MECHANISTIC BASIS OF THE ACUTE SAFETY PROFILE OF RESE-CEL, AN AUTOLOGOUS CD19-CAR T, IN PATIENTS WITH AUTOIMMUNE DISEASE TREATED IN FOUR ONGOING PHASE 1/2 CLINICAL TRIALS

D Nunez[1,2] J Volkov[1,2] D Thompson[1] F Hadi-Nezhad[1] D Braccia[1] J Stadanlick[1] T Furmanak[1] M Werner[1] Z Vorndran[1] L Ishikawa[1] A Ellis[1] S Flanagan[1] J Williams[1] J Cicarelli[1] D Kobulsky[1] Q Lam[1] C Little[1] Y White[1] S Sheikh[3] V Derebail[3] N Grover[3] G Gulati[4] M Abedi[4] M Sise[5] M Frigault[5] C Palma[6] P Reagan[6] C Edens[7] S Kosuri[7] C Elgarten[8] J Burnham[8] C Ulane[9] R Reshef[9] T Mozaffar[10] E Naddaf[11] N Chahin[12] EM Wilfong[13] D Khanna[14] M Ghosh[14] A Shah[15] J Hogan[1] R Estremera[1] R Tummala[1] DJ Chang[1] GK Binder[1] S Basu[1]

1: Cabaletta Bio, 2: Co-first authors, 3: University of North Carolina at Chapel Hill, 4: University of California, Davis, 5: Massachusetts General Hospital, 6: University of Rochester, 7: University of Chicago, 8: Children's Hospital of Philadelphia, 9: Columbia University, 10: University of California, Irvine, 11: Mayo Clinic Rochester, 12: Oregon Health and Science University, 13: Vanderbilt University, 14: University of Michigan, 15: Duke University

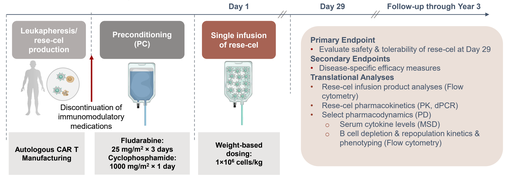
INTRODUCTION

INTRODUCTION & AIMS

Autologous CD19-directed CAR T therapies have been utilized across a wide range of B cell driven autoimmune diseases (ADs), including idiopathic inflammatory myopathies (IIM), systemic lupus erythematous (SLE), systemic sclerosis (SSc), and myasthenia gravis (MG). To date, different CD19-CAR T therapies have delivered drug-free responses in AD patients. However, the safety profile of CD19-CAR T therapies across different ADs has yet to be fully explored. This is especially true for cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) and their association to a variety of biomarkers. Cabaletta Bio is investigating the safety and efficacy of resecabtagene autoleucel (rese-cel, formerly CABA-201), an autologous CD19 directed 4-1BBz CAR T therapy, across four separate Phase I/II clinical trials in IIM, SLE, SSc, and MG.

The schematic below depicts commonalities in study design among each ongoing Phase I/II RESET™ clinical trial. All patients were treated with a single weight-based dose of rese-cel at 1×10^6 cells/kg following a standard preconditioning regimen and discontinuation of immunomodulatory medications (IM).

The aim of these analyses is to investigate key pharmacokinetic (PK) and pharmacokinetic (PD) profiles of rese-cel across 4 Phase I/II RESET trials and relate these to the incidence and severity of CRS and ICANS in these patients.



RESULTS

As of October 30th, 2025, 40 patients with active disease refractory to standard of care have been treated with rese-cel and have completed at least 29 days of follow-up across four ongoing Phase I/II clinical trials in IIM (15 patients; RESET-Myositis: NCT06154252), SLE (10 patients; RESET-SLE: NCT06121297), SSc (9 patients; RESET-SSc: NCT06328777), and MG (6 patients; RESET-MG: NCT06359041). Baseline characteristics and the incidence, severity and timing of onset of CRS and ICANS are shown in Tables 1 and 2, respectively. The accompanying translational correlative analyses include data from 38 patients (excludes JIIM-1 and SSc-Organ-5; data unavailable at time of data cut).

BASELINE CHARACTERISTICS & SAFETY

Table 1. Baseline characteristics of AD patients treated with rese-cel.

	RESET-Myositis	RESET-SLE	RESET-SSc	RESET-MG
Number of patients	15	10	9	6
Age, mean (SD)	51.7 (14.6)	30.4 (7.6)	53.1 (12.3)	57.5 (9.8)
Sex, % female	53.3	80.0	66.7	66.7
Duration of disease, mean (SD)	5.4 (3.7)	9.8 (5.0)	2.2 (1.3)	5.1 (5.3)

Table 2. Incidence, severity and onset of CRS and ICANS in the first 29 days following rese-cel treatment in AD patients.

	RESET-Myositis	RESET-SLE	RESET-SSc	RESET-MG	Total
CRS[‡], n (%)	5 (33.3)	3 (30.0)	4 (44.4)	1 (16.7)	13 (32.5)
CRS Grade 1, n (%)	5 (33.3)	3 (30.0)	3 (33.3)	0 (0.0)	11 (27.5)
CRS Grade 2, n (%)	_	_	1 (11.1)	1 (16.7)	2 (5.0)
Time to CRS onset, days* (mean)	7.4	7.3	8.5	7.0	7.7
CRS duration[†], days (mean)	4.6	3.0	3.0	2.0	3.5
ICANS[‡] n (%) (Grade)	_	1 (10) (G4)	1 (11.1) (G3)	_	2 (5.0)
Time to ICANS onset. days (mean)	_	9.0	8.0	_	8.5
ICANS duration, days (mean)	_	3.0	3.0	_	3.0

*Days relative to rese-cel infusion
†Events occurring within 7 days of each other are considered as 1 episode. IMNM-3 CRS duration includes preceding event of fever which was consistent with CRS definition.
‡Graded per ASTCT Consensus Grading Criteria

RESULTS

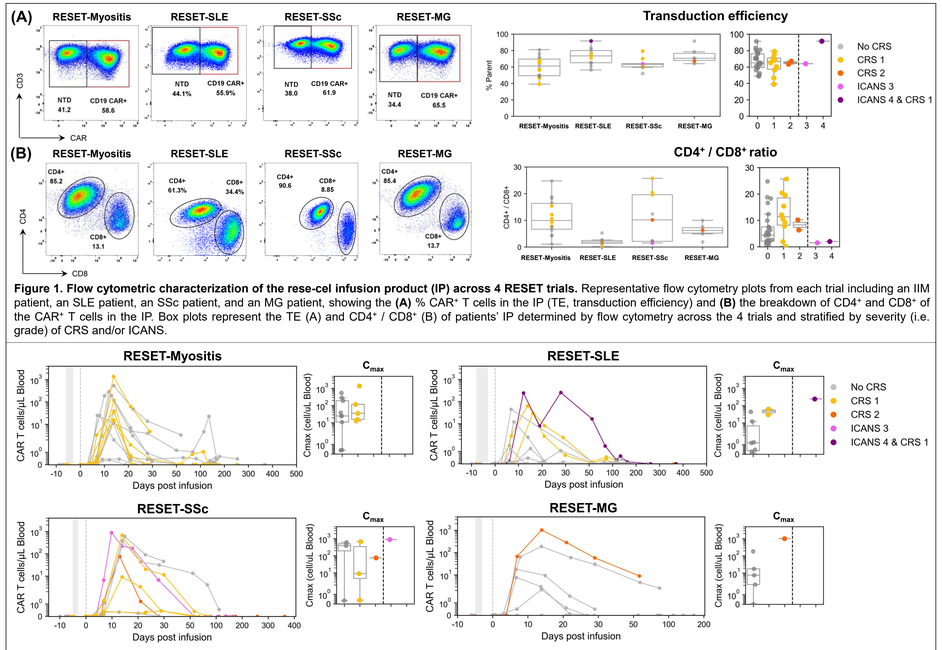


Figure 1. Flow cytometric characterization of the rese-cel infusion product (IP) across 4 RESET trials. Representative flow cytometry plots from each trial including an IIM patient, an SLE patient, an SSc patient, and an MG patient, showing the **(A)** % CAR⁺ T cells in the IP (TE, transduction efficiency) and **(B)** the breakdown of CD4⁺ and CD8⁺ of the CAR⁺ T cells in the IP. Box plots represent the TE (A) and CD4⁺ / CD8⁺ (B) of patients' IP determined by flow cytometry across the 4 trials and stratified by severity (i.e. grade) of CRS and/or ICANS.

Figure 2. Pharmacokinetic (PK) profile of rese-cel reported as CAR T cells per µL of blood in 38 patients across 4 RESET clinical trials. Left plot per trial is CAR T cells per µL of blood to latest follow-up following rese-cel infusion. Patients are color coded by exhibited safety events, gray vertical shading on each plot represents the cumulative time of preconditioning administration per trial, and vertical gray dotted line signifies day of rese-cel infusion (day 0, Study Visit Day 1). Right plot per trial is maximum CAR T cell concertation (C_{max}) for each patient grouped by severity (i.e. grade) of CRS and/or ICANS, when present. PK profiling was measured in PBMC samples using dPCR.

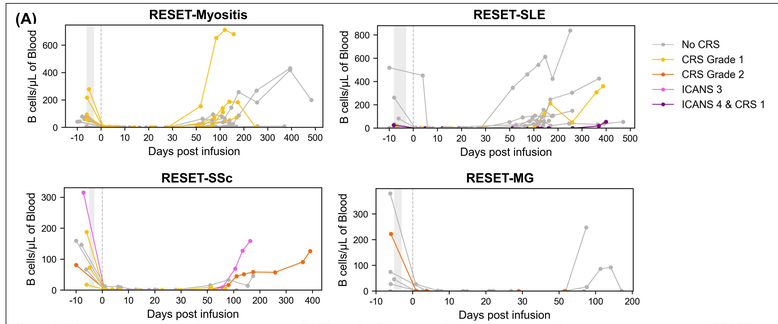


Figure 3. Pharmacodynamic profile (A) and serum BAFF levels (B) induced following rese-cel infusion in patients across 4 RESET trials. (A) Peripheral B cell counts over time before pre-conditioning (baseline) and to latest follow-up after rese-cel infusion, determined by flow cytometry, per RESET trial. Patients color coded by exhibited safety events, gray vertical shading on each plot represents the cumulative time of preconditioning administration per trial, and vertical gray dotted line signifies day of rese-cel infusion (day 0, Study Visit Day 1). **(B)** Serum levels of B cell activating factor (BAFF, in pg/mL) at baseline before pre-conditioning and the maximum levels (Max) following rese-cel infusion per RESET trial. Patients color coded by safety events. Note: AChR-Neg-3 and SLE-2 BAFF levels were not available at the time of the data cut.

As of 30 October 2025. Abbreviations: AChR, acetylcholine receptor; AD, autoimmune disease; ASyS, antisynthetase syndrome; AUC, area under the curve; AUCd30, AUC from baseline to 30 days post-infusion; BAFF, B-cell activating factor; CAR, chimeric antigen receptor; C_{max}, maximum concentration; CRS, cytokine release syndrome; DM, dermatomyositis; dPCR, digital polymerase chain reaction; ICANS, immune effector cell-associated neurotoxicity syndrome; IFN-γ, interferon gamma; IL-6, interleukin-6; IL-8, interleukin-8; IIM, idiopathic inflammatory myopathies; IM, immunomodulatory medications; IMNM, immune mediated necrotizing myopathy; IP, infusion product; LN, lupus nephritis; JIIM, juvenile idiopathic inflammatory myopathies; MG, myasthenia gravis; MSD, mesoscale discovery; PBMC, peripheral blood mononuclear cell; PC, preconditioning; PD, pharmacodynamic; PK, pharmacokinetic; rese-cel, resecabtagene autoleucel; RESET, REstoring SElf-Tolerance; SSc, systemic sclerosis; SLE, systemic lupus erythematosus; TE, transduction efficiency; TCR, T cell receptor.
Cabaletta Bio, data on file.

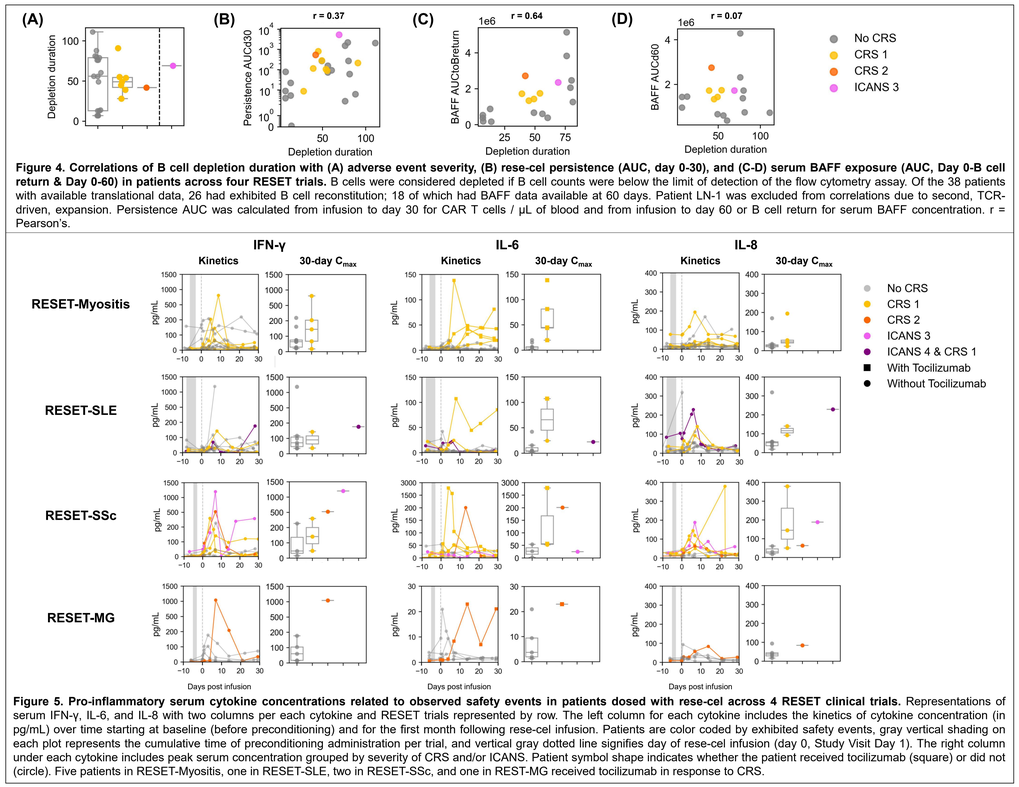


Figure 4. Correlations of B cell depletion duration with (A) adverse event severity, (B) rese-cel persistence (AUC, day 0-30), and (C-D) serum BAFF exposure (AUC, Day 0-B cell return & Day 0-60) in patients across four RESET trials. B cells were considered depleted if B cell counts were below the limit of detection of the flow cytometry assay. Of the 38 patients with available translational data, 26 had exhibited B cell reconstitution; 18 of which had BAFF data available at 60 days. Patient LN-1 was excluded from correlations due to second, TCR-driven, expansion. Persistence AUC was calculated from infusion to day 30 for CAR T cells / µL of blood and from infusion to day 60 or B cell return for serum BAFF concentration. r = Pearson's.

Figure 5. Pro-inflammatory serum cytokine concentrations related to observed safety events in patients dosed with rese-cel across 4 RESET clinical trials. Representations of serum IFN-γ, IL-6, and IL-8 with two columns per each cytokine and RESET trials represented by row. The left column for each cytokine includes the kinetics of cytokine concentration (in pg/mL) over time starting at baseline (before preconditioning) and for the first month following rese-cel infusion. Patients are color coded by exhibited safety events, gray vertical shading on each plot represents the cumulative time of preconditioning administration per trial, and vertical gray dotted line signifies day of rese-cel infusion (day 0, Study Visit Day 1). The right column under each cytokine includes peak serum concentration grouped by severity of CRS and/or ICANS. Patient symbol shape indicates whether the patient received tocilizumab (square) or did not (circle). Five patients in RESET-Myositis, one in RESET-SLE, two in RESET-SSc, and one in REST-MG received tocilizumab in response to CRS.

CONCLUSIONS

- At the time of the data cut, 40 patients with AD were dosed with rese-cel* and completed one month of follow-up across 4 Phase I/II trials (RESET-Myositis, RESET-SLE, RESET-SSc, and RESET-MG).
- Rese-cel was generally well tolerated (67.5% did not experience CRS & 95% did not experience ICANS).
  - CRS events were low grade and resolved quickly with standard management.
  - In the two reported cases of transient ICANS, both may have been confounded by ongoing occult infections and resolved with standard treatments without clinical sequalae.†
- Maximum circulating rese-cel concentration was similar between patients with CRS/ICANS & patients without.
- Increases in serum BAFF were observed in all patients during the B cell depletion phase following rese-cel infusion (average maximum BAFF concentrations were 34,663; 43,350; 26,960; and 20,544 pg/mL for RESET-Myositis, RESET-SLE, RESET-SSc, and RESET-MG, respectively).
  - Magnitude of BAFF increases did not correspond to incidence or severity of CRS/ICANS.
- The median time to B cell reconstitution was 63 ± 26 days across the 4 RESET trials.
  - B cell depletion duration weakly correlated with rese-cel persistence.
  - BAFF levels over the duration of B cell aplasia weakly correlated with depletion duration.
- There was no relationship observed between persistence AUCd30 and clinical outcome.
- Peak serum pro-inflammatory cytokine levels were higher in patients with CRS/ICANS than in patients without; timing of peak varied per cytokine but mostly coincided with timing of the safety event.

* All patients discontinued IM agents prior to rese-cel dosing except for one MG patient, which was a protocol deviation.
† Protocol controls were implemented to ensure patients did not have active infections prior to infusion; no ICANS has been reported since.