Clinical Impact of C-CAR168, a Novel Anti-CD20/BCMA Composite Autologous CAR-T Therapy, in Refractory Lupus Nephritis

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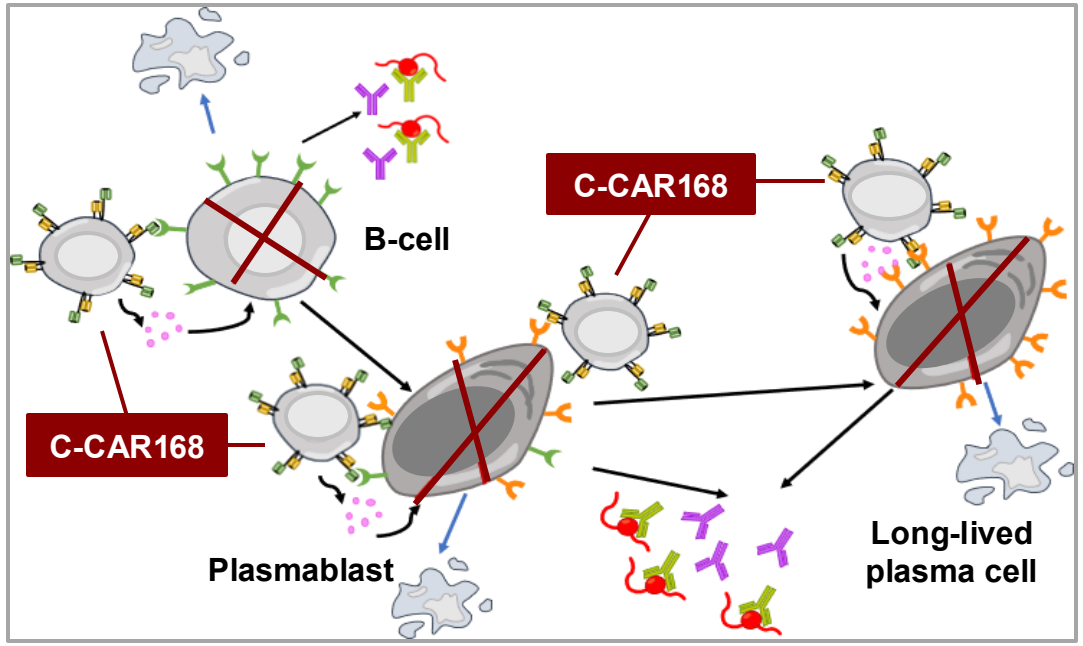
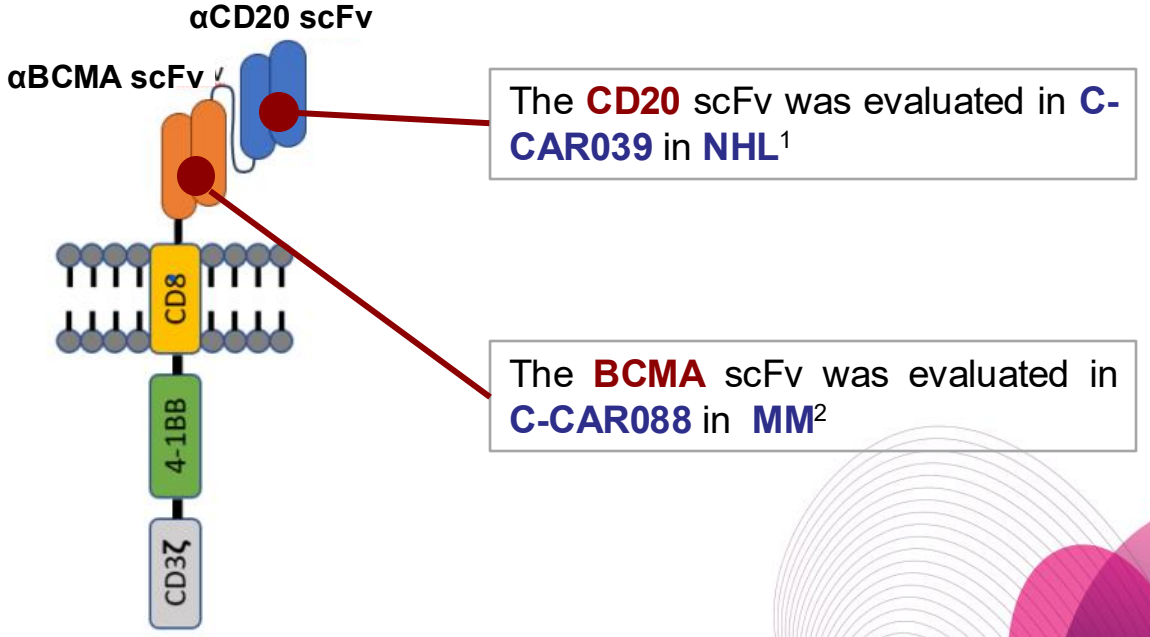
Faculty Disclosure

- I consult for several pharmaceutical companies including AbelZeta on SLE programs.

C-CAR168: A 2nd Generation Bispecific CAR-T Targeting CD20 and BCMA

- **B cells and plasma cells** drive autoimmunity via both antibody-dependent and -independent mechanisms;
- Targeting antibody-secreting cells shows broad efficacy across autoimmune diseases;
- Our strategy is to target both **CD20** and **BCMA** that depletes B cells, plasmablasts, short- and long-lived plasma cells, as well as CD20dim T cells.





1. Yu et al, *Blood* (2025) 145 (14): 1526–1535
2. Qu X, et al. *J Immunother Cancer*. 2022;10:e005145

CAR-AID Study: Phase 1, Open Label, First-in-human IIT of C-CAR168 in Chinese Patients with Refractory Autoimmune Disease

LUPUS TORONTO 2025

Key Inclusion Criteria

SLE

- Diagnosed with SLE for ≥ 6 months, with renal biopsy proven LN
- Had failed ≥ 2 immunosuppressants (IS) or biologic agents
- SLEDAI-2K ≥ 7, AND clinical SLEDAI-2K ≥ 6
- UTP ≥ 1g/24h or UPCR ≥ 1.0g/g
- ANA ≥ 1:80, OR a positive anti-dsDNA, OR a positive anti-Sm

Other CTD

- IMNM
- SSc

Neurology

- MS
- NMOSD
- MG

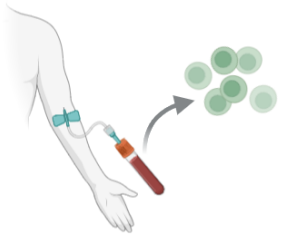
Key Exclusion Criteria

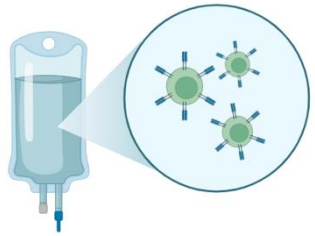
- Active infection
- Impaired organ function

SLE: Systemic Lupus Erythematosus; LN: Lupus nephritis; SSc: Systemic Sclerosis; IMNM: Immune-Mediated Necrotizing Myopathy; NMOSD: Neuromyelitis Optica Spectrum Disorders; MS: Multiple Sclerosis; MG: Myasthenia Gravis; IS: Immunosuppressants; BA: Biologic agents

Study Design

≤28d	Day-5 ~Day-3	Day 0	Day 28	M6	~ M24
Screening	Leukapheresis Lympho-depletion	Single infusion of C-CAR168	DLT evaluation	Primary analysis	Follow-up





T cell isolated (autologous CAR T)

FLU 25 mg/m^2/d
CYC 300 mg/m^2/d

DL1: 0.75×10^6 /kg
DL2: 1.5×10^6 /kg

C-CAR168 manufacturing (~20 days)

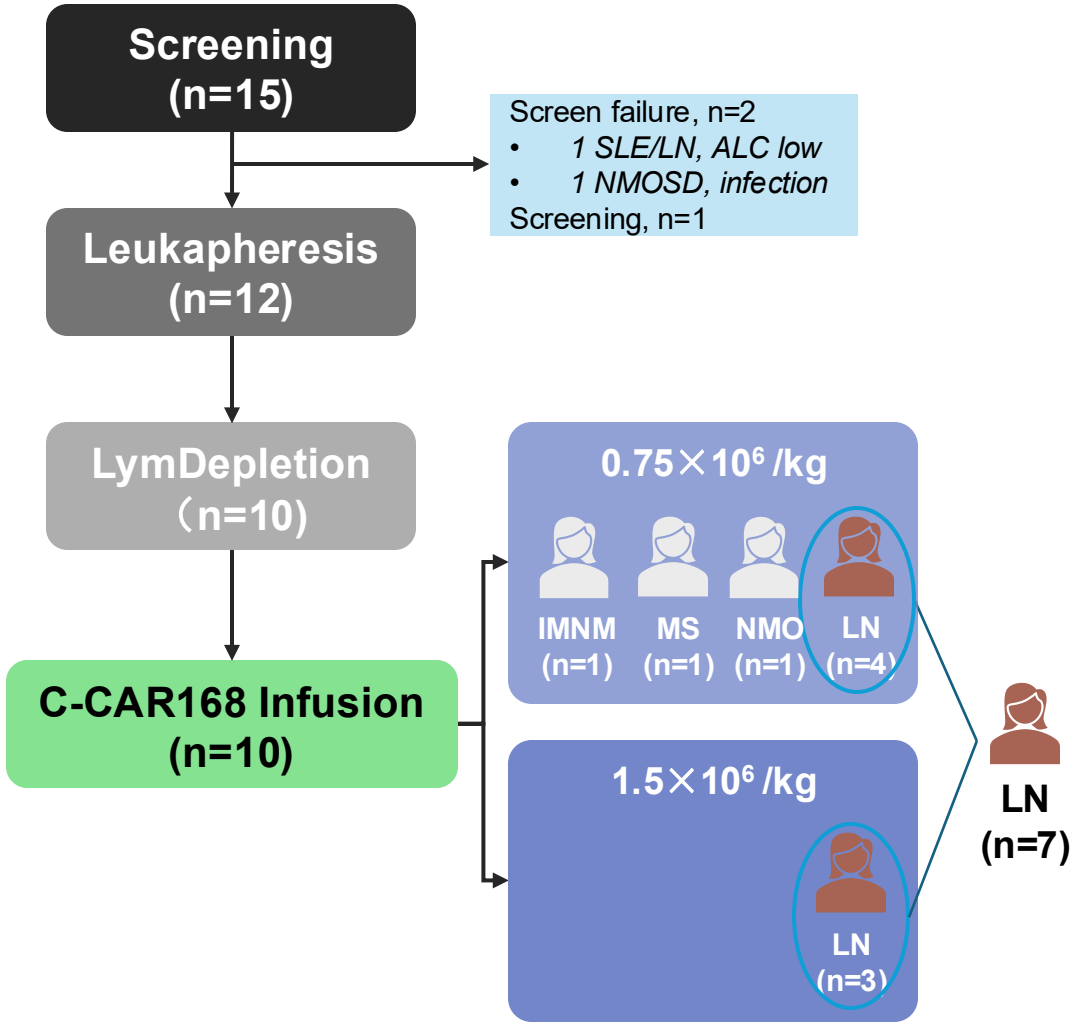
All AEs and C-CAR168 related AEs

Safety and Efficacy Assessment

- **Safety**
  - CTCAE v5.0
  - CRS and ICANS by ASTCT 2019
- **SLE Disease Activity**
  - SLEDAI-2K, SELENA-SLEDAI, PGA, BILAG-2004
  - DORIS, LLDAS, SRI-4
- **LN Clinical Response**
  - 2024 KDIGO criteria: CR / PR / NR

FLU: Fludarabine； CYC: Cyclophosphamide; DL: Dose level; DLT: Dose-limiting toxicity; AE: Adverse event; CTCAE: Common Terminology Criteria for Adverse Events; CRS: Cytokine Release Syndrome; ICANS: Immune effector Cell-Associated Neurotoxicity Syndrome; SLEDAI: Systemic lupus erythematosus disease activity index; ASTCT: American Society for Transplantation and Cellular Therapy; PGA: physician global assessment; BILAG: British Isles Lupus Assessment Group; DORIS: Definition Of Remission In SLE; LLDAS: Lupus Low Disease Activity State; SRI: Systemic Lupus Erythematosus Responder Index; KDIGO: Kidney Disease Improving Global Outcomes; CR: complete remission; PR: partial remission; NR: no renal remission

Patient Allocation and Baseline Characteristics of Involved Patients



Characteristics of Patients with Refractory LN

Demographics

- Age (yr): 30 (26-41)
- Female, n(%): 6 (85.7)
- SLE duration (yr): 9 (5-14)
- LN duration (yr): 5 (2-9)

Clinical assessment

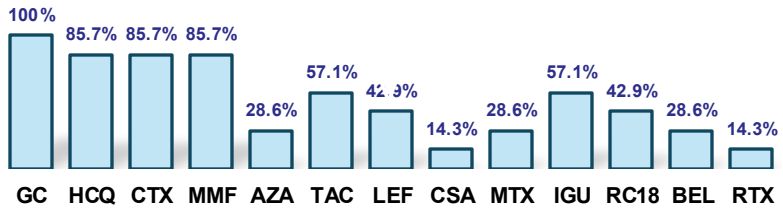
- SLEDAI-2K: 12 (8-24)
- PGA: 1.5 (1.1-2.4)
- 24h UP (g/24h): 3.71 (1.23-8.16)
- UPCR (g/g): 2.64 (1.64-10.84)
- Low complement, n (%): 6 (85.7)

LN ISN/RPS, n (%)

- III+V: 2 (28.6)
- IV+V: 3 (42.9)
- III/IV+V: 1 (14.3)
- V: 1 (14.3)

Previous treatment

- No. of IS/biologics, n (range): 4 (3-8)



C-CAR168 is Well Tolerated in Terms of Low-grade CRS, no ICANS, no Severe Infection

	0.75×10^6 /kg (n=4)	1.5×10^6 /kg (n=3)	Total (n=7)
Treatment emergent SAE	0	1*	1
C-CAR168-related SAE	0	0	0
CRS			
Any Grade	1	3	4
Grade 1	1	2	3
Grade 2	0	1	1
Grade ≥ 3	0	0	0
Median to onset, day	2	2	2
Median duration, days	8	8	8
Tocilizumab use	0	2	2
Dexamethasone use	0	2	2
ICANS	0	0	0
DLT	0	0	0
Grade ≥ 3 Infection	0	0	0
Long-term hematological toxicities	0	0	0

*: Pt C009 experienced G4 thrombocytopenia at M2 caused by disease flare. The patient was fully recovered with GC, TPO, transfusion treatment

Robust SLE and LN Responses to C-CAR168 6 Months Post Treatment

- 4 patients completed M6 efficacy evaluation, **all achieved SRI-4**
- Pt C004/C007 have not yet reached the M6 evaluation timepoint
- Pt C009 flared at M3 and withdrew from the study thereafter
- All patients discontinued IS/biologics after lymphodepletion
- Most patients reached steroids free after C-CAR168 infusion

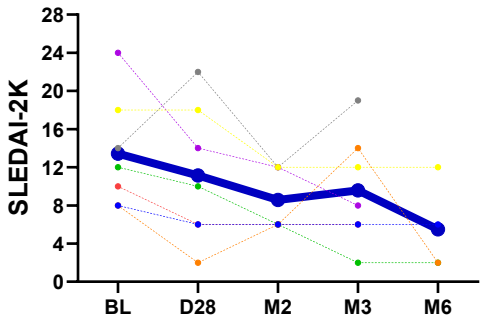
DL	Pt No	SLE response at M6			LN response at M6	
		DORIS	LLDAS	SRI-4	CR	PR
0.75×10^6 cells/kg	C001			√		√
	C002	√	√	√	√	
	C003	√	√	√	√	
1.5×10^6 cells/kg	C006			√		
	C009	/	/	/	/	/

C-CAR168 Alleviates Disease Activity and Reduces Proteinuria

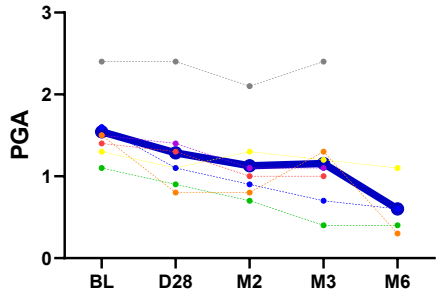
- 6 patients were under follow up and showed downward trend in SLEDAI score, PGA and proteinuria, of whom 3 maintained with low dose steroids, 3 were steroids free;
- C002 and C003 reached LN-CR
- C009 flared at M3

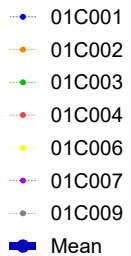
Disease Activity

SLEDAI-2K



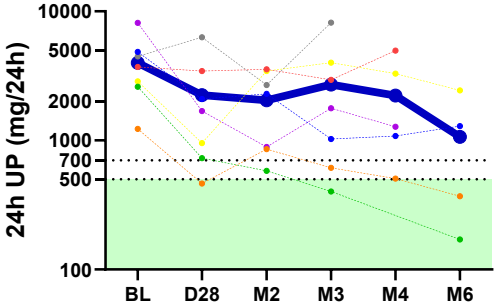
PGA



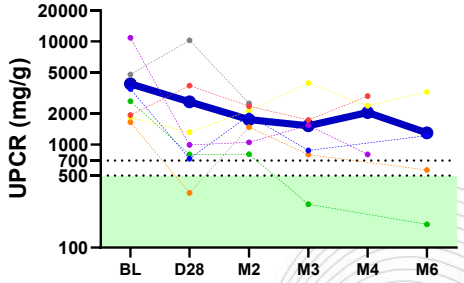


Proteinuria

24h Proteinuria



UPCR

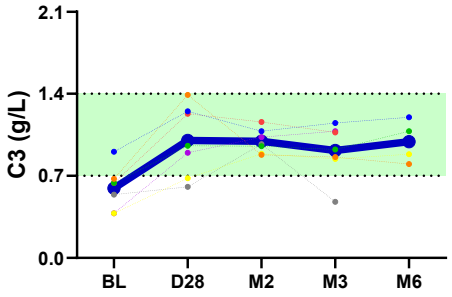


C-CAR168 Results in Complement Recovery, Autoantibody Reduction, and Renal Function Stabilization

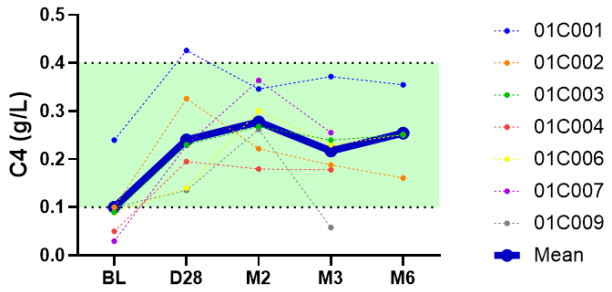
- Early recovery of complement levels was observed in all patients, with 6/7 achieving normal levels during follow-up
- All patients showed stable renal function, with no deterioration in eGFR
- A downward trend in anti-dsDNA level was observed in most patients

Complement Levels

C3

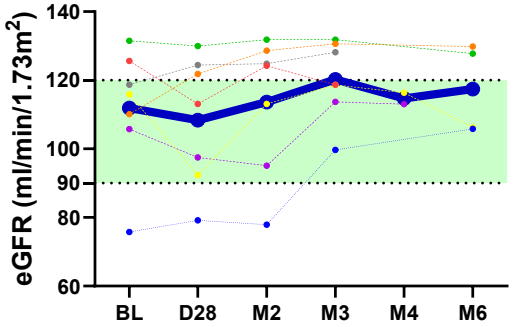


C4



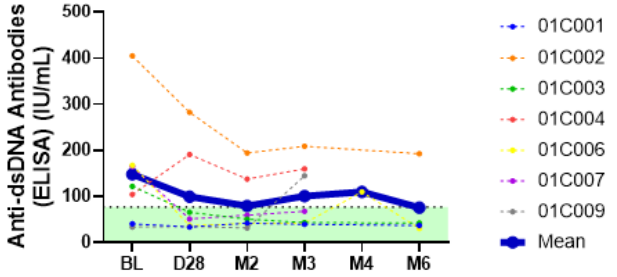
Renal Function

eGFR-EPI Cr



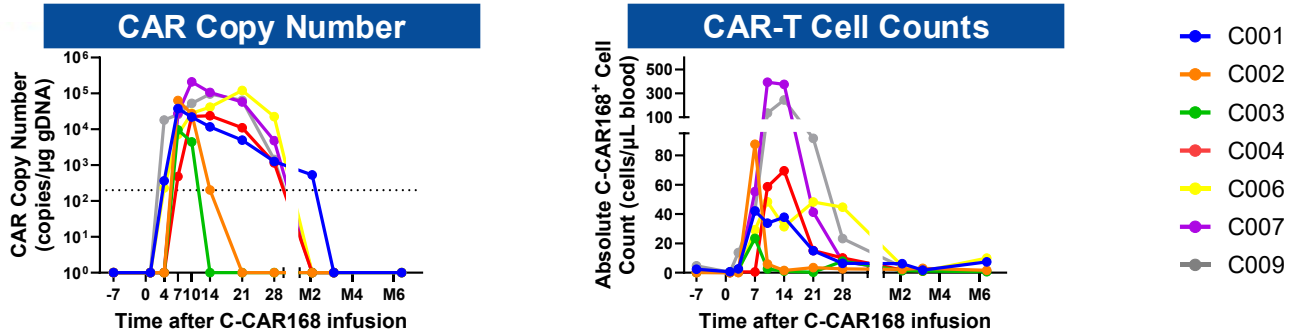
Autoantibody Level

Anti-dsDNA

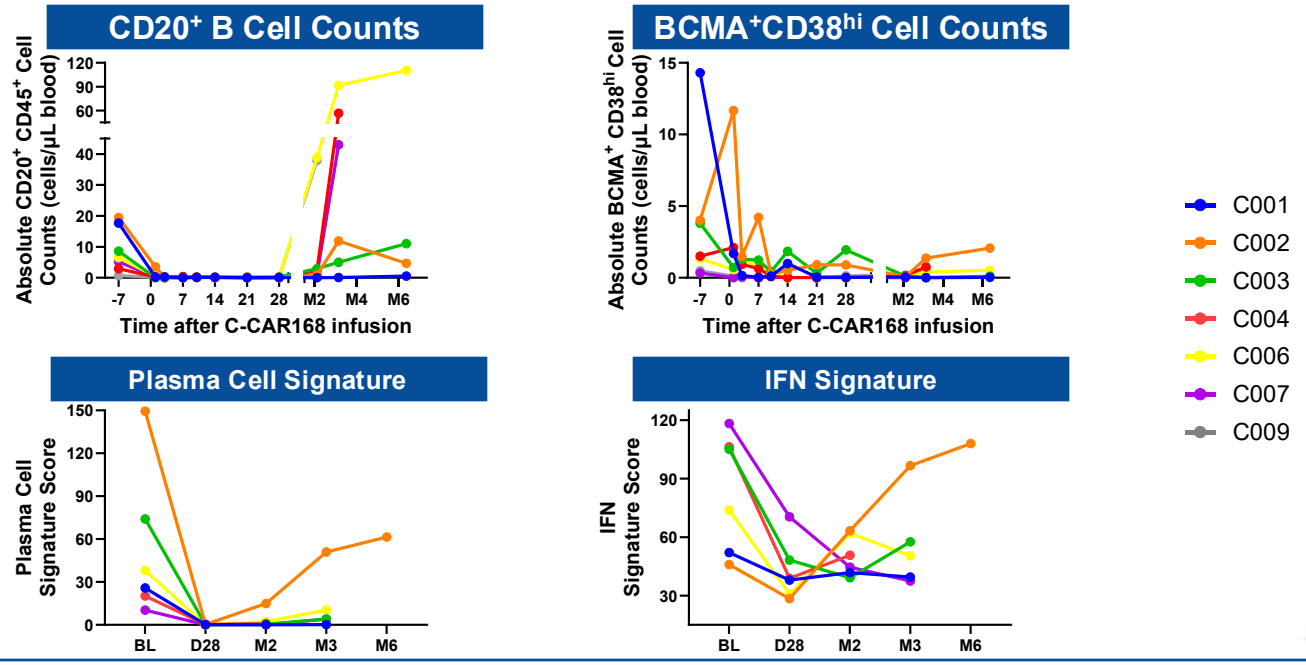


Pharmacokinetics and Pharmacodynamics of C-CAR168 in LN

Pharmacokinetics



Pharmacodynamics

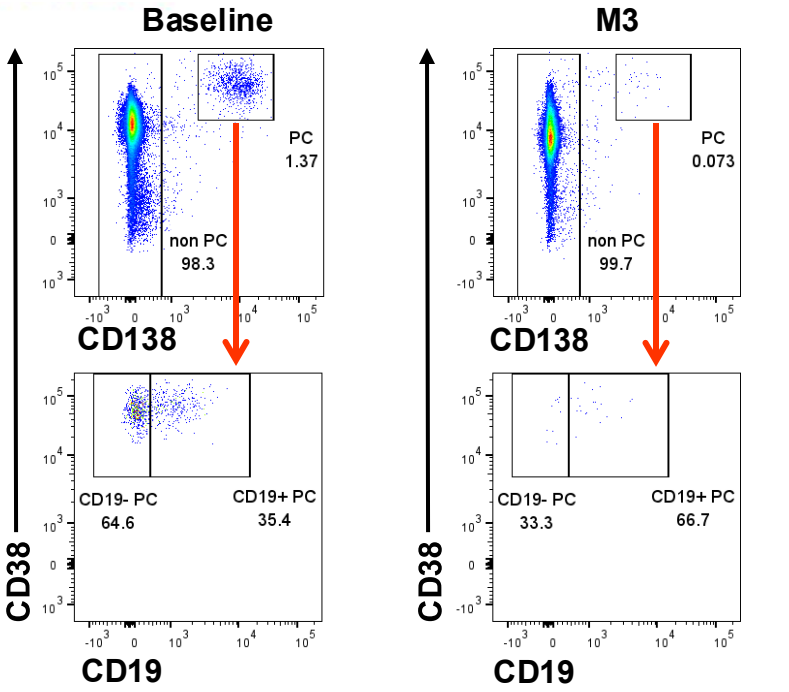


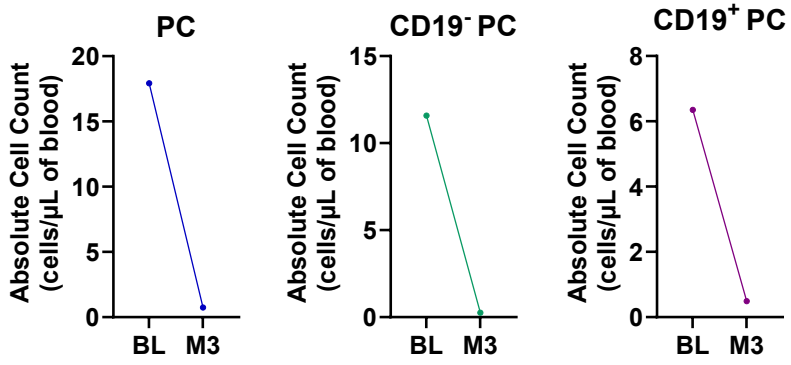
- Rapid C-CAR168 expansion was observed in the peripheral blood in all patients (median T_{max}: 11 days (range: 7 to 21 days)
- CAR-T cells persisted for 1 to 3 months in 5 patients. Two patients in DL1 group (Pt 02 and Pt 03) had shorter persistence
- Rapid and profound depletion of circulating B cells and plasma cells were observed
- Gene signature analysis further supported deep depletion of plasma cells and alleviation of type I IFN pathway activity

The plasma cell signature score and type I IFN signature score were computed based on RNAseq data available for 6 patients of the indicated follow up. Plasma cell signature: Streicher K, et al., Arthritis Rheumatol. 2014 Jan;66(1):173-84.. IFN signature (21-gene): Yao Y, et al., Hum Genomics Proteomics. 2009 Nov 17;2009:374312.

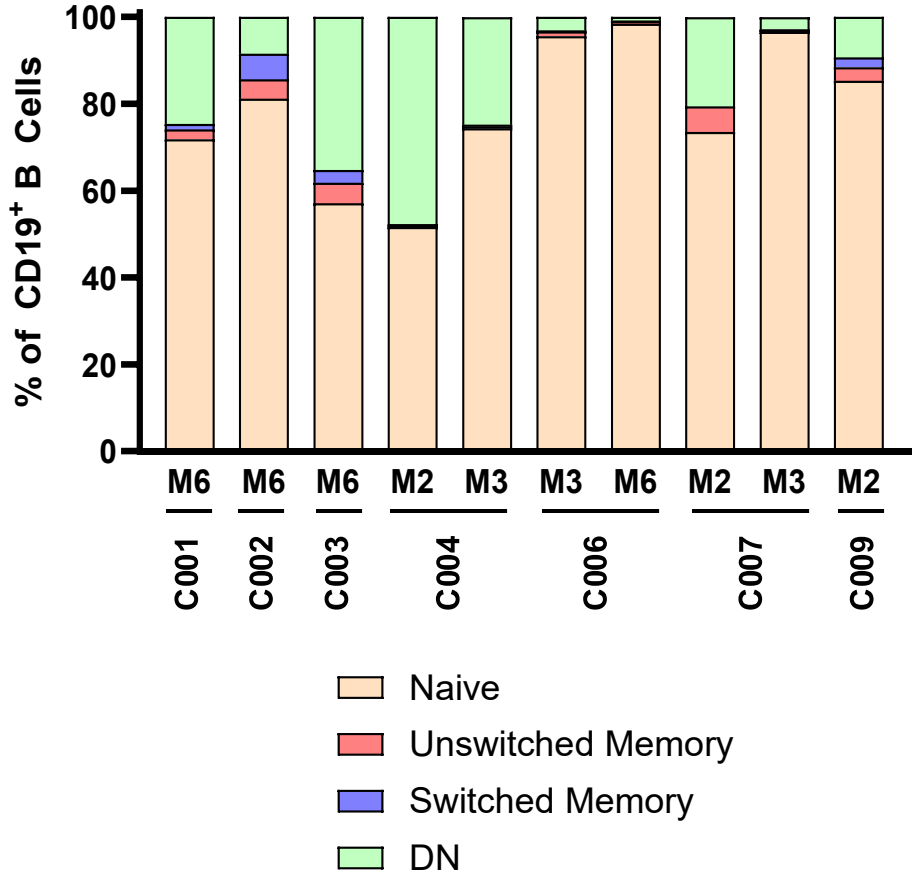
C-CAR168 Eliminates Long-Lived Plasma Cells in Bone Marrow and Induces Immune Reset

BM PCs of Pt C009





Phenotype of Recovered B Cells



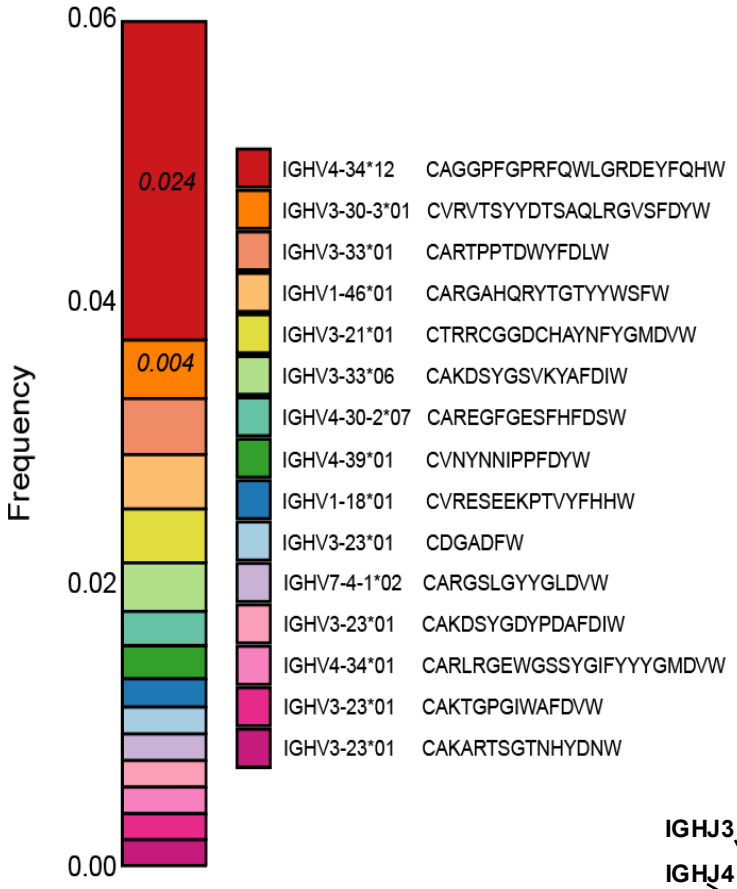
(Data is available for 7 patients of indicated follow up)

- Analysis of a bone marrow biopsy (Pt C009) indicated that both $CD19^+$ PCs and $CD19^-$ long-lived PCs were eliminated by C-CAR168
- Analysis of peripheral blood samples demonstrated that most recovered B cells were naïve cells, implying immune reset

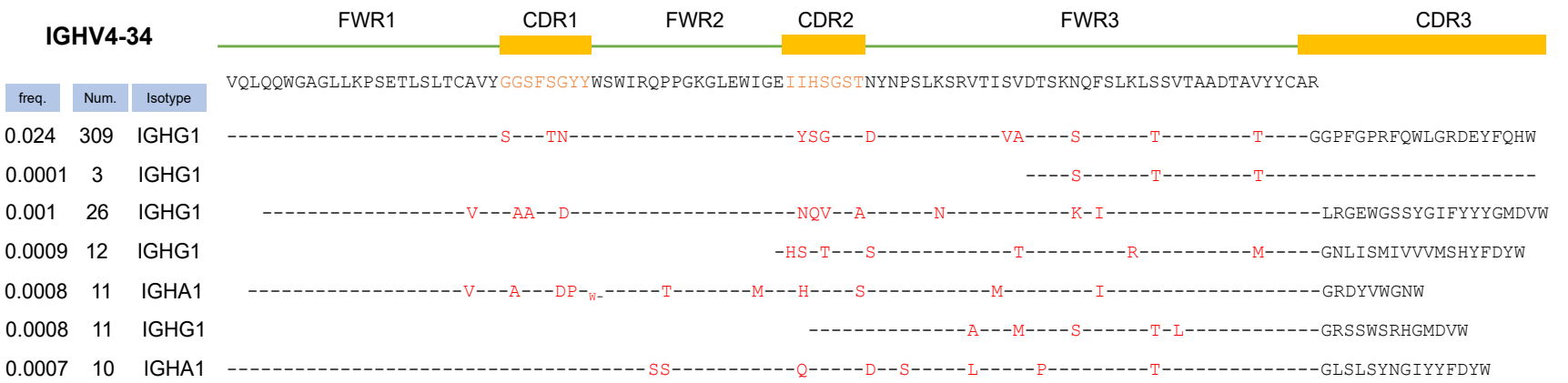
C-CAR168 Eliminates Dominant B Cell Clone and Reshapes the BCR Repertoire

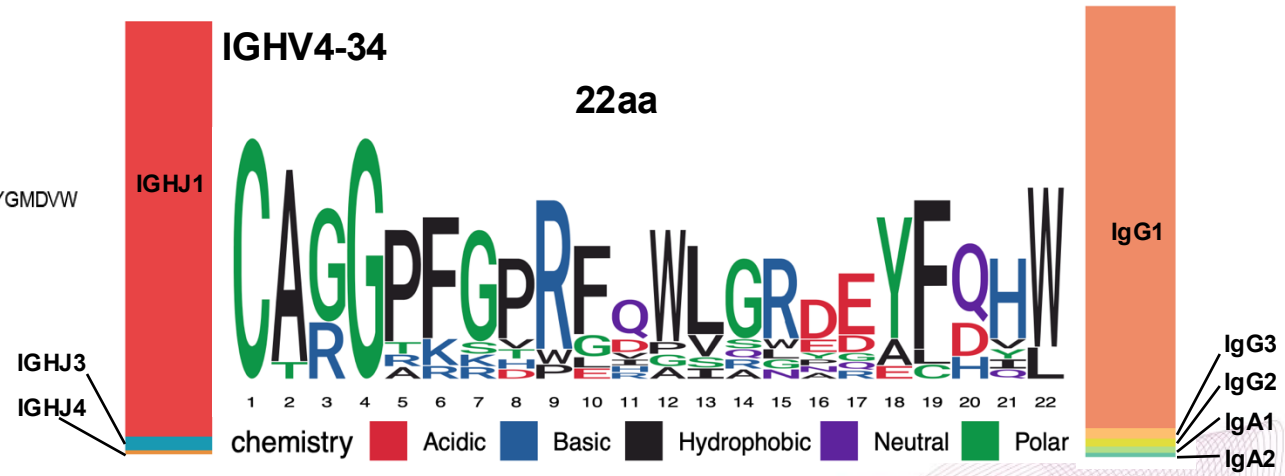
IGHV4-34 is predominantly used in Pt C001 at baseline and be effectively eliminated after treatment

Top15 clone at baseline

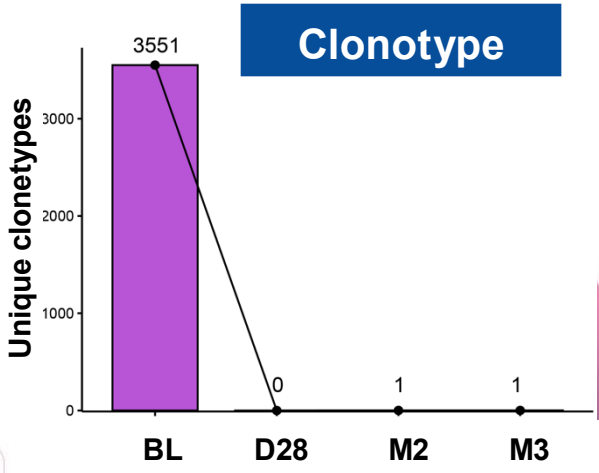


Amino acid mutations in the large IGHV4-34+ clonotypes at baseline





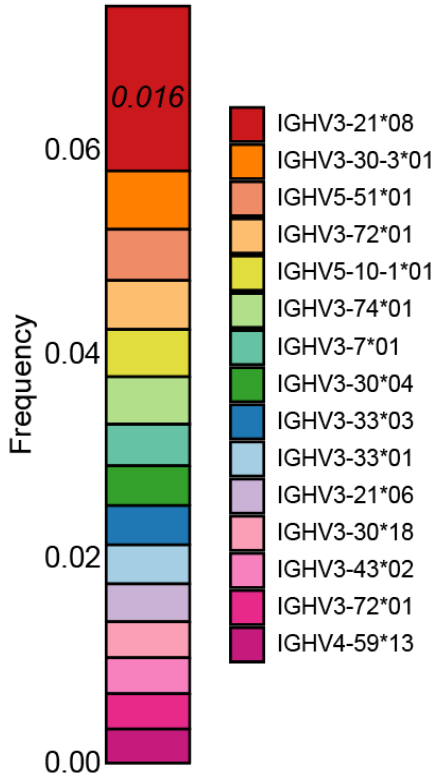
Clonotype



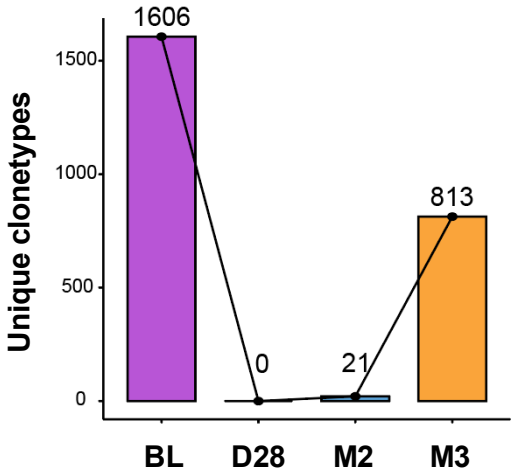
C-CAR168 Eliminates Dominant B Cell Clone and Reset the BCR Repertoire

BCR repertoire dynamics of Pt C007

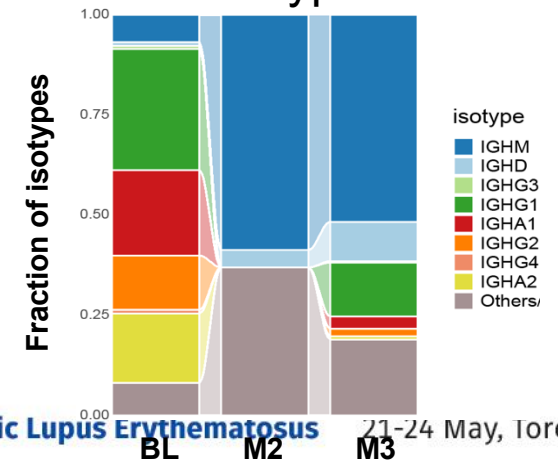
Top15 clone at baseline



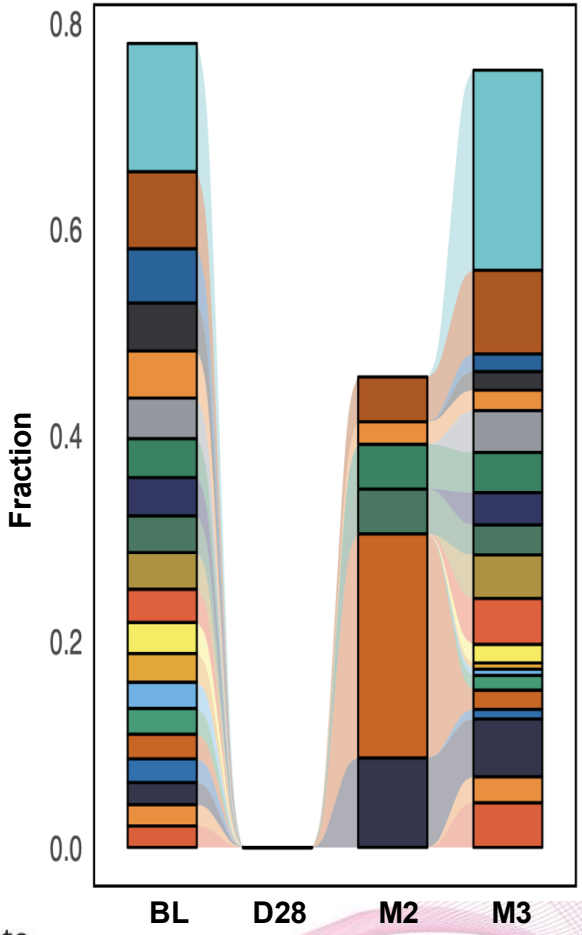
Clonotype



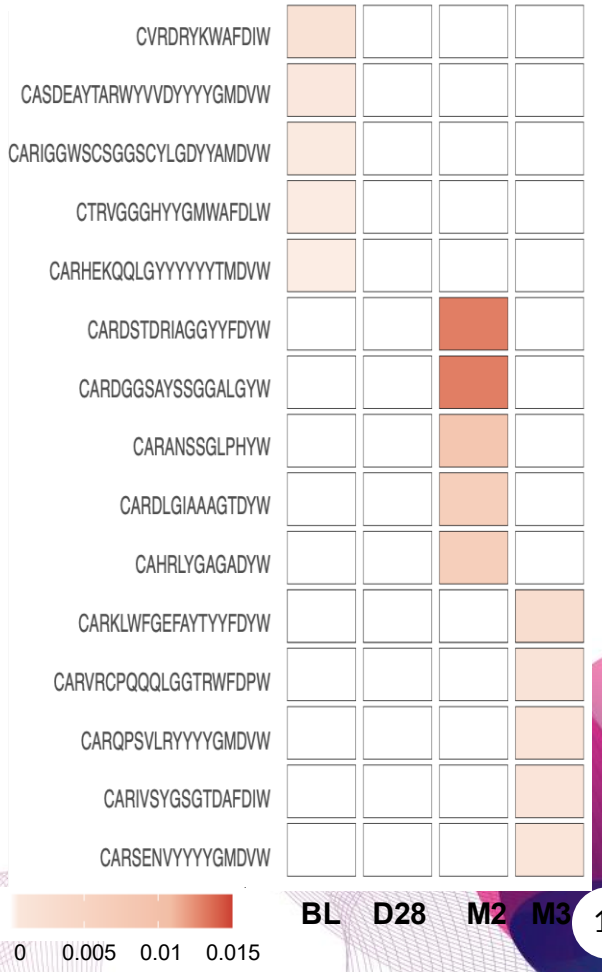
Isotype



V gene usage



Top 5 clone



CASE Study of C-CAR168 in a Secondary Progressive MS Patient

Patient information

31-year-old male

MS history: Initially diagnosed with relapsing-remitting multiple sclerosis (RRMS) in 2014, diagnosed with secondary progressive multiple sclerosis (SPMS) in 2024

Recent relapses: Two relapses in the past 12 months, evidenced by MRI deterioration and exhibited mild intellectual impairment

Prior treatment: GC, Betaferon (Recombinant human interferon beta-1b), Teriflunomide, AZA (Azathioprine)

MRI at the base line: approximately 20-50 lesions in the brain and brainstem, diffuse cervical and thoracic spinal cord lesions

C-CAR168 treatment

0.75×10^6 cells/kg and was IS/steroid free after infusion

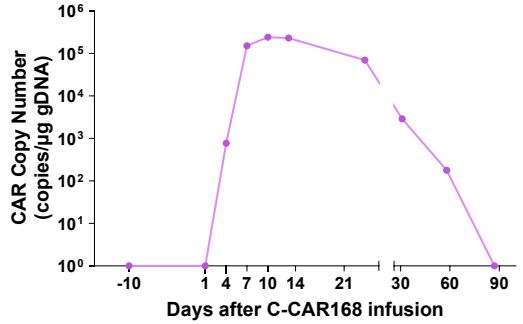
Safety

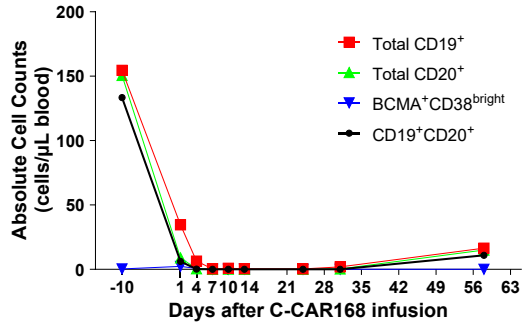
Grade 1 CRS and totally recovered without tocilizumab and dexamethasone treatment

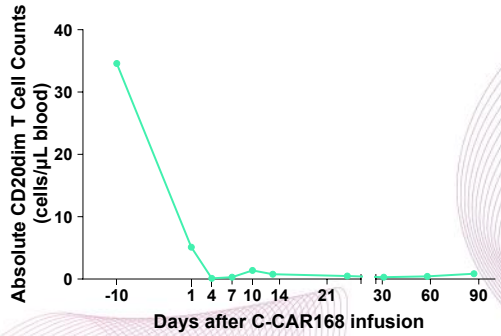
No ICANS, no SAE, no infection≥G3

PK/PD profile

Robust CAR-T expansion, complete depletion of B cells, plasma cells and CD20dim T cell in blood





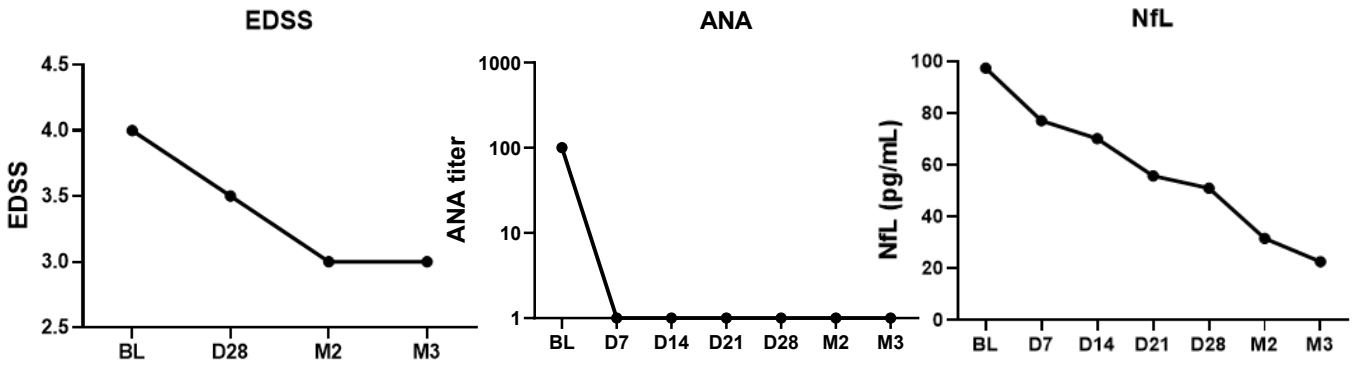


C-CAR168 Showed Early Promising Efficacy in a Secondary Progressive MS Patient

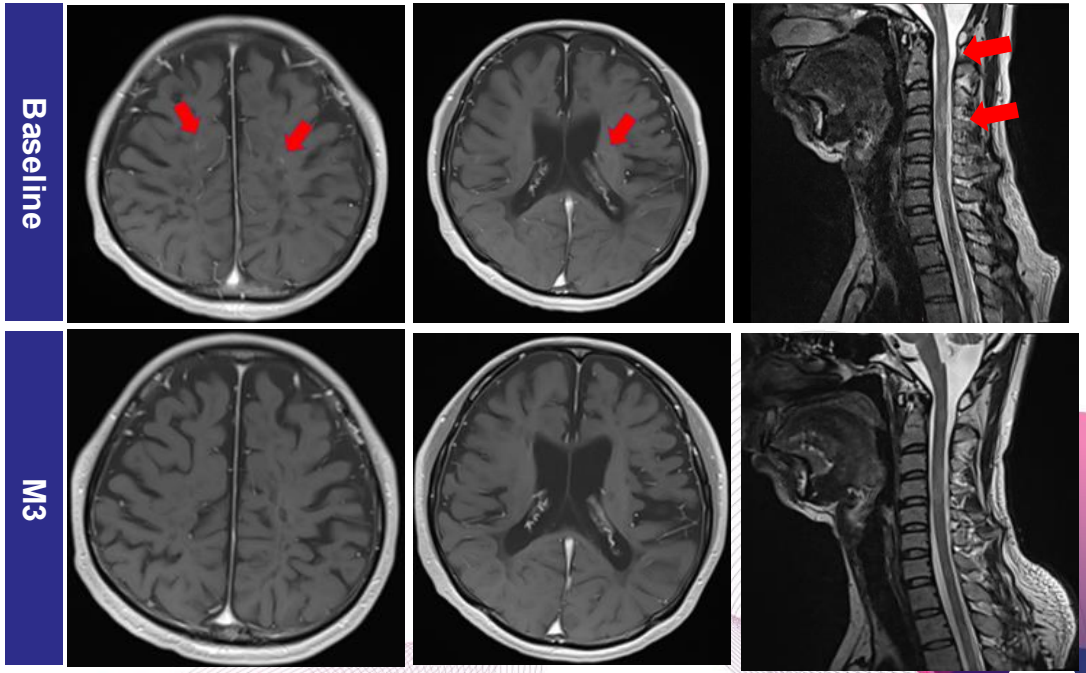
Improved test scores in 9-Hole Peg Test (9-HPT), the timed 25-foot walk(T25-FW) and Mini-Mental State Examination(MMSE)

	9-HPT (s)			T25-FW (s)				MMSE
	R	L	Ave	devices	1st	2nd	Ave	/
BL	35.38	37.13	36.26	N	7.9	7.2	7.6	24
D28	31.25	34.27	32.76	N	6.1	6.2	6.2	25
M2	32.25	34.11	33.18	N	5.8	7.6	6.7	26
M3	29.55	32.15	30.85	N	5.5	6.1	5.8	24

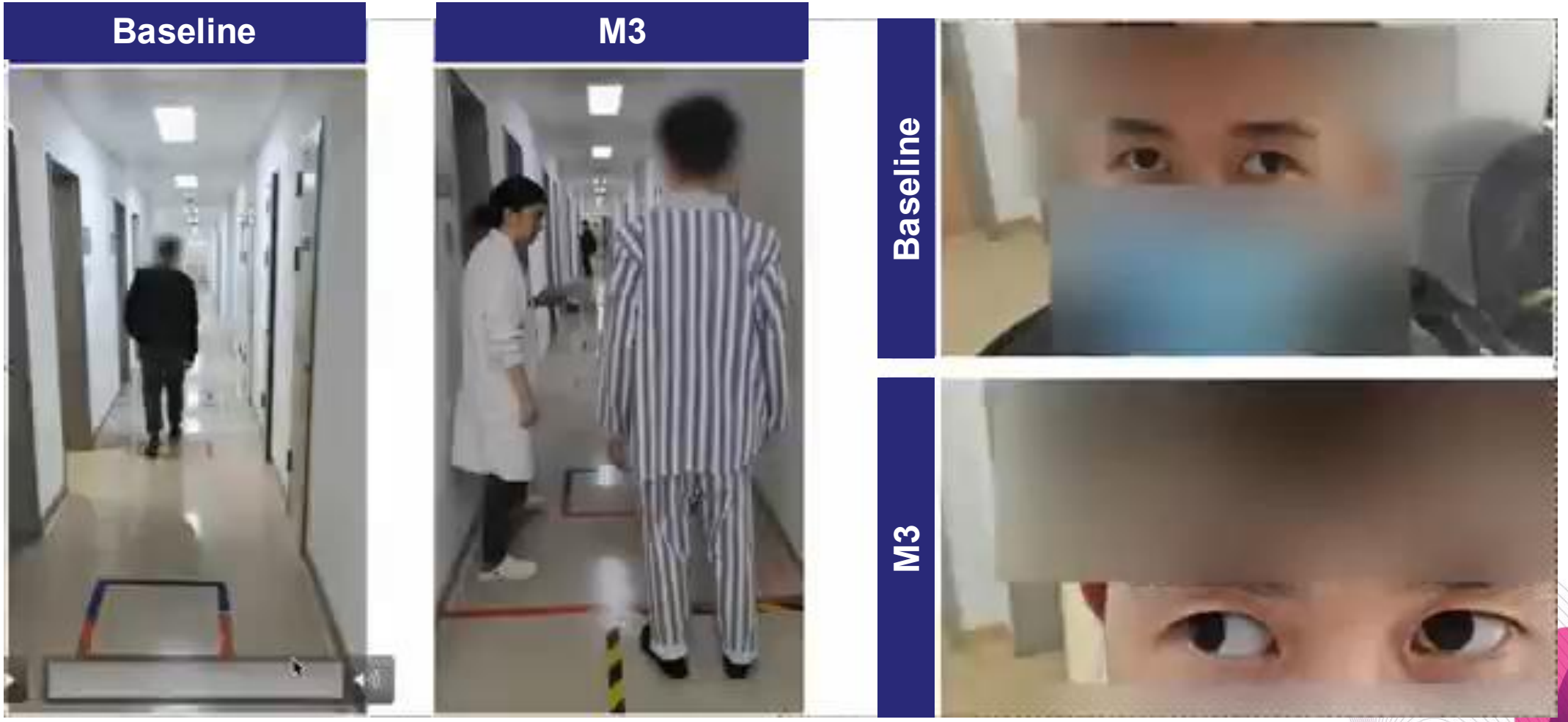
Improved EDSS scores and decrease of ANA and NFL levels



- Reduction in periventricular/paraventricular enhancing lesions on T1-weighted imaging
- No new T1-enhancing lesions, no new T2-enlarging/new lesions found by M3



Improvement in Gait, Orbital Movement after Treatment

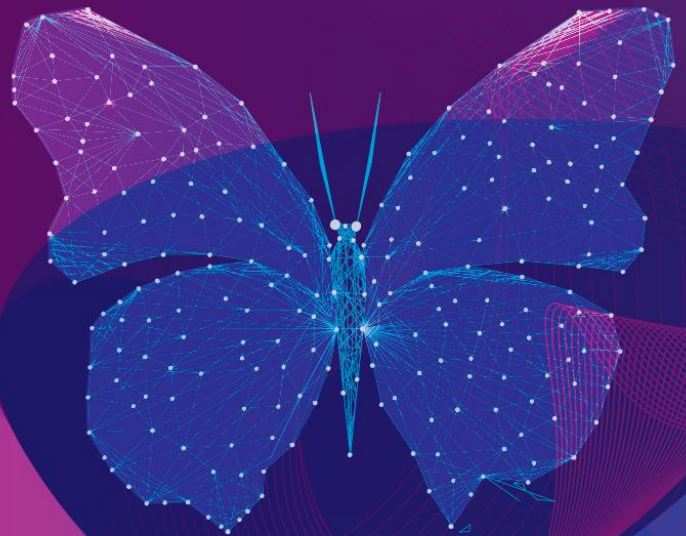


CLICK TO PLAY VIDEO

Conclusion

- C-CAR168 shows promising efficacy in highly refractory LN, with reduction in proteinuria, preserved renal function, and improvement in laboratory and extra-renal features of LN, including enabling withdrawal of IS
- Robust PK/PD profile, excellent safety, and efficacy signals in a SPMS patient
- Continued IIT in China will enroll more patients with LN and/or SLE, progressive MS, and indications such as NMOSD, SSc to explore and confirm the clinical utility of C-CAR168 in a variety of autoimmune and neurological diseases

Thank You!



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