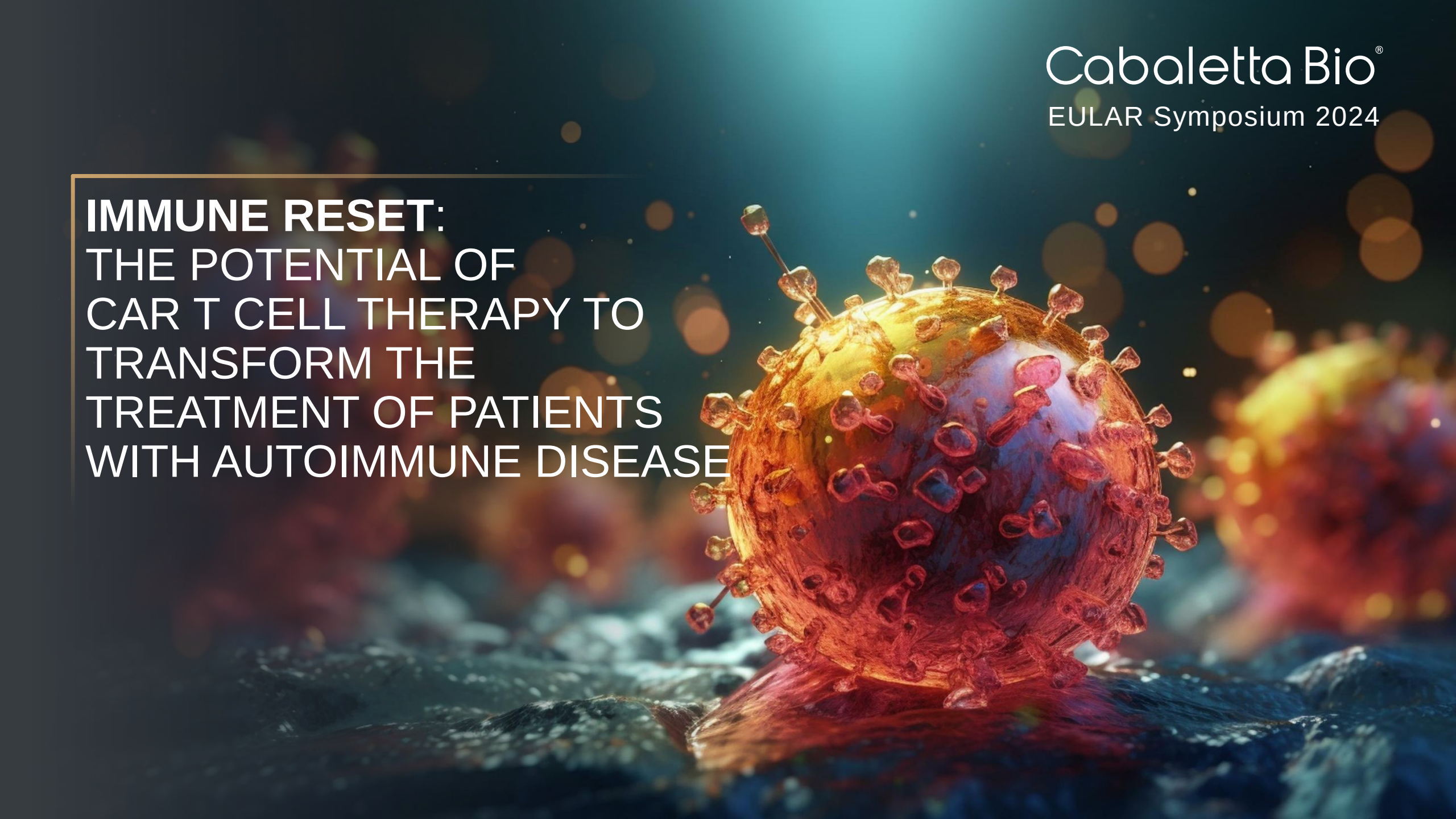
Cabaletta Bio®

EULAR Symposium 2024

IMMUNE RESET: THE POTENTIAL OF CAR T CELL THERAPY TO TRANSFORM THE TREATMENT OF PATIENTS WITH AUTOIMMUNE DISEASE



Symposium Speakers

Carl H. June, MD
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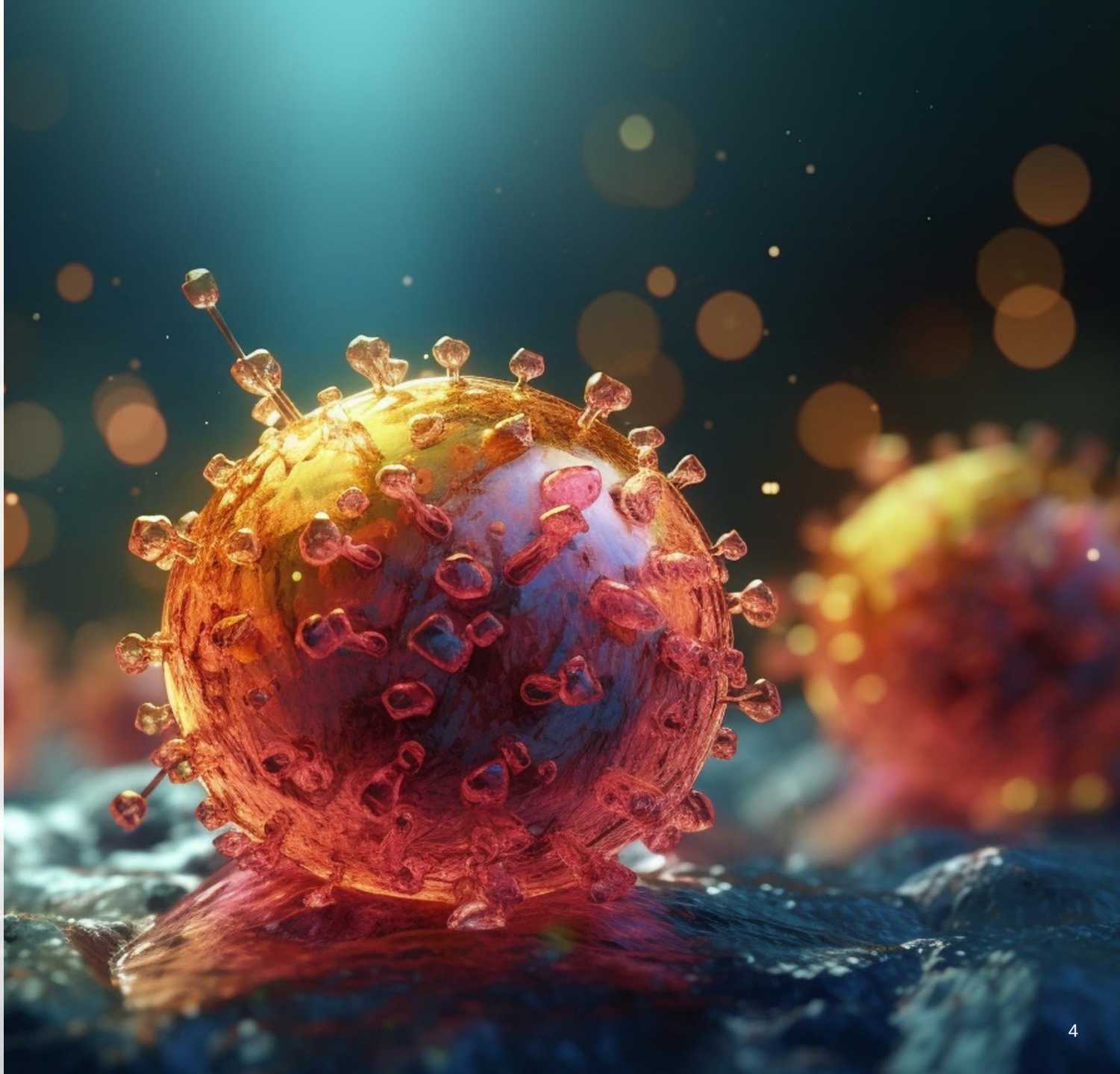
Drs Georg Schett and Carl June are members of Cabaletta Bio's Scientific Advisory Board.

Agenda

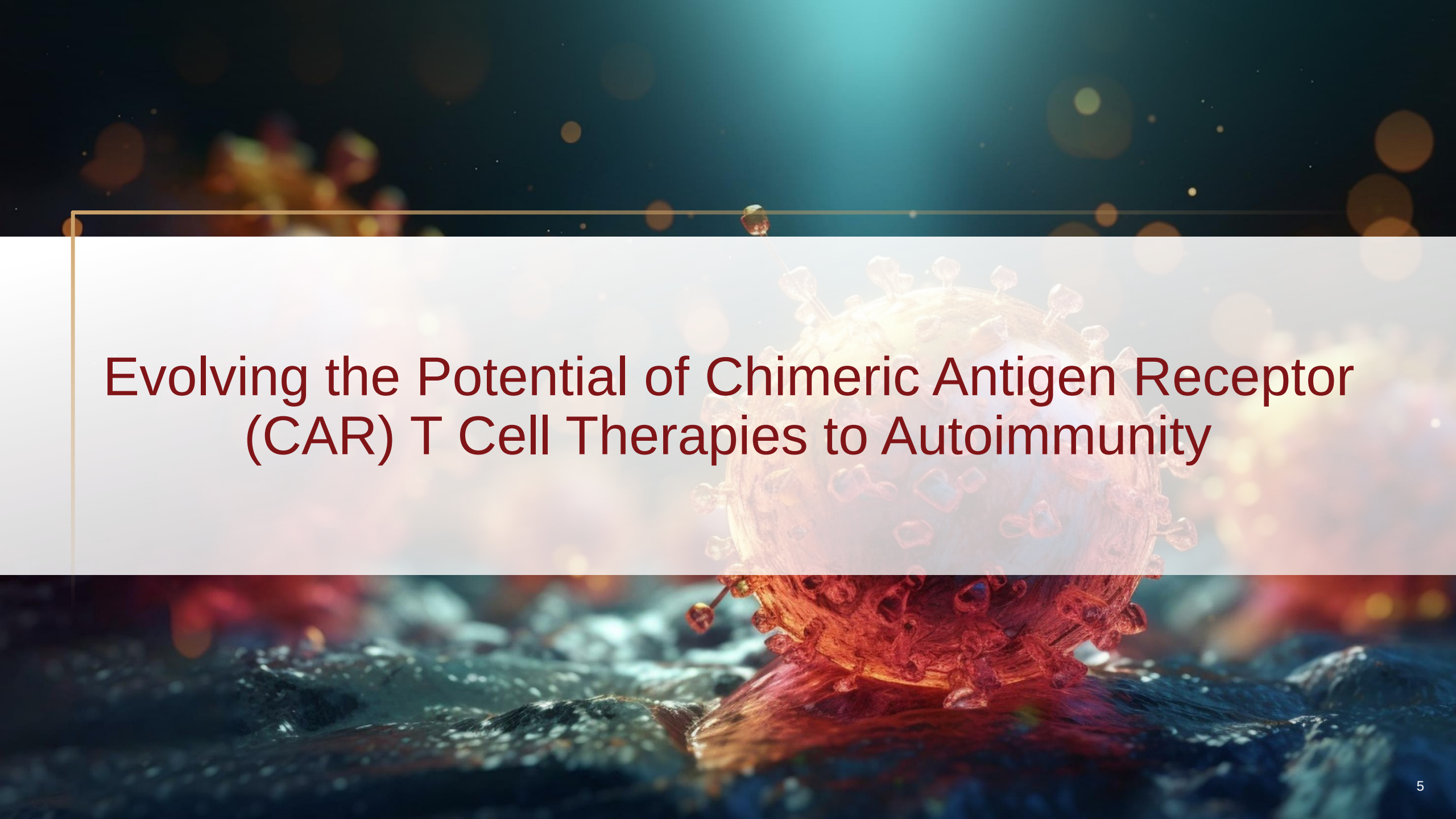
8:15 AM-8:20 AM	8:20 AM-8:35 AM	8:35 AM-8:50 AM	8:50 AM-9:15 AM	9:15 AM-9:30 AM
Welcome and introductions *David J. Chang, MD, MPH, FACR*	**Evolving the potential of chimeric antigen receptor (CAR) T cell therapies to autoimmunity** *Carl H. June, MD*	**Resetting the immune system of patients with autoimmune disease** *Georg Schett, MD*	**Unlocking the potential of CD19-CAR T cell therapy in myositis and lupus** *David J. Chang, MD, MPH, FACR*	**Questions and answers**

Learning Objectives

- Learn about the history of CAR T cell therapies in oncology and their potential in autoimmunity
- Review the role of B cells in autoimmune disease and the potential for CD19-CAR T cell therapy to transform treatment
- Understand the potential of CD19-CAR T cell therapy to reset the immune system in myositis and lupus

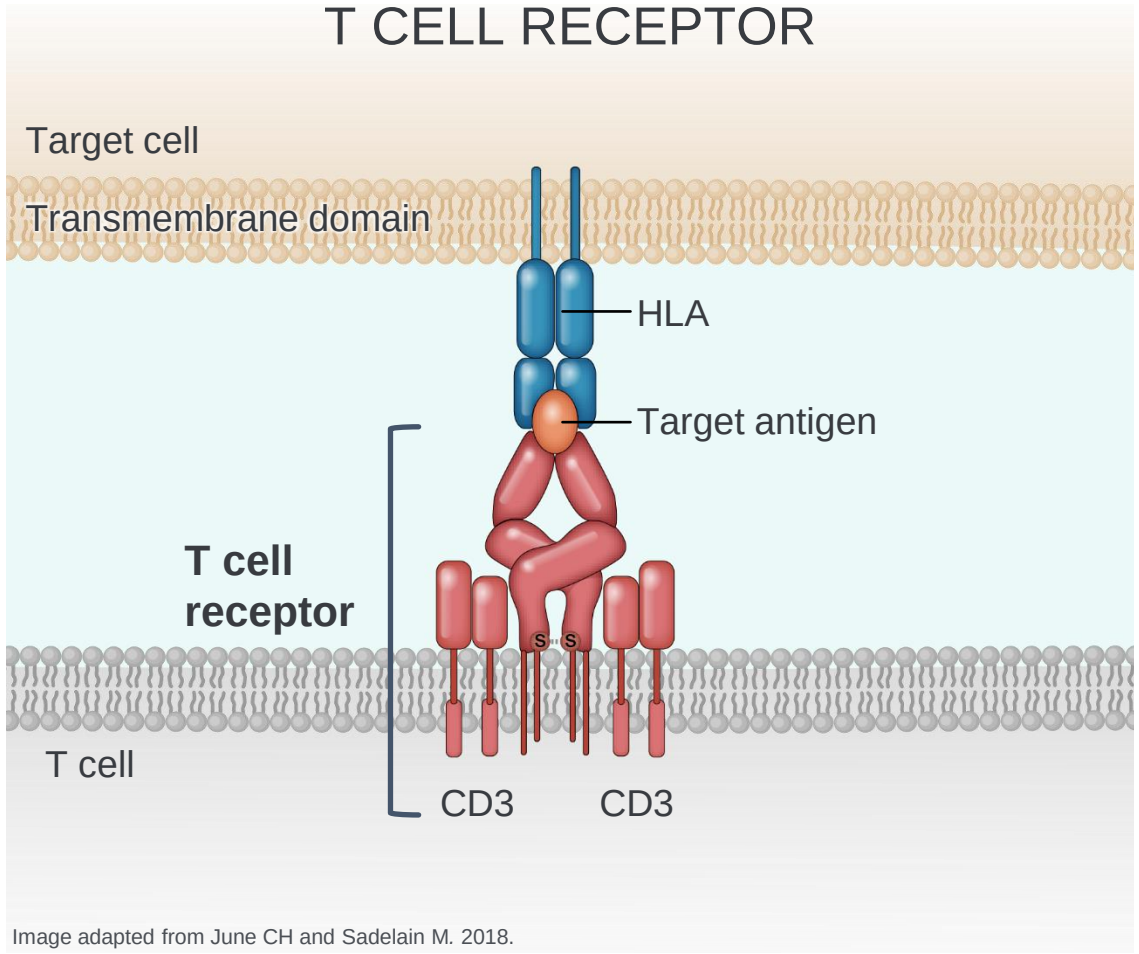


Evolving the Potential of Chimeric Antigen Receptor (CAR) T Cell Therapies to Autoimmunity



What Are Chimeric Antigen Receptor (CAR) T Cells?

Engineered T cells that combine the targeting ability of antibodies with the cell-killing machinery of T cells



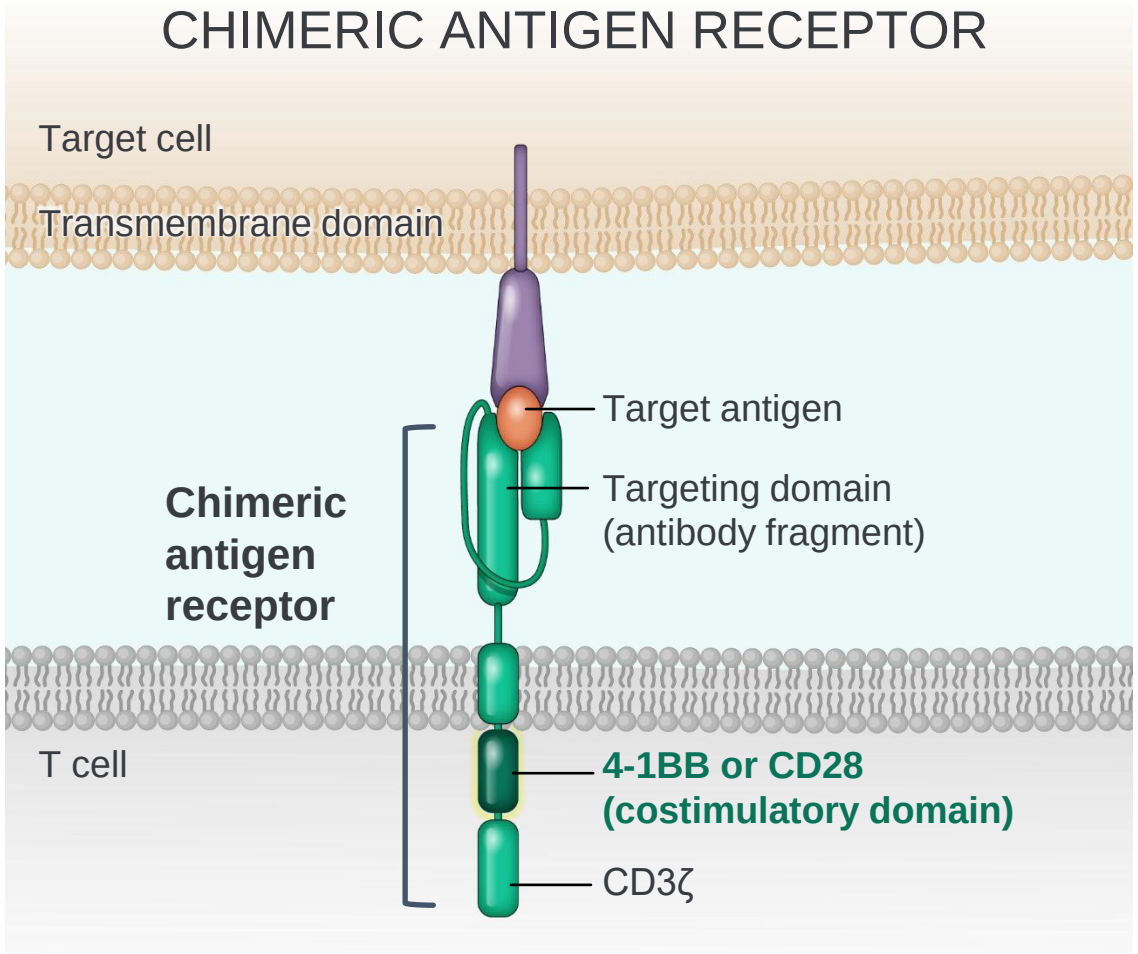


Image adapted from June CH and Sadelain M. 2018.

CD, cluster of differentiation; HLA, human leukocyte antigen.

June CH, Sadelain M. *N Engl J Med.* 2018;379;64-73.

Personalized Manufacturing of CAR T Cells

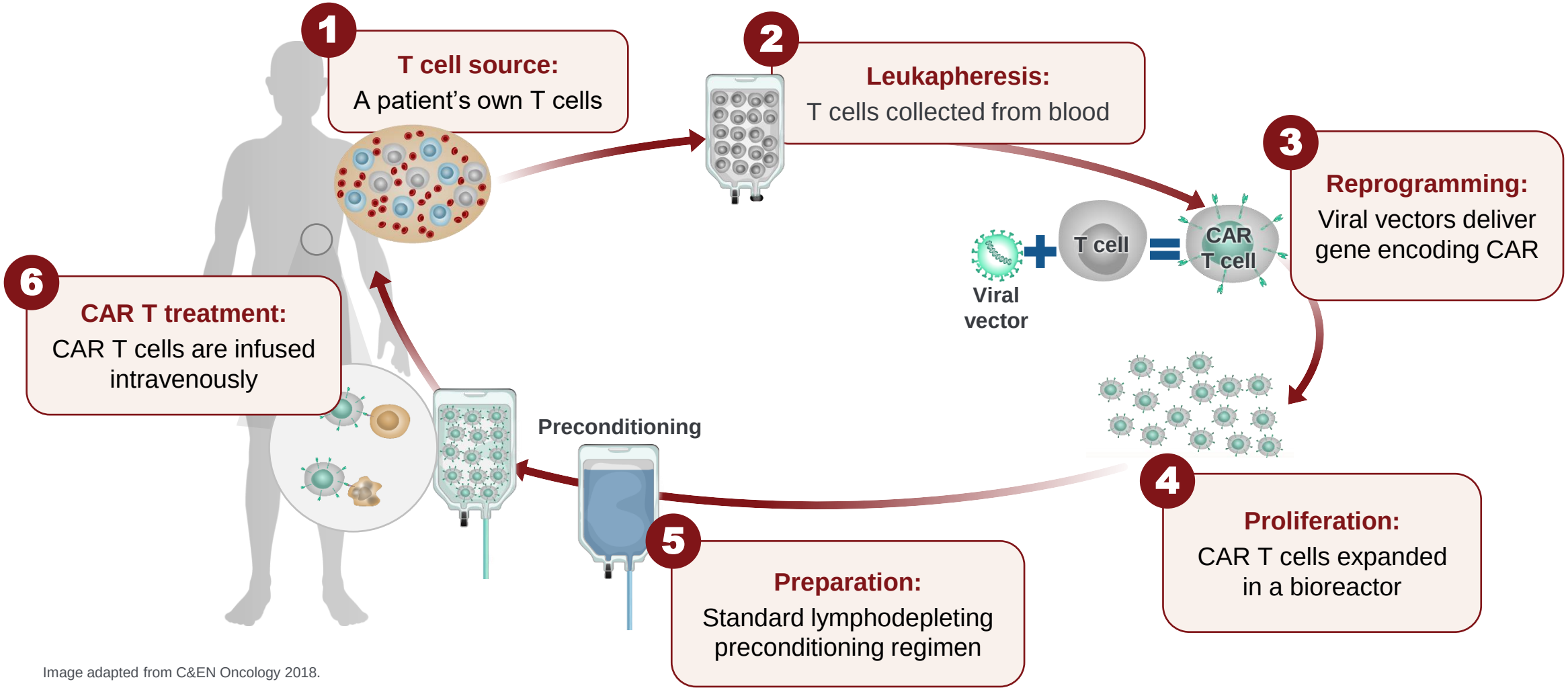


Image adapted from C&EN Oncology 2018.

C&EN Oncology. Accessed June 10, 2024. https://cen.acs.org/pharmaceuticals/oncology/Controlling-CAR-T-scientists-plan/96/i19.

Considerations and Efficacy Outcomes of CAR T in Cancer

Personalized cell therapy product that behaves as a ‘living drug’ by fully eliminating target cells in the body[1]

- **CAR T is a ‘living drug’[1]**
  - Engrafts & expands in the body
  - Penetrates across tissues
- **Activated by target cells[1]**
- **Preconditioning key in oncology[2]**
  - Eliminates cytokine sinks
  - Increases CAR T expansion, persistence & activity

CD19-CAR T cells have been FDA approved for lasting remission of B cell cancers[1]

2017	2017	2020	2021
Kymriah (tisagenlecleucel) **4-1BB**	**Yescarta** (axicabtagene ciloleucel) **CD28**	**Tecartus** (brexucabtagene autoleucel) **CD28**	**Breyanzi** (lisocabtagene maraleucel) **4-1BB**

COMPLETE remission rate:
40%-67%[3-7]

LONG-TERM remission rate:
30%-59%[6-9]

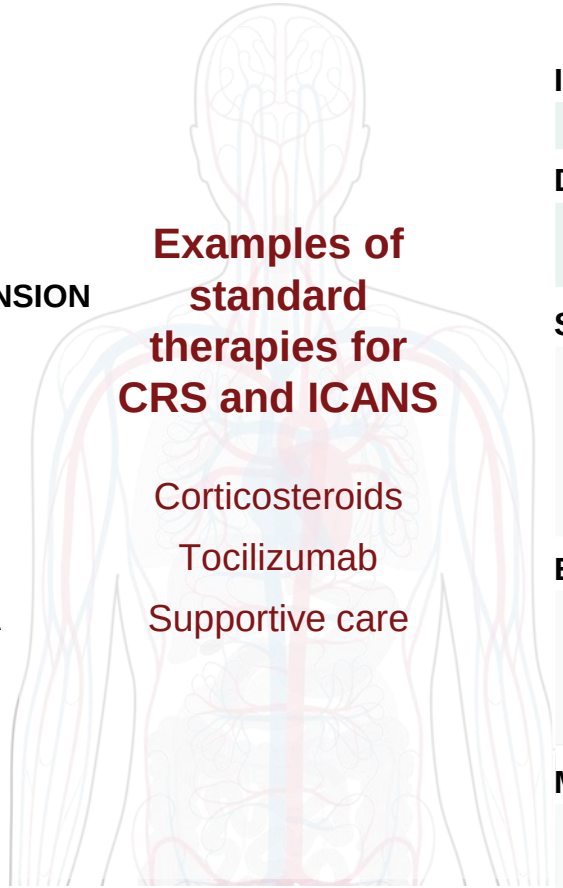
FDA, US Food and Drug Administration.
1. Holzinger A, Abken H. *Pharmacology.* 2022;107(9-10):446-463. 2. Pietrobon V, et al. *Int J Mol Sci.* 2021;22(19):10828. 3. Maude SL, et al. *N Engl J Med.* 2018;378(5):439-448. 4. Schuster SJ, et al. *N Engl J Med.* 2019;380(1):45-56. 5. Locke FL, et al. *Lancet Oncol.* 2019;20(1):31-42. 6. Abramson JS, et al. *Lancet.* 2020;396(10254):839-852. 7. Wang M, et al. *N Engl J Med.* 2020;382(14):1331-1342. 8. Schuster SJ, et al. *Lancet Oncol.* 2021;22(10):1403-1415. 9. Neelapu SS, et al. *Blood.* 2023;141(19):2307-2315.

Common Adverse Events Associated With CAR T Cell Therapy

Familiarity with CAR T-associated AEs has increased in oncology, enabling potential outpatient administration

CRS
(cytokine release syndrome)

		Grade 1	Grade 2	Grade 3	Grade 4
FEVER	Temperature ≥38°C				
	with				
HYPOTENSION	No vasopressors				
	Vasopressor +/- vasopressin				
	Multiple vasopressors				
	and/or				
HYPOXIA	Low-flow nasal cannula or blow-by				
	High-flow nasal cannula face mask, nonrebreather mask, or Venturi mask				
	Positive pressure (CPAP, BiPAP)				



Examples of standard therapies for CRS and ICANS

Corticosteroids

Tocilizumab

Supportive care

ICANS
(immune effector cell-associated neurotoxicity syndrome)

	Grade 1	Grade 2	Grade 3	Grade 4
ICE SCORE	7-9	3-6	0-2	Unarousable/unable to perform ICE
DEPRESSED LEVEL OF CONSCIOUSNESS	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Unarousable or requires vigorous tactile stimuli to arouse or coma
SEIZURE	None	None	Any clinical seizure that resolves rapidly or nonconvulsive seizure that resolves with intervention	Life-threatening prolonged seizure (>5 min) or repetitive clinical or electrical seizures with no return to baseline in between
ELEVATED ICP/CEREBRAL EDEMA	None	None	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; papilledema; or Cushing's triad
MOTOR FINDINGS	None	None	None	Deep focal motor weakness such as hemiparesis or paraparesis

Diagram adapted from Zhang Y, et al. 2023.

AE, adverse event; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, immune effector cell encephalopathy; ICP, intracranial pressure.

Zhang Y, et al. *J Clin Med*. 2023;12(19):6124.

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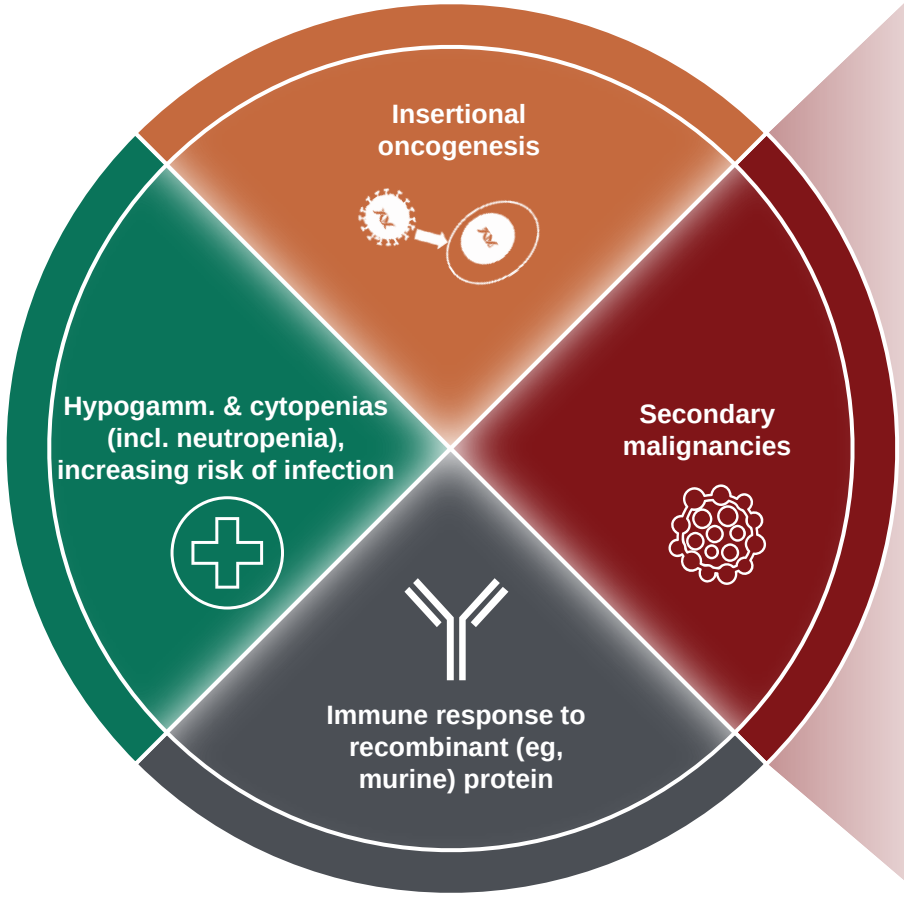
Potential Adverse Events After CAR T Cell Therapy in Cancer



Secondary malignancies

- In November 2023, the FDA reported identifying 22 cases of T cell cancers that occurred among the 34,000 patients who previously received treatment with CAR T products[2]
- In April 2024, the FDA required approved CAR T products (CD19 and BCMA targeted) to add a boxed warning for T cell malignancy when used in patients treated for hematologic malignancies[4]
- In January 2024, the Director of FDA's CBER suggested the risk:benefit profile of CAR T is not in question in oncology or in moving forward development programs in autoimmune diseases[5,6]

Image adapted from Bonifant CL, et al. 2016,[1] Verdun N and Marks P. 2024,[2] Adkins S, et al. 2019.[3]

1. Bonifant CL, et al. *Mol Ther Oncolytics.* 2016;3:16011. 2. Verdun N, Marks P. *N Eng J Med.* 2024;390(7):584-586. 3. Adkins S. *J Adv Pract Oncol.* 2019;10(suppl 3):21-28. 4. FDA. Accessed June 10, 2024. https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/fda-requires-boxed-warning-t-cell-malignancies-following-treatment-bcma-directed-or-cd19-directed.
5. Wu L. Accessed June 10, 2024. https://endpts.com/jpm24-fdas-peter-marks-says-some-secondary-cancer-cases-after-car-t-therapy-may-be-causal-but-benefits-still-outweigh-risks/. 6. Expediting the Development of Cell and Gene Therapy. Accessed June 10, 2024. https://www.youtube.com/watch?v=jt3CNgsCXAk.
CBER, Center for Biologics Evaluation and Research.

Differences in CD19-CAR T Constructs

A human CD19 binder and 4-1BB costimulatory domain may be ideal for a CD19-CAR T construct

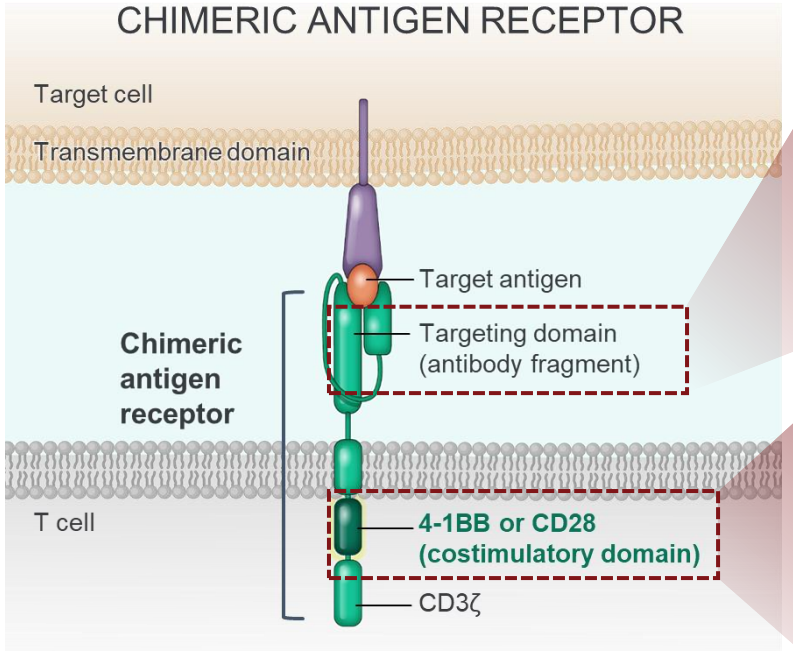


Image adapted from June CH and Sadelain M. 2018.[1]

IMMUNOGENICITY[2]

Sources of CAR constructs

Chimeric

Approved products (FMC63)

Humanized

Fully human

Candidates under development with potentially lower risk of immune responses

Image adapted from Brekke OH and Inger Sandlie. 2003.[2]

SAFETY[3] Product in lymphoma study[a]	Costim domain	CRS		ICANS		Requiring tocilizumab	Requiring steroids
		All Gr	Gr ≥3	All Gr	Gr ≥3		
Axicabtagene ciloleucel[4]	CD28	93%	13%	64%	28%	43%	27%
Brexucabtagene autoleucel[5]	CD28	91%	15%	63%	31%	59%	22%
Tisagenlecleucel[6]	4-1BB	58%	22%	21%	12%	14%	10%
Lisocabtagene maraleucel[7]	4-1BB	42%	2%	30%	10%	18%	10%

In oncology, a 4-1BB costimulatory domain is associated with a reduced incidence and severity of CRS and ICANS events[6,7]

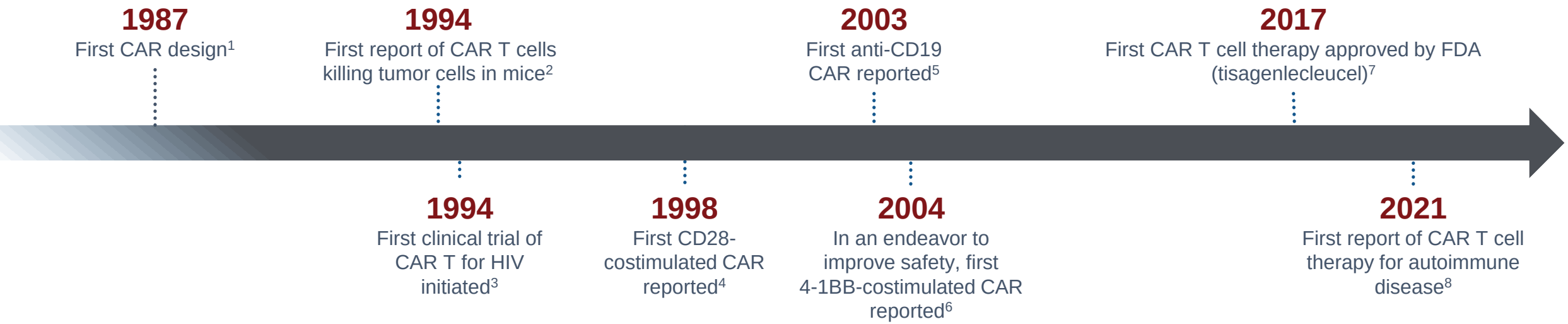
[a]Similar safety outcomes comparing 4-1BB and CD28 costimulatory domains were also demonstrated in patients with B-ALL.[8,9]

B-ALL, B cell acute lymphoblastic leukemia; Costim, costimulatory. Gr, grade.

1. June CH, Sadelain M. *N Engl J Med*. 2018;379:64-73. 2. Brekke OH, Sandlie I. *Nat Rev Drug Discov.* 2003;2(1):52-62. 3. Cappell KM, Kochenderfer JN. *Nat Rev Clin Oncol.* 2021;18(11):715-727. 4. Neelapu SS, et al. *N Engl J Med.* 2017;377(26):2531-2544. 5. Wang M, et al. *N Engl J Med.* 2020;382(14):1331-1342. 6. Schuster SJ, et al. *N Engl J Med.* 2019;380(1):45-56. 7. Abramson JS, et al. *Lancet.* 2020;396(10254):839-852. 8. Zhao X, et al. *Mol Ther Oncolytics.* 2020;18:272-281. 9. Wu L, et al. *Cancers (Basel).* 2023;15(10):2767.

Success of CAR T in Oncology Established Over Decades

Significant experience with CAR T in B cell cancers provided the foundation for autoimmune application



- Multiple types of cell therapies are in phase 1/2 studies, with the majority being autologous CAR T cell therapy[9]
- Over 800 ongoing CAR T trials, with the majority in the US and China[10]

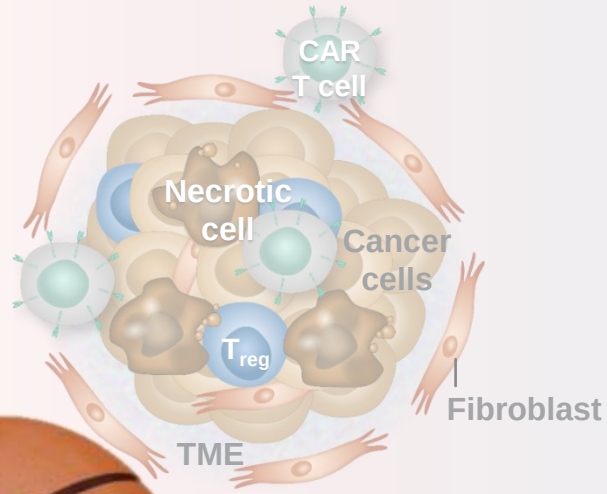
Experience in oncology has established foundation for application in autoimmune disease

1. Kuwana Y, et al. *Biochem Biophys Res Commun.* 1987;149(3):960-968. 2. Moritz D, et al. *Proc Natl Acad Sci USA.* 1994;91:4318-4322. 3. Roberts MR, et al. *Blood.* 1994;84(9):2878-2889. 4. Krause A, et al. *J Exp Med.* 1998;188:619-626. 5. Brentjens RJ, et al. *Nat Med*. 2003;101(4):1637-1644. 6. Imai C, et al. *Leukemia.* 2004;18:676-684. 7. O'Leary MC, et al. *Clin Cancer Res.* 2019;25(4):1142-146. 8. Mougiakakos D, et al. *N Engl J Med.* 2021;385(6):567-569. 9. Krishnamurthy A, et al. Wells Fargo, November 2017. 10. Clinicaltrials.gov. Accessed June 10, 2024. https://clinicaltrials.gov/search?intr=chimeric%20antigen%20receptor.

Considerations for CAR T Therapy in Cancer and Autoimmunity

Factors that predict adverse events and relapse are minimized in autoimmune diseases[1]

Cancer



Cancer (DLBCL)
~10 trillion cells

High risk[1-5]

Risk of side effects related to target B cell burden[1,2]

Risk of treatment failure due to mutational load (antigen escape)[1,2]

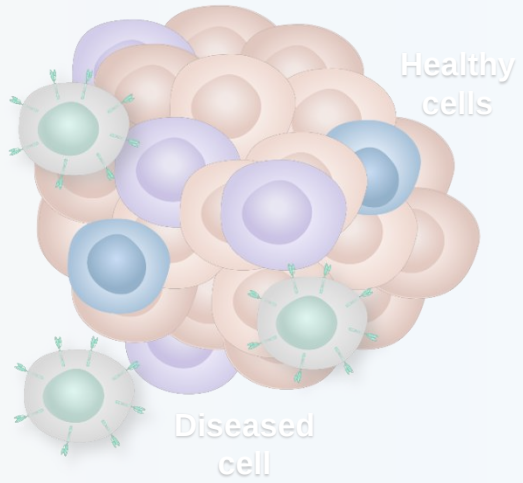
Risk of permanent B cell aplasia due to prior bone marrow damage[2]

Risk of environmental barriers for CAR T cell infiltration

Safety, including CRS, ICANS, and prolonged B cell aplasia[3-5]

Anticipated risk of suboptimal outcomes

Autoimmune disease



Healthy B cells
300 billion cells[7]

Lower Risk[1,6]

Images adapted from Baker DJ, et al. 2023.[1]

TME, tumor microenvironment.

1. Baker DJ, et al. *Nature.* 2023;619(7971):707-715. 2. Sterner RC, Sterner RM. *Blood Cancer J.* 2021;11(4):69. 3. Breyanzi. Prescribing information; 2024. 4. Yescarta. Prescribing information; 2024. 5. Kymriah. Prescribing information; 2022. 6. Müller F, et al. *N Engl J Med.* 2024;390(8):687-700. 7. Sender, R et al. *PNAS* 2023 e2308511120.

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Key Takeaways

Evolving the Potential of CAR T Cell Therapies to Autoimmunity

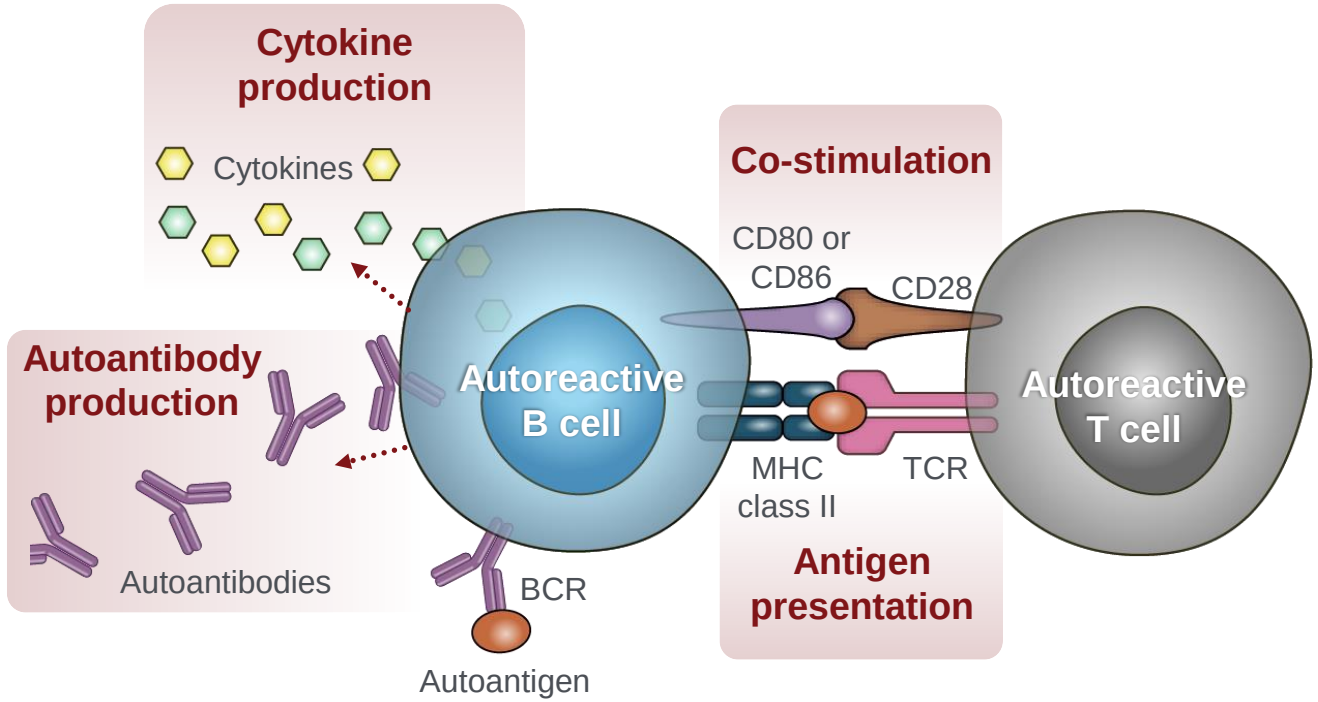
- CAR T cells are engineered T cells that are designed to combine the targeting ability of antibodies with the cell-killing machinery of T cells[1]
- Key learnings from oncology have the potential to accelerate the adoption of CAR T cell therapy for autoimmune disease[2,3]
- Differences in CD19-CAR T costimulatory domains seem to impact safety in cancer[3-5]
- Many factors that drive adverse events & disease relapse post-CAR T are not at play in autoimmune disease driven by B cells[3,6]
  - Potentially lower risk of CRS & ICANS due to lower B cell burden

1. Holzinger A, Abken H. *Pharmacology.* 2022;107(9-10):446-463. 2. Baker DJ, et al. *Nature.* 2023;619(7971):707-715. 3. Cappell KM, Kochenderfer JN. *Nat Rev Clin Oncol.* 2021;18(11):715-727. 4. Davey AS, et al. *Cancers.* 2021;13(38). 5. Zhao X, et al. *Molecular Therapy Oncolytics.* 2020;18. 6. Müller F, et al. *N Engl J Med.* 2024;390(8):687-700.

Resetting the Immune System of Patients With Autoimmune Disease

B Cells Play a Central Role in the Pathogenesis of Autoimmune Diseases

- **B cells contribute to autoimmunity through a variety of mechanisms[1,2]**
  - Autoantibody production
  - Antigen presentation
  - T cell co-stimulation
  - Production of proinflammatory cytokines
- **While circulating B cells are sensitive to depletion, tissue-resident B cells easily escape depletion[2]**



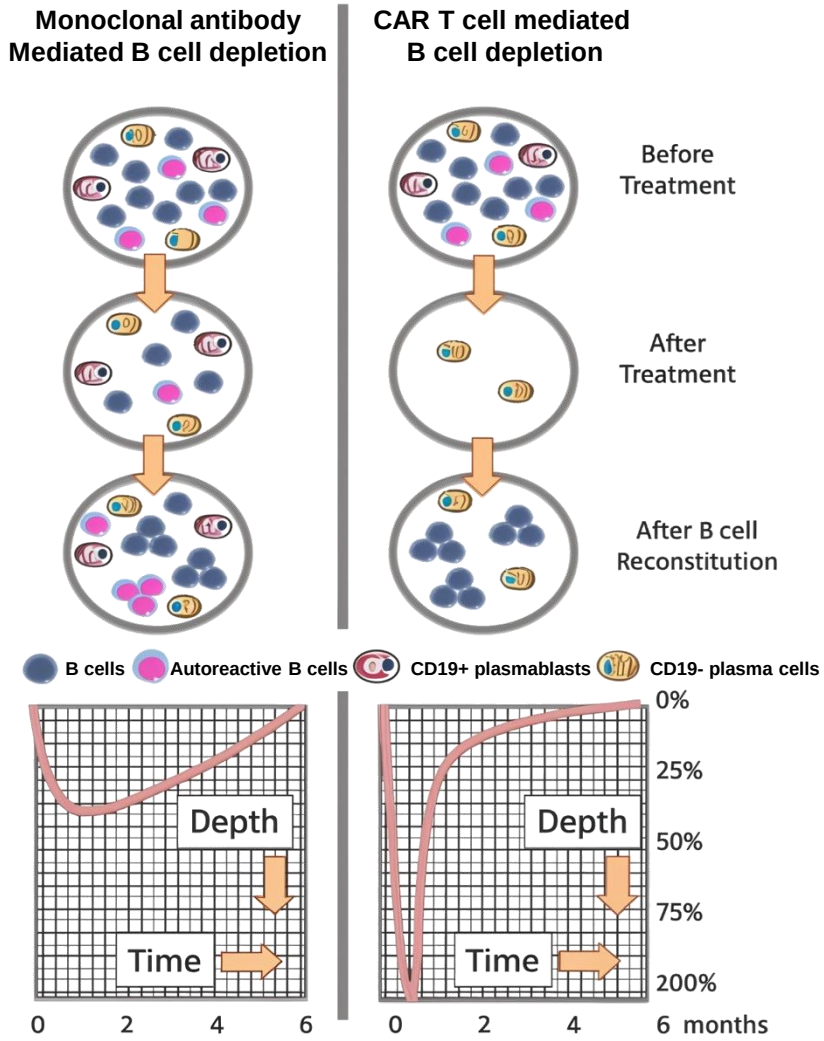
Images adapted from Rubin SJS, et al. 2019[2]

BCR, B cell receptor; MHC, major histocompatibility complex.

1. Barnas JL, et al. *Curr Opin Immunol.* 2019;61:92-99. 2. Rubin SJS, et al. *Nat Rev Rheumatol.* 2019;15(5):303-315.

Current Therapies for B Cell Driven Autoimmune Disease Rarely Achieve Drug-Free Remission

- **Current challenges**
  - Despite good peripheral B cell depletion, bispecific and antibody-based B cell targeting therapies rarely induce stable drug-free remission in autoimmune disease
  - Shallow B cell depletion that does not tackle resident autoimmune B cell clones may be the reason for this limitation
- **Goals of newer therapies**
  - Deeper B cell depletion with a ‘living drug’ to allow targeting resident autoimmune B cell clones, enabling potential immune tolerance such that long-term drug therapy is not needed
  - Reversibility of B cell depletion enabling a good safety profile



1. Schett G, et a. *Ann Rheum Dis.* 2024. PMID: 38777374. 2. Bucci, L. et al. *Nat Med*. 2024; PMID 38671240.

Emerging Academic Evidence of CD19-CAR T in Autoimmunity

15 patients with refractory systemic autoimmune disease

- Age range of 18 to 60 years; 60% female
- All patients with disease duration >12 months
- All patients had inadequate response to ≥2 lines of therapy
- ~50% of patients received B cell depletion therapy

Myositis (n=3)	Muscle and lung involvement median CK of 4298 U/L
SLE (n=8)	Median SLEDAI-2K score of 13; all had LN class III or IV
SSc (n=4)	All had active skin and lung involvement

All patients received a single dose of 1x10^6/kg CD19-CAR T cells following Flu/Cy preconditioning

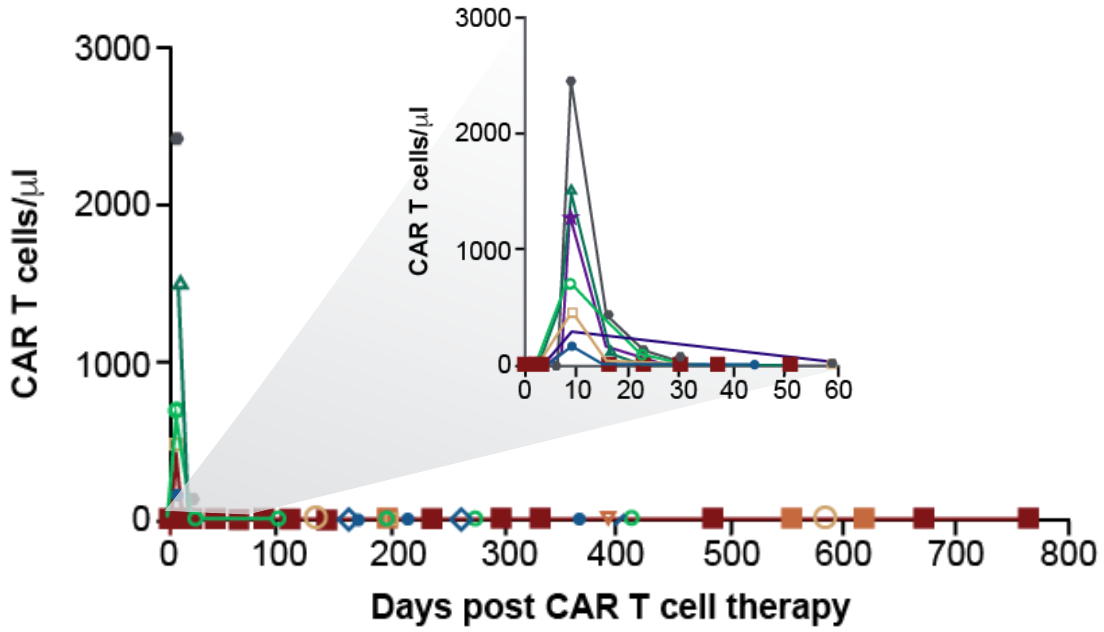
CK: creatinine kinase; Flu/Cy, fludarabine/cyclophosphamide; LN, lupus nephritis; SLE, systemic lupus erythematosus; SLEDAI-2K, systemic lupus erythematosus disease activity index 2K.

Müller F, et al. *N Engl J Med.* 2024;390(8):687-700.

CD19-CAR T Cells Can Result in Targeted B Cell Depletion

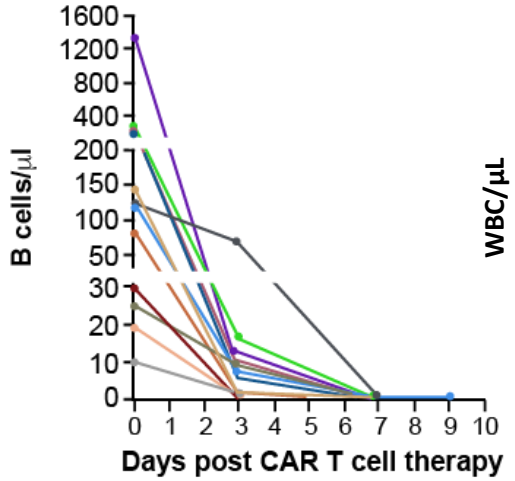
Preconditioning results in transient WBC decrease, though B cell depletion is sustained

CD19-CAR T cells



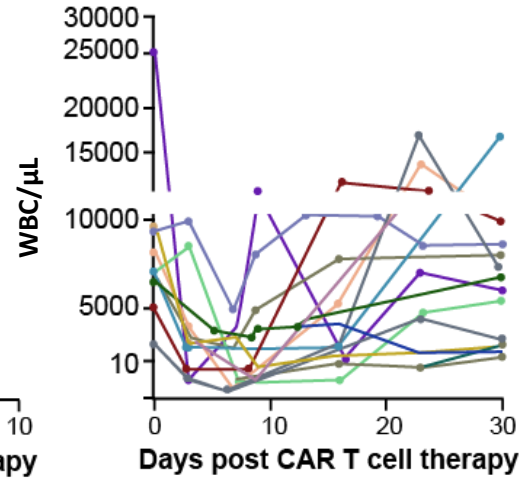
Circulating CAR T cell numbers after CD19-CAR T treatment (N=15)

CD19⁺ B cells



Circulating CD19⁺ B cells within first 10 days after treatment (N=15)

WBC



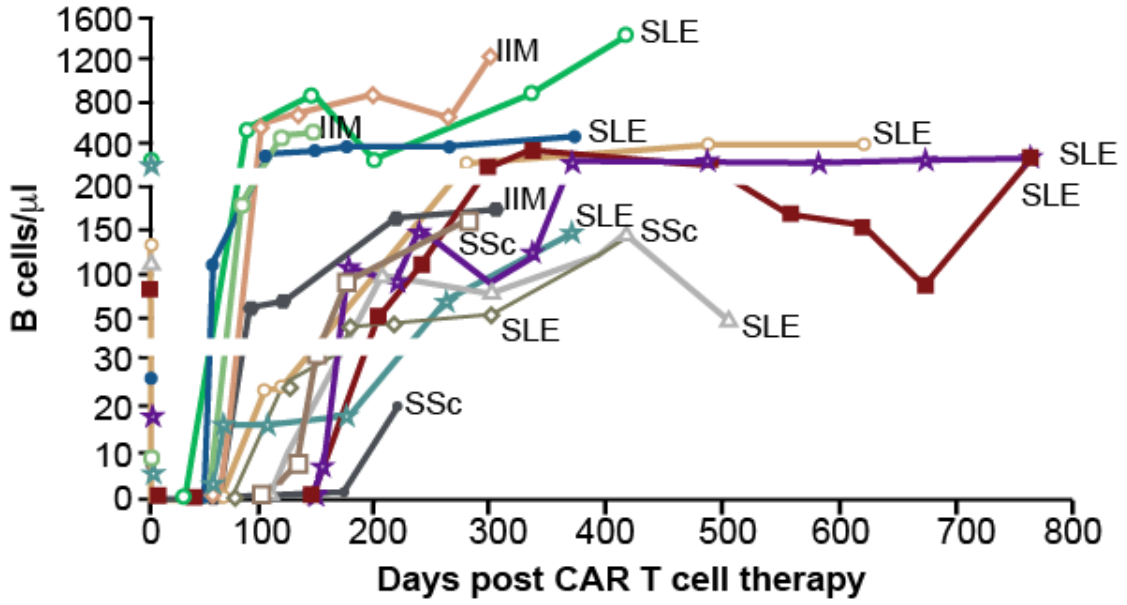
Circulating total WBCs within first 30 days after treatment (N=15)

WBC, white blood cell.

Müller F, et al. *N Engl J Med.* 2024;390(8):687-700.

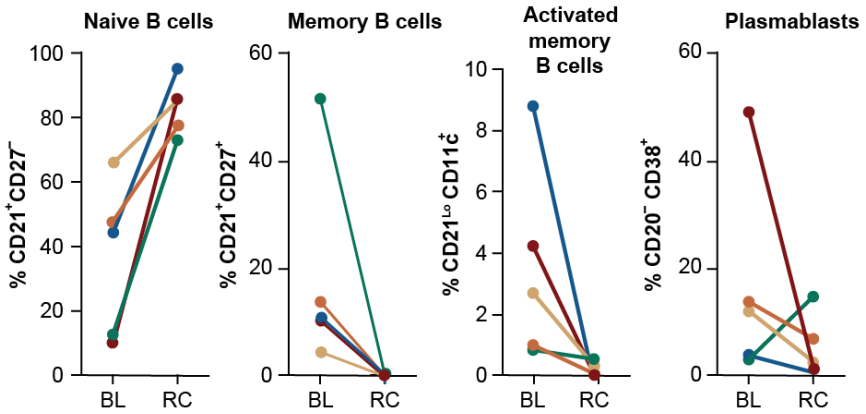
Reconstitution With Naïve B Cells Within 7 Months[1]

B cell reconstitution

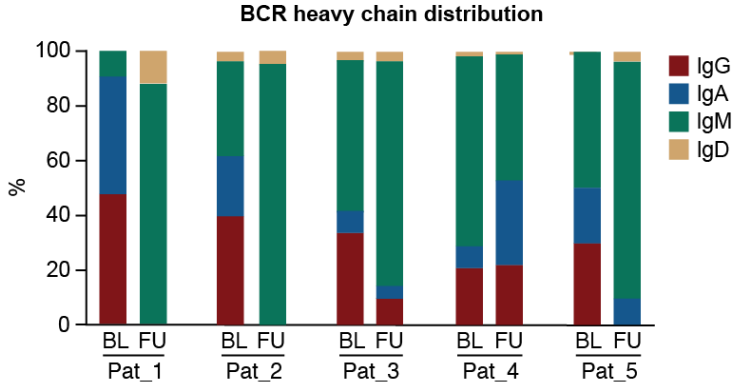


Circulating B cell numbers after CD19-CAR T treatment (N=15)[1]

Changes in B cell subtype numbers from baseline to B cell reconstitution (n=5)[2]



Distribution of heavy chain in the BCRs at baseline and after B cell reconstitution by mRNA sequencing (n=5)[2]



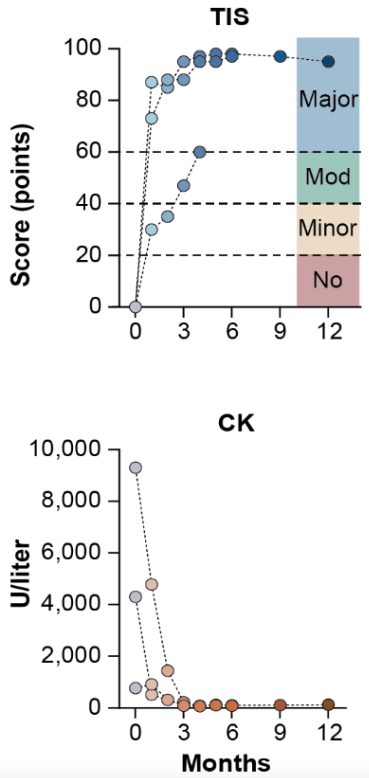
BL, baseline; FU, follow-up; Ig, immunoglobulin; IIM, idiopathic inflammatory myopathy; RC, reconstitution.

1. Müller F, et al. *N Engl J Med.* 2024;390(8):687-700. 2. Mackensen, Andreas A, et al. *Nature Medicine*. 2022;28(10):1-9.

Long-term Efficacy Outcomes With CD19-CAR T Cells

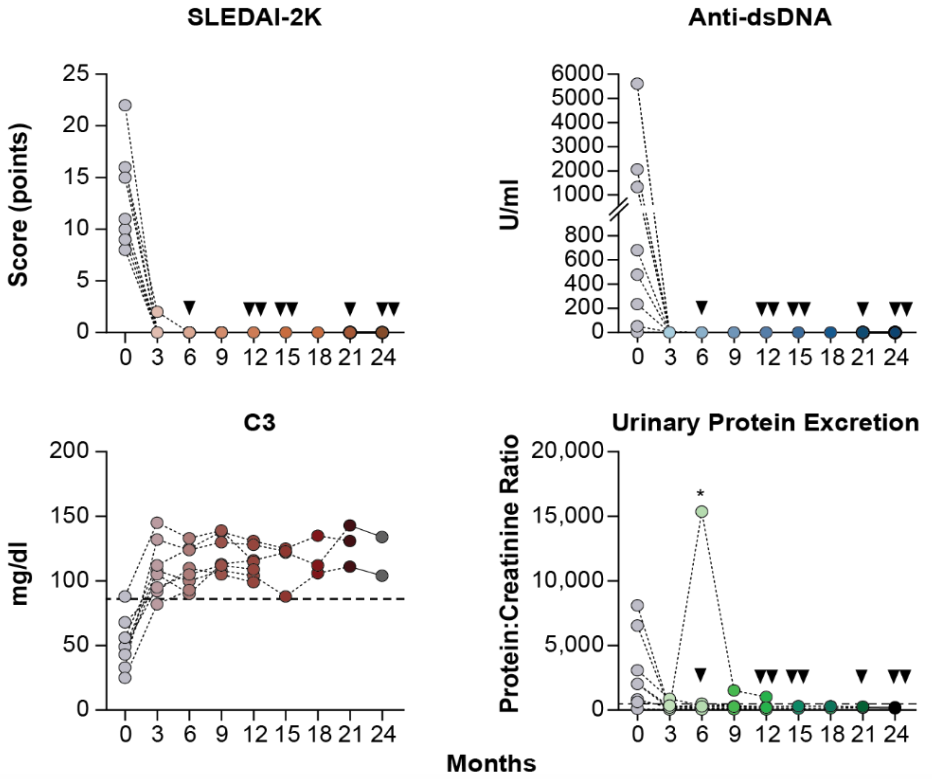
Patients maintained off immunosuppressive therapies, suggesting an ‘immune reset’ is possible

Myositis (n=3, ASyS)



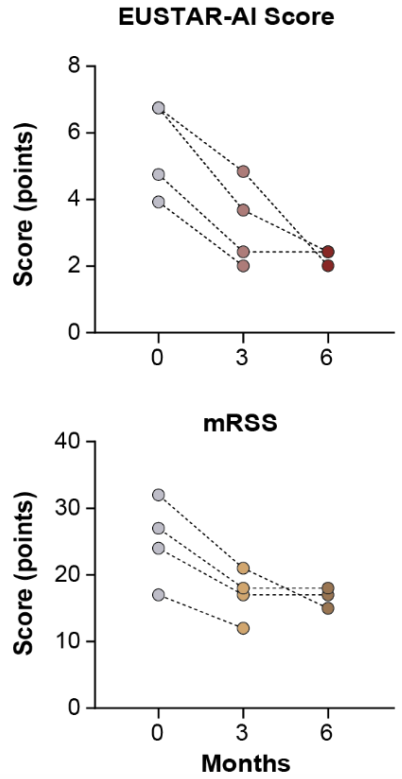
Achieved initial responses by 3 months

SLE (n=8)



Achieved response by 6 months

SSc (n=4)



Decreased disease activity by 6 months

Figures adapted from Müller F, et al. 2024.
C3, complement component 3; EUSTAR-AI, European Scleroderma Trials and Research Group activity index; dsDNA, double stranded DNA; mRSS, modified Rodnan skin score; TIS, total improvement score.
Müller F, et al. *N Engl J Med.* 2024;390(8):687-700.

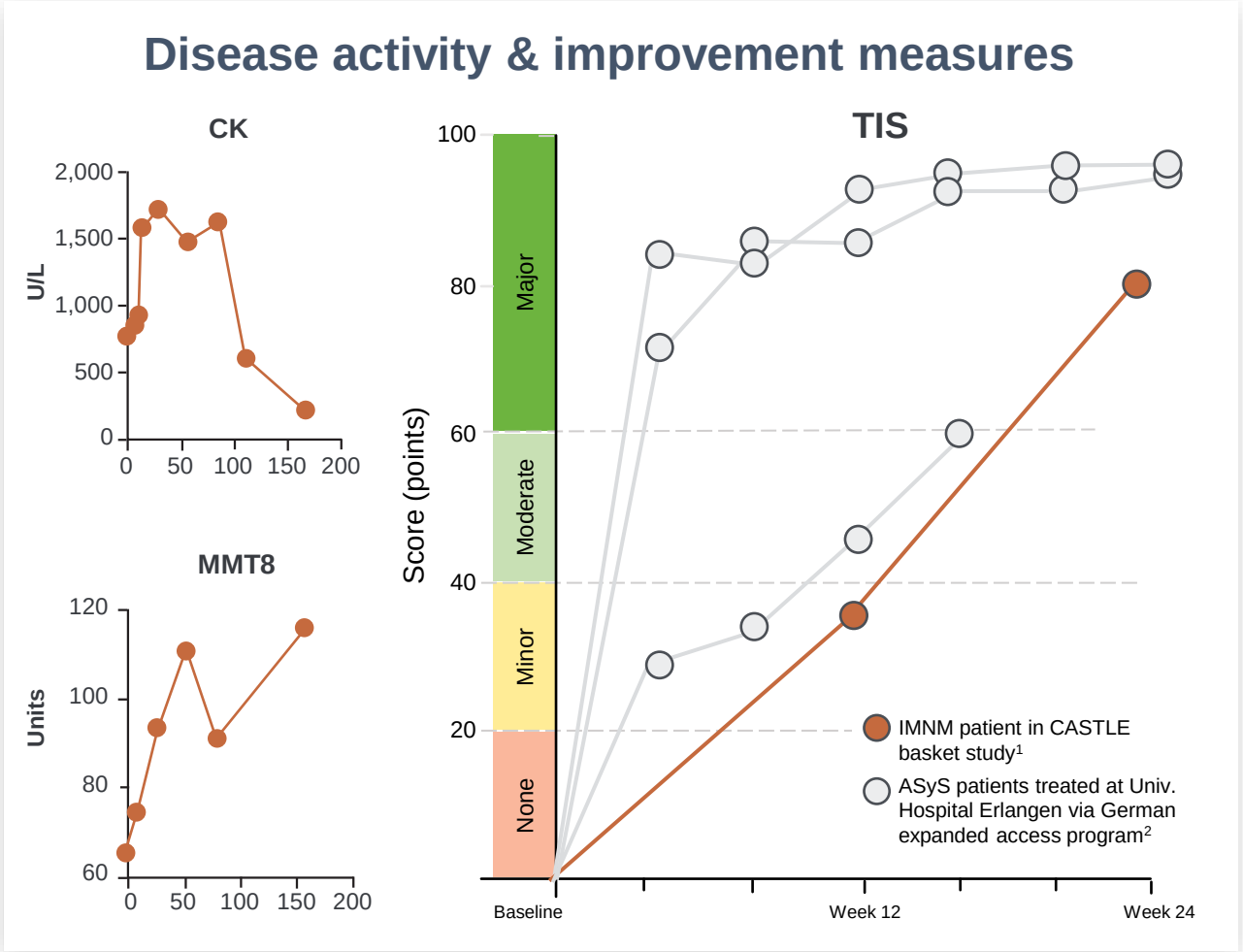
Cabaletta Bio®

Initial HMGCR IMNM Patient Treated With CD19-CAR T[1]

Preliminary academic data suggests potential slower IMNM improvement due to muscle-predominant disease[1,2]

- 81-year-old woman with HMGCR IMNM
  - Myositis subtype involving primarily muscle
  - Manifestations may affect response kinetics
- Treated with CD19-CAR T in CASTLE study

Potential for disease-specific timing & magnitude of response to CD19-CAR T



1. Patient treated in CASTLE Phase I/II basket study. CK and MMT8 data as presented at the Global Conference on Myositis in March 2024 and TIS data at Week 12 and 24 provided via personal communication with Dr. Georg Schett. 2. Müller F, et al. *N Engl J Med.* 2024;390(8):687-700.

Safety & Tolerability of CD19-CAR T in Autoimmunity[1]

AE profile consisted primarily of fever in 4-1BB costimulatory domain-containing CD19-CAR T

Cytokine release syndrome

- **67%** (10 of 15 patients) with only grade 1 (**fever**)
- **1 patient with myositis with grade 2**
  - Preexisting ILD with increased oxygen requirement for 1 day while febrile
- 6 patients received tocilizumab

ICANS

- Possible **grade 1 ICANS in 1 ASyS patient**
  - Mild dizziness at 2w post-infusion
  - Resolved following oral steroids

Hypogammaglobulinemia

- **5 patients** developed hypogamm.[a]
- 2 patients required IVIg supplementation[b]
- **Vaccine titers remained stable**

Infection

- **1 hospitalization due to pneumonia**[c]
- All other infections were mild and mostly manifested as URTIs (including COVID)
- 2 events of herpes zoster reactivation

[a]2 patients (1 SLE, 1 myositis) had preexisting hypogammaglobulinemia due to previous rituximab exposure [b]1 patient had preexisting hypogammaglobulinemia. [c]Pneumonia occurred in an SLE patient 7 weeks after CAR T cell therapy.
ILD, interstitial lung disease; IVIG, intravenous immunoglobulin; URTI, upper respiratory tract infection.
1. Müller F, et al. *N Engl J Med.* 2024;390(8):687-700.

Key Takeaways

Academic Data Demonstrates Drug-free and Durable Responses in Patients With Myositis, SLE and SSc

- Case series provides preliminary support for the feasibility, efficacy and safety of a 4-1BB CD19-CAR T in patients with autoimmune disease[1,2]
  - Durable disease- and drug-free remission
  - Acute adverse events post-CAR T consisted primarily of fever
  - Repopulation with naïve B cells within 7 months
  - Most infections were mild in severity, with only one case of pneumonia requiring hospitalization

1. Müller F, et al. *N Engl J Med.* 2024;390(8):687-700. 2. Mackensen, Andreas A, et al. *Nat Med.* 2022;28(10):1-9.

Unlocking the Potential of CD19-CAR T Cell Therapy in Myositis and Lupus

REstoring **SE**lf-**T**olerance (**RESET™**) Development Program

Designed to replicate and expand on the academic clinical data that generated interest in the field

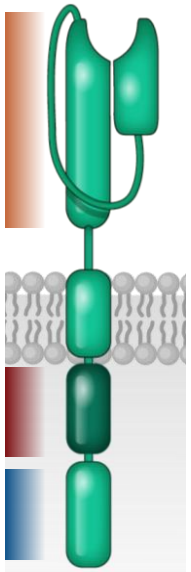
CABA-201 designed to optimize the potential safety and efficacy of CD19-CAR T for patients with autoimmune disease

Fully human anti-CD19 binder
Similar binding affinity and biologic activity to FMC63, with binding to the same epitopes[1,2]

Safety data in ~20 oncology patients evaluated and reported by IASO as part of a dual-CAR[3]

4-1BB costimulatory domain
Same domain as used in academic studies

CD3-zeta signaling domain



CABA-201

Key Questions for RESET Phase 1/2 Studies

Safety of CABA-201
- CABA-201 AE profile
- *CRS, ICANS, SAEs*

Dose selection
1 x 10^6 cells/kg
- PK – CAR T persistence
- PD – B cell depletion
- Autoantibody reduction
- Clinical outcomes

PK, pharmacokinetics; PD, pharmacodynamics, SAEs: serious adverse events

1.Peng, BinghaoJ, et al. Presented at: American Society Gene and Cell Therapy 26th Annual Meeting; 2023 May 19; Los Angeles, CA. 2. Dai, Zhenyu, et al. *Journal of Cellular Physiology*. 2021;236(8): 5832-5847. 3. Evaluated as part of CT120, a dual-CD19xCD22 CAR T product candidate under development by Nanjing IASO Biotherapeutics, Co., Ltd. (IASO Bio).

Phase 1/2 Myositis Study for CABA-201[1]

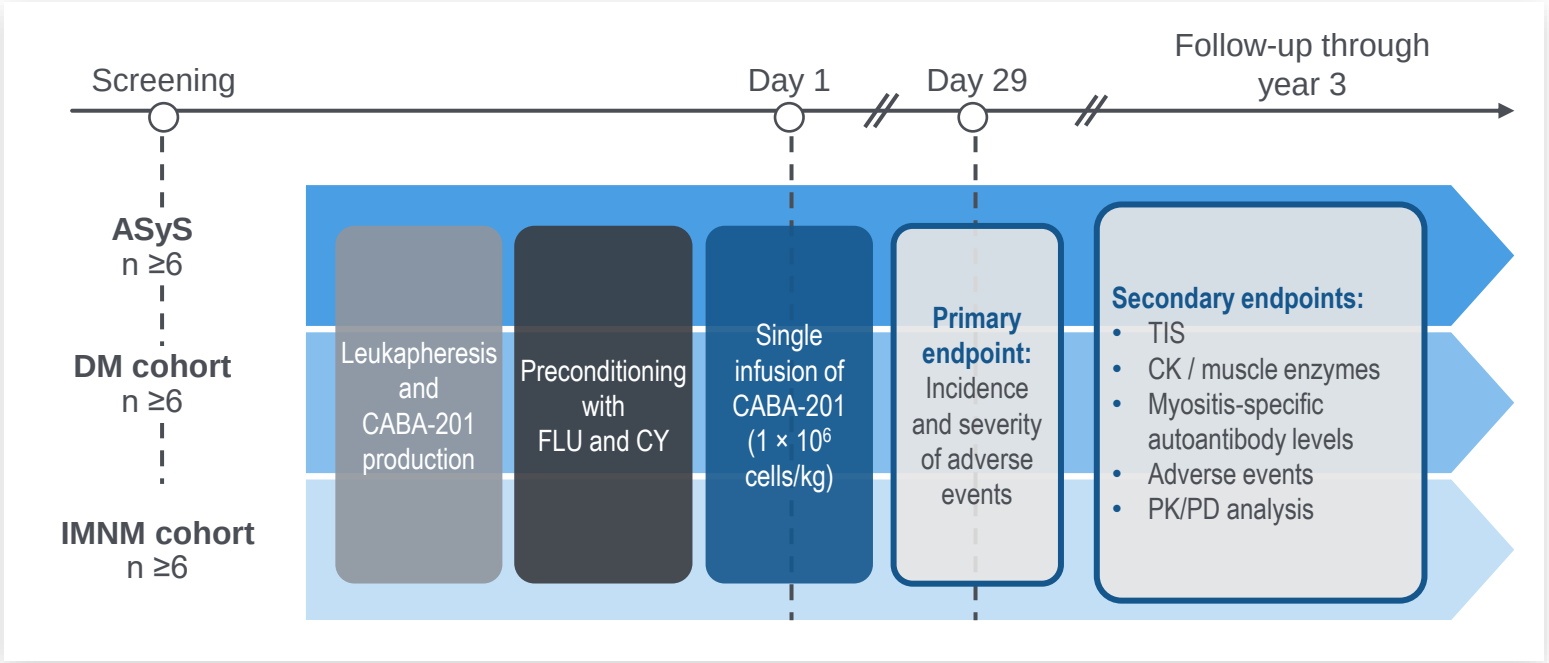
RESET Myositis™

Key inclusion criteria

- Age ≥18 and ≤75 with a definite or probable clinical diagnosis of IIM (2017 EULAR/ACR classification criteria)
- Diagnosis of antisynthetase syndrome (ASyS), dermatomyositis (DM), or immune-mediated necrotizing myopathy (IMNM) based on presence of serum myositis-specific antibodies
- Evidence of active disease despite prior or current treatment with standard of care

Key exclusion criteria

- Cancer-associated myositis
- Significant lung or cardiac impairment
- B cell-depleting agent within prior ~6 months
- Previous CAR T cell therapy and/or HSCT



Juvenile IIM cohort recently incorporated into trial

CY, cyclophosphamide; EULAR/ACR, European Alliance of Associations for Rheumatology/America College of Rheumatology; FLU, fludarabine; HSCT, hematopoietic stem cell transplantation. TIS, Total Improvement Score.

1. ClinicalTrials.gov. Accessed June 10, 2024. https://classic.clinicaltrials.gov/ct2/show/NCT06154252.

Phase 1/2 Lupus Study for CABA-201[1]

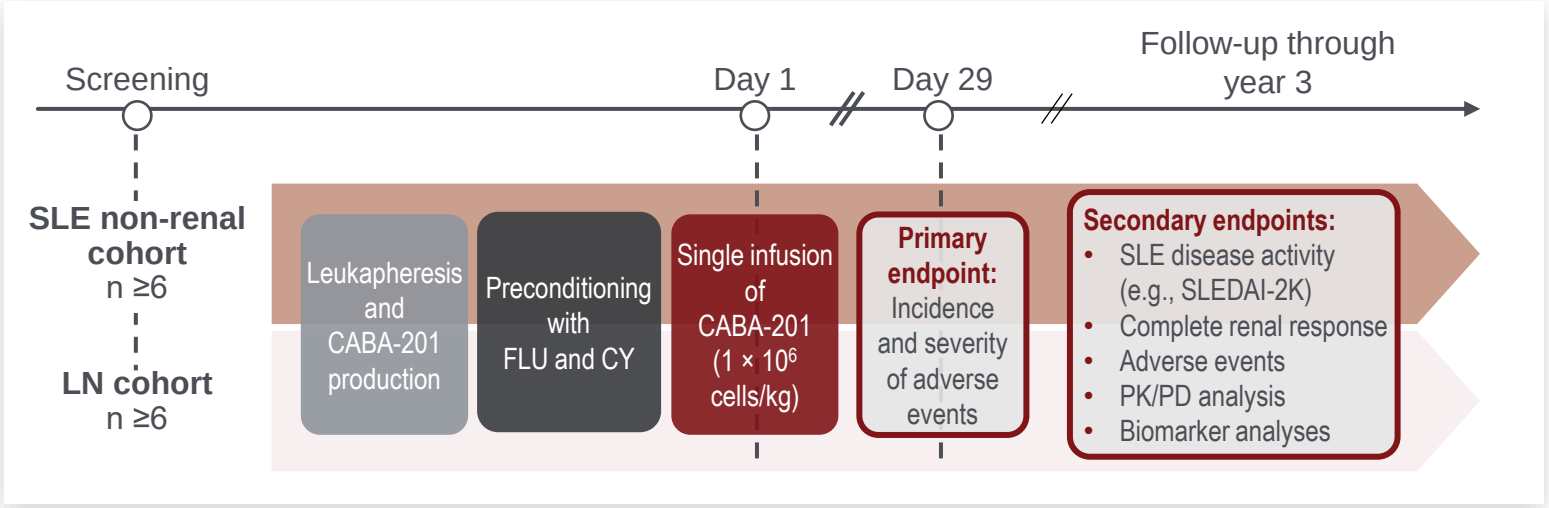
RESET SLE™

Key inclusion criteria

- Age ≥18 to ≤65 with an SLE diagnosis (2019 EULAR/ACR classification criteria)
- ANA+ or anti-dsDNA+ at screening
- For SLE (non-renal) cohort: active, moderate to severe SLE, SLEDAI-2K ≥8 despite standard therapy
- For Lupus Nephritis cohort: active, biopsy-proven LN class III or IV, ± class V

Key exclusion criteria

- B cell-depleting agent within prior ~6 months
- Previous CAR T cell therapy and/or HSCT
- Presence of kidney disease other than LN

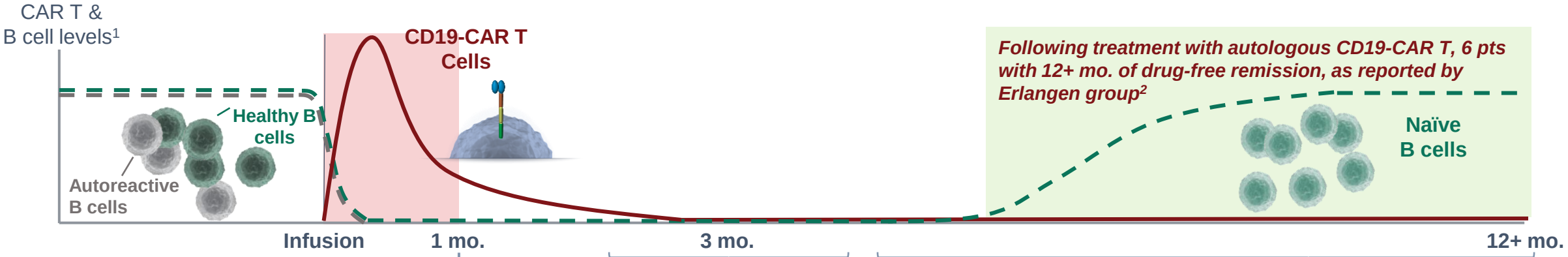


ANA, antinuclear antibody; SELENA-2K, Systemic Lupus Erythematosus Disease Activity Index-2K.

1. ClinicalTrials.gov. Accessed June 10, 2024. https://classic.clinicaltrials.gov/ct2/show/NCT06121297.

Metrics To Assess Outcomes of B Cell Depletion In Autoimmunity

Translational & clinical parameters inform framework to evaluate advanced modalities in autoimmunity



Metrics of evaluation	Within 1 month	~3 months	Up to 12+ months
Translational measures	☑ B cell depletion: Timing & depth ☑ CAR T expansion: Magnitude & timing	☑ Autoantibody changes ☑ Vaccine titer changes ☑ Inflammatory marker changes	☑ Time to B cell repopulation ☑ B cell phenotype[a] ❑ Autoantibody changes
Clinical data	☑ Rate of CRS more severe than fever ☑ Rate & grade of ICANS ☑ Rate & severity of infection	☑ Early efficacy signals ☑ Rate & severity of infection	❑ Durability of clinical activity ❑ Rate & severity of infection
Patient experience	☑ Hospitalization requirements ☑ Apheresis & preconditioning ☑ Single vs. multiple infusions	☑ Chronic maintenance therapy / concomitant medications, if any	❑ Chronic maintenance / concomitant medications, if any

✓Indicates data being presented for either or both of the first two patients in the RESET™ clinical program.
[a]Flow phenotyping data; confirmatory analyses ongoing.

1. Illustrative graphic, adapted from Taubmann J, et al. OPO141. Abstract presented at: EULAR; May 31, 2023; Milan, Italy. 2. Müller F, et al. *N Engl J Med.* 2024;390(8):687-700.

IMNM: High Unmet Need & Limited Therapeutic Options[1]

Idiopathic inflammatory myopathy (IIM, myositis)

♀ > ♂

Immune-mediated necrotizing myopathy

Dermatomyositis

Antisynthetase syndrome

- IMNM-associated antibodies include anti-SRP & anti-HMGCR
- Muscle disease (weakness, elevated CK) predominant
- No therapies approved by the FDA or EMA for IMNM
- Often refractory despite combination therapy (e.g., IVIg, rituximab)

Myositis Prevalence: ~1 million globally[2]

HMGCR IMNM patient treated in CASTLE CD19-CAR T study with minor response by 3 months improved to major response at 6 months with no additional therapy[3]

Cohort for first patient treated with CABA-201

DM, dermatomyositis; EMA, European Medicines Agency; ESRD, end-stage renal disease; IMNM, immune-mediated necrotizing myopathy; HMGCR: HMG-CoA reductase

1. Suh J, et al. *Muscle Nerve*. Published online May 27, 2024. doi:10.1002/mus.28114. 2. Khoo T, et al. *Nat Rev Rheumatol.* 2023;19(11):695-712. 3. Patient treated in third-party CASTLE Phase I/II basket study.

SLE: Variable Disease Course & Limited Treatments[1-6]

Systemic lupus erythematosus (SLE)

- Highly heterogenous with potentially life-threatening complications
- Two biologic therapies approved with 52-week efficacy endpoint
- Incomplete responses & need for long-term therapy very common
- ~40% with LN, with Class V LN often resistant to therapy

Non-renal systemic lupus erythematosus

Lupus nephritis

♀ > ♂

Academic CD19-CAR T data in SLE patients with predominantly renal disease suggest potential for clinical response by 3 months[7]

SLE Prevalence: >3 million globally[1]

Cohort for first patient treated with CABA-201

LN, lupus nephritis.

1. Tian J, et al. *Ann Rheum Dis.* 2023;82(3):351-356. 2. Hoover PJ, Costenbader KH. *Kidney Int*. 2016;90(3):487-92. 3. Benlysta. Package insert. GSK; 2018. 4. Saphnelo. Package Insert. AstraZeneca. 2021. 5. Hahn BH, et al. *Arthritis Care Res (Hoboken)*. 2012; 64(6): 797–808. 6. Aziz F, Chaudhary, K. *Curr Clin Pharmacol.* 2018;13(1):4-13. 7. Mackensen, Andreas A, et al. Nature Medicine. 2022;28(10):1-9.

Baseline Characteristics of First Two Patients in RESET Trials

Both patients had refractory disease, including to B cell-targeting antibodies & other agents

	RESET-Myositis Patient #1	RESET-SLE Patient #1
Age (years), sex	33, male	26, male
Cohort	IMNM	Non-renal SLE
Disease duration	~2 years	~6 years
Prior disease-specific therapy	IVIG, rituximab, MTX, glucocorticoids	Cyclophosphamide, voclosporin, belimumab, tacrolimus
Disease-specific therapy at screening	MTX, glucocorticoids	MMF, hydroxychloroquine, glucocorticoids
Autoantibodies	SRP, Ro-52	ANA, dsDNA
Disease activity[a]	MMT-8: 130, CK: 617	SLEDAI-2K: 26
Disease manifestations[a,b]	Muscle weakness, dysphagia	Vasculitis, arthritis, alopecia, hematuria, proteinuria (isolated class V LN), low complement

Expanding CD19-CAR T experience in IMNM & non-renal SLE

[a]Baseline=pre-preconditioning visit. [b]Disease manifestations were according to Myositis Disease Activity Assessment Tool (MDAAT) and SLEDAI-2K for myositis and SLE, respectively.
dsDNA, double-stranded DNA; IMNM, immune-mediated necrotizing myopathy; MMF, mycophenolate mofetil; MMT-8, manual muscle testing of 8 muscles; MTX, methotrexate; Ro-52, ribonucleoprotein 52; SRP, signal recognition particle.

CABA-201 was Well-tolerated in Initial Patients

No CRS, ICANS or infections reported through follow-up period[a]

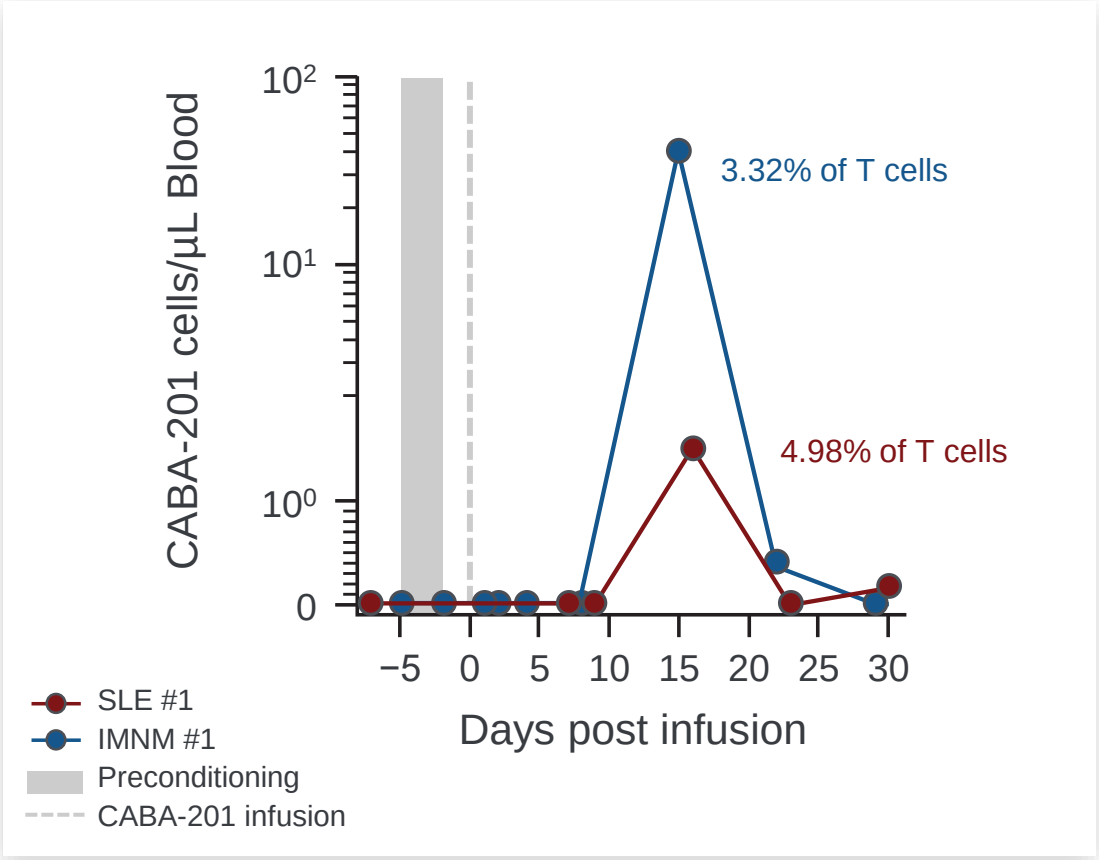
		RESET-Myositis Patient #1	RESET-SLE Patient #1
Dose of CABA-201		83 million (1 x 10^6/kg) CAR^+ cells	63 million (1 x 10^6/kg) CAR^+ cells
Duration of inpatient monitoring[b]		4 days	4 days
Adverse events[d]	CRS	None	None
	ICANS	None	None
	Infections	None	None
	Hypogammaglobulinemia	None	None
	Serious adverse events	None	None
Concomitant disease-specific therapy		Discontinued MTX prior to infusion; Prednisone discontinued day 3 post-infusion	Discontinued MMF and HCQ prior to infusion; Ongoing taper from prednisone 10mg daily by 8 weeks[c]
Duration of follow-up[a]		84 days	28 days

Both patients discharged after 4 days of monitoring post-infusion & neither received tocilizumab

[a]Data cut-off as of 28 May 2024. [b]Protocol requires a minimum of 4-day hospitalization for monitoring. [c]PI-directed taper from 10mg daily prednisone. [d]Grade 4 leukopenia, neutropenia and lymphopenia reported for SLE Patient #1, the Grade 4 cytopenias resolved and were attributed to the preconditioning regimen (fludarabine and cyclophosphamide).

CABA-201 Expansion in Anticipated Range

CABA-201 exhibited anticipated profile of expansion and contraction[1-5]



- Expansion of CAR T cells to anticipated range suggests target engagement
- Peripheral peak CAR T expansion occurred at approximately 2 weeks[a]
- Rapid contraction suggests systemic B cell aplasia has been achieved

[a]Response appears to be consistent with published data of cryopreserved CAR T products as well as the expansion profile of BCMA-CAR T products in patients with multiple myeloma, in which the number of target cells is more similar to autoimmune disease than to B cell leukemias and lymphomas

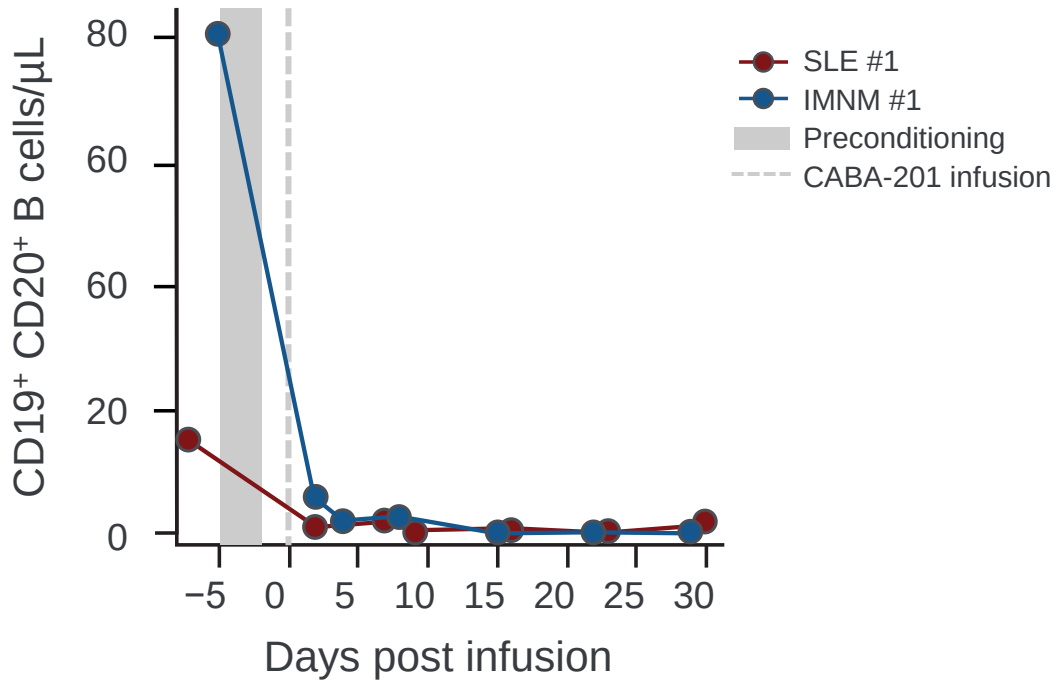
BCMA, B cell maturation antigen.

1. Shah BD, et al. *Lancet*. 2021;398(10299):491-502. 2. Awasthi R, et al. *Blood Adv*. 2020;4(3):560-572. 3. Munshi NC, et al. *N Engl J Med*. 2021;384(8):705-716. 4. Cohen AD, et al. *Blood Cancer J*. 2022;12(2):32. 5. Müller F, et al. *N Engl J Med.* 2024;390(8):687-700.

Systemic B Cell Depletion With CABA-201

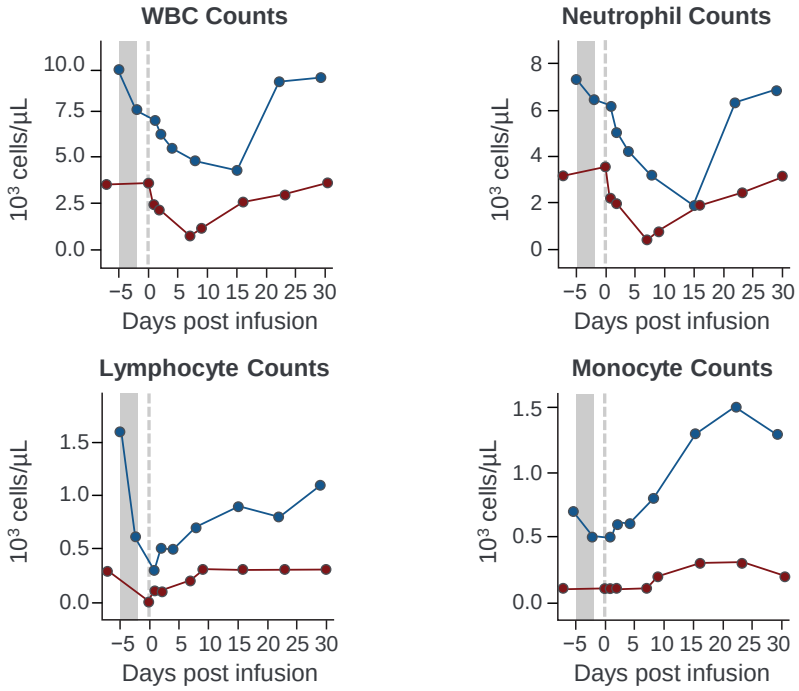
Complete B cell depletion achieved by day 15 on flow cytometry & maintained in context of WBC recovery

$CD19^+$ $CD20^+$ B cell count



B cell depletion was achieved & maintained in follow up or until naïve B cell recovery

Leukocyte counts

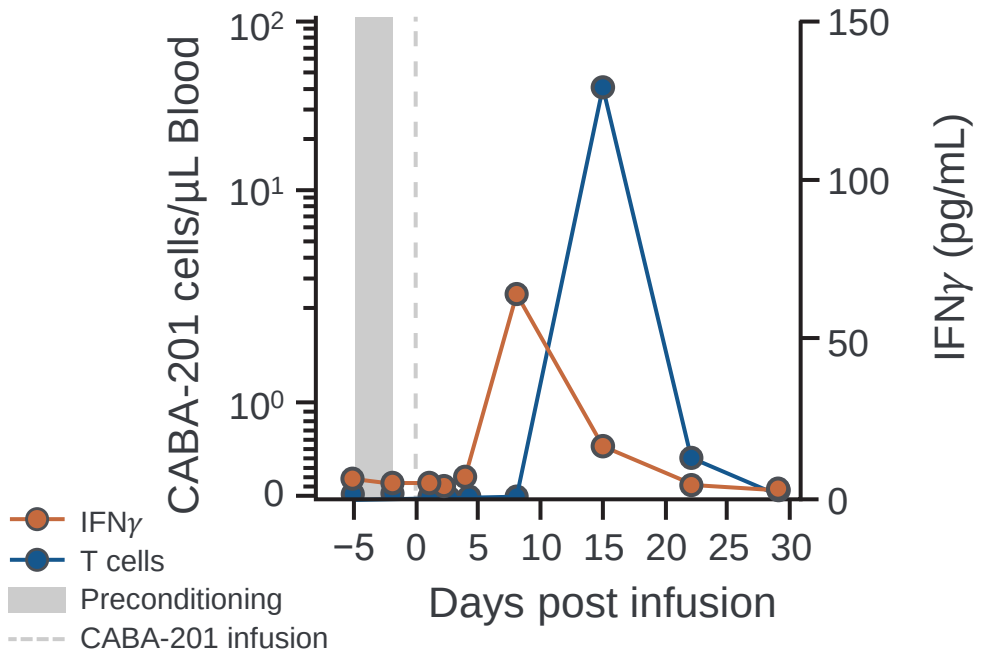


Early, transient leukopenia observed in both patients, as expected with preconditioning[a]

[a]Nadir of lymphocyte count following fludarabine and cyclophosphamide administration estimated based on respective product labels.[1,2]
WBC, white blood cell.
1. Fludarabine phosphate injection. Prescribing information. 2010. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022137s003lbl.pdf. 2.Cyclophosphamide. Prescribing information. 2013. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/012141s090,012142s112lbl.pdf.

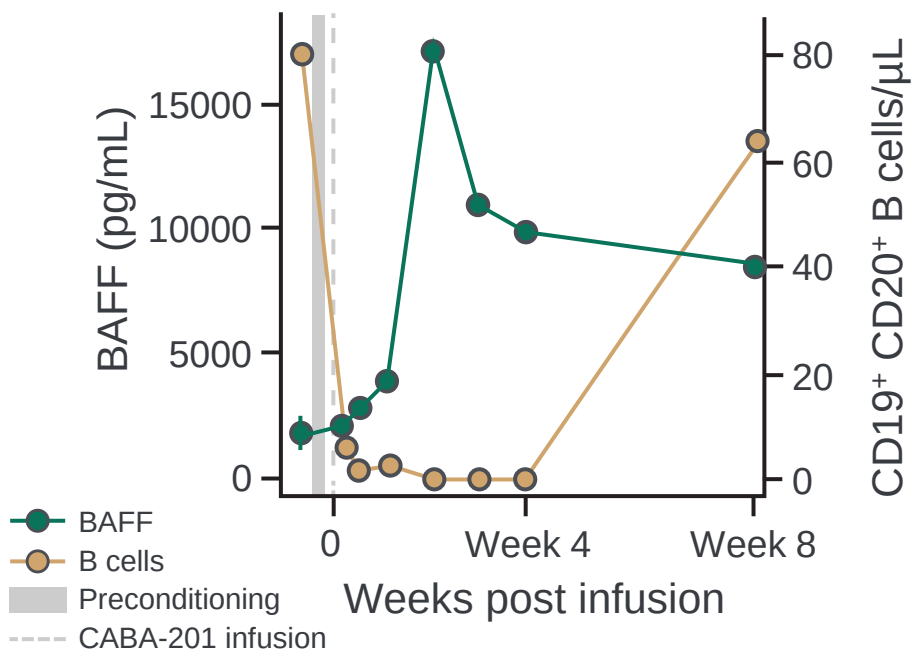
Immunologic Effects of CABA-201

CABA-201 pharmacokinetics



IFNγ peak prior to peripheral CABA-201 peak suggests tissue-resident B cell cytotoxicity

CABA-201 pharmacodynamics



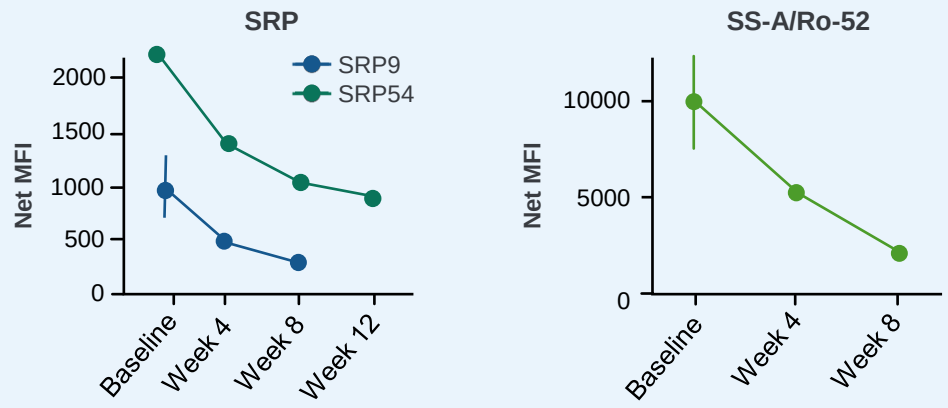
Systemic B cell depletion triggers BAFF to encourage bone marrow B cell repopulation

CK Reduction & Clinical Improvement Observed in SRP IMNM

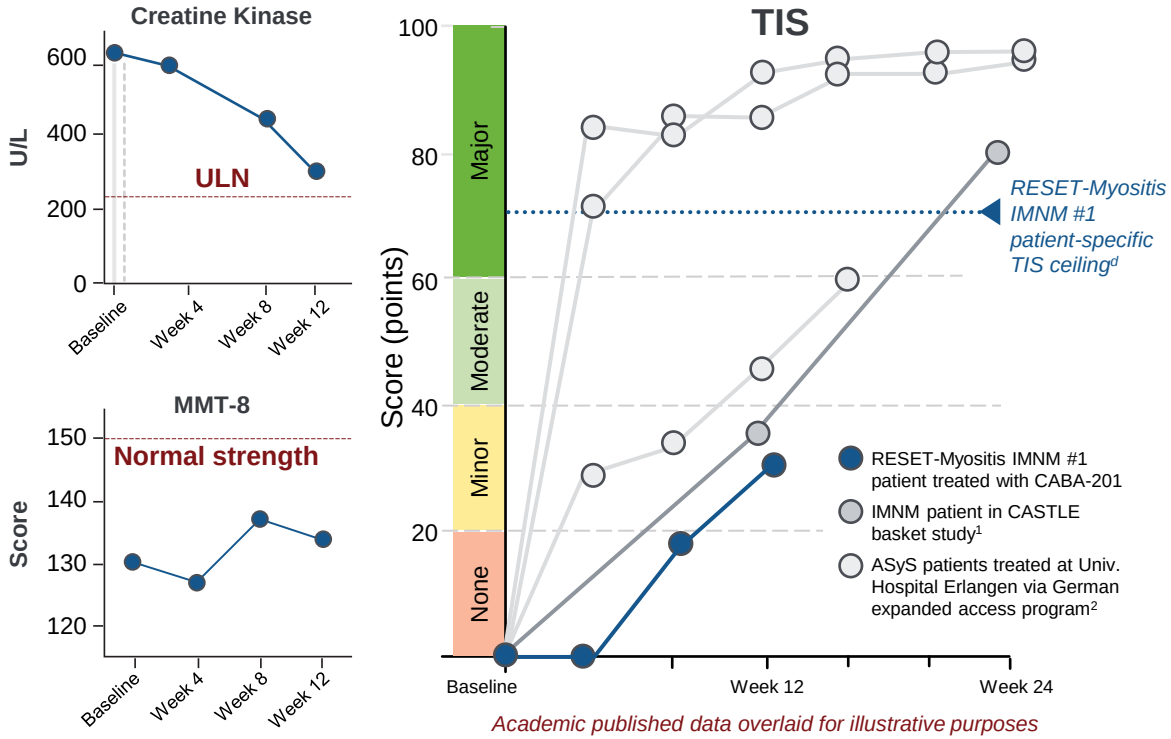
Antibody reduction & clinical improvement in disease activity as anticipated with follow-up of 12 weeks

- Discontinued all disease-specific therapies
- Disease markers continuing to trend positively
- Patient reported symptoms as much improved

Quantitative translational assay shows ongoing reduction in SRP & Ro-52 antibodies[b,c]



Disease activity & improvement measures



12-week TIS consistent with IMNM case report[1]

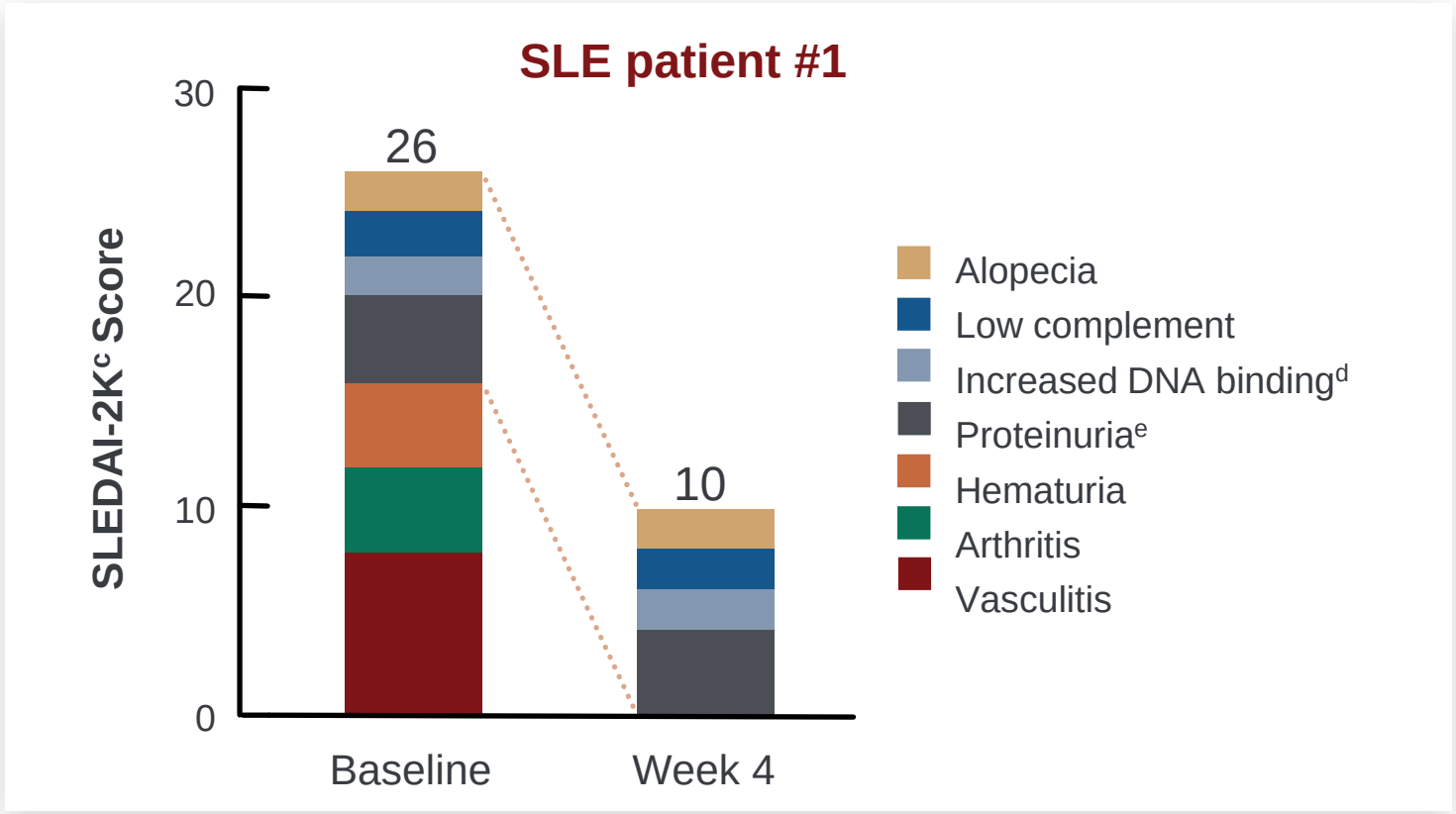
[a]Data cut-off as of 28 May 2024. [b]Luminex assay developed and performed by Cabaletta Labs. [c]Qualitative commercial assay (Myositis Antigen Panel, performed at National Jewish Health Advanced Diagnostic Laboratories) suggests SRP54 antibody remains strongly positive at Week 12; Ro-52 normalizes by week 8. [d]Based on patient's moderate level of muscle disease at baseline, mild-moderate disability and limited extramuscular manifestations, the maximum achievable score is 70 points on the 100-point TIS scale.

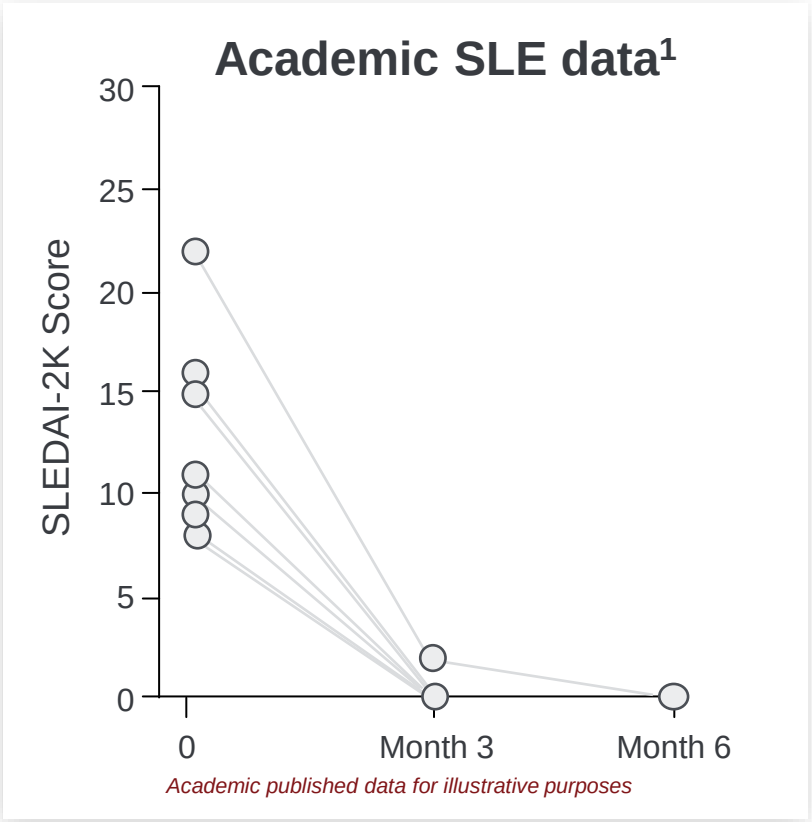
1. Patient treated in third-party CASTLE Phase I/II basket study, TIS data at Week 12 and 24 provided via personal communication with and as presented by Dr. Georg Schett. 2. Müller F, et al. *N Engl J Med.* 2024;390(8):687-700.

SRP9, signal recognition particle 9; SSA, Sjögren's syndrome–related antigen A autoantibody; TRIM21, tripartite motif 21; ULN, upper limit of normal; CK, creatine kinase.

Early Efficacy Signals in Non-Renal SLE[a]

Trend toward improvement in disease manifestations with follow up of 4 weeks[b]



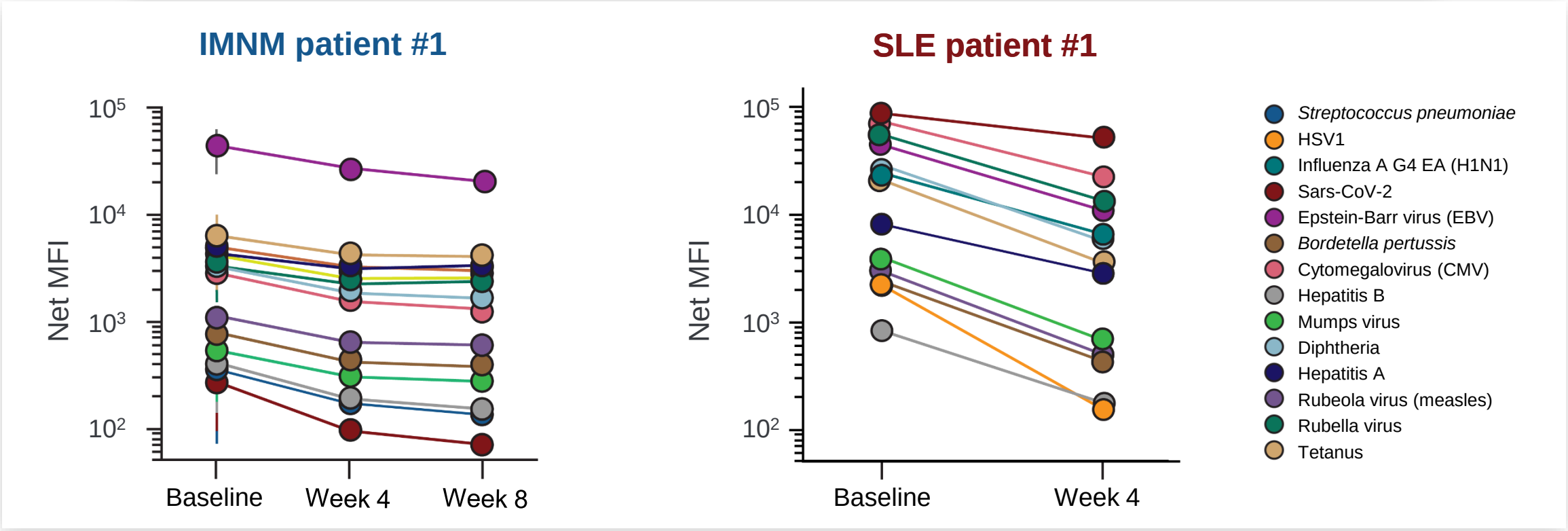


Vasculitis, arthritis and hematuria resolved within 4 weeks despite discontinuation of all therapies at infusion other than ongoing taper from prednisone 10mg per day

[a]Patient in non-renal SLE cohort due to isolated Class V LN. [b]Data cut-off as of 28 May 2024. [c]Baseline and Day 29 SLEDAI-2K score are reflective of disease activity at study visit day. [d]Urine Protein Creatinine Ratio decreased from 1.08 to 0.80 from Baseline to Week 4. [e]Anti-dsDNA antibody titer decreased from 1:40 to 1:10 from Baseline to Week 4.

1. SLE patients treated at Univ. Hospital Erlangen via German expanded access program; Müller F, et al. *N Engl J Med.* 2024;390(8):687-700.

CABA-201 Effects on Vaccine & Infection Antibody Titers



Titers preserved post-infusion, with no reported infections in the duration of follow-up period[a]

[a]Data cut-off as of 28 May 2024.

B Cell Repopulation with Naïve B Cells

Initial patient phenotyping data consistent with potential immune system reset; confirmatory analyses ongoing

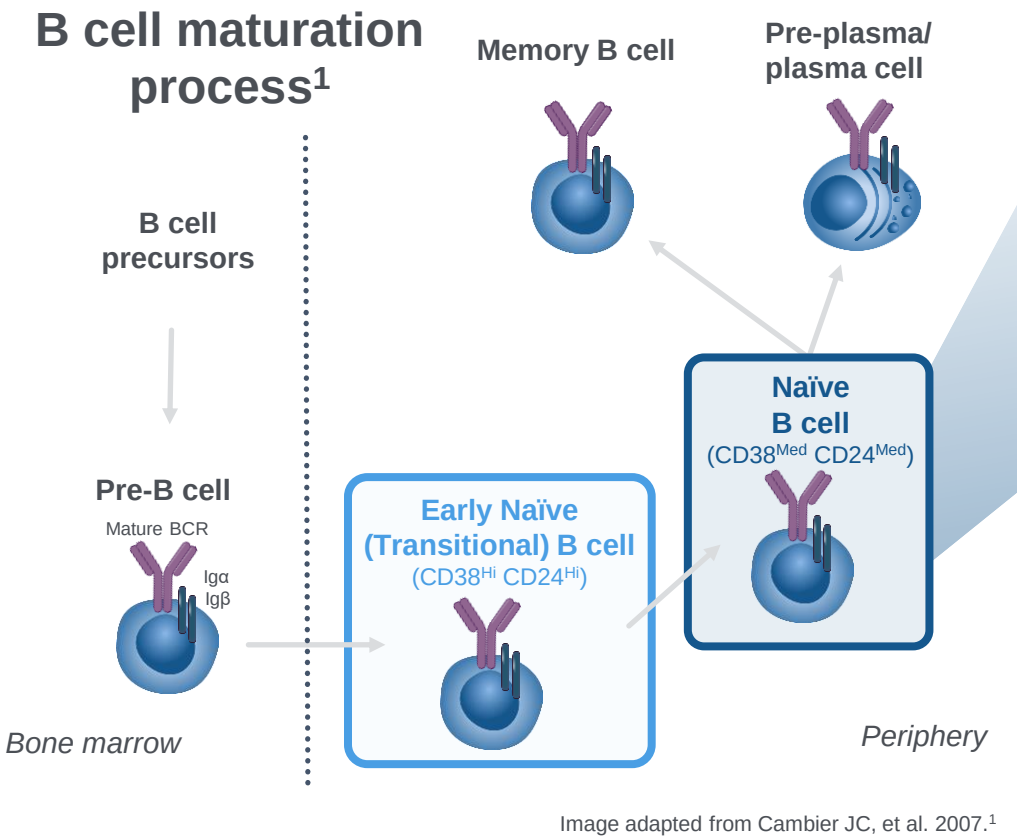
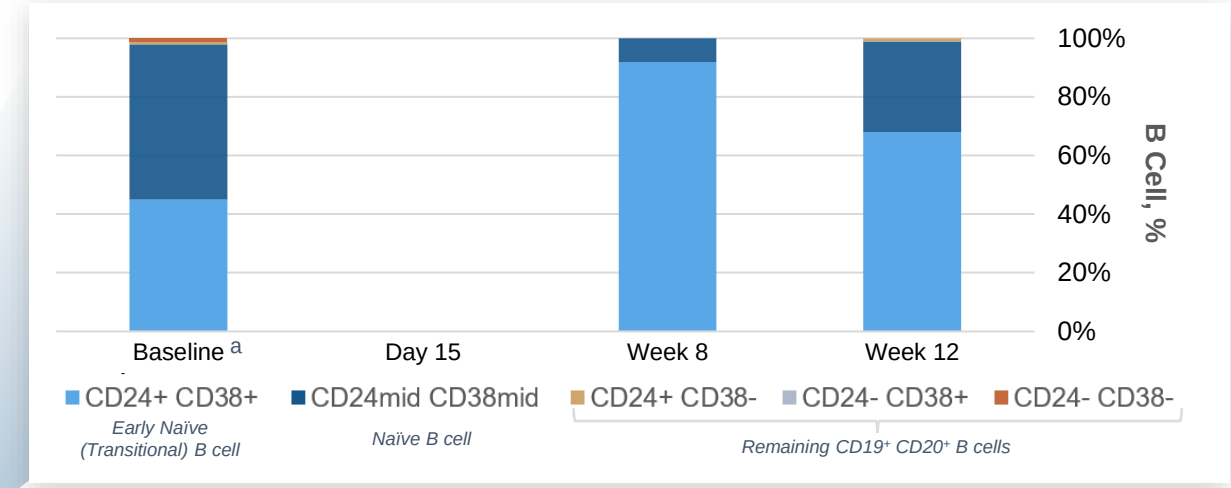
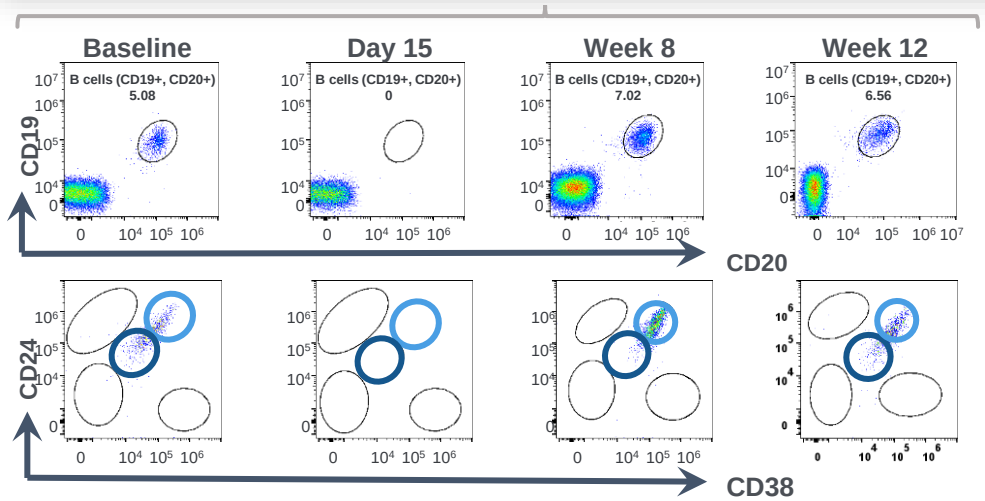


Image adapted from Cambier JC, et al. 2007.[1]





B cell phenotyping data

Note: Flow plot gating reflects CD19+ CD20+ live lymphocytes. [a]Patient received multiple courses of rituximab, with most recent dose approximately 9 months prior to CABA-201 infusion.
BCR, B cell receptor.

1. Cambier JC, et al. *Nat Rev Immunol*. 2007;7(8):633-643.

Key Takeaways

- **CABA-201**: Designed for autoimmune patients to optimize the potential product profile of CD19-CAR T
- **Safety**: In the first 2 patients (IMNM & SLE), CABA-201 was well-tolerated
  - No CRS, ICANS or infections reported through follow-up period
- **Dose**: Clinical & translational data support the selected dose of CABA-201
  - PK: IFNγ peak prior to peak of CABA-201 suggests tissue-level B cell cytotoxicity
  - PD: Systemic B cell depletion followed by repopulation with naïve B cells
  - Autoantibody levels: Decline generally consistent with Univ. Hospital Erlangen data[1]
  - Clinical & translational data: Improvement consistent with reported CD19-CAR T data[1,2]

18 clinical sites now enrolling patients in the CABA-201 RESET™ program with four trials open – myositis, SLE/LN, systemic sclerosis and myasthenia gravis

1. Müller F, et al. *N Engl J Med.* 2024;390(8):687-700. 2. Castle Phase 1/2 basket study.

Questions & Answers

You are invited to stop by at Booth S18-19 for additional engagement with Cabaletta Bio!

Please use the EULAR app to complete an evaluation form

To learn more, please visit **CabalettaBio.com** &

contact us at **clinicaltrials@cabalettabio.com**