# *ACR 23 Any Updates ??*

*Dalia Fayez*
*Ain Shams University*

# *Agenda*

- Can Lupus Be Prevented
- Disease Modification in Lupus Nephritis
- Meet the panel: the latest in Lupus Treatment
- The future of APS: 2023 ACR/EULAR APS Classification Criteria α Beyond
- The future of APS: Disentangling APS through pathogenesis-informed sub-phenotyping

UT Southwestern
Medical Center

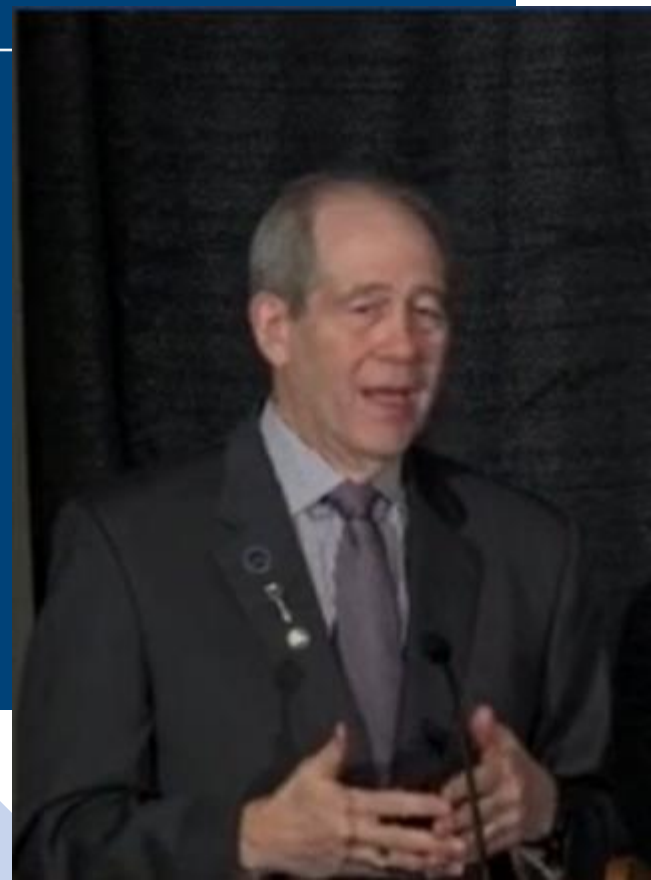
# Can Lupus Be Prevented?

David R. Karp, MD, PhD

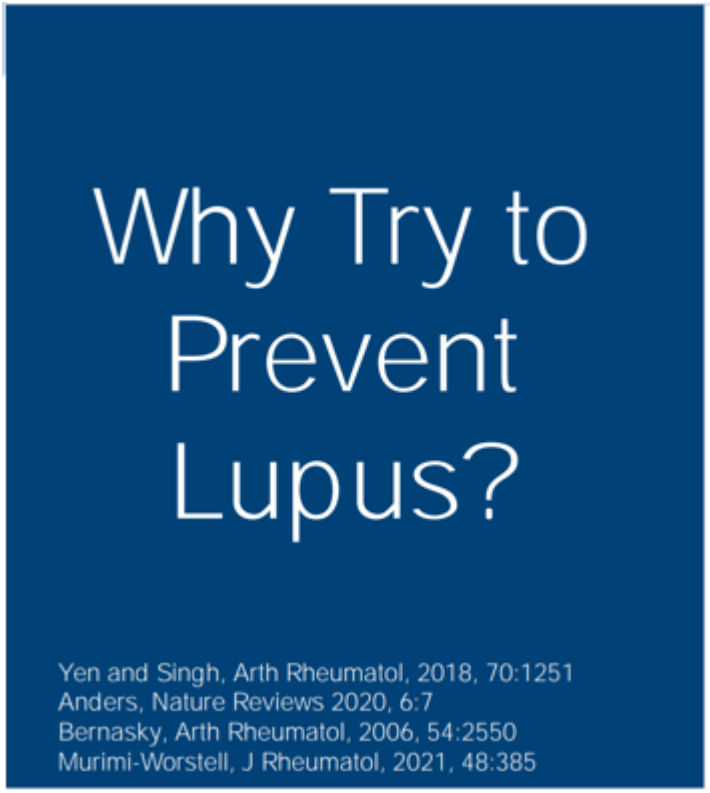
Professor and Chief, Rheumatic Diseases Division

University of Texas Southwestern Medical Center

Dallas, Texas

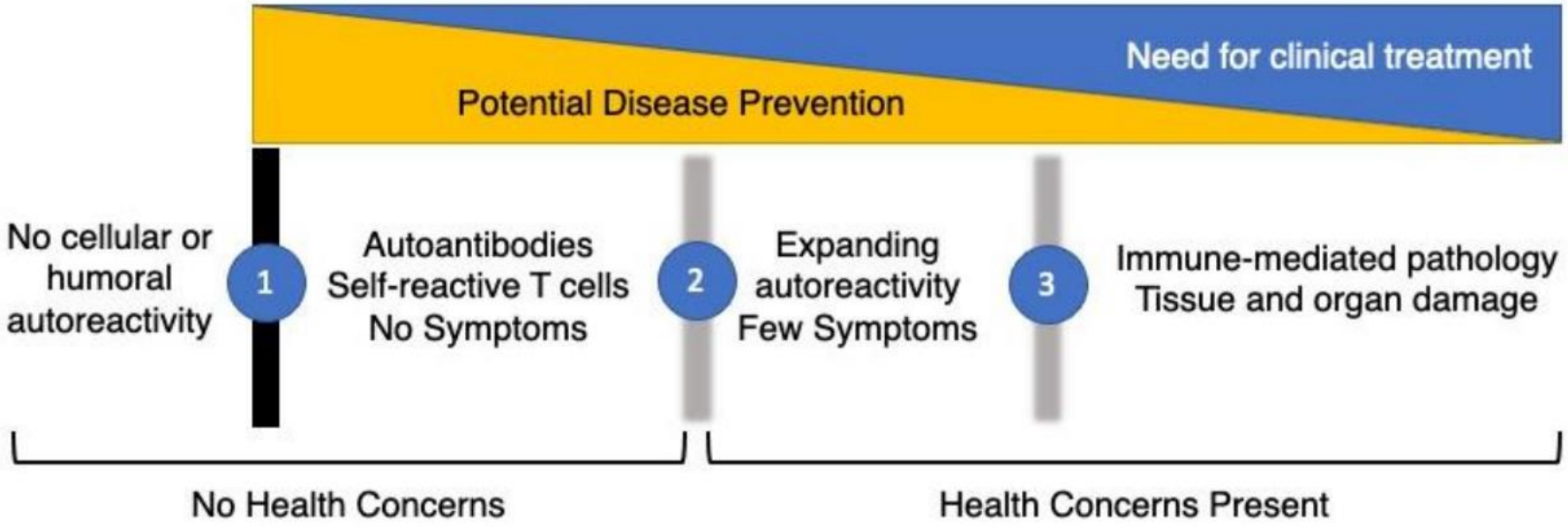


# *Try To Prevent Lupus*




- SLE is the 5$^{th}$ leading cause of non-traumatic mortality in Black and Hispanic females ages 15-24 in the US
- 60% of lupus patients have lupus nephritis during their disease and up to 20% develop end-stage renal disease within 10 yr.
- From 2011-2015, 25.7% of lupus patients had >ED visit, 13.7% had >1 hospitalization per year and the mean annual cost for treatment was 52,951 $

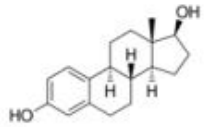
# A General Scheme for Pre-Classification Autoimmunity – Setting the Stage for Lupus




Pre-Stage 1 – At risk
Stage 1 – Evidence of autoimmunity but no symptoms
Stage 2 – Few symptoms and more autoimmunity
Stage 3 – Classifiable disease

# Setting the Stage for Lupus

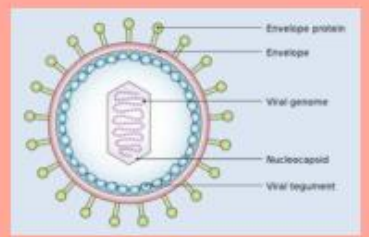
Diet, etc.



1. 2. 3. 4.

N R I

A R I

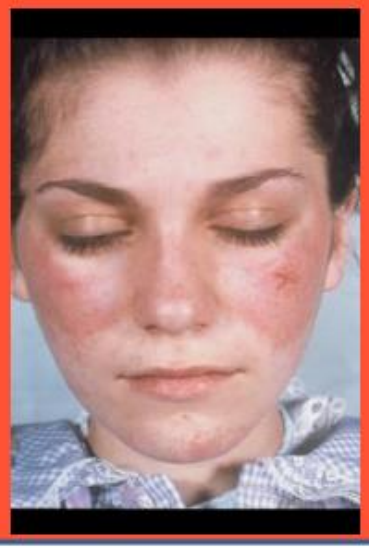



ANA, anti-Ro, anti-La
Dysregulated cytokines and chemokines
Altered gene expression in B cells and monocytes
Re-activation of EBV

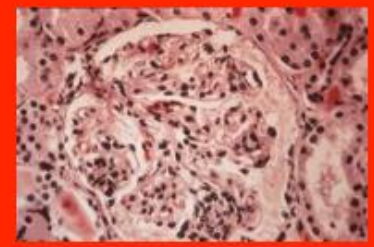
Incomplete Lupus Erythematosus
ILE

Leukopenia
Low platelets
Low C4, C3
Isolated rash
Isolated joints

Classified Disease Multi-Criteria



Irreversible Tissue Damage

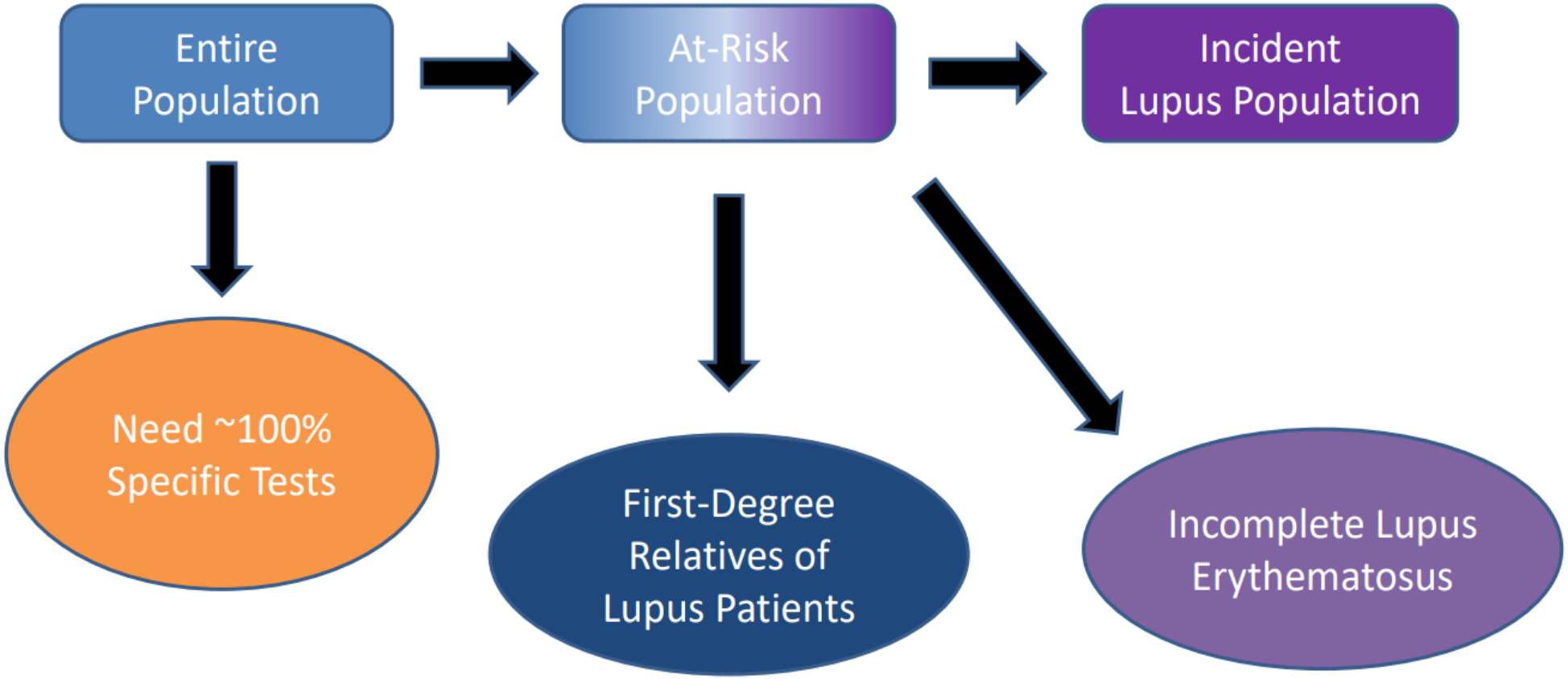


1. Altered Immunity
2. Symptoms
3. Diagnosis
4. Damage

Window for screening and prevention

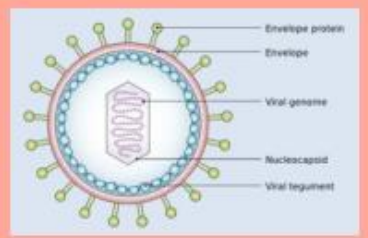
NRI – No Risk Individuals; ARI At Risk Individuals

# Deciding Whom to Screen: Practical Issues



# Deciding Whom to Treat: Clues From Studying Incomplete Lupus

1.




ANA, anti-Ro, anti-La
Dysregulated cytokines and chemokines
Altered gene expression in B cells and monocytes
Re-activation of EBV

How many?
How fast?
Which ones?

2.

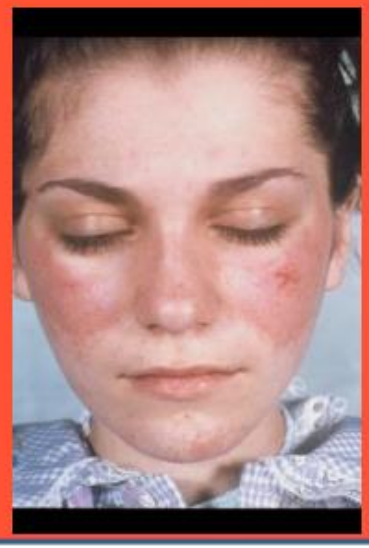
Incomplete Lupus Erythematosus
ILE

Leukopenia
Low platelets
Low C4, C3
Isolated rash
Isolated joints

How many?
How fast?
Which ones?

3.

Classified Disease
Multi-Criteria



Window for screening and prevention

ILE

3 of 22 ILE became SLE over 2.4 y; Female, # and titers of auto Ab (La, LC1, C1q, PCNA, hemocyanin, β2M) predicted progression. Olsen, N. J., et al. (2012). Arthritis Res Ther **14**(4): R174.

56 of 264 ILE with 2.7±1.0 ACR criteria progressed to SLE over 6.3±4.3 y. 161 remained ILE. Oral ulcers, anti-dsDNA, and active urinary sediment predicted progression. Al Daabil, M., et al. (2014). Int J Clin Pract **68**(12): 1508-1513.

13 of 77 CLE became SLE over 8.03±6.2 y. Only 5 of 13 had mild systemic symptoms. Wieczorek, I. T., et al. (2014). JAMA Dermatol **150**(3): 291-296.

8 of 87 Spanish ILE became SLE in 2.2±2.4 y. Photosensitivity, anti-dsDNA, and low C' predicted progression. Vila, L. M., et al. (2000). Lupus **9**(2): 110-115.

SLE

2%-5% per year of ILE patients become SLE

# *Is There an Acceptable Treatment to Prevent Lupus*

**Based on**

### *Pathogenesis*

- ✓ B-cell depletion- Anti-CD20;Anti-BLyS
- ✓ T-cell activation- Abatacept
- ✓ Type I interferon: Hydroxychloroquine Anifrolimab

### *Safety*

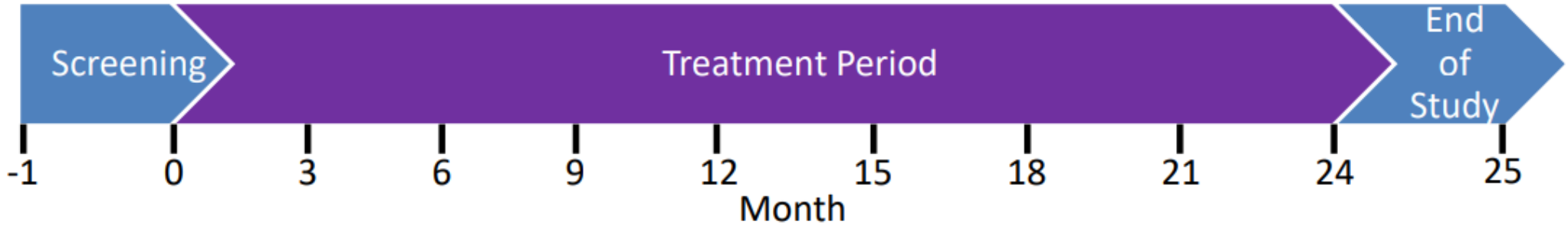
- ✓ Targeted population will have few, if any, symptoms
- ✓ Therapy may be short and intense, or long-term

### *Acceptability to patients*

- ✓ Oral preferred to parenteral
- ✓ Need to demonstrate effectiveness

# SMILE – Study of Anti-Malarials in Incomplete Lupus Erythematosus NCT03030118

| | |
|---|---|
| **Patient Population** | • F/M 15-49<br>• ANA ≥ 1:80 by Hep2 Indirect Immunofluorescence<br>• 1-2 additional 2012 SLICC Criteria for SLE<br>• No other autoimmune disease or fibromyalgia |
| **Sample Size** | • 240 Enrolled (120 per arm)<br>• 7 Sites |
| **Treatment** | • 1:1 Hydroxychloroquine or matching placebo<br>• 200 mg/d for ≤ 40 kg; 400 mg/d for > 40 kg<br>• Randomization stratified by site and # criteria |




| | | |
|---|---|---|
| **Outcomes** | • 1° Rate of accumulation of SLICC Criteria | |
| | • 2° Transition to SLE (SLICC/ACR) | Autoantibodies (Clinical; array) |
| | • Cytokine/Chemokine levels | PROMIS |
| | • Retinal toxicity | Genomics/Transcriptomics |

# Screening and Preventing Lupus – A Scorecard

- **Is there a recognized latent stage?**
  - Yes, clearly there are humoral and cellular immune changes preceding clinical signs and symptoms.
- **Are there suitable and acceptable tests to screen for lupus?**
  - Most likely, but genetic testing in individuals without a family history may be questioned, and accuracy of antibody/cytokine screening over time in different populations is not known.
- **Is the natural history of the latent stage known?** Yes and no.
  - Definition of lupus 'Stages' is not agreed upon.
  - The progression of biomarkers is not yet known
- **Is there a policy of whom to treat?** No
- **Is there an acceptable treatment?** Not yet

# Disease Modification in Lupus

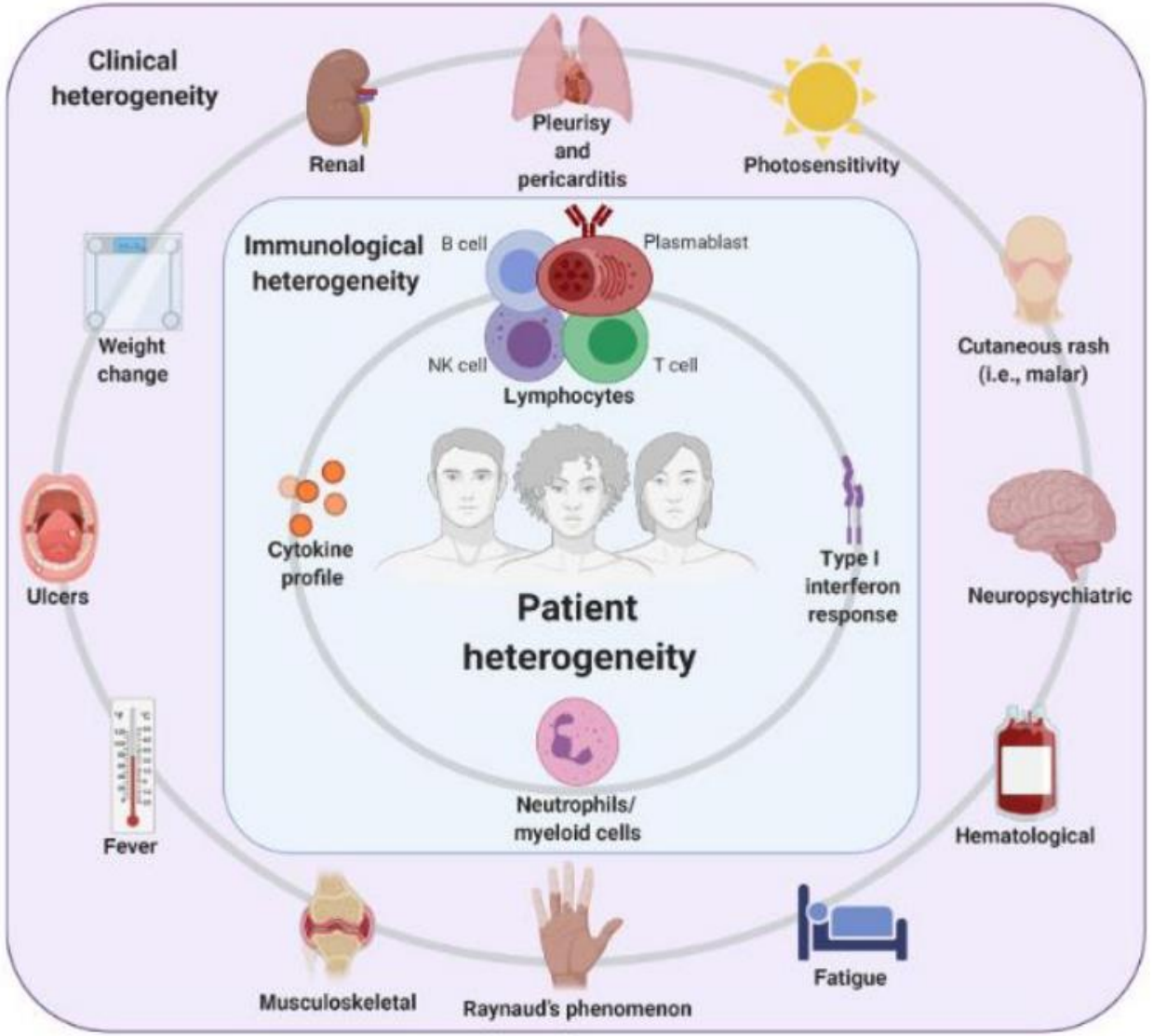
Anca D. Askanase MD, MPH

COLUMBIA | COLUMBIA UNIVERSITY IRVING MEDICAL CENTER


## Anca D. Askanase, MD, MPH

Columbia University Irving Medical Center, New York, NY

# Should having an impact on the underlying pathophysiology be part of the definition?

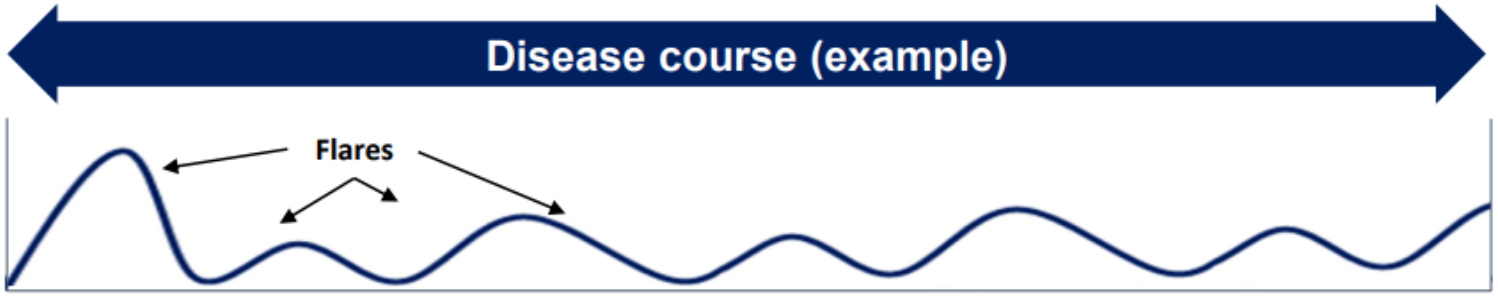



- Varied presentations in disease severity and expression
- SLE is more frequent, more severe, has higher disease activity, and more damage accrual in non-Caucasian populations (Hispanics, African descendants and Asians) than in Caucasians
- **The pathophysiology of SLE is complex and heterogeneous, but not yet fully elucidated, and the evaluation of biomarkers needs further development**

Allen, ME et al. *Trends Mol Med*. 2021;27(2):152-171.

# SLE disease course

A disease of waxing and waning activity and progressive organ damage




## What is organ damage in SLE?

**Organ damage** is an irreversible tissue injury occurring after SLE diagnosis and lasting at least 6 months, regardless of cause, which could include:[2]

- **SLE disease activity/ flares**
- **Medication side-effects**
- **Concomitant disease**

## Early organ damage

Key driver:

- **Persistent disease activity**[1]

*Disease-related organ damage includes: renal, pulmonary, gastrointestinal, and skin manifestations*

## Late organ damage

Key driver:

- **Drug side effects** (especially chronic exposure to corticosteroids)[1]

*Corticosteroid-related organ damage includes: ocular and musculoskeletal manifestations*

1. Doria, et al. Autoimmun Rev. 2014;13(7):770–7. 2. Gladman, et al. Arthritis Rheum. 1996;39(3):363–9.

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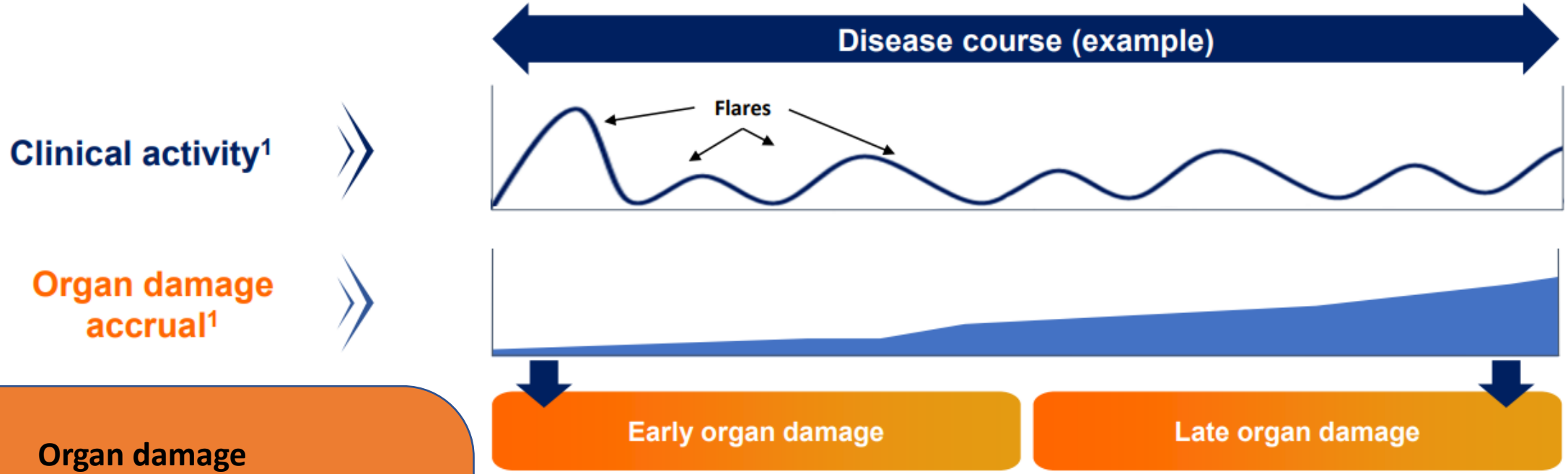


**Organ damage**

Is an irreversible tissue injury occurring after SLE diagnosis and lasting at least 6 months, regardless of cause, which could include:

- ✓ SLE disease activity/flares
- ✓ Medication side-effects
- ✓ Concomitant disease

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- **Persistent disease activity**[1]

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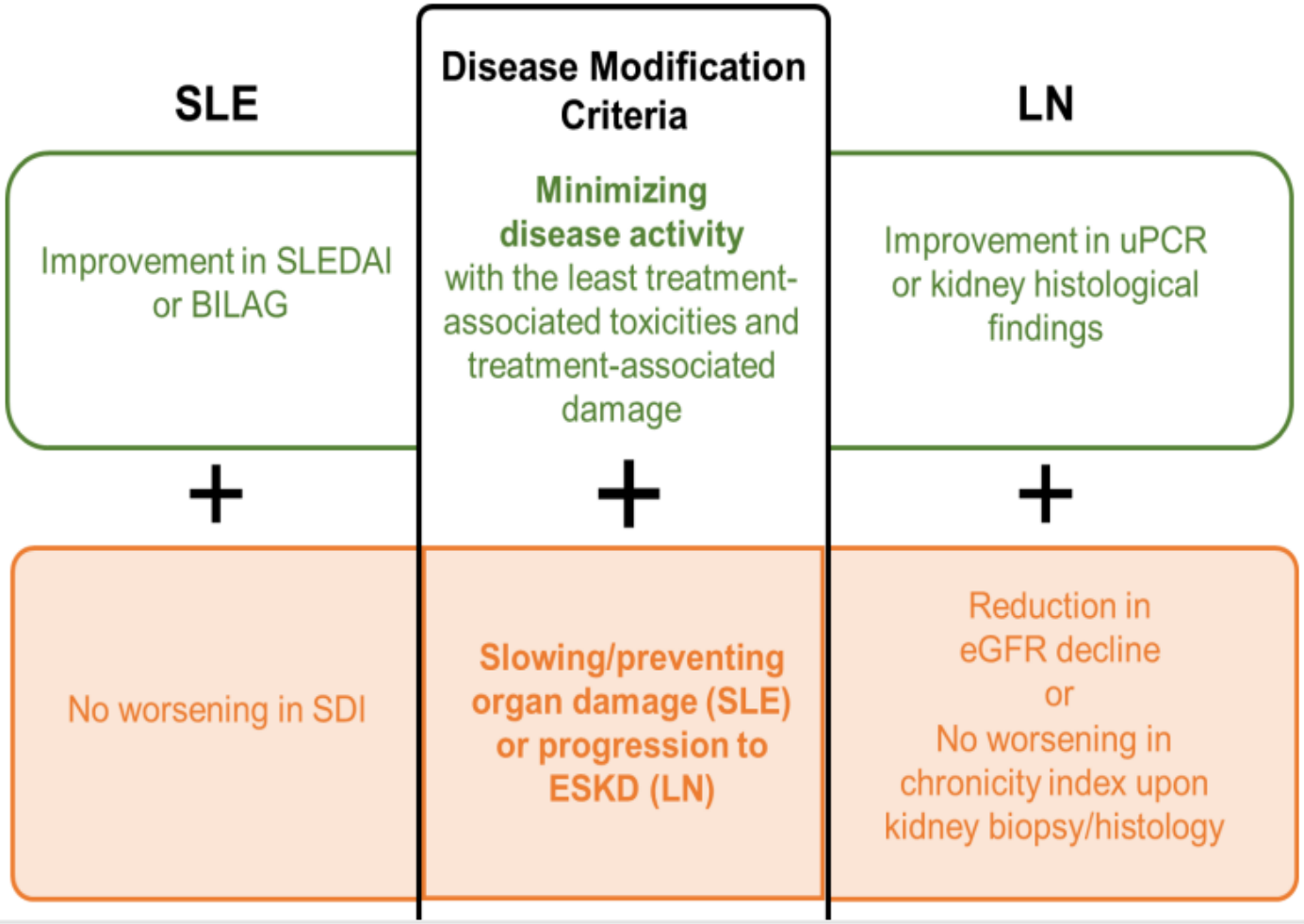
# Disease modification in SLE: An emergent conceptual framework

**SLE and LN**, the definition **must also accommodate specific nuances**, varied clinical manifestations, unclear pathophysiology, unpredictable disease course.

The proposed definition of disease modification:

***"Minimizing disease activity with the least treatment-associated toxicities and slowing or preventing organ damage progression (or, in the case of LN, progression to ESKD"***




Van Vollenhoven ARD 2022

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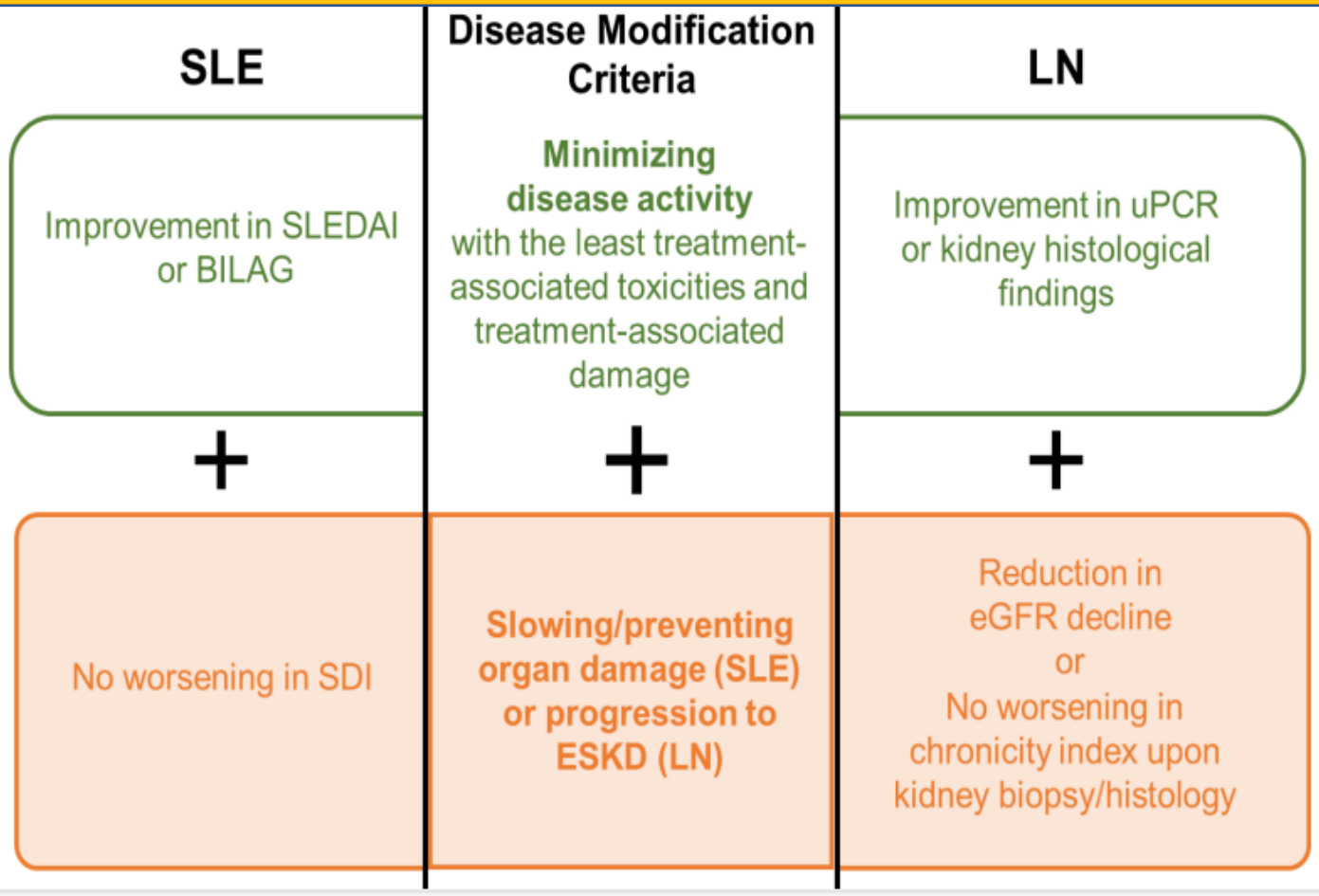


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# Proposed matrix for SLE DM

**Table 2** Proposed matrix for application of the SLE-specific disease modification criteria in clinical trials and clinical practice

| Disease Modification definition category | | Interim timepoints for assessment of disease modification POTENTIAL in clinical trials (vs standard therapy alone) and clinical practice (no comparison) | | Disease modification CONFIRMED |
|---|---|---|---|---|
| | | Outcomes year 1 | Outcomes years 2–5 | Outcomes year >5 |
| Extra renal | Minimising disease activity with minimal treatment-associated toxicity AND Slowing/Preventing organ damage progression | ► Significant reduction in disease activity measured using a validated tool (ie, SELENA-SLEDAI, BILAG, SRI-4)<br>► Significant reduction in severe flare measured using a validated tool (ie, SFI or BILAG)<br>► Reduction in use of steroids* and/or immunosuppressants | ► Sustained improvement in multiple organ domains/no worsening in multiple organ domains<br>► Prevention of severe flares<br>► Continued reduction in use of steroids* and/or immunosuppressants | No change in SDI or delayed progression |
| Renal | Minimising disease activity with minimal treatment-associated toxicity AND Slowing/Preventing organ damage progression | ► Significant improvement in uPCR or kidney activity index via biopsy<br>► Significant reduction in renal flare<br>► Minimise eGFR decline (ie, ≤30%)<br>► Reduction in use of steroids* and/or immunosuppressants | ► Sustained improvement in uPCR or no worsening in kidney chronicity index via biopsy<br>► Prevention of renal flares<br>► Minimise further decline in eGFR (ie, <30%)<br>► Continued reduction in steroids* and/or immunosuppressants | No change in SDI or delayed progression |

*≤7.5 mg/day per 2019 EULAR SLE treatment guidelines and LLDAS;[36 64] ≤5 mg/day per DORIS remission definition.[63]
BILAG, British Isles Lupus Assessment Group; DORIS, Definitions Of Remission In SLE; eGFR, estimated glomerular filtration rate; EULAR, European Alliance of Associations for Rheumatology; GC, glucocorticoid; LLDAS, Lupus Low Disease Activity State; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SELENA, Safety of Estrogens in Lupus Erythematosus National Assessment; SFI, SELENA-SLEDAI Flare Index; SLEDAI, SLE Disease Activity Index; SRI-4, SLE Responder Index-4; uPCR, urinary protein-creatinine ratio.

# Application of the DM definition to new therapies/clinical trials at the 3 timepoints:

Year 1: Clinical trials endpoints include
Reduction in disease activity
Reduction in severe flares
Reduction in use of steroids
FDA approved medications meet DM criteria at 1 year

Years 2-5: LTE studies of approved therapies evaluate
Sustained improvement
Prevention of severe flares
Continued reduction in steroids and/or immunosuppressants

Years > 5: No change in SDI or delayed progression – not standardized
CAR-T

- Belimumab : >5 year- No change in SDI or delayed progression
- Anifrolumab –1,2-4 year ;Significant reduction in disease activity and steroid dose

# Paving the Road to Disease Modification in Lupus Nephritis

Maria Dall'Era, M.D.
University of California, San Francisco
ACR Convergence 2023

UCSF
University of California
San Francisco

# Disease Modification in Lupus Nephritis- Time is Kidney!

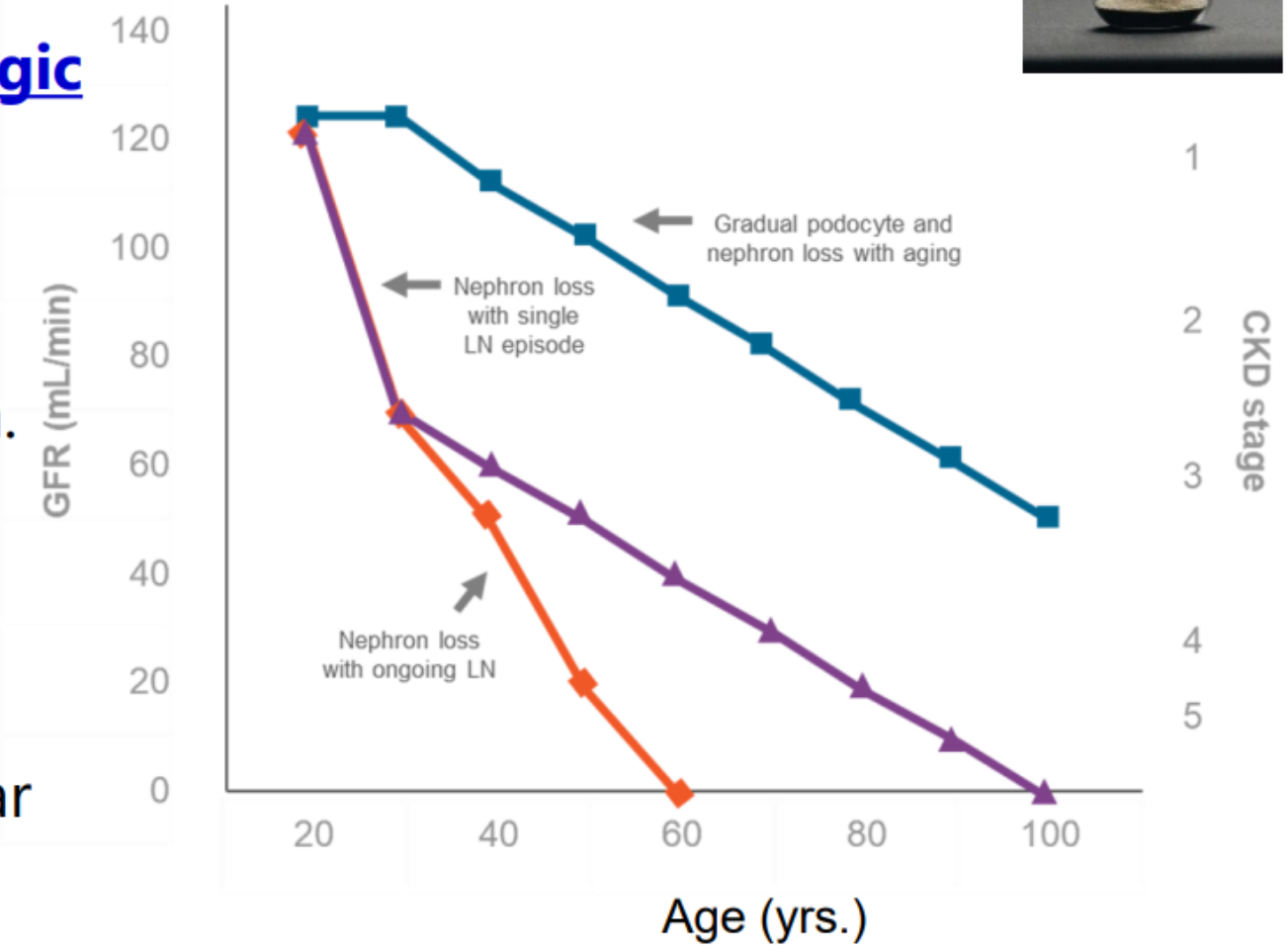
**Immunologic** and **non-immunologic** mechanisms of kidney injury in LN.

## Immunologic

- Immune complex deposition.
- Soluble inflammatory mediators.
- Cellular infiltrates.
- Immune aggregates.

## Non-immunologic

- Disruption of cell-cell interactions.
- Tissue hypoxia.
- Tubular dysfunction.
- Proteinuria.
- Intraglomerular hypertension/ hyperfiltration.




Davidson A, Nat Rev Rheum, 2016

Anders HJ et al., Nat Rev Dis Primers, 2020

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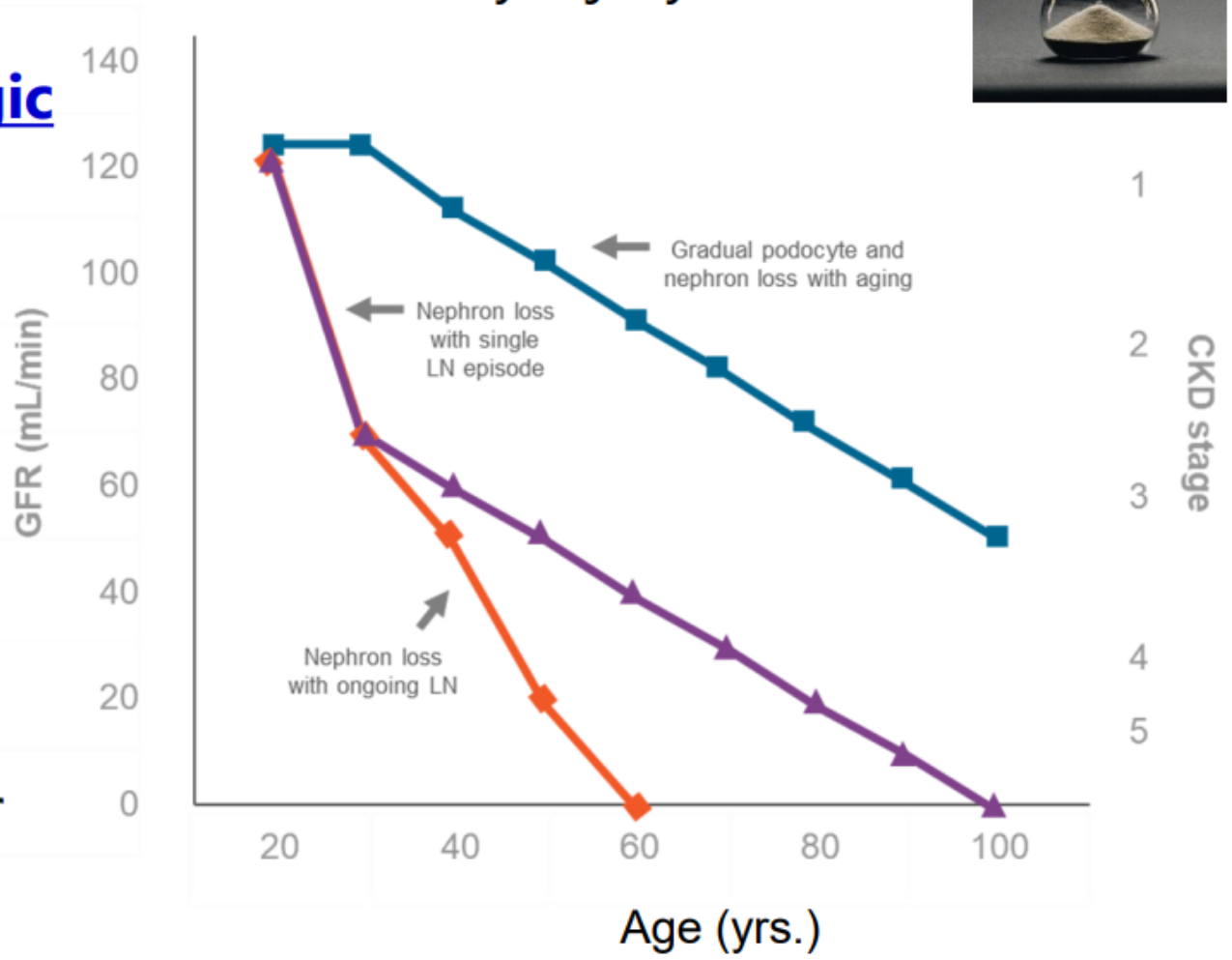


Davidson A, Nat Rev Rheum, 2016

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# Limitations of our Conventional Therapeutic Approaches

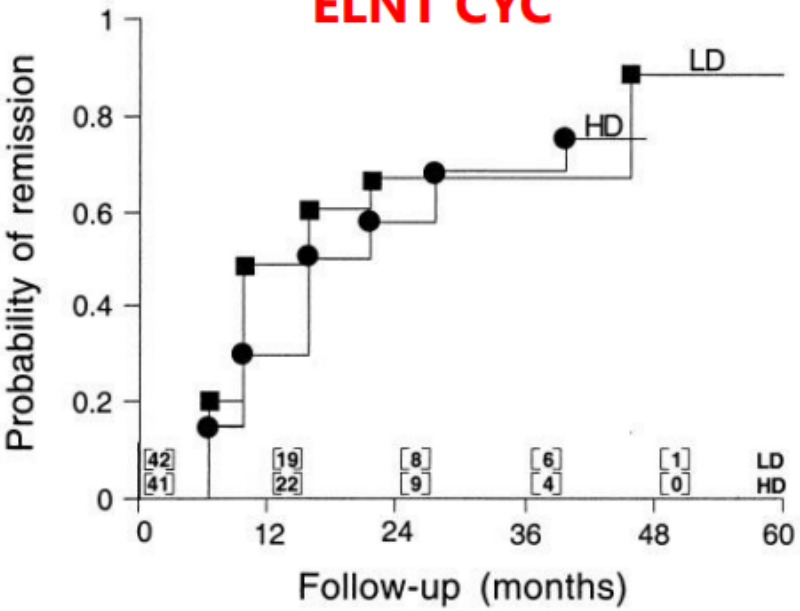
- Incomplete renal response and prolonged time to renal response.
- Substantial rates of renal flare.
- Significant rates of CKD, ESKD, and mortality.
- Toxicities of concomitant glucocorticoids.
- Suboptimal tolerability of conventional immunosuppressive agents.

**Conventional Therapies and Renal Response**

| Trial | % With Baseline Prot > 3g | CRR (%) at 6 Months |
|---|---|---|
| ELNT-low | 42 | 25 |
| ELNT-high | 45 | 24 |
| ACCESS-ELNT | 52 | 23 |
| ALMS-MMF | 57 | 21 |
| ALMS-IVC | 60 | 22 |

Wofsy D et al., Arth. Rheum, 2015

**ELNT CYC**

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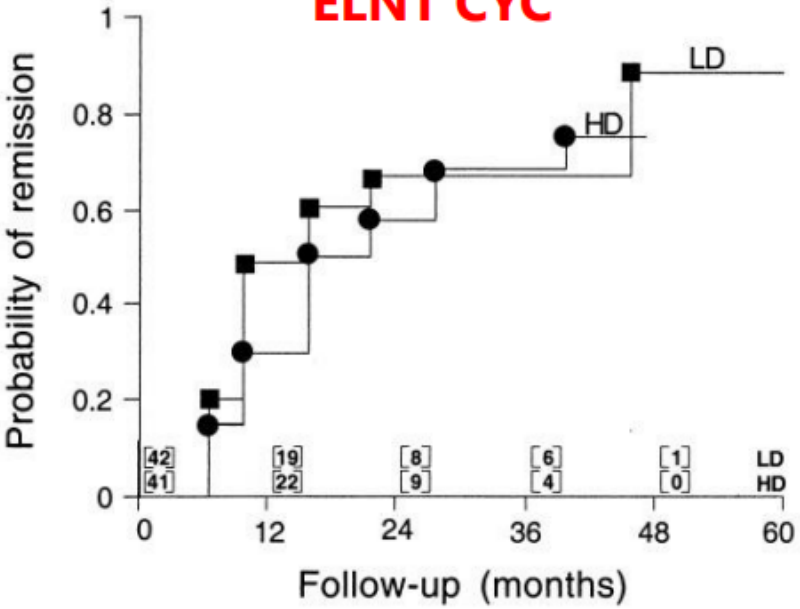
## ELNT CYC



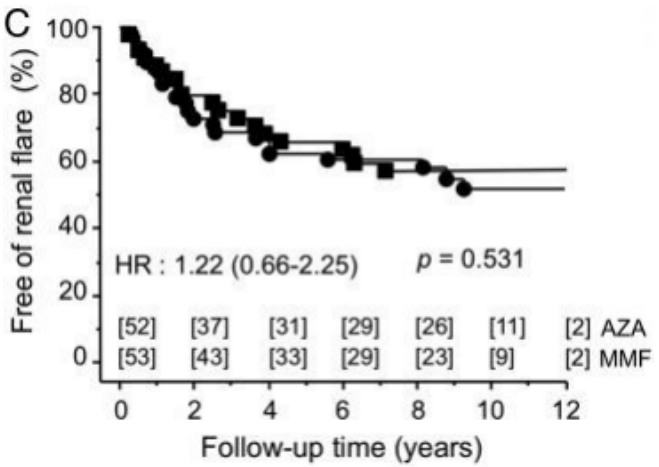

Houssiau FA et al., Arth. Rheum, 2002

# High Rates of LN Flares with Conventional Therapies

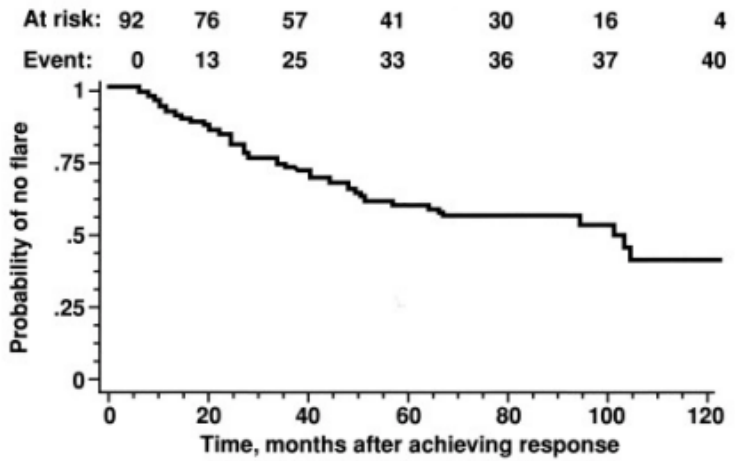
## NIH Trials

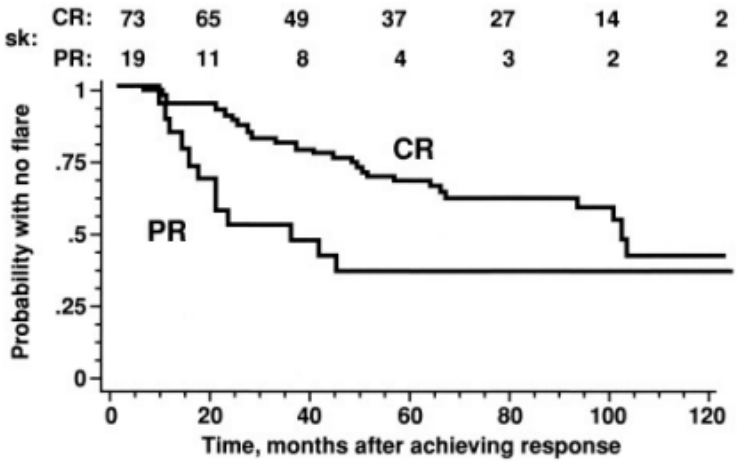
- 145 Class III or IV LN patients randomized to monthly pulse methylprednisolone, IV CYC, or combination.
- Median follow-up: 120 mo.
- 40% patients with CR had LN flare after median 41 mo.
- 63% patients with PR had LN flare after median 11.5 mo.
- "Severe nephritic flare" (LR 11.8) and lack of CR (LR 7.0) associated with progression to ESKD.

## MAINTAIN Trial




## LN Flares over Time



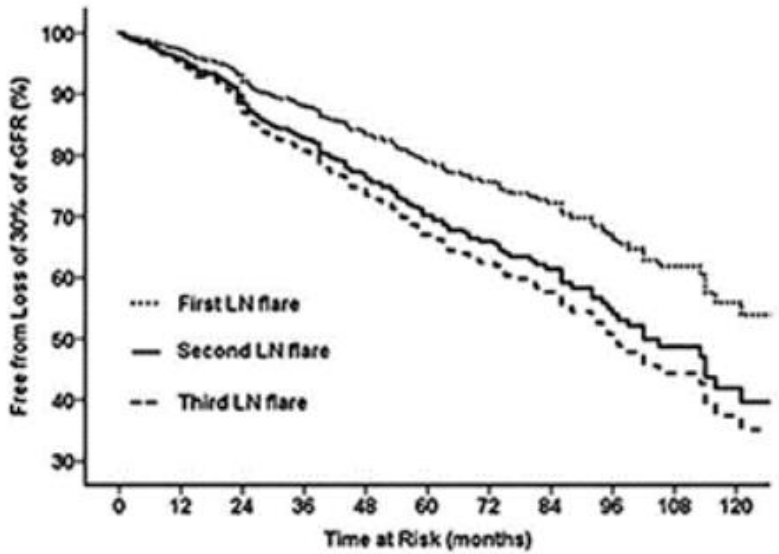

Illei GG et at., Arthritis Rheum, 2002

Tamirou F et al., Ann Rheum Dis, 2016

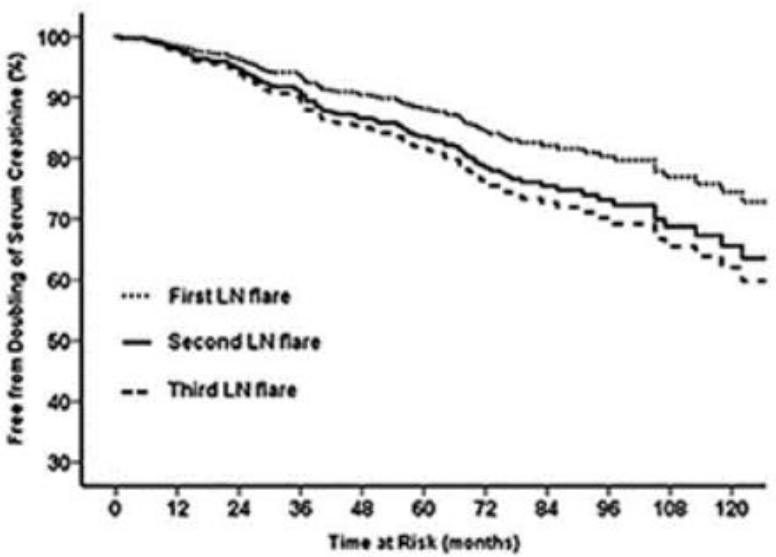
# Lupus Nephritis Flares are Associated with Progressive CKD

- 441 patients with active III, IV, V LN (years 2008-2018).
- 58%- first LN flare, 23%- second LN flare, 19%- third LN flare.

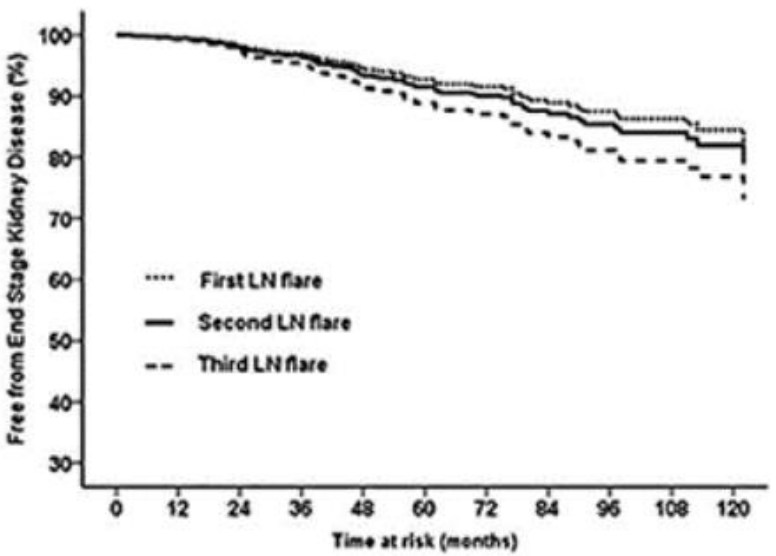
**30%↓ in eGFR**




**Doubling SCr**

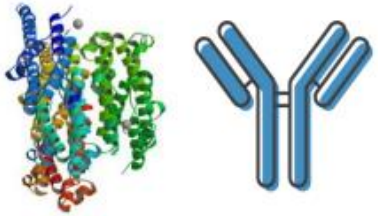



**ESKD**




Perez-Arias, A et al., NDT, 2022

# How Can We Best Achieve Disease Modification in LN?



- **Develop therapeutic strategies that:**
  - Impact both innate **and** adaptive immune responses.
  - Target key immunologic pathways/cells/mediators that are important in disease pathogenesis.
  - Act in a synergistic or complementary manner to mitigate ongoing autoimmunity and inflammation.
- **Apply a holistic treatment approach targeting immunologic and non-immunologic mechanisms of kidney injury.**
- **Diagnose and treat early.**
- **Understand when and how to taper maintenance therapy.**
- **Help our patients adhere to their therapies.**
- **Consider the role for therapeutic drug monitoring if applicable.**

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# *Combination Therapy to Achieve Disease Modification in LN*

## *Step- down approach*

### *What*

- ✓ Treatment with HCQ+lower- dose GC
  +
  Combination immunosuppressive / targeted biologic therapy
- ✓ Maximize non-immunosuppressive kidney- protective therapies

### *Why*

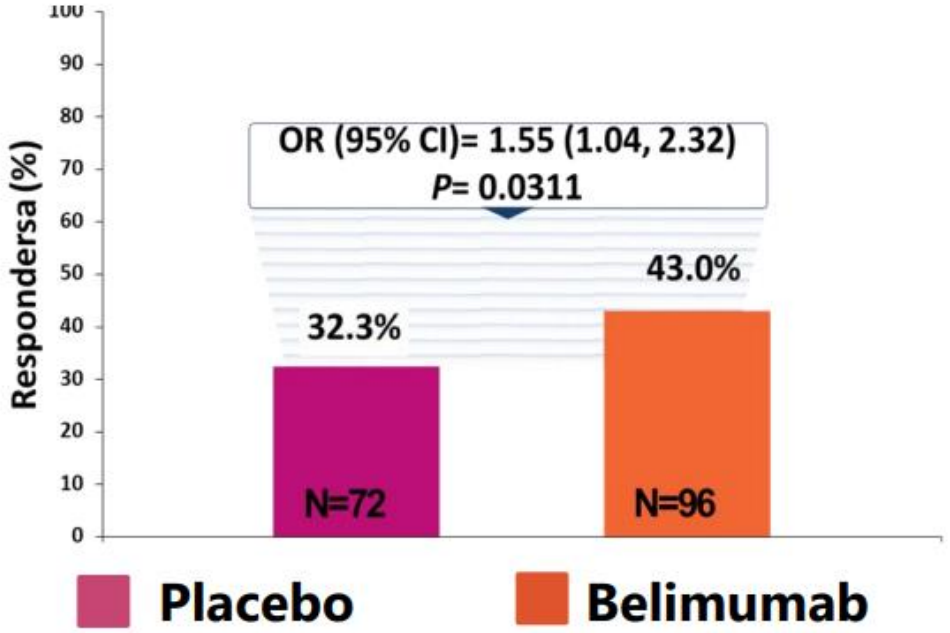
- ✓ To achieve and sustain an initial renal response
- ✓ prevent flares
- ✓ slow/prevent CKD progression

**Over time, one or more of the therapies will be tapered and potentially discontinued**

# Belimumab and Voclosporin: Primary Endpoints from Phase III Trials

## BLISS-LN: Belimumab in LN

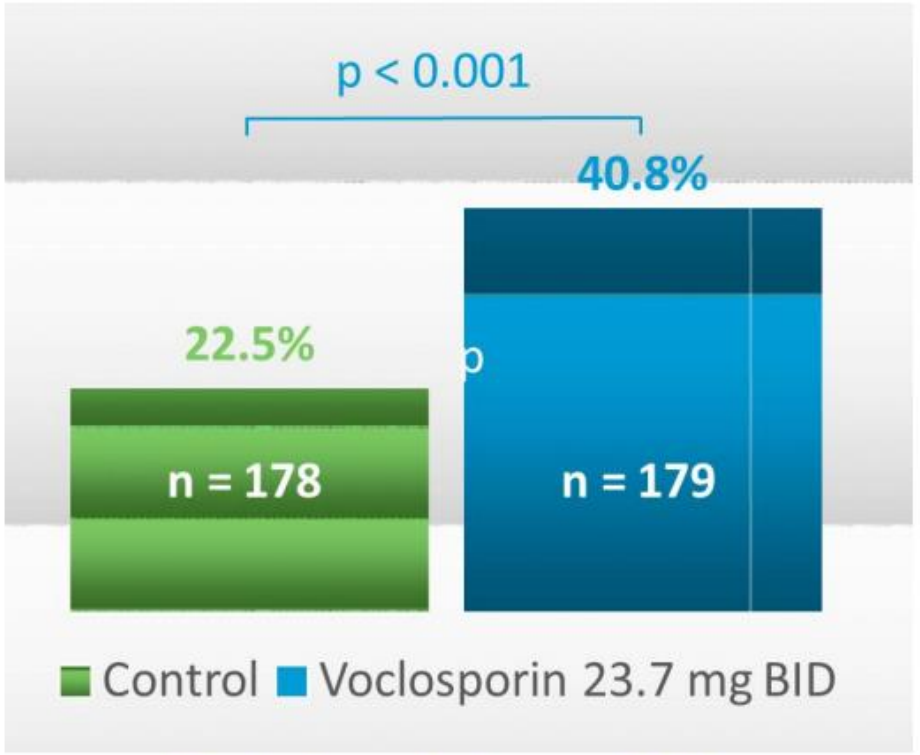
**Primary Endpoint: PERR at Week 104**




Furie R et al., NEJM, 2020

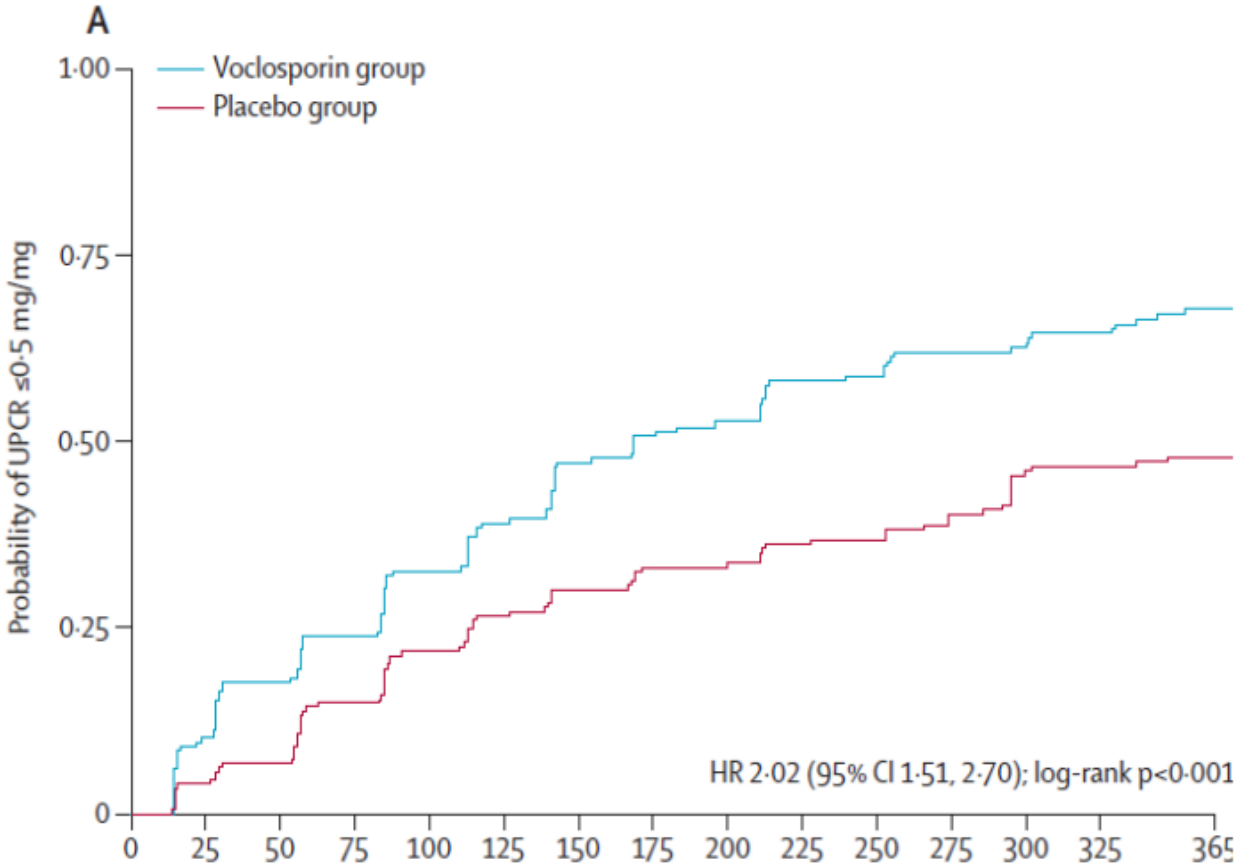
## AURORA 1: Voclosporin in LN

**Primary Endpoint: CR at Week 52**



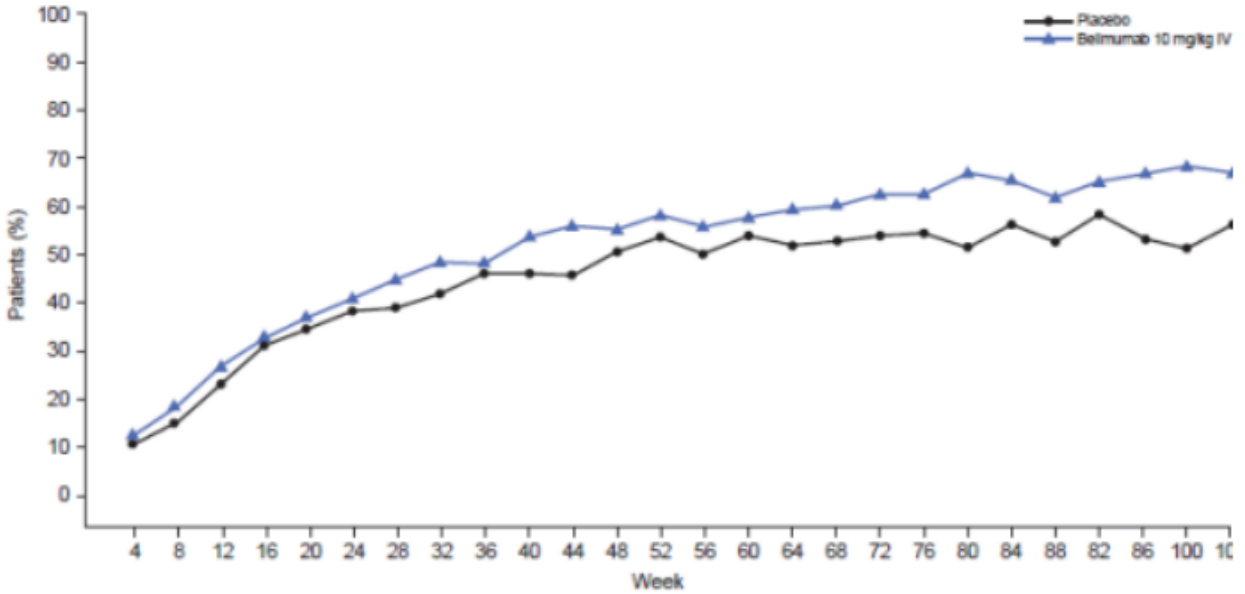

Rovin B et al., Lancet, 2021

## AURORA 1




**Time to UPCR ≤ 0.5**

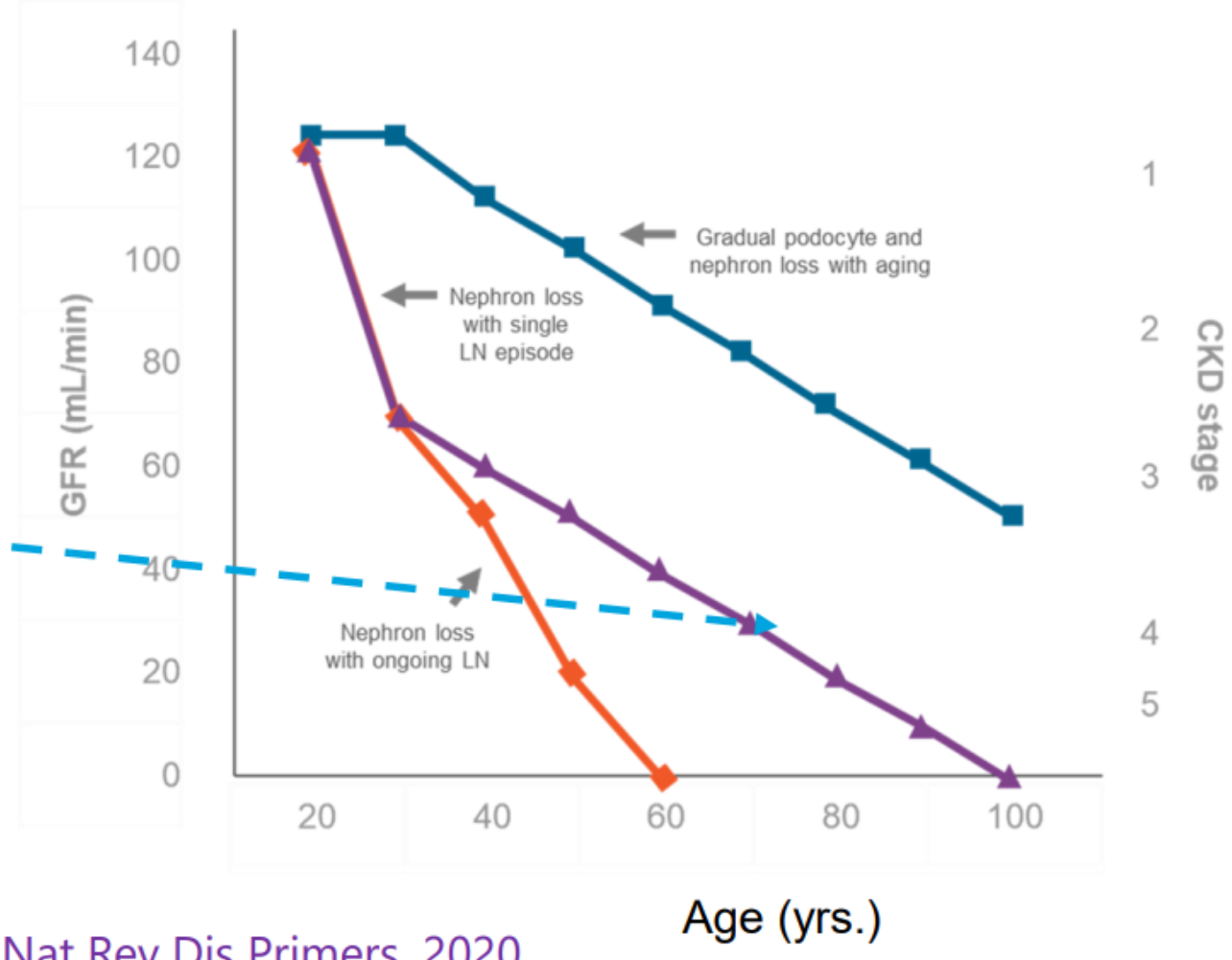
## BLISS-LN




**Patients with proteinuria shift from ≥ 0.5 to <0.5.**

# Reducing Progression of CKD After the Active LN is Treated

- **Targeting non-immunologic pathways.**
  - Reduce proteinuria.
  - Control hypertension.
  - RAAS inhibition.
  - Salt restriction.
  - Healthy body weight.
  - SGLT2 inhibition.
  - Avoid nephrotoxic meds.
  - Strategies for adherence.



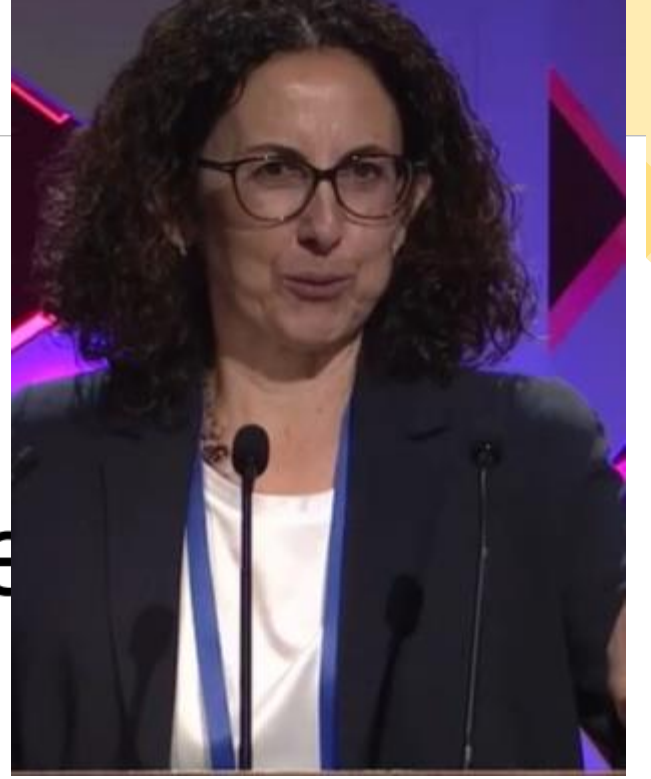

Anders HJ et al., Nat Rev Dis Primers, 2020

# Meet the Panel: The Latest in Lupus Treatment


Maria Dall'Era, MD
Chief, Division of Rheumatology
UCSF Health
Professor of Medicine
University of California, San Francisco

Richard Furie, MD
Chief, Division of Rheumatology
Northwell Health
Professor of Medicine
Zucker School of Medicine at Hofstra Northwell

Marta Mosca, MD, PhD
Chief, Rheumatology Unit
Professor of Rheumatology
University of Pisa, Italy



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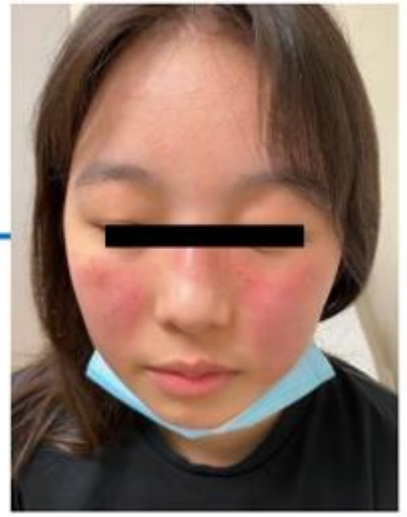
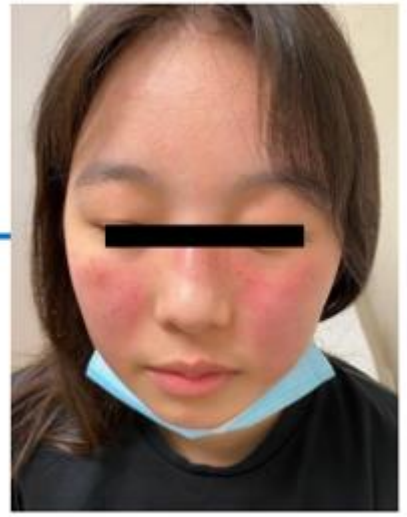
# Case I



- 31 y. old female with a history of SLE diagnosed 1 year ago with manifestations of malar rash, oral ulcers, arthritis of wrists and small joints of hands
- ANA, dsDNA, anti-Sm: +Ve; normal C3and C4, +ve LA
- Clinical manifestations had been well controlled on HCQ 200mg/d, MTX12.5 mg/wk, and prednisone 5m/d.
- Currently presents with nocturia, puffy eyes, and swollen feet/ankles of 4 wks duration
- Reports that she has been taking ibuprofen for headaches x 6 wks

# *Case I*



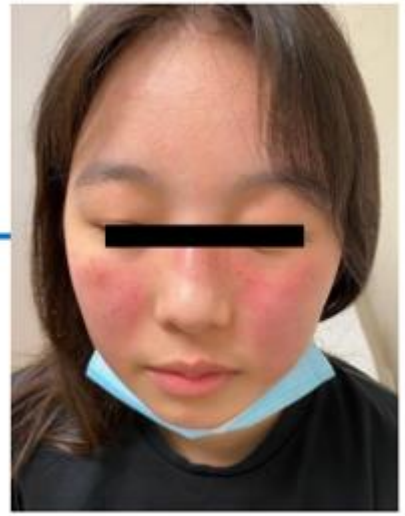
**Exam**:BP160/90, P90/m, mild periorbital swelling, normal heart and lungs, moderate symmetric pedal edema.
Labs: normal CBC, S.creat0.90 (eGFR 82), ANA1/160 speckled, anti-ds DNA 65, C3 45, C4 10, UA: +11-20 RBCs, +5-10WBCs, spot UPCR 4.4.

**Kidney biopsy:**

Class IV+ V LN
AI:9/24
CI: 2/12
No vascular abnormalities

# Case I

**What is the proper management**



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**Kidney biopsy:**

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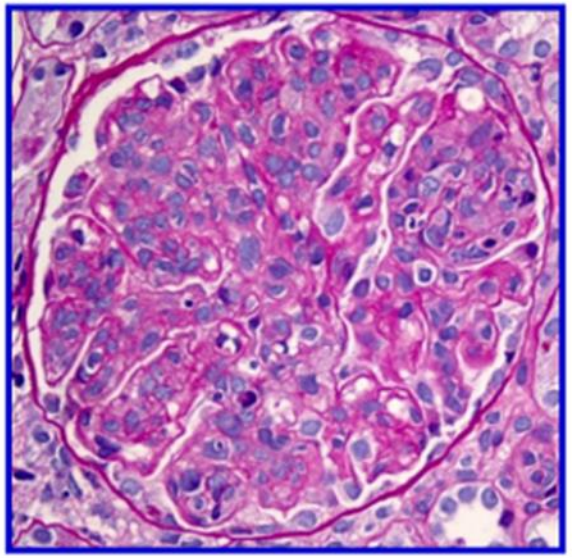
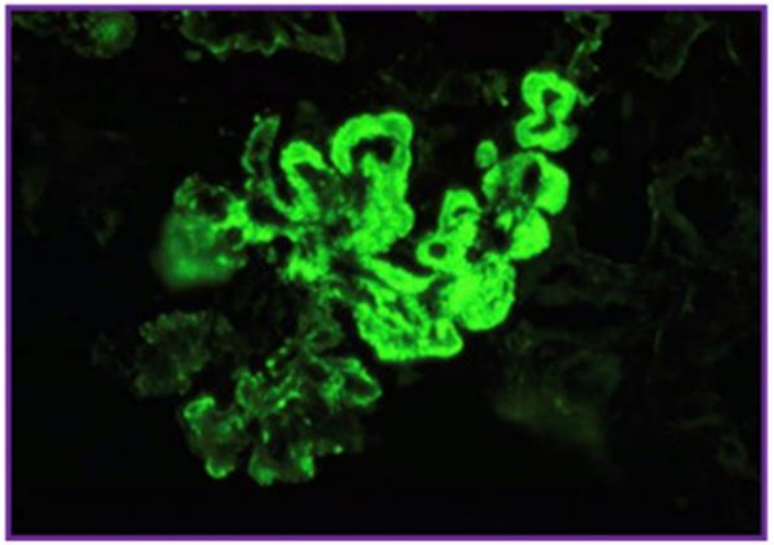
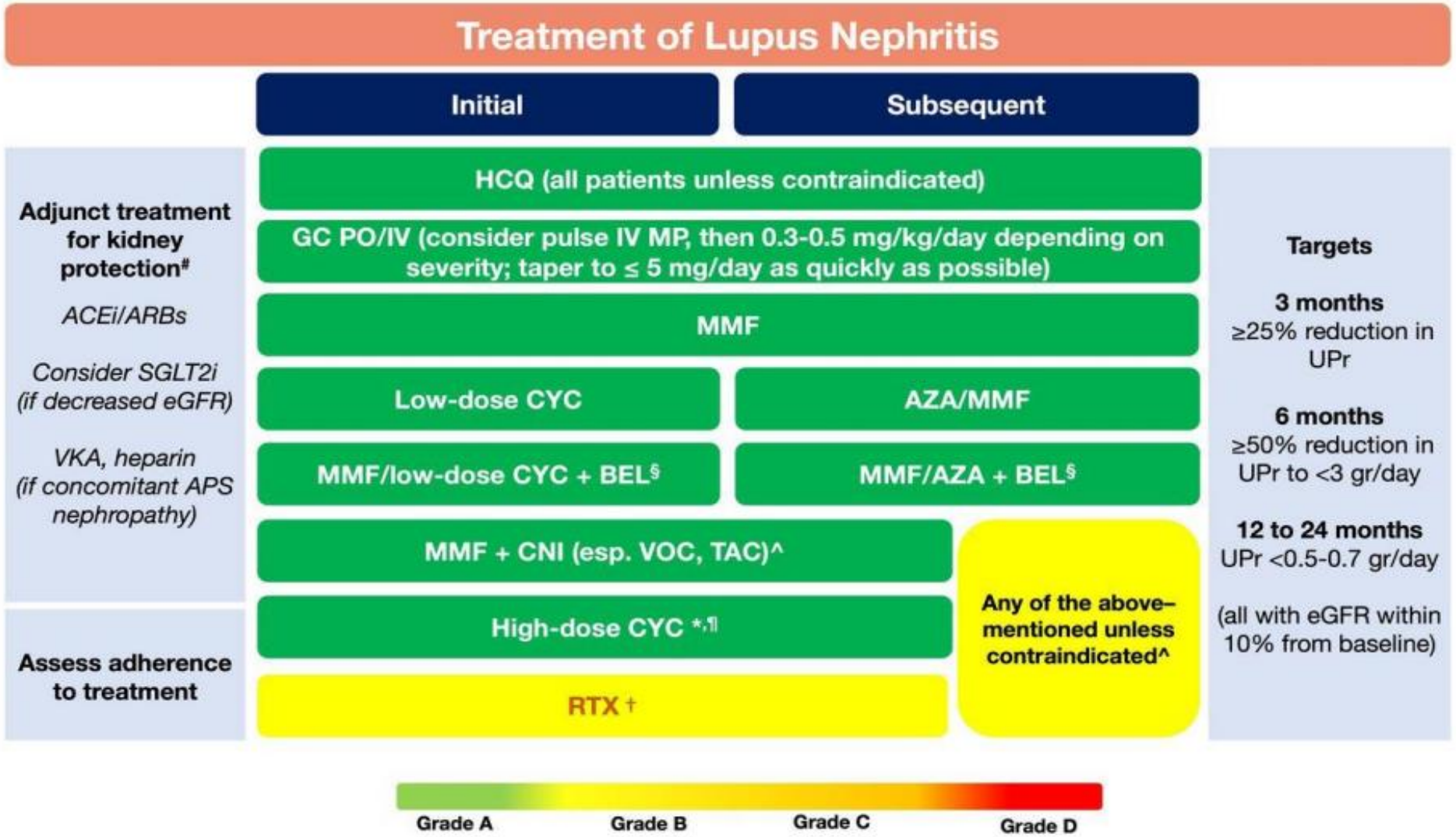




# EULAR 2023 LN Treatment Guidelines




Fanouriakis A et al., ARD, 2023

# Safety Profile of Belimumab and Voclosporin

## BLISS-LN

**Table 3. Adverse Events, Adverse Events of Special Interest, and Suicidality in the Safety Population.***

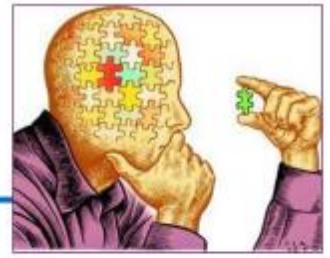
| Event | Belimumab (N=224) | Placebo (N=224) |
|---|---|---|
| | *no. of patients (%)* | |
| All adverse events† | 214 (96) | 211 (94) |
| All treatment-related adverse events† | 123 (55) | 119 (53) |
| Upper respiratory tract infection | 26 (12) | 24 (11) |
| Urinary tract infection | 15 (7) | 13 (6) |
| Herpes zoster | 13 (6) | 10 (4) |
| Bronchitis | 11 (5) | 10 (4) |
| Nasopharyngitis | 8 (4) | 8 (4) |
| Headache | 9 (4) | 5 (2) |
| Nausea | 8 (4) | 5 (2) |
| Rash | 6 (3) | 5 (2) |
| All serious adverse events† | 58 (26) | 67 (30) |
| All treatment-related serious adverse events† | 23 (10) | 25 (11) |
| Most common treatment-related serious adverse events, according to system organ class, occurring in ≥1% of patients in either group | | |
| Infections and infestations | 15 (7) | 18 (8) |
| Respiratory, thoracic, and mediastinal disorders | 5 (2) | 1 (<1) |
| Blood and lymphatic system disorders | 3 (1) | 2 (1) |
| Nervous system disorders | 0 | 3 (1) |
| Most common treatment-related serious adverse events occurring in ≥1% of patients in either group | | |
| Pneumonia | 3 (1) | 4 (2) |
| Herpes zoster | 3 (1) | 2 (1) |
| Adverse events resulting in discontinuation of trial drug | 29 (13) | 29 (13) |
| Adverse events of special interest‡ | | |
| Cancer | | |
| Excluding nonmelanoma skin cancer§ | 2 (1) | 0 |
| Including nonmelanoma skin cancer§ | 3 (1) | 0 |
| Postinfusion reactions¶ | 26 (12) | 29 (13) |
| All infections of special interest, including opportunistic infections, herpes zoster, tuberculosis, and sepsis | 30 (13) | 34 (15) |
| Serious infections | 9 (4) | 7 (3) |
| Depression, suicide, or self-injury | 11 (5) | 16 (7) |
| C-SSRS suicidal ideation or behavior during trial intervention | 7 (3) | 12 (5) |
| Death | 6 (3) | 5 (2) |
| Fatal serious adverse events that began during trial intervention | 4 (2) | 3 (1) |
| Fatal serious adverse events that did not begin during trial intervention | 2 (1) | 2 (1) |

## AURORA 1

| | Control (n=178) n (%) | Voclosporin (n=179) n (%) |
|---|---|---|
| Adverse Event (AE) | 158 (88.8) | 162 (91.0) |
| Serious Adverse Event (SAE) | 38 (21.3) | 37 (20.8) |
| SAE System Organ Class of Infection | 20 (11.2) | 18 (10.1) |
| Treatment-related SAE | 8 (4.5) | 8 (4.5) |
| AE leading to study drug discontinuation | 26 (14.6) | 20 (11.2) |
| Death* | 5 (2.8) | 1 (0.6) |
| Treatment-related AE leading to death | 0 | 0 |

**Unknown: chronic CNI-associated nephrotoxicity**

# Putting it All Together- Using Data to Inform Therapy



## Favors Belimumab

- eGFR ≤ 45 and/or significant chronicity on kidney biopsy.
- Low level of proteinuria (< 3g).
- History of major infections/concern for safety.
- Difficulty with adherence to oral therapy/prefers parenteral therapy.
- Concomitant extra-renal disease such as cutaneous LE or arthritis.

## Favors Voclosporin

- eGFR > 45 without significant chronicity on kidney biopsy.
- High level of proteinuria (≥3 g).
- Prefers oral therapy/able to adhere to combinations of oral therapy.

# Case II

- **2010**: SLE consisting of arthritis, pleuritis treated with HCQ and intermittent prednisone.
- **2016**: UPCR:2; kidney biopsy: III-S(A) and V ; treated with prednisone and MMF with reduction in UPCR to 0.9; serologies improved.
- **2020:** kidney biopsy: persistent proteinuria and active serologies;III/V (AI:4/24, CI:3/12); treated with maximal dose MMF(3g/d) and belimumab (200mg/wk)

***How can you manage this patient with refractory lupus nephritis ?***

***2023: Labs***

- ✓ S.creat: 0.81
- ✓ UPCR:2.0
- ✓ C3/C4: 58/5
- ✓ DNA Ab: 452 (<30)

# What Advice Would You Give to My Patient?

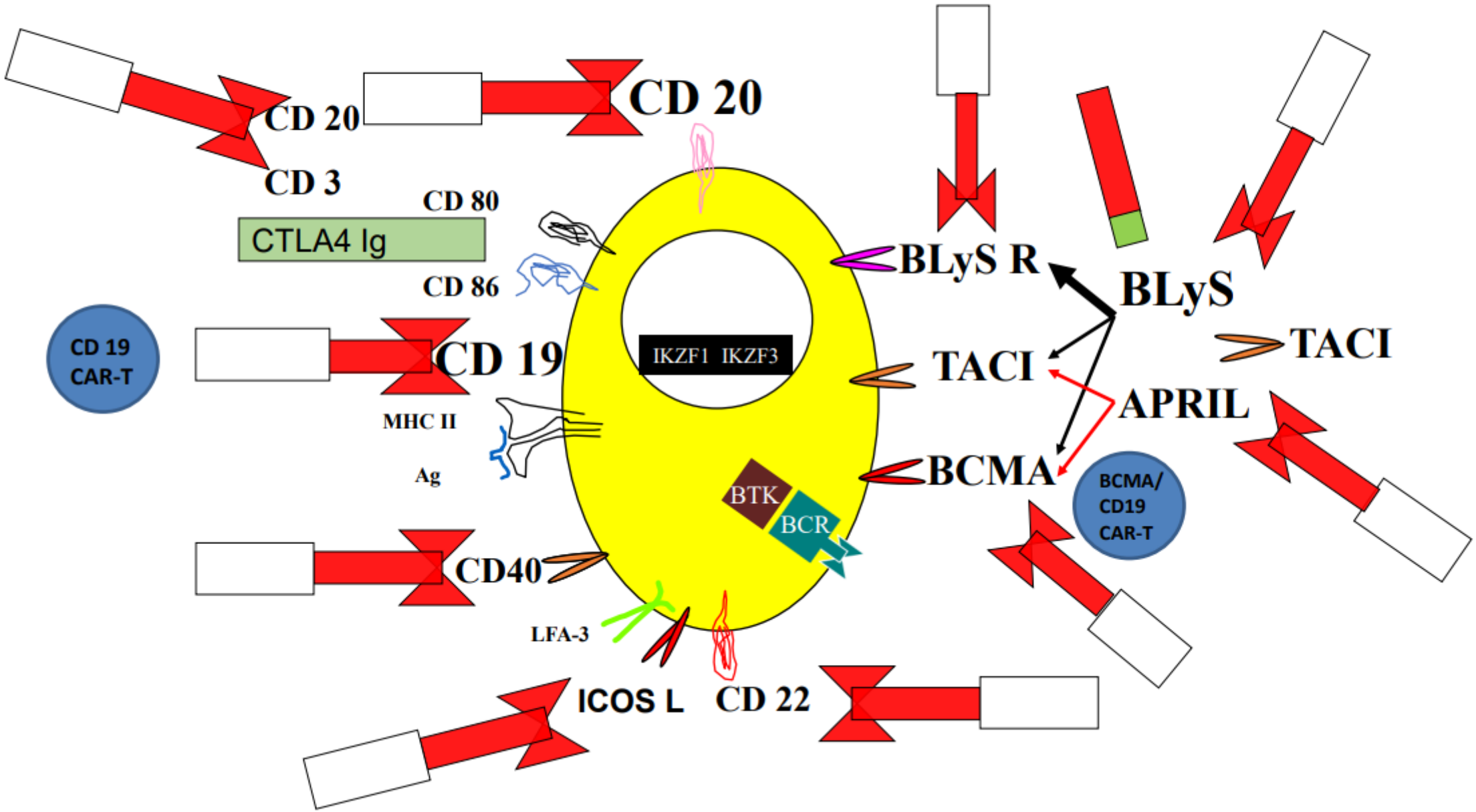
**I suggested:**

- Another biopsy

**I discussed (assuming continued activity):**

- Cyclophosphamide
- Voclosporin
- Obinutuzumab
- CAR-T

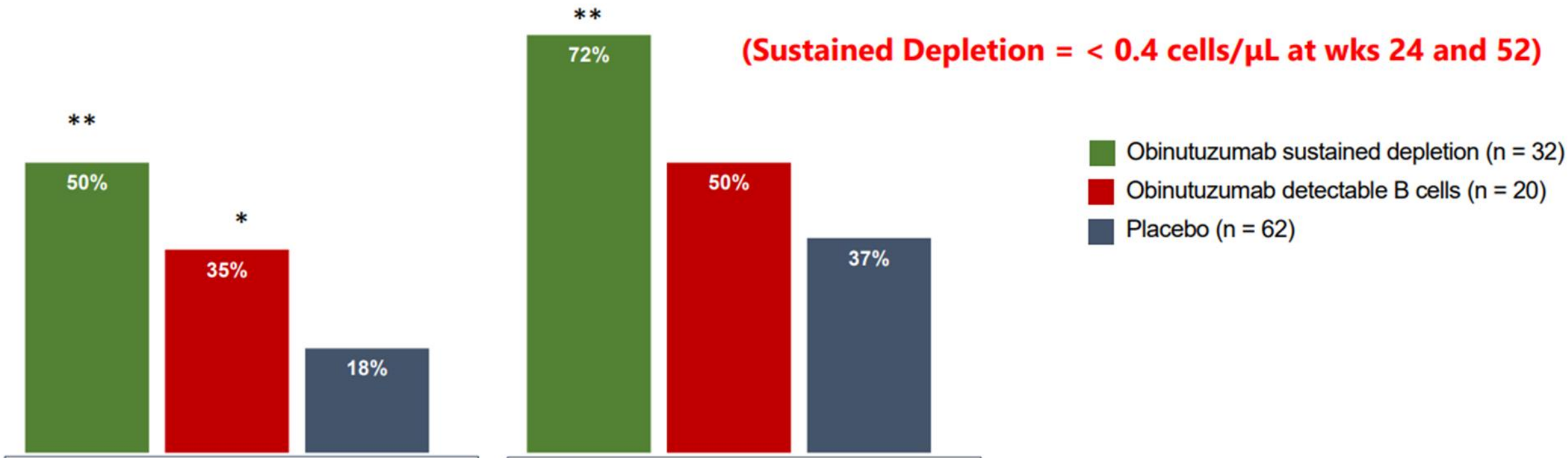
# B Cell-Directed Therapies: Targets



# Week 76 Modified CRR by B-Cell Depletion Status

**1/3 of patients had BL Cr ≤ 0.65 (response rate ~50% less in this group)**

**(Sustained Depletion = < 0.4 cells/µL at wks 24 and 52)**




**CRR required all of:**
- UPCR < 0.5
- Serum creatinine ≤ upper limit of normal
- Serum creatinine **≤ 115%** of baseline value
- < 10 RBC/hpf without RBC casts

**Modified CRR required:**
- UPCR < 0.5
- Serum creatinine ≤ the upper limit of normal

* *P* < 0.2 vs placebo group. ** *P* < 0.05 vs placebo group.

Eleven patients in the obinutuzumab group with insufficient data to determine depletion status are excluded.

PRR, partial renal response

# Chimeric Antigen Receptor T-Cells (CAR-T)

nature medicine

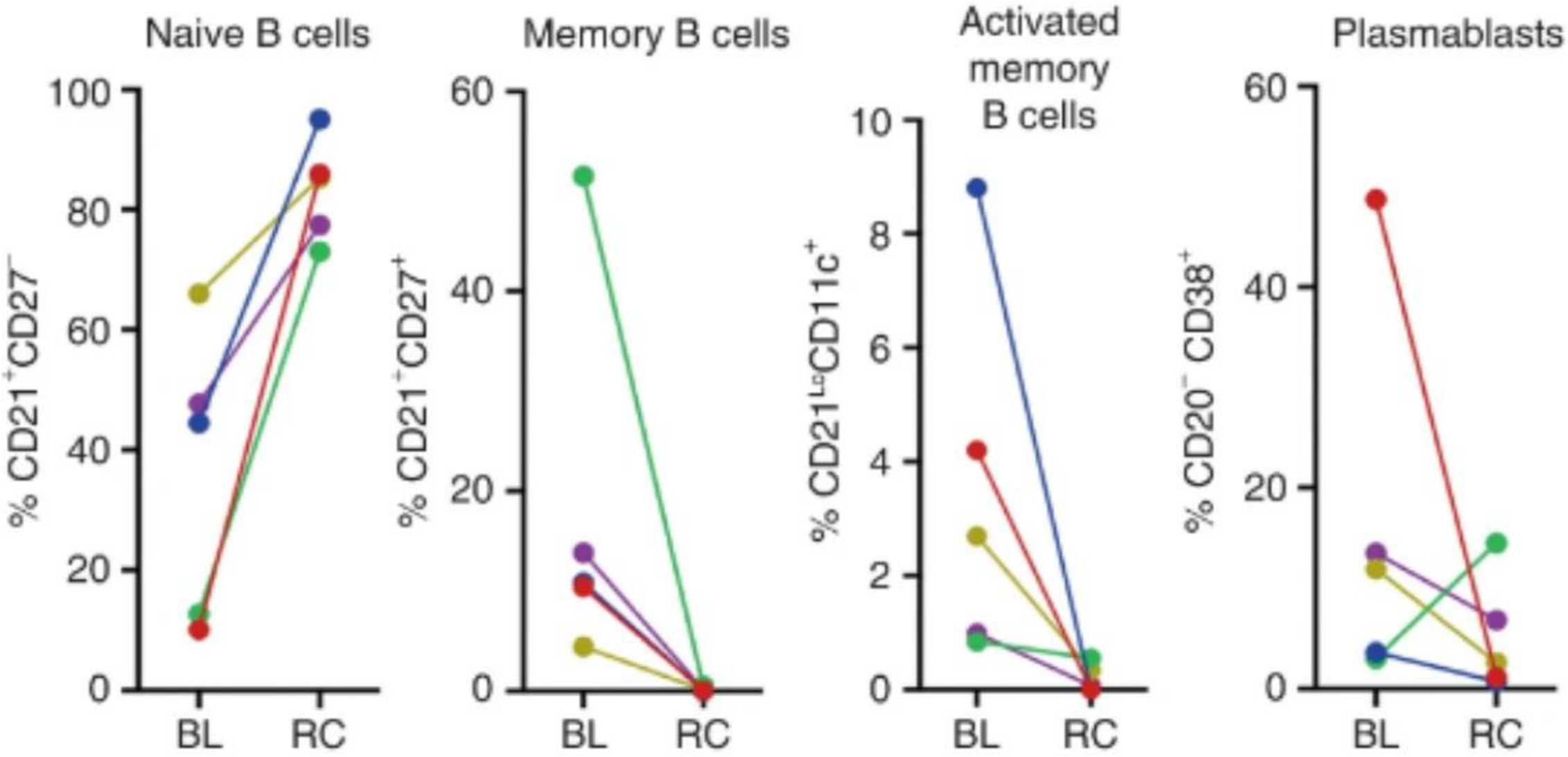
ARTICLES

https://doi.org/10.1038/s41591-022-02017-5



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

Andreas Mackensen[1,2,8], Fabian Müller[1,2,8], Dimitrios Mougiakakos[1,2,3,8], Sebastian Böltz[2,4], Artur Wilhelm[2,4], Michael Aigner[1,2], Simon Völkl[1,2], David Simon[2,4], Arnd Kleyer[2,4], Luis Munoz[2,4], Sascha Kretschmann[1,2], Soraya Kharboutli[1,2], Regina Gary[1,2], Hannah Reimann[1,2], Wolf Rösler[1,2], Stefan Uderhardt[2,4], Holger Bang[5], Martin Herrmann[2,4], Arif Bülent Ekici[6], Christian Buettner[6], Katharina Maria Habenicht[7], Thomas H. Winkler[7], Gerhard Krönke[2,4,8] and Georg Schett[2,4,8] ✉


Naive B cells
% CD21+CD27−
100
80
60
40
20
0
BL
RC
Memory B cells
% CD21−CD27+
60
40
20
0
BL
RC
Activated memory B cells
% CD21LoCD11c+
10
8
6
4
2
0
BL
RC
Plasmablasts
% CD20− CD38+
60
40
20
0
BL
RC

# Case III

**European ancestry female, 32 years old**

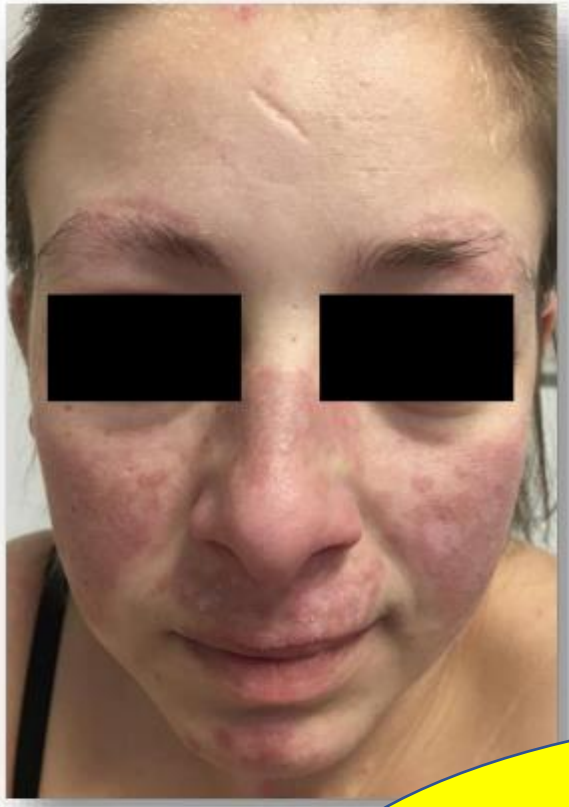
Disease onset: constitutional manifestations

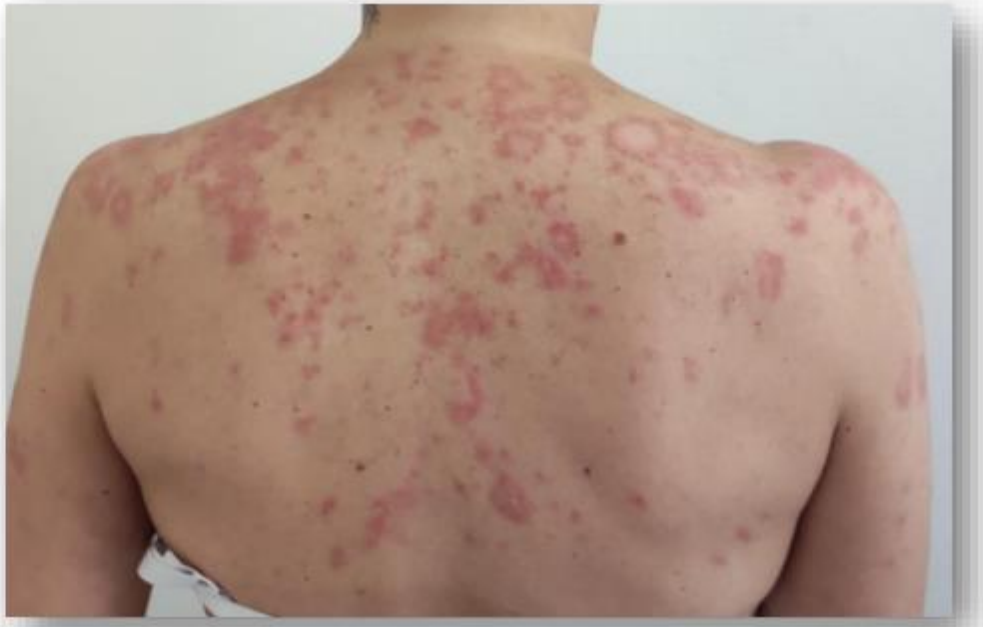
- ✓ Non erosive arthritis hands and wrists
- ✓ Diffuse subacute cutaneous lupus
- ✓ Discoid lesions on her face
- ✓ Low complement, mild leukopenia, ANA+ve; anti ROSSA +ve
- ✓ Negative prognostic factors: smoker
- ✓ She wants a pregnancy

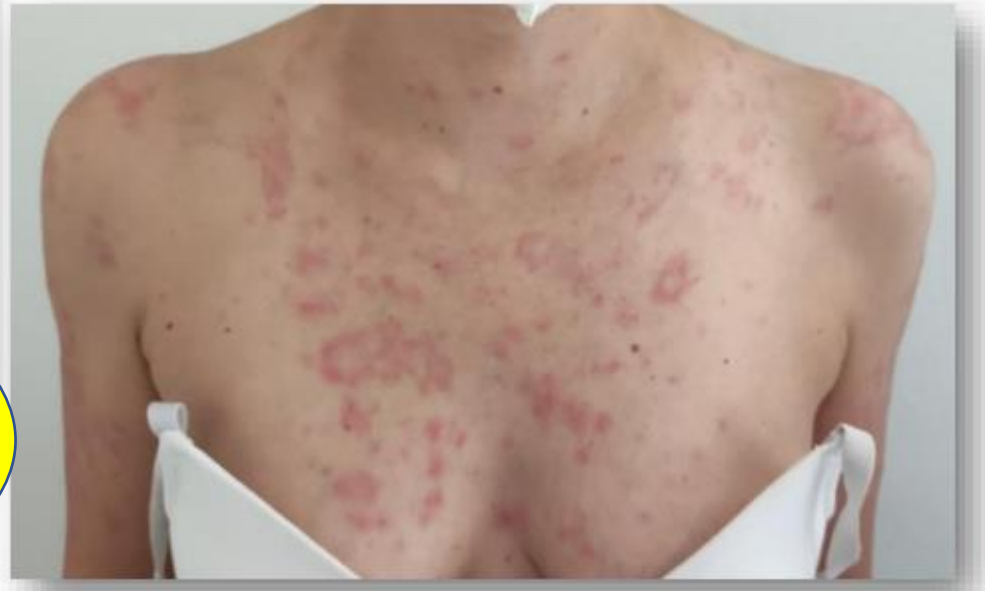
## *Follow Up*

- Relapsing remitting disease with subacute cutaneous lupus, persistence of discoid manifestations/ scarring
- Treatment: to be discussed
- Self medication with increased PDN doses
- Scarring on her face

# Case 3







***What is the best treatment for her ?***

# Treatment of Non-Renal Systemic Lupus Erythematosus

**General measures**

Sun protection
Exercise
No smoking
Balanced diet
Vaccinations
Normal body weight
Blood pressure, lipid, glucose control

Acetylsalicylic acid, VKA
(in aPL+/APS)

**Assess adherence to treatment**

| Mild* | | Moderate* | | Severe* | |
|---|---|---|---|---|---|
| 1st line | 2nd line | 1st line | 2nd line | 1st line | 2nd line |
| HCQ (all patients unless contraindicated) | | | | | |
| GC PO/IV (if needed, short-term use to control active disease; taper to ≤5 mg/day as quickly as possible and discontinue, if possible) | | | | | |
| MTX | | | | | |
| AZA | | | | | |
| MMF | | MMF | | | |
| BEL† | | | | | |
| ANI † | | | | | |
| | | CNI | CNI | | |
| | | | | CYC | |
| | | | | RTX | RTX |

Grade A — Grade B — Grade C — Grade D

**Target**

**Remission**
Clinical SLEDAI=0
HCQ
GC ≤ 5 mg/day

*or*

**Low disease activity**
SLEDAI ≤4
HCQ
GC ≤ 5 mg/day

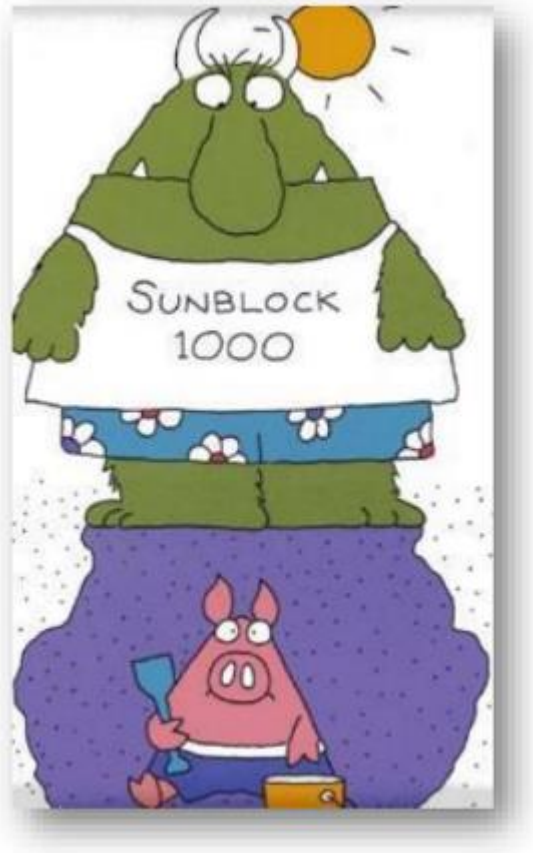
Immunosuppressive or biological agents at stable, tolerated dose

# *EULAR 2023 Recommendations skin involvement*

- Adherence to preventive measures and role of lifestyles (sun protection, smoking), adherence to therapy
- GC sparing in non renal lupus
- Role of new therapies: when it is early? Effect on skin manifestations GC sparing

***Lifestyle***

- Avoid UV exposure; peak sun 11-3pm and reflective surfaces (e.g. water, sand)
- Check photosensitizing drugs
- Wear protective clothing
- Broad-spectrum sunscreens
- Avoid smoking

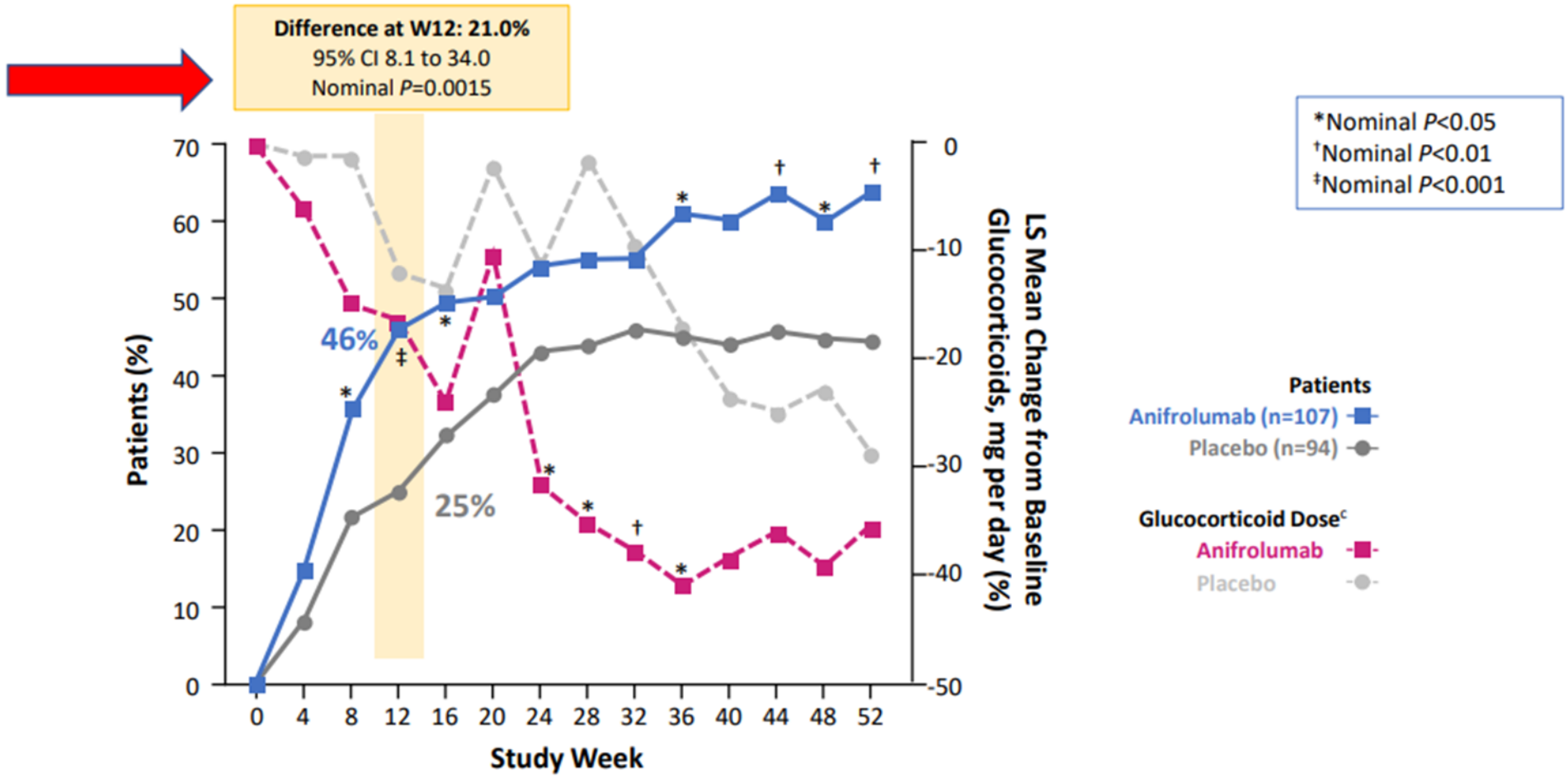


# Comparison between 2019 and 2023 updates

| 2019- SKIN | 2023- SKIN |
| --- | --- |
| • First line treatment of skin disease in SLE includes **topical agents (GC, Calcineurin inhibitors)(2b/B), antimalarials (HCQ, quinacrine) (1a/A), and/or systemic GC (4/C)**<br>• In **non responsive cases** or cases requiring high dose GC, methotrexate (3a/B), retinoids (4/C), dapsone or mycophenolate (4/C) can be added | • Treatment of active skin disease should include **topical agents (glucocorticoids, calcineurine inhibitors) (2b/B), antimalarials (HCQ, quinacrine) (1a/A), and/or systemic glucocorticoid as needed**, with **methotrexate (1b/B), mycophenolate (4/C), anifrolumab (1a/A) or belimumab (1a/B)** considered as **second line therapy** |

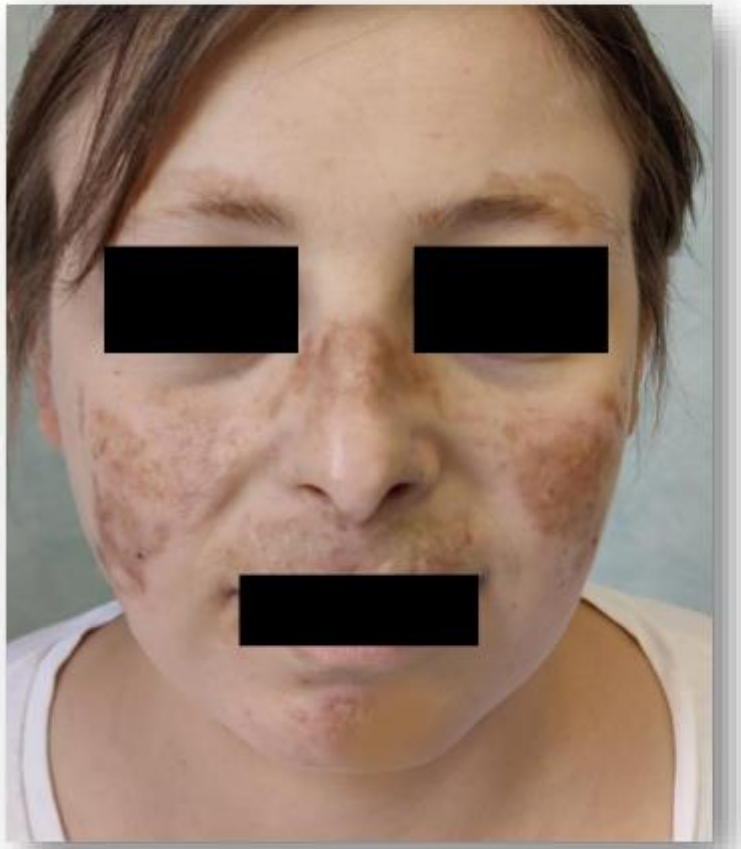
# CLASI-A Response Over Time

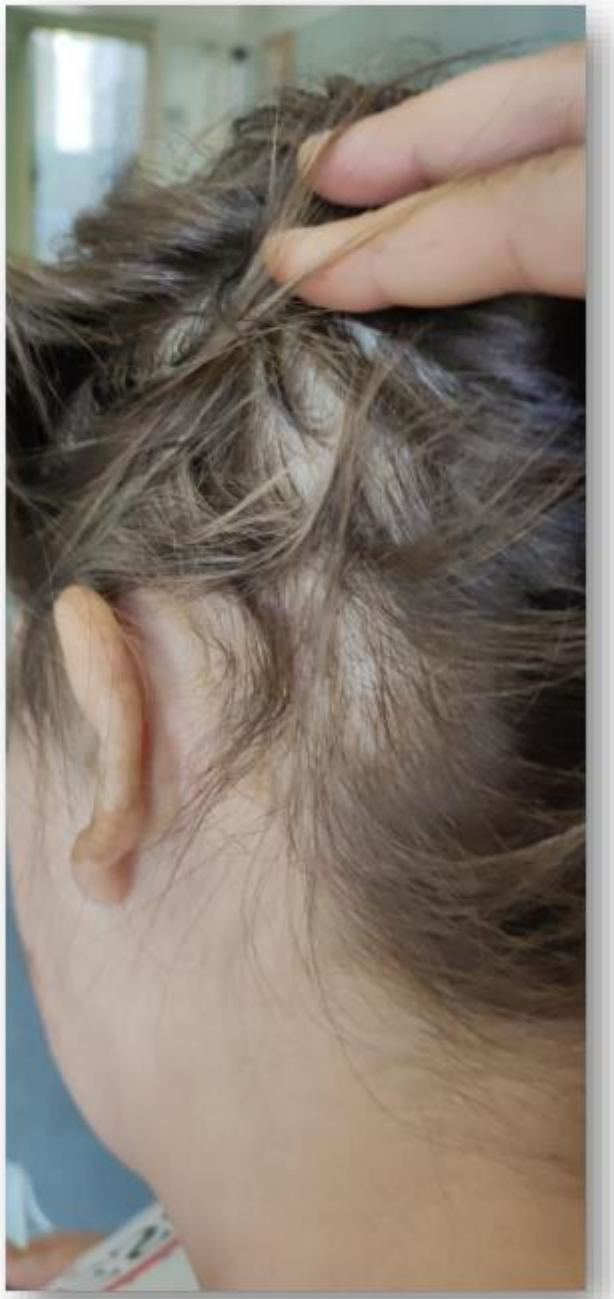
## Pooled TULIP-1 and TULIP-2




**Even with a reduction in corticosteroid dose, patients with a baseline CLASI-A >10 treated with anifrolumab had a greater response which was maintained over time compared with placebo**

# 24 weeks of treatment





ACR Convergence
Where Rheumatology Meets
#ACR23

# The Future of Antiphospholipid Syndrome (APS): 2023 ACR/EULAR APS Classification Criteria & Beyond

## Rethinking APS with the Guidance of 2023 ACR/EULAR APS Classification Criteria


**Doruk Erkan, MD, MPH**

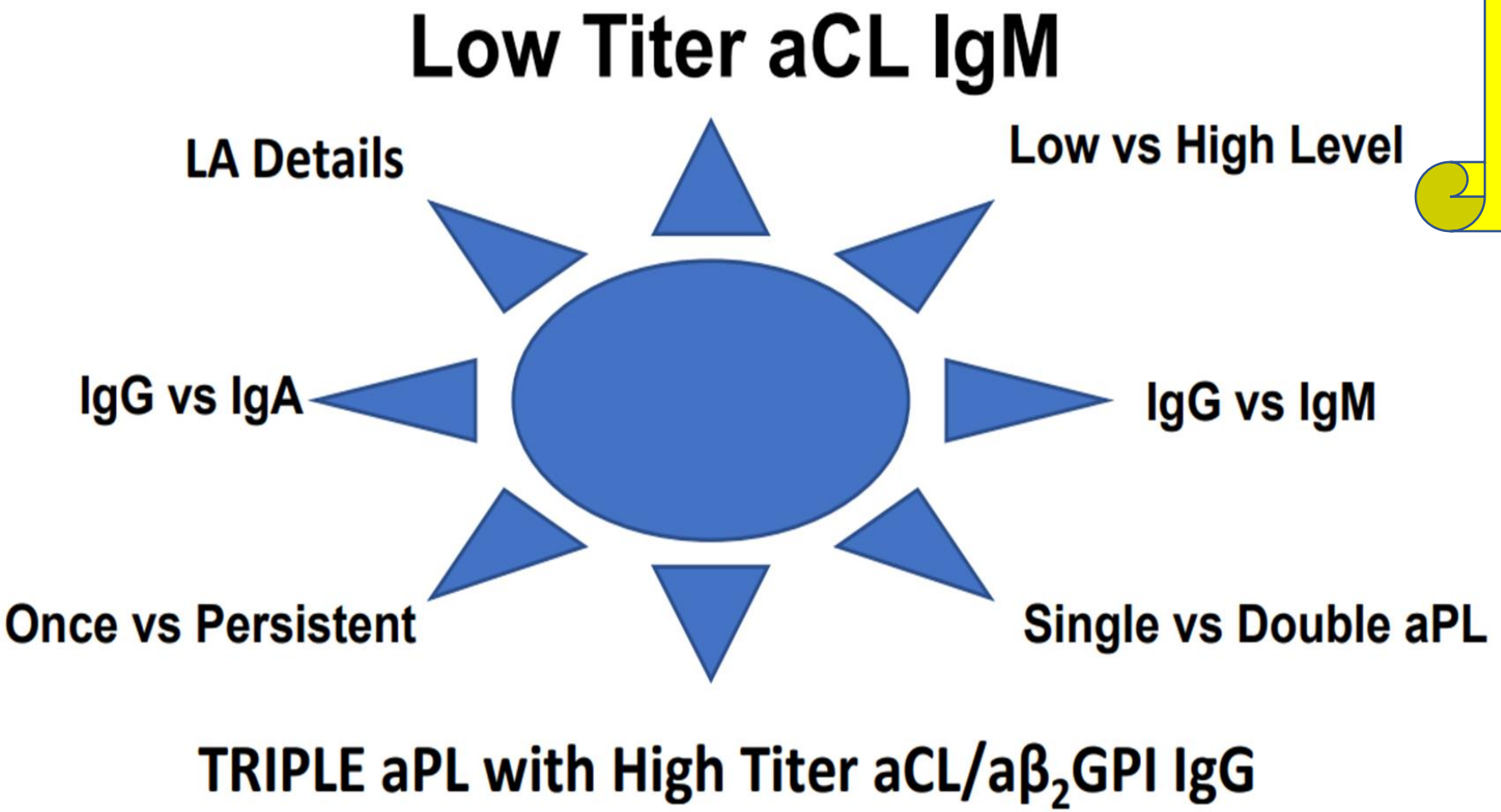
**Barbara Volcker Center for Women and Rheumatic Diseases**

**Attending Rheumatologist, Hospital for Special Surgery**

**Professor of Medicine, Weill Cornell Medicine, NY, NY**

# What is APS

Systemic Autoimmune Disease with Thrombotic, Obstetric, and Non-Thrombotic Manifestations



# *What is APS ?*

## CLINICAL PHENOTYPE

American College of Rheumatology
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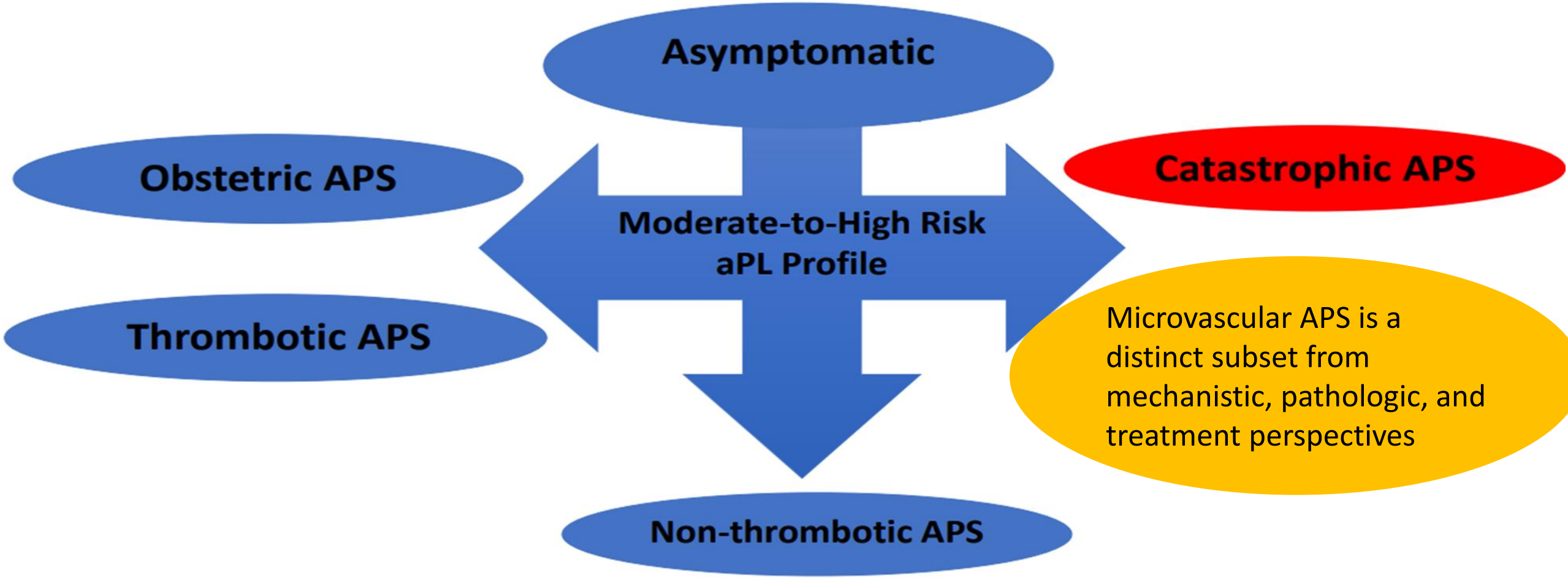
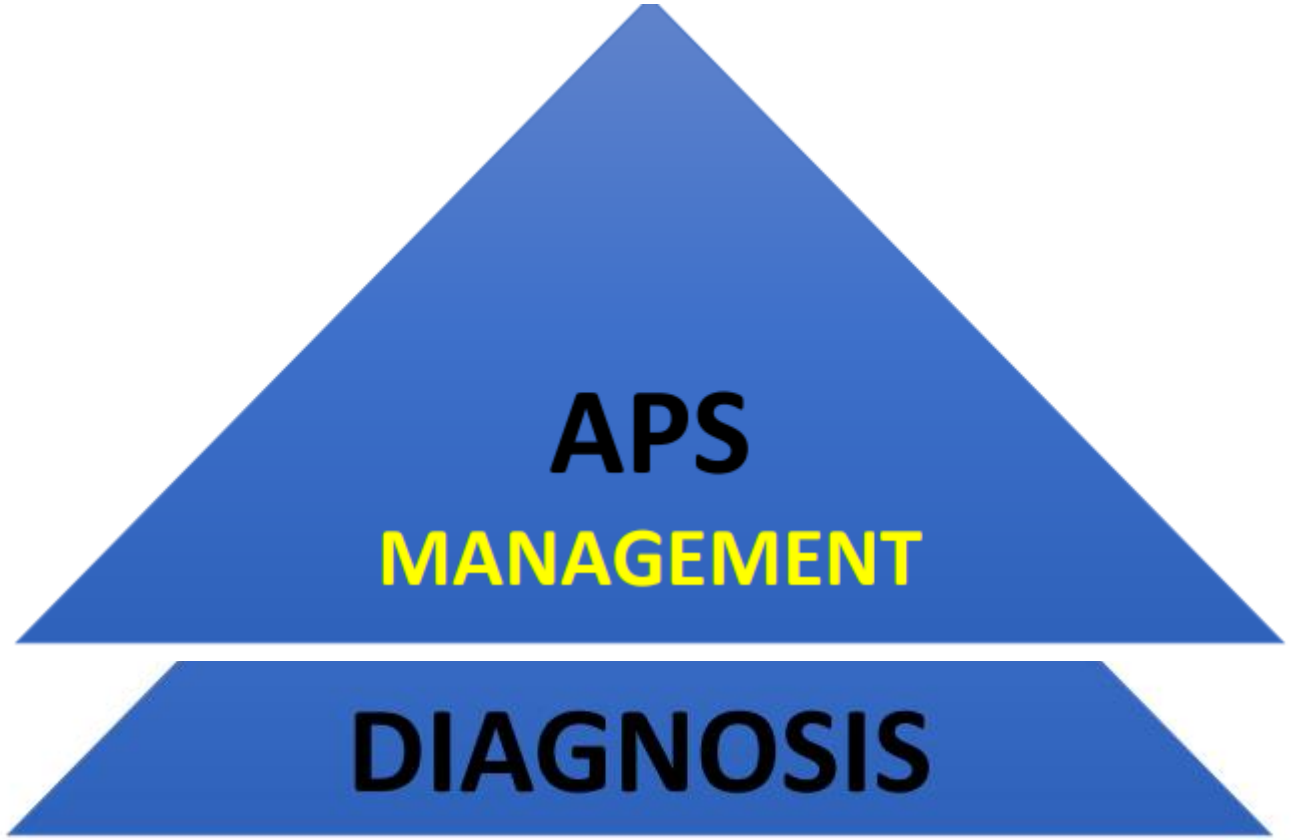


# CLINICIAN'S ROLE






aPL Profile

Other (Risk) Factors

# CLINICAL PHENOTYPE

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**Obstetric APS**

**Primary/Secondary Prevention:**

- **Who is at risk?**
- **ASA?**
- **LMWH?**
- **ASA+LMWH?**
- **Others?**

**Pre - Early - Late Fetal Loss**
**Without Other Pregnancy Morbidity**

**Placental Vascular Problems, e.g.,**

**aPL Profile**

De Jesus GR et al. In: APS (DOI 10.1007/978-3-319-55442-6_12)

# CLINICAL PHENOTYPE

American College of Rheumatology
*Empowering Rheumatology Professionals*

**Obstetric APS**

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**aPL Profile**

De Jesus GR et al. In: APS (DOI 10.1007/978-3-319-55442-6_12)

# CLINICAL PHENOTYPE

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**Microvascular APS**

## Treatment

- **Predictors of Microvascular APS?**
- **Anticoagulation?**
- **Immunosuppression?**
  - **Which one?**
  - **Most effective target?**
  - **Organ specific approach?**

**aPL Profile**

**Arthritis & Rheumatology**
Vol. 0, No. 0, Month 2021, pp 1–11
DOI: 10.1002/art.41891


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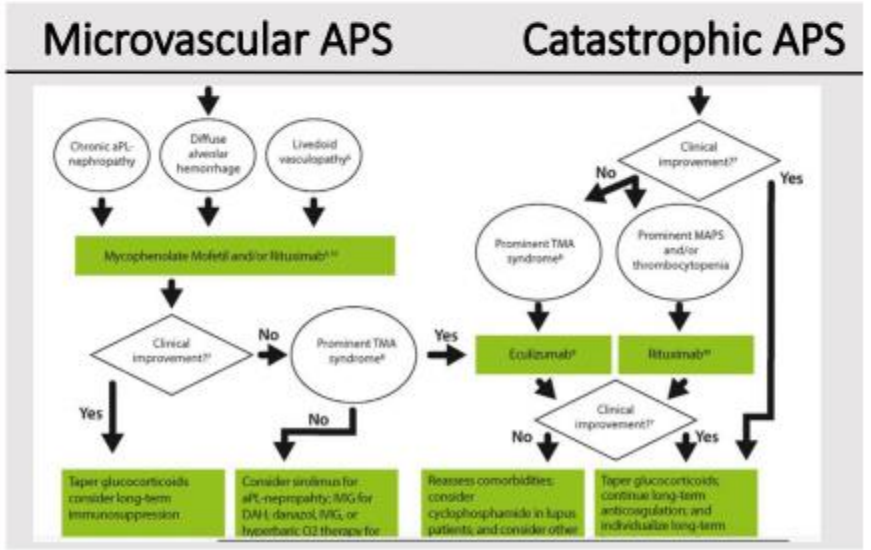
EXPERT PERSPECTIVES ON CLINICAL CHALLENGES

### Expert Perspective: Management of Microvascular and Catastrophic Antiphospholipid Syndrome

Doruk Erkan



# RETHINKING APS – PART B

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## 2023 ACR/EULAR Antiphospholipid Syndrome Classification Criteria

Medha Barbhaiya,[1*] Stephane Zuily,[2*] Ray Naden,[3†] Alison Hendry,[4] Florian Manneville,[5] Mary-Carmen Amigo,[6] Zahir Amoura,[7] Danieli Andrade,[8] Laura Andreoli,[9] Bahar Artim-Esen,[10] Tatsuya Atsumi,[11] Tadej Avcin,[12] Michael H. Belmont,[13] Maria Laura Bertolaccini,[14] D. Ware Branch,[15] Graziela Carvalheiras,[16] Alessandro Casini,[17] Ricard Cervera,[18] Hannah Cohen,[19] Nathalie Costedoat-Chalumeau,[20] Mark Crowther,[21] Guilherme de Jesus,[22] Aurelien Delluc,[23] Sheetal Desai,[24] Maria De Sancho,[25] Katrien M. Devreese,[26] Reyhan Diz-Kucukkaya,[27] Ali Duarte-Garcia,[28] Camille Frances,[29] David Garcia,[30] Jean-Christophe Gris,[31] Natasha Jordan,[32] Rebecca K. Leaf,[33] Nina Kello,[34] Jason S. Knight,[35] Carl Laskin,[36] Alfred I. Lee,[37] Kimberly Legault,[38] Steve R. Levine,[39] Roger A. Levy,[40] Maarten Limper,[41] Michael D. Lockshin,[1] Karoline Mayer-Pickel,[42] Jack Musial,[43] Pier Luigi Meroni,[44] Giovanni Orsolini,[45] Thomas L. Ortel,[46] Vittorio Pengo,[47] Michelle Petri,[48] Guillermo Pons-Estel,[49] Jose A. Gomez-Puerta,[50] Quentin Raimboug,[51] Robert Roubey,[52] Giovanni Sanna,[53] Surya V. Seshan,[54] Savino Sciascia,[55] Maria G. Tektonidou,[56] Angela Tincani,[10] Denis Wahl,[2] Rohan Willis,[57] Cecile Yelnik,[58] Catherine Zuily,[59] Francis Guillemin,[5] Karen Costenbader,[60] and Doruk Erkan,[1] on Behalf of the ACR/EULAR APS Classification Criteria Collaborators

**Arthritis Rheumatol.** 2023 Aug 28
doi: 10.1136/ard-2023-224609

## 2023 ACR/EULAR antiphospholipid syndrome classification criteria

Medha Barbhaiya,[1] Stephane Zuily,[2] Ray Naden,[3] Alison Hendry,[4] Florian Manneville,[5] Mary-Carmen Amigo,[6] Zahir Amoura,[7] Danieli Andrade,[8] Laura Andreoli,[9] Bahar Artim-Esen,[10] Tatsuya Atsumi,[11] Tadej Avcin,[12] Michael H Belmont,[13] Maria Laura Bertolaccini,[14] D Ware Branch,[15] Graziela Carvalheiras,[16] Alessandro Casini,[17] Ricard Cervera,[18] Hannah Cohen,[19] Nathalie Costedoat-Chalumeau,[20] Mark Crowther,[21] Guilherme de Jesús,[22] Aurelien Delluc,[23] Sheetal Desai,[24] Maria De Sancho,[25] Katrien M Devreese,[26,27] Reyhan Diz-Kucukkaya,[28] Ali Duarte-García,[29] Camille Frances,[30] David Garcia,[31] Jean-Christophe Gris,[32] Natasha Jordan,[33] Rebecca K Leaf,[34] Nina Kello,[35] Jason S Knight,[36] Carl Laskin,[37] Alfred I Lee,[38] Kimberly Legault,[39] Steve R Levine,[40] Roger A Levy,[41,42] Maarten Limper,[43] Michael D Lockshin,[1] Karoline Mayer-Pickel,[44] Jack Musial,[45] Pier Luigi Meroni,[46] Giovanni Orsolini,[47] Thomas L Ortel,[48] Vittorio Pengo,[49] Michelle Petri,[50] Guillermo Pons-Estel,[51] Jose A Gomez-Puerta,[52] Quentin Raimboug,[53] Robert Roubey,[54] Giovanni Sanna,[55] Surya V Seshan,[56] Savino Sciascia,[57,58] Maria G Tektonidou,[59] Angela Tincani,[9] Denis Wahl,[2] Rohan Willis,[60] Cécile Yelnik,[61] Catherine Zuily,[62] Francis Guillemin,[5] Karen Costenbader,[63] Doruk Erkan,[1] on Behalf of the ACR/EULAR APS Classification Criteria Collaborators

**Ann Rheum Dis.** 2023 Aug28
doi: 10.1002/art.42624

# C1. REMINDER



**#1. Positive aPL with no history of thrombosis**

**$aB_2GPI$ IgG: 34U & 35U (12w apart) (LA/aCL Negative)**

**1st Pregnancy and on low dose aspirin**

*"Does history of skin rash and presence of thrombocytopenia qualify her meeting clinical criteria for APS. If so, it may influence our decision of using prophylactic LMWH during pregnancy"*

**Classification Criteria Should not be Used for Treatment Decisions**

# C1. REMINDER

# C2. THE PAST & PRESENT



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**#2. Positive aPL with no history of thrombosis**

**aCL IgM: 53U – a$B_2$GPI: IgM 41U (12w)(rest of aPL negative)**

*"Need for primary prophylaxis with low dose aspirin and/or hydroxychloroquine"*

Classification criteria should not be used for treatment decisions

# C1. REMINDER
# C3. REMINDER

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**If a case does not meet the APS classification criteria, the case may still be uncertain or equivocal, rather than "not APS"**

- Uncertain or controversial cases should be studied separately to guide future updates of the new criteria

**After publication, all ACR/EULAR-approved criteria sets are expected to undergo intermittent updates**

# C3. REMINDER


**Table 6.** High-priority antiphospholipid syndrome (APS) research agenda to guide the future update of the 2023 ACR/EULAR APS classification criteria

**Patients with clinical AND laboratory criteria but NOT fulfilling the APS classification criteria**

- Venous thromboembolism (VTE) or arterial thrombosis (AT) alone, i.e., no other clinical criteria, in patients with high-risk VTE or CVD profiles, AND laboratory criteria score ≥3
- Otherwise unexplained 3 or more consecutive prefetal deaths (<10 weeks) and/or early fetal death (10 weeks 0 days to 15 weeks 6 days) alone, i.e., no other clinical criteria, AND laboratory criteria score ≥3
- Otherwise unexplained 1 or more fetal death (16 weeks 0 days to 34 weeks 0 days) alone, i.e., no other clinical criteria, AND laboratory criteria score ≥3
- Moderate-titer (40–79 units) or high-titer (≥80) IgM anticardiolipin (aCL) or IgM anti–$\beta_2$-glycoprotein I (anti-$\beta_2$GPI) antibodies based on enzyme-linked immunosorbent assays (ELISAs) alone, i.e., no other antiphospholipid antibody (aPL) test positivity, and clinical criteria score ≥3

**Patients fulfilling the clinical criteria but NOT the laboratory criteria**

- Other aCL/anti-$\beta_2$GPI testing platforms, e.g., automated laboratory systems, to determine the "moderate" and "high" thresholds corresponding to ELISA
- "Other" solid-phase assay–based aPL tests to determine their relevance

**Patients fulfilling the laboratory criteria but NOT the clinical criteria**

- "Other" potential aPL-related clinical manifestations to determine their specificity and frequency (see ref. 8)

# C4. IMMUNOSUPPRESSION



- #3 - 53yo male, triple aPL (+) with high titer (>80U) aCL/a$\beta_2$GPI IgG & unprovoked DVT
- 3-month history of worsening shortness of breath and dry cough
- Afebrile, hypoxic, and hypertensive; livedo racemosa of the upper extremities with three painful skin ulcers on bilateral lower extremities

- Hemoglobin 8.7 mg/dL with no schistocytes, platelet count 78 x $10^3$/mL, INR 2.1, creatinine 2.9 mg/dL (baseline 1.5 mg/dL), and urine protein-to-creatine ratio (UP/C) 1.75 (baseline 0.5).

- CXR with extensive patchy bilateral airspace opacities
- Chest CT with diffuse ground glass opacities (infection workup negative).
- BAL with alveolar hemorrhage with persistent bloody returns, demonstrating neutrophilic predominance and high percentage of hemosiderin-laden macrophages

Sevim E, Willis R, Erkan D. Is There a Role For immunosuppression in APS? Hematol Educ Program 2019;2019:426.

# C4. IMMUNOSUPPRESSION

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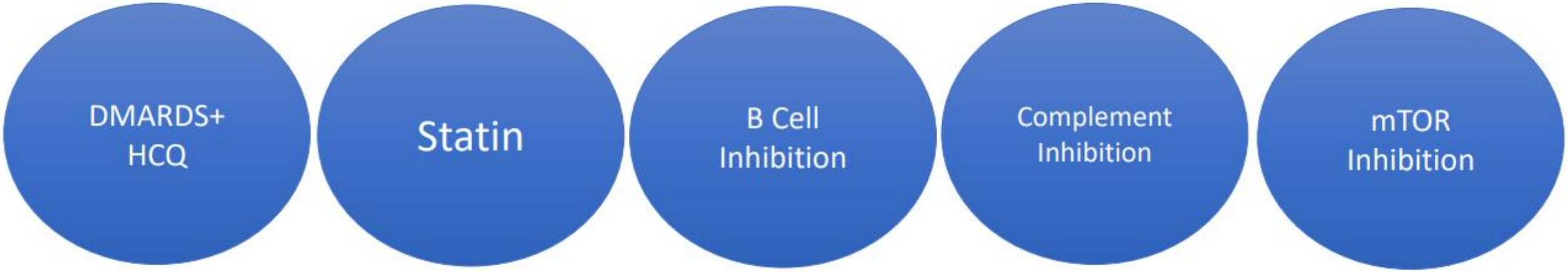


The supporting (pre) clinical evidence is limited

The management is mostly based on theoretical and preclinical evidence, very limited clinical evidence in humans, and the “expert” opinion.

*We need clinical studies other than case reports/series to accumulate more evidence*

Sevim E, Willis R, Erkan D. Hematol Educ Program 2019;2019:426 - Erton ZB, Erkan D. Curr Opin Pharmacol 2022;65:102212

# C5. SUB-PHENOTYPING

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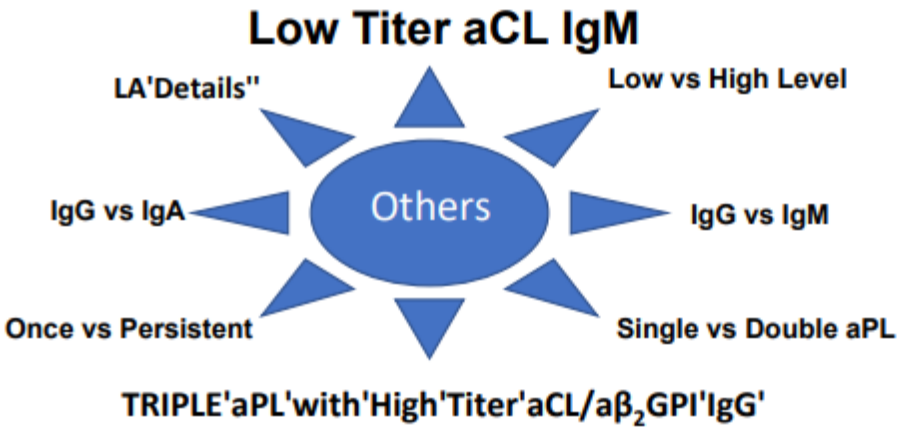
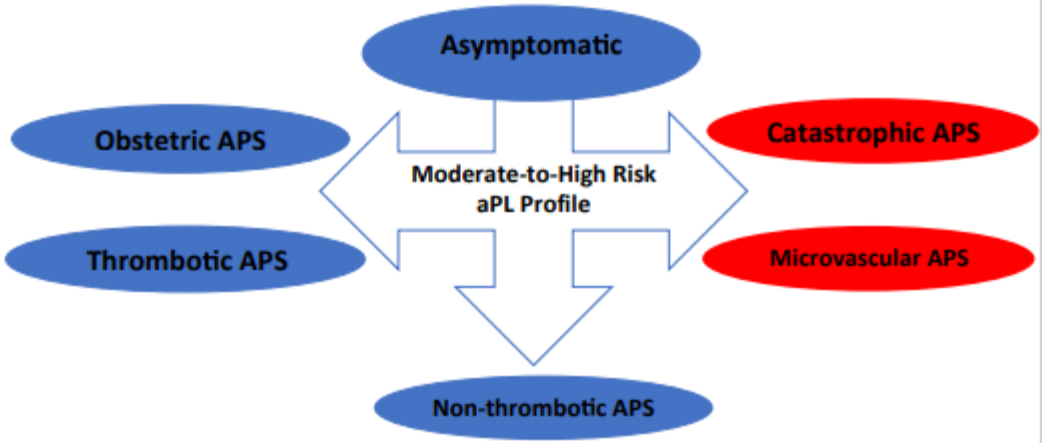
## APL PROFILE




## CLINICAL PHENOTYPE




## October 31, 2023:

| | | |
|---|---|---|
| #4 | 66 yo F | Thrombocytopenia + DAH |
| #5 | 18 yo M | Thrombocytopenia + Valve Disease + Stroke |
| #6 | 62 yo F | aPL-Nephropathy + Livedoid Vasculopathy |

# C5. SUB-PHENOTYPING

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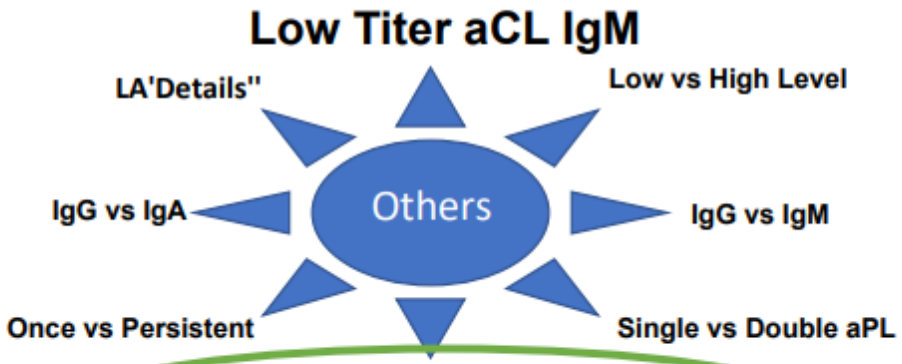
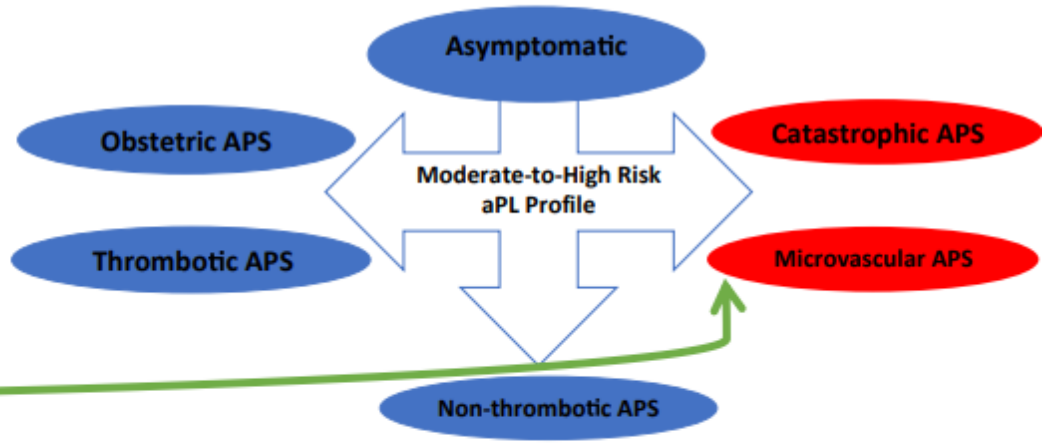
## APL PROFILE

## CLINICAL PHENOTYPE

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# CONCLUSIONS

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**Part A:**

- We need high-quality research to better define APS and its management

**Part B:**

- Now we have a highly specific classification system for research purposes

**Part C:**

- Sub-phenotyping APS, beyond aPL profile and different clinical phenotypes, is critical

ACR Convergence
Where Rheumatology Meets
#ACR23

# *The future of APS:* Disentangling APS through pathogenesis-informed sub-phenotyping

**Jason S. Knight, MD, PhD**
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**Additive clinical and laboratory criteria**[a]

Do not count a clinical criterion if there is an equally or more likely explanation than APS.
Within each domain, only count the highest weighted criterion towards the total score.

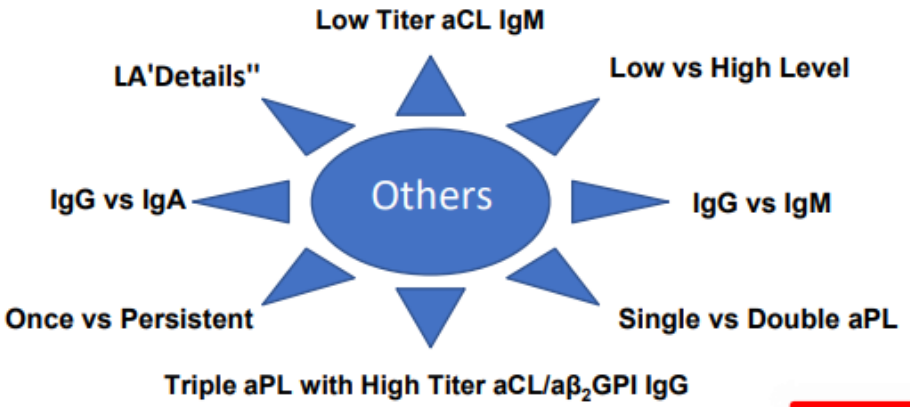
| Clinical domains and criteria | Weight |
|---|---|
| **D1. Macrovascular (Venous Thromboembolism [VTE])** | |
| VTE with a high-risk VTE profile[c] | 1 |
| VTE without a high-risk VTE profile[c] | 3 |
| **D2. Macrovascular (Arterial Thrombosis [AT])** | |
| AT with a high-risk CVD profile[c] | 2 |
| AT without a high-risk CVD profile[c] | 4 |
| **D3. Microvascular** | |
| Suspected (one or more of the following) | 2 |
| Livedo racemosa (exam) | |
| Livedoid vasculopathy lesions (exam) | |
| Acute/chronic aPL-nephropathy (exam or lab) | |
| Pulmonary hemorrhage (symptoms and imaging) | |
| Established (one of more of the following) | 5 |
| Livedoid vasculopathy (pathology[d]) | |
| Acute/chronic aPL-nephropathy (pathology[d]) | |
| Pulmonary hemorrhage (BAL or pathology[d]) | |
| Myocardial disease (imaging or pathology) | |
| Adrenal hemorrhage (imaging or pathology) | |
| **D4. Obstetric** | |
| ≥3 Consecutive pre-fetal (<10w) and/or early fetal (10w 0d -15w 6d) deaths | 1 |
| Fetal death (16w 0d – 33w 6d) in the absence of pre-eclampsia (PEC) with severe features or placental insufficiency (PI) with severe features | 1 |
| **D5. Cardiac Valve** | |
| Thickening | 2 |
| Vegetation | 4 |
| **D6. Hematology** | |
| Thrombocytopenia (lowest 20-130x$10^9$/L) | 2 |

Some of these manifestations present acutely, while others present more insidiously

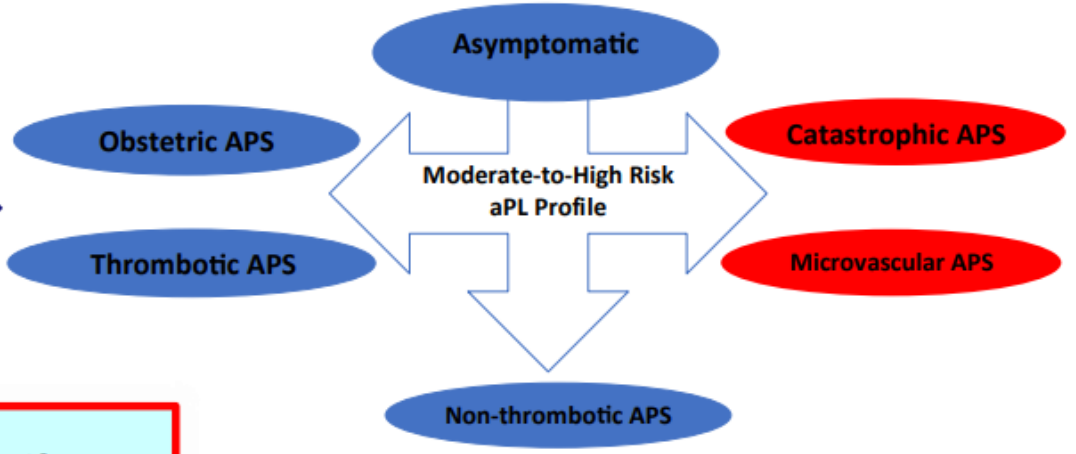
2023 ACR/EULAR APS CLASSIFICATION CRITERIA

# Sub-phenotyping APS: an aspirational future

## APL PROFILE




## CLINICAL PHENOTYPE




Let's talk about other approaches that are *(hopefully)* on the horizon…

**Table 3** Frequency of autoantibodies in each cluster over time

| | Cluster 1 (n=137) | | | Cluster 2 (n=376) | | | Cluster 3 (n=80) | | | Cluster 4 (n=212) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Antibody | Enrolment | Y3 | Y5 | Enrolment | Y3 | Y5 | Enrolment | Y3 | Y5 | Enrolment | Y3 | Y5 |
| Sm | 78.8 | 69.3 | 50.4 | 5.3 | 1.3 | 3.2 | 11.3 | 6.3 | 6.3 | 21.7 | 10.4 | 15.1 |
| U1RNP | 95.6 | 90.5 | 74.5 | 8.8 | 6.6 | 6.6 | 12.5 | 10.0 | 12.5 | 25.0 | 19.3 | 22.6 |
| DFS70 | 1.5 | 1.5 | 2.2 | 8.8 | 9.8 | 9.6 | 5.0 | 5.0 | 3.8 | 4.7 | 4.8 | 2.8 |
| β2GP1 IgG | 4.4 | 4.4 | 3.7 | 4.8 | 4.3 | 3.7 | 46.3 | 40.0 | 40.0 | 7.1 | 5.2 | 9.0 |
| β2GP1 IgM | 9.5 | 9.5 | 2.2 | 9.6 | 10.9 | 3.5 | 46.3 | 46.3 | 31.3 | 10.4 | 13.2 | 3.3 |
| Cardiolipin IgG | 13.1 | 6.6 | 12.4 | 8.0 | 3.7 | 6.4 | 55.0 | 37.5 | 37.5 | 20.3 | 7.1 | 13.7 |
| Cardiolipin IgM | 1.5 | 1.5 | 2.2 | 5.1 | 2.9 | 4.8 | 33.8 | 22.5 | 23.8 | 2.4 | 4.2 | 3.3 |
| β2GP1-domain 1 | 6.6 | 4.4 | 3.7 | 6.4 | 4.0 | 2.7 | 45.0 | 50.1 | 47.5 | 6.6 | 4.7 | 4.7 |
| Lupus anticoagulant | 8.6* | 10.7† | 8.6* | 16.0‡ | 12.4§ | 8.3‡ | 64.8¶ | 70.2** | 60.6¶ | 15.0†† | 14.5‡‡ | 10.6†† |
| PS/PT IgG | 15.3 | 19.0 | 10.9 | 9.8 | 8.8 | 5.9 | 71.3 | 63.8 | 61.3 | 21.7 | 25.0 | 20.3 |
| PS/PT IgM | 19.0 | 16.8 | 13.9 | 17.6 | 16.5 | 8.2 | 78.8 | 77.5 | 62.5 | 27.8 | 20.3 | 16.0 |
| dsDNA | 35.0 | 38.7 | 33.6 | 18.9 | 11.2 | 9.3 | 36.3 | 41.3 | 40.0 | 59.0 | 56.1 | 56.1 |
| Histone | 29.2 | 21.2 | 21.2 | 15.7 | 6.9 | 10.9 | 33.8 | 21.3 | 26.3 | 59.4 | 46.7 | 43.4 |
| PCNA | 16.8 | 10.2 | 13.9 | 7.4 | 4.8 | 12.8 | 17.5 | 6.3 | 18.8 | 29.2 | 18.4 | 31.1 |
| Ribosomal P | 33.6 | 28.5 | 26.3 | 11.4 | 6.1 | 8.5 | 23.8 | 15.0 | 18.8 | 41.5 | 36.3 | 36.8 |
| Ro52/TRIM21 | 39.4 | 29.9 | 37.2 | 22.3 | 18.1 | 21.3 | 16.3 | 17.5 | 25.0 | 71.2 | 69.8 | 70.8 |
| SSA/Ro60 | 48.9 | 42.3 | 46.0 | 25.5 | 22.3 | 26.3 | 21.3 | 21.3 | 25.0 | 76.4 | 79.7 | 73.6 |
| SSB/La | | | | | | | | | | | | |
| Centromere B | | | | | | | | | | | | |
| Jo-1 | | | | | | | | | | | | |

So many antibodies to work with beyond diagnosis/classification!

Darker red shading indicates higher frequency, lighter shading indicates lower frequency of autoantibody.

Choi MY, *et al*. *Ann Rheum Dis* 2023;**82**:927–936. doi:10.1136/ard-2022-223808

# Details important for our antigen-specific future…

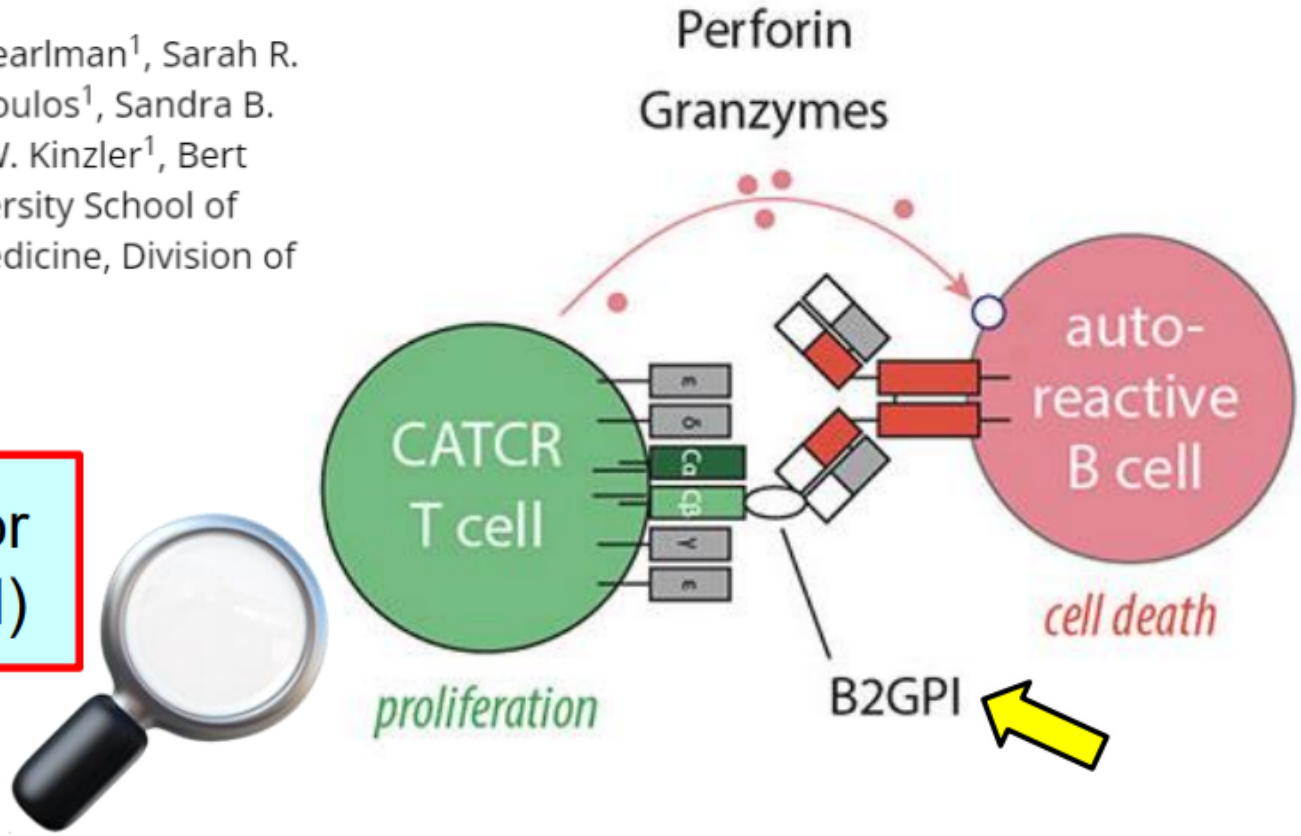
ABSTRACT NUMBER: 1677

## Chimeric Autoantigen-T Cell Receptor (CATCR)-T Cell Therapies to Selectively Target Autoreactive B Cells

Brian J. Mog[1], Elana R. Shaw[1], Michael S. Hwang[1], Alexander H. Pearlman[1], Sarah R. DiNapoli[1], Suman Paul[1], Chetan Bettegowda[1], Nickolas Papadopoulos[1], Sandra B. Gabelli[1], Michelle Petri[2], Antony Rosen[1], Shibin Zhou[1], Kenneth W. Kinzler[1], Bert Vogelstein[1] and **Maximilian F. Konig**[1], [1]The Johns Hopkins University School of Medicine, Baltimore, MD, [2]Johns Hopkins University School of Medicine, Division of Rheumatology, Baltimore, MD

**Meeting: ACR Convergence 2022**

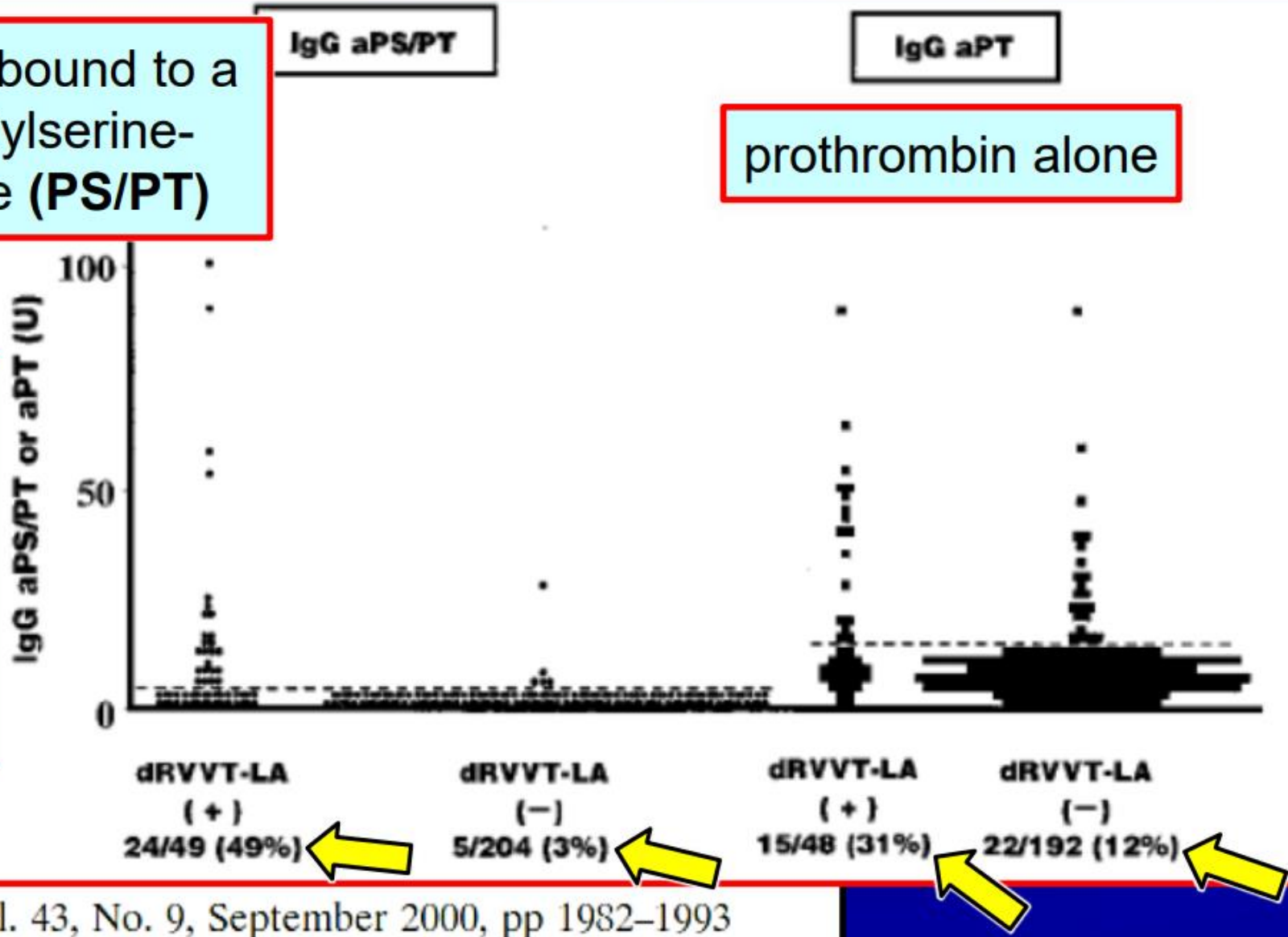
CAR T-like cells, on the hunt for specific BCRs (e.g., anti-$\beta_2$GPI)



# Will anti-PS/PT antibodies help us risk stratify?

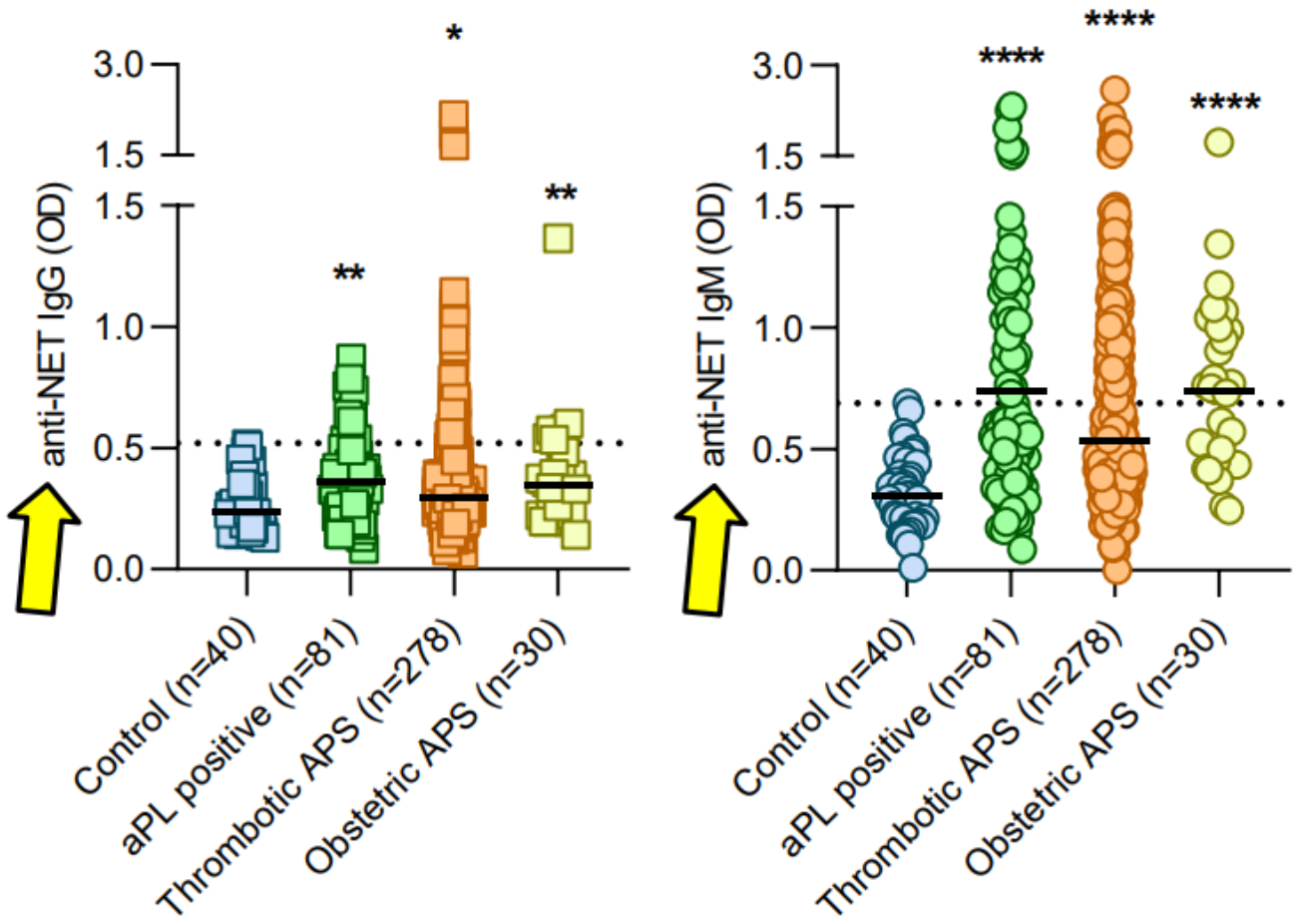
prothrombin bound to a phosphatidylserine-coated plate **(PS/PT)**

**Opinion alert:** We can have a more interesting conversation about anti-PS/PT if we figure out relevant downstream mechanisms…




ARTHRITIS & RHEUMATISM Vol. 43, No. 9, September 2000, pp 1982–1993

# Anti-NET antibodies 🕸️👀




Samples from APS ACTION: especially Brazil, Italy, and USA

First published: 02 March 2023 | https://doi.org/10.1002/art.42489

# Who's talking about complement inhibition?

| | Total (n = 11) | Responders (n = 5) | Nonresponders (n = 6) |
|---|---|---|---|
| Age, median (IQR), y | 48 (24) | 46 (40) | 53 (23) |
| Female, n | 8 | 4 | 4 |
| **CAPS clinical features** | | | |
| Cardiac failure | 6 | 3 | 3 |
| Cutaneous (livedo reticularis, necrosis) | 8 | 5 | 3 |
| Renal failure | 10 | 4 | 6 |
| Cerebrovascular involvement | 4 | 3 | 1 |
| Venous thrombosis | 4 | 1 | 3 |
| Peripheral artery thrombosis | 2 | 1 | 1 |
| Adrenal ischemic hemorrhag | | | |
| Diffuse alveolar hemorrhage | | | |
| Liver infarct | | | |
| Gastrointestinal involvement | | | |
| Thrombocytopenia | | | |
| Median (IQR) platelet count before, × 10⁹/L | 19 (96) | 14 (54) | 79 (207) |
| Median (IQR) platelet count after, × 10⁹/L | 89 (165) | 89 (113) | 111 (212) |
| MAHA | 6 | 4 | 2 |

Preliminary evidence that patients with thrombocytopenia and microangiopathic features respond best…

# Quantifying complement at the cell surface…

## Measuring complement? #ACR23

| Complement Biomarkers | Total (n=52) | New Thrombosis (n=27) | No New Thrombosis (n=25) | p-value |
|---|---|---|---|---|
| Elevated sC5b-9 (# patients (%)) | 44/50 (88) | 23/26 (89) | 21/24 (88) | 1.00 |
| sC5b-9 level, ng/ml (median (±IQR)) | 412 (±307) | 491 (±367) | 346 (±308) | 0.20 |
| sC5b-9 in acute* samples, ng/ml | | 482 (±295) | | |
| Elevated C4d | NA | NA | NA | NA |
| C4d levels, µg/ml (median (±IQR)) | 3.63 (±3.18) | 4.21 (±3.39) | 2.87 (±2.56) | **0.041** |
| C4d in acute* samples, µg/ml | | 4.27 (3.7) | | |
| Elevated Bb (# patients (%)) | 15/50 (30) | 10/26 (39) | 5/24 (21) | 0.17 |
| Bb level, µg/ml (median (±IQR)) | 1.06 (±0.59) | 1.03 (±0.77) | 1.16 (±0.53) | 0.71 |
| Bb in acute* samples, µg/ml | | 1.41 (±1.54) | | |
| Positive mHAM (# of patients) | 9/51 (18) | 8/27 (30) | 1/24 (4) | **0.026** |

# Any progress on small-vessel vasculopathy?

This study investigates the vascular pathology of APS in patients who met well-defined clinical criteria for the diagnosis of the syndrome. The data indicate that several organs are involved by a spectrum of pathology that includes thrombosis and arterial intimal hyperplasia.

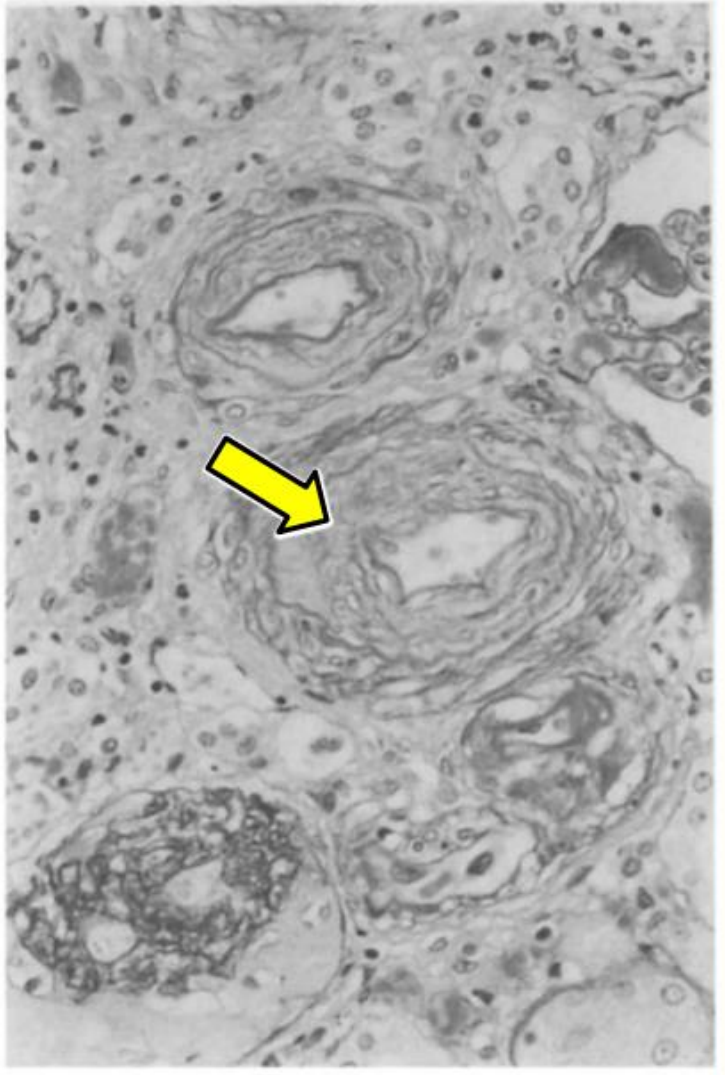
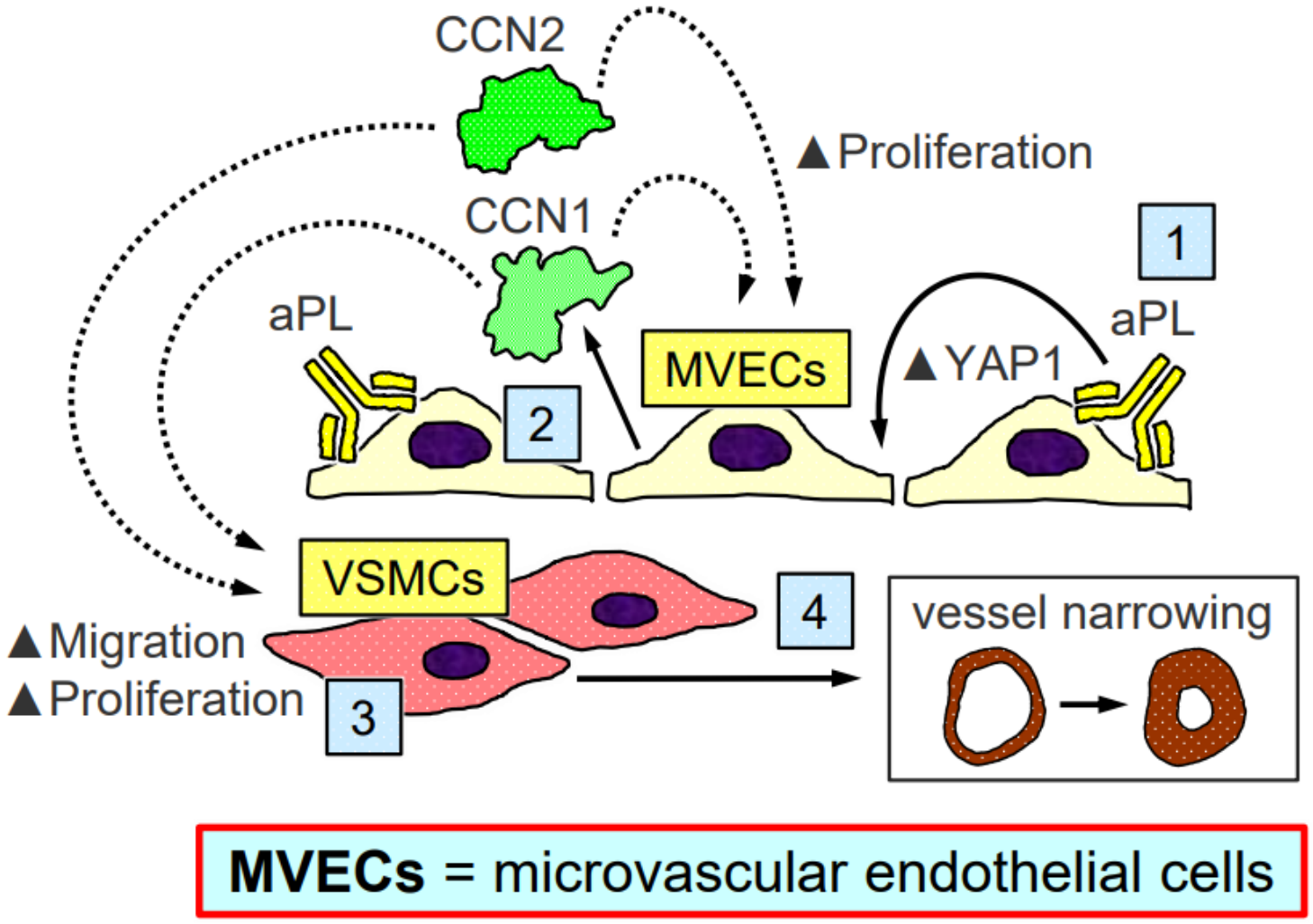


**FIGURE 6.** Patient no. 1. In kidney tissue obtained at autopsy, an interlobular artery displays concentric intimal fibrosis indistinguishable from hypertensive vascular disease. (Periodic acid–Schiff–hematoxylin stain; original magnification ×250.)

Hum Pathol. 1995 Jul;26(7):716-24. doi: 10.1016/0046-8177(95)90218-x.

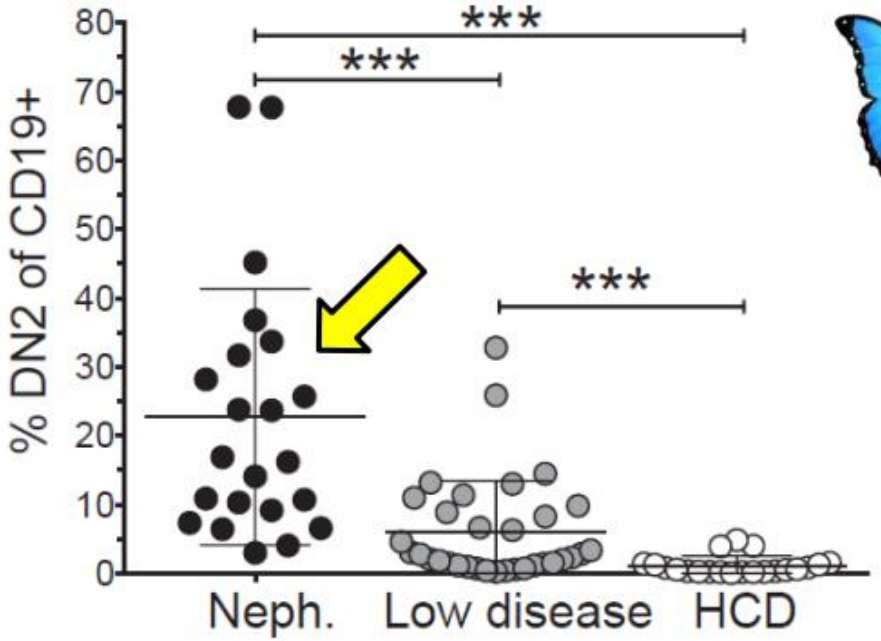
# Progress on small-vessel vasculopathy? #ACR23




**MVECs** = microvascular endothelial cells

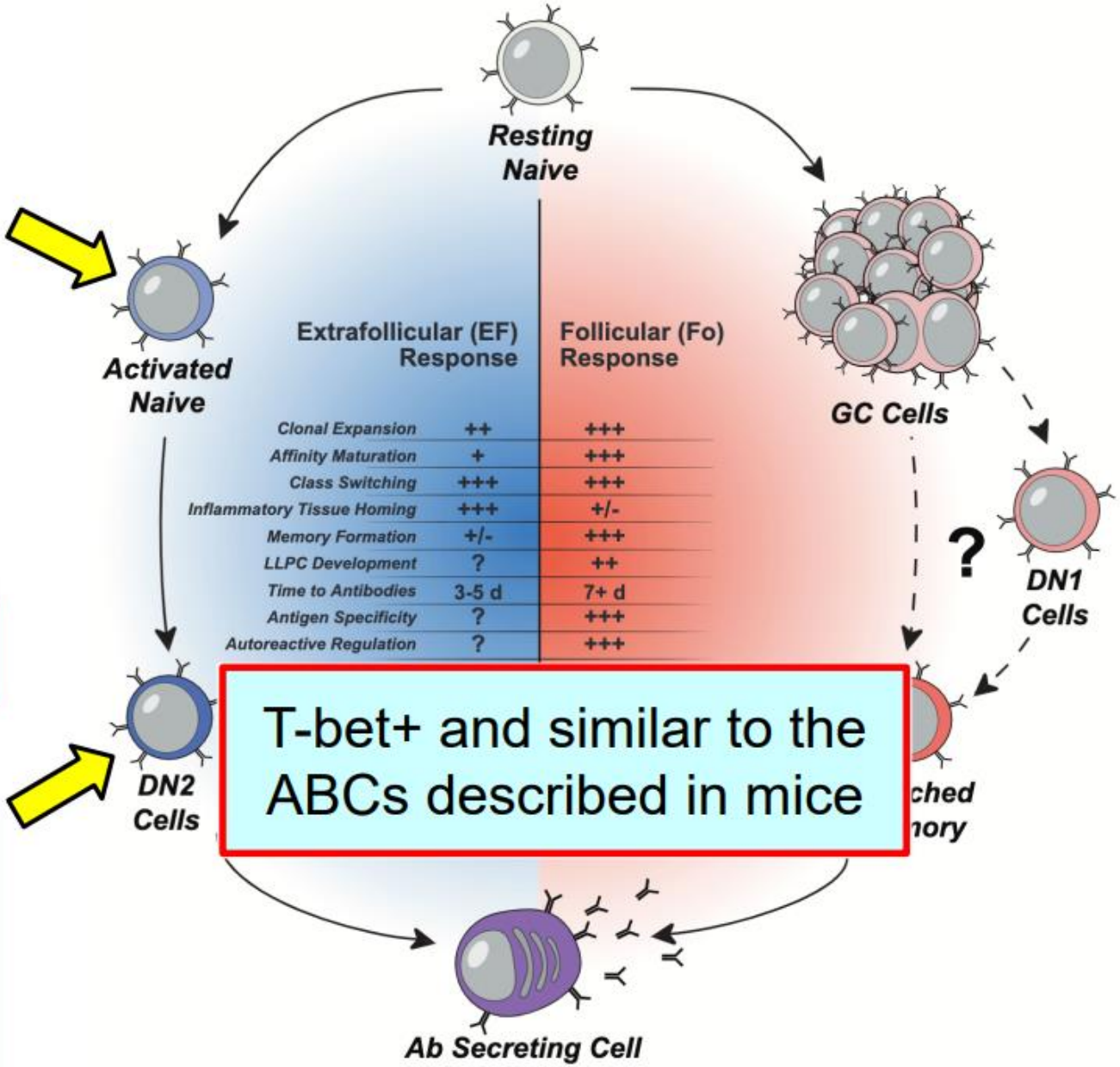
**CCN1/CCN2**

- **Secreted** proteins
- Regulators of cell **proliferation** and chemotaxis
- Implicated in **fibrosis** (mostly) but also in neointima formation
- Classic targets of **Hippo-YAP1/TAZ**




**DN** = double-negative = IgD- CD27-

Expansion of “extrafollicular” B cells that appear to bypass normal germinal center checkpoints




T-bet+ and similar to the ABCs described in mice

Immunity *49*, 725–739, October 16, 2018

# What do we know about B cells in APS?

Journal of *Clinical Medicine*

MDPI

*Review*

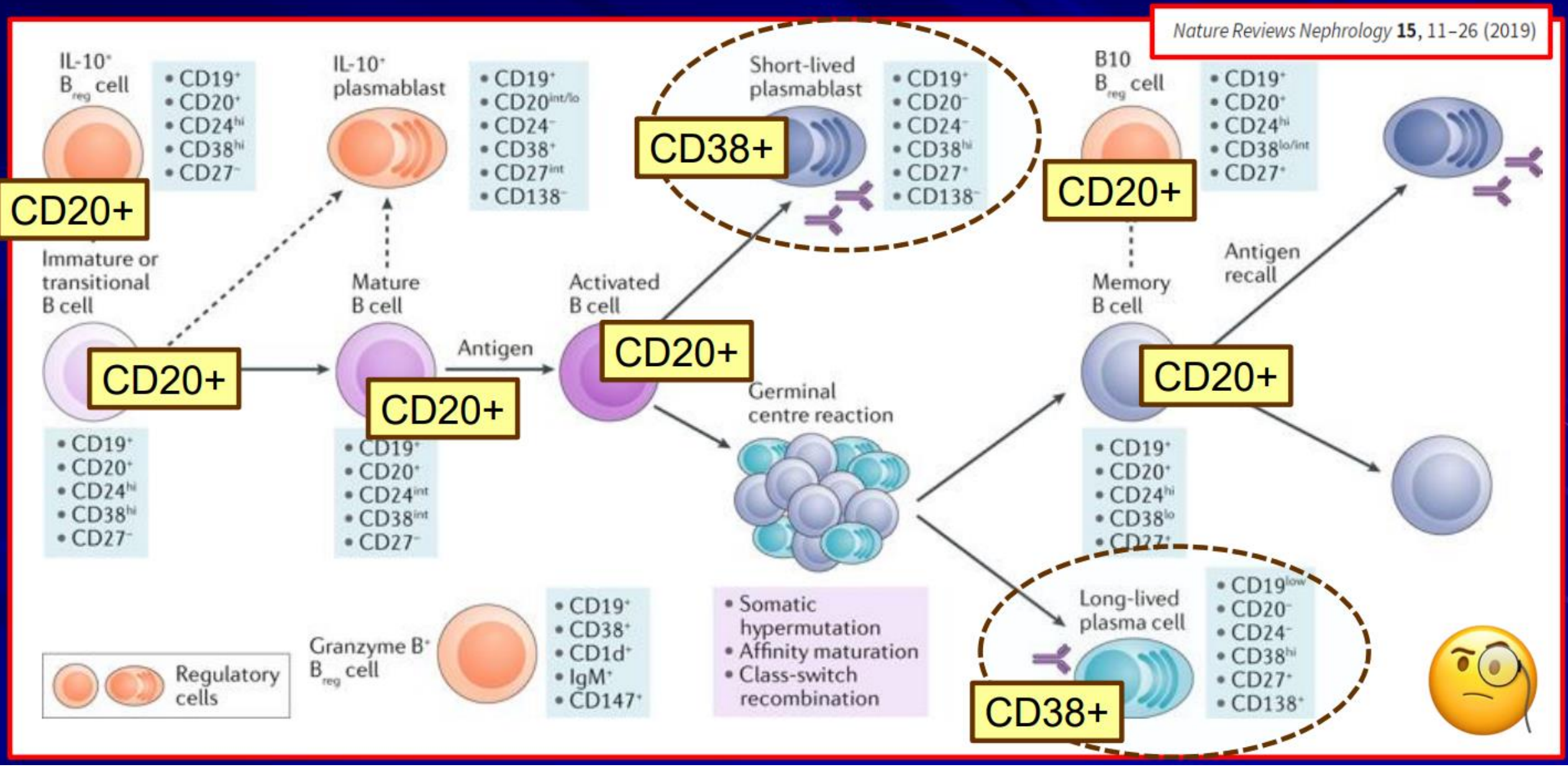
## B-Cells and BAFF in Primary Antiphospholipid Syndrome, Targets for Therapy?

Lucas L. van den Hoogen [1,2] and Radjesh J. Bisoendial [3,4,*]

Check out this nice review for the current landscape…

*J. Clin. Med.* **2023**, *12*, 18. https://doi.org/10.3390/jcm12010018

# Anti-CD38 for plasma cell depletion in APS?



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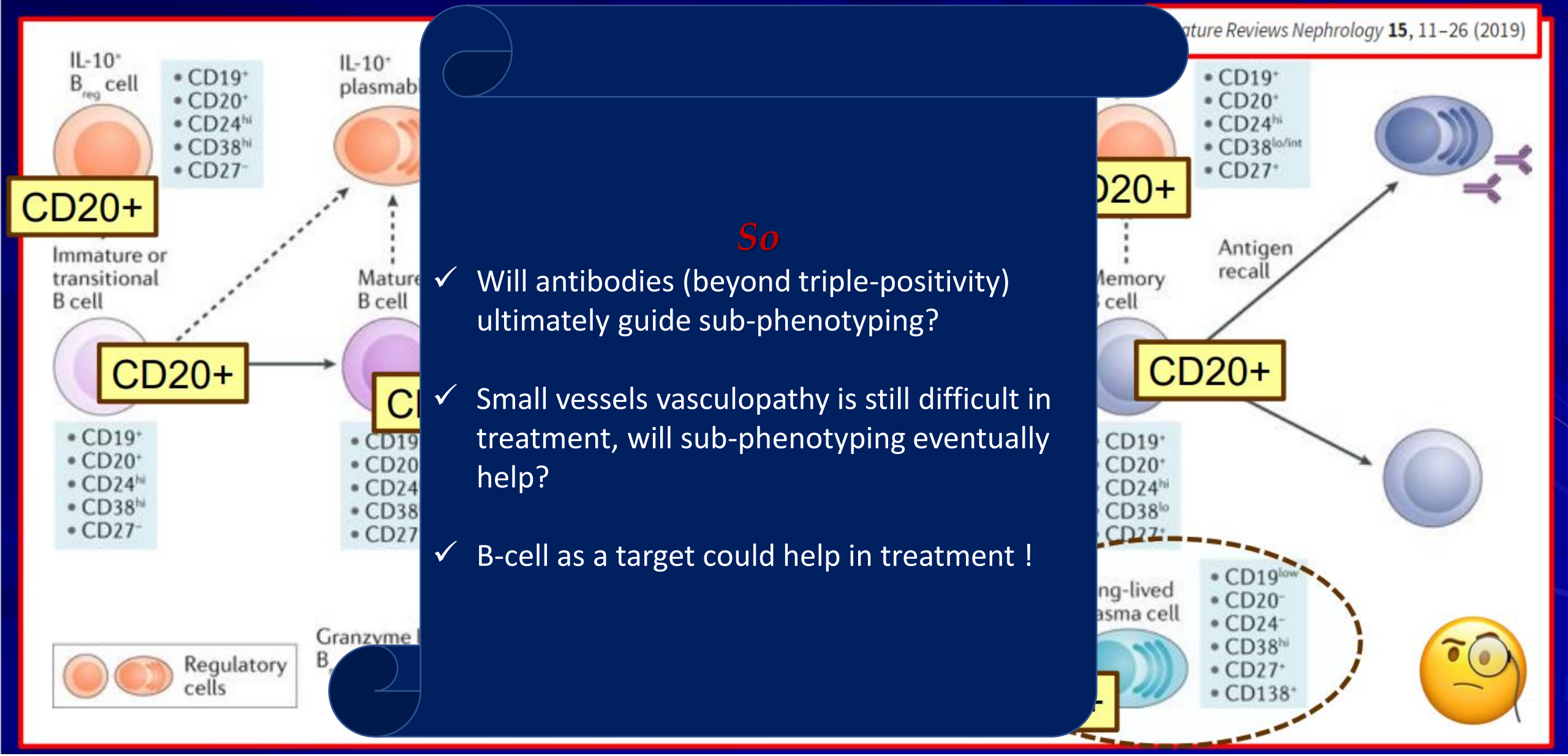


*So*

- ✓ Will antibodies (beyond triple-positivity) ultimately guide sub-phenotyping?
- ✓ Small vessels vasculopathy is still difficult in treatment, will sub-phenotyping eventually help?
- ✓ B-cell as a target could help in treatment !

THANK YOU