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RESET-SLE™: Clinical Trial Evaluating Rese-cel (Resecabtagene Autoleucel), A Fully Human, Autologous 4-1BB Anti-CD19 CAR T Cell Therapy in Non-Renal SLE and Lupus Nephritis: Correlative Findings

J. Stadanlick[1], L. Ishikawa[1], T. Furmanak[1], M. Werner[1], Z. Vorndran[1], A. Ellis[1], J. Williams[1], J. Cicarelli[1], S. Flanagan[1], D. Kobulsky[1], Q. Lam[1], F. Hadi-Nezhad[1], Y. White[1], C. DiCasoli[1], R. Estremera[1], S. Sheikh, V[2]. Derebail[2], N. Grover[2], G. Gulati[3], M. Abedi[2], M. Sise[5], M. Frigault[2], C. Palma[6], P. Reagan[6], C. Edens[7], S. Kosuri[7], C. Elgarten[4], J. Burnham[4], J. Hogan[1], R. Tummala[1], D. Chang[1], S. Basu[1], D. Nunez[1], J. Volkov[1]

1: Cabaletta Bio, Philadelphia, PA, USA; 2: University of North Carolina, Chapel Hill, NC; 3: University of California, Davis, CA, USA; 4: Children's Hospital of Philadelphia, Philadelphia, PA, USA; 5: Massachusetts General Hospital, Boston, MA, USA; 6: University of Rochester, Rochester, NY, USA; 7: University of Chicago, Chicago, IL, USA

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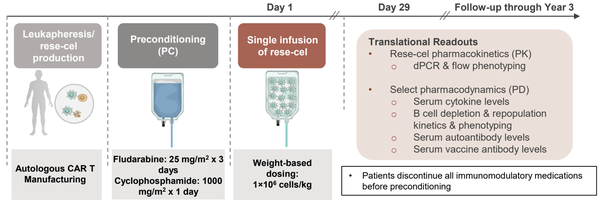
Background

Current therapies for systemic lupus erythematosus (SLE) aim to control disease activity, reduce organ damage, and decrease long-term morbidity and mortality. Achieving durable clinical responses without chronic immunosuppressive drugs is desired. CD19-targeting chimeric antigen receptor (CAR) T cells have demonstrated durable, drug-free responses in SLE patients in an academic program. Rese-cel (resecabtagene autoleucel, formerly 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 without chronic immunosuppression. RESET-SLE™ (NCT06121297) is an ongoing Phase 1/2 trial evaluating the safety and efficacy of rese-cel in two cohorts of non-renal SLE and lupus nephritis (LN).



Methods

Rese-cel cell pharmacokinetic (PK) profiles were assessed by dPCR for transgene in PBMC samples. PK was reported as cells per µL of blood and was estimated by including the patient's white blood cell count per visit and the vector copy number for each patient's manufactured product 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 the patient's PBMC count was determined using combined lymphocyte and monocyte 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 and CD4/CD8 expression in CAR+ T cells. B cell numbers were also quantified using flow cytometry (via CD19 and CD20 expression) and evaluated to assess maturity (via CD24 and CD38). All flow cytometry was performed using custom multi-color antibody panels. Samples and controls were read on the Novocyte Quanteon flow cytometer (Agilent), and data were analyzed using FlowJo Software. Rese-cel cytotoxicity assays were performed *in vitro* using the IncuCyte® platform. Serum antibody panels were used to measure select lupus- and vaccine-associated antibodies in patient sera utilizing the Luminex FlexMap instrument. Serum antibody levels were reported as net median fluorescence intensity (MFI). T cell receptor (TCR) sequencing was performed on peripheral blood mononuclear cell (PBMC) samples isolated from LN-1 at various timepoints before and throughout the first month post-infusion. CAR+ (CD8+, CD8-CD4- and CD4+, where possible) and CAR- T cell populations were sorted via the MACSQuant Tyto prior to sequencing. Short-read sequencing (Illumina) of these populations was performed on libraries prepared using primer pools that amplify the beta chains of each TCR (Adaptive Biotech). A unique TCR clone was defined as a unique complementarity-determining region 3 nucleotide sequence. Baseline characteristics and time of latest follow up for each patient are shown in **Tables 1** and **2**, respectively.

Data cut for this poster is 31Mar2025. [1] Baumer et al. 2018 Scientific Reports, [2] Boris et al. 2020 Molecular Therapy Methods & Clinical Development.

Table 1. Baseline characteristics of first 7 patients in RESET-SLE™.

Baseline characteristics							
Patient / Cohort	**SLE-1†**	**SLE-2**	**SLE-3**	**SLE-4**	**LN-1**	**LN-2**	**LN-3**
Age, sex	26 M	36 F	44 F	37 F	24 F	35 F	26 F
Disease dur. (y)	~6	~17	~9	~10	~2	~8	~16
Autoantibodies	dsDNA, Sm	dsDNA	dsDNA	dsDNA, Sm	dsDNA, Sm	dsDNA, Sm	Sm

*Baseline disease activity = activity before preconditioning. †Enrollment in the LN cohort requires class III/IV +/- V LN. SLE-1 had isolated class V LN and extra-renal SLE disease activity that met inclusion criteria for the non-renal cohort; dsDNA, double-stranded DNA; Sm, Smith.

Table 2. Time of latest follow up

	Non-renal SLE				LN		
Patient	**SLE-1***	**SLE-2**	**SLE-3**	**SLE-4**	**LN-1**	**LN-2**	**LN-3**
Latest follow-up	Week 44	Week 28	Week 20	Week 20	Week 32	Week 16	Week 4

Results

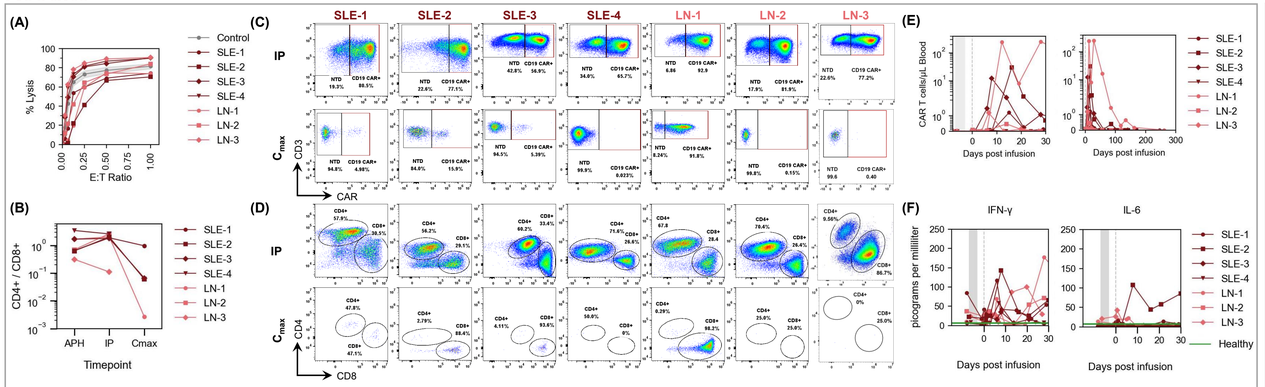


Figure 1. Rese-cel characterization. (A) In vitro lysis of GFP+CD19+ NALM6 target cells by CD19-CAR T cells from patient's IP. Area under the curve (AUC) generated for each effector to target (E:T) ratio (ranging from 0:1 to 1:1) by plotting the number of GFP+CD19+ NALM6 target cells over time (120 hours). 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. **(B)** Changes in the frequency of CD8+ or CD4+ T cells between apheresis (APH), IP, and C_{max}. **(C)** Flow cytometry plots showing percentage of T cells that are CAR+ in the IP and post-infusion PBMCs at the time of maximum rese-cel exposure (C_{max}; study visits Day 15 for SLE-1, SLE-2, and LN-1, Day 8 for SLE-3, no CAR+ T cells detected in SLE-4, LN-2, LN-3). **(D)** Flow cytometry plots showing the percentage of CAR+ T cells expressing CD4 and CD8 in the IP and post-infusion C_{max}. In **(E-F)** vertical gray shading indicates window in time for pre-conditioning across all subjects and vertical dotted line indicates infusion at day 0. **(E)** Rese-cel PK profile in patients over time in days elapsed from rese-cel infusion (left: 30 day follow up, right: all follow up). **(F)** Levels of serum cytokines (IFN-γ and IL-6) over the first 30 days following rese-cel infusion.

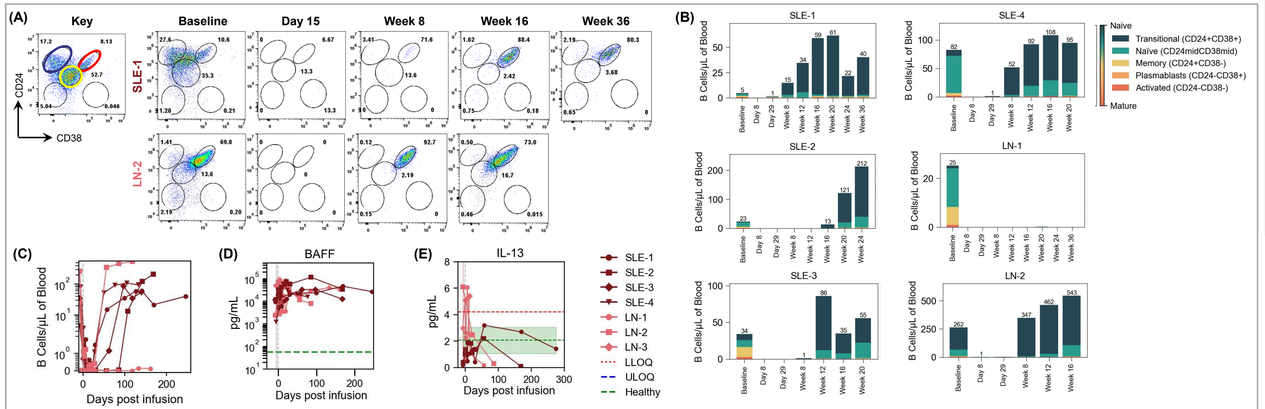


Figure 2. Characterization of B-cells and humoral responses. (A) Phenotype of CD19+CD20+ B cells in SLE and LN patients from baseline (pre-preconditioning; pre-PC) and at indicated study visits were characterized by flow cytometry with CD24 and CD38. Dot plot on the left indicates key gates of interest: transitional naïve B cells (red), mature naïve B cells (yellow), and memory B cells (blue). **(B)** Bar graphs enumerating the numbers of specific CD19+CD20+ B cell subsets per µL of blood as classified by CD24 and CD38 expression. Data not reported for LN-3 who had no measurable B cells at any time point. **(C)** B cell counts in blood measuring live CD19+CD20+ cells by flow cytometry. Data reported in concentration over time in days elapsed from rese-cel infusion over all time. Pre-infusion B cell levels were measured in PBMCs from pre-PC visit for all subjects. **(D)** Serum BAFF levels from pre-PC through all time. **(E)** Total serum IL-13 levels (pg/mL) at pre-PC and over time after rese-cel infusion. IL-13 levels are low, but quantifiable in some subjects at early time points.

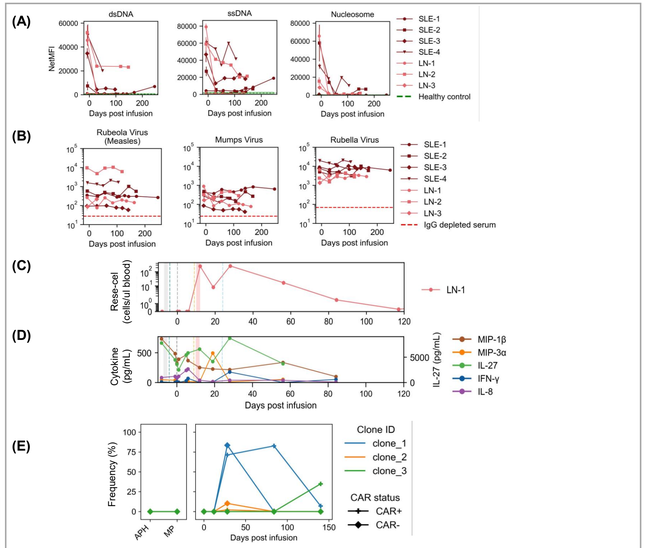


Figure 3. Translational antibody levels and clinical measures. (A) Disease associated antibodies for double-stranded DNA (dsDNA), single-stranded DNA (ssDNA), and nucleosome. Y-axis is net MFI and dashed green horizonal lines with shading depict mean healthy donor sera levels ±1SD. **(B)** Serum levels of vaccine antibodies before and after rese-cel infusion. Red dashed line indicates IgG-depleted serum. **(C)** Rese-cel PK overlaid on timeline of clinical events reported in LN-1. Vertical dashed lines represent hospitalization with a fever of indeterminate etiology (blue), CABA-201 infusion (grey), CRS (orange), fever with pancytopenia (blue). Shaded areas represent timing of lymphodepletion (grey) and grade 4 ICANS (day 10-12; red). **(D)** Serum cytokine levels following rese-cel infusion. MIP-1β, MIP-3α, IL-27, and IL-8 were either not elevated or detected in other subjects. **(E)** TCR sequencing depicting the top 3 clones in the apheresis, MP, and PBMCs collected at days 12 and 28 post-infusion in LN-1. Apheresis samples were sorted into CD4+ and CD8+ populations. Other samples were sorted into CAR- or CAR+. Day 28 T cells comprised of three dominant clones (clones 1-3), regardless of the CAR expression. CAR+ T cell population diversified over time and were undetectable by month 9 post-infusion.

Conclusions

- We report on early translational data from 7 patients (4 SLE, 3 LN) treated in RESET-SLE.
- Peak expansion (C_{max}) occurred between study visit Day 8 and Day 15 with LN-1 exhibiting a second expansion peak at Day 29, which was TCR-driven.
- CAR+ T cells in the infusion product were CD4+ dominant in all patients except LN-3. CAR+ T cells at C_{max} exhibited an increase in CD8+ proportion in patients with detectable CAR T cells.
- Peripheral B cells were rapidly reduced in all patients following rese-cel infusion and began to reconstitute as early as 8 weeks post-infusion.
  - Newly emerging B cells exhibited a primarily transitional naïve phenotype with many patients exhibiting a further maturation to naïve B cells.
  - Antibodies associated with SLE and LN decreased in patients throughout the post-treatment period, while vaccine and infectious pathogen antibodies remained stable.
- 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. Clinical safety & efficacy data from RESET-SLE will be shared at the EULAR Congress in June 2025.