

Lupus Nefritis: is er meer dan B-cel therapie?

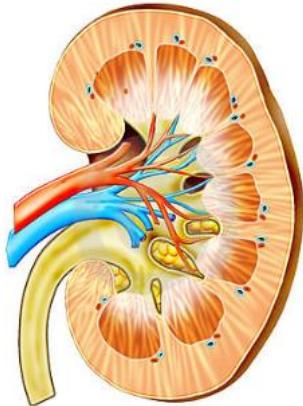
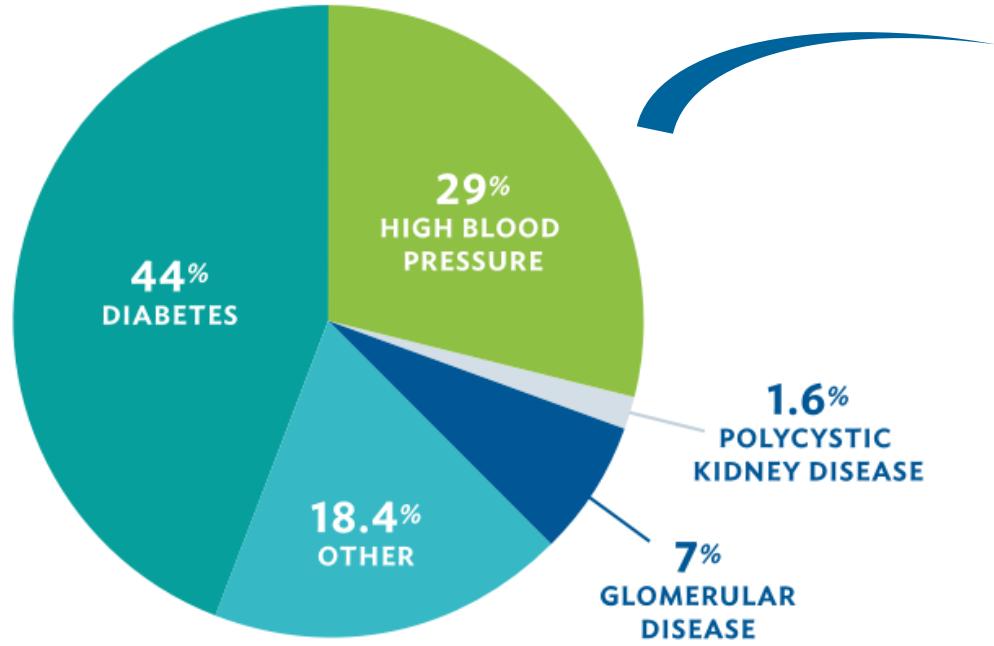
Y.K. Onno Teng

Afdeling Nierziekten

LEIDS UNIVERSITAIR MEDISCH CENTRUM

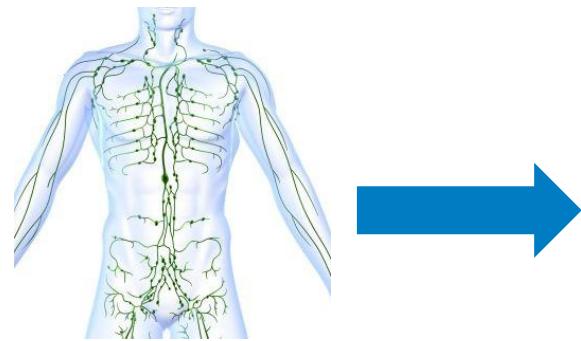


Zijn Nefrologen eigenlijk wel 'Nier'-dokters?

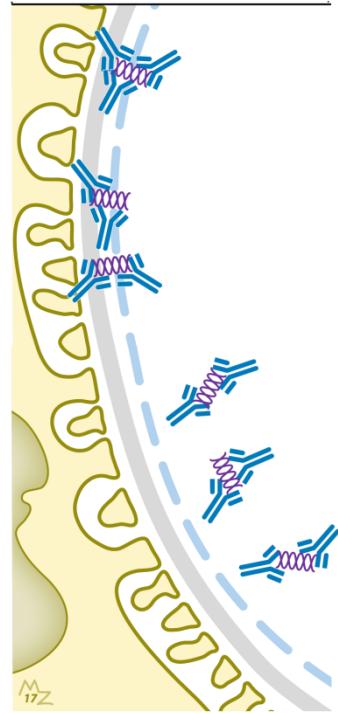
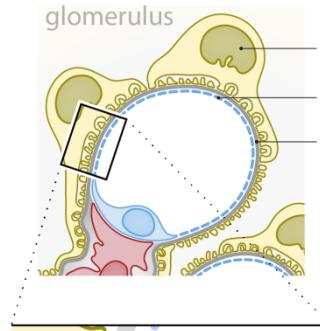


**Metabole & hormonale
ontregeling**

Lupus Nefritis: Immuuncomplex-gemedieerde nefritis



Immunologische
ontregeling



*Immunocomplex-
Gemedieerde
Endotheelschade*

ANA
Anti-DNA, anti-Nucl.

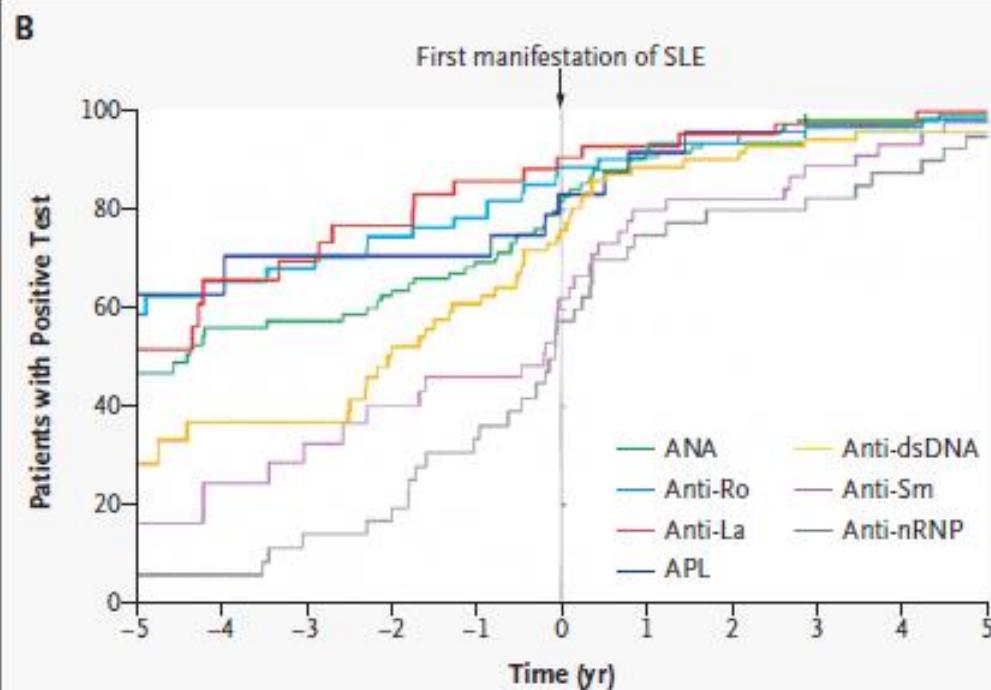
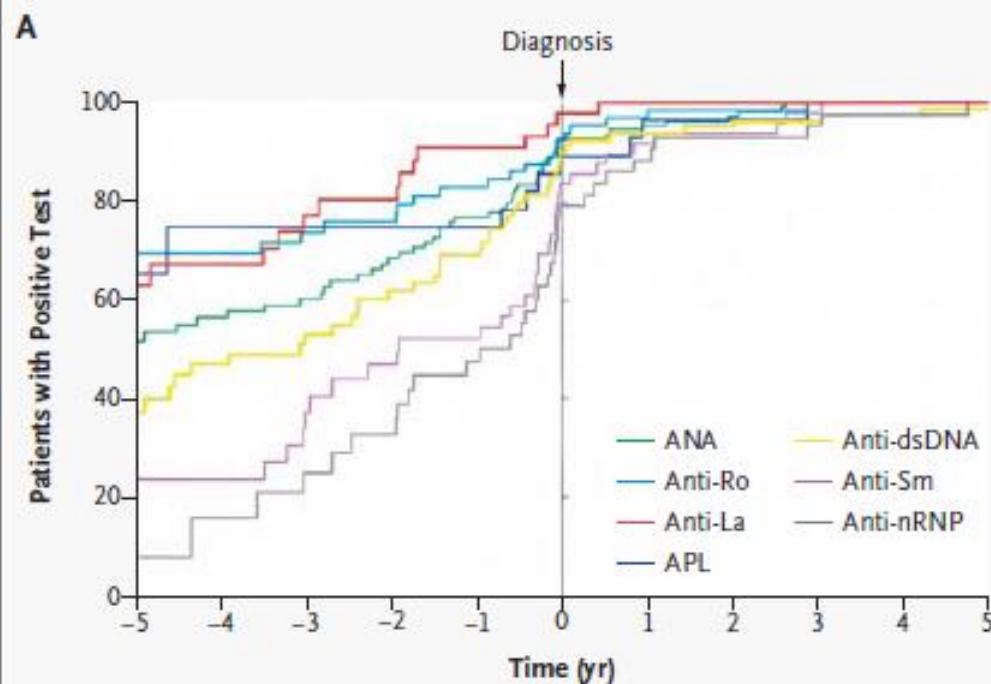


Metabole
ontregeling

Auto-immunitéit

ontstaat jaren
vooraf aan

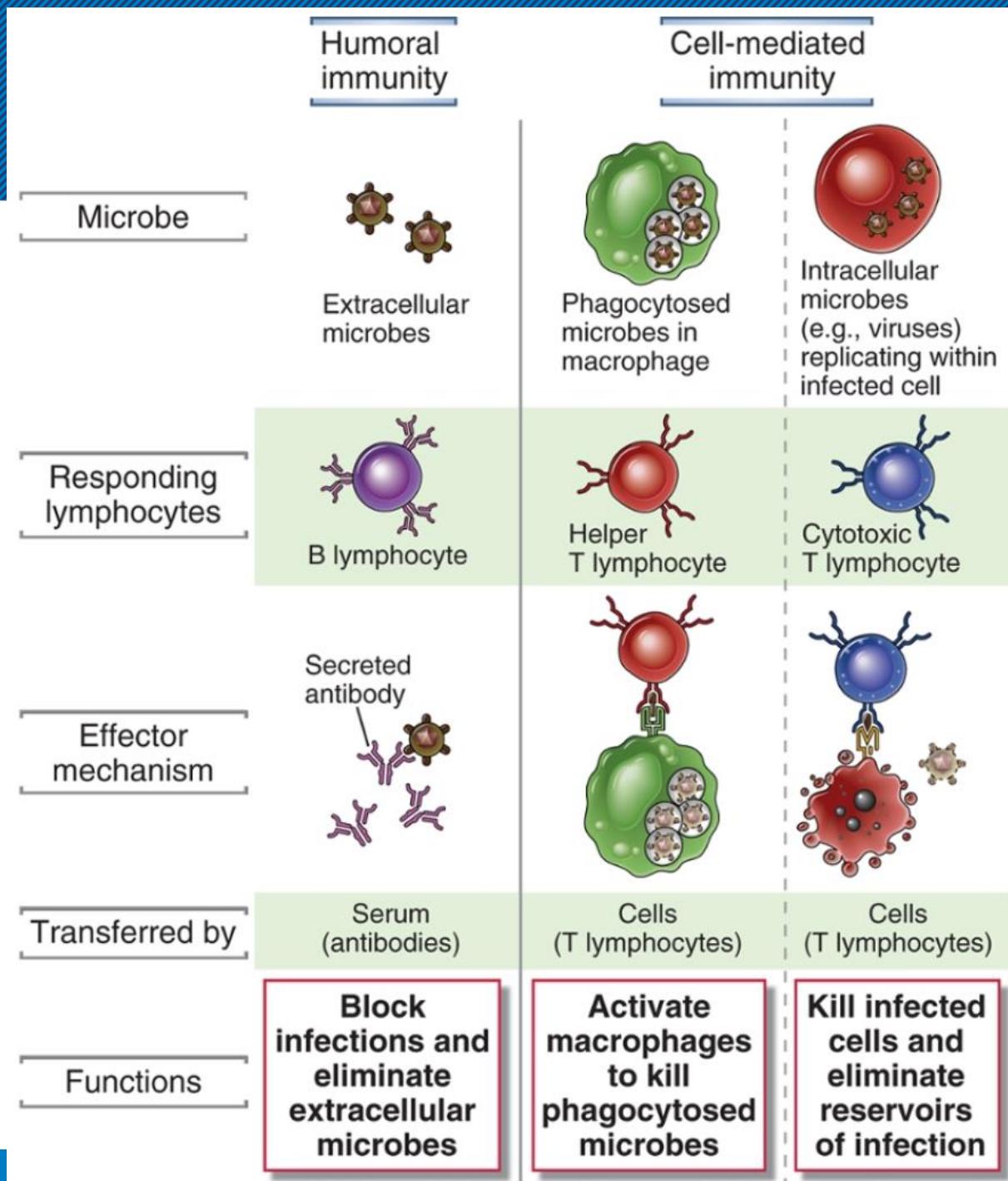
Auto-immuunziekte



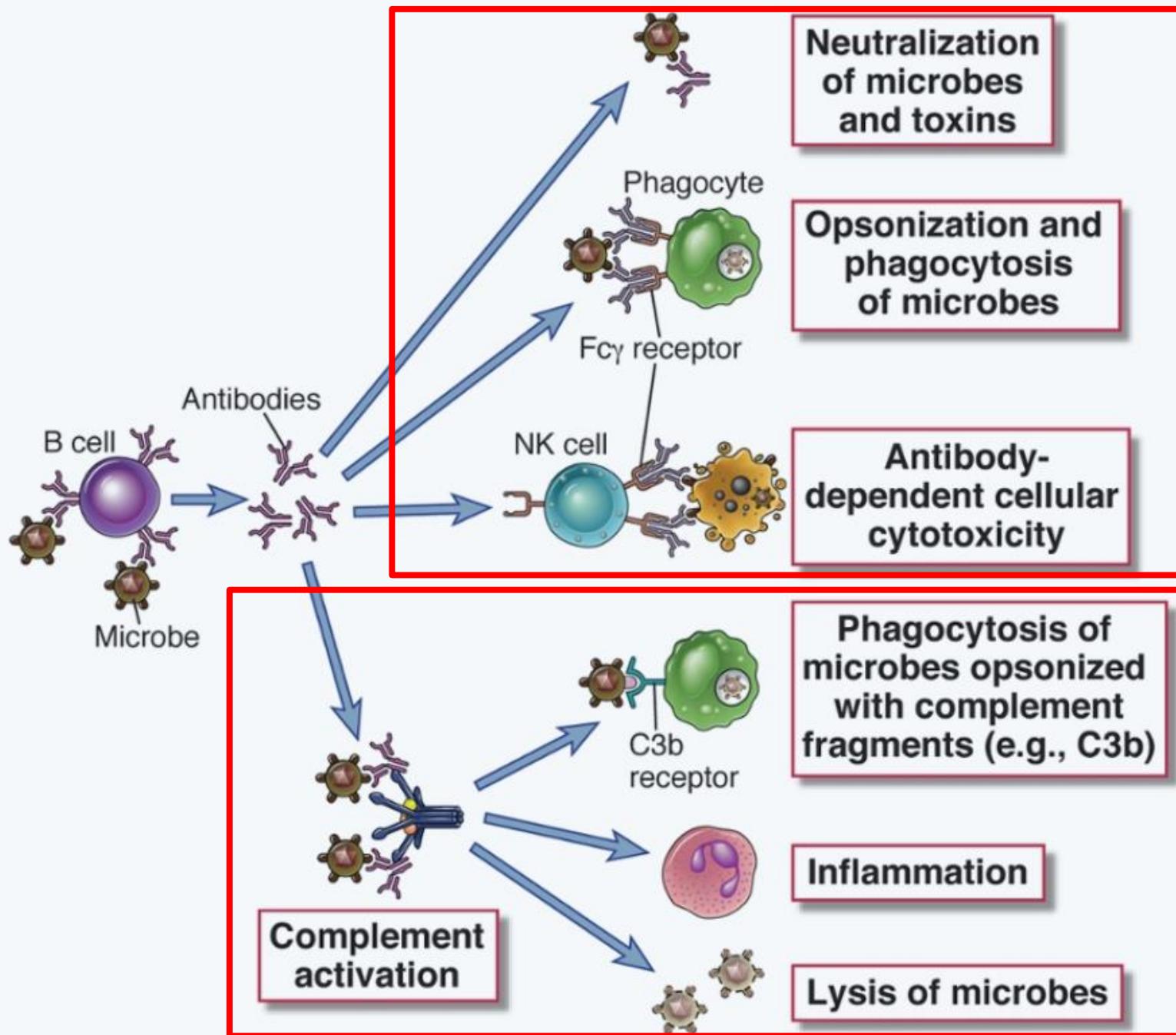
Overzicht: Is er meer dan B-cel therapie alleen?

1. B-cel immunologie & Humorale Autoimmuniteit
2. Meer dan anti-CD20 targeting in LN
 - a. Post LUNAR tijdperk
 - b. Gecombineerde B-cel therapie

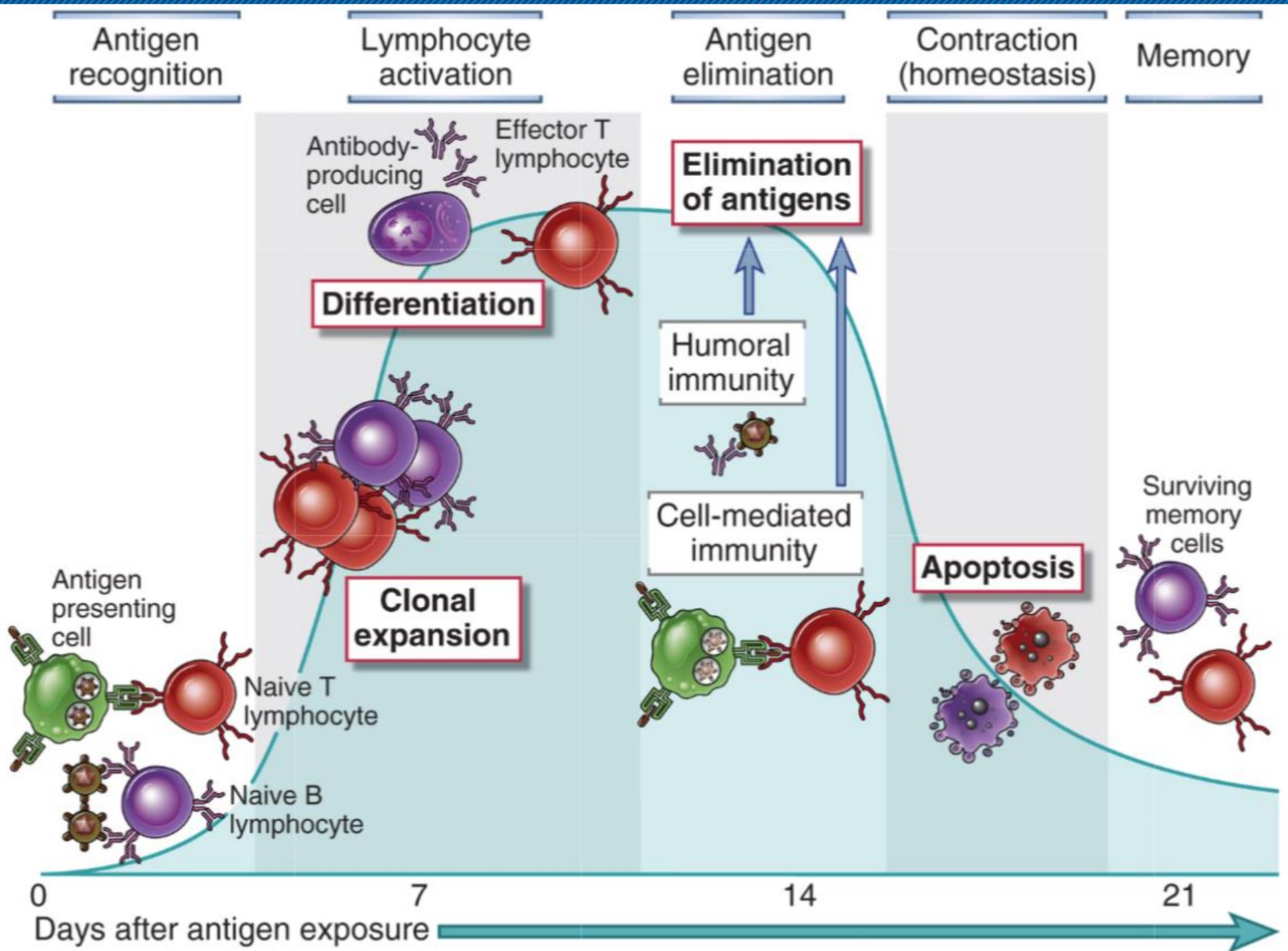
Humorale Immunitéit



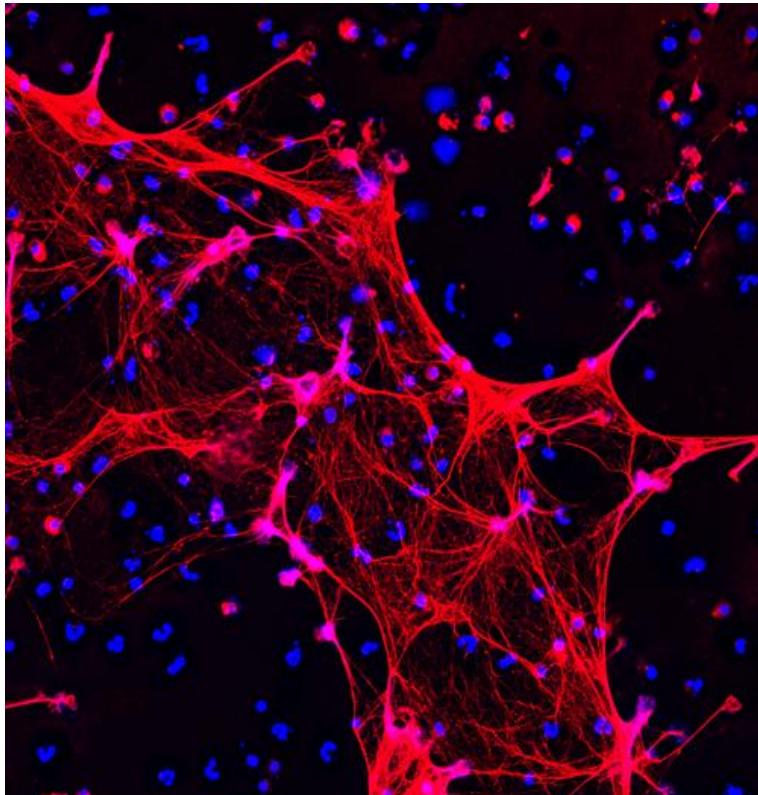
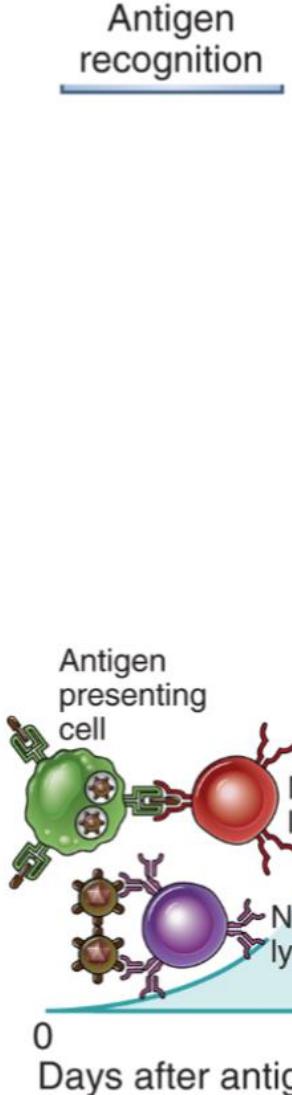
Humorale Immunitéit



Biologicals
Lupus Nefritis



Extracellulair DNA als auto-antigenen



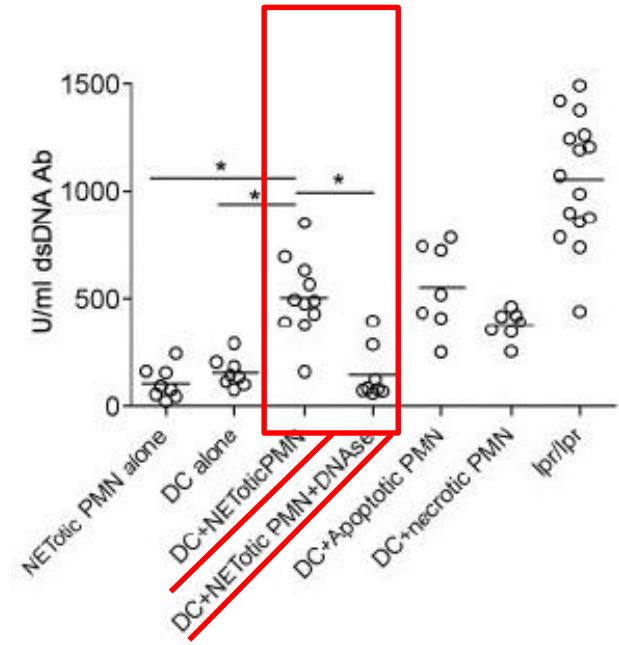
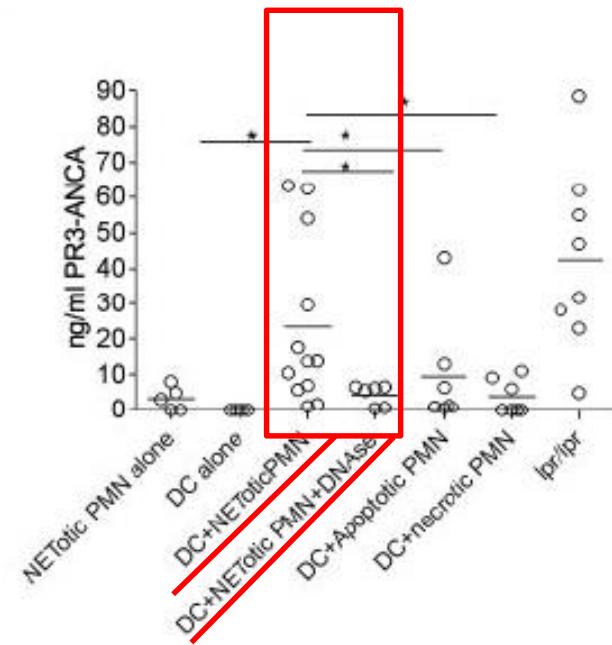
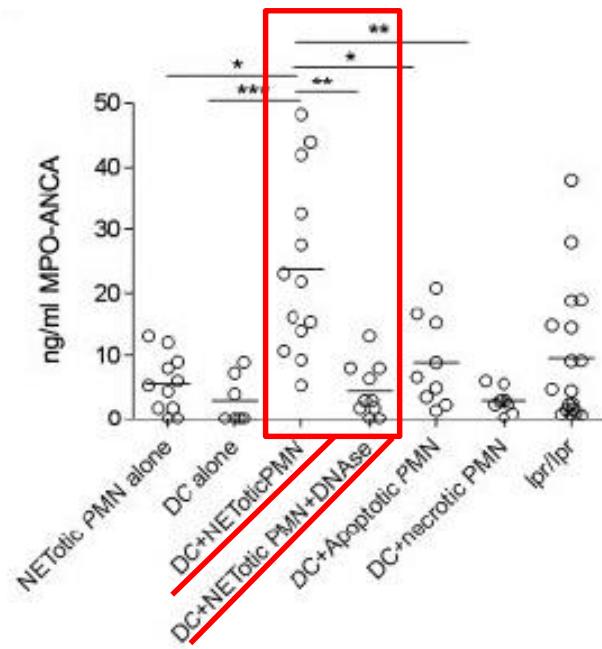
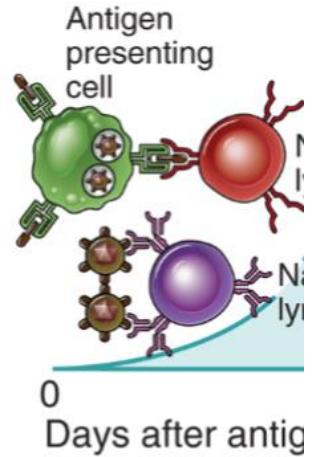
70% histones
30% proteins

dsDNA	→ SLE
Histones	→ SLE, RA
MPO	→ ANCA vasculitis
PR3	→ ANCA vasculitis
Cit-Vimentin	→ RA
Cit-Enolase	→ RA

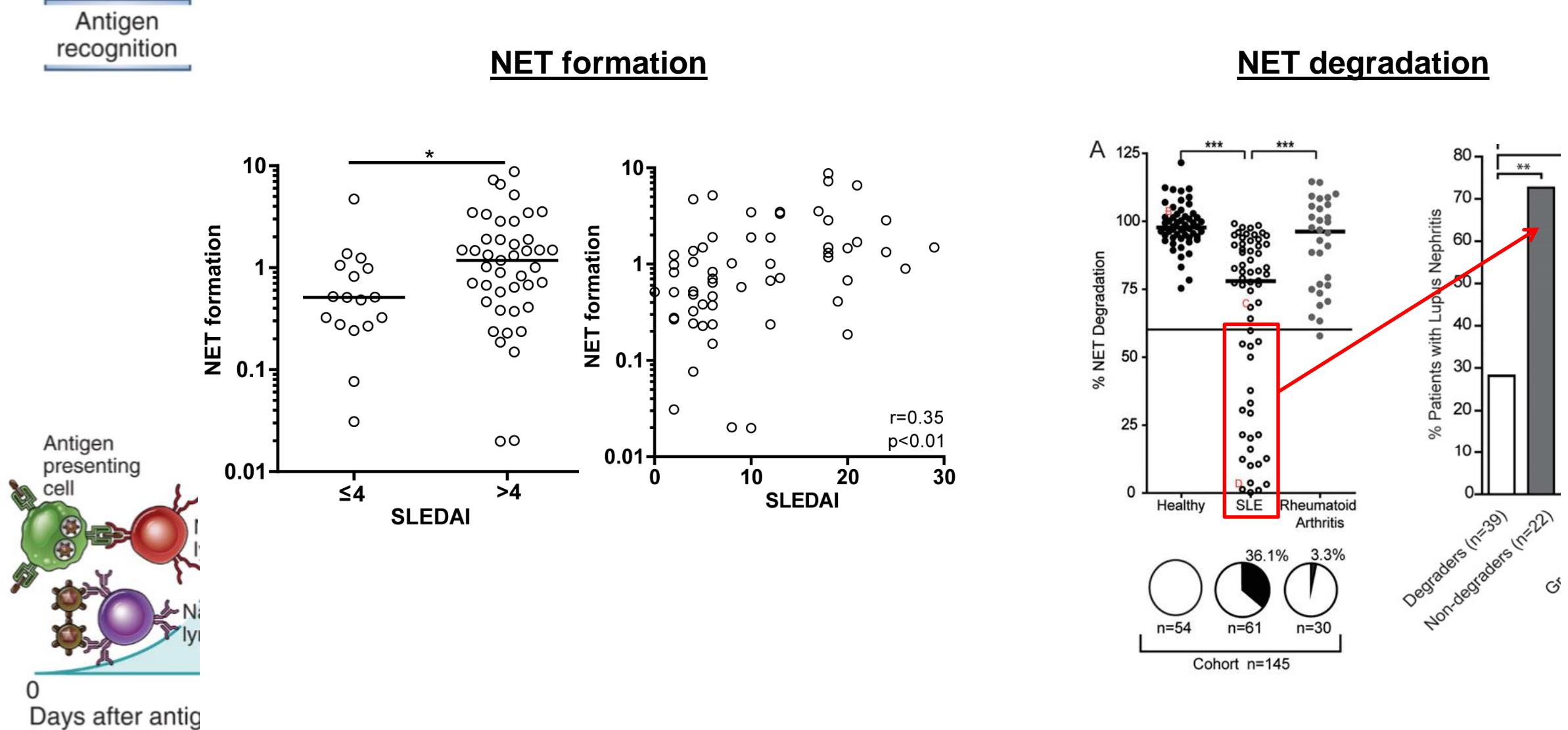
Kessenbrock et al. *Nat Med* 2009
Villaneuva et al. *JI* 2011
Garcia-Romo et al. *Sci Trans Med* 2011
Lande et al. *Nature* 2007 & *Sci Trans Med* 2011
Khandpur et al. *Sci Trans Med* 2013
Grayson et al. *A&R* 2015
Lood et al. *Nature Med* 2016
Carmona-Riviera et al. *JCI Insight* 2017
Carmona-Riviera et al. *Science Immunology* 2017

Extracellulair DNA als auto-antigenen

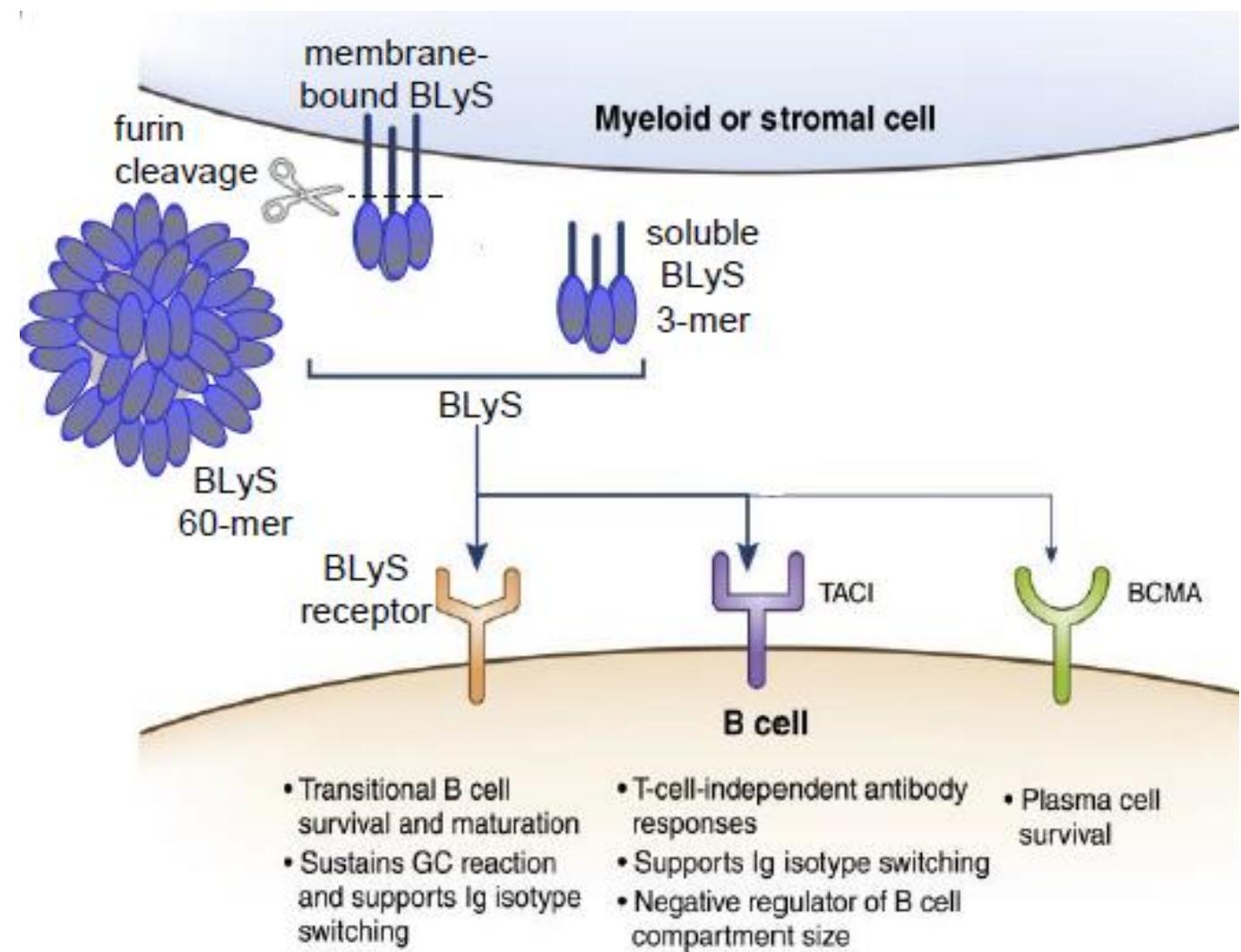
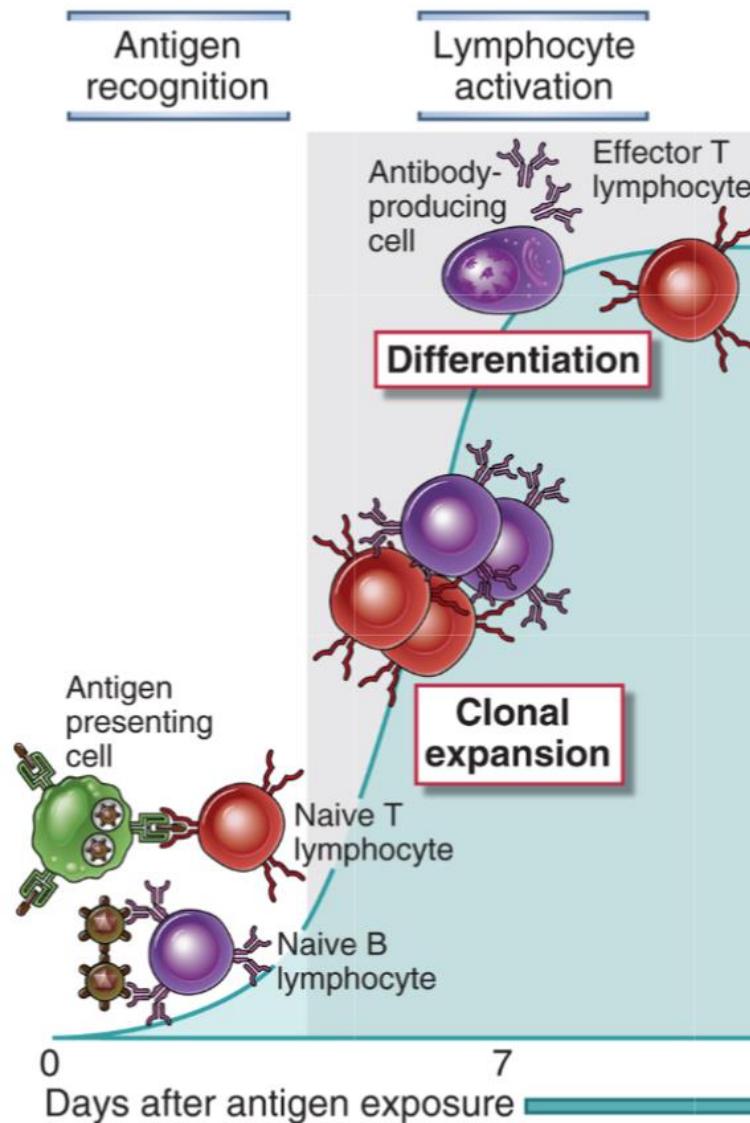
Antigen recognition



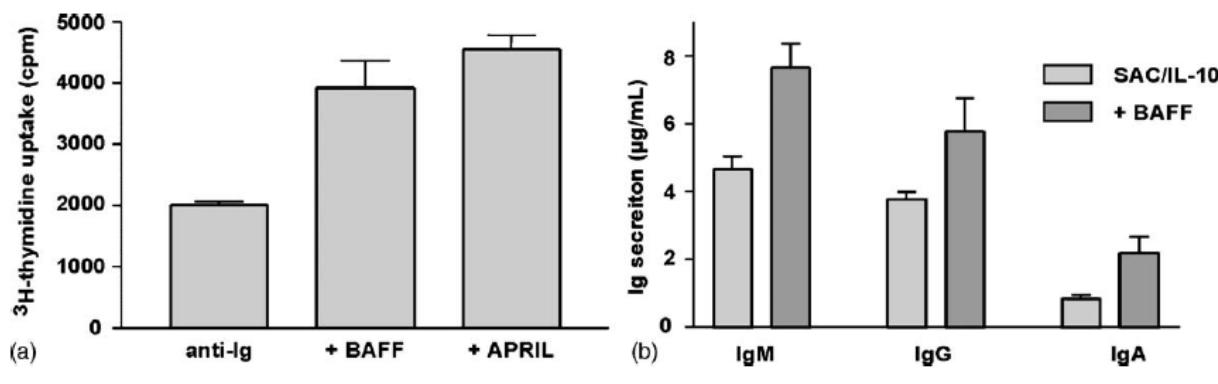
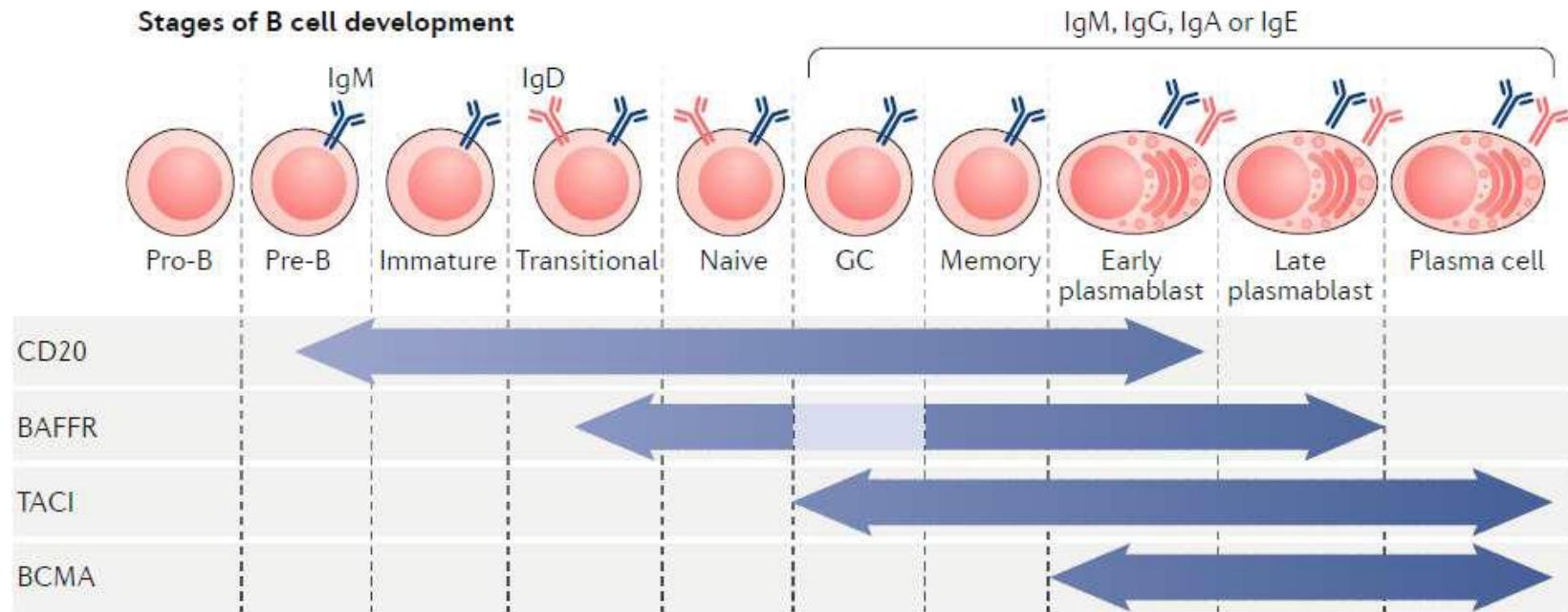
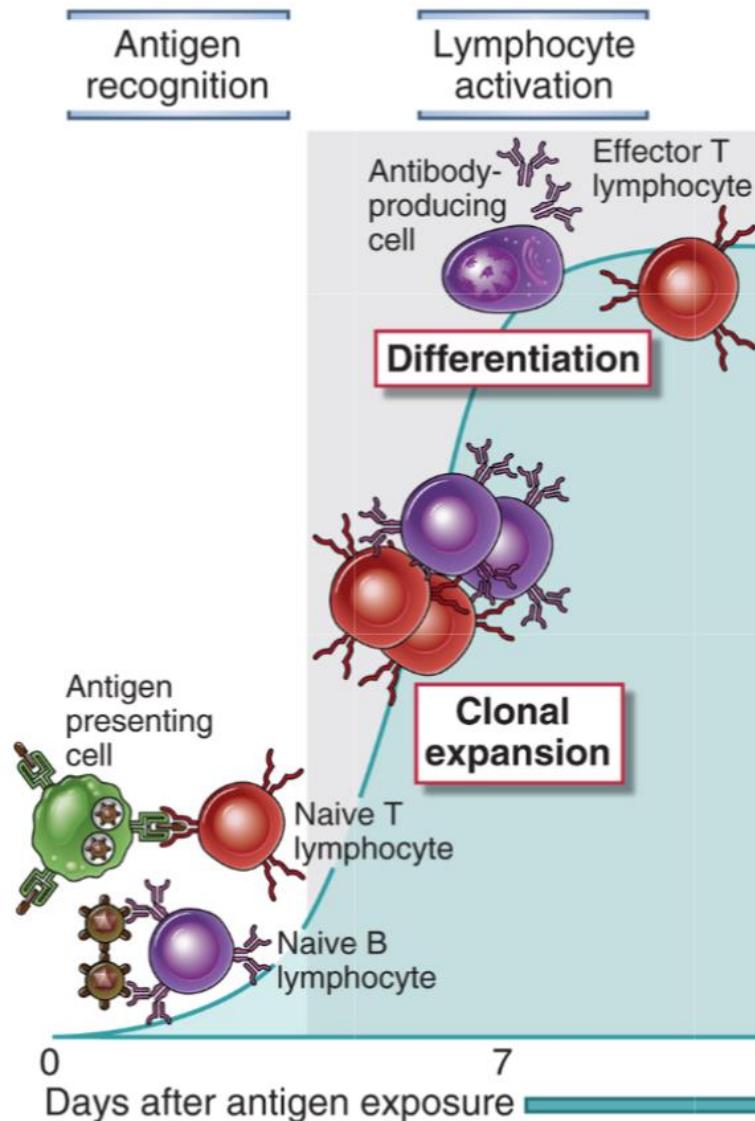
Extracellular DNA als auto-antigenen



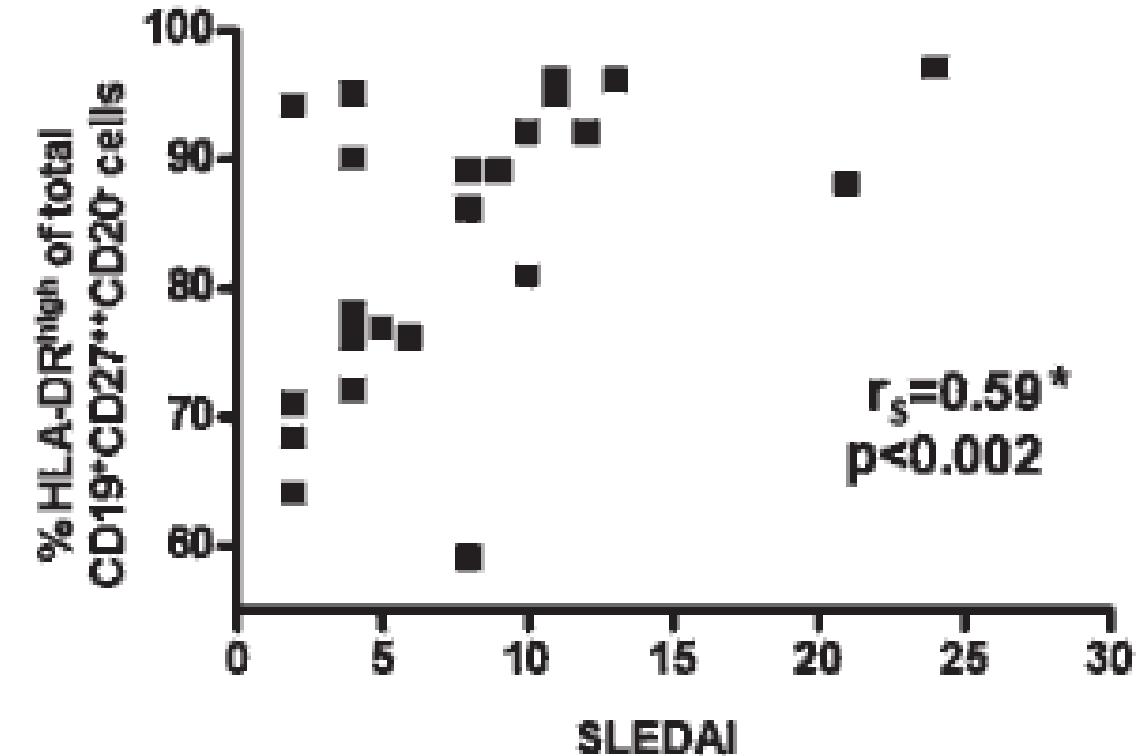
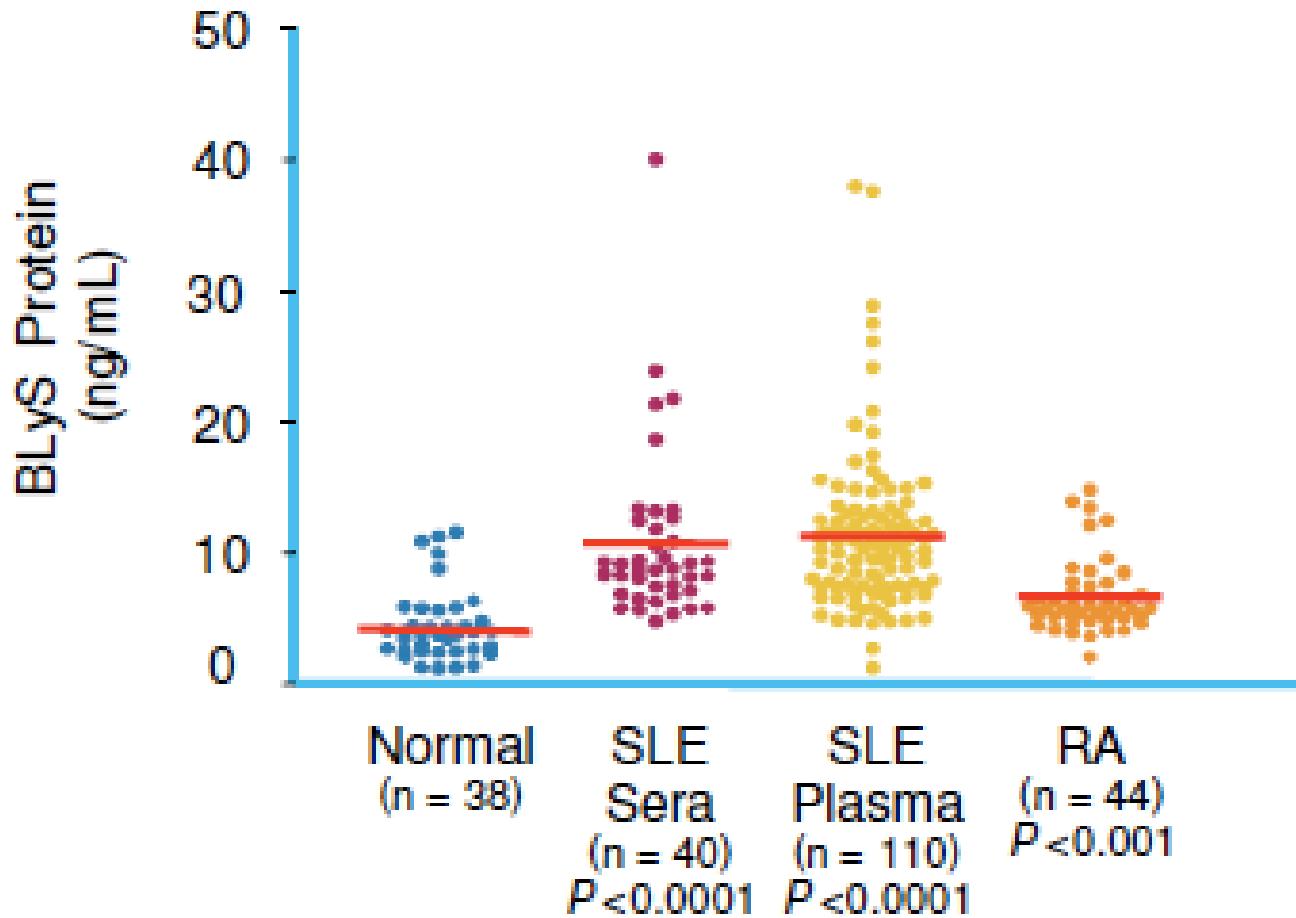
BAFF (=BlyS): B-cell activating factor



BAFF (=BlyS): B-cell activating factor

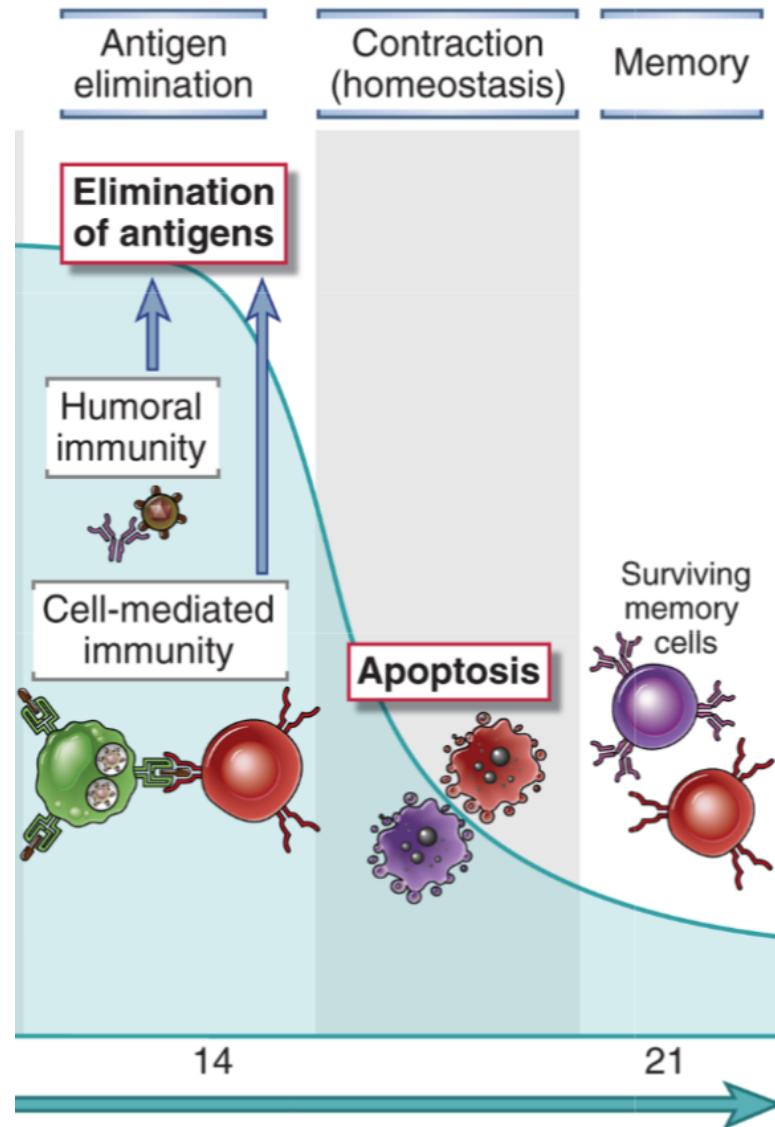


BAFF levels zijn verhoogd in SLE patienten

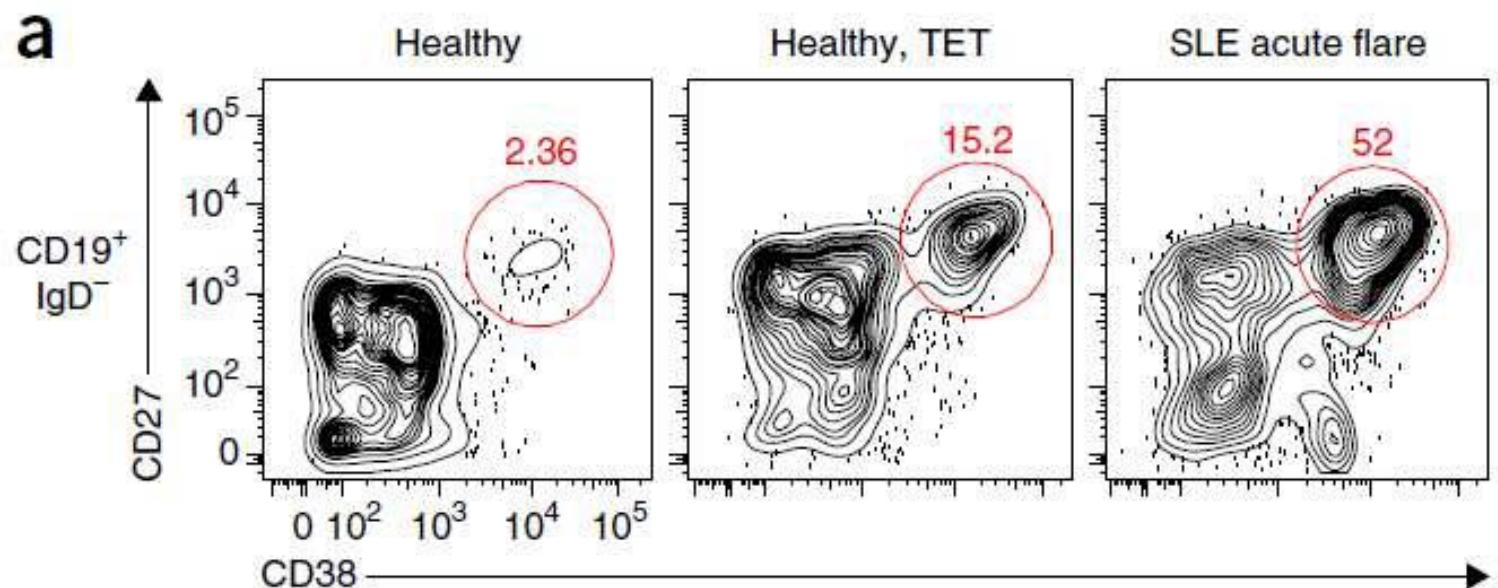
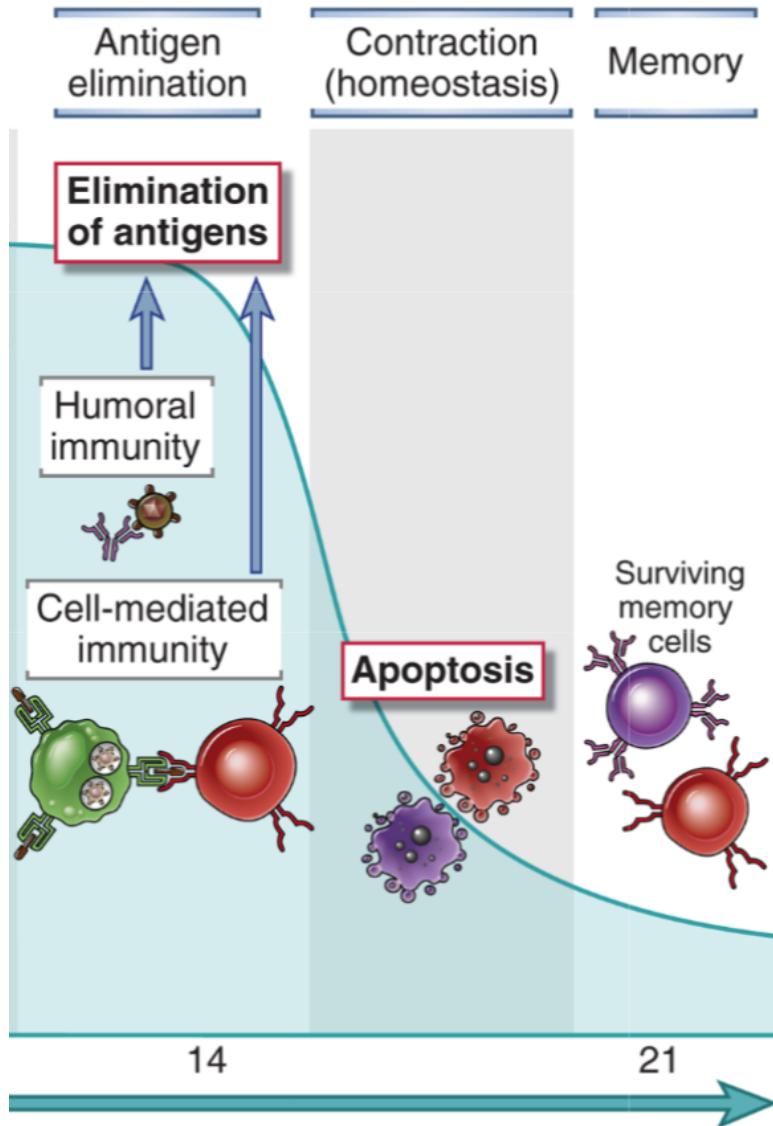


Zhang J et al. *J Immunology*. 2001;166:6-10

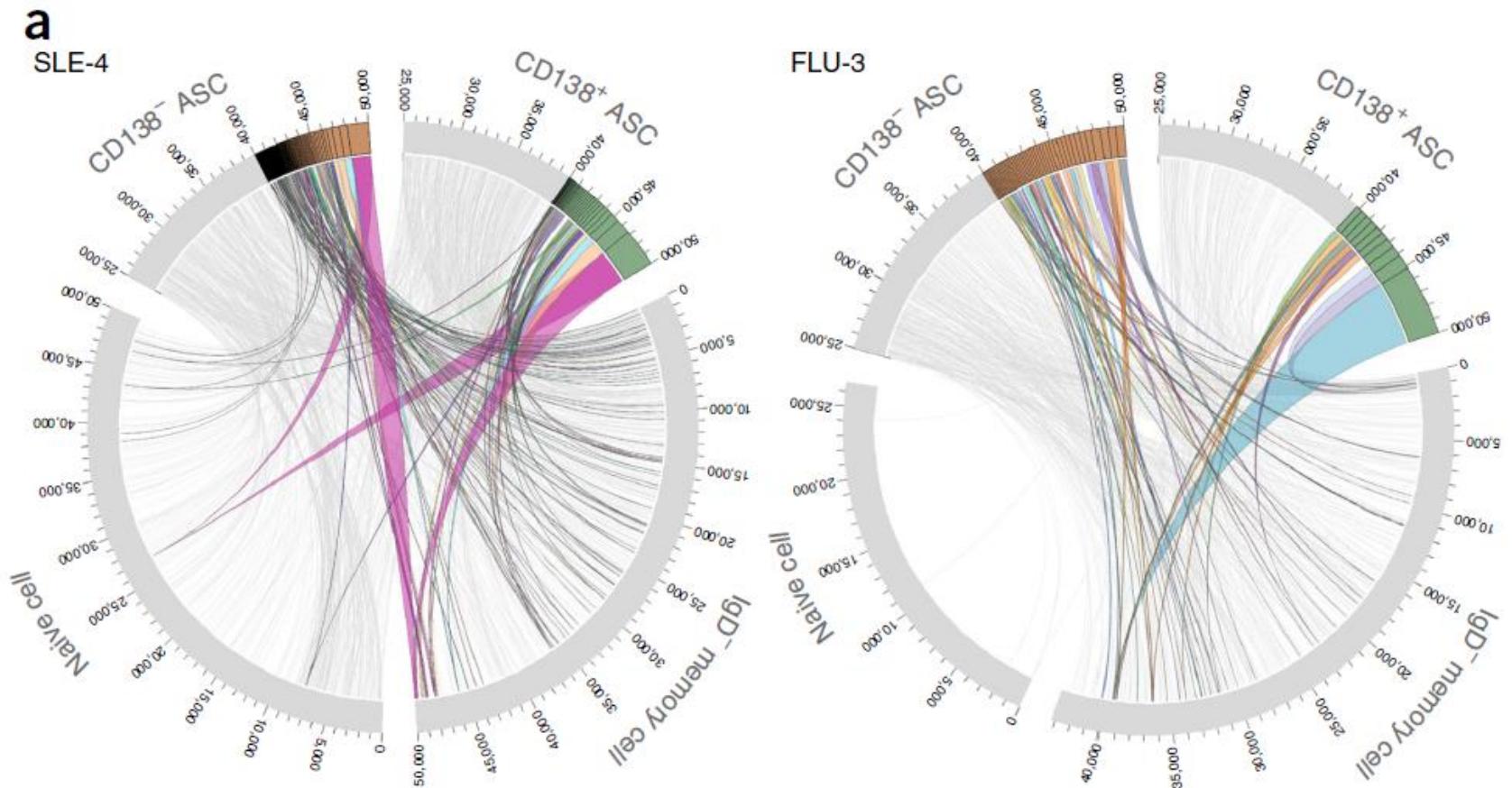
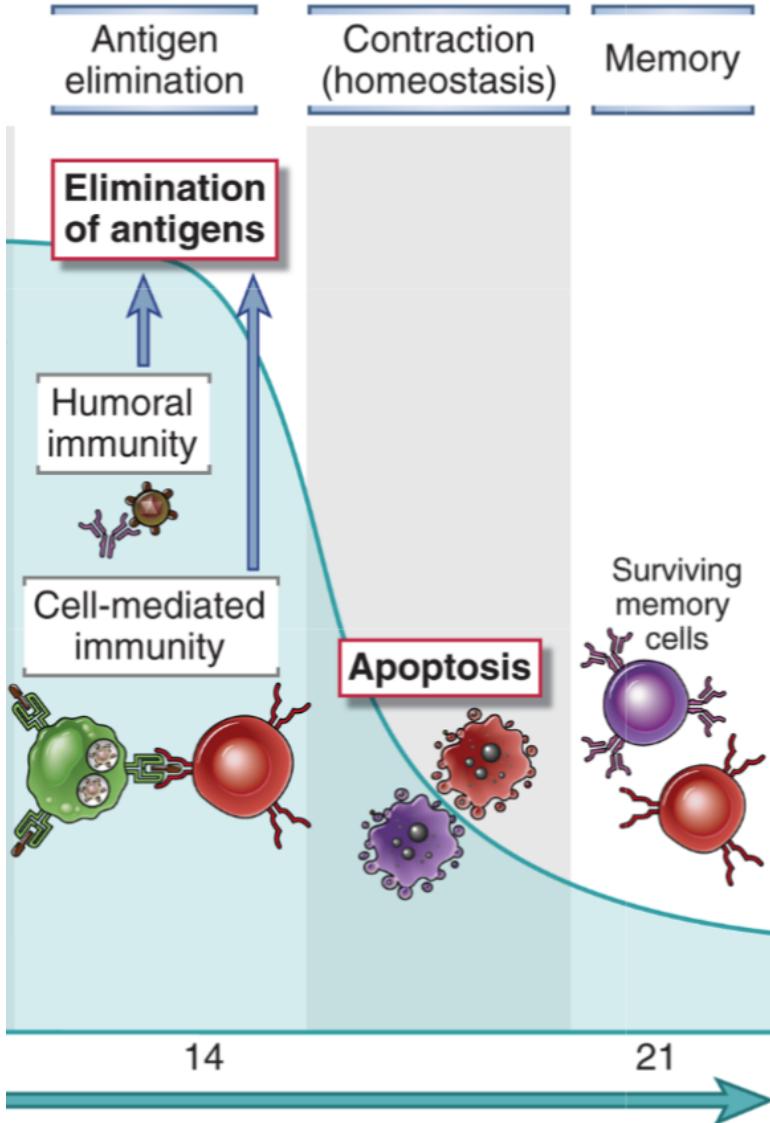
B-cell immunitéit: Immuun-contractie



B-cell immuneit & memory in SLE

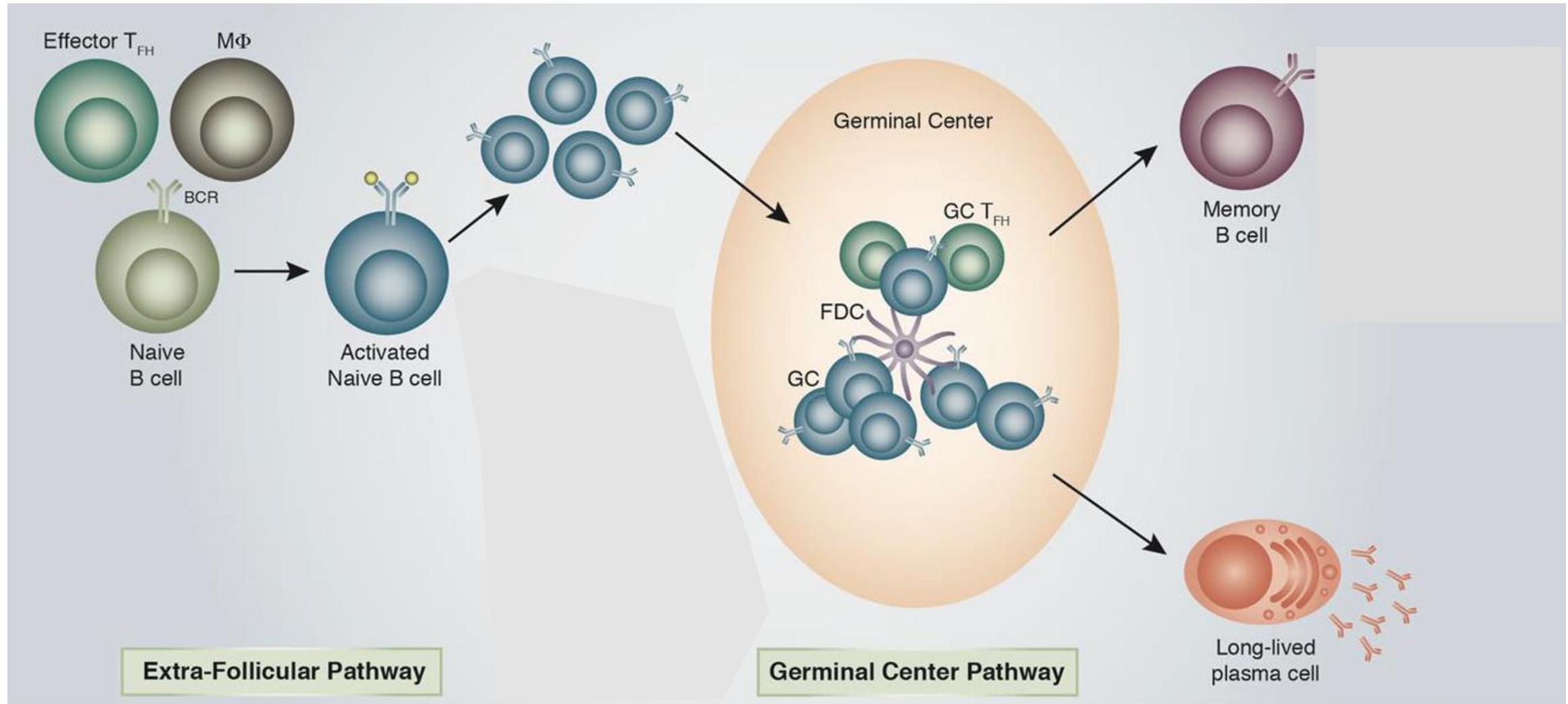


B-cell immuneit & memory in SLE



Next generation sequencing VDJ repertoire

B-cell immuneit & memory in SLE



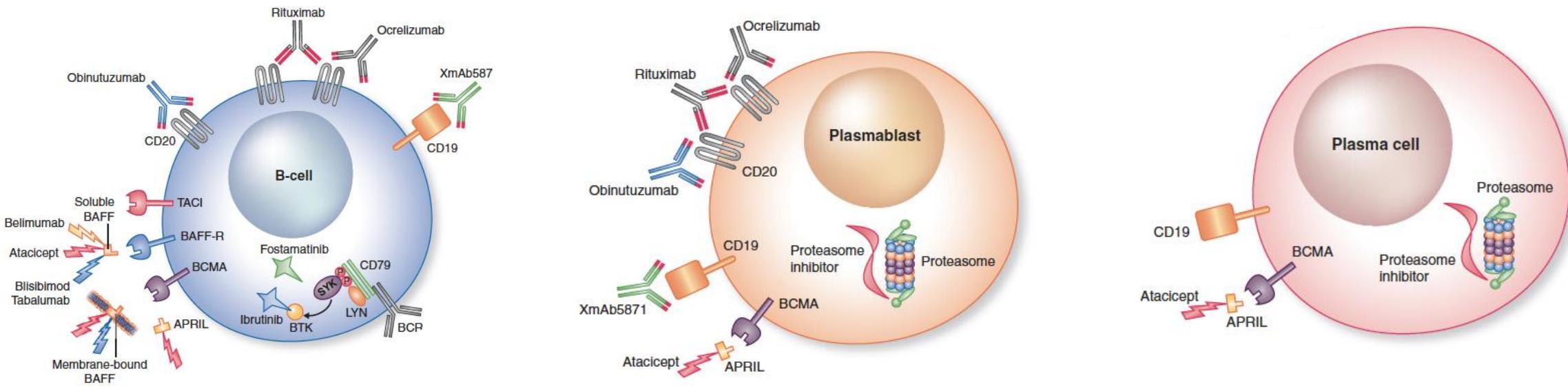
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Pijplijn anti-B cel therapie voor LN

Study name	Target	Phase RCT	
Mesenchymal stem cells	Umbilical cord MST (Asia)	Phase 2 blinded	Due end 2020
Mizoribine	Mizoribine (Asia)	Phase 3 open-label	Due end 2019
BLISS-LN (Belimumab)	Anti-BlyS mAb	Phase 3 blinded	Due end 2019
AURORA (Voclosporin)	3 rd generation CNI	Phase 3 blinded	Due end 2020
IGeLU (Iguratimod)	DMARD (Asia)	Phase 3 blinded	Recruiting
Obinutuzumab	3 rd generation anti-CD20	Phase 2 blinded	Recruiting
TULIP-LN1 (Anifrolimumab)	IFNaR blockade	Phase 2 blinded	Recruiting
CFZ533	Anti-CD40 mAb	Phase 2 blinded	Recruiting
BI 655064	Anti-CD40 mAb	Phase 2 blinded	Recruiting
Synbiose-2 (Belimumab + Rituximab)	Anti-BlyS + Anti-CD20	Phase 2 open label	Recruiting
APL-2	C3 complement mediator	Phase 2 open label	Recruiting
ACTHar	Corticotropine injecties	Phase 2 open label	Recruiting
KZR-616	Immunoproteasome inhibitor	Phase 1b/2 open label	Recruiting
OMS-721	Anti-MASP2 mAB	Phase 1b/2 open label	Recruiting

Anti-B cel therapie: kies uw target



Rituximab voor LN: LUNAR post-hoc analyses

LUNAR – Negatieve studie

T = 52 weken	Placebo (N=72)	Rituximab (N=72)
Complete respons	31%	26%
Partiele respons	15%	31%
<i>Totale delta respons*</i>		11%
MMF dosis	2,4g	2,7g

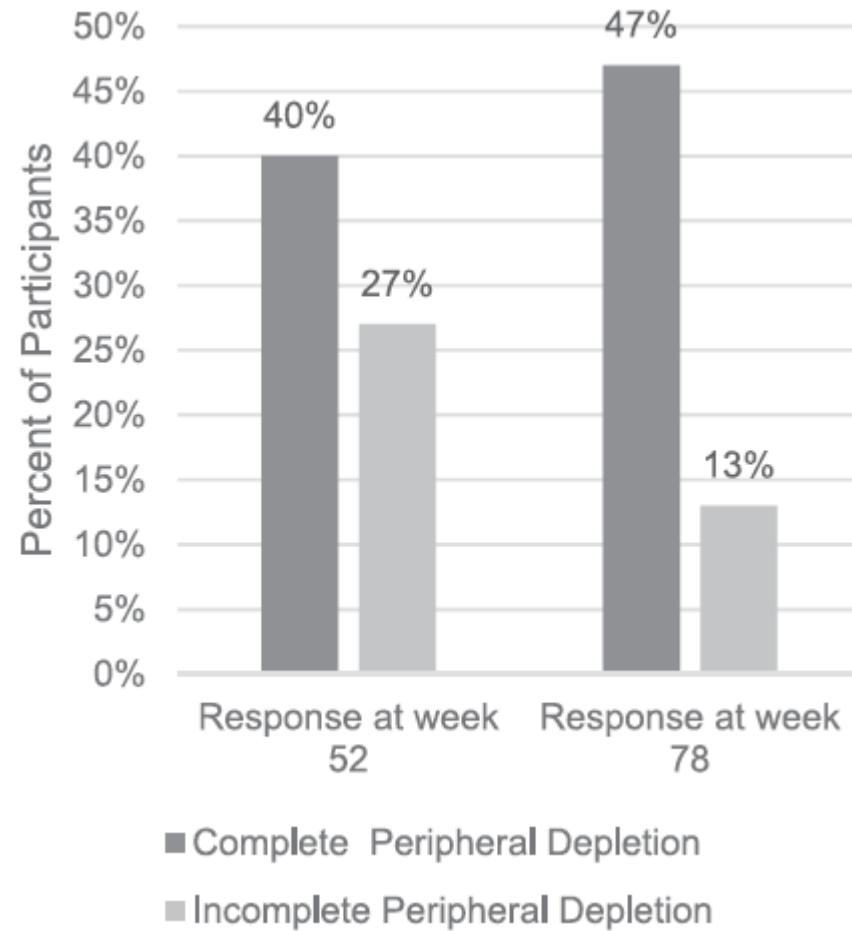
* Superioriteit- studie: power op een delta van 20%

Rituximab voor LN: LUNAR post-hoc analyses

LUNAR – Negatieve studie

T = 78 weken	Placebo (N=72)	Rituximab (N=72)	P-waarde
Proteinurie: $\Delta >50\%$	54%	71%	0.04
Cyclofosfamide voor week 52	11%	0%	0.006
Cyclofosfamide voor week 78	15%	3%	0.02
Gemid. Prednison 1 ^e jaar	12.8 ± 6.5	10.9 ± 4.1	0.05

Rituximab voor LN: LUNAR post-hoc analyses



B-cel depletie =

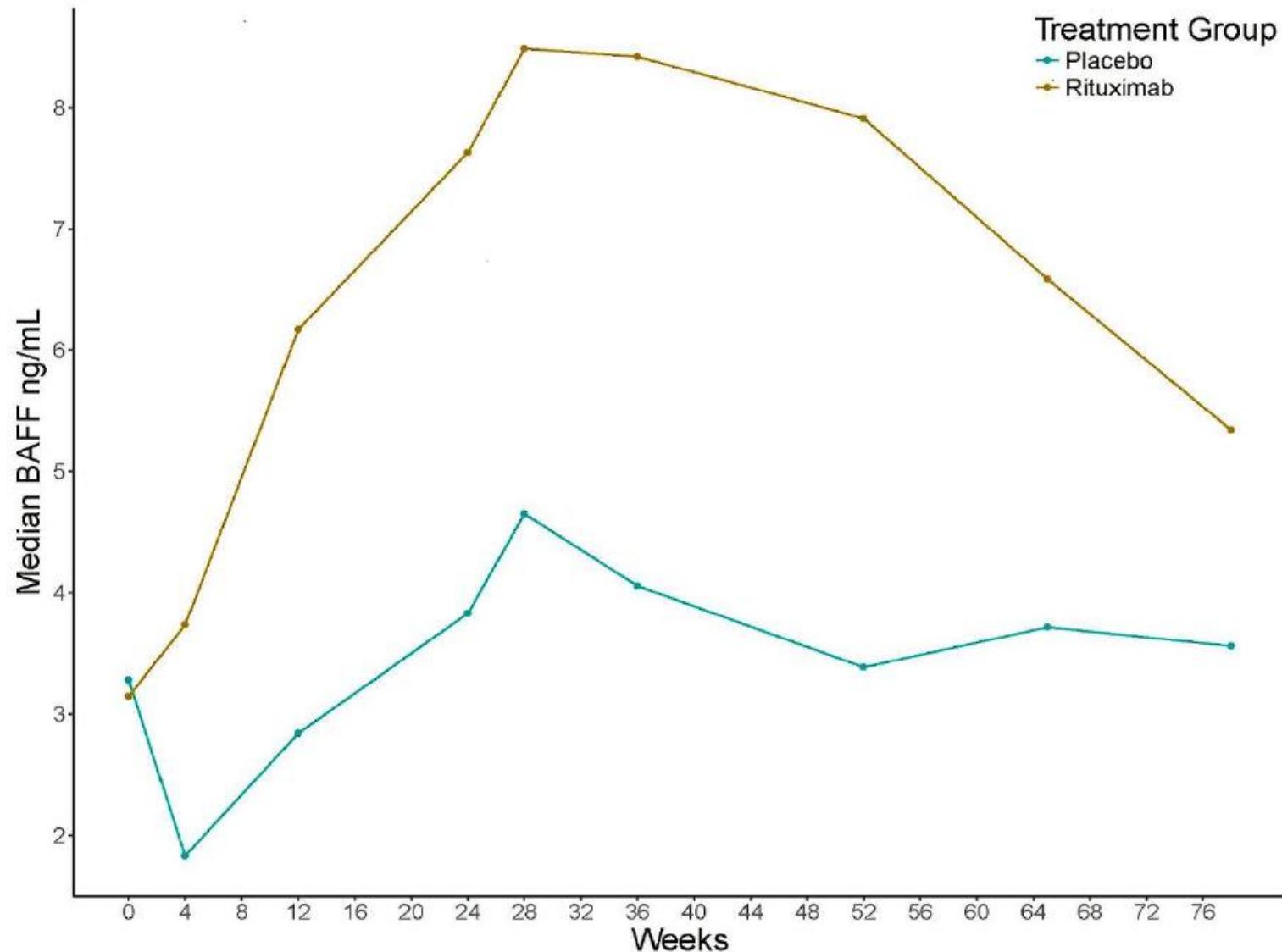
LUNAR study report: $< 20 \times 10^6 / L$ ~ 20 cells/uL
Phase 1 studies: $< 5 \times 10^6 / L$ ~ 5 cells/ uL
Post-hoc: $< 1 \times 10^6 / L$ ~ 1 cells/ uL

Post-hoc

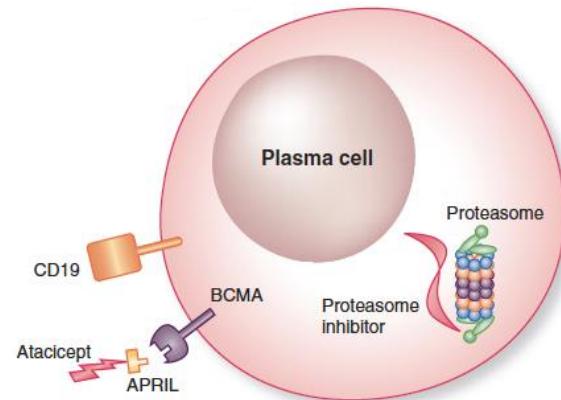
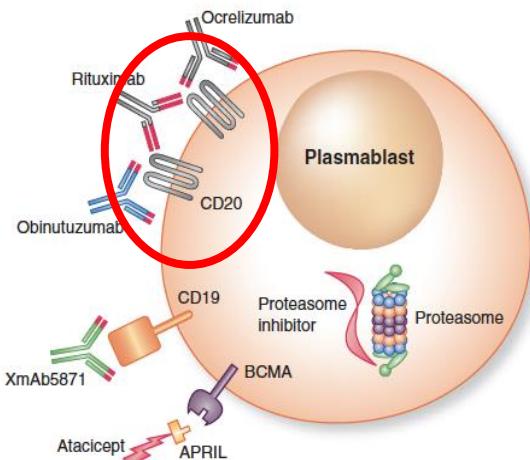
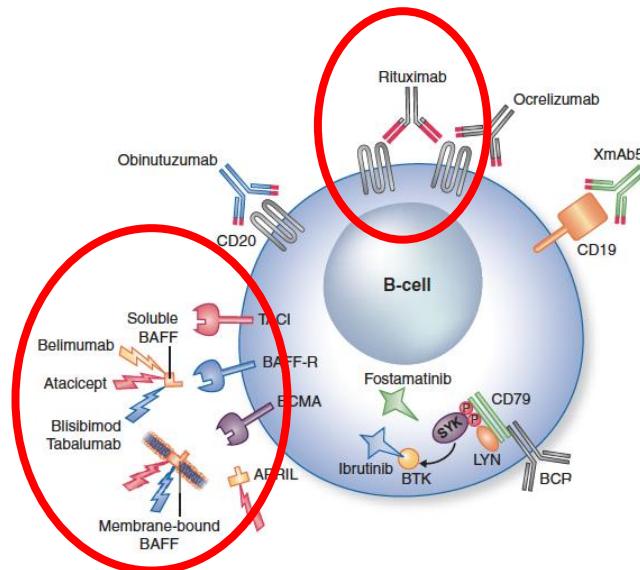
53 ptn bereikten 'complete depletion'
15 ptn bereikten geen 'complete depletion'

Week 78: OR 5.8 (1,2-28); p=0.03

Rituximab voor LN: LUNAR post-hoc analyses



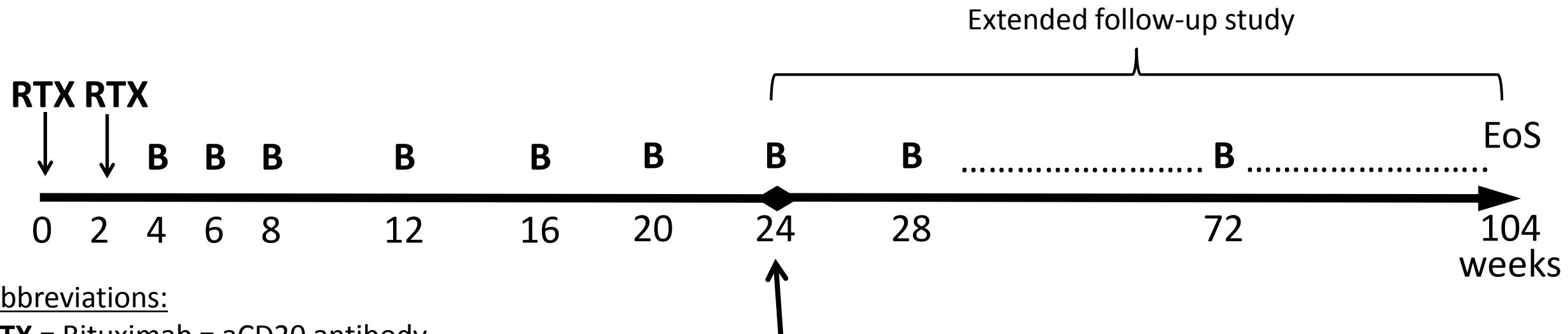
Optimaliseren van anti-B cel therapie?



Combining anti-CD20 with anti-BAFF in humans

YEAR	AUTHORS	JOURNAL	PATIENTS
2014	Teng et al.	Rheumatology	2 LN patients
2014	Fabris et al.	Clin Exp Rheum	1 Sjogren patient with MALT lymphoma
2016	Ruiz-Irastorza et al.	Clin Exp Rheum	1 LN patient
2016	Chizzolini et al.	Joint Bone Spine	1 LN patient

Optimaliseren anti-B-cel therapie: Synbiose 1 studie



Abbreviations:

RTX = Rituximab = aCD20 antibody

B = Belimumab = aBAFF antibody

RTX = 2x 1000mg

BLM = 10mg/kg

- I. - Reduction of pathogenic autoantibodies
- Inhibition of NETosis

- II. - Seroconversion
- Complement normalization
- Safety & feasibility
- Clinical response

Patient karakteristieken (n=16)

Demographics

Age, median (range)	31 (19-51)
Female sex	88%
Race	
White/Caucasian	31%
Black/African American	63%
Asian/Oriental	6%

SLE history

Disease duration in years, median (range)	11 (2-24)
No. of relapses, median (range)	3 (1-6)
SLICC ^A damage index, median (range)	1 (0-4)

Treatment history

Steroids	100%
Mycophenolate mofetil	100%
Cyclophosphamide	44%
Azathioprine	56%
Tacrolimus	6%
Rituximab	25%
Hydrochloroquine	88%

SLE at inclusion

Reasons for inclusion

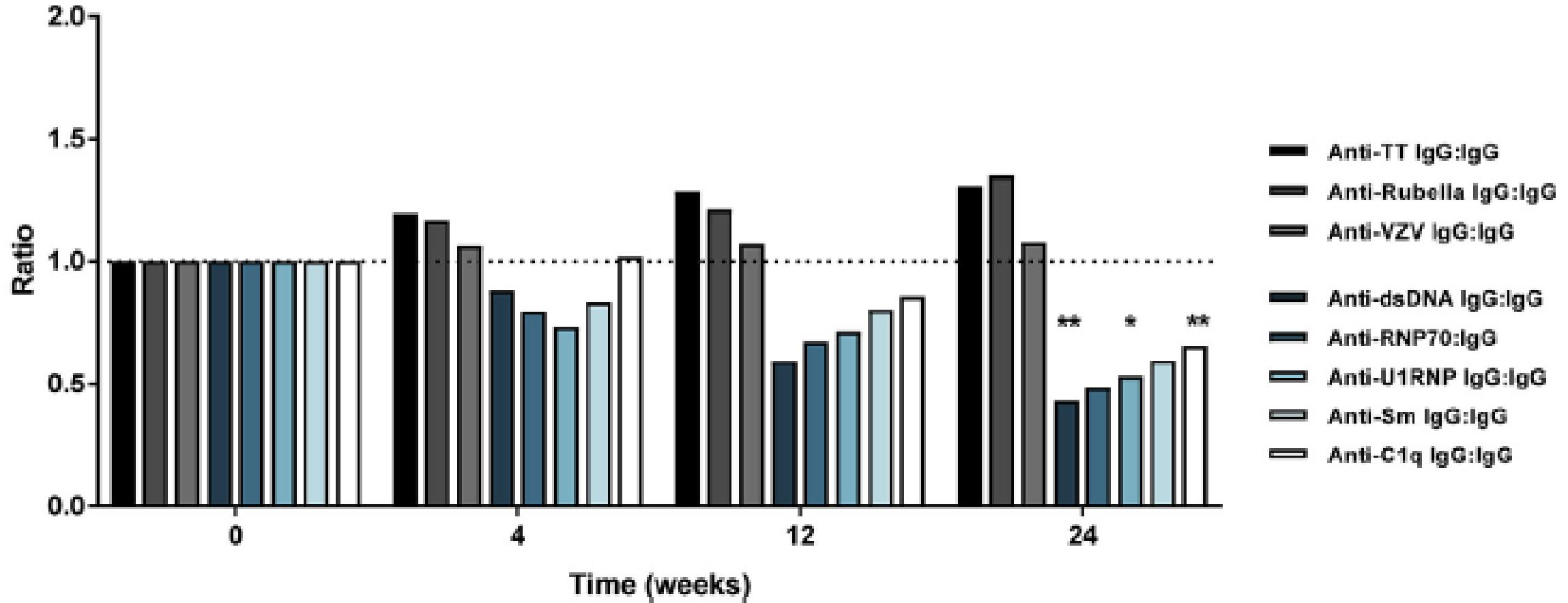
Renal flare 81%

Myelitis transversa 6%

Persistent disease activity despite treatment 13%

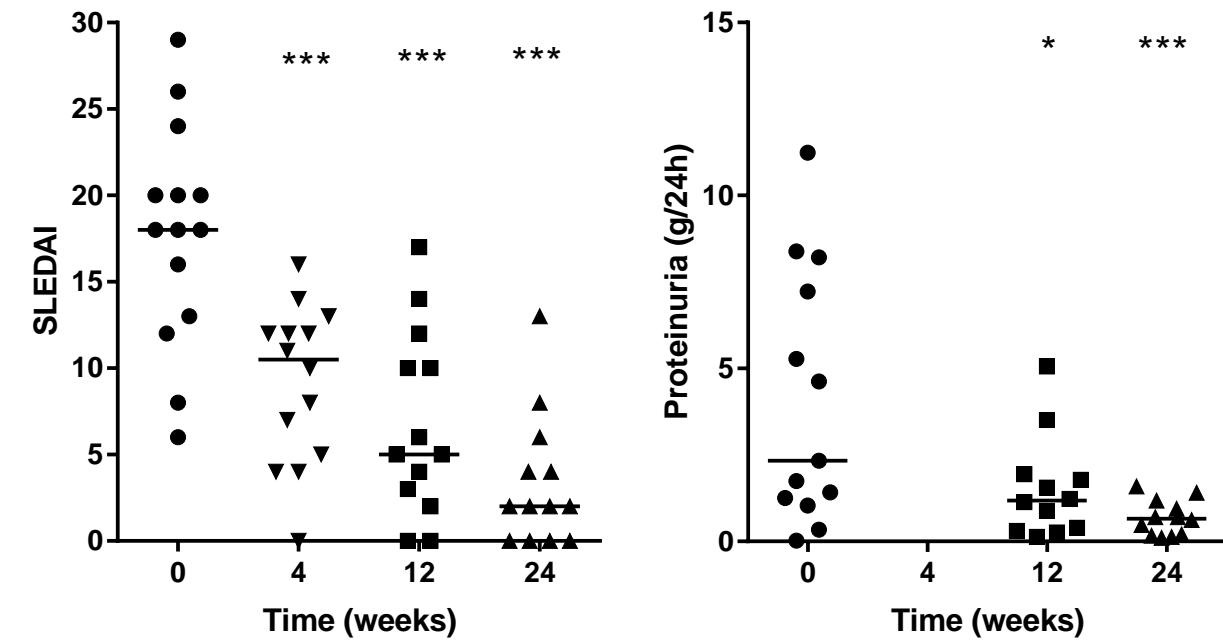
SLEDAI score, median (range) 18 (6-29)

Specifieke reductie ANAs na RTX+BLM

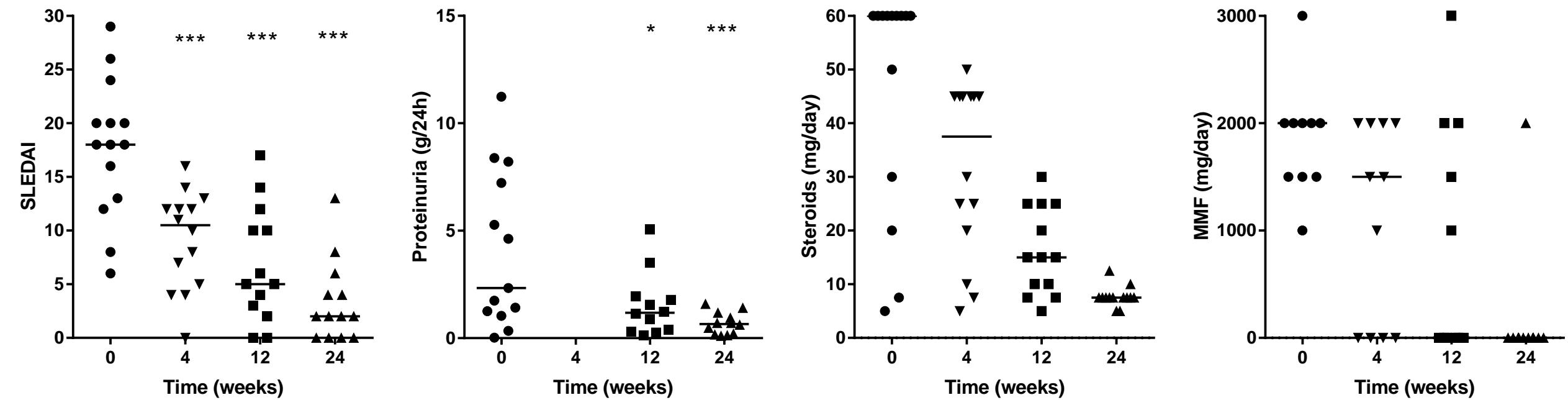


69% anti-DNA seroconversion

Goede klinische respons na RTX+BLM



Goede klinische respons na RTX+BLM mét tapering van immuunsuppressie

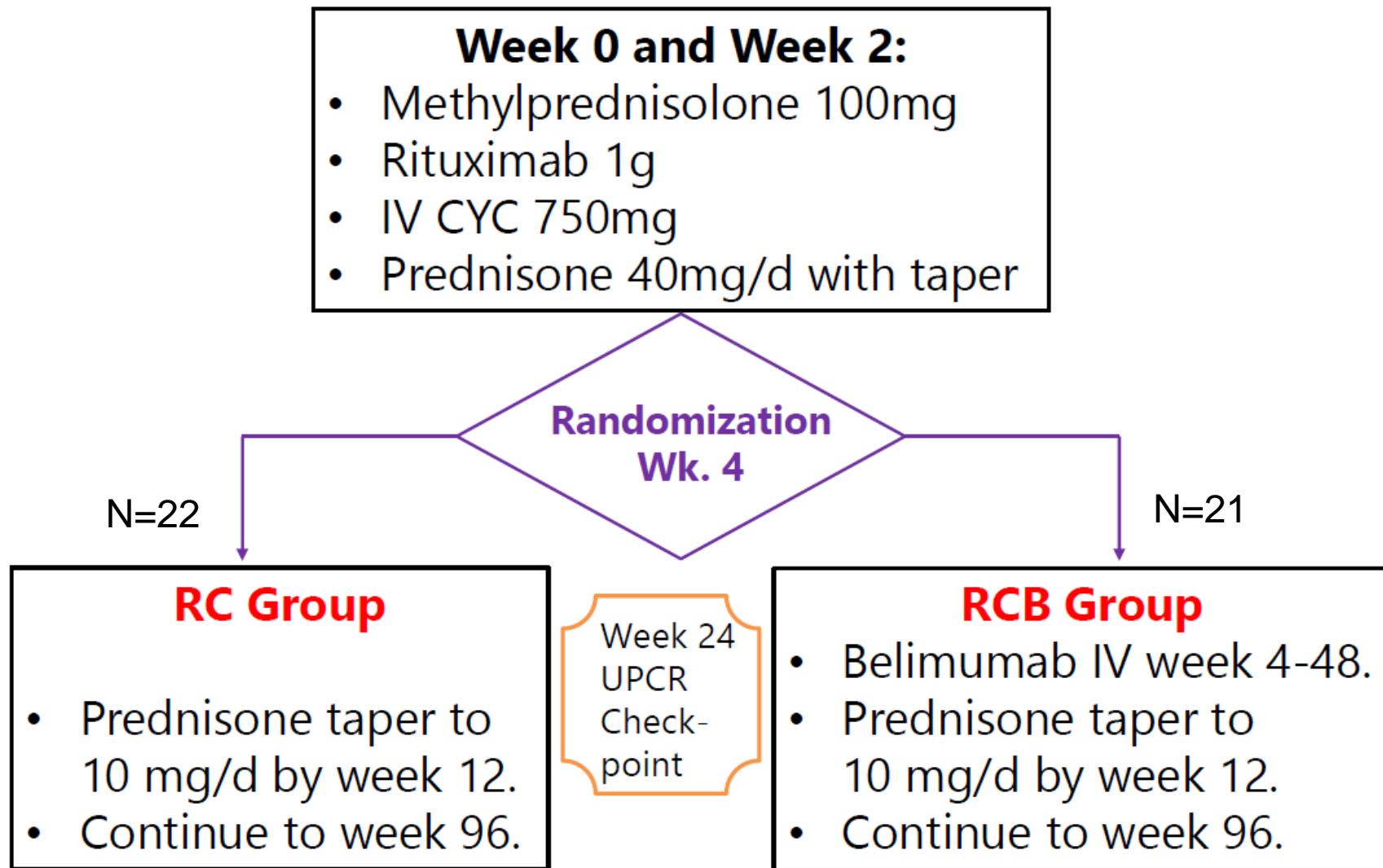


Adverse events

Any adverse event	41
Major infection/hospitalization	1 (2%)
Minor infection	15 (37%)
<i>Upper respiratory tract</i>	6
<i>Lower respiratory tract</i>	3
<i>Urinary tract</i>	3
<i>Sinusitis</i>	1
<i>Influenza</i>	1
<i>Herpes simplex</i>	1
HACA formation	4 (10%)
<i>Symptomatic</i>	1
<i>Asymptomatic</i>	3
Hypogammaglobulinemia (<4.0 g/l)	3 (7%)
Steroid-induced mood disorder/psychosis	1 (2%)
Diarrhea	5 (12%)
Myalgia	3 (7%)
Infusion-related reaction	2 (5%)
Headache	1 (2%)
Nausea	1 (2%)
OtherC	5 (12%)

Lange termijns klinische response

CALIBRATE studie (USA)



CALIBRATE studie (USA)

PRIMARY ENDPOINT

Grade 3 Infectious AE: MITT Sample

	RC (N=22)	RCB (N=21)	P value
Subjects with \geq 1 grade 3 or higher infectious AE through week 48	5 (23%)	2 (9%)	0.254

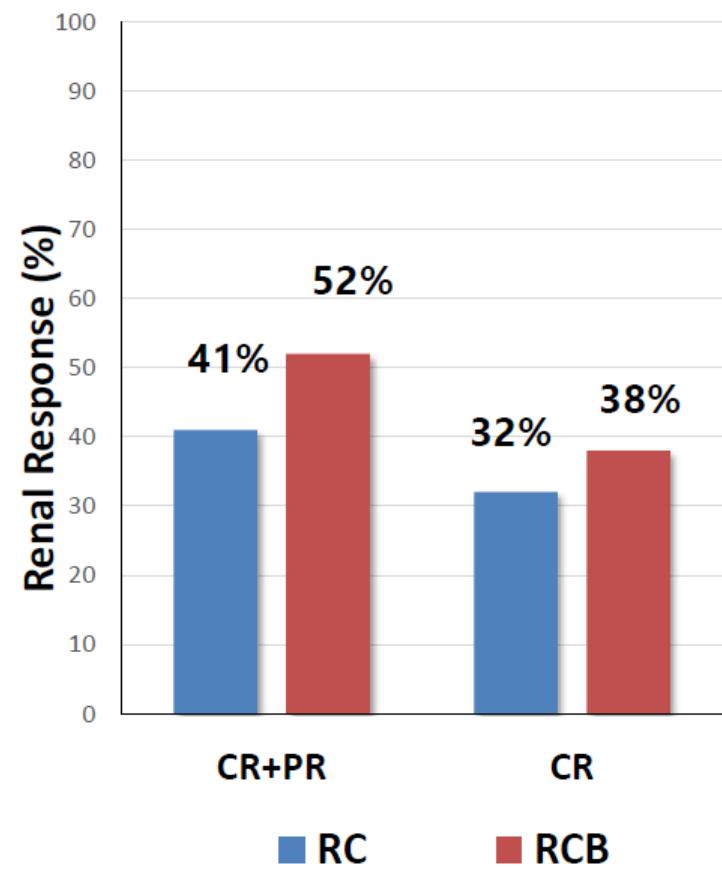
RC group: 2 pneumonia, 2 urinary tract infections, 1 cellulitis.

RCB group: 1 urinary tract infection, 1 soft tissue abscess + cellulitis.

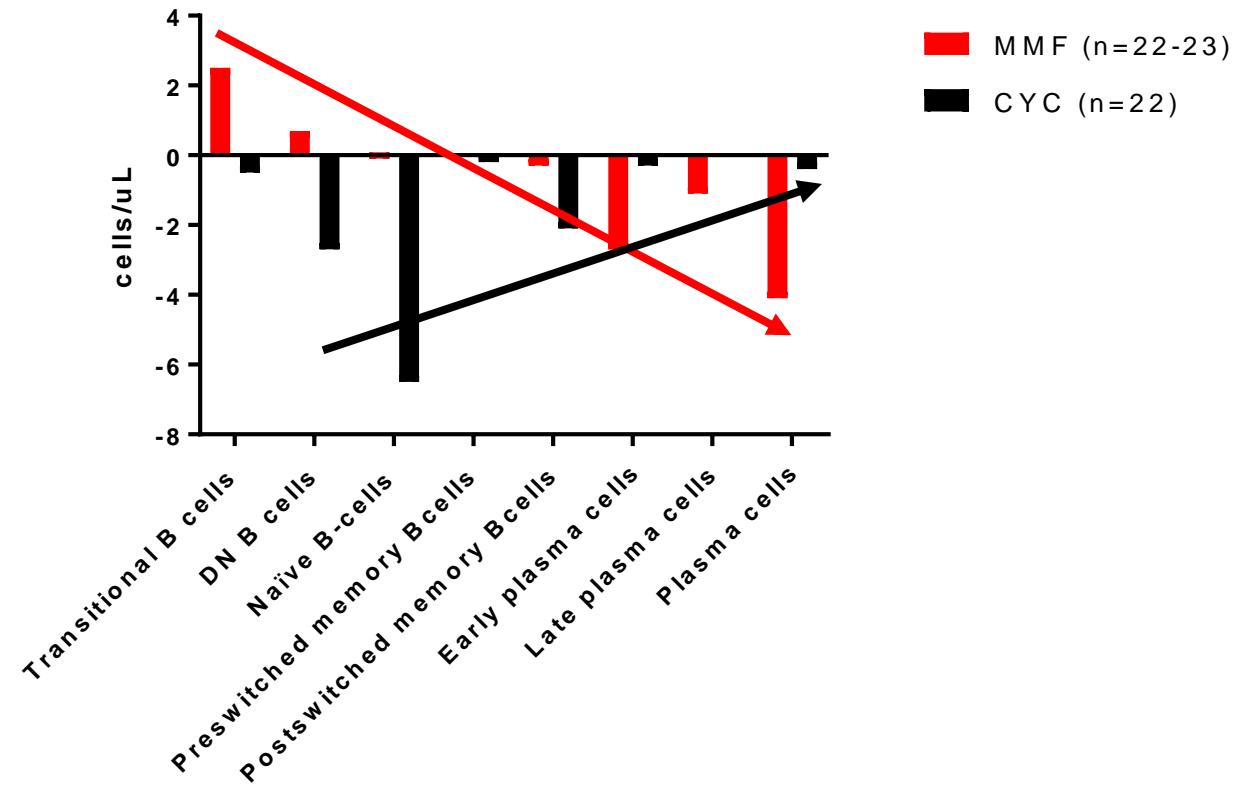
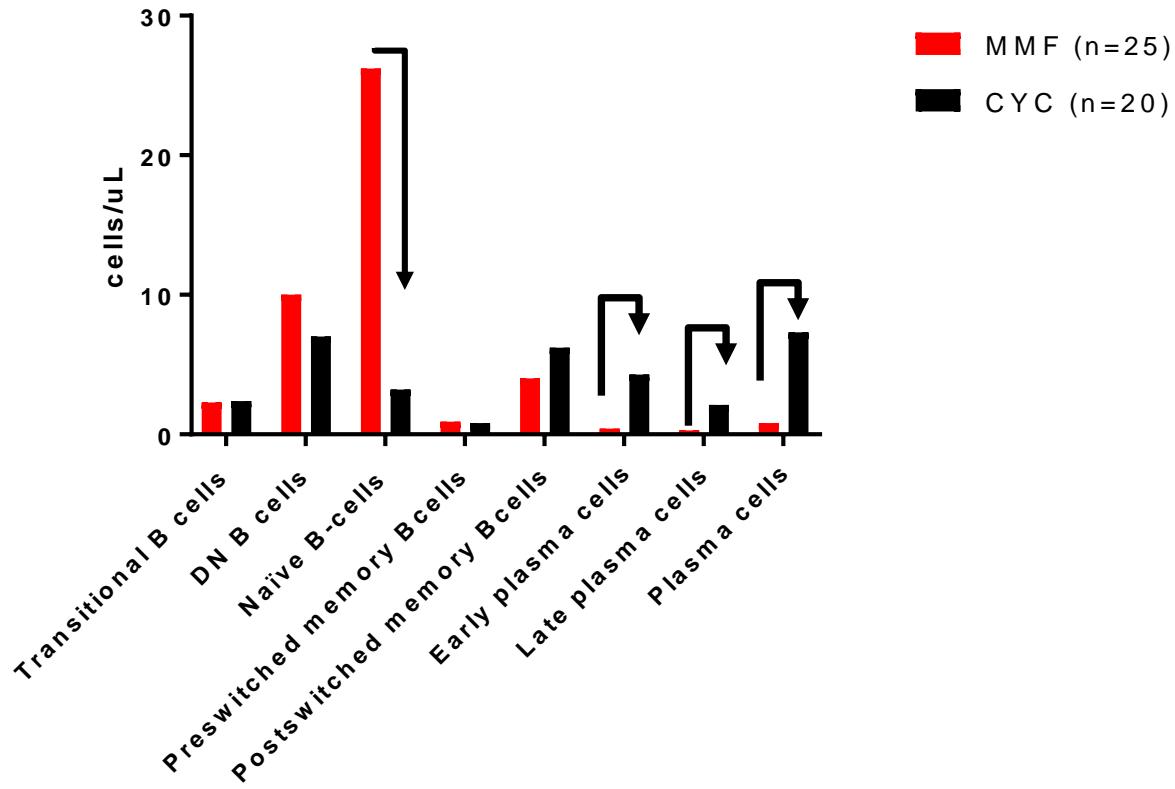
All AEs resolved

SECONDARY ENDPOINT

Week 48



B-cel immuniteit ten tijde van MMF versus CYC

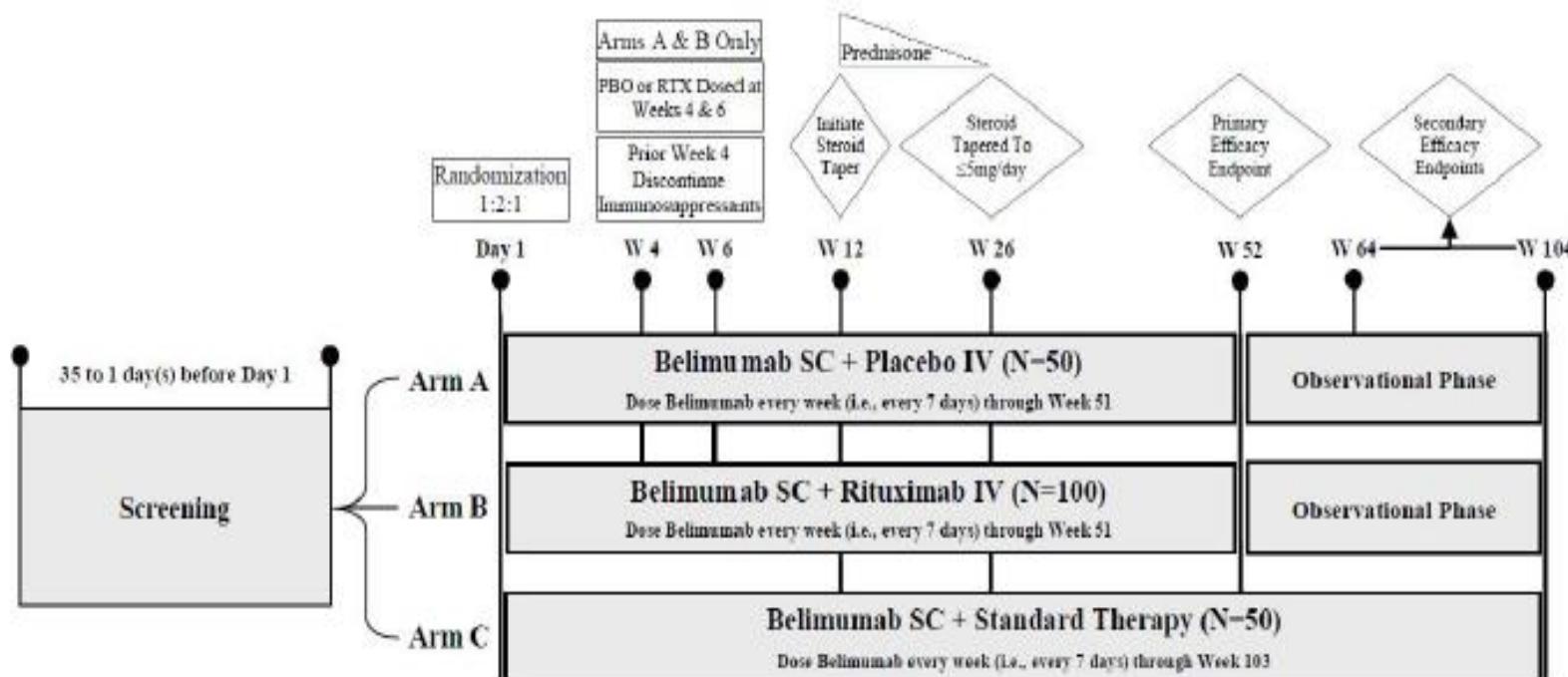


Studies naar combinatietherapie Rituximab + Belimumab

Non-renal SLE

BEAT-LUPUS (Phase 2 RCT, UC London) → Add-on RTX+placebo versus RTX + BLM

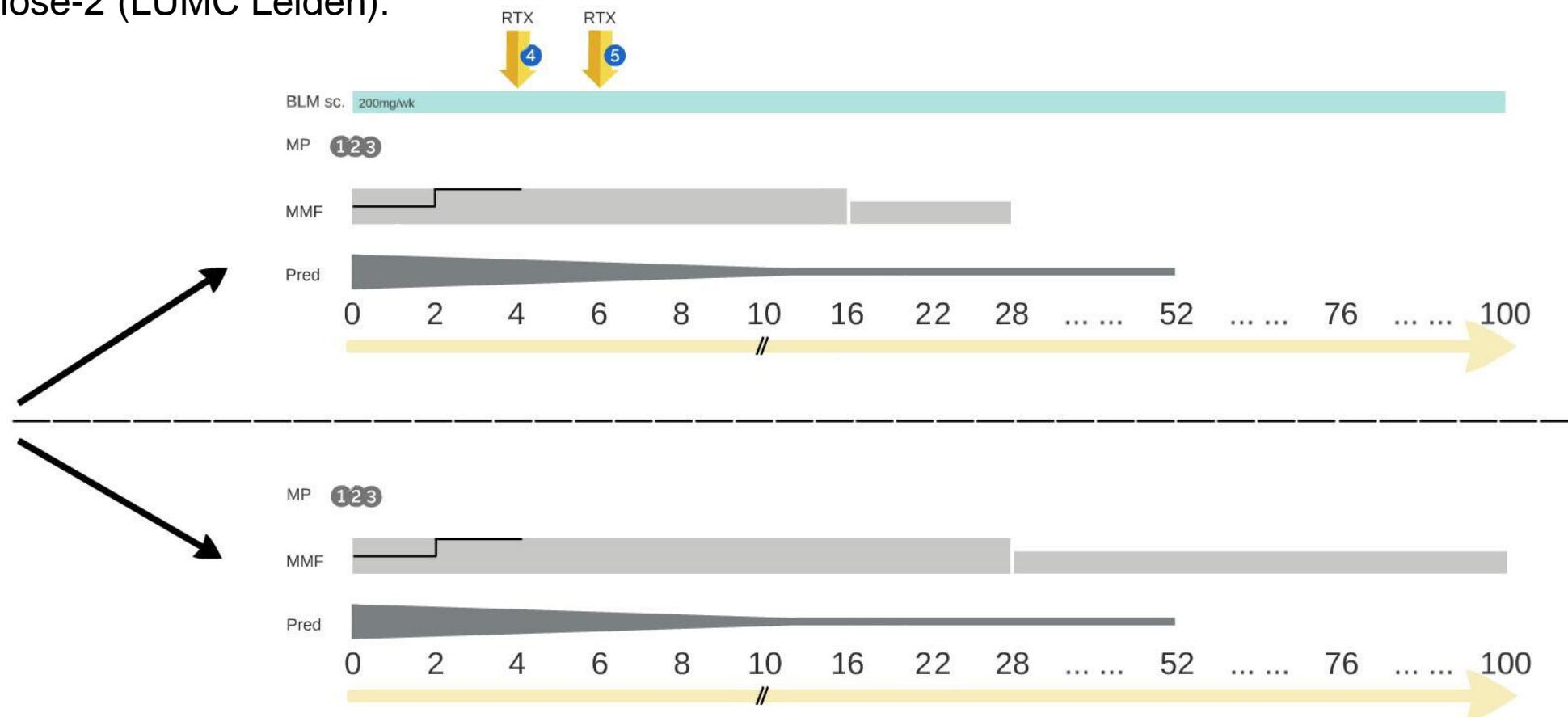
BLISS-BELIEVE (Phase 3 RCT, Global - GSK)



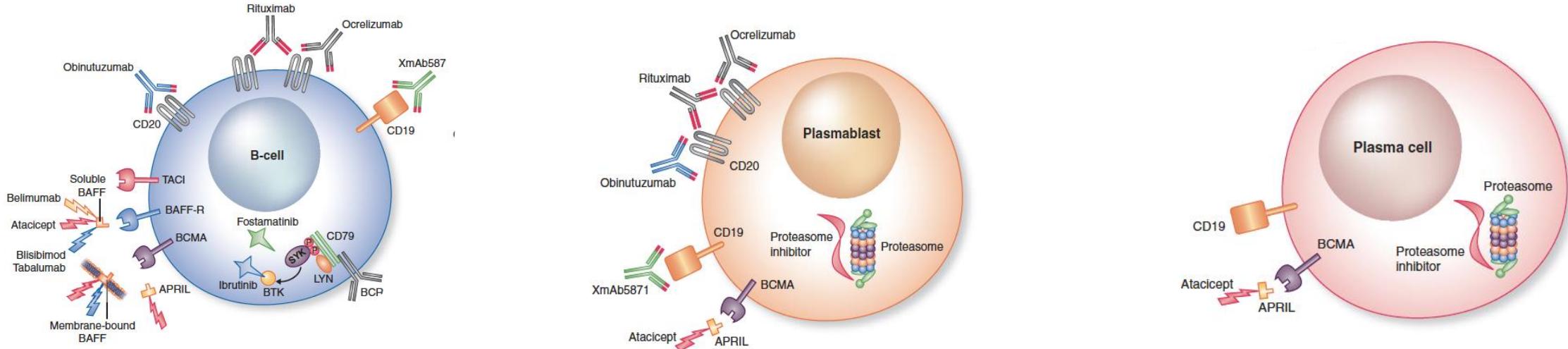
Studies naar combinatietherapie Rituximab + Belimumab

Lupus Nefritis

Synbiose-2 (LUMC Leiden):



Optimaliseren van anti-B cel therapie?



Rituximab

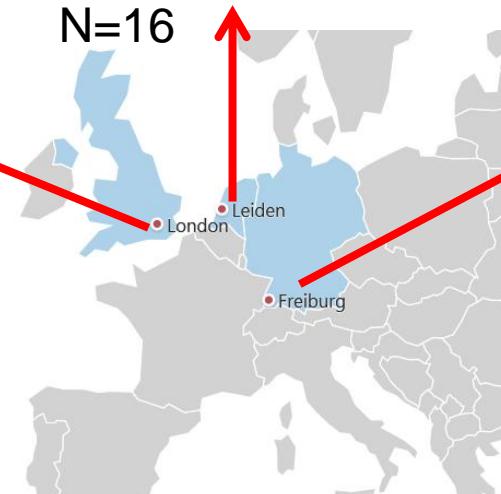
N=16

Rituximab + Belimumab

N=16

Bortezomib

N=12



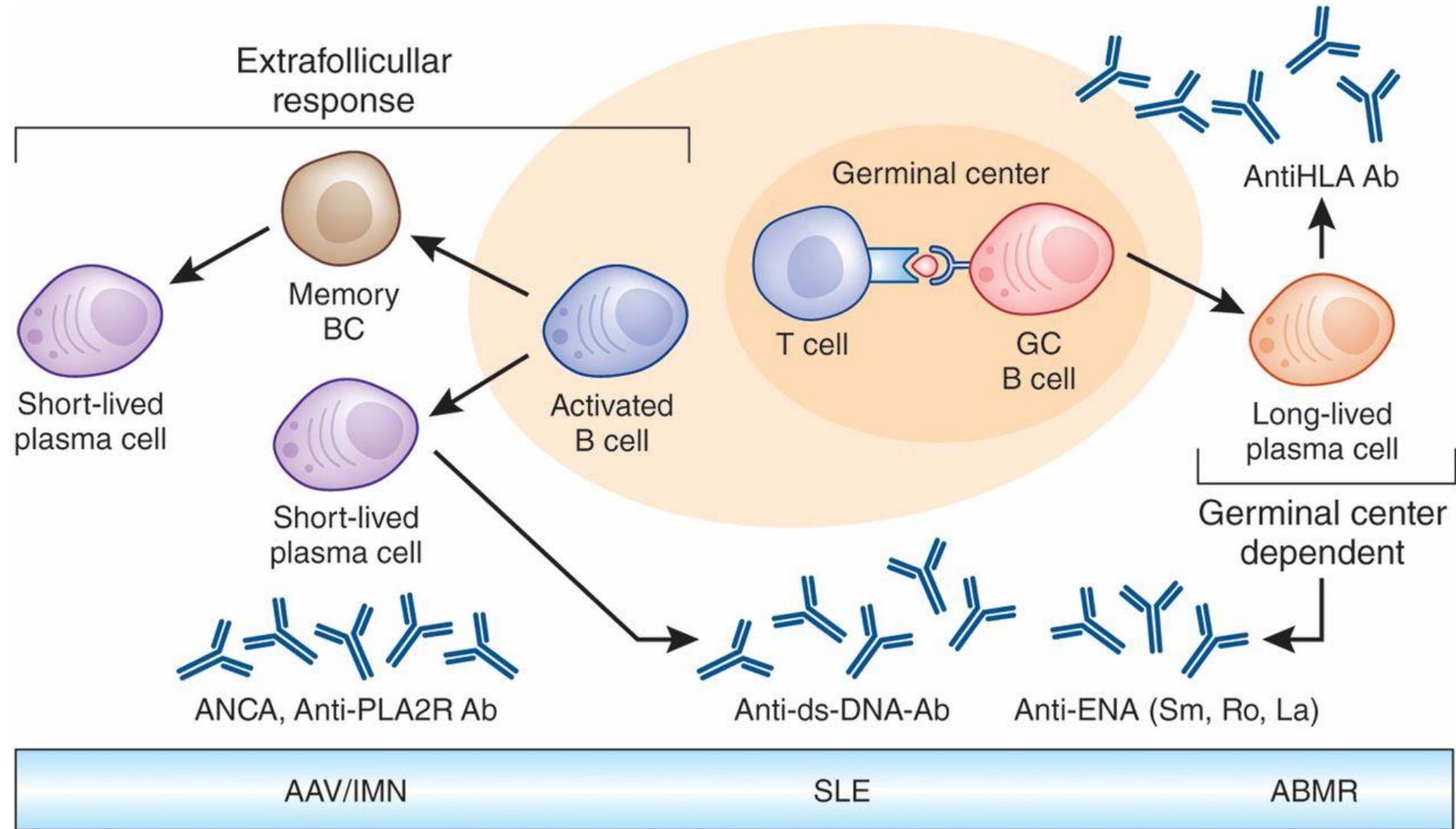
Optimaliseren van anti-B cel therapie?



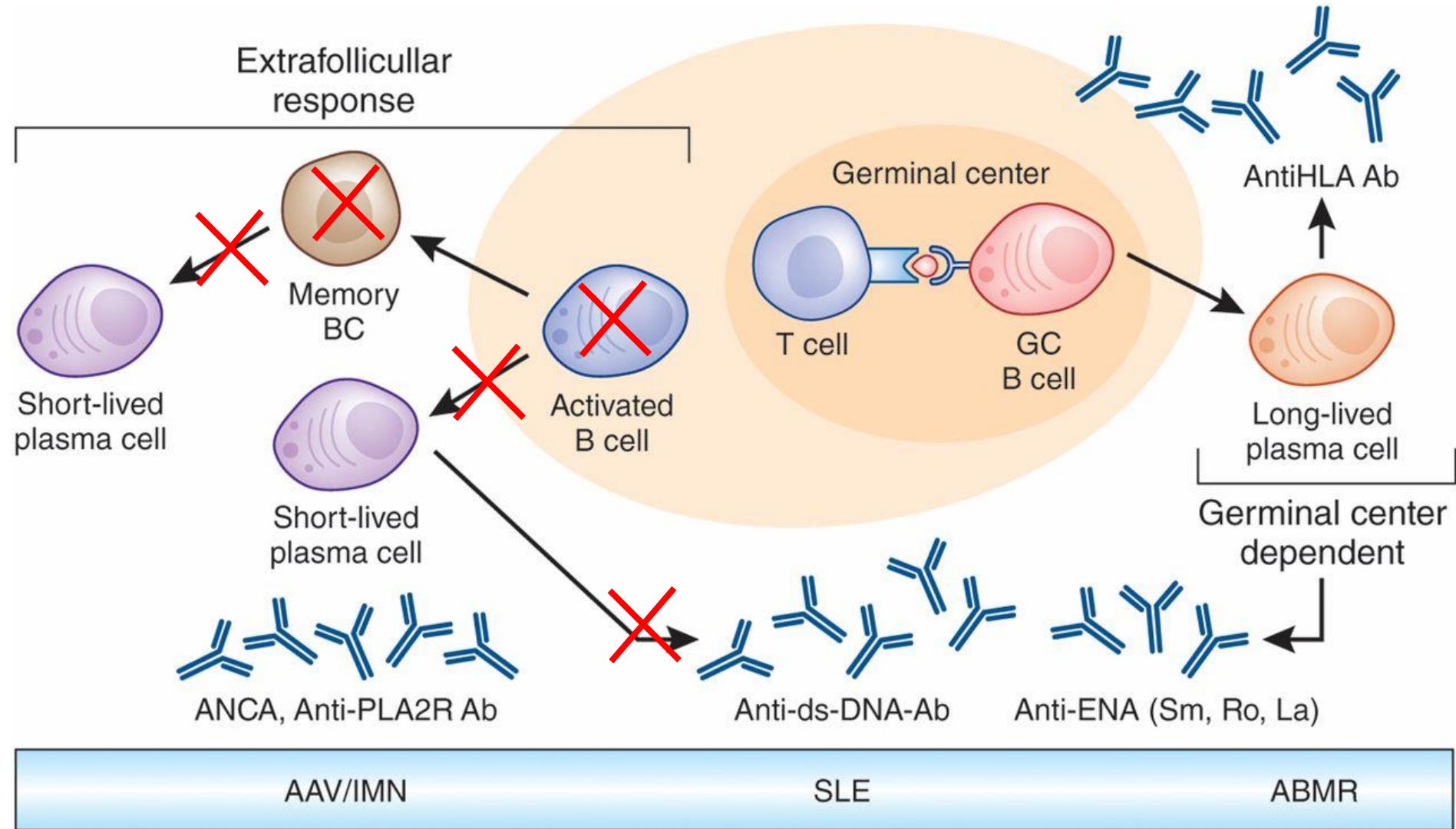
Optimaliseren van anti-B-cel therapie

Take Home Messages:

Abberante B-cel immuniteit bij LN



Take Home Messages: Combinatietherapie Rituximab + Belimumab



LuVaCs ExpertiseCentrum

Lupus, Vasculitis & Complement gemedieerde Systeemziekten

Patients and their families

Blood donors

Dept. of Nephrology, LUMC

Drs. T. Kraaij

Drs. S. Kamerling

Drs. L.S. van Dam

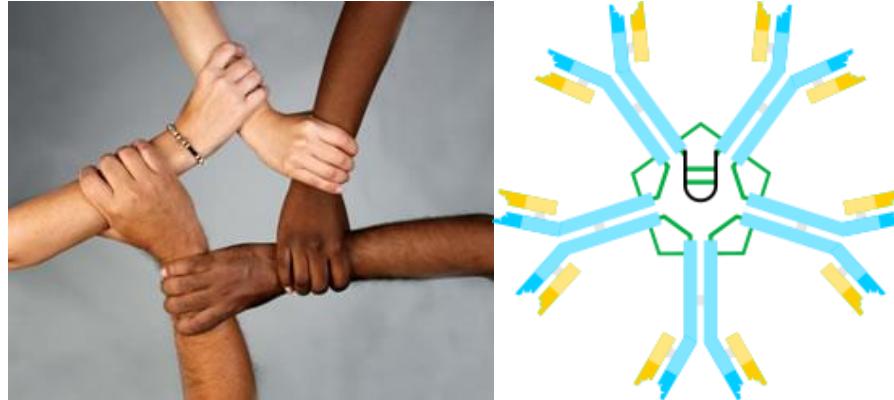
Drs. E.J. Arends

Drs. O.W. Bredewold

Prof. dr. A.F. Cohen

Prof. dr. C. van Kooten

Prof. dr. T.J. Rabelink



Dept. of Rheumatology, LUMC

Dr. U. Scherer

Dr. J. Desai

Prof. dr. R.E.M. Toes

Prof. dr. T.W.J. Huizinga

Dept. of Clinical Chemistry, LUMC

Dr. J.A. Bakker

Dept. of Pulmonology, LUMC

Dr. M.K. Ninaber

Dept. of ENT, LUMC

Dr. C.C. Wever

Dr. A.P.M. Langeveld

Dept. of Pathology, LUMC

Dr. I.M. Bajema

Dept. of Clinical Epidemiology, LUMC

Prof. Dr. O.M. Dekkers



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