LUPUS MANAGEMENT AND TRIALS

Will Pendergraft, M.D., Ph.D.

UNC KIDNEY CENTER

OUR PLAN…

1. Discuss current state of affairs with management of lupus nephritis, including resistant disease
2. Describe the current state of biologics in lupus nephritis
3. Highlight hot topics in the field of lupus nephritis
4. Review active lupus nephritis clinical trials at UNC
5. Suggest potential window into the future

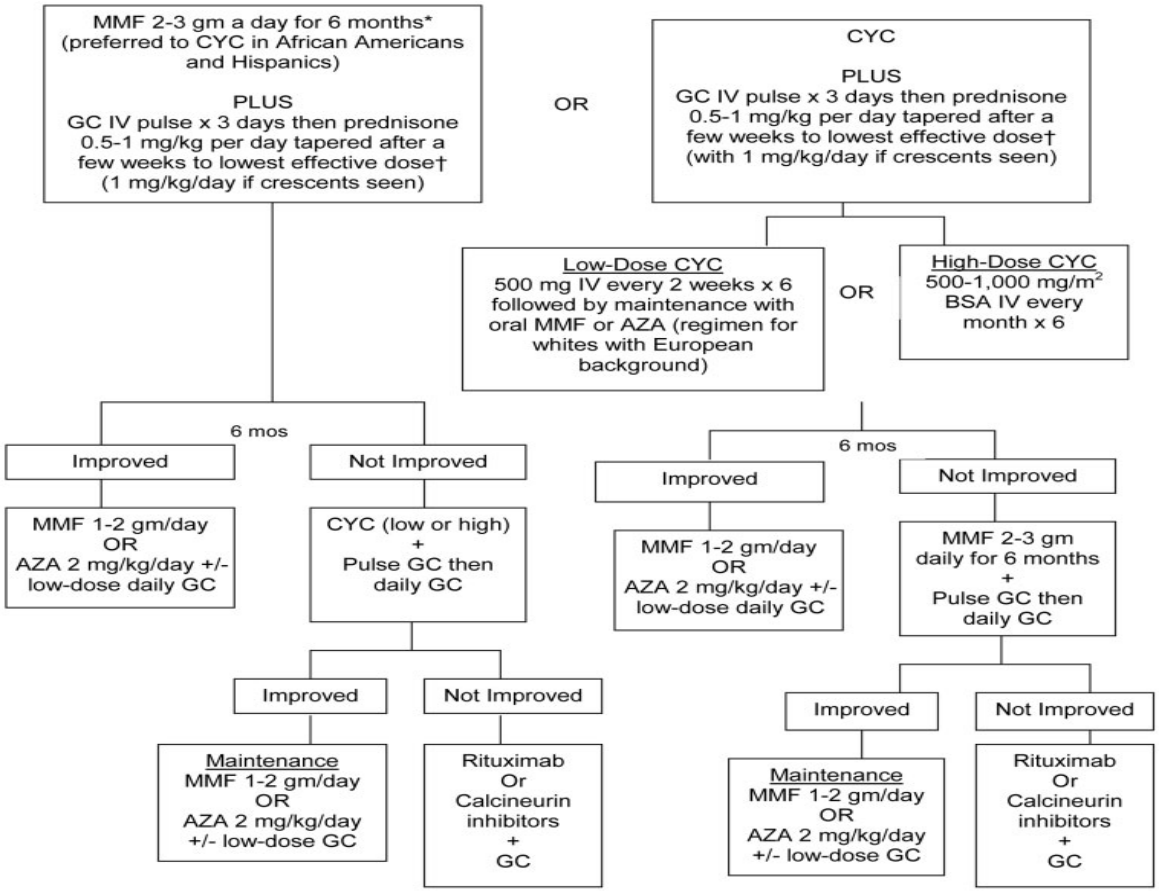
“Lupa Stella”

32♀ with newly-diagnosed class IV-G/A lupus nephritis

Past Medical History: none

Social History: professional athlete

Lupus Nephritis: Induction Therapy



Hahn, et al. ACR guidelines for screening, treatment and management of lupus nephritis. AC&R 64(6): 797-808, 2012

“Lupa Stella”

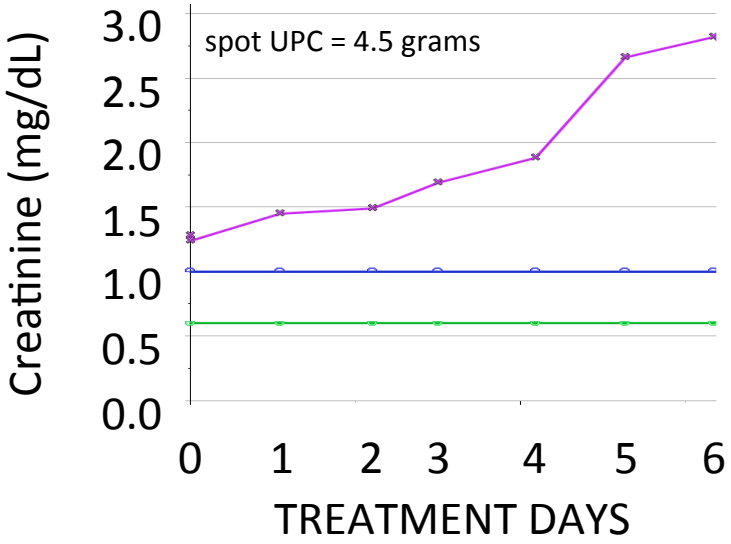
32♀ with newly-diagnosed class IV-G/A lupus nephritis

Past Medical History: none

Social History: professional athlete

Remission Induction Treatment Regimen:
Methylprednisolone 7 mg/kg IV QD x 3 doses
Prednisone 60 mg PO daily
Cyclophosphamide 500 mg IV Q2weeks x 6 doses
Hydroxychloroquine 200 mg PO BID

“Lupa Stella”



WHY ISN’T SHE IMPROVING?

WHAT DO WE DO?

Issues to consider with resistant disease

1. Review the native kidney biopsy in detail (ATN, IFTA, TMA).
2. Consider re-biopsy.
3. Consider the patient and his/her ability to adhere to regimen.
4. Consider other factors (co-infections, other meds, other organs).

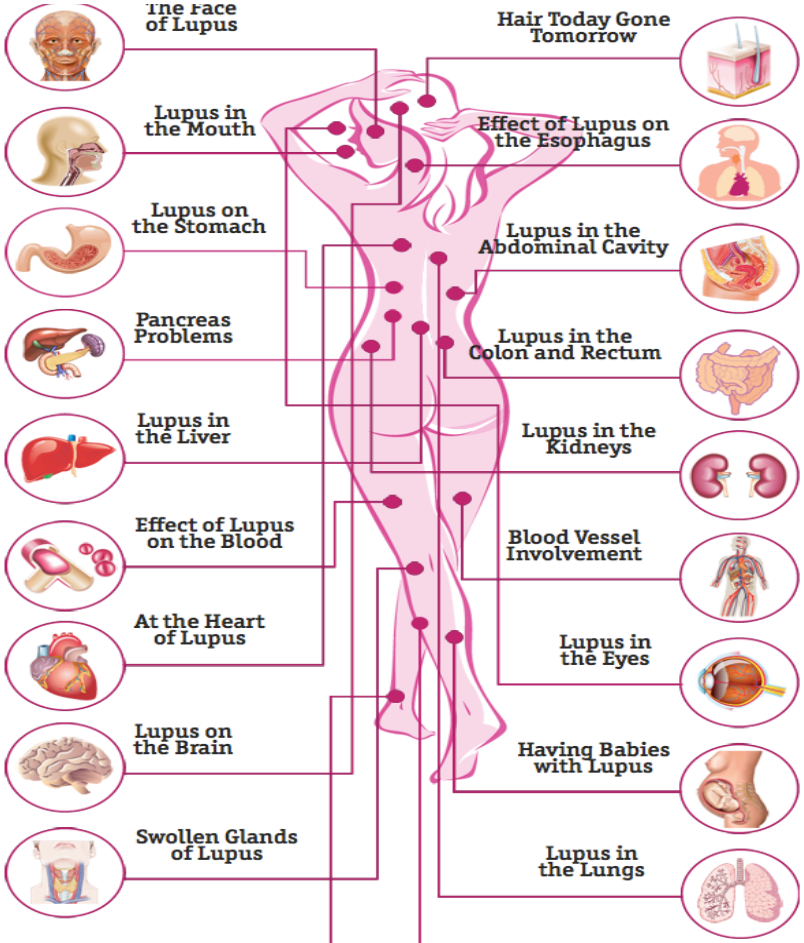
Lupus nephritis is already resistant to current remission induction therapies

This begs the question…

How can we treat resistant lupus nephritis if we are already poor at treating garden variety lupus nephritis?

What makes lupus nephritis resistant?

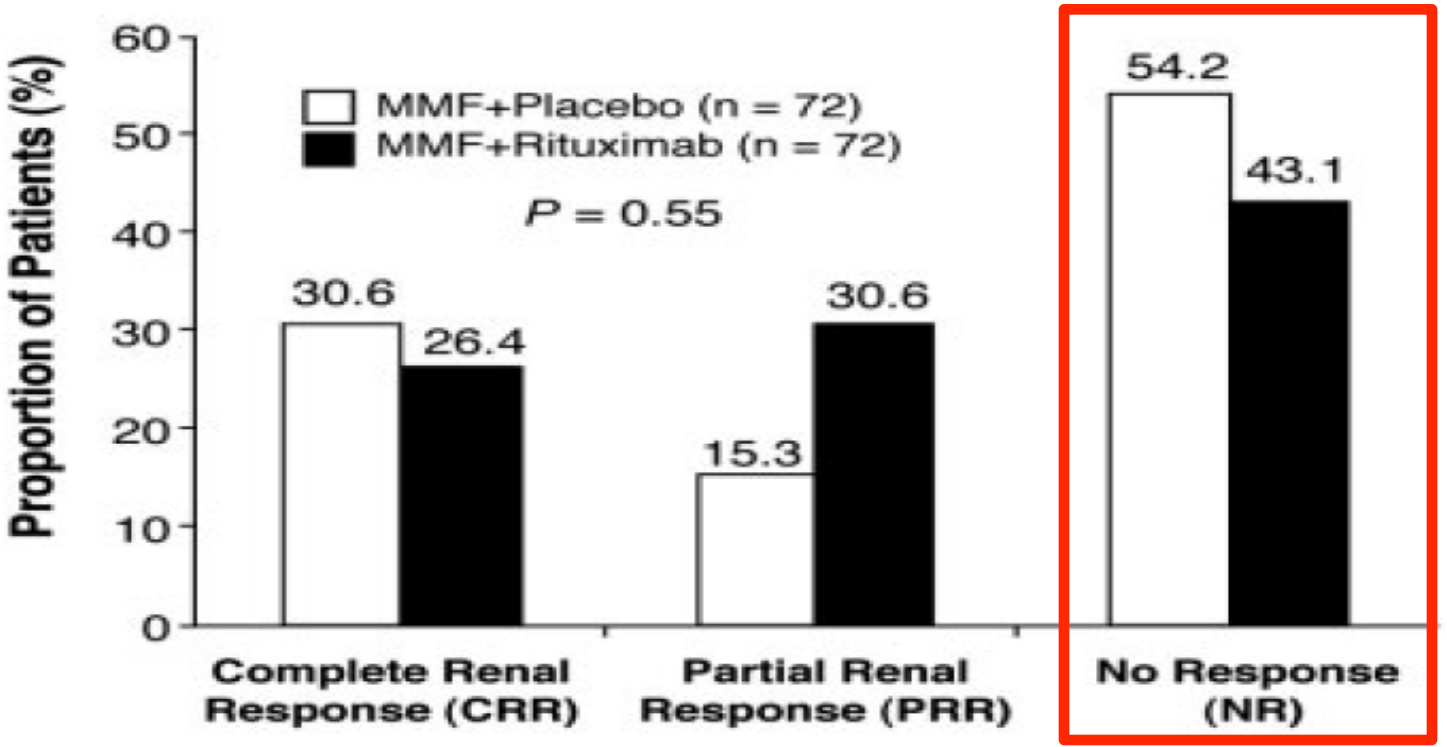
Lupus is a complex disease with a vast phenotypic spectrum



LACK OF DURABLE REMISSION IS MADDENING

Efficacy and Safety of Rituximab in Patients With Active Proliferative Lupus Nephritis

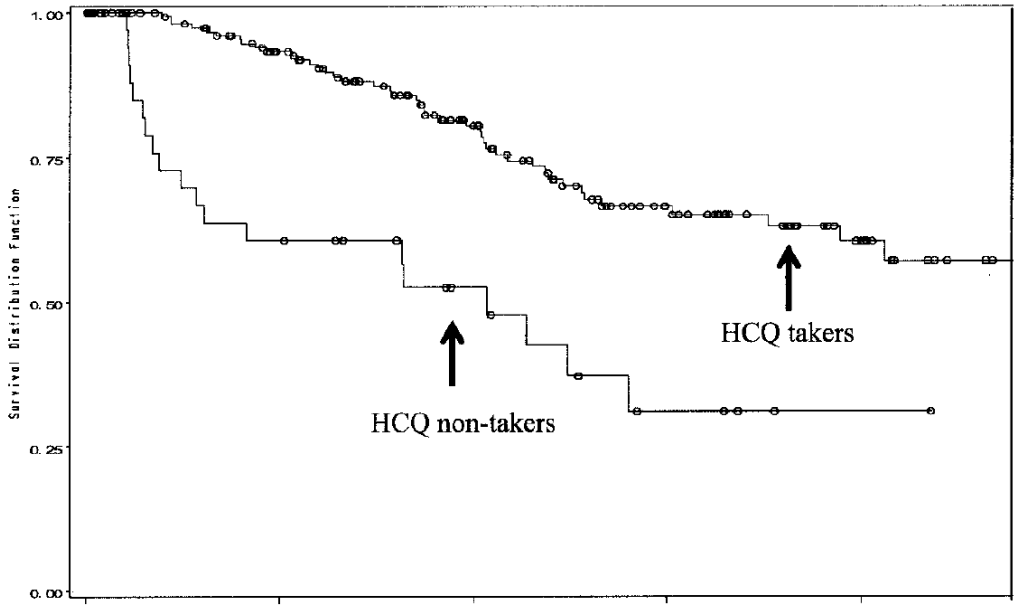
The Lupus Nephritis Assessment With Rituximab Study



Rovin and colleagues, Arthritis Rheum 64(4): 1215-26, April 2012

The ability to adhere to a plan may be difficult for some.

% renal happiness = % lacking renal damage

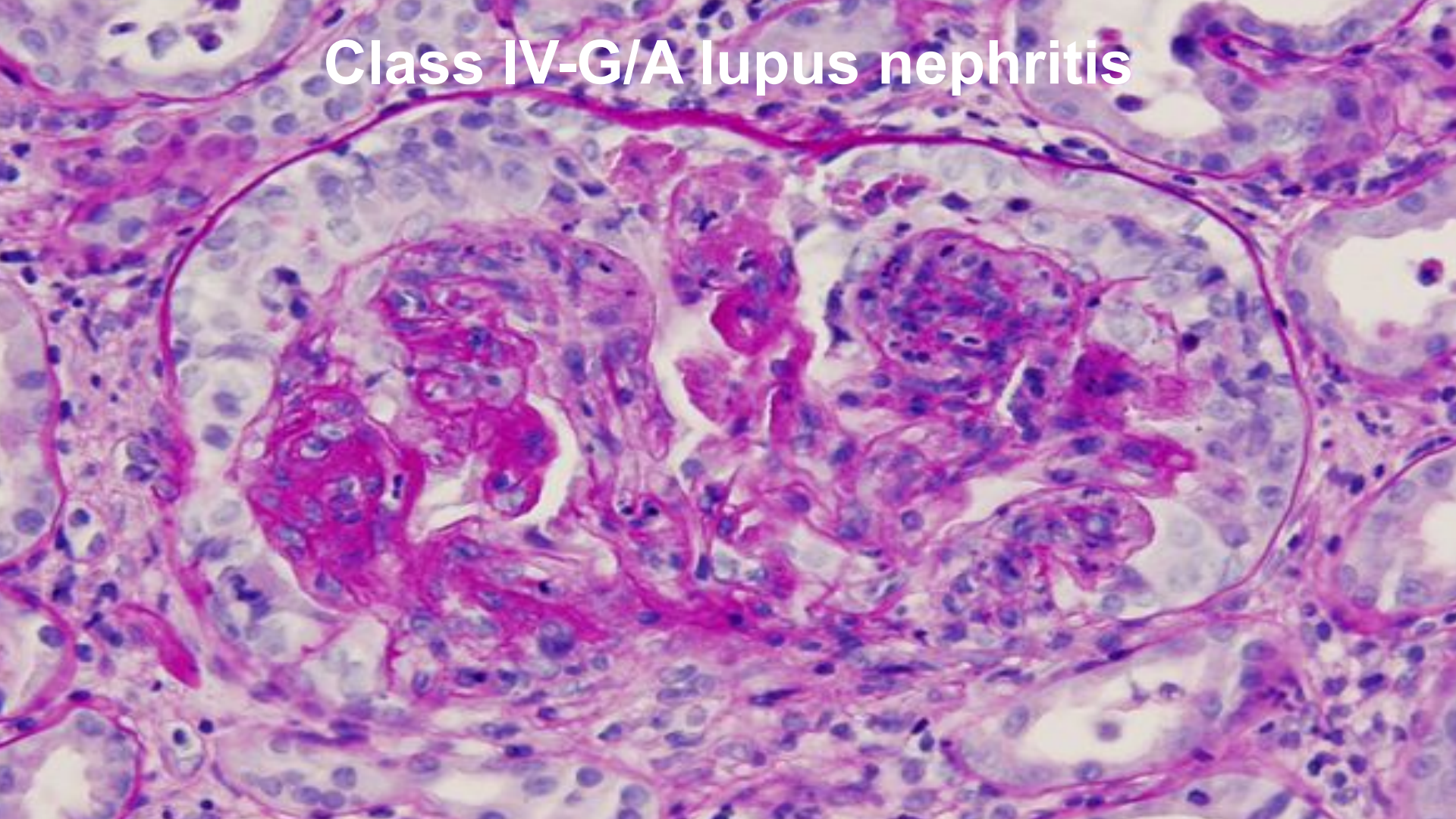


Time (years)	0	2.5	5	7.5	10
Hydroxychloroquine (HCQ) takers	161	131	83	45	20
Hydroxychloroquine non-takers	42	20	11	4	1

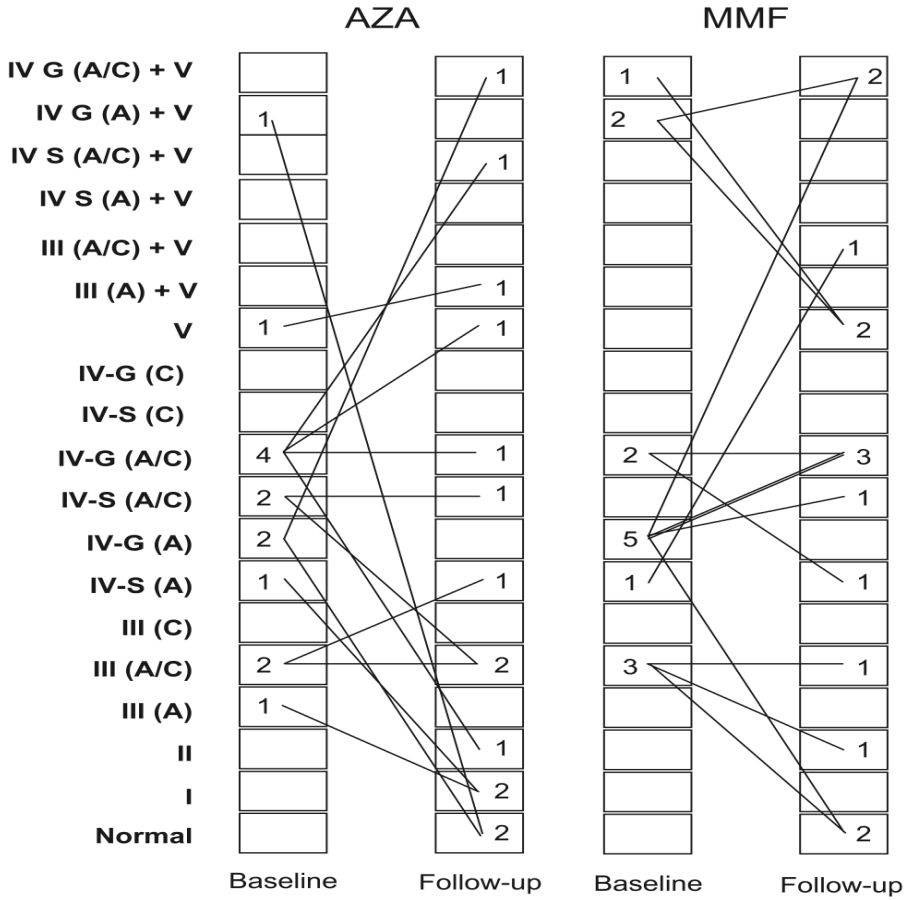
Pons-Estel and colleagues for Nature vs Nurture Study, Arthritis Rheum 61(6): 830-9, June 2009

Clinical versus histologic remission remains a problem

Class IV-G/A lupus nephritis



REPEAT BIOPSY EXPERIENCE IN MAINTAIN TRIAL

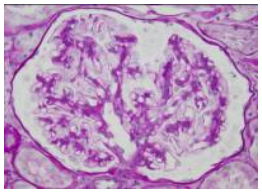


n = 30 patients
no difference

Stoenoiu and colleagues. *NDT* 27: 1924-1930, 2012

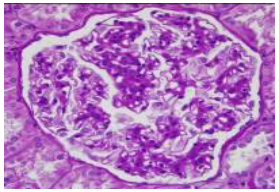
VARIABLE LANDSCAPE OF LUPUS NEPHRITIS OVER TIME

I



Histologically Normal Glomeruli

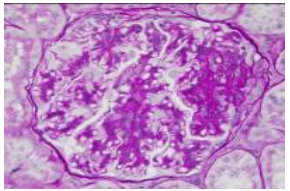
II

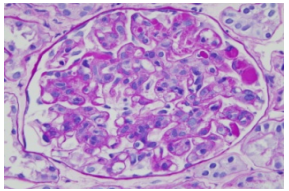


Focal or Diffuse Mesangioproliferative Glomerulonephritis

III

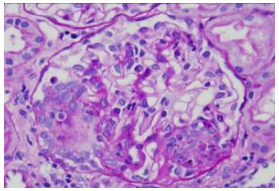
A A/C





IVG

Focal or Diffuse Proliferative or Necrotizing Glomerulonephritis

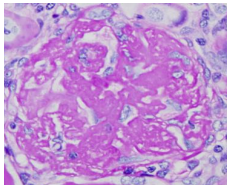


IVS

III C

IV C

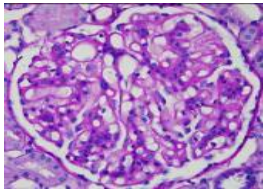
VI



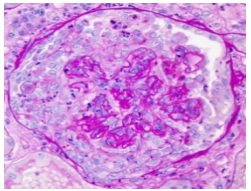
Focal or Diffuse Sclerosing Glomerulonephritis

V

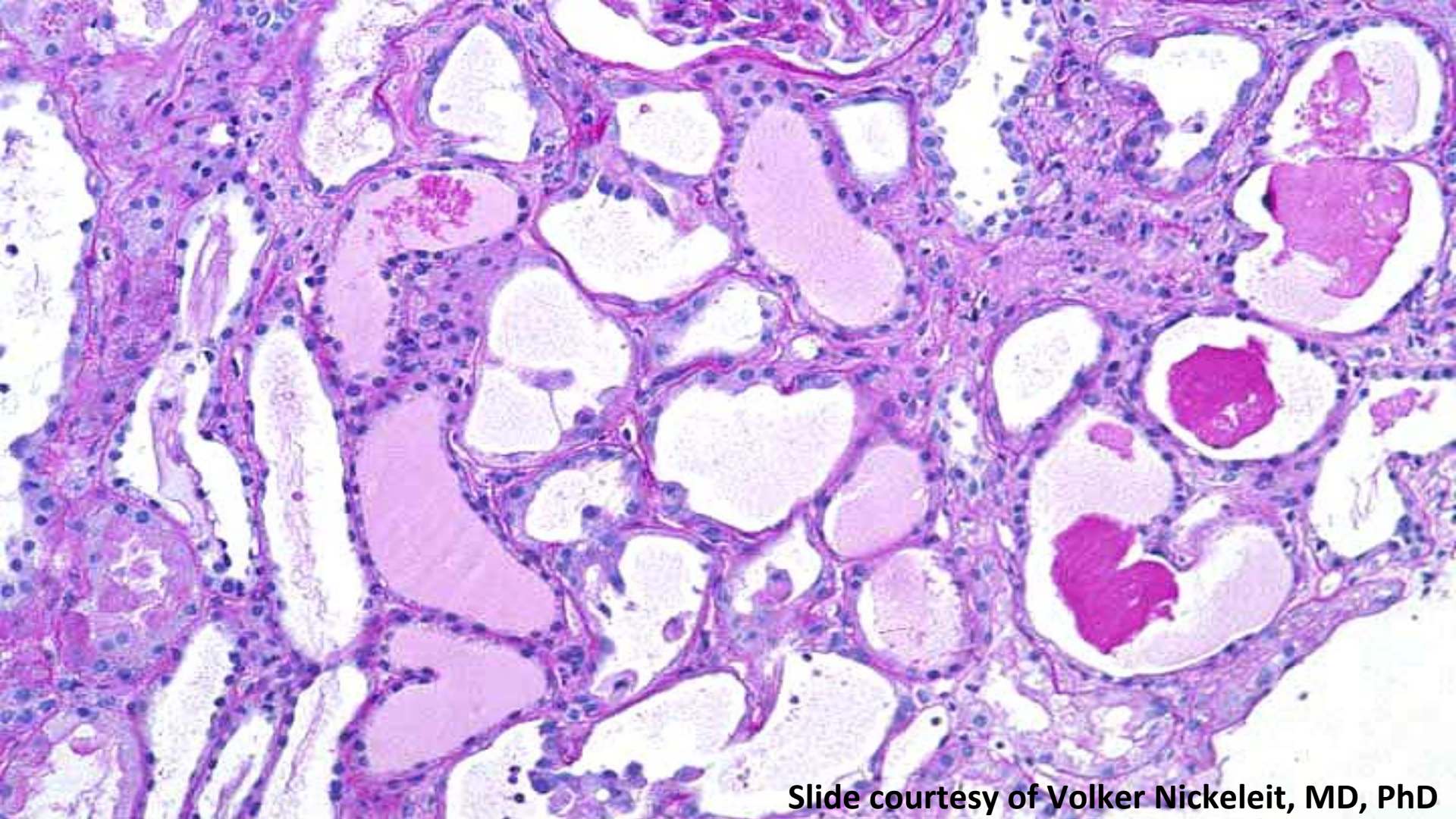
Membranous Glomerulonephritis



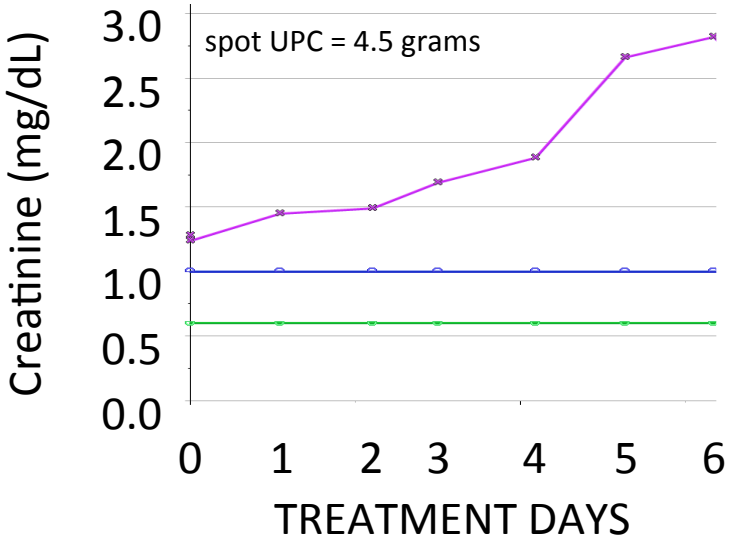
Crescentic Glomerulonephritis



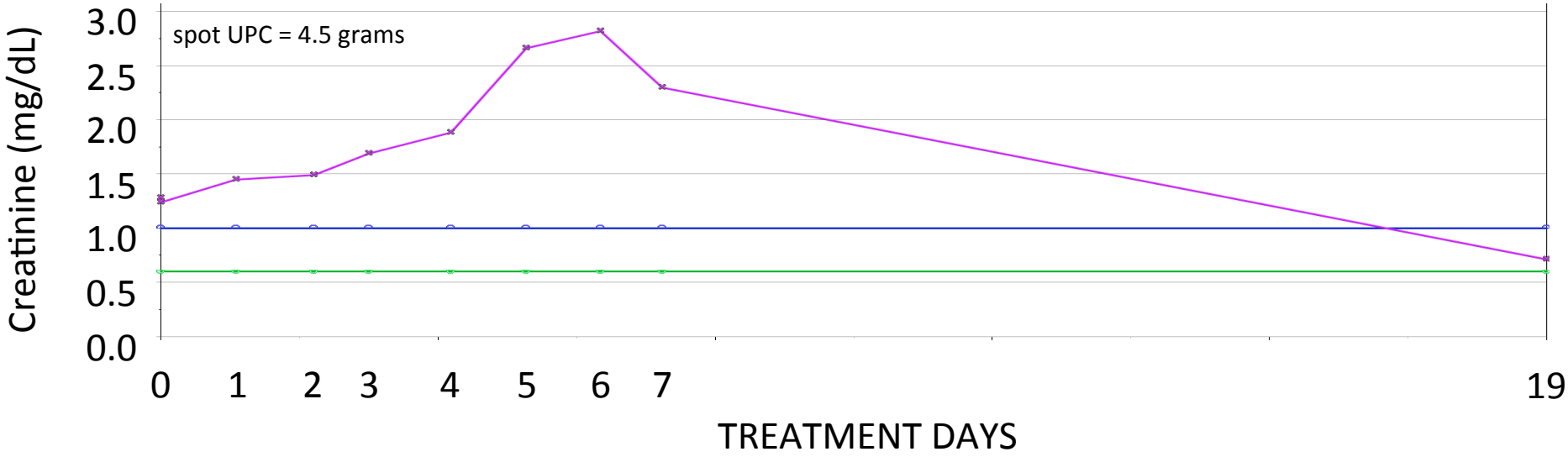
Now back to the patient…


Slide courtesy of Volker Nickeleit, MD, PhD

“Lupa Stella”


spot UPC = 4.5 grams
Creatinine (mg/dL)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
1
2
3
4
5
6
TREATMENT DAYS

“Lupa Stella”


spot UPC = 4.5 grams
Creatinine (mg/dL)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
1
2
3
4
5
6
7
19
TREATMENT DAYS

OUR PLAN…

1. Discuss current state of affairs with management of lupus nephritis, including resistant disease
2. **Describe the current state of biologics in lupus nephritis**
3. Highlight hot topics in the field of lupus nephritis
4. Review active lupus nephritis clinical trials at UNC
5. Suggest potential window into the future

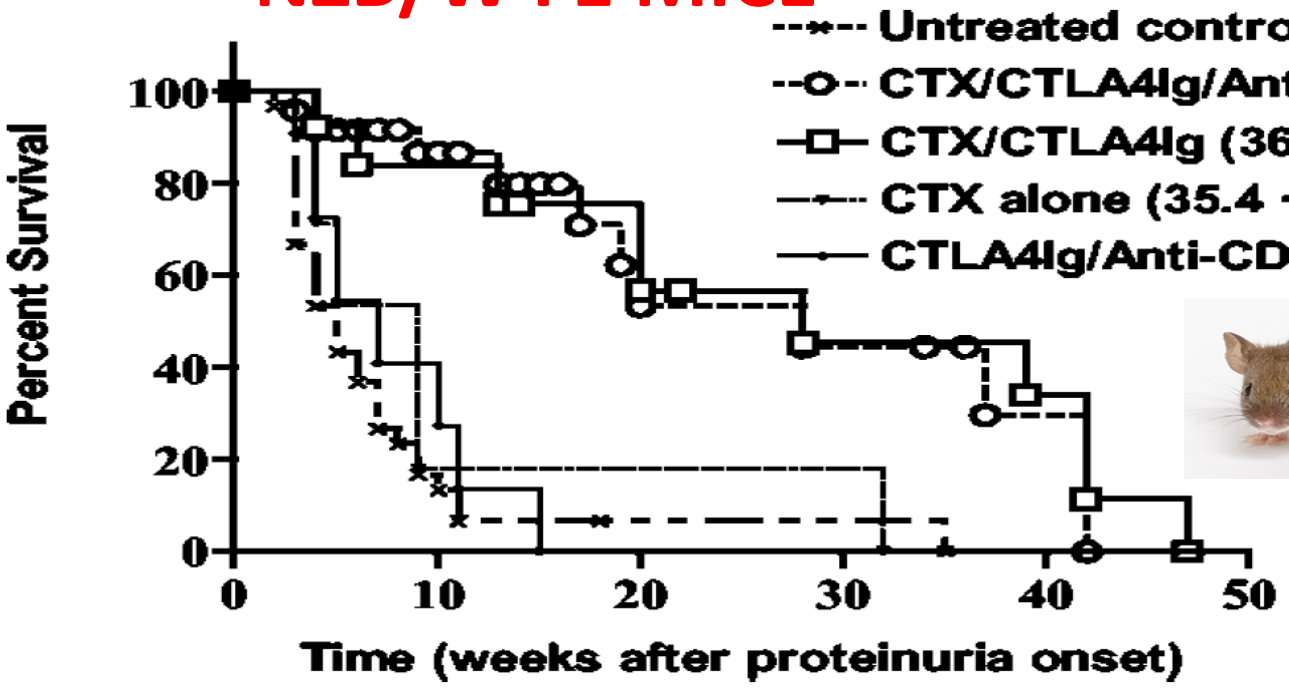
The Biologic Clinical Trial Landscape Has Been Bleak…

Drug	Class	Target	Clinical Trial Status
Abatacept-BMS	CTLA4-Ig	CTLA4-B7	Phase 2/3-FAILED
Abatacept-ACCESS	CTLA4-Ig	CTLA4-B7	Phase 2-FAILED
Laquinamod	Small Molecule	Inflammation	Phase 2-ENCOURAGING *but* Development Discontinued
Rituximab	Monoclonal Antibody	CD20	Phase 3-FAILED
Sirukumab	Monoclonal Antibody	IL-6	Phase 2-FAILED
Bortezomib	Proteasome Inhibitor	Plasma Cells	Phase 4-STOPPED
Anti-CD40 Ligand	Monoclonal Antibody	CD40 Ligand	Phase 2-STOPPED
Tabalumab	Monoclonal Antibody	BLyS	Phase 3-FAILED
Anti-TWEAK	Monoclonal Antibody	TWEAK	Phase 2-FAILED

SLIDE COURTESY OF BRAD ROVIN

Mice with lupus nephritis are not humans with lupus nephritis

NZB/W F1 MICE



ACCESS TRIAL RESPONSE RATES

Treatment of Lupus Nephritis With Abatacept

The Abatacept and Cyclophosphamide Combination Efficacy and Safety Study

The ACCESS Trial Group

Patients
n = 134

African Americans
n = 52 (39%)

Background therapy:
Euro-Lupus CYC
500 mg IV Q2 weeks
- 6 doses total

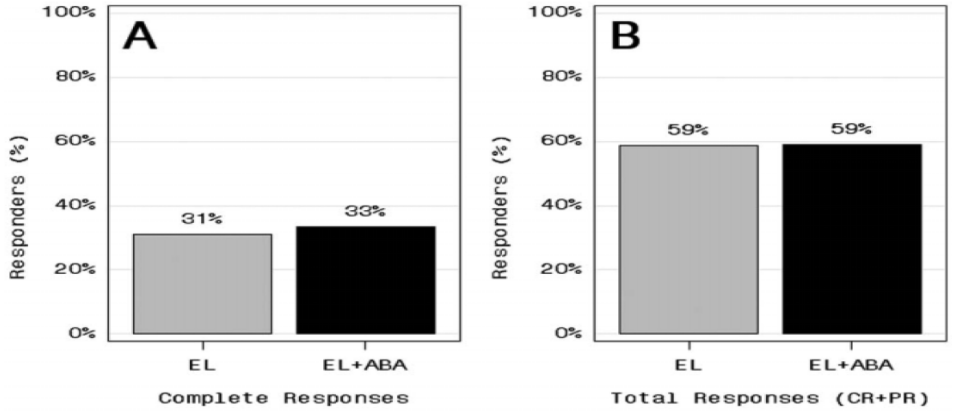
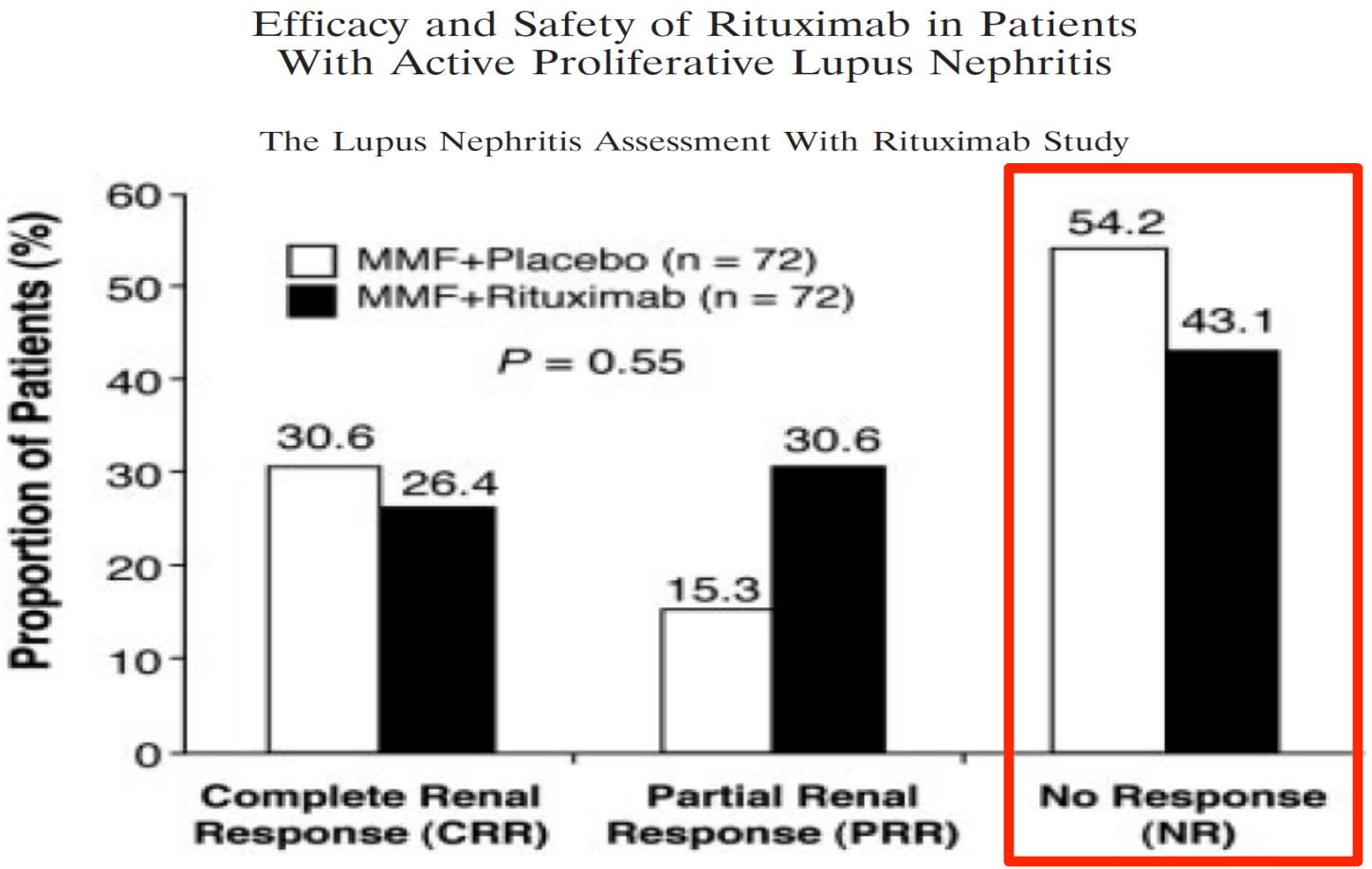


Figure 2. Complete response (CR) rate (**A**) and total response rate (complete responses plus partial responses [PR]) (**B**) at week 24 among control subjects treated with either the Euro-Lupus (EL) Nephritis Trial regimen or the Euro-Lupus Nephritis Trial regimen plus abatacpet (EL + ABA).

UNC KIDNEY CENTER

ARTHRITIS & RHEUMATOLOGY
Vol. 66, No. 11, November 2014, pp 3096–3104

Maybe our biologics are not getting to the tissue?



Rovin and colleagues, Arthritis Rheum 64(4): 1215-26, April 2012

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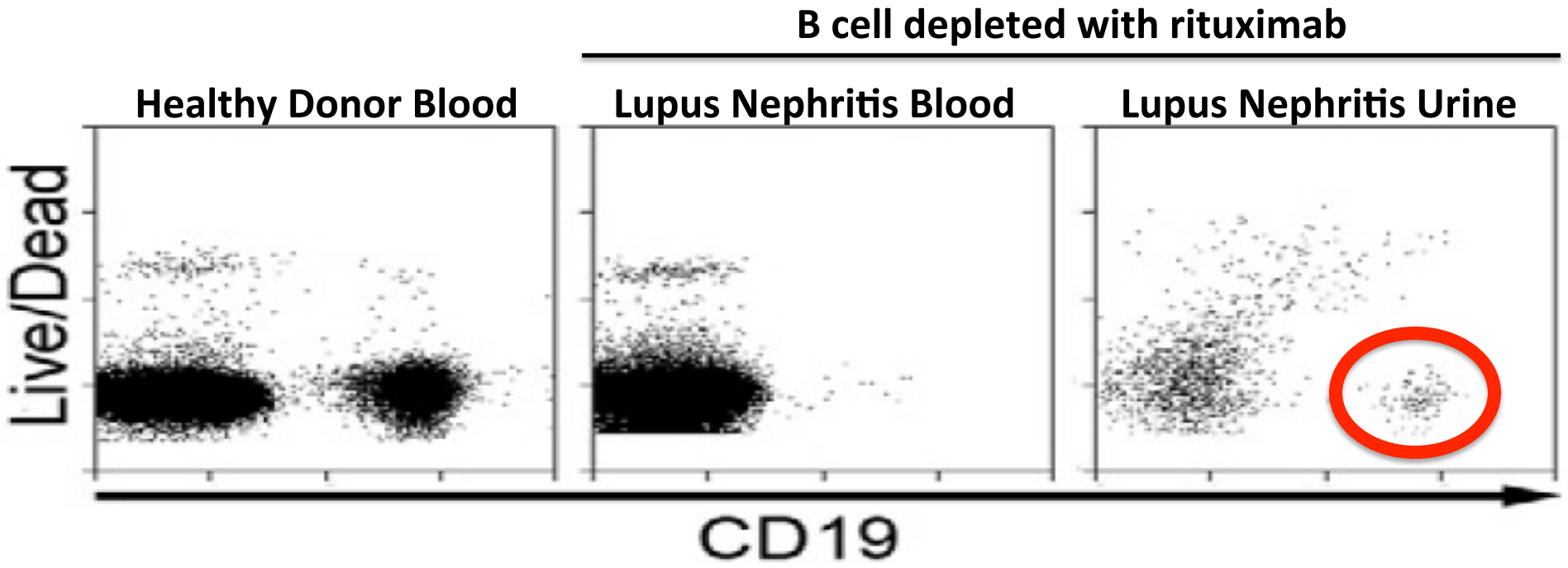


Scott and colleagues, Clin Immunol 168: 16-24, July 2016

CONSIDER BIOLOGICS THAT HAVE NOT BEEN CONSIDERED

Daratumumab (HuMax®-CD38)

Daratumumab is a human IgG1k monoclonal antibody (mAb) that binds with high affinity to the CD38 molecule, which is highly expressed on the surface of multiple myeloma cells. It is believed to induce rapid tumor cell death through programmed cell death, or apoptosis, and multiple immune-mediated mechanisms, including complement-dependent cytotoxicity, antibody-dependent cellular phagocytosis and antibody-dependent cellular cytotoxicity.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma

Meletios A. Dimopoulos, M.D., Albert Oriol, M.D., Hareth Nahi, M.D., Jesus San-Miguel, M.D., Nizar J. Bahlis, M.D., Saad Z. Usmani, M.D., Neil Rabin, M.B., B.S., Ph.D., Robert Z. Orlowski, M.D., Mieczyslaw Komarnicki, M.D., Kenshi Suzuki, M.D., Torben Plesner, M.D., Sung-Soo Yoon, M.D., Dina Ben Yehuda, M.D., Paul G. Richardson, M.D., Hartmut Goldschmidt, M.D., Donna Reece, M.D., Steen Lisby, M.D., Nushmia Z. Khokhar, M.D., Lisa O'Rourke, M.S.N., Christopher Chiu, Ph.D., Xiang Qin, M.S., Mary Guckert, M.S.N., Tahamtan Ahmadi, M.D., and Philippe Moreau, M.D., for the POLLUX Investigators*

N Engl J Med 2016; 375:1319-1331 | October 6, 2016 | DOI: 10.1056/NEJMoa1607751

HOT TOPICS

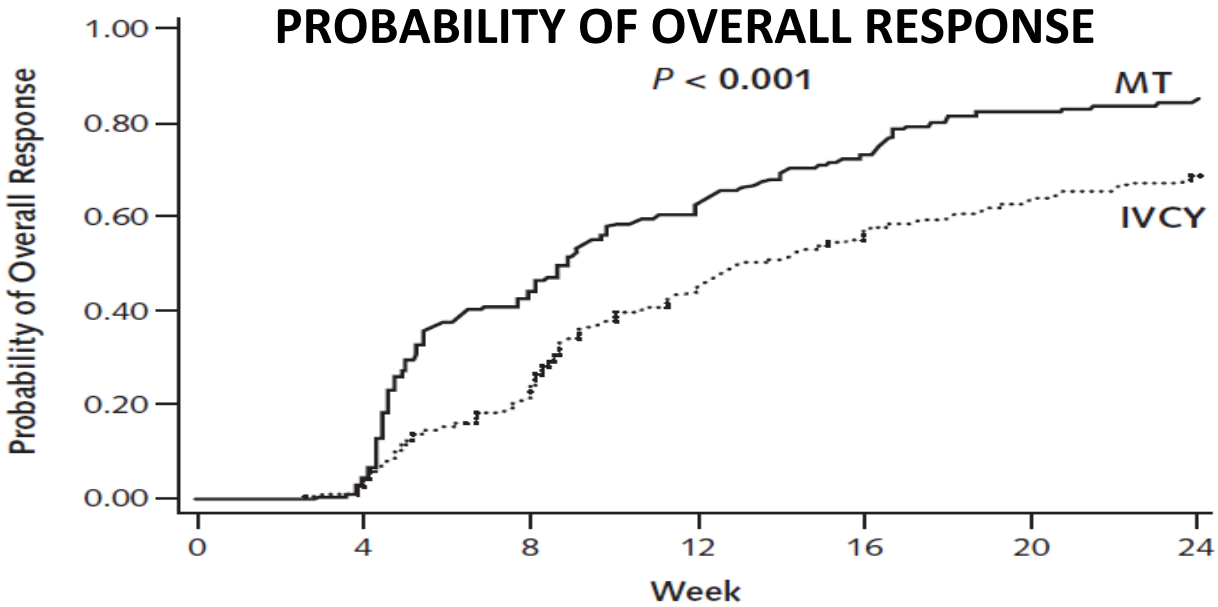
Multi-drug induction regimens may help.

ORIGINAL RESEARCH

Annals of Internal Medicine

Multitarget Therapy for Induction Treatment of Lupus Nephritis

A Randomized Trial



Patients at risk, *n*

MT	181	175	98	67	45	29	20
IVCY	181	176	132	91	71	58	45

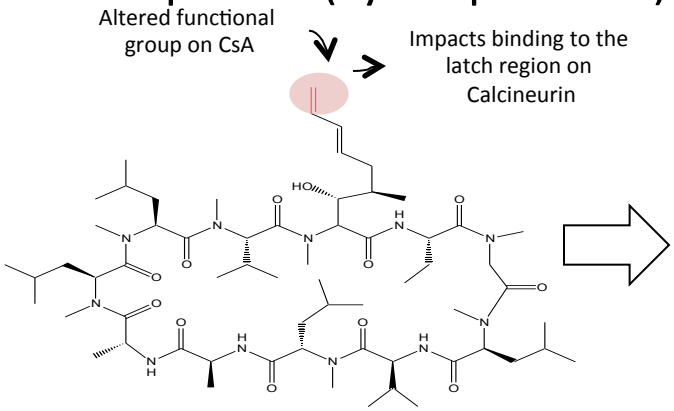
Corticosteroids
Tacrolimus
MMF

Corticosteroids
IV cyclophosphamide

Ann Intern Med. 2015;162:18-26. doi:10.7326/M14-1030

Voclosporin: a *best in class* calcineurin inhibitor allowing for significant clinical differentiation

- Voclosporin has a modified functional group on the periphery of the cyclosporine molecule which allows the molecule to offer several advantages vs. its parent (cyclosporine A) and other CNI's



Voclosporin

Modification results in:

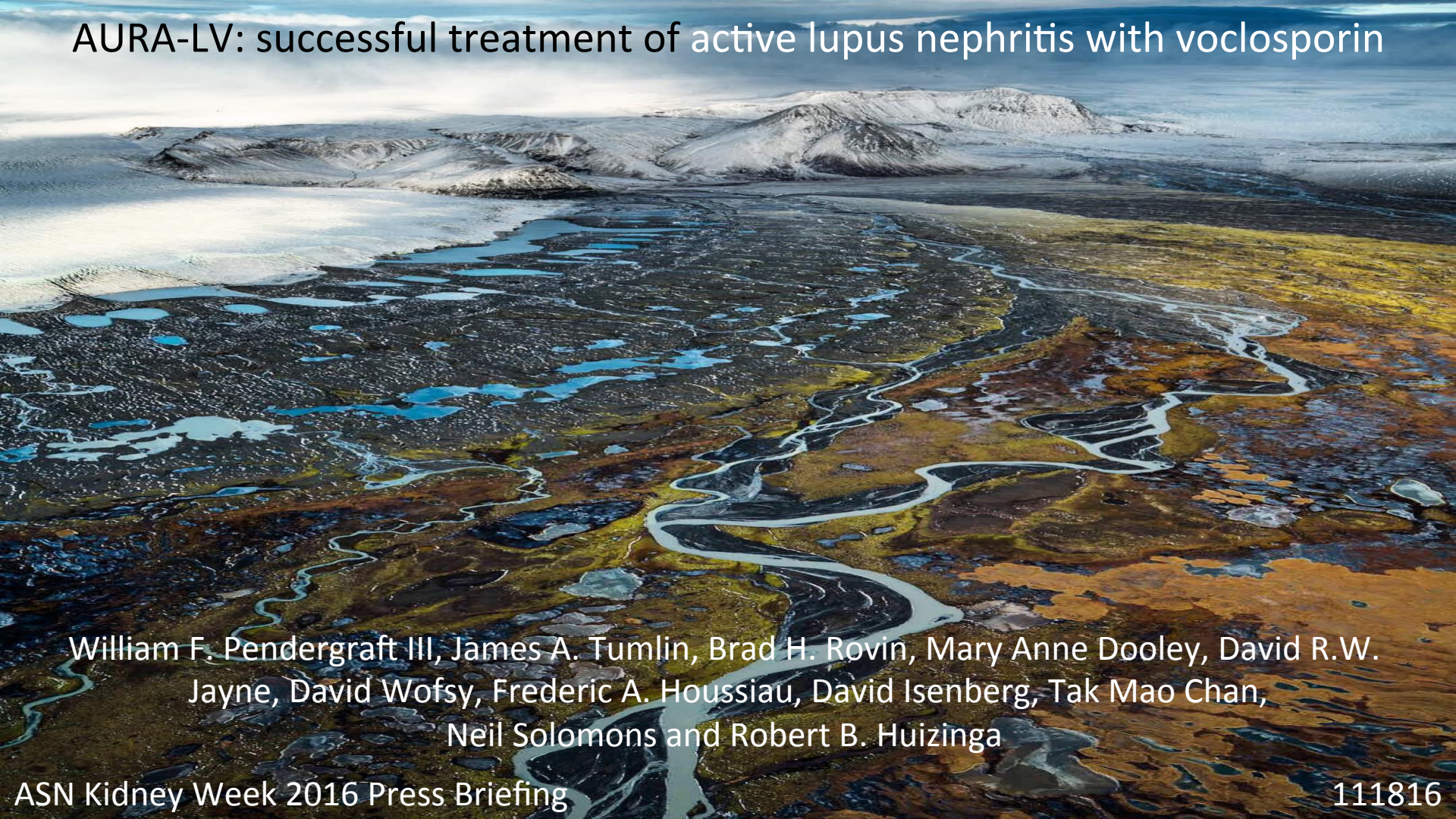
1) Predictable PK/PD relationship
2) Increased potency 3-4 fold (vs. CSA)
3) Altered metabolic profile and faster elimination of resultant metabolites

Clinical benefits*:

- Allows for flat dosing
- Improved lipid profile (vs. CSA)
- Reduced risk of diabetes (vs. TAC)
- No impact on CellCept® levels when used in combination (vs. CSA)

**Existing CNI's (cyclosporine & tacrolimus) are not approved for Lupus in the EU/US*

AURA-LV: successful treatment of active lupus nephritis with voclosporin



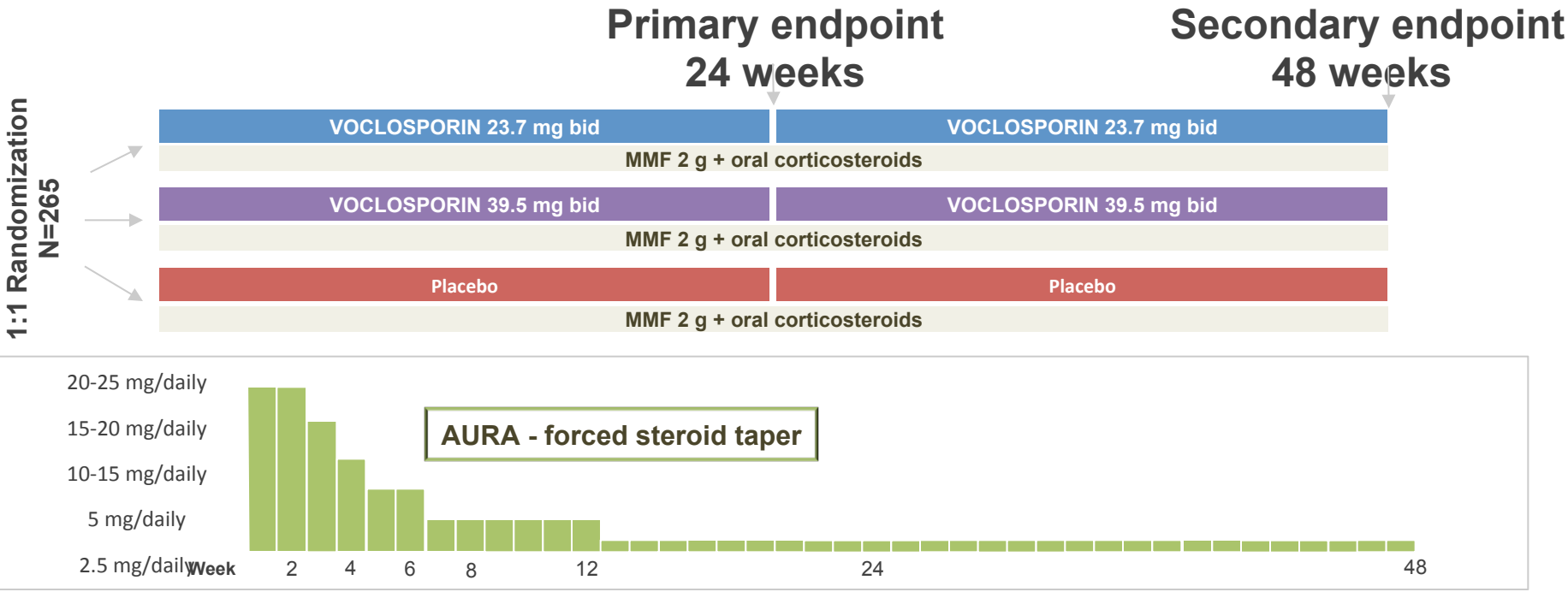
William F. Pendergraft III, James A. Tumlin, Brad H. Rovin, Mary Anne Dooley, David R.W. Jayne, David Wofsy, Frederic A. Houssiau, David Isenberg, Tak Mao Chan, Neil Solomons and Robert B. Huizinga

ASN Kidney Week 2016 Press Briefing

111816

AURA-LV Study Design: Phase IIB

AIMS: To demonstrate that voclosporin added to standard of care can increase speed of remission & overall remission rates in the presence of extremely low steroid exposure.



AURA-LV Key Inclusion Criteria and Outcome Measures

KEY INCLUSION CRITERIA

- Diagnosis of SLE according to ACR criteria
- Biopsy proven LN [Class III, IV or Class V (alone or in combination w/Class III or IV)]
- Proteinuria of ≥1.5 mg/mg OR ≥2 mg/mg*

Indicative of highly active disease

PRIMARY OUTCOME MEASURES

The proportion of subjects achieving complete remission (CR) at 24 weeks

- **CR** is defined as: Confirmed urinary protein/creatinine ratio of ≤0.5 mg/mg (FMV)
- \+ Normal, stable renal function (≥60 mL/min/1.73m^2 or no confirmed decrease from baseline in eGFR of ≥20%)
- Presence of sustained, low dose steroids (≤10mg prednisone from week 16-24)
- No administration of rescue medications

KEY SECONDARY OUTCOME

Partial Remission, Time to Remission, Time to Partial Remission, Durability of remission and extra-renal activity (SLEDAI) at 24 & 48 weeks

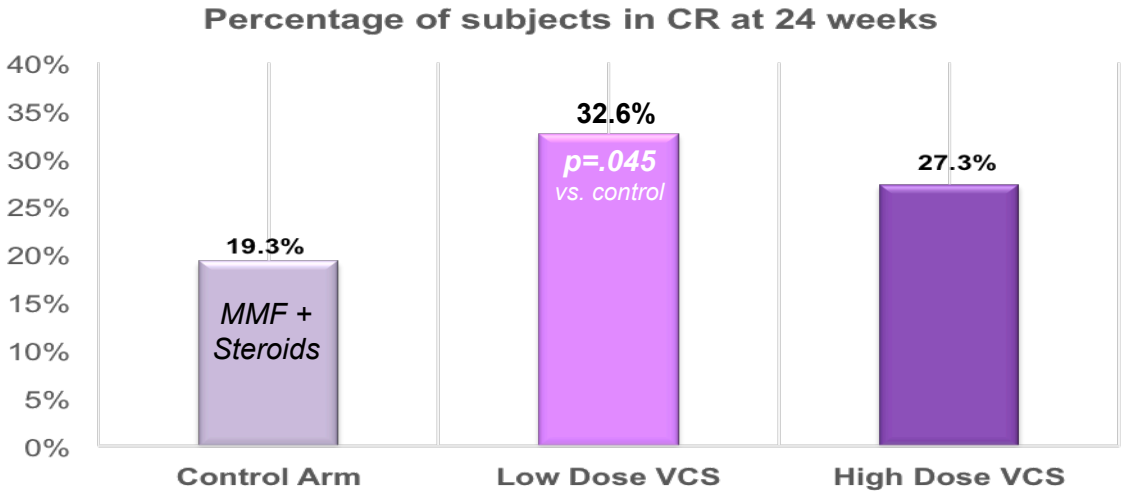
*≥2 mg/mg refers to Class V patients

Primary endpoint: complete remission at 24 weeks

First therapeutic agent to meet primary endpoint in global clinical trial for active LN

PRIMARY OUTCOME MEASURES

32.6% of patients in **low dose voclosporin arm achieved CR (*p=0.045*);** compared to **27.3% (p=0.204)** in **high-dose arm** and **19.3% in control arm - Odds Ratio (95% CI) vs. Control = 2.03**

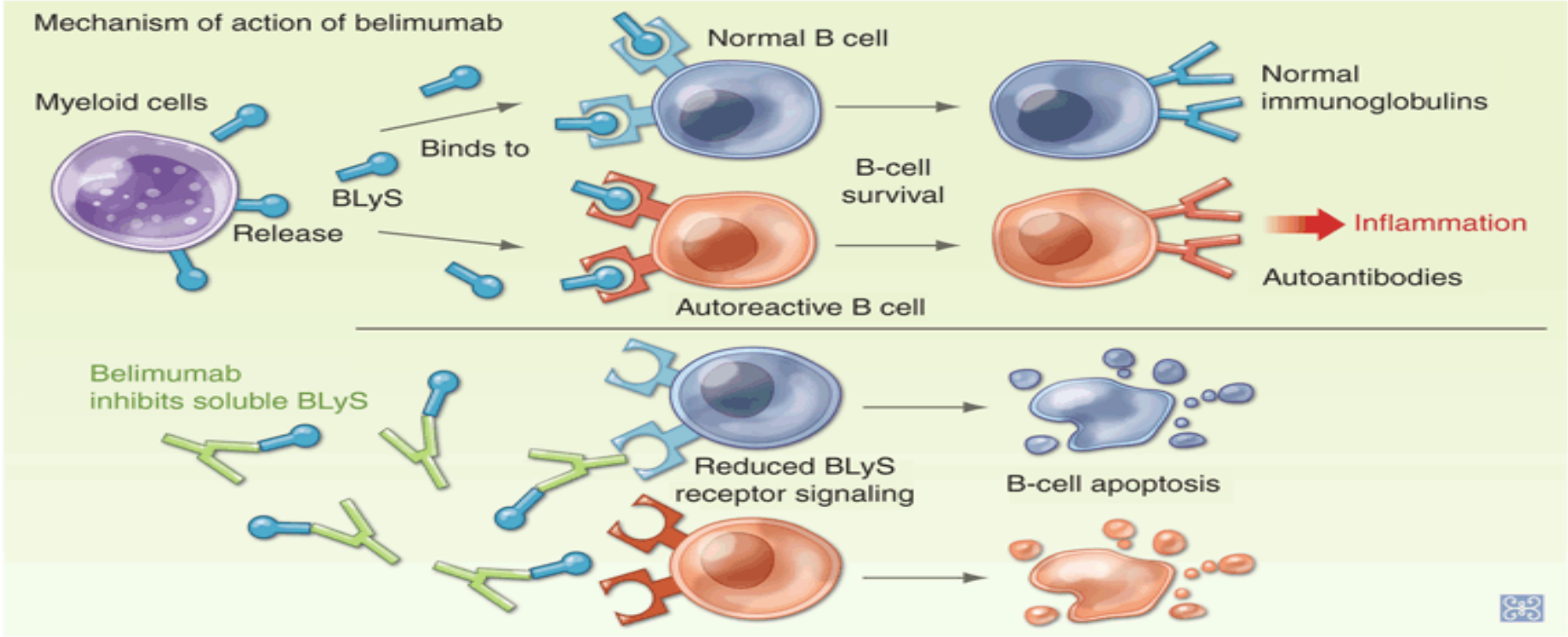


CR in AURA is a **composite end-point** which includes *efficacy, safety and low-dose steroids*

- UPCR ≤ 0.5mg/mg (confirmed)
- eGFR >60ml/min or within 20% of baseline
- Steroids ≤ 10mg/day

Study was powered to show a difference in either arm vs. control arm, not between doses

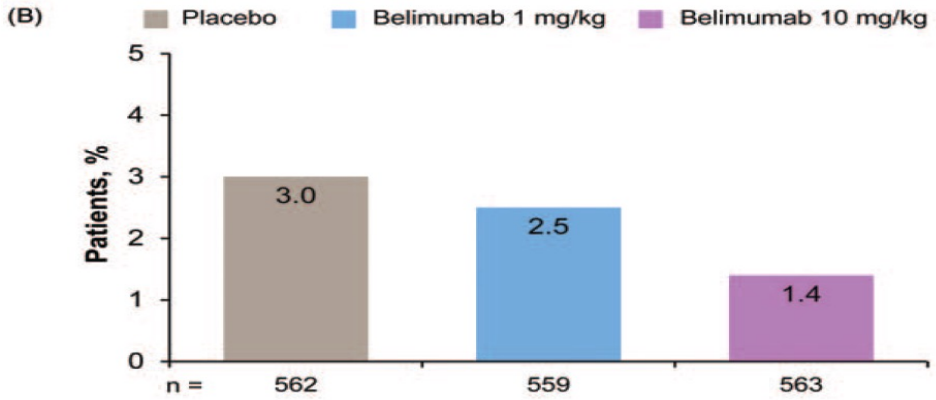
BELIMUMAB INHIBITS SOLUBLE BLyS



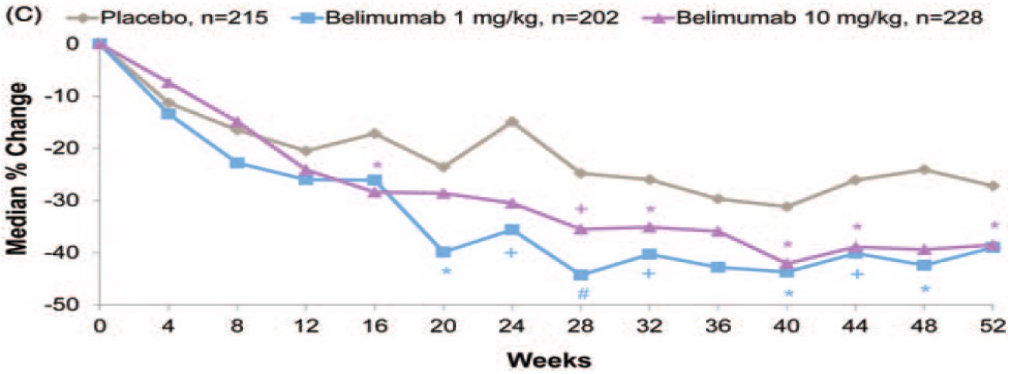
Schober and Pendergraft. *Lupus Science & Medicine* 2015.

BELIMUMAB IN LUPUS NEPHRITIS

Pooled post-hoc analysis of renal outcomes in BLISS-52 and BLISS-76



Renal flares

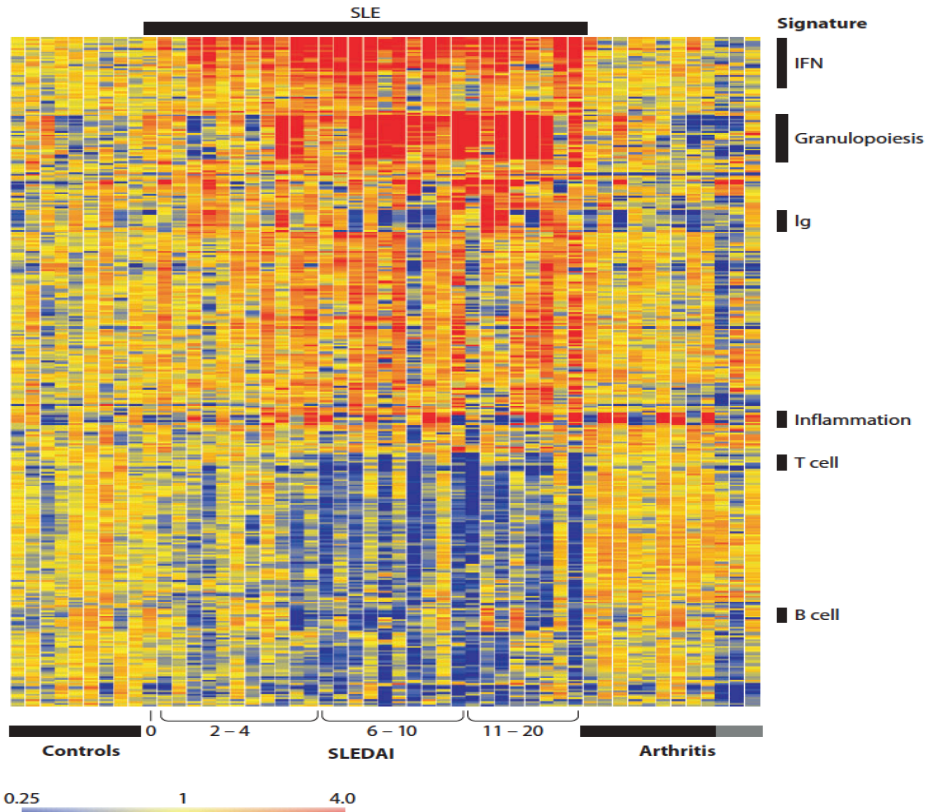


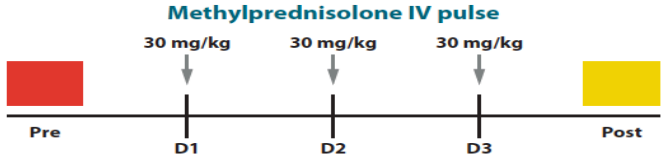
Proteinuria

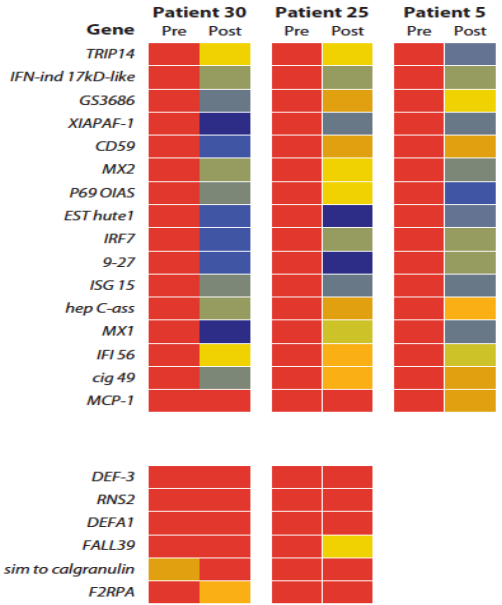
Dooley and colleagues. *Lupus* 22: 63-72, 2013.

WE HAVE INFORMING DATA

SLE TYPE I INTERFERON SIGNATURE





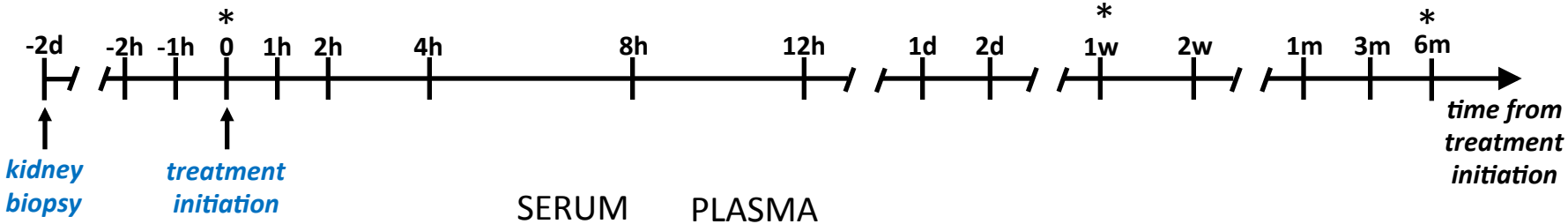


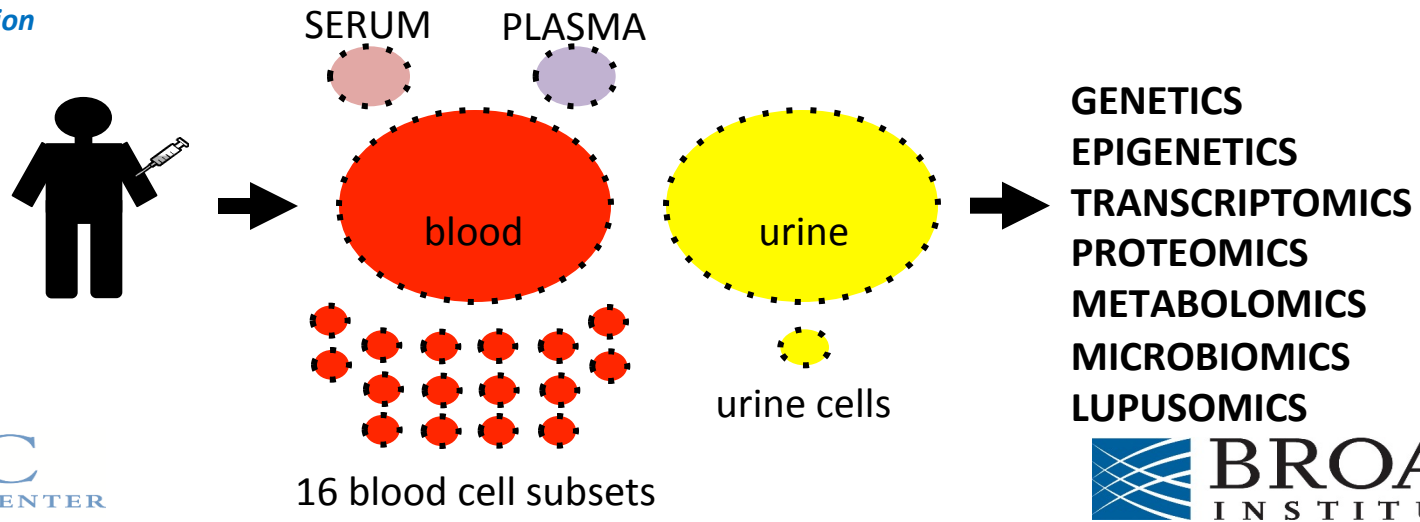
Pascual, V., et al. A genomic approach to human autoimmune diseases. Annu Rev Immunol 28: 535-571, 2010.

STOP SLE

Systems-wide Temporal Observation of Patients with SLE

GOAL: To identify predictors of treatment response in lupus nephritis.

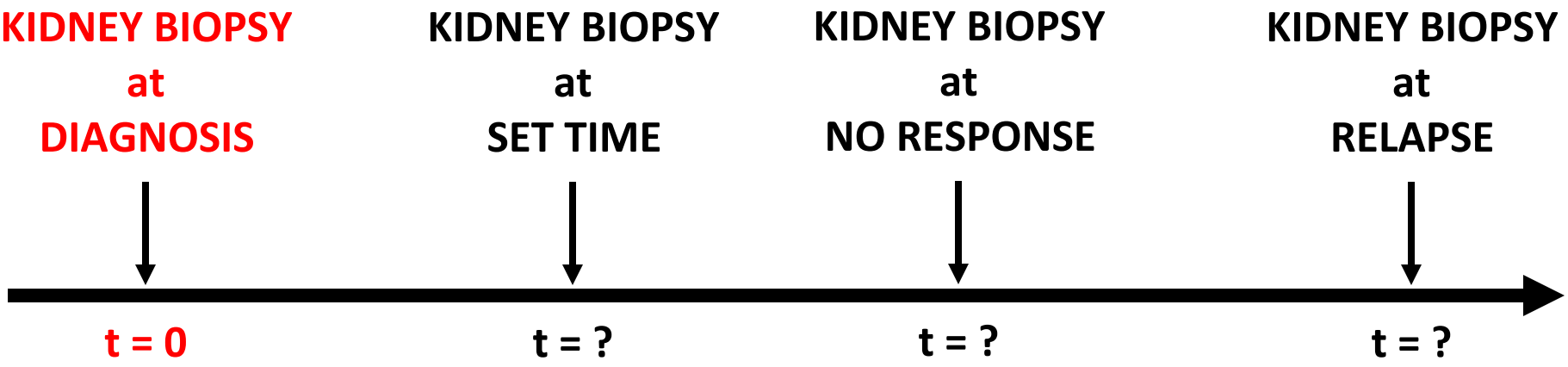




UNC KIDNEY CENTER

BROAD INSTITUTE

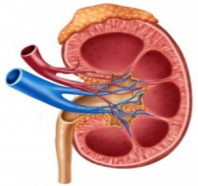
WE NEED REPEAT KIDNEY BIOPSIES IN LUPUS NEPHRITIS TO HELP GUIDE NEXT STEPS IN MANAGEMENT



OUR PLAN…

1. Discuss current state of affairs with management of lupus nephritis, including resistant disease
2. Describe the current state of biologics in lupus nephritis
3. Highlight hot topics in the field of lupus nephritis
4. **Review active lupus nephritis clinical trials at UNC**
5. Suggest potential window into the future

ACTIVE LUPUS NEPHRITIS TRIALS



1. BLISS-LN

- corticosteroids and MMF or Euro-Lupus +/- belimumab

2. AURORA

- corticosteroids and MMF +/- voclosporin (new CNI)

3. TULIP

- corticosteroids and MMF +/- anifrolumab (anti-IFN)

4. 1293-10 Phase 2 trial

- corticosteroids and MMF +/- anti-CD40

Just closed enrollment…

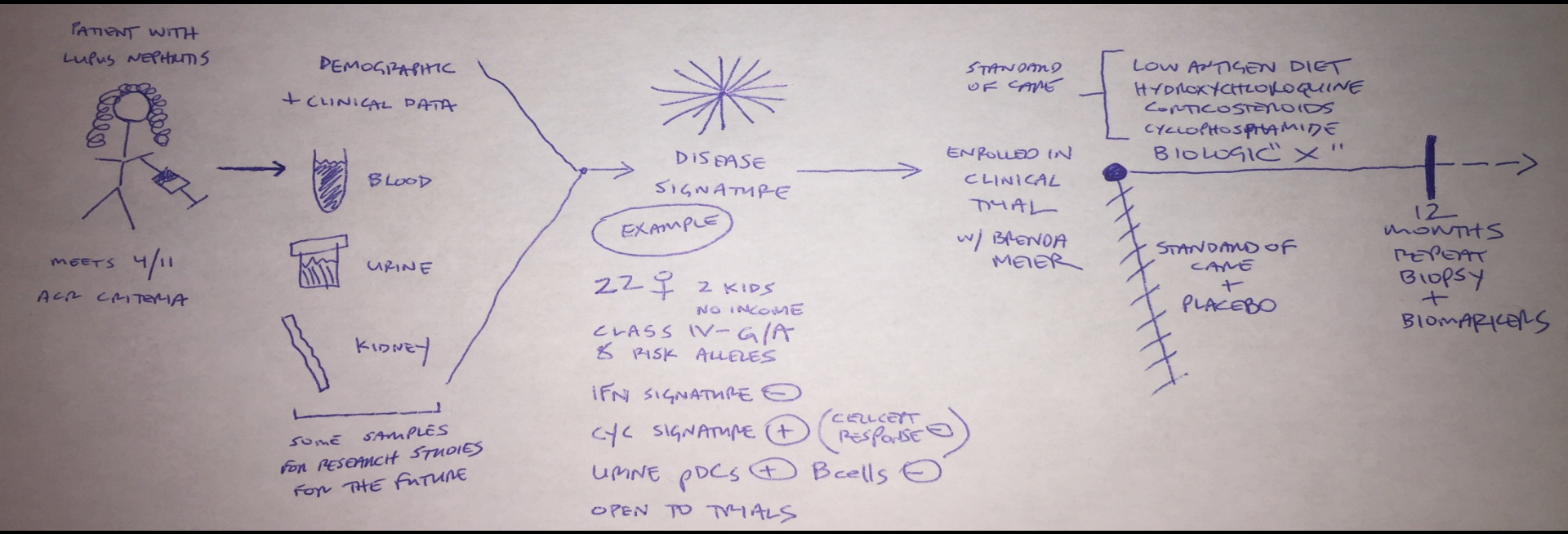
1. CALIBRATE (relapsing lupus nephritis)

- corticosteroids, cyclophosphamide and rituximab
- belimumab for maintenance

OUR PLAN…

1. Discuss current state of affairs with management of lupus nephritis, including resistant disease
2. Describe the current state of biologics in lupus nephritis
3. Highlight hot topics in the field of lupus nephritis
4. Review active lupus nephritis clinical trials at UNC
5. **Suggest potential window into the future**

A PROPOSED ROADMAP FOR THE FUTURE



THANKS

QUESTIONS, CONCERNS, PATIENTS WHO NEED HELP, TRIALS, RESEARCH?

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