Recent progress in the treatment of lupus nephritis

Vladimir Tesar
Department of Nephrology,
Charles University, Prague

Disclosure of Interests

AstraZeneca,

Bayer,

Boehringer-Ingelheim,

Calliditas

Novartis,

Omeros,

Otsuka

Travere

(consultancy, advisory board)

Ferdinand, Ritter von Hebra (1816-1880)
among his colleagues in the University of Vienna

description of lupus vulgaris and erythematosus by Hebra (1856)

Cazenave, Kaposi and Lupus erythematosus

A Centennial and a Sesquicentennial

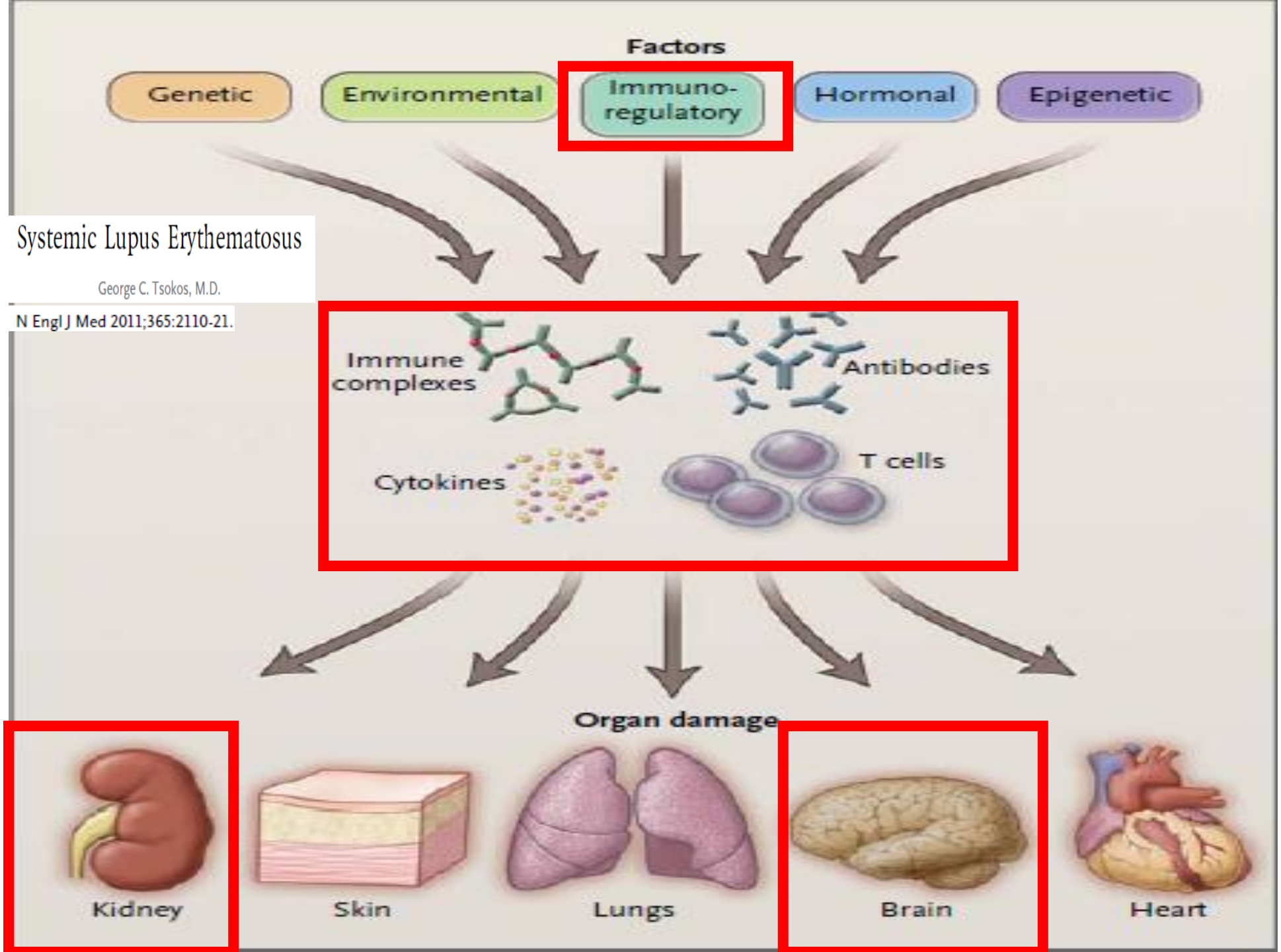
Karl Holubar[a] Stella Fatović-Ferenčić[b]

Dermatology 2001;203:118–120

Keith NM, Rowntree LG: A study of renal complications of lupus erythematosus: report of four cases. *Trans Assoc Am Physicians* 37: 487—502, 1922

Louis-Alphée Cazenave (1795-1867)
used the term SLE for the first time in 1851

Moritz Kaposi (1837 – 1901)
provided detailed description of organ involvement in SLE


Factors
Genetic
Environmental
Immuno-regulatory
Hormonal
Epigenetic
Systemic Lupus Erythematosus
George C. Tsokos, M.D.
N Engl J Med 2011;365:2110-21.
Immune complexes
Antibodies
Cytokines
T cells
Organ damage
Kidney
Skin
Lungs
Brain
Heart

Neandertals and Moderns Made Imperfect Mates

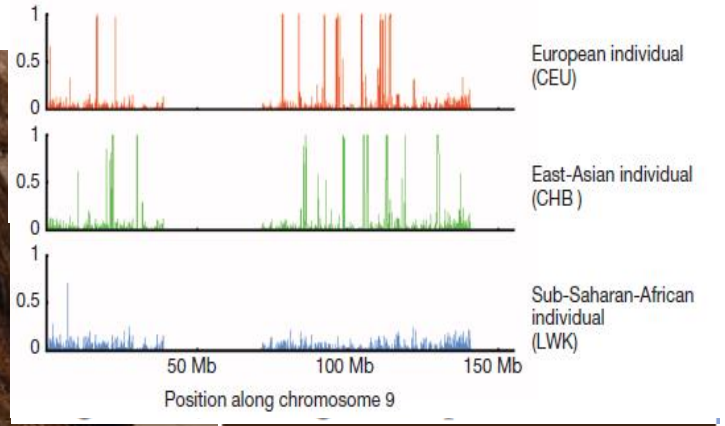
31 JANUARY 2014 VOL 343 SCIENCE www.sciencemag.org

1% to 3% of the genome in Europeans and East Asians comes from Neandertals.

IRF5 – G allele enriched in European population

rs12531711

Great-great-great-Grandma? Living people may carry more genes from Neandertal females, like the one in this artist's reconstruction, than from Neandertal males.



Conditions Associated With Neandertal Alleles

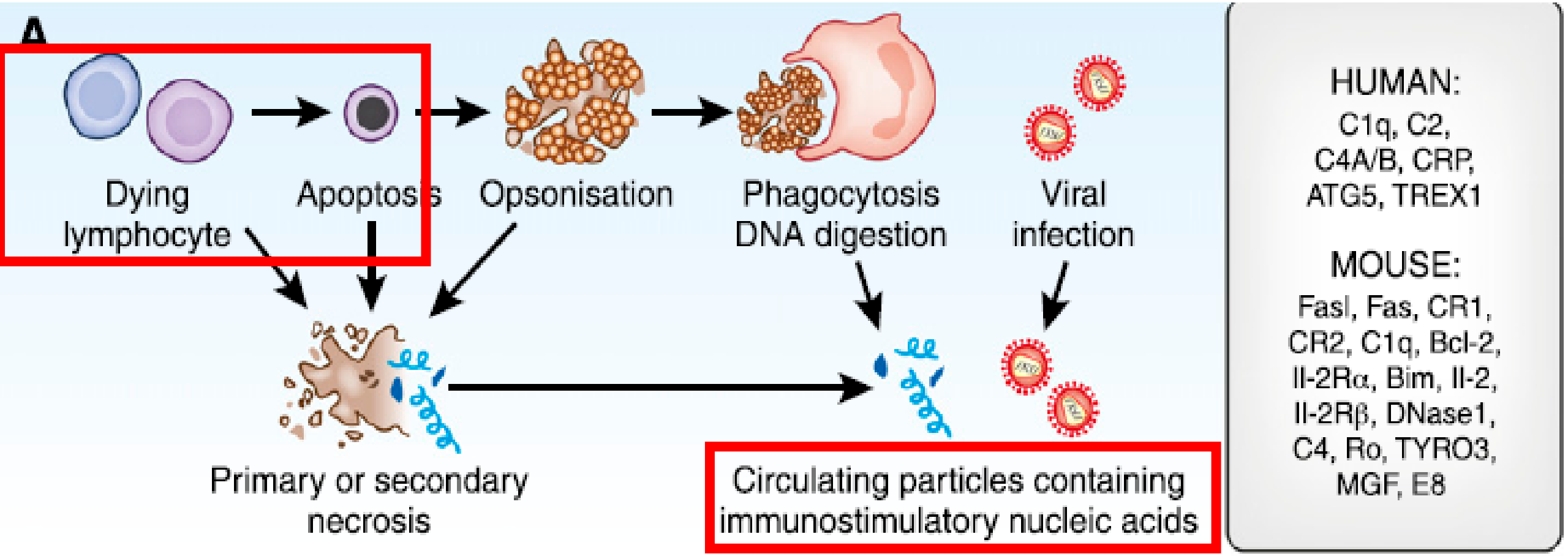
- Lupus
- Primary biliary cirrhosis
- Crohn's disease (2 alleles)
- Type 2 diabetes
- Variation in keratin in skin and hair (several alleles)
- Variation in interleukin-18 levels
- Variation in optic disc size
- Variation in smoking behavior

The Pathogenesis of Lupus Nephritis

Maciej Lech and Hans-Joachim Anders

J Am Soc Nephrol 24: ●●●–●●●, 2013.

Cell death with incomplete chromatin digestion resulting in the exposure of nuclear particles to the immune system

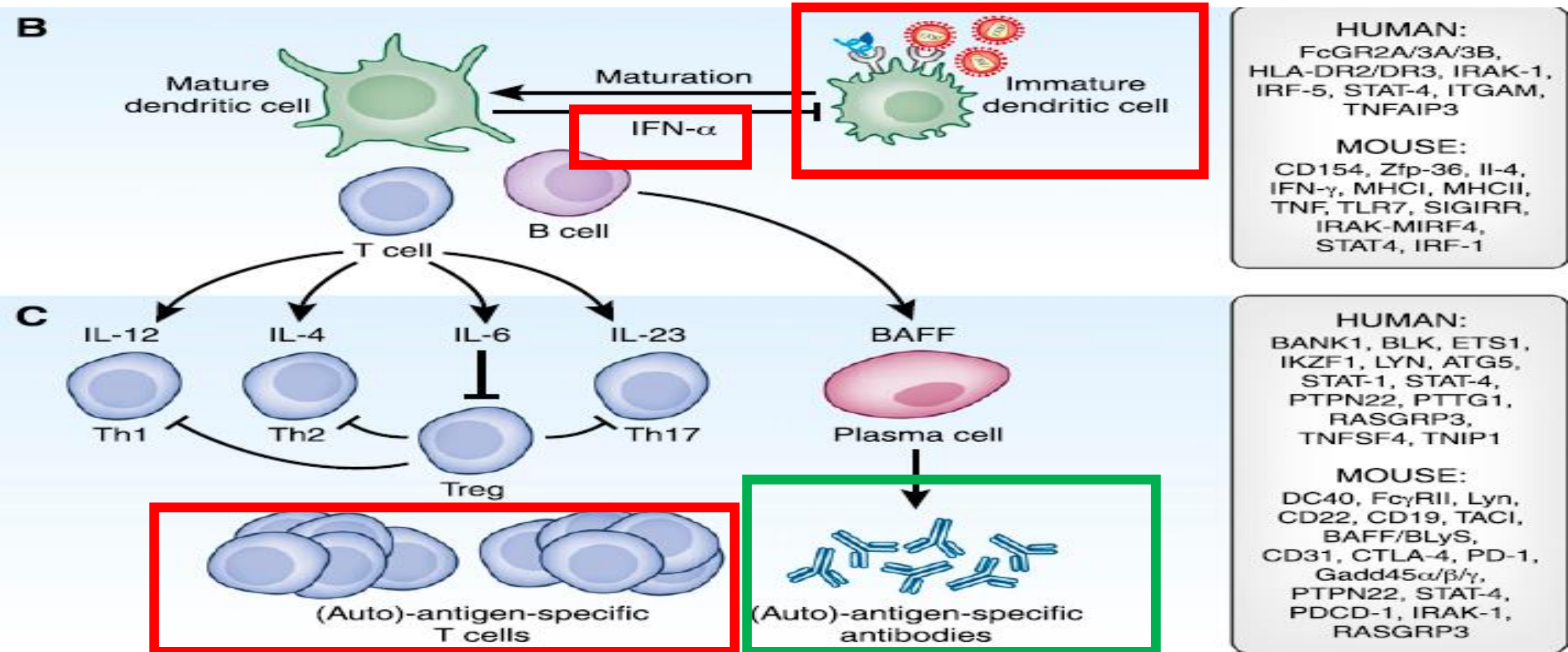


The Pathogenesis of Lupus Nephritis

J Am Soc Nephrol 24: ●●●–●●●, 2013.

Maciej Lech and Hans-Joachim Anders

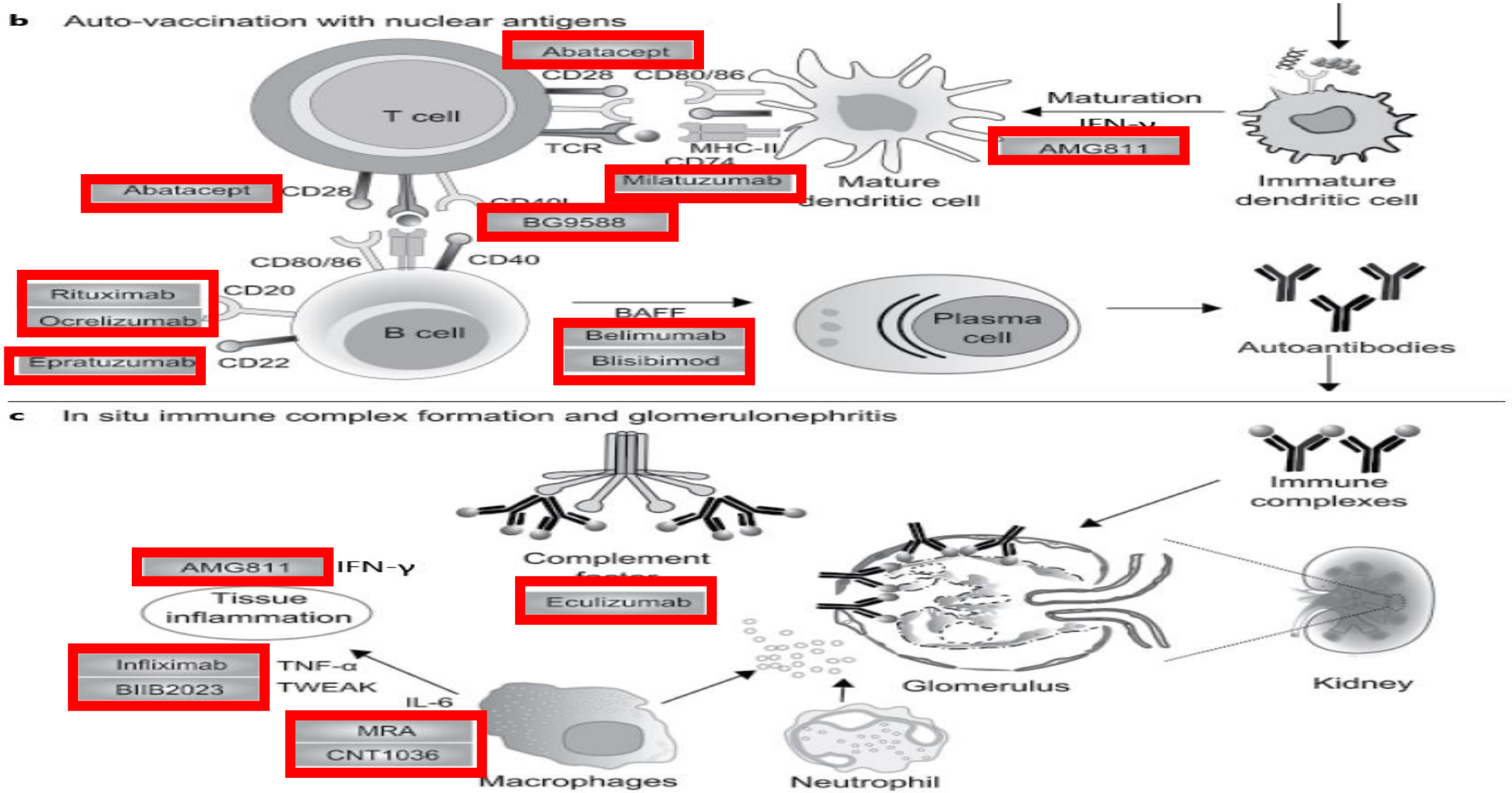
Pseudo-viral particles activate TLRs and antigen presentingresulting in polyclonal expansion of T and B cells



Lupus Nephritis: From Pathogenesis to Targets for Biologic Treatment

Nephron Clin Pract Published online: November 8, 2014

Yujuan Liu Hans-Joachim Anders



Lupus nephritis – ISN/RPS classification

Weening et al.: Kidney Int., 2004, 65: 521-30

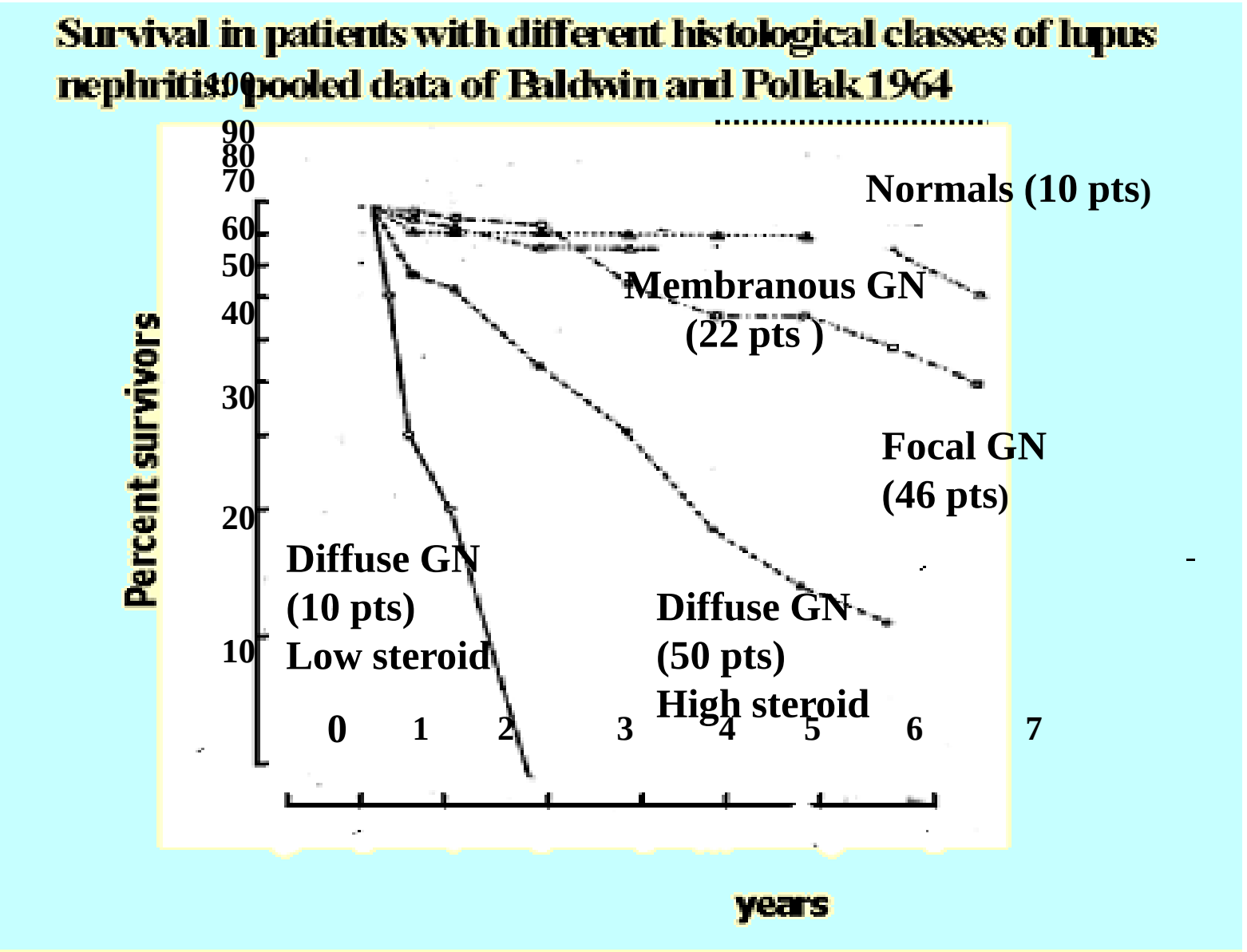
1. type I – II – mesangiopathy

2. type III – IV – proliferative LN

3. *type V – membranous LN*

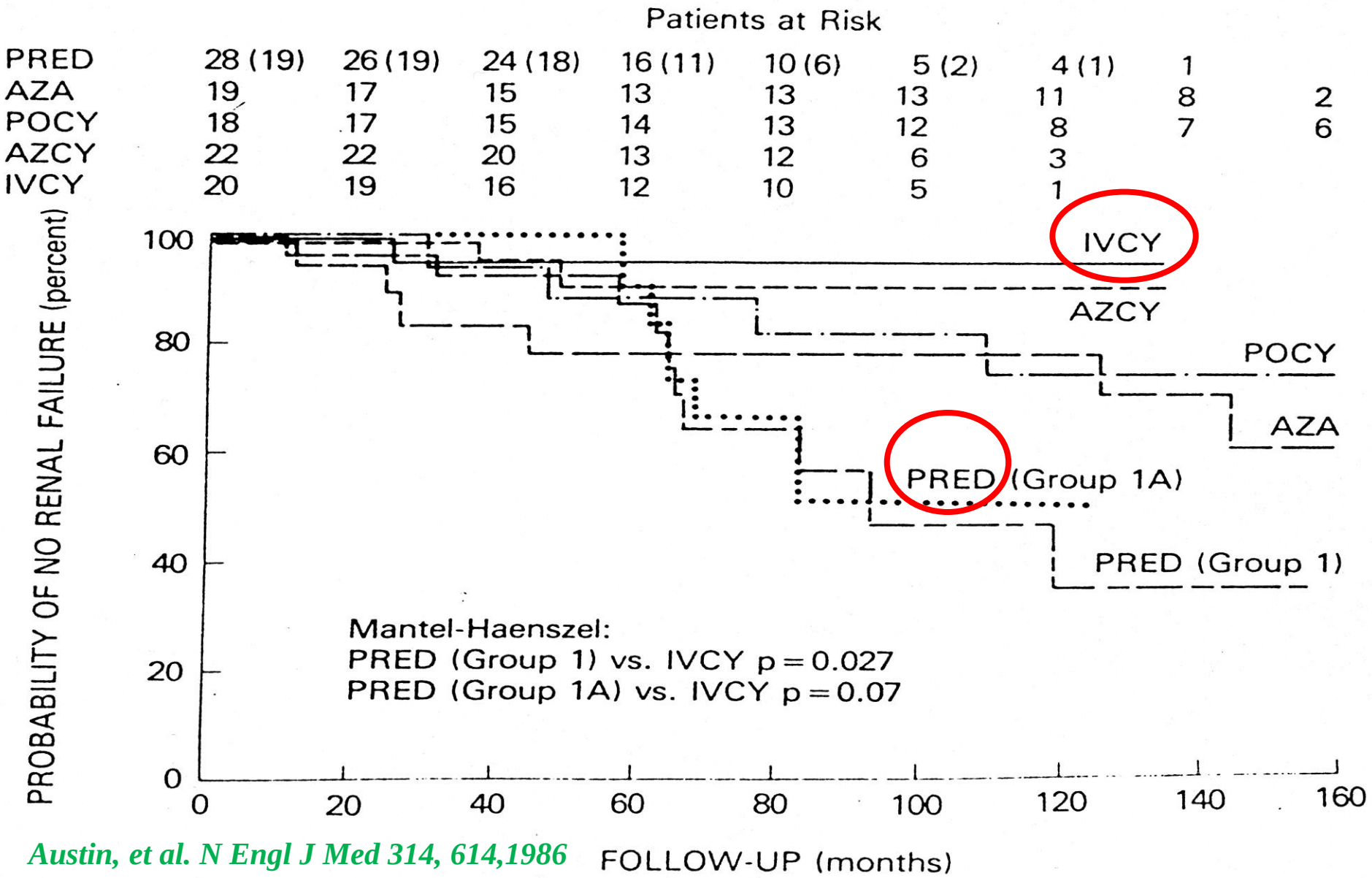
4. type VI – sclerosing lesions

5-year survival in lupus nephritis in 1964



Type III	65%
Type IV	25%
Type V	90%

Survival without renal failure

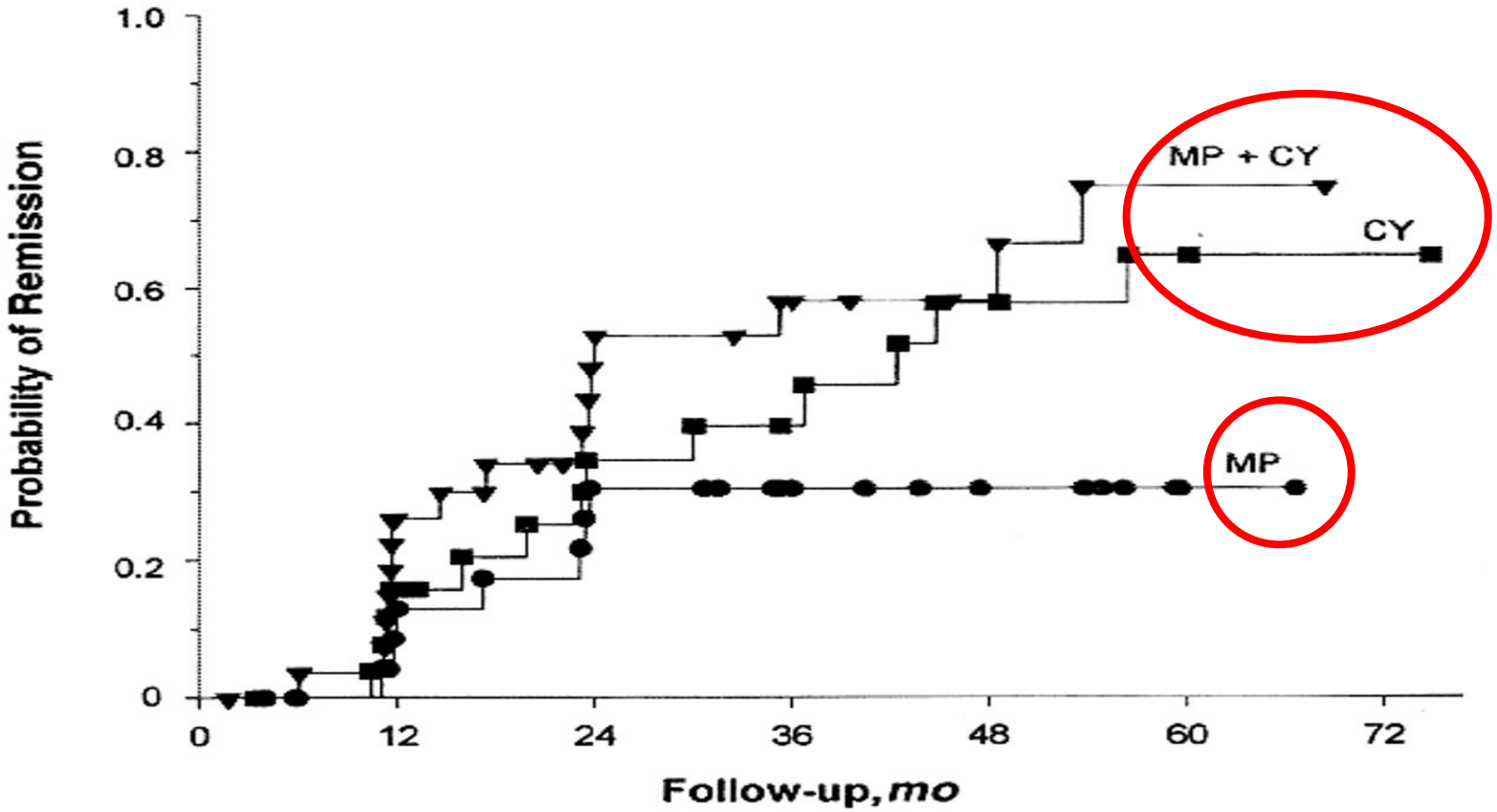


Austin, et al. N Engl J Med 314, 614,1986

CPH increased the remission rate

Number of patients eligible at each year

Year	0	1	2	3	4	5
MP + CY	28	19	11	8	5	3
MP	27	20	16	11	6	1
CY	27	21	13	10	7	5



Dimitrios Boumpas

Gourley, M. F. et. al. Ann Intern Med 1996;125:549-557

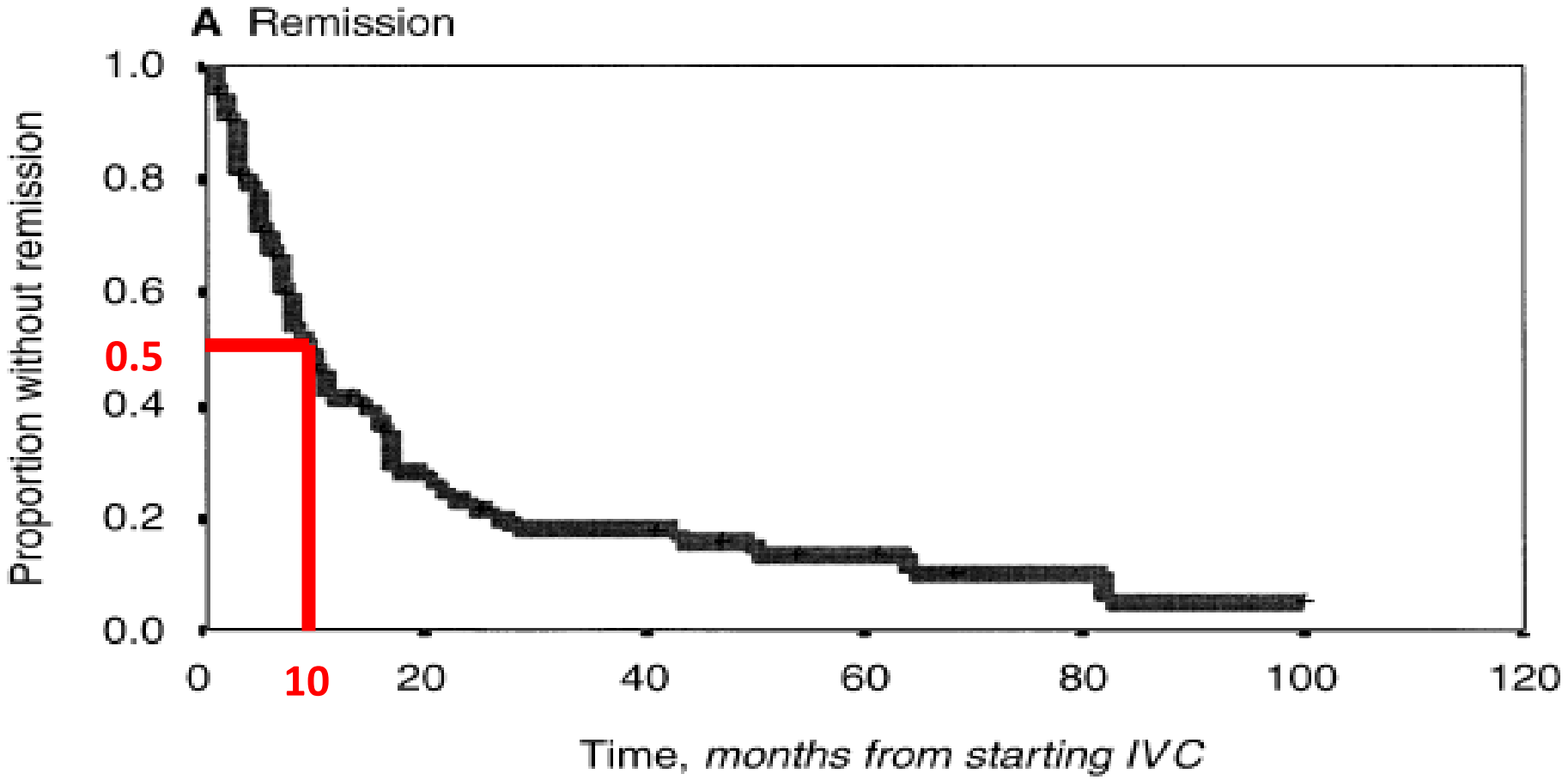
Annals of Internal Medicine

Remission, relapse, and re-remission of proliferative lupus nephritis treated with cyclophosphamide

Kidney International, Vol. 57 (2000), pp. 258–264

JOHN P.A. IOANNIDIS, KYRIAKI A. BOKI, MARIA E. KATSORIDA, ALEXANDROS A. DROSOS, FOTINI N. SKOPOULI, JOHN N. BOLETIS, and HARALAMPOS M. MOUTSOPOULOS

In 85 Greek patients with class III (33 pts) and IV (52 pts) LN median time to remission was 10 months

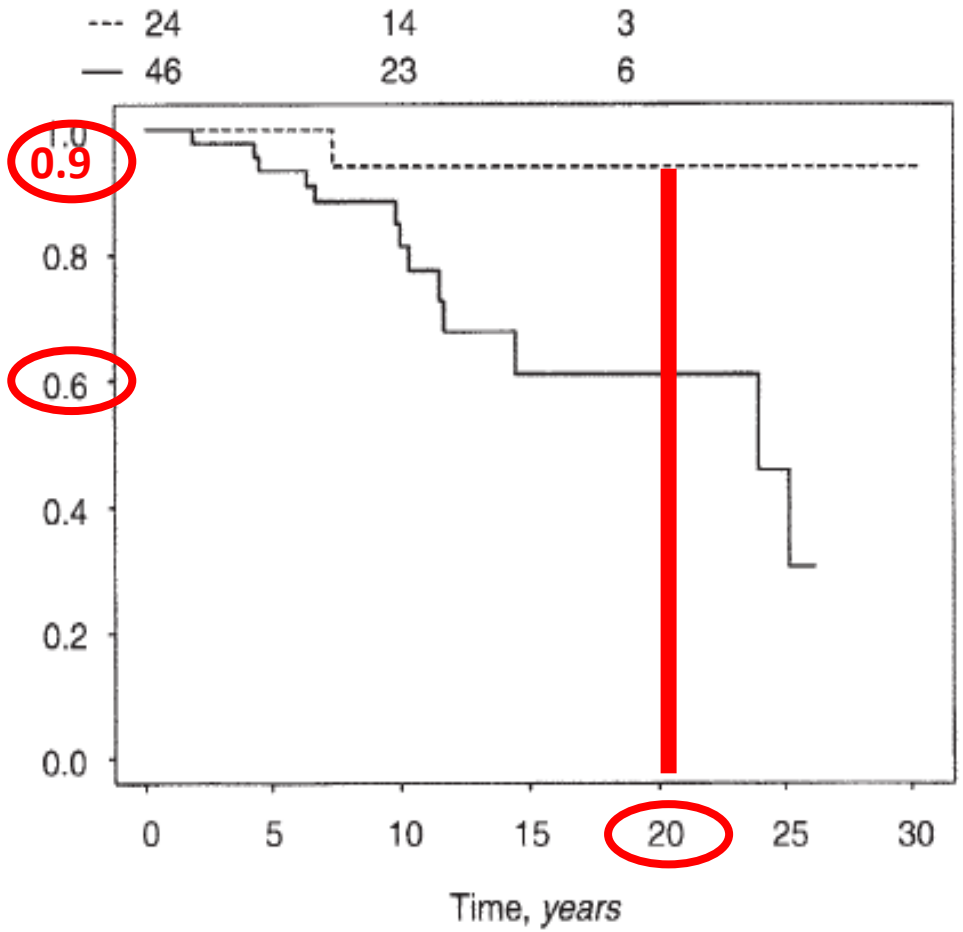


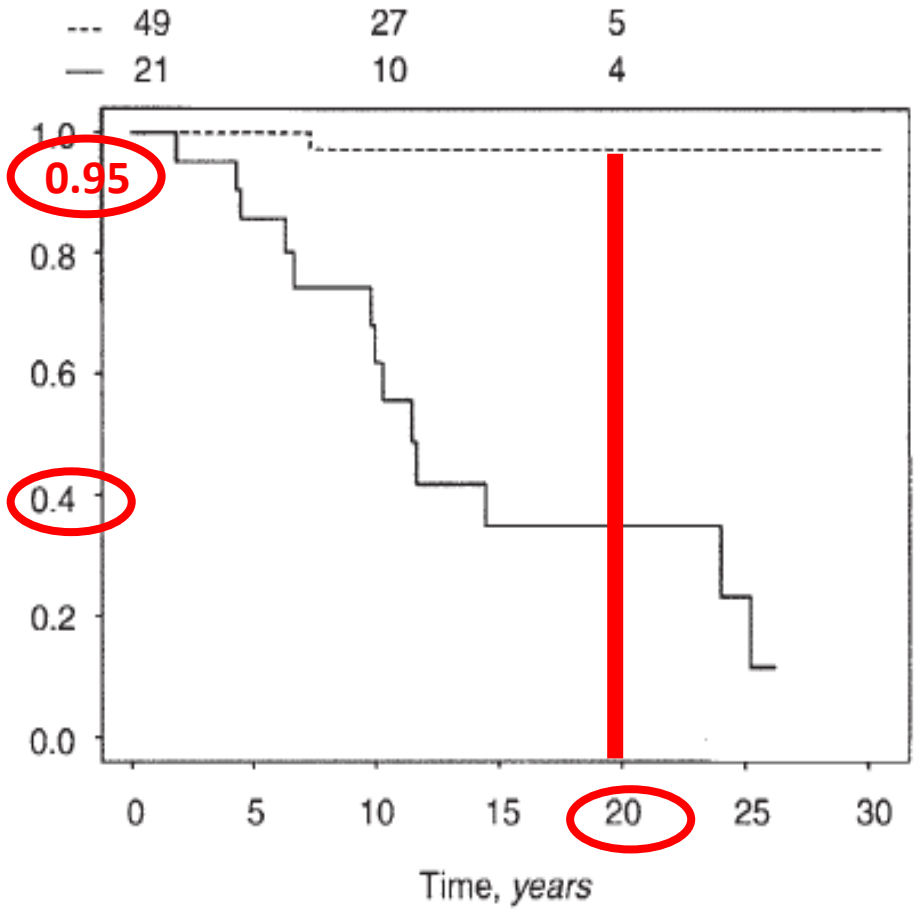
"Nephritic flares" are predictors of bad long-term renal outcome in lupus nephritis

GABRIELLA MORONI, SILVANA QUAGLINI, MASSIMO MACCARIO, GIOVANNI BANFI, and CLAUDIO PONTICELLI

Kidney International, Vol. 50 (1996), pp. 2047–2053

In non- relapsing patients survival without DSC much better than with („nephritic") relapses





Lupus Nephritis

J Am Soc Nephrol 10: 413–424, 1999 J. STEWART CAMERON

Outcome of pts with SLE and (proliferative) lupus nephritis dramatically improved

Table 4. Five-year actuarial survival for lupus, lupus nephritis, and WHO class IV nephritis over the past 40 years[a]

Period	% 5-Year Actuarial Survival (Weighted Mean of Published Series)		
	All Lupus	Lupus Nephritis	Class IV Nephritis
1953–1969	(4) 49%	(3) 44%	(2) 17%
1970–1979	(6) 82%	(13) 67%	(9) 55%
1980–1989	(5) 86%	(6) 82%	(3) 80%
1990–1995	(3) 92%	(5) 82%	(4) 82%

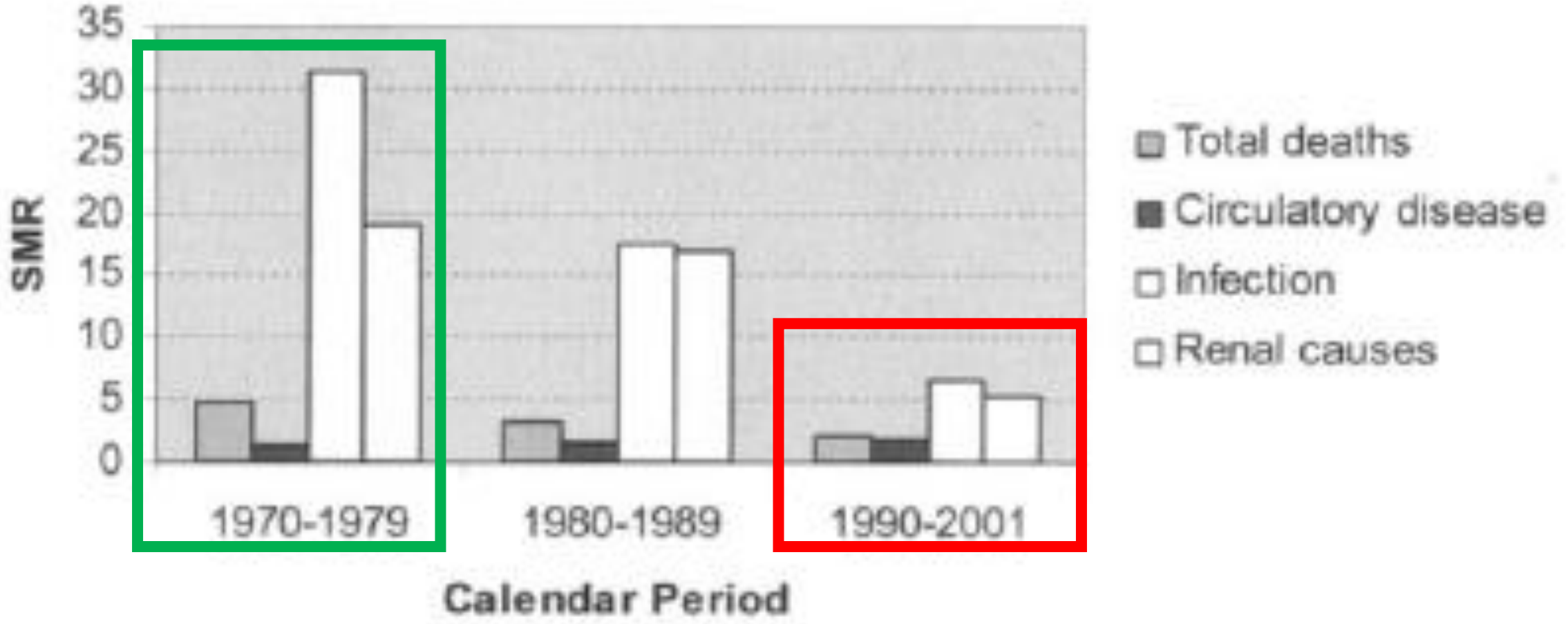
[a] Based on an analysis of the published literature. The number of articles for a given period is shown in parentheses.

Mortality in Systemic Lupus Erythematosus

S. Bernatsky,[1] J.-F. Boivin,[2] L. Joseph,[3] S. Manzi,[4] E. Ginzler,[5] D. D. Gladman,[6] M. Urowitz,[6] P. R. Fortin,[6] M. Petri,[7] S. Barr,[8] C. Gordon,[9] S.-C. Bae,[10] D. Isenberg,[11] A. Zoma,[12] C. Aranow,[13] M.-A. Dooley,[14] O. Nived,[15] G. Sturfelt,[15] K. Steinsson,[16] G. Alarcón,[17] J.-L. Senécal,[18] M. Zummer,[19] J. Hanly,[20] S. Ensworth,[21] J. Pope,[22] S. Edworthy,[8] A. Rahman,[11] J. Sibley,[23] H. El-Gabalawy,[24] T. McCarthy,[24] Y. St. Pierre,[1] A. Clarke,[1] and R. Ramsey-Goldman[25]

ARTHRITIS & RHEUMATISM
Vol. 54, No. 8, August 2006, pp 2550–2557

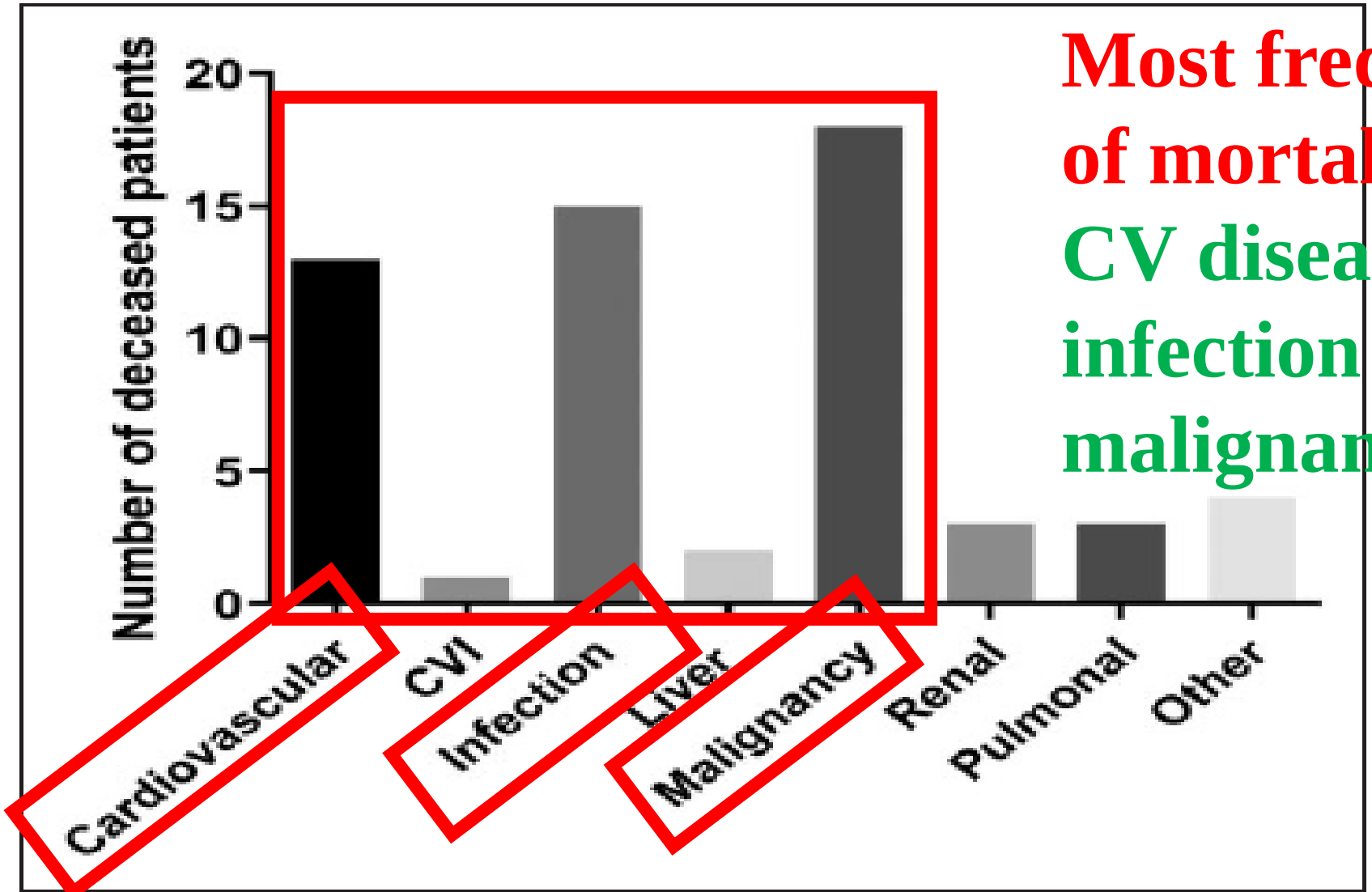
SMR dramatically decreased (infection, renal)



The majority of Swedish systemic lupus erythematosus patients are still affected by irreversible organ impairment: factors related to damage accrual in two regional cohorts

Lupus (2019) 28, 1261–1272

M Frodlund[1], S Reid[2], J Wetterö[1], Ö Dahlström[3], C Sjöwall[1] and D Leonard[2]



Most frequent causes of mortality:
CV disease, infection malignancy

(N Engl J Med THERAPY OF LUPUS NEPHRITIS 1986; 314:614-9.)

Controlled Trial of Prednisone and Cytotoxic Drugs

HOWARD A. AUSTIN, III, M.D., JOHN H. KLIPPEL, M.D., JAMES E. BALOW, M.D., NICOLE G.H. LE RICHE, M.D., ALFRED D. STEINBERG, M.D., PAUL H. PLOTZ, M.D., AND JOHN L. DECKER, M.D.

Table 5. Complications Observed among Patients within Each Treatment Group.

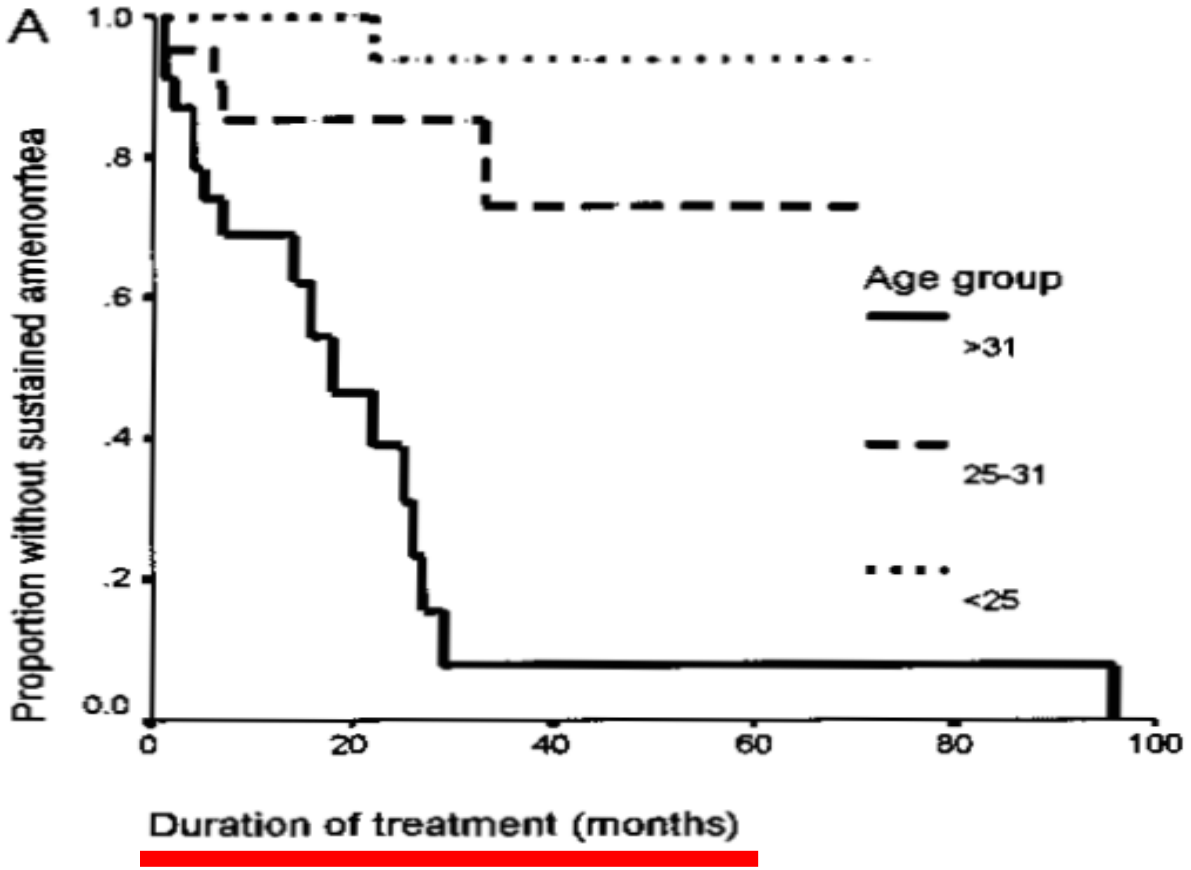
COMPLICATION	TREATMENT GROUP*				
	PRED	AZA	POCY	AZCY	IVCY
	% of the patients at risk				
Major infection	25	11	17	14	10
Herpes zoster†	7	11	33	32	25
Hemorrhagic cystitis‡	0	0	17	14	0
Cancer	0	11	17	0	0
Premature ovarian failure§	8	18	71	53	45

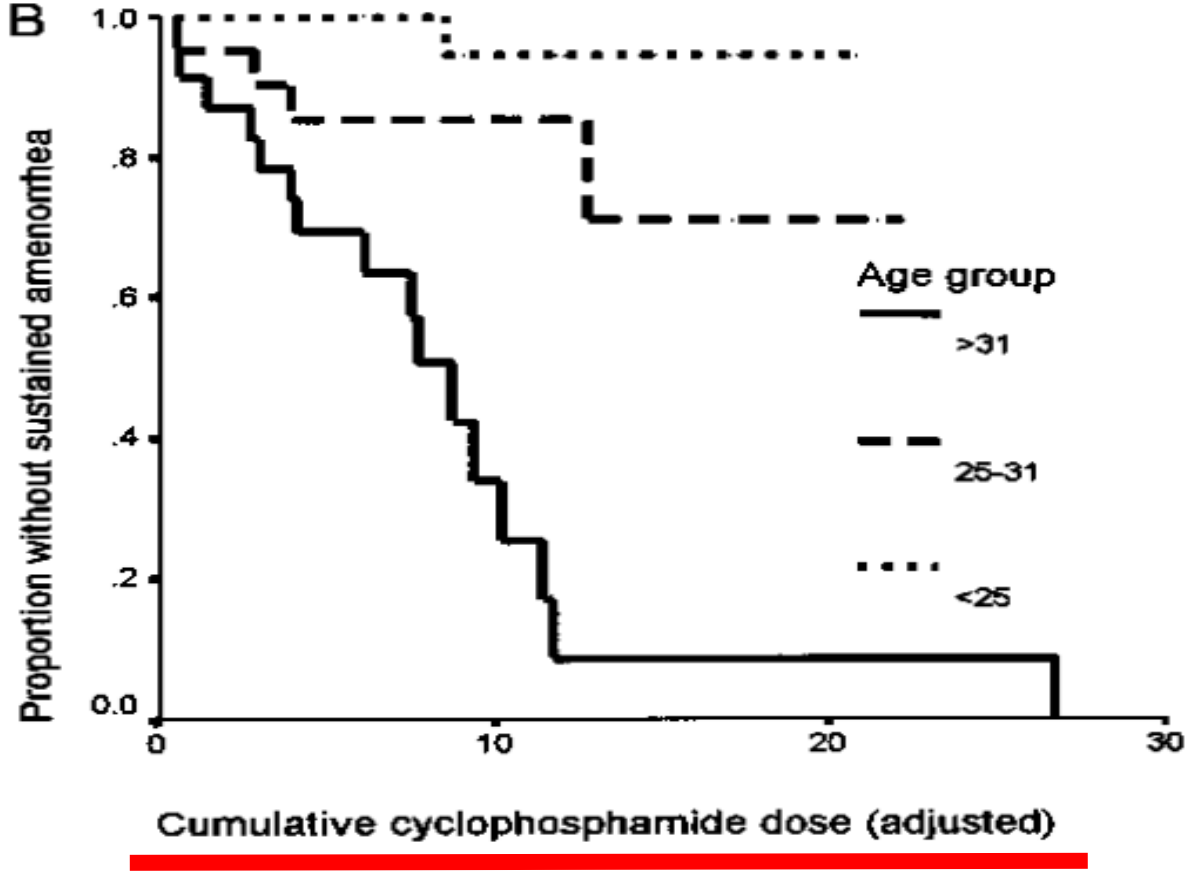
Predictors of Sustained Amenorrhea from Pulsed Intravenous Cyclophosphamide in Premenopausal Women with Systemic Lupus Erythematosus

JOHN P.A. IOANNIDIS, GIKAS E. KATSIFIS, ATHANASIOS G. TZIOUFAS, and HARALAMPOS M. MOUTSOPOULOS

J Rheumatol 2002;29:2129–35

Predictors of sustained amenorrhea in 67 pts with SLE (59 out of them with LN)
age, cumulative dose of CPH and duration of treatment





Anti–Müllerian Hormone and Ovarian Reserve in Systemic Lupus Erythematosus

ARTHRITIS & RHEUMATISM
Vol. 65, No. 1, January 2013, pp 206–210

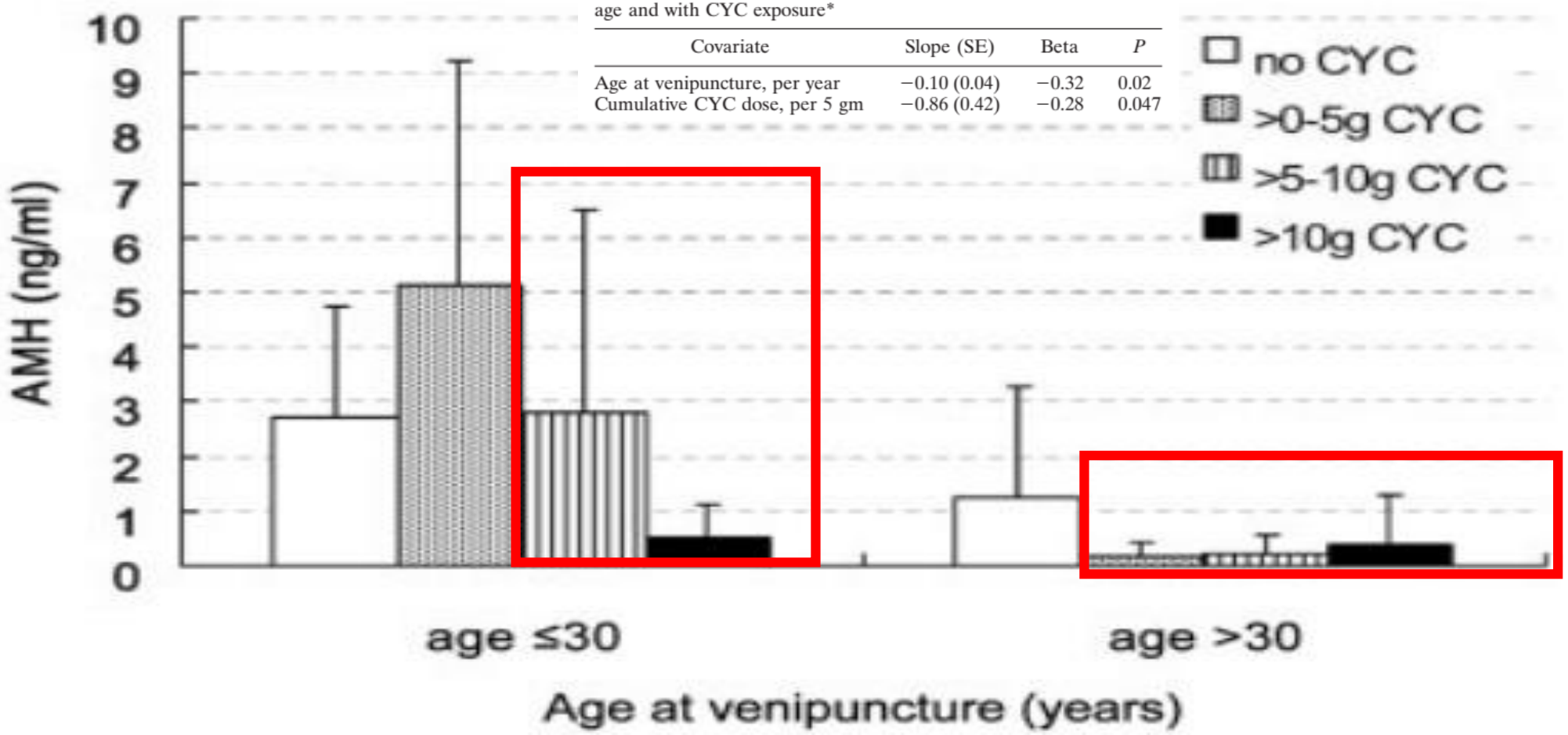
C. C. Mok, P. T. Chan, and C. H. To

AMH measured in 216 premenopausal SLE pts

divided based on age and CPH use

Table 3. Linear regression analysis of the correlation of AMH with age and with CYC exposure*

Covariate	Slope (SE)	Beta	*P*
Age at venipuncture, per year	−0.10 (0.04)	−0.32	0.02
Cumulative CYC dose, per 5 gm	−0.86 (0.42)	−0.28	0.047



Immunosuppressive Therapy in Lupus Nephritis

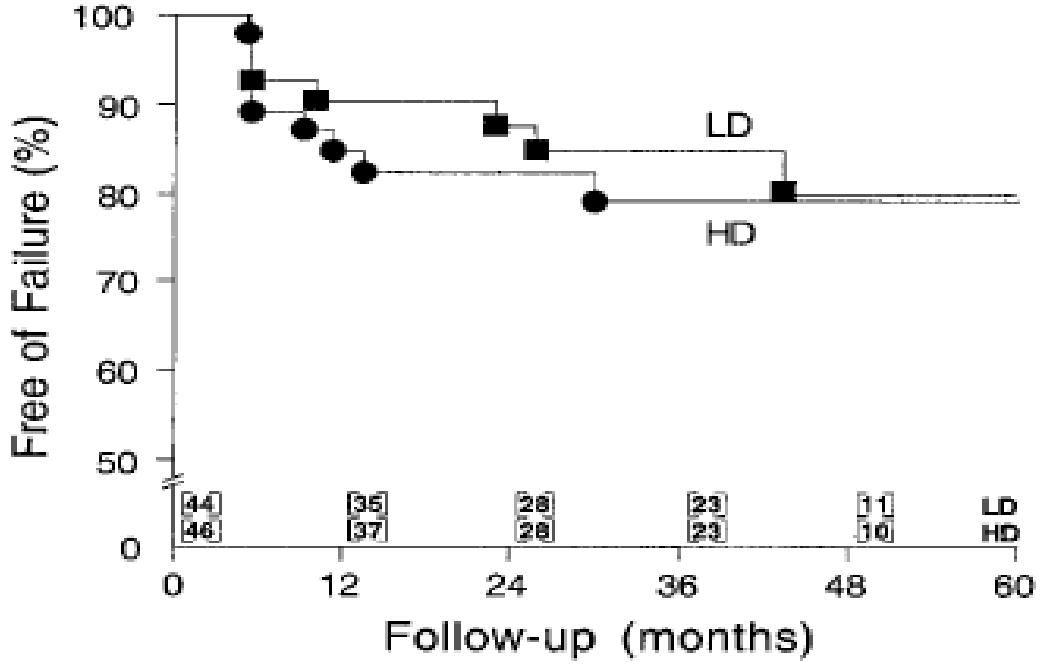
The Euro-Lupus Nephritis Trial, a Randomized Trial of Low-Dose Versus High-Dose Intravenous Cyclophosphamide

Frédéric A. Houssiau,[1] Carlos Vasconcelos,[2] David D'Cruz,[3] Gian Domenico Sebastiani,[4] Enrique de Ramon Garrido,[5] Maria Giovanna Danieli,[6] Daniel Abramovicz,[7] Daniel Blockmans,[8] Alessandro Mathieu,[9] Haner Direskeneli,[10] Mauro Galeazzi,[11] Ahmet Gül,[12] Yair Levy,[13] Peter Petera,[14] Rajko Popovic,[15] Radmila Petrovic,[16] Renato Alberto Sinico,[17] Roberto Cattaneo,[18] Josep Font,[19] Geneviève Depresseux,[1] Jean-Pierre Cosyns,[1] and Ricard Cervera[19]

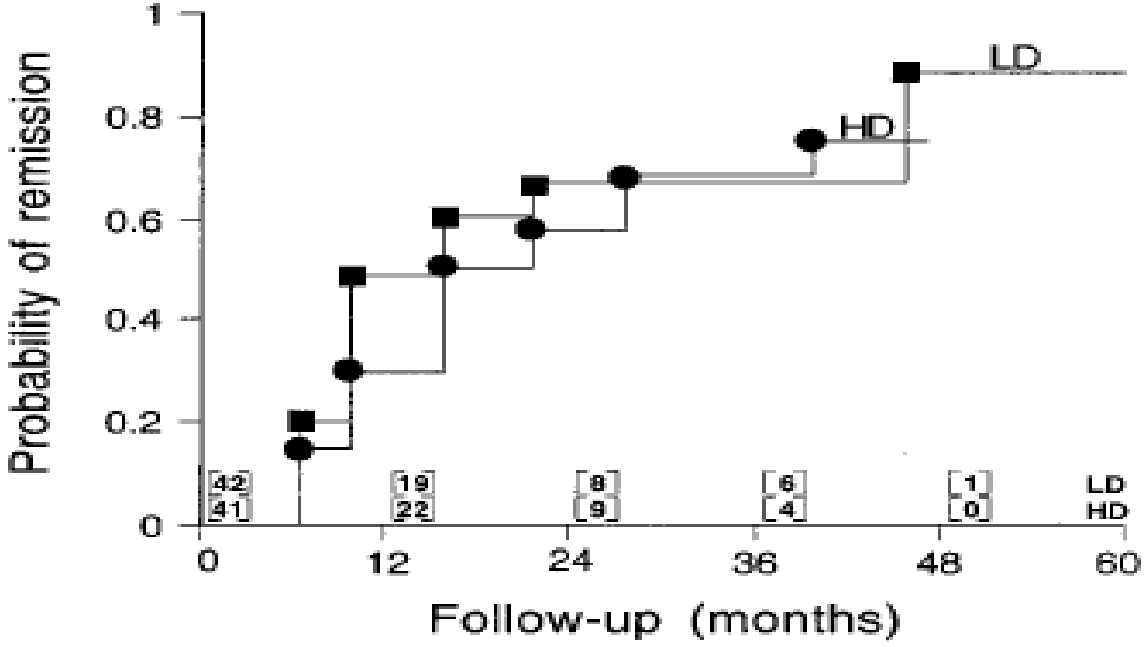
ARTHRITIS & RHEUMATISM
Vol. 46, No. 8, August 2002, pp 2121–2131
DOI 10.1002/art.10461

Euro-Lupus study

compared low-dose (3 g) versus high dose CPH (almost 9g)



Treatment failure

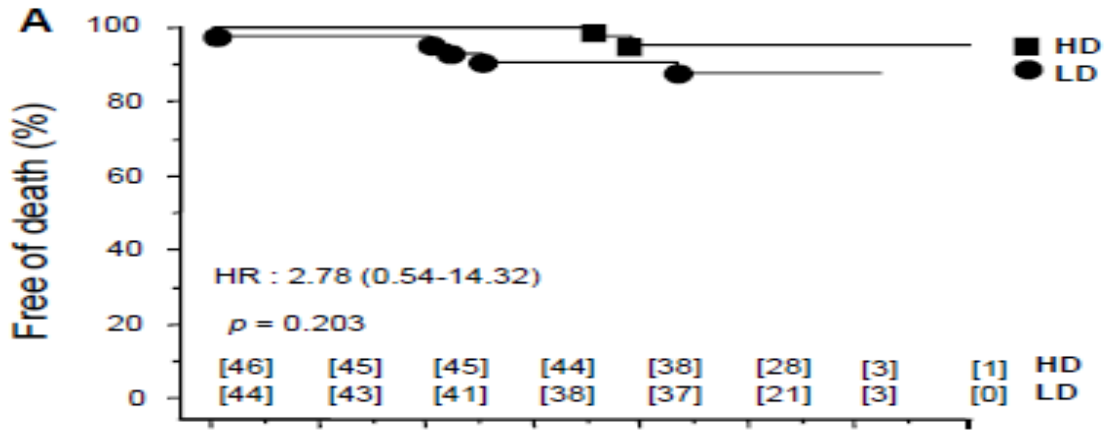


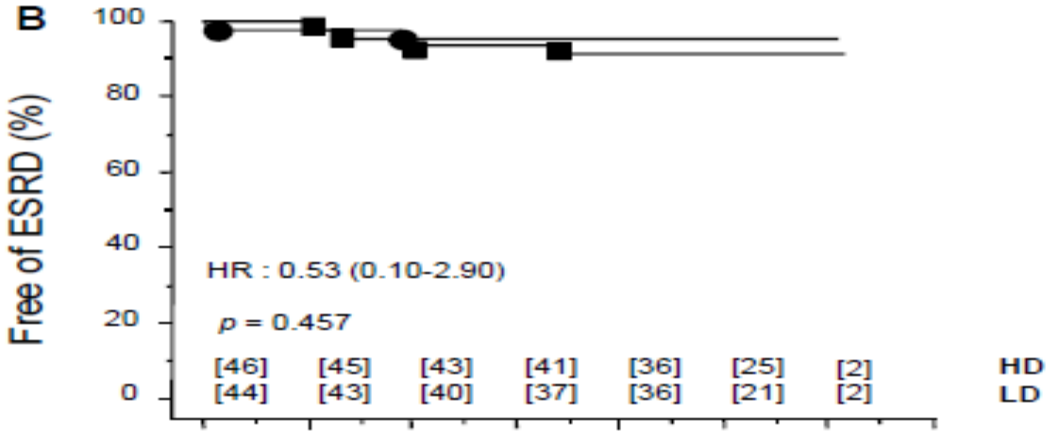
Renal remission

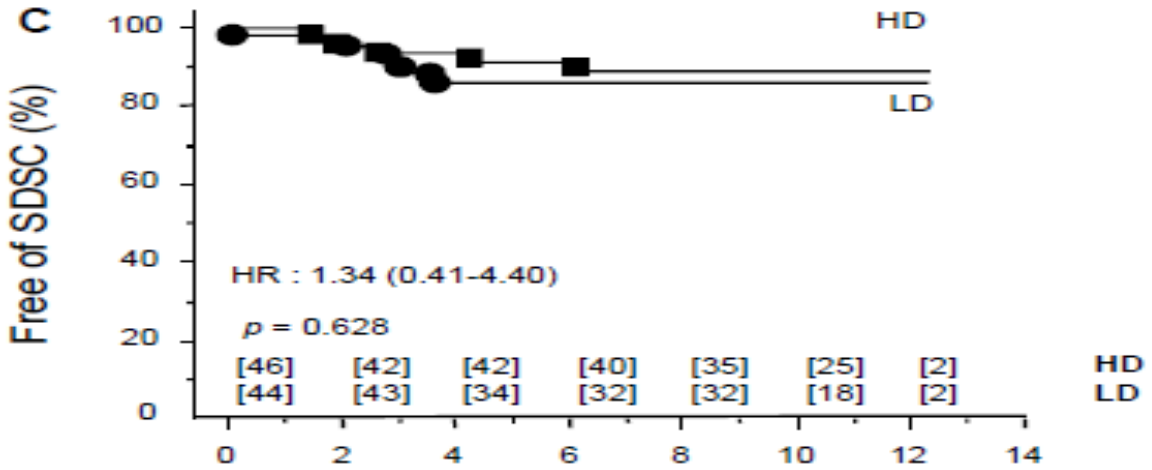
The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose versus high-dose intravenous cyclophosphamide

Frédéric A Houssiau, Carlos Vasconcelos, David D'Cruz, Gian Domenico Sebastiani, Enrique de Ramon Garrido, Maria Giovanna Danieli, Daniel Abramovicz, Daniel Blockmans, Alberto Cauli, Haner Direskeneli, Mauro Galeazzi, Ahmet Gül, Yair Levy, Peter Petera, Rajko Popovic, Radmila Petrovic, Renato A Sinico, Roberto Cattaneo, Josep Font, Geneviève Depresseux, Jean-Pierre Cosyns and Ricard Cervera

Ann Rheum Dis published online 20 Jan 2009;
doi:10.1136/ard.2008.102533





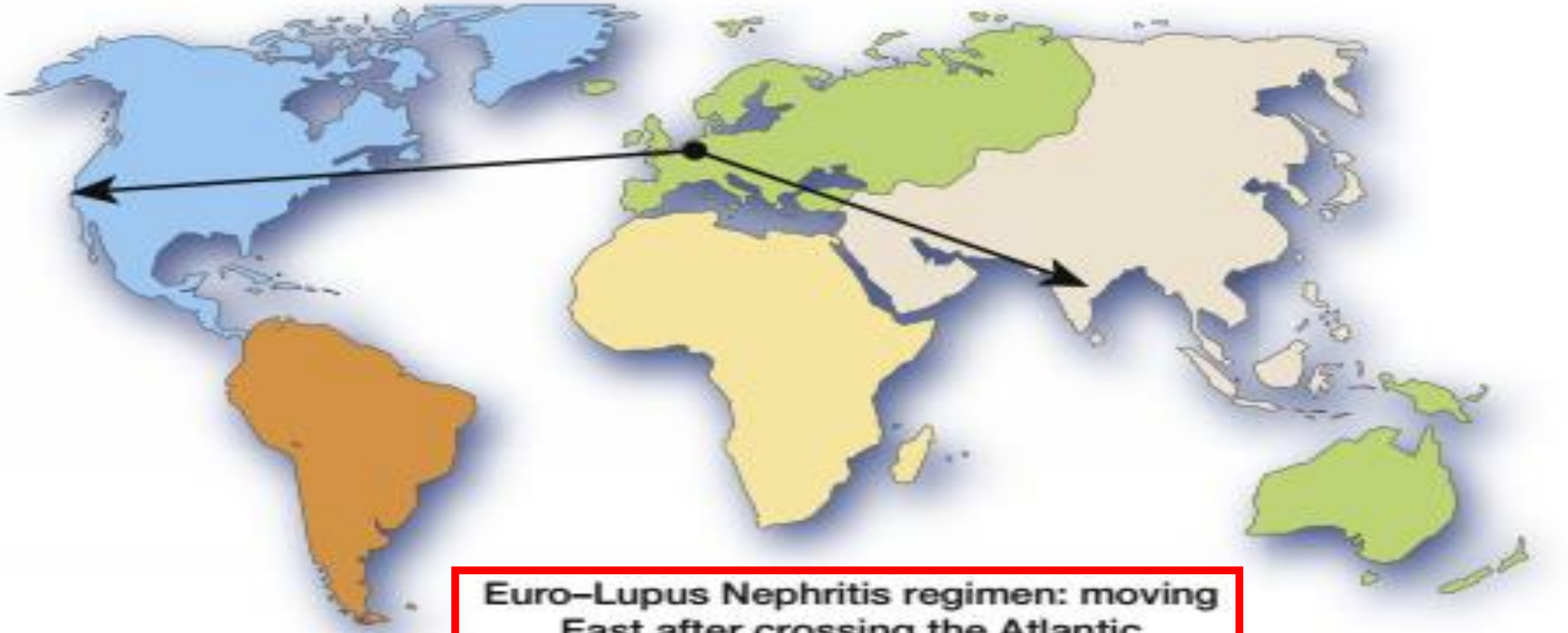


	LD	HD
Death	11%	4%
DSC	14%	11%
ESKD	5%	9%
Severe infection	11%	22%

Moving East: the Euro–Lupus Nephritis regimen in Asia

Frédéric A. Houssiau[1]

Kidney International (2016) **89,** 25–27



Euro–Lupus Nephritis regimen: moving East after crossing the Atlantic

Mycophenolate Mofetil *versus* Cyclophosphamide for Induction Treatment of Lupus Nephritis

J Am Soc Nephrol 20: 1103–1112, 2009.

Gerald B. Appel,* Gabriel Contreras,† Mary Anne Dooley,‡ Ellen M. Ginzler,§ David Isenberg,‖ David Jayne,¶ Lei-Shi Li,** Eduardo Mysler,†† Jorge Sánchez-Guerrero,‡‡ Neil Solomons,§§ David Wofsy,‖‖ and the Aspreva Lupus Management Study Group

In the ALMS study (358 pts with LN)

MMF better than CPH only in „other“ (mostly black) pts

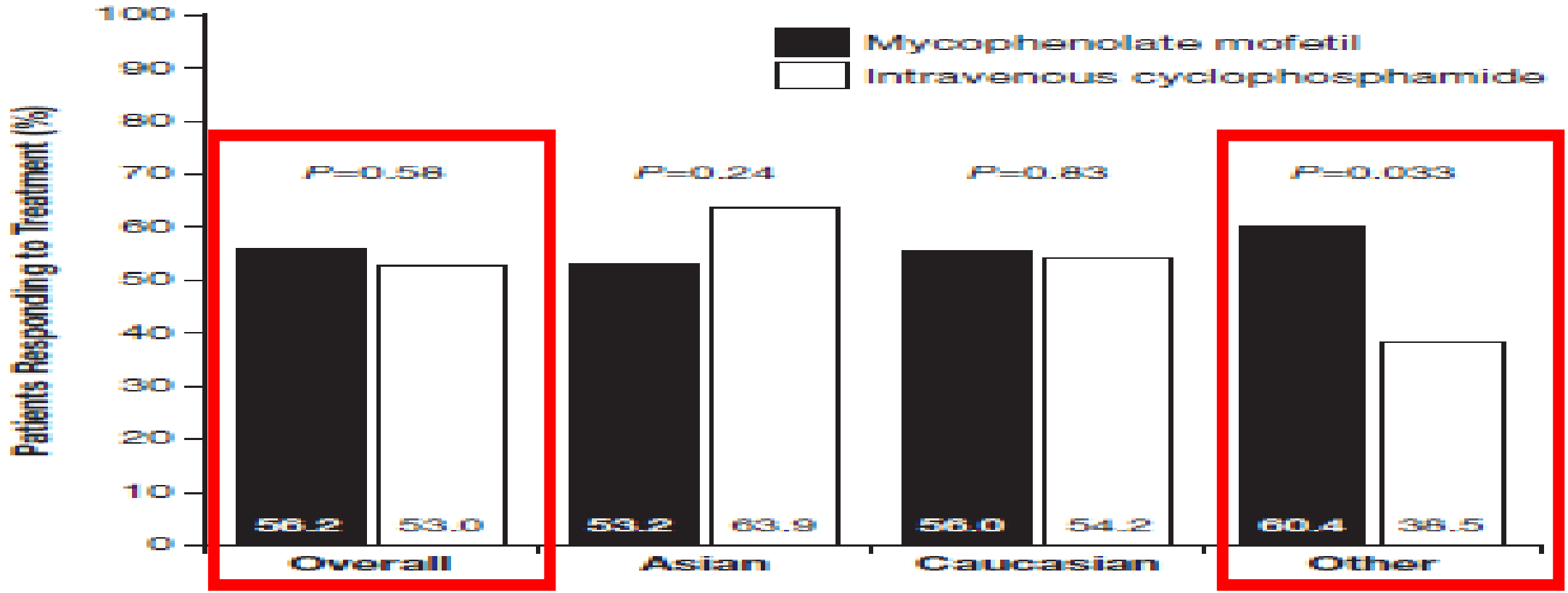


Figure 2. Response rates of study population and by racial group.

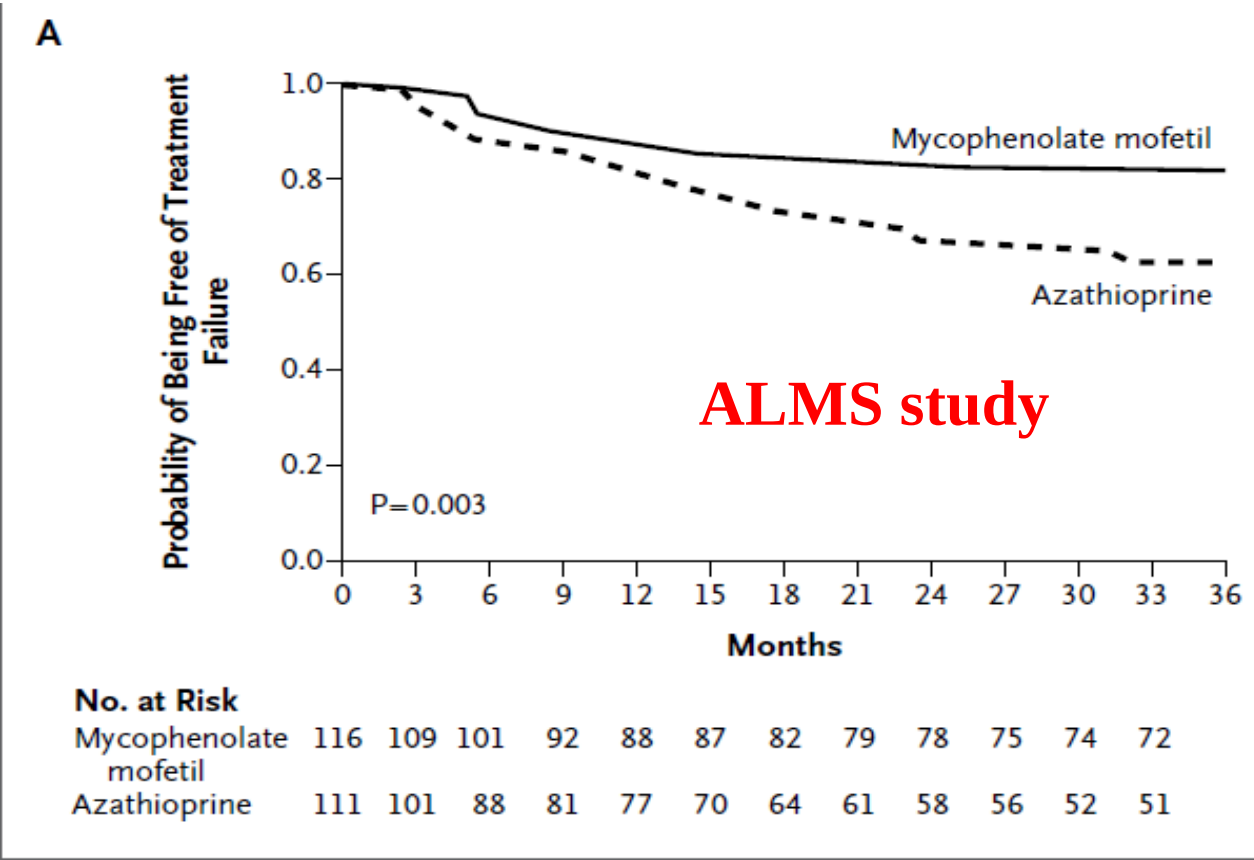
Mycophenolate versus Azathioprine as Maintenance Therapy for Lupus Nephritis

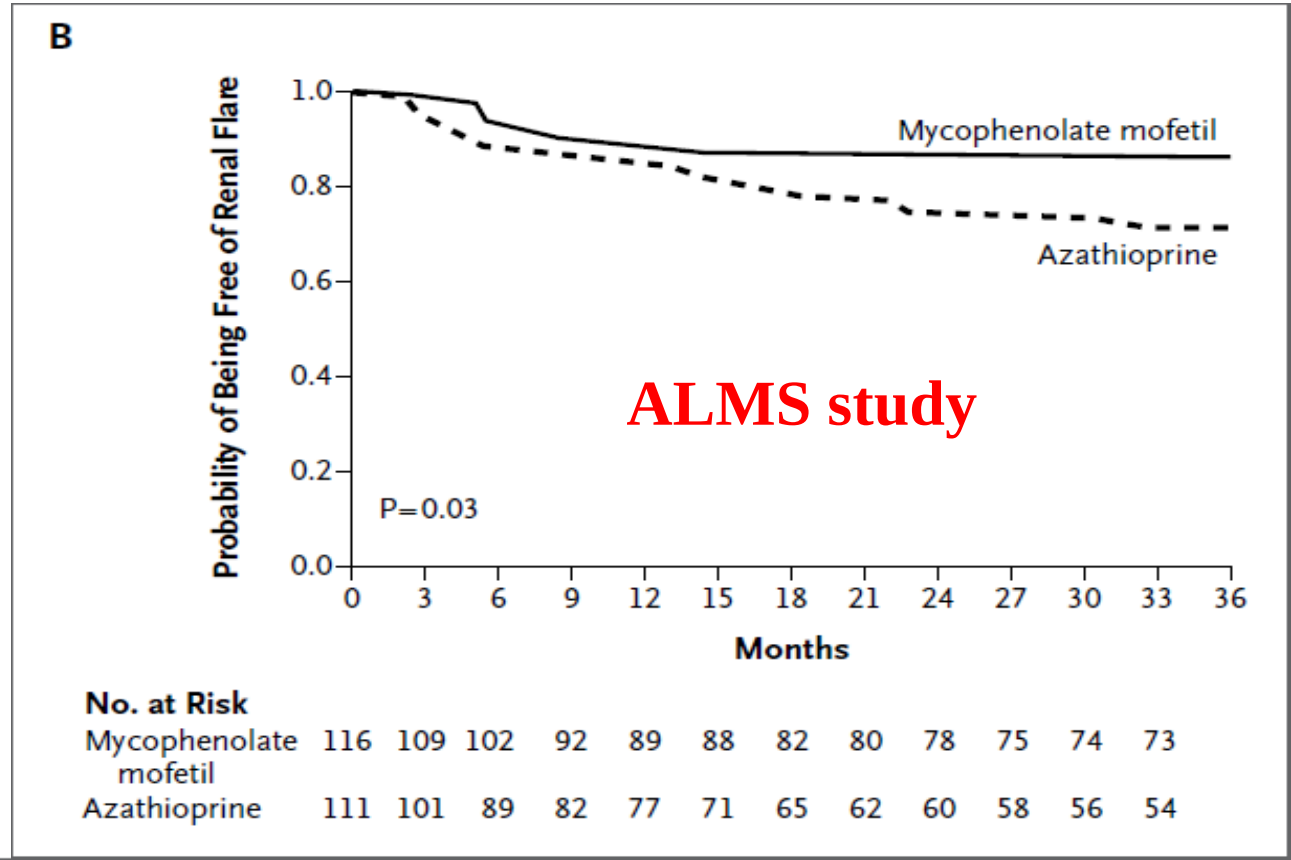
Mary Anne Dooley, M.D., M.P.H., David Jayne, M.D., Ellen M. Ginzler, M.D., M.P.H., David Isenberg, M.D., Nancy J. Olsen, M.D., David Wofsy, M.D., Frank Eitner, M.D., Gerald B. Appel, M.D., Gabriel Contreras, M.D., M.P.H., Laura Lisk, B.Sc., and Neil Solomons, M.D., for the ALMS Group*

N Engl J Med 2011;365:1886-95.

In 227 pts in ALMS study compared maintenance treatment with MMF and AZA (2mg/kg)

MMF - lower risk of treatment failure and lower risk of relapses





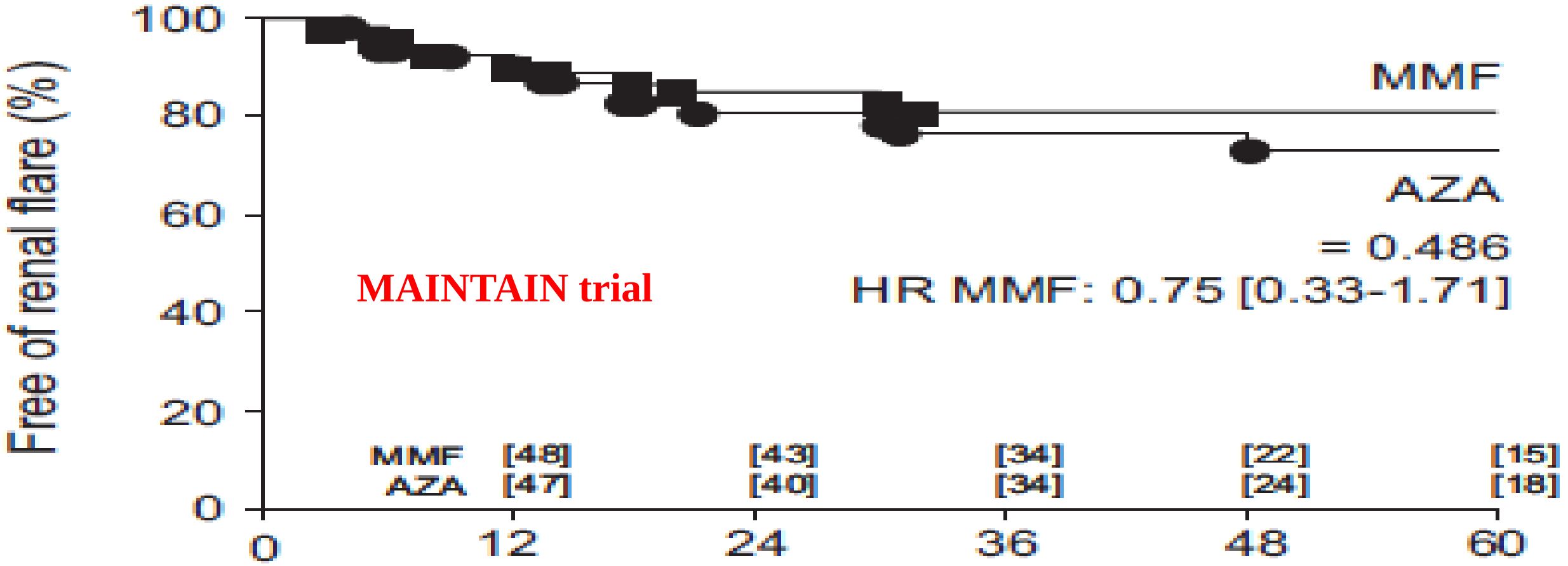
Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial

Ann Rheum Dis 2010 69: 2083-2089

Frédéric A Houssiau, David D'Cruz, Shirish Sangle, et al.

In 105 mostly Caucasian pts with LN III-IV treated with Euro-lupus-like induction MMF compared with AZA

No difference in relapse rate and time to relapse



Mycophenolate Mofetil *versus* Cyclophosphamide for Induction Treatment of Lupus Nephritis

J Am Soc Nephrol 20: 1103–1112, 2009.

Gerald B. Appel,* Gabriel Contreras,† Mary Anne Dooley,‡ Ellen M. Ginzler,§ David Isenberg,‖ David Jayne,¶ Lei-Shi Li,** Eduardo Mysler,†† Jorge Sánchez-Guerrero,‡‡ Neil Solomons,§§ David Wofsy,‖‖ and the Aspreva Lupus Management Study Group

No difference in mortality and all AE, different drug specific AE

Table 4. Incidences of adverse events reported by >10% of patients[a]

Parameter	Patients Who Experienced at Least One AE	
	MMF (*n* = 184)	IVC (*n* = 180)
Deaths	9 (4.9)	5 (2.8)
Withdrawals as a result of AEs	24 (13.0)	13 (7.2)
All AEs	177 (96.2)	171 (95.0)
diarrhea	52 (28.3)	23 (12.8)
headache	38 (20.7)	47 (26.1)
peripheral edema	35 (19.0)	30 (16.7)
arthralgia	29 (15.8)	43 (23.9)
nausea	27 (14.7)	82 (45.6)
hypertension	26 (14.1)	25 (13.9)
nasopharyngitis	25 (13.6)	29 (16.1)
vomiting	25 (13.6)	68 (37.8)
cough	24 (13.0)	16 (8.9)
anemia	23 (12.5)	12 (6.7)
alopecia	20 (10.9)	64 (35.6)
abdominal pain	19 (10.3)	13 (7.2)
back pain	19 (10.3)	16 (8.9)
muscle spasms	19 (10.3)	17 (9.4)
rash	19 (10.3)	21 (11.7)
urinary tract infection	19 (10.3)	17 (9.4)

The effects of cyclophosphamide and mycophenolate on end-stage renal disease and death of lupus nephritis

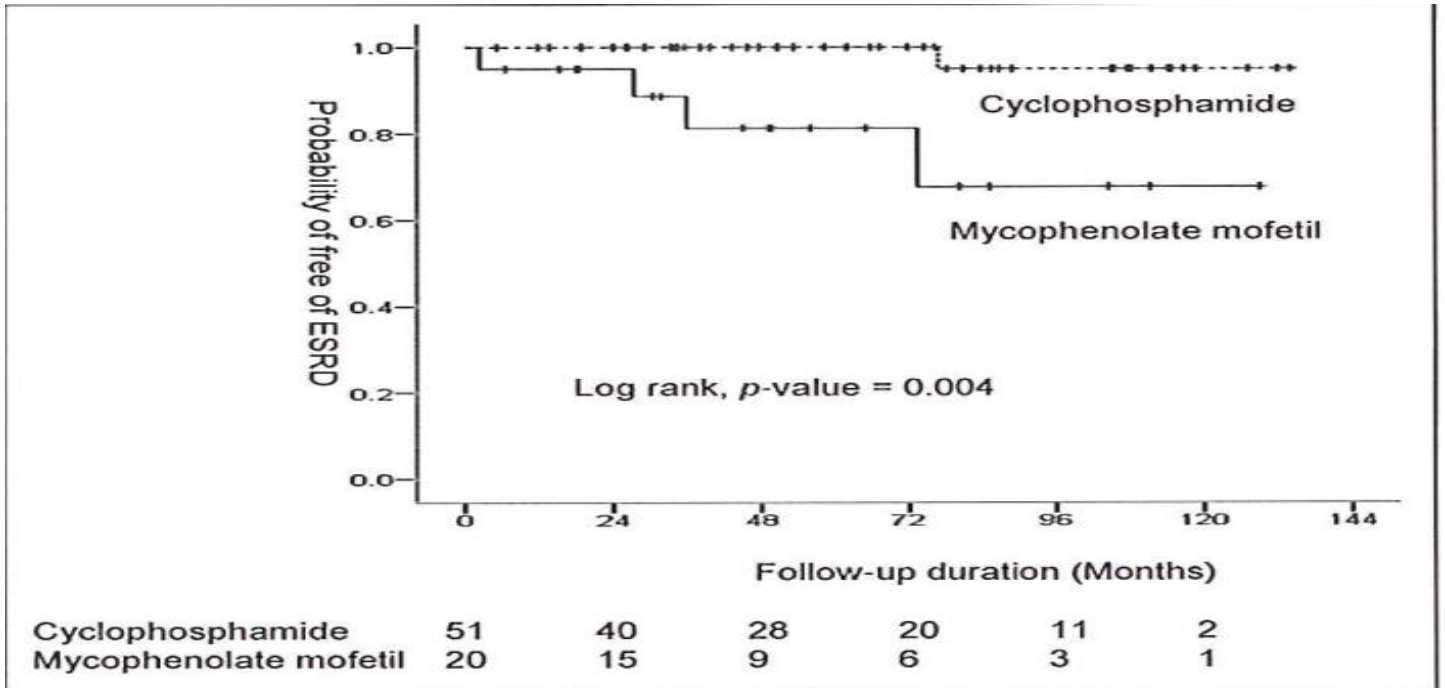
Lupus (2011) 20, 1442–1449

HS Koo[1], YC Kim[2], SW Lee[2], DK Kim[2], K-H Oh[2], KW Joo[2], YS Kim[2], C Ahn[2], JS Han[2], S Kim[2,3] and HJ Chin[4]

Despite the same short-term response to MMF and CPH, higher risk of ESRD in MMF treated pts

Table 3 Assessment of renal response between the two groups

	MMF (n = 19)	*CYC (n = 49)*	p-*value*
Complete Remission	9 (47.4%)	19 (38.7%)	0.374
Partial remission	1 (5.3%)	9 (18.4%)	
No response	9 (47.4%)	21 (42.9%)	



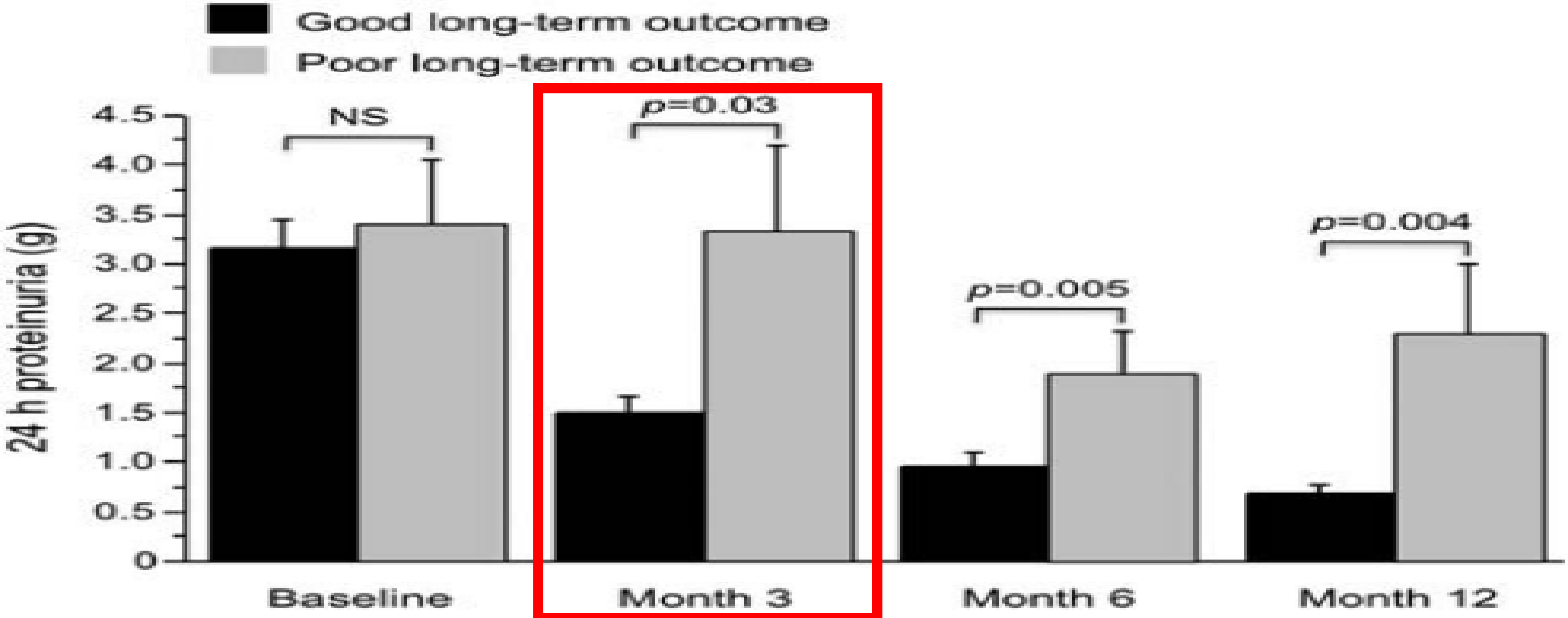
Long-term follow-up of the *MAINTAIN* Nephritis Trial, comparing azathioprine and mycophenolate mofetil as maintenance therapy of lupus nephritis

Farah Tamirou,[1] David D'Cruz,[2] Shirish Sangle,[2] Philippe Remy,[3] Carlos Vasconcelos,[4] Christoph Fiehn,[5] Maria del Mar Ayala Guttierez,[6] Inge-Magrethe Gilboe,[7] Maria Tektonidou,[8] Daniel Blockmans,[9] Isabelle Ravelingien,[10] Véronique le Guern,[11] Geneviève Depresseux,[1] Loïc Guillevin,[11] Ricard Cervera,[12] Frédéric A Houssiau,[1] and the *MAINTAIN* Nephritis Trial Group

Ann Rheum Dis 2016;**75**:526–531

10-yr FU of 87 pts from MAINTAIN study

Predictive role of early decrease of proteinuria



A proteinuria cut-off level of 0.7 g/day after 12 months of treatment best predicts long-term renal outcome in lupus nephritis: data from the *MAINTAIN Nephritis Trial*

Lupus Science & Medicine 2015;**2**:e000123.

Farah Tamirou,[1] Bernard R Lauwerys,[1] Maria Dall'Era,[2] Meggan Mackay,[3] Brad Rovin,[4] Ricard Cervera,[5] Frédéric A Houssiau,[1] on behalf of the *MAINTAIN Nephritis Trial* investigators

Proteinuria 0.7 g/day at 12 mo and longterm outcome of LN

Table 1 Sensitivity, specificity, PPV and NPV for good long-term renal outcome according to target definition

Target at 12 months	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Proteinuria <0.7 g/day	71 (48/68)	75 (9/12)	94 (48/51)	31 (9/29)
Proteinuria <0.7 g/day and sCr ≤1 mg/dL	63 (43/68)	83 (10/12)	96 (43/45)	29 (10/31)
Proteinuria <0.7 g/day and sCr ≤1 mg/dL and RBC ≤5/hpf	41 (28/68)	67 (8/12)	97 (28/29)	21 (8/38)

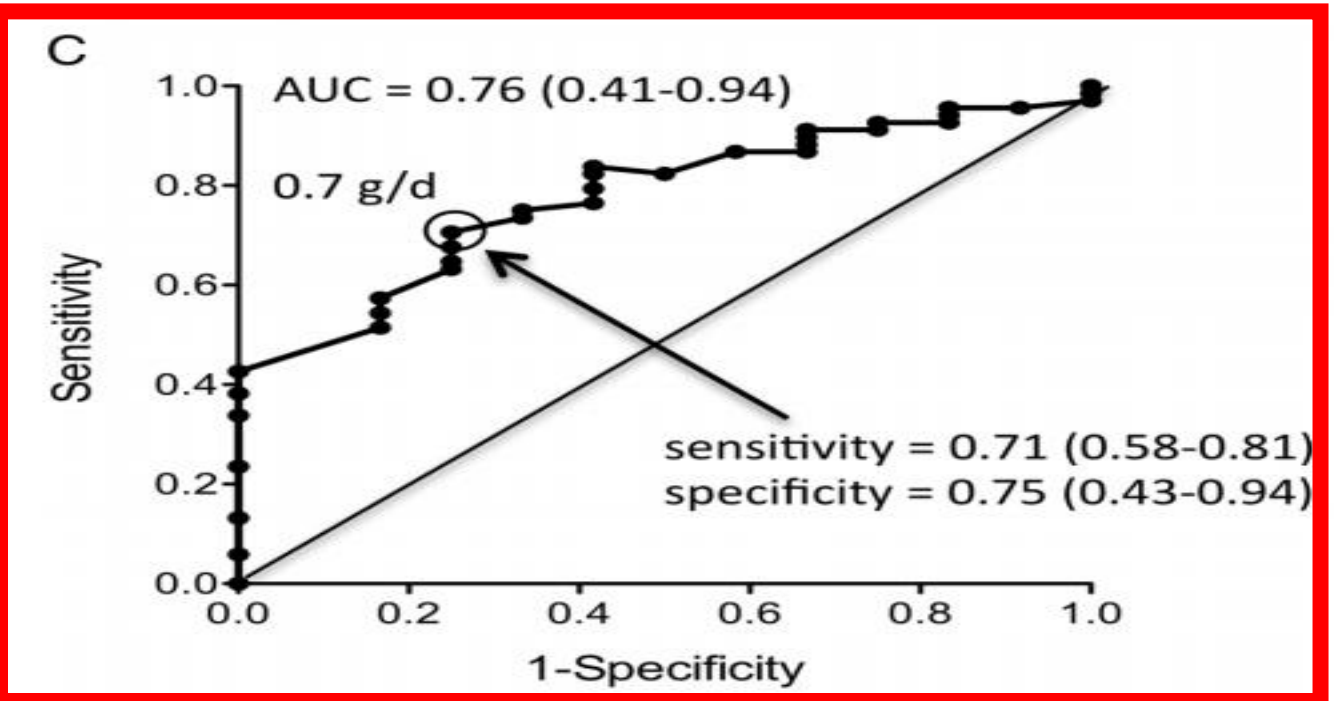


Table 2 NPV of a proteinuria <0.7 g/day at 12 months according to baseline proteinuria

Baseline proteinuria (g/day)	NPV (%)
According to mean	
<3.3 (n=48)	44 (7/16)
≥3.3 (n=32)	15 (2/13)
According to median	
<2.4 (n=37)	46 (6/13)
≥2.4 (n=43)	11 (3/16)

Treatment of proliferative lupus nephritis: a slowly changing landscape

Tesar, V. & Hruskova, Z. *Nat. Rev. Nephrol.* 7, 96–109 (2011);

Vladimir Tesar and Zdenka Hruskova

Box 1 | Clinical course and outcomes of proliferative lupus nephritis

- Patient survival and renal survival in proliferative lupus nephritis have improved, but a significant proportion of patients still progress to end-stage renal disease
- Race, ethnicity and presenting renal histology are the most important predictors of patient and renal outcome
- Definitions of responses to treatment differ substantially between individual studies as until recently no uniform definition existed
- Remission rates are lower in black and Hispanic patients than in white patients
- Median time to remission is usually long (10–15 months)
- Disease activity is not suppressed quickly enough by the available induction treatment, and most patients go into remission only while on maintenance treatment
- The relapse rate is still high, and nephritic relapses have a negative impact on renal outcome
- Although current maintenance treatments have decreased the relapse rate, they do not completely prevent relapse

Calcineurin inhibitors in the treatment of lupus nephritis

Cyclosporine

Combination of tacrolimus and MMF

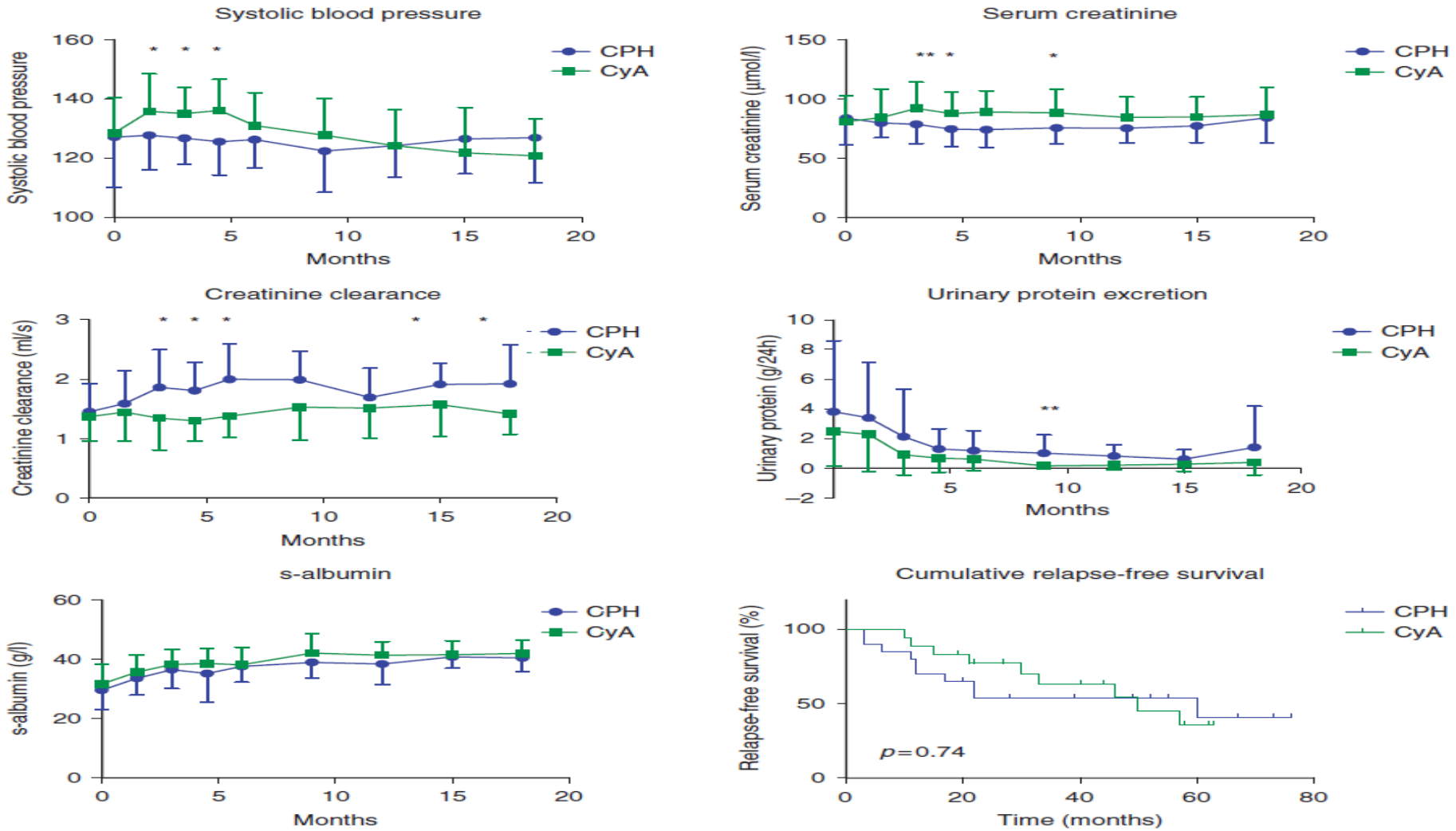
Voclosporin

Cyclosporine A or intravenous cyclophosphamide for lupus nephritis: the Cyclofa-Lune study

Lupus (2010)

J Závada[1,*], SS Pešičková[2,*], R Ryšavá[2], M Olejárova[1], P Horák[3], Z Hrnčíř[4], I Rychlík[5], M Havrda[5], J Vítová[6], J Lukáč[7], J Rovenský[7], D Tegzova[1], J Böhmova[8], J Zadražil[3], J Hána[6], C Dostál[1] and V Tesar[2]

In 40 Caucasian pts with LN III-IV cyclosporine similarly effective compared to iv CPH pulses



Extended follow-up of the CYCLOFA-LUNE trial comparing two sequential induction and maintenance treatment regimens for proliferative lupus nephritis based either on cyclophosphamide or on cyclosporine A

Lupus (2013)

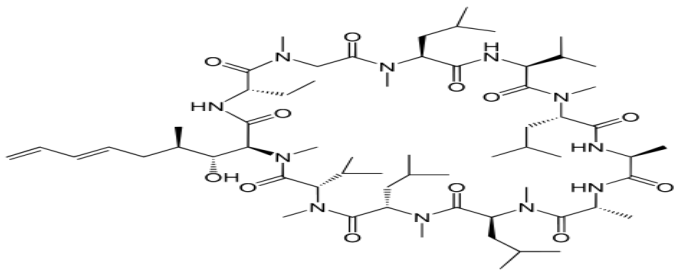
J Závada[1,2], S Sinikka Pešičková[2], R Ryšavá[2], P Horák[3], Z Hrnčíř[4], J Lukáč[5], J Rovenský[5], J Vítová[6], M Havrda[7], I Rychlík[7], J Böhmova[8], V Vlasáková[9], J Slatinská[10], J Zadražil[3], M Olejárová[1], D Tegzova[1] and V Tesar[2]

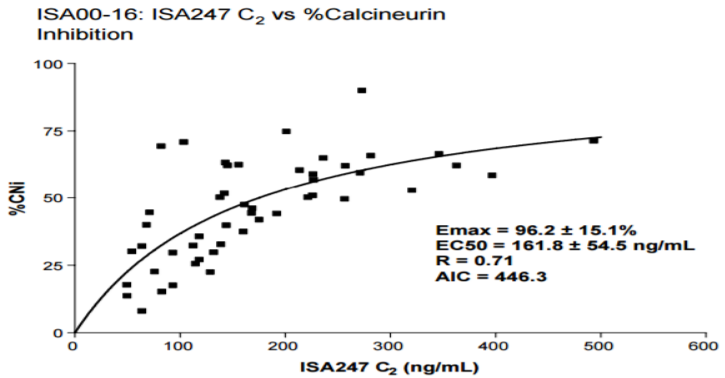
Extended FU (7.7 years) available in 38 pts, without significant difference between both limbs

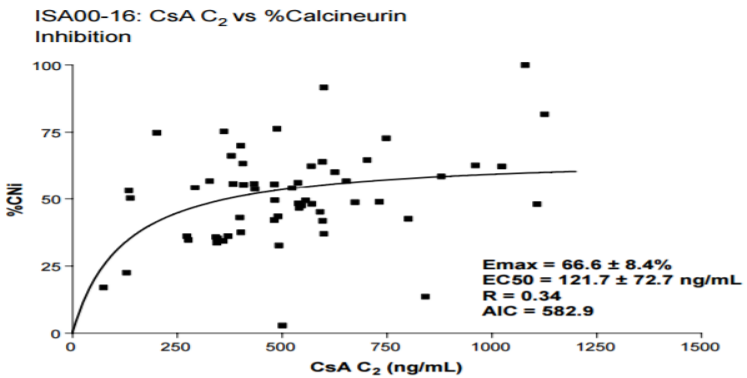
Table 1 Long-term renal outcomes in patients enrolled in the CYCLOFA-LUNE trial with available extended follow-up data

	All (n=38)	*CPH (n=19)*	*CyA (n=19)*
Age, years, mean (SD)	39 (10)	37 (5)	38 (8)
Female, *n*	27 (71)	13 (68)	14 (74)
Follow-up, years, median (range)	7.7 (5.0–10.3)	7.4 (5.0–9.7)	8.3 (5.3–10.3)
50% increase in creatinine concentration	5 (13)	3 (16)	2 (11)
Non-sustained doubling of the creatinine concentration	2 (5)	1 (5)	1 (5)
Sustained doubling of serum creatinine	2 (5)	1 (5)	1 (5)
End-stage renal disease	2 (5)	1 (5)	1 (5)
Current serum creatinine, μmol/l	67 (19)	71 (23)	63 (15)
Current 24 h proteinuria, g	0.4 (0.6)	0.5 (0.5)	0.4 (0.7)

Multitarget therapy more effective compared to iv CPH, complete remission at 24 weeks (45.9 vs. 25.6%, p < 0.001)





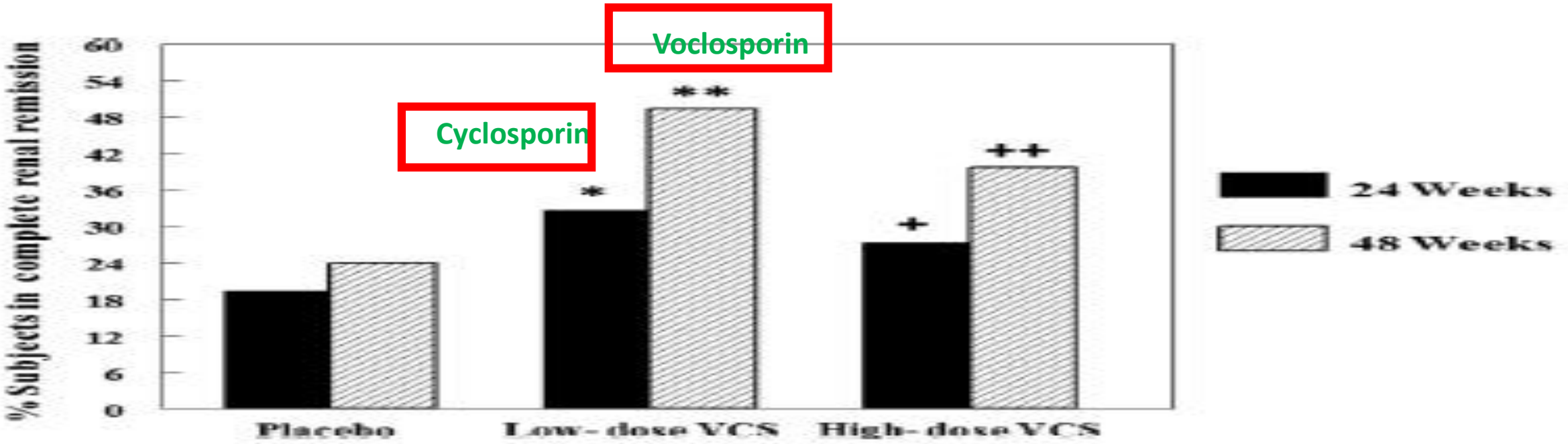


A randomized, controlled double-blind study comparing the efficacy and safety of dose-ranging voclosporin with placebo in achieving remission in patients with active lupus nephritis

Voclosporin – a new CNI with more predictable relation between its plasma levels and calcineurin inhibition

Brad H. Rovin[1], Neil Solomons[2], William F. Pendergraft III[3], Mary Anne Dooley[3], James Tumlin[4], Juanita Romero-Diaz[5], Lidia Lysenko[6], Sandra V. Navarra[7] and Robert B. Huizinga[2]; for the AURA-LV Study Group[8]

Kidney International (2019) **95,** 219–231;



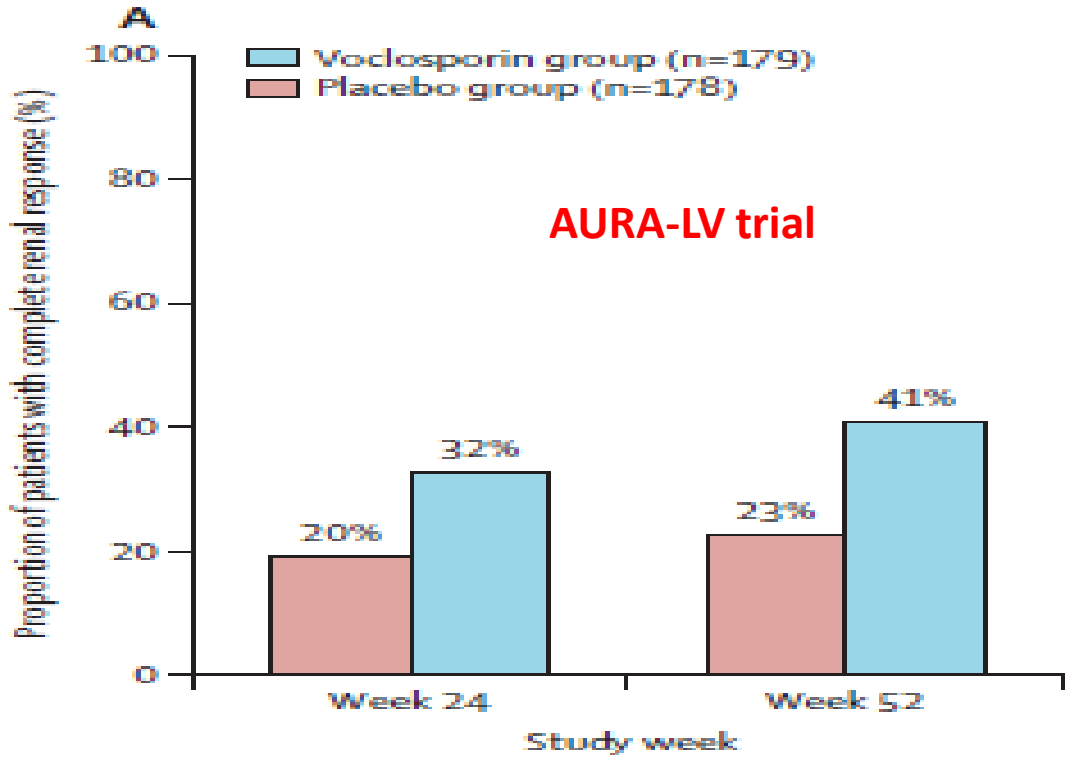
Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial

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

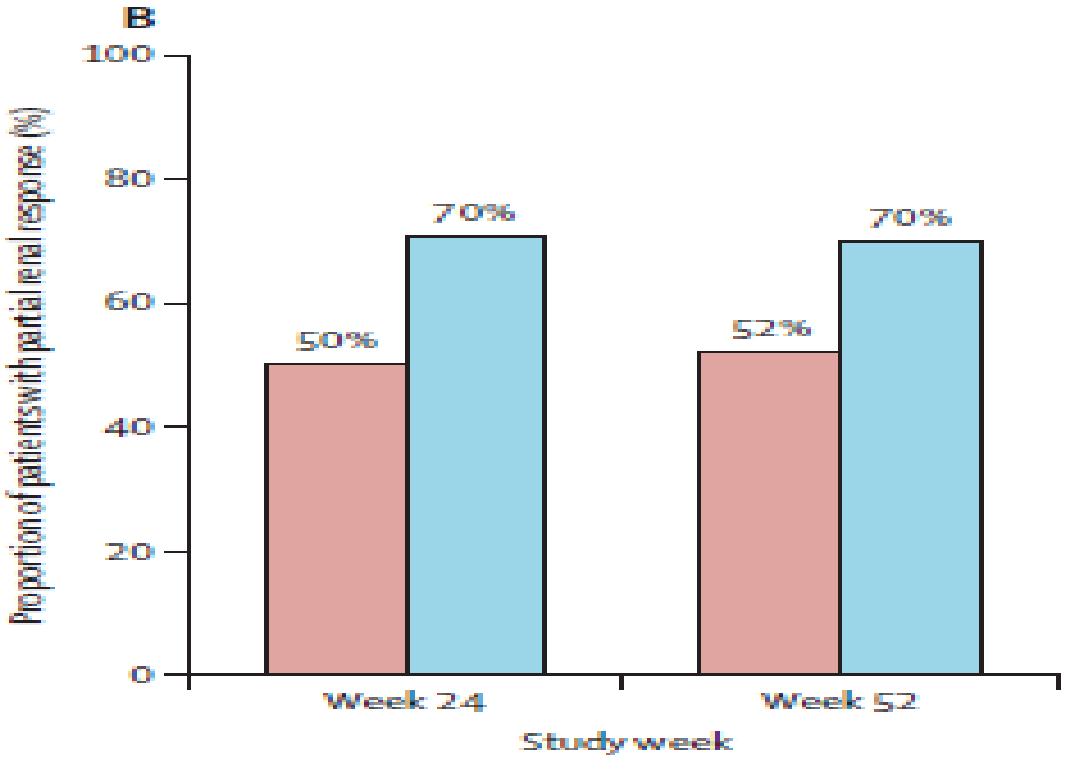
www.thelancet.com Published online May 7, 2021

265 pts randomized to either to 23.7 mg or 39.5 mg of voclosporin twice daily, or placebo as an add-on to the standard care with MMF and CS (forced taper to 5 mg by week 8)

Complete renal remission more common in voclosporin-treated pts



AURA-LV trial

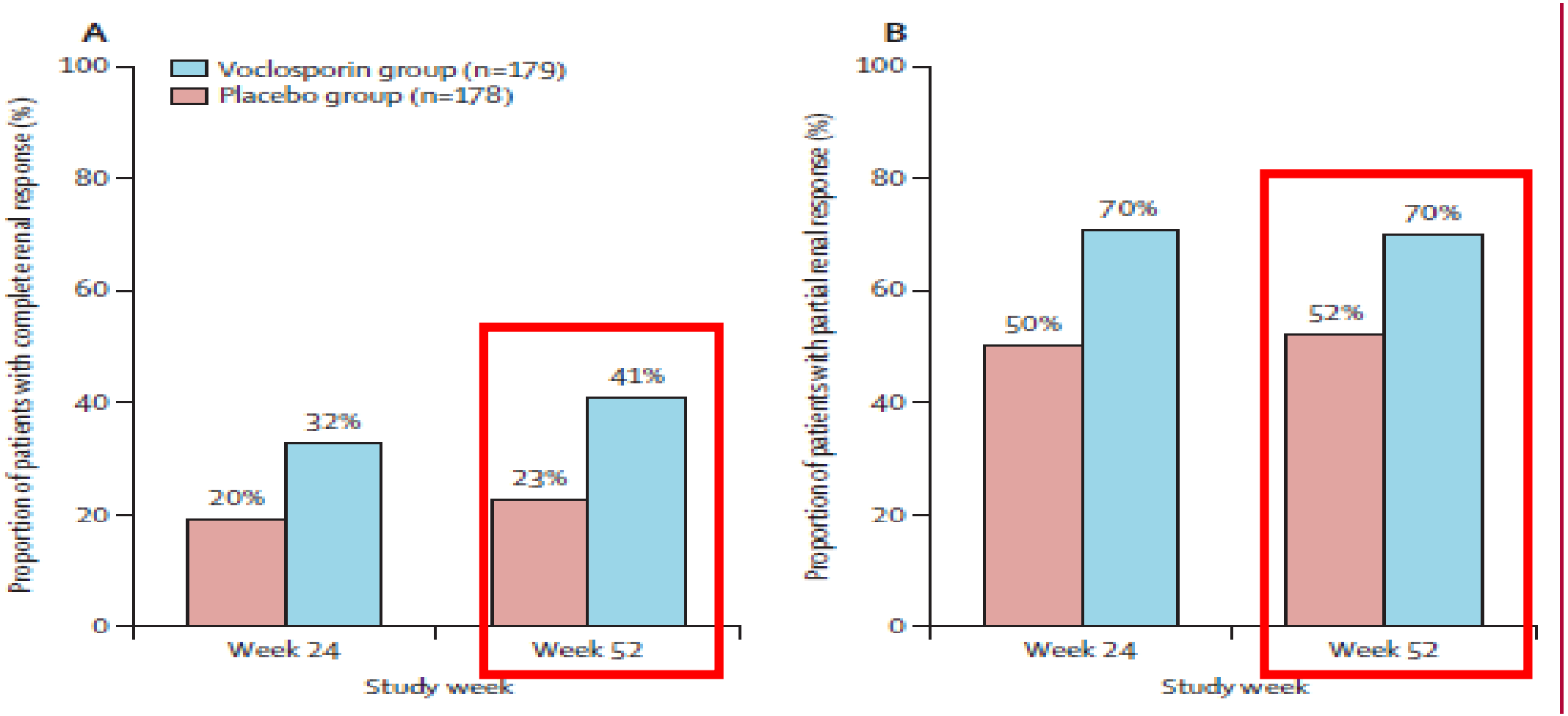


Complete renal remission

Durability of complete renal remission

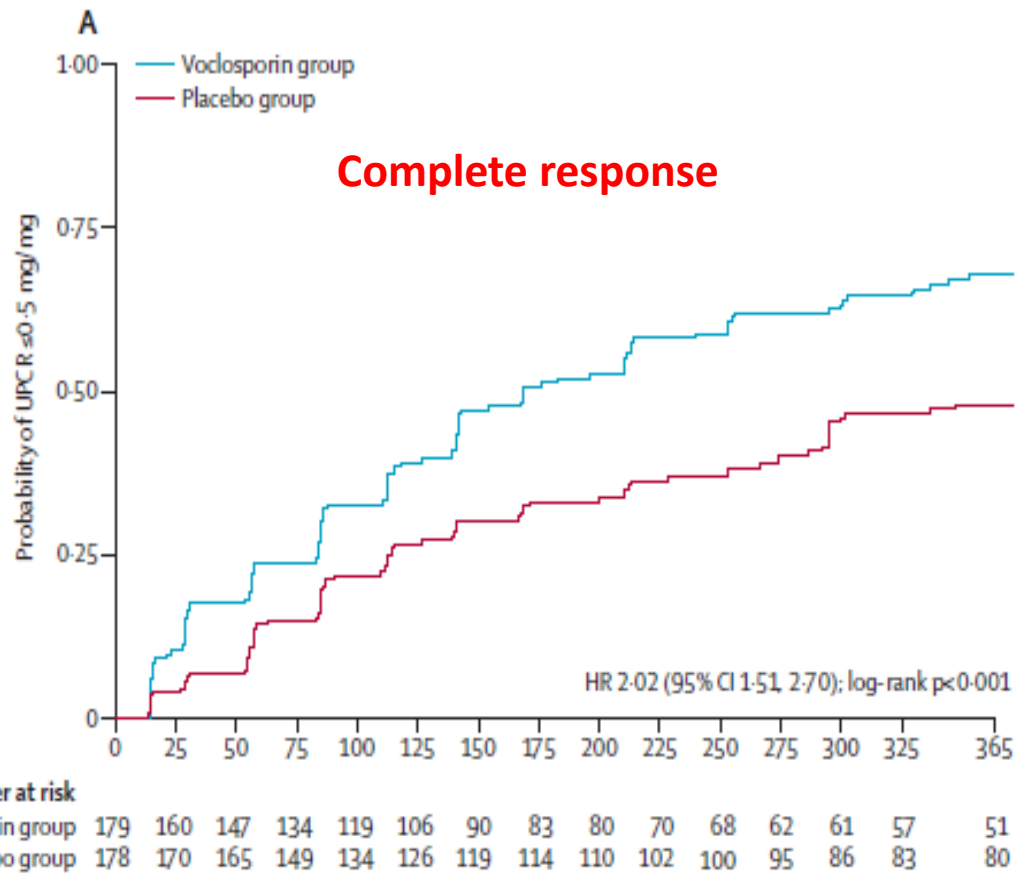
In the phase 3 trial (AURORA 1) 357 pts with LN III-V randomized to either 23.7 mg of voclosporin twice daily, or placebo as an add-on to the standard care with MMF and CS (forced taper to 5 mg by week 8)

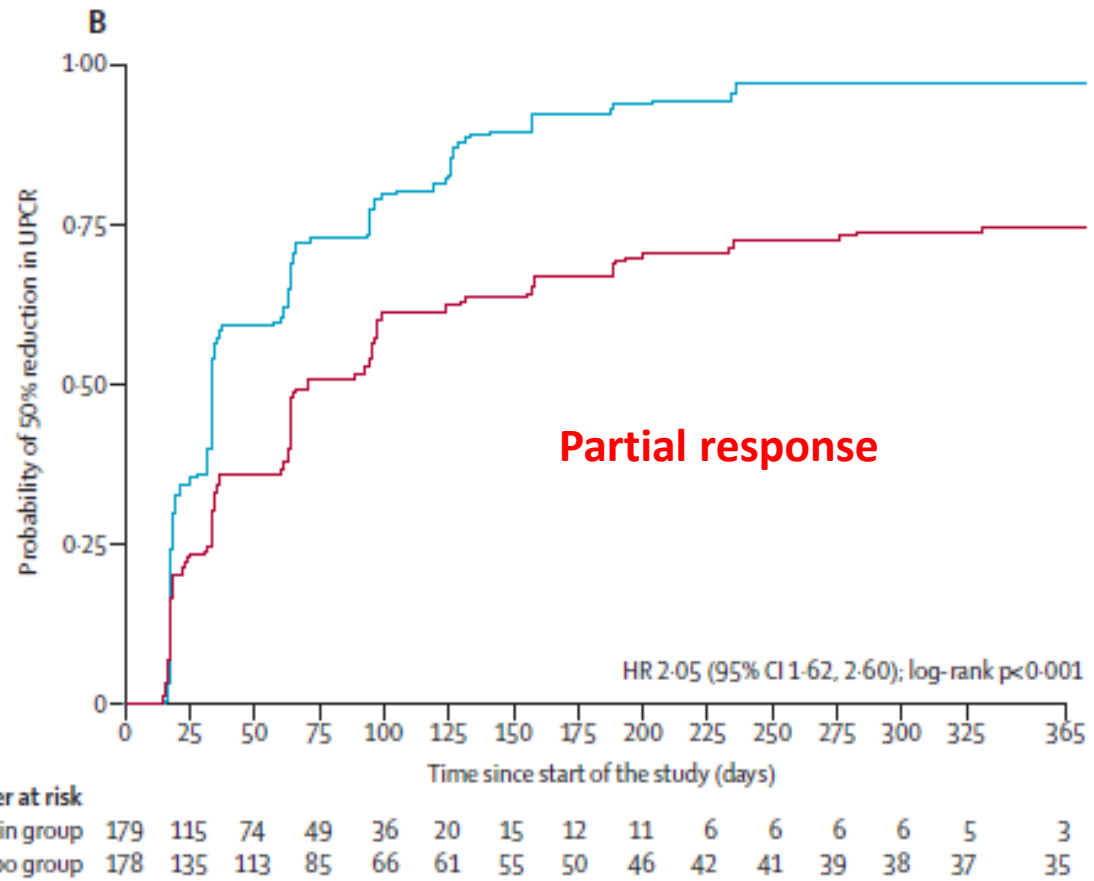
Complete and partial response more common in voclosporin-treated pts



In the phase 3 trial (AURORA 1) 357 pts with LN III-V randomized to either 23.7 mg of voclosporin twice daily, or placebo as an add-on to the standard care with MMF and CS (forced taper to 5 mg by week 8)

Complete and partial response more common in voclosporin-treated pts





Efficacy of Voclosporin in Recent Onset Lupus Nephritis

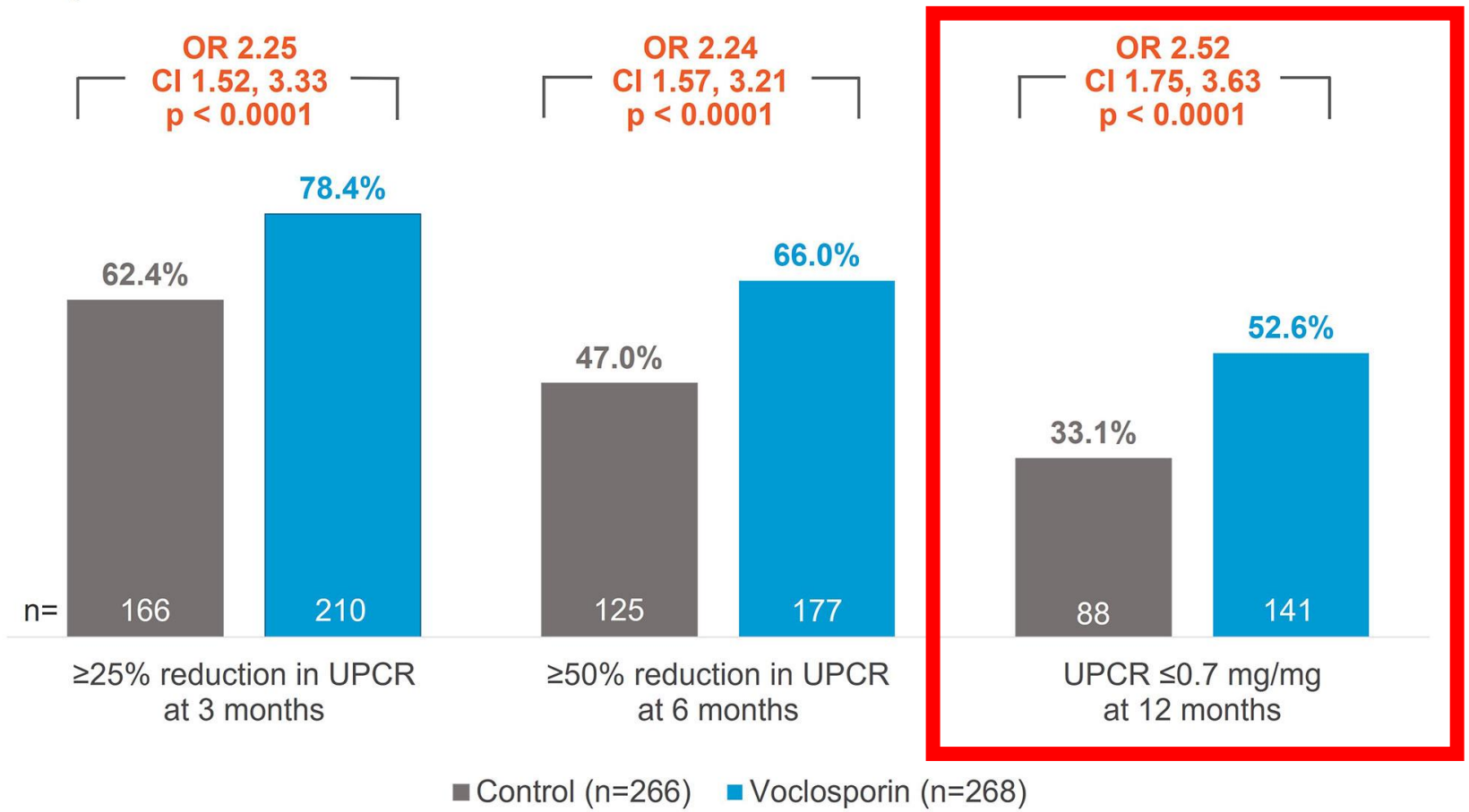
Arthritis Rheumatol. 2022; 74 (suppl 9).

ACR Convergence 2022

Meggan Mackay[1], Matt Truman[2], Nicole England[2], Vanessa Birardi[3]

Recommended treatment targets achieved more frequently in voclosporin-treated patients

Figure 1. Achievement of UPCR Treatment Targets per EULAR/ERA Lupus Nephritis Recommendations



Efficacy of Voclosporin in Recent Onset Lupus Nephritis

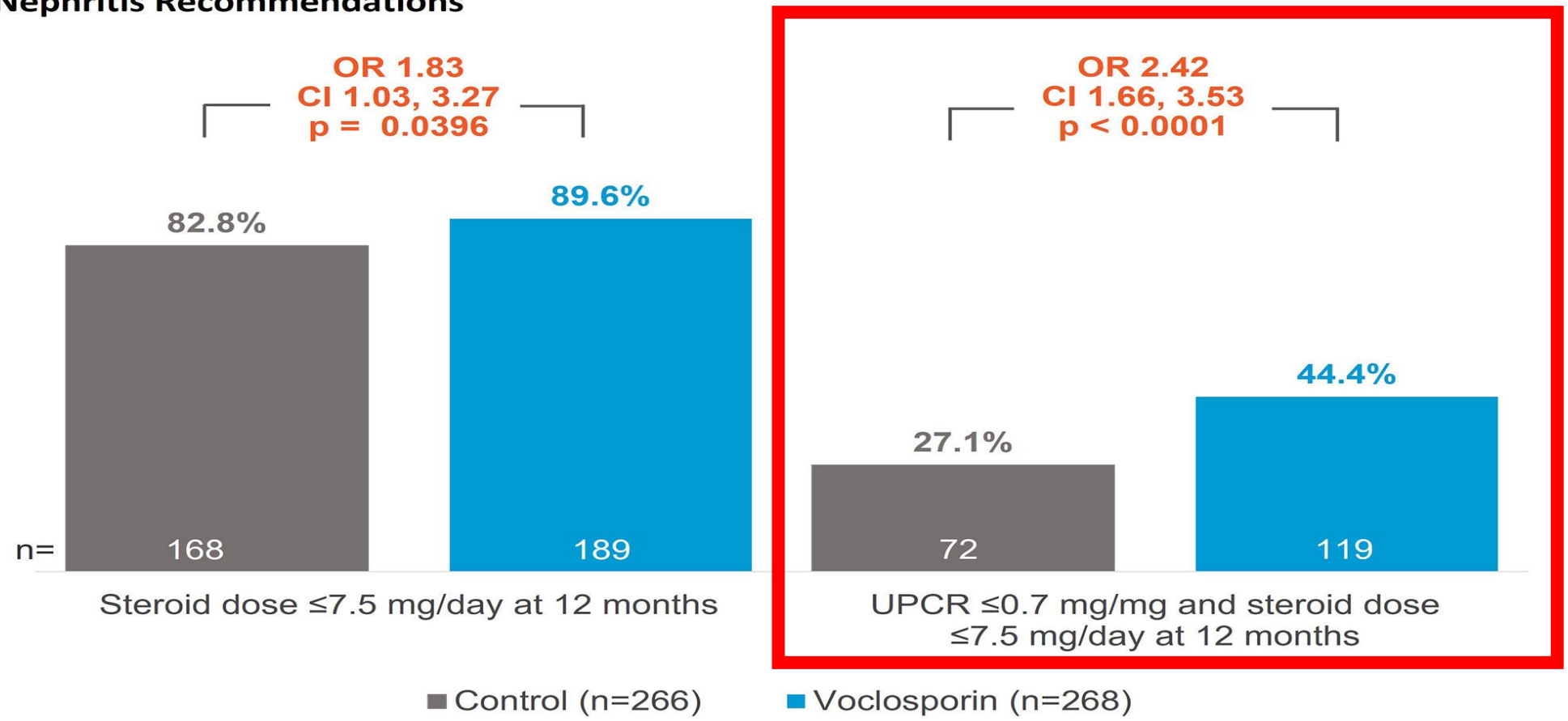
Arthritis Rheumatol. 2022; 74 (suppl 9).

ACR Convergence 2022

Meggan Mackay[1], Matt Truman[2], Nicole England[2], Vanessa Birardi[3]

Reduction of CS more successful in voclosporin-treated patients

Figure 2. Achievement of Steroid Treatment Targets per EULAR/ERA Lupus Nephritis Recommendations



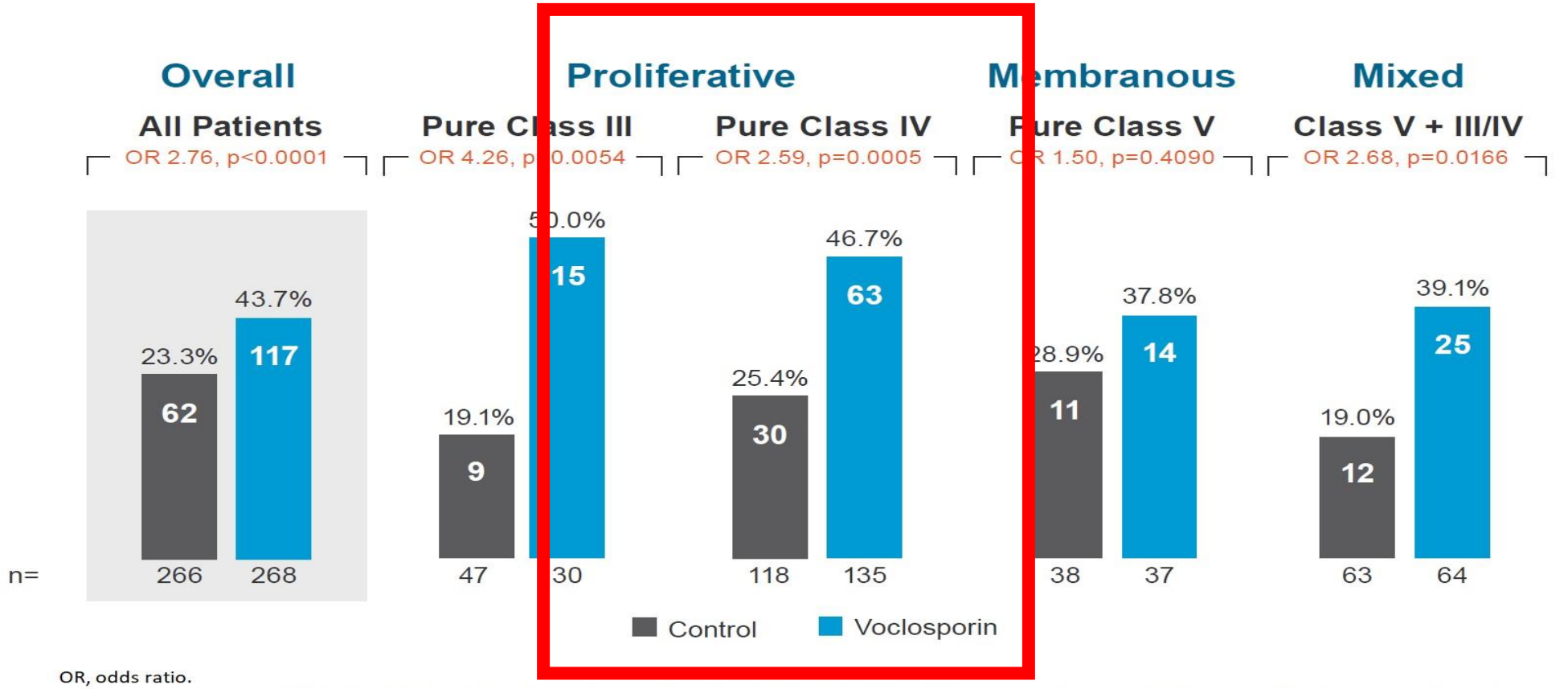
Safety and Efficacy of Long-Term Voclosporin Treatment for Lupus Nephritis in the Phase 3 AURORA 2 Clinical Trial

Arthritis Rheumatol. 2022; 74 (suppl 9).

ACR Convergence 2022

Anit Saxena,[1] Ellen M. Ginzler,[2] Keisha Gibson,[3] Bancha Satirapoj,[4] Adolfina Elizabeth Zuta Santillán,[5] Olena Levchenko,[6] Sandra Navarra,[7] Tatsuya Atsumi,[8] Shinsuke Yasuda,[9] Nilirno Noel Chavez-Perez,[10] Cristina Arriens,[11] Samir V. Parikh,[12] Dawn J. Caster,[13] Vanessa Birardi,[14] Simrat Randhawa,[15] Laura Lisk,[16] Robert B. Huizinga,[17] and Y. K. Onno Teng[18]

Efficacy of voclosporin similar in recent onset and later onset lupus nephritis



OR, odds ratio.

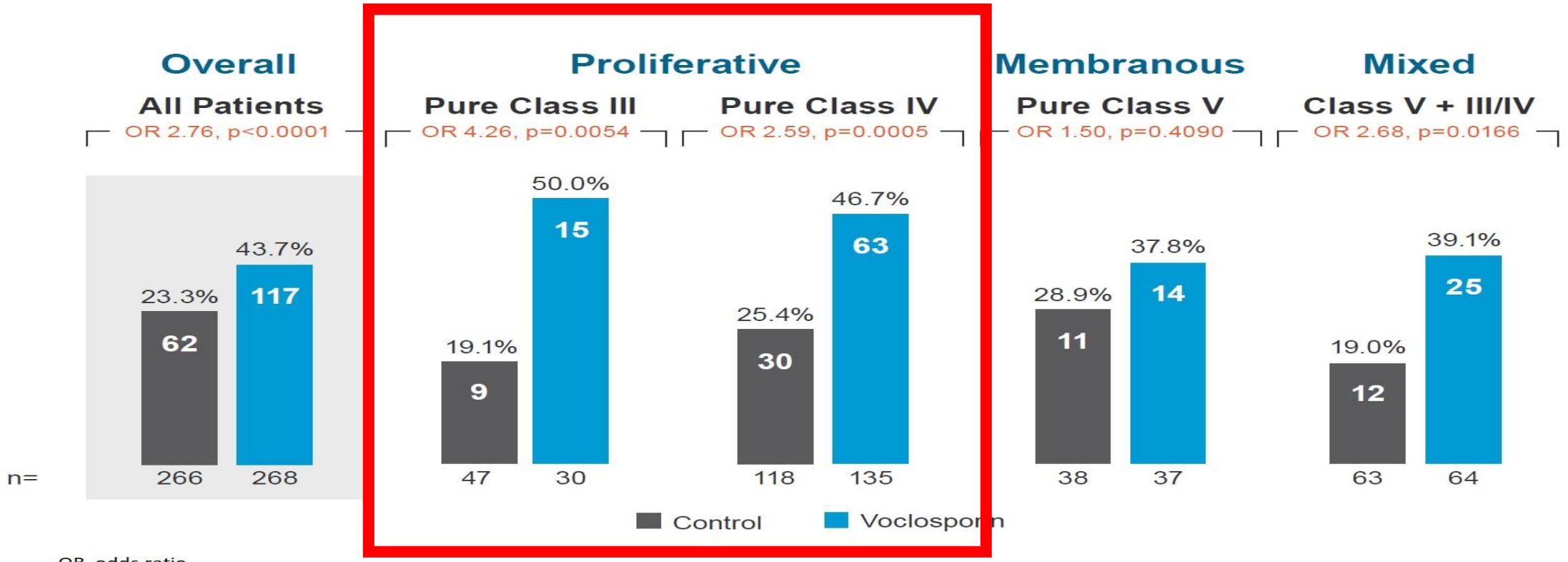
Complete renal response defined as UPCR ≤0.5 mg/mg, stable renal function (eGFR ≥60 mL/min/1.73 m^2 or no decrease >20% from baseline), presence of sustained, low-dose steroids (in the 8 weeks prior to assessment) and no rescue medication. Pooled analysis at approximately one year included Week 48 data from AURA-LV and Week 52 data from AURORA 1.

Arthritis & Rheumatology
Vol. 0, No. 0, Month 2023, pp 1–9
DOI 10.1002/art.42657

Arthritis Rheumatol. 2022; 74 (suppl 9).

ACR Convergence 2022

Longterm renal outcome of voclosporin-treated patients better



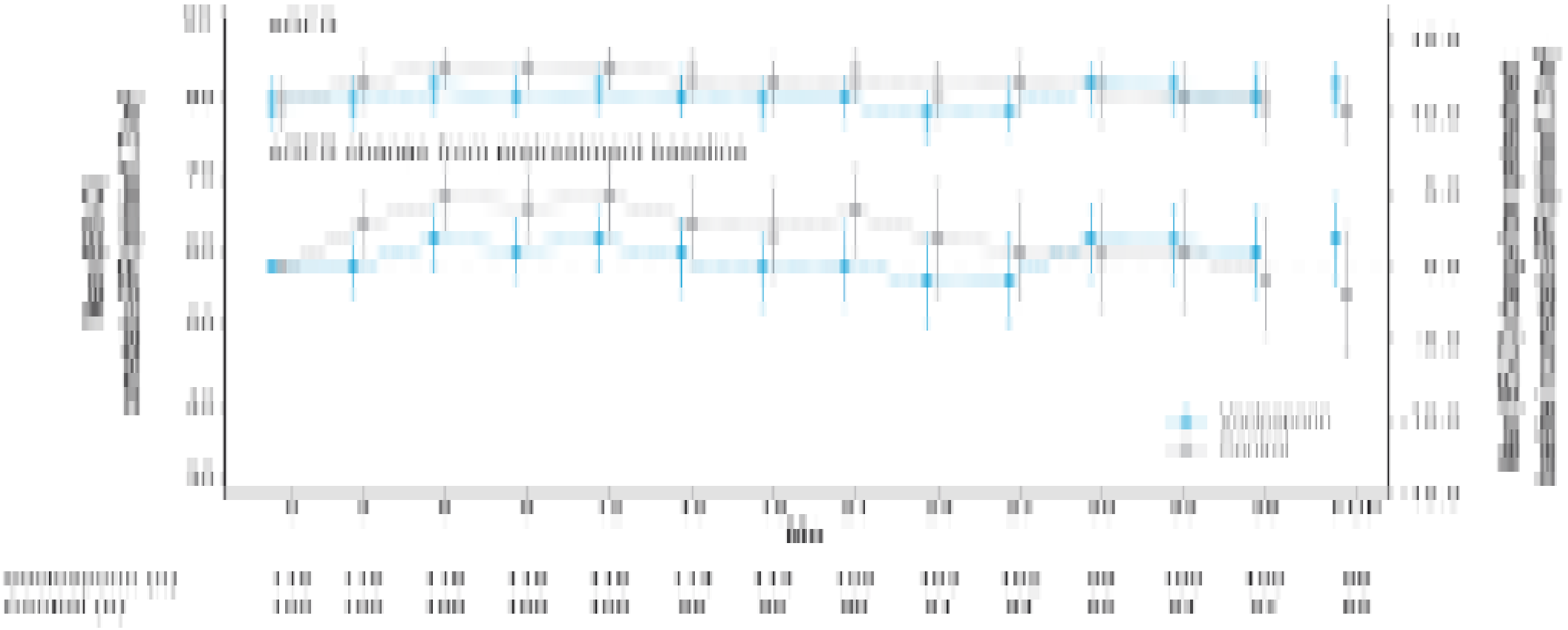
OR, odds ratio.
Complete renal response defined as UPCR ≤0.5 mg/mg, stable renal function (eGFR ≥60 mL/min/1.73 m^2 or no decrease >20% from baseline), presence of sustained, low-dose steroids (in the 8 weeks prior to assessment) and no rescue medication. Pooled analysis at approximately one year included Week 48 data from AURA-LV and Week 52 data from AURORA 1.

Safety and Efficacy of Long-Term Voclosporin Treatment for Lupus Nephritis in the Phase 3 AURORA 2 Clinical Trial

Amit Saxena,[1] Ellen M. Ginzler,[2] Keisha Gibson,[3] Bancha Satirapoj,[4] Adolfina Elizabeth Zuta Santillán,[5] Olena Levchenko,[6] Sandra Navarra,[7] Tatsuya Atsumi,[8] Shinsuke Yasuda,[9] Nilmo Noel Chavez-Perez,[10] Cristina Arriens,[11] Samir V. Parikh,[12] Dawn J. Caster,[13] Vanessa Birardi,[14] Simrat Randhawa,[15] Laura Lisk,[16] Robert B. Huizinga,[17] and Y. K. Onno Teng[18]

Arthritis & Rheumatology
Vol. 0, No. 0, Month 2023, pp 1–9
DOI 10.1002/art.42657

eGFR during the course of AURORA 1 and AURORA 2 study



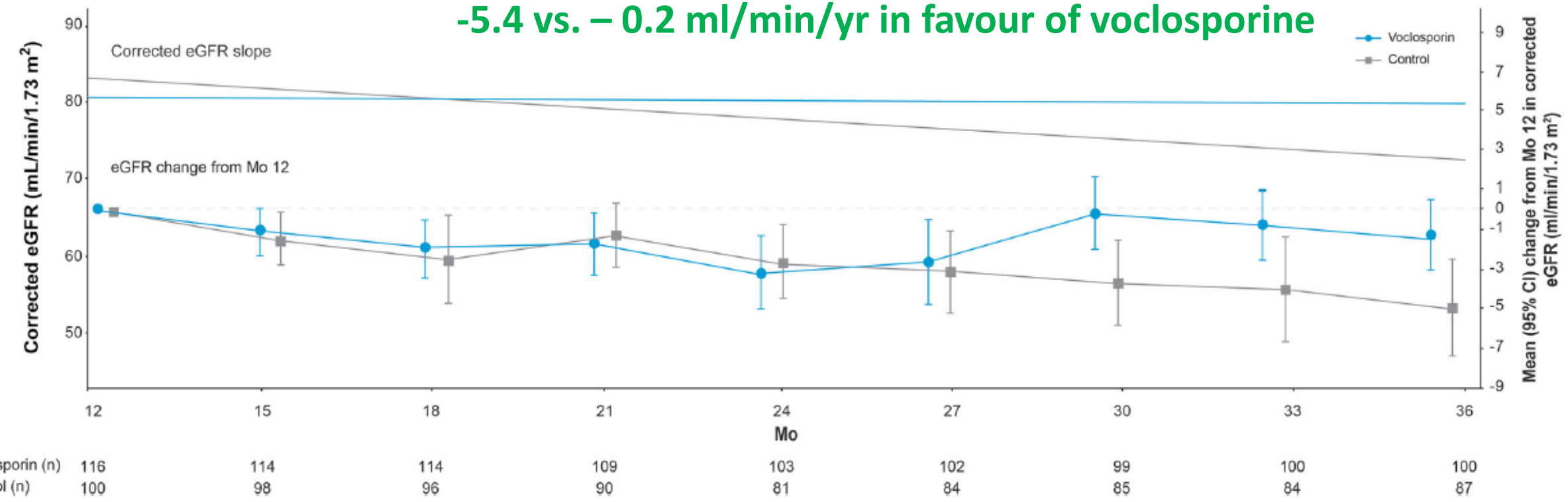
Safety and Efficacy of Long-Term Voclosporin Treatment for Lupus Nephritis in the Phase 3 AURORA 2 Clinical Trial

Amit Saxena,[1] Ellen M. Ginzler,[2] Keisha Gibson,[3] Bancha Satirapoj,[4] Adolfina Elizabeth Zuta Santillán,[5] Olena Levchenko,[6] Sandra Navarra,[7] Tatsuya Atsumi,[8] Shinsuke Yasuda,[9] Nilmo Noel Chavez-Perez,[10] Cristina Arriens,[11] Samir V. Parikh,[12] Dawn J. Caster,[13] Vanessa Birardi,[14] Simrat Randhawa,[15] Laura Lisk,[16] Robert B. Huizinga,[17] and Y. K. Onno Teng[18]

Arthritis & Rheumatology
Vol. 0, No. 0, Month 2023, pp 1–9
DOI 10.1002/art.42657

Slope of eGFR during the course of AURORA 2 clinical trial

-5.4 vs. – 0.2 ml/min/yr in favour of voclosporine



Voclosporin (n)	116	114	114	109	103	102	99	100	100
Control (n)	100	98	96	90	81	84	85	84	87

In the phase 3 trial (AURORA 1) adverse events similarly frequent in voclosporin and placebo limb, respectively

	Voclosporin group (n=178)	Placebo group (n=178)
Adverse event summary		
Adverse event	162 (91%)	158 (89%)
Serious adverse event	37 (21%)	38 (21%)
Serious adverse event of infections and infestations	18 (10%)	20 (11%)
Treatment-related serious adverse event	8 (4%)	8 (4%)
Adverse event leading to study drug discontinuation	20 (11%)	26 (15%)
Death*	1 (<1%)	5 (3%)
Treatment-related adverse event leading to death	0	0

Biologic treatment for lupus nephritis

Rituximab

Belimumab

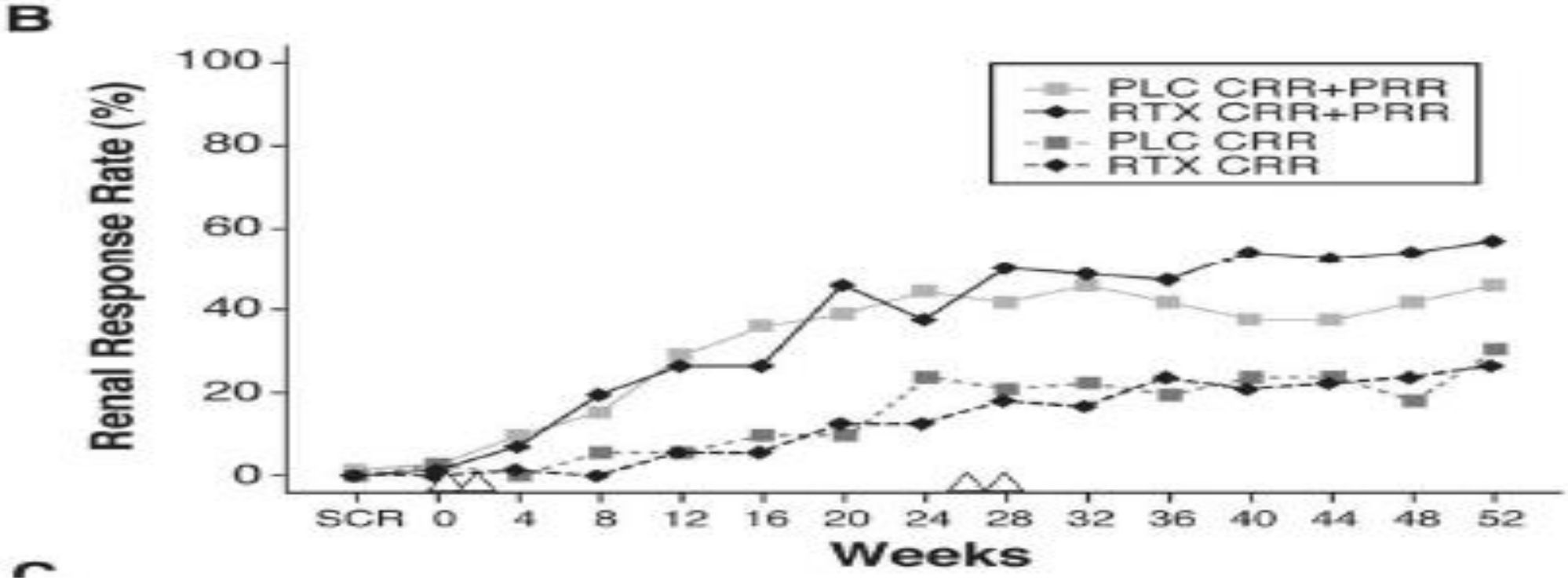
Obinutuzumab

Anifrolumab

Efficacy and Safety of Rituximab in Patients With Active Proliferative Lupus Nephritis

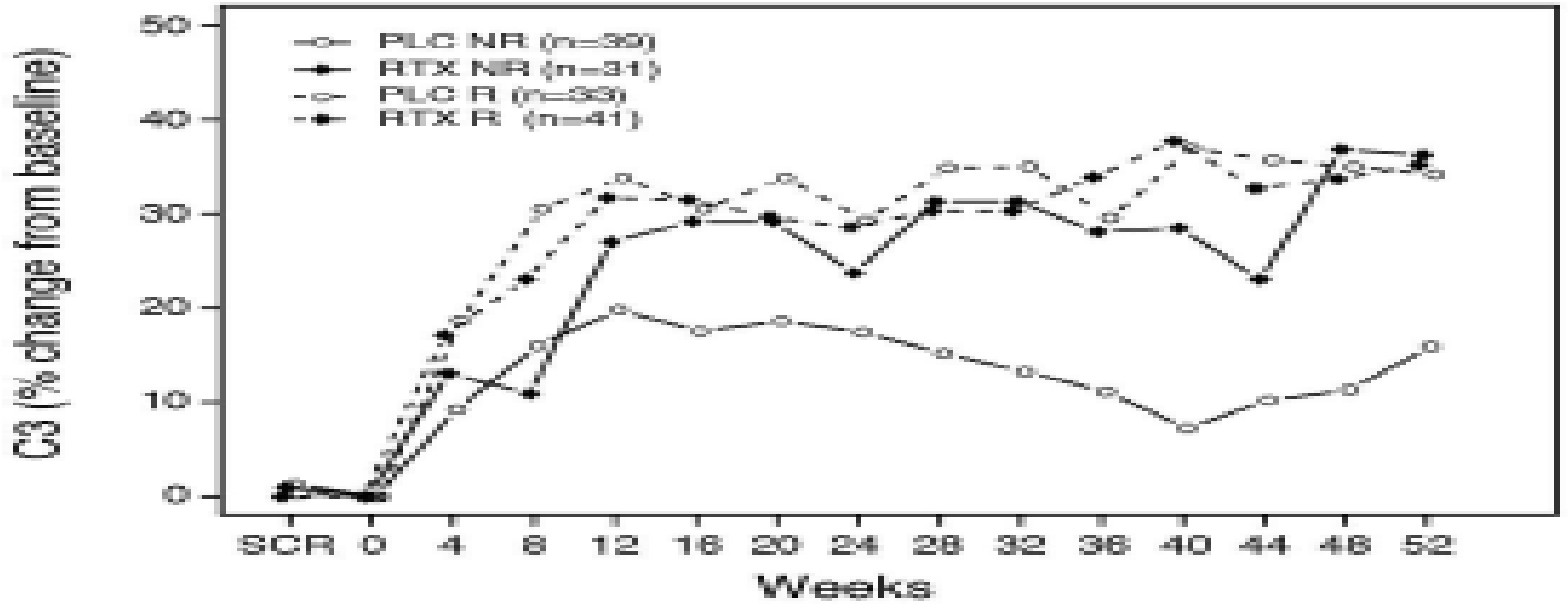
ARTHRITIS & RHEUMATISM
Vol. 64, No. 4, April 2012, pp 1215–1226

The Lupus Nephritis Assessment With Rituximab Study



144 pts with LN III-IV on CS and MMF randomized to RTX, or placebo with a FU of 52 weeks

No significant difference in remission rate and renal response rate…



Peripheral Blood B Cell Depletion after Rituximab and Complete Response in Lupus Nephritis

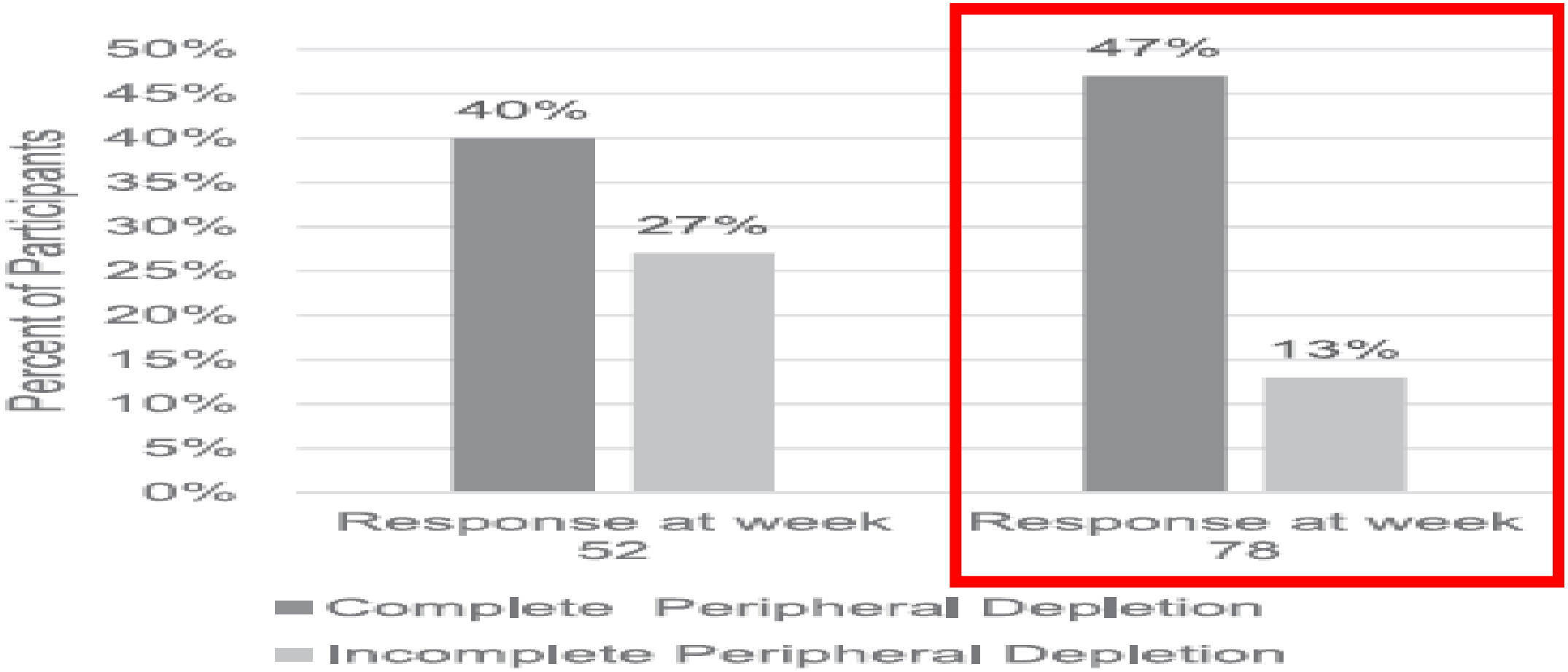
Liliana Michelle Gomez Mendez,[1] Matthew D. Cascino,[2] Jay Garg,[2] Tamiko R. Katsumoto,[2] Paul Brakeman,[1] Maria Dall'Era,[1] Richard John Looney,[3] Brad Rovin,[4] Leonard Dragone,[2] and Paul Brunetta[2]

Clin J Am Soc Nephrol 13: ●●●–●●●, 2018.

Only 78% of pts reached complete peripheral depletion

Complete response achieved 47% of pts with and in only 13% of pts without complete B cell depletion (p = 0.03)

Complete response associated with time to B cell depletion and its duration



Implications of rituximab pharmacokinetic and pharmacodynamic alterations in various immune-mediated glomerulopathies and potential anti-CD20 therapy alternatives

Jan Miroslav Hartinger[1*], Vojtech Kratky[2], Zdenka Hruskova[2], Ondrej Slanar[1] and Vladimir Tesar[2]

Front. Immunol. 13:1024068.
doi: 10.3389/fimmu.2022.1024068

TABLE 2 The half-lives of RTX in various autoimmune diseases.

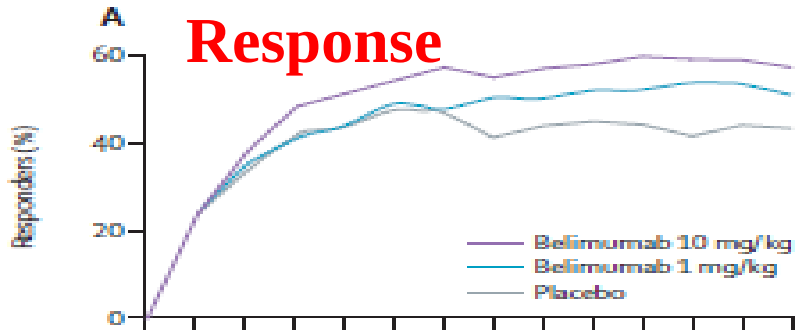
Drug/disease	Half-life
RTX/AAV	23 days = 552 hours (74)
RTX/MN	11.4 ± 5.4 days = 275 ± 130 hours (11)
	11.5 days = 276 hours (82)
RTX/NS in children	23 days = 554 hours (34)
RTX/RA	19-22 days = 456-528 hours (62)

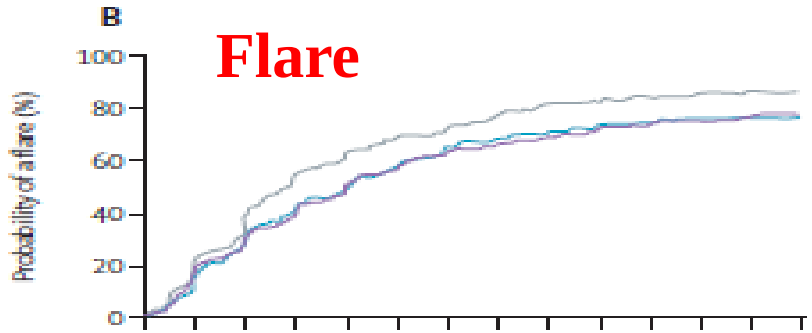
Effect of belimumab treatment on renal outcomes: results from the phase 3 belimumab clinical trials in SLE

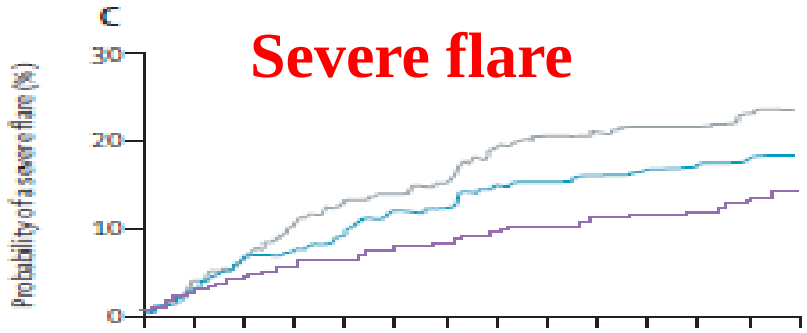
Lupus (2013) 22, 63–72

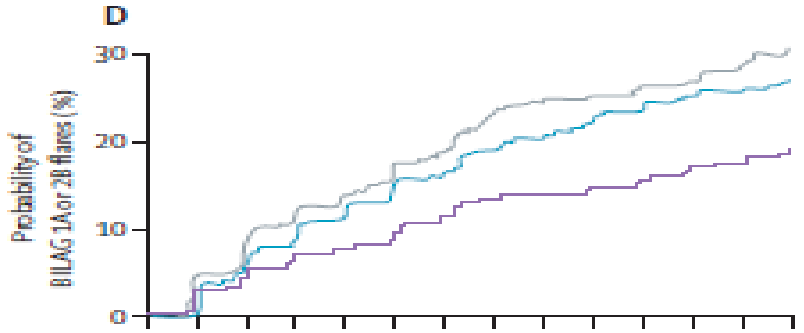
MA Dooley[1], F Houssiau[2], C Aranow[3], DP D'Cruz[4], A Askanase[5], DA Roth[6], ZJ Zhong[7], S Cooper[7], WW Freimuth[7] and EM Ginzler[8], for the BLISS-52 and -76 Study Groups

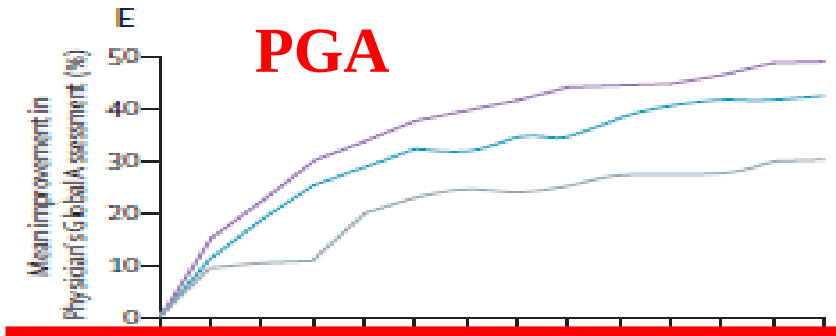
Similar efficacy of belimumab in BLISS-52 study

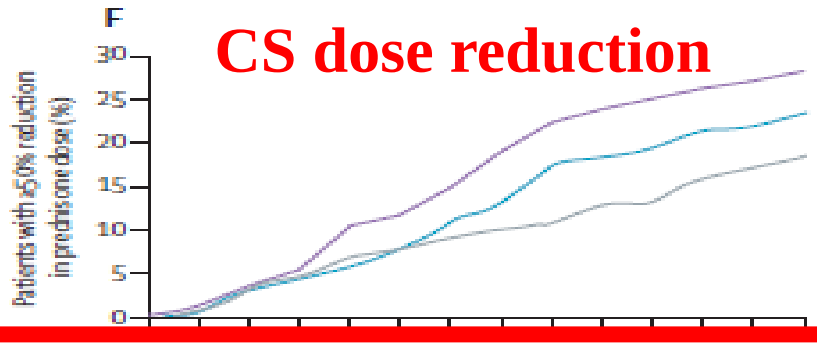


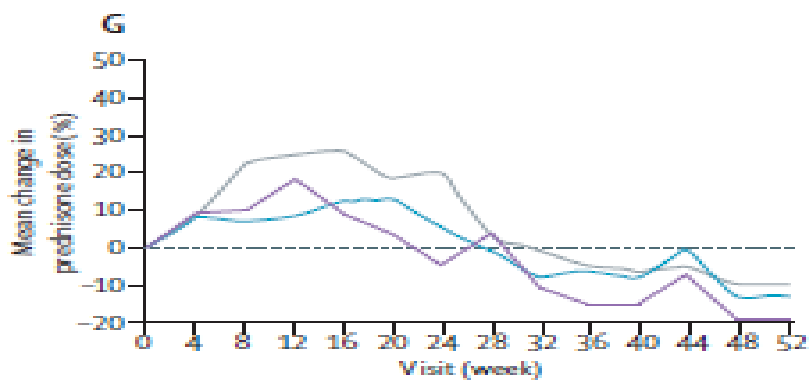


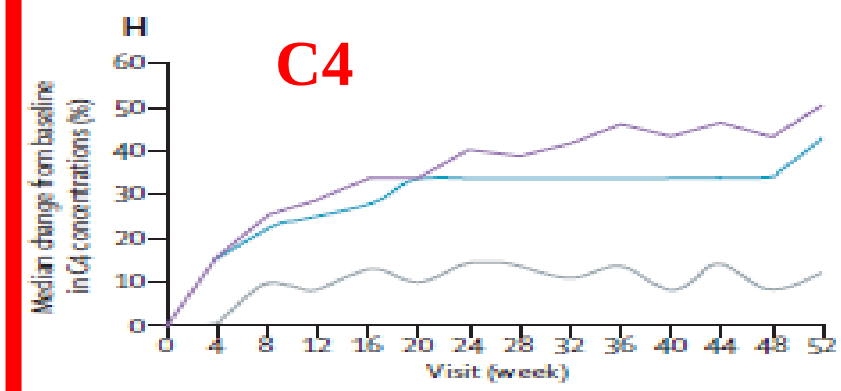


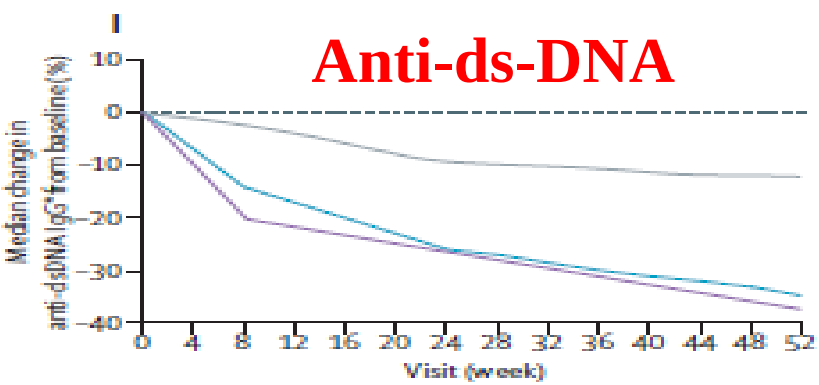








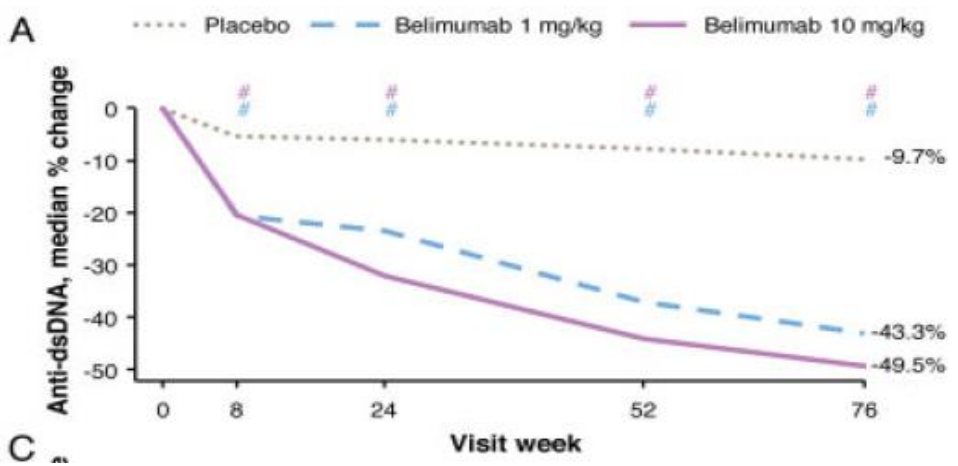


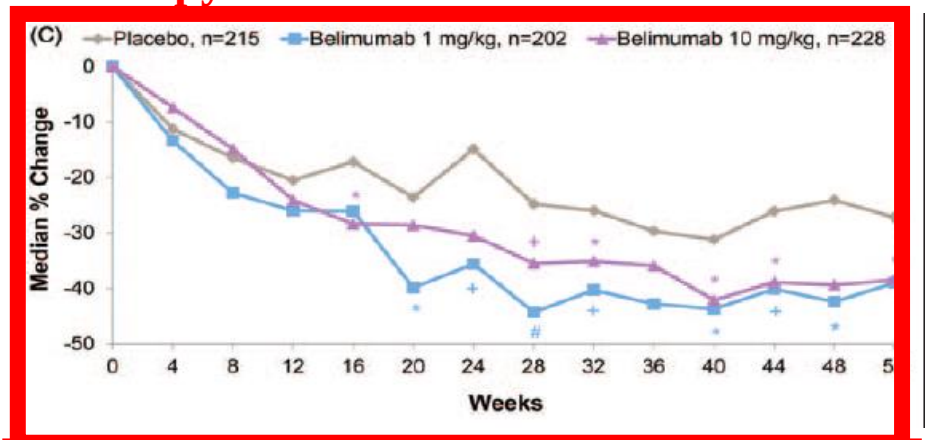


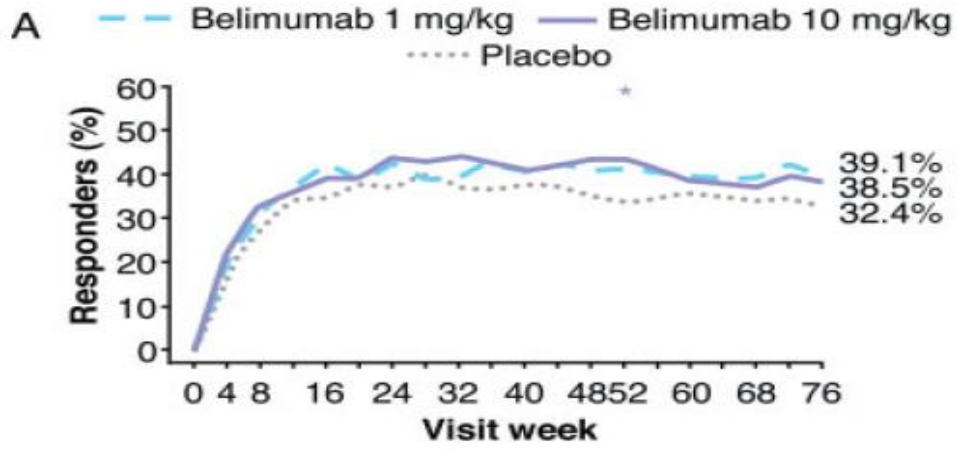
ARTHRITIS & RHEUMATISM
Vol. 63, No. 12, December 2011, pp 3918–3930

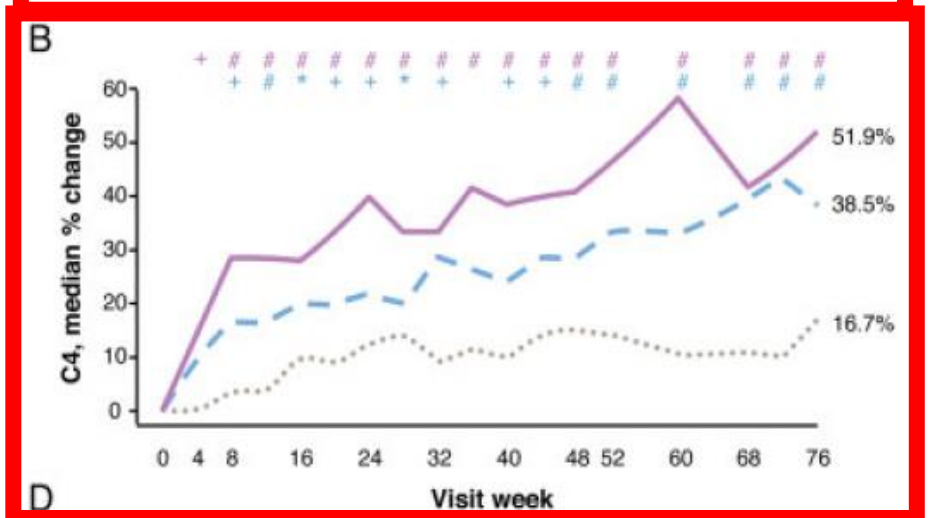
Dana Tegzová,[6] Jorge Sanchez-Guerrero,[7] Andreas Schwarting,[8] Joan T. Merrill,[9] W. Winn Chatham,[10] William Stohl,[11] Ellen M. Ginzler,[12] Douglas R. Hough,[13] Z. John Zhong,[13] William Freimuth,[13] and Ronald F. van Vollenhoven,[14] for the BLISS-76 Study Group

Belimumab approved by FDA and then by EMA in 2011 for an add-on therapy in adult patients with active autoantibody-positive SLE, with a high degree of disease activity (e.g. positive anti-dsDNA and low C3) despite standard therapy







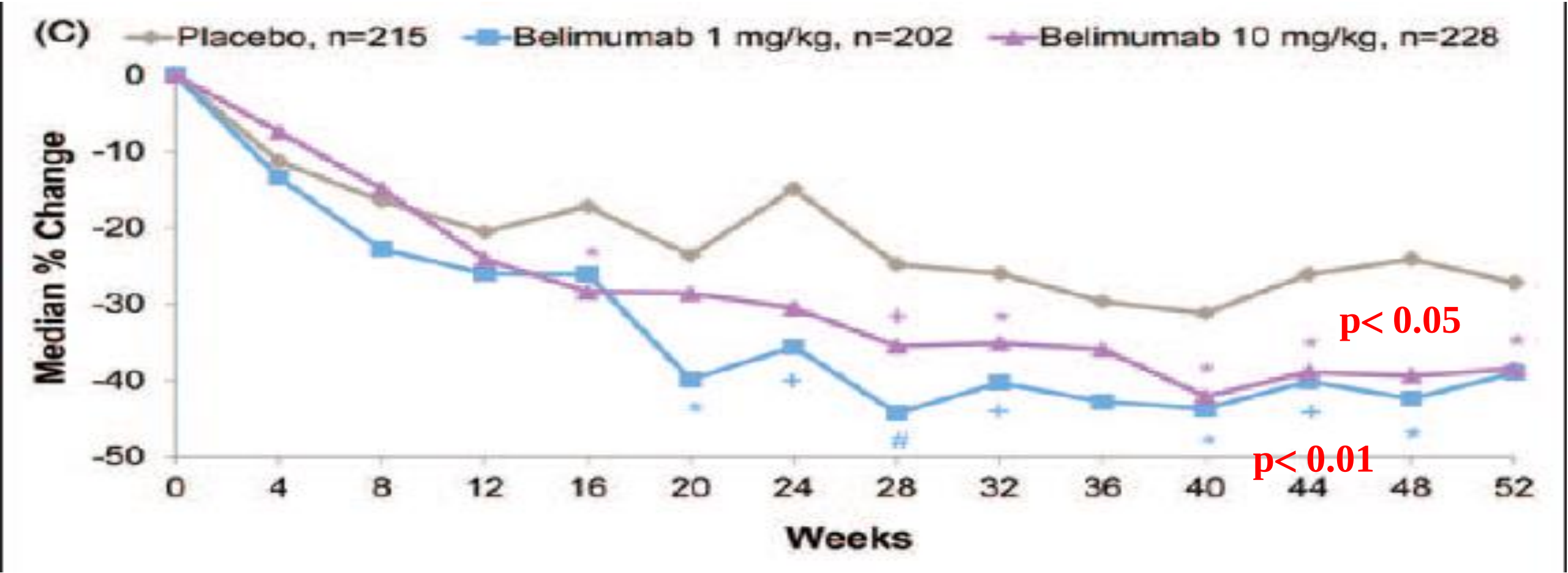


Effect of belimumab treatment on renal outcomes: results from the phase 3 belimumab clinical trials in patients with SLE

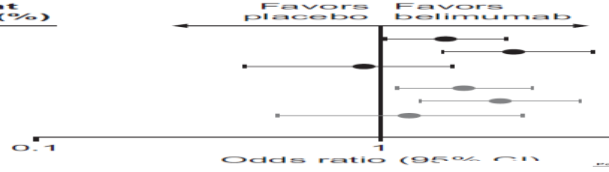
Lupus (2013) 22, 63–72

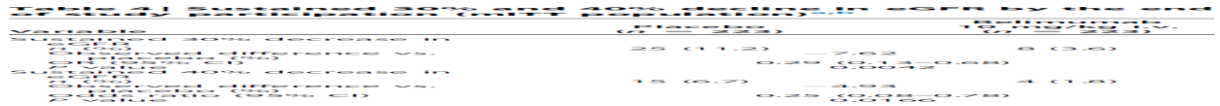
MA Dooley[1], F Houssiau[2], C Aranow[3], DP D'Cruz[4], A Askanase[5], DA Roth[6], ZJ Zhong[7], S Cooper[7], WW Freimuth[7] and EM Ginzler[8], for the BLISS-52 and -76 Study Groups

In a subanalysis of 267 (out of 1684) pts from BLISS-76 and BLISS-52 studies with renal involvement belimumab decreased proteinuria

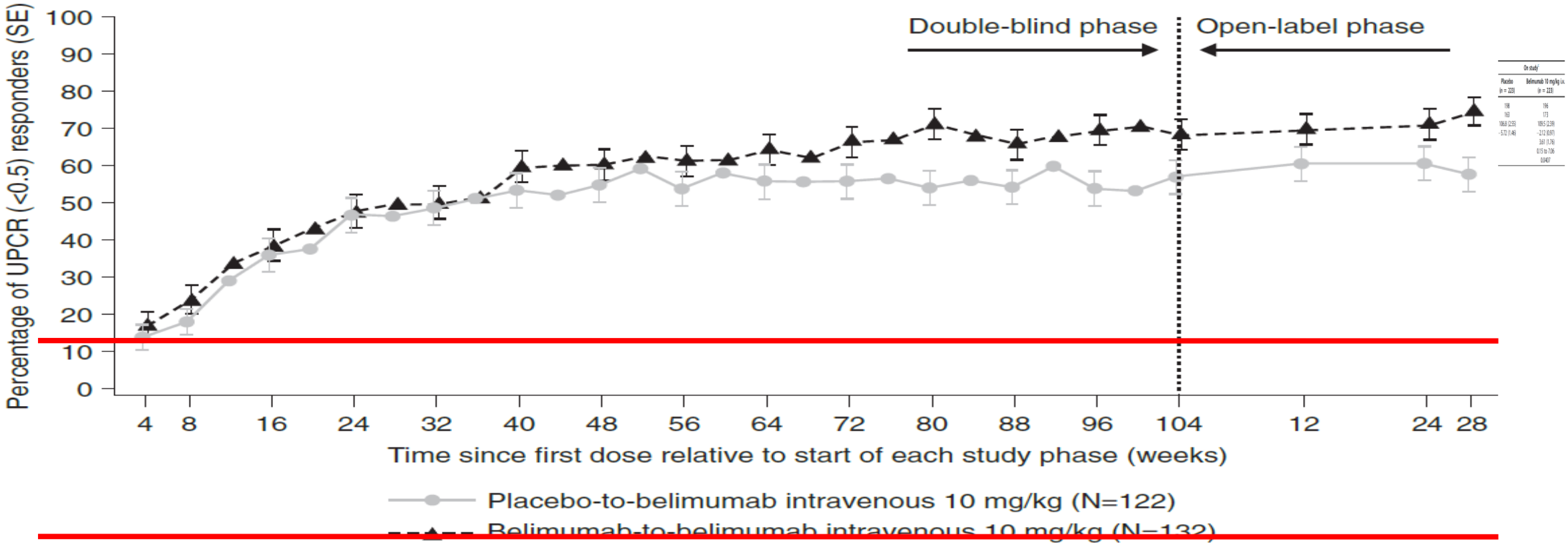


Response type	Baseline proteinuria level[b]	Responders, n (%) Placebo (n = 223)	Belimumab 10 mg/kg i.v. (n = 223)	Treatment difference (%)	Odds ratio (95% CI)	P value
PERR	Overall	72 (32.3)	96 (43.0)	10.8	1.55 (1.04, 2.32)	0.0311
	Low[c]	44 (33.6)	72 (54.5)	21.0	2.44 (1.46, 4.08)	
	High[d]	28 (30.4)	24 (26.4)	−4.1	0.85 (0.44, 1.63)	
CRR	Overall	44 (19.7)	67 (30.0)	10.3	1.74 (1.11, 2.74)	0.0167
	Low[c]	29 (22.1)	51 (38.9)	16.5	2.18 (1.26, 3.78)	
	High[d]	15 (16.3)	16 (17.6)	1.3	1.20 (0.54, 2.64)	

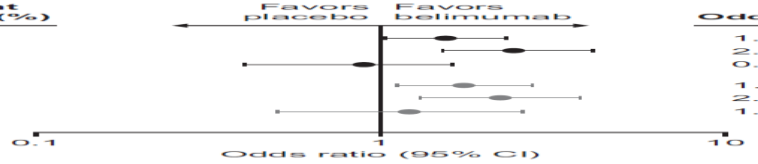


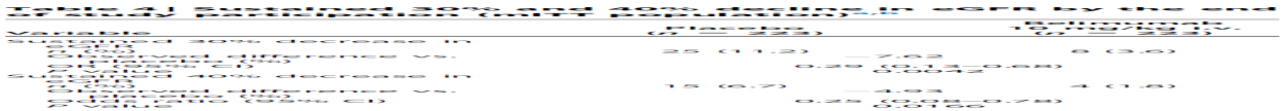


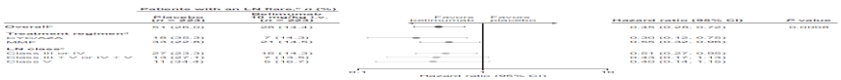
Post-hoc analysis of BLISS-LN study – sustained 30% and 40% decline in eGFR by the end of study



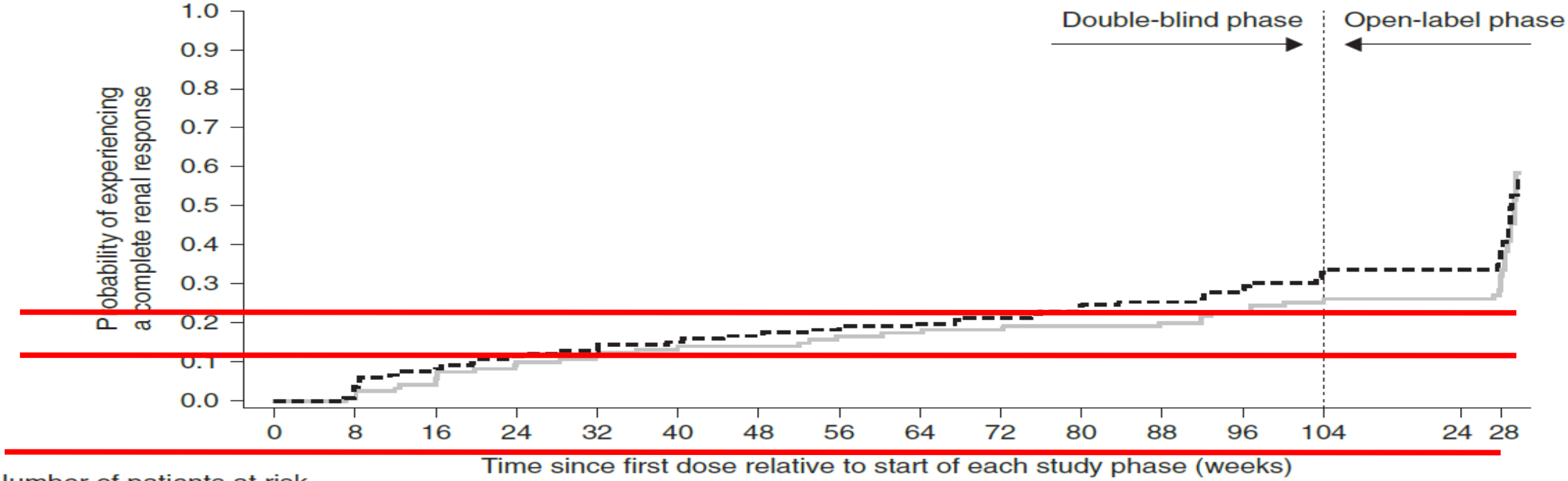
Response type	Baseline proteinuria level[b]	Responders, n (%) Placebo (N = 223)	Belimumab 10 mg/kg I.V. (N = 223)	Treatment difference (%)	Odds ratio (95% CI)	P value
PERR	Overall	72 (32.3)	96 (43.0)	10.8	1.55 (1.04, 2.32)	0.0311
	Low[c]	44 (33.6)	72 (54.5)	21.0	2.44 (1.46, 4.08)	
	High[d]	28 (30.4)	24 (26.4)	−4.1	0.85 (0.44, 1.63)	
CRR	Overall	44 (19.7)	67 (30.0)	10.3	1.74 (1.11, 2.74)	0.0167
	Low[c]	29 (22.1)	51 (38.9)	16.5	2.18 (1.26, 3.78)	
	High[d]	15 (16.3)	16 (17.6)	1.3	1.20 (0.54, 2.64)	







Post-hoc analysis of BLISS-LN study – time to first LN flare from week 24



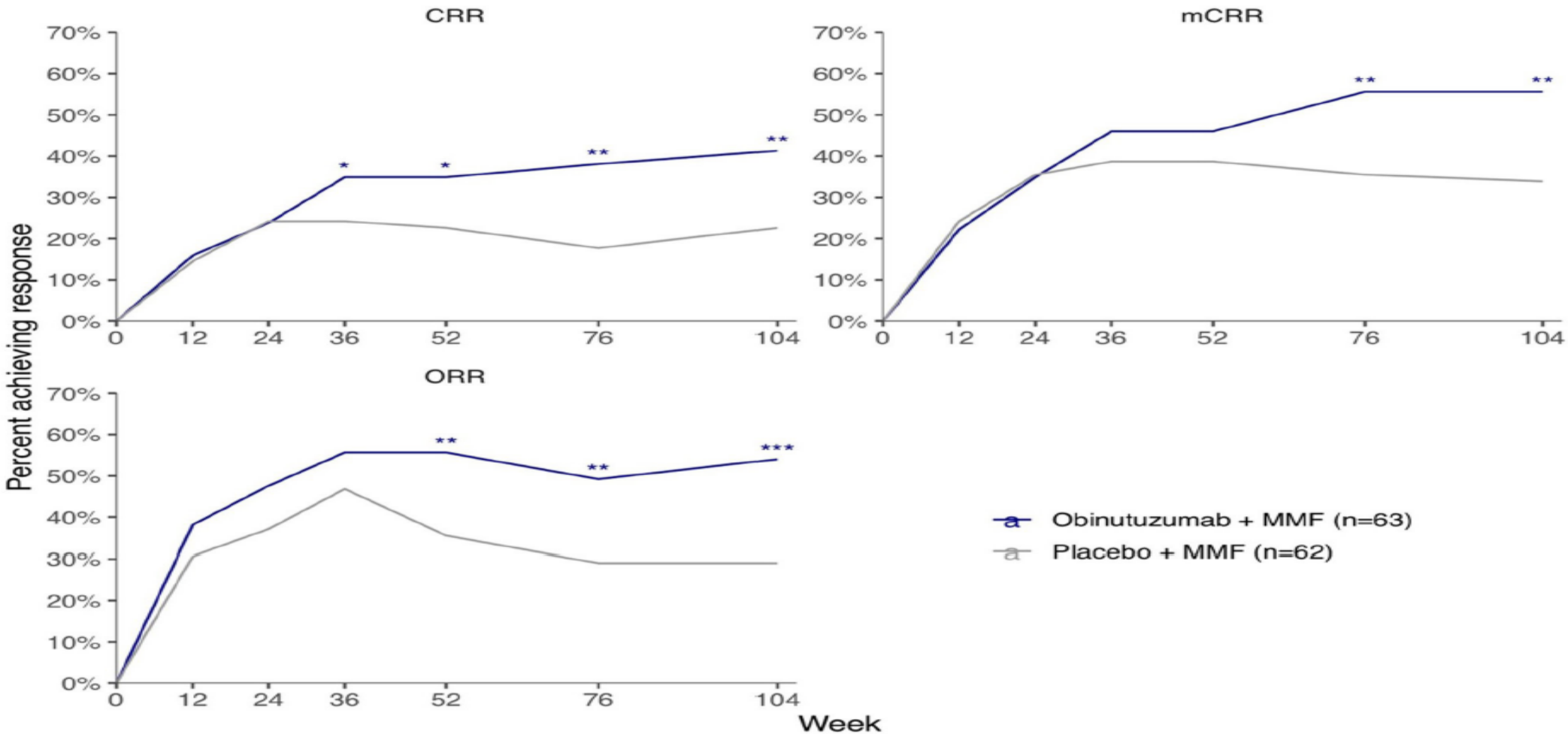
Number of patients at risk

Placebo-to-belimumab	120	116	110	107	105	104	98	96	95	93	91	88	84	82	56
Belimumab-to-belimumab	130	122	117	114	110	107	105	102	98	96	92	89	83	70	51

Placebo-to-belimumab intravenous 10 mg/kg (N=122)

Belimumab-to-belimumab intravenous 10 mg/kg (N=132)

Open-label 28 mo extension of BLISS-LN study –
Probabillity of experiencing PERR

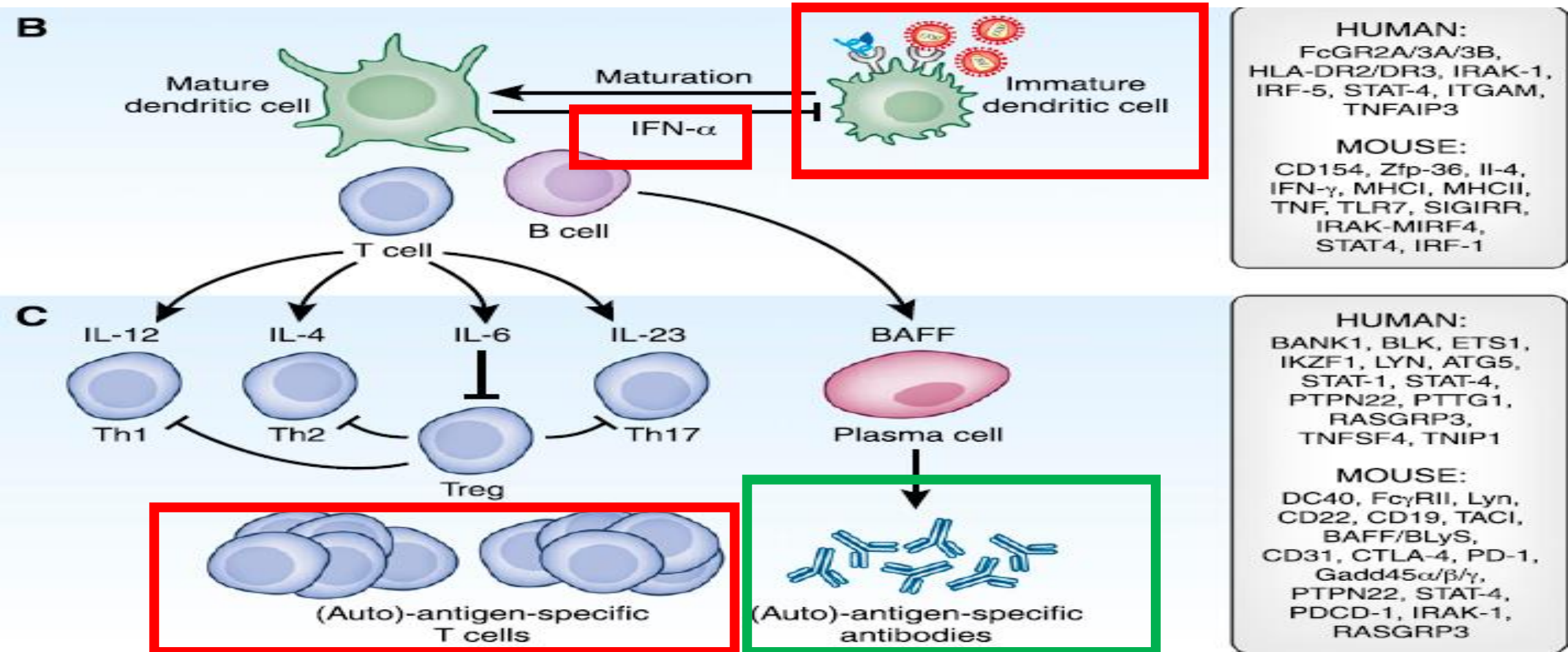


The Pathogenesis of Lupus Nephritis

J Am Soc Nephrol 24: ●●●–●●●, 2013.

Maciej Lech and Hans-Joachim Anders

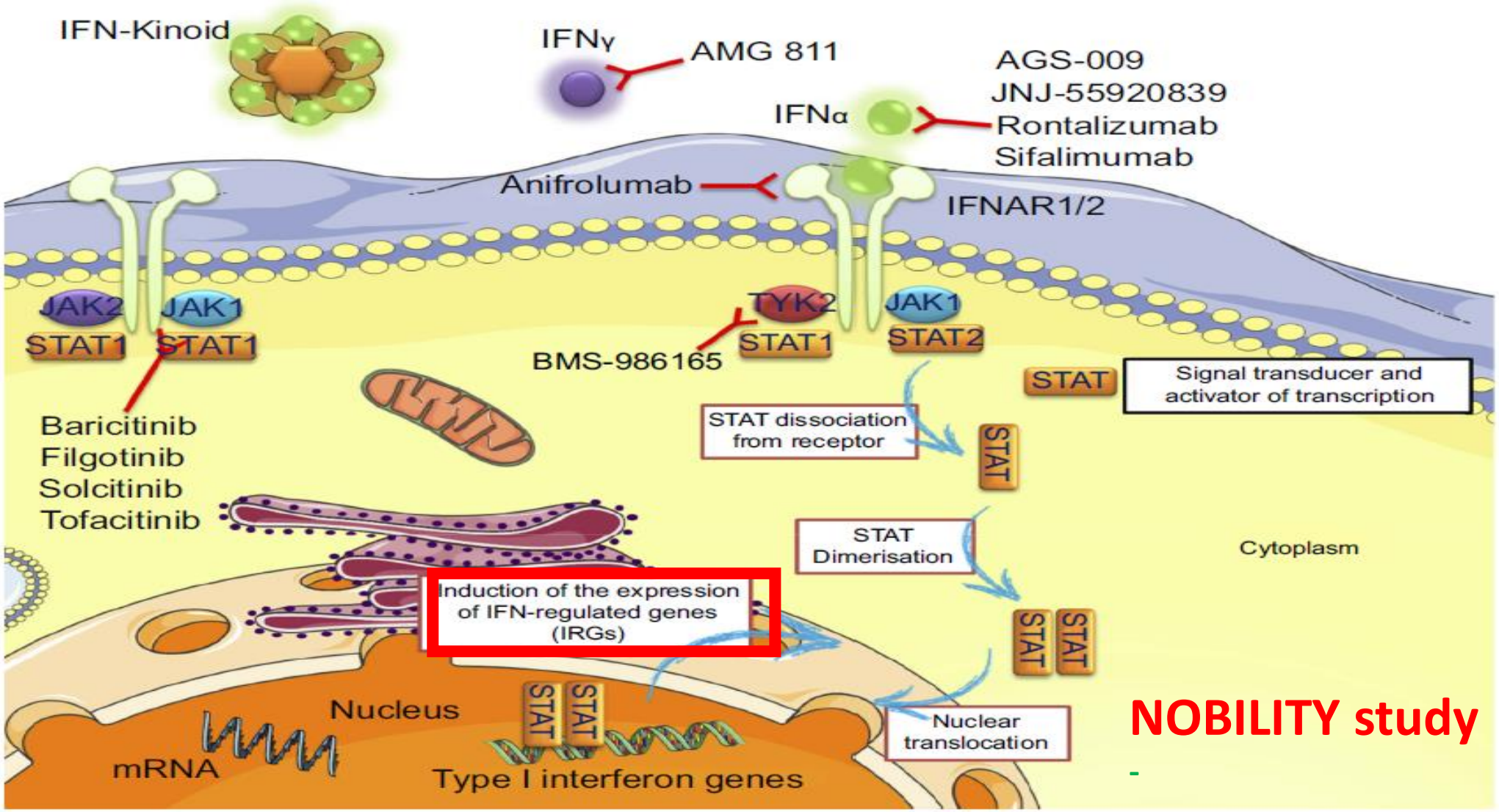
Pseudo-viral particles activate TLRs and antigen presentingresulting in polyclonal expansion of T and B cells



Spotlight on anifrolumab and its potential for the treatment of moderate-to-severe systemic lupus erythematosus: evidence to date

Renaud Felten[1–3]
Florence Scher[1,3]
Françoise Chasset[1,3]
Laurent Arnaud[1,3,4]

Drug Design, Development and Therapy 2019:13 1535–1543



NOBILITY study

-

TULIP 2 – phase 3 study

– 373 pts with SLE, anifrolumab vs placebo

Primary endpoint - decrease of BICLA at 52 weeks reached

TULIP LN – phase 2 study

– 147 pts with SLE, anifrolumab vs placebo

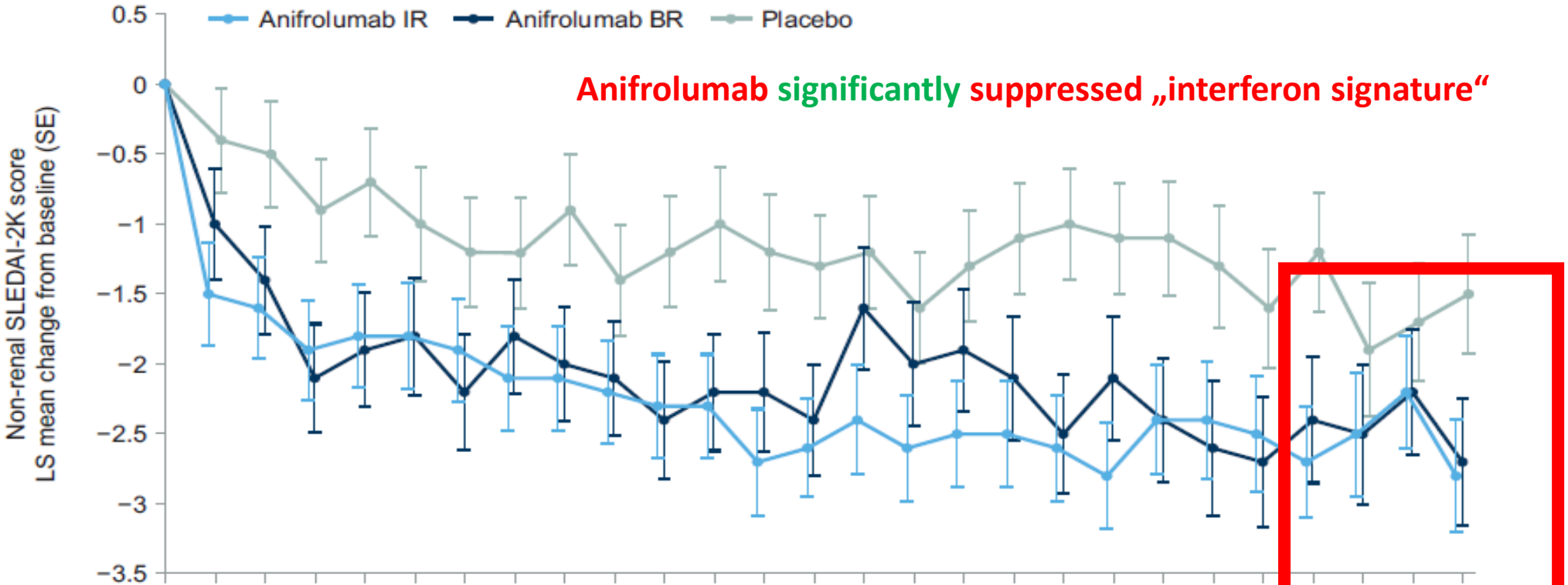
Primary endpoint - decrease of BICLA at 52 weeks reached

Anifrolumab in lupus nephritis: results from second-year extension of a randomised phase II trial

David Jayne,[1] Brad Rovin,[2] Eduardo Mysler,[3] Richard Furie,[4] Frédéric Houssiau,[5] Teodora Trasieva,[6] Jacob Knagenhjelm,[6] Erik Schwetje,[7] Weifeng Tang,[7] Raj Tummala,[7] Catharina Lindholm[6]

147 pts with LN III-IV randomized to basic or intensified anifrolumab regimen, or placebo,

Anifrolumab significantly suppressed „interferon signature“



Patients at risk

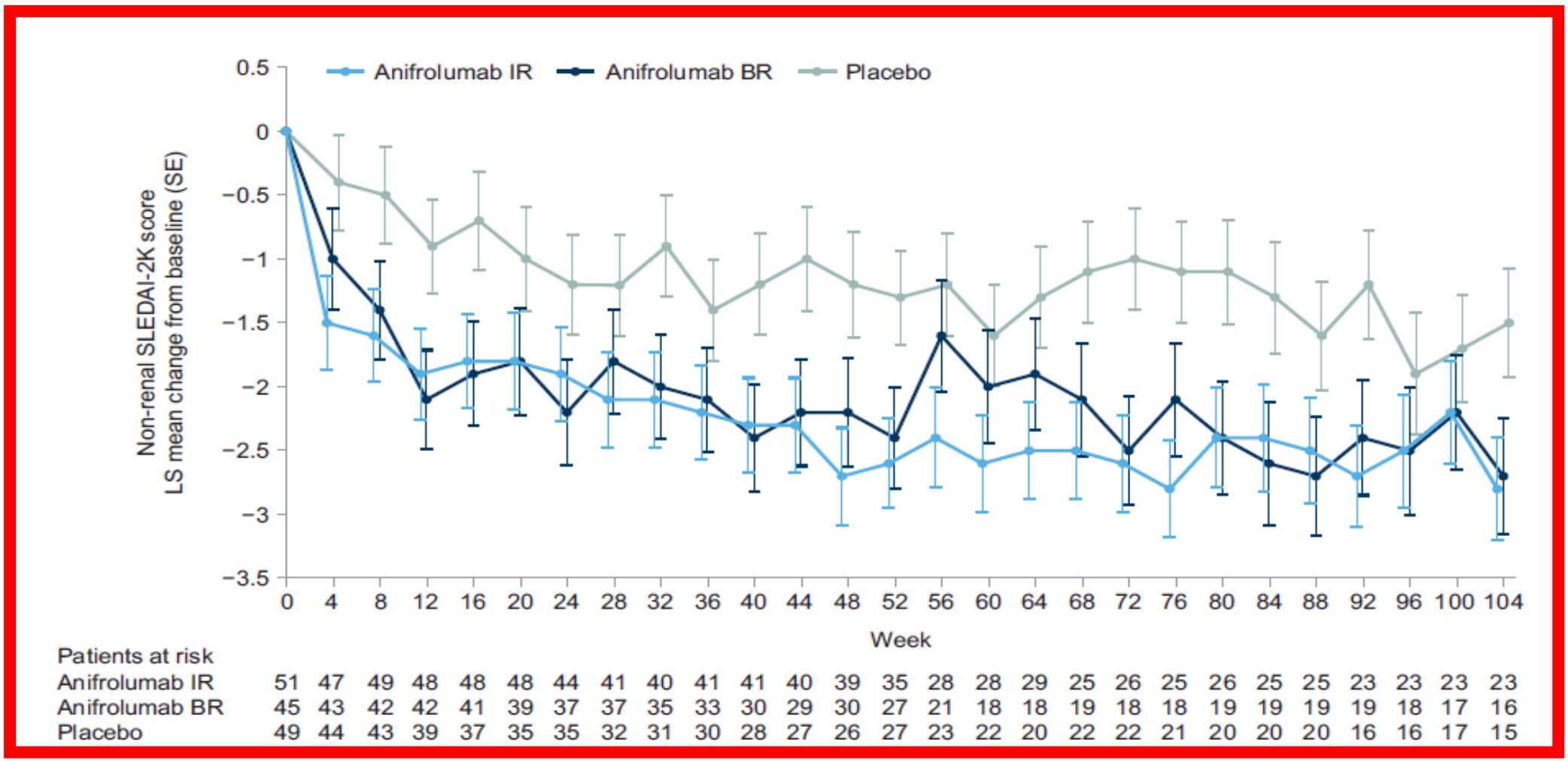
Anifrolumab IR	51	47	49	48	48	48	44	41	40	41	41	40	39	35	28	28	29	25	26	25	26	25	25			
Anifrolumab BR	45	43	42	42	41	39	37	37	35	33	30	29	30	27	21	18	18	19	18	18	19	19	19	19	18	17	16
Placebo	49	44	43	39	37	35	35	32	31	30	28	27	26	27	23	22	20	22	22	21	20	20	20	16	16	17	15

Martin Aringer, Marta E. Alarcón-Riquelme, Megan Clowse,
Guillermo J. Pons-Estel, Edward M. Vital and Maria Dall'Era

Lupus Science & Medicine
2023;**10**:e000910. doi:10.1136/lupus-2023-000910

David Jayne [1], Brad Rovin [2], Eduardo Mysler [3], Richard Furie [4], Frédéric Houssiau [5], Teodora Trasieva,[6] Jacob Knagenhjelm,[6] Erik Schwetje,[7] Weifeng Tang,[7] Raj Tummala,[7] Catharina Lindholm[6]

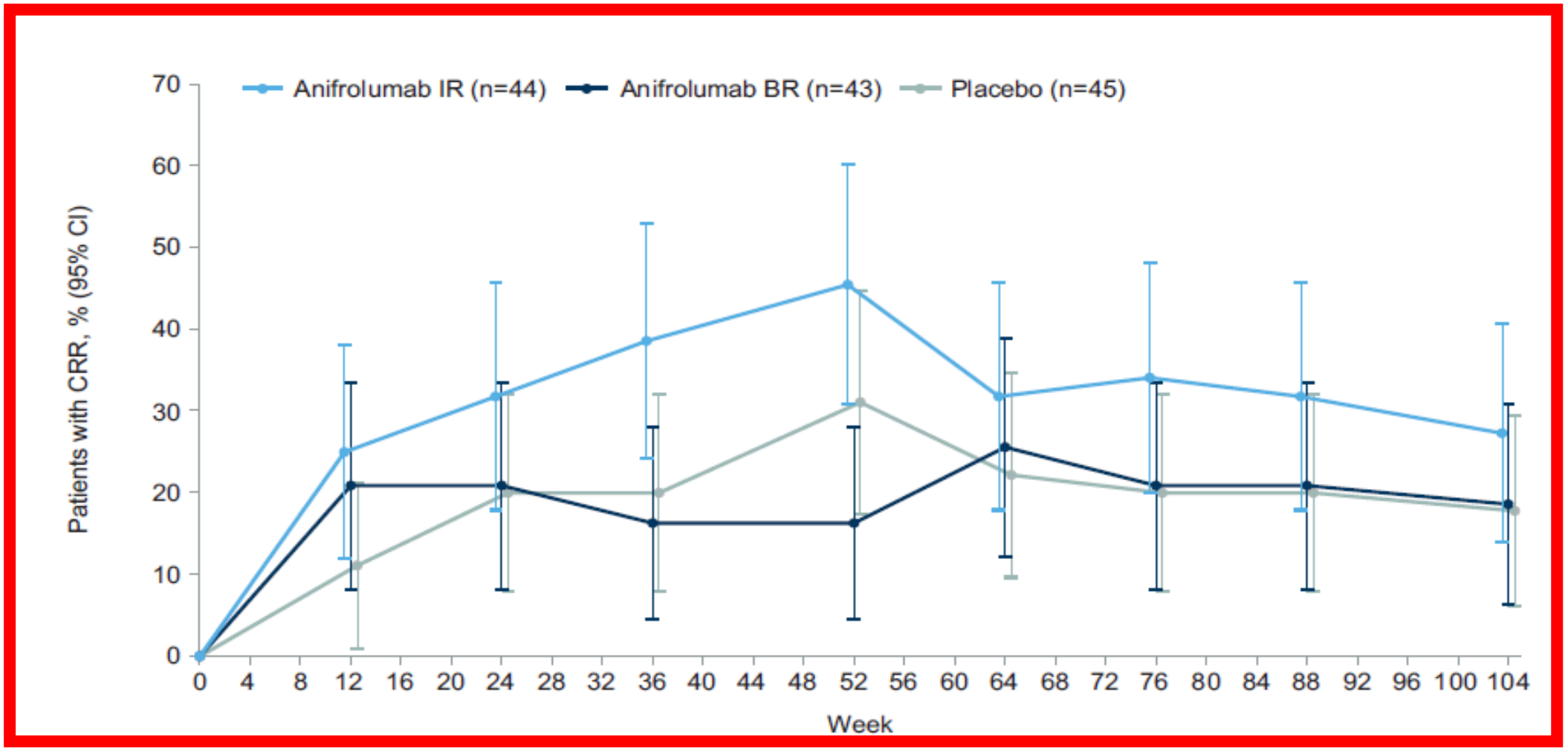
Anifrolumab in LN – second-year extension of randomised phase II trial – SLEDAI-2K score



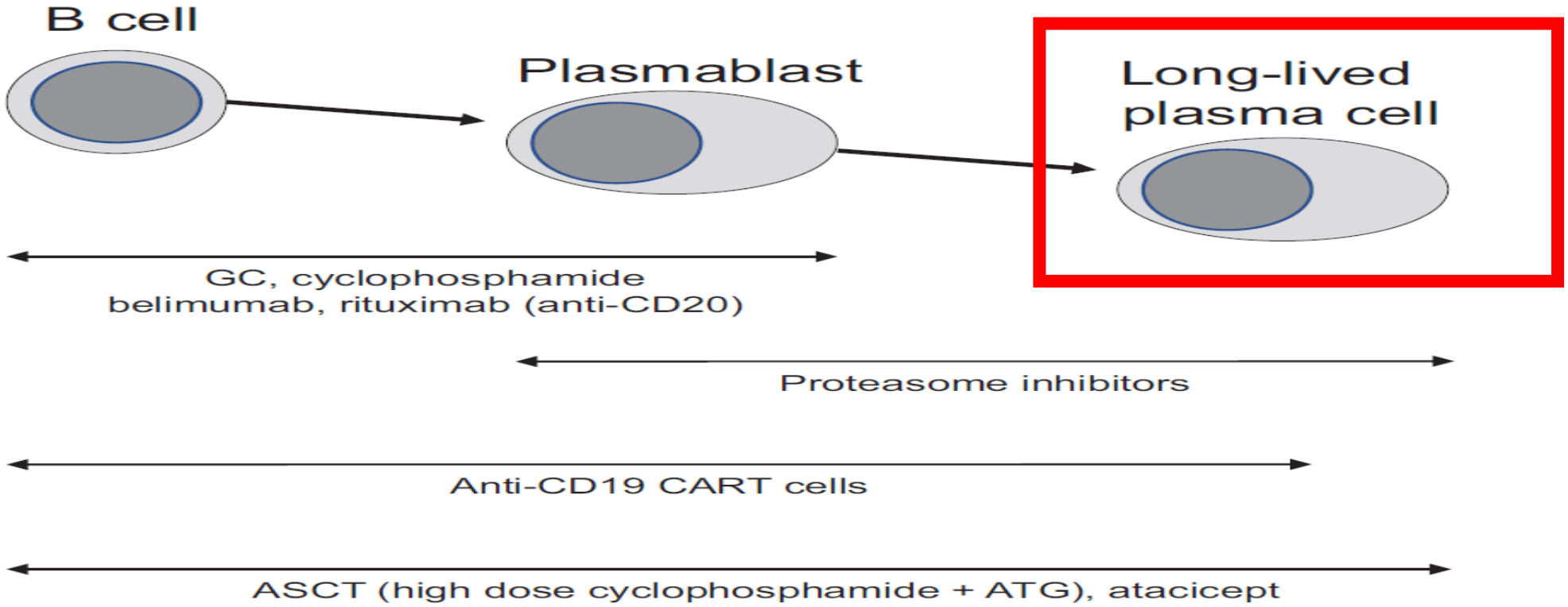
Martin Aringer, Marta E. Alarcón-Riquelme, Megan Clowse,
Guillermo J. Pons-Estel, Edward M. Vital and Maria Dall'Era
David Jayne,[1] Brad Rovin,[2] Eduardo Mysler,[3] Richard Furie,[4]
Frédéric Houssiau,[5] Teodora Trasieva,[6] Jacob Knagenhjelm,[6] Erik Schwetje,[7]
Weifeng Tang,[7] Raj Tummala,[7] Catharina Lindholm[6]

Lupus Science & Medicine
2023;**10**:e000910. doi:10.1136/
lupus-2023-000910

Anifrolumab in LN – second-year extension of randomised phase II trial – % of pts with CRR



Curative options in SLE need to eliminate both plasmablasts and long-lived plasma cells



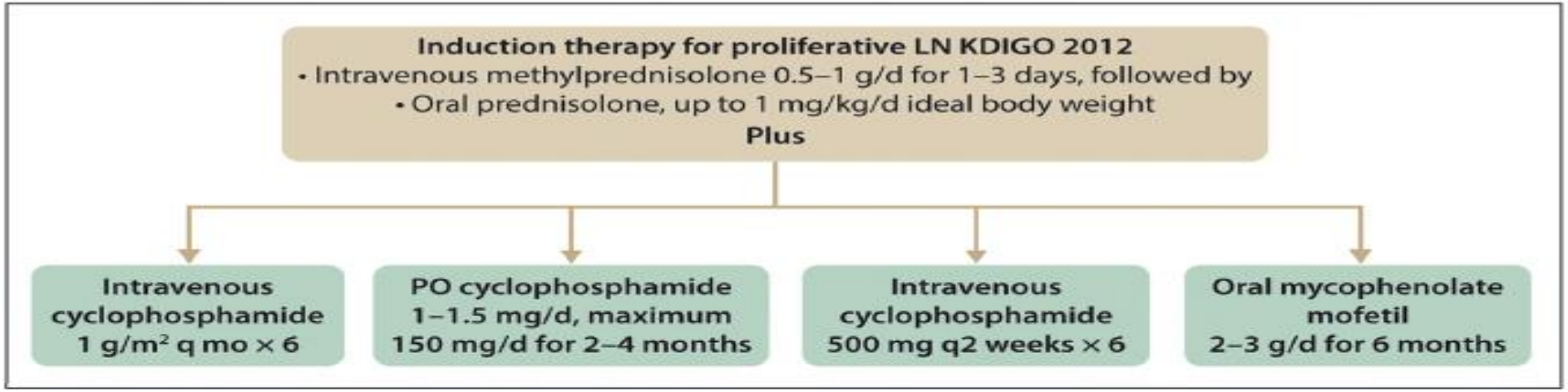
2023 update of 2021 KDIGO guidelines and EULAR 2023 guidelines

KDIGO CLINICAL PRACTICE GUIDELINE ON GLOMERULAR DISEASES

Chapter 10: Lupus nephritis

Kidney International (2021) 100, 753–779

Recommended initial first-line treatment of proliferative LN according to 2012 KDIGO guidelines



10.2.3.1 Initial therapy of active Class III/IV lupus nephritis

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 glucocorticoids plus either low-dose intravenous cyclophosphamide or MPAA *(1B)*.

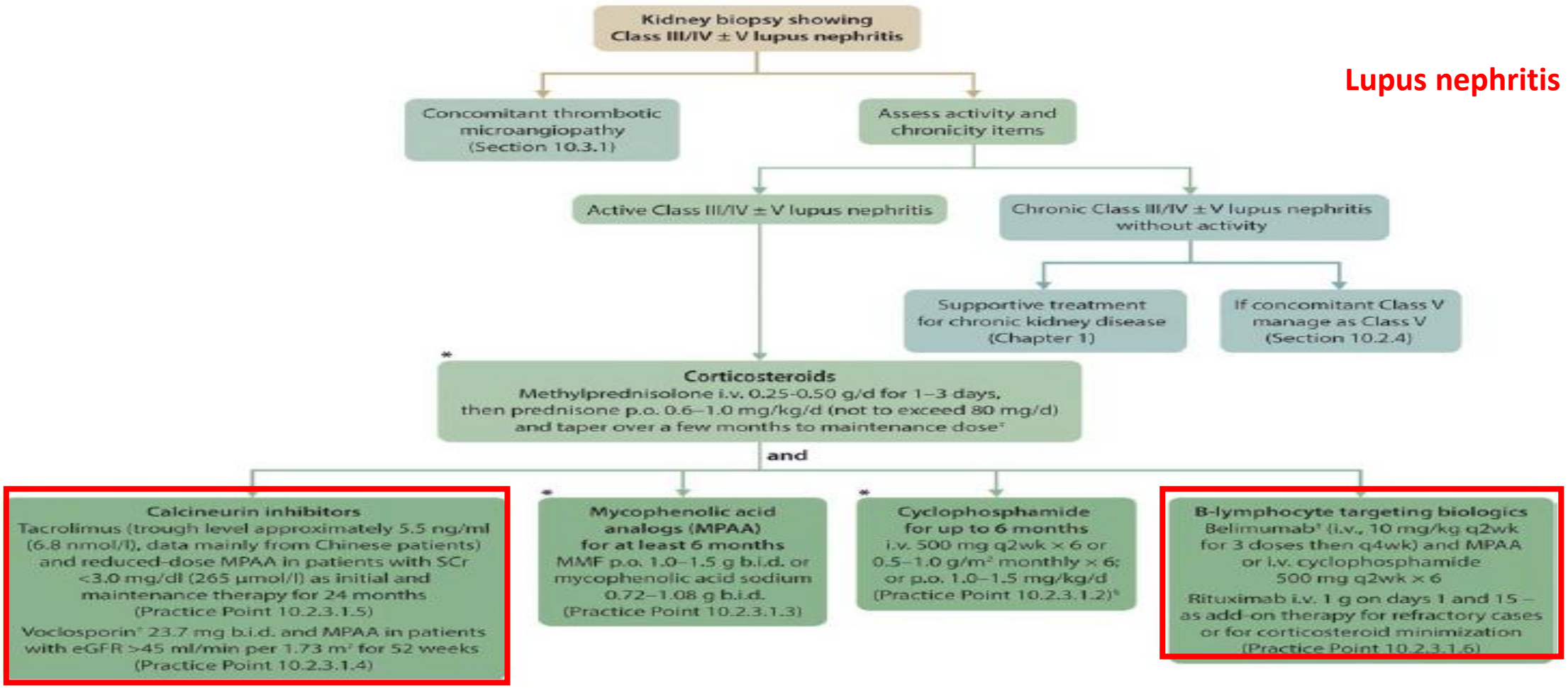
KDIGO CLINICAL PRACTICE GUIDELINE ON GLOMERULAR DISEASES

Chapter 10: Lupus nephritis

Kidney International (2021) 100, 753–779

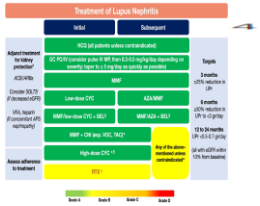
Recommended approach for initial therapy of active class III-IV LN according to 2021 KDIGO guidelines

Lupus nephritis



Antonis Fanouriakis, Myrto Kostopoulou, Jeanette Andersen, Martin Aringer, Laurent Arnaud, Sang-Cheol Bae, John Boletis, Ian N Bruce, Ricard Cervera, Andrea Doria, Thomas Dörner, Richard A Furie, Dafna D Gladman, Frederic A Houssiau, Luis Sousa Inês, David Jayne, Marios Kouloumas, László Kovács, Chi Chiu Mok, Eric F Morand, Gabriella Moroni, Marta Mosca, Johanna Mucke, Chetan B Mukhtyar, György Nagy, Loreto P. Santra, Ioannis Parodis, José M Pego-Reigosa, Bernardo A Pons-Estel, Matthias Schneider, Josef S S, Yoshiya Tanaka, Maria G Tektonidou, Angela Tincani, Edward M Vital, Chris Wincup, George Bertsias

Ann Rheum Dis 2023;0:1–15.



Recommended approach for initial therapy of active class III-IV±V LN according to 2023 KDIGO LN guidelines

Kidney biopsy showing Class III/IV ± V lupus nephritis

- Concomitant thrombotic microangiopathy (Section 10.3.1)
- Assess activity and chronicity items
  - Active Class III/IV ± V lupus nephritis
  - Chronic Class III/IV ± V lupus nephritis without activity
    - Supportive treatment for chronic kidney disease (Chapter 1)
    - If concomitant Class V manage as Class V (Section 10.2.4)

Corticosteroids
Methylprednisolone i.v. 0.25-0.50 g/d for 1–3 days, 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)† (Practice Point 10.2.3.1.1)

and

CNI + MPAA
Voclosporin 23.7 mg b.i.d. and MPAA in patients with eGFR >45 ml/min per 1.73 m²
(Practice Point 10.2.3.1.4)
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 maintenance therapy
Consider cyclosporine when voclosporin and tacrolimus are not available
CNI duration up to 3 years‡

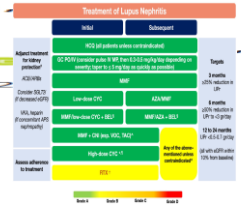
Mycophenolic acid analogs (MPAA) for at least 6 months
MMF p.o. 1.0–1.5 g b.i.d. or mycophenolic acid sodium 0.72–1.08 g b.i.d.
(Practice Point 10.2.3.1.3)

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
(Practice Point 10.2.3.1.2)§

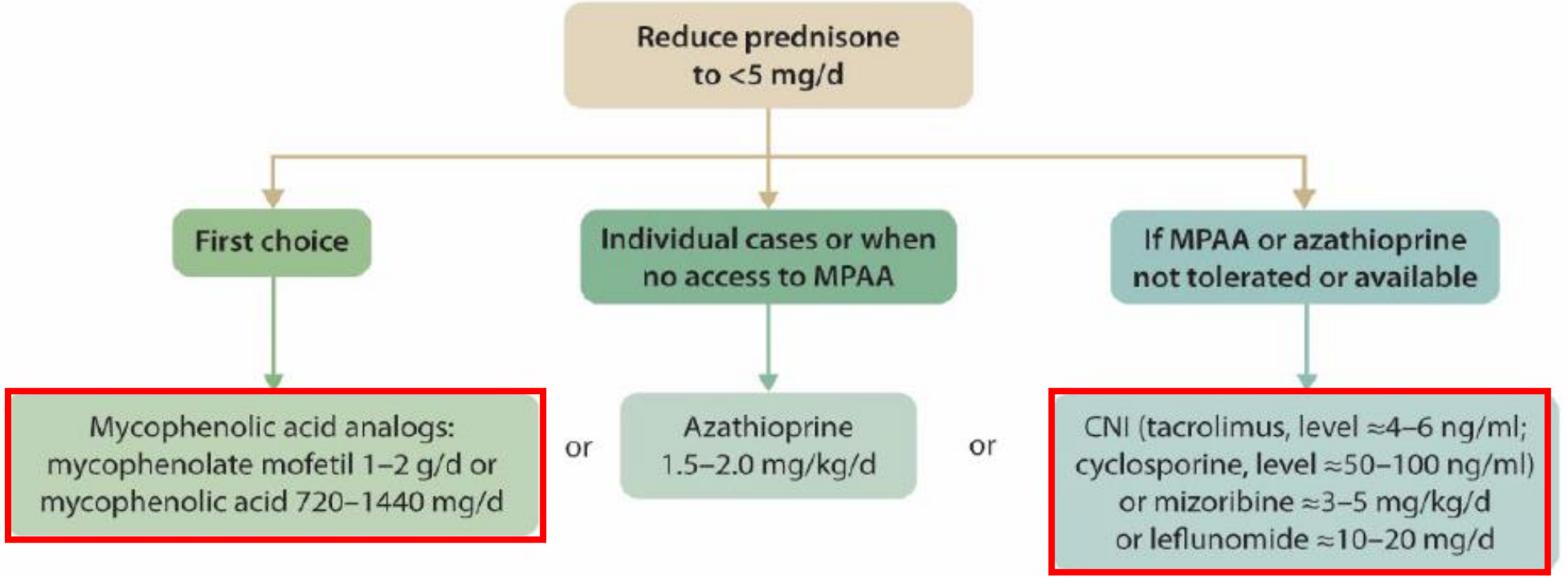
Belimumab + MPAA or reduced-dose cyclophosphamide
Belimumab (i.v., 10 mg/kg q2wk for 3 doses then q4wk) and MPAA or i.v. cyclophosphamide 500 mg q2wk × 6
(Practice Point 10.2.3.1.5)
Belimumab duration up to 2.5 years

Antonis Fanouriakis, Myrto Kostopoulou, Jeanette Andersen, Martin Aringer, Laurent Arnaud, Sang-Cheol Bae, John Boletis, Ian N Bruce, Ricard Cervera, Andrea Doria, Thomas Dörner, Richard A Furie, Dafna D Gladman, Frederic A Houssiau, Luis Sousa Inês, David Jayne, Marios Kouloumas, László Kovács, Chi Chiu Mok, Eric F Morand, Gabriella Moroni, Marta Mosca, Johanna Mucke, Chetan B Mukhtyar, György Nagy, Sandra Navarra, Ioannis Parodis, José M Pego-Reigosa, Michelle Petri, Bernardo A Pons-Estel, Matthias Schneider, Josef S, Elisabet Svenungsson, Yoshiya Tanaka, Maria G Tektonidou, Yk Onno Teng, Angela Tincani, Edward M Vital, Chris Wincup, George Bertsias

Ann Rheum Dis 2023;0:1–15.



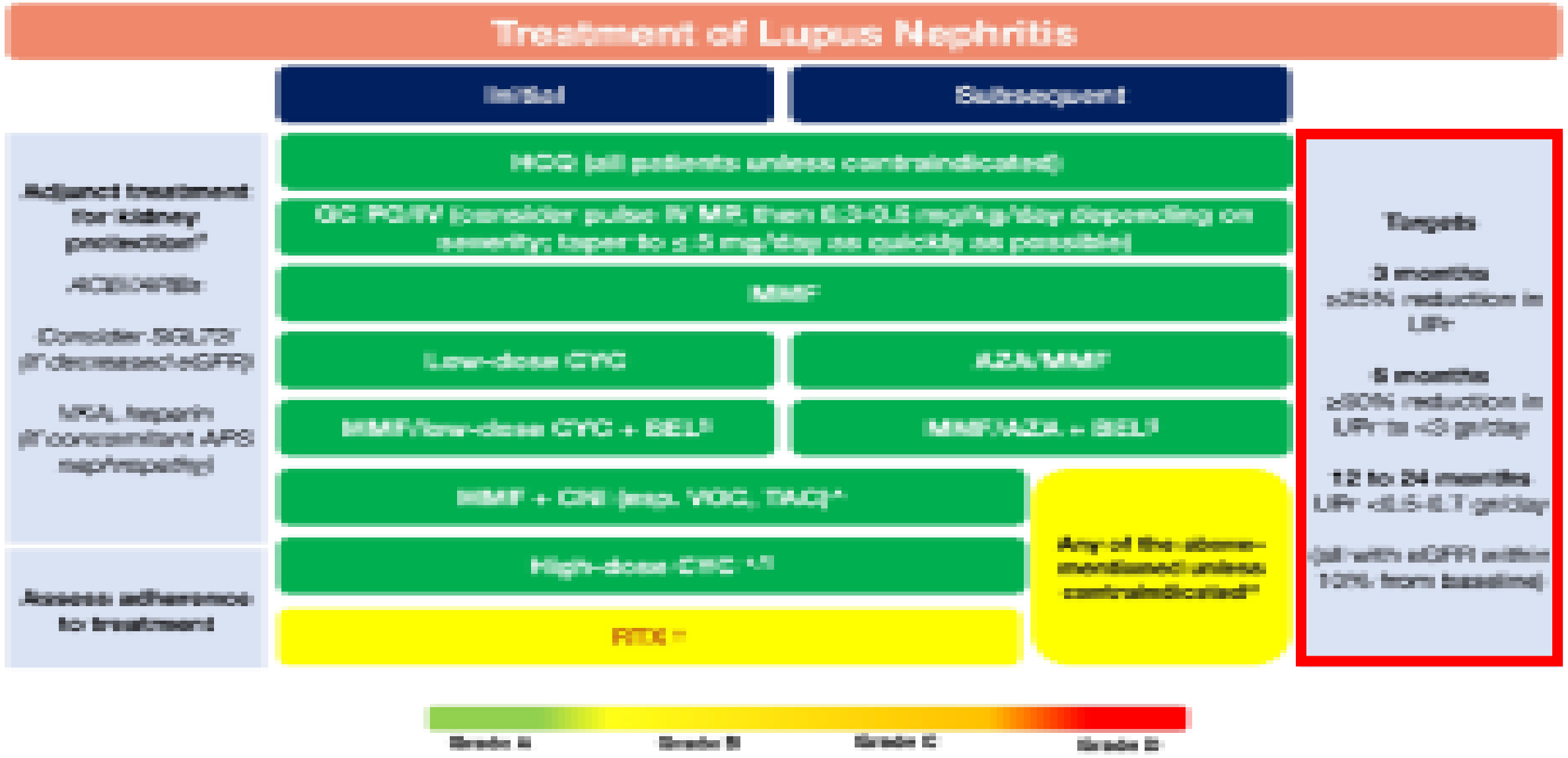
Recommended maintenance therapy for Class III and Class IV lupus nephritis.



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

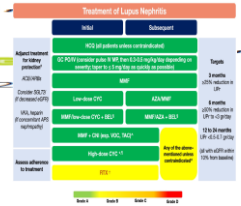
Ann Rheum Dis 2023;**0**:1–15.

Antonis Fanouriakis ,[1] Myrto Kostopoulou ,[1] Jeanette Andersen,[2]



Antonis Fanouriakis, Myrto Kostopoulou, Jeanette Andersen, Martin Aringer, Laurent Arnaud, Sang-Cheol Bae, John Boletis, Ian N Bruce, Ricard Cervera, Andrea Doria, Thomas Dörner, Richard A Furie, Dafna D Gladman, Frederic A Houssiau, Luis Sousa Inês, David Jayne, Marios Kouloumas, László Kovács, Chi Chiu Mok, Eric F Morand, Gabriella Moroni, Marta Mosca, Johanna Mucke, Chetan B Mukhtyar, György Nagy, Sandra Navarra, Ioannis Parodis, José M Pego-Reigosa, Michele Petri, Bernardo A Pons-Estel, Matthias Schneider, Josef S Elisabet Svenungsson, Yoshiya Tanaka, Maria G Tektonidou, Yk Onno Teng, Angela Tincani, Edward M Vital, George Bertsias, Chris Wincup

Ann Rheum Dis 2023;0:1–15.



Management of unsatisfactory response to treatment

1	Verify adherence to treatment
2	Ensure adequate dosing of immunosuppressive medications by measuring plasma drug levels if applicable or available (check mycophenolic acid level if on mycophenolic acid analogs/check infusion records if on cyclophosphamide)
3	Repeat biopsy if concern for chronicity or other diagnosis (e.g., thrombotic microangiopathy)
4	Consider switching to an alternative first-line regimen when there is persistent disease activity
5	Consider the following in patients refractory to first-line treatment regimens: • Addition of rituximab or other biologic therapies • Extended course of i.v. pulse cyclophosphamide • Enrollment in clinical trials if eligible

Conclusions

1. Better understanding of the pathogenesis of SLE and LN resulted in the identification of new therapeutic targets
2. New modes of treatment should be at least similarly effective, but less toxic
3. Current treatment can induce longterm remission, but the risk of relapses after withdrawal still remains high
3. None of recommended modes of treatment is curative

Thank you for your attention and your questions