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RESET-SSc™: Clinical Trial Evaluating Rese-cel (Resecabtagene Autoleucel), A Fully Human, Autologous 4-1BB Anti-CD19 CAR T Cell Therapy in Systemic Sclerosis: Correlative Findings

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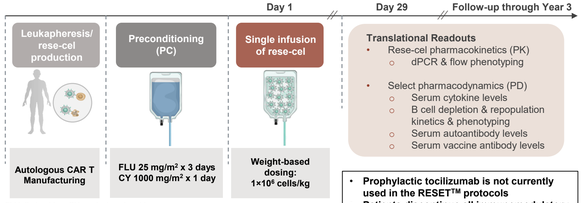
Background

Treatments for systemic sclerosis (SSc) aim to control disease activity, limit progression of organ damage, and decrease morbidity and mortality but many fail to provide durable clinical responses without requiring chronic immunosuppression. CD19-targeting chimeric antigen receptor (CAR) T cells produced durable, drug-free responses in SSc patients in an academic program. Rese-cel (resecabtagene autoleucel, formerly referred to as CABA-201) is a fully human, autologous 4-1BB anti-CD19-CAR T cell therapy, designed to deeply and transiently deplete CD19 positive B cells following a one-time weight-based infusion of 1x10^6 CAR T cells/kg. Rese-cel may enable durable responses in patients without the need for chronic immunosuppression. RESET-SSc™ (NCT06328777) is an ongoing Phase 1/2 trial evaluating rese-cel in two cohorts of adults with SSc and either severe skin (SSc-Skin) or organ (SSc-Organ) involvement. Here we report on initial pharmacokinetic (PK), pharmacodynamic (PD), and additional correlative data from the first patient dosed in the RESET-SSc™ clinical trial.



FLU, fludarabine; CY, cyclophosphamide

Methods

Rese-cel CAR T PK profiles were assessed by dPCR in pre- and post-infusion peripheral blood mononuclear cells (PBMC) samples. CAR T cells / µL blood reported values were determined with the patient's white blood cell count and the vector copy number for the infusion product (IP). CAR T cells per µL blood was calculated using the following equation:

$$\frac{CAR\ T\ cells}{\mu L\ blood} = \frac{CAR\ copies}{\mu g\ DNA} * \frac{1 \mu g\ DNA}{1e5\ cells} * \frac{PBMC}{\mu L\ blood} * \frac{1}{VCN}$$

where an estimation of 1 µg DNA per 1x10^5 cells was used[1] and cell number was approximated using lymphocytes + monocytes counts[2]. Serum cytokines were measured via a multiplexed V-plex or U-plex mesoscale discovery (MSD) immunoassay. Flow cytometric analyses were performed on cell samples from apheresis, infusion product (IP), and post-infusion PBMC samples to assess CAR expression in T cells CD4/CD8, CD45RA/CCR7, and HLA-DR expression in CAR+ T cells. Flow cytometry was also used to quantify B cell numbers (via CD19 and CD20) , phenotype (via CD24 and CD38) and evaluate surface IgG expression (via IgG). All flow cytometry was performed using custom antibody panels read on the Novocyte Quanteon flow cytometer (Agilent). Flow cytometry data was analyzed using FlowJo Software. Rese-cel cytotoxicity assay was performed *in vitro* using the IncuCyte® platform. Serum antibody panels were used to measure select autoantibodies and vaccine-associated antibodies in patient sera before and after rese-cel infusion utilizing the Luminex FlexMap platform. Serum antibody levels were reported as net median fluorescence intensity (MFI).

Data cut for this poster was 31-Mar-2025. [1] Baumer et al. 2018 Scientific Reports, [2] Boris et al. 2020 Molecular Therapy Methods & Clinical Development.

Patient Characteristics

Table 1. Baseline characteristics for SSc-Skin-1 in RESET-SSc™.

Cohort	Age, sex	Ethnicity	Weight (kg)	Total cells dosed (CAR T cells)	Disease duration (in years)
Severe skin cohort	66 F	white	59.9	6 x10^7	~2

Results

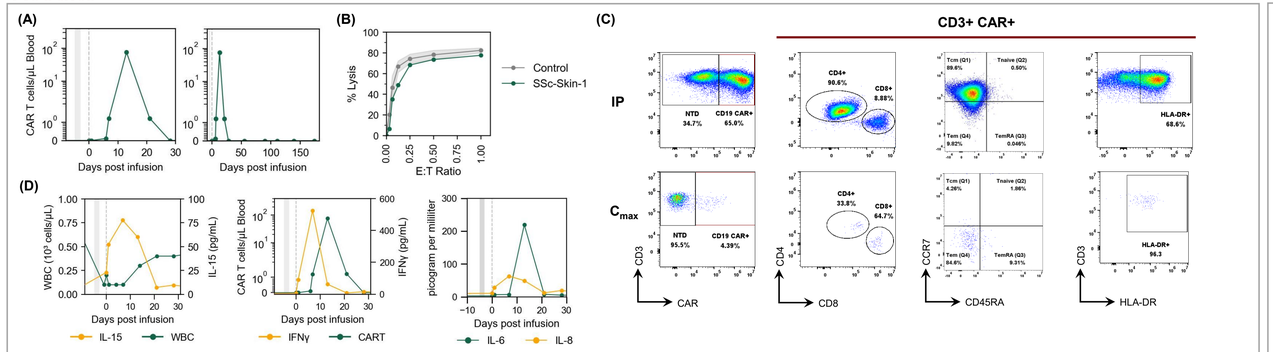


Figure 1. Rese-cel characterization for SSc-Skin-1. (A) Rese-cel PK profile in patients over time in days elapsed from infusion (left: 30-day follow-up, right: all time). Vertical gray shading indicates window in time for preconditioning (PC) and vertical dotted line indicates infusion at day 0. **(B)** In vitro lysis of GFP+CD19+ NALM6 target cells by CD19-CAR T cells from patient's IP. Area under the curve (AUC) generated for each effector to target (E:T) ratio (ranging from 0:1 to 1:1) by plotting the number of GFP+CD19+ NALM6 target cells over time (120 hours). Percent lysis determined by the difference between each $AUC_{E:T}$ and $AUC_{0:1}$ divided by the $AUC_{0:1}$ then multiplied by 100. **(C)** Flow cytometry plots of the IP and PBMCs at the time of maximum rese-cel exposure post-infusion (C_{max}; Day 13 for SSc-Skin-1). Flow cytometry plots representing the percentage of T cells that are CAR+, percentage of CAR+ T cells expressing CD4 and CD8, percentage of CAR+ T cells expressing CD45RA and CCR7, and percentage of CAR+ T cells expressing HLA-DR are shown. **(D)** Levels of selected serum cytokines over time in days elapsed from rese-cel infusion. IL-15 is overlaid on white blood cell counts, IFNγ is overlaid on PK, and IL-6 is overlaid on IL-8.

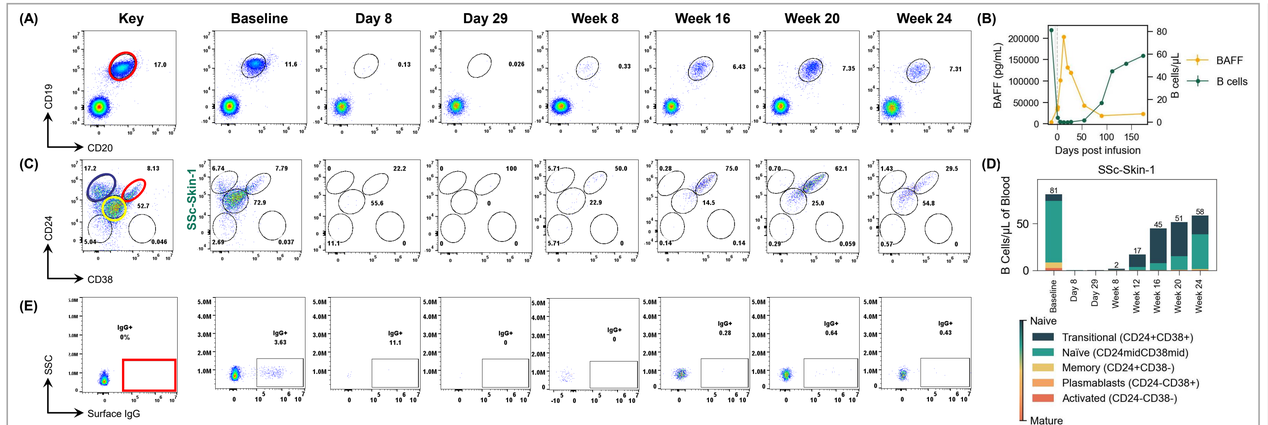


Figure 2. Characterization of B cells and humoral responses following rese-cel infusion in SSc-skin-1. (A) Phenotype of lymphocytes pre-infusion through reconstitution were characterized by flow cytometry and gated for CD19+ and CD20+ (B cells). Dot plot on the left ("Key") indicates gating strategy for CD19+CD20+ B cells on internal control cell population (circled in red) . **(B)** Serum BAFF levels from pre-PC through 24 weeks post rese-cel infusion overlayed on B cell counts as determined by flow cytometry (CD19+CD20+). **(C)** Phenotype of CD19+CD20+ B cells pre-infusion and through reconstitution post-infusion were characterized by flow cytometry with CD24 and CD38. Dot plot on the left indicates key gates of interest: transitional naïve B cells (red), naïve B cells (yellow), and memory B cells (blue). **(D)** Phenotypes as gated in C expressed as B cells/µL of blood. Numbers above each bar represents the total number of CD19+/CD20+ B cells. **(E)** IgG surface expression on CD19+CD20+ B cell population. Timepoints include pre-PC and through reconstitution after rese-cel. Dot plot on the left ("Key") indicates gating strategy (in red) on internal control IgG+ fluorescence minus one (FMO) sample.

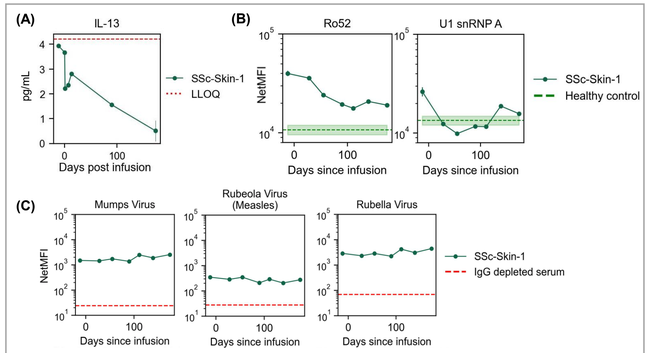


Figure 3. (A) Serum levels of IL-13 in pg/mL over time in days post rese-cel infusion, red line is the lower limit of quantification (LLOQ). **(B)** Serum autoantibody (Left: Ro52 and Right: U1snRNP A) and **(C)** vaccine/pathogen antibody levels at baseline (pre-PC) and various time points after rese-cel infusion. Y-axis is net mean fluorescent intensity (MFI), dashed green horizonal lines with shading depict healthy donor sera levels represented as mean ±1 SD in a pool of 3 healthy donors across runs, and red dashed line represents IgG depleted serum across runs.

Conclusions

- We report on the early translational data from the first systemic sclerosis (SSc) patient with skin involvement treated with rese-cel.
- Rese-cel exhibited rapid expansion in the first 2 weeks post-infusion followed by contraction to undetectable levels by 28 days post-infusion.
  - Peak expansion of rese-cel (C_{max}) was observed 13 days post-infusion.
  - Rese-cel infusion product CAR T cells were activated CD4, central memory dominant and exhibited an inversion to CD8, effector memory dominance at C_{max}. At peak expansion, CAR+ T cells maintained expression of HLA-DR.
- Peripheral B cells were rapidly and deeply depleted following rese-cel infusion and began to reconstitute by 8 weeks post-infusion.
  - Peripheral B cells were depleted within the first month after rese-cel infusion.
  - Reconstituted B cells primarily exhibited a transitional naïve phenotype upon reconstitution at week 8 and moved to a more mature naïve phenotype by 24-week post-infusion.
  - Serum levels of disease- and vaccine-associated antibodies decreased slightly and remained stable, respectively, over the 24-week period after rese-cel treatment.
- Early clinical data have indicated emergence of a drug-free clinical response[3]. Additional clinical safety and efficacy data from the RESET-SSc trial will be shared at the EULAR Congress in June 2025.
- These data further support the potential for rese-cel to provide an immune system reset that could lead to durable disease response without the need for chronic immunosuppression.

[3] Sheikh, et al. *Safety and Efficacy of CABA-201, a Fully Human, Autologous 4-1BB Anti-CD19 CAR T Cell Therapy in Patients with Immune-Mediated Necrotizing Myopathy and Systemic Lupus Erythematosus from the RESET-Myositis™ and RESET-SLE™ Clinical Trials.* Presented at ACR Convergence 2024. Abstract 1733.