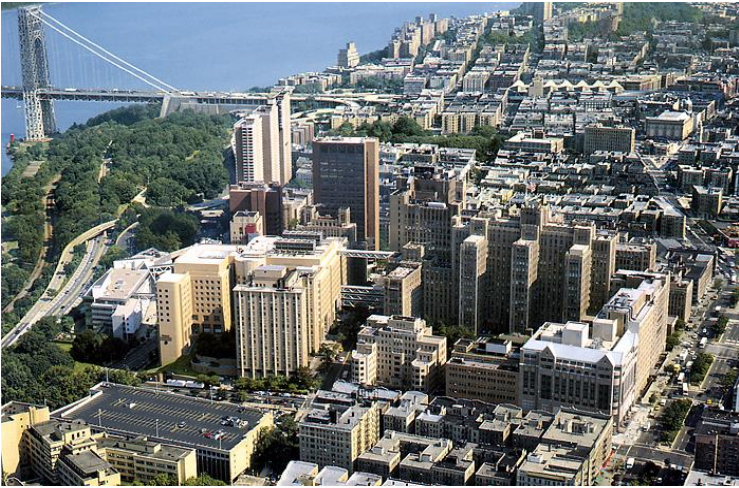




Lupus Nephritis in 2026 – New Guidelines, New Treatments, and New Challenges

Gerald B. Appel, M.D.

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Division of Nephrology

Columbia University Medical Center



G.Appel -Potential Conflicts of Interest

Dr. Appel has research grants with Achillion-Alexion, Apellis, Vera, Vertex, Novartis, and NIH.

He has consultantships with : Alexion-Achillion, Apellis, Aurinia, Glaxo , Calliditas, Roche-Genentech, Up-to-Date, Genzyme-Sanofi , Travers, Novartis, Vertex, Vera.

He has lectureships with Glaxo on LN ; Calliditas on Mechanisms of IgA Nephropathy, Travers on mechanisms and treatment of Focal Glomerulosclerosis.

He has no major conflicting stock holdings.

Lupus Nephritis— Still a Rare Disease ?

Estimated number of patients with SLE
200,000 to 300,000

Up to 45% of SLE patients have LN

Of these 70% patients with LN are class III, IV, or V

Up to 40-60% develop CKD
Up to 15% reach ESKD

Fanouriakis A, et al. EULAR Rec. for SLE w Kdy Dis Ann Rheumatic Dis 85:75-90 2026

Tektonidou MG, et al Arthritis Rheumatol. 68:1432, 2016.

Dall'Era et al. *Arthritis Rheum.* 69(10):1996-2005,. 2017

Somers et al. Abstract presented at: 2019 ACR/ARP Nov. 2019.

LN Pts at High Risk for ESKD – Up to 15% will progress to ESKD

Risk Factors for CKD Progression

Reduce GFR < 60 cc/min/m² at baseline
Nephrotic range proteinuria at baseline
Hypertension at baseline

Male Gender
Pediatric group
Some AA descent + ApoL1 risk genes

Flares of Disease
Increased chronicity on Bx (w activity)
Crescents
Severe tubulointerstitial inflammation

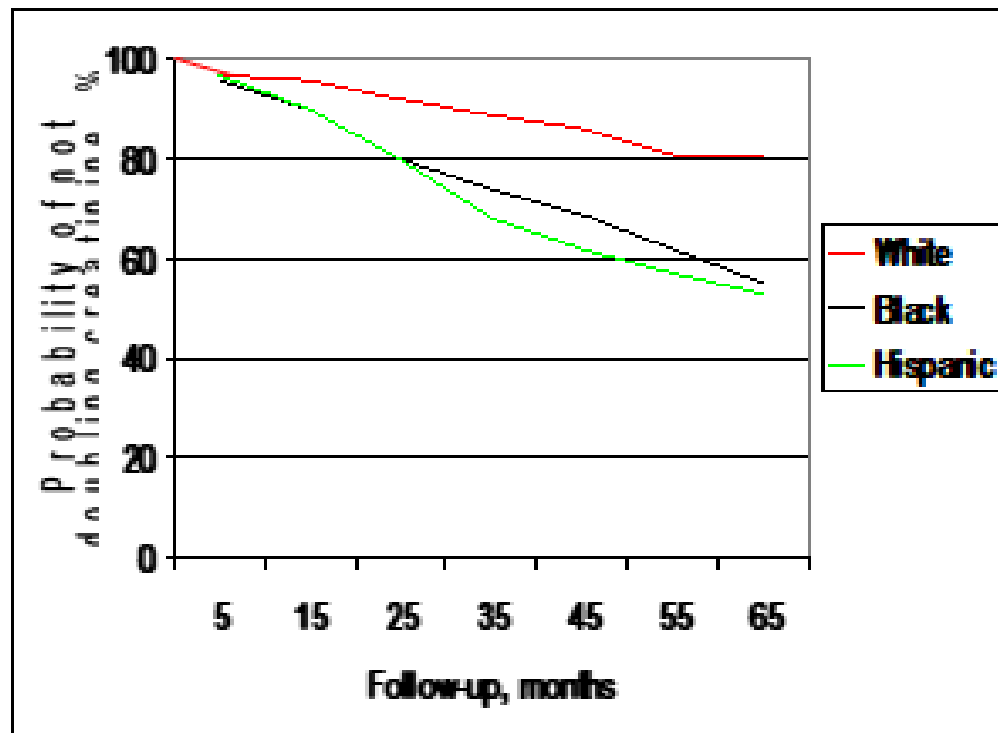
Risk for Flares

Younger age < 30 yo
Male gender
Nonadherence to Rx
Shorter duration Rx (<3yrs)
Incomplete response to initial Rx
Ongoing extrarenal and serologic activity
No use of HCQ
Residual histologic activity

Modified from A. Fanouriakis et al EULAR recommendations for Rx SLE with Kidney Involvement
Ann Rheum Dis 85: 75-90 2026.

Effect of Ancestral Background on Renal Survival

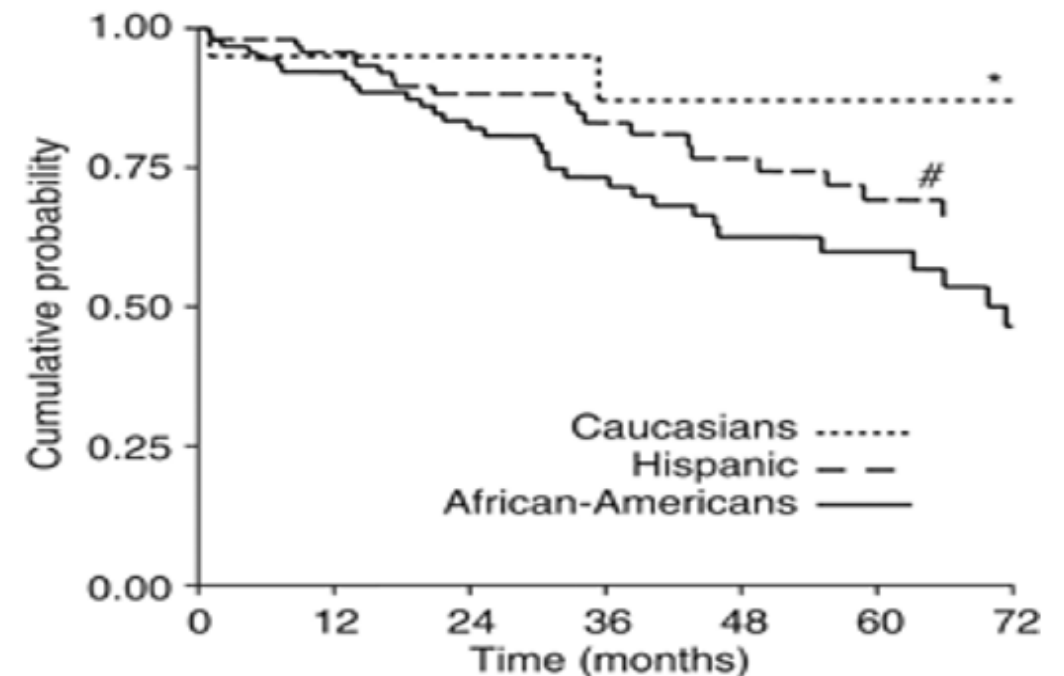
Renal Survival LN III and IV
CUMC N=129



Barr RG, Seliger S, Appel GB et al.
Nephrol Dial Trans 2003; 18: 2039–2046

Outcomes in African Americans and
Hispanics with LN U Miami N=213

Contreras et al KI 69:1846, 2006

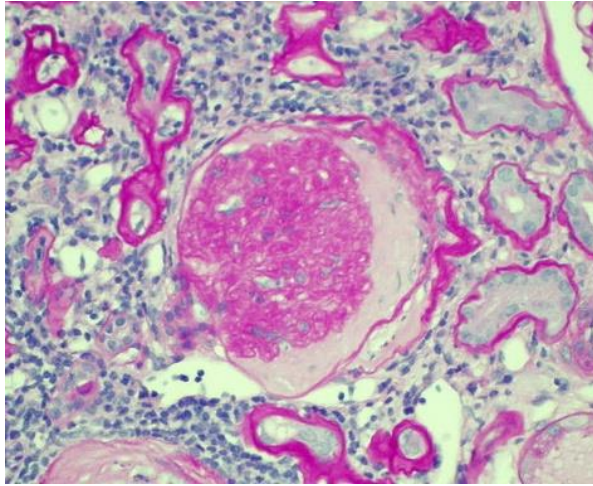


Contreras et al KI 69:1846, 2006

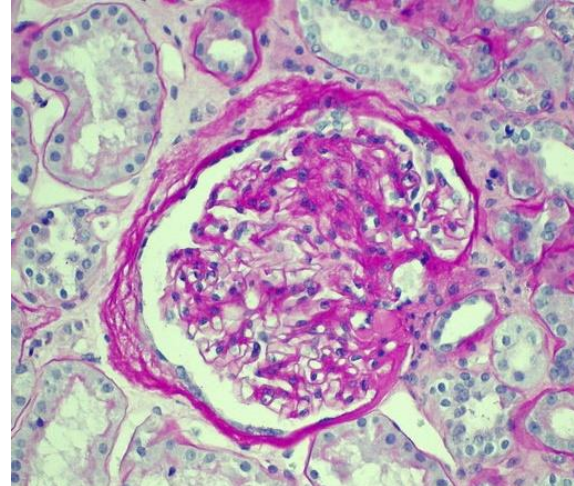
Spectrum of *APOL1*-associated nephropathy (ApoL1 G1G2,G1G1,G2G2)

**Focal Global
Glomerulosclerosis**

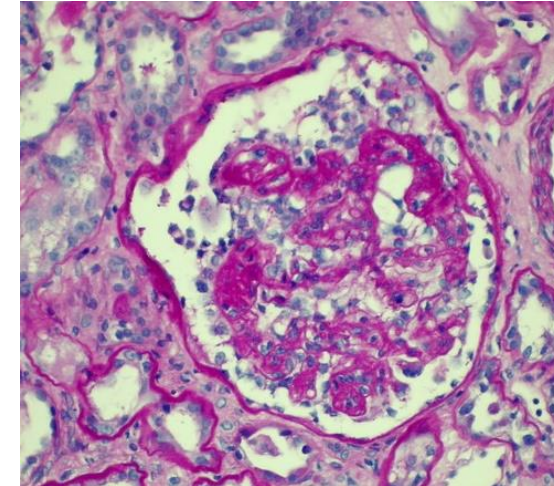
“Hypertension-attributed”



**Focal Segmental
Glomerulosclerosis**



**Collapsing FSGS
(HIVAN + **COVAN**)**

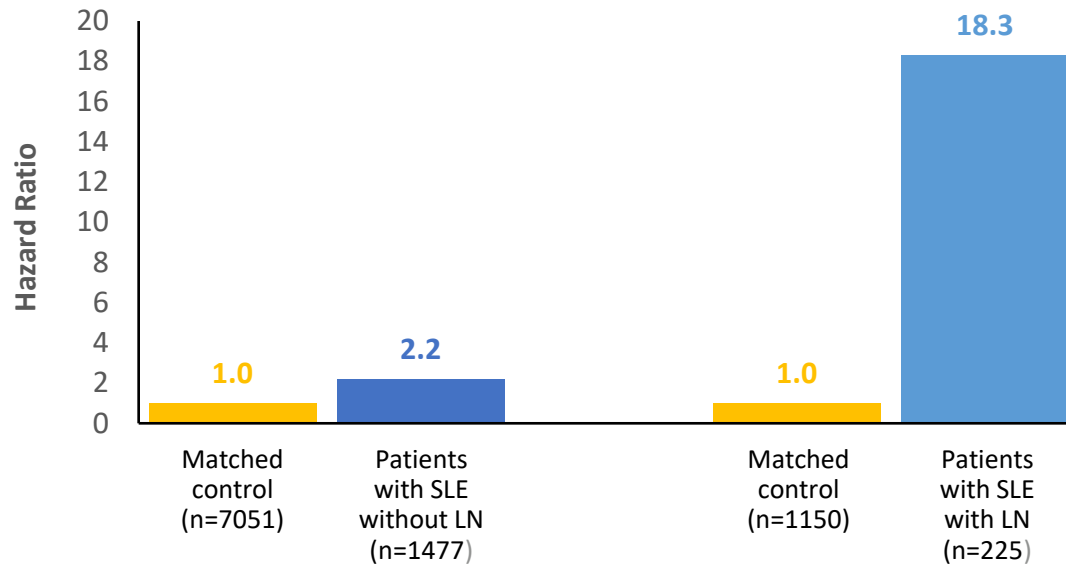


Proteinuria & nephropathy progression rate

Severe lupus nephritis

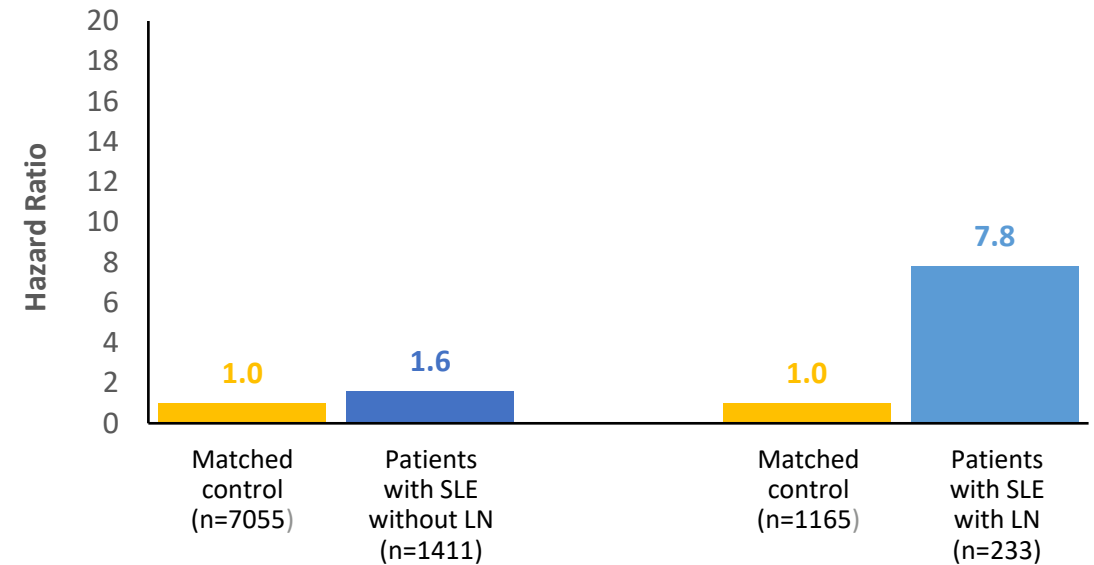
LN Increases the Risk of CV Events and CV Mortality

Hazard Ratios of MI in Patients With SLE
With and Without LN



>8x increased risk for MI
(HR=8.5; 95% CI: 2.2-33; $P=0.002$)

Hazard Ratios of CV Mortality in Patients With SLE
With and Without LN



>4x increased risk for CV mortality
(HR=4.9; 95% CI: 1.8-13.7; $P=0.002$)

Hermansen et al. *Rheumatology (Oxford)*. 2017;56(5):709-715.

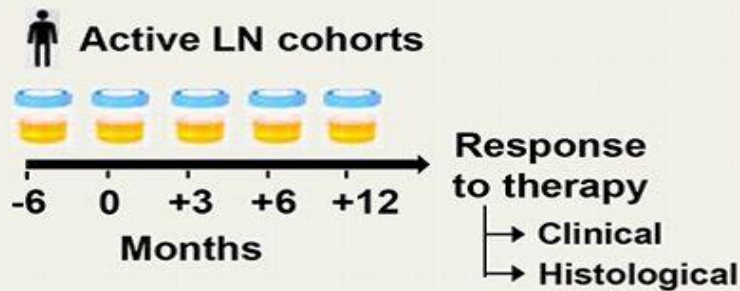
Urinary soluble CD163: a novel non-invasive biomarker of activity for lupus nephritis

METHODS

Cross-sectional

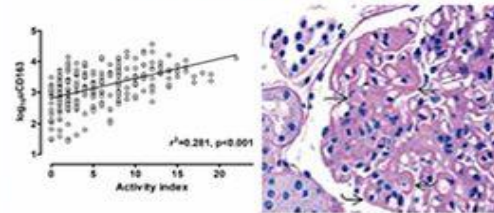


Longitudinal



OUTCOME Urine sCD163 levels:

Correlate with LN histologic activity



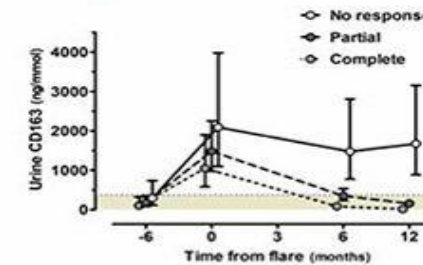
6-month values predict 12-month response

- ✓ Sensitivity: >87%
- ✓ Specificity: >87%

Identify histologic remission in patients with persistent proteinuria



Vary with treatment and response to therapy



- ↑ At flare
- ↓ Responders
- Non-responders

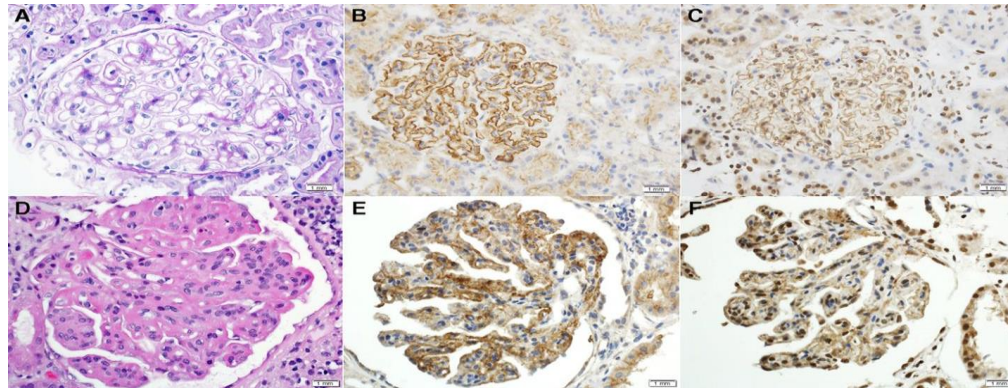
Agree with histology on repeat biopsy



Proteinuria: moderate
uCD163: perfect

CONCLUSION Urinary sCD163 may be a valuable LN activity biomarker that reflects histologic inflammation in LN and varies over time with activity and treatment.

Incidence of ESKD in LM patients Over 10 yrs



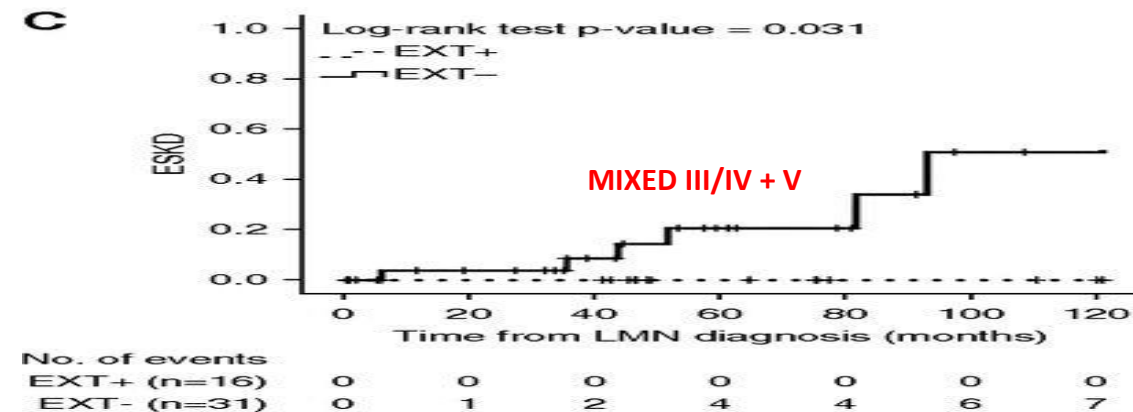
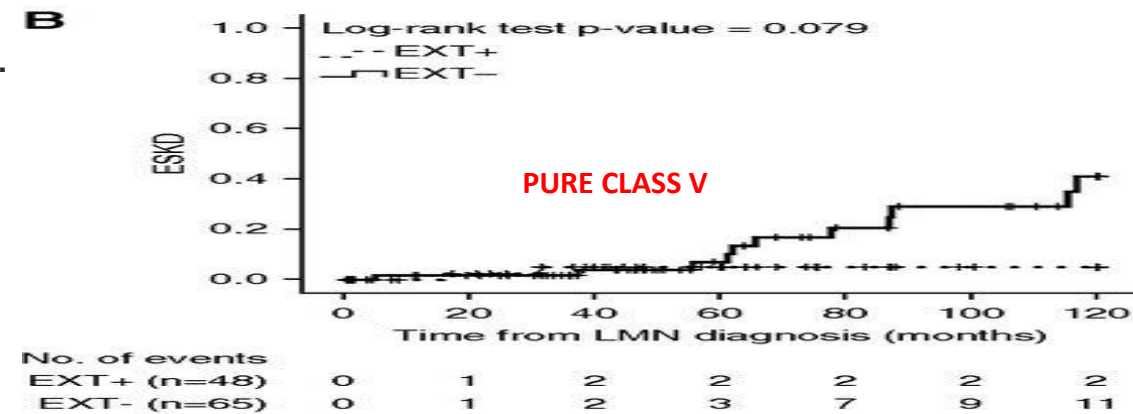
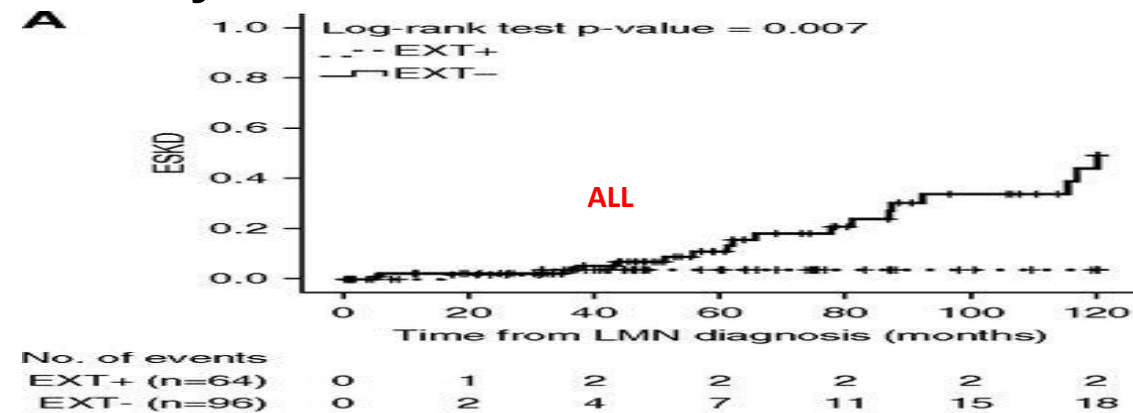
374 Pts LN V 122 (32.6%) Bx + EXT1/EXT2 252 (67.4%) neg..

EXT1/EXT2- Positive : younger ($P=0.01$), lower serum creatinine levels ($P=0.02$), more with proteinuria ≥ 3.5 g/24 h ($P=0.009$) BUT less chronicity features

EXT1/EXT2-negative pts evolved to ESKD faster and more frequently (18.8% versus 3.1%; $P=0.003$).

EXT1/EXT2 Positivity confirms MLN, predicts better course.

A Ravindran et al. JASN 32:695-706,2021



Glomerular Exostosin as a Subtype and Activity Marker of Class 5 Lupus Nephritis

Chengyu Wang,^{1,2} Yang Liu,^{1,3} Mingchao Zhang,⁴ Fan Yang,⁴ Feng Xu,⁴ Shaolin Shi ,⁴ Caihong Zeng,⁴ Xin Chen,⁴ Yiqi Miao,⁴ Zhengzhao Liu,⁴ and Weixin Hu^{1,4}

Abstract

Background and objectives There have been only several studies on the correlation between glomerular exostosin expression and membranous lupus nephritis. In this study, we validate the previous findings in Chinese patients with class 5 lupus nephritis.

Design, setting, participants, & measure One hundred sixty-five patients with class 5 lupus nephritis and varying numbers of control patients were included. Exostosin1/exostosin2 staining was performed by immunohistochemistry, and the staining intensity was quantified using an imaging analysis system. Between-group comparisons were tested for statistical significance using the Pearson chi-squared test, the Fisher exact test

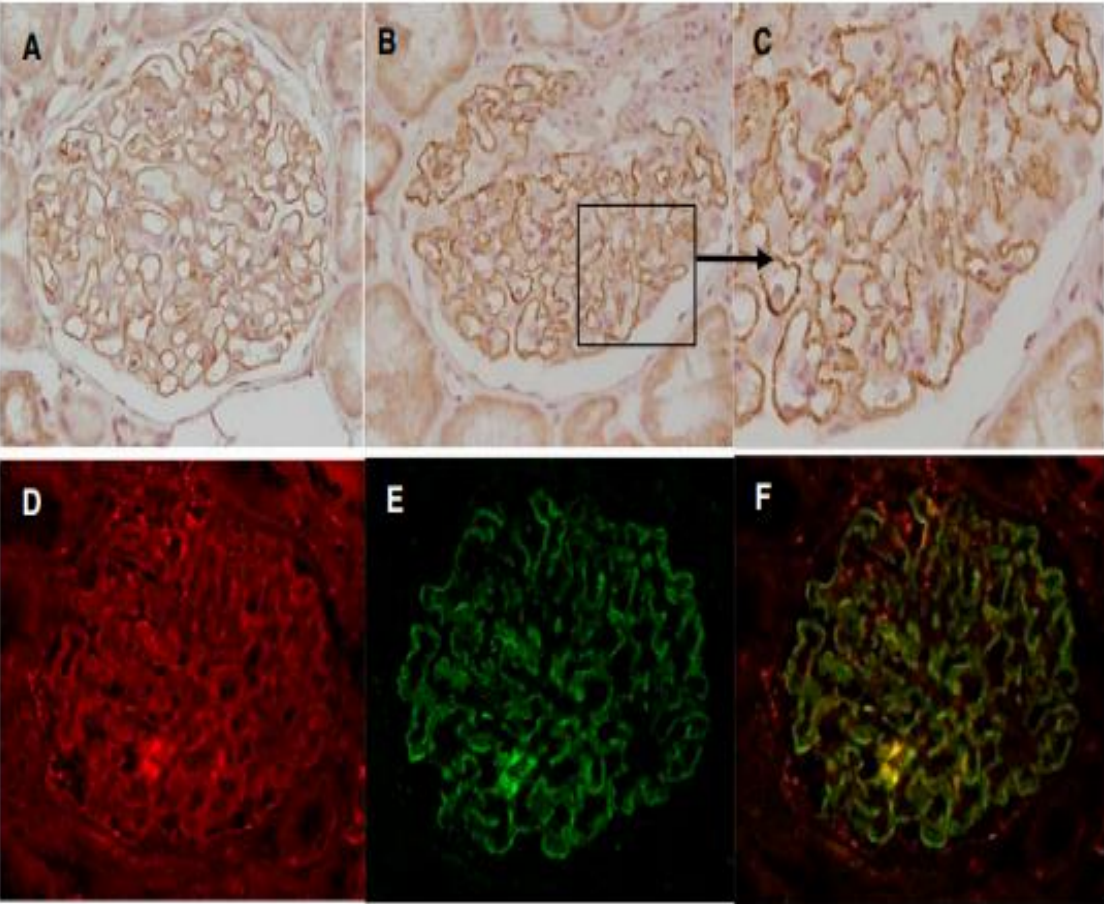


Table 4. Treatment response and outcomes in the cases of exostosin-positive and exostosin-negative class 5 lupus nephritis

Variable	Exostosin Positive, n=75	Exostosin Negative, n=90
Treatment		
Pred + Tac	31 (41)	18 (20)
Multitarget	14 (19)	21 (23)
Pred + TW	17 (23)	29 (32)
Pred + IV-CYC	6 (8)	14 (16)
Others	7 (9)	8 (9)
Efficacy		
Complete remission	63 (84)	74 (82)
Partial remission	5 (6.7)	7 (8)
Follow-up time, mo	72.0 (33.0–102.0)	84.5 (59.3–107.8)
Kidney end point	5 (7)	6 (7)
Relapse	34 (48)	45 (51)

Data were presented as *n* (percentage) or median (interquartile range). Multitarget indicates Pred plus Tac plus mycophenolate mofetil. Pred, prednisone; Tac, tacrolimus; TW, *Tripterygium wilfordii*; IV-CYC, intravenous cyclophosphamide.

Glomerular Exostosin- Positivity is Associated with Disease Activity and Outcome in Patients With Membranous Lupus Nephritis



The First Affiliated
Hospital of Sun Yat-Sen
University, China



85% female
(n= 283)



January 2006
to June 2022



Median age= 29years
(IQR 22-38)



Primary endpoints:
Adverse renal events-
Death, Dialysis & Renal
transplant



EXT1/ EXT2 Positive
biopsy has less activity/
chronicity indicator



Chronicity features

Tubular atrophy, p= 0.002

Glomerulosclerosis, p=<0.001

Interstitial fibrosis, p= 0.006



Activity indicators

Endocapillary hypercellularity,
p= 0.012

Fibrocellular crescent, p= 0.007

Cellular crescent, p= <0.001



EXT1/ EXT2
Negative
(n= 200)

EXT1/ EXT2
Positive
(n= 83)

p- value



Median time
(Onset of lupus
& Biopsy)

12m
(IQR, 3-49)

6m
(IQR, 2-25)

p= 0.008



Median time
(Onset of LN &
Biopsy)

6m
(IQR, 2-23)

3m
(IQR, 2-18)

p= 0.039



SLE DAI

14
(IQR, 10-18)

12
(IQR, 8-16)

p= 0.015



Adverse
renal
events

16%

2.4%

p= 0.001

EXT= Exostosin; SLE DAI= SLE disease activity index; LN= Lupus nephritis; m= month (s)

KIREPORTS
Kidney International Reports

Xia X et al, 2024

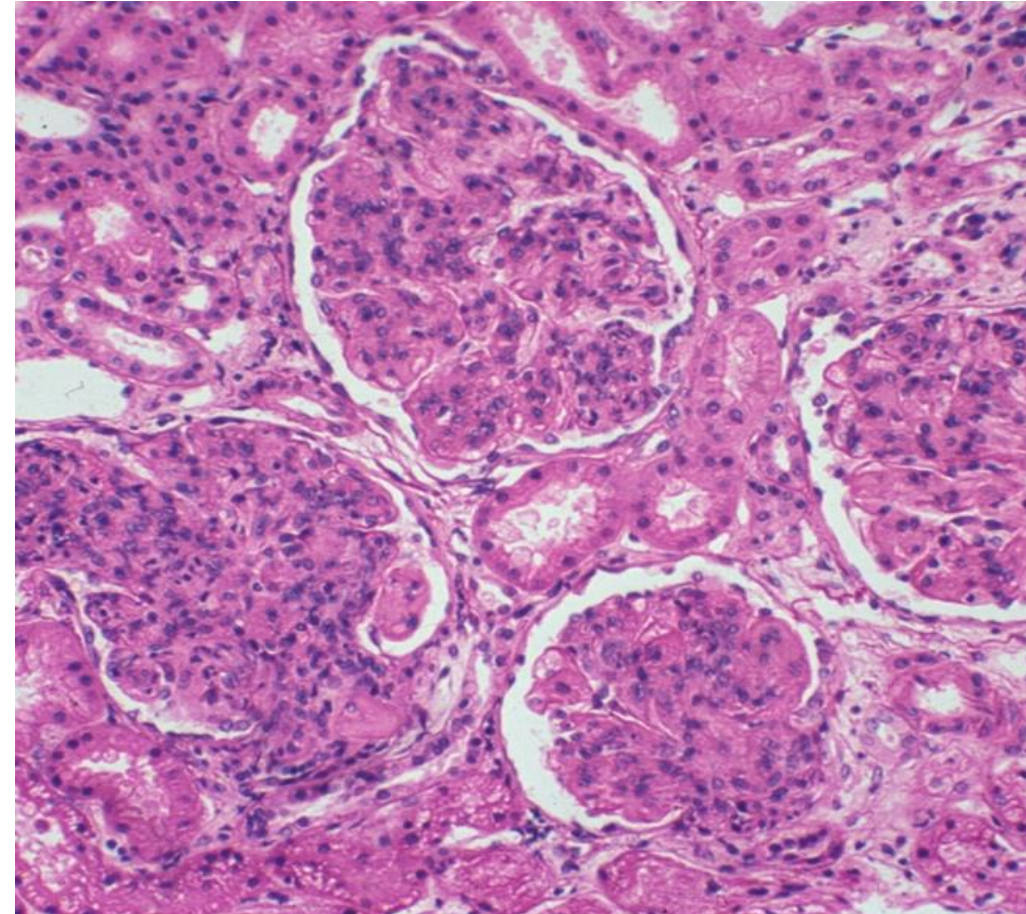
Visual abstract by:
Abdul Qader, MD

✉ @md_abdulqader83

Conclusion Compared with EXT1/ EXT2- negative patients, the EXT1/EXT2-positive patients presented with lower disease activity and were less likely to experience adverse renal events in relation with the chronicity index.

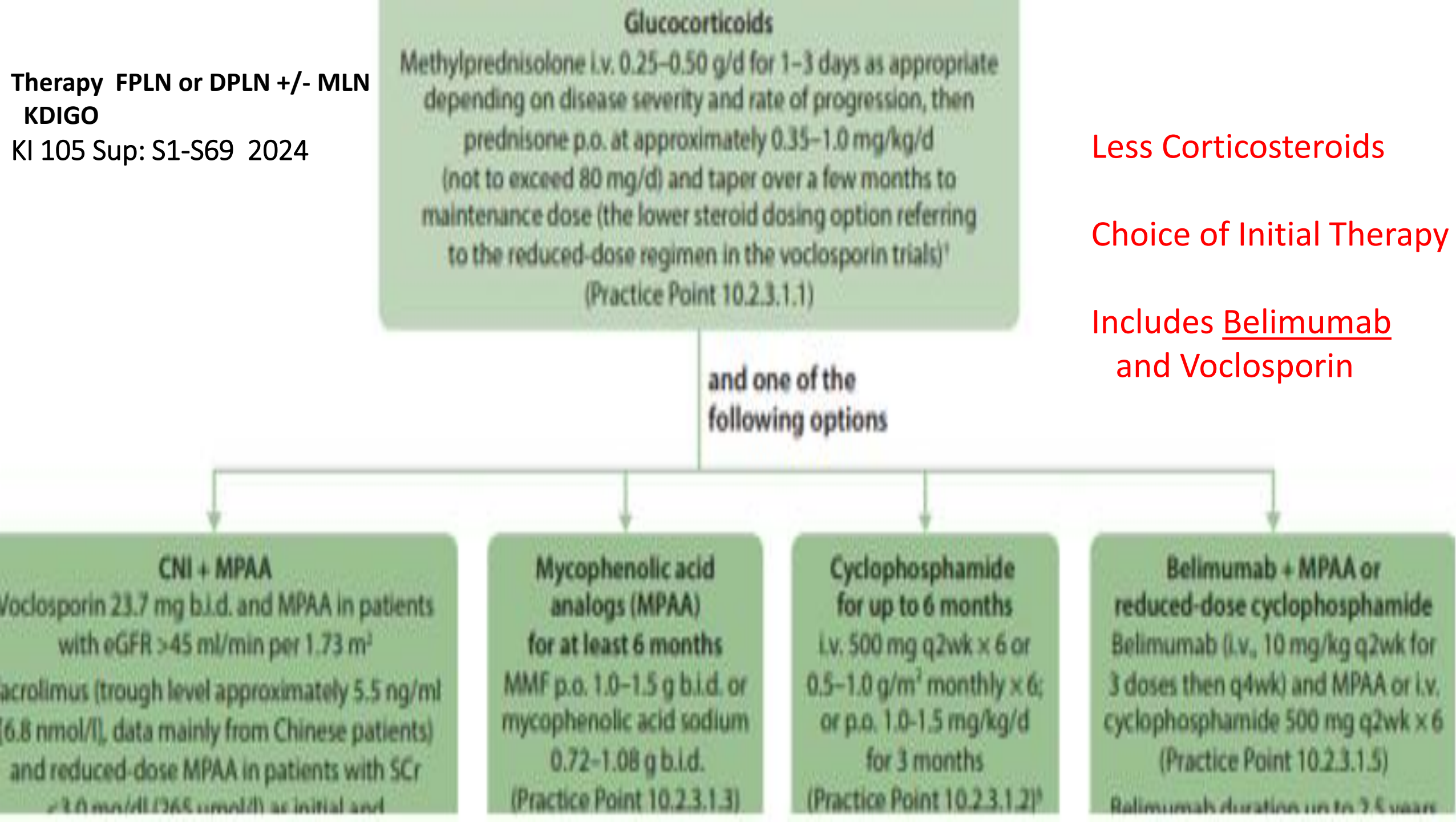
28 yo F with new onset SLE and Diffuse Proliferative LN

- Evaluation shows a BP 145/88 weight 102# afeb and 1+ bilat pedal edema.
- BUN 28 mg/dl creat 1.2 mg/dl alb 3.3 g/dl U/A 3+ prot 3+ bld
- Anti DNA 95 (high) , C3 and C4 low, ESR 68
- **Bx – DPLN with 22/34 glom with proliferative lesions, IF w IgG, IgA, IgM, C3, C1q staining, and EDD in mesangium and many subendothelial.**
- **AI 8/24 CI 1/12.**
- **How would you treat this patient in 2026?**



Therapy FPLN or DPLN +/- MLN
KDIGO

KI 105 Sup: S1-S69 2024



Less Corticosteroids

Choice of Initial Therapy

Includes Belimumab
and Voclosporin

American College of Rheumatology (ACR) 2024 LN

Guideline-Treatment Overview

Class III/IV ± V
Active, newly diagnosed, or flare

Pure Class V*
Active, newly diagnosed, or flare

Hydroxychloroquine and RAAS-I[†]

FIRST LINE (CONTINUOUS) THERAPY
Preferred:

TRIPLE THERAPY

GC pulse/oral taper to ≤5 mg/day by 6 mo.

+

MPAA

+

BEL^a or CNI^b

Alternatives:

TRIPLE THERAPY

GC pulse/oral taper to ≤5 mg/d by 6 mo.

+

Low-dose CYC[‡] + BEL

DUAL THERAPY if TRIPLE THERAPY
Is not available or not tolerated

FIRST LINE (CONTINUOUS) THERAPY
Preferred:

TRIPLE THERAPY

GC pulse/oral taper to ≤5 mg/day by 6 mo.

+

MPAA

+

CNI

Alternatives:

TRIPLE THERAPY

GC pulse/oral taper to ≤5 mg/d by 6 mo.

+

MPAA + BEL or Low-dose CYC[‡] + BEL

DUAL THERAPY if TRIPLE THERAPY
Is not available or not tolerated

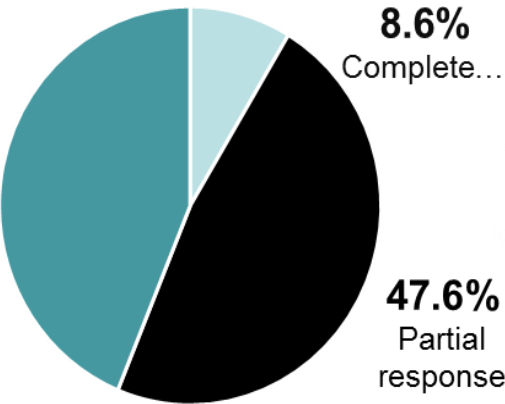
EULAR recommendations for SLE w Kidney Disease

Fanouriakis et al. Ann Rheum Disease 2026: 85:75-90

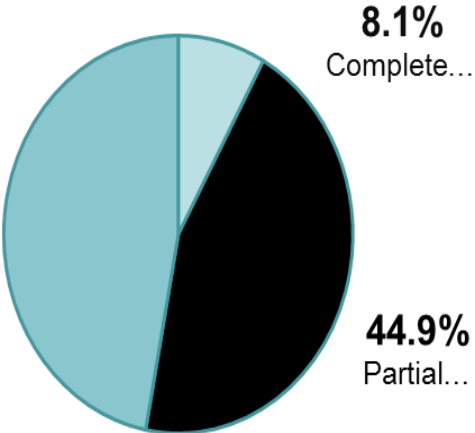
- Kidney Bx for all with evidence of kdy disease (proteinuria > 0.5 g/d ,or 500mg Prot/g Creat. Glom hematuria, unexplained low GFR)
- Goal - Reduction proteinuria 25% by 3 mo, 50% by 6mo and Upr/Ucr < 0.7g/g by 12 mo.
- IV pulse methylpred followed by oral steroids w reduction to < 5 mg/d by 4-6 mo
- For Active LN - triple therapy (steroids + MMF or IV cyclophos with belimumab or steroids + MMF + CNI or steroids + MMF +obinutuzumab. Alt single agent + steroids (double therapy).
- Maintenance therapy for at least 3 years

In Past Complete Response Rates Were Low With Standard-of-Care First-line Therapies

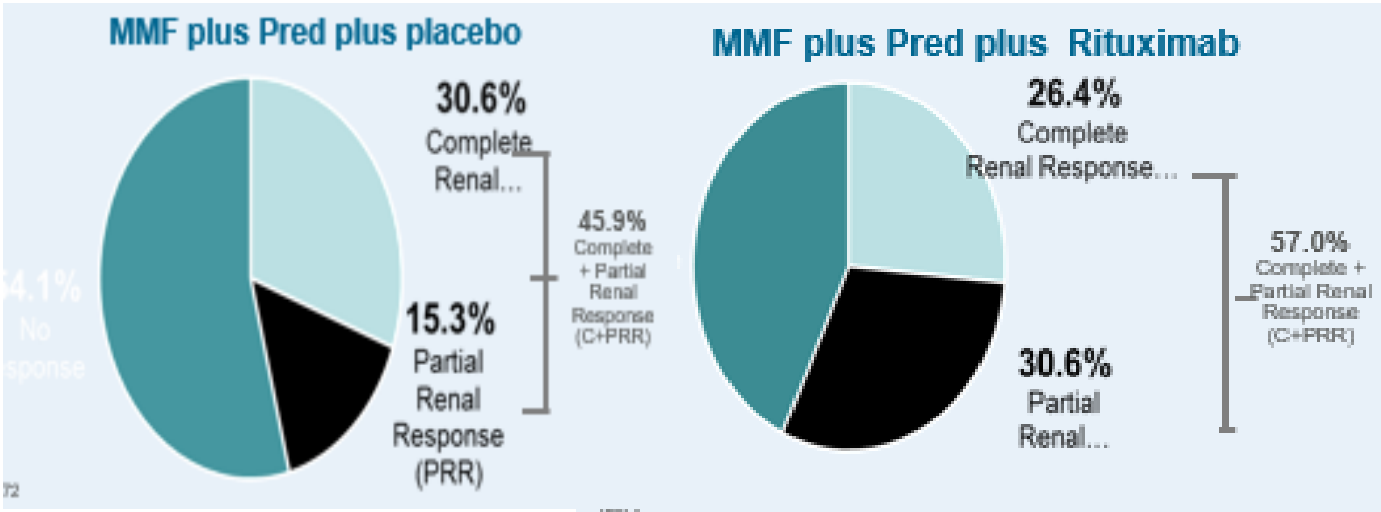
ALMS study MMF



ALM Study Cyclophos



LUNAR Trial MMF + Pred w or w/o Rituximab



Response at 24 weeks

Appel , Contreras, Dooley et al *JASN*. 2009

Response at 52 weeks

Rovin B, ... , Appel GB, et al. *Arth and Rheum*. 2012

Available Newer Treatment Choices for FPLN or DPLN in 2026

- Rituximab
- Belimumab
- Voclosporin (new CNI)
- Obinutuzumab

Ginzler EM Are New Treatments for LN on the Horizon. Kid Int 99:295 2021.

Costedoat-Chalumeau, Houssiau F Improving Adherence in LN. Kid Int. 99:285, 2021.

Anders HJ, Lei Y, Rovin BH Induction and Maintenance of LN Kid Int 99: 288-291,2021.

Furie RA et al. Efficacy and Safety of Obinutuzumab in Active LN NEJM 2025.

Guidelines recommend a proactive approach with triple therapy for initial treatment for III/IV LN¹⁻³

ACR 2024 Guidelines^{2†‡}

recommend triple Rx
preferred initial
treatment for pts with
active, newly diagnosed,
or flaring disease[‡]

KDIGO 2024 Guidelines^{3†}

Recommend triple
therapy as an initial
treatment for patients
with active class III or
IV ± V lupus nephritis

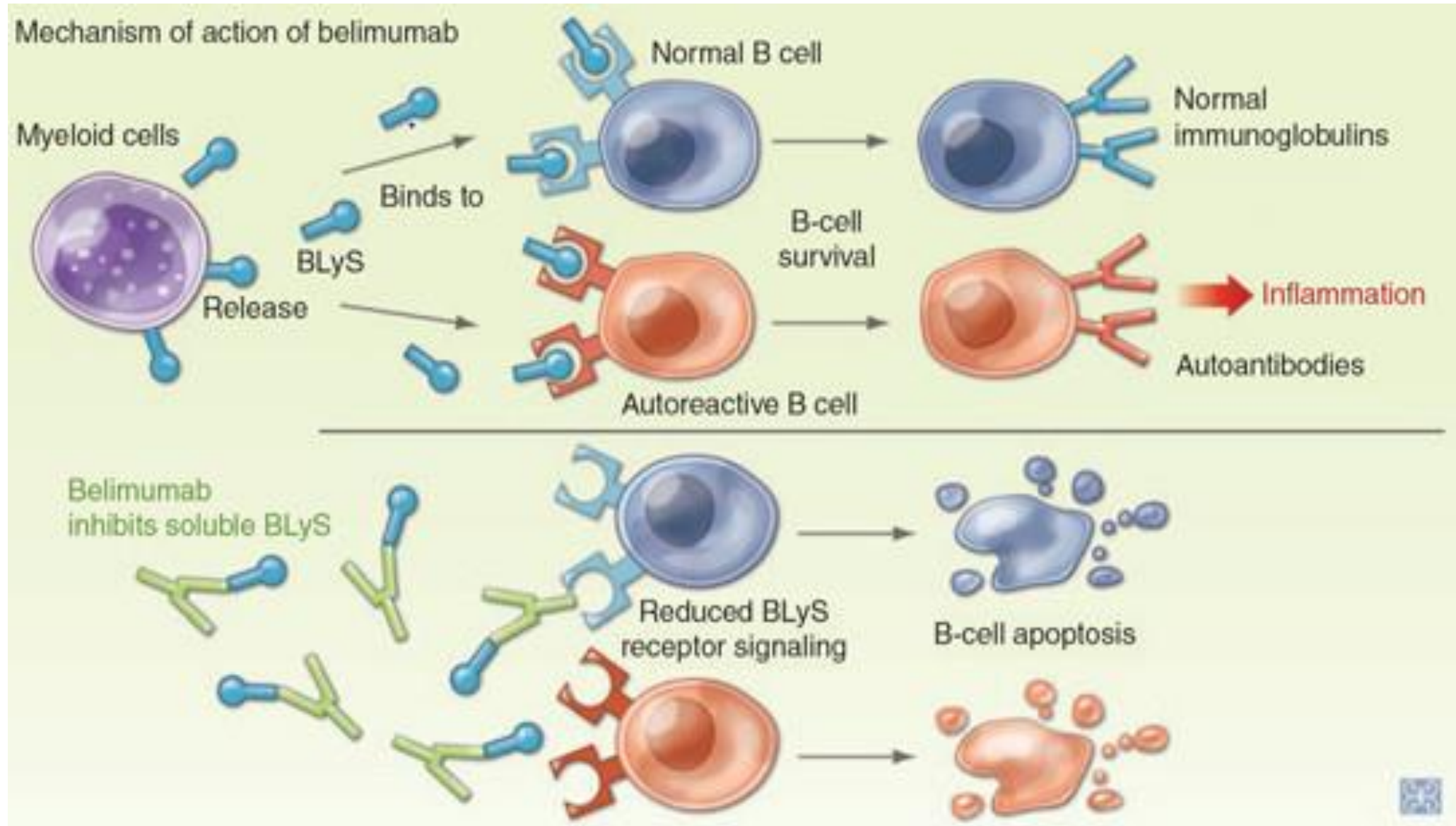
EULAR 2025 Guidelines¹

Recommend early use of
combination therapy for
patients with active lupus
nephritis, especially those
with poor prognostic
factors

**Triple Therapy is Glucocorticoids, MMF + something else (belimumab, tacrolimus or Voclosporin, rituximab /obinutuzumab)
Or Glucocorticoids + Cyclophosphamide + belimumab**

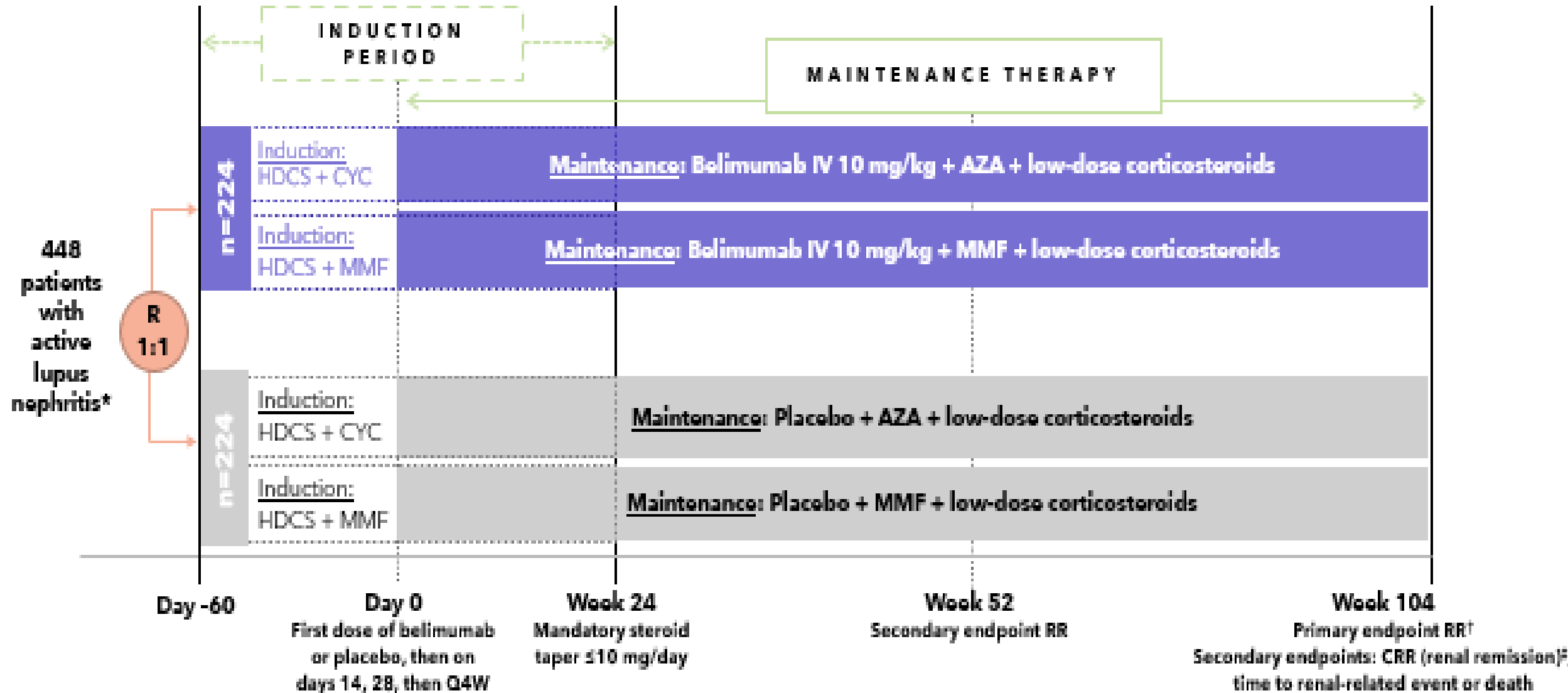
References: 1. Fanouriakis A, et al. *Ann Rheum Dis*. Published online October 16, 2025. doi:10.1016/j.ard.2025.09.007 2. Sammaritano LR. *Arthritis Care Res (Hoboken)*. 2025;77:1045-1065.
3. Kidney Disease: Improving Global Outcomes (KDIGO) Lupus Nephritis Work Group. *Kidney Int*. 2024;105(suppl 1):S1-S69. 4. Patel AM. Poster 1546 presented at: ACR Convergence 2024.

Mechanism of Action of Belimumab in LN



Two year Randomized, controlled Trial of Belimumab in LN

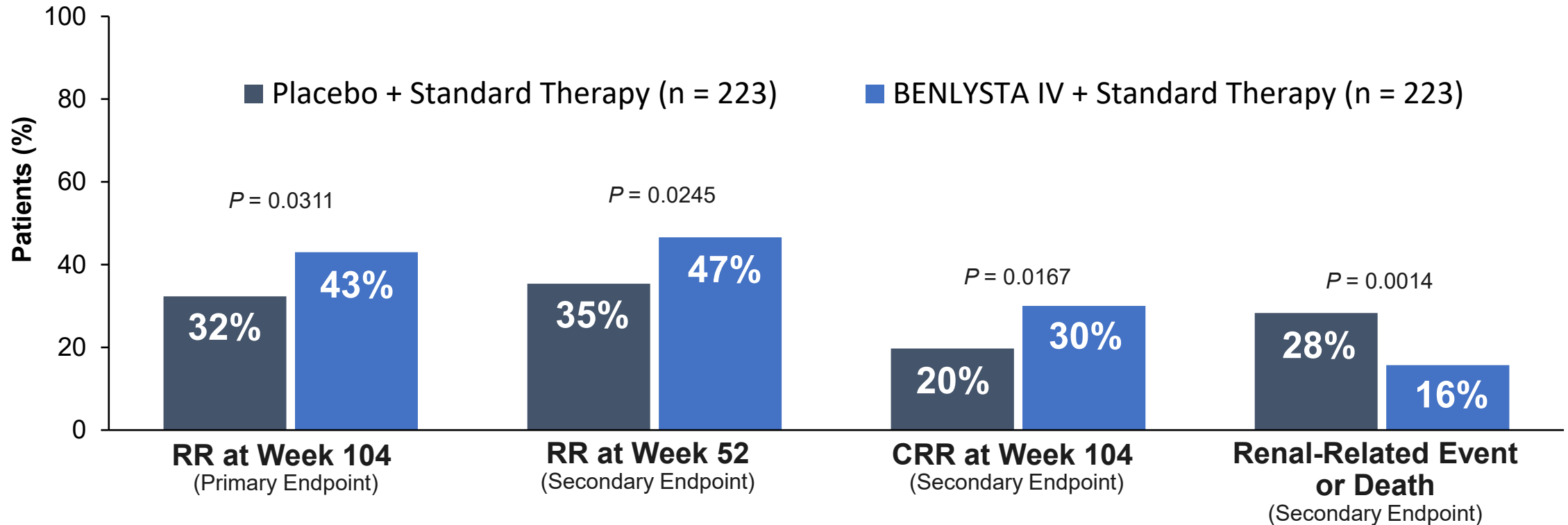
Furie R, Rovin B, Houssiau F, et al NEJM 383: 1117 2020



Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis

Furie R, Rovin B, Houssiau F, et al. NEJM 383:1117, Sept 2020

BLISS-LN Results for Primary and Secondary Endpoints^{1,2}



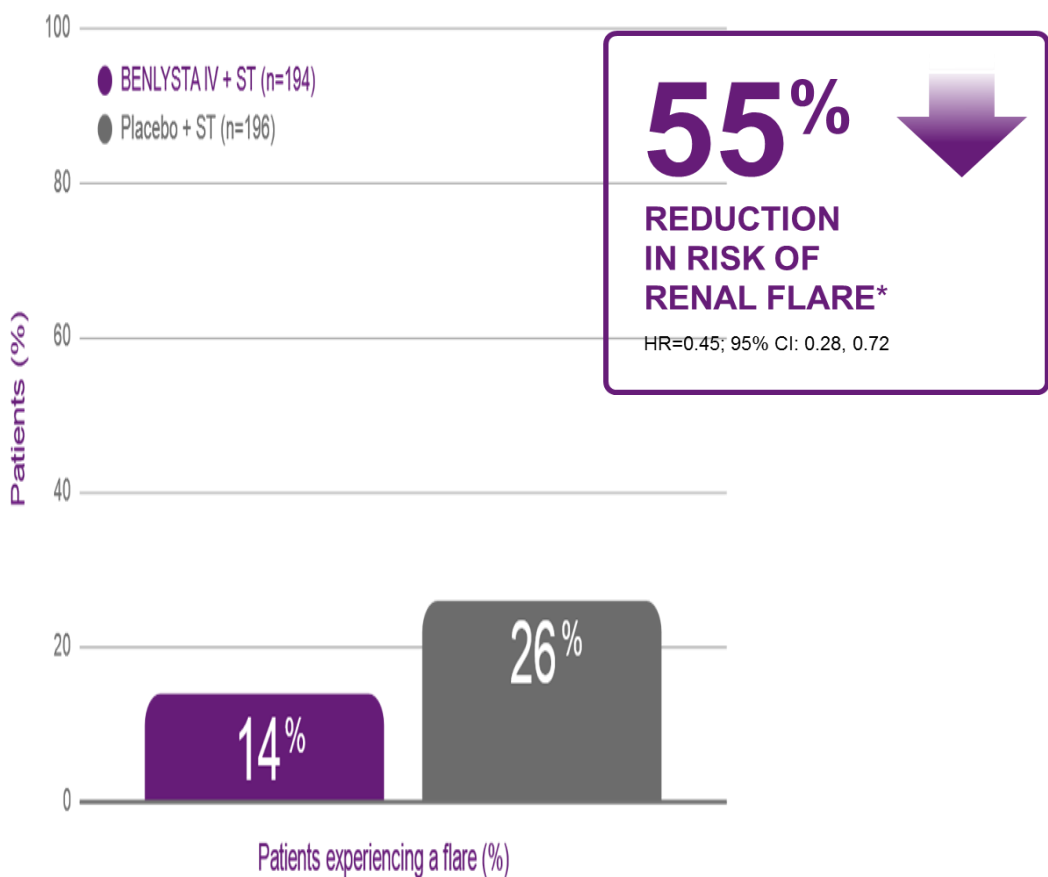
Standard Therapy :

Mycophenolate mofetil (MMF) + glucocorticoids **OR**
cyclophosphamide/azathioprine + glucocorticoids

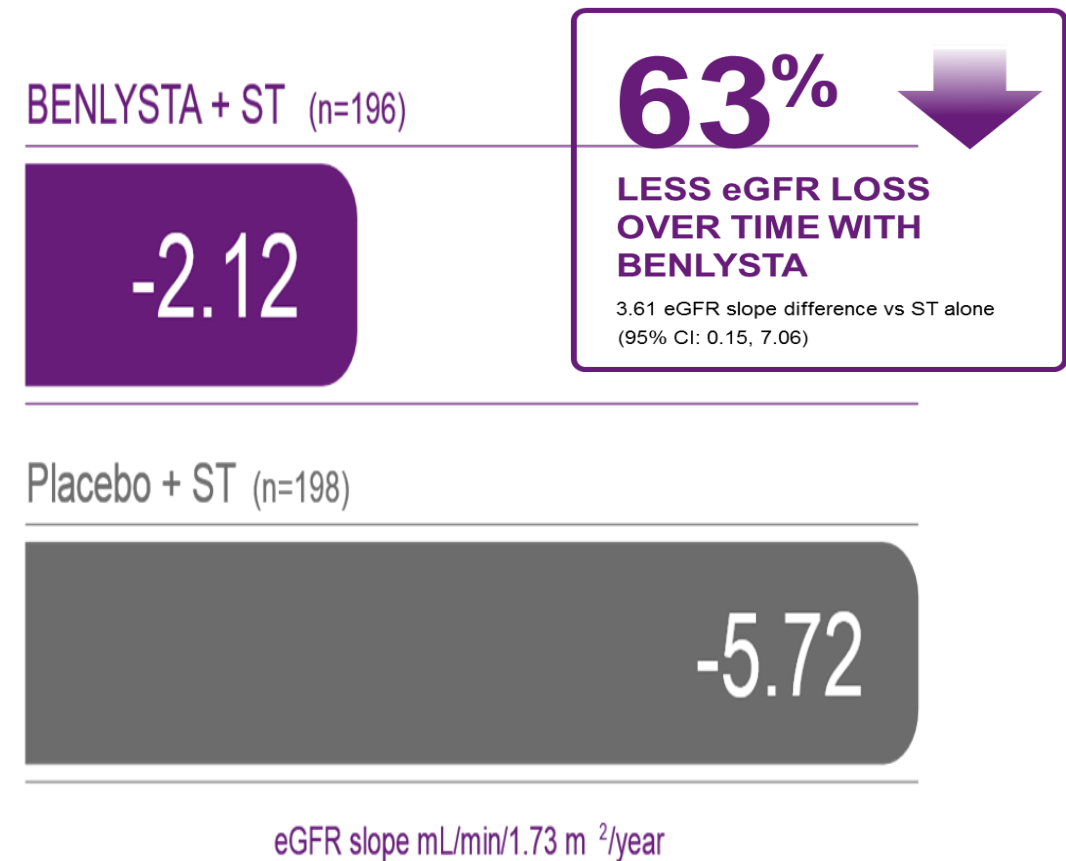
Post Hoc Analysis of BLISS LN Trial

Rovin BH, Furie R, Teng YKO, et al. *Kidney Int.* 2022;101(2):403-413

Patients having ≥ 1 renal flare (Week 24 to 104)

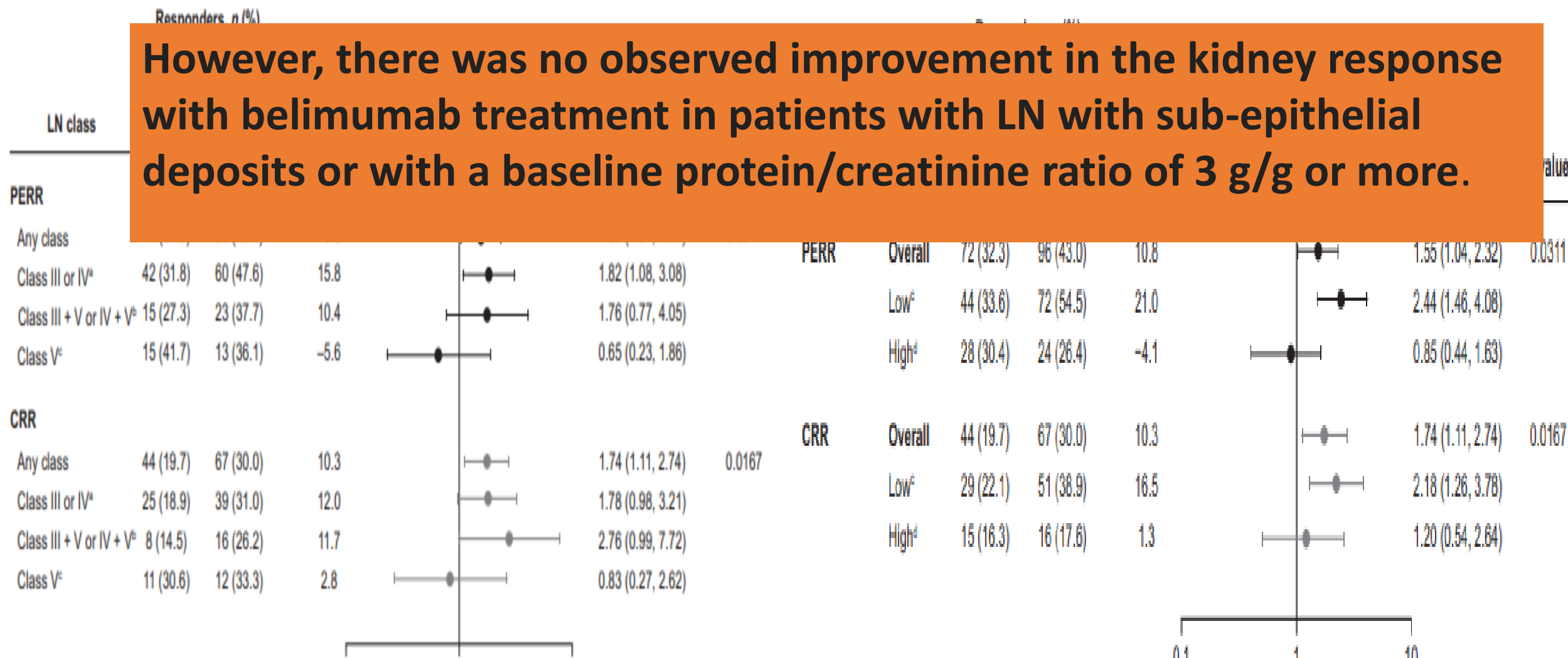


eGFR slope (Week 24 to 104)



Secondary analysis of Belimumab International Study in LN – effects on kidney outcomes, and preservation of kidney function

Rovin BH, Furie R, Teng Y. et al. *Kidney Int.* 2022;101(2):403-413



Results of a subgroup analysis on renal remission (CRR)

In a post hoc subgroup analysis of the secondary endpoint of complete renal response (renal remission) at Week 104¹

Complete renal response (renal remission) results at Week 104 by induction regimen and baseline uPCR level¹

	MMF		CYC	
	<3 g/g	≥3 g/g	<3 g/g	≥3 g/g
BENLYSTA + ST	43.0% (n=100)	20.3% (n=64)	25.0% (n=32)	11.1% (n=27)
Placebo + ST	22.4% (n=98)	16.7% (n=66)	21.2% (n=33)	15.4% (n=26)

The mITT subpopulation from the BLISS-LN trial was analyzed based on current treatment guidelines and expert opinion.^{2,3}

Post hoc analysis. Results are descriptive. Caution should be used when interpreting the data due to limitations such as small sample size and no adjustments for multiplicity.

mITT = modified Intention-to-Treat; MMF = mycophenolate mofetil; ST = standard therapy; uPCR = urine protein: creatinine ratio.
1. Data on file. GSK. **2.** Rovin BH, et al. *Kidney Int.* 2022; 101(2):403-413. **3.** Fancouriakis A, et al. *Ann Rheum Dis.* 2024;83(1):15-29.

Insights from the BLISS-LN Phase 3 study of biomarker associations with kidney response to belimumab in lupus nephritis

kidney
INTERNATIONAL



Aim

To evaluate **biomarker responses** and identify predictive **biomarkers of kidney response to belimumab** in patients with LN from the previously published BLISS-LN study

Methods



BLISS-LN
(NCT01639339)

104-week, double-blind study
446 adults (mITT population)
with active LN



Belimumab IV
10 mg/kg
N=223

R
1:1



Placebo
N=223

In addition to standard therapy:
CYC/AZA or MMF

Clinical measures

- PERR at Week 104
- CRR at Week 104

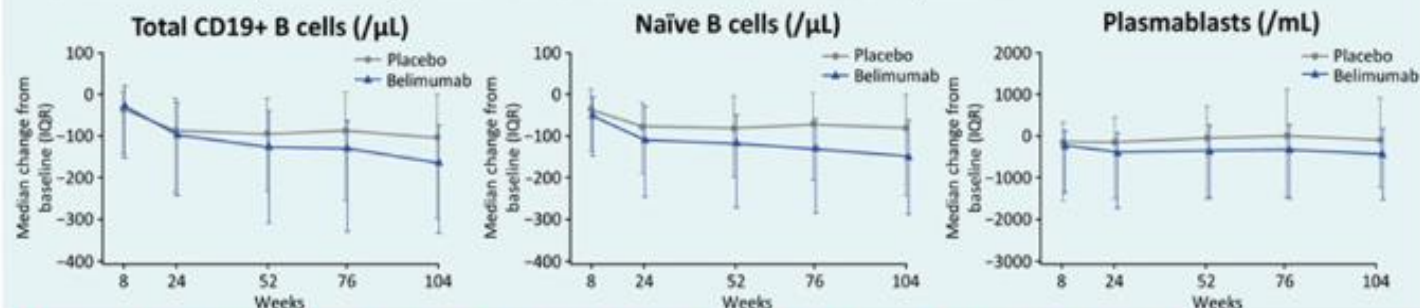
Biomarkers over 104 weeks

- Complement
- Immunoglobulins
- Autoantibodies
- CD19+ B cells
- B-cell subsets

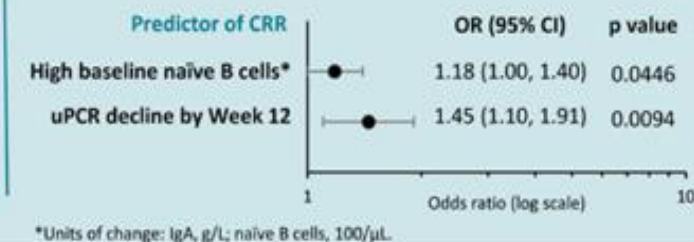
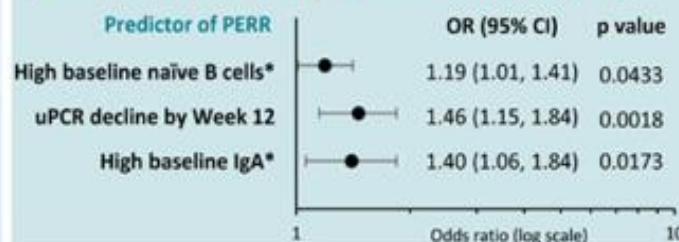
Results

Descriptive biomarker analysis over 104 weeks

- 36% and 14% of patients receiving belimumab and placebo, respectively, shifted from **positive to negative anti-dsDNA antibodies**
- Belimumab-treated patients had greater absolute reductions** than placebo-treated patients in:



Strongest predictive biomarkers of kidney response (PERR or CRR) in belimumab-treated patients at Week 104 (by univariate analysis)



Rovin et al. 2025

This analysis of the BLISS-LN study (GSK Study BEL114054; NCT01639339) was funded by GSK.

AZA, azathioprine; CI, confidence interval; CRR, complete renal response; CYC, cyclophosphamide; dsDNA, double-stranded deoxyribonucleic acid; Ig, immunoglobulin; IV, intravenous; LN, lupus nephritis; mITT, modified intention-to-treat; MMF, mycophenolate mofetil; OR, odds ratio; PERR, primary efficacy renal response; R, randomization; uPCR, urine protein/creatinine ratio.

CONCLUSION

Belimumab- versus placebo-treated patients had a better overall improvement in serologies. Additionally, novel baseline or early change from baseline biomarkers were identified as predictive of kidney response to belimumab at 2 years.

A prospective multi-center randomized controlled trial preemptive increase in immunosuppression for asymptomatic serological reactivation in patients with lupus nephritis in clinical remission

kidney
INTERNATIONAL



Methods and Cohort



Clinically stable lupus nephritis (LN) patients with asymptomatic serological reactivation receiving maintenance treatment with low-dose prednisolone (Pred) and mycophenolate (MMF) or azathioprine (AZA)

Prospective multi-center RCT to compare **pre-emptive treatment (PT)** vs. **observant management (Control)**

Primary outcome: 24-month survival free of renal flares

Secondary outcomes: survival free of extra-renal flares, change in renal and immunological parameters, adverse events (AEs)

Intervention

PT: ↑Pred from ≤ 5 mg/D to 0.4-0.5 mg/kg/D and
↑MMF to 1.5 g/D or
↑AZA to 100 mg/D

then taper Pred to original dose by 12 weeks

V.S.

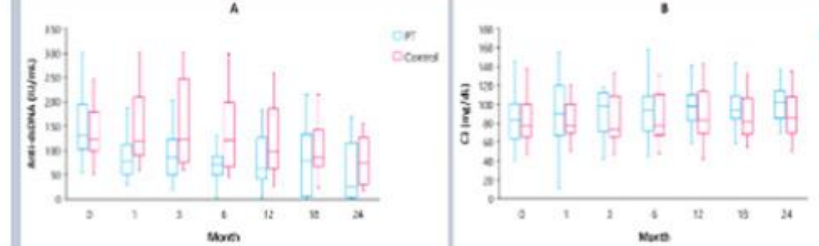
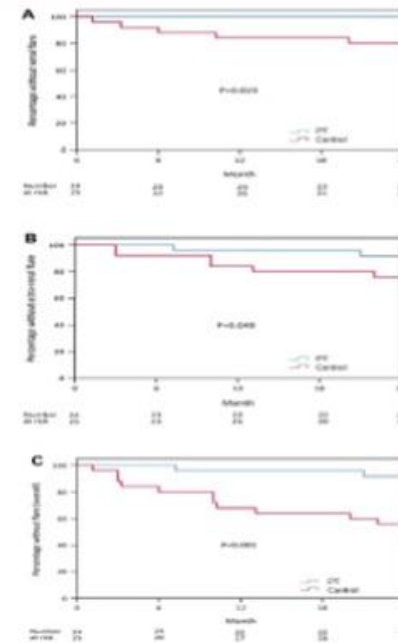
Control: Current immunosuppressive treatment unchanged



Patients followed for 24 months after randomization

Findings

49 patients randomized (PT – 24 ; Control - 25)



Preemptive treatment reduced anti-dsDNA titre



Preemptive treatment did not increase AE



Stable kidney function in both groups

PT - superior 24-month survival rate free of renal (also extra-renal & overall) flare

	Renal Flares	Extra-renal Flares	Any Clinical Flares
NNT to prevent one flare	5	4	2

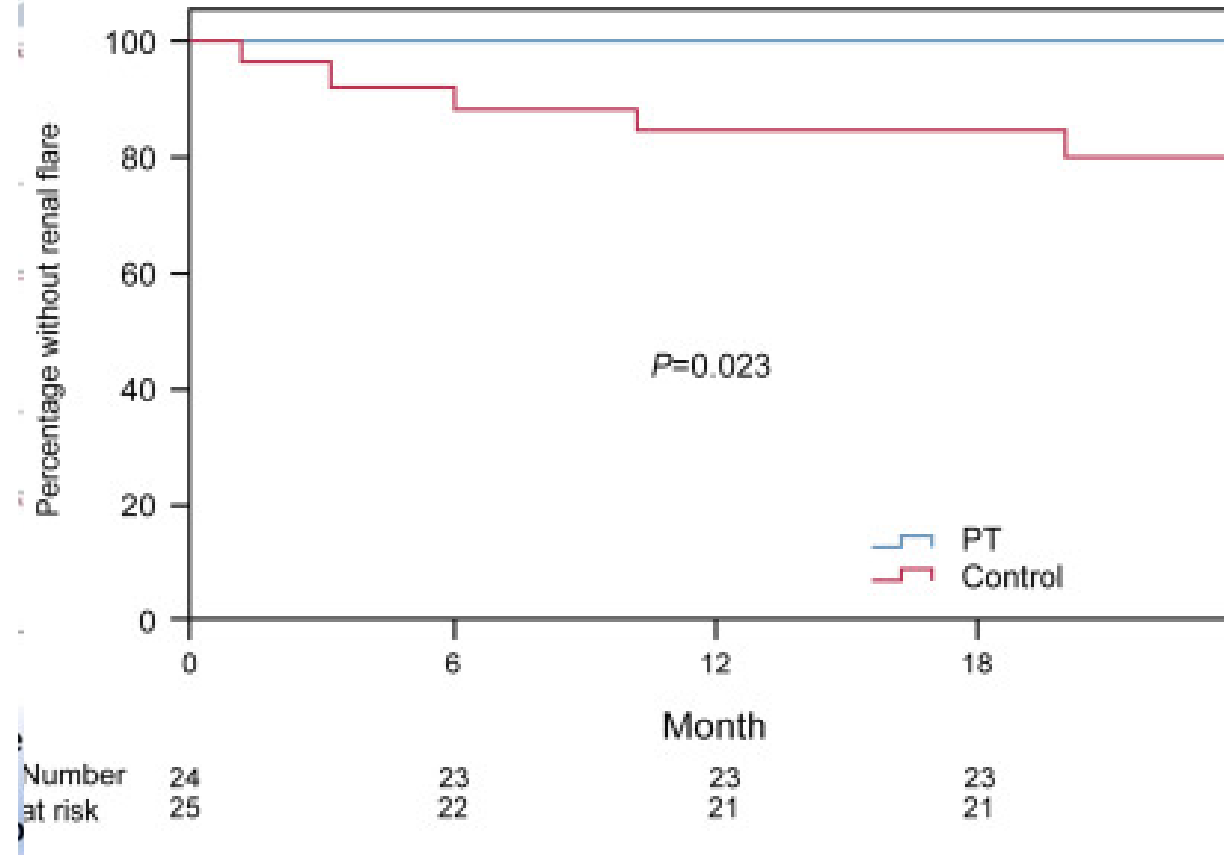
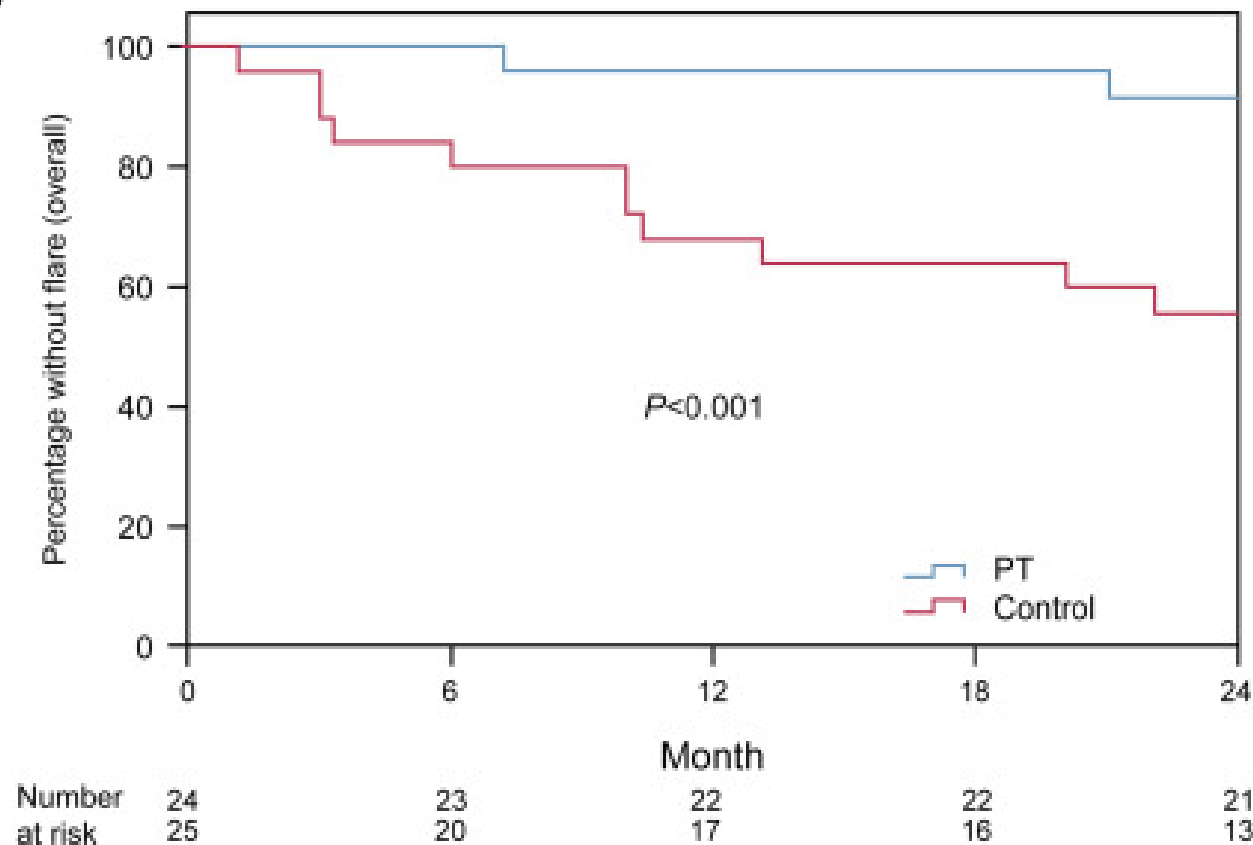
YAP DY, et al. 2026

CONCLUSION

Preemptive moderate increase of immunosuppression was effective in preventing renal flares in LN patients with asymptomatic serological reactivation, and was well-tolerated.

A prospective multi-center randomized controlled trial preemptive increase in immunosuppression for asymptomatic serological reactivation in patients with lupus nephritis in clinical remission

C



YAP DY, et al. 2026

CONCLUSION

Preemptive moderate increase of immunosuppression was effective in preventing renal flares in LN patients with asymptomatic serological reactivation, and was well-tolerated.



Methods



142 hospitals
27 countries
Double-blind



357 patients with
active class III-V
lupus



All received 2g/day
MMF and tapered
steroids

Complete Renal Response

- ✓ UPCR < 5 mg/mg
- ✓ stable GFR
- ✓ no rescue Rx

52 week

24 week

Serious Adverse Events

Placebo

n=178



23%

OR 2.65

95% CI (1.64-4.27)

Voclosporin

n=179



41%

20%

OR 2.23

95% CI (1.34-3.72)

21%

21%

Conclusions: There was superior efficacy of voclosporin compared with placebo in combination with MMF and low-dose steroids in the treatment of class III-V lupus nephritis, with comparable safety profile.

Rovin BH et al. Lancet 2021.
PMID 33971155



@katierizzolo

Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1) The Lancet May 7, 2021

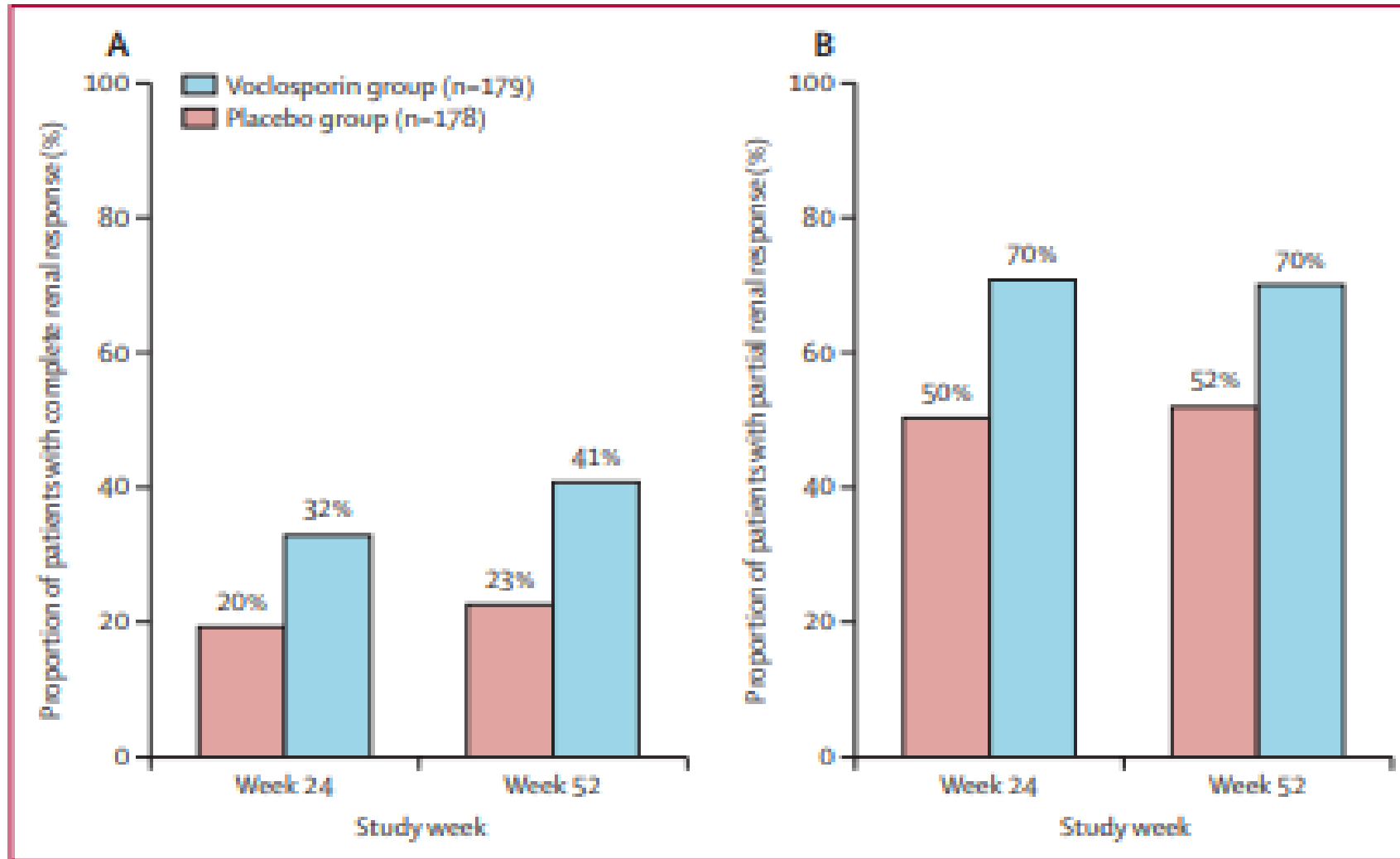
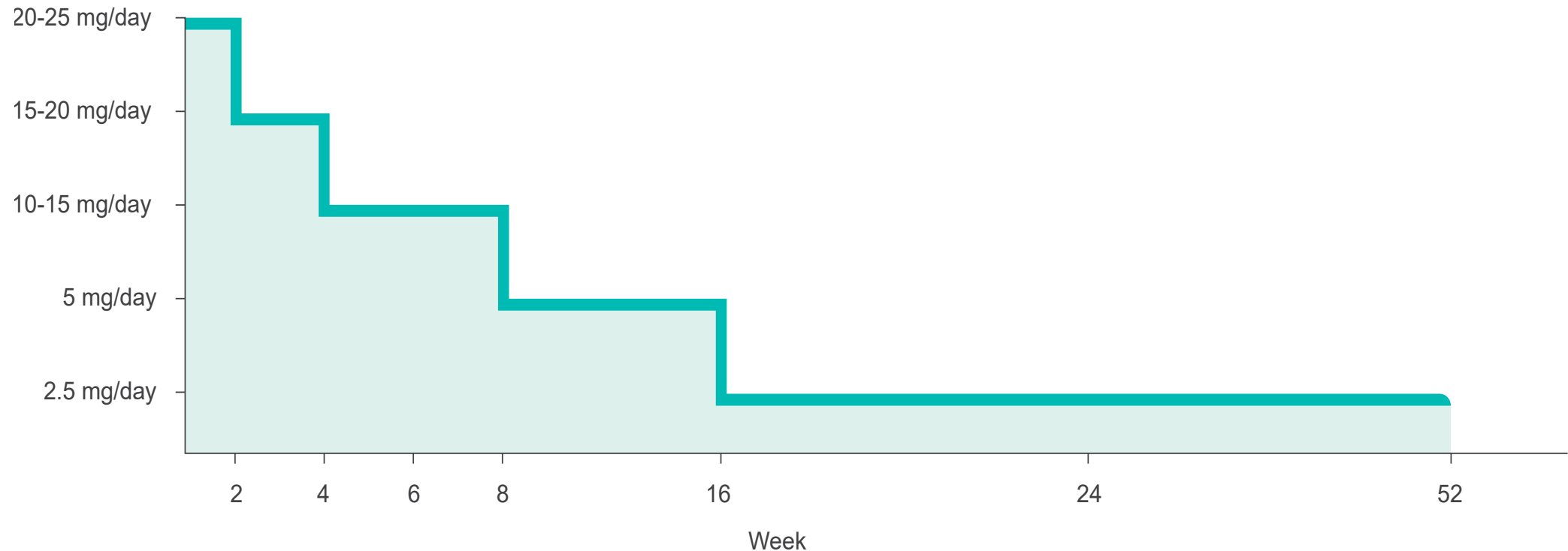


Figure 2: Complete and partial renal response endpoints (intention-to-treat population)

Efficacy and safety of voclosporin vs PBO for lupus nephritis (AURORA 1) The Lancet May 7, 2021

Study included scheduled steroid taper from 20-25 mg/day at Week 1 to 2.5 mg/day by Week 16¹.

^a **>80%** of patients were able to achieve a steroid taper to ≤ 2.5 mg/day by Week 16^{1,2}
^a (LUPKYNIS, n=142/174; control, n=138/171)



Long-Term Voclosporin Treatment for Lupus Nephritis Is Safe and Effective

1 3 years of voclosporin treatment studied

AURORA 1
Randomized One-year
Phase 3 Clinical Trial

AURORA 2
Continuation Two-year
Phase 3 Clinical Trial

Voclosporin + MMF
+ GC (n=179)

Voclosporin + MMF + GC (n=116)

Placebo + MMF +
GC (n=178)

Placebo + MMF + GC (n=100)

GC target 2.5 mg/day by week 16 and thereafter; MMF target 2 gm/day

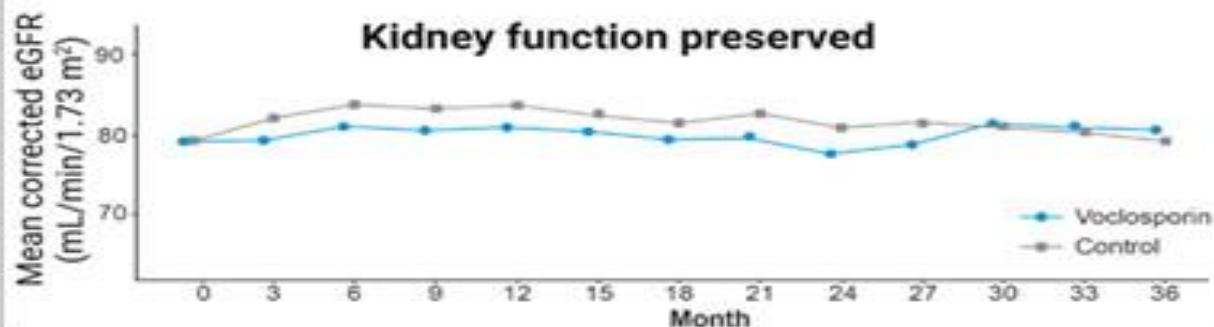
2 Long-term voclosporin treatment safe and well-tolerated



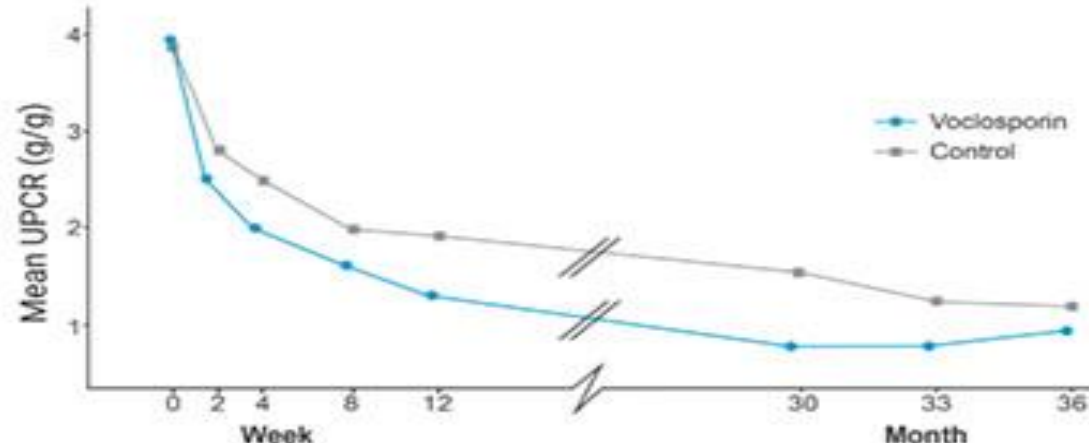
86.1%
completed
AURORA 2



Comparable AEs in
both groups



3 Rapid and persistent proteinuria reductions



Voclosporin-treated patients had more rapid and greater reductions in UPCR compared to control, maintained with continued treatment

Complete Renal Response at Month 36



AE = adverse event; CI = confidence interval; eGFR = estimated glomerular filtration rate; GC = glucocorticoid; MMF = mycophenolate mofetil; UPCR = urine protein-to-creatinine ratio.

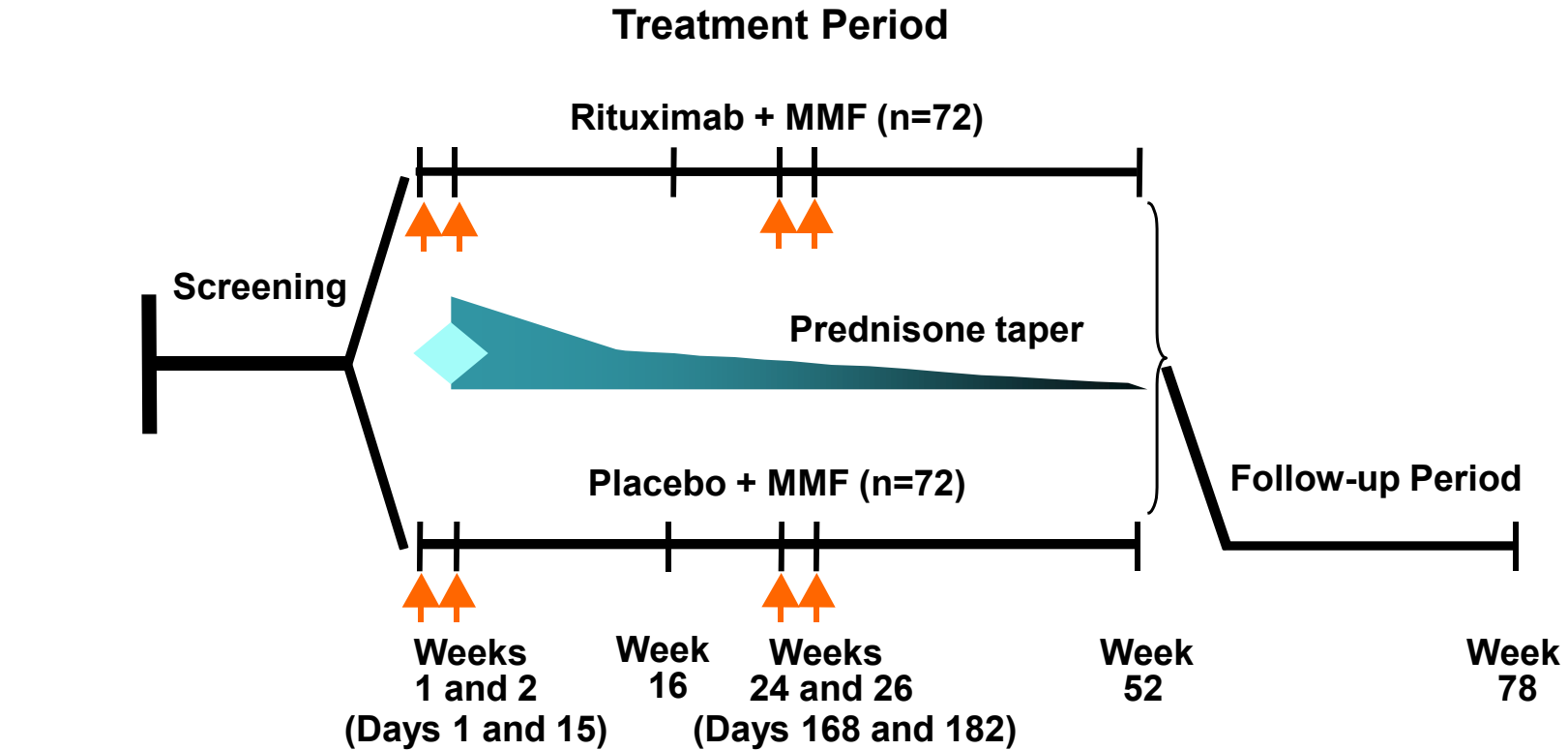
Saxena A, Ginzler E, Gibson K, et al. Safety and efficacy of long-term voclosporin treatment for lupus nephritis in the Phase 3 AURORA 2 clinical trial. *Arthritis Rheumatol* 2023.

Arthritis & Rheumatology ACR
American College of Rheumatology

Saxena A, Ginzler E, Gibson K et al. *Arthritis and Rheumatol*. 76:59-67, 2024

LUNAR – RITUXIMAB Study Design

Rovin B, Furie R, Latinas K , Appel GB et al Arthritis and Rheum 2012.



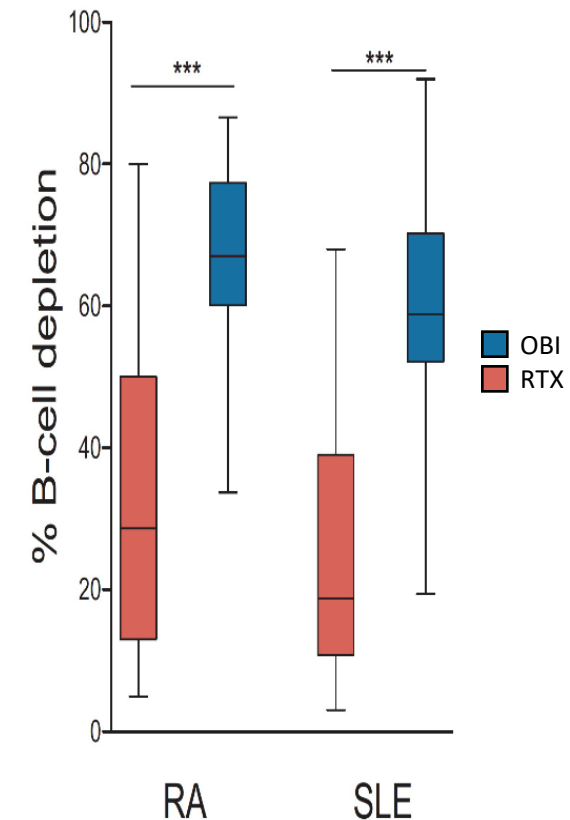
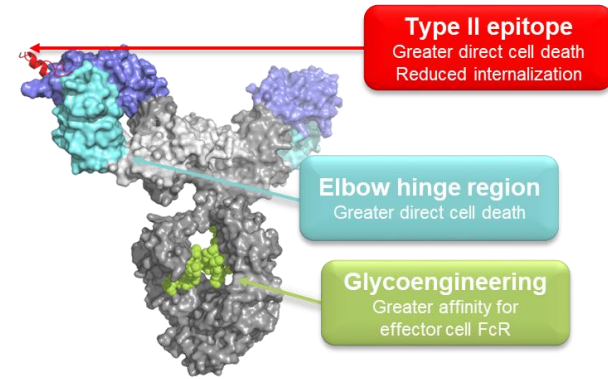
↑ = Study drug infusion.

◆ = Corticosteroids:

- 1000 mg IV methylprednisolone given at days 1 and then days 2, 3, or 4
- Oral prednisone initiated at 0.75 mg/kg/day after IV steroids and then tapered to 10 mg/day by day 112

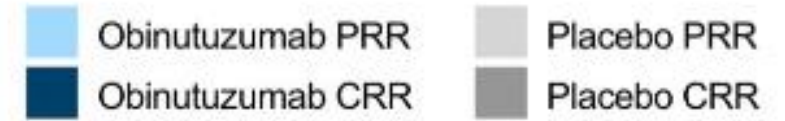
Obinutuzumab

- A **humanized** type II anti-CD20 monoclonal antibody **FDA approved** for combination treatment of CLL and follicular lymphoma¹.
- Compared to rituximab it has:
 - **Glycoengineering**: Up to 100x antibody-dependent cytotoxicity^{2,3}
 - **Type II binding conformation**: Greater direct cell death, reduced internalization, less reliance on complement-dependent cytotoxicity^{2,3}
- **Obinutuzumab results in superior B cell depletion vs. rituximab in tissue³ and SLE patient samples⁴**
- Obinutuzumab was superior to rituximab in head-to-head trials in B-cell malignancies^{5,6}

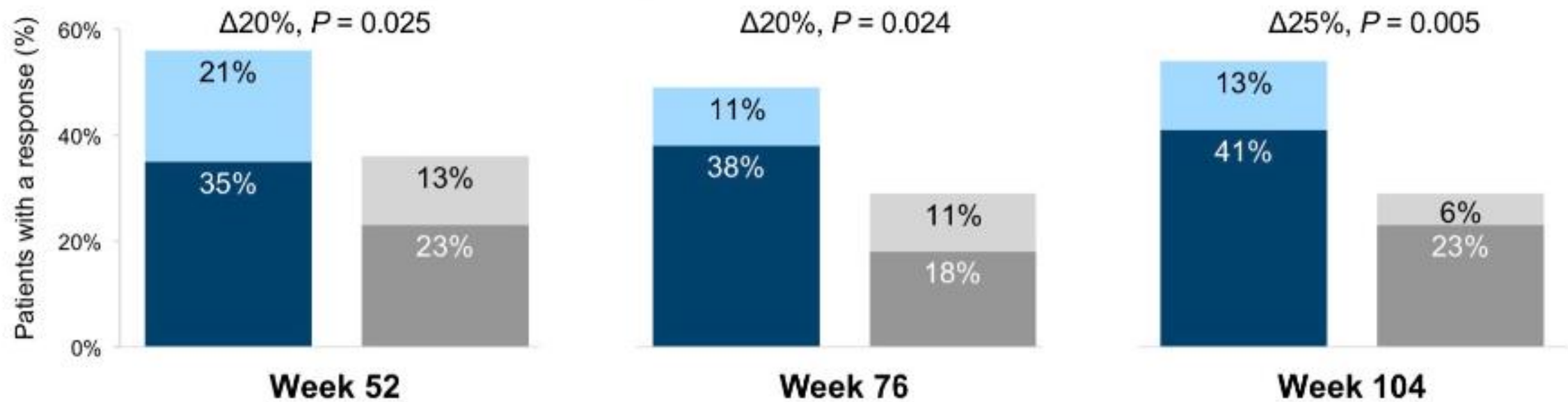


Phase 2 Randomized, Controlled Trial of Obinutuzumab w Mycophenolate and Corticosteroids in Proliferative Lupus Nephritis -NOBILITY

Renal response endpoints



Overall renal response (CRR or PRR)



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

PRR required all of:

- UPCR ≥ 50% reduction to <1 (to <3 if baseline ≥3)
- Serum creatinine ≤ 115% of baseline value
- RBC ≤50% above baseline or <10 RBC/hpf

ORIGINAL ARTICLE

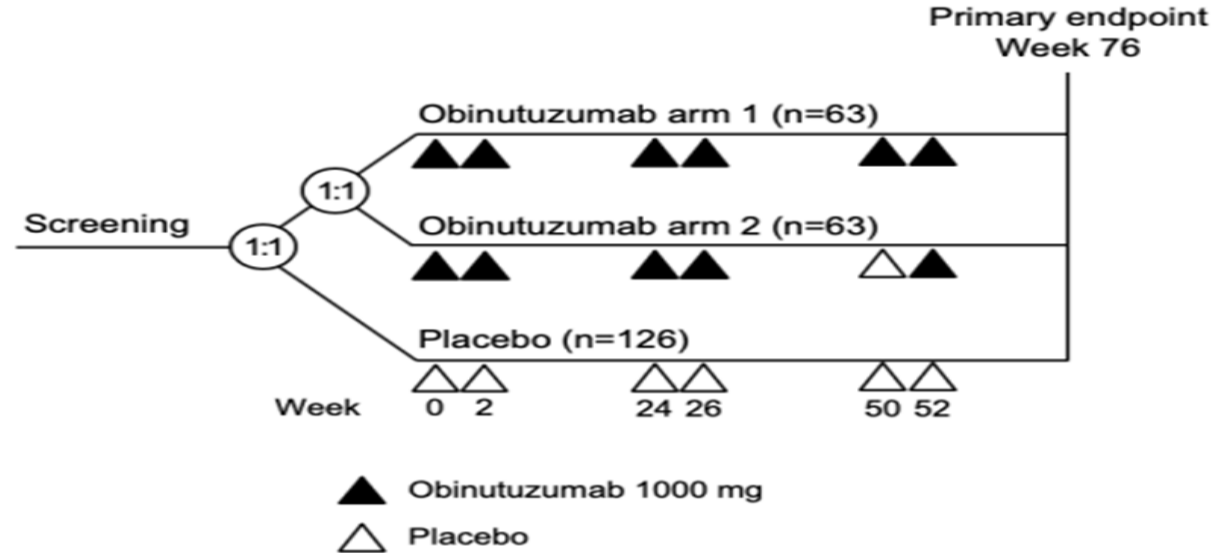
Efficacy and Safety of Obinutuzumab in Active Lupus Nephritis

R.A. Furie,¹ B.H. Rovin,² J.P. Garg,³ M.B. Santiago,^{4,5,6} G. Aroca-Martínez,^{7,8} A.E. Zuta Santillán,⁹ D. Alvarez,¹¹ C. Navarro Sandoval,¹⁰ A.M. Lila,¹³ J.A. Tumlin,¹⁴ A. Saxena,¹⁵ F. Irazoque Palazuelos,¹⁶ H. Raghu,³ B. Yoo,³ I. Hassan,¹⁷ E. Martins,¹⁸ H. Sehgal,¹⁸ P. Kirchner,¹⁸ J. Ross Terres,³ T.A. Omachi,³ T. Schindler,¹⁸ W.F. Pendergraft III,³ and A. Malvar,¹² for the REGENCY Trial Investigators*

ABSTRACT

BACKGROUND

Obinutuzumab, a humanized type II anti-CD20 monoclonal antibody, provided significantly better renal responses than placebo in a phase 2 trial involving patients with lupus nephritis receiving standard therapy.



All patients receive MMF and a prednisone taper

Phase 3 randomized, internat. trial . 271 Pts
1:1 Obi vs PBO w all pts getting MMF + low dose pred.

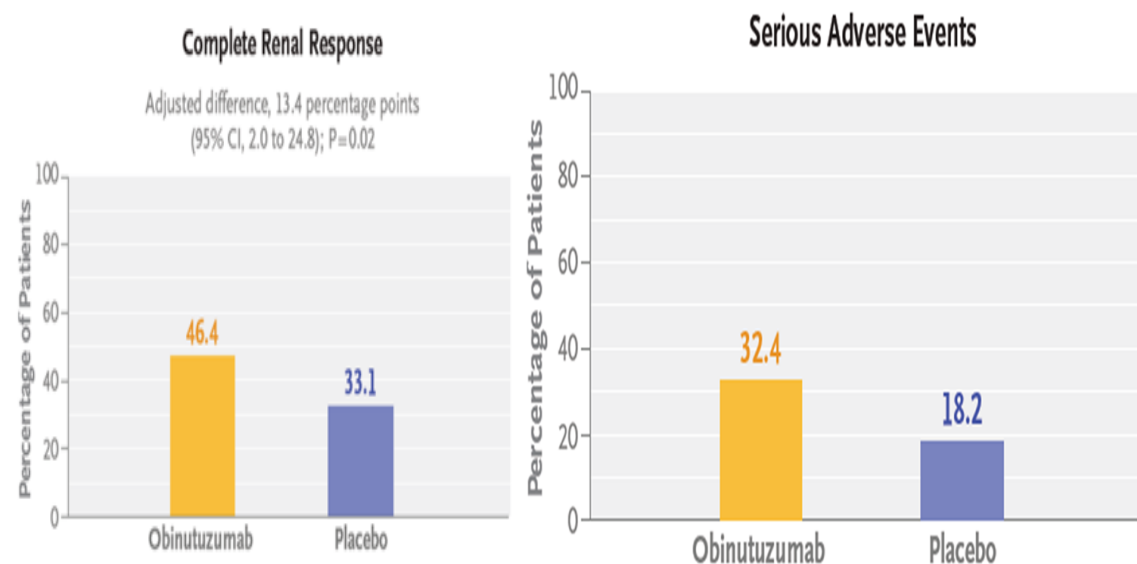
Primary endpoint CRR by wk 76 w UpUcr <0.5 , eGFR 85% baseline, no intercurrent bad event

Secondary endpoint wk 76 CRR + < 7.5 mg pred.

CRR at wk 76 46% Obi and 33% PBO.

Uprot/Ucreat < 0.8 in 55% Obi and 41% PBO .

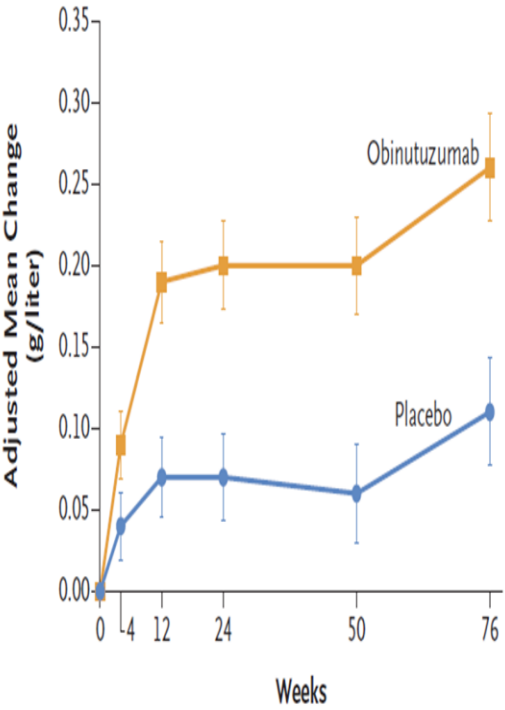
No difference in SAE except more COVID with Obi



Efficacy and safety of Obinutuzumab in LN

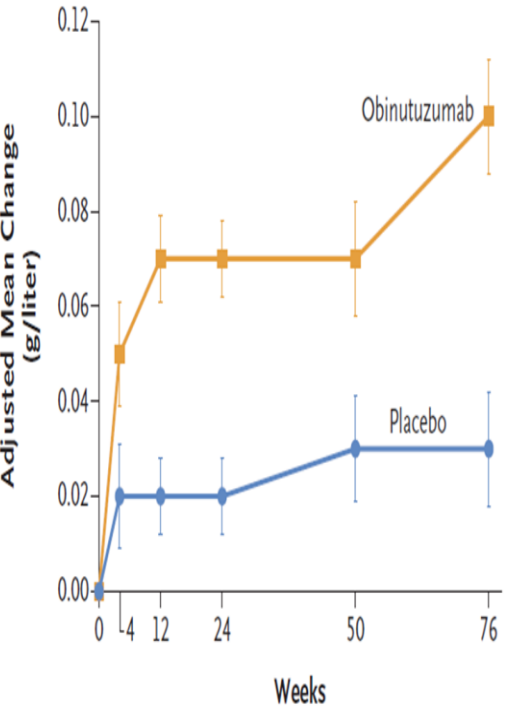
Furie et al. NEJM Feb 7 , 2025

A Change in C3 Complement Level from Baseline



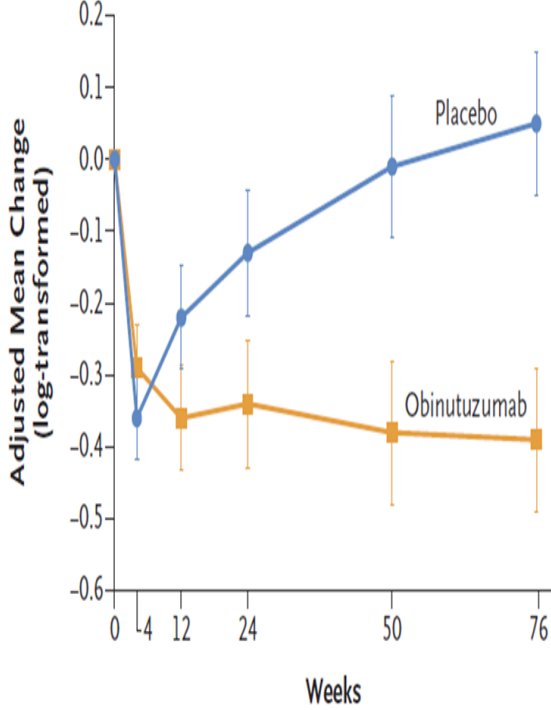
No. of Patients	271	271	271	271	271	271
No. with Missing Data	0	10	10	14	22	26

B Change in C4 Complement Level from Baseline



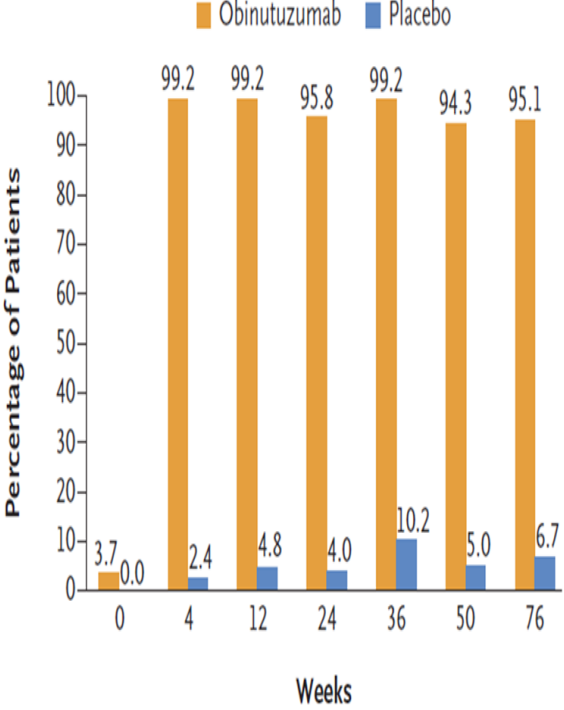
No. of Patients	271	271	271	271	271	271
No. with Missing Data	1	11	11	16	24	27

C Change in Anti-dsDNA Antibody Level from Baseline



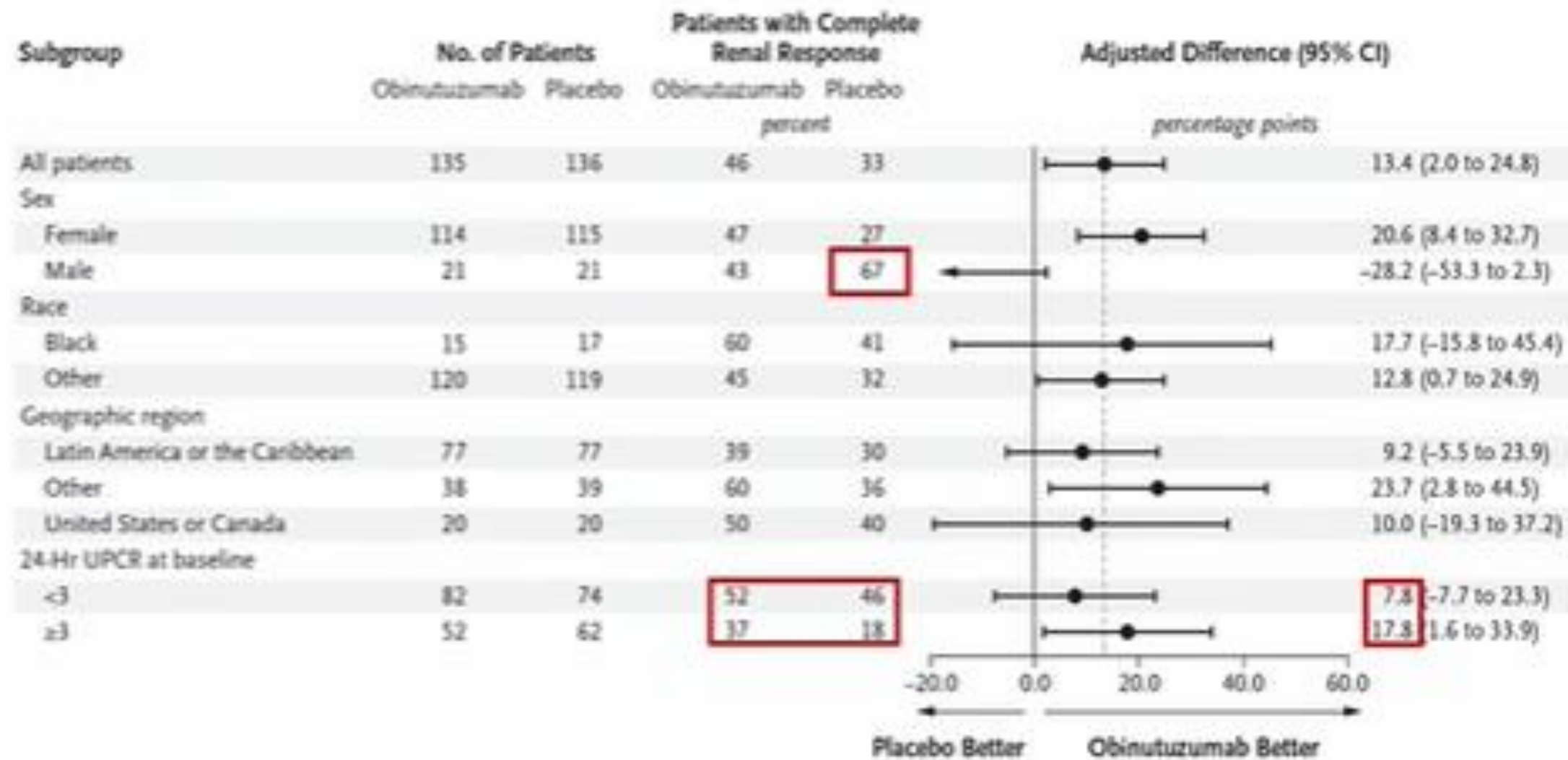
No. of Patients	271	271	271	271	271	271
No. with Missing Data	0	7	10	22	27	27

D Patients with B-Cell Depletion over Time



No. of Patients	135	132	128	125	127	126	119	125	126	128	123	120	123	120
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Phase 3 REGENCY Subgroup Analysis



ORIGINAL ARTICLE

Efficacy and Safety of Obinutuzumab in Active Systemic Lupus Erythematosus

R.A. Furie,^{1,2} M. Dall'Era,³ E.M. Vital,^{4,5} J.P. Garg,⁶ F. Irazoque Palazuelos,⁷ A.E. Zuta Santillán,⁸ J. Ravelo-Hernández,⁹ M.B. Santiago,^{10,12} B. Zazueta Montiel,¹³ S. Botha,¹⁴ P. Leszczyński,¹⁵ V.A. de Souza,¹⁶ S.A. Sicsik,¹⁷ L. Bellatin,¹⁸ A. Naidoo,¹⁹ Z. Amoura,²⁰ M.A. D'Agostino,^{21,22} S. Kumar,²³ B. Workeneh,²⁴ J. Rae,⁶ H.A. Mao,²⁵ F. Erblang,²⁶ O. Meier,²⁶ J.C. Maller,⁶ and A.D. Askanase,²⁷ for the ALLEGORY Trial Investigators*

ABSTRACT

BACKGROUND

Obinutuzumab, a glycoengineered type II anti-CD20 monoclonal antibody, induces potent B-cell depletion and is approved for the treatment of active lupus nephritis. Its efficacy and safety in patients with active systemic lupus erythematosus (SLE) are yet to be determined.

METHODS

We conducted a phase 3, multicenter, double-blind, placebo-controlled trial involving adults with active SLE but without proliferative or membranous lupus nephritis who were receiving standard therapy. Patients were randomly assigned in a 1:1 ratio to receive obinutuzumab (1000 mg) or placebo on day 1 and weeks 2, 24, and 26. In the prespecified analysis, the primary end point at week 52 was a response on the SLE Responder Index 4 (SRI-4), defined by a reduction from baseline of at least 4 points in the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score, no worsening of disease as assessed by the British Isles Lupus Assessment Group (BILAG) 2004 index and Physician's Global Assessment, and no intercurrent events (i.e., major concomitant-therapy violation, receipt of rescue medication, or early discontinuation of trial participation due to death, lack of efficacy, or adverse events).

The authors' full names, academic degrees, and affiliations are listed at the end of the article. Richard A. Furie can be contacted at rfurie@northwell.edu or at the Division of Rheumatology, Northwell, 865 Northern Blvd., Suite 302, Great Neck, NY 11021.

*A complete list of investigators in the ALLEGORY trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on March 6, 2026, and last updated on June 1, 2026, at NEJM.org.

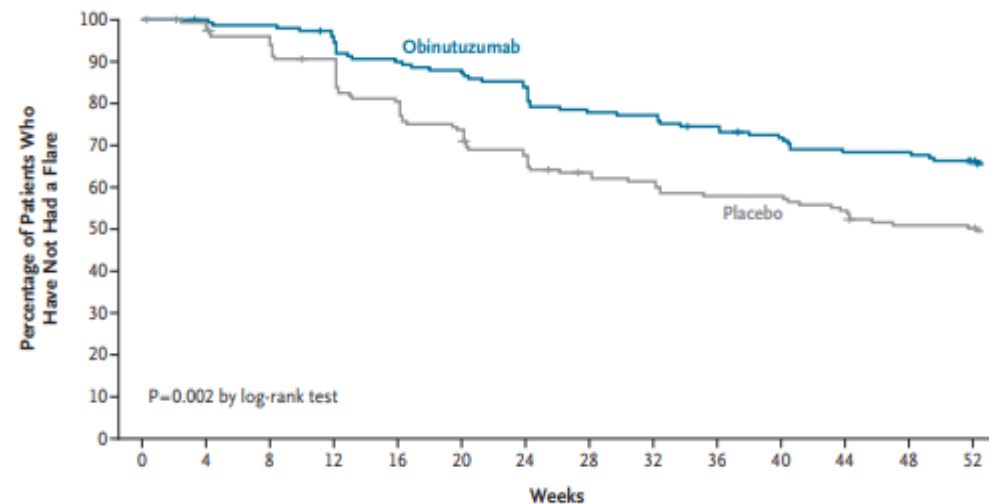
N Engl J Med 2026;395:243–54.
DOI: 10.1056/NEJMoa2516150
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CME

Table 2. Results for Primary and Secondary Efficacy End Points (Intention-to-Treat Population).

End Point	Obinutuzumab (N=151)*	Placebo (N=152)*	Adjusted Difference or Hazard Ratio (95% CI)*	P Value†
Primary end point: SRI-4 response at wk 52 (95% CI) — %‡§	76.7 (69.8–83.5)	53.5 (45.3–61.6)	23.1 (12.5–33.6)	<0.001
Supplementary treatment policy analysis¶	85.4 (79.6–91.2)	68.5 (60.7–76.3)	16.8 (7.1–26.4)	<0.001
Key secondary end points‡				
BICLA response at wk 52 (95% CI) — %	62.0 (54.2–69.8)	40.1 (32.1–48.1)	21.9 (10.8–32.9)	<0.001
Reduction in glucocorticoid dose to ≤7.5 mg/day, sustained from wk 40 to wk 52 (95% CI) — %**	80.0 (71.5–88.5)	54.1 (43.5–64.7)	26.1 (12.7–39.5)	<0.001
SRI-4 response at wk 40, sustained to wk 52 (95% CI) — %††	72.0 (64.6–79.3)	46.4 (38.3–54.6)	25.4 (14.6–36.2)	<0.001
SRI-6 response at wk 52 (95% CI) — %‡‡	68.9 (61.4–76.5)	38.9 (31.0–46.9)	30.0 (19.2–40.7)	<0.001
Median time to first BILAG flare through wk 52 — wk§§	Could not be estimated	52.3	0.58 (0.40–0.82)	0.002

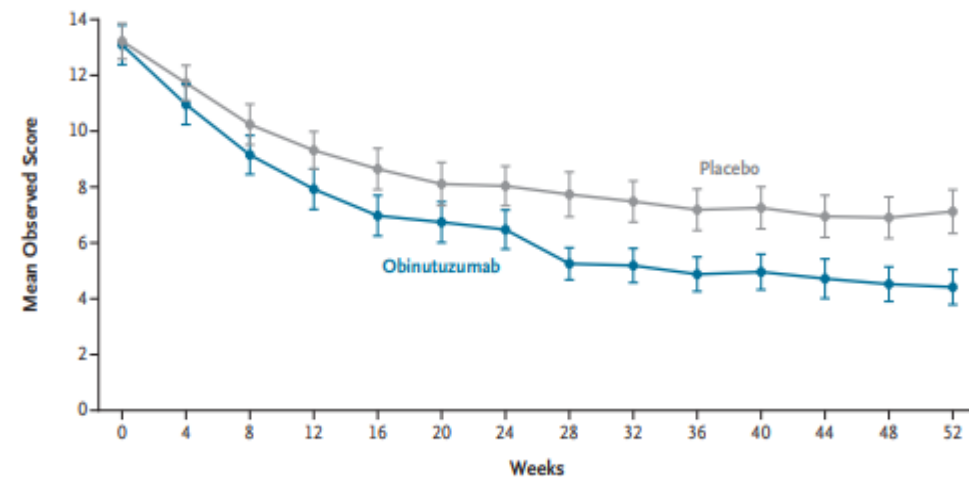
A Time to First BILAG Flare



No. at Risk

Obinutuzumab	151	150	148	143	134	131	125	116	115	110	105	100	100	95
Placebo	152	149	143	134	119	109	99	91	88	83	83	78	72	71

B SLEDAI-2K Score



No. of Patients

Obinutuzumab	151	146	146	145	146	146	139	139	139	144	144	141	140	143
Placebo	152	150	145	146	141	139	136	128	139	135	134	132	134	132

Figure 1. Flares over Time and Disease Activity.

ORIGINAL ARTICLE

Efficacy and Safety of Obinutuzumab in Active Systemic Lupus Erythematosus

R.A. Furie,^{1,2} M. Dall'Era,³ E.M. Vital,^{4,5} J.P. Garg,⁶ F. Irazoque Palazuelos,⁷ A.E. Zuta Santillán,⁸ J. Ravelo-Hernández,⁹ M.B. Santiago,^{10,12} B. Zazueta Montiel,¹³ S. Botha,¹⁴ P. Leszczynski,¹⁵ V.A. de Souza,¹⁶ S.A. Sicsik,¹⁷ L. Bellatin,¹⁸ A. Naidoo,¹⁹ Z. Amoura,²⁰ M.A. D'Agostino,^{21,22} S. Kumar,²³ B. Workeneh,²⁴ J. Rae,⁶ H.A. Mao,²⁵ F. Erblang,²⁶ O. Meier,²⁶ J.C. Maller,⁶ and A.D. Askanase,²⁷ for the ALLEGORY Trial Investigators*

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RESULTS

The authors' full names, academic degrees, and affiliations are listed at the end of the article. Richard A. Furie can be contacted at rfurie@northwell.edu or at the Division of Rheumatology, Northwell, 865 Northern Blvd., Suite 302, Great Neck, NY 11021.

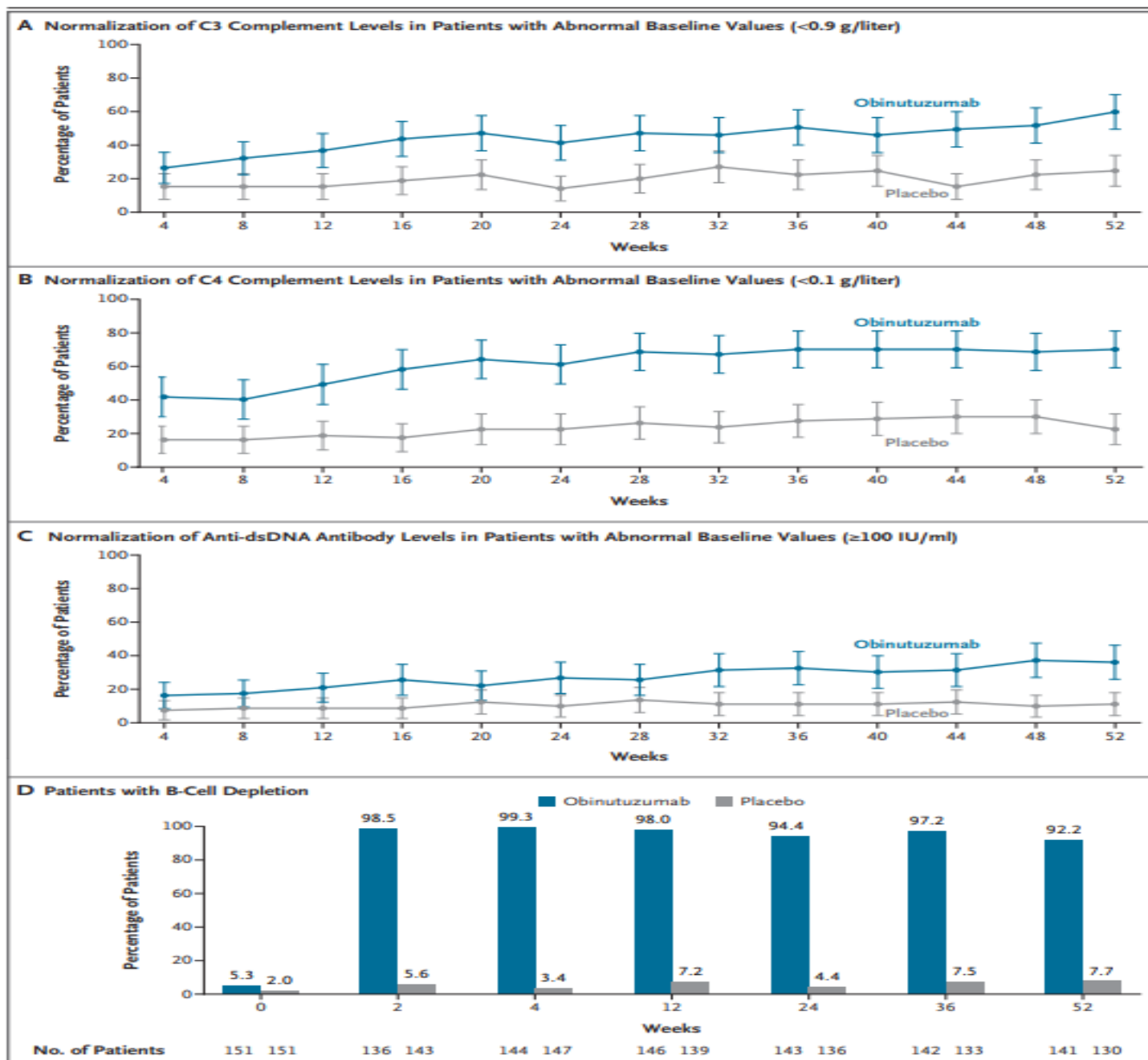
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N Engl J Med 2026;395:243-54.

DOI: 10.1056/NEJMoa2516150

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How I treat FPLN and DPLN +/- MLN

Assess disease severity :

- Clinical SLE
- Renal Involvement

Consider Bx (Class + AI + CI) - crescents, fibrinoid necrosis,
tubulo-interstitial fibrosis.

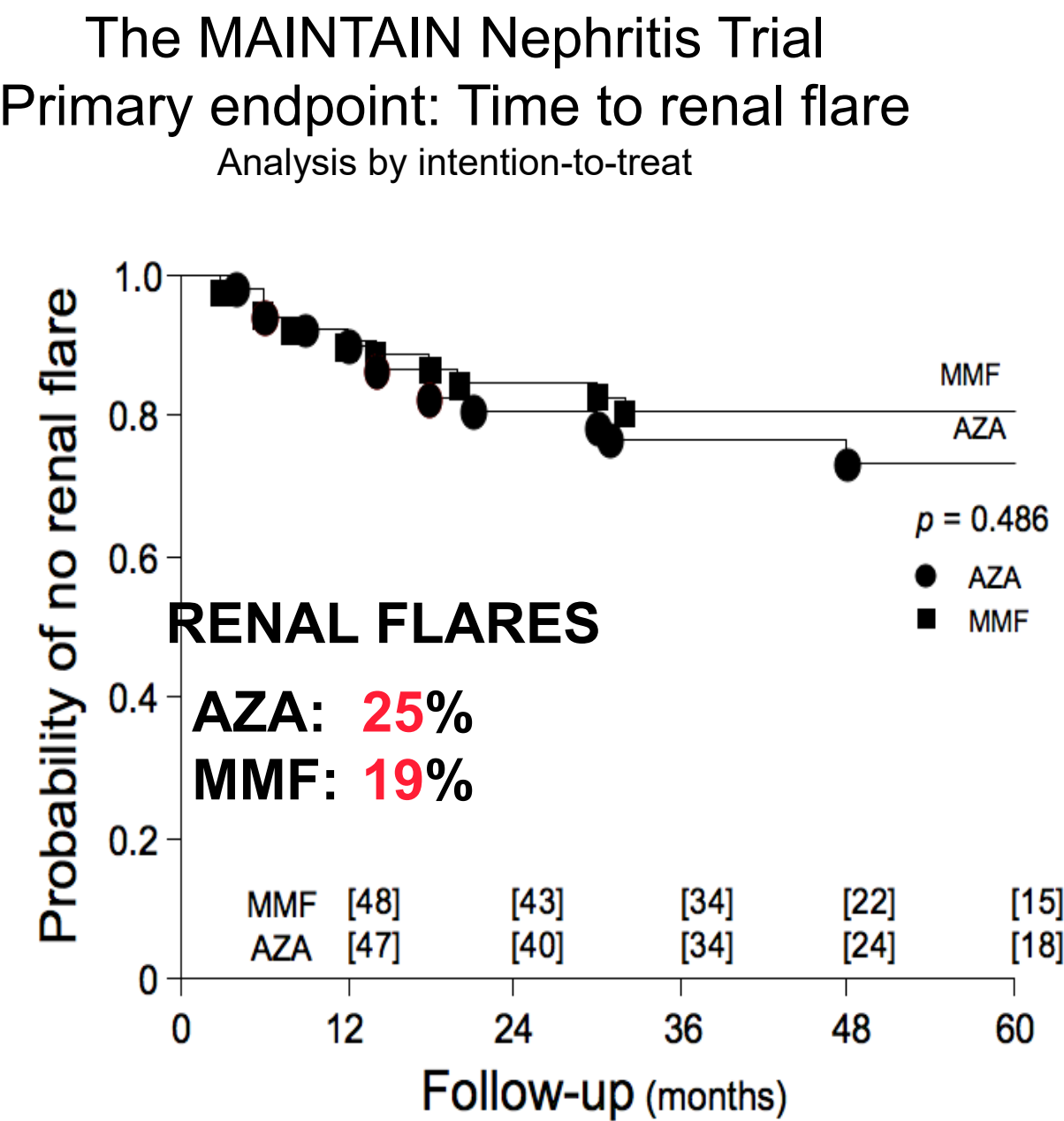
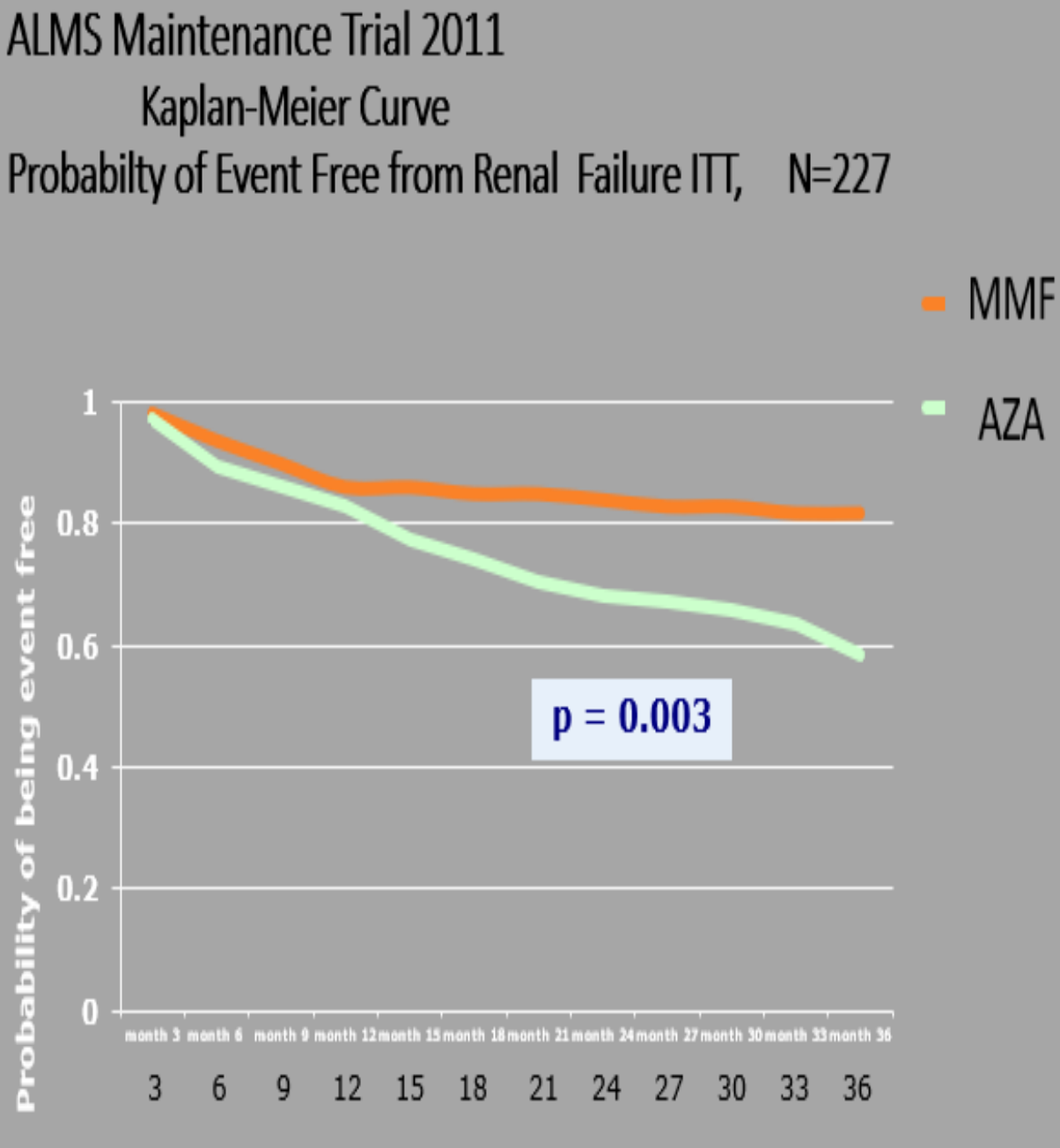
Treat aggressively :

I often **start with triple therapy** with steroids , MMF , and belimumab or CNI or obinutuzumab

If already on MMF and steroids and not reaching goals (protein reduction etc) by 3 months I add either belimumab or voclosporin or obinutuzumab.

If failed prior therapy with MMF I consider cyclophosphamide, or rituximab or Obinutuzumab.

If resistant I consider rituximab or obinutuzmab.



KDIGO 2024 CLINICAL PRACTICE GUIDELINE FOR THE MAINTENANCE OF LUPUS NEPHRITIS – KI 105 Sup: S1-S69 January 2024

Maintenance Immuno-suppressive regimens	Low-dose glucocorticoids AND				
	Mycophenolic acid analogs	Azathioprine	Belimumab and mycophenolic acid analogs or azathioprine	CNI and mycophenolic acid analogs	CNI (such as voclosporin, tacrolimus or cyclosporine)
Comments	Preferred treatment based on high-certainty evidence; lower flare rate than azathioprine maintenance	Low medication cost; safe in pregnancy	Efficacy and safety of belimumab demonstrated in BLISS-LN (104-wk) and open-label extension trials (28-wk) [Practice Point 10.2.3.2.5]	Efficacy and safety of voclosporin demonstrated in AURORA 1 (52-wk) and AURORA 2 continuation trials (2-yr); efficacy and safety of tacrolimus demonstrated in 'Multitarget Therapy' trial in Chinese patients in which tacrolimus and reduced-dose MPAA were given for 24 months [Practice Point 10.2.3.2.5]	Tacrolimus and cyclosporine safe in pregnancy; insufficient pregnancy data on voclosporin

How I maintain FPLN and DPLN patients over time.

- I make certain they are in remission after induction ? reBX???
- I consider former therapies.
- I prefer MMF to Azathioprine. I have no problem using voclosporin with MMF and very low dose steroids or belimumab + azathioprine or MMF + low dose steroids. Less data on CNIs and Obinutuzumab.
- Maintenance 3-4 years.
- If planning pregnancy use Aza over MMF and Tac over Voclosporin. Little data on belimumab in pregnancy and lactation.

KDIGO 2024 GUIDELINE FOR THE MANAGEMENT OF MLN

– KI 105 Sup: S1-S69 January 2024

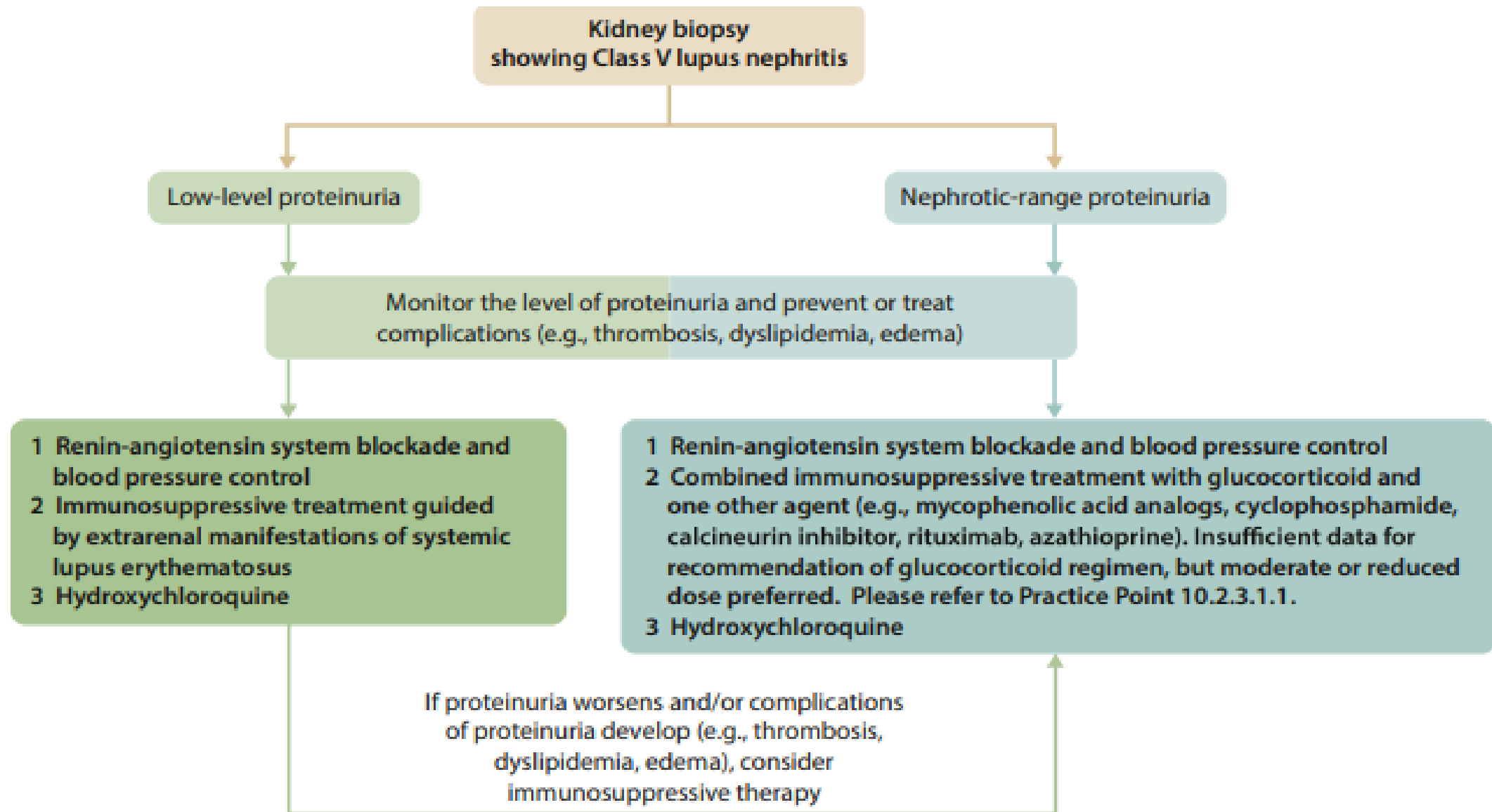


Figure 10 | Management of patients with pure Class V lupus nephritis.

American College of Rheumatology (ACR) 2024 LN

Guideline-Treatment Overview

Class III/IV ± V
Active, newly diagnosed, or flare

Pure Class V*
Active, newly diagnosed, or flare

Hydroxychloroquine and RAAS-I[†]

FIRST LINE (CONTINUOUS) THERAPY
Preferred:

TRIPLE THERAPY

GC pulse/oral taper to ≤5 mg/day by 6 mo.

+

MPAA

+

BEL^a or CNI^b

Alternatives:

TRIPLE THERAPY

GC pulse/oral taper to ≤5 mg/d by 6 mo.

+

Low-dose CYC[‡] + BEL

DUAL THERAPY if TRIPLE THERAPY
Is not available or not tolerated

FIRST LINE (CONTINUOUS) THERAPY
Preferred:

TRIPLE THERAPY

GC pulse/oral taper to ≤5 mg/day by 6 mo.

+

MPAA

+

CNI

Alternatives:

TRIPLE THERAPY

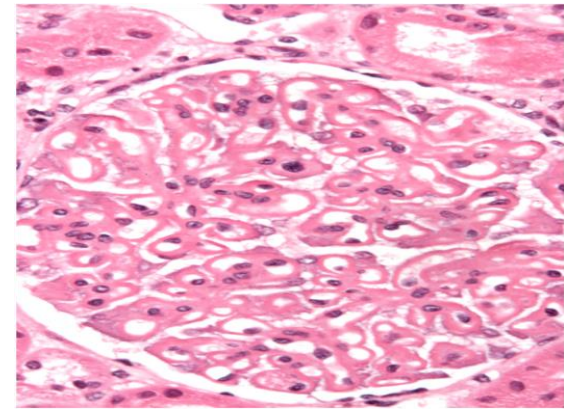
GC pulse/oral taper to ≤5 mg/d by 6 mo.

+

MPAA + BEL or Low-dose CYC[‡] + BEL

DUAL THERAPY if TRIPLE THERAPY
Is not available or not tolerated

How I treat Membranous LN



- 1) For LMN with FPLN or DPLN (Class V+III or Class V + IV) Treat as III or IV.
- 2) For isolated LMN with normal GFR, and low proteinuria ($< 1\text{g/day}$) I use ACEinhib/ARBs, hydroxychloroquine, and in some SGLT2 inhibitors.
- 3) For LMN with heavier proteinuria, consider former treatments , risks of delaying therapy, cosmetic concerns- pregnancy-etc .

I prefer to use CNI + MMF + low dose steroids as initial therapy or obi + MMF + steroids

CD19 CAR T-Cell Therapy in Autoimmune Disease — A Case Series with Follow-up

Fabian Müller, M.D., Jule Taubmann, M.D., Laura Bucci, M.D., Artur Wilhelm, Ph.D., Christina Bergmann, M.D., Simon Völkl, Ph.D., Michael Aigner, Ph.D., Tobias Rothe, Ph.D., Ioanna Minopoulou, M.D., Carlo Tur, M.D., Johannes Knitza, M.D., Soraya Kharboutli, M.D., Sascha Kretschmann, Ph.D., Ingrid Vasova, M.D., Silvia Spoerl, M.D., Hannah Reimann, Ph.D., Luis Munoz, M.D., Roman G. Gerlach, Ph.D., Simon Schäfer, Ph.D., Ricardo Grieshaber-Bouyer, M.D., Anne-Sophie Korganow, M.D., Dominique Farge-Bancel, M.D., Dimitrios Mougiakakos, M.D., Aline Bozec, Ph.D., Thomas Winkler, Ph.D., Gerhard Krönke, M.D., Andreas Mackensen, M.D., and Georg Schett, M.D.

ABSTRACT

BACKGROUND

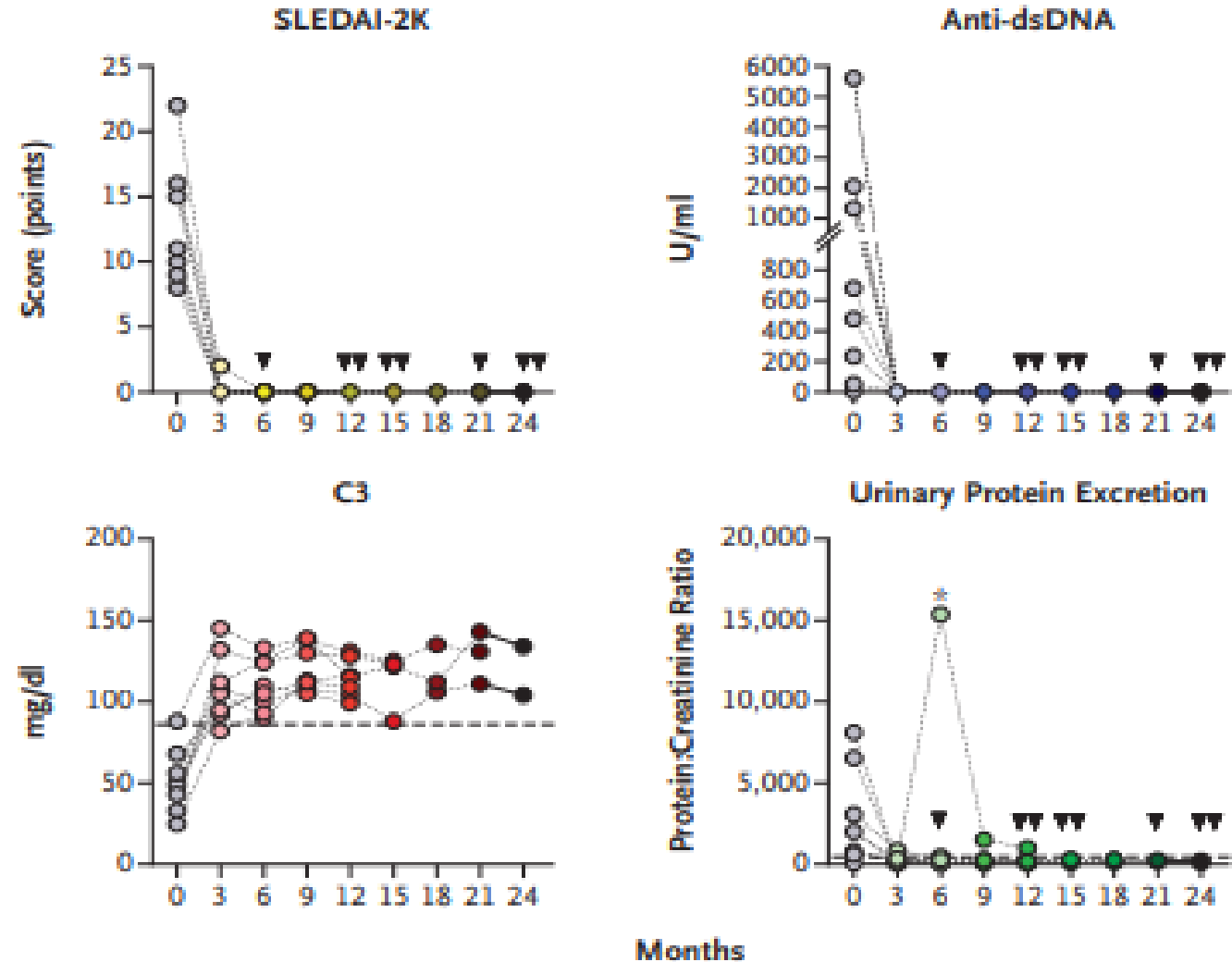
Treatment for autoimmune diseases such as systemic lupus erythematosus (SLE), idiopathic inflammatory myositis, and systemic sclerosis often involves long-term immune suppression. Resetting aberrant autoimmunity in these diseases through deep depletion of B cells is a potential strategy for achieving sustained drug-free remission.

The authors' affiliations are listed in the Appendix. Dr. Schett can be contacted at georg.schett@uk-erlangen.de or at the Department of Internal Medicine 3—Rheumatology and Immunology, Friedrich-

15 pts with autoimmune disease treat with a single infusion of CD19 Targeted chimeric antigen receptor T cells. At mean of 15 mo all in remission

Uncontrolled heterogenous group with 8 w SLE

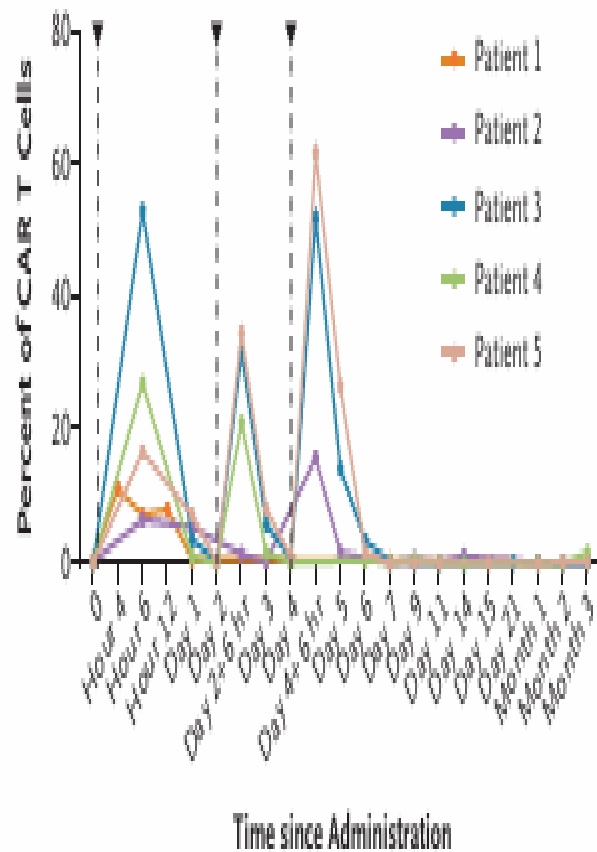
B Long-Term Outcomes in Patients with SLE (N=8)



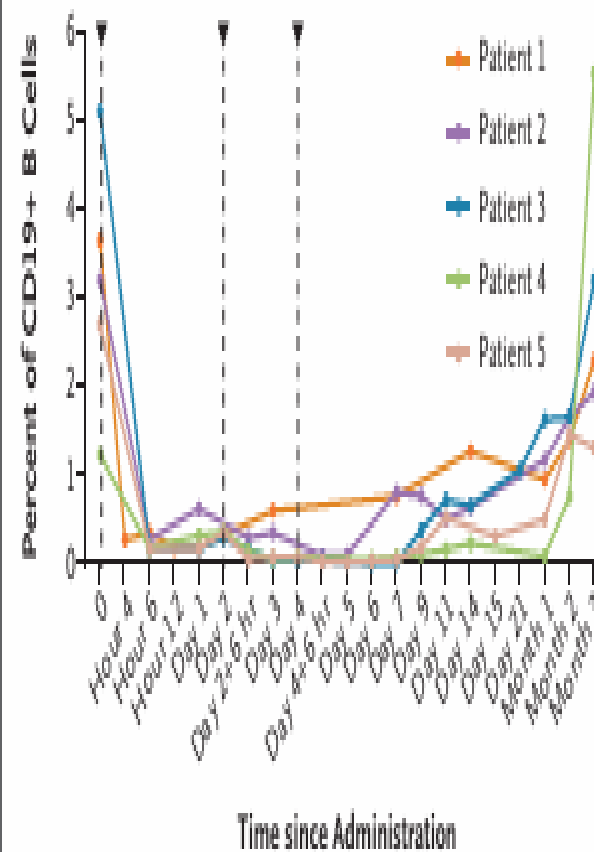
In Vivo CD19 CAR T-Cell Therapy of Refractory SLE

Wang et al NEJM 393: 1542-1544 Oct 2025

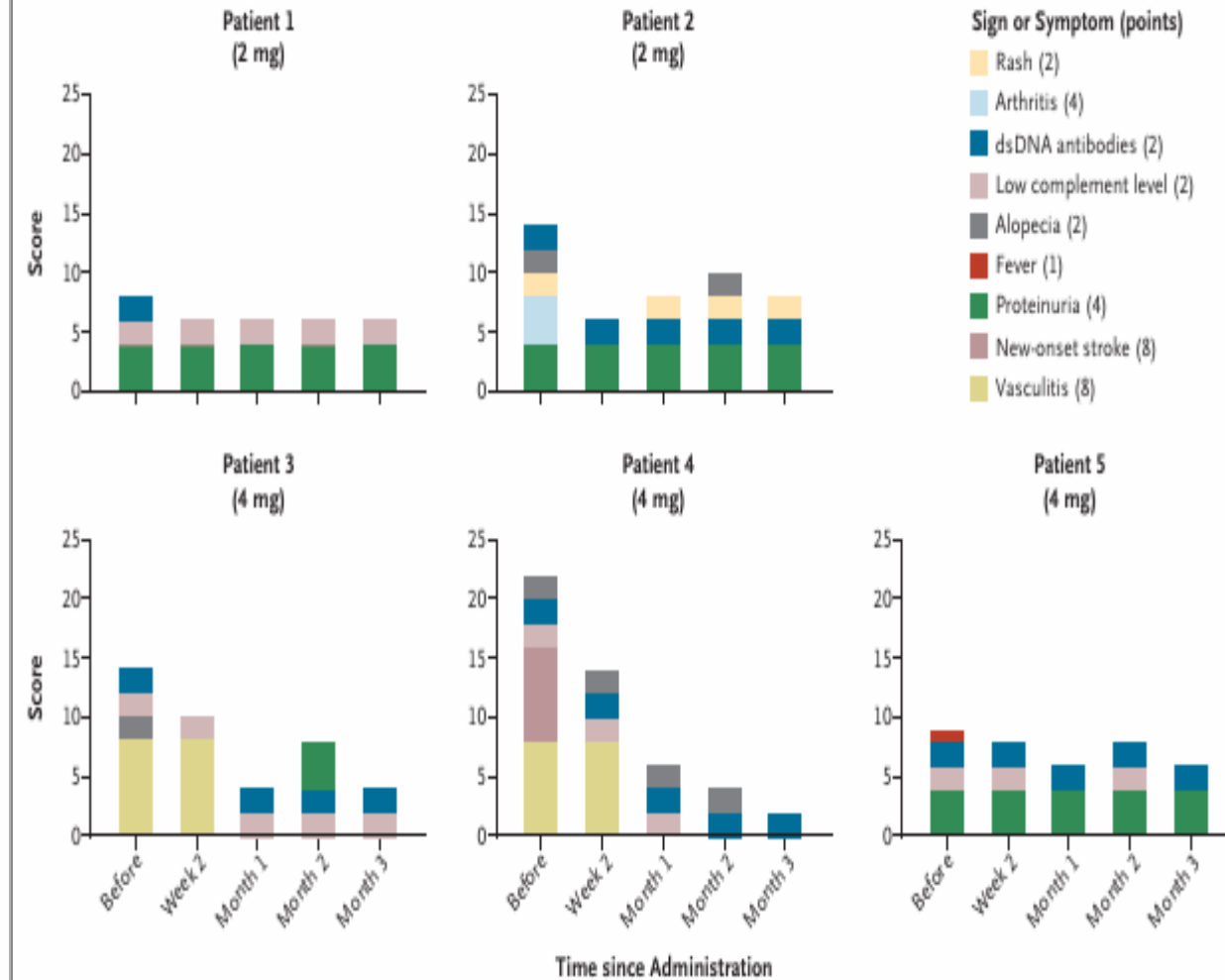
B Percent of CAR T Cells Relative to CD8+ T Cells in Peripheral Blood after Administration of HN2301



C Percent of CD19+ B Cells Relative to Total Lymphocytes in Peripheral Blood after Administration of HN2301



D Systemic Lupus Erythematosus Disease Activity Index 2000 after Administration of HN2301



Newer IgAN Agents Acting on BAFF and APRIL

Atacicept, Povatacept, Telitacept

Human TACI-IgG1 fusion protein

Binds to BLyS/BAFF and APRIL
Inhibits B cell activation and
Ig production

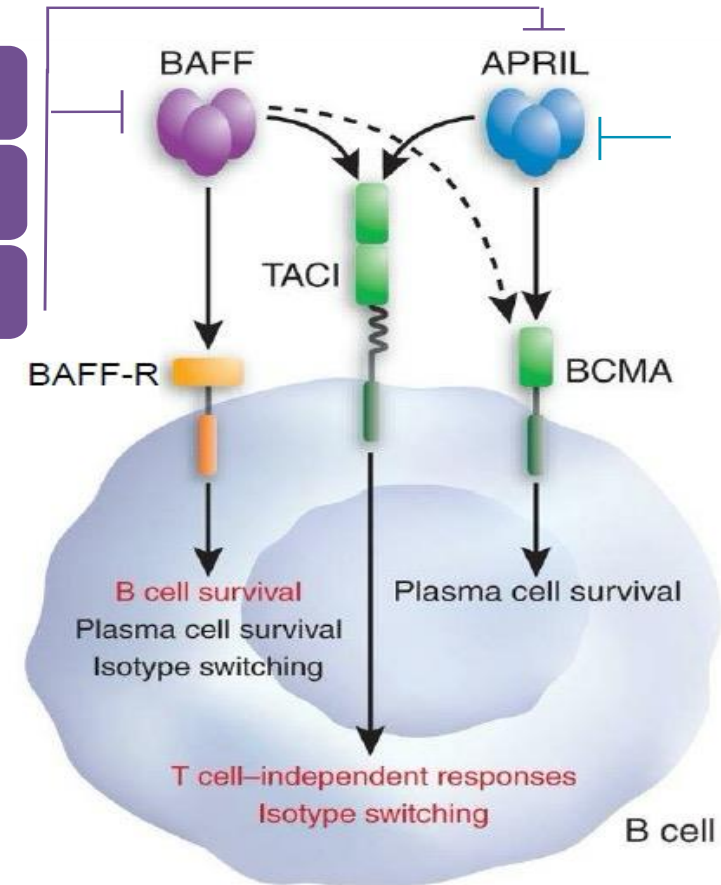
Dual BAFF/APRIL
Inhibitors

Atacicept

Povetacept

Telitacept

APRIL
Inhibitors



Modified from Cheung CK, et al. *Front Nephrol.* 2024;3:1346769.

A Phase 3 Trial of Telitacicept for Systemic Lupus Erythematosus

Ronald F. van Vollenhoven, M.D.,¹ Li Wang, M.D.,² Joan T. Merrill, M.D.,³ Yi Liu, M.D.,⁴ Chunde Bao, M.D.,⁵ Fen Li, M.D.,⁶ Jiankang Hu, M.M.,⁷ Chenghui Huang, M.M.,⁸ Jianhong Zhao, M.D.,⁹ Cibo Huang, M.M.,¹⁰ Hanyou Mo, M.D.,¹¹ Wei Wei, M.D.,¹² Fu'ai Lu, M.M.,¹³ Jingyang Li, M.D.,¹⁴ Dongbao Zhao, M.D.,¹⁵ Wenxiang Wang, Ph.D.,¹⁶ Lin Li, M.D.,¹⁶ Qing Zuraw, M.D.,¹⁷ Xiaofei Wang, M.D.,¹⁸ Xuebin Wang, M.D.,¹⁹ Jianmin Fang, Ph.D.,^{16,20} and Fengchun Zhang, M.D.,² for the 18C010 Trial Investigators*

ABSTRACT

BACKGROUND

Telitacicept, a new dual inhibitor of the cytokines B-lymphocyte stimulator (BLyS) and

Serum biomarkers

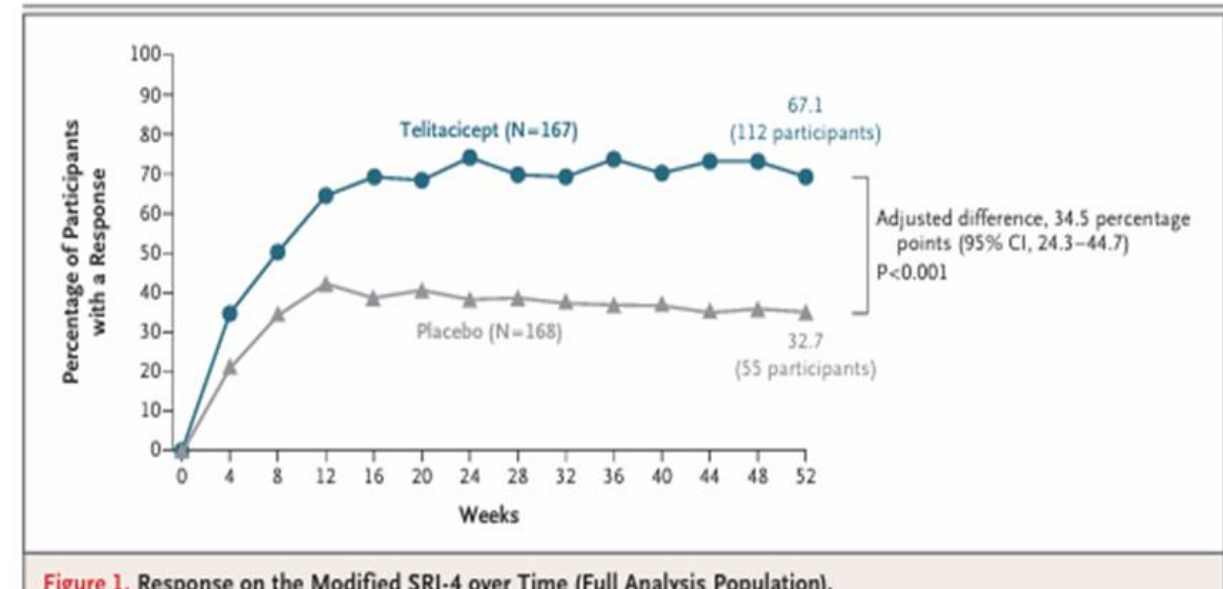
Low level of C3, C4, or both — no. (%)	119 (71.3)	118 (70.2)
Positivity for antinuclear antibodies — no. (%)	160 (95.8)	165 (98.2)
Positivity for anti-dsDNA antibodies — no./total no. (%)	99/163 (60.7)	98/165 (59.4)
Urine protein level — g/24 hr	1.40±1.57	1.24±1.34
Quantitative classification of 24-hr urine protein level — no. (%)		
≤0.5 g	57 (34.1)	70 (41.7)
>0.5 g	110 (65.9)	98 (58.3)
Daily dose of glucocorticoid or prednisone equivalent — mg	15.2±11.1	13.9±10.5
Combination therapy — no. (%)		
Glucocorticoid + antimalarial agent	25 (15.0)	26 (15.5)
Glucocorticoid + immunosuppressive drug	23 (13.8)	24 (14.3)
Glucocorticoid + immunosuppressive drug + antimalarial agent	117 (70.1)	114 (67.9)

A Phase 3 trial of Telitacicept for SLE

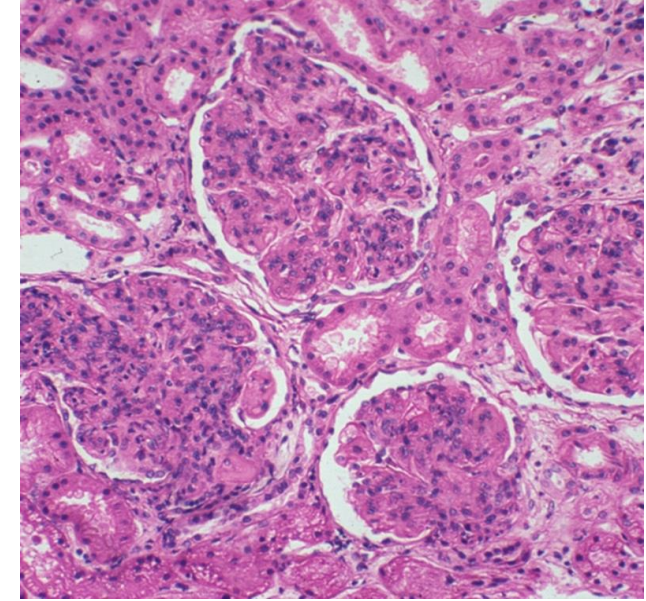
R van Vollenhoven et al NEJM 393: 1475-85 2025

335 adults w active SLE in China teli vs PBO + SOC meds
SQ weekly for 1 yr
Response modified SLR Responder index (SRI-4) and
SLEDAI-SLENA

67% reponse Teli vs 33% PBO AE's 75% teli vs 50% PBO
(URI, low Ig, injection site reactions)



Treating Lupus Nephritis in 2026



- 1) We have new and better medicines to treat LN.
- 2) We have better goals (e.g. reduction of proteinuria, preservation of GFR) that correlate with outcome.
- 3) Biopsy is best “biomarker”. **Biopsy early and reduce steroids.**
- 4) We have large controlled, blinded, randomized trials w efficacy and safety.
- 5) Not everyone will benefit from Obinutuzumab, Belimumab, or Voclosporin, but do not be reluctant to use them - **Think Triple Therapy**
- 6) **Obinutuzumab** formerly for truly resistant LN patients – now for many more.
- 7) **We need comparative studies w triple therapy regimens and still need new meds for LN .**