



# Treatment of Systemic Lupus Erythematosus *Taking into consideration outcomes and new trials*

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# Disclosures: Janet Pope

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- **Grants/research:** Frensenius Kabi, Mallinckrodt Pharmaceuticals, Seattle Genetics
- **Consultant:** AbbVie, Amgen, Astra Zeneca, BI, BMS, Celltrion, EMERALD, Frensenius Kabi, Galapagos, GSK, Janssen, Lilly, Mallinckrodt Pharmaceuticals, Medexus, Mitsubishi Tanabe Pharma, Novartis, Pfizer, Roche, Sandoz, Samsung, Sobi, Viatris
- **Speaker/advisory board:** AbbVie, Amgen, Astra Zeneca, BI, BMS, Frensenius Kabi, Galapagos, GSK, Janssen, Lilly, Novartis, Organon, Pfizer, Sandoz, UCB, Viatris
  
- **Committees:**
- **CRA:** Scientific Committee (chair), Education, Therapeutics, Guidelines, Human Resources, LEAP (chair)
- **ORA:** Committee for AGM (chair), Access, Therapeutics

**Clinical  
Heterogeneity  
of SLE**



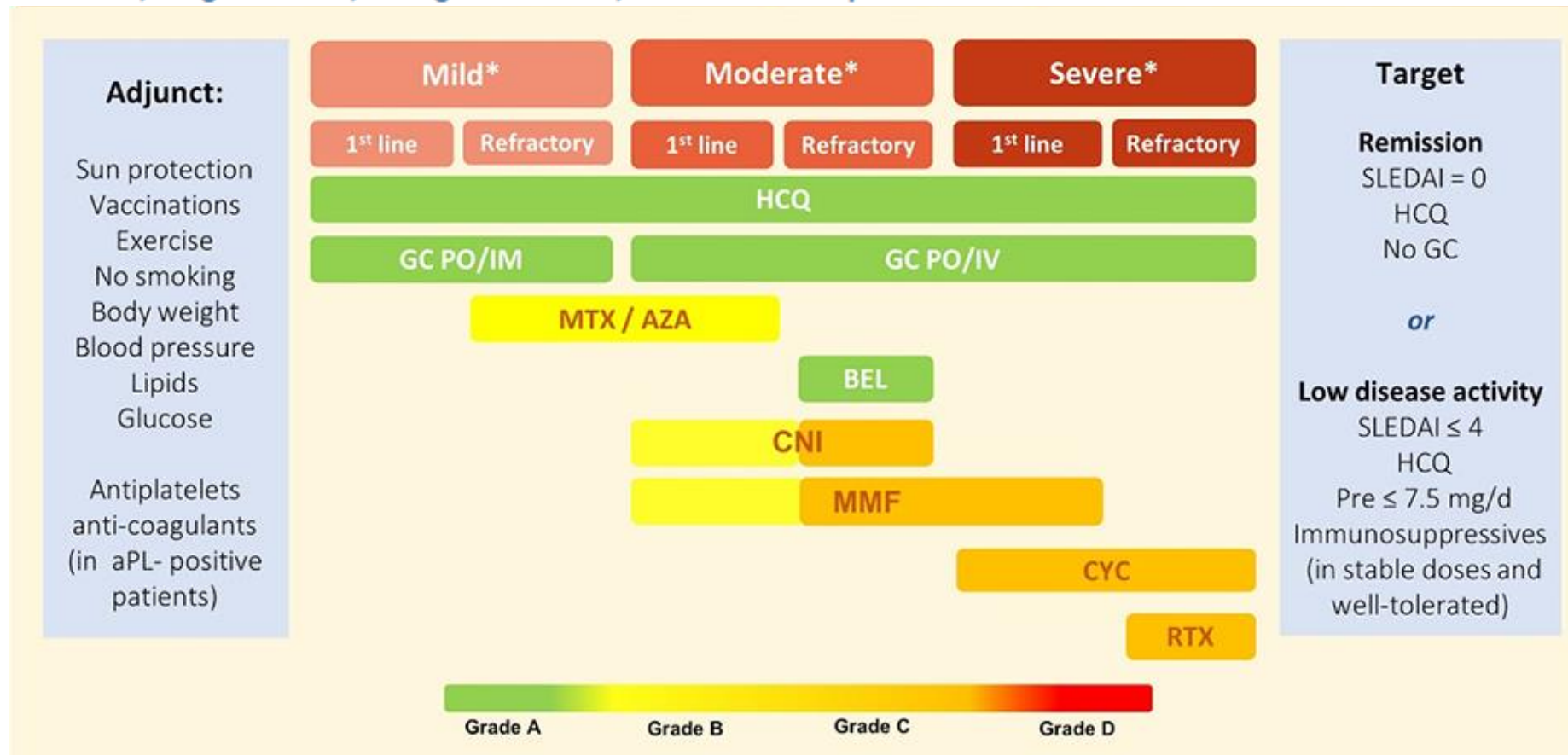
# Objectives

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- To be updated on new studies in SLE
- To critique clinical trial design in SLE RCTs
- To be aware of outcome measurements in SLE
  - Advantages and disadvantages

# 2019 UPDATE OF THE EULAR RECOMMENDATIONS FOR THE MANAGEMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS

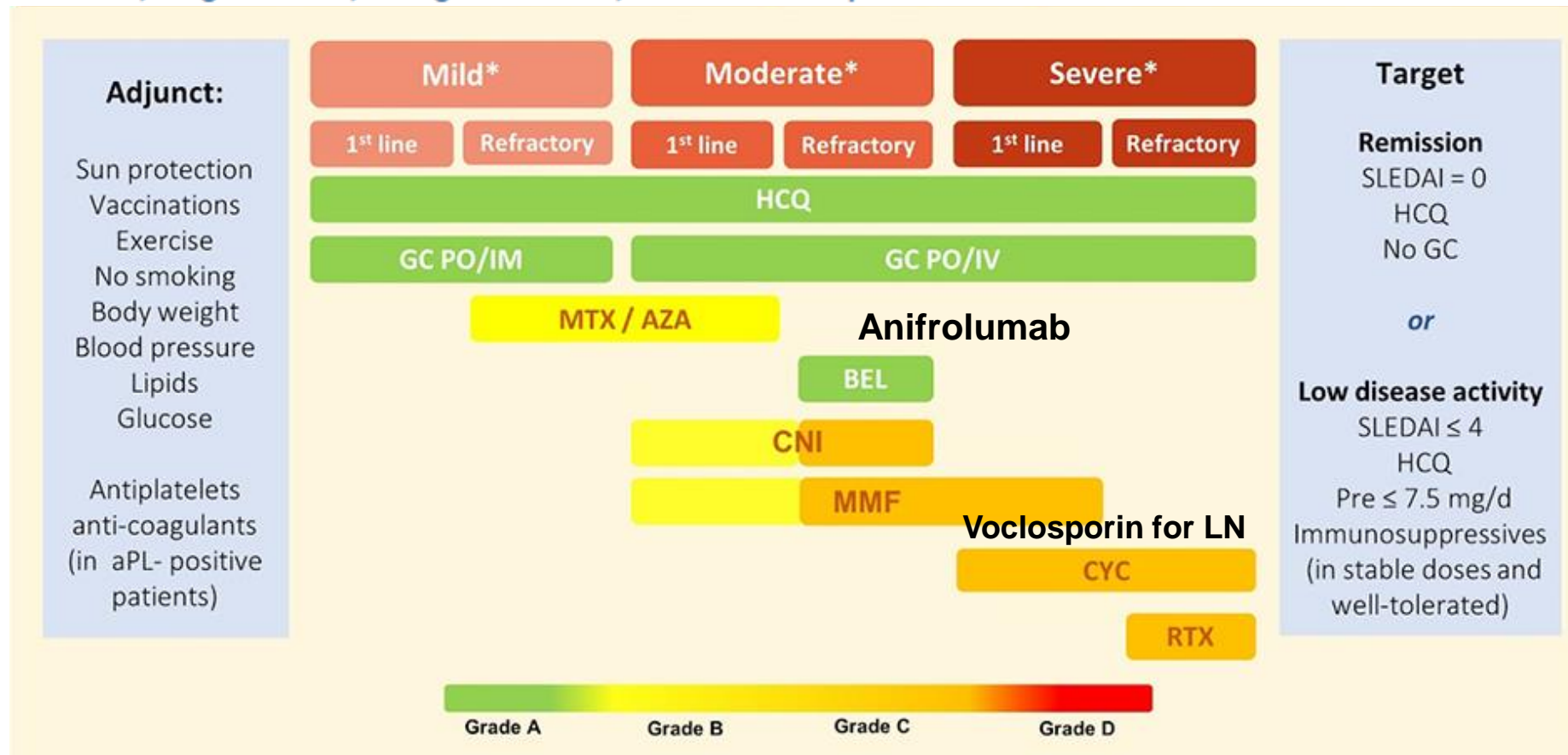
**Antonis Fanouriakis<sup>1</sup>, Myrto Kostopoulou<sup>2</sup>, Alessia Alunno<sup>3</sup>, Martin Aringer<sup>4</sup>, Ingeborg Bajema<sup>5</sup>, John N. Boletis<sup>6</sup>, Ricard Cervera<sup>7</sup>, Andrea Doria<sup>8</sup>, Caroline Gordon<sup>9</sup>, Marcello Govoni<sup>10</sup>, Frederic Houssiau<sup>11</sup>, David Jayne<sup>12</sup>, Marios Kouloumas<sup>13</sup>, Annegret Kuhn<sup>14</sup>, Janni Lisander Larsen<sup>15</sup>, Kirsten Lerstrom<sup>16</sup>, Gabriela Moroni<sup>17</sup>, Marta Mosca<sup>18</sup>, Matthias Schneider<sup>19</sup>, Josef S. Smolen<sup>20</sup>, Elisabet Svenungsson<sup>21</sup>, Vladimir Tesar<sup>22</sup>, Angela Tincani<sup>23</sup>, Anne Troldborg<sup>24</sup>, Ronald van Vollenhoven<sup>25</sup>, Jörg Wenzel<sup>26</sup>, George Bertsias<sup>27</sup>, Dimitrios Boumpas<sup>1</sup>**



**Mild:** constitutional symptoms/ mild arthritis/ rash ≤9% BSA/PLTs 50-100 x 10<sup>9</sup>/mm<sup>3</sup>; SLEDAI≤6; BILAG C or ≤1 BILAG B manifestation  
**Moderate:** RA-like arthritis/ rash 9-18% BSA/cutaneous vasculitis ≤18% BSA; PLTs 20-50x10<sup>3</sup>/mm<sup>3</sup>/serositis; SLEDAI 7-12; ≥2 BILAG B manifestations  
**Severe:** major organ threatening disease (nephritis, cerebritis, myelitis, pneumonitis, mesenteric vasculitis; thrombocytopenia with platelets <20x10<sup>3</sup>/mm<sup>3</sup>; TTP-like disease or acute hemophagocytic syndrome; SLEDAI>12; ≥1 BILAG A manifestations

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# SLE metrics

## SLE clinical remission<sup>2</sup>

- Clinical SLEDAI-2K = 0 (increased anti-dsDNA and low complement were excluded)
- Prednisone  $\leq 5$  mg/d
- Stable immunosuppressants and/or antimalarials

## LLDAS<sup>1</sup>

- SLE disease activity index 2000 (SLEDAI-2K)  $\leq 4$ 
  - No major organ activity
  - No new disease activity
  - Physician Global Assessment (0–3)  $\leq 1$
  - Prednisolone  $\leq 7.5$  mg/d
  - Well-tolerated immunosuppressant dosages

## BICLA

- BILAG-2004 improvement
  - All A scores at baseline improved to B/C/D, and all B scores improved to C/D
- No worsening in disease activity
  - No new BILAG A or >1 new BILAG B score
- No worsening of SLEDAI-2K score from baseline
- No >10% worsening in PhysGA
- No treatment failure
  - Initiation of non-protocol treatment

## SRI-4

- $\geq 4$ -point reduction in SELENA-SLEDAI score
- No new BILAG A or >1 new BILAG B score
- No  $\geq 0.3$ -point deterioration from baseline in PhysGA

## What do you use for inflammatory arthritis in SLE after Hydroxychloroquine?

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- A Low dose steroids
- B Rituximab
- C Azathioprine
- D Mycophenolate mofetil
- E Belimumab
- F Methotrexate
- G JAKi

## What do I do for SLE arthritis?

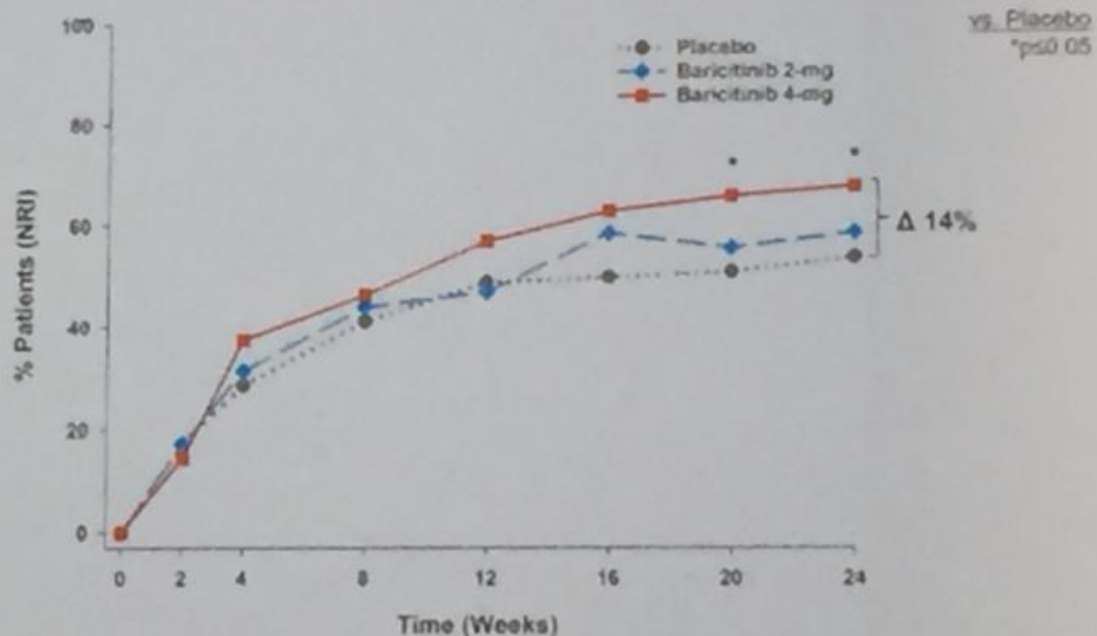
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- Treatment depends on phenotype
- If CCP+/RF+/erosive:
  - Then patient can be considered a RA overlap and treat like RA
- If reducible subluxations, non-erosive
- TNFis don't work well (my opinion)



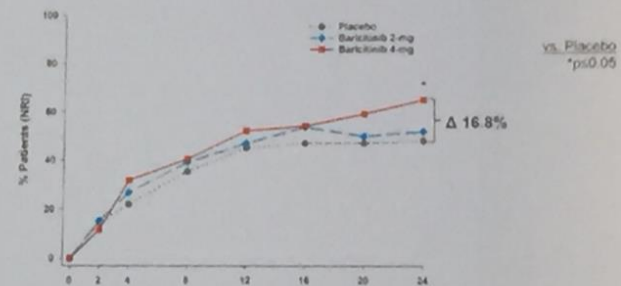
## Primary Endpoint: Resolution of Arthritis or Rash (SLEDAI-2K)

Baricitinib phase 2 SLE



## Secondary Endpoint: SRI-4 Response

Baricitinib phase 2 SLE



|                                   | Placebo<br>(N=105) | Baricitinib 2-mg<br>(N=105) | Baricitinib 4-mg<br>(N=104) |
|-----------------------------------|--------------------|-----------------------------|-----------------------------|
| Week 24                           |                    |                             |                             |
| SRI-4, n (%)                      | 50 (47.6)          | 54 (51.4)                   | 67 (64.4)*                  |
| 24-point improvement in SLEDAI-2K | 51 (48.6)          | 55 (52.4)                   | 67 (64.4)*                  |
| No worsening (≥1A/2B) by BILAG    | 80 (76.2)          | 82 (78.1)                   | 85 (81.7)                   |
| No worsening by PGA               | 78 (74.3)          | 82 (78.1)                   | 84 (80.8)                   |

BILAG-British Isles Lupus Assessment Group; NRI=nonresponder imputation; PGA=Physician's Global Assessment of Disease Activity; SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index 2000; SRI=Systemic Lupus Erythematosus Response Index. \*P-values for comparisons to placebo are based on a logistic regression model with treatment, region, baseline disease activity and baseline anti-dsDNA status in the model.

## Safety

No VTE signal (1 in 4mg bari)  
No MACE, malignancy

Phase 3 SLE-BRAVE-II did not meet endpoint of SRI-4 response.

Key secondary endpoints were not met in either study.

<https://investor.lilly.com/news-releases/news-release-details/updates-olumiantr-baricitinib-phase-3-lupus-program-and-fda>

[Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 2 trial.](#)

Wallace DJ, Furie RA, Tanaka Y, Kalunian KC, Mosca M, Petri MA, Dörner T, Cardiel MH, Bruce IN, Gomez E, Carmack T, DeLozier AM, Janes JM, Linnik MD, de Bono S, Silk ME, Hoffman RW. Lancet. 2018 Jul 21;392(10143):222-231. doi: 10.1016/S0140-6736(18)31363-1. Erratum in: Lancet. 2018 Aug 11;392(10146):476.

PMID: 30043749

## SLE-BRAVE-I and -II: Efficacy and safety of baricitinib in SLE

- 2 Phase 3, 52-week, multicenter DBRCTs: SLE-BRAVE-I (n=760) and SLE-BRAVE-II (n=775)<sup>1</sup>
  - BARI 2 mg, 4 mg, or PBO + stable standard of care; glucocorticoid (GC) tapering encouraged
  - Primary endpoint: SRI-4 response at Week 52
  - Baseline SLEDAI-2K: 10.1 for both trials

| Efficacy measure                        | SLE-BRAVE-I |                   |                   | SLE-BRAVE-II |                   |                   |
|---|-------------|-------------------|-------------------|--------------|-------------------|-------------------|
|   | PBO (n=253) | BARI 2 mg (n=255) | BARI 4 mg (n=252) | PBO (n=256)  | BARI 2 mg (n=261) | BARI 4 mg (n=258) |
| SRI-4 at Week 52, n (%) <sup>a</sup>    | 116 (46)    | 126 (50)          | 142 (57)*         | 116 (46)     | 120 (46)          | 121 (47)          |
| SRI-4 at Week 24, n (%)                 | 99 (39)     | 114 (45)          | 117 (47)          | 98 (39)      | 104 (40)          | 108 (42)          |
| Severe flares (n, events)               | 38 (15)     | 34 (13)           | 26 (10)           | 26 (10)      | 29 (11)           | 29 (11)           |
| Time to first severe flare, HR (95% CI) | NA          | 0.8 (0.52, 1.32)  | 0.7 (0.40, 1.08)  | NA           | 1.1 (0.65, 1.89)  | 1.1 (0.67, 1.94)  |
| GC sparing at Week 52                   | 36 (31)     | 31 (29)           | 36 (34)           | 33 (32)      | 34 (30)           | 36 (34)           |
| LLDAS at Week 52                        | 66 (26)     | 65 (26)           | 74 (30)           | 59 (23)      | 62 (24)           | 65 (25)           |

\*P=0.05 vs PBO

- Primary endpoint in SLE-BRAVE-II failed, as did all secondary endpoints in both trials
- Pooled safety of Phase 2/3 trials: no increased VTE or malignancy; numerically more dose-related SIE, HZ, and MACE<sup>2</sup>

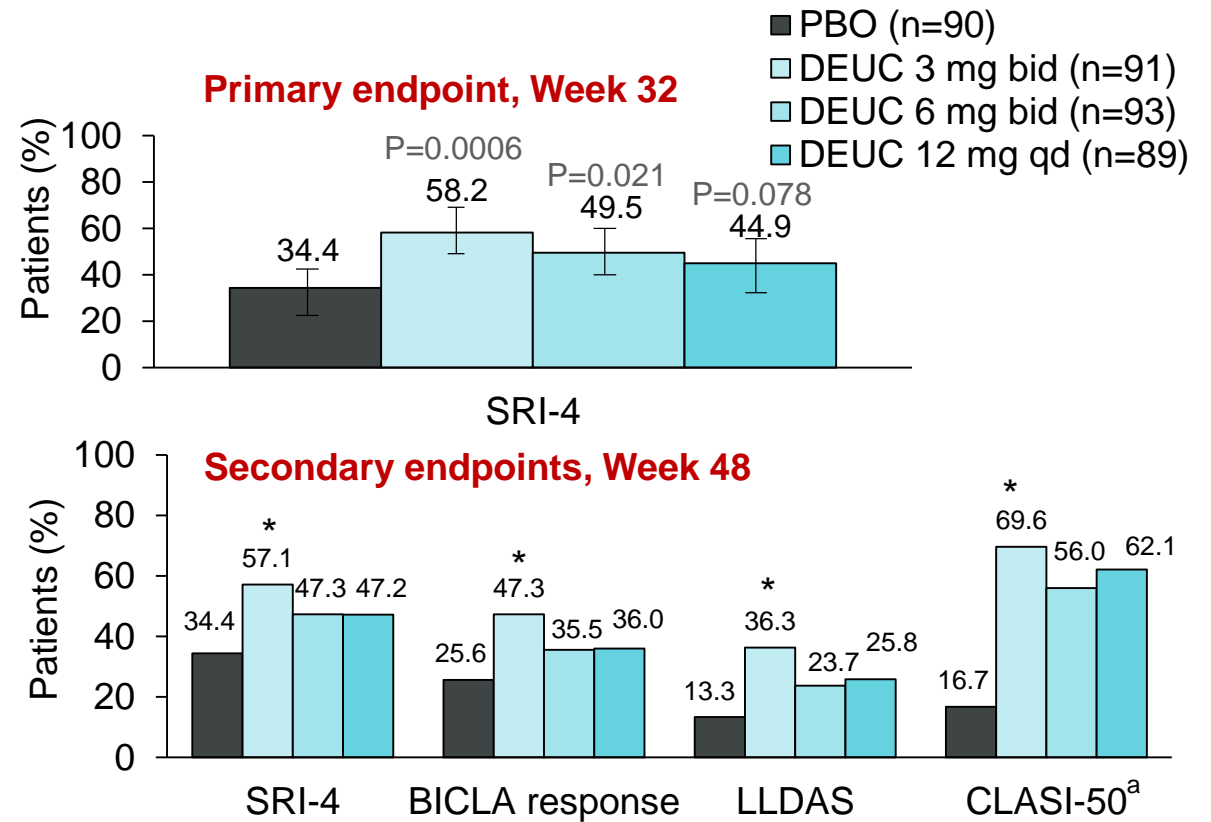
<sup>a</sup>Nonresponder imputation and multiple imputation. LLDAS, Lupus Low Disease Activity State; SRI-4, SLE Responder Index-4

1. Morand EF, et al. EULAR 2022, Copenhagen, POS0190; 2. Dorner T, et al. Ibid, POS0714

## PAISLEY: Deucravacitinib Phase 2 in SLE

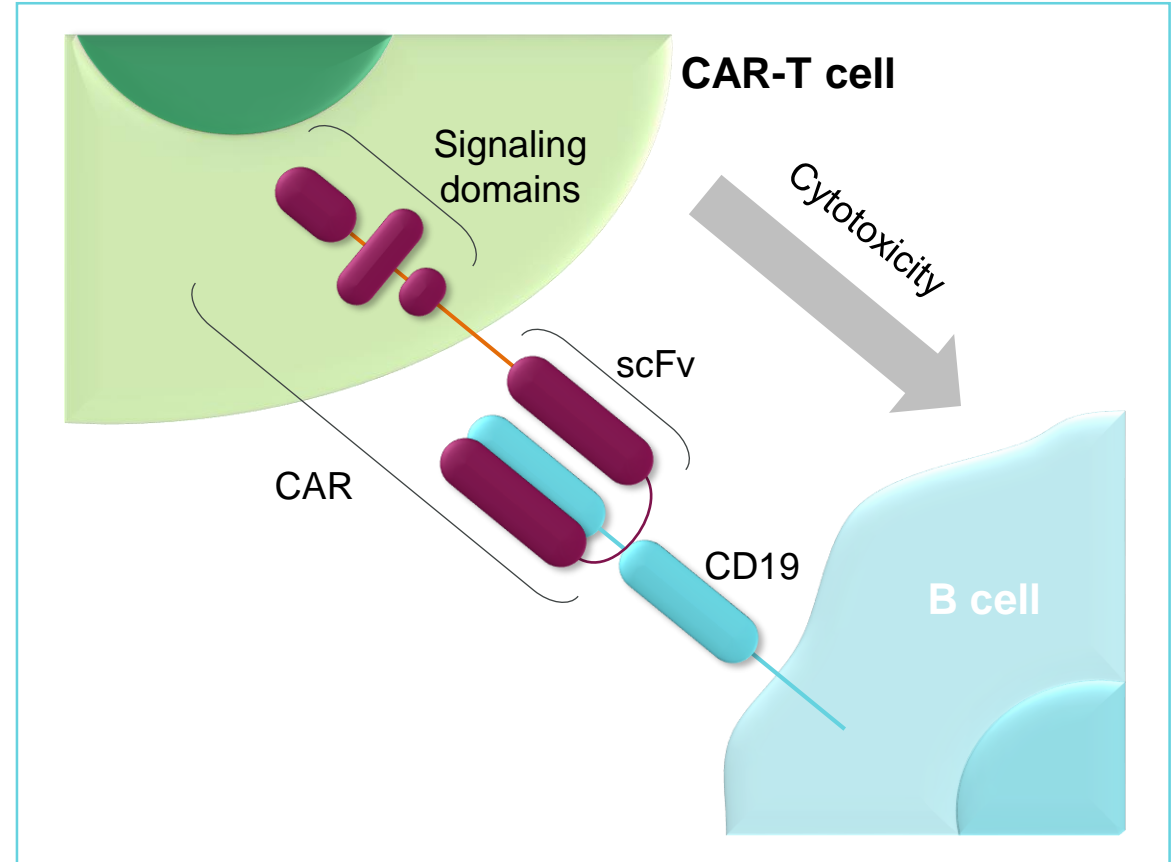
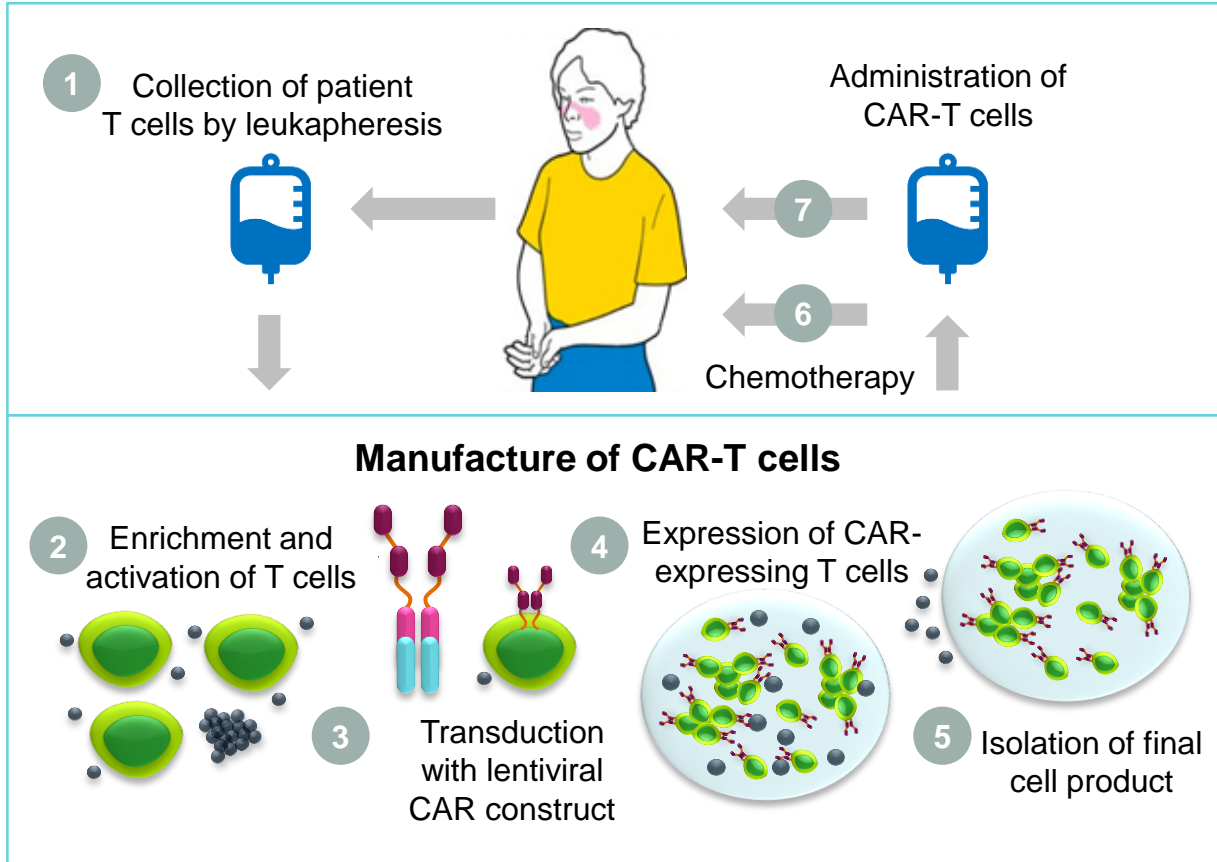
- TYK2 mediates signaling of type I IFN, IL-23, and IL-12: key cytokines in SLE
- Deucravacitinib: oral TYK2 inhibitor
- Phase 2, 48-week DBRCT in active SLE on standard care
  - PBO or Deucravacitinib (3, 6, 12 mg qd)
  - Oral GC tapering to 7.5 mg/day required from Wk 8–20
- SLICC criteria for SLE; + ANA/anti-DNA/or anti-Sm; SLEDAI 2K  $\geq 6$ ;  $\geq 1$  BILAG A or  $> 2$  B from MSK or MC domain
- Primary endpoint: % patients achieving SRI-4 at Wk 32
- Safety: increased acneiform rash DEUC 12 mg – no signal for SAE, infections (SIE, TB, HZ), malignancy, MACE, VTE
- Lab abnormalities - no signal with Deucavacitinib

### Efficacy outcomes (nonresponder imputation)



\*Significant vs PBO in multiplicity-controlled prespecified analysis. <sup>a</sup>n patients with baseline CLASI-A score  $\geq 10$ ; MSK, musculoskeletal; MC, mucocutaneous; Sm, Smith; SOC, standard of care. Morand E, et al. EULAR 2022, Copenhagen, LB0004

# Chimeric antigen receptor (CAR)-T cell treatment in SLE<sup>1,2</sup>



**Anti-CD19 CAR construct** = FMC63 scFv, CD8-derived hinge region, TNFRSF19-derived transmembrane domain, 4-1BB co-stimulatory domain, CD3 $\zeta$  intracellular domain

scFv, single-chain variable fragment

1. Adapted from: Hucks G, et al. Blood Cancer Journal. 2019;9:10

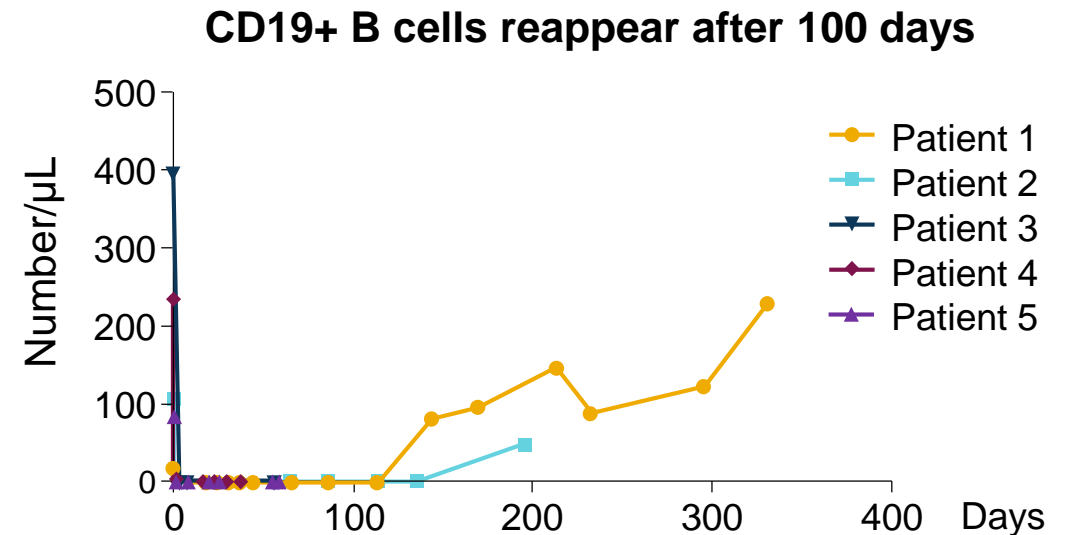
2. Adapted from: <https://bpsbioscience.com/car-t-cell-therapy-technical-note>

## CAR-T cell treatment of refractory SLE

- Patients with severe multiorgan SLE refractory to all therapies treated with anti-CD19 CAR-T cells
  - Stopped all SLE therapies (except low-dose prednisolone), conditioned with CYC/fludarabine, and then given single infusion of  $1 \times 10^6$  CD19–CAR-T cells/kg of body weight

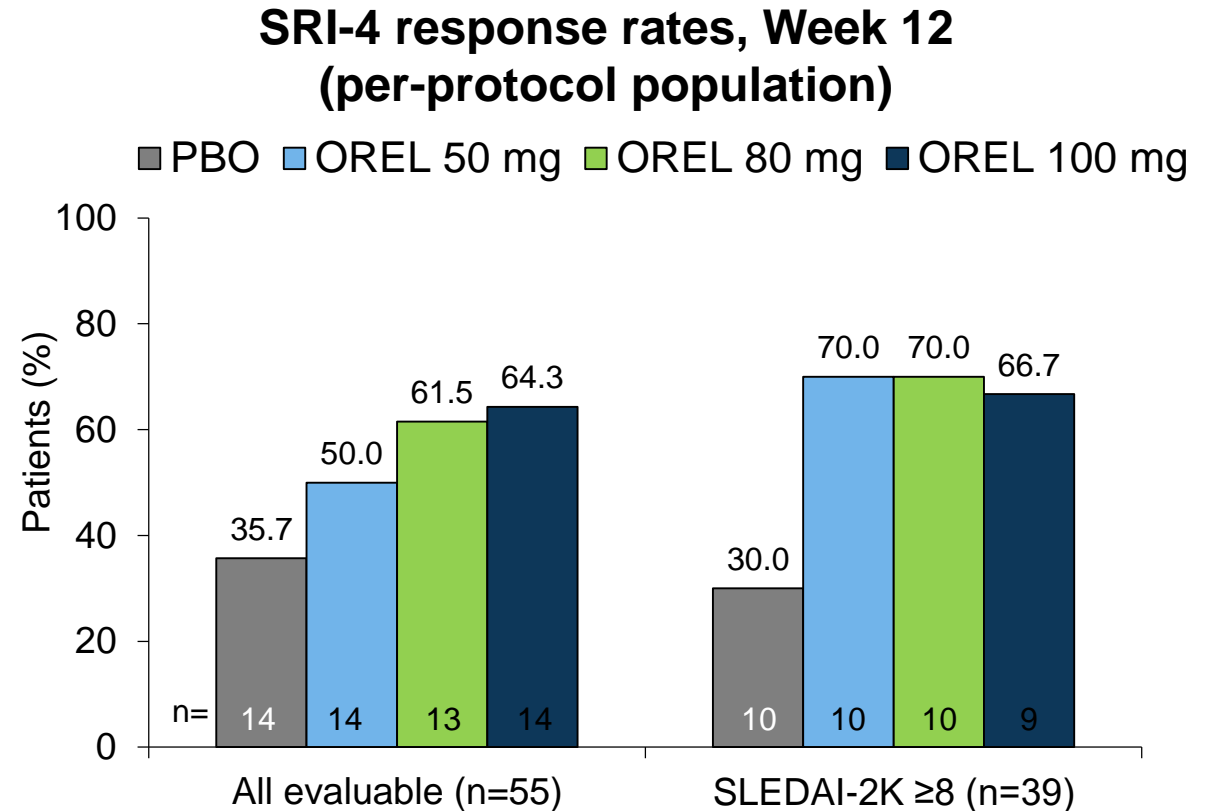
| Patient, age, sex | Follow-up (months) | Baseline SLEDAI-2K | Follow-up SLEDAI-2K |
|-------------------|--------------------|--------------------|---------------------|
| 20 y, F           | 12                 | 16                 | 0, ANA/dsDNA neg    |
| 22 y, M           | 9                  | 16                 | 2, ANA/dsDNA neg    |
| 22 y, F           | 4                  | 10                 | 0                   |
| 24 y, F           | 3                  | 8                  | 0                   |
| 18 y, F           | 1                  | 9                  | 0                   |

- % total CAR/total T cells (at Day 9): 11.5–59.1%
- Toxicity: fever; no other cytokine-release syndrome symptoms, neurotoxicity, or infections
- All patients in remission and able to stop prednisolone and immunosuppressives



## Orelabrutinib: Bruton kinase inhibitor in SLE

- OREL: oral selective irreversible BTK inhibitor
- Phase 1b/2a 12-week DBRCT in SLE
  - Safety, tolerability, PK/PD, biomarkers, efficacy
- OREL 50, 80, 100 mg or PBO + standard of care
  - 55 patients; baseline SLEDAI-2K  $\geq 5$ , auto-Ab+
- Results
  - 24-hour almost complete BTK occupancy at all doses
  - Proportional increase in OREL plasma concentration
  - “Trends” in reduced proteinuria, dsDNA Abs, IgG, and B cells; increased C4
  - 3 treatment-related SAEs – 1 grade 3 (what were they?)

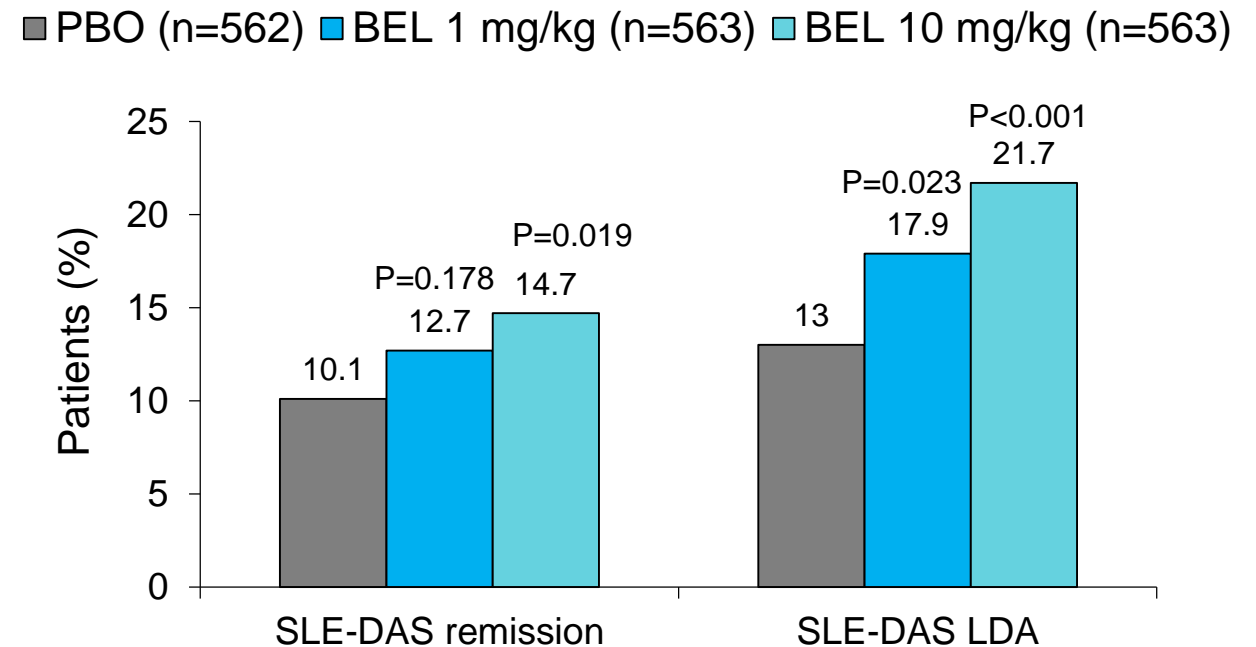


# Can SLE-DAS discriminate active drug from placebo in Phase 3 RCTs?

- Post hoc analysis of 2 Phase 3 trials of Belimumab (BLISS-52 and BLISS-76)
- BEL 1 and 10 mg/kg vs PBO in SLE
- No new BILAG A,  $\geq 1$  new BILAG B and no PhysGA increase of  $\geq 0.3$  if patients achieved SLE-DAS LDA/remission
- SLE-DAS remission and LDA associated with improved HRQoL and fatigue

SLE-DAS calculator: <http://sle-das.eu/>

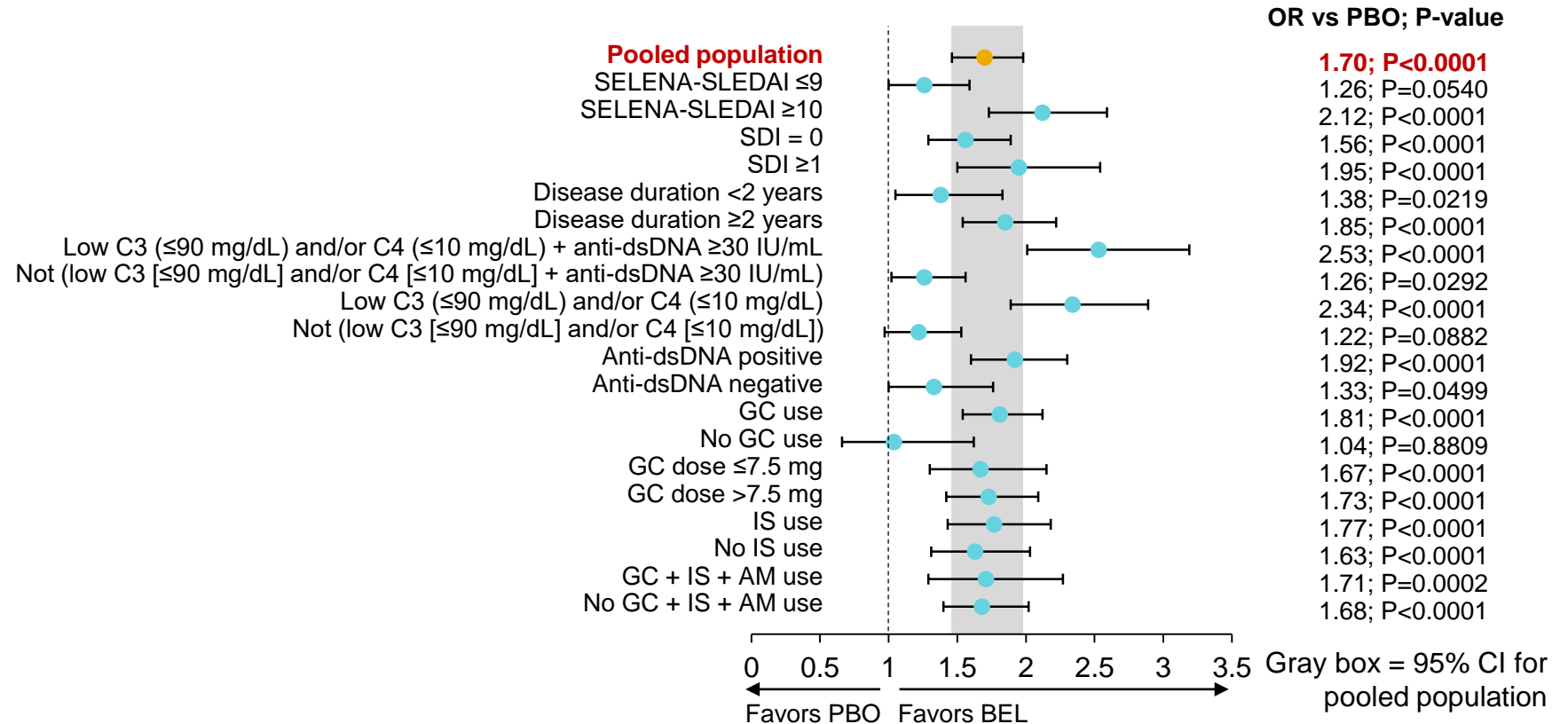
## Attainment of SLE-DAS Boolean remission and LDA at Week 52



# Integrated analysis of belimumab in SLE from 5 clinical trials

## SRI-4 response at Wk 52 by baseline characteristics

- Post hoc analysis in 3086 patients from BLISS-52, -76, -NEA, -SC, and EMBRACE (BEL n=1869; PBO n=1217)
- BEL 10 mg/kg IV q4w or 200 mg SC weekly vs PBO + standard of care
- SRI-4 response BEL vs PBO
  - **Week 8:** 38.4% vs 33.3%; OR 1.25 (95% CI: 1.07, 1.46); P=0.0060
  - **Week 52:** 54.8% vs 41.6%; OR 1.70 (95% CI: 1.46, 1.98); P<0.0001



# Impact of stopping corticosteroids in SLE

- Retrospective US cohort study 2015–2019; 12-month pre-index baseline, using IBM MarketScan Commercial/Medicare supplemental claims database
- 17,759 patients
- Evaluated flares (mild, moderate, severe), corticosteroid restarts, CS-free periods
- Higher BL cumulative corticosteroid dose → greatest risk of flare
- No information on concomitant therapy

## Outcomes in SLE patients treated with corticosteroid

| Measure  | Mean ( $\pm$ SD) or % |
|--|-----------------------|
| <b>Prior to initial corticosteroid discontinuation</b> |                       |
| Duration of corticosteroid use, days                   | 103.6 ( $\pm$ 129.5)  |
| Oral corticosteroid dose tertile                       | 26.6 ( $\pm$ 126.3)   |
| $\leq$ 5 mg/day  | 13.5%                 |
| 6–20 mg/day  | 58.6%                 |
| $>$ 20 mg/day  | 28.0%                 |
| <b>After initial corticosteroid discontinuation</b>    |                       |
| Corticosteroid treatment restart                       | 73.2%                 |
| No corticosteroid treatment $\geq$ 6 months            | 76.7%                 |
| Any flare  | 90.4%                 |
| Mild-to-moderate                                       | 72.4%                 |
| Severe   | 50.7%                 |
| Number of flares                                       | 6.9 ( $\pm$ 6.4)      |

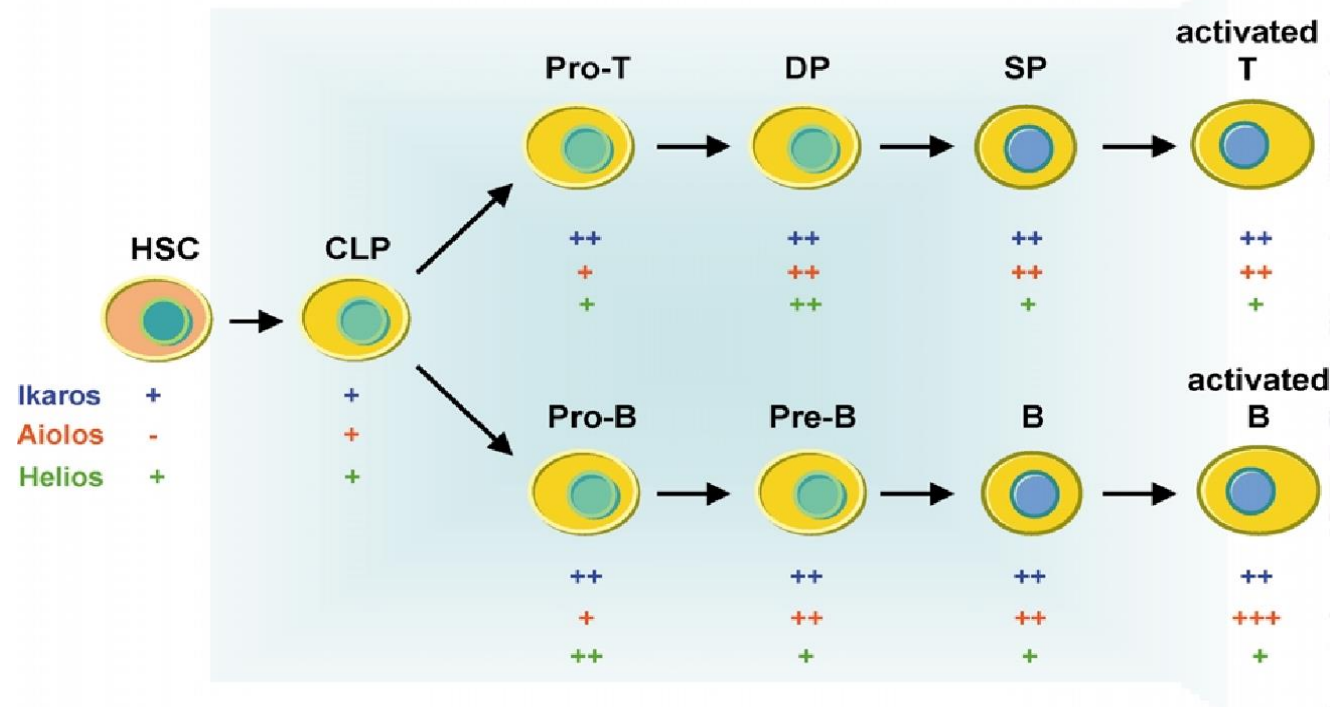
# Sustained Efficacy and Safety of Iberdomide to Week 52 in Patients with Active Systemic Lupus Erythematosus (SLE) in a Phase 2, Randomized, Placebo-Controlled Study

Merrill J, Werth V, Furie R, van Vollenhoven R, Majdan M, Weiswasser M, Korish S, Liu Z, Schafer P, Delev N

Merrill J, et al. ACR 2021

## Background/Rationale

- Iberdomide: a high-affinity cereblon ligand that promotes proteasomal degradation of Ikaros (*IKZF1*) and Aiolos (*IKZF3*), 2 key transcription factors linked to SLE.

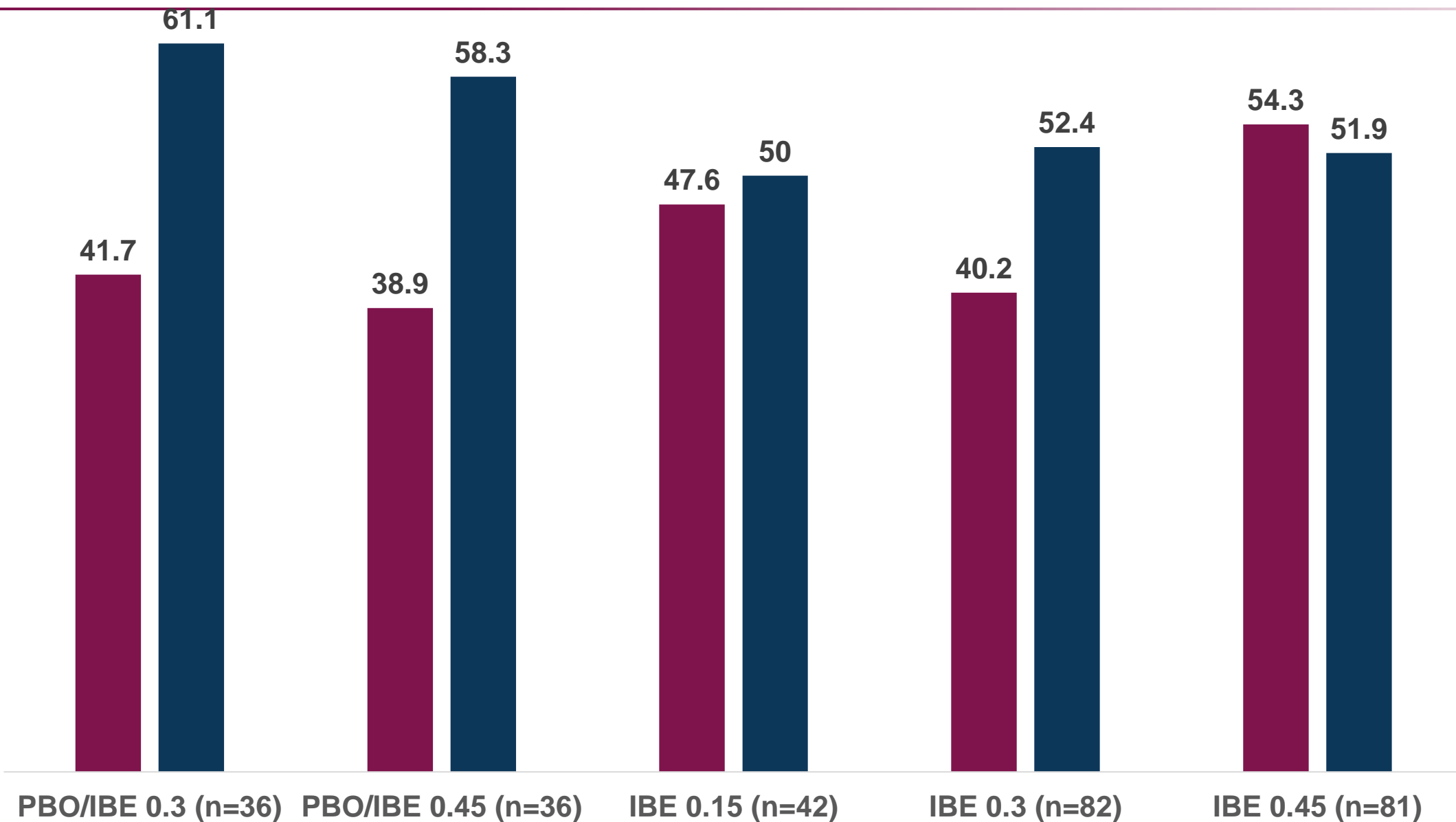


# Iberdomide vs Placebo in active SLE

SRI-4 (%)

Total N=217

70  
60  
50  
40  
30  
20  
10  
0



■ w24 (SRI-4)  
■ w52 (SRI-4)

# Iberdomide vs Placebo in active SLE

## BICLA (%)

60

50

40

30

20

10

0

40.6

50

42.3

42.3

37.1

42.9

33.3

43.3

37.3

45.8

w24 (BICLA)

w52 (BICLA)

PBO/IBE 0.3 (n=36)

PBO/IBE 0.45 (n=36)

IBE 0.15 (n=42)

IBE 0.3 (n=82)

IBE 0.45 (n=81)

Merrill J, et al. ACR 2021

# Improvement in individual mucocutaneous manifestations in patients with systemic lupus erythematosus treated with anifrolumab

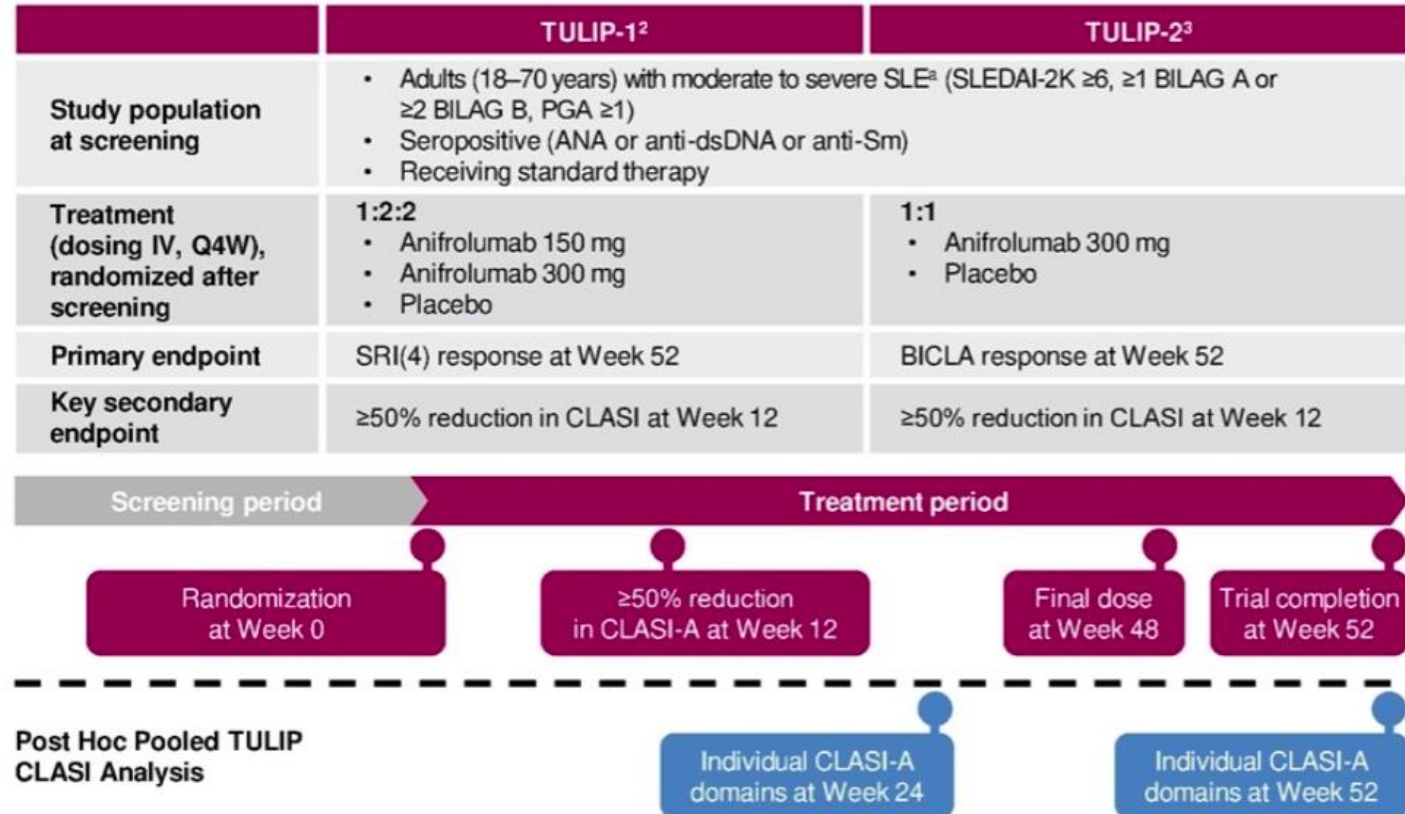
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- Background
- Anifrolumab is a fully human monoclonal antibody that binds to subunit 1 of the type I interferon (IFN) receptor, blocking the activity of type I IFN
- Approved in many countries for the treatment of SLE

# Improvement in individual mucocutaneous manifestations in systemic lupus erythematosus treated with anifrolumab

- Data from Anifrolumab trials were used to determine the effects of specific features (mucocutaneous) of SLE
- Combining data from TULIP-1 and TULIP-2 RCTs
- Comparing Active vs placebo all added to standard of care
- Creating the CLASI responses

Figure 1. Trial Design for TULIP-1 and TULIP-2 and Pooled Post Hoc Analysis



## Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)

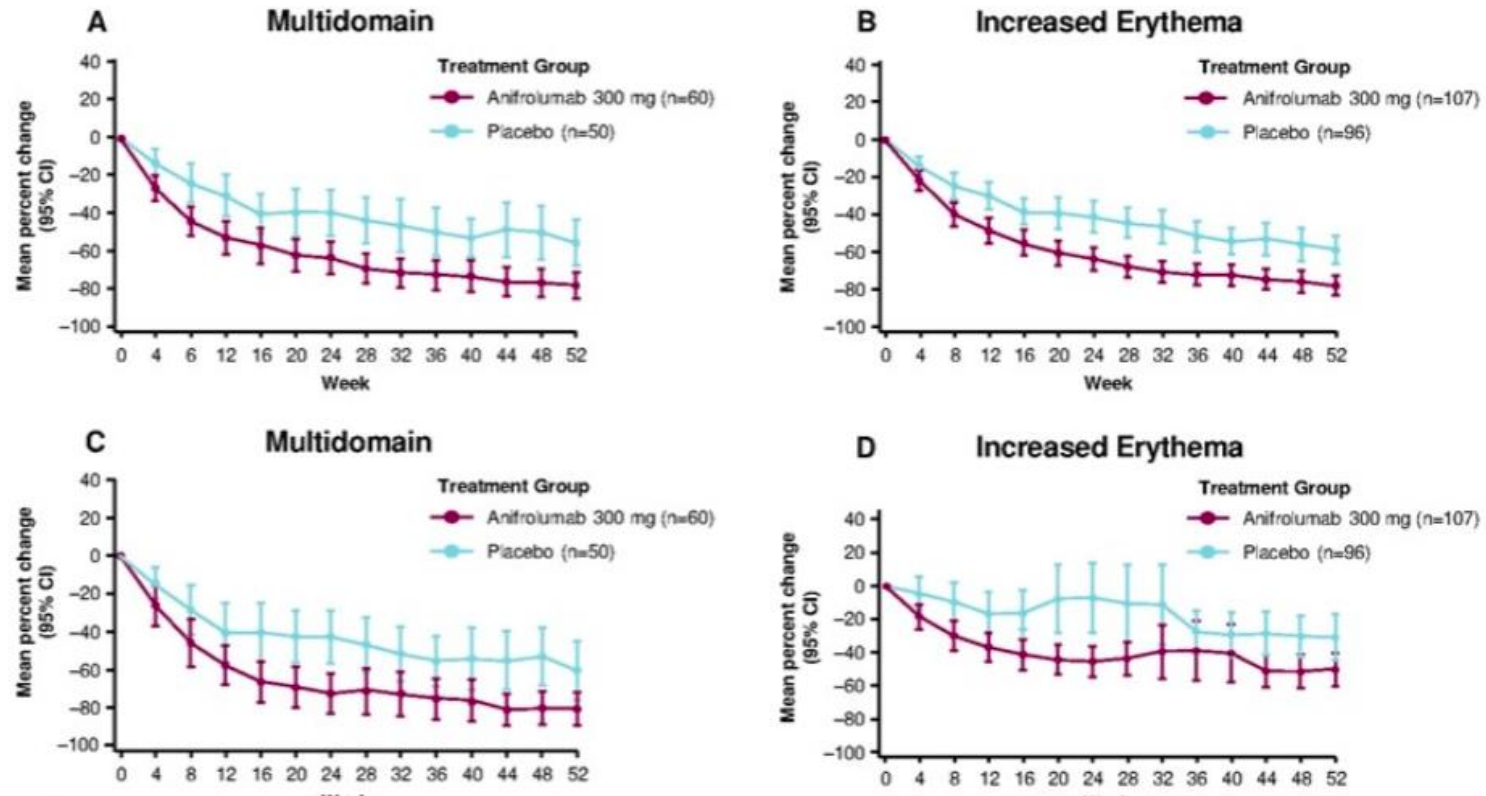
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- Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)
- Quantifies disease activity and damage in cutaneous lupus erythematosus (CLE).
- Activity score is based on the degree of erythema, scale, mucous membrane lesions, and nonscarring alopecia.

[https://jamanetwork.com/journals/jamadermatology/fullarticle/426652#:~:text=in%20disease%20activity.-,The%20Cutaneous%20Lupus%20Erythematosus%20Disease%20Area%20and%20Severity%20Index%20\(CLASI,membrane%20lesions%2C%20and%20nonscarring%20alopecia.](https://jamanetwork.com/journals/jamadermatology/fullarticle/426652#:~:text=in%20disease%20activity.-,The%20Cutaneous%20Lupus%20Erythematosus%20Disease%20Area%20and%20Severity%20Index%20(CLASI,membrane%20lesions%2C%20and%20nonscarring%20alopecia.)

# Improvement in individual mucocutaneous manifestations in systemic lupus erythematosus treated with anifrolumab

Figure 2. Mean Percent Change From Baseline in (A, B) Erythema and (C, D) Scale/Hypertrophy in the Multidomain and Increased Erythema Patient Subgroups Through Week 52



## Conclusions / Lessons Learned

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- Anifrolumab is superior to placebo on mucocutaneous manifestations of SLE
- Reassuring to have consistent results of efficacy when symptoms/signs of SLE are sub-setted
- This is what a majority of our patients have as symptoms
- Skin, joints, oral/nasal ulcers

## Do you treat to a target in SLE?

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Yes

Sometimes

No

## If you do, what target do you use?

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Remission

Low Lupus Disease Activity

Other

# MODERATE RATES OF TREATMENT INTENSIFICATION IN SLE PATIENTS WITH RESIDUAL DISEASE ACTIVITY

POS0366

Ourania Gioti<sup>1</sup>, Myrto Nikoloudaki<sup>2</sup>, Katerina Chavatza<sup>3</sup>, Eleni Kalavri<sup>1</sup>, Antonia Elezoglou<sup>1</sup>, Prodromos Sidiropoulos<sup>2</sup>, George Bertias<sup>2</sup>, Dimitrios Boumpas<sup>3</sup>, Antonis Fanouriakis<sup>4</sup>  
<sup>1</sup> "Asklepieio" General Hospital, Department of Rheumatology, Athens, Greece, <sup>2</sup>University Hospital Heraklion, Rheumatology, Clinical Immunology and Allergy, Crete, Greece, <sup>3</sup>"Attikon" University Hospital, Rheumatology and Clinical Immunology, Athens, Greece, <sup>4</sup>"Laikon" General Hospital, 1st Department of Propaedeutic Internal Medicine, Athens, Greece

- Background
- Most patients with SLE are not in remission and have residual disease activity
- As in RA, pts with SLE with residual disease activity may or may not have treatment intensification

# MODERATE RATES OF TREATMENT INTENSIFICATION IN SLE PATIENTS WITH RESIDUAL DISEASE ACTIVITY

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<sup>1</sup> "Asklepieio" General Hospital, Department of Rheumatology, Athens, Greece, <sup>2</sup>University Hospital Heraklion, Rheumatology, Clinical Immunology and Allergy, Crete, Greece, <sup>3</sup>"Attikon" University Hospital, Rheumatology and Clinical Immunology, Athens, Greece, <sup>4</sup>"Laikon" General Hospital, 1st Department of Propaedeutic Internal Medicine, Athens, Greece

Cross sectional study of 3 centres in Greece

Pts were categorized by their disease state and if treatment was intensified

Analyses by logistic regression and ROC analysis for SLEDAI-2K cut offs

- 332 patients were included, 93.1% female.
- Mean (SD) age was 48.5 (14.7) years and median (IQR) disease duration 6.5 (12.4) years.

**Table 1. Disease activity states, n %**

|  |             |
|--|-------------|
| Remission off-therapy                    | 28 (8.4%)   |
| Remission on-therapy                     | 49 (14.8%)  |
| LDA                                      | 122 (36.7%) |
| Non-optimally controlled/ Active disease | 133 (40.1%) |

# Features of treatment intensification

Features are common and/or severe that require treatment intensification

Arthritis

Rash

Alopecia – but what treatment actually works?

Proteinuria

**Half of active disease did NOT have Rx**

Figure 1. Application of treatment intensification according to disease activity state at last visit

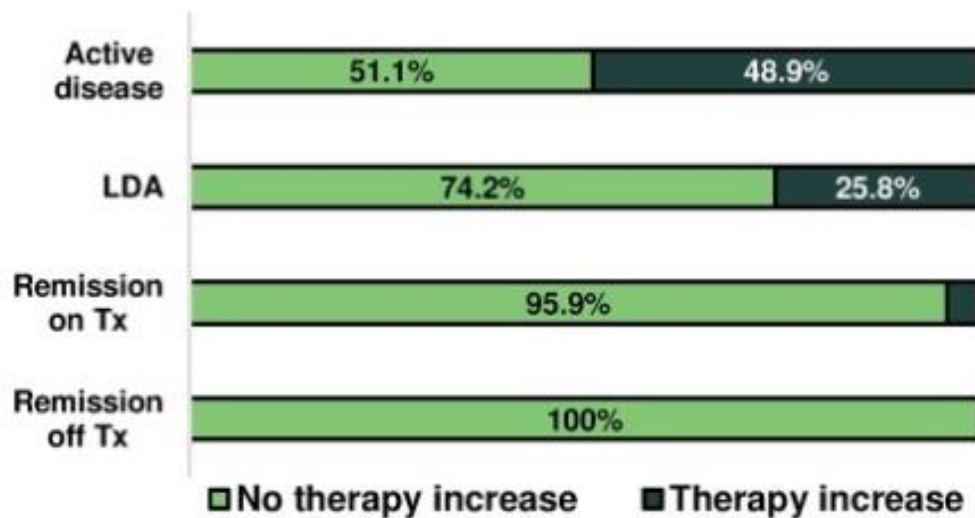


Table 2. Factors associated with Tx intensification at last visit

|                    | Univariable |                    | Multivariable |                   |
|--------------------|-------------|--------------------|---------------|-------------------|
|                    | OR          | 95% CI             | OR            | 95% CI            |
| Male sex           | 0.46        | 0.15-1.38          | 0.59          | 0.16–2.12         |
| Age                | 1.01        | 0.99-1.02          | 1.00          | 0.99–1.02         |
| Disease duration   | 0.99        | 0.97-1.02          |               |                   |
| Arthritis          | <b>5.40</b> | <b>3.25 - 8.99</b> | <b>5.48</b>   | <b>3.20-9.40</b>  |
| Skin rash          | <b>3.28</b> | <b>1.95 - 5.53</b> | <b>3.23</b>   | <b>1.81-5.75</b>  |
| Mucosal ulcers     | 1.75        | 0.77 - 3.95        |               |                   |
| Alopecia           | <b>2.06</b> | <b>1.13 - 3.75</b> | 1.50          | 0.76–2.97         |
| Proteinuria        | <b>3.64</b> | <b>1.26-10.53</b>  | <b>6.78</b>   | <b>2.06–22.25</b> |
| Hematuria          | 0.97        | 0.25-3.84          |               |                   |
| Thrombocytopenia   | 0.91        | 0.17-4.75          |               |                   |
| Serologic activity | 0.76        | 0.43-1.33          |               |                   |

# Conclusions

---

- There are many pts with SLE who are not in remission
- Many of these do NOT have Rx altered
- ?Unmet need for appropriate Rx, Rx pathways and obtaining remission

# Early (3 months) improvement in physician global assessment of disease activity predicts long-term retention of belimumab treatment in SLE: a multicentre observational study of 184 patients

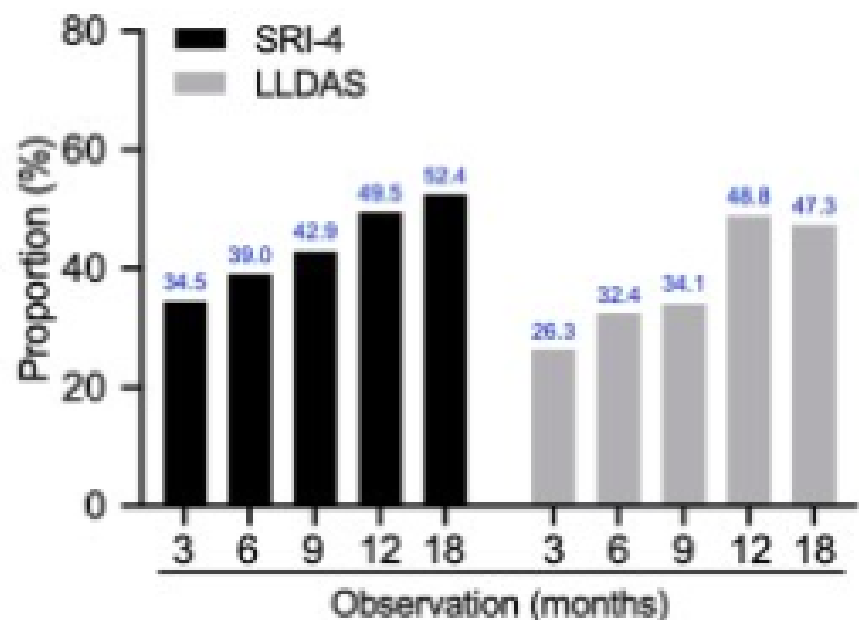


POS0368

Myrto Nikoloudaki<sup>1</sup>, Dionysis Nikolopoulos<sup>2</sup>, Sofia Koutsoviti<sup>1</sup>, Irini Flouri<sup>1</sup>, Argyro Repa<sup>1</sup>, Pelagia Katsimbri<sup>2</sup>, Evangelos Theotikos<sup>1</sup>, Sofia Pitsigevaki<sup>1</sup>, Katerina Pateronichelaki<sup>1</sup>, Anastasios Eskitzis<sup>1</sup>, Antonia Elezoglou<sup>3</sup>, Prodromos Sidropoulos<sup>1</sup>, Antonis Fanourakis<sup>2,3</sup>, Dimitrios Boumpas<sup>1</sup>, George Bertsis<sup>1</sup>

<sup>1</sup>Rheumatology, Clinical Rheumatology and Allergy, University of Crete Medical School, Heraklion, Greece; <sup>2</sup>Rheumatology Clinic, Fourth Department of Internal Medicine, Atzikon Hospital, Athens, Greece; <sup>3</sup>Department of Rheumatology, 'Asklepeion' General Hospital, Voula, Athens, Greece

Early improvement in SLE with belimumab predicts still being on Rx over time



**Figure 2.** Proportion of SLE patients started on belimumab who attained SRI-4 and LLDAS states (no. patients as shown in Figure 1).

## Results:

- A total 184 patients treated with belimumab for at least 3 months were included (women 95.6%; mean  $\pm$  SD age  $48.8 \pm 13.4$  years; disease duration  $9.2 \pm 11.3$  years).
- Baseline characteristics of the cohort are summarized in **Table 1**.

| Table 1.  | N (%)             |
|---|-------------------|
| <b>Prior use of immunosuppressants or biologics</b> |                   |
| Methotrexate  | 135 (73.4%)       |
| Leflunomide   | 33 (17.9%)        |
| Cyclosporine  | 16 (8.7%)         |
| Azathioprine  | 99 (53.8%)        |
| Mycophenolate                                       | 25 (13.6%)        |
| Cyclophosphamide                                    | 31 (16.9%)        |
| Rituximab   | 18 (9.8%)         |
| Other biologic                                      | 3 (1.6%)          |
| <b>Concomitant treatments (baseline)</b>            |                   |
| Glucocorticoids                                     | 123 (66.9%)       |
| >5 mg/day (prednisone equivalent)                   | 81 (44.0%)        |
| Hydroxychloroquine (HCQ)                            | 145 (78.8%)       |
| Methotrexate  | 68 (37.0%)        |
| Leflunomide   | 8 (4.3%)          |
| Cyclosporine  | 5 (2.7%)          |
| Azathioprine  | 37 (20.1%)        |
| Mycophenolate                                       | 17 (8.2%)         |
| <b>Organ damage (SDI &gt;0; baseline)</b>           | <b>73 (39.7%)</b> |

# Lessons Learned

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- The 1000 Faces of Lupus registry has also shown unmet need where remission is often NOT obtained in prevalent pts with SLE<sup>1</sup>
- 1/3 had clinically important SLE activity.
- % in LOW disease activity who moved to a higher activity level varied from 30% to 49% from 1 to 3 years, and 54% at 5 years
- If in MOD to VHIGH activity, 2/3 were still active at 3 years
- Higher SLEDAI-2K at cohort entry remained a significant predictor of higher SLEDAI-2K in subsequent years.


Multicenter Study > J Rheumatol. 2019 Feb;46(2):166-175. doi: 10.3899/jrheum.171454.

Epub 2018 Sep 15.

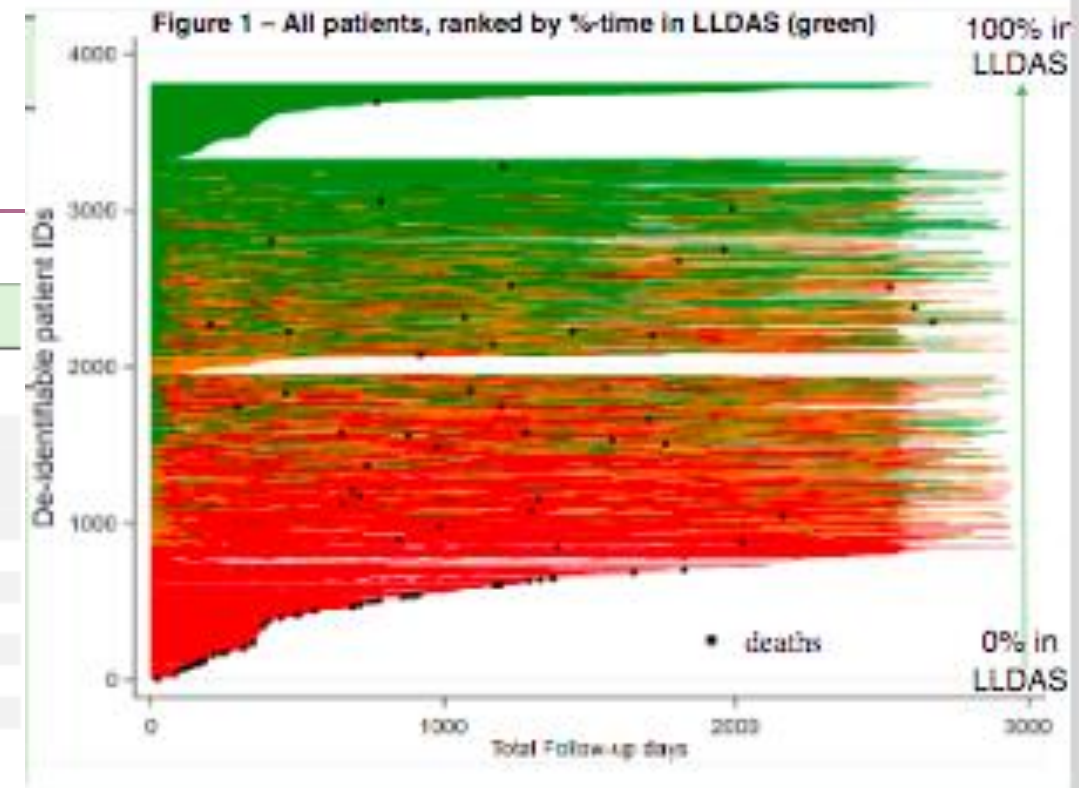
## 1 Persistent Disease Activity Remains a Burden for Patients with Systemic Lupus Erythematosus

Christine A Peschken<sup>1 2</sup>, Yishu Wang<sup>3 4</sup>, Michal Abrahamowicz<sup>3 4</sup>, Janet Pope<sup>3 4</sup>, Earl Silverman<sup>3 4</sup>, Aryn Sayani<sup>3 4</sup>, Sandra Iczkowitz<sup>3 4</sup>, Jorge Ross<sup>3 4</sup>, Michel Zummer<sup>3 4</sup>, Lori Tucker<sup>3 4</sup>, Christian Pineau<sup>3 4</sup>, Deborah Levy<sup>3 4</sup>, Marie Hudson<sup>3 4</sup>, Carol A Hitchon<sup>3 4</sup>, Adam M Huber<sup>3 4</sup>, C Douglas Smith<sup>3 4</sup>, Antonio Avina-Zubieta<sup>3 4</sup>, Hector Arbillaga<sup>3 4</sup>, Gaëlle Chédeville<sup>3 4</sup>, Willy Wynant<sup>3 4</sup>, Paul R Fortin<sup>3 4</sup>, CaNIOS 1000 Faces Investigators

# 0865. Lupus Low Disease Activity State Attainment Provides Significant Protection Against Mortality: A Multi-National, Longitudinal Observational Study

 Rangika Kandane-Rathnayake

| Table 1                            | All patients (n=4,106)       | Deceased patients (n=91)     | Univariable associations          | Multivariable Model 1             | Multivariable Model 2 <sup>†</sup> |
|------------------------------------|------------------------------|------------------------------|-----------------------------------|-----------------------------------|------------------------------------|
| <b>Demographics</b>                | <b>Median [IQR] or n (%)</b> | <b>Median [IQR] or n (%)</b> | <b>HR (95% CI)</b>                | <b>HR (95% CI)</b>                | <b>HR (95% CI)</b>                 |
| Age (years)                        | 39 <sup>†</sup> [30, 50]     | 41 <sup>†</sup> [28, 54]     | 1.00 <sup>‡</sup> (0.99, 1.02)    |                                   |                                    |
| Disease duration (years)           | 29 <sup>†</sup> [21, 39]     | 31 <sup>†</sup> [21, 39]     | 0.99 <sup>‡</sup> (0.98, 1.01)    |                                   |                                    |
| Males                              | 328 (8%)                     | 9 (10%)                      | 1.62 (0.82, 3.26)                 |                                   |                                    |
| Asian ethnicity                    | 3632 (89%)                   | 81 (90%)                     | 1.11 (0.55, 2.23)                 |                                   |                                    |
| Current smoker                     | 216 (5%)                     | 9 (10%)                      | 2.52 (1.26, 5.04)***              | 1.96 (0.92, 4.18)                 | 2.06 (1.96, 4.42)*                 |
| Tertiary-level education           | 2,045 (53%)                  | 29 (35%)                     | 0.60 (0.37, 0.98)*                |                                   |                                    |
| GDP (PPP) per capita <Int\$20,000  | 1458 (35%)                   | 44 (48%)                     | 2.06 (1.30, 3.25)**               | 2.80 (1.72, 4.56)***              | 2.68 (1.66, 4.33)***               |
| <b>Clinical indications</b>        |                              |                              |                                   |                                   |                                    |
| TAM SLEDAI-2K (AMS)                | 2.9 [1.3, 4.7]               | 5.1 [2.7, 7.1]               | 1.22 (1.16, 1.29)***              | 1.04 (0.95, 1.14)                 | 1.17 (1.09, 1.25)***               |
| TAM PGA                            | 0.4 [0.2, 0.7]               | 0.9 [0.5, 1.4]               | 1.67 <sup>‡</sup> (1.49, 1.86)*** | 1.54 <sup>‡</sup> (1.30, 1.82)*** |                                    |
| Cumulative PNL dose                | 3.5 [0.7, 9.3]               | 6.0 [2.1, 12.5]              | 1.03 <sup>‡</sup> (1.00, 1.06)*   | 0.90 <sup>‡</sup> (0.81, 1.32)    | 1.18 <sup>‡</sup> (0.86, 1.61)     |
| No. of Mild/Moderate/Severe flares | 1 [0, 2]                     | 2 [0, 3]                     | 1.12 (1.05, 1.19)**               | 1.00 (0.91, 1.10)                 | 1.98 (0.90, 1.07)                  |
| SDI score <sup>§</sup>             | 0 [0, 1]                     | 2 [0, 5]                     | 1.51 (1.37, 1.66)***              | 1.45 (1.30, 1.62)***              | 1.53 (1.38, 1.69)***               |



N=4106 in combined SLE cohorts  
 Asia Pacific lupus collaboration  
 91 died  
 Mortality  
 Time in lupus low disease activity  
 LLDAS  
 Time in Clinical Remission on  
 treatment  
 CROT

| Table 2       | Multivariable Cox regression models |
|---------------|-------------------------------------|
| ≥50%-time in: | HR <sup>†</sup> (95% CI), p-value   |
| LLDAS         | 0.44 (0.26, 0.75), p=0.003          |
| CROT-PNL≤5    | 0.49 (0.27, 0.89), p=0.018          |
| CROT-PNL<5    | 0.30 (0.12, 0.74), p=0.009          |
| CROT-PNL0     | 0.13 (0.02, 0.90), p=0.039          |

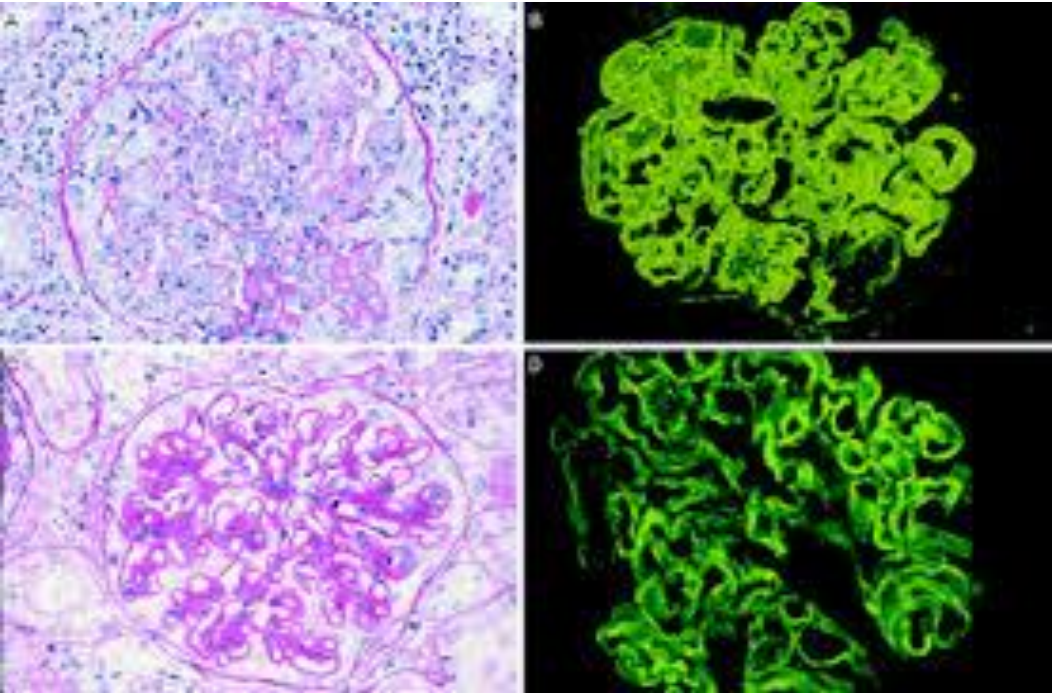
<sup>†</sup>HR = Hazard ratios adjusted for GDP (PPP), current smoking status and SDI score.

## Conclusions

LLDAS and remission conferred significant protection against mortality in SLE. Compared to LLDAS, clinical remission on treatment was not more protective unless lower PNL thresholds were applied. Clinical remission off steroids was maximally protective and should be the goal of treatment in SLE.

# Lupus Nephritis

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**Class I:** Minimal mesangial lupus nephritis

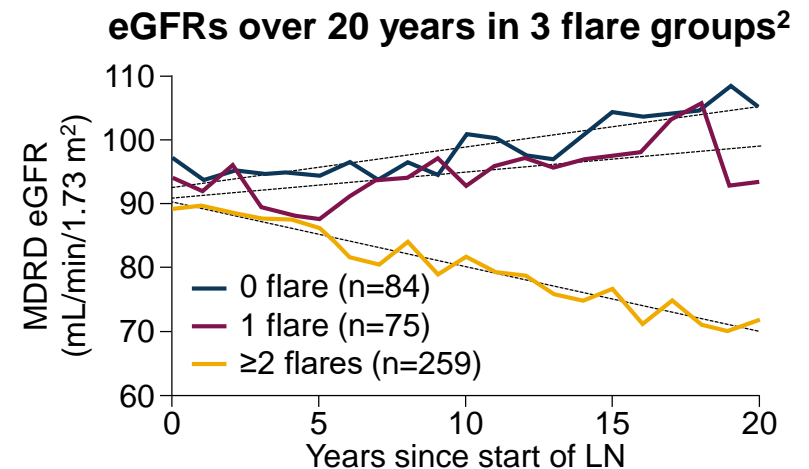
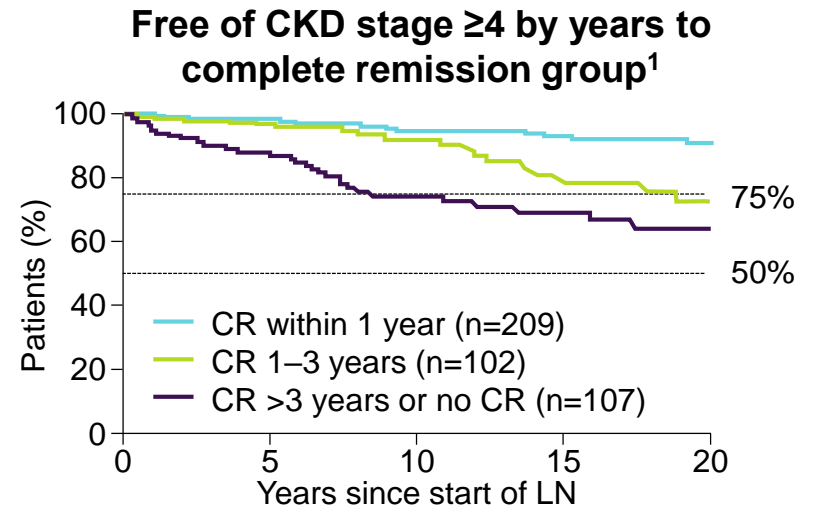
**Class II:** Mesangial proliferative nephritis.

**Class III:** Focal lupus nephritis (active and chronic, proliferative and sclerosing)

**Class IV:** Diffuse lupus nephritis (active and chronic, proliferative and sclerosing, segmental and global)

# Lupus nephritis: Advanced chronic kidney disease (CKD) risk factors

- All treated LN patients (confirmed clinically [ $>0.5$  g/d proteinuria] or by biopsy) followed for  $\geq 5$  years
  - Remission: proteinuria  $<0.5$  g/d, no active sediment, creatinine  $\leq 120\%$  of baseline
  - Flare: proteinuria  $>0.5$  g/d after remission
- Results (n=418 patients)<sup>1,2</sup>
  - 66 patients (15.8%) developed stage IV/V (n=39/37) at mean 9.5 y follow-up
    - CR within 1st year protects against advanced CKD
  - 1 flare (2.7 $\times$ ) and  $\geq 2$  flares (3.6 $\times$ ) increased risk for advanced CKD
  - Longer time on immunosuppressive medications ( $>3$  y) after remission protects from advanced CKD
  - **Early remission and flare prevention with prolonged immune suppressives maximizes renal survival in LN**



# Need to target rapid remission in lupus nephritis to preserve renal function over time

---

**Can a patient with SLE and quiescent disease stop Hydroxychloroquine?**

---

## Results: Crude flare rates and adjusted HRs, HCQ maintenance vs reduction

Incidence, first SLE flare : Crude rates/100 person-years (95% CI) + aHRs

| Disease activity time zero | Maintenance       | Reduction         | Adjusted HR (95% CI) |
|----------------------------|-------------------|-------------------|----------------------|
| Remission (N=196)          | 13.2 (9.5, 18.4)  | 26.2 (20.1, 34.1) | 2.14 (1.34, 3.42)    |
| Not remission (N=1146)     | 41.7 (37.8, 46.0) | 46.3 (41.9, 51.1) | 1.14 (0.98, 1.32)    |
| Low (N=815)                | 27.8 (24.5, 31.6) | 37.5 (33.2, 42.4) | 1.32 (1.10, 1.60)    |
| Not low (N=527)            | 39.8 (34.3, 46.1) | 43.9 (38.0, 50.6) | 1.04 (0.84, 1.29)    |

Low disease activity: SLEDAI-2Ks4, pred ≤7.5 mg/day (+/-antimalarials, immunosuppressives, biologics)  
Complete remission off therapy: SLEDAI-2K=0 and no prednisone or immunosuppressives use in past year

If you stop HCQ you are more apt to flare in SLE

## Results: Crude flare rates and adjusted HR HCQ maintenance vs discontinuation

Incidence, first SLE flare : Crude rates/100 person-years (95% CI) + aHRs

| Disease activity time zero | Maintenance       | Discontinuation   | Adjusted HR (95% CI) |
|----------------------------|-------------------|-------------------|----------------------|
| Remission (N=196)          | 12.2 (8.0, 18.8)  | 24.7 (17.7, 34.6) | 2.77 (1.46, 5.26)    |
| Not remission (N=1146)     | 41.7 (37.8, 46.0) | 46.3 (41.9, 51.1) | 1.50 (1.25, 1.81)    |
| Low (N=815)                | 26.6 (22.8, 30.9) | 35.5 (30.4, 41.3) | 1.62 (1.28, 2.05)    |
| Not low (N=527)            | 36.4 (30.5, 43.5) | 53.6 (44.7, 64.2) | 1.60 (1.22, 2.09)    |

Low disease activity: SLEDAI-2Ks4, pred ≤7.5 mg/day (+/-antimalarials, immunosuppressives, biologics)  
Complete remission off therapy: SLEDAI-2K=0 and no prednisone or immunosuppressives use in past year

Sasha Bernatsky, MD,

7S123. Plenary II (0956–0961)

Bernatsky, S, et al. ACR21,#0959

# Do you stop MMF in SLE patients

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If in remission, sustained

Only if contemplating pregnancy

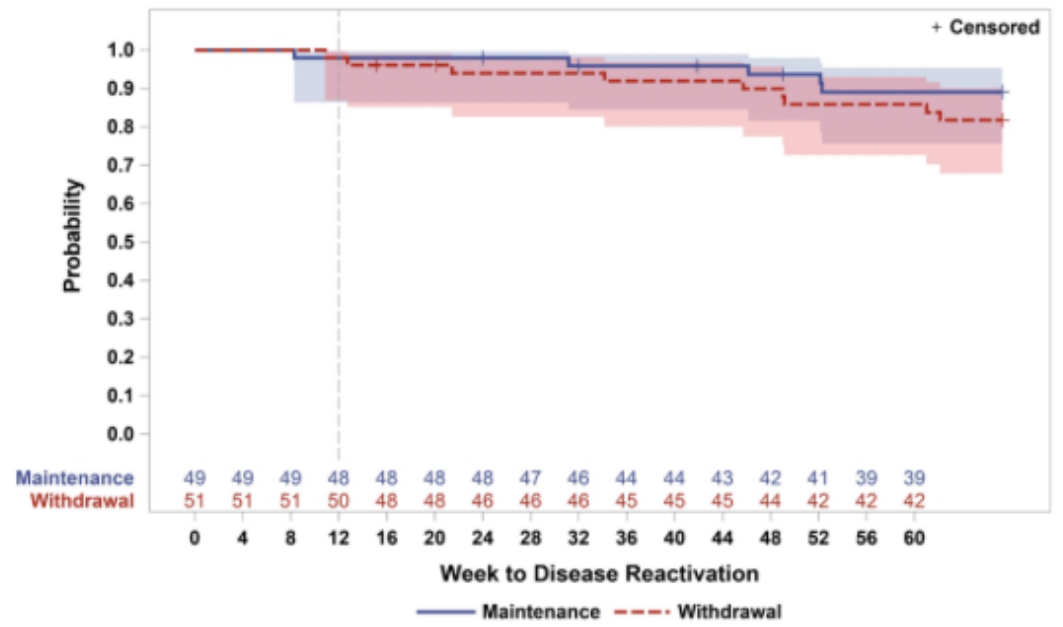
If patient preference to have less medications

# Disease Reactivation

|   | Maintenance<br>(n=49)         | Withdrawal<br>(n=51)          | Difference                     |
|---|-------------------------------|-------------------------------|--------------------------------|
| Clinically Significant Disease Reactivation   | 5 (10.2)                      | 9 (17.6)                      |                                |
| Kaplan-Meier Estimate of Disease Reactivation |                               |                               |                                |
| Estimate (95% CI)                             | <b>0.11</b><br>(0.047, 0.243) | <b>0.18</b><br>(0.099, 0.321) | <b>0.07</b><br>(-0.068, 0.214) |
| Weeks to Disease Reactivation                 |                               |                               |                                |
| Mean (SD)                                     | 38.0 (18.71)                  | 38.5 (19.62)                  |                                |
| Median  | 46.1                          | 45.7                          |                                |
| Min,Max                                       | 8,52                          | 11,62                         |                                |

**Withdrawal of MMF in lupus remission doesn't result in more flares over 1 year**

## Clinically Significant Disease Reactivation



### Successful withdrawal of mycophenolate mofetil in Quiescent SLE: Results from a randomized trial

#OP0167  
 Session: Advances in treating SLE and lupus nephritis  
 Eular 2020 | Aho | 4. June 2020 10:50 - 10:55 | 413 views

### Successful Withdrawal of Mycophenolate Mofetil in Quiescent SLE: Results from a randomized trial

OP0167



The Kaplan-Meier estimate of risk difference by Week 60 is: Risk<sub>withdrawal</sub> - Risk<sub>maintenance</sub> = 0.07 (95%CI: -0.068, 0.214)

## Can you stop MMF in SLE nephritis patients

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If in remission, sustained

No

Don't know



## WIN-Lupus

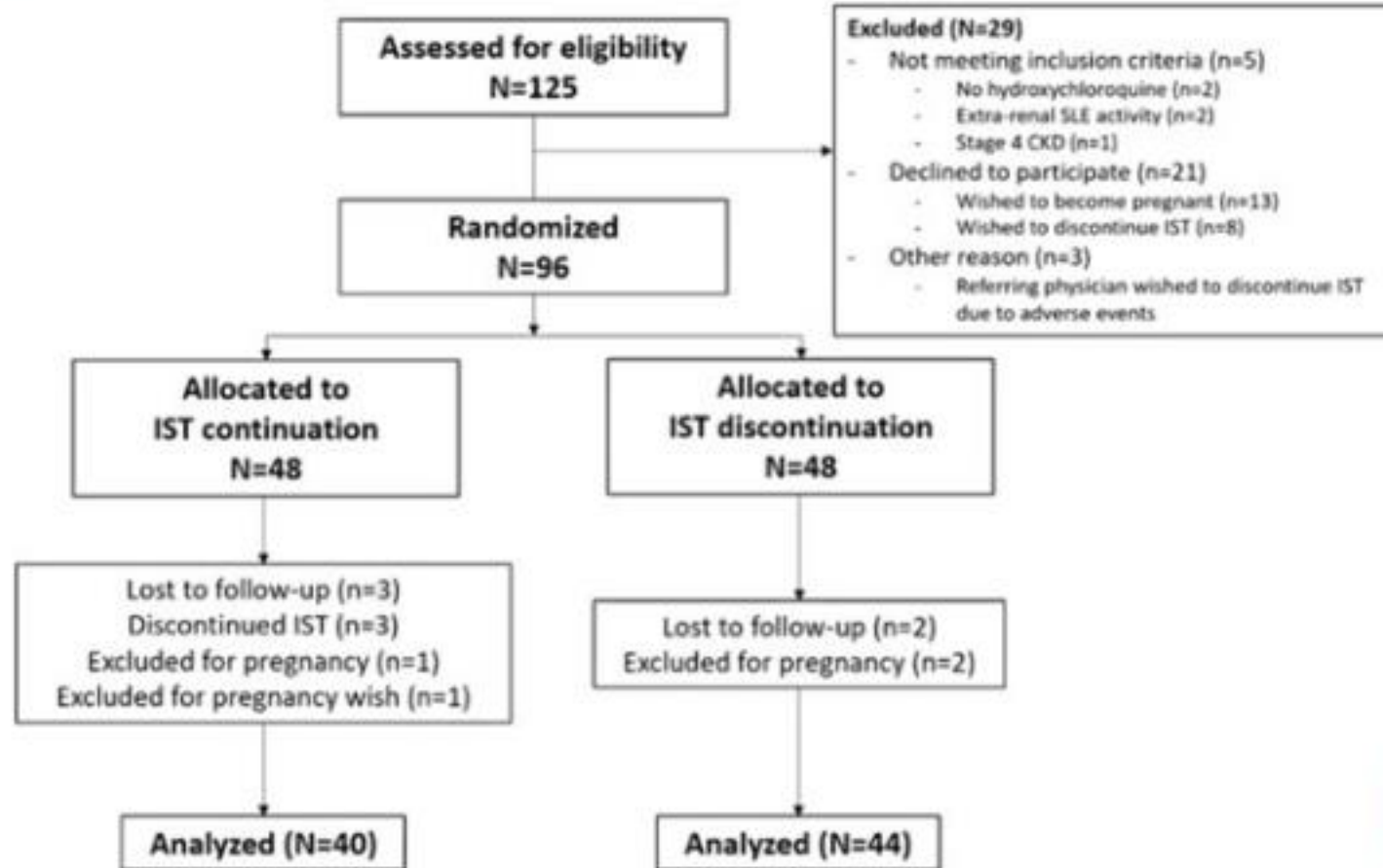
### Weaning of Immunosuppression in Lupus Nephritis: a Multicenter Randomized Controlled Trial



EULAR – 3 Jun 2022  
Pr Noémie Jourde-Chiche

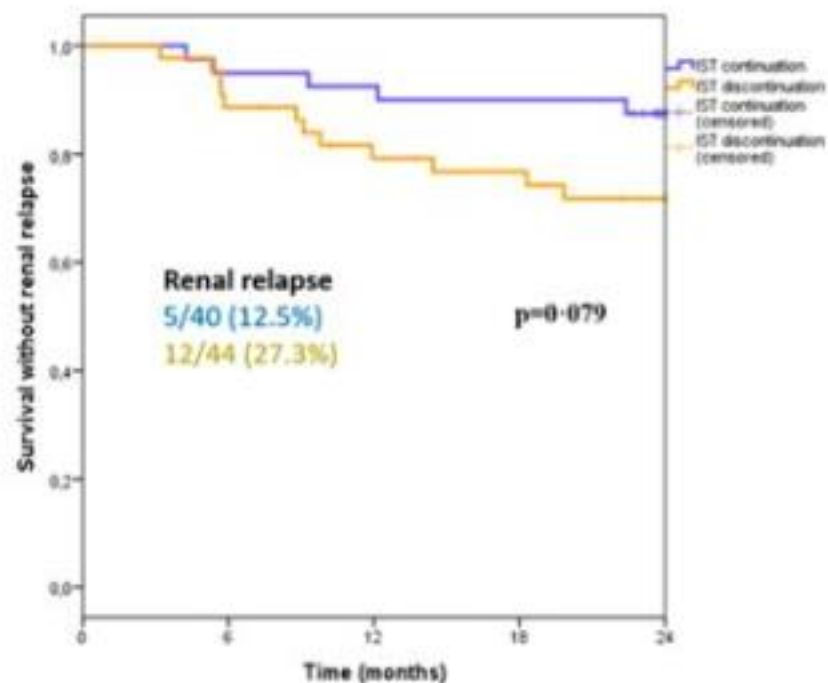


## WIN-Lupus: Flow-Chart

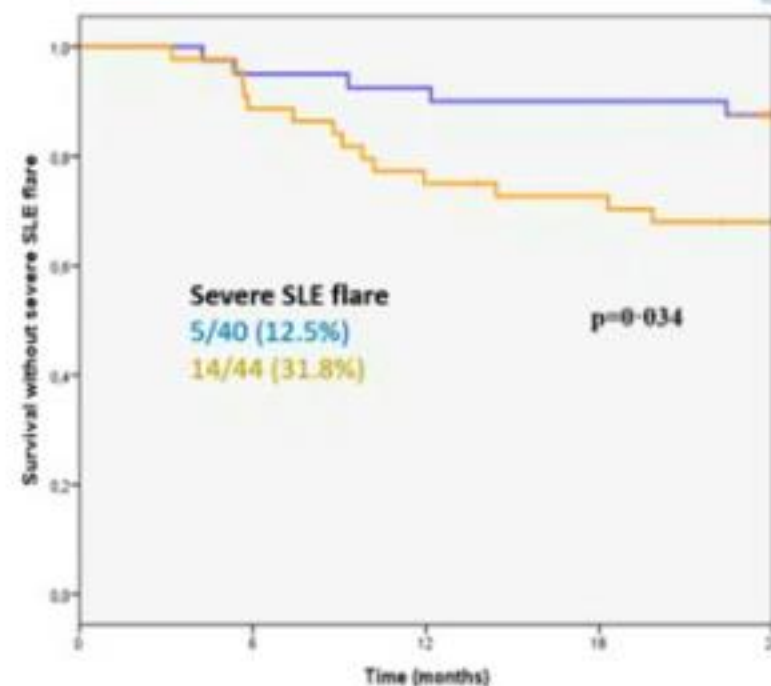




## WIN-Lupus: Survival without renal relapse & without severe flare



Non-inferiority of IST discontinuation: not demonstrated.  
Renal relapse : no significant difference between groups.



More severe SLE flares (renal or extra-renal)  
in the IST discontinuation group.





## WIN-Lupus : Conclusion



- WIN-Lupus is the first randomized trial of IST weaning in proliferative lupus nephritis.
- 96 patients were randomized (out of 200 planned).
- Non-inferiority of maintenance IST discontinuation after 2-3 years was NOT DEMONSTRATED.
- Patients who discontinued IST had a higher risk of severe flares of lupus (renal or extra-renal).
- However, the majority of patients who discontinued IST did not experience a flare.
- The most important challenge remains the identification of patients who can be safely weaned from IST.

# Conclusions

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- There are potentially new mechanisms of action in SLE
- T2T improves SLE
- Withdrawal of Rx doesn't always work
  - Steroids
  - MMF in SLE nephritis



# Hydroxychloroquine Blood Levels Are Associated with Reduced SLE Disease Activity and Improvements in Cardiovascular Risk Factors

Laurence Magder<sup>1</sup>, Michelle Petri<sup>2</sup> and Daniel Goldman<sup>2</sup>, <sup>1</sup>University of Maryland, Baltimore, Baltimore, <sup>2</sup>Johns Hopkins University School of Medicine, Baltimore,

- High hydroxychloroquine (HCQ) blood levels over time are associated with retinopathy.
- To determine HCQ levels needed to have good SLE disease activity
- Hopkins Lupus cohort of 10,370 clinic visits from 1095 SLE patients

- **1000 ng/ml may be a good target** to achieve protection without accruing a high risk of retinopathy.
- Higher HCQ blood levels were associated with:
  - lower mean SLEDAI
  - lower urine protein-creatinine ratio
  - lower systolic blood pressure
  - higher platelet counts
  - .Within a patient, increases in HCQ concentration were associated with
    - decreases in urine protein-creatinine ratio,
    - decreases in systolic blood pressure
    - increases in platelets
    - **Surprisingly, changes in blood concentration were not significantly associated with changes in skin or joint manifestations of SLE**

Would you do HCQ levels if you could?

- Are you impressed with the results?

## Clinical Events and Treatment Consequences

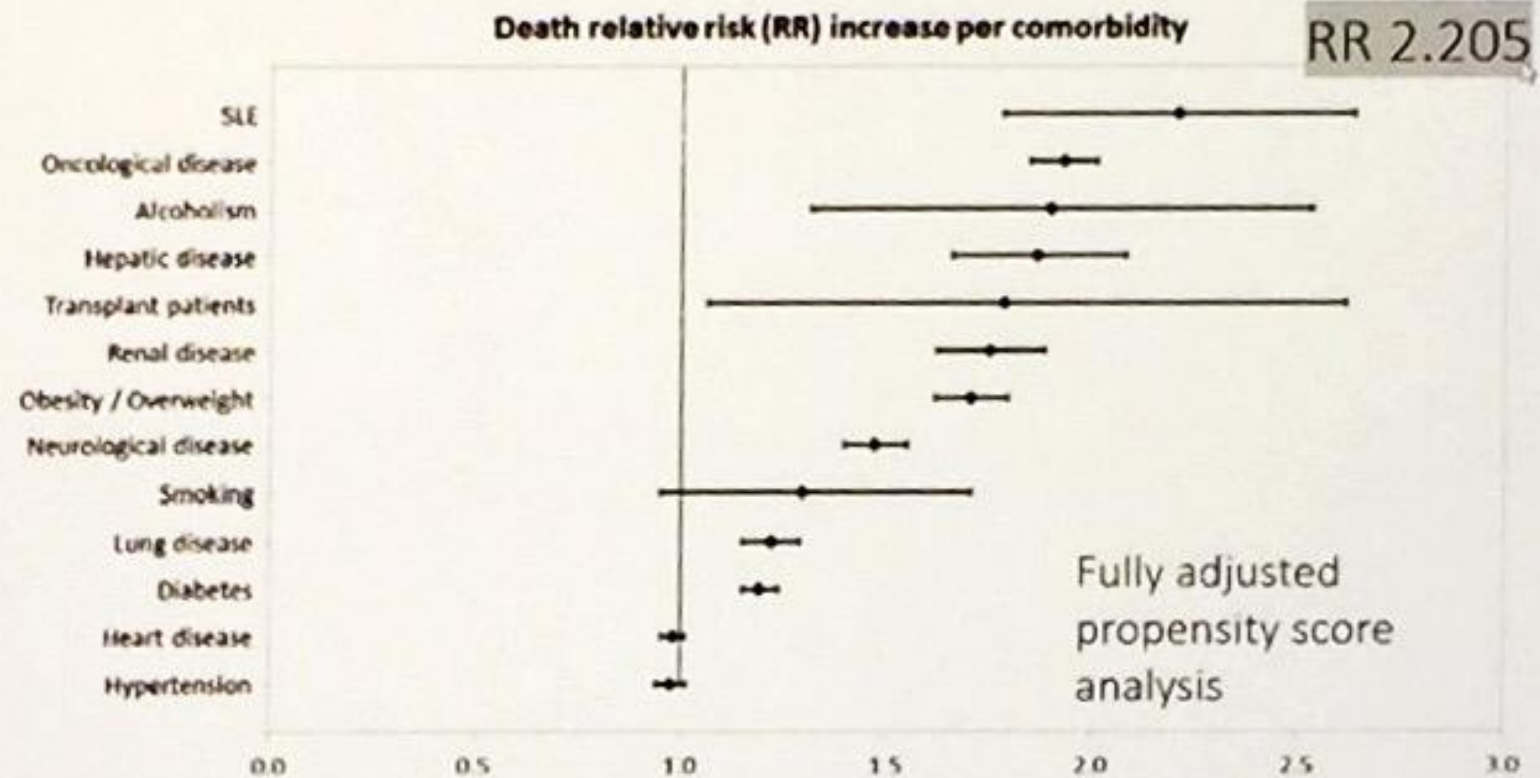


# SLE patients do not have an increased risk of flaring with COVID-19 vaccinations



# COVID-19 in Hospitalized SLE carries significantly higher risks of death and poor outcomes

Nationwide Registry Brazil  
312 047 pts. Hospitalized  
382 SLE pts.



SLE („chronic interferonopathy“) appears as independent risk factor for increased mortality and morbidity of SARS-Cov2 infection

## Failure to achieve LLDAS **and/or** cumulative GC dosages significantly associated with damage & mortality

3384 SLE over 30,313 visits (median follow-up 2.4 years).  
813 patients (24%) never achieved LLDAS.

Despite combined therapy (dual/triple) in 71.1%.

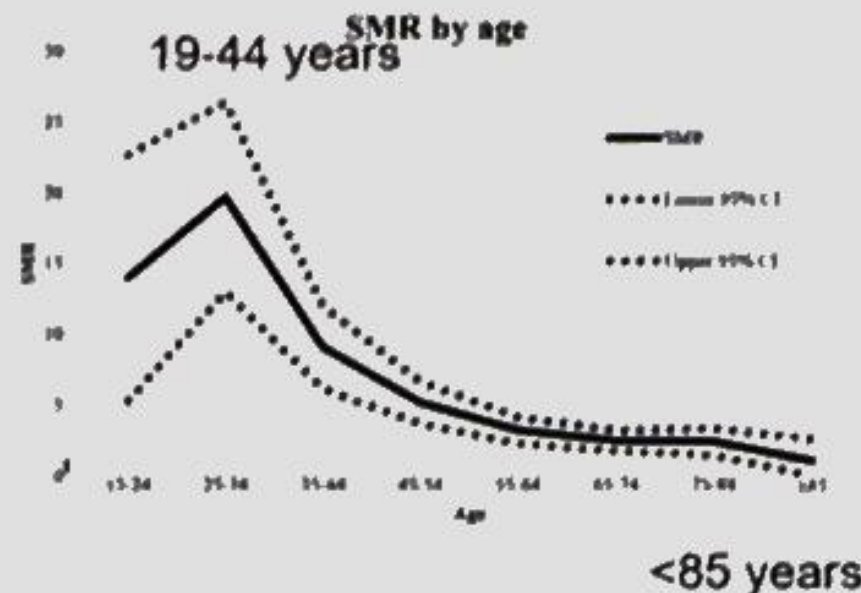
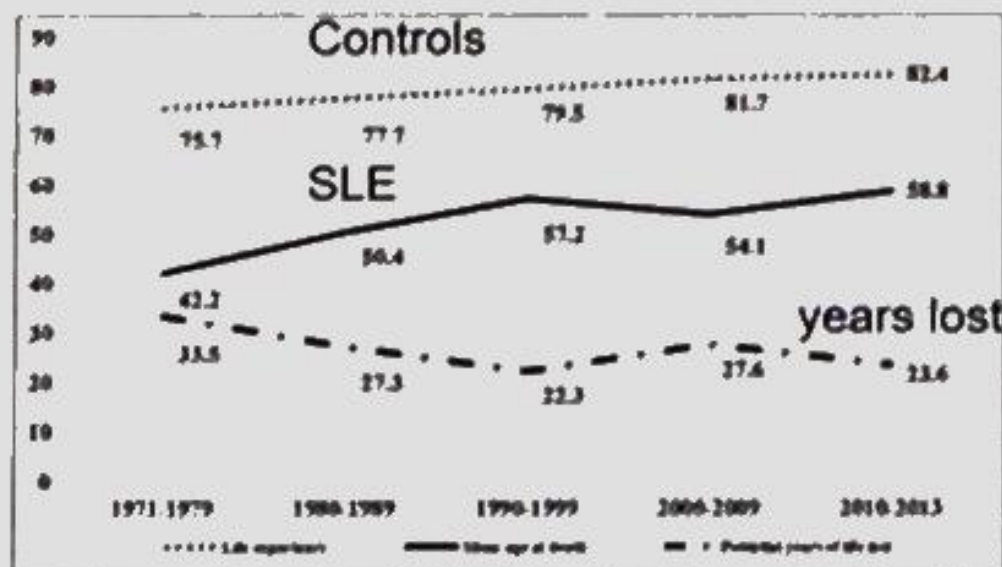
| Outcomes                             | LLDAS-never                       |
|--------------------------------------|-----------------------------------|
|                                      | HR <sup>1</sup> (95% CI), p-value |
| <b>Damage accrual</b>                |                                   |
| Unadjusted                           | 1.52 (1.31, 1.76), p < 0.001      |
| Adjusted <sup>a</sup>                | 1.46 (1.26, 1.69), p < 0.001      |
| <b>Mortality</b>                     |                                   |
| Unadjusted                           | 6.64 (2.83, 15.6), p < 0.001      |
| Adjusted <sup>b</sup>                | 4.98 (2.07, 12.0), p < 0.001      |
|                                      | RC <sup>2</sup> (95% CI), p-value |
| <b>Cumulative prednisolone (PNL)</b> |                                   |
| Unadjusted                           | 5.61 (5.34, 5.88), p < 0.001      |
| Adjusted <sup>c</sup>                | 5.71 (5.38, 6.03), p < 0.001      |

# Premature mortality remains high among SLE patients

## Toronto Lupus Clinic

Between 1971 and 2013, 1732 patients were followed

The all-cause and cause-specific SMR decreased over time



SMR, standardized mortality rate.

Tselios K, et al Ann Rheum Dis 2019;78:802-806.

SLE - among the top 10 causes of death in young women

# Renal Lupus

## Data about association treatment with RTX and CTX

- Zhang J, Cell Biochemistry and Biophysics 2015: RTX plus with CTX showed a better therapeutic efficacy compared to CTX, and it significantly improved the prognosis of refractory and severe LN.
- Roccatello D, Autoimmune Review 2015: A promising role of RTX in an intensified protocol including CTX of induction therapy can be envisaged in severe forms of LN
- Catapano F, NDT 2010: Ten of 11 (91%) patients with active glomerulonephritis achieved a renal response after treatment with CTX and RTX.
- Gunnarsson I, Arthritis Rheum 2007: At 6 months of follow-up, all patients had responded both clinically and histopathologic to combination therapy RTX and CTX

# Renal Lupus

## Predictors of increase in chronicity index and of kidney function impairment at repeat biopsy in Lupus Nephritis. *Moroni G et al. submitted*

Among 203 LN subjects, 61 (30%) repeated kidney biopsy 49 months after the basal biopsy.

**At repeat biopsy, chronicity index increased in 72% participants  
and did not increase in 28%.**

**Predictors of chronicity index increase:**

- Nephritic syndrome - serum creatinine  $>1.6\text{mg/dl}$  at presentation and
- development of renal flares and of nephritic flares in particular  
correlated with chronicity index increase

**Cyclophosphamide therapy protects against chronicity index increase**

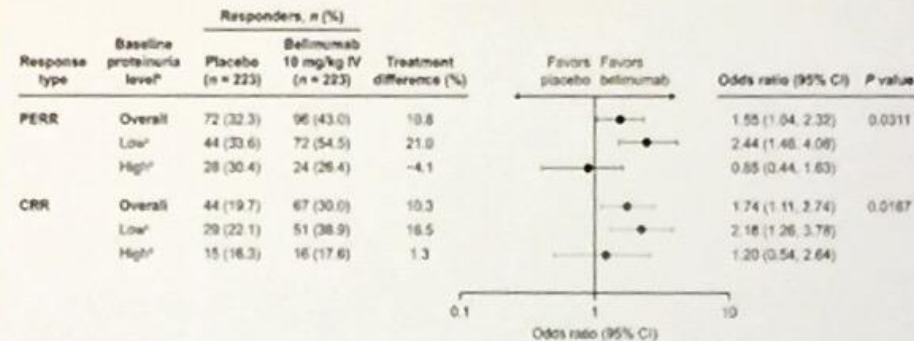
# Renal Lupus

## A secondary analysis of the Belimumab International Study in LN trial examined effects of belimumab on kidney outcome and preservation of kidney function in Lupus Nephritis patients

Rovin BH, *Kidney Int.* 2021 Sep 22;S0085-2538(21)00862-

Add-on belimumab was most effective in achieving PERR and CR in pts with proliferative LN and a basal urine prot/creat ratio <3 g/g.

No observed improvement in pts with LN and sub-epithelial deposits or with a basal prot/creat ratio of  $\geq 3$  g/g.



- Belimumab significantly reduced the risk of kidney-related events or death and lupus nephritis flare in the overall population.
- Belimumab reduced the risk of a sustained 30% or 40% decline in eGFR versus standard treatment alone and attenuated the annual rate of eGFR decline in patients who remained on-study.

## Very Recent Trial Reports Phase 3 in SLE

### Ustekinumab –

Janssen Press Release 26 June 2020

Discontinuation of Phase 3 LOTUS Study of STELARA® (ustekinumab) in Systemic Lupus Erythematosus (SLE) due to lack of efficacy in SLE.

### Baricitinib –

Discordant Results in BRAVE-I and BRAVE-II (EULAR 2022 Presentations)

Morand E et al., Efficacy and Safety of Baricitinib in Patients with Systemic Lupus Erythematosus: Results from two Randomised, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 3 Studies

Dörner T et al. Pooled Safety Analysis of Baricitinib in Patients with Systemic Lupus Erythematosus: Results from Three Randomised, Double-Blind, Placebo-Controlled, Clinical Trials. EULAR poster

### BLISS-BELIEVE –

Lack of efficacy of Subcutaneous Belimumab and Rituximab Sequential Therapy in SLE.

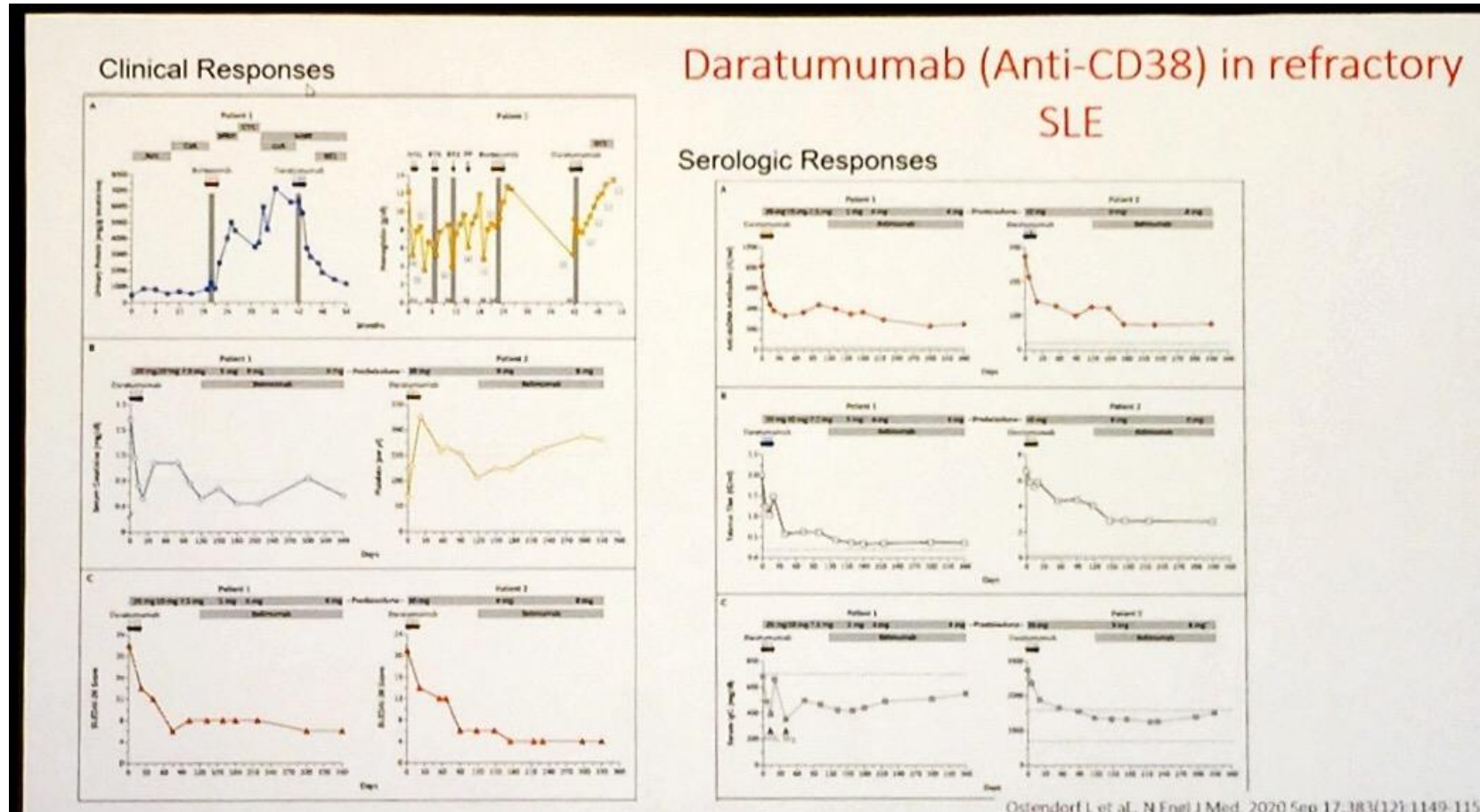
Aranow C, et al. Poster presented at: ACR Convergence; November 1-10, 2021; virtual.

### BEAT LUPUS ++

Achieved primary endpoint (decrease of anti-dsDNA levels at week 52) and prevented BILAG (A and 2B) flares

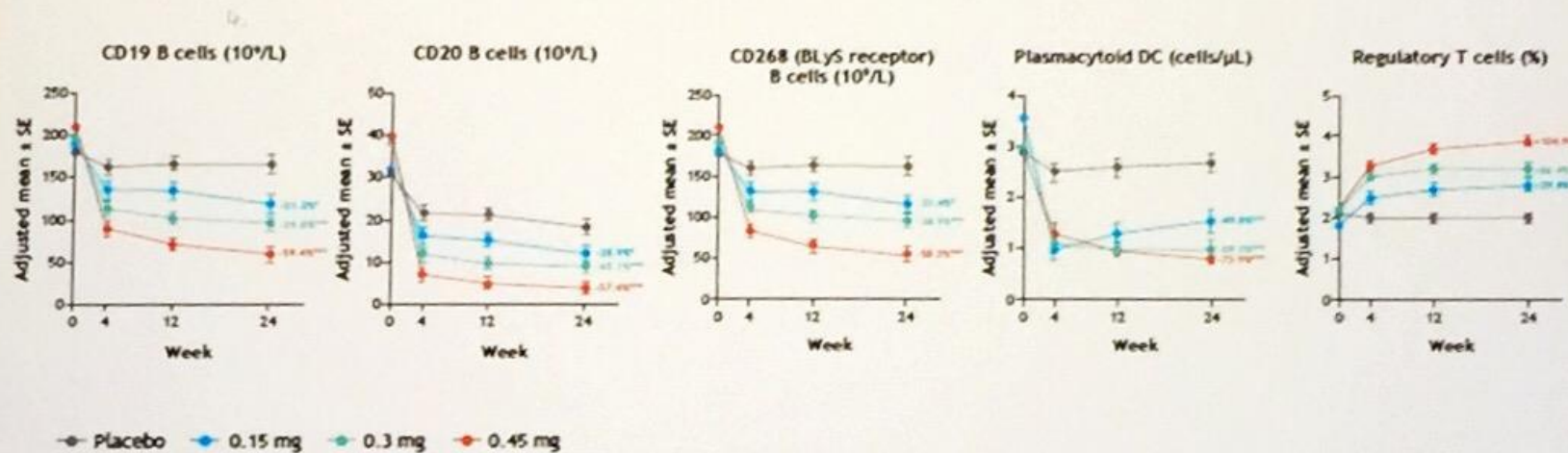
Shipa M et al. Ann Intern Med. 2021; 174(12):1647-1657. doi:10.7326/M21-2078

# ?Future Rx in refractory SLE

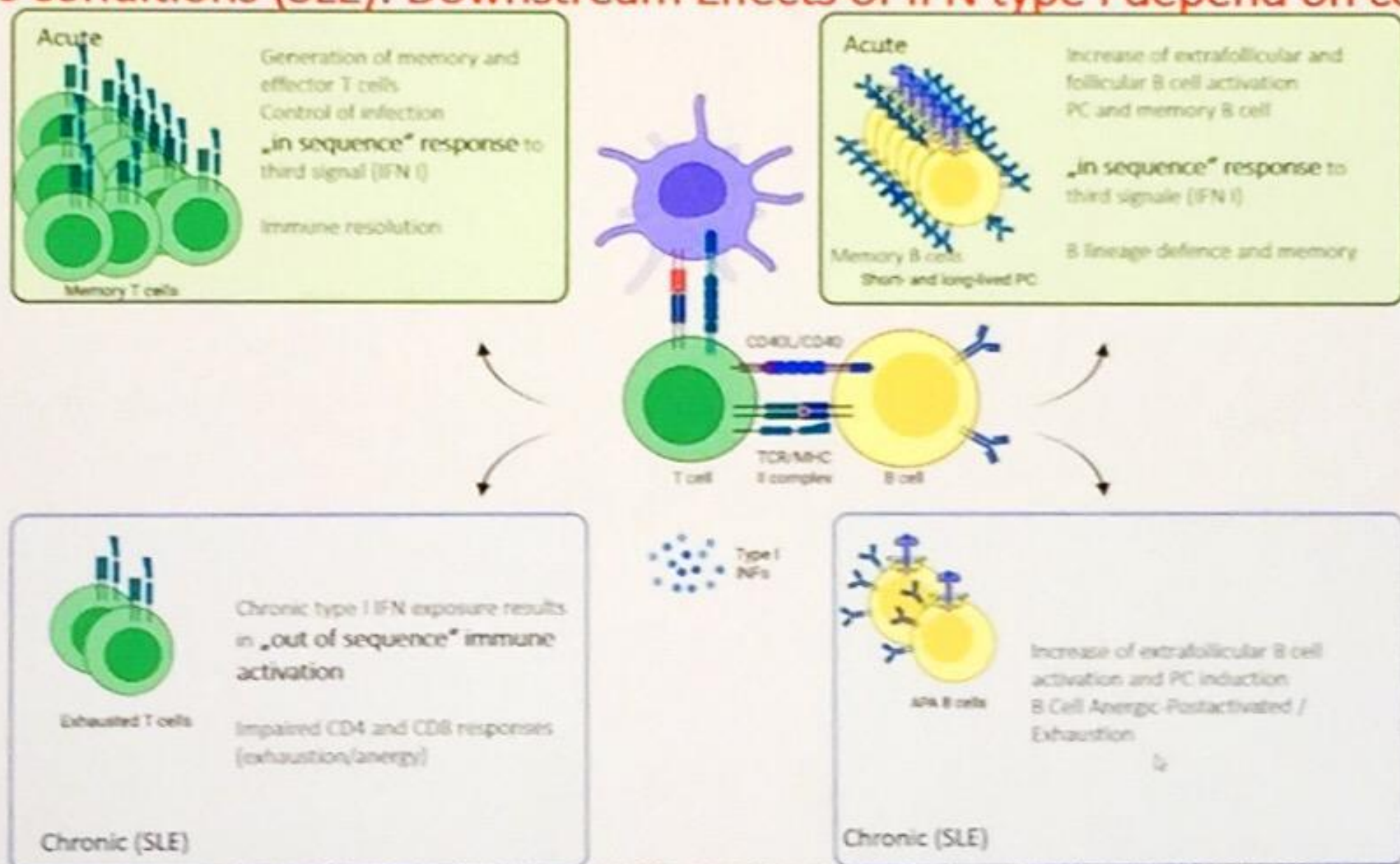


## Biomarkers under Iberdomide Treatment – Impact of Targeting Ikaros and Aiolos on Cell Subsets

Time course of change from baseline of CD19, CD20 B-cells, pDCs, and Treg cells



# Role of type I interferons in T & B cell immunity in acute (virus infection) and chronic conditions (SLE): Downstream Effects of IFN type I depend on context



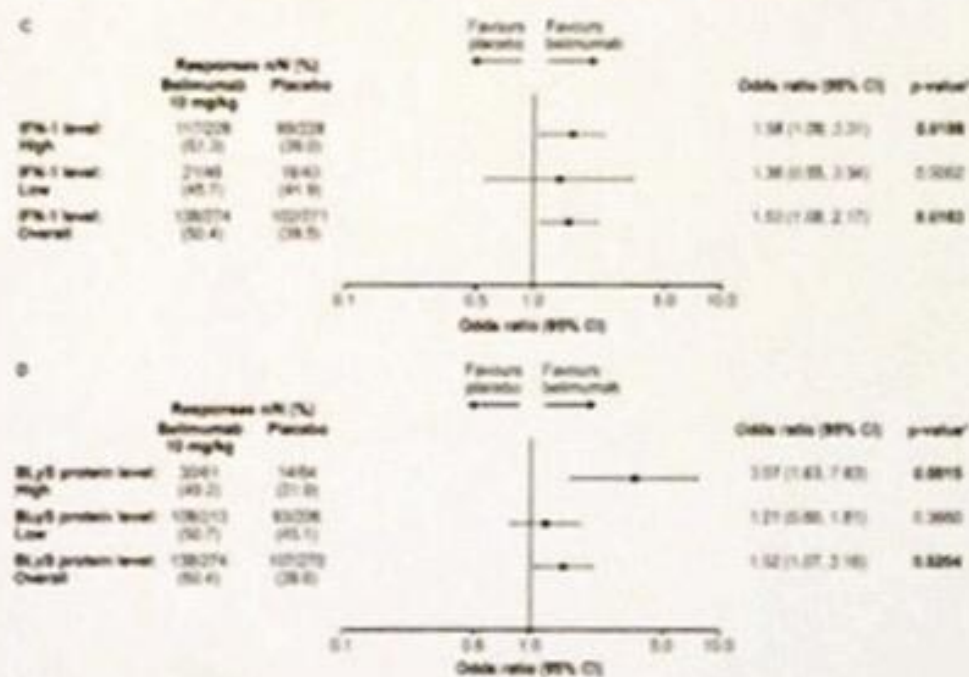
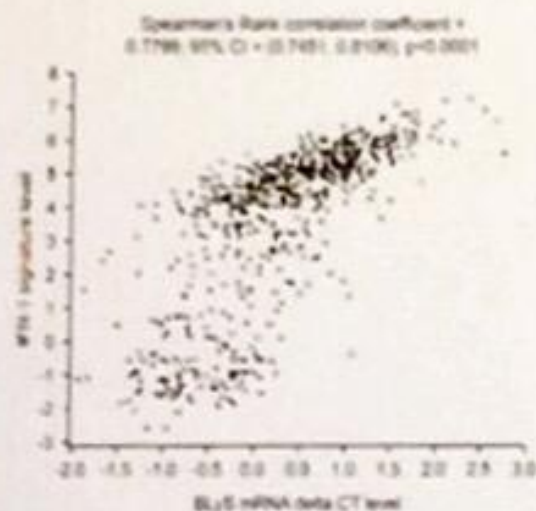
# Do SLE Patients with the IFN and BlyS Signature overlap or represent distinct populations?



Post hoc meta-analysis: improved response to intravenous belimumab 10mg/kg versus SoC in patients with **high baseline BlyS protein and IFN-1 mRNA levels and medium/high BlyS mRNA levels** (554 pts)

## SRI-4 Response and Protein Level

### Correlation mRNA BlyS – IFN-1

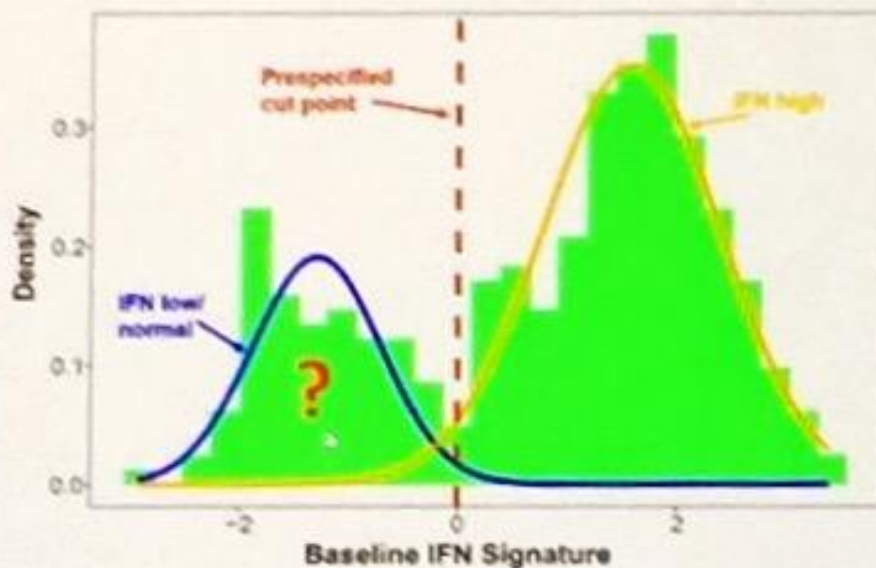


Open question:

Responder profile distinct between belimumab versus anifrolumab

?Need to revisit?

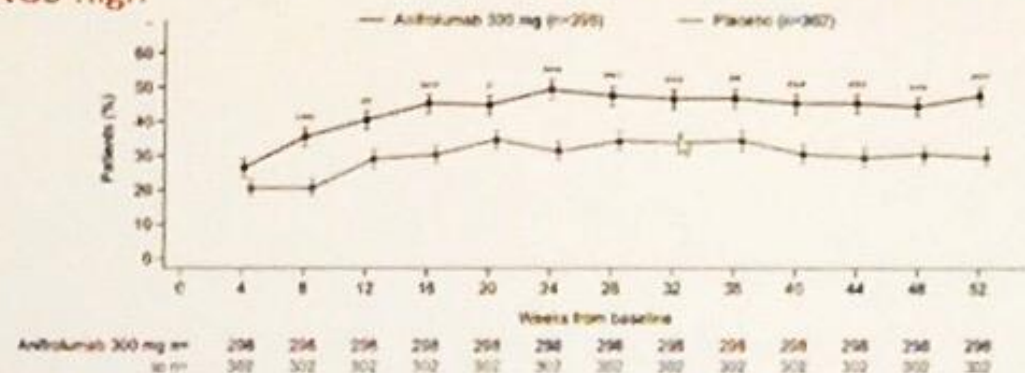
## Bimodal type I IFN signature distribution in SLE



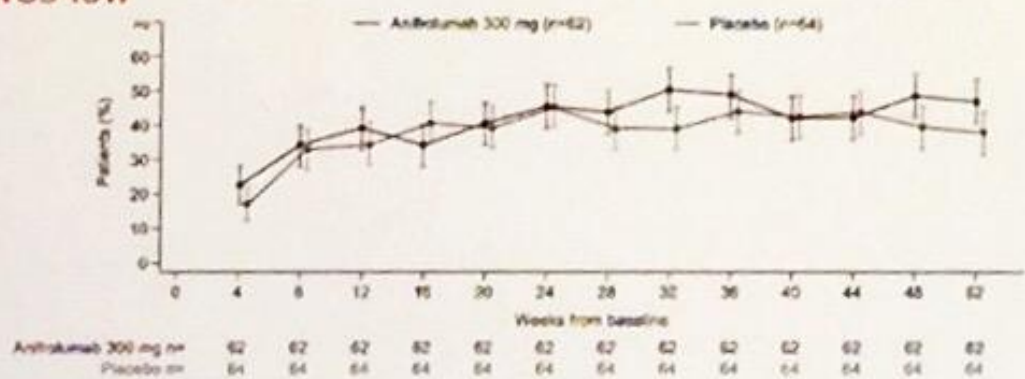
Confounding variable of anti-IFN antibodies in relation to the IFN signature?

## Efficacy (BICLA) and Safety of 300mg Anifrolumab in Type I IFNGS-high and IFNGS-low patients in pooled TULIP data

### IFNGS-high



### IFNGS-low

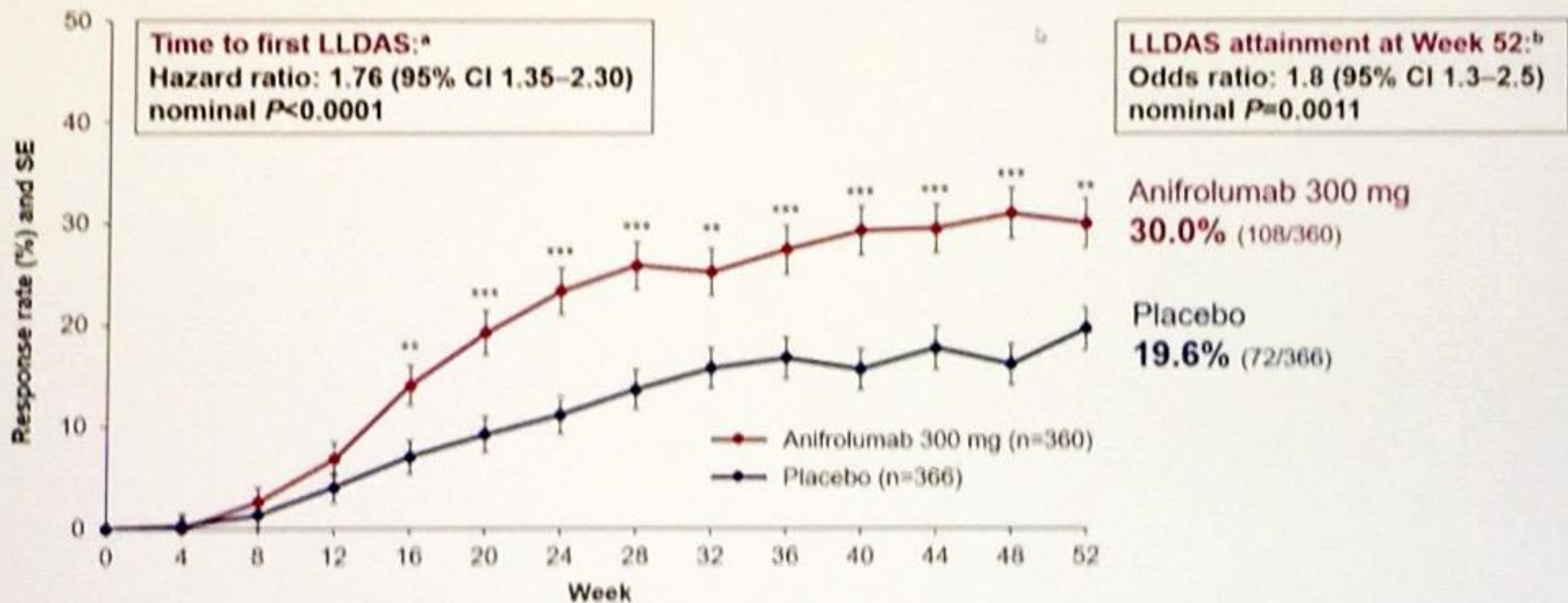


**Responder Profile to 300mg AFR:**  
 IFNGS high patients and/or serologically active  
 18-65 years

Consistent response across various subsets  
 baseline SLE activity  
 GC  $\geq$  10mg  
 demographic and clinical subgroups

?Responder profile among IFNGS-low?

# LLDAS Attainment by Treatment Group (Time to First LLDAS and LLDAS at Week 52)



CI, confidence interval; CMH, Cochran–Mantel–Haenszel; LLDAS, Lupus Low Disease Activity State; SE, standard error; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.  
<sup>a</sup>Time to first LLDAS was derived as the date of the visit when LLDAS was attained minus the date of first administration of investigational product; hazard ratios and 95% CIs were estimated using Cox regression model with stratification factors of SLEDAI-2K at screening, glucocorticoid dosages at Day 1, type I IFN gene signature at screening, and study. <sup>b</sup>Responder rates were calculated using a stratified CMH approach, with the same stratification factors as for the Cox regression; odds ratios, 95% CIs, and nominal  $P$ -values were calculated using logistic regression with the same stratification factors as for the Cox regression. \*\*nominal  $P < 0.01$ ; \*\*\*nominal  $P < 0.001$ .