CAR-T in Autoimmune Diseases

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Disclosures

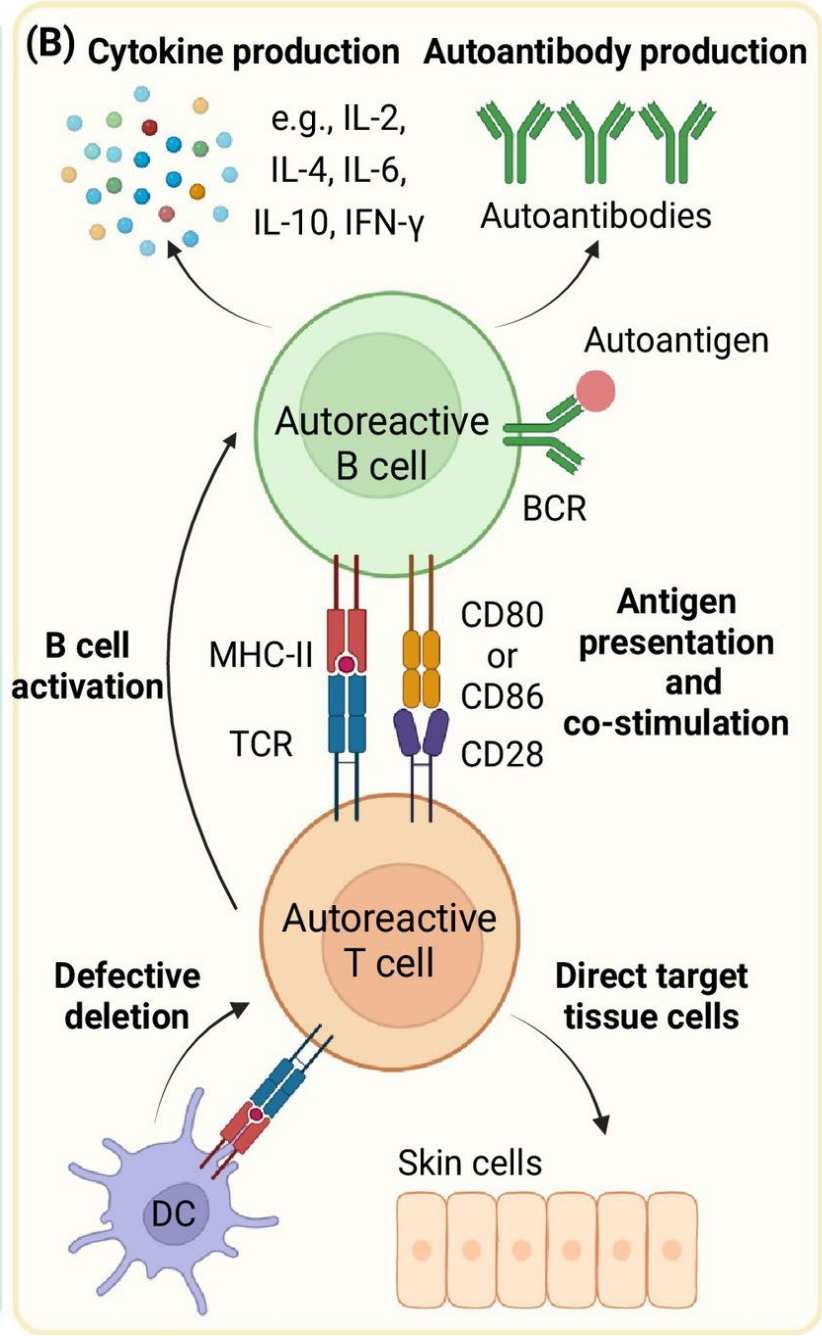
BMS-Speaker’s Bureau

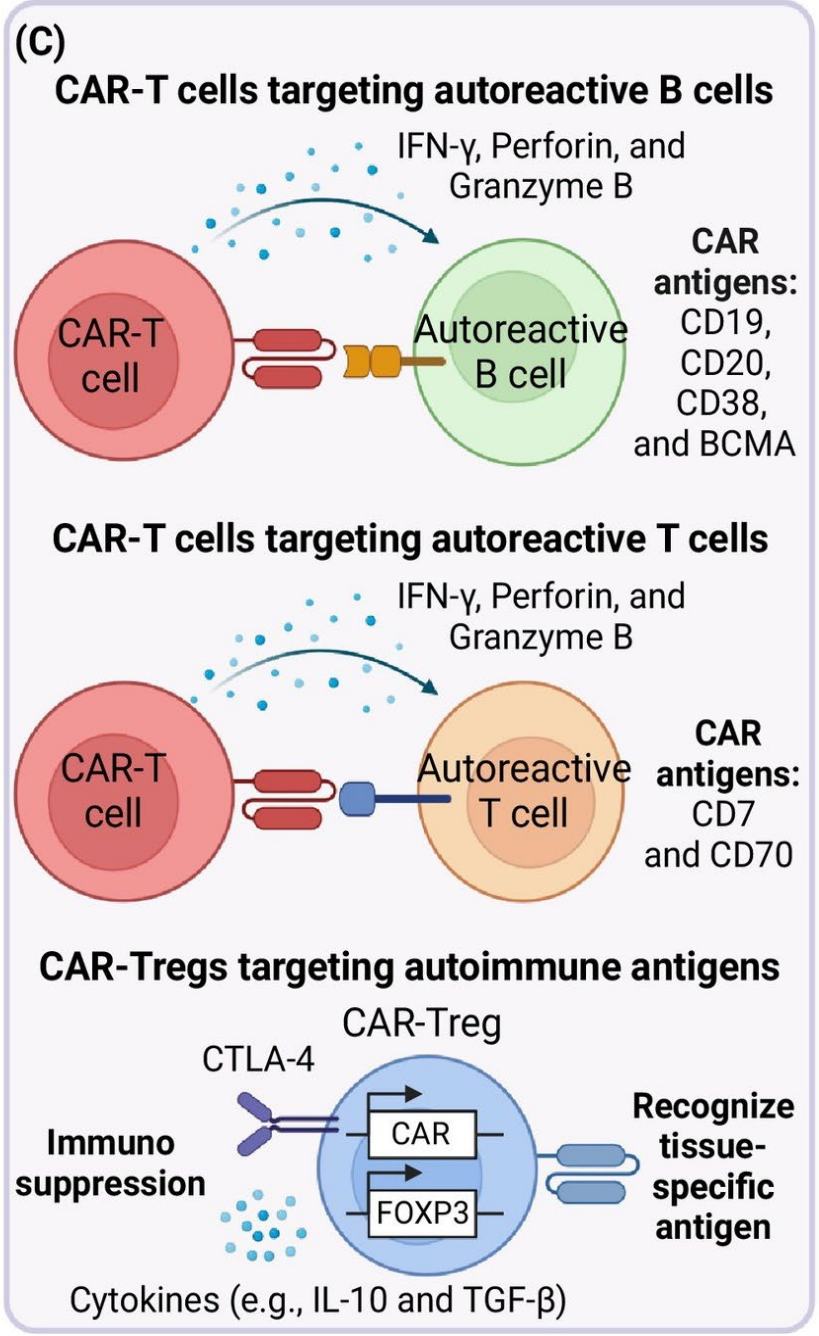
I have autoimmune alopecia

(skin in the game?)

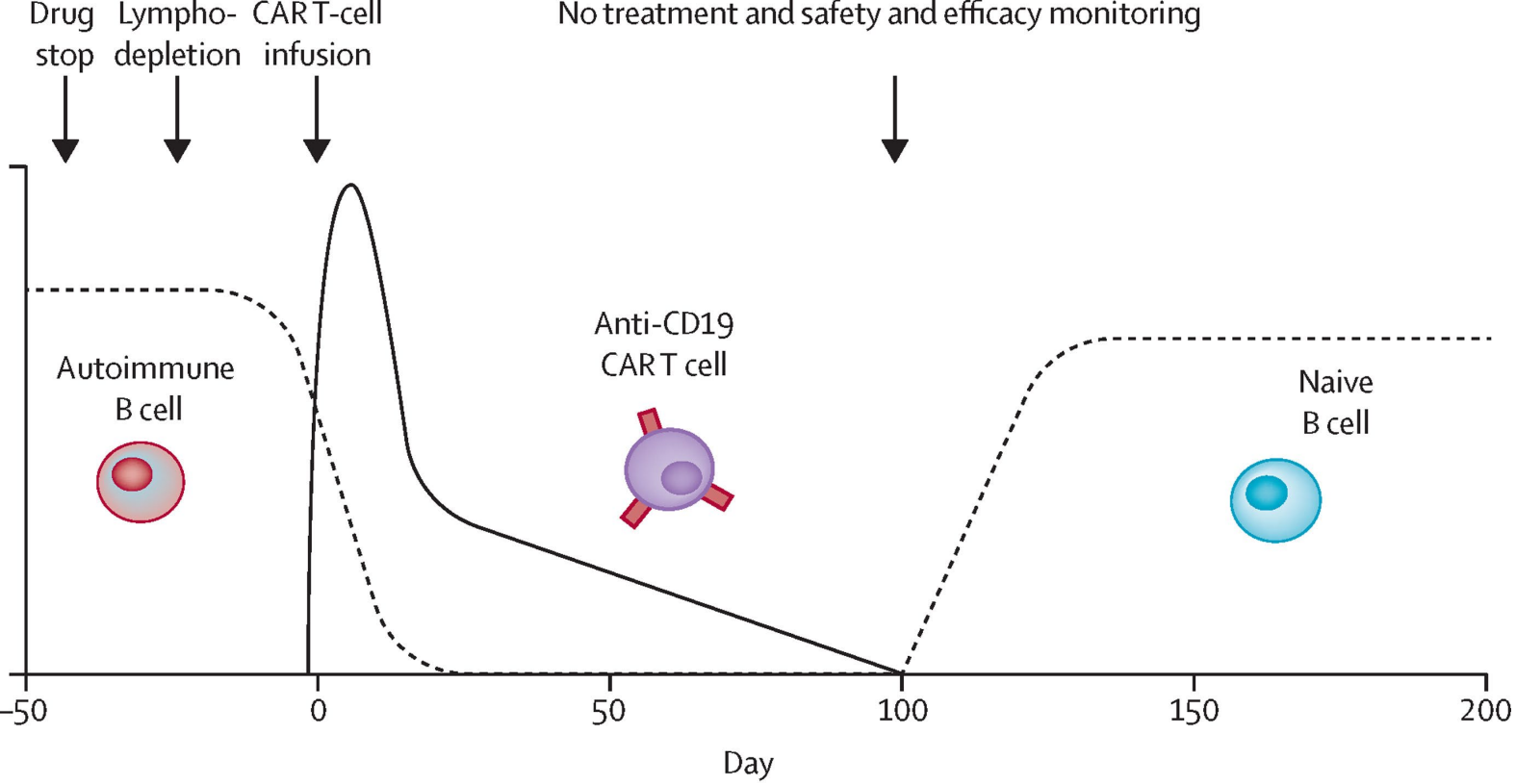
Background

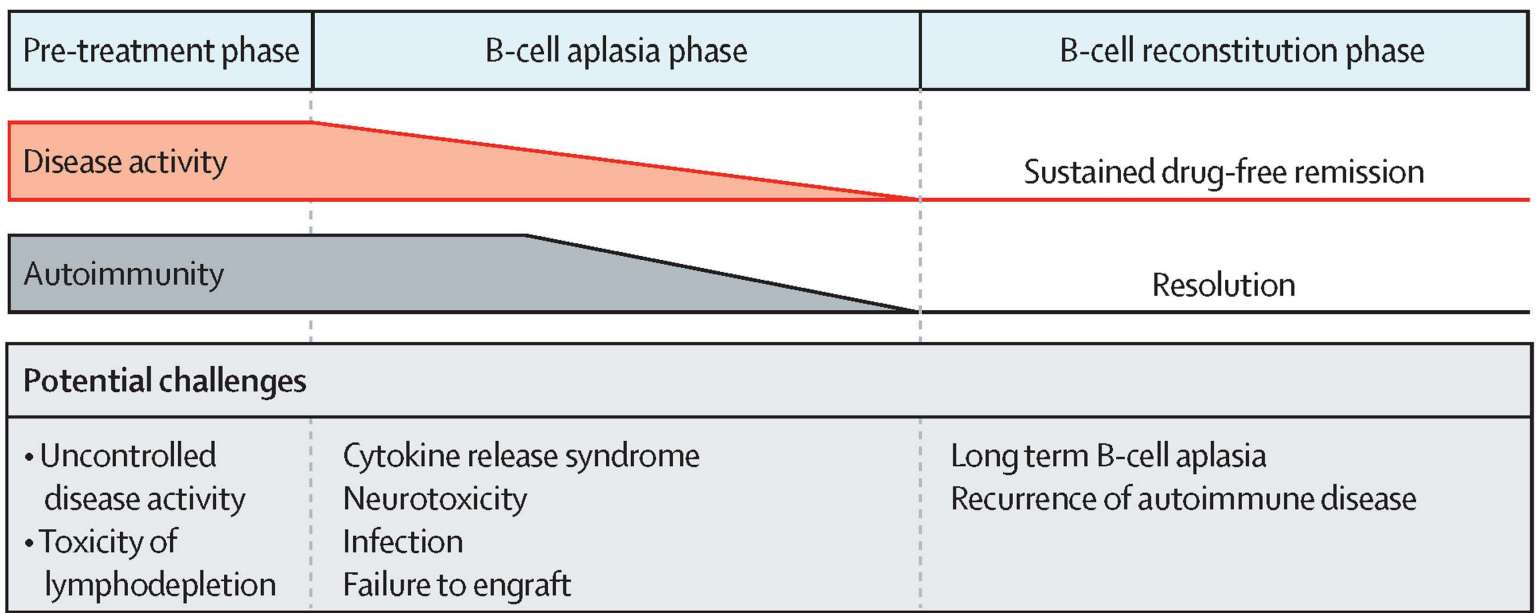
- Autoimmune disorders driven by autoreactive B and T cells.
- Indefinite Monoclonal antibody therapy results in incomplete control
- CAR-T cell therapy mitigates autoimmune diseases by targeting specific markers on B cells (CD19, CD20, CD38, BCMA) and T cells (CD7, CD70).





Li YR, et al. Frontiers in CAR-T cell therapy for autoimmune diseases. Trends Pharmacol Sci. 2024 Sep

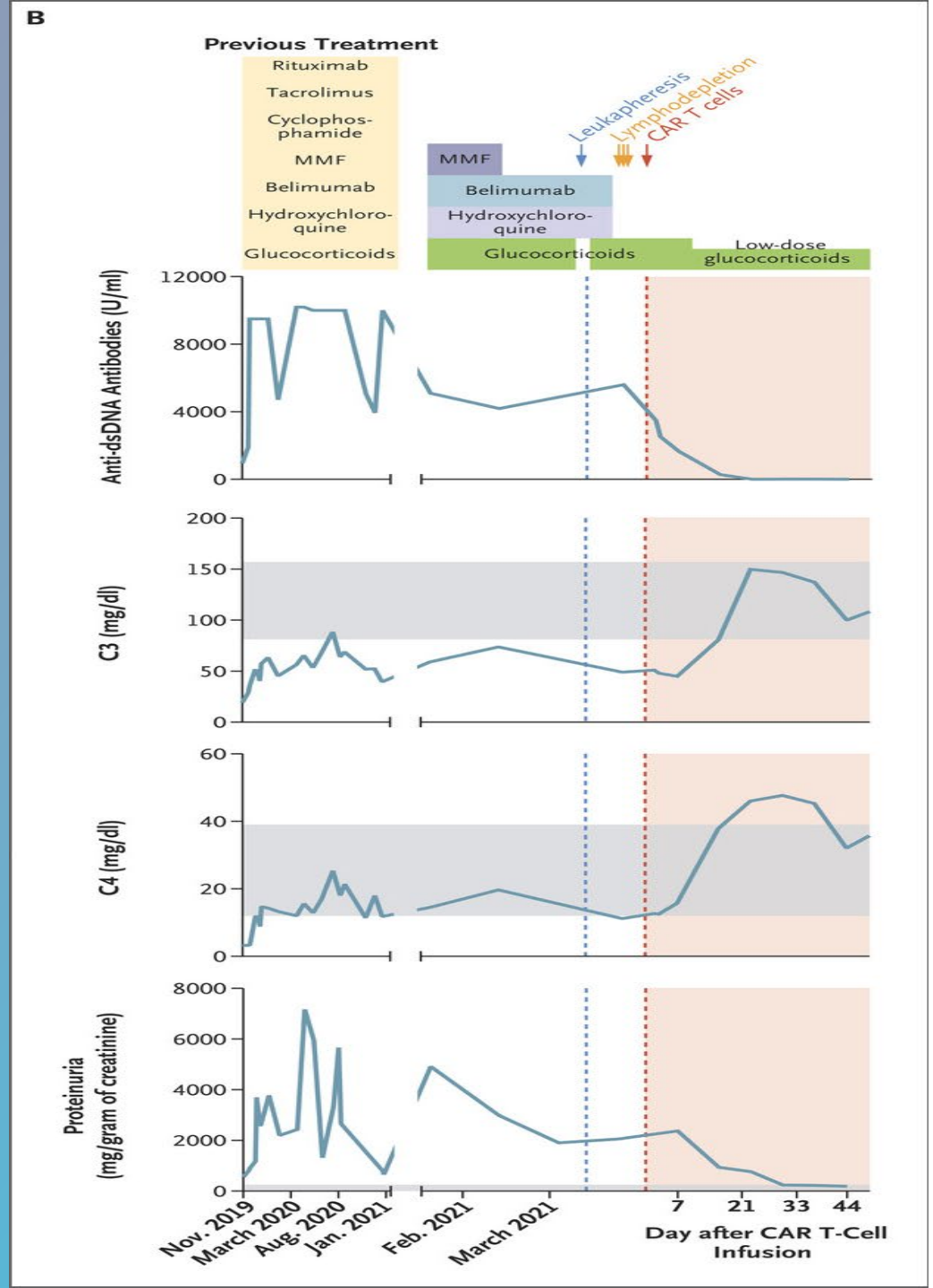




- First, we need to stop immunosuppressive therapy prior to leukapheresis
- After lymphodepleting chemotherapy and CAR T-cell infusion/expansion, patients experience B-cell aplasia, corresponding with decrease in disease activity and autoimmunity
- Finally with naïve B-cell recurrence and reconstitution, patients may enter a phase of (indefinite?) drug-free remission.

Schett, Georg et al. The Lancet. Nov 2023.

CD19-CAR-T for SLE



20 yo woman with:

- active lupus nephritis (World Health Organization class IIIA, indicating focal proliferative disease with active lesions)
- nephrotic syndrome
- Pericarditis
- Pleurisy
- Rash
- Arthritis
- history of Libman–Sacks endocarditis

Mougiakakos, et al.

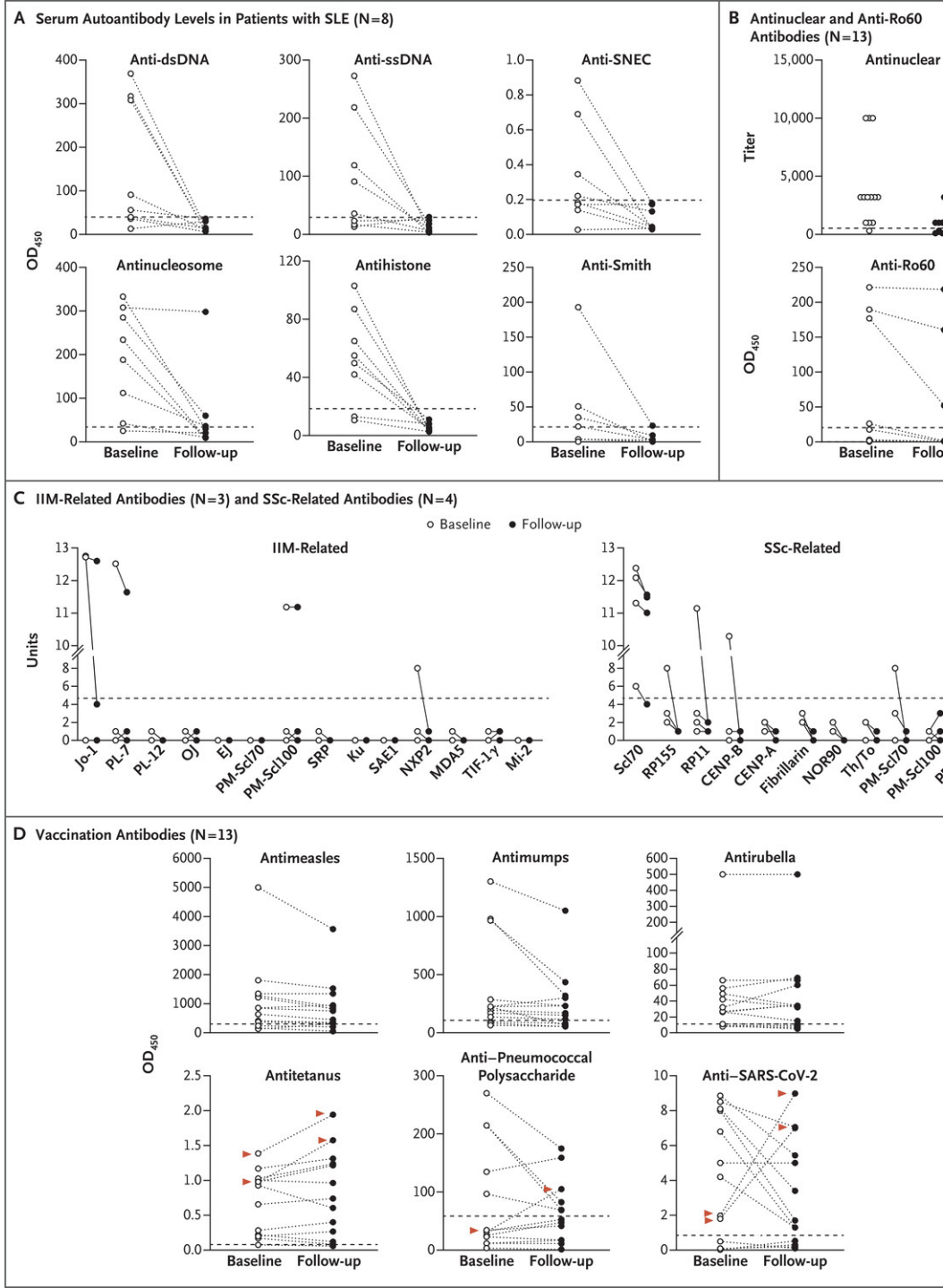
August 4, 2021

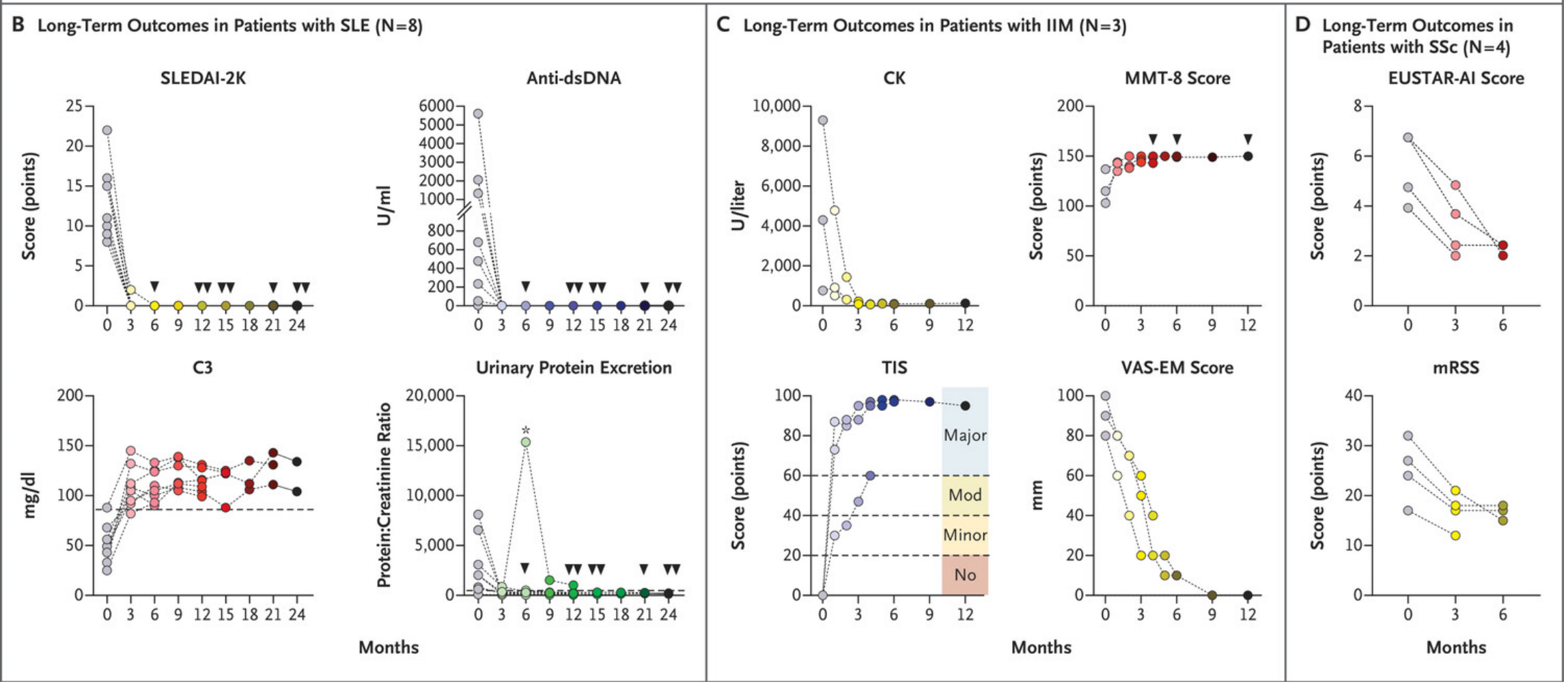
15 patient case series

systemic lupus erythematosus (SLE)
idiopathic inflammatory myositis (IIM)
systemic sclerosis (SSc)

- Median follow-up = 15 months (4-29)
- Mean duration of B-cell aplasia: 112+/- 47 days
- Grade 1 cytokine release syndrome occurred in 10 patients. One patient each had grade 2 cytokine release syndrome, grade 1 immune effector cell–associated neurotoxicity syndrome, and pneumonia that resulted in hospitalization.
- seroconversion of antibodies against dsDNA, single-stranded DNA, secondary necrotic cells, nucleosomes, and Smith protein
- vaccination-related antibodies were not eliminated (implying CD19-negative plasma cells were not depleted)

Muller et al, NEJM Feb 21, 2024.



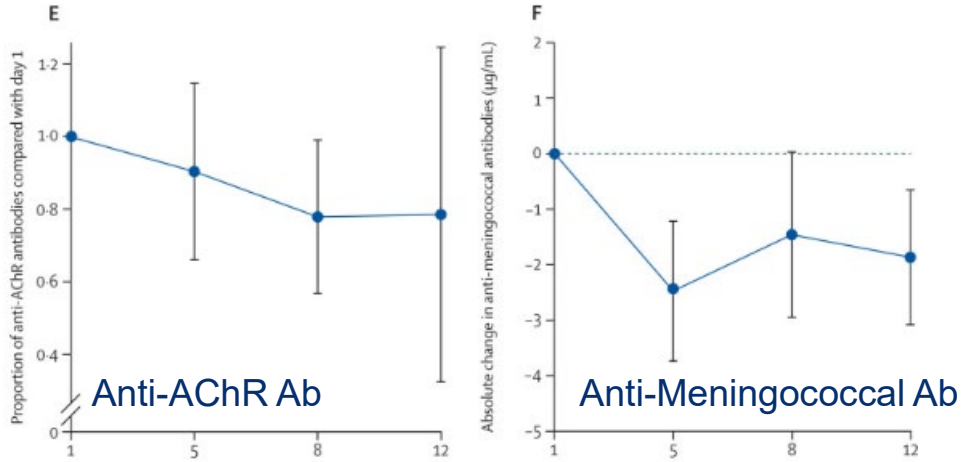


- All the patients with SLE had DORIS remission
- All the patients with idiopathic inflammatory myositis had an ACR–EULAR major clinical response
- All the patients with systemic sclerosis had a decrease in the score on the EUSTAR activity index.
- Immunosuppressive therapy was completely stopped in all the patients.

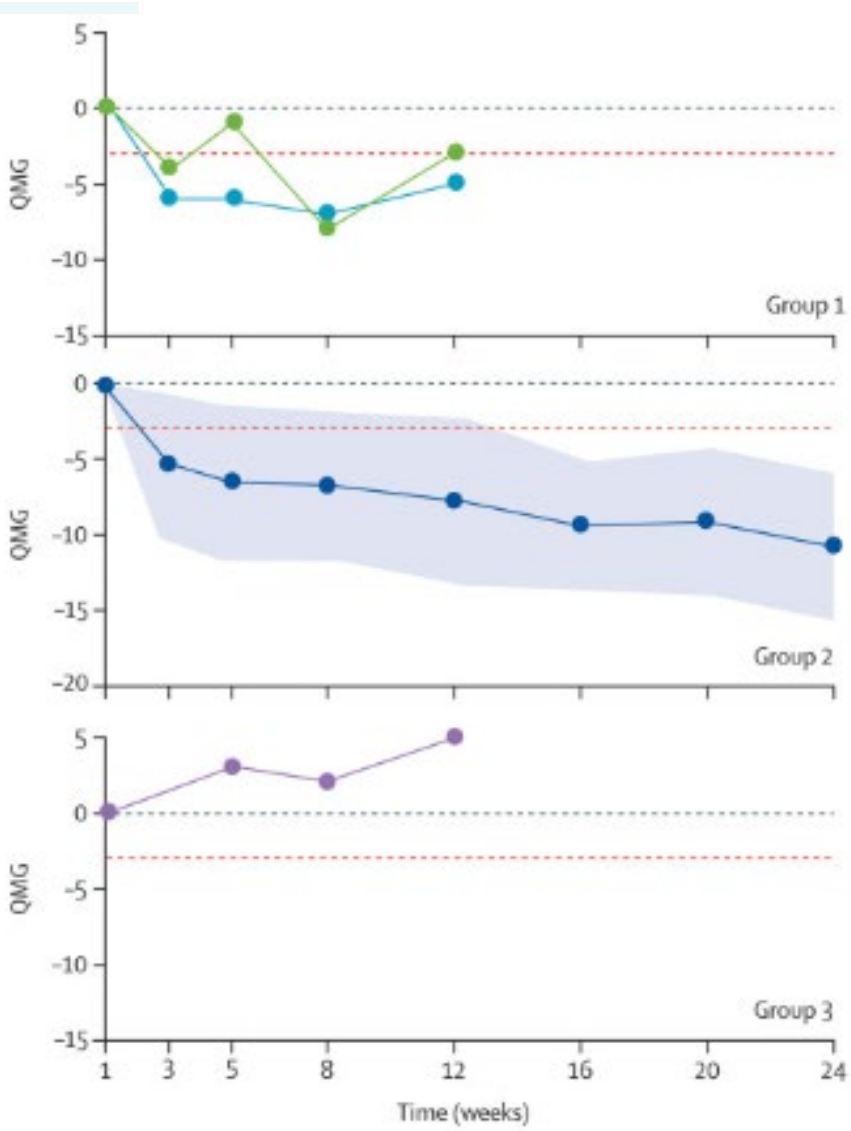
Muller et al, NEJM Feb 21, 2024.

BCMA-CAR-T for MG

- Phase 1b/2a trial (MG-001) with 14 patients with MG treated with Descartes-08
- Autologous ex-vivo mRNA-engineered $CD8^+$ CAR-T cells did not require LD chemotherapy
- Total 6 doses infused:
- MTD = $52{\cdot}5 \times 10^6$ CAR^+ cells/kg
  - No dose-limiting toxicity or major adverse events like cytokine release syndrome or neurotoxicity.
  - Clinically significant improvements in myasthenia gravis severity scores.



Quantitative Myasthenia Gravis Score (QMG)



n=2
2x-week

n=7
weekly

n=1
monthly

Granit V, et al; (MG-001): Lancet Neurol. 2023

Ongoing Clinical trials

	ARCELLX	BMS	CARIBOU	NOVARTIS	KYVERNA	Autolus Therapeutics
Product	**anitocabtagene autoleucel (anito-cel)**	**lisocabtagene maraleucel (NEX-T platform)**	**CB-010**	**rapcabtagene autoleucel**	**KYV-101**	**obecabtagene autoleucel (obe-cel)**
Phase	1, escalation + expansion	1, escalation + expansion	1	2	2	2
Target/product	BCMA/auto	CD19/auto	CD19/allo (CRISPR)	CD19/auto	CD19/auto	CD19/auto
Target disease	-**Generalized Myasthenia Gravis (GMG),** Myasthenia Gravis Foundation of America [MGFA] Grade 2 to 4a	-Systemic Lupus Erythematosus (**SLE**) -Idiopathic Inflammatory Myopathy (**IIM**) -Systemic Sclerosis (**SSc**)	-Refractory Systemic Lupus Erythematosus (**SLE**)	-Severe Active Granulomatosis with Polyangiitis (**GPA**) -Microscopic Polyangiitis (**MPA**) **[lupus nephritis]**	-Refractory, Progressive **Multiple Sclerosis**	-Severe, Refractory **SLE** **-Lupus Nephritis**

Questions?

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