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# Nieuwe behandelingen voor systemische lupus erythematodes (SLE)

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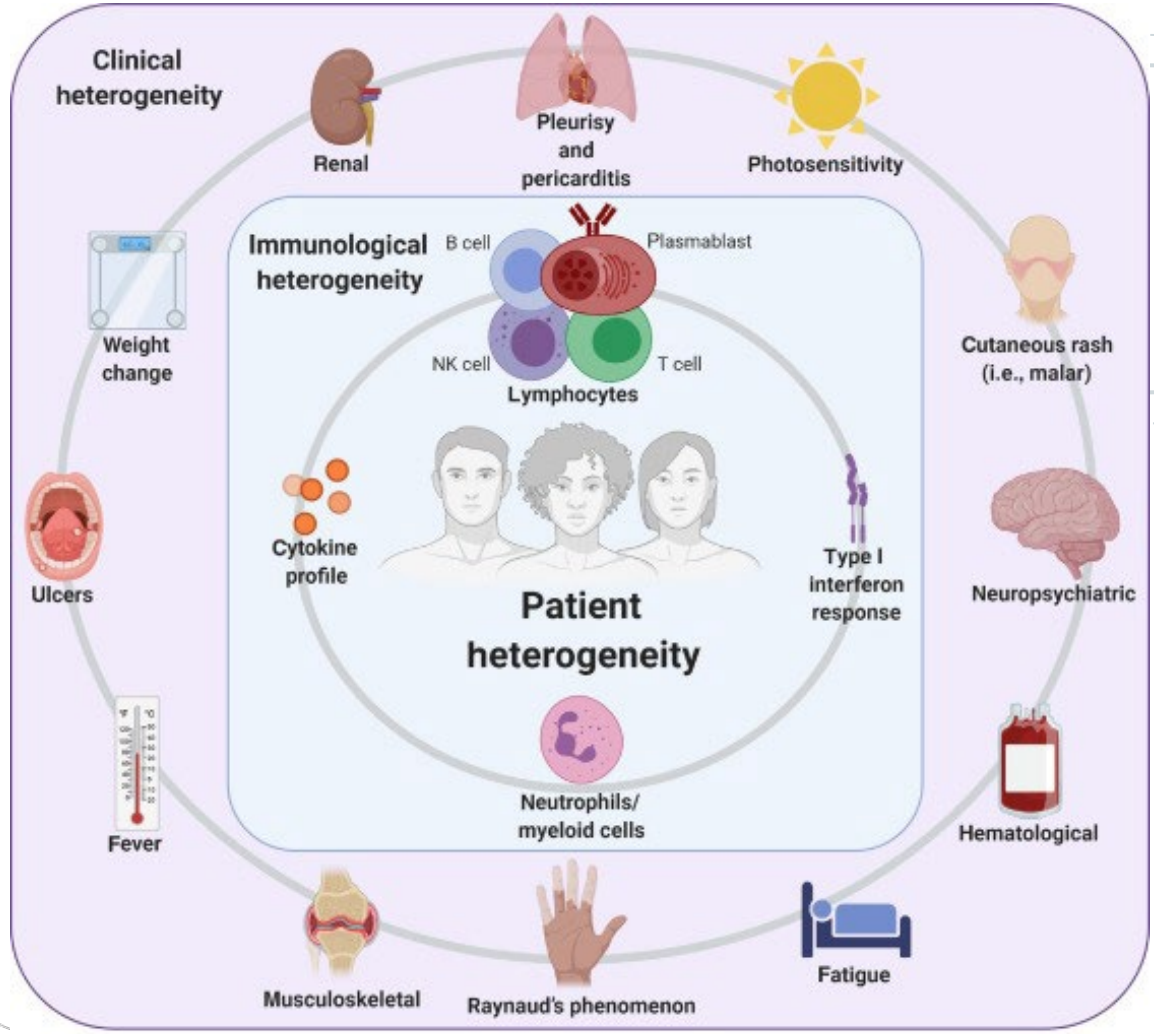
Mei 2023




Trends in Molecular Medicine

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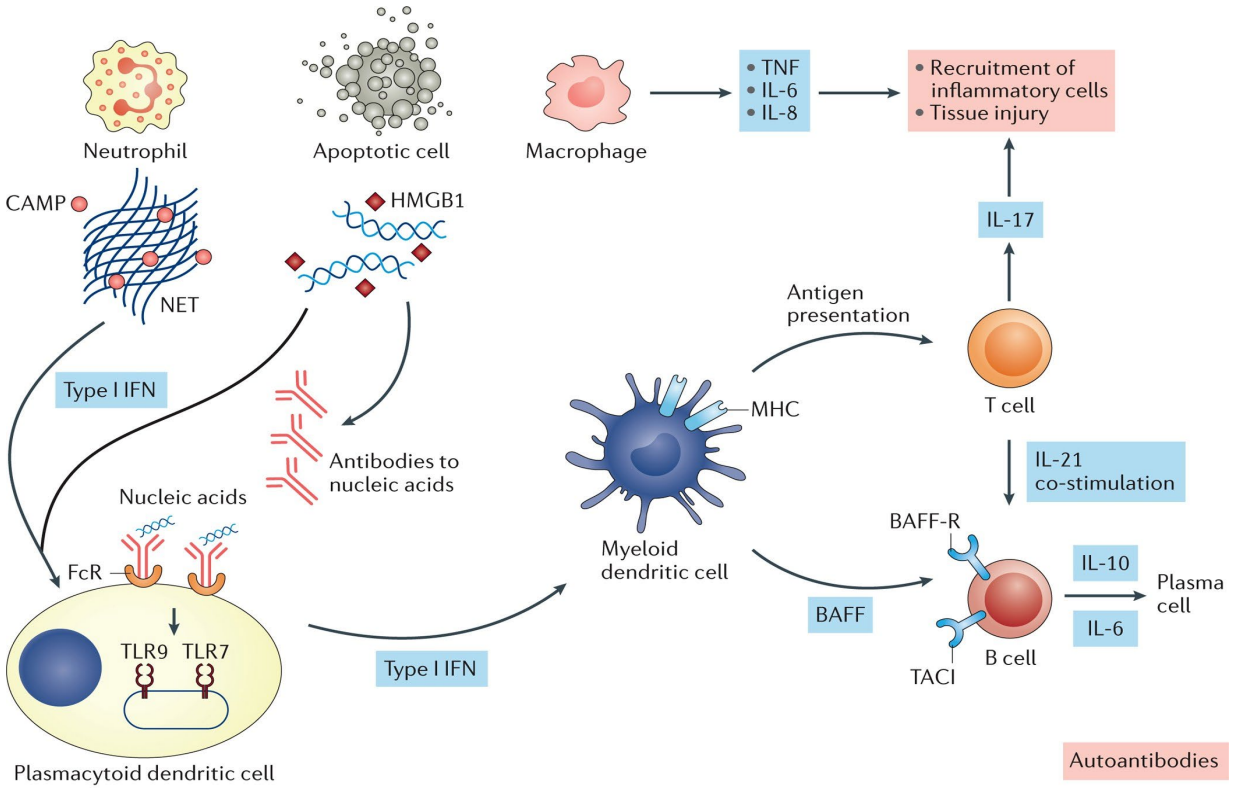
European Reference Network | Connective Tissue and Musculoskeletal Diseases (ERN ReCONNET)

# Ontstaan SLE




Tsokos, G. C. *et al.* (2016) New insights into the immunopathogenesis of systemic lupus erythematosus *Nat. Rev. Rheumatol.* doi:10.1038/nrrheum.2016.186

Nature Reviews | Rheumatology

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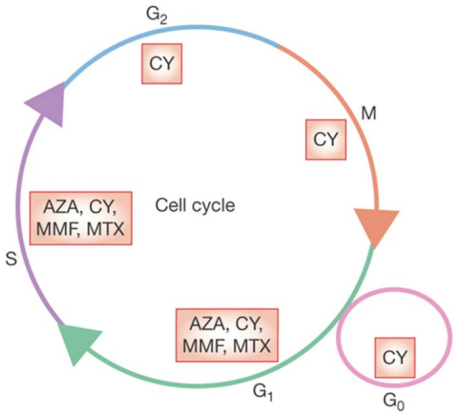
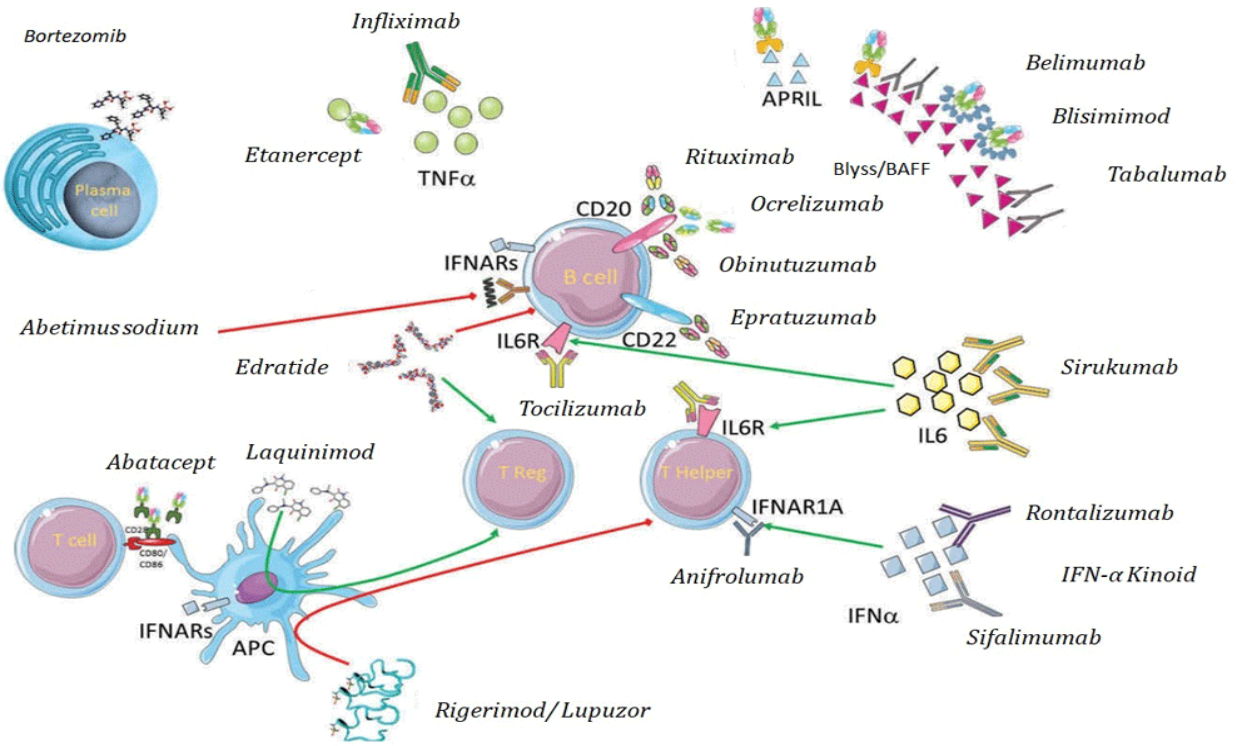
# SLE: behandeling (DMARDs)

- Vermijd zonlicht; UV-blockers
- Glucocorticoiden: prednison, dexamethason
- Hydroxychloroquine (plaquenil)
- Azathioprine (imuran)
- Methotrexaat
- Cyclofosfamide
- Mycofenolaat mofetil (cellcept)



# Immunotherapie




Sciascia S, Radin M, Roccatello D et al. Recent advances in the management of systemic lupus erythematosus. F1000Research 2018, 7:970 (doi: 10.12688/f1000research.13941.1)

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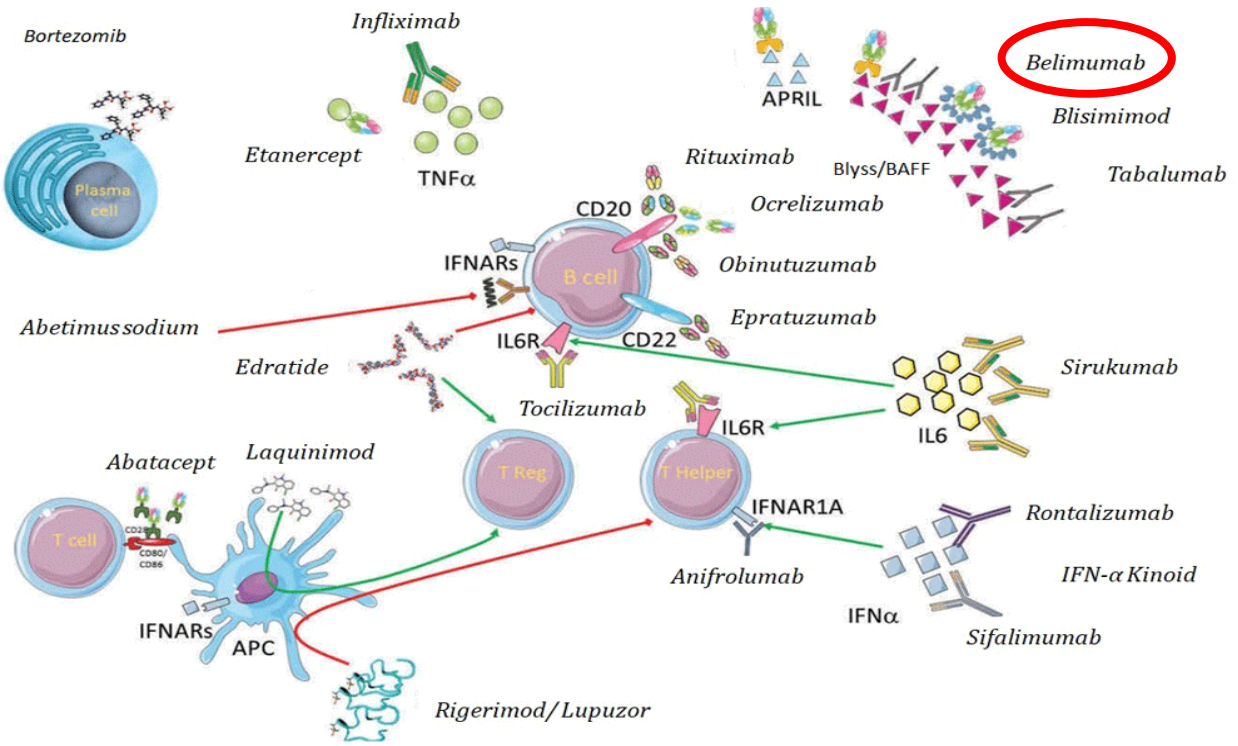
# Nieuwe medicijnen

- belimumab
- anifrolumab
- voclosporin

# Immunotherapie




Sciascia S, Radin M, Roccatello D et al. Recent advances in the management of systemic lupus erythematosus. F1000Research 2018, 7:970 (doi: 10.12688/f1000research.13941.1)

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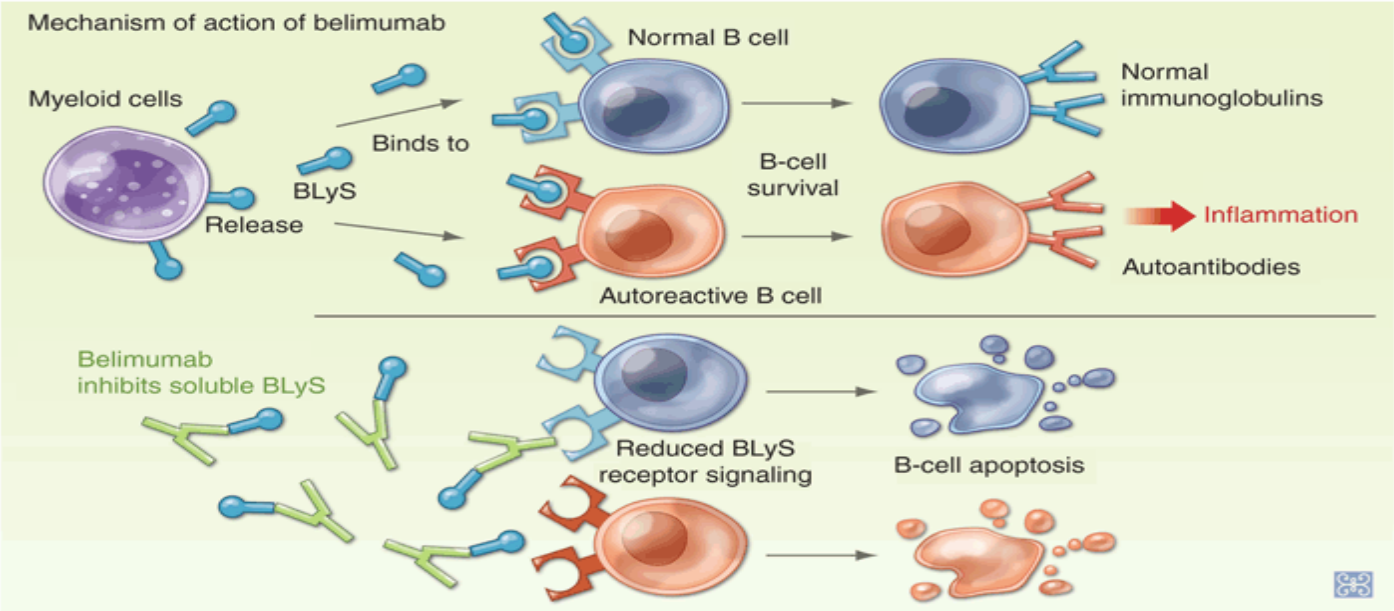
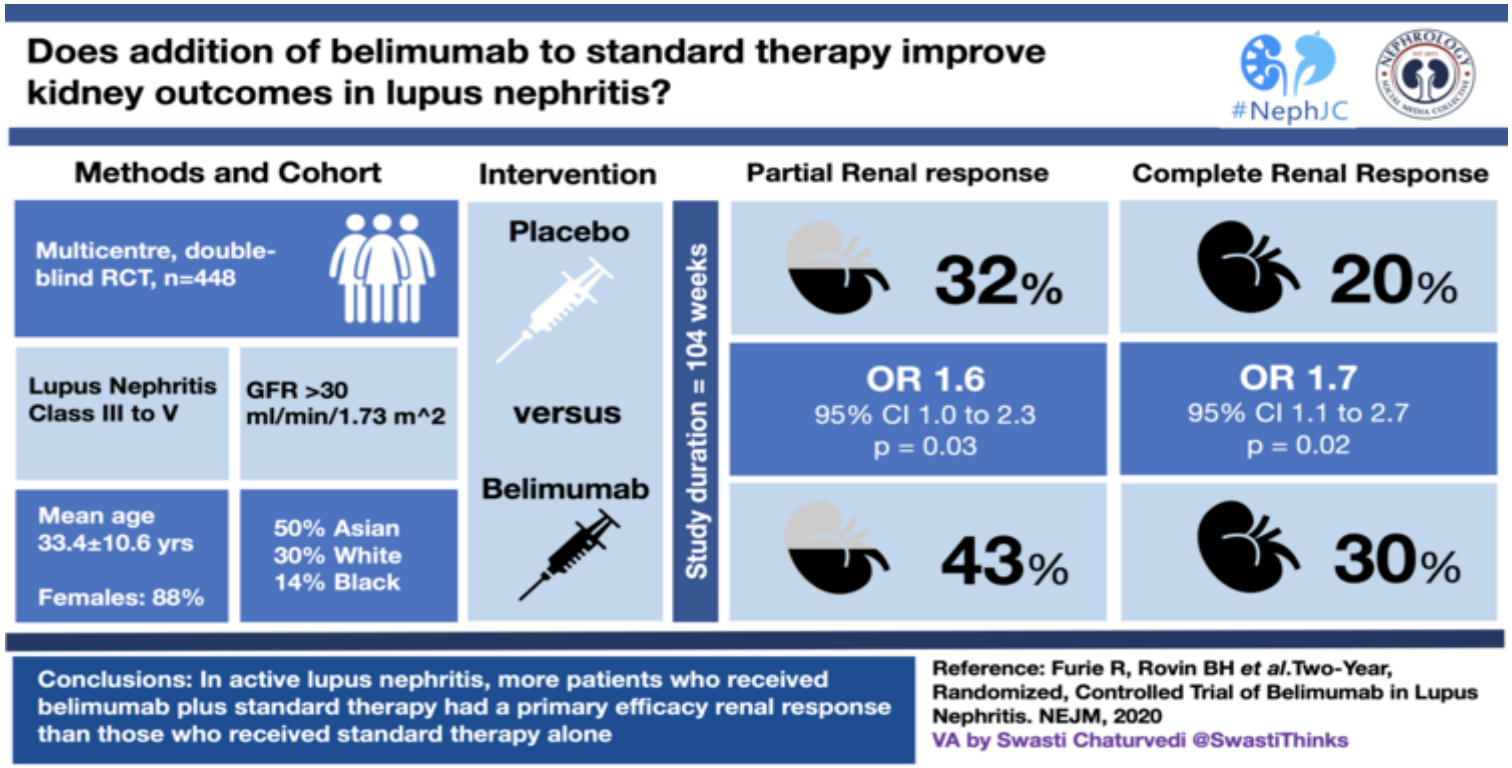
# Belimumab: werkingsmechanisme

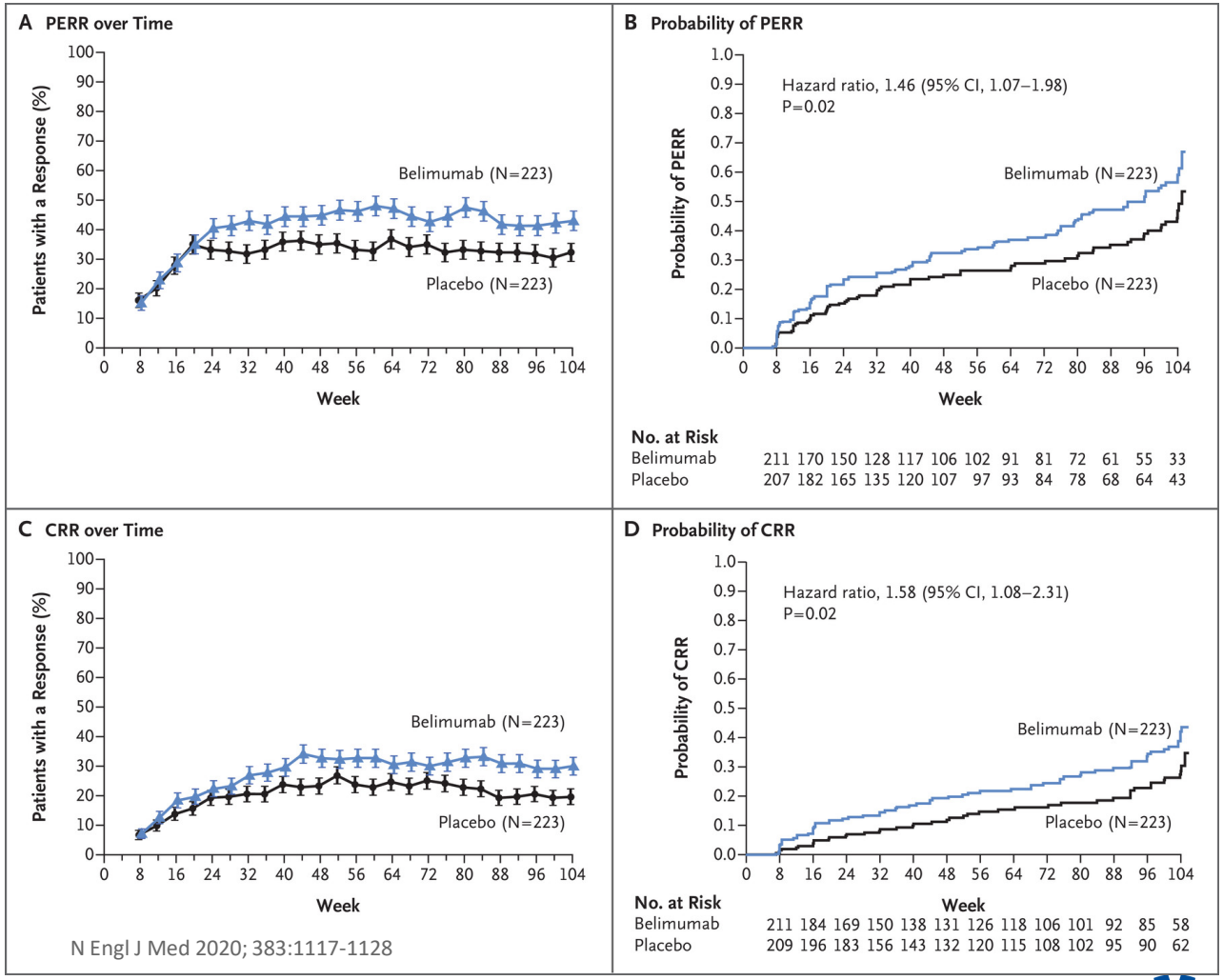
I.v. of s.c.; EMA-goedgekeurd 2011, actieve SLE met SLEDAI > 6



# BLISS-LN




http://www.nephjc.com/news/2020/11/24/visual-abstract-for-bliss




N Engl J Med 2020; 383:1117-1128

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**Table 3. Adverse Events, Adverse Events of Special Interest, and Suicidality in the Safety Population.***

| Event | Belimumab (N = 224) | Placebo (N = 224) |
|---|---|---|
| | *no. of patients (%)* | |
| All adverse events† | 214 (96) | 211 (94) |
| All treatment-related adverse events† | 123 (55) | 119 (53) |
| Upper respiratory tract infection | 26 (12) | 24 (11) |
| Urinary tract infection | 15 (7) | 13 (6) |
| Herpes zoster | 13 (6) | 10 (4) |
| Bronchitis | 11 (5) | 10 (4) |
| Nasopharyngitis | 8 (4) | 8 (4) |
| Headache | 9 (4) | 5 (2) |
| Nausea | 8 (4) | 5 (2) |
| Rash | 6 (3) | 5 (2) |
| All serious adverse events† | 58 (26) | 67 (30) |
| All treatment-related serious adverse events† | 23 (10) | 25 (11) |
| Most common treatment-related serious adverse events, according to system organ class, occurring in ≥1% of patients in either group | | |
| Infections and infestations | 15 (7) | 18 (8) |
| Respiratory, thoracic, and mediastinal disorders | 5 (2) | 1 (<1) |
| Blood and lymphatic system disorders | 3 (1) | 2 (1) |
| Nervous system disorders | 0 | 3 (1) |
| Most common treatment-related serious adverse events occurring in ≥1% of patients in either group | | |
| Pneumonia | 3 (1) | 4 (2) |
| Herpes zoster | 3 (1) | 2 (1) |
| Adverse events resulting in discontinuation of trial drug | 29 (13) | 29 (13) |
| Adverse events of special interest‡ | | |
| Cancer | | |
| Excluding nonmelanoma skin cancer§ | 2 (1) | 0 |
| Including nonmelanoma skin cancer§ | 3 (1) | 0 |
| Postinfusion reactions¶ | 26 (12) | 29 (13) |
| All infections of special interest, including opportunistic infections, herpes zoster, tuberculosis, and sepsis | 30 (13) | 34 (15) |
| Serious infections | 9 (4) | 7 (3) |
| Depression, suicide, or self-injury | 11 (5) | 16 (7) |
| C-SSRS suicidal ideation or behavior during trial intervention | 7 (3) | 12 (5) |
| Death | 6 (3) | 5 (2) |
| Fatal serious adverse events that began during trial intervention | 4 (2) | 3 (1) |
| Fatal serious adverse events that did not begin during trial intervention | 2 (1) | 2 (1) |

* Only adverse events that occurred during the intervention period (from the first infusion to the first missed infusion or the last infusion, whichever was later, plus 28 days) are listed. Patients were counted once in each row and column for any adverse event that met the criterion. Adverse events were coded with the use of the *Medical Dictionary for Regulatory Activities* (MedDRA), version 22.0.
† This category includes all patients who had at least one event. Relatedness of the intervention to the event was determined by the site investigators.
‡ These events were determined according to a custom MedDRA query.
§ This category includes tumors of unspecified cancer that were adjudicated as cancer.
¶ These events were determined according to a custom MedDRA query or sponsor adjudication.

N Engl J Med 2020; 383:1117-1128

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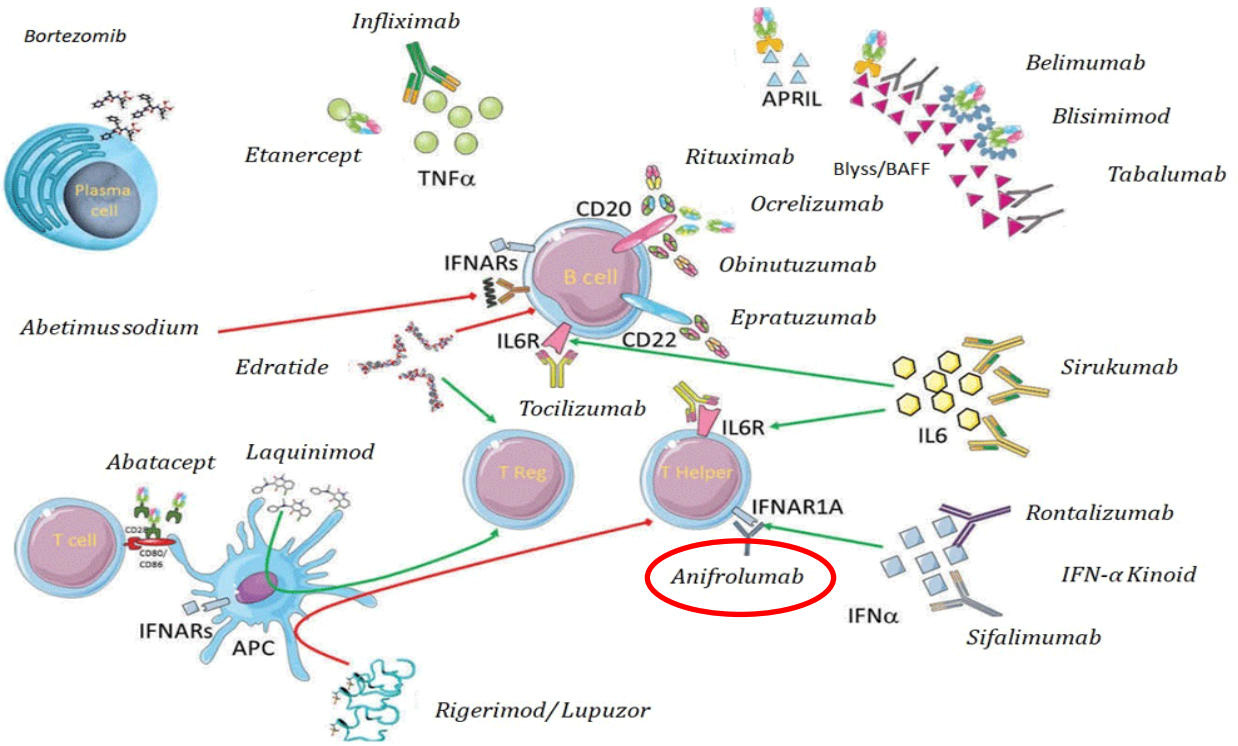
# Belimumab

- Sinds 2021 gereigstreerd als add-on behandeling lupus nefritis
- Onderzoek naar combinatietherapie rituximab/belimumab bezig, phase 2-studies veelbelovend, fase 3-studie (BLISS-BELIEVE) negatieve resultaten
- Mogelijk meer effectief bij zeer actieve SLE -> SYNBIOSE-2


1. Ann Intern Med doi:10.7326/M21-2078
2. Nephrol Dial Transplant. 2021;36(8):1474-83
3. ACR abstract L13 2021

# Immunotherapie




Sciascia S, Radin M, Roccatello D et al. Recent advances in the management of systemic lupus erythematosus. F1000Research 2018, 7:970 (doi: 10.12688/f1000research.13941.1)

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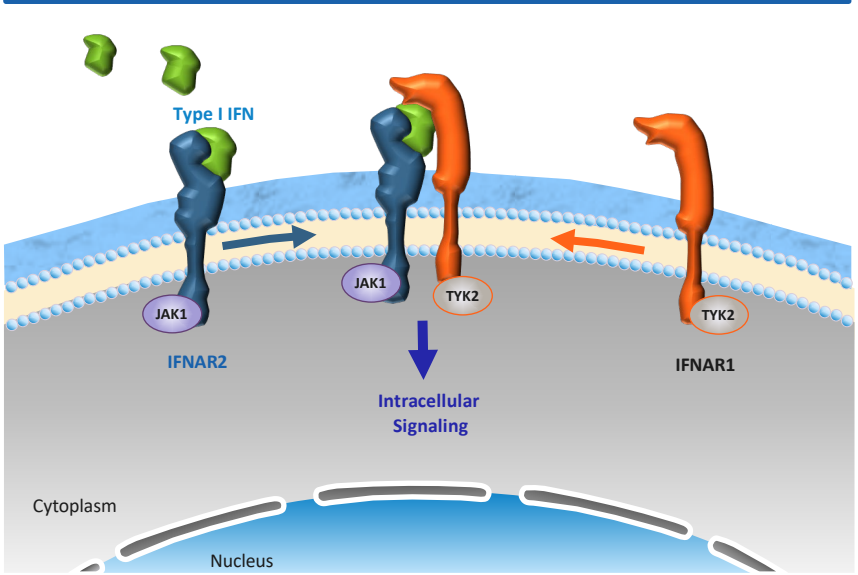
# Anifrolumab

- Humaan IgG-monoklonaal tegen IFN-receptor
- Fase 2b-trial (MUSE)[1]
- Twee fase 3-trials (TULIP-1 en -2)[2, 3]

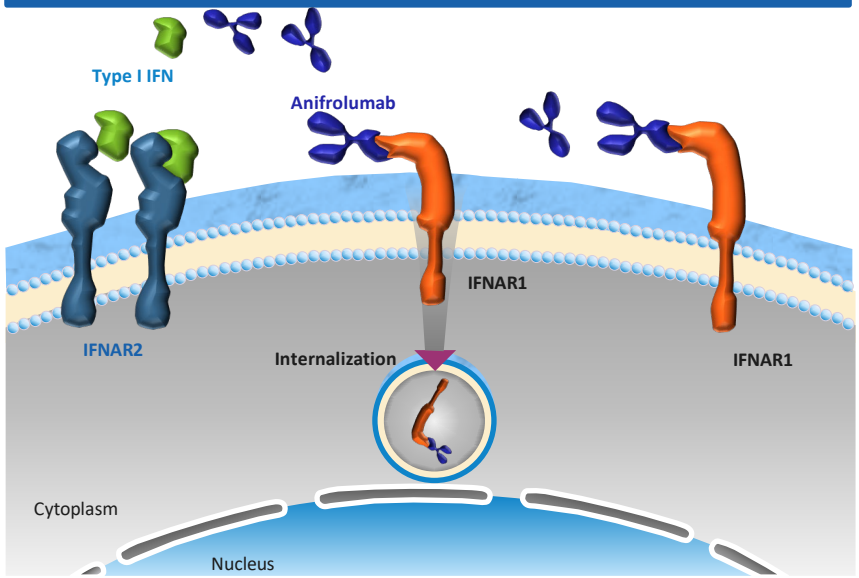

1. Arthritis Rheumatol. 2017 Feb; 69(2): 376–386
2. Furie RA, et al. *Lancet Rheumatol*. 2019;1:e208–19
3. Morand EF, et al. *N Engl J Med*. 2020;382:211–21

# Anifrolumab

Type I IFN binds to IFNAR causing dimerization resulting in intracellular signaling[1]




Anifrolumab binds to the Type I IFN Receptor and blocks receptor dimerization and induces receptor internalization[1]




IFN = interferon; IFNAR = IFN-α receptor; JAK = janus kinase; TYK = tyrosine kinase.

1. Riggs JM et al. *Lupus Sci Med*. 2018;5(1):e000261. 2. Ivashkiv LB, Donlin LT. *Nat Rev Immunol*. 2014;14(1):36-49.

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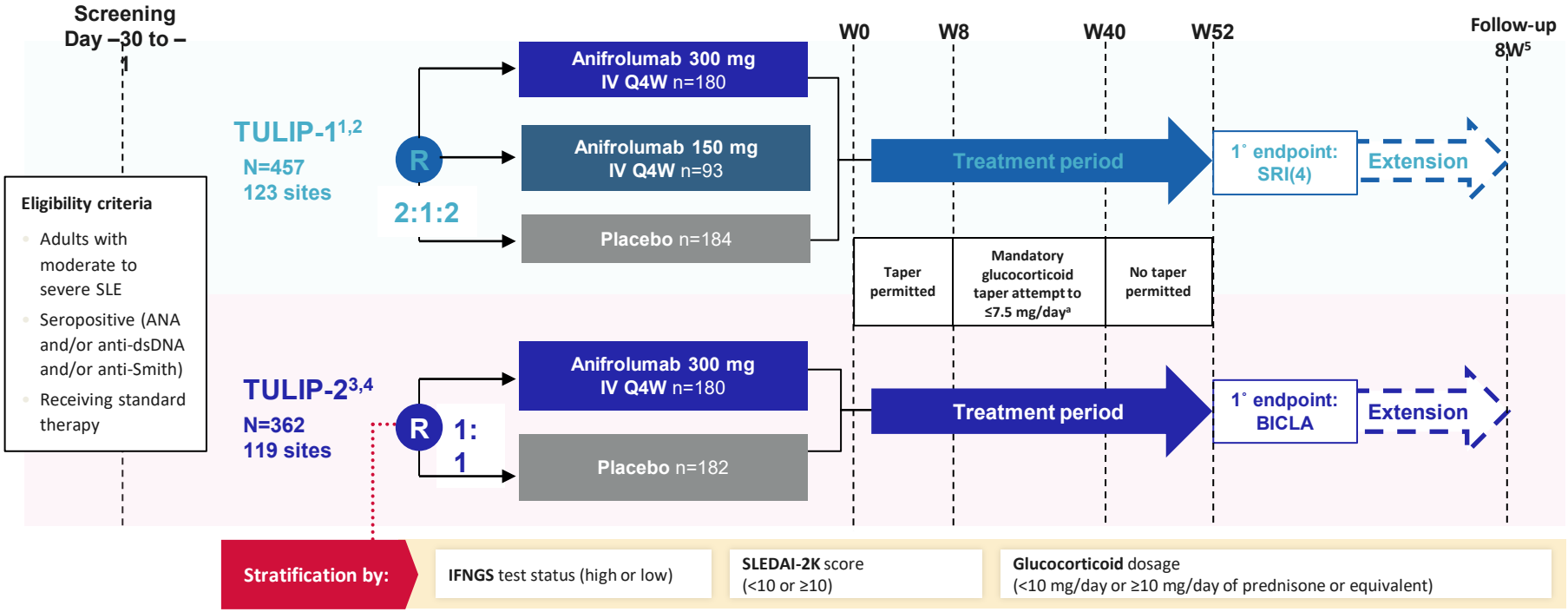
# TULIP-1 and -2




ANA, antinuclear antibody; anti-dsDNA, anti–double-stranded DNA; BICLA, British Isles Lupus Assessment Group–based Composite Lupus Assessment; IFNGS, interferon gene signature; IV, intravenous; LTE, long-term extension; Q4W, every 4 weeks; R, randomization; SLE, systemic lupus erythematosus; SLEDAI-2K, SLE Disease Activity Index 2000; SRI(4), SLE Responder Index of 4; W, week.

[a]For patients with baseline glucocorticoid dosage ≥10 mg/day prednisone or equivalent.

1. Furie RA, et al. Supplementary Appendix. *Lancet Rheumatol*. 2019;1:e208–19. 2. Furie RA, et al. *Lancet Rheumatol*. 2019;1:e208–19.
3. Morand EF, et al. *N Engl J Med*. 2020;382:211–21. 4. Morand EF, et al. Supplementary Appendix. *N Engl J Med*. 2020;382:211–21.
5. Morand EF, et al. Poster 1828 presented at: American College of Rheumatology All-Virtual Annual Meeting; November 5–9, 2020.



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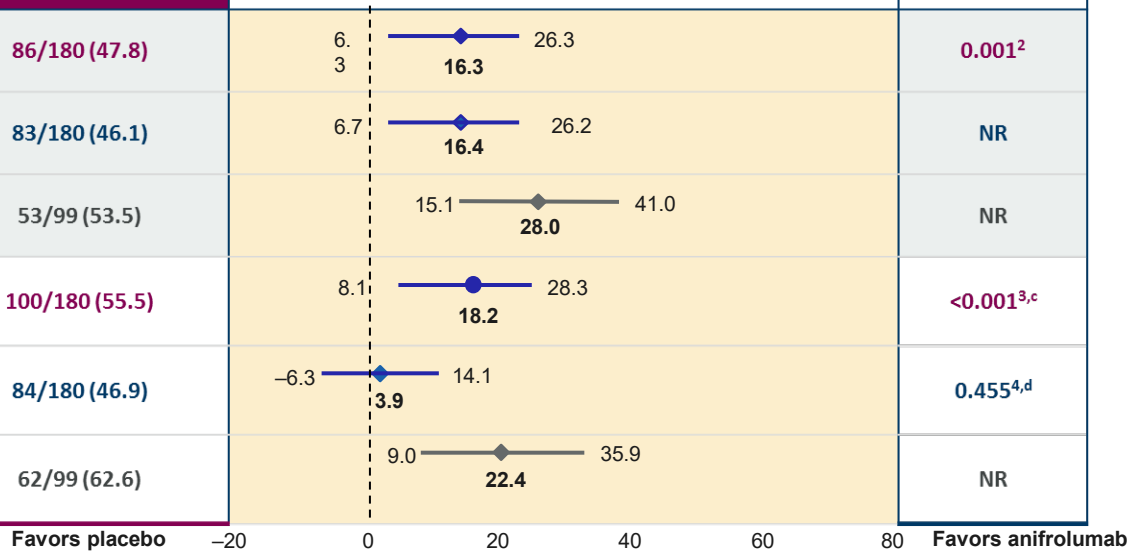
# Primaire eindpunten

| Primary Endpoint | | Placebo n/N (%) | Anifrolumab 300 mg, n/N (%) | Treatment Difference (95% CI) | *P*-value |
|---|---|---|---|---|---|
| BICLA, W52 (TULIP-2)[1] | TULIP-2 | 57/182 (31.5) | 86/180 (47.8) | 6.3 **16.3** 26.3 | 0.001[2] |
| | TULIP-1[a] | 54/184 (29.6) | 83/180 (46.1) | 6.7 **16.4** 26.2 | NR |
| | MUSE[b] | 26/101 (25.7) | 53/99 (53.5) | 15.1 **28.0** 41.0 | NR |
| SRI(4), W52 (TULIP-1)[1] | TULIP-2 | 68/182 (37.3) | 100/180 (55.5) | 8.1 **18.2** 28.3 | <0.001[3,c] |
| | TULIP-1[a] | 79/184 (43.0) | 84/180 (46.9) | −6.3 **3.9** 14.1 | 0.455[4,d] |
| | MUSE[b] | 41/102 (40.2) | 62/99 (62.6) | 9.0 **22.4** 35.9 | NR |




BICLA, BILAG–based Combined Lupus Assessment; BILAG-2004, British Isles Lupus Assessment Group-2004; CI, confidence interval; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; SRI(4), Systemic Lupus Erythematosus Responder Index of 4; W, Week.
Analytic methods and definitions differ across trials.
[a]Value after the restricted medication rules were amended to correct for inappropriately classified NSAID use; [b]The primary publication of MUSE[5] expressed these data as odds ratios rather than CIs; [c]Nominal *P*-value that is not multiplicity adjusted; [d]The primary outcome in TULIP-1 was not significant per the prespecified analysis plan, so all other comparisons were considered nonsignificant.
1. Tanaka Y, Tummala R. *Mod Rhematol.* 2020;1–12;doi:10.1080/14397595.2020.1812201. 2. Morand EF, et al. *N Engl J Med*. 2020;382:211–21. 3. Morand EF, et al. Supplementary Appendix. *N Engl J Med*. 2020;382:211–21. 4. Furie RA, et al. *Lancet Rheumatol*. 2019;1:e208–19. 5. Furie R, et al. *Arthritis Rheumatol*. 2017;69:376–86.

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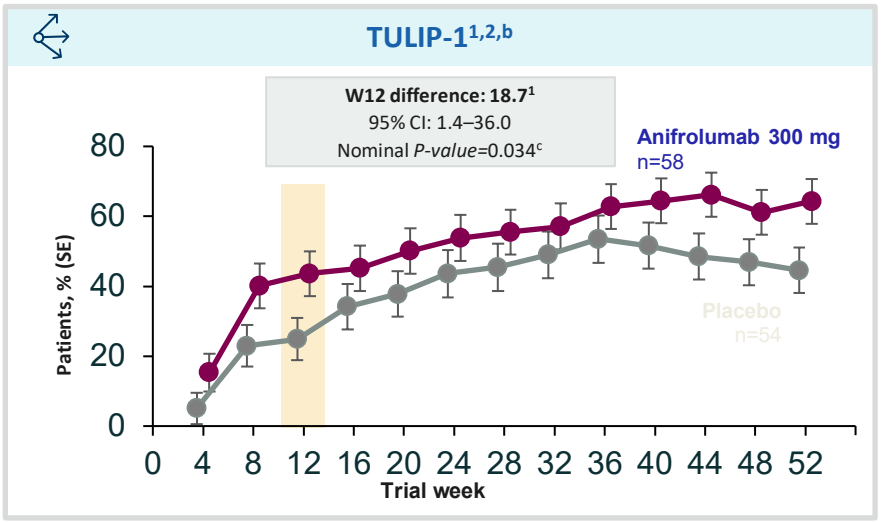
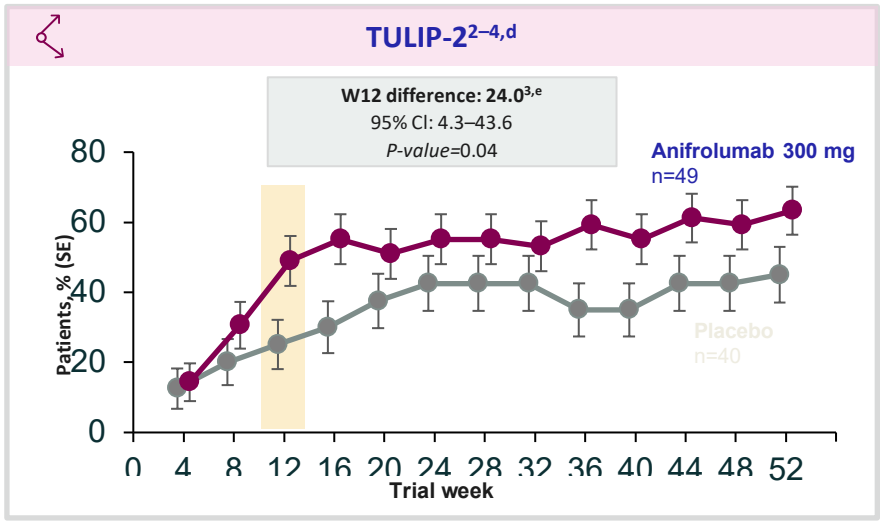
# CLASI-respons

**Proportion of Patients With a ≥50% Reduction in CLASI Activity Score[a]**




CI, confidence interval; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; NSAID, nonsteroidal anti-inflammatory; SE, standard error; W, week.
[a]Among patients with at least moderately active skin disease (CLASI activity score ≥10) at baseline; [b]Restricted medication rules were amended to correct for inappropriately classified NSAID use; [c]As the primary outcome was not significant per the prespecified analysis plan, all other comparisons were considered nonsignificant; [d]Amended restricted medication rules from TULIP-1 were applied before study unblinding; [e]The differences between the two groups and the associated 95% CIs were adjusted for the factors which randomization was stratified using the stratified Cochran–Mantel–Haenszel method. *P*-values were adjusted with the use of a weighted Holm procedure.

1. Furie RA, et al. *Lancet Rheumatol.* 2019;1:e208–19. 2. AstraZeneca Data on File. 3. Morand EF, et al. Supplementary Appendix. *N Engl J Med*. 2020;382:211–21.
3. Tanaka Y, Tummala R. *Mod Rhematol*. 2020;1–12;doi:10.1080/14397595.2020.1812201.



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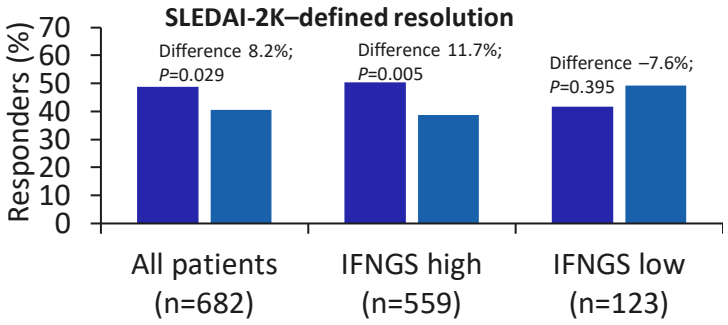
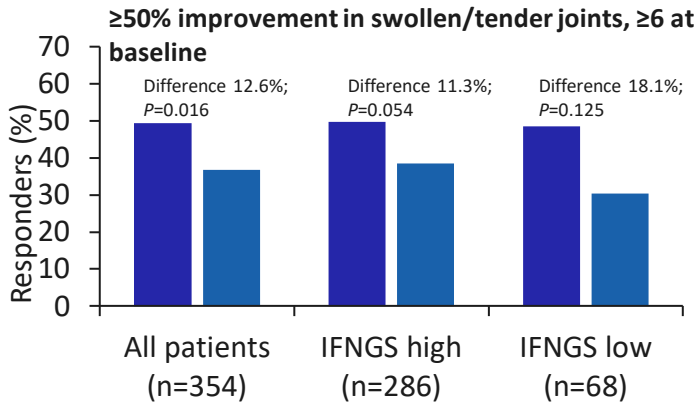
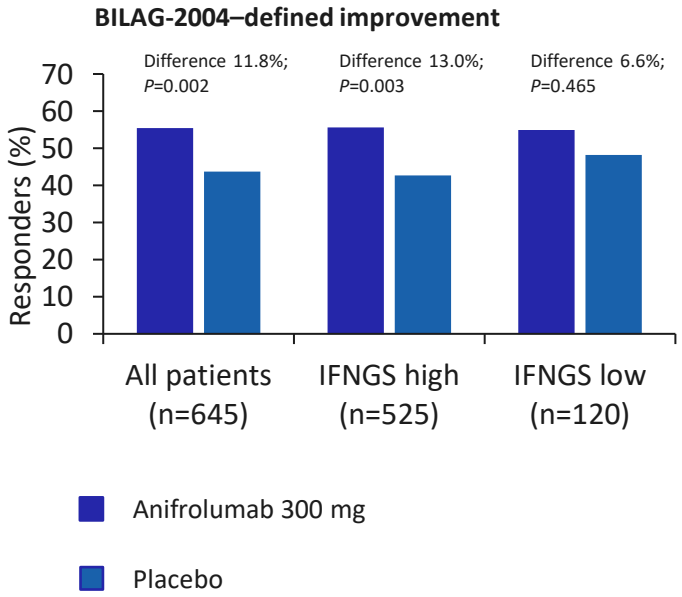
# Effect anifrolumab op gewrichten




BILAG-2004, British Isles Lupus Assessment Group-2004; IFNGS, interferon gene signature; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.
Data pooled from TULIP-1 and TULIP-2 trials.
Resolution defined as SLEDAI-2K arthritis component score of 0 in patients with SLEDAI-2K arthritis component score of ≥4 at baseline; improvement defined as BILAG-2004 arthritis, musculoskeletal baseline score A change to B, C, or D, or baseline B change to C or D. All *P*-values are nominal.

Merril JT, Werth VP, Furie RA et al. Anifrolumab Effects on Rash and Arthritis in Patients With SLE and Impact of Interferon Signal in Pooled Data From Phase 3 Trials. Oral presentation at EULAR 2021



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**Table 1** AEs in patients during treatment in pooled MUSE, TULIP-1 and TULIP-2 data

| | Anifrolumab 300 mg (n=459) | | Placebo (n=466) | | EAIR risk difference (anifrolumab 300 mg – placebo) (95% CI) |
|---|---|---|---|---|---|
| | n (%) | EAIR | n (%) | EAIR | |
| Any AE* | 399 (86.9) | 290.1 | 370 (79.4) | 225.2 | NR |
| SAE | 54 (11.8) | 13.6 | 78 (16.7) | 20.7 | −7.2 (−12.5 to −1.9) |
| Death | 2 (0.4) | 0.5 | 0 | 0 | 0.5 (−0.5 to 1.7) |
| DAE | 19 (4.1) | 4.5 | 24 (5.2) | 6.0 | −1.4 (−4.7 to 1.7) |
| AESI†‡ | 61 (13.3) | 15.5 | 47 (10.1) | 12.2 | 3.3 (−1.5 to 8.2) |
| Non-opportunistic serious infections | 22 (4.8) | 5.4 | 26 (5.6) | 6.6 | −1.3 (−4.7 to 2.1) |
| Opportunistic infections | 1 (0.2) | 0.2 | 1 (0.2) | 0.2 | −0.0 (−1.2 to 1.1) |
| Anaphylaxis | 0 | 0 | 0 | 0 | 0 |
| Malignancy | 3 (0.7) | 0.7 | 3 (0.6) | 0.7 | −0.0 (−1.5 to 1.4) |
| Herpes zoster | 28 (6.1) | 6.9 | 6 (1.3) | 1.5 | 5.4 (2.8 to 8.4) |
| Active TB | 0 | 0 | 0 | 0 | 0 |
| Latent TB§ | 4 (0.9) | 1.0 | 1 (0.2) | 0.2 | 0.7 (−0.5 to 2.2) |
| Influenza | 12 (2.6) | 2.9 | 9 (1.9) | 2.3 | 0.6 (−1.7 to 3.0) |
| Non–SLE-related vasculitis | 0 | 0 | 2 (0.4) | 0.5 | −0.5 (−1.8 to 0.4) |
| Major adverse cardiovascular event | 1 (0.2) | 0.2 | 3 (0.6) | 0.7 | −0.5 (−2.0 to 0.7) |

EAIR was reported per 100 patient-years and calculated as the number of patients with an event/[sum of time at risk in days/(365.25×100)].
*AEs were coded by MedDRA V.22.1. An AE during intervention period was defined as an AE with a date of onset on or after the day of the first dose of anifrolumab or placebo and on or before the day of the last dose of anifrolumab or placebo plus 28 days.
†AESIs differed from the individual MUSE and TULIP trials and were identified using standardised MedDRA queries and custom preferred term groupings.
‡Hypersensitivity was included as an AESI in MUSE but not in the TULIP trials and is not included in this table.
§Patients with latent TB (not active TB) were interferon gamma release assay positive without radiographic or clinical manifestations of active TB.
AE, adverse event; AESI, AE of special interest; DAE, AE leading to discontinuation of investigational product; EAIR, exposure-adjusted incidence rate; MedDRA, Medical Dictionary for Regulatory Activities; NR, not reported; SAE, serious AE; TB, tuberculosis.

Tummala R, *et al. Lupus Science & Medicine* 2021;**8**:e000464. doi:10.1136/lupus-2020-000464

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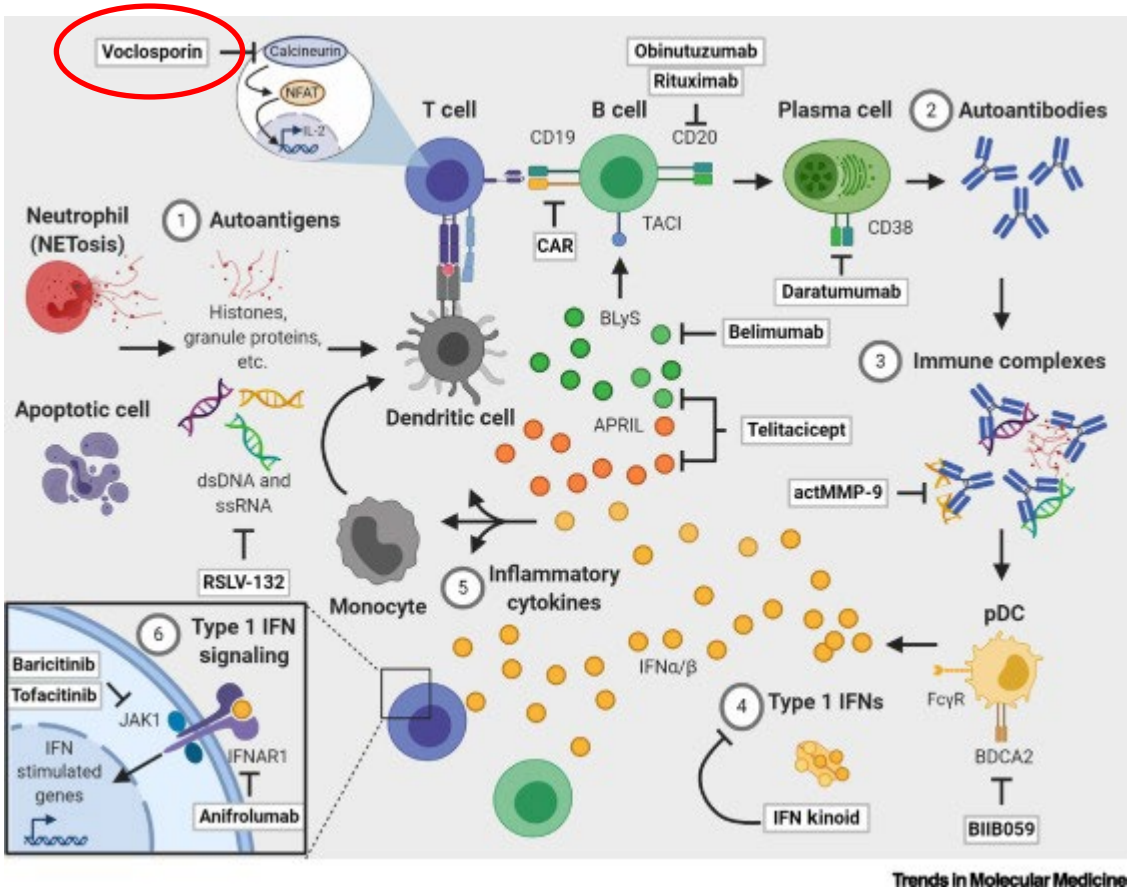
# Anifrolumab

- EMA-goedgekeurd 2022
- Studies naar lupus-nefritis bezig

# Voclosporin

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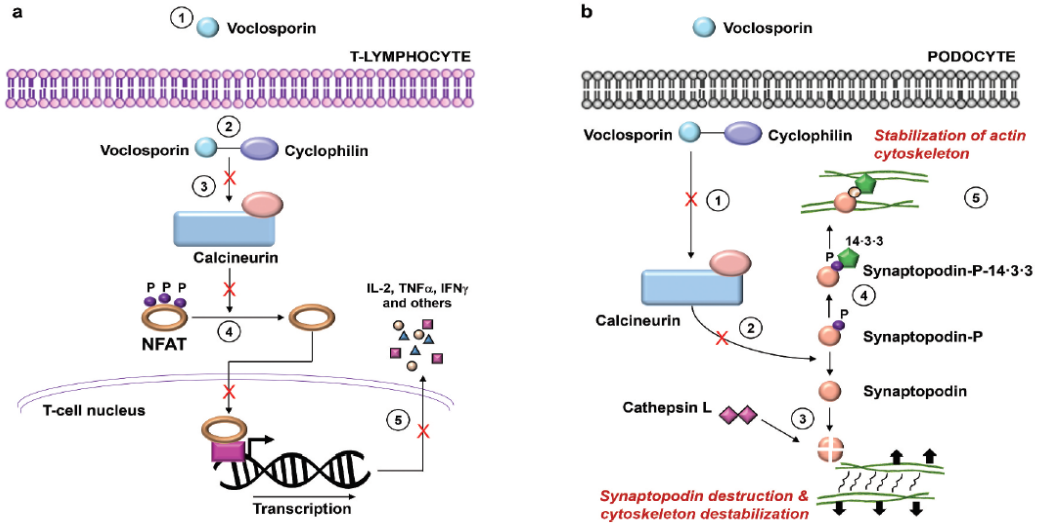
# Voclosporin

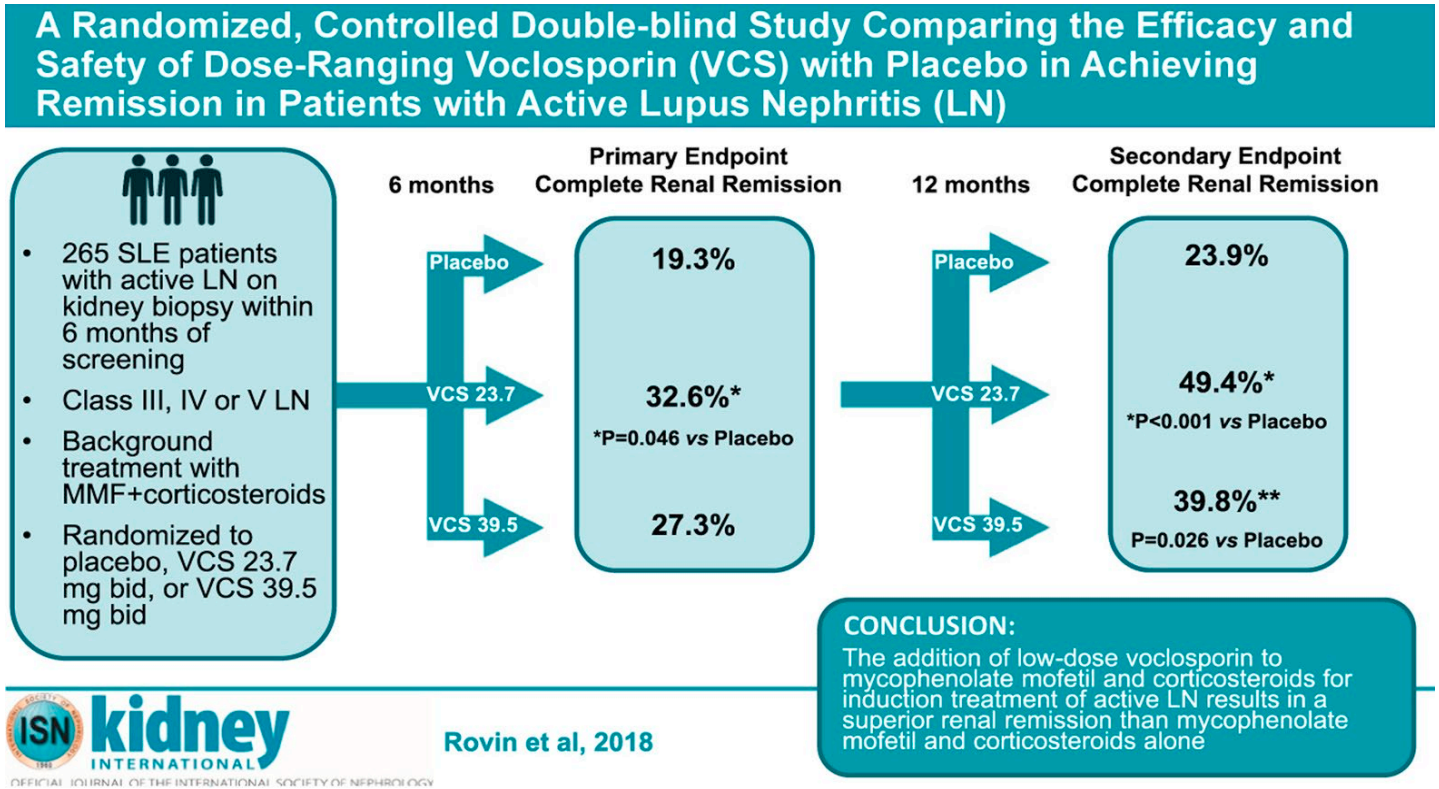
Calcineurineremmer

FDA-geregistreerd voor behandeling van lupus-nefritis




Expert Review of Clinical Immunology, 2021;17:9, 937-945

# Fase 2 – AURA-LV

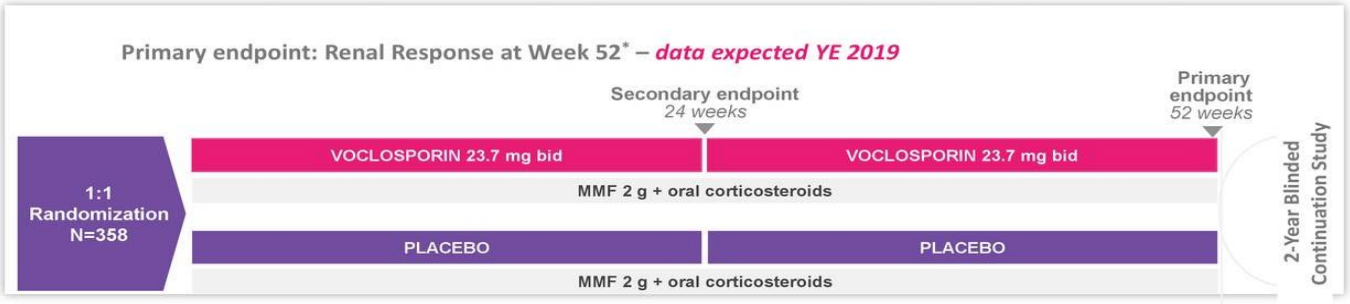


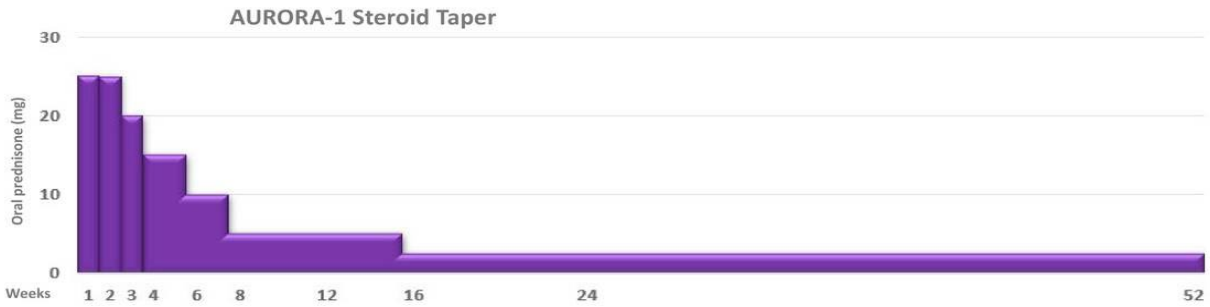

Kidney Int. 2019 Jan;95(1):219-231

# Fase 3 – AURORA

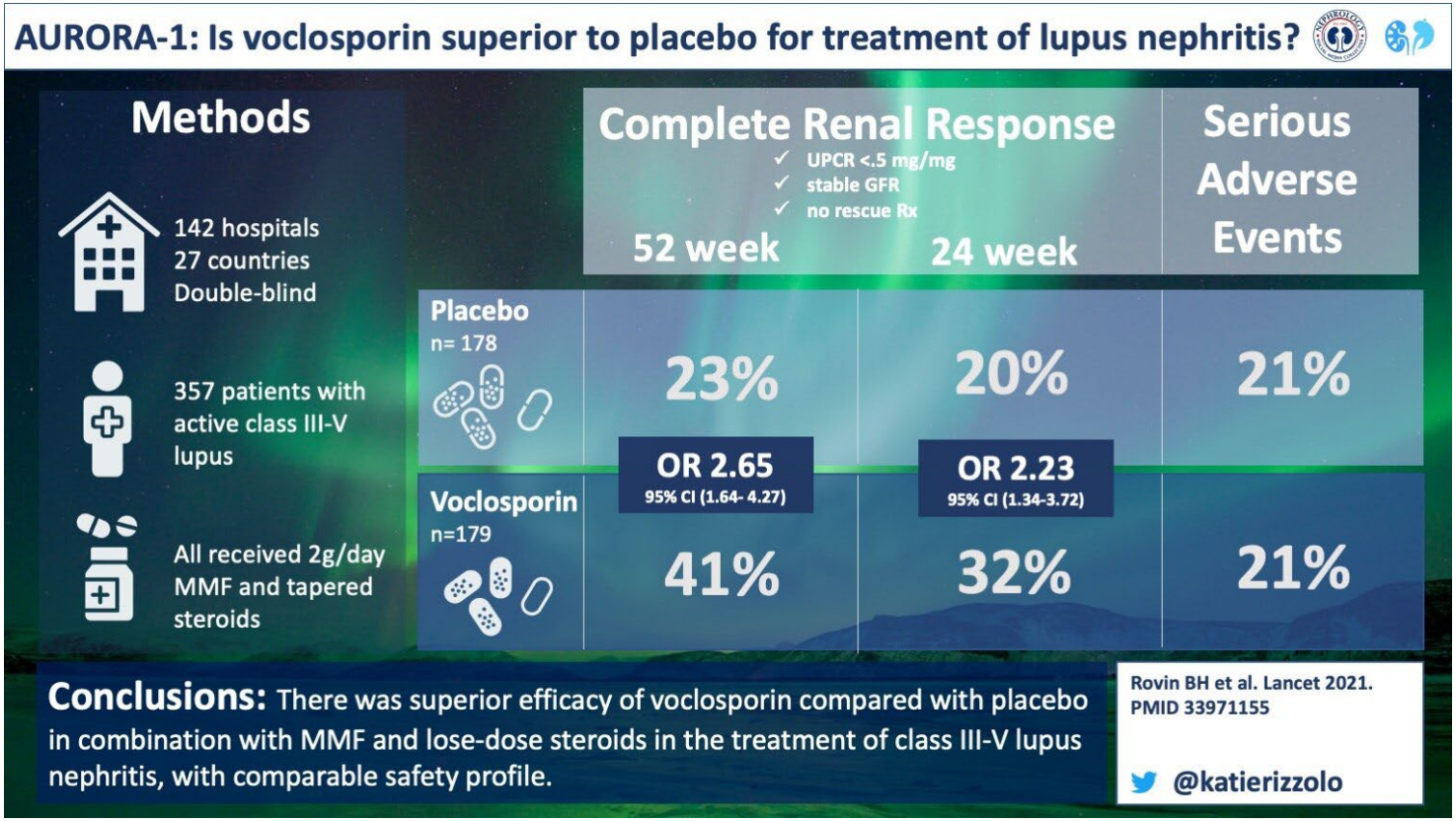
## AURORA Phase 3 Study Design Mimics AURA Phase 2 Study

Global, double-blind, placebo controlled study to evaluate whether voclosporin in combination w/background standard of care of MMF/CellCept® can increase speed of & overall remission rates in the presence of low steroids;
*Target enrollment of 324 patients was surpassed due to high patient demand with 358 subjects randomized*



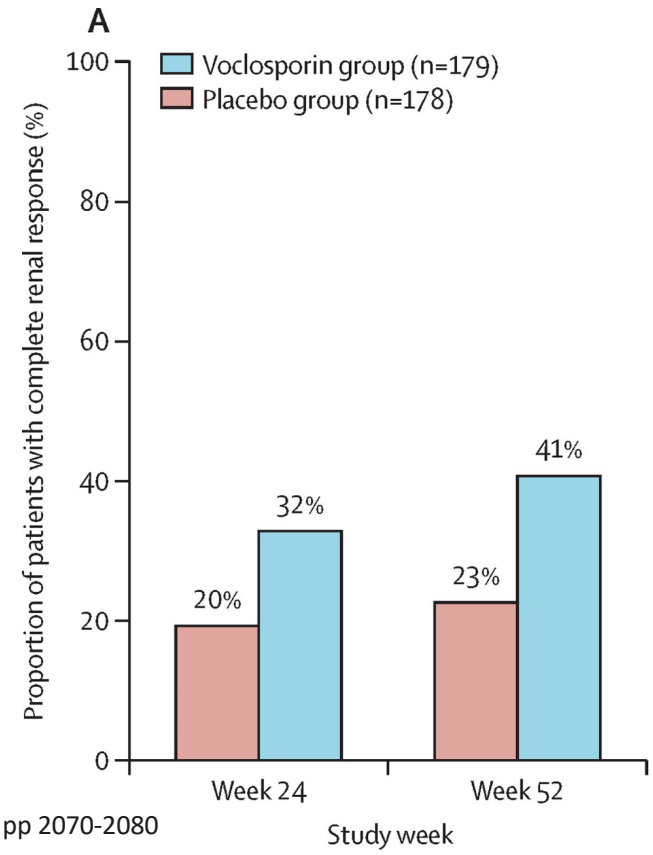



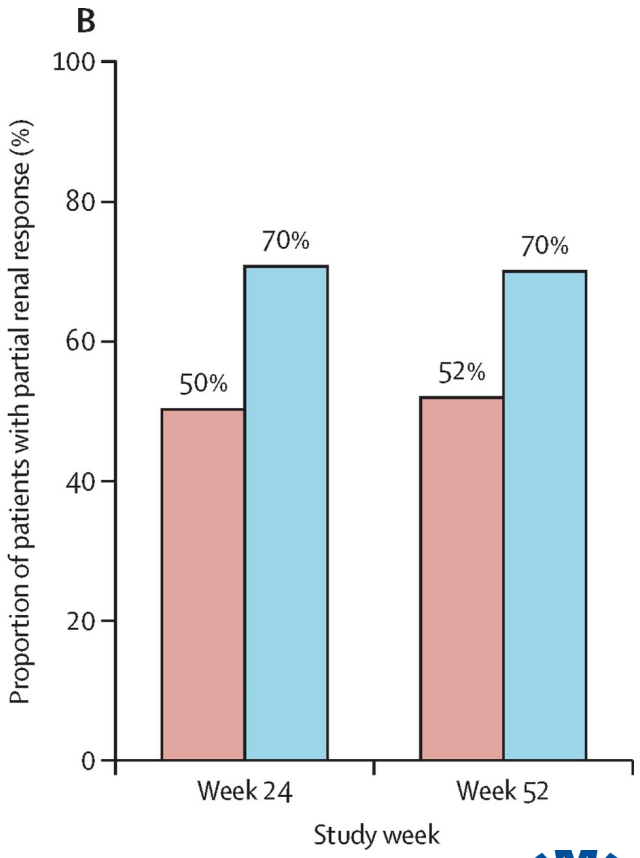

*Similar to AURA-LV definition of complete remission, ref: Kidney Int. 2019 Jan;95(1):219-231. doi: 10.1016/j.kint.2018.08.025. Epub 2018 Nov 9.




http://www.nephjc.com/news/2021/6/21/the-aurora-1-visual-abstract

# AURORA: primair/secundair eindpunt




The Lancet 2021, pp 2070-2080

European Reference Network | Connective Tissue and Musculoskeletal Diseases (ERN ReCONNET)

UMC Utrecht

| | Voclosporin group (n=178) | Placebo group (n=178) |
|---|---|---|
| **Adverse event summary** | | |
| Adverse event | 162 (91%) | 158 (89%) |
| Serious adverse event | 37 (21%) | 38 (21%) |
| Serious adverse event of infections and infestations | 18 (10%) | 20 (11%) |
| Treatment-related serious adverse event | 8 (4%) | 8 (4%) |
| Adverse event leading to study drug discontinuation | 20 (11%) | 26 (15%) |
| Death* | 1 (<1%) | 5 (3%) |
| Treatment-related adverse event leading to death | 0 | 0 |
| **Adverse events (reported ≥4% of patients)** | | |
| Infections and infestations | 115 (65%) | 101 (57%) |
| Gastrointestinal disorders | 83 (47%) | 61 (34%) |
| Investigations and infestations | 60 (34%) | 31 (17%) |
| Nervous system disorders | 47 (26%) | 27 (15%) |
| Skin and subcutaneous tissue disorders | 42 (24%) | 31 (17%) |
| Musculoskeletal and connective tissue disorders | 40 (22%) | 46 (26%) |
| Vascular disorders | 38 (21%) | 23 (13%) |
| General disorders and administration site conditions | 36 (20%) | 32 (18%) |
| Blood and lymphatic system disorders | 35 (20%) | 29 (16%) |
| Respiratory, thoracic, and mediastinal disorders | 26 (15%) | 17 (10%) |
| Renal and urinary disorders | 26 (15%) | 37 (21%) |
| Metabolism and nutritional disorders | 25 (14%) | 37 (21%) |

Adverse events are defined as an adverse event that occurs on or after the day of the first dose and up to 30 days after the last dose of voclosporin or placebo, with the exception of death. *Includes two deaths in placebo group and one death in voclosporin group that occurred >30 days after discontinuation of study drug.

*Table 3*: Adverse events (safety population)

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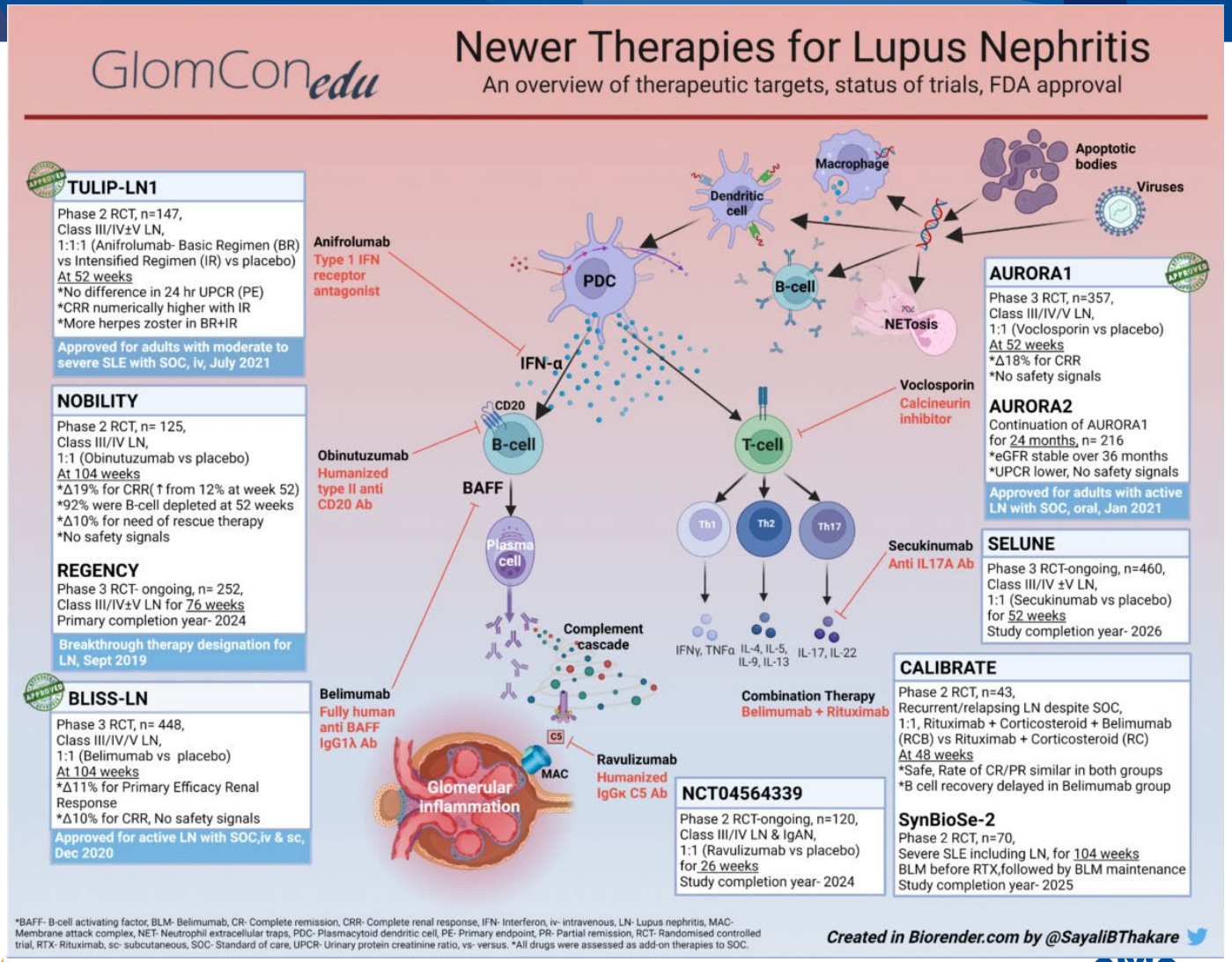


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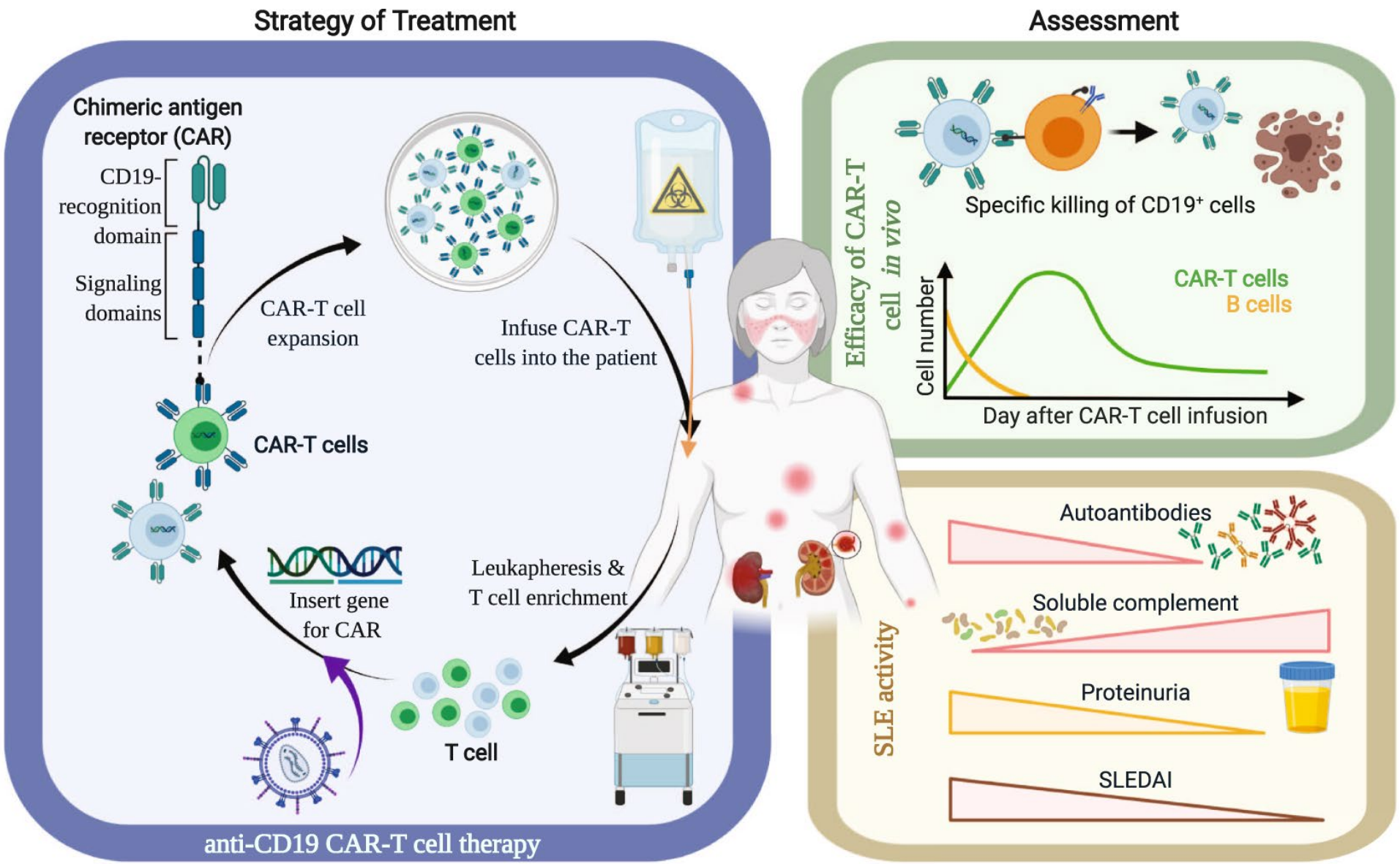
# CAR-T-cells


Strategy of Treatment
Assessment
Chimeric antigen receptor (CAR)
CD19-recognition domain
Signaling domains
CAR-T cell expansion
Infuse CAR-T cells into the patient
CAR-T cells
Insert gene for CAR
Leukapheresis & T cell enrichment
T cell
anti-CD19 CAR-T cell therapy
Efficacy of CAR-T cell in vivo
Specific killing of CD19+ cells
Cell number
CAR-T cells
B cells
Day after CAR-T cell infusion
SLE activity
Autoantibodies
Soluble complement
Proteinuria
SLEDAI

ARTICLES
https://doi.org/10.1038/s41591-022-02017-5
nature medicine



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

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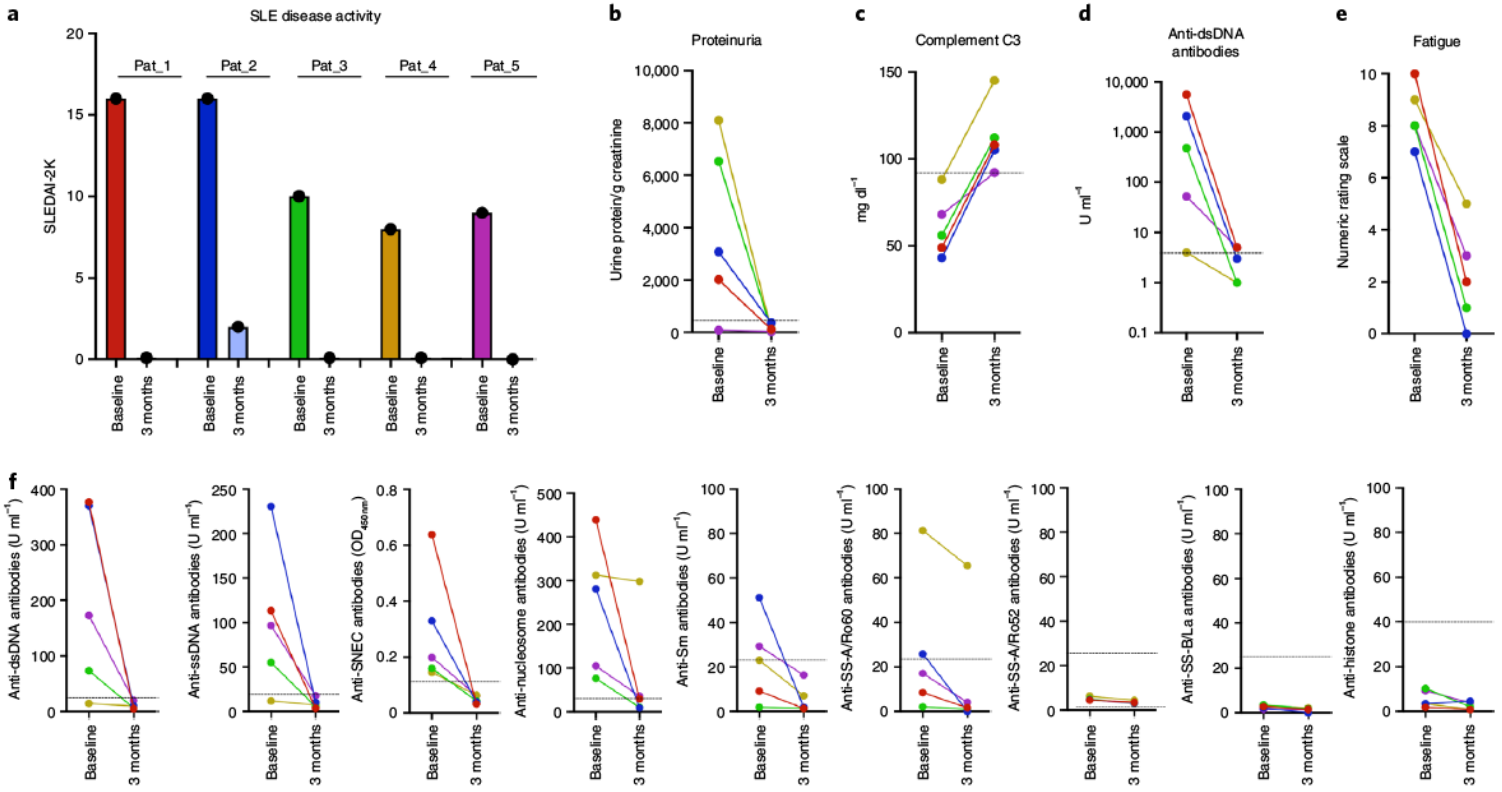

# Conclusie

- In laatste jaren nieuwe middelen voor SLE
- Belimumab / anifrolumab nu te gebruiken
- Voclosporin komt eraan
- Nieuwe middelen niet beter dan oude, maar toevoeging
- Behandeling met CAR-T-cells veelbelovend, maar nog ver van dagelijkse praktijk

# QUESTIONS

## FOUND IN GOOGLE AUTOCOMPLETE

WHY DO WHALES JUMP
WHY ARE WITCHES GREEN
WHY ARE THERE MIRRORS ABOVE BEDS
WHY DO I SAY UH
WHY IS SEA SALT BETTER
WHY ARE THERE TREES IN THE MIDDLE OF FIELDS
WHY IS THERE NOT A POKEMON MMO
WHY IS THERE LAUGHING IN TV SHOWS
WHY ARE THERE DOORS ON THE FREEWAY
WHY ARE THERE SO MANY SVCHOST.EXE RUNNING
WHY AREN'T THERE ANY COUNTRIES IN ANTARCTICA
WHY ARE THERE SCARY SOUNDS IN MINECRAFT
WHY IS THERE KICKING IN MY STOMACH
WHY ARE THERE TWO SLASHES AFTER HTTP
WHY ARE THERE CELEBRITIES
WHY DO SNAKES EXIST
WHY DO OYSTERS HAVE PEARLS
WHY ARE DUCKS CALLED DUCKS
WHY DO THEY CALL IT THE CLAP
WHY ARE KYLE AND CARTMAN FRIENDS
WHY IS THERE AN ARROW ON AANG'S HEAD
WHY ARE TEXT MESSAGES BLUE
WHY ARE THERE MUSTACHES ON CLOTHES
WHY ARE THERE MUSTACHES ON CARS
WHY ARE THERE MUSTACHES EVERYWHERE
WHY ARE THERE SO MANY BIRDS IN OHIO
WHY IS THERE SO MUCH RAIN IN OHIO
WHY IS OHIO WEATHER SO WEIRD
WHY ARE THERE MALE AND FEMALE BIKES
WHY ARE THERE BRIDESMAIDS
WHY DO DYING PEOPLE REACH UP
WHY AREN'T THERE VARSITY ARTISTS
WHY ARE OLD KUNGONS DIFFERENT
WHY AREN'T DINOSAUR GHOSTS


WHY IS PROGRAMMING SO HARD
WHY IS THERE A 0 OHM RESISTOR
WHY DO AMERICANS HATE SOCCER
WHY DO RHYMES SOUND GOOD
WHY DO TREES DIE
WHY IS THERE NO SOUND IN SPACE
WHY AREN'T POKEMON REAL
WHY AREN'T BULLETS SHARP
WHY DO DREAMS SEEM SO REAL
WHY IS THERE HELL IF GOD FORGIVES

WHY DO TESTICLES MOVE
WHY ARE THERE PSYCHICS
WHY ARE HATS SO EXPENSIVE
WHY IS THERE CAFFEINE IN MY SHAMPOO
WHY DO YOUR BOOBS HURT
WHY DO IGUANAS DIE

WHY ARE THERE SLAVES IN THE BIBLE
WHY DO TWINS HAVE DIFFERENT FINGERPRINTS
WHY ARE AMERICANS AFRAID OF DRAGONS
WHY IS YKK ON ALL ZIPPERS

WHY IS HTTPS CROSSED OUT IN RED
WHY IS THERE A LINE THROUGH HTTPS
WHY IS THERE A RED LINE THROUGH HTTPS ON FACEBOOK
WHY IS HTTPS IMPORTANT


WHY ARE THERE WEEKS
WHY DO I FEEL DIZZY

WHY AREN'T ECONOMISTS RICH
WHY DO AMERICANS CALL IT SOCCER
WHY ARE MY EARS RINGING
WHY ARE THERE SO MANY AVENGERS
WHY ARE THE AVENGERS FIGHTING THE X MEN
WHY IS WOLVERINE NOT IN THE AVENGERS
WHY IS THERE LAVA

WHY ARE THERE SWARMS OF GNATS
WHY IS THERE PHLEGM
WHY ARE THERE SO MANY CROWS IN ROCHESTER,
WHY IS PSYCHIC WEAK TO BUG
WHY DO CHILDREN GET CANCER
WHY IS POSEIDON ANGRY WITH ODYSSEUS
WHY IS THERE ICE IN SPACE
WHY IS MN

WHY ARE THERE ANTS IN MY LAPTOP

WHY IS EARTH TILTED
WHY IS SPACE BLACK
WHY IS OUTER SPACE SO COLD
WHY ARE THERE PYRAMIDS ON THE MOON
WHY IS NASA SHUTTING DOWN
WHY ARE THERE FEMALE MR MIMES


WHY IS THERE AN OWL IN MY BACKYARD
WHY IS THERE AN OWL OUTSIDE MY WINDOW
WHY IS THERE AN OWL ON THE DOLLAR BILL
WHY DO OWLS ATTACK PEOPLE
WHY ARE AK 47s SO EXPENSIVE
WHY ARE THERE HELICOPTERS CIRCLING MY HOUSE
WHY ARE THERE GODS
WHY ARE THERE TWO SPOCKS
WHY IS MT VESUVIUS THERE
WHY DO THEY SAY T MINUS
WHY ARE THERE OBELISKS
WHY ARE WRESTLERS ALWAYS WET
WHY ARE OCEANS BECOMING MORE ACIDIC
WHY IS ARWEN DYING
WHY AREN'T MY QUAIL LAYING EGGS
WHY AREN'T MY QUAIL EGGS HATCHING
WHY AREN'T THERE ANY FOREIGN MILITARY BASES IN AMERICA
WHY IS LIFE SO BORING

WHY ARE MY BOOBS ITCHY
WHY ARE CIGARETTES LEGAL
WHY ARE THERE DUCKS IN MY POOL
WHY IS JESUS WHITE
WHY IS THERE LIQUID IN MY EAR
WHY DO Q TIPS FEEL GOOD
WHY DO GOOD PEOPLE DIE


WHY ARE ULTRASOUNDS IMPORTANT
WHY ARE ULTRASOUND MACHINES EXPENSIVE
WHY IS STEALING WRONG

WHY ARE THERE TINY SPIDERS IN MY HOUSE
WHY DO SPIDERS COME INSIDE
WHY ARE THERE HUGE SPIDERS IN MY HOUSE
WHY ARE THERE LOTS OF SPIDERS IN MY HOUSE
WHY ARE THERE SPIDERS IN MY ROOM
WHY ARE THERE SO MANY SPIDERS IN MY ROOM
WHY DO SPIDER BITES ITCH
WHY IS DYING SO SCARY

WHY IS THERE NO GPS IN LAPTOPS
WHY DO KNEES CLICK
WHY AREN'T THERE E GRADES
WHY IS ISOLATION BAD
WHY DO BOYS LIKE ME
WHY DON'T BOYS LIKE ME
WHY IS THERE ALWAYS A JAVA UPDATE
WHY ARE THERE RED DOTS ON MY THIGHS
WHY IS LYING GOOD


WHY IS GPS FREE

WHY ARE DOGS AFRAID OF FIREWORKS
WHY IS THERE NO KING IN ENGLAND