Therapies New and Old for Lupus Nephritis

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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

- Describe lupus nephritis impact
- Consider current treatments and risks
- Review new treatments for lupus nephritis

Frequency of Lupus Nephritis

	All	Male	Female	Caucasians	African-Americans
Proteinuria	42.1%	51.2%	41.3%	31.4%	56.0%
Nephrotic Syndrome	17.8%	24.1%	17.3%	10.9%	26.8%
Hematuria	28.9%	34.4%	28.4%	21.9%	36.7%
Renal Insufficiency	19.9%	31.7%	18.9%	15.2%	27.0%
Renal Failure	8.3%	15.8%	7.6%	5.5%	12.4%
Renal Biopsy	27.8%	36.4%	27.1%	19.7%	37.0%

There were 487 SLE patients who had renal biopsies.

Tan TC et al. *J Rheumatol*. 2012;39:759-69.

Anti-C1q Is Associated with Renal Lupus

Variable	Renal Lupus (%)[1]	No Renal Lupus (%)[1]	Adjusted P value for Age and Race
Anti-C1q	45.5	19.3	<0.0001
Anti-dsDNA	80.2	44.4	<0.0001
Anti-Sm	29.7	15.0	0.03
Low complement	78.2	50.2	0.0006

C1q=complement 1 subcomponent Q; dsDNA=double-stranded DNA; Sm-Smith

Orbai AM, et al. Abstract 1375. Presented at: American College of Rheumatology. 2011

Who is Going to do Badly?

ESRD in Hopkins Lupus Cohort

- In SLE patients like those in our cohort, we estimate that 9.6% will develop renal failure within 20 years.

- Among those who satisfy the ACR-11 definition of renal disease within 1 year of SLE diagnosis, the risk of renal failure within 20 years is 23.2%.

- Risks are higher among men, African Americans, those diagnosed at a young age, and among those with immunologic markers such as low complement and anti-dsDNA.

- Among the immunologic markers, low C3 is the strongest predictor

Petri M, Magder LS, Barr E. *J Rheumatol*. pii: jrheum.191094, 2020.

Progression to ESRD Has Not Decreased Over Time and Varies by Race and SES

**ESRD Due to Lupus Nephritis
Incidence by Race/Ethnicity**
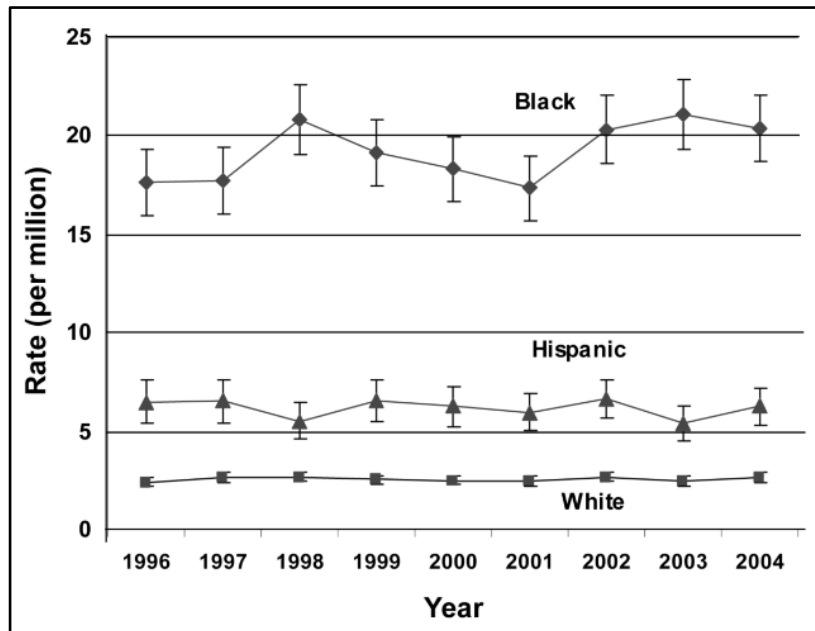
**ESRD Due to Lupus Nephritis
Incidence by Socioeconomic Status (SES)**
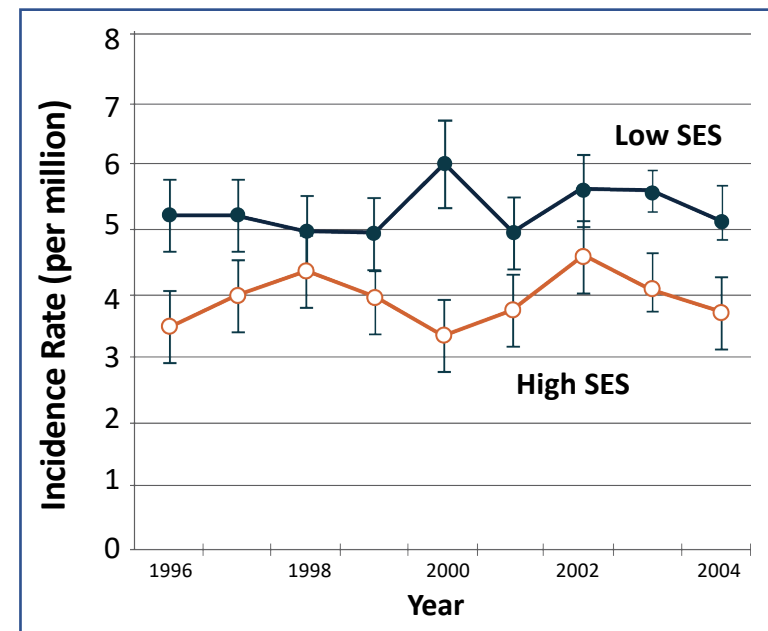
Patients aged ≥15 years with incidence of ESRD due to lupus nephritis were identified using the US Renal Data System, a national population-based registry of all patients needing chronic renal replacement therapy for ESRD. Incidence rates were age-, sex-, and race-adjusted to the composition of the US population. Mean age was 40.9 years, 82% of patients were female, 43% were white, 48% were black, 14.7% were Hispanic, 4.6% were Asian/Pacific Islander, 1.1% were Native American, and 2.7% were "other."

Ward MM. *J Rheumatol*. 2009;36:63-67.

How Do We Measure Renal Disease Activity?

Gold Standard is Still the Renal Biopsy

- ISN Class
  - I   Mesangial
  - II   Mesangioproliferative
  - III   Focal
  - IV   Diffuse
  - V   Membranous
  - VI   Sclerotic
- Activity Index
- Chronicity Index

Glomerulocentric was WRONG.

Tubulointerstial inflammation is also KEY.

How Do We Follow Lupus Nephritis?

Better Ways to Measure Urine Protein

- Spot urine protein/creatinine ratio

Christopher-Stine L, Petri M, Astor BC, Fine D. *J Rheumatol*. 2004;31(8):1557-9.
Fine DM, et al. *Kidney Int*. 76:1284-1288. 2009.

SLICC Renal Activity Score

- This score is derived from a regression analysis using the physician rating of renal activity as the gold standard.

proteinuria of 0.5 to 1 gm/day	3 points
proteinuria of 1 to 3 gm/day	5 points
proteinuria of > 3 gm/day	11 points
urine red blood cells > 5/hpf	3 points
urine white blood cells > 5/hpf	1 point

Petri M, et al. Systemic Lupus Erythematosus Clinical Studies Systemic Lupus International Collaborating Clinics renal activity/response exercise: Development of a renal activity score and renal response index. *Arthritis Rheum*. 2008;58:1784-1788 (erratum *Arthritis Rheum*. 2008;58:2823).

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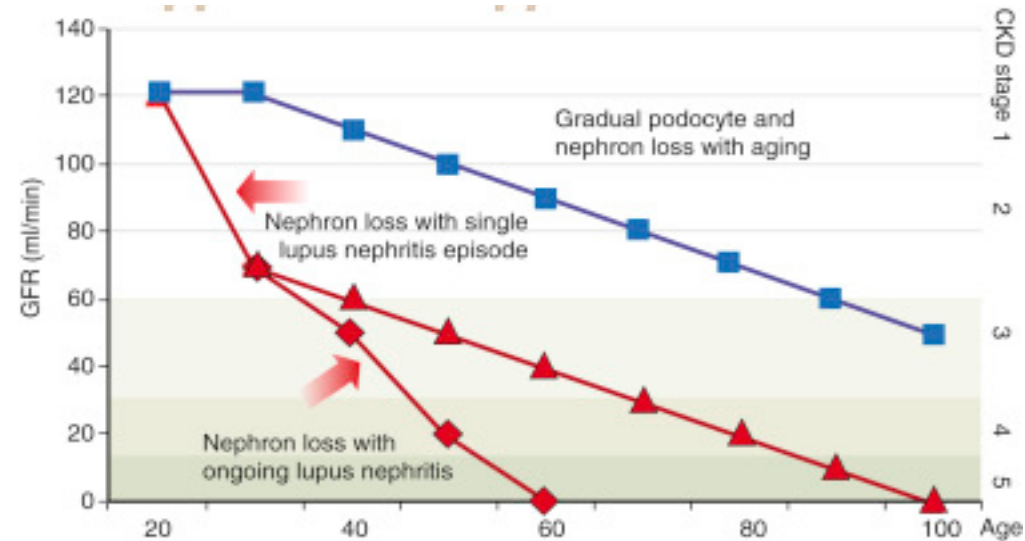
GFR = glomerular filtration rate; CKD = chronic kidney disease.
Anders HJ, et al. *Kidney Int*. 2016;90(3):493-501.

The Goal in Treatment of Lupus Nephritis

NEVER have a flare.

- check urine protein/cr often
- check adherence

DON'T put remaining nephrons at risk

- no NSAIDS
- no CT dye
- no kidney toxins

Stop the Blind Trust in Proteinuria

A protocol kidney biopsy is the only way to know for sure that treatment is sufficient

Malvar A et al. *Nephrol Dial Transplant*. 2017;32:1338-1344

Biopsy Risk is Very Low (Hematoma)

- 3%
  - Low platelets
  - Hypertension (severe)
  - Uremia
  - Anticoagulants

Chen et al. *Lupus* 2012;21:848-54

A Kidney Biopsy Could Change Approach If:

- Very active disease
  - more immunosuppression
  - check adherence
- Delayed kidney repair
- Discovery of another kidney disease
- Renal scarring

The Goal for Proteinuria

- Urine pr/cr
  - 0.5

    Houssiau FA, et al. Ann Rheum Dis 2010;69:2083–9

  - 0.7

    Tamirou F, et al. Ann Rheum Dis 2015; 2016;75:526–531

- RAPID resolution is best

  Dall'Era M et al. Arthritis Rheumatol 2015;67:1305-13.

Urine Biomarkers are Not Yet Ready for Prime Time

VCAM-1

Seron D et al.Nephrol Dial Transplant 6:917, 1991.
Kiani AN, et al. J Rheumatol 39:1231-1237, 2012.

CXCL 16

Wu T et al. J Rheumatol 179:7166, 1007

NGAL (lipocalin)

Pitashny M et al. Arthritis Rheum 56:1894, 2007

MCP-1

Stahl RA et al. Kidney Int 44:1036, 1993.
Rovin BH et al. Am J Kidney Dis 27:640, 1996.
Kiani AN et al. J Rheumatol, 36:2224-2230, 2009.

IL-8

Mezzano S et al. J Am Soc Nephrol 8:234, 1997
Cockwell P, et al. Kidney Int 55:852-1999

OPG

Petri M et al. J Rheumatol 36:2224, 2009

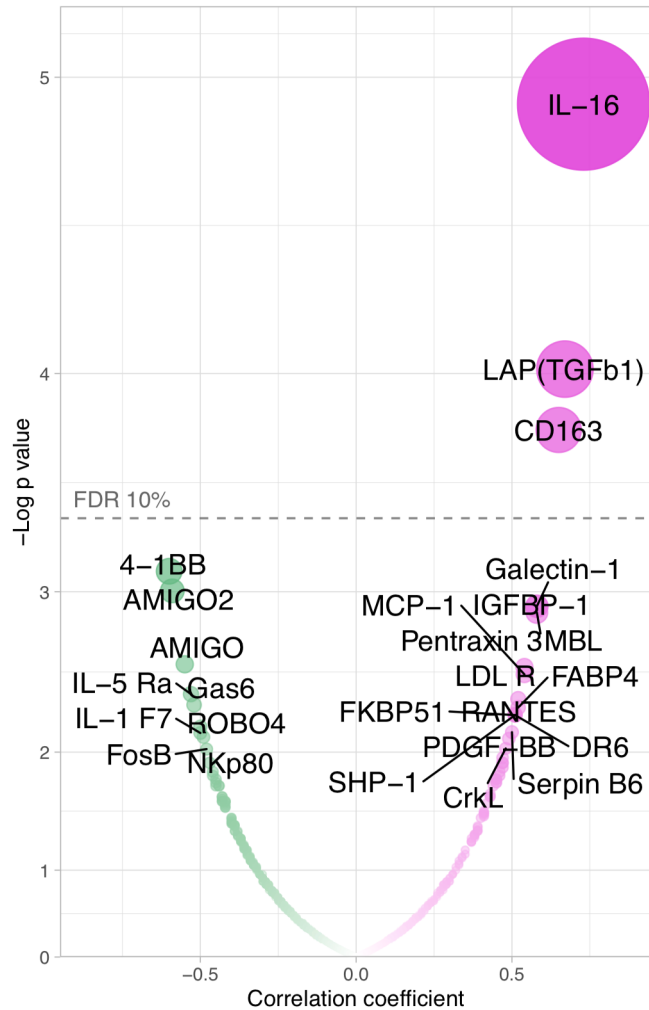# What are the urinary proteins enriched in lupus nephritis?
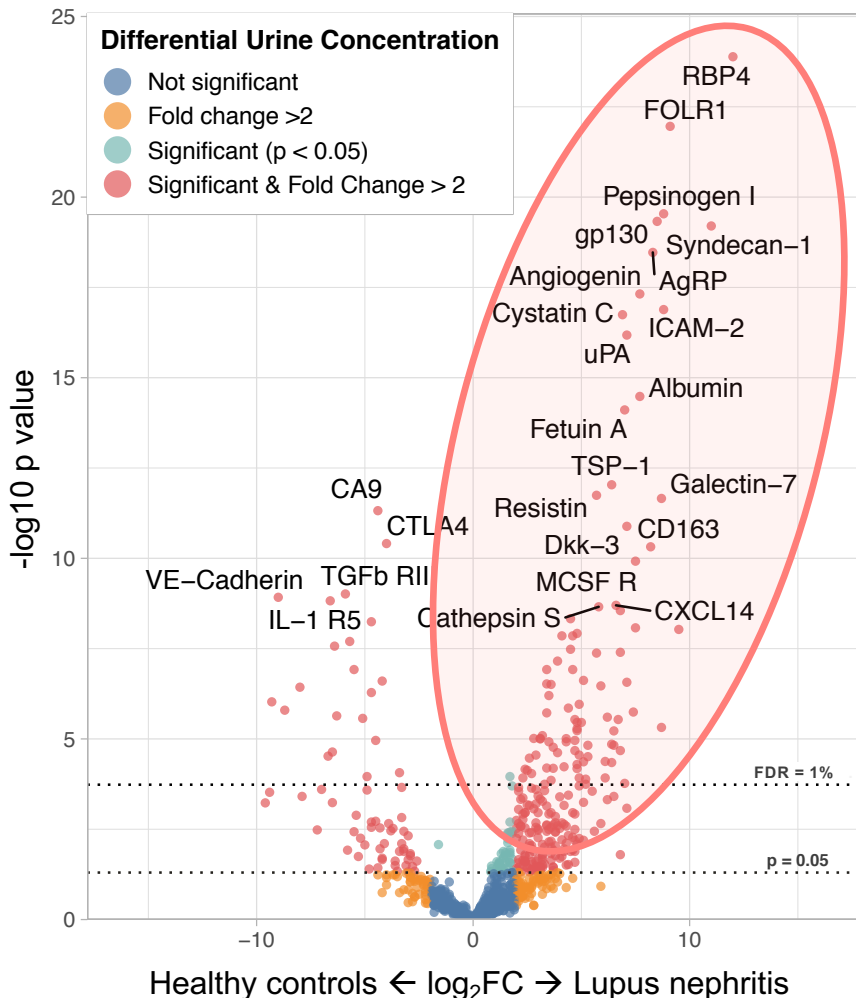
273 urinary proteins (FDR 10%) were elevated in SLE vs healthy

Non-overlapping pathways enriched in lupus nephritis
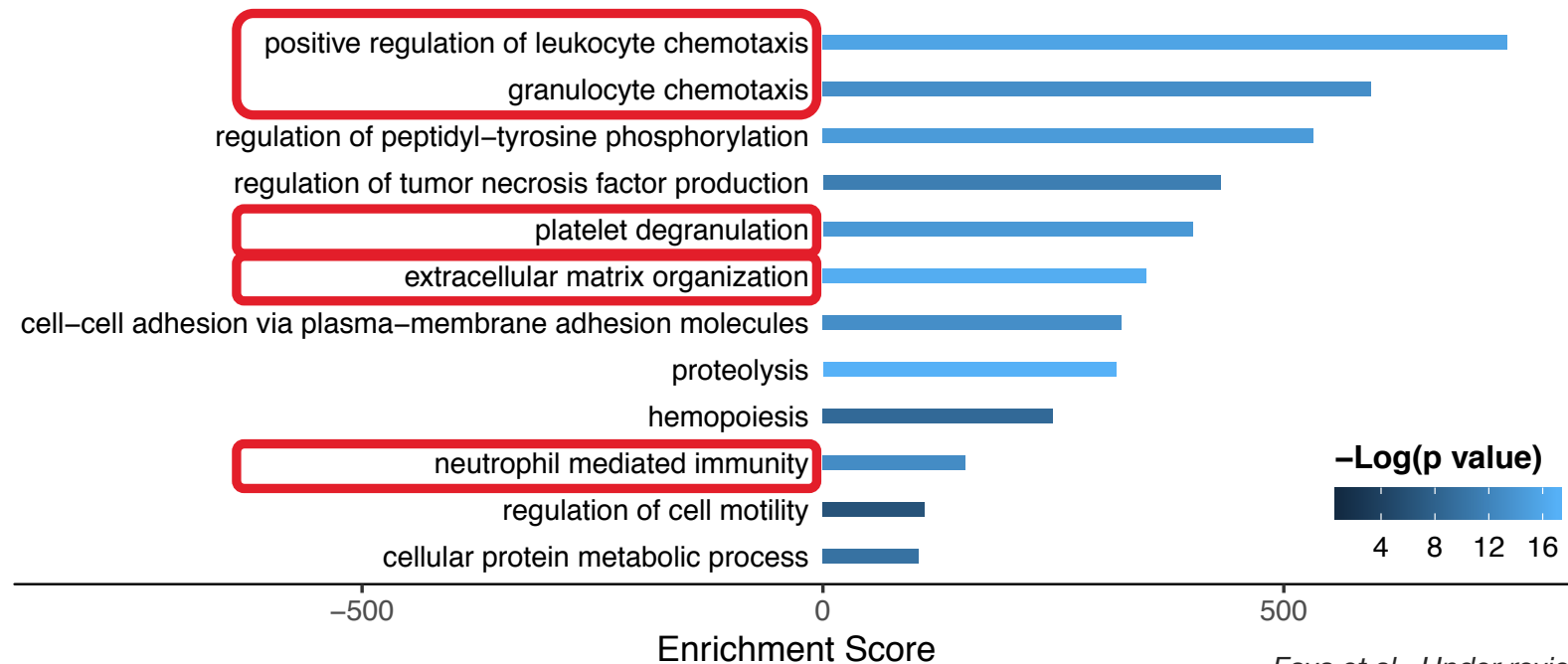
IL-16, TGFb, and CD163 were highly correlated with histological activity
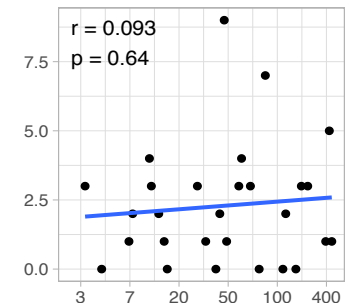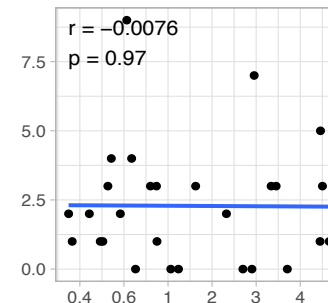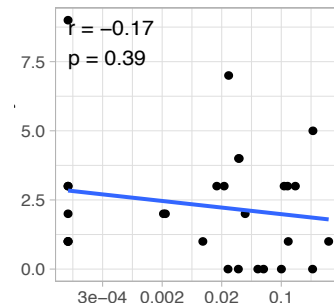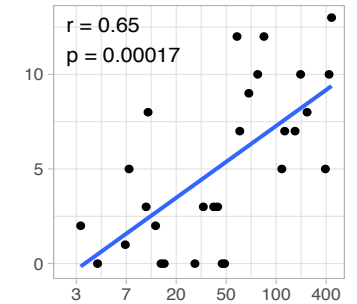
Correlation with NIH _activity_ index
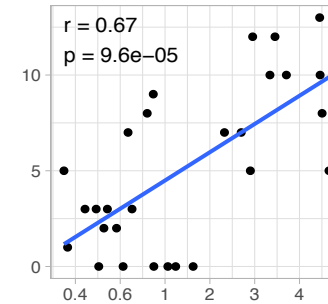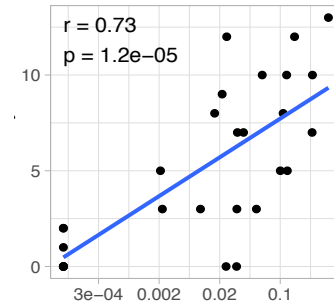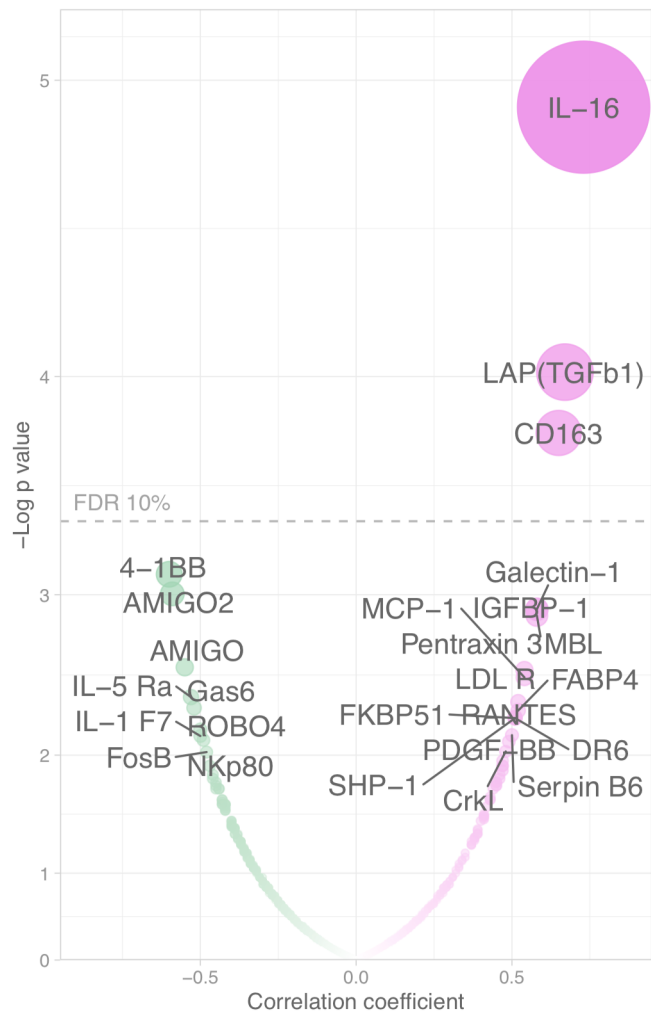
IL-16 is "independent" of proteinuria

Correlation with NIH activity index
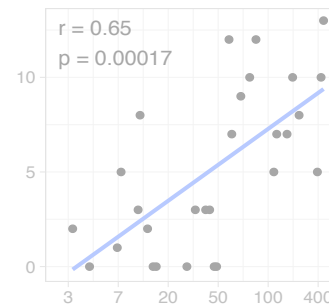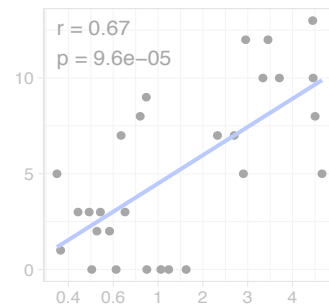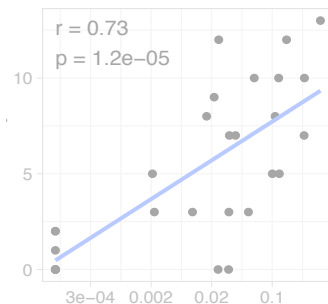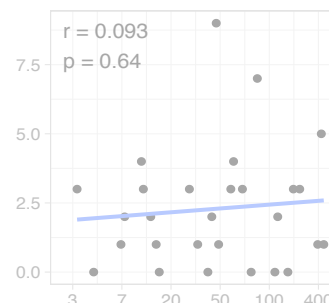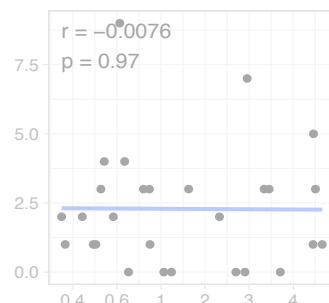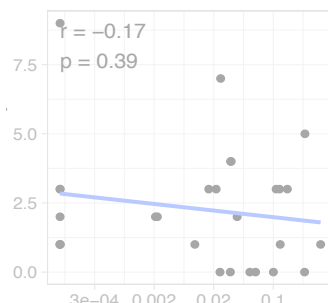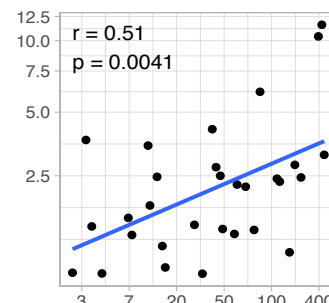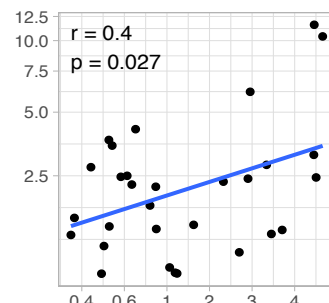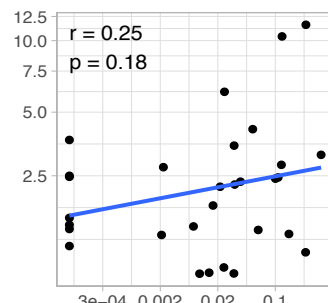
IL16 is abundantly expressed by kidney infiltrating immune cells

Kidney single cell RNA sequencing
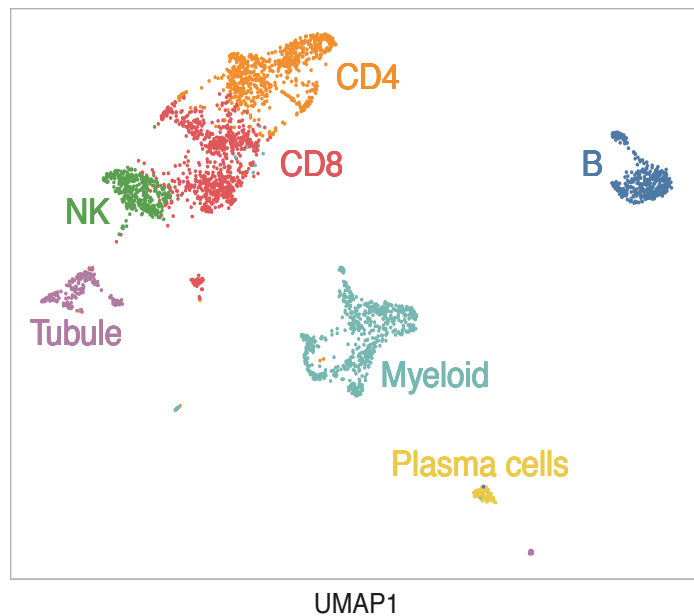
IL16 expression

IL16

CD163

TGFB1

Arazi et al., Nat Immunol 2019
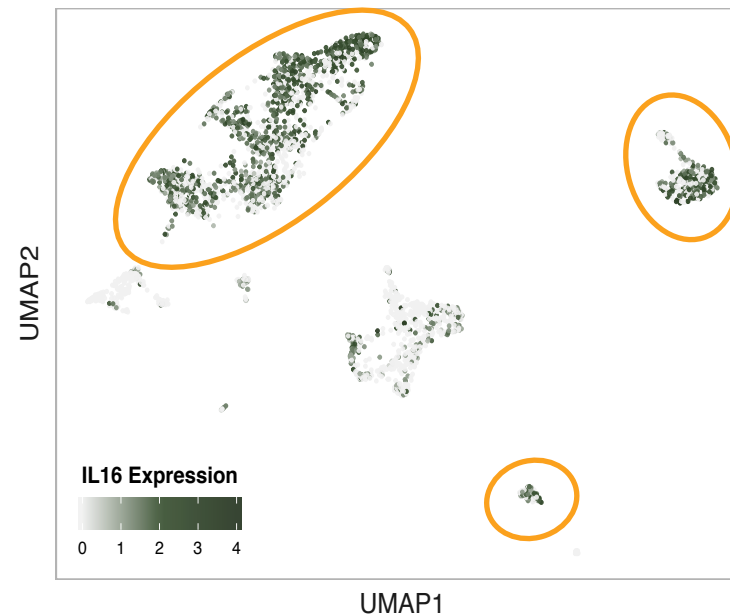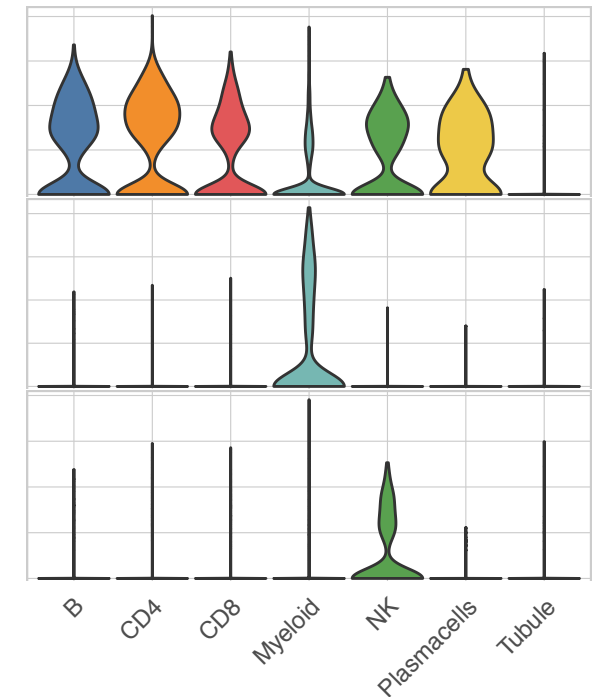
ACR Guidelines for Kidney Biopsy

Indications for Kidney Biopsy*

Increasing serum creatinine without compelling alternative causes (eg, sepsis, hypovolemia, or medication)

Confirmed proteinuria of 1.0 gm/24 hours (either 24-hour urine specimens or spot protein-creatinine ratios)

Combinations of the following, assuming the findings are confirmed in at least 2 tests done within a short period of time and in the absence of alternative causes:
- Proteinuria 0.5 gm per 24 hours plus hematuria, defined as 5 RBCs per HPF
- Proteinuria 0.5 gm per 24 hours plus cellular casts

*All recommendations are level of evidence C.
Hahn BH, et al. *Arthritis Care Res.* 2012;64:797-808.

EULAR/ERA-EDTA Guidelines for Kidney Biopsy

Indications for Kidney Biopsy	Level of Evidence	Level of Agreement (SD)
1.1 Kidney biopsy should be considered when there is evidence of kidney involvement, especially in the presence of persistent proteinuria ≥0.5 g/24 hours (or UPCR ≥500 mg/g in morning first void urine), and/or an unexplained decrease in GFR.	2b	9.84 (0.54)
1.2 Kidney biopsy remains indispensable and its diagnostic and prognostic value cannot be substituted by other clinical or laboratory variables.	2b	9.96 (0.20)
6.3 Repeat kidney biopsy should be considered in selected cases, such as worsening of kidney variables, non-responsiveness to immunosuppressive or biologic treatment (as defined above); or at relapse, to demonstrate possible histologic class transition or change in chronicity and activity indices; to provide prognostic information; and detect other pathologies.	2b	9.84 (0.37)

Fanouriakis A, et al. *Ann Rheum Dis.* 2020;79:713-723.

The Value of Renal Biopsy at Lower Levels of Proteinuria in Patients Enrolled in the Lupus Accelerating Medicines Partnership

Objectives

To address whether UPCR between 0.5 and 1 differs from higher ratios with regard to clinical, serologic and histologic variables and whether clinical characteristics can distinguish patients with UPCR <1 based on renal pathology

Methods

283 patients included were age ≥18, were SLE by ACR or SLICC criteria, had a research core obtained during a clinically-indicated kidney biopsy showing Class I, II, III, IV, V, III/V, IV/V, or VI lupus nephritis

Key Results

- Patients with UPCR <1 had increased mesangial histology but frequencies of other classes and activity/chronicity were similar among all proteinuria levels.
- No serologic variables distinguished patients with UPCR <1 with mesangial histology, from those with UPCR <1 and proliferative or membranous histology.
- Nearly half of patients with UPCR <1 and proliferative or membranous histology had no active sediment.

Conclusion

A significant proportion of patients with a UPCR <1 have proliferative histology and activity and chronicity scores similar to patients with nephrotic range proteinuria in the absence of urinary sediment. These results support renal biopsy at thresholds lower than a UPCR of 1 irrespective of sediment.

Carlucci P, et al., Abstract 1516
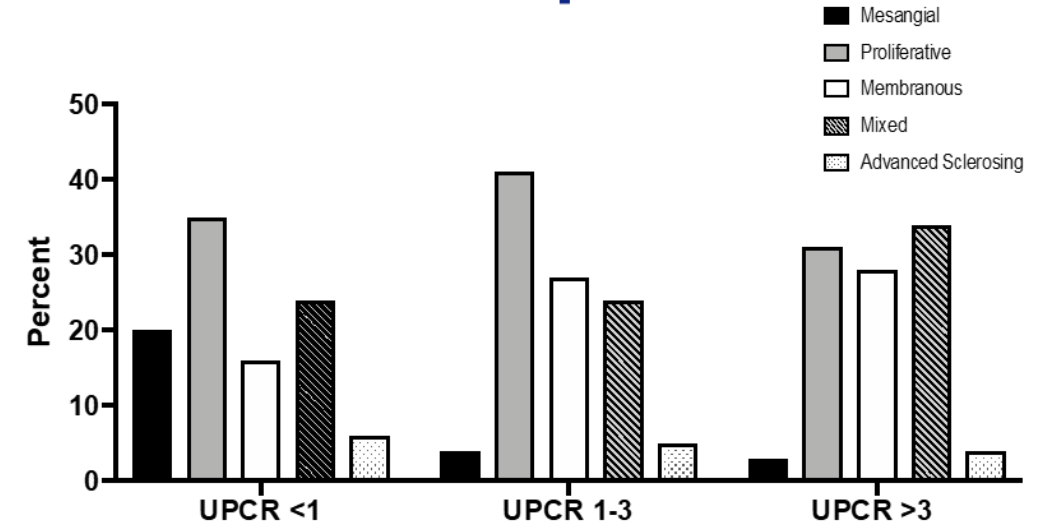
Urinary Sediment	Class I or II N=11	Class III, IV, V, Mixed N=41
No Sediment, %	88%	42%
Hematuria, %	11%	29%
Pyuria, %	0%	34%
Casts, %	0%	0%

Table shows data for patients with UPCR <1 only

How Do We Treat Lupus Nephritis?

Management of Lupus Nephritis

1. ACEi/ARB

2. Hydroxychloroquine

3. Vitamin D

4. Mycophenolate vs Cyclophosphamide

5. Steroids

6. New therapies: belimumab, voclosporin

Adjunctive Therapy for Proteinuria

- ACE-inhibitor

- Angiotensin receptor blocker
  Duran-Barragan S, et al. *Rheumatology* 2008 47:1093-1096.

- Spironolactone 25 mg or eplerenone 50 mg
  Epstein. *Am J Med* 2006;119:912-919.

Hydroxychloroquine for Lupus Nephritis

- Continuing hydroxychloroquine improves complete response rates with mycophenolate mofetil.
Kasitanon et al. Lupus 2006;15:366-70.

- No need to check G6PD
Mohammad S et al. Arthritis Care Res. 2018;70:481-5

ACR Guidelines: Adjunctive Therapies

All SLE patients with nephritis should be treated with a background of hydroxychloroquine unless there is a contraindication (level C evidence)

EULAR/ERA-EDTA Guidelines: Adjunctive Therapies

HCQ should be coadministered,
[level of evidence 2a; level of agreement 9.28 (SD 1.40)]

at a dose not to exceed 5 mg/kg/day and adjusted for the GFR.
[level of evidence 3b]

Hahn BH, et al. *Arthritis Care Res.* 2012;64:797-808.
Fanouriakis A, et al. *Ann Rheum Dis.* 2020;79:713-723..

Adjusted QTc Was Comparable Between HCQ vs. NO HCQ
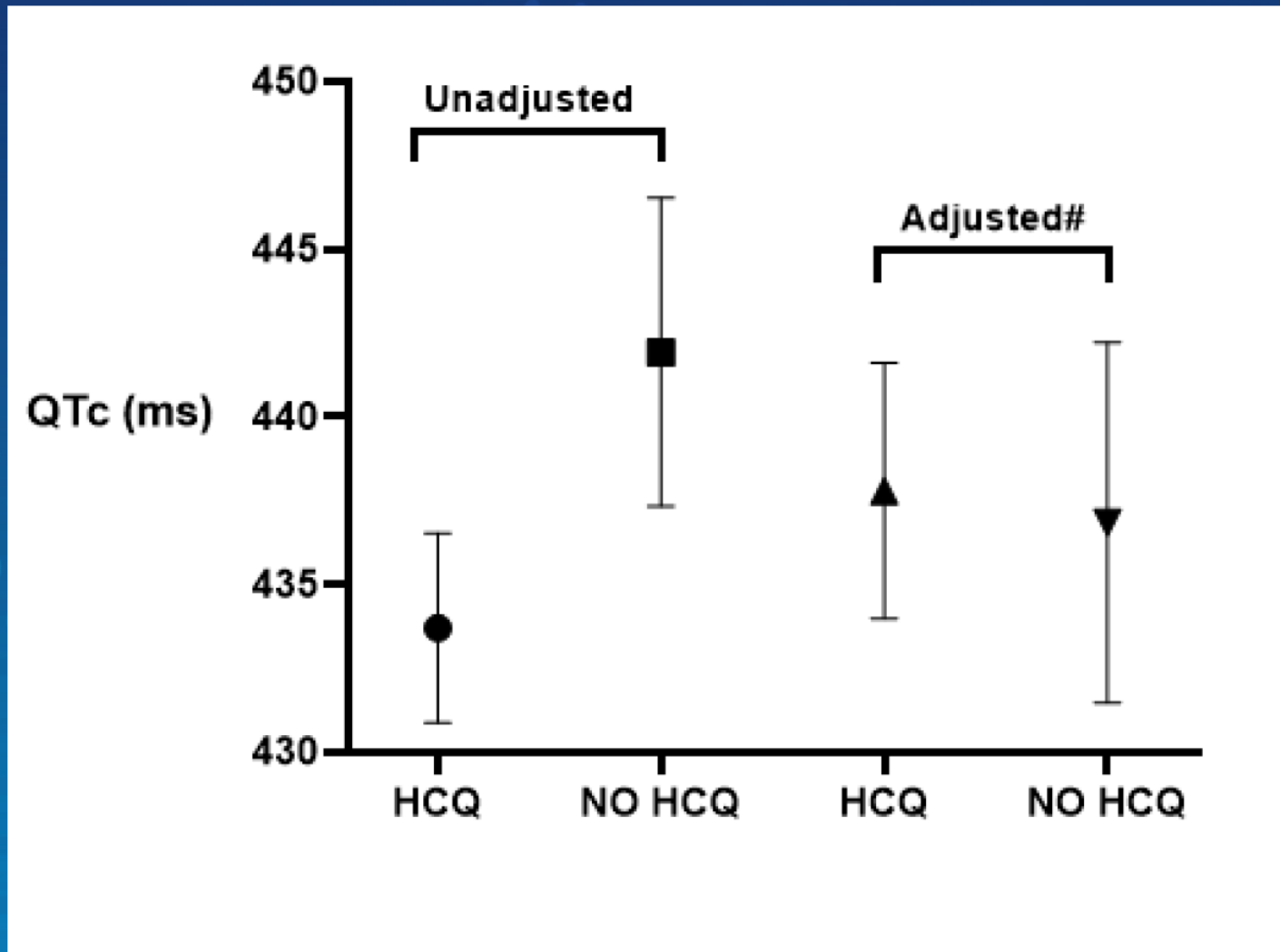
Figure 1. QTc length and 95% CI in HCQ vs. NO HCQ in combined SLE/RA cohorts

#Adjusting for age, race, current prednisone use, hypertension, current smoking, diabetes, and aspirin use, anti-microbial use

Park E, et al. Arthritis Rheumatol. 2020; 72 (suppl 10):Abstract No. 0431.

Increasing 25-Hydroxy Vitamin D Modestly 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.
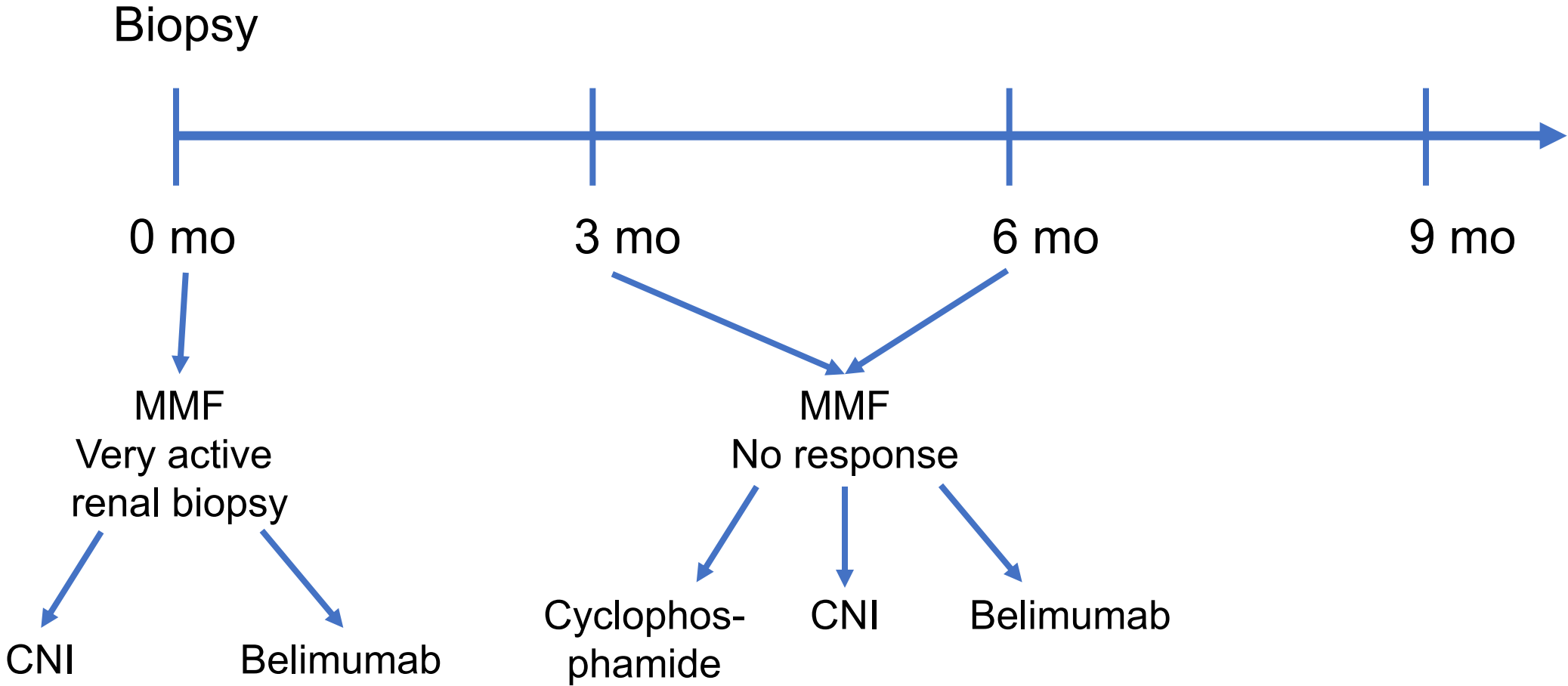
Initial Therapy: Class IV

- ACR
  - Mycophenolate mofetil (2-3 gm total daily orally) or IV cyclophosphamide along with glucocorticoids is recommended (level A evidence)
    - Evidence suggestions that mycophenolate mofetil may be more likely to induce improvement in patients who are African American or Hispanic

- EULAR/ERA-EDTA
  - 4.3 For patients with class III or IV (±V) LN, MMF (target dose: 2 to 3 g/day, or MPA at equivalent dose) [LoE 1a, LoA 9.84 (SD 0.37)] or low-dose intravenous CY (500 mg every 2 weeks for a total of 6 doses) [LoE 1a] in combination with glucocorticoids, are recommended as they have the best efficacy/toxicity ratio.
  - 4.4 Combination of MMF (target dose: 1 to 2 g/day, or MPA at equivalent dose) with a CNI (especially TAC) is an alternative, particularly in patients with nephrotic-range proteinuria. [LoE 1a, LoA 9.32 (SD 0.93)]

Hahn BH, et al. *Arthritis Care Res.* 2012;64:797-808.
Fanouriakis A, et al. *Ann Rheum Dis.* 2020;79:713-723.

Influence of Race on Treatment
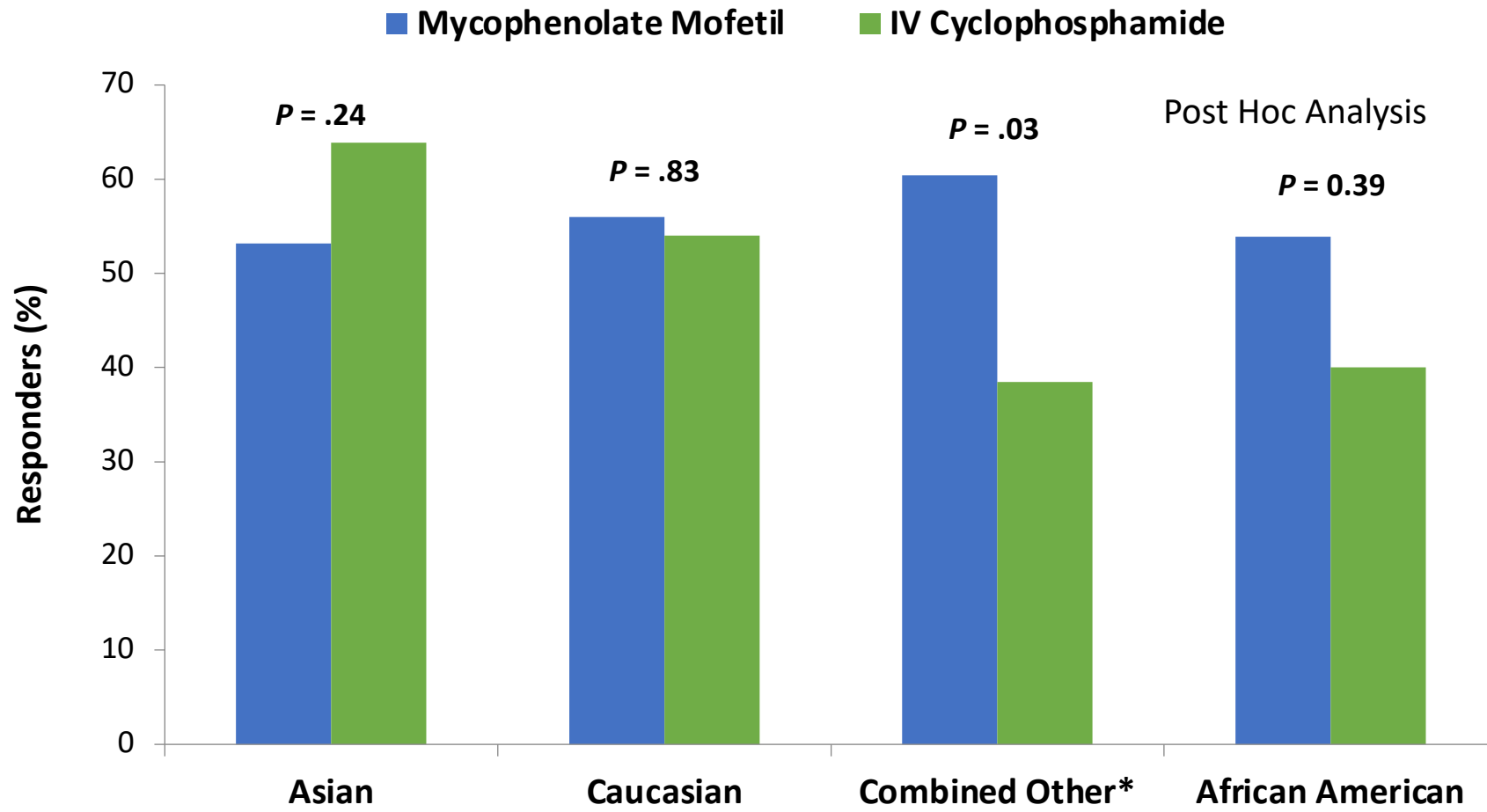
*Includes African Americans.
Isenberg D, et al. *Rheumatology (Oxford).* 2010;49:128-140.

Mycophenolate Mofetil: Induction Therapy

	Comparator	Result
Chan et al	oral cytoxan	equivalent
Hu et al	IV cytoxan	MMF superior
Ong et al	IV cytoxan	equivalent
Ginzler et al	IV cytoxan	equivalence (but MMF better in Af.-Amer.)
ALMS[1]	IV cytoxan	equivalence (but MMF better in Non-Cauc)
Meta-analysis[2]	IV cytoxan	equivalence

[1]Appel, G. B., et al. *J Am Soc Nephrol* 2009;20:1103-12
[2]Touma Z, et al. *J Rheumatol*. 2011;38:69-78.

How Much Prednisone?
As Little As Possible!

Initial Therapy: Class IV (continued)

- ACR
  - Pulse IV glucocorticoids (500-1000 mg methylprednisolone daily for 3 doses) in combination with immunosuppressive therapy is recommended, followed by daily oral glucocorticoids (0.5-1 mg/kg/day), followed by a taper to the minimal amount necessary to control disease (level C evidence)

- EULAR/ERA-EDTA
  - To reduce cumulative glucocorticoid dose, the use of intravenous pulses methylprednisolone (total dose 500–2500 mg, depending on disease severity) is recommended, followed by oral prednisone (0.3–0.5 mg/kg/day) for up to 4 weeks, tapered to ≤7.5 mg/day by 3 to 6 months. [LoE 2b, LoA 9.48 (SD 0.90)]

Hahn BH, et al. *Arthritis Care Res.* 2012;64:797-808.
Fanouriakis A, et al. *Ann Rheum Dis.* 2020;79:713-723.

High Dose Prednisone had Higher 12 Month Complete Renal Remissions

	Medium prednisone (≤30mg/day, n=103)	High prednisone (>40mg/day, n=103)	P-value
Complete remission* (n=206)	39 (38.2%)	63 (61.8%)	0.024
Complete and partial remission** (n=206)	58 (59.8%)	66 (66.7%)	0.411
Proliferative LN (classes III, IV) (n=82)	11/41 (26.8%)	27/41 (65.8%)	0.001
Non-proliferative LN (classes II, V) (n=28)	6/14 (42.9%)	9/14 (64.3%)	0.257

*Complete remission: proteinuria<0.5g/day and serum creatinine <120% of the baseline value

**Partial remission: proteinuria <50% and serum creatinine <120% of the baseline values

But the High Prednisone Group Paid a Price in Higher Damage Accrual

	Medium prednisone (≤30mg/day)	High prednisone (>40mg/day)	P-value
Cumulative prednisone dose (g)	6.8 + 3.0	8.5 + 3.7	0.001

Prednisone Is Directly or Indirectly Responsible for 80% of Organ Damage over 15 Years
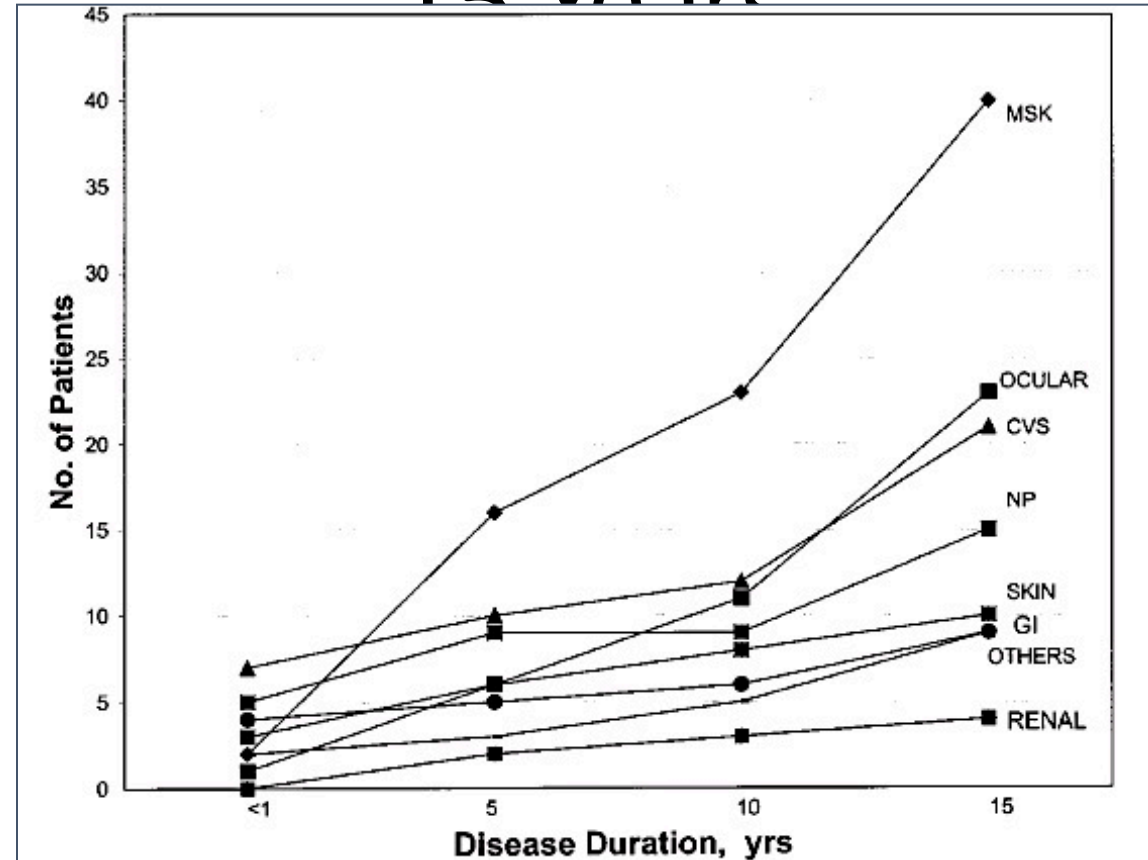
CVS=cardiovascular system; GI=gastrointestinal; MSK=musculoskeletal
NP=neuropsychiatric

Gladman DD, et al. *J Rheum*. 2003;30(9):1955-1959

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.

Maintenance Therapy: Class IV

- ACR
  - Either azathioprine or mycophenolate mofetil may be used for maintenance therapy (level A evidence)

- EULAR/ERA-EDTA
  - If improvement after initial treatment is achieved, subsequent immunosuppression is recommended with either MMF/MPA (dose: 1 to 2 g/day)—especially if it was used as initial treatment— [LoE 1a, LoA 9.80 (SD 0.49)] or AZA (2 mg/kg/day)—preferred if pregnancy is contemplated—in combination with low-dose prednisone (2.5–5 mg/day) when needed to control disease activity. [LoE 1a]
  - Gradual withdrawal of treatment (glucocorticoids first, then immunosuppressive drugs) can be attempted after at least 3 to 5 years therapy in complete clinical response. HCQ should be continued long-term. [LoE 2b, LoA 9.40 (SD 0.75)]

Hahn BH, et al. *Arthritis Care Res.* 2012;64:797-808.
Fanouriakis A, et al. *Ann Rheum Dis.* 2020;79:713-723.

Withdrawal of MMF Is Safe in Quiescent Renal and Non-Renal SLE: Results from a Multicenter Randomized Trial

Objectives

To describe the effects of withdrawal from MMF (structured 12 week taper) on risk of clinically significant disease reactivation in quiescent SLE patients who have been on long-term MMF therapy

Methods

Multicenter, randomized, open-label 60-week study: 102 randomized

- Quiescent SLE (mSLEDAI <4); stable or decreasing MMF >2 years for renal disease, >1 year for non-renal disease
- HCQ >12 weeks prior to baseline and continuation through the study required
- 1º endpoint: clinically significant disease reactivation by 60 weeks
- 2º endpoints: BILAG flares, SELENA-SLEDAI flares; time to flare
- Subset analysis of 78 participants with history of renal disease

Key Results

- Kaplan-Meier estimate of risk difference for all outcomes overlapped.
- Few serious flares occurred in the maintenance or withdrawal groups.

Conclusion

Withdrawal of MMF may be safely considered in some SLE patients with prolonged quiescent disease.

Chakravarty EF, et al., Abstract 0989

Clinically Significant Disease Reactivation
All Eligible Participants (n=100)

| Maintenance | 49 49 49 48 48 48 48 47 46 44 44 43 42 41 39 39 |
| Withdrawal | 51 51 51 50 48 48 46 46 46 45 45 45 44 42 42 42 |

Week to Disease Reactivation
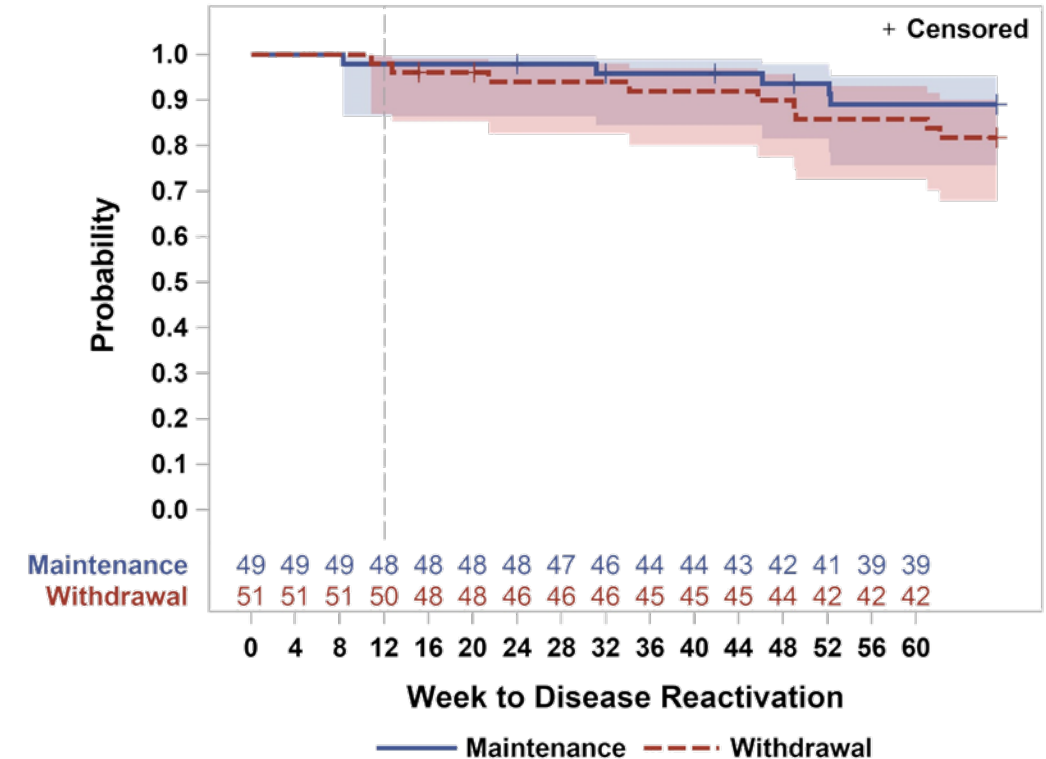
Kaplan-Meier estimate of risk difference by Week 60:
$Risk_{withdrawal} - Risk_{maintenance} = 0.07$ (95%CI: -0.068, 0.214)

ALMS Maintenance Trial:
MMF is Superior to Azathioprine
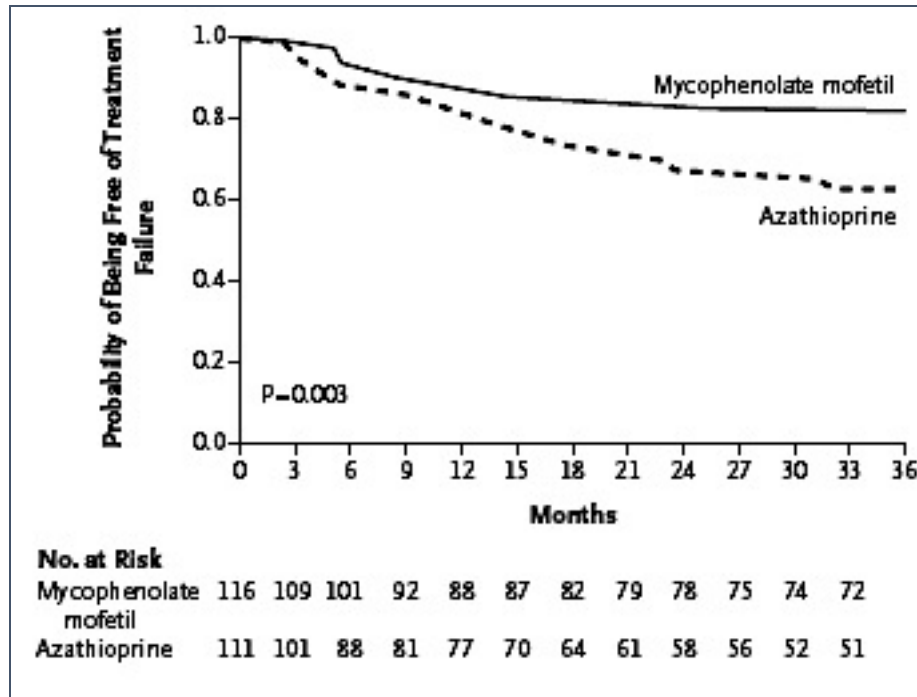
N=227

Time to treatment failure   Time to renal flare
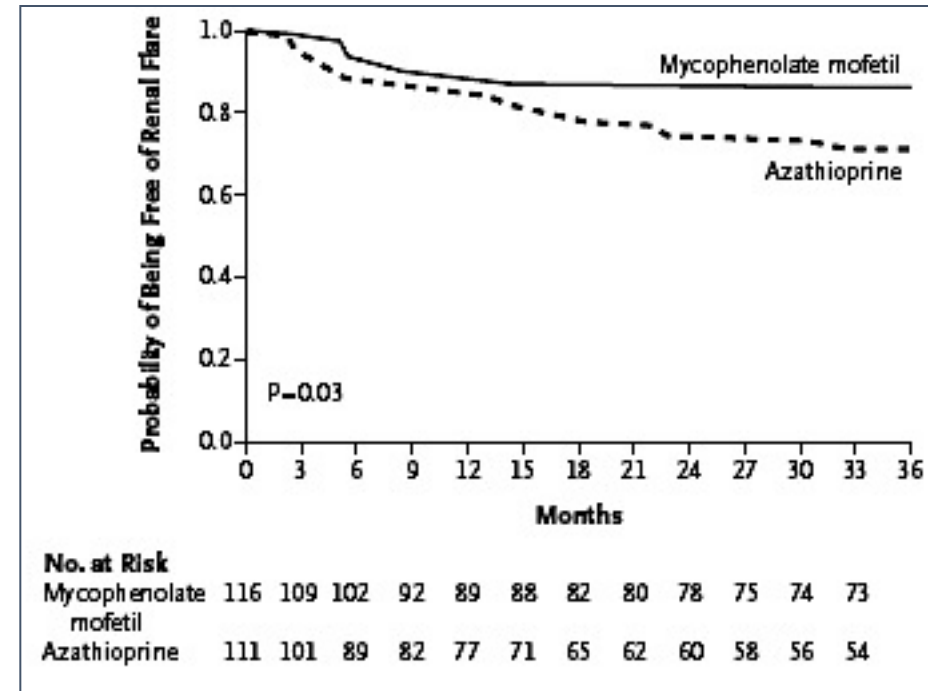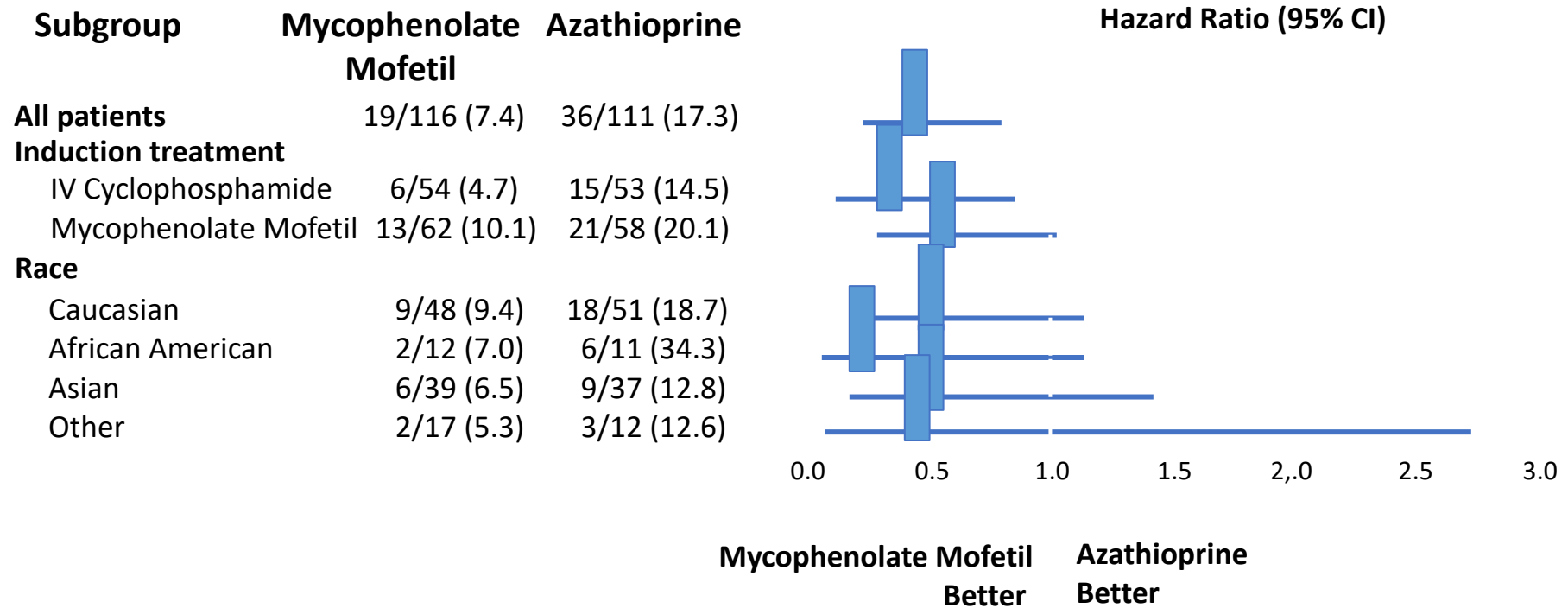
Dooley MA, et al. *N Engl J Med.* 2011;365:1886-95.

ALMS Maintenance Trial

Subgroup	Mycophenolate Mofetil	Azathioprine
All patients	19/116 (7.4)	36/111 (17.3)
Induction treatment		
IV Cyclophosphamide	6/54 (4.7)	15/53 (14.5)
Mycophenolate Mofetil	13/62 (10.1)	21/58 (20.1)
Race		
Caucasian	9/48 (9.4)	18/51 (18.7)
African American	2/12 (7.0)	6/11 (34.3)
Asian	6/39 (6.5)	9/37 (12.8)
Other	2/17 (5.3)	3/12 (12.6)

Hazard Ratio (95% CI)

0.0 0.5 1.0 1.5 2,0 2.5 3.0

Mycophenolate Mofetil Better   Azathioprine Better

Mycophenolate Mofetil: Maintenance Therapy

Study	Groups	Result
Contreras et al	azathioprine IV cytoxan	aza = MMF MMF better & safer than IVC
Chan et al	oral cytoxan/aza	equivalent
MAINTAIN	azathioprine	aza = MMF
ALMS	Azathioprine	MMF better p=0.003

Mycophenolate Hints

- Must be split dosing
- Induction dosing differs by ethnicity
  - Asians 2,000 mg
  - Caucasians 2,000 – 3,000 mg
  - African-Americans 3,000 mg

MMF Warnings

- Infection (including PML)

- Lymphoma and malignancy

- Pregnancy loss and congenital malformation (new information: interaction with OCPs)

- Neutropenia and red cell aplasia

REMS

PML = progressive multifocal leukoencephalopathy; OCPs = oral contraceptive pills.
MMF (mycophenolate mofetil) FDA Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/
2008/050722s018lbl.pdf. Accessed April 22, 2012.

Only Complete Renal Response Matters
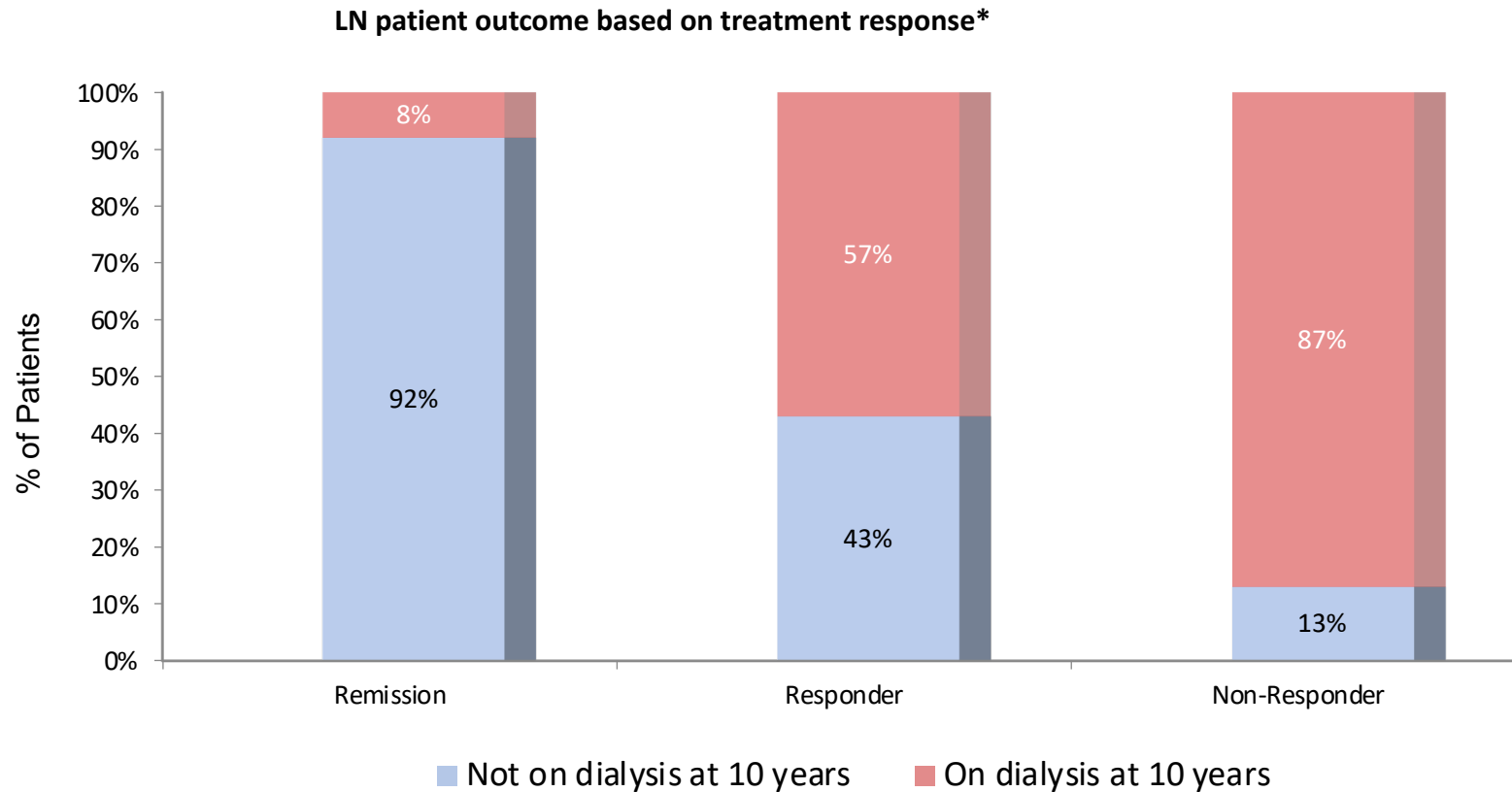
LN patient outcome based on treatment response*

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

M. Ramanujam and A. Davidson. Arthritis Research and Therapy. 2004. 6:197-202.
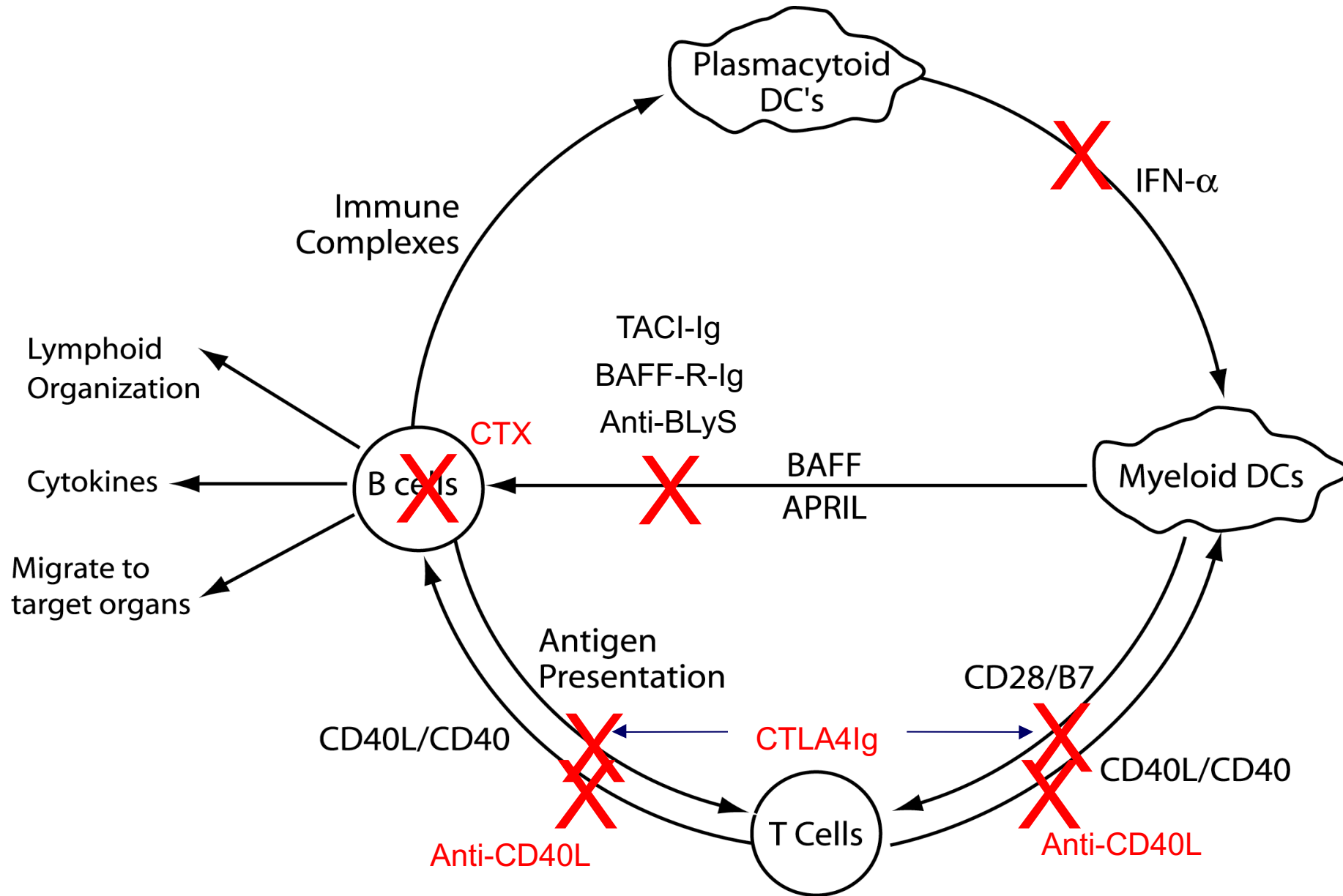
RESULTS
Primary and key secondary endpoints

Endpoint, n (%)	Placebo n=223	Belimumab 10 mg/kg IV n=223	Treatment difference (%)	OR/HR (95% CI) vs placebo	p-value
Primary endpoint:					
PERR at Week 104*†	72 (32.3)	96 (43.0)	10.8	OR 1.6 (1.0, 2.3)	0.0311
Secondary endpoints:					
CRR at Week 104*†	44 (19.7)	67 (30.0)	10.3	OR 1.7 (1.1, 2.7)	0.0167
PERR at Week 52*†	79 (35.4)	104 (46.6)	11.2	OR 1.6 (1.1, 2.4)	0.0245
Time to renal-related event or death‡	63 (28.3)‖	35 (15.7)‖	–	HR 0.5 (0.3, 0.8)	0.0014
ORR at Week 104§†					
Complete response	44 (19.7)	67 (30.0)	10.3		
Partial response	38 (17.0)	39 (17.5)	0.4		0.0096
Non-responders	141 (63.2)	117 (52.5)	−10.8		

*OR (95% CI) and p-value are from regression model comparing belimumab and placebo with covariates for treatment group, induction regimen (CYC vs MMF), race (Black African Ancestry vs other), baseline uPCR, and baseline eGFR; †study WD, TF, and IPD were imputed as non-responders; ‡HR and p-value are from Cox proportional hazards model adjusted for induction regimen (CYC vs MMF), race (Black African Ancestry vs other), baseline uPCR, and baseline eGFR; §p-value is from rank ANCOVA model comparing belimumab and placebo with covariates for treatment group, induction regimen (CYC vs MMF), race (Black African Ancestry vs other), baseline uPCR, and baseline eGFR; ‖number/proportion of patients reporting the event
ANCOVA, analysis of covariance; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IPD, investigational product discontinuation; OR, odds ratio; TF, treatment failure; WD, withdrawal

RESULTS
PERR and CRR by visit

PERR by visit

Placebo (n=223)
Belimumab 10 mg/kg IV (n=223)

CRR by visit

Placebo (n=223)
Belimumab 10 mg/kg IV (n=223)
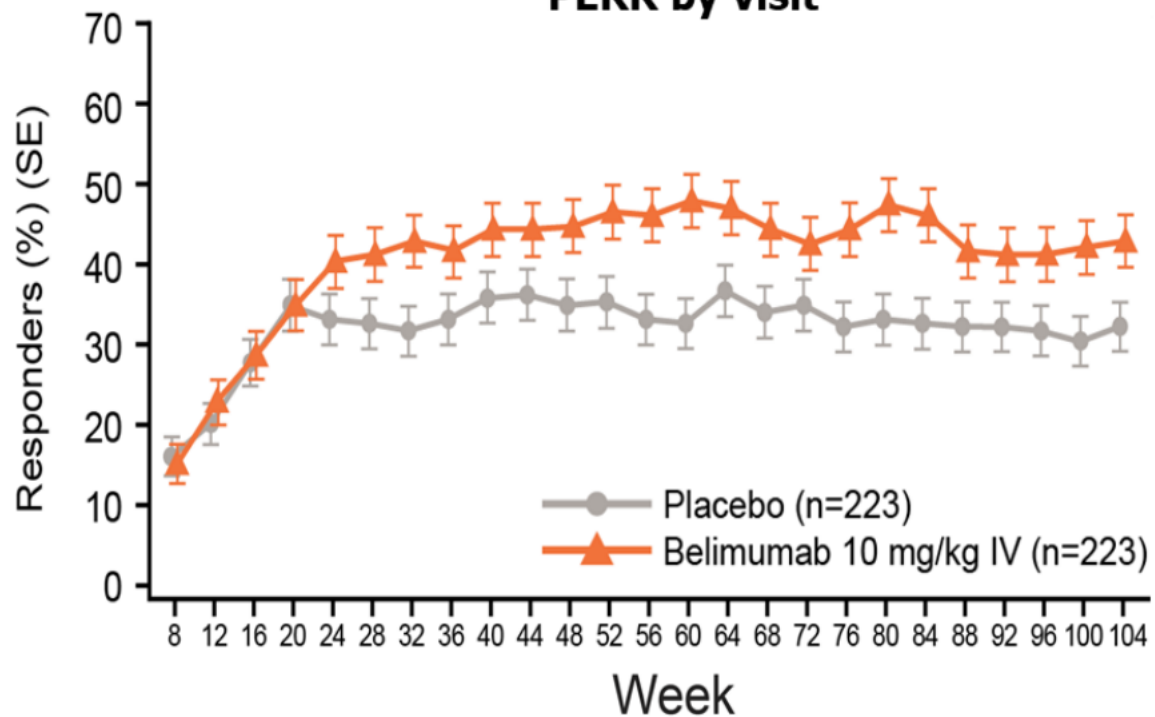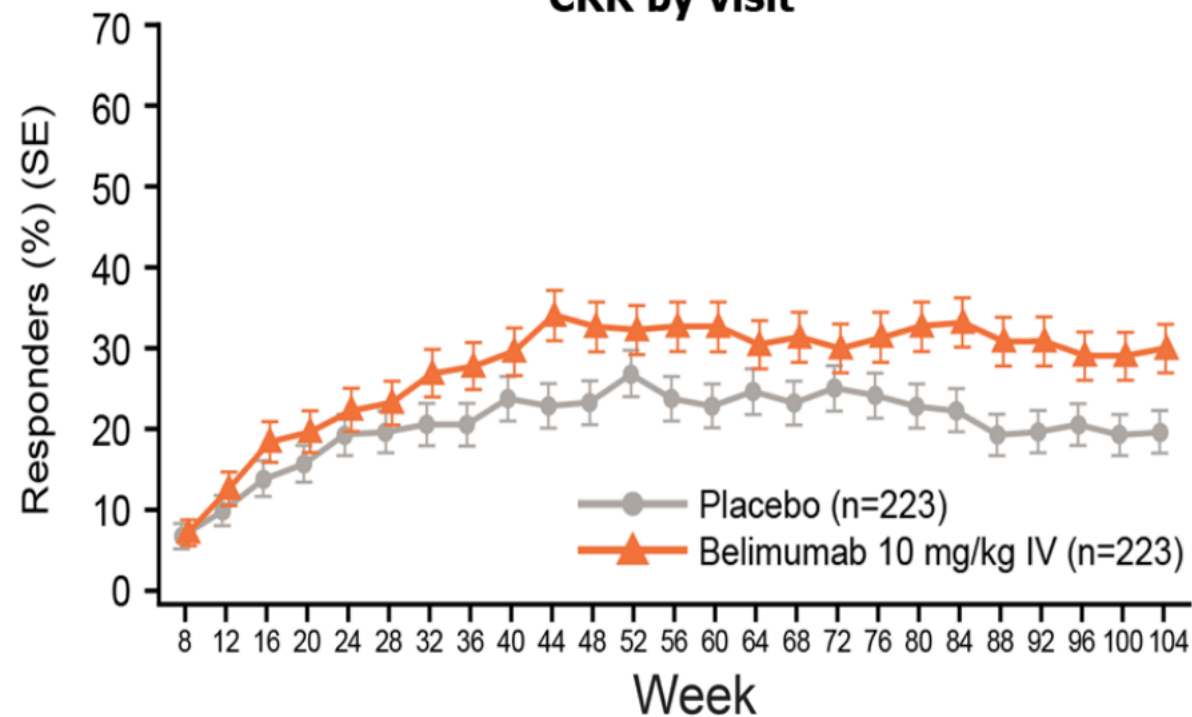
PERR is defined as uPCR ≤0.7, *and* eGFR no worse than 20% below pre-flare value or ≥60 ml/min/1.73 m^2, *and* not a treatment failure; CRR is defined as uPCR <0.5, *and* eGFR no worse than 10% below pre-flare value or ≥90 ml/min/1.73 m^2, *and* not a treatment failure
SE, standard error

RESULTS
PERR at Week 104 by treatment regimen, LN class, and race

		Responders, n (%)		Treatment difference (%)	Favors placebo	Favors belimumab	OR (95% CI)	p-value
		Placebo n=223	Belimumab 10 mg/kg IV n=223					
PERR* — Treatment regimen	**CYC/AZA** PBO, n=59; BEL, n=59	16 (27.1)	20 (33.9)	6.8			1.5 (0.7, 3.5)	0.3272
	MMF PBO, n=164; BEL, n=164	56 (34.1)	76 (46.3)	12.2			1.6 (1.0, 2.5)	0.0501
LN class	**Class III or IV** PBO, n=132; BEL, n=126	42 (31.8)	60 (47.6)	15.8			1.8 (1.1, 3.1)	0.0250
	Class III+V or IV+V PBO, n=55; BEL, n=61	15 (27.3)	23 (37.7)	10.4			1.8 (0.8, 4.0)	0.1796
	Pure Class V PBO, n=36; BEL, n=36	15 (41.7)	13 (36.1)	−5.6			0.6 (0.2, 1.9)	0.4196
Race	**Black African Ancestry** PBO, n=32; BEL, n=31	5 (15.6)	7 (22.6)	7.0			2.2 (0.6, 9.2)	0.2613
	Other PBO, n=191; BEL, n=192	67 (35.1)	89 (46.4)	11.3			1.5 (1.0, 2.3)	0.0465

OR (95% CI): axis 0.1 — 1 — 10

*Defined as uPCR ≤0.7, *and* eGFR no worse than 20% below pre-flare value or ≥60 ml/min/1.73 m^2, *and* not a treatment failure
BEL, belimumab; PBO, placebo

Change in kidney function between 24 and 104 weeks (*post hoc*)
mITT population*

	On-treatment		On-Study (some no longer on study treatment)	
	Placebo (n=223)	Belimumab 10 mg/kg IV (n=223)	Placebo (n=223)	Belimumab 10 mg/kg IV (n=223)
Patients at any visit, n	198	196	198	196
Patients at Week 104, n	128	140	163	173
Mean eGFR (SE) at Week 24[†]	106.6 (2.49)	109.4 (2.36)	106.8 (2.55)	109.5 (2.39)
eGFR slope (ml/min/1.73m^2/year) (SE)[†]	**−3.18 (1.10)**	**−0.99 (0.77)**	**−5.72 (1.47)**	**−2.12 (0.97)**
eGFR slope difference vs placebo (SE)[†] 95% CI p-value	-	2.19 (1.34) (−0.45, 4.84) 0.1041	-	3.61 (1.76) (0.15, 7.06) 0.0407

Rovin BH, Houssiau F, Furie R, Malvar A, Teng YKO, Mok CC et al. *ASN Kidney Week Annual Meeting* October 22-25, 2020.

*Defined as all randomized patients who received ≥1 dose of investigational treatment, excluding 2 patients (N=446); [†]statistics are from a linear mixed model consisting of treatment group (belimumab vs placebo), analysis visit (weeks), and their interaction, and random intercept and slope at the patient level. Covariance structure for random intercept and slope is unstructured and heterogeneous for treatment groups

Time to first decline in eGFR by 30% and 40% (*post hoc*)

	Censored at withdrawal or treatment discontinuation		Censored at withdrawal	
	Placebo (n=223)	Belimumab 10 mg/kg IV (n=223)	Placebo (n=223)	Belimumab 10 mg/kg IV (n=223)
Patients with 30% decrease in eGFR	12.6%	6.7%	17.0%	8.5%
30% decrease in eGFR, HR 95% CI p-value		0.52 (0.28, 0.98) 0.0429		0.47 (0.27, 0.83) 0.0084
Patients with 40% decrease in eGFR	6.7%	2.7%	11.7%	4.5%
40% decrease in eGFR, HR 95% CI p-value		0.38 (0.15, 0.98) 0.0457		0.35 (0.17, 0.74) 0.0056

HR, hazard ratio

Time to first renal flare after week 24 (*post hoc*)

Renal Flare Definitions

- **Week 24 uPCR and eGFR values were used as baseline:**
    - Reproducible increase in uPCR to >1 g if the baseline value (Week 24) was <0.2 g, to >2 g if the baseline value (Week 24) was between 0.2 g and 1 g, or more than twice the value at baseline if the baseline value (Week 24) was >1 g

    AND/OR
    - Reproducible decrease in GFR of >20%, accompanied by proteinuria (>1 g), and/or RBC and/or WBC cellular casts

    AND/OR
    - Renal-related treatment failure

	Placebo* (n=223)	Belimumab* 10 mg/kg IV (n=223)
Total patients (n)	196	194
Patients who flared, n (%)	51 (26.0)	28 (14.4)
HR 95% CI p-value	-	0.45 (0.28, 0.72) 0.001

Rovin BH, Houssiau F, Furie R, Malvar A, Teng YKO, Mok CC et al. *ASN Kidney Week Annual Meeting* October 22-25, 2020.
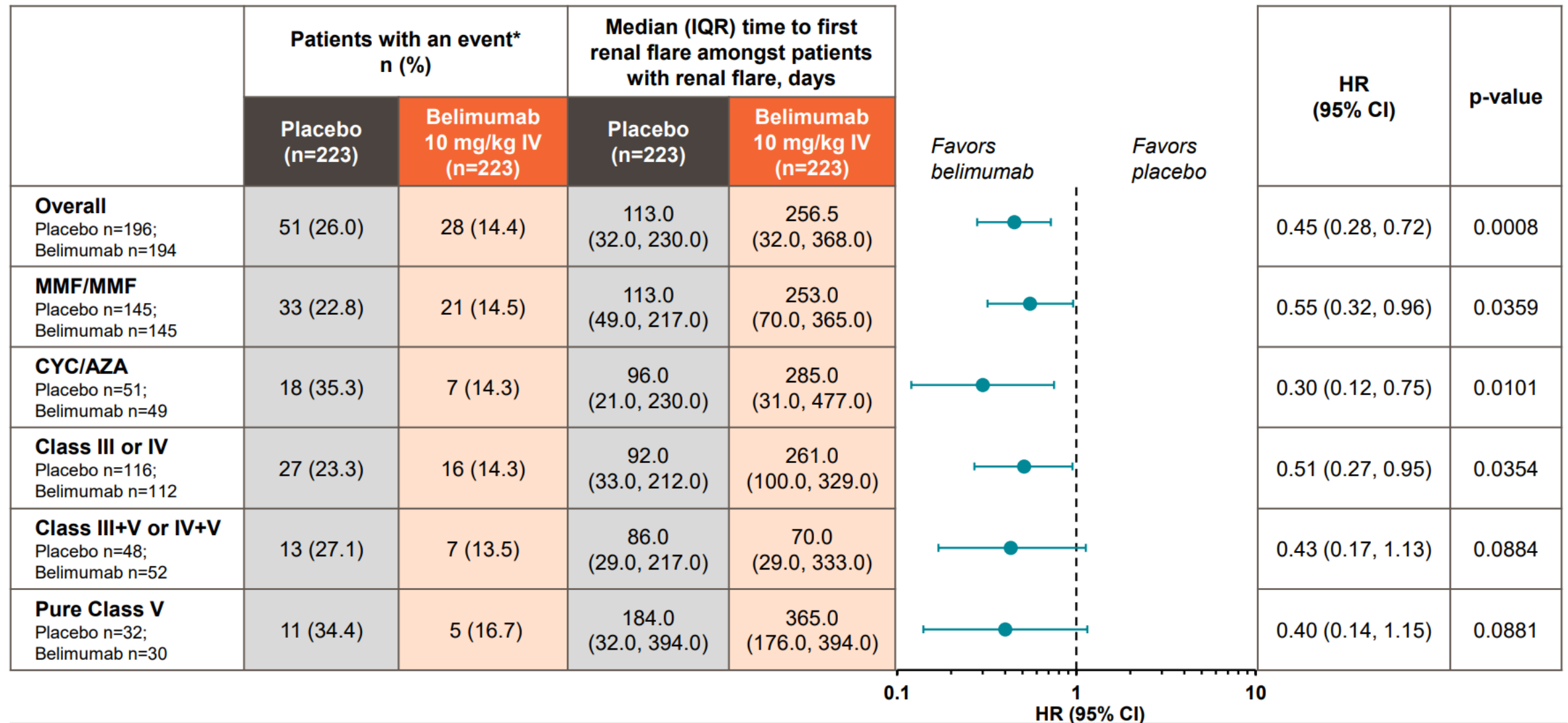
*Censored for treatment discontinuation or withdrawal or treatment failure not related to renal flare

RBC, red blood cell; WBC, white blood cell

Time to first renal flare from Week 24 (*post hoc*)

By induction/maintenance regimen and LN Class

	Patients with an event* n (%)		Median (IQR) time to first renal flare amongst patients with renal flare, days				HR (95% CI)	p-value
	Placebo (n=223)	Belimumab 10 mg/kg IV (n=223)	Placebo (n=223)	Belimumab 10 mg/kg IV (n=223)	*Favors belimumab*	*Favors placebo*		
Overall Placebo n=196; Belimumab n=194	51 (26.0)	28 (14.4)	113.0 (32.0, 230.0)	256.5 (32.0, 368.0)			0.45 (0.28, 0.72)	0.0008
MMF/MMF Placebo n=145; Belimumab n=145	33 (22.8)	21 (14.5)	113.0 (49.0, 217.0)	253.0 (70.0, 365.0)			0.55 (0.32, 0.96)	0.0359
CYC/AZA Placebo n=51; Belimumab n=49	18 (35.3)	7 (14.3)	96.0 (21.0, 230.0)	285.0 (31.0, 477.0)			0.30 (0.12, 0.75)	0.0101
Class III or IV Placebo n=116; Belimumab n=112	27 (23.3)	16 (14.3)	92.0 (33.0, 212.0)	261.0 (100.0, 329.0)			0.51 (0.27, 0.95)	0.0354
Class III+V or IV+V Placebo n=48; Belimumab n=52	13 (27.1)	7 (13.5)	86.0 (29.0, 217.0)	70.0 (29.0, 333.0)			0.43 (0.17, 1.13)	0.0884
Pure Class V Placebo n=32; Belimumab n=30	11 (34.4)	5 (16.7)	184.0 (32.0, 394.0)	365.0 (176.0, 394.0)			0.40 (0.14, 1.15)	0.0881

HR (95% CI) — 0.1   1   10

*Censored for treatment discontinuation or withdrawal not related to renal flare

IQR, interquartile range

Rovin BH, Houssiau F, Furie R, Malvar A, Teng YKO, Mok CC et al. *ASN Kidney Week Annual Meeting* October 22-25, 2020.

Two-Year Results from a Randomized, Controlled Study of Obinutuzumab for Proliferative Lupus Nephritis

Objectives

Two-year results from the NOBILITY trial are reported here.

Methods

Patients with class III/IV LN received MMF and steroids and were randomized to blinded obinutuzumab (OBI) or placebo (PBO) infusions on weeks 0, 2, 24, and 26. Patients were followed through week 104.
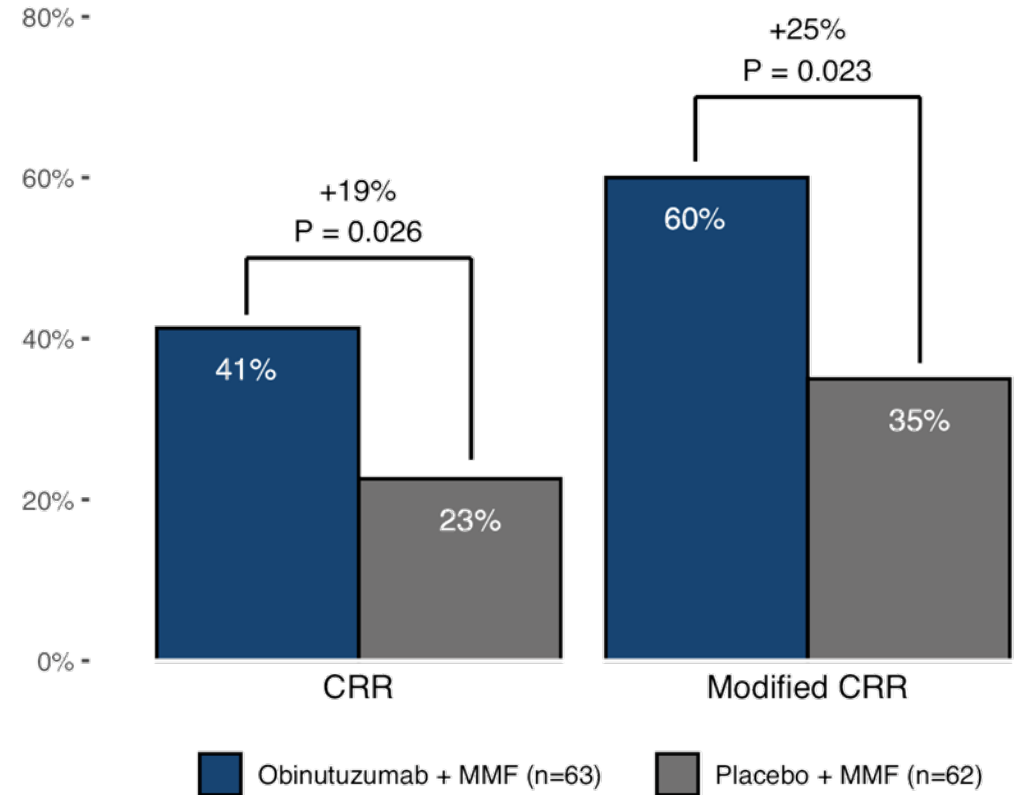
Key Results

- CRR was greater with OBI than PBO at week 52 (35% vs 23%, P=0.115), week 76 (40% vs 18%, P=0.007), and week 104 (41% vs 23%, P=0.026).
- At week 104, OBI patients had greater improvements in eGFR, UPCR, anti-dsDNA, C3, and C4.
- Serious adverse events (OBI 25% vs PBO 30%), serious infections (8% vs 18%) and deaths (1 vs 4) were not increased with OBI.

Conclusion

NOBILITY demonstrated a sustained benefit of OBI through week 104, 18 months after the last OBI treatment. There were no unexpected safety findings. OBI use in LN will be further evaluated in the Phase 3 REGENCY trial.

Furie R, et al., Abstract 0988

Renal Responses at Week 104

CRR: Obinutuzumab + MMF 41%, Placebo + MMF 23% (+19%, P = 0.026)
Modified CRR: Obinutuzumab + MMF 60%, Placebo + MMF 35% (+25%, P = 0.023)

Obinutuzumab + MMF (n=63) | Placebo + MMF (n=62)

CRR: UPCR < 0.5, SCr ≤ ULN and ≤ 115% of baseline, and inactive urinary sediment

Modified CRR: UPCR < 0.5 and SCr ≤ ULN

AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

AURORA: Phase 3 Voclosporin Trial
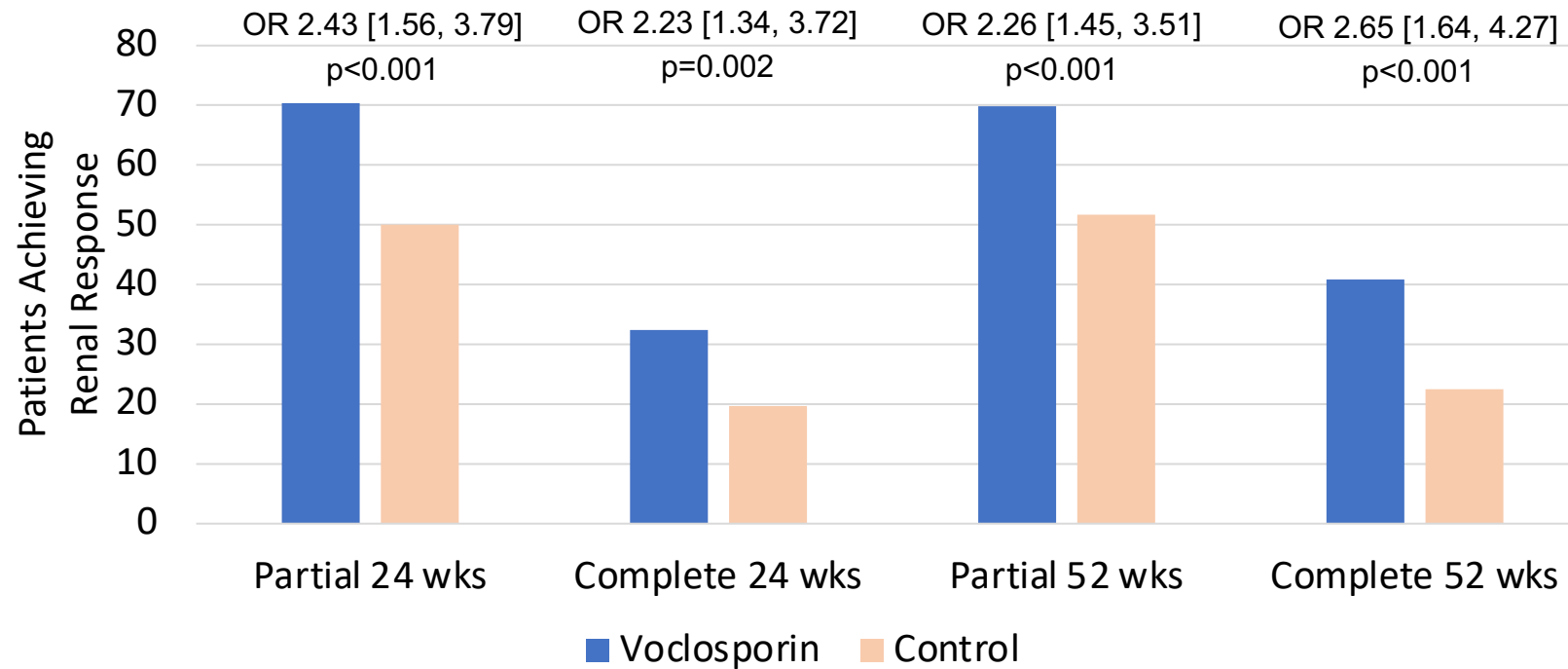
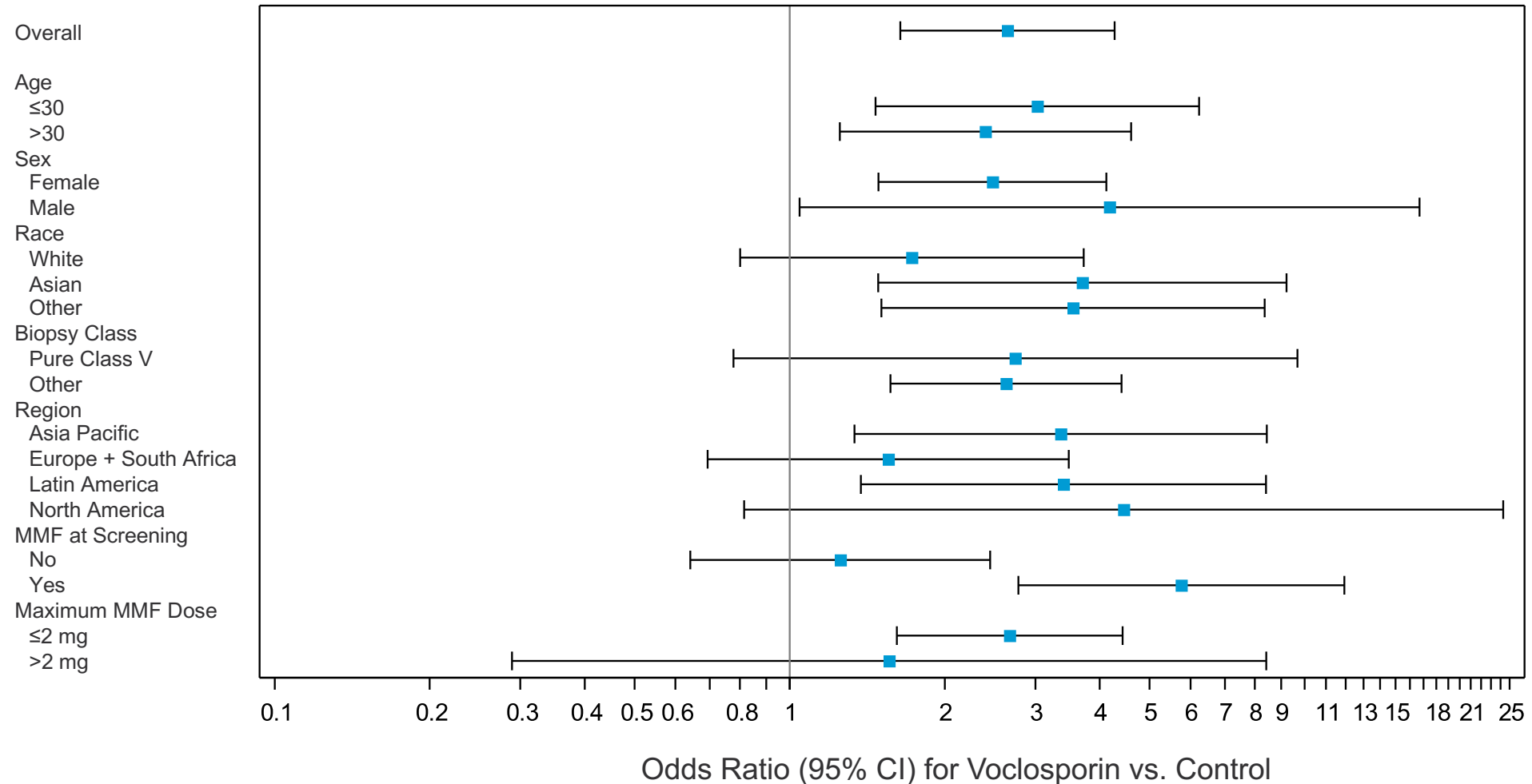| Measure	Result	Hazard Ratio [95% CI]	p-value
Time to UPCR ≤0.5	Voclosporin faster than Control	2.02 [1.51, 2.70]	p<0.001
Time to 50% reduction in UPCR	Voclosporin faster than Control	2.05 [1.62, 2.60]	p<0.001

AURORA Efficacy Benefit Seen Across Subgroups

Forest Plot of Odds Ratio for Renal Response at Week 52

Odds Ratio (95% CI) for Voclosporin vs. Control

AURORA Renal Response by Race

	Asian (n=109)	White (n=129)	Black (n=45)	Mixed* (n=74)
p-value	p = 0.005	p = 0.165	p = 0.045	p = 0.054
Control	17.9% (10, n=56)	29.5% (18, n=61)	15.8% (3, n=19)	21.4% (9, n=42)
Voclosporin	41.5% (22, n=53)	38.2% (26, n=68)	46.2% (12, n=26)	40.6% (13, n=32)

■ Control   ■ Voclosporin
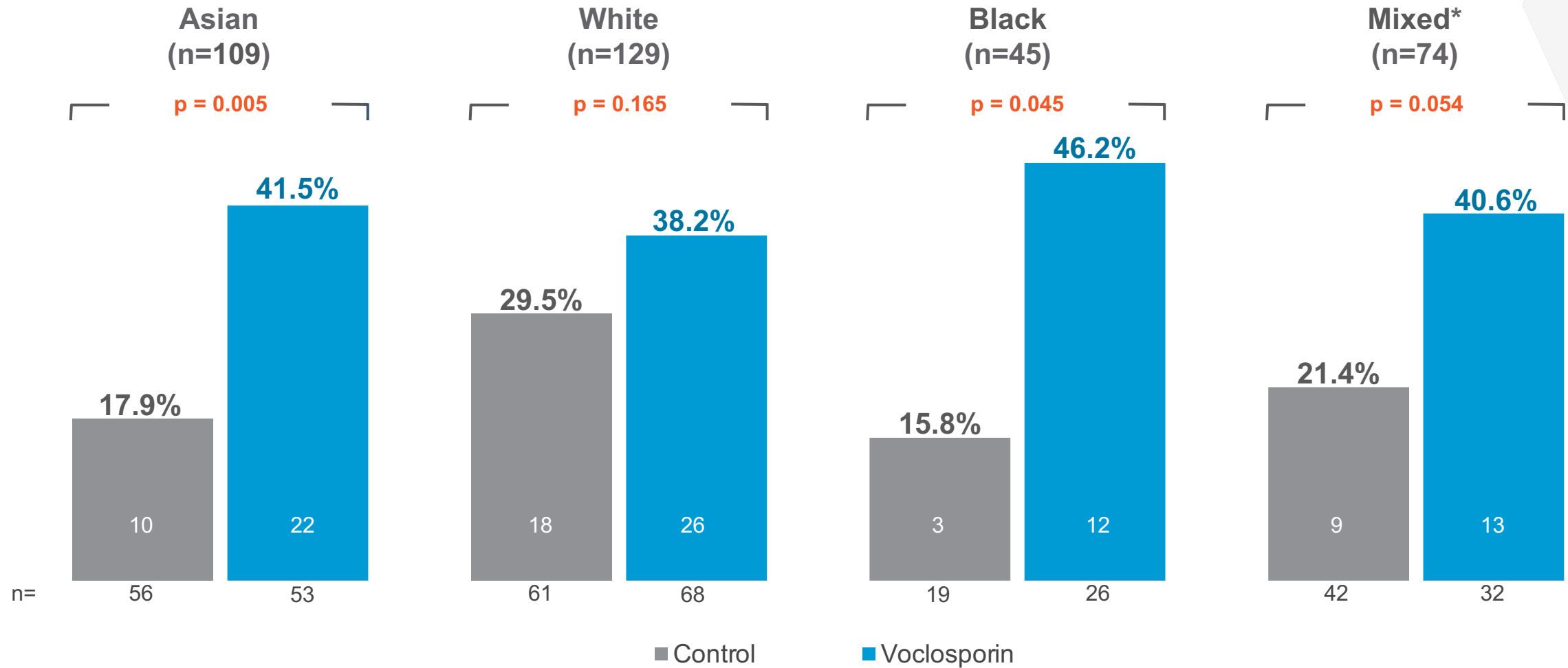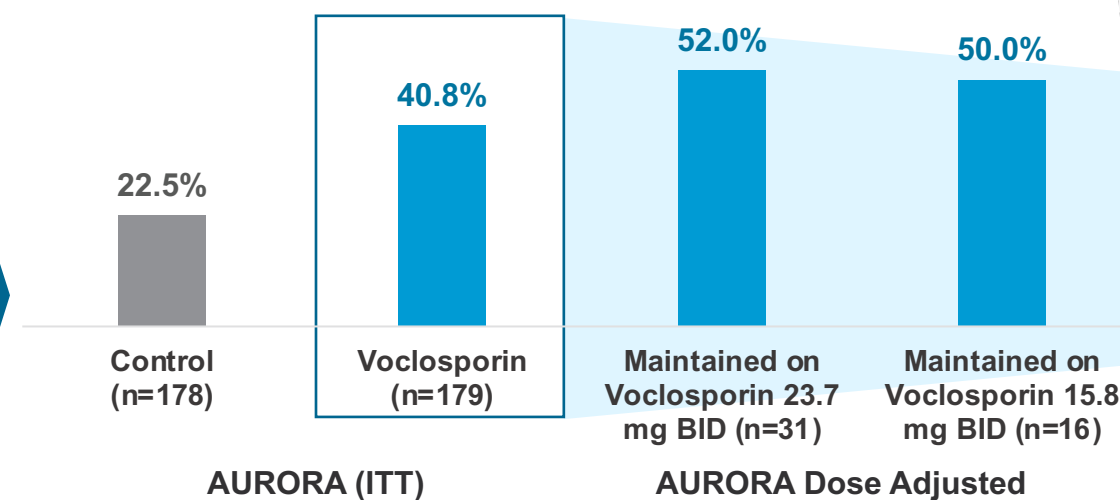
* Mestizo, Mulato, Other

Aurinia™

eGFR-Based Flat-Dosing Algorithm used in Clinical Trials

- Dose adjustments (interruption, reduction and re-escalation) were implemented according to protocol guidance after excluding potential contributing factors

Voclosporin Dose Adjustments Based on eGFR

| Confirmed eGFR Decrease From Baseline	Dosing Recommendation
≥30%*	• Stop administration of voclosporin • Restart voclosporin upon eGFR recovery at a lower dose and increase dose as tolerated based on renal function
>20% and <30%*	• Repeat eGFR within 2 weeks and reduce dose by 7.9-15.8 mg BID[†]
≤20%	• Maintain voclosporin dose and monitor renal function

Renal Response at Week 52

Control (n=178): 22.5%
Voclosporin (n=179): 40.8%
Maintained on Voclosporin 23.7 mg BID (n=31): 52.0%
Maintained on Voclosporin 15.8 mg BID (n=16): 50.0%

AURORA (ITT)   AURORA Dose Adjusted

*Accompanied by eGFR <60ml/min/1.72m^2
[†]After consultation with medical monitor to discuss if medically appropriate and confirmation that change in eGFR is not due to potential contributing factors (e.g. NSAID use, dehydration, lupus flare).
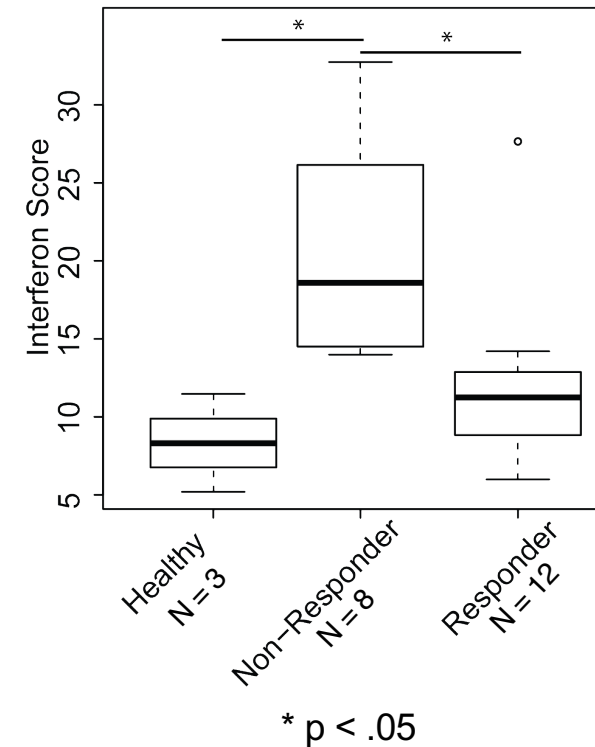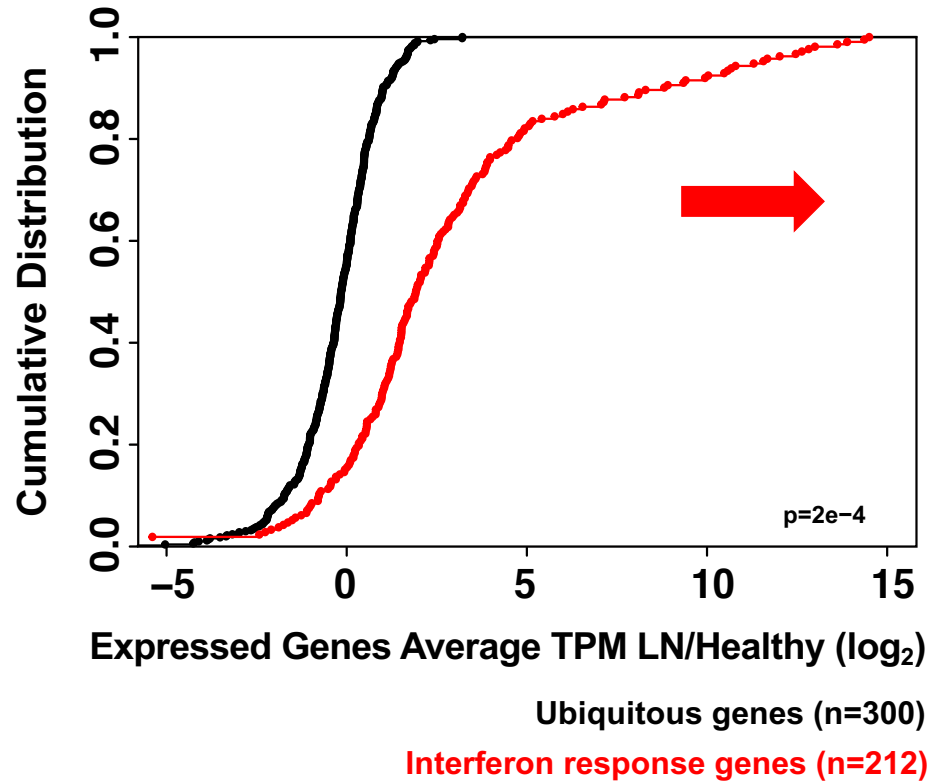
Aurinia™

CD19-Targeted CAR T Cells In Refractory SLE
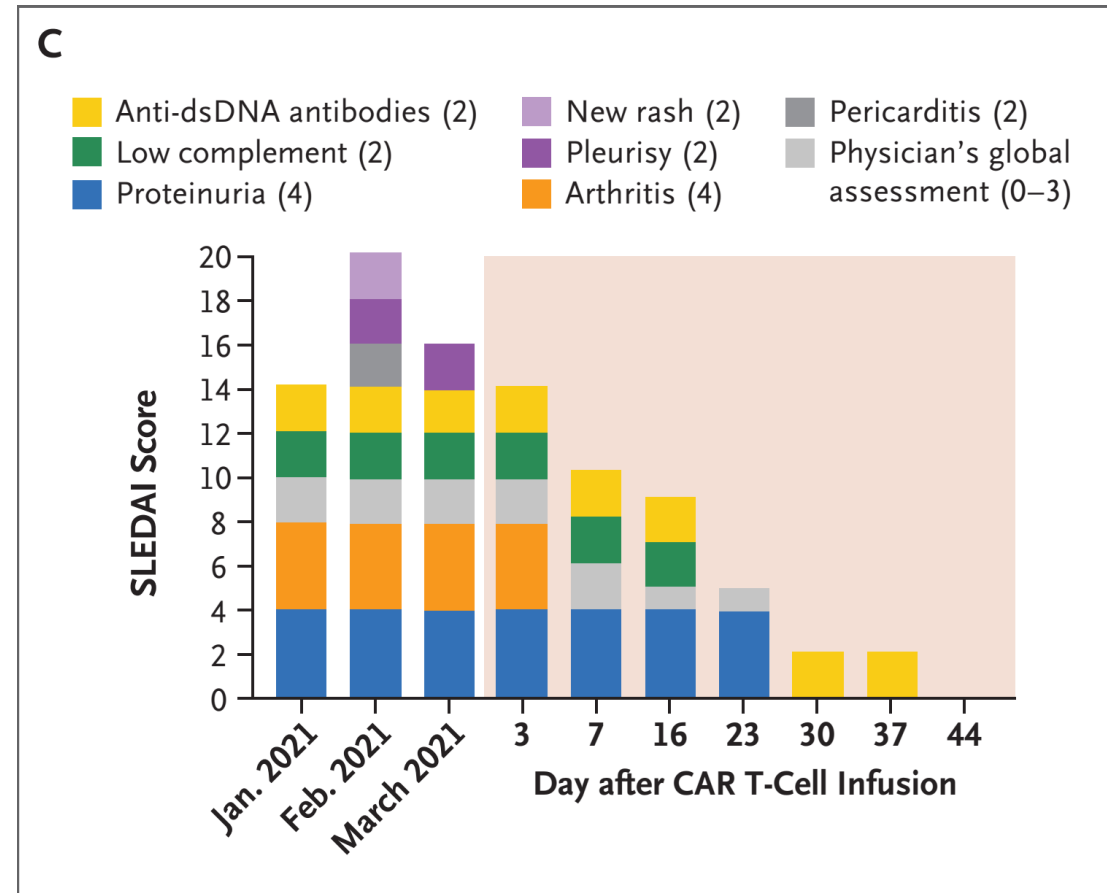
New Insights in Basic Science

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

Ubiquitous genes (n=300)

Interferon response genes (n=212)

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

Randomized, Controlled, Phase 2 Trial of Type 1 IFN Inhibitor Anifrolumab in Patients with Active Proliferative Lupus Nephritis

Anifrolumab Basic Regimen (n=45)	**Anifrolumab** Intensified Regimen (n=51)	vs.	**Placebo** (n=49)
31.0%			31.1%

BUT

Anifrolumab Intensified Regimen	vs.	**Placebo**
45.5%		31.1%

Jayne D, et al. *Ann Rheum Dis*. 2021;80(suppl. 1):592.

# Non-responders Exhibit Upregulation of Fibrotic Pathways in Tubular Cells
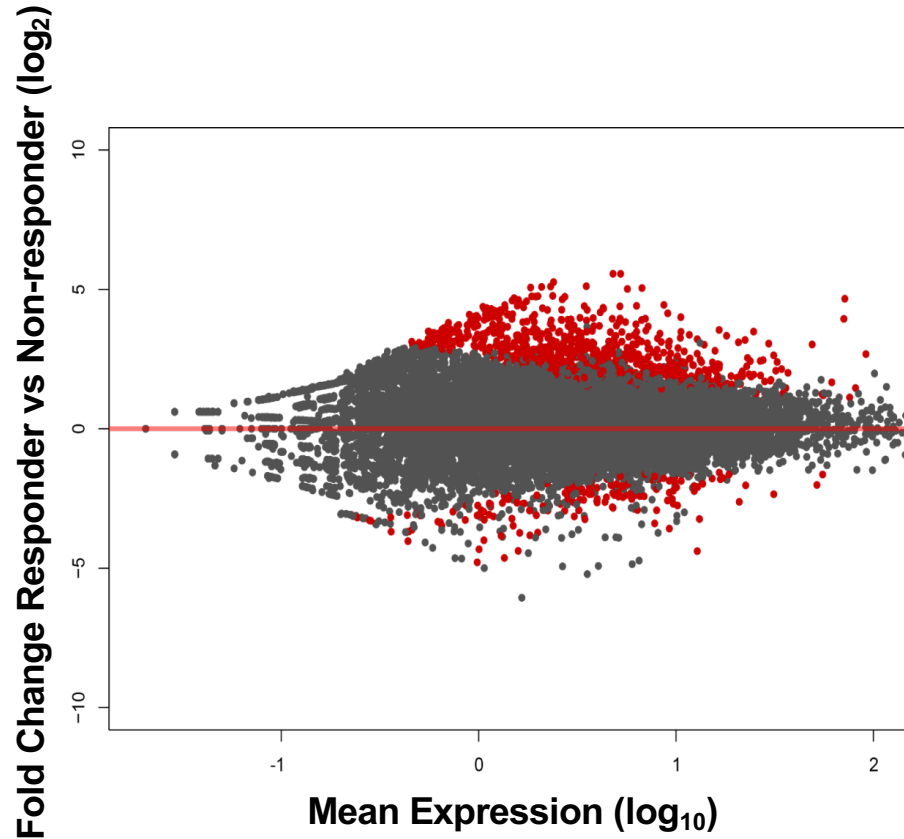
Upregulated pathways in non-responders

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.

Microbiome

		Healthy	SLE low	SLE high	P value
Family	Veillonellaceae	1.68%	3.41%	12.27%	0.009
Family	Ruminococcaceae	26.51%	11.68%	15.11%	0.019
Genus	Lachnospira	1.19%	0.25%	0.62%	0.045
Genus	Faecalibacterium	1.08%	0.65%	0.53%	0.026
G		0.64%	1.76%	3.15%	0.013
Species	Faecalibacterium prausnitzii	1.07%	0.64%	0.52%	0.022
Species	Bacteroides uniformis	1.95%	0.87%	0.35%	0.016
Species	Lachnospiraceae Sp.	0.23%	1.19%	2.11%	0.006

High disease activity associated with greater *Lachnospiraceae* outgrowths

Silverman GJ, et al. *Arthritis Rheumatol*. 2017; 69 (suppl 10):abstract 1786.

Serum IgG Anti-Lachnospiraceae Species Levels Identify Lupus Nephritis in Three Independent Cohorts
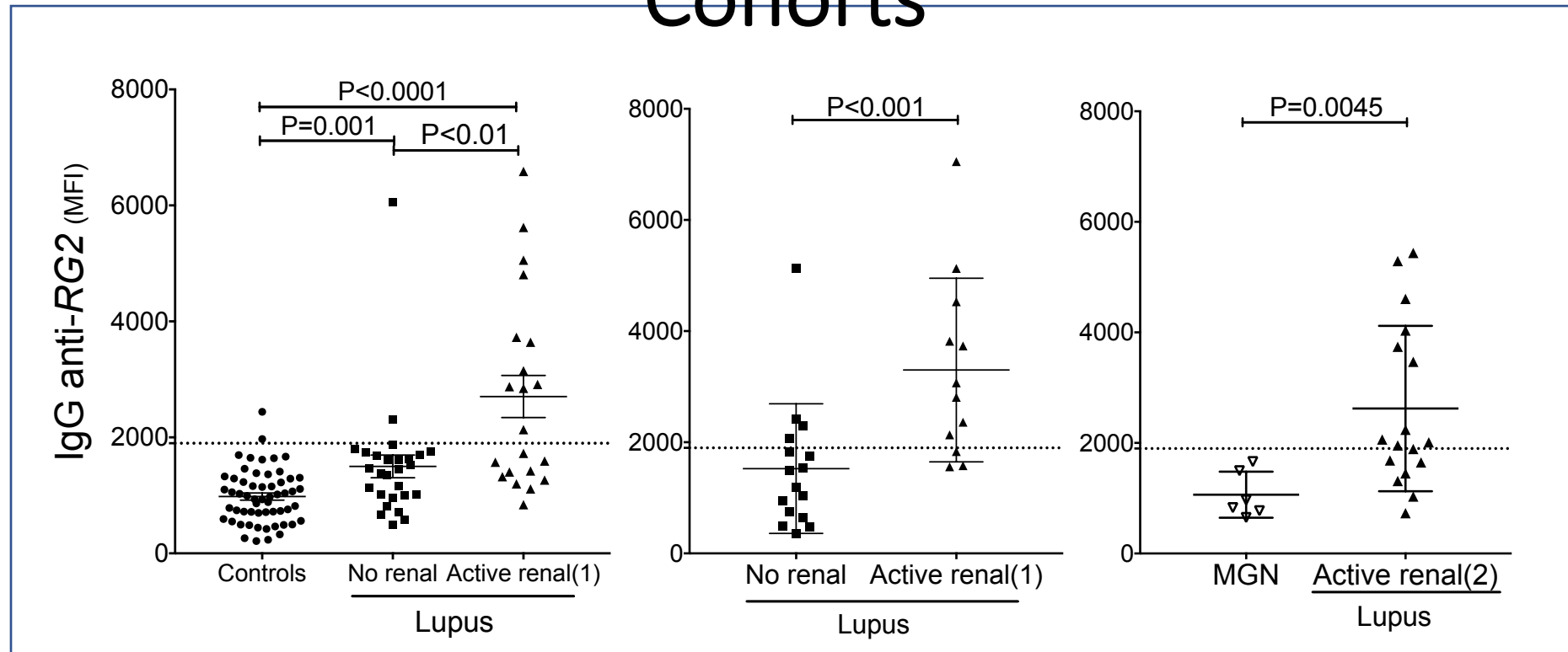
1   Serum laboratory criteria
2   Renal biopsy –WHO criteria

MGN- primary membranous glomerulonephritis

Silverman GJ, et al. *Arthritis Rheumatol*. 2017; 69 (suppl 10):abstract 1786.

El Greco – *St. Sebastian* (Prado)