CAR-T oltre i confini dell'oncologia: la terapia cellulare nelle malattie autoimmuni

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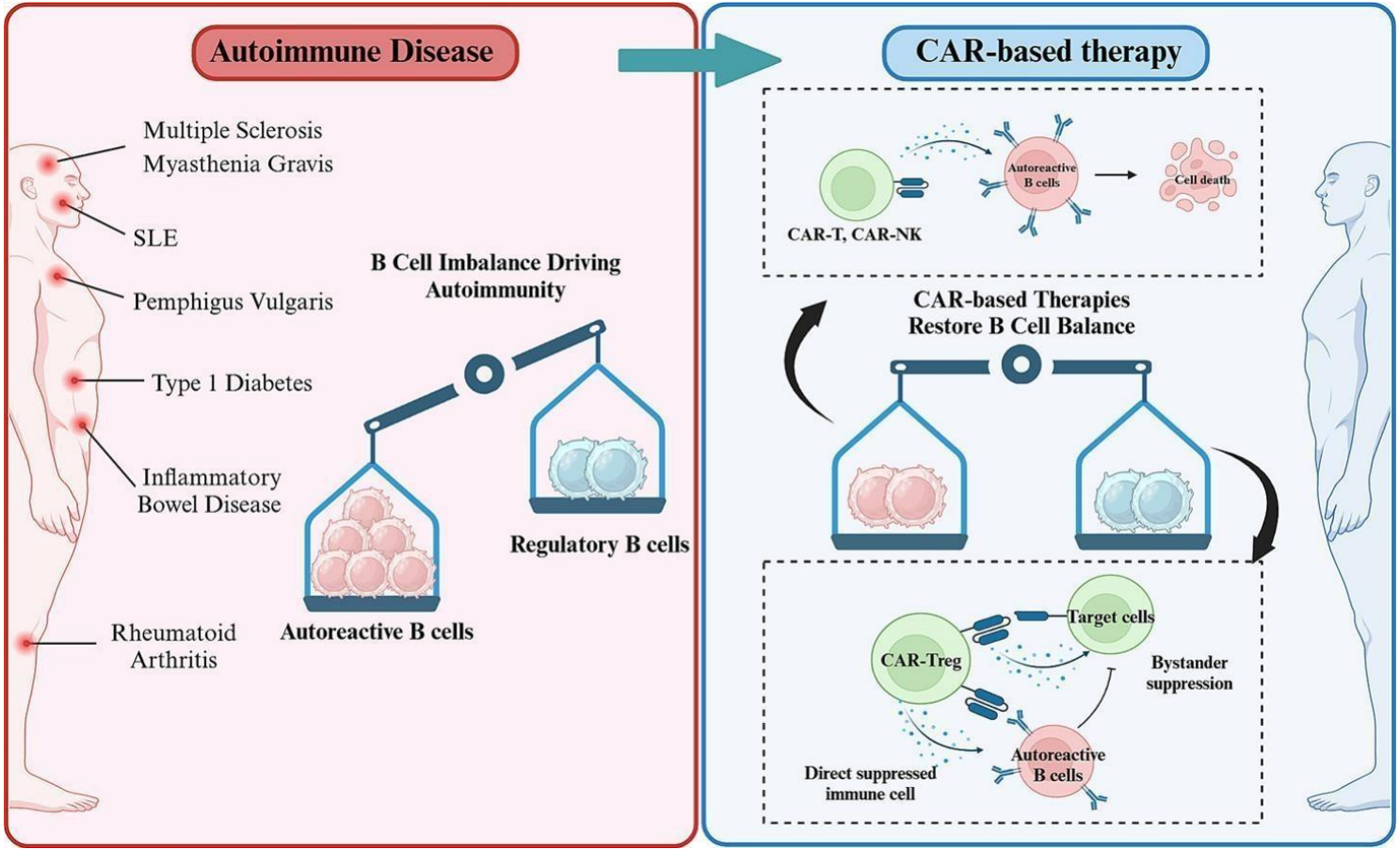
CONGRESSO NAZIONALE AIEOP
ROMA, 22-24 Settembre 2025
CENTRO CONGRESSI
UNIVERSITÀ CATTOLICA
DEL SACRO CUORE

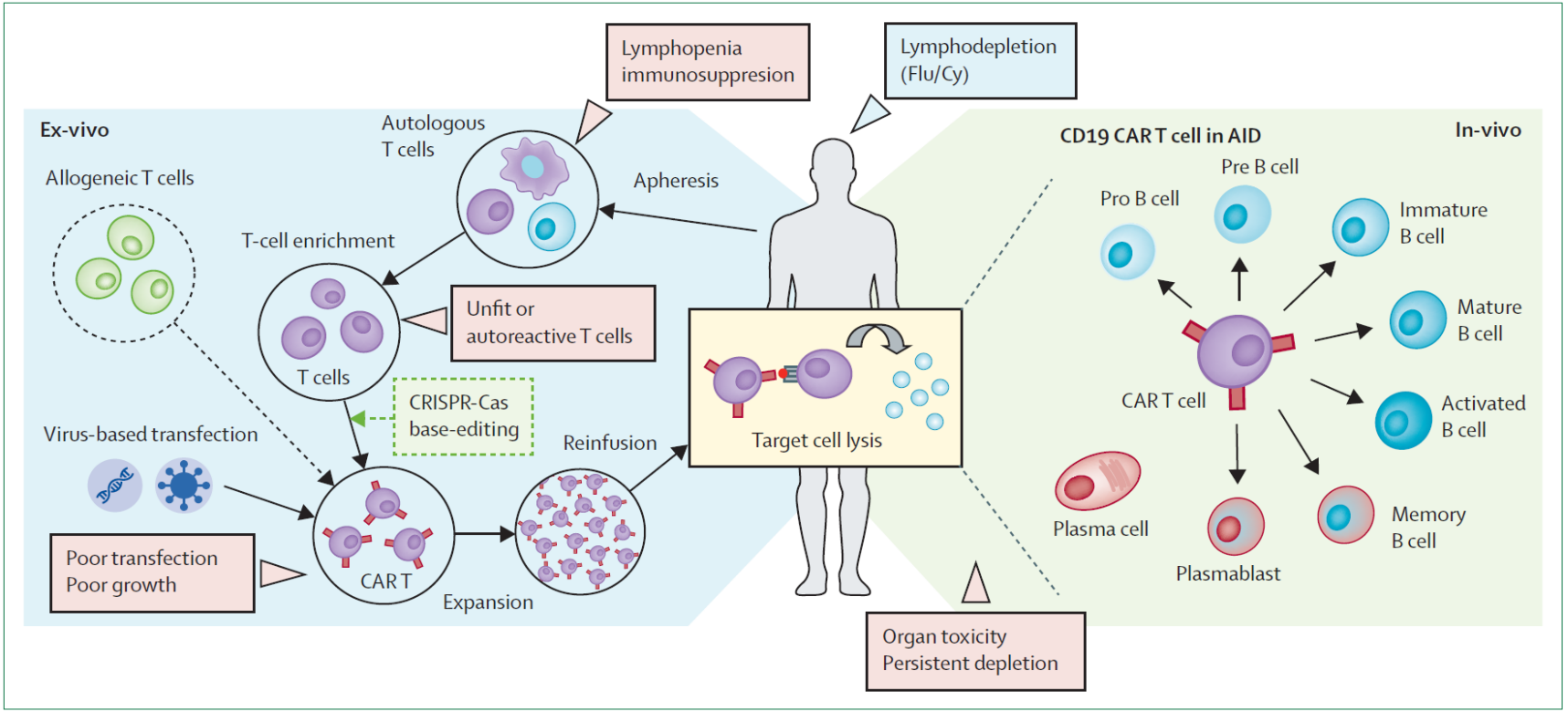
Disclosures of Franco Locatelli

Name of Company	Research Support	Employee	Consultant	Stockholder	Speaker's Bureau	Advisory Board	Other
Miltenyi					X		
Amgen					X	X	
Novartis					X	X	
BMS					X		
GILEAD					X		
Sanofi						X	
SOBI					X		
Vertex						X	



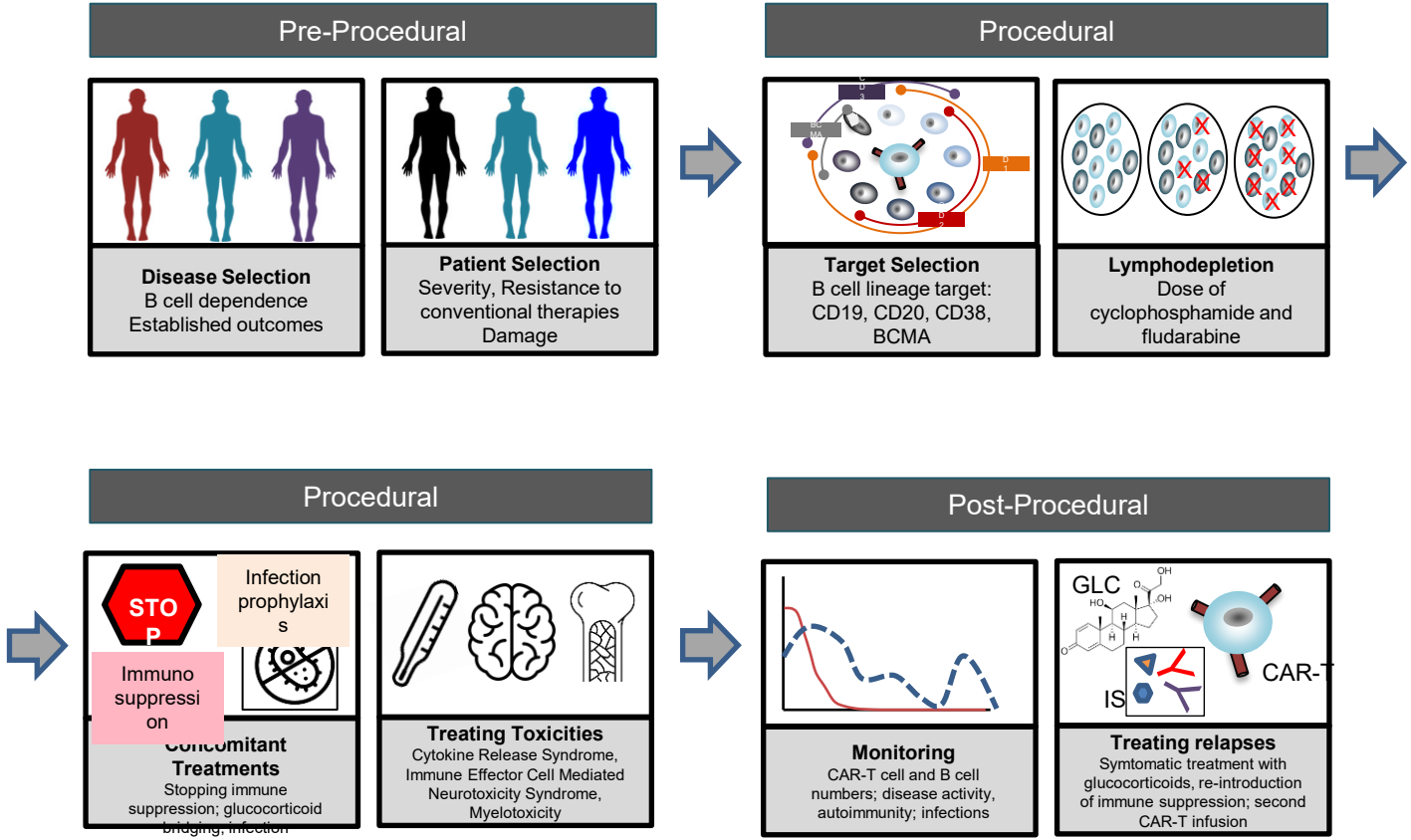
Wen R et al.
Autoimmun Rev 2025

CAR T cells in B-cell mediated Autoimmune Diseases



Schett G et al. Lancet 2023

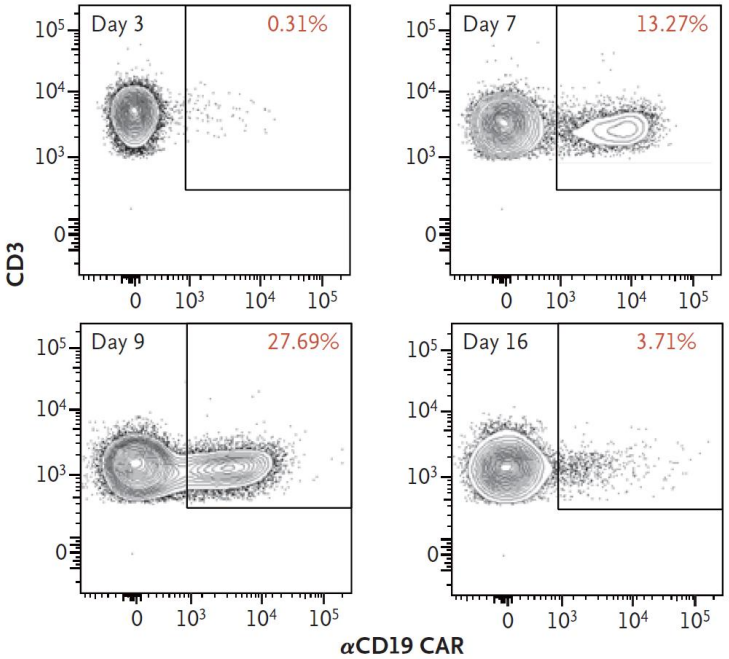
Advancements and challenges in CAR T cell therapy in autoimmune diseases

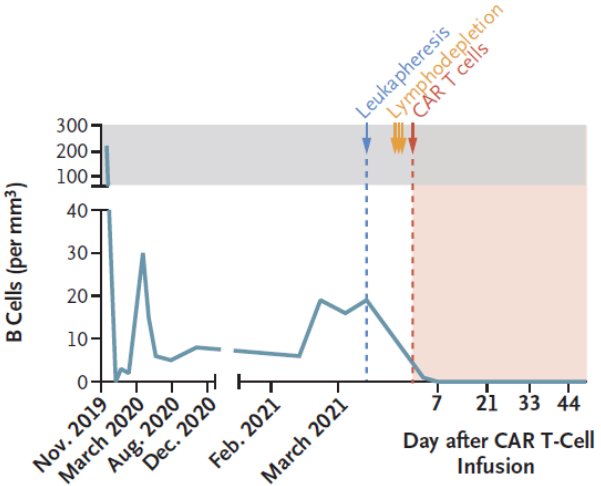


Georg Schett[1,2] ✉, Fabian Müller[2,3], Jule Taubmann[1,2], Andreas Mackensen[2,3], Wei Wang[4], Rich A. Furie[5], Ralf Gold[6], Aiden Haghikia[7], Peter A. Merkel[8,9], Roberto Caricchio[10], Maria-Antonietta D'Agostino[11], Franco Locatelli[12], Carl H. June[13] & Dimitrios Mougiakakos[14,15]

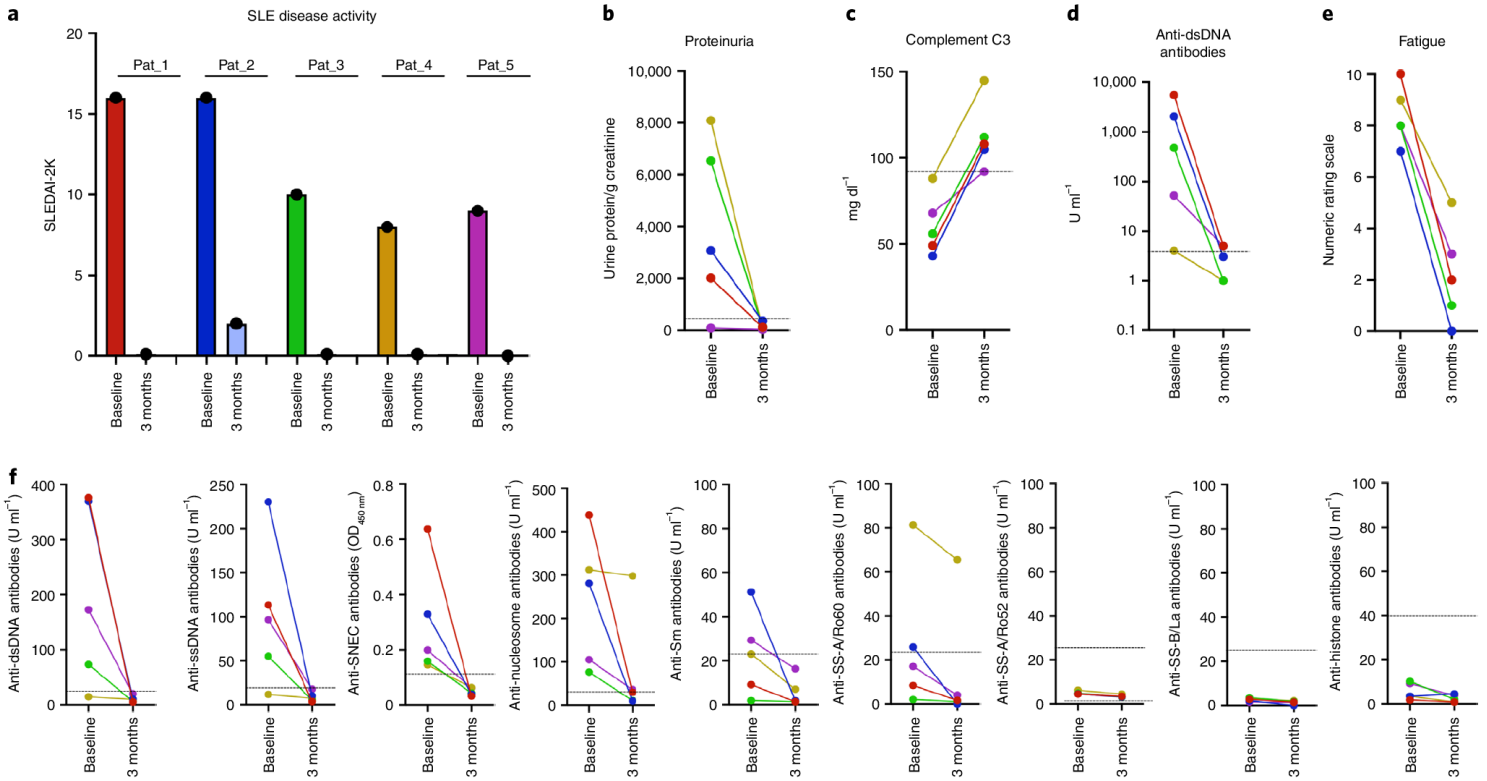
Nature Reviews Rheumatology | Volume 20 | September 2024 | 531–544

CD19-Targeted CAR T Cells in Refractory Systemic Lupus Erythematosus





Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus

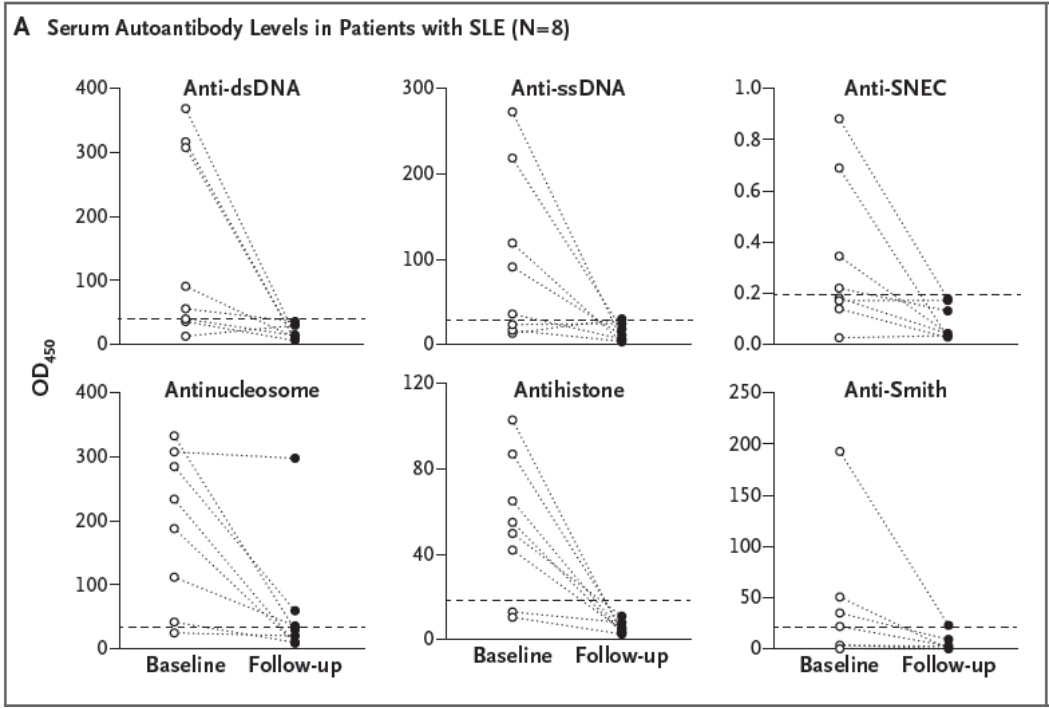


The NEW ENGLAND JOURNAL of MEDICINE

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.



N Engl J Med 390;8 February 22, 2024

nature reviews rheumatology

https://doi.org/10.1038/s41584-025-01272-3

Perspective

Check for updates

CAR T cell therapy for children with rheumatic disease: the time is now

Holly Wobma[1], Stacy P. Ardoin[2,3], Challice L. Bonifant[4], Jennifer C. Cooper[5], Hanna Kim[6], Rebecca E. Sadun[7], Laura Lewandowski[8], Michael Keller[9,10], Robert A. Colbert[11], Cuoghi Edens[12], Kimberly DeQuattro[13], Kyla Driest[2,3], Julia Shalen[14], Ivana Stojkic[2,3], Andrea Knight[15], Colleen Annesley[16,17], Kathryn S. Torok[18], Caitlin W. Elgarten[19], Toshihiro Onishi[20], Shaun W. Jackson[21,22], Susan Prockop[23], Nirali N. Shah[24], Kaveh Ardalan[25,36] & Margaret Lamb[26,36] ✉ on behalf of the Integrated Multidisciplinary Paediatric Autoimmunity and Cell Therapy (IMPACT) working group**

Characteristics of patients

Patient	#1	#2	#3	#4	#5
Age	17	12	17	13	5
Sex	F	M	F	F	F
Ethnicity	White	White	White	White	White
Disease	pSLE†	JDM*	pSLE†	JDM*	JDM*§
Duration	3 years and 6 months	6 years	4 months	5 years	1 year/9 months
	Immunological features				
Autoantibodies	ANA dsDNA	ANA No MSA/MAA	ANA dsDNA DAT	None at screening (anti-NXP2 at onset)	neg
Complement levels	low	-	low	-	-
	Organ involvement				
Skin	Malar rash	Severe diffuse rash, ulcerations	Malar rash, alopecia	Typical rash, ulcerations, microcirculatory abnormalities	Ulcerations Microcirculatory abnormalities (livedo reticularis), malar rash
Joints/muscles	Arthritis	Diffuse myositis	Arthritis	Myositis	Myositis
Kidney	Class II/V LN	-	Class V LN, Tubulointerstitial nephritis	-	-
Lung	ILD/PAH	-	ILD/DAH	-	ILD
Heart	-	-	-	-	-
Serositis	+	-	+	-	-
Hematology	Thrombocytopenia, AIHA	-	Thrombocytopenia, AIHA	-	-
Others	-	Calcinosis universalis	Optical neuritis	Calcinosis universalis	Calcinosis (elbows)
Score	SLEDAI-2k=22	mDAS=8 sDAS=9	SLEDAI-2k=38	mDAS=8 sDAS=9	mDAS=9 sDAS=5

According to 2019† and 2017* EULAR/ACR criteria

§ Mosaicism trisomy 21

cSLE: childhood Systemic Lupus Erythematosus
JDM: Juvenile dermatomyositis

F: female; M: male;
LN: lupus nephritis;
ILD: interstitial lung disease;
PAH: pulmonary hypertension;
DAH: diffuse alveolar hemorrhage; AIHA: autoimmune hemolytic anemia.

Previous immunosuppressive therapy

	#1	#2	#3	#4	#5
Glucocorticoids	+	+	+	+	+
HCQ	+	+	+	+	+
Azathioprine	+	-	-	-	-
Mycophenolate mofetil	+	+	+	+	+
Rituximab	+	+	-	+	+
Belimumab	+	-	-	-	-
JAK inhibitors	-	-	-	+	-
Methotrexate	-	+	-	+	+
CNI inhibitors	-	+	-	+	+
CYC	+	+	+	-	-
IVIGs	+	+	+	+	+
Plasmapheresis	-	+	+	+	+
Others	-	-	-	Infliximab	Anakinra

Median previous lines

9 (range: 6-10)

Zorpocabtagene-autoleucel

T cells transduced with a **second-generation (4.1BB) CD19-directed CAR** (Miltenyi®)

Lentiviral vector

Single infusion of **fresh-to-fresh**, **autologous**, anti-CD19 CAR T product manufactured on the CliniMACS Prodigy device

Lymphodepletion:

- Cyclophosphamide 500 mg/sqm/day (D-4/-3)
- Fludarabine 30 mg/sqm/day (D-5/-4/-3)

CD19-CAR T-cell dose: **1 x 10^6 CAR T cells/kg**

Patient identification

Screening before apheresis

Autologous PBMCs collection (fresh)

DAYS 0-2 CD4/CD8 enrichment and cell activation(Transact)

DAY 2 Transduction of activated CD3 cells

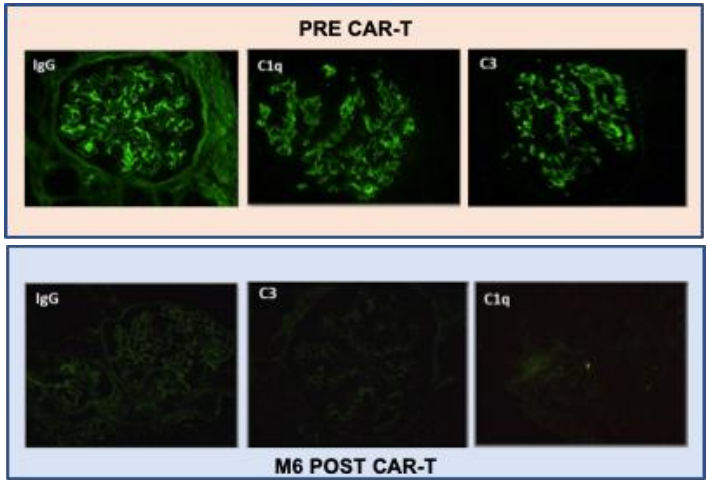
DAYS 2-12 Expansion

Filling for infusion

Immunosuppressive therapy was discontinued before the CAR T-cell infusion

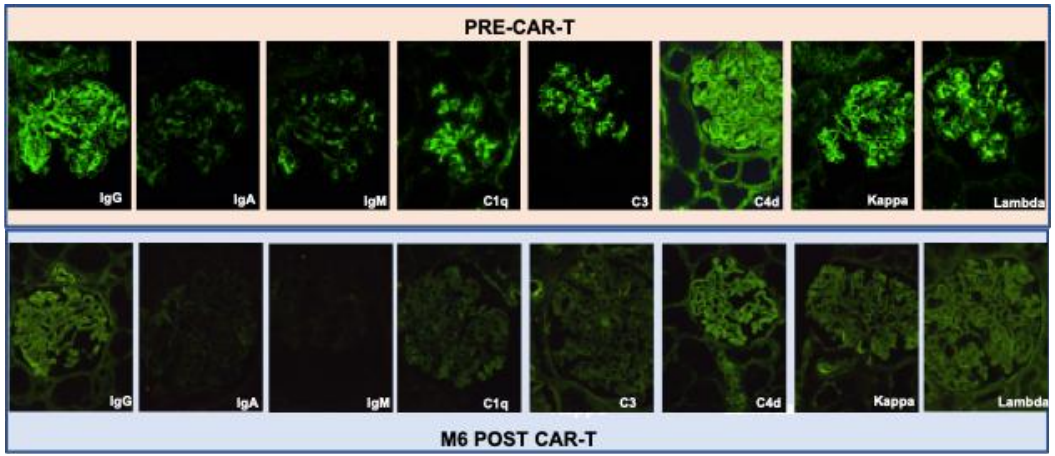
Efficacy – Lupus Nephritis

(Pt #1)



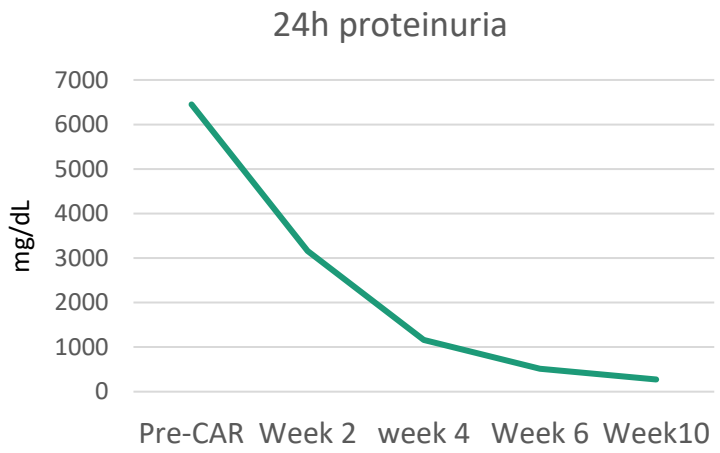
De Benedetti F, Diomedi Camassei F, Locatelli F.
N Engl J Med. 2024.

(Pt #3)



Unpublished. Please, do not post.

Outcome of the 2° patient with SLE (currently 19 months after infusion)

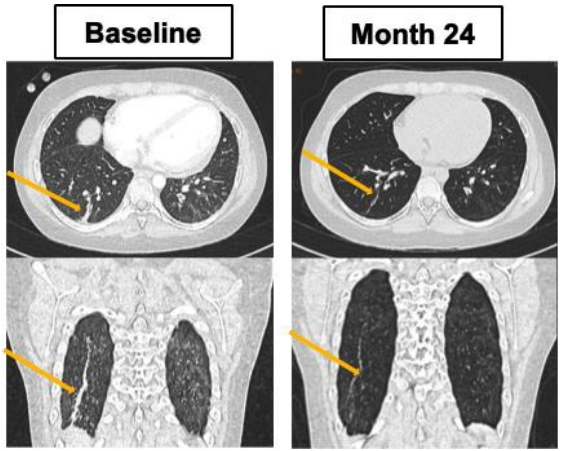


Treatment	Baseline	4 Months
Glucocorticoids	+++	-
Hydroxychloroquine	+	-
Mycophenolate mofetil	+	-
Plasmapheresis	+	-
Ciclophosphamide	+	-
SUPPORTIVE THERAPIES		
Insulin	++	-
Oxygen supply	+++	-
Hypertension treatment	+++	-

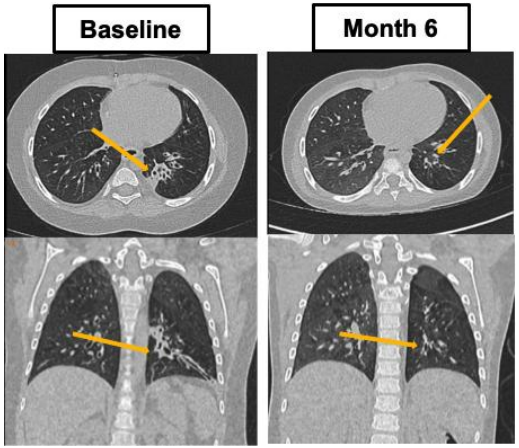
Clinical presentation before CAR T-cell infusion	Status at 9 months
Restrictive pneumopathy requiring continuous oxygen supply	**RESOLVED**
Lupus nephritis (grade V)	**RESOLVED**
Bilateral optical neuropathy	**RESOLVED**
DAT/IAT +	**RESOLVED**
Steroid-associated diabetes	**RESOLVED**
Steroid-associated hypertension	**RESOLVED**
Steroid-associated osteopoenia with multiple vertrebral collapses	**STABILIZED**

Efficacy – Interstitial Lung Disease

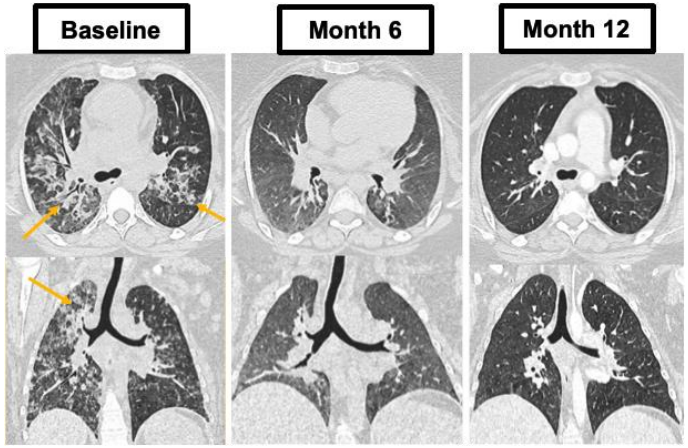
(Pt #1 - pSLE)



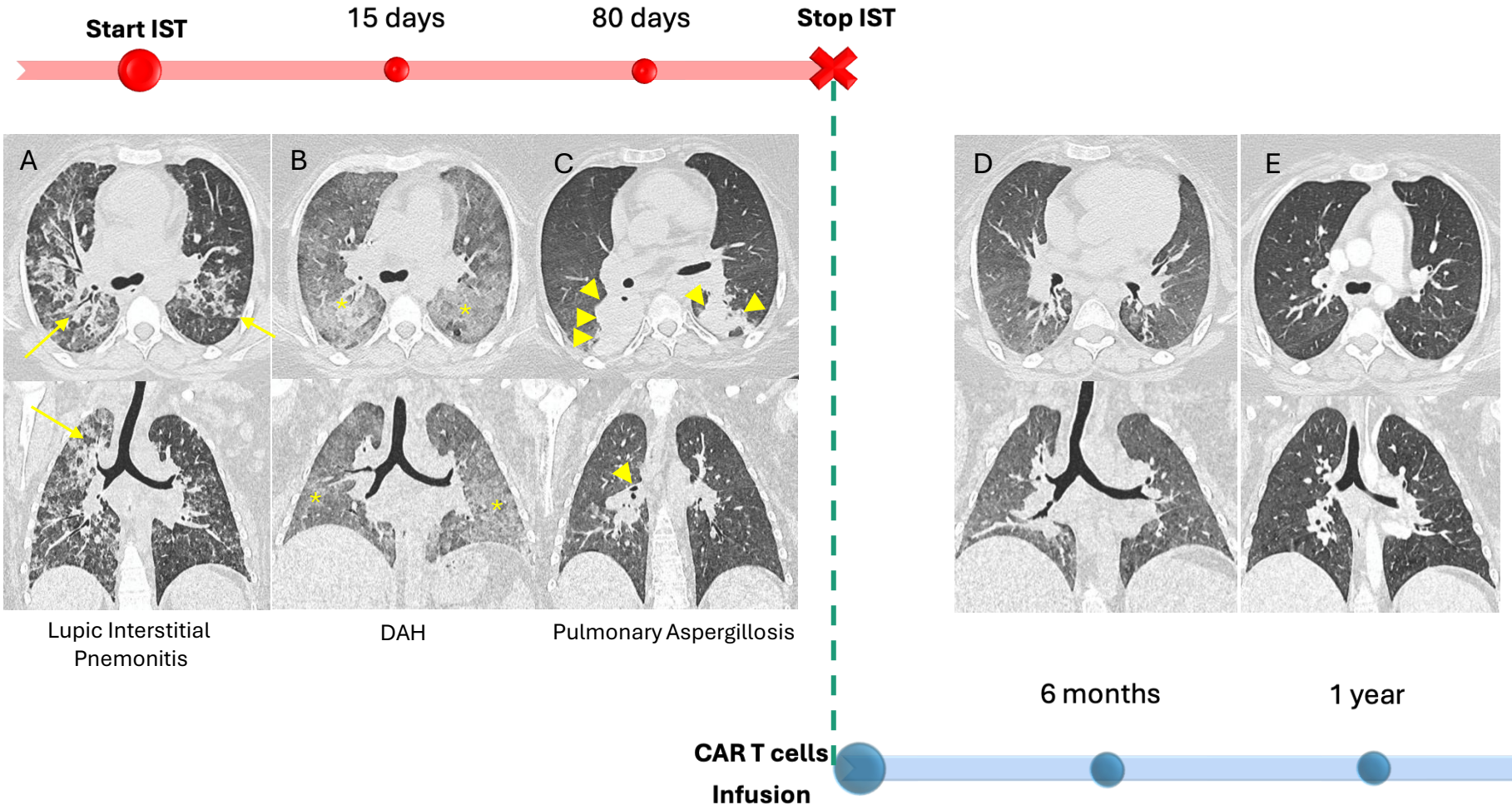
(Pt #3 - pSLE)



(Pt #5 - jDM)

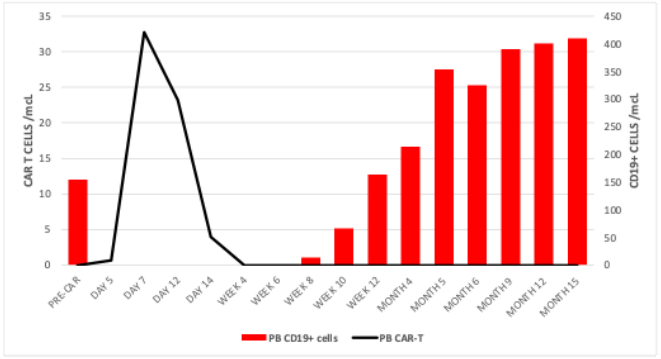


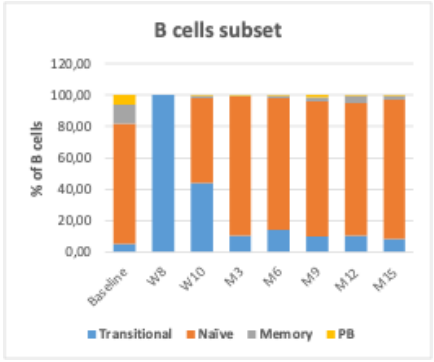
Radiological findings of ILD, characterized by interstitial and bronchial wall thickening along with parenchymal and subpleural bands, improved in all patients.


Start IST
15 days
80 days
Stop IST
A
B
C
D
E
Lupic Interstitial Pnemonitis
DAH
Pulmonary Aspergillosis
6 months
1 year
CAR T cells Infusion

Pt #2 – FU 18 months

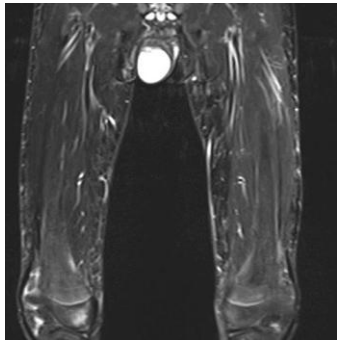
No immunosuppressive therapy



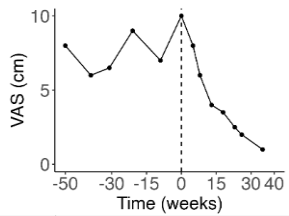


Baseline

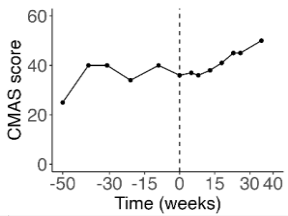
Month 6



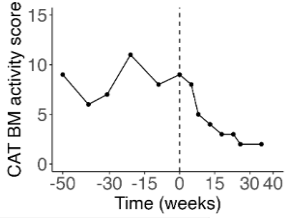
PGA



CMAS



CAT



Niccolai R et al, Arthritis and Rheumatology 2024 Oct;76(10):1560-1565

Refractory Immune Thrombocytopenia of SLE

38-year-old female, SLE-ITP

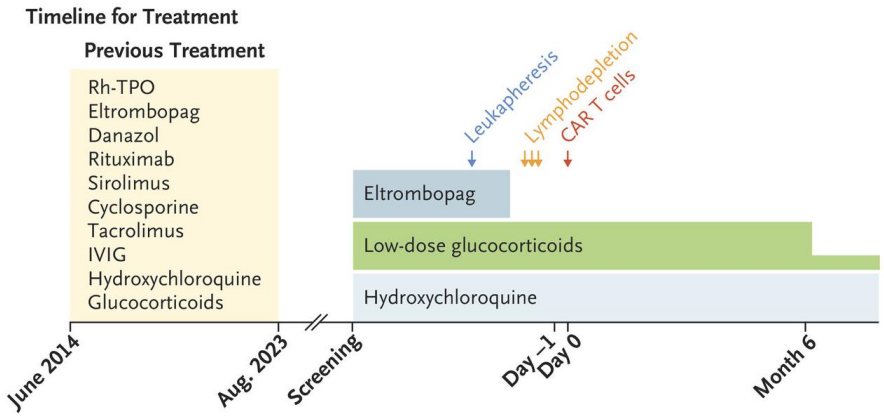
Drug product: Inaticabtagene autoleucel (0,5 x 10^6/kg)

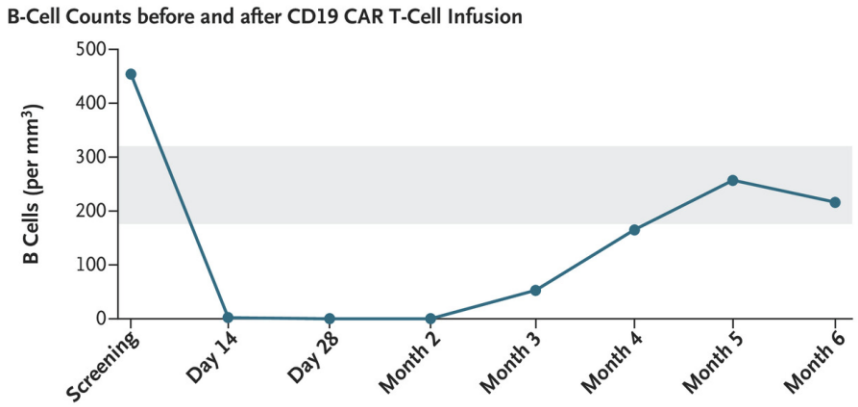
Anti-CD19, second generation (41BB), lentivirus

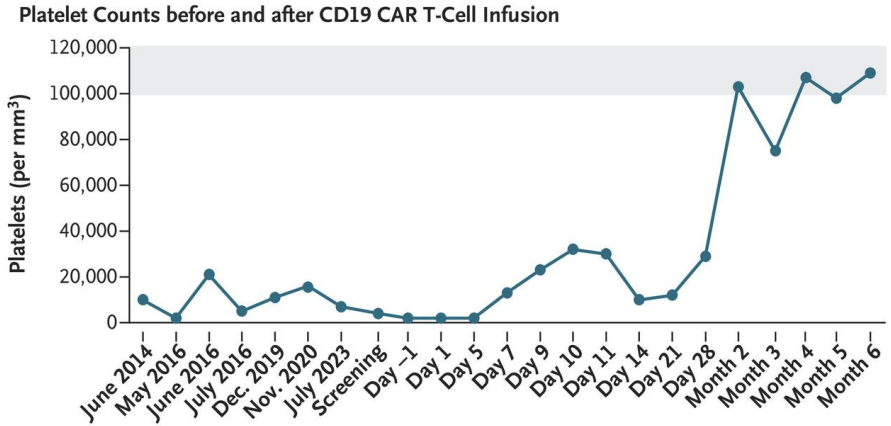
Fludara 30 mg/m^2/day D-5, -4, -3 + Cy 250 mg/m^2/day D-5, -4

Expansion: peak on day 14 (35% of T cells)

Persistence: up to 6 months







Li M, et al. N Engl J Med. 2024

Refractory Primary Immune Thrombocytopenia

35-year-old male, **ITP** with detected **anti-platelet Abs against gpIIb/IIIa**

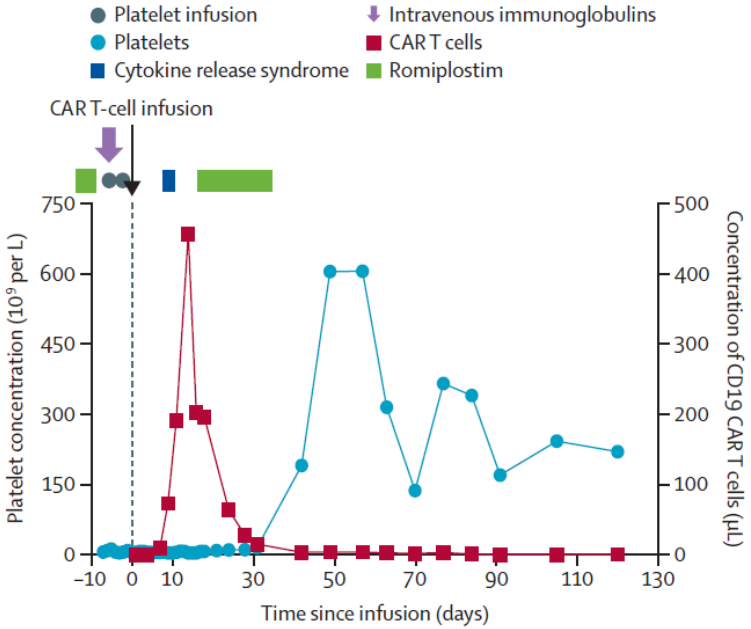
- **Previous therapies:**

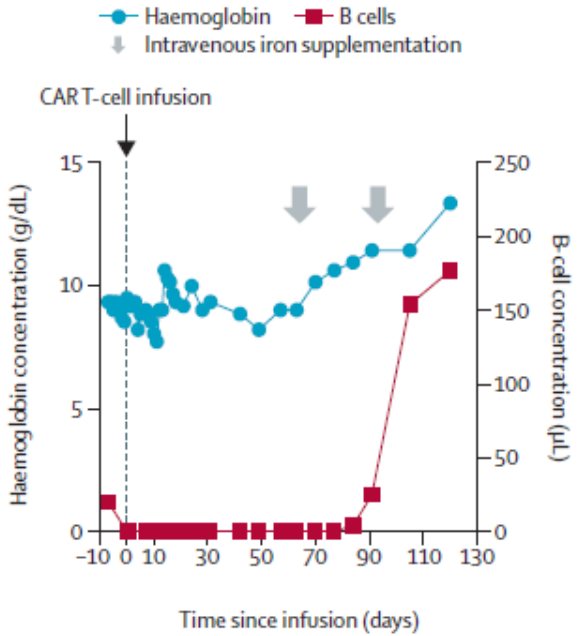
Glucocorticoids, Rituximab, Romiplostim, Eltrombopag, Avatrombopag, Fostamatinib, IVIG, HCQ, MMF, Splenectomy, Cyclosporine

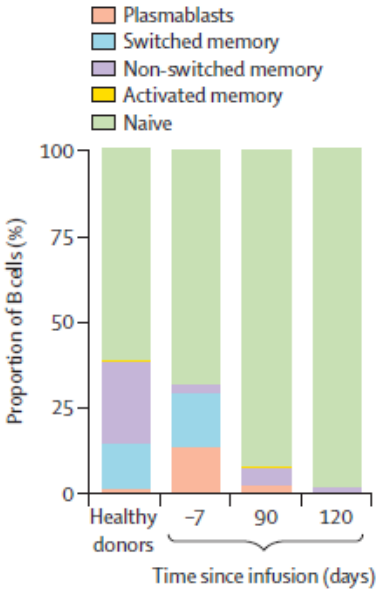
Drug product: KYV-101 (1 x 10^6/kg)

Anti-CD19, second generation (CD28), fully human

Fludara 30 mg/m²/day + Cy 300 mg/m²/day D-5, -4, -3







Anti-platelet Abs against gpIIb/IIIa undetectable by day 42.

Trautmann-Grill K, et al. Lancet. 2025

Refractory Autoimmune Hemolytic Anemia

5 patients treated in a compassionate use program

+ 3 patients in phase I clinical trial (NCT06231368)

Drug product: autologous CD19-CAR T cells

i) 1 x 10^6/kg (compassionate use)

ii) 0,5 x 10^6/kg (DL1 phase I clinical trial)

Fludara 25 mg/m^2/day D-5, -4, -3 + Cy 1 g/m^2/day D-3

- Peak of CAR T-cell expansion:

  10 days (range: 7-11 days)

  118.8 cells/μl (range: 44.9 to 244.6 cells/μl)

Median follow-up: 6.8 months (range: 0.8-10.5 months)

- 7 evaluable patients for efficacy: all obtained CR
- One relapse 6.8 months after CD19-CAR T-cell infusion

  - All patients G1-2 CRS
  - One patient G1 ICANS
  - No severe infections

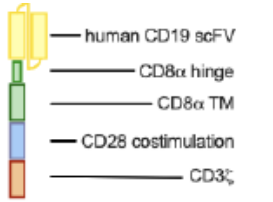
- Reset of the B-cell compartment was confirmed through scRNA-seq and single-cell V(D)J sequencing

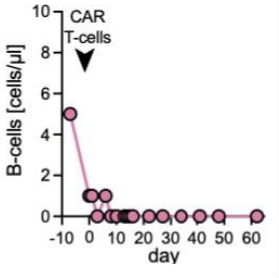
The 66th ASH Annual Meeting Abstracts ORAL ABSTRACTS; Li R et al, Blood 2024; 144 (Supplement 1): 682.

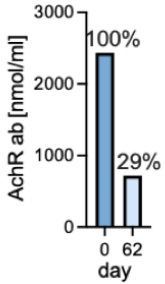
Bambino Gesù
OSPEDALE PEDIATRICO

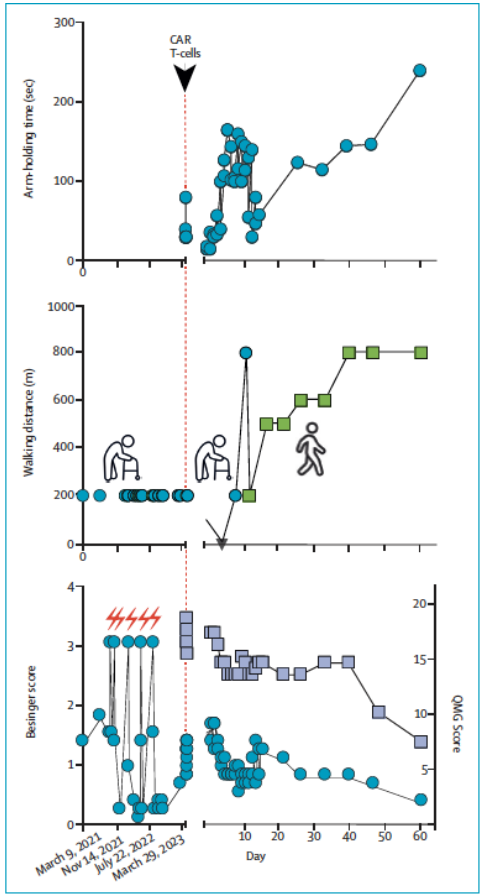
Myasthenia Gravis

KYV-101 CAR CONSTRUCT







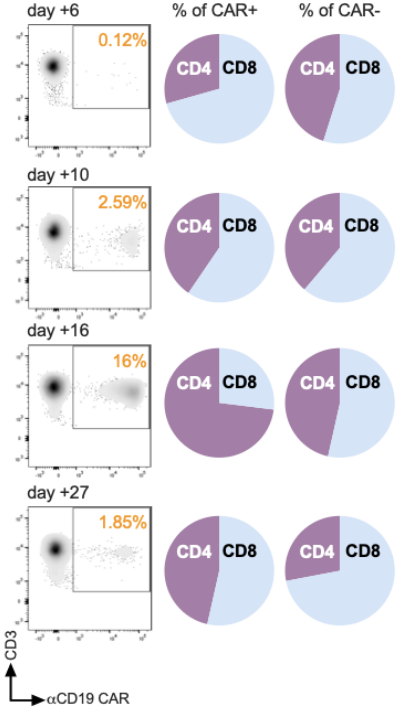


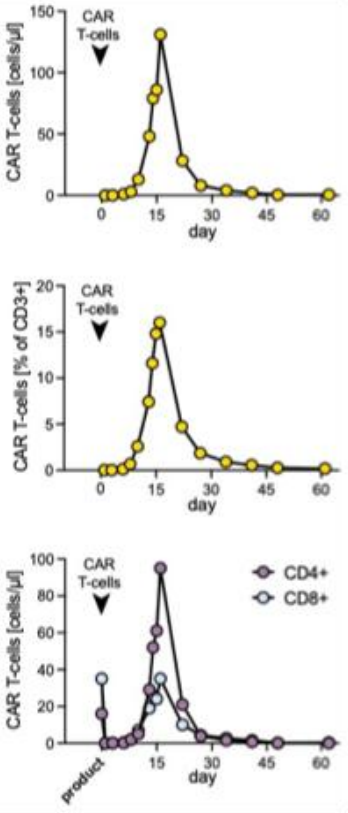
Correspondence

Anti-CD19 CAR T cells for refractory myasthenia gravis

Aiden Haghikia [a] ✉, Tobias Hegelmaier [a], Denise Wolleschak [b], Martin Böttcher [b], Christiane Desel [a], Dominic Borie [c], Jeremias Motte [d], Georg Schett [f], Roland Schroers [e], Ralf Gold [d], Dimitrios Mougiakakos [b]

THE LANCET Neurology





Bambino Gesù
OSPEDALE PEDIATRICO

Myasthenia Gravis

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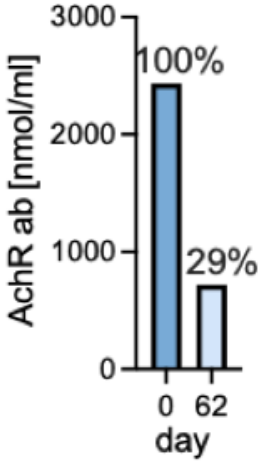
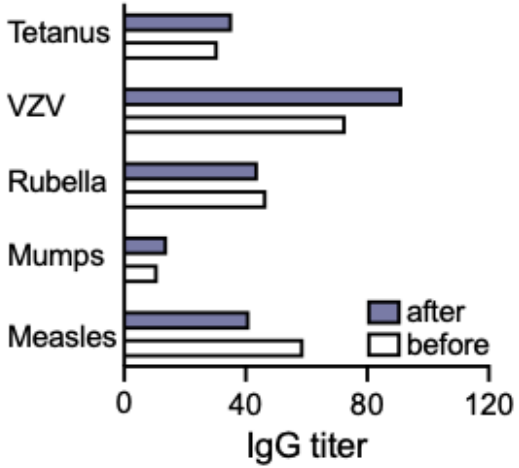
THE LANCET
Neurology

Protective vaccination IgG titer were maintained





- A substantial proportion of pathogenic anti-AchR autoantibodies is produced by plasma blasts and short-lived plasma cells, which do express CD19
- Protective antibodies are produced by bone marrow long-lived plasma cells that do not express CD19

In conclusion

- CD19-CAR (and maybe BCMA-CAR) T cells are a promising, **feasible** and **well-tolerated**, **potentially curative**, therapeutic option for patients with severe and/or refractory autoimmune diseases mediated by autoreactive B-cells;
- This novel approach can provide a **durable drug-free remission (DFR)**, rescuing patients from *side effects of chronic IST*, even in previously recalcitrant B-cell mediated autoimmune diseases;
- Available evidence indicates patients experience a remarkable improvement of **QoL;**
- **Clinical trials** in patients are underway to confirm these promising results;
- **Long-term follow-up** is needed to fully define the safety profile of the approach.

ACKNOWLEDGEMENTS

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Concetta Quintarelli, Biagio De Angelis, Francesca Del Bufalo, ***Enrico Velardi, Chiara Agrati, Mara Vinci***

Fred Hutchinson Cancer Research Center

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Stefania Macchia

All Team!

National University of Singapore

Dario Campana, Allen Yeoh Eng Jug, Elaine Coustan-Smith

Medisix

Andrew Bruce, Peiying Chuan

BCM/CAGT Houston

Malcolm Brenner