Lupus 2022

Sheetal Desai MD MSEd

Chief of Rheumatology

Professor of Medicine

University of California, Irvine

Disclosures

Consultant/Speakers Bureau

- Janssen
- GSK
- Astrazeneca
- Aurinia
- Alexion

Agenda

- Diagnosis
- Epidemiology
- Co-Morbidities
- Management
- Lupus Nephritis

SLE Diagnosis

Lupus Classification Criteria history

1971 ACR first classification criteria, revised 1982 &1997

Sensitivity 83% Specificity 96%

Not good for early disease

2012 SLICC/ACR criteria

Sensitivity 97% Specificity 84%

TABLE 1. Classification criteria for SLE

	1997 ACR criteria[11]	2012 SLICC/ACR criteria[12]
No. of clinical criteria	9	11
Dermatological	1. Malar rash (fixed erythema, flat or raised, over the malar prominence, tending to spare the nasolabial folds) 2. Photosensitivity	1. Acute cutaneous lupus (malar rash, photosensitive rash, bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular rash) OR subacute cutaneous lupus rash
Dermatological	3. Discoid lupus (typical)	2. Chronic cutaneous lupus (classic discoid, hypertrophic [verrucous] lupus, panniculitis [profundus], mucosal lupus, lupus tumidus, chilblains lupus, discoid lupus/ lichen planus overlap)
Mucosal	4. Oral/nasal ulcers (usually painless, observed by physician)	3. Oral/nasal ulcers
Alopecia	-	4. Non-scarring diffuse alopecia (excluding alopecia areata, androgenic alopecia, or other causes, eg, drugs)
Musculoskeletal	5. Non-erosive arthritis in ≥2 joints (tender, swollen or effusion)	5. Synovitis ≥2 joints (swelling or effusion) OR tenderness ≥2 joints and ≥30 minutes of morning stiffness
Serositis	6. Pleurisy OR pericarditis	6. Typical pleurisy >1 day OR pleural effusion OR pleural rub; typical pericardial pain >1 day OR pericardial effusion OR pericardial rub OR pericarditis by electrocardiography
Haematologic	7. Haemolytic anaemia with reticulocytosis OR leukopenia (<4000/mm^3 at least twice) OR lymphopenia (<1500/mm^3 at least twice) OR thrombocytopenia (<100/cm^3)	7. Haemolytic anaemia 8. Leukopenia (<4000/mm^3 at least once) OR lymphopenia (<1000/mm^3 at least once) 9. Thrombocytopenia (<100/cm^3 at least once)
Renal	8. Proteinuria >500 mg/day or >3+ by dipstick OR cellular cast (RBC, haemoglobin, granular, tubular, or mixed)	10. Urine protein-to-creatinine ratio (or 24-hour urine protein) >500 mg protein/24 hours OR RBC casts
Neuropsychiatric	9. Seizure OR psychosis	11. Seizures, psychosis, mononeuritis multiplex, myelitis, peripheral OR cranial neuropathy
No. of serological criteria	2	6
Immunologic/ serological	1. Positive ANA (not induced by drugs) 2. Positive for anti-dsDNA OR anti-Sm OR antiphospholipid antibodies (IgG/IgM anticardiolipin; lupus anticoagulant; or a false positive serologic test for syphilis known to be positive for ≥6 months)	1. Positive ANA (above laboratory reference range) 2. Anti-dsDNA (above laboratory reference range or >2-fold the reference range if tested by ELISA) 3. Anti-Sm positivity 4. Antiphospholipid antibody positivity: positive lupus anticoagulant, false positive result for rapid plasma regain, medium-/high-titre anticardiolipin (IgG/A/M), or anti-β_2 glycoprotein I (IgG/A/M) 5. Low complements (C3/C4/CH50) 6. Positive direct Coombs' test (in the absence of haemolytic anaemia)
Total No. of criteria	11	17
SLE classification	≥4/11 Criteria	≥4/17 Criteria

Abbreviations: ACR = The American College of Rheumatology; ANA = antinuclear antibody; ELISA = enzyme-linked immunosorbent assay; Ig = immunoglobulin; RBC = red blood cells; SLE = systemic lupus erythematosus; SLICC = Systemic Lupus International Collaborating Clinics

Entry criterion

Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria

Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight
Constitutional	
Fever	2
Hematologic	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Neuropsychiatric	
Delirium	2
Psychosis	3
Seizure	5
Mucocutaneous	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous OR discoid lupus	4
Acute cutaneous lupus	6
Serosal	
Pleural or pericardial effusion	5
Acute pericarditis	6
Musculoskeletal	
Joint involvement	6
Renal	
Proteinuria >0.5g/24h	4
Renal biopsy Class II or V lupus nephritis	8
Renal biopsy Class III or IV lupus nephritis	10

Immunology domains and criteria	Weight
Antiphospholipid antibodies	
Anti-cardiolipin antibodies OR	
Anti-β2GP1 antibodies OR	
Lupus anticoagulant	2
Complement proteins	
Low C3 OR low C4	3
Low C3 AND low C4	4
SLE-specific antibodies	
Anti-dsDNA antibody* OR	
Anti-Smith antibody	6

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

SLE Classification Criteria (EULAR/ACR 2019)

- Used data driven methods with a multicenter Delphi exercise
- Entry criterion positive ANA
- Highest weighted in each domain
- Need a total score of 10 or more
- Sensitivity 96% Specificity 93%

SLE Classification Criteria (EULAR/ACR 2019)

ENTRY CRITERION: ANA titer ≥1:80 on Hep-2 cells OR an equivalent positive test (ever)

CLINICAL CRITERIA* (Must have ≥1)

CONSTITUTIONAL	
Fever	2
HEMATOLOGIC	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
NEUROPSYCHIATRIC	
Delirium	2
Psychosis	3
Seizure	5
MUCOCUTANEOUS	
Nonscarring alopecia	2
Oral ulcers	2
Subacute cutaneous OR discoid lupus	4
Acute cutaneous lupus	6
SEROSAL	
Pleural or pericardial effusion	5
Acute pericarditis	6
MUSCULOSKELETAL	
Joint involvement	6
RENAL	
Proteinuria >0.5 g/24h	4
Renal biopsy Class II or V lupus nephritis	8
Renal biopsy Class III or IV lupus nephritis	10

IMMUNOLOGY CRITERIA*

ANTIPHOSPHOLIPID ANTIBODIES		**COMPLEMENT PROTEINS**		**SLE-SPECIFIC ANTIBODIES**	
Anticardiolipin OR anti-β2GP1 OR lupus anticoagulant	2	Low C3 OR low C4	3	Anti-dsDNA* OR Anti-Sm	6
		Low C3 AND low C4	4		

Classify as SLE if TOTAL SCORE is ≥10

*For these criteria: occurrence on ≥1 occasion is sufficient, simultaneous occurrence is not required, and only highest weighted criterion is scored in each domain.

ACR, American College of Rheumatology; β2GP1, Beta 2 glycoprotein; EULAR, European League Against Rheumatism; HEp, human epithelial cells.

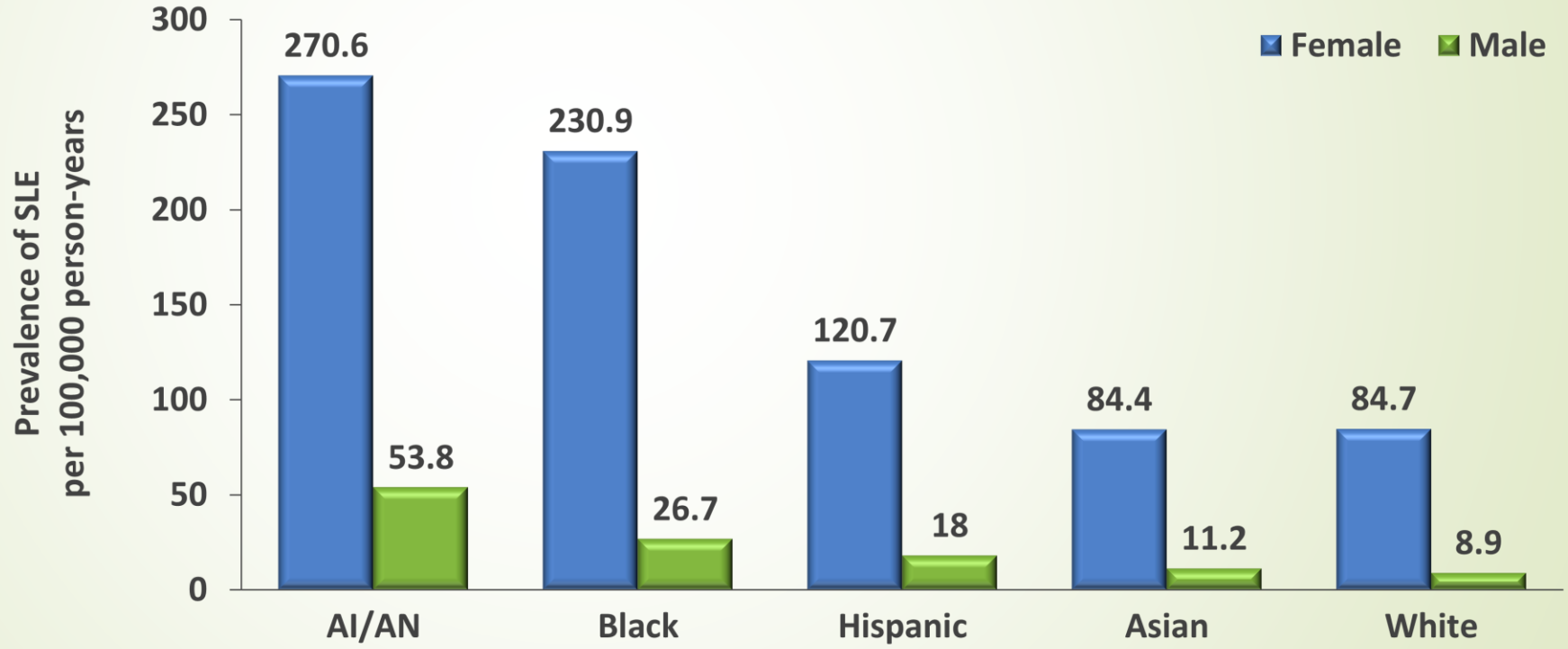
Aringer M, et al. *Ann Rheum Dis*. 2019;78:1151.

SLE Epidemiology

National Lupus Patient Registry

- 2003 Congress established the National Lupus Patient Registry
- First comprehensive research study to assess the prevalence and incidence of lupus in the United States
- Conducted by CDC
- Developed registries in different regions to study 1-2 race/ethnicity
- Georgia, Michigan, San Francisco, Manhattan, Indian Health Services Lupus Registry

CDC National Lupus Registry



Defined by ACR 1997 revised classification criteria. Includes 4 registries from CA, GA, MI, and NY, and the Indian Health Service.
AI/AN, American Indian/Alaska Native.
Izmirly PM, et al. *Arthritis Rheumatol*. 2021;73:991-996. ample Footer Text

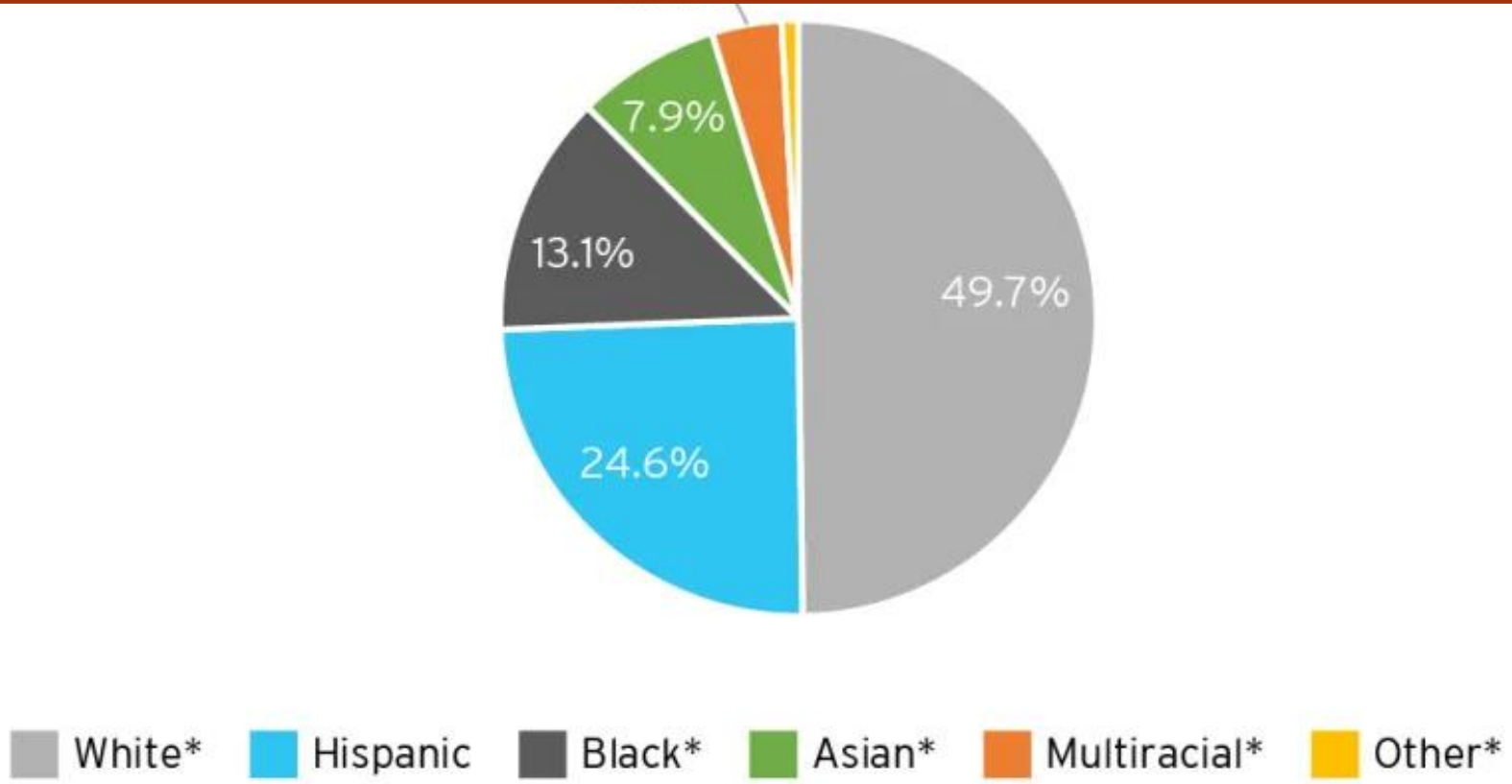
Lupus Disparities

- Incidence, morbidity, mortality all much higher among nonwhite than white racial and ethnic groups in the U.S.
- Prevalence: higher in women and nonwhite descent; highest in those of African heritage
- Mean age of onset: younger in black people
- Disease damage accrues more quickly in black people
- Mortality rates: 3 times as high in non white people vs white people

SamDemas KL, Costenbader KH. Disparities in lupus care and outcomes. Curr Opin Rheumatol. 2009;21(2):102-9.ple Footer Text

2045 US projections

FIGURE 1



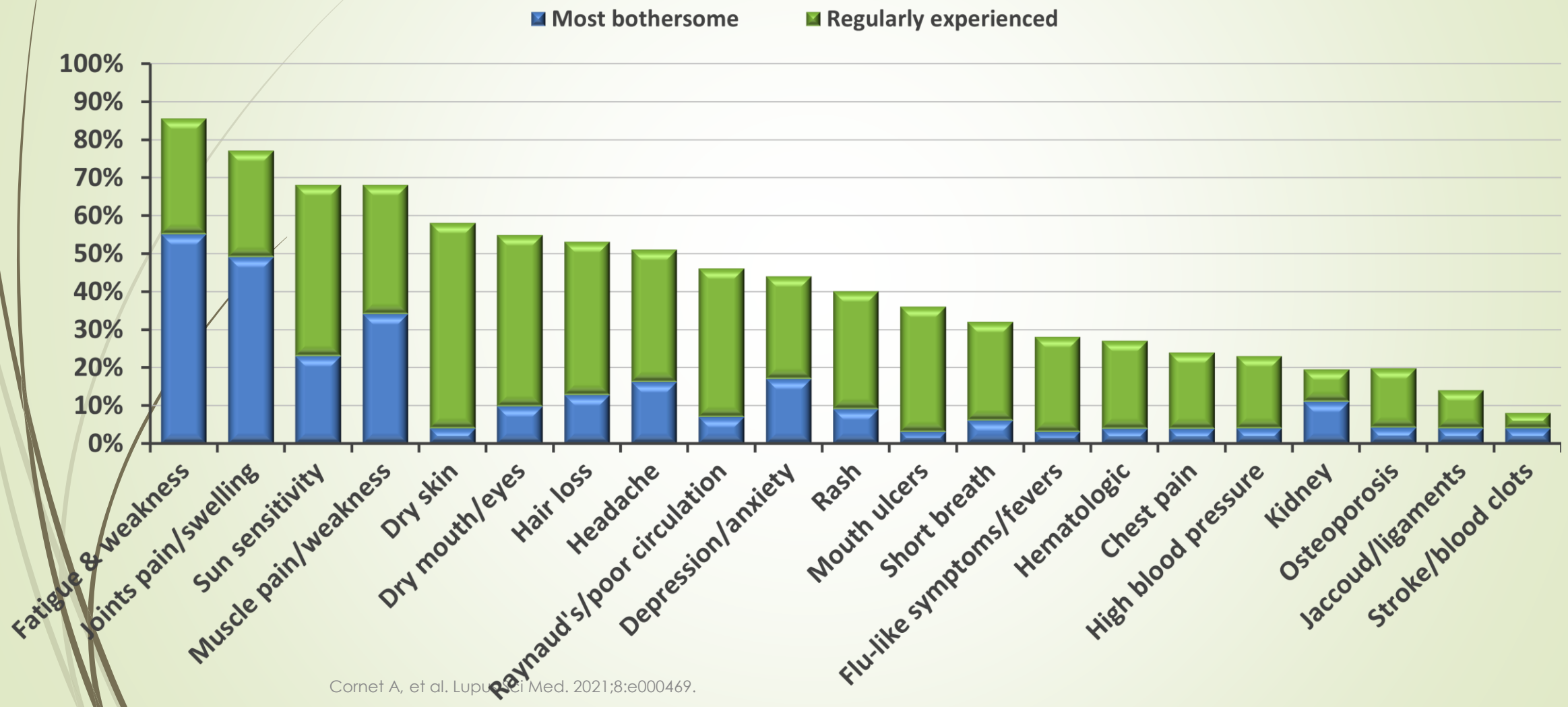
* *Non-Hispanic members of race*

Source: William H Frey analysis of U.S. Census population projections released March 13, 2018

Metropolitan Policy Program at BROOKINGS

SLE Co-Morbidities and Damage

Most Common and Bothersome Symptoms Reported by Patients With SLE



Cornet A, et al. Lupus Sci Med. 2021;8:e000469.

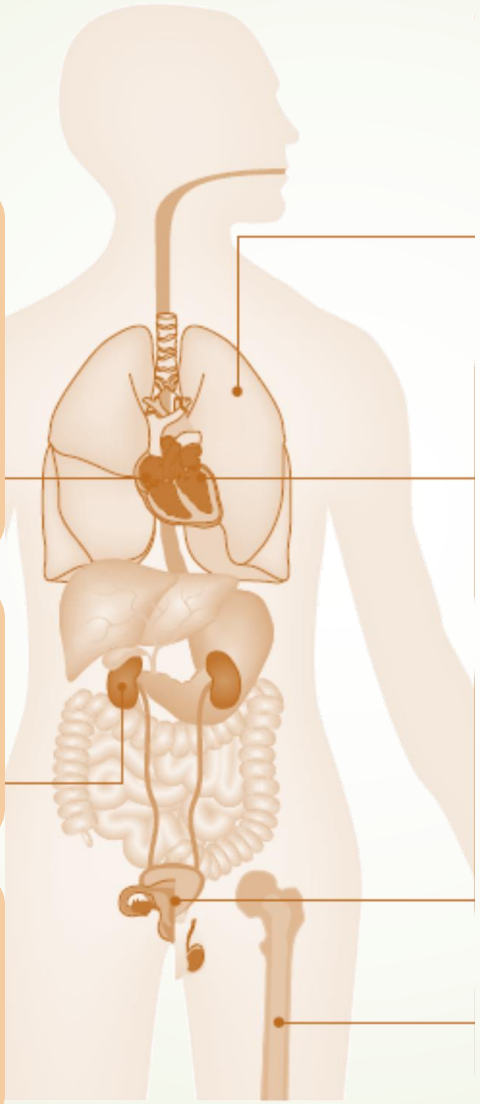
Comorbidities Secondary to SLE and Its Treatment

Comorbidities

Cardiovascular
- HTN
- Dyslipidemia
- CKD-related vascular effects
- CVD
- DM

Renal
- CKD (anemia, bone & mineral disease, ESKD)
- Nephrotic syndrome

Malignancy
- Lymphoma
- Other solid tumors
- Leukemia



Treatment-associated adverse events

Infections
- *Pneumocystis jiroveci pneumonia*
- Herpes
- Latent tuberculosis

Cardiovascular
- HTN
- Dyslipidemia
- Accelerated atherogenesis
- CVD

Reproductive
- Premature ovarian failure
- Adverse pregnancy outcomes
- Reduced male fertility & teratogenicity

Osteoporosis
- Fractures

CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; ESKD, end-stage kidney disease.

Adapted from: ; Anders HJ, et al. *Nat Rev Dis Primers*. 2020;6:7; González LA, et al. *Exp Rev Clin Immunol*. 2017;13:753-768.

1996 SLICC/ACR Damage Index

Ocular
- Any cataract ever — 1
- Retinal change or optic atrophy — 1

Neuropsychiatric
- Cognitive impairment or major psychosis — 1
- Seizures requiring therapy for 6m — 1
- CVA ever (2 pts if> 1) — 1,2
- Cranial or peripheral neuropathy — 1
- Transverse myelitis — 1

Renal
- Estimated or measured GFR <50% — 1
- Proteinuria >3.5 gm/24h — 1
- ESRD — 3

Pulmonary
- PH — 1
- Pulmonary fibrosis (physical & radiograph) — 1
- Shrinking lung (radiograph) — 1
- Pleural fibrosis (radiograph) — 1
- Pulmonary infarction (radiograph) — 1

CV
- Angina or coronary artery bypass — 1
- MI ever (2 pts if > I) — 1,2
- Cardiomyopathy (ventricular dysfunction) — 1
- Valvular disease (diastolic, murmur, or systolic murmur >3/6) — 1
- Pericarditis for 6m, or pericardiectomy — 1

Peripheral vascular — 1,2
- Claudication for 6m — 1
- Minor tissue loss (pulp space) — 1
- Significant tissue loss ever (eg, digit loss; 2 pts if >1 site) — 1
- Venous thrombosis with swelling, ulceration, or venous stasis — 1,2

GI
- Infarction or resection of bowel below duodenum, spleen, liver, or gall bladder ever (2 pts if> 1 site) — 1
- Mesenteric insufficiency — 1
- Chronic peritonitis — 1
- Stricture or upper GI tract surgery ever — 1

Musculoskeletal
- Muscle atrophy or weakness — 1
- Deforming or erosive arthritis — 1
- Osteoporosis with fracture or vertebral collapse — 1
- Avascular necrosis (2 pts if >I) — 1,2
- Osteomyelitis — 1

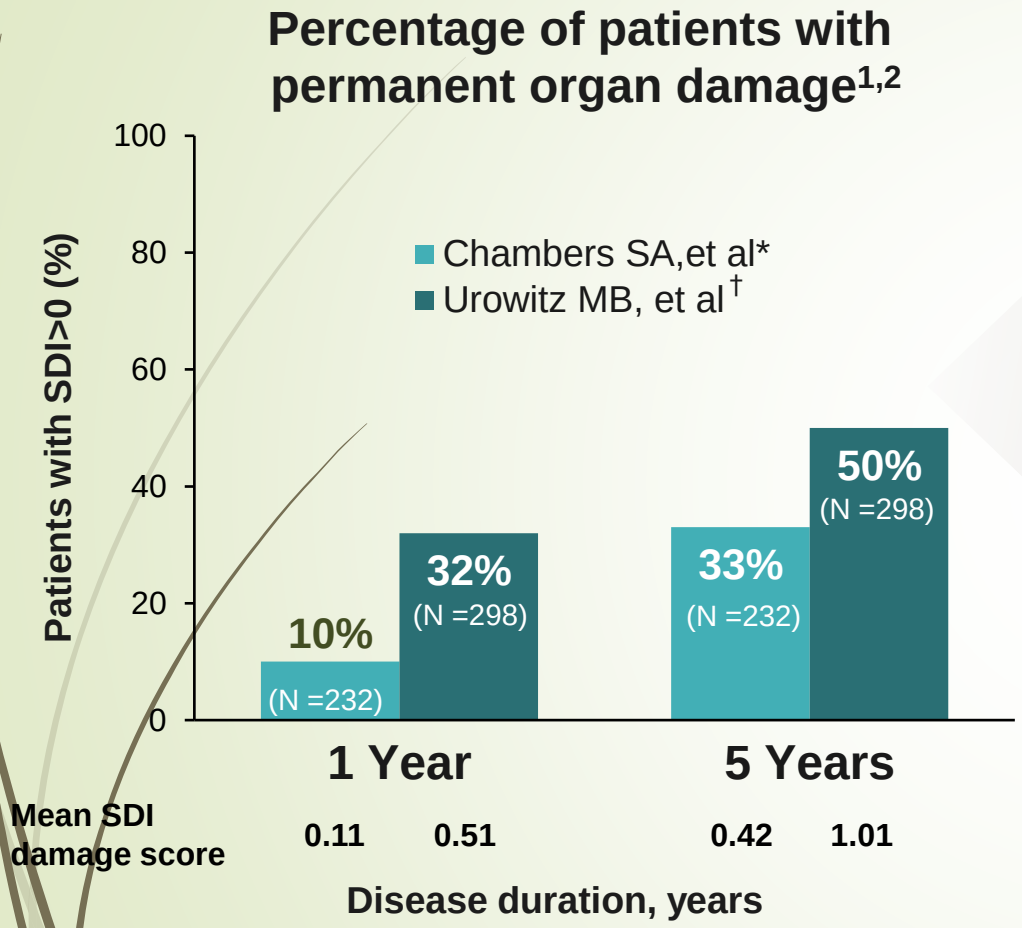
Skin
- Scarring chronic alopecia — 1
- Extensive scarring or panniculum other than scalp & pulp space — 1
- Skin ulceration (excluding thrombosis) >6m — 1

Premature gonadal failure — 1

Diabetes (regardless of treatment) — 1,2

Malignancy (exclude dysplasia) (2 pts if> I site)

Organ Damage Accrual in SLE



of patients with SLE accrued organ damage within 5 years of diagnosis[1,2]

Organ damage is measured by the **SDI**, an internationally validated tool that captures damage caused by ongoing disease activity, flares, and medications used to manage symptoms[3]

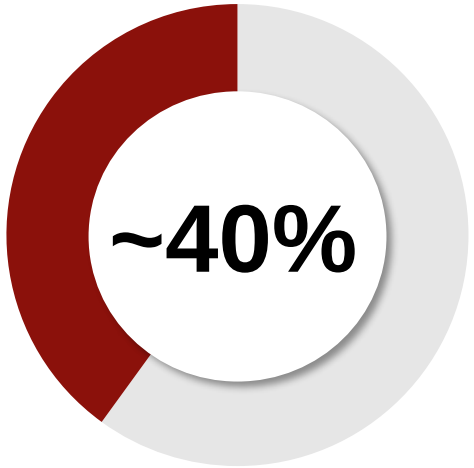
Early organ damage in patients with SLE is a predictor of poor prognosis[4,‡]

*Retrospective analysis of records from 401 patients (232 patients with ≥10 years of consistent follow-up) attending the University College London Hospital SLE clinic between 1978-2004. Year 0 represents time of diagnosis. †Cohort analysis (2009) of 298 patients followed for a minimum of 5 years by the Systemic Lupus International Collaborating Clinics International Research Network, comprising 27 centers from 11 countries. Year 0 represents time of enrollment. ‡Prospective analysis of 263 patients with SLE from the Toronto Lupus Clinic followed for 10 years or until death. At initial assessment, 28% of patients had early damage (defined as SDI score of ≥1) compared with 72% of patients with no damage.

SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

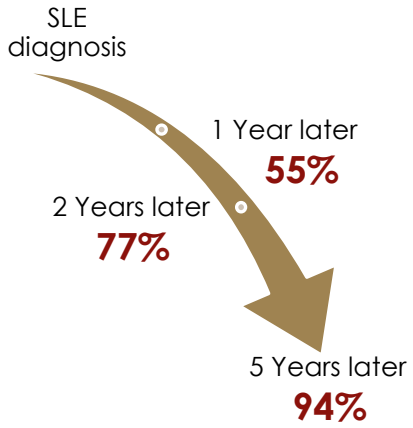
References: 1. Chambers SA, et al. *Rheumatology (Oxford)*. 2009;48(6):673-675. **2.** Urowitz MB, et al. *Arthritis Care Res (Hoboken)*. 2012;64(1):132-137. **3.** Gladman D, et al. *Arthritis Rheum.* 1996;39(3):363-369. **4.** Rahman P, et al. *Lupus.* 2001;10(2):93-96.

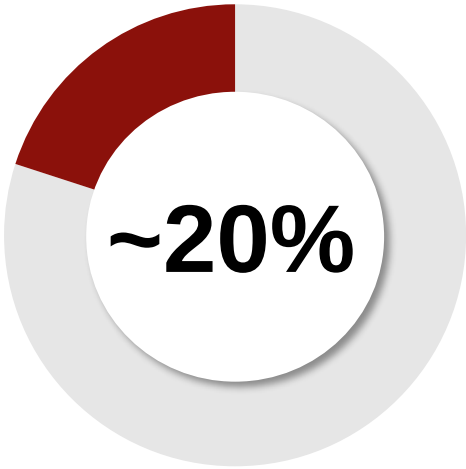
Kidney Damage in SLE



of patients with SLE will develop lupus nephritis[1,2,*]

Majority of patients developed lupus nephritis in the **first 5 years** after SLE diagnosis[3,†]





of patients with lupus nephritis will develop end-stage kidney disease in the 10 years after diagnosis[4]

Lupus nephritis is a severe manifestation of SLE and is a major risk factor for overall morbidity and mortality regardless of treatment[5]

Click on the link to view risk factors of poor prognosis for patients with LN

*With or without biopsy-proven lupus nephritis. †Patients (≥16 years old) with SLE from the Oslo County cohort (N = 325) were followed from January 1, 1999, through January 1, 2008. Lupus nephritis was defined by the ACR criteria (proteinuria >0.5 g/24 hour and/or relevant casts in urine sediment). A patient who fulfilled the ACR criteria for lupus nephritis but did not have a renal biopsy available was defined as clinical lupus nephritis.
ACR = American College of Rheumatology.

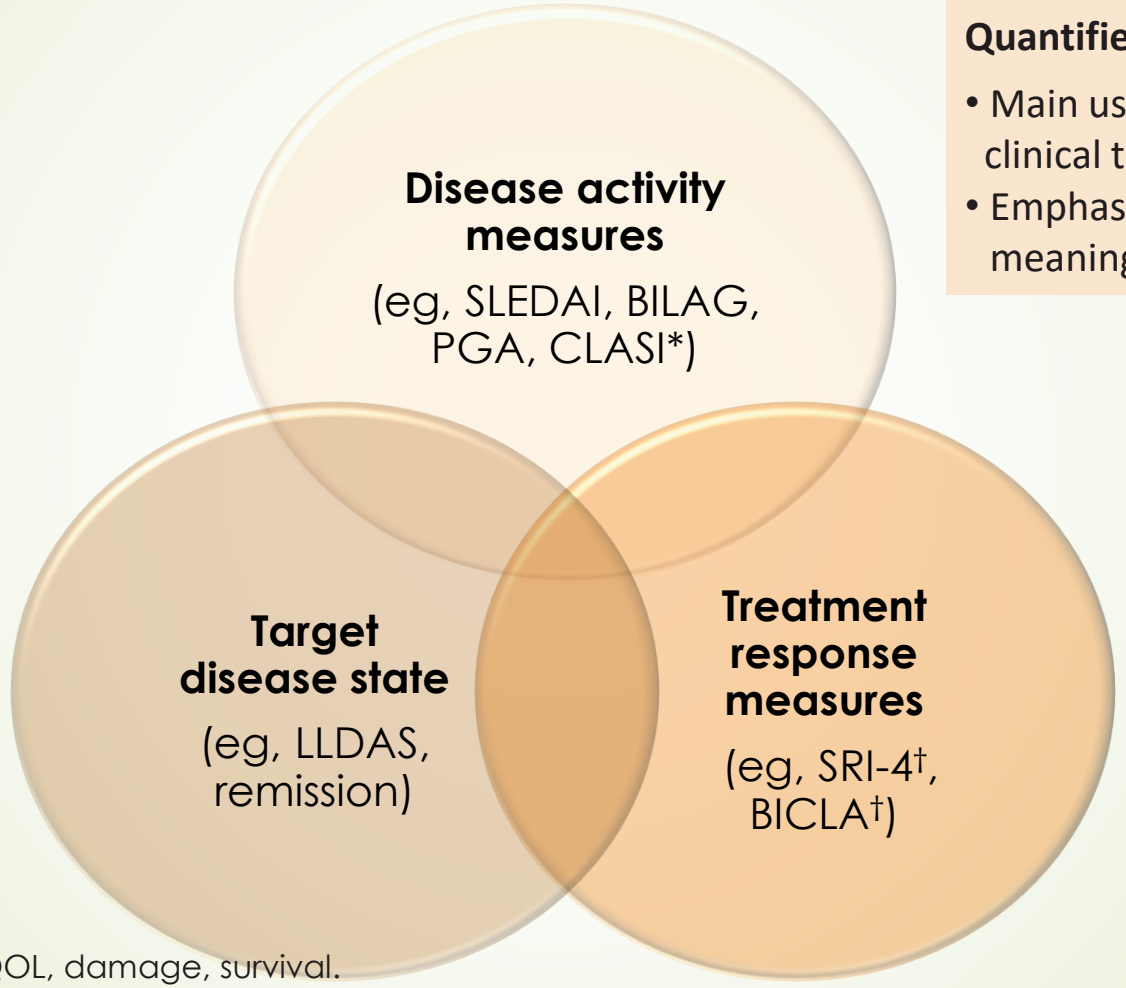
References: 1. Hanley JG, et al. *Rheumatology*. 2016;55:252-262. **2.** Alarcon GS, et al. *Lupus.* 2002;11(2):95-101. **3.** Reppe Moe SE, et al. *Lupus*. 2019;28(7):818-825. **4.** Tektonidou MG, et al. *Arthritis Rheumatol.* 2016;68(6):1432-1441. **5.** Anders HJ, et al. *Nat Rev Dis Primers*. 2020;6(1):7. doi: 10.1038/s41572-019-0141-9.

SLE Disease Activity Measures and Targets

Measures of Disease in SLE

Forms a treatment target to guide treatment escalation

- Main use: clinical practice; clinical trials (target endpoint)
- Emphasis: achievability & association with meaningful health outcomes



Quantifies current disease activity

- Main use: observational cohorts; clinical trials
- Emphasis: reliability, association with meaningful health outcomes, & feasibility

Captures clinically meaningful improvement in response to therapy

- Main use: clinical trials
- Emphasis: sensitivity to change, discriminatory capacity, association with meaningful health outcomes, & interpretability

Note: Meaningful health outcomes include QOL, damage, survival.

BICLA, BILAG-based Composite Lupus Assessment; BILAG, British Isles Lupus Assessment Group; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Score; LLDAS, lupus low disease activity state; PGA, Physician Global Assessment; SLEDAI, SLE Disease Activity Index; SRI-4, SLE Responder Index, ≥4-point reduction.

*Measure of both activity and damage. †Composite index.

Adapted from: Connelly K, et al. *Lancet Rheumatol*. 2021;3:e595-e603.

SELENA-SLEDAI: Disease Activity and Flares

Safety of Estrogens in Lupus Erythematosus National Assessment - SLE Disease Activity Index (SELENA-SLEDAI)

- Modified version of the SLEDAI originally devised for use in the SELENA study
- Manifestations are either present or absent at the time of visit or in the preceding 30 days (ie, improvement or worsening not measured)
- Maximum score of 105
- Score of 4-8 mild/moderate activity
- Score 8 and above high activity

Weight[1]	Check if Present[1]	Descriptor[1]
8	☐	Seizure
8	☐	Psychosis
8	☐	Organic brain syndrome
8	☐	Visual disturbance
8	☐	Cranial nerve disorder
8	☐	Lupus headache
8	☐	CVA
8	☐	Vasculitis
4	☐	Arthritis
4	☐	Myositis
4	☐	Urinary casts
4	☐	Hematuria
4	☐	Proteinuria
4	☐	Pyuria
2	☐	Rash
2	☐	Alopecia
2	☐	Mucosal ulcers
2	☐	Pleurisy
2	☐	Pericarditis
2	☐	Low complement
2	☐	Increased DNA binding
1	☐	Fever
1	☐	Thrombocytopenia
1	☐	Leukopenia

CVA = cerebrovascular accident; SLE = systemic lupus erythematosus

Reference: Petri M, et al. *N Engl J Med*. 2005;353:2550-2558.

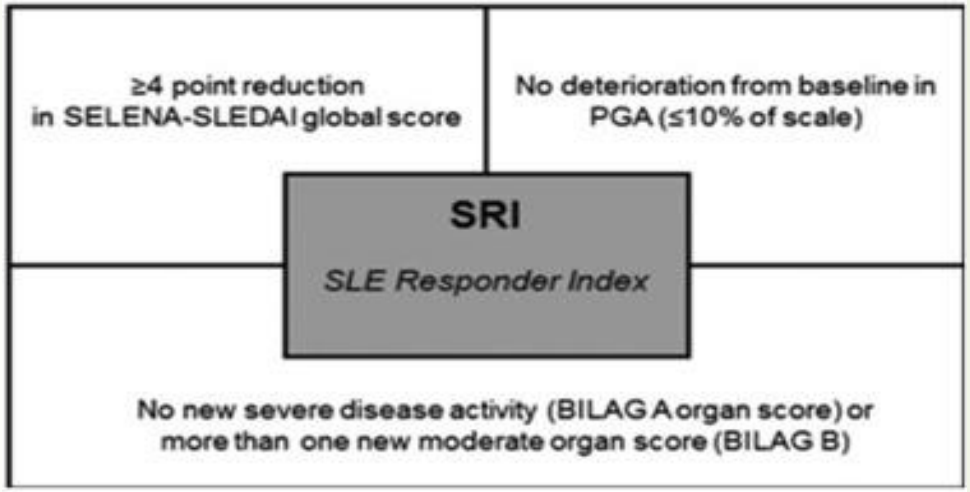
PGA: Disease Activity and Flares

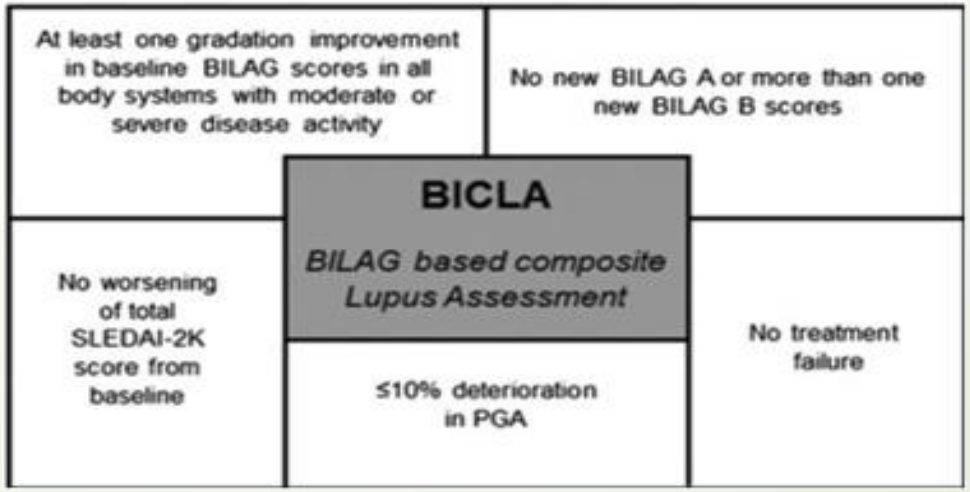
The Physician's Global Assessment (PGA)[1,2]

- Assesses the patient's overall condition
- A 10-cm visual analog scale ranging from 0 to 3 (higher score = more severe disease activity)

Reference: 1. Petri M, et al. *Lupus.* 1999;8(8):685-691. **2.** Furie RA, et al. *Arthritis Rheum.* 2009;61(9):1143-1151.

SRI4 and BICLA
clinical trial composite endpoints





DORIS Definitions of Clinical vs Complete Remission

DORIS Definition

Clinical Remission on Treatment

- Clinical SLEDAI=0
- Serological activity allowed
- SELENA-SLEDAI PGA ≤0.5 (scale 0–3)
- Low-dose GCs (eg, prednisone 5 mg/d) allowed
- Maintenance antimalarials, immunosuppressives and/or stable (maintenance) biologics allowed

Complete Remission

- Clinical SLEDAI=0
- No serological activity
- SELENA-SLEDAI PGA ≤0.5 (scale 0–3)
- No GCs
- Maintenance antimalarials allowed, but no immunosuppressives and/or biologics

Golder V, Tsang-A-Sjoe MW. *Rheumatology*. 2020;59:v19-v28.

Lupus Low Disease Activity Score

Domain and Items	Mean Agreement Score* in Delphi Round 2
Disease activity	
1. SLEDAI-2K ≤4, with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever) and no hemolytic anemia or gastrointestinal activity	5.0
2. No new features of lupus disease activity compared with the previous assessment	4.7
3. SELENA-SLEDAI physician global assessment (PGA, scale 0–3) ≤1	4.8
Immunosuppressive medications	
4. Current prednisolone (or equivalent) dose ≤7.5 mg daily	4.5
5. Well tolerated standard maintenance doses of immunosuppressive drugs and approved biological agents, excluding investigational drugs	4.5

CNS, central nervous system; SELENA, Safety of Estrogens in System Lupus Erythematosus National Assessment.
Franklyn K, et al. *Ann Rheum Dis*. 2016;75:1615-21.

SLE Patient Reported Outcome Measures

PRO	Measure	Content	Recall
SF-36[a]	**HRQoL**	**Generic measure of physical & mental functioning with 36 items contributing to 8 subscales: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, & mental health**	**Standard: 4w Acute: 1w**
LupusQoL	**HRQoL**	34 items, 8 domains: physical health, pain, planning, body image, burden to others, intimate relationships, emotional health, & fatigue	4w
LupusPRO	**HRQoL**	30 items in 8 HRQoL domains: lupus symptoms, lupus medications, cognition, procreation, physical health, emotional health, pain-vitality & body image. 13 items in 3 non-HRQoL domains: desires/goals, available social support & coping, and satisfaction with medical care	4w
L-QoL	**HRQoL Impact**	25 items investigating fatigue and impacts (eg, daily activities, emotional/psychological, social functioning, & relationships)	At the moment
SLEQOL	**HRQoL**	40 items in 6 subsections: physical functioning, activities, symptoms, treatment, mood, & self-image	1w
SSC	**Symptoms**	38 items measuring disease-related and treatment-related symptoms and their burden	1m
SLAQ[b]	**Symptoms**	24 items measuring symptoms of disease activity	3m
Lup-QOL	**HRQoL**	Incorporates the Medical Outcomes Study SF-36 and FACIT-Fatigue. Includes 19 items with generic and disease-specific components including symptoms and interference, cognitive & confidence and planning	Varies
SSD	**Symptoms**	17 items measuring SLE symptoms (including: energy/vitality, joint or muscle pain/stiffness/swelling, cognition and skin symptoms), and current steroid dose	1d
SIQ	**Impact**	30 items measuring SLE impacts (eg, daily activities; social, physical & emotional functioning; & work productivity)	7d

HRQoL, health-related quality of life; PRO, patient-reported outcome.

Mathias SD, et al. *J Patient-Reported Outcomes.* 2018;2:11.

SF-36 Form

Today's date:_____/_____/_____ **ID No:**_____

First name:_____
Surname:_____

SF-36 Questionnaire

This questionnaire asks for your views about your health. For ALL questions, please tick, cross or color the circle that most closely matches your response. There are no right or wrong answers. Please answer ALL questions.

1. In general, would you say your health is:	Poor ○	Fair ○	Good ○	Very good ○	Excellent ○
2. Compared to one year ago, how would you rate your general health now?	Much worse now than one year ago ○	Somewhat worse than one year ago ○	About the same as one year ago ○	Somewhat better than one year ago ○	Much better than one year ago ○

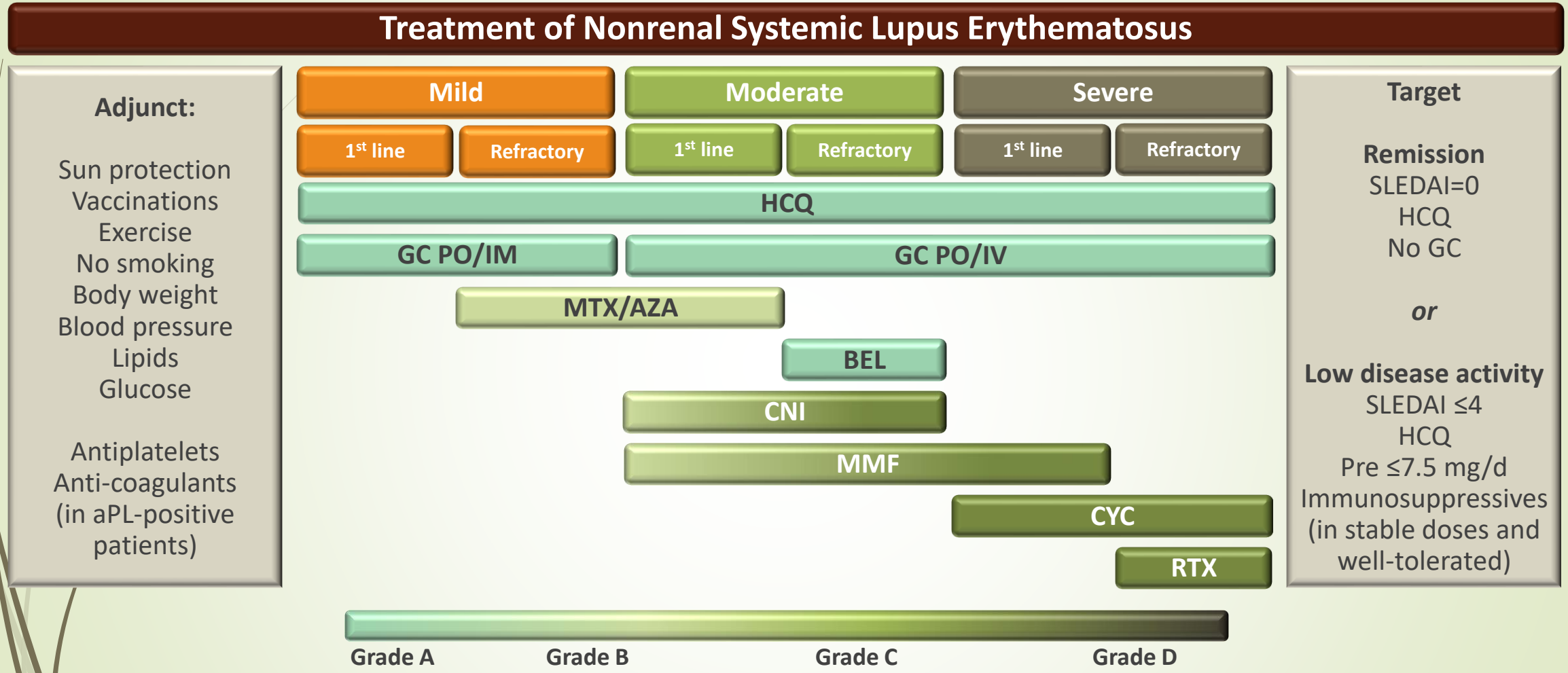
3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	No, not limited at all	**Yes, limited a little**	**Yes, limited a lot**
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	○	○	○
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing	○	○	○
c. Lifting or carrying groceries	○	○	○
d. Climbing <u>several</u> flights of stairs	○	○	○
e. Climbing <u>one</u> flight of stairs	○	○	○
f. Bending, kneeling or stooping	○	○	○
g. Walking more than a mile	○	○	○
h. Walking several blocks	○	○	○
i. Walking one block	○	○	○
j. Bathing or dressing yourself	○	○	○

Available at: https://www.eviq.org.au/getmedia/97326ca3-24bc-4a41-b49e-ec0aed52af61/Self-health-assessment-SF-36.pdf.aspx

Treatment Landscape of Lupus

Approach to the Treatment of SLE: 2019 EULAR Recommendations



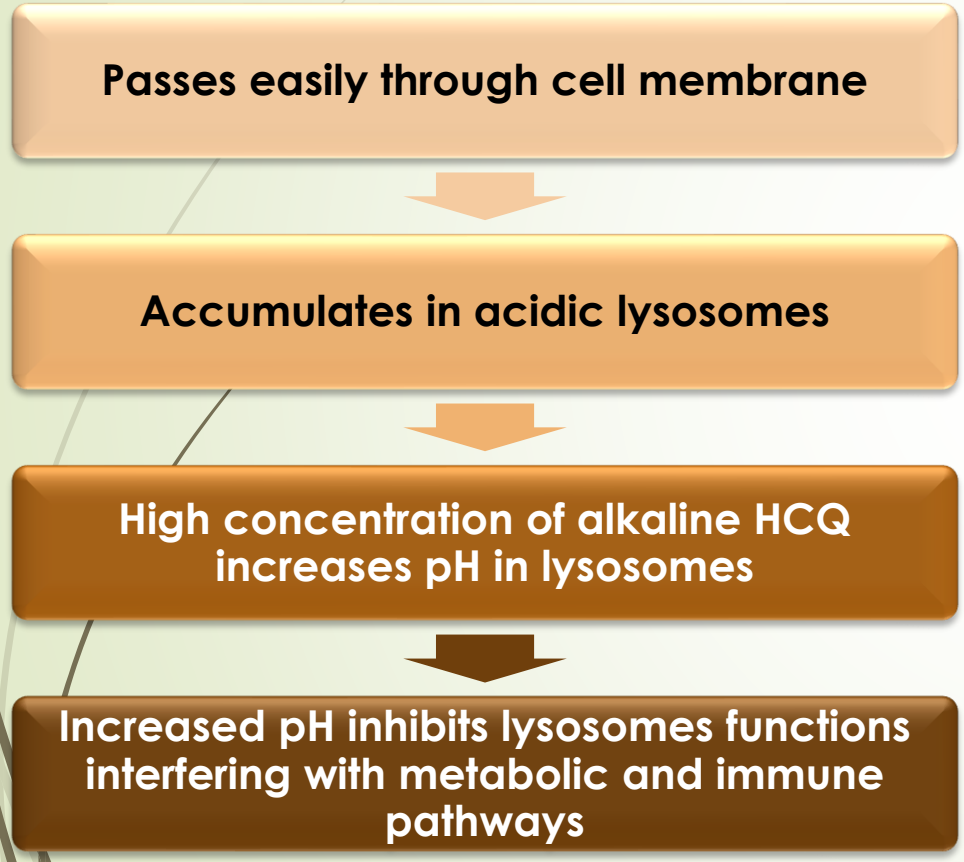
Mild: Constitutional symptoms/mild arthritis/rash ≤9% BSA/PLTs 50-100 x 10^3/mm^3; SLEDAI ≤6; BILAG C or ≤1 BILAG B manifestation
Moderate: RA-like arthritis/rash 9-18% BSA/cutaneous vasculitis ≤18% BSA; PLTs 20-50 x 103/mm^3/serositis; SLEDAI 7-12; ≤2 BILAG B manifestations
Severe: Major organ threatening disease (nephritis; cerebritis, myelitis pneumonitis, mesenteric vasculitis; thrombocytopenia with platelets <20 x 103/mm^3; TTP-like disease or acute hemophagocytic syndrome; SLEDAI >12; ≤1 BILAG A manifestations

aPL, antiphospholipid antibody; AZA, azathioprine; BEL, belimumab; BSA, body surface area; CNI, calcineurin inhibitor; CYC, cyclophosphamide; IM, intramuscular; IV, intravenous; MMF, mycophenolate mofetil; MTX, methotrexate; PO, by mouth; PLT, platelet; Pre, prednisone; RA, rheumatoid arthritis; RTX, rituximab; TTP, thrombotic thrombocytopenic purpura.

Fanouriakis A, et al. *Ann Rheum Dis*. 2019;78:736.

The Role of Hydroxychloroquine in SLE

Primary mechanism of action of HCQ

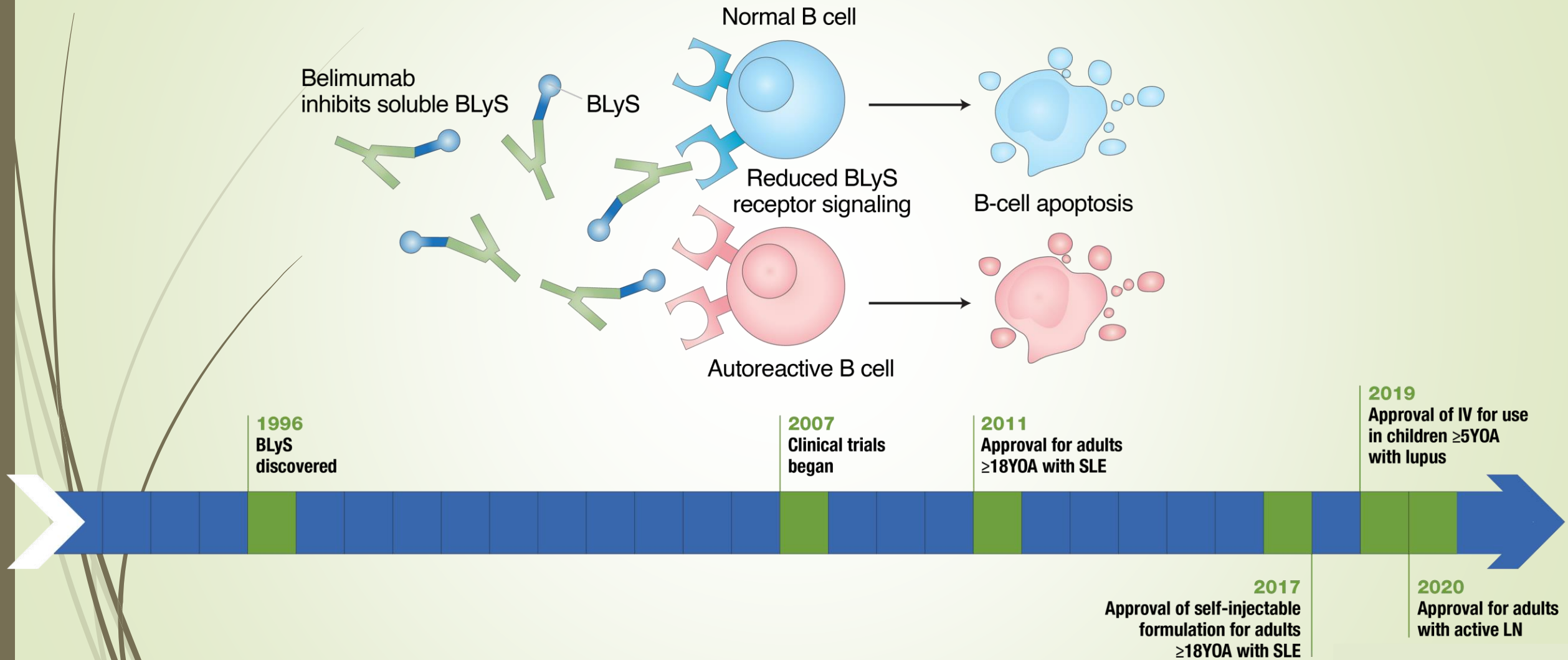


- **Efficacy**
  - **Reduces risk of flares**
  - **Reduces risk of nephritis**
  - **Reduces organ damage**
  - **Increases longevity**
  - **Prevents thrombotic effects of APLAs**
  - **Reduces renal transplant rejection**
- **Safety**
  - **Generally safe**
  - **May be used during pregnancy**
  - **Caution regarding retinopathy with prolonged use (rare but serious complication)**

APLA, antiphospholipid antibody.

Ponticelli C, Moroni G. *Expert Opin Drug Saf.* 2017;16:411-419.

History of Anti-BlyS/BAFF Belimumab for Treatment of Lupus



BlyS, B lymphocyte stimulator; LN, lupus nephritis; YOA, years of age.
Dennis GJ. *Clin Pharmacol Ther*. 2012;91:143-149.

FDA Phase III Adult Pivotal Trials

Clinical Trials	Treatment Arms	Patients Enrolled	Duration of Study	Select Inclusion Criteria	Select Exclusion Criteria
BLISS-52[1,4] 	BENLYSTA IV 1 mg/kg*, 10 mg/kg + ST vs. Placebo + ST	**N = 865** (288/290/287)	52 weeks	• **SELENA-SLEDAI score ≥6** • Positive ANA or anti-dsDNA antibody at screening • SLE diagnosis according to ACR criteria	**Severe active lupus nephritis** • Proteinuria >6 g over 24 hours or equivalent using spot urine protein to creatinine ratio • Serum creatinine >2.5 mg/dL • Required hemodialysis within 90 days of study entry • Required high-dose prednisone (>100 mg/day) within 90 days of study entry **Severe active CNS lupus:** Patient required therapeutic intervention for seizures, psychosis, organic brain syndrome, CVA, cerebritis, or CNS vasculitis within 60 days of study entry **Other biologics or IV cyclophosphamide were not permitted**
BLISS-76[2,4] 	BENLYSTA IV 1 mg/kg*, 10 mg/kg + ST vs. Placebo + ST	**N = 819** (271/273/275)	76 weeks (with primary endpoint at 52 weeks)		
BLISS-SC[3,4] 	BENLYSTA SC 200 mg + ST vs. Placebo + ST	**N = 836** (556/280)	52 weeks	• **SELENA-SLEDAI score ≥8** • Positive ANA or anti-dsDNA antibody at screening • SLE diagnosis according to ACR criteria	

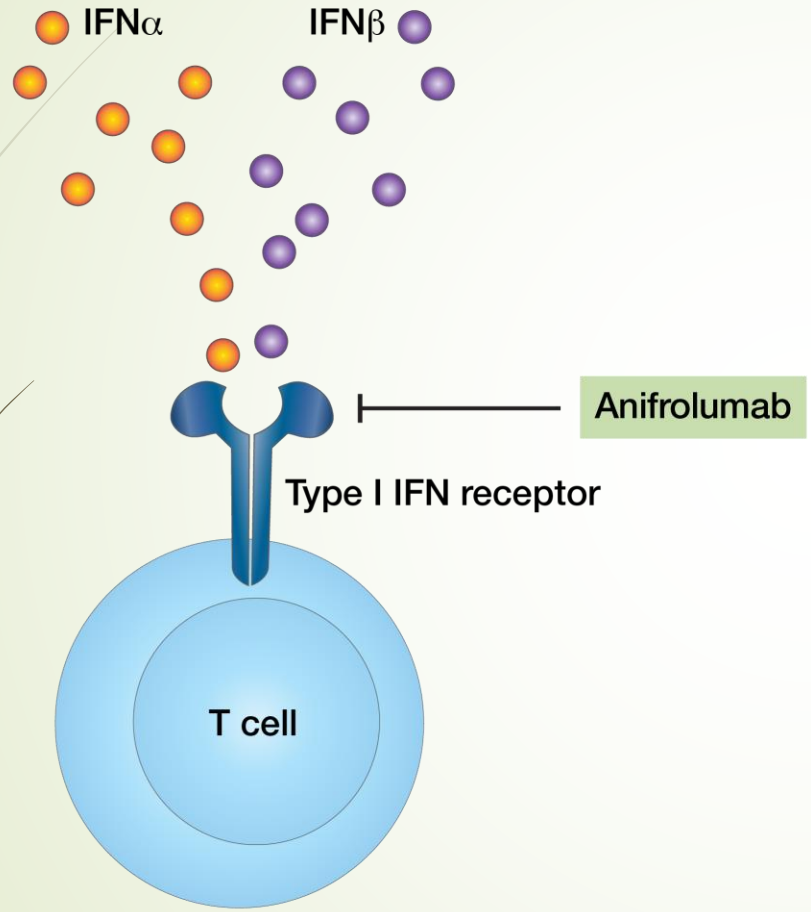
- Primary Endpoint for all trials was SRI-4 response at week 52.
- Specified changes to standard therapy were allowed.

Click on the link for definitions and details of the clinical tools used

Click on the link to view baseline levels of renal involvement

*The 1-mg/kg dose is not recommended.
ACR = American College of Rheumatology; ANA = antinuclear antibody; CNS = central nervous system; CVA = cerebrovascular accident; dsDNA = double-stranded DNA; SELENA-SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index;
SRI-4 = Systemic Lupus Erythematosus Responder Index 4; ST = standard therapy.

Anti-IFNAR Anifrolumab for the Treatment of SLE



2019

- Meets primary endpoints in patients with SLE (TULIP 2)

2021

- Shows benefit across measures of skin & joint disease activity in patients with SLE
- Granted FDA approval for moderate-to-severe SLE

IFN, interferon.

Niewold TB. *Nature Rev Rheumatol*. 2016;12:377-378.

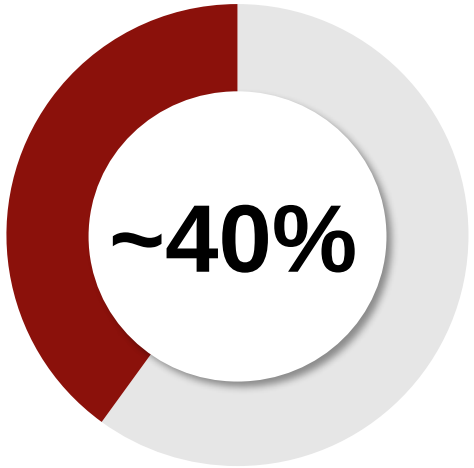
Safety of Anifrolumab

Event	Placebo (N=182)	Anifrolumab 300 mg (N=180)
	Number (percent)	
Any AE	153 (84.1)	159 (88.3)
Serious AE	31 (17.0)	15 (8.3)
Death	0	1 (0.6)†
AE leading to discontinuation	13 (7.1)	5 (2.8)
AEs of special interest‡	18 (9.9)	25 (13.9)
Herpes zoster	2 (1.1)	13 (7.2)
Nonopportunistic serious infections	10 (5.5)	5 (2.8)
Influenza	6 (3.3)	4 (2.2)
Tuberculosis	0	3 (1.7)
Major adverse cardiovascular event	0	1 (0.6)
Cancer	1 (0.5)	0
Serious AE occurring in ≥2 patients		
Pneumonia	7 (3.8)	3 (1.7)
Gastroenteritis, viral	0	2 (1.1)
Worsening of SLE§	6 (3.3)	1 (0.6)
Radius fracture	2 (1.1)	0

Event	Placebo (N=182)	Anifrolumab 300 mg (N=180)
	Number (%)	
AEs with frequency of >5% in the anifrolumab group		
Upper respiratory tract infection	18 (9.9)	39 (21.7)
Nasopharyngitis	20 (11.0)	28 (15.6)
Infusion-related reaction	14 (7.7)	25 (13.9)
Bronchitis	7 (3.8)	22 (12.2)
Urinary tract infection	25 (13.7)	20 (11.1)
Herpes zoster	2 (1.1)	13 (7.2)
Sinusitis	9 (4.9)	12 (6.7)
Arthralgia	6 (3.3)	10 (5.6)
Back pain	3 (1.6)	10 (5.6)
Cough	6 (3.3)	10 (5.6)

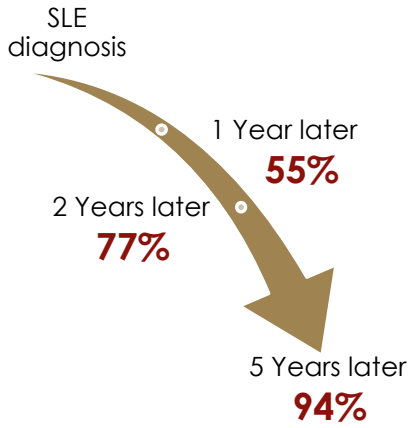
Morand EF, et al. *N Engl J Med*. 2020;382:211-221.

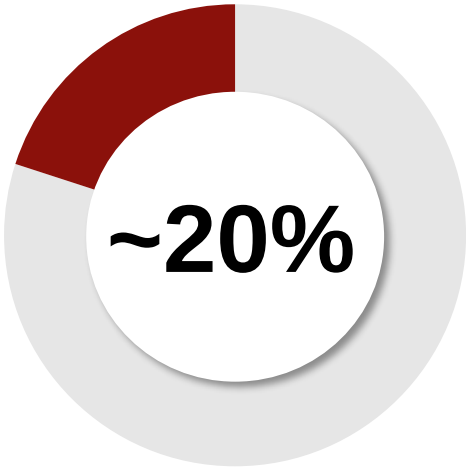
Kidney Damage in SLE



of patients with SLE will develop lupus nephritis[1,2,*]

Majority of patients developed lupus nephritis in the **first 5 years** after SLE diagnosis[3,†]





of patients with lupus nephritis will develop end-stage kidney disease in the 10 years after diagnosis[4]

Lupus nephritis is a severe manifestation of SLE and is a major risk factor for overall morbidity and mortality regardless of treatment[5]

Click on the link to view risk factors of poor prognosis for patients with LN

*With or without biopsy-proven lupus nephritis. †Patients (≥16 years old) with SLE from the Oslo County cohort (N = 325) were followed from January 1, 1999, through January 1, 2008. Lupus nephritis was defined by the ACR criteria (proteinuria >0.5 g/24 hour and/or relevant casts in urine sediment). A patient who fulfilled the ACR criteria for lupus nephritis but did not have a renal biopsy available was defined as clinical lupus nephritis.
ACR = American College of Rheumatology.

References: 1. Hanley JG, et al. *Rheumatology*. 2016;55:252-262. **2.** Alarcon GS, et al. *Lupus.* 2002;11(2):95-101. **3.** Reppe Moe SE, et al. *Lupus*. 2019;28(7):818-825. **4.** Tektonidou MG, et al. *Arthritis Rheumatol.* 2016;68(6):1432-1441. **5.** Anders HJ, et al. *Nat Rev Dis Primers*. 2020;6(1):7. doi: 10.1038/s41572-019-0141-9.

BLISS-LN: Belimumab for the Treatment of LN

Methods & Cohort

- Multicenter, double-blind RCT, n=448
- LN Class III to V
- GFR >30 ml/min/1.73m^2
- Mean age 33.4 ± 10.6Y
- Females: 88%
- 50% Asian, 30% White, 14% Black

104 weeks

PlaceboSOC

Belimumab

Primary Efficacy Renal Response

32%

OR 1.6
95% CI 1.0 to 2.3
P = 0.03

43%

Complete Renal Response

20%

OR 1.7
95% CI 1.1 to 2.7
P = 0.02

30%

More patients who received belimumab plus standard therapy had a primary efficacy renal response vs those who received standard therapy alone.

Note: The safety profile of belimumab was consistent with that in previous trials.

Furie R, et al. *NEJM.* 2020;383:1117-1128.

Renal Endpoints

A responder must meet all of the criteria listed[1,2]

	Renal Response (RR)	Complete Renal Response (CRR)*
For RR and CRR endpoints, response must be reproducible by a repeat measurement at a separate visit to be considered a responder.		
eGFR	No worse than 20% below pre-flare value ***OR*** ≥60 mL/min/1.73m^2	No worse than 10% below pre-flare value ***OR*** ≥90 mL/min/1.73m^2
Urinary protein: creatinine ratio (uPCR)	≤0.7	<0.5
Not a treatment failure†	Yes	Yes
***CRR is a more stringent endpoint for reduction in proteinuria and preservation of renal function than RR**		

Time to Renal-related Event or Death[1,2]

This is a composite outcome that evaluates the prevention of renal worsening events

First of the following:

End stage kidney disease

Doubling of serum creatinine

Renal worsening as evidenced by increased proteinuria and/or impaired renal function

Renal disease-related treatment failure‡

Death

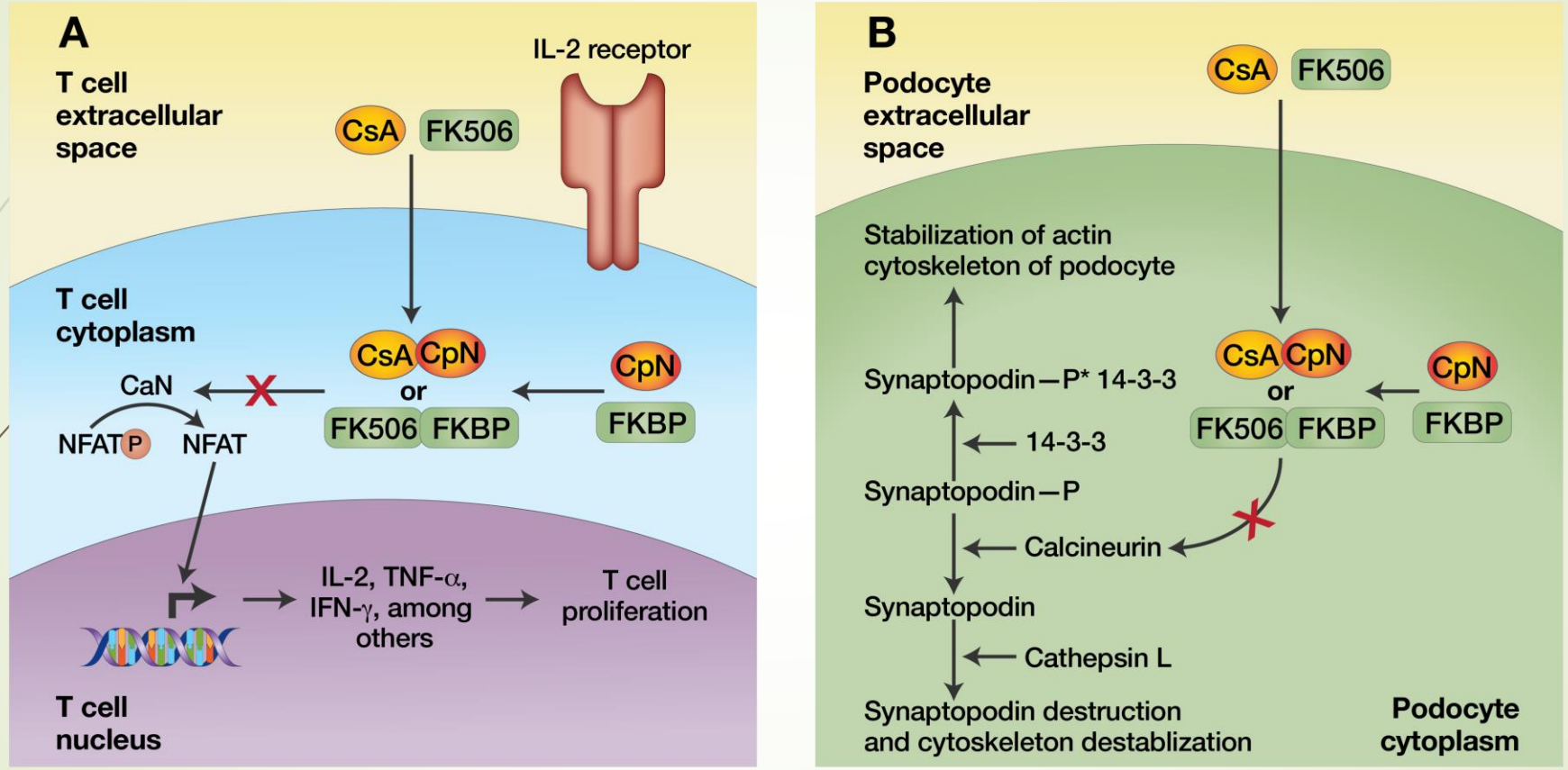
‡(Use of protocol-prohibited rescue medication such as prednisone above 10 mg/day after Week 24 for treatment of renal SLE-related disease activity or new immunosuppressants outside of the induction and maintenance regimens)

†Treatment failure was defined as patients taking a protocol-prohibited or restricted medication, including corticosteroids above 10 mg/kg for treatment of a renal event after Week 24.

eGFR = estimated glomerular filtration rate.

References: 1. Furie R, et al. *N Engl J Med.* 2020;383(12):1117-1128. **2.** Data on File. GSK.

The Role of Calcineurin Inhibitors in Treating Lupus Nephritis



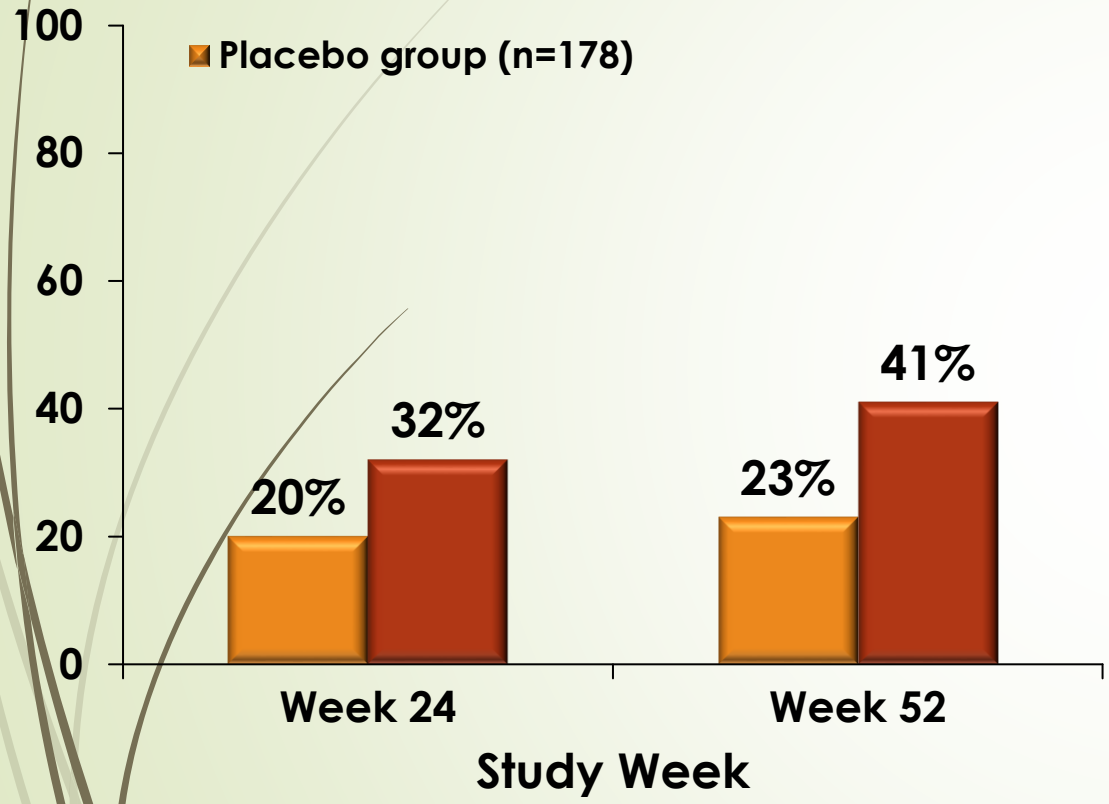
Calcineurin inhibition results in both decreased T cell proliferation (A) and in podocyte stabilization (B).

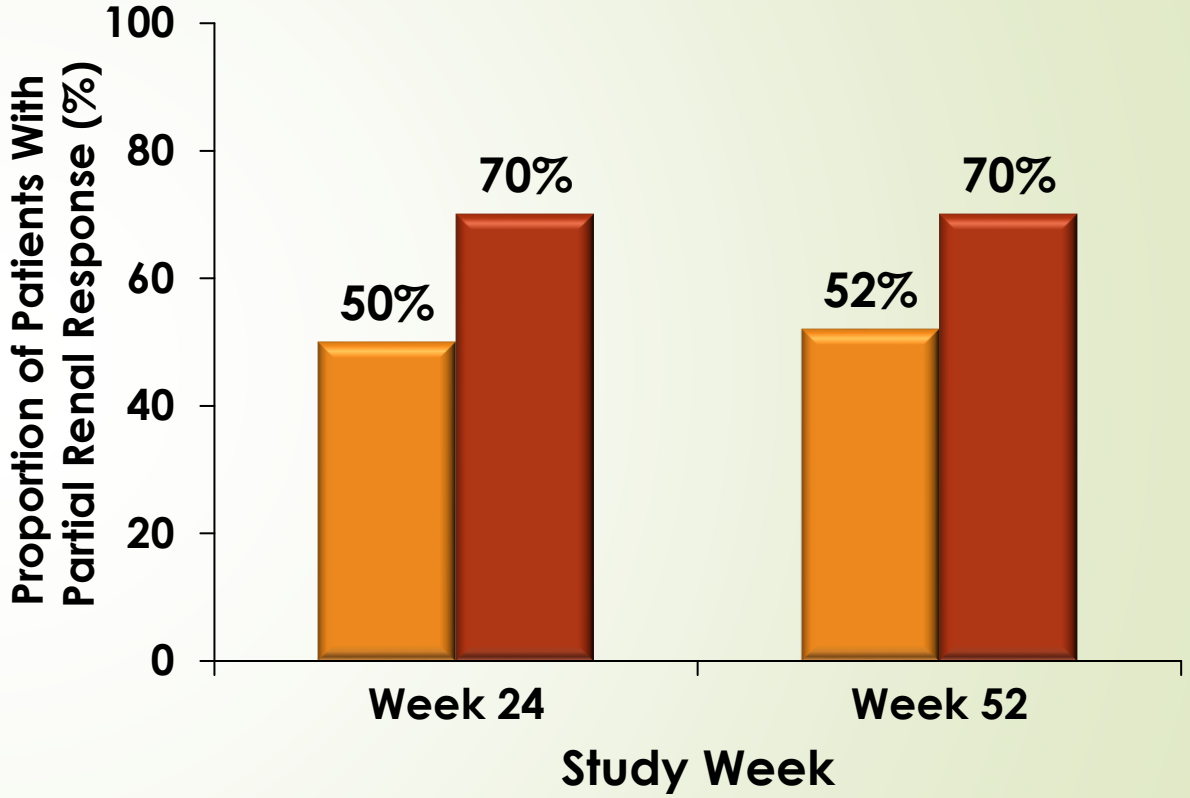
CpN, cyclophilin; CsA, cyclosporine A; NFAT, nuclear factor of activated T cells.

Peleg Y, et al. *Clin J Am Soc Nephrol*. 2020;15:1066-1072.

Efficacy and Safety of the Calcineurin Inhibitor Voclosporin for Lupus Nephritis

AURORA1

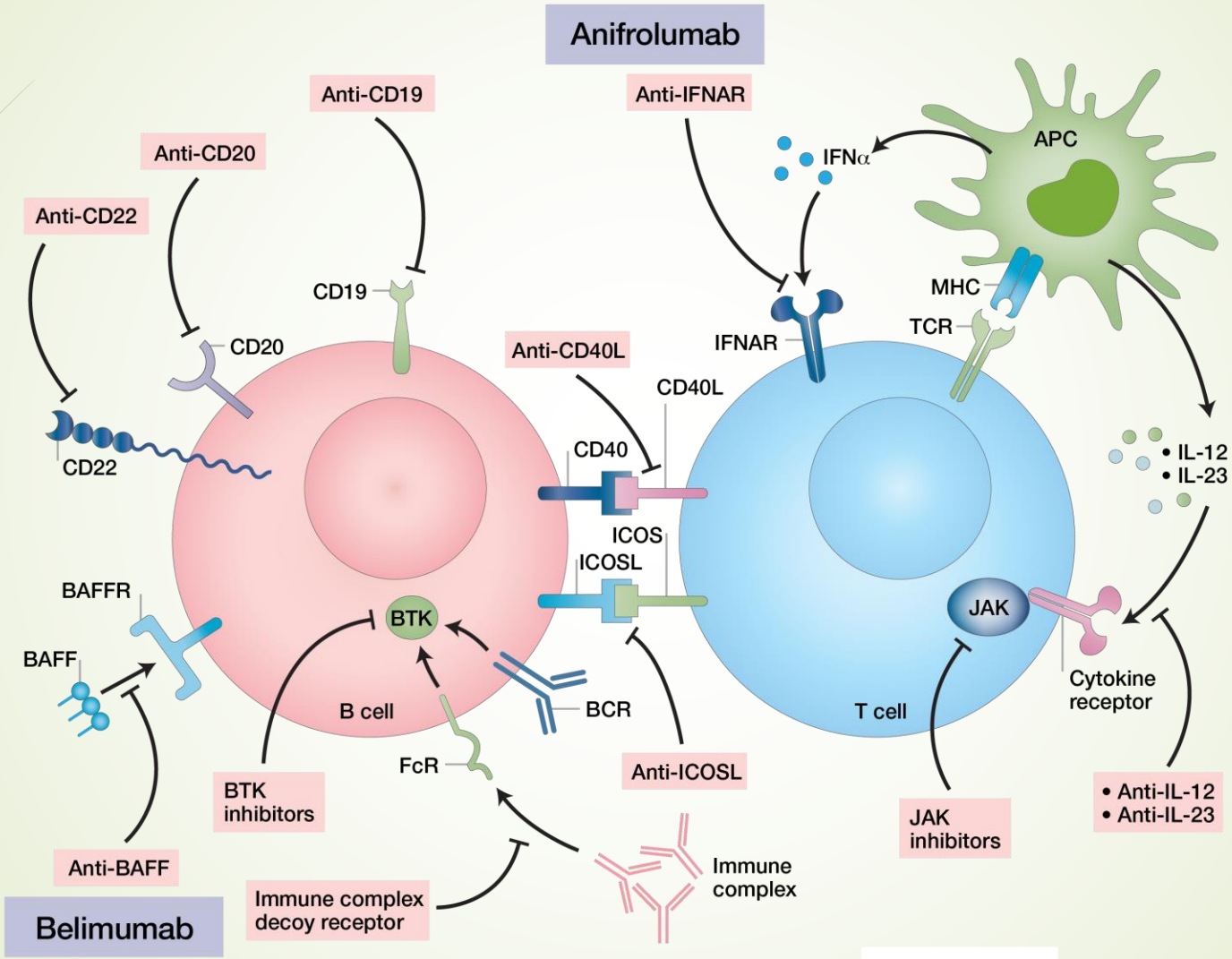




Note: AEs were balanced between groups; the most frequent serious AE involving infection was pneumonia.

Rovin BH, et al. *Lancet*. 2021;397:2070-2080.

The Current Landscape of Therapeutic Targets in SLE



*Mechanism of action not fully elucidated. APC, antigen-presenting cell; BCR, B-cell receptor; BTK, Bruton's tyrosine kinase; CD, cluster of differentiation; ICOSL, inducible T-Cell costimulatory ligand; IFNAR, interferon alpha/beta receptor; JAK, janus kinase; TCR, T-cell receptor.
Adapted from: Murphy G, et al. *Nat Rev Rheumatol*. 2019;15:403-412.

The time is ripe, the time is now, to improve the care of patients with SLE

- Updated 2019 ACR/EULAR Classification Criteria with sens/spec 90s
- Improved understanding of epidemiology of Lupus with higher incidence, prevalence, morbidity and mortality in all non white patient populations
- Plethora of disease activity measures and treatment targets
- Appreciation of co-morbidities and damage in Lupus
- New composite indices for Lupus clinical trials with the SRI4 and BICLA
- Several new therapeutics/indications for treatment
  - Anifrolumab for non renal lupus
  - Benlysta for LN multitargeted therapy
  - Voclosporin for LN multitargeted therapy

Thank you!