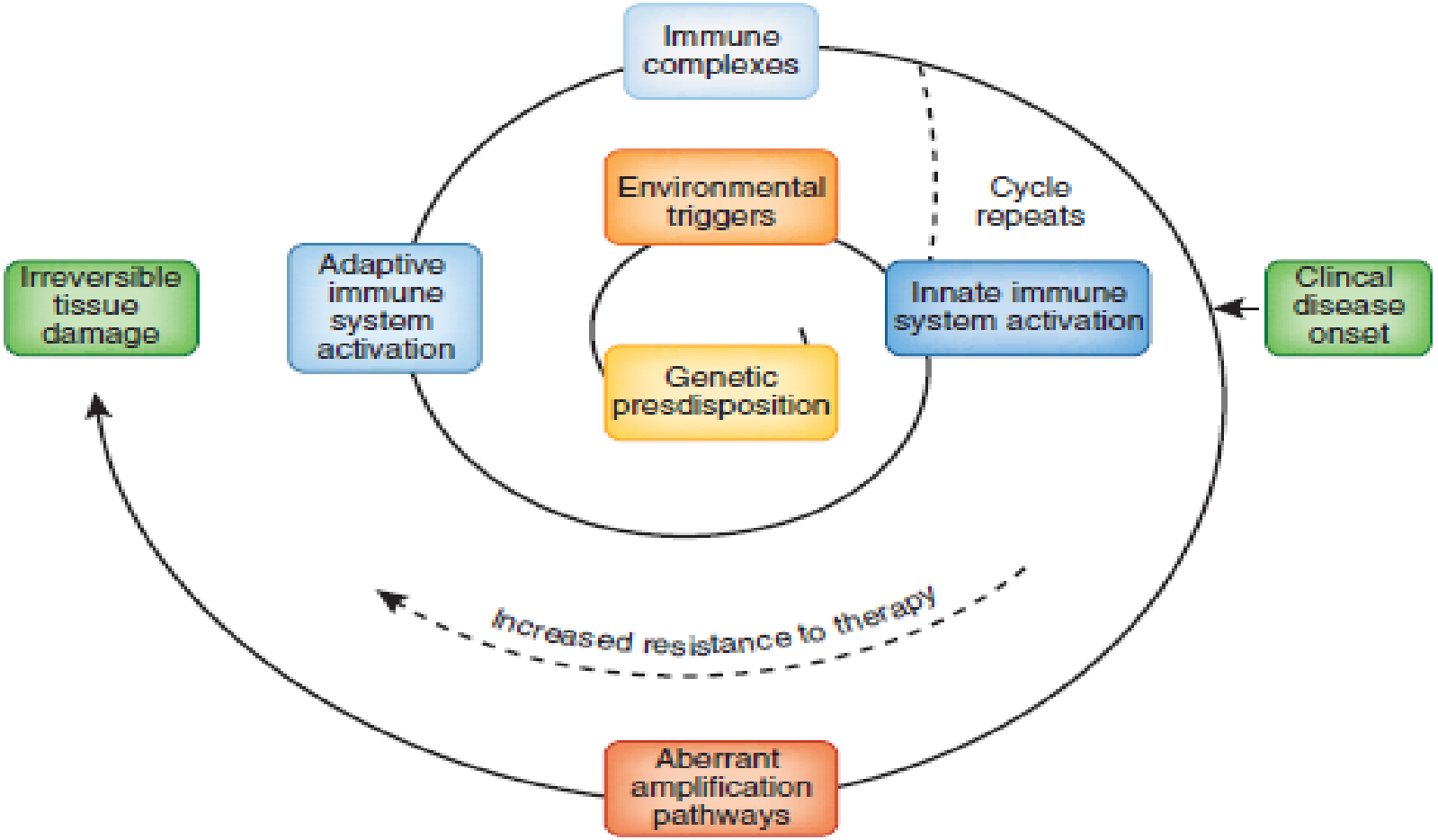
Novel biological agents for lupus nephritis

Lai-Shan Tam, MD
Professor
Head
Division of Rheumatology
Department of Medicine & Therapeutics
The Chinese University of Hong Kong

Objective

- To update on the new therapeutic targets in lupus nephritis
- To understand the problems behind clinical trials in lupus nephritis

Figure 1 The spiral of disease progression in SLE.



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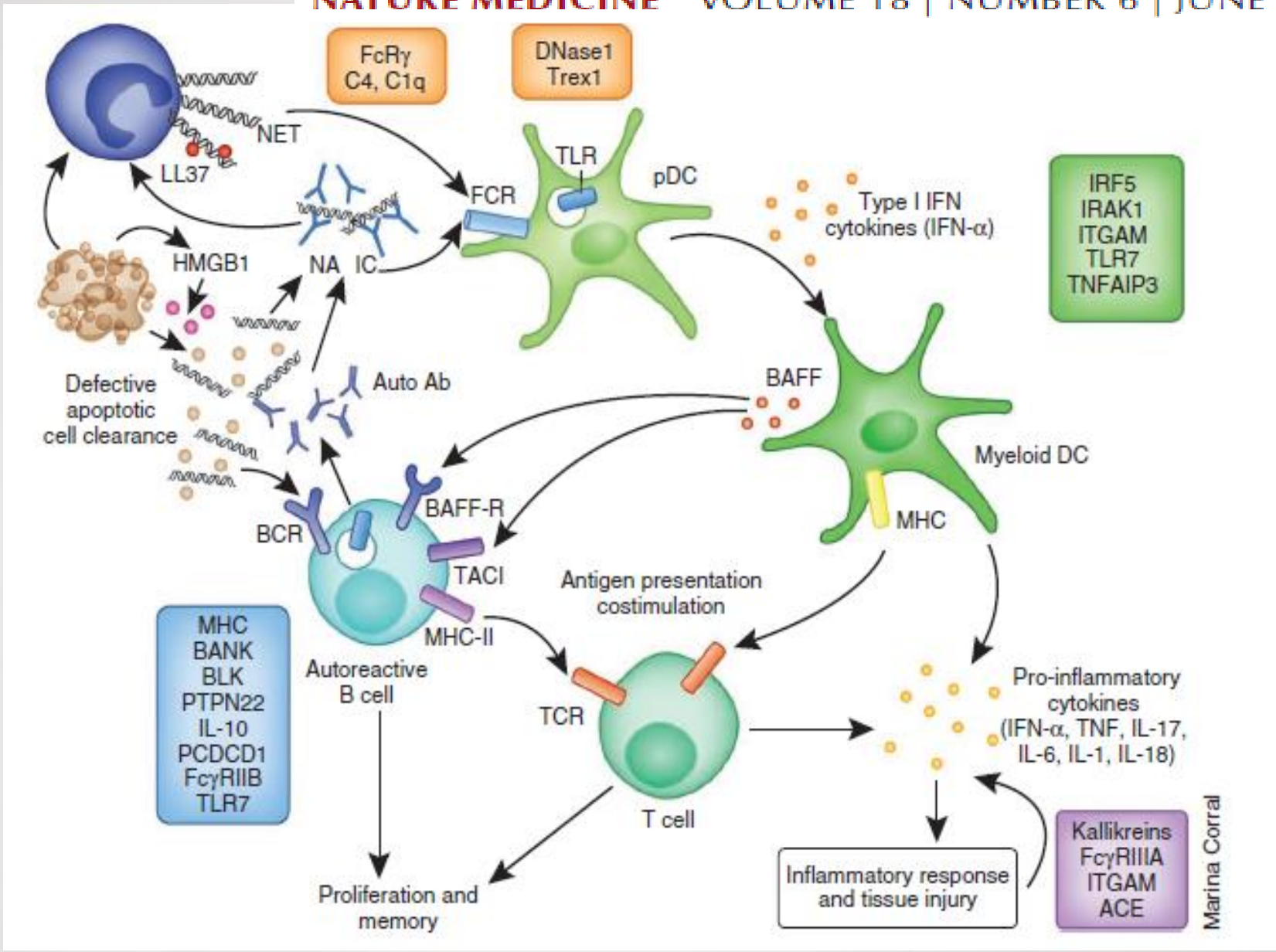

FcRγ
C4, C1q
DNase1
Trex1
NET
LL37
TLR
pDC
FCR
HMGB1
NA IC
Type I IFN
cytokines (IFN-α)
IRF5
IRAK1
ITGAM
TLR7
TNFAIP3
Defective
apoptotic
cell clearance
Auto Ab
BAFF
Myeloid DC
BCR
BAFF-R
MHC
TACI
Antigen presentation
costimulation
MHC
BANK
BLK
PTPN22
IL-10
PCDCD1
FcγRIIB
TLR7
MHC-II
Autoreactive
B cell
TCR
Pro-inflammatory
cytokines
(IFN-α, TNF, IL-17,
IL-6, IL-1, IL-18)
T cell
Kallikreins
FcγRIIIA
ITGAM
ACE
Inflammatory response
and tissue injury
Proliferation and
memory
Marina Corral

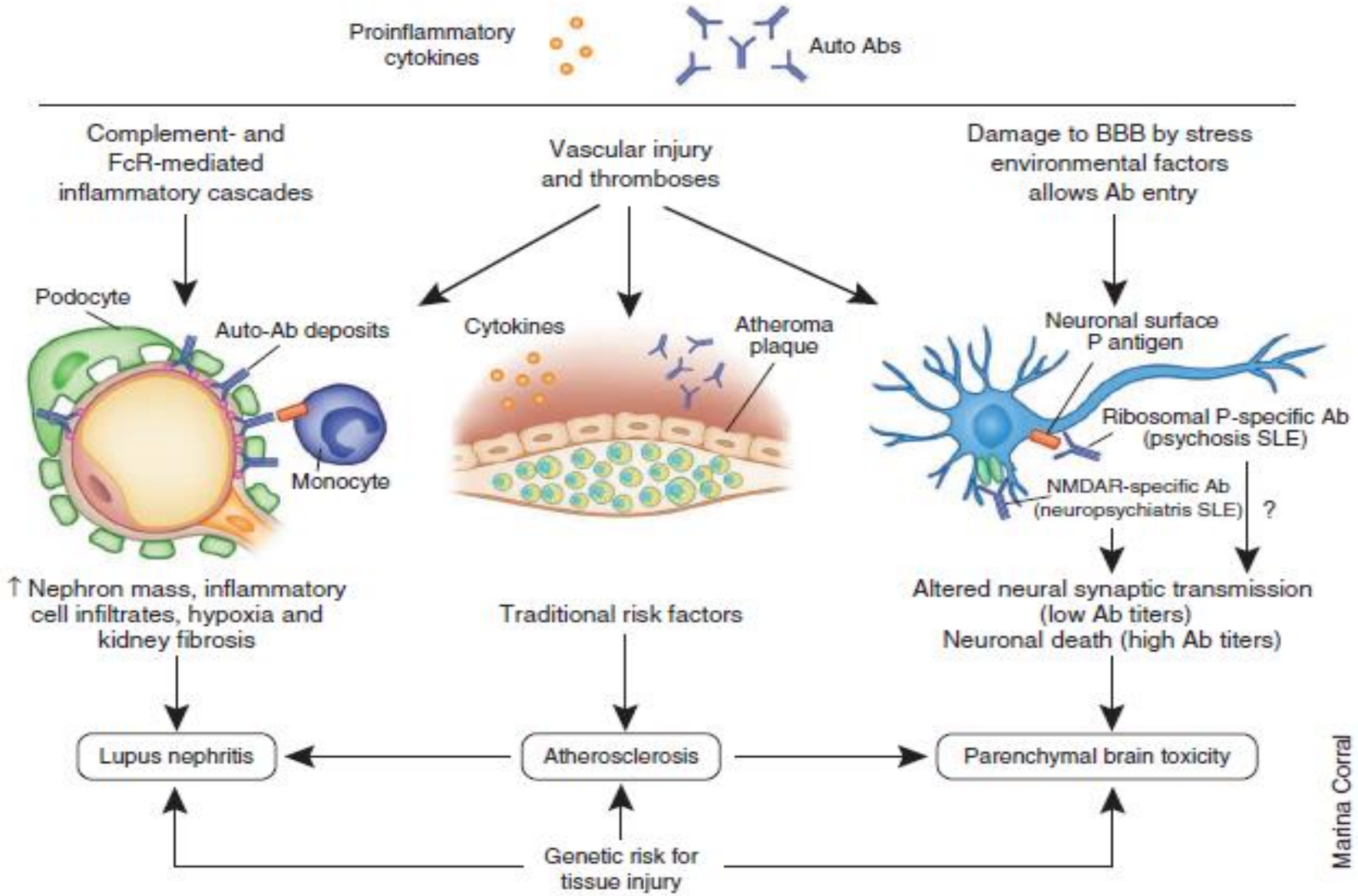
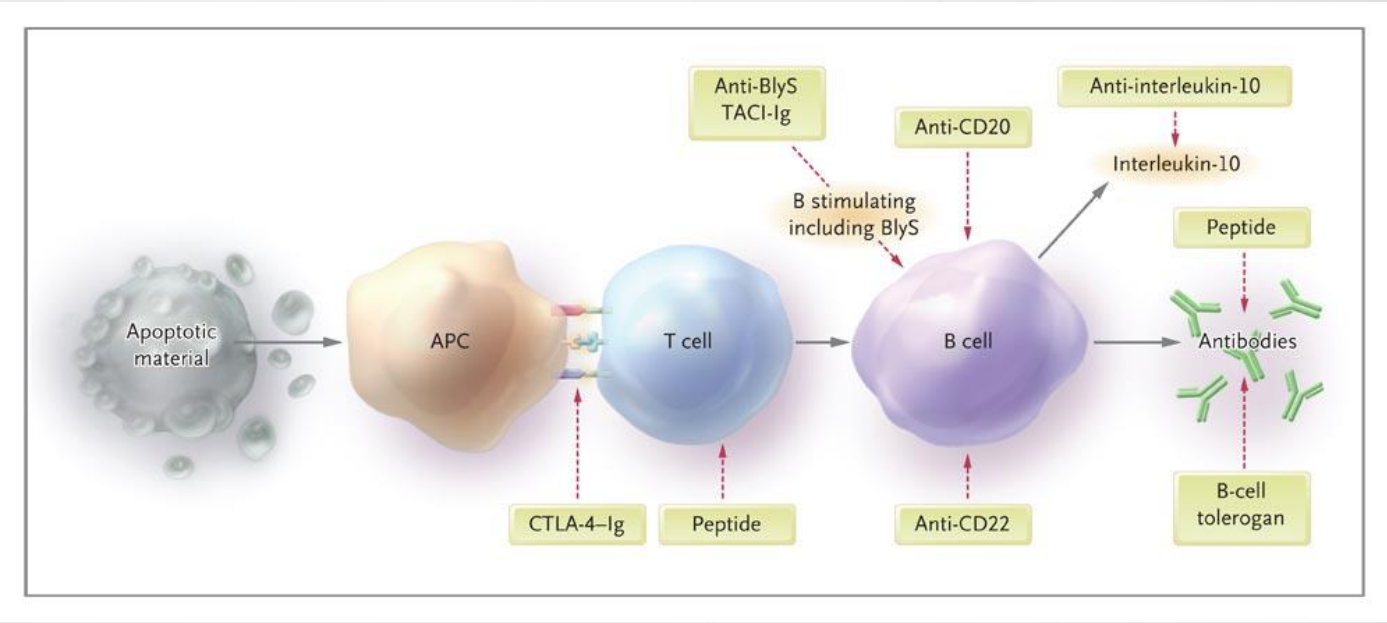


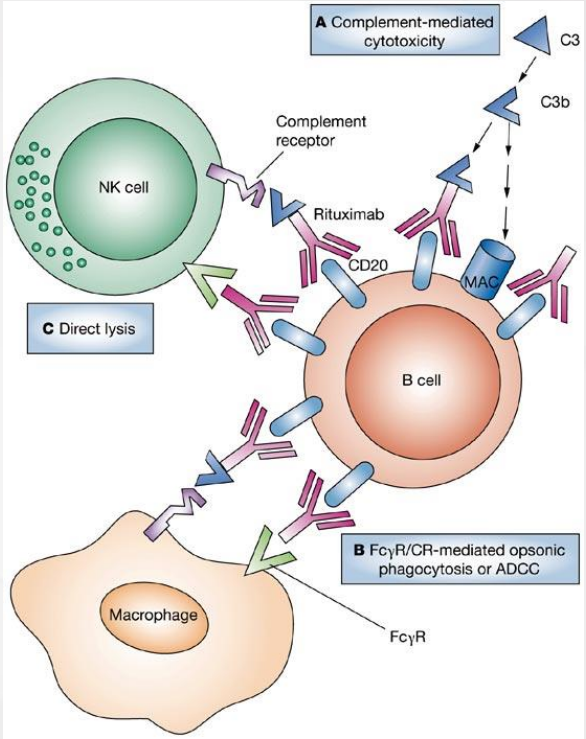
Figure 4 Mechanisms for organ damage.

Targeted Therapeutic Approaches in Systemic Lupus Erythematosus



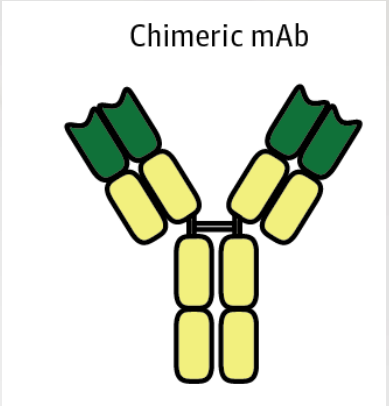
Rahman A and Isenberg D. N Engl J Med 2008;358:929-939

Figure 1 Rituximab-opsonized B cells are subject to attack and killing by at least three pathways



Taylor RP and Lindorfer MA (2007) Drug Insight: the mechanism of action of rituximab in autoimmune disease—the immune complex decoy hypothesis
Nat Clin Pract Rheumatol **3:** 86–95 doi:10.1038/ncprheum0427

Rituximab



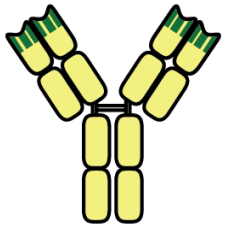
- Rescue therapy ↓
- UP↓ at week 72
- ↓C3C4
- ↓↓anti-ds DNA

Table 2 Randomized controlled trials of rituximab in SLE

	No. and ethnicity	Study duration and comparator	Inclusion	Main results	Adverse events
EXPLORER (phase III)[46]	257 (42% Asians, Hispanics or Africans)	52 weeks RTX (1 g × 2) versus PBO in addition to steroid and background therapies	≥ 1 BILAG A (except severe or organ-threatening disease) or ≥ 2 BILAG B score	Major clinical response at week 52 (RTX *vs.* PBO: 12% *vs.* 16%); partial clinical response (RTX *vs.* PBO: 17% *vs.* 13%) (differences NS)	AEs, SAEs and infusion reactions similar between RTX and PBO
LUNAR (phase III)[47]	144 (69% Asians, Hispanics or Africans)	RTX (1 g × 2) versus PBO in addition to high-dose steroid and MMF (3 g/day)	Biopsy-confirmed active class III/IV lupus nephritis with urine P/Cr ratio > 1.0	Complete renal response at week 52 (RTX *vs.* PBO: 26% *vs.* 31%); partial renal response (RTX *vs.* PBO: 31% *vs.* 15%) (differences NS)	AEs, SAEs, rates of infusion reaction and infection similar between RTX and PBO; neutropenia, leukopenia and hypotension more common with RTX

AE, adverse events; BILAG, British Isles Lupus Assessment Group; MMF, mycophenolate mofetil; NS, not significant; PBO, placebo;; P/Cr, protein to creatinine ratio; RTX, rituximab; SAE, serious adverse events; SLE, systemic lupus erythematosus.

Ocrelizumab (BELONG)



CU Medicine HONG KONG

Table 3. Renal response rates at week 48, overall and by background standard of care (modified intent-to-treat population)*

Response	Placebo + standard of care (n = 75)	Ocrelizumab 400 mg + standard of care (n = 75)	Ocrelizumab 1,000 mg + standard of care (n = 73)	Ocrelizumab Combined + standard of care (n = 148)
All patients				
CRR, no. (%)	26 (34.7)	32 (42.7)	23 (31.5)	55 (37.2)
PRR, no. (%)	15 (20.0)	18 (24.0)	26 (35.6)	44 (29.7)
ORR, no. (%)	41 (54.7)	50 (66.7)	49 (67.1)	99 (66.9)
95% CI for the ORR, %	43.4, 65.9	56.0, 77.3	56.3, 77.9	59.3, 74.5
Adjusted treatment difference, % (95% CI)†	–	12.1 (−3.3, 27.5)	13.9 (−1.4, 29.2)	12.7 (−0.8, 26.1)
P‡	–	–	–	0.065
ELNT regimen§				
CRR, no. (%)	7 (25)	14 (45)	8 (24)	22 (34)
PRR, no. (%)	5 (18)	9 (29)	11 (33)	20 (31)
ORR, no. (%)	12 (43)	23 (74)	19 (58)	42 (66)
95% CI for the ORR, %	24.5, 61.2	58.8, 89.6	40.7, 74.4	54.0, 77.3
Adjusted treatment difference, % (95% CI)†	–	31.3 (7.4, 55.3)	14.7 (−10.0, 39.6)	22.8 (1.1, 44.5)
P‡	–	–	–	0.065
MMF§				
CRR, no. (%)	19 (40)	18 (41)	15 (38)	33 (39)
PRR, no. (%)	10 (21)	9 (20)	15 (38)	24 (29)
ORR, no. (%)	29 (62)	27 (61)	30 (75)	57 (68)
95% CI for the ORR, %	47.8, 75.6	47.0, 75.8	61.6, 88.4	57.9, 77.8
Adjusted treatment difference, % (95% CI)†	–	−0.3 (−20.0, 19.7)	13.3 (−6.0, 32.6)	6.2 (−11, 23.3)
P‡	–	–	–	0.57

IVMP
11%
Vs
51%

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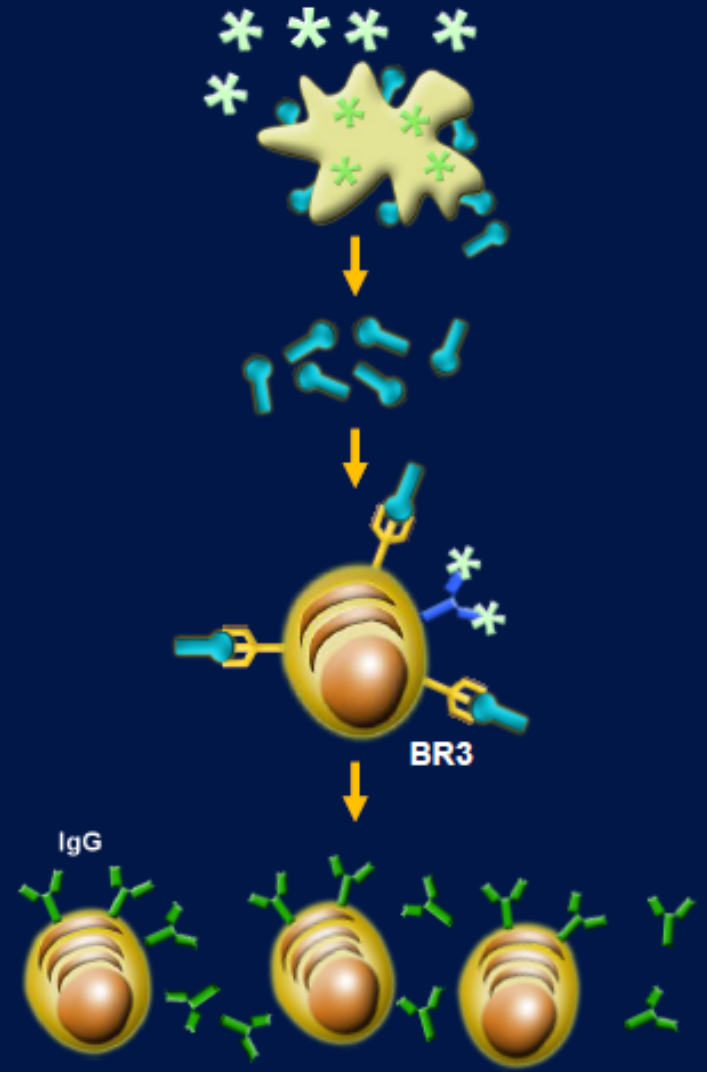
BLyS Activates B Cells



* Antigens present in periphery and activate monocytes, which release BLyS

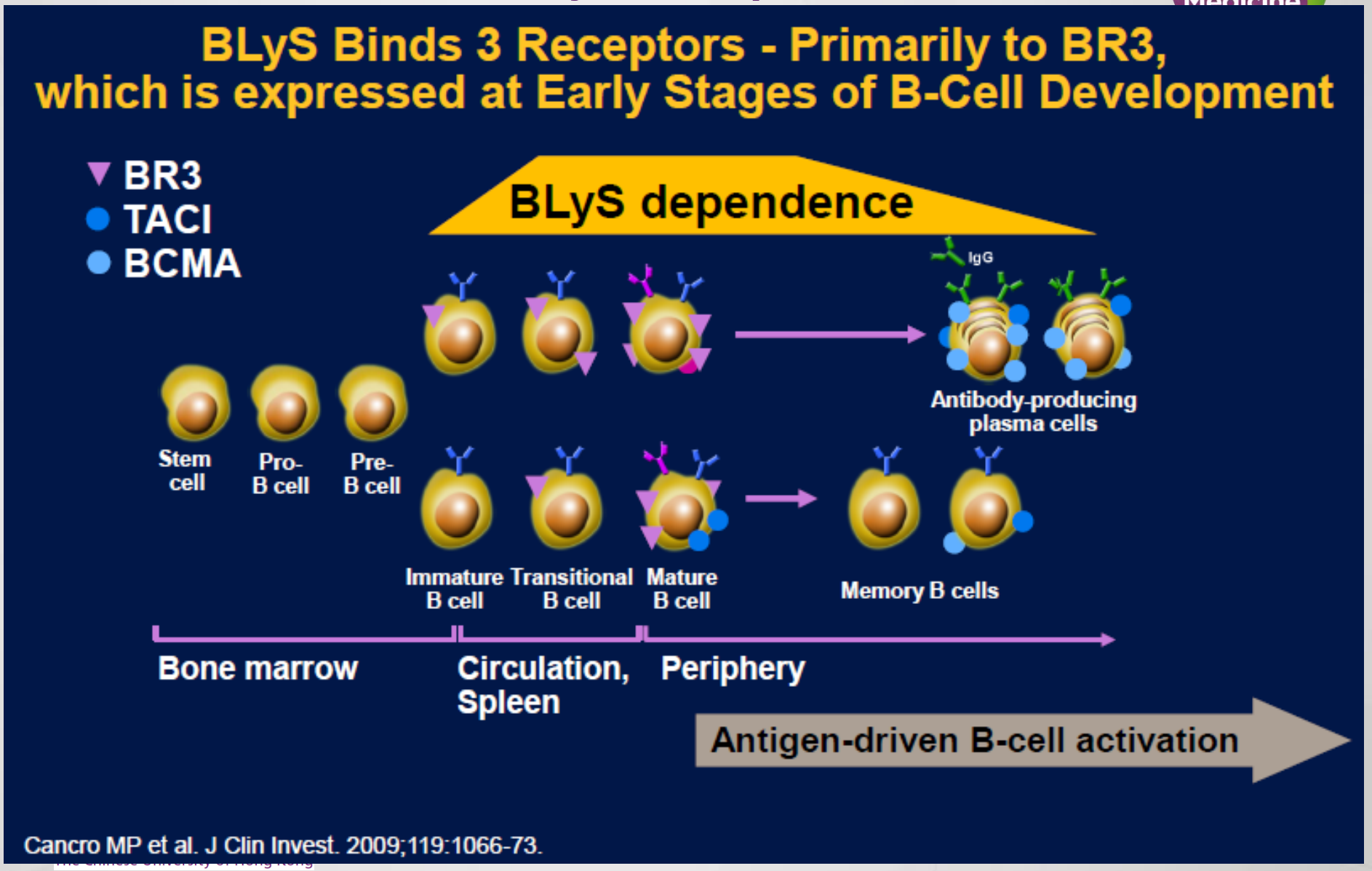
BLyS is cleaved to active, soluble form

Soluble BLyS binds to and activates B cells

B cells proliferate and differentiate to antibody-producing plasma cells; elevated BLyS levels contribute to abnormal B-cell development

Cancro MP et al. J Clin Invest. 2009;119:1066-73.

B-Cell Subsets and BLyS Receptors



Cancro MP et al. J Clin Invest. 2009;119:1066-73.

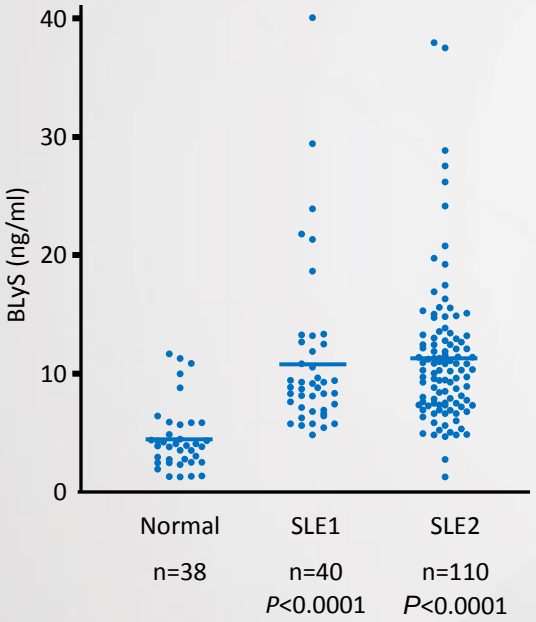
Summary of preclinical studies

- **B-lymphocyte stimulator (BLyS)[1]**
  - Expressed by monocytes, activated neutrophils, T cells and dendritic cells
  - Has been shown to bind to three receptors on the surface of B cells (BR3, TACI and BCMA)
  - Has been shown to promote B-cell survival and isotype switching (IgM/IgD to IgG)

1. Cancro MP, *et al. J Clin Invest* 2009; **119:**1066–1073; 2. Mackay F, *et al. J Exp Med* 1999; **190:**1697–1710; 3. Khare SD, *et al. Proc Natl Acad Sci USA* 2000; **97:**3370–3375; 4. Ramanujam M, *et al. Arthritis Rheum* 2010;

Elevated BLyS levels in SLE patients correlated with high anti-dsDNA titres and changes in SELENA-SLEDAI score

BLyS levels found to be elevated in patients with SLE[1]



Two independent sets of SLE sera (SLE1) and plasmas (SLE2) were collected and assayed.

* Multivariate analysis of the association of BLyS level with a change in SELENA-SLEDAI (SS) score from previous visit. SELENA-SLEDAI was administered and plasma BLyS autoantibodies were measured at baseline, 3, 6, 9, 12, 18 and 24 months and at any unscheduled visits.

1. Zhang J, *et al. J Immunol* 2001; **166:**6–10;
2. Petri M, *et al. Arthritis Rheum* 2008; **58:**2453–2459.

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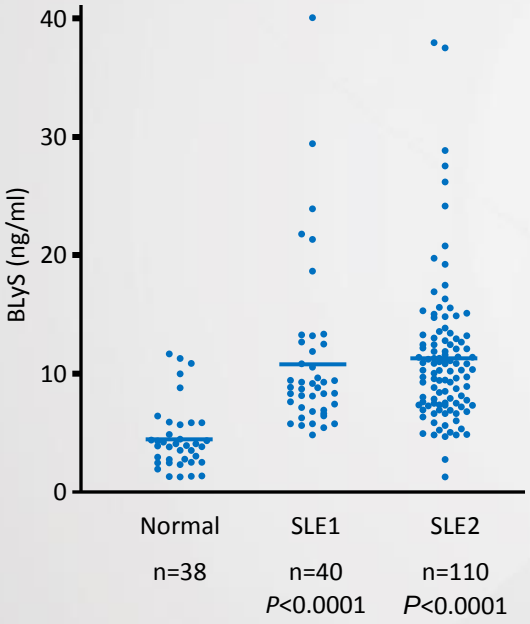

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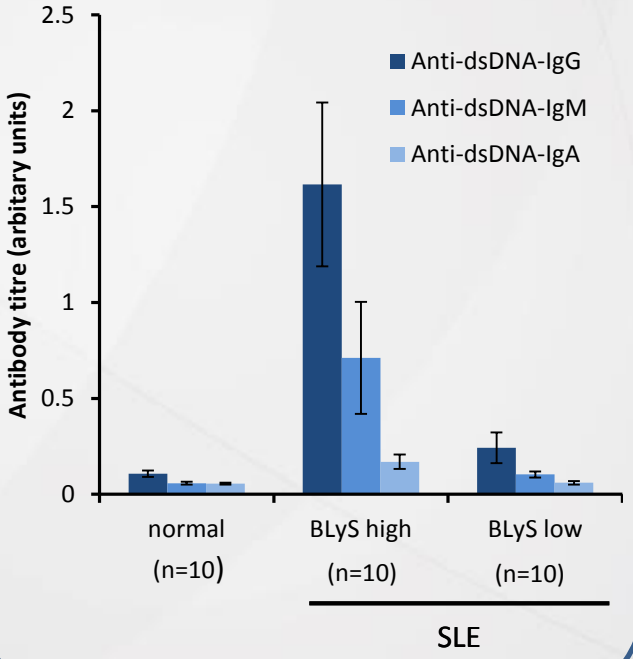

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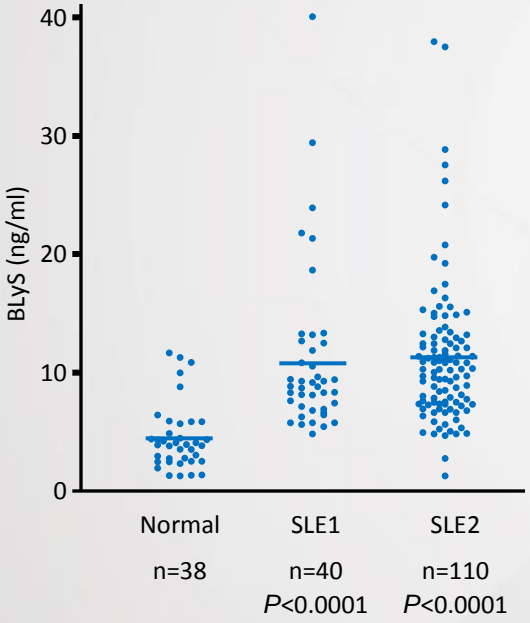

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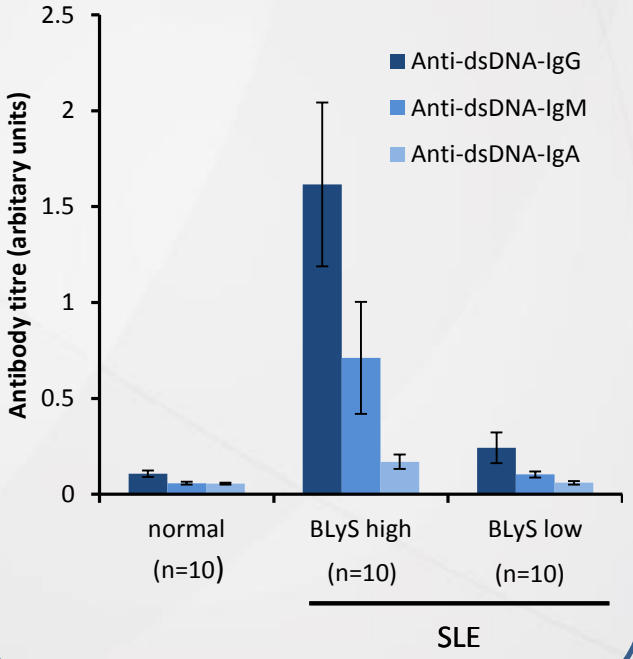

Increased BLyS levels associated with worsening of SLE[2]*

Independent variable	Relationship to increase in SS
BLyS level at previous visit	Positive *P*=0.0042
Change in BLyS level from previous visit	Positive *P*=0.0007

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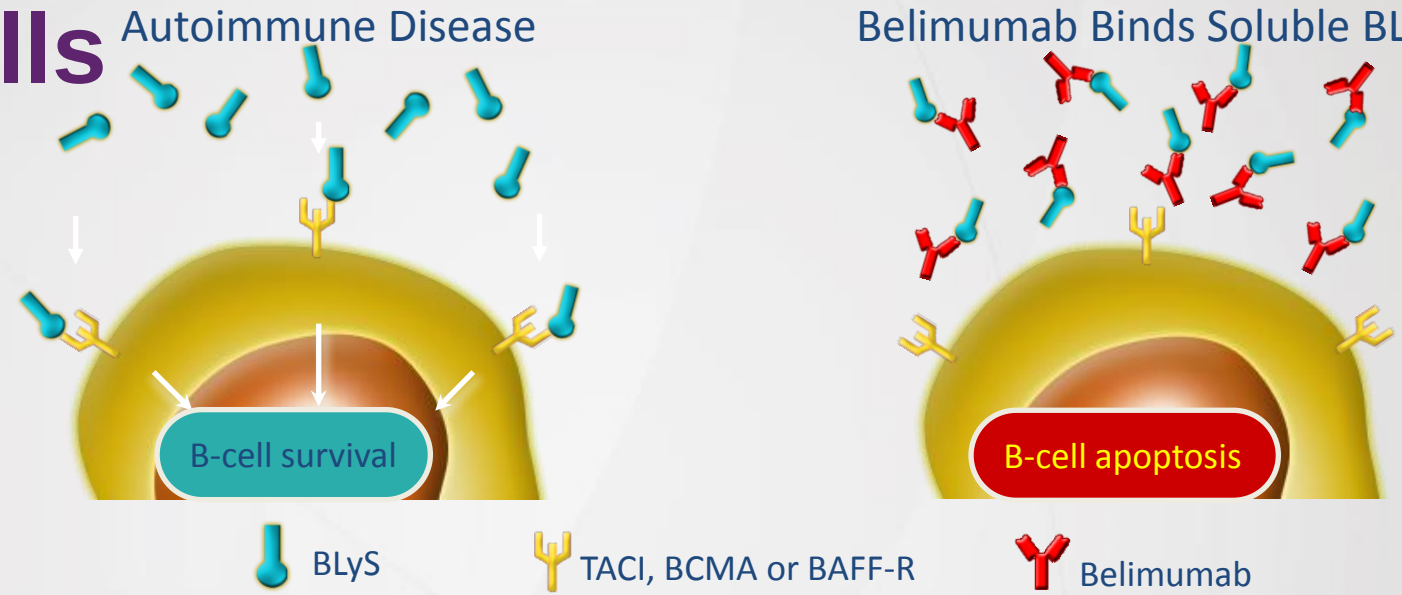
1. Zhang J, *et al. J Immunol* 2001; **166:**6–10;
2. Petri M, *et al. Arthritis Rheum* 2008; **58:**2453–2459.

BLyS Antagonists Facilitate Apoptosis of Autoreactive B Cells



BLyS Inhibition Helps Promote Apoptosis in Autoreactive B Cells

Fully human monoclonal antibody

Selectively targets and inhibits the biological activity of soluble BLyS

Inhibition of BLyS may result in autoreactive B-cell apoptosis

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The Chinese University of Hong Kong

Do RKG et al. *J Exp Med*. 2000;192:953-964; Ammana et al. *J Immunol*. 2003;170:4593-4600.
Baker KP et al. Arthritis Rheum. 2003;48:3253-65.

Belimumab

Table 1: BLISS-52 (*n*=865) comparative analysis after 52 weeks

	SLE responder index at week 52	SLE responder index at week 76	SELENA-SEDAI reduction of ≥4
Belimumab 1 mg/kg (*n*=288)	51.4%**	NR	53.1%**
Belimumab 10 mg/kg (*n*=290)	57.6%**	NR	58.3%**
Placebo + standard therapy (*n*=287)	43.6%	NR	46%

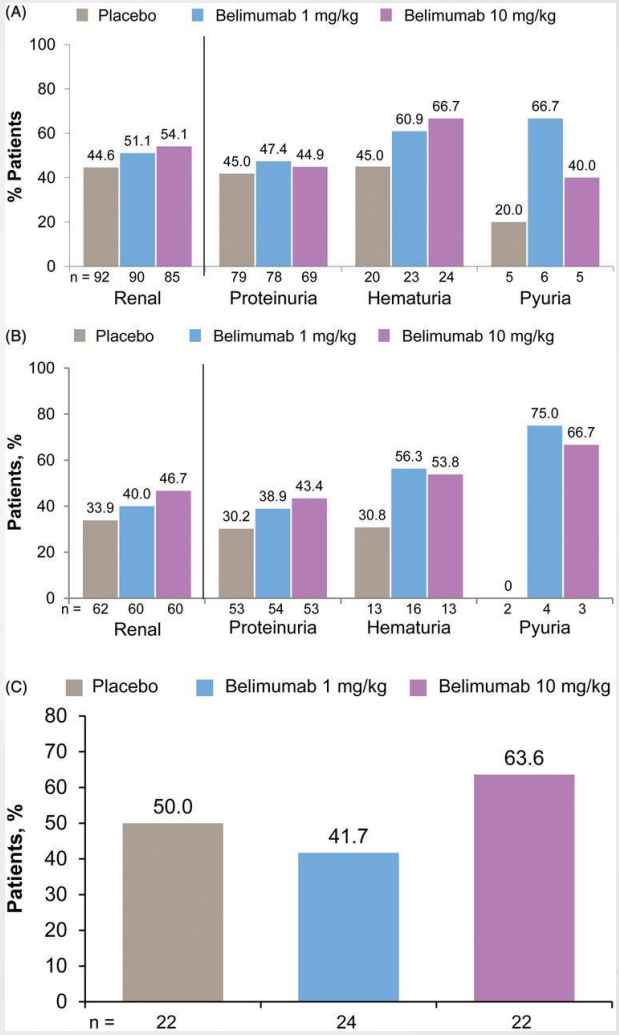
*BILAG: British isles lupus activity group. **Indicates statistical significance ($P<0.05$) vs. placebo. SLE=sys
of Estrogens in Lupus Erythematosus National Assessment version of the SLE Disease Activity Index, PG

Table 2: BLISS-76 (*n*=819) comparative analysis after 76 weeks

	SLE responder index at week 52	SLE responder index at week 76	SELENA-SEDAI reduction of ≥4
Belimumab 1 mg/kg (*n*=271)	40.6%	39.1%	42.1%**
Belimumab 10 mg/kg (*n*=273)	43.2%**	38.5%	41.1%**
Placebo + standard therapy (*n*=275)	33%	32.4%	33.8%

Frieri M, et al. J Pharmacol Pharmacother 2015;6:71-6.

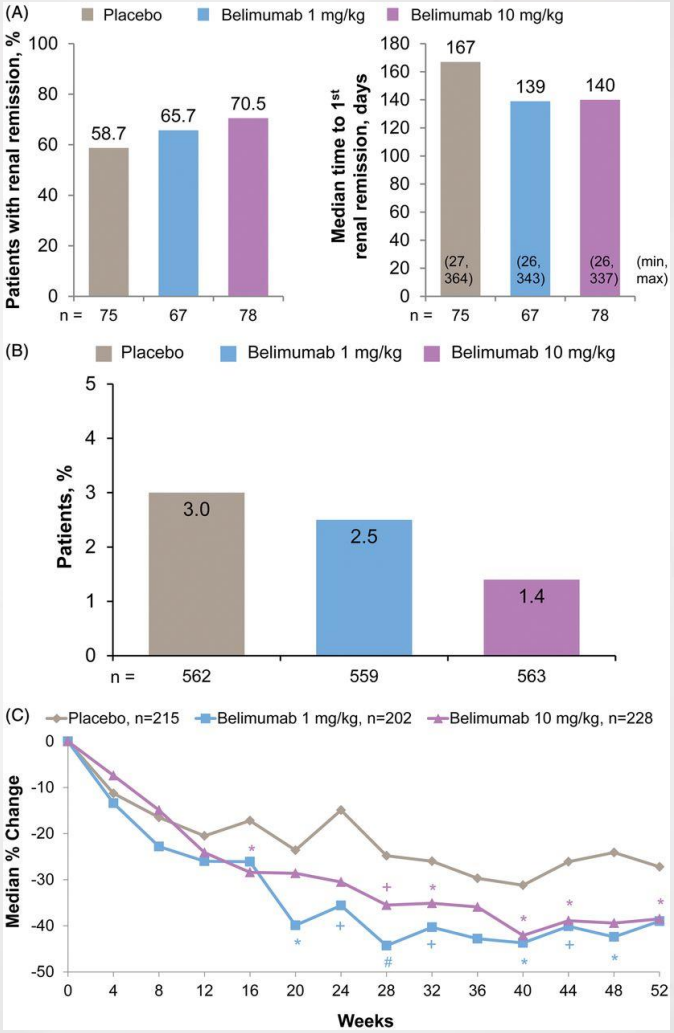
Figure 1 Renal improvement at week 52 in patients with renal involvement at baseline.



MA Dooley et al. Lupus 2012;22:63-72

Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index renal organ system and item improvement in
(A)pooled population and
(B) subgroup with low complement levels and anti-double-stranded DNA positivity at baseline.
(C) British Isles Lupus Assessment Group renal organ system improvement in patients with renal A or B score and active renal disease at baseline.

Figure 2 Renal remission and flare, and changes in proteinuria over 52 weeks in the pooled population.



MA Dooley et al. Lupus 2012;22:63-72

(A)Renal remission rates and median times to first renal remission in patients with baseline proteinuria 1 g/24 h.

(B) Renal flare rates in the full pooled population.

C) Median percent reductions in proteinuria in patients with baseline proteinuria >0.2 g/24 h (n¼643). *p<0.05; þp<0.01; #p<0.001.

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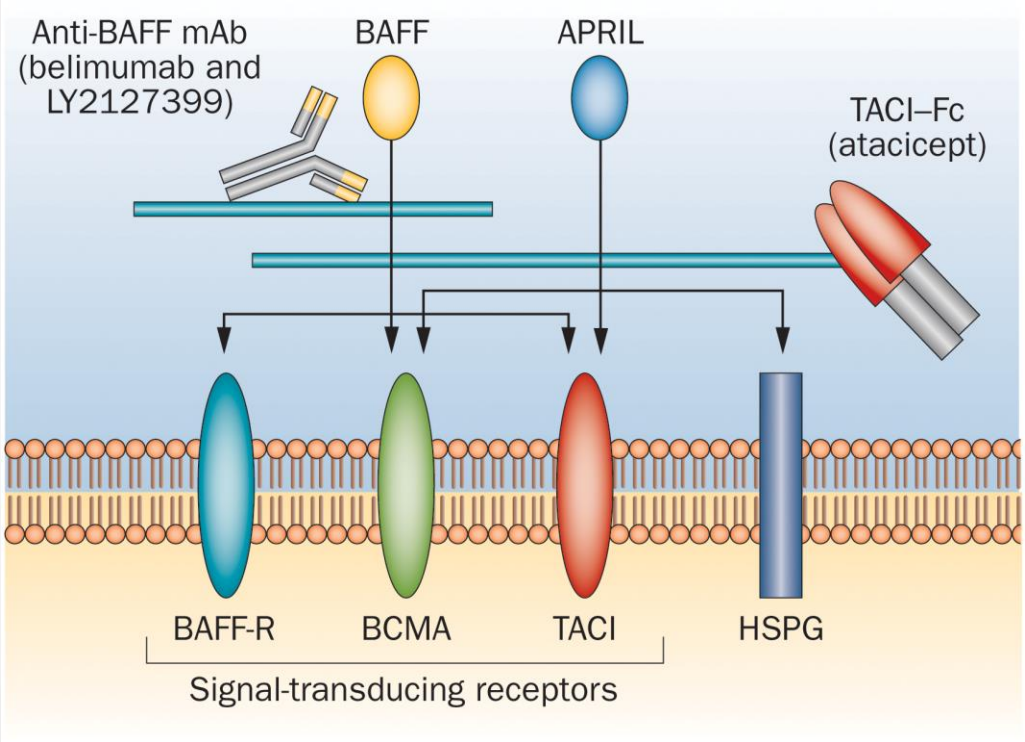
Atacicept blocking Blys and APRIL

- A proliferation inducing ligand (APRIL)



Krumbholz, M. *et al.* (2012) B cells and antibodies in multiple sclerosis pathogenesis and therapy *Nat. Rev. Neurol.* doi:10.1038/nrneurol.2012.203

nature REVIEWS NEUROLOGY

Atacicept

Table 1 Demographic characteristics, disease history, duration on study and reasons for discontinuation

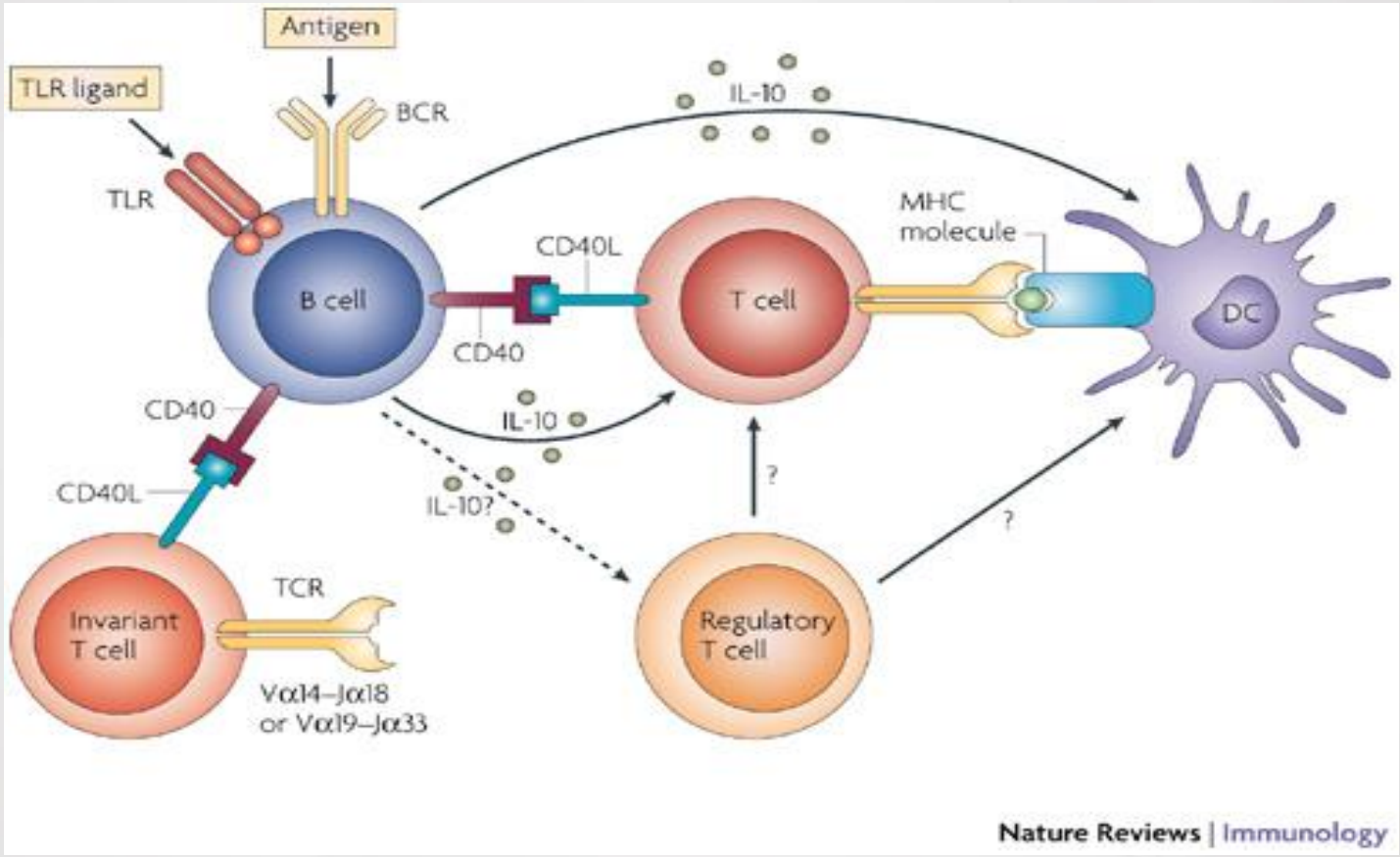
Patient #	Race	Disease history[a]			Prior therapy		Study drug treatment duration (Days)	Reason for discontinuation
		SLE (Months)	LN (Months)	Prior renal flare	MMF	CTX		
2	African American	38	< 1	-	-	-	148	Leukocytoclastic vasculitis
8	Caucasian	46	38	+	+	-	85	Study termination
3	African American	< 1	< 1	-	-	-	29	*H. influenzae* pneumonia, IgG < 3 g/l
5	African American	3	< 1	-	-	-	230	Study termination
13	African American	52	52	+	+	+	31	IgG < 3 g/l[b]
14	Asian	32	< 1	+	+	+	18	IgG < 3 g/l

Patients' mean (SD) height and weight were 169.3 (9.7) cm and 83.3 (20.8) kg, respectively. Patients #2 and #8 randomized to placebo; Patients #3, #5, #13 and#14 randomized to atacicept 150 mg subcutaneously twice weekly (4 weeks), then 150 mg weekly (48 weeks). [a]Disease history: time between SLE/LN diagnosis and consent. All patients had Class IV renal disease. [b]Patient #13 diagnosed with severe *Legionella* pneumonia on Day 34, 1 day after study discontinuation. CTX, cyclophosphamide; IgG, immunoglobulin G; LN, lupus nephritis; MMF, mycophenolate mofetil; SLE, systemic lupus erythematosus.

- Infection risk not seen in RA
- MMF, ↓Ig, Nephrosis responsible for the high infection risk

Ginzler *et al. Arthritis Research & Therapy* 2012, **14**:R33

TheCD40-CD40L interaction results in B- cell differentiation, germinal center formation, and anti- body isotype switching



Simon Fillatreau, et al. Nature Reviews Immunology 8, 391-397 (May 2008)

BG9588 (anti-human CD40L antibody)

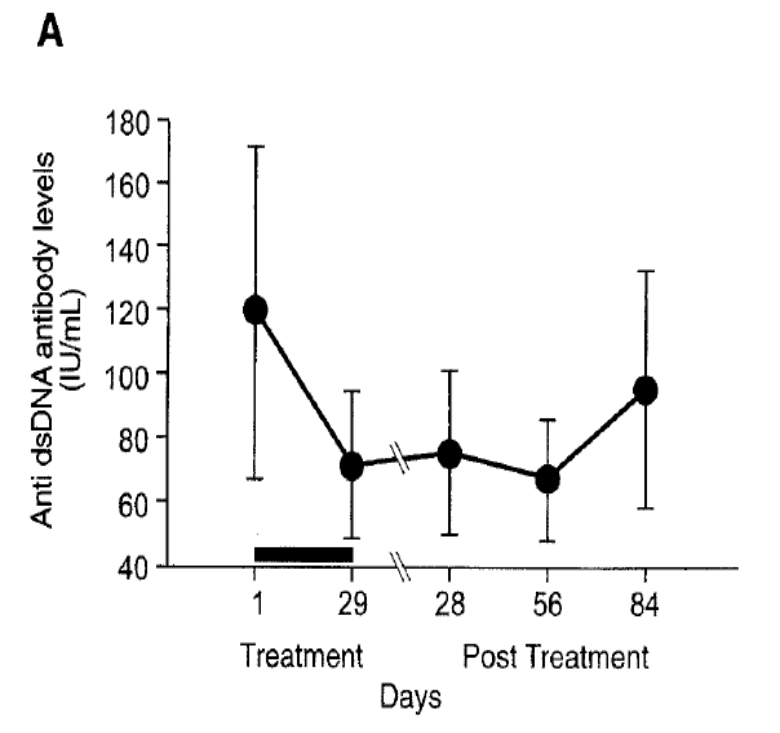
Table 2. Occurrence of serious adverse events during the study period

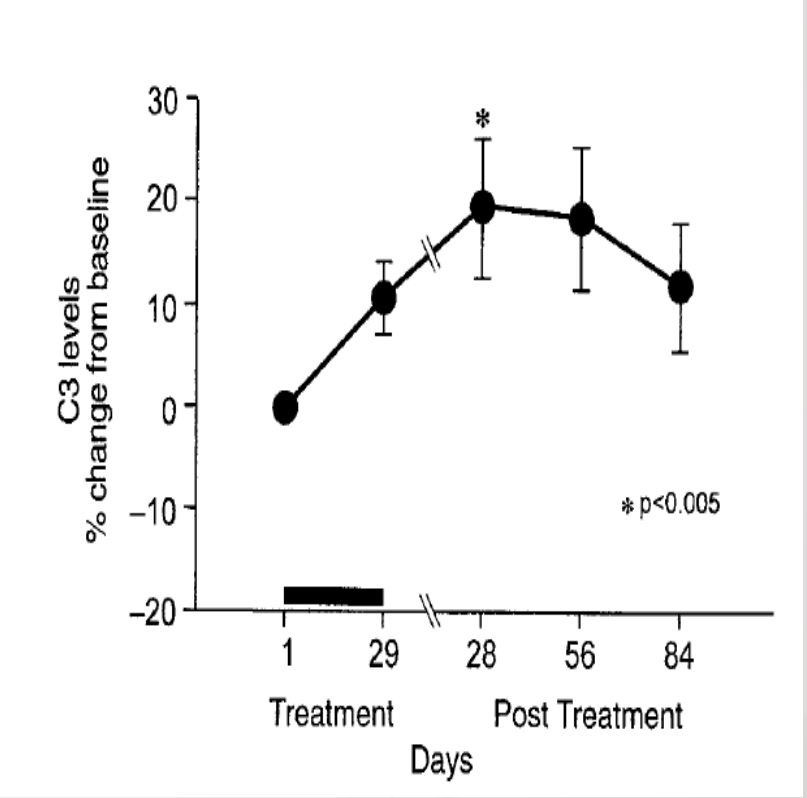
Event*	Day after first infusion	Severity as judged by investigator	Comment
Fever and chills	29	Mild	
Tracheobronchitis	117	Severe	
Fetal death	145	Moderate	Patient receiving known teratogenic treatment (coumadin prophylaxis) during pregnancy
Worsening renal function	2	Severe	Worsened during screening period; progressed to end-stage renal disease after a single BG9588 infusion
Myocardial infarction	59	Severe	
Myocardial infarction	9	Severe	

* Each of these events occurred in 1 patient.

Boumpas DT et al. ARTHRITIS & RHEUMATISM. Vol. 48, No. 3, March 2003, pp 719–727

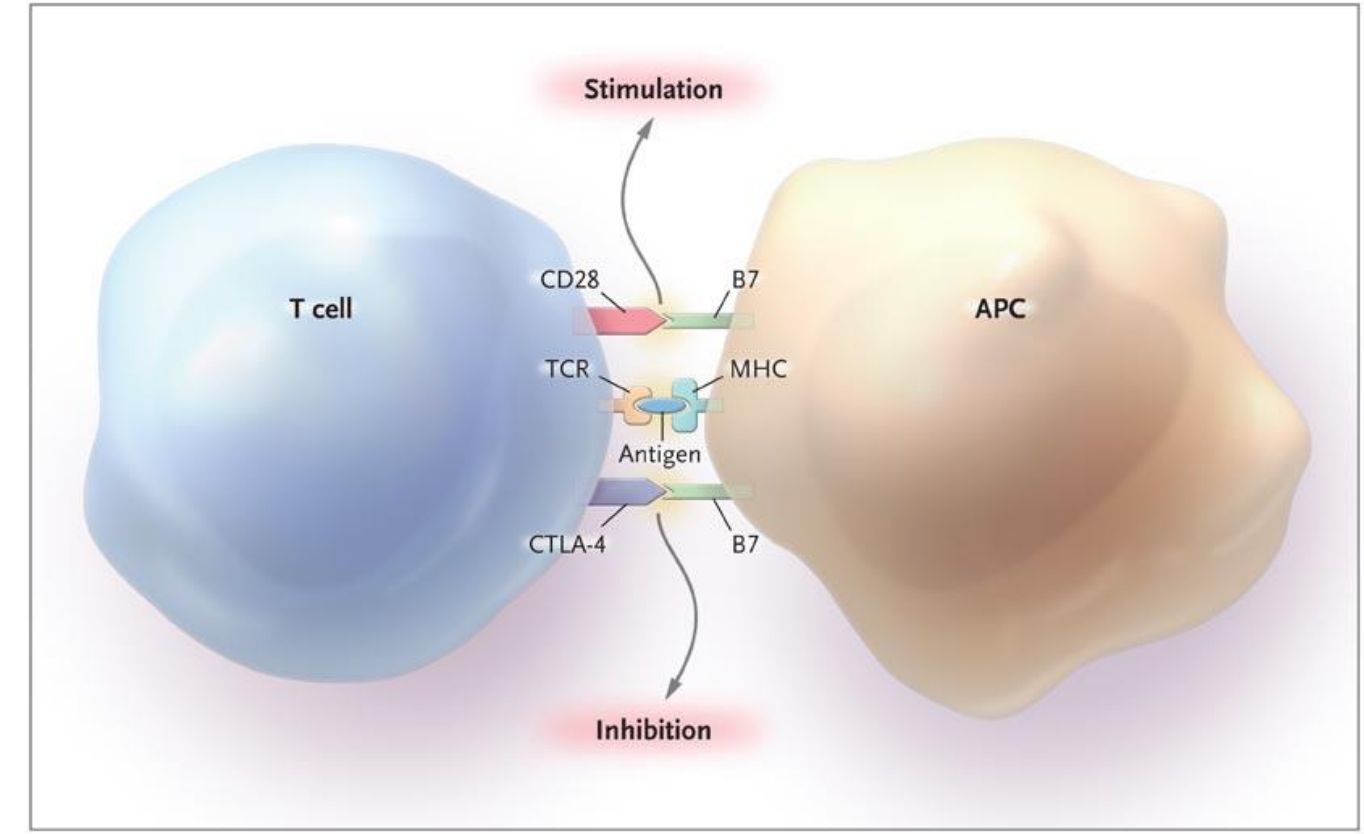
BG9588 (anti-human CD40L antibody)



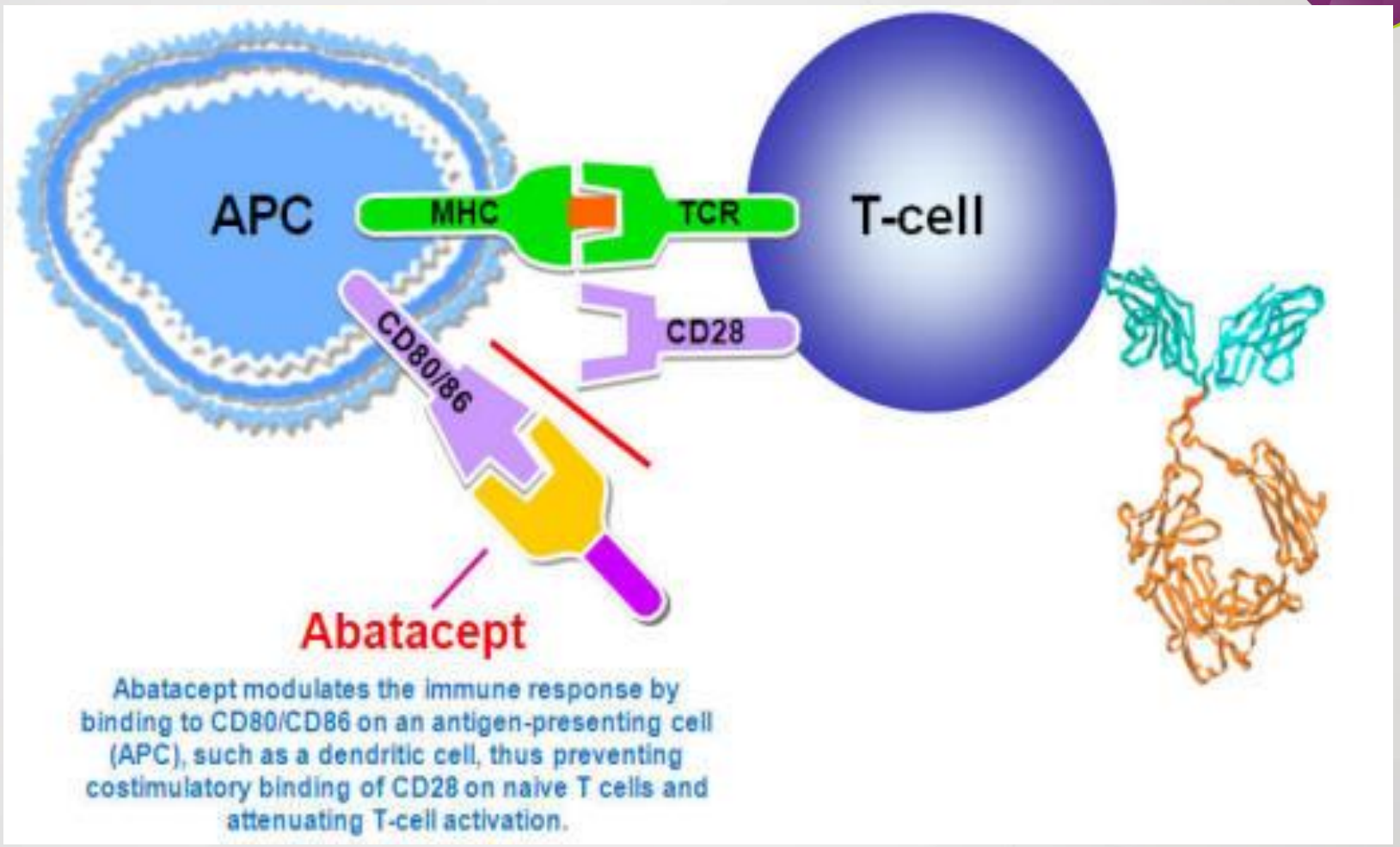


Boumpas DT et al. ARTHRITIS & RHEUMATISM. Vol. 48, No. 3, March 2003, pp 719–727

Interaction between a T Cell and an Antigen-Presenting Cell (APC)



Rahman A and Isenberg D. N Engl J Med 2008;358:929-939


APC
MHC
TCR
T-cell
CD28
CD80/86
Abatacept
Abatacept modulates the immune response by binding to CD80/CD86 on an antigen-presenting cell (APC), such as a dendritic cell, thus preventing costimulatory binding of CD28 on naive T cells and attenuating T-cell activation.

Reference	Molecule	Mode of action	Trial acronym	Phase	Patients, n	Class	SOC	SD	Primary outcome	Conclusions
Rovin et al. [10]	Rituximab RTX	Anti-CD20 B cell depleting mAb	LUNAR	III	144	III/IV	i.v. MP GC MMF	1 g on days 1, 15, 168 and 182	Superior renal response (CR and PR) rate with RTX at week 52	CR+PR rate at week 52 P: 45.8% SD: 56.9%
Mysler et al. [11]	Ocrelizumab OCR	Fully humanized anti-CD20 B cell depleting mAb	BELONG	III	381	III/IV	i.v. MP GC MMF or EL i.v. CY	400 or 1,000 mg on day 1, week 2, week 16, then q 16 weeks *ad* week 96	Superior renal response (CR and PR) rate with OCR at week 48	Higher rate of serious infections on MMF background leads to early termination CR+PR rate at week 48 (if ≥32 weeks of Rp) P: 54.7% OCR 400: 56.9% OCR 1,000: 67.1%
Furie et al. [12]	Abatacept ABA	CTLA-4/Ig fusion protein binding to CD80/86 and inhibiting interactions with CD28		II/III	298	III/IV±V	GC MMF	10/10 group: 10 mg/kg on days 1, 15, 29 and 57 and q month *ad* 12 months 30/10 group: 30 mg/kg on days 1, 15, 29 and 57; then 10 mg/kg q month *ad* 12 months	Time to confirmed CR	CR at week 52 P: 8.0% ABA 30/10: 9.1% ABA 10/10: 11.1%
Frogoso-Loyo et al. [13]	Abatacept ABA	CTLA-4/Ig fusion protein binding to CD80/86 and inhibiting interactions with CD28	ACCESS	II	134	III/IV±V	GC EL i.v. CY followed by AZA	500–1,000 mg at week 0, 2, 4 and then q 4 weeks	CR rate at week 24	CR at week 24 P: 31% ABA: 33%
Ginzler et al. [14]	Atacicept ATA	Soluble recombinant fusion protein inhibiting BLyS and APRIL		II/III	6	III/IV	GC MMF	150 mg s.c. twice weekly for 4 weeks; then q 4 weeks *ad* week 52		Early termination Severe hypogammaglobulinemia and severe infectious adverse events
Jayne et al. [15]	Laquinimod LAQ	Antigen-presenting cell modulator; downregulation of proinflammatory cytokines; upregulation of IL-10		IIa	46	IIa	GC MMF	0.5 or 1.0 mg/day	ALMS response criteria at week 24 (see [33])	ALMS response at week 24 P: 33% LAQ 0.5 mg: 62% LAQ 1.0 mg: 40%
van Vollenhoven et al. [16]	Sirukumab SIR	Anti-IL-6 mAb		II	25	III/IV	GC MMF or AZA	10 mg/kg q 4 weeks *ad* week 24	% reduction from baseline in proteinuria	P: 43% proteinuria increase SIR: 0% proteinuria increase

N = Number of patients; Class = according to ISN/RPS classification; SOC = standard of care; SD = study drug; mAb = monoclonal antibody; i.v. = intravenous; MP = methylprednisolone; GC = glucocorticoids; MMF = mycophenolate mofetil; CR = complete response; PR = partial respone; P = placebo; EL = Euro-Lupus; CY = cyclophosphamide; AZA = azathioprine; ALMS = Aspreva Lupus Management Study.

Abatacept in Lupus Nephritis Trials

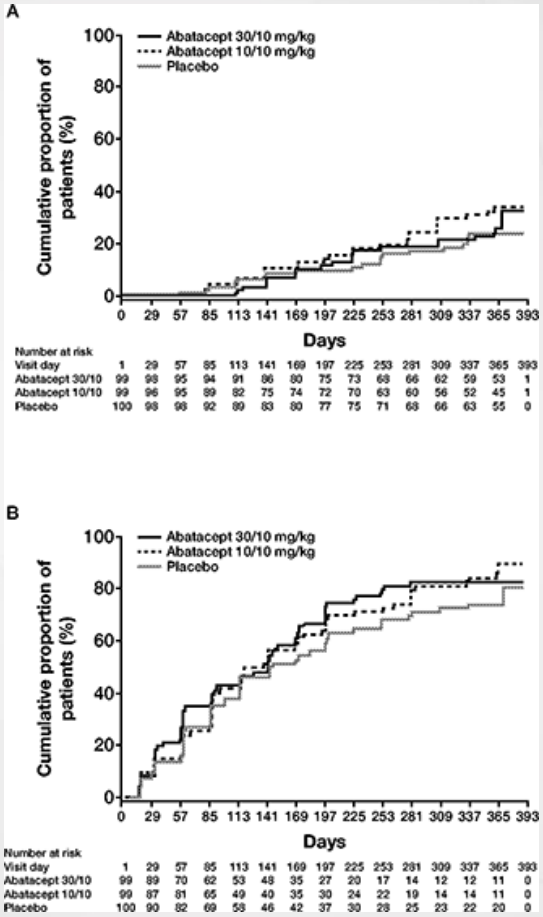
Table 1. Definitions of complete response in lupus nephritis trials: distinguishing features*

Source of criteria	Urine protein: creatinine ratio, gm/gm	Creatinine or estimated glomerular filtration rate	Urinalysis, cells or casts	Steroid taper required	Criteria must be met on 2 successive visits
BMS trial	≤0.26	Within 10% of screening or baseline value	Normal	No	Yes
ACR recommendations	≤0.20	Within 25% of screening or baseline value	Normal	Not addressed	No
LUNAR trial	≤0.50	Within 15% of screening or baseline value	Normal	Yes	No
ALMS trial	≤0.50	Normal	Normal	Yes	No
ACCESS trial	≤0.50	Normal or within 25% of baseline value	Not a component	Yes	No

* The Bristol-Myers Squibb (BMS) trial allowed enrollment of patients with urine protein:creatinine ratios of ≥0.44 gm/gm. The Lupus Nephritis Assessment with Rituximab (LUNAR) trial and the Abatacept and Cyclophosphamide Combination: Efficacy and Safety Study (ACCESS) trial restricted enrollment to patients with urine protein:creatinine ratios of ≥1.0 gm/gm. The Aspreva Lupus Management Study (ALMS) trial restricted enrollment to patients with proteinuria of ≥1 gm/24 hours, abnormal serum creatinine levels, and/or abnormal urinalysis results. ACR = American College of Rheumatology.

Wolfy D. ARTHRITIS & RHEUMATISM. Vol. 64, No. 11, November 2012, pp 3660–3665

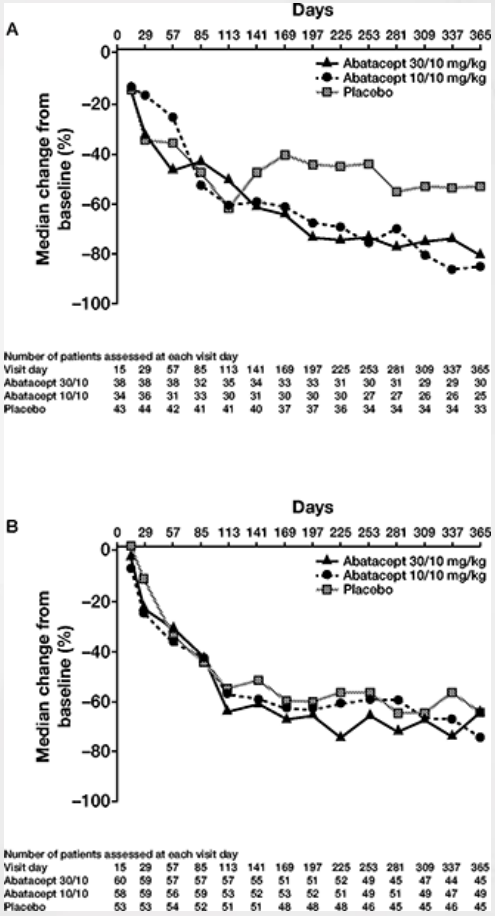
Efficacy and Safety of Abatacept in Lupus Nephritis: A Twelve-Month, Randomized, Double-Blind Study



A. Time to achievement of confirmed complete response, by treatment group.
B. Time to achievement of renal improvement, by treatment group.

Arthritis & Rheumatology
Volume 66, Issue 2, pages 379-389, 27 JAN 2014 DOI: 10.1002/art.38260
http://onlinelibrary.wiley.com/doi/10.1002/art.38260/full#art38260-fig-0001

Change in mean urinary protein-to-creatinine ratio



A. nephrotic-range proteinuria at baseline

B. No nephrotic-range proteinuria at baseline

Arthritis & Rheumatology
Volume 66, Issue 2, pages 379-389, 27 JAN 2014 DOI: 10.1002/art.38260
http://onlinelibrary.wiley.com/doi/10.1002/art.38260/full#art38260-fig-0002

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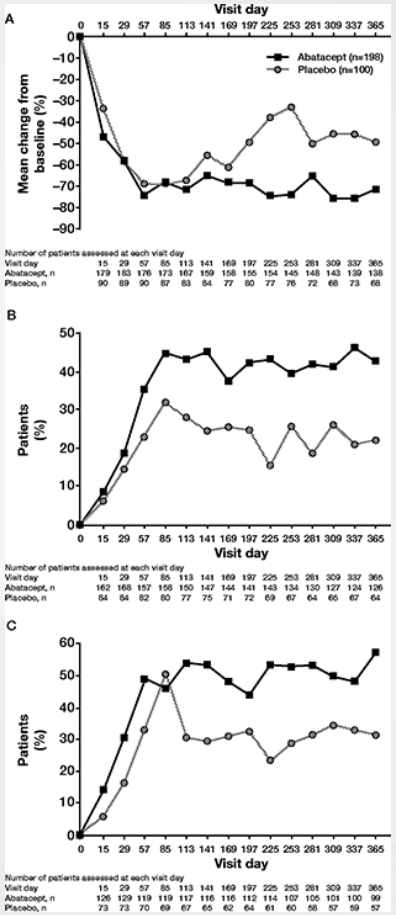
Changes in biomarker levels



A, anti–double-stranded DNA antibody

B, Percentage of patients with low complement C3 levels at baseline whose C3 levels normalized.

C, Percentage of patients with low complement C4 levels at baseline whose C4 levels normalized.

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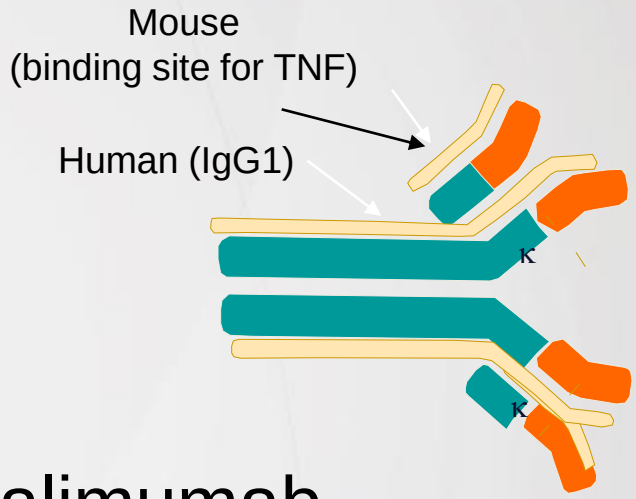
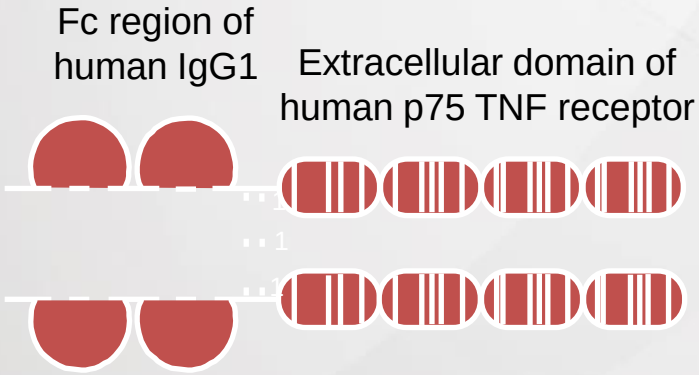
Anti-TNF

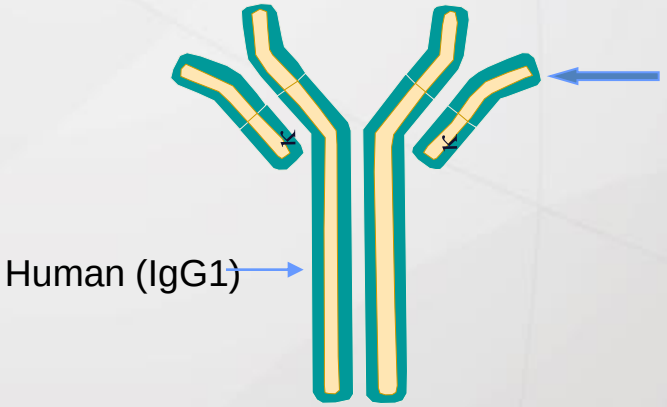
Infliximab



Etanercept (Enbrel)



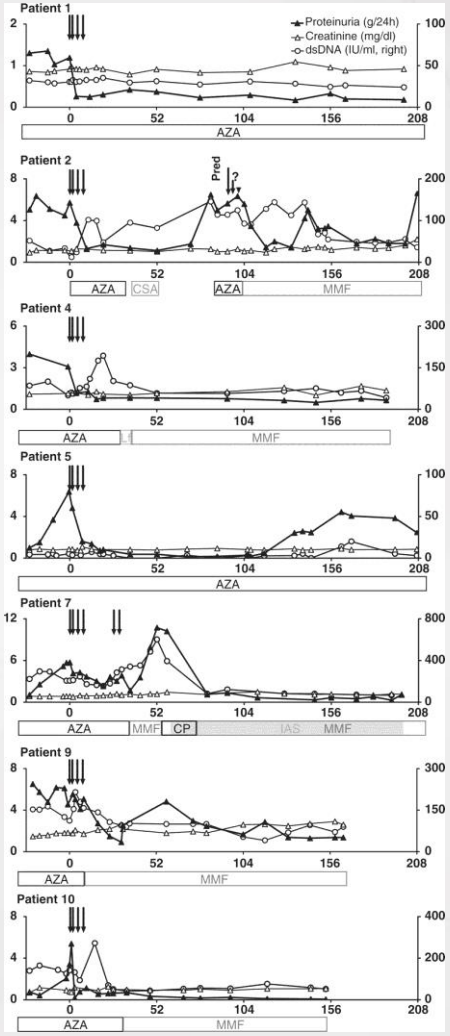
Adalimumab
Golimumab, certolizumab



Long-term follow-up of seven patients with lupus nephritis treated with infliximab.

TABLE 1. Patients, adverse events within 6 months after infliximab therapy, and

Patient	Therapy 12 months before infliximab	Infliximab, g	Adverse events
Short term			
1	AZA, steroids	4 ×/1.2	None
2	AZA, steroids, CP, IAS	4 ×/1.2	UTI
3	MTX, steroids	4 ×/1.2	None
4	AZA, steroids	4 ×/1.2	UTI
5	AZA, steroids	4 ×/1.2	UTI
8	AZA, steroids, CP	4 ×/1.2	None
9	AZA, steroids, CP	4 ×/1.2	Enteritis (*Salmonella*)
10	AZA, steroids, CsA	4 ×/1.2	DVT
12	AZA, steroids, CP	5 ×/1.1	Abscess secondary to molluscum contagiosum
13	AZA, steroids	5 ×/1.5	Macular rash
Long term			
6	AZA, steroids, MTX	16 ×/4.8	Cerebral lymphoma
7	AZA, steroids	6 ×/2.2	UTI
11	AZA, steroids, MMF, rituximab, CP	8 ×/1.6	Fatal pneumonia (*Legionella*)



The levels of proteinuria (black triangles, left *y*-axis), serum creatinine (white triangles, left *y*-axis) and anti-dsDNA antibodies (RIA, right *y*-axis) are shown.

Martin Aringer et al. Rheumatology 2009;48:1451-1454

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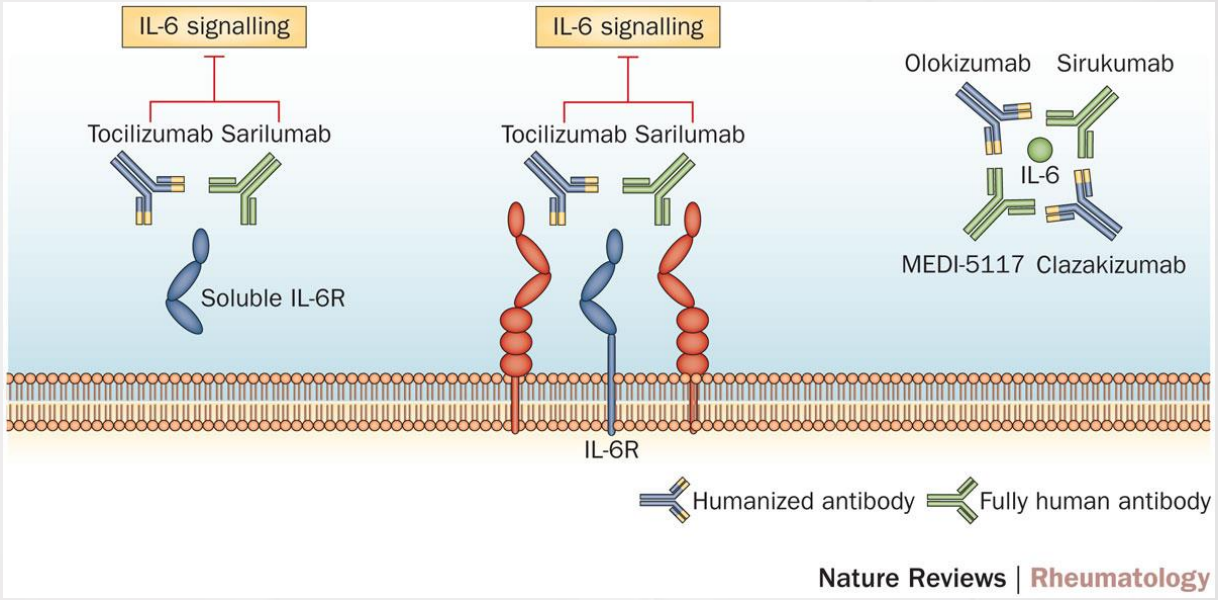
RHEUMATOLOGY

Figure 1 Antibodies directed against IL-6 signalling



Ruderman, E. M. (2015) IL-6 inhibition in RA—déjà vu all over again?
Nat. Rev. Rheumatol. doi:10.1038/nrrheum.2015.58

Sirukumab

Table. Summary of primary and major secondary efficacy endpoints at wk 24	Placebo	CNTO 136
Modified intent-to-treat pts	4	20 [a]
Proteinuria % change from baseline at wk24[a]		
Median	43.3	0.00
(95% CI)		(-61.8, 39.6)
Pts with decrease ≥50% in proteinuria at wk24[a]	0	4/20 (20.0%)
95% confidence interval		(5.7, 43.7)
Pts with meaningful reduction in proteinuria at wk24[a,b]	0	3/20 (15.0%)
95% confidence interval		(3.2, 37.9)
Pts with no worsening in GFR at wk24	3 (75.0%)	10/18 (55.6%)
95% confidence interval		(30.8, 78.5)

[a]A last-observation-carried-forward procedure was used to impute missing proteinuria values if a pt had data for ≥1 post- baseline evaluation. Of 21 randomized patients, 20 were included in the efficacy analyses.

[b]Meaningful reduction in proteinuria was defined as P/C (protein/creatinine) ratio < 0.5 for non-nephrotic pts; and ≥50% reduction in P/C ratio and P/C ratio < 3.0 for nephrotic pts.

R. van Vollenhoven et al. Ann Rheum Dis 2014;73:78

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AE

- 5 withdrawal because of an AE: anaphylactic reaction, increased liver enzymes, neutropenia, pneumonia, and LN worsening.
- No deaths occurred.
- Approximately half (47.5%, 10/21) of sirukumab-treated pts had ≥1 serious AE, the majority of which were infections.

Reference	Molecule	Mode of action	Trial acronym	Phase	Patients, n	Class	SOC	SD	Primary outcome	Conclusions
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Lessons learned

Definitions of Complete Response

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Wolfy D. ARTHRITIS & RHEUMATISM. Vol. 64, No. 11, November 2012, pp 3660–3665

Alternative Definitions of Complete Response Support Conflicting Conclusions

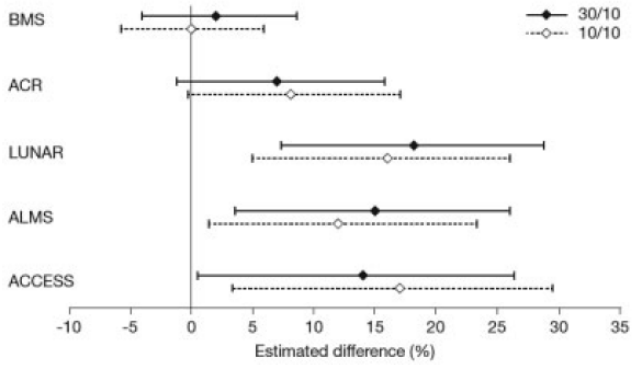

Figure 1. Difference in rates of complete response in each of the abatacept treatment groups (12 months of treatment at 10 mg/kg every 28 days [10/10] or 12 months of treatment at 30 mg/kg every 28 days for 5 months followed by 10 mg/kg every 28 days for the remainder of the treatment period [30/10]) compared to the rate in the standard-of-care control group, with complete response defined according to the criteria from the Bristol-Myers Squibb study IM101075 protocol (BMS), the American College of Rheumatology (ACR) recommendations, and the Lupus Nephritis Assessment with Rituximab (LUNAR), Aspreva Lupus Management Study (ALMS), and Abatacept and Cyclophosphamide Combination: Efficacy and Safety Study (ACCESS) trials. Bars show the 95% confidence interval.

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Lessons learned

- Background Medicines
- Geography – SAE
- Racial Differences - Efficacy
- Duration of the Trial

Ocrelizumab

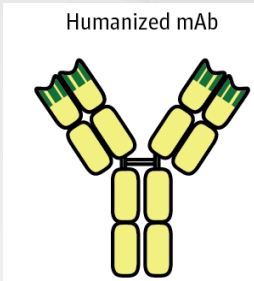

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Table 3. Renal response rates at week 48, overall and by background standard of care (modified intent-to-treat population)*

Response	Placebo + standard of care (n = 75)	Ocrelizumab 400 mg + standard of care (n = 75)	Ocrelizumab 1,000 mg + standard of care (n = 73)	Ocrelizumab Combined + standard of care (n = 148)
All patients				
CRR, no. (%)	26 (34.7)	32 (42.7)	23 (31.5)	55 (37.2)
PRR, no. (%)	15 (20.0)	18 (24.0)	26 (35.6)	44 (29.7)
ORR, no. (%)	41 (54.7)	50 (66.7)	49 (67.1)	99 (66.9)
95% CI for the ORR, %	43.4, 65.9	56.0, 77.3	56.3, 77.9	59.3, 74.5
Adjusted treatment difference, % (95% CI)†	–	12.1 (−3.3, 27.5)	13.9 (−1.4, 29.2)	12.7 (−0.8, 26.1)
P‡	–	–	–	0.065
ELNT regimen§				
CRR, no. (%)	7 (25)	14 (45)	8 (24)	22 (34)
PRR, no. (%)	5 (18)	9 (29)	11 (33)	20 (31)
ORR, no. (%)	12 (43)	23 (74)	19 (58)	42 (66)
95% CI for the ORR, %	24.5, 61.2	58.8, 89.6	40.7, 74.4	54.0, 77.3
Adjusted treatment difference, % (95% CI)†	–	31.3 (7.4, 55.3)	14.7 (−10.0, 39.6)	22.8 (1.1, 44.5)
P‡	–	–	–	0.065
MMF§				
CRR, no. (%)	19 (40)	18 (41)	15 (38)	33 (39)
PRR, no. (%)	10 (21)	9 (20)	15 (38)	24 (29)
ORR, no. (%)	29 (62)	27 (61)	30 (75)	57 (68)
95% CI for the ORR, %	47.8, 75.6	47.0, 75.8	61.6, 88.4	57.9, 77.8
Adjusted treatment difference, % (95% CI)†	–	−0.3 (−20.0, 19.7)	13.3 (−6.0, 32.6)	6.2 (−11, 23.3)
P‡	–	–	–	0.57

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Lessons learned

- Background Medicines
- Geography – SAE
- Racial Differences - Efficacy
- Duration of the Trial

Take home messages

- An expanded understanding of immunopathogenesis of SLE has resulted in the ability to supply the lupus community with the reagents needed to perform clinical trials.
- Belimumab has been approved for patients with SLE through the traditional route of randomized controlled trials.
- The basis for our failures relates to trial design issues, confounding by background medicines, and the multiplicity of active biologic pathways in this disease.
- Despite the obstacles, there currently is unprecedented clinical trial activity in lupus nephritis, which most likely will lead to new drug approval

Thank you!

Head of Division: Professor Lai-Shan Tam

Clinical Staff

Prof. Edmund K Li, Clinical Honorary Professor

Dr. Kong-Chiu Wong, Consultant

Dr. Priscilla CH Wong, Associate Consultant

Dr. Lydia Tam, Resident Specialist

Nurses:

Ms. Eleven Lau

Ms. Tena Li

Ms. Tracy Yu

Ms. Emily Lau

Research Assistants:

Ms. Michelle Pui

Mr Issac Cheng

Ms. Queenie Mak

PhD Student:

Mr. Jiang Yue

Post-doc Fellows:

Dr Jiayun Shen

Dr Yvonne Kam

Senior Technician:

Dr. Martin Li

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