What’s New in SLE?

ΕΠΕΜΥ, Ηράκλειο, Σεπτέμβριος 2023

Σταμάτης - Νίκος Λιόσης
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Πανεπιστήμιο Πατρών

Σύγκρουση Συμφερόντων

Καμμία

The dynamic epigenetic regulation of the inactive X chromosome in healthy human B cells is dysregulated in lupus patients

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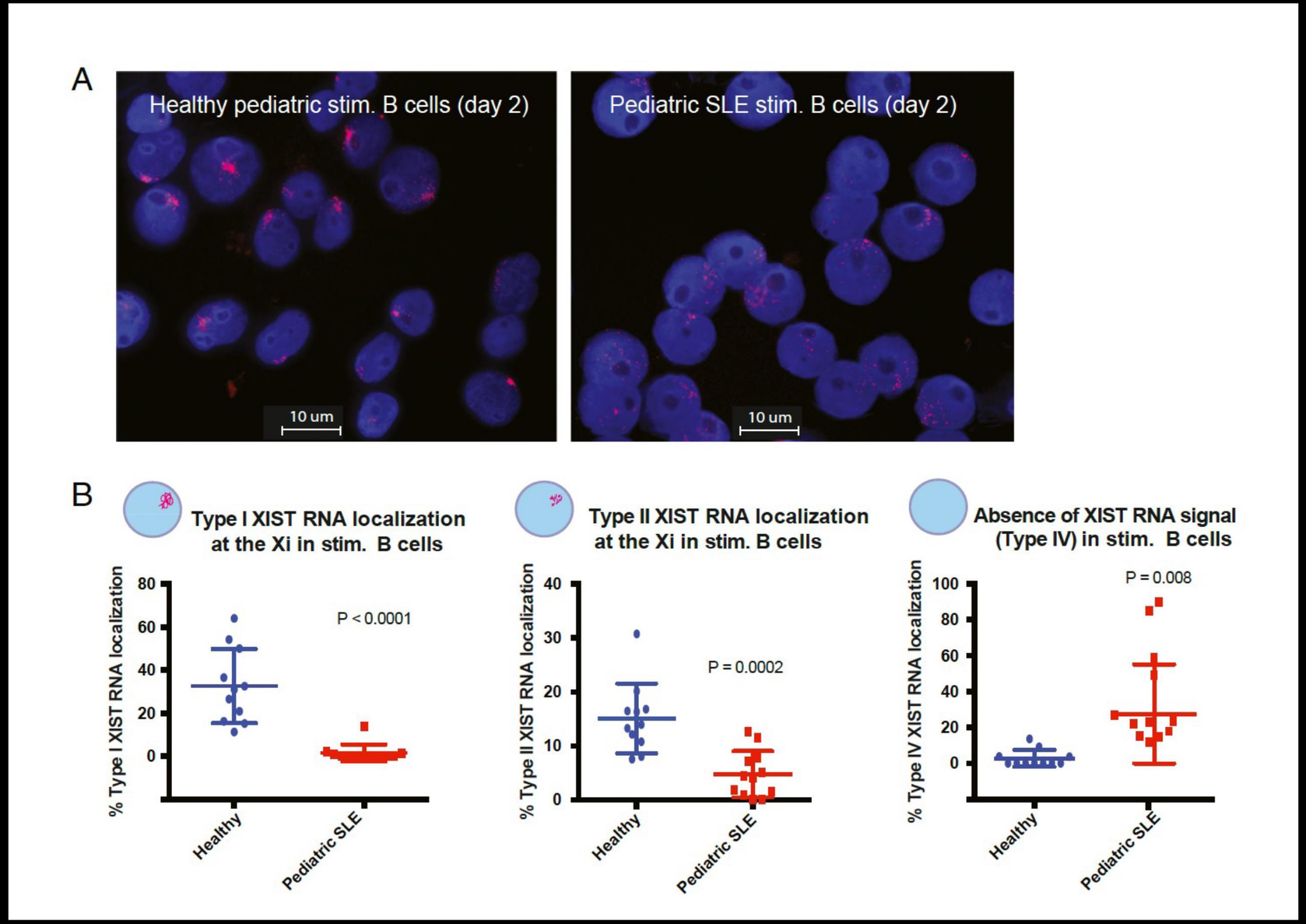
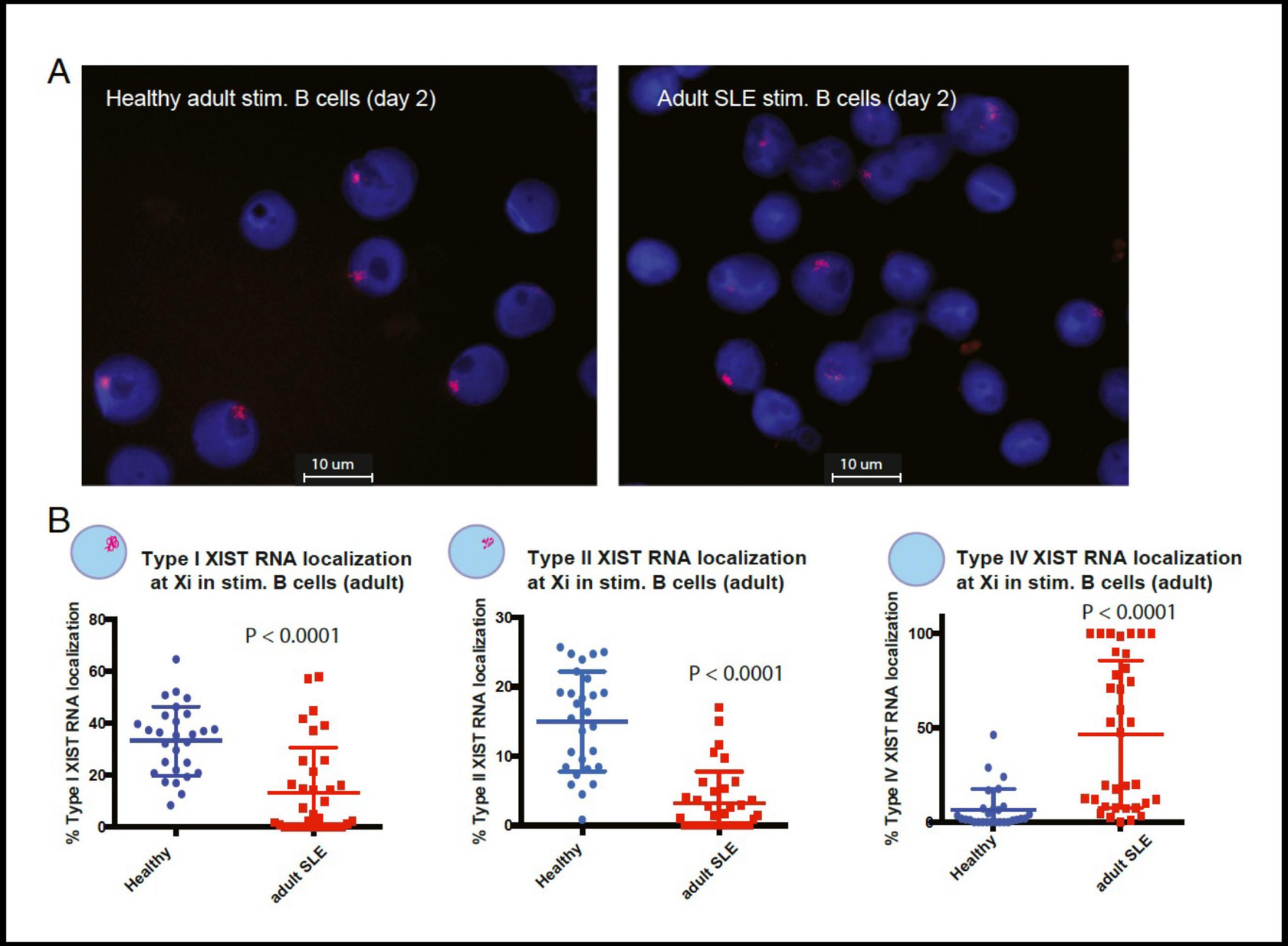
Abnormal X chromosome inactivation in lupus B cells

- Individuals with at least 2 X chromosomes are at increased risk for SLE.
- The well-known X chromosome inactivation in lymphocytes **is not static**.
- Several mechanisms apply to X chromosome genes suppression.
- 3% of murine and 15 - 25% of human X genes **escape inactivation.**

Deranged X inactivation in lupus B cell subsets



Deranged X inactivation in lupus B cell subsets



Deranged XCI in lupus B cell subsets

Normal B cells are “almost normal”

- B cells from paediatric lupus patients: Decreased or even **ABSENT** X-chromosome gene silencing.

- B cells from adult lupus patients: Decreased X-chromosome gene silencing that is **INDEPENDENT** of disease activity.

- **Decreased adult B cell XCI is therefore inherent to the disease.**

TLR7 gain-of-function genetic variation causes human lupus

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TLR7 mutation

7yr old girl
Aggressive SLE

De novo Mutation

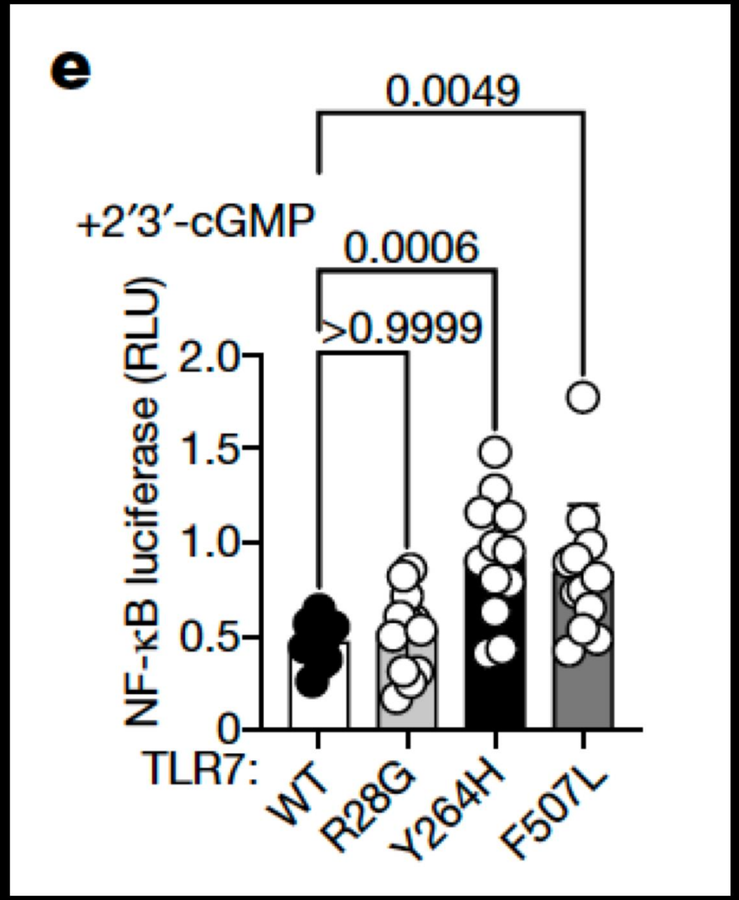
Refractory immune thrombocytopenia
Inflammatory arthritis
CNS involvement (chorea)
Constitutional
Renal involvement
ANA & Low C

A novel TLR7 mutation

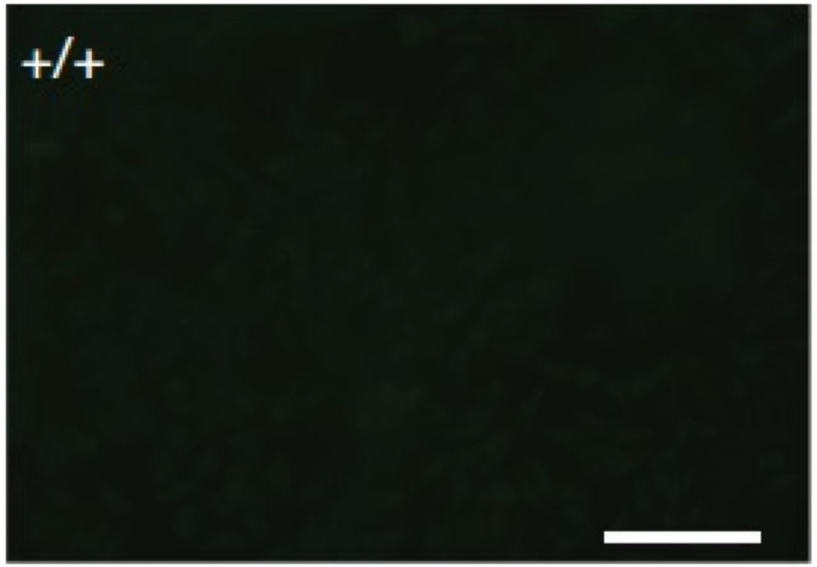
Occurred *de novo*

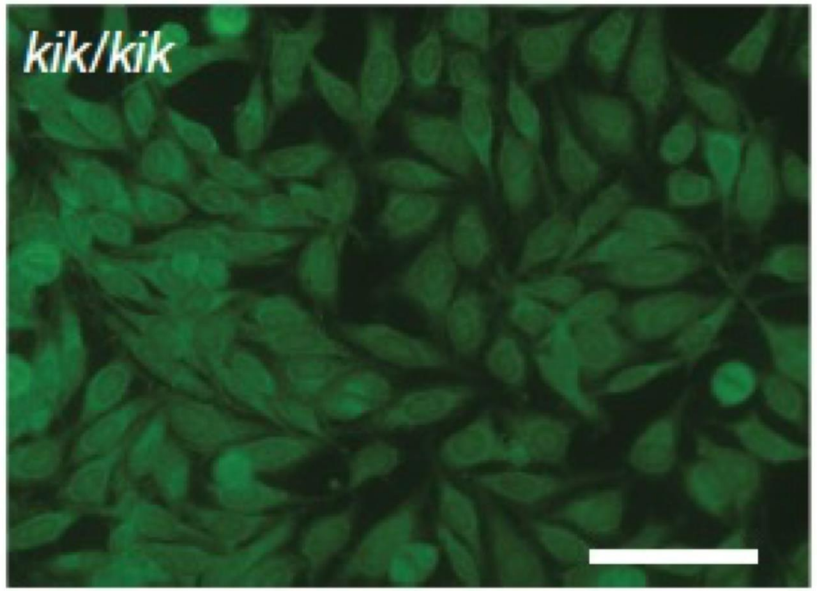
- TLR7 is a sensor of viral RNA
- Binds to guanosine

- **This was a Gain-of-Function mutation**
- Enhanced binding to Guanosine and to 2,3-cGMP

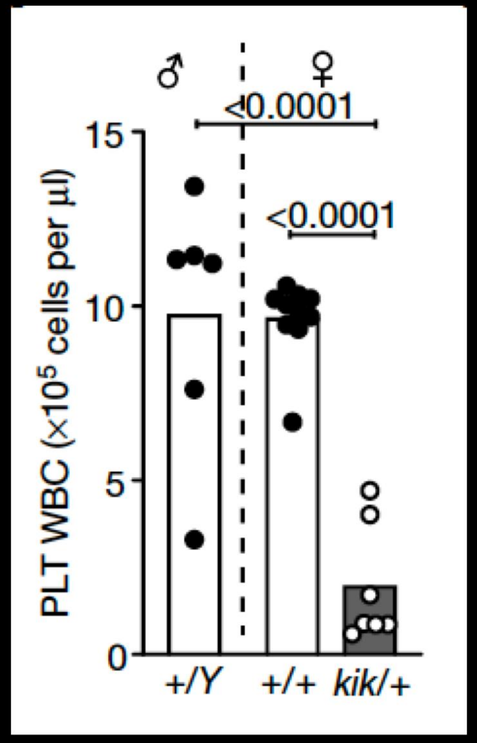


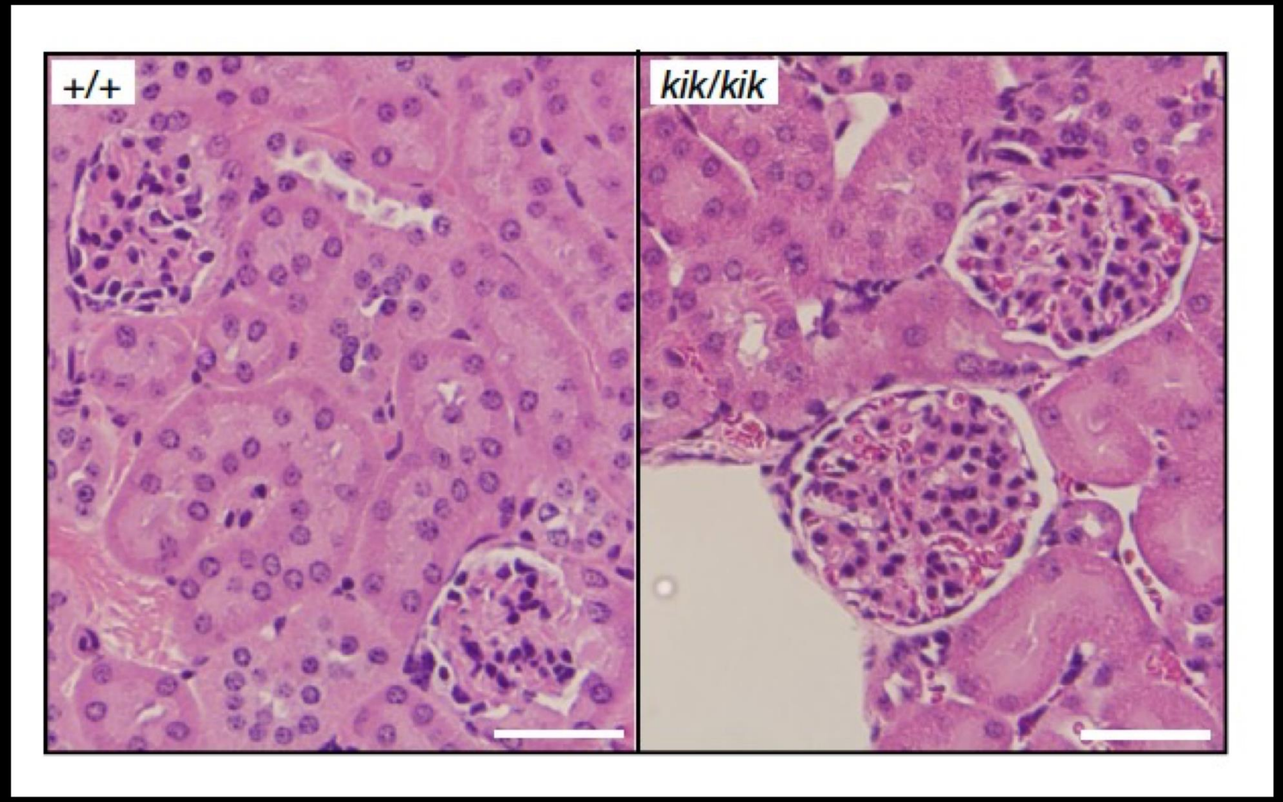
TLR7^{Y264H} CAUSES AUTOIMMUNITY IN MICE



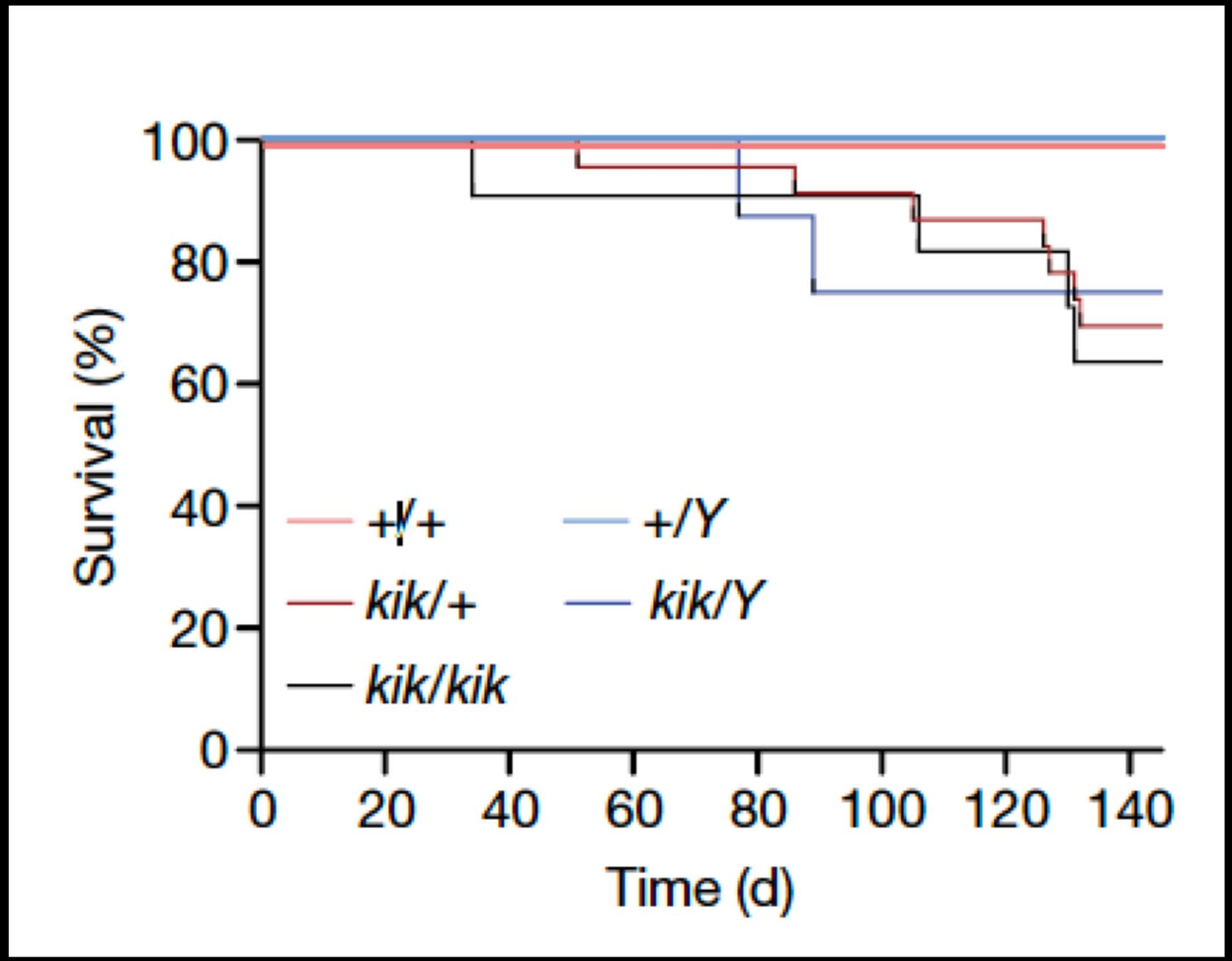


TLR7^{Y264H} CAUSES AUTOIMMUNITY IN MICE

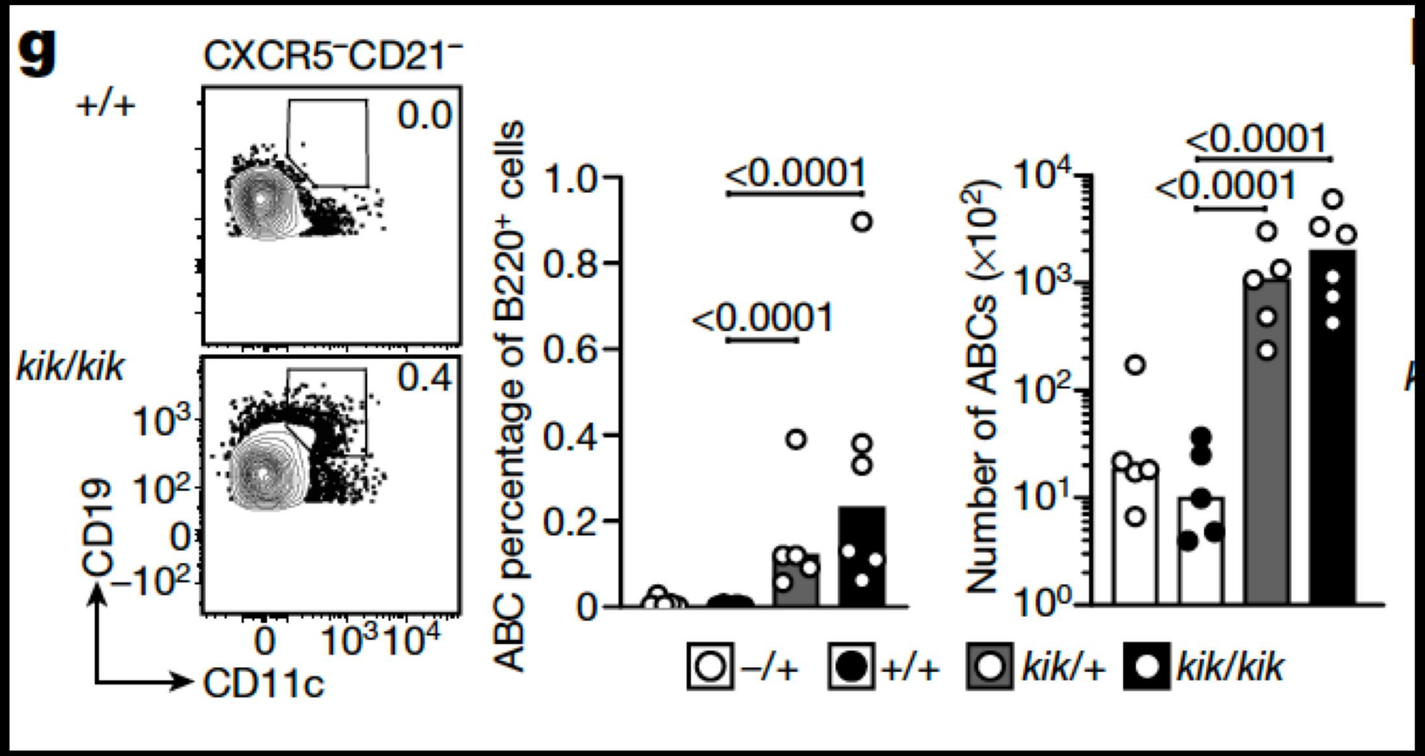




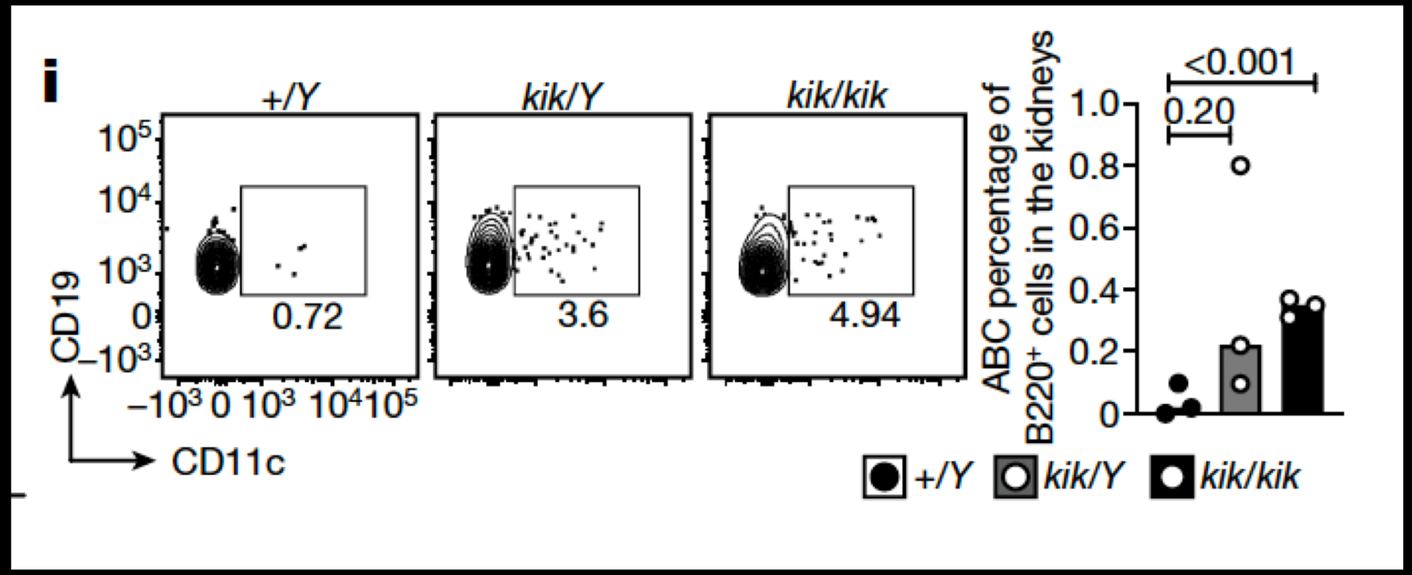
TLR7^{Y264H} CAUSES A LETHAL AUTOIMMUNE DISEASE IN MICE



TLR7^{Y264H} CAUSES B CELL-INTRINSIC DEFECTS



TLR7^{Y264H} CAUSES B CELL-INTRINSIC TISSUE-DAMAGING (RENAL) DEFECTS



BCR-initiated signalling is abnormally increased in SLE

B Cells from Patients with Systemic Lupus Erythematosus Display Abnormal Antigen Receptor–mediated Early Signal Transduction Events

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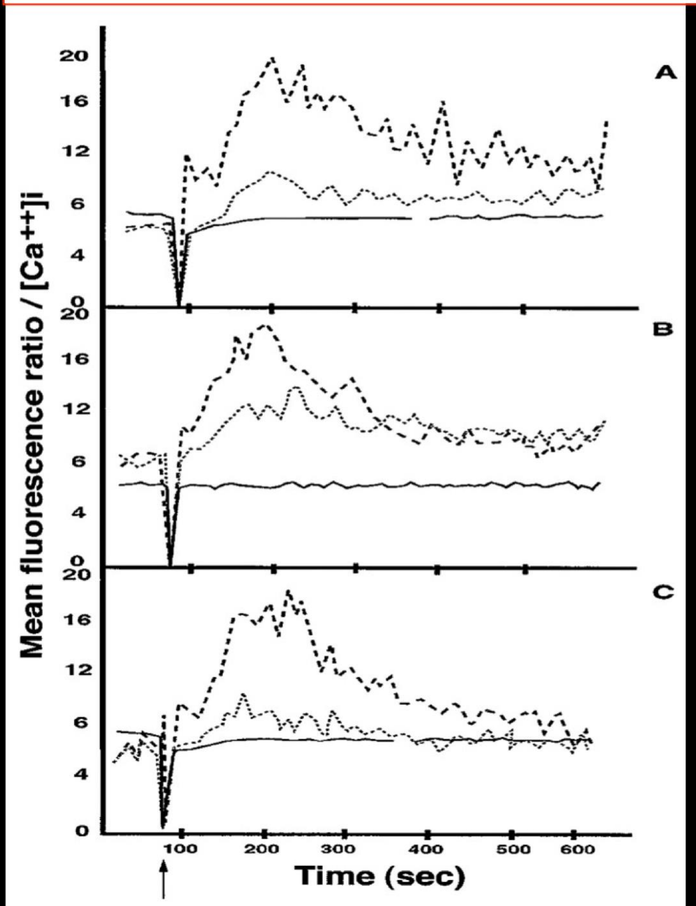

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ΚΛΙΝΙΚΕΣ ΜΕΛΕΤΕΣ

Phase II randomised trial of type I interferon inhibitor anifrolumab in patients with active lupus nephritis

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Jayne D, *et al*. *Ann Rheum Dis* 2022;**81**:496–506.

Table 1 Patient demographics and disease characteristics

		Anifrolumab combined (n=96)	Anifrolumab BR (n=45)	Anifrolumab IR (n=51)	Placebo (n=49)
Patient demographics					
Age, years	Median (range)	34.5 (18, 67)	34.0 (19, 67)	35.0 (18, 65)	32.0 (18, 58)
Sex	Female, n (%)	82 (85.4)	37 (82.2)	45 (88.2)	38 (77.6)
Weight	Mean (SD), kg	65.4 (15.0)	62.7 (12.3)	67.7 (16.8)	65.6 (13.3)
BMI	Mean (SD)	25.1 (5.06)	24.0 (3.77)	26.0 (5.85)	24.5 (3.93)
	>28 kg/m^2, n (%)	23 (24.0)	7 (15.6)	16 (31.4)	9 (18.4)
Race, n (%)	White	42 (43.8)	17 (37.8)	25 (49.0)	24 (49.0)
	Black/African American	6 (6.3)	2 (4.4)	4 (7.8)	1 (2.0)
	Asian	18 (18.8)	11 (24.4)	7 (13.7)	10 (20.4)
	Native Hawaiian/ Pacific Islander	1 (1.0)	1 (2.2)	0	0
	American Indian/ Alaska Native	4 (4.2)	3 (6.7)	1 (2.0)	0
	Other	25 (26.0)	11 (24.4)	14 (27.5)	14 (28.6)
Hispanic or Latino ethnicity, n (%)		45 (46.9)	22 (48.9)	23 (45.1)	20 (40.8)
Geographic region, n (%)	Asia Pacific	18 (18.8)	10 (22.2)	8 (15.7)	9 (18.4)
	Europe	26 (27.1)	10 (22.2)	16 (31.4)	15 (30.6)
	Latin America	34 (35.4)	14 (31.1)	20 (39.2)	16 (32.7)
	North America	18 (18.8)	11 (24.4)	7 (13.7)	9 (18.4)
Baseline disease characteristics					
Time from initial LN diagnosis to randomisation, mean (range), months		6.8 (0.4, 306.9)	3.4 (1.1, 212.7)	15.7 (0.4, 306.9)	37.0 (0.7, 328.3)
Renal biopsy result at screening, n (%)	Class III	17 (17.7)	7 (15.6)	10 (19.6)	6 (12.2)
	Class III+V	11 (11.5)	7 (15.6)	4 (7.8)	5 (10.2)
	Class IV	53 (55.2)	26 (57.8)	27 (52.9)	30 (61.2)
	Class IV+V	15 (15.6)	5 (11.1)	10 (19.6)	8 (16.3)
24-hour UPCR, mg/mg	Mean (SD)	3.10 (2.18)	3.36 (2.50)	2.86 (1.85)	3.71 (3.20)
	>3.0, n (%)	36 (37.5)	19 (42.2)	17 (33.3)	23 (46.9)
eGFR* mL/min/1.73 m^2	Mean (SD)	97.1 (44.77)	100.2 (46.77)	94.4 (43.22)	87.3 (35.43)
	≥60, n (%)	73 (76.0)	35 (77.8)	38 (74.5)	39 (79.6)
SLEDAI-2K† score	Mean (SD)	10.7 (4.83)	10.4 (4.63)	11.0 (5.04)	11.3 (4.38)
	≥10, n (%)	51 (53.1)	23 (51.1)	28 (54.9)	29 (59.2)
Non-renal SLEDAI-2K† score	Mean (SD)	4.7 (3.12)	5.2 (3.44)	4.2 (2.74)	4.7 (2.30)
IFNGS status	High, n (%)	91 (94.8)	44 (97.8)	47 (92.2)	46 (93.9)
Serology, n (%)	ANA positive‡	90 (93.8)	44 (97.8)	46 (90.2)	49 (100)
	Anti-dsDNA positive§	76 (79.2)	37 (82.2)	39 (76.5)	39 (79.6)
	Low C3¶	57 (59.4)	30 (66.7)	27 (52.9)	42 (85.7)
	Low C4¶	24 (25.0)	10 (22.2)	14 (27.5)	20 (40.8)
Baseline treatments					
Oral glucocorticoids**	Yes, n (%)	94 (97.9)	43 (95.6)	51 (100)	48 (98.0)
	Dosage, mean (SD), mg/day	22.6 (10.63)	21.9 (10.4)	23.2 (10.88)	21.9 (11.20)
	≥20 mg/day, n (%)	67 (69.8)	31 (68.9)	36 (70.6)	33 (67.3)
MMF before randomisation	Yes, n (%)	72 (75.0)	36 (80.0)	36 (70.6)	33 (67.3)
	Dosage, mean (SD), g/day	1.81 (0.502)	1.82 (0.551)	1.79 (0.460)	1.77 (0.469)
Concomitant ACEI/ARB treatment, n (%)		63 (65.6)	27 (60.0)	36 (70.6)	33 (67.3)
Antimalarials, n (%)		57 (59.4)	31 (68.9)	26 (51.0)	35 (71.4)

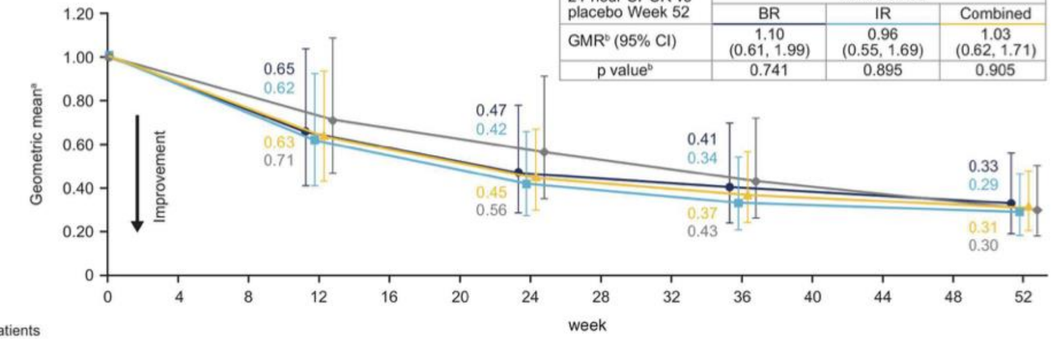
Primary endpoint

- **<u>Ελάττωση της λευκωματουρίας</u>** (24 h UPCR) στο anifrolumab group [συνήθης δόση (n = 45) / ενισχυμένη δόση (n = 51)] συγκριτικά με το placebo group (n = 49) μετά απο 1 έτος.

- Η λευκωματουρία βελτιώθηκε σε:
  - **69% στο anifrolumab group**
  - **70% στο placebo group**

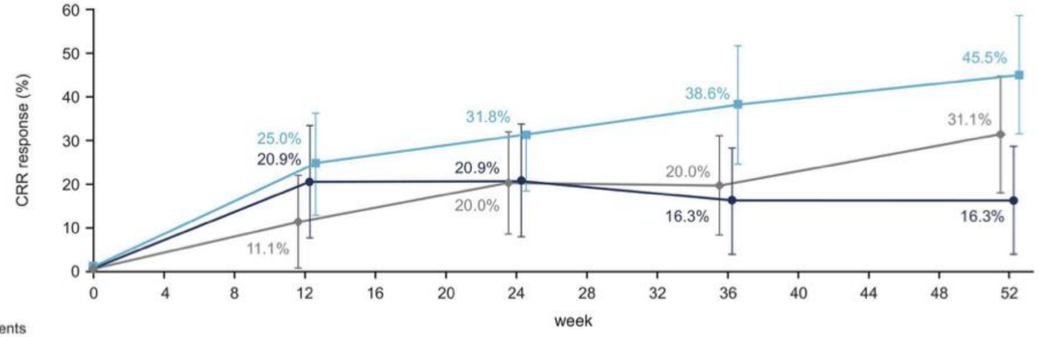
A GM change from baseline in 24-hour UPCR over time

24-hour UPCR vs placebo Week 52	Anifrolumab		
	BR	IR	Combined
GMR[b] (95% CI)	1.10 (0.61, 1.99)	0.96 (0.55, 1.69)	1.03 (0.62, 1.71)
p value[b]	0.741	0.895	0.905



Number of patients					
Anifrolumab BR	45	35	35	30	29
Anifrolumab IR	51	43	45	32	37
Anifrolumab combined	96	78	80	62	66
Placebo	49	36	32	28	25

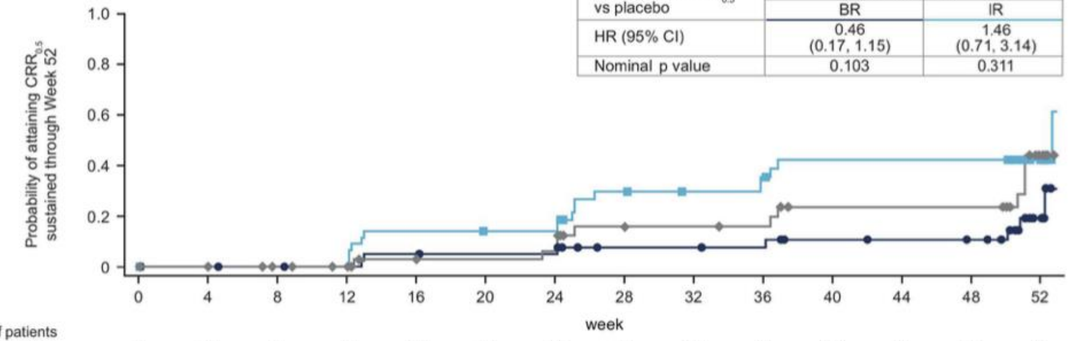
B Percentage of patients with a CRR over time[c]



Number of patients					
Anifrolumab BR	43	43	43	43	43
Anifrolumab IR	44	44	44	44	44
Placebo	45	45	45	45	45

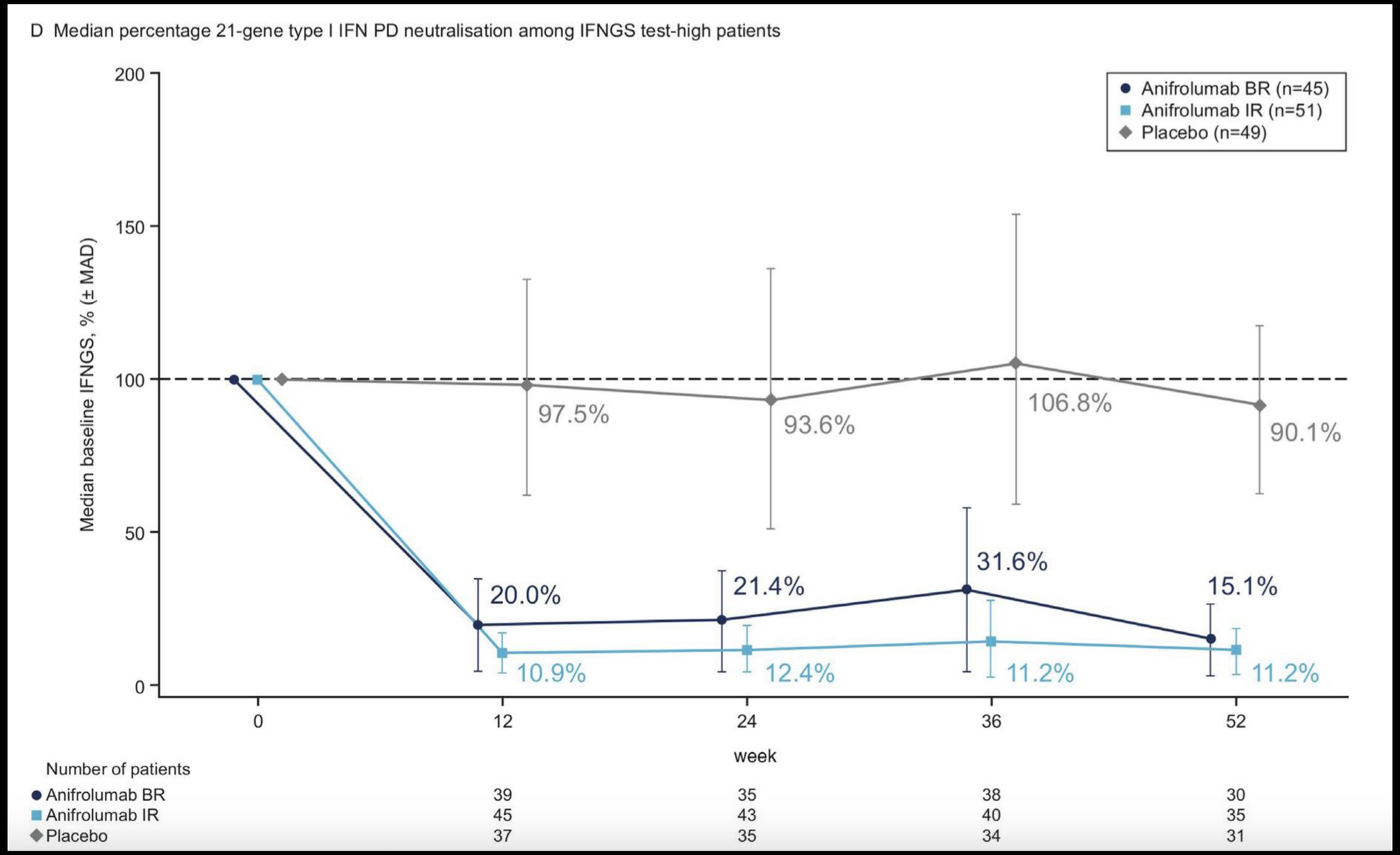
C Time to $CRR_{0.5}$ sustained through week 52[c,d]

Difference in $CRR_{0.5}$ vs placebo	Anifrolumab	
	BR	IR
HR (95% CI)	0.46 (0.17, 1.15)	1.46 (0.71, 3.14)
Nominal p value	0.103	0.311



Number of patients														
Anifrolumab BR	43	42	41	40	38	37	37	31	31	30	27	26	25	11
Anifrolumab IR	44	43	43	43	37	36	36	26	24	22	19	19	19	11
Placebo	45	42	39	37	32	31	30	24	23	22	18	18	18	7

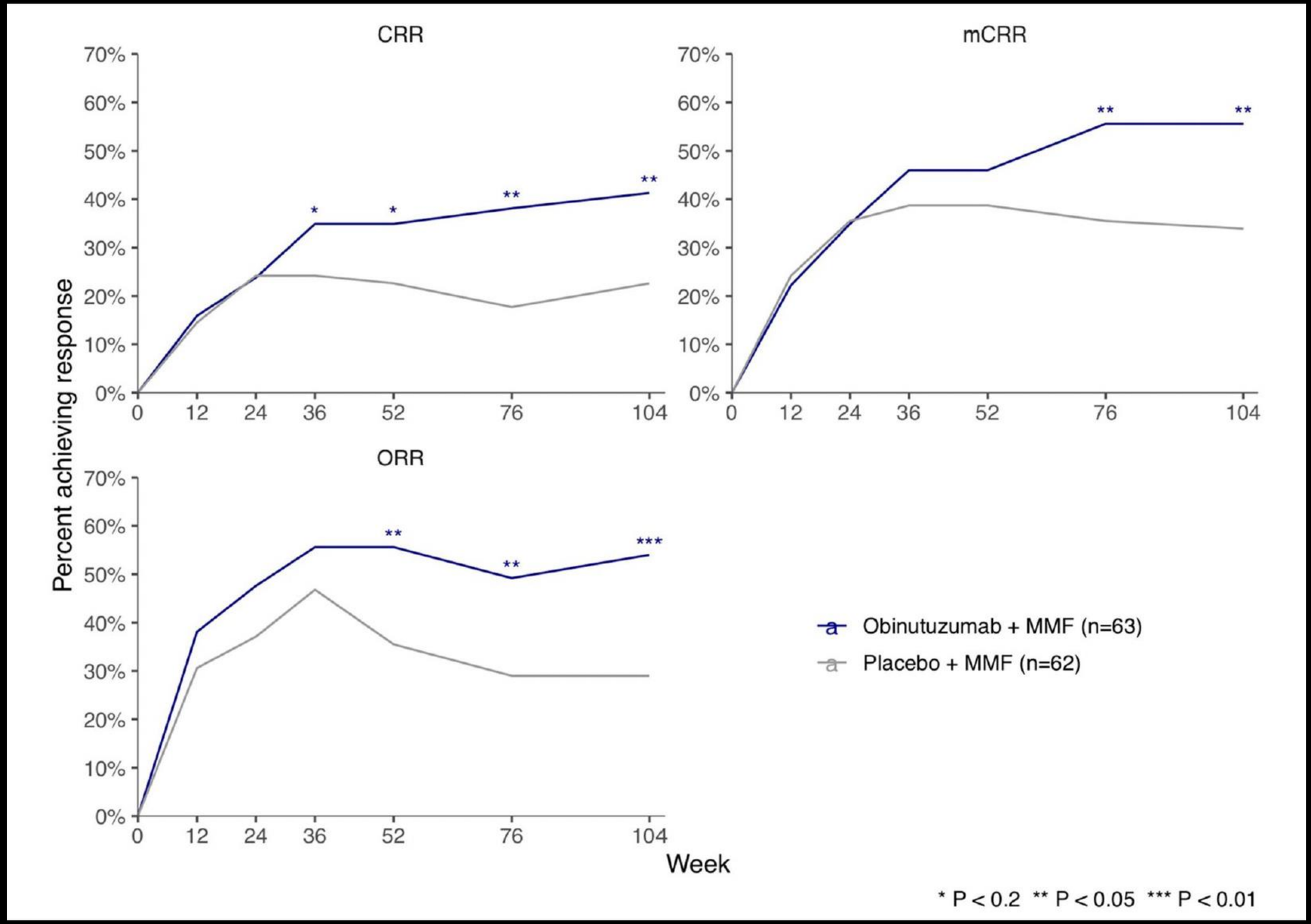
…. IFN signature



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

Richard A Furie,[1] Gustavo Aroca,[2] Matthew D Cascino,[3] Jay P Garg,[3] Brad H Rovin,[4] Analia Alvarez,[5] Hilda Fragoso-Loyo,[6] Elizabeth Zuta-Santillan,[7] Thomas Schindler,[8] Paul Brunetta,[3] Cary M Looney,[3] Imran Hassan,[9] Ana Malvar[10]

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



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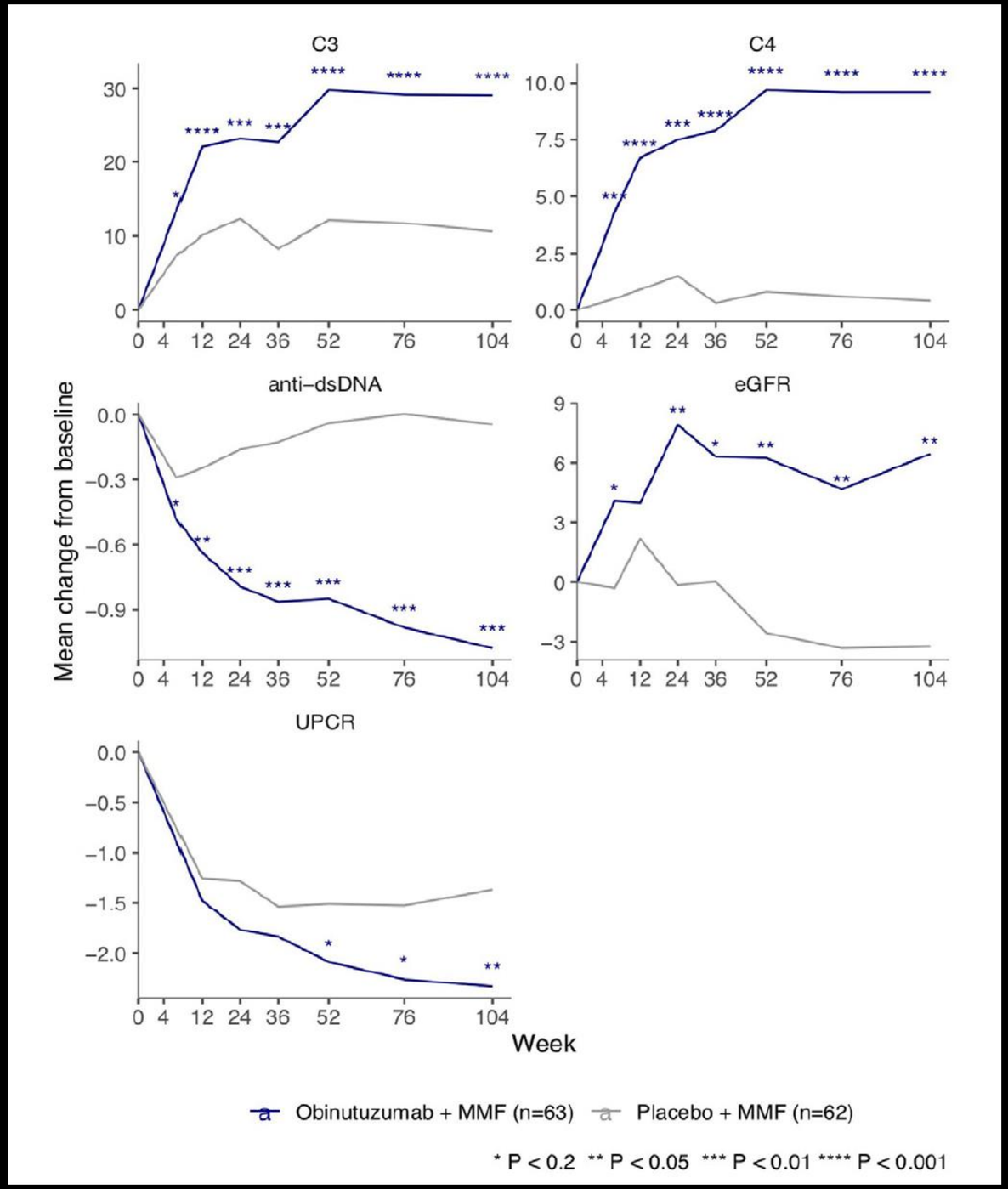


Furie RA, *et al*. *Ann Rheum Dis* 2022;**81**:100–107. doi:10.1136/annrheumdis-2021-220920

Table 2 Primary and secondary endpoints at weeks 52 and 104

	Week 52				Week 104*			
	Obinutuzumab (n=63)	Placebo (n=62)	Difference (95% CI)	P value	Obinutuzumab (n=63)	Placebo (n=62)	Difference (95% CI)	P value
Primary endpoint								
CRR, n (%)	22 (35)	14 (23)	12 (–3.4 to 28)	0.115	26 (41)	14 (23)	19 (2.7 to 35)	0.026
Secondary endpoints								
mCRR, n (%)	29 (46)	24 (39)	7 (–10 to 25)	0.373	35 (56)	21 (34)	22 (5 to 39)	0.015
ORR (CRR or PRR), n (%)	35 (56)	22 (36)	20 (3.0 to 37)	0.025	34 (54)	18 (29)	25 (8.2 to 42)	0.005
Change in C3 from baseline, mean† (SE)	30 (3.4)	12 (3.5)	18 (8.0 to 27)	<0.001	29 (3.4)	11 (3.4)	19 (8.9 to 28)	<0.001
Change in C4 from baseline, mean† (SE)	9.7 (1.3)	0.8 (1.3)	8.8 (5.2 to 12)	<0.001	9.6 (1.3)	0.4 (1.3)	9.3 (5.7 to 13)	<0.001
Change in log anti-dsDNA titre from baseline, mean† (SE)	–0.91 (0.12)	–0.10 (0.12)	–0.81 (–1.1 to 0.48)	<0.001	–1.1 (0.13)	–0.05 (0.13)	–1.0 (–1.4 to 0.67)	<0.001
Renal response components								
UPCR <0.5, n (%)	33 (52)	24 (39)	14 (–3.6 to 31)	0.102	39 (62)	23 (37)	25 (7.8 to 42)	0.005
SCr ≤15% increase from baseline and ≤ULN	48 (76)	38 (61)	15 (–1.2 to 31)	0.080	45 (71)	32 (52)	20 (3.1 to 37)	0.019
Urinary RBCs <10/HPF without RBC casts	52 (83)	51 (82)	0.3 (–13 to 13)	0.987	49 (78)	41 (66)	12 (–4.0 to 27)	0.154
No rescue immunosuppression or early discontinuation	57 (91)	53 (86)	5 (–6.4 to 16)	0.414	51 (81)	38 (61)	20 (4.1 to 35)	0.012
CRR in prespecified subgroups								
Baseline proteinuria, n (%)								
UPCR <3 (n=73)	13 (38)	12 (31)	7.5 (–14 to 29)	0.468	16 (47)	12 (31)	16 (–5.9 to 39)	0.147
UPCR ≥3 (n=47)	8 (31)	2 (10)	21 (–0.5 to 43)	0.163	8 (31)	2 (10)	21 (–0.5 to 43)	0.098
Baseline biopsy class, n (%)								
Class III (n=31)	5 (36)	6 (35)	0.4 (–33 to 34)	0.952	3 (21)	7 (41)	–19 (–52 to 12)	0.338
Class IV (n=94)	17 (35)	8 (18)	17 (–0.5 to 34)	0.068	23 (47)	7 (16)	31 (14 to 49)	0.001
Baseline biopsy class, n (%)								
No class V (n=88)	17 (40)	9 (20)	20 (0.8 to 38)	0.054	17 (40)	10 (22)	17 (–1.7 to 36)	0.117
Class V (n=37)	5 (25)	5 (29)	–4.4 (–33 to 24)	0.825	9 (45)	4 (24)	22 (–8.2 to 51)	0.187
Post hoc endpoints								
UPCR <0.8, n (%)	41 (65)	31 (50)	15 (-2.1 to 32)	0.085	45 (71)	28 (45)	26 (9.6 to 43)	0.003

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

Table 3 Safety summary through week 104

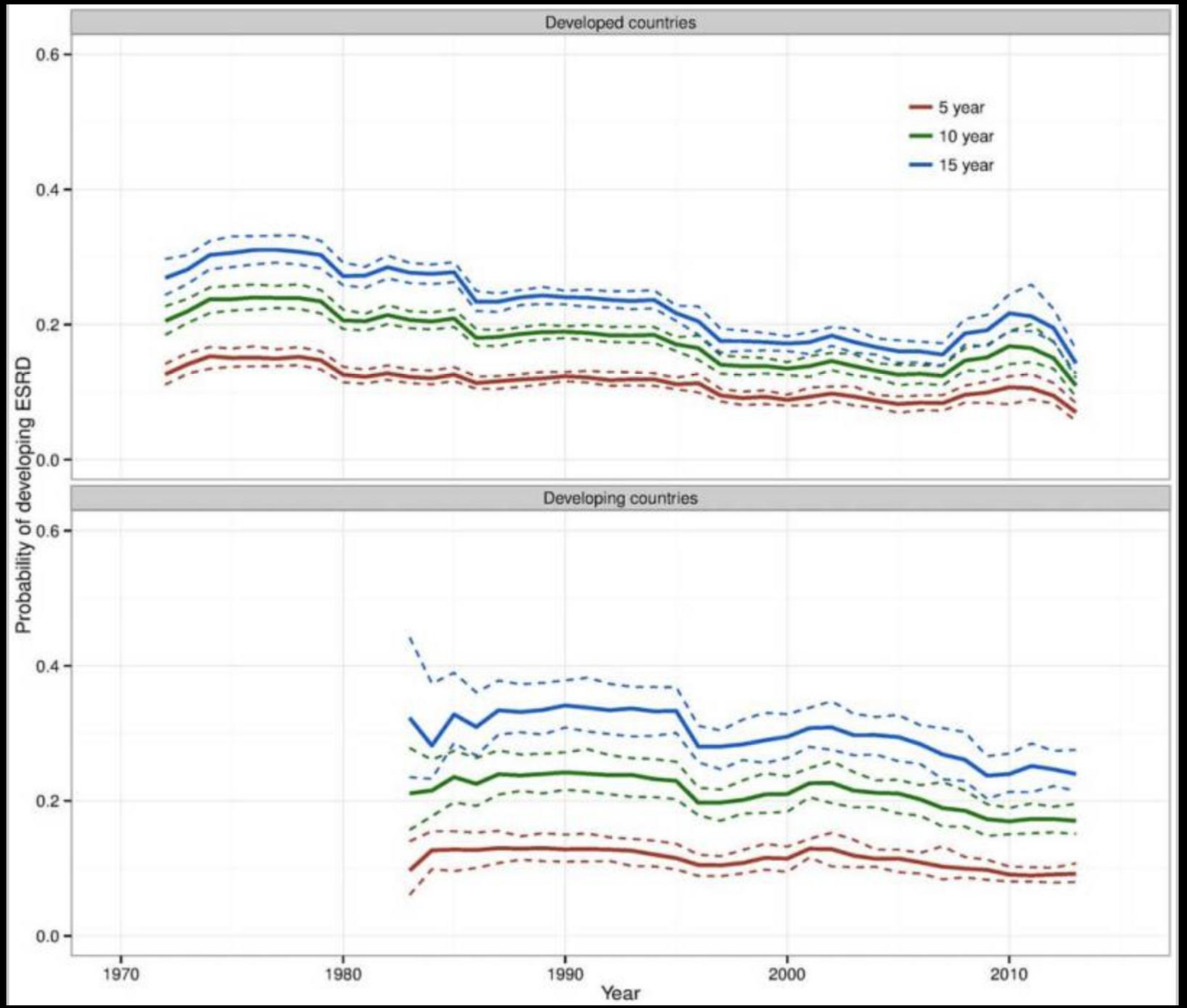
	Obinutuzumab n=64	Placebo n=61
Any adverse event	58 (91)	54 (89)
Deaths	1 (2)	4 (7)
Serious adverse events	16 (25)	18 (30)
Serious infection adverse events	5 (8)	11 (18)
Infection adverse event	48 (75)	38 (62)
Most common adverse events*		
Urinary tract infection	15 (23)	13 (21)
Bronchitis	12 (19)	5 (8)
Herpes zoster	9 (15)	6 (10)
Abdominal pain	7 (11)	3 (5)
Infusion-related reaction	7 (11)	6 (10)
Nausea	6 (9)	3 (5)
Upper respiratory tract infection	6 (9)	5 (8)
Hypertension	6 (9)	3 (5)
Anaemia	5 (8)	4 (7)
Nasopharyngitis	5 (8)	6 (10)
Pharyngitis	5 (8)	4 (7)
Arthralgia	5 (8)	4 (7)
Headache	5 (8)	4 (7)
Conjunctivitis	4 (6)	2 (3)
Influenza	4 (6)	2 (3)
Neutropaenia	3 (5)	3 (5)
Diarrhoea	3 (5)	5 (8)
Peripheral oedema	3 (5)	3 (5)
Gastroenteritis	3 (5)	6 (10)
Sinusitis	3 (5)	0
Insomnia	3 (5)	4 (7)
Frequent urination	3 (5)	0
Cough	3 (5)	1 (2)
Infusion-related reaction†	10 (16)	6 (10)
Serious infusion related reaction	0	0
Progressive multifocal leukoencephalopathy	0	1 (2)

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

Πόσο καλά τα καταφέρνουμε

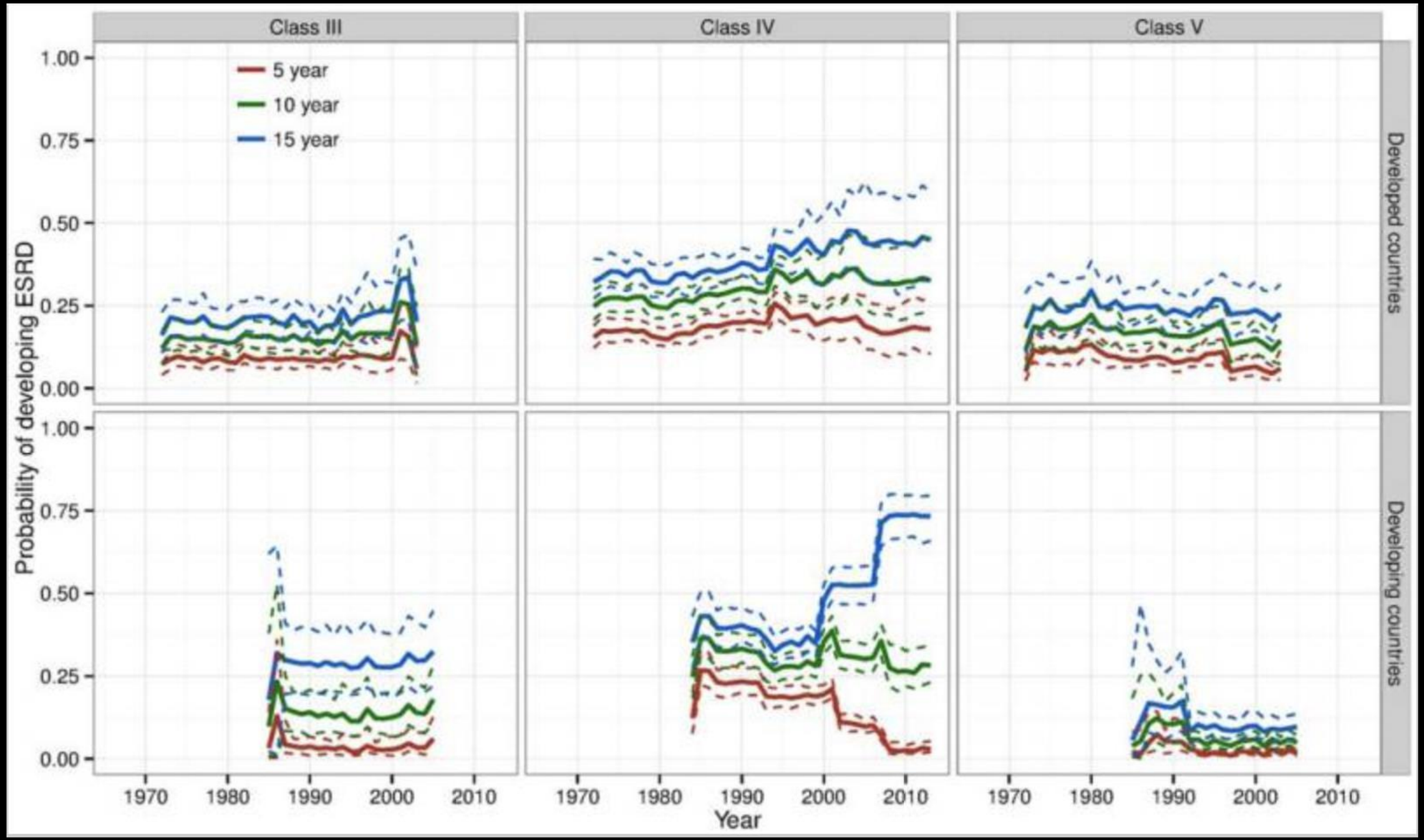
- **20% των ασθενών με Νεφρίτιδα του Λύκου θα αναπτύξουν ΧΝΝ τελικού σταδίου μετά από 15 χρόνια.**

- **Αυτό το ποσοστό ΔΕΝ έχει αλλάξει τα τελευταία χρόνια** (παρά την εισαγωγή ισχυρών ανοσοκατασταλτικών παραγόντων)



Κίνδυνος για ΧΝΝ Τελικού Σταδίου σε ασθενείς με LN

Tektonidou MG et al. A&R 2016; 68:1432.

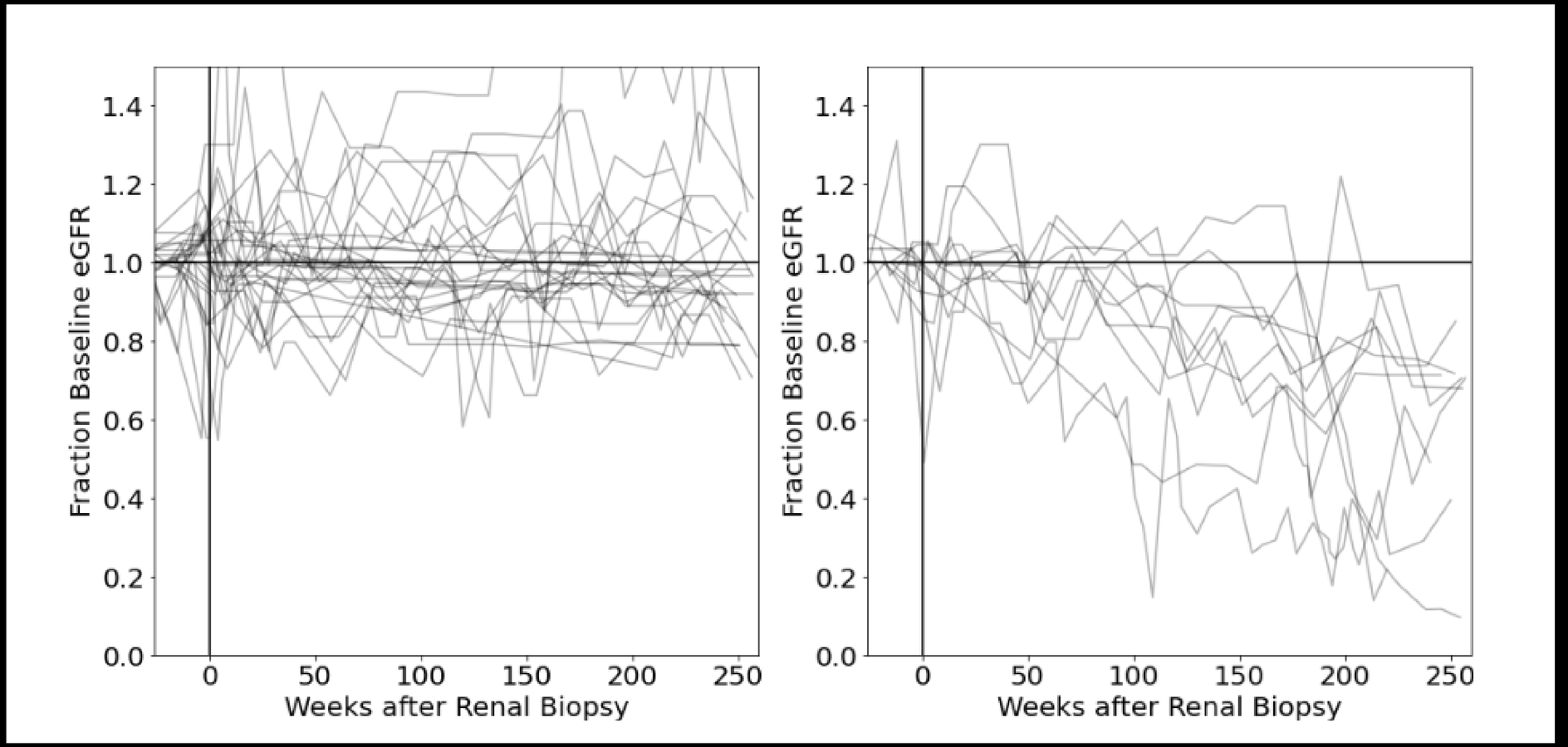

Class III
Class IV
Class V
5 year
10 year
15 year
Developed countries
Developing countries
Probability of developing ESRD
1.00
0.75
0.50
0.25
0.00
1970
1980
1990
2000
2010
Year

One-third of patients with lupus nephritis classified as complete responders continue to accrue progressive renal damage despite resolution of proteinuria

Emma Weeding [1], Andrea Fava [1], Laurence Magder,[2] Daniel Goldman,[1] Michelle Petri [1]

Weeding E, *et al. Lupus Science & Medicine* 2022;**9**:e000684.

Οι ασθενείς που ανταποκρίνονται στο SoC χωρίζονται σε 2 ομάδες….



Οι ασθενείς που ανταποκρίνονται στο SoC χωρίζονται σε 2 ομάδες….

Lupus nephritis

Table 4 Response status (based on proteinuria <500 mg/g) at 1 year per eGFR trajectory group

	eGFR trajectory group		
Response status at 1 year	**Stable**	**Decline**	
Responder	12	6	33% with eGFR decline
Non-responder	12	5	29% with eGFR decline
	50% classified as responders	55% classified as responders	

Αλλά και εκείνοι που δεν ανταποκρίνονται στο SoC επίσης χωρίζονται σε 2 (ίδιες) ομάδες….

Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus

Andreas Mackensen[1,2,8], Fabian Müller[1,2,8], Dimitrios Mougiakakos[1,2,3,8], Sebastian Böltz[2,4], Artur Wilhelm[2,4], Michael Aigner[1,2], Simon Völkl[1,2], David Simon[2,4], Arnd Kleyer[2,4], Luis Munoz[2,4], Sascha Kretschmann[1,2], Soraya Kharboutli[1,2], Regina Gary[1,2], Hannah Reimann[1,2], Wolf Rösler[1,2], Stefan Uderhardt[2,4], Holger Bang[5], Martin Herrmann[2,4], Arif Bülent Ekici[6], Christian Buettner[6], Katharina Marie Habenicht[7], Thomas H. Winkler[7], Gerhard Krönke[2,4,8] and Georg Schett[2,4,8] ✉

NATURE MEDICINE | VOL 28 | OCTOBER 2022 | 2124–2132

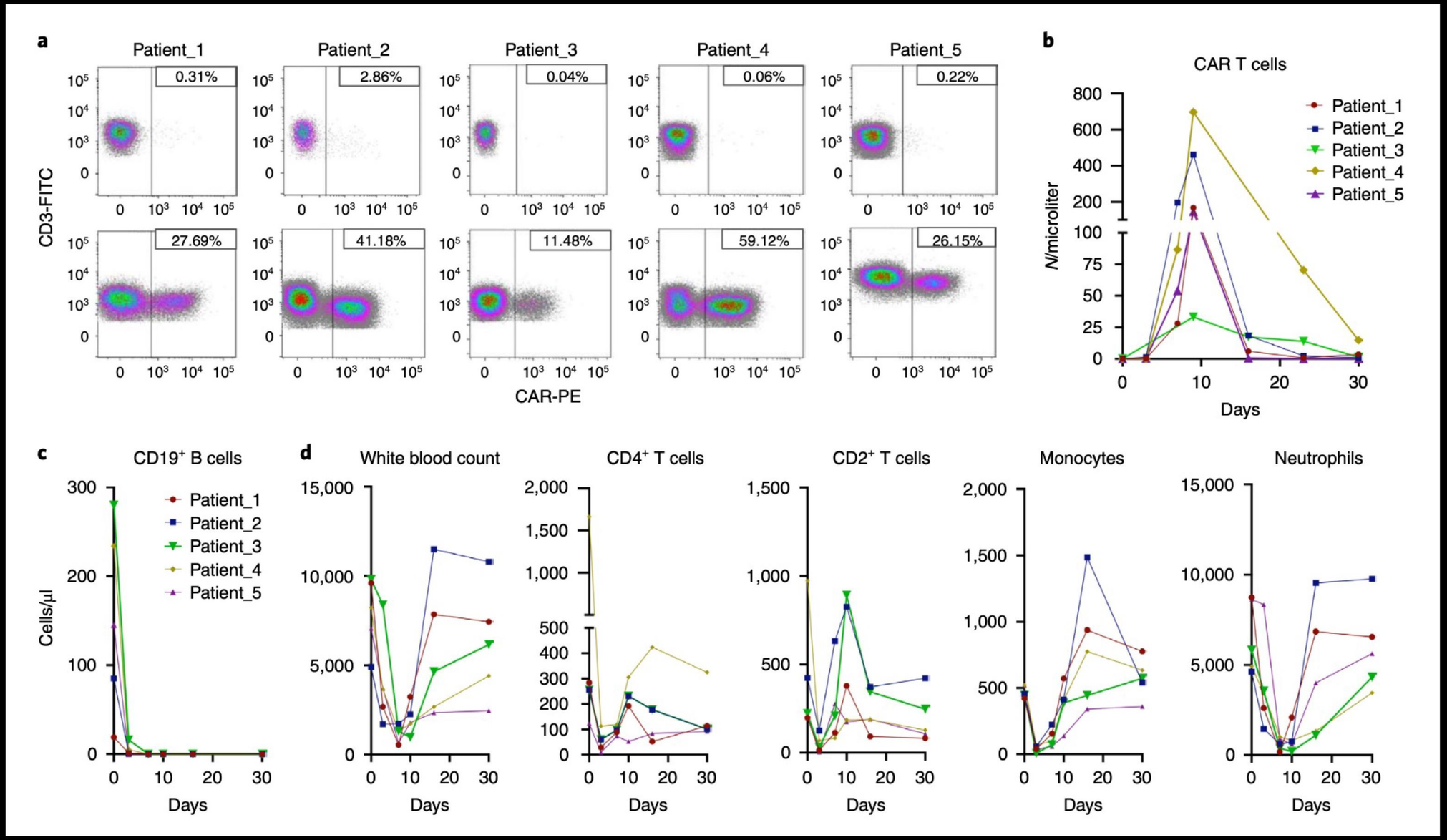
Table 1 | Patient characteristics at baseline

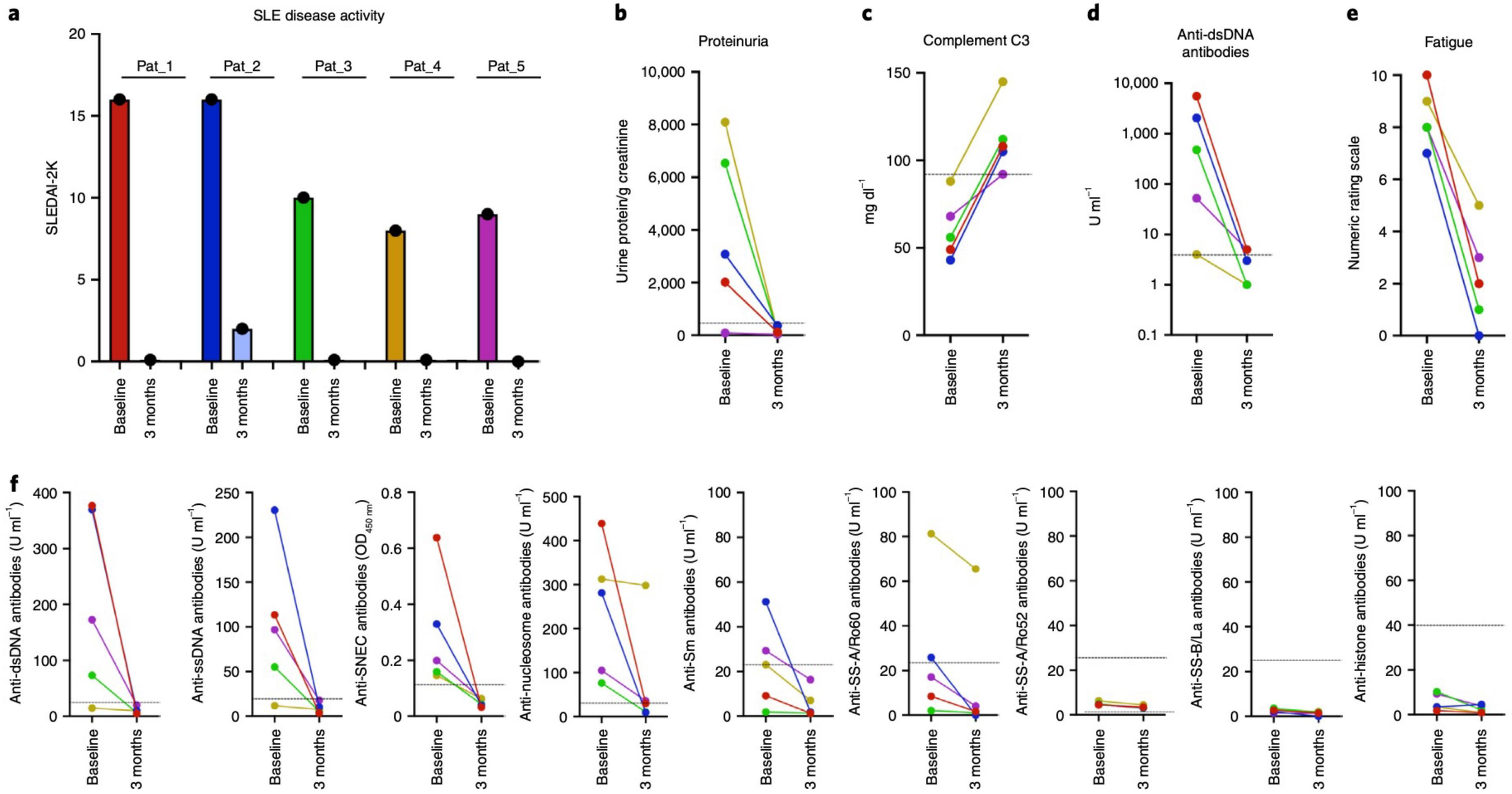
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Demographics					
Age (years)	22	23	22	24	18
Sex (female/male)	F	M	F	F	F
Disease duration (years)	4	1	6	9	3
Disease activity SLEDAI-2K (score)	16	16	10	8	9
Laboratory values					
Baseline hemoglobin (g dl^{-1})	10.0	14.60	9.60	13.10	12.20
Baseline white blood cells (*N* μl^{-1})	8.69	5.36	5.85	3.88	7.25
Baseline lymphocytes (*N* μl^{-1})	0.7	1.2	1.4	1.4	1.4
Baseline platelets (*N* μl^{-1})	279	188	198	398	278
Baseline C3 (mg dl^{-1})	49	43	56	88	68
Baseline anti-dsDNA (U ml^{-1})	5,600	2,060	479	4	52
Baseline ANA (titer)	1:10,000	1:3,200	1:10,000	1:3,200	1:1,000
Proteinuria (mg per 24 h)	2,015	3,080	6,539	8,096	88
Other autoantibodies	NUC, Sm	NUC, Sm Ro60	NUC, PCNA	NUC, Sm, Ro60	NUC, Sm, Ku
Organ involvement					
Skin (presence/absence)	+	+	+	+	+
Kidney (presence/absence)	+ (stage III)	+ (stage III)	+ (stage IV)	+ (stage III/V)	+ (stage III/V)
Joints (presence/absence)	–	+	+	+	+
Lungs (presence/absence)	+	–	+	+/–	–
Heart (presence/absence)	+	–	–	+	–
Other (presence/absence)	HEM	–	SER	MYO	HEM
Treatments					
Glucocorticoid pulses (yes/no)	+	+	+	+	+
Hydroxychloroquine (yes/no)	+	+	+	+	+
MMF (yes/no)	+	+	+	+	+
Azathioprine (yes/no)	–	–	–	+	+
Cyclophosphamide (yes/no)	+	+	+	–	–
Rituximab (yes/no)	+	–	–	–	–
Belimumab (yes/no)	+	+	+	+	+
Other (yes/no)	TAC	–	–	MTX, LEF	–

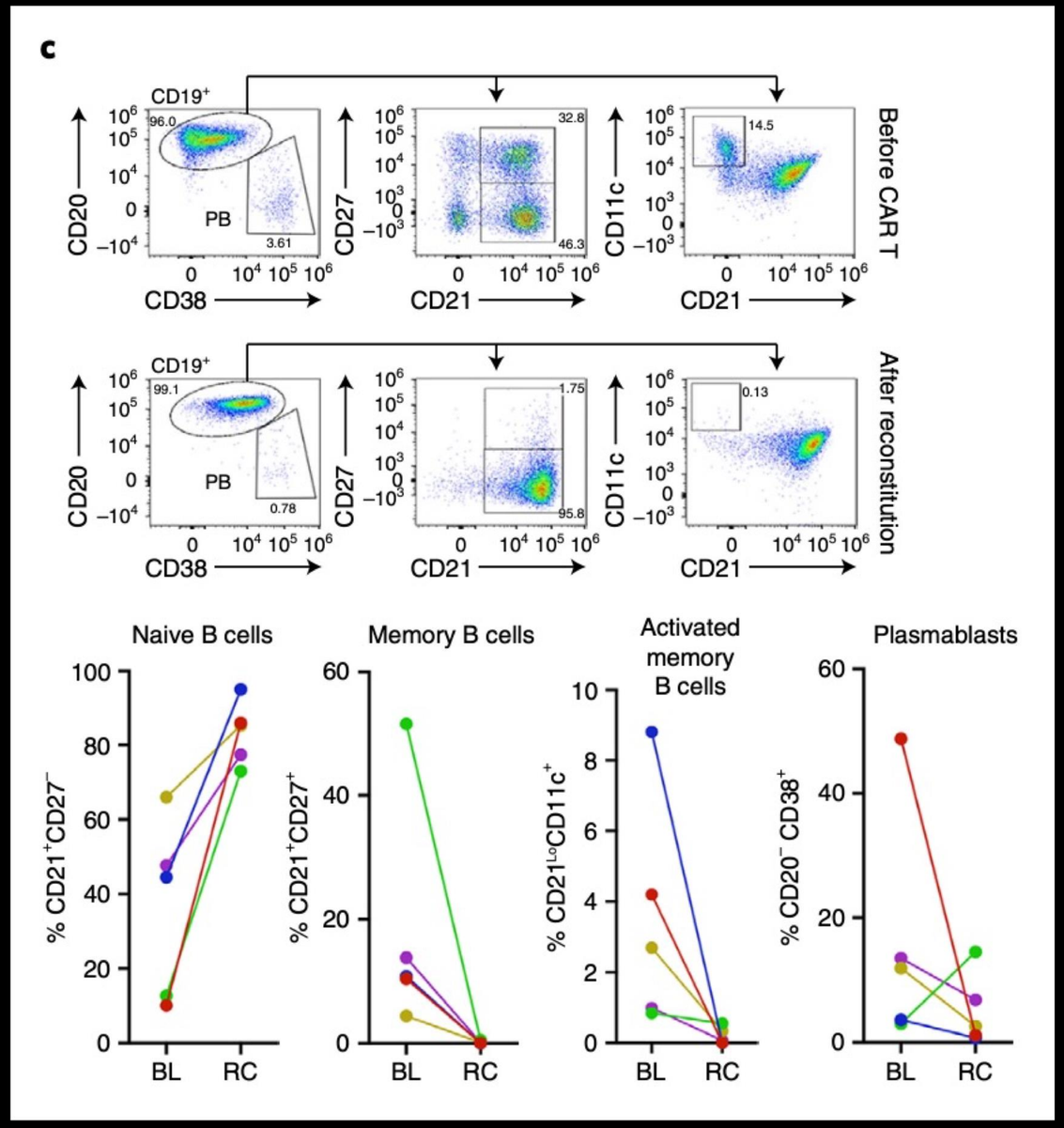
ANA, antinuclear antibody; C3, complement factor C3; HEM, hematologic abnormalities of SLE; LEF, leflunomide; MTX, methotrexate; MYO, myositis; NUC, anti-nucleosome antibodies; PCNA, proliferating cell nuclear antigen; SER, serositis; TAC, tacrolimus.

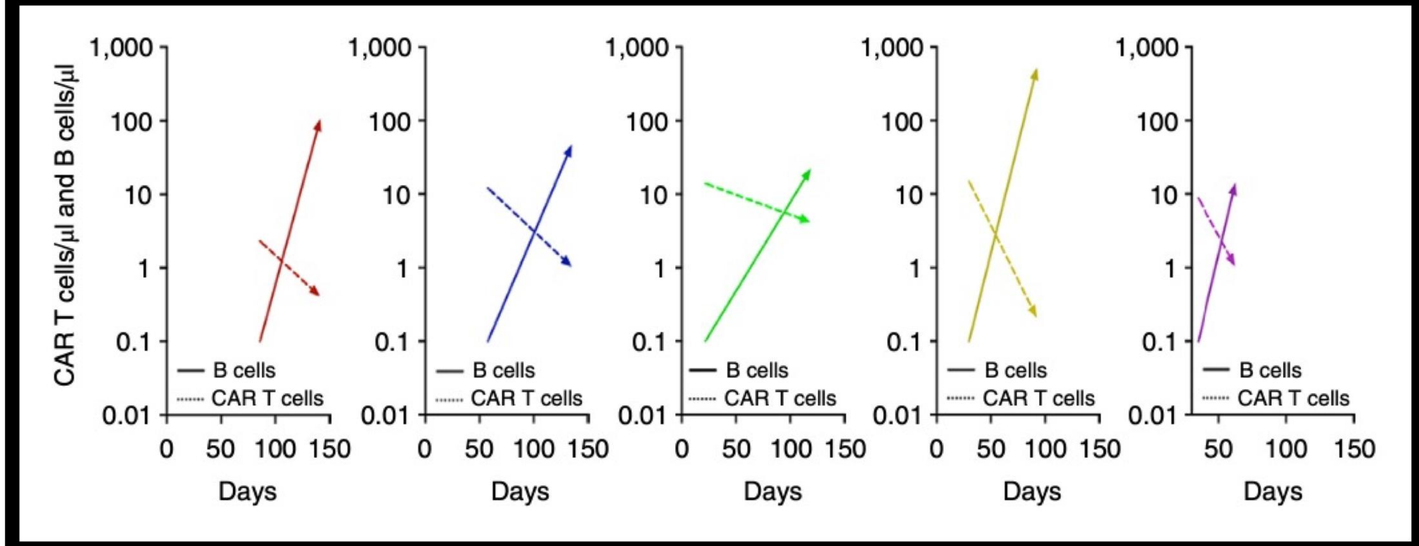
ΟΧΙ
ΚΝΣ

ΕΚΠΤΥΞΗ ΤΩΝ CAR T cells
ΕΞΑΦΑΝΙΣΗ ΤΩΝ B cells




a
SLE disease activity
SLEDAI-2K
Pat_1
Pat_2
Pat_3
Pat_4
Pat_5
Baseline
3 months
b
Proteinuria
Urine protein/g creatinine
c
Complement C3
mg dl−1
d
Anti-dsDNA antibodies
U ml−1
e
Fatigue
Numeric rating scale
f
Anti-dsDNA antibodies (U ml−1)
Anti-ssDNA antibodies (U ml−1)
Anti-SNEC antibodies (OD450 nm)
Anti-nucleosome antibodies (U ml−1)
Anti-Sm antibodies (U ml−1)
Anti-SS-A/Ro60 antibodies (U ml−1)
Anti-SS-A/Ro52 antibodies (U ml−1)
Anti-SS-B/La antibodies (U ml−1)
Anti-histone antibodies (U ml−1)


c
CD19+
96.0
PB
3.61
CD20
CD38
32.8
46.3
CD27
CD21
14.5
CD11c
CD21
Before CAR T
99.1
0.78
1.75
95.8
0.13
After reconstitution
Naive B cells
Memory B cells
Activated memory B cells
Plasmablasts
% CD21+CD27−
% CD21+CD27+
% CD21Lo CD11c+
% CD20− CD38+
BL
RC


CAR T cells/µl and B cells/µl
1,000
100
10
1
0.1
0.01
B cells
CAR T cells
0
50
100
150
Days

FOLLOW-UP

- Follow up: 5 – 11 μήνες
- B cell reconstitution ≈ 100d

- Κλινικά: **DRUG FREE REMISSION**

- Η εξεργασία της νεφρίτιδας: **σταμάτησε**
- Αρθρίτιδα, κόπωση: εξαφανίστηκαν

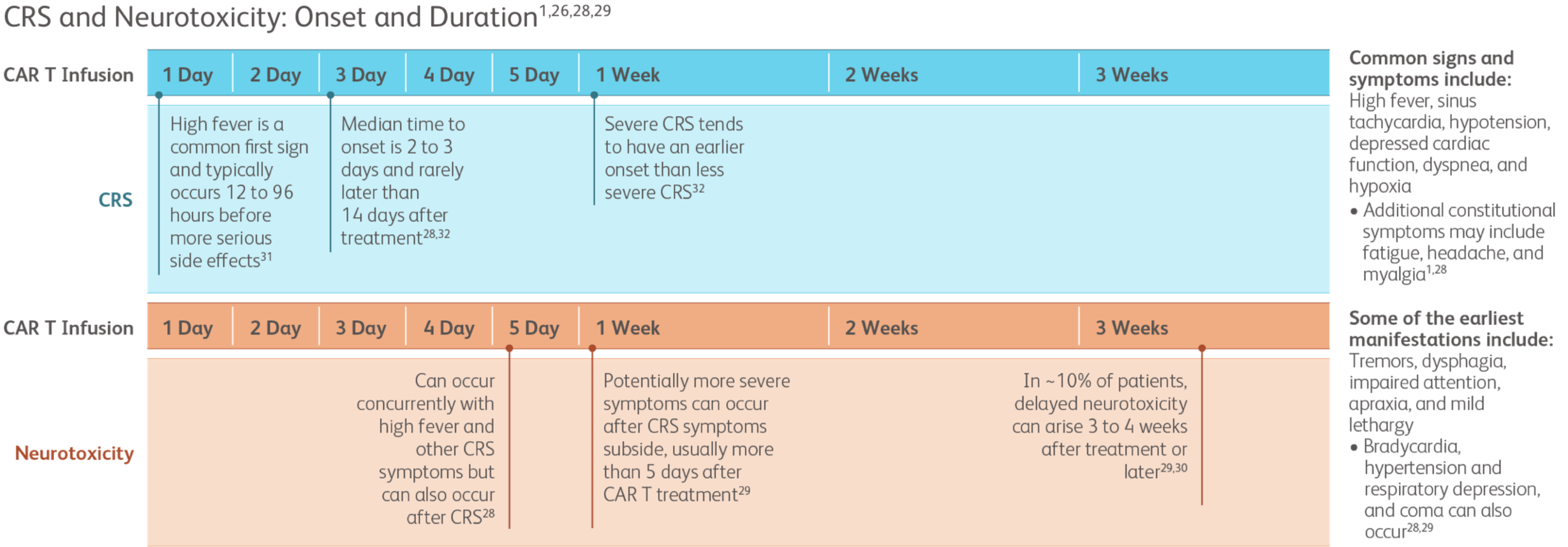
- CAR-T cells: εξαφανίστηκαν γρήγορα

- Υπο-γ-σφαιριναιμία: ΟΧΙ

- Επίπεδα Ab από εμβόλια: ΔΕΝ ελαττώθηκαν

- **Ίνωση καρδιακών βαλβίδων και διάμεση πνευμονική ίνωση: ΕΞΑΦΑΝΙΣΤΗΚΑΝ**

Cytokine Release Syndrome (CRS) & Immune effector Cell Associated Neurotoxicity Syndrome (ICANS)



https://www.cartcellscience.com/car-t-associated-toxicities/

ΣΥΜΠΕΡΑΣΜΑΤΙΚΑ

”What’s New in SLE?”

- Not much

- Λίγες **εντυπωσιακές** μελέτες που φωτίζουν την Παθογένεια

- Πολυάριθμες νέες Κλινικές Μελέτες. Πολλά μόρια που παρεμβαίνουν σε διάφορα βιοχημικά μονοπάτια / κυτταροκίνες / κύτταρα.

- Μερικές με ενθαρρυντικά αποτελέσματα. »Κοντόφθαλμα» ?? time points?

- **Ζούμε ξεκάθαρα στον Αστερισμό του Lupus B cell.**