These handouts are designed to complement the expert presentations. We strongly encourage you to view the full sessions before drawing conclusions based solely on the handout content.

This information is current at the time of recording and is subject to change as new information becomes available.

T-Cell Engagers & CAR-T Therapy: Can We RESET Autoimmunity?

Teja Kapoor, MD

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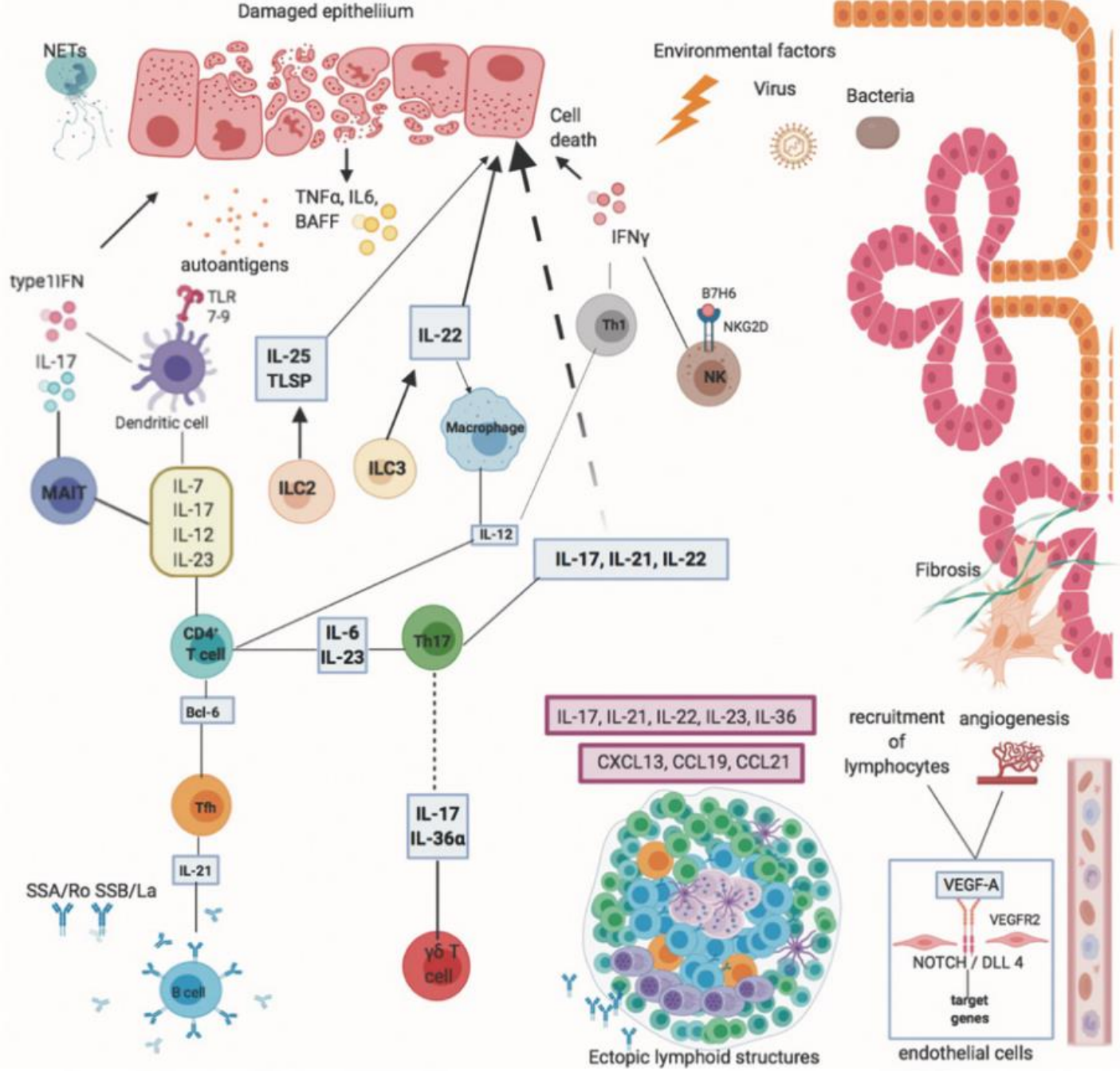
Disclosures

- Argenx- advisory board member
- Novartis- advisory board member

Presentation Outline

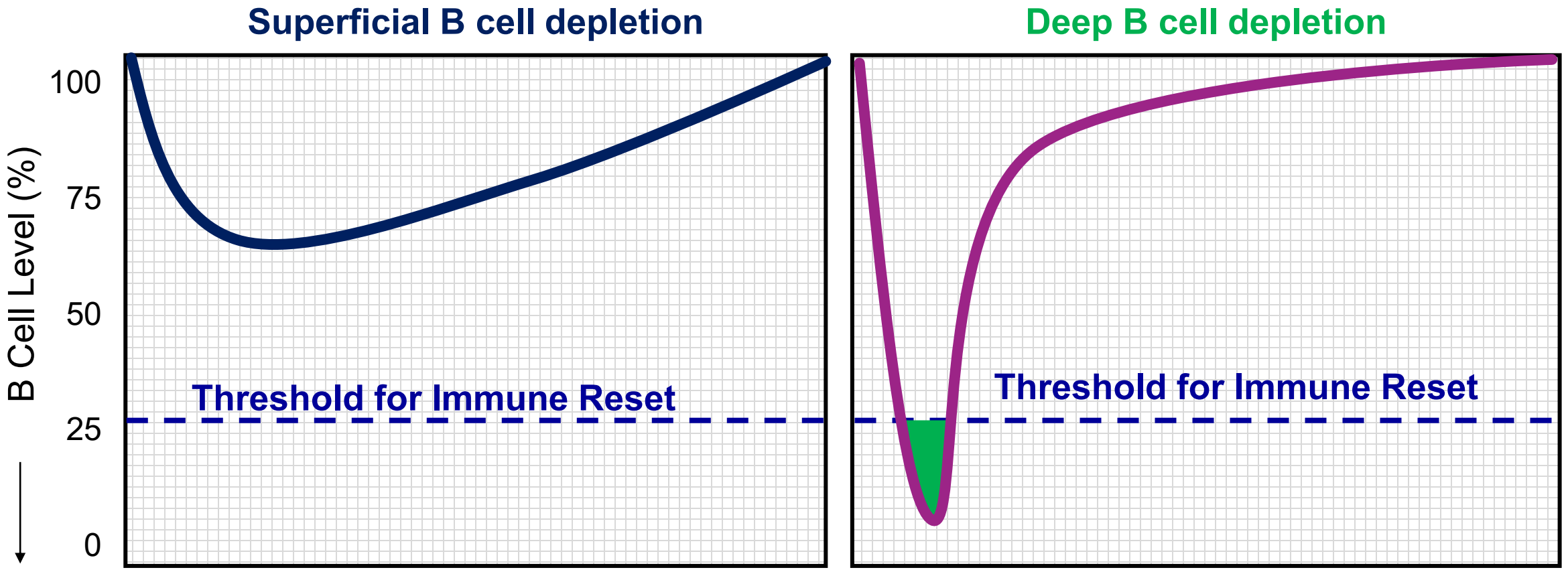
1. Introduction to CAR-T and T-Cell Engagers
2. Studies in Autoimmune Rheumatologic Disease
3. The Cullinan/CLN-978 CD19-directed T Cell Engager Trial in Sjögren's
4. Summary/Take-Home Messages

Pathophysiology of Sjögren's Disease



Fasano S, Mauro D, Macaluso F, et al. *Pathogenesis of primary Sjögren's syndrome beyond B lymphocytes.* Clin Exp Rheumatol. 2020;38(Suppl 126):S315-S323.

Hypothesis: A Lasting Sjögren's Remission Requires Deep B-cell Depletion



Persistence of abnormal B cells

Eradication of abnormal B cells

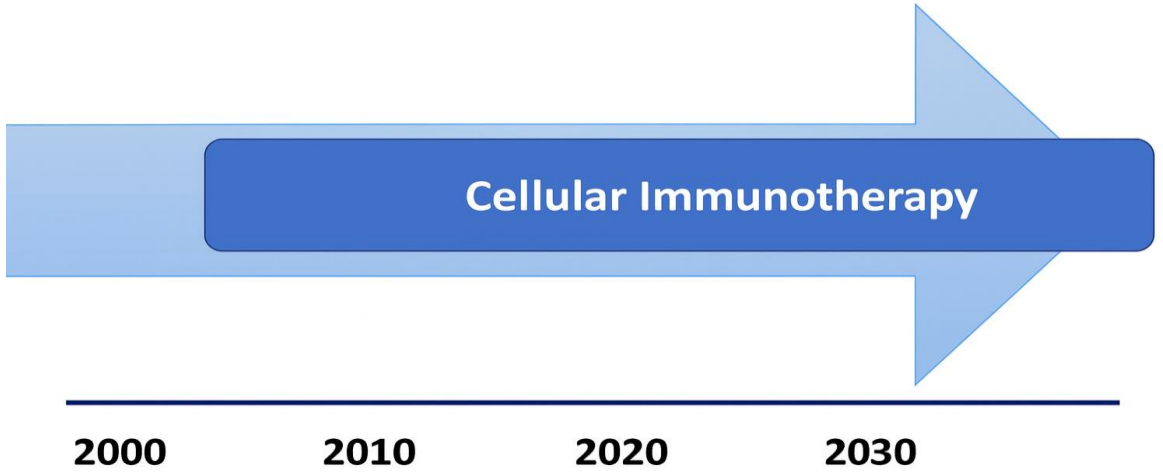
➡ Successful immune **RESET**

cullinan™ THERAPEUTICS

Cell Therapy *"living drugs"*

- Using the body's own immune cells to treat, and prevent diseases

- Potentially transformative, rapidly expanding area that may drive biomedical research and clinical care for the next decades

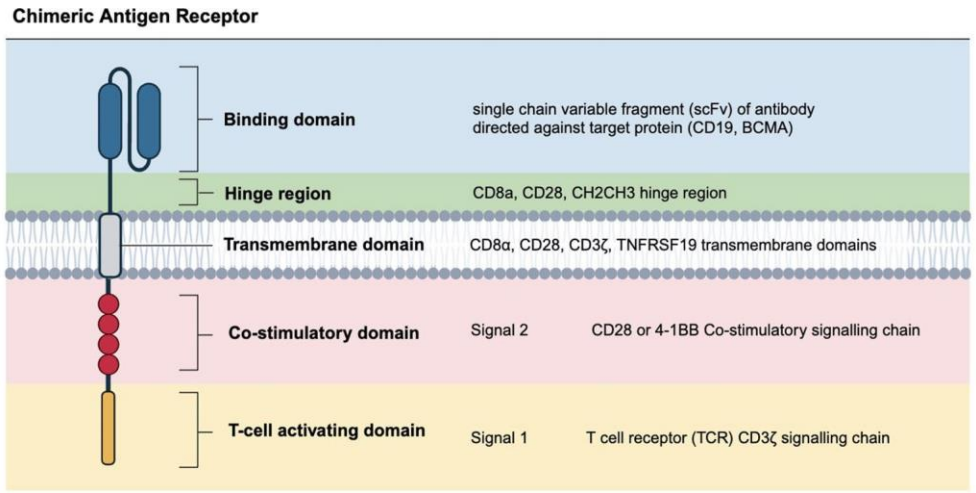


Cellular immunotherapy

- Established clinical use in **oncology**
- Being evaluated in **transplant** to prevent or treat rejection and graft-vs-host disease
- Therapeutic/curative potential in **autoimmune** diseases

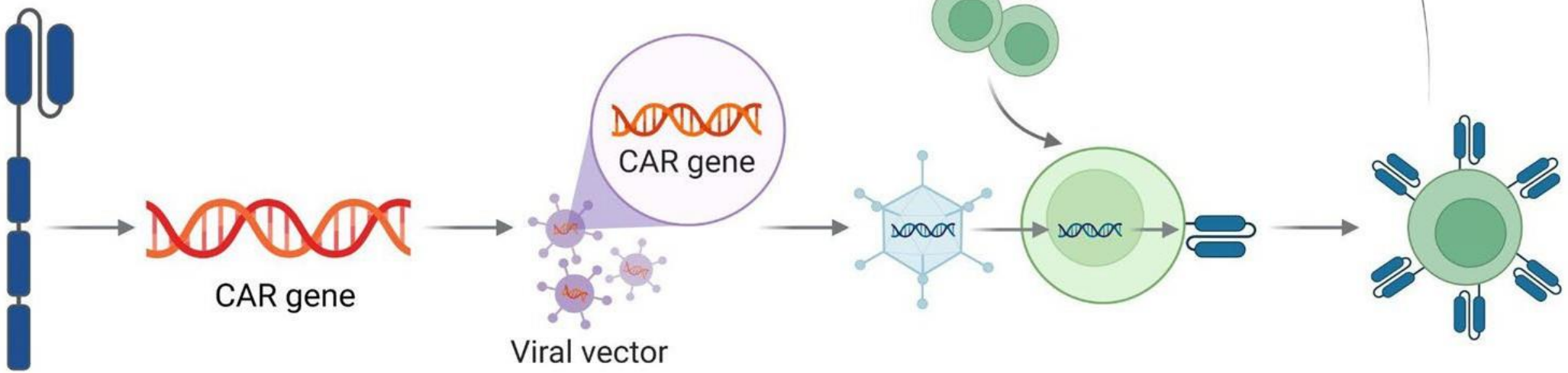
El-Kadiry AE et al. Front Med (Lausanne). 2021 Nov 22;8:756029.

CAR T-cells: Basic Concept



Chimera

Greek mythology fire-breathing creature with a lion's body, a goat's head on its back, and a serpent tail



A Chimeric Antigen Receptor (CAR) is designed to target a specific antigen (e.g. CD19 B-cell)

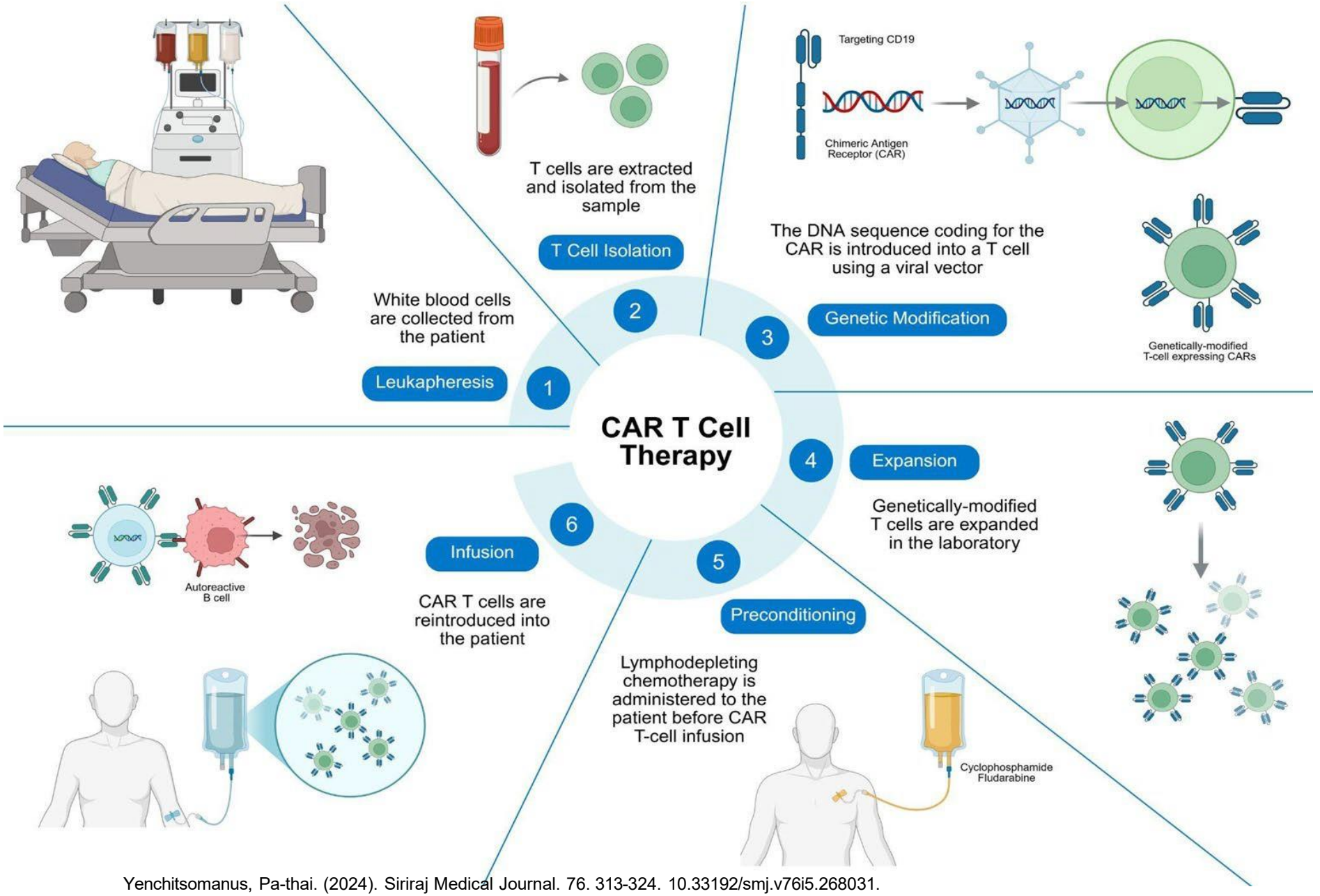
The gene for the **CAR** is inserted into a **viral vector**

The CAR's DNA sequence is inserted into **T-cells** using the viral vector

The genetically-modified T cells expressing the CARs are infused into the patient

Nordmann-Gomes A, Khalili L, et al. Semin Arthritis Rheum. 2025 Jul 16;74:152786.
Feins S et al. Am J Hematol. 2019 May;94(S1):S3-S9.

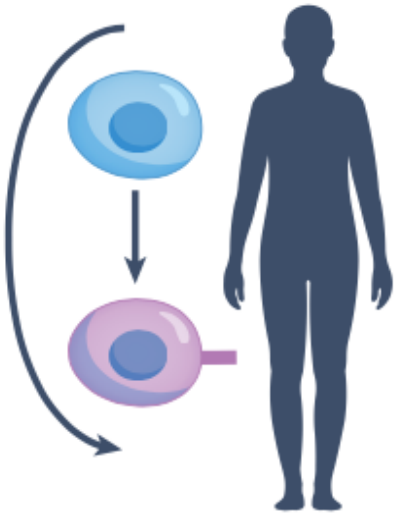
Complexity of Autologous CAR-T Cell Therapy



Yenchitsomanus, Pa-thai. (2024). Siriraj Medical Journal. 76. 313-324. 10.33192/smj.v76i5.268031.

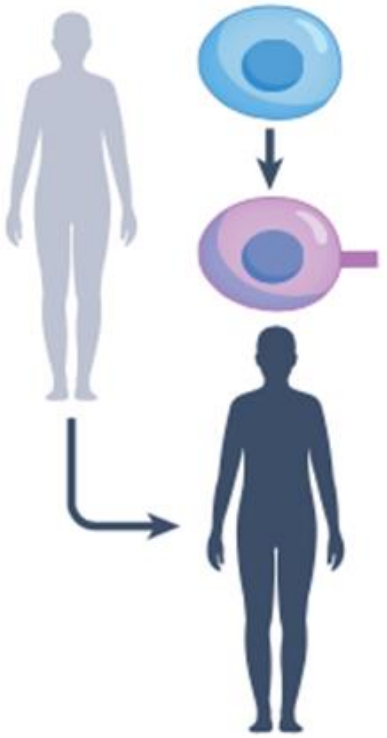
Autologous vs Allogeneic CAR T-cells (Oncology patients)

Autologous



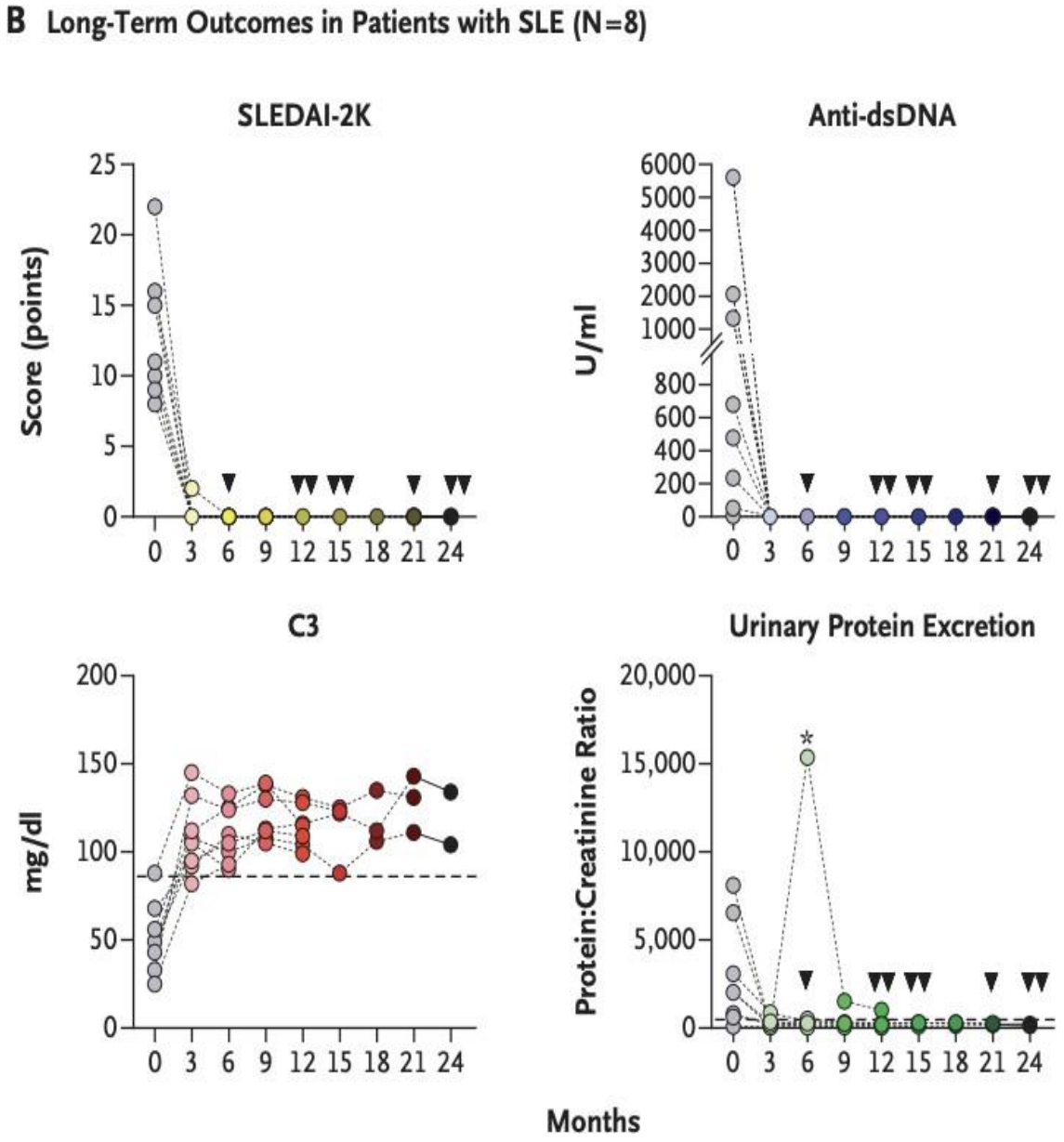
	Autologous CAR-T	Allogeneic CAR-T
Dosing	Single dose	Repeat dosing can be adapted to patient response
Expansion	In the patient	In the dish
Manufacturing time	~2-4 weeks plus additional release testing, often requiring bridging therapy	Off-the-shelf, available on demand No apheresis, bridging or other patient burden
Administration setting	Large, academic centers, requires inpatient observation	Shorter inpatient post-infusion observation
Safety	May have higher rates of CRS and ICANS with frequent hospital admission	Manageable infusion-related effects and reversible cytopenias
Product kinetics	Requires expansion after single infusion to ensure effective activity	Multiple infusions

Allogeneic



Locke FL et al. J Clin Oncol. 2025 May 10;43(14):1695-1705 Li YR et al. Med. 2025 Aug 8;6(8):100677.

CAR T-cell Therapy in SLE



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 22, 2024 VOL. 390 NO. 8

CD19 CAR T-Cell Therapy in Autoimmune Disease — A Case Series with Follow-up

Fabian Müller, M.D., Jule Taubmann, M.D., Laura Bucci, M.D., Artur Wilhelm, Ph.D., Christina Bergmann, M.D., Simon Völkl, Ph.D., Michael Aigner, Ph.D., Tobias Rothe, Ph.D., Ioanna Minopoulou, M.D., Carlo Tur, M.D., Johannes Knitza, M.D., Soraya Kharboutli, M.D., Sascha Kretschmann, Ph.D., Ingrid Vasova, M.D., Silvia Spoerl, M.D., Hannah Reimann, Ph.D., Luis Munoz, M.D., Roman G. Gerlach, Ph.D., Simon Schäfer, Ph.D., Ricardo Grieshaber-Bouyer, M.D., Anne-Sophie Korganow, M.D., Dominique Farge-Bancel, M.D., Dimitrios Mougiakakos, M.D., Aline Bozec, Ph.D., Thomas Winkler, Ph.D., Gerhard Krönke, M.D., Andreas Mackensen, M.D., and Georg Schett, M.D.

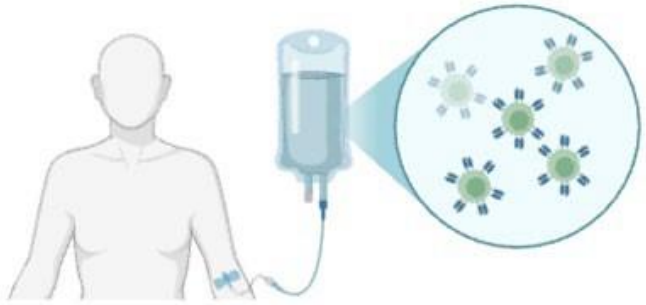
- All 8 patients achieved **remission** after 6 months
  - Symptoms improved. Labs normalized (Anti-dsDNA, complements, proteinuria)
- By 1 year: reconstituted B cells showed a **naïve B-cell** phenotype (“**Immune reset**”)
- On final follow up at 29 months: all patients **discontinued immunosuppressants with remission of SLE.**

Müller F et al. N Engl J Med. 2024 Feb 22;390(8):687-700

Systematic Review of CAR-T in Lupus

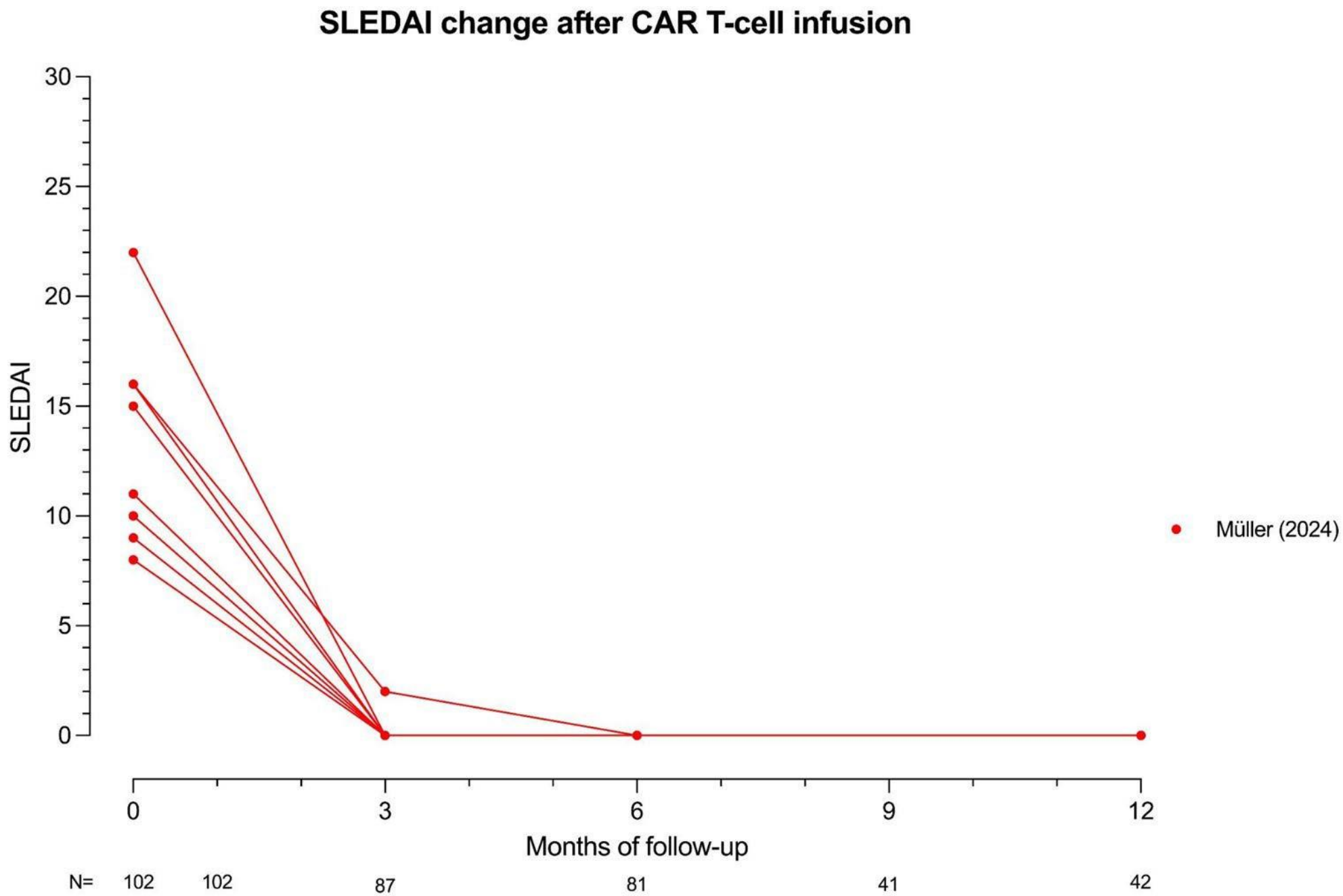
	Feng, J (2023)	He, X (2024)	Marasco, E (2024)	Müller, F (2024)	Podoll, A (2024)	Wang, W (2024)	Shu, J (2025)	Yang, C (2025)	Wang, D (2025)	Schett, G. (2024)	Schett, G (2025)	Sheikh, S (2025)	Gao, J (2025)	Sandhu, V (2025)	Morand, E (2025)	Fu, Q (2025)
Patients (n)	12	2	1	8	2	13	8	4	3	11	10	8	27	5	21	10
Population	Adult	Pediatric	Pediatric	Adult	Adult	Mixed	Adult	Adult	Adult	Adult	Adult	Adult	Adult	Adult	Adult	Adult
Study Type	Phase 1	Case Series	Case Report	Case Series	Phase 1	Phase 1	Phase 1	Pilot Study	Pilot Study	Phase 1	Phase 1/2 CASTLE	Phase 1/2	Phase 1	Phase 1	Phase 1/2	Phase 1/2
Target	CD19-BCMA	CD19	CD19	CD19	CD19	CD19-BCMA	CD19	CD19	CD19	CD19	CD19	CD19	CD19 (NK)	CD19	CD19	CD19-BCMA
CAR Construct: Hinge	Unknown	Unknown	CD8α	CD8α	CD8α	Unknown	Unknown	Unknown	Unknown	CD8α	CD8α	CD8α	Unknown	Unknown	CD8α	Unknown
CAR Construct: Trans.	Unknown	Unknown	TNFRSF-19	TNFRSF-19	CD8α	Unknown	Unknown	Unknown	Unknown	TNFRSF-19	TNFRSF-19	CD8α	Unknown	Unknown	CD8α	Unknown
CAR Construct: TCR	Unknown	CD3ζ	CD3ζ	CD3ζ	CD3ζ	CD3ζ	CD3ζ	Unknown	Unknown	CD3ζ	CD3ζ	CD3ζ	Unknown	CD3ζ (1xx)	CD3ζ	Unknown
CAR Construct: Co-stim.	Unknown	4-1BB	4-1BB	4-1BB	CD28	4-1BB (CD19) CD28 (BCMA)	4-1BB	Unknown	Unknown	4-1BB	4-1BB	4-1BB	Unknown	CD28	4-1BB	Unknown
Manufacture	Autologous	Autologous	Autologous	Autologous	Autologous	Autologous	Autologous	Allogeneic	Allogeneic	Autologous	Autologous	Autologous	Allogeneic	Allogeneic (iPSC)	Autologous	Autologous
Producer	Shanghai YaKe Bio.	Chongqing Precision Biotech	Miltenyi Biotech	Miltenyi Biotech	Kyverna Therap.	iCell Gene Therap.	JW Therap. (Shanghai)	BRL Medicine Inc.	BRL Medicine Inc.	Bristol Myers Squibb	Miltenyi Biotech	Cabaletta Bio	Rui Therap.	Fate Therap.	Novartis Pharm.	Gracell Biotech. Ltd.
Drug Name	Unknown	MC-1-50	MB-CART19.1	MB-CART19.1	KYV-101	ICG-119	Relma-cel	TyU19 (BRL-301)	TyU19 (BRL-301)	CC-97540	MB-CART19.1	Rese-cel (CABA-201)	KN5501	FT819	YTB323	GC012F (AZD0120)
Dose	1 - 2 x 10^6/kg	1 x 10^5/kg	1 x 10^6/kg	1 x 10^6/kg	0.5 x 10^8	3 x 10^6/kg	25-100 x 10^6	1 x 10^6	1 x 10^8	10 - 25 x 10^6	1 x 10^6/kg	1 x 10^6/kg	0.7 - 1.5 - 3 - 4.5 x 10^9	3.6 x 10^8	12.5 x 10^6	1 – 2 – 3 x 10^5/kg
Center	Multicenter	Single center	Single center	Multicenter	Multicenter	Multicenter	Single center	Single center	Single center	Multicenter	Multicenter	Multicenter	Single center	Multicenter	Multicenter	Single center
Country	China	China	Italy	Germany	USA	China	China	China	China	Germany USA	Germany Austria Italy	USA	China	USA	Spain Germany	China
Longest Follow-up	17 mo.	5 mo.	3 mo.	29 mo.	3 mo.	48 mo.	12 mo.	9 mo.	12 mo.	11 mo.	9 mo.	9 mo.	21 mo.	12 mo.	12 mo.	18 mo.

16
studies

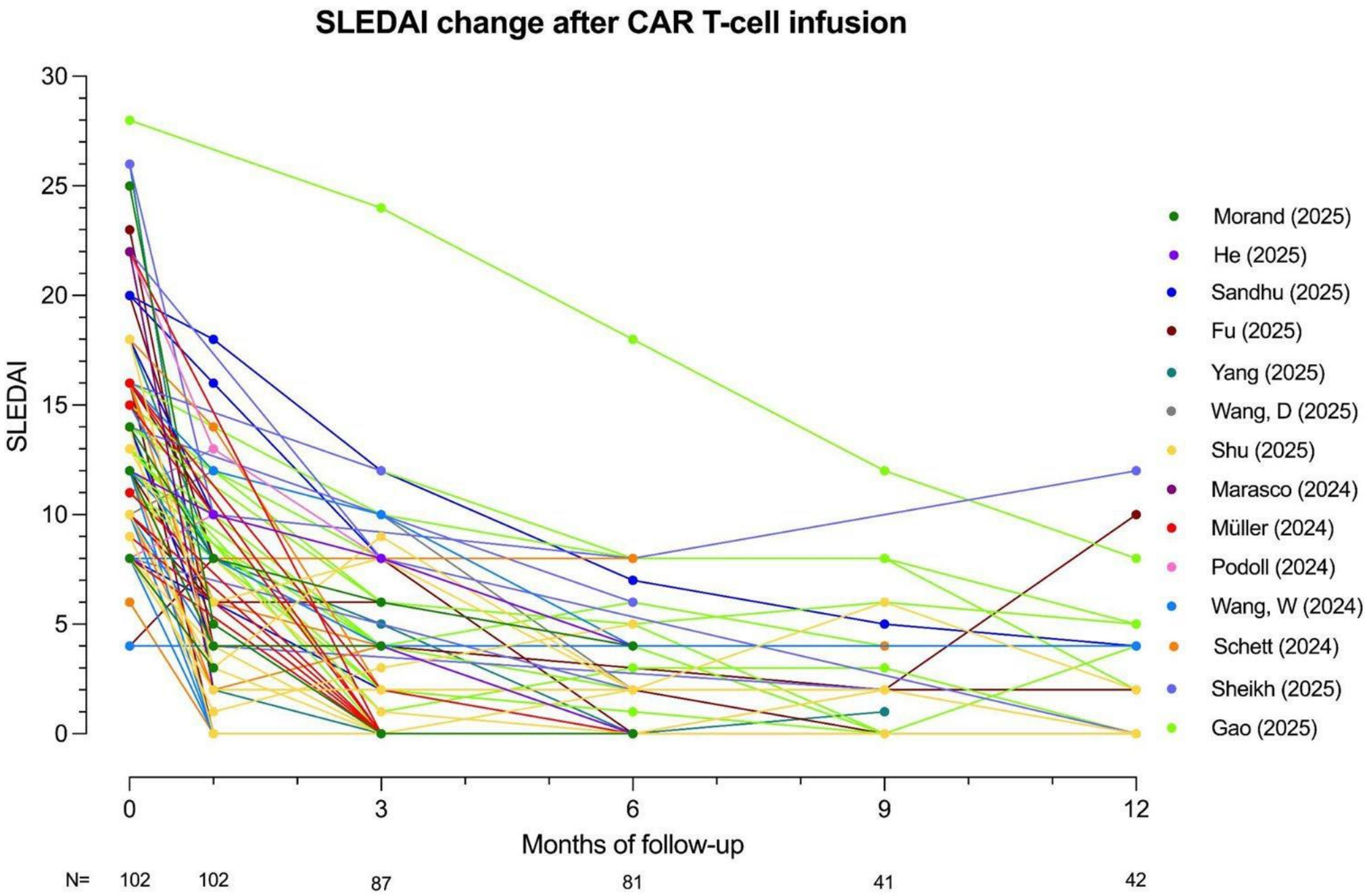


145
patients with SLE

Nordmann-Gomes A, Khalili L, et al. Semin Arthritis Rheum. 2025 Jul 16;74:152786.

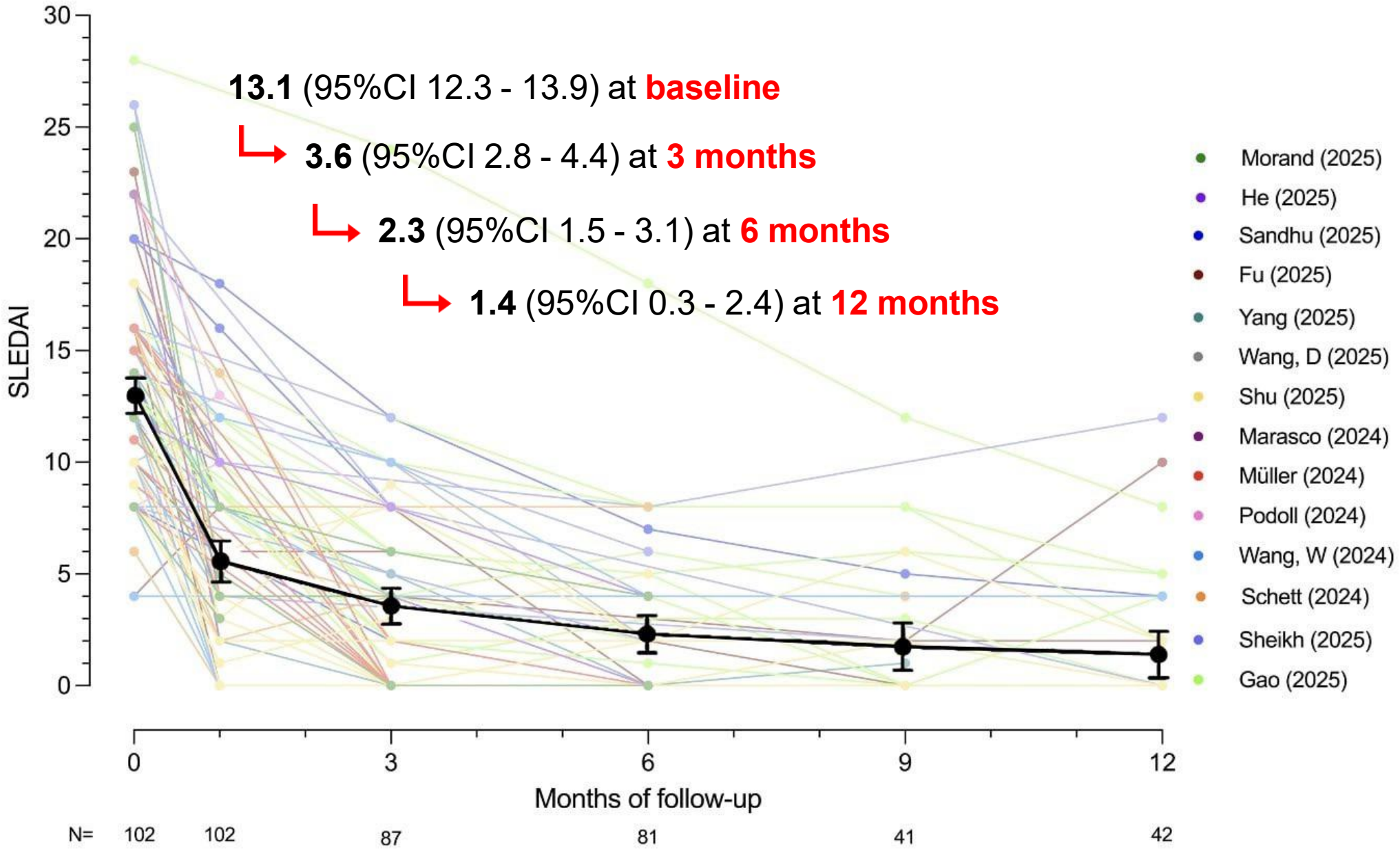


Nordmann-Gomes A, Khalili L, et al. Semin Arthritis Rheum. 2025 Jul 16;74:152786.



Nordmann-Gomes A, Khalili L, et al. Semin Arthritis Rheum. 2025 Jul 16;74:152786.

SLEDAI change after CAR T-cell infusion



Nordmann-Gomes A, Khalili L, et al. Semin Arthritis Rheum. 2025 Jul 16;74:152786.

Efficacy Outcomes

- Efficacy outcomes were reported for **133**/145 patients (92%)
- Of these, **106** (80%) had follow-up of at least 6 months
- Efficacy outcomes were variably reported

No statistically significant difference in efficacy outcomes:

- autologous and allogeneic

70% achieved **Remission** (45/64)

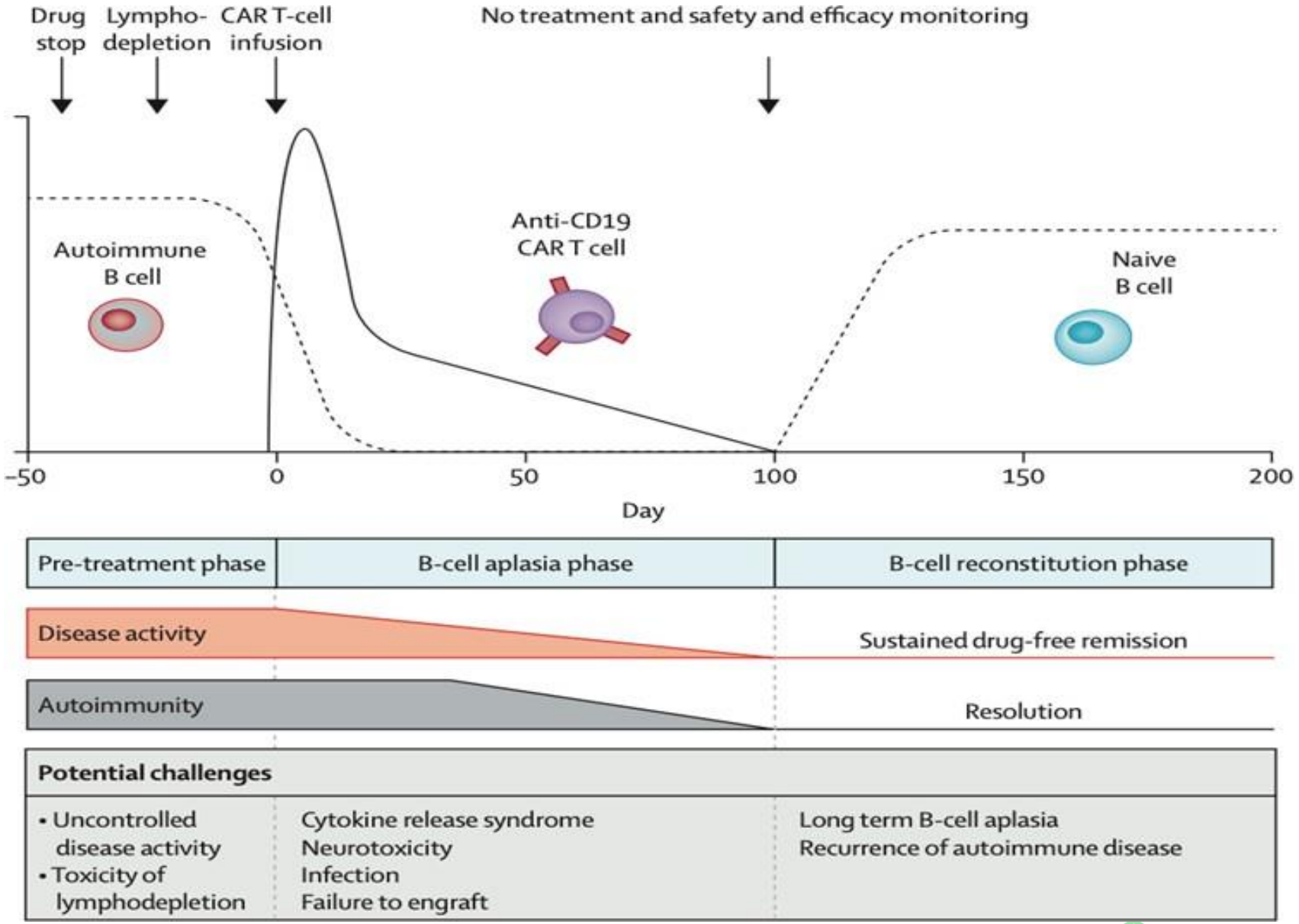
89% achieved **Low-level disease activity** (50/56)

84% achieved **Drug-free** remission (76/91)

Nordmann-Gomes A, Khalili L, et al. Semin Arthritis Rheum. 2025 Jul 16;74:152786.

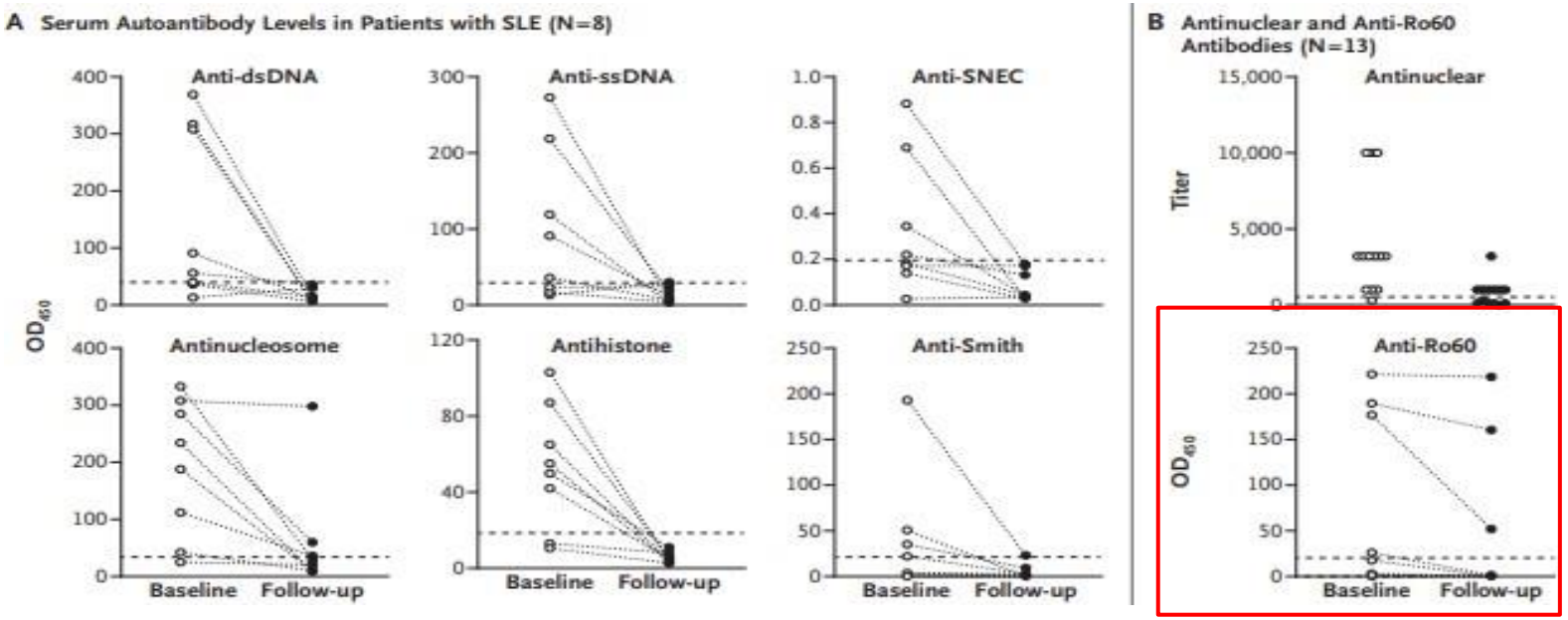
B-cell Depletion & Reconstitution

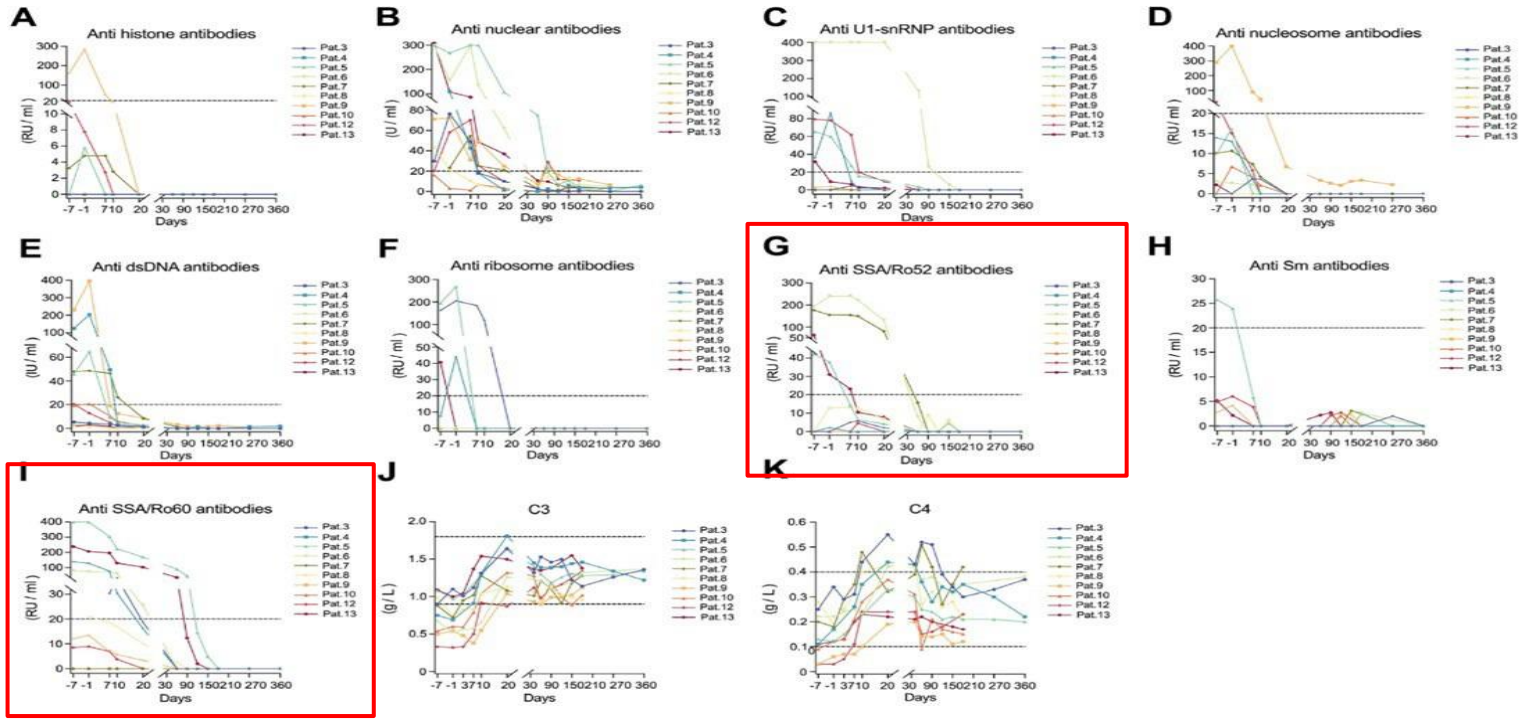
- All groups reported successful B-cell **depletion**, typically achieved within **1-3 weeks**
- B-cell **reconstitution** in most groups around **2-3 months** post-infusion, with some groups reporting **reconstitution as early as 40 days or as late as 6 months**



Nordmann-Gomes A, Khalili L, et al. Semin Arthritis Rheum. 2025 Jul 16;74:152786. Ikegame K. Intern Med. 2024 Aug 28.

Autoantibodies and Complement





- **<u>C3 and C4</u>** normalized in **75/79** (95%)
- **<u>Anti-dsDNA</u>** decreased in **72/79** patients (91%) and normal in **47/79** (60%)
- Several groups also reported decrease in other autoantibodies:
  - Difficult to eradicate antibodies (including anti-SSA/Ro60, and anti-SSA/Ro52) - produced by LLPCs normalized in **12/13** patients (92%) treated with the bispecific CD19 CAR T-cell by iCell Gene Therapeutics study

Nordmann-Gomes A, Khalili L, et al. Semin Arthritis Rheum. 2025 Jul 16;74:152786.

B-cell Depleting Therapies

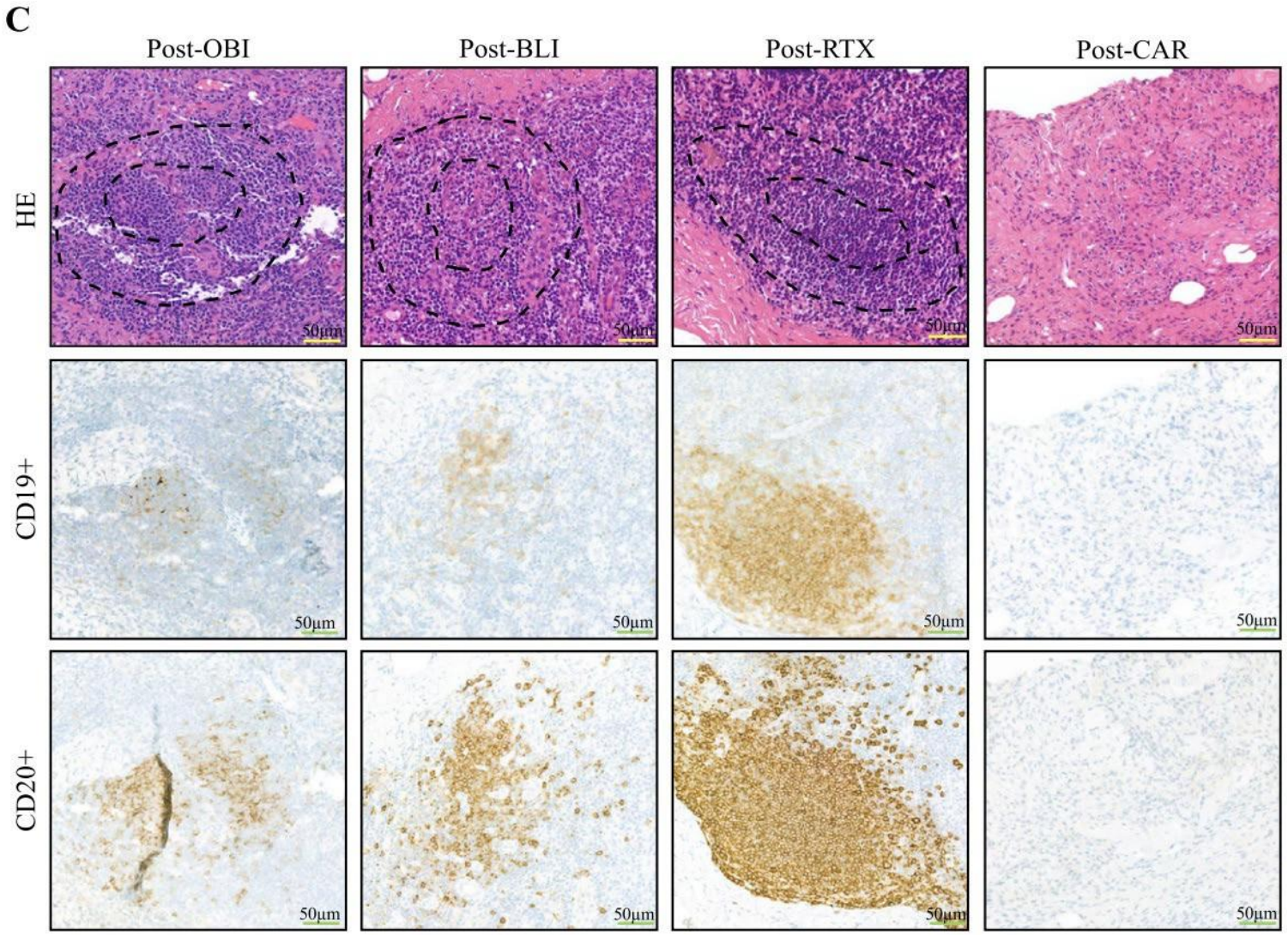
- Comparing efficacy of four B-cell depleting therapies in 24 patients with autoimmune diseases (SLE, RA, Myositis, SSc)
  - Rituximab (n=4), Obinutuzumab (n = 4), Blinatumomab (n = 4), CAR t-cell therapy (n=12)
- All patients underwent sequential inguinal lymph node biopsies to assess B-cell depletion in the tissues

	OBI 1	OBI 2	OBI 3	OBI 4	BLI 1	BLI 2	BLI 3	BLI 4	RTX 1	RTX 2	RTX 3	RTX 4
	SLE	IIM	SLE	SLE	RA	RA	RA	RA	RA	RA	IIM	IIM
LN Clearance												
Clinical response												
Remission												
Drug-Free State												
	CAR 1	CAR 2	CAR 3	CAR 4	CAR 5	CAR 6	CAR 7	CAR 8	CAR 9	CAR 10	CAR 11	CAR 12
	SLE	SSc	SLE	SSc	SLE	SLE	SSc	SSc	SSc	SSc	IIM	SSc
LN Clearance												
Clinical response												
Remission		n.a.		n.a.				n.a.	n.a.	n.a.		n.a.
Drug-Free State												

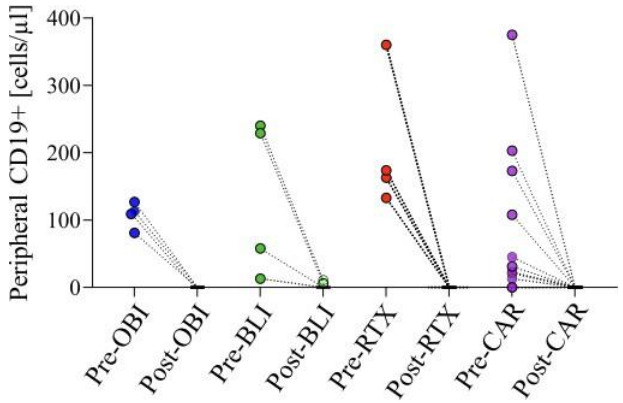
Color legend: **green** indicates achievement, **orange** indicates nonachievement and **blue** indicates not available

Tur C et al. Ann Rheum Dis. 2025 Jul 11:S0003-4967(25)04174-3.

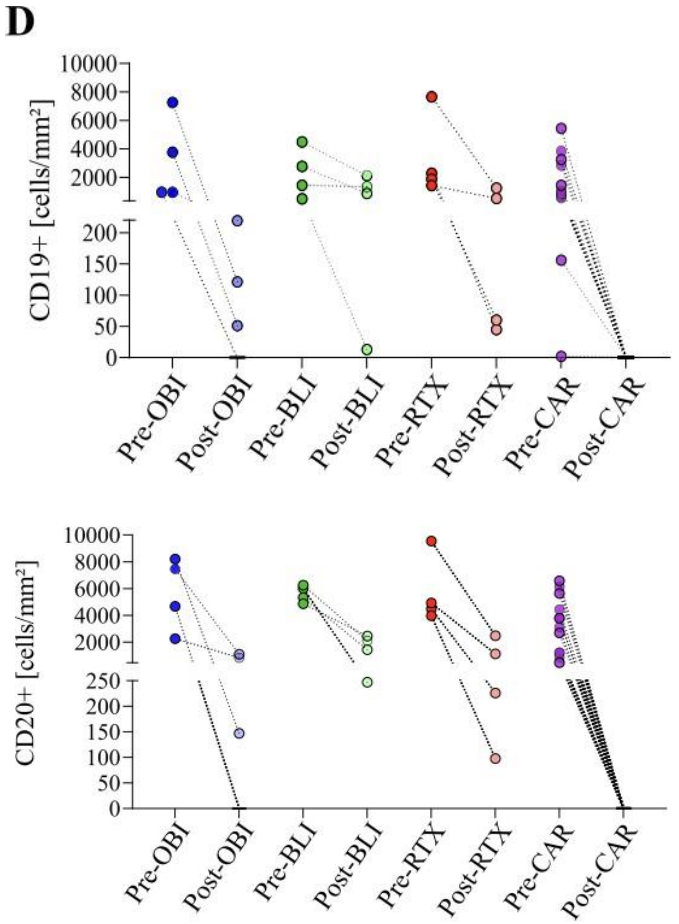
B-cell Depletion in Lymph Nodes



Peripheral

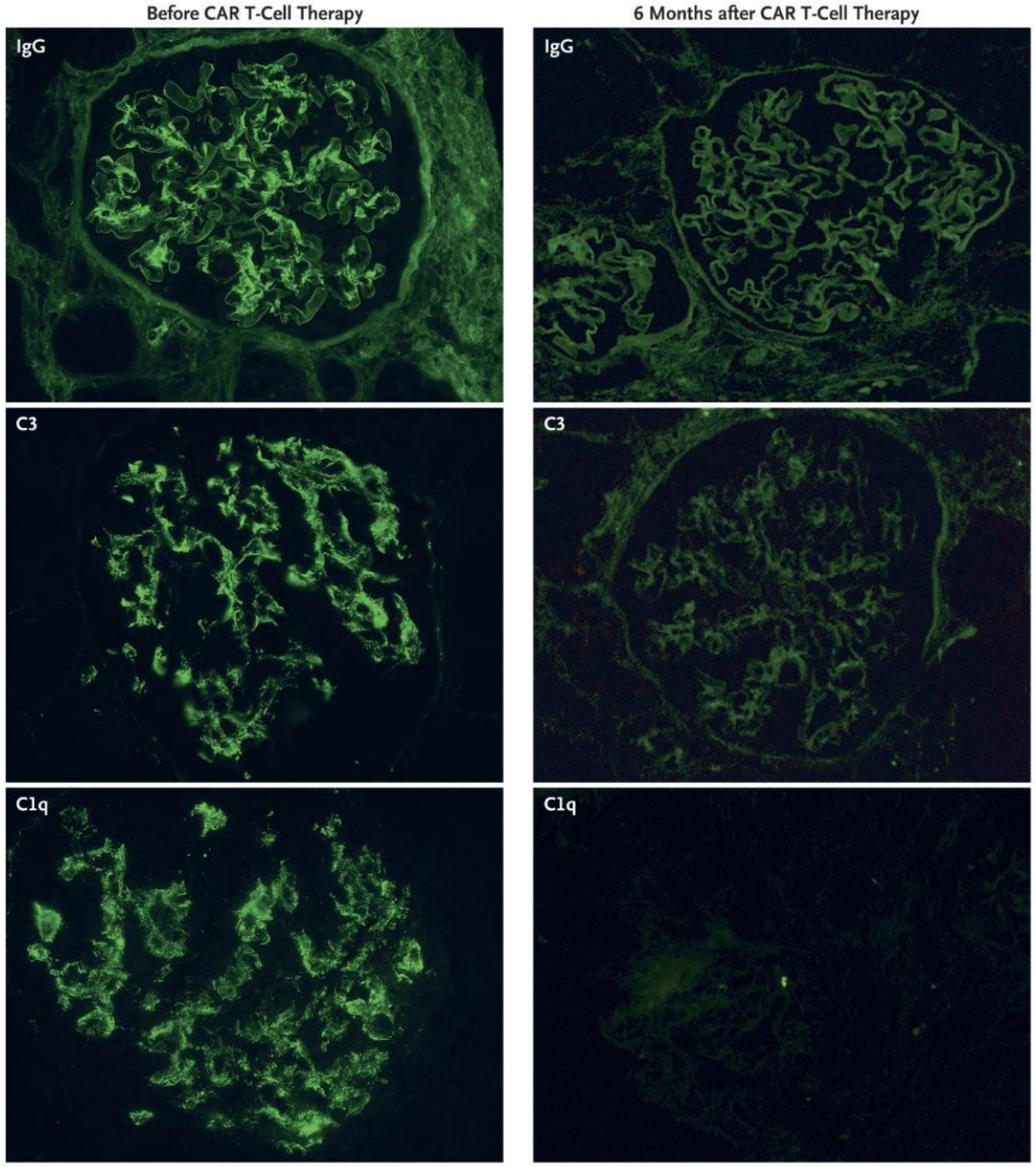


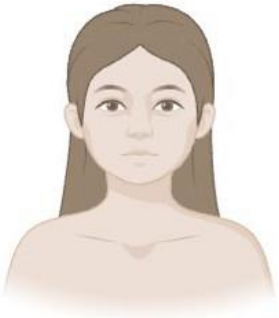
Lymph nodes



Tur C et al. Ann Rheum Dis. 2025 Jul 11:S0003-4967(25)04174-3.

Immune clearance in the kidneys





16-year-old girl with childhood-onset, severe refractory SLE with pulmonary hypertension and **lupus nephritis**

Immunofluorescence Analysis Showing Intense Glomerular Deposits of IgG, C3, and C1q before CAR T-Cell Therapy and an Absence of Immune Deposits 6 Months after Such Therapy.

Clinically: Drug-free remission achieved at 3 months, sustained up to the last follow-up at 9 months, with normalization of proteinuria and lung pressure

Fabrizio De Benedetti et al. NEJM. 2024

Efficacy Outcomes

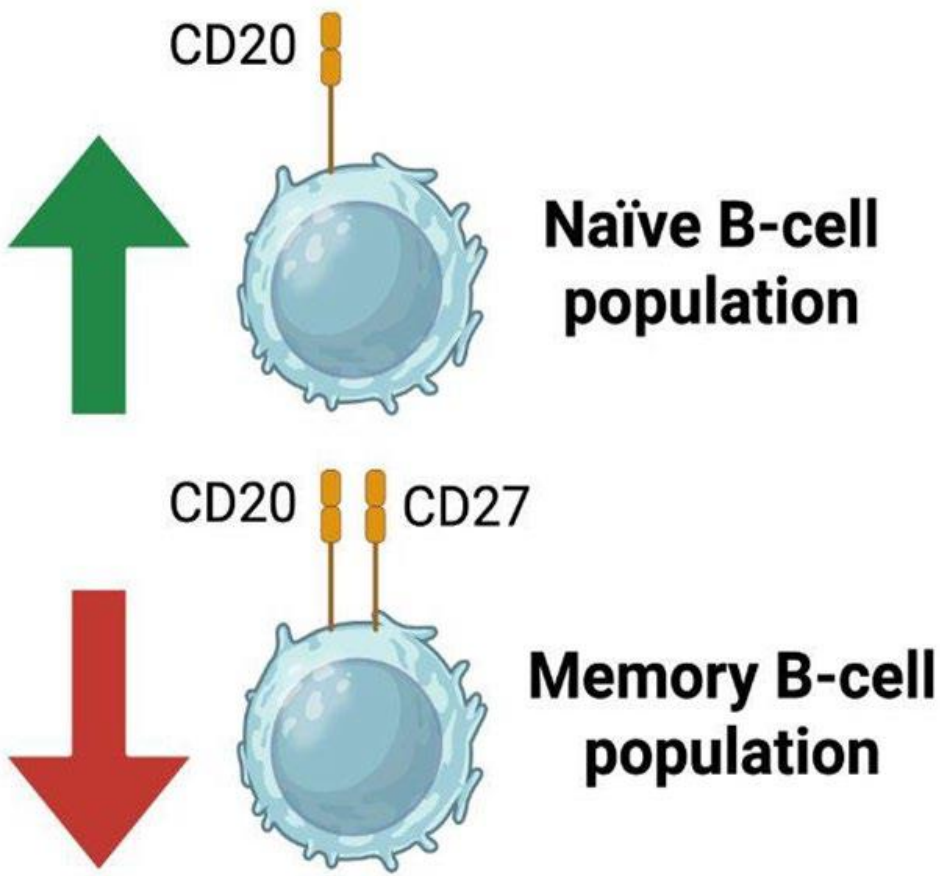
- Some patients did not achieve DORIS Remission or Low disease activity (LLDAS)
  - 40% -- persistent anti-dsDNA titers
  - ~10% -- persistent abnormal complement levels

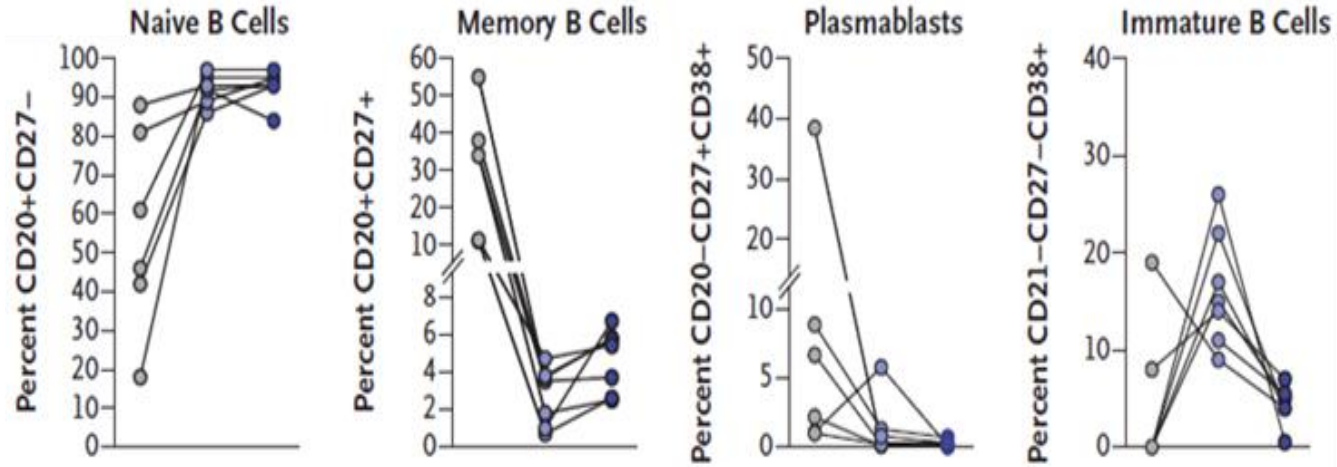
This **persistence of autoantibody production** and **residual disease activity** -even at low levels- suggests that small numbers of autoreactive B-cells may continue to reside within tissues.

All patients reported successful expansion of CAR-Ts, so why is this happening?
→ Not complete depletion of tissue B cells?
→ Product variability?
→ Recurrence of autoreactive cells after reconstitution?
→ Other mechanisms besides B cell driven disease activity

Nordmann-Gomes A, Khalili L, et al. Semin Arthritis Rheum. 2025 Jul 16;74:152786.

B-cell Reconstitution: An Autoimmunity Reset?



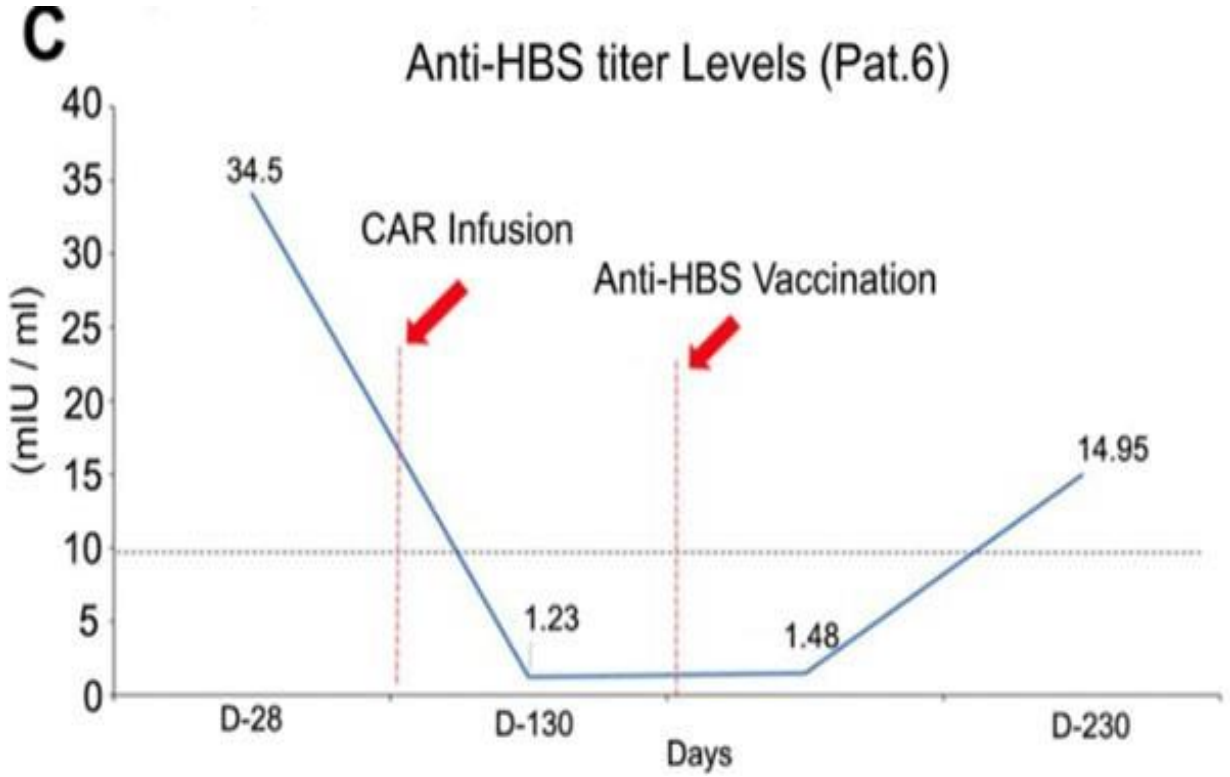


Nordmann-Gomes A, Khalili L, et al. Semin Arthritis Rheum. 2025 Jul 16;74:152786.

Protective Antibodies

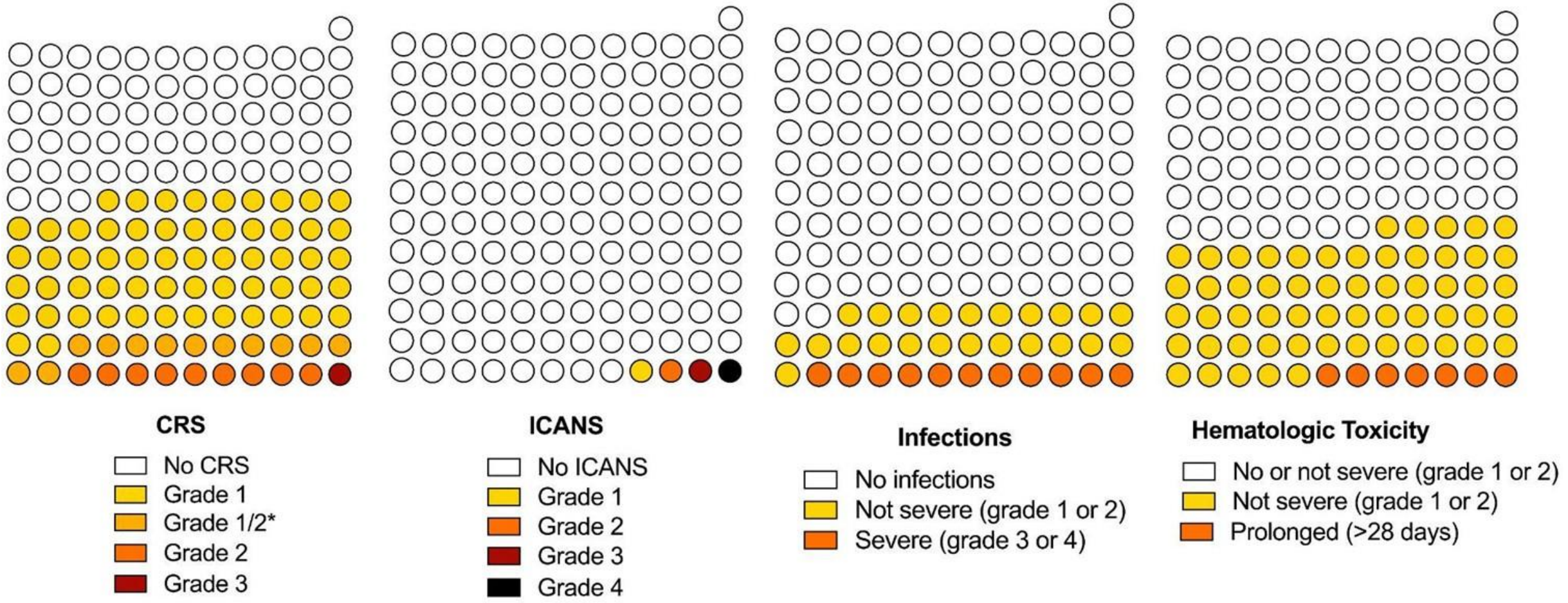
- Long-lived Plasma Cells also sustain long-term antibody responses to infections and vaccines, a reduction in protective IgG antibodies was also reported by some studies

- **These titers recovered following vaccination, and no increase in infection rates was observed**



Nordmann-Gomes A, Khalili L, et al. Semin Arthritis Rheum. 2025 Jul 16;74:152786.

Safety Outcomes



Nordmann-Gomes A, Khalili L, et al. Semin Arthritis Rheum. 2025 Jul 16;74:152786.

Cytokine Release Syndrome (CRS)

Total	Grade 1	Grade 2	Grade 3	Grade 4
81 (56%)	80 (55%)		1 (1%)	0 (0%)

- **Onset**: within 1-10 days
- **Duration**: 2-5 days for most cases
- All 81 events **resolved**:
  - No treatment – 34
  - Supportive care or **NSAIDS** - 17
  - **Tocilizumab** - 26
  - **Glucocorticoids** - 4

Grade	Fever	Hypotension	Hypoxia
1	✓*	✗	✗
2	✓*	✓ **NOT** requiring vasopressors	✓ Requiring **low-flow nasal cannula** only †
3	✓*	✓ Requiring **1 vasopressor**§	✓ Requiring **high-flow nasal cannula, non-rebreather mask, or venturi mask**
4	✓*	✓ Requiring **multiple vasopressors**⁑	✓ Requiring **positive pressure ventilation**∆

* with or without constitutional symptoms (myalgia, arthralgia, malaise)
† low-flow nasal cannula (6 L/minute) or blow-by
§ with or without vasopressin
⁑ excluding vasopressin
∆ CPAP, bilevel positive airway pressure, intubation, mechanical ventilation

Nordmann-Gomes A, Khalili L, et al. Semin Arthritis Rheum. 2025 Jul 16;74:152786.
Lee DW et al. Biol Blood Marrow Transplant. 2019 Apr;25(4):625-638

Immune effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Total	Grade 1	Grade 2	Grade 3	Grade 4
4 (3%)	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)

- Symptoms ranged from: **tremors**, **dysphagia**, **speech difficulties**, **ataxia**, **lethargy**, **altered mental status**, and subclinical **seizure** activity
- Onset: within day 8-10
- Treated with glucocorticoids ± anakinra
- No neurological sequelae were reported

Grade	ICE Score	Level of Consciousness	Seizure	Motor findings	Elevated ICP
1	7-9	Awakens **spontaneously**	✗	✗	✗
2	3-6	Awakens to **voice**	✗	✗	✗
3	0-2	Awakens to **tactile** stimuli	**< 5 minutes**	✗	**Focal edema** on imaging
4	0	**Unarousable***, stupor, or **coma**	**≥ 5 minutes**	**Hemiparesis** or **paraparesis**	**Diffuse edema** on imaging †

* Or difficult to arouse.
† Or posturing, or Cushing's triad

Nordmann-Gomes A, Khalili L, et al. Semin Arthritis Rheum. 2025 Jul 16;74:152786.
Lee DW et al. Biol Blood Marrow Transplant. 2019 Apr;25(4):625-638

Sjögren's FOUNDATION

Safety Outcomes Compared to Oncology

CRS

	SLE n = 145	DLBCL n = 1193	ALL n = 1908
Total	**56%**	67%	30%
Grade 3 or 4	**1%**	13%	13.8%

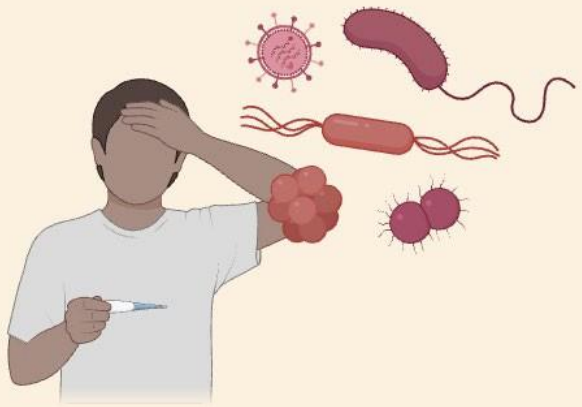
ICANS

	SLE n = 145	Hematologic malignancies n = 3,184
Total	**3%**	26.9%
Grade 3 or 4	**1.5%**	10.5%

This improved safety profile in patients with autoimmune conditions compared to those with B-cell malignancies is hypothesized to result from the **lower B-cell burden** in SLE

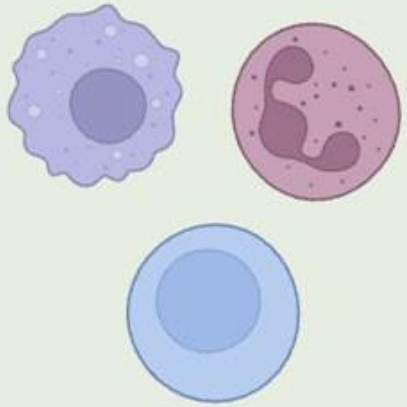
Rodrigues Dos Santos *et al. Hematol Transfus Cell Ther.* 2024.2024;46(Suppl 6):S306–S315.
Elsallab M *et al*. Cancer Gene Ther. 2023 Jun;30(6):845-854.
Han MW et al. Front Neurol. 2024 Oct 15;15:1392831.
Nordmann-Gomes A, Khalili L, et al. Semin Arthritis Rheum. 2025 Jul 16;74:152786.

Safety Outcomes



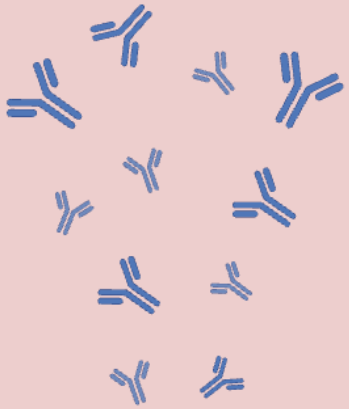
Infections

- 28 (19%) infections
- 11 (7.6%) were **severe**
  - 9 pneumonias
  - 1 UTI
  - 1 meningitis
- **1 Death** from **pneumococcal meningitis (pt declined vaccination)**
  - 11 months after CD19 CAR T-cell
  - No pneumococcal vaccination pre or post infusion



Cytopenias

- **Severe** (grade 3 or 4): 58 (40%)
  - Expected from CAR therapy and lymphodepletion
- **Prolonged** (>28 days): 7 (5%)

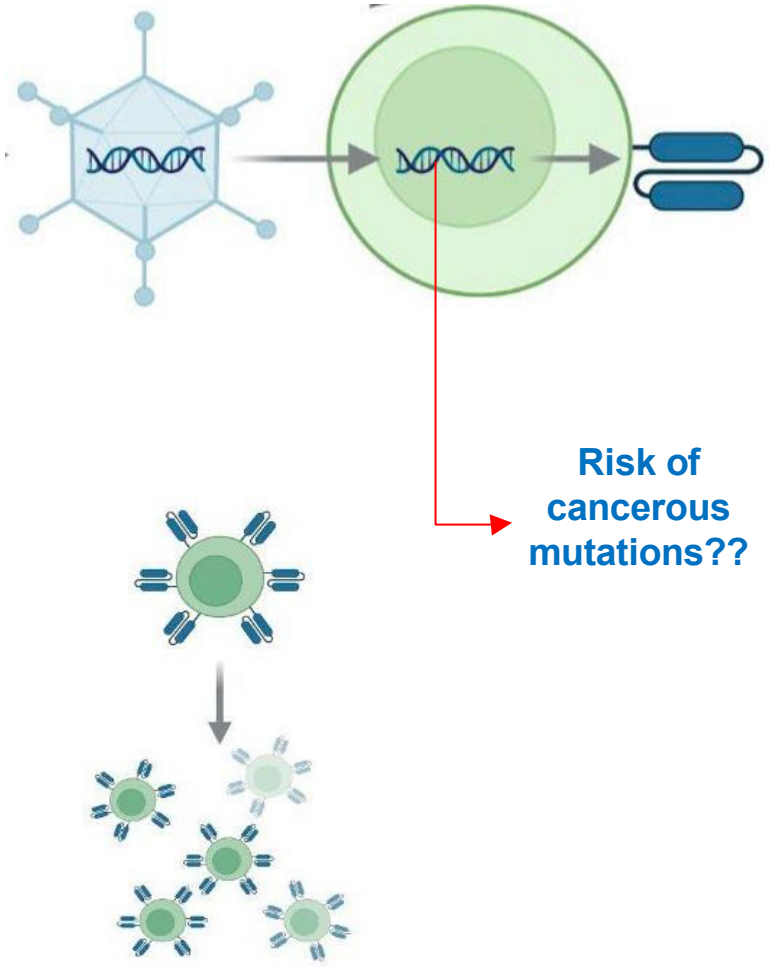


Other

- **Hypogammaglobulinemia**: 37 (26%)
  - 8 received IVIG
- **Macrophage Activating Syndrome (MAS)**: 2 patients

Nordmann-Gomes A, Khalili L, et al. Semin Arthritis Rheum. 2025 Jul 16;74:152786.

Concern for Secondary Malignancies?



- Patients w/ B-cell lymphoma have a 4.7 fold higher incidence of developing second primary T-cell lymphoma
- Question: can CAR-T treatment further increase the risk for secondary T-cell Lymphoma?
- French DESCAR-T registry database → 3,066 oncology patients who received CAR T cell since 2018
  - **One (0.03%) oncology patien**t developed a T cell malignancy *due* to CAR T infusion
    - Primary cutaneous CD30⁺ T cell lymphoma
    - 3 years after receiving tisagenlecleucel therapy for DLBCL
    - Integration of the CAR clone into the tumor suppressor gene *PLAAT4* (phospholipase A and acyltransferase 4)

Hamilton MP et al. N Engl J Med. 2024 Jun 13;390(22):2047-2060. Dulery R et al. Nat Med. 2025 Apr;31(4):1130-1133

Secondary T-cell Malignancies in Oncology Patients

As of Sept 2023: 34,000 individuals received CAR T treatment commercially[2]

FDA investigating 20 reports of T cell malignancy, including T cell lymphomas and leukemias

- Many unknowns about these cases, including age, prior therapies, immune status, etc[2]
  - Recommendation to monitor patients who have received these therapies lifelong for new malignancies[2]

- **One published case** of confirmed CAR+ T-cell malignancy **may have been due to a gene mutation present <u>before</u>** CAR T-cell manufacturing[3]

European Medical Agency monitoring over 40,000 patients worldwide with CAR T-cell therapies[4]

As of April 2024, EMA is investigating 27 cases of T-cell lymphoma or leukemia, some overlapping with those reported in FAERS[4]

AML, acute myeloid leukemia; CAR, chimeric antigen receptor; EMA, European Medicines Agency; FAERS, FDA Adverse Events Reporting System; FDA, Food and Drug Administration.

1. FDA Investigating Serious Risk of T-cell Malignancy Following BCMA-Directed or CD19-Directed Autologous Chimeric Antigen Receptor (CAR) T cell Immunotherapies. Accessed April 19, 2024. https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/fda-investigating-serious-risk-t-cell-malignancy-following-bcma-directed-or-cd19-directed-autologous 2 Levine BL et al. *Nat Med*. 2024. doi: 10.1038/s41591-023-02767-w. 3. Harrison SJ et al. *Blood* 2023;142:6939-6940. 4. Pharmacovigilance Risk Assessment Committee (PRAC) Recommendation 11 April 2024. Single assessment report on secondary malignancy of T-cell origin with CAR T-cell products.

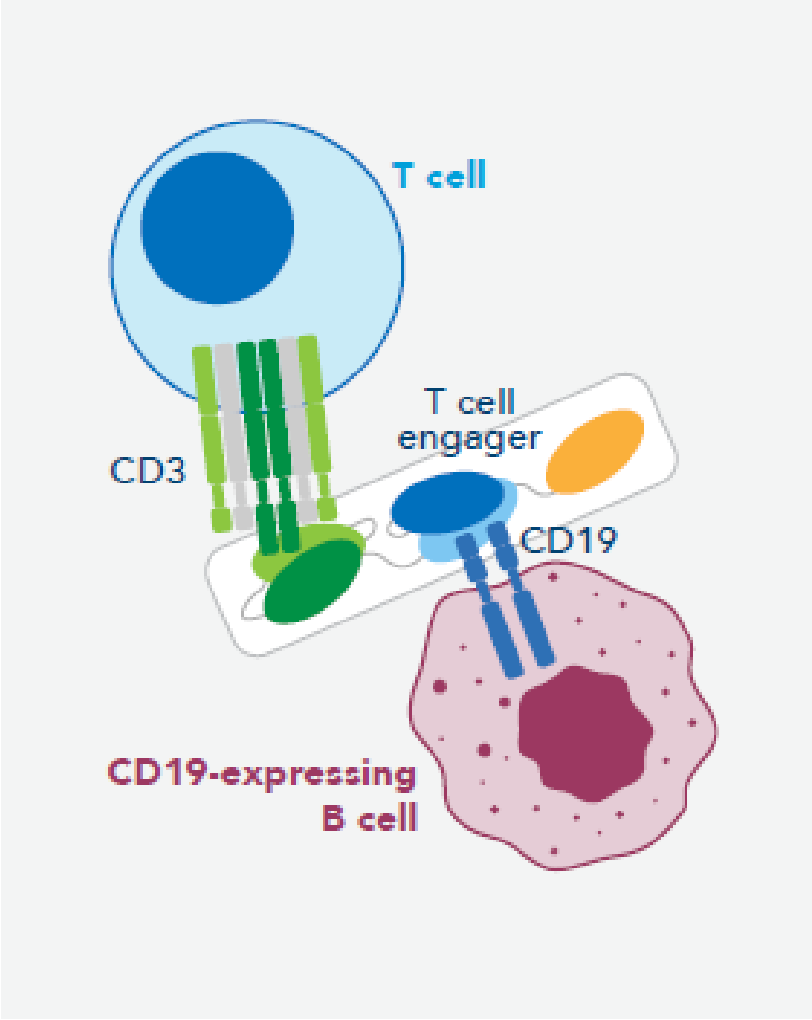
Current Stance:

- Risk for 2nd T-cell malignancy appears *very low*—only a handful of cases have been reported among tens of thousands of patients worldwide.
- French registry of more than 3,000 people, one developed a T-cell cancer years later, which is about **0.03%**.
- Most secondary cancers seen after CAR-T are not related to the therapy itself.
- Scientists continue to monitor long-term safety carefully, but so far, CAR-T remains a safe and promising approach for autoimmune diseases.

A New Treatment Approach – T Cell Engagers

- In the body's immune system, we have special cells called **T cells** that find and destroy harmful cells.
- **B cells** are another type of immune cell that usually help fight infections. Sometimes, B cells can make proteins that cause diseases like Sjögren's disease.
- **T cell engagers** are a type of treatment that works by guiding the body's own T cells to find B cells.
- Each **T cell engager** molecule sticks to a T cell and a B cell, which makes the T cell destroy the B cell.

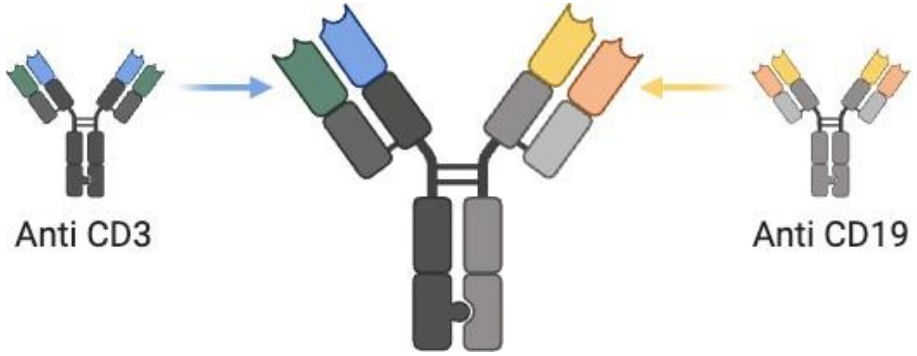
CD-19 Targeted T Cell Engager



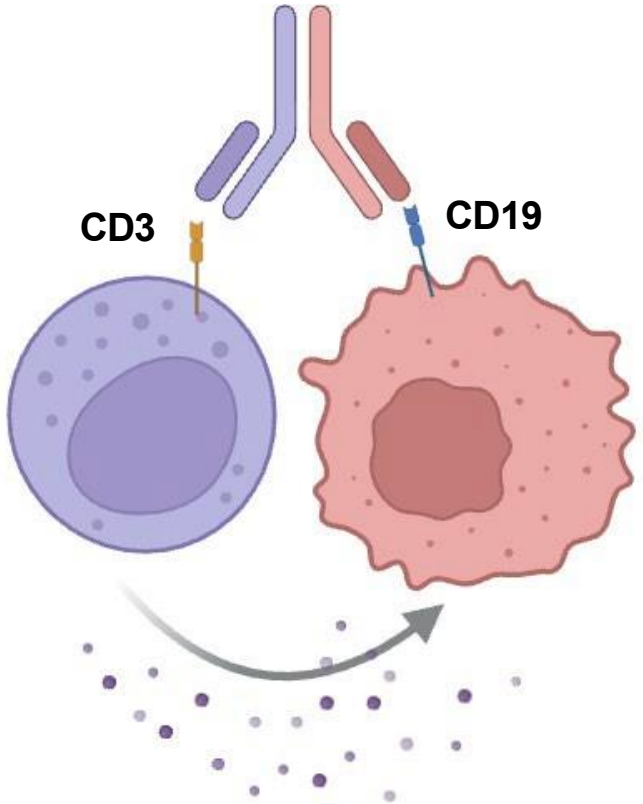
CD19 targeted **T cell engagers** have high therapeutic potential for deep **B cell** depletion

cullinan™ THERAPEUTICS

T Cell Engagers (TCE)



- Bispecific Ab: an engineered antibody with **2 different binding sites**
- T-Cell Engager: a type of Bispecific antibody that binds one part to **cytotoxic T-cells, redirecting it** to recognize and kill tumor or pathogenic cells
  - One arm binds → **CD3 T-cell**
  - Other arm binds → **CD19 B-cell**



Albayrak G et al. Br J Cancer. 2025 Jul 23.

nature medicine

Article

https://doi.org/10.1038/s41591-024-02964-1

Bispecific T cell engager therapy for refractory rheumatoid arthritis

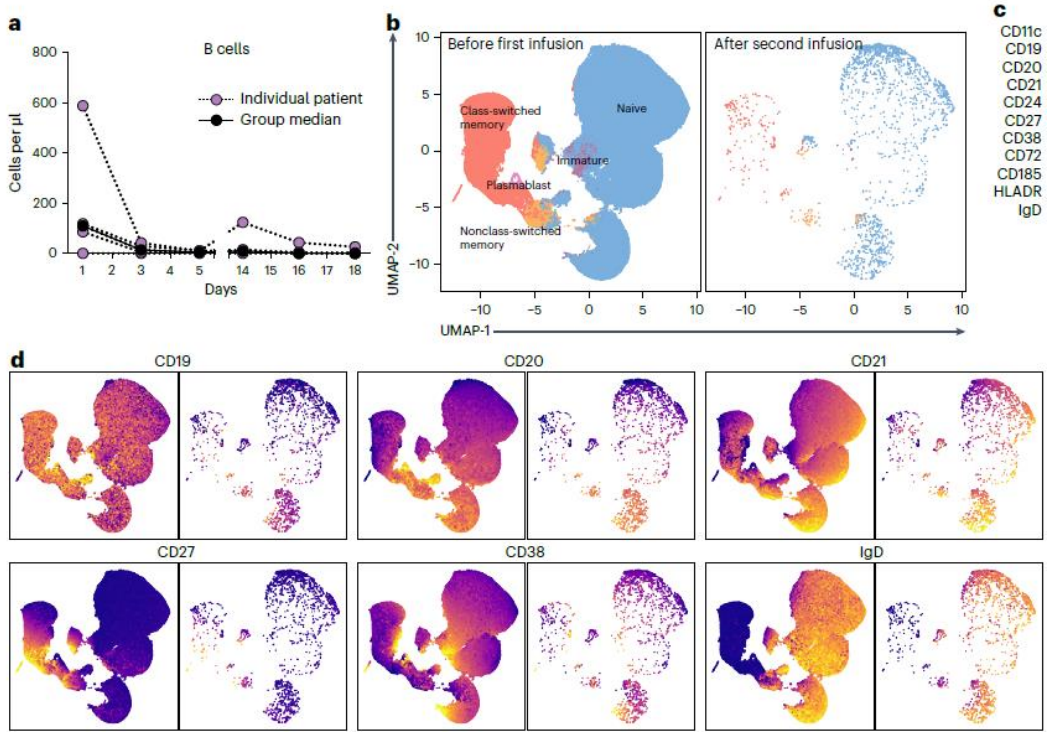
Received: 13 December 2023

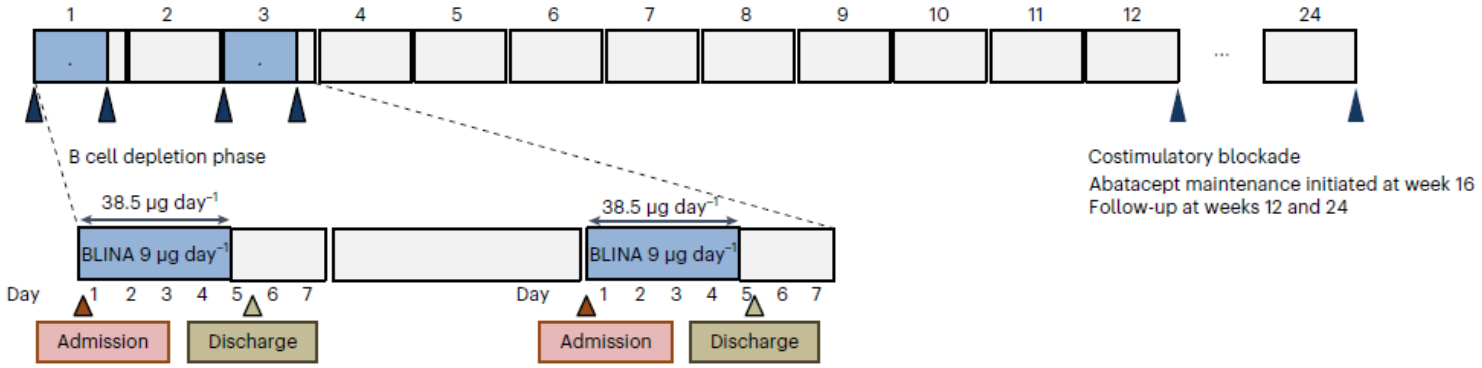
Accepted: 1 April 2024

Published online: 26 April 2024

Check for updates

Laura Bucci[1,2,7], Melanie Hagen[1,2,7], Tobias Rothe[1,2], Maria Gabriella Raimondo[1,2], Filippo Fagni[1,2], Carlo Tur[1,3], Andreas Wirsching[1,2], Jochen Wacker[1,2], Artur Wilhelm[1,4], Jean-Philippe Auger[1,2], Milena Pachowsky[1,2], Markus Eckstein[5], Stefano Alivernini[3], Angelo Zoli[3], Gerhard Krönke[1,4], Stefan Uderhardt[1,2], Aline Bozec[1,2], Maria-Antonietta D'Agostino[3], Georg Schett[1,2,3,6,8] ✉ & Ricardo Grieshaber-Bouyer[1,2,8]





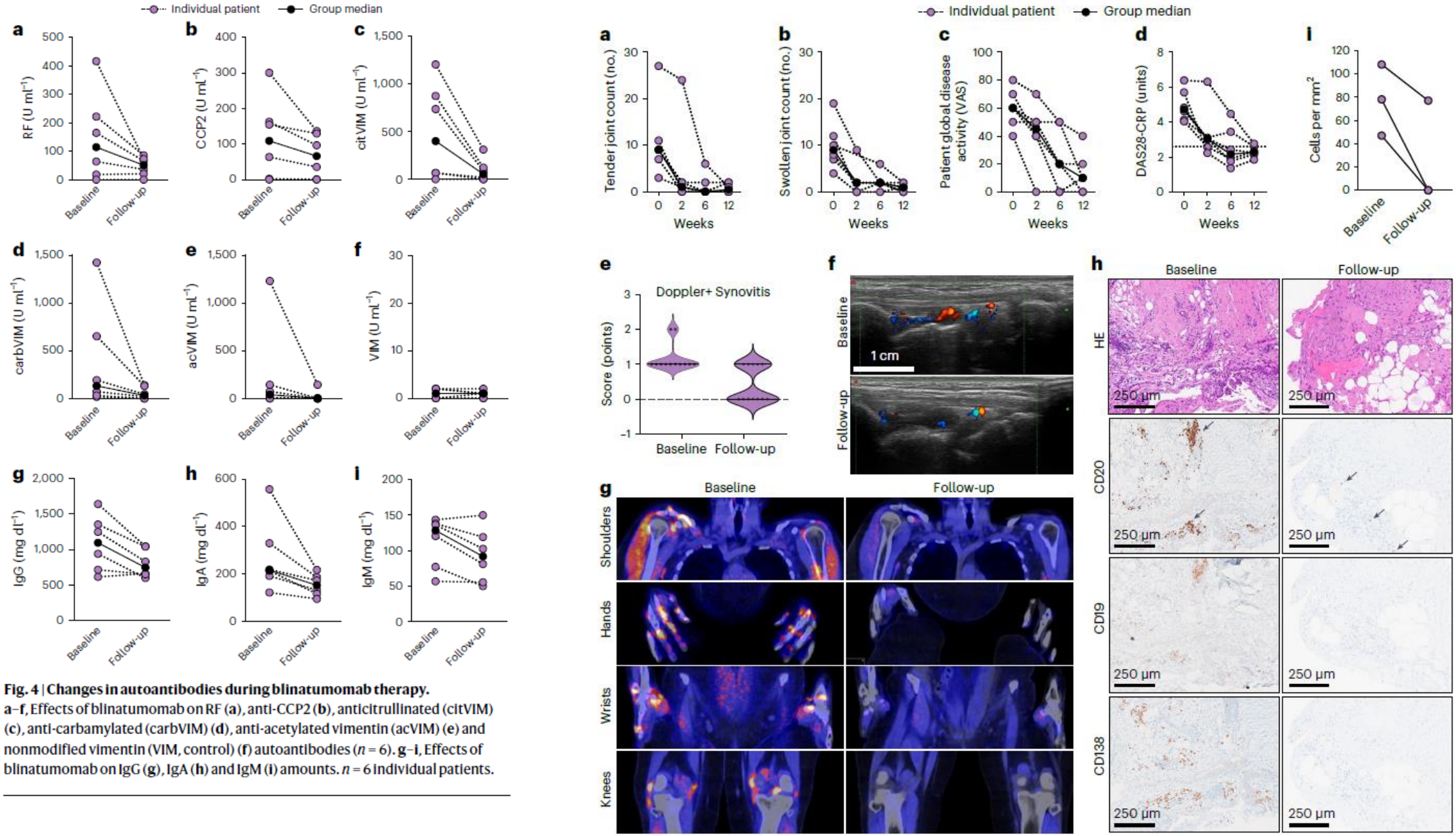
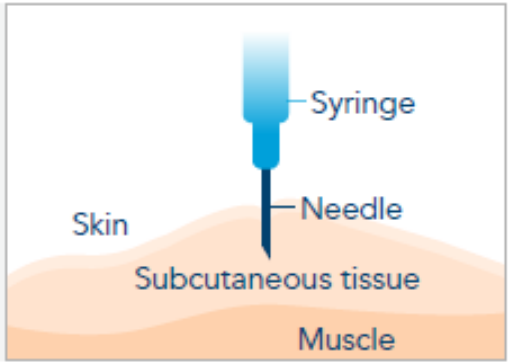


Fig. 4 | Changes in autoantibodies during blinatumomab therapy. **a**–**f**, Effects of blinatumomab on RF (**a**), anti-CCP2 (**b**), anticitrullinated (citVIM) (**c**), anti-carbamylated (carbVIM) (**d**), anti-acetylated vimentin (acVIM) (**e**) and nonmodified vimentin (VIM, control) (**f**) autoantibodies ($n = 6$). **g**–**i**, Effects of blinatumomab on IgG (**g**), IgA (**h**) and IgM (**i**) amounts. $n = 6$ individual patients.

CLN Phase 1B Trial

How is CLN-978 Given?

CLN-978 is given as an injection under the skin called a subcutaneous injection. This provides flexible and convenient dosing.



Who Can Participate in the Clinical Trial?

The trial will enroll eligible people living with active, moderate to severe Sjögren's disease who have:

EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) score >/=5 (moderate to severe Sjögren's disease)

had an inadequate response to at least two treatments

tested positive for one or more Sjögren's-related antibodies

What Should Participants Expect?

Before treatment begins:

- Participants will attend one or more screening visits before the study treatment period begins.
- Certain tests and procedures will be done to make sure patients are eligible to participate in the study, such as blood sample collections and a physical exam.

Study treatment:

- Prior to CLN-978 treatment, one tissue biopsy will be performed.
- Following a subcutaneous (under the skin) injection of CLN-978, participants will be monitored for two days in an inpatient setting, such as a hospital. Participants may receive up to four weekly injections in total and will stay in the hospital for two days after at least the first two injections.
- All participants will receive CLN-978. No one in the study will receive a placebo. A placebo is a substance that does not have the active ingredient being studied.

Post-treatment follow-up:

- Participants will attend eight follow-up visits to check on their health for one year after receiving the investigational therapy (approximately one visit every one to two months). Eight weeks after CLN-978 is given, one tissue biopsy will be done.
- These visits will include procedures such as physical exams and blood sample collections.

Long-term follow-up (optional):

- There is an additional longer-term year-long follow-up period available to interested participants with four visits in total (every three months).

Sjögren's FOUNDATION

T Cell Engagers & CAR T Therapy

T Cell Engagers

- ✓ May be very effective; B cell depletion in tissue
- ✓ Potential to address the root cause of Sjögren's (disease modifying)
- ✓ Potential to reset the immune system
- ✓ Standard manufacturing & storage (available "off-the-shelf") and ease of administration
- ✓ Dosing flexibility to extend remissions
- ✓ Free from access issues and complex coordination between specialists
- ✓ Free from chemotherapy to prepare for treatment

CAR T

- ✓ May be very effective; B cell depletion in tissue
- ✓ Potential to address the root cause of Sjögren's (disease modifying)
- ✓ Potential to reset the immune system
- ✗ Lengthy manufacturing process tailored to each person; complex administration
- ✗ Single dose without opportunity to re-dose
- ✗ Can have access issues and involves complex coordination between specialists
- ✗ Requires chemotherapy to prepare for treatment

T CELL REDIRECTING THERAPIES

cullinan™ THERAPEUTICS

Key Points

- T cell engagers and CAR-T therapies represent a new frontier aiming to reset immune dysregulation in autoimmune disease
- Safety and durability are key
- Cullinan's CLN-978 trial is the first targeted effort in Sjögren's, potentially redefining therapeutic paradigms