(S246) A PHASE I STUDY OF AUTOLOGOUS DUAL-EPITOPE NANOBODY-BASED ANTI-CD5 CAR T CELLS IN RELAPSED/REFRACTORY T-ALL/LBL AND PTCL/CTCL

Topic: 20. Other aggressive lymphomas

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Background

Patients with relapsed or refractory T-lymphoblastic leukemia/lymphoma(T-ALL/LBL) and peripheral T-cell lymphoma (PTCL) have dismal outcomes. We previously demonstrated that a naturally selected anti-CD7 CAR-T platform can overcome fratricide without gene editing or protein blockade (Blood 2022; 2025). CD5 is a pan–T-cell antigen, particularly in cutaneous T-cell lymphoma (CTCL); however, effective CD5-directed cellular therapies remain limited.

Aims

This first-in-human phase I study (NCT06874946) evaluated the safety, preliminary efficacy, and recommended phase II dose (RP2D) of autologous CD5-directed CAR-T cells (SL105) in patients with R/R T-ALL/PTCL.

Methods

Autologous CD5-directed CAR-T cells incorporating a tandem camelid-derived dual-epitope nanobody were generated using a natural selection platform to mitigate fratricide. Following fludarabine/cyclophosphamide lymphodepletion, patients were treated in a 3+3 dose-escalation phase I design (0.5, 1.0, and 2.0 $\times 10^6$ cells/kg). Single-cell RNA sequencing of peripheral blood at 1–3 months post-infusion was performed to characterize immune reconstitution and its association with viral complications.

Results

As of March 1, 2026, 22 patients had received SL105 and completed the 28-day DLT assessment. The median age was 37 years (range, 16–57), and 22.7% had prior HSCT. Diagnoses included T-ALL/LBL (n=11) and PTCL (n=11), including mycosis fungoides/Sézary syndrome (n=3) and other CTCL (n=2). Median follow-up was 6 months (range, 1–11). No dose-limiting toxicities were observed, and the RP2D was determined as 2.0 $\times 10^6$ CAR-T cells/kg. Median time to peak CAR-T expansion was 14 days by qPCR, with a median peak level of 6.3×10^4 copies/μg.
Grade 1 CRS occurred in 50% and grade 2 CRS in 22.7%; one patient experienced grade 1 ICANS. The best overall response rate (ORR) was 81.8%, including CRc/CMR in 54.5% and PR of extramedullary disease in 27.3%. At the RP2D level, ORR was 100%, with CR/CMR in 62.6%. Three patients with PR of extramedullary disease at M1 remain under follow-up, with ongoing responses. All responding patients with bone marrow involvement achieved MRD negativity by flow cytometry. All four non-responders exhibited low CAR-T expansion (peak <500 copies/μg). Five responders proceeded to consolidative allo-HSCT. EBV viremia or clinically diagnosed EBV-PTLD occurred in 9 patients (41%), and CMV viremia in 6 patients (27.3%).

Single-cell RNA sequencing of peripheral blood (M1–M3) from patients with viral infections revealed a time-dependent expansion of cytotoxic $CD56^{dim}$ $CD16^{hi}$ GZMH+ NK cells exclusively in the EBV-only group, whereas NK expansion was limited in CMV-only or EBV+CMV co-infection. Expanded NK cells showed stress-related transcriptional signatures without exhaustion features, suggesting virus-specific functional remodeling during T-cell reconstitution following CD5 CAR-T therapy.

Summary/Conclusion

SL105, a first-in-human dual-epitope nanobody CD5-directed CAR-T therapy, demonstrated a favorable safety profile and promising antitumor activity in R/R T-ALL/PTCL, including cutaneous T-cell lymphoma such as mycosis fungoides, a population with limited effective treatment options. The RP2D has been established, supporting further evaluation in an ongoing phase II study.