KYV-101 Anti-CD19 CAR T-Cell Therapy: The Future of Autoimmune Disease Treatment

NOVEMBER 18, 2024

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This presentation includes results from named patient activities. Named patient activities are not part of our clinical trials for KYV-101 and data from these trials and activities are reported by the relevant investigators and physicians. Such data are not obtained using a single protocol or designed to be aggregated or reported as study results and may be highly variable. While we do not expect to be able to use the results from these investigator-initiated trials or named patient activities in our applications for marketing approval to the U.S. Food and Drug Administration or other foreign regulatory agencies, we believe that this strategy may provide some competitive advantage as we will be able to acquire additional clinical insights beyond highly focused clinical trials in specific geographies.

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Why We Are Here... Patients Are Our Why

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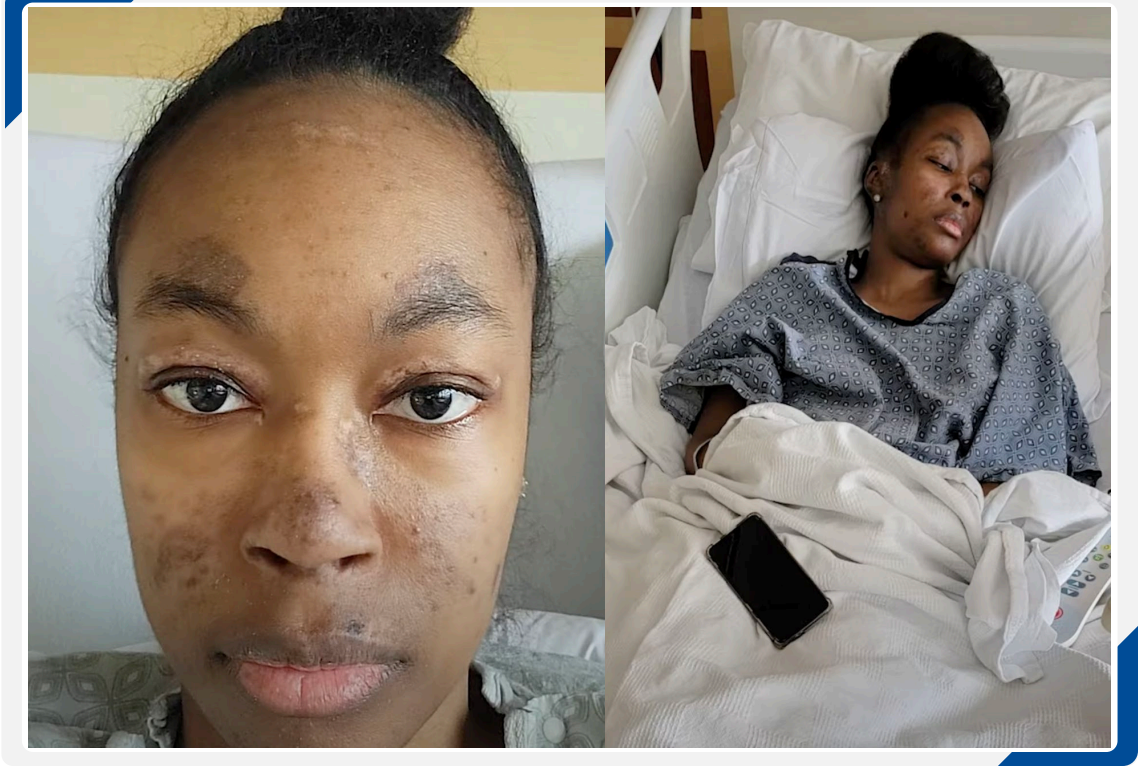
Leading the Way to Life Changing Impacts for Patients

Before KYV-101

- Severe Disease
- Rash
- SLEDAI score 27



After KYV-101

- Disease Free
- No immunosuppressants
- No glucocorticoids

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Working with Leaders and Trailblazing the Autoimmune CAR-T Field

Autoimmune CAR-T Milestones

2018

Kyverna Founded

BRUDNO[1]
2020
20 patients with B-cell malignancies treated with KYV-101 construct

Demonstrated Safety & Feasibility with KYV-101 in B-cell Malignancy

SCHETT[2]
2021
1st autoimmune disease patient treated (lupus nephritis)

1st to Tackle Autoimmune Disease

Partnered with NIH to Deliver KYV-101

HAGHIKIA[3]
2023
1st neuroinflammatory disease patient treated (KYV-101 in myasthenia gravis)

1st Company To Dose Autoimmune Patient

SCHETT[4]
2024
Single-center case series in rheumatology

Largest Clinical Experience Using KYV-101

2024

Differentiated with RMAT and FASTRACK Designations

Kyverna Milestones

Differentiated Fully Humanized CD-19

Best Access for Patients with Global Clinical Trial and Manufacturing

1. Brudno JN, et al. *Nat Med*. 2020;26(2):270-280; 2. Mougiakakos D, et al. *N Engl J Med*. 2021;385(6):567-569; 3. Haghikia A, et al. *Lancet Neurol*. 2023;22(12):1104-1105; 4.Muellller F, et al. *N Engl J Med*. 2024;390(7):687-700.

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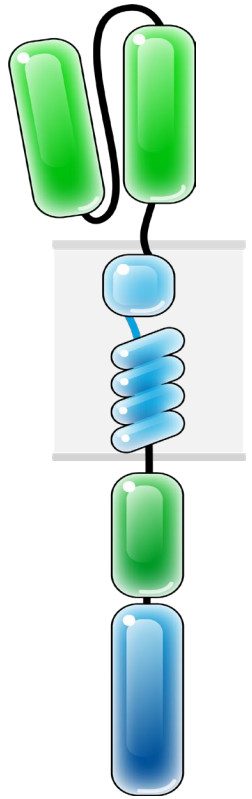
KYV-101: Uniquely Designed to Impact the Unmet Need in Autoimmune Disease

KYV-101 Design

KYV-101 (Hu19-CD828Z)



Human **Anti-CD19 scFv**

Human **CD8α Hinge**

Human **CD8α TM**

Human **CD28 Costim**

Human **CD3ζ**

Designed for **POTENCY**

- The only construct with **highly potent CD28**
- **Maximal B-cell depletion** and **immune reset** ability

Potential for **TRANSFORMATIVE EFFICACY**

- Largest clinical experience across **15+ indications**
- Potential **life-changing efficacy** in refractory patients
- "One and Done" **impacting chronic disease**

Engineered for **SAFETY**

- Unique CAR **designed to minimize toxicity**
- **Fully human** single-chain variable fragment
- CD8α hinge and TM domains

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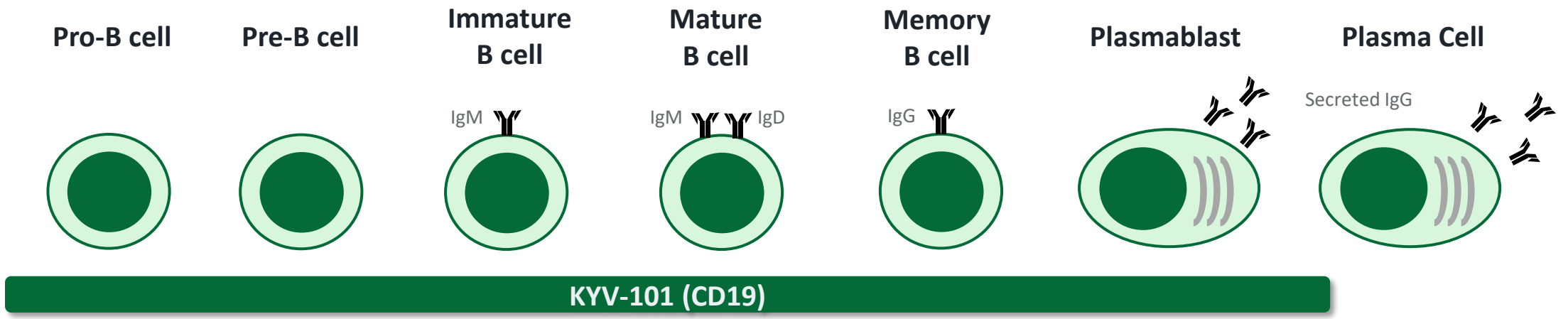
Differentiated Broad Impact of KYV-101: The Value of CD19



Maximizing the depth of B cell cleanout is how we reset the disease

CD19-targeted depletion eliminates the broadest range of B-cell subsets showing promising efficacy while preserving humoral immunity

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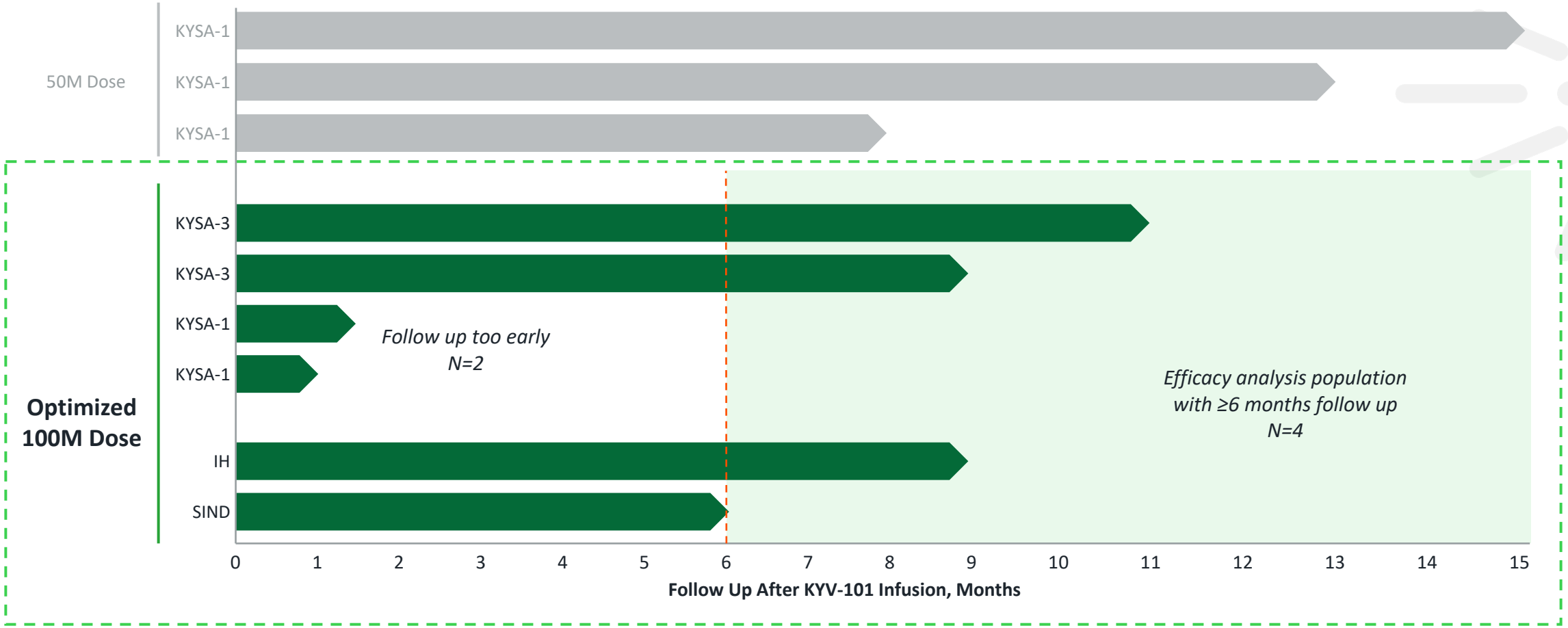
Growing Multi-Center, Multi-Country Experience for KYV-101 in Lupus Nephritis



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IH, Individueller Heilversuch; SIND, single-patient Investigational New Drug Application.

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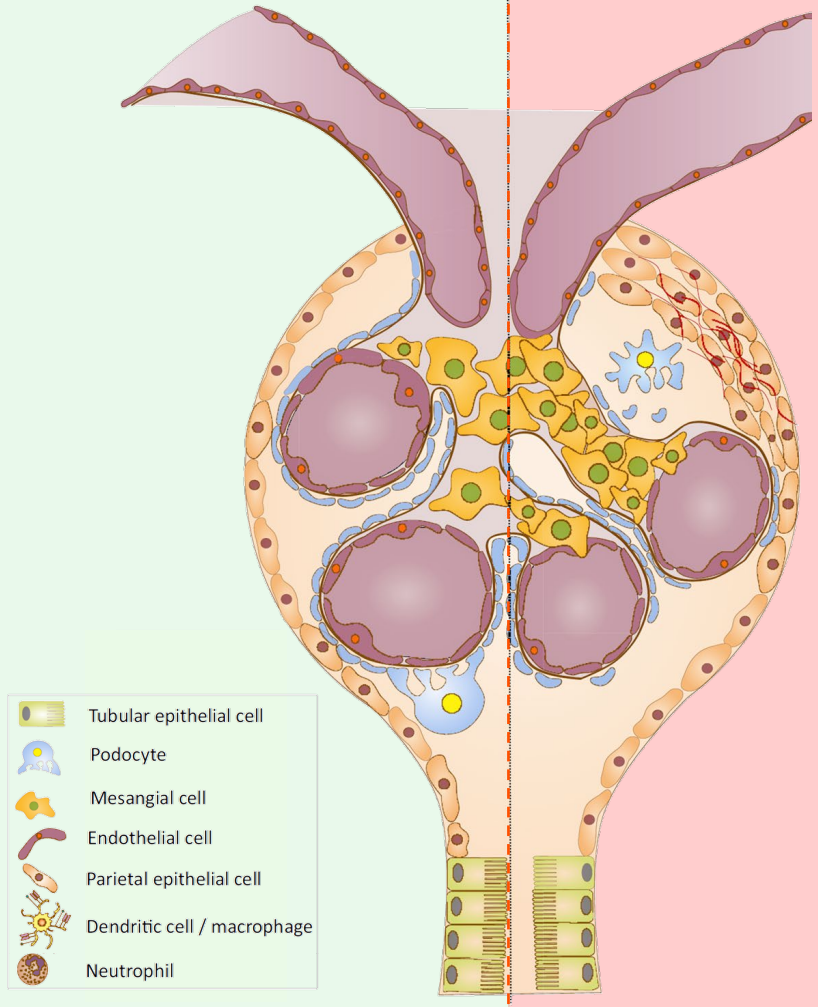
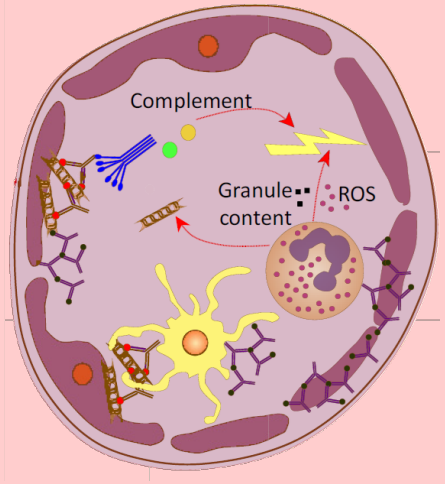
Uncontrolled Inflammation Drives Accumulating Damage in Refractory LN

Healthy Glomerulus



Injured Glomerulus

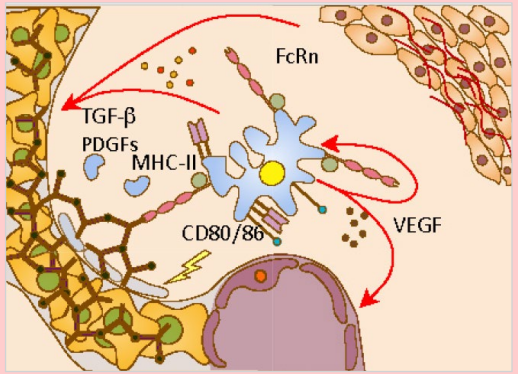
High activity associated with inflammatory processes



- B cells produce anti-dsDNA antibodies which drive immune complex deposition
- Complement activation and consumption
- Immune cell infiltration

Uncontrolled Inflammation

High chronicity due to accumulated kidney damage



- Extracellular matrix deposition
- Podocyte injury and effacement of foot processes

Clinical Measures

- ↑ Anti-dsDNA antibodies
- ↓ Circulating C3+C4
- ↑ Proteinuria
- ↓ eGFR

Adapted from Flores-Mendoza G, et al. *Trends Mol Med*. 2018;24(4):364-378.

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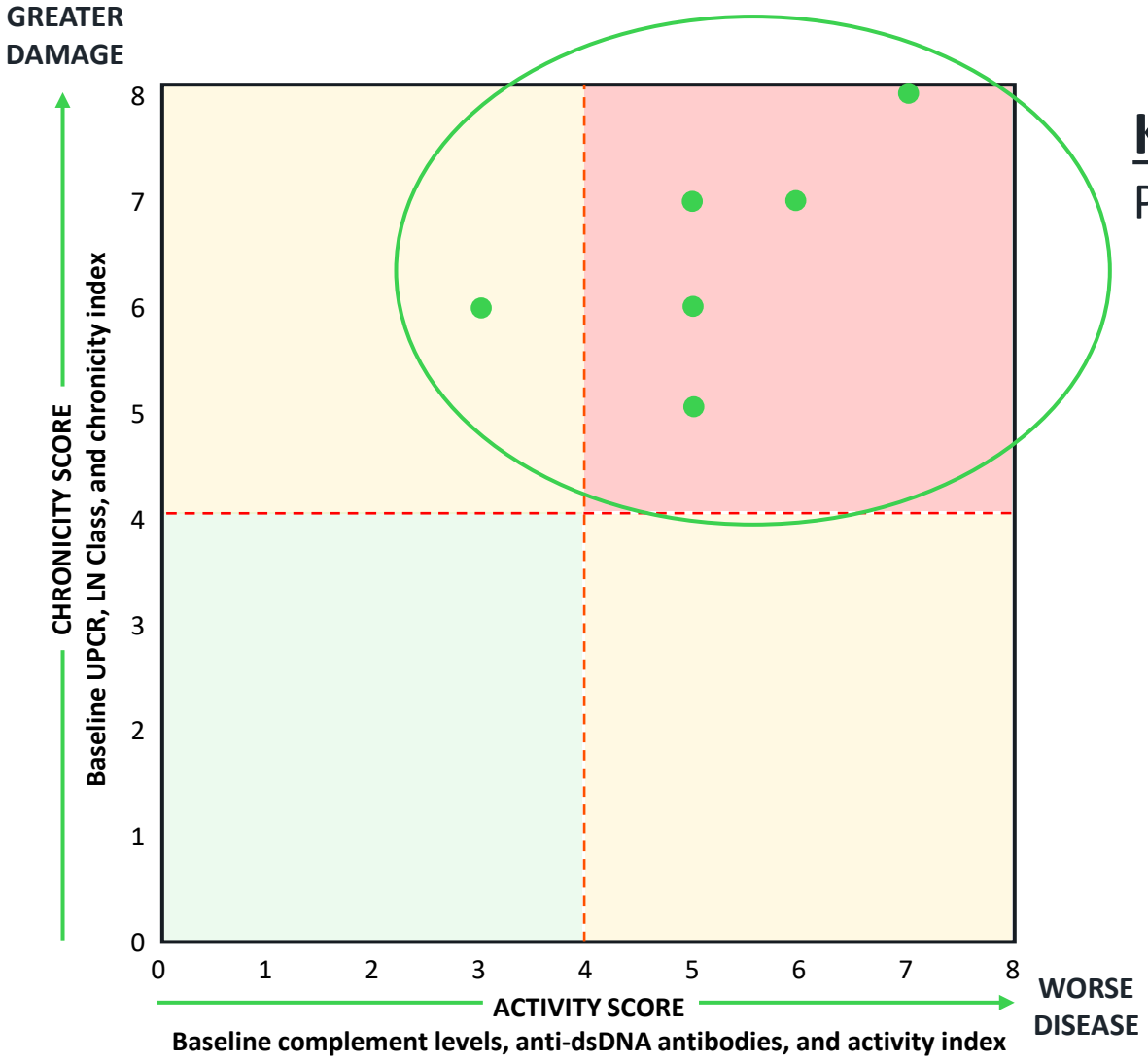
KYV-101 Refractory LN Patients Have High Disease Activity and Kidney Damage



KYV-101 100M Target Dose

Patient Baseline Characteristics

- Refractory LN patients experience uncontrolled inflammation and accumulated kidney damage
- KYV-101 patients have particularly high baseline disease activity and kidney damage
  - Activity: Low complement, high levels of anti-dsDNA antibodies, and high activity indices by biopsy
  - Chronicity: High levels of proteinuria, Class II-V histology, and high chronicity indices by biopsy

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LN, lupus nephritis; UPCR, urine protein creatinine ratio.

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Pillars to Define Success of CAR T-Cell Therapy in Lupus Nephritis

1. Preservation of Kidney Function

- Stabilization of eGFR
- Decreasing Proteinuria
- Avoiding Dialysis

2. Improvement of SLE

- Decrease in SLEDAI
- Decrease in anti-dsDNA
- Normalization of complement

3. Reduction or Elimination of Therapy

- No immunosuppressants
- No or physiological glucocorticoids

eGFR, estimated glomerular filtration rate; SLEDAI, Systematic Lupus Erythematosus Disease Activity Index.

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Leading Pipeline Recognized for Addressing Clinical Unmet Need

Actively enrolling studies in the US and Europe

Technology	Candidates	Target	Indication	Discovery / Validation	Preclinical	Clinical Phase 1	Clinical Phase 2	Clinical Phase 3	Regulatory Milestone
Autologous CAR T	KYV-101 Rheumatology	CD19	Lupus nephritis	KYSA-1, KYSA-3	Phase 1/2				Fast Track
			Systemic sclerosis	KYSA-5	Phase 1/2				ODD
	KYV-101 Neurology	CD19	Myasthenia gravis	KYSA-6	Phase 2				ODD, RMAT
			Multiple sclerosis	KYSA-7	Phase 2				Fast Track
			Stiff person syndrome	KYSA-8	Phase 2				ODD, RMAT
Allogeneic CAR T	KYV-201	CD19	Multiple						

Fast track designation does not assure that we will experience a faster development process, regulatory review or regulatory approval process compared to conventional FDA procedures.
CAR, chimeric antigen receptor; FDA, Food and Drug Administration; ODD, orphan drug designation; RMAT, regenerative medicine advanced therapy.

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B-Cell Targeting With CAR T in Autoimmune Diseases

GEORG SCHETT, MD

FRIEDRICH-ALEXANDER-UNIVERSITY ERLANGEN-NÜRNBERG

DZI Deutsches Zentrum Immuntherapie

FAU FRIEDRICH-ALEXANDER UNIVERSITÄT ERLANGEN-NÜRNBERG

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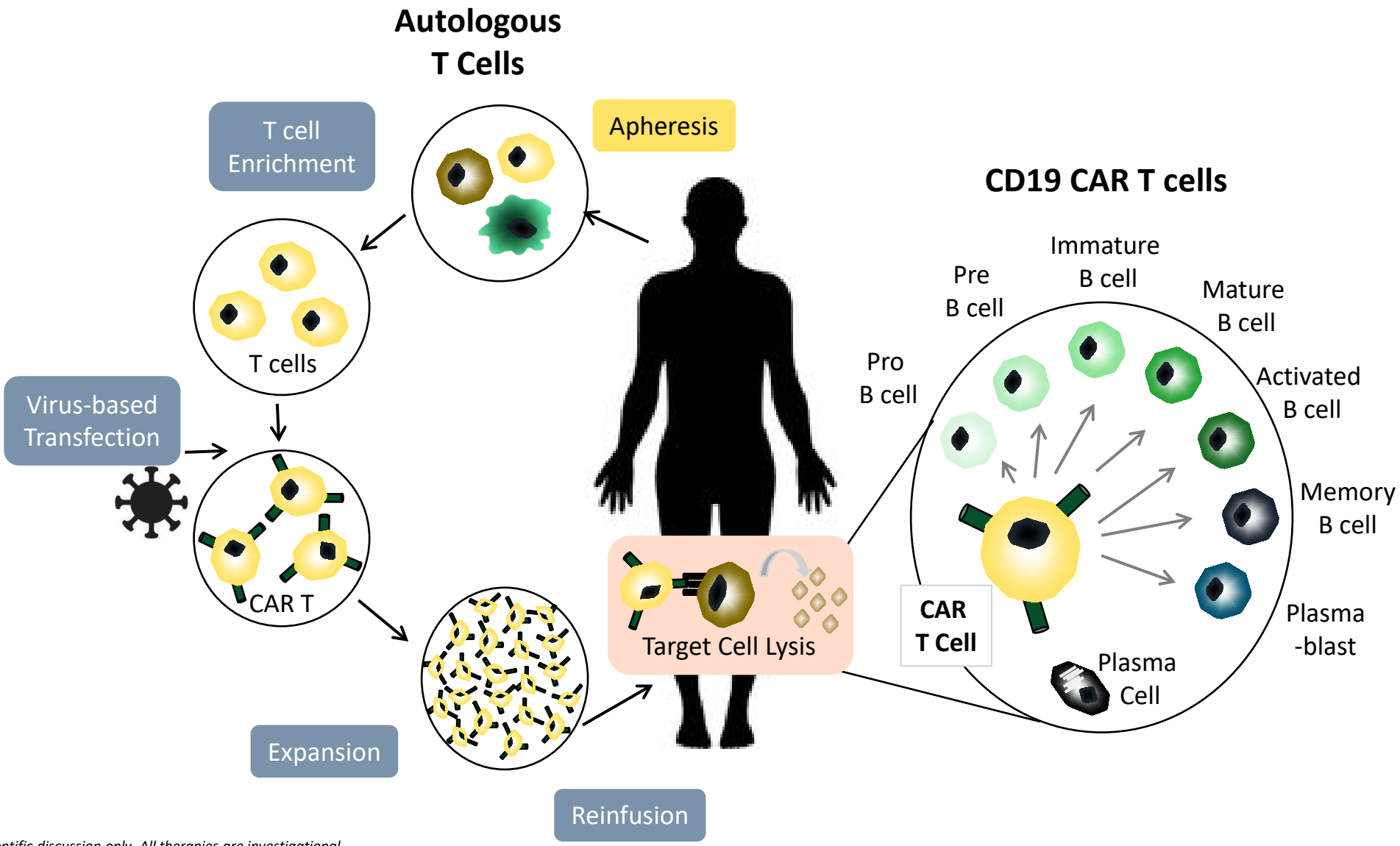
Principle of Autologous CAR T-Cell Therapy



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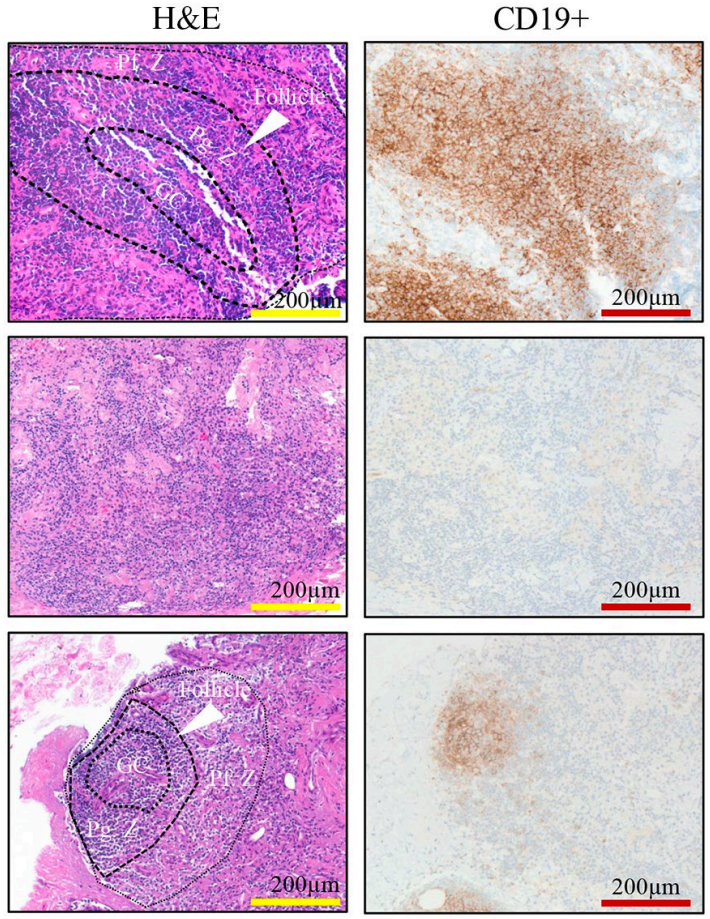
Deep Depletion of Tissue Resident B Cells with CAR T Therapy

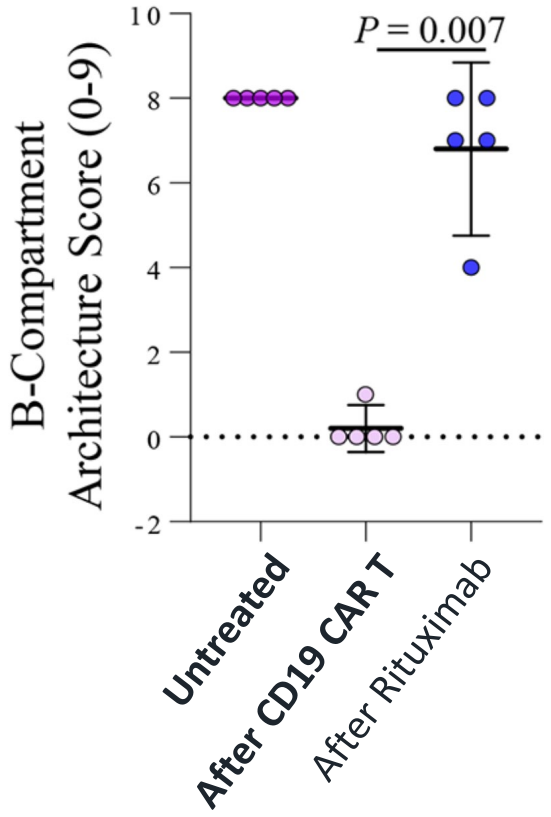
Anti-CD19 CAR T deeply depletes B cells in lymph nodes and disrupts B-cell follicular architecture



Most B-cell are in the Tissues

Deep Tissue Depletion of B-cells

Incomplete Tissue Depletion of B-cells



Tur C, et al. *Ann Rheum Dis*. 2024 Sep 11;0:1–8:ard-2024-226142.

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Lupus Nephritis: Key Challenge in SLE

Clinical

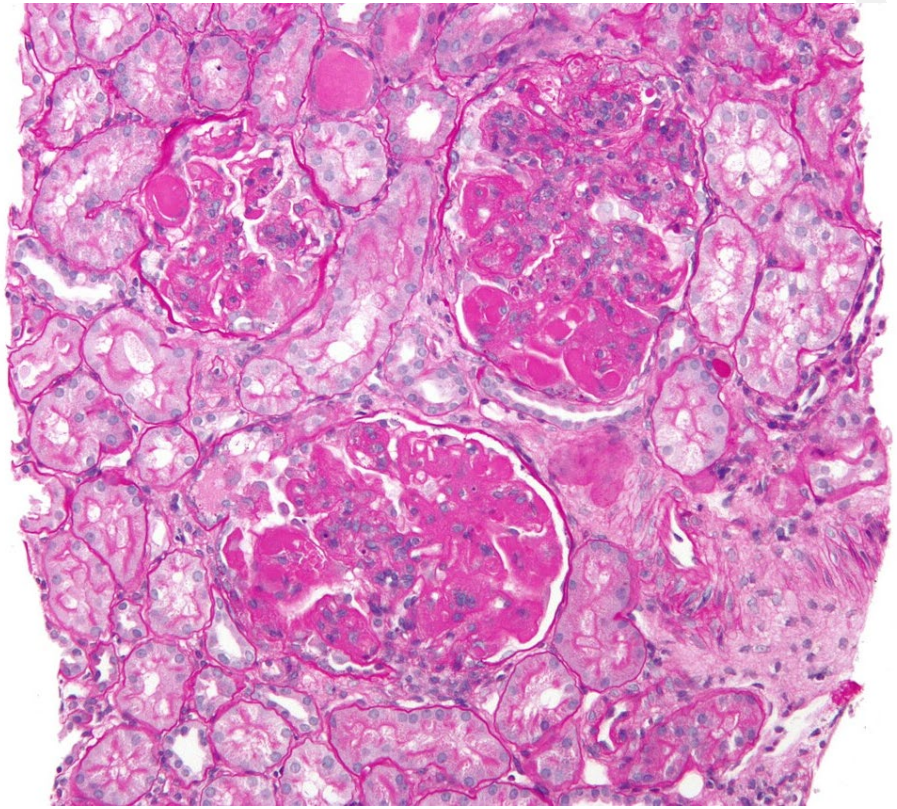
Significant burden of disease with ***frequent and more severe flares*** and ***substantial health care costs*** from hospital stays[1,2]

Damage

Uncontrolled inflammation damages kidneys[3] with 30% risk of developing ***end stage renal disease*** needing dialysis or transplant and ***higher mortality risk***[4-6]

Treatment

Treatment with ***immunosuppressants*** such as MMF, cyclophosphamide, belimumab, voclosporin, and tacrolimus in combination with ***glucocorticoids***[7]



https://en.wikipedia.org/wiki/Lupus_nephritis#/media/File:Diffuse_proliferative_lupus_nephritis_-_high_mag.jpg

1. Kharawala S, et al. *Lupus*. 2022;31(9):1029-1044; 2. Thompson JC, et al. *Rheumatol Ther*. 2022;9(1):25-47; 3. Anders HJ, et al. *Semin Immunopathol*. 2014;36(4):443-459; 4. Fanouriakis A, et al. *Lupus Sci Med*. 2019;6(1):e000310; 5. Lateef A, Petri M. *Arthritis Res Ther.* 2012;14(Suppl 4):S4; 6. Yap DY, et al. *Nephrol Dial Transplant*. 2012;27(8):3248-3254; 7. Lupus nephritis: Initial and subsequent therapy for focal or diffuse lupus nephritis. UpToDate Accessed October 28, 2024.

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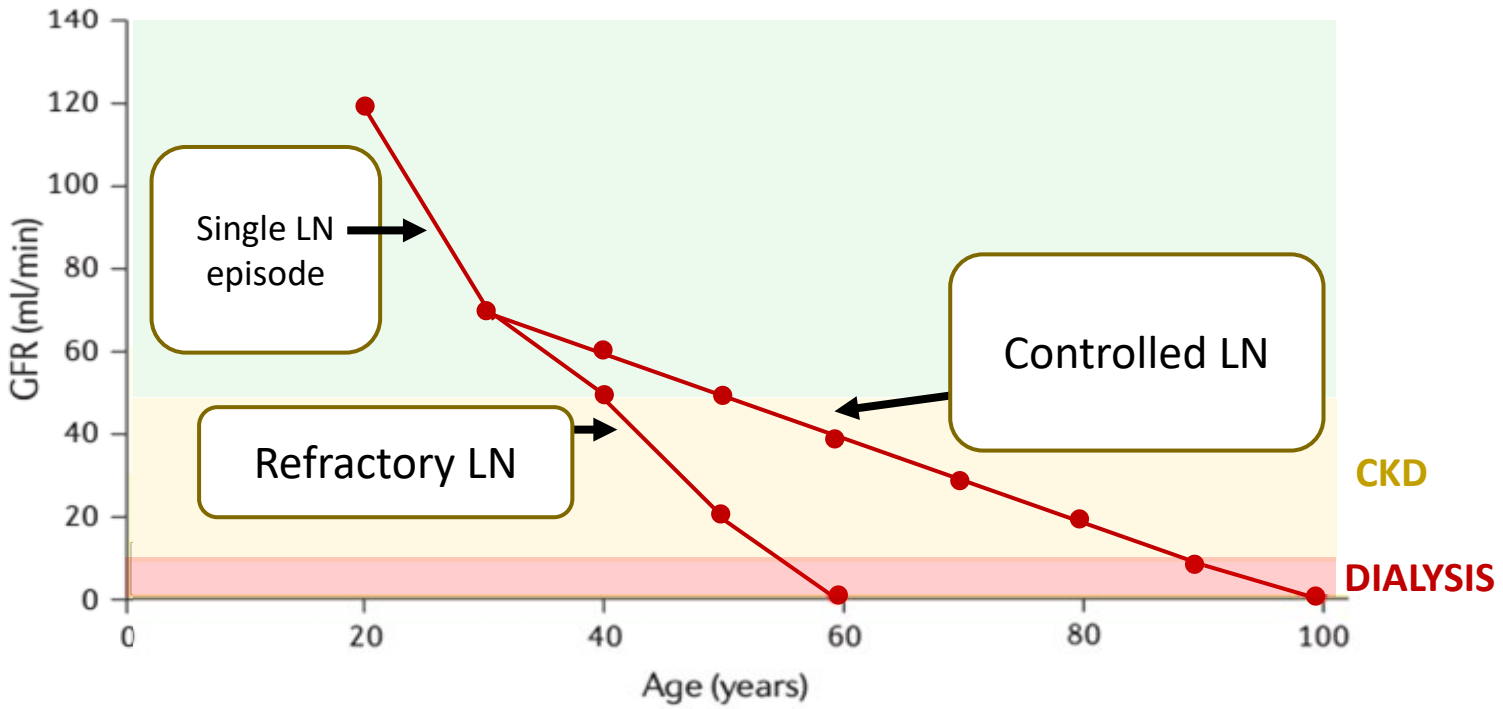
Steep Loss of Kidney Function in Refractory Lupus Nephritis

Loss of Kidney Function in LN Over Time[1]



- Despite therapy, patients progress with eGFR decline and loss of Kidney Function
- Single episodes can impact the slope of decline significantly
- Risk of Dialysis, Kidney Transplantation and Death increase, as eGFR declines

30% with progressive eGFR loss despite treatment[2]

Anders H-J, et al. *Nat Rev Disease Primers*. 2020;6(1):7; Weeding E, et al. *Lupus Sci Med*. 2022;9(1):e000684.

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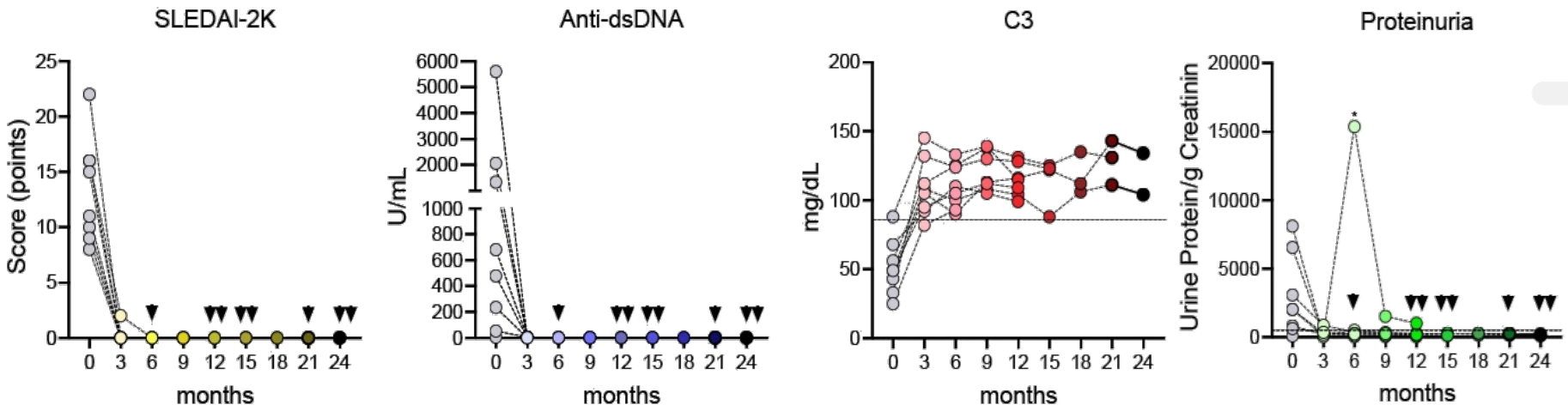
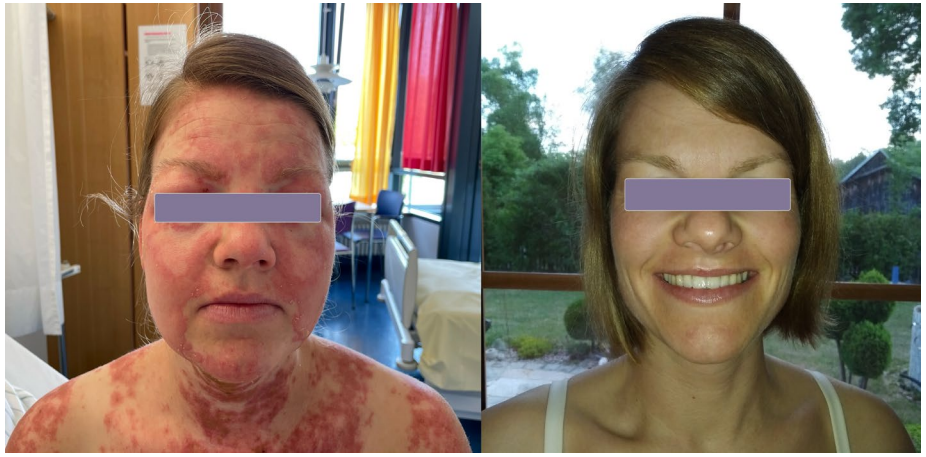
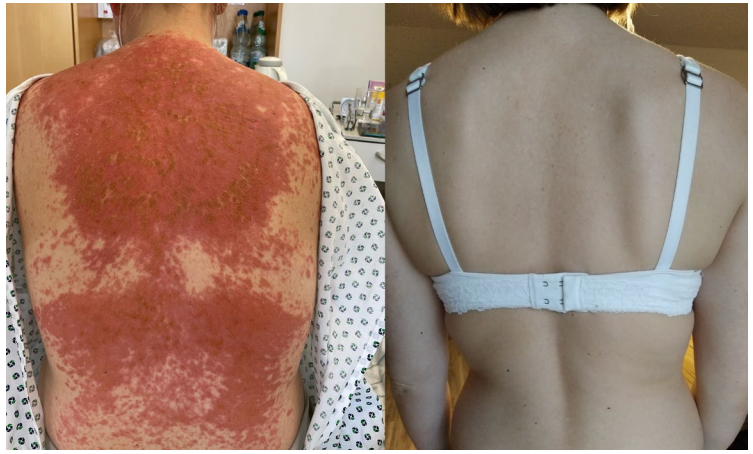
Robust Responses With CD19 CAR T-Cell Therapy in Lupus Nephritis

Consistent effects demonstrated across disease domains in 8 patients





Baseline 6 months



Baseline 6 months

Müller F, Taubmann J, et al. *N Engl J Med*. 2024;390(8):687-700

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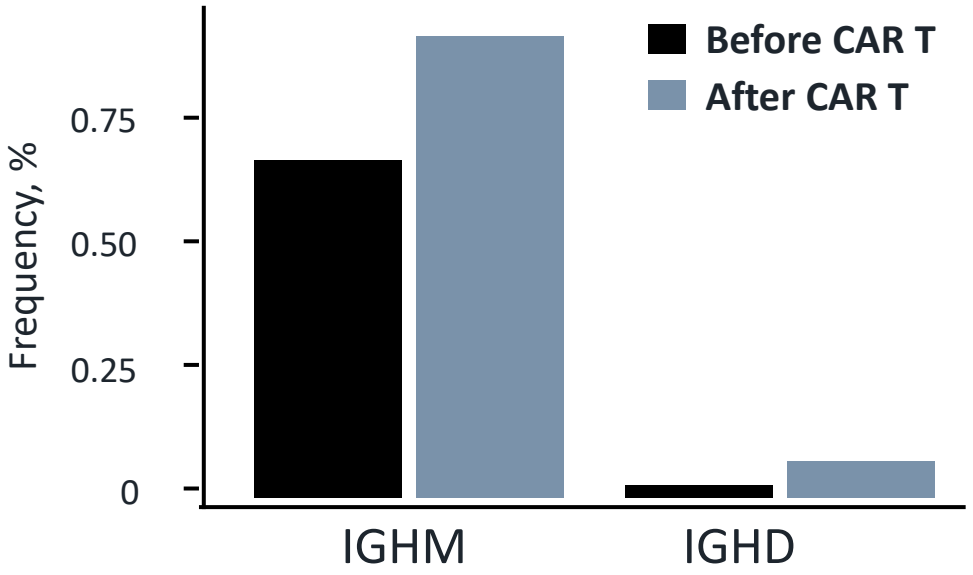
Evidence of Immune Reset After CAR T Therapy

New B cells show a naive IgD/IgM-based heavy chain pattern in 7 patients

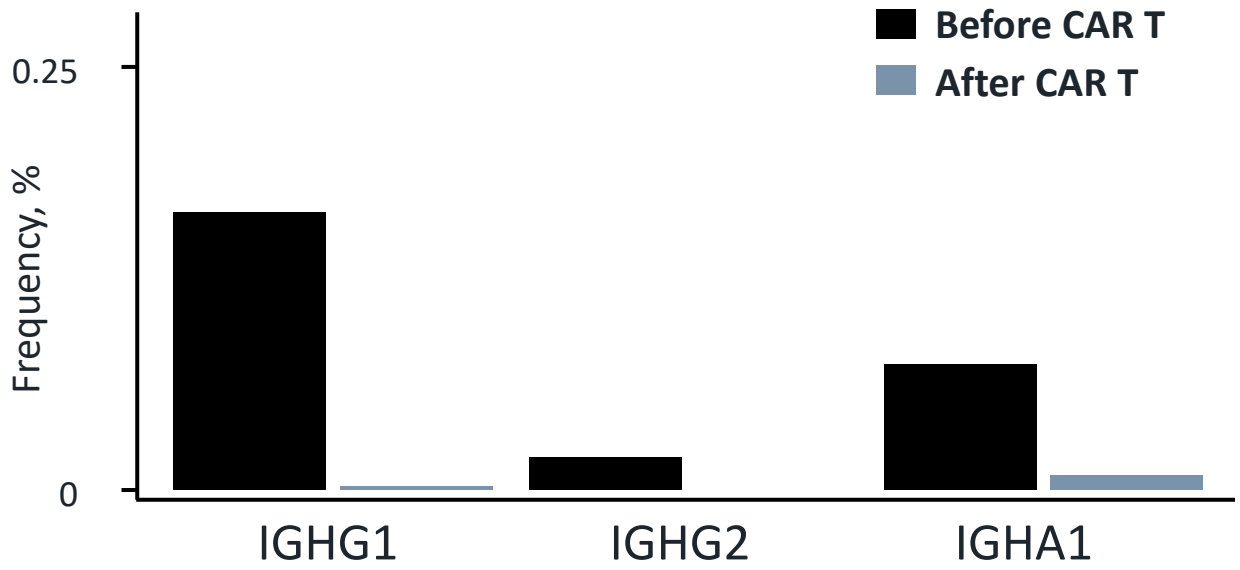
Increase in non-class-switched B-cells

IgM and IgD heavy chains are expressed before class-switching



Virtual absence of class-switched B-cells

IgG and IgA heavy chains indicate class-switching



Adapted from Müller F, et al. *N Engl J Med*. 2024;390(8):687-700.

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KYV-101: Phase 1/2 Multi-Center, Multi-Country Studies in Refractory Lupus Nephritis

KYSA-1 Phase 1 Design

3+3 Dose-Escalation

Dose Level 1
0.5×10^8 CAR+ T cells
Standard lymphodepletion

Dose Level 2
1×10^8 CAR+ T cells
Standard lymphodepletion

KYSA-3 Phase 1 Design

Dose Level
1×10^8 CAR+ T cells
Standard lymphodepletion

Key Eligibility Criteria	Adult patients with active biopsy-proven Class III or IV lupus nephritis
Primary Objectives	Safety and tolerability
Key Secondary Objectives	▪ Efficacy ▪ PK/PD ▪ Disease-related biomarkers ▪ Immunogenicity ▪ PROs

PK/PD, pharmacokinetics/pharmacodynamics; PRO, patient reported outcomes.

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KYV-101: Treatment of Heavily Pretreated LN Patients

Demographic summary of patients receiving 1×10^8 CAR T-cells

Patient Characteristic	*N=6*
Age (Range)	29 – 55 years
Sex (Female : Male)	4:2
Prior Lines Of Therapy	3 – 7
SLEDAI-2K	8 – 27
Histologic Class of Nephritis (WHO)	II – V
UPCR (Range)	1.4 – 8.0

4 of 6 patients with ≥6 months follow up included in efficacy analysis

2 of 6 patients with <2 months follow up not in efficacy analysis (too short follow-up to assess efficacy)

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LN, lupus nephritis; UPCR, urine protein-creatinine ratio.

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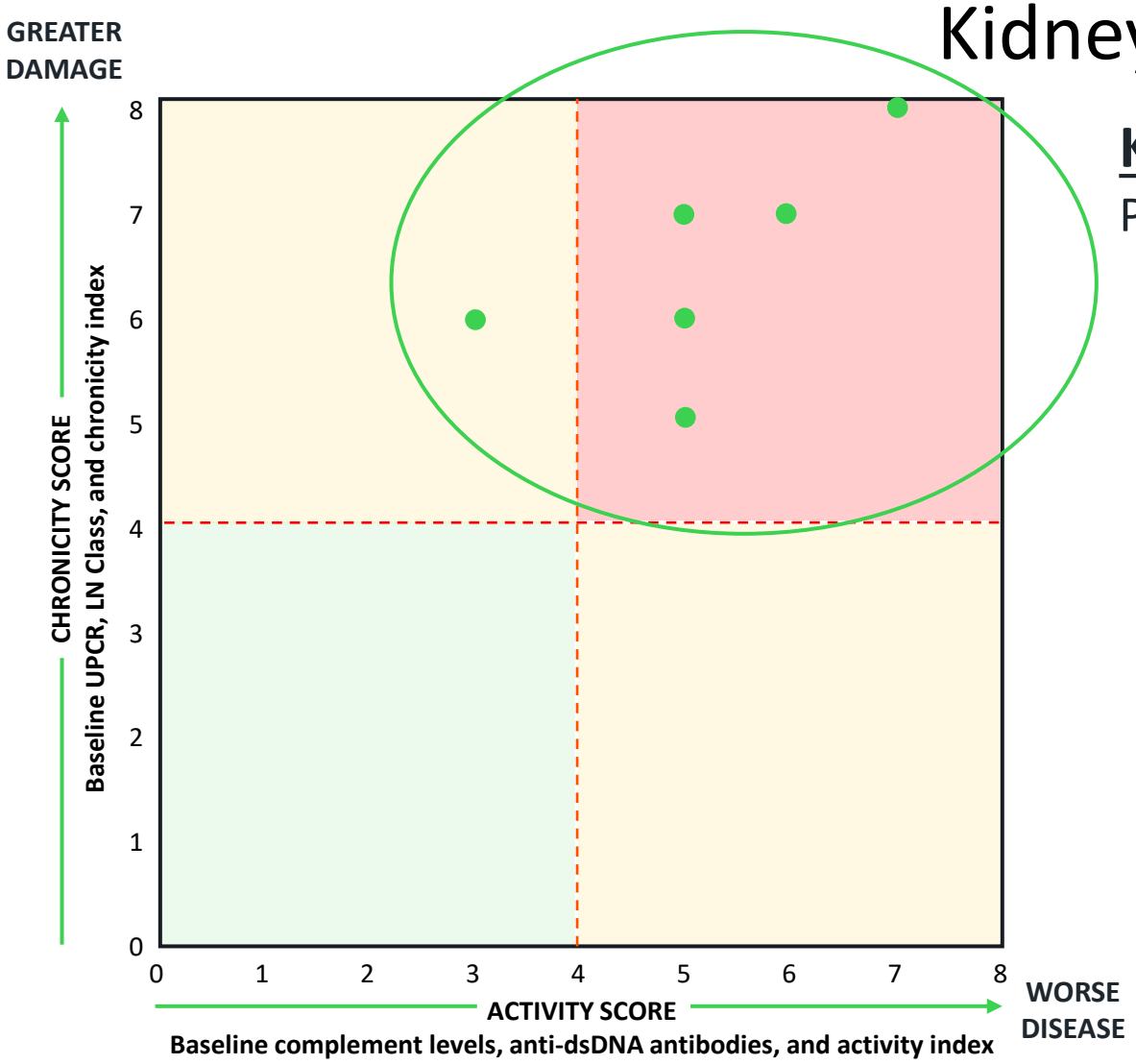

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- Normalization of complement

3. Reduction or Elimination Therapy

- No immunosuppressants
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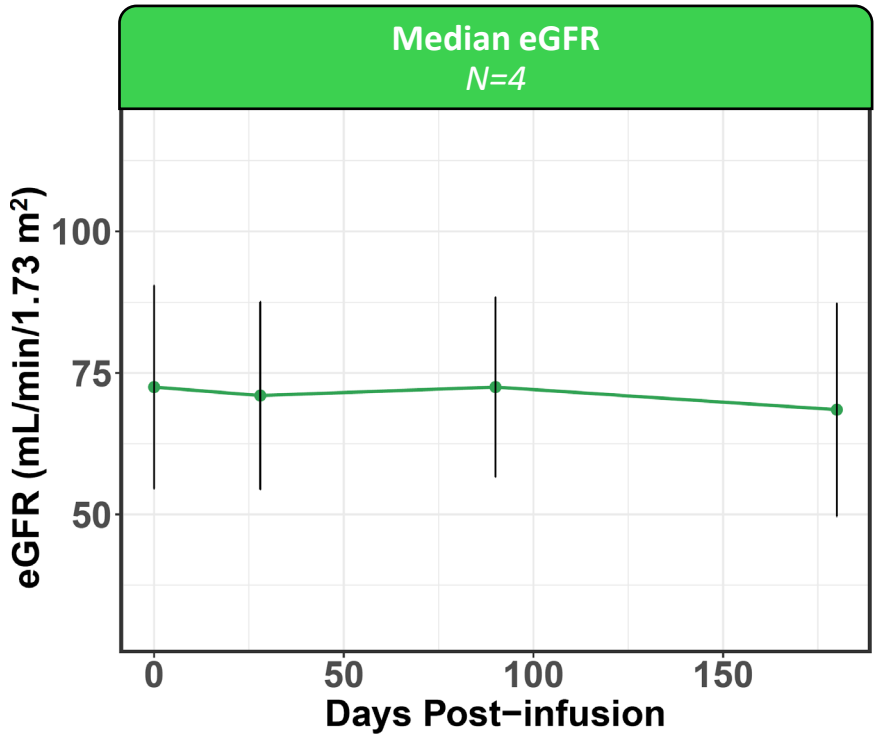
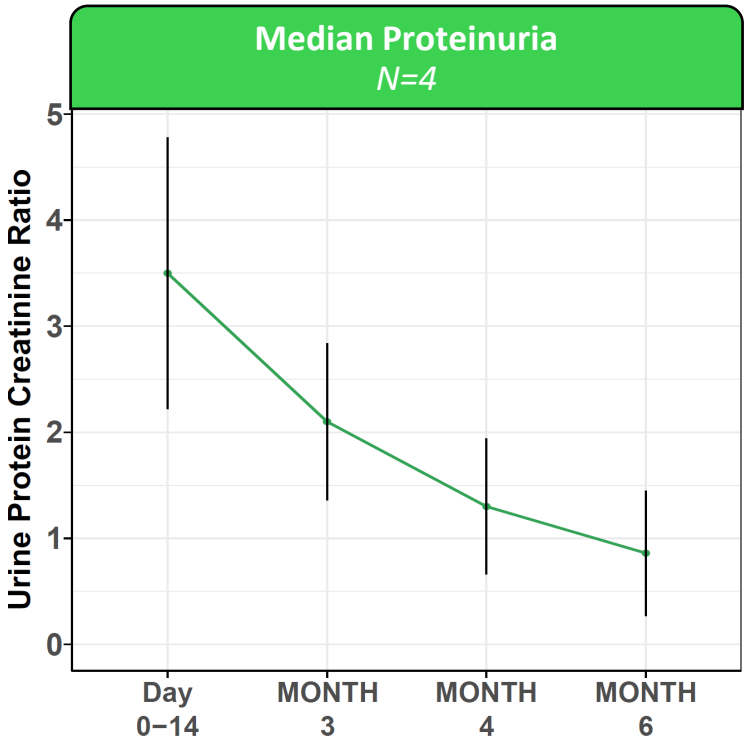
Pillar 1: KYV-101 Potential for Preservation of Kidney Function

Stable and Durable Kidney Function



Clinically Meaningful Decline in Proteinuria



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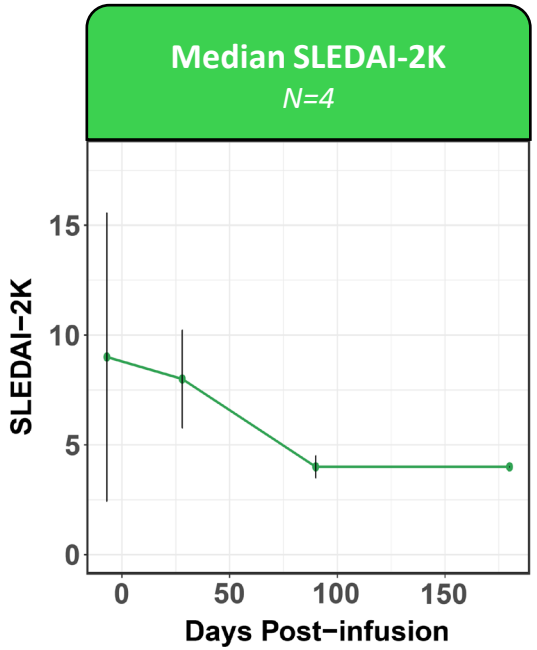
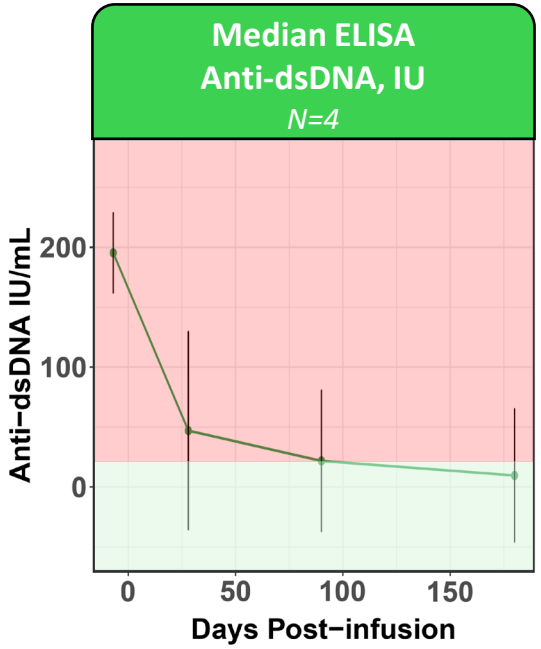
Pillar 2: KVY-101 Potential for Improvement of SLE

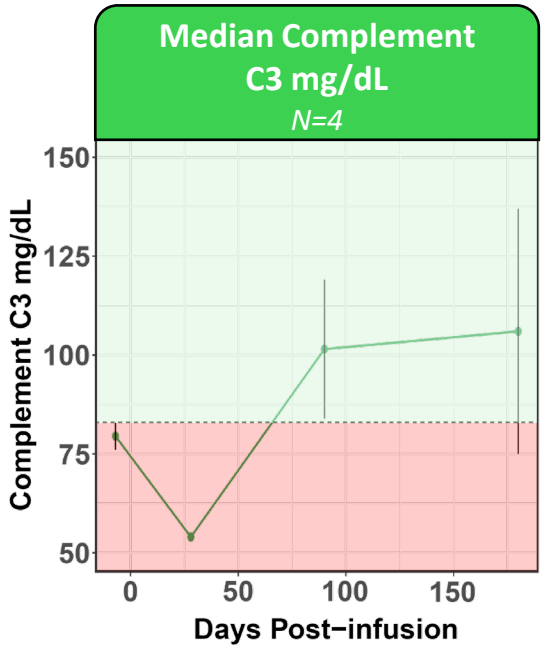
Reduction in SLEDAI Score

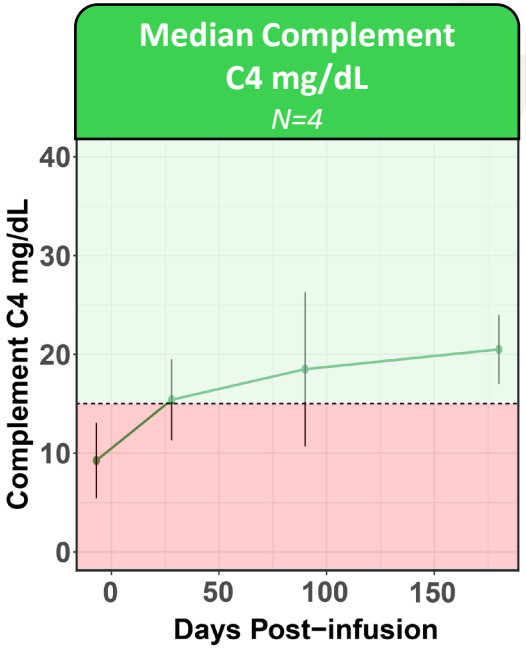


Reduction in Autoantibodies



Normalization of Complement





Patients from Kyverna-sponsored clinical trials, investigator-reported named patient, and investigator-initiated trial experience as of October 31, 2024. These observations are derived from separate clinical settings, including information from case reports. Future clinical trials may not confirm the clinical safety observations discussed in these case reports and studies.

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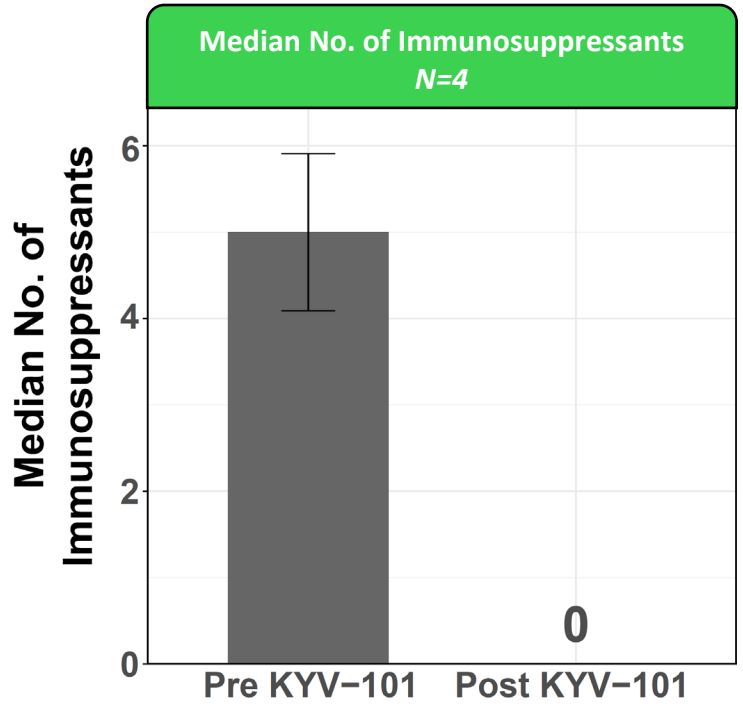
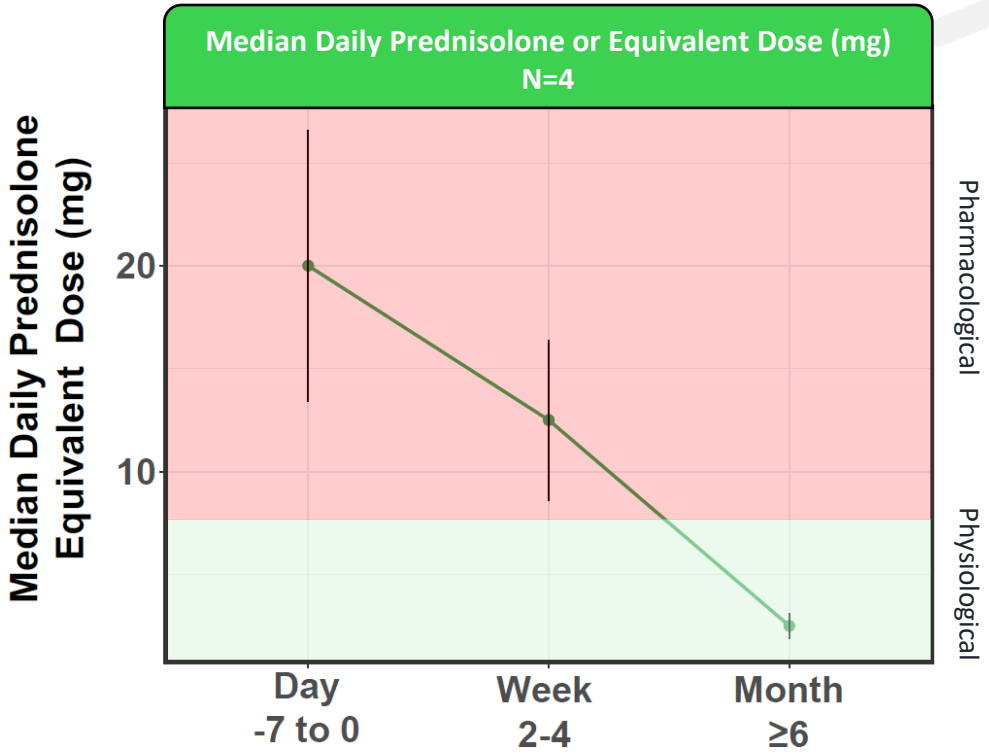
Pillar 3: KYV-101 Potential to Eliminate Immunosuppressants and Reduce Glucocorticoids

Eliminating Immunosuppressants



Reducing Glucocorticoids to Physiological Levels



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KYV-101: Potential to Redefine Success in Lupus Nephritis

1. Preservation of Kidney Function

- Stabilization of eGFR
- Decreasing Proteinuria
- Avoiding Dialysis

2. Improvement in SLE

- Decrease in SLEDAI
- Decrease in anti-dsDNA
- Normalization of complement

3. Reduction or Elimination of Therapy

- No immunosuppressants
- No or physiological glucocorticoids

After a single infusion of KYV-101 (1×10^8 CAR T cells), none of the patients require active treatment for LN

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KYV-101: Potential for Predictable, Well Tolerated, and Robust Safety Profile in First 50 Patients Across Different Autoimmune Diseases

KYV-101 All 15+ AID indications

RHEUMATOLOGY

- Rheumatoid arthritis
- Systemic sclerosis
- Lupus nephritis
- ANCA-associated vasculitis
- Anti-Synthetase Syndrome
- And others

NEUROLOGY

- Stiff-person syndrome
- Myasthenia gravis
- Multiple sclerosis
- NMOSD
- CIDP
- And others

Indication Category	CRS	ICANS
	Grade 3/4	Grade 2–4
Neuroimmunology	0	0
Rheumatology	0	0
Other Autoimmune	0	0

In the 6 patients with LN treated with 1×10^8 KYV-101 cells, **no grade 3/4 CRS or no grade 2-4 ICANS** observed

Observed CRS and ICANS events were transient, low-grade, and manageable

Patients from Kyverna-sponsored clinical trials, investigator-reported named patient, and investigator-initiated trial experience as of October 31, 2024. These observations are derived from separate clinical settings, including information from case reports. Future clinical trials may not confirm the clinical safety observations discussed in these case reports and studies.

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KYV-101: Potential for Immune System Reset in Lupus Nephritis

UNMET NEED

LN is a severe condition with **high risk to develop kidney failure**

PROMISE OF KYV-101

KYV-101 achieves potential for significant progress in the treatment of LN via:

- Preserving kidney function
- Improving SLE activity
- Eliminating immunosuppression
- Predictable and robust safety profile

NEXT STEPS

KYSA-1 and KYSA-3 continuing to enroll and treat patients in order to bring a **new, transformative treatment option** to patients with LN

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KYV-101 Anti-CD19 CAR T-Cell Therapy: The Future of Autoimmune Disease Treatment

1 **Welcome and Introduction**
Sham Dholakia, MD, DPhil Kyverna Therapeutics

2 **B-Cell Targeting With CAR T in Autoimmune Diseases**
Georg Schett, MD Friedrich-Alexander-University Erlangen-Nürnberg

3 **Biomarkers to Uncover Mechanistic Drivers of CAR T-Cell Therapy**
Jörg Distler, MD Heinrich Heine University Düsseldorf

4 **Exploring Opportunities Across Different Diseases**
Lorinda Chung, MD, MS Stanford University

5 **Panel Discussion**
Roberto Caricchio, MD Jörg Distler, MD Lorinda Chung, MD, MS Georg Schett, MD

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Biomarkers to Uncover Mechanistic Drivers of CAR T-Cell Therapy for Autoimmune Diseases

JÖRG DISTLER, MD

HEINRICH HEINE UNIVERSITY DÜSSELDORF

Heinrich Heine Universität Düsseldorf

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Debilitating Effects of Systemic Sclerosis

SSc Overview[1]

- SSc is characterized by ***fibrosis of the skin and internal organs***, as well as ***vasculopathy***
- SSc is rare, with an estimated ***global incidence of 0.5-5.6 per 100,000 persons/yr***
- SSc has a ***10-year mortality rate of 23% - 43%***

SSc Treatment[2,3]

- Majority of patients receive ***symptomatic management only***, with systemic immunosuppressants[1,2]
  - Nintedanib and tocilizumab are approved to treat SSc-related interstitial lung disease (but not underlying disease)
- ***Stem cell transplants reserved for severe cases*** with organ/lung involvement[3,4]
  - Risk of treatment-related mortality
  - Limited availability
  - Strict selection criteria

Current therapies are focused on managing SSc symptoms and complications

1. Denton CP, et al. *Lancet*. 2017;390(10103):1685-1699; 2. Pope JE, et al. *Nat Rev Rheumatol*. 2023;19(4):212-226; 3. Walker UA, et al. *RMD Open*. 2018;4(2):e000533; 4. Spierings J, et al. *Ther Adv Musculoskelet Dis*. 2021;13(1):1759720X211035196.

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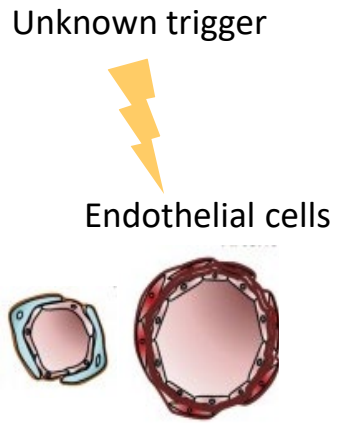
Immune Memory Drives Persistent Fibrotic Tissue Remodeling in SSc



Distler J, et al. *Nat Rev Rheumatol*. 2019;15(12):705-730; Distler J, et al. *Arthritis Rheumatol*. 2017;69(2):257-267.

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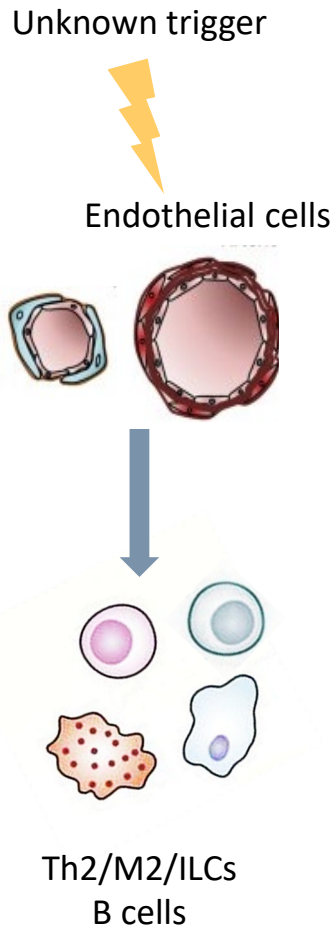

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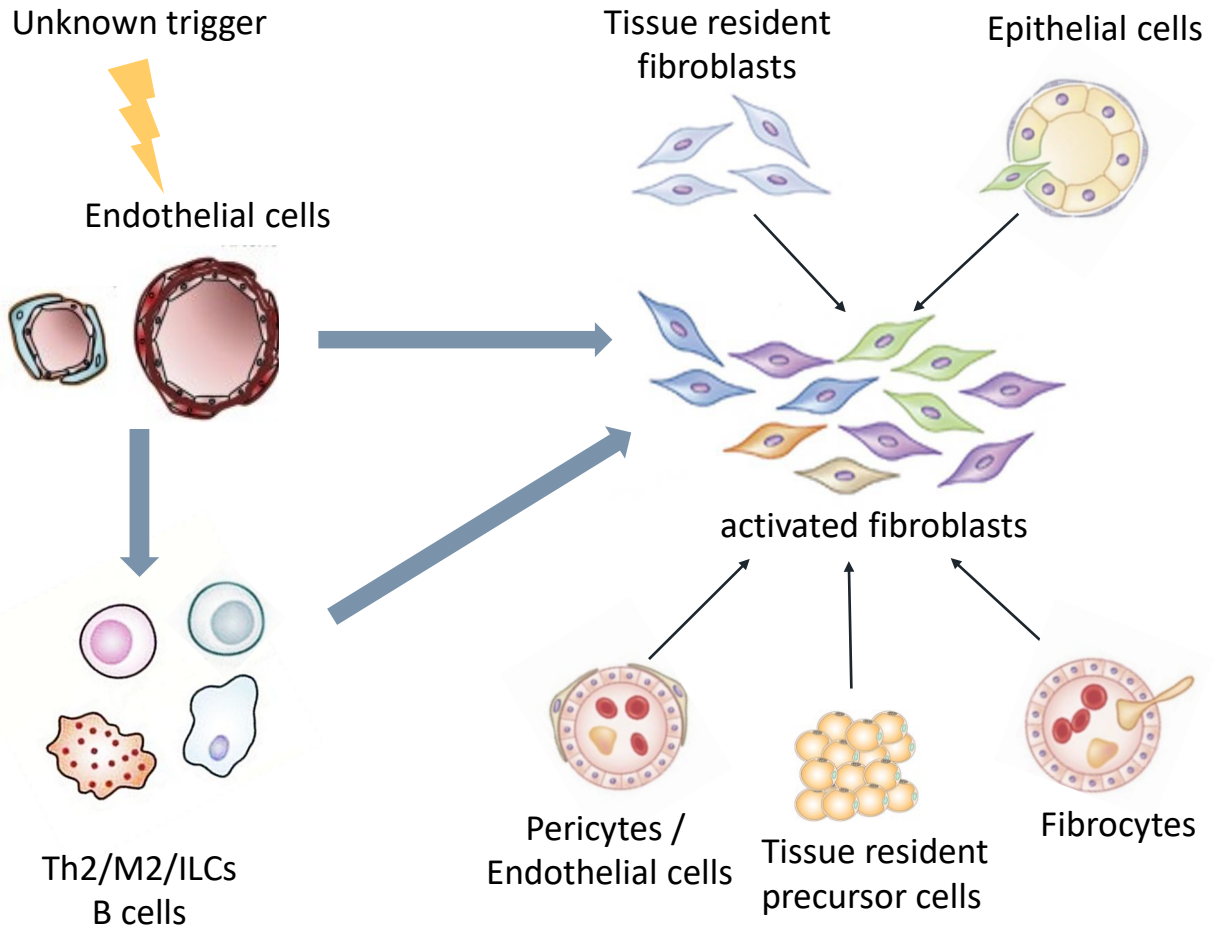

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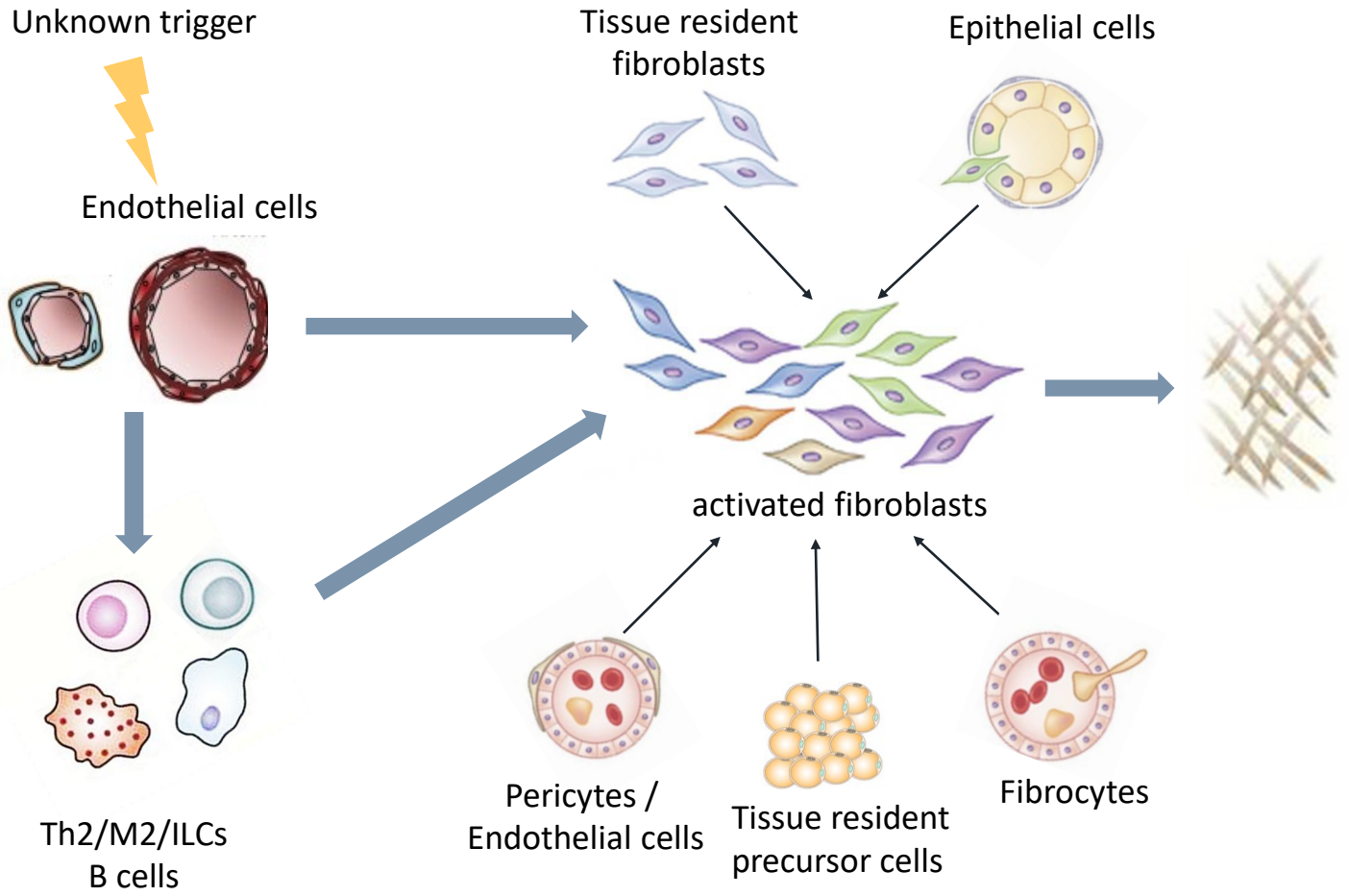

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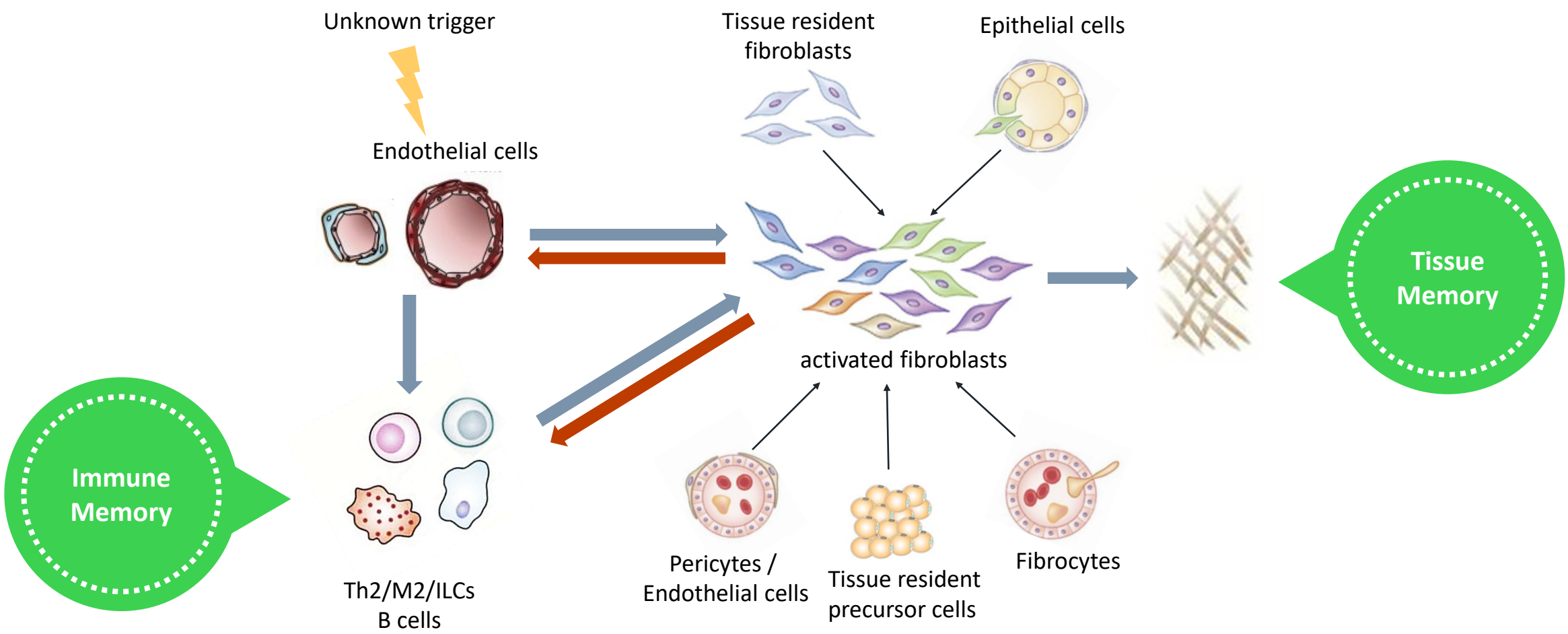

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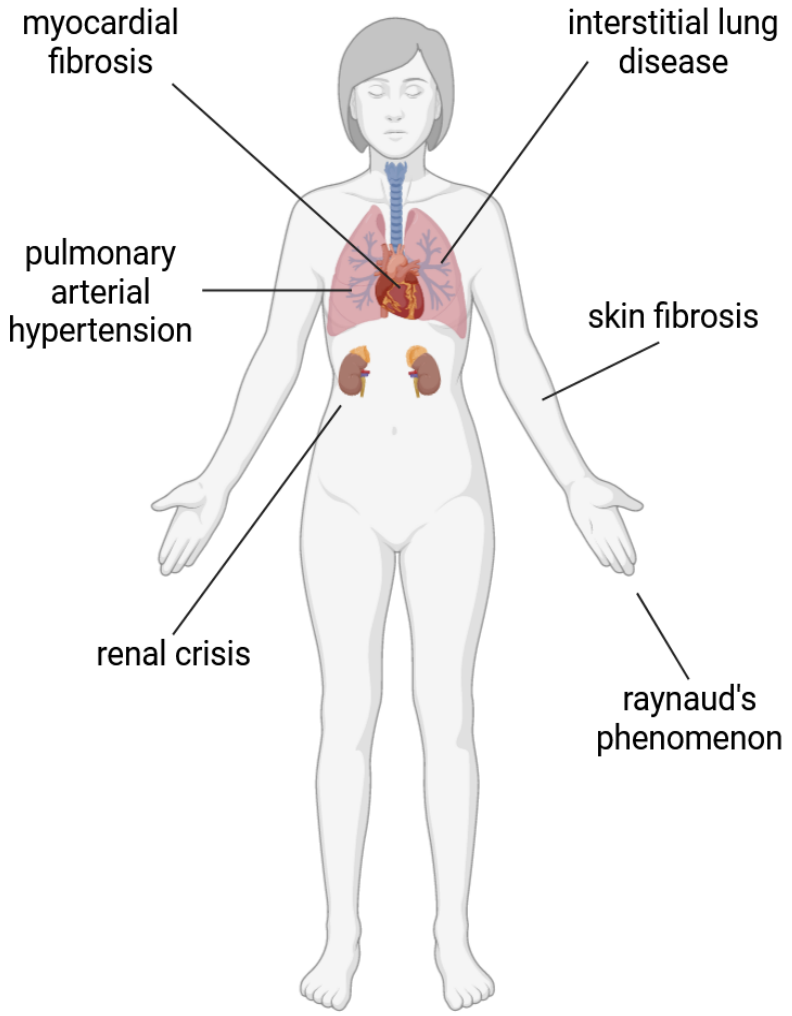
B Cells Play a Significant Role in SSc Pathophysiology

- Elevated levels of B-cell stimulating factors[1]
- Disturbed B-cell homeostasis with expansion of naïve and decrease of memory B cells[2]
- Significantly increased CD19 expression in naïve and memory B cells in SSc[2]
- Significant skin improvement upon CD20-targeting antibody rituximab[3]
- Hematopoietic stem cell transplantation shows promising results and favorably alters the autoantibody repertoire[4-8]

CD19-targeting CAR T cell therapy as a potential treatment in Systemic Sclerosis



1. Matsushita T, et al. *Arthritis Rheum*. 2006;54(1):192-201; 2. Sato S, et al. *Arthritis Rheum*. 2004;50(6):1918-1927; 3. Ebata S, et al. *Lancet Rheumatol*. 2021;3(7):e489-e497;
4. Ayoglu B, et al. *Ann Rheum Dis*. 2023;82(5):670-680; 5. Assassi S, et al. *Ann Rheum Dis*. 2019;78(10):1371-1378; 6. van Laar JM, et al. *JAMA*. 2014;311(24):2490-2498.

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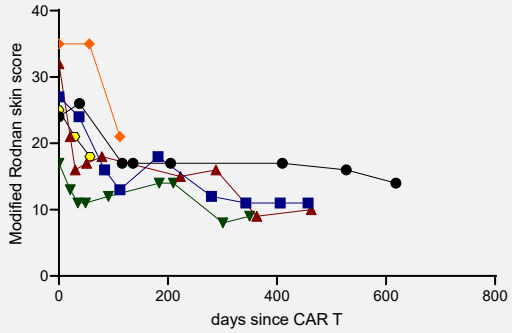
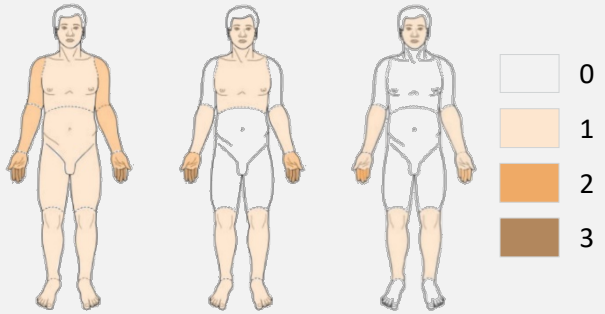
Improvements Shown in Skin and Hand Manifestations

Among 6 patients with SSc treated with anti-CD19 CAR T-cell therapy

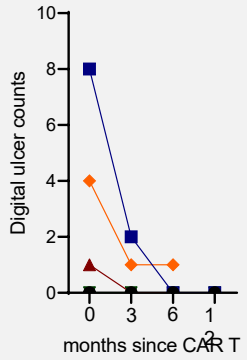
Modified Rodnan Skin Score

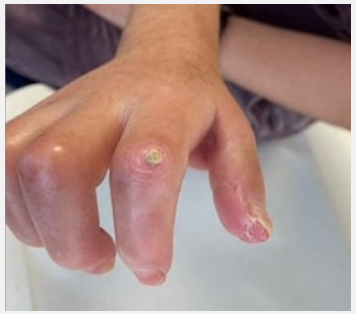




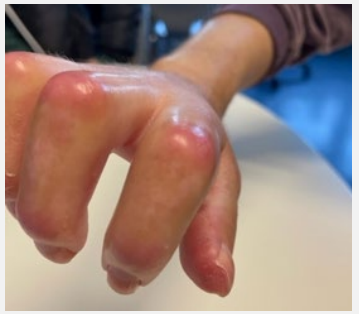
Pre CAR T 3 months 12 months

Digital Ulcerations



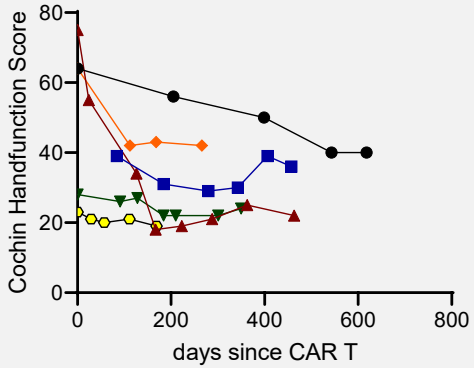


Before CAR T therapy

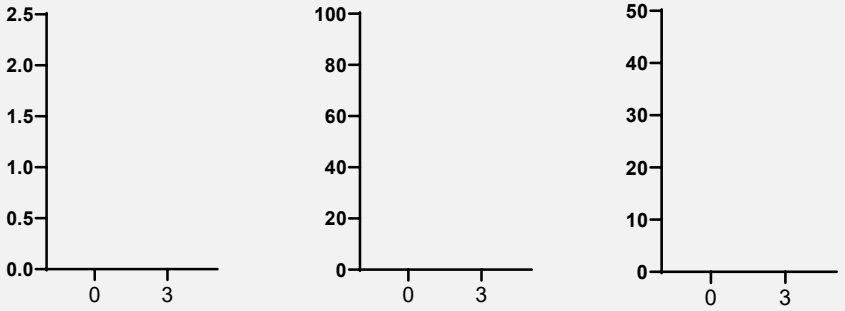


4 weeks after CAR T

Cochin Hand Function Scale



Raynaud's Phenomenon



Auth J, et al. *Lancet Rheumatology*, in press.

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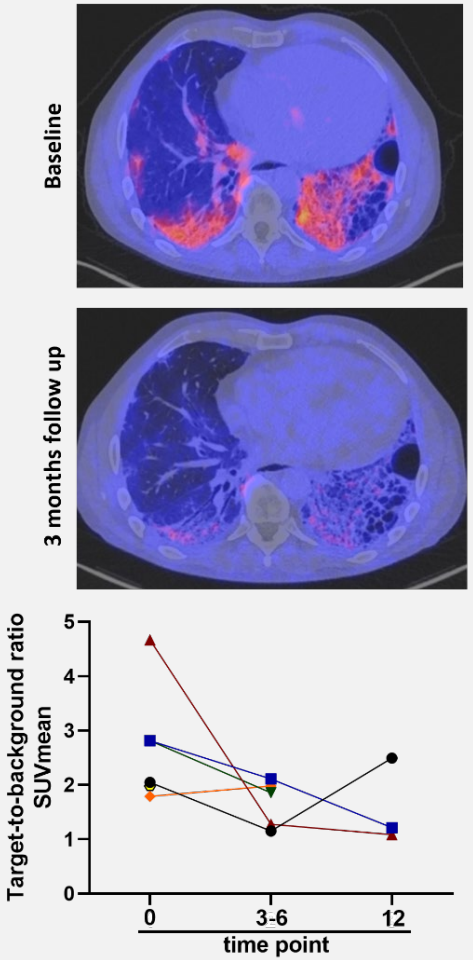
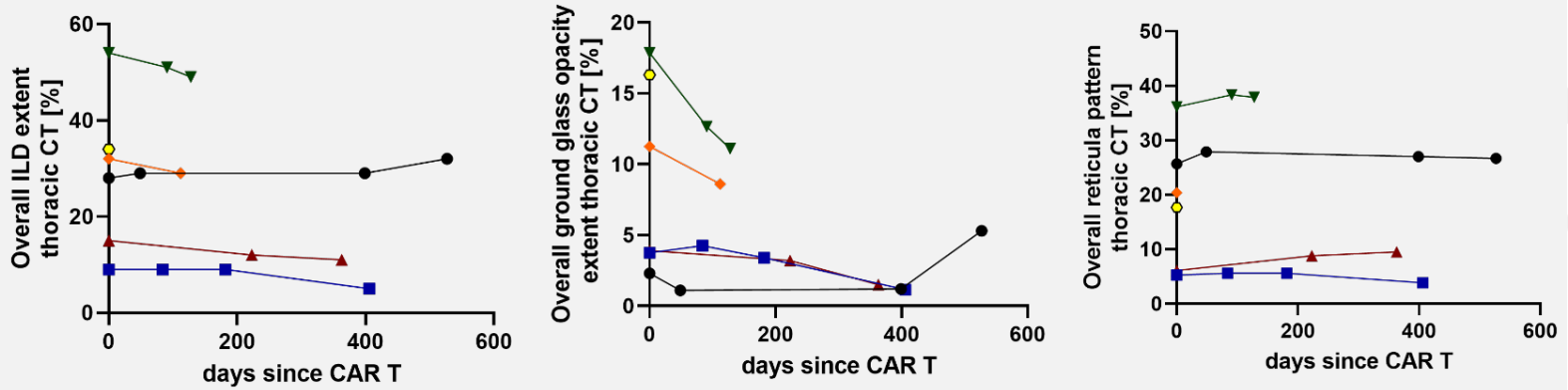
Stabilization Demonstrated of Pre-Existing ILD

Among 6 patients with SSc treated with anti-CD19 CAR T-cell therapy

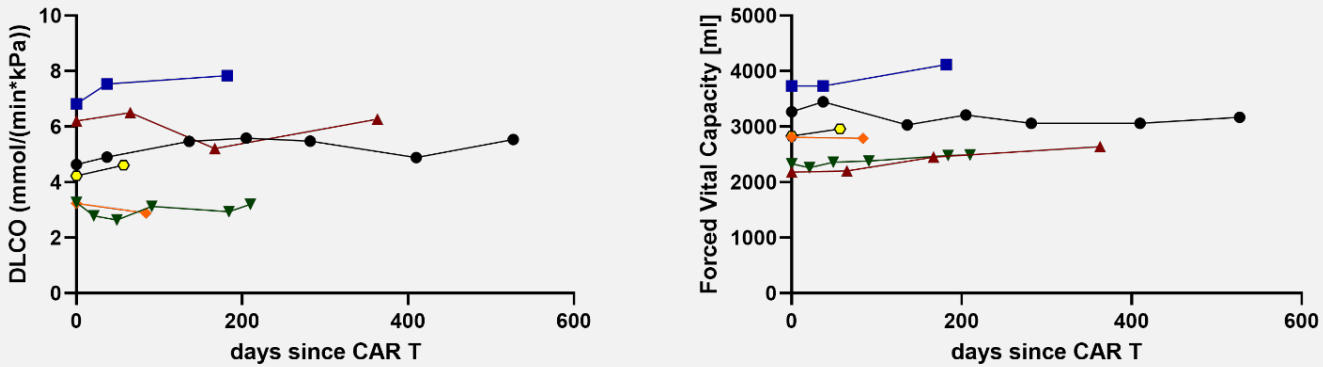
^{68}Ga-FAPI-04-PET-CT



Thoracic CT



Pulmonary Function



patient 1 patient 2 patient 3 patient 4 patient 5 patient 6

Auth J, et al. *Lancet Rheumatology*, In press.

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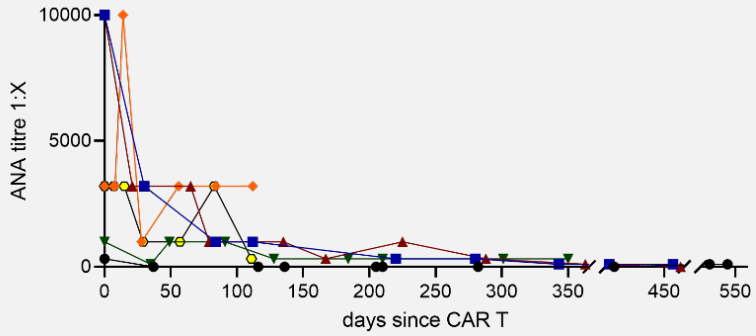
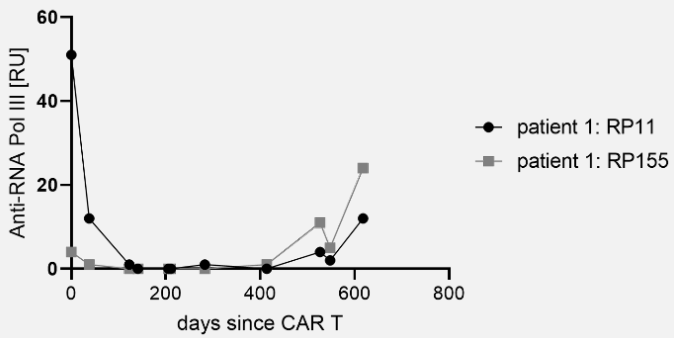
Reductions Demonstrated in Auto-Antibodies

Among 6 patients with SSc treated with anti-CD19 CAR T-cell therapy

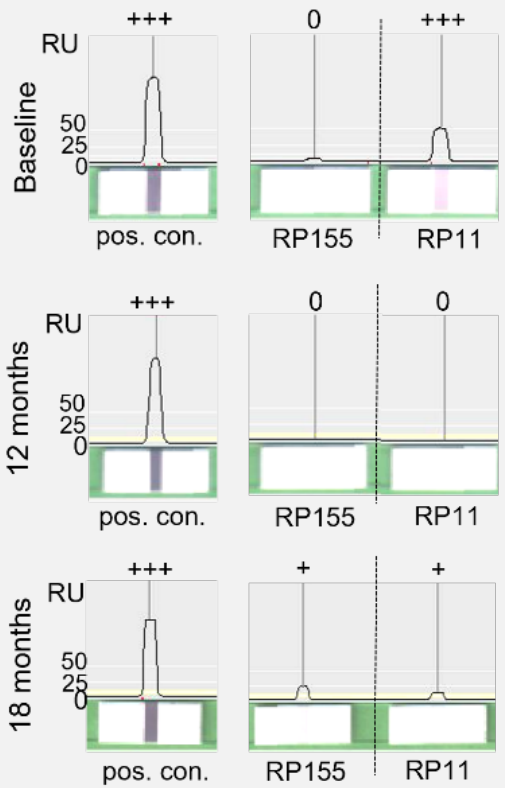
Anti-Nuclear Antibodies



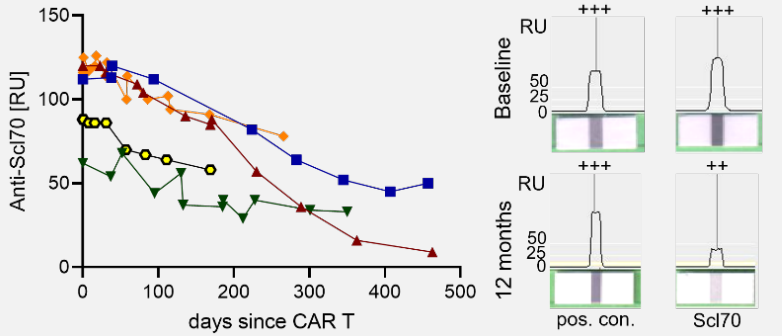
Anti-RNA Polymerase III Immunoblot



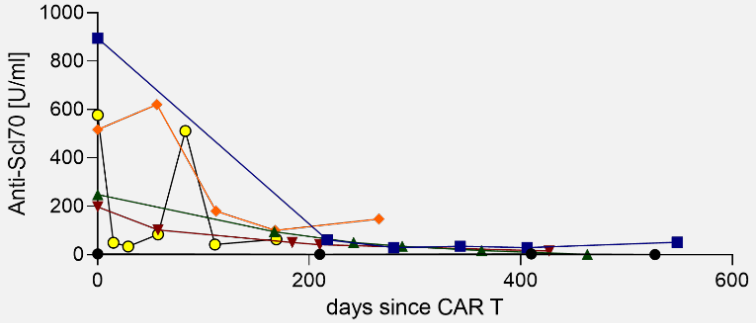
RP, RP155, RP11 Activity



Anti-Scl70 Immunoblot



Anti-Scl70 ELISA



patient 1 patient 2 patient 3 patient 4 patient 5 patient 6

Auth J, et al. *Lancet Rheumatology*, In press.

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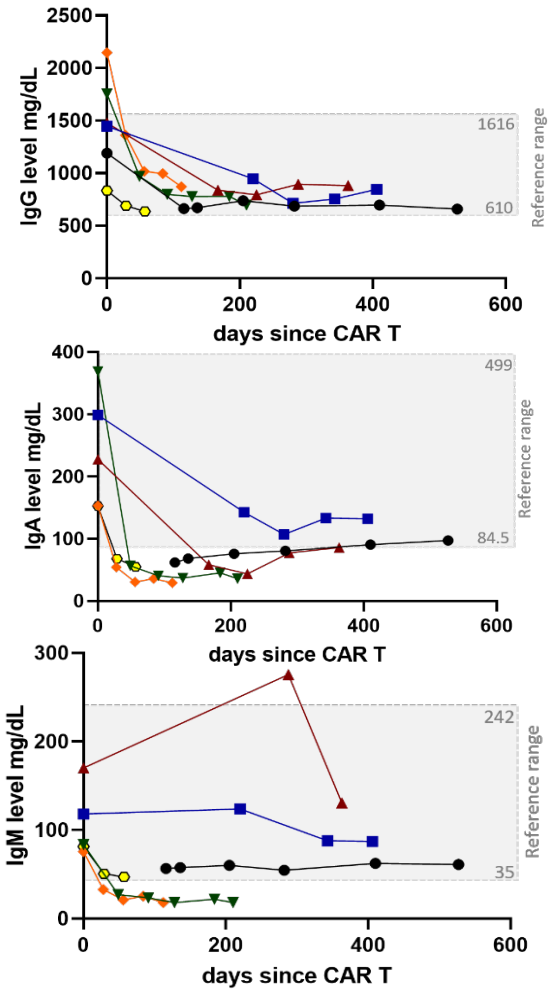
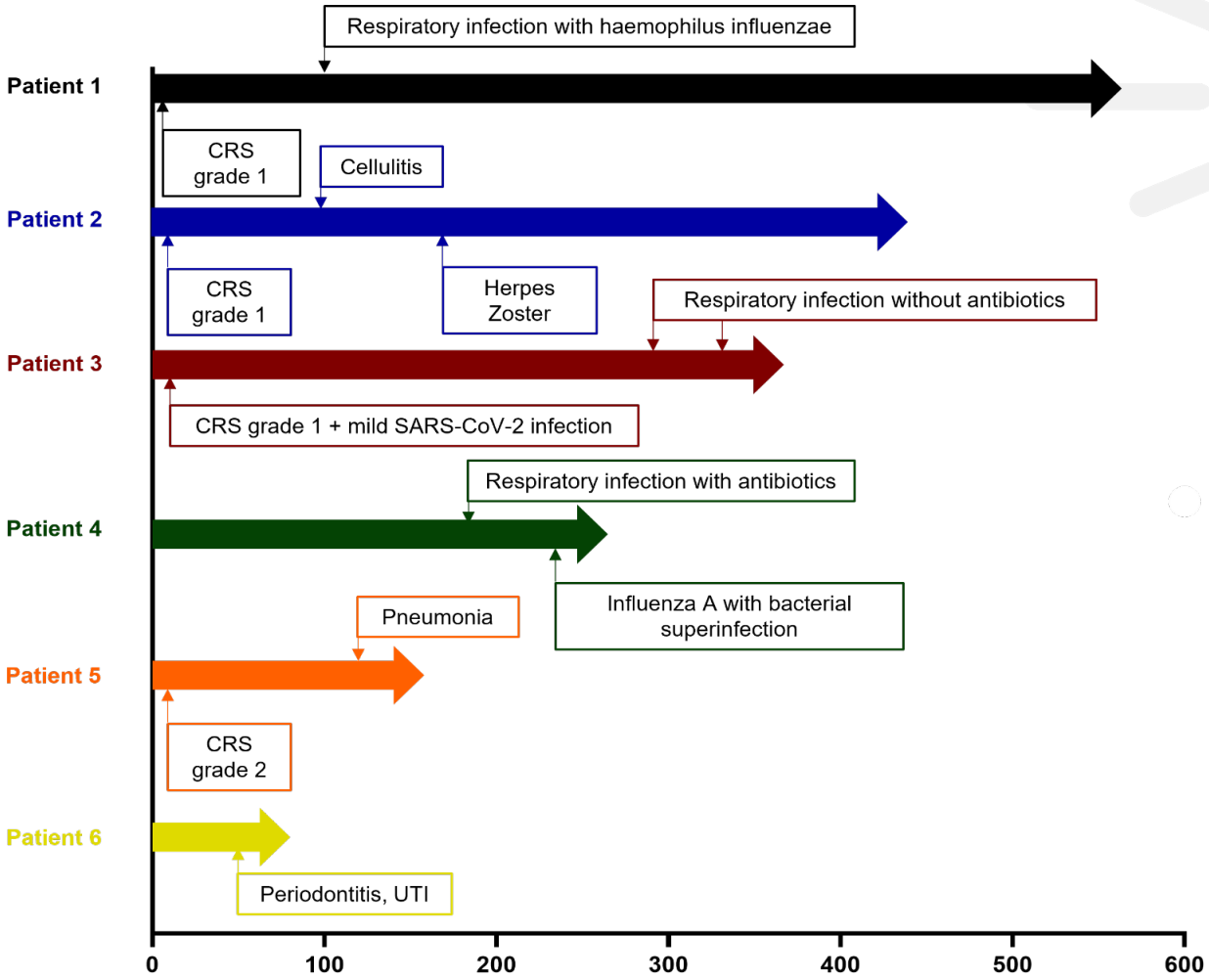
Safety Profile

Among 6 patients with SSc treated with anti-CD19 CAR T-cell therapy

Reductions in Immunoglobulins



Low Grade AEs



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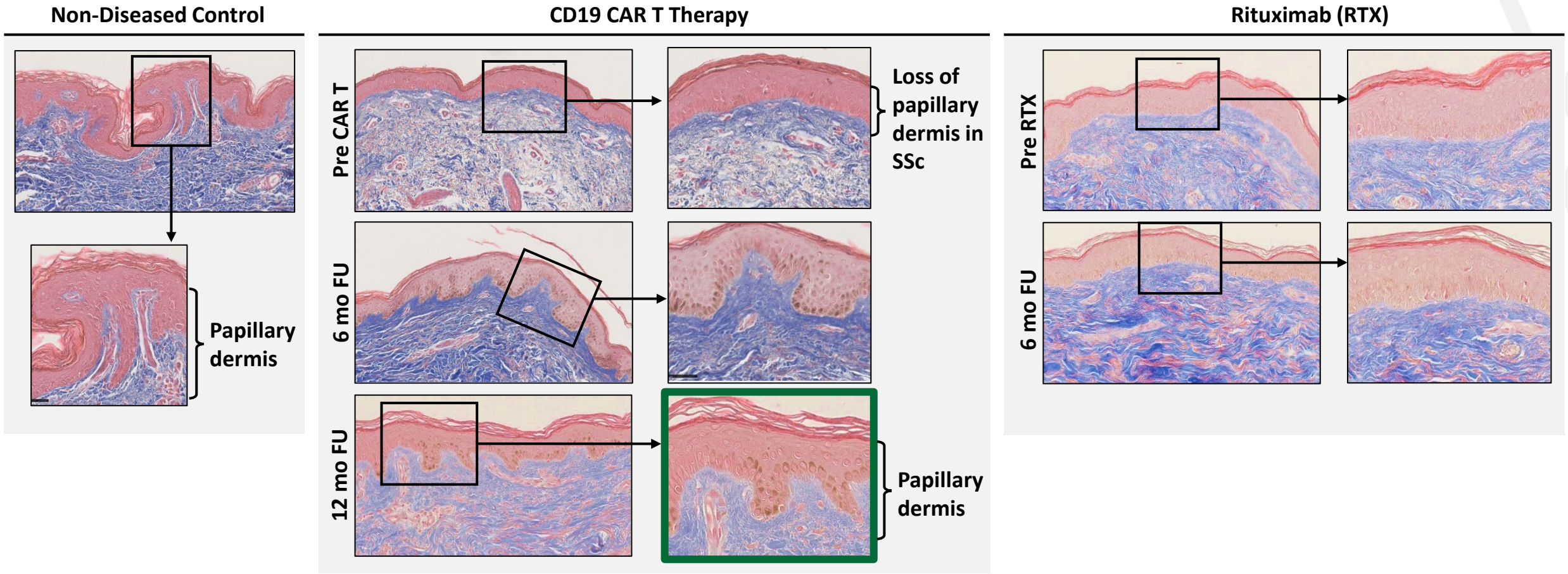
Anti-CD19 CAR T in SSc: Regeneration? Potential Surrogate for Other Tissues



Regeneration of skin architecture in a patient with SSC demonstrated in H&E sections after treatment with anti-CD19 CAR T-cell therapy

Auth J, et al. *Lancet Rheumatology*, In press.

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Future Directions: Characterizing B-Cell Depletion & Predicting Response

	B-Cell Depletion & Immune Reset	Predicting Patient Response
Open Questions	• Does CD19.CAR-T cell therapy completely ***deplete auto-antigen-specific B cell clones in the peripheral blood and in target tissues*** (immune reset)? - How ***persistent is the reset*** of the immune memory? - Is the reset of the immune memory associated with a ***reset of the tissue memory***?	• Does the presence of a particular set of disease specific ***B cell clones identify patients most likely to respond*** the CD19.CAR-T cell therapy? • Is the ***clone-specific depletion*** associated with ***durable response*** to therapy and does the ***return of these specific clones*** correlate with ***disease relapse***?
Approach	***Multi-OMICs-based, spatially resolved profiling*** of altered tissue responses after CD19.CAR-T cell therapy Assessment of ***the immune receptor repertoires and BCR reactivities*** in the ***peripheral blood and target tissues*** before and after CD19.CAR-T treatment	Development of a multiplexed single cell PCR-based assay and a spatial B-cell repertoires sequencing assay to ***assess clonal B-cell repertoire dynamics*** after CD19.CAR-T cell therapy

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Summary and Outlook: Anti-CD19 CAR T Holds Significant Promise in SSc

Growing number of autoimmune patients treated CD19.CAR-T cells, some with ***follow-up for up to three years*** post CAR-T

Loss of auto-antibodies in some patients (immune reset / eradication of immune memory), and reduction in auto-antibodies in others

So far ***good tolerability***, despite the selection for patients with severe and often advanced disease (that would not qualify for HDCT/SCT)

Often impressive improvement of clinical manifestations, including ***preliminary evidence of regression of histological changes*** (eradication of tissue memory?)

Molecular mechanism underlying these therapeutic effects ***require further studies***

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Exploring Opportunities Across Different Diseases

LORINDA CHUNG, MD, MS

STANFORD UNIVERSITY

Stanford

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Stanford CIT: Bringing Cell Therapy to Autoimmune & Transplant Patients

Stanford MEDICINE
School of Medicine
Cellular Immune Tolerance (CIT)

Cellular Immune Tolerance (CIT) Vision:

Development and clinical translation of ***cutting-edge curative cell therapies to restore immune tolerance*** in autoimmune and transplant patients.

- ***Cell therapy trials involve an elaborate infrastructure***, predominately cancer-focused
- Academic teams are needed to specifically focus on ***immune cell tolerance trials***
- An infrastructure has been developed to ***bring together clinical, scientific, regulatory, and operational experts*** from within the Department of Medicine to collaborate on Clinical Trial Operations

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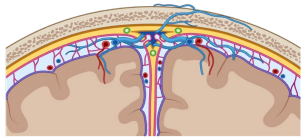
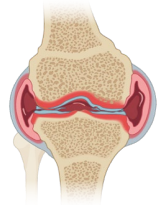
Kyverna Collaboration Brings Transformative CAR T to Stanford

Stanford HEALTH CARE

Collaboration between multiple departments at Stanford Medicine…



Neuroimmunology

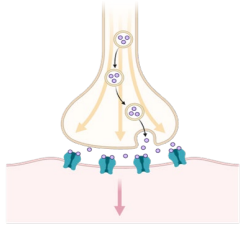


Rheumatology

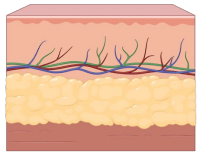
Stanford MEDICINE

School of Medicine

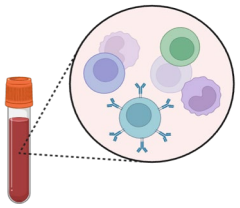
Cellular Immune Tolerance (CIT)



Neurology



Dermatology



Hematology

…Gathering extensive experience with KYV-101 for autoimmune conditions

KYSA-1
LUPUS NEPHRITIS

KYSA-5
SYSTEMIC SCLEROSIS

KYSA-6
MYASTHENIA GRAVIS

KYSA-7
MULTIPLE SCLEROSIS

IITs in Dermatomyositis and Multiple Sclerosis

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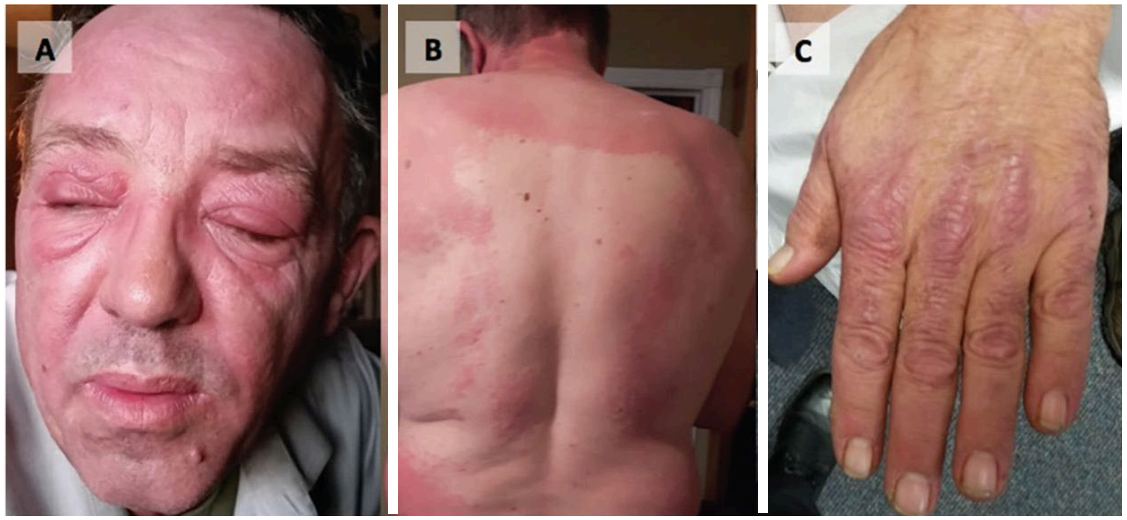
DM Is a Severe Disease Primarily Affecting the Skin, Muscles, and Lung

Dermatomyositis (DM) Overview[1–3]

- DM is a ***type of idiopathic inflammatory myopathy*** (IIM)
- DM is rare, with an estimated ***global incidence of 1-3 per 100,000 persons/yr***
- ***Progressive proximal muscle weakness*** and characteristic ***skin findings*** are hallmarks of DM
  - ***Interstitial lung disease*** is a major cause of morbidity and mortality
  - DM patients are at ***higher risk*** for associated ***cancers***, especially for patients with certain autoantibody types

Typical DM Skin Manifestations[4]



Heliotrope rash around the eyes | Shawl sign on upper back | Gottron papules on the hand

1. Osman M, et al. Sci Rep. 2023;13(1):16444. 2. Lundberg IE, et al. Nat Rev Dis Primers. 2021;7(1):86. 3. Oldroyd AGS, et al. Nat Rev Rheumatol. 2023;19(12):805-817. 4. Chu LL and Rohekar G. CMAJ. 2019; 191(12):E340.

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No Curative Therapies for DM

DM Treatment[1–3]

- DM is primarily treated with ***corticosteroids, immunosuppressants, and IVIG***
- Severe and/or refractory patients often require ***multiple*** and/or ***more potent immunosuppressants***
- However, efficacy is often ***unpredictable and modest*** in magnitude, and patients often suffer from ***intolerable side effects*** due to their medications
- There is currently ***no cure*** for DM, and the majority of patients require ***life-long therapy***

1. Lundberg IE, et al. *Nat Rev Dis Primers*. 2021;7(1):86. 2. Aggarwal R, et al. *N Engl J Med*. 2022;387(14):1264-1278. 3. Franco C, et al. *Curr Opin Rheumatol*. 2021;33(6):522-528.

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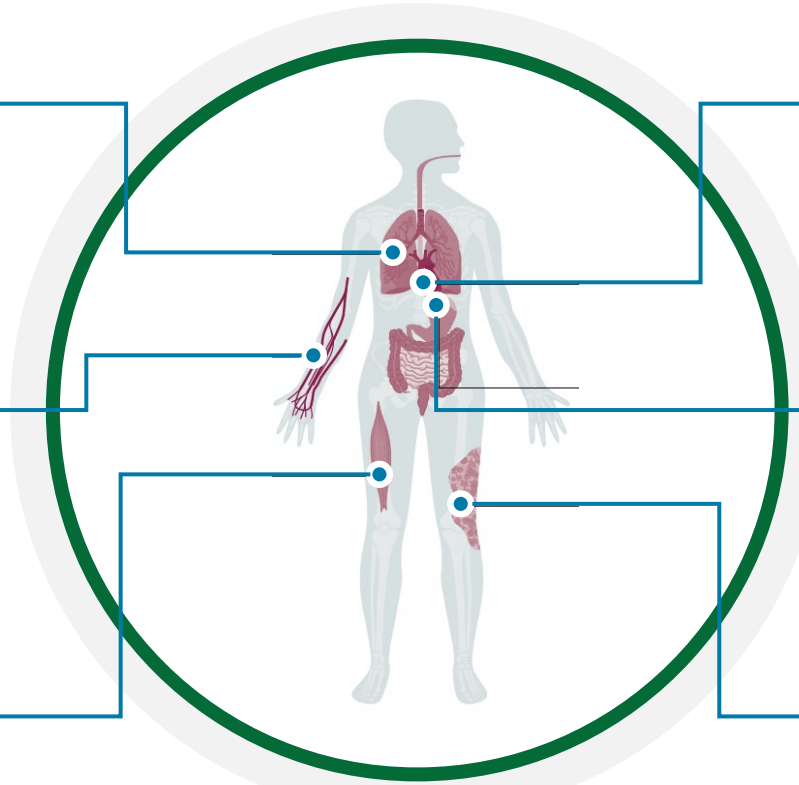
DM Has a Heterogeneous Presentation Across Multiple Organ Systems

Highlighted complications have significant impact on patient mortality and/or quality of life

Pulmonary System
- **Interstitial lung disease**

Peripheral Vascular System
- Raynaud phenomenon
- Digital ischemia

Musculoskeletal System
- **Muscle weakness**
- Arthritis



Cardiovascular System
- **Myocarditis**

Gastrointestinal System
- Dysphagia
- Ulceration/perforation

Dermatological System
- **Rash**
- Cutaneous ulceration
- Calcinosis

Increased Cancer Risk

Lundberg IE, et al. *Nat Rev Dis Primers*. 2021;7(1):86.

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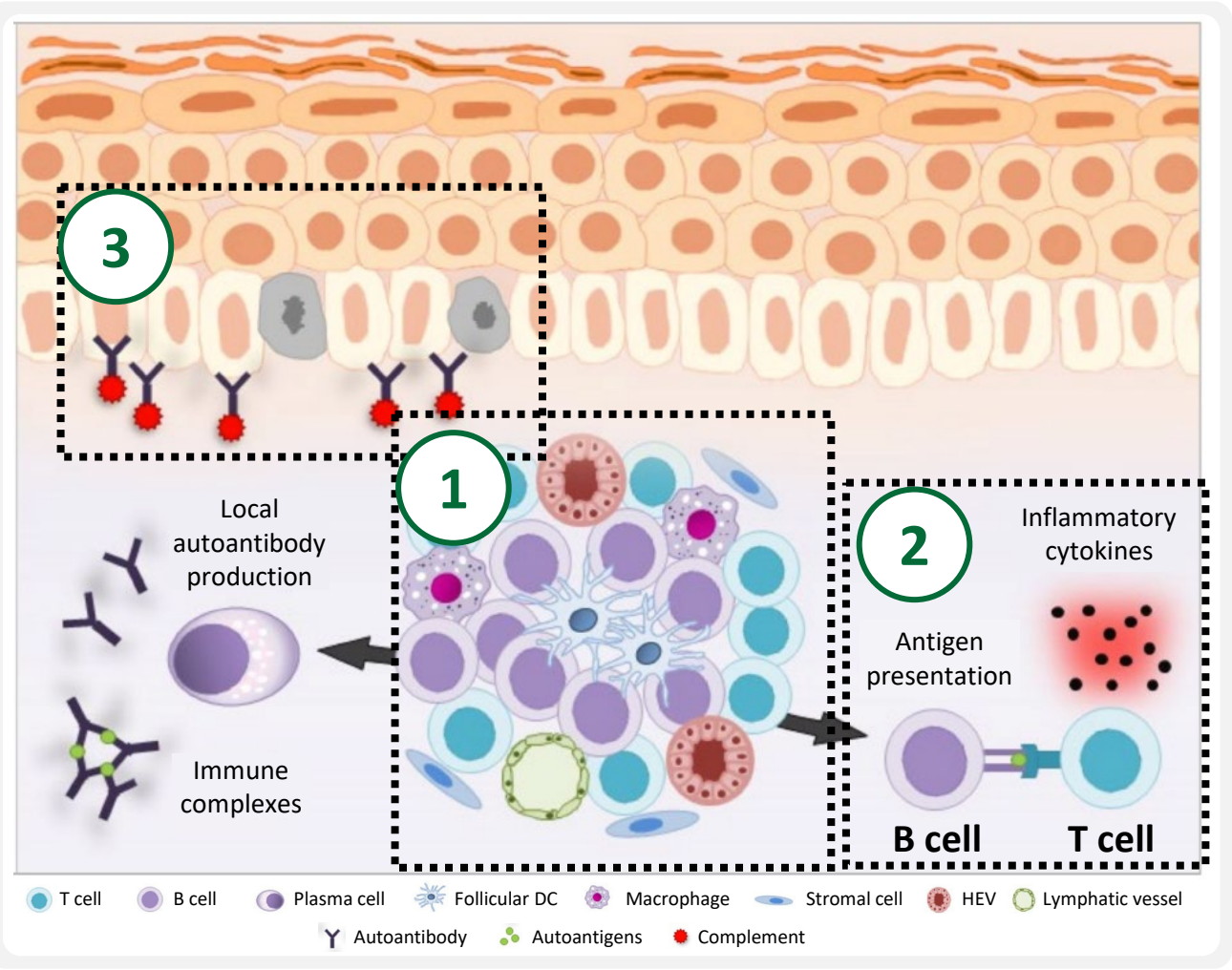
B Cells Are Central to Autoimmune Disease Pathology in DM



Adapted from Melissaropoulos K, et al. *Front Immunol*. 2022;13:933468.

1 Tertiary Lymphoid Structure (TLS) Formation

Lymphoid and stromal cells within the skin form TLSs rich in survival factors and ***inaccessible to traditional B-cell depleting therapies***

2 Immune Dysregulation

TLS-resident ***B cells secrete autoantibodies*** and/or ***present autoantigens to T cells***

3 Chronic Inflammation

Autoantibodies, cytokines, and activated autoreactive T cells ***perpetuate chronic inflammation***

Fetter T, et al. *Cells*. 2020;9(12):2627.

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Why Is it So Challenging to Develop Treatments for DM?

Complex Mechanism of Disease

Inaccessible Tissue-Resident B Cells

Patient-To-Patient Heterogeneity

Multi-Organ Involvement

Anti-CD19 CAR-T therapy depletes B cells in the blood and tissues with the aim to trigger an immune reset and is a promising therapy for this devastating disease

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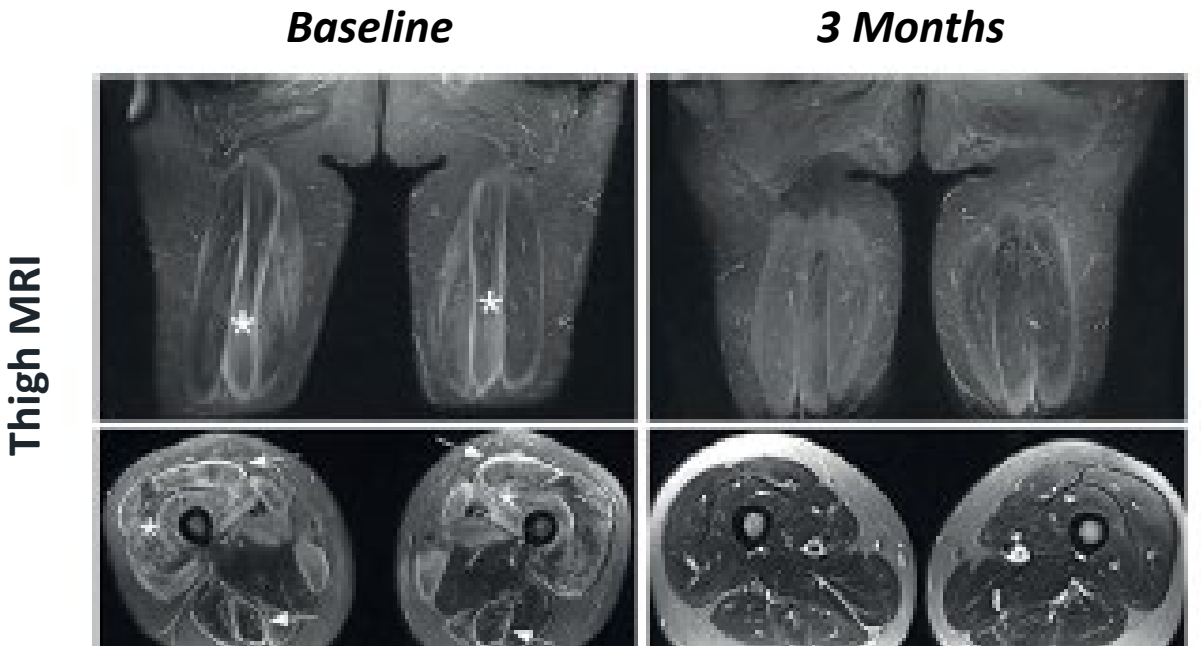
Anti-CD19 CAR T in ASyS (IIM Subtype): Disease Remission in a Patient

41-year-old male patient with Jo1+ IIM, periorbital edema, active myositis, and ILD achieved ***complete remission in 3 months, including:***

- Discontinuation of immunosuppressive drugs
- Complete resolution of myositis lesions
- Improvement in respiratory symptoms
- Discontinuation of supplemental oxygen

Resolution of Inflammation in Quads and Hamstrings



ASyS, antisynthetase syndrome.
Müller F, et al. *Lancet*. 2023 Mar 11;401(10379):815-818.

Anti-CD19 CAR T in ASyS (IIM Subtype): Disease Remission in a Patient

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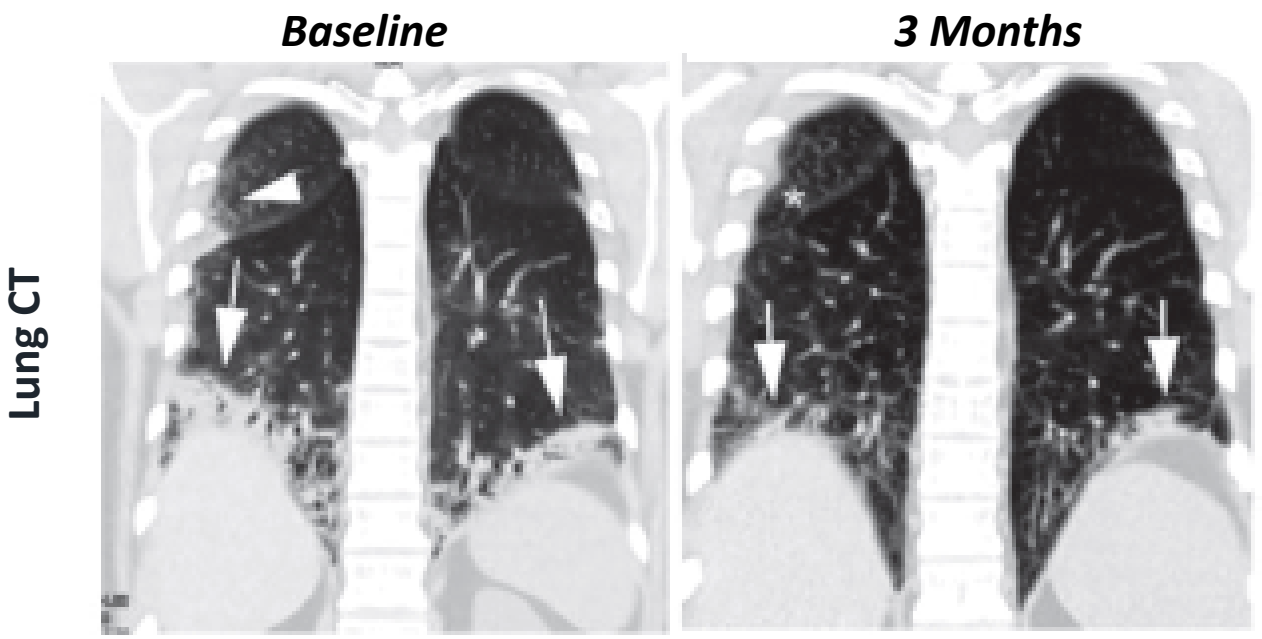
- Improvement in respiratory symptoms
- Discontinuation of supplemental oxygen

Full Regression of Alveolitis



ASyS, antisynthetase syndrome.
Müller F, et al. *Lancet*. 2023 Mar 11;401(10379):815-818.

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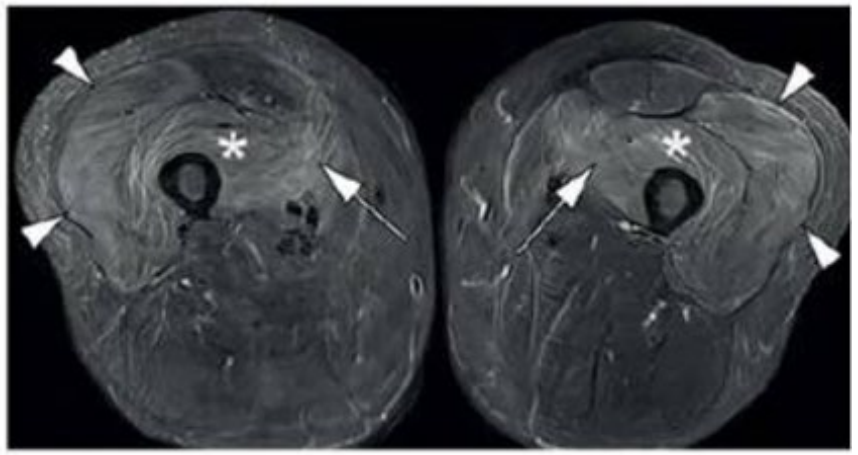
Anti-CD19 CAR T in ASyS (IIM Subtype): Disease Remission in a Patient

44-year-old female patient with Jo1+, PM/Scl+, ANA+ myositis, polyarthritis, **holster sign**, **V-sign**, and **Gottron papules** achieved **major improvement according to the 2016 ACR/EULAR TIS*, including:***

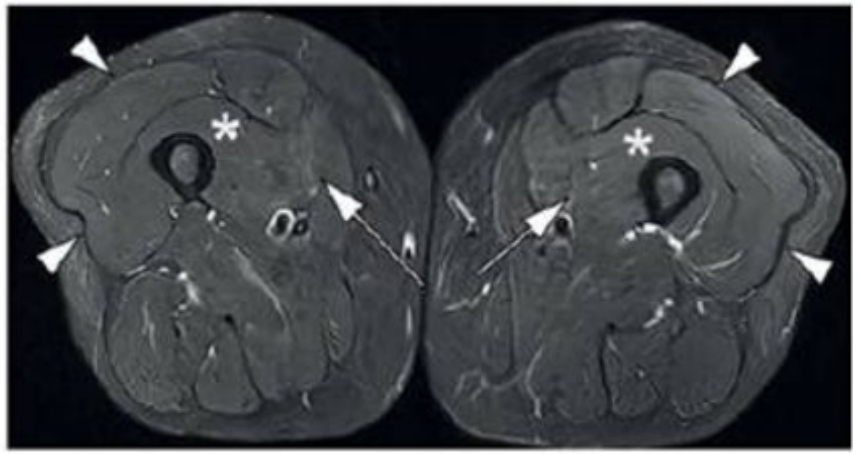
- Complete resolution of myositis by MRI
- Drug-free (including glucocorticoid-free) remission
- Regained muscle strength with a manual muscle test score of 103/150 at baseline to full strength (150/150) at the Day 150+

Complete Resolution of Myositis in the Thigh

Baseline



3 Months



ACR/EULAR, American College of Rheumatology/European League Against Rheumatism; ANA, antinuclear antibodies; ASyS, antisynthetase syndrome; PM/Scl, polymyositis/scleroderma; TIS, total improvement score.

Taubmann J, et al. *Rheumatology*. 2024;63(1):e12-e14.

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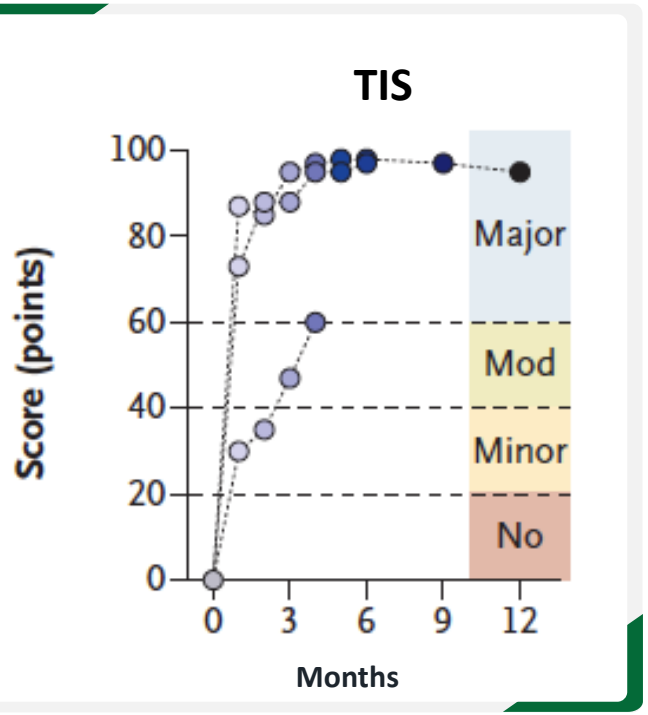
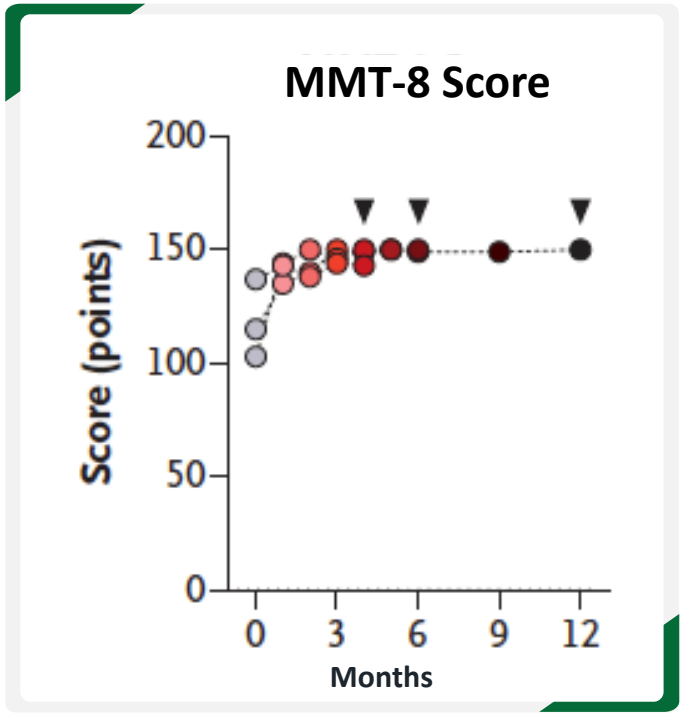
Anti-CD19 CAR T in IIM: Improved Muscle Function, Off Immunosuppressants

Improvement in Clinical Status
N=3



Normalized Muscular Function
N=3



Reduction or Elimination of IS Therapy

Patient #	Glucocorticoid-free State	No Immunosuppressant Drugs
Patient 1	+	+
Patient 2	+	+
Patient 3	+	+

These early anti-CD19 CAR-T experiences in IIM provides compelling rationale to study CAR T use in DM

MMT-8, Manual Muscle Test-8; TIS, ACR-EULAR Total Improvement Score.

Müller F, et al. *N Engl J Med*. 2024;390(8):687-700.

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Investigator Initiated Phase 1B Study of KYV-101 in Dermatomyositis

Key Eligibility Criteria

- ≥25 and ≤72 years old
- Diagnosis of probable or definite (>55%) DM
- Refractory to steroids and ≥2 immunomodulatory therapies
- Active muscle with MMT-8 <142 OR skin disease with CDASI ≥19 and ≥2 abnormal CSM

Phase 1B Design *(N≤21)*

- **Dose:** 1×10^8 CAR+ T cells
- **Standard Lymphodepletion (LD) (CYC/FLU)** *(n=3)*

Safety & PD Evaluation

- **Dose:** 1×10^8 CAR+ T cells
- **Reduced Intensity LD (CYC/FLU)** *(n=3-6)*

- **Dose:** 1×10^8 CAR+ T cells
- **Bendamustine LD** *(n=3-6)*

Endpoints

- **Primary:** Safety and tolerability
- **Key Secondary (Efficacy)**
  - Myositis response rate, defined as increase in TIS by ≥ 20, at 24 weeks
  - Change in CDASI-a at 12, 24, and 52 weeks
  - Change in TIS at 12, 24, and 52 weeks
  - If ILD, change in FVC and DLCO at 24 and 52 weeks
  - Change in MRI at 24 weeks
  - Optional: change in FAPI PET at 24 weeks

NCT06400303

CAR, chimeric antigen receptor; CDASI, Cutaneous Dermatomyositis Disease Area and Severity Index; CSM, core set measures; CYC, cyclophosphamide; DLCO, diffusion capacity for carbon monoxide; FAPI PET, fibroblast activation protein inhibitor positron emission tomography; FLU, fludarabine; FVC, forced vital capacity; MMT-8, Manual Muscle Testing and a Subset of Eight Muscle; ILD, interstitial lung disease; PK/PD: pharmacokinetics/pharmacodynamics; PRO, patient reported outcome, RP2D, recommended phase 2 dose; TIS, total improvement score.

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Stanford IIT in DM: Exploring Alternative Lymphodepletion With KYV-101

	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	
Standard LD Regimen	Cyclophosphamide (300mg/m^2) + Fludarabine (30mg/m^2)	Cyclophosphamide (300mg/m^2) + Fludarabine (30mg/m^2)	Cyclophosphamide (300mg/m^2) + Fludarabine (30mg/m^2)	*Rest*				**KYV-101 INFUSION** *Day 0*
Reduced Intensity LD	Cyclophosphamide (150mg/m^2) + Fludarabine (15mg/m^2)	Cyclophosphamide (150mg/m^2) + Fludarabine (15mg/m^2)	Cyclophosphamide (150mg/m^2) + Fludarabine (15mg/m^2)	*Rest*				
Alternative LD			Bendamustine (90mg/m^2)	Bendamustine (90mg/m^2)	*Rest*			

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Understanding Mechanism of KYV-101 In Dermatomyositis

Blood Assessments

Tracked Biomarker	Informs
Blood IFN Gene Signature	Proxy for skin and muscle disease activity
Autoantibody Profile	Assess change in myositis-specific and myositis-associated levels
B- and T-Cell Subsets	Explore concept of immune reset by assessing immune repertoire over time via flow cytometry

Skin Assessments

Tracked Biomarker	Informs
Type 1 IFN Signature	Correlation between B cell depletion and skin inflammation
Immune Cell Populations	Profile changes in immune composition with treatment
BCR / TCR Sequencing	Monitor stability and changes in immune cell repertoire over time

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Broadening the Impact of KYV-101: Transformative Potential Across Diseases

KYV-101 drives deep B-cell depletion to achieve an immune reset and holds ***great promise for treating autoimmune diseases***

The CIT program at Stanford is ***exploring KYV-101 across a broad range of autoimmune conditions***

This is just a starting point and we have much to **learn from the ongoing studies** which will inform us regarding the **applicability to other autoimmune diseases**[1-4]

1.https://autoimmune.org › 1-in-5-Brochure. Accessed on October 24, 2024; 2. Schett G, et al. *Lancet*. 2023;402:2034-20442; 3. Pope JE, et al. *Nat Rev Rheumatol.* 2023 Feb 27;19:212-26; 4. Aggarwal R, et al. *N Engl J Med*. 2022 Oct 6;387(14):1264-78.

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Thank You to the Cellular Immune Tolerance (CIT) Team

CIT Team


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Everett Meyer


Sally Arai


Lori Panu


Monali Manohar


Renata Gilfanova


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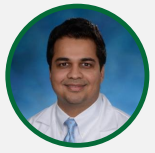
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Kavita Sarin


PJ Utz

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KYV-101 Anti-CD19 CAR T-Cell Therapy: The Future of Autoimmune Disease Treatment

1 **Welcome and Introduction**
Sham Dholakia, MD, DPhil Kyverna Therapeutics

2 **B-Cell Targeting With CAR T in Autoimmune Diseases**
Georg Schett, MD Friedrich-Alexander-University Erlangen-Nürnberg

3 **Biomarkers to Uncover Mechanistic Drivers of CAR T-Cell Therapy**
Jörg Distler, MD Heinrich Heine University Düsseldorf

4 **Exploring Opportunities Across Different Diseases**
Lorinda Chung, MD Stanford University

5 **Panel Discussion**
Roberto Caricchio, MD Jörg Distler, MD Lorinda Chung, MD Georg Schett, MD

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