XIX Congresso della Società GITMO

RIUNIONE NAZIONALE GITMO

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CAR-T nelle malattie autoimmuni

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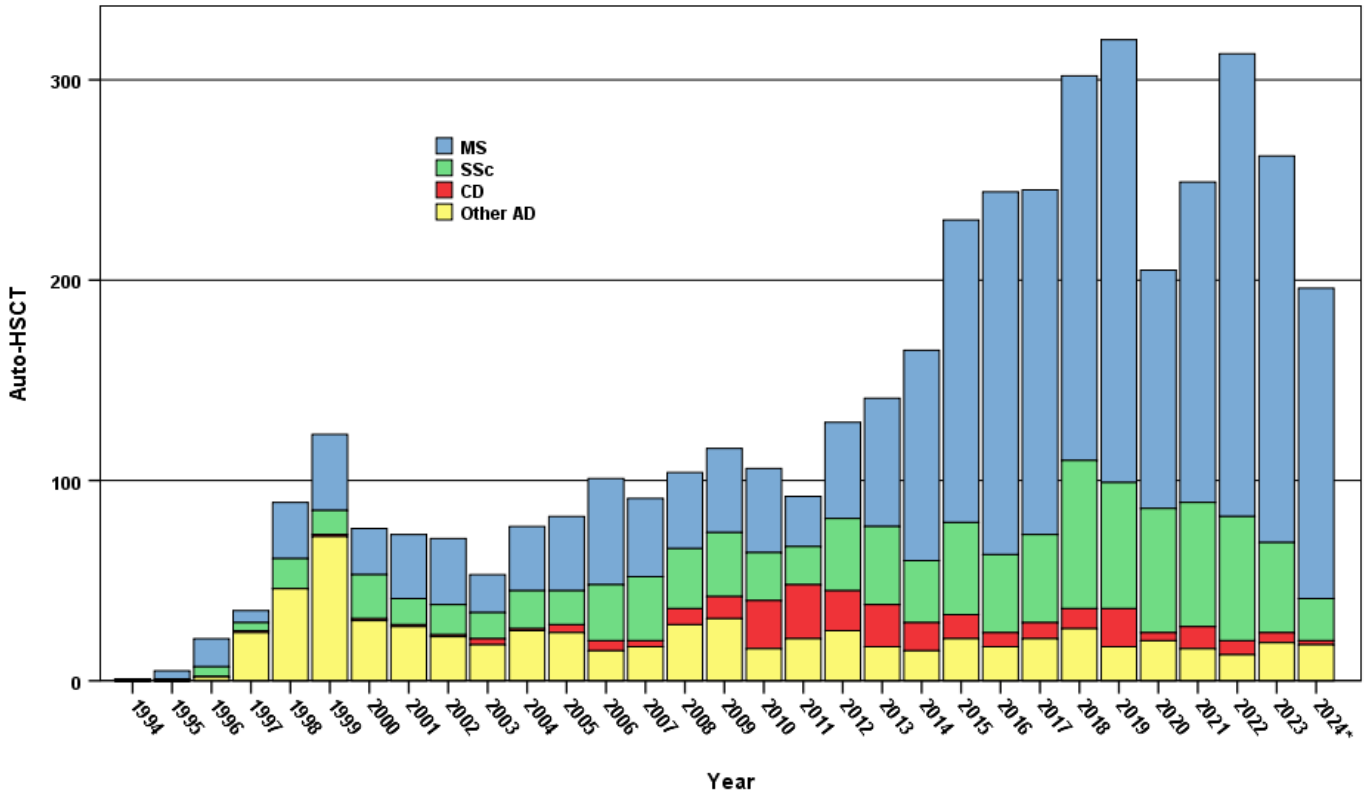
Disclosures of Raffaella Greco

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Biotest					x		
Pfizer						x	
Medac					x		
Qiagen					x		
Kyverna					x		
Magenta					x		
Neovii					x		
BMS						x	
MSD						x	

HCT activity in autoimmune diseases: ADWP registry

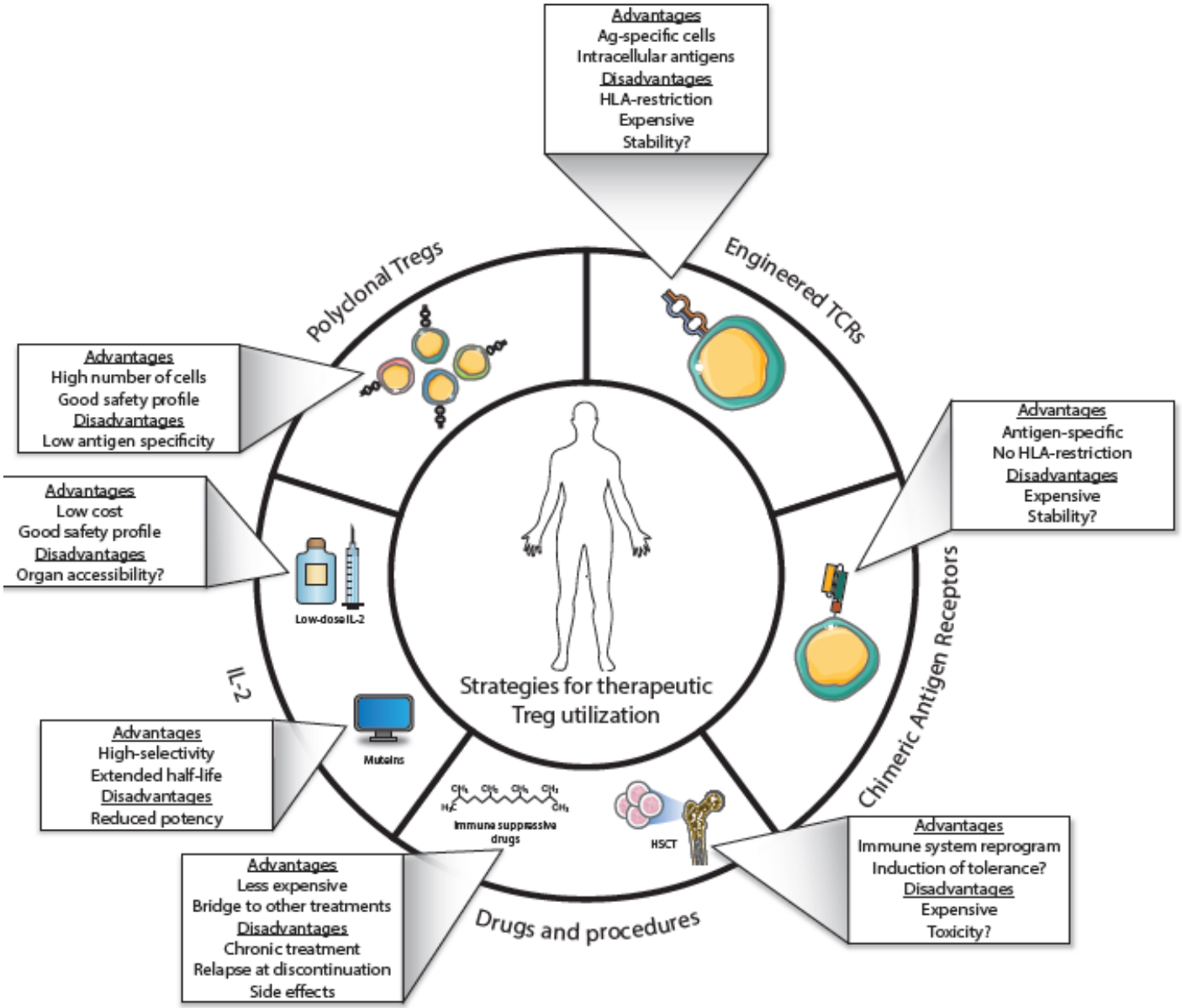
EBMT-ADWP Registry Data 1994-2024



- HCT has evolved over the last 3 decades as a specific treatment for patients with severe autoimmune diseases (ADs) through the eradication of the pathogenic immunologic memory and profound immune renewal.
- HCT for ADs is recently facing a unique *developmental phase* (**n=4656**) across EBMT transplant centres.
- **MS and SSc** cover around 80% of transplants performed for ADs, where HCT has become an *integral and standard-of-care part of treatment algorithms*.

Alexander T, Greco R, BMT 2022; Snowden et al, BMT 2022

Innovative therapeutic approaches for ADs

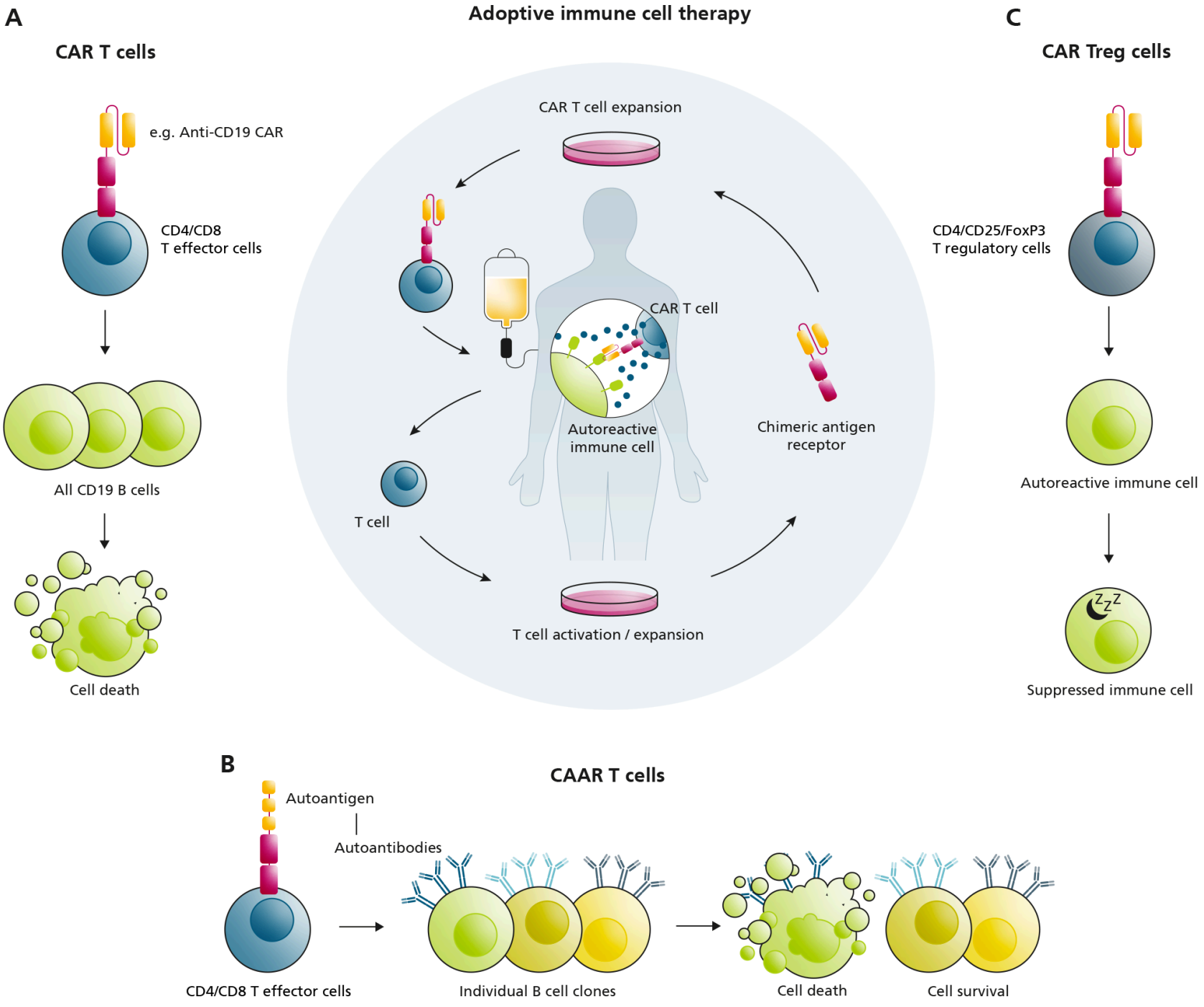


Adoptive T-cell therapy: polyclonal or engineered T-cells [Chimeric Antigen Receptors (CARs) or T Cell Receptors (TCRs)].

CARs *novel approach with promising results in ADs*, recognize extra-cellular antigens and are MHC-independent.
The CAR-expressing cells applied so far in ADs have typically been T cells that recognize B cell-specific (CD19) or plasma cell-specific antigens (BCMA).

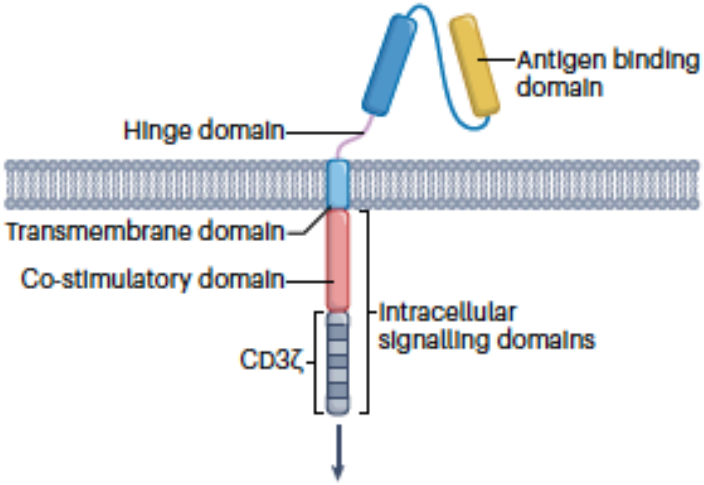
Doglio et al, JACI 2022

Adoptive immune cell therapy in ADs



Blache et al, RMD Open 2023

Vector constructs used for CAR-T cell generation in ADs

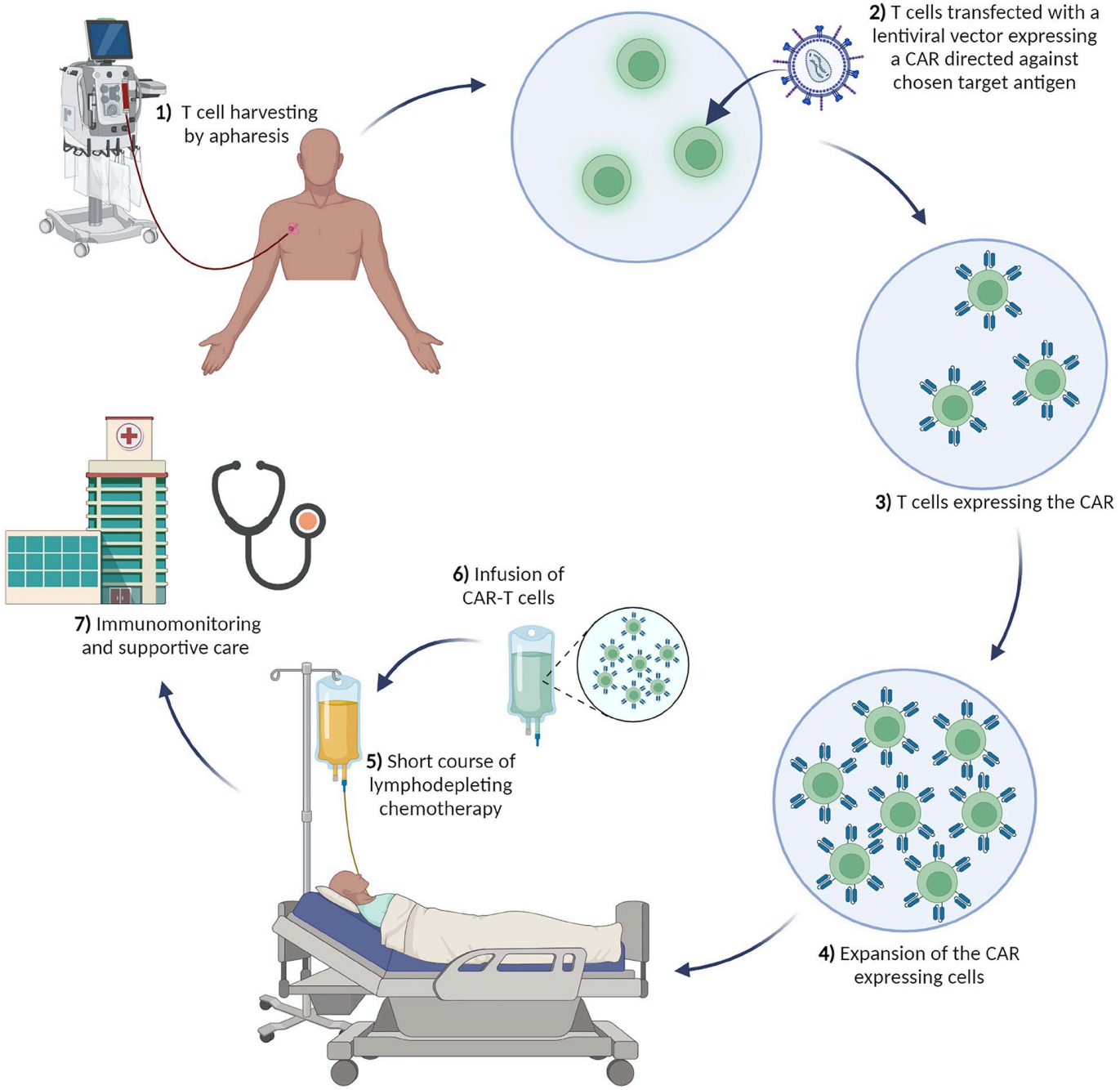


Antigen-binder	Hinge	Transmembrane	Co-stimulation	TCR signal
Anti-CD19 (FMC63)	CD8α	TNFRSF19	4-1BB	CD3ζ
Anti-CD19 (47G4)	CD8α	CD8α	CD28	CD3ζ
Anti-CD19 (FMC63)	CD8α	CD8α	4-1BB	CD3ζ
Anti-CD19 (FMC63)	CD8α	TNFRSF19	4-1BB	CD3ζ
Anti-CD19 (IC78)	CD8α	CD8a	4-1BB	CD3ζ
Anti-CD19 (FMC63)	CH2CH3	CD28	4-1BB · CD28	CD3ζ
Anti-BCMA	Whitlow 218 linker	CD8α	4-1BB	CD3ζ
Anti-CD19	Unknown	Unknown	4-1BB	CD3ζ
Anti-BCMA	Unknown	Unknown	CD28	CD3ζ

Current lentiviral-based vector constructs used for the generation of CD19-targeted or BCMA-targeted CAR-T cell

Schett et al, Nature Reviews Rheumatology 2024

CAR-T cell approach in ADs

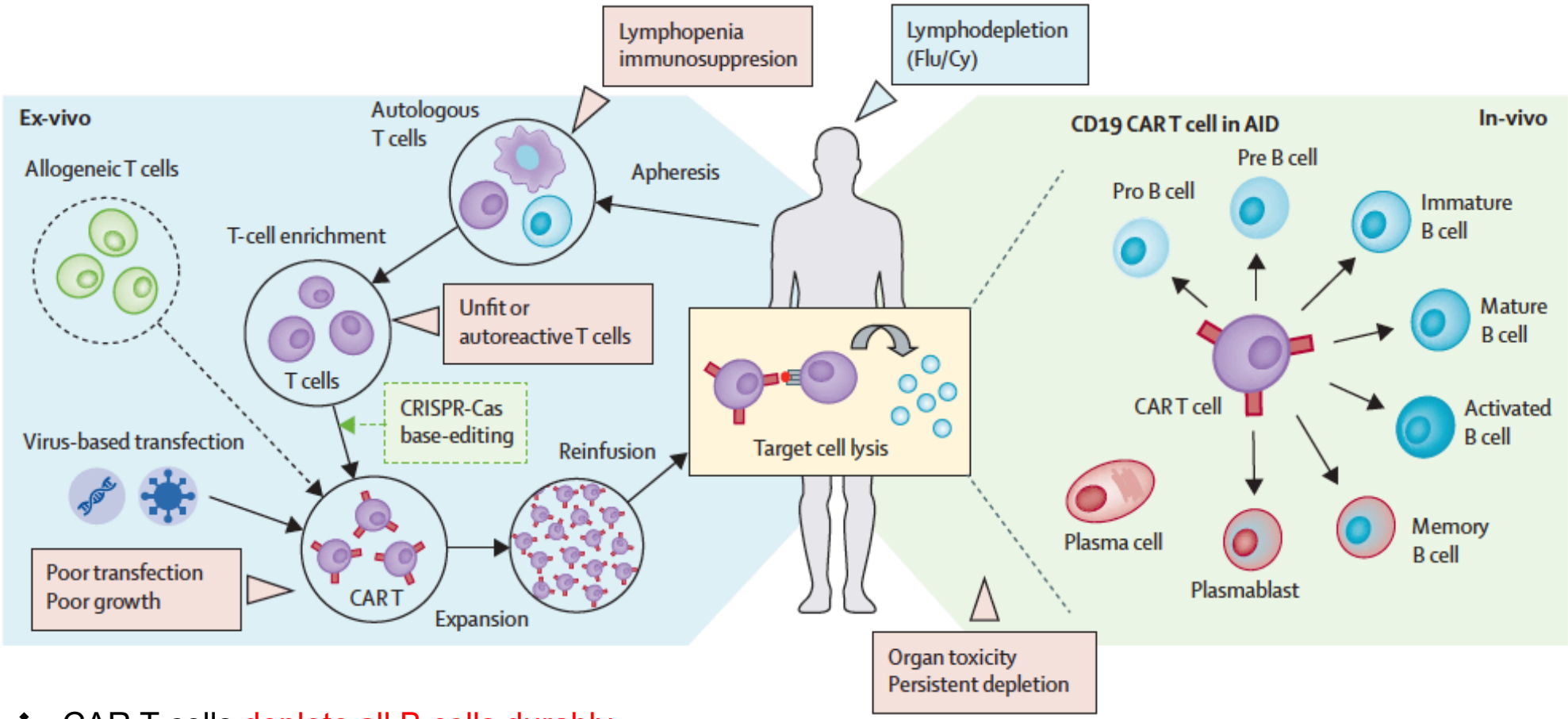


MDT strongly recommended!

Critical patient selection and **careful monitoring** for both *efficacy* and *toxicity* are paramount for successful treatment with CAR-T cells.

Brittain et al, Ann Neurol 2024

Targeting B cells with CAR T cells in ADs



- CAR T cells deplete all B cells durably when applied to lymphoma patients (antiCD20 mAb deplete most of the B cells, however, often some remain in the peripheral blood)
- CAR T cells can actively invade tissue whereas antibodies passively diffuse
- CD19 is broader than CD20 (also tackles plasmablasts)

B-cell lineage differentiation

Tumour cells antigen	Pro B cell	Prä B cell	Imm B B cell	Mature B cell	Memory B cell	Plasma blast	Plasma cell	Target
CD19	■	■	■	■	■	■		B cell
CD20		■	■	■	■			Bcell
CD22		■	■	■	■			B cell
BCMA					■	■	■	PC
CD38					■	■	■	PC
CD138							■	PC

Schett G et al, Lancet 2023

CAR-T cells in RMD

CAR-T cells in lupus nephritis

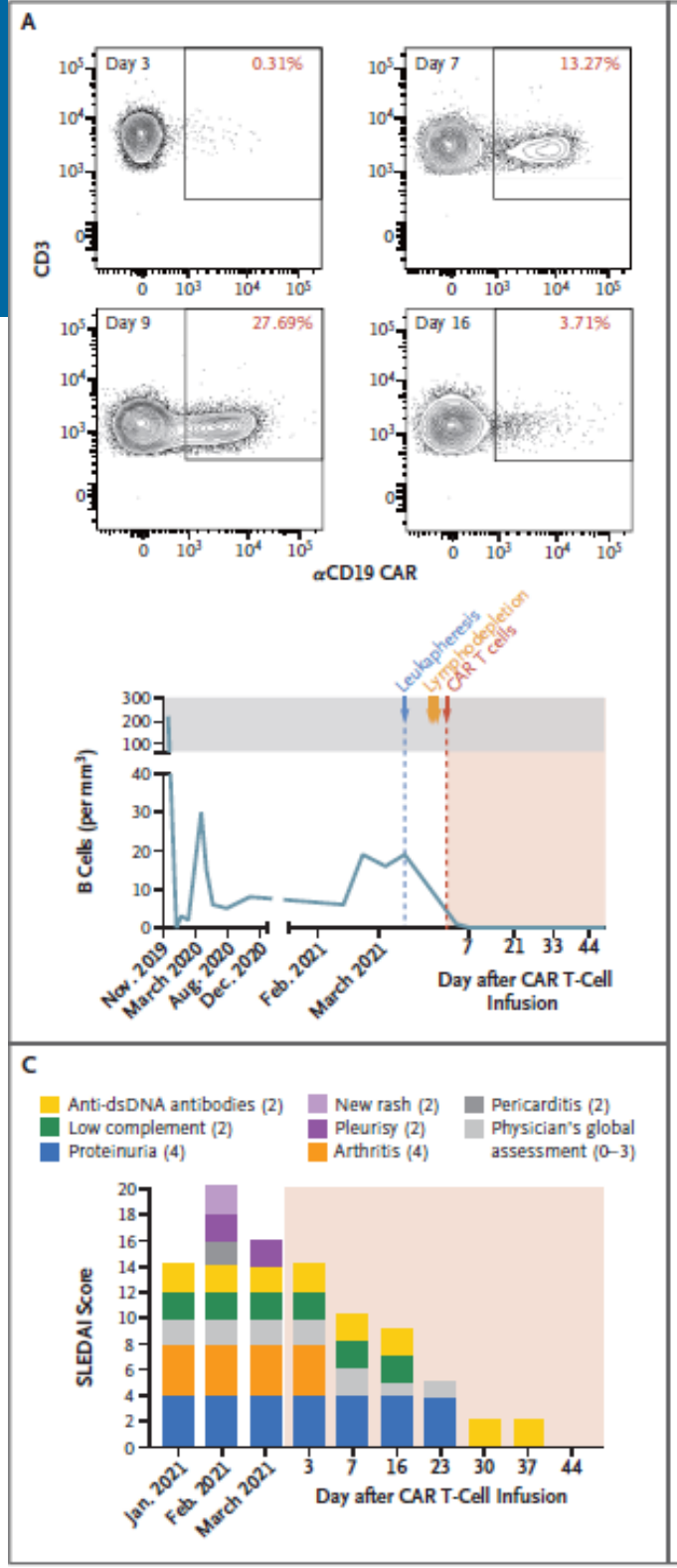
A CAR T cell approach, genetically engineered to recognize the B cell surface antigen CD19, may induce a **more robust B cell depletion** compared to the use of anti-CD19 directed monoclonal antibodies, **both in circulation and tissues**.

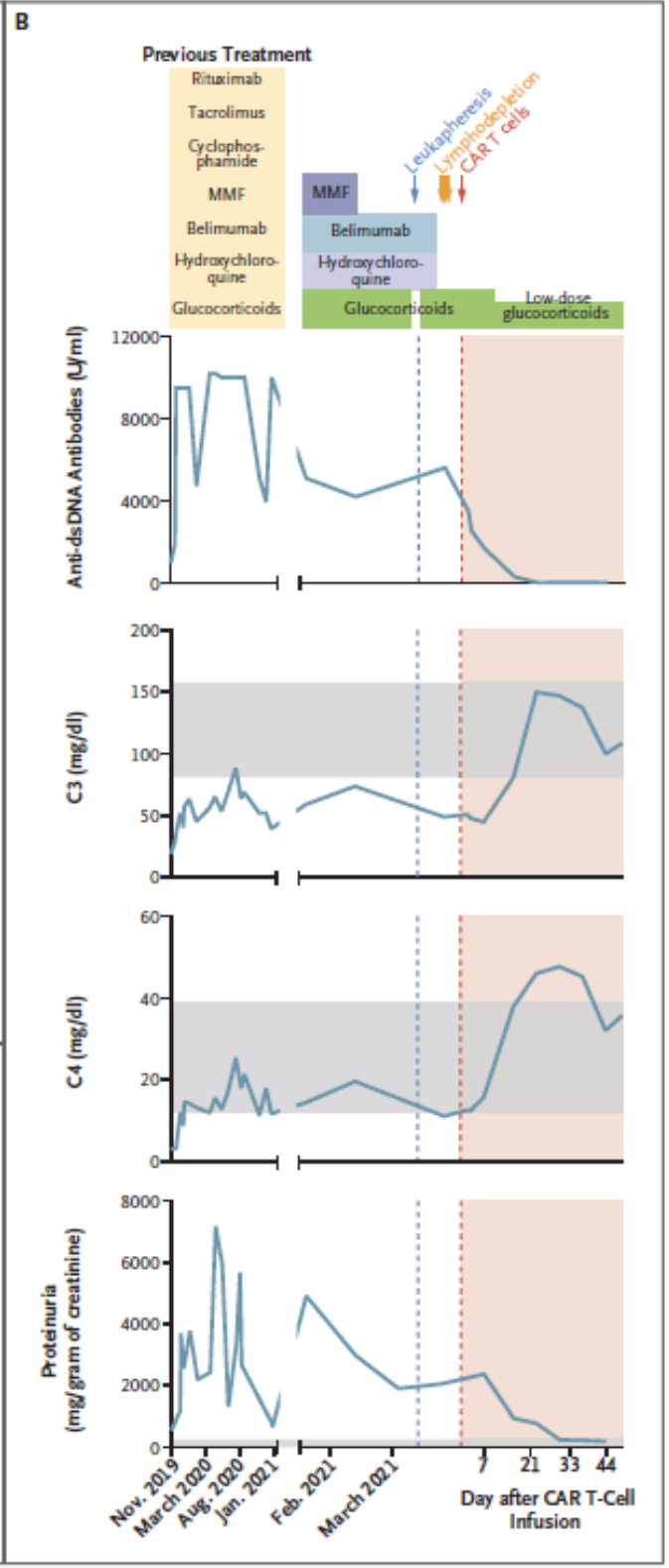
Recently, first data on the use of *autologous* CAR-T cell strategy in a patient with **refractory & active lupus nephritis** showed a rapid clinical remission without notable adverse effects, accompanied by sustained depletion of circulating B cells and a **rapid disappearance of anti-ds DNA antibodies**.

The patient received preparatory lymphodepleting chemotherapy before receiving an infusion of autologous CAR T cells, genetically engineered to recognize the B cell surface antigen CD19.

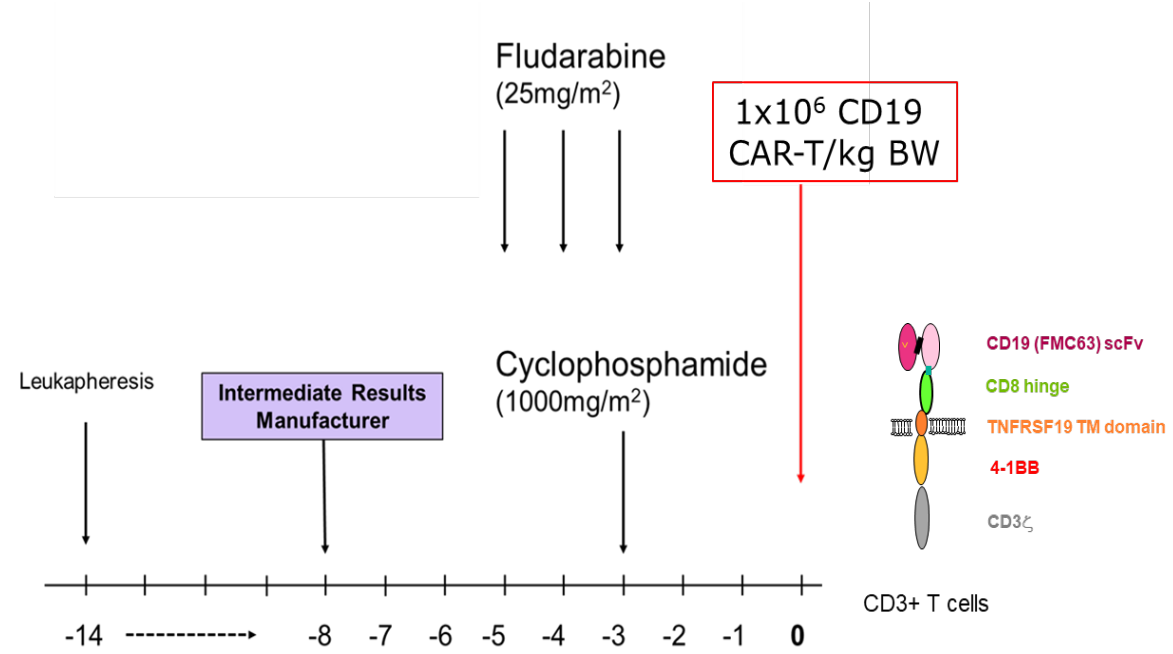
Following the infusion, the CD19 CAR T cells expanded in vivo, increasing to 28% of total circulating T cells at day 9 and remaining detectable during the subsequent 7 weeks. ***The strategy was well tolerated and induced rapid remission.***

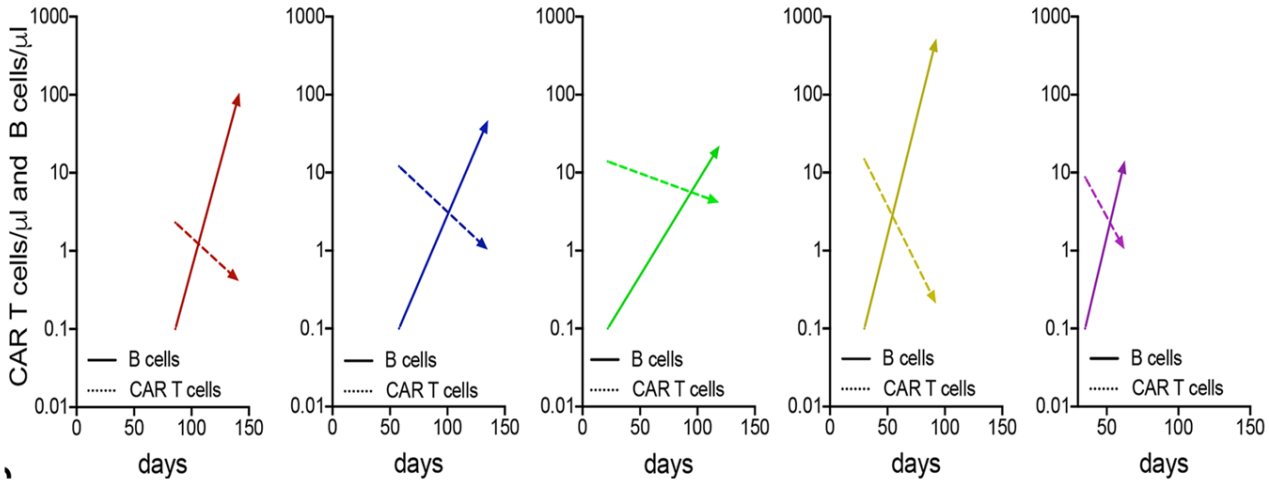
Mougiakakos et al. NEJM 2021





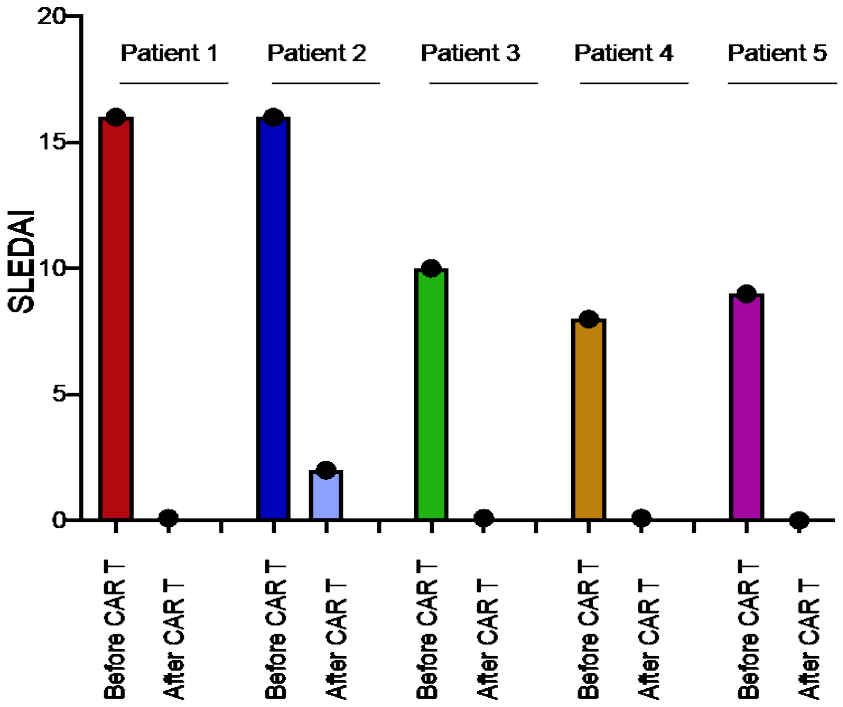
SLE





The strategy was ***well tolerated and induced rapid remission in 5 severe refractory SLE,*** instead of re-appearance of B cells 100 days after CAR-T transfer.

Data on long-term follow up are warranted.

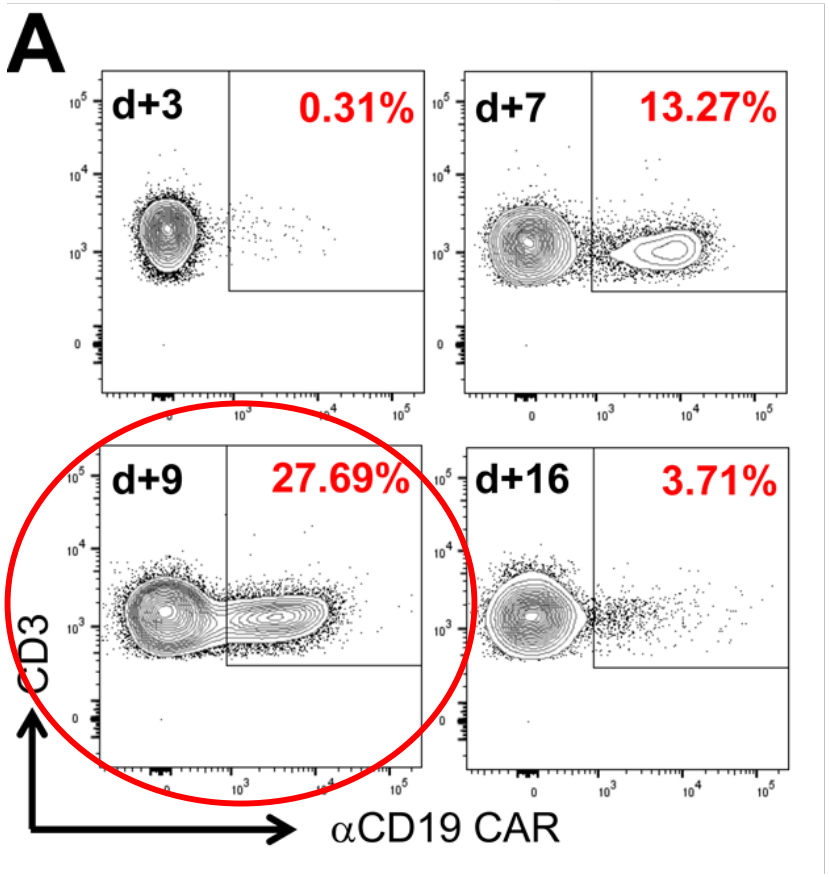


CART cells expansion on D9.
Sustained **depletion of circulating B cells** and **rapid disappearance of anti-ds DNA antibodies**.

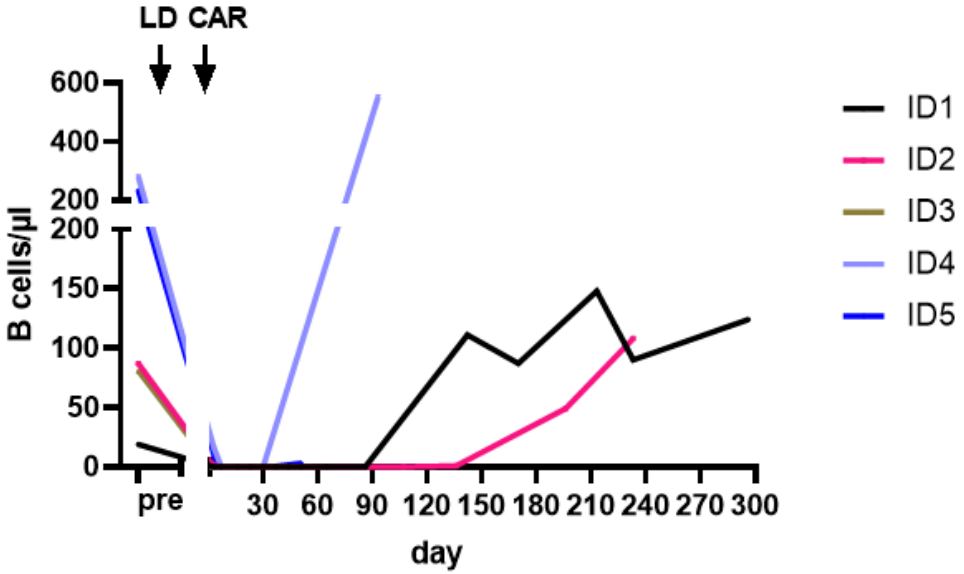
A. Mackensen, F. Müller*, et al., Nat. Med. 2022*

CD19 CAR T expansion & B-Cell depletion after CAR T

CAR-T Cell expansion



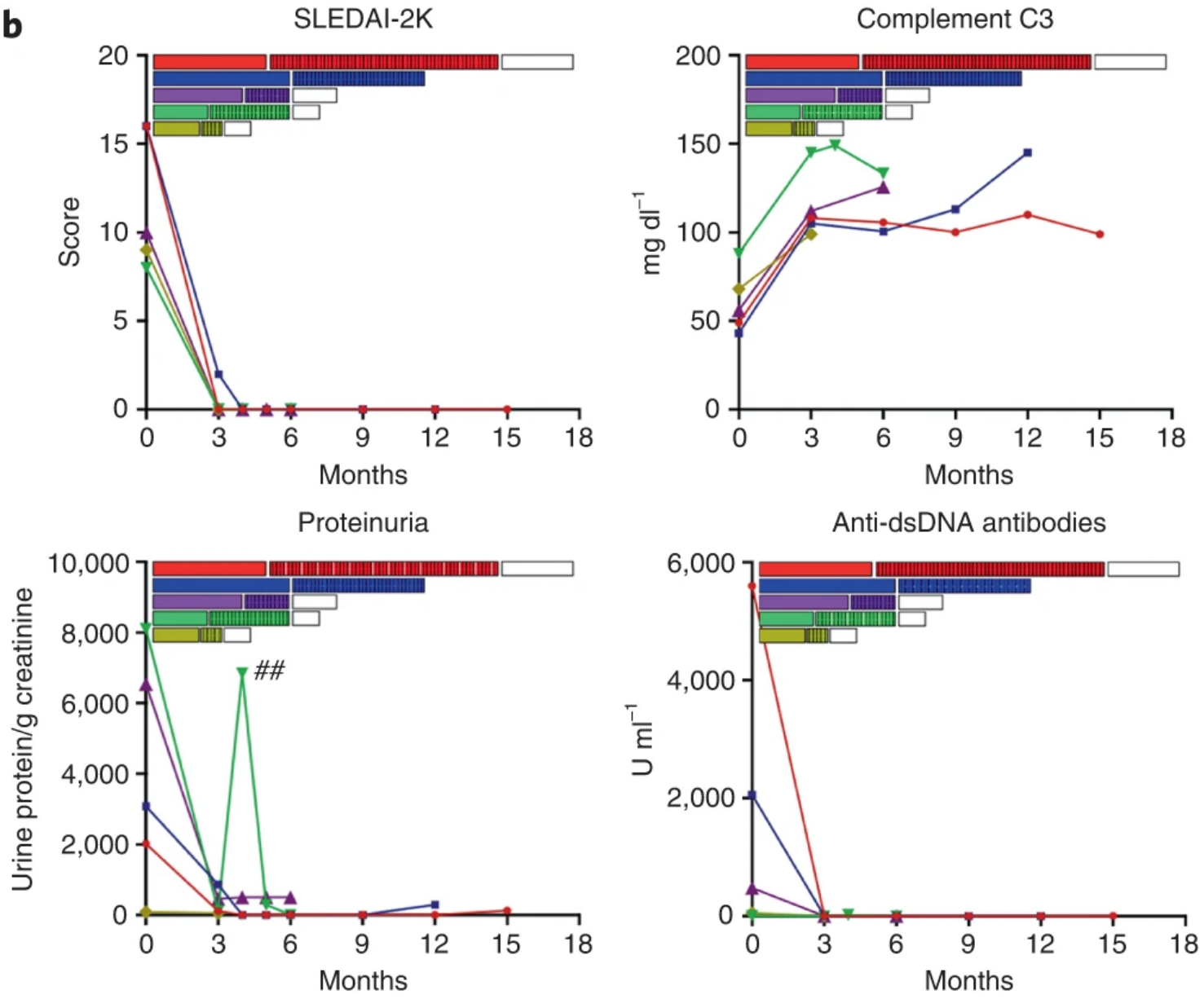
B cells come back after 90 to 120 days



Patients remain in remission despite the reoccurring B cells!

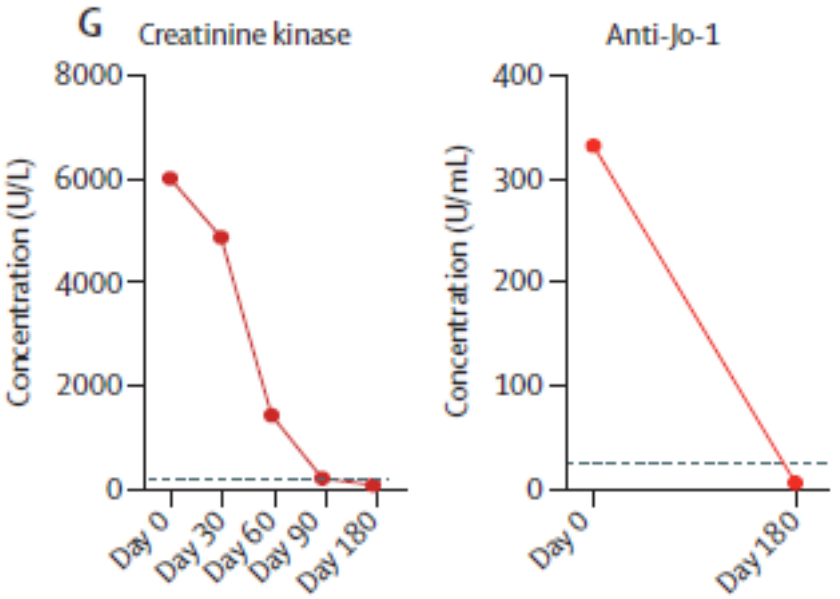
Courtesy of A. Mackensen & F.Muller

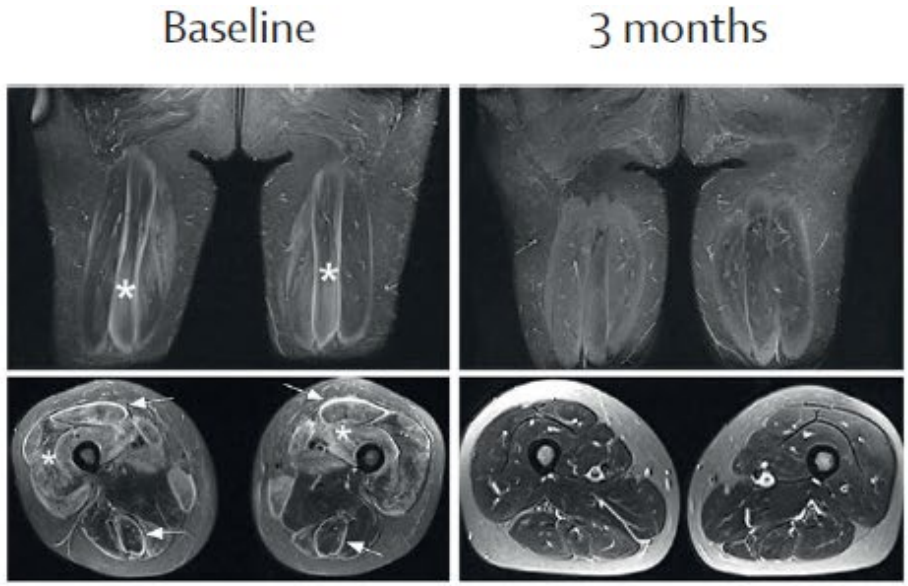
Clinical results of SLE patients treated with CAR T cells



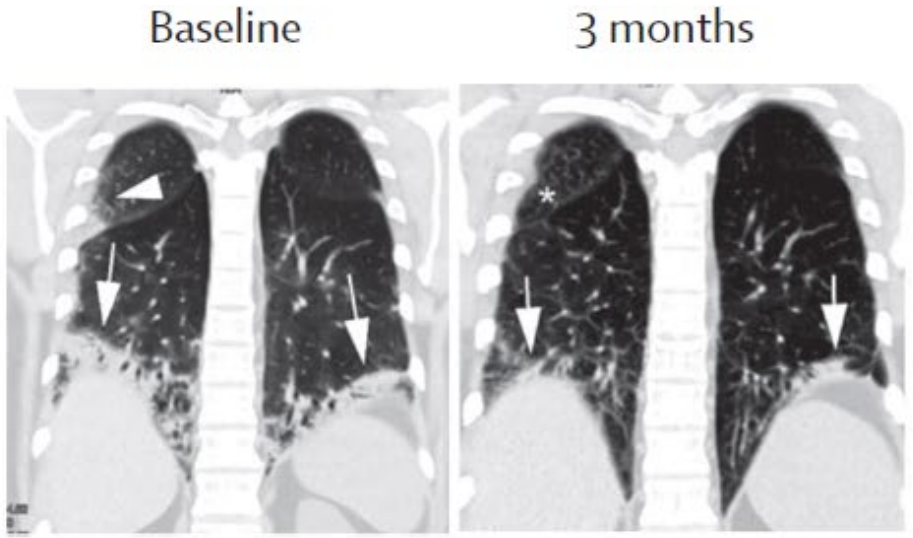
A. Mackensen, F. Müller*, et al., Nat. Med. 2022*

Anti Synthetase Syndrome





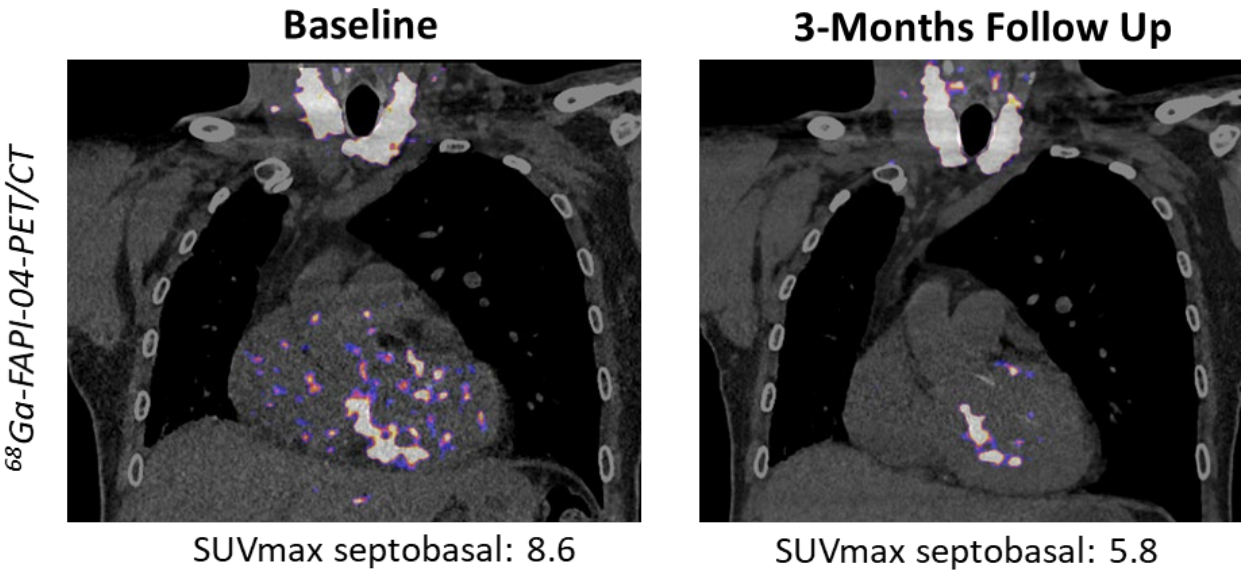
Complete resolution of muscle and fascial inflammatory alterations 3 months after treatment.

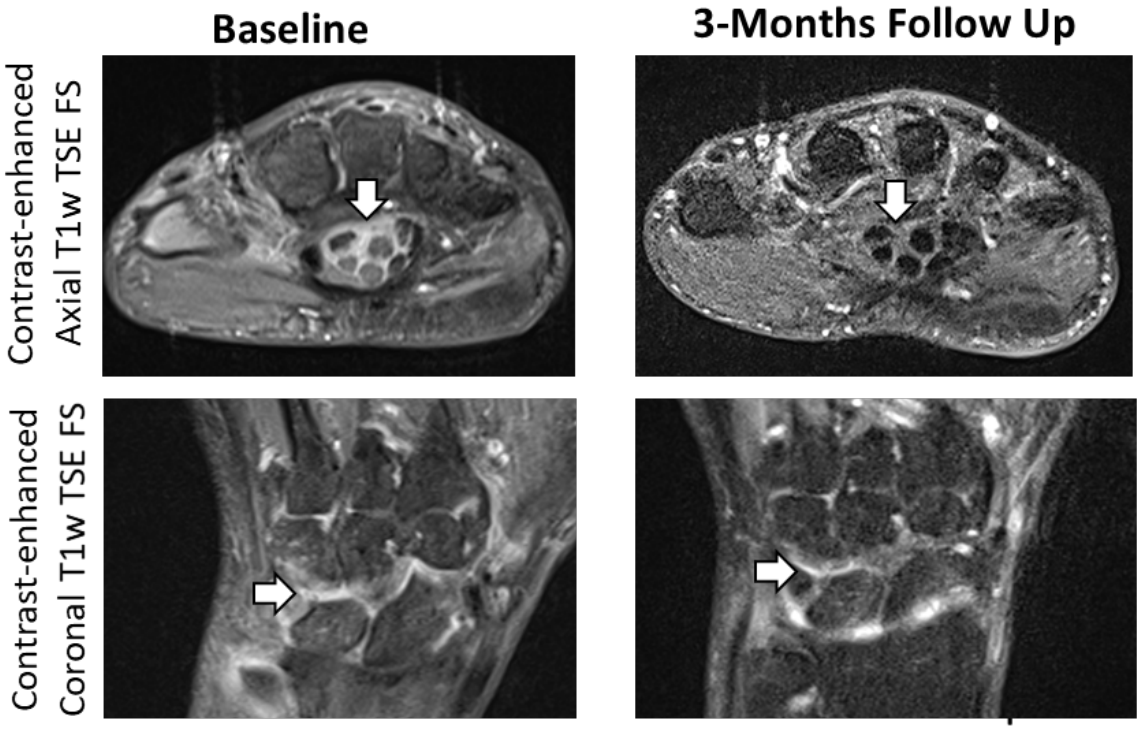


Complete resolution of right upper lobe findings *(asterisk)* and alveolitis, and minor residual findings of basal interstitial lung disease *(arrows)*

Müller et al. Lancet 2023

Systemic Sclerosis

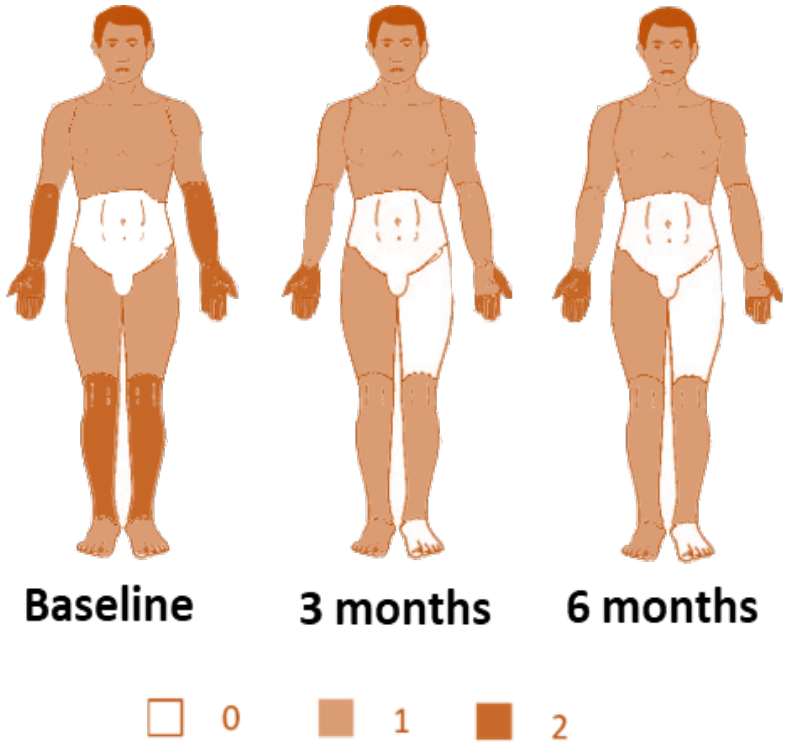




PET showing resolution of fibroblast activation protein inhibitor (^{68}Ga-FAPI-04) tracer accumulation in the **heart** at baseline and 3 months after CAR-T.

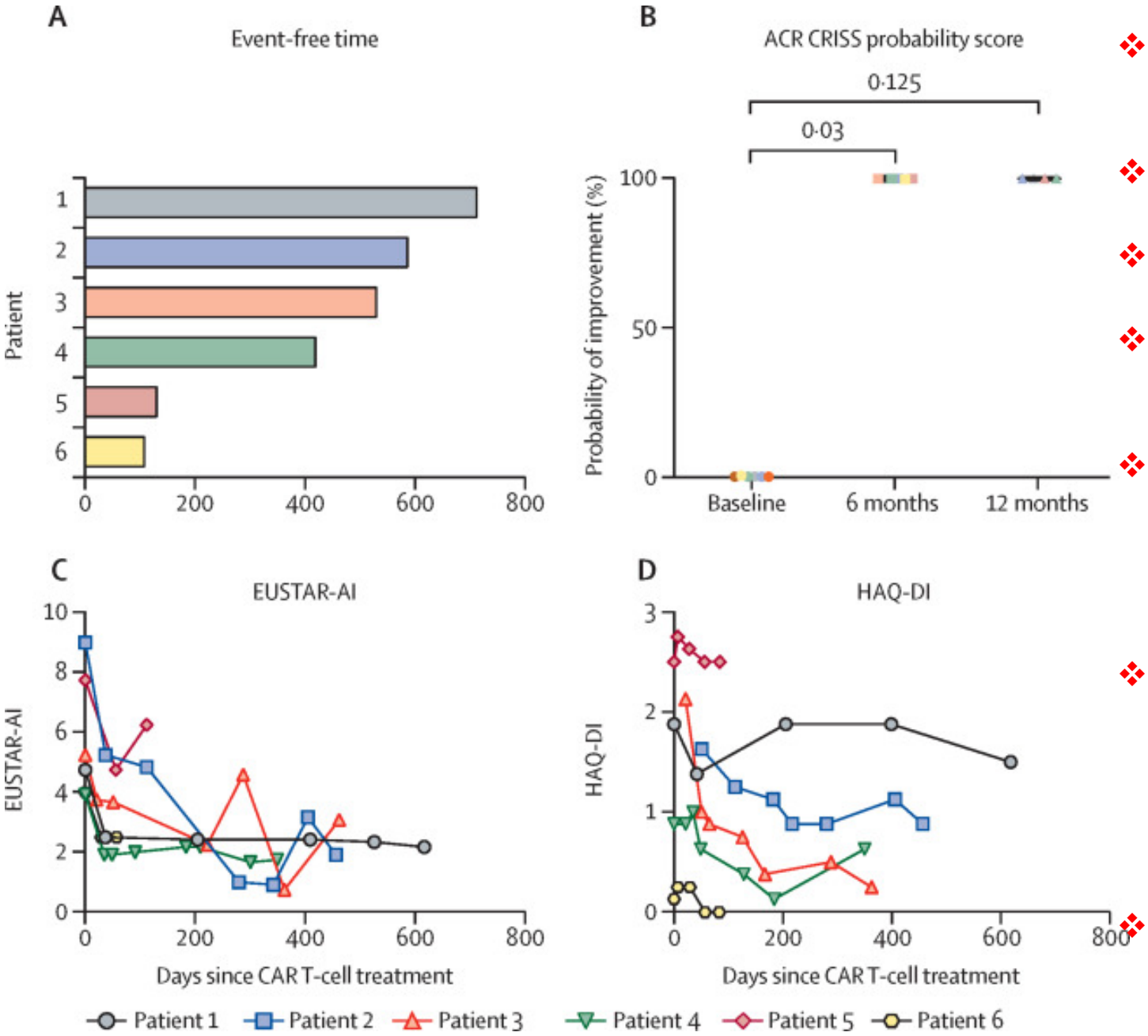
Axial and coronal sections of T1-weighted contrast-enhanced **MRI** of the **hands** at baseline and 3 months after CAR-T.

mRSS and **lung function** parameters at baseline and 3 months after CAR-T.



Bergmann, Müller* et al. 2023*
Ann. Rheum. Disease

Systemic Sclerosis – Clinical results in 6 pts

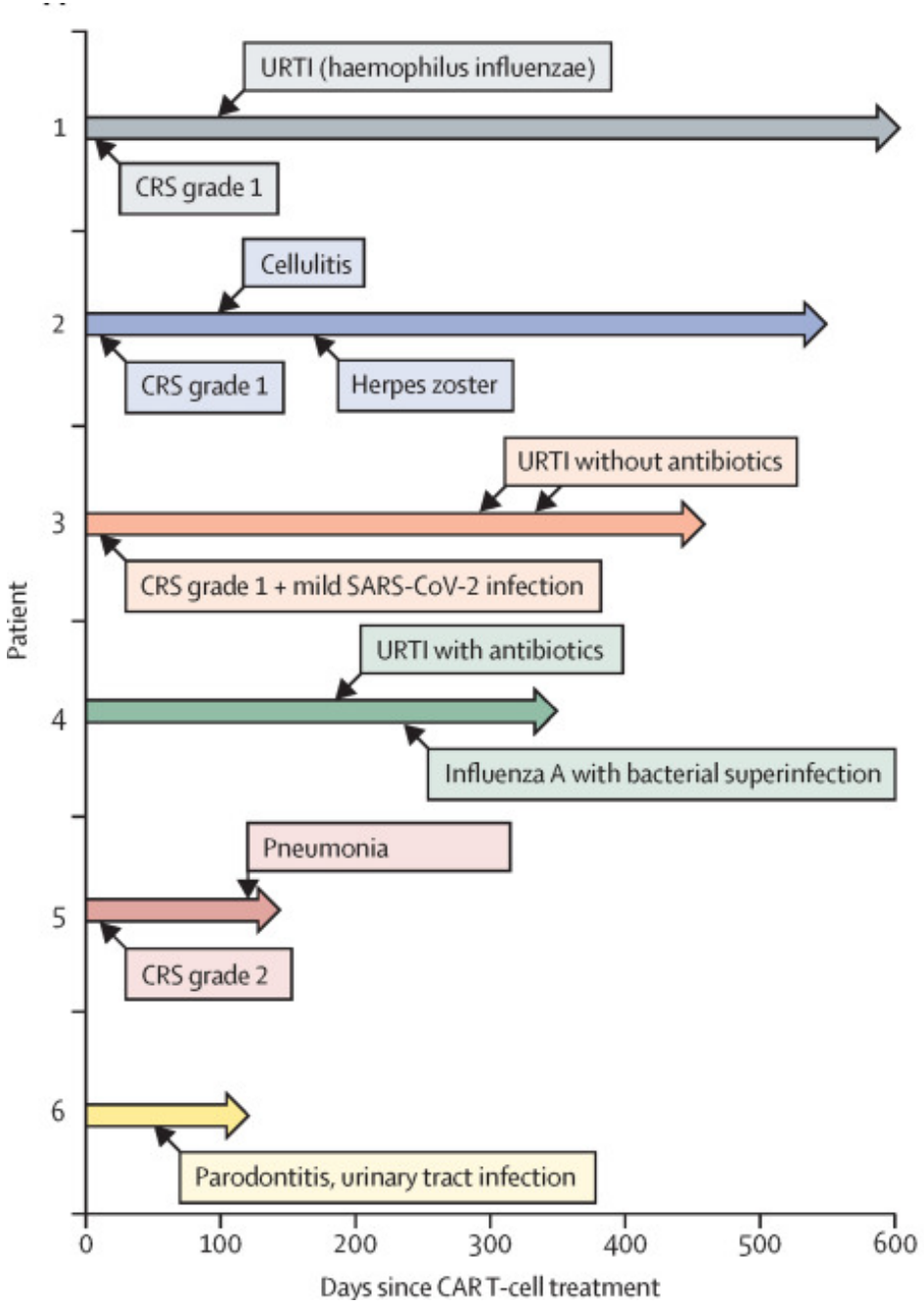


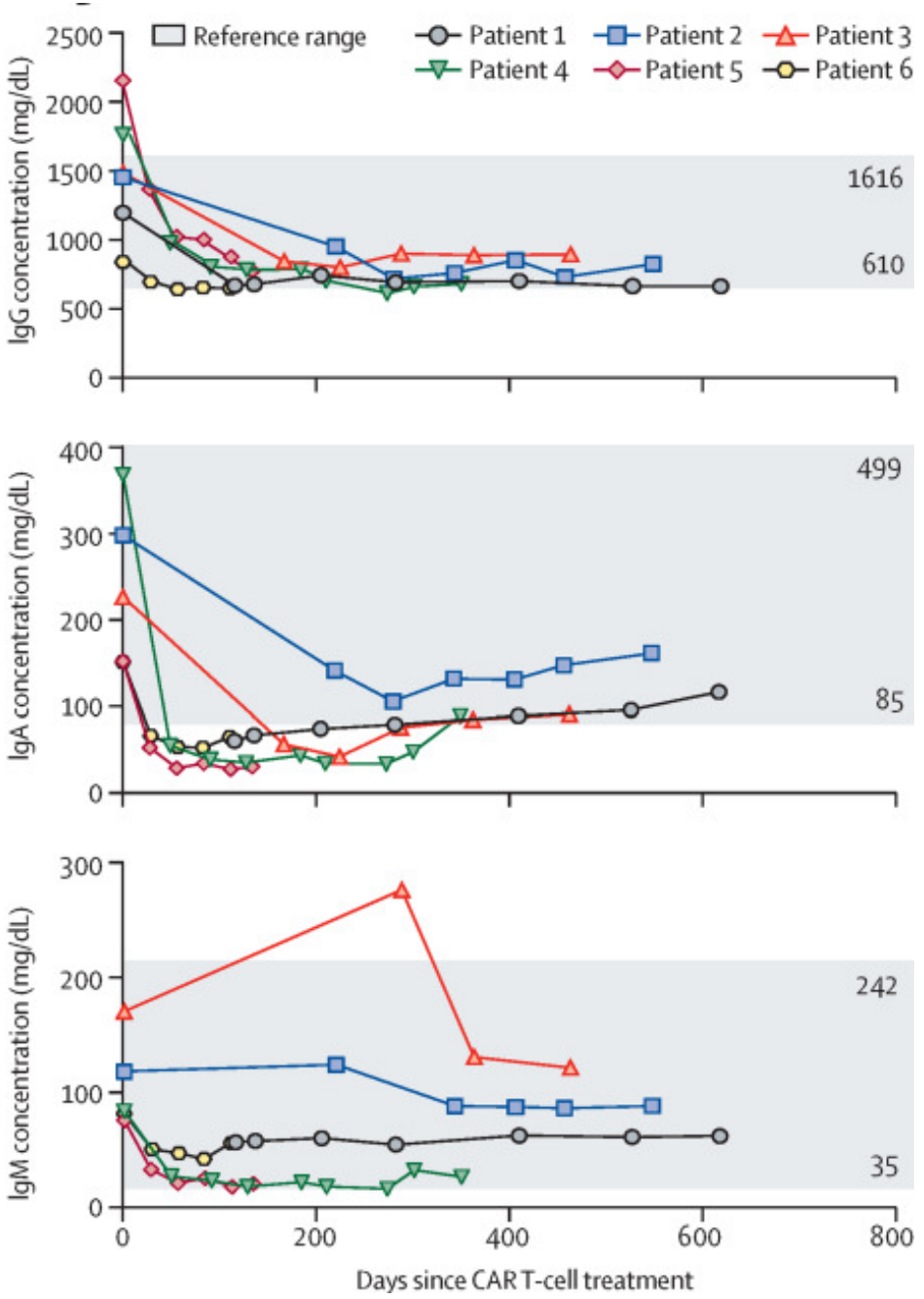
- **6 pts** with severe diffuse SSc (insufficient response to at least 2 tp).
- CD19-targeting CAR T-cell (1×10^6 CAR T/kg).
- Median follow-up 487 days (IQR 342–585).
- Probability of improvement in ACR-CRISS score increased to a median of 100% at 6mo.
- Median mRSS decreased by 31% (IQR 29–38), corresponding to a median of 8 points (IQR 7–13) within 100 days.
- The extent of disease on CT scan decreased by a median of 4% (IQR 3–4) due to reduction of ground-glass opacities while the reticular pattern remained stable.
- Forced vital capacity improved by a median of 195 mL (IQR 18–275) at the latest FU

CART might intercept with the progression of fibrotic organ manifestations.

Auth et al. 2025 Lancet. Rheum.

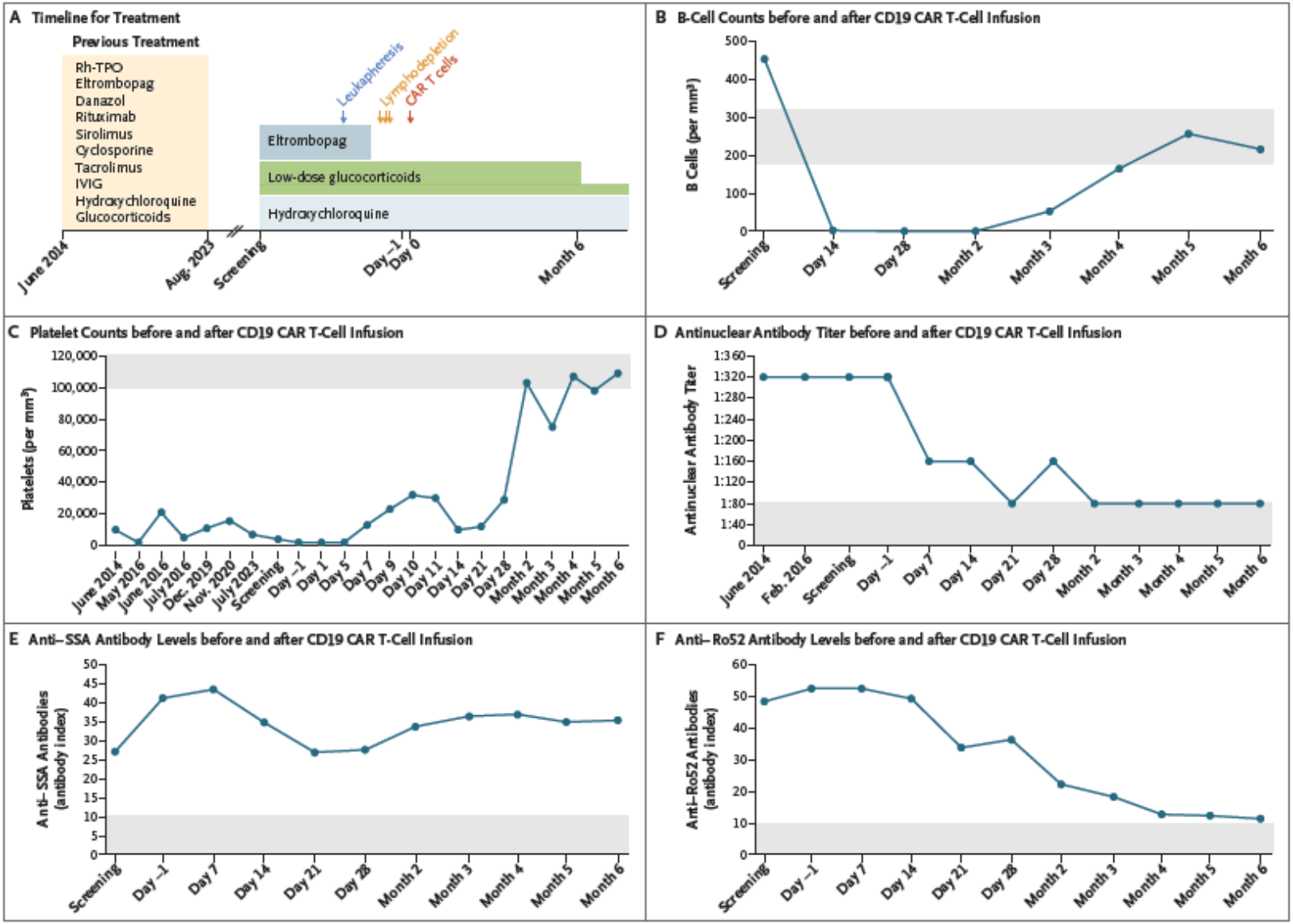
Systemic Sclerosis – Safety results in 6 pts





Auth et al. 2025 Lancet. Rheum.

Anti–CD19 CAR T in Refractory Immune Thrombocytopenia of SLE



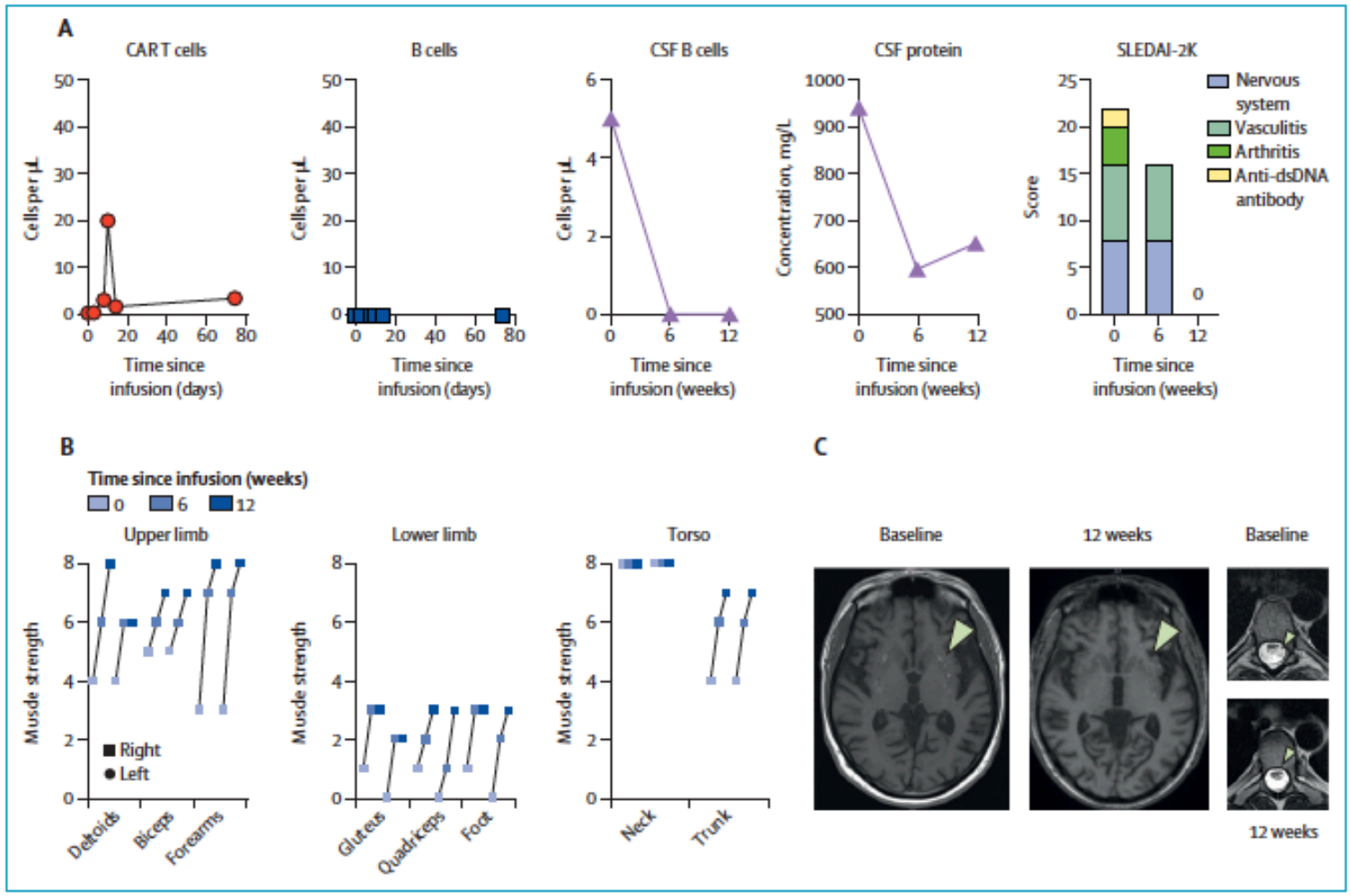
Autologous CD19 CAR T-cell (inaticabtagene autoleucel [inati-cel], Juventas Cell Therapy).

CAR T-cell numbers rapidly reached the expansion peak on day 14.

The *platelet count* per cubic millimeter rose from 4000 at screening to 29,000 at day 28, 75,000 at 3 months, and *109,000 at 6 months*.

Mengtao et al. NEJM 2024

Treatment of CNS SLE with CD19 CART



SLE with **CNS+**; 1 pt M.

CD19 CAR, 4-1BB.
Flu (25mg/m2 day-5 -4 -3) and Cy (1000mg/m2 day-3); **Dex** (10 mg/die days 1-3).

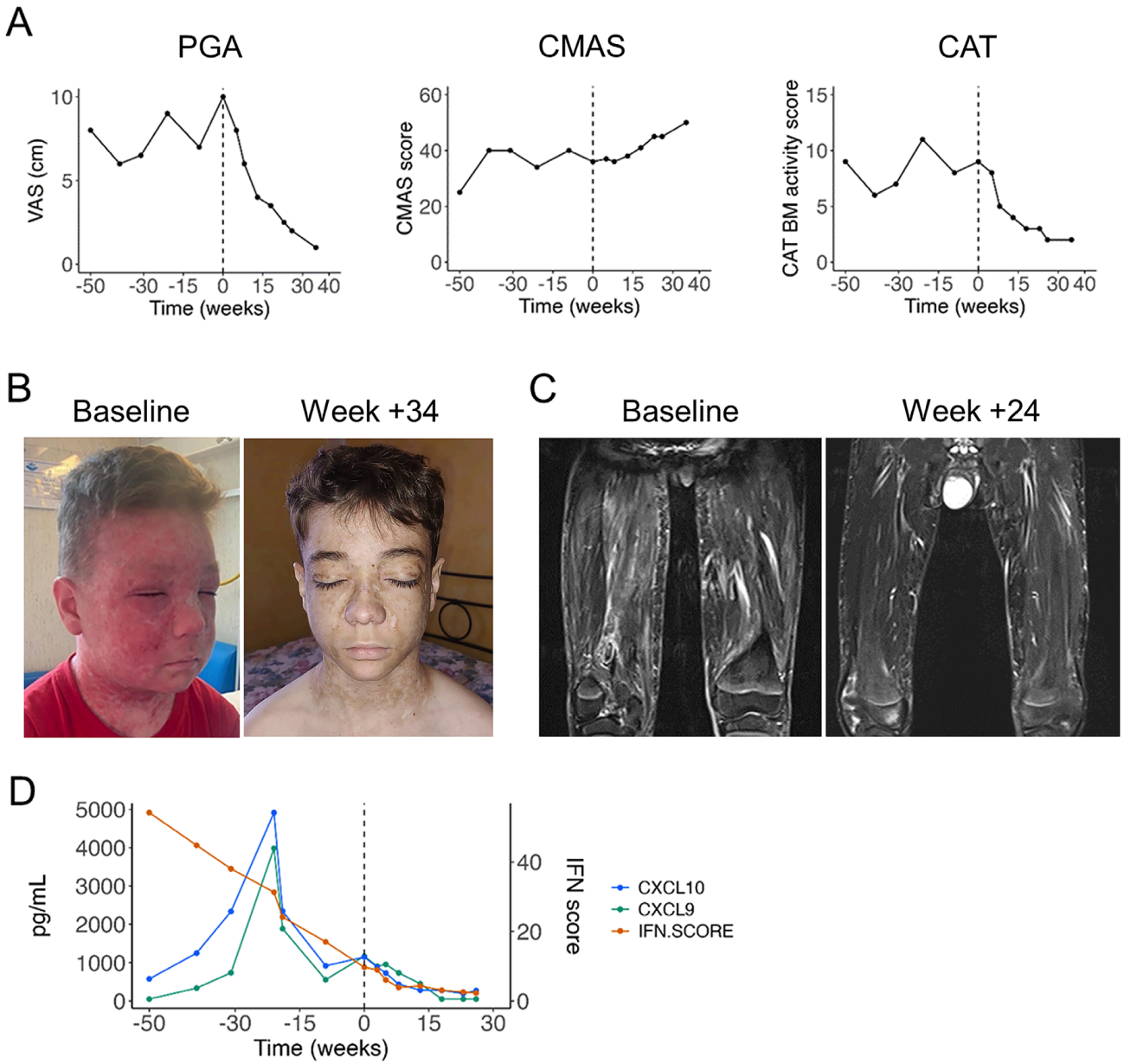
No CRS/ICANS.
Transient decrease in Hb.

At 12w:

- anti ds-DNA Ab seroconverted;
- SLEDAI-2K decreased from 22 at baseline to 0 at 12w;
- neurological status improved, MRI lesions in the brain and spinal cord regressed.

Hagen et al Lancet 2025

Autologous CD19 CAR T in Refractory Juvenile Dermatomyositis



12y-old boy with severe, chronically active JDM refractory to multiple IST lines, including RTX.

CAR T cells expanded significantly (peak at day 7, 32.69 cells/μL).

Pt achieved sustained B cell depletion and *IST drug-free clinical and radiologic improvement* 8 months after a single infusion of anti-CD19 CAR T.

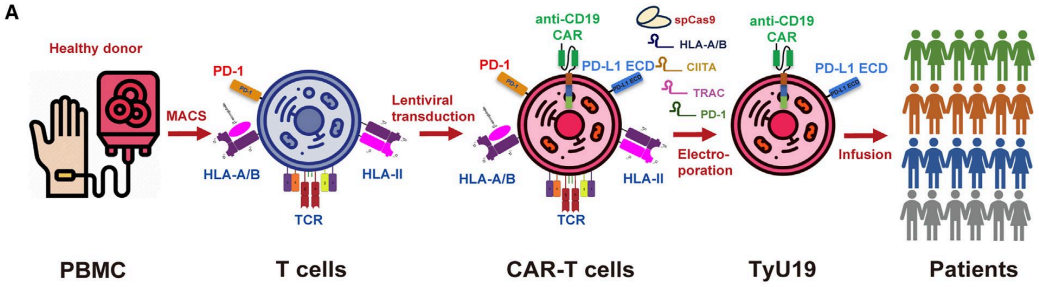
Laboratory tests, MRI imaging, disease activity scores for myositis showed remarkable progressive improvement that persists over time, even after B cell recovery.

Nicolai et al, Arthritis & Rheumatology 2024

Allogeneic CD19-targeted CAR-T in severe myositis and SSc

Wang et al, Cell 2024

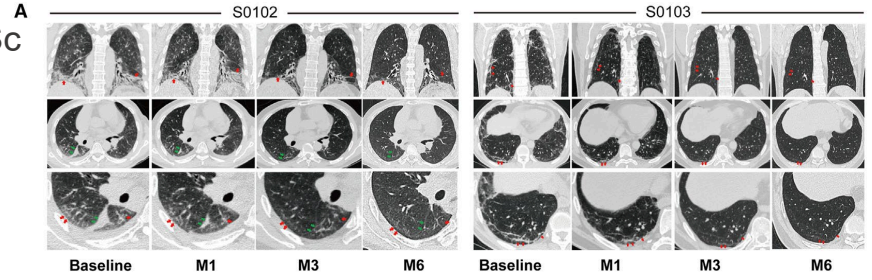
TyU19, a genetically engineered using CRISPR-Cas9, *healthy donor-derived CD19* CAR-T, was used for refractory IMNM (n=1) and SSc (n=2).

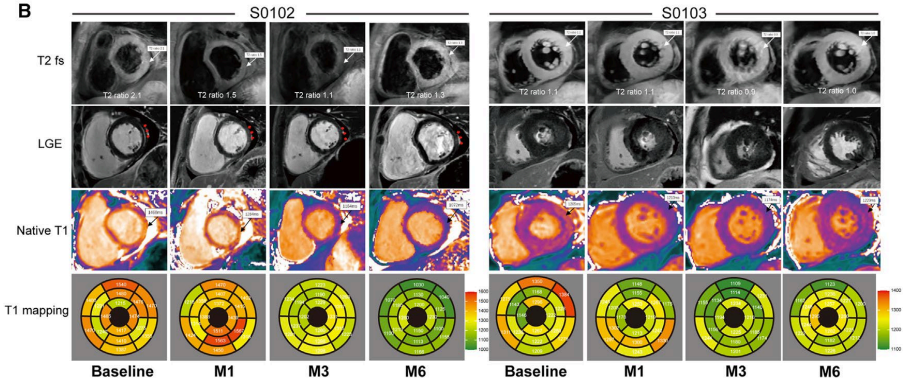


TyU19 (NCT05859997):

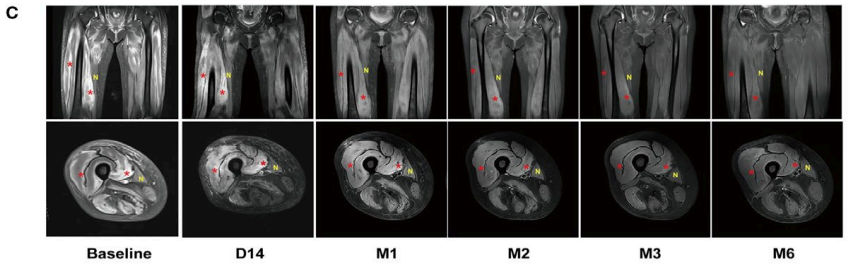
- caused *B cell depletion* in all refractory ADs, cells persisted for over 3 months
- determined *significant improvement in clinical response index scores* for the 2 diseases
- *reversed extensive fibrotic damage* to critical organs in 2 pts with dcSSc
- *alleviated severe skeletal muscle damage* in 1 refractory IMNM.

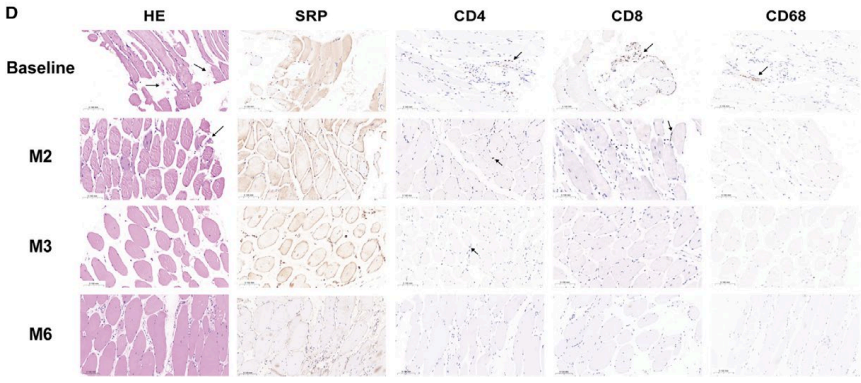
dcSSc





IMNM





BCMA CD19 COMPOUND CART (cCAR) IN LUPUS NEPHRITIS (LN)

Open label ph1 clinical trial.

- 10 refractory LN patients who failed multiple lines of therapy
- Age range: 16-46
- Renal biopsy: Class IV/V most common (6 of 10)
- Mean baseline eGFR 134
- Mean 24-hr protein at screening 1722 mg/day, and increased to 2955 mg/day at baseline

cCAR:

- well tolerated, no SAE
- no CRES, no ICANS and no CRS > 1
- Infections: Covid, g1 UTI
- Bcells/IgM recovery within 150 days and IgA/IgG within 1y
- AutoAbs disappear and not return when B cells/Ig recovered
- Complete humoral reset that results in elimination of autoAbs, medication-free symptom and renal function improvement.

Ma et al, Oral presentation EULAR24, Annals of the Rheumatic Diseases 2024

CD19 CAR T cells in 15 RMD patients

Data on 15 patients with severe **SLE** (n=8), idiopathic inflammatory **myositis** (n=3), or **SSc** (n=4) who received a single infusion of CD19 CAR T cells after FluCy. Median follow-up: 15 months (range 4-29).

Table 1. Characteristics of 15 Patients with Autoimmune Disease at Baseline.*

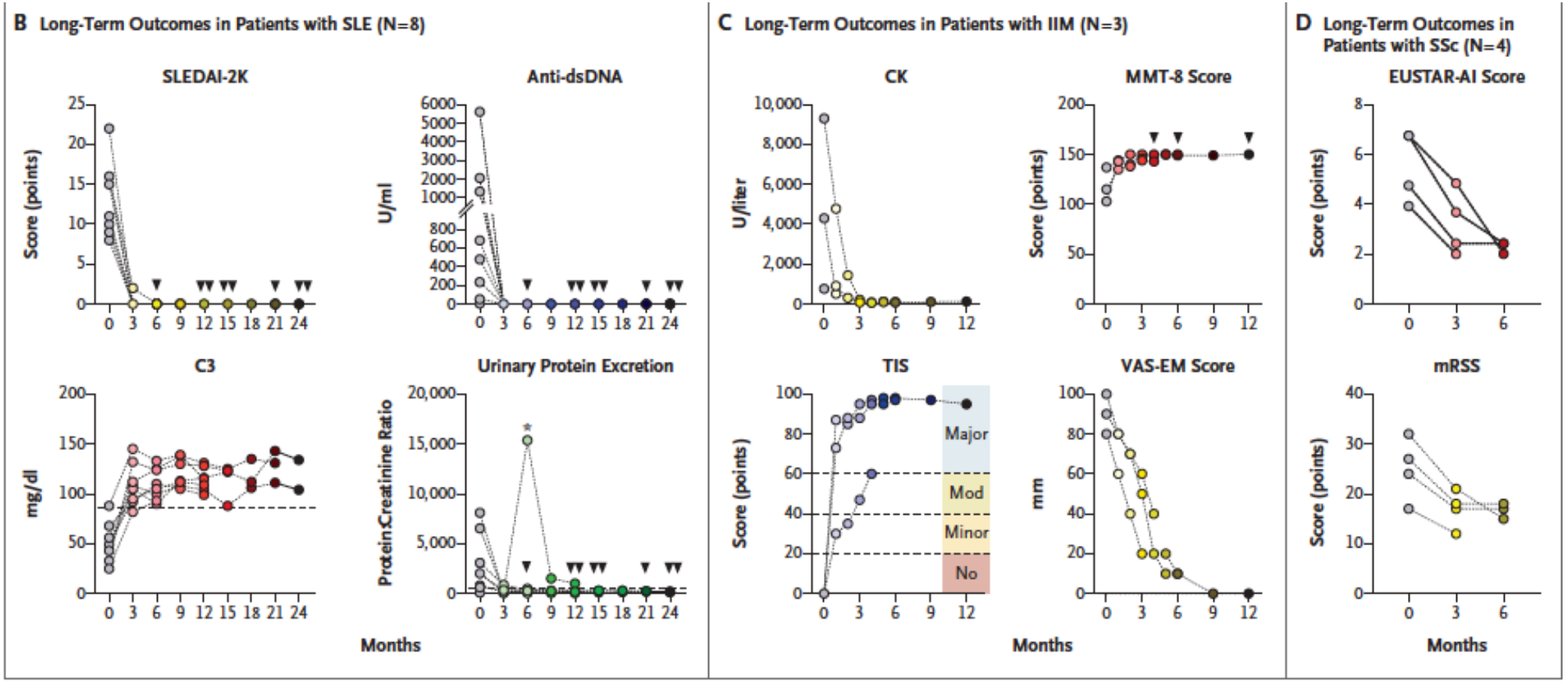
Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14	Patient 15
Age (yr)	20	23	22	24	18	38	33	35	41	43	42	60	36	37	47
Sex	F	M	F	F	F	F	F	F	M	F	M	M	M	F	M
Disease	SLE	SLE	SLE	SLE	SLE	SLE	SLE	SLE	IIM	IIM	IIM	SSc	SSc	SSc	SSc
Disease duration (yr)	4	1	6	9	3	18	1	20	2	5	1	2	2	1	11
Follow-up (mo)	29	25	21	19	15	15	12	6	18	18	5	13	10	7	4
Autoantibodies															
Lead	dsDNA	dsDNA	dsDNA	Sm	dsDNA	dsDNA	dsDNA	dsDNA	Jo-1	Jo-1	PL-7	RNAP III	Scl70	Scl70	Scl70
Co-lead	—	Sm	—	—	Sm	Sm	—	—	—	Pm-Scl100	—	—	—	—	—
Other	—	—	PCNA	Ro60	Ku	Ro52/60	RNP	RNP	—	Ro52	Ro52	—	—	Ro60	—
Organ involvement															
Skin	+	+	+	+	+	+	+	+	+	0	0	+	+	+	+
Kidney	+	+	+	+	+	+	+	+	0	0	0	0	0	+†	0
Nephritis (WHO grade)	III	III	IV	III–V	III–V	IV	IV	IV	0	0	0	0	0	0	0
Lungs	+	0	+	+	0	0	0	+	+	+	+	+	+	+	+
Heart	+	0	0	+	0	0	0	0	0	0	0	+	+	0	0
Bone marrow	+	0	0	0	+	+	0	0	0	0	0	0	0	0	0
Muscles	0	0	0	0	0	0	0	0	+	+	+	0	0	0	0
Joints	0	+	+	+	+	+	0	+	0	+	0	+	+	0	0

F. Müller, et al., NEJM 2024

Clinical Results

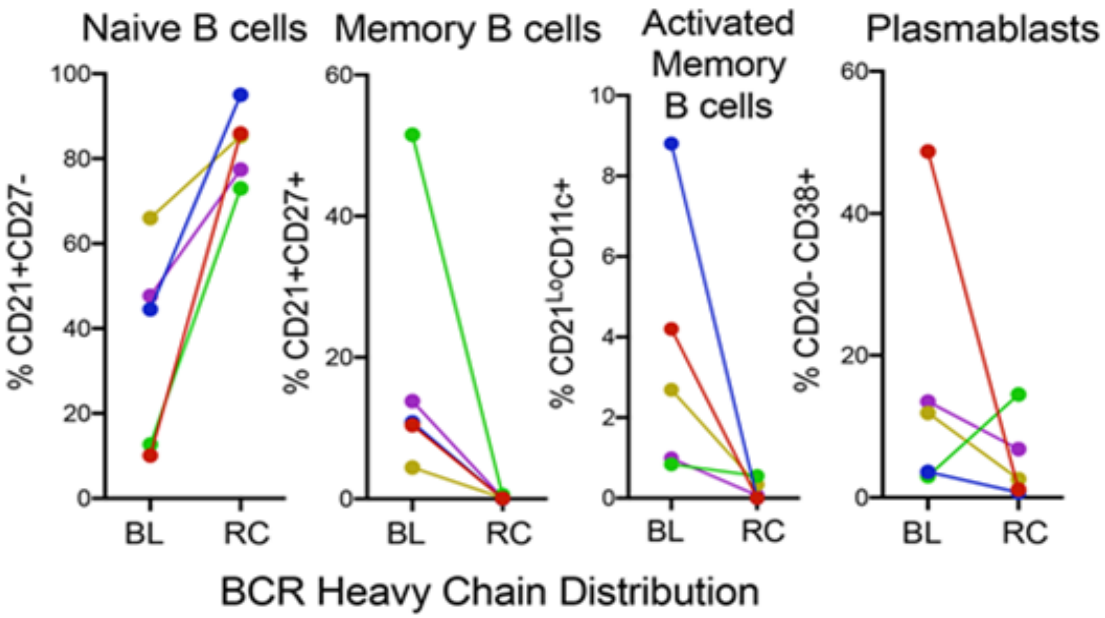
A Short-Term Efficacy of CD19 CAR T-Cell Therapy in Autoimmune Disease

Patient No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Disease	SLE								IIM			SSc			
DORIS Remission	+	+	+	+	+	+	+	+*	N/A			N/A			
LLDAS	+	+	+	+	+	+	+	+*							
SLEDAI-2K Score	0	0	0	0	0	0	0	0							
ACR–EULAR Major Clinical Response	N/A								+	+	+*				
Normalization of CK Level									+	+	+*				
Change in EUSTAR-AI Score									N/A			−2.3	−4.7	−4.3	−1.9*
Change in mRSS												−7	−9	−17	−5*
Glucocorticoid-free State	+	+	+	+	+	+	+	+*	+	+	+*	+	+	+	+*
No Immunosuppressive Drugs	+	+	+	+	+	+	+	+*	+	+	+*	+	+	+	+*

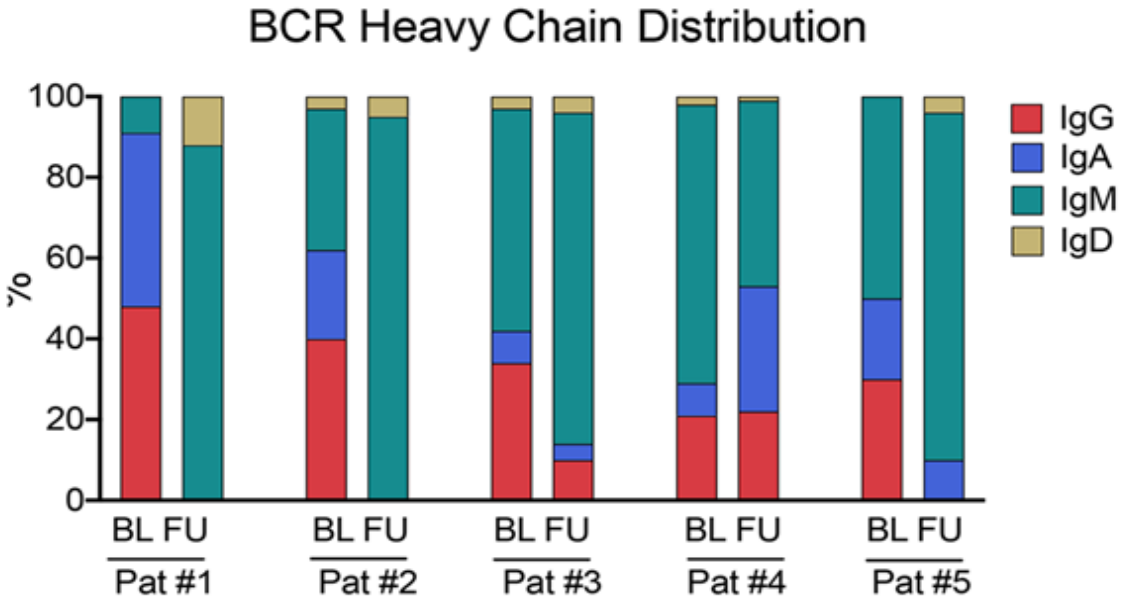


F. Müller, et al., NEJM 2024

Re-appearing B cells are of a naïve phenotype



Changes from baseline (BL) to B cell reconstitution (RC) following CAR T

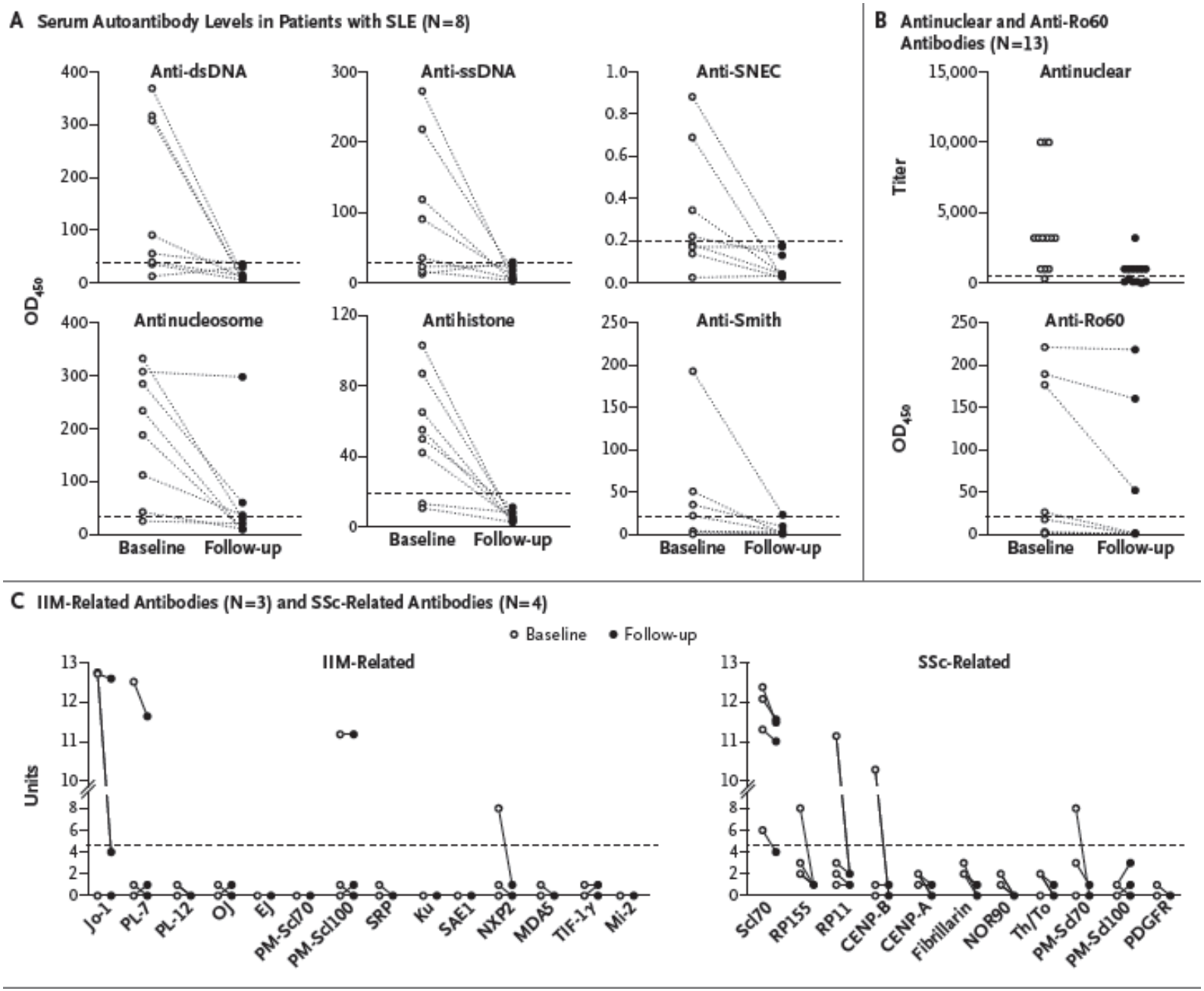


In line with naive B cells at reconstitution, surface Ig is of IgM and IgD (Ab seroconversion)

→ Reset of the B cells in the peripheral blood.

A. Mackensen, F. Müller*, et al., Nat. Med. 2022 Sep 15.*

Antibody Repertoires after CAR T-Cell Therapy



F. Müller, et al., NEJM 2024

Data on short/medium-term safety

Grade 1 CRS occurred in *10 patients*. Tocilizumab was administered in 6 patients.

One patient had **grade 2 CRS**, **grade 1 ICANS** (treated with steroids), and pneumonia requiring hospitalization.

No case of prolonged (>28 days) or biphasic BM suppression occurred.
One patient had grade 4 neutropenia at 120 days after CAR T, which resolved after cessation of sertraline, pregabalin, and doxazosin, and after three injections of GCSF.

Table 2. Short-Term Safety of CD19 CAR T-Cell Therapy in Autoimmune Disease.*

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14	Patient 15
Disease	SLE	SLE	SLE	SLE	SLE	SLE	SLE	SLE	IIM	IIM	IIM	SSc	SSc	SSc	SSc
CRS (grade)	0	1	1	1	0	1	0	1	1	1	2	1	1	1	0
ICANS (grade)	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
Bone marrow toxicity†	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
TOC treatment	0	0	0	+	0	+	0	+	+	+	+	0	0	0	0
GLC treatment	0	0	0	0	0	0	0	0	0	+	0	0	0	0	0
Low IgG	+	+	+	0	0	0	0	+‡	+‡	0	0	0	0	0	0
IgG substitution	0	+	0	0	0	0	0	+	0	0	0	0	0	0	0

F. Müller, et al., NEJM 2024

Data on long-term safety

Table 3. Long-Term Safety of CD19 CAR T-Cell Therapy in Autoimmune Disease.*

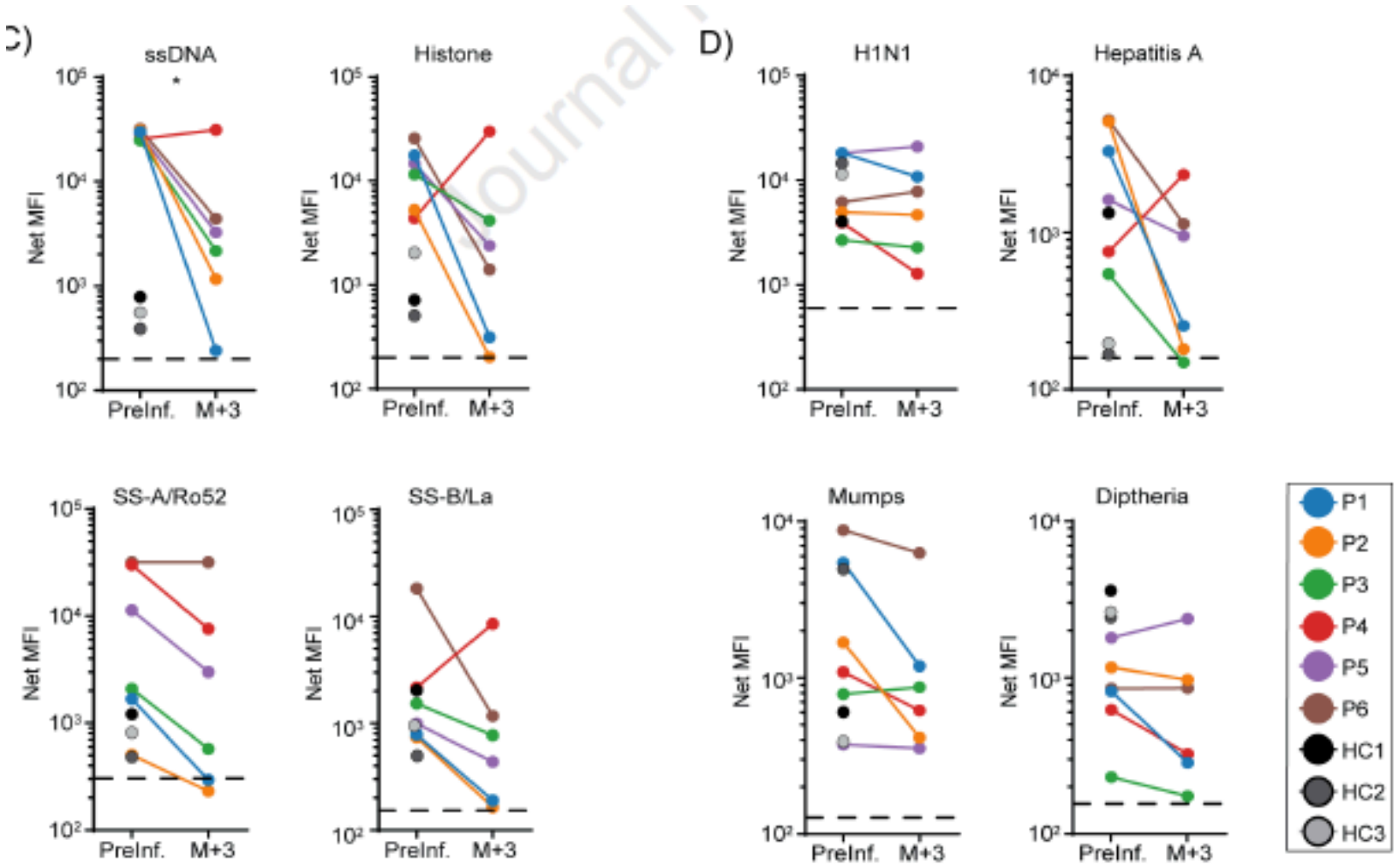
Patient No.	Disease	<3 Months	3–6 Months	6–12 Months	>12 Months
1	SLE	UTI	0	0	URTI (nonspecified)
2	SLE	0	0	URTI (SARS-CoV-2†)	URTI (nonspecified)
3	SLE	URTI (SARS-CoV-2)	0	URTI (nonspecified)	URTI (SARS-CoV-2) and herpes zoster
4	SLE	0	0	0	Otitis
5	SLE	0	URTI (SARS-CoV-2†)	0	0
6	SLE	0	URTI (SARS-CoV-2† and RSV)	URTI (SARS-CoV-2†)	URTI (nonspecified)
7	SLE	0	0	0	
8	SLE	Pneumonia	0		
9	IIM	0	Enteritis (nonspecified)	0	0
10	IIM	0	Herpes simplex	0	0
11	IIM	URTI (nonspecified)	0		
12	SSc	0	URTI (*Haemophilus influenzae*)	0	0
13	SSc	0	Cellulitis	Herpes zoster	
14	SSc	URTI (SARS-CoV-2†)	0		
15	SSc	0			

F. Müller, et al., NEJM 2024

Impact of CD19+ B-cell depletion on pre-existing humoral immunity in SLE patients

Assessment of patient sera for Ab to 14 different infectious agents and vaccines.

Results from **no change** to **mild/moderate decreases** in pathogen or *vaccine associated Ab titers* following anti-CD19 CAR T-cell infusion. No titers became negative.



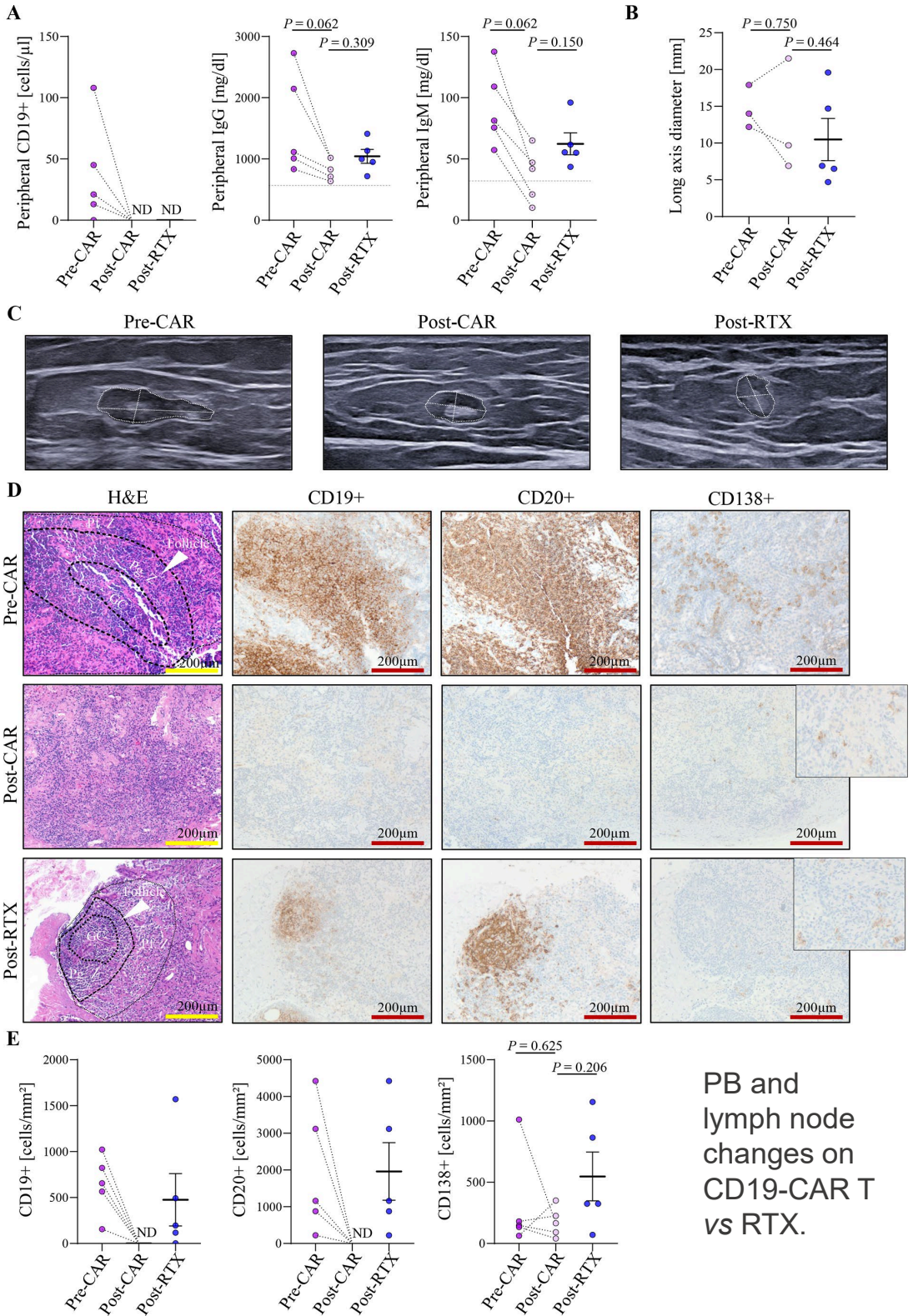
Nunez D et al., Molecular Therapy: Methods & Clinical Development (2023)

CD19-CAR T induces deep tissue depletion of B cells

By performing *sequential lymph node biopsies*, this study shows that CD19-CAR T-cell in conjunction with standard lymphodepleting therapy leads to the complete depletion of B cells (CD19+ and CD20+) from lymph nodes — an effect that has not been observed with Ab-based B-cell depletion therapies, such as rituximab (RTX).

Plasma cells, T cells and macrophages in the lymph nodes remained unchanged. Follicular structures were disrupted and FDCs were depleted in the lymph nodes after CD19-CAR T, but not after RTX. Non-lymphoid organs were completely depleted of B cells.

Tur C, et al. Ann Rheum Dis 2024



PB and lymph node changes on CD19-CAR T *vs* RTX.

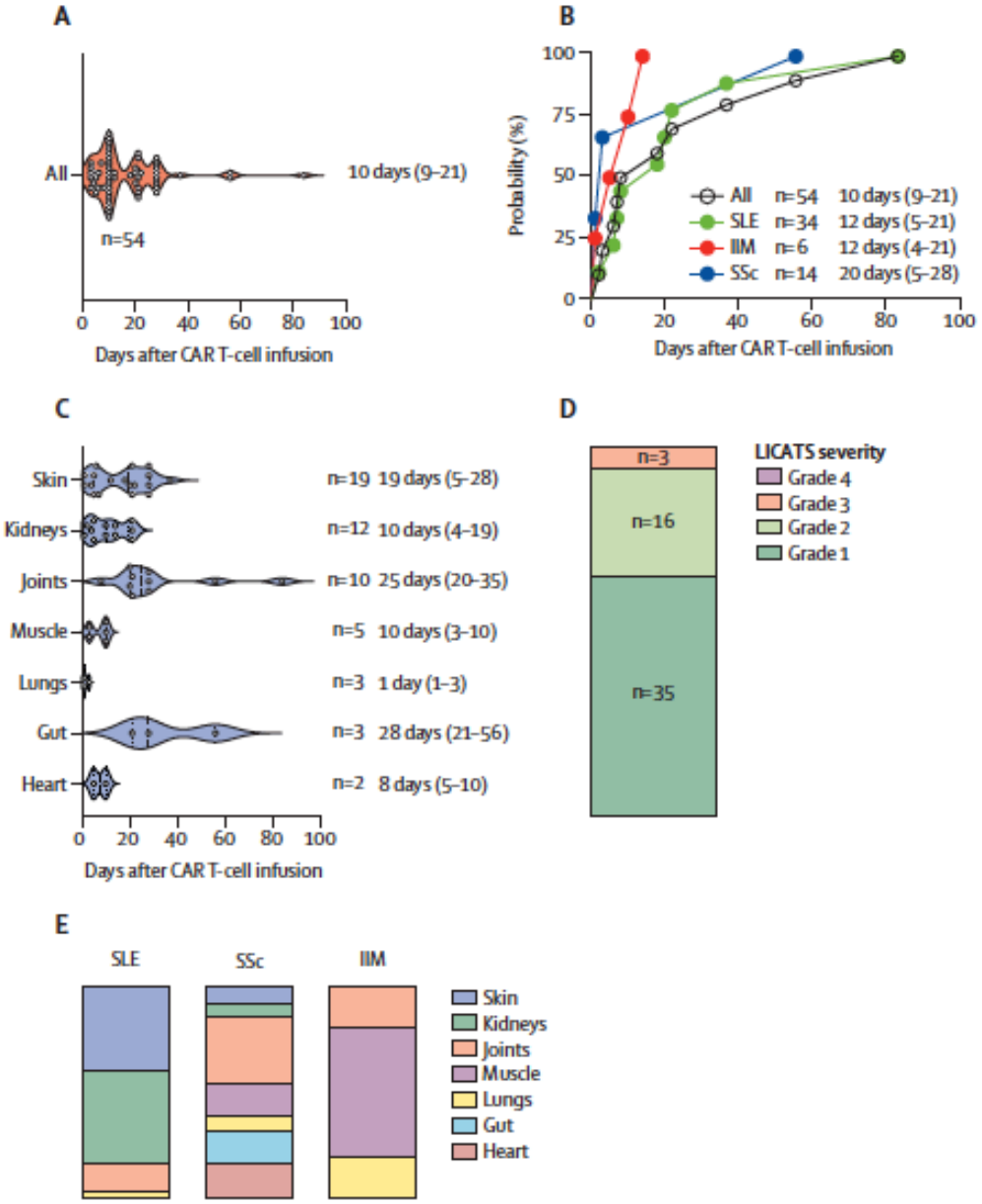
Local immune effector cell-associated toxicity syndrome (LICATS)

39 pts with ADs were treated with CD19- CAR T (20 SLE, 13 SSc, 6 IIM).

LICATS >> 54 local reactions, in 30 (77%) pts with a median time of onset of 10 days (IQR 9–21) from CAR infusion and a median duration of 11 days (5–14).

LICATS exclusively occurred during the B-cell aplasia and only involved **organs previously affected by the respective ADs**. The most frequently affected organs were the **skin** (19 [35%] of 54) and the **kidneys** (12 [22%]).

Most cases of LICATS were **mild** (grade 1: 35 [65%]; grade 2: 16 [30%]).
Only 3 cases were grade 3. All events of LICATS **resolved without sequelae**.



Hagen, et al. Lancet Rheumatol 2025

Treatment of Relapse after CD19-CAR T-cells: **BCMA-CAR T-cells** in idiopathic inflammatory myositis

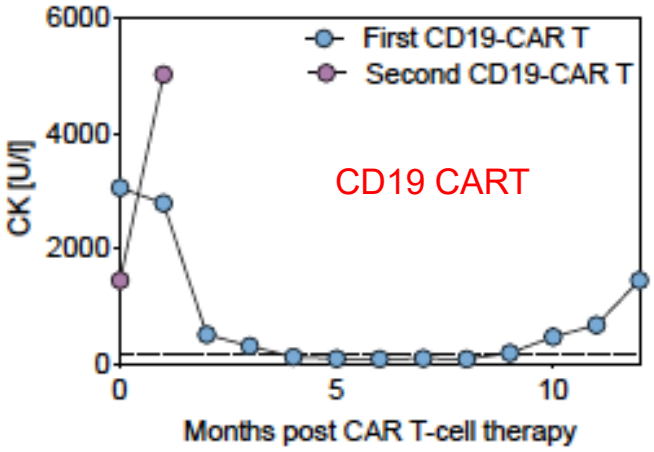
Antisynthetase syndrome
Jo-1+ (*refractory to CD19 CART x2 & daratumumab*): 1 pt

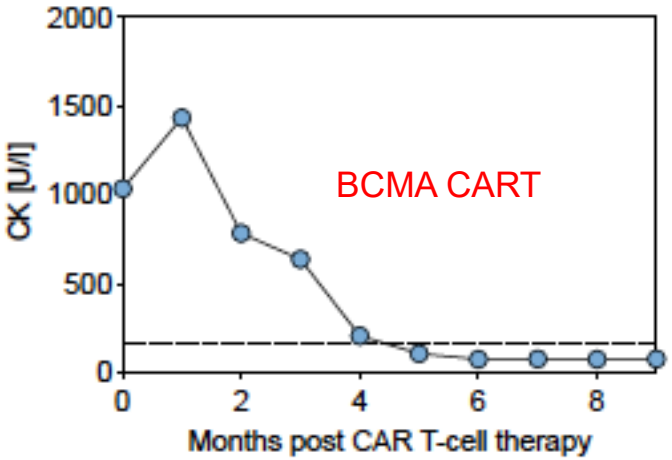
BCMA CAR (IdeCel) under expanded access program.

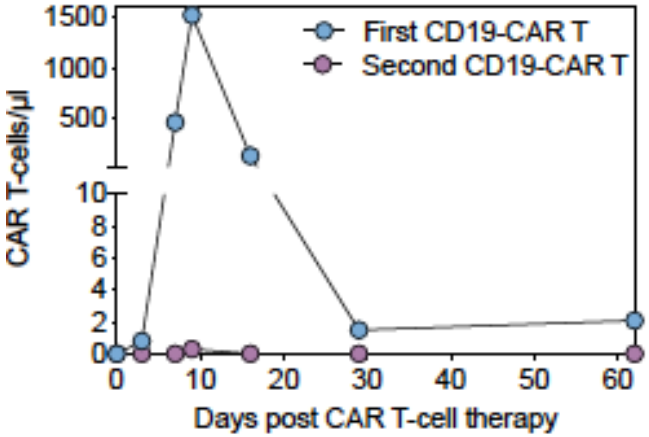
Flu (30mg/m2 day-5 -4 -3) and Cy (300mg/m2 day-5 -4-3).

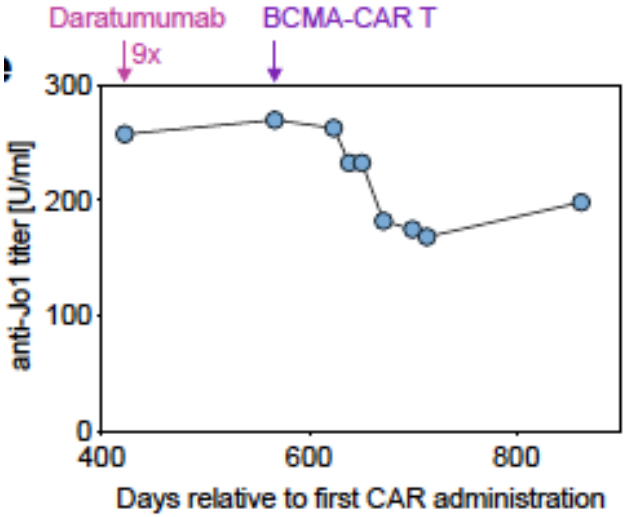
CRS g1.
Letermovir prophylaxis.

Clearance of plasma cells in lymphoid tissue;
reduced autoAb;
re-induced stable drug-free remission, disappearance of muscular impairment.









These data demonstrate that:
- switch of CAR T target can restore drug-free remission after relapse after the 1st CART
- repeated treatment with the same CART product can be hampered by anti-CAR T-cells preventing engraftment
- immunosuppressive effects of lymphodepletion is not effective to influence AD in the absence of CAR T-cell proliferation.

Muller et al., Nat Med 2025

Overview on CART cells literature for RMDs

Adapted from EBMT Handbook 2024

	AD	CAR-T CELL	LYMPHODEPLETION	CRS/ ICANS	OTHER TOXICITIES	DISEASE RESPONSE	FOLLOW UP
Mougiakakos et al (2021)	**SLE** (active lupus nephritis); 1 pt	Autologous, CD19 CAR, 4-1BB co-stimulatory domain	Flu 25 mg/m2/d i.v. on days -5, -4, -3 and Cy 1000 mg/m2/d i.v. on day -3	none	none	Clinical remission (proteinuria, SLEDAI), serologic remission (dsDNA Ab; C3/C4)	44 days
Mackensen et al (2022)	**SLE** (multiorgan involvement, lupus nephritis all); 5 pts	Autologous, CD19 CAR, 4-1BB co-stimulatory domain	Flu 25 mg/m2/d i.v. on days -5, -4, -3 and Cy 1000 mg/m2/d i.v. on day -3	CRS g1 (3/5); no ICANS	no infections	Resolution of nephritis and disease-related symptoms, serologic remission (5/5)	8 months
Müller et al (2023)	**Antisynthetase syndrome**; 1 pt	Autologous, CD19 CAR lentiviral vector	Flu 25 mg/m2/d i.v. days -5, -4, -3, Cy 1000 mg/m2/d i.v. day -3	CRS g1, transient CRS-related symptoms	Decreased Ig levels	Improvement in muscle strength & endurance, serologic remission, MRI resolution of myositis	200 days
Bergmann et al (2023)	**SSc** (diffuse cutaneous, heart/ lung fibrosis, lung hypertension) 1 pt	Autologous, CD19 CAR lentiviral vector	Flu 12.5 mg/m2; days −5, −4 and −3 and Cy 500 mg/m², day −3 (50% dose-reduced due to renal impairment)	CRS g1; no ICANS	none	Improvement of heart, joint and skin manifestations, serologic remission, stable pulmonary fibrosis	6 months
Pecher et al (2023)	**Antisynthetase syndrome** (interstitial lung disease); 1 pt	Autologous, CD19 lentiviral vector	Flu (25mg/m2 day-5 -4 -3) and Cy (1000mg/m2 day-3); MMF (2 g/d) by day35	CRS g1	Expansion of CD8+ T cells with disease flare at day+ 7	Muscle and pulmonary function tests improved, no detectable myositis on MRI; reduction in anti-Jo-1 Ab	8 months
Müller et al (2024)	**SLE** (n=8), II **myositis** (n=3), **SSc** (n=4)	Autologous, CD19 4-1BB CAR, lentiviral vector (MB-CART19.1)	Flu 25 mg/m2/d i.v. on days -5, -4, -3 and Cy 1000 mg/m2/d i.v. on day -3; 2 pts (due to dialysis) received 50% dose reduced LD	CRS g1 (n=10), CRS g2 & ICANS g1 (n=1); tocilizumab (n=6)	Pneumonia & hospitalization (n=1), transient neutropenia g4 (n=1)	DORIS remission in SLE, ACR–EULAR major clinical response in IIM, decrease in EUSTAR activity index for SSc; reduction in Ab titers	15. months
Mengtao et al (2024)	**SLE** (active lupus: severe and refractory **SLE–ITP**); 1 pt	Autologous CD19 CAR T (inaticabtagene autoleucel [inati-cel], Juventas Cell Therapy)	Flu (at a dose of 25 mg per square meter of body-surface area) per day on days −5, −4, −3 and Cy (at a dose of 250 mg per square meter) on days −5 and −4 before CAR T	CRS g1	None	PLT 109,000 at 6 months; antibody titers decreased	6 months
Nicolai et al (2024)	**JDM**; 1 pt (*paediatric*)	Autologous, 2nd-generation CD19 CART, lentiviral vector, manufactured on Prodigy device	Flu 90 mg/m2 over 3 days, Cy 1,000 mg/m2 over 2 days	CRS g1	Transient g2 anemia and g4 neutropenia	Sustained B cell depletion, ongoing IST drug-free clinical and radiologic improvement	8 months
Krickau et al (2024)	**SLE** (severe lupus nephritis, ongoing haemodialysis); 1 pt (*paediatric*)	Autologous, CD19 4-1BB CAR, lentiviral vector	Flu 12·5 mg/m² on days –5, –4, –3 and Cy 500 mg/m² on day –3. Haemodialysis before the start of CT and 18 h after the last CT infusion on days –3,–2, 0	CRS g1	CT-associated transient g4 granulocytopenia, pre-existing anaemia	SLE activity decreased, arthritis solved, C3/C4 normalised, anti-dsDNA Ab disappeared, renal function improved (dialysis-free, partial renal response)	6 months
Wang et al (2024)	Refractory **myositis** (n=1) and **SSc** (n=2)	Allogeneic CD19 CART, CRISPR-Cas9, lentiviral vector (TyU19)	Flu 25 mg/day/m2 from day-5 to day-3, Cy 300 mg/day/m2 on day-5 and day-4	none	No GvHD, no relevant clinical symptoms	Significant improvement in the clinical response index scores for the 2 diseases, and reversal of inflammation and fibrosis	6 months

Overview on CART cells literature for RMDs

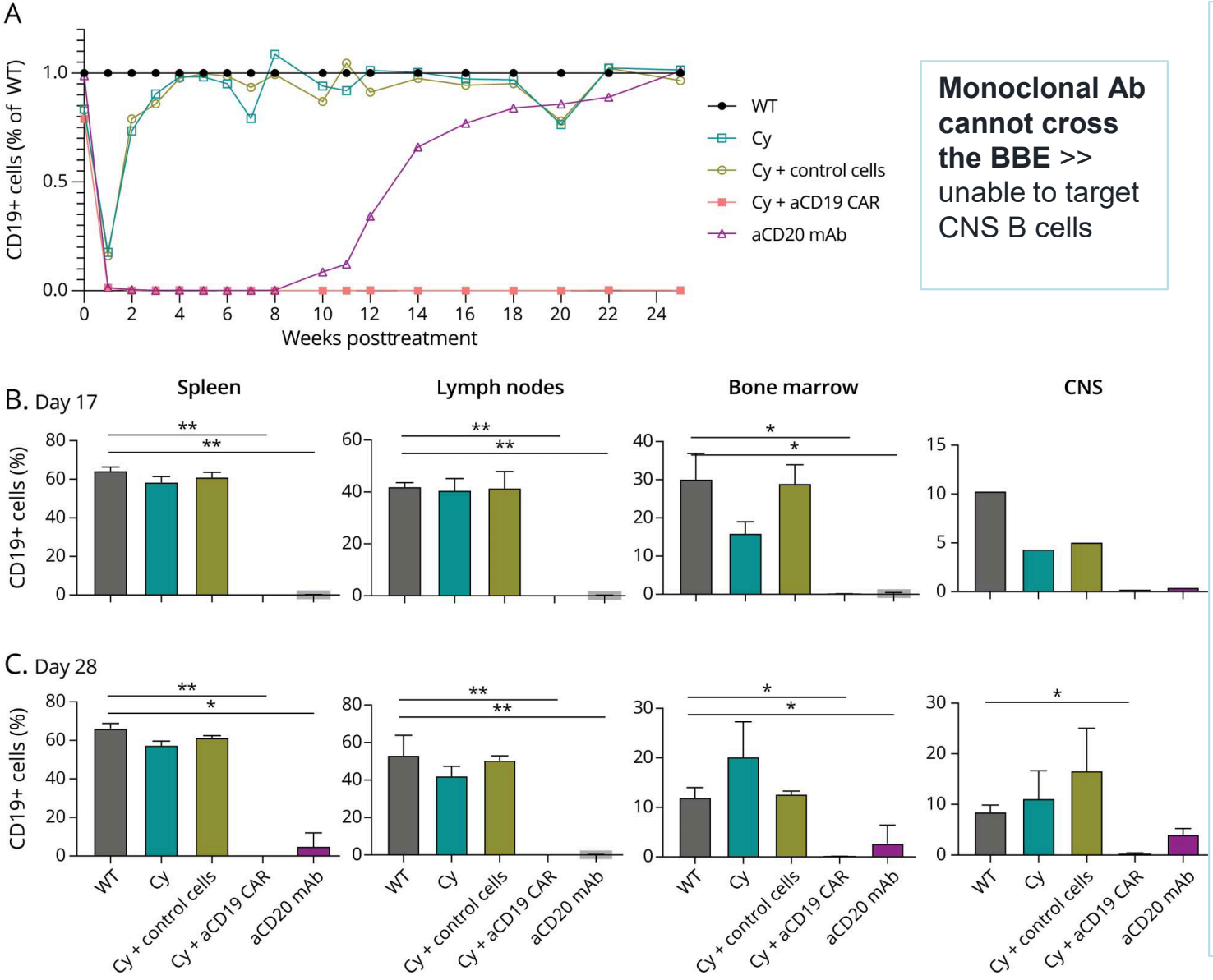
Adapted from EBMT Handbook 2024

	AD	CAR-T CELL	LYMPHODEPLETION	CRS/ ICANS	OTHER TOXICITIES	DISEASE RESPONSE	FOLLOW UP
Auth et al (2024)	**SSc** (diffuse & severe;insufficient response to at least 2 treatments); 6 pt	Autologous, CD19 CAR, 4-1BB co-stimulatory domain	Flu 25 mg/m2/d i.v. on days -5, -4, -3 and Cy 1000 mg/m2/d i.v. on day -3	CRS: 3 patients with g1, and 2 patients with g2)	Infections: influenza with bacterial superinfection (n=1)	Improvement in the ACR-CRISS score, median mRSS decreased ;FVC improved; the extent of disease on CT scan decreased	487 days
Hagen et al. (2024)	**SLE** with **CNS+**; 1 pt	Autologous, CD19 CAR, 4-1BB co-stimulatory domain	Flu (25mg/m2 day-5 -4 -3) and Cy (1000mg/m2 day-3); **Dex** (10 mg/die days 1-3)	None	Hb levels showed a transient decrease (minimum on day14)	Anti ds-DNA Ab seroconverted; SLEDAI-2K decreased from 22 at baseline to 0 at 12w. Neurological statusimproved, MRI lesions in the brain and spinal cord regressed.	12 weeks
Muller et. Al (2025)	**Antisynthetase syndrome** Jo-1+ (*refractory to CD19 CART x2 & daratumumab*); 1 pt	Autologous, BCMA CAR (*idecabtagene vicleucel*) under an expanded access program	Flu (30mg/m2 day-5 -4 -3) and Cy (300mg/m2 day-5 -4-3)	CRS g1	None (Letermovir prophylaxis)	Clearance of plasma cells in lymphoid tissue, reduced autoAb levels, and re-induced stable drug-free remission with disappearance of muscular impairment	9 mo
Haase et al (2025)	**Antisynthetase syndrome** Jo-1+ (*refractory to anti CD38 tp*); 1 pt	Autologous, CD19 CAR-T (KYV-101), CD28 co-stimulatory domain	Flu (30mg/m2 day-5 -4 -3) and Cy (300mg/m2 day-5 -4-3) Under low-dose prednisolone (5 mg/d) in the first 6 mo.	CRS g2 (treated with Tocilizumab, anakinra and dexamethasone- in reoccurring mild grade CRS to prevent higher grade toxicity)	Neutropenia (CTCAE grade 3) was noted on day 7 to 10 >> single dose G-CSF. A transient elevation of transaminases (g2) self-limiting.	Significant and rapid improvement in muscle strength, arthritis, and pulmonary function. Normalization of muscle enzymes and inflammatory markers. AutoAb levels remained unchanged. Transient skin alterations resolved with low-dose glucocorticoids.	6 months

EBMT

CAR-T cells in neurological ADs

CAR-T Cell–Mediated B-Cell Depletion in CNS Autoimmunity



Monoclonal Ab cannot cross the BBE >> unable to target CNS B cells

CD19 CAR-T in a B-cell–dependent **EAE model**.

- ✓ *Clinical scores and lymphocyte infiltration were reduced* in mice treated with CD19 CAR-T.
- ✓ *B-cell depletion* was observed in *peripheral lymphoid tissue and CNS* of mice treated with CD19 CART.
- ✓ CD19 CAR-T ameliorated EAE.
- ✓ Th1 or Th17 populations did not differ in CD19 CAR-T, control, or Cy > clinical benefit independently of Ag specificity or B-cell depletion

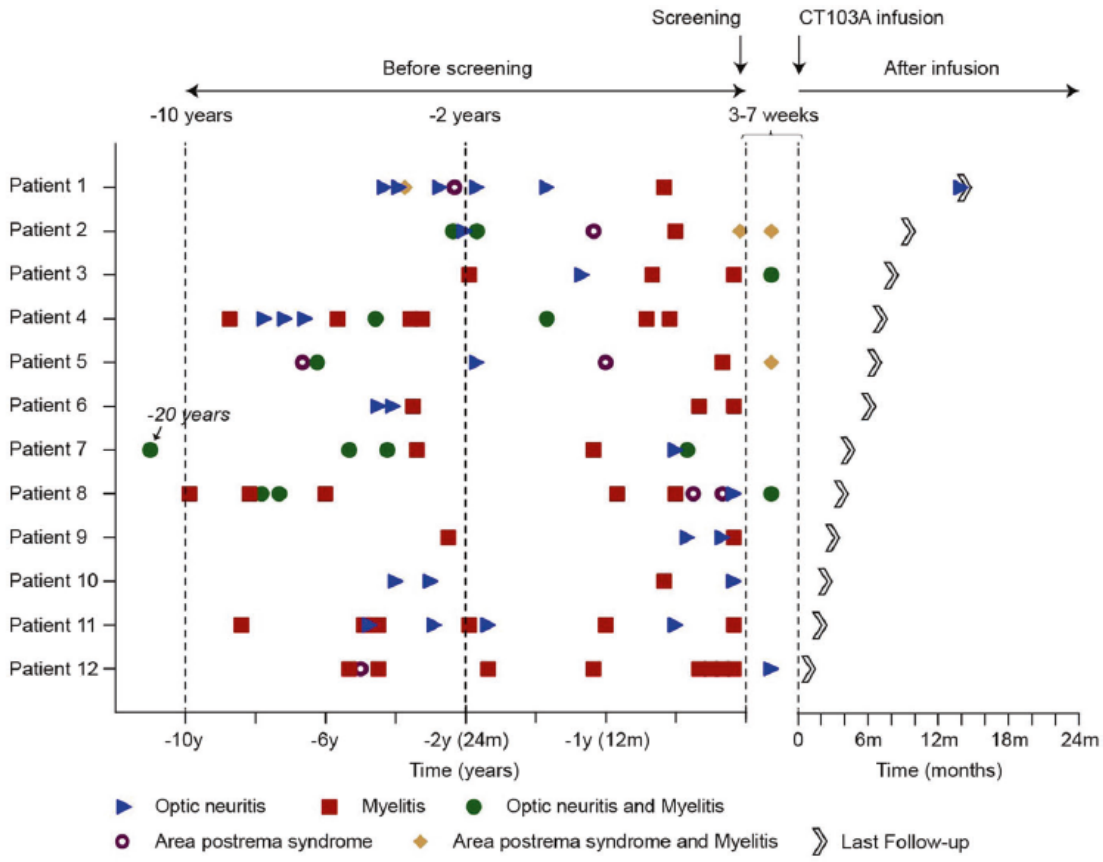
Gupta et al, Neurology 2023

CAR-T cells in NMO

An ongoing, investigator-initiated, open-label, single-arm, **phase 1** clinical trial to investigate CT103A, a self-developed **BCMA-targeting CART** in patients with AQP4-IgG seropositive NMOSD (n=12).

AE:

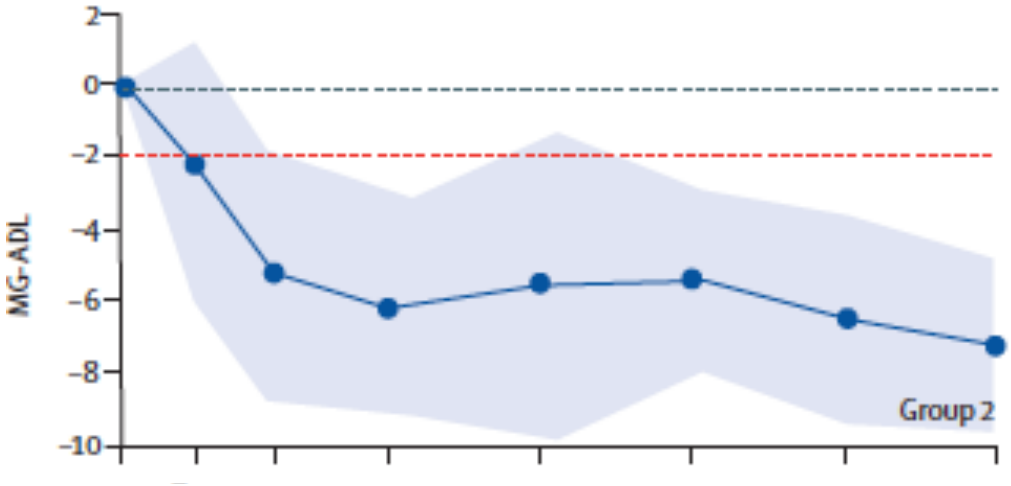
- 7 pts (58%) infections, but no grade 4
- CRS in all patients (only grade 1 or 2)
- CR in 11 pts at median follow-up of 5.5 months
- improvement in disabilities and QoL in all pts
- reduction of AQP-4 antibodies in serum in 11 pts
- CAR T-cell expansion associated with responses, persisted > 6 months in 17% pts.

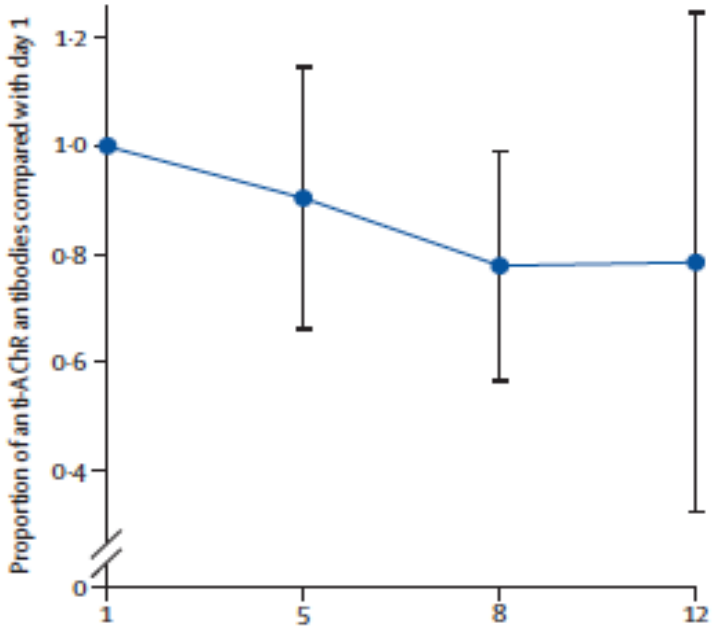


Chuan Qin et al. Signal Transduction and Targeted Therapy 2023

Anti-BCMA RNA autologous CART in Myasthenia Gravis (MG-001)

Phase 1b/2a study of Descartes-08 (clinicaltrials.gov, NCT04146051).
14 pts with generalised myasthenia gravis with MG-ADL score ≥6.
Lymphodepletion chemotherapy was not used.
In part 2 (phase 2a), participants received 6 doses at the maximum tolerated dose in an outpatient setting.
Median follow-up: 5 months (range 3–9).
No DLT/CRS/ICANS, but only infusion-related AEs.
Improvements in MG-related scores (decrease on myasthenia gravis severity scales at up to 9 months of follow-up).





8 pts: **anti-AChR** (acetylcholine receptor) Ab; in 5/8 (63%) Ab decreased by 22% after CART.

1 pt with anti-MuSK Ab at screening: no change was observed during treatment.

Granit V et al. Lancet Neurol 2023

Anti-CD19 CART in Myasthenia Gravis

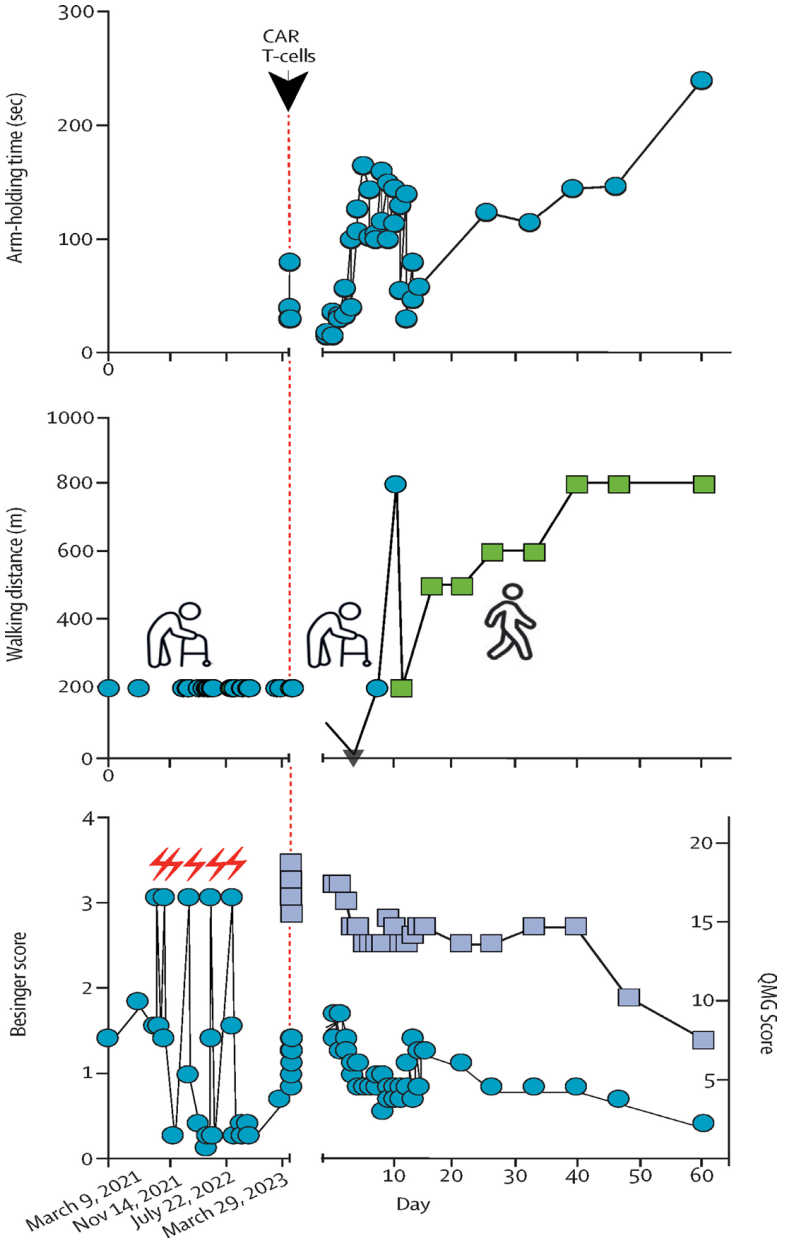
One pt (33y F) affected by severe, treatment-refractory, anti-AchR-positive generalised MG. Several myasthenic crises rrequiring invasive ventilation.

CART cells: fully human autologous anti-CD19 CAR, lower cytokine production and toxicity construct (KYV-101, Kyverna, comprising a fully human CD19 binding domain, a CD28 costimulatory domain, and a CD3ξ activation domain).

Lynphodepletion: Flu (30 mg/m2 on day –6, –5, and –4) and Cy (300 mg/m2 on day –6, –5, and –4).

CAR peak expansion on d+16 (still detectable by d+62).
No AE expect for g1 transaminitis.
B cells: eliminated by d+8 and have not reconstituted as of d+62.
70% reduction in pathogenic anti-AchR Ab, whereas protective vaccination IgG titres were maintained (selective effect on CD19).

Clinical improvement: muscle strength and fatigue (steady increase in the time that the patient could hold out her arm horizontally, enhanced walking ability without any supportive devices), reduction of the clinical disease related scores.



Haghikia A et al. Lancet Neurol 2023

CD19-CART in a patient with MG and coexisting RA

37y-old woman with refractory AChR (acetylcholine receptor)-Ab positive MG (2013) and ACPA (anticitrullinated protein antibody) positive RA (2020).

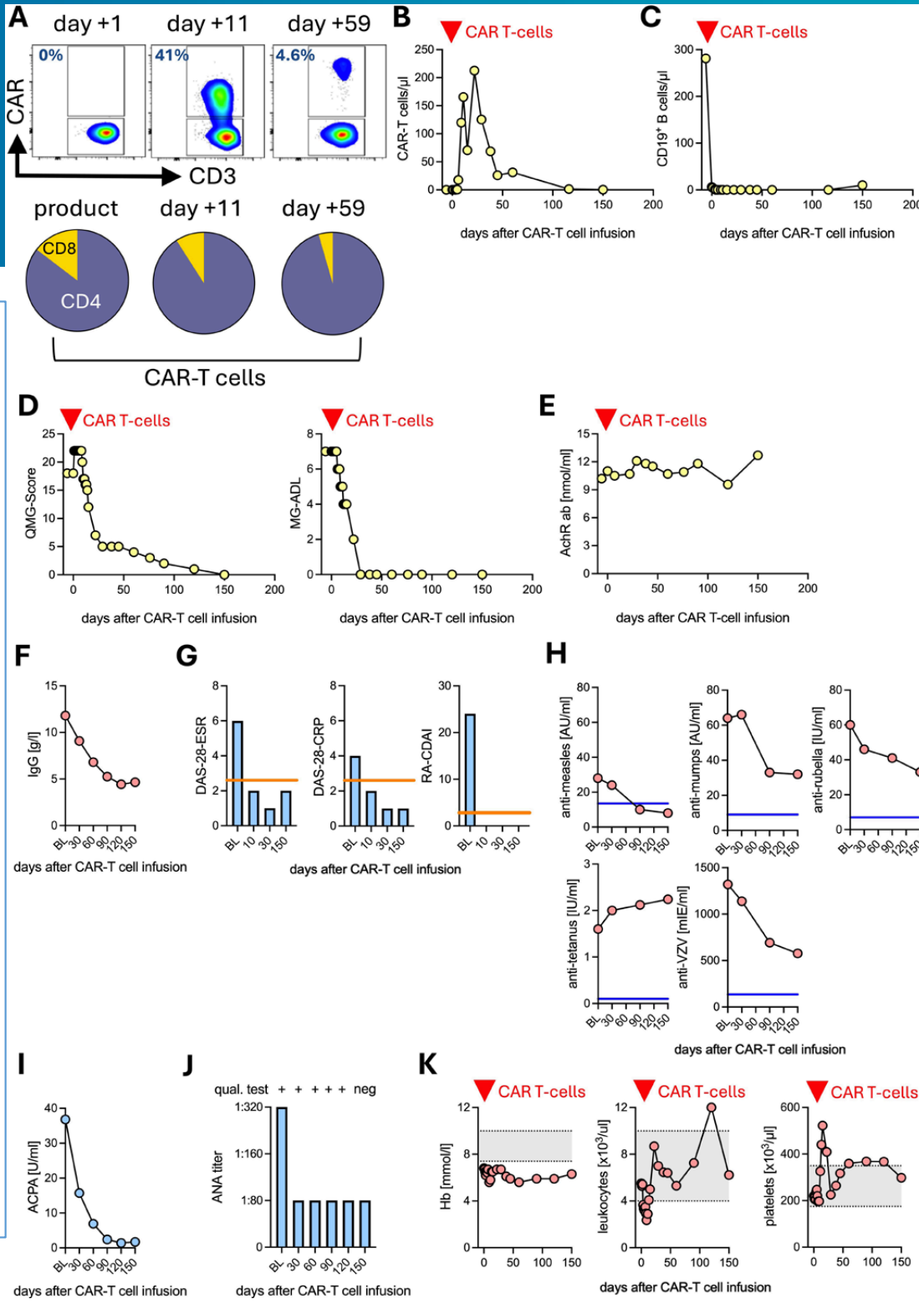
CD19 CAR (**KYV-101**).

Dominance of CD4+T cells among CAR T in the product and in vivo. CAR T cell kinetics: biphasic pattern (peaks d11 & d22), persistence until d120.

Circulating B cells undetectable at d+4 and slowly reconstitute at d150.

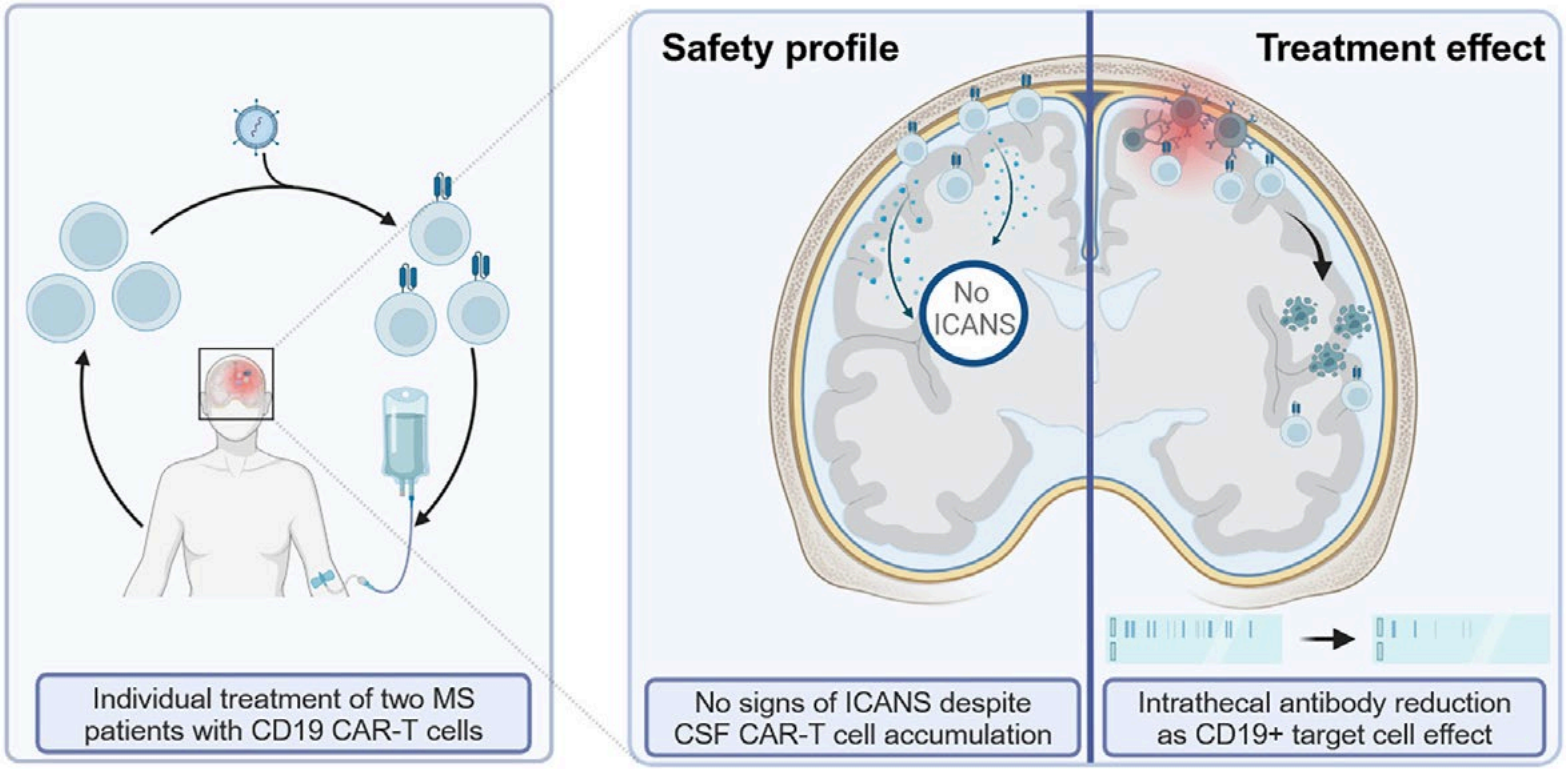
MG activity rapidly abated, ultimately reaching complete disease remission. While total IgG decreased, anti-AChR Ab stable (levels do not always correlate with disease activity.
RA also improved (ACPA levels seroconverted).

CRS g1. Protective IgG responses to standard vaccinations slightly declined, but were overall maintained.



Haghikia et al, Ann Rheum Dis 2024

CD19 CART in two patients with progressive MS



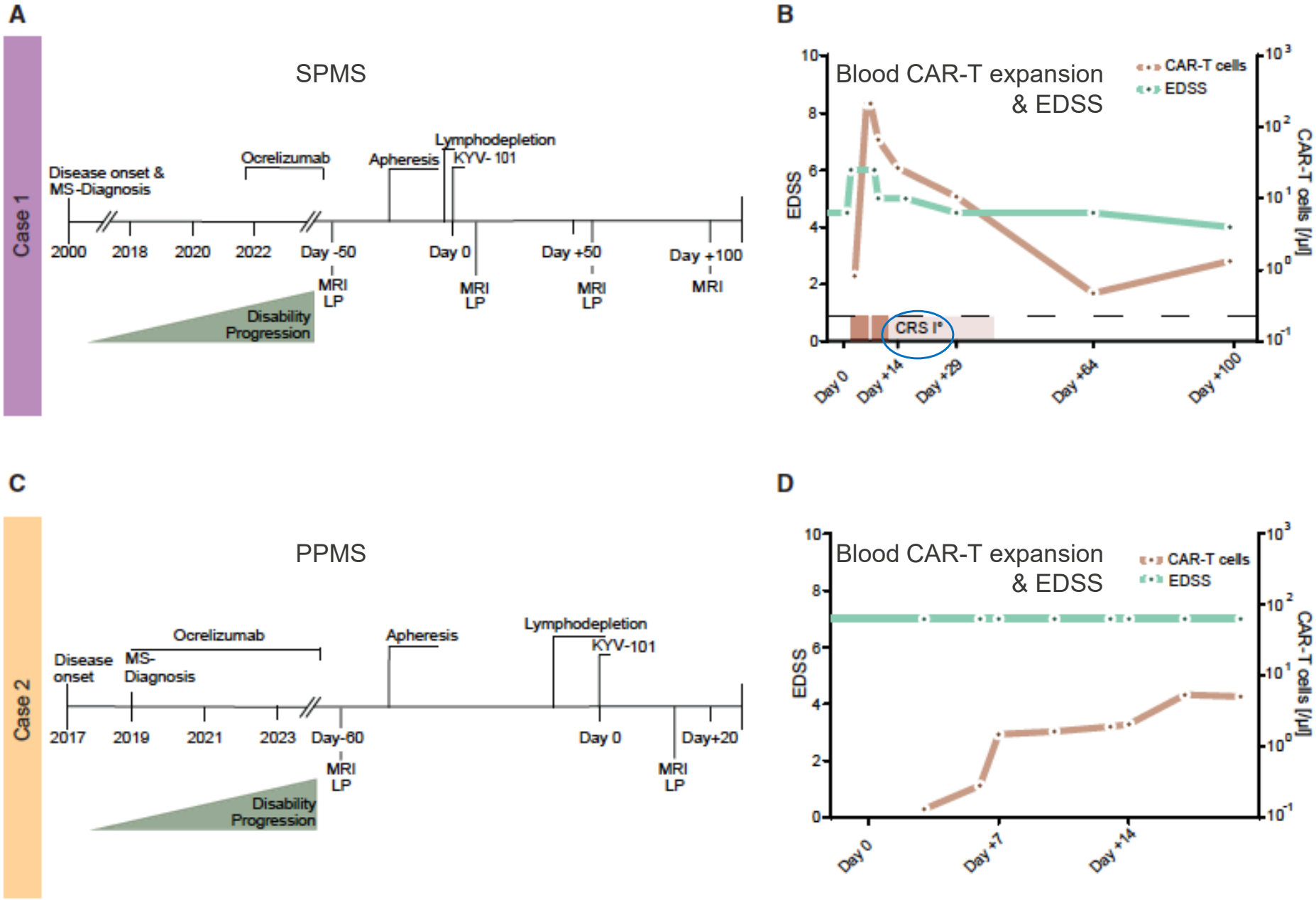
5 pts:
3 RRMS
1 PPMS
1 SPMS

After CD20 MAb failure

- ✓ **KYV-101**, a first-in-class CD19 CAR-T cell therapy, includes a fully human CAR (Hu19-CD828z)
- ✓ CAR-T cell expansion was observed in cerebrospinal fluid without ICANS
- ✓ Intrathecal Ab production decreased after CAR-T cell infusion in 1 pt
- ✓ CNS expansion is not associated with ICANs; transient and easily manageable CRS

Fischbach et al, Med 2024; EU CART Meeting 2025 Oral presentation

Therapy overview and safety profile

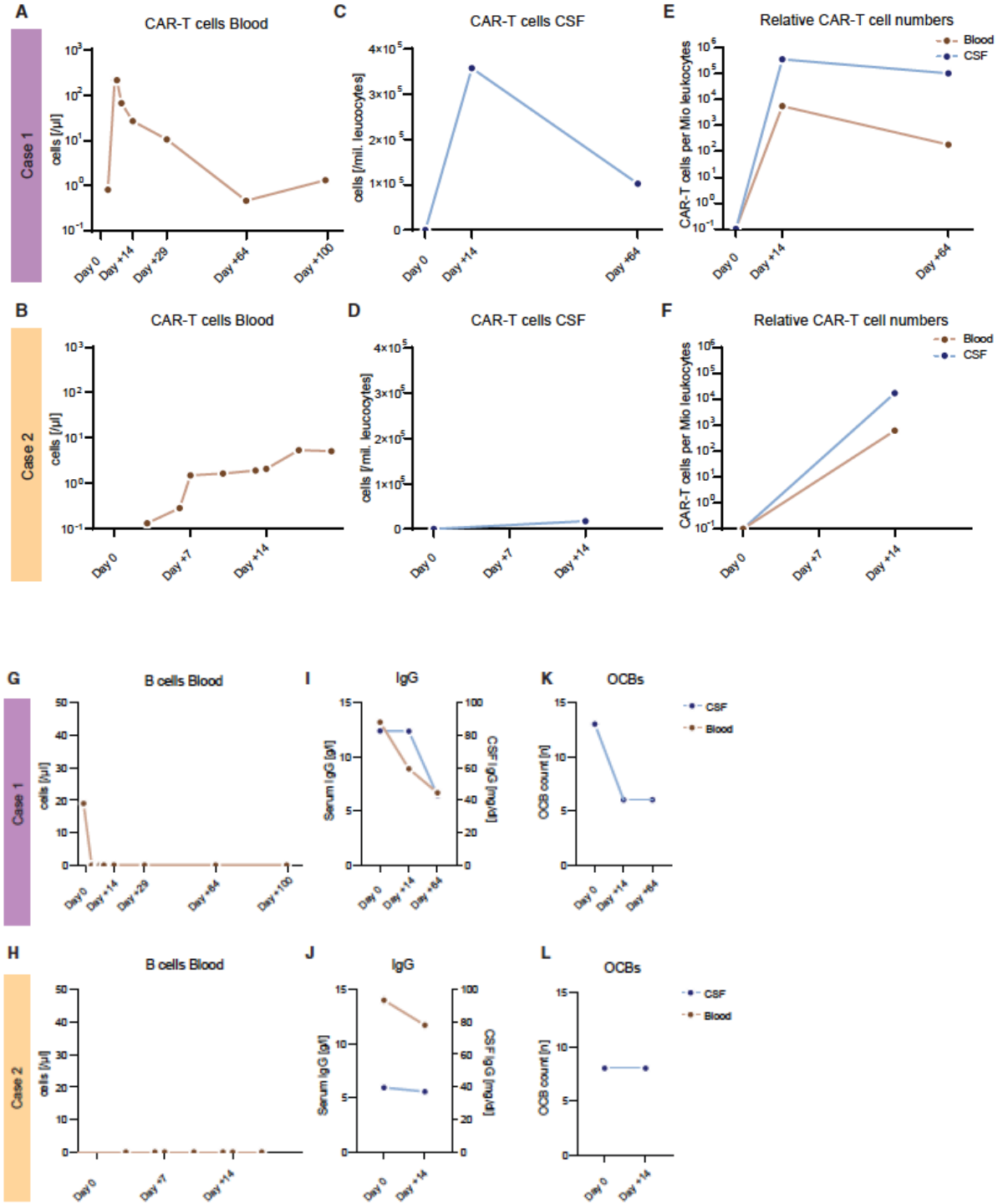


Acceptable safety profile. Only g1 CRS in pt1. No ICANS (5 pts overall).
Uhthoff's phenomenon at fever in pt1, then EBDD stable in 2 pts.

Fischbach et al, Med 2024

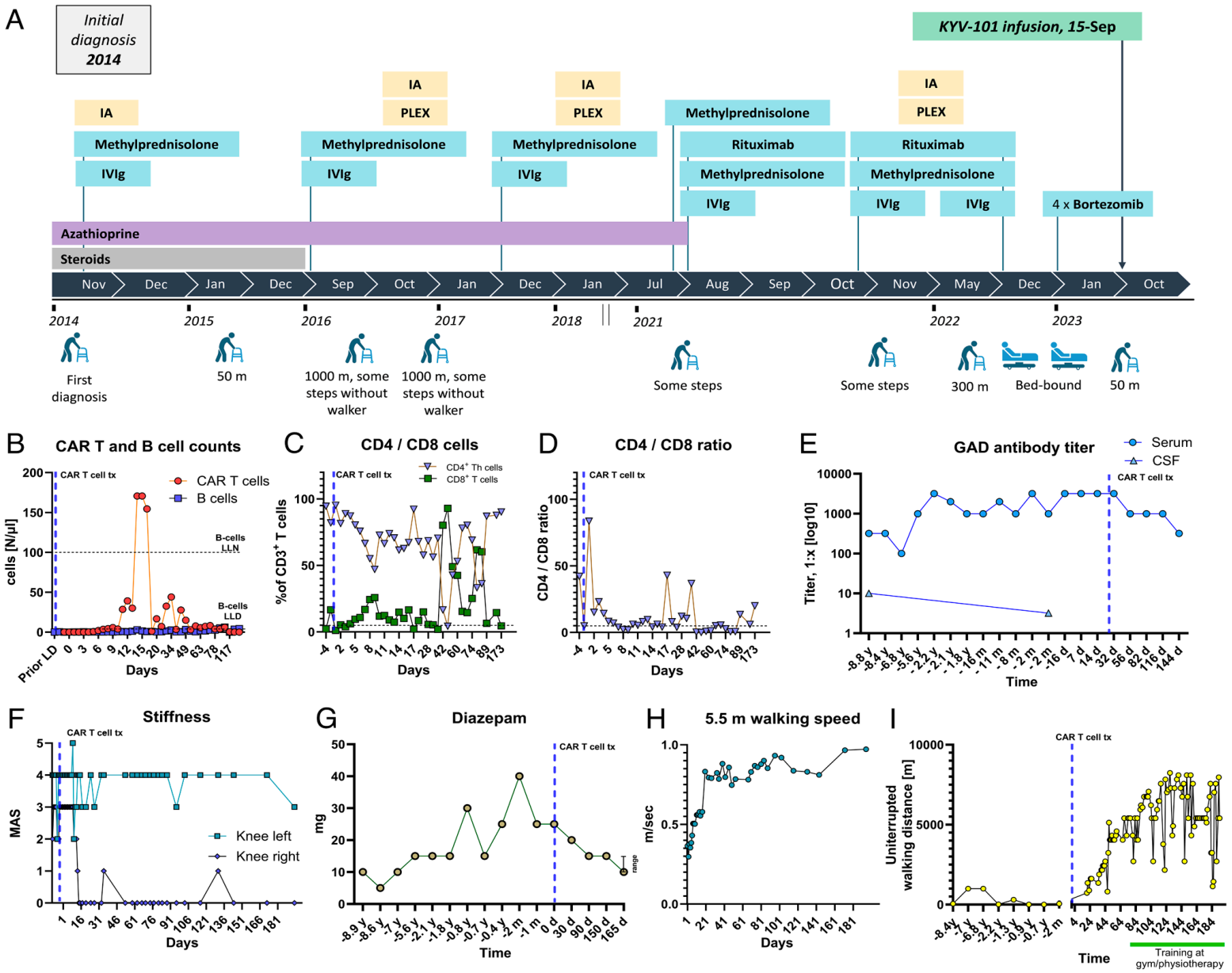
CAR-T cell presence and expansion in CNS & blood

Bcell depletion & IgG reduction



Fischbach et al, Med 2024

CD19 CAR T in severe treatment-refractory Stiff-person Syndrome (SPS)



69y-old female with a 9-y history of treatment-refractory SPS received autologous anti-CD19 CAR T (**KYV-101**).

At 6mo CAR T resulted in reduced leg stiffness, drastic *improvement* in gait, walking speed increase over 100%, and daily walking distance improvement from less than 50 m to over 6 km within 3 mo. GABAergic medication (benzodiazepines) was reduced by 40%.

KYV-101 CAR T cells were *well tolerated* with only low-grade CRS.

Faissner et, PNAS 2024

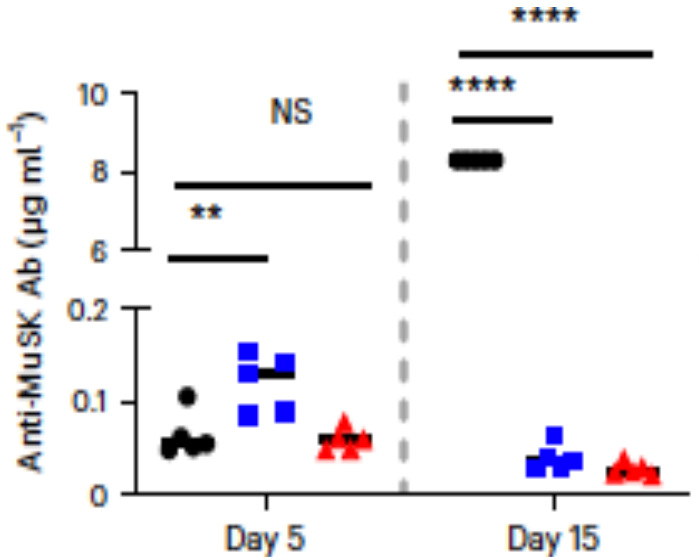
MuSK-CAART in Myasthenia Gravis

Engineered T cells to express a MuSK chimeric autoAb receptor with CD137-CD3ζ signaling domains (**MuSK-CAART**) for precision *targeting of B cells expressing anti-MuSK autoAb*.

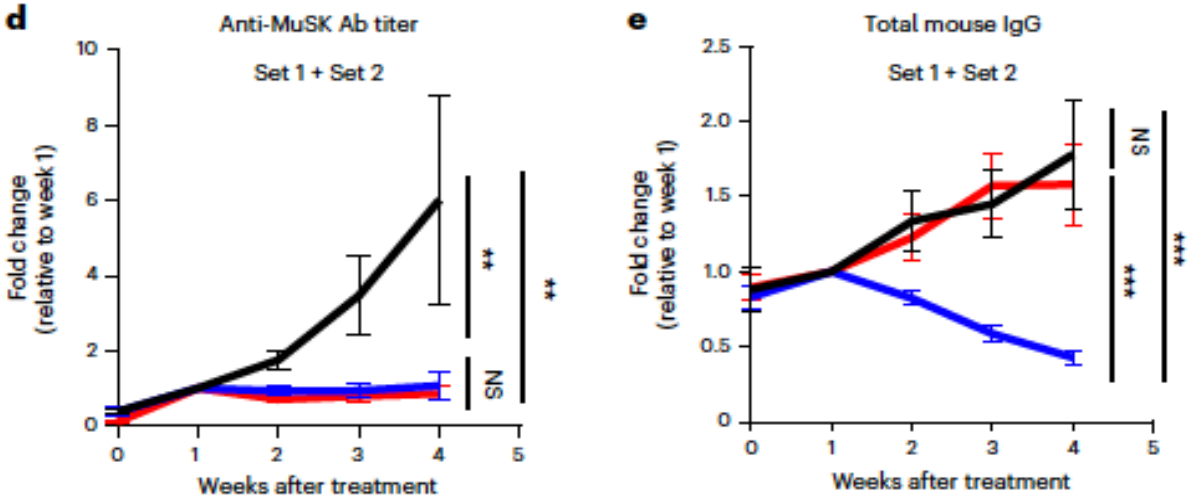
MuSK-CAART demonstrated similar efficacy as anti-CD19 CART for depletion of anti-MuSK B cells.

In an experimental autoimmune MG mouse model, MuSK-CAART reduced anti-MuSK IgG without decreasing B cells or total IgG levels, reflecting MuSK-specific B cell depletion.

No specific off-target interactions.



Anti-MuSK Ab titer in PB on d5 and 15 after target cell injection



MuSK-CAART reduces anti-MuSK IgG but not total IgG or B cell counts.

Oh et al, Nature Biotechnology 2023

Overview on CART cells literature for neurological ADs

Adapted from EBMT Handbook 2024

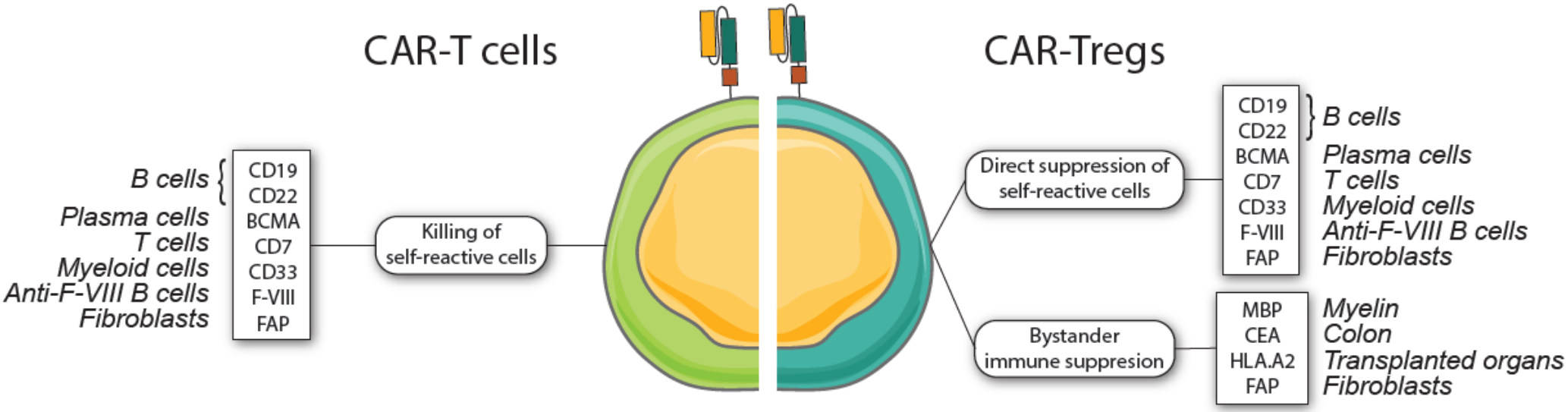
	AD	CAR-T CELL	LYMPHODEPLETION	CRS/ ICANS	OTHER TOXICITIES	DISEASE RESPONSE	FOLLOW UP
Qin et al (2023)	**NMOSD**; 12 pts	BCMA CAR	Flu 30 mg/m2/d i.v and Cy 500 mg/m2/d i.v. . on days -4, -3, -2	CRS g 1-2 (12/12); no ICANS	common hematotox; 58% infections (no g4); 25% CMV	Drug-free and serologic remission (11/12), improvement in disabilities (12/12)	5.5 months
Granit et al (2023)	**MG** (MG-001 trial); 14 pts	BCMA, RNA-based CAR-T (Descartes-08)	None (multiple cell infusions)	No DLT, no CRS, no ICANS	Headache, nausea, vomiting & fever, solved in 24 h	Clinically meaningful decreases on myasthenia gravis severity scales	9 months
Haghikia et al (2023)	**MG**; 1 pt	CD19 CAR-T (KYV-101)	Flu (30 mg/m2 on day –6, –5, –4) , Cy (300 mg/m2 on day –6, –5, –4)	No	G1 transaminitis	Clinical improvement, 70% reduction of Ab	62 days
Haghikia et al (2024)	**MG** (AChR-Ab pos) & RA (ACPA pos); 1 pt	CD19 CAR-T (KYV-101)	Flu (30 mg/m2 from day −5 to −3) , Cy (300 mg/m2 from day −5 to −3)	CRS g1	none	MG: complete disease remission (anti-AChR Ab stable -levels do not always correlate with disease activity); RA also improved (ACPA levels seroconverted).	200 days
Fischbach et al (2024)	**MS** (SP-MS, PP-MS); 2 pts	CD19 CAR-T (KYV-101), CD28 costimulatory domain	Flu (30 mg/m2 on days 5, 4, 3) Cy (300 mg/m2 on days 5, 4, 3)	CRS g1	Uhthoff's phenomenon (pt1), transaminitis G2 (pt1) and G3 (pt2)	Stable EDSS,.Intrathecal Ab production decreased after CAR-T in one patient	100 days
Faissner et (2024)	**SPS** (GAD+); 1 pt	CD19 CAR-T (KYV-101)	Flu (30 mg/m2 on day –6, –5, –4) , Cy (300 mg/m2 on day –6, –5, –4)	CRS g2	Sore throat and cervical LN swelling; 4-fold increases in liver transaminases	Reduced leg stiffness, drastic improvement in gait, walking speed increase over 100%, daily walking distance improvement	6 months

CAR-T regs

Treg-based CAR-T in ADs

Ongoing debate:

? resetting immune-balance (not complete eradication) provides better outcomes?



CAR-Tconvs
- Longer persistence
- Depletion of autoreactive cells
- Cell-to-cell contact
- Limited targets
- Known toxicities

CAR-Tconvs > Immune depletion.

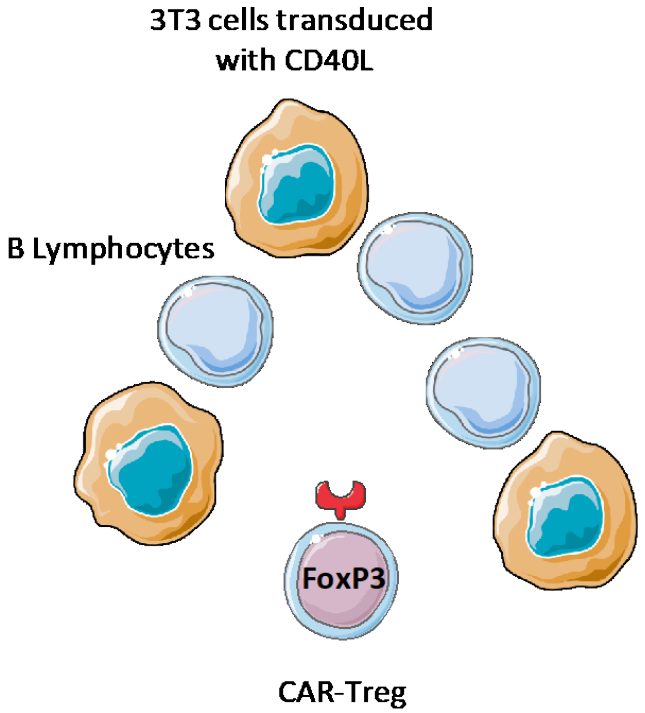
CAR-Tregs
- Short persistence
- Immune regulation
- Multiple suppressive strategies
- Self-antigens
- Safety profile?

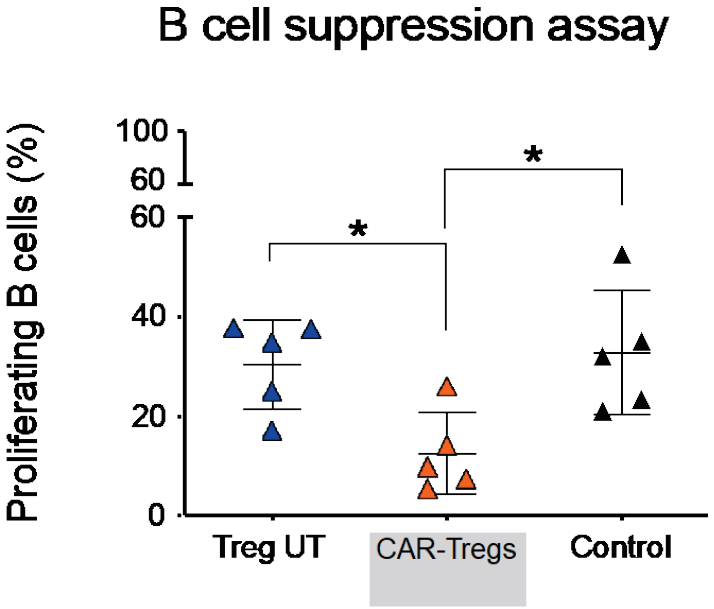
CAR-Tregs > Immune regulation.

Doglio et al, JACI 2022

CAR-Tregs generation: Ag-specific suppression

A platform for the generation of CAR-Tregs, starting from healthy donors' PBMCs, was developed. Isolated CD4+CD25+ Tregs were stimulated with anti-CD3/CD28 beads and cultured in the presence of IL-2 and rapamycin to prevent the expansion of contaminant Tcons.
After the activation, Tregs were transduced with a lentiviral vector encoding for a **second-generation anti-CD19 CAR**.

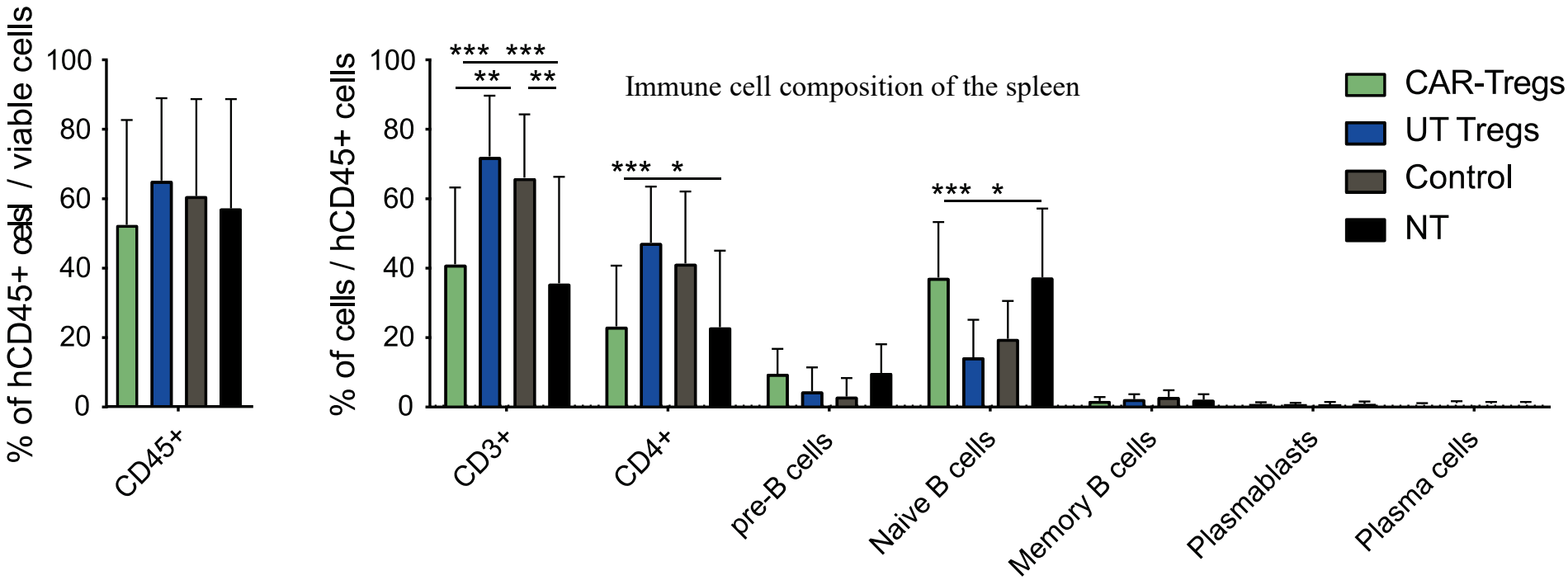




CAR-Tregs could suppress the proliferation of activated B lymphocytes compared to untransduced cells, demonstrating that CAR molecules could *redirect the suppressive capacities of Tregs in an Ag-specific manner*.

Doglio M et al, Nat Comm 2024

CAR-Treg immunomodulation



We analyzed the composition of the spleen in terms of human immune cells at sacrifice. Altered B cell compartment in lupus mice compared to humanized mice without the disease. *Only CAR-Tregs restored the composition of the spleen to normal levels* compared to untransduced Tregs, supporting their immunomodulatory effect already detected in PB.

Doglio M et al, Nat Comm 2024

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Innovative cellular therapies for autoimmune diseases: expert-based position statement and clinical practice recommendations from the EBMT practice harmonization and guidelines committee

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Recommendations for general screening and eligibility before CT

Criterion	EBMT/EHA recommendations (adapted from Hayden et al 2022)	AD-specific recommendations
Performance status	ECOG <2, Karnofsky >60% or Lansky >60%	Same as hematological indications for all CTs (MSC, CART, Tregs) in ADs
Prior treatments, including prior immunosuppressive treatment	Relative contraindication. Any systemic immunosuppressive treatment may impair the efficacy of CART.	Consider balance of active disease, sequelae, damage and the possibility of withdrawing immunosuppressive therapies in the time window required to perform CTs. Specific wash out periods for CART cell process are described.
Infections	Active infection is a contraindication. In most cases, active infection requires only a temporary deferral. Nasopharyngeal PCR for SARS-CoV-2 before CT should be negative. Treatment should be delayed in cases of positive COVID-19 PCR. Some latent infections e.g., HIV, are a contraindication to manufacturing for several (but not all) commercial and trial CART products. When proceeding to CART in cases of latent HBV, HCV or HIV infections, prophylactic anti-viral treatment is required.	Same as hematological indications for all CTs (MSC, CART, Tregs) in ADs
CNS involvement	EBMT recommendations consider risk / benefit ratio. Anticonvulsant prophylaxis is mandatory in CNS involvement when using CART cell approaches.	There is no evidence suggesting substantially increased ICANS risk in AD patients receiving CART cells, however CNS involvement and peripheral neuropathy should be assessed at baseline and individual patient risk has to be considered, especially in CART.
Disease confirmation	Diagnosis should be confirmed using appropriate tests.	Activity, damage and organ involvement should be carefully assessed before CTs in ADs.
Bilirubin **AST/ALT**	<34 mmol/l in trials; higher limit acceptable (<43 mmol/l) with Gilbert's syndrome. <4 ULN a contraindication in some trials.	Specific AD involvement should be ruled out before CTs.
Creatinine clearance	>30 ml/min.	Same as hematological indications for all CTs (MSC, CART, Tregs) in ADs.
Hepatitis B and C	As per national guidelines Serology/molecular testing.	Same as hematological indications for all CTs (MSC, CART, Tregs) in ADs.
HIV	Leukapheresis for some CART cells (e.g., tisagenlecleucel [Kymriah] manufacturing) will not be accepted from patients with a positive test for active HBV, HCV or HIV (SPC).	Same as hematological indications for all CTs (MSC, CART, Tregs) in ADs.
Cardiac function	TTE to assess cardiac function and exclude significant pericardial effusions and structural abnormalities. dLVEF <40% (via 4DEF or Simpson's biplane method) is a relative contraindication. ECG to exclude significant arrhythmias. Cardiac biomarkers (troponin and NT-proBNP) at baseline. CMR to assess extent of disease with cardiac involvement.	Extensive cardiac function assessment is mandatory in AD patients undergoing CTs (MSC, CART, Tregs,).
CNS imaging and lumbar puncture	MRI not required except in those with a history of CNS disease or current neurological symptoms. Lumbar puncture not required except in those with a history of CNS disease or current neurological symptoms	In case of underlying diagnosis of SLE and neurological ADs, a detailed clinical examination, Montreal Cognitive Assessment (MOCA), MRI +/- EEG are strongly recommended.
Fertility	Females of childbearing potential must have a negative serum or urine pregnancy test. Test must be repeated and confirmed negative within 8 days of the CART cell infusion	Same as hematological indications for all CTs (MSC, CART, Tregs) in ADs. Fertility assessment and preservation should be proposed to AD patients before a CT.

Greco R et al, eclin med 2024

Eligibility criteria, specific concerns/contraindications and disease assessments

Rheumatic ADs:

- ❖ SLE
- ❖ SSc
- ❖ Polymyositis
- ❖ Rheumatoid arthritis
- ❖ Sjögren's syndrome

Systemic Lupus Erythematosus	• Age: ≥18 yrs • EULAR-ACR classification criteria 2019[44] • Anti-DsDNA or anti-histone or anti-SM or anti-nucleosome antibody positive • With active disease (defined by not being in remission according to DORIS criteria or in low disease activity state [LLDAS])[45–47] • With at least one active organ system involvement[48] • With one BILAG A score (severe) or more than 2 BILAG B scores (moderate disease activity)[49] and with insufficient response to glucocorticoids and to at least 2 of the following treatments for at least 3 months each: cyclophosphamide, mycophenolate mofetil or its derivatives, belimumab, azathioprine, anifrolumab, methotrexate, rituximab, obinutuzumab, cyclosporin, tacrolimus or voclosporin.	• Life-threatening end-organ damage defined as: - FVC <45% and/or DLCO (corrected for Hb) <30% predicted - LVEF <40% cardiac echocardiography - Pulmonary hypertension: baseline resting systolic PAP >50 mmHg by echocardiography • Active liver disease: AST, ALT> 3 × N • History of malignancy, unless being free of the disease for ≥2 years (except basal or squamous cell carcinoma of the skin; carcinoma in situ of the cervix or breast), mainly for CART[39] • Neutropenia <0.5 × 10^9 ANC/L, Thrombocytopenia: <30 × 10^9 platelet cell count/L, Anemia: Hb < 8 g/dL, Lymphopenia: lymphocyte cell count <100 × 10^9/L • Uncontrolled infection • Unvaccinated against SARS-CoV-2 unless previous exposure • Psychological, sociological or geographical conditions precluding compliance	• Autologous MSC intrinsic abnormalities • Allogeneic cells triggering immunization when injected repeatedly • Fertility preservation • Lymphopenia may inhibit feasibility for CART production • Pre-existing irreversible kidney damage
Systemic Sclerosis	• Age: ≥18 yrs • SSc according to ACR/EULAR 2103 criteria[50] • Disease duration ≤5 yrs and i) mRSS of >20 and (ESR >25 mm and/or Hb < 11 g/dL), or ii) mRSS >15 and ≥1 major organ involvement: - Lung: DLCO and/or FVC <80% + interstitial lung disease (chest X-ray and/or HRCT scan); - Kidney: past renal crisis and/or stage 2 or 3 chronic kidney disease (Crcl: 30–89 ml/min); - Heart: reversible congestive heart failure, atrial or ventricular rhythm disturbances and/or mild to moderate pericardial effusion. • Insufficient response to at least two of the following mycophenolic acid, methotrexate, tocilizumab, rituximab, nintedanib, methotrexate, cyclophosphamide for a minimum of 3 months, and Contraindication, inadequate response or unwillingness to undergo AHCT (determined by patient and physician judgement)	• As above	• As above • Pre-existing excessive and irreversible fibrotic damage • Autologous MSC intrinsic abnormalities • Allogeneic cells triggering immunization when injected repeatedly • Fertility preservation
Rheumatoid Arthritis	• Age: ≥18 yrs	• As above	• Presence of "activity" based on non-inflammatory domains • Autologous MSC intrinsic abnormalities • Allogeneic cells triggering immunization when injected repeatedly • Fertility preservation • Lymphopenia may inhibit feasibility for CART production
Sjögren's syndrome	• Age: ≥18 yrs • Sjögren's syndrome according to 2016 ACR/EULAR) with–persistent high activity defined by EULAR ESSDAI >5[52] - Presence of extra-glandular domains such as vasculitis, or hematologic, lung, kidney and neuronal involvement - Serological activity defined as hypocomplementemia or elevated CRP/eESR/IgG/RF level (excluding acute or chronic infection and other factors). - Poor response to previous treatments with glucocorticoids and at least 2 of the following drugs: cydophosphamide, azathioprine, MMF, methotrexate, rituximab or belimumab.	• As above	• Autologous MSC intrinsic abnormalities • Allogeneic cells triggering immunization when injected repeatedly • Fertility preservation • Lymphopenia may inhibit feasibility for CART production • Pre-existing irreversible damage • Consider risk of concomitant lymphoma
Polymyositis	• Age: ≥18 yrs • Idiopathic Inflammatory Myopathy (IIM) according to EULAR/ACR criteria[53] • Active myositis on MRI or biopsy, with or without the presence of interstitial lung disease • In case of amyositic disease course, presence of interstitial lung disease (ILD) involvement is mandatory • Presence of myositis specific autoantibodies • Incomplete response to high doses of glucocorticoids combined with at least 2 of the following treatments: iv IGs, methotrexate, azathioprine, cyclophosphamide, tacrolimus, JAK inhibitors or rituximab.		• Challenge of rapid progressive disease especially in ILD • Consider risk of concomitant cancer • Autologous MSC intrinsic abnormalities • Allogeneic cells triggering immunization when injected repeatedly • Fertility preservation • Lymphopenia may inhibit feasibility for CART production

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Eligibility criteria, specific concerns/contraindications and disease assessments

Rheumatic ADs:

- SLE
- SSc
- Polymyositis
- Rheumatoid arthritis
- Sjögren's syndrome

Neurological ADs:

- MS
- NMOSD
- MG
- CIDP

Type of disease	Indications	Contraindications	Concerns
MS	CART: ▪ RRMS–Active disease despite the use of highly active DMTs (or patients who cannot receive autologous HCT because of co-morbidities) ▪ PPMS–Treatment option for patients with clinical or radiological evidence of inflammation ▪ Contraindication, inadequate response or unwillingness to undergo autologous HCT (determined by patient and physician judgement). MSC: ▪ Progressive MS ▪ Contraindication, inadequate response or unwillingness to undergo autologous HCT (determined by patient and physician judgement).	Stable disease (adequately treated or unrated)	Potential central or peripheral nervous system toxicity mainly with BCMA CART, although such AEs have not been seen in CAR-T trials for MG and NMOSD.[36,37] Prophylactic use of anticonvulsant is mandatory in CART.
NMOSD	CART: ▪ AQP4+ disease failing at least one biological treatment	Stable disease	
MG	CART: ▪ Ab + disease refractory to second line treatment	Stable disease	
CIDP	CART: ▪ Disease refractory to conventional treatments	Stable disease	

Greco R et al, eclin med 2024

Recommendations on washout period before CT, leukapheresis, LD specifically for ADs

Type of therapy	Specific recommendations in ADs	Comments
Steroids	may be administered at dosages ≤10 mg/d prednisone (or equivalent), by 7 days before leukapheresis and before LD; after leukapheresis and before LD, steroids may be administered at higher doses as needed for bridging therapy.	Depending on the patient's clinical picture; topic/inhaled steroids permitted.
Hydroxychloroquine	no specific need for a washout period	Individualized decision
Mycophenolate Mofetil, Azathioprine, Calcineurin inhibitors, mTOR inhibitors JAK inhibitors	discontinued at least 2 weeks before leukapheresis	Tapering can be considered based on individual disease
Dimethyl fumarate, Fingolimod	discontinued at least 6 weeks before leukapheresis	
Bortezomib/Proteasome inhibitors§	discontinued at least 3 weeks before leukapheresis	
Cladribine	discontinued at least 6 months before leukapheresis	try to avoid if T cell therapy is planned
Cyclophosphamide Methotrexate	discontinued at least 3 weeks before leukapheresis	the washout period is recommended to ensure T-cell activity at time of collection and to reduce potential toxicity for patients
Belimumab, B cell targeting antibodies (e.g. anti CD20)	discontinued at least 1 week before leukapheresis	irrelevant for T cell apheresis and CART production;
Anti-cytokine antibodies Natalizumab (humanized anti α4-integrin)	discontinued at least 1 month before leukapheresis discontinued at least 6 weeks before leukapheresis	the washout period is recommended to reduce toxicity (ie. infections, such as PML) for patients and impact on B-cell, while preserving disease control, especially for CART
Alemtuzumab (anti CD52 mAb) Daratumumab (anti-CD38 mAb)§ ATG§	discontinued at least 6 weeks before leukapheresis	try to avoid anti T cell directed antibody therapy (CD52, ATG, CD38) if B cell targeted CART is considered as next treatment

Greco R et al, eclin med 2024

Recommendations on supportive care, management of short/medium term complications and long-term follow-up

	EBMT/EHA recommendations (adapted from Hayden et al 2022, Rejeski/Subklewe et al 2023)	Specific recommendations in ADs
pRBC/ platelet transfusions in CART	As per institutional standards, based on patient risk profile For pRBC: consider using 1 product per time to reduce iron overload Irradiation of blood products; Start 7 days prior to leukapheresis until at least 90 days post CAR-T	As for hematological patients; monitoring of blood counts is mandatory in ADs (e.g. at every visit and as clinically indicated, including long-term follow up to evaluate risk of ICAHT).
G-CSF in CART	Prophylactic G-CSF: On day +2 in patients with a high-risk profile for ICAHT (e.g. high CAR-HEMATOTOX score and risk profile) In patients at low risk for ICAHT, G-CSF not necessary Reduced risk of febrile neutropenia (without increasing the risk of severe, or grade ≥3, CRS nor ICANS). No detrimental effect on CART expansion kinetics or treatment outcomes	The CAR-HEMATOTOX score is not validated in ADs. With only few patients reported so far, no prolonged hematotoxicity has occurred in AD. Administration of G-CSF may induce disease flare in ADs. Prophylactic use of G-CSF is not recommended.
	Therapeutic G-CSF: Severe neutropenia (ANC <500/mcl) neutropenia with or without infectious complications Patients with intermittent neutrophil recovery often rapidly respond to G-CSF stimulation, while aplastic patients are often G-CSF unresponsive	HLH can be causally related to underlying ADs and should be considered as differential diagnosis in case of prolonged cytopenia. In case of prolonged grade 3-4 neutropenia, the use of G-CSF should be considered according to the risk/benefit evaluation and EBMT guidelines. Use of G-CSF may potentially favour an AD flare.
WBC, biochemistry panel, AST, ALT, bilirubin, LDH, fibrinogen, CRP	Standard follow-up At every visit and as clinically indicated	As hematological patients.
CMV, EBV, adenovirus, COVID-19	Viral reactivation/infection (post-allogeneic HCT) As clinically indicated	As hematological patients; quarterly evaluation at least during the first year after CT, in consideration of past immunosuppression. MDT evaluation recommended.
Endocrine function and other standard late effects testing appropriate to age	Standard follow-up Yearly or as clinically indicated	As hematological patients. The occurrence of secondary ADs should be investigated.

Greco R et al, eclin med 2024

Recommendations on supportive care, management of short/medium term complications and long-term follow-up

	EBMT/EHA recommendations (adapted from Hayden et al 2022, Rejeski/Subklewe et al 2023)	Specific recommendations in ADs
Antibacterial prophylaxis	In patients with a low risk for ICAHT, not recommended. In patients with a high-risk profile for ICAHT, prophylaxis may be considered once ANC <500/mcl. As per institutional standards (e.g. levofloxacin or ciprofloxacin). Look at local bacterial epidemiology. Warning in case of colonization by MDR pathogens.	As hematological patients Pre-exisiting humoral immune responses appear to be only marginal impacted by CD19 CART in SLE patients, but probably reduced more dramatically following BCMA CART. The risk of infection depends on the AD and degree of immunosuppression, and management should be carefully discussed upfront by a multidisciplinary team meeting (disease specialist, infection-disease specialist, hematologists and CART experts). A follow-up of potential infectious complications should be considered mandatory. Sufficiently long anti-viral and antibacterial prophylaxis should be maintained according to patient individual risk and in line with institutional guidelines and current EBMT guidelines.
Anti-viral	All patients Start from LD conditioning until 1-year post-CART infusion AND/OR until CD4+ count > 0.2 × 10^9/l Valaciclovir 500 mg bid or aciclovir 800 mg bid	
Anti-pneumocystis	All patients To start from LD conditioning until 1-year post-CART infusion AND/OR until $CD4^+$ count >0.2 x 10^9/l Co-trimoxazole 480 mg once daily or 960 mg three times each week In case of co-trimoxazole allergy, pentamidine inhalation (300 mg once every month) are recommended, dapsone 100 mg daily or atovaquone 1500 mg once daily can be considered	
Systemic primary anti-fungal prophylaxis	Anti-fungal prophylaxis should be considered in severe neutropenia (ANC <500/ mcl) with a high-risk profile for ICAHT (e.g. CAR HEMATOTOX score and risk profile) and/or prolonged neutropenia Mold-active prophylaxis for 1-3 months (depending on the duration of neutropenia and use of steroids): posaconazole (300 mg/day) or micafungin (50 mg i.v./day) In patients with prior allogeneic HCT, prior invasive aspergillosis and those receiving corticosteroids after CAR- T cells (long-term >72 h, or high dose), prophylaxis is recommended	As for hematological patients. The risk of infection may depend on the AD and degree and duration of immunosuppression before CTs. Management should be carefully discussed upfront by a multidisciplinary team meeting (disease specialist, infection-disease specialist, hematologists and CART experts). A follow-up of potential infectious complications should be considered mandatory.
Quantitative Ig	Consider i.v. (or s.c.) immunoglobulin replacement Consider in adults with serious/ recurrent infections with encapsulated organisms and hypogammaglobulinemia (<4 g/l)	As hematological patients; consider to replace immunoglobulins in case of hypogammaglobulinemia (<4 g/l) in AD patients, due to the risk of recurrent infections. Quarterly MDT evaluation is recommended.

Greco R et al, eclin med 2024

Recommendations on supportive care, management of short/medium term complications and long-term follow-up

	EBMT/EHA recommendations (adapted from Hayden et al 2022, Rejeski/Subklewe et al 2023)	Specific recommendations in ADs
Vaccine strategy in CART	*Influenza vaccine* Pre-CART: preferably vaccinate 2 weeks before LD. In B-cell aplasia low likelihood of serological response. Post-CART: >3 months after CART patients should be vaccinated irrespective of immunological reconstitution. Comments: where there is incomplete immune reconstitution or ongoing immunosuppression, there is a high likelihood of lower vaccine responses. Consensus view is that vaccination may still be beneficial to reduce rates of infection and improve clinical course. Consider boost upon B-cell recovery. *SARS-CoV-2* Pre-CART: Preferably vaccinate before CART; in B-cell aplasia low likelihood of serological response. Post-CART: >3 months after CART infusion. Comments: Limited data is available on vaccine response after CART, and early reports suggest impaired serological responses in patients treated for haematological malignancies. SARS-CoV-2 vaccine-induced protection relies heavily on T-cell-mediated immunity, therefore B-cell aplasia does not seem to be a contraindication; no T-cell threshold has been defined. Postvaccination response monitoring is desirable. Guidance on re-vaccination post- CART and frequency/dosing of booster vaccines will vary between countries. National guidelines should be followed in this area of rapidly evolving clinical practice. *Killed/inactivated vaccines* Post-CART: >6 months after CART and >2 months after immunoglobulin replacement. Comments: Contraindications include concurrent immunosuppressive or cytotoxic therapy. *Live and non-live adjuvant vaccines* Post-CART: 1 year after CAR-T and fully immune reconstituted, defined as absolute CD4 T cells >0.2 x 10^9/l, CD19 or CD20 positive B cells >0.2 x 10^9/l, no concomitant immunosuppressive or cytotoxic therapy. Comments: contraindications include, <8 months after completion of immunoglobulin replacement.	Vaccinations status should be assessed and updated before LD. Vaccination is a balance between reducing the risk of infection but comes with a theoretical risk of triggering immune events, which is a concern in the setting of ADs. Measurements of specific antibody titers may be helpful in deciding whether to vaccinate or not. Recently, ADWP has also provided specific COVID-19 vaccine recommendations in patients with ADs. Vaccination after CART therapy is effective and risk consideration should guide the decision to vaccinate before the procedure. In AD patients, as per hematological patients, re-vaccinations can be started from >3 months after CART therapy in fully immune reconstituted, defined as absolute CD4 T cells >0.2 x10^9/l, CD19 or CD20 positive B cells >0.2 x 10^9/l, no concomitant immunosuppressive or cytotoxic therapy in line with EBMT guidelines. Vaccinations before full immune reconstitution can be effective and must be based on an individualized risk-assessment. Live vaccines are contraindicated in AD patients.

Recommendations on follow-up

	EBMT/EHA recommendations (adapted from Hayden et al 2022, Rejeski/Subklewe et al 2023)	Specific recommendations in ADs
CRS, ICANS and ICAHT in CART	To be monitored and managed according to EBMT/EHA guidelines.	As hematological patients. The early and prompt treatment of these complications is highly recommended in AD setting. Anticonvulsive prophylaxis according to institutional guidelines; mandatory in case of CNS involvement. Higher-grade toxicities were not observed in the patients with ADs already treated with CART. MDT clinical monitoring of AD patients after CART is strongly recommended.

- For hospitalization and distance to the accredited treating center, we refer to current EBMT guidelines for CT and ideally up to 14 days for AD patients without severe reactions. Patients should be located within 60 min of the center with the continuous presence of a caregiver educated to identify the potential complications maintained for a year. Given the intrinsic frailty of AD patients, related to both the underlying disease and prolonged immunosuppressive treatments, a case by case evaluation is recommended by MDT.

- Due to the complexity of the treatment in combination with the underlying AD, we recommend a joint follow-up period in a multidisciplinary team composed of disease specialist and a CART expert (hematologist) for at least 6 months after which, individual decisions can be made.

- Hematologists should be continued to be involved in monitoring of side effects according to EBMT handbook recommendations with a quarterly MDT assessments during the first year, and yearly thereafter with data collection and reporting in the EBMT registry.

Greco R et al, eclin med 2024

Conclusions

CONCLUSION.
CAR-T in ADs

- New insights are emerging in the complexity and power of innovative cellular therapies.
- Different types of **cellular therapies**, including **CAR T cells**, have been developed to **restore immunologic self-tolerance** in AD patients.
- CAR-T cell use in ADs requires:

  - a **careful selection of patients**
  - a consideration of therapeutic alternatives, with **risks and benefits**
  - the **centre expertise & MDT**

- Preliminary experiences with CART cells >> **B-cell depletion** and cotargeting of **plasmablasts** with CD19-targeting CAR T cells deeply **resets B-cell immunity.**
- Initial trials suggest a **rapid AD response** to CART therapy, leading to impressive drug-free remission in patients refractory to standard therapies. These findings show that the generation and administration of CART in AD is **feasible and safe**.
- **Extended follow-up** is needed to determine long-term efficacy and safety.

EBMT Autoimmune Diseases Working Party (ADWP)

"Cross fertilization of specialities"

THANKS to all the members and the staff of the ADWP, patients and their families!

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Thanks!