Nieuwste behandelingen in SLE

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Klinisch immunoloog

Afdeling Reumatologie & Klinische Immunologie

UMCG

Disclosure belangen spreker

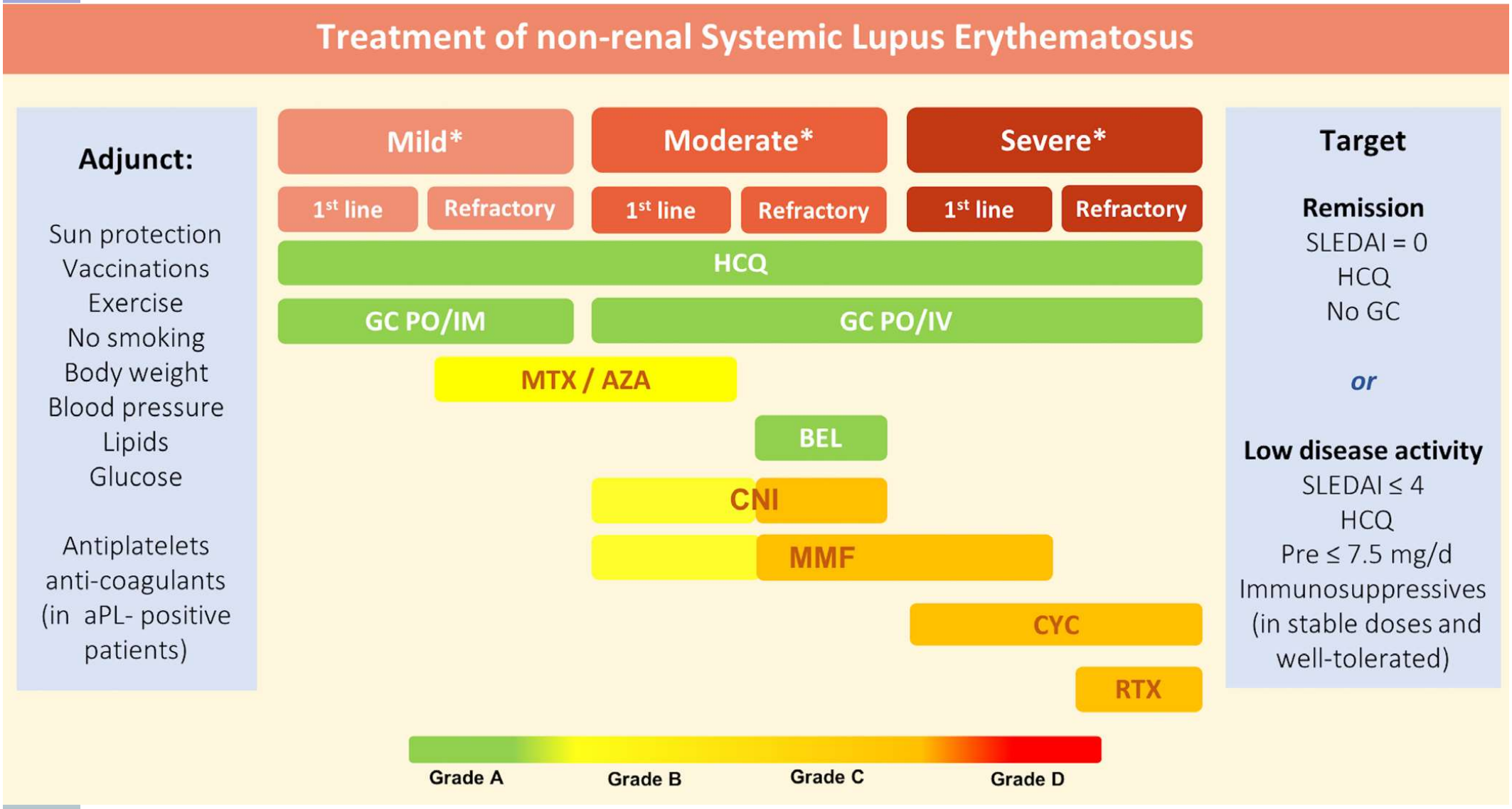
(potentiële) belangenverstrengeling	geen
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Bedrijfsnamen
• Adviesraad	• GSK • Astra Zeneca • Otsuka

Behandeling SLE

- Complex
- Heterogene aandoening
- Actieve ziekte vs remissie
- Vele middelen, weinig RCTs
- Bijwerkingen medicatie:
  - Infecties
  - Atherosclerose
  - Osteoporose


SOMETHING OLD,
SOMETHING NEW,
SOMETHING of the future

EULAR recommendations



Fanouriakis et al, ARD 2019

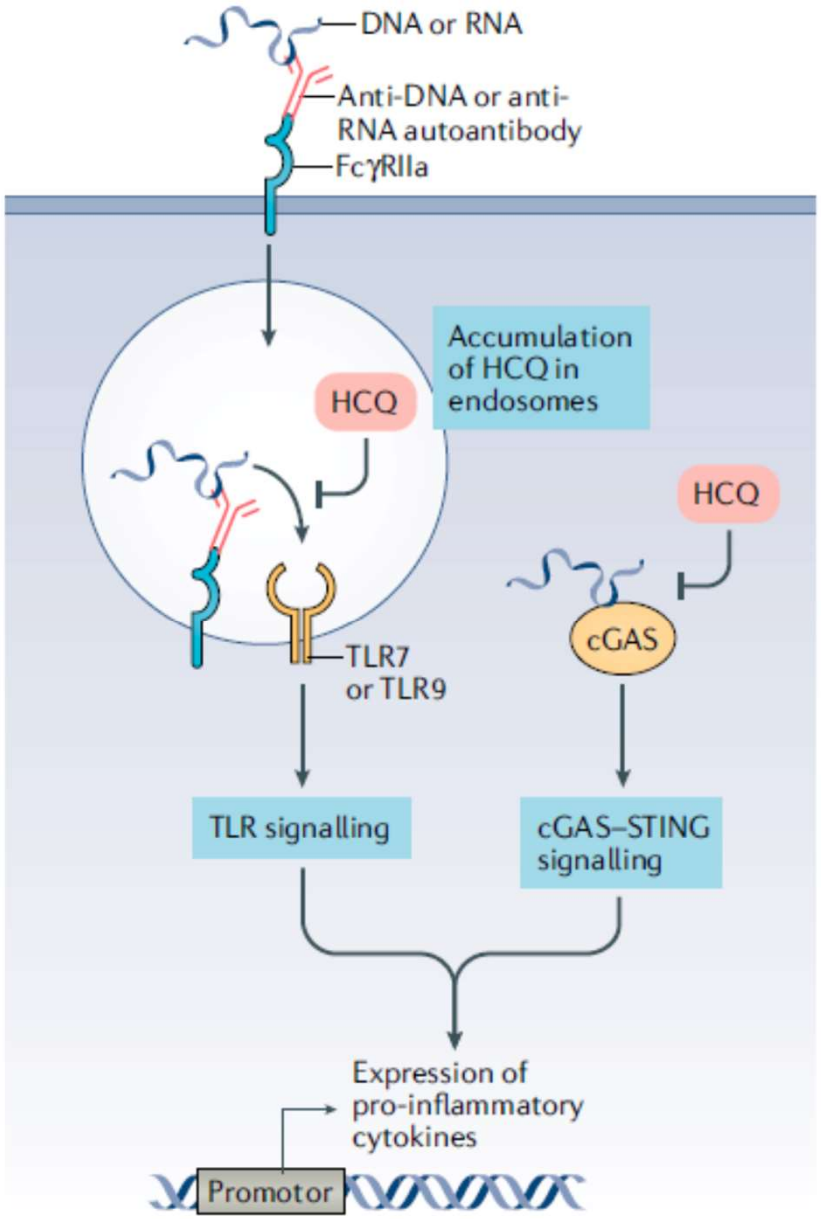
Something old

- Hydroxychloroquine

- Prednisolon maar dan juist minder!

Hydroxychloroquine

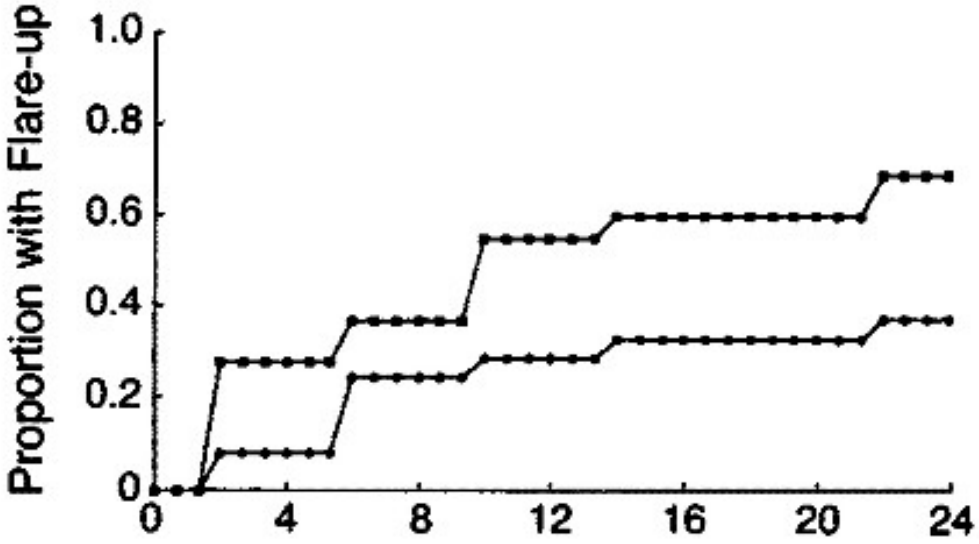
- Aanbevolen voor elke patient
- Effecten in SLE zelf
- Andere positieve effecten
- Veilig tijdens zwangerschap
- Belangrijkste bijwerking: retinale toxiciteit
- Therapietrouw…. (7-44%)



Schrezenmeier et al, Nat Reviews Rheum 2020
Costedoat et al, J Rheum 2015

Effecten in SLE

- Algemeen:
  - Betere survival
  - Minder ziekte activiteit
- Nefritis:
  - Minder corticosteroïden
  - Langere tijd tot relapse
  - Langere tijd tot nierfalen

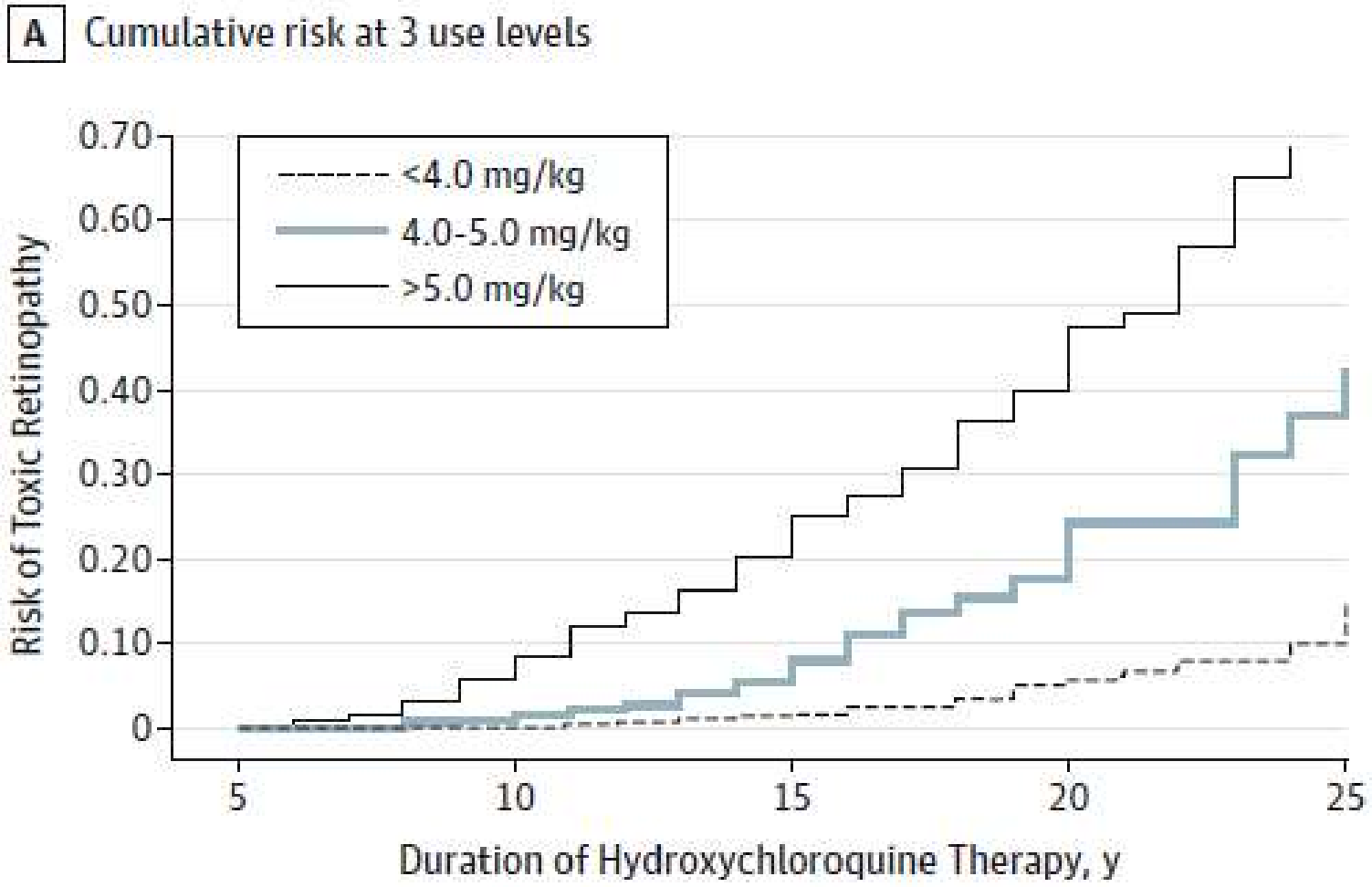


Number of Patients at Risk

Hydroxychloroquine	25	23	18	17	16	16	15
Placebo	22	16	14	10	9	9	6

Canadian HCQ group, NEJM 1991

Retinopathie



No. at risk					
<4.0 mg/kg	1196	766	387	136	34
4.0-5.0 mg/kg	632	386	190	61	12
>5.0 mg/kg	533	310	139	41	6

Melles et al, JAMA 2014

Something old

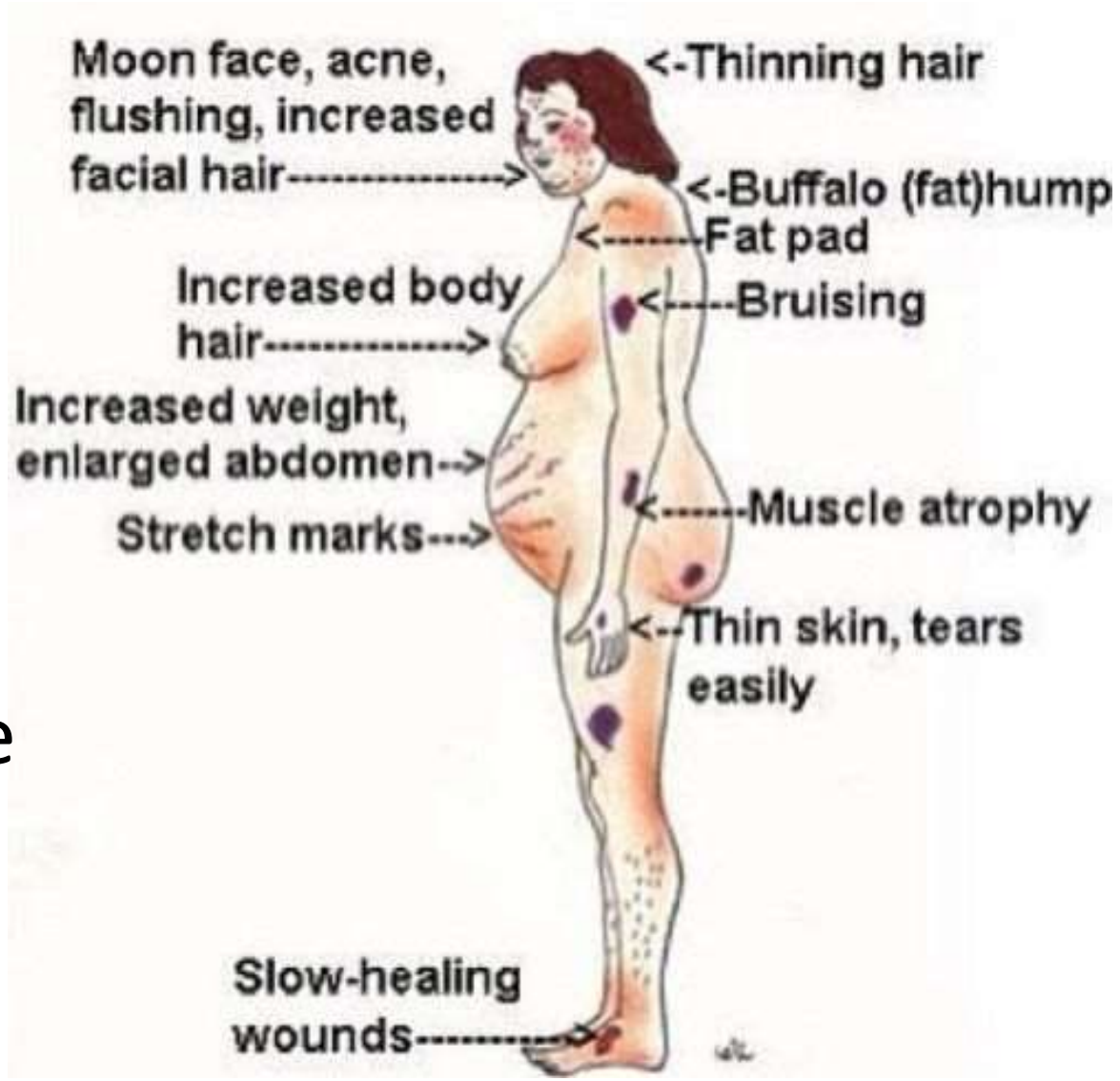
- Hydroxychloroquine
- Prednisolon, maar dan juist minder!

Dosering prednisolon

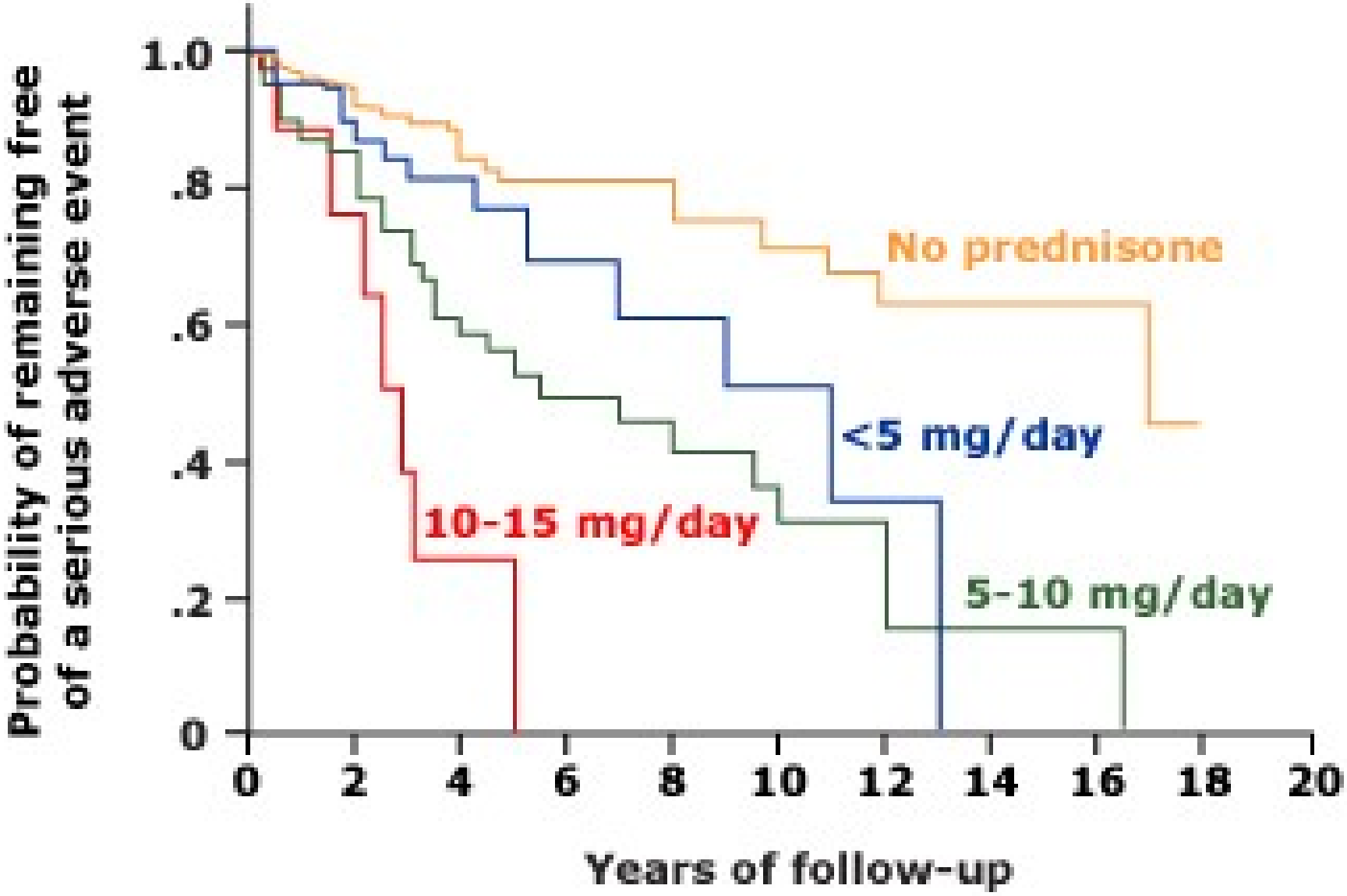
- Vele verschillende afbouwschema's
- Vaak lang en relatief hoge dosering
- Echter veel bijwerkingen en schade (SLICC) door prednisolon

Bijwerkingen

- Infecties
- Cataract
- Osteoporose
- Osteonecrose
- Diabetes
- Gewichtstoename
- Huid
- Atherosclerose



Cumulatief effect - relatie dosering



Saag, KG et al. Am J Med 1994; 96:115

Conclusie prednisolon

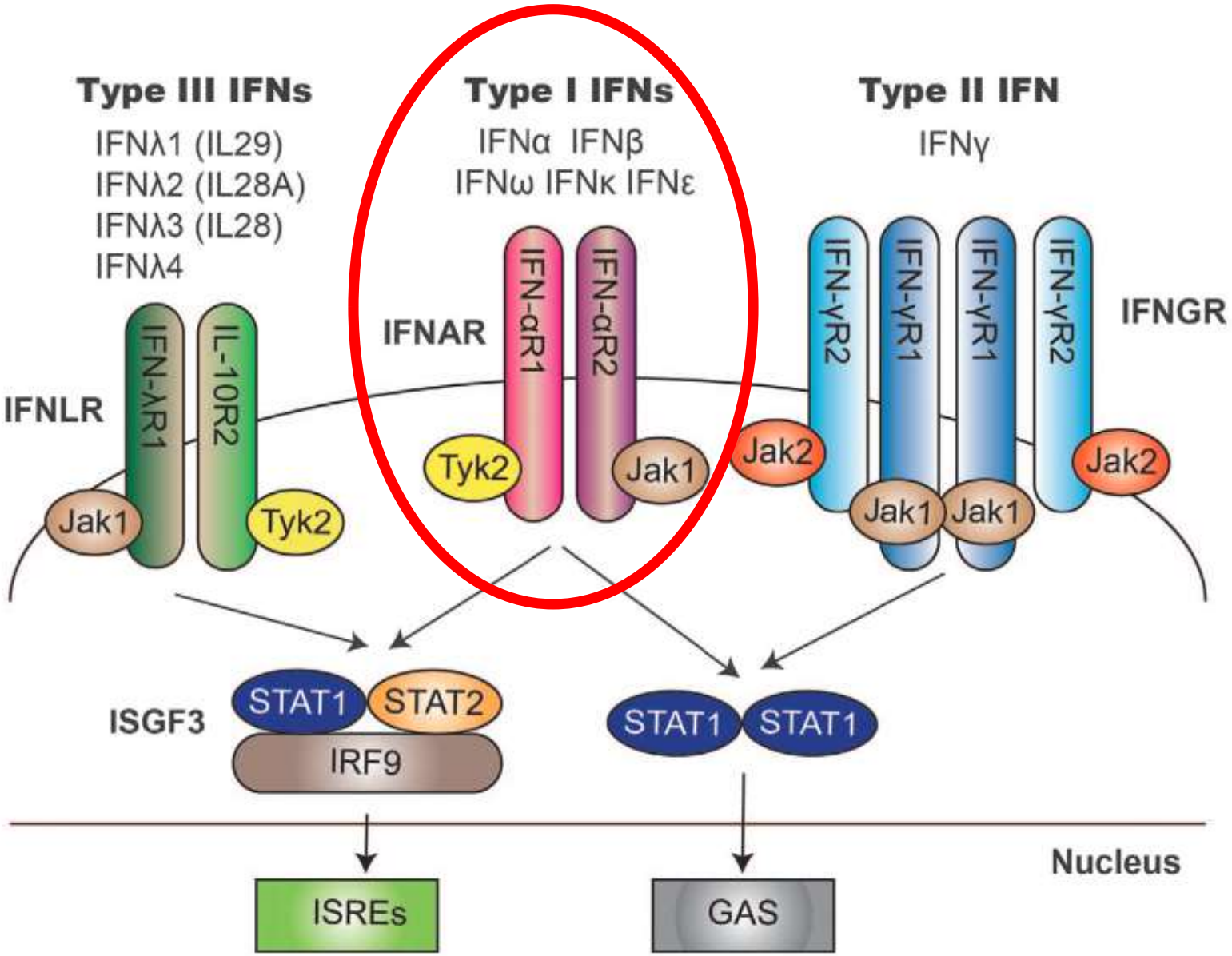
Zorg voor lage cumulatieve dosering:

- Sneller afbouwen
- Lagere onderhoudsdosering nastreven:
  - Treat to target: prednisolon ≤5 mg/dag
- Eerder prednisolonsparend middel overwegen
- Wellicht meer iv en dan geen of veel lagere orale dosis

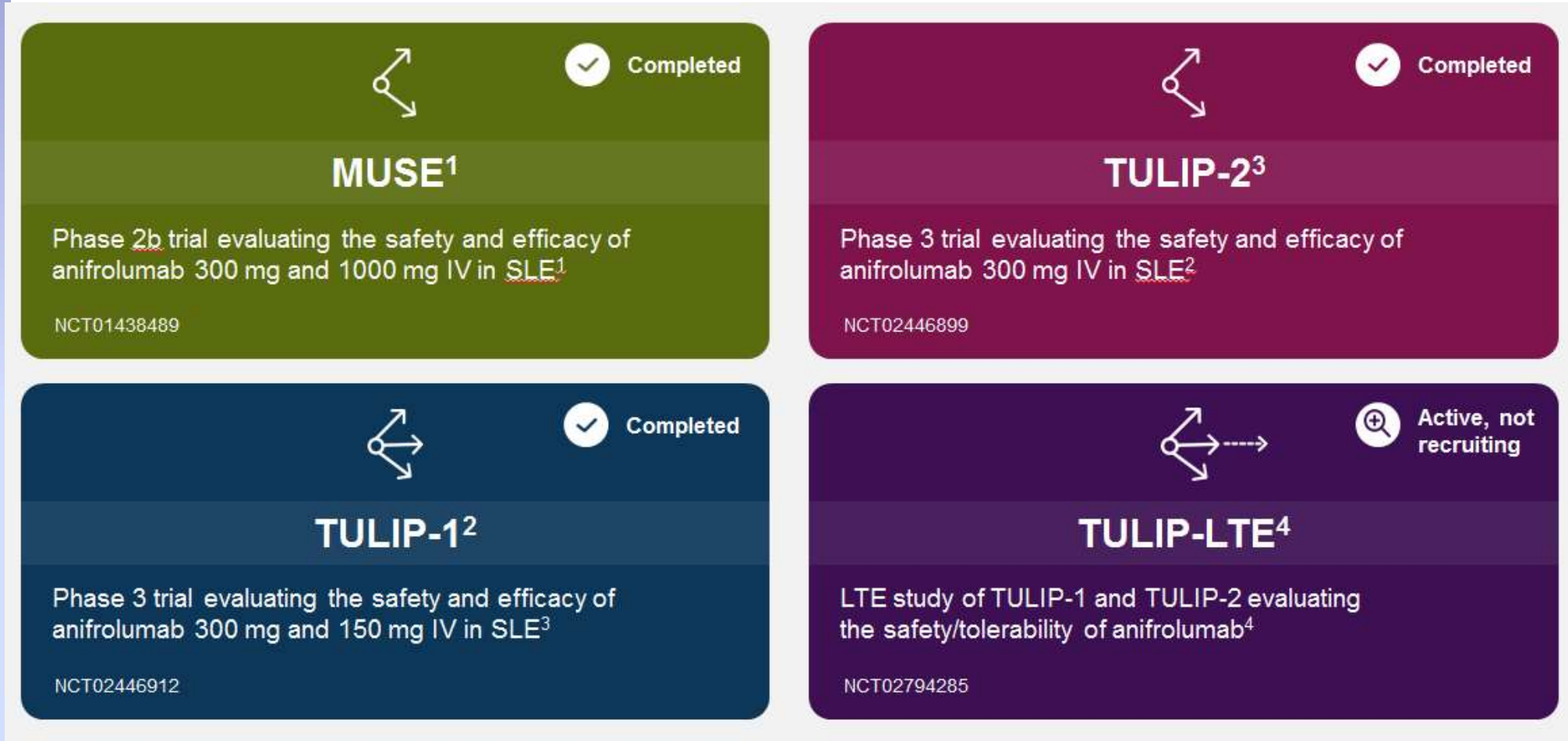
Something new

- Anifrolumab

Anifrolumab = humaan monoklonaal antilichaam tegen IFNAR



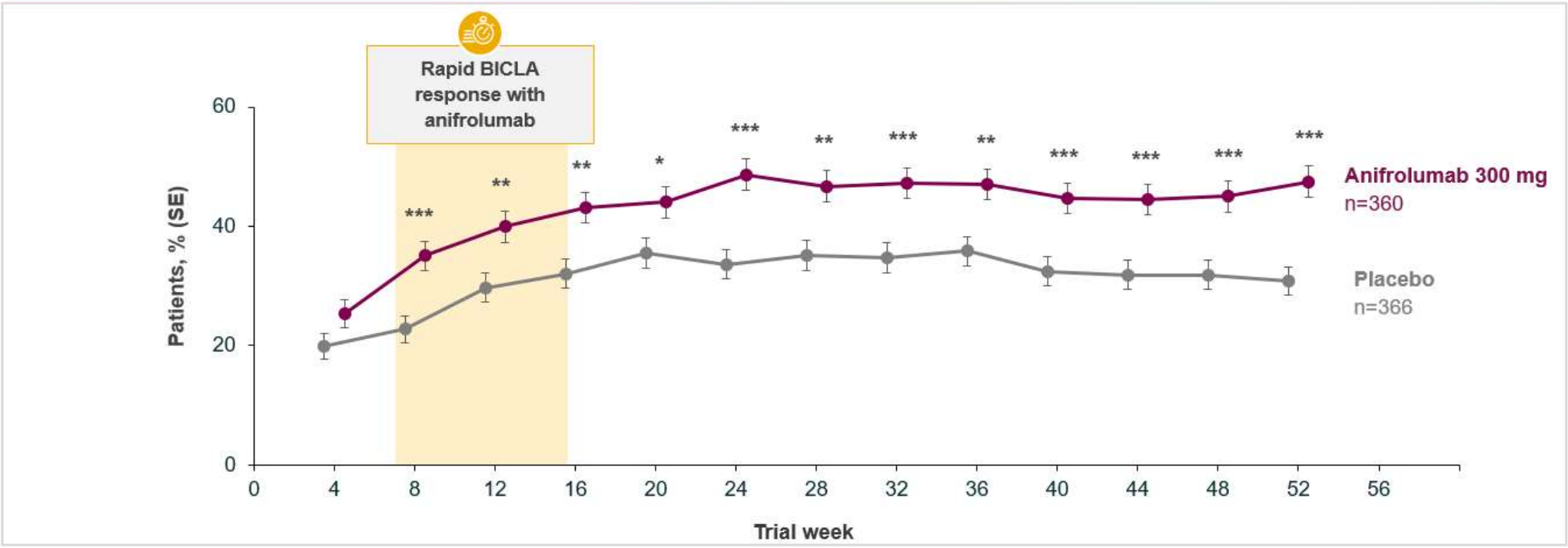
Trials met Anifrolumab



1. Furie R, et al. *Arthritis Rheumatol*. 2017
2. Furie RA, et al. *Lancet Rheumatol*. 2019
3. Morand EF, et al. *N Engl J Med*. 2020
4. Trial NCT02794285. ClinicalTrials.gov

BICLA respons

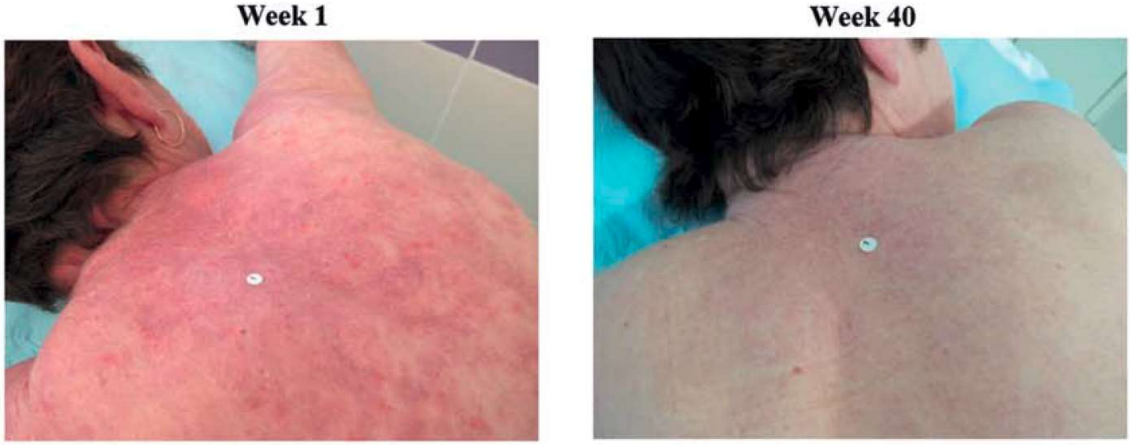
Proportion of Patients With BICLA Response Over Time[1,2]



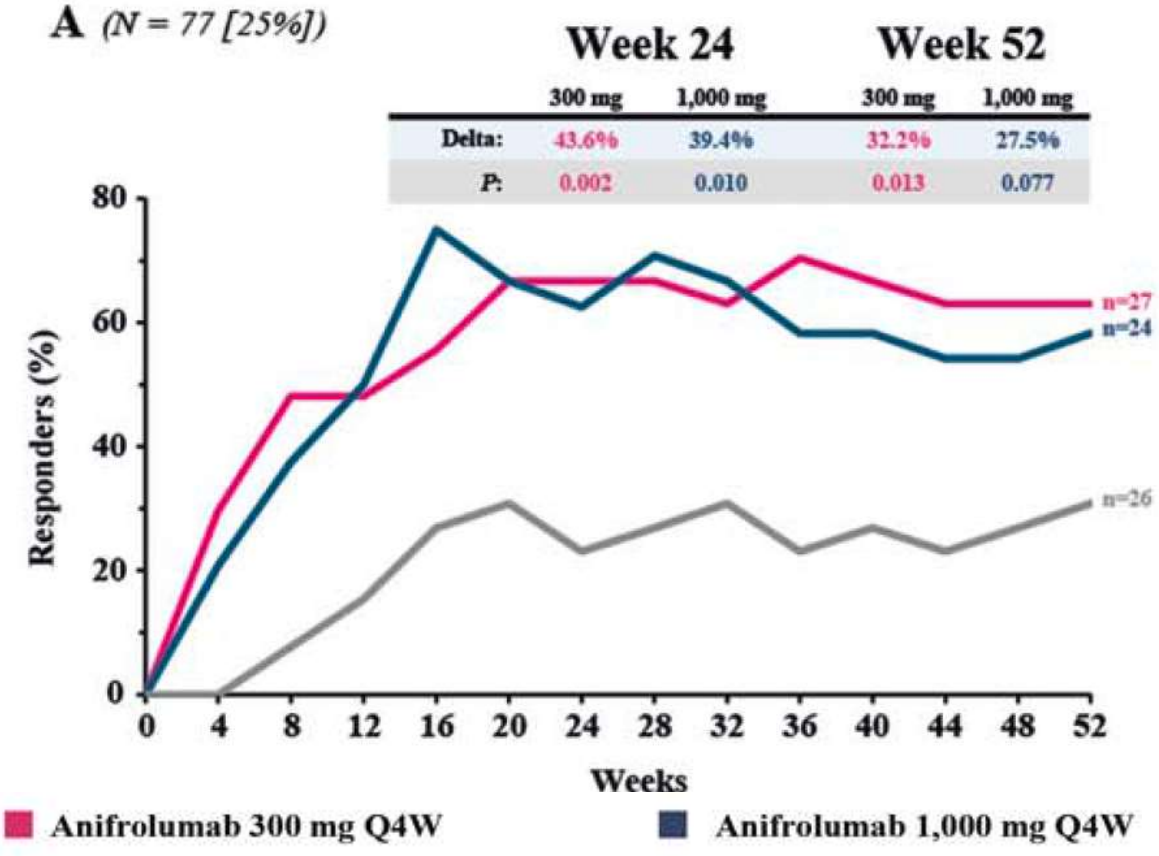
More patients showed a BICLA response as early as W8 and W12 in the anifrolumab group vs placebo, a significant difference that persisted over the duration of the trial[2]

Vooral effect op huid en gewrichten

Effect op de huid: CLASI score



Patient was receiving anifrolumab 300 mg Q4W



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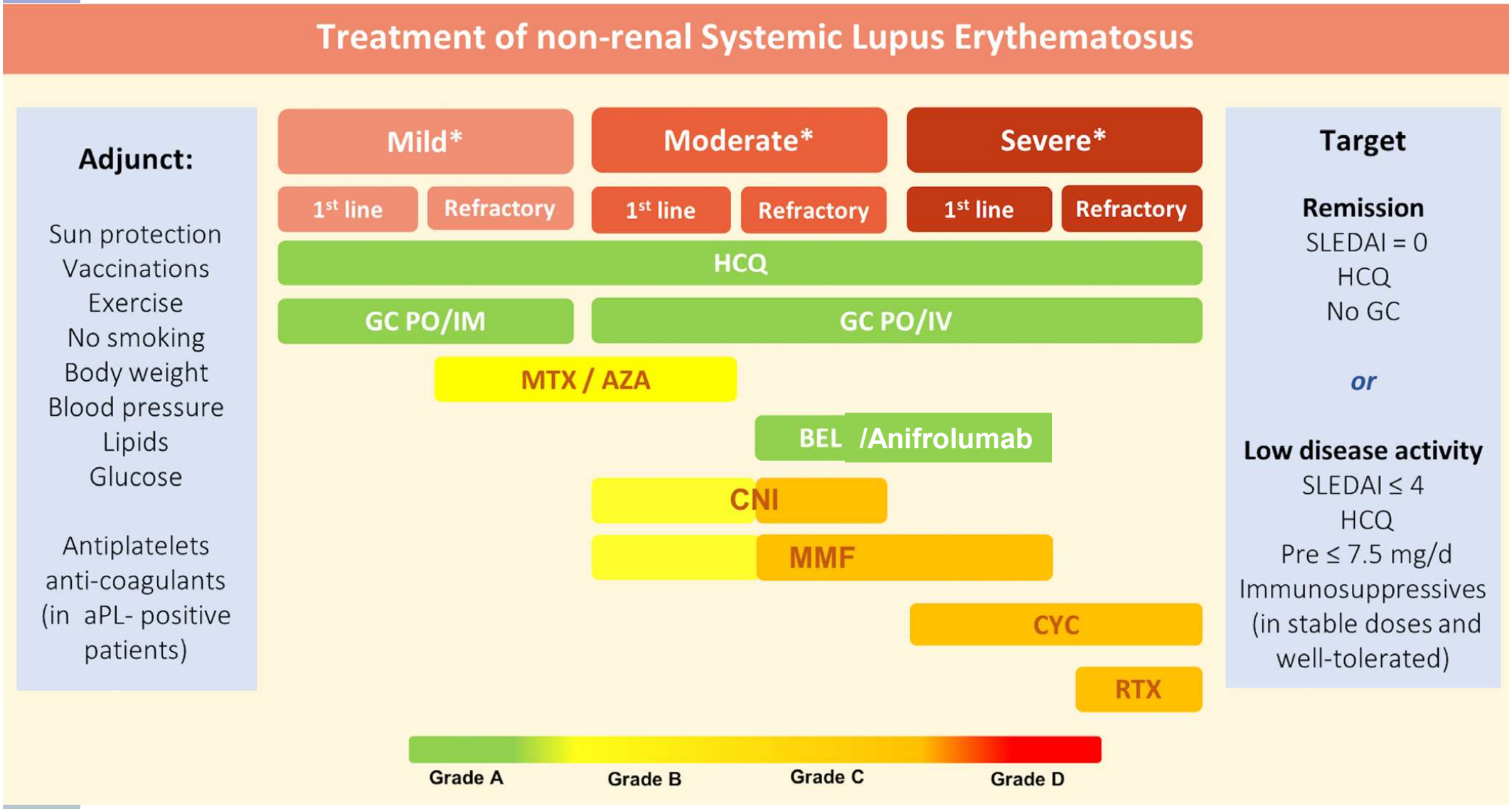
Furie et al A&R, 2016

Anifrolumab

- Goedgekeurd als add-on therapie voor behandeling van SLE patienten met matige tot ernstige ziekteactiviteit ondanks standaard behandeling
- Met name huid manifestaties en arthritis
- Overweeg herpes zoster vaccinatie

EULAR recommendations



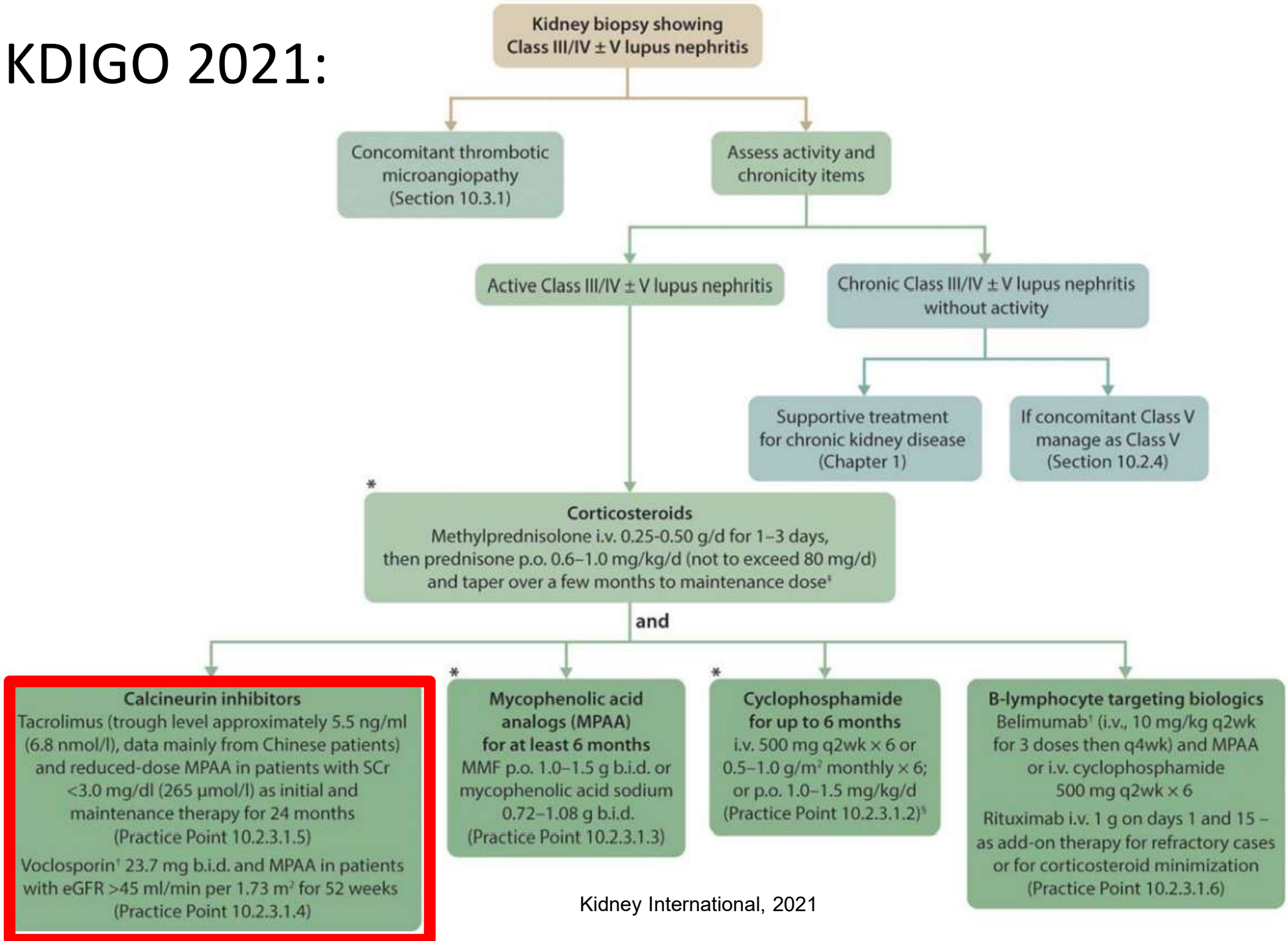
Fanouriakis et al, ARD 2019

Something relative new

- Anifrolumab
- Calcineurine remmers
  - Voclosporine

Lupus nephritis

KDIGO 2021:



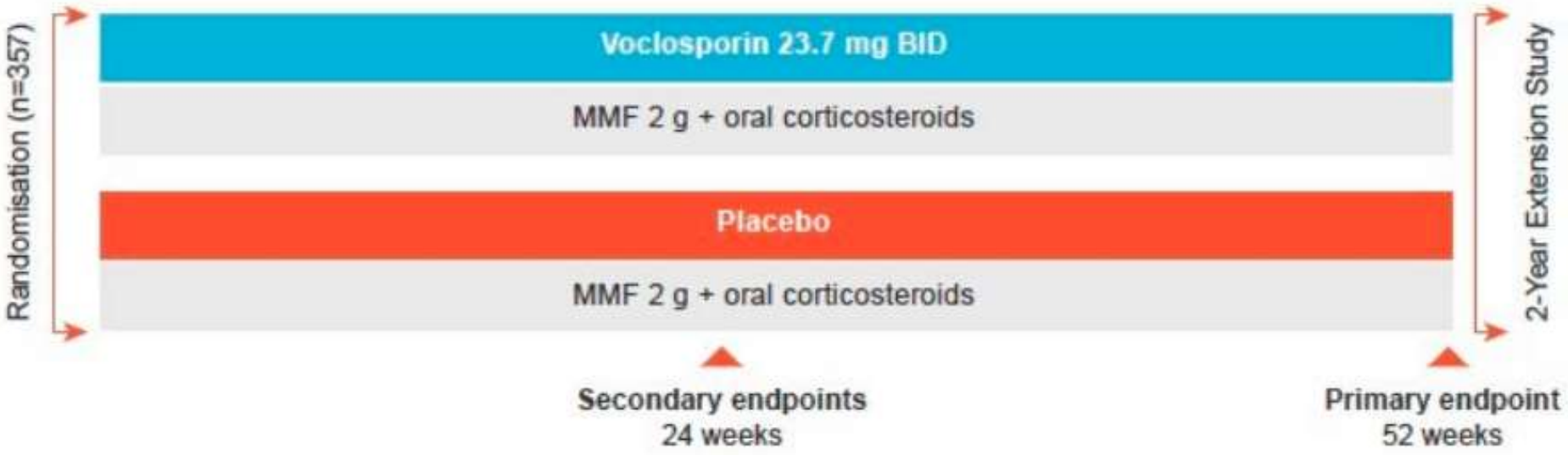
Kidney International, 2021

Calcineurine remmers in LN

Effectiviteit	**Toxiciteit**
<u>1e generatie: ciclosporine</u> Gelijk aan CYC/AZA	<u>1e generatie: ciclosporine</u> Significante toxiciteit: daling eGFR Hypertensie Flushes

Meest recente RCT: Aurora

- N = 357
- Lupus nefritis



Rovin et al 2021; May 29; 397

AURORA phase 3

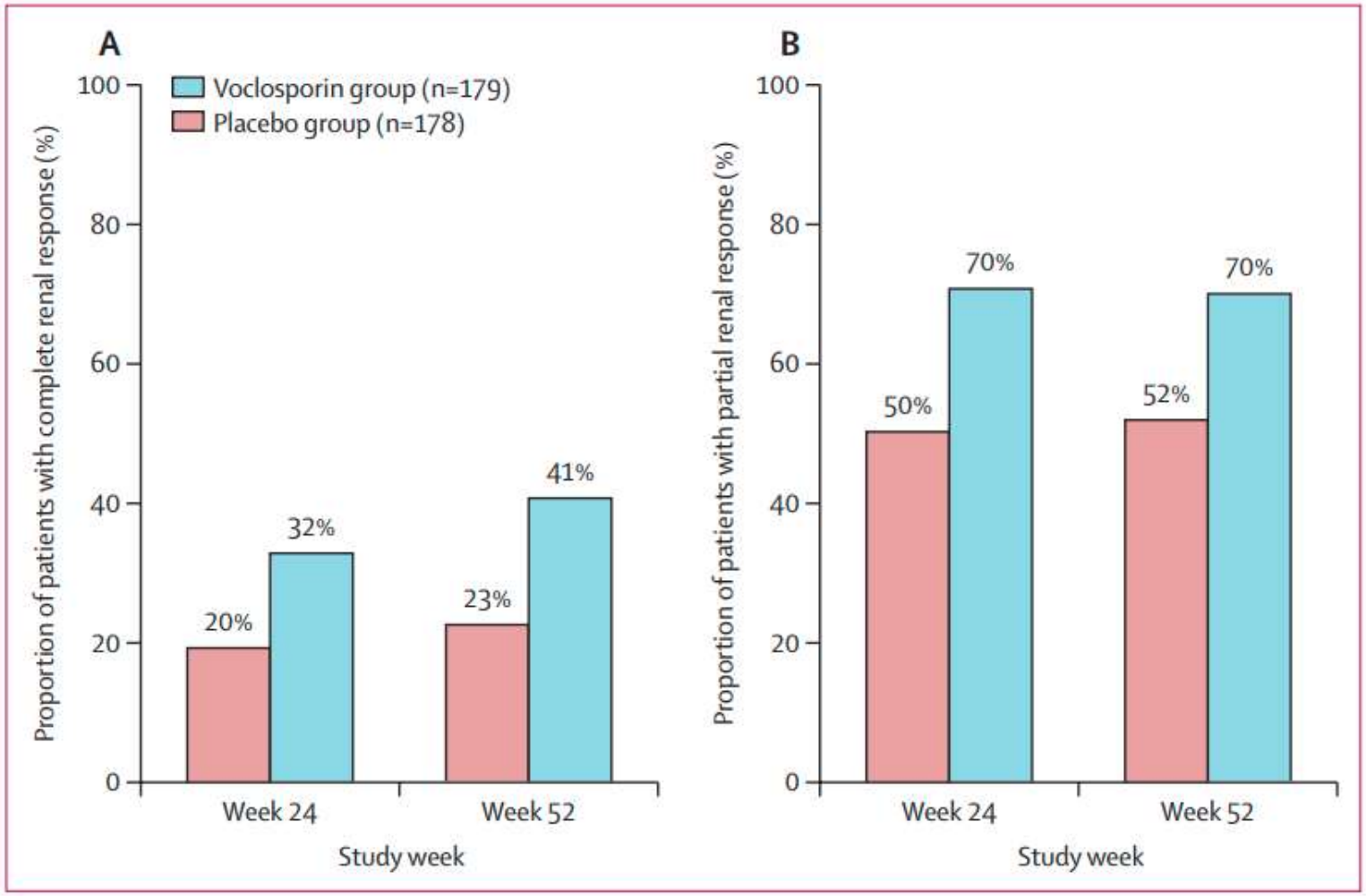


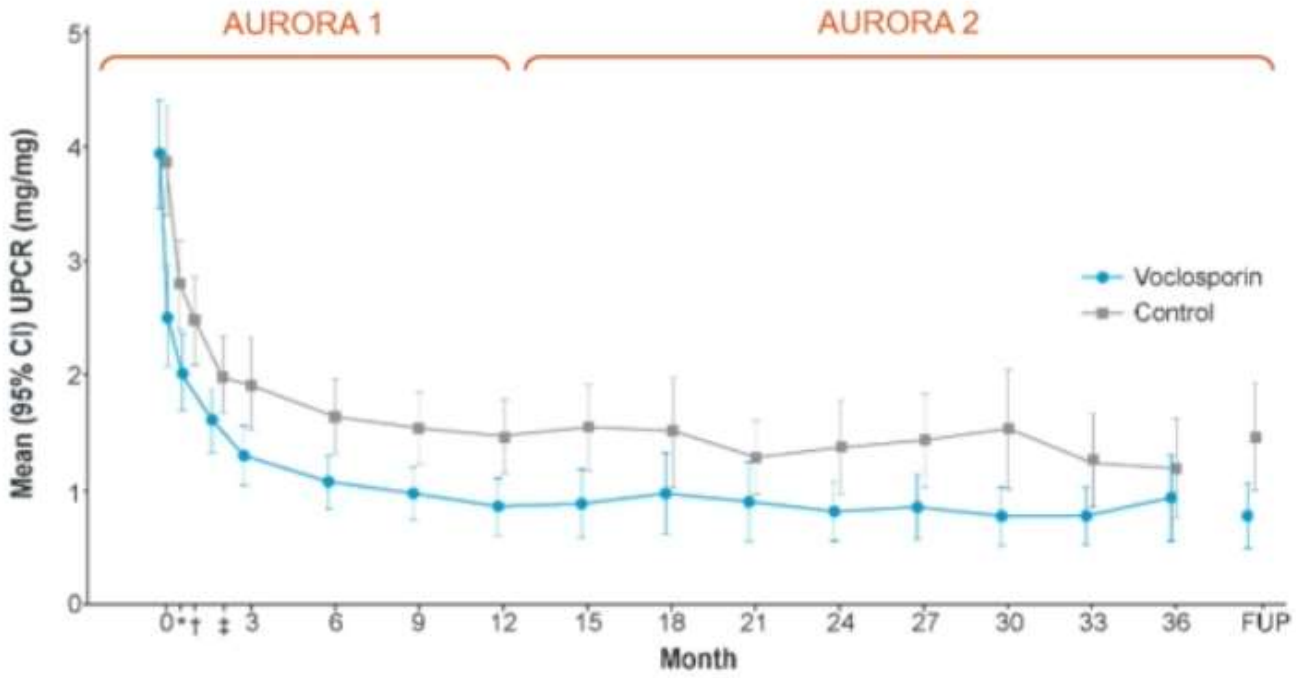
Figure 2: **Complete and partial renal response endpoints (intention-to-treat population)**

- 20% meer response
- Geen verhoogde kans op bijwerkingen inclusief infecties, hypertensie of nierfunctieverslechtering

Lange termijn uitkomsten AURORA

Mean UPCR Over Time

- The mean reductions in UPCR observed in AURORA 1 were maintained out to three years, with no increase in UPCR at the follow-up visit 4 weeks after study drug discontinuation

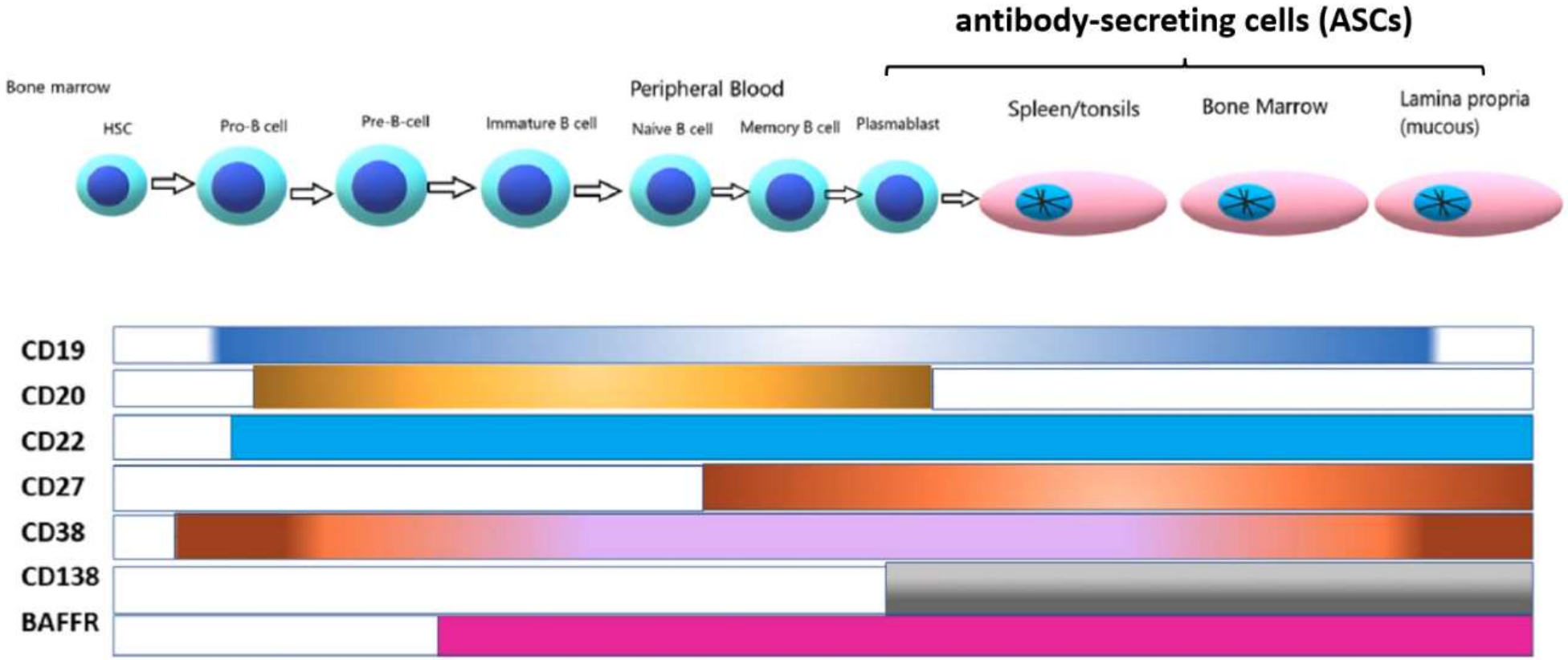


Voclosporin (n)	116	111	116	116	116	113	113	109	105	102	100	99	99	95
Control (n)	100	100	100	100	100	96	96	90	81	86	87	84	87	85

Something of the future

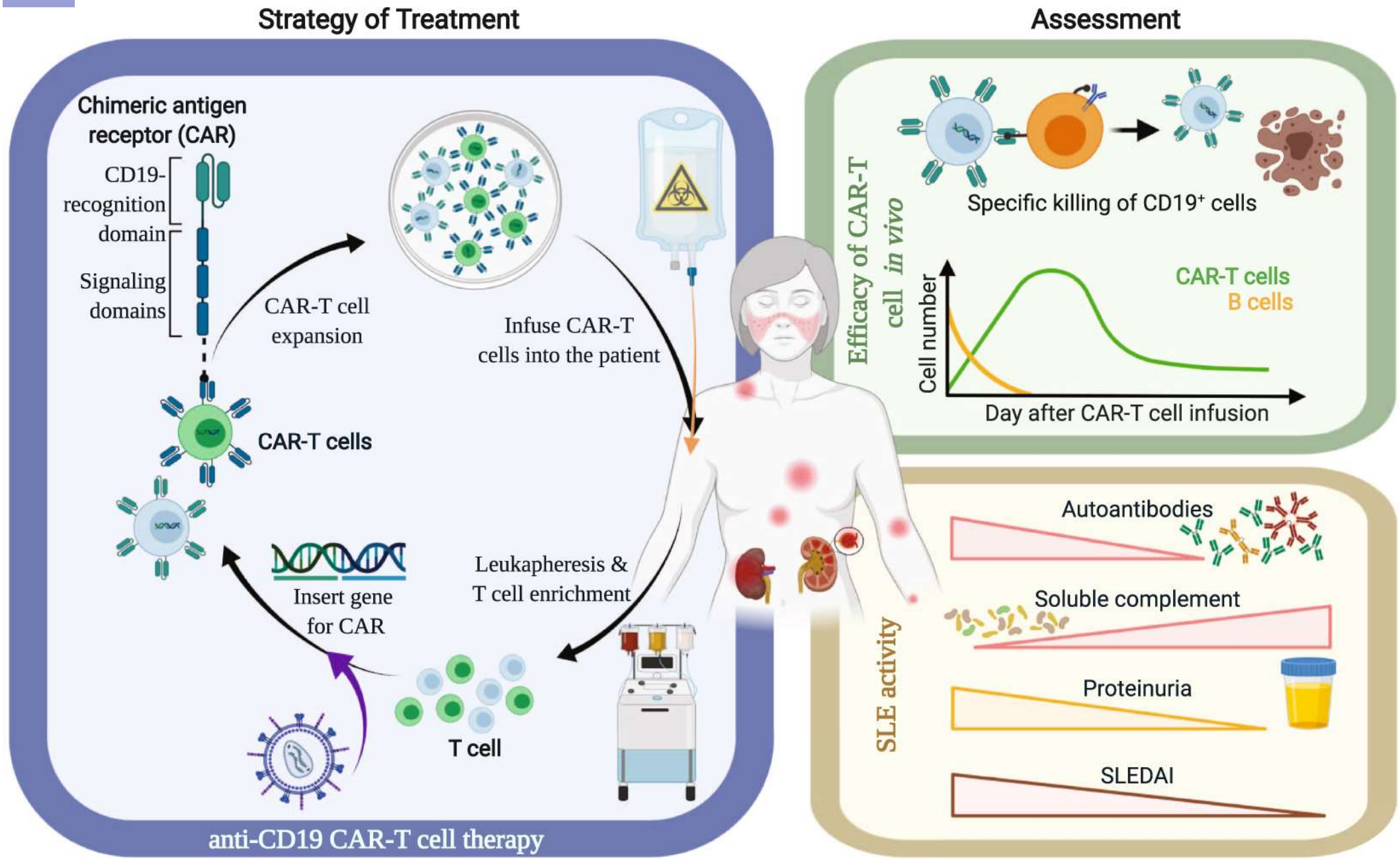
- CAR T cellen
- Clustering

CAR T-cellen tegen CD19



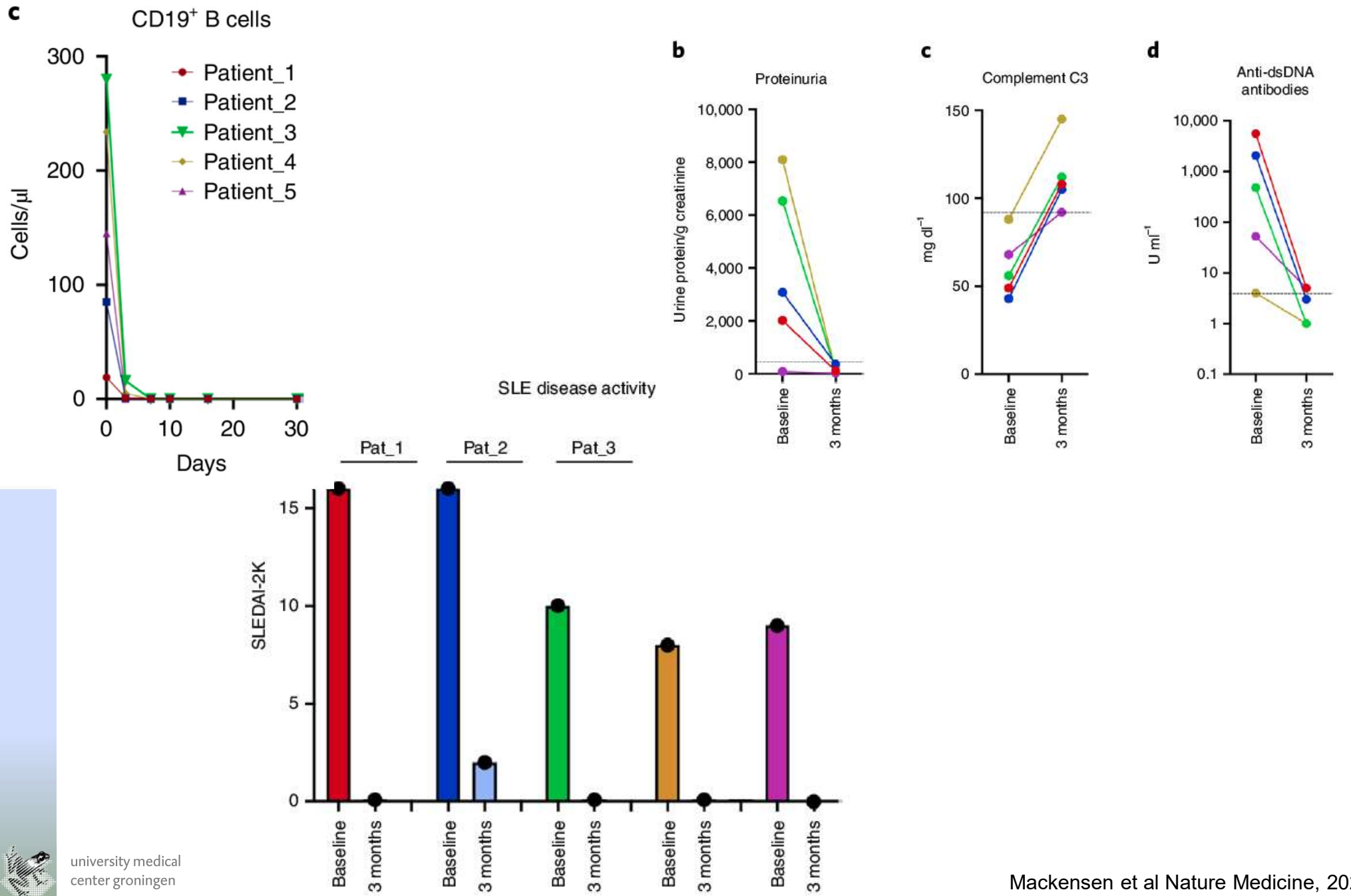
Bryl et al, Immun Letter 2021

CAR-T cellen in SLE



Jin et al Nature 2021

CAR T cellen in refractaire SLE



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Mackensen et al Nature Medicine, 2022

Something of the future

- CAR T cellen
- Deucravacitinib (TYK2 inhibitor)
- Clustering

Clusteren van patiënten

Transcriptomics -> voorspellen response?

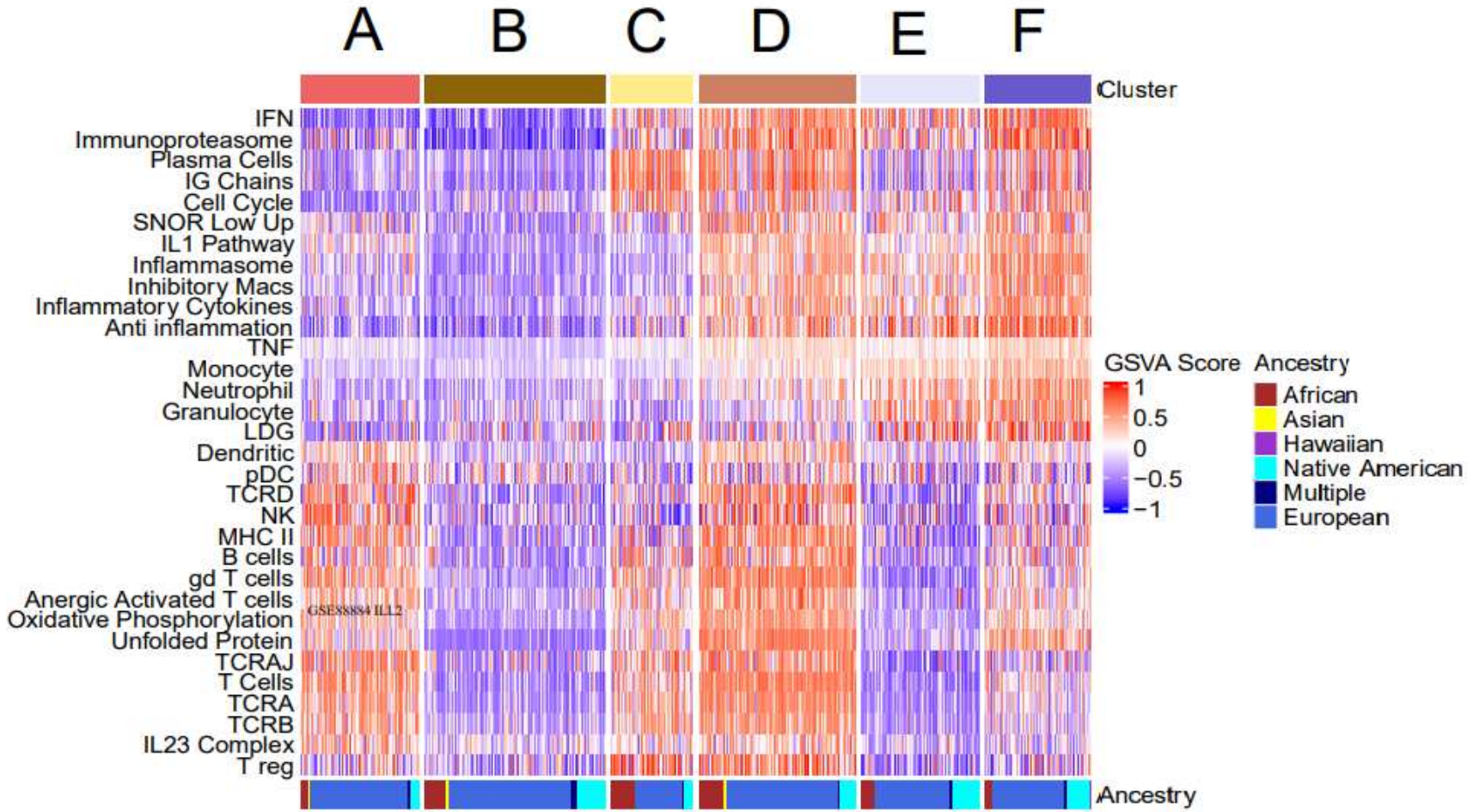

Figure 1. Endotypes in Adult SLE

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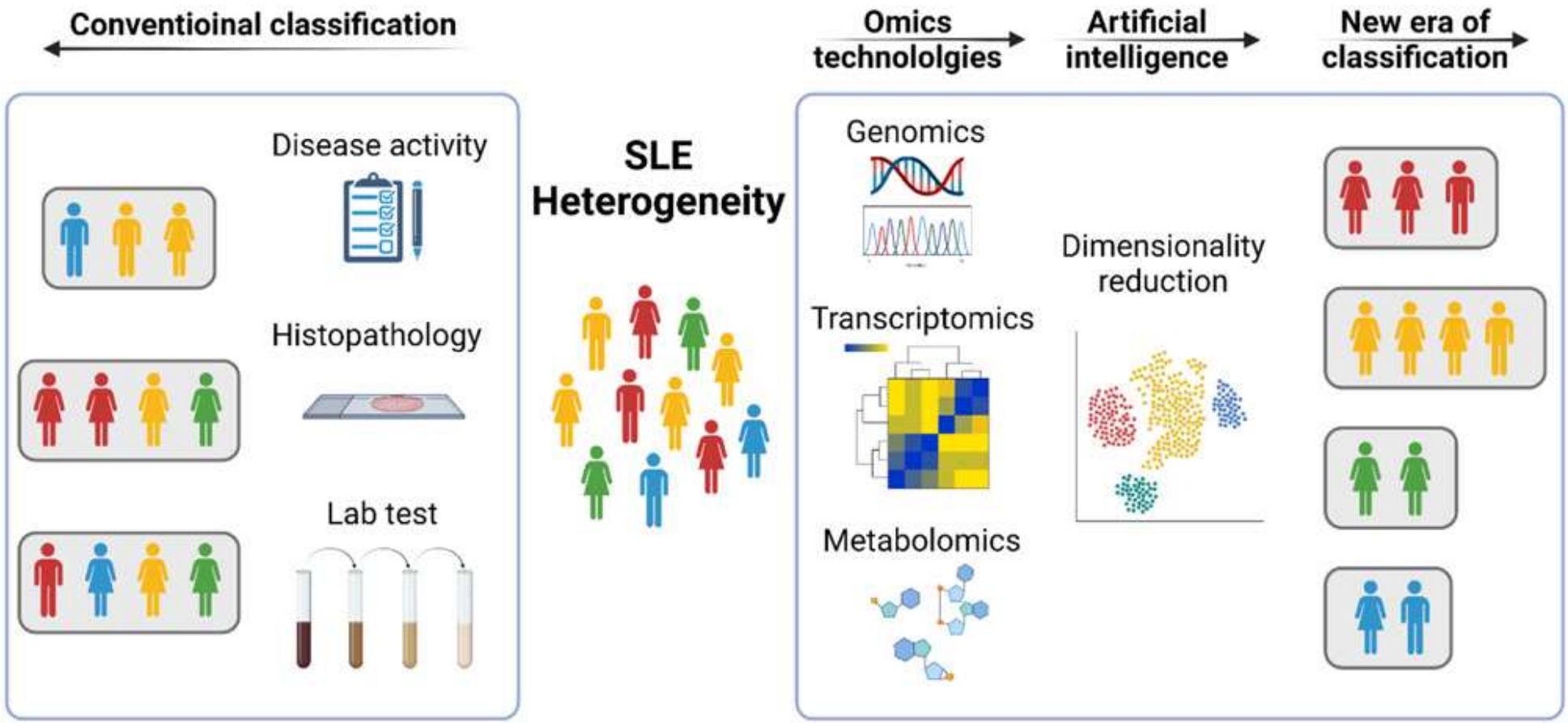
Hubbard et al, abstract ACR 2022

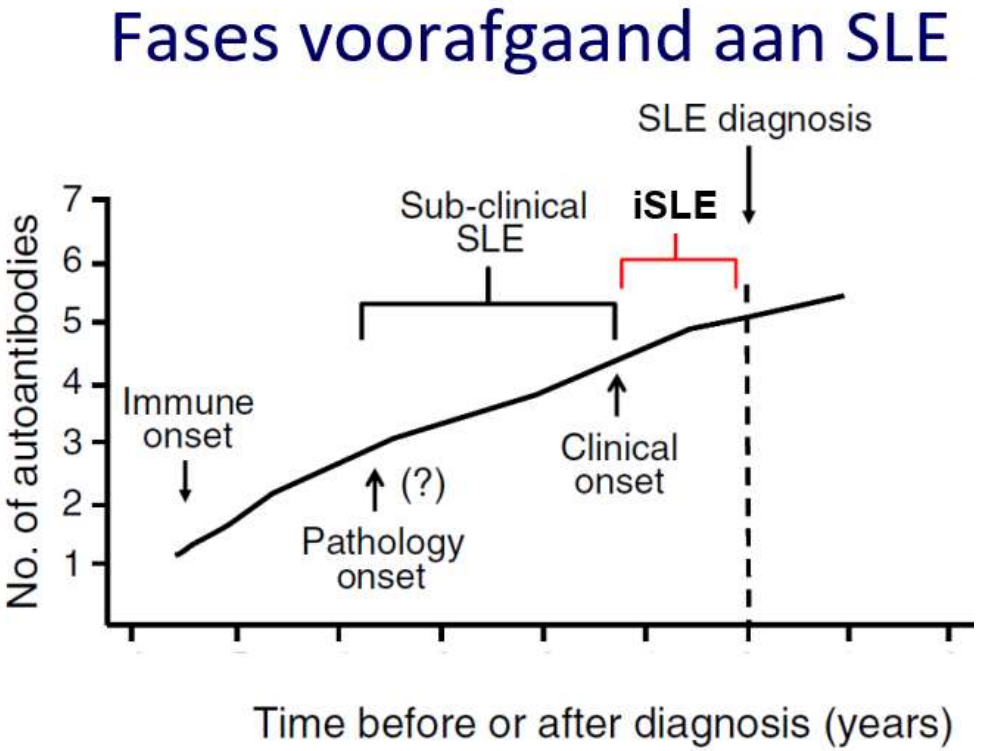
Clusteren van patiënten



Puri et al, Rheum&Autoimmunity 2021

Lopende onderzoeken UMCG

- Incomplete SLE
- TOPAZ-2: anti-BDCA2
- Synbiose 2
- Zwangerschap



SOMETHING OLD,

SOMETHING NEW,

SOMETHING of the future

to ask?

Belimumab vs voclosporin

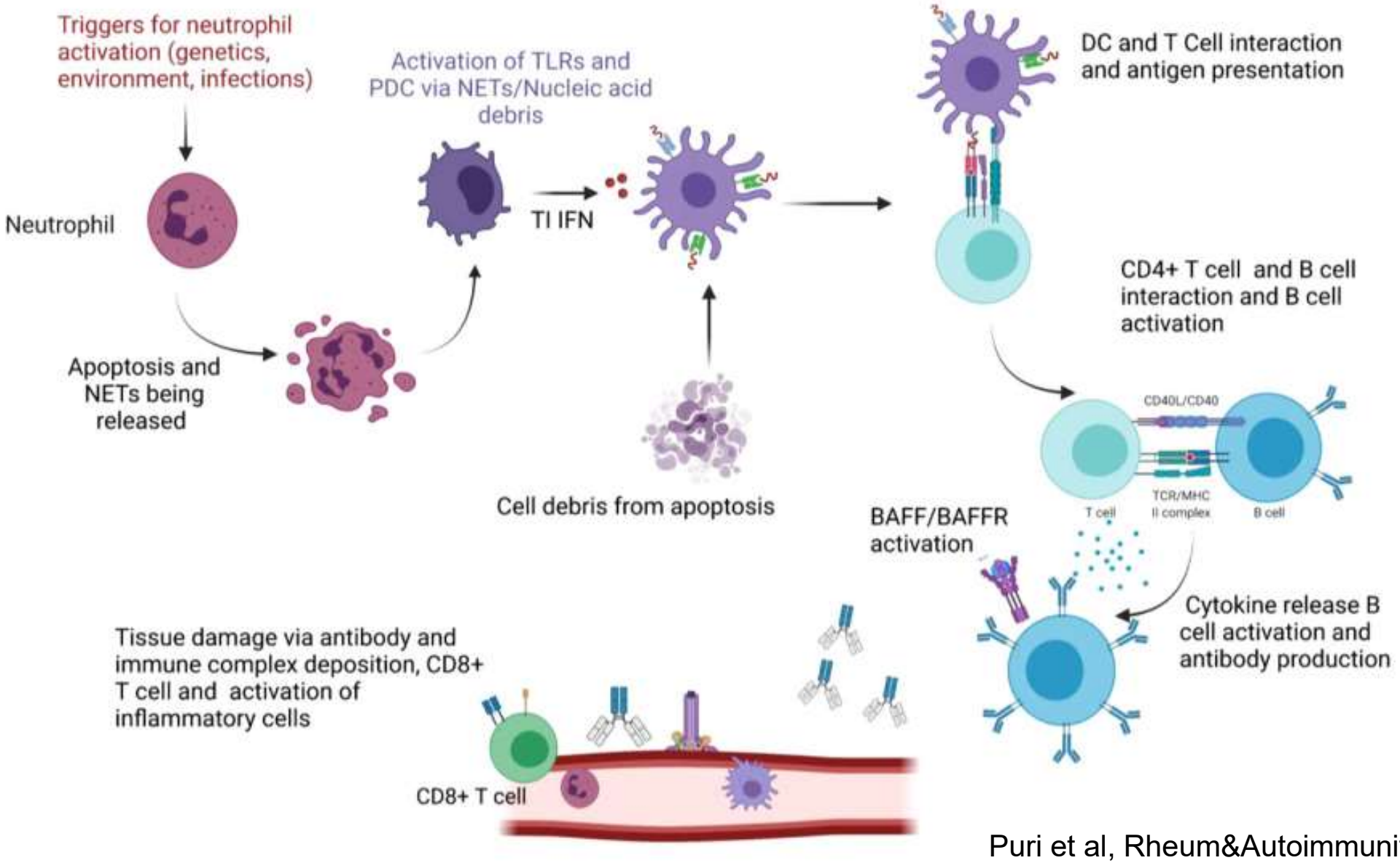
Favors Belimumab

- eGFR < 45 ml/min
- Low level of proteinurie (<3g)
- History of major infections
- Difficulty with adherence to more tablets
- Extra renal disease (cutaneous or arthritis)

Favors voclosporin

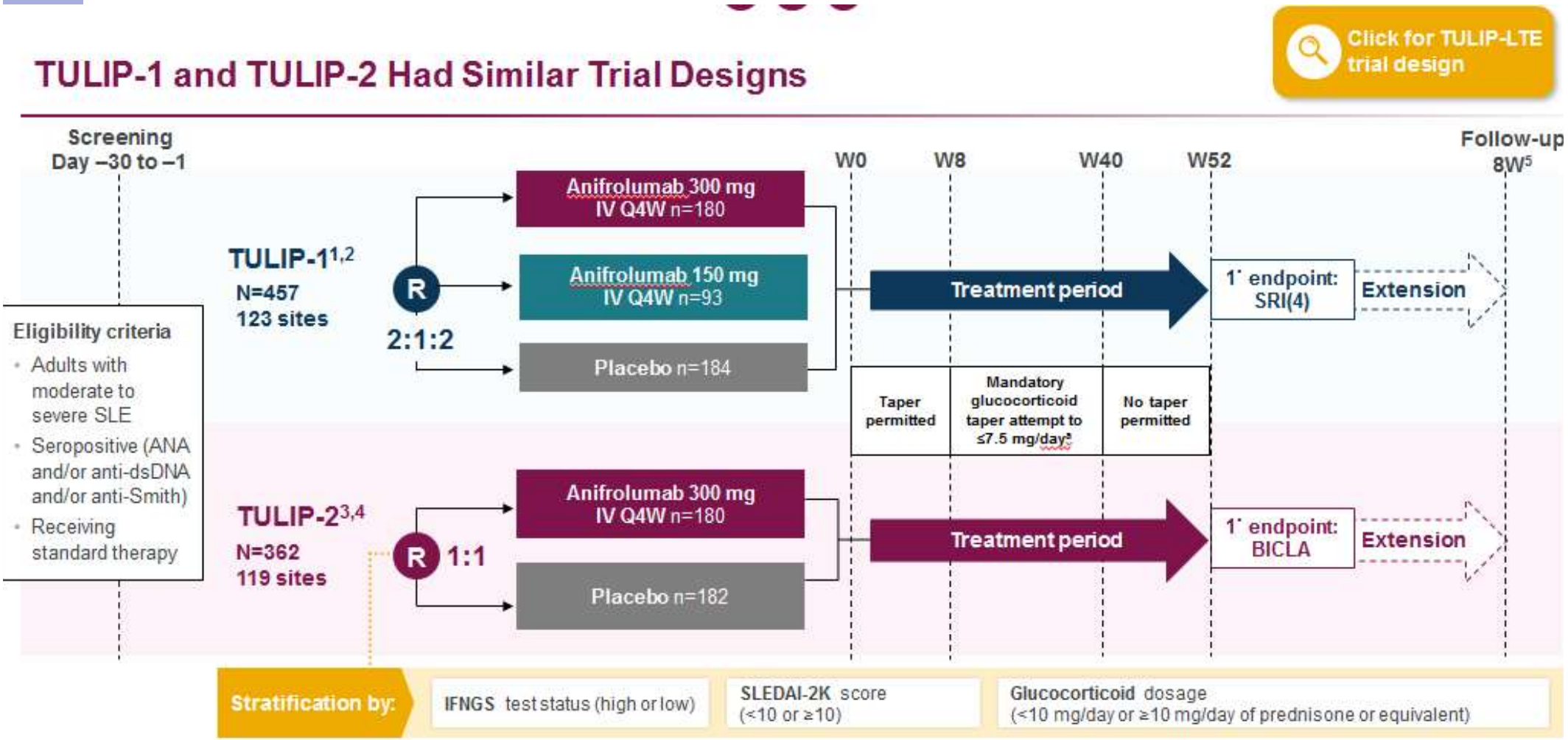
- eGFR > 45
- High level of proteinuria
- Prefers oral therapy

Take home – pathogenese SLE



Puri et al, Rheum&Autoimmunity 2021

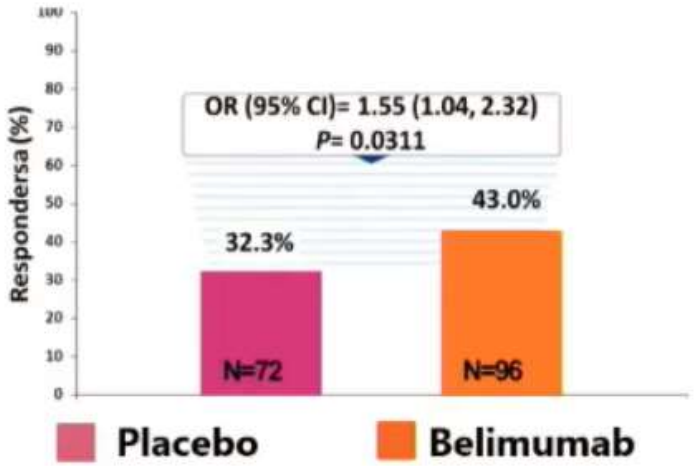
TULIP-1 and TULIP-2



Outcome BLISS and AURORA

BLISS-LN: Belimumab in LN

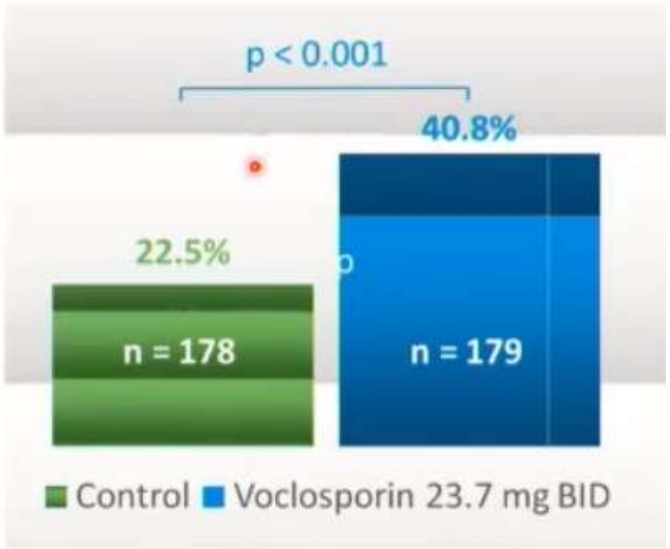
Primary Endpoint: PERR at Week 104



Furie R et al., NEJM, 2020

AURORA 1: Voclosporin in LN

Primary Endpoint: CR at Week 52



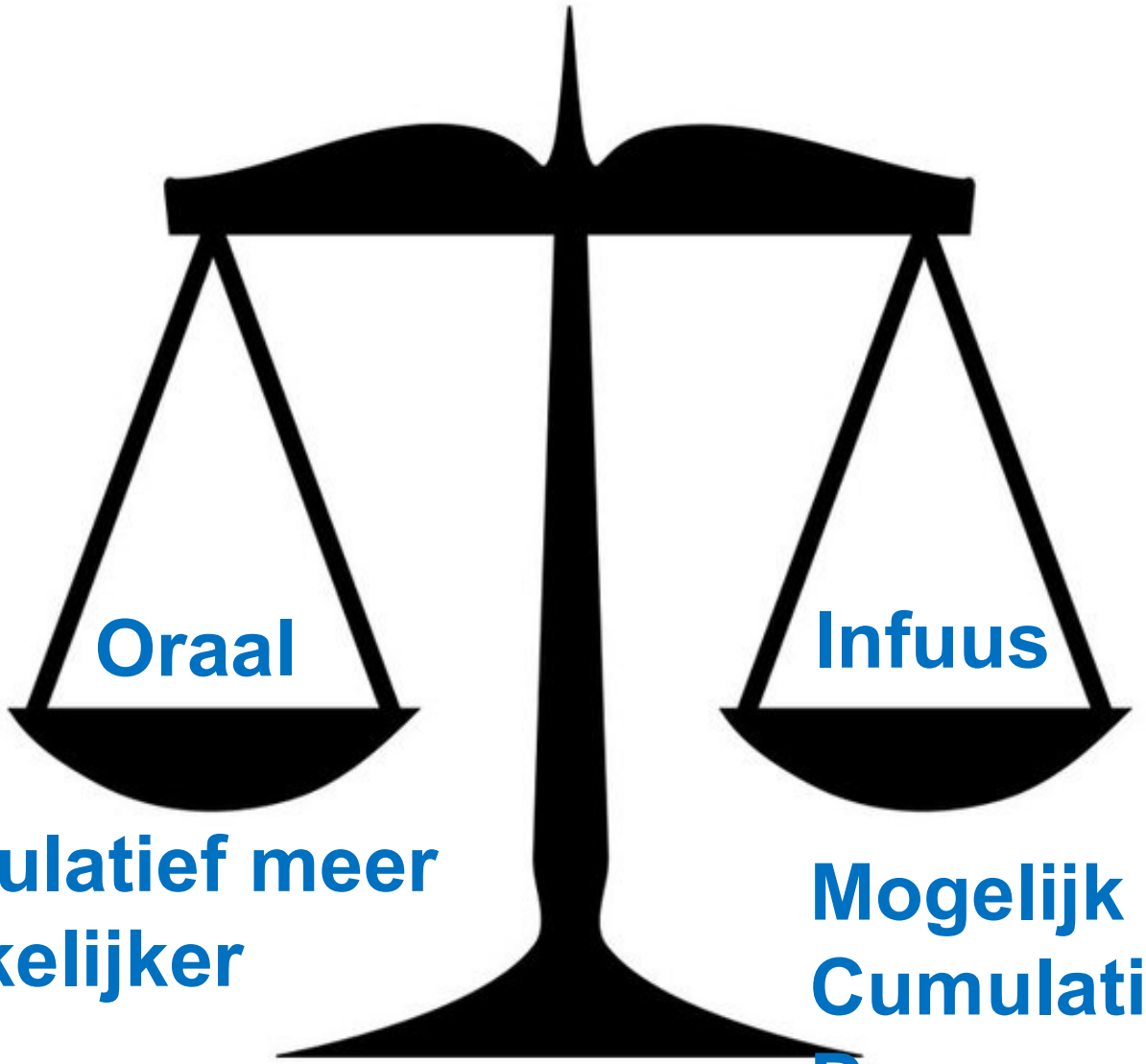
Rovin B et al., Lancet, 2021

Richtlijn oogheelkunde HCQ

- **Risicofactoren:**
  - > 5 jaar gebruik
  - Hogere dosering dan 5 mg/kg ideaal gewicht.
  - adipositas
  - nier/ leverfunctie ↓
  - leeftijd > 60 jaar
  - Pre existente retina afwijkingen

- **Baseline screening (binnen 1 jaar na starten medicatie):**
- **Follow up:**
  - geen risicofactoren: na 5 jaar en daarna jaarlijks.
  - risicofactoren: jaarlijks

Oraal versus methylprednisolon



Cumulatief meer
Makkelijker

Mogelijk effectiever
Cumulatief minder
Dagopnames

Verschil effectiviteit

- Genomische vs non-genomische effecten

Genomische effecten

Genomische pathway:

1e effect

- GCs bind the cytosolic-GC receptor (cGR)
- GC-cGR complex is translocated into the nucleus
- Interfering genomic transcription of inflammatory molecules

2e effect

- Increasing intranuclear concentration of GCs -> a second process named transactivation starts.
- Stimulates transcription of some inhibitory genes,
- But mainly mediates the activation of gluconeogenesis, insulin resistance, skin atrophy, and the inhibition of bone formation, all well-known adverse effects

Non-genomic effects

1. GC-cGR complex directly blocks activation of phospholipase A2 and thus production of arachidonic acid (transcription-independent)
2. Activation of membrane-bound GR (mGR) leads to reduction of lymphocyte activity via the p38 MAP kinase
3. Nonspecific interactions with cellular membranes of immune cells result in inhibition of ATP production and thus decrease cell activity

Therapeutische effect

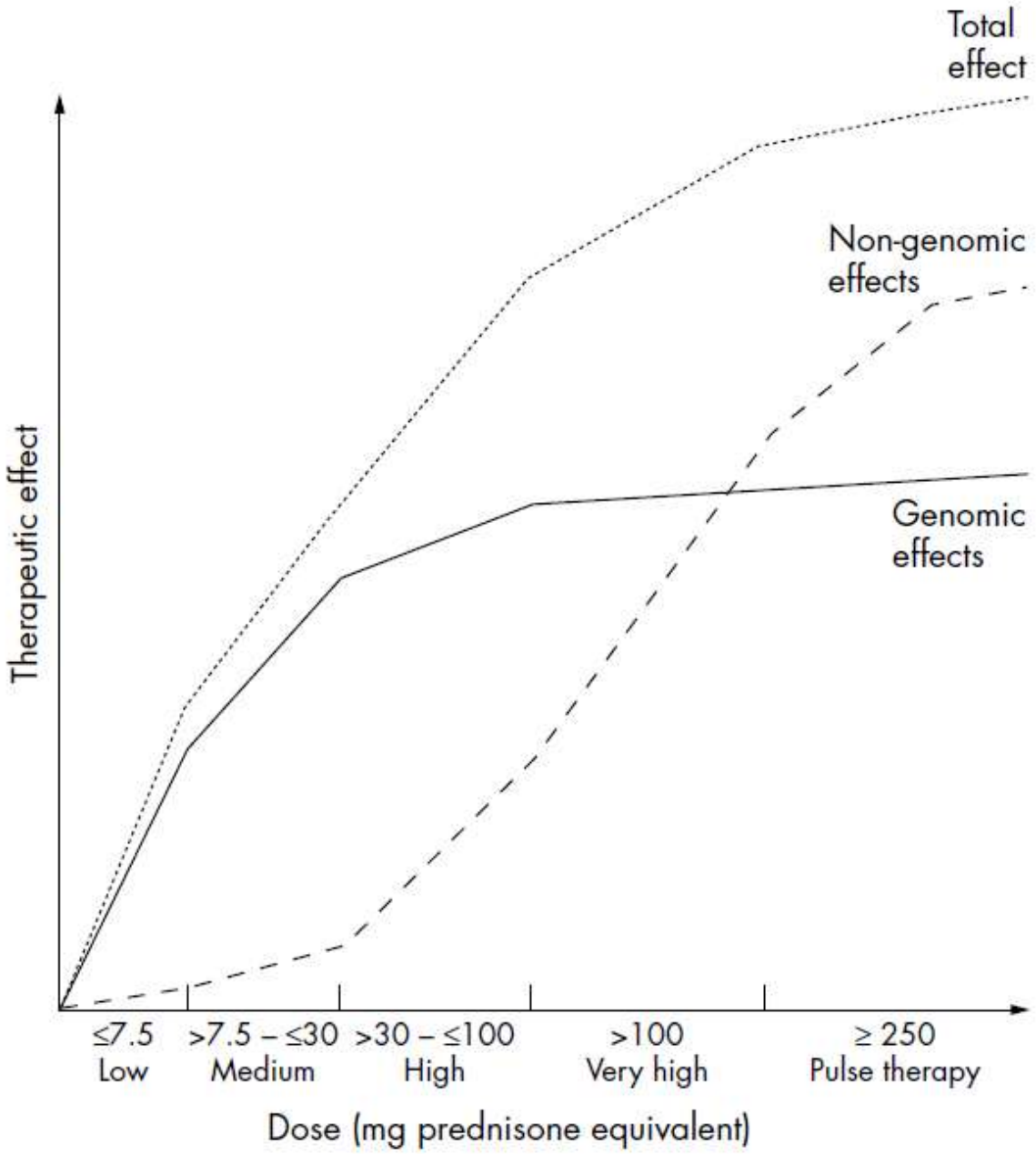
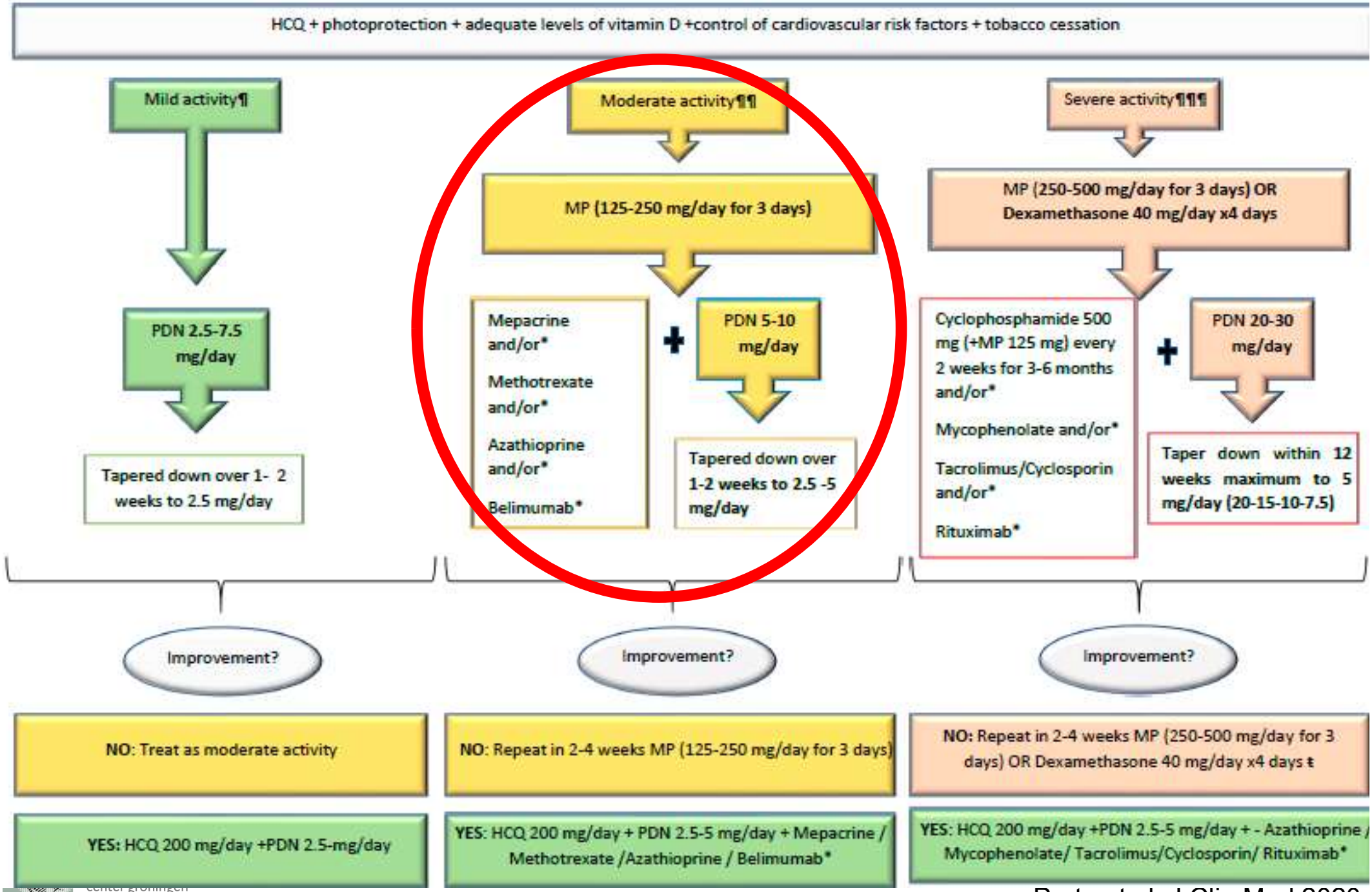


Table genomic vs non-genomic

Table 2. Summary of the mechanisms of action of glucocorticoids.

	Genomic Pathway	Non-Genomic Pathway
Cells targeted	All the organism	Inflammatory cells
Mechanism of action	Genomic modulation	Membrane receptor and intracellular inflammatory pathways
Start of action	~4 to 6 h	~15 min
Saturation dose of the immunosuppressive – anti-inflammatory effects	~100% at 30 to 40 mg/day of prednisone-equivalent	Unknown
Minimum effective dose	2.5 to 5 mg/day of prednisone-equivalent	Over 100 mg of prednisone-equivalent
Maximum effective doses that minimize adverse effects	30 to 40 mg/day of prednisone-equivalent (for trans-repression)	500/day mg of methylprednisolone
Damage accrual with cumulative doses	Proven	Not proven
Glucocorticoids acting by this way	All	Mainly methylprednisolone and dexamethasone

New paradigm in SLE?



Porta et al. J Clin Med 2020