EHA-1743

First-in-human Study of CD19xBCMA Dual-targeting FastCAR-T GC012F(AZD0120) for Patients with Refractory Systemic Lupus Erythematosus

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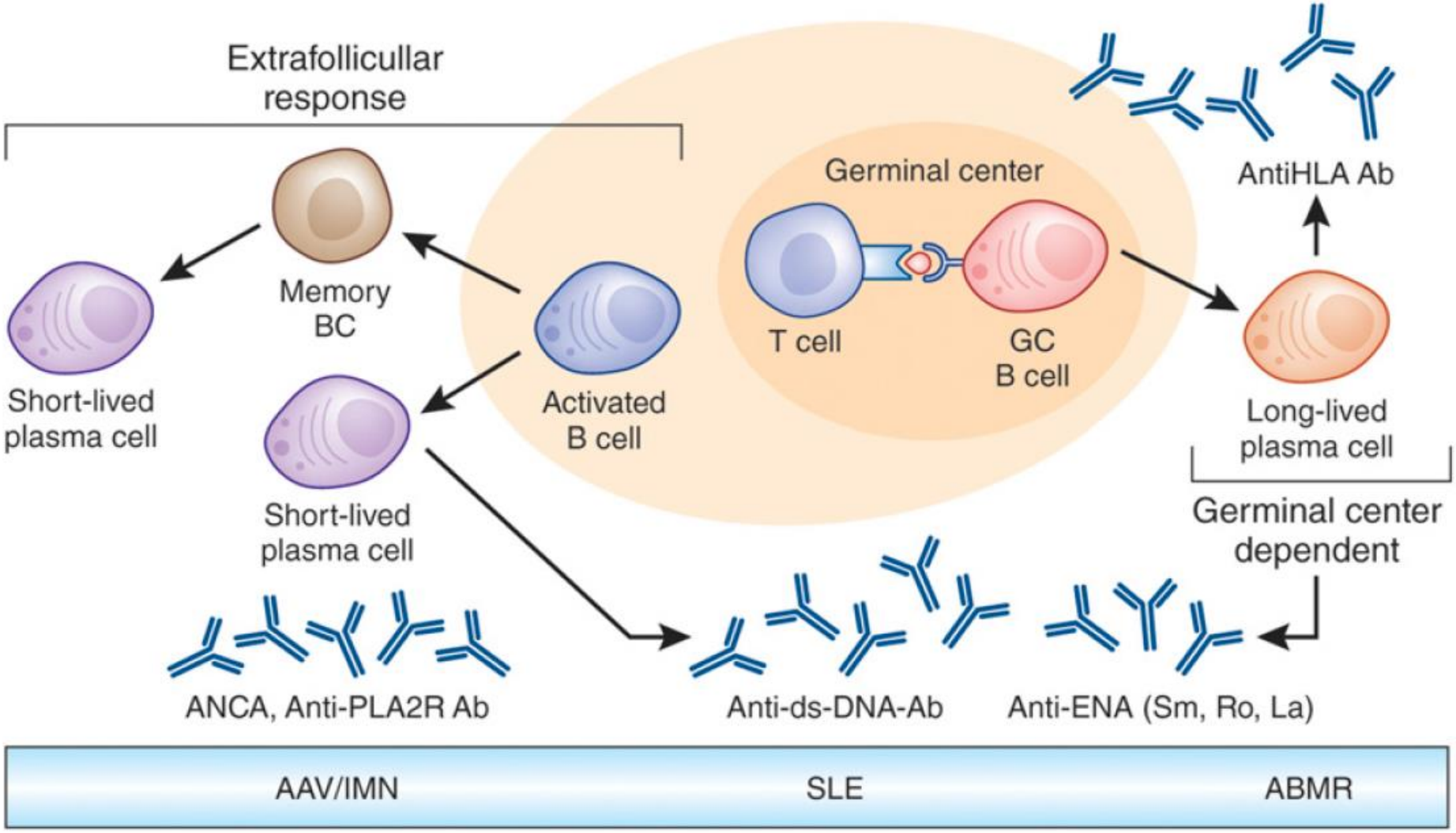
Disclosures

I have nothing to disclose

Introduction

B cell as pathogenic drivers in SLE

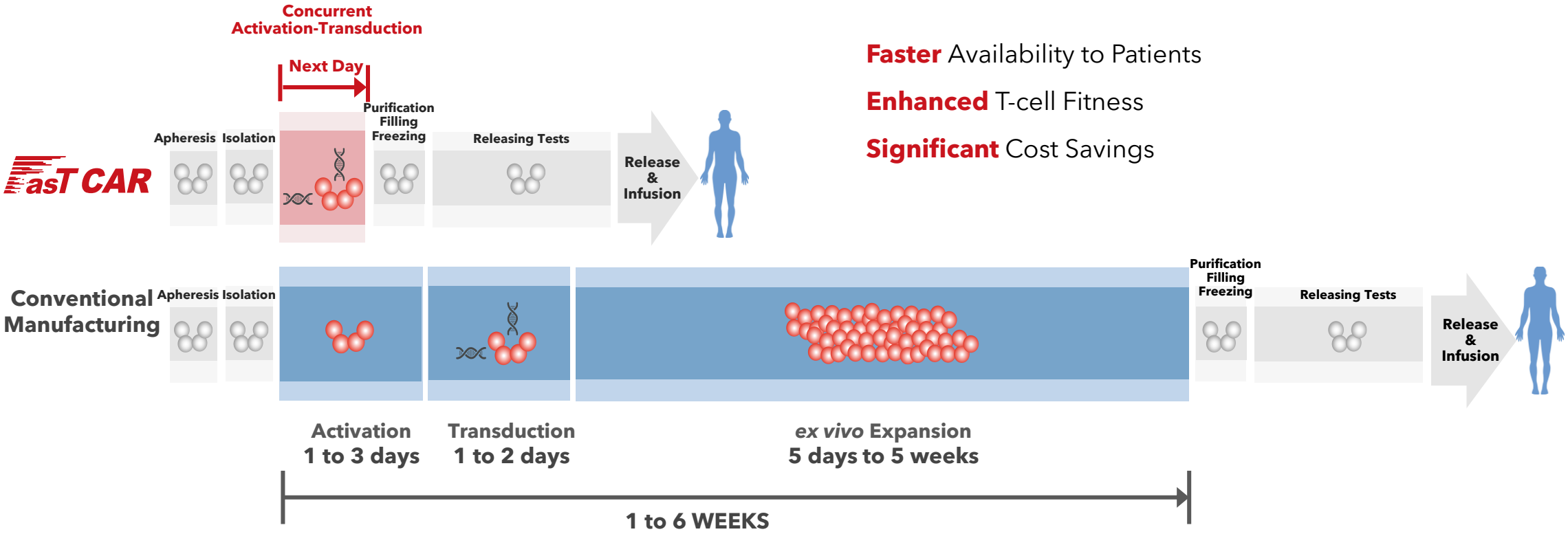


Schrezenmeier, Eva1 et al. JASN March 2018. | DOI: 10.1681/ASN.2017040367

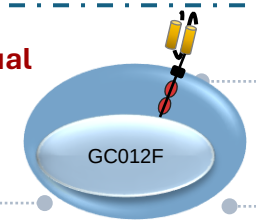
Introduction

GC012F, a CD19xBCMA dual targeting CAR-T manufactured by the FasT CAR platform

FasT CAR Platform Significantly Shortens CART Manufacturing Time and Improves T Cell Fitness



CD19xBCMA –dual target CAR-T



Dosage Form
Injection

Specification
50mL/Bag

Administration
Intravenous drip

Preclinical Studies suggest:

- ✓ High transduction efficiency and high CAR-positive rate
- ✓ Specific killing of CD19+ and BCMA+ cells in vitro
- ✓ Specific elimination of CD19+ and BCMA+ cells in mouse models in vivo
- ✓ Favorable safety profile in preclinical studies

Methods

Study design (NCT05858684)

Target Population

- Male or Female aged from 18 to 70 years
- Diagnosed with SLE and meeting the 2019 EULAR/ ACR classification criteria for SLE
- At least two immunosuppressants and at least one approved biologics were used more than 6 months without achieving LLDAS
- SELENA-SLEDAI score ≥ 8
- No prior CD19 or BCMA-targeted therapy

Study Objective & Endpoint

Primary objective: Safety and tolerability of GC012F in subjects with refractory SLE

Primary endpoints:

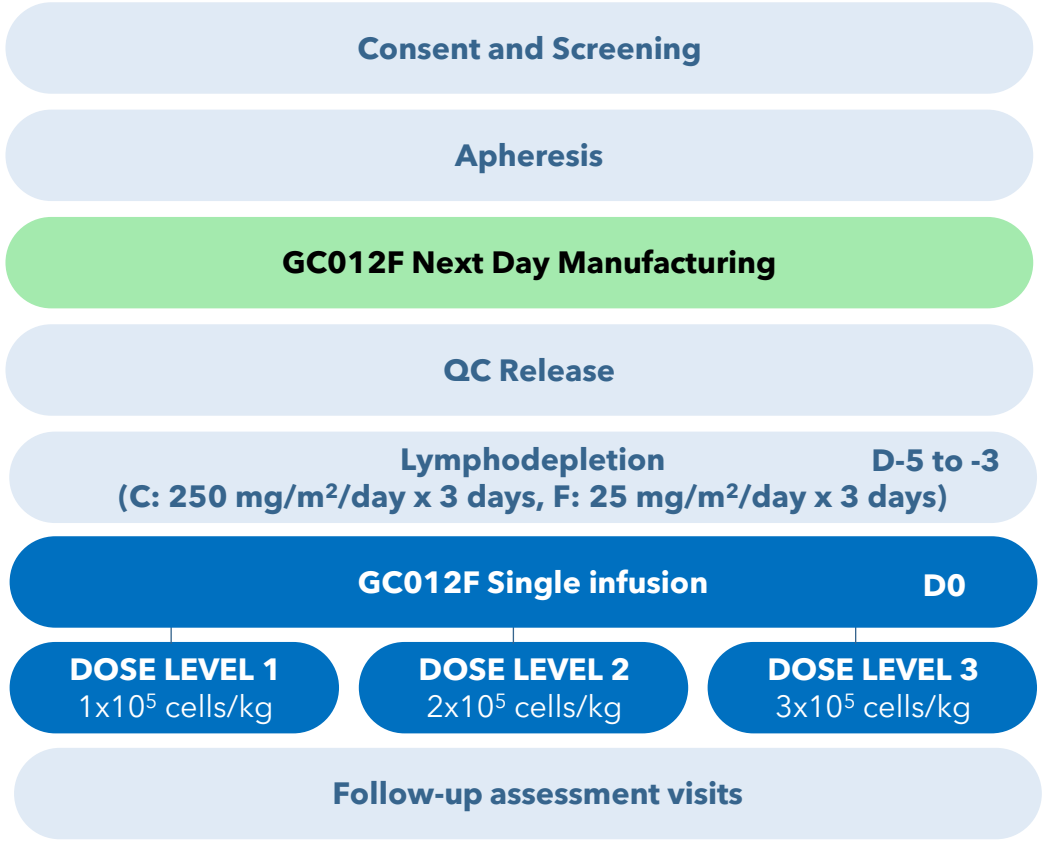
- The proportion of subjects with dose-limiting toxicity within 28 days after infusion
- The proportion of subjects with adverse events

Key Secondary objective: Efficacy of GC012F in subjects with refractory SLE

Key Secondary endpoints:

- Proportion of subjects achieving LLDAS or DORIS
- Pharmacokinetics / Pharmacodynamics

EULAR: 2019 European League Against Rheumatism
ACR: American College of Rheumatology



Data cut off on Jan 03, 2025

Results

Baseline Characteristics

		Dose level 1 N = 4	Dose level 2 N = 3	Dose level 3 N = 3	Total N = 10
Median age (range), years		25 (21,34)	26 (22,42)	31 (19,35)	26.5 (19,42)
Sex, n	**Male**	1	0	1	2
	Female	3	3	2	8
Median SLE duration (range), years		10.0 (2.4,14.1)	2.9 (2.4,18.8)	5.4 (4.5,7.9)	**5.9 (2.4,18.8)**
Median follow-up duration (range), months		13.7 (12.3,16.2)	10.4 (10.3,11.1)	7.6 (7.0,11.3)	**14.7 (7.0,16.2)**
Median SLEDAI-2K (range)-screening		12 (10, 20)	14 (8, 16)	10 (10, 16)	**12 (8, 20)**
Baseline Organ Involvement, n (%)	**Skin**	1 (25.00)	0 (0.00)	2(66.67)	3 (30.0)
	Arthritis	2 (50.00)	0 (0.00)	1 (33.33)	3 (30.0)
	Proteinuria (urine protein > 0.5g/24h)	4 (100.00)	2(66.67)	3 (100.00)	**9 (90.0)**
	Lupus Nephritis	**4 (100.0)**	**3 (100.0)**	**3 (100.0)**	**10 (100.0)**
SLE Historic Treatment	**OGC, n (%)**	4 (100.0)	3 (100.0)	3 (100.0)	10 (100.0)
	Immunosuppressants, median (range)	4 (3, 5)	4 (3, 6)	5 (4, 5)	4 (3, 6)
	Biologics, median (range)	2 (1, 3)	1 (1, 1)	1 (1, 1)	1 (1, 3)

- Follow-up (FU) duration is from 7.0 ms~16.2ms, median FU duration is 14.7 ms.
- All patients had active SLE with SLEDAI-2K median score of 12 across three dose levels at screening.
- 100% patients had Lupus Nephritis involvement (Grade III: n=1, IV: n=5, V: n=1,III+V: n=1, IV+V: n=2), with 90% of patients having proteinuria.

Results

GC012F was generally well tolerated across all dose levels

Dose limiting toxicity (DLT) criteria were not met.

Follow-up adverse effects (AEs*) related to CAR T infusion, number of patients (%)				
SOC/PT, n (%)	Any grade (N = 10)	Grade 3 or higher	Any grade (N = 10)	Grade 3 or higher
	≤ 12 weeks post-CAR		> 12 weeks post-CAR	
Hematologic TEAEs* (≥25%)				
White blood cell count decreased	9 (90.0)	3 (30.0)	3 (30.0)	0 (0.0)
Lymphocyte count decreased	7 (70.0)	6 (60.0)	0 (0.0)	0 (0.0)
Neutrophil count decreased	8 (80.0)	4 (40.0)	2 (20.0)	2 (20.0)
Anaemia	5 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-Hematologic TEAEs* (≥25%)				
Hypogammaglobulinemia	10 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fever	9 (90.0)	1 (10.0)	1 (10.0)	0 (0.0)
Upper respiratory tract infections	4 (40.0)	0 (0.0)	3 (30.0)	0 (0.0)

CRS	1×10^5 (n = 4)	2×10^5 (n = 3)	3×10^5 (n = 3)	Overall (n = 10)
Any Grade	3 (75%)	2 (66%)	2 (66%)	7 (70%)
Grade 1	3 (75%)	2 (66%)	1 (33%)	6 (60%)
Grade 2	0	0	1 (33%)	1 (10%)
Grade 3	0	0	0	0
Grade 4	0	0	0	0

CRS any grade	Median (days)	Range (days)
Time to onset	7	6, 14
Duration	1	1, 4

- **CRS** events were reported in 70% of patients, with the majority being grade 1 (6/10), 1 grade 2 CRS. All resolved with SOC within 2 weeks.
- **No ICANS** observed.
- All AEs were reversible. No grade 3/serious infections or opportunistic infections were collected. And hypogammaglobulinemia do not had any clinical impact in safety.

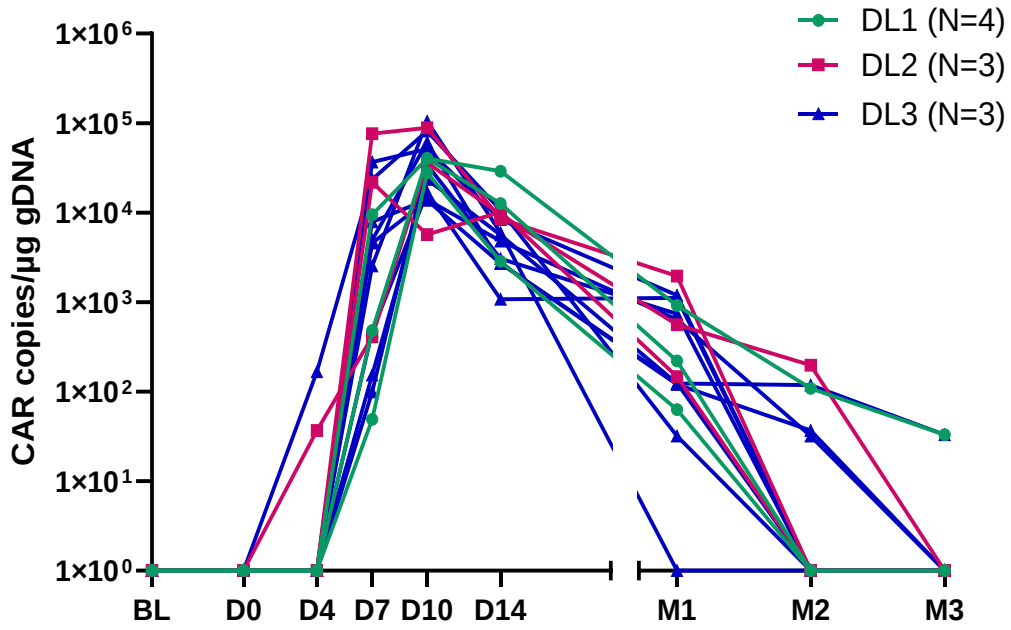
* AEs were graded according to CTCAE v5.0, TEAE - treatment emergent adverse event

Results

GC012F shows robust CAR-T cell expansion and results in immune reset

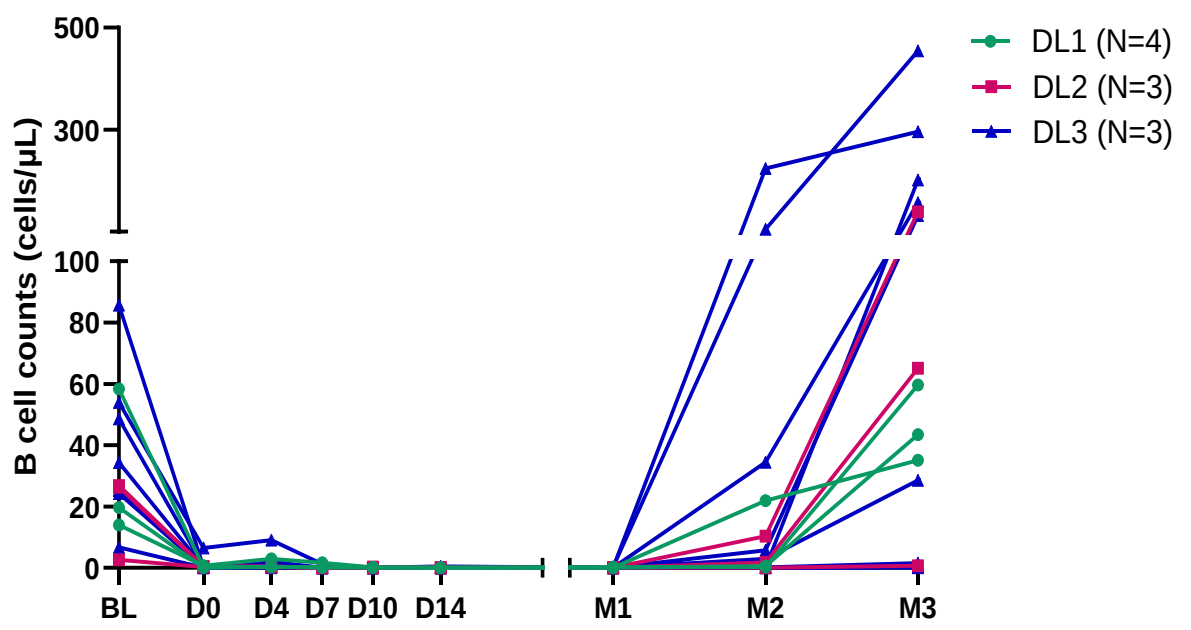
B cell aplasia achieved in all patients with median duration of 84 days. Upon B cell reconstitution, 94.62% cells show naive phenotype.

CAR-T cell expansion



- Cmax, copies/µg gDNA, median(range) = 20180 (11482-50316)
- Tmax, days, median(range) = 10 (7-10)
- AUC_{0-28}, copies/µg gDNA*Days, median(range) = 123165 (56652-210819)

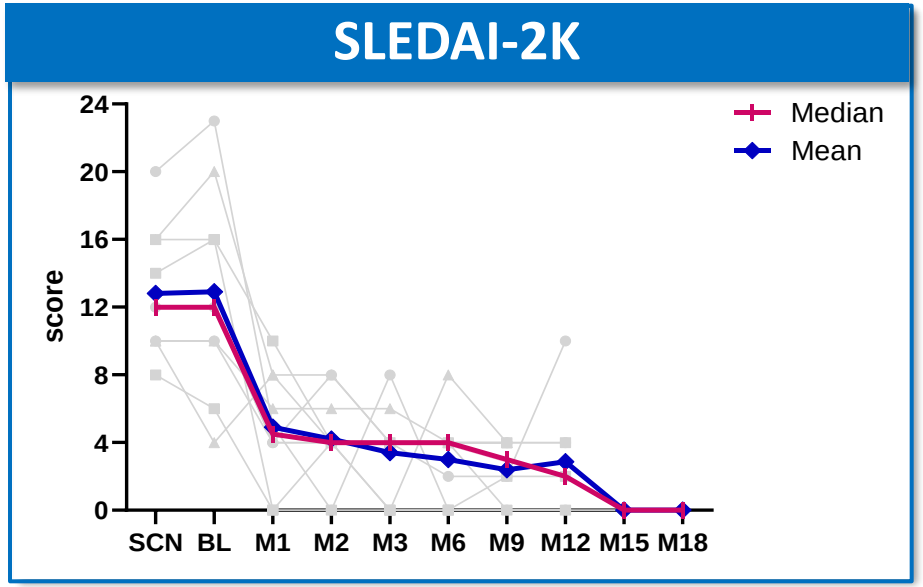
B cell depletion and reconstitution

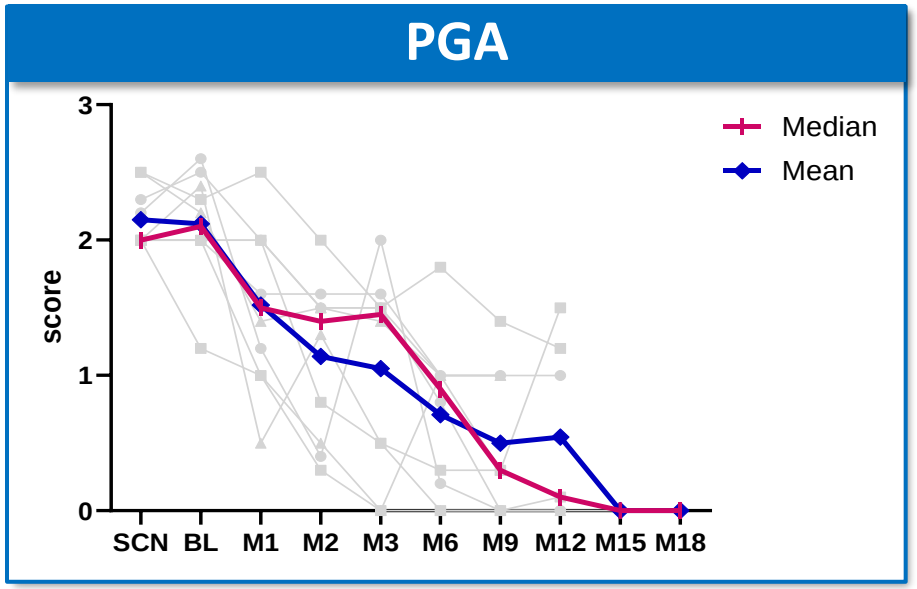


- B cell recovery, days, median(range) = 84 (84-168)
- B cell recovery, cells/µl, median(range) = 9.83 (1.16-101.28)

Results

Significant decline in SLEDAI-2K and PGA scores in all patients post GC012F infusion





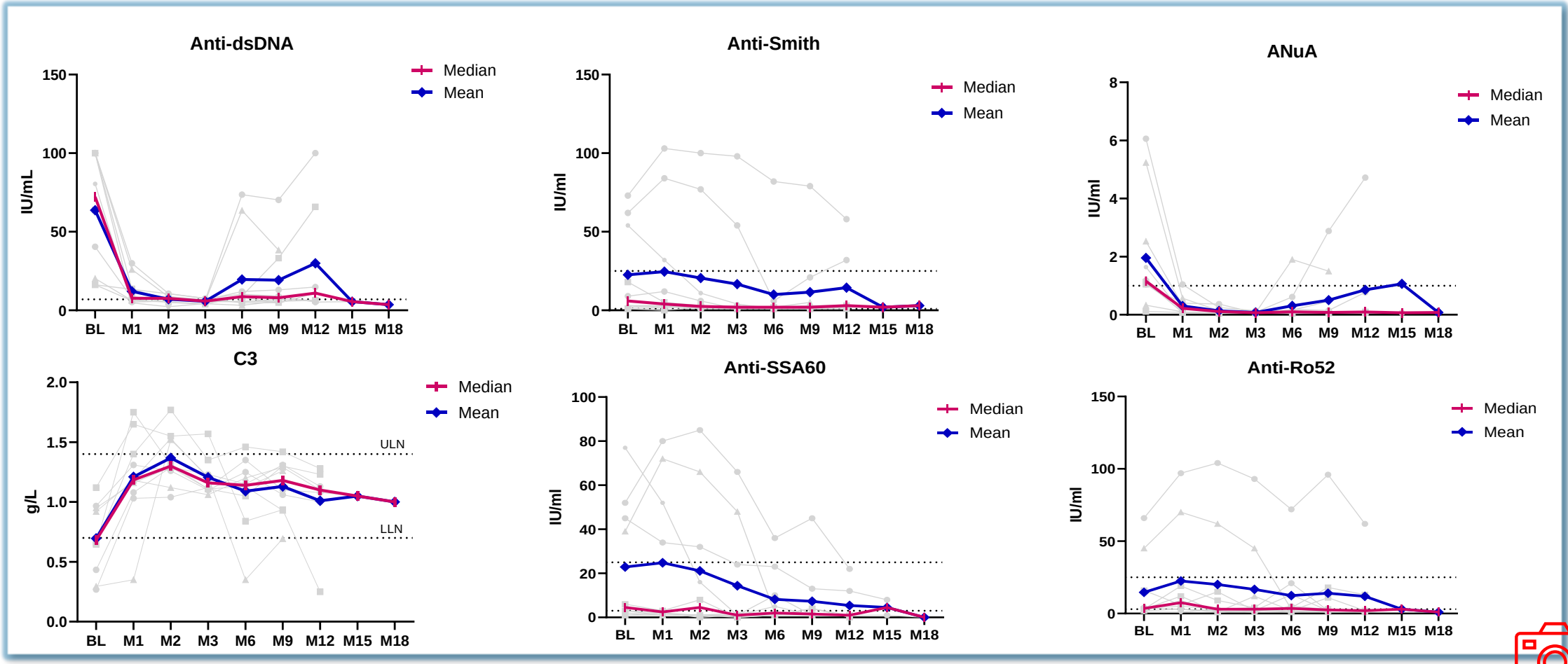
SLE disease assessment		SRI-4 N = 10	DORIS remission N = 10
SLE remission	Week 12	10/10 (100%)	3/10 (30%)
	Week 24	10/10 (100%)	4/10 (40%)
	Week 36	10/10 (100%)	6/10 (60%)
Glucocorticoid Free		6/10 (60%)	
Immunosuppressant Free		10/10 (100%)	
No biologics		10/10 (100%)	

***DORIS remission was not achieved in some cases due to residual proteinuria (SLEDAI-2K = 4).**

Results

Rapid serological improvement post GC012F infusion

- Anti-dsDNA and complement levels rapidly normalized following CAR-T cell infusion.
- Other ENA autoantibodies, including ANuA, Anti-Smith, Anti-SSA60, Anti-Ro52, declined gradually and remained stable in eight out of ten patients.

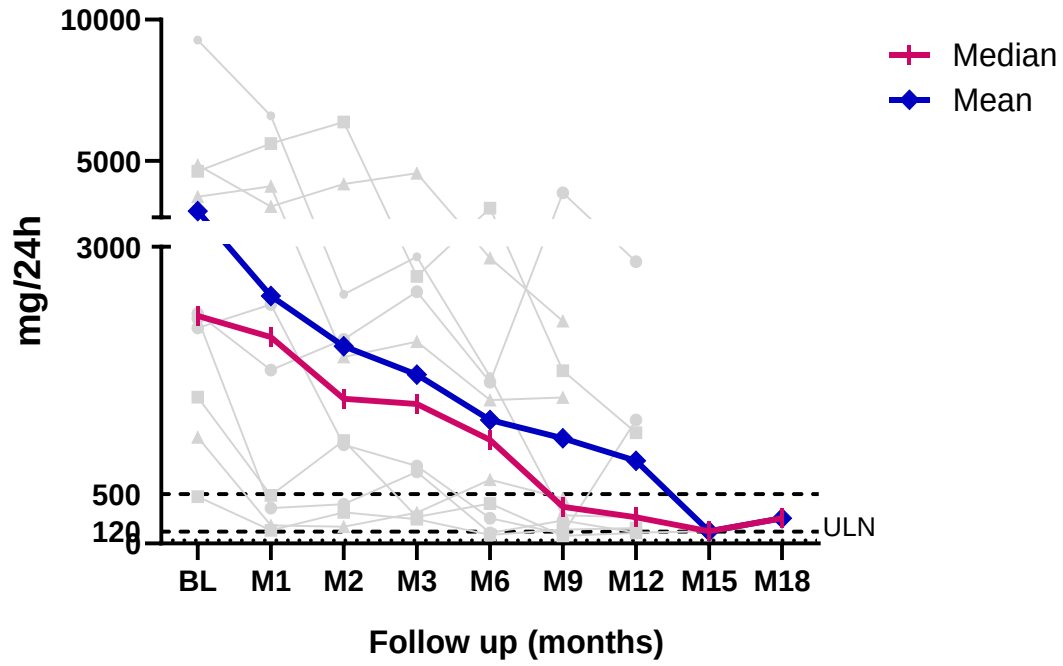


Results

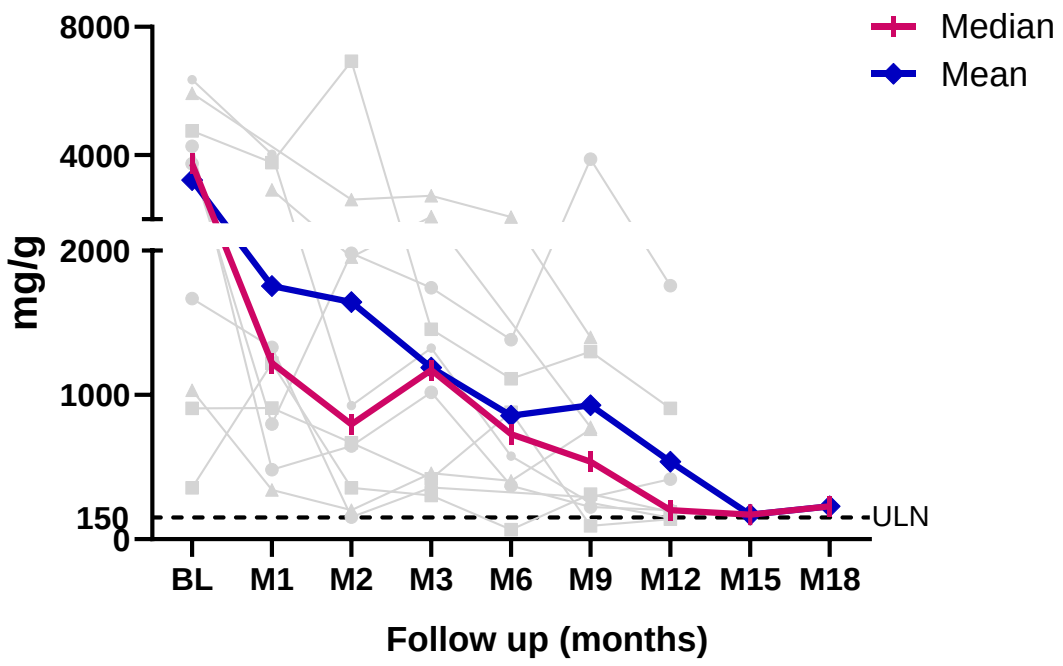
Significant improvement in kidney function

- A significant reduction in proteinuria was observed in eight out of ten patients by week 36.
- 4 out of 10 subjects did not achieve DORIS remission at week 36 because of residual proteinuria
  - None exhibited other active SLEDAI-2K scores, active sediment, or UPCR decline.

24h Urine protein



UPCR



Three subjects who did not achieve DORIS remission consented to a repeat renal biopsy at 6–9 months post CAR-T cell treatment.

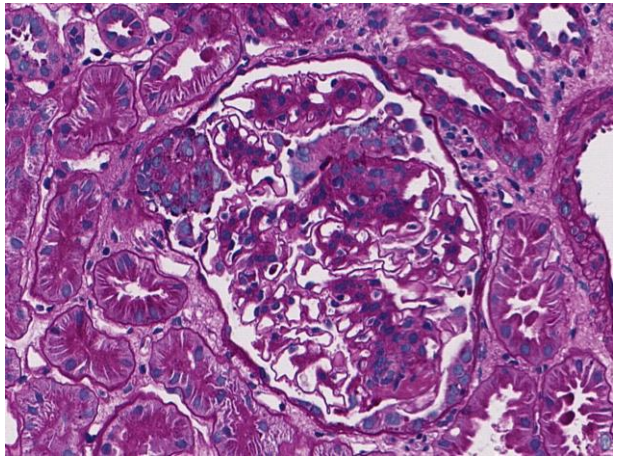
UPCR: Urine Protein Creatinine Ratio

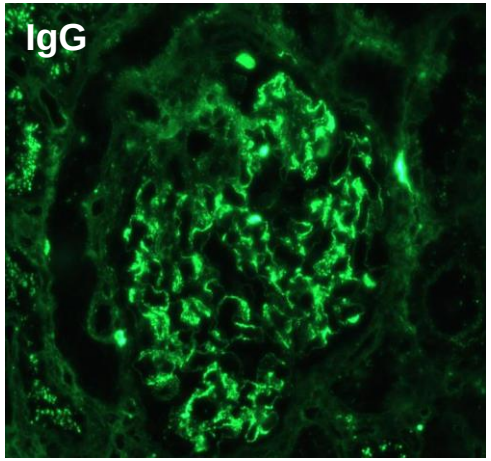
Results
Renal re-biopsy results - Patient-06

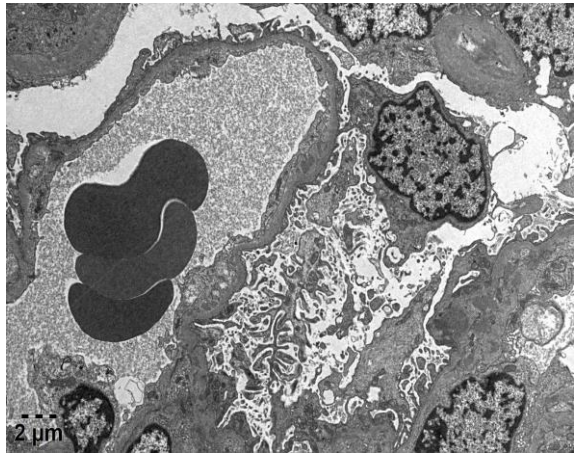
- Immunofluorescence (middle) reveals a marked reduction in IgG deposition in the kidney tissue.
- Electron microscopy (right) shows electron-dense deposits undergoing dissolution and absorption.

P06

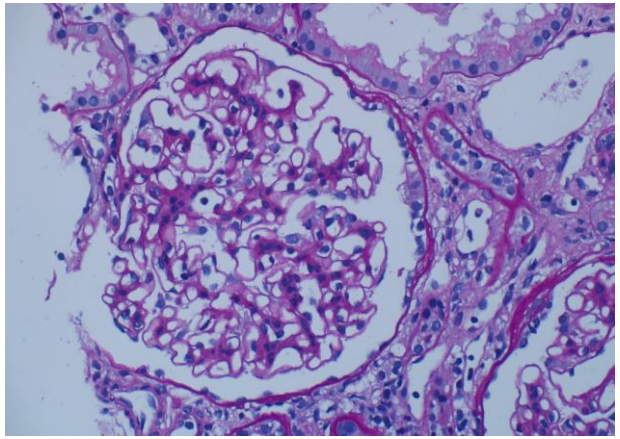
Prior. CAR

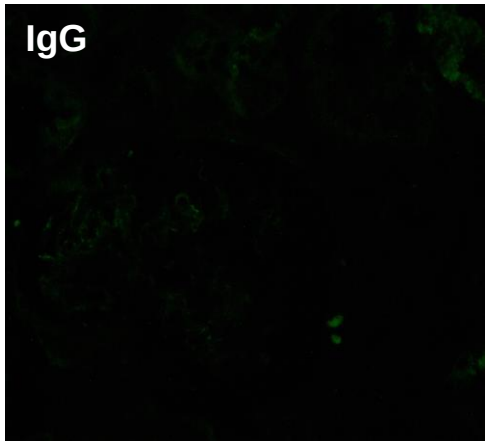


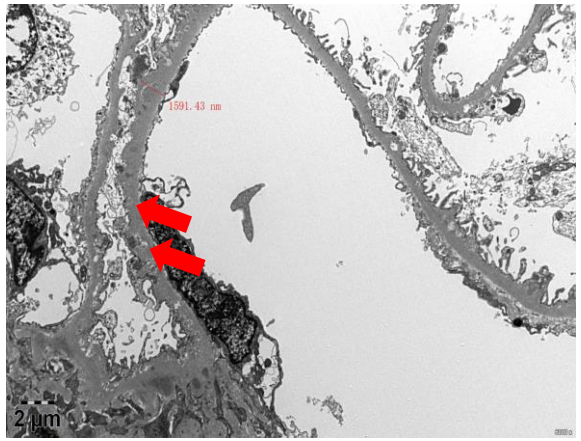




Post. CAR





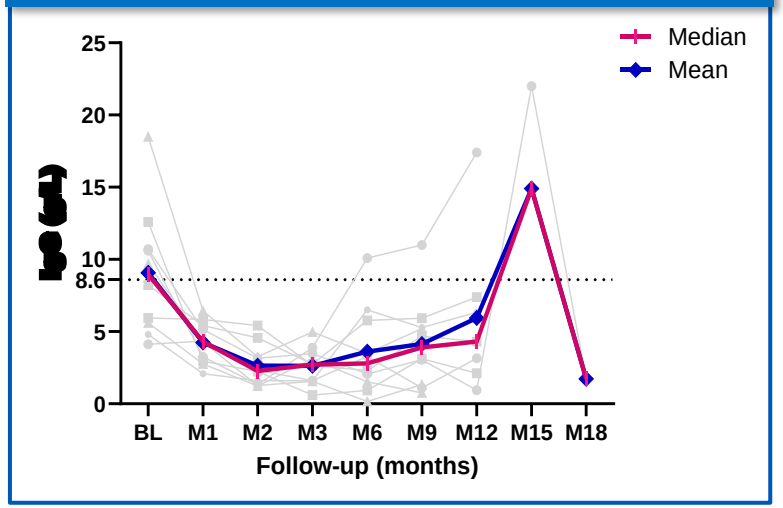


Results

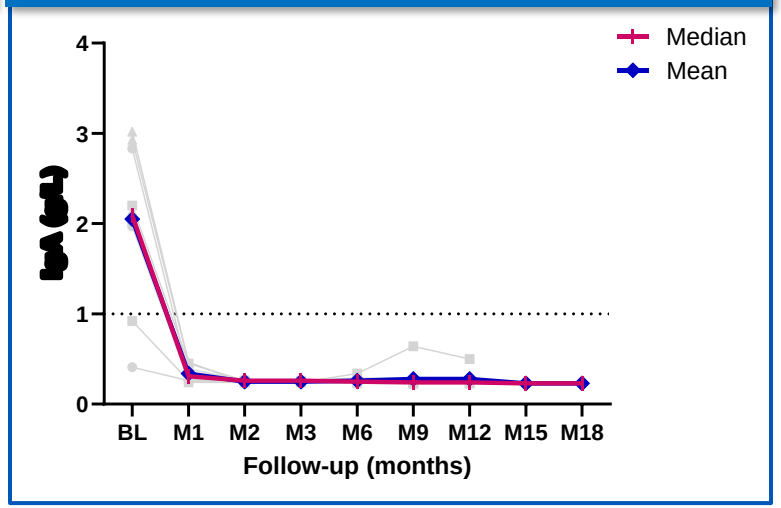
Immunoglobulin levels post GC012F infusion

- All patients exhibited a reduction in serum IgA, IgG, and IgM levels after CAR-T cell infusion
- IVIG was administered on demand.

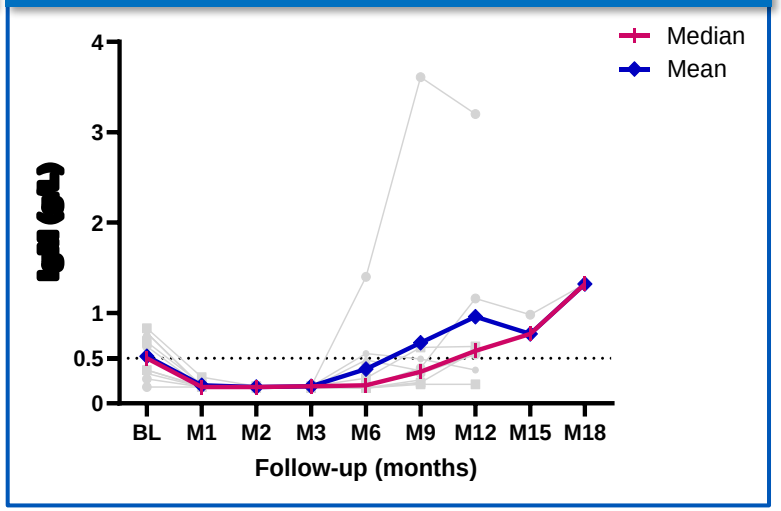
IgG



IgA



IgM



Conclusions

- GC012F was generally well tolerated across all dose levels and no DLT signals identified.
- CK analysis revealed robust GC012F cell expansion.
- GC012F demonstrated rapid, deep, and durable responses in patients with refractory SLE(100%LN):
  - All patients experienced considerable reduction in SLEDAI-2K and PGA, with promising results/trending in DORIS remission rate and SRI-4.
  - Significant improvement in anti-dsDNA, ANuA, ENA profile, complement levels and proteinuria level.
  - B cell aplasia was achieved after GC012F infusion in all patients and predominantly naïve B cell phenotype was observed upon B cell reconstitution .
  - Most subjects who did not achieve DORIS remission by M9 (4/10) had residual proteinuria, which was likely attributed to prior kidney damage rather than lupus activity, based on repeated renal biopsy results.
- GC012F offers a promising therapeutic strategy for patients with an unmet medical need
  - Phase 1/2 IND studies (US: NCT06897930; China: NCT06530849) are ongoing.

Acknowledgements

We would like to thank the patients, their families, the investigators and all the caregivers involved in this study and AstraZeneca/Gracell Biotechnologies for providing FasT CAR™ GC012F.

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