



Brigham and Women's Hospital

Founding Member, Mass General Brigham

Basic Concepts of Immunology in Autoimmune Kidney Disease

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- Clinical and research focus:
Telenephrology outcomes and best practices
Glomerular disease mechanisms



DISCLOSURES

Dr. Bonegio is a full-time employee of the Veterans Administration and Associate Chief of Nephrology for VA-Boston. He directs the VA Telenephrology Enterprise-Wide Initiative.

He has no financial disclosures.



OBJECTIVES

Introducing the immune system

- Innate immunity
- Adaptive immune cells

A few new things to be aware of

- Where is the immune system?
- B cell maturation factors
- The plastic T cell subtypes

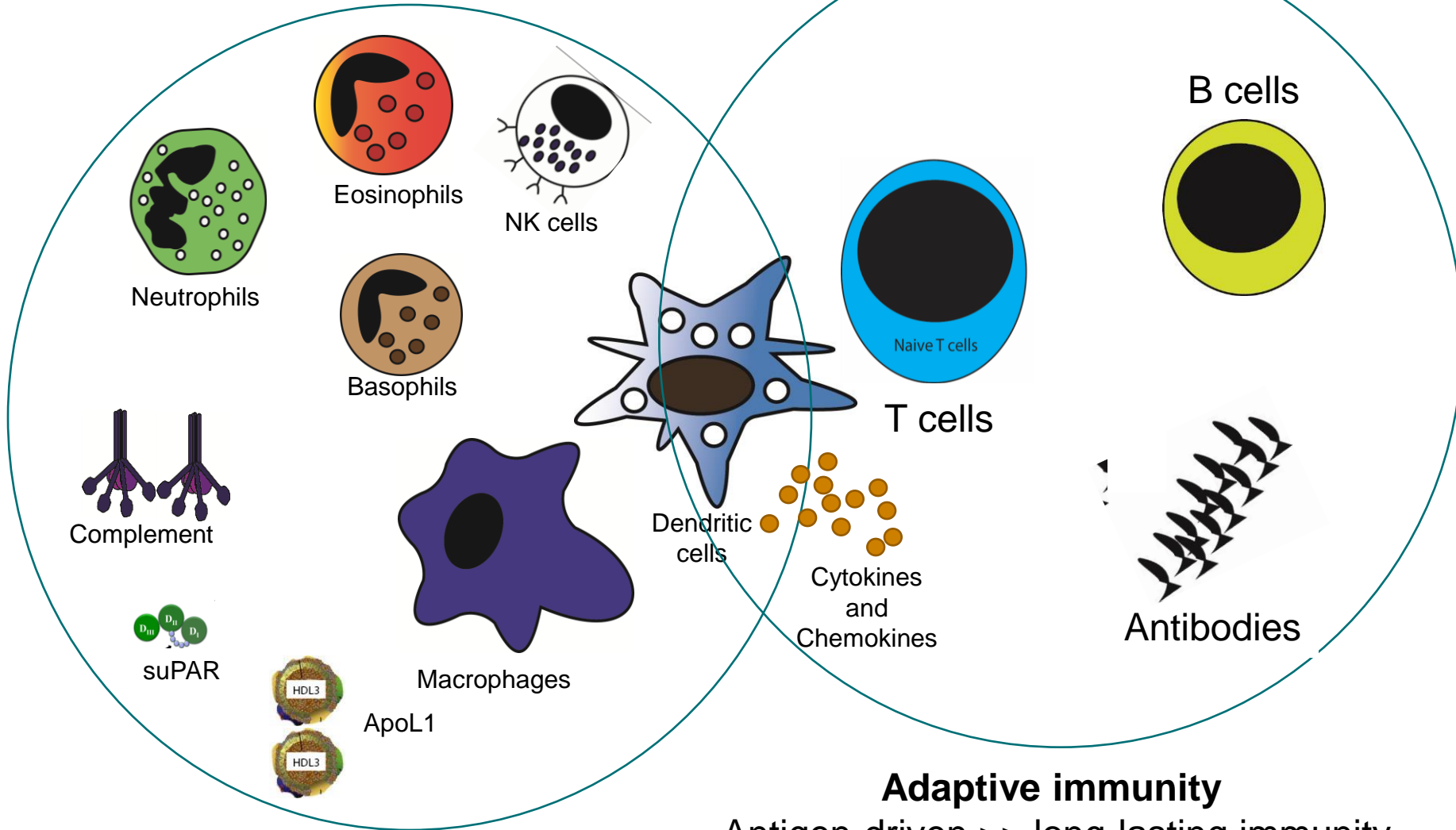
A few cases with possible therapeutic implications

Conclusions



Parts of the immune system

Innate immunity
PRR >> inflammation



Adaptive immunity
Antigen-driven >> long-lasting immunity

Where is the immune system?

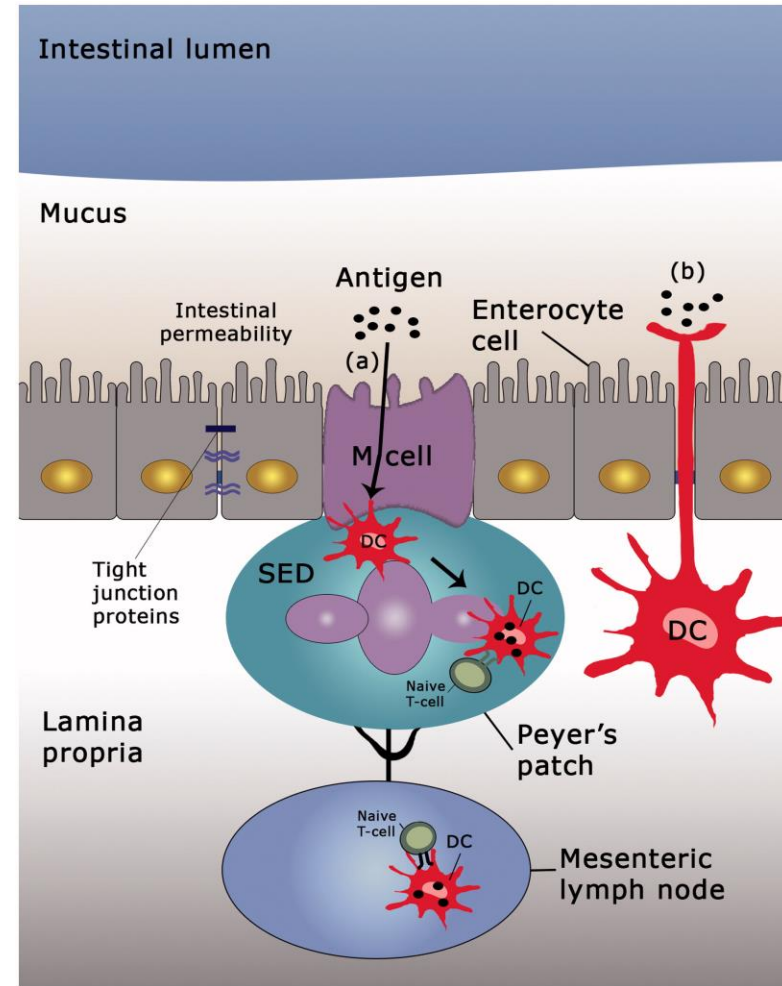


Where is the immune system?



Gut-associated lymphoid tissue samples antigens from the gut lumen

- Critical site of defense
- Critical site tolerance vs effector responses



NefIgArd – Efficacy and safety of a targeted-release formulation of budesonide in patients with IgA nephropathy (NefIgArd): 2-year results from a randomized phase 3 trial

Screening

Optimized and
Stable RAS blockade

9 month

Double blinded treatment
Nefecon 16mg/d vs Placebo

15 month

Double blinded follow-up



	Nefecon 16 mg/day (n=182)	Placebo (n=182)
Age, years	43 (36–50)	42 (34–49)
<45 years	98 (54%)	104 (57%)
Sex		
Male	117 (64%)	123 (68%)
Female	65 (36%)	59 (32%)
Race		
White	138 (76%)	137 (75%)
Asian	43 (24%)	40 (22%)
Black or African American	0	0
Other	1 (1%)	5 (3%)
Baseline blood pressure, mm Hg		
Systolic	126 (121–132)	124 (117–130)
Diastolic	79 (76–84)	79 (74–84)
Baseline UPCR, g/g	1.48 (0.85), 1.28 (0.90–1.76)	1.48 (1.15), 1.25 (0.88–1.74)
Baseline proteinuria, g/24 h	2.71 (1.73), 2.29 (1.61–3.14)	2.71 (2.20), 2.17 (1.53–3.39)
<2 g/24 h	78 (43%)	79 (43%)
≥2 g/24 h	104 (57%)	103 (57%)
Baseline UACR, g/g	1.16 (0.68), 0.99 (0.68–1.40)	1.16 (0.84), 0.98 (0.66–1.42)
Baseline total urine albumin, g/24 h	2.12 (1.34), 1.77 (1.24–2.49)	2.11 (1.58), 1.70 (1.12–2.54)
eGFR*, mL/min per 1.73 m ²	56.14 (45.50–70.97)	55.11 (45.96–67.74)
<60 mL/min per 1.73 m ²	109 (60%)	109 (60%)
≥60 mL/min per 1.73 m ²	73 (40%)	73 (40%)
Microhaematuria at randomisation		
Yes	123 (68%)	127 (70%)
No	59 (32%)	55 (30%)
Time since IgA nephropathy biopsy diagnosis at	2.4 (0.6–6.9)	2.6 (0.6–6.5)

Outcomes

- **Primary** = time-weighted eGFR
- **Secondary** = -30% eGFR or ESRD

Completed treatment for 9 months

- Nefecon group (16mg/d)
158/182 (87%)
- Placebo group
165/182 (91%)

Adherence to treatment (80% of capsules taken) was high (94%)

NefIgArd – Efficacy and safety of a targeted-release formulation of budesonide in patients with IgA nephropathy (NefIgArd): 2-year results from a randomized phase 3 trial

Supplementary Figure S4. Subgroups summary of time-weighted average of eGFR over 2 years us

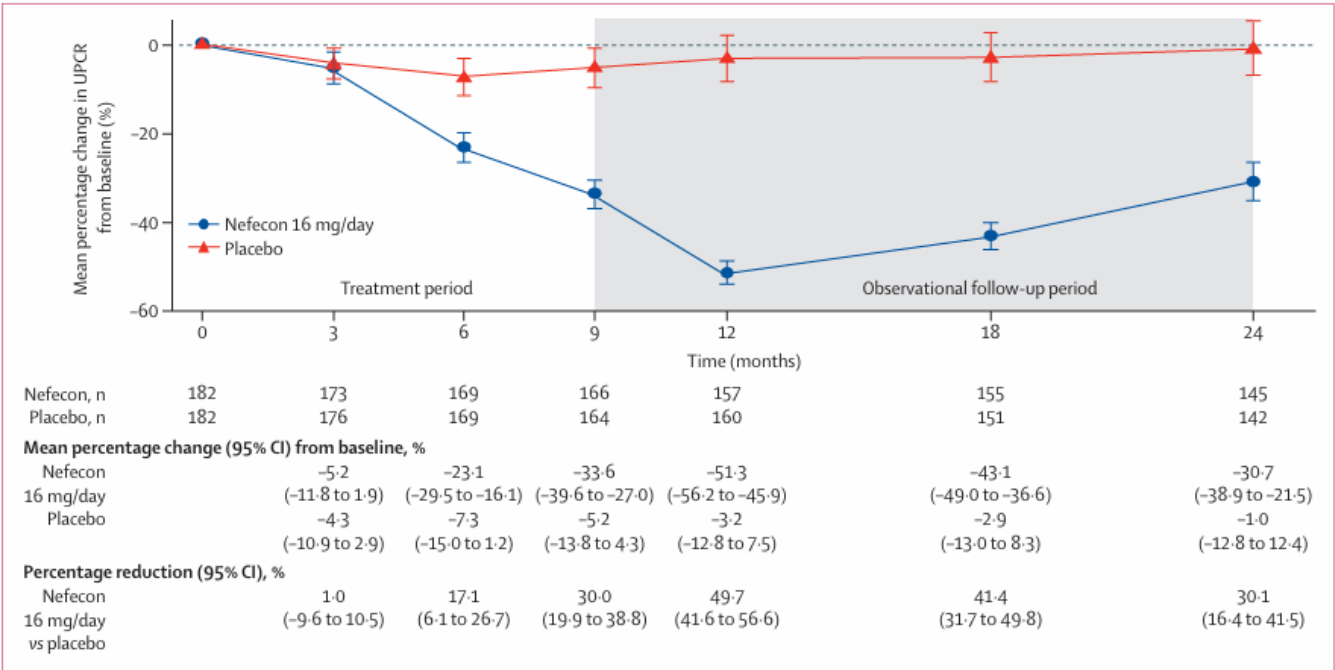
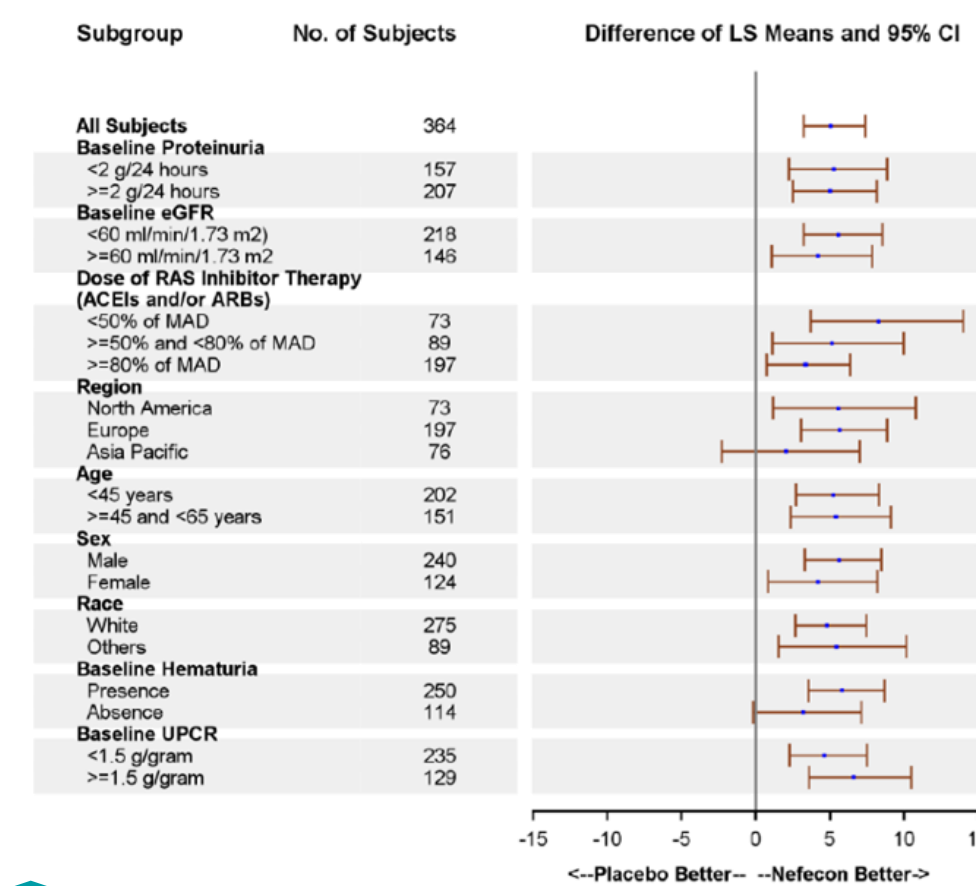
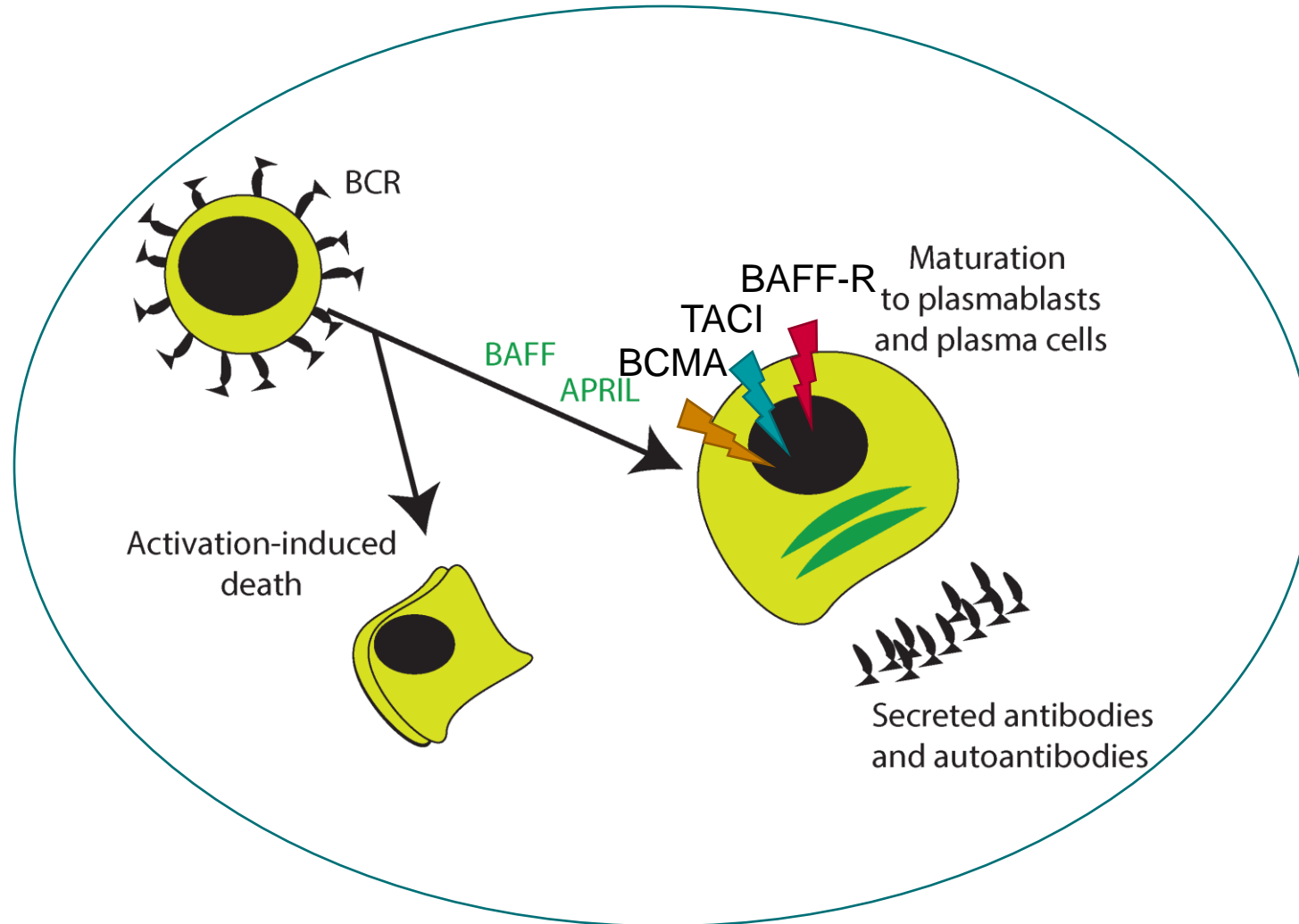


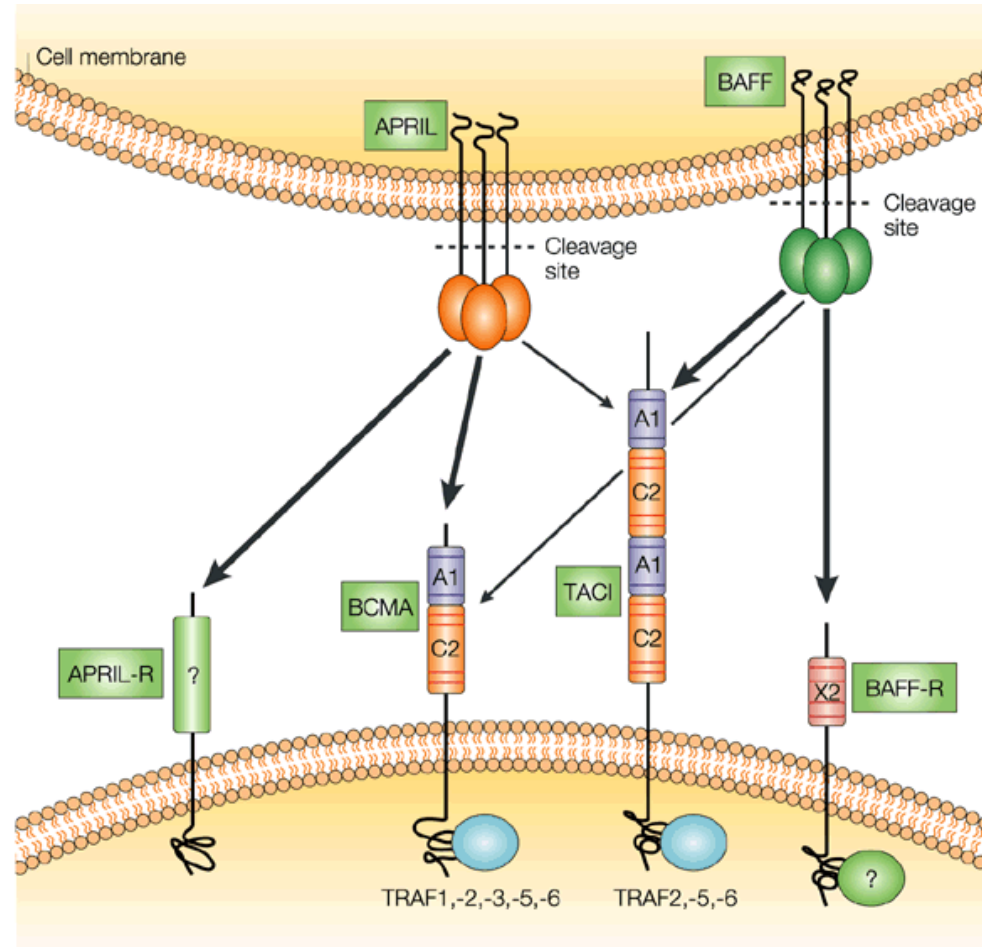
Figure 2: Mean percentage change in UPCR (g/g) from baseline to 24 months (full analysis set)



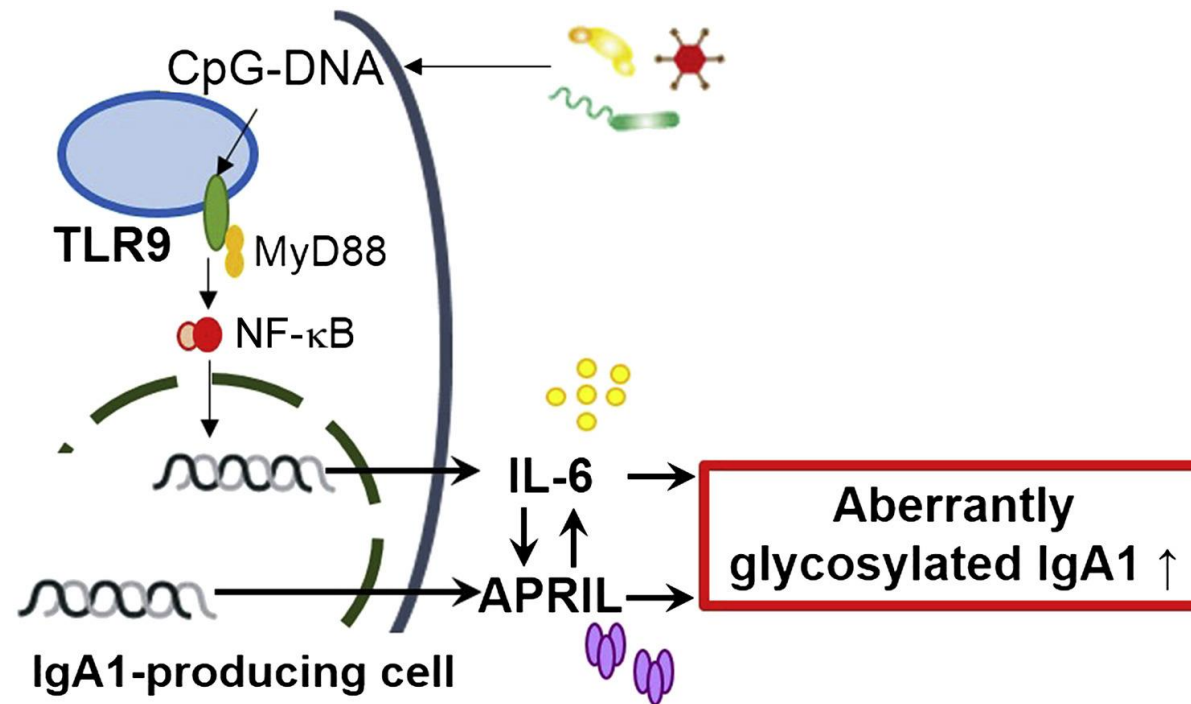
Adaptive immunity: TNF family members regulate maturation and growth of B cells



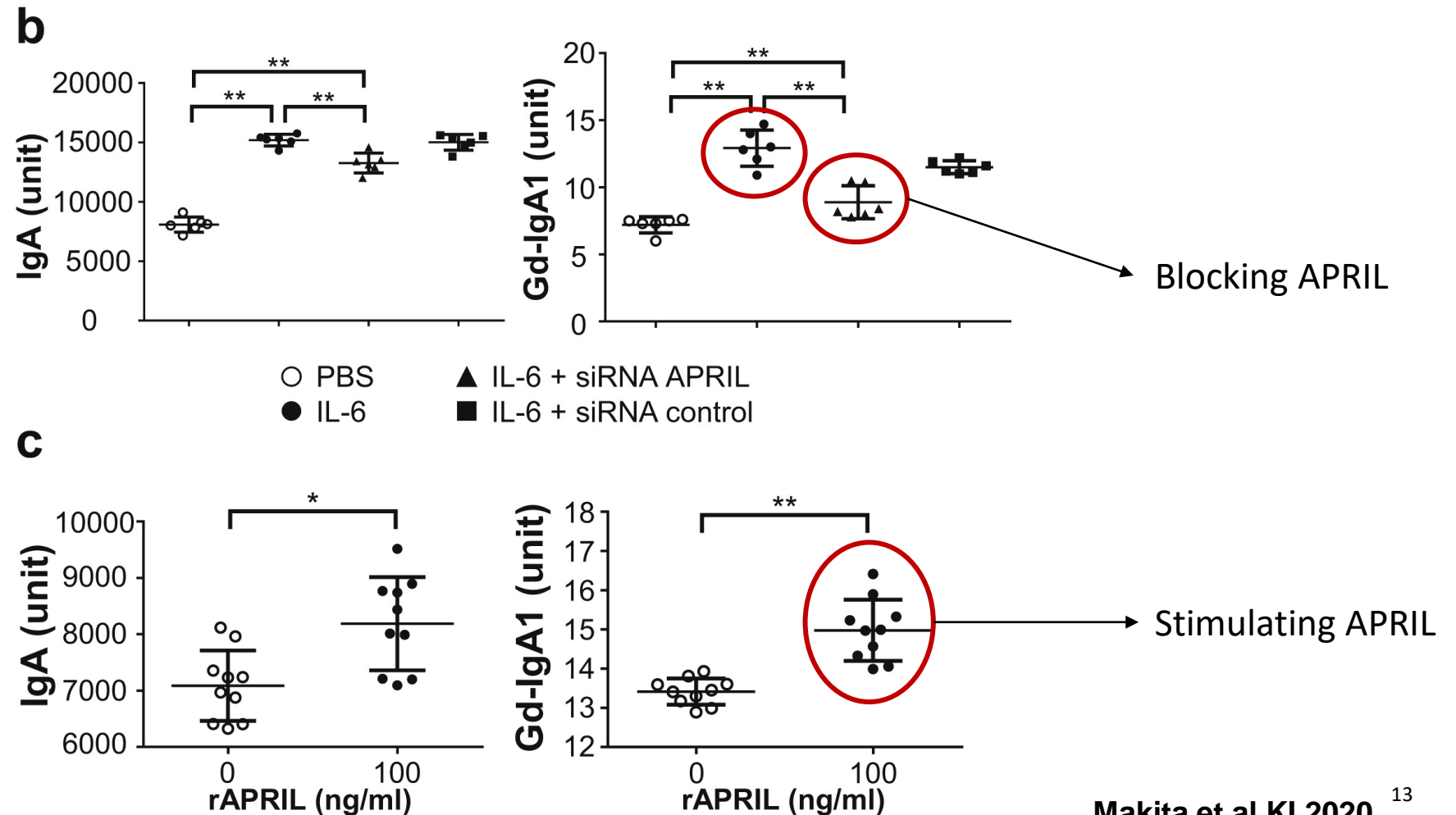
Adaptive immunity: TNF family members regulate the maturation and growth of B cells



APRIL and IL-6 synergistically activate IgA producing cells to induce aberrant IgA glycosylation

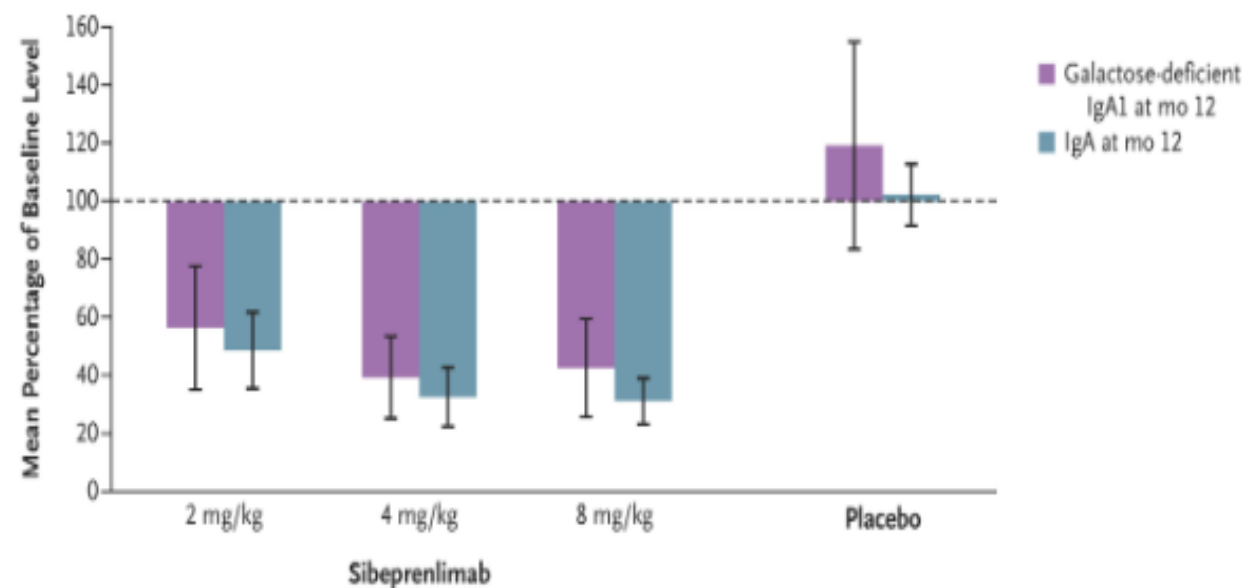


APRIL and IL-6 synergistically activate IgA producing cells to induce aberrant IgA glycosylation

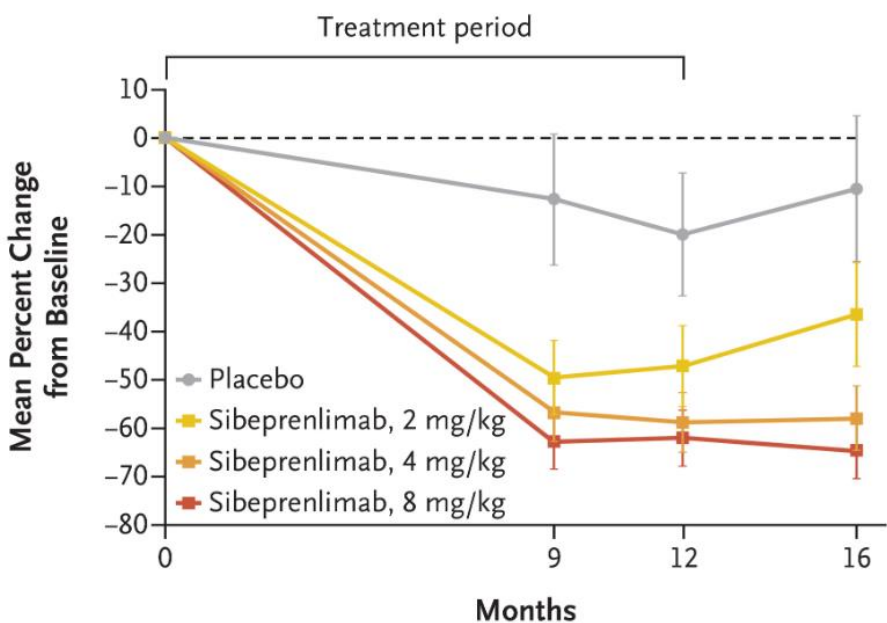


A Phase 2 Trial of Sibeprenlimab (an APRIL inhibitor) in Patients with IgA Nephropathy

Galactose-deficient IgA1 and IgA levels at Month 12 of Siberprenlimab/placebo



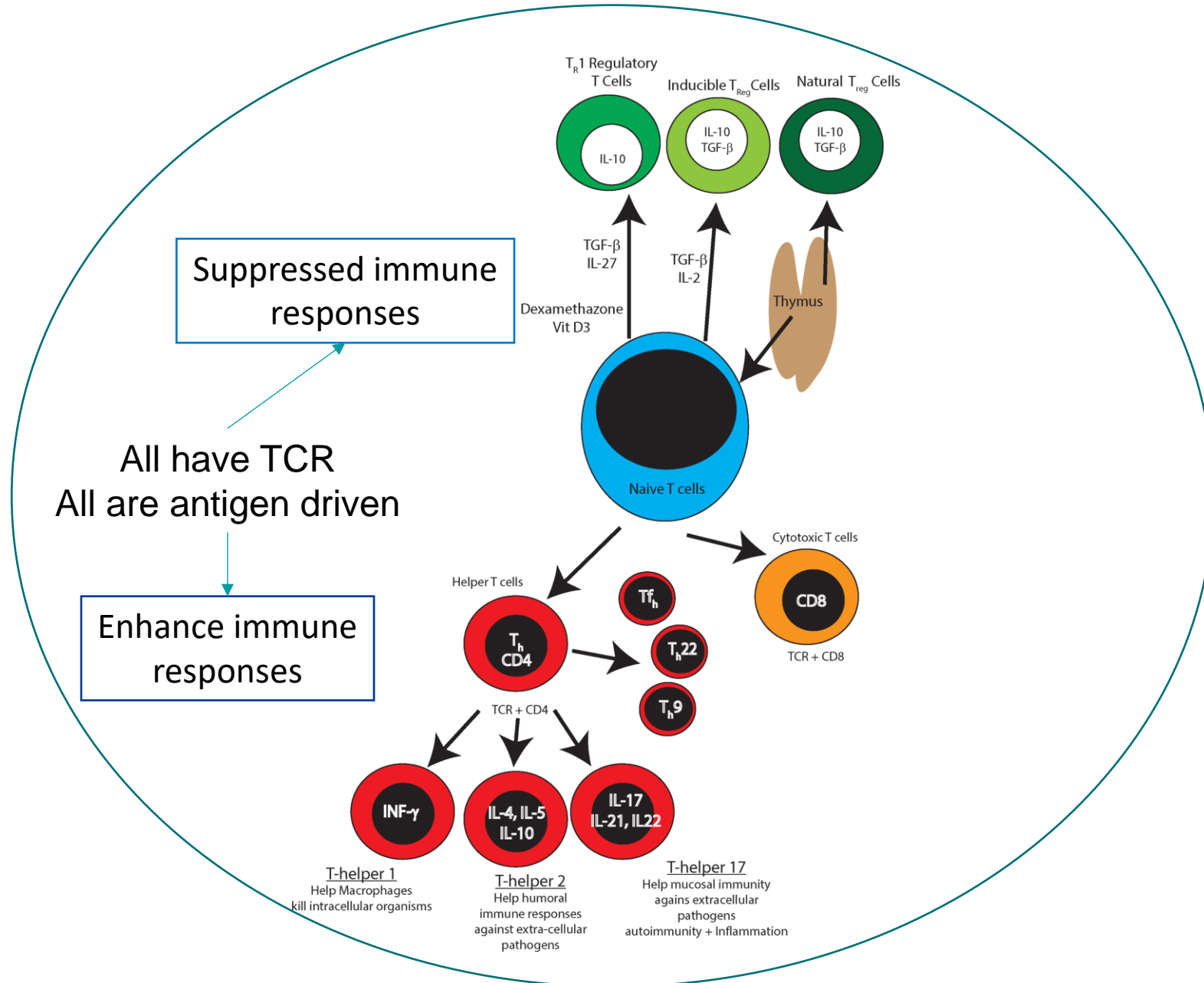
Change in 24-hour urine PCR during treatment with Siberprenlimab/placebo



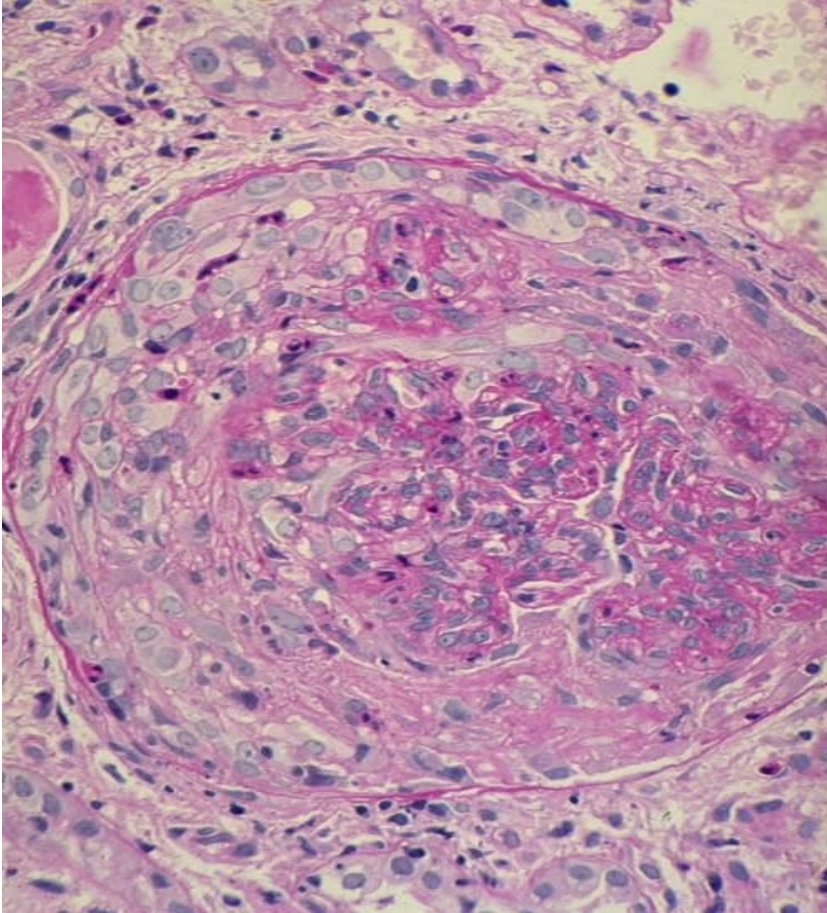
No. of Patients				
Placebo	38	35	35	35
Sibeprenlimab, 2 mg/kg	38	35	35	35
Sibeprenlimab, 4 mg/kg	41	40	38	38
Sibeprenlimab, 8 mg/kg	38	36	37	37



Adaptive immunity: T cell personalities and immune functions

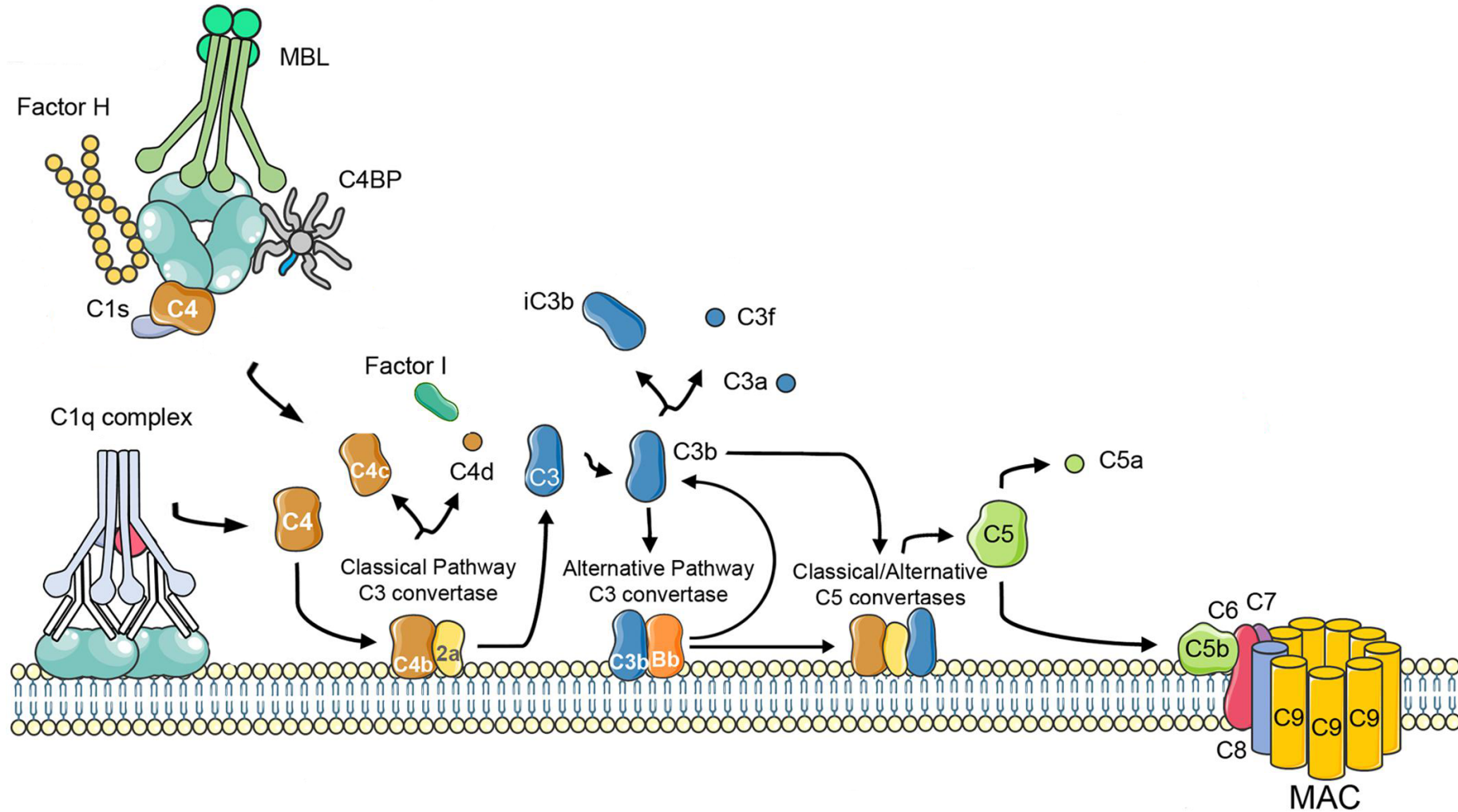


Q1. A 62-year-old woman presents with ANCA-associated RPGN. Which of the following factors **IS LEAST LIKELY** to contribute to the severity of her glomerular injury?

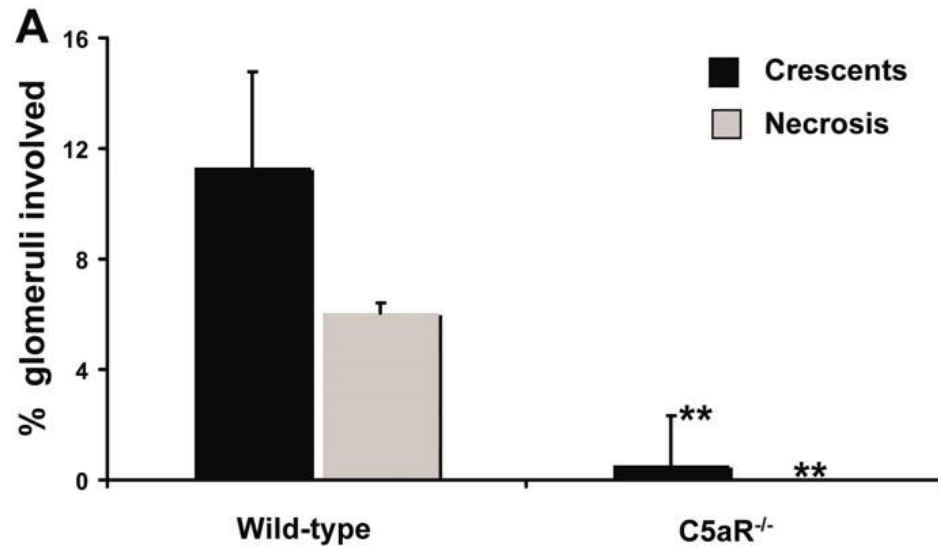


- 1) Neutrophils
- 2) B cells and plasma cells
- 3) Complement C5a
- 4) The complement membrane attack complex (C5b-9)
- 5) Autoantibodies targeting proteinase 3 or myeloperoxidase

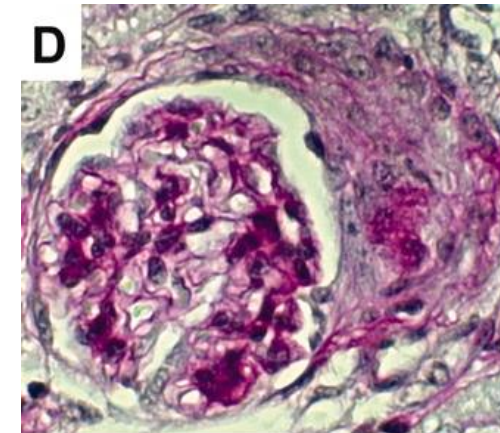
Complement activation



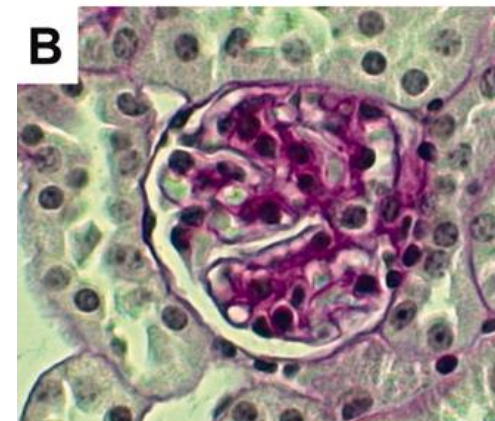
C5aR is required for neutrophil recruitment to glomeruli and crescent formation



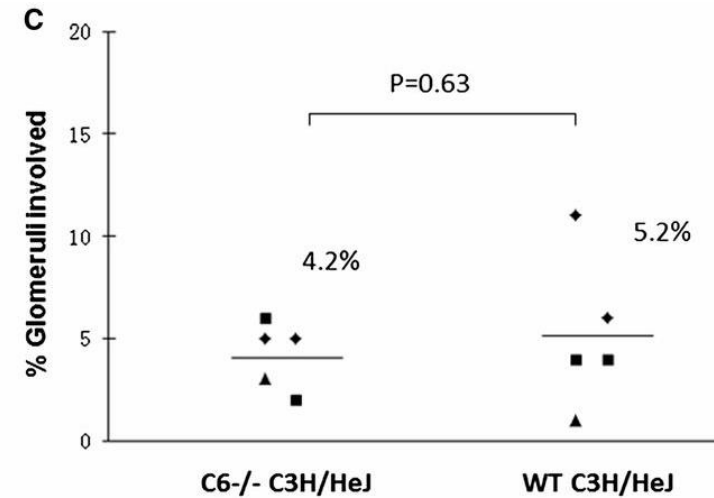
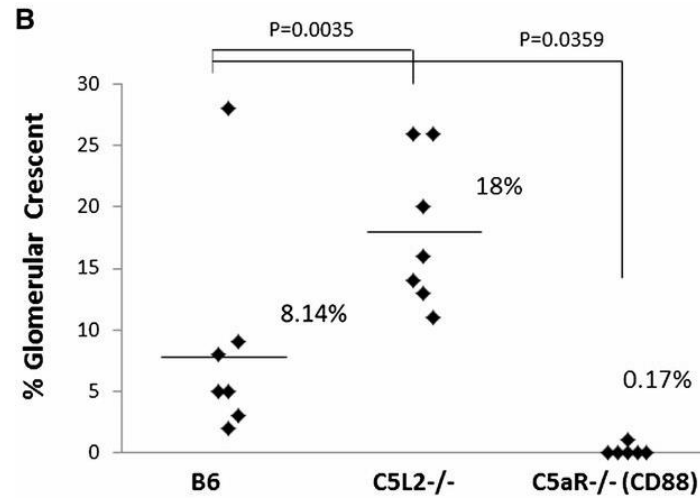
Wild-type



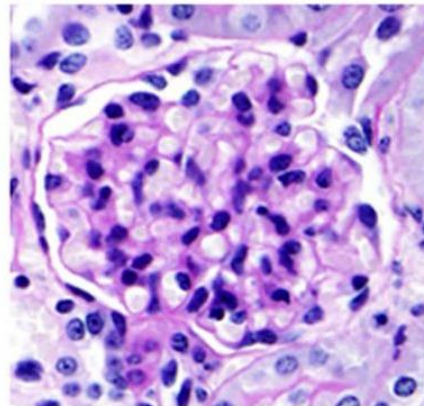
C5aR^{-/-}



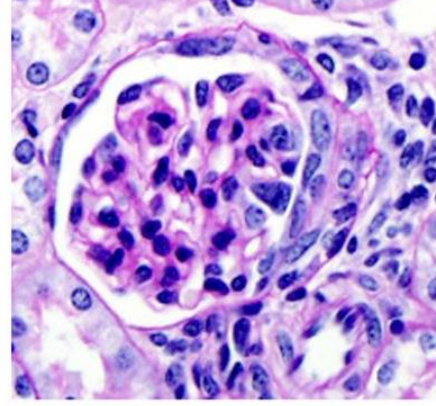
C5aR but not the MAC is required for crescent formation



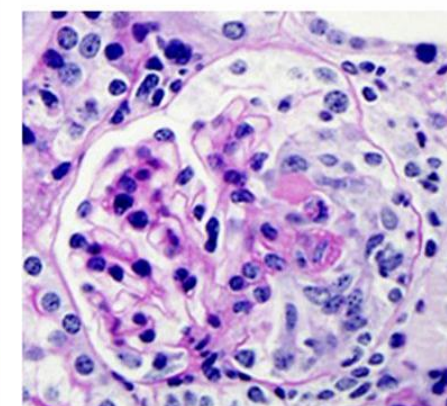
C5aR-/-



C6-/-



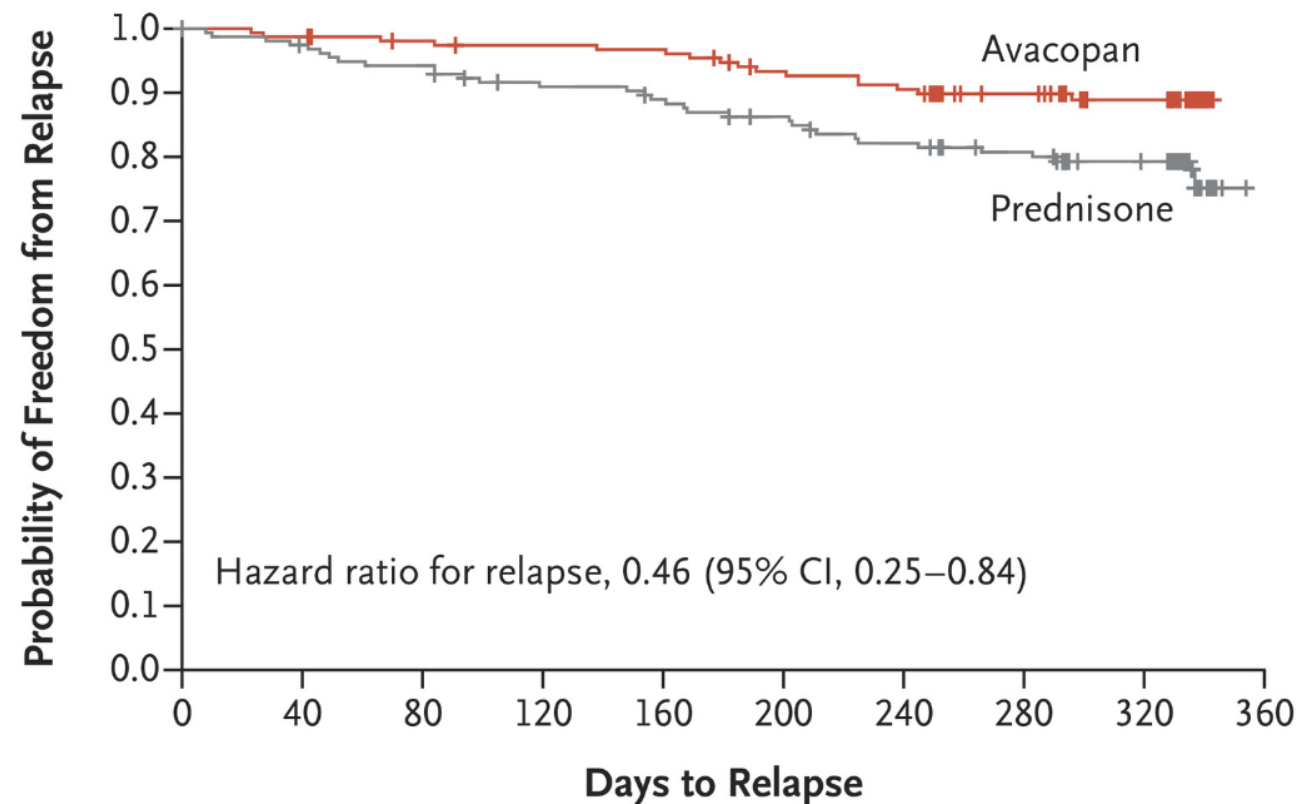
C5aR-/- with hC5aR



C5aR inhibition in human AAV

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Avacopan (N=166)	Prednisone (N=164)
Age — yr	61.2±14.6	60.5±14.5
Sex — no. (%)		
Male	98 (59.0)	88 (53.7)
Female	68 (41.0)	76 (46.3)
Race — no. (%)†		
White	138 (83.1)	140 (85.4)
Asian	17 (10.2)	15 (9.1)
Black	3 (1.8)	2 (1.2)
Other	8 (4.8)	7 (4.3)
Body-mass index‡	26.7±6.0	26.8±5.2
Median duration of ANCA-associated vasculitis (range) — mo	0.23 (0–362.3)	0.25 (0–212.5)
Vasculitis disease status — no. (%)		
Newly diagnosed	115 (69.3)	114 (69.5)
Relapsed	51 (30.7)	50 (30.5)
ANCA status — no. (%)		
Antiproteinase 3 positive	72 (43.4)	70 (42.7)
Antimyeloperoxidase positive	94 (56.6)	94 (57.3)

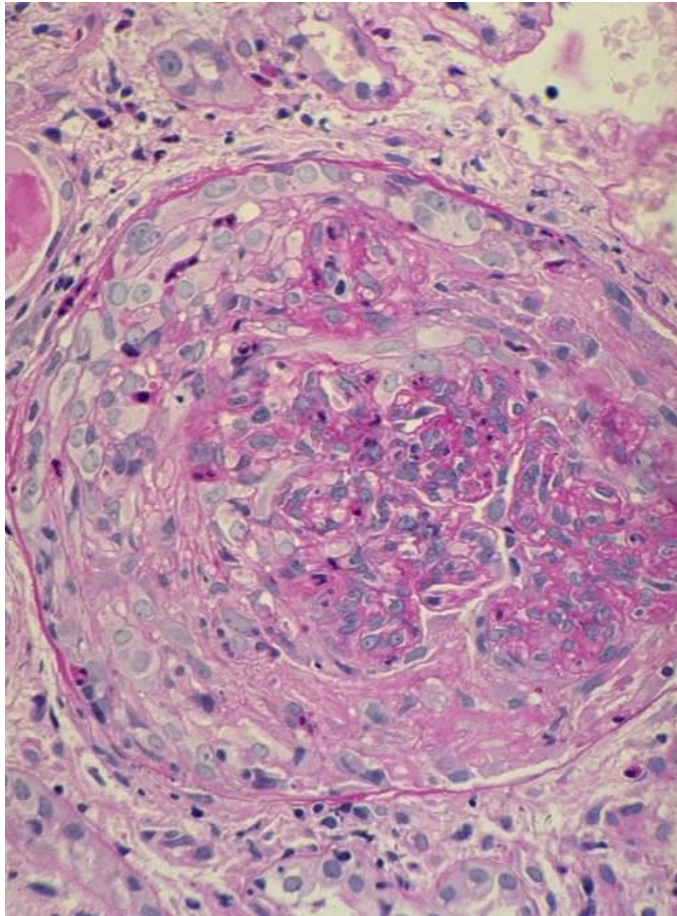


No. at Risk

Avacopan	158	153	149	146	145	133	129	115	92	0
Prednisone	157	151	146	137	133	126	119	111	90	0



Q1. A 62 year-old woman presents with ANCA-associated RPGN. Which of the following factors **IS LEAST LIKELY** contribute to the severity of her glomerular injury?

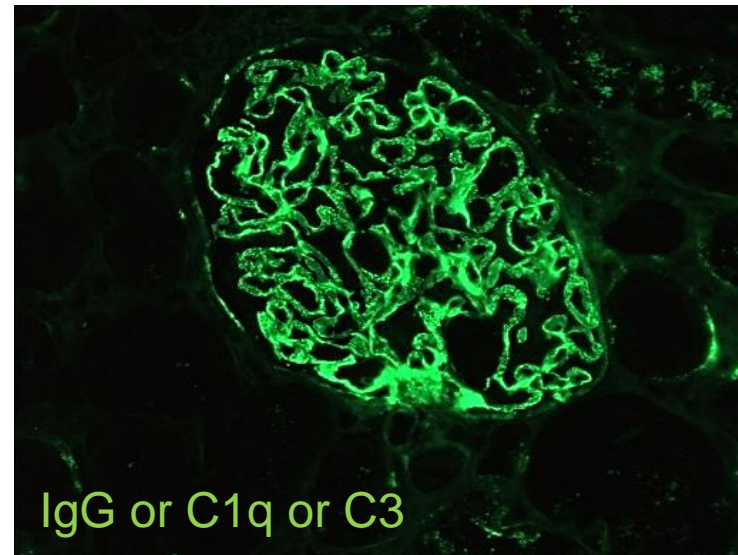
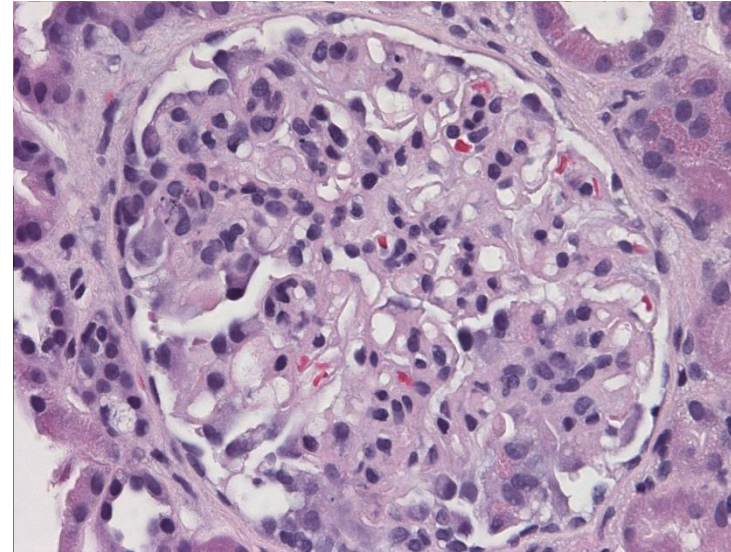


- 1) Neutrophils
- 2) B cells and plasma cells
- 3) Complement C5a
- 4) The complement membrane attack complex (C5b-9)
- 5) Autoantibodies targeting proteinase 3 or myeloperoxidase

Q2. A 24-year-old woman presents with nephrotic range proteinuria and an active urinary sediment. She complains of photosensitivity, hair loss and arthritis

Which of the following are likely targets that may ameliorate disease

- 1) The TNF pathways
- 2) Type 1 interferon pathways
- 3) C2
- 4) B cell activation factor (BAFF)
- 5) B cells



Anti-TNF induced lupus

TABLE 2. Features of patients with ATIL based on case reports and case series to date

ACR diagnostic criteria for lupus	BSRBR data [47], (Britain) (n= 41)	Costa <i>et al.</i> , 2008 [31], (USA) (n=33)	Ramos-Casal <i>et al.</i> , 2007 [45], (Spain) (n=72)	De Bandt <i>et al.</i> , 2005 [44], (France) (n=12)
Malar rash, n (%)	— ^a	— ^a	— ^a	5 (42)
Discoid rash, n (%)	25 (61) ^a	24 (73) ^a	48 (67) ^a	0
Photosensitivity, n (%)	4 (10)	— ^a	— ^a	5 (42)
Oral ulcers, n (%)	5 (12)	1 (3)	3 (4)	0
Arthritis, n (%)	3 (7)	17 (52)	22 (31)	6 (50)
Serositis, n (%)	0	3 (18)	9 (12)	3 (25)
Renal disorder, n (%)	0	3 (9)	5 (7)	0
Neurological disorder, n (%)	0	0	2 (3)	0
Haematological disorder, n (%)	1 (2)	20 (61)	Cytopenia—16 (22)	6 (50)
Immunological disorder, n (%)	4 (10)	29 (88)	dsDNA—52 (72) ^b anti-Sm—7 (10)	11 (92)
Anti-nuclear antibodies, n (%)	13 (32)	32 (97)	57 (79)	12 (100)

^aData on cutaneous features not given; subdivided into individual categories. Also includes 'unspecified rash' as a category. ^bIndividual patient data not listed, so unable to ascertain if some patients had more than one of these features.

TABLE 3. Autoantibody profiles of reported cases of ATIL/lupus-like syndrome

Autoantibody	Costa <i>et al.</i> , 2008 [31], (Britain) (n=33)	Ramos-Casals <i>et al.</i> , 2007 [45], (Spain) (n=72)	De Bandt <i>et al.</i> , 2005 [44], (France) (n=12)
ANA, n (%)	32/32 ^a (100)	57 (79)	12 (100)
dsDNA, n (%)	29/32 (91)	52 (72)	11 (92)
Histone, n (%)	16/28 (57)	NR	2 (17)
aPL, n (%)	NR	8 (11)	6 (50)
ENAs (any), n (%)	10/19 (53)	Anti-Sm 7 (10) ^b Anti-Ro/La 9 (12) Anti-RNP 5 (7)	5 (42)

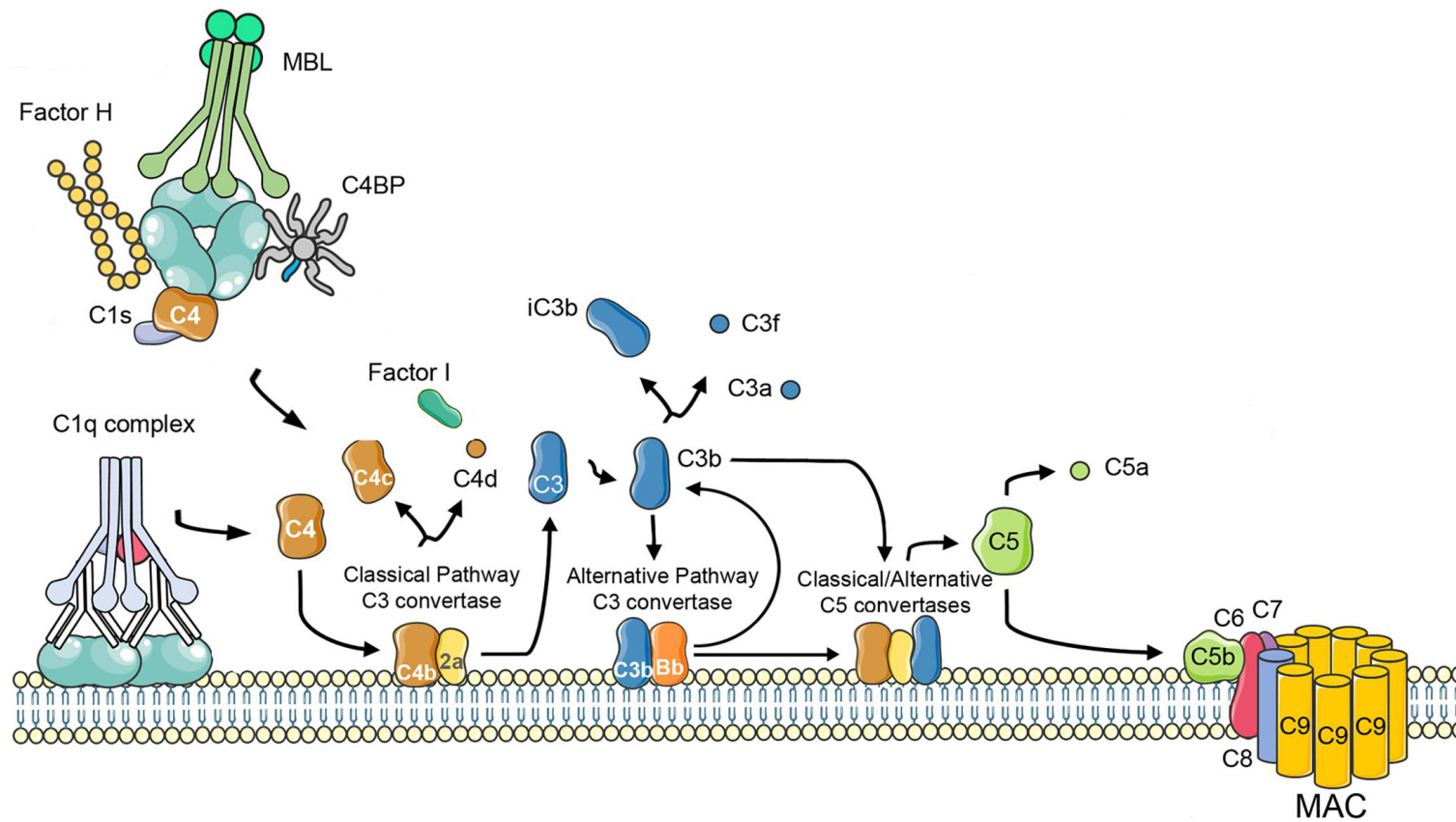
NR: not reported. ^aANA/dsDNA reported in only 32 subjects. ^bUnclear from data given whether some patients had more than one positive ENA or if these all occurred in separate patients.

61-84%
Cut. Lupus

< 9 %
Renal dis.



Complement activation



C2 and C4 deficiency is strongly associated with SLE risk

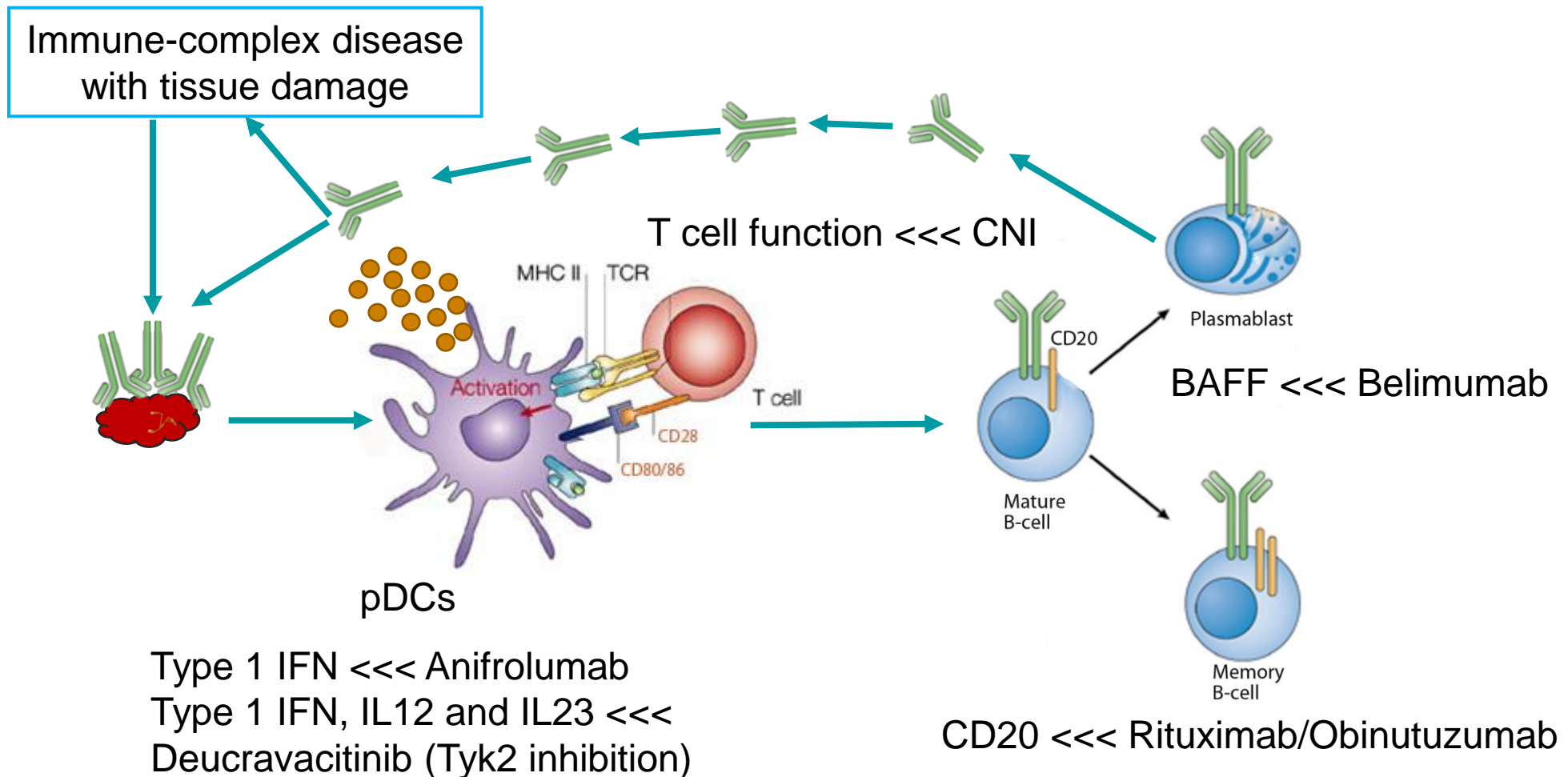
Table 1 Selected complement deficiencies and associated clinical findings

Complement protein	Inheritance pattern	Pathway impacted	Main clinical presentation	Autoantibody profile characteristics (if applicable)
C1q	Autosomal recessive	CP	Infection, SLE	ANA, ENA antibody commonly positive; dsDNA antibody negative
C1r/C1s	Autosomal recessive	CP	Infection, SLE	
C4	Autosomal recessive	CP, LP	Infection, SLE, IgA nephropathy, Henoch-Schönlein purpura, chronic hepatitis, scleroderma, membranous nephropathy, panencephalitis, diabetes mellitus type 1	ANA, ENA antibody positive
C2	Autosomal recessive	CP, LP	Infection, SLE, rash, glomerulonephritis	Low titer ANA ~25 %, negative dsDNA antibody, Ro antibody ~25–50 %
C3	Autosomal recessive	CP, LP, AP	Infection, SLE, membranoproliferative glomerulonephritis, rash	Negative
C5–8	Autosomal recessive	Terminal	Recurrent neisserial infections	
MBL	Autosomal recessive	LP	Infections, SLE (increased risk of arterial thrombosis)	
Factor B	Autosomal recessive	AP	Infection	
Factor D	Autosomal recessive	AP	Neisserial infections	
Factor I	Autosomal recessive	AP	Infections	
Factor H	Autosomal recessive	AP	Hemolytic uremic syndrome, membranoproliferative glomerulonephritis, macular degeneration	
Properdin	X-linked recessive	AP	Neisserial infections	
C1 inhibitor	Autosomal dominant	CP	Angioedema	

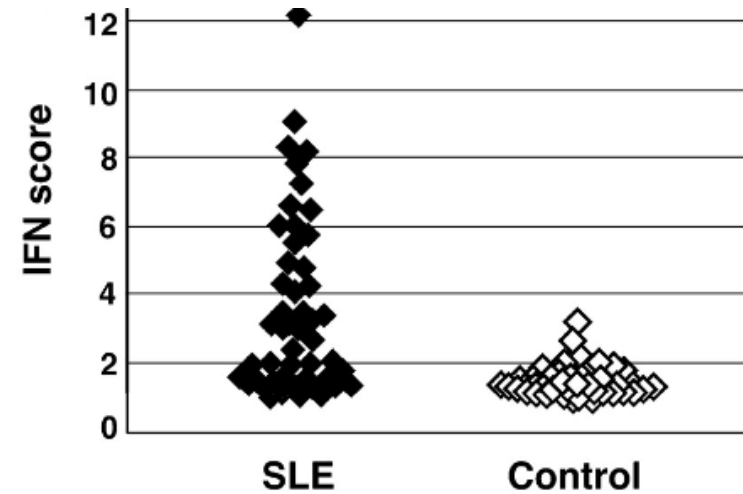
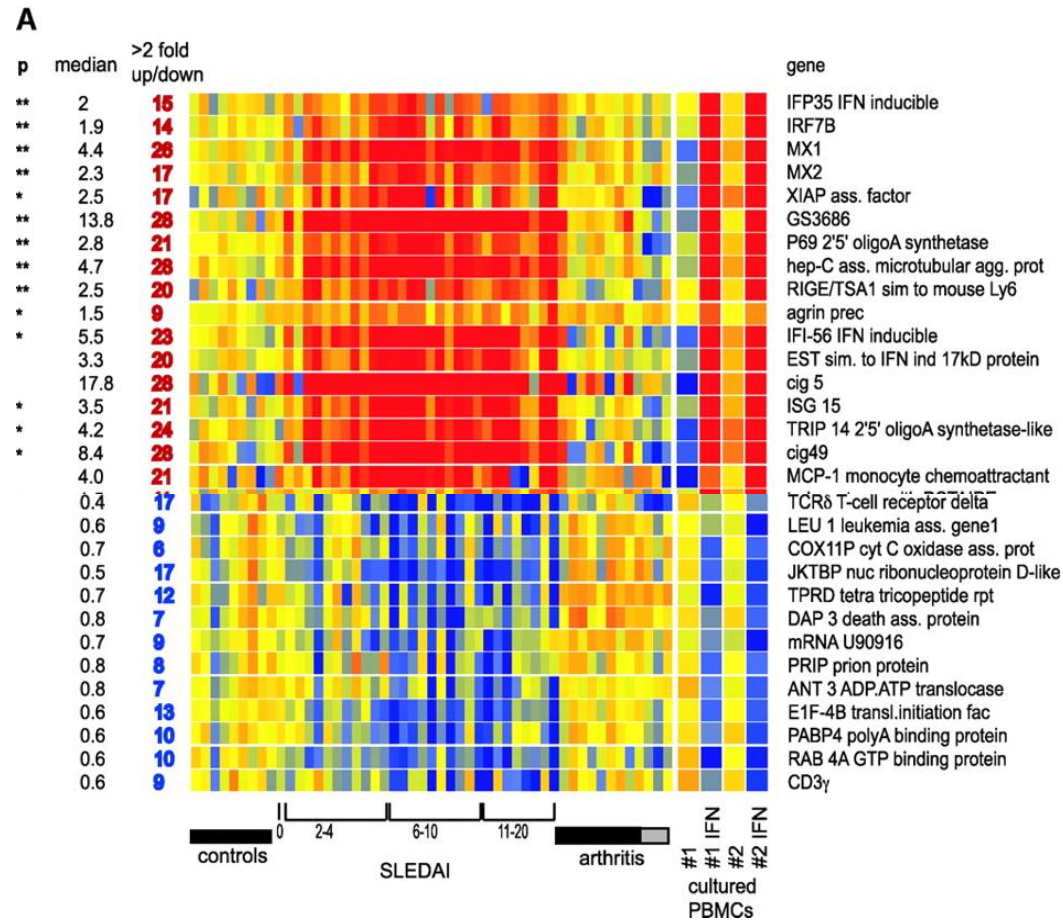
CP classical pathway, *AP* alternative pathway, *LP* lectin pathway, *SLE* systemic lupus erythematosus, *ANA* anti-nuclear antibody, *ENA* extractable nuclear antigens, *dsDNA* double-stranded DNA



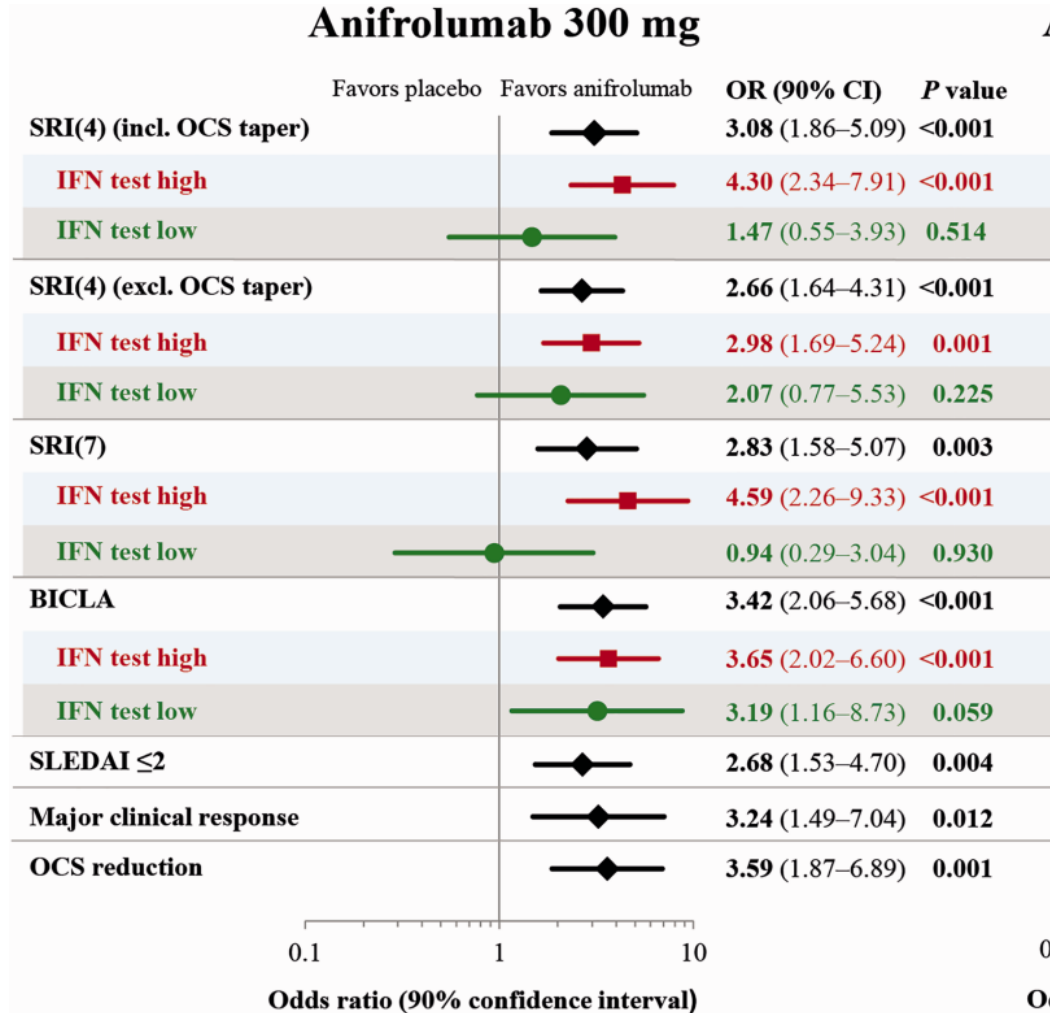
Lupus -Targeted therapy



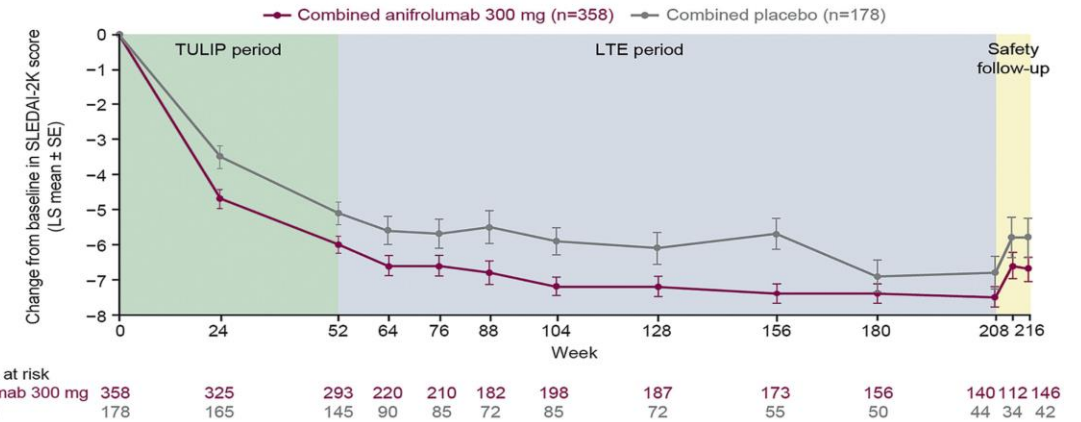
Type 1 interferon as a target in SLE



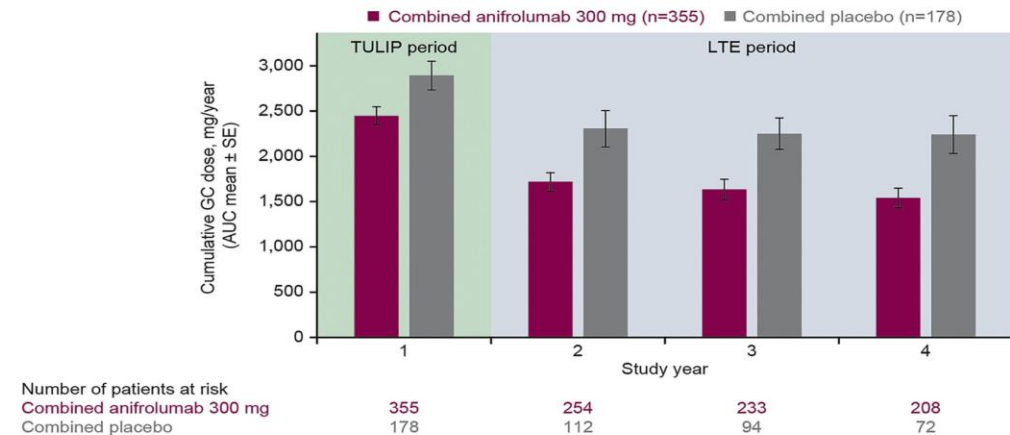
Treatment of lupus nephritis: Anifrolumab phase 1-2



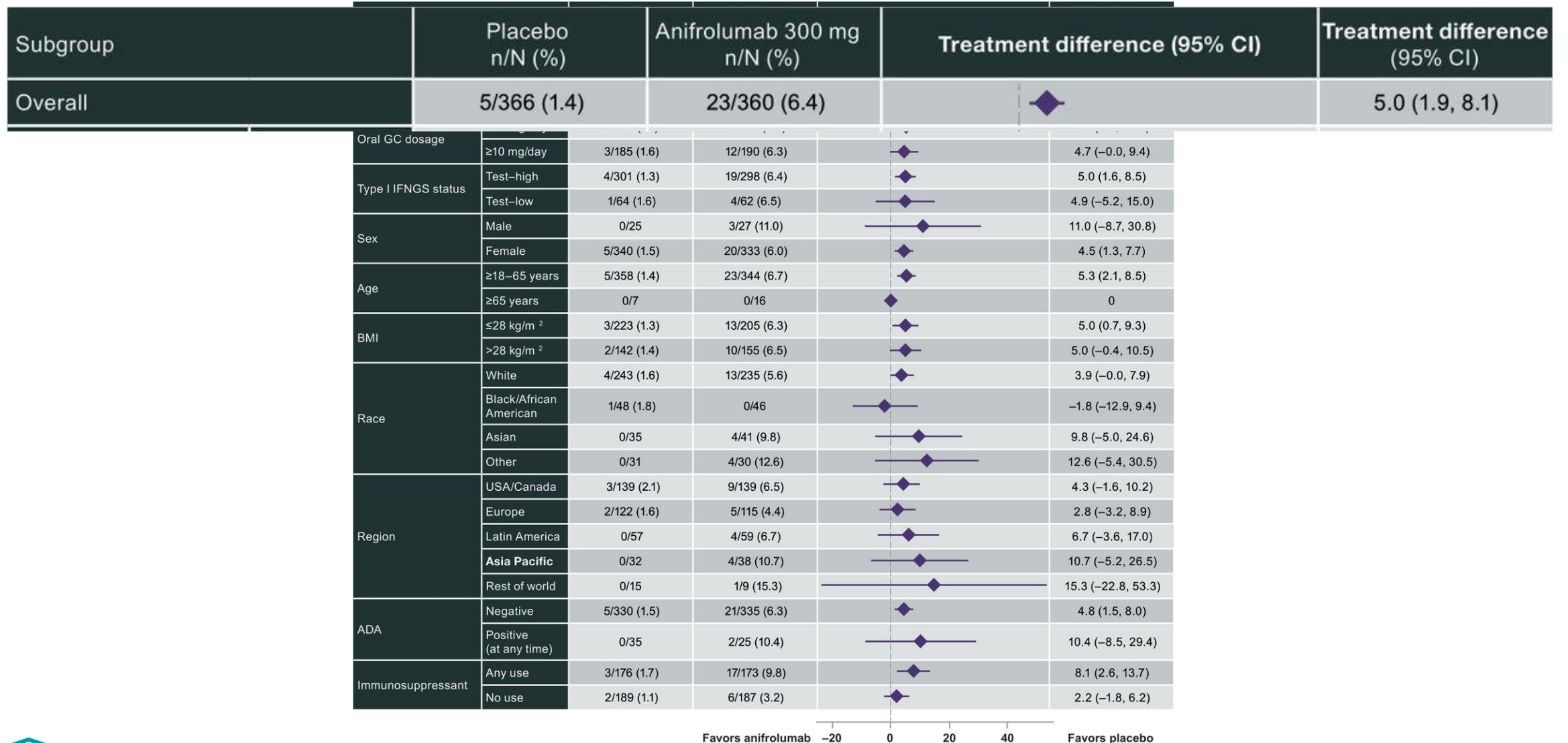
A



B



Anifrolumab safety – cumulative risk of Herpes Zoster



Anifrolumab safety

Table 3. AEs, SAEs, deaths, AESIs, and EAIRs in any category during treatment and follow-up during weeks 0–216 (TULIP + LTE years 1–4)*

	All anifrolumab (n = 560; exposure 1,568.0 patient-years†)		Combined anifrolumab 300 mg (n = 358; exposure 1,026.2 patient-years†)		All placebo (n = 360; exposure 587.1 patient-years†)	
	No. (%)	EAIR (per 100 patient-years)‡	No. (%)	EAIR (per 100 patient-years)‡	No. (%)	EAIR (per 100 patient-years)‡
Any AE	522 (93.2)	33.3	338 (94.4)	32.9	318 (88.3)	54.2
Any SAE (including events with outcome of death)	147 (26.3)	9.4	92 (25.7)	9.0	91 (25.3)	15.5
Any AE with outcome of death	10 (1.8)	0.6	5 (1.4)	0.5	2 (0.6)	0.3
Any DAE	59 (10.5)	3.8	35 (9.8)	3.4	30 (8.3)	5.1
Any AE of severe intensity	102 (18.2)	6.5	67 (18.7)	6.5	46 (12.8)	7.8
Any death of COVID-19 infection	2 (0.4)	0.1	1 (0.3)	0.1	0	0
Any AESI	180 (32.1)	11.5	113 (31.6)	11.0	61 (16.9)	10.4
Any AESI of herpes zoster	75 (13.4)	4.8	45 (12.6)	4.4	13 (3.6)	2.2
Any AESI of non-opportunistic serious infections	55 (9.8)	3.5	37 (10.3)	3.6	29 (8.1)	4.9
Non-opportunistic serious infections of COVID-19	9 (1.6)	0.6	6 (1.7)	0.6	0	0
Any AESI of influenza	36 (6.4)	2.3	20 (5.6)	1.9	11 (3.1)	1.9
Any AESI of latent tuberculosis§	27 (4.8)	1.7	20 (5.6)	1.9	4 (1.1)	0.7
Any AESI of opportunistic infections	3 (0.5)	0.2	1 (0.3)	0.1	4 (1.1)	0.7
Any AESI of anaphylaxis	1 (0.2)	0.1	0	0	0	0
Any AESI of malignancy	12 (2.1)	0.8	7 (2.0)	0.7	4 (1.1)	0.7
Any AESI of major acute cardiovascular events	12 (2.1)	0.8	6 (1.7)	0.6	3 (0.8)	0.5
Any AESI of vasculitis	0	0	0	0	0	0

* Data presented are combined from the Treatment of Uncontrolled Lupus via the Interferon Pathway (TULIP) trials and the extension study. Only descriptive statistics were performed. See Table 2 for other definitions.

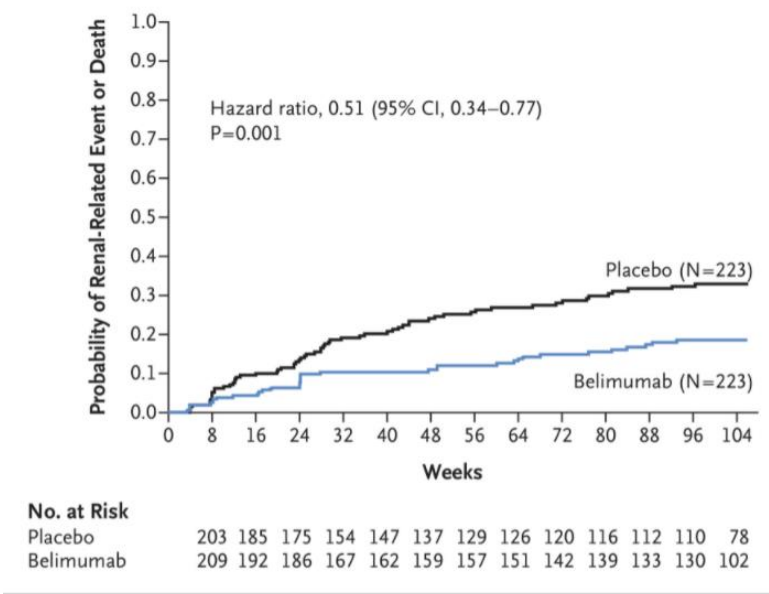
† Exposure in days for each patient was calculated as: the earlier of either (i.e., date of last dose of treatment + 84 days, or date of study discontinuation) – date of first dose of treatment + 1 day.

‡ The EAIR per 100 patient-years was defined as the number of patients with the specific event divided by the total exposure in years × 100. The exposure time was defined as from the date of first administration of treatment to death, end of treatment + 84 days, or end of study, whichever came first.

§ Latent tuberculosis was defined as a positive interferon-γ release assay result. All patients were required to be tested at least annually and, in some cases, more often, depending on the result. No active cases of tuberculosis were reported.

Targeting B cell activation is effective

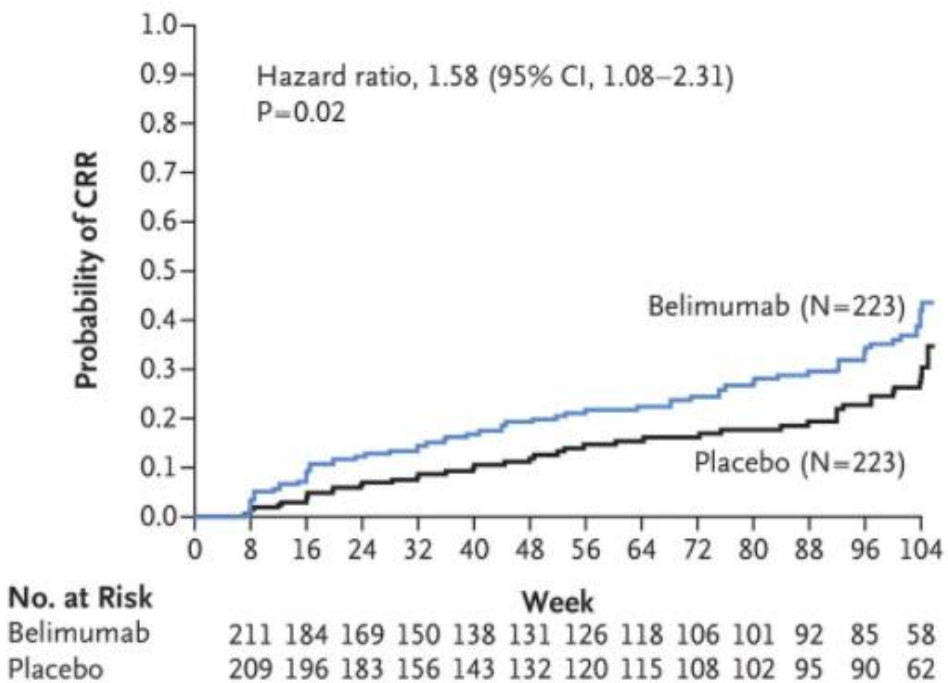
Renal event or Death



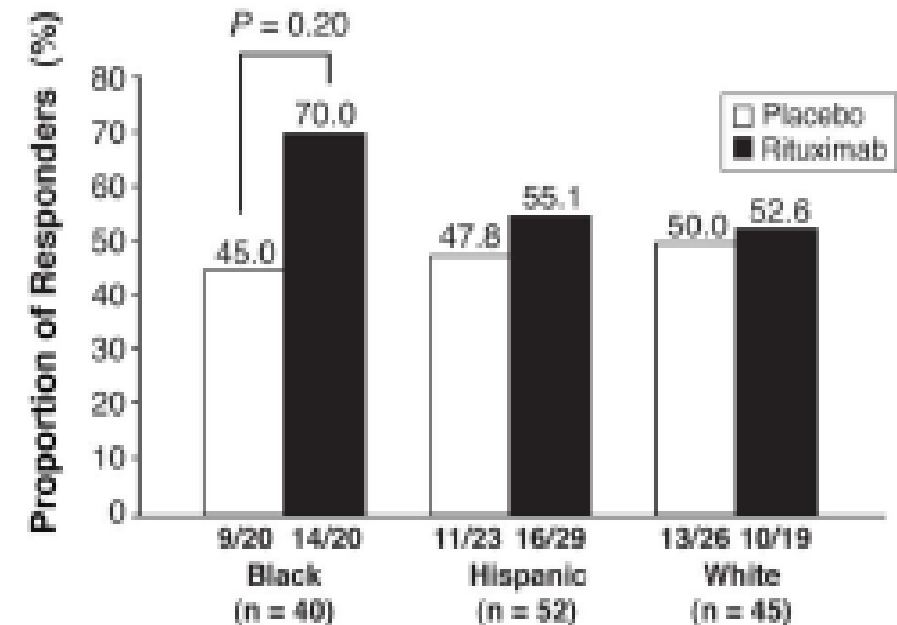
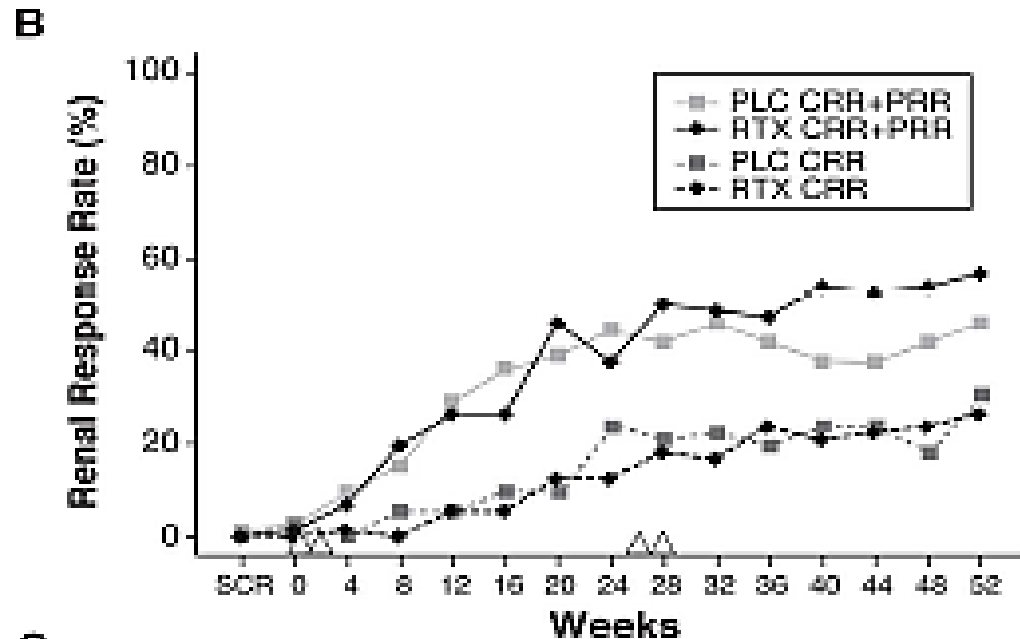
B

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

Complete Remission



Rituximab in lupus nephritis – LUNAR III



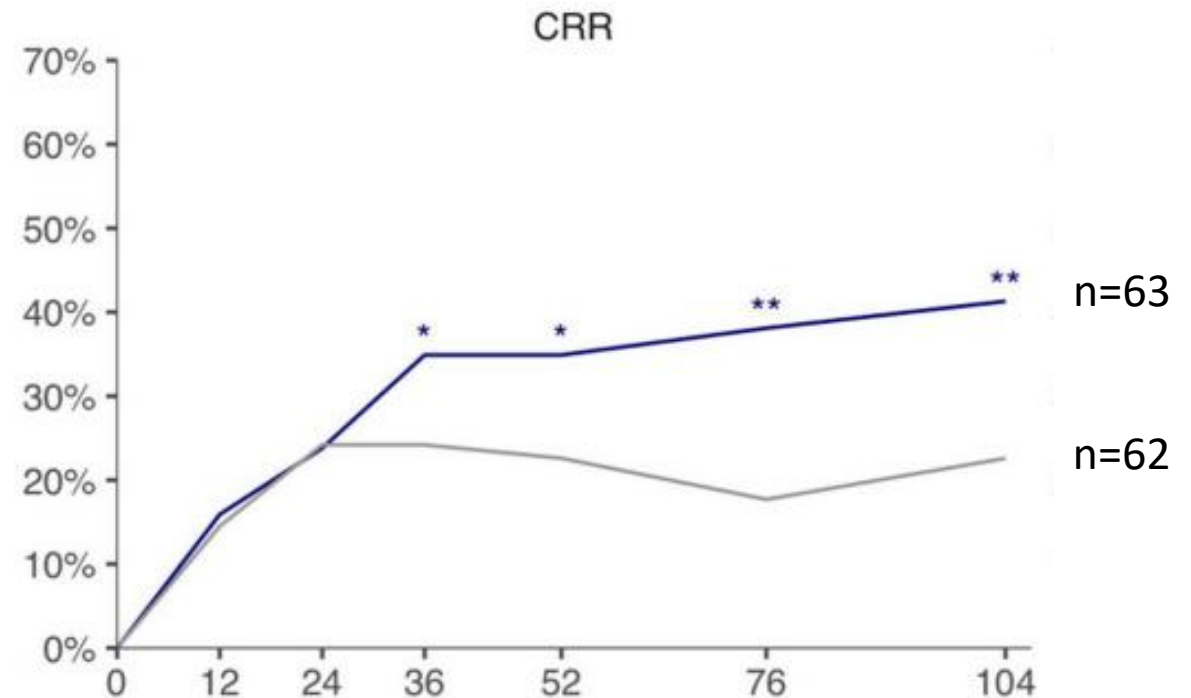
Obinutuzumab added to SOC increased CRR at 104 weeks in a phase 3 RCT of patients with lupus nephritis

Table 1 Baseline characteristics and demographics

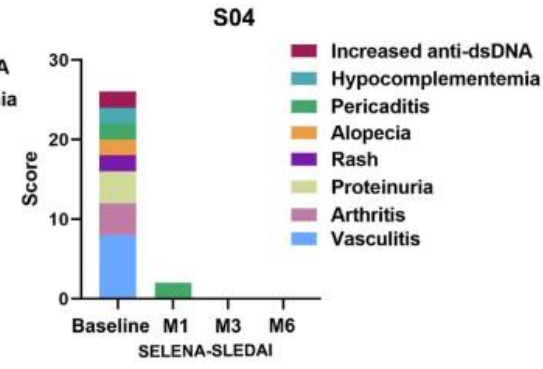
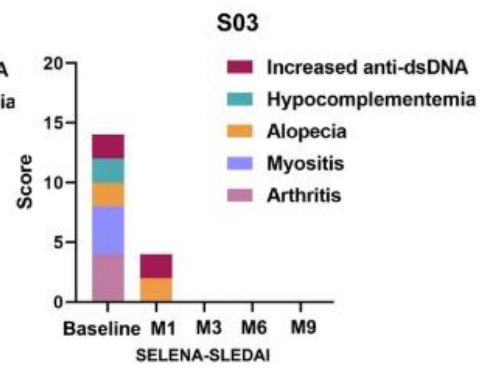
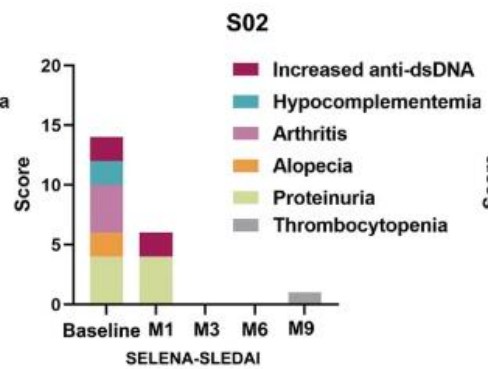
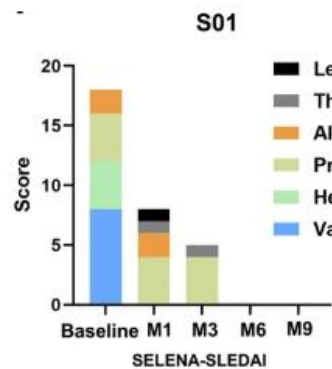
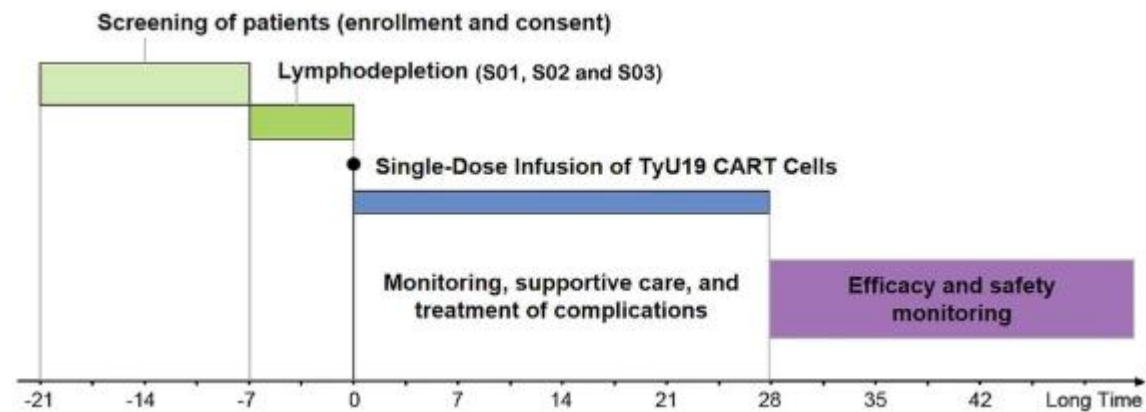
	Obinutuzumab (n=63)	Placebo (n=62)
Age—years	33.1±9.8	31.9±10.1
Female—no (%)	55 (87)	51 (82)
Region—no (%)		
Latin America and the Caribbean	38 (60)	47 (76)
Europe and Israel	18 (29)	7 (11)
USA	7 (11)	8 (13)
Hispanic or Latino ethnicity—no (%)	42 (67)	49 (79)
Race—no (%)		
White	28 (44)	26 (42)
American Indian or Alaska Native	11 (18)	17 (27)
Black or African American	6 (10)	5 (8)
Asian	3 (5)	2 (3)
Other or unknown	15 (24)	12 (20)
Prior history of lupus nephritis—no (%)	32 (51)	32 (52)
Class IV lupus nephritis—no (%)	40 (64)	35 (57)
Concomitant class V lupus nephritis—no (%)	20 (32)	17 (27)
Serum creatinine—mg/dL	0.87±0.34	0.80±0.33
eGFR—mL/min/1.73 m ²	102.0±30.6	102.1±32.9
UPCR—g/g	3.3±2.7	2.9±2.5
Anti-dsDNA Ab >30 IU/mL—no (%)	42 (67)	46 (74)
C3 <90 mg/dL—no (%)	43 (68)	37 (60)
C4 <16 mg/dL—no (%)	37 (59)	44 (71)

eGFR was calculated using the CKD-EPI creatinine equation.

Ab, antibody; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; ULN, upper limit of normal; UPCR, urine protein-to-creatinine ratio.



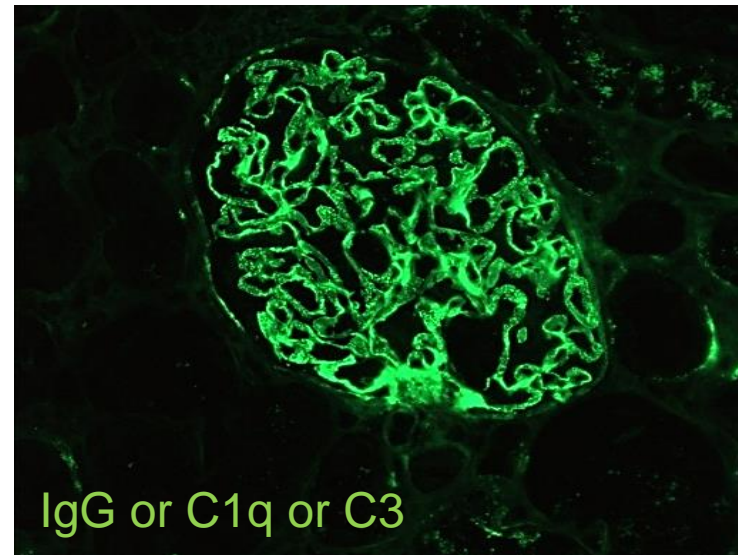
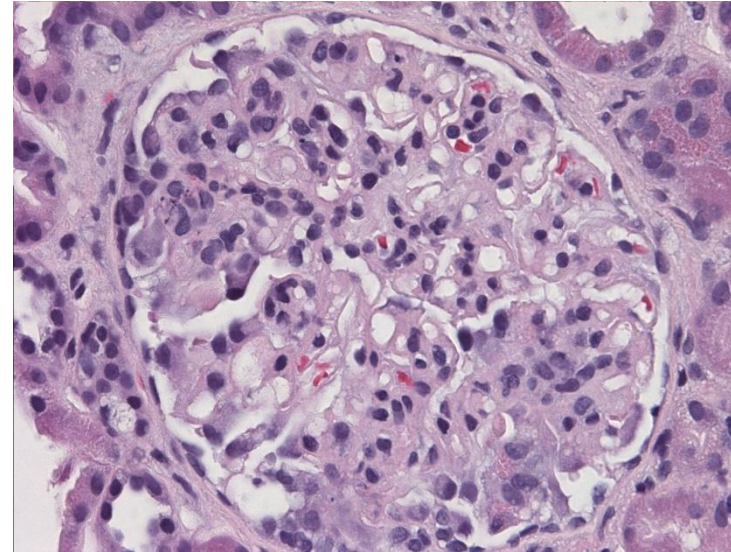
Allogeneic anti-CD19 CAR-T cells induce remission in refractory lupus



Q2. A 24 year-old woman presents with nephrotic range proteinuria and an active urinary sediment. She complains of photosensitivity, hair loss and arthritis

Which of the following are likely targets that may ameliorate disease

- 1) ~~The TNF pathways~~
- 2) Type 1 interferon pathways
- 3) ~~C2~~
- 4) B cell activation factor (BAFF)
- 5) CD20+ B cells – Obinutuzumab/CAR-T cell



TAKE HOME MESSAGES

Introducing the immune system

- Innate immunity
- Adaptive immune cells

A few new things to be aware of

- MALT and GALT
- BAFF and APRIL as important B cell maturation regulators
- T cell subtypes
 - effector T cells (Th1, Th2 and Th17) vs regulatory T cells

A few cases with possible therapeutic implications

- The role of C5a and the C5aR in AAV
- Targeting specific cell types and cytokine pathways in autoimmune kidney disease like IgA nephropathy and lupus nephritis



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