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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

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RESET SSc™

June 2025

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# Disclosures

| Author | | Disclosures |
|---|---|---|
| Dinesh Khanna | | AbbVie, Bristol Myers Squibb, AstraZeneca, Fate Therapeutics, Nkarta, Novartis, Cabaletta Bio |
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# Systemic Sclerosis: Profound Unmet Need and Limited Options

Affects ~90K people in the U.S. and ~60K people in Europe; associated with progressive morbidity and high mortality[1–6]

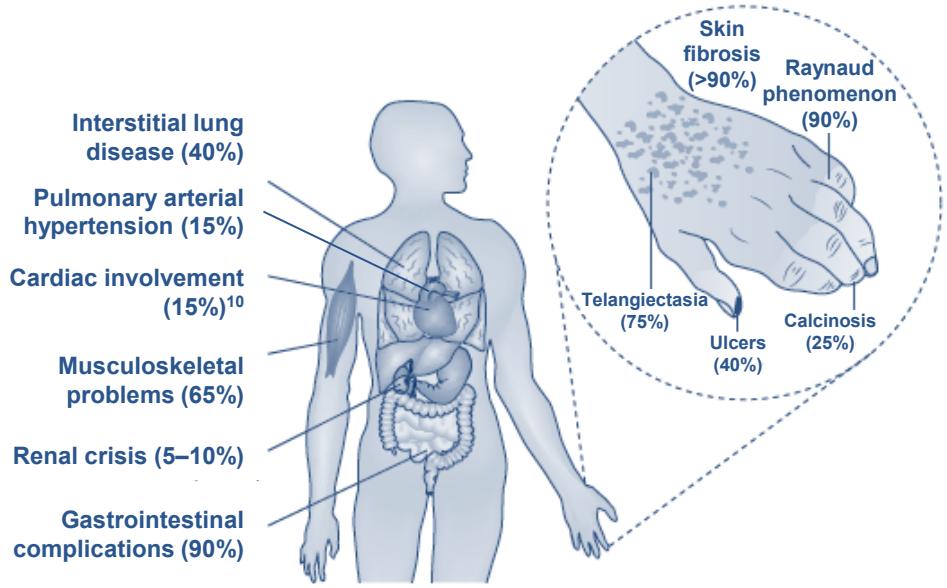
## A rare, potentially fatal chronic autoimmune disease[5]

- Characterized by progressive skin and internal organ fibrosis[5]
- Deep, tissue-level B cell-driven autoimmunity, with activated B cells and autoantibodies, promotes inflammation and organ damage[7]

## High burden on function & quality of life

- Disproportionately impacts women, with less favorable outcomes in people of color[5]
- SSc is associated with the highest mortality of all rheumatological diseases and significant burden from persistent skin and organ manifestations[8,9]
- There is a need for disease-modifying therapies across all SSc subsets[9]
    - Most treatments for skin disease have limited effect
    - AHSCT improves outcomes in selected patients but carries substantial treatment-related risks

## Potential manifestations and classification[5]




**Progressive fibrosis and scarring of the skin and internal organs in SSc, may lead to severe and potentially life-threatening complications**

AHSCT, autologous hematopoietic stem cell transplantation; SSc, systemic sclerosis.

1. Fan Y, et al. *J Manag Care Spec Pharm*. 2020;26(12):1539–1547. 2. Bergamasco A, et al. *Clin Epidemiol*. 2019;11:257–273. 3. Kremer K, et al. *Akt Dermatol*. 2012;38:44-52. 4. ERN ReCONNET Disease: Systemic Sclerosis. Available online at: https://reconnet.ern-net.eu/disease-ssc/ (accessed May 2025). 5. Allanore Y, et al. *Nat Rev Dis Primers*. 2015;1:15002. 6. Denton CP, et al. *Lancet*. 2017;390(10103):1685–1699. 7. Thoreau B, et al. *Front Immunol*. 2022;13:933468. 8. Truchetet ME, et al. *Clin Rev Allergy Immunol*. 2023;64(3):262–283. 9. Pope JE, et al. Nat Rev Rheumatol. 2023;19(4):212–226. 10. Steen, V & Medsger, T. Arthritis & Rheumatology. 2000, 43(11): 2437-2444.

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# B Cells Play a Central Role in the Pathogenesis of Systemic Sclerosis

Current therapeutic options often result in incomplete B cell depletion in tissues and lymphoid organs[1]

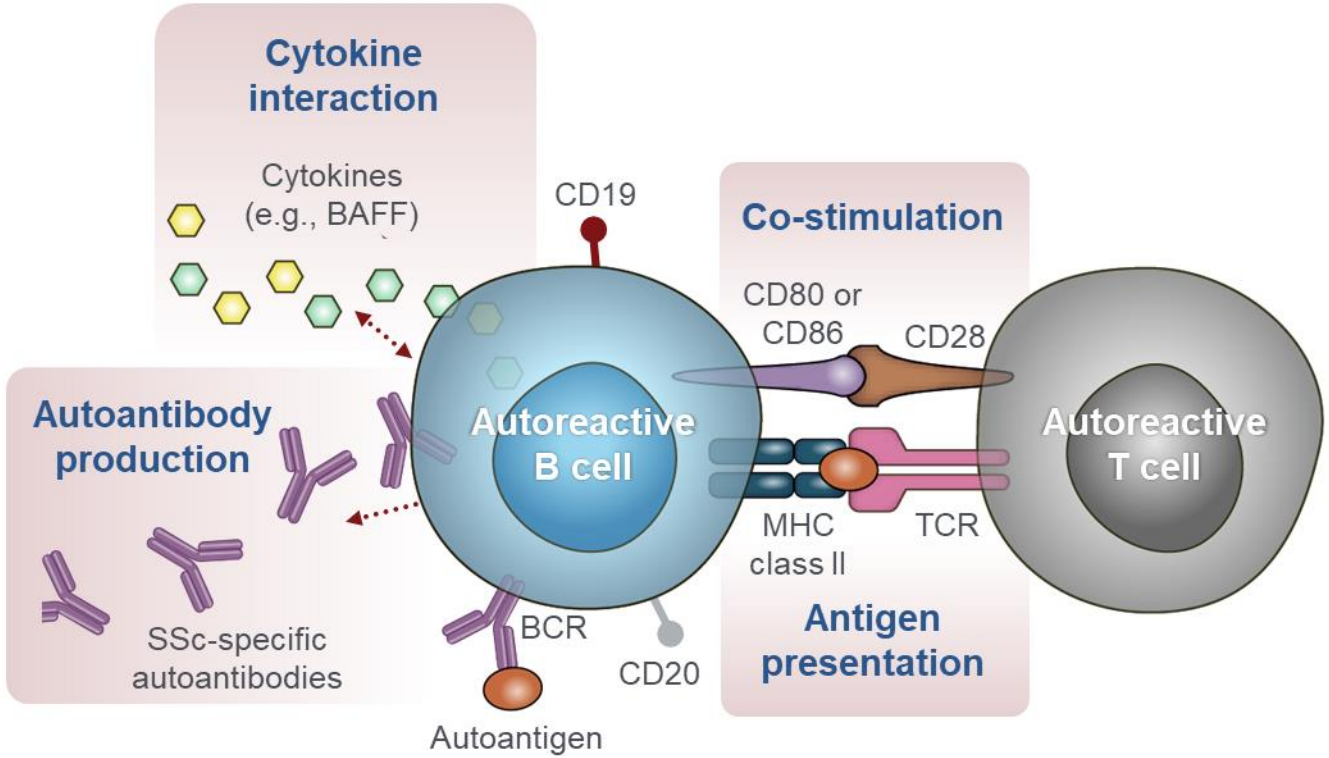



Image adapted from Rubin SJS, et al. 2019[2]

**In SSc:**

- B cells are key drivers of immune dysregulation through multiple mechanisms[3]
- B cell-targeted therapies offer a promising approach for treatment-refractory cases[3]
- Persistent B cell activity in skin and lung tissue may contribute to treatment resistance using currently available therapies[3]

BAFF, B cell activating factor; BCR, B cell receptor; CD, cluster of differentiation; MHC, major histocompatibility complex; SSc, systemic sclerosis; TCR, T cell receptor.

1. Schett G, et al. *Ann Rheum Dis*. 2024;83(11):1409–1420. 2. Rubin SJS, et al. *Nat Rev Rheumatol.* 2019;15(5):303–315. 3. Scaletti C, et al. *Clin Exp Immunol*. 2025;219(1):uxae098.

# Rese-cel (CABA-201): CD19-CAR T Designed For Autoimmunity

Cabaletta's CD19 binder with similar in vitro & in vivo activity to FMC63[1,2] (binder used in academic report[3])

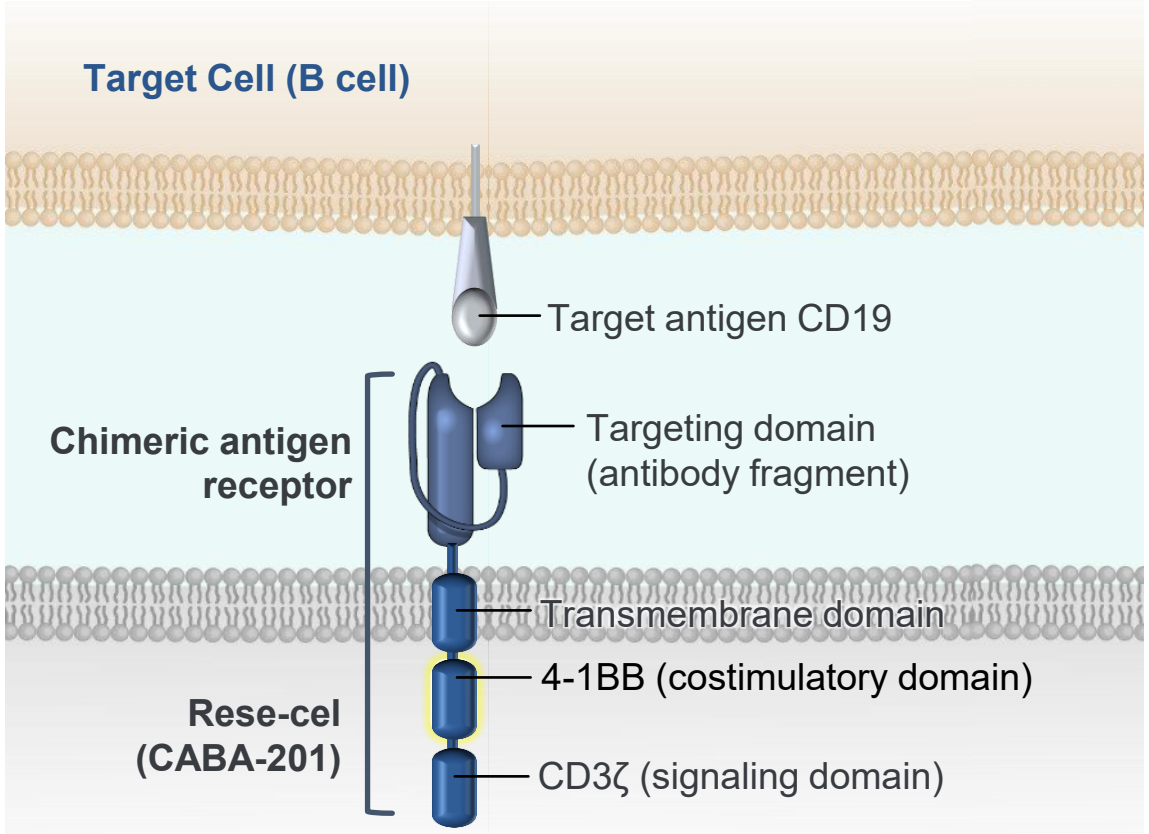



Image adapted from June CH and Sadelain M. 2018.[4]

## Rese-cel product design and clinical/translational data

**4-1BB costimulatory domain with fully human binder[1]**

- Binder with similar affinity and biologic activity to academic FMC63 binder while binding to the same epitopes[1,2]

**Same weight-based dose as in academic studies[3,5]**

- Potential to provide immune reset based on initial clinical and translational data[5]

**Initial patients treated with rese-cel have shown compelling clinical responses with safety data that supports development in autoimmune diseases[6]**

CAR, chimeric antigen receptor; rese-cel, resecabtagene autoleucel.

1. Peng BJ, et al. *Mol Ther Methods Clin Dev*. 2024;32(2):101267. 2. Dai Z, et al. *J Cell Physiol*. 2021;236(8):5832–5847. 3. Müller F, et al. *N Engl J Med*. 2024;390(8):687–700. 4. June CH, Sadelain M. *N Engl J Med*. 2018;379(1):64–73. 5. Volkov J, et al. *Mol Ther*. 2024;32(11):3821–3828. 6. Sheikh S, et al. *Arthritis Rheumatol*. 2024;76 (Suppl 9). Abstr. No. 1733.

# Autologous CAR T Cell Therapy: How Rese-cel is Manufactured

Designed to combine antibodies' targeting ability with the cell-killing machinery of a patient's own T cells[1,2]

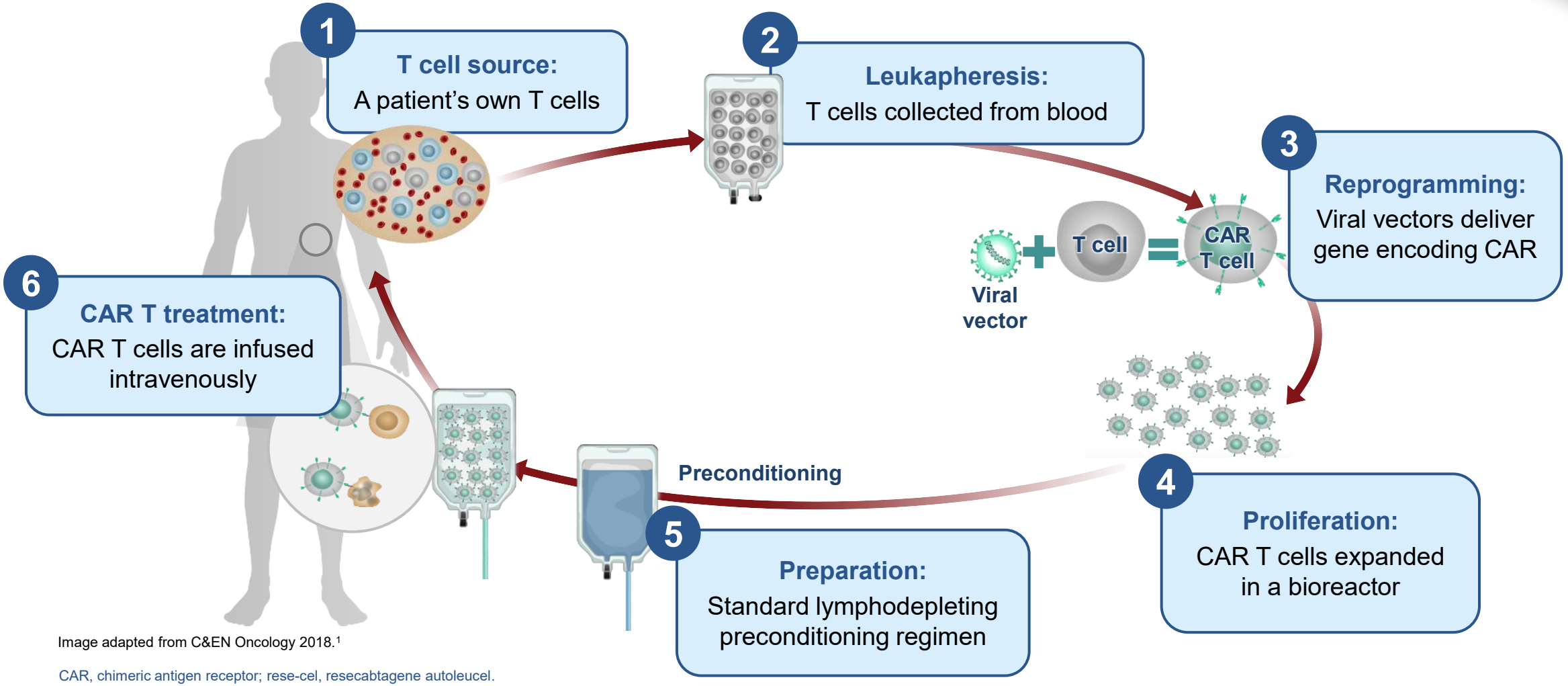


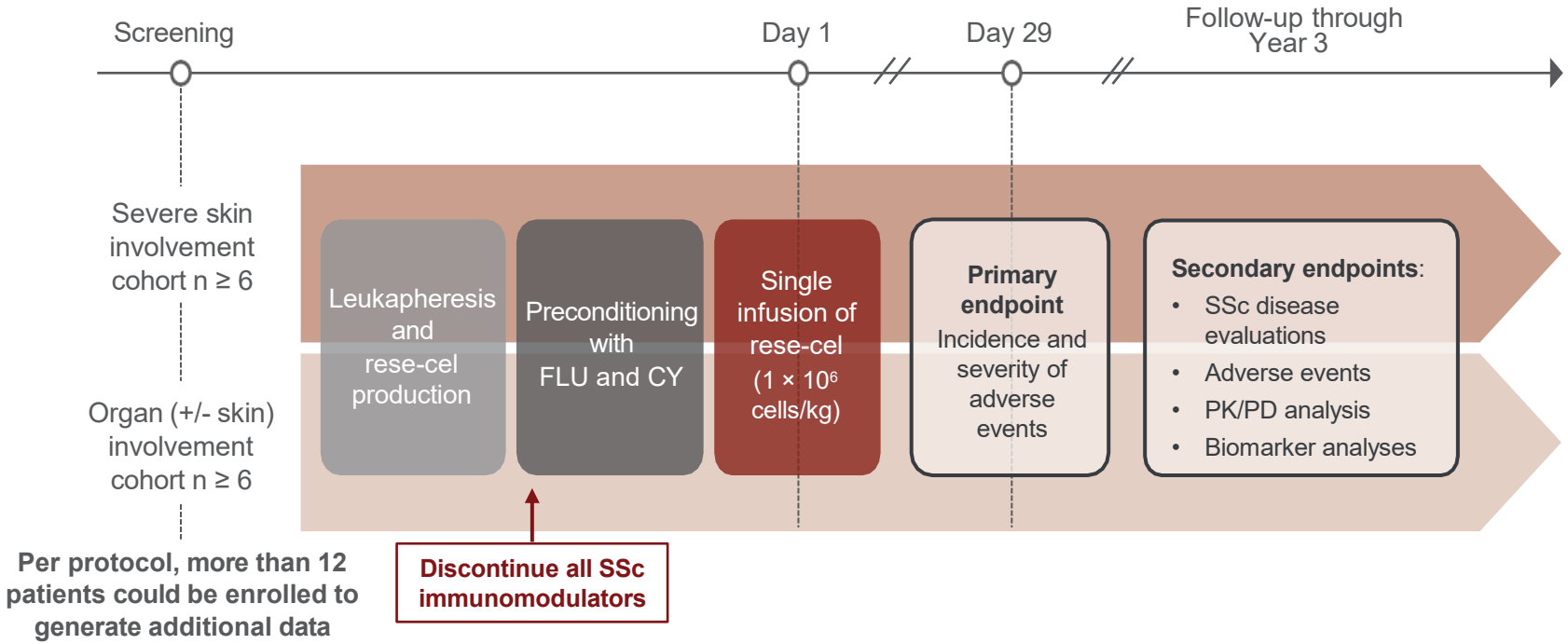

Image adapted from C&EN Oncology 2018.[1]

CAR, chimeric antigen receptor; rese-cel, resecabtagene autoleucel.

1. C&EN Oncology. 2024. Available at: https://cen.acs.org/pharmaceuticals/oncology/Controlling-CAR-T-scientists-plan/96/i19 (accessed May 2025). 2. Peng BJ, et al. *Mol Ther Methods Clin Dev*. 2024;32(2):101267.

# RESET-SSc™ Study Design[1,2]

## Enrolling patients with moderate to severe disease that is refractory to standard of care




### Key Inclusion Criteria[1,2]

- Age ≥18 and ≤75 with a limited or diffuse SSc diagnosis (2013 EULAR/ACR classification criteria)
- Early, active disease
- Evidence of significant skin, pulmonary, renal, or cardiac involvement

### Key Exclusion Criteria[1,2]

- Severe lung or cardiac impairment
- Treatment with B cell-depleting agent within prior ~6 months
- Previous CAR T cell therapy and/or HSCT

ACR, American College of Rheumatology; CAR, chimeric antigen receptor; CY, cyclophosphamide; EULAR, European Alliance of Associations for Rheumatology; FLU, fludarabine; HSCT, hematopoietic stem cell transplant(ation); PD, pharmacodynamic; PK, pharmacokinetic; rese-cel, RESET™, resecabtagene autoleucel, REstoring Self Tolerance.

1. Cabaletta Bio – Data on File. 2. NCT06328777. Available online at: www.clinicaltrials.gov/study/NCT06328777 (accessed May 2025).

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# Baseline Characteristics: First 2 Patients in the RESET-SSc Program

| | RESET-SSc™ | |
|---|---|---|
| **Patient / Cohort** | **SSc-Skin-1**<br>(Severe skin cohort) | **SSc-Skin-2**<br>(Severe skin cohort) |
| **Age, sex** | 66 F | 55 F |
| **Disease duration (y)** | ~2 | ~0.5 |
| **Autoantibodies** | RNA Pol III | Scl-70 |
| **Baseline* mRSS** | **42** | **38** |
| **Baseline* HAQ-DI** | 2.25 | 2.125 |
| **Baseline* PFTs (% predicted)** | FVC: 91<br>DLCO: 70 | FVC: 93<br>DLCO: 58 |
| **ILD presence†** | ✓ | - |
| **Therapies at Screening** | MMF (1500 mg BID) | MMF (1500 mg BID), GC |
| **Other prior therapies** | HCQ, BRX (Investigational) | None |
| **Glucocorticoid dose at Screening (mg/day)** | 0 | 5 |

As of May 6, 2025.
*Baseline disease activity = activity before preconditioning. †Per patient history and HRCT
BID, twice per day; BRX, brentuximab vedotin; DLCO, % predicted diffusing capacity for carbon monoxide; FVC, forced vital capacity; GC, glucocorticoid; HAQ-DI, Health Assessment Questionnaire Disability Index; HCQ, hydroxychloroquine; ILD, interstitial lung disease; MMF, mycophenolate mofetil; mRSS, modified Rodnan skin score; PFT, pulmonary function test; RESET, REstoring SElf-Tolerance; RNA Pol III, ribonucleic acid polymerase III; SSc, systemic sclerosis; y, years.
Cabaletta Bio: Data on File.

# Incidence of Relevant and Related Serious Adverse Events*

| SSc-Skin-1 | SSc-Skin-2 |
|---|---|
| • CRS Grade 2† on Day +10<br>  • Transient hypotension resolved with IV hydration<br>  • No tocilizumab administered<br>• No ICANS<br>• No other SAEs related to rese-cel‡ | • No CRS<br>• Grade 3 ICANS†<br>  • Productive cough + fever prior to infusion<br>  • Low grade fever & rigors on Day +8, treated with IV cefepime, vancomycin, and morphine<br>  • On Day +9, developed ICE score of 3, progressed to ICE score of 1 on Day +10<br>  • Arousable; able to speak and follow commands but answered all questions to the ICE assessment incorrectly.<br>  • No evidence of seizure, elevated intracranial pressure or cerebral edema<br>  • Resolved within 2 days following dexamethasone<br>• Grade 1 neutropenic fever<br>• No other SAEs related to rese-cel‡ |

*As of May 6, 2025; primary endpoint is incidence and severity of adverse events through Day 29.
†Graded per ASTCT Consensus Grading Criteria. Both patients received medication for seizure prophylaxis.
‡As assessed per US Food and Drug Administration guidelines.
ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, immune effector cell-associated encephalopathy; SAE, serious adverse event.
Cabaletta Bio: Data on File.

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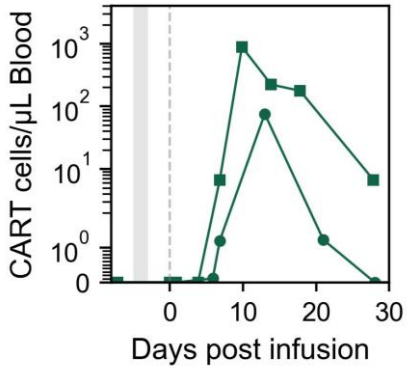
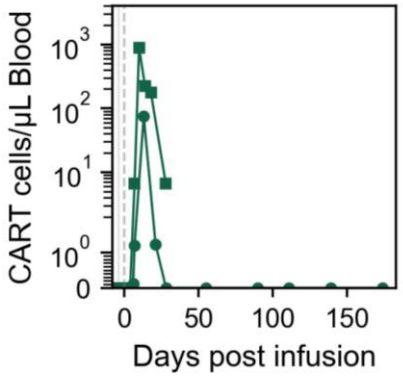
# Rese-cel Expansion and B Cell Kinetics

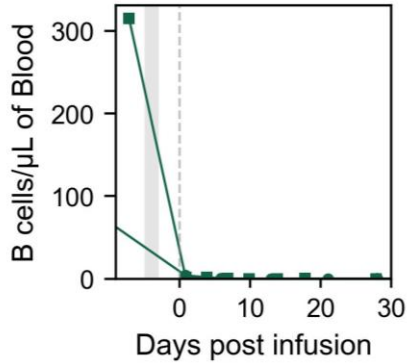
Peak rese-cel expansion and transient peripheral B cell depletion occurred by 13 days post infusion

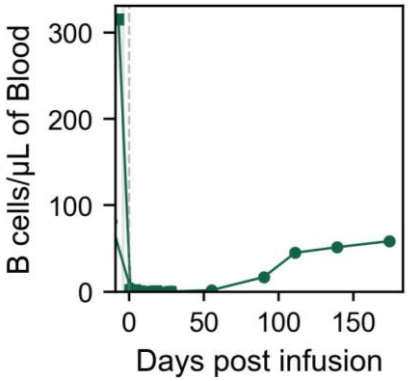
## Rese-cel Pharmacokinetics




## B Cell Kinetics




SSc-Skin-1
SSc-Skin-2

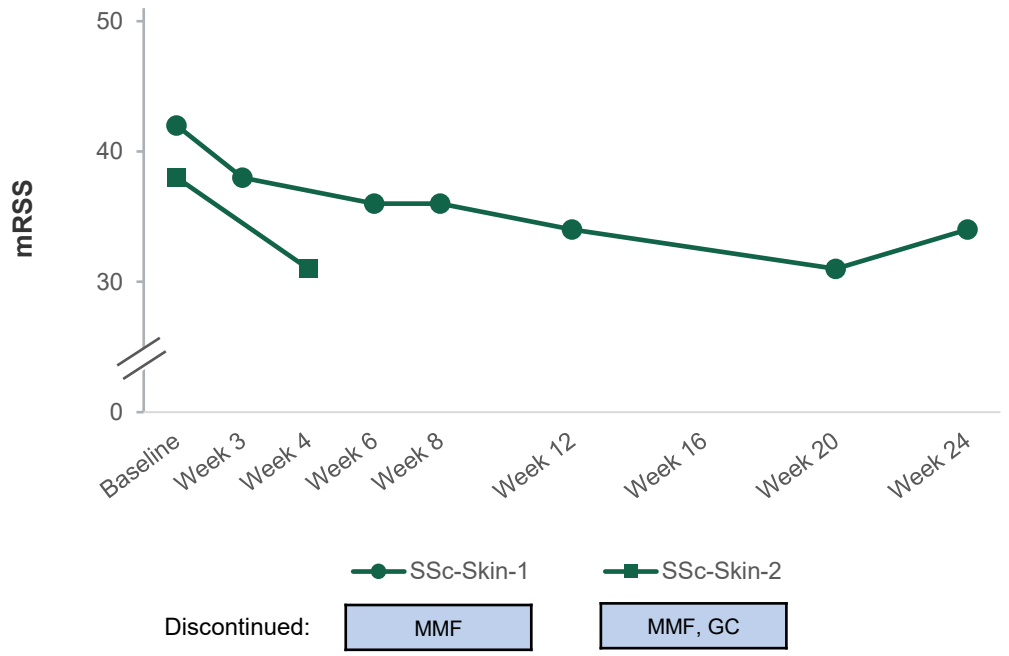
**Early repopulating B cells at 8 weeks post-infusion in SSc-Skin-1 display a transitional naïve phenotype**

CAR, chimeric antigen receptor; rese-cel, resecabtagene autoleucel; SSc, systemic sclerosis.
Cabaletta Bio: Data on file.

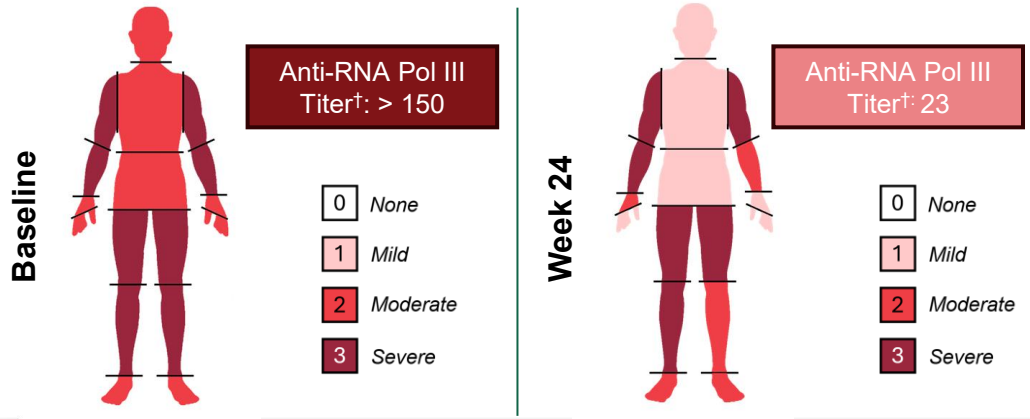
# Efficacy Data Following Rese-cel Infusion[1]

Improvements in both SSc patients after discontinuing immunomodulatory drugs and steroids

## Overall mRSS (N=2)




## mRSS by body area (SSc-Skin-1)




## Pulmonary Evaluations (SSc-Skin-1)‡

| | Baseline | Week 12 | Week 24 |
|---|---|---|---|
| **DLCO** | 70% | 85% | 81% |
| **FVC** | 91% | 97% | 105% |
| **ILD** | Mild stabilization on HRCT | | |

**SSc-Skin-1 met revised CRISS response criteria starting at Week 12, supporting potential for a drug-free clinical response***

*As of May 6, 2025. †RNA Pol III IgG level performed locally at U Mich. ‡ Pulmonary evaluations not available for SSc-Skin-2 at Week 4.

CRISS, Composite Response Index in Systemic Sclerosis; DLCO, % predicted diffusing capacity for carbon monoxide; FVC, % predicted forced vital capacity; GC, glucocorticoid; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; MMF, mycophenolate mofetil; mRSS, modified Rodnan Skin Score (measure of skin thickness in SSc across 17 body areas, with a maximum score of 51[2]); RNA Pol III, ribonucleic acid polymerase III; rese-cel, resecabtagene autoleucel; SSc, systemic sclerosis.

1. Cabaletta Bio: Data on File. 2. Khanna D, et al. *J Scleroderma Relat Disord*. 2017;2(1):11–18;.

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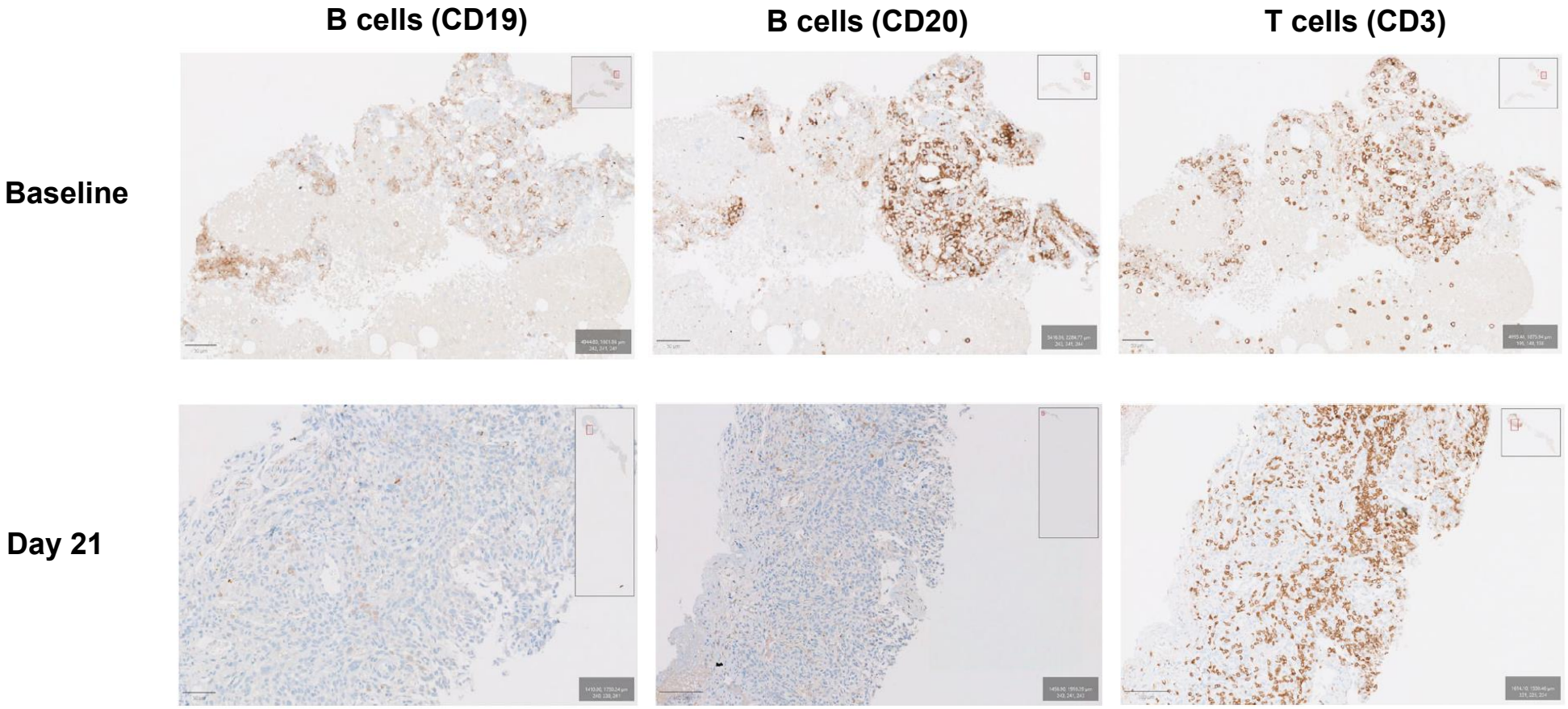
# Lymph Node B Cell Depletion in SSc-Skin-1[1]

## Lymph node B cell depletion is contemporaneous with peripheral B cell depletion*



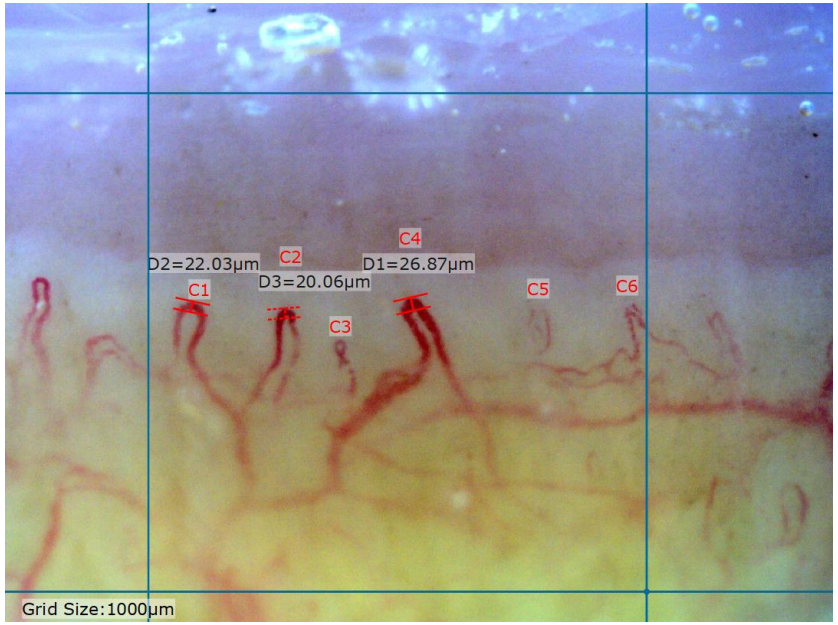

**B cell depletion observed to date is consistent with an academic study in autoimmune disease showing CD19-CAR T cell therapy achieves deeper depletion than mAbs[2]**

*Lymph node biopsies were from the left inguinal area using USG at U. Mich. by Dr. Khanna.
CAR, chimeric antigen receptor; rese-cel, resecabtagene autoleucel; mAb, monoclonal antibody; RESET, REstoring SElf-Tolerance; SSc, systemic sclerosis.
1. Cabaletta Bio: Data on File. 2. Tur C, et al. *Ann Rheum Dis.* 2025;84(1):106–114.

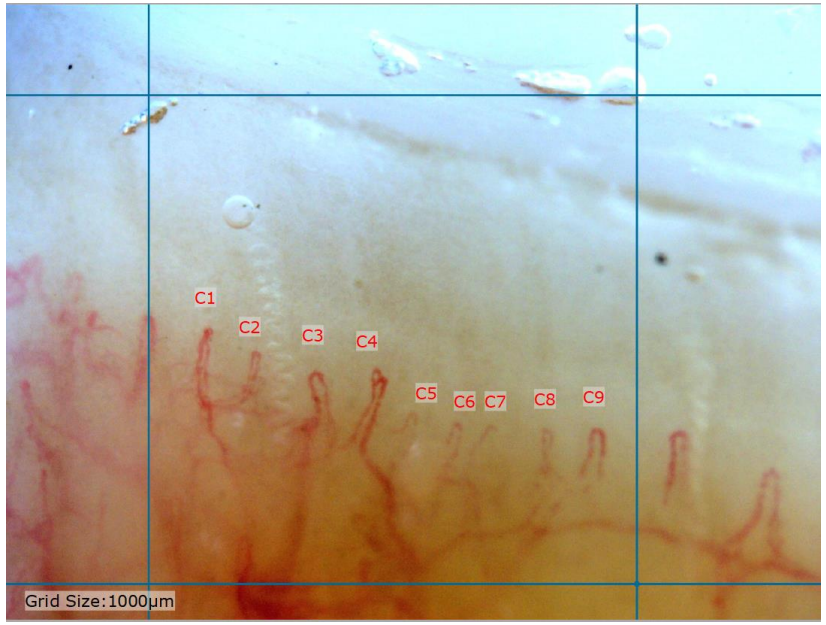
# Nailfold Capillaroscopy for SSc-Skin-1 After Rese-cel

## Preliminary evidence of vascular recovery or stabilization in the majority of fingers

**Baseline**




**Week 24**




rese-cel, resecabtagene autoleucel; RESET, REstoring SElf-Tolerance; SSc, systemic sclerosis.
Cabaletta Bio: Data on File.

# Summary from Clinical and Translational Data: RESET SSc™

- No unexpected safety findings in two SSc patients treated with rese-cel to date*
  - Transient Grade 2 CRS (fever + hypotension) in one patient
  - Transient Grade 3 ICANS in one patient based on confusion (no seizure, motor findings, or cerebral edema) associated with a peak in serum IL-8, but not IL-6
- Rese-cel provided evidence of efficacy off all immunomodulatory meds and steroids, which was sustained out to 6 months in the first patient
- Rese-cel peak expansion was observed at approximately 11 days after infusion
- B cells rapidly and transiently depleted in peripheral blood and tissue following rese-cel infusion
  - Evidence of tissue level B cell depletion in SSc-Skin-1 at 21 days post-infusion
  - B cells begin repopulating by week 8 post-infusion in 1 of 2 patients (SSc-Skin-2 has limited follow-up)
- Systemic sclerosis registrational discussions with FDA anticipated in fourth quarter of 2025[1]

*As of May 6, 2025.
CRS, cytokine release syndrome; FDA, US Food and Drug Administration; ICANS, immune effector cell-associated neurotoxicity syndrome; rese-cel, resecabtagene autoleucel; RESET, REstoring SElf-Tolerance; SSc, systemic sclerosis.
[1]Cabaletta Bio. (15 May 2025), [Press Release], https://www.cabalettabio.com/news-media/press-releases/detail/128/cabaletta-bio-announces-2027-rese-cel-bla-submission

# Acknowledgments


## Patients and caregivers involved in the RESET™ clinical program

## Site investigators and staff involved with these patients from the RESET™ clinical program

- University of Michigan
- Duke University

## Cabaletta Bio team

- Biostatistics
- Clinical Development
- Clinical Operations
- Computational Biology
- Manufacturing
- Medical Affairs
- Translational Medicine
- Regulatory Affairs

# Back Up Slide

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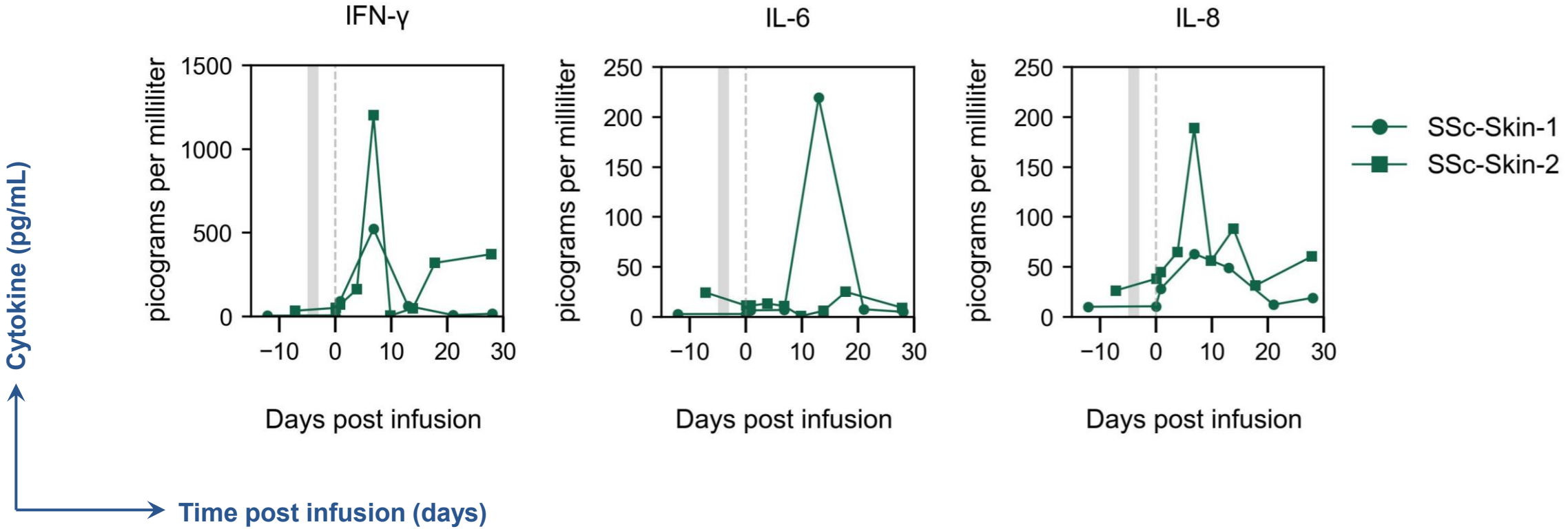
# Serum cytokine levels following rese-cel infusion

IFN-γ increased as expected with rese-cel activation, only SSc-Skin-2 exhibited high levels of IL-8




**SSc-Skin-2 with ICANS demonstrated high levels of IFN-γ and IL-8 but not IL-6[1]**

[1]Teachey, DT et al. *Cancer Discov*. 2016;6(6):664-679.
Serum cytokine levels quantified using mesoscale discovery (MSD) platform. $C_{max}$, maximum concentration; IFN-γ, interferon-gamma; IL, interleukin; SSc, systemic sclerosis.
Cabaletta Bio: Data on file.