Novel Treatments of Lupus Nephritis

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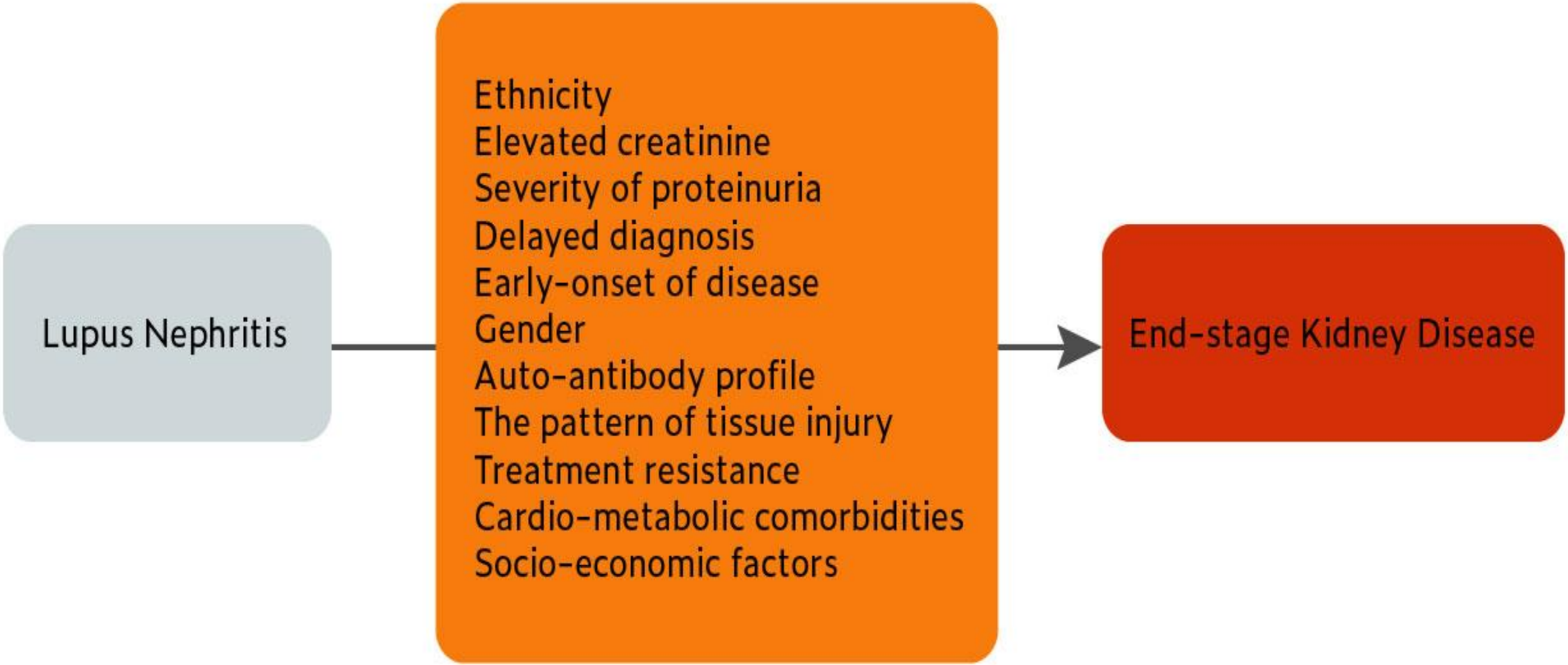
December 2023

Lupus Nephritis is very Important

- ✓ **Lupus Nephritis** is common and occurs in about 50-60% of patients with SLE.
- ✓ **LN is severe** and yet **10-30%** of these patients progress to **ESKD** within 15 years.
- ✓ **Complete Remission** occurs in less than **50%** with **SOC**
- ✓ **Subsequent renal flares occur in 27- 66%**
- ✓ While **conventional immunosuppressive treatments** improved the outcome of LN, **Novel therapies** continue to emerge and management of LN has evolved considerably over the past years.

- There has been significant progress in understanding of the pathophysiology of LN and identification of Antigenic targets within the kidney which provided new treatments for management of LN.

- Patient stratification by clinical phenotypes, pathologic classification, biomarkers and molecular profiles will help to select the best treatment protocol and application of novel therapies of LN.

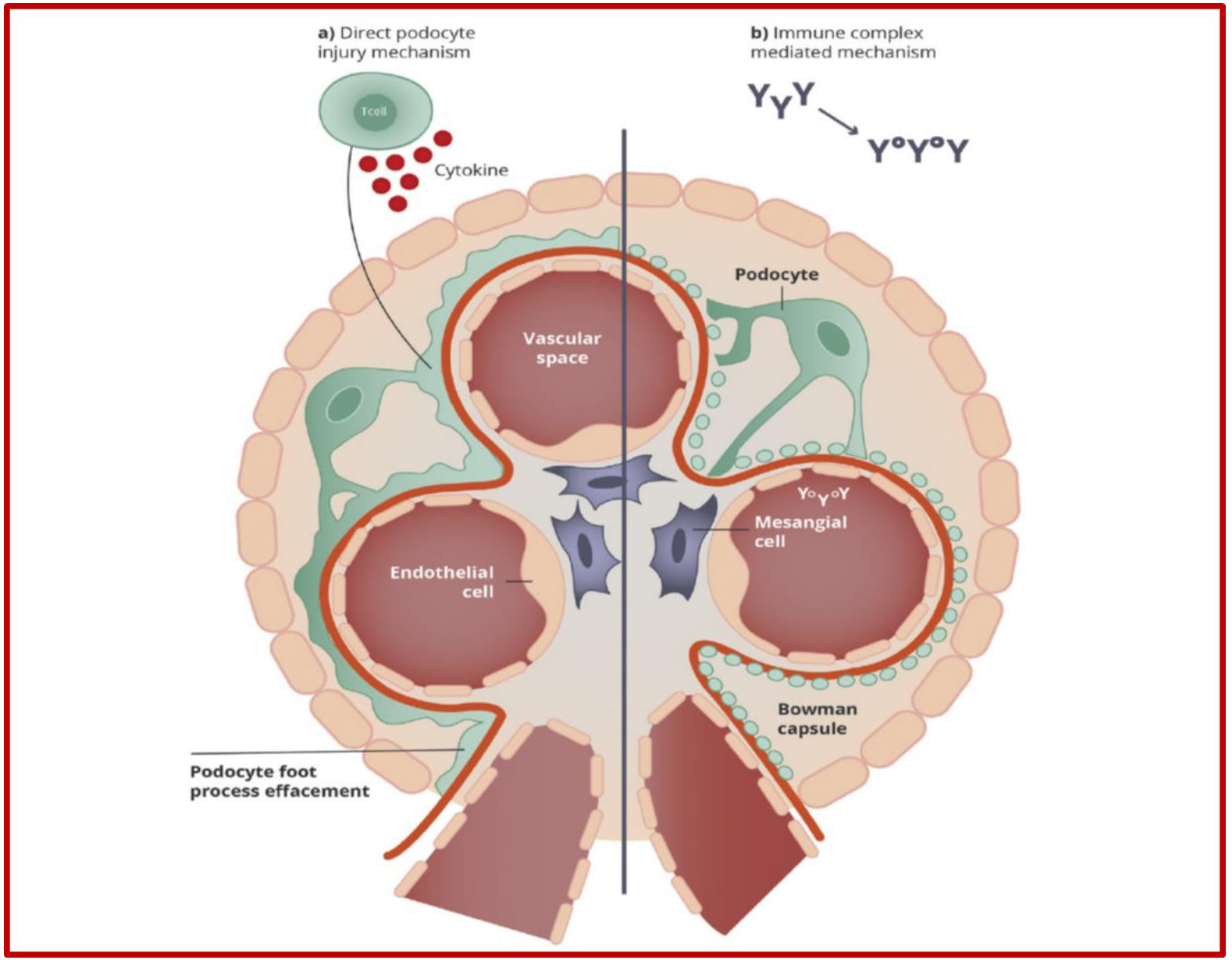


Riskfactors for progression of lupus nephritis to end-stage kidney disease

Table 3. The Classification of Lupus Nephritis, Including Lupus Podocytopathy, With Associated Clinical Presentation

Class	Biopsy Findings	Clinical Features	Patients Presenting with Nephrotic Syndrome, %
Class I: minimal mesangial LN	No LM abnormalities; isolated mesangial IC deposits on IF and/or EM	Normal urine or microscopic hematuria	0
Class II: mesangial proliferative LN	Mesangial hypercellularity or matrix expansion with mesangial IC deposits on IF and/or EM	Microscopic hematuria and/or low-grade proteinuria	0
Lupus podocytopathy	Normal glomeruli, FSGS, or mesangial proliferation on LM; IC deposits absent or limited to mesangium on IF and/or EM; diffuse and severe foot process effacement on EM	Nephrotic syndrome	>90
Class III: focal LN	<50% of glomeruli on LM display segmental (<50% of glomerular tuft) or global (>50% of glomerular tuft) endocapillary and/or extracapillary proliferation or sclerosis; mesangial and focal subendothelial IC deposits on IF and EM	Nephritic urine sediment and subnephrotic proteinuria	30
Class IV: diffuse LN	≥50% of glomeruli on LM display endocapillary and/or extracapillary proliferation or sclerosis; mesangial and diffuse subendothelial IC deposits on IF and EM	Nephritic and nephrotic syndromes, hypertension, reduced kidney function	50
Class V: membranous LN	Diffuse thickening of the glomerular capillary walls on LM with subepithelial IC deposits on IF and EM with or without mesangial IC deposits	Nephrotic syndrome	80
Class VI: advanced sclerosing LN	>90% of glomeruli on LM are globally sclerosed with no residual activity	Advanced CKD	<10

Abbreviations: EM, electron microscopy; FSGS, focal segmental glomerulosclerosis; IC, immune complex; IF, immunofluorescence micro-


a) Direct podocyte injury mechanism
b) Immune complex mediated mechanism
Tcell
Cytokine
Podocyte
Vascular space
Endothelial cell
Mesangial cell
Bowman capsule
Podocyte foot process effacement

Review Article

Kidney360

Management of Lupus Nephritis: New Treatments and Updated Guidelines

Rupali Avasare[1], *Yelena Drexler*[2], *Dawn J. Caster*,[3] *Alla Mitrofanova*[2], *and J. Ashley Jefferson*[4]

Management of lupus nephritis has evolved considerably over the past years. Here, we provide a comprehensive review of clinical trials that form the basis for the Kidney Disease: Improving Global Outcomes and EULAR/ERA-EDTA updated guidelines and present day trials that will change the landscape of lupus nephritis therapy in years to come. In addition, we highlight the issues related to cost of therapy, resistant disease, and downstream adverse effects of specific therapies.

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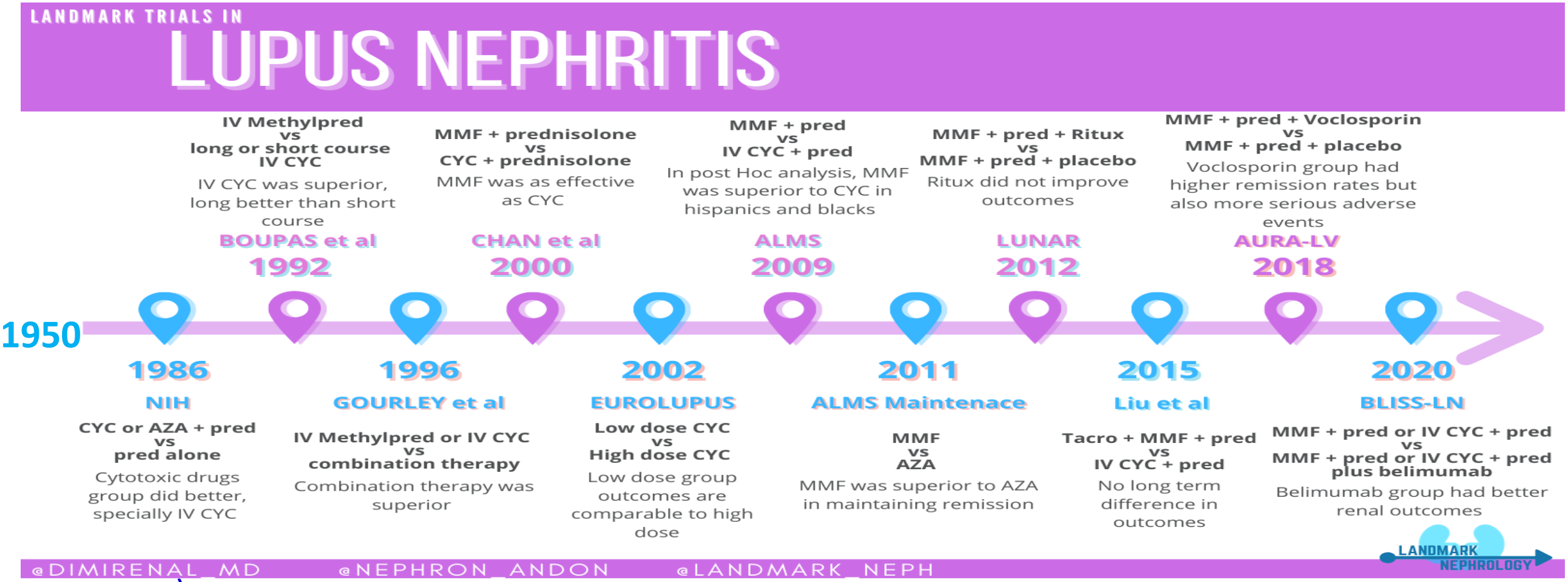


1-GC(1950) was the mainstay of treatment.

2-CYC(1970-1990) improved the outcome of LN.

3-EUROLUPUS(2002) revealed that low dose was comparable to high dose.

4-MPA & MMF(2000, First study W/ MMF in LN)- HK group

5-ALMS (2009, Multinational & Multiethnic cohort)- No deference in remission induction between MMF & CYC

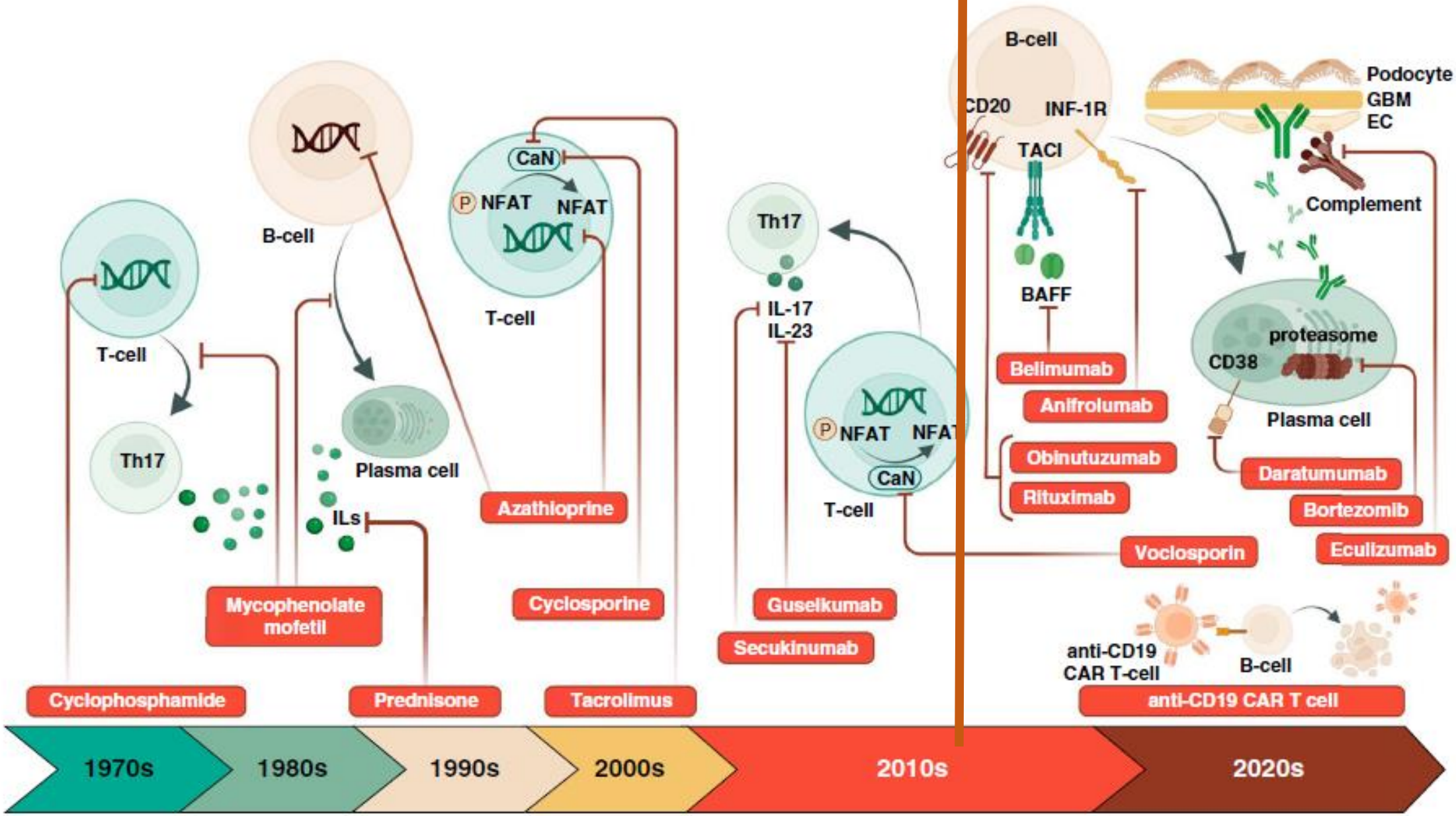
6-ALMS Maintenance(2011), MMF was superior to AZA

7-Multitarget Therapy(CNI+SOC)-(2015, 2017

8-LUNAR (2012)

9- AURORA(2018)

10-BLISS(2020)


B-cell
T-cell
Th17
Plasma cell
ILs
CaN
P NFAT
NFAT
T-cell
Th17
IL-17
IL-23
P NFAT
NFAT
CaN
T-cell
B-cell
CD20
INF-1R
TACI
BAFF
Podocyte
GBM
EC
Complement
proteasome
CD38
Plasma cell
Cyclophosphamide
Mycophenolate mofetil
Prednisone
Azathioprine
Cyclosporine
Tacrolimus
Guselkumab
Secukinumab
Belimumab
Anifrolumab
Obinutuzumab
Rituximab
Voclosporin
Daratumumab
Bortezomib
Eculizumab
anti-CD19 CAR T-cell
B-cell
anti-CD19 CAR T cell
1970s
1980s
1990s
2000s
2010s
2020s

Novel Therapeutic Targets for LN

Individualized treatments

EXPERT REVIEW OF CLINICAL PHARMACOLOGY
2022, VOL. 15, NO. 11, 1283–1292
https://doi.org/10.1080/17512433.2022.2138340

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REVIEW

Novel and emerging treatment strategies for lupus nephritis

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ABSTRACT

Introduction: Lupus nephritis (LN) is a key predictor for kidney failure and death in patients with systemic lupus erythematosus. While conventional immunosuppressive treatments have improved the outcome of LN, novel therapies continue to emerge. These new agents targetspecific immune-reactive cells, cytokines and signaling pathways in LN pathogenesis.

Areas covered: New therapeutic approaches that target B cells, T cells, crucial cytokines and their signaling pathways in LN.

Expert opinion: Although earlier studies of rituximab fail to show benefit, a newer generation anti-CD20 biologic, obinutuzumab, is promising in LN. Inhibition of B-cell activating factor by belimumab confers superior renal response when added to the standard of care (SOC) regimens, leading to its recent approval for LN. Therapies targeting plasma cells (proteasome inhibitors, anti-CD38) in LN are being developed. A newer generation calcineurin inhibitor, voclosporin, when combined with SOC, results in better renal responses in LN. Other innovative strategies include targeting type I interferon, co-stimulatory signals, complement cascade (anti-C5b) and intracellular proliferation signals (e.g. mTOR, JAK1/2, BTK). While these novel agents improve the short-term renal responses without increased toxicities, long-term data on disease progression and safety remain to be established. Patient stratification by clinical phenotypes, biomarkers and molecular profiles helps enhance the efficacy and cost-effectiveness of novel therapies of LN.

ARTICLE HISTORY

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KEYWORDS

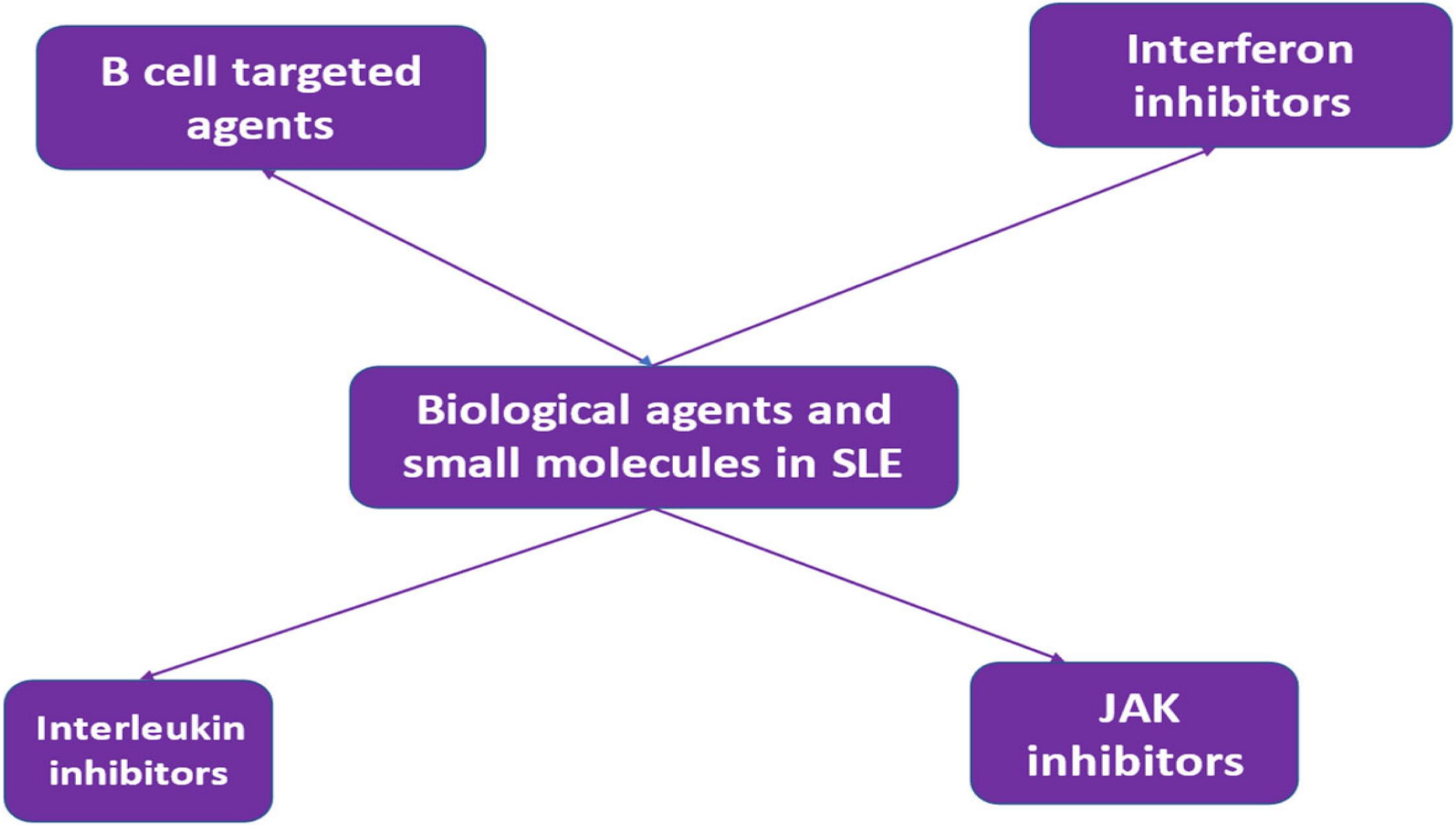
Novel; lupus; nephritis; anti-CD20; calcineurin; BAFF; belimumab

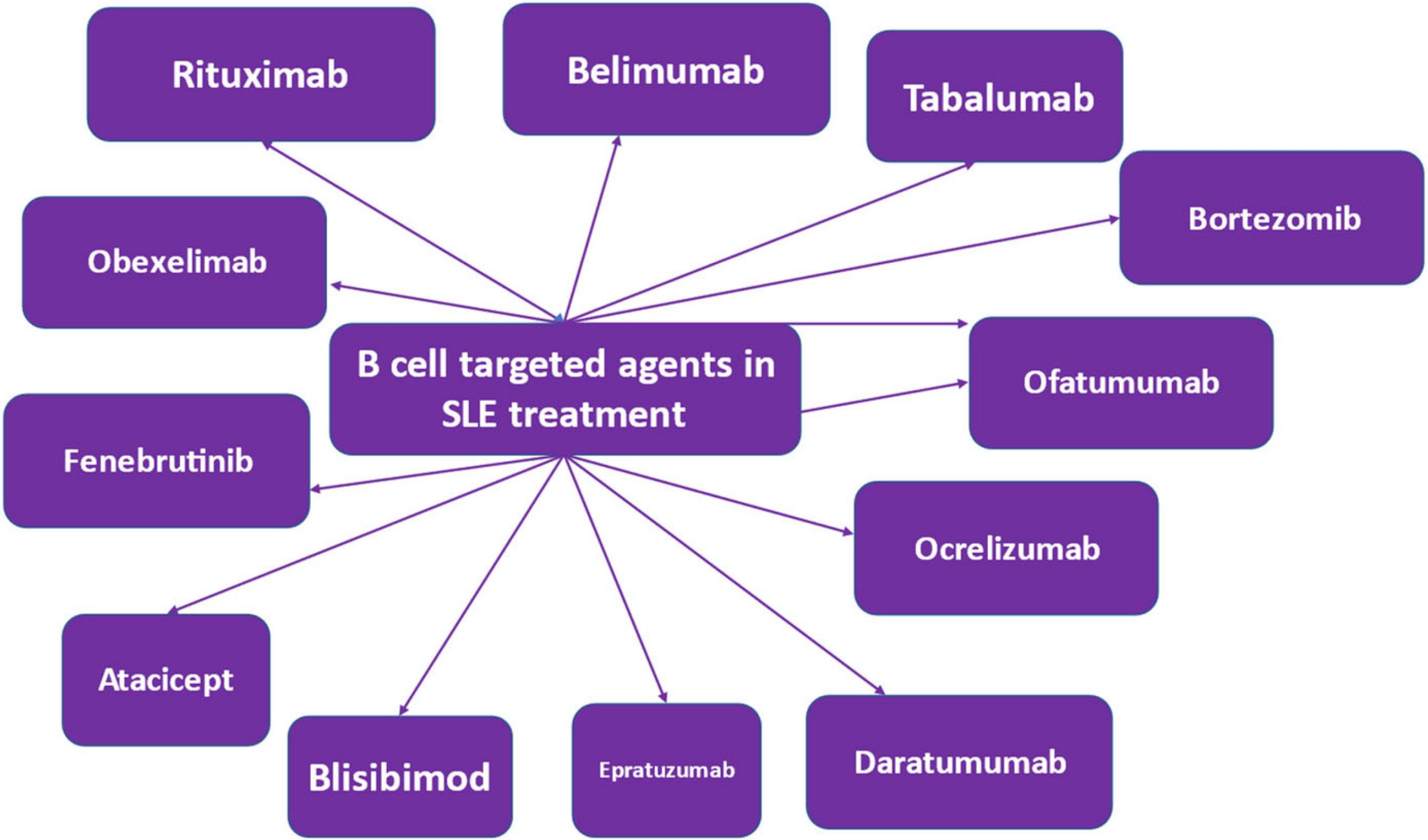
The pathogenesis of SLE & LN is highly complicated.

Table 1. Emerging therapies in lupus nephritis and the relevant therapeutic targets or mechanisms.

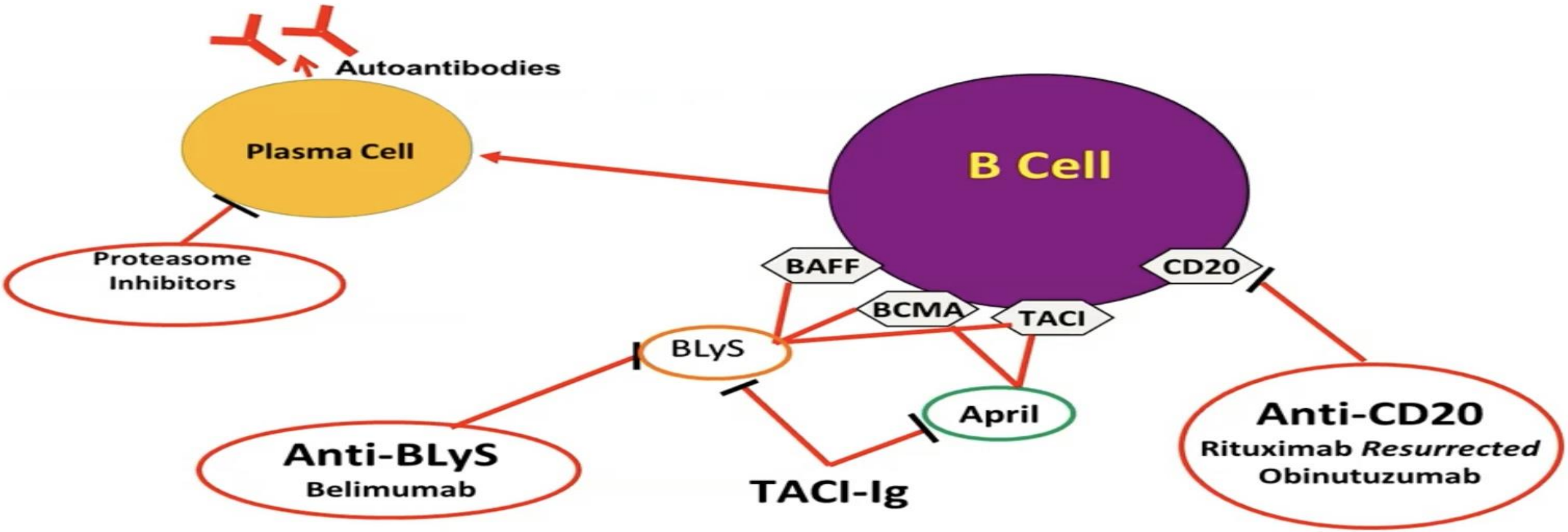
Therapeutic targets/mechanisms	Available drugs or compounds under development
B cell repertoire & plasma cells	
CD20	Rituximab (anti-CD20)
	Obinutuzumab (anti-CD20)
CD19	CAR-T
BAFF	Belimumab (anti-BAFF)
BAFF/ICOSL	Rozibafusp (bispecific antibody against BAFF & ICOSL)
B cell/BAFF	Ianalumab (bispecific antibody directly against B cell and BAFF)
Proteosomes	Bortezomib, ixazomib (proteasome inhibitors)
CD38	Daratumumab (anti-CD38)
Zinc finger transcription factor (Ikaros & Aiolos)	Iberdomide (cereblon modulator)
T cell activation	
Calcineurin/IL-2 synthesis	TAC, Voclosporin (CNI)
Co-stimulatory signals	Abatacept (CTLA4 Ig)
	BI655064 (anti-CD40)
	CFZ533 (anti-CD40)
	Dapirolizumab pegol (a pegylated Fab anti-CD40L)
Cytokines	
Type I IFN	Anifrolumab (anti-type I IFN receptor)
	Litifilimab (anti-BDCA2 mAb vs dendritic cells)
IL-17/IL-23 axis	Secukinumab (anti-IL-17A)
	Guselkumab (anti-IL-23)
IL-2	Efavaleukin alfa (IL-2 mutein)
Complement cascade	
C5a/C5b	Eculizumab (anti-C5b)
Intracellular signaling pathways	
JAK	Baracitinib (JAK1/2 inhibitor)
BTK	Fenebrutinib (BTK inhibitor)
mTOR	Sirolimus (mTOR inhibitor)

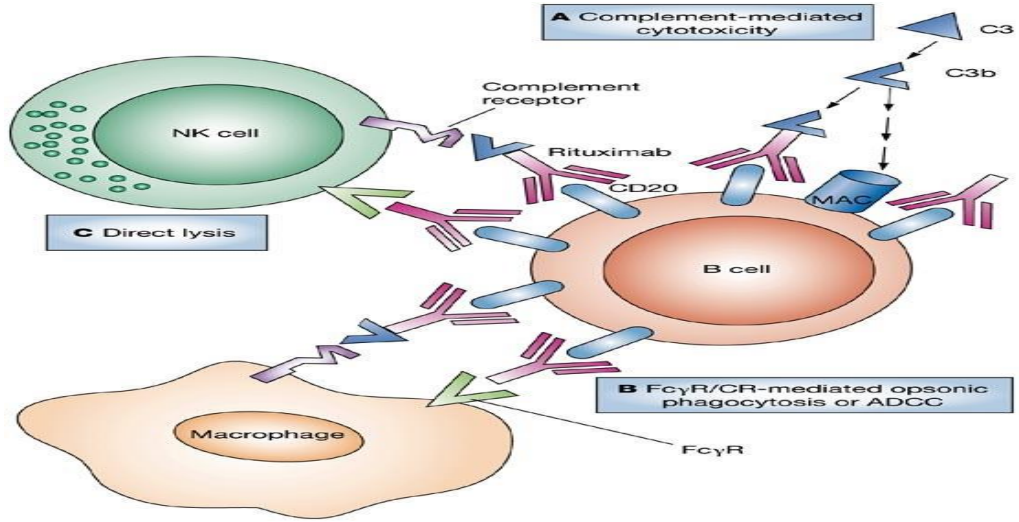
BAFF, B cell activating factor; BTK, Bruton's tyrosine kinase; CAR-T; Chimeric antigen receptor–modified T cells CNI, calcineurin inhibitor; ICOSL, inducible T cell co-stimulator ligand; IFN, interferon; JAK, janus kinase; mTOR, mammalian target of rapamycin


B cell targeted agents
Interferon inhibitors
Biological agents and small molecules in SLE
Interleukin inhibitors
JAK inhibitors


Rituximab
Belimumab
Tabalumab
Bortezomib
Obexelimab
B cell targeted agents in SLE treatment
Ofatumumab
Fenebrutinib
Ocrelizumab
Atacicept
Blisibimod
Epratuzumab
Daratumumab

B Cell Targeted Therapies





LUNAR trial

- Randomized, placebo-controlled LUpus Nephritis Assessment with Rituximab (LUNAR) trial
  - renal response: RTX 57% v. placebo 45.9%
    - American Society of Nephrology (ASN) 2009.

RITUXIMAB IN LN

- LUNAR study:
  - Phase III randomized, double-blind, placebo-controlled, multi-center study
  - 144 patients with Class III or IV LN
  - 60 sites in the U.S., Canada, Mexico, Argentina and Brazil
  - Study of Rituximab plus MMF and steroids in pts with LN
  - The primary endpoint : evaluate improvements in kidney response as measured by standard lab. tests
- Did not meet its primary endpoint of significantly reducing disease activity at 52 weeks

LANDMARK TRIALS IN

RITUXIMAB FOR LUPUS NEPHRITIS

2009

EXPLORER

RCT with SLE patients with no nephritis showed no difference in outcomes with Rituximab

2009

Observational study with 18 patients who received Rituximab for induction

RITUXIRESCUE

2012

LUNAR

RCT -inducation with MMF and steroids plus placebo or Rituximab. No difference in outcomes

2013

Observational study with 50 patients who received Rituximab+ steroids for induction

RITUXILUP

LANDMARK NEPHROLOGY

GlomCon Mini Review

Kidney Medicine

Novel Therapeutics for Management of Lupus Nephritis: What Is Next?

Sayali B. Thakare, Paolo Nikolai So, Sonia Rodriguez, Mohamed Hassanein, Edgar Lerma, and Nasim Wiegley, on behalf of the GlomCon Editorial Team

Lupus nephritis is a severe, organ-threatening manifestation of systemic lupus erythematosus. The current standard of care in the treatment of lupus nephritis is limited to broad-spectrum immunosuppressants, which have significant concerns of short- and long-term toxicity. With traditional approaches, kidney survival and patient outcomes have remained suboptimal. Robust research in the therapeutics of lupus nephritis has resulted in development of many novel drugs targeting specific inflammatory response pathways. Some newer agents have shown a definitive signal of benefit when added to standard of care. With the advent of precision medicine in nephrology, lupus nephritis treatment may undergo a shift toward incorporating approaches using these newer drugs and individualizing care of our patients. This review highlights major advances in management of lupus nephritis over the last 25 years and explores the ongoing trials of emerging therapies in lupus nephritis.

Complete author and article information provided before references.

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GlomCon*edu*

Newer Therapies for Lupus Nephritis

An overview of therapeutic targets, status of trials, FDA approval

TULIP-LN1

Phase 2 RCT, n=147,
Class III/IV±V LN,
1:1:1 (Anifrolumab- Basic Regimen (BR) vs Intensified Regimen (IR) vs placebo)
At 52 weeks
*No difference in 24 hr UPCR (PE)
*CRR numerically higher with IR
*More herpes zoster in BR+IR

Approved for adults with moderate to severe SLE with SOC, iv, July 2021

NOBILITY

Phase 2 RCT, n= 125,
Class III/IV LN,
1:1 (Obinutuzumab vs placebo)
At 104 weeks
*Δ19% for CRR(↑ from 12% at week 52)
*92% were B-cell depleted at 52 weeks
*Δ10% for need of rescue therapy
*No safety signals

REGENCY

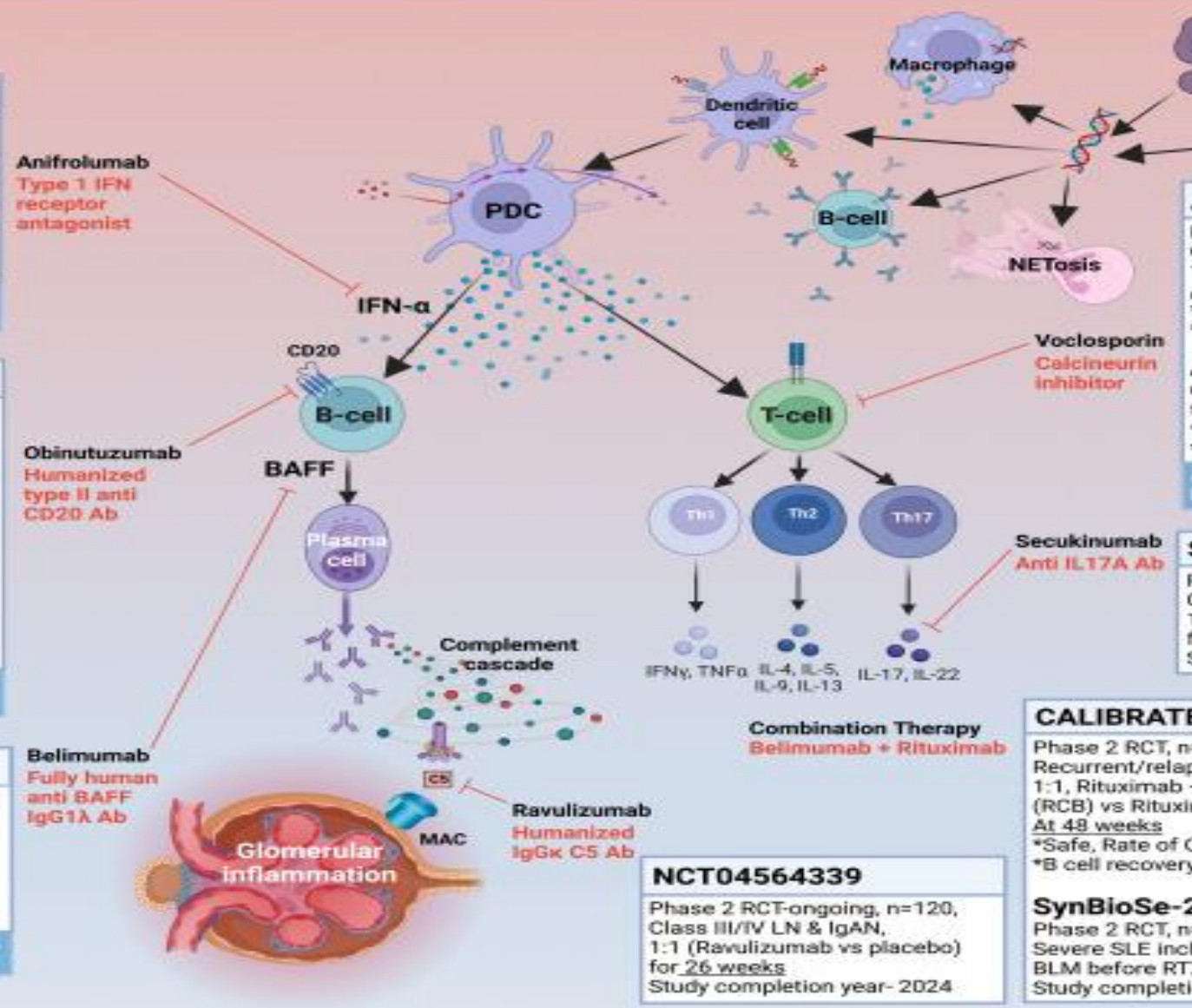
Phase 3 RCT- ongoing, n= 252,
Class III/IV±V LN for 76 weeks
Primary completion year- 2024

Breakthrough therapy designation for LN, Sept 2019

BLISS-LN

Phase 3 RCT, n= 448,
Class III/IV/V LN,
1:1 (Belimumab vs placebo)
At 104 weeks
*Δ11% for Primary Efficacy Renal Response
*Δ10% for CRR, No safety signals

Approved for active LN with SOC,iv & sc, Dec 2020



AURORA1

Phase 3 RCT, n=357,
Class III/IV/V LN,
1:1 (Voclosporin vs placebo)
At 52 weeks
*Δ18% for CRR
*No safety signals

AURORA2

Continuation of AURORA1 for 24 months, n= 216
*eGFR stable over 36 months
*UPCR lower, No safety signals

Approved for adults with active LN with SOC, oral, Jan 2021

SELUNE

Phase 3 RCT-ongoing, n=460,
Class III/IV ±V LN,
1:1 (Secukinumab vs placebo)
for 52 weeks
Study completion year- 2026

CALIBRATE

Phase 2 RCT, n=43,
Recurrent/relapsing LN despite SOC,
1:1, Rituximab + Corticosteroid + Belimumab (RCB) vs Rituximab + Corticosteroid (RC)
At 48 weeks
*Safe, Rate of CR/PR similar in both groups
*B cell recovery delayed in Belimumab group

SynBioSe-2

Phase 2 RCT, n=70,
Severe SLE including LN, for 104 weeks
BLM before RTX,followed by BLM maintenance
Study completion year- 2025

NCT04564339

Phase 2 RCT-ongoing, n=120,
Class III/IV LN & IgAN,
1:1 (Ravulizumab vs placebo)
for 26 weeks
Study completion year- 2024

@SayaliBThakare

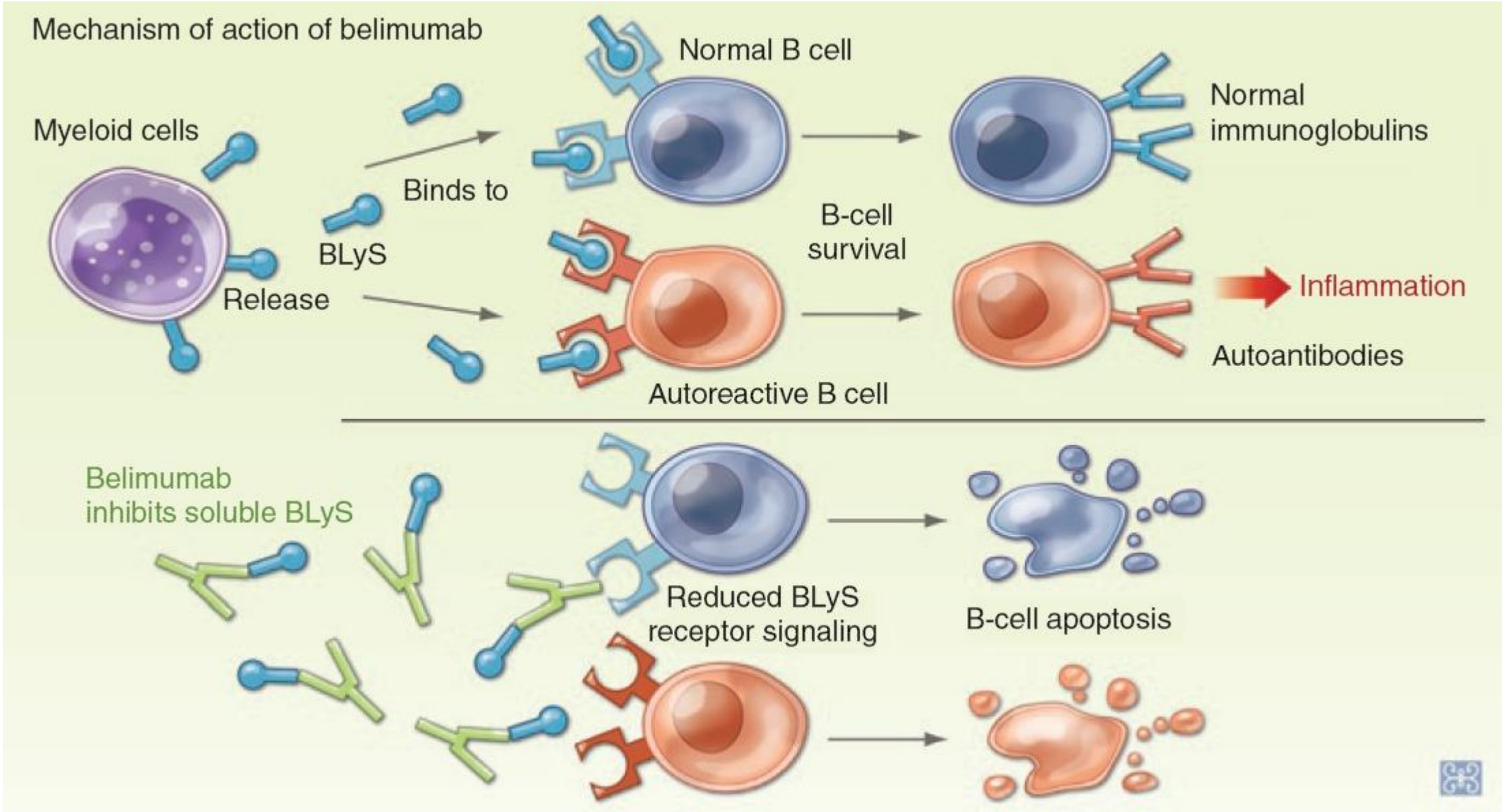
Table 2. Key findings of recent lupus nephritis trials with positive results (BLISS-LN, NOBILITY and Aurora-1).

Trial	Study Design	Patients	Sample Size	Primary & Secondary outcomes	Key Findings
BLISS-LN [31] (Belimumab)	Phase 3 RCT IV belimumab (10 mg/kg) or Placebo on D1, D15, D29 then every 28 days, both in combination with standard therapy (EURO-LUPUS or ALMS regimen) for 104 weeks	Class III/IV ± V or pure V within 6 months; eGFR≧30 ml/min/ 1.73 m^2	N = 448 (Belimumab N = 224; placebo N = 224)	Primary endpoint: PERR at 104 weeks (UPC ≤0.7, eGFR no worse than 20% below the pre-value or ≧60 ml/ min/1.73^2) Secondary endpoint: CRR at 104 weeks (UPC ≤0.5, eGFR that no worse than 10% below the pre-value or ≧90 ml/min/1.73 m^2); time to sustained PERR and CRR; changes in UPC, eGFR & biomarkers	Belimumab vs. Placebo: PERR – 43% vs. 32% (OR 1.6, 95% CI 1.0–2.3, p = 0.03) CRR – 30% vs. 20% (OR 1.7, 95% CI 1.1–2.7, p = 0.02) Risk of renal related event or death: HR 0.51, 95% CI 0.34–0.77, p = 0.001 SAE – 26% vs. 30%
NOBILITY [21] (Obinutuzumab)	Phase 2 RCT IV obinutuzumab (1 g) or placebo on D1 and week 2, 24 and 26, both in combination with corticosteroids + MMF (2–2.5 g/D); followed for 104 weeks	Class III/IV (A or A/C) ± V; UPC >1; eGFR≧30 ml/min/ 1.73 m^2	N = 126 Obinutuzumab N = 64 Placebo N = 62	Primary endpoint: CRR at week 52 (UPC<0.5, normal renal function and inactive urinary sediment) Secondary endpoints: PRR at 52 weeks (>50% in UPC to <1 or < 3 if baseline 3); ORR (i.e. CRR + PRR); changes in renal and serological parameters	Obinutuzumab vs. Placebo: CRR at 52 weeks – 35% vs. 23%, 95% CI 3.4–28%, p = 0.115 CRR at 104 weeks – 41% vs. 23%, 95% CI 2.7–35%, p = 0.026 SAE – 25% vs. 30% Serious infection – 8% vs. 18% More improvements in UPC, eGFR and serology in obinutuzumab group
AURORA-1 [62] (Voclosporin)	Phase 3 RCT Voclosporin 23.7 mg BD vs. placebo, both in combination with corticosteroids + MMF 1 g BD for 52 weeks	Class III, IV or V (alone or in combination with III or IV); UPC >1.5 mg/mg; eGFR≧ 45 ml/min/1.73 m^2	N = 357 (Voclosporin N = 179; Placebo N = 178)	Primary endpoint: CRR at 52 weeks [composite of UPC <0.5, stable renal function (eGFR ≥60 mL/ min/1 · 73 m^2 or no confirmed decrease from baseline in eGFR of >20%), no administration of rescue medication, and no >10 mg prednisone/day for >3 days or >7 days during weeks 44–52] Secondary endpoints: UPC <0.5; PRR (50% in UPC), CRR at 24 weeks; changes in UPC, eGFR, serological markers & SELENA-SLEDAI	Voclosporin vs. Placebo: CRR at 52 weeks – 42% vs. 23%, OR 2.65, 95%CI 1.64–4.27, p < 0.001 CRR at 24 weeks – 32% vs. 20%, OR 2.23, 95% CI 1.56–3.79, p < 0.001 PRR at 52 weeks – 70% vs. 52%, OR 2.26, 95% CI 1.45–3.51, p < 0.001 PRR at 24 weeks – 70% vs. 50%, OR 2.43, 95% CI 2.43, 95% CI 1.56–3.79, p < 0.001 SAE – 21% vs. 21% Serious infections – 10% vs. 11%

CRR, complete renal response; eGFR, estimated glomerular filtration rate; MMF, mycophenolate mofetil; ORR, overall renal response; PERR, primary efficacy renal response; PRR, partial renal response; UPC, urine protein-to-creatinine ratio

- Abnormal B lymphocyte hyperreactivity is a characteristic feature in the pathogenesis of SLE. B-cell activating factor (**BAFF, also known as B lymphocyte stimulator BLyS**) is a cytokine expressed in B cell lineage cells and acts as a potent B cell activator.

- **Belimumab** may be preferred in patients treated with MPAA in contrast to cyclophosphamide, and when prevention of disease flares and adverse kidney outcomes assumes high priority such as in patients with significant CKD.


Mechanism of action of belimumab
Normal B cell
Myeloid cells
Binds to
BLyS
Release
B-cell
survival
Normal
immunoglobulins
Inflammation
Autoantibodies
Autoreactive B cell
Belimumab
inhibits soluble BLyS
Reduced BLyS
receptor signaling
B-cell apoptosis

BLISS-LN

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

A multinational, multicenter, randomized trial conducted at 107 sites in 21 countries during 104 weeks

448 LN patients

- 88% female, about 33 yrs
- 50% Asian
- 58% Class III or IV
  26% Class III + V or IV + V
  16% Class V only
- eGFR mean 100 ml/min
- UPCR mean 3.4 g/g
- 72% antimalarial
- 67% ACE inhibitor or ARB

Belimumab 10 mg/kg IV
(day 0, 14, 28, then every 28 days) **+ standard-of-care**

104 weeks

Placebo + standard-of-care

Standard-of-care

Steroids (pulses, then 0.5-1 mg/kg/d with taper) plus

- 74%: MMF (3 g/d initially, 1-3 g/d for maintenance)
- 26%: Cyclophosphamide (Euro-Lupus)
  + Azathioprine maintenance

Primary endpoint:

'Primary Efficacy Renal Response

PERR

at week 104

1. eGFR ≥ 60 mL/min/1.73 m^2 or no more than 20% below pre-flare value, and
2. Urine protein:creatinine ratio ≤ 0.7, and
3. not a treatment failure[a]

Secondary endpoint:

Complete Renal Response

at week 104

CRR

1. eGFR ≥ 90 mL/min/1.73 m^2 or no more than 10% below pre-flare value, and
2. Urine protein:creatinine ratio < 0.5, and
3. not a treatment failure[a]

Secondary endpoint:

Time to renal-related event or death

1. End stage kidney disease, or
2. Doubling of s-creatinine from baseline, or
3. Renal worsening (⇧ protein-uria and/or impaired kidney function), or
4. Renal disease-related treatment failure[a]

[a] Treatment failure defined as patients who dropped out of the trial early or received prohibited medications.
For these endpoints, in order to be considered a responder, steroid dose had to be reduced to ≤ 10 mg/day from Week 24.

Table 2. Primary and Major Secondary Efficacy End Points in the Modified Intention-to-Treat Population.

End Point	Belimumab (N = 223)	Placebo (N = 223)	Difference	Odds Ratio or Hazard Ratio (95% CI)*	P Value
	number (percent)		*percentage points*		
Primary end point: primary efficacy renal response at wk 104†	96 (43)	72 (32)	11	1.6 (1.0 to 2.3)	0.03
Major secondary end points					
Complete renal response at wk 104‡	67 (30)	44 (20)	10	1.7 (1.1 to 2.7)	0.02
Primary efficacy renal response at wk 52§	104 (47)	79 (35)	11	1.6 (1.1 to 2.4)	0.02
Time to renal-related event or death¶	NA	NA	NA	0.5 (0.3 to 0.8)	0.001
Ordinal renal response without urinary sediment at wk 104‖					
Complete renal response	67 (30)	44 (20)	10	NA	0.01
Partial renal response**	39 (18)	38 (17)	<1	NA	
No response	117 (52)	141 (63)	−11	NA	

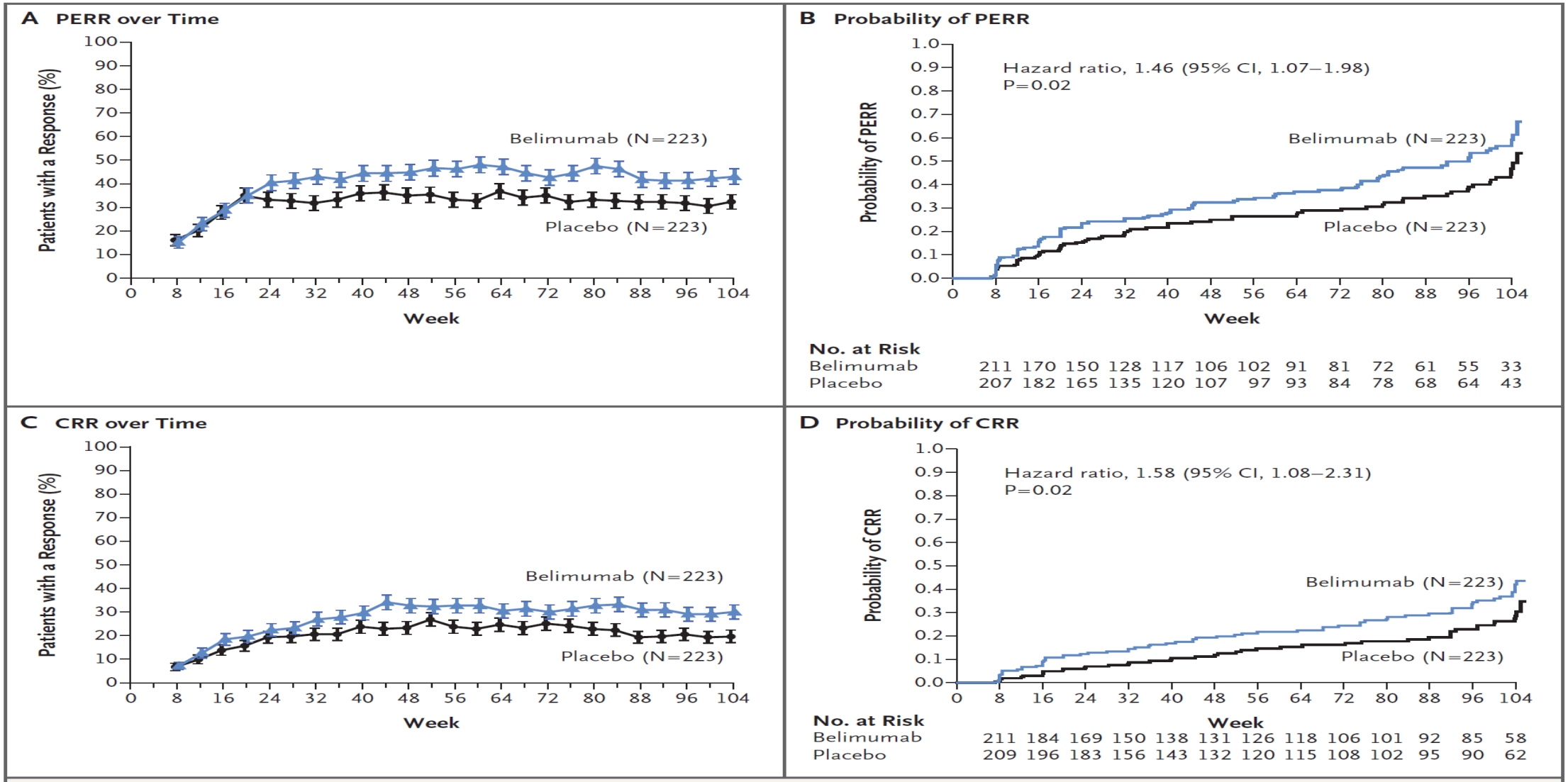
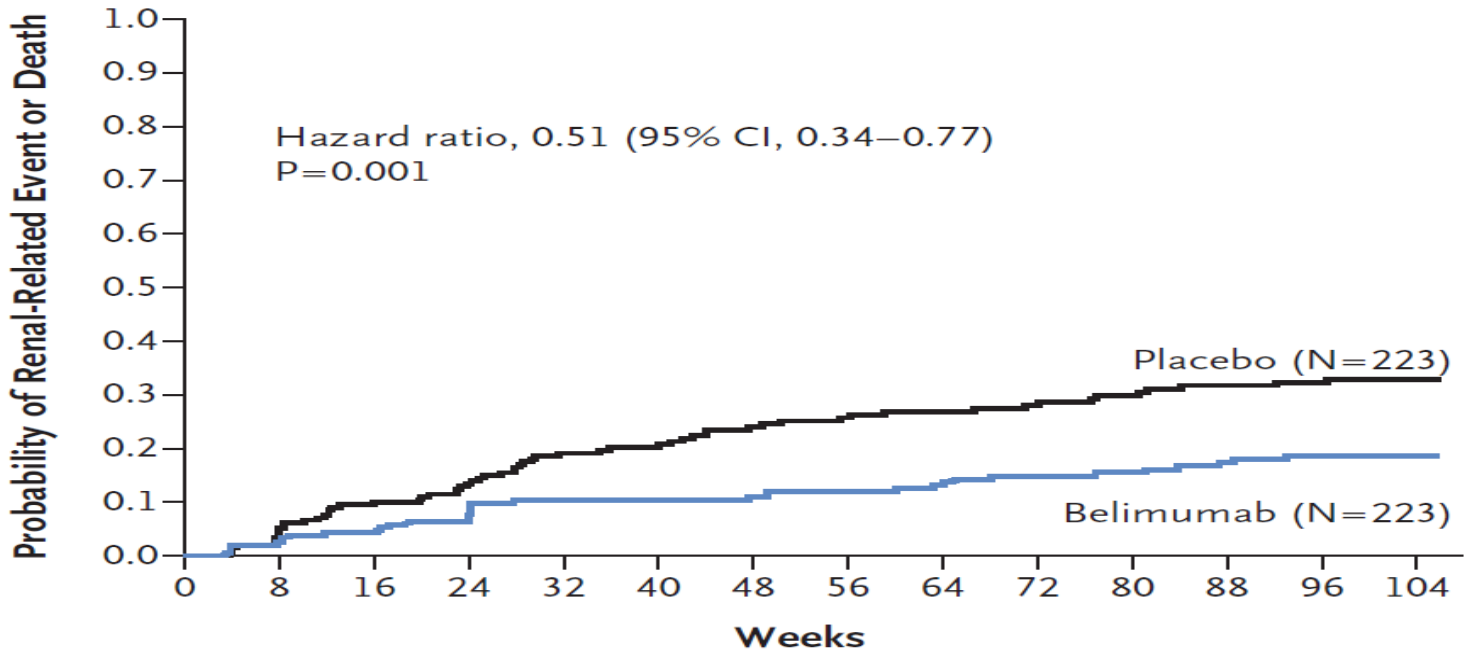


Figure 1. Renal Responses over Time in the Modified Intention-to-Treat Population.

Panel A shows the primary efficacy renal responses (PERRs) over time. Panel B shows the probability of a PERR that was sustained through week 104. Patients who discontinued belimumab or placebo, had treatment failure, or withdrew from the trial were counted as not having had a response. Panel C shows the complete renal response (CRR) over time. Panel D shows the probability of a CRR that was sustained through week 104 (discontinuation of belimumab or placebo, treatment failure, or withdrawal from the trial were counted as a nonresponse). Data on patients who did not have a PERR or a CRR at week 104 were censored at the last available visit up through week 104. Data on patients who discontinued belimumab or placebo, had treatment failure, withdrew from the trial, were lost to follow-up, or died were censored. The time to event in days was calculated as the event date minus the treatment start date plus 1. I bars indicate standard errors. CI denotes confidence interval.

A



No. at Risk

Placebo	203	185	175	154	147	137	129	126	120	116	112	110	78
Belimumab	209	192	186	167	162	159	157	151	142	139	133	130	102

B

Event	Belimumab (N=223)	Placebo (N=223)
	no.	
Any event	35	63
Death from any cause	1	2
Progression to ESKD	0	1
Doubling of creatinine level from baseline	1	1
Increased proteinuria, impaired kidney function, or both	17	39
Treatment failure related to kidney event	16	20

Does addition of belimumab to standard therapy improve kidney outcomes in lupus nephritis?

#NephJC

Methods and Cohort

Multicentre, double-blind RCT, n=448

Lupus Nephritis Class III to V

GFR >30 ml/min/1.73 m^2

Mean age 33.4±10.6 yrs

Females: 88%

50% Asian
30% White
14% Black

Intervention

Placebo

versus

Belimumab

Study duration = 104 weeks

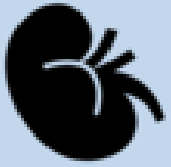
Partial Renal response

32%

OR 1.6
95% CI 1.0 to 2.3
p = 0.03

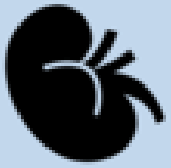
43%

Complete Renal Response



20%

OR 1.7
95% CI 1.1 to 2.7
p = 0.02



30%

Conclusions: In active lupus nephritis, more patients who received belimumab plus standard therapy had a primary efficacy renal response than those who received standard therapy alone

Reference: Furie R, Rovin BH *et al.*Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis. NEJM, 2020

VA by Swasti Chaturvedi @SwastiThinks

Efficacy and Safety of Belimumab in Patients With Lupus Nephritis

Setting & Participants

*Parent **BLISS-LN** study: Phase 3, randomized double-blind placebo-controlled trial of 448 adults with LN from 21 countries. In the full study, more patients in belimumab + standard therapy group had a PERR* than those who received standard therapy alone (OR, 1.6 [95% CI, 1.0-2.3])*

Current study: Pre-specified BLISS-LN subgroup analyses of East Asian adult patients with active LN (N = 142)

Mainland China	79	**Hong Kong**	6
South Korea	43	**Taiwan**	14

Intervention

104-wk double-blind phase

n = 68
Placebo IV + **Standard Therapy**

vs

n = 74
Belimumab 10 mg/kg IV + **Standard Therapy**

Standard Therapy: *Oral glucocorticoids and either cyclophosphamide for induction followed by azathioprine for maintenance, or mycophenolate mofetil for both induction and maintenance*

Primary Outcome

PERR* at Week 104

OR 1.76
(95% CI, 0.88-3.51)

Placebo IV 37%
Belimumab 53%

Belimumab reduced the risk of a kidney-related event or death vs placebo (HR, **0.37** [95% CI, 0.15-0.91])

Safety results were similar across both groups

PERR: Primary Efficacy Renal Response
(urine protein-creatinine ratio [UPCR] ≤0.7, eGFR no more than 20% below pre-flare value or ≥60 mL/min/1.73 m^2, and no treatment failure)

CONCLUSION: Safety and efficacy profiles were consistent with BLISS-LN overall population, supporting benefits of belimumab treatment in the East Asian population with LN.

Xueqing Yu, Nan Chen, Jun Xue, et al
@AJKDonline | DOI: 10.1053/j.ajkd.2022.06.013

AJKD
AMERICAN JOURNAL OF KIDNEY DISEASES

Journal of
Clinical Medicine

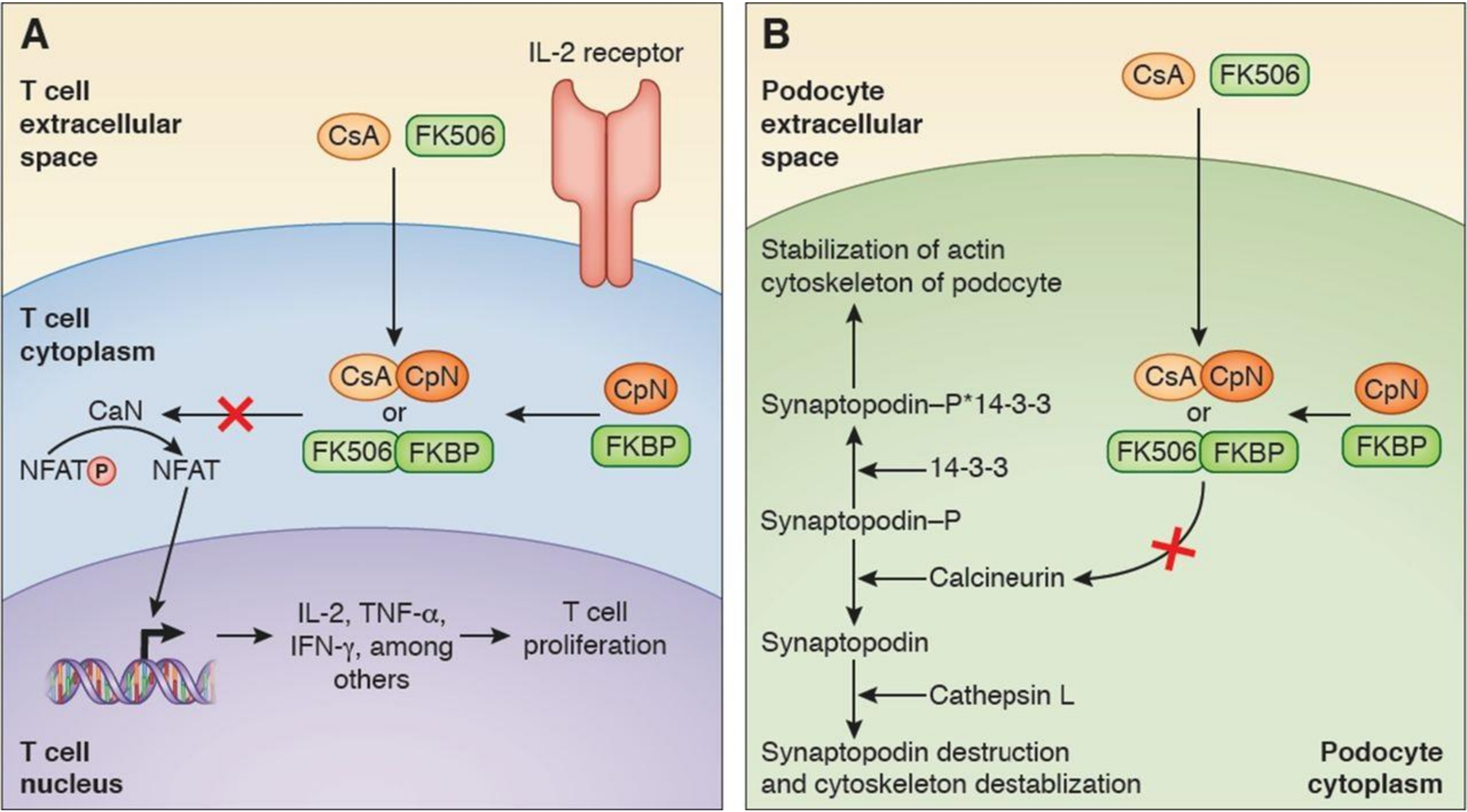
MDPI

Review

Old and New Calcineurin Inhibitors in Lupus Nephritis

Claudio Ponticelli [1,*,†], Francesco Reggiani [2] and Gabriella Moroni [2]

In addition to its immunomodulatory effects, the **calcineurin inhibitors** also are able to decrease proteinuria by direct podocyte stabilization and afferent arteriole vasoconstriction


A
T cell extracellular space
IL-2 receptor
CsA
FK506
T cell cytoplasm
CsA
CpN
or
FK506
FKBP
CpN
FKBP
CaN
NFAT
P
NFAT
IL-2, TNF-α, IFN-γ, among others
T cell proliferation
T cell nucleus
B
Podocyte extracellular space
CsA
FK506
Stabilization of actin cytoskeleton of podocyte
Synaptopodin–P*14-3-3
14-3-3
Synaptopodin–P
Calcineurin
Synaptopodin
Cathepsin L
Synaptopodin destruction and cytoskeleton destablization
CsA
CpN
or
FK506
FKBP
CpN
FKBP
Podocyte cytoplasm

JAMA Network Open

Original Investigation | Rheumatology

Effect of Tacrolimus vs Intravenous Cyclophosphamide on Complete or Partial Response in Patients With Lupus Nephritis

A Randomized Clinical Trial

Zhaohui Zheng, MD; Haitao Zhang, MD; Xiaomei Peng, MD; Chun Zhang, MD, PhD; Changying Xing, MD; Gang Xu, MD; Ping Fu, MD; Zhaohui Ni, MD; Jianghua Chen, MD; Zhonggao Xu, MD; Ming-hui Zhao, MD; Shaomei Li, MD; Xiangyang Huang, MD; Lining Miao, MD; Xiaonong Chen, MD; Bicheng Liu, MD; Yongcheng He, MD; Jing Li, MSc; Lijun Liu, MD; Haishan Kadeerbai, MS; Zhangsuo Liu, MD; Zhihong Liu, MD

In this study, oral tacrolimus appeared noninferior to IVCY for initial therapy of active LN, with a more favorable safety profile than IVCY. Tacrolimus may be an alternative to IVCY as initial therapy for LN.

JAMA Network Open. 2022;5(3):e224492.

Randomized Controlled Trial > Ann Rheum Dis. 2020 Aug;79(8):1070-1076.
doi: 10.1136/annrheumdis-2020-217178. Epub 2020 May 24.

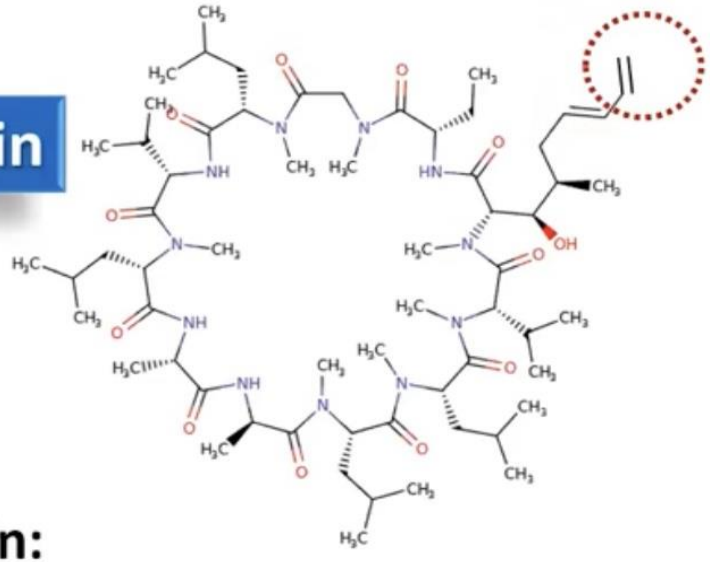
Long-term outcome of a randomised controlled trial comparing tacrolimus with mycophenolate mofetil as induction therapy for active lupus nephritis

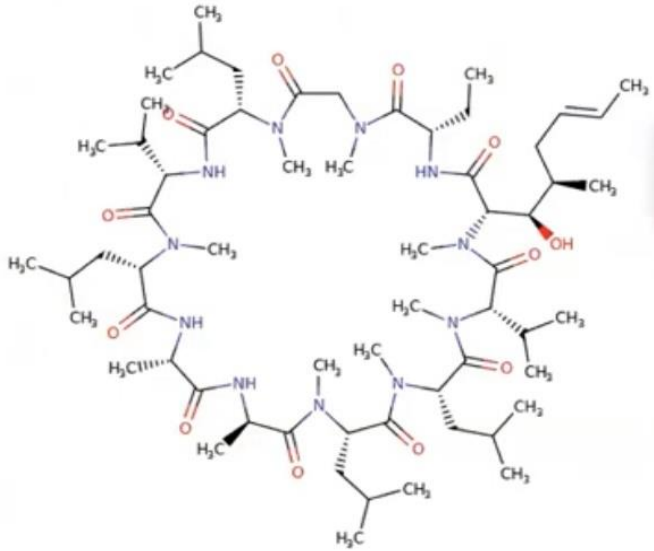
Chi Chiu Mok [1], Ling Yin Ho [2], Shirley King Yee Ying [3], Man Chi Leung [4], Chi Hung To [2], Woon Leung Ng [4]

✓**Long-term data confirmed non-inferiority of TAC to MMF as induction therapy of LN.**

The structural modification (addition of a single carbon extension to the amino acid-1 position) produces a molecule with high potency and a favorable metabolic profile, without the need for therapeutic drug monitoring.

Voclosporin

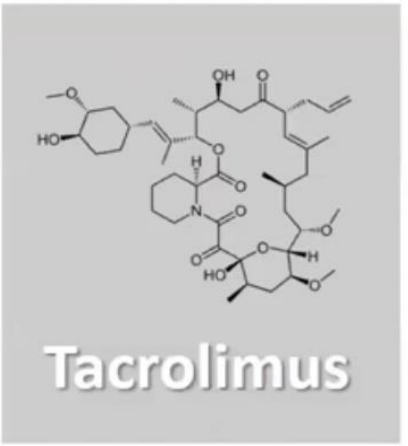




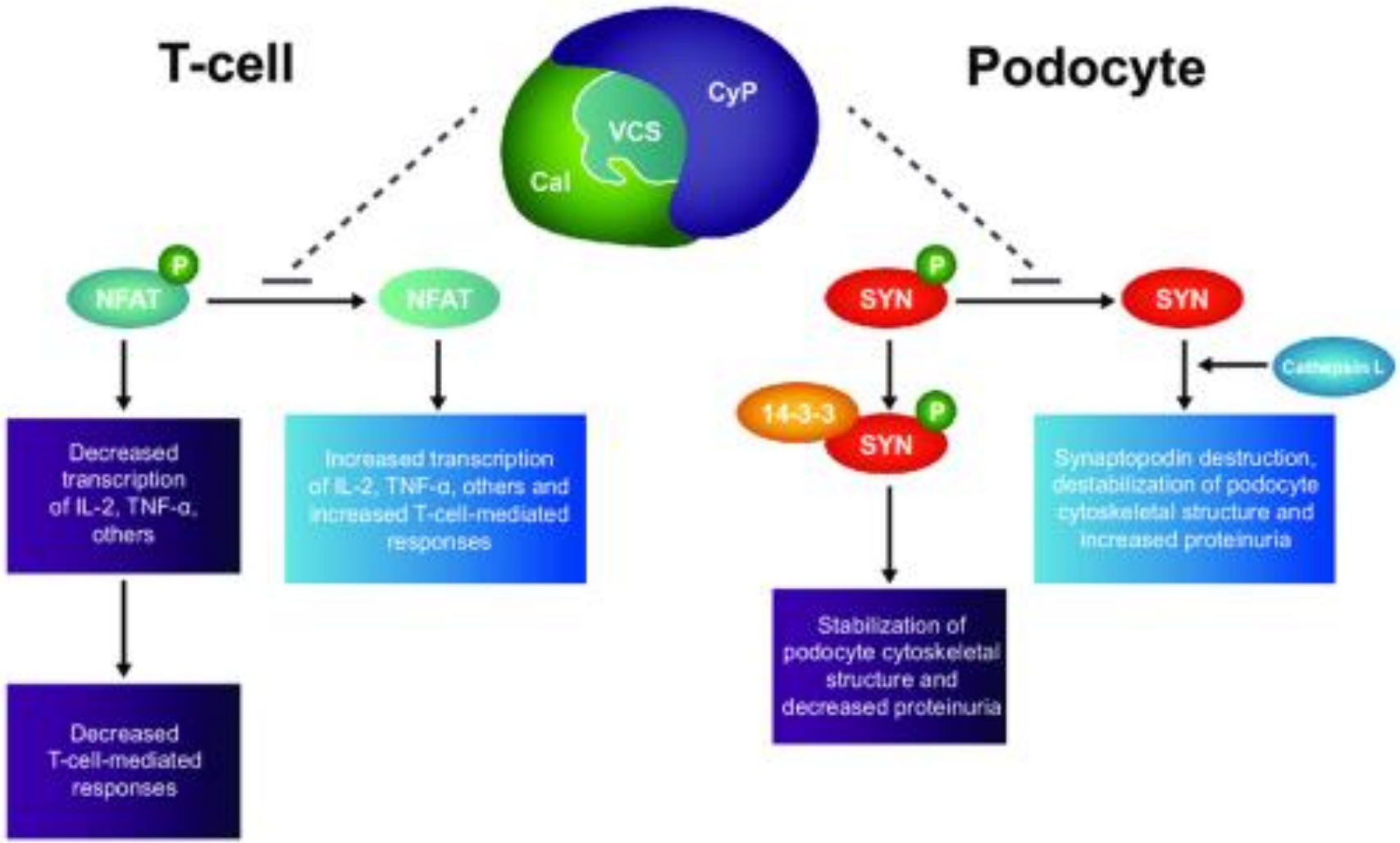
Cyclosporin A

Voclosporin:

- Stable pharmacokinetics, no trough level controls needed[1]
- No dose adaption in mild to moderate eGFR reduction[5]
- Higher potency vs CyA[2], no interaction with MMF[4]
- Better lipid- and glucose-profile vs other CNI[3,6]



1. Rovin BH, et al. *Lancet*. 2021;397:2070; 2. Ling SY, et al. *J Clin Pharmacol.* 2013;53:1303; 3. Kuglstatter, A, et al. *Acta Crystallogr D Biol Crystallogr.* 2011;2:119; 4. van Gelder T, et al. *Arthritis Rheumatol*. 2020;72(Suppl10):1706; 5; 5. Busque S, et al. *Am J Transplant*. 2011;11:2675; 6. Li Y ,et al Clin Pharmacol. 2020;12:83


T-cell
Podocyte
CyP
VCS
CaI
NFAT
P
NFAT
SYN
P
SYN
Cathepsin L
14-3-3
SYN
P
Decreased transcription of IL-2, TNF-α, others
Increased transcription of IL-2, TNF-α, others and increased T-cell-mediated responses
Synaptopodin destruction, destabilization of podocyte cytoskeletal structure and increased proteinuria
Decreased T-cell-mediated responses
Stabilization of podocyte cytoskeletal structure and decreased proteinuria


AURORA study

Lancet 2021; 397: 2070–80

Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial

Brad H Rovin, Y K Onno Teng, Ellen M Ginzler, Cristina Arriens, Dawn J Caster, Juanita Romero-Diaz, Keisha Gibson, Joshua Kaplan, Laura Lisk, Sandra Navarra, Samir V Parikh, Simrat Randhawa, Neil Solomons, Robert B Huizinga

Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial

Brad H Rovin, Y K Onno Teng, Ellen M Ginzler, Cristina Arriens, Dawn J Caster, Juanita Romero-Diaz, Keisha Gibson, Joshua Kaplan, Laura Lisk, Sandra Navarra, Samir V Parikh, Simrat Randhawa, Neil Solomons, Robert B Huizinga

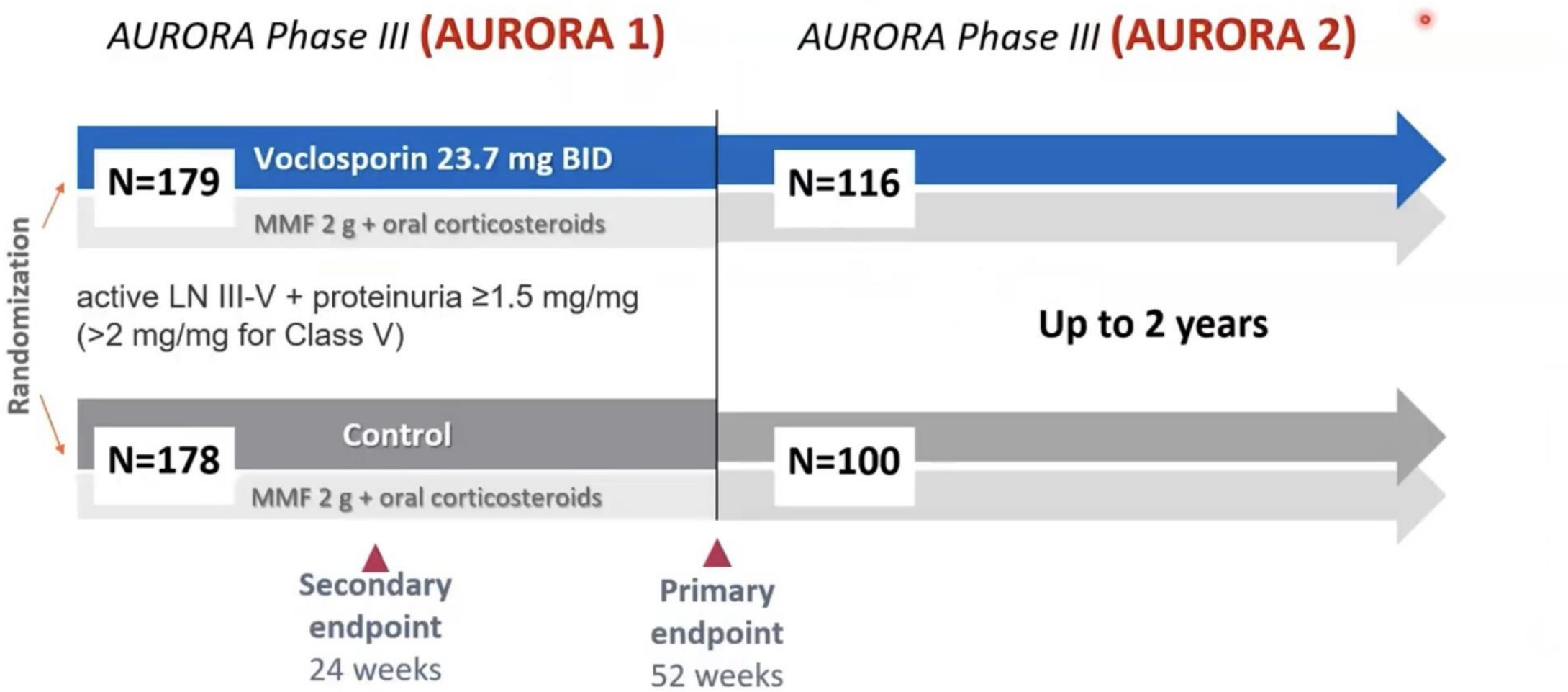
Summary

Background Voclosporin, a novel calcineurin inhibitor approved for the treatment of adults with lupus nephritis, improved complete renal response rates in patients with lupus nephritis in a phase 2 trial. This study aimed to evaluate the efficacy and safety of voclosporin for the treatment of lupus nephritis.

Methods This multicentre, double-blind, randomised phase 3 trial was done in 142 hospitals and clinics across 27 countries. Patients with a diagnosis of systemic lupus erythematosus with lupus nephritis according to the American College of Rheumatology criteria, and a kidney biopsy within 2 years that showed class III, IV, or V (alone or in combination with class III or IV) were eligible. Patients were randomly assigned (1:1) to oral voclosporin (23·7 mg twice daily) or placebo, on a background of mycophenolate mofetil (1 g twice daily) and rapidly tapered low-dose oral steroids, by use of an interactive web response system. The primary endpoint was complete renal response at 52 weeks defined as a composite of urine protein creatinine ratio of 0·5 mg/mg or less, stable renal function (defined as estimated glomerular filtration rate [eGFR] ≥60 mL/min/1·73 m² or no confirmed decrease from baseline in eGFR of >20%), no administration of rescue medication, and no more than 10 mg prednisone equivalent per day for 3 or more consecutive days or for 7 or more days during weeks 44 through 52, just before the primary endpoint assessment. Safety was also assessed. Efficacy analysis was by intention-to-treat and safety analysis by randomised patients receiving at least one dose of study treatment. The trial is registered with ClinicalTrials.gov, NCT03021499.

Findings Between April 13, 2017, and Oct 10, 2019, 179 patients were assigned to the voclosporin group and 178 to the placebo group. The primary endpoint of complete renal response at week 52 was achieved in significantly more patients in the voclosporin group than in the placebo group (73 [41%] of 179 patients *vs* 40 [23%] of 178 patients; odds ratio 2·65; 95% CI 1·64–4·27; p<0·0001). The adverse event profile was balanced between the two groups; serious adverse events occurred in 37 (21%) of 178 in the voclosporin group and 38 (21%) of 178 patients in the placebo group. The most frequent serious adverse event involving infection was pneumonia, occurring in 7 (4%) patients in the voclosporin group and in 8 (4%) patients in the placebo group. A total of six patients died during the study or study follow-up period (one [<1%] patient in the voclosporin group and five [3%] patients in the placebo group). None of the events leading to death were considered by the investigators to be related to the study treatments.

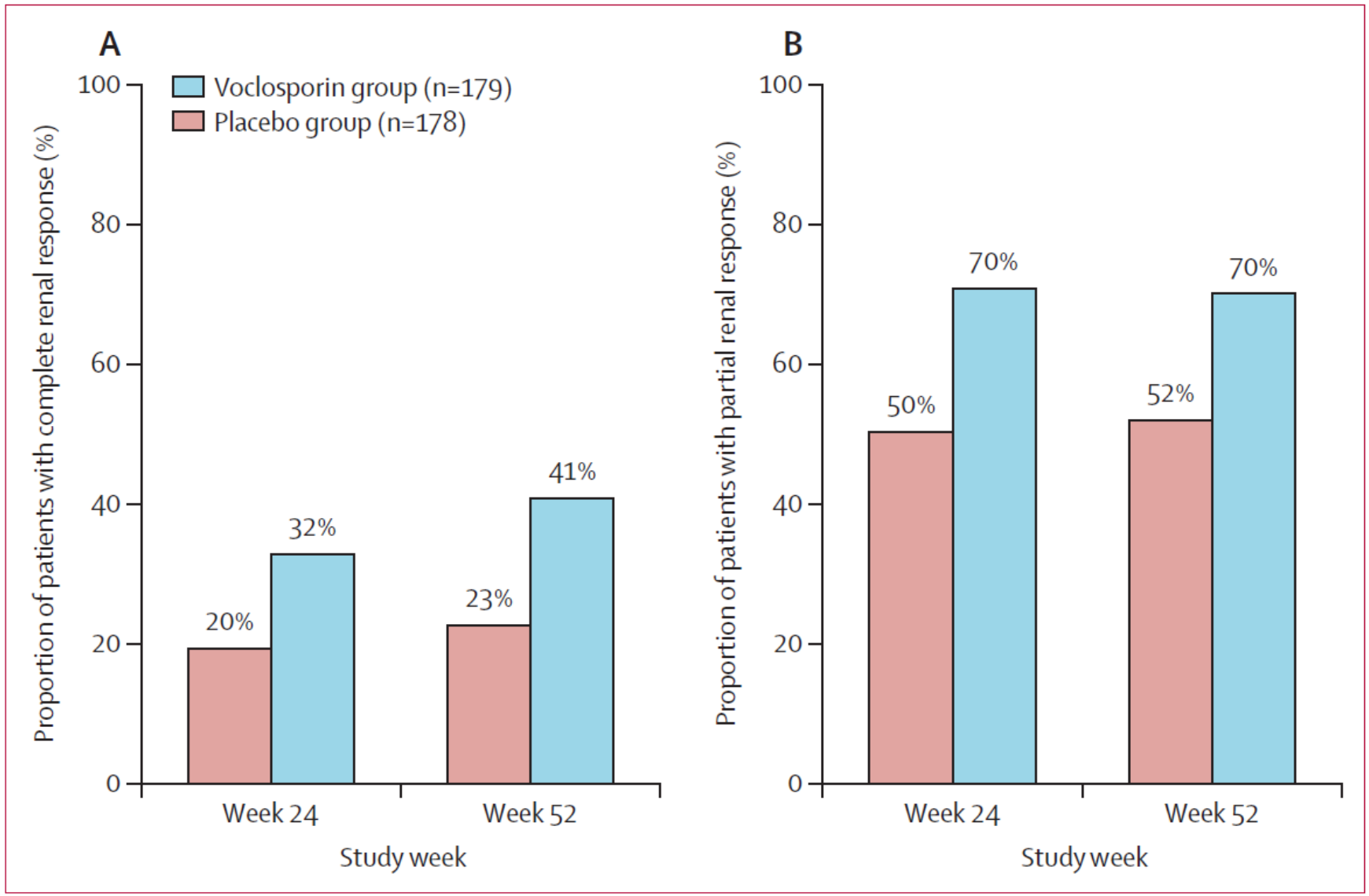
Interpretation Voclosporin in combination with MMF and low-dose steroids led to a clinically and statistically superior complete renal response rate versus MMF and low-dose steroids alone, with a comparable safety profile. This finding is an important advancement in the treatment of patients with active lupus nephritis.

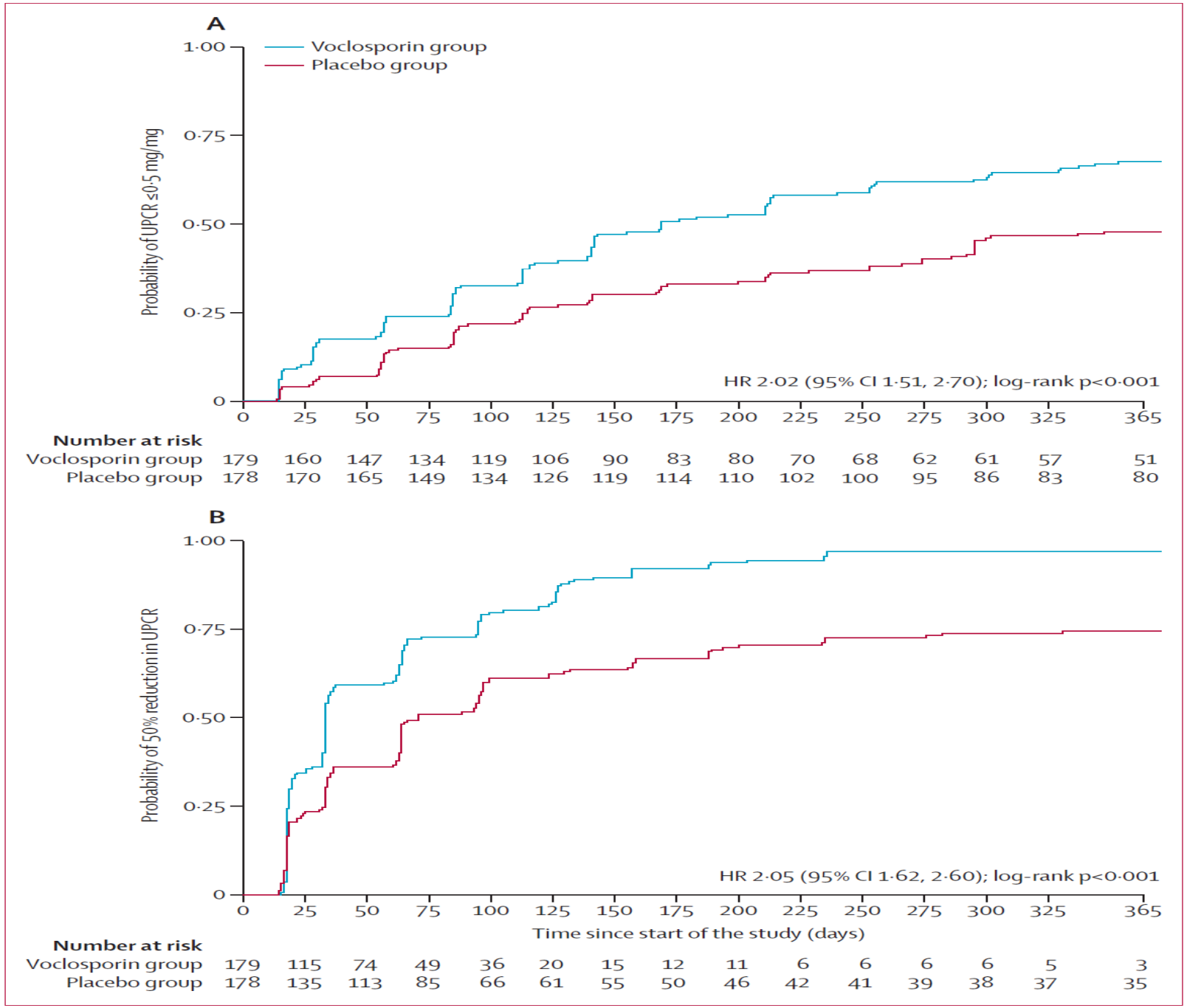

AURORA Phase III (AURORA 1)
AURORA Phase III (AURORA 2)
Randomization
N=179
Voclosporin 23.7 mg BID
MMF 2 g + oral corticosteroids
active LN III-V + proteinuria ≥1.5 mg/mg
(>2 mg/mg for Class V)
N=178
Control
MMF 2 g + oral corticosteroids
N=116
N=100
Up to 2 years
Secondary endpoint
24 weeks
Primary endpoint
52 weeks

	Voclosporin group (n=179)	Placebo group (n=178)	OR or HR (95% CI)	p value
Primary endpoint*				
Complete renal response at 52 weeks	73 (41%)	40 (23%)	OR 2·65 (1·64–4·27)	<0·0001
Secondary endpoints				
Complete renal response at 24 weeks	58 (32%)	35 (20%)	OR 2·23 (1·34–3·72)	0·002
Partial renal response at 24 weeks	126 (70%)	89 (50%)	OR 2·43 (1·56–3·79)	<0·001
Partial renal response at 52 weeks	125 (70%)	92 (52%)	OR 2·26 (1·45–3·51)	<0·001
Time to UPCR ≤0·5 mg/mg, days	169 (141–214)	372 (295–NC)	HR 2·02 (1·51–2·70)	<0·001
Time to 50% reduction in UPCR, days	29 (29–32)	63 (57–87)	HR 2·05 (1·62–2·60)	<0·001

Data are n (%) or median (95% CI), unless otherwise specified. OR=odds ratio. HR=hazard ratio. UPCR=urine protein creatinine ratio. NC=non-calculable. *The model is based on a logistic regression with terms for treatment, baseline UPCR, biopsy class, mycophenolate mofetil use at baseline, and region.

***Table 2:* Summary of complete and partial renal responses at weeks 24 and 52 (intention-to-treat population)**


A
Voclosporin group (n=179)
Placebo group (n=178)
Proportion of patients with complete renal response (%)
100
80
60
40
20
0
20%
32%
23%
41%
Week 24
Week 52
Study week
B
Proportion of patients with partial renal response (%)
100
80
60
40
20
0
50%
70%
52%
70%
Week 24
Week 52
Study week


A
Voclosporin group
Placebo group
Probability of UPCR ≤0·5 mg/mg
1·00
0·75
0·50
0·25
0
HR 2·02 (95% CI 1·51, 2·70); log-rank p<0·001
0 25 50 75 100 125 150 175 200 225 250 275 300 325 365
Number at risk
Voclosporin group 179 160 147 134 119 106 90 83 80 70 68 62 61 57 51
Placebo group 178 170 165 149 134 126 119 114 110 102 100 95 86 83 80
B
Probability of 50% reduction in UPCR
1·00
0·75
0·50
0·25
0
HR 2·05 (95% CI 1·62, 2·60); log-rank p<0·001
0 25 50 75 100 125 150 175 200 225 250 275 300 325 365
Time since start of the study (days)
Number at risk
Voclosporin group 179 115 74 49 36 20 15 12 11 6 6 6 6 5 3
Placebo group 178 135 113 85 66 61 55 50 46 42 41 39 38 37 35

AURORA 1: Is voclosporin safe and effective for the treatment of lupus nephritis?

Study design

- 27 countries Phase 3
- Pts with active class III, IV and/or V lupus nephritis
- All received 2g/day MMF and rapid steroid taper
- Treated for 52 weeks

Double-blinded

Placebo n= 178

Voclosporin n=179

Randomization

	Complete Renal Response (UPCR <.5 mg/mg, Stable GFR, No rescue treatment)	Serious Adverse Events	Mortality (n)
Placebo	20% (24 weeks) / 23% (52 weeks)	21%	5
Voclosporin	32% (24 weeks) / 41% (52 weeks)	21%	1
	OR 2.23 (95% CI (1.34- 3.72))		
	OR 2.65 (95% CI (1.64- 4.27))		

Conclusion: Voclosporin in combination with MMF and low-dose steroids led to a clinically and statistically superior complete renal response rate versus MMF and low-dose steroids alone, with a comparable safety profile.

Reference: Rovin et al. *Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial.* 2021. 10.1016/S0140-6736(21)00578-X

Visual abstract by Priti Meena MD DNB (Nephrology) @priti899

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
Randomization: Voclosporin + MMF + GC (n=179)	→ Voclosporin + MMF + GC (n=116)
Randomization: Placebo + MMF + GC (n=178)	→ Placebo + MMF + GC (n=100)

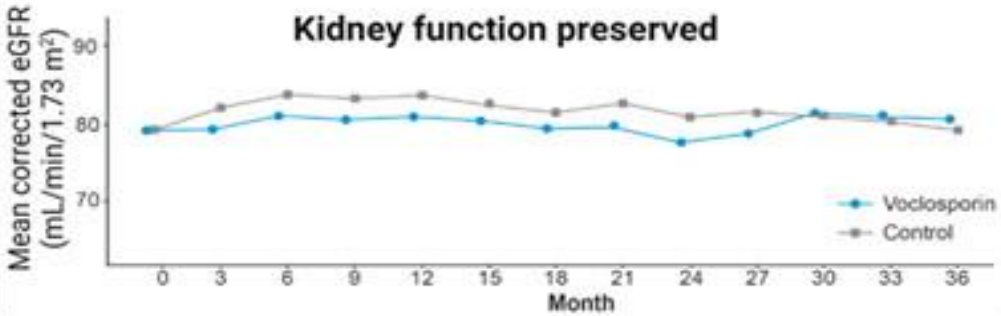
GC target 2.5 mg/day by week 16 and thereafter; MMF target 2 gm/day

2 Long-term voclosporin treatment safe and well-tolerated

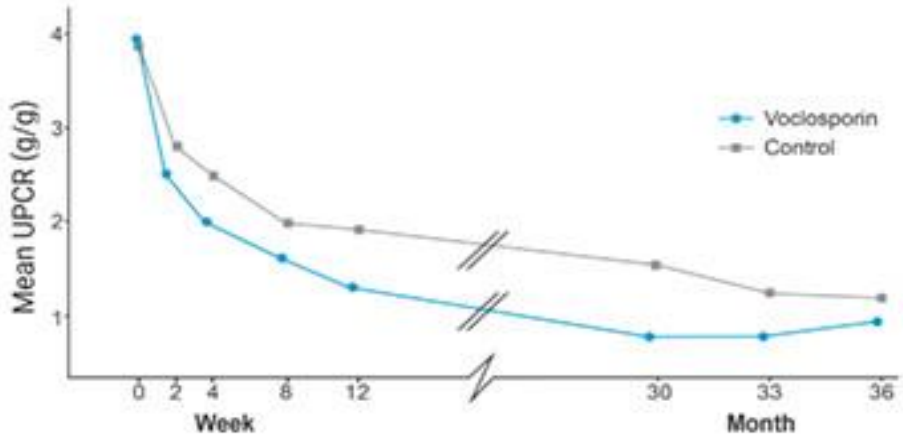
86.1% completed AURORA 2

Comparable AEs in both groups

Kidney function preserved

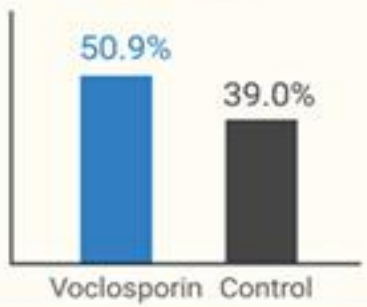


3 Rapid and persistent proteinuria reductions



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.

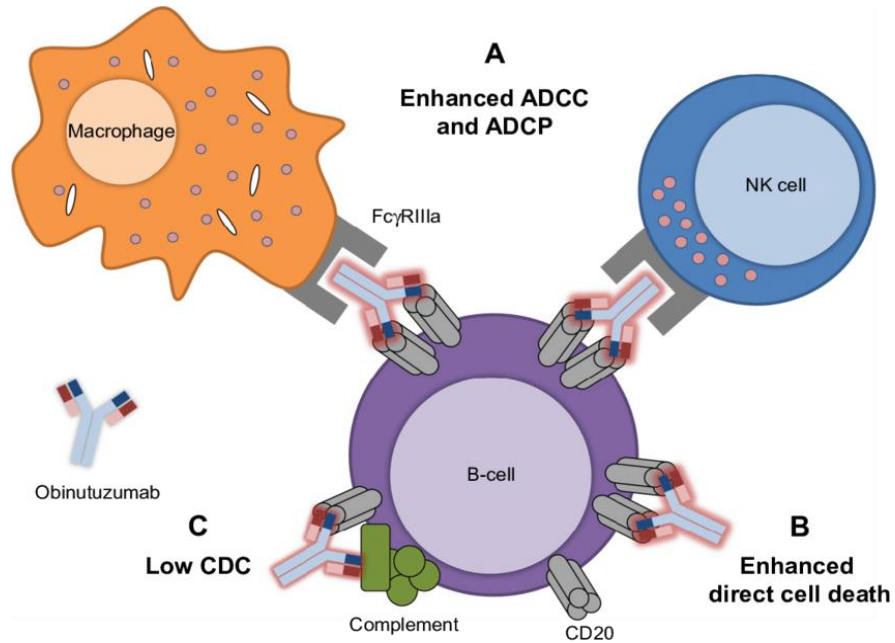
Saxena A, Ginzler E, Gibson K, et al. Safety and efficacy of long-term voclosporin treatment for lupus nephritis in the Phase 3 AURORA 2 clinical trial. Arthritis Rheumatol 2023.

Arthritis & Rheumatology ACR

eular Furie RA, *et al*. *Ann Rheum Dis* 2022;**81**:100–107. doi:10.1136/annrheumdis-2021-220920 BMJ

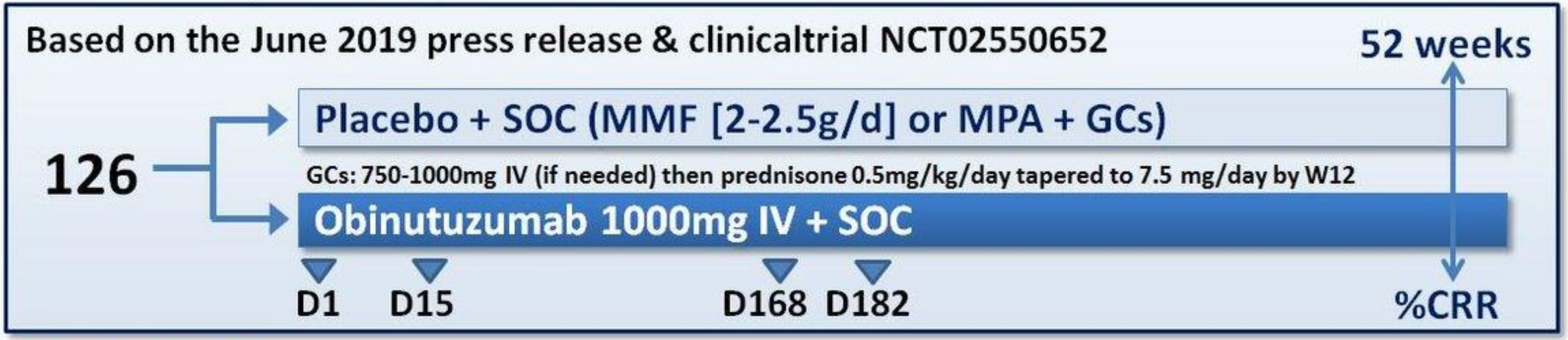
CLINICAL SCIENCE

B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis: a randomised, double-blind, placebo-controlled trial



Obinutuzumab in Lupus nephritis

NOBILITY (Phase 2) TRIAL



Selected Inclusion Criteria:

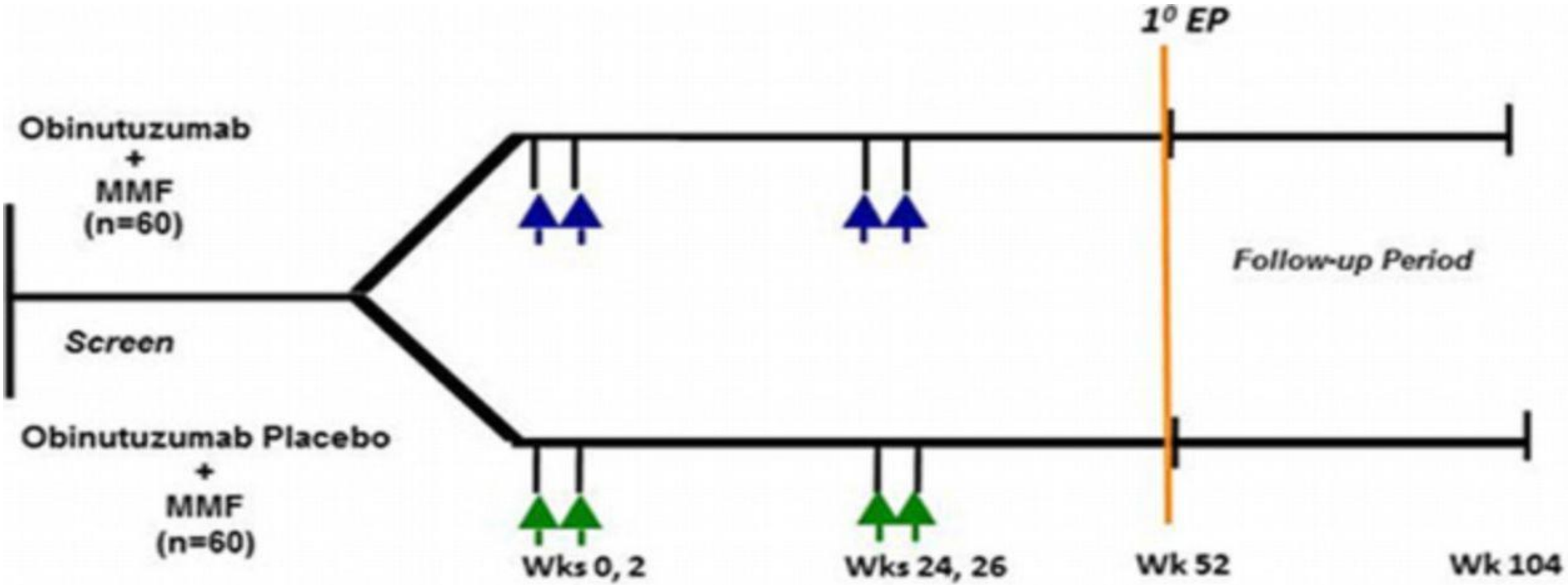
- Diagnosis of SLE, according to 1997 ACR criteria
- Diagnosis of ISN/RPS 2003 Class III or IV (+/- V) LN as evidenced by renal biopsy performed within 6 months prior to or during screening
- Proteinuria (urine protein to creatinine ratio) greater than (>) 1.0

Selected Exclusion Criteria:

- Presence of rapidly progressive glomerulonephritis or severe renal impairment with GFR <30mL/min or the need for dialysis / renal transplant
- Greater than 50% of glomeruli with sclerosis on renal biopsy
- Retinitis or CNS involvement that is currently active and resulting from SLE

Primary Outcome Measure:

- Proportion of participants who achieve protocol defined Complete Renal Response (CRR) [Time Frame: Week 52]

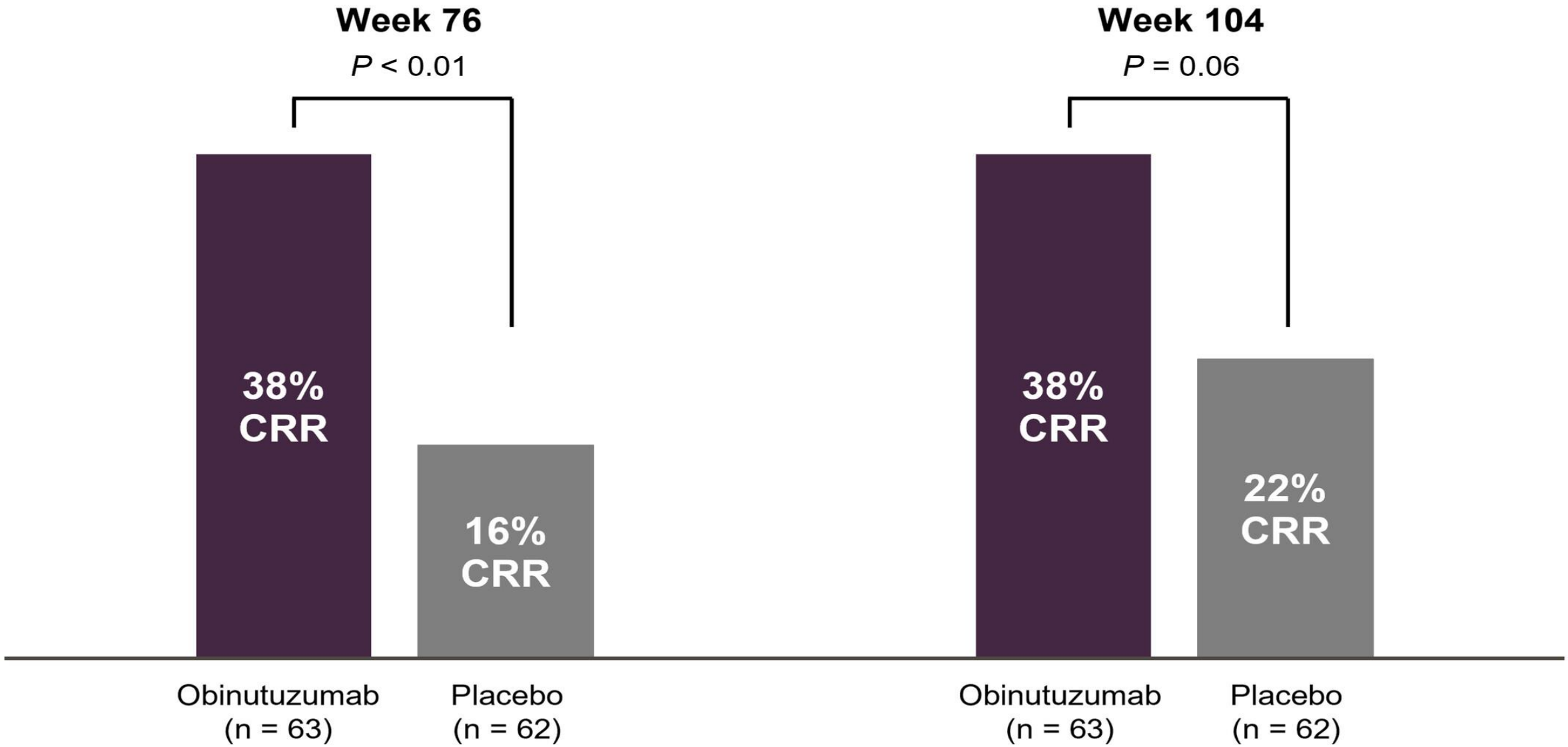


= Obinutuzumab infusion 1000mg

= Placebo infusion

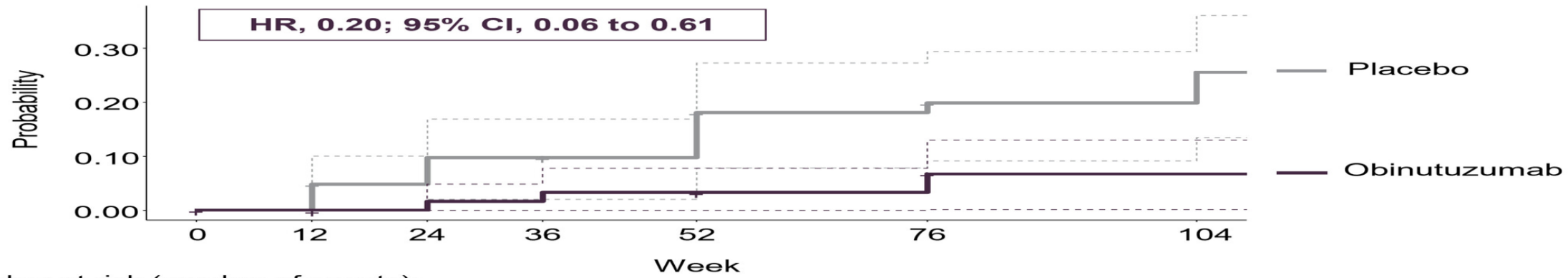
Obinutuzumab dosing: 1000 mg x 2 (Days 1, 15) repeated at Month 6
Target MMF dose: 2.0–2.5 g/day
IV Methylprednisolone: 1–3 infusions of 1000 mg prior to randomization
Prednisone dose: 0.5 mg/kg tapered over 12 weeks

CRR and 7.5 mg/day or less of prednisone*



A

Time to first 30% eGFR decline from baseline

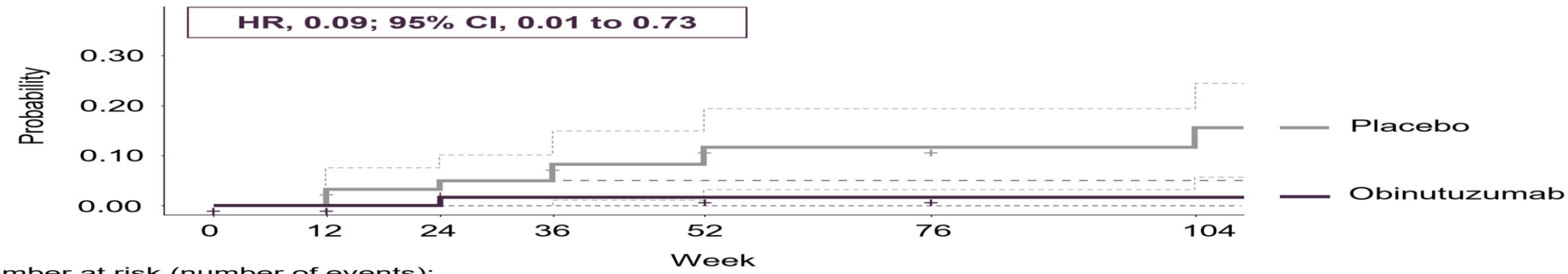


Number at risk (number of events):

Obinutuzumab	63 (0)	62 (0)	60 (1)	59 (1)	58 (0)	56 (2)	51 (0)
Placebo	62 (0)	62 (3)	58 (3)	55 (0)	54 (5)	46 (1)	42 (3)

B

Time to first 40% eGFR decline from baseline

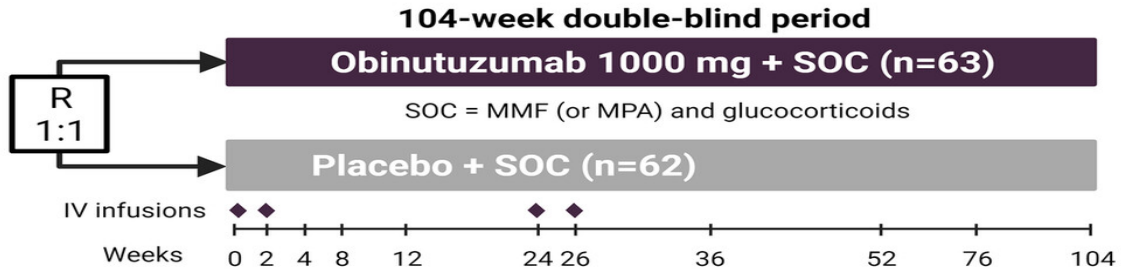


Number at risk (number of events):

Obinutuzumab	63 (0)	62 (0)	60 (1)	59 (0)	59 (0)	57 (0)	54 (0)
Placebo	62 (0)	62 (2)	58 (1)	57 (2)	54 (2)	48 (0)	45 (2)

Kidney Outcomes With Obinutuzumab in Patients With Lupus Nephritis: A Post Hoc Analysis of the NOBILITY Trial

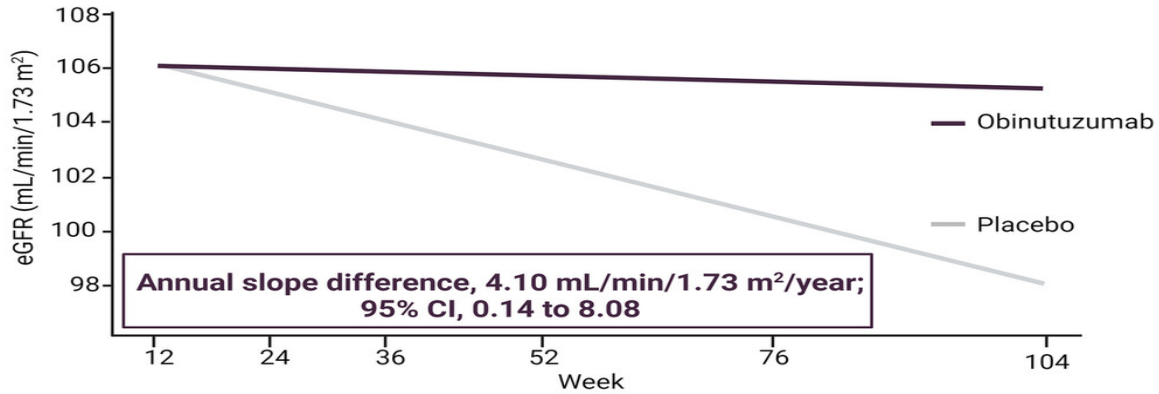
2 years of obinutuzumab treatment studied in patients with active lupus nephritis (NCT02550652)



At Weeks 52 (primary endpoint), 76, and 104, achievement of CRR was greater with obinutuzumab than placebo; no new safety signals were identified[1]

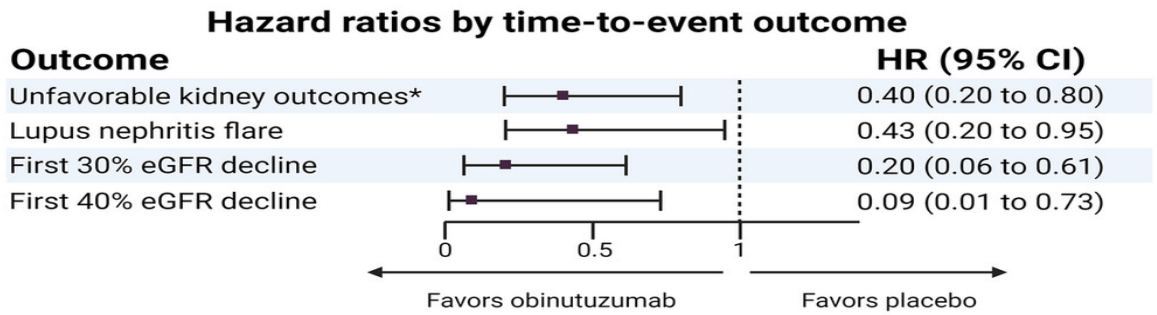
CRR, complete renal response; IV, intravenous; MMF, mycophenolate mofetil; MPA, mycophenolic acid; R, randomization; SOC, standard of care. 1. Furie RA, et al. Ann Rheum Dis. 2022;81:100-107.

Obinutuzumab significantly attenuated eGFR slope decline



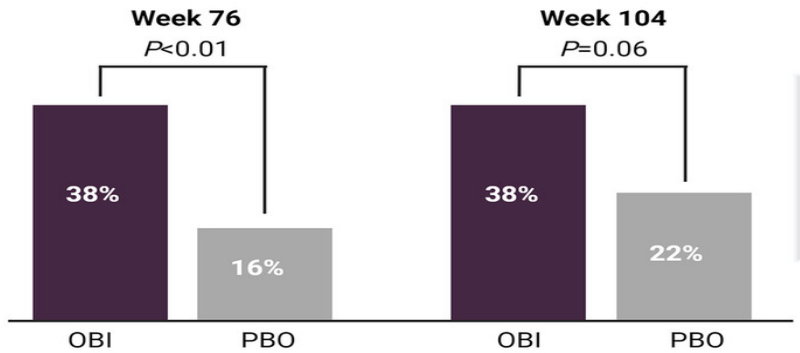
eGFR, estimated glomerular filtration rate.

Obinutuzumab significantly reduced the risk of adverse kidney outcomes



eGFR, estimated glomerular filtration rate; HR, hazard ratio.
*Composite endpoint of treatment failure, doubling of serum creatinine and death.

More patients achieved CRR and ≤7.5 mg/day of prednisone with obinutuzumab



Week 64-76 median cumulative prednisone dose:

Obinutuzumab: 525 mg
Placebo: 630 mg

CRR, complete renal response; OBI, obinutuzumab; PBO, placebo.

Rovin BH, Furie RA, Ross Terres JA, et al. Kidney outcomes and preservation of kidney function with obinutuzumab in patients with lupus nephritis: a post hoc analysis of the NOBILITY trial. Arthritis Rheumatol 2023.

Arthritis & Rheumatology
ACR American College of Rheumatology

KDIGO 2023 CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF LUPUS NEPHRITIS

KDIGO: Class III or Class IV lupus nephritis

Intravenous cyclophosphamide: in patients who may have difficulty adhering to an oral regimen.

An MPAA-based regimen: for patients at high risk of infertility, patients who have a moderate to high prior cyclophosphamide exposure.

Initial therapy with an immunosuppressive regimen that includes a CNI: patients with relatively preserved kidney function and nephrotic-range proteinuria, as well as patients who cannot tolerate standard-dose MPAA or are unfit for or will not use cyclophosphamide-based regimens.

KDIGO: Class III or Class IV lupus nephritis

A triple immunosuppressive regimen of belimumab with glucocorticoids and either MPAA or reduced-dose cyclophosphamide may be considered in patients with repeated renal flares or at high-risk for progression to kidney failure.

Rituximab may be considered for patients with persistent disease activity or inadequate response to initial standard-of-care therapy.

- **Practice Point : Intravenous cyclophosphamide should be used as the initial therapy for active Class III and Class IV LN in patients who may have difficulty adhering to an oral regimen.**

- **Practice Point : An MPAA-based regimen is the preferred initial therapy of proliferative LN for patients at high risk of infertility, patients who have a moderate to high prior cyclophosphamide exposure.**

- **Practice Point : Initial therapy with an immunosuppressive regimen that includes a CNI (voclosporin, tacrolimus, or cyclosporine) may be preferred in patients with relatively preserved kidney function and nephrotic-range proteinuria likely due to extensive podocyte injury, as well as patients who cannot tolerate standard-dose MPAA or are unfit for or will not use cyclophosphamide-based regimens.**

- **Practice Point : A triple immunosuppressive regimen of belimumab with glucocorticoids and either MPAA or reduced-dose cyclophosphamide may be considered in patients with repeated renal flares or at high-risk for progression to kidney failure.**

MPAA as maintenance therapy

- Azathioprine is an alternative to MPAA after completion of initial therapy in patients who do not tolerate MPAA, who do not have access to MPAA, or who are considering pregnancy.

- Glucocorticoids should be tapered to the lowest possible dose during maintenance, except when glucocorticoids are required for extrarenal lupus manifestations; discontinuation of glucocorticoids can be considered after patients have maintained a complete clinical renal response for ≥12 months.

- The dose of mycophenolate mofetil (MMF) in the early maintenance phase is approximately 750–1000 mg twice daily, and for mycophelolic acid (MPA), approximately 540–720 mg twice daily.

- The total duration of initial immunosuppression plus combination maintenance immunosuppression for proliferative LN should be ≥36 months.

- Patients treated with triple immunosuppressive regimens that include belimumab or a CNI in addition to standard immunosuppressive therapy can continue with triple immunosuppressive regimen as maintenance therapy.

- If MPAA and azathioprine cannot be used for maintenance, CNIs or mizoribine or leflunomide can be considered.

2021

Class III or IV

Recommendation 10.2.3.1.1: We recommend that patients with active Class III or IV LN, with or without a membranous component, be treated initially with steroids plus either low-dose IV cyclophosphamide or MPAA (1B).

2023

Class III or IV

Recommendation 10.2.3.1.1: We recommend that patients with active Class III or IV LN, with or without a membranous component, be treated initially with steroids plus either one of the following:

- **mycophenolic acid analogues (MPAA) (1B); or**
- **low-dose intravenous cyclophosphamide (1B); or**
- **belimumab and either MPAA or low-dose IV cyclophosphamide (1B); or**
- **MPAA and a calcineurin inhibitor (CNI) when kidney function is not severely impaired** (for example eGFR ≤45 ml/min per 1.73 m^2) **(1B).**

New: draft 3/2023

KDIGO. Kidney Int 2021;100:S1–S276 and
KDIGO. Public review draft 2023.

Practice points in guiding selection of initial therapy for class III + IV:

- **IV cyclophosphamide:** **if difficulty adhering to an oral regimen**
- **MPAA:** **if high risk of infertility following prior cyclophosphamide**
- **CNI** (voclosporin, tacrolimus, CyA): **if relatively preserved kidney function and nephrotic-range proteinuria or if standard-dose MPAA or cyclophosphamide not tolerated**
- **Belimumab:** **with glucocorticoids + standard-dose MPAA or reduced-dose cyclophosphamide if repeated renal flares or at high-risk for progression to kidney failure.**
- Azathioprine or leflunomide: with glucocorticoids, if intolerance, lack of availability, or cost concerns, but associated with inferior efficacy.
- Rituximab: consider if persistent disease activity or inadequate response to initial therapy.

	Standard-dose scheme	Moderate-dose scheme	Reduced-dose scheme
Methylprednisolone intravenous pulses	Nil or 0.25–0.5 g/day up to 3 days as initial treatment	0.25–0.5 g/day up to 3 days often included as initial treatment	0.25–0.5 g/day up to 3 days usually included as initial treatment
Oral prednisone equivalent (/day)			
Week 0–2	0.8–1.0 mg/kg (max 80 mg)	0.6–0.7 mg/kg (max 50 mg)	0.5–0.6 mg/kg (max 40 mg)
Week 3–4	0.6–0.7 mg/kg	0.5–0.6 mg/kg	0.3–0.4 mg/kg
Week 5–6	30 mg	20 mg	15 mg
Week 7–8	25 mg	15 mg	10 mg
Week 9–10	20 mg	12.5 mg	7.5 mg
Week 11–12	15 mg	10 mg	5 mg
Week 13–14	12.5 mg	7.5 mg	2.5 mg
Week 15–16	10 mg	7.5 mg	2.5 mg
Week 17–18	7.5 mg	5 mg	2.5 mg
Week 19–20	7.5 mg	5 mg	2.5 mg
Week 21–24	5 mg	<5 mg	2.5 mg
Week >25	<5 mg	<5 mg	<2.5 mg

2021

Class III or IV

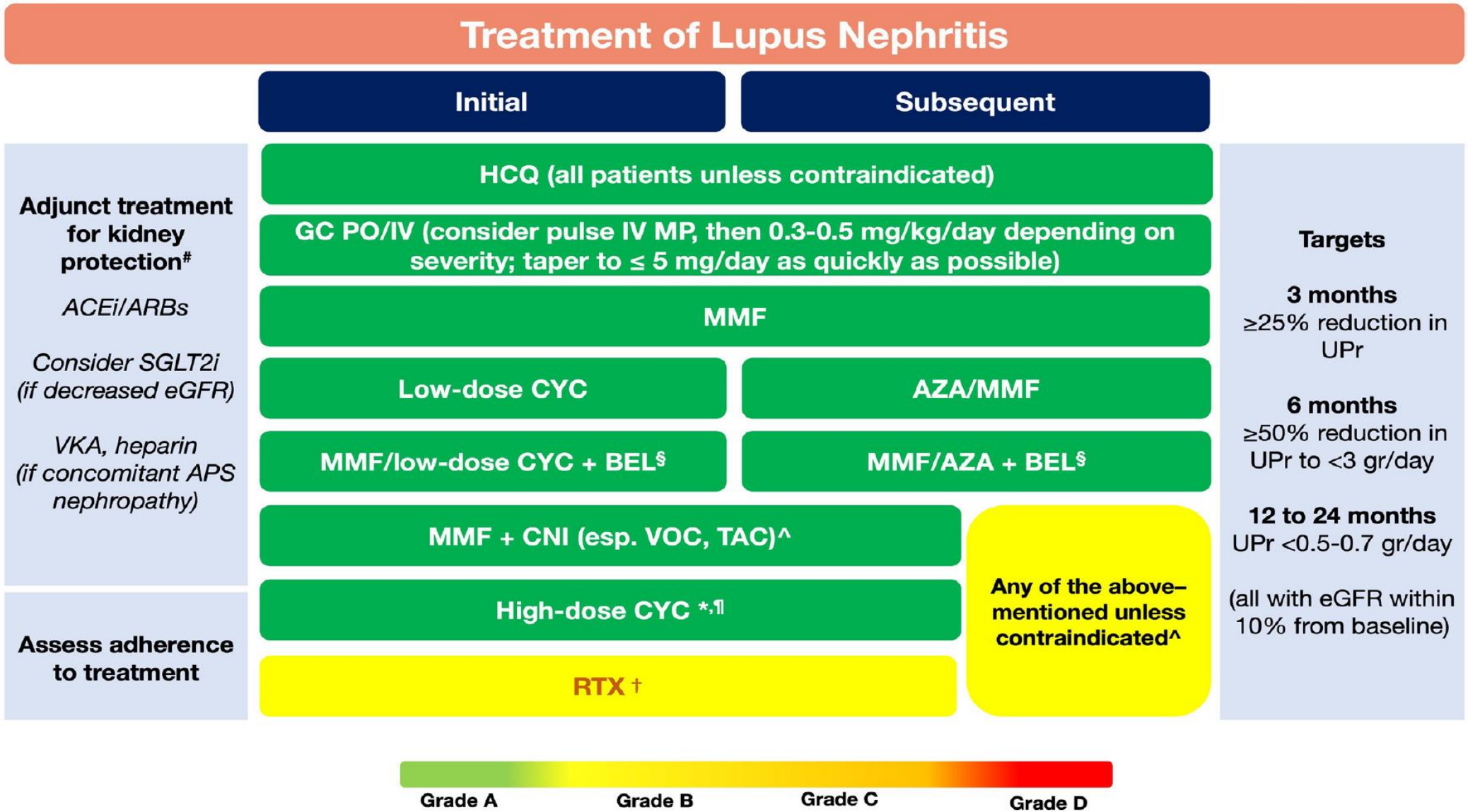
Recommendation 10.2.3.2.1. We recommend that after completion of initial therapy patients should be placed on MPAA for maintenance (1B).

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 **Preferred**	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 **Continue in maintenance if good response initially** 24 months [Practice Point 10.2.3.2.5]	Tacrolimus and cyclosporine safe in pregnancy; insufficient pregnancy data on voclosporin

New: draft 3/2023

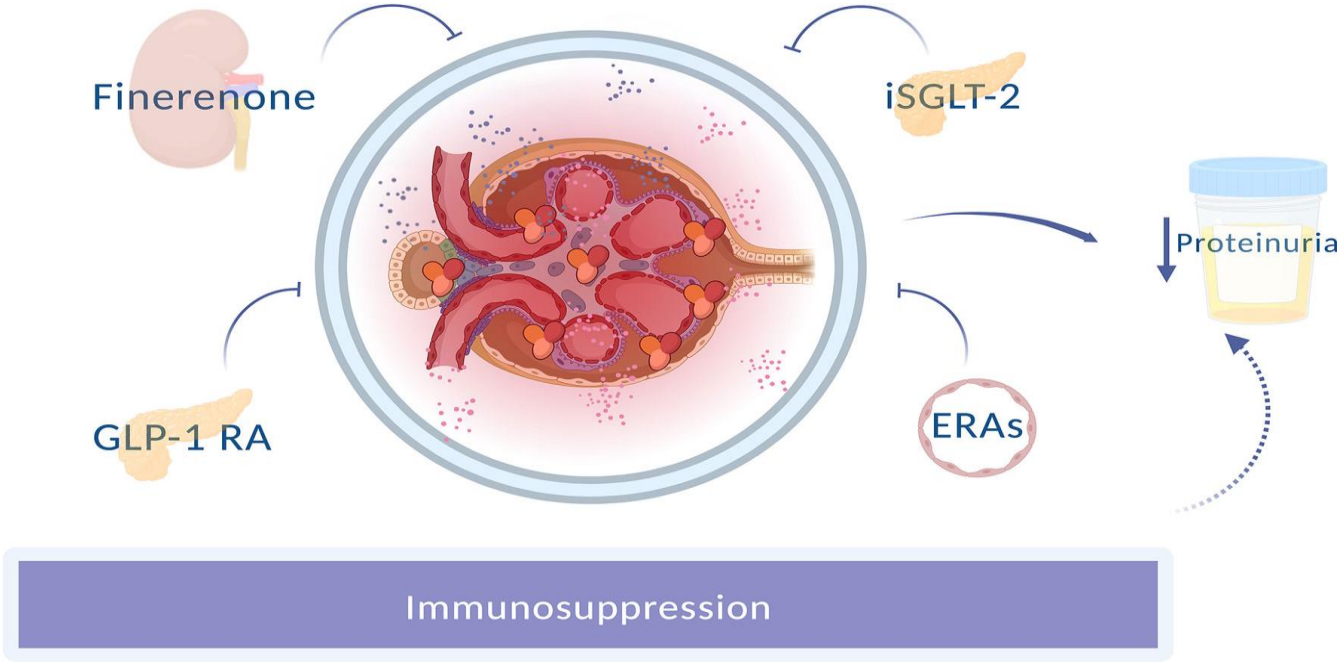
EULAR recommendations for the management of systemic lupus erythematosus: 2023 update

Treatment of Lupus Nephritis



Treatment goals in patients with LN include preserving renal function and preventing ESKD; these outcomes can be assessed by renal biopsy and other clinical indicators of damage, such as estimated glomerular filtration rate (eGFR) slope and chronic kidney disease (CKD) staging

Nephroprotection is a cornerstone in preserving renal damage in patients with lupus nephritis



Executive summary of the 2024 update of the KDIGO Lupus Nephritis Guideline

OPEN

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The Kidney Disease: Improving Global Outcomes (KDIGO)

ince publication of the Kidney Disease Improving

Conclusions

1- Induction : Cyclophosphamide, MMF

2-Maintenance: MMF is preferred

3-**Belimumab** may be preferred when prevention of disease flares and adverse kidney outcomes assumes high priority

4- CNI in patients in podocytopathy

5-**Voclosporin** when kidney function is not severely impaired (GFR ≥45cc/min/1.73m2 and there is significant proteinuria

6- Non-immunosuppressive renoprotective treatments