

Treating Lupus Nephritis in 2025 – New Guidelines, New Medications, and New Challenges

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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 , Novartis, Vertex, Vera.

He has lectureships with Aurinia and Glaxo on LN and Calliditas on Mechanisms of IgA Nephropathy.

Lupus Nephritis— Still a Rare Disease

PREVALENCE in the US

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

45% of patients with SLE have LN

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

Pts with LN are likely to be
Female (90% of pts with SLE).

Blacks, Asians, and those
of Hispanic ethnicity are more
likely to develop LN than whites

Lim et al. *Arthritis Rheum.* 2014;66(2):357-368.

Somers et al. *Arthritis Rheum.* 2014;66(2):369-378.

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

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

2019-21 Guidelines for Screening and Diagnosis of LN

	EULAR/ERA-EDTA 2019-2020
Monitoring for LN in patients with SLE	<ul style="list-style-type: none"> • Every 3 months in those at high risk of kidney involvement
Criteria for kidney biopsy	<ul style="list-style-type: none"> • Proteinuria ≥ 0.5 g/24 hr • Glomerular hematuria and/or cellular casts • Unexplained decrease in GFR
Kidney biopsy	<ul style="list-style-type: none"> • Recommended for classification and treatment

Screening ACR Nov 2024 Guidelines

- Strong recommendation to screen SLE pts at least **every 6-12 mo** for proteinuria even SLE pts without known kidney disease,
- Conditional recommendation to **perform a kidney biopsy** in patients with SLE who have **high levels of proteinuria (>0.5 g/g)** and/or **impaired kidney function not otherwise explained.**

Fanouriakis et al. *Ann Rheum Dis.* 2019;78(6):736-745.
 Fanouriakis et al. *Ann Rheum Dis.* 2020;79(6):713-723
 Amer College of Rheum Nov 2024

LN Pts at High Risk for Poor Renal Outcome

10 to 30% of LN pts progress to kidney failure

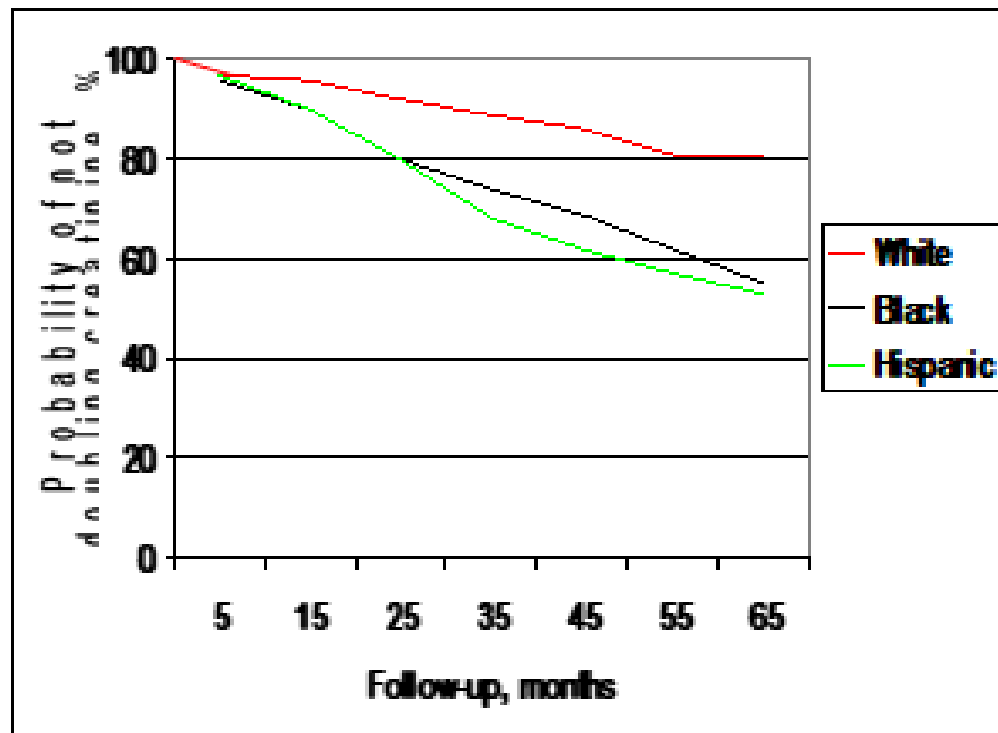
Lupus nephritis patients at high risk for poor renal outcome (risk increases with the number of risk factors present)

Patient characteristics	Serological characteristics	Histologic characteristics
<ul style="list-style-type: none">• African or Hispanic ancestry• Male• Pediatric onset• Frequent relapses• Incomplete remission• Proteinuria >4 g/d at diagnosis	<ul style="list-style-type: none">• Antiphospholipid syndrome• Persistent hypocomplementemia• High titer dsDNA Abs• High titer C1q antibodies	<ul style="list-style-type: none">• Crescentic glomerulonephritis• Thrombotic microangiopathy• Extensive tubulointerstitial damage

1. Anders HJ, et al. *Nat Rev Dis Primers*. 2020;6(1):7. **2.** Mahajan A, et al. *Lupus*. 2020;29(9):1011.
3. Tektonidou MG, et al. *Arthritis Rheumatol*. 2016;68(6):1432-1441 **4.** Parikh SV, et al. *AJKD* . 2020;76(2):265-281.

Effect of Ancestral Background on Renal Survival

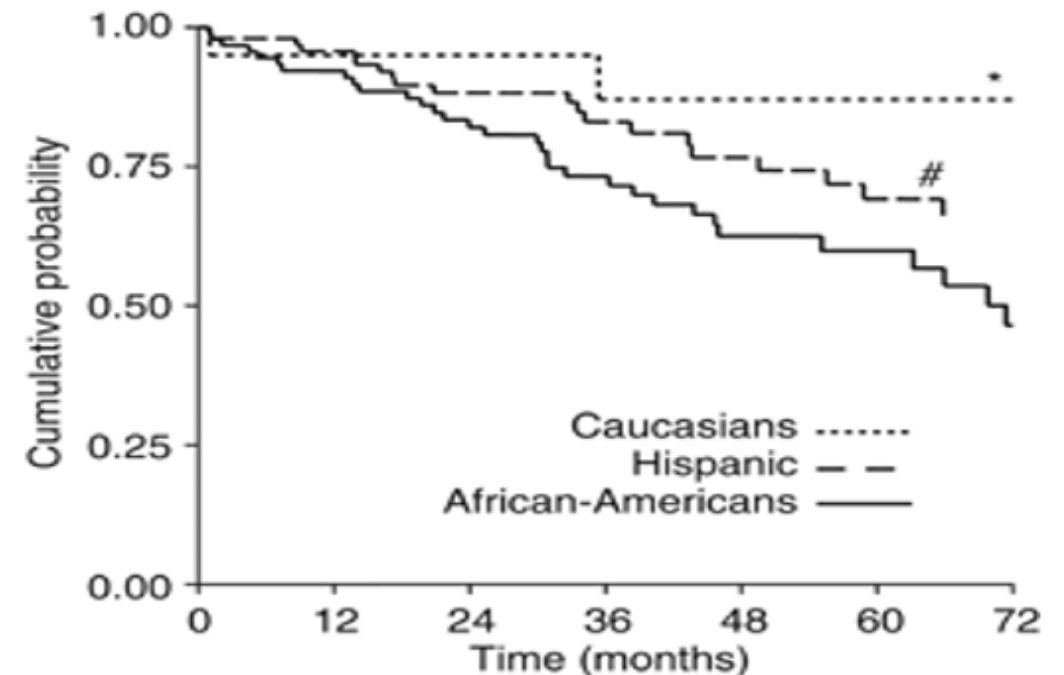
Renal Survival LN III and IV
CUMC N=129



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

Who has FSGS? Shaq? Alonzo?
Answer: Not Dr. Appel!



APOL1 Mediated Kidney Disease (AMKD)

African American make up 13% of the population but 30% of the ESKD population.

APOL1-mediated kidney disease is caused by 2 **risk variants of the *APOL1* gene (G1/G1, G1/G2, or G2/G2)** and a second hit.

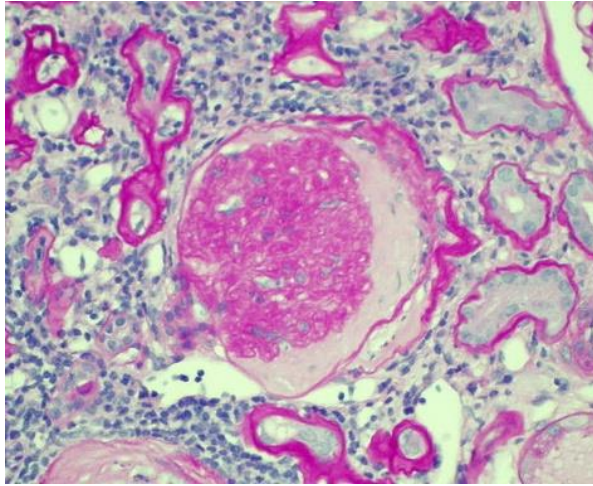
***APOL1* risk variants** damage the podocytes and glomerular endothelial cells **by creating channels in these cells, resulting in glomerular dysfunction and proteinuria.**

Not all people with 2 risk variants will develop AMKD. A **second hit of infection or inflammation is required to trigger disease.**

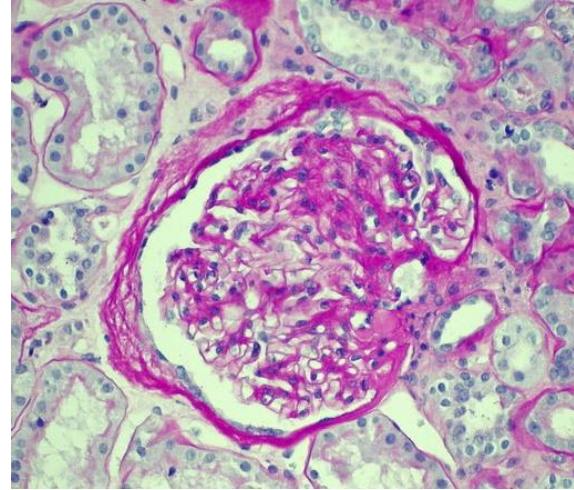
Spectrum of *APOL1*-associated nephropathy (ApoL1 G1G2,G1G1,G2G2)

**Focal Global
Glomerulosclerosis**

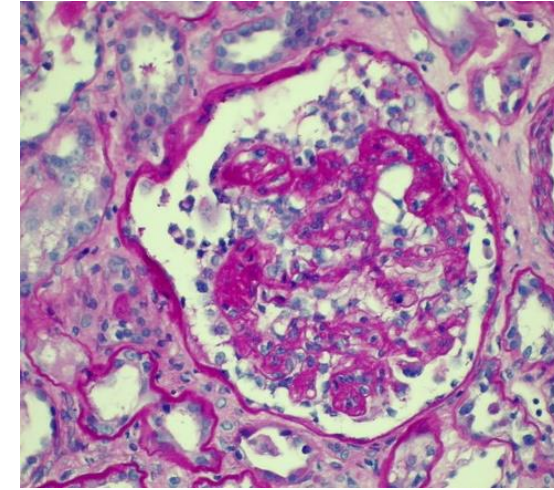
“Hypertension-attributed”



**Focal Segmental
Glomerulosclerosis**



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

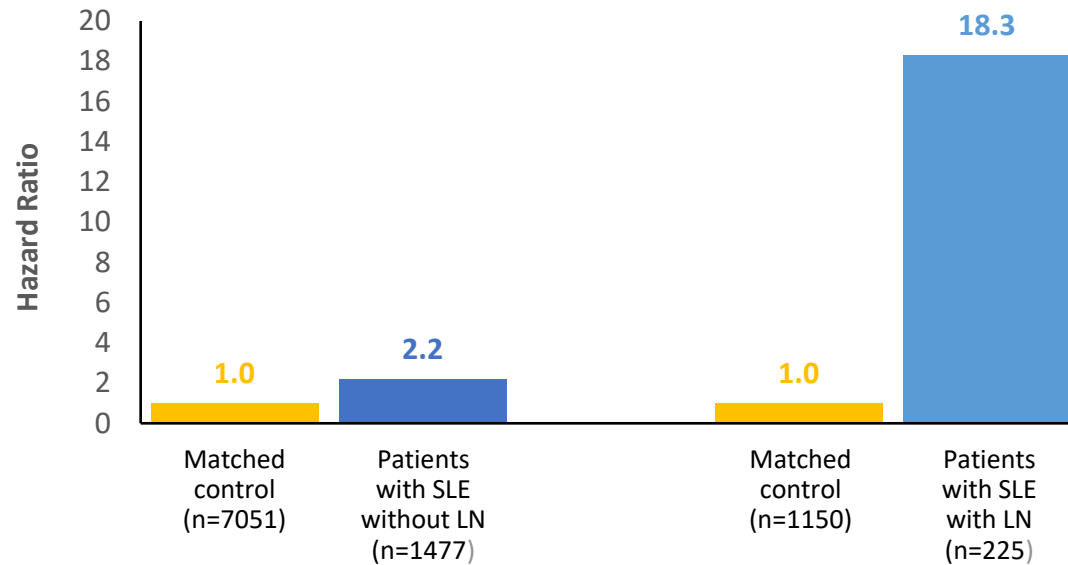


Proteinuria & nephropathy progression rate

Severe lupus nephritis

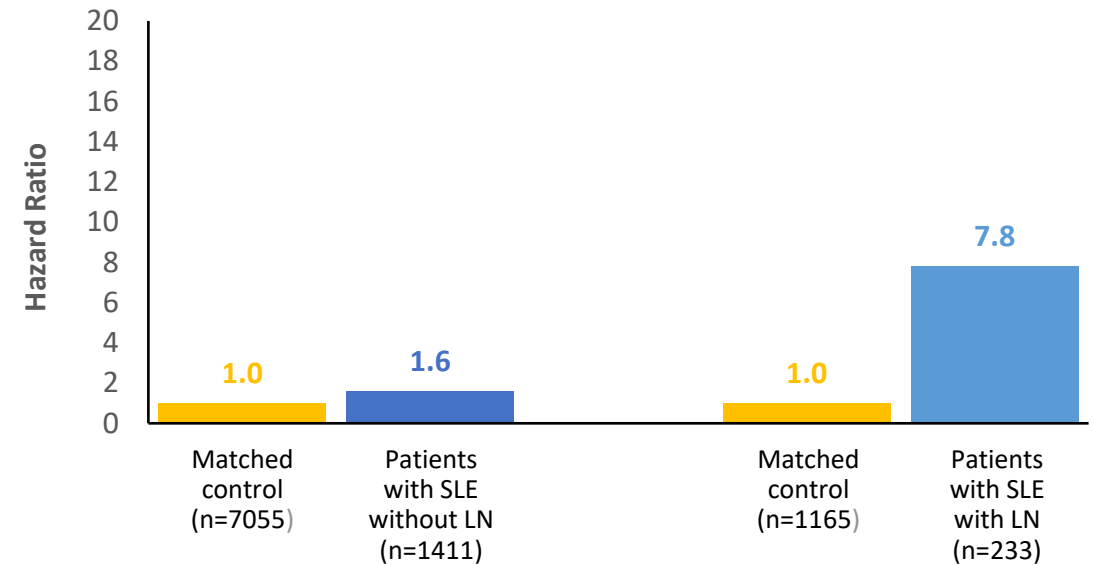
LN Increases the Risk of CV Events and CV Mortality

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.

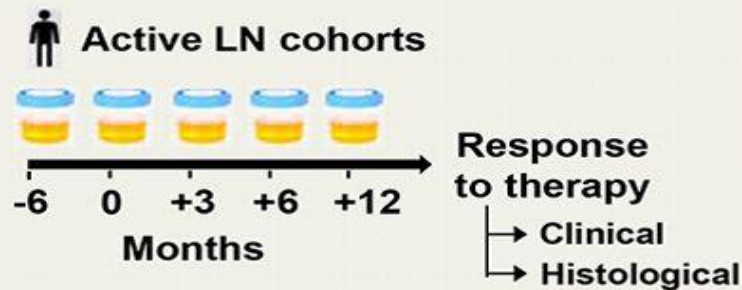
Urinary soluble CD163: a novel non-invasive biomarker of activity for lupus nephritis

METHODS

Cross-sectional

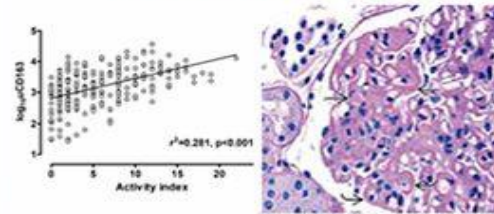


Longitudinal



OUTCOME Urine sCD163 levels:

Correlate with LN histologic activity



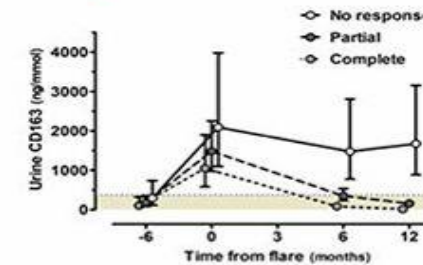
6-month values predict 12-month response

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

Identify histologic remission in patients with persistent proteinuria



Vary with treatment and response to therapy



- ↑ At flare
- ↓ Responders
- Non-responders

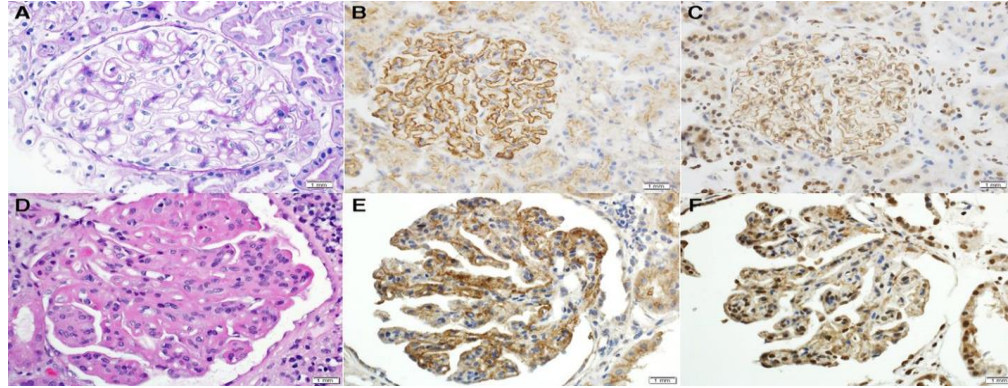
Agree with histology on repeat biopsy



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



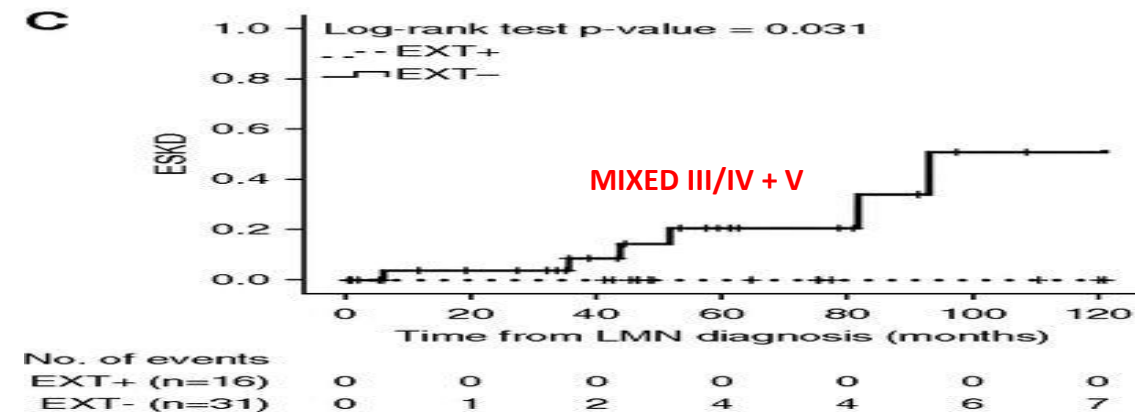
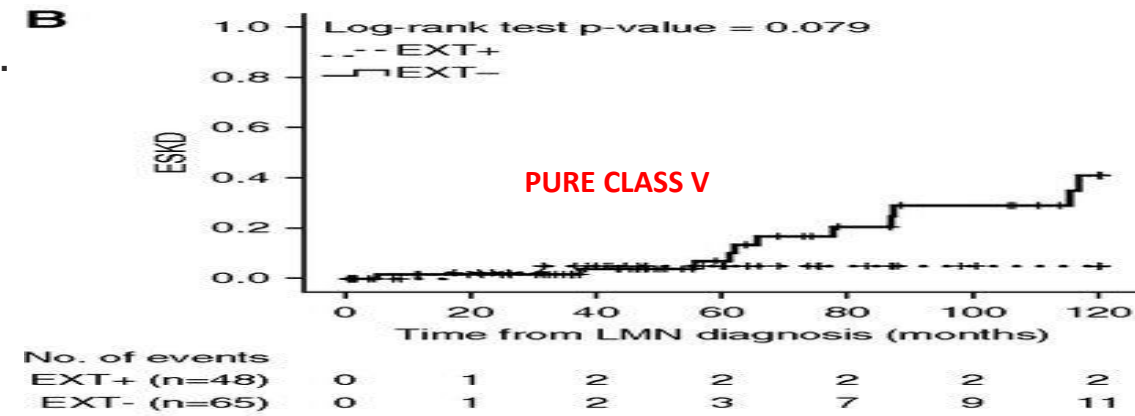
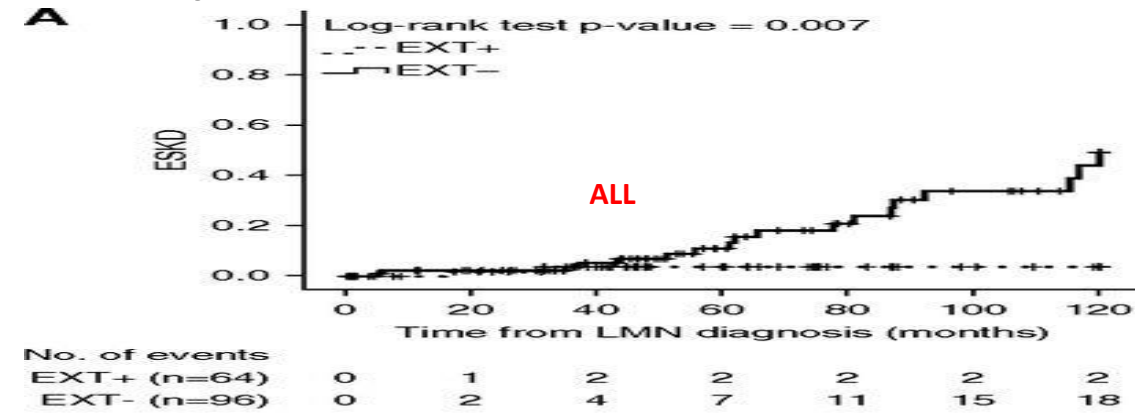
374 Pts LN V 122 (32.6%) Bx + EXT1/EXT2 252 (67.4%) neg..

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

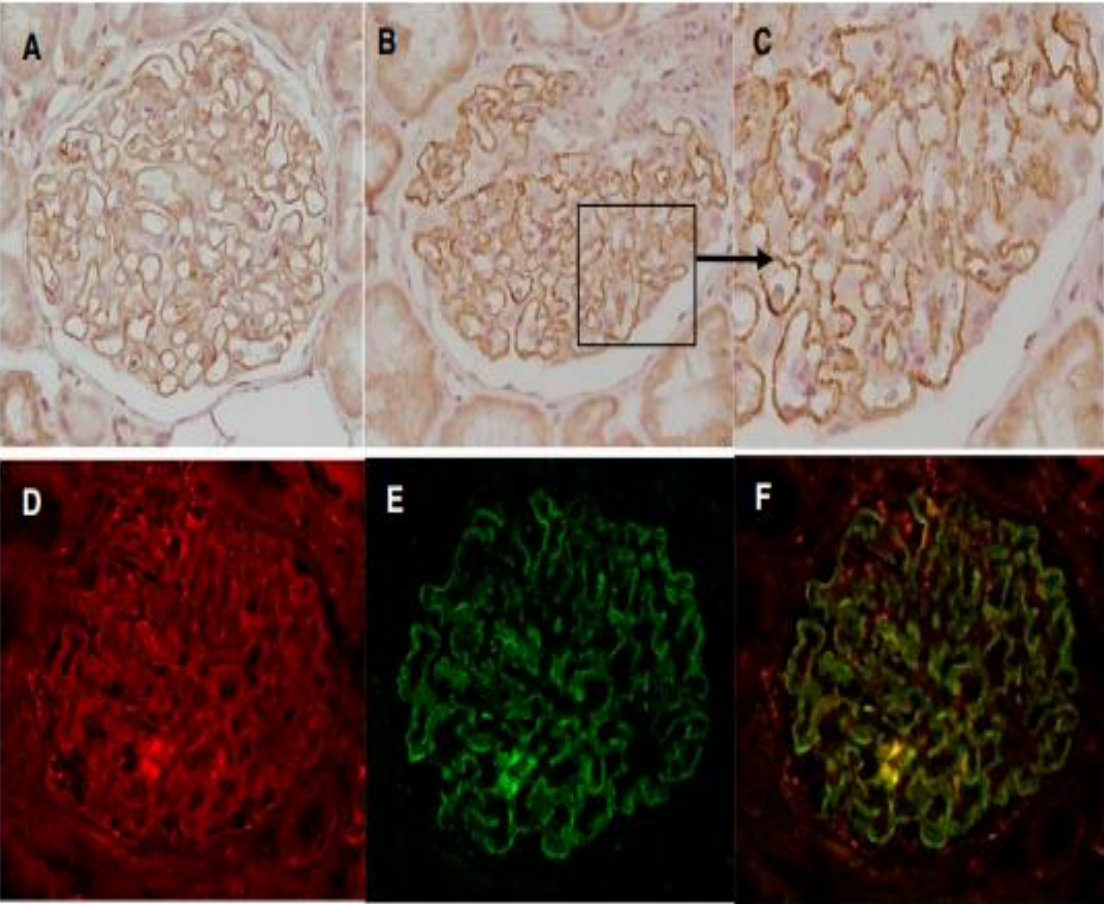


Table 4. Treatment response and outcomes in the cases of exostosin-positive and exostosin-negative class 5 lupus nephritis

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

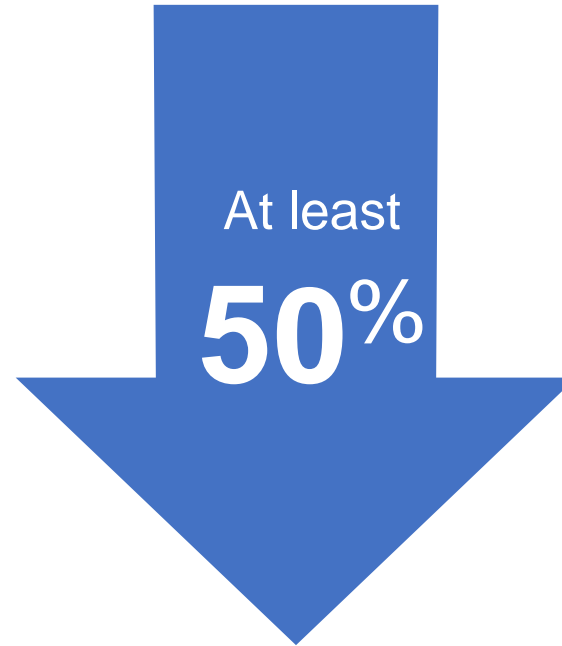
Conclusion Compared with EXT1/ EXT2- negative patients, the EXT1/EXT2-positive patients presented with lower disease activity and were less likely to experience adverse renal events in relation with the chronicity index.

2019-20 EULAR/ERA-EDTA Recommendations to Optimize Kidney Function Based on Proteinuria Reduction

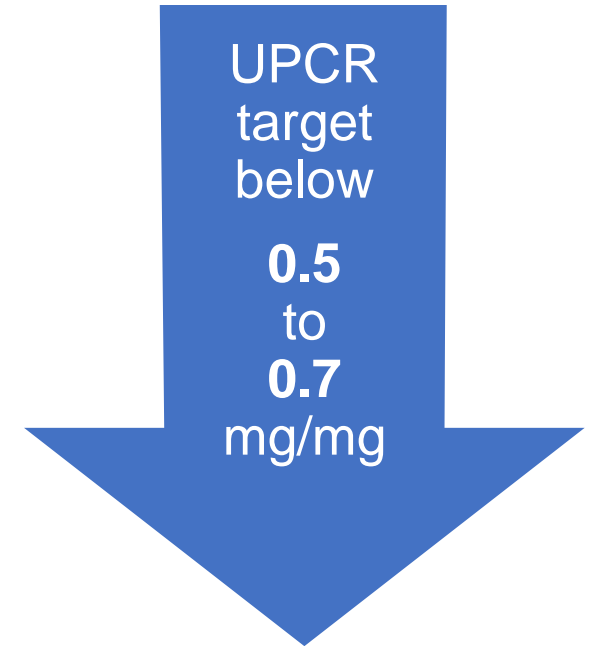
Target Proteinuria



by 3 months



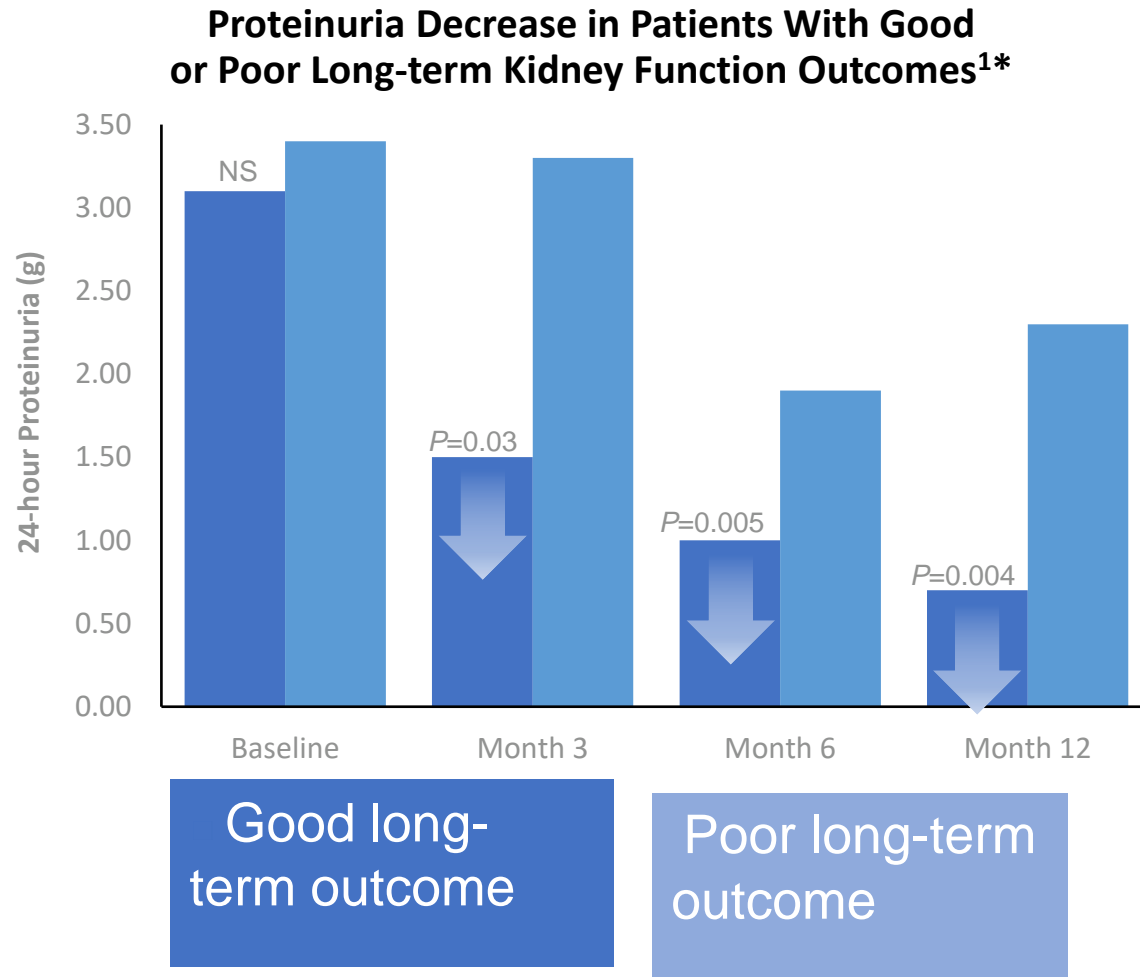
by 6 months



by 12 months

Fanouriakis et al. *Ann Rheum Dis*. 2020;79(6):713-723.

Early Decrease in Proteinuria Levels Predicts Improved Kidney Function Outcomes



- Patient baseline proteinuria did not predict long-term kidney function outcomes¹
- Proteinuria decrease alone was a good marker of long-term kidney outcome. (Inclusion of SCr and urinalysis did not increase the positive predictive value)

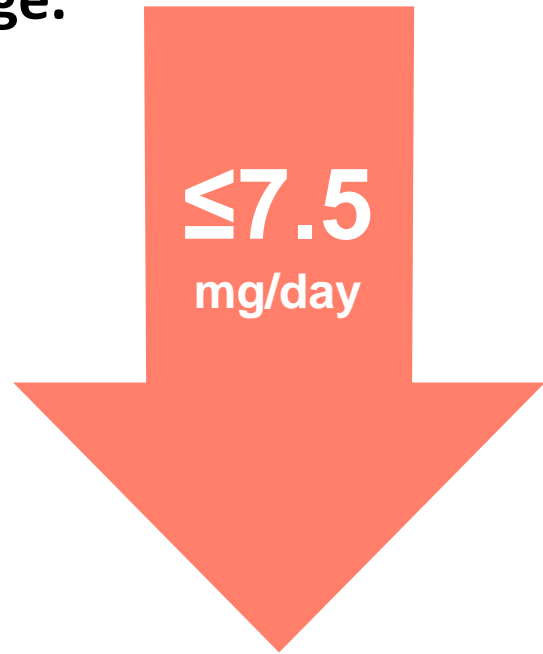
Long-term follow-up (median 110 months) of patients enrolled in MAINTAIN trial

Good long-term kidney function outcome was defined as SCr \leq 120% of baseline value (n=83); poor long-term kidney function outcome was defined as SCr >120% of baseline value (n=21).

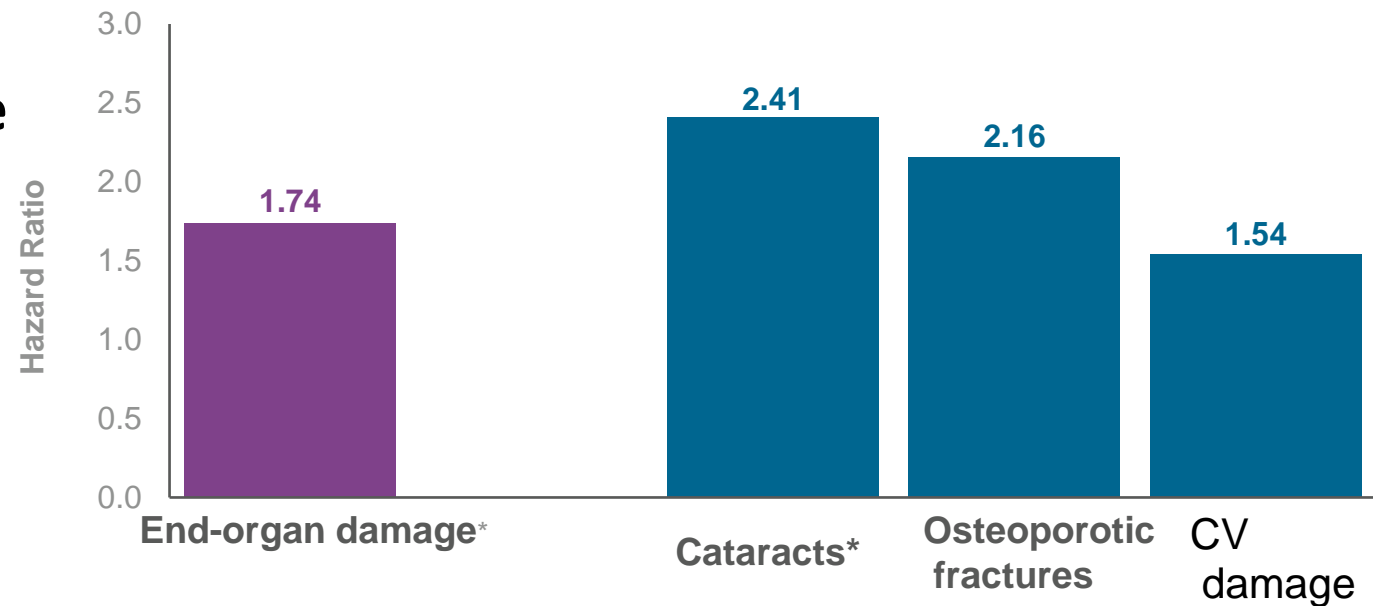
Recent Lupus Nephritis Guidelines Recommend Aggressive Goals for Reducing Steroids During Treatment

Guidelines from both EULAR and KDIGO offer similar recommendations for steroid reductions²

Target steroid reduction to 7.5 mg daily by the 3-6th month to prevent irreversible end organ damage.



Damage Associated W Mean Prednisone Daily Dose ≥ 7.5 mg Versus < 7.5 mg



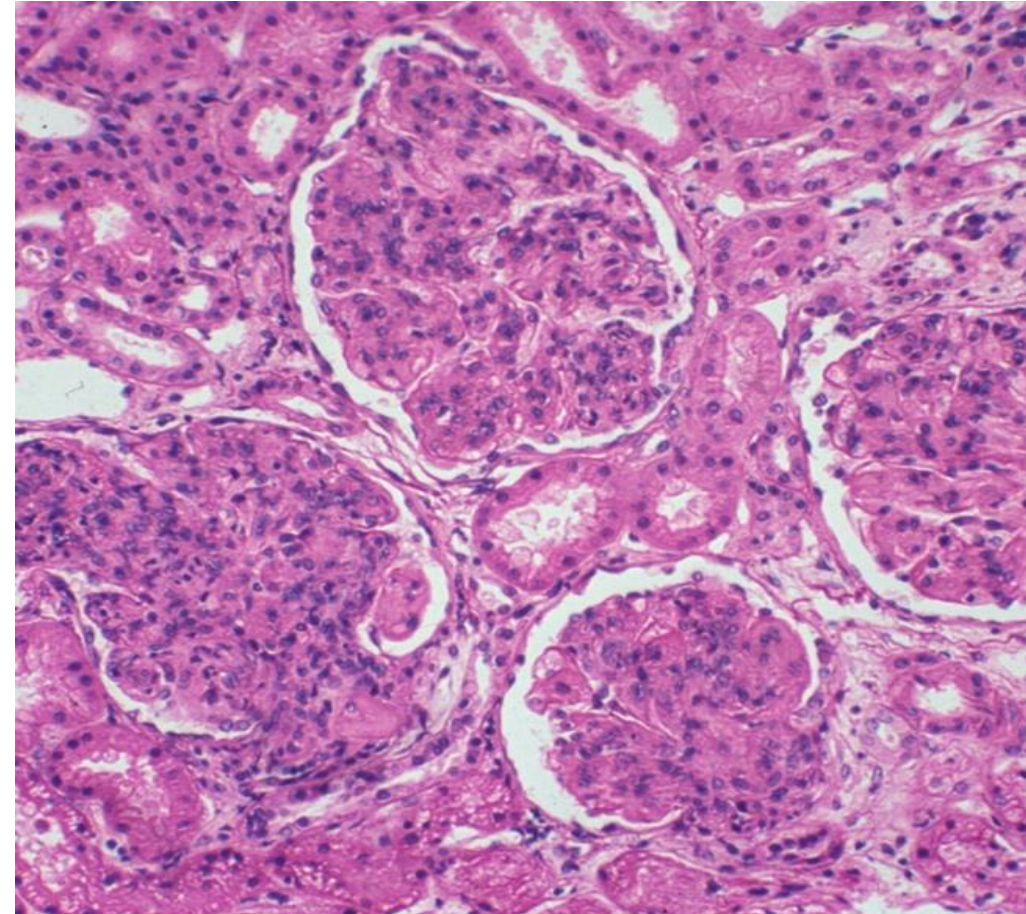
Analysis of the Hopkins Lupus Cohort of 2265 patients with SLE followed a mean of 6.2 years
Al Sawah et al. *Lupus Sci Med.* 2015;2(1):e000066.

1. Fanouriakis A, et al. *Ann Rheum Dis.* 2020;79(6):713-723.

2. KDIGO 2021 Clinical Practice Guidelines for the Management of Glomerular Diseases. *Kidney Int.* 2021;100(45):S1-S276

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?**



Induction therapy for proliferative LN KDIGO 2021

- Intravenous methylprednisolone **0.25–0.5 g/d** for 3 days, followed by
- Oral prednisolone **0.6–1 mg/kg/d** ideal body weight, taper to ≤ 7.5 mg/d by end of 3 months

Plus

Intravenous cyclophosphamide
500 mg q2 weeks \times 6

Or

Oral mycophenolate mofetil
2–3 g/d for 6 months

Therapy FPLN or DPLN +/- MLN
KDIGO

KI 105 Sup: S1-S69 2024

Glucocorticoids
Methylprednisolone i.v. 0.25–0.50 g/d for 1–3 days as appropriate depending on disease severity and rate of progression, then prednisone p.o. at approximately 0.35–1.0 mg/kg/d (not to exceed 80 mg/d) and taper over a few months to maintenance dose (the lower steroid dosing option referring to the reduced-dose regimen in the voclosporin trials)¹
(Practice Point 10.2.3.1.1)

Less Corticosteroids

Choice of Initial Therapy

Includes Belimumab
and Voclosporin

and one of the
following options

CNI + MPAA
Voclosporin 23.7 mg b.i.d. and MPAA in patients with eGFR >45 ml/min per 1.73 m²
tacrolimus (trough level approximately 5.5 ng/ml [6.8 nmol/l], data mainly from Chinese patients) and reduced-dose MPAA in patients with SCr <3.0 mg/dL (265 μmol/l) as initial and

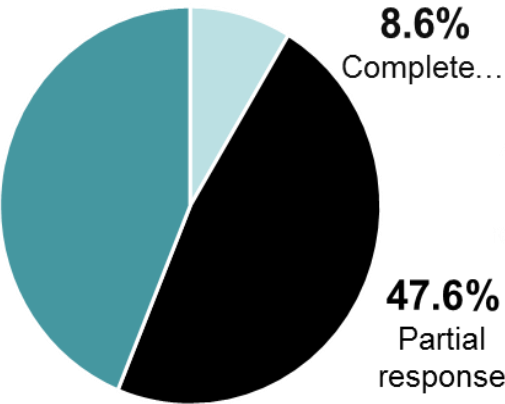
Mycophenolic acid analogs (MPAA) for at least 6 months
MMF p.o. 1.0–1.5 g b.i.d. or mycophenolic acid sodium 0.72–1.08 g b.i.d.
(Practice Point 10.2.3.1.3)

Cyclophosphamide for up to 6 months
i.v. 500 mg q2wk × 6 or 0.5–1.0 g/m² monthly × 6; or p.o. 1.0–1.5 mg/kg/d for 3 months
(Practice Point 10.2.3.1.2)¹

Belimumab + MPAA or reduced-dose cyclophosphamide
Belimumab (i.v., 10 mg/kg q2wk for 3 doses then q4wk) and MPAA or i.v. cyclophosphamide 500 mg q2wk × 6
(Practice Point 10.2.3.1.5)
Belimumab duration up to 3.5 years

Complete Response Rates Have Been Are Low With Standard-of-Care First-line Therapies

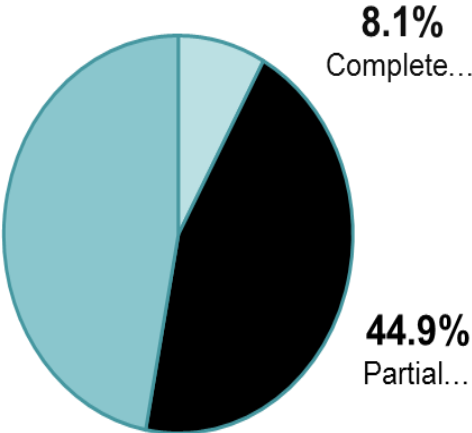
ALMS study MMF



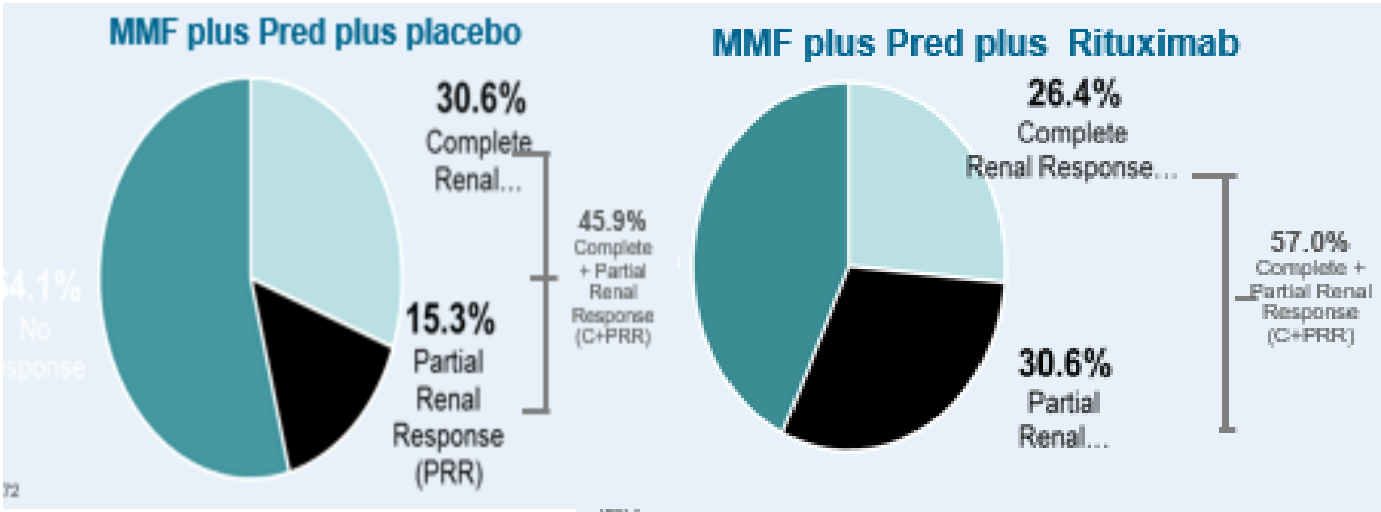
Response at 24 weeks

Appel , Contreras, Dooley et al JASN. 2009

ALM Study Cyclophos



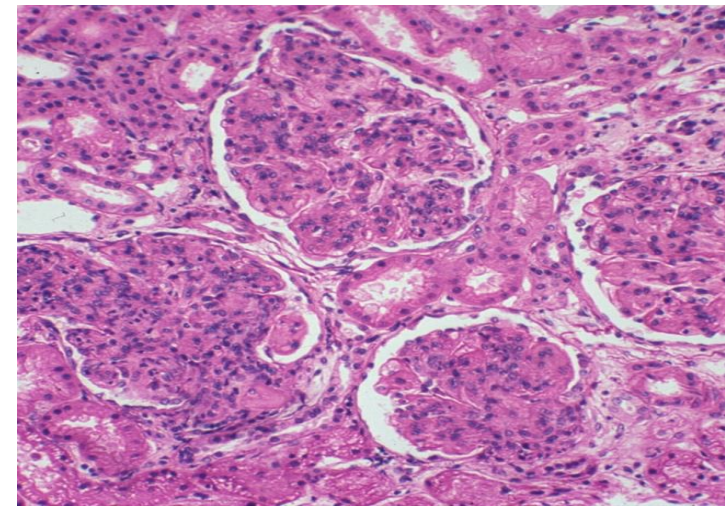
LUNAR Trial MMF + Pred w or w/o Rituximab



Response at 52 weeks

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

When to use the Newer Agents in Proliferative LN



- **Patient with newly diagnosed lupus nephritis**
- **Patient not adequately responding to treatment**
- **Patient with newly flaring lupus nephritis**
- **Patient with lupus nephritis who remains stable with MMF + steroids, but has not reached treatment goals**

If a flare or not responding to therapy ----Before new therapies ask
“Is it truly resistance, - a failure to reach goal, and/or not responding to therapy ???

Check for **Compliance** ; Consider USG and rebiopsy - **scarring vs active treatable LN.**

Current Available Treatment Choices for FPLN or DPLN in 2025

Additional Available Treatment Choices for 2025

- Anifrolimab
- 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 ahead of print.

Anifrolumab for Systemic Lupus Erythematosus

MULTICENTER, RANDOMIZED, DOUBLE-BLIND TRIAL

362 Patients with
moderately
to severely active SLE



Anifrolumab

300 mg every 4 wk
for 48 wk

(N=180)



Placebo

(N=182)

Response at 52 wk
(British Isles Composite
Lupus Assessment)

47.8%

31.5%

Difference, 16.3 percentage points;
95% CI, 6.3 to 26.3; P=0.001

**More patients had a response
to anifrolumab than placebo,**

in contrast to results of similar trial with different primary end point

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 Knitz, 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

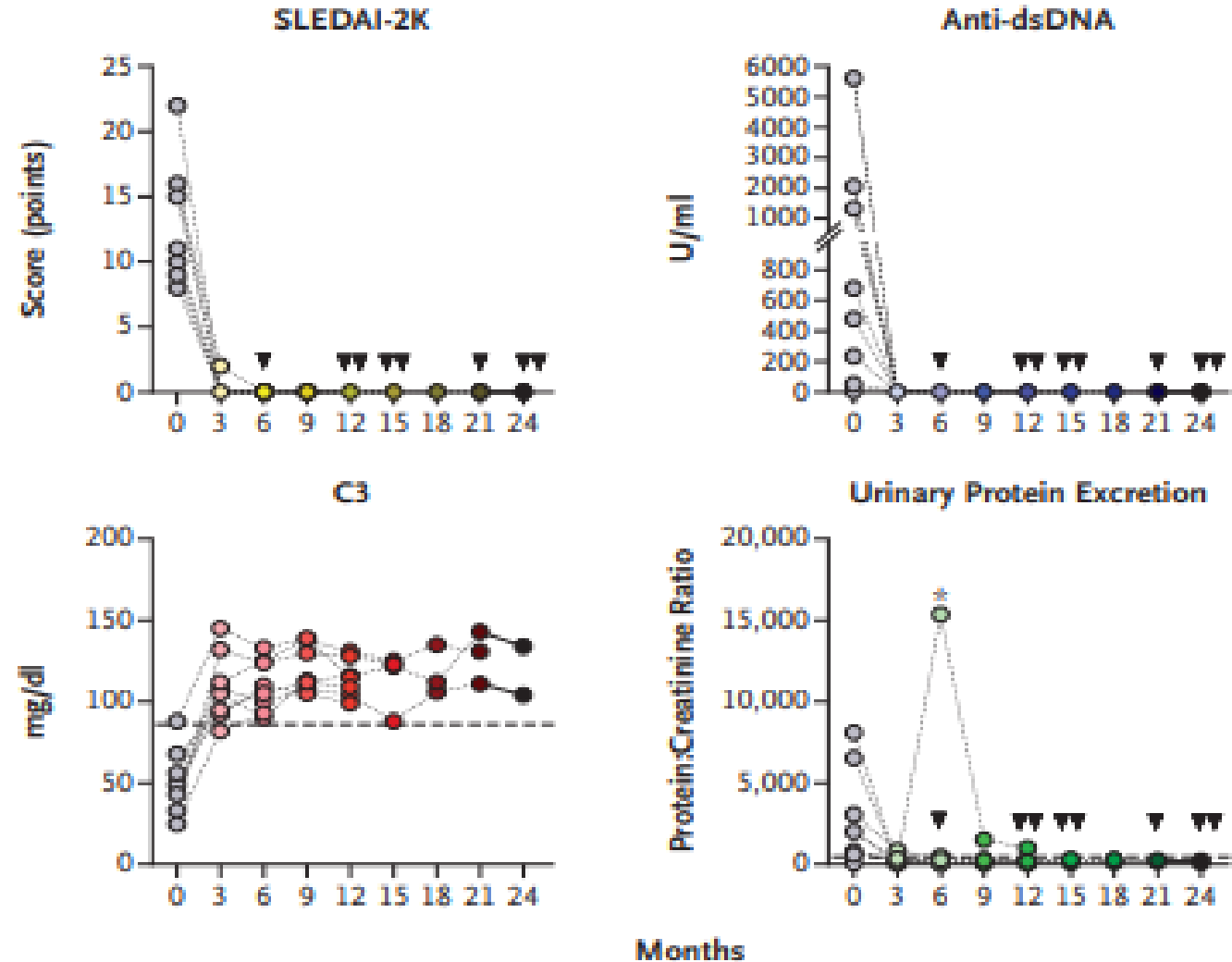
Treatment for autoimmune diseases such as systemic lupus erythematosus (SLE), idiopathic inflammatory myositis, and systemic sclerosis often involves long-term immune suppression. Resetting aberrant autoimmunity in these diseases through deep depletion of B cells is a potential strategy for achieving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

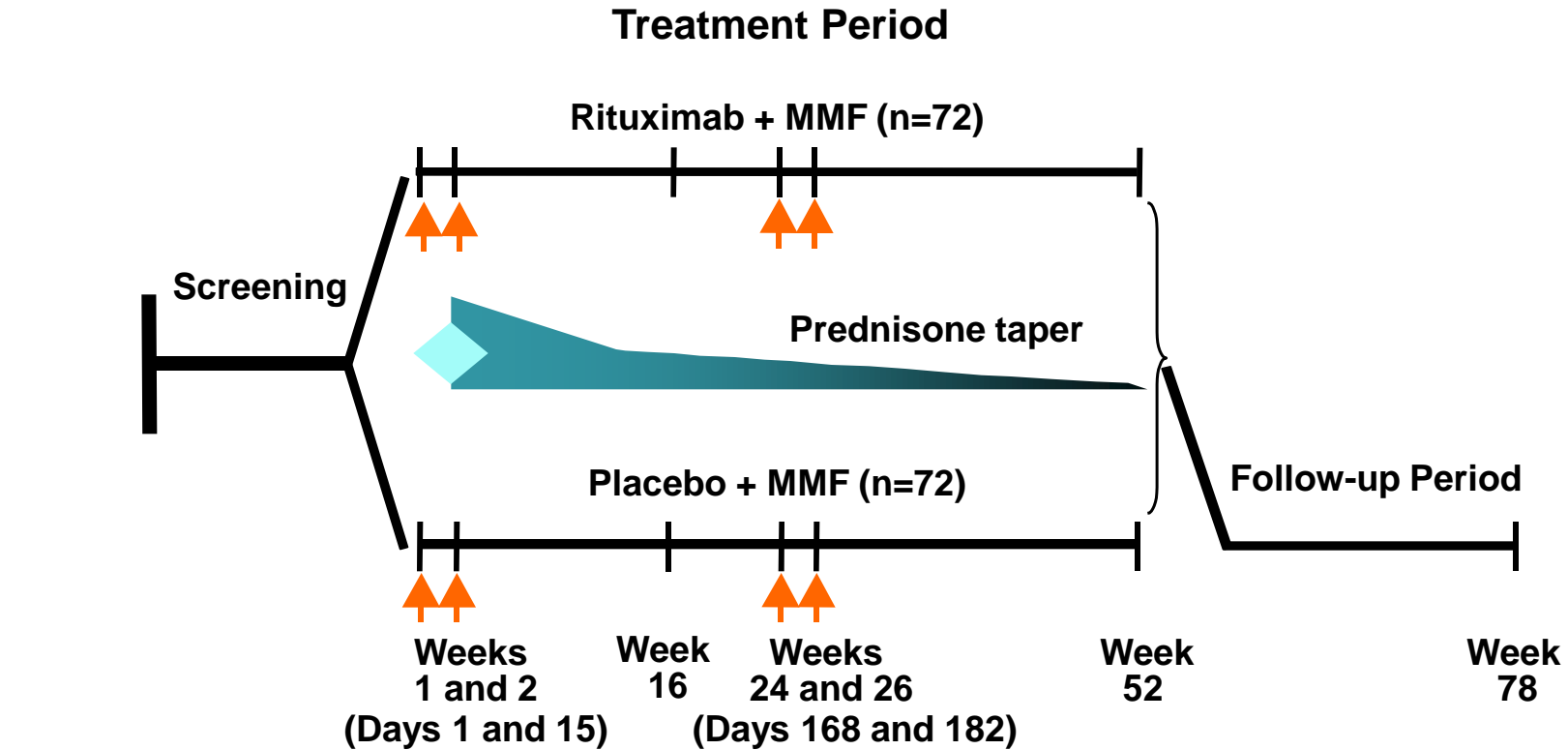
Uncontrolled heterogenous group with 8 w SLE

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



LUNAR – RITUXIMAB Study Design

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

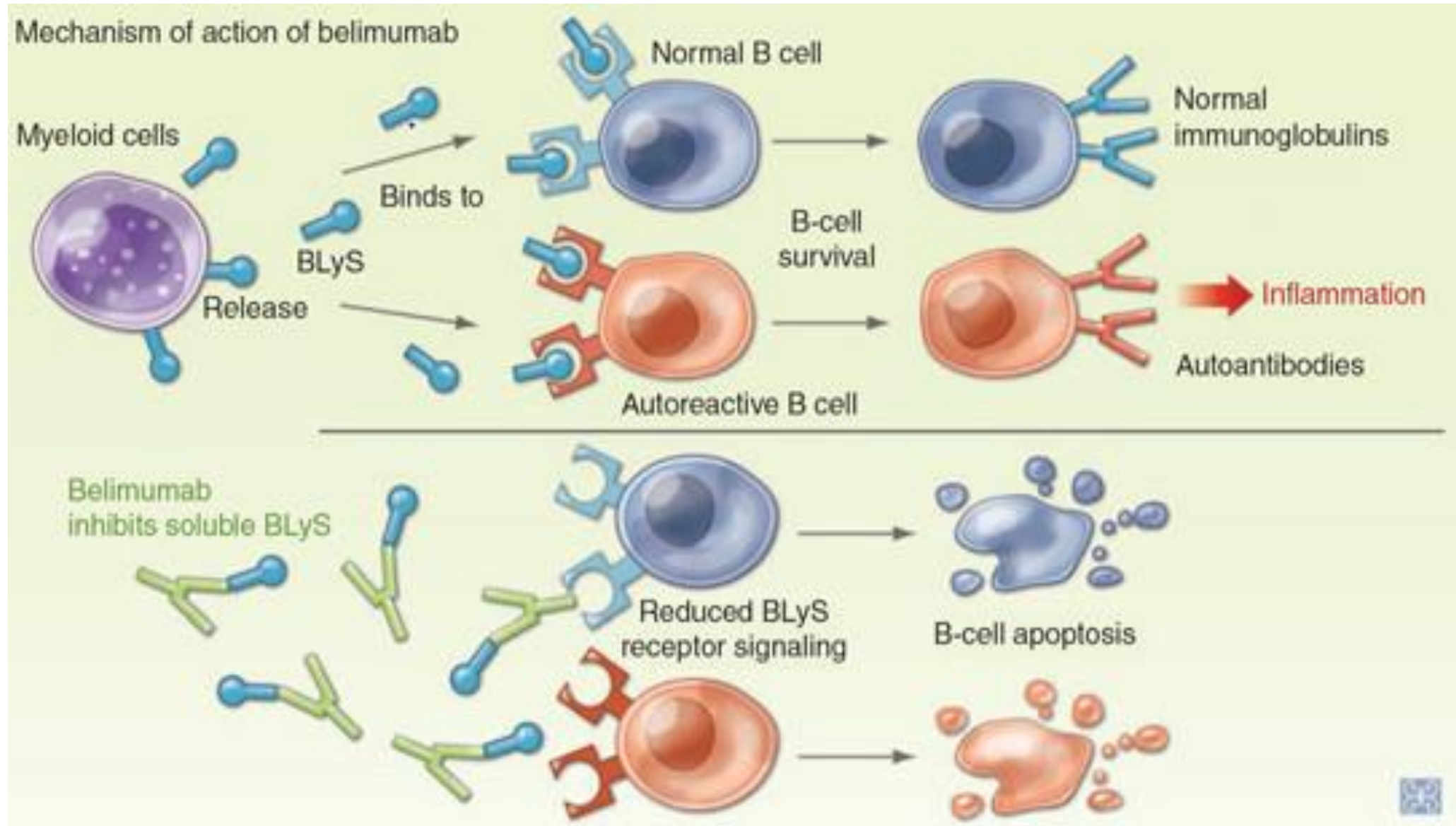


↑ = Study drug infusion.

◆ = Corticosteroids:

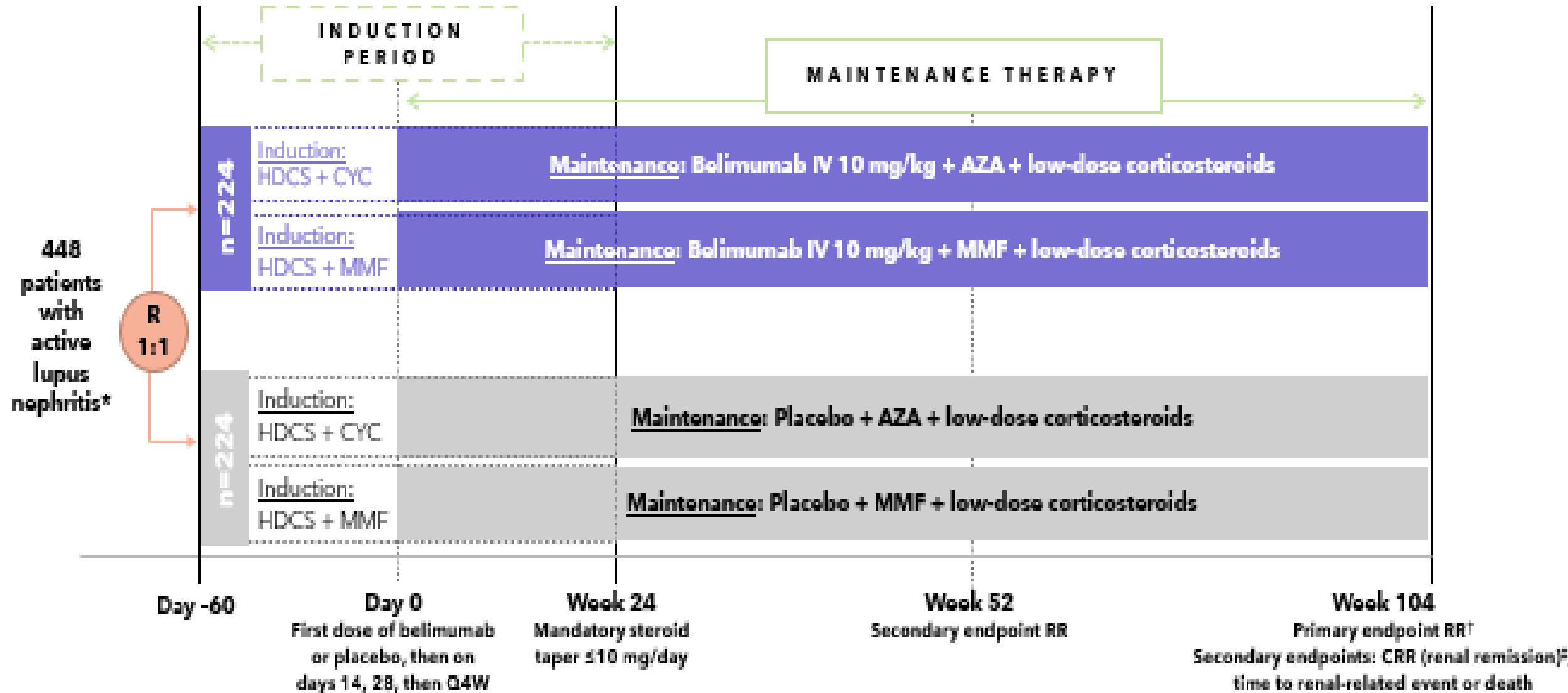
- 1000 mg IV methylprednisolone given at days 1 and then days 2, 3, or 4
- Oral prednisone initiated at 0.75 mg/kg/day after IV steroids and then tapered to 10 mg/day by day 112

Mechanism of Action of Belimumab in LN



Two year Randomized, controlled Trial of Belimumab in LN

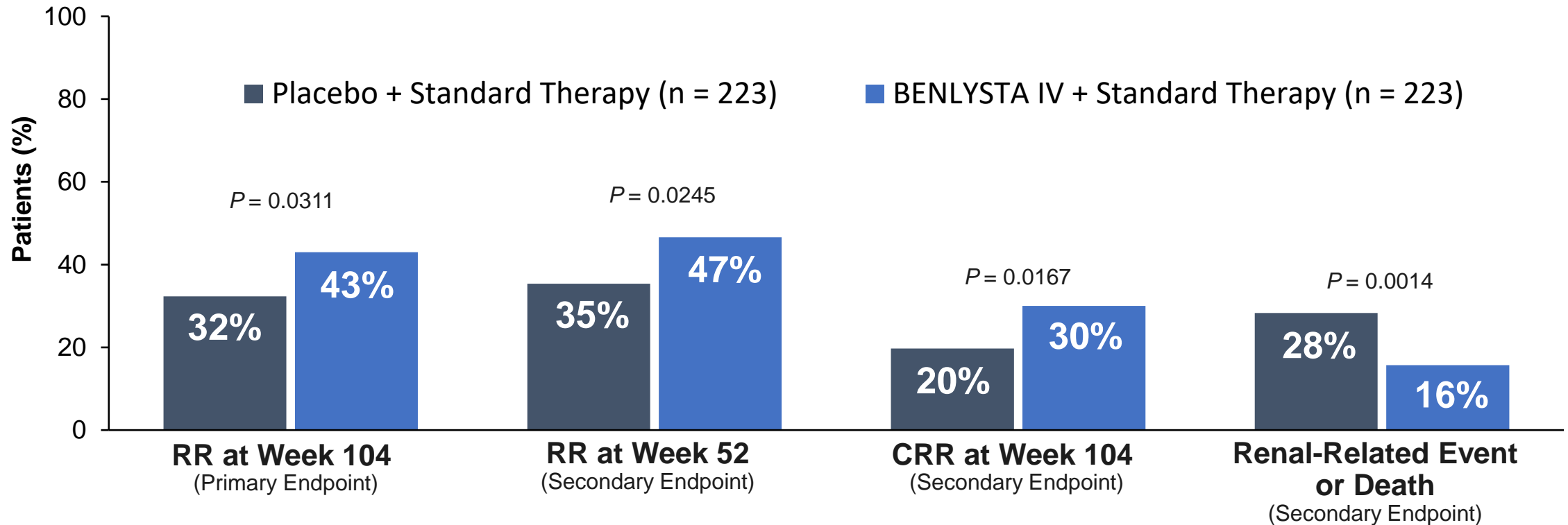
Furie R, Rovin B, Houssiau F, et al NEJM 383: 1117 2020



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}



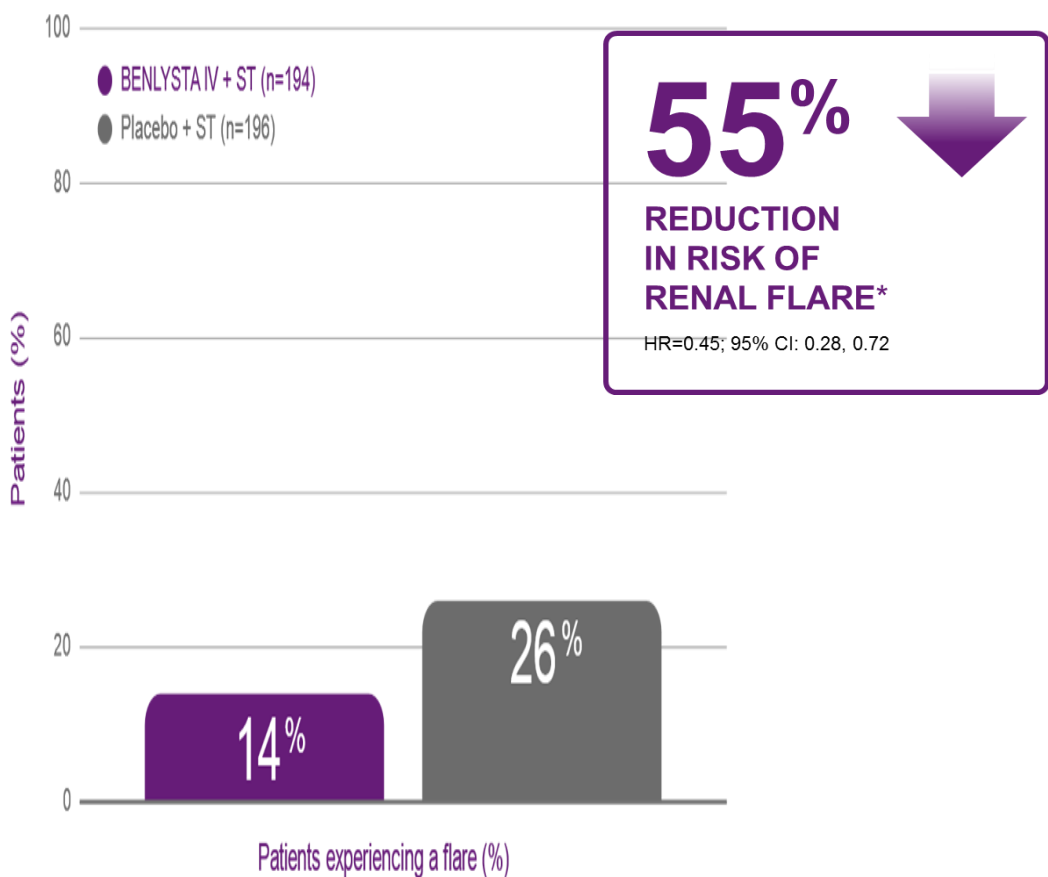
Standard Therapy :

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

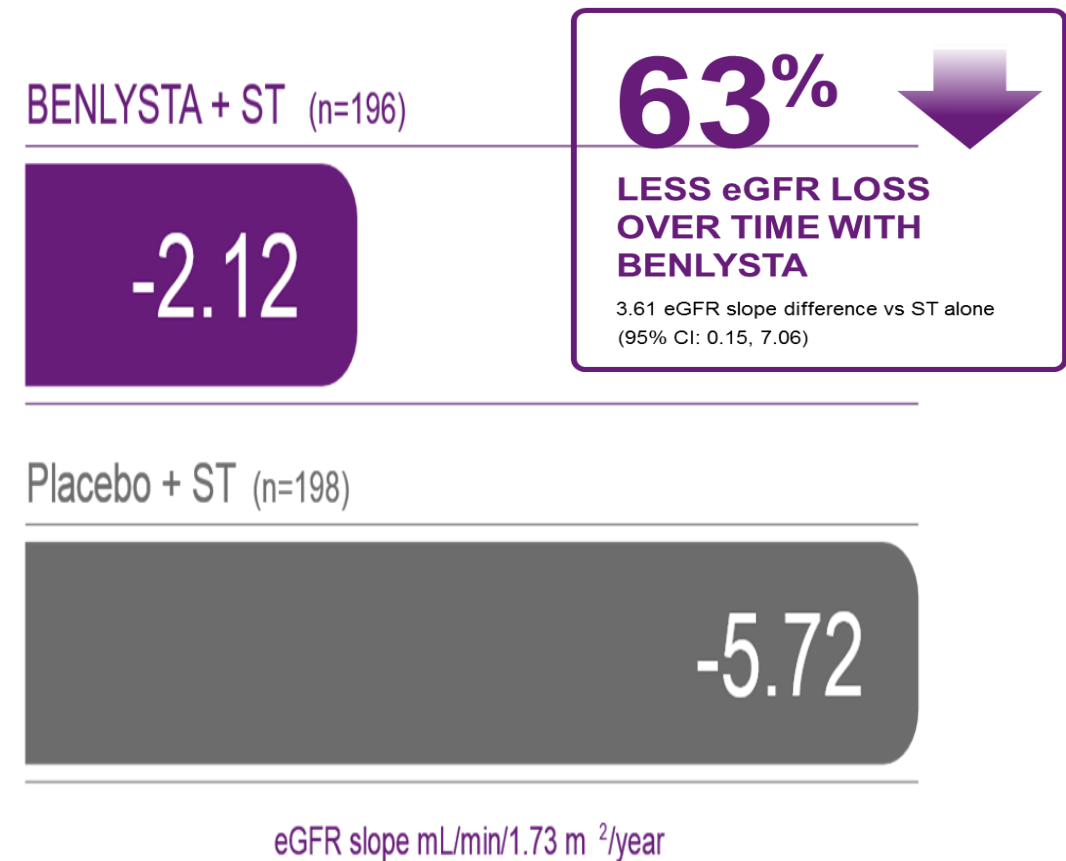
Post Hoc Analysis of BLISS LN Trial

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

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

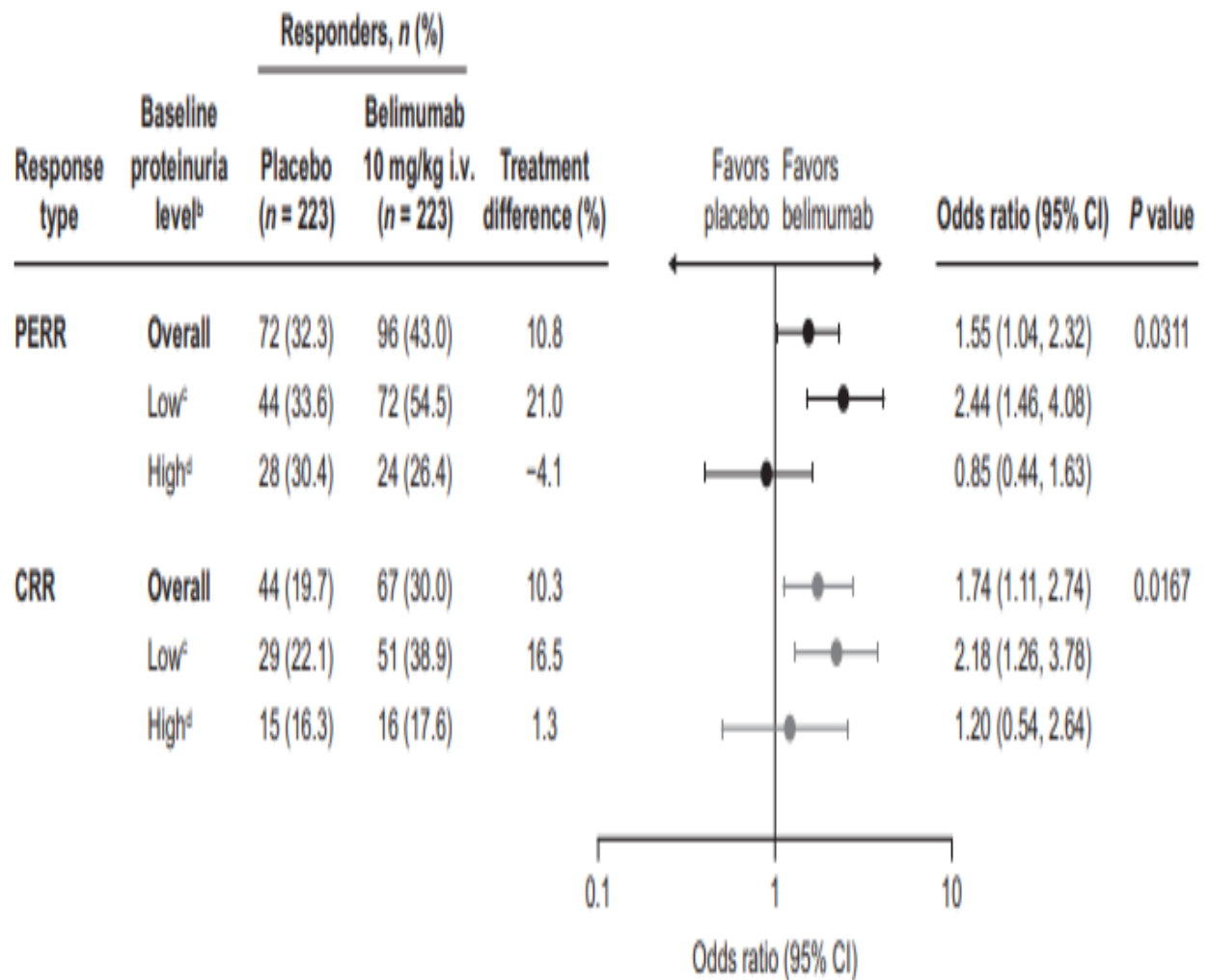
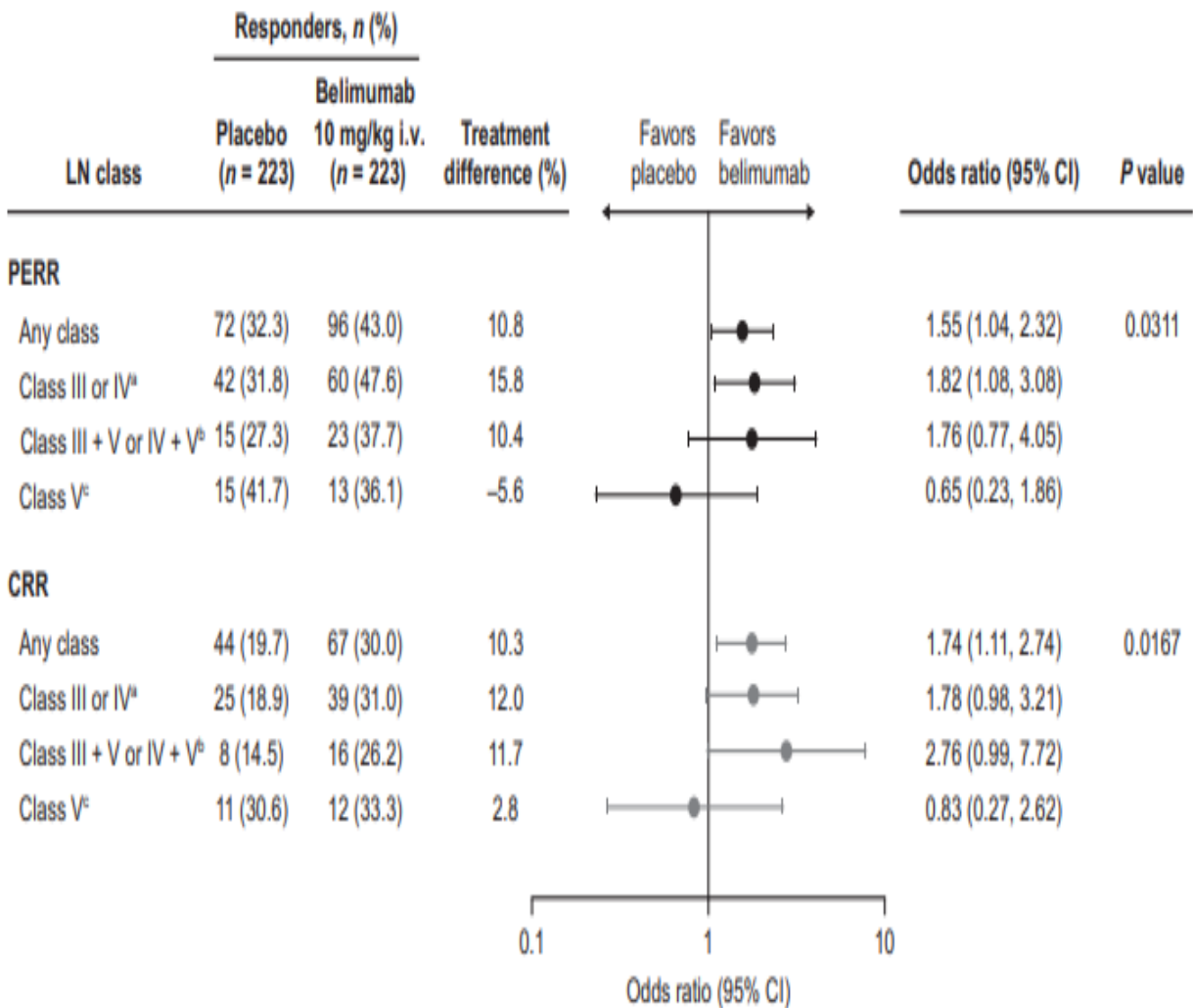


eGFR slope (Week 24 to 104)



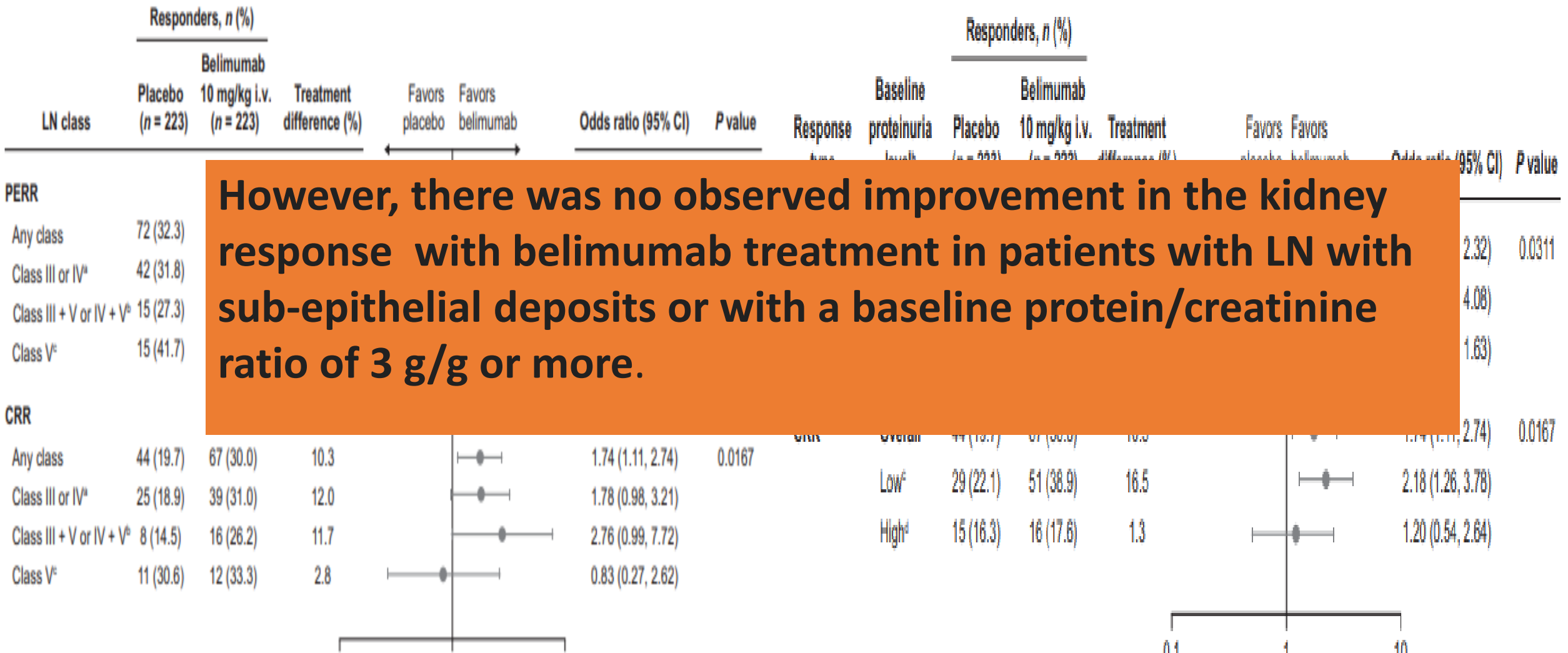
Secondary analysis of Belimumab International Study in LN – effects on kidney outcomes, and preservation of kidney function

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



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



However, there was no observed improvement in the kidney response with belimumab treatment in patients with LN with sub-epithelial deposits or with a baseline protein/creatinine ratio of 3 g/g or more.

BLISS LN Study -My Conclusions

Positive Points of Study:

Broad population background and different LN classes.

Study used both SOC meds : MMF and IV Cyclophosphamide

Effective –reaching all end points including complete remit.

Good steroid tapering.

Little toxicity in this study less with belimumab.

Can be self administered subcutaneously.

Limitations:

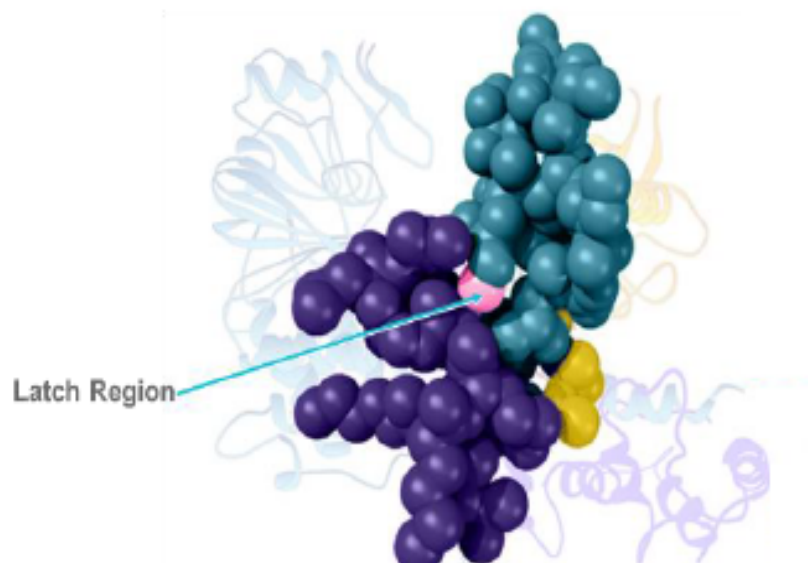
Patients did not have very reduced GFR and may not be sickest.

Still have many treatment failures at 1 and 2 yrs.

.

?s about those with > 3 g proteinuria and subepithelial EDD (MLN –Class V)

Voclosporin: A Novel CNI



- Novel CNI developed as a structural change from cyclosporine A, incorporating a single carbon extension with a double-bond
- Voclosporin has a consistent dose response potentially eliminating the need for therapeutic drug monitoring
- 4x potency over cyclosporine A

CNIs in Renal Disease: Two Separate Mechanisms of Action

1 Inhibition of calcineurin reduced cytokine activation of t-cells



2 Potential disease-modifying podocyte stabilization, which protects against proteinuria

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

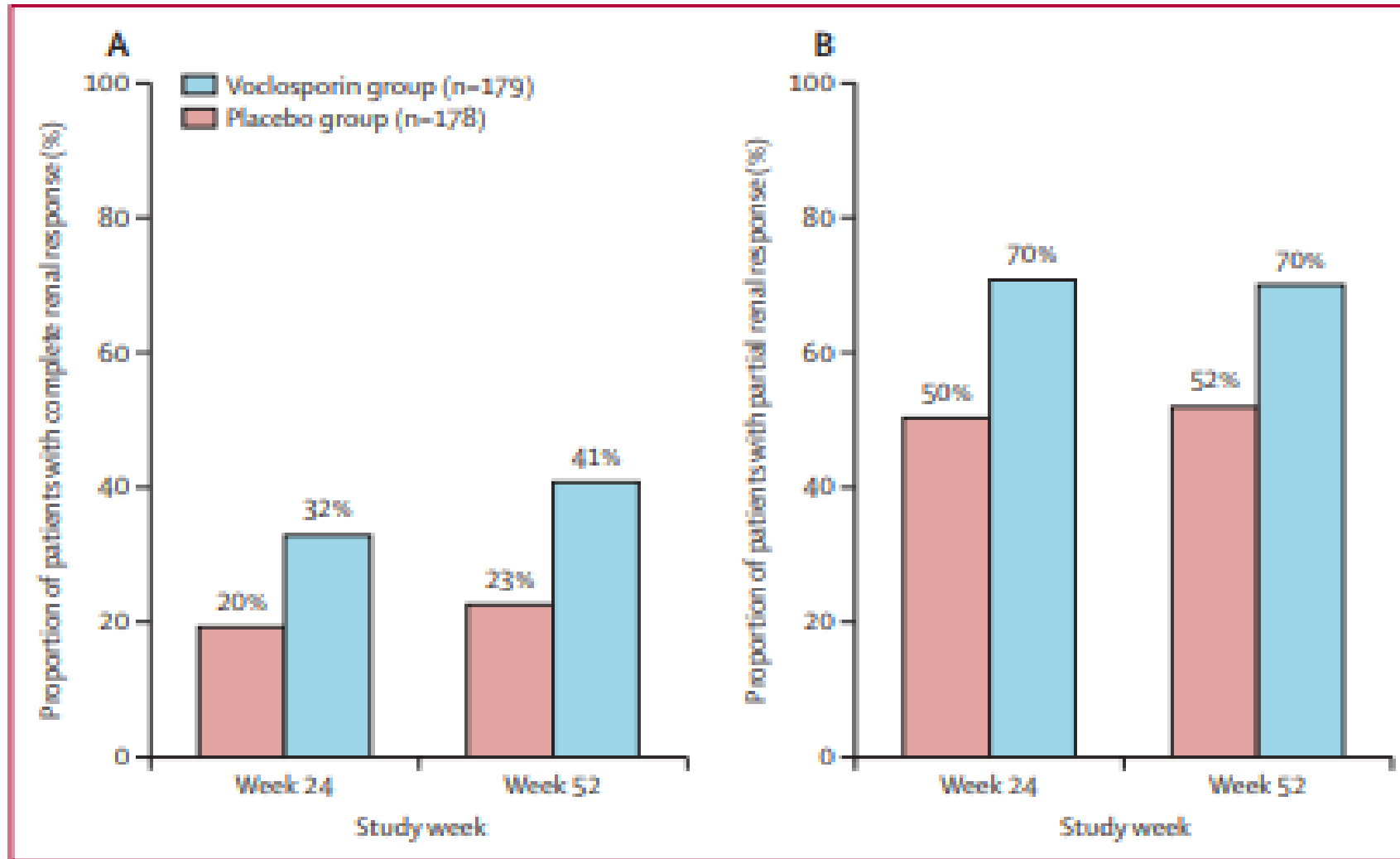
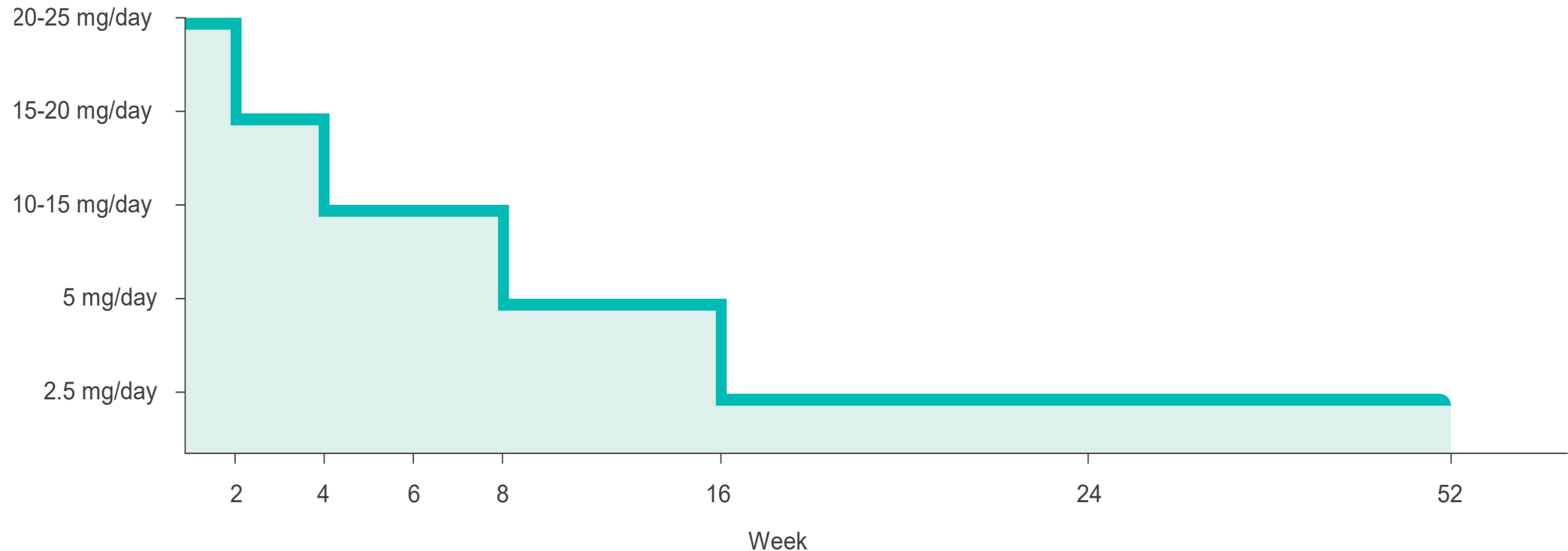


Figure 2: Complete and partial renal response endpoints (intention-to-treat population)

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

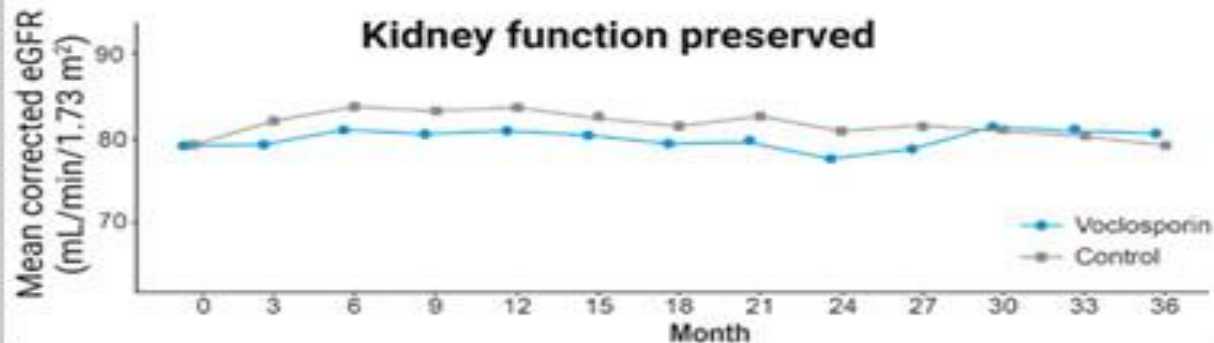


86.1%
completed
AURORA 2

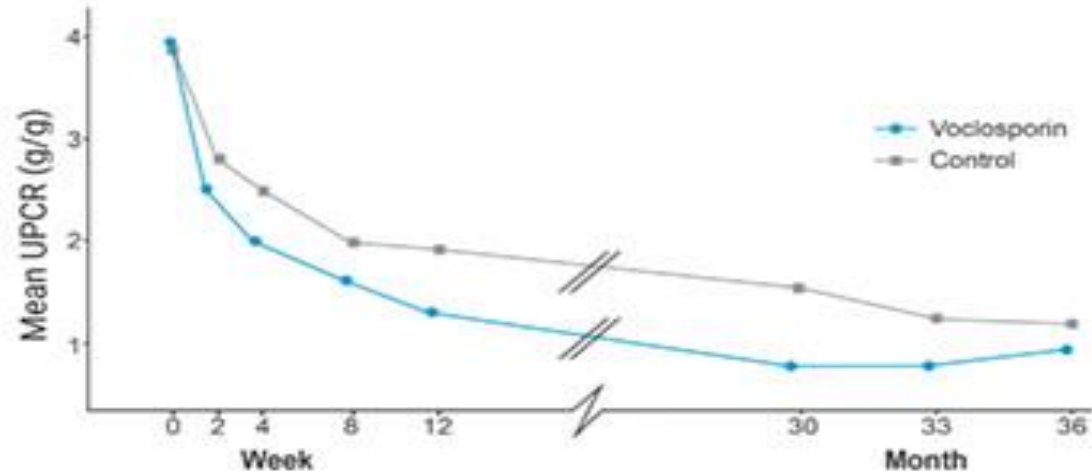


Comparable AEs in
both groups

Kidney function preserved



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.

Aurora Voclosporin Study My Conclusions

Positive points of study:

Broad patient background and Classes of LN

Effective –reaching all end points.

Good steroid tapering to **very low** levels.

Little toxicity in this study.

No CNI level measurement necessary. Adjust Dose to creatinine – GFR.

Limitations:

May not be the sickest patients

Only complete data at one year

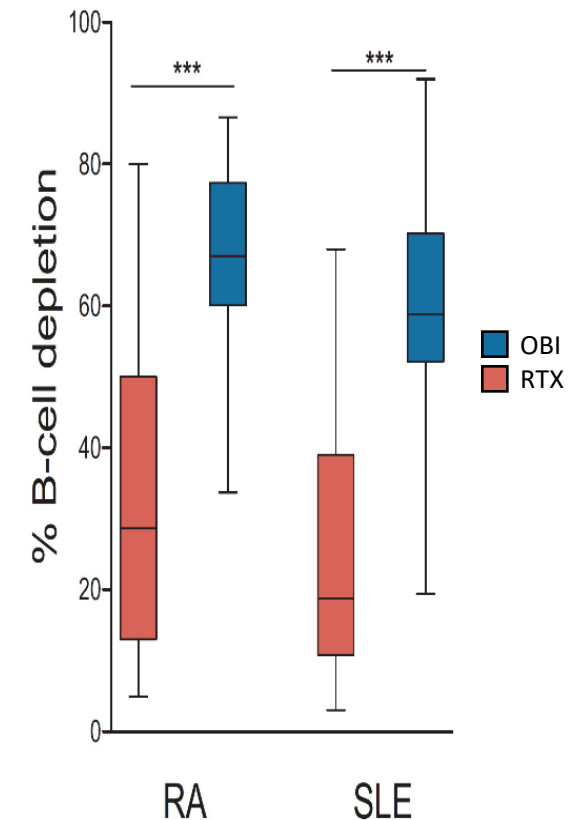
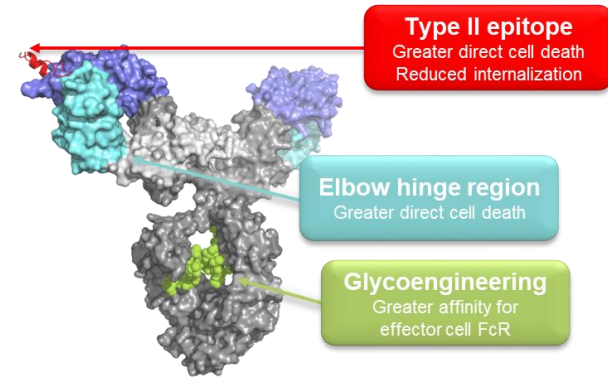
Only studied w MMF induction and 2 g (not 3 g) and not Cyclophosphamide.

CNI – always concerned about long-term Nephrotoxicity. Drug interactions CYP enzymes.

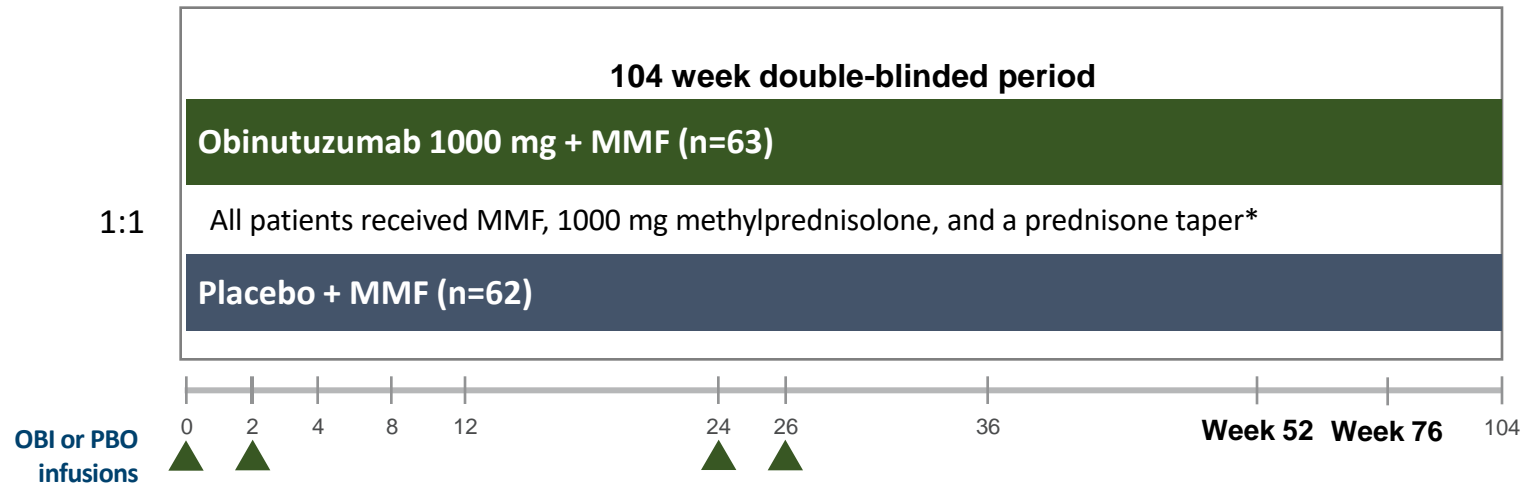
Needs dose reduction at low GFR.

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}



A Phase 2 Randomized, Controlled Study of Obinutuzumab with Mycophenolate and Corticosteroids in Proliferative Lupus Nephritis -NOBILITY



Key inclusion criteria:

- ISN/RPS Class III or IV LN w/i six months, concomitant class V permitted
- UPCR ≥ 1 on 24-hour collection
- :

Key exclusion criteria:

- Rapidly progressive GN
- eGFR < 30 mL/min
- $> 50\%$ of glomerulosclerosis
- :

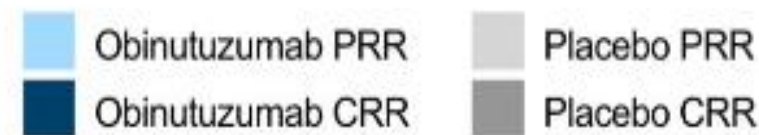
Primary endpoint

- Complete renal response (CRR) at week 52

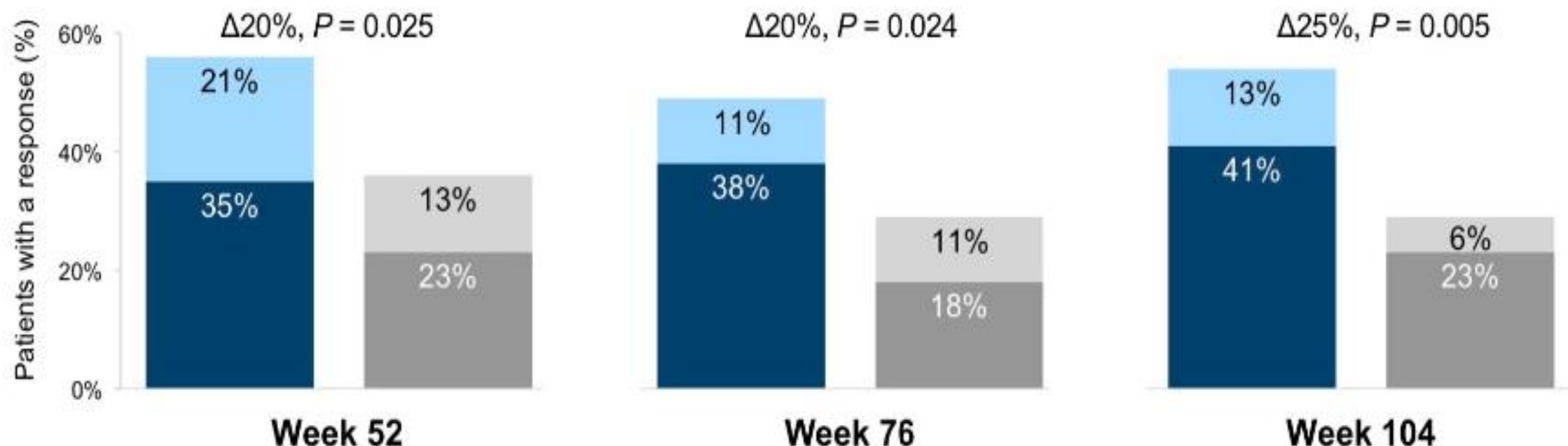
Key secondary endpoints:

- Overall renal response (CRR or PRR)
- Change in dsDNA, C3, C4

Renal response endpoints



Overall renal response (CRR or PRR)



CRR required all of:

- UPCR < 0.5
- Serum creatinine \leq upper limit of normal
- Serum creatinine \leq 115% of baseline value
- < 10 RBC/hpf without RBC casts

PRR required all of:

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

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. R. J. Meuwert,¹⁹ J. L. H. J. van der Woude,¹² for the REGENCY Trial Investigators*

NEJM Feb 7, 2025

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.

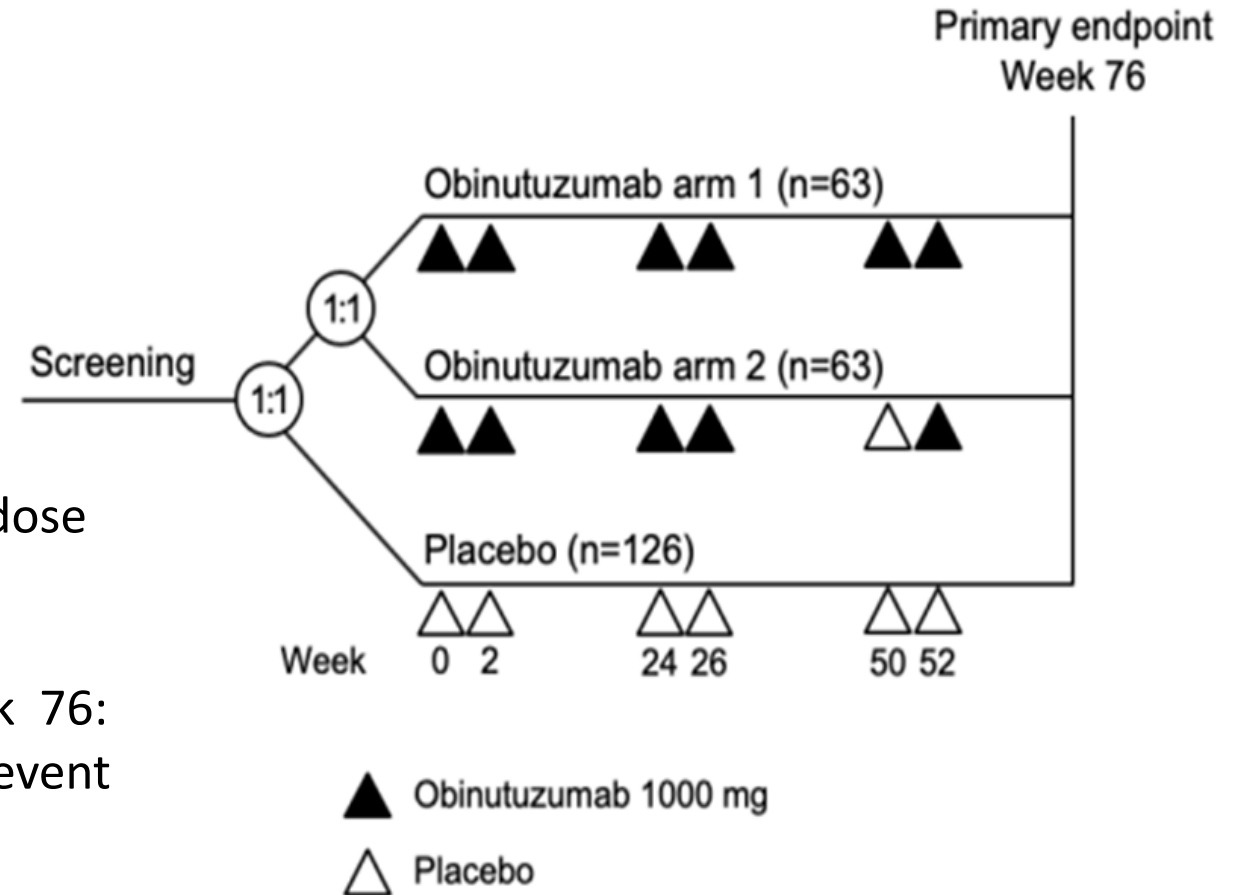
Phase 3 randomized, international, controlled trial .
1:1 active LN obi vs pbo w all pts getting MMF + low dose pred.

Primary endpoint Complete renal response CRR by wk 76:
UpUcr <0.5 , eGFR 85% baseline, no intercurrent bad event
Secondary endpoint wk 76 CRR + < 7.5 mg pred.

271 pts (135 Obi) - **Complete renal response at wk 76**
46% Obi and 33% PBO.

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

No difference in adverse events except more COVID with Obi



All patients receive MMF and a prednisone taper

Randomized trial of Obinutuzumab vs PBO on Day 1 + Weeks 2, 24, 26, d 52

- 270 SLE Pts with **Class III or IV LN**
- Urine protein-to-creatinine ratio ≥ 1
- ANA titer $\geq 1:80$ (or equivalent positive test)

Complete Renal Response at Week 76

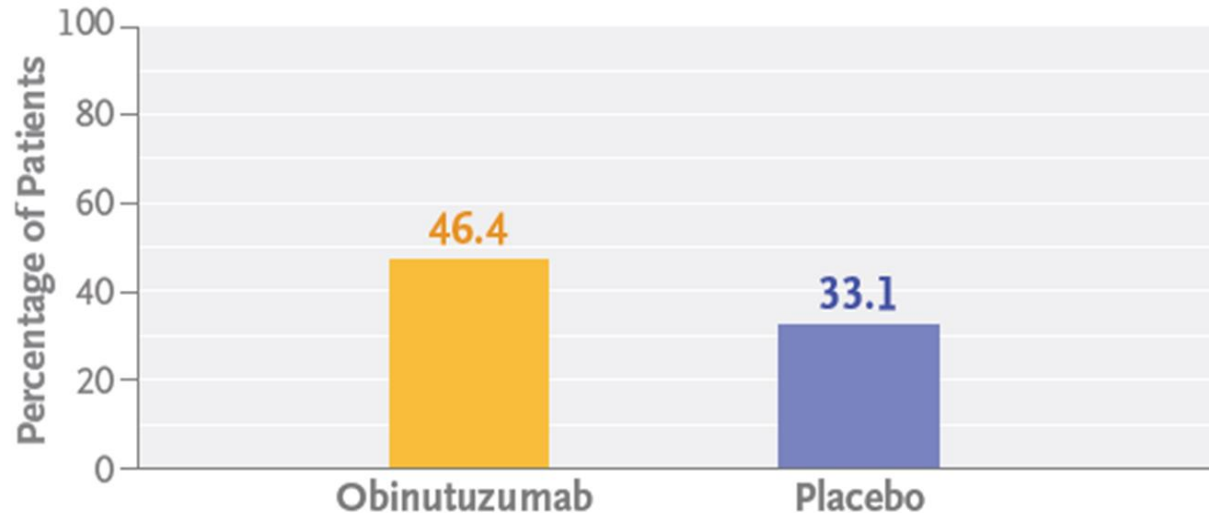
Urine protein-to-creatinine ratio < 0.5

eGFR $\geq 85\%$ of baseline

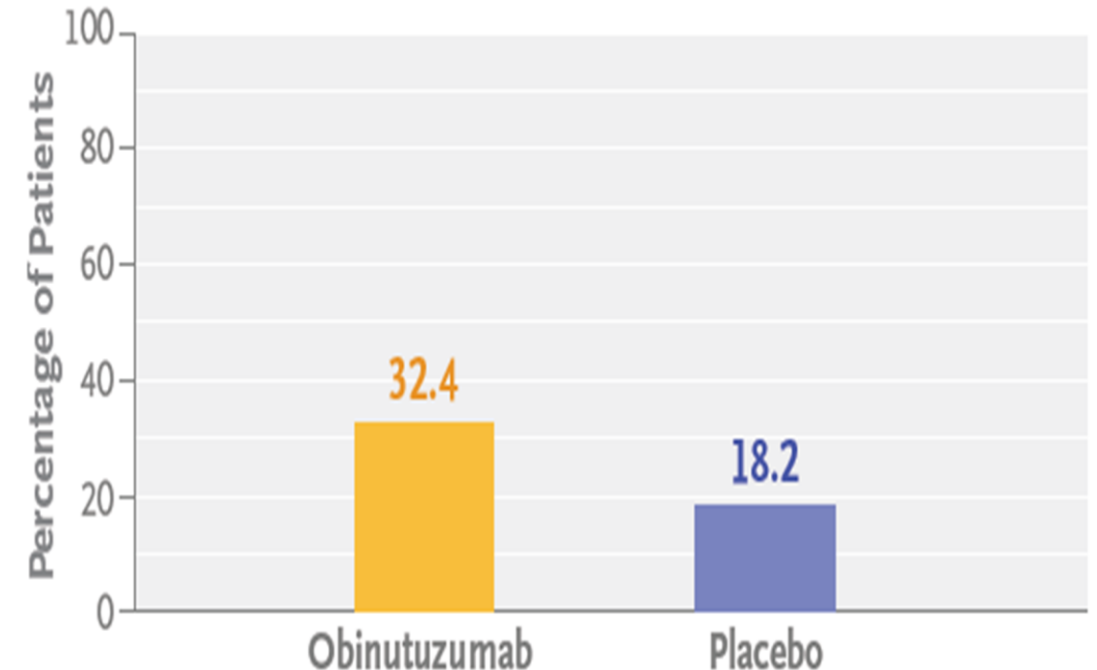
No intercurrent event

Complete Renal Response

Adjusted difference, 13.4 percentage points
(95% CI, 2.0 to 24.8); P=0.02



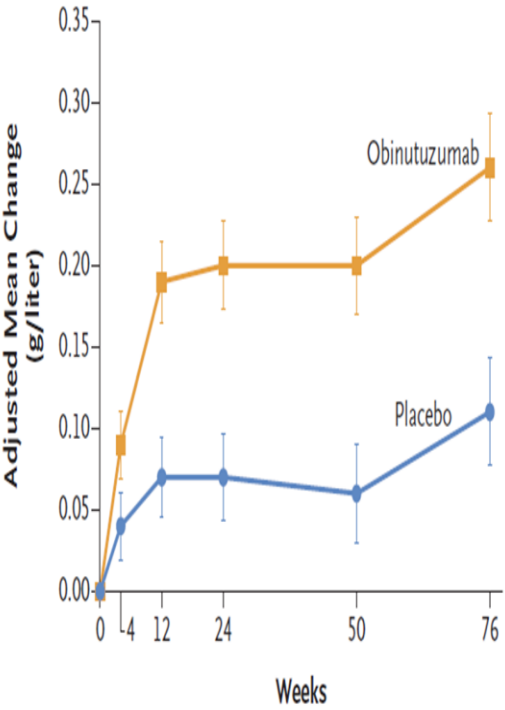
Serious Adverse Events



Efficacy and safety of Obinutuzumab in LN

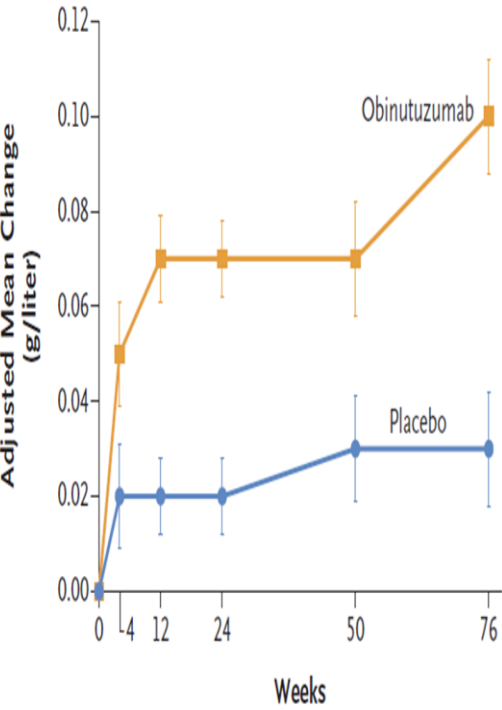
Furie et al. NEJM Feb 7 , 2025

A Change in C3 Complement Level from Baseline



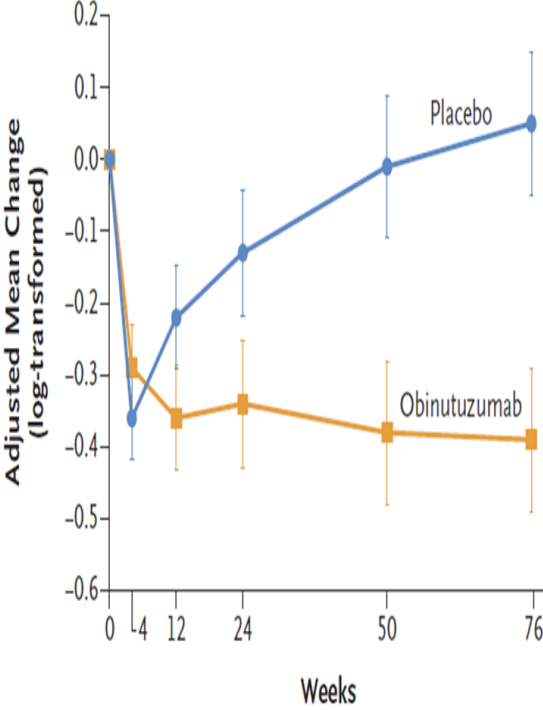
No. of Patients	271	271	271	271	271	271
No. with Missing Data	0	10	10	14	22	26

B Change in C4 Complement Level from Baseline



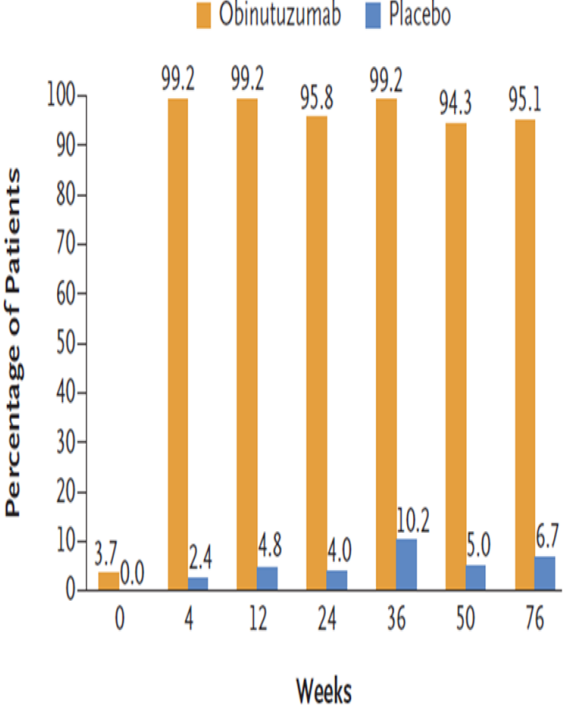
No. of Patients	271	271	271	271	271	271
No. with Missing Data	1	11	11	16	24	27

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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How I treat FPLN and DPLN +/- MLN

Assess disease severity :

- Clinical SLE activity – HBP, anemia, edema, residua from former treatments, serology (anti-DNA, Complement).
- Renal Involvement – creatinine (GFR), Proteinuria (Uprotein/Ucreatinine).
Consider Bx (Class + AI + CI) - crescents, fibrinoid necrosis,
tubulo-interstitial fibrosis.

Treat aggressively :

I often start with steroids and MMF – If not reaching goals (protein reduction etc) by 3-6 months I add either belimumab or voclosporin. At present if very heavy proteinuria and + Class V prefer Voclosporin.

If resistant I consider rituximab or obinutuzmab.

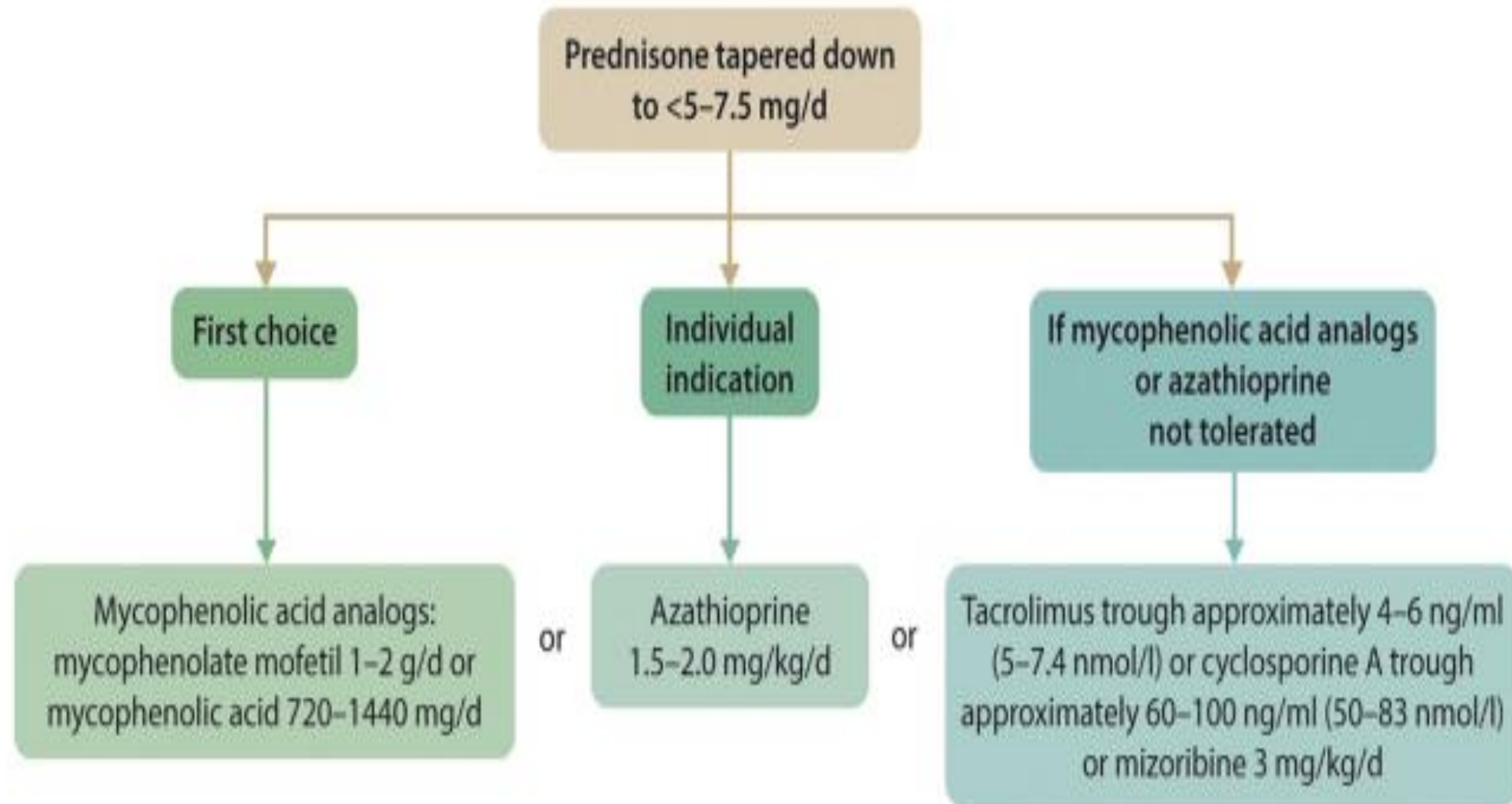
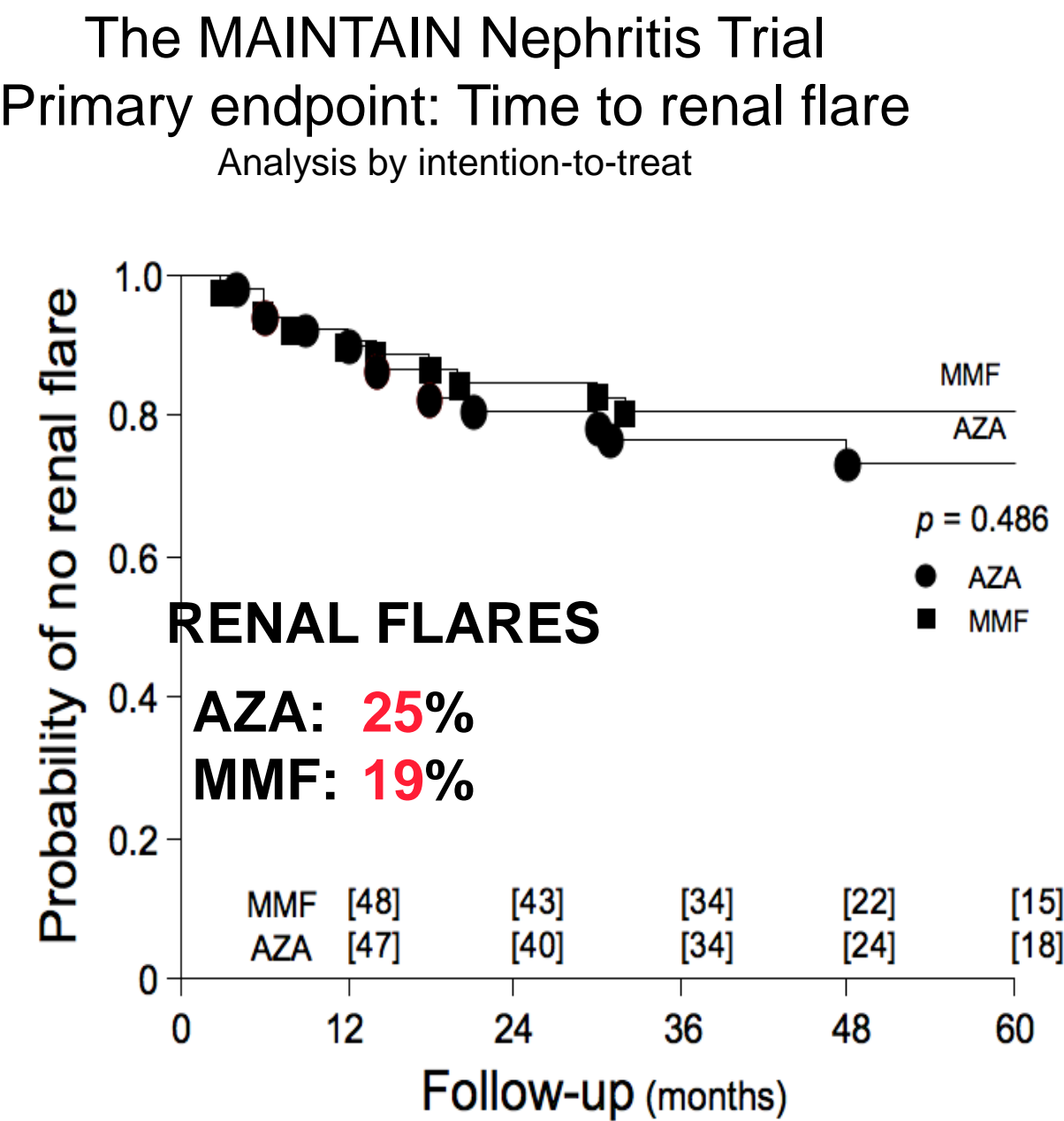
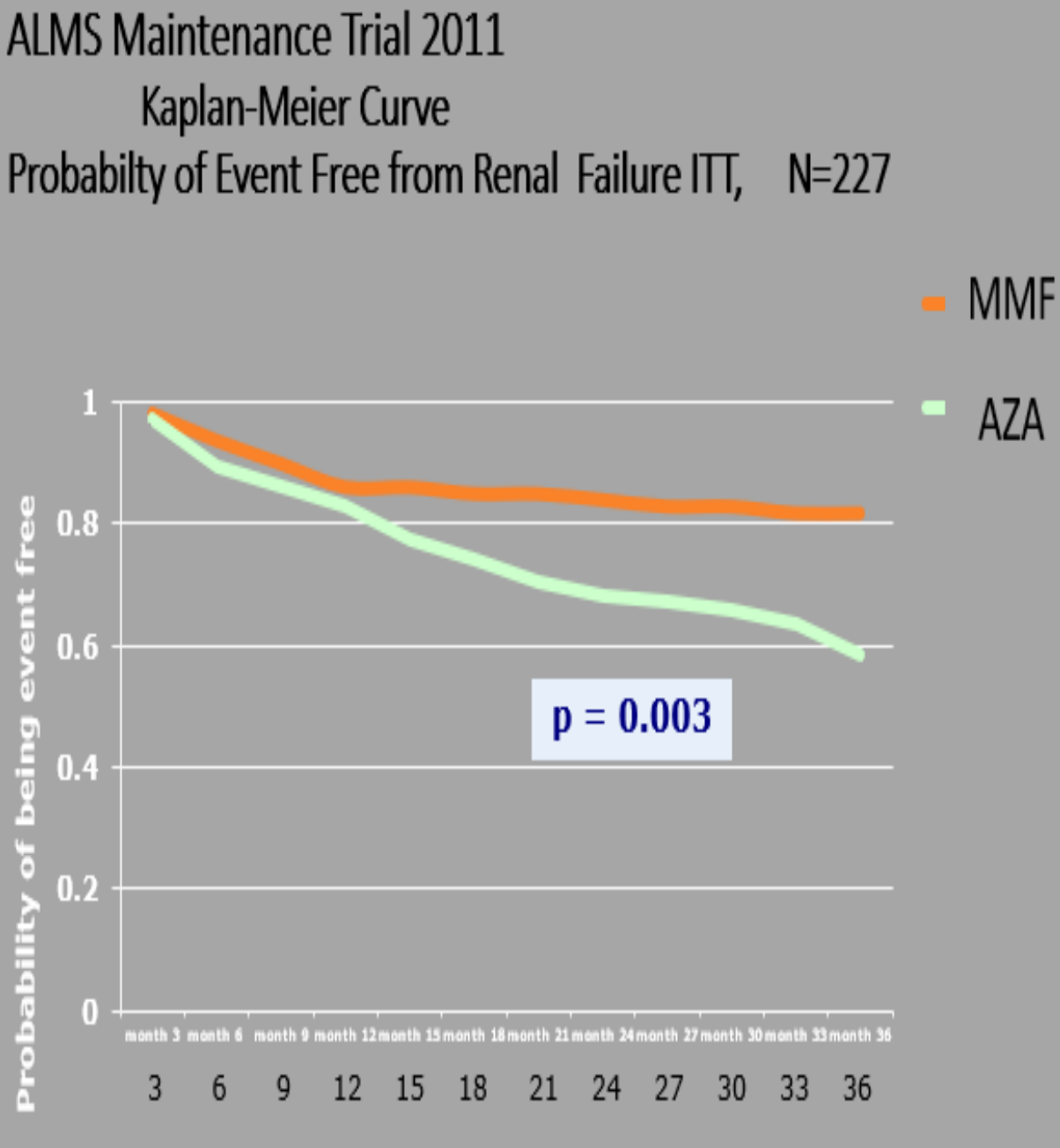


Figure 28 | Maintenance therapy for Class III and Class IV LN. The target ranges for CNIs have been based on the transplant literature. The



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.
- 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

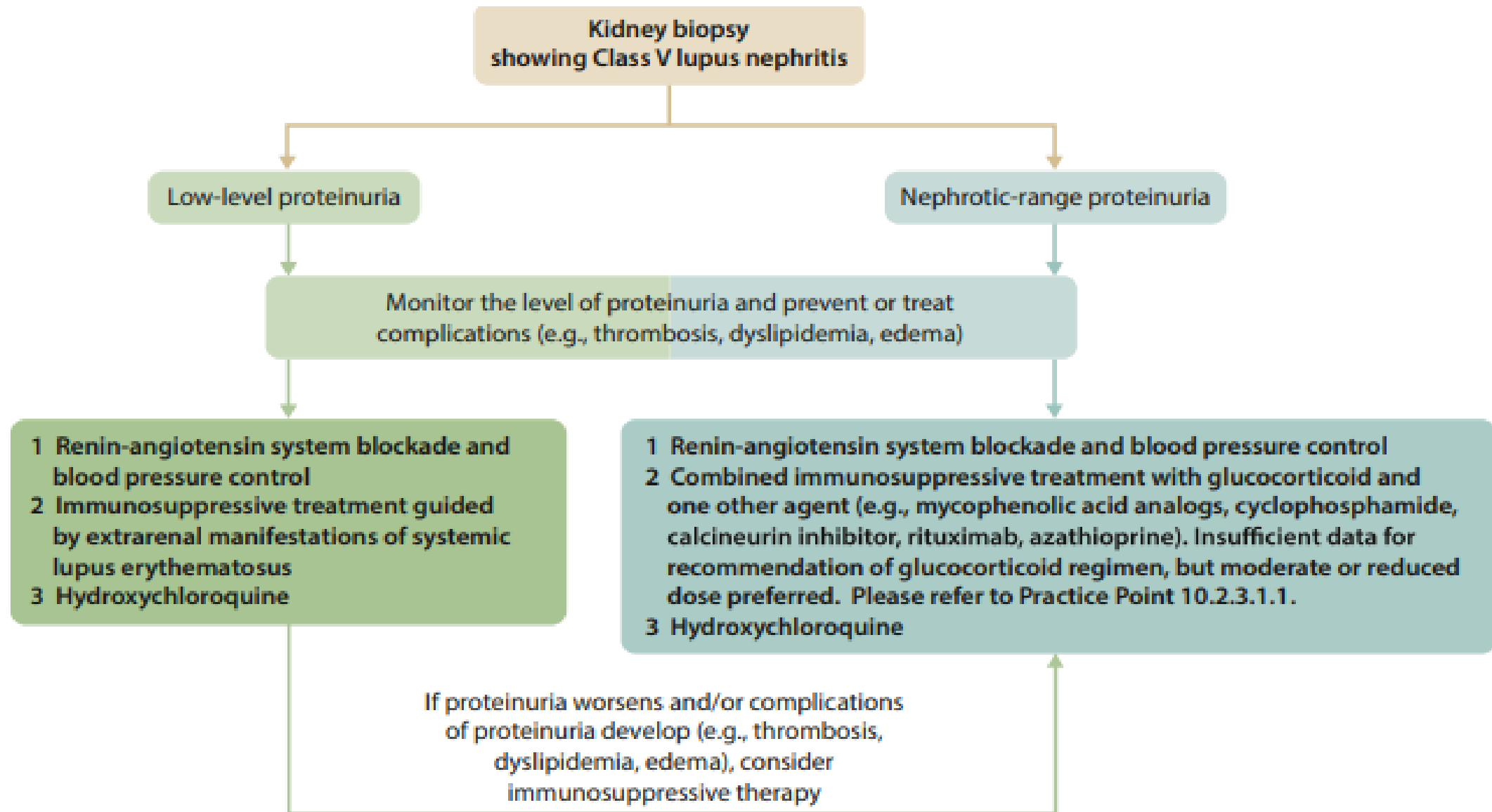
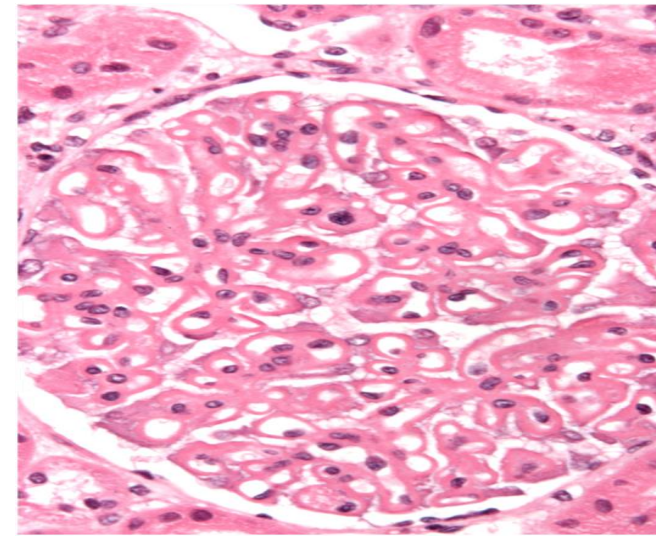


Figure 10 | Management of patients with pure Class V lupus nephritis.

How I treat Membranous LN



- 1) For LMN (Class V+III (FPLN) or Class V + IV (DPLN) 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- pregnancy-etc considerations.

I prefer to use MMF + low dose steroids as initial therapy.

If not reaching goals of protein reduction I add either CNI or rituximab. Voclosporin has good data on very low dose steroid therapy and OK with heavy proteinuria. Belimumab? Consider using rituximab or Obinutuzumab.

The New Medicines for LN – Belimumab, Voclosporine, Obinutuzumab.

- 1) We needed and now have new medicines to treat LN.
- 2) We have better goals (e.g. reduction of proteinuria) that correlate with outcome.
- 3) We have large controlled, blinded, randomized trials that show the new meds work.
- 4) We need to reduce corticosteroids
- 5) Not everyone will benefit from Obinutuzumab, Belimumab, or Voclosporin, but do not be reluctant to try them
- 6) Rituximab and Obinutuzumab for truly resistant LN patients.

