19-IL18 manufactured with CDNPs • Objective Response Rate (ORR) • Progression Free Survival (PFS) • Overall Survival (OS) • Duration of Response (DOR)
Exploratory	• Pharmacokinetics of huCART19-IL18 manufactured with CDNPs • Systemic Soluble Immune Factors • Immunophenotyping

Synecta™ T1 Cell-Derived Nanoparticles (CDNPs)



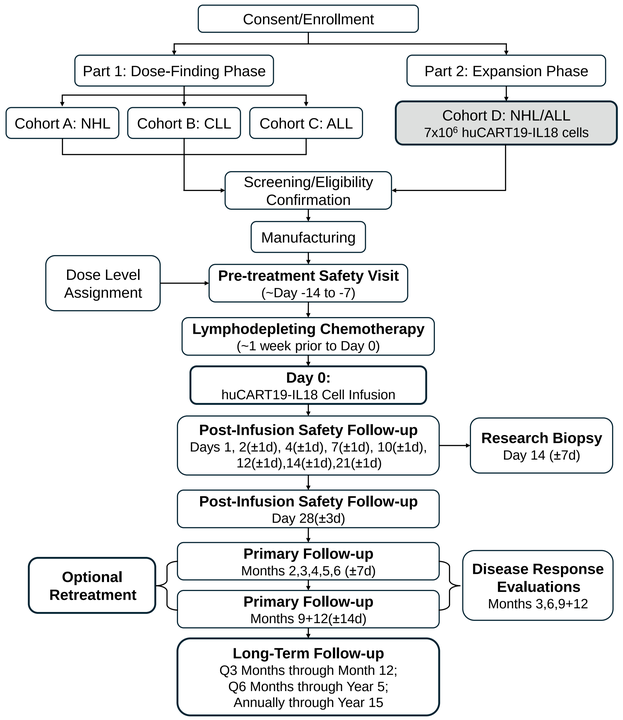
Synecta™ T1 Cell-Derived Nanoparticles (CDNPs) is a novel activation technology displaying membrane bound co-stimulatory molecules and cytokines

- Derived from a human cell line
  - Safety tested per regulatory guidelines
  - Fully biodegradable
  - No intact cells in the final reagent
  - Adhesion molecules support immunological synapse formation
- Stimulatory ligands and membrane-bound cytokines for balanced activation



In preclinical testing, CDNPs enabled robust expansion of patient samples from prior manufacturing failures, indicating the potential to recover material that might otherwise be unusable for dosing

Study Design



Bioanalytical and Biomarker Plan

Pharmacokinetic profile and bioactivity	• Kinetics of expansion and persistence by flow cytometry and qPCR • Systemic soluble immune factors, including IL-18, in serum
Ex vivo expansion	• Expansion profile of patient samples with different activation reagents. • Phenotypical assessment of T cell drug product • Drug product potency by IFN-γ release testing
Low level disease characterization	• Assessment of leukemia and B cells via polychromatic flow cytometry • Presence or absence of malignant B cells by Next-Generation Immunoglobulin heavy chain Sequencing

Summary

- huCART19-IL18 has activity in patients with CD19+ lymphomas after prior anti-CD19 CAR T-cell failure, but over one third of patients did not meet the target dose using expedited 3-day manufacturing (Svoboda et al, NEJM 2025).
- Our current trial in progress (Cohort D) was opened to evaluate the use of Synecta T1 CDNP, an alternative T-cell activation reagent to manufacture huCART19-IL18 for patients with CD19+ NHL/ALL with the goal to improve manufacturing feasibility with a short manufacturing cycle.
- Assessment of Synecta as an alternative to current technology includes harvest yields at reduced seeding number, transduction efficiency following Day 0 transduction, clinical response and persistence of Synecta-activated CAR-T cells
- Cohort D secondary objectives are to evaluate safety and efficacy of huCAR19-IL18 cells manufactured with the novel technology

References

- *Svoboda, Jakub, et al. "Enhanced CAR T-cell therapy for lymphoma after previous failure." New England Journal of Medicine 392.18 (2025): 1824-1835.*
- *Di Blasi, Roberta, et al. "Outcomes of patients with aggressive B-cell lymphoma after failure of anti-CD19 CAR T-cell therapy: a DESCAR-T analysis." Blood, The Journal of the American Society of Hematology 140.24 (2022): 2584-2593.*
- *Lemoine, Jean, Marco Ruella, and Roch Houot. "Born to survive: how cancer cells resist CAR T cell therapy." Journal of Hematology & Oncology 14.1 (2021): 199.*

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Phase I Trial of huCART19-IL18 Cells in Patients With Relapsed or Refractory CD19+ Cancers

https://clinicaltrials.gov/study/NCT04684563?term=NCT04684563&rank=1#study-overview