Abstract: P1189

Title: CD22-TARGETED CAR T CELL SINGLE CELL MULTIOMIC FEATURES LINKED TO PATIENT OUTCOMES IN CD19-CAR RESISTANT LARGE B CELL LYMPHOMA

Abstract Type: Poster Presentation

Topic: Aggressive Non-Hodgkin lymphoma - Clinical

Background:

In a Phase 1b trial (NCT04088890), we evaluated an autologous CAR T-cell therapy targeting CD22 (CAR22), constructed from the m971 single chain variable fragments and 41BB/CD3z endodomains, for the treatment of adult patients with relapsed/refractory large B-cell lymphoma (R/R LBCL) who have progressed after CAR19.

Aims:

All patients have a minimum of 1 year follow-up, and here we report overall response rate, complete response (CR) rates, progression free survival (PFS), and overall survival (OS). We identify CAR22 cellular characteristics that are associated with better** outcomes.

Methods:

Single-cell RNA transcriptome, surface protein expression, and TCR clonotype was determined via droplet-based sequencing (10X). We tracked individual T cell clonotypes from pre-manufacture apheresis material, final CAR22 products and at Day 14 (peak) and Day 28 post-infusion.

Results:

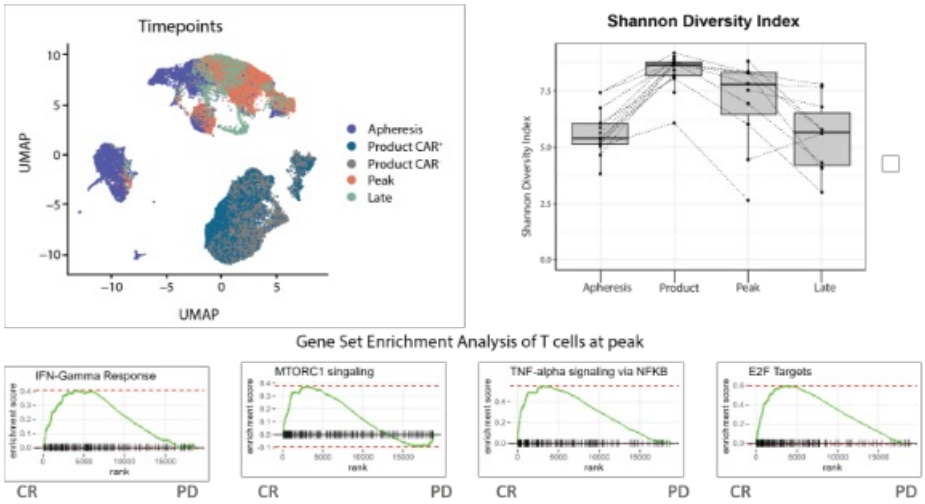
From October 17, 2019 to October 19, 2022, 38 patients were infused with CAR22, 19 (50%) of these patients had serial samples collected for single cell multiomic analysis. The median follow-up from date of CAR22 infusion to the data cutoff date of Feb 1, 2024 was 31.4 mo (range, 14.8 to 51.4). The ORR and CR rates were 68% (95% confidence interval [CI], 51% to 83%) and 53% (95% CI 36% to 69%). Response rates were similar between DL1 (1 million CAR+ cell/kg) and DL2 (3 million CAR+ cell/kg), however DL2 was found to be too toxic. At DL1 (median follow-up of 29.8 mo), the recommended phase 2 dose (RP2D), the median PFS and OS for all patients was 3.0 mo (95% CI, 1.6 to NE) and 25.7 mo (95% CI, 9.2 to NE). The estimated 2-year survival at DL1 is 52%. Of the 20 patients achieving CR, only four (20%) patients relapsed (at 3, 6, 22 and 24 months respectively). For those who achieved a CR, the median PFS, duration of response, and OS have not been reached. No grade 3 or higher CRS and ICANS occurred at DL1.

We applied our computational pipeline to a cohort of 19 patients for whom adequate CAR22 T cells were available for subsequent analysis. Patients included in the analysis were representative of the study population in terms of age, sex, cell dose, adverse events, and clinical outcome. A total of 70 samples, including 781,747 cells in total and 280,449 unique TCR clonotypes, was analyzed. Differential expression analysis revealed the upregulation of transcription factors from the AP-1 family in CAR T products associated with CR. Conversely, patients with higher proportions of terminal effector memory cells in the product experienced inferior outcomes. Source T cells from apheresis material exhibited clonal restriction, infusion CAR T cells displayed increased clonal diversity, and post-infusion CAR T cells demonstrated an increasing degree of clonal restriction. Increased clonal diversity in CAR22 products was associated with CR. Genes significantly enriched at peak in T cells of those achieving CR were associated with IFN-γ signaling, cell cycling, and proliferation. Additional data will be reported at the meeting.

Summary/Conclusion:

We created a CAR22 T cell atlas that enables lineage tracing at scale. We identified phenotypes impacting efficacy and are further studying the potentially actionable depletion of undesirable cellular populations or functional states during manufacturing. CAR22 is a highly effective and safe salvage therapy for patients with

CAR19-relapsed LBCL. A multicenter phase 2 clinical trial is enrolling (NCT05972720).



Keywords: CAR-T, RNA-seq, Phase I, Diffuse large B cell lymphoma