# TITLE

# First-in-patient proof of safety and efficacy of a 4th generation chimeric antigen receptor-modified T cells for the treatment of relapsed or refractory CD30 positive lymphomas

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## OBJECTIVES

Many lymphoma patients cannot be cured by standard chemo-radiotherapy. CD30 is expressed in Hodgkin's lymphoma (HL), anaplastic large cell lymphoma (ALCL), diffuse large B cell lymphoma, and peripheral T/NK cell lymphoma. Brentuximab Vedotin(SGN-35), an antibody-drug against CD30, has been approved by U.S. Food and Drug Administration (FDA) for the treatment of relapsed or refractory classical HL and systemic ALCL. However, SGN-35 is not available or approved in many countries. Nevertheless, CD30 represents an attractive target for chimeric antigen receptor (CAR)-based immune cell therapy. This study reports the safety and efficacy of a 4th generation CAR T cell treatment for the management of relapsed and refractory CD30 positive lymphomas (www.clinicaltrials.gov; #NCT02274584).

## METHODS

Lymphoma patients with relapsed or progressive CD30 positive disease are recruited. T cells are transduced with lentiviral CAR containing anti-CD30-scFv and T cell signaling domains including CD28/CD137/CD27 and CD3zeta. The CAR is fused with an apoptosis-inducing gene, FKBP-caspase 9 (iCasp9), to establish a safety-improved CAR (4S-CAR). CAR T cells and cytokines in blood are detected by quantitative PCR and ELISA, respectively.

## RESULTS

A 22-year-old male, diagnosed with stage III HL (Nodular Sclerosis, NS) in December 2011, had been heavily treated with three lines of chemotherapy and auto-transplantation. The patient relapsed in May 2014 and has been enrolled in this study. He received a conditioning regimen of three daily doses of fludarabine 25mg/m^2 and cyclophosphamide 250mg/m^2 one week before CAR T infusion. The total cell number infused was 3.2x10^8, of which 5% were CAR-positive. There were no infusion-related toxicities. 35 days and 2.5 months after infusion, CT scan showed resolution of multiple tumor nodules, which indicated partial remission. However, 5 months after infusion, disease slowly progressed based on CT scan. The CAR T cells peaked on day 45 accounting for >20% of circulating lymphocytes. Peak levels of interferon-γ and interleukin-6 were detected around day 40 coincided with peak CAR T detection.

## CONCLUSIONS

We demonstrate for the safety and efficacy of CD30 4S-CAR T cells in a heavily-treated, relapsed late-stage CD30 positive HL patient. Compared with leukemia and other subtypes of lymphoma, HL has unique pathological characteristics. The NS subtype is the most common HL characterized by dense bands of collagen fibrosis and an overt immunosuppressive tumor niche. Such feature may result in the difficulty of CAR T cells to penetrate into the tumor mass. We are designing new treatment regimens to overcome this obstacle. Expansion of patient cohort and long term follow-up are in progress.

## References

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