Systemic Lupus Erythematosus

Michelle Petri, MD, MPH
Professor of Medicine
The Johns Hopkins University School of Medicine
Baltimore, Maryland

Faculty Disclosures

Michelle Petri, MD, MPH, discloses the following:

- Consultant: Abbvie, Amgen, AstraZeneca, Blackrock, BMS, Exagen, Glenmark, GSK, IQVIA, Janssen, Lilly, Merck EMD Serono, Novartis, Sanofi Japan, Thermofisher, UCB.
- Grant Support: AstraZeneca, Eli Lilly, Exagen, GSK, Thermofisher.

I will reference treatments for SLE that are not FDA approved.

Learning Objectives

- Review classification criteria for SLE.
- Consider “feed forward loops” leading to SLE immunologic activity.
- Critique recent clinical trials of new therapies in SLE.

SLE = systemic lupus erythematosus.

Prevalence of Systemic Lupus Erythematosus in the USA

Objective

To estimate SLE prevalence in the US based on registries with racial and ethnic diversity

Methods

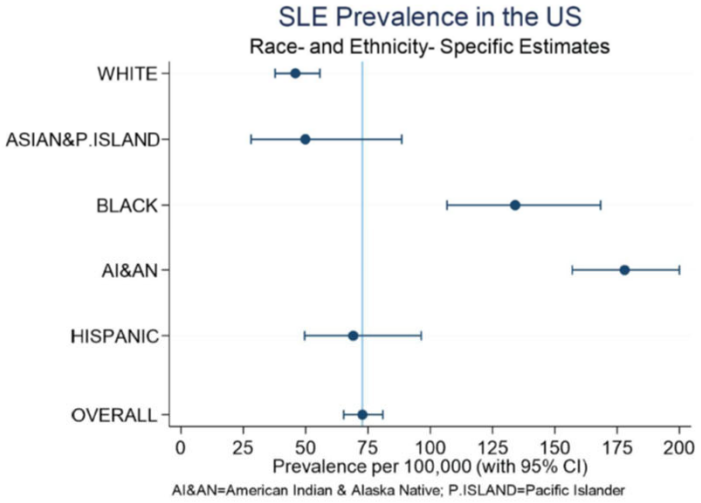
- We performed a meta-analysis (with random effects models) of data from the CDC-funded network of National Lupus Registries.
- SLE cases were classified according to ACR criteria.

Key Results

- SLE prevalence overall: 72.8 per 100,000 (95% CI 65.3, 81.0)
- Rates were highest for Amer Indian/Alaska Natives and blacks.

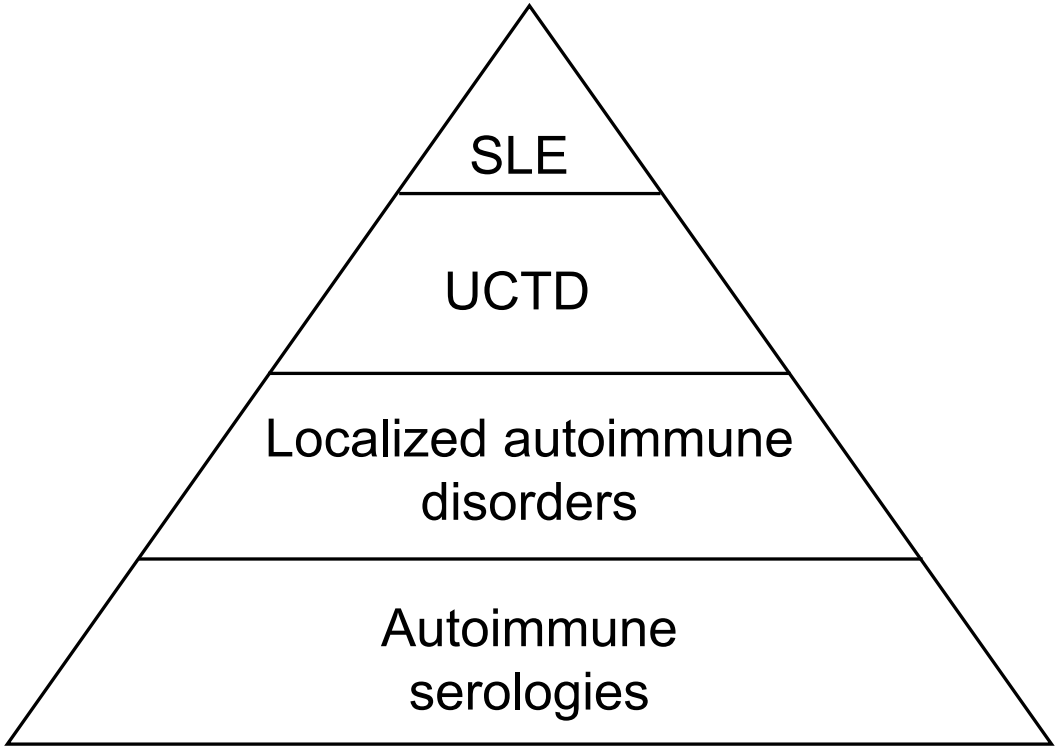
Conclusion

Applied to US Census data, 198,677 persons in the US are estimated to have SLE (179,186 female, 19,491 male).



Somers E, et al. Presented at: ACR/ARP Annual Meeting; November 13, 2019; Atlanta, GA. Abstract 2886.

Systemic Lupus Erythematosus (SLE): The Tip of the Iceberg



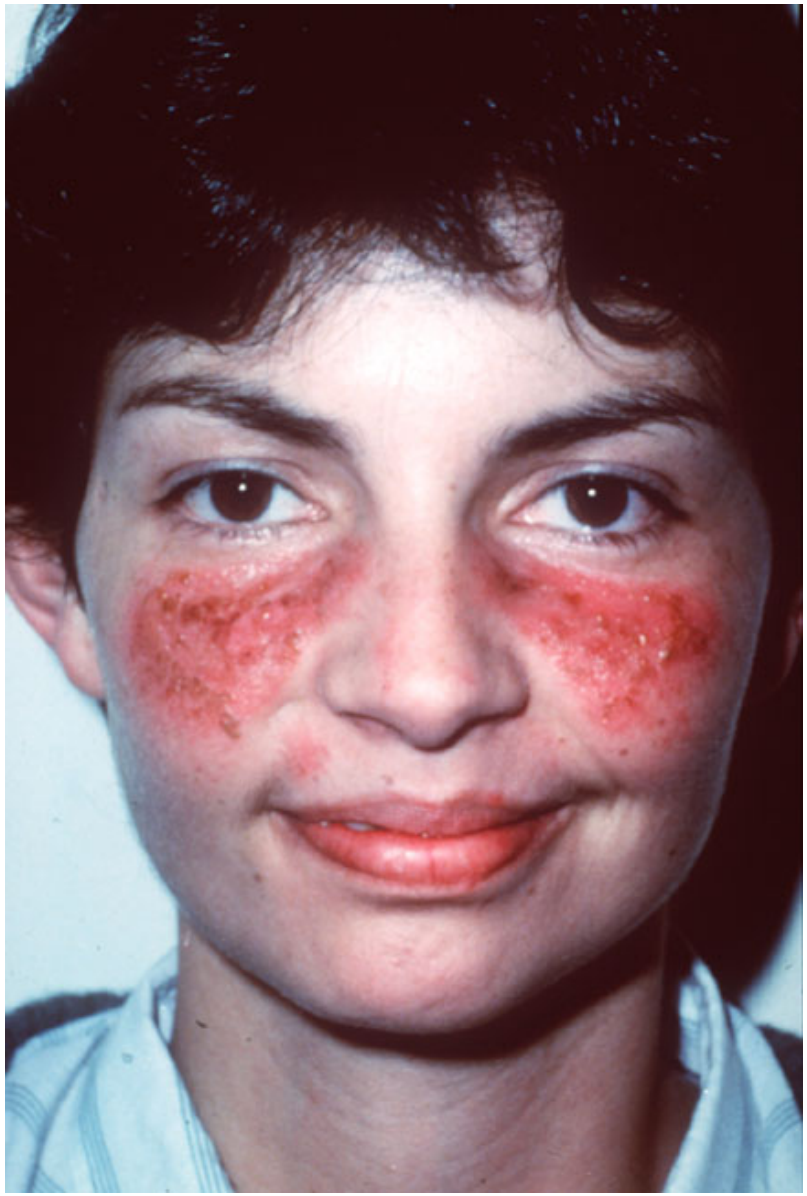
SLICC Revision of the ACR Classification Criteria

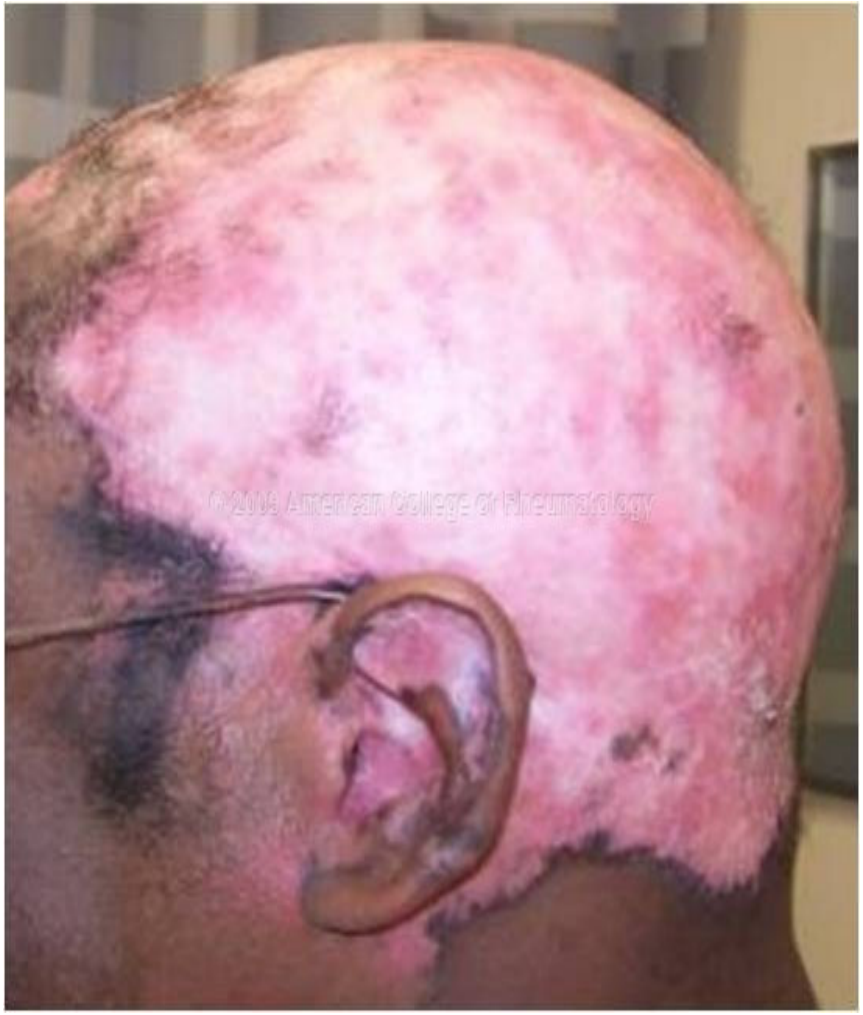
Clinical Criteria
1. Acute/subacute cutaneous lupus
2. Chronic cutaneous lupus
3. Oral/Nasal ulcers
4. Nonscarring alopecia
5. Inflammatory synovitis with physician-observed swelling of two or more joints OR tender joints with morning stiffness
6. Serositis
7. Renal: Urine protein/creatinine (or 24 hr urine protein) representing at least 500 mg of protein/24 hr or red blood cell casts
8. Neurologic: seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, cerebritis (acute confusional state)
9. Hemolytic anemia
10. Leukopenia (< 4000/mm^3 at least once) OR Lymphopenia (< 1000/mm^3 at least once)
11. Thrombocytopenia (<100,000/mm^3) at least once

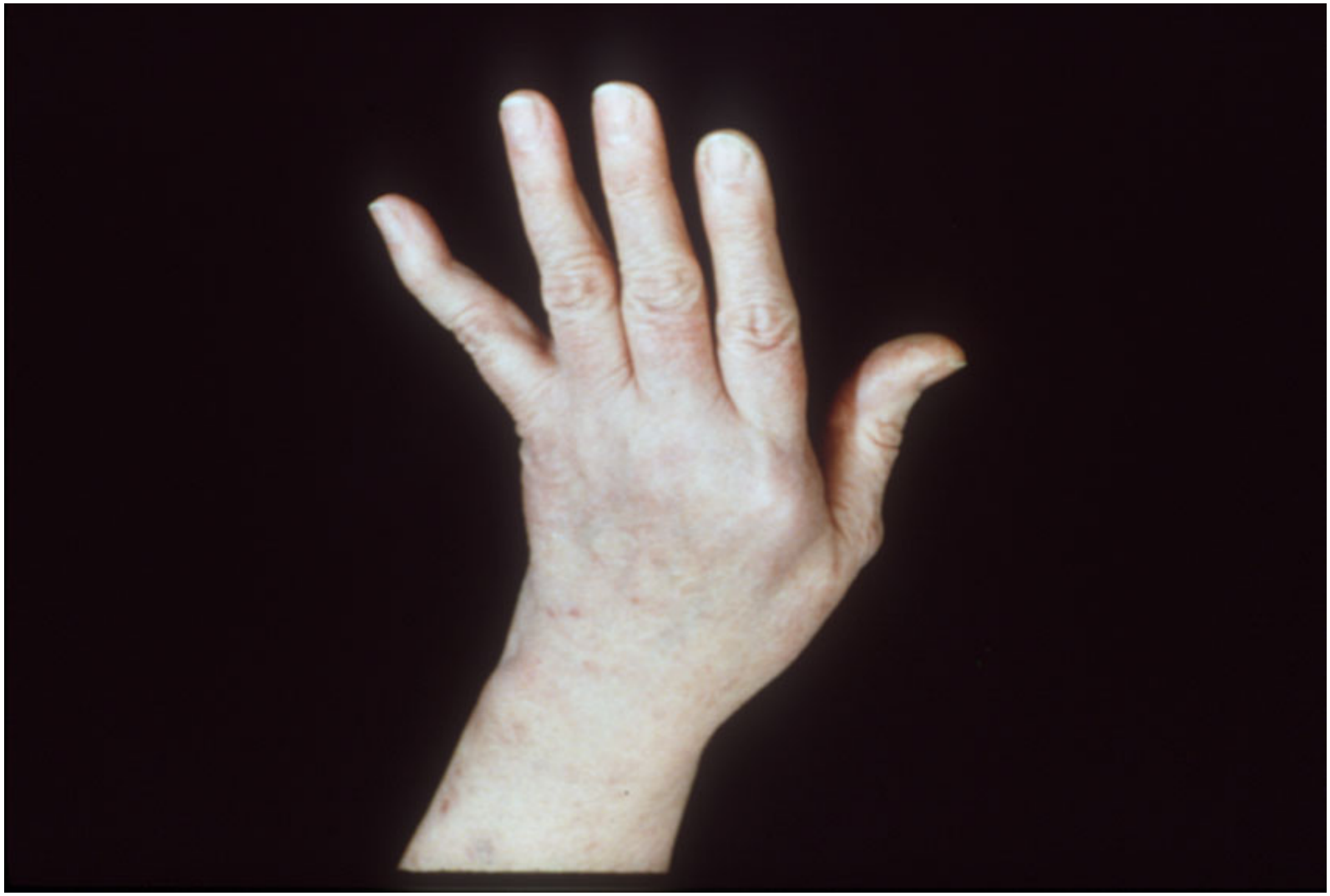
SLICC Revision of the ACR Classification Criteria

Immunologic Criteria
1. ANA above laboratory reference range
2. Anti-dsDNA above laboratory reference range (except ELISA: twice above laboratory reference range)
3. Anti-Sm
4. Antiphospholipid antibody lupus anticoagulant false-positive test for syphilis anticardiolipin – at least twice normal or medium-high titer anti-β_2 glycoprotein 1
5. Low complement low C3 low C4 low CH50
6. Direct Coombs test in absence of hemolytic anemia

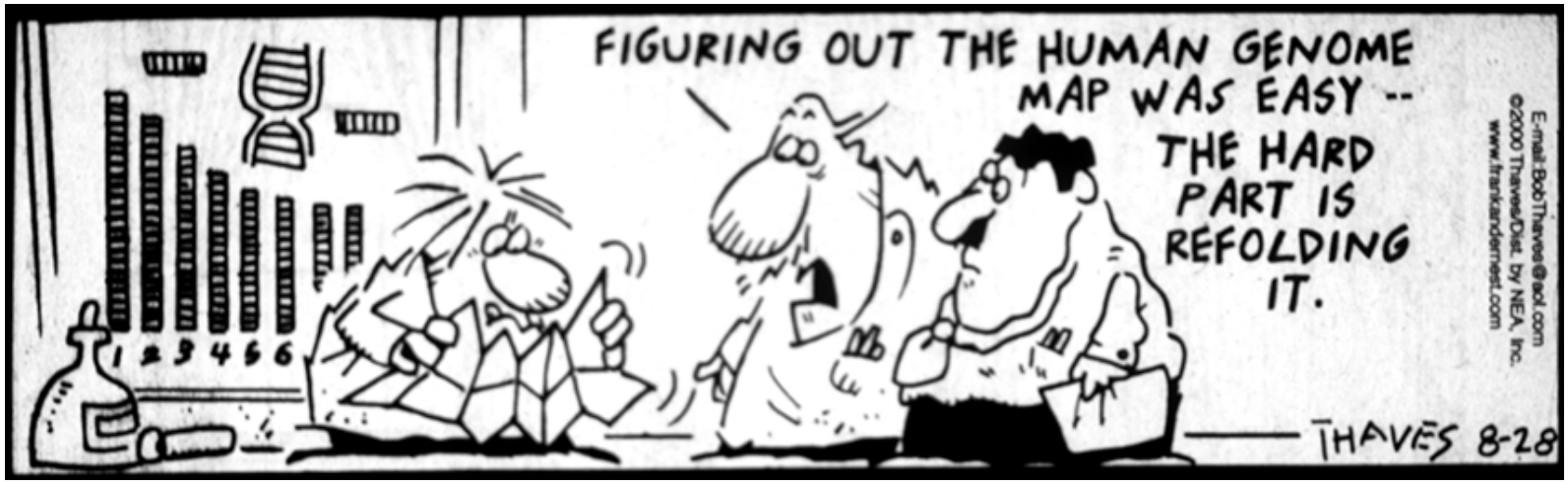
Recognize It When You See It




© 2009 American College of Rheumatology



What Causes SLE?


FIGURING OUT THE HUMAN GENOME MAP WAS EASY --
THE HARD PART IS REFOLDING IT.
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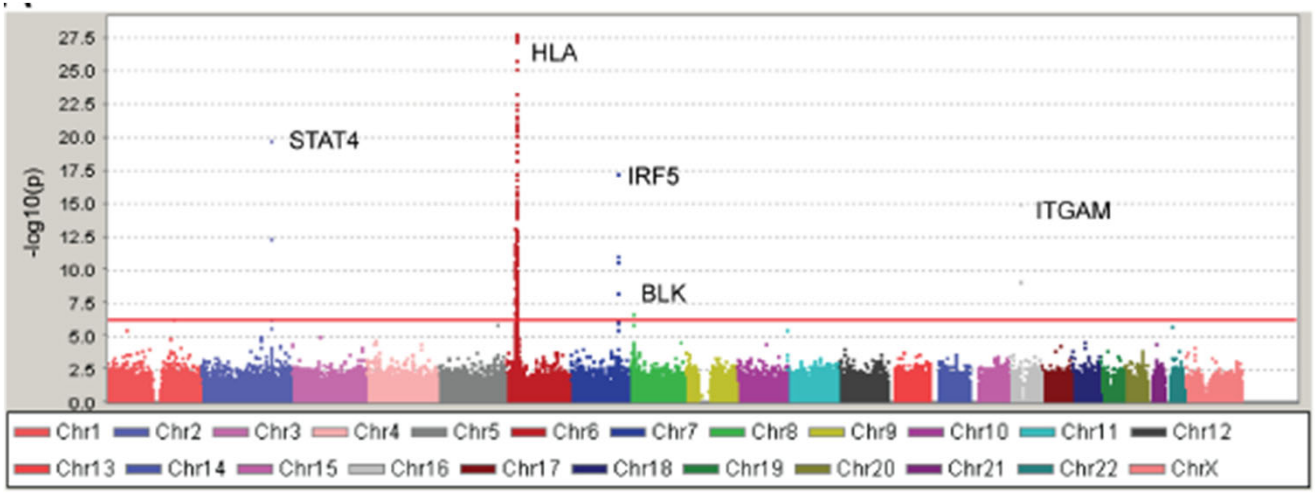
SLE is 1/2 Genetics!



Hom G, et al. *N Engl J Med* 2008;358:900-9

SLE is 1/2 Environmental

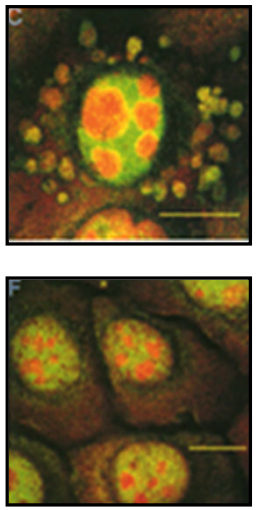
- Ultraviolet light
- Drugs/supplements (echinacea, trimethoprim/sulfamethoxazole)
- Smoking
- Infections
- Silica
- Mercury
- Pesticides

Parks CG, et al. *Arthritis Rheum*. 2002;46:1840–1850; Chiou SH, et al. *Lupus*. 2004;13:442–449; Zarmbinski MA, et al. *J Rheumatol*. 1992;19:1380–1384; Cooper GS, et al. *J Rheumatol.* 2004;31:1928; Costenbader KH, et al. *Arthritis Rheum.* 2004;50(3):849-857.Karlson EW. *Autoimmunity* 2005;38(7):541-547; Freemer, MM, et al. *Annals Rheum Dis.* 2006;65:581-584; Majka DS, Holers VM. *Annals Rheum Dis.* 2006;65:561-563.

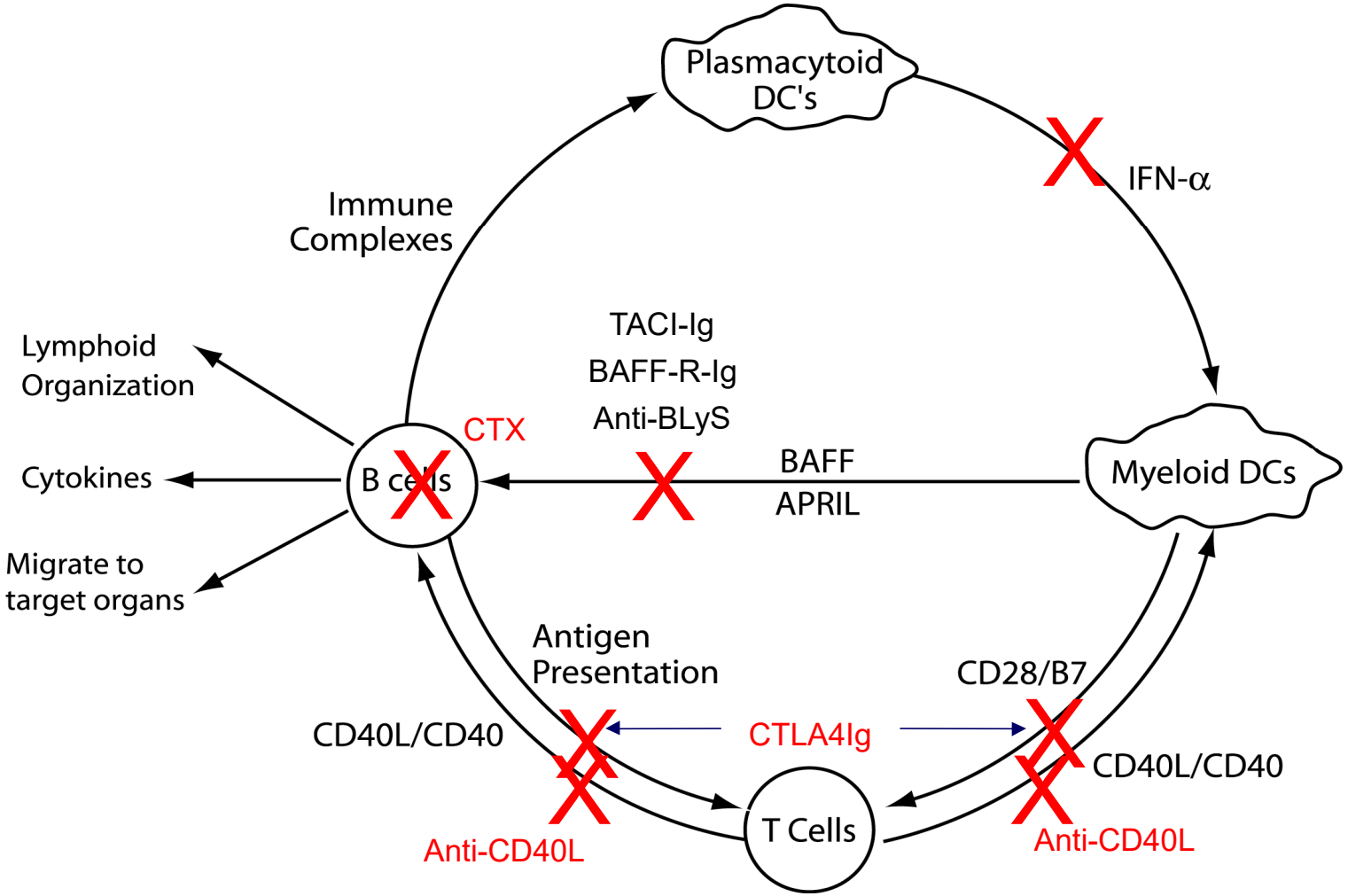
How Does it Start?

Apoptosis in SLE

- Apoptotic cells contain surface blebs rich in autoantigens like Ro, La, nucleosomes
- Mice defective in apoptotic pathways (MRL, C1q, IgM, SAP, DNase) produce autoantibodies and develop SLE
- SLE patients have more apoptotic cells in peripheral blood, and do not process apoptotic cells in a noninflammatory way



Casciola-Rosen et al. *Proc Natl Acad Sci U S A.* 1996;96:1624-1629.



M. Ramanujam and A. Davidson. Arthritis Research and Therapy. 2004. 6:197-202.

Prednisone is Poison!

Effect of Prednisone on Organ Damage

Adjusting for Confounding by Indication Due to SLE Disease Activity

Prednisone Average Dose	Hazard Ratio
> 0-6 mg/day	1.16
> 6-12 mg/day	1.50
>12-18 mg/day	1.64
> 18 mg/day	2.51

Thamer M, et al. *J Rheumatol*. 2009;36:560–564.

Prednisone Itself Increases the Risk of Cardiovascular Events

Prednisone use	Observed number of CVE	Rate of events/1000 person years	Age-adjusted rate ratios (95% CI)	P value
Never taken	22	13.3	1.0 (reference group)	
Currently taking				
1-9 mg/d	32	12.3	1.3 (0.8, 2.0)	.31
10-19 mg/d	**31**	**20.2**	**2.4 (1.5, 3.8)**	**.0002**
20+mg/d	**25**	**35.4**	**5.1 (3.1,8.4)**	**<.0001**
Cumulative past dose				
<3650 mg[1]	14	9.9	0.9 (0.4,1.6)	.56
3650-10,950 mg[2]	26	13.8	1.2 (0.7, 2.2)	.49
10,950-36,499 mg[3]	41	12.8	1.1 (0.6, 1.8)	.83
36,500+[4]	**30**	**25.3**	**2.2 (1.2,3.7)**	**.0066**

1. 3650 mg equals 10 mg/day for 1 year, or an equivalent cumulative exposure; 2. 1-3 years with 10 mg/day or an equivalent cumulative exposure; 3. 3-10 years with 10 mg/day or an equivalent cumulative exposure; 4.10+ years with 10 mg/day or an equivalent cumulative exposure; CVE=cardiovascular events

Magder LS, Petri M. *Am J Epidem.* 176:708-19, 2012.

Lupus Low Disease Activity State (LLDAS)

- SLEDAI <=4
- PGA <=1.0
- no major organ activity
- no new activity
- Allows for prednisone use <= 7.5 mg/d and immunosuppressants

Franklyn K, et al. *Ann Rheum Dis* 2016;75:1615-1621.

LLDAS Reduces Later Organ Damage

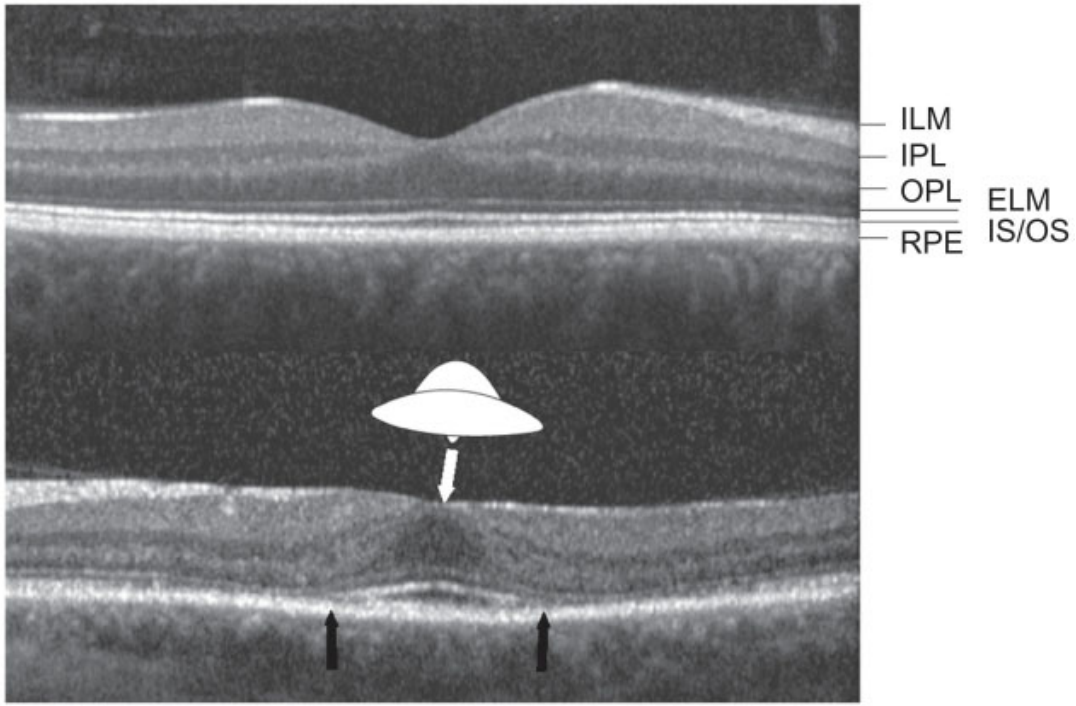
Percentage of Prior Months in:	Rate of damage per 100 person months	Rate Ratios	P-values
LLDAS			
None	1.53	1.0 (Ref)	
< 25%	1.27	0.83 (0.65, 1.06)	0.14
25% to 50%	1.02	0.66 (0.51, 0.85)	0.0013
50% to 75%	0.73	0.48 (0.37, 0.61)	<0.0001
75%+	0.62	0.40 (0.30, 0.54)	<0.0001

Petri M, Magder LS. *Arthritis Rheumatol* 70:1790-1795, 2018. doi: 10.1002/art.40571.

Current Treatment Approaches

Hydroxychloroquine Should Be Background Therapy in All SLE Patients

- Reduction in flares
  Canadian Hydroxychloroquine Study Group. *N Engl J Med*. 1991;324(3):150-154.
- Reduction in organ damage
  Fessler BJ, et al. *Arthritis Rheum*. 2005;52(5):1473-1480.
- Reduction in lipids
  Petri M. *Lupus*. 1996;5(Suppl 1):S16-S22.
  Wallace DJ, et al. *Am J Med*. 1990;89(3):322-326.
- Reduction in thrombosis
  Pierangeli SS, et al. *Lupus*. 1996;5(5):451-455.
  Petri M. *Curr Rheumatol Rep*. 2011;13(1):77-80.
- Triples mycophenolate response in lupus nephritis
  Kasitanon N, et al. *Lupus*. 2006;15(6):366-370.
- Improvement in survival
  Alarcon GS, et al. *Ann Rheum Dis.* 2007;66:1168-1172.
  Ruiz-Irastorza G, et al. *Lupus*. 2006;15:577-583.



Top: Normal Spectralis® spectral domain optical coherence tomography (SD OCT) image with intact photoreceptor inner segment/outer segment (IS/OS) junction. Bottom: Spectralis SD OCT from the left eye of patient 10 showing the "flying saucer" sign of hydroxychloroquine retinopathy, an ovoid appearance of the central fovea created by preservation of central foveal outer retinal structures (seen between the black arrows) surrounded by perifoveal loss of the photoreceptor IS/OS junction, and perifoveal outer retinal thinning.

ILM = internal limiting membrane; IPL = inner plexiform layer; OPL = outer plexiform layer; ELM = external limiting membrane; RPE = retinal pigment epithelium.

Chen E, et al. *Clin Ophthalmol*. 2010;4:1151-1158.

Increasing 25-Hydroxy Vitamin D Helps Disease Activity and Urine Protein/CR

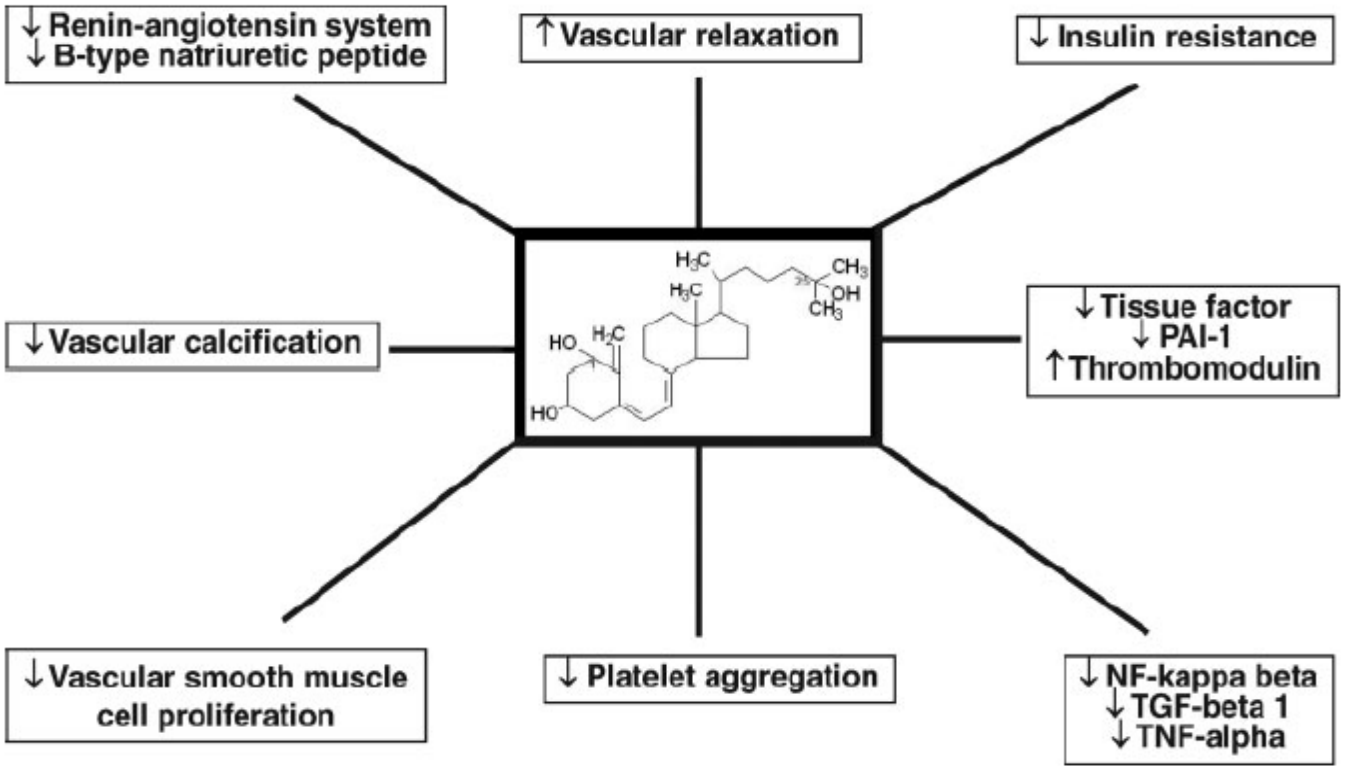
Model allowing slope to differ before and after 40 ng/mL

Disease Measure	Slope over range of 0-40 ng/mL (95% CI)	*P*-value	Slope over range of ≥40 ng/mL (95% CI)	*P*-value
Physician's Global Assessment	–0.04 (–0.08, –0.01)	**0.026**	0.01 (–0.02, 0.04)	0.50
SELENA-SLEDAI	–0.22 (–0.41, –0.02)	**0.032**	0.12 (–0.01, 0.24)	0.065
Log Urinary Protein/Creatinine	–0.03 (–0.05, –0.02)	**0.0004**	–0.01 (–0.01, 0.00)	0.24

SELENA-SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index.

Petri M et al. *Arthritis Rheum.* 2013;65:1865-1871.

Vitamin D May Have Cardiovascular and Hematologic Benefits



Targher G et al. *Semin Thromb Hemostasis.* 2012;38:114-124.

Immunosuppressive Approaches

- Drugs
  - Mycophenolate mofetil*
  - Methotrexate
  - Azathioprine
- Biologics
  - Rituximab§
  - Belimumab

*Chan TM, et al. *N Engl J Med*. 2000;343:1156–1162; Ginzler E, et al. *Arthritis Rheum*. 2003;48(9, Suppl.):S647.; Contreras G, et al. *N Engl J Med* 2004;350(10):971-80.
§Leandro MJ, et al. *Arthritis Rheum*. 2002;46:2673–2677.

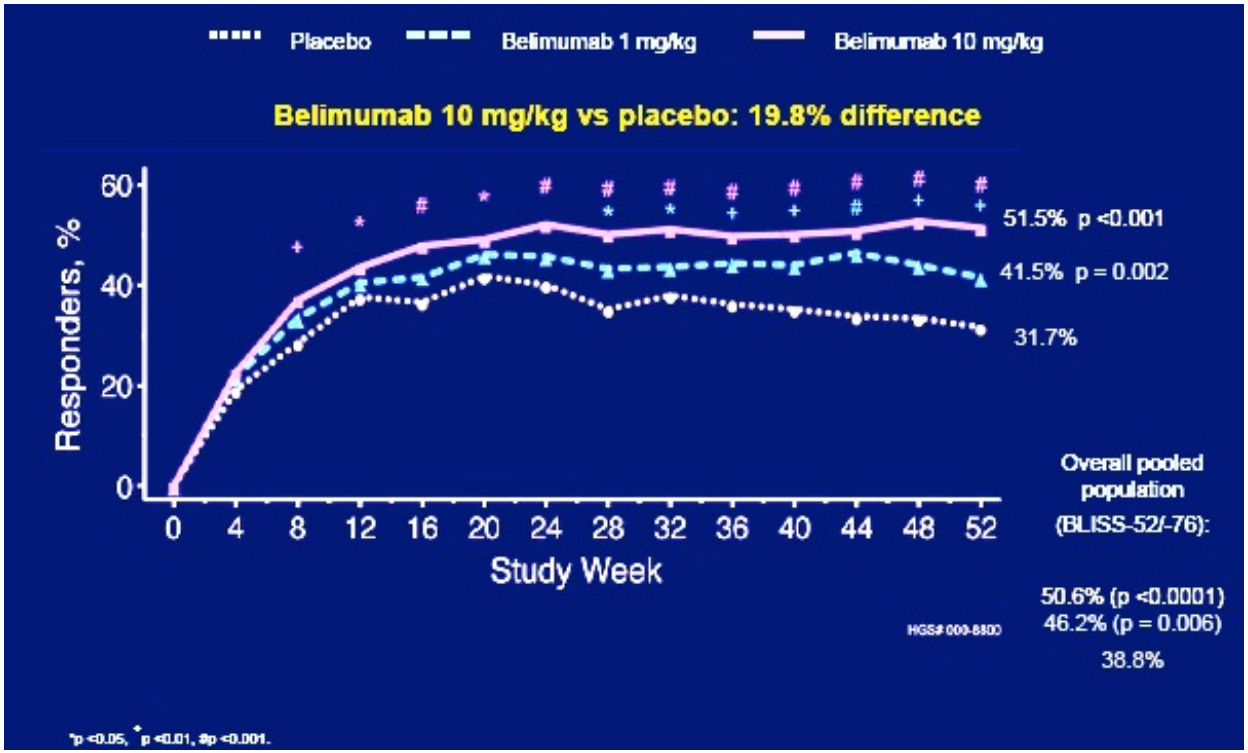
What Is Non-renal Lupus?

- Type 1 = Classic signs/symptoms of SLE
  - Clear-cut relationship to autoimmunity
  - Assessed by SLEDAI

- Type 2 = Non-inflammatory
  - Do not respond to immunosuppression
  - Examples: fatigue, diffuse pain, cognitive dysfunction, sleep disturbance, anxiety/depression, brain fog

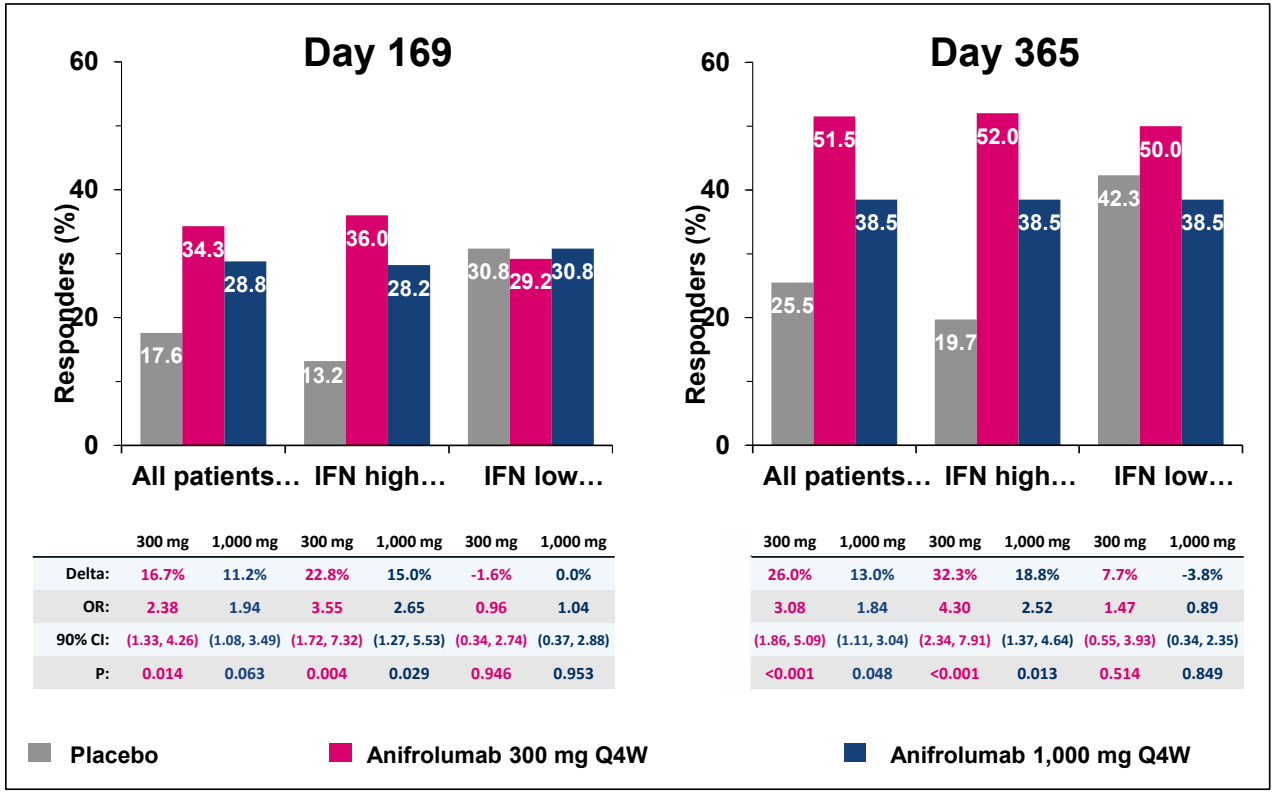
Pisetsky DS, et al. *Arthritis Care Res* (Hoboken). 2019;71(6):735-741.

The Subgroup with BOTH High Anti-dsDNA and Low Complement is About 20% More Likely to Respond to Belimumab



van Vollenhoven RF, et al. Presented at EULAR 2011; May 25-28, 2011; London, UK

Anifrolumab Primary Endpoint in Phase 2: SRI(4) including OCS Taper



	300 mg	1,000 mg	300 mg	1,000 mg	300 mg	1,000 mg
Delta:	16.7%	11.2%	22.8%	15.0%	-1.6%	0.0%
OR:	2.38	1.94	3.55	2.65	0.96	1.04
90% CI:	(1.33, 4.26)	(1.08, 3.49)	(1.72, 7.32)	(1.27, 5.53)	(0.34, 2.74)	(0.37, 2.88)
P:	0.014	0.063	0.004	0.029	0.946	0.953

300 mg	1,000 mg	300 mg	1,000 mg	300 mg	1,000 mg
26.0%	13.0%	32.3%	18.8%	7.7%	-3.8%
3.08	1.84	4.30	2.52	1.47	0.89
(1.86, 5.09)	(1.11, 3.04)	(2.34, 7.91)	(1.37, 4.64)	(0.55, 3.93)	(0.34, 2.35)
<0.001	0.048	<0.001	0.013	0.514	0.849

Dropouts and patients whose medication use exceeded protocol threshold were imputed as failure

SRI = SLE responder index;
OCS = oral corticosteroid;
IFN = interferons;
Delta = dosage vs placebo;
OR = odds ratio;
CI = confidence interval;
Q4W = every 4 weeks.

Furie R, et al. *Arthritis Rheumatol*. 2017;69(2):376-386.

Phase 3 trial of anifrolumab in patients with moderate to severe SLE (TULIP-1)

Objectives

To evaluate efficacy and safety of anifrolumab vs placebo in adults with moderate to severe, autoantibody-positive SLE who were receiving standard-of-care (SOC) treatment

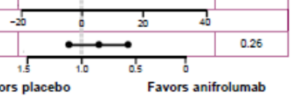
Methods

Efficacy and safety in SLE patients randomized to intravenous anifrolumab 300 mg, 150 mg, or placebo (2:1:2) Q4W while receiving stable SOC with attempts to taper OCS were assessed in prespecified and post-hoc analyses with amended restricted medication rules.

Conclusion

The primary endpoint, SRI(4) for anifrolumab 300 mg vs placebo, was not achieved; several secondary endpoints (steroid reduction, skin disease response, and BICLA) and post-hoc analyses suggest efficacy compared with placebo.

Primary and Select Secondary Endpoints[a]	Analysis	Placebo (n=184)	Anifrolumab 300 mg (n=180)	Plot of Treatment Difference (95% CI)	Nominal *P*-Value
Primary: SRI(4) at wk 52, %	Prespecified	40.4	36.2		0.41
	Amended	43.0	46.9		0.46
SRI(4) at wk 52 in IFNGS Test–High patients, %	Prespecified	39.3	35.9		0.55
	Amended	41.8	48.2		0.26
BICLA Response at wk 52, %	Prespecified	27.0	37.1		N/A
	Amended	29.6	46.1		N/A
Sustained OCS Reduction to ≤7.5 mg/d wk 40–52, %	Prespecified	32.1	41.0		0.18
	Amended	32.1	48.8		0.01
≥50% Reduction in CLASI Activity Score From BL to wk 12, %	Prespecified	24.9	41.9		0.05
	Amended	24.9	43.6		0.03
≥50% Reduction in Active (Swollen and Tender) Joints at wk 52,[b] %	Prespecified	32.3	47.0		N/A
	Amended	32.3	53.0		N/A
Annualized Flare Rate to wk 52[c]	N/A	0.72	0.60		0.26



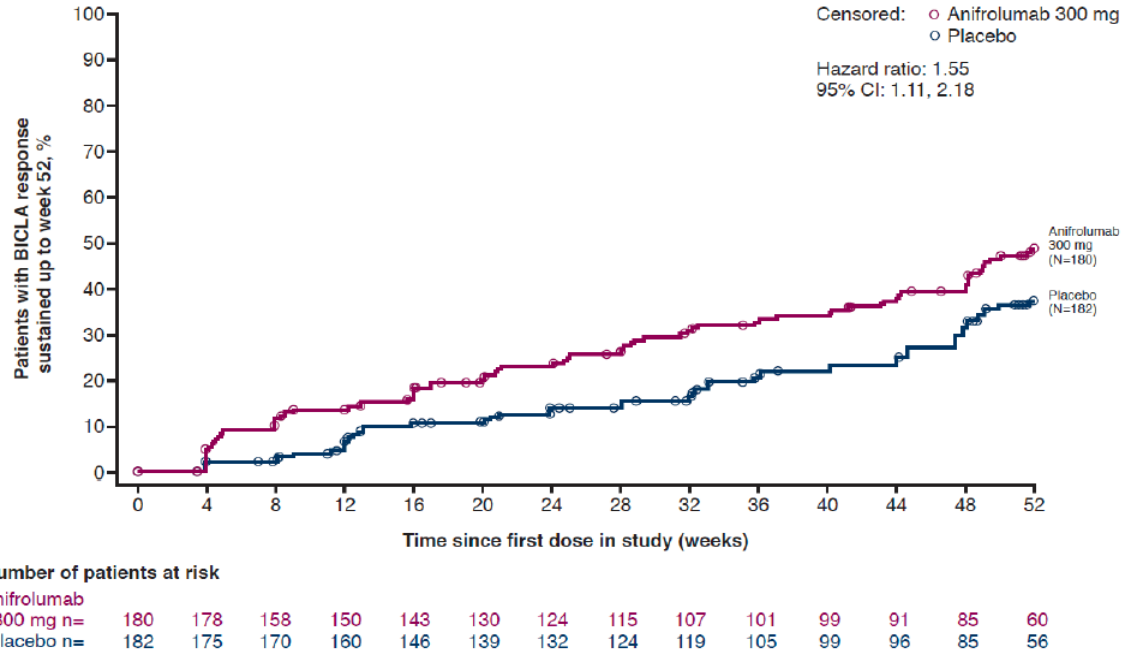
[a]For responder rates, the difference in response rates and associated 95% CIs are weighted and calculated using a stratified Cochran–Mantel–Haenszel approach. Because the primary endpoint was not statistically significant, per the prespecified analysis plan, all other comparisons are nonsignificant. [b]In patients with ≥8 swollen and ≥8 tender joints at baseline. [c]Flare rate calculations did not incorporate amended restricted medication rules; therefore, values for the prespecified and post-hoc analyses are identical.

Furie R, et al. *Lancet Rheumatol*. 2019;1:e208-e219.

Phase 3 Trial of Anifrolumab (TULIP-2) Time to Onset of a BICLA Response

Figure S2. Time to Onset of a BICLA Response That Was Sustained From Attainment Through to Week 52.*

Note: Evaluated using a Cox proportional hazards model.

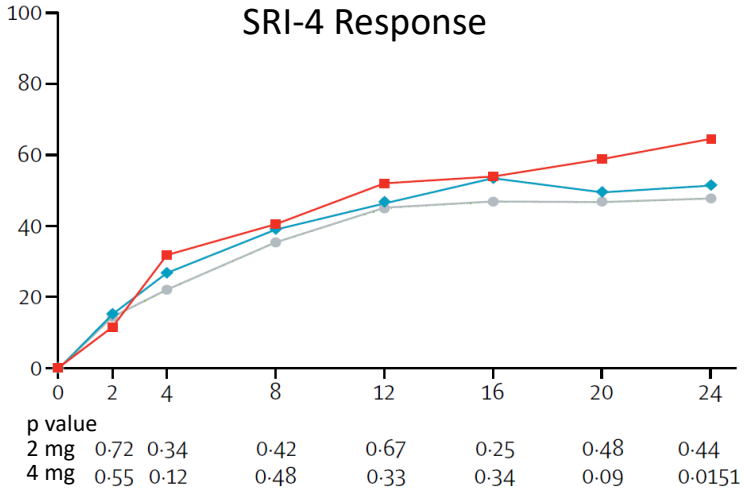


BICLA = British Isles Lupus Assessment Group (BILAG)–based Composite Lupus Assessment.

EF Morand, et al. *N Engl J Med*. 2020;382(3):211-221.

Baricitinib in SLE

- JAK 1/2 inhibitor
- MOA: IL-6, type I interferon
- Successful phase 2 trial



JAK = Janus kinase; MOA = mechanism of action.

Wallace DJ, et al. *Lancet*. 2018;392(10143):222-231.

Low-Dose IL-2 in SLE Improves SRI-4 Response

	Week - 12		Week - 24	
	IL-2	SOC	IL-2	SOC
	55.2%	30.0%	65.5%	36.7%
	P = 0.052		P = 0.027	
Lupus Nephritis			53.9%	16.7%
			P = 0.036	

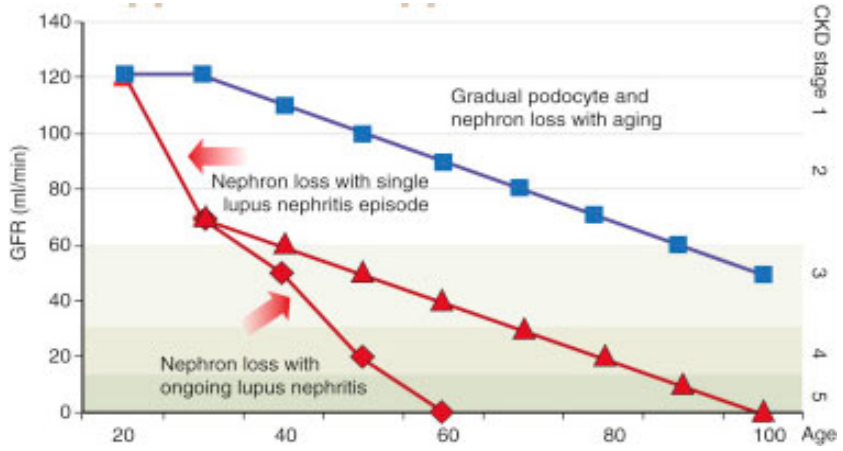
SOC = standard of care.

He J, et al. *Ann Rheum Dis*. 2020;79(1):141-149.

Nephrons Once Lost Are Gone Forever!

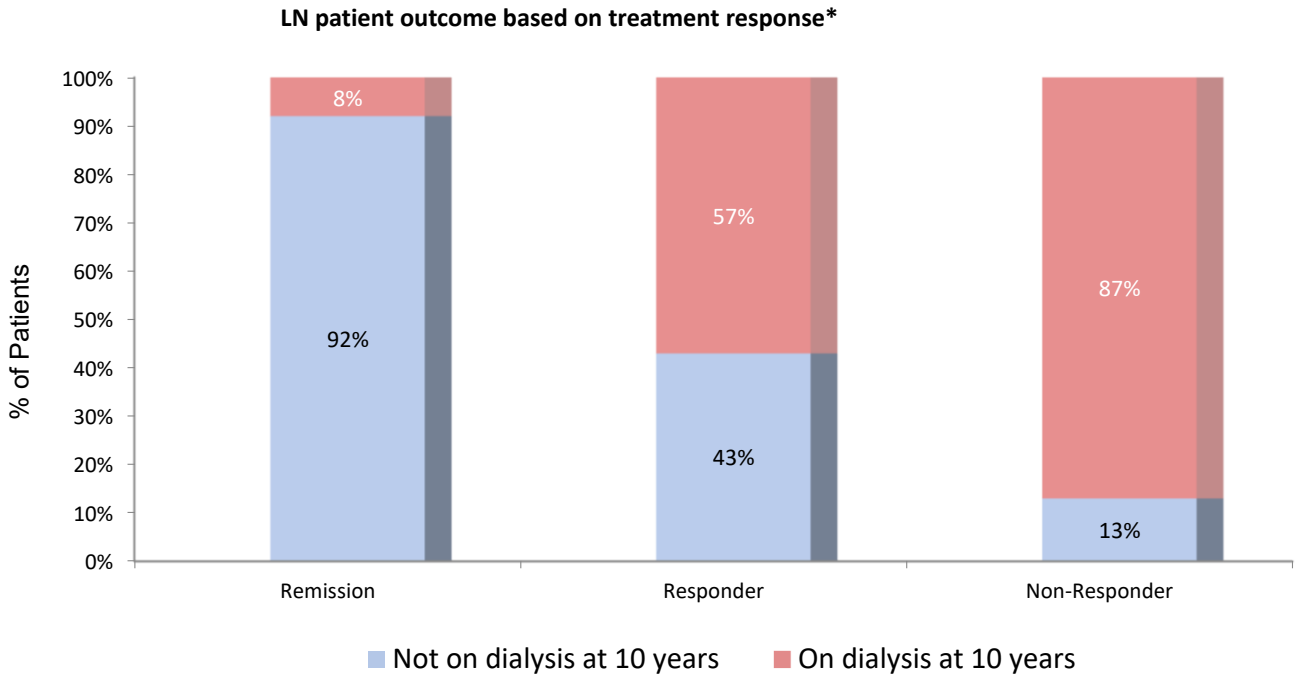
- First lupus nephritis (LN) episode might lead to a 1/3 loss of nephrons
- Remaining nephrons hypertrophy (so we overestimate the remaining renal function)
- Add to this the expected gradual loss of podocytes and nephrons with aging

MOST of our LN patients will be on dialysis by age 70!



GFR = glomerular filtration rate; CKD = chronic kidney disease.
Anders HJ, et al. *Kidney Int*. 2016;90(3):493-501.

Only Complete Renal Response Matters



^Response = 50% reduction in proteinurea Remission = Proteinurea <.33 g/day
^Complete remission by urinary protein

Chen YE, et al. *Clin J Am Soc Nephrol*. 2008;3(1):46-53.

BLISS-Lupus Nephritis Study: Phase 3

Primary Efficacy Renal Response at 2 years

43% vs 32%

OR 1.55 (1.04-2.32), p=0.0311

GSK. https://www.gsk.com/en-gb/media/press-releases/gsk-announces-positive-headline-results-in-phase-3-study-of-benlysta-in-patients-with-lupus-nephritis/. Accessed February 12, 2020.

Obinutuzumab for proliferative lupus nephritis (NOBILITY)

Objectives

To assess obinutuzumab, a type II anti-CD20 that induces potent B-cell depletion, for proliferative lupus nephritis (LN)

Methods

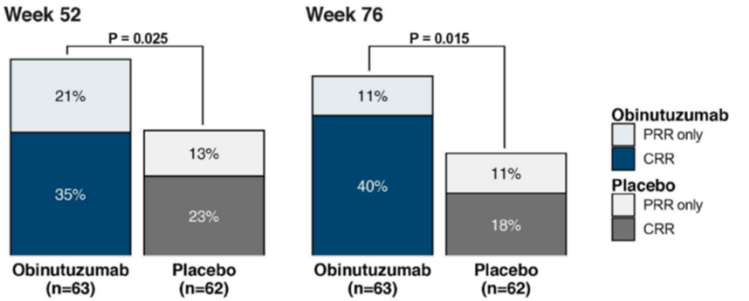
Phase II randomized, placebo-controlled trial of obinutuzumab vs placebo on background MMF and steroids

Key Results

- Primary and secondary endpoints were met at week 52.
- Increased complete renal response rate at week 76
- No increase in serious adverse events or death

Conclusion

Obinutuzumab was superior to placebo in achieving renal response and improving serologies in patients with proliferative LN and did not increase key safety events.



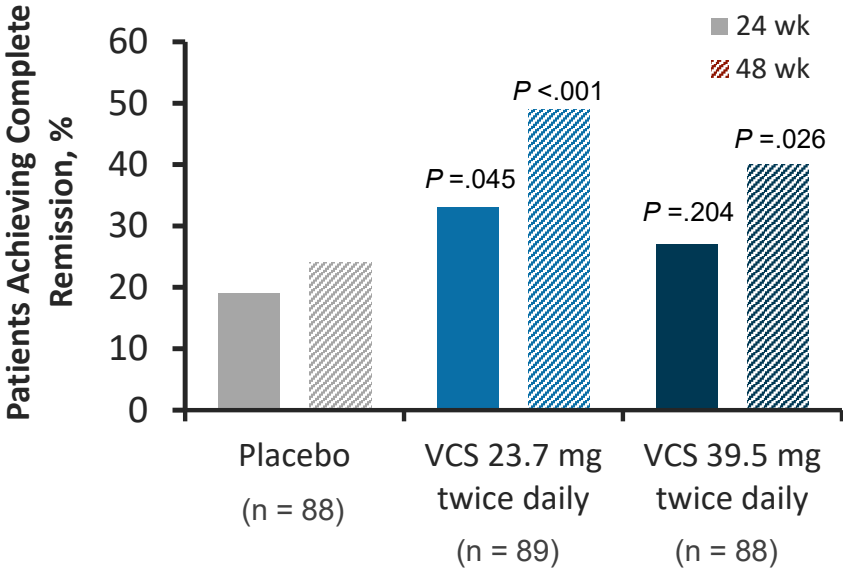
Week 76 Safety	Obinutuzumab (n=63)	Placebo (n=62)
Deaths	1 (2%)	4 (7%)
≥1 Serious Adverse Event	15 (24%)	18 (29%)
≥1 Serious Infection	4 (6%)	11 (18%)
Infusion-Related Reactions	10 (16%), all nonserious	6 (10%), all nonserious

Furie R, et al. Presented at: ACR/ARP Annual Meeting; November 8-13, 2019; Atlanta, GA. Abstract 696361.

Voclosporin, a Novel Calcineurin Inhibitor

Phase 2 Lupus Nephritis Study

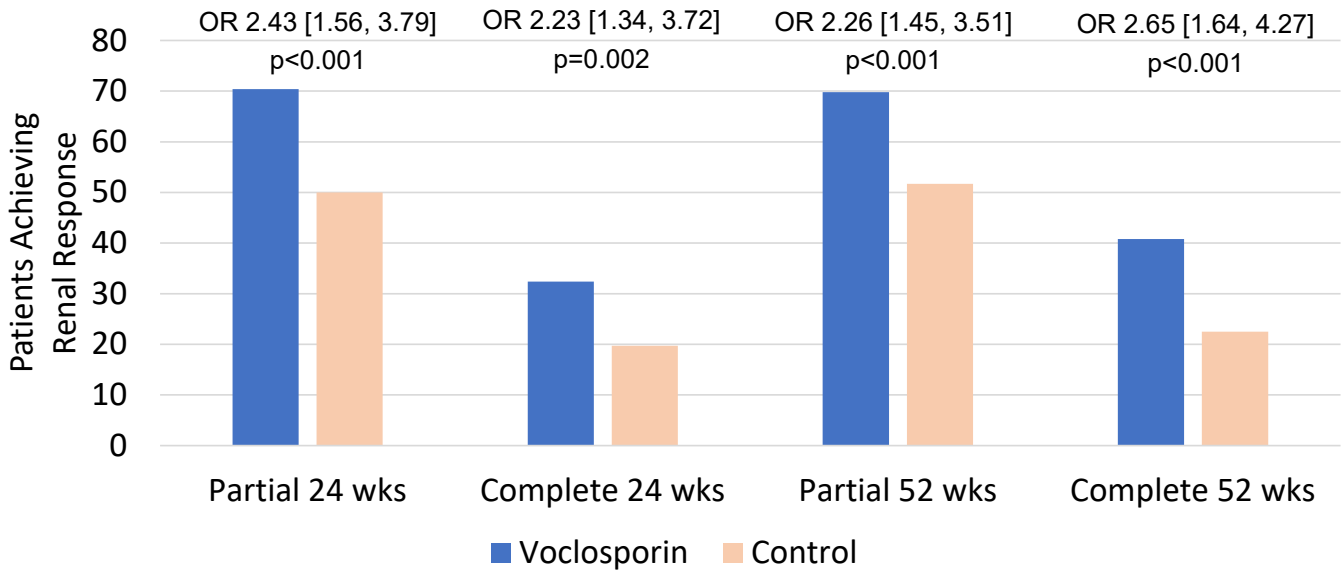
- 265 patients with active lupus nephritis were randomized to VCS 23.7 mg twice daily or VCS 39.5 mg twice daily or placebo with background therapy of MMF 2 g/d
- Safety issues
  - GFR reduced (low dose vs placebo: -12.6 mL/min/m^2)
  - Cr rose 20-25% compared with placebo (0.8-1.0%)
  - Deaths
    - 1/13 (placebo)
    - 12/13 (VCS 23.7 mg twice daily or VCS 39.5 mg twice daily)



VCS = voclosporin; MMF = mycophenolate mofetil.

Parikh SV, et al. Presented at: National Kidney Foundation (NKF) Spring Clinical Meetings; April 18-22, 2017; Orlando, FL. Poster 381. Dooley MA, et al. *Arthritis Rheumatol*. 2016;68(Suppl 10). Presented at: ACR/ARHP Annual Meeting; November 15, 2016; Washington, DC. Abstract 5L.

AURORA: Phase 3 Voclosporin Trial



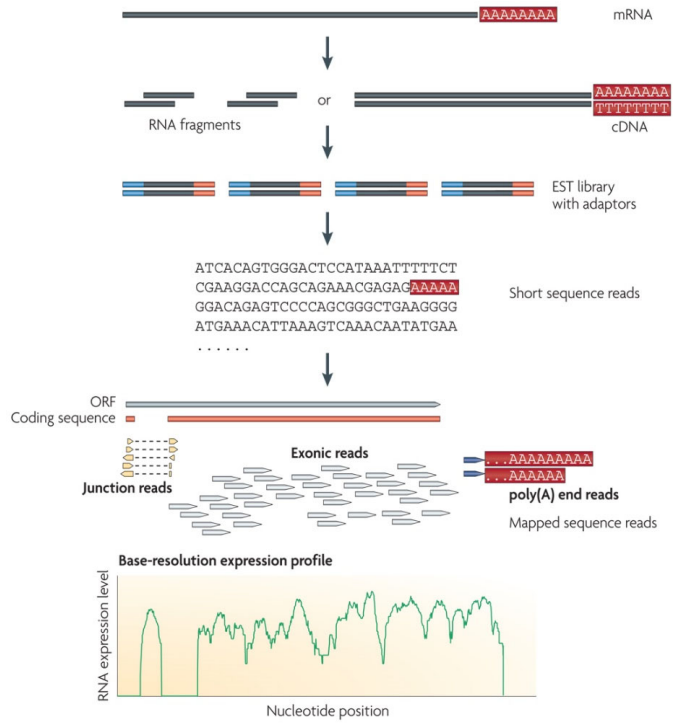
Measure	Result	Hazard Ratio [95% CI]	p-value
Time to UPCR ≤0.5	Voclosporin faster than Control	2.02 [1.51, 2.70]	p<0.001
Time to 50% reduction in UPCR	Voclosporin faster than Control	2.05 [1.62, 2.60]	p<0.001

UPCR = urinary protein-to-creatinine ratio.

Business Wire. https://www.businesswire.com/news/home/20191204005890/en/Aurinia-Announces-Positive-AURORA-Phase-3-Trial. Accessed February 13, 2020.

AMP: Single-cell RNA Sequencing (scRNA-seq)

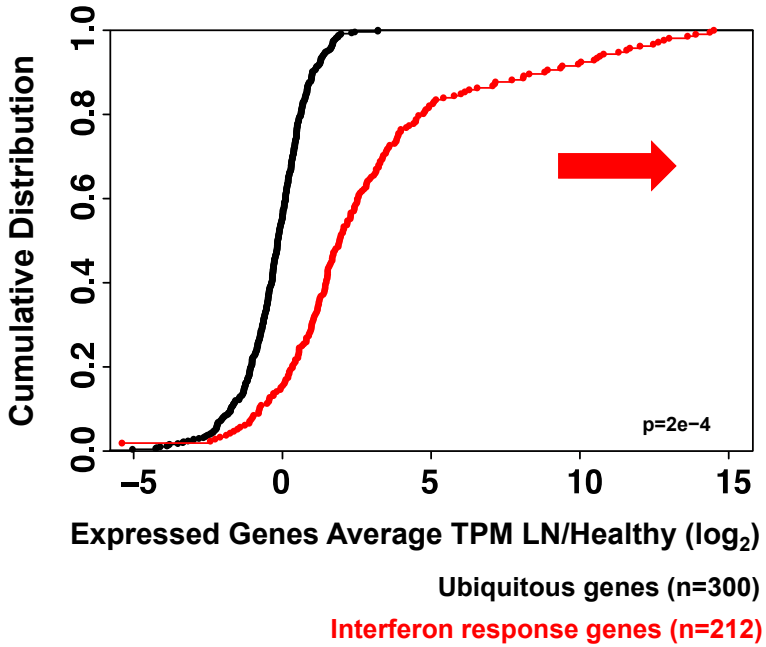
- Single-cell transcriptome resolution
- Heterogeneity
- Unbiased
- Does not rely on surface markers
- Nanoliter volume

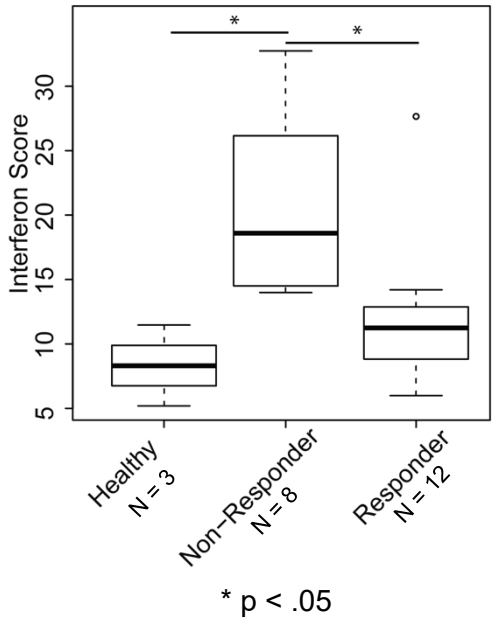


AMP = Accelerering Medicines Partnership.

Der E, et al. *Nat Immunol*. 2019;20(7):915-927. Wang Z, et al. *Nat Rev Genet*. 2009;10(1):57-63.

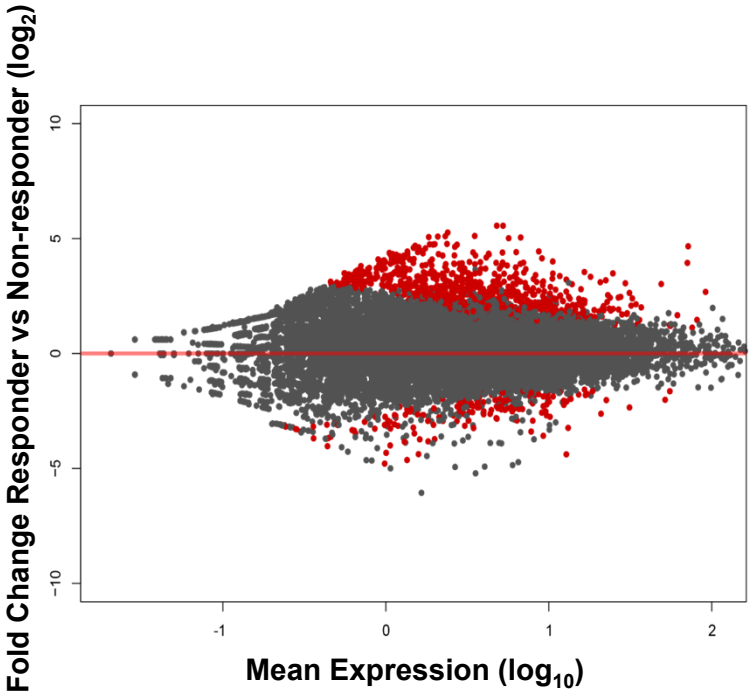
Tubular Cells from Patients with Lupus Nephritis Express Higher Levels of Interferon Response Genes





Der E, et al. *Nat Immunol*. 2019;20(7):915-927.

Non-responders Exhibit Upregulation of Fibrotic Pathways in Tubular Cells



Upregulated pathways in non-responders

Pathway	Genes	P-value
Extracellular matrix (ECM)	26	4.70E-11
ECM-receptor interaction	12	2.70E-06
PI3K-Akt signaling pathway	21	6.10E-05
Collagen	12	3.20E-06

Der E, et al. *Nat Immunol*. 2019;20(7):915-927.

El Greco – *St. Sebastian* (Prado)