Lupus nephritis

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Disclosure of Interests

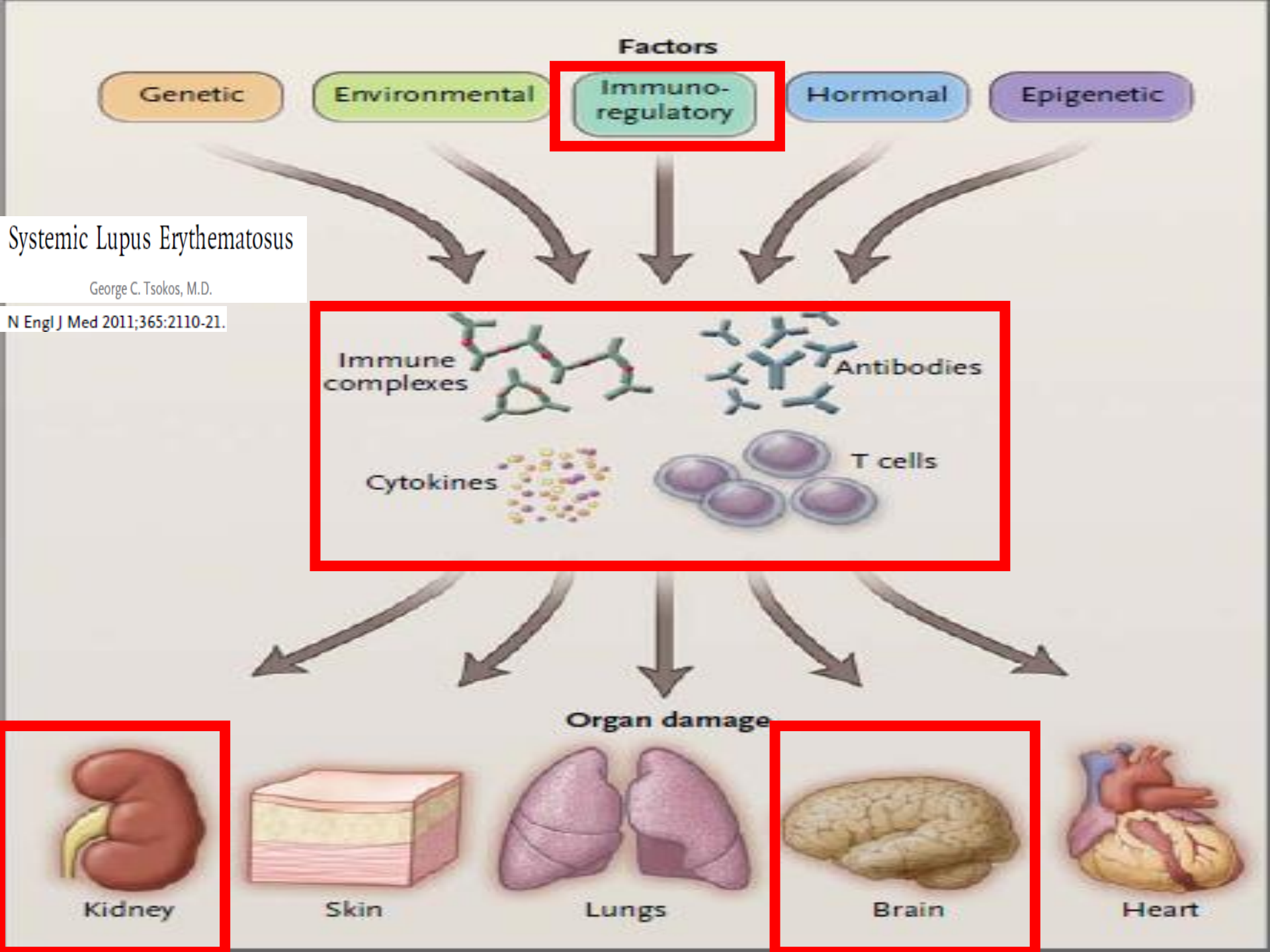
Abbvie, Amgen, Baxter, Bayer, Boehringer-Ingelheim, Calliditas, Chemocentryx, Daichi-Sankyo Fresenius Medical Care

(consultancy, advisory board)

Systemic Lupus Erythematosus

George C. Tsokos, M.D.

N Engl J Med 2011;365:2110-21.



Lupus nephritis – ISN/RPS classification

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

1. type I – immune deposits in the mesangium w/o hypercellularity
2. type II – mesangial hypercellularity with immune deposits
3. type III – focal GN (< 50% gls) –
   a) active lesions
   b) active and chronic lesions
   c) chronic lesions
4. type IV – diffuse GN (> 50% gls) –
   IV-S >50% segmental lesions (a,b,c)
   IV-G>50% global lesions (a,b,c)
5. type V – membranous lupus nephritis
6. type VI – advanced sclerosing lesions (> 90% gls)

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 – sklerosing lesions

Outline of the lecture

1. Efficacy and toxicity of high-dose cyclophosphamide
2. Mycophenolate mofetil and calcineurin inhibitors in LN
3. Biologic treatment in LN
4. Low dose cyclophosphamide
   – high efficacy, relatively low toxicity
5. Conclusions

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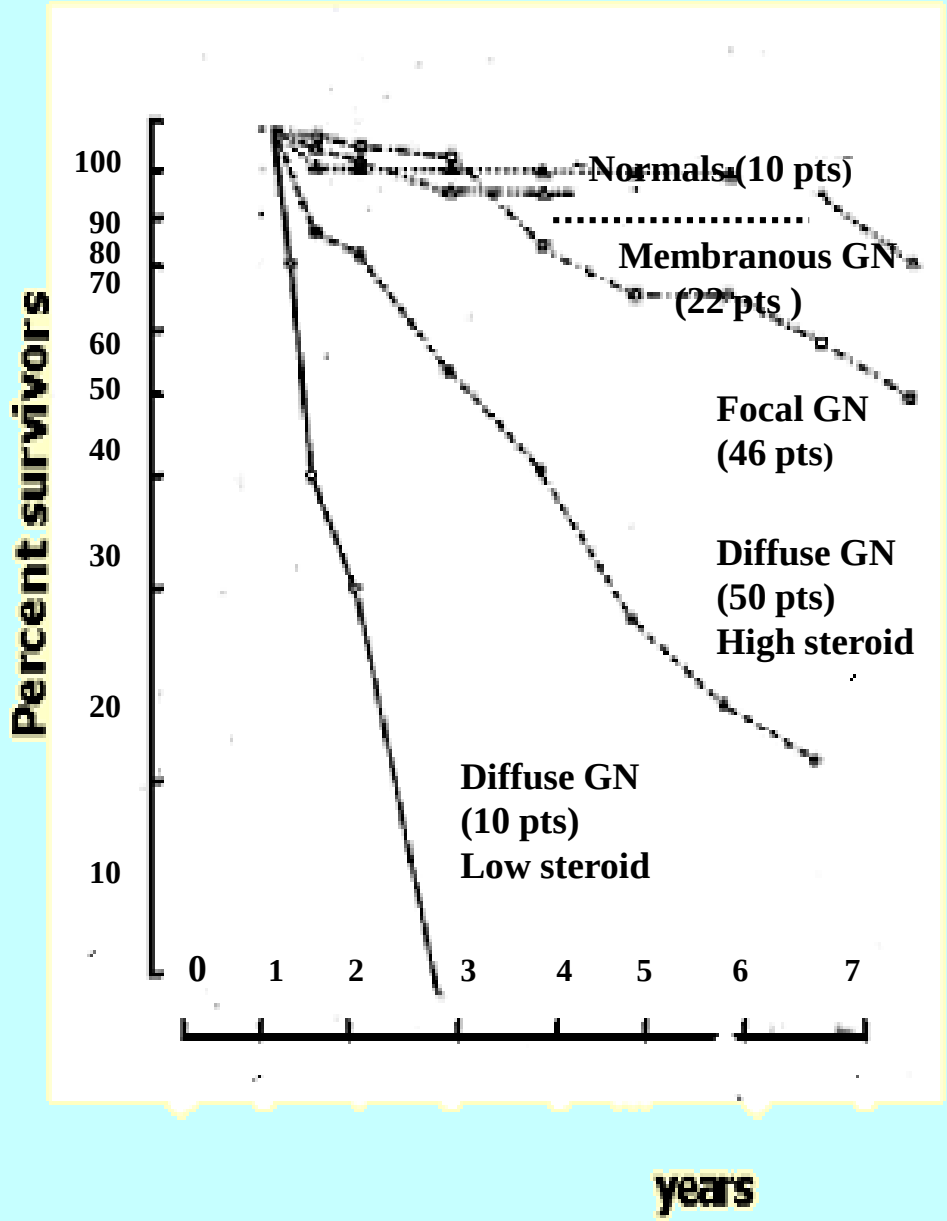
Survival in patients with different histological classes of lupus nephritis: pooled data of Baldwin and Pollak 1964



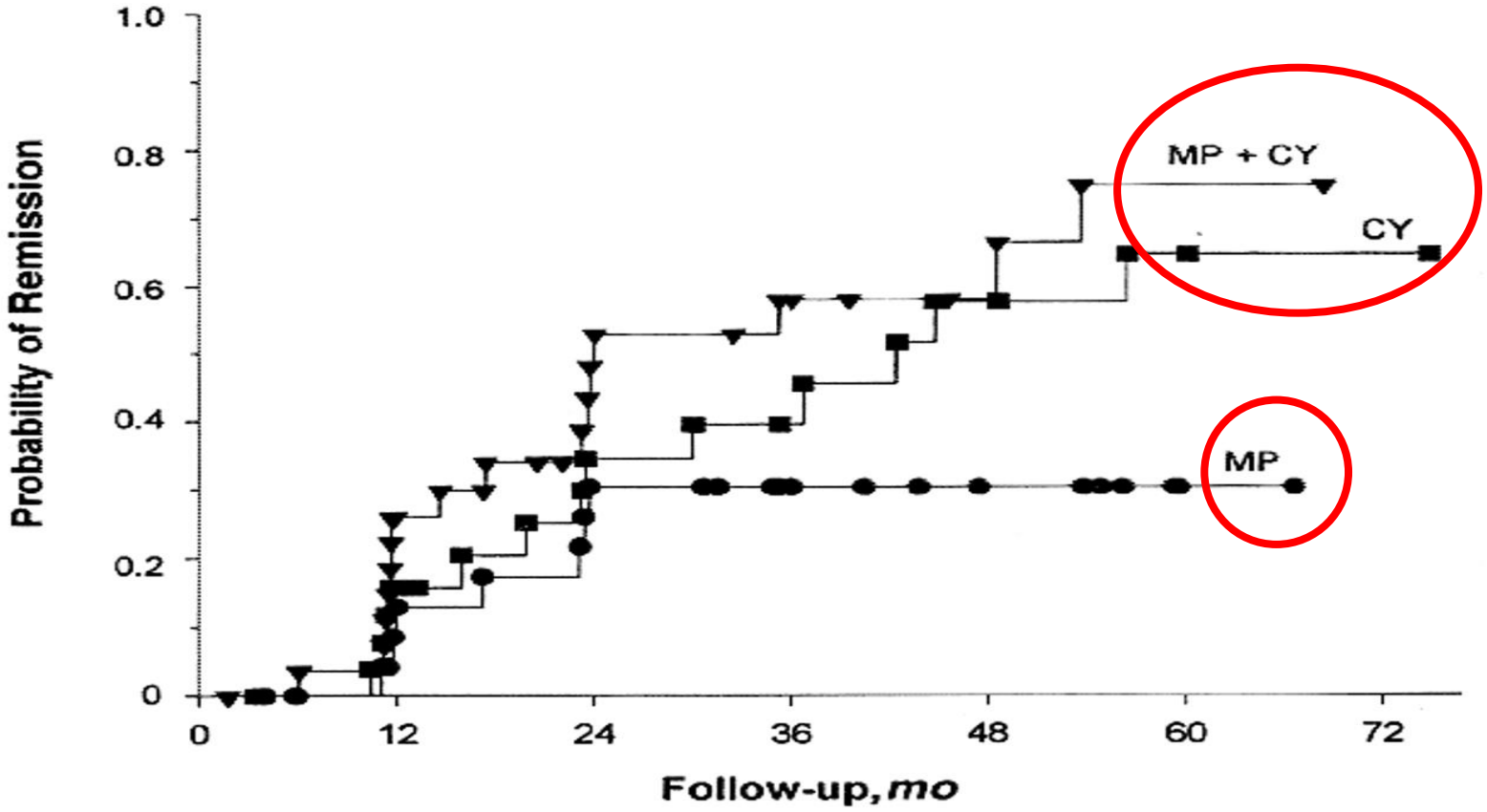
5-year survival

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

CPH increased the remission rate

Number of patients eligible at each year

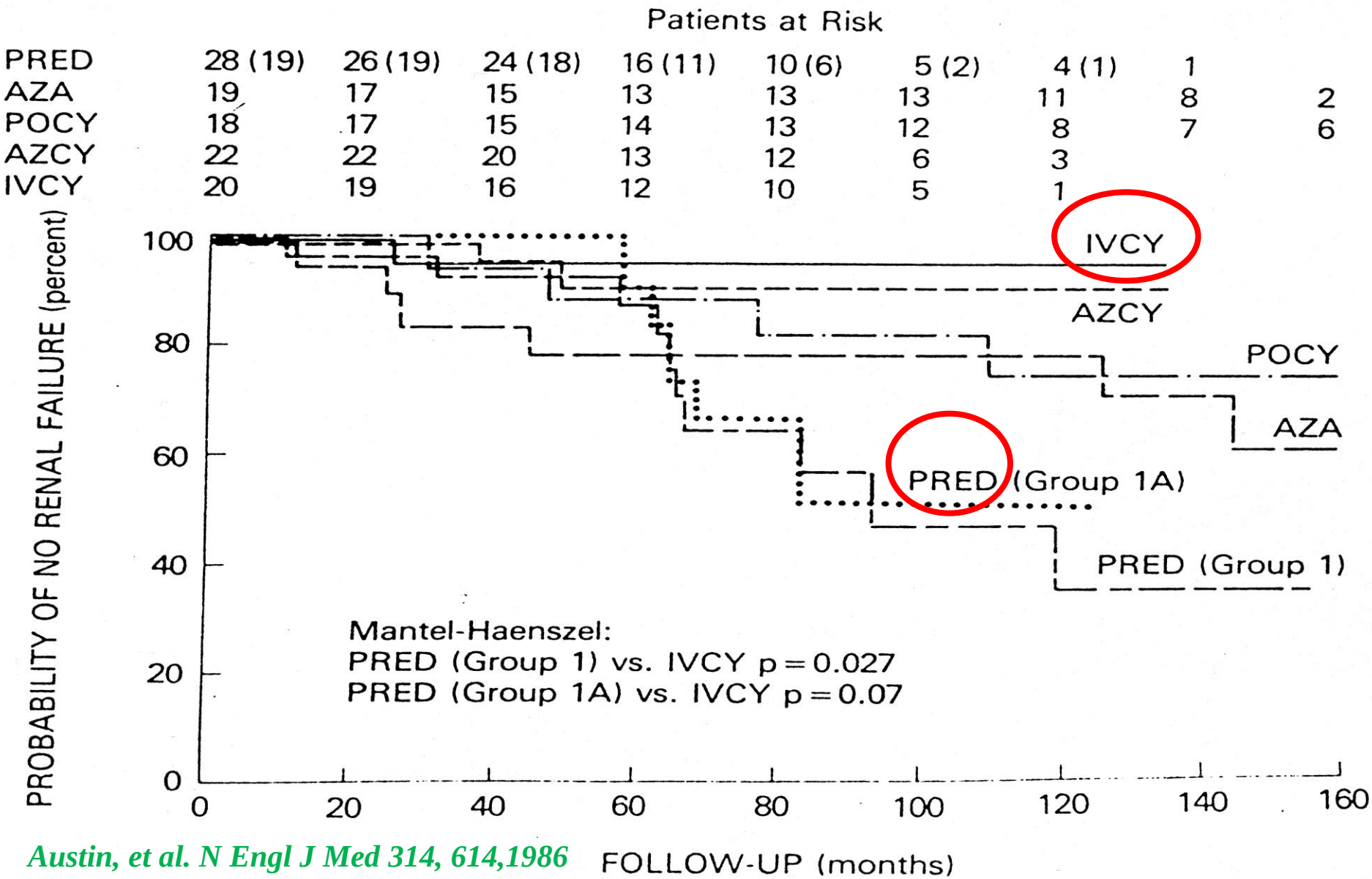
Year	0	1	2	3	4	5
MP + CY	28	19	11	8	5	3
MP	27	20	16	11	6	1
CY	27	21	13	10	7	5



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

Annals of Internal Medicine

Survival without renal failure



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

Induction treatment

(usually 3-6 months)

3 i.v. MP pulses (a 0,5 - 1 g)
Prednisone 0.5 - 1 mg/kg/day

Oral cyclophosphamide 1 -2 mg/kg/day
Pulsed cyclophosphamide 15 mg/kg/2-4 weeks

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

Outcome of pts with (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%

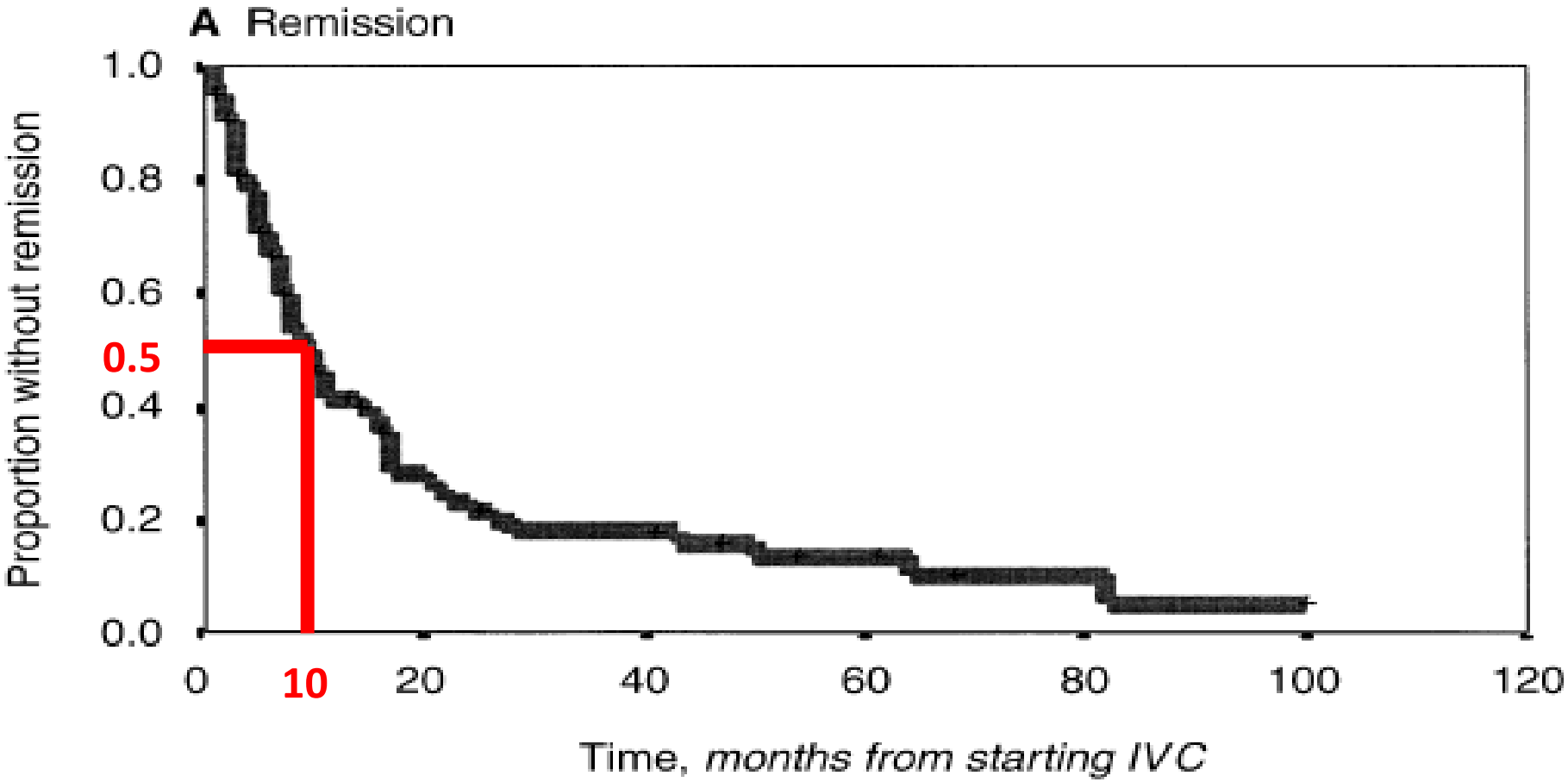
[a] Based on an analysis of the published literature. The number of articles for a given period is shown in parentheses.

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



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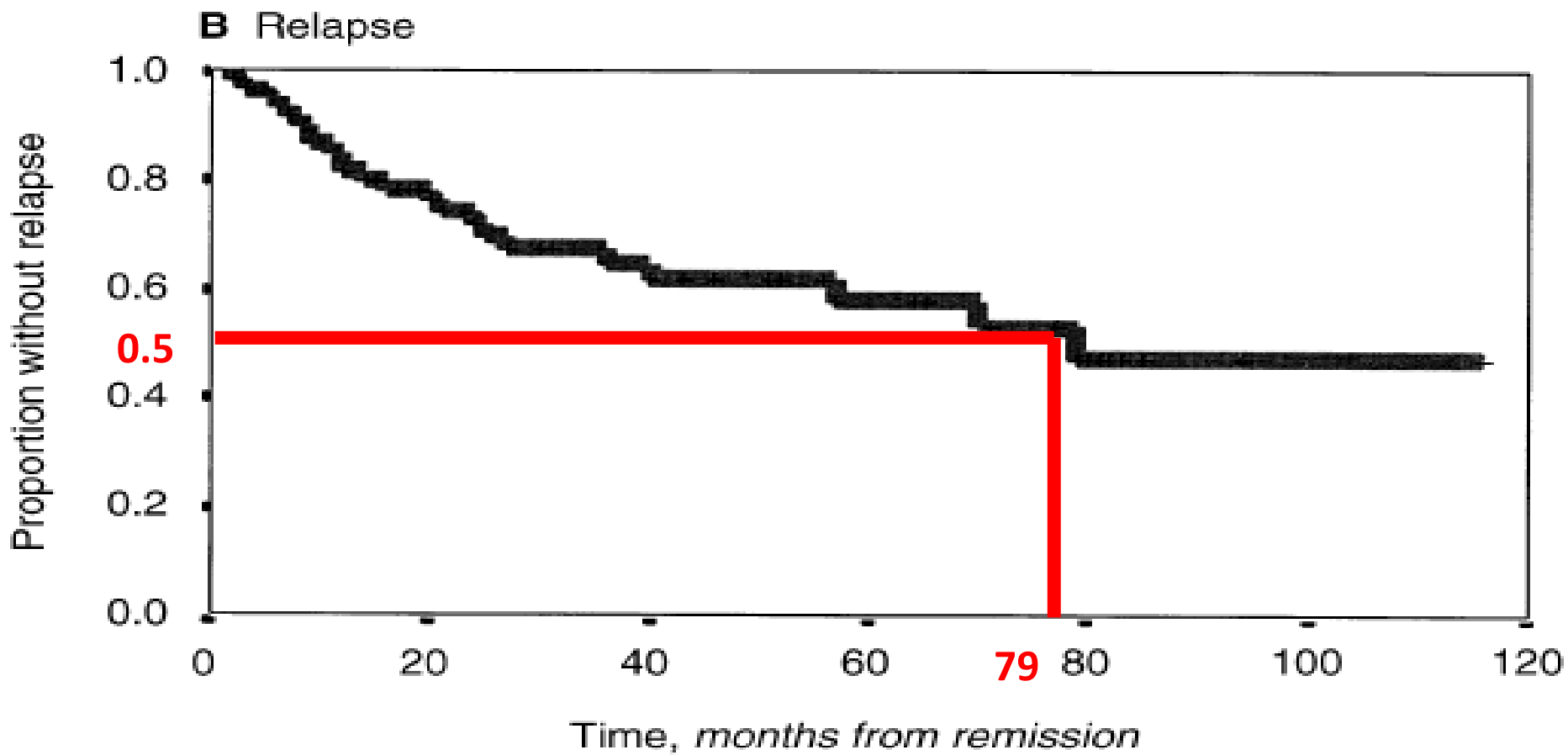
Relapses were frequent and median time to relapse was 79 months

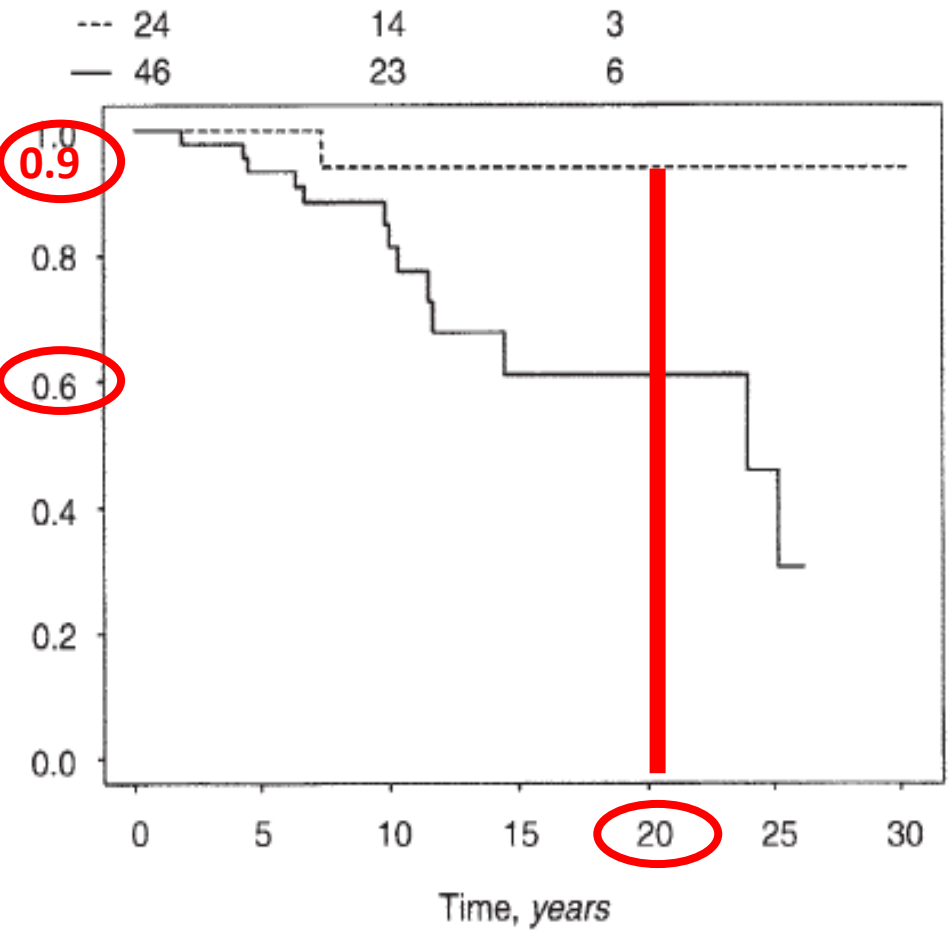


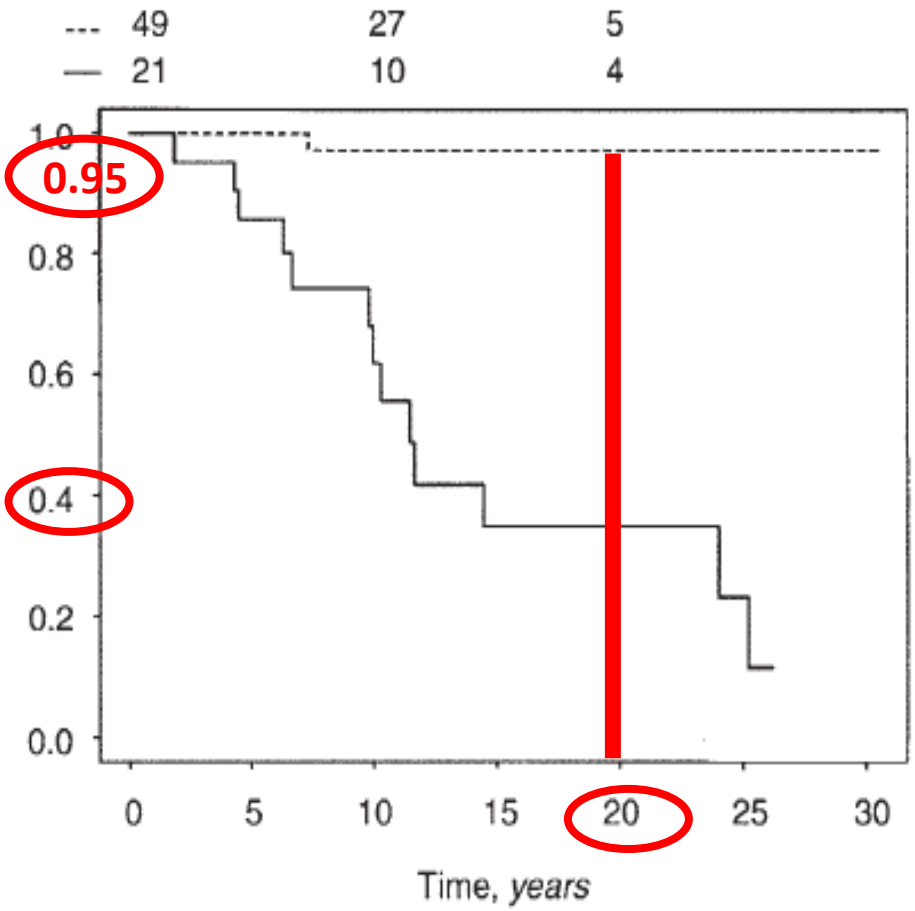
"Nephritic flares" are predictors of bad long-term renal outcome in lupus nephritis

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





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

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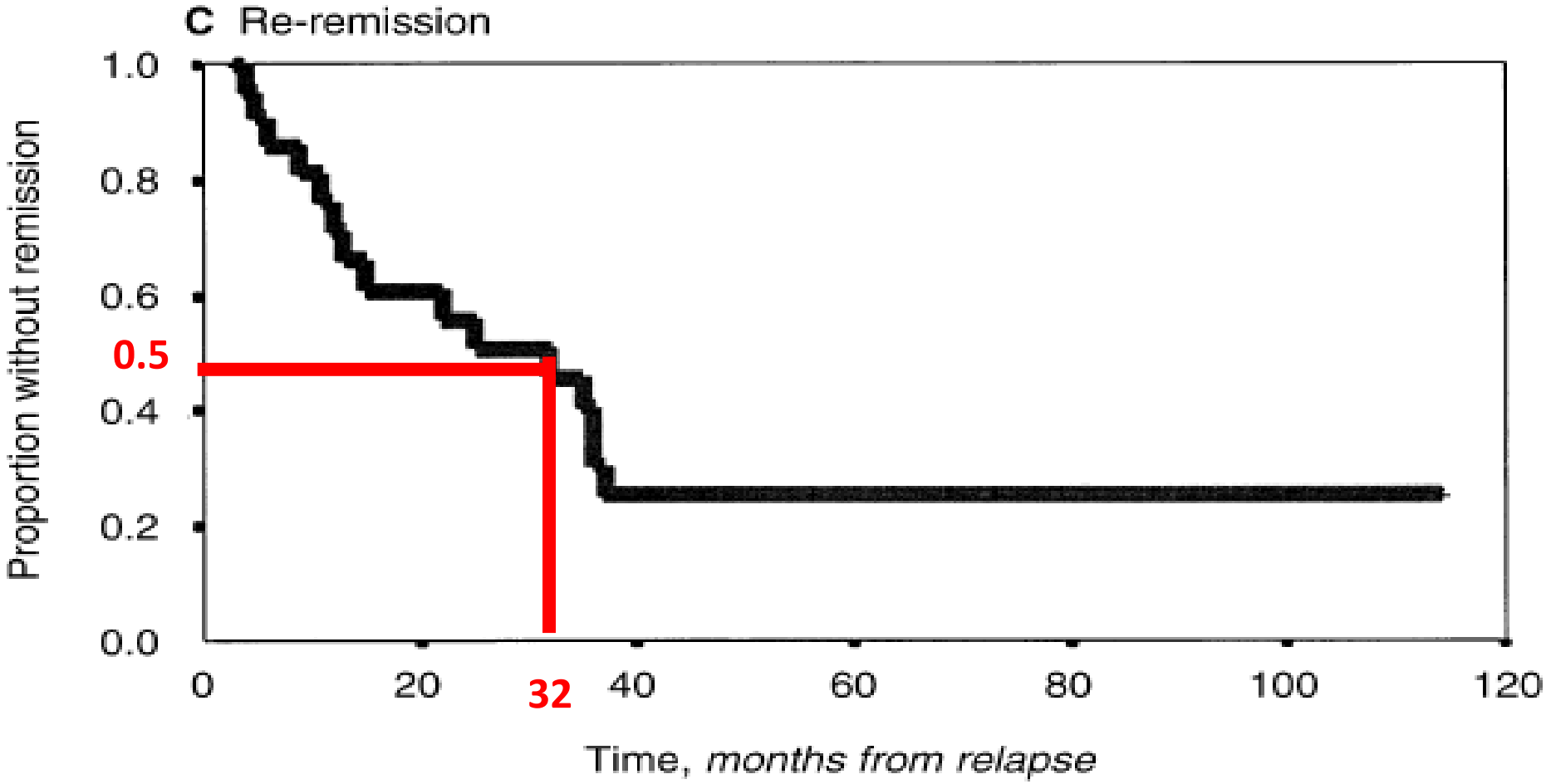
To induce remission in relapsing patients was more difficult and median time to re-remission was 32 months



(N Engl J Med 1986; 314:614-9.)

THERAPY OF LUPUS NEPHRITIS

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 2 Non-Renal Deaths According to Treatment Group

TREATMENT GROUP	NO. OF PATIENTS	CAUSE OF DEATH
Prednisone	3	Sepsis, central nervous system lupus (2 patients)
Azathioprine	2	Sepsis, suicide
Oral cyclophosphamide	2	*Pneumocystis carinii* pneumonia, pulmonary embolus
Oral azathioprine plus cyclophosphamide	3	Thrombotic thrombocytopenic purpura, central nervous system lupus, pulmonary hemorrhage
Intravenous cyclophosphamide	3	Sepsis, epiglottitis, sudden death

(N Engl J Med 1986; 314:614-9.)

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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

Incidence of ovarian failure in systemic lupus erythematosus after treatment with pulse cyclophosphamide

Annals of the Rheumatic Diseases 1996; **55:** 224–229

Elizabeth M McDermott, Richard J Powell

In 35 pts with SLE treated with pulse CPH (31.4% with LN) between 1987-1995

54% of pts developed ovarian failure (premature menopause)

Table 4 Differences in cyclophosphamide (CY) treatment between those who continued to menstruate and those who developed ovarian failure

	Menstruating group	*Ovarian failure group*
Duration of treatment (months)	5·63 (0·5–14·5)	9·45 (1–28·5)
Age at start of treatment (yr)		
< 30	8	3
30–39	7	9
≥ 40	1	7
Dose of CY (mg)	11750 (3000–20500)	16834 (3000–65250)
Use of the oral contraceptive pill during treatment		
Yes	4	2
No	11	17

Ovarian failure in systemic lupus erythematosus patients treated with pulsed intravenous cyclophosphamide

GE Katsifis and AG Tzioufas*

Lupus (2004) 13, 673–678

Incidence of ovarian failure in SLE pts treated with pulsed CPH (13 – 59% of pts)

Table 1 Summary of the risk of sustained amenorrhea after cyclophosphamide treatment from various published studies

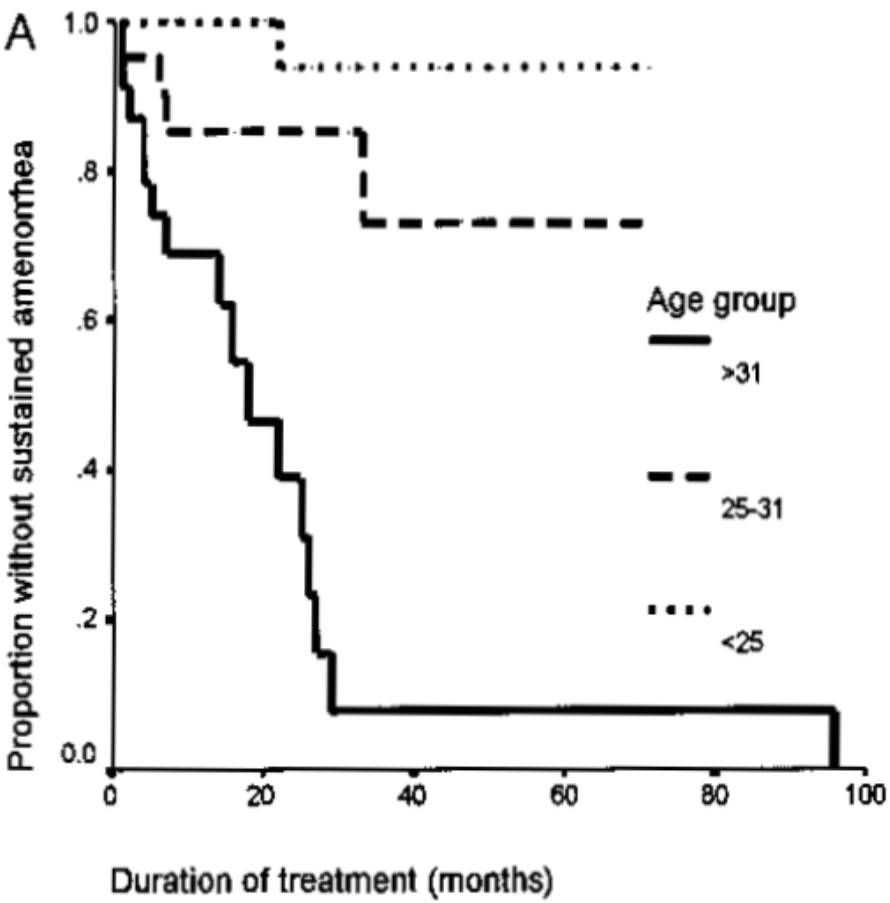
Reference	*No. of patients studied*	*Route of CYC administration*	*Regimen*	*Incidence of ovarian failure %*
Warne *et al.* [11]	20	Oral	25–200 mg day	55
Kumar *et al.* [12]	8	Oral	3 mg/kg/day	25
Uldall *et al.* [13]	34	Oral	40–120 mg day	50
Langevitz *et al.* [14]	17	IV pulse	10 mg/kg every 7–14 days, followed by monthly pulses	24
Wang *et al.* [15]	92	Oral	1–2 mg/kg/day	27
McDermort and Powell[16]	35	IV pulse	1 gm weekly for 4 weeks, then every other week for 8 weeks, then monthly for 3 months	54
Boumpas *et al.* [1]	39	IV pulse	Short CYC: 0.5–1 g/m^2 monthly for 7 doses	12
			Long CYC: 0.5–1 g/m^2 monthly for >15 doses	39
Belmont *et al.* [17]	27	IV pulse	0.5–1 g/m^2 monthly for 6 months, followed by a pulse once every 3 months	11
Austin *et al.* [3]	33	IV pulse	0.5–1 g/m^2 once every 3 months	45
		Oral	CYC 1–4 mg/kg/day or CYC 50 mg/day combined with AZA 50 mg/day	59
Mok *et al.* [18]	54	IV pulse	0.5–1 g/m^2 monthly for 6 months, followed by a pulse once every 3 months	13
	16	Oral	1–2 mg/kg/day	30
Ioannidis *et al.* [19]	67	IV pulse	0.5–1 g/m^2 monthly for 6 months, followed by a pulse once every 2 months for 12 months, and then a pulse every 3 months for another year	30

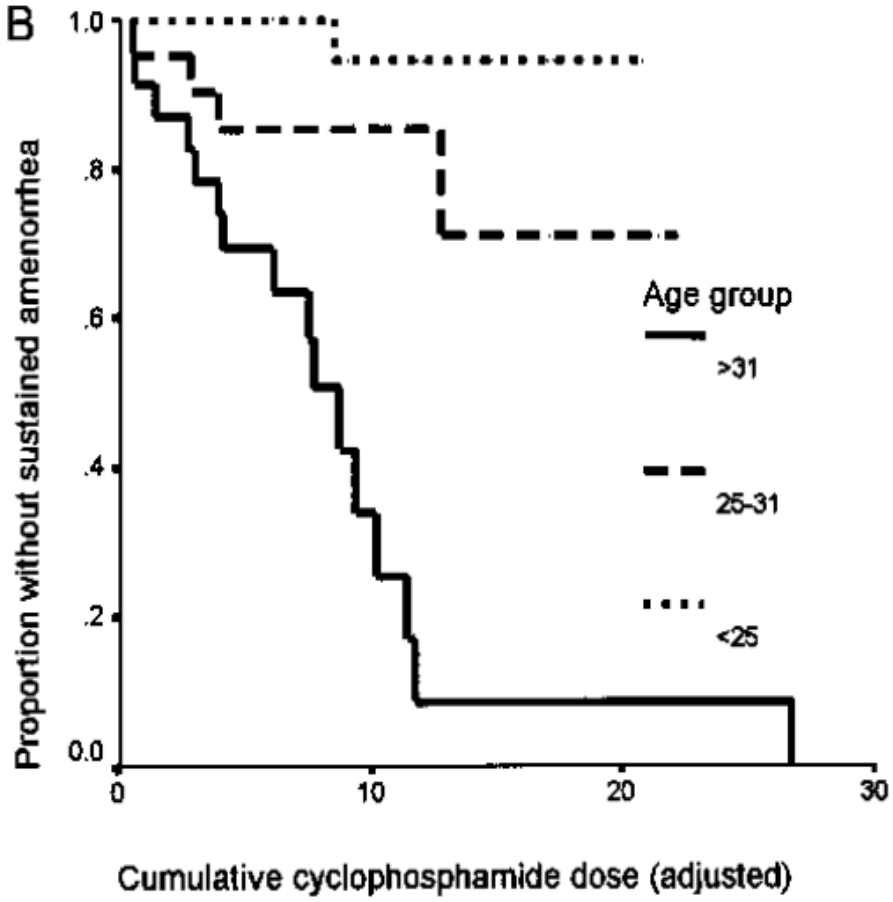
Predictors of Sustained Amenorrhea from Pulsed Intravenous Cyclophosphamide in Premenopausal Women with Systemic Lupus Erythematosus

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





Treatment of proliferative lupus nephritis: a slowly changing landscape

Vladimir Tesar and Zdenka Hruskova

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

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

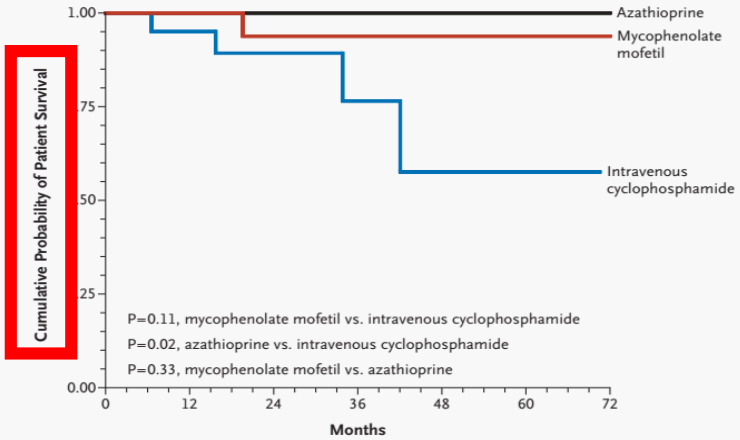
Sequential Therapies for Proliferative Lupus Nephritis

N ENGL J MED 350;10 WWW.NEJM.ORG MARCH 4, 2004

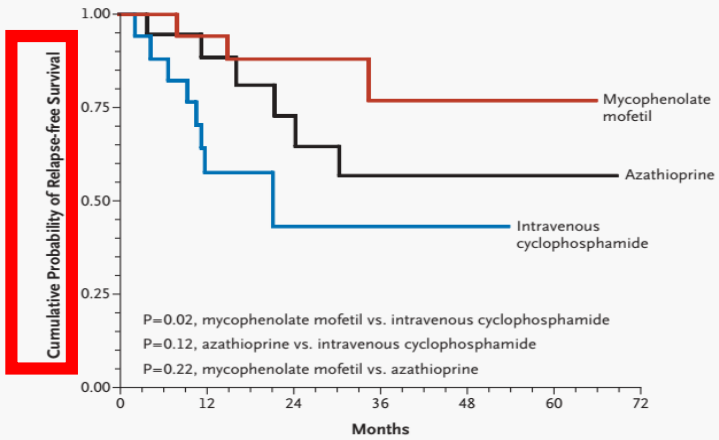
Gabriel Contreras, M.D., M.P.H., Victoriano Pardo, M.D., Baudouin Leclercq, M.D., Oliver Lenz, M.D., Elaine Tozman, M.D., Patricia O'Nan, R.N., and David Roth, M.D.

59 pts with LN (mostly III and IV) induced into remission with high-dose CPH pulses randomized to AZA, MMF, or quartely PHD pulses

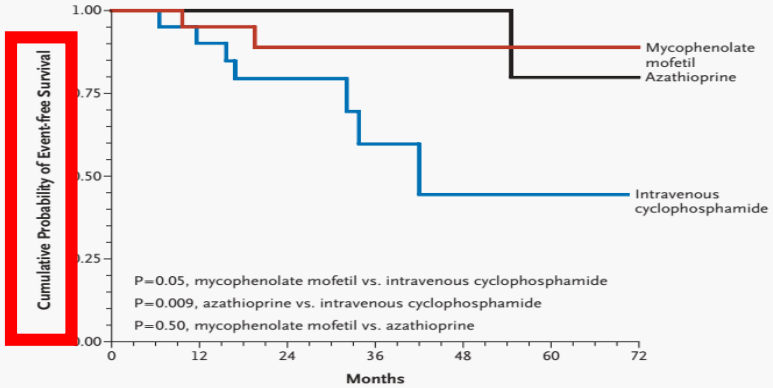
Quarterly iv CPH inferior in terms of survival, event-free and relapse-free survival



No. at Risk							
Azathioprine	19	19	15	10	9	4	2
Intravenous cyclophosphamide	20	19	12	6	3	2	1
Mycophenolate mofetil	20	20	14	11	6	2	2



No. at Risk							
Azathioprine	19	15	10	6	4	3	1
Intravenous cyclophosphamide	17	10	4	2	2	1	1
Mycophenolate mofetil	19	17	12	8	3	2	1



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N ENGL J MED 350;10 WWW.NEJM.ORG MARCH 4, 2004

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Amenorrhea, infections, nausea and vomiting more frequent in ivCPH vs. AZA and MMF

Table 3. Rates of Amenorrhea, Infections, and Other Adverse Events during Maintenance Therapy.*

Adverse Event	Azathioprine Group	Mycophenolate Mofetil Group	Cyclophosphamide Group	P Value for Comparison with Azathioprine	P Value for Comparison with Mycophenolate Mofetil
		percent			
Amenorrhea†	8	6	32	0.03	0.03
Infection					
Total	29	32	77	0.002	0.005
Major	2	2	25	0.01	0.02
Pneumonia	2	2	15	0.05	0.06
Sepsis with bacteremia	0	0	8	—	—
Meningitis	0	0	3	—	—
Minor	28	30	52	0.06	0.11
Upper respiratory tract	22	14	32	0.34	0.08
Urinary tract	2	10	3	0.83	0.20
Herpes zoster	4	6	17	0.05	0.13
Leukopenia‡	6	2	10	0.43	0.15
Nausea§	7	14	65	<0.001	<0.001
Vomiting§	4	10	55	<0.001	<0.001
Diarrhea	9	12	12	0.97	0.63

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1. Efficacy and toxicity of high-dose cyclophosphamide
2. **Mycophenolate mofetil and calcineurin inhibitors in LN**
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Treatment of proliferative lupus nephritis: a slowly changing landscape

Vladimir Tesar and Zdenka Hruskova

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

Table 2 | Selected studies of maintenance treatment in proliferative lupus nephritis

Study	Patients	Race/ethnicity	Proliferative LN class	Follow-up duration	Results	Adverse events
MMF vs AZA vs intravenous CyA						
Contreras *et al.* (2004)[68]	Patients who achieved remission with i.v. CYC randomized to AZA (n=19), MMF (n=20), or i.v. CYC (n=20)	29 Hispanic, 27 black, 3 white	46 class IV, 12 class III, 1 class Vb	72 months	Event-free survival rate*: higher in MMF and AZA than CYC; relapse-free survival: higher in MMF vs CYC (P=0.02)	Infections, severe infections, amenorrhea, nausea and vomiting more frequent with CYC
MMF vs AZA						
Houssiau *et al.* (2009)[74]	105 patients who achieved remission with Euro-Lupus regimen randomized to MMF or AZA	Mainly white	Class III, IV, Vc, or Vd	53 months	No difference in time to renal flare and severe systemic flare	Infectious side effects similar; hematological cytopenias more frequent with AZA (P=0.03)
Wofsy *et al.* (2010)[67]	Patients who achieved treatment response in ALMS were randomized to MMF (n=116) or AZA (n=111)	43% white, 10% black, 33% Asian, 13% other	Not available	36 months	MMF superior to AZA in primary end point‡ (P=0.003), regardless of induction treatment	No difference in treatment-emergent adverse events, including infections
CyA vs AZA						
Moroni *et al.* (2006)[73]	Patients in remission after CYC induction randomized to CyA (n=36) or AZA (n=33)	100% white	60 class IV, 9 class Vc or Vd	4 years	7 vs 8 flares (n.s.); no difference in proteinuria and SCr at end of follow-up	Minor infections and leukopenia more frequent with AZA; gastrointestinal disorders and arthralgias more frequent with CyA

Treatment of diffuse proliferative LN
MMF vs. CPH

Chan TM et al N Engl J Med 343,1156,2000

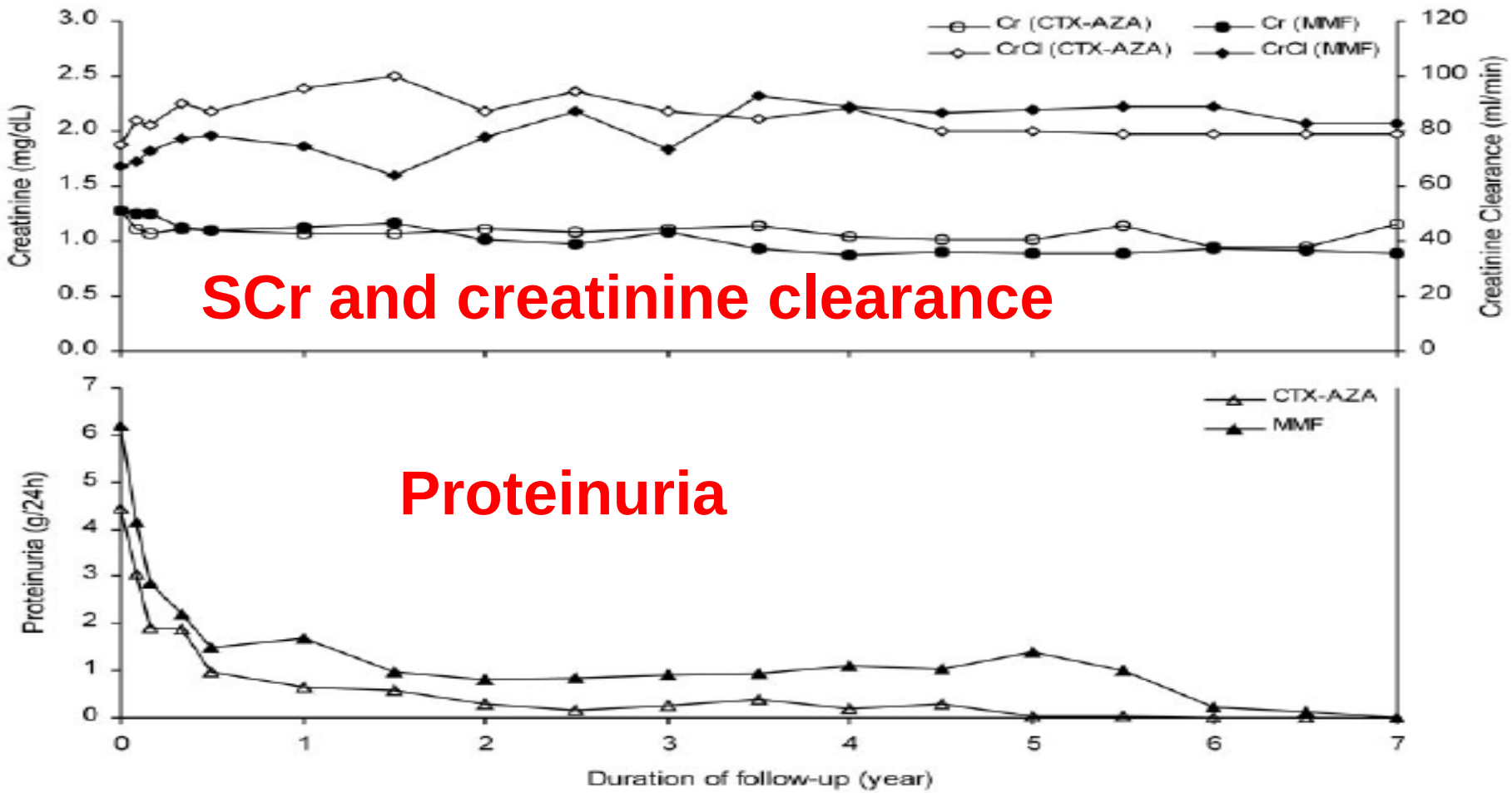
64 Chinese pts randomized to either:

MMF (2g/day 6 months,
followed by 1g/day
for further 6 months)
vs.
Oral cyclophosphamide 6 months followed
by
AZA for further 6 months

Long-Term Study of Mycophenolate Mofetil as Continuous Induction and Maintenance Treatment for Diffuse Proliferative Lupus Nephritis

Tak-Mao Chan, Kai-Chung Tse, Colin Siu-On Tang, Mo-Yin Mok, and Fu-Keung Li, for the Hong Kong Nephrology Study Group

J Am Soc Nephrol 16: 1076-1084, 2005.



Long-term follow-up (63 months)

Chan et al., J. Am. Soc. Nephrol., 2005, 16:1076

	MMF	CPH-Aza	P
Patients	33	31	
ESRD/death	0	4	0.062
Doubling of Scr	2	3	
Relapses	9	11	
Infections	4 (12.5%)	12 (40%)	0.013

Mycophenolate Mofetil or Intravenous Cyclophosphamide for Lupus Nephritis

Ellen M. Ginzler, M.D., M.P.H., Mary Anne Dooley, M.D., M.P.H., Cynthia Aranow, M.D., Mimi Y. Kim, Sc.D., Jill Buyon, M.D., Joan T. Merrill, M.D., Michelle Petri, M.D., M.P.H., Gary S. Gilkeson, M.D., Daniel J. Wallace, M.D., Michael H. Weisman, M.D., and Gerald B. Appel, M.D.

N Engl J Med 2005;353:2219-28.

MMF compared with high-dose pulsed CPH also in multiethnic US population

Table 1. Characteristics of Patients at the Beginning of Induction Therapy.*

Characteristic	Mycophenolate Mofetil (N=71)	Intravenous Cyclophosphamide (N=69)	P Value†
Age — yr	32.5±10.0	31.0±9.0	0.35
Female sex — no. (%)	61 (86)	65 (94)	0.10
Duration of SLE — mo	43.7±66.9	58.7±80.6	
Race or ethnic group — no. (%)‡			0.38
Black	43 (61)	36 (52)	0.32
White	12 (17)	12 (17)	0.94
Hispanic	10 (14)	18 (26)	0.08
Asian	6 (8)	2 (3)	0.16
Other		1	
Renal biopsy according to WHO class — no. (%)§			0.99
III	11 (15)	11 (16)	0.94
IV	39 (55)	37 (54)	0.88
V	14 (20)	13 (19)	0.90
Mixed membranoproliferative	7 (10)	8 (12)	0.74

Mycophenolate Mofetil or Intravenous Cyclophosphamide for Lupus Nephritis

Ellen M. Ginzler, M.D., M.P.H., Mary Anne Dooley, M.D., M.P.H., Cynthia Aranow, M.D., Mimi Y. Kim, Sc.D., Jill Buyon, M.D., Joan T. Merrill, M.D., Michelle Petri, M.D., M.P.H., Gary S. Gilkeson, M.D., Daniel J. Wallace, M.D., Michael H. Weisman, M.D., and Gerald B. Appel, M.D.

N Engl J Med 2005;353:2219-28.

	MMF 3 g/ day 6 months	CPH 1g /month 6 months	p
Patients	71	69	
Complete remission	14	4	0.014
Complete and partial remission	21	14	0.034

Mycophenolate mofetil as induction and maintenance therapy for lupus nephritis: rationale and protocol for the randomized, controlled Aspreva Lupus Management Study (ALMS)

A Sinclair[1], G Appel[2], MA Dooley[3], E Ginzler[4], D Isenberg[5], D Jayne[6], D Wofsy[7] and N Solomons[1]*

Lupus (2007) 16, 972–980

Phase III study randomised 358 pts with LN to induction treatment either with MMF (3 g/day, minimum 2 g/day), or CPH (0.5 – 1 g/m2) in combination with CS

Patients in remission again randomised to maintenance treatment either with MMF or AZA, in combination with CS

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

Mycophenolate more effective only in other (mostly black) patients

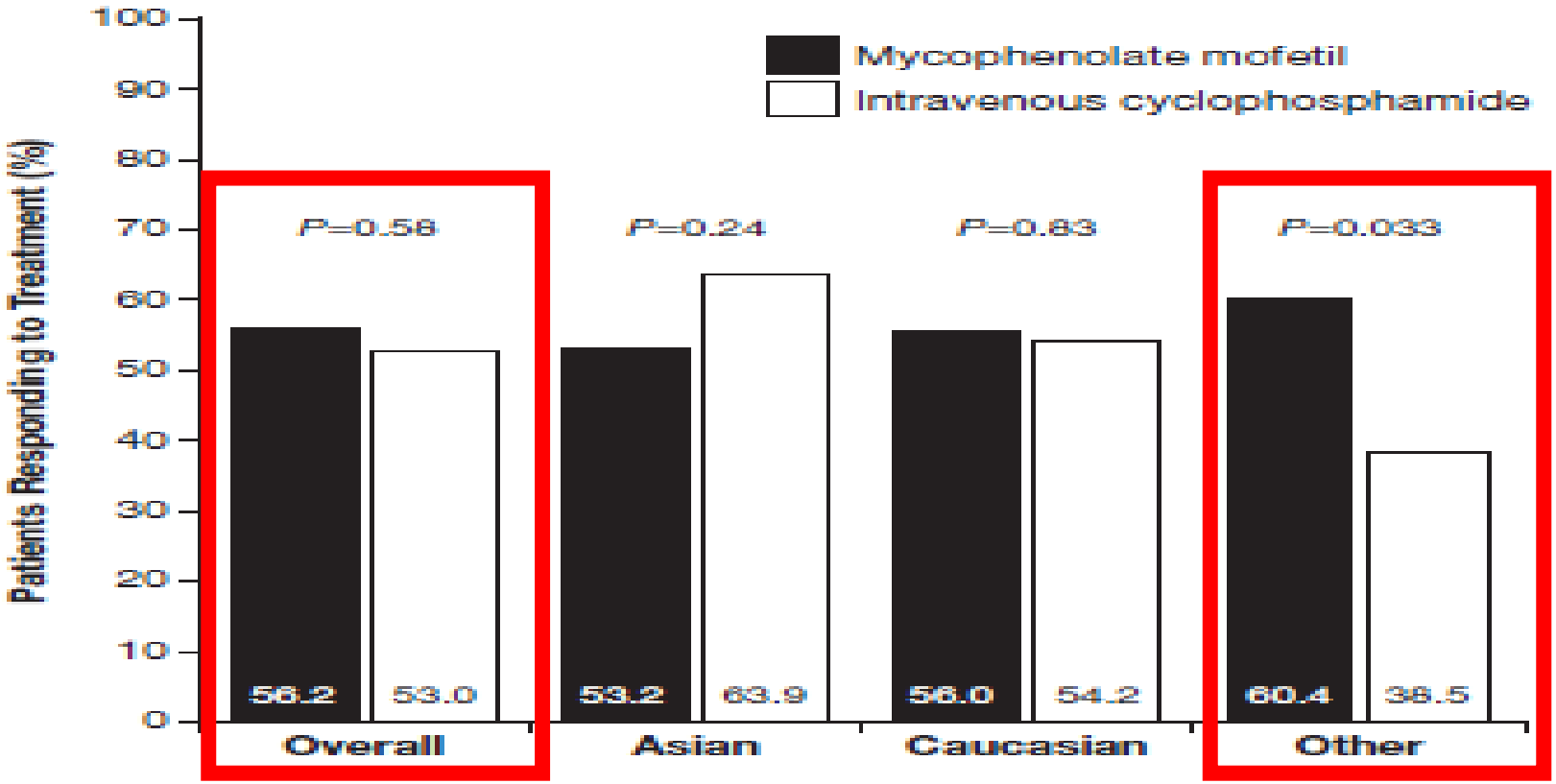


Figure 2. Response rates of study population and by racial group.

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

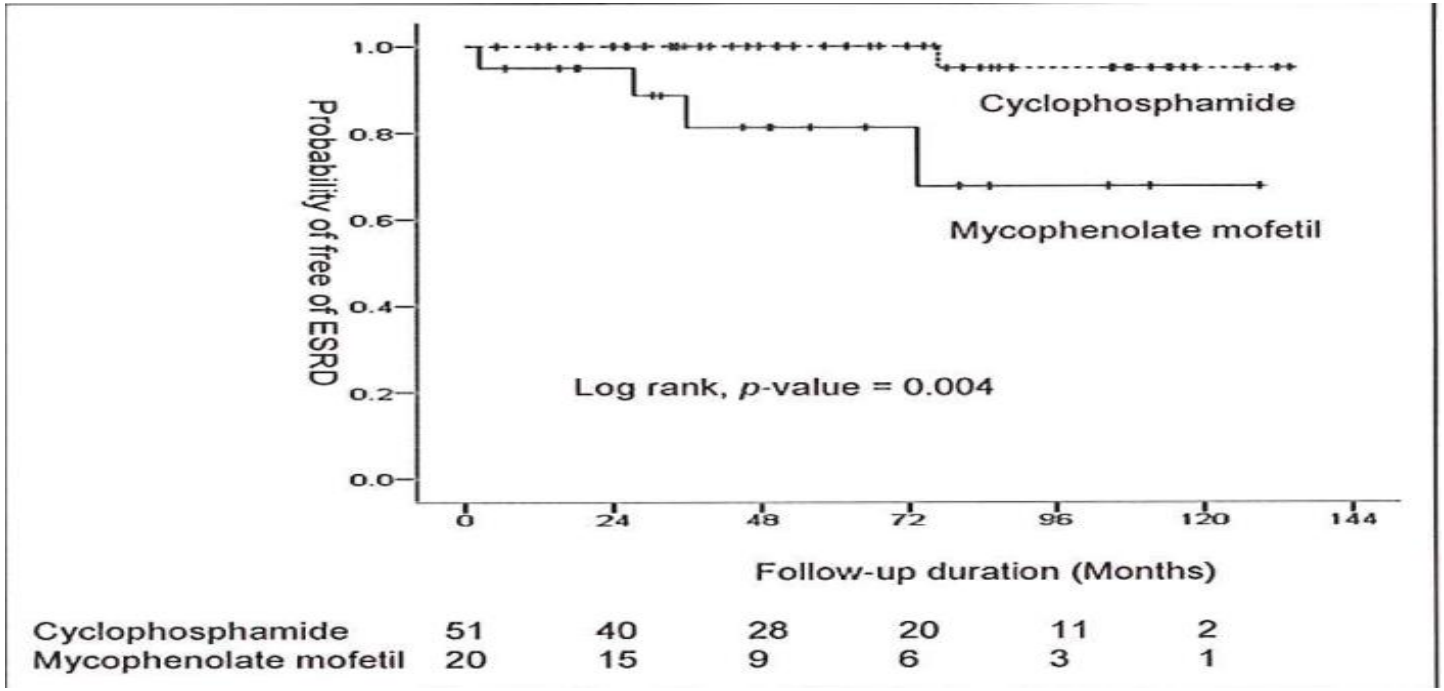
Lupus (2011) 20, 1442–1449

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%)	



Lupus Nephritis: Induction Therapy in Severe Lupus Nephritis—Should MMF Be Considered the Drug of Choice?

Clin J Am Soc Nephrol 8: 147–153, 2013.

Brad H. Rovin, Samir V. Parikh,* Lee A. Hebert,* Tak Mao Chan,† Chi Chiu Mok,‡ Ellen M. Ginzler,§ Lai Seong Hooi,‖ Paul Brunetta,¶ Romeo Maciuca,¶ and Neil Solomons***

Renal outcome in CPH and MMF treated patients

	CPH	MMF	
ESRD-free surival at 5 years			
Koo et al., 2011	100%	81%	p = 0.04
Treatment failure at 3 years (death, ESRD, doubling of SCr, flare, need for rescue medication	4.7% (MMF)	10% (MMF)	p = n.s.
Dooley et al., 2011	14.5% (AZA)	20.1% (AZA)	p= n.s.

Lupus Nephritis: Induction Therapy in Severe Lupus Nephritis—Should MMF Be Considered the Drug of Choice?

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Conclusions

The bulk of the existing data suggests that, in the short term, MMF and intravenous or oral cyclophosphamide are equally effective induction therapies for severe LN, with severity defined histologically or as impaired kidney function. However, these definitions of severity are imperfect, and a more explicit definition, including levels of kidney function and histologic injury, may reveal short-term differences. Long-term kidney outcome data, while limited, suggest that cyclophosphamide may preserve renal function better than MMF. On this basis, we suggest that MMF cannot yet be considered the drug of choice for induction therapy of severe LN. Studies to examine this

Successful Treatment of Class V+IV Lupus Nephritis with Multitarget Therapy

J Am Soc Nephrol 19: 2001–2010, 2008.

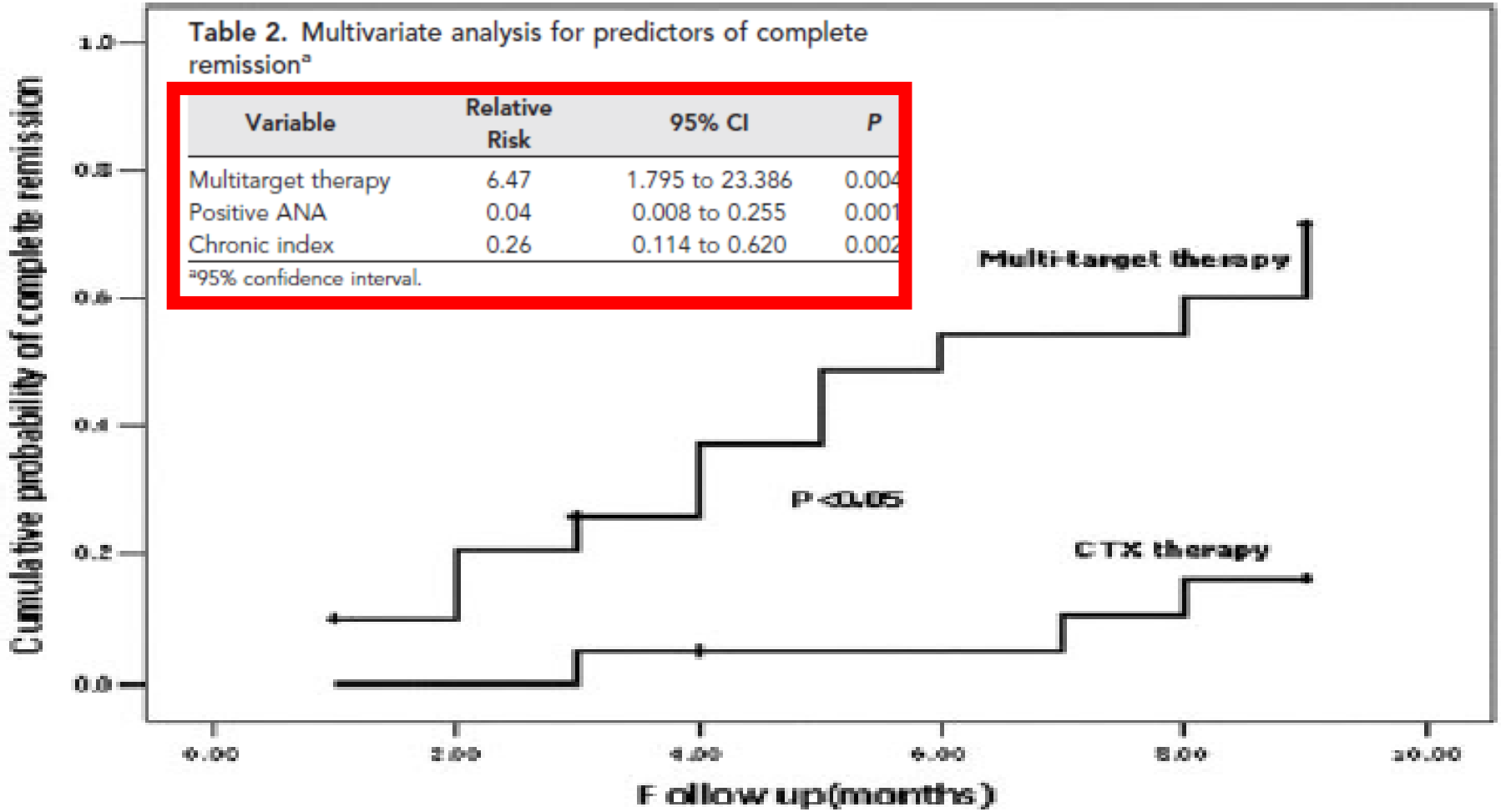
Hao Bao, Zhi-Hong Liu, Hong-Lang Xie, Wei-Xin Hu, Hai-Tao Zhang, and Lei-Shi Li

Treatment with CPH pulses and CS compared in 40 pts with IV+V LN with the combination of MMF, tacrolimus and CS, completete remission much more frequent in pts on multitarget treatment

Table 2. Multivariate analysis for predictors of complete remission[a]

Variable	Relative Risk	95% CI	P
Multitarget therapy	6.47	1.795 to 23.386	0.004
Positive ANA	0.04	0.008 to 0.255	0.001
Chronic index	0.26	0.114 to 0.620	0.002

[a]95% confidence interval.



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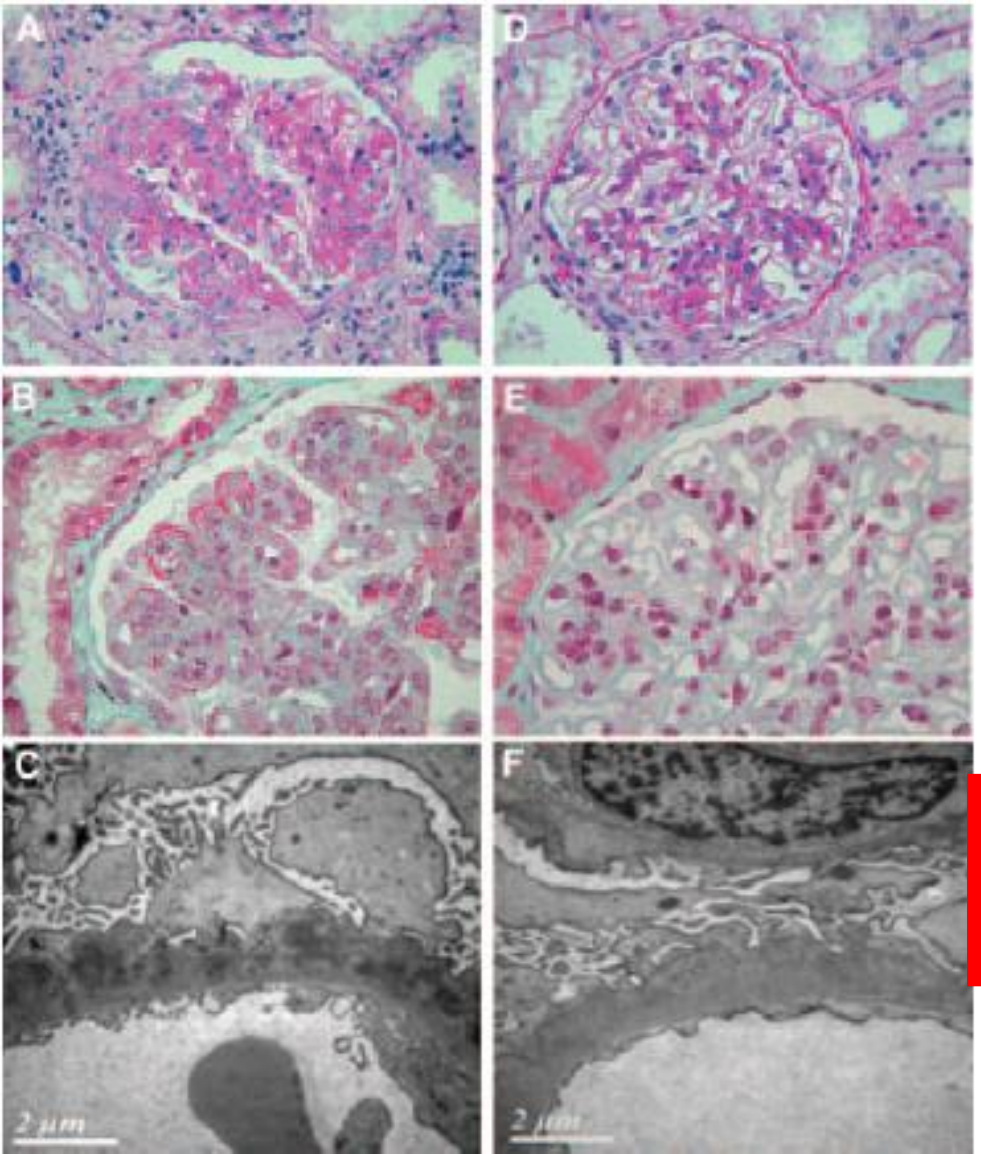


On rebiopsy ↓ activity and less expressed ↑ chronicity in pts on multitarget therapy

Table 5. Pathological changes after the induction therapy

Parameter	Before Therapy	After Therapy	Difference (95% CI)	P
CR (n = 9)[a]				
Active index	10.6 ± 5.0	3.7 ± 2.1	6.9 (4.1 to 9.7)	0.000
Chronic index	0.7 ± 0.5	1.7 ± 0.7	−1.0 (−1.8 to −0.1)	0.028
Not CR (n = 6)[b]				
Active index	7.3 ± 2.6	4.5 ± 4.7	2.8 (−4.2 to 9.8)	0.346
Chronic index	1.6 ± 0.5	4.2 ± 2.3	−2.5 (−4.7 to −0.3)	0.032

Multitarget Therapy for Induction Treatment of Lupus Nephritis

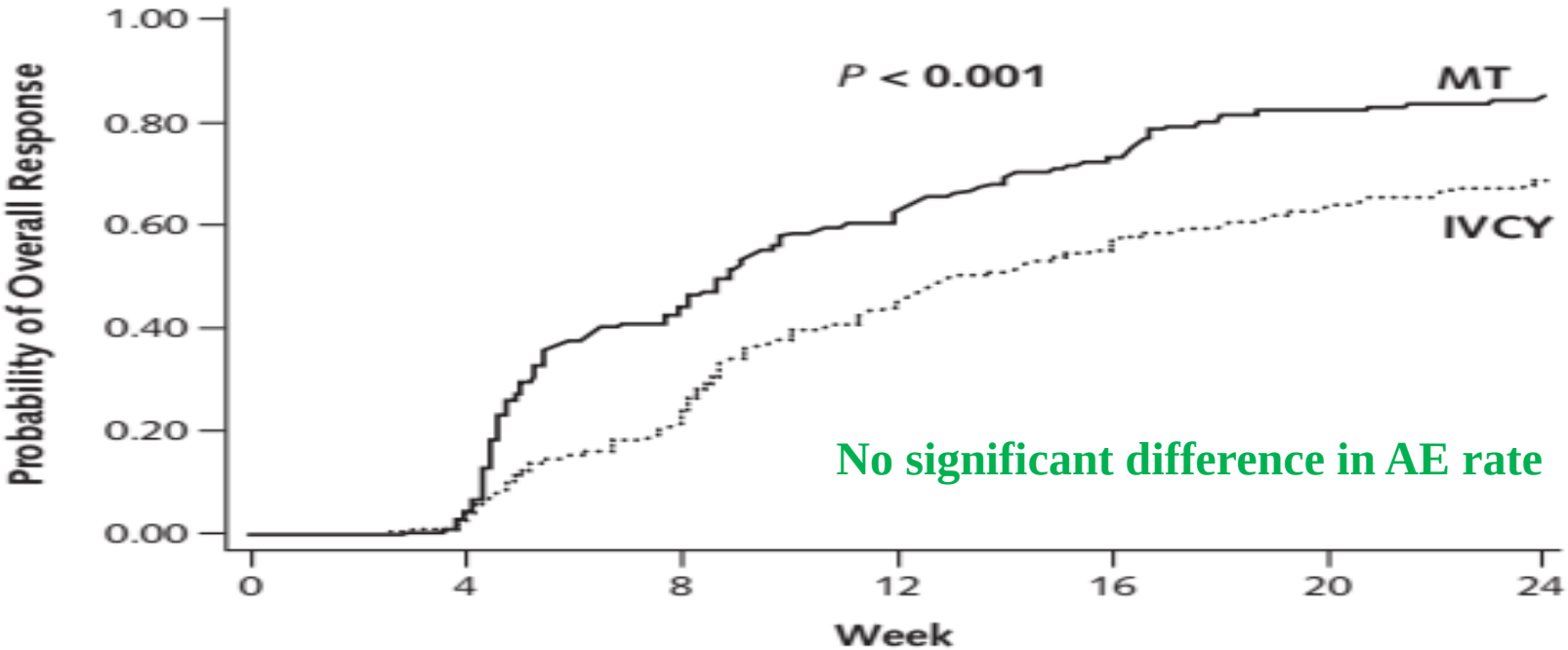
A Randomized Trial

Ann Intern Med. 2015;162:18-26.

Zhihong Liu, MD; Haitao Zhang, MD; Zhangsuo Liu, MD; Changying Xing, PhD; Ping Fu, MD; Zhaohui Ni, MD; Jianghua Chen, MD; Hongli Lin, MD; Fuyou Liu, MD; Yongcheng He, MD; Yani He, MD; Lining Miao, MD; Nan Chen, MD; Ying Li, MD; Yong Gu, MD; Wei Shi, MD; Weixin Hu, MD; Zhengzhao Liu, MD; Hao Bao, MD; Caihong Zeng, PhD; and Minlin Zhou, MD

368 Chinese pts with (mostly class III-IV) LN randomized to either multitarget therapy TAC 4 mg/day, MMF 1g/day and CS, or iv CPH (0.75 g/m2 each 4 weeks) and CS

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



No significant difference in AE rate

Patients at risk, *n*							
MT	181	175	98	67	45	29	20
IVCY	181	176	132	91	71	58	45

Multitarget Therapy for Induction Treatment of Lupus Nephritis

A Randomized Trial

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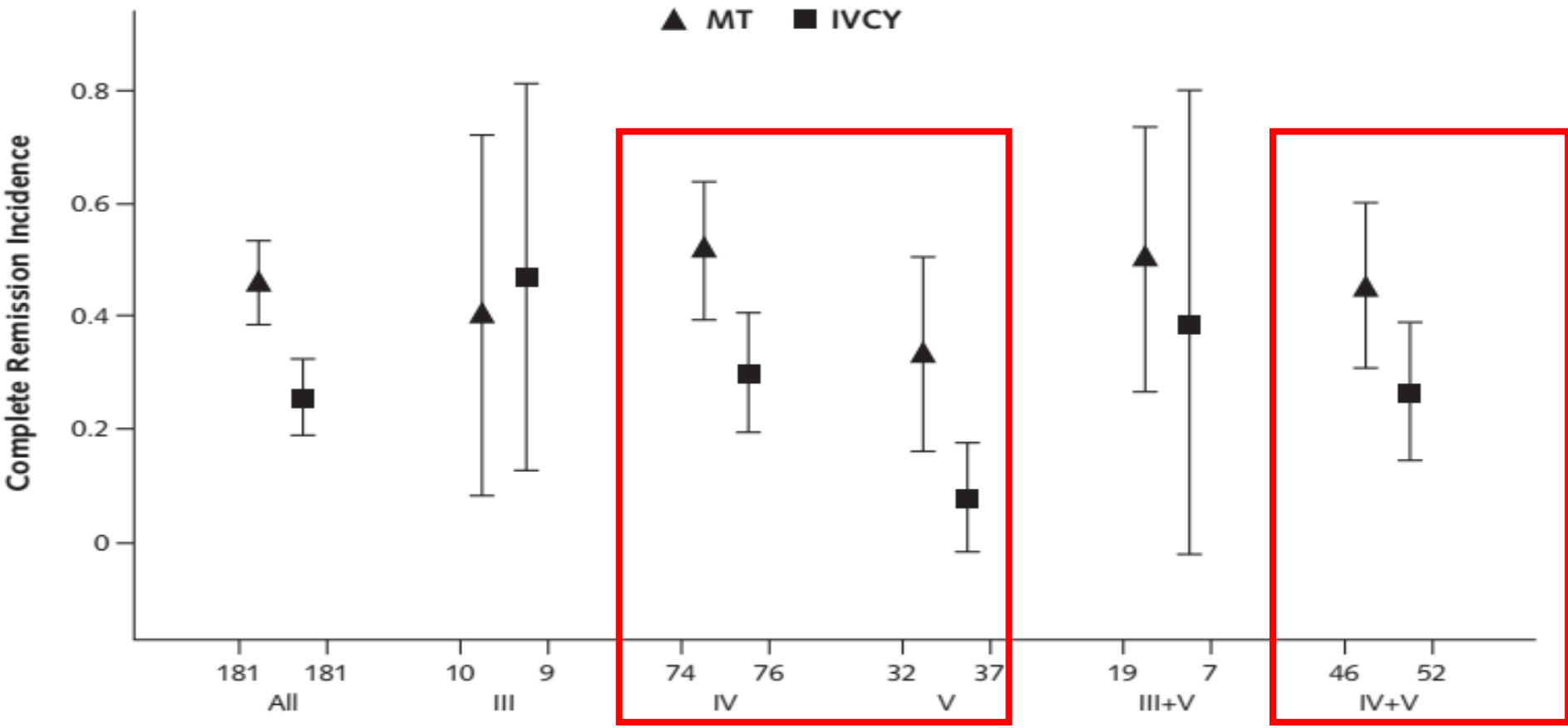
Efficacy of multitarget therapy present over all classes of LN



Patients, *n*

LN Pathologic Class Subgroup by Treatment

Multitarget Therapy for Induction Treatment of Lupus Nephritis

A Randomized Trial

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368 Chinese pts with (mostly class III-IV) LN randomized to either multitarget therapy TAC 4 mg/day, MMF 1g/day and CS, or iv CPH (0.75 g/m2 each 4 weeks) and CS

Adverse events rate similar in pts on the multitarget therapy

Table 2. Adverse Experience Data for Multitarget Therapy and Intravenous Cyclophosphamide Therapy*

Type of Adverse Event	Multitarget (n = 181), n (%)	Intravenous Cyclophosphamide (n = 181), n (%)
Serious	13 (7.2)	5 (2.8)
Pneumonia	7 (3.9)	1 (0.6)
Varicella zoster virus	2 (1.1)	1 (0.6)
Upper respiratory tract infection	2 (1.1)	0
Skin and soft tissue infection	0	1 (0.6)
Epilepsy	1 (0.6)	0
Septicemia	0	1 (0.6)
Doubling of serum creatinine level	1 (0.6)	0
Pregnant	1 (0.6)	1 (0.6)
All (includes serious)	91 (50.3)	95 (52.5)
Infections	51 (28.2)	46 (25.4)
Varicella zoster virus	12 (6.6)	6 (3.3)
Herpes simplex	3 (1.7)	4 (2.2)
Pneumonia	11 (6.1)	5 (2.8)
Urinary tract infection	3 (1.7)	5 (2.8)
Skin and soft tissue infection	1 (0.6)	4 (2.2)
Upper respiratory tract infection	23 (12.7)	22 (12.2)
Other infections	6 (3.3)	3 (1.7)

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]

40 pts Caucasian pts with proliferative LN randomized to the initial treatment with ivCPH or CyA

Table 1 Baseline characteristics of the patients

Parameter	*CPH* (n = *21*)	*CyA* (n = *19*)	p-*value*
Gender – M/F	6/15	5/14	1.00
LN class – ¾	7/14	9/10	0.37
Pathological activity index	9.3 ± 2.9	9.9 ± 2.8	0.91
Pathological chronicity index	3.5 ± 2.5	4.0 ± 2.4	0.75
Age (years)	30 ± 9	28 ± 5	0.45
Serum creatinine (μmol/l)	83.8 ± 22.7	80.7 ± 22.5	0.66
Creatinine clearance (ml/s/1.73 m^2)	1.46 ± 0.47	1.36 ± 0.42	0.50
Urinary protein excretion/24 hr (g/l)	3.8 ± 4.9	2.5 ± 2.4	0.29
Serum albumin	29.6 ± 6.6	29.9 ± 9.9	0.89
Serum C3 (g/l)	0.54 ± 0.27	0.58 ± 0.27	0.63
Serum C4 (g/l)	0.08 ± 0.04	0.06 ± 0.03	0.17
Systolic blood pressure (mmHg)	127.1 ± 17.3	128.5 ± 12.1	0.77
Diastolic blood pressure (mmHg)	81.2 ± 10.7	80.8 ± 5.6	0.88
SLEDAI	19.9 ± 7.9	19.3 ± 4.5	0.76
Non-renal SLEDAI	10.2 ± 7.1	9.7 ± 3.7	0.79
Hematuria present/absent	16/5	14/5	0.85
Anti-dsDNA positive/negative	15/6	18/1	0.09
Low C3/normal C3	16/5	16/3	0.41
Low C4/normal C4	16/5	16/3	0.41
ACEI or ARB used	10/21	14/19	0.26

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Remission and response comparable, ↓ Pu in CyA limb

Table 2 Outcomes of treatment

Parameter	*Month 9* *CPH (n = 21)*	*CyA (n = 19)*	*p-value*	*Month 18* *CPH (n = 21)*	*CyA (n = 19)*	*p-value*
Remission	5 (24%)	5 (26%)	0.86	3 (14%)	7 (37%)	0.15
Response	11 (52%)	8 (43%)	0.52	8 (38%)	11 (58%)	0.21
Remission or Response criterion met						
– stable/improved serum creatinine	18 (86%)	9 (47%)	0.02	12 (57%)	11 (58%)	0.96
– 50% decrease in urinary protein[a]	13 (62%)	16 (84%)	0.24	11 (52%)	14 (74%)	0.16
– urinary protein <0.3	8 (38%)	13 (68%)	0.06	8 (38%)	14 (74%)	0.02
– inactive urinary sediment	12 (57%)	15 (79%)	0.19	14 (67%)	15 (79%)	0.49
– normal/improved C3	18 (86%)	15 (79%)	0.57	16 (76%)	16 (84%)	0.53
Treatment failure	7 (33%)	3 (16%)	0.28	6 (29%)	3 (16%)	0.46
Treatment failure criterion met						
– serum creatinine (increase >50 μmol/l)	1 (5%)	0 (0%)	1.00	2 (10%)	1 (5%)	1.00
– urinary protein >3.5 g/24 h	2 (9%)	0 (0%)	0.49	2 (10%)	1 (5%)	1.00
– persistent nephritic activity[b]	4 (19%)	3 (16%)	1.00	4 (19%)	1 (5%)	0.34

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

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Leukopenia ↑ in pts on CPH, ↑ BP and temporary ↑ Screat on CyA

Table 4 Adverse events (patients who experienced at least one adverse event)

Parameter	*CPH* n (%)	*CyA* n (%)
Deaths	0 (0%)	0 (0%)
Leukopenia	4 (20%)	2 (11%)
Hair loss	1 (5%)	0 (0%)
Increased facial hair	0 (0%)	1 (5%)
Increased blood pressure	6 (29%)	10 (53%)
Amenorrhea	1 (5%)	0 (0%)
Transient increase in serum creatinine	0 (0%)	3 (16%)
Generalized seizure	0 (0%)	1 (5%)
Herpes Zoster infection	2 (10%)	1 (5%)
Urinary tract infection	1 (5%)	1 (5%)
Sepsis	1 (5%)	0 (0%)
Perianal abscess	0 (0%)	1 (5%)
Transient ischemic attack	0 (0%)	1 (5%)

CPH, cyclophosphamide; CyA, Cyclosporine A.

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

Lupus (2010)

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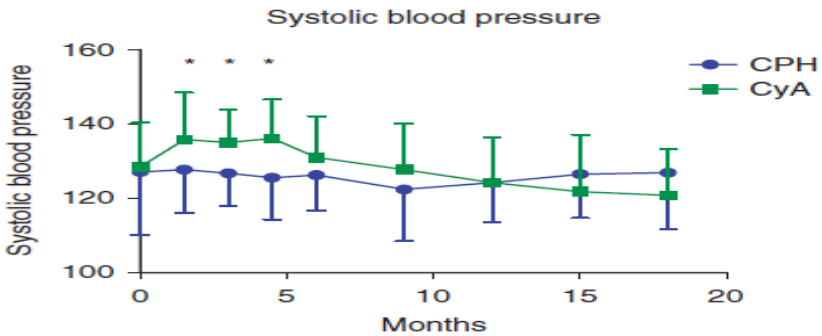
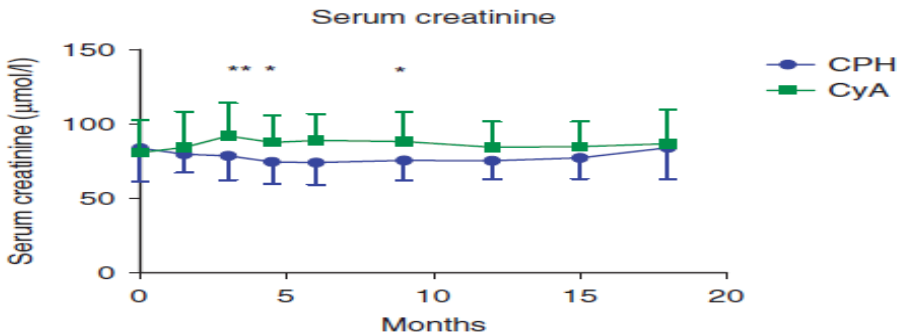
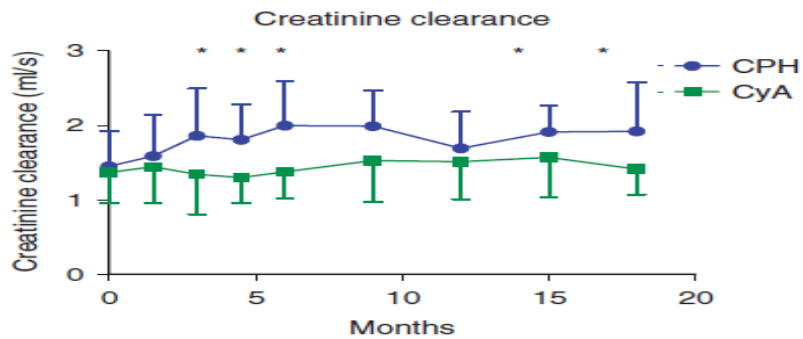
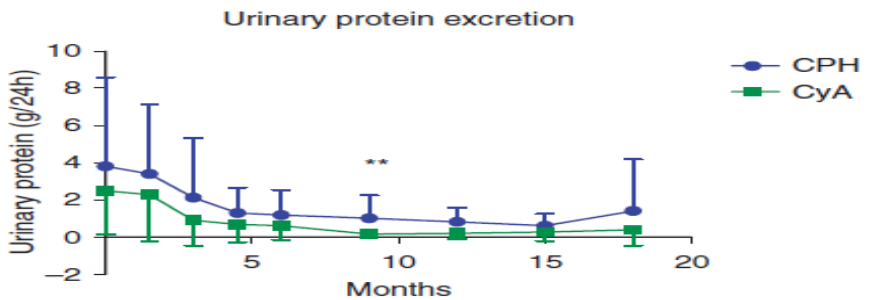
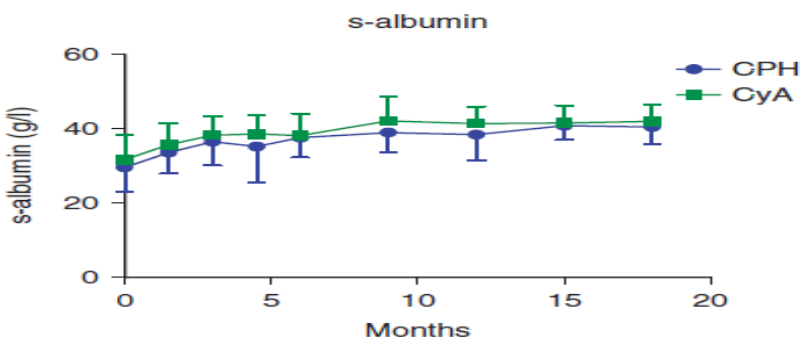
In 40 Caucasian pts cyclosporine similarly effective compared to iv CPH pulses

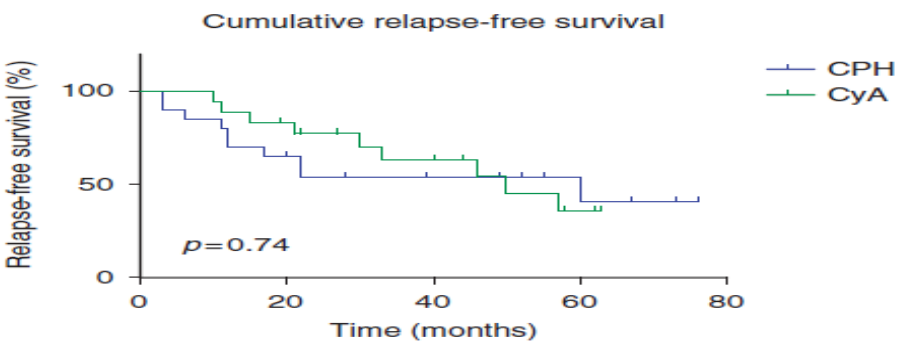












Extended follow-up of the CYCLOFA-LUNE trial comparing two sequential induction and maintenance treatment regimens for proliferative lupus nephritis based either on cyclophosphamide or on cyclosporine A

Lupus (2013)

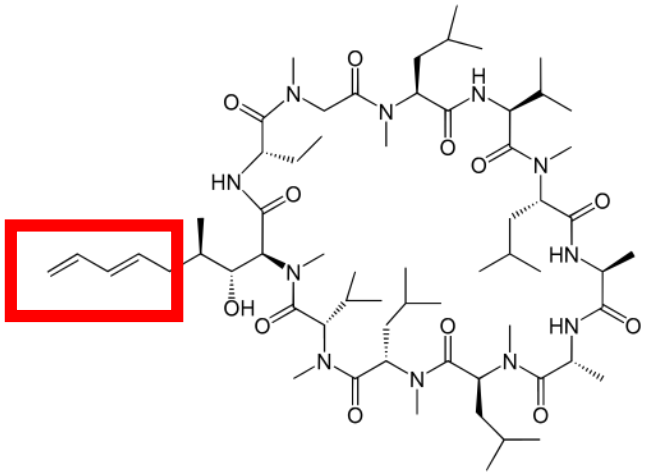
J Závada[1,2], S Sinikka Pešičková[2], R Ryšavá[2], P Horák[3], Z Hrnčíř[4], J Lukáč[5], J Rovenský[5], J Vítová[6], M Havrda[7], I Rychlík[7], J Böhmova[8], V Vlasáková[9], J Slatinská[10], J Zadražil[3], M Olejárová[1], D Tegzova[1] and V Tesar[2]

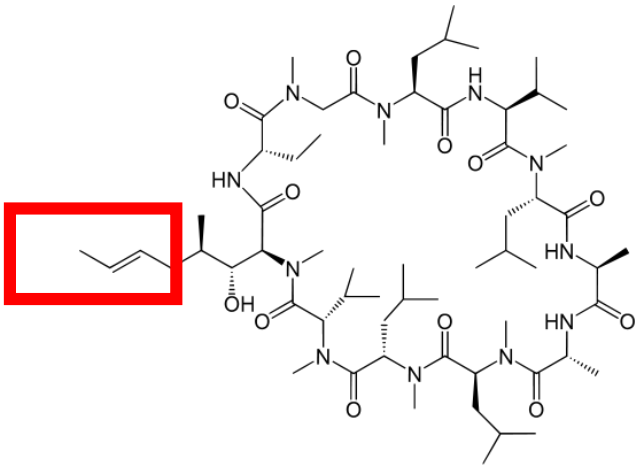
Extended FU (7.7 years) available in 38 pts, without significant difference between both limbs

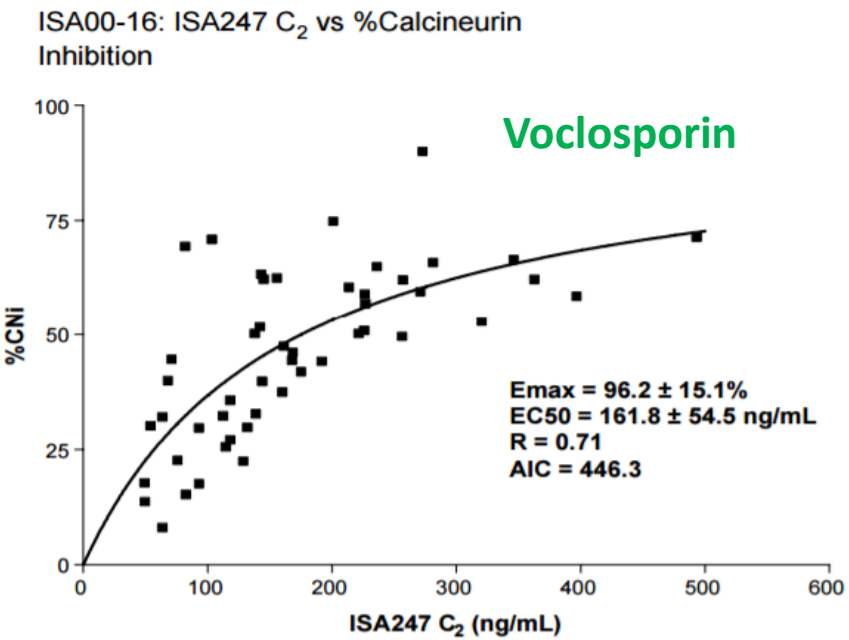
Table 1 Long-term renal outcomes in patients enrolled in the CYCLOFA-LUNE trial with available extended follow-up data

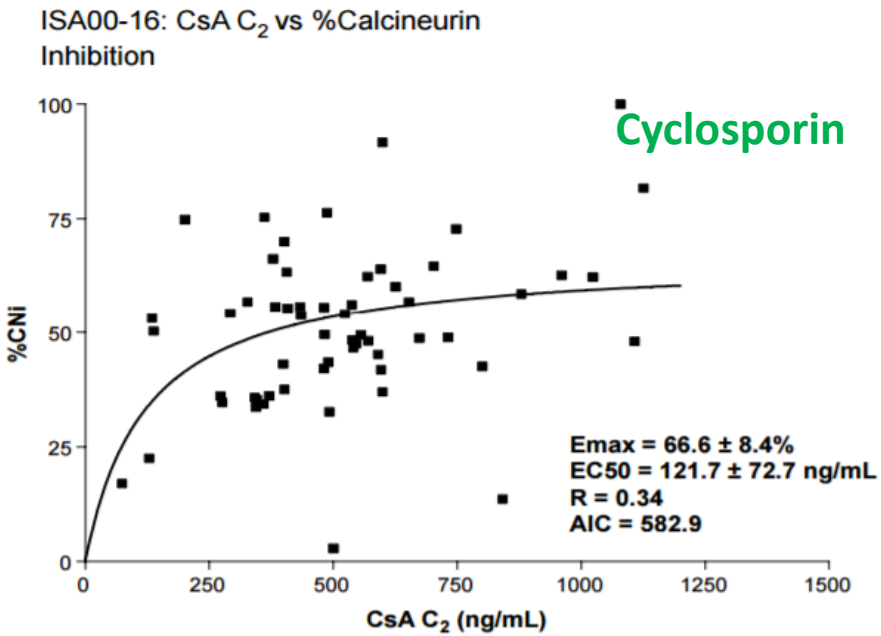
	All (n=*38*)	*CPH* (n=*19*)	*CyA* (n=*19*)
Age, years, mean (SD)	39 (10)	37 (5)	38 (8)
Female, *n*	27 (71)	13 (68)	14 (74)
Follow-up, years, median (range)	7.7 (5.0–10.3)	7.4 (5.0–9.7)	8.3 (5.3–10.3)
50% increase in creatinine concentration	5 (13)	3 (16)	2 (11)
Non-sustained doubling of the creatinine 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)

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









AURA-LV Trial
"Successful Treatment of Active Lupus Nephritis with Voclosporin"

Pendergraft et al., ASN Kidney Week 2016, November 19 in Chicago

Study enrolled 265 patients who were randomized to receive either to 23.7 mg or 39.5 mg of voclosporin twice daily, or placebo.
The experimental treatment was taken as an add-on to the standard care with mycophenolate mofetil and steroids (forced taper to 5 mg by week 8).

After 24 weeks of treatment, 32.6% of patients in the low-dose group and 27.3% of those in the high-dose group achieved complete remission, compared to 19.3% in the placebo group (OR = 2, statistically significant).

Both voclosporin doses were also better than placebo in achieving partial remission

Outline of the lecture

1. Efficacy and toxicity of high-dose cyclophosphamide
2. Mycophenolate mofetil and calcineurin inhibitors in LN
3. **Biologic treatment in LN**
4. Low dose cyclophosphamide
   – high efficacy, relatively low toxicity
5. Conclusions

Systemic Lupus Erythematosus

George C. Tsokos, M.D.

N Engl J Med 2011;365:2110-21.

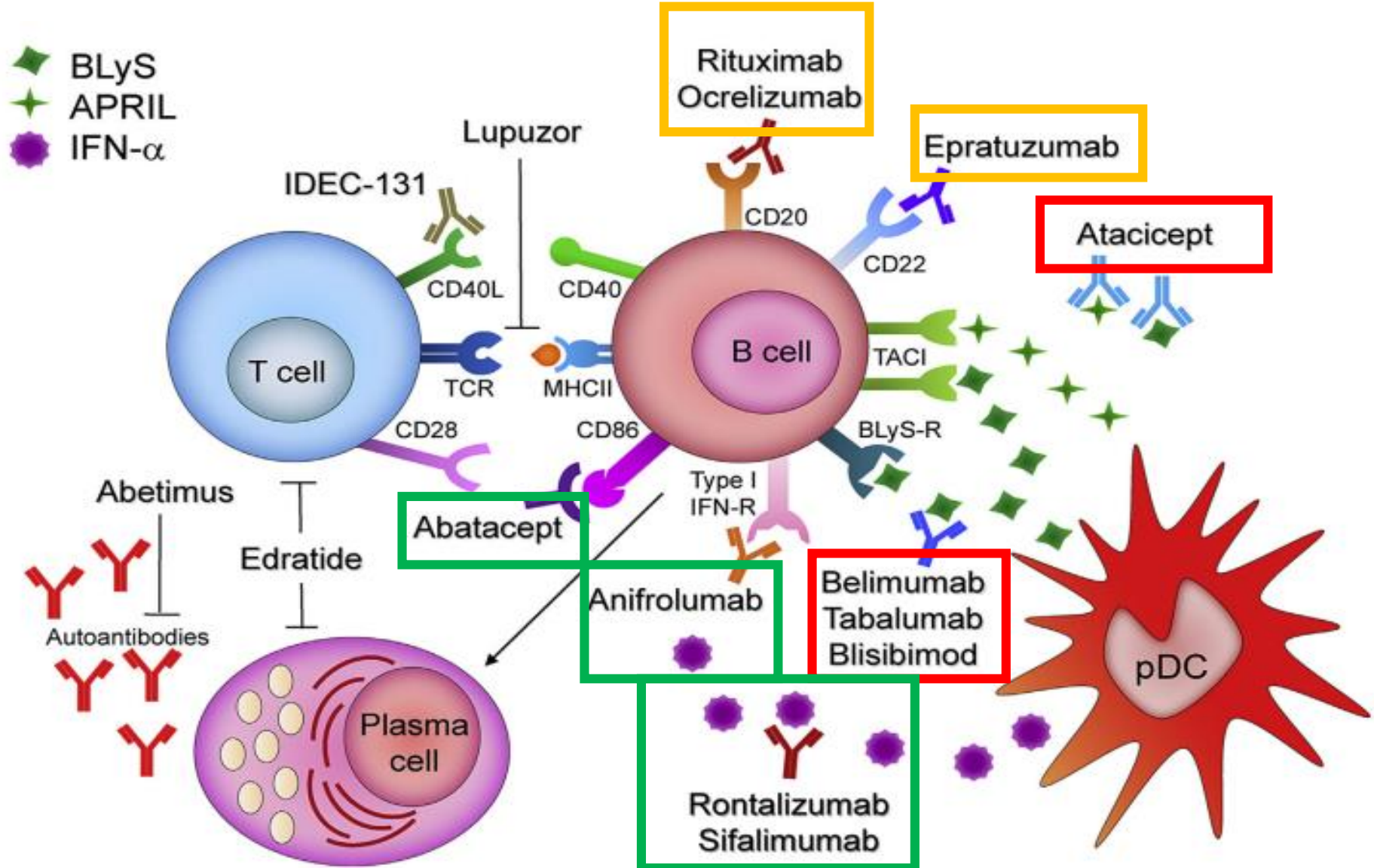
Table 2. Treatment Approaches for SLE.*

- Aspirin†
- Glucocorticoids†
- Immunosuppressive agents
  - Cyclophosphamide
  - Methotrexate
  - Azathioprine
  - Mycophenolate mofetil
- Modulation of B-cell function or numbers
  - Reestablishment of tolerance
  - B-cell depletion
  - B-cell–directed cytokines
    - Blockade of B-lymphocyte stimulator (belimumab)†
    - TACI–immune globulin (atacicept)
    - Blockade of the interleukin-6 receptor (tocilizumab)
- Interruption of T-cell–B-cell interaction
  - Blockade of CD40 ligand
  - CTLA4–immune globulin
  - Blockade of inducible costimulator
- Reestablishment of tolerance in T cells
  - Autoantigen-derived peptides
- Blockade of type I interferon
- Inhibition of toll-like receptor
  - Hydroxychloroquine†
- Hormone manipulation (dehydroepiandrosterone)
- Modulation of cell signaling
  - Spleen tyrosine kinase (fostamatinib)
  - Janus kinase
  - Rho kinase
  - Calcium/calmodulin-dependent protein kinase IV
  - Calcineurin (dipyridamole)
  - Mammalian target of rapamycin (sirolimus)

Success and failure of biological treatment in systemic lupus erythematosus: A critical analysis

Journal of Autoimmunity 74 (2016) 94–105

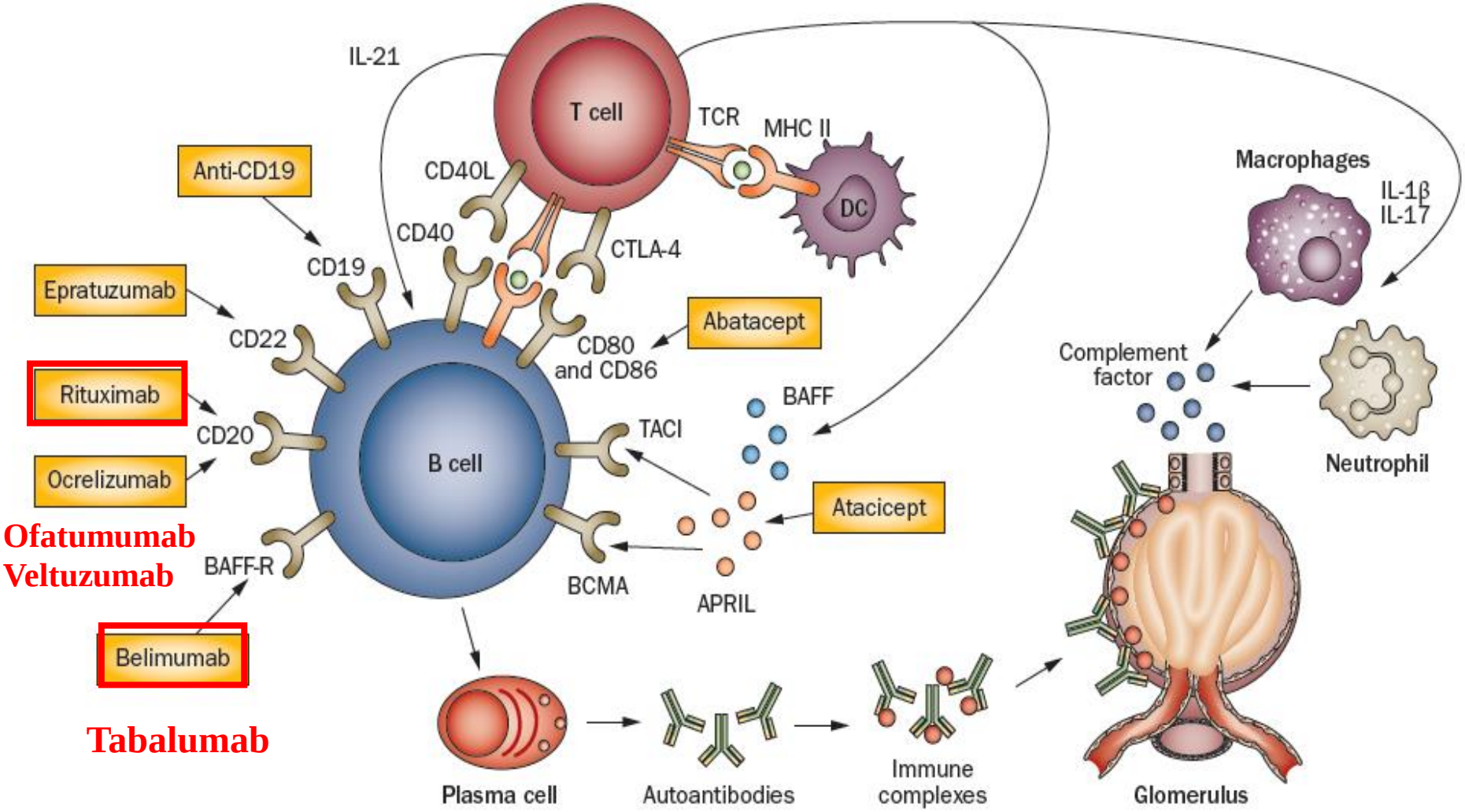
Mariele Gatto, Francesca Saccon, Margherita Zen, Silvano Bettio, Luca Iaccarino, Leonardo Punzi, Andrea Doria*



B-cell depletion in the treatment of lupus nephritis

Nat. Rev. Nephrol. advance online publication 17 July 2012: doi:10.1038/nrneph.2012.141

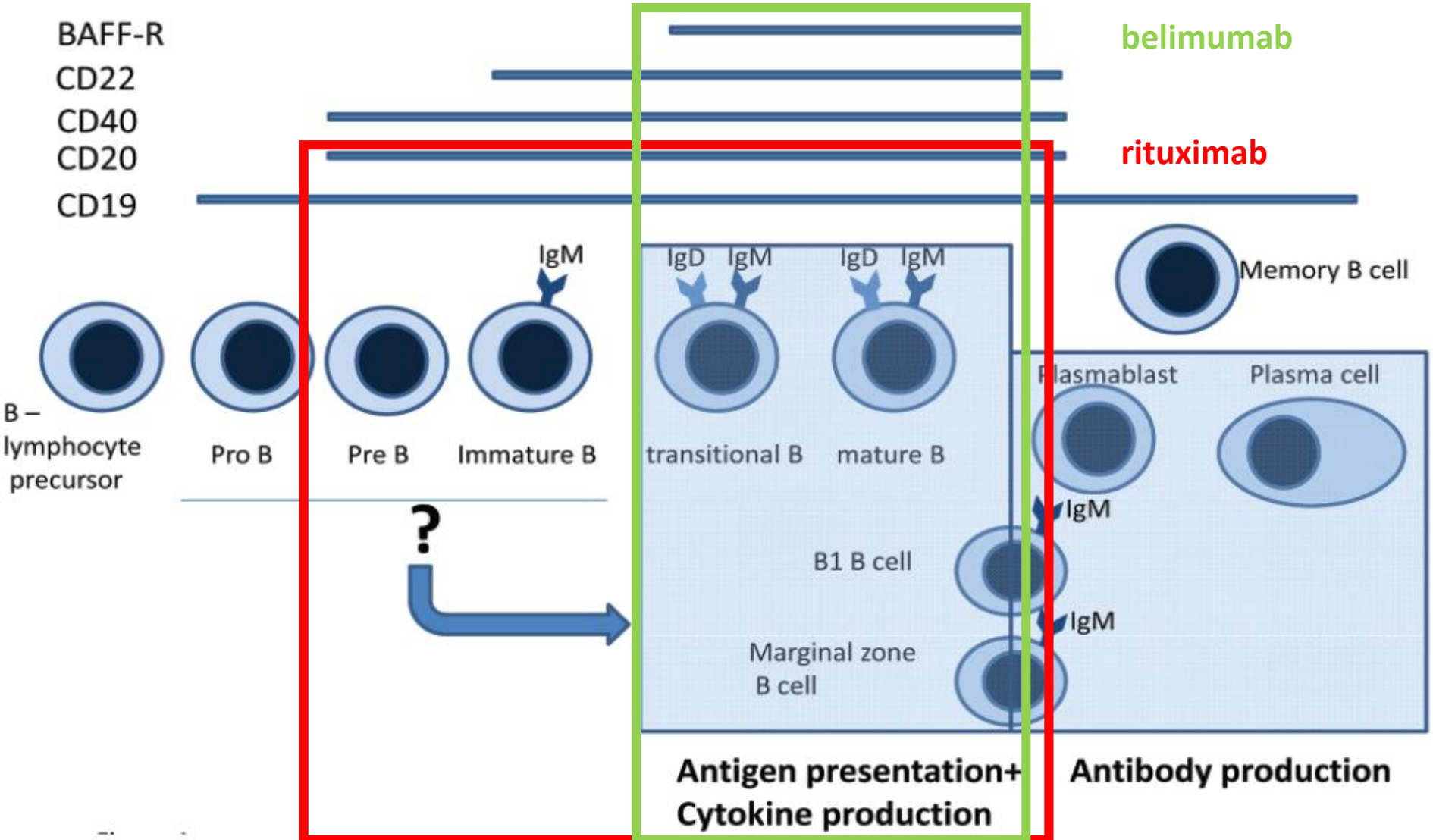
Jon W. Gregersen and David R. W. Jayne



B-cell targeted therapeutics in clinical development

Arthritis Research & Therapy 2013, 15(Suppl 1):S4

Stephan Blüml[1,2], Kathleen McKeever[3], Rachel Ettinger[3], Josef Smolen[1,2] and Ronald Herbst*[3]

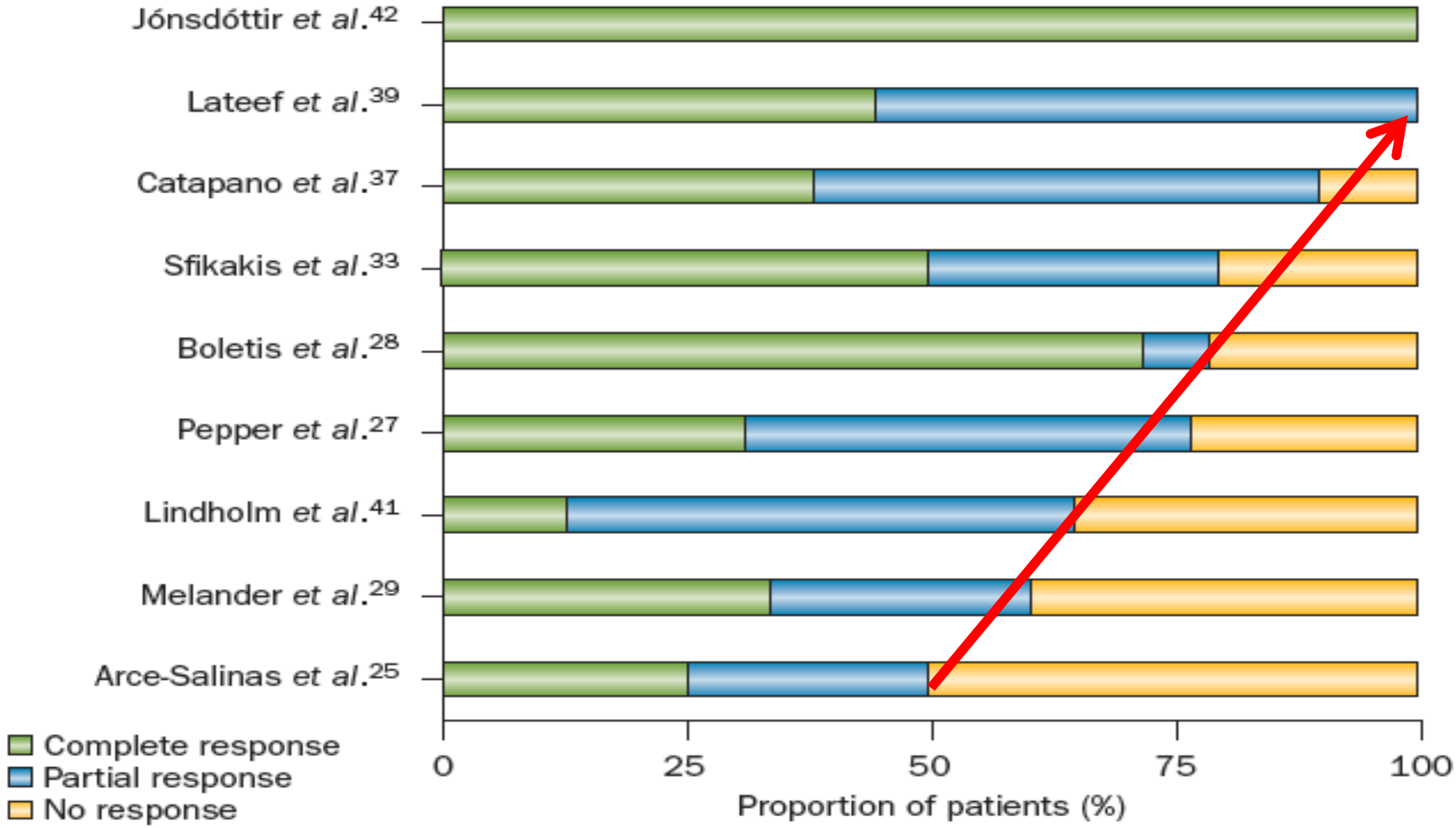


B-cell depletion in the treatment of lupus nephritis

Nat. Rev. Nephrol. advance online publication 17 July 2012: doi:10.1038/nrneph.2012.141

Jon W. Gregersen and David R. W. Jayne

Very variable efficacy with at least partial response in 50 -100% pts with (mostly) refractory LN



Efficacy of rituximab in 164 patients with biopsy-proven lupus nephritis: Pooled data from European cohorts

Cándido Díaz-Lagares [a], Sara Croca [b], Shirish Sangle [c], Edward M. Vital [d], Fausta Catapano [e,j], Agustín Martínez-Berriotxoa [f], Francisco García-Hernández [g], José-Luis Callejas-Rubio [h], Javier Rascón [i], David D'Cruz [c], David Jayne [e], Guillermo Ruiz-Irastorza [f], Paul Emery [d], David Isenberg [b], Manuel Ramos-Casals [a,*], Munther A. Khamashta [c] and The UK-BIOGEAS Registry [1]

Autoimmunity Reviews 11 (2012) 357–364

Therapeutic response to RTX in 2/3 of pts with LN

Table 1

Baseline characteristics at diagnosis of lupus nephritis in 164 patients treated with rituximab. Data presented in all cases and separated according to the renal biopsy.

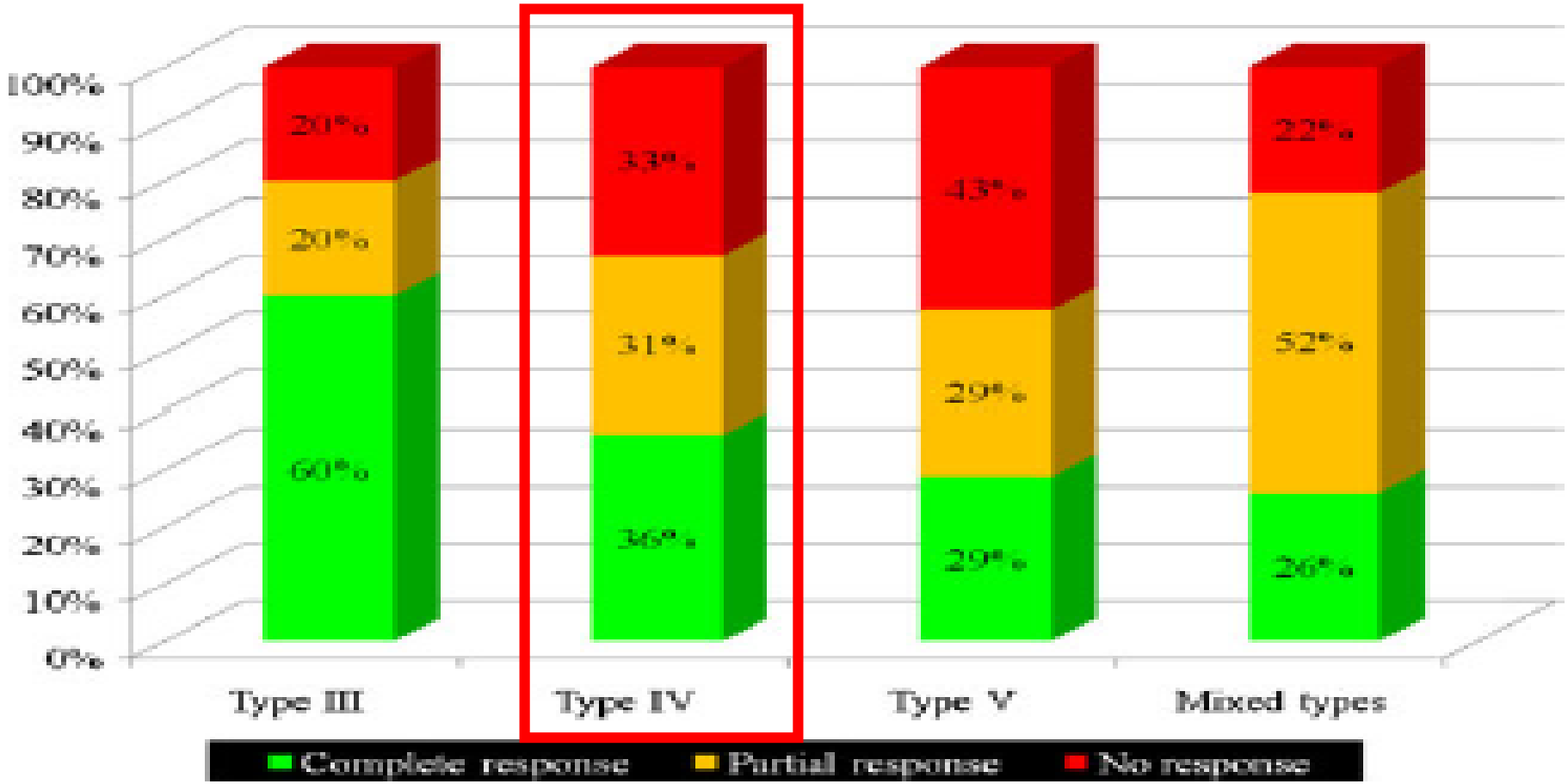
	All patients N = 164	Type IV N = 93	Type III N = 26	Type V N = 20	Mixed types N = 19	Type II N = 6
Therapeutic response (6 m)[2]						
- Complete remission	30/110 (27%)	10/62 (16%)	10/21 (48%)	3/11 (27)	8/16 (50%)	1/6 (17%)
- Partial remission	44/110 (40%)	28/62 (45%)	6/21 (27%)	5/11 (46%)	4/16 (50%)	2/6 (33%)
- No response	36/110 (33%)	24/62 (39%)	5/21 (24%)	3/11 (27%)	4/16 (50%)	3/6 (50%)
Therapeutic response (12 m)^						
- Complete remission	38/126 (30%)	16/71 (22%)	10/16 (62%)	3/17 (18%)	8/16 (50%)	1/6 (17%)
- Partial remission	46/126 (37%)	29/71 (41%)	3/16 (19%)	8/17 (47%)	4/16 (25%)	2/6 (33%9
- No response	42/126 (33%)	26/71 (37%)	3/16 (19%)	6/17 (35%)	4/16 (25%)	3/6 (50%)

Rituximab Therapy in Lupus Nephritis: Current Clinical Evidence

Clinic Rev Allerg Immunol (2011) 40:159–169

Manuel Ramos-Casals · Candido Diaz-Lagares · Maria-Jose Soto-Cardenas · Pilar Brito-Zeron · María-José Cuadrado · Giovanni Sanna · Laura Bertolaccini · Munther A. Khamashta

Response to RTX different in different classes of LN
- better response in type III compared to type IV
(analysis of 106 pts)



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

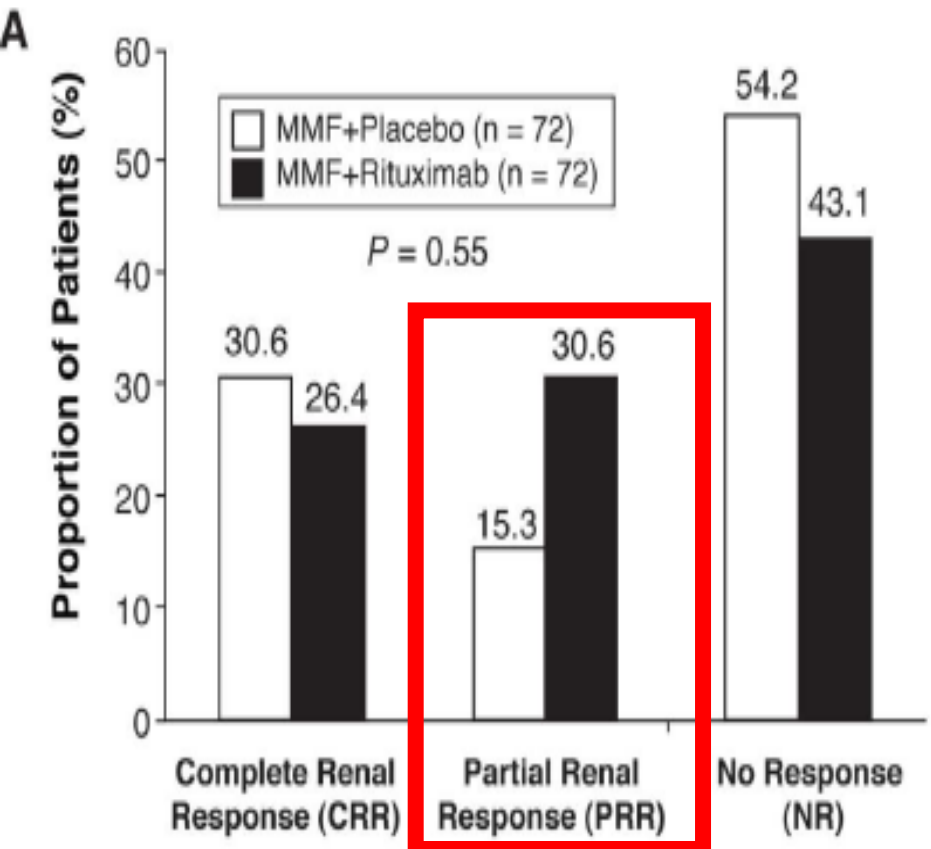
The Lupus Nephritis Assessment With Rituximab Study

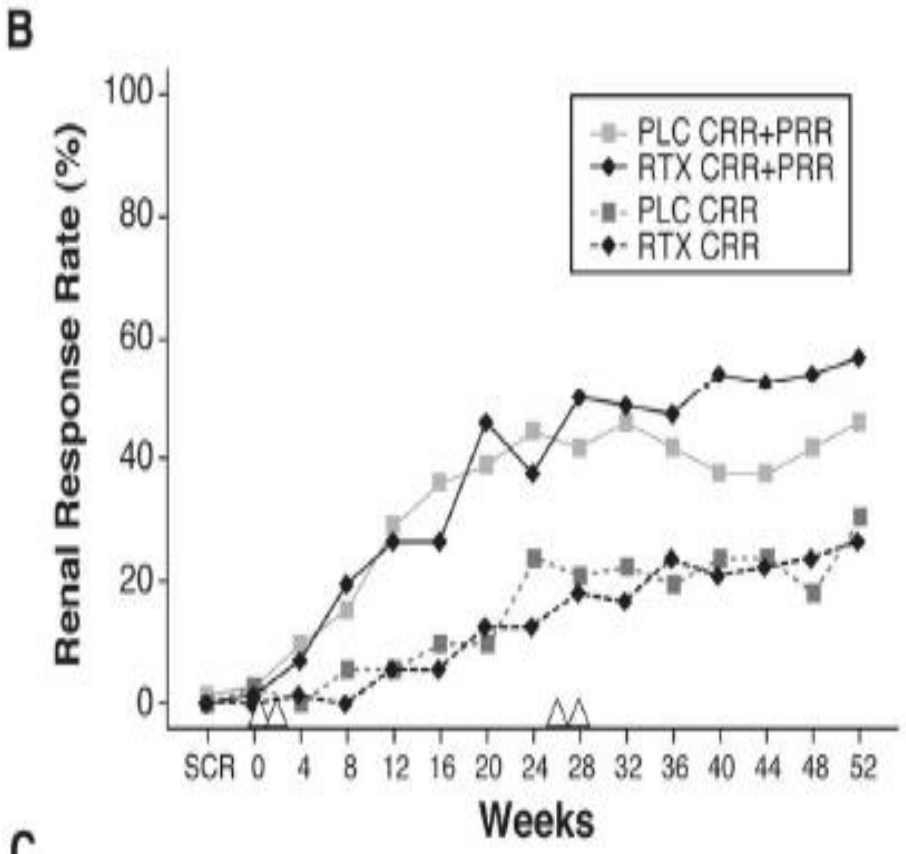
Brad H. Rovin,[1] Richard Furie,[2] Kevin Latinis,[3] R. John Looney,[4] Fernando C. Fervenza,[5] Jorge Sanchez-Guerrero,[6] Romeo Maciuca,[7] David Zhang,[7] Jay P. Garg,[7] Paul Brunetta,[7] and Gerald Appel,[8] for the LUNAR Investigator Group

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

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…





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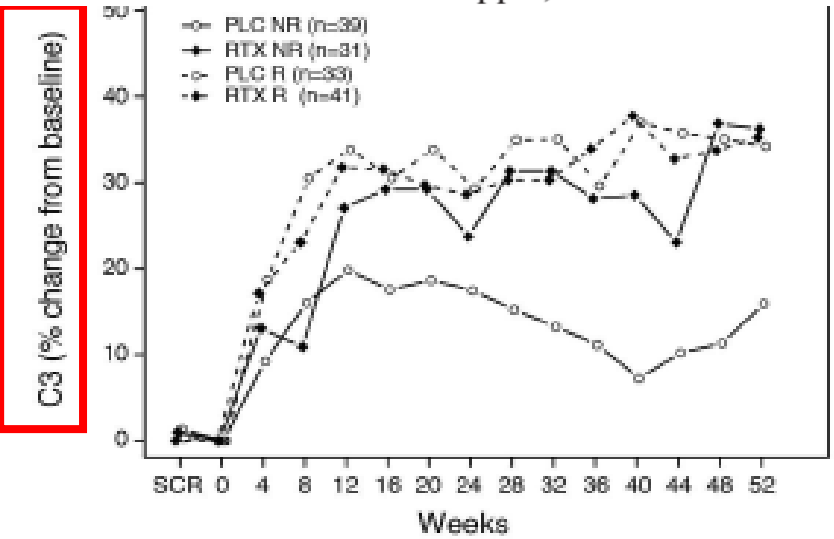
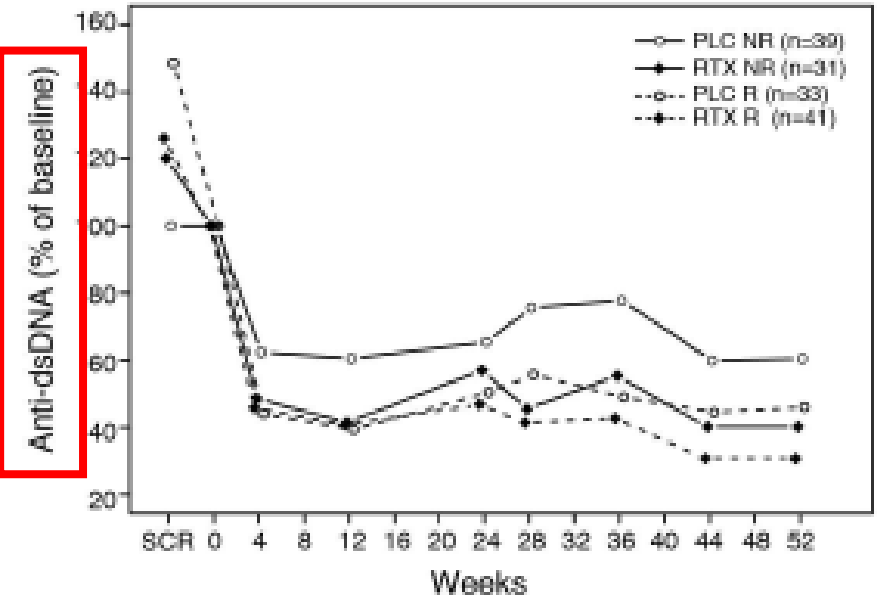


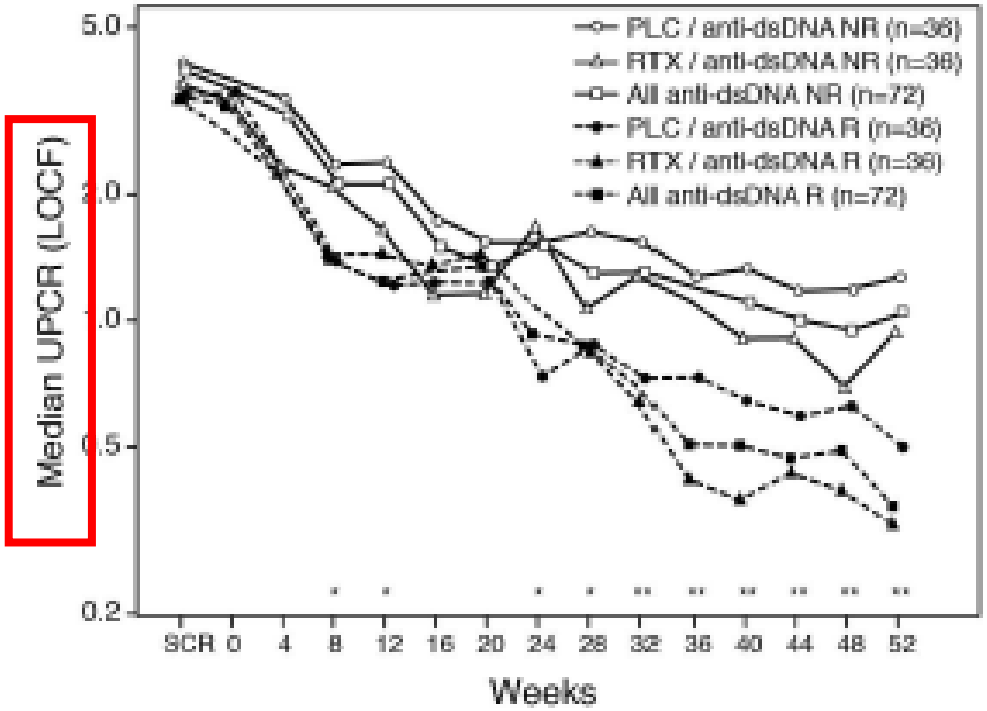
… but, in pts treated with RTX

↑ C3 a ↓ anti-ds-DNA …

Too short FU in pts with relatively mild disease and strong background therapy?

Low number of pts?





Probable predictors of the response to RTX

Ethnicity
Genetic factors (FcγIIIA or IL2/IL21 polymorphism)
Efficacy of B cell depletion (RTX levels)
Number of cycles of RTX treatment (duration of B cell depletion)
Concomitant treatment (CPH better than MMF?)
Class of LN
Crescents
Proteinuria
Renal function

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

CJASN ePress. Published on August 8, 2018

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]

In a post-hoc analysis of 68 pts from LUNAR trial

only 78% of pts achieved complete B cell depletion during FU

Pts who achieved B cell depletion - ↓ proteinuria and ↑ anti-Sm Ab

Table 2. Comparison of baseline characteristics of patients from the LUNAR trial treated with rituximab who achieved complete peripheral depletion versus those who never achieved complete peripheral depletion

Characteristics	Complete Peripheral Depletion, *n*=53	Incomplete Peripheral Depletion, *n*=15
Age, yr, mean±SD	32±8	31±10
Women	48 (90%)	11 (73%)
Duration of lupus nephritis, mo, median (range)	10.5 (0.4–210)	17.8 (0.4–130)
Race		
White	15 (28%)	4 (26%)
Hispanic	21 (39%)	6 (41%)
Black	15 (28%)	4 (26%)
Asian	2 (4%)	1 (7%)
Biopsy class		
Class III only	6 (11%)	2 (13%)
Class III and V	11 (21%)	5 (33%)
Class IV only	28 (53%)	7 (47%)
Class IV and V	8 (15%)	1 (7%)
Baseline CD19, cells/μl, median (range)	166 (11–1477)	106 (20–1839)
Creatinine, mg/dl, mean±SD	0.95±0.4	1.17±0.5
eGFR, ml/min, mean±SD	79±33	58±24
Urine protein/creatinine ratio, mg/mg, mean±SD	3.3±2.3	5.2±2.45
Albumin, g/dL, mean±SD	2.8±0.67	2.1±0.87
Nephrotic syndrome present	15 (28%)	11 (73%)
IgG, g/L, median (range)	9.9 (3.4–22)	7.7 (1.2–20)
C3, mg/dl, median (range)	69 (23–151)	59 (32–130)
C4, mg/dl, median (range)	13 (5–42)	9.5 (5–24)
Anti-dsDNA positivity	42 (80%)	13 (87%)
Anti-Smith positivity	17 (32%)	1 (7%)
BAFF levels, ng/ml, median (range)	3.1 (0.1–19)	3.5 (1.4–24)
Peak rituximab levels, μg/ml, median (range)	456 (290–1070)	386 (293–565)

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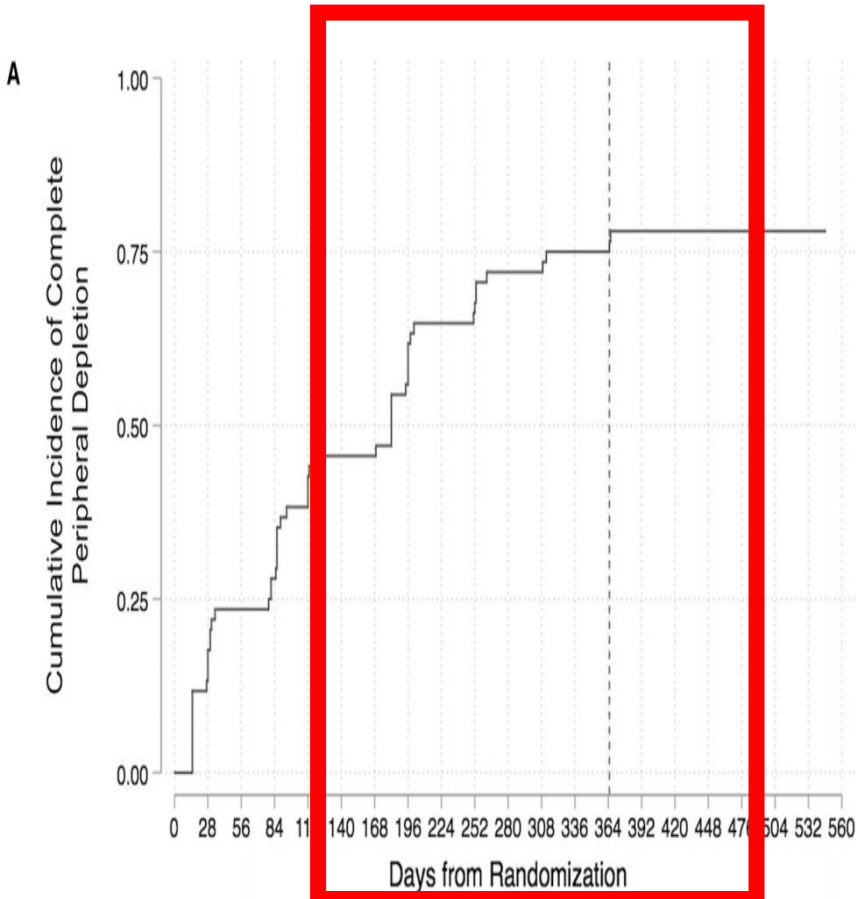
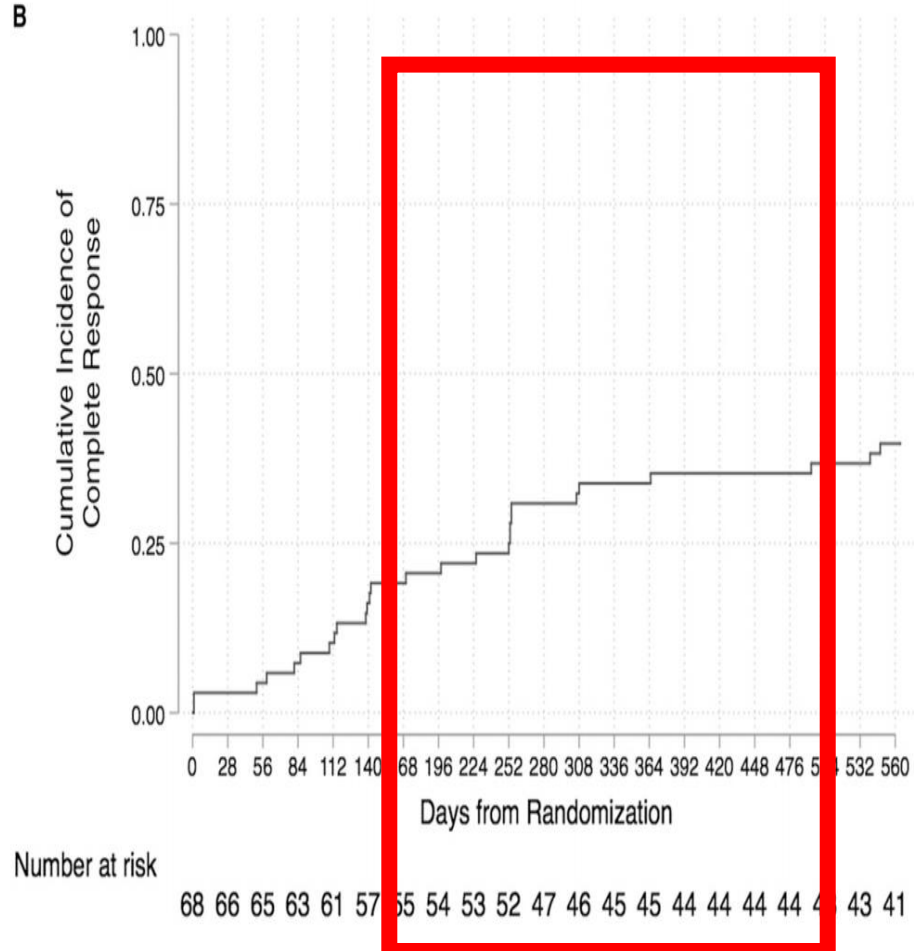
Time course of complete B cell depletion and complete response





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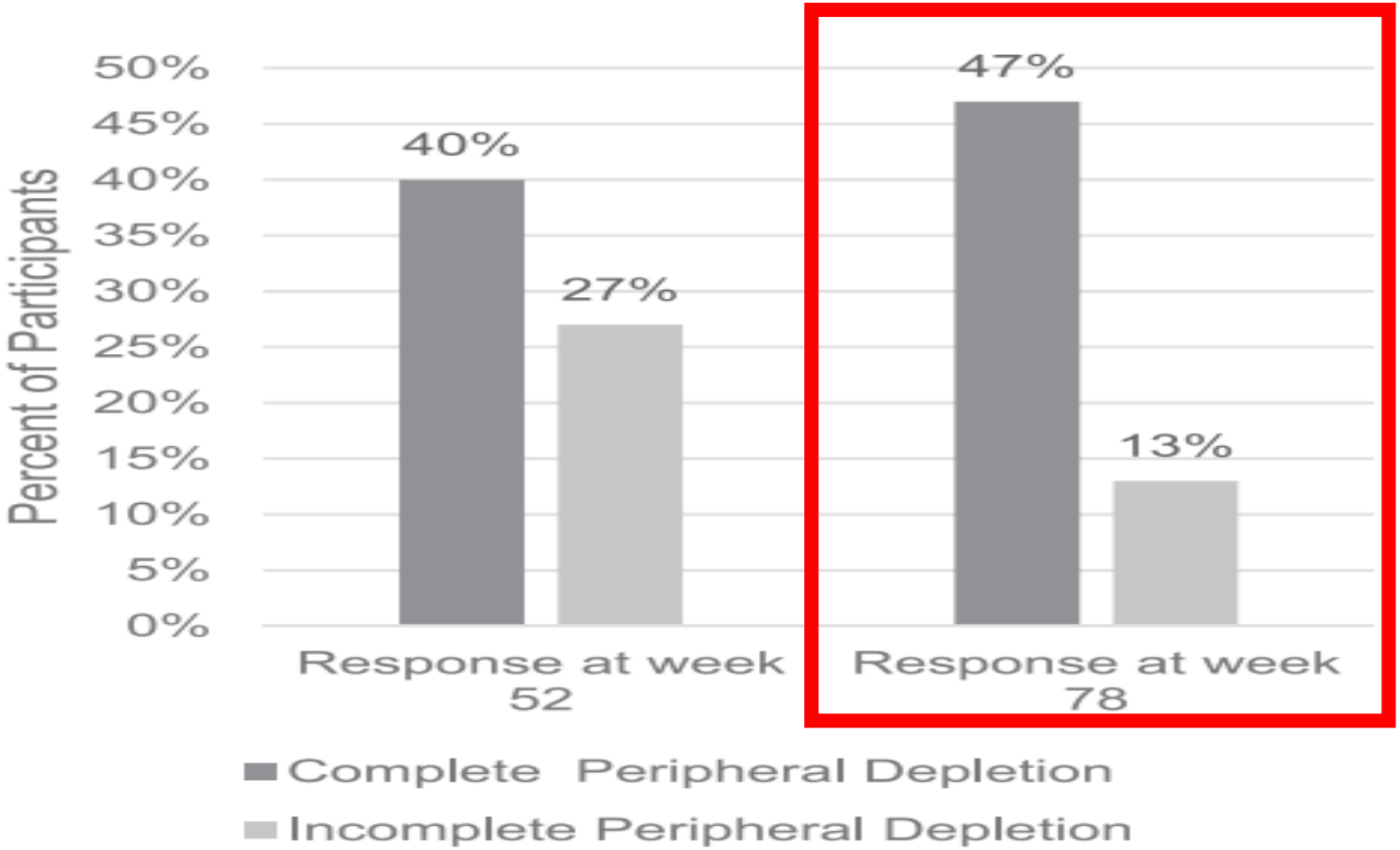
Complete remission more common in pts who achieved complete B cell depletion at week 52 and 78



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Complete response associated with achieving complete B cell depletion and its duration

Table 3. Univariable logistic regressions assessing whether characteristics of complete peripheral depletion associate with complete response at week 78

Characteristics	Complete Response, *N* (%)	Unadjusted Odds Ratio (95% CI)	*P* Value
Complete peripheral depletion		5.8 (1.2 to 28)	0.03
Achieved (*n*=53)	25 (47)		
Never achieved (*n*=15)	2 (13)		
Duration of complete peripheral depletion		4.1 (1.5 to 11)	0.008
≥71 d (*n*=34)	19 (70)		
<71 d (*n*=34)	8 (30)		
Each incremental delay of 30 d to complete peripheral depletion	53 (78)	0.89 (0.81 to 0.98)	0.02

95% CI, 95% confidence interval.

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Complete B cell depletion associated with proteinuria, anti-Sm Ab and rituximab levels

Table 4. Multivariable logistic regression model including the three variables that significantly associated with complete peripheral depletion by week 78 when evaluated in a univariable model

Variables	Odds Ratio (95% CI)	*P* Value
Baseline nephrotic syndrome	0.12 (0.03 to 0.50)	0.004
Baseline anti-Smith positivity	13.8 (1.4 to 136)	0.02
Each 100 μg/ml increment above 440 μg/ml in peak rituximab levels	2.3 (0.98 to 5.2)	0.05

Efficacy of rituximab in 164 patients with biopsy-proven lupus nephritis: Pooled data from European cohorts

Cándido Díaz-Lagares [a], Sara Croca [b], Shirish Sangle [c], Edward M. Vital [d], Fausta Catapano [e,j], Agustín Martínez-Berriotxoa [f], Francisco García-Hernández [g], José-Luis Callejas-Rubio [h], Javier Rascón [i], David D'Cruz [c], David Jayne [e], Guillermo Ruiz-Irastorza [f], Paul Emery [d], David Isenberg [b], Manuel Ramos-Casals [a,*], Munther A. Khamashta [c] and The UK-BIOGEAS Registry [1]

Autoimmunity Reviews 11 (2012) 357–364

Take-home messages

- Rituximab in lupus nephritis (LN) currently seems to be good in real life, but bad in controlled trials.
- We present the results of the use of rituximab in 164 patients with biopsy-proven LN, the majority refractory to standard therapies, with a clinical response in two thirds of patients at both 6 and 12 months, and a rate of CR of 27% at 6 months rising to 30% at 12 months.
- We found a different rate of response according to the ISN/RPS histopathological classification, with a 4-fold higher rate of CR at 12 months in patients with mixed proliferative-membranous LN (70%) in comparison with those with type IV LN (16%).
- The main baseline features associated with not achieving CR were nephrotic syndrome and renal failure.

B-cell depletion in SLE: clinical and trial experience with rituximab and ocrelizumab and implications for study design

Arthritis Research & Therapy 2013, 15(Suppl 1):S2

Venkat Reddy*[1], David Jayne[2], David Close[3] and David Isenberg[1]

Table 5. Adverse events reported in published studies[a] during or after rituximab-induced B-cell depletion therapy

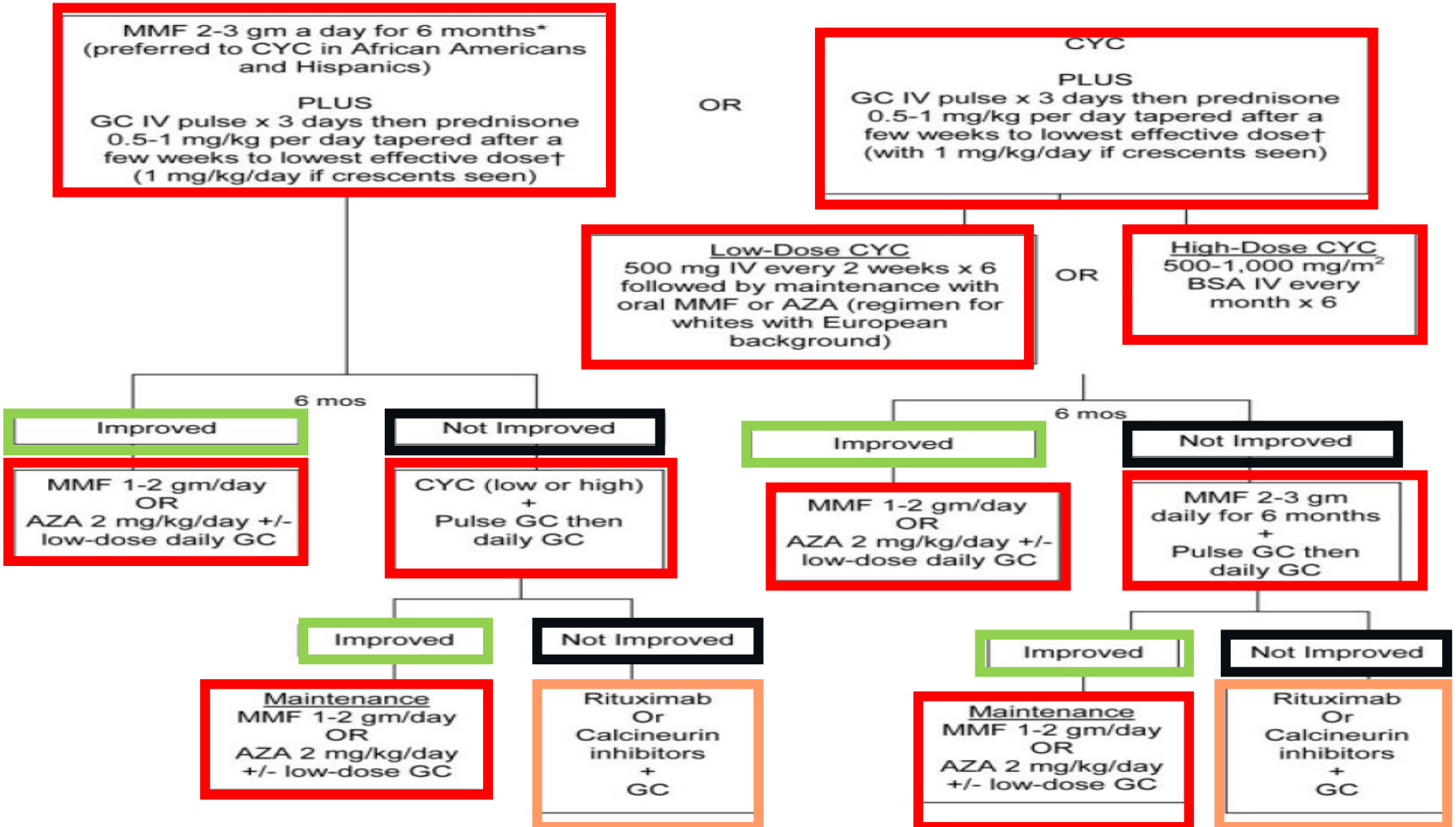
Infections	Pneumonia[b]
	Shingles[b]
	Thigh abscess, subcutaneous abscess
	Urinary tract infection
	Septicaemia
	Psuedomonas infection
	Staphyloccal abscess
	Streptococcal viridans infection
	Necrotising fasciitis
	Fatal histoplasmosis
Haematological	Neutropenia[b]
Pulmonary	Pneumonia
	Pulmonary haemorrhage
	Pulmonary embolism
	Respiratory failure[c]
	Breathlessness
Cardiac	Cardiac failure[c]
	Fatal pancarditis[c]
	Pericarditis
	Tachycardia
Neurological	Insomnia
	Transient ischaemic attack
Skin	Localised or widespread rash[b]
	Pruritis
	Urticaria
Miscellaneous	Infusion reactions[b]
	Serum sickness reaction
	Hypogammaglobulinaemia
	Anaphylaxis
	Deep vein thrombosis
	Dyspepsia
	Malaise
	Pyrexia
	Polyarthralgia

American College of Rheumatology Guidelines for Screening, Treatment, and Management of Lupus Nephritis

BEVRA H. HAHN,[1] MAUREEN A. McMAHON,[1] ALAN WILKINSON,[1] W. DEAN WALLACE,[1] DAVID I. DAIKH,[2] JOHN D. FITZGERALD,[1] GEORGE A. KARPOUZAS,[1] JOAN T. MERRILL,[3] DANIEL J. WALLACE,[4] JINOOS YAZDANY,[2] ROSALIND RAMSEY-GOLDMAN,[5] KARANDEEP SINGH,[1] MAZDAK KHALIGHI,[1] SOO-IN CHOI,[1] MANEESH GOGIA,[1] SUZANNE KAFAJA,[1] MOHAMMAD KAMGAR,[1] CHRISTINE LAU,[1] WILLIAM J. MARTIN,[1] SEFALI PARIKH,[1] JUSTIN PENG,[1] ANJAY RASTOGI,[1] WEILING CHEN,[1] AND JENNIFER M. GROSSMAN[1]

Arthritis Care & Research
Vol. 64, No. 6, June 2012, pp 797–808

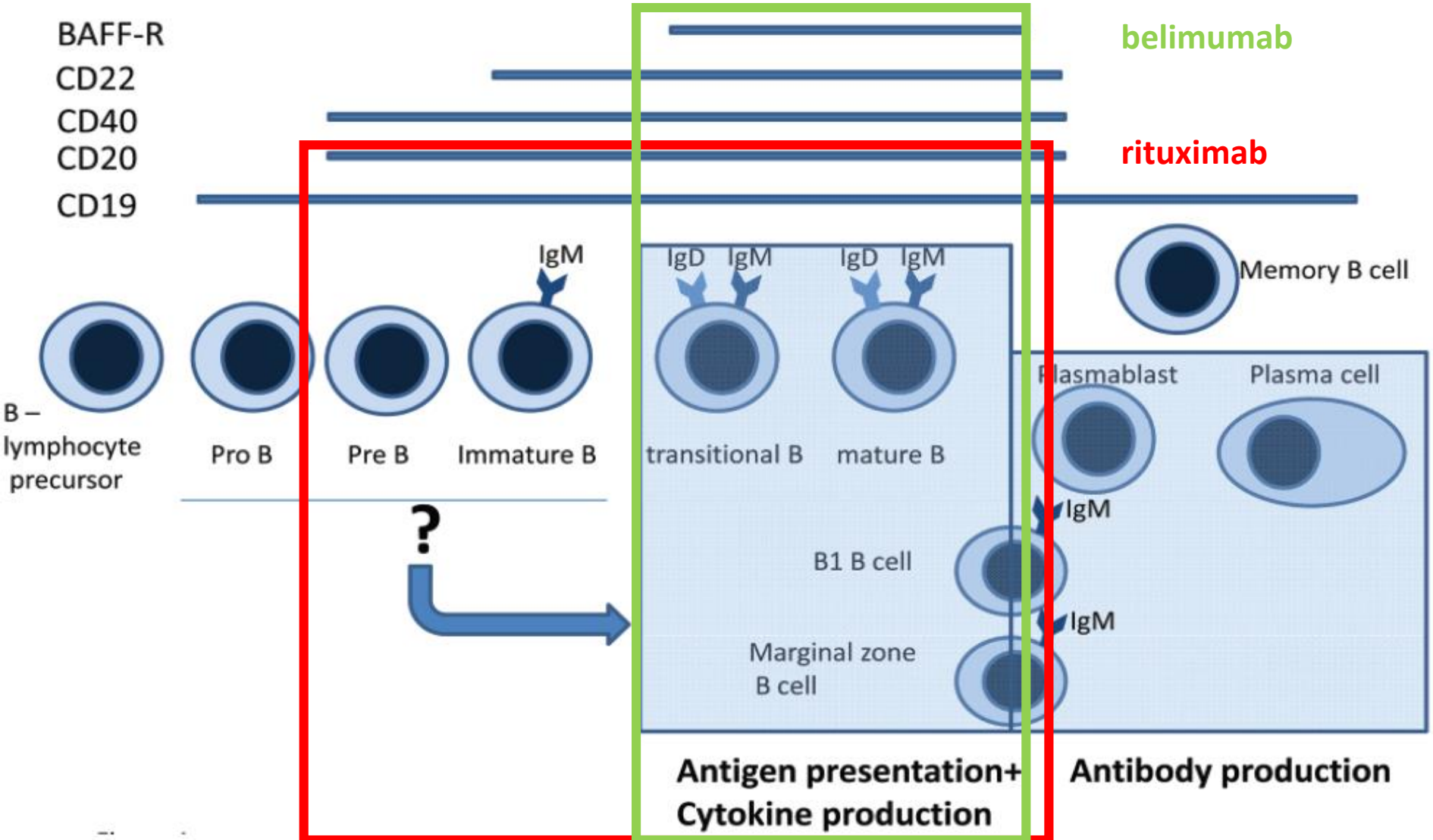
In proliferative LN RTX recommended only as an off-label treatment of pts refractory to CPH and MMF



B-cell targeted therapeutics in clinical development

Arthritis Research & Therapy 2013, 15(Suppl 1):S4

Stephan Blüml[1,2], Kathleen McKeever[3], Rachel Ettinger[3], Josef Smolen[1,2] and Ronald Herbst*[3]

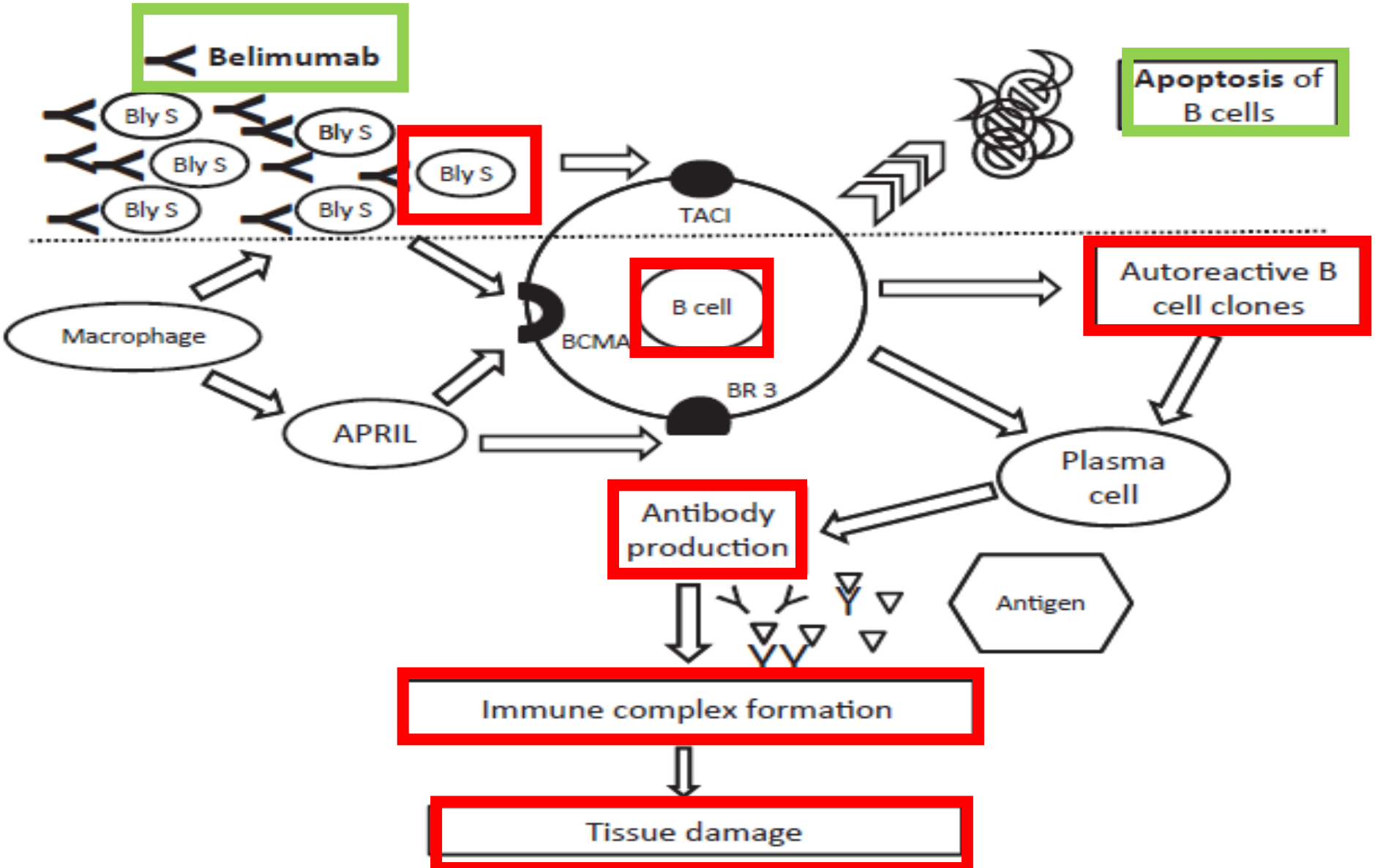


Belimumab: targeted therapy for lupus

Preeta K. CHUGH and Bhupinder S. KALRA

International Journal of Rheumatic Diseases 2013; 16: 4–13

Blocking BlyS (BAFF) with belimumab results in the apoptosis of B cells



A Phase III, Randomized, Placebo-Controlled Study of Belimumab, a Monoclonal Antibody That Inhibits B Lymphocyte Stimulator, in Patients With Systemic Lupus Erythematosus

Richard Furie,[1] Michelle Petri,[2] Omid Zamani,[3] Ricard Cervera,[4] Daniel J. Wallace,[5] 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

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

BLISS-76

In 819 mostly white pts with SLE with SELENA/SLEDAI > 6 belimumab (10 mg/kg) achieved SRI response in 43.2% pts compared to 33.5% in placebo limb (p< 0.02)

Table 1. Baseline demographic and clinical characteristics of the treated patients*

Characteristic	Placebo (n = 275)	Belimumab 1 mg/kg (n = 271)	Belimumab 10 mg/kg (n = 273)
Female, no. (%)	252 (91.6)	253 (93.4)	259 (94.9)
Race, no. (%)†			
Indigenous American‡	36 (13.1)	33 (12.2)	34 (12.5)
White/Caucasian	188 (68.4)	192 (70.8)	189 (69.2)
Black/African American	39 (14.2)	40 (14.8)	39 (14.3)
Asian	11 (4.0)	6 (2.2)	11 (4.0)
Hispanic or Latino origin, no. (%)§	55 (20.0)	62 (22.9)	56 (20.5)

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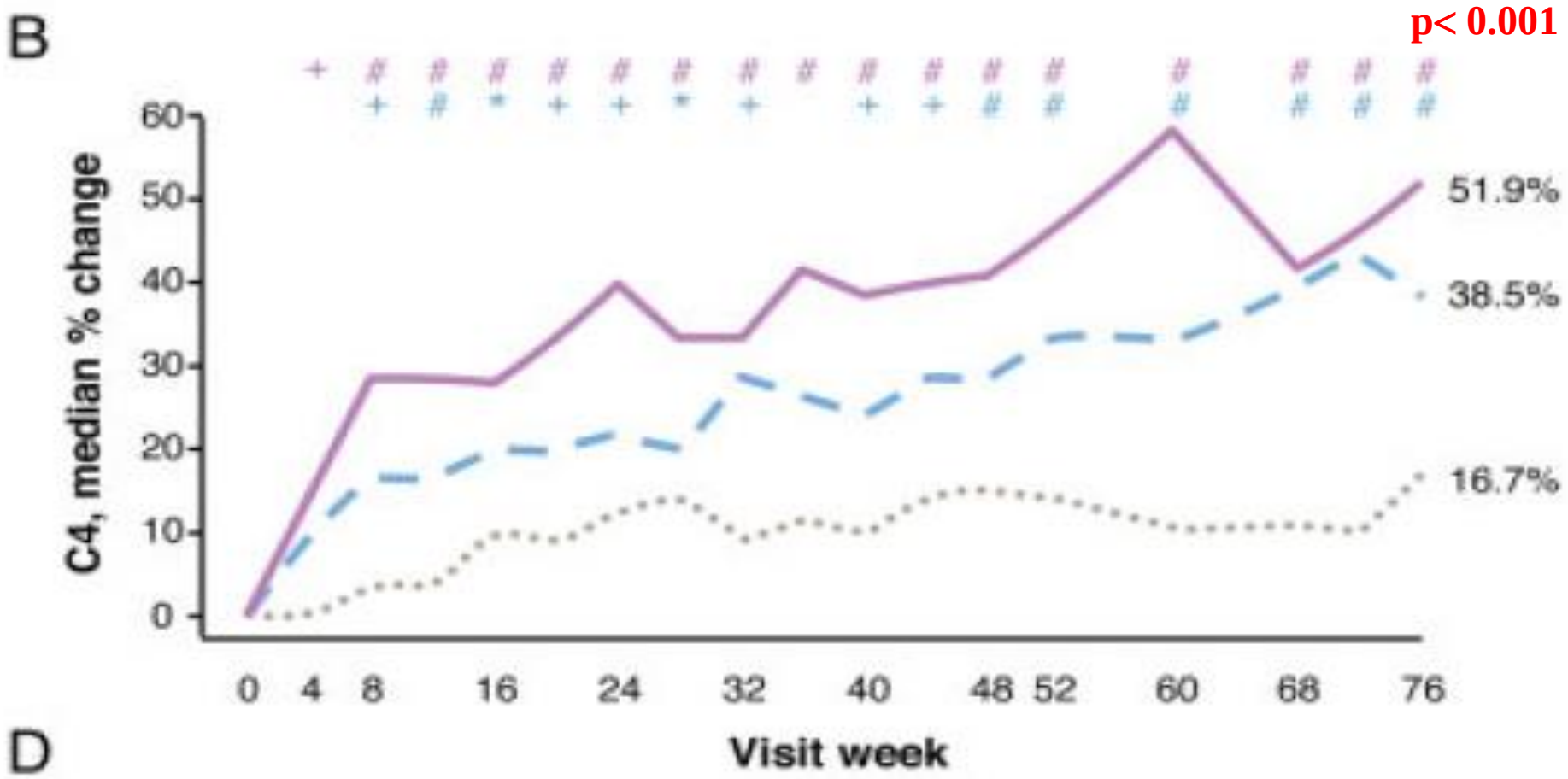
ARTHRITIS & RHEUMATISM
Vol. 63, No. 12, December 2011, pp 3918–3930

High C4 (a C3) in pts treated with belimumab



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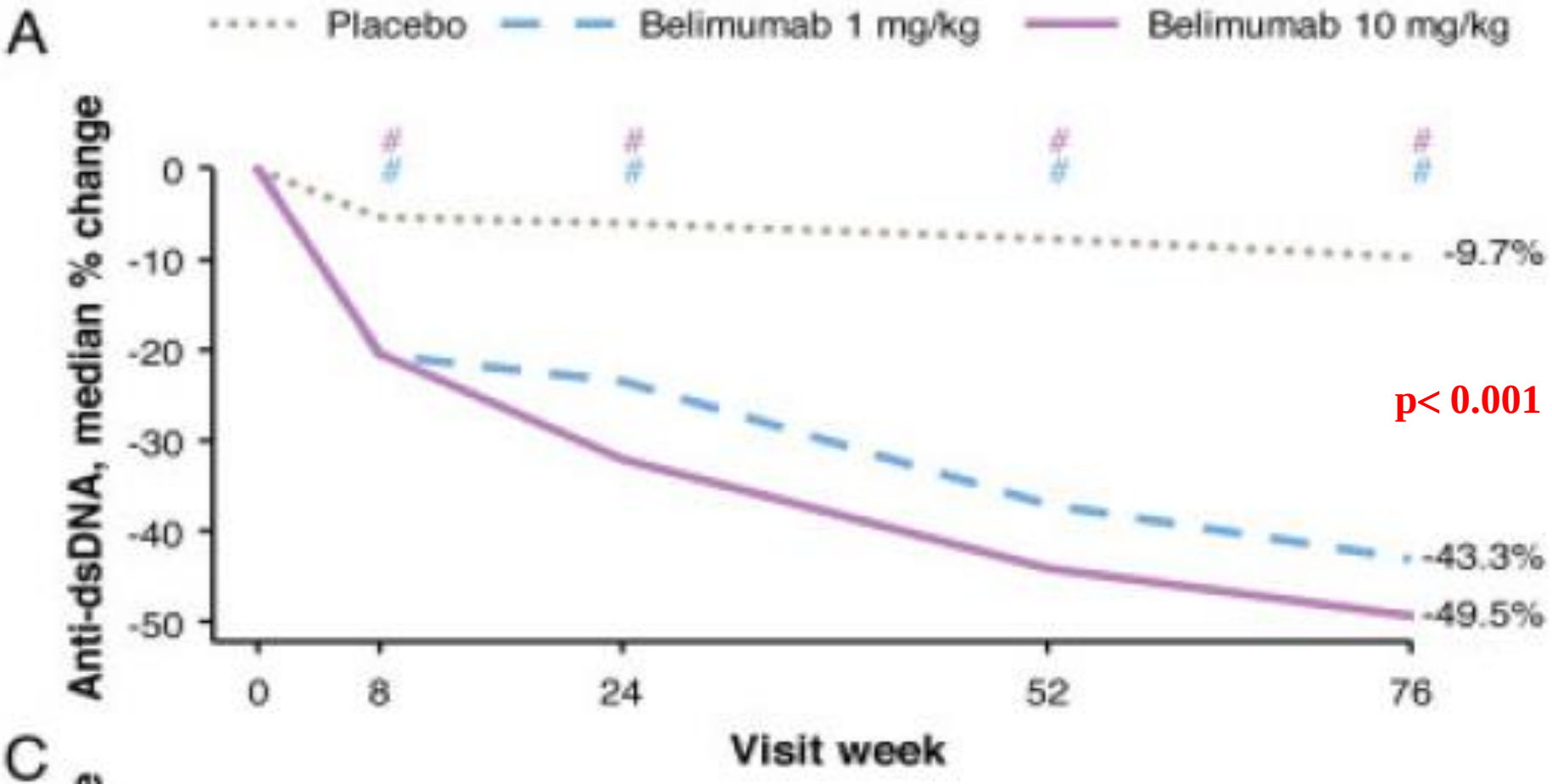
ARTHRITIS & RHEUMATISM
Vol. 63, No. 12, December 2011, pp 3918–3930

Much more pronounced decrease of anti-ds-DNA in pts treated with belimumab



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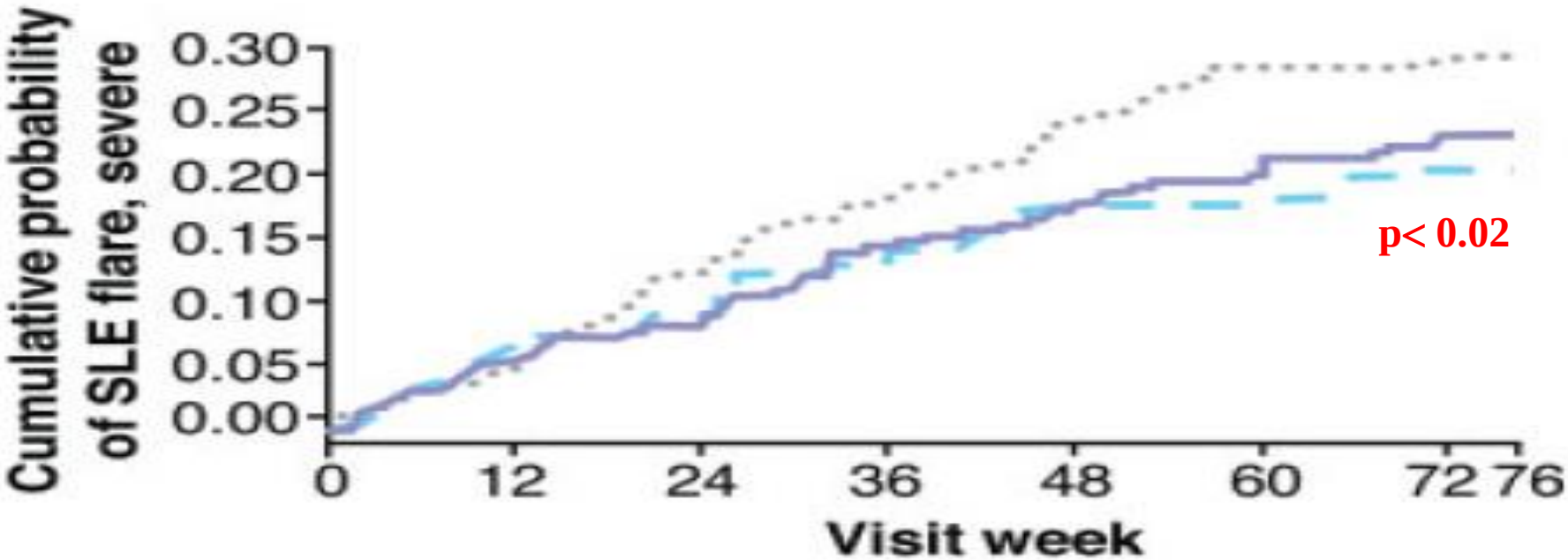
ARTHRITIS & RHEUMATISM
Vol. 63, No. 12, December 2011, pp 3918–3930

Less frequent relapses in pts treated with belimumab 1 mg/kg



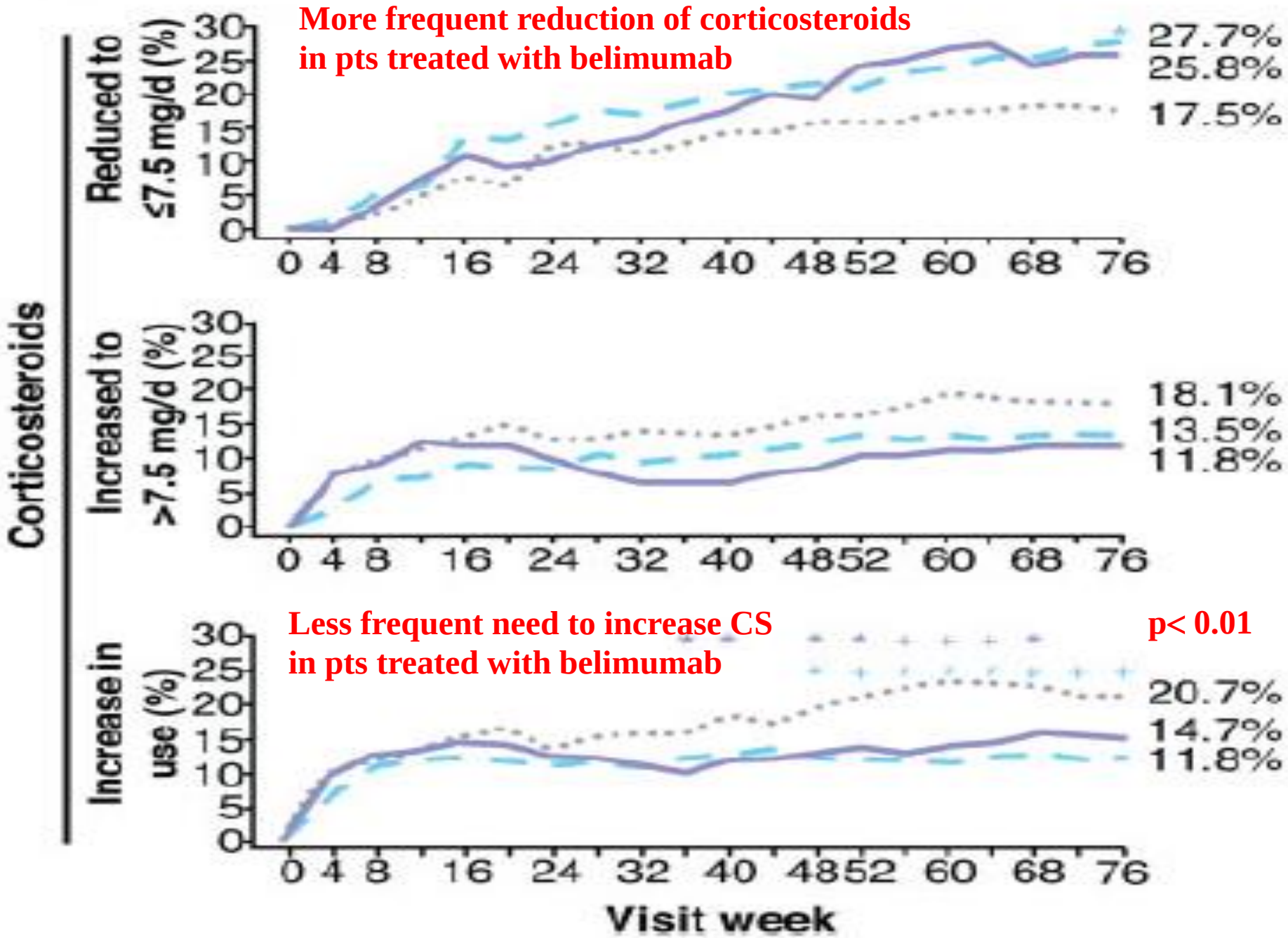
Flare rate:
- Placebo: 26.5%
- 1 mg/kg: 18.5%
- 10 mg/kg: 20.5%

Hazard ratio:
- 1 mg/kg: 0.66; $P = 0.023$
- 10 mg/kg: 0.77; $P = 0.13$

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

E

p< 0.05

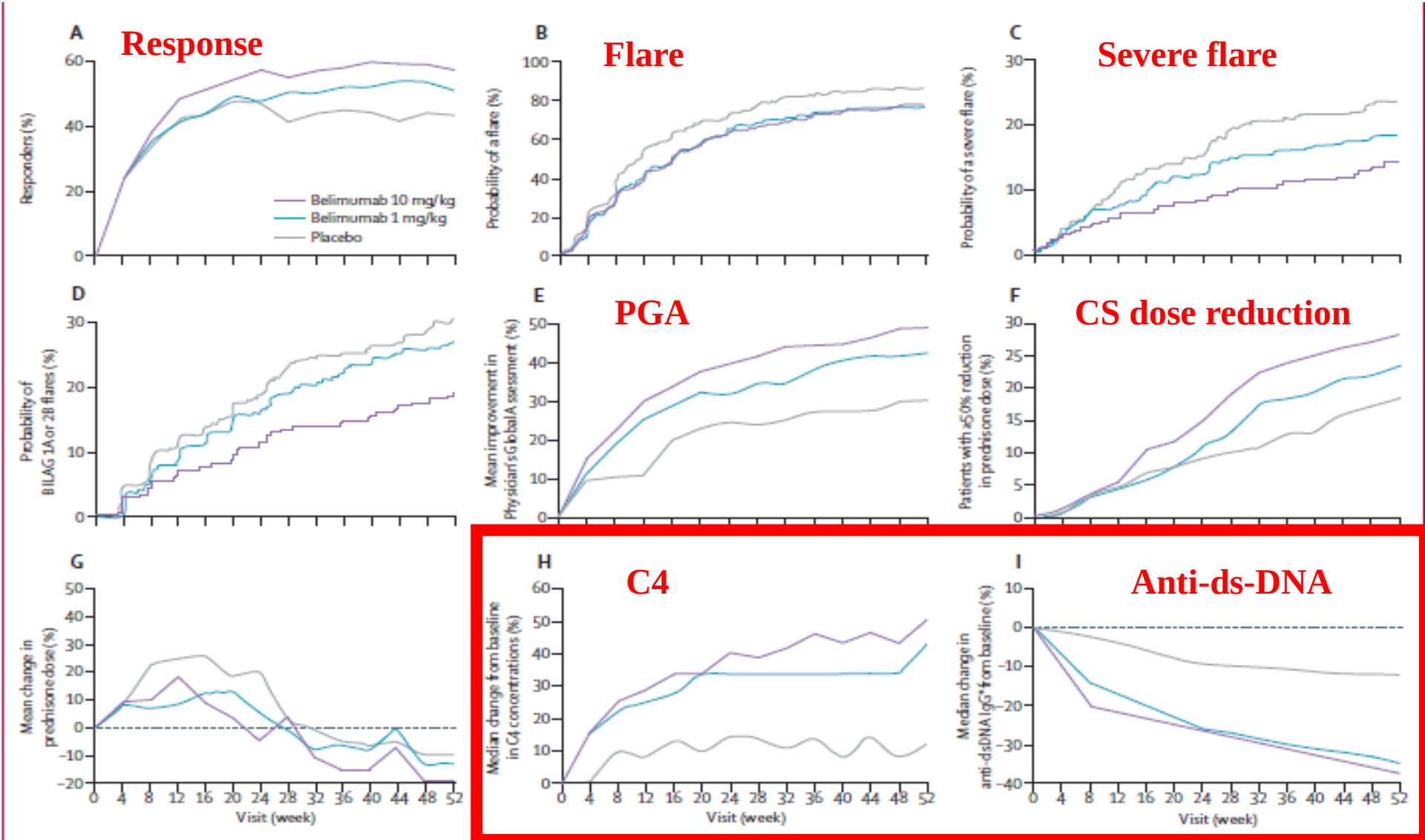


Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial

Lancet 2011; 377: 721-31

Sandra V Navarra, Renato M Guzmán, Alberto E Gallacher, Stephen Hall, Roger A Levy, Renato E Jimenez, Edmund K-M Li, Mathew Thomas, Ho-Youn Kim, Manuel G León, Coman Tanasescu, Eugeny Nasonov, Joung-Liang Lan, Lilia Pineda, Z John Zhong, William Freimuth, Michelle A Petri, for the BLISS-52 Study Group

Similar efficacy of belimumab in BLISS-52 study

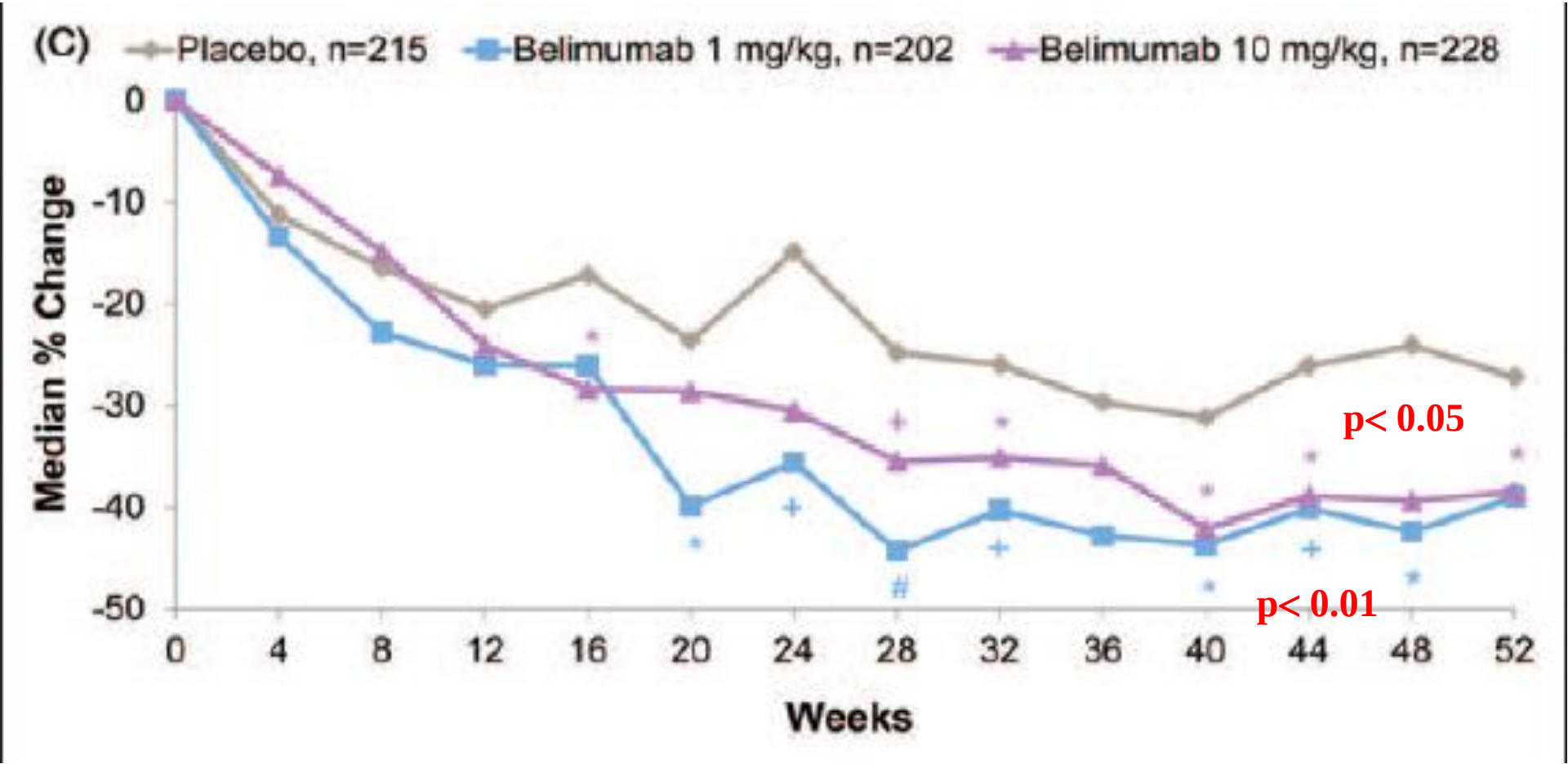


Effect of belimumab treatment on renal outcomes: results from the phase 3 belimumab clinical trials in patients with SLE

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



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

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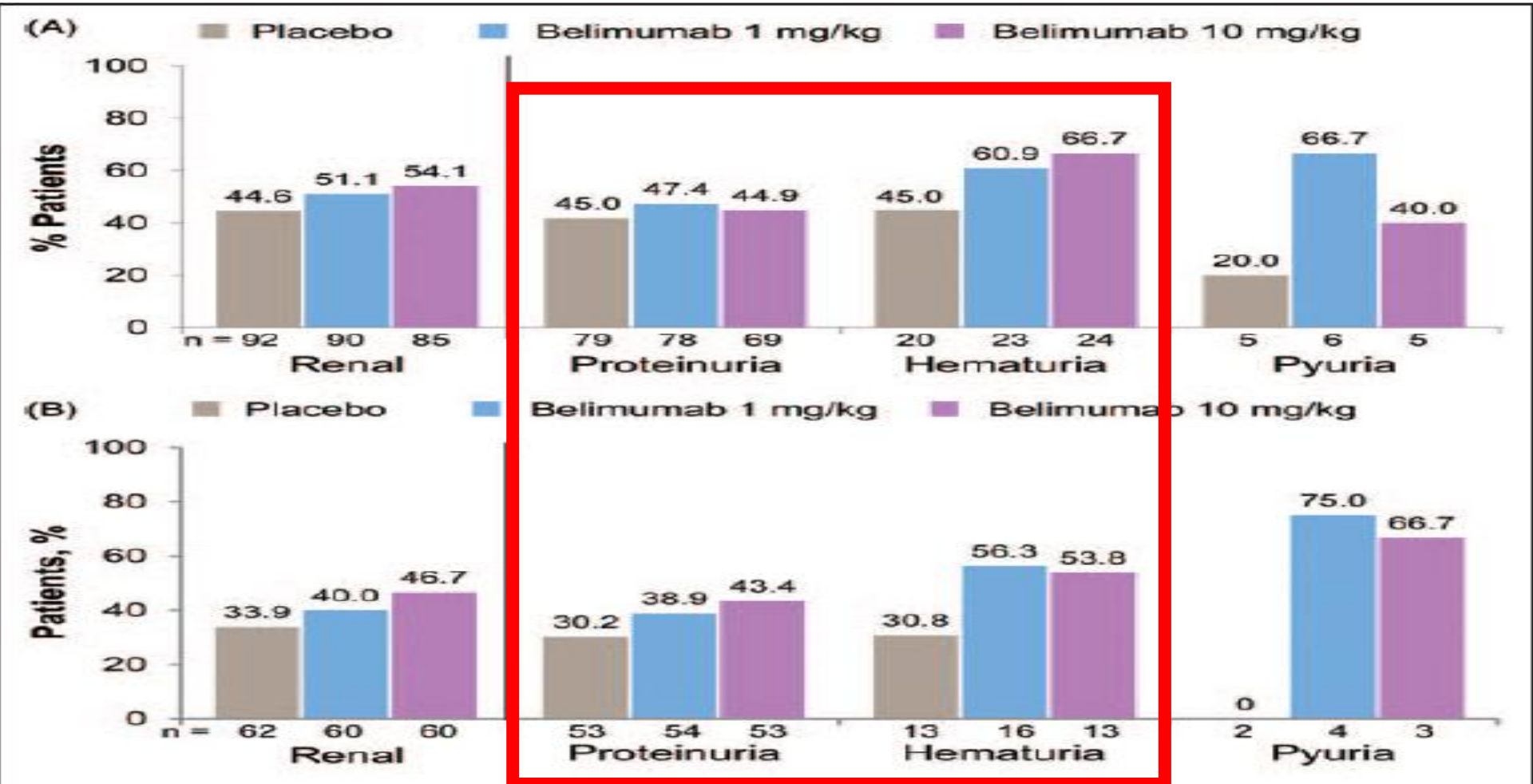
Renal response to belimumab more pronounced in seropositive pts and pts treated with MMF



Breaking the ice in systemic lupus erythematosus: belimumab, a promising new therapy

Lupus (2013) 22, 361–371

J Mosak and R Furie

5. ***Should belimumab be administered to patients with lupus nephritis?*** The BLISS studies excluded patients with severe active lupus nephritis as well as those with excessive proteinuria (>6 g/24 h). However, the results of a BLISS Phase III subgroup analysis of patients with renal involvement (n = 267) suggest that treatment with belimumab plus standard of care may have a beneficial effect on renal outcomes compared with placebo plus standard of care.[26] During the BLISS Phase III trials, belimumab was administered to 261 patients with moderate renal impairment (CrCl ≥30 and <60 ml/min) and 14 patients with severe renal impairment (CrCl ≥15 and <30 ml/min). Although clearance of belimumab decreased with decreasing creatinine clearance and increased with proteinuria (≥2 g/d), these effects were within the expected range of variability. No dose adjustment is required.[27]

BLISS-LN study (NCT 01639339)

Belimumab 10 mg/kg vs placebo for 52 weeks,
Primary endpoint - renal remission

Standard care CPH + AZA or MMF + MMF

464 pts

Results expected in 2019

Belimumab in the management of systemic lupus erythematosus – an update

Vladimir Tesar and Zdenka Hruskova

EXPERT OPINION ON BIOLOGICAL THERAPY, 2017
VOL. 17, NO. 7, 901–908

Expert opinion: Belimumab currently has its established role in the treatment of patients with SLE with serologic activity and clinical activity namely in mucocutaneous and musculoskeletal domains despite standard of care treatment. Better identification of patients who can benefit from treatment with belimumab is warranted. Data from ongoing studies in lupus nephritis and other data from observational studies are eagerly awaited.

Systemic lupus erythematosus and lupus nephritis

Toli Koutsokeras and Tina Healy

Nature Reviews Drug Discovery | AOP, published online 14 February 2014;

Table 1 | **Systemic lupus erythematosus and lupus nephritis therapeutics — pipeline products in Phase II and III (2013)**

Molecule (brand)	Company	Mechanism of action	Molecule type	Phase
Systemic lupus erythematosus				
Blisibimod	Anthera	Anti-BLYS (soluble and membrane-bound BLYS)	Recombinant protein	III
Epratuzumab	UCB/Immunomedics	Anti-CD22	Monoclonal antibody	III
Rigerimod (Lupuzor)	ImmuPharma	CD4 modulator	Synthetic peptide	III
Tabalumab	Eli Lilly	Anti-BLYS (soluble and membrane-bound BLYS)	Monoclonal antibody	III
Atacicept	Merck Serono	Anti-BLYS, anti-APRIL	Recombinant protein	II
GSK-2586184	GSK/Galapagos	JAK1 inhibitor	Small molecule	II
INV-103	Invion	Modified chaperonin 10	Recombinant protein	II
PF-04236921	Pfizer	Anti-IL-6	Monoclonal antibody	II
Rontalizumab	Genentech-Roche	Anti-IFNα	Monoclonal antibody	II
Sifalimumab	MedImmune	Anti-IFNα	Monoclonal antibody	II
Anifrolumab	MedImmune	Anti-IFNα receptor	Monoclonal antibody	II
SM-101	SuppreMol	FcγRIIB agonist	Recombinant protein	II
Lupus nephritis				
Abatacept (Orencia)	Bristol-Myers Squibb	Anti-CD80, anti-CD86	Recombinant protein	III
Belimumab (Benlysta)	GSK	Anti-BLYS (soluble BLYS)	Monoclonal antibody	III
BIIB-023	Biogen Idec	Anti-TWEAK	Monoclonal antibody	II
Laquinimod sodium	Teva/Active Biotech	Immunomodulator	Small molecule	II
Sirukumab	Johnson & Johnson/GSK	Anti-IL-6	Monoclonal antibody	II

Lessons learned from the failure of several recent trials with biologic treatment in systemic lupus erythematosus

Zdenka Hruskova and Vladimir Tesar

EXPERT OPINION ON BIOLOGICAL THERAPY
https://doi.org/10.1080/14712598.2018.1504918

Drug	Target	Clinical Trial Identifier/ Reference	Trial status
Rituximab	B cells – CD20	EXPLORER [10]	Phase II/III – failed
		LUNAR [11]	Phase III – failed
Ocrelizumab	B cells – CD20	BELONG [13]	Phase III – failed and stopped early
Tabalumab	B cells – BAFF	ILLUMINATE-1 [15]	Phase III – failed
		ILLUMINATE-2 [17]	Phase III – partially successful
Epratuzumab	B cells – CD22	EMBODY 1 and EMBODY 2 [20]	Phase III – failed

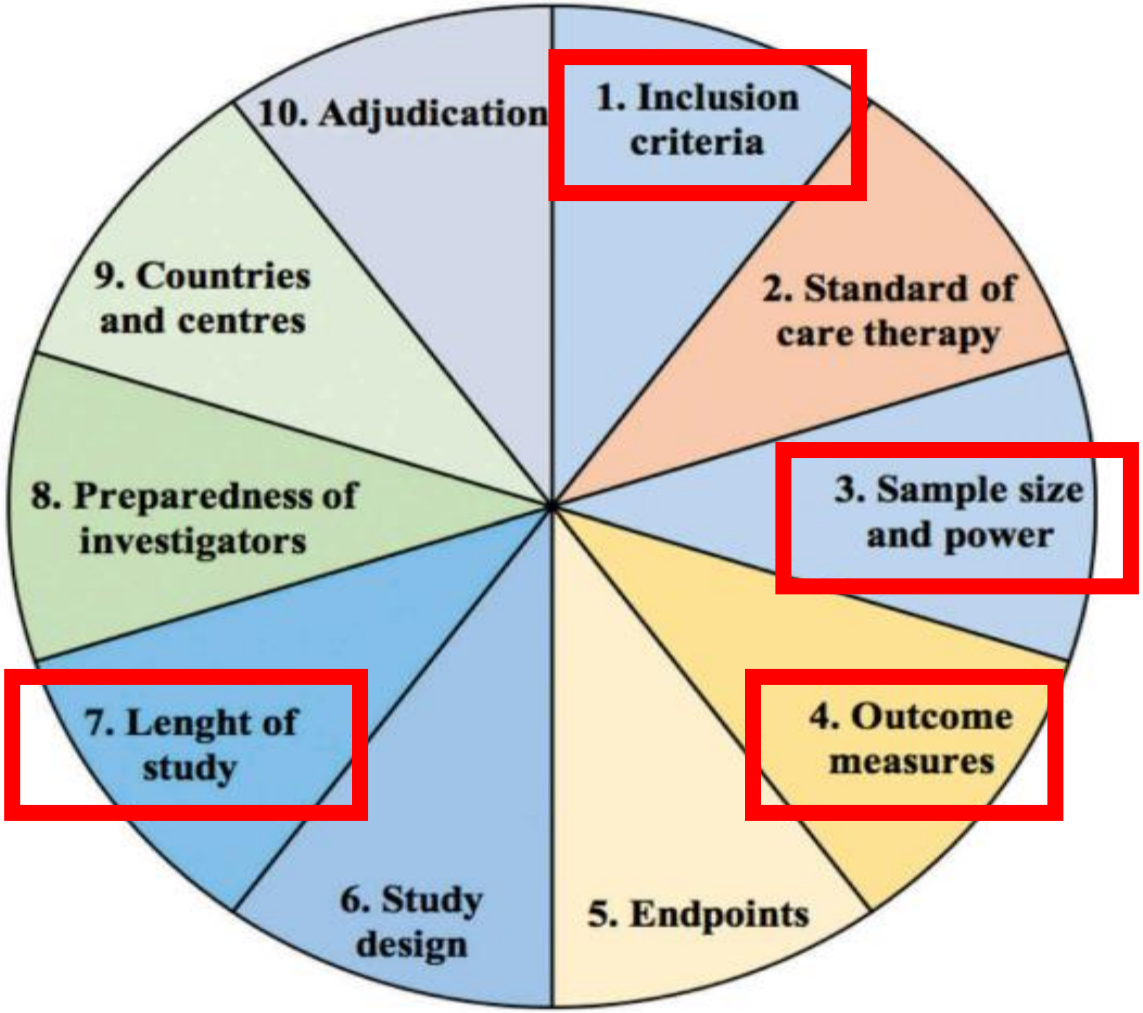
Drug	Target	Clinical Trial Identifier/ Reference	Trial status
Atacicept	B cells – BAFF and APRIL	APRIL-SLE [24]	Phase II/III - higher dose arm prematurely terminated
		ADDRESS II [26]	Phase IIb - failed
Sirukumab	IL-6	NCT01273389 [27]	Phase II – failed
Rontalizumab	IFNα	ROSE [28]	Phase II – failed
Abatacept	T cells – blocking co-stimulation	ACCESS [29]	Phase II

Recent advances in the biologic therapy of lupus: the 10 most important areas to look for common pitfalls in clinical trials

EXPERT OPINION ON BIOLOGICAL THERAPY, 2016
VOL. 16, NO. 10, 1225–1238

Jorge Medina-Rosas, Hanan Al-Rayes, Ahmed T. Moustafa and Zahi Touma

Most important pitfalls in clinical trials with biologics in SLE



Lessons learned from the failure of several recent trials with biologic treatment in systemic lupus erythematosus

EXPERT OPINION ON BIOLOGICAL THERAPY
https://doi.org/10.1080/14712598.2018.1504918

Zdenka Hruskova and Vladimir Tesar

Article highlights

- Treatment of SLE should result in preventing organ damage, reducing morbidity, improving patient survival and health-related quality of life.
- Despite expectations, most clinical trials performed in SLE and lupus nephritis in the last decade did not reach primary outcome, and the only biologic drug that has been licensed is belimumab.
- Reasons for failure of the trials include: design of the trials, sample size, entry criteria, definition of endpoints, outcome measures, heterogeneity of the disease, geographical and ethnic differences, strong 'background' medication, or too short follow-up.
- Future studies should recruit patients with similar organ involvement, well-defined disease activity, and similar severity.
- New drugs should be tested not only as 'add-on' treatment, but also as a way to reduce (or completely avoid) the (potentially toxic) background therapy.
- New drugs should be also tested in the settings of severe SLE (namely lupus nephritis and CNS involvement) where the greatest unmet need is present.

Outline of the lecture

1. Efficacy and toxicity of high-dose cyclophosphamide
2. Mycophenolate mofetil and calcineurin inhibitors in LN
3. Biologic treatment in LN
4. **Low dose cyclophosphamide – high efficacy, relatively low toxicity**
5. Conclusions

Treatment of proliferative lupus nephritis: a slowly changing landscape

Vladimir Tesar and Zdenka Hruskova

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

Table 1 | Selected recent studies of induction treatment in proliferative LN

Study	Patients	Race/ethnicity	Proliferative LN class	Follow-up duration	Results	Adverse events
Low-dose vs high-dose intravenous CYC						
Houssiau *et al.* (2002)[53]	44 on low-dose CYC vs 46 on high-dose CYC*	76 white, 6 Asian, 8 Afro-Caribbean	62 class IV, 21 class III, 7 class Vc/Vd	Median 41 months	Treatment failure: 16% vs 20% (n.s.); renal remission: 71% vs 54% (n.s.); renal flare: 27% vs 29% (n.s.)	No significant difference
Houssiau *et al.* (2010)[54]	41 on low-dose CYC vs 43 on high-dose CYC	Similar to above (exact numbers unknown)	Similar to above (exact numbers unknown)	10 years	Death: 11% vs 4% (n.s.); sustained SCr doubling: 14% vs 11% (n.s.); ESRD: 5% vs 9% (n.s.)	Not reported
AZA vs CYC						
Grootscholten *et al.* (2006)[58]	37 on oral AZA+MP pulses vs 50 on CYC+MP pulses	80% white in CYC limb, 70% Caucasian in AZA limb	90% class IV or Vd, 10% class III or Vc	5.7 years	SCr doubling: more frequent in AZA limb (RR 4.1); relapse: more frequent in AZA limb (RR 8.8); renal remission: no difference	Infections more frequent in AZA limb; no difference in ovarian function

Low vs. high doses of cyclophosphamide in mostly Caucasian population

Houssiau et al Arthritis and Rheum. 2002

Induction treatment - 3 iv MP pulses a 750 mg

- **High dose of CPH**
- 8 IV CPH pulses (1g)
- mean **8.5±1.9 g**

- **Low dose of CPH**
- 6 pulses of CPH a 500mg a 2 weeks
- mean **3 g**

- Azathioprine 2mg/kg/day 13th – 30th month

Azathioprine 2mg/kg/day 4th - 30th month

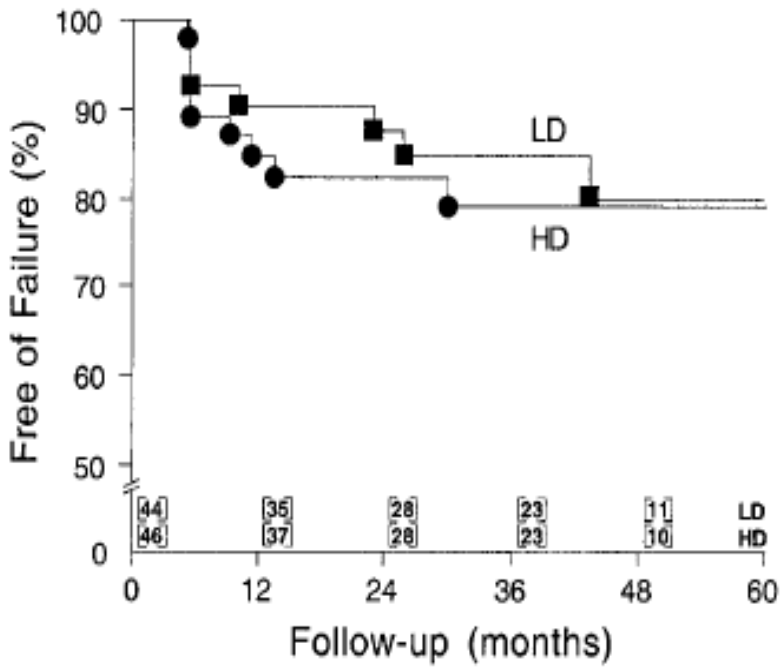
Immunosuppressive Therapy in Lupus Nephritis

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

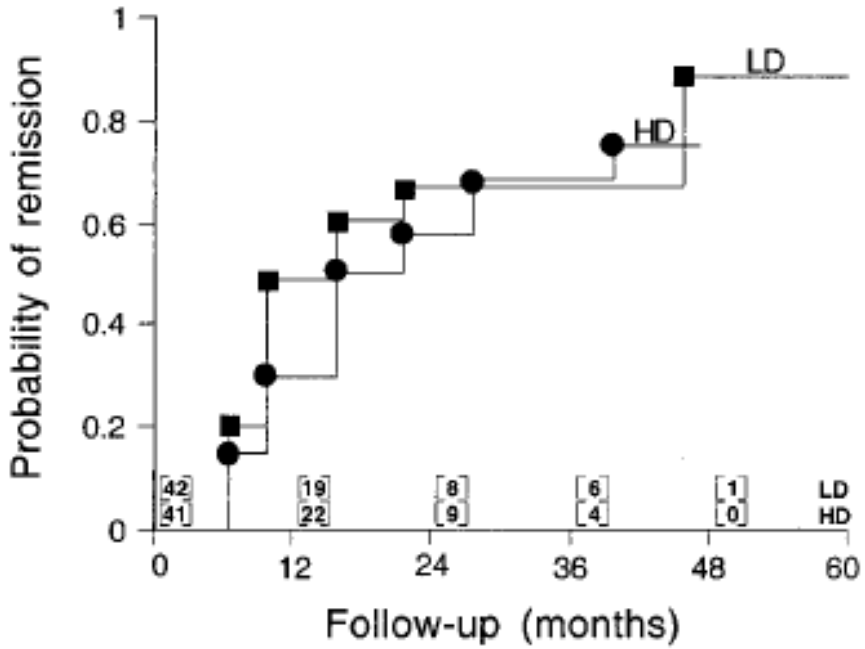
Frédéric A. Houssiau,[1] Carlos Vasconcelos,[2] David D'Cruz,[3] Gian Domenico Sebastiani,[4] Enrique de Ramon Garrido,[5] Maria Giovanna Danieli,[6] Daniel Abramovicz,[7] Daniel Blockmans,[8] Alessandro Mathieu,[9] Haner Direskeneli,[10] Mauro Galeazzi,[11] Ahmet Gül,[12] Yair Levy,[13] Peter Petera,[14] 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

Low-dose CPH similary effective…



Treatment failure



Renal remission

EURO-LUPUS TRIAL

mean follow-up of 41 months

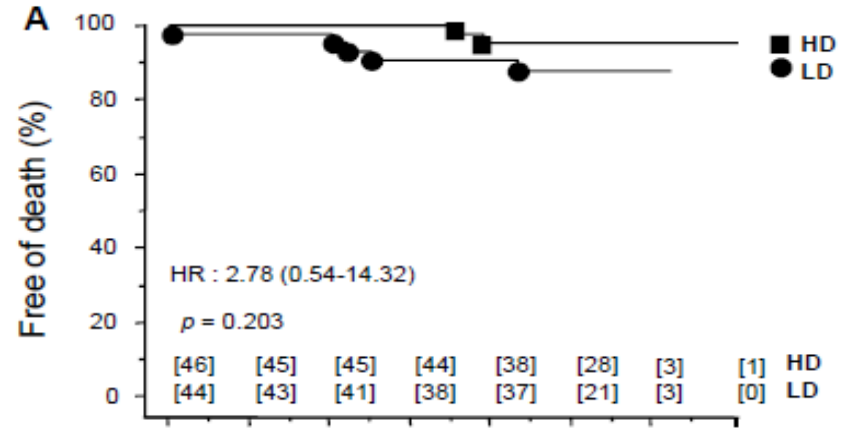
	High CPH 45 pts	Low CPH 44 pts
Renal failure	6.6%	9.0%
Death	0	4.5%
Renal relapses	29%	26%
Renal remission	54%	70%
Treatment failure	20%	16%
Severe infections	22%	11%

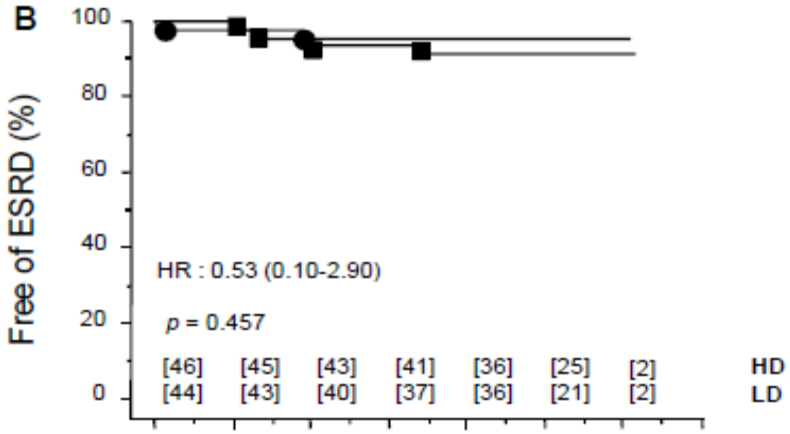
The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose versus high-dose intravenous cyclophosphamide

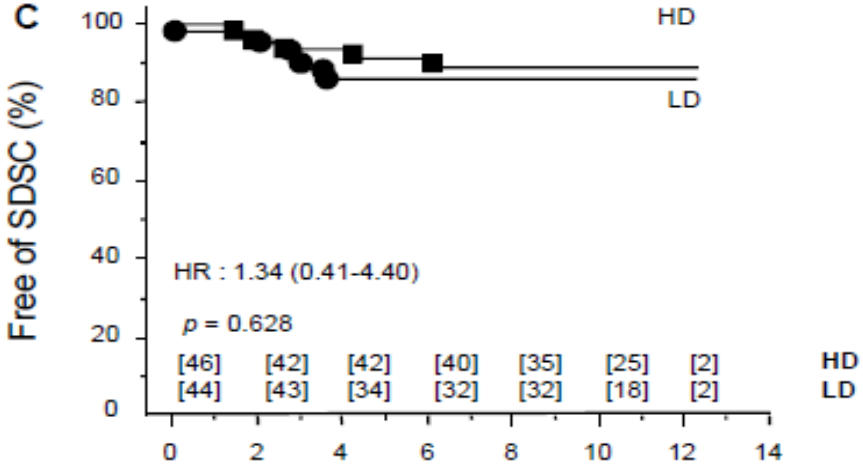
Frédéric A Houssiau, Carlos Vasconcelos, David D'Cruz, Gian Domenico Sebastiani, Enrique de Ramon Garrido, Maria Giovanna Danieli, Daniel Abramovicz, Daniel Blockmans, Alberto Cauli, Haner Direskeneli, Mauro Galeazzi, Ahmet Gül, Yair Levy, Peter Petera, Rajko Popovic, Radmila Petrovic, Renato A Sinico, 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

Efficacy maintained during 10 yr FU







	LD	HD
Death	11%	4%
DSC	14%	11%
ESRD	5%	9%

Treatment of Lupus Nephritis With Abatacept

The Abatacept and Cyclophosphamide Combination Efficacy and Safety Study

The ACCESS Trial Group

ARTHRITIS & RHEUMATOLOGY
Vol. 66, No. 11, November 2014, pp 3096–3104

Low dose CPH used in ACCESS trial in multiethnic population (39% African Americans, 40% Hispanics)

Table 1. Patient demographics and baseline characteristics*

Variable	Control (n = 68)	Abatacept (n = 66)
Age, mean ± SD years	32.7 ± 12.0	32.0 ± 10.1
Female	64 (94)	58 (88)
Primary race		
White	33 (49)	34 (51)
African American	25 (37)	27 (41)
Asian	3 (4)	3 (5)
Mixed or undeclared	7 (10)	2 (3)
Ethnicity		
Hispanic/Mestizo	28 (41)	25 (38)

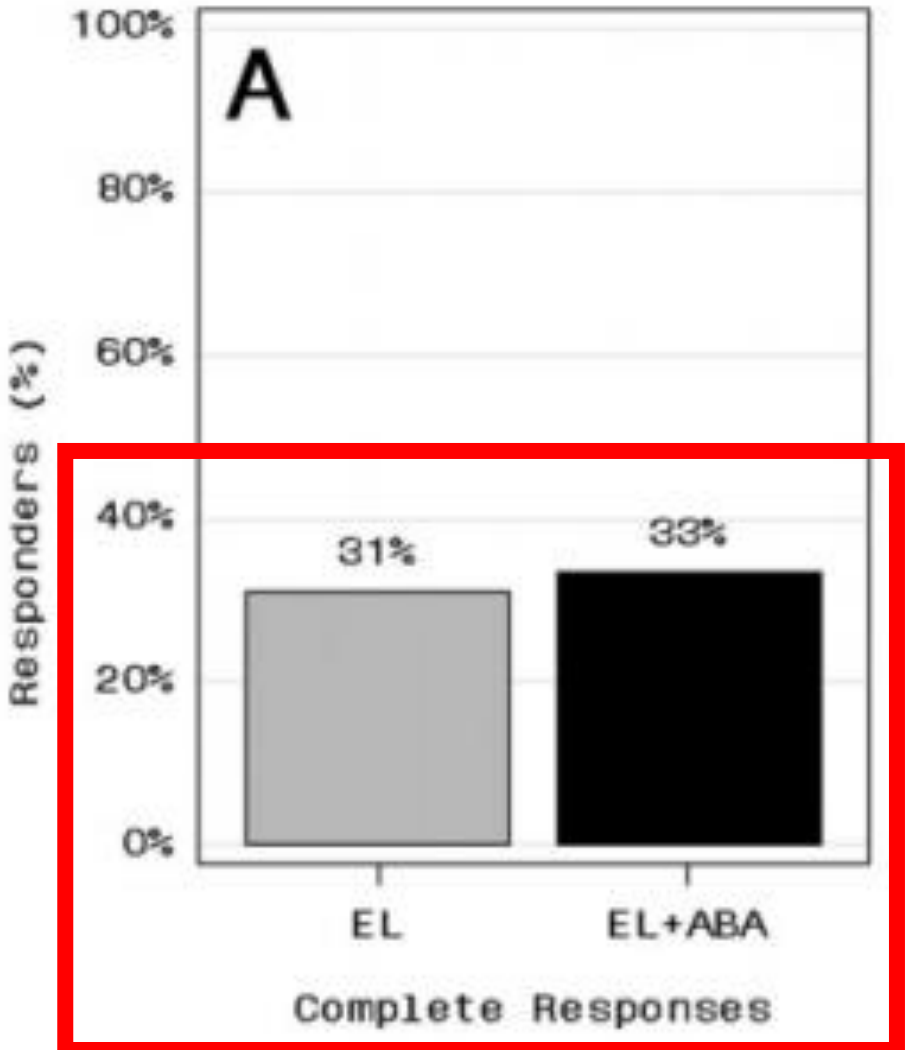
Treatment of Lupus Nephritis With Abatacept

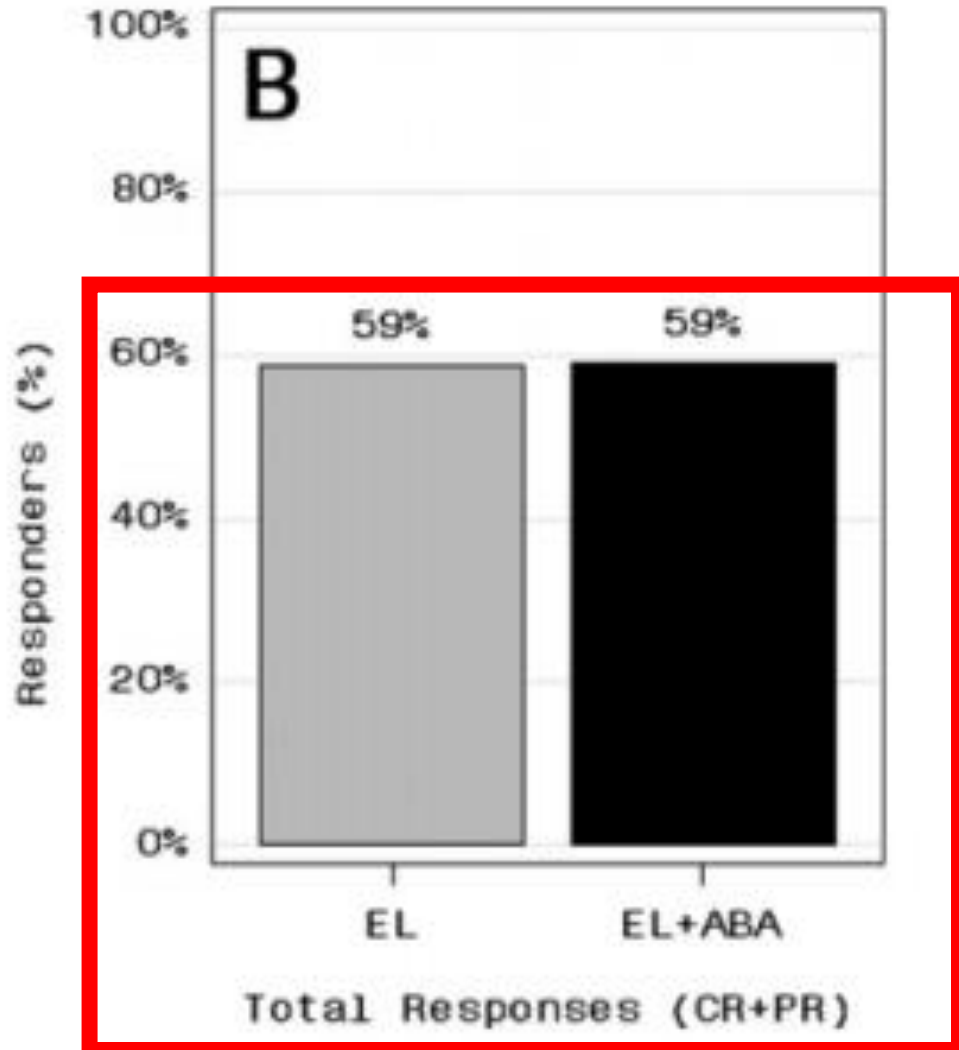
The Abatacept and Cyclophosphamide Combination Efficacy and Safety Study

The ACCESS Trial Group

ARTHRITIS & RHEUMATOLOGY
Vol. 66, No. 11, November 2014, pp 3096–3104

Complete response rate was 33%, total response rate 59% …





Crossing the Atlantic: The Euro-Lupus Nephritis Regimen in North America

ARTHRITIS & RHEUMATOLOGY
Vol. 67, No. 5, May 2015, pp 1144–1146

David Wofsy,[1] Betty Diamond,[2] and Frédéric A. Houssiau[3]

… quite comparable to ELNT and MMF and high-dose CPH in ALMS trial

Based on available evidence, and the principle of first doing no harm, the ELNT regimen should be considered an option for all patients with lupus nephritis.

Treatment regimen	% with proteinuria >3 gm/24 hours at baseline†	Complete response rate (%) at 6 months‡
ELNT–low dose (n = 36)	42	25
ELNT–high dose (n = 38)	45	24
ACCESS (n = 66)	52	23
ALMS–MMF (n = 169)	57	21
ALMS–CYC (n = 171)	60	22

Comparison of low-dose intravenous cyclophosphamide with oral mycophenolate mofetil in the treatment of lupus nephritis

CrossMark

Kidney International (2016) **89**, 235–242

Manish Rathi[1], Ajay Goyal[1], Ajay Jaryal[1], Aman Sharma[2], Pramod K. Gupta[3], Raja Ramachandran[1], Vivek Kumar[1], Harbir S. Kohli[1], Vinay Sakhuja[4], Vivekanand Jha[1] and Krishan L. Gupta[1]

Low dose CPH compared with MMF in 100 Indian pts (class III-V LN).

Both limbs comparable except for ↑ Pu at presentation in CPH limb

Table 1 | Baseline characteristics of the study population

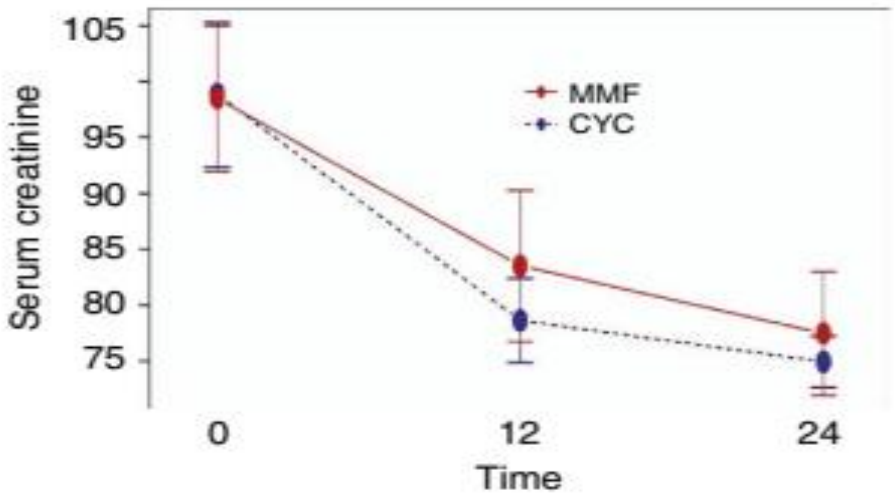
Variable	CYC *n* = 50	MMF *n* = 50	*P*-value
Gender, n *(%)*			
Female	45 (90)	47 (94)	0.715
Male	5 (10)	3 (6)	
Kidney biopsy class, n *(%)*			
III/III+V	6 (12)	11 (22)	0.414
IV/IV+V	30 (60)	27 (54)	
V	14 (28)	12 (24)	
Age (years)	30.6 ± 9.5	28.3 ± 9.5	0.237
Body mass index (kg/m^2)	22.3 ± 3.1	22.5 ± 3.6	0.85
SLEDAI score[a]	18.1 ± 6.2	17.9 ± 5.6	0.866
Anti-dsDNA positive, *n* (%)	45 (90)	44 (88)	1
Hypocomplementemia (↓ C3 or C4), *n* (%)	46 (92)	38 (76)	0.056
Hemoglobin (g/l)	89 ± 18	94.4 ± 24	0.203
Leukocyte count (x10^9/l)[b]	6.5 (4, 8)	6.8 (4.8, 9.1)	0.311
Platelet count (x10^9/l)[b]	143.5 (108, 264.8)	220 (133.8, 269)	0.177
Blood urea nitrogen (mmol/l)[b]	6.7 (5.5, 10)	6.0 (4.5, 8.5)	0.178
Serum creatinine (μmol/l)[b]	77.3 (70.7, 123.8)	79.6 (70.7, 123.8)	0.942
Urine protein/creatinine ratio[b]	3.0 (1.9, 4.4)	2.2 (1.6, 3.4)	**0.024**
eGFR (ml/min)[c]	75.8 ± 31.2	78.3 ± 32.9	0.693
Serum albumin (g/l)	24.7 ± 7.0	27.4 ± 8.0	0.082

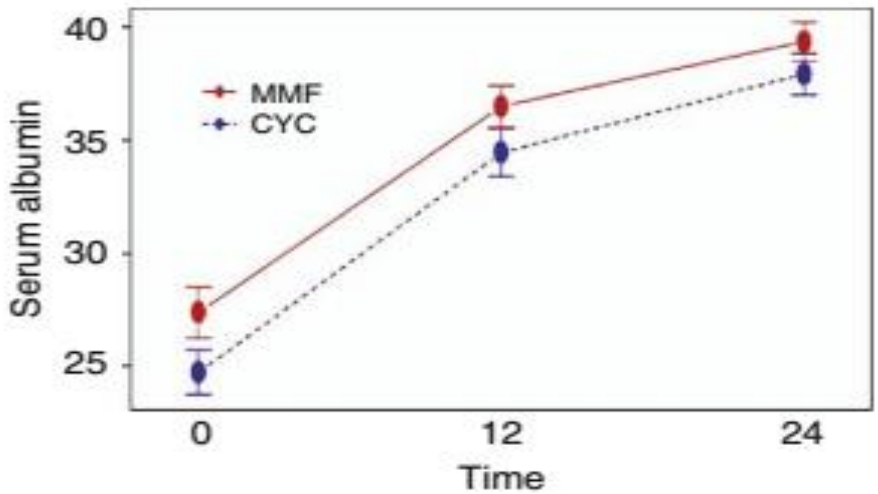
Comparison of low-dose intravenous cyclophosphamide with oral mycophenolate mofetil in the treatment of lupus nephritis

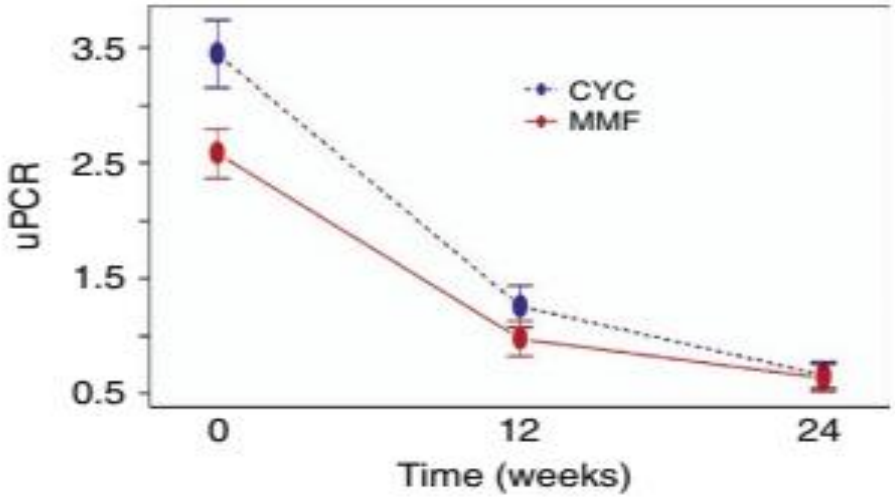
Kidney International (2016) **89**, 235–242

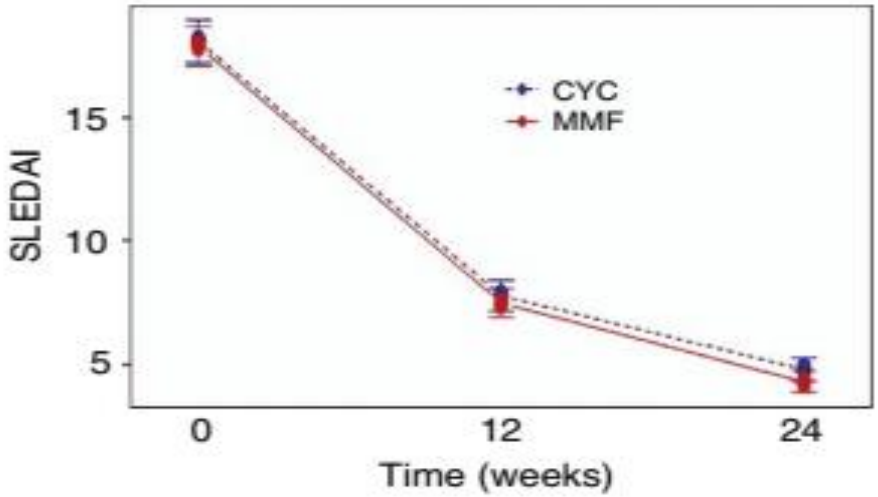
Manish Rathi[1], Ajay Goyal[1], Ajay Jaryal[1], Aman Sharma[2], Pramod K. Gupta[3], Raja Ramachandran[1], Vivek Kumar[1], Harbir S. Kohli[1], Vinay Sakhuja[4], Vivekanand Jha[1] and Krishan L. Gupta[1]

No difference in SLEDAI, proteinuria, serum creatinine and albumin







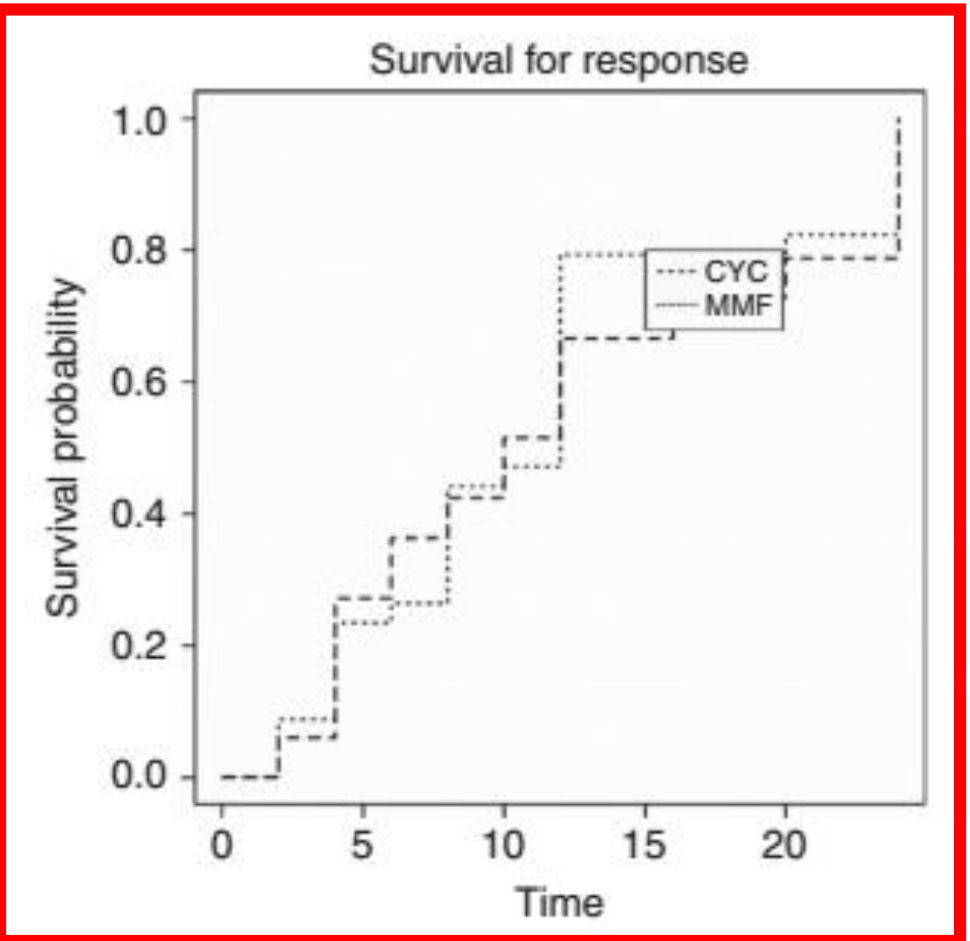


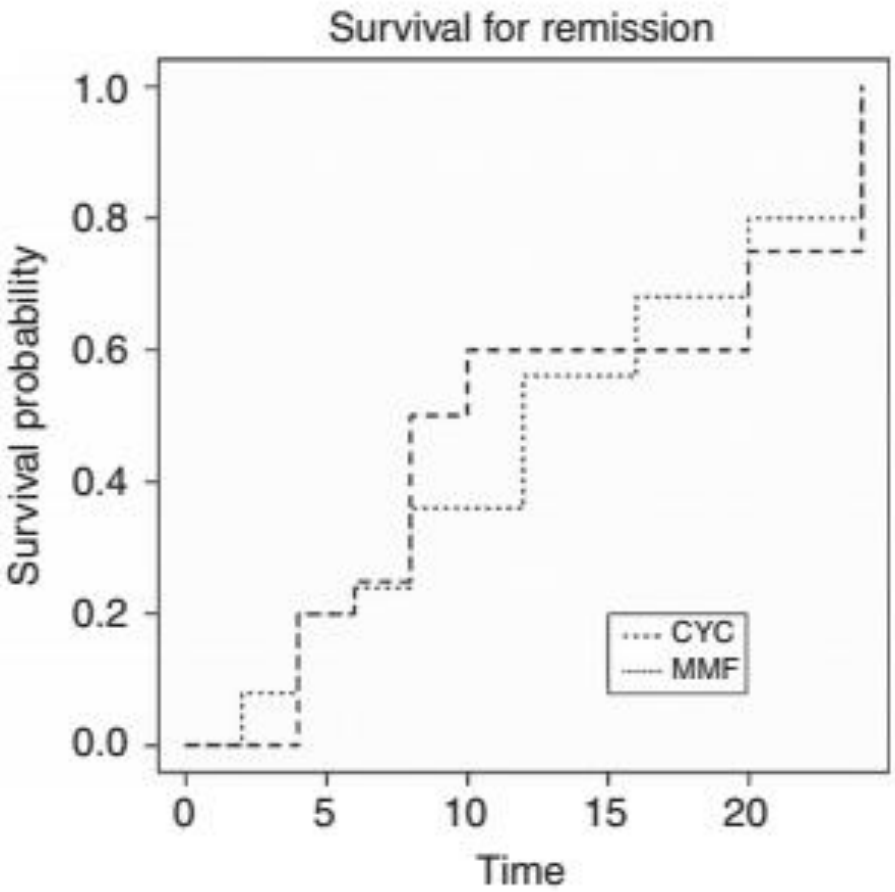
Comparison of low-dose intravenous cyclophosphamide with oral mycophenolate mofetil in the treatment of lupus nephritis

Kidney International (2016) **89**, 235–242

Manish Rathi[1], Ajay Goyal[1], Ajay Jaryal[1], Aman Sharma[2], Pramod K. Gupta[3], Raja Ramachandran[1], Vivek Kumar[1], Harbir S. Kohli[1], Vinay Sakhuja[4], Vivekanand Jha[1] and Krishan L. Gupta[1]

Response and remission rate very similar in MMF and low-dose CPH limb





Comparison of low-dose intravenous cyclophosphamide with oral mycophenolate mofetil in the treatment of lupus nephritis

CrossMark
Kidney International (2016) 89, 235–242

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AE rate similar in both limbs, but much ↑rate of GI events in MMF limb

Table 3 | Adverse events during 24-week induction phase

Adverse events	CYC $n = 50$	MMF $n = 50$
Death	2 (4.0)	5 (10)
Patients with at least one AE	25 (50)	32 (64)
Infections (total)	13	10
Pneumonia	4	4
Urinary tract infection	3	1
Esophageal candidiasis	0	1
Breast abscess	0	1
Gluteal abscess	1	0
Herpes zoster	5	3
Pulmonary tuberculosis	0	1
Acute parotitis	0	1
Shock	1	1
GI symptoms	**2 (4.0)**	**26 (52)***
Gastric ulcer	1	0
Transaminitis	0	1
Cytopenia	5	7
Leg ulcers	3	0
Steroid induced diabetes	1	2
Deep vein thrombosis	2	1
Neurological		
Headache	0	1
Seizures	3	1
Stroke	0	1
Psychosis	1	0
Worsened GFR	1	1
Menorrhagia	1	0
Amenorrhea	1	2
Alopecia	1	0
Diffuse alveolar hemorrhage	0	1

Moving East: the Euro–Lupus Nephritis regimen in Asia

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

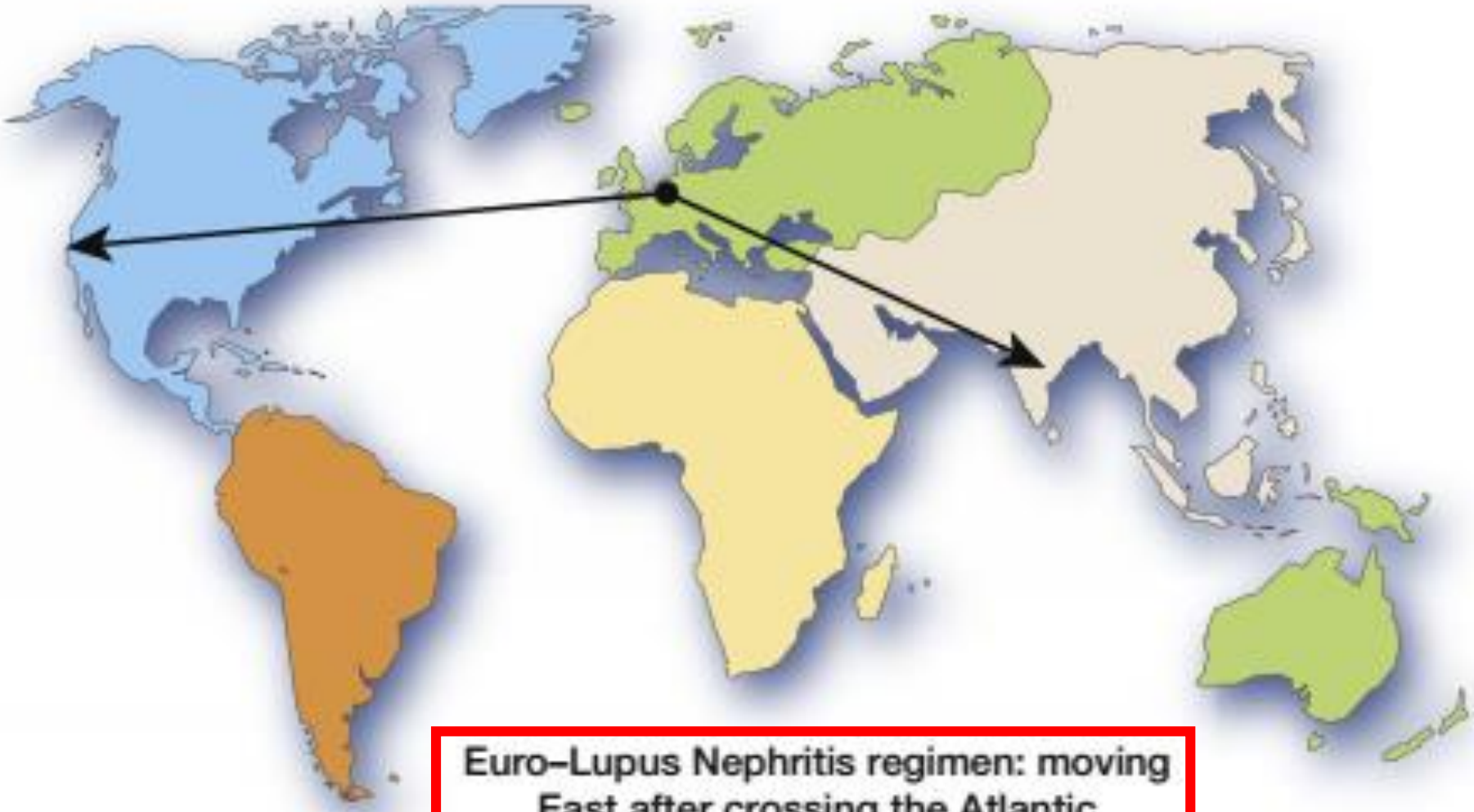
Frédéric A. Houssiau[1]

Treatment of lupus nephritis is more evidenced-based than ever. Yet many areas of uncertainty persist. The article by Rathi *et al.* brings a piece to the puzzle by comparing, in a group of Indian patients, the Euro-Lupus low-dose i.v. cyclophosphamide regimen with mycophenolate mofetil. Although some caveats must be raised, the results suggest that, after crossing the Atlantic, the Euro-Lupus regimen may well be moving East.

Moving East: the Euro–Lupus Nephritis regimen in Asia

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

Frédéric A. Houssiau[1]



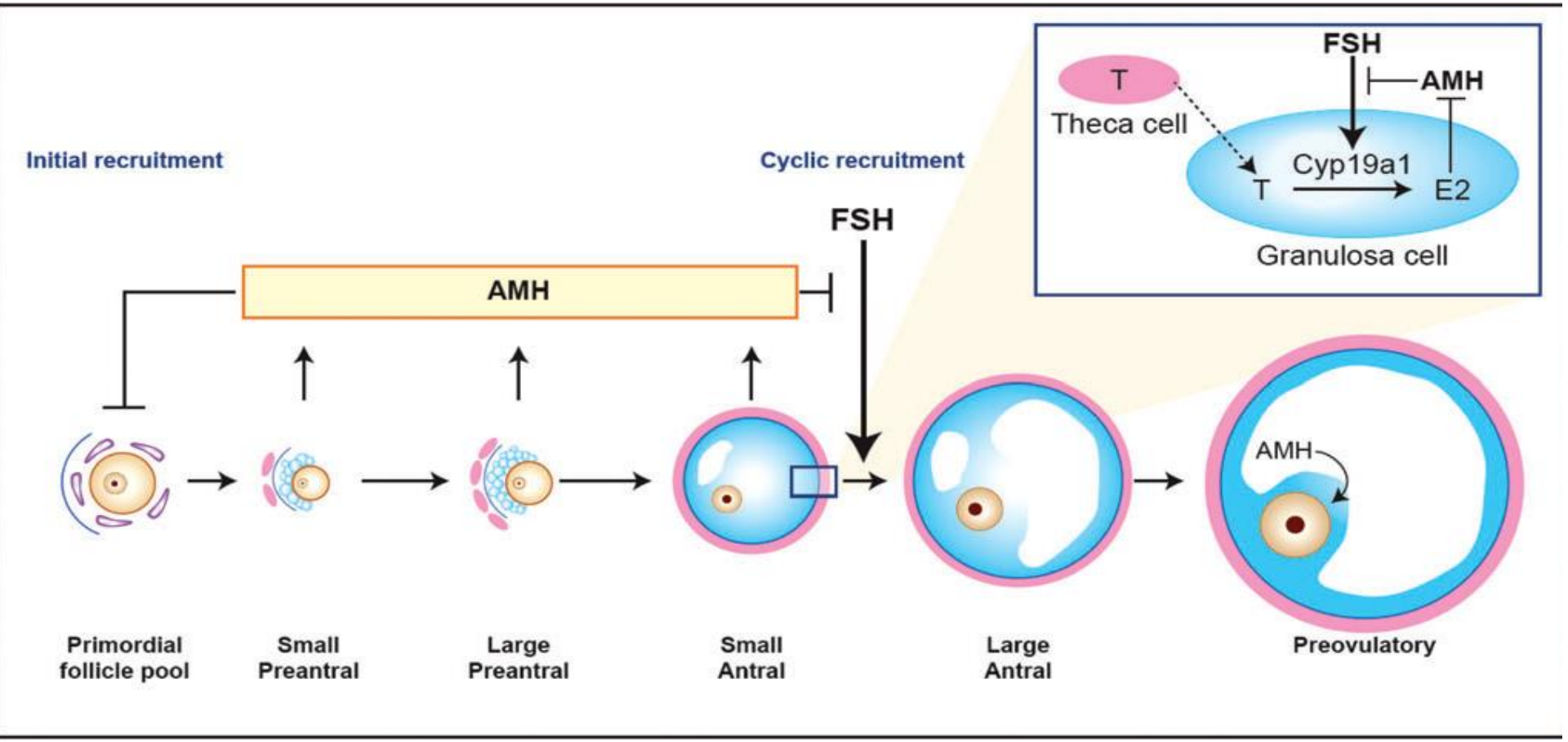
Euro–Lupus Nephritis regimen: moving East after crossing the Atlantic

The physiology and clinical utility of anti-Müllerian hormone in women

Didier Dewailly[1,*], Claus Yding Andersen[2], Adam Balen[3],

Human Reproduction Update, Vol.20, No.3 pp. 370–385, 2014

AMH inhibits initial follicle recruitment and FSH-dependent growth of small antral follicles

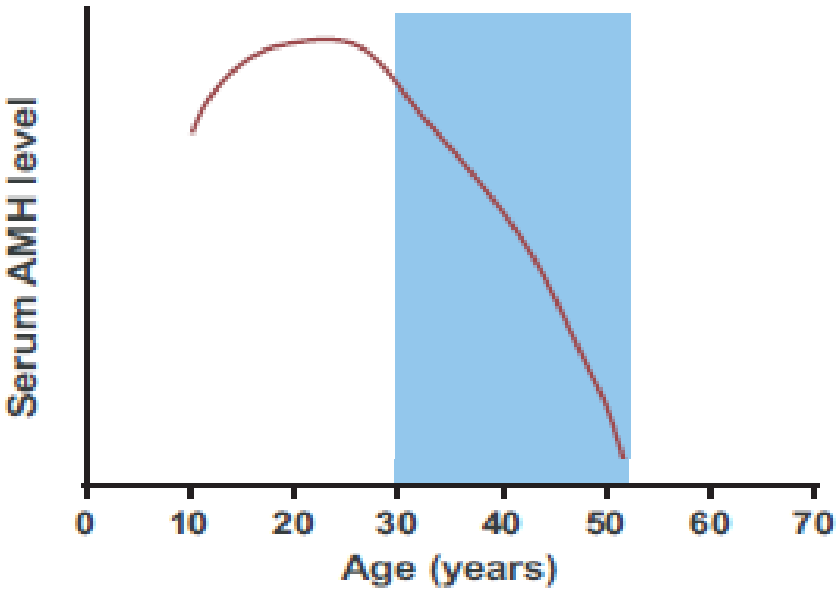


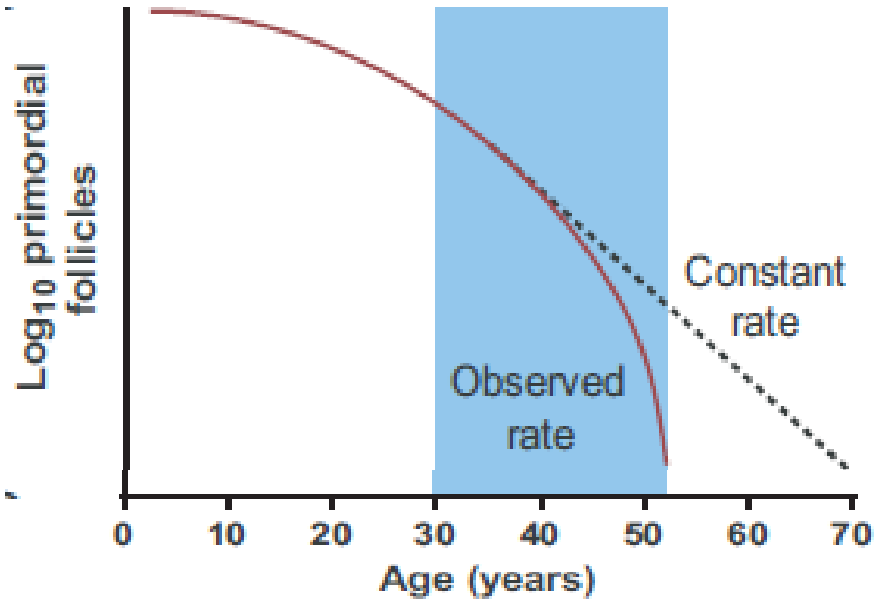
A putative role for anti-Müllerian hormone (AMH) in optimising ovarian reserve expenditure

Journal of Endocrinology
(2017) **233**, R1–R13

Michael W Pankhurst

AMH levels correlate with the ovarian reserve





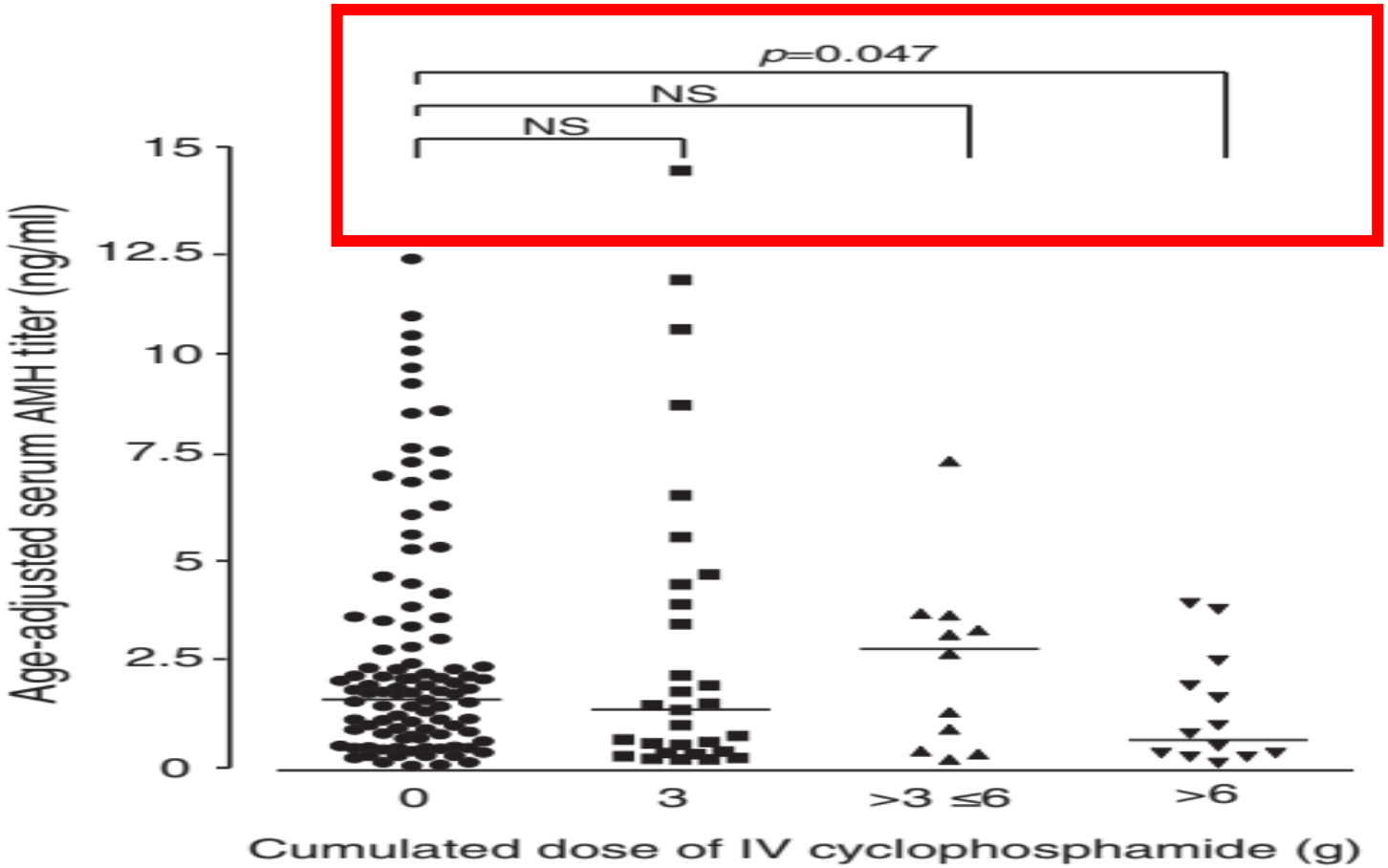
The Euro-Lupus Low-Dose Intravenous Cyclophosphamide Regimen Does Not Impact the Ovarian Reserve, as Measured by Serum Levels of Anti–Müllerian Hormone

ARTHRITIS & RHEUMATOLOGY
Vol. 69, No. 6, June 2017, pp 1267–1271

Farah Tamirou, Séverine Nieuwland Husson, Damien Gruson, Frédéric Debiève, Bernard R. Lauwerys, and Frédéric A. Houssiau

Anti-müllerian hormone (AMH - marker of ovarian reserve) measured in 155 premenopausal SLE pts

(30 treated with low-dose CPH, 24 high-dose CPH, the rest not treated with CPH)



Anti–Müllerian Hormone and Ovarian Reserve in Systemic Lupus Erythematosus

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

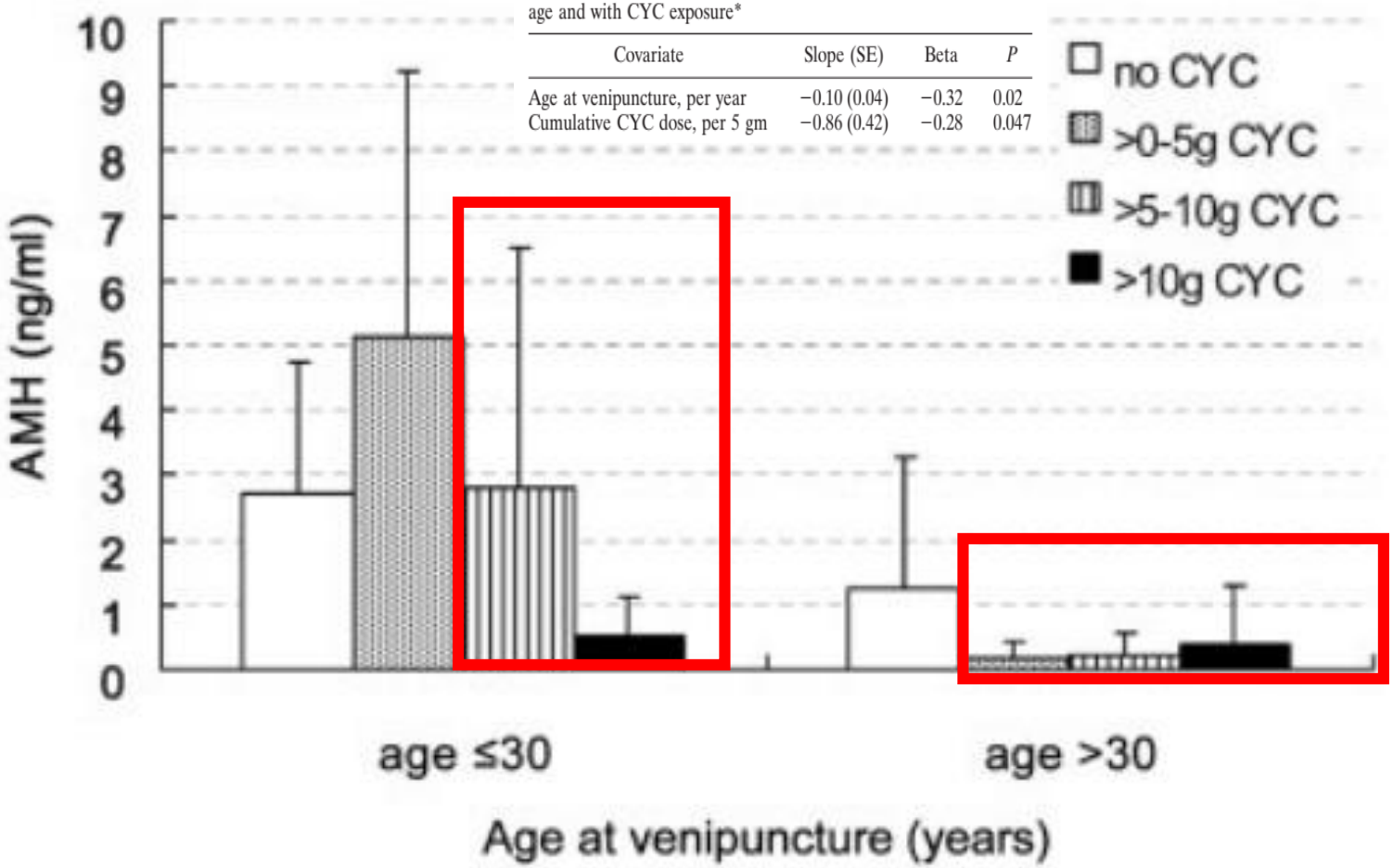
C. C. Mok, P. T. Chan, and C. H. To

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



The relationship between cancer and medication exposures in systemic lupus erythaematosus: a case–cohort study

Ann Rheum Dis 2008;**67**:74–79.

S Bernatsky,[1] L Joseph,[2] J-F Boivin,[1] C Gordon,[4] M Urowitz,[5] D Gladman,[5] P R Fortin,[5] E Ginzler,[6] S-C Bae,[7] S Barr,[8] S Edworthy,[8] D Isenberg,[9] A Rahman,[9] M Petri,[10] G S Alarcón,[11] C Aranow,[12] M-A Dooley,[13] R Rajan,[14] J-L Sénécal,[15] M Zummer,[16] S Manzi,[17] R Ramsey-Goldman,[18] A E Clarke[2]

246 cancer cases compared 538 control SLE pts without cancer

increased risk of haematological cancer after lag-time of 5 yrs related to IST

Table 3 Adjusted hazard ratio (HR) estimates for haematological cancer occurrence in systemic lupus erythaematosus (SLE) after immunosuppressive exposure, lag-time 5 years*

Exposure†	HR	95% CI
Immunosuppressive exposure	2.29	1.02–5.15
Anti-malarial agents	1.88	0.86–4.11
Systemic glucocorticoids	1.63	0.72–3.66
NSAIDs	0.71	0.27–1.86
Aspirin	0.88	0.33–2.36
Tobacco use‡	0.79	0.54–1.15
Age ≥65	2.71	0.96–7.61
Female sex	1.99	0.56–7.10
White	1.04	0.50–2.14
Damage§	2.10	1.01–4.40
Residence in North America	1.08	0.43–2.71
Sjögren syndrome¶	1.08	0.35–3.37
Cohort entry before 1990	2.38	1.07–5.32

Lymphoma risk in systemic lupus: effects of disease activity versus treatment

ARD Online First, published on January 8, 2013

Sasha Bernatsky,[1,2] Rosalind Ramsey-Goldman,[3] Lawrence Joseph,[1,2] Jean-Francois Boivin,[2] Karen H Costenbader,[4] Murray B Urowitz,[5] Dafna D Gladman,[5]

75 SLE pts with lymphoma compared to 4961 cancer-free controls

Lymphoma risk may be associated with both CPH and CS exposure

Table 2 Results of the unadjusted, partially adjusted and fully adjusted models to assess the HR of exposures in lymphoma development in patients with systemic lupus erythematosus (SLE)

Variable	Unadjusted HR (95% CI)	Partially adjusted model (95% CI)	Fully adjusted HR (95% CI)
Outside North America	0.81 (0.46 to 1.45)	–	0.91 (0.44 to 1.90)
Calendar year	1.02 (0.99 to 1.04)	–	0.99 (0.96 to 1.02)
Male	2.74 (1.45 to 5.19)	2.64 (1.39 to 5.02)	2.70 (1.38 to 5.28)
Age	1.04 (1.03 to 1.06)	1.04 (1.02 to 1.06)	1.04 (1.02 to 1.06)
White race/ethnicity	1.11 (0.67 to 1.84)	–	0.91 (0.53 to 1.56)
Sjogren's syndrome	2.08 (1.13 to 3.8)	1.94 (1.04 to 3.61)	1.79 (0.88 to 3.62)
Glucocorticosteroids ever used	1.69 (0.95 to 3.03)	–	0.79 (0.25 to 2.45)
Cumulative glucocorticosteroids >3.5 g*	1.82 (1.06 to 3.14)	1.94 (1.11 to 3.39)	2.57 (0.94 to 7.04)
Cyclophosphamide ever used	2.07 (1.13 to 3.81)	1.90 (1.02 to 3.53)	2.80 (0.87 to 8.98)
Cumulative cyclophosphamide >6 g	1.68 (0.80 to 3.55)	–	0.68 (0.18 to 2.59)
Azathioprine (AZA) ever used	0.72 (0.41 to 1.27)	–	0.84 (0.32 to 2.25)
Cumulative AZA >36.5 g	0.55 (0.27 to 1.11)	–	0.59 (0.18 to 1.92)
Methotrexate ever used	1.06 (0.50 to 2.26)	–	0.74 (0.31 to 1.78)
Mycophenolate ever used	1.47 (0.61 to 3.54)	–	1.47 (0.58 to 3.71)
Antimalarial drugs ever used	1.63 (0.94 to 2.84)	–	1.55 (0.81 to 2.96)
High disease activity†	0.62 (0.34 to 1.13)	0.65 (0.35 to 1.22)	0.68 (0.36 to 1.29)

Outline of the lecture

1. Efficacy and toxicity of high-dose cyclophosphamide
2. Mycophenolate mofetil and calcineurin inhibitors in LN
3. Biologic treatment in LN
4. Low dose cyclophosphamide
   – high efficacy, relatively low toxicity
5. Conclusions

Conclusions

1. **Low dose CPH effective and (relatively) safe**
   (not only in Caucasian, but also in African American, Hispanic and Asian pts with LN)

2. **Newer drugs not superior to CPH,**
   but reasonable alternative
   (to avoid gonadotoxicity, excessive cumulative doses of CPH, in pts intolerant or refractory to CPH)

3. **Further more personalized studies**
   (with the aim to avoid not only CPH, but also high-dose steroids) **warranted**