Treatment of Severe Lupus Nephritis:

Beyond Standard Regimens- A New Role for Biologics?

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QUESTION #2A

- **A 23 year old woman with a 7 year history of Systemic Lupus Erythematosus develops nephrotic syndrome (urine protein excretion of 5.6gms/d, serum albumin of 2.4gms/dL). Her serum creatinine is 1.30mg/dL (115µM/L; eGFR- CKD-EPI-creatinine= 58ml/min/1.73m2). A C3 is 46mg/dL and a C4 is 9mg/dL/ The anti-dsDNA titer is 1:1280. A pregnancy test is negative. She indicates a desire to eventually have children.**

QUESTION #2A

- **A renal biopsy reveals Severe Lupus Nephritis Class IV- Segmental; a+c; 15 % of the glomeruli show crescents. Moderate interstitial nephritis is present. IF shows moderate (3+) segmental deposits of IgG, C3, C1q. EM shows mesangial and sub-endothelial electron dense deposits and scanty sub-epithelial deposits. Tubulo-reticular inclusions are present in endothelial cells.**

QUESTION #2A

- **In addition to 3 doses of IV methylprednisolone (500mg each), which one of the following treatments would you start now?**

A. Oral MMF at 2.0gms/d + oral prednisone at 60mg/d

B. IV cyclophosphamide 500mg every two weeks for 3 months+ oral prednisone at 60mg/d

C. IV cyclophosphamide 1000mg/m2 monthly for 6 months+ oral prednisone at 60mg/d

D. Oral cyclophosphamide 2mg/kg/d or 3 months + oral prednisone at 60mg/d

E. Rituximab 375m/m2 every week times 4 weeks + oral prednisone at 60mg/d

F. Cyclosporine 4mg/kg/d + MMF 2 gms/d + oral prednisone at 60mg/d

QUESTION #2A

- The “correct” answer (my best choice) is ***A-MMF + Prednisone, but a regimen involving cyclophosphamide is also reasonable given the crescentic involvement***

Severe Lupus Nephritis*:

Standard Treatment Regimens

KDIGO-GN- CPG- July 2012

[*ISN/RPS Class III/IV (G or S; A or A/C)]

- ***Induction***
  - Oral CYC (1-1.5mg/kg/d) + steroids (2-4 months)- ***LNCSG*** Protocol
  - IV CYC (0.5-1.0g/m2) monthly + steroids (6 months) **– *NIH*** Protocol
  - IV CYC (low dose; 500 mg every 2 weeks) + steroids (3 months)- ***EUROLUPUS*** Protocol
  - Oral MMF (2-3gms/d + steroids) (3-6 months) **– ALMS** Protocol

- ***Maintenance***
  - Oral MMF (2-3gms/d) + low dose steroids x 24 months (+) (***ALMS*** protocol)
  - Oral AZA (2mg/kg/d)+ low dose steroids x 24 months (+)-(***EUROLUPUS*** Protocol) do not use if MMF used for Induction
  - CNI (CsA or Tac) + low dose steroids if intolerant of MMF or AZA (***Ponticelli/Moroni*** Protocol)

Severe Lupus Nephritis:
Treatment Modifications-I

- **Use IV CYC with great caution in renal failure; adjust dose of oral or IV CYC according to eGFR. Do not use CYC in liver failure**
- **CYC based regimens effective in Caucasians and Blacks (except Euro-Lupus- not tested); perhaps less so in Hispanics and Asians**
- **MMF based induction and maintenance regimens may be preferred in Blacks, Hispanics and Asians**

Severe Lupus Nephritis:
Treatment Modifications

- **ISN/RPS Class IV (G) + V may respond better to a MMF + Tac + steroid induction regimen ("Multi-Target Therapy")- not tested in Blacks or Caucasians**
- **ISN/RPS Class V lesion may respond better to CYC- or CNI- based regimens -not tested in Blacks or Asians**
- **ISN/RPS Class III >50% (called IV (Q) by Schwartz et al) may be a forme-fruste of SVV (ANCA ±) and respond better to CYC than MMF**

Unfortunately only about *60-70%* of patients with severe LN will respond with a Complete or Partial remission to one or the other of the *"Standard"* regimens, often requiring over 6 months of treatment (greater unresponsiveness is seen in males and Blacks)

Renal relapses (nephritic and nephrotic) remain *frequent* with *"Standard"* treatment and maintenance regimens (About 8-10 relapses per 100 treated patient per year for the first 5 years after induction) and frequency/severity predict later onset of ESRD

Cumulative toxicity of *"Standard"* treatment regimens (particularly steroids) due to *delayed remission and frequent relapses* contribute significantly to morbidity and mortality

Safe and effective regimens beyond *"Standard"* care are needed for management of "refractory" *(treatment resistant)* patients with severe LN and for those with *frequent relapses* and treatment related toxicity (especially steroids)

Is there a role for new *Biologic Agents* in the management of severe *Lupus Nephritis?*

A. For primary induction of remission

B. For "rescue" of treatment refractory disease

C. For maintenance of remission and avoidance of steroids (steroid-sparing)

New Biologic Agents in Treatment of Severe Lupus Nephritis

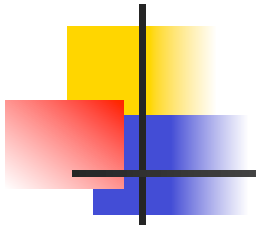
- **Rituximab** (chimeric anti-CD20 MoAb- B cells and ? Th-17 cells)
- **Belimumab*** (anti-Blys/BAFF MoAb- B-cells)
- **Abatacept** (CTLA-4/Ig fusion protein-inhibits CD80 and T-cell co-stimulation)
- **Atacicept** (Fusion protein that inhibits Blys + APRIL- B-Cells)
- **Epratuzimab** (anti-CD20 MoAb- B-cells)
- **Ocreluzimab** (fully humanized anti-CD20 MoAb-B-cells)
- **Eculizimab**** (anti-C5A MoAb)
- **ACTH gel*** (natural, porcine)

(*approved by FDA for treatment of SLE, but not specifically LN;**approved by FDA for use in atypical HUS)

RITUXIMAB

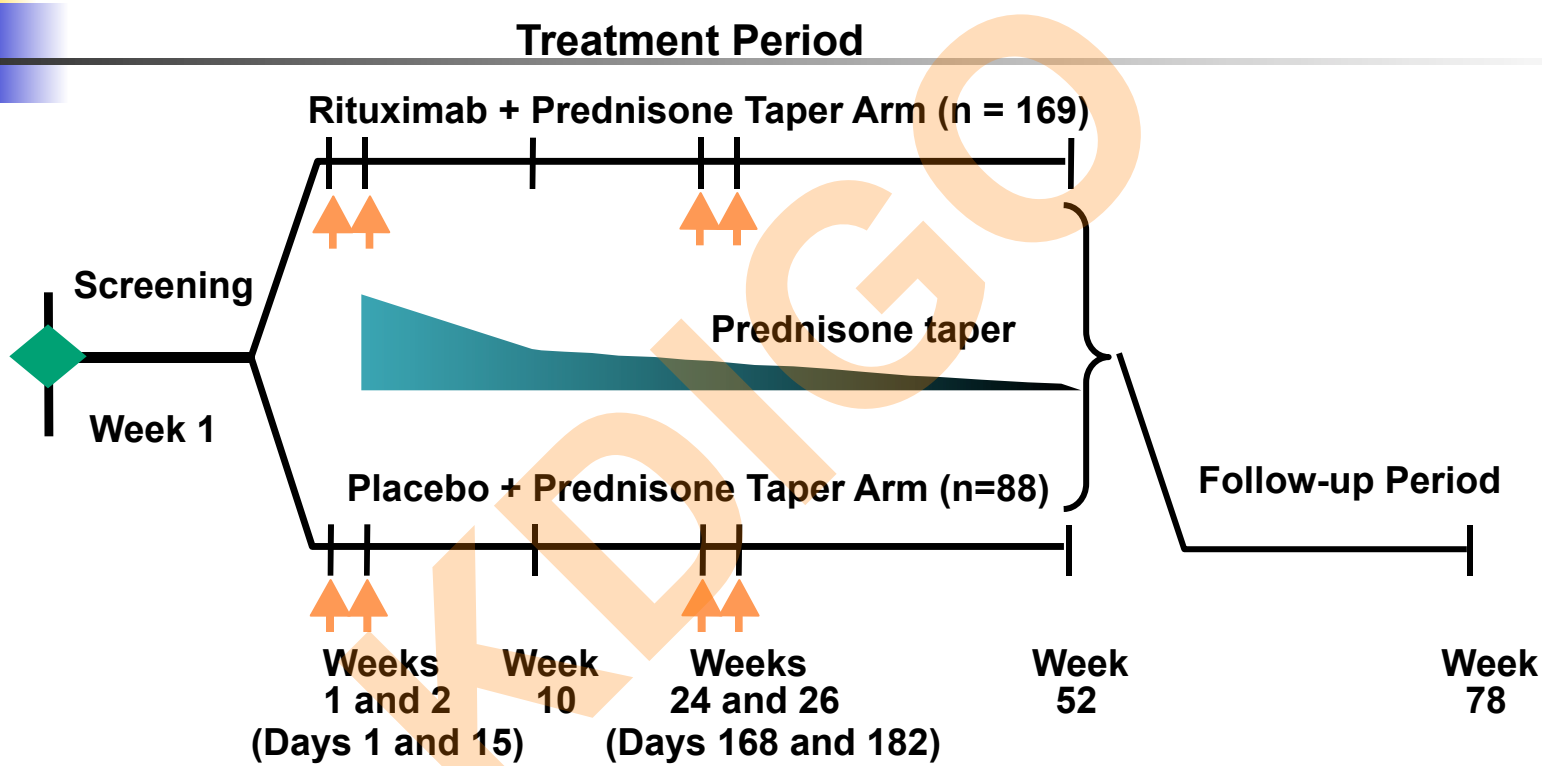
RITUXIMAB for INDUCTION of REMISSION IN SYSTEMIC LUPUS ERYTHEMATOSUS and SEVERE LUPUS NEPHRITIS:

The EXPLORER and LUNAR Trials



EXPLORER
(SLE without LN)

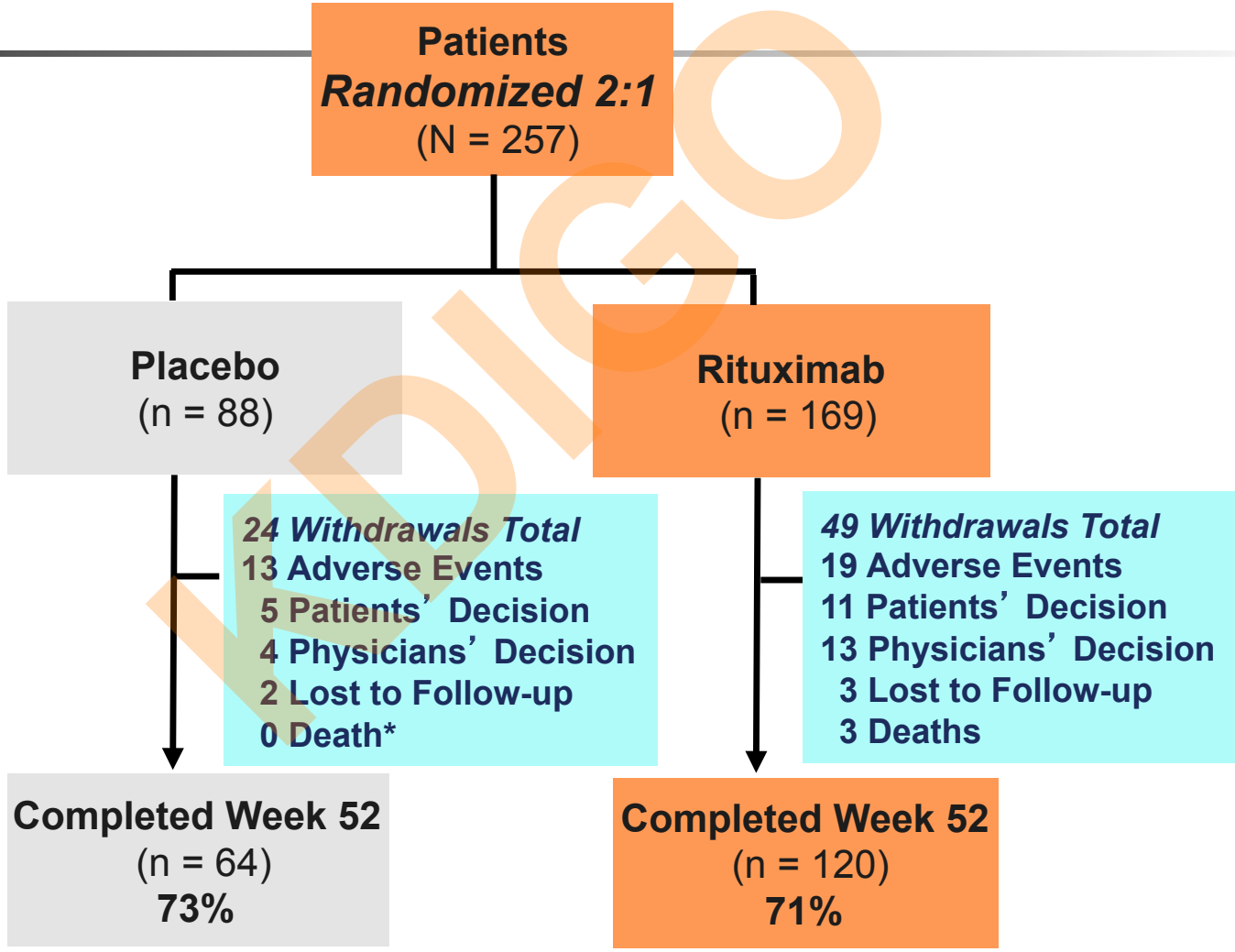
EXPLORER - *A Randomized, Blinded Phase II/III Study Efficacy and Safety of Rituximab in Moderately to Severely Active SLE*



= Study drug infusion; 2 x 1000 mg Rituximab/Placebo

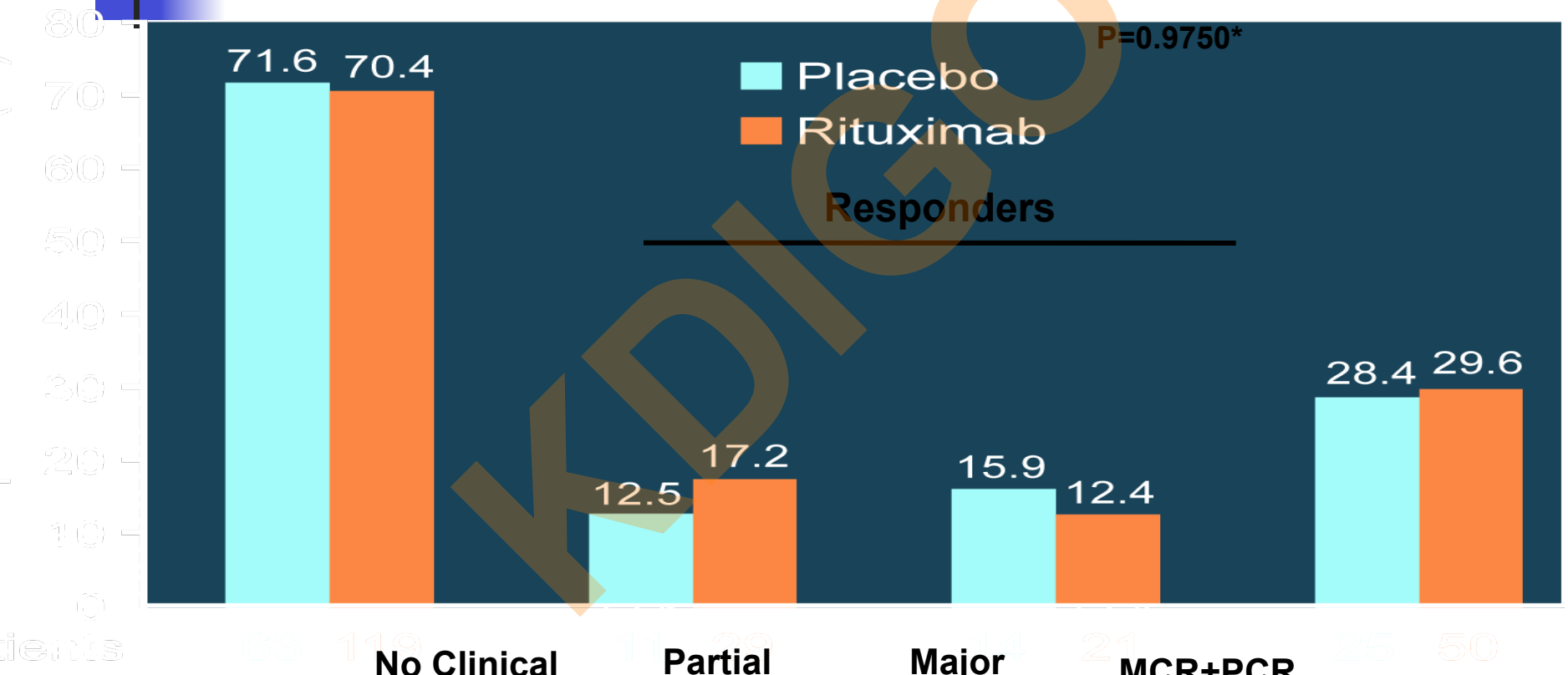
Merrill JT et al. Arthritis and Rheum 62:222-233, 2010

EXPLORER TRIAL -
Patient Disposition



*One patient withdrew due to AE, and died one month later.

Primary Endpoint: *Patients Achieving Clinical Response* (ITT Population)

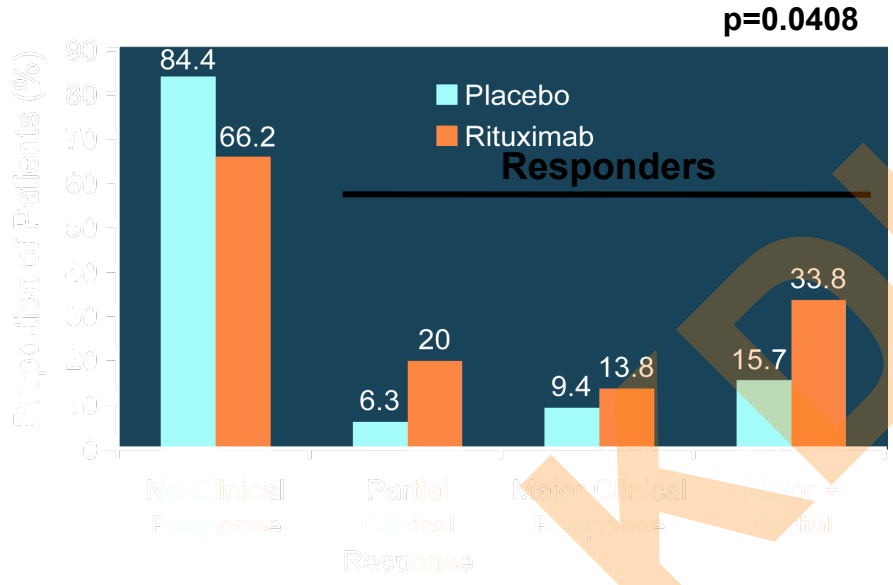


All early terminations treated as NCR.

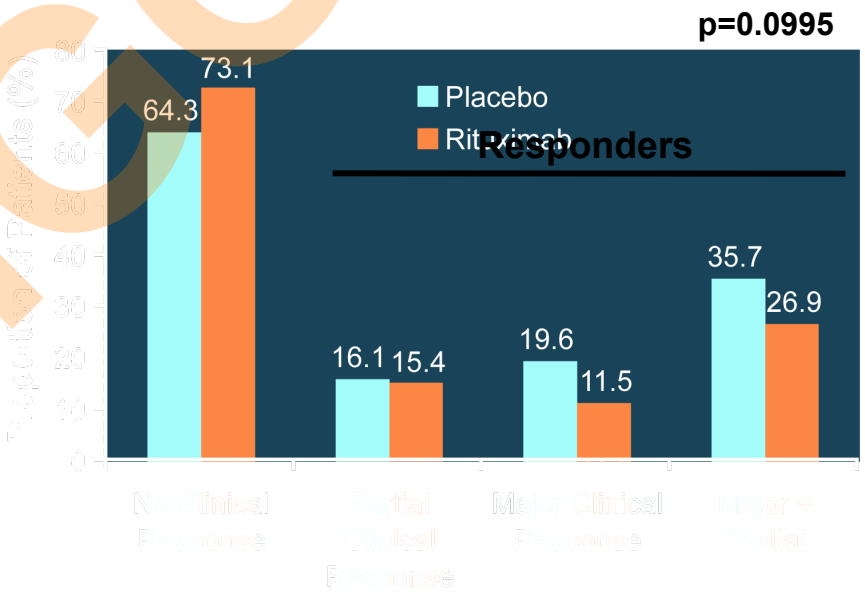
*p value is based on Wilcoxon Rank sum test stratified by race and baseline assigned prednisone dose.

Pre-specified Exploratory Analysis:
Clinical Response by Ethnicity

African-Americans/Hispanics



Other

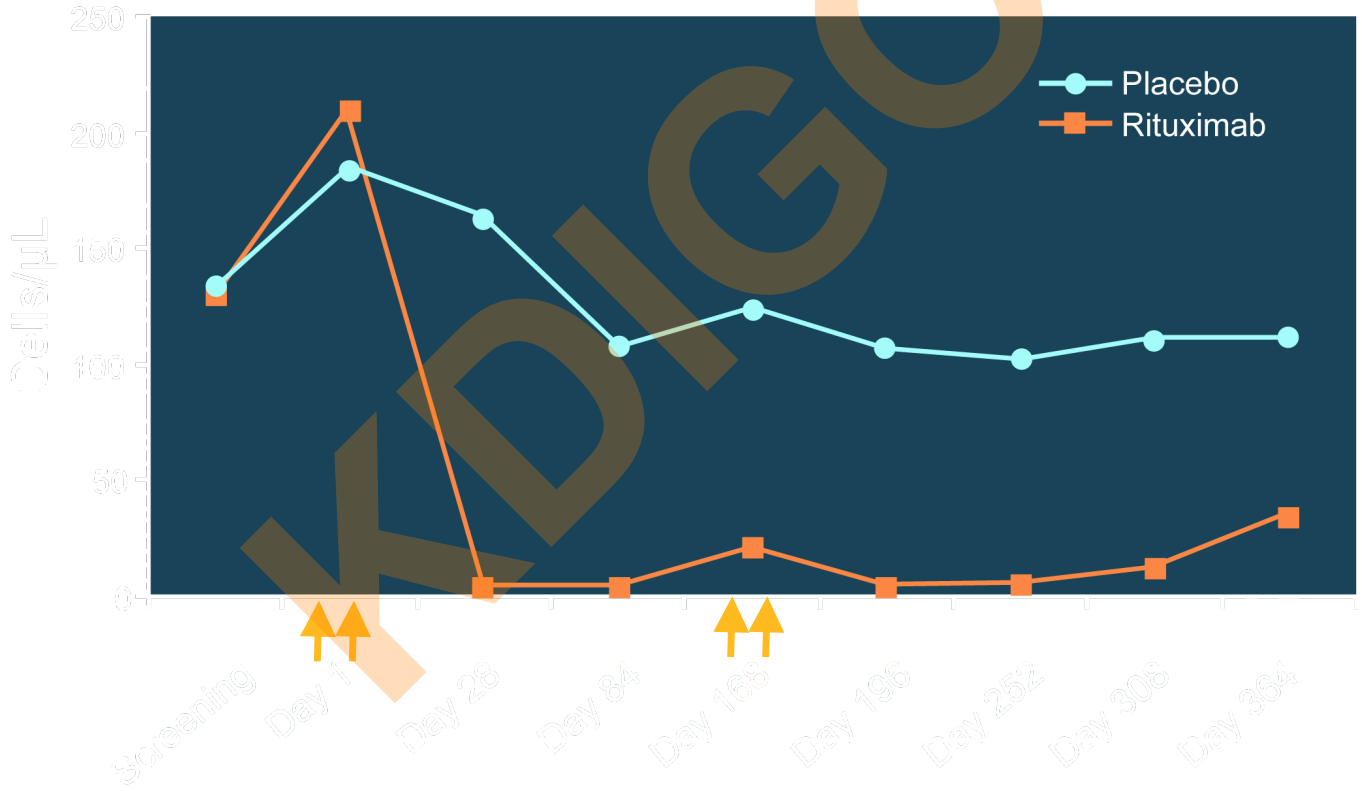


African-American/Hispanic subgroup showed significant response in the rituximab-treated group compared with the placebo group.

The other (ethnic) group trended toward a worsening response with rituximab, but not statistically significant.

*

Pharmacodynamics: Mean CD19+ B-cell Counts Over 52 Weeks (Safety Population)

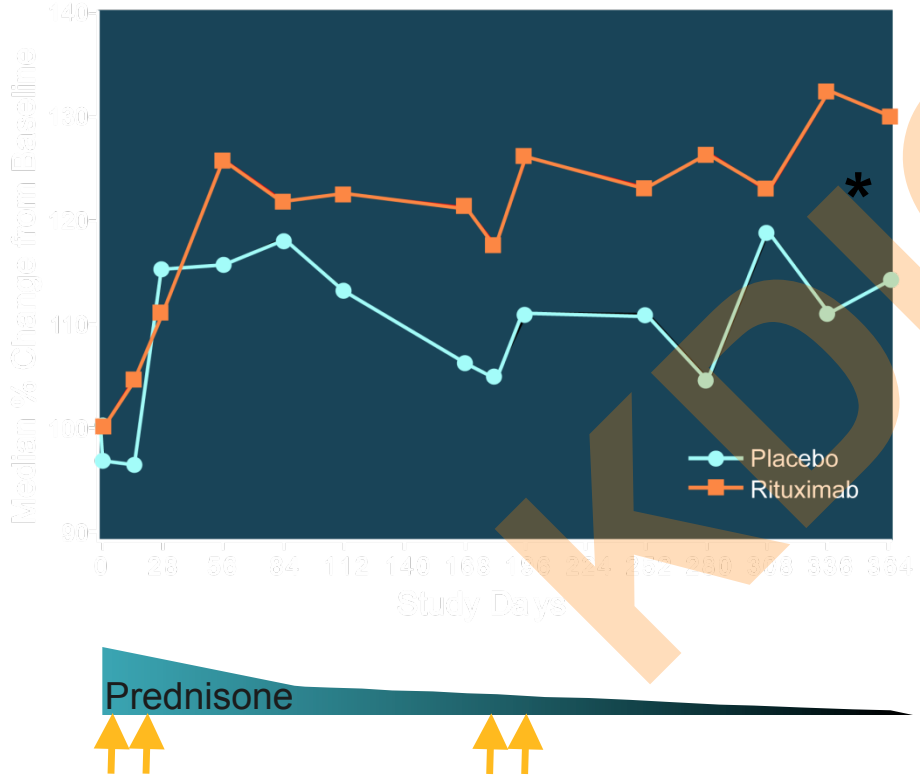


1000 mg rituximab infusions
At Days 1, 15, 168, and 182

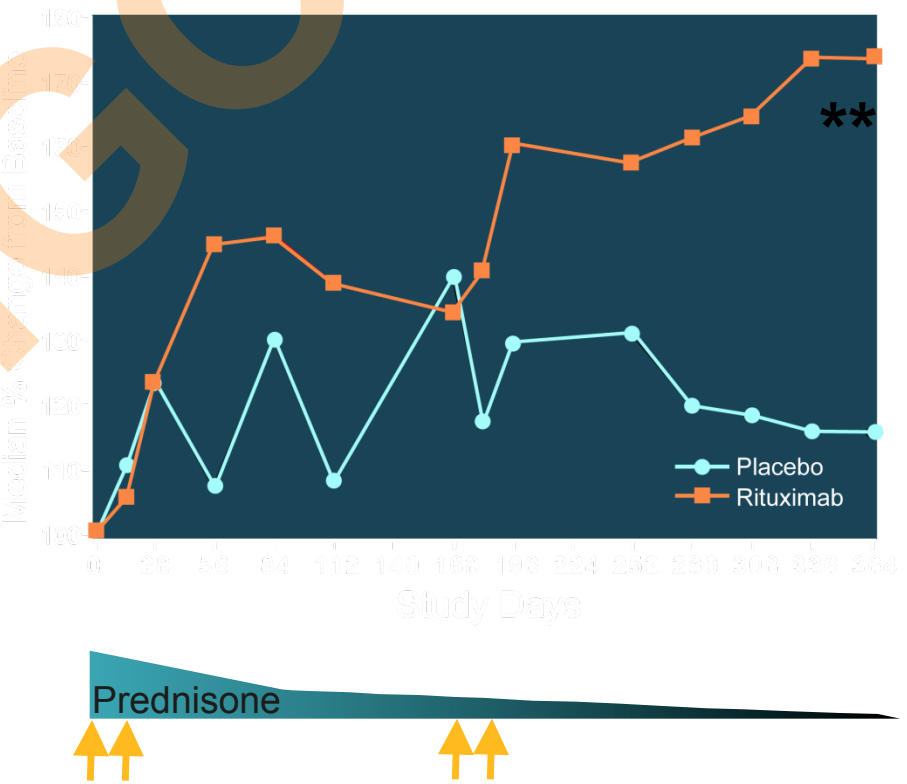
3.4% of placebo patients were HACA +

Biomarkers: Increased Complement Levels in Rituximab-treated Patients

C3 Complement



C4 Complement



1000 mg rituximab infusions
At Days 1, 15, 168, and 182

*p=0.0029
**p=0.0045
P values based on Wilcoxon rank sum test

EXPLORER:

CONCLUSIONS

- **Primary and Secondary Endpoints**

- **EXPLORER evaluated patients with moderate to severe active extra-renal SLE on immunosuppression with steroid treatment and used a high bar for response**
- **Rituximab depleted CD19+ B cells.**
- **There were no statistically significant differences between rituximab and placebo in primary or secondary endpoints**
- **The subgroup of AA or Hispanic Patients may benefit**
- **Serology (anti-dsDNA and complement) appeared to respond better with Rituximab**
- **Adverse events balanced and not excessive**

Safety and Efficacy of Rituximab in SLE:
136 Pts in the French Autoimmunity Registry-Observational Uncontrolled

- 136 SLE patients treated and evaluated by SELENA-SLEDAI
- 71% pts responded – no difference between RTX monotherapy and RTX + concurrent therapy.
- Improvements by Organ System –
  Articular (72%)
  Cutaneous (70%)
  Hematologic (88%)
  Renal (74%)
- 41% relapse with response again in 91% with retreatment

- Severe infections in 9% most within 3 months of RTX
- 5 Deaths - 3 due to infection , 2 refractory disease.

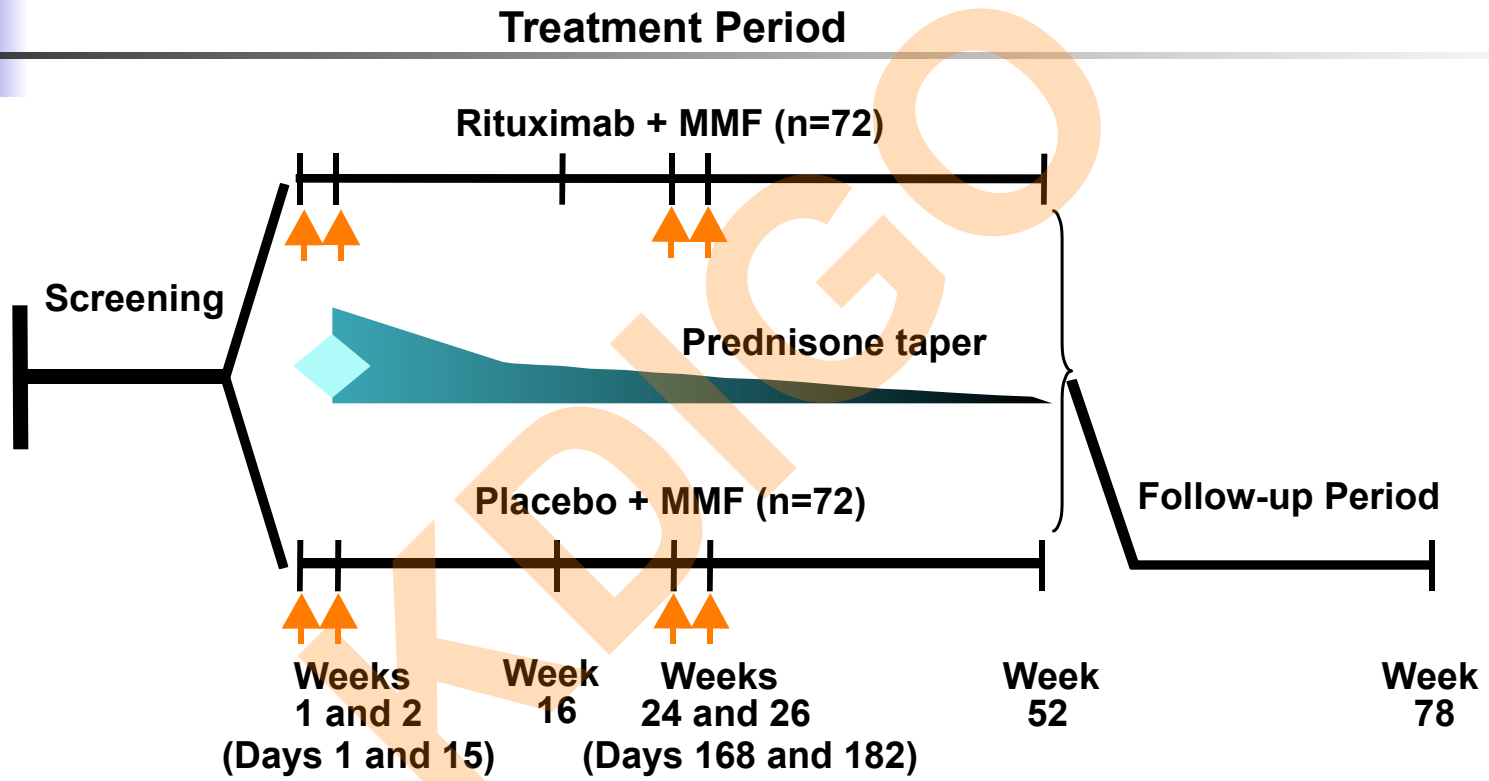
Arthritis and Rheumatism 62:2458-2466, 2010

LUNAR

SLE + Nephritis

(Rovin B, et al Arthritis Rheum 2012; 64:1215-1226)

LUNAR Study Design



= Study drug infusion.

= Corticosteroids:

- 1000 mg IV methylprednisolone given at days 1 and then days 2, 3, or 4
- Oral prednisone initiated at 0.75 mg/kg/day after IV steroids and then tapered to 10 mg/day by day 112

LUNAR

Key Inclusion and Exclusion Criteria

- **Inclusion Criteria**
  - Age 16-75 years with SLE by ACR criteria,
  - ISN/RPS Class III or IV lupus nephritis (A or A/C) with a renal biopsy within 12 months
  - Proteinuria, with urine Protein /Creat ratio >1.0

- **Exclusion Criteria**
  - >50% of glomeruli with sclerosis and/or interstitial fibrosis on renal biopsy
  - Estimated glomerular filtration rate <25 mL/min per 1.73 m^2 or ESRD
  - CNS disease
  - Thrombocytopenia at high risk for significant bleeding

LUNAR: *Primary Endpoint* (Renal Response at 52 wks)

Complete Renal Response (CRR)

- Normalization of serum creatinine OR ≤15% greater than baseline if day 1 serum creatinine within normal range of central lab
- Inactive urinary sediment
- Urinary protein to creatinine ratio <0.5

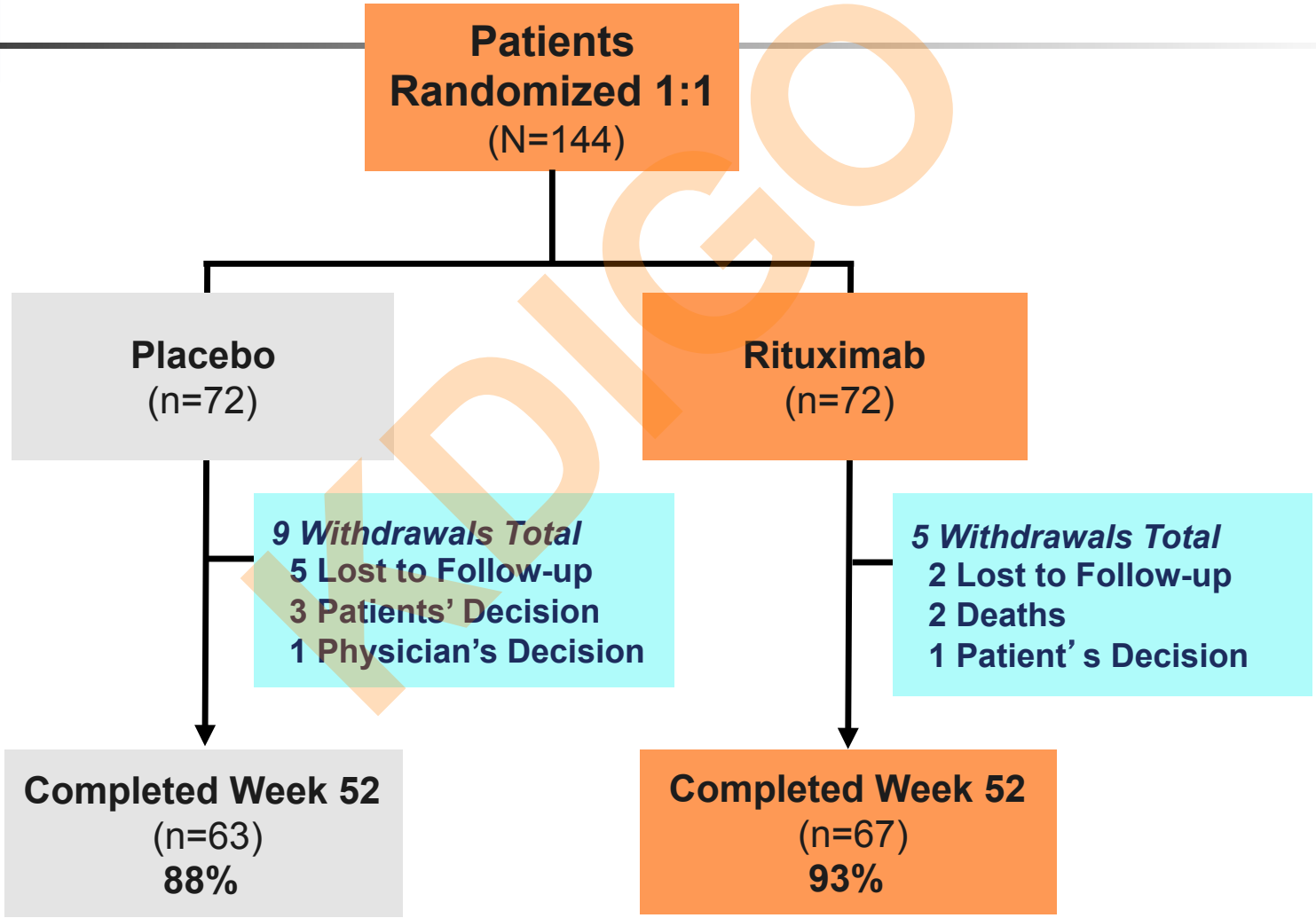
Partial Renal Response (PRR)

- Serum creatinine ≤15% above baseline value
- No worsening of urinary sediment
- 50% improvement in the urine protein to creatinine ratio,
- If baseline ratio ≤3.0, then urine P/Cr ratio <1.0
- If baseline ratio >3.0, then urine P/Cr ratio <3.0

Non-Response (NR)

- No response
- All early terminations and patients starting a new immunosuppressant were considered non-responders

LUNAR-
Patient Disposition

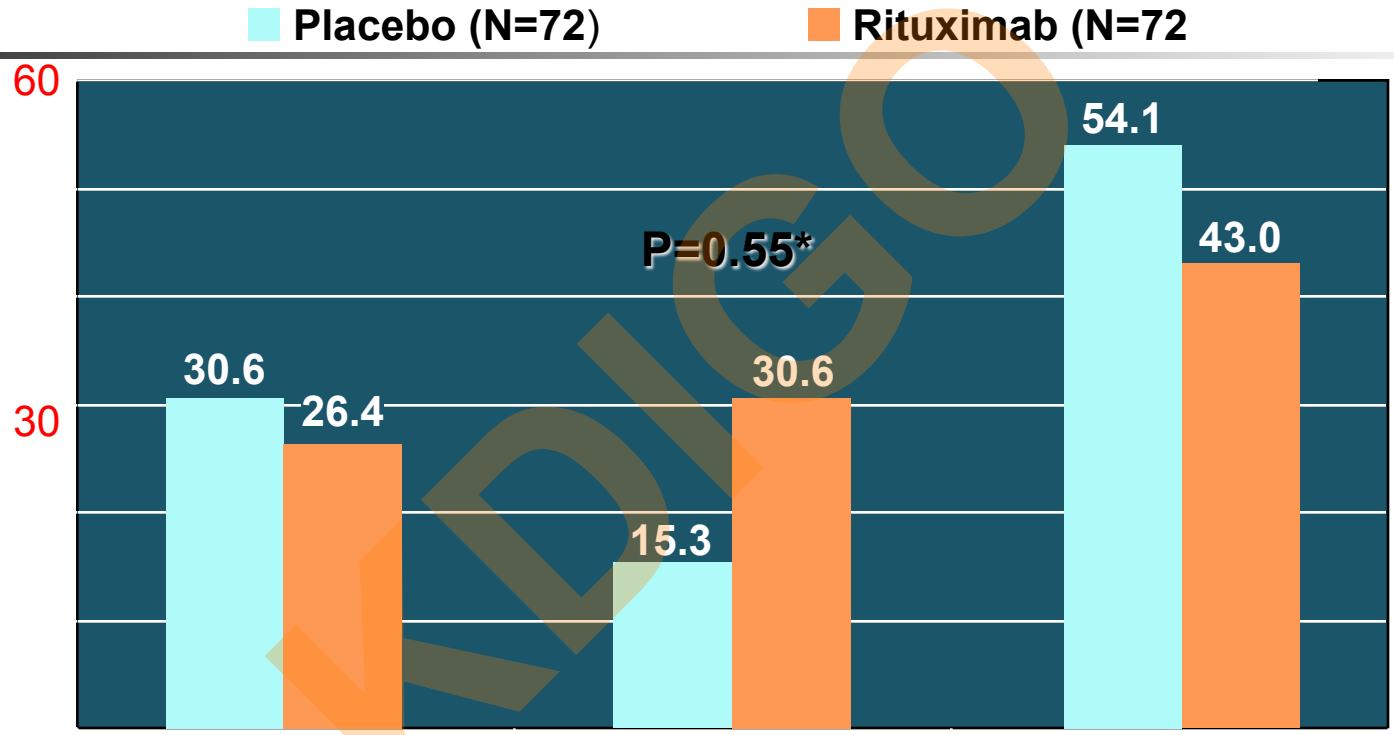


LUNAR:
Patient Disease Characteristics

	Placebo (N=72)	Rituximab (N=72)
Urine protein:creatinine ratio, mean (SD)	4.2 (3.0)	3.8 (2.8)
Serum creatinine, mg/dL, mean (SD)	1.0 (0.5)	1.0 (0.5)
Estimated GFR (mL/min), mean (SD) <60, n (%) ≥60, n (%)	96.0 (51.1) 20 (27.8) 52 (72.2)	87.7 (34.9) 17 (23.6) 55 (76.4)
Serum albumin, g/L, mean (SD)	2.6 (0.7)	2.7 (0.8)
ISN/RPS classification, n (%) Class III Class IV Class V (coexistent)	 24 (33.3) 48 (66.7) 23 (31.9)	 25 (34.7) 47 (65.3) 26 (36.1)
BILAG index global score, mean (SD)	15.3 (6.2)	15.3 (6.4)

LUNAR:Primary Endpoint:

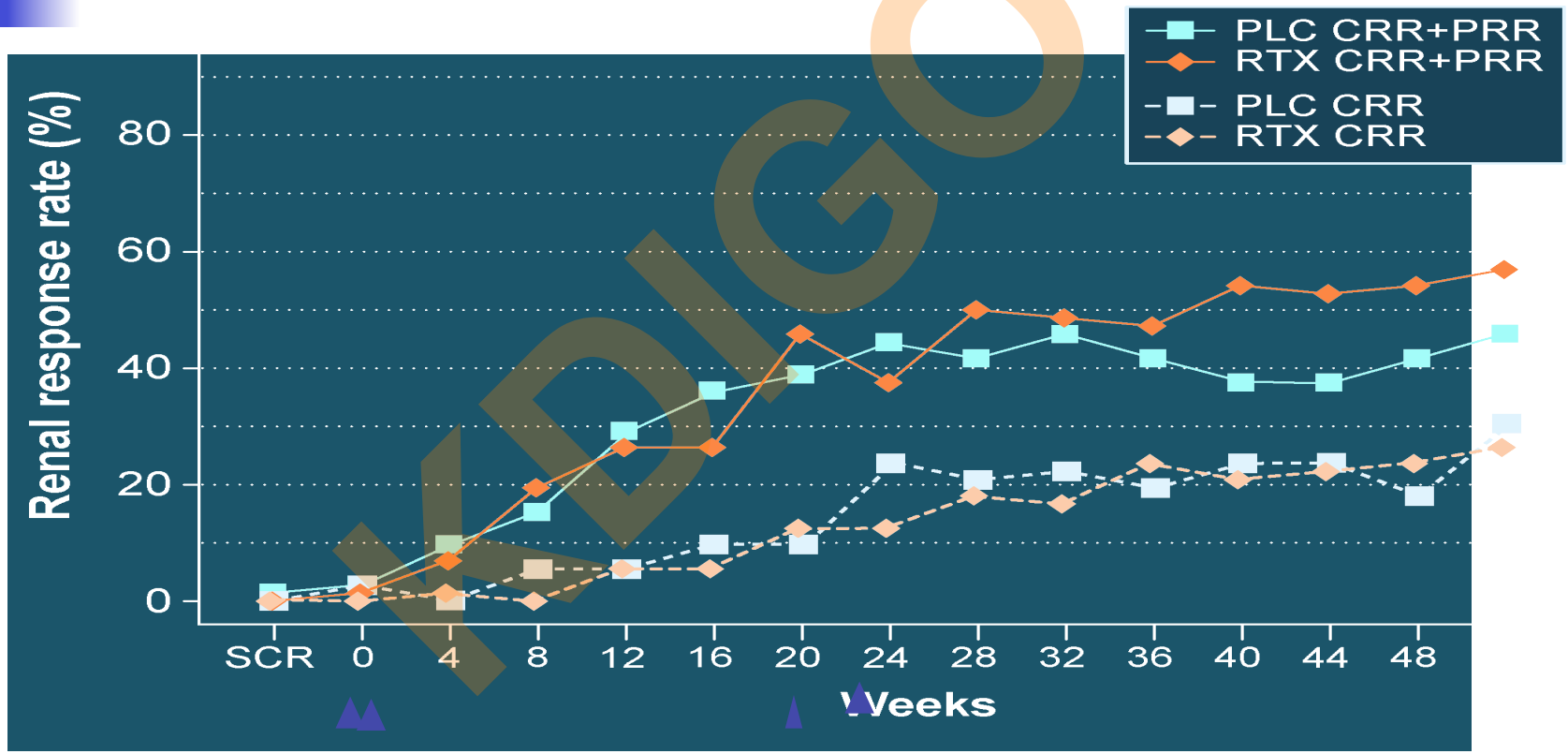
Renal Response at Week 52



* Wilcoxon Rank-sum test to compare the proportions of (CRR, PRR, NR) between rituximab and placebo

Mean MMF dose: Placebo: 2.4±0.62 g; Rituximab: 2.7±0.41 g

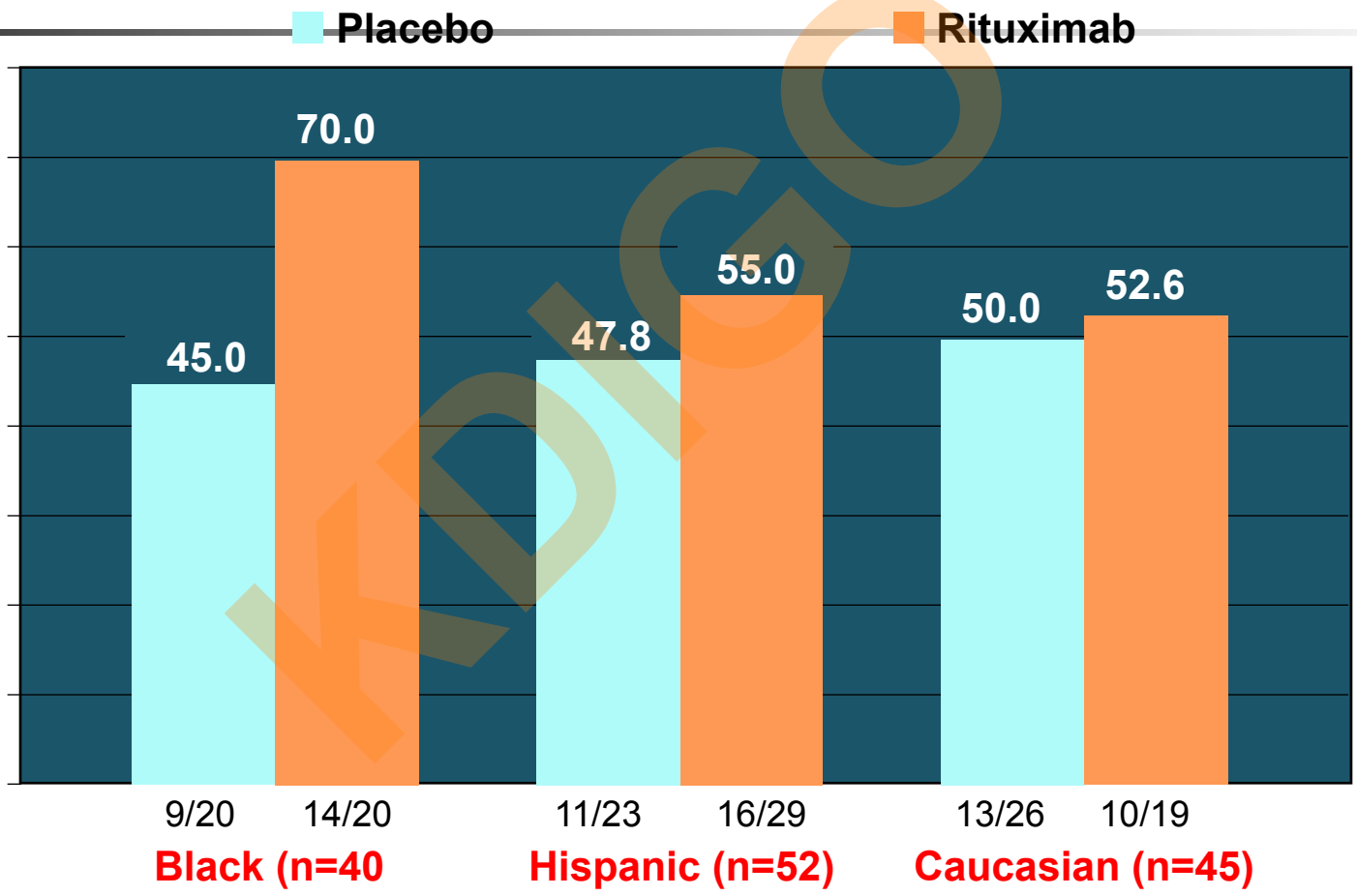
LUNAR:
Renal Response Rates Over Time



▲ **Rituximab infusions (1000 mg)**

PLC=placebo, RTX=rituximab, CRR=complete renal response, PRR=partial renal response

LUNAR0Pre-Specified Analysis: *Proportion of Subjects Achieving Response by Race*



LUNAR:
Safety Summary

n (%)	Placebo (N=71)	Rituximab (N=73)
Any adverse event (AE)	68 (95.8)	71 (97.3)
Serious adverse event (SAE)	25 (35.2)	22 (30.1)
Infectious AE	61 (85.9)	61 (83.6)
Infectious SAE	12 (16.9)	12 (16.4)
Infusion-related AE	29 (40.8)	25 (34.2)
Infusion-related SAE	2 (2.8)*	1 (1.4)**
AE leading to withdrawal from study	3 (4.2)	1 (1.4)
Human anti-chimeric antibody (HACA)-positive	4 (5.6)***	8 (11.1)
Death	0 (0)	2 (2.7)

** Urticaria requiring interruption of infusion (HACA titer 35,000 ng/mL)
*** One subject received open-label RTX

LUNAR:
Conclusions

- **LUNAR is the largest randomized, placebo-controlled trial to evaluate Rituximab as a therapeutic intervention (induction of remission) in LN, when combined with "standard" immunosuppression (MMF + steroids)**

- **Although there were more renal responders with Rituximab (57% vs. 46%), the study did not show a statistically significant difference in primary or secondary endpoints at week 52**

- **Rituximab had a statistically significant effect on levels of anti-dsDNA and C levels. AA may have a better renal response**

- **Adverse events and serious adverse events were similar in frequency between groups, with no new or unexpected safety signals**

Rituximab is *not currently indicated (or approved by the FDA)* for induction of Remission in Lupus Nephritis; with or without concurrent therapy with MMF or CYC

RITUXIMAB THERAPY for *REFRACTORY* LUPUS NEPHRITIS

(No Renal Response [CRR or PRR] after 3-6 months of CYC or MMF + steroids for Induction)

Rituximab in "Refractory" or Relapsing LN

(Catapano F, et al NDT 2010; 25: 35686-3592)

- **31 patients with "refractory" or "relapsing" SLE (11 with LN) treated with Rituximab 375mg/m2 x 4 or 1000mg x 2 and followed for a median of 30 months.**
- ***27/31 (87%) achieved a CR or PR. 10/11 with LN achieved a CRR or PRR***
- **18/31 (53%) relapsed in 11 months on or after B-cell return in 10 but in the absence of B-cell return in 8**
- **Infusion reactions were common (58%) and infection developed in 26%**

Rituximab in *"Refractory"* LN

(Diaz-Lagares C, et al Autoimmun Rev 2012; 11: 357-364)

- **146 patients with Class III, IV or V LN treated with Rituximab and CYC (n=124 or MMF (n=55)- uncontrolleld**
- **6 months- CRR= 27%; PRR= 40%**
- **12 months- *CRR= 30%; PRR= 37%***
- **Better response in Class III compared to Class IV or V**
- **Poorer response in NS or AKI**

Rituximab in *"Refractory"* LN

(Bang SY, et al Autoimmune Dis 2012)

- 39 patients with SLE (44% wth LN) refractory to treatment with CYC (44%) or MMF (49%) were treated with Rituximab and followed for 24 months.
- SLEDAI score- 11 → 5.5 at 24 months
- *28/39 (72%) had a CRR or PRR*
- Relapse at 25 months in 4/28 (14%)responders
- Infections in <10%

Rituximab in Severe LN:

Early B Cell Depletion Affects Long-Term Renal Outcome

(Melander et al CJASN 4: 579-587, 2009)

- **20 Patients treated with RTX for LN and followed at least 12 months.**
- **19F/1M Active IV (n=15) or V (n=5)**
- **12 Patients refractory to standard therapy , 6 cases relapsing disease, 2 patients first line therapy**
- **3 concurrent cyclophosphamide, 10 continued RTX as maintenance**

Rituximab in Severe LN:

Early B Cell Depletion Affects Long-Term Renal Outcome

(Melander et al CJASN 4: 579-587, 2009)

- **At 22 months complete or partial renal remission in 12/20 (60%) .**
- **LN relapsed in 1 patients who responded to another RTX course**
- **Side effects: 5 infections and 4 moderate neutropenias (late onset)**
- **B cell depletion 1 month post-Rituximab was strongly associated with renal response (negatively associated with Black race and hypoalbuminemia)**
- ***RPGN with crescentic disease did not respond.***

Rituximab in "*Refractory*" LN

(Jonsdottir T, et al, Rheumatology (Oxford) 2013; 52:847-855)

- 25 patients with LN "refractory" to standard therapy treated with Rituximab. Followed for a mean of 36 months.
- 22/25 *(88%)* had a PRR or CRR after median of 12 months; 16/25 (64%) had a CRR after a median of 24 months
- 6/22 (27%) responders had a relapse
- Longer B-cell depletion time associated with a better outcome

Rituximab in *"Refractory"* LN: *Systematic Review*

(Weidenbusch M, et al NDT 2013; 28:106-111)

- **Systematic Review of 26 published reports of use of Rituximab for "Refractory" LN (n=300; all observational; mean follow-up 60m)**
- **Class III- CRR/PRR= 87%; CRR= 60%**
- **Class IV—CRR/PRR= 76%; CRR= 45%**
- **Class V-- CRR/PRR= 67%; CRR= 40%**
- **Class III/IV + V = 76%; CRR= 24%**

Observational studies of Rituximab therapy shows "beneficial" effects in *"Refractory" or "Relapsing"* LN (60-80% CRR + PRR) but relapses common (15-30%). Late onset neutropenia of concern. No benefit in RPGN with crescents

RITUXIMAB for *STEROID-FREE MAINTENANCE* and for TREATMENT of *RELAPSES*

Treatment of Class IV LN with MMF and Rituximab with NO Oral Steroids

- 50 Patients; average age 35 years
- ISN/RPS Class IV Salb 2.2 g/dl Scr= 129 umol/L
- Treated with 2 doses Rituximab 1 g + IV methylprednisolone pulses 500mg 2 wks apart and then maintained on MMF. No oral steroids.
- Followed at 35 +/- 14 months

Condon MB, et al. Ann Rheum Dis 2013)

Treatment of Class IV LN with MMF and Rituximab with N0 Oral Steroids

- 45/50 (90%) CRR/PRR - Mean time- 37 weeks
- 36/50 (72%) CRR - Mean time- 32 weeks 6 months
- 11 patients (22%) relapsed by 65 weeks
- 9 Hospitalizations (18%)- 10% for a serious infection episode , 1 PVD died post surgery.

Condon MB, , Griffith M, Cook HT, Levy J, Lightstone, L,Cairns T ASN 2010

Rituximab in SLE and LN: *Conclusions*

- **Rituximab appears to be beneficial as rescue therapy for some patients (Class III/IV LN) with relapsing or refractory (to standard therapy) disease.**
- **Rituximab is mostly used with other therapies – however, steroid-free maintenance with Rituximab is possible**
- **The role of Rituximab as a first line agent in Induction for LN remains to be defined. May have a role in certain populations – Blacks and Hispanics.**
- **In general, Rituximab it has been well tolerated, expt for late onset leucopenia; Infusion reactions are uncommon but can be severe. Infection rate is low. PML rate is low but not zero**
- **Rituximab is "an interesting therapeutic option" for difficult to treat LN**

BELIMUMAB

BELIMUMAB (Benlysta®) for Lupus Nephritis

- ***Belimumab*** **is approved by FDA for treatment of SLE (without nephritis) based on a positive Phase III RCT) .Efficicy in African-Americans is uncertain**
- **A post-hoc pooled analysis of all Phase III trials in SLE patients with LN at baseline (n=267 of 1684 total) was conducted***
- **Trends (not significant) for improved renal outcomes (proteinuria , BILAG, serology) seen in Belimumab vs placebo. Greater improvement was seen in subjects receiving MMF who were serologically active**

(*Dooley MA, et al. Lupus, 2013)

OCRELUZIMAB

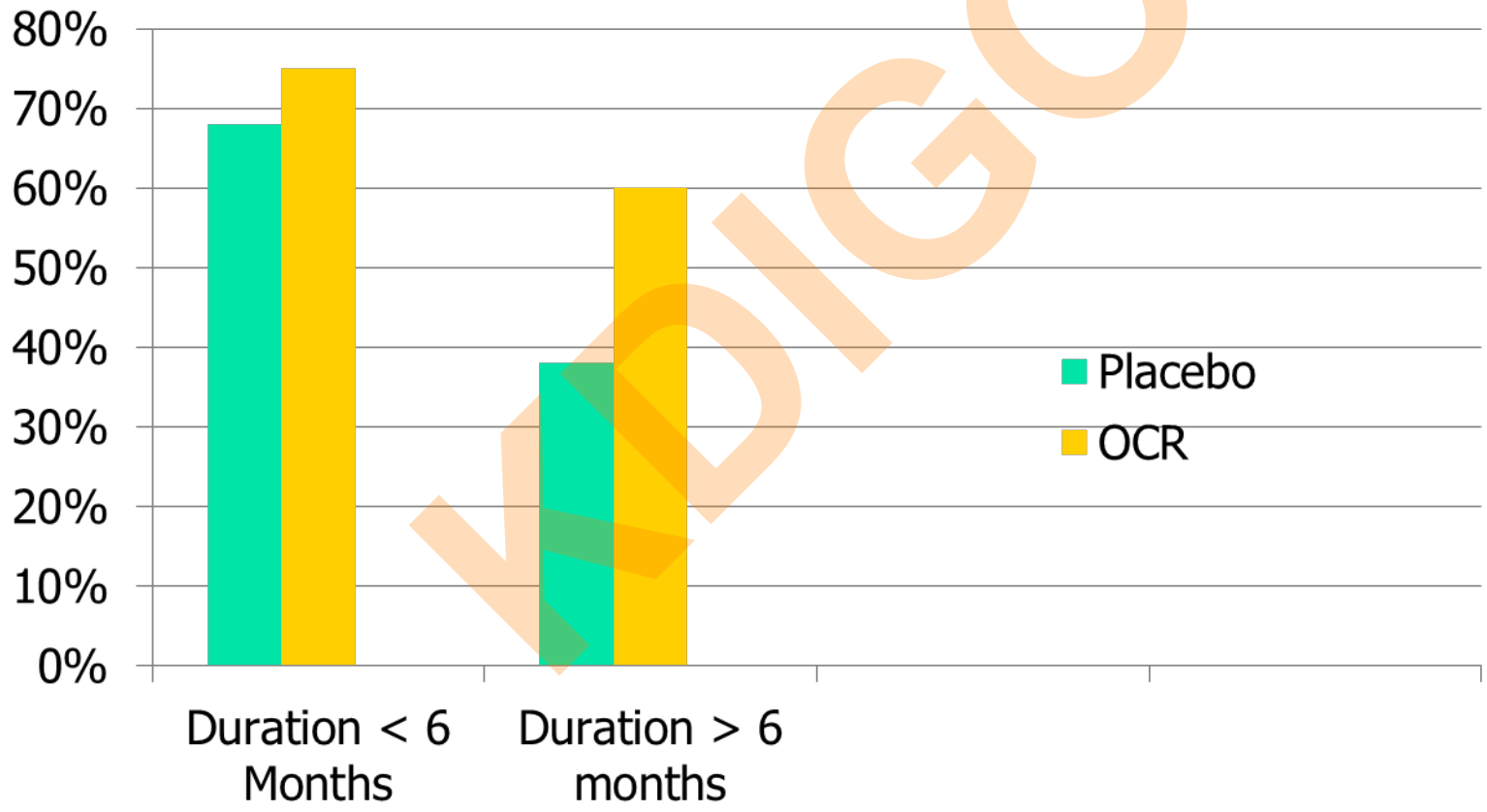
Ocreluzimab for Lupus Nephritis (BELONG)

- ***Ocreluzimab*** **(OCR)+ MMF or CYC (Eurolupus protocol) vs Placebo + MMF or CYC underwent a Phase III pivotal trial in LN but the study was stopped prematurely due to excess infection rates in the active drug treated groups**

- **At the time of discontinuation no difference in efficacy (ITT) between OCR + MMF or CYC and Placebo + MMF or CYC groups**

Efficacy of OCR in LN:

Exploratory (post-hoc) analysis of % Renal Response according to duration of disease prior to randomization



ABATACEPT

ABATACEPT (Orencia®) for Lupus Nephritis

(Wofsy D, et al Arthritis Rheum 2012; 64: 3660-3665)

- **A Phase III trial of *Abatacept* (IM101075) for induction of remission in Lupus Nephritis on a background of MMF and steroids *failed* to meet the primary outcome (frequency of CRR at 12 months)**

- **However a *post-hoc* analysis of the trial, using different end-point criteria (ALMS, LUNAR and ACCESS)- showed significant differences. Using LUNAR criteria a CRR was seen in 6% of controls vs 22-24% in the Abatacept arms (2 dosing levels)**

- **The choice of *how a CRR is defined* can determine if a LN trial is a success or a failure!!!**

Issues Concerning Selection of "Correct" Surrogate End-Points for Evaluation of Novel Drugs for LN

- **The *Kidney Health Initiative* (a consortium of ASN, FDA, CDC, NIH, CMO, Pharma and Device Companies, CMS, Patients and Providers) to foster innovations in treatment of Kidney Disease**

- **One of 3 initial pilot projects (headed by Brad Rovin, MD- Ohio State and partnered with the Lupus Nephritis Trial Network) will examine the strengths and weaknesses of existing surrogate endpoints and make consensus recommendations for *new outcome measures, biomarkers, remission and relapse definitions and surrogate end-points for trials of LN* going forward**

(see www.kidneyhealthinitiative.org)

Other Biologic Agents

Other Biologic Agents in Lupus Nephritis

- Ataticept
- Epratuzumab
- Abetimus
- CTLA4Ig
- Anti-TWEAK
- Anti-CD40L
- Eculizumb*
- ACTH**

(* approved by FDA for treatment of atypical HUS, not LN; ** approved by FDA for treatment of SLE)

Other Biologic Agents in SLE and LN

- ***Atacicept***- NCT-01369628- Serono- Terminated for toxicity
- ***Epratuzumab***- NCT- 01262365 (EMBODY-1)-Active Phase III- UCB- (Japan only)
- ***Eculizumab***- No Trials in SLE or Nephritis
- ***ACTH (Acthar Gel)-*** NCT-01769937 (single site) and NCT-012753401 (multi-site- Phase IV- placebo-RCT- QuestCor
- ***Abetimus (Riquent)-***NCT-00089804- Terminated –ineffective- La Jolla Pharm
- ***Anti-TWEAK (ATLAS)-***NCT-0149935- Active- Phase II- Biogen
- ***CTLA4Ig-*** NCT-00094381- Active Phase II- (NIH)
- ***Anti-CD40L (9588)--*** NCT00001789- Active – Phase II –(NIH)

SUMMARY-

New Biologics in Treatment of Lupus Nephritis- I

- ***Rituximab*** **(anti-CD20 chimeric MoAb) shows great promise for treatment of refractory and/or relapsing LN. Steroid-free remissions may be maintained by periodic Rituximab infusions (? 500-1000 mg every 4-6 months). Long-term safety and efficacy (hard end-points of mortality or ESRD) still uncertain, but short term safety seems reasonable. Efficacy for induction unknown. No positive RCT (yet)- Evidence level B/C**

SUMMARY-

New Biologics in Treatment of Lupus Nephritis- II

- **Other Biologic agents of uncertain value- (incompletely assessed)- need more RCT and observation studies**
- **Abatacept is promising, but a confirmed positive result in a RCT is needed**
- **Abetimus, Ocrelizumab, Atacicept not effective or unsafe**
- **Combinations of MoAb's or fusion protein receptor antagonists (anti-CD20 + CTLA4Ig or anti-Blys/BAFF might be efficacious- not tested)_**

SUMMARY-

New Biologics in Treatment of Lupus Nephritis-III

- **Long-term safety (especially for latent viral diseases like PML) is a nagging concern– risk seems low (<1:30,000 patient years)**

- **Rituximab is contra-indicated if concomitant Hepatitis B viral infection is present (reactivation of viral replication)**

QUESTION #2B

- **A 23 year old woman with a 7 year history of Systemic Lupus Erythematosus develops nephrotic syndrome (urine protein excretion of 5.6gms/d, serum albumin of 2.4gms/dL). Her serum creatinine is 1.30mg/dL (115µM/L; eGFR- CKD-EPI-creatinine= 58ml/min/1.73m2). A C3 is 46mg/dL and a C4 is 9mg/dL/ The anti-dsDNA titer is 1:1280. A pregnancy test is negative. She indicates a desire to eventually have children.**

QUESTION #2B

- **A renal biopsy reveals Severe Lupus Nephritis Class IV- Segmental; a+c; 15 % of the glomeruli show crescents. Moderate interstitial nephritis is present. IF shows moderate segmental deposits of IgG, C3, C1q. EM shows mesangial and sub-endothelial electron dense deposits and scanty sub-epithelial deposits. Tubulo-reticular inclusions are present in endothelial cells.**

QUESTION #2B

- **In addition to 3 doses of IV methylprednisolone (500mg each), which one of the following treatments would you start now?**

A. Oral MMF at 2.0gms/d + oral prednisone at 60mg/d

B. IV cyclophosphamide 500mg every two weeks for 3 months+ oral prednisone at 60mg/d

C. IV cyclophosphamide 1000mg/m2 monthly for 6 months+ oral prednisone at 60mg/d

D. Oral cyclophosphamide 2mg/kg/d or 3 months + oral prednisone at 60mg/d

E. Rituximab 375m/m2 every week times 4 weeks + oral prednisone at 60mg/d

F. Cyclosporine 4mg/kg/d + MMF 2 gms/d + oral prednisone at 60mg/d