

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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II. Supplementary methods

A. Patient inclusion and exclusion criteria

Inclusion Criteria

- Idiopathic MN diagnosed by renal biopsy (original biopsy needs to include light, immunofluorescence and electron microscopy) showing subepithelial projections (“spikes”) along the capillary walls on methenamine silver stain by light microscopy, granular deposition of IgG and C3 along the capillary walls on immunofluorescence microscopy and subepithelial deposits are seen on electron microscopy; pathology report must be adjudicated by a study PI (Dr. Fervenza or Dr. Cattran, or documented delegate) prior to randomization.
- Age 18-80 years inclusive
- If female, must be post-menopausal, surgically sterile or practicing a medically approved method of contraception (with exception of no birth-control pill given the potential for increased risk of thromboembolism in the nephrotic setting).
- Patient must be off prednisone or mycophenolate mofetil for >1 month and alkylating agents for >6 months. The rationale is to minimize the potential confounding effect of delayed benefits from previous immunosuppressive agents and to reduce the risk of too much immunosuppression from the combined previous drug exposure plus trial drug exposure, e.g. infections.
- Treatment with an ACEi and/or ARB, for ≥3 months prior to randomization and adequate blood pressure control (target BP is <130/80 mm Hg in >75% of the readings, but subjects with BP <140/80 mmHg in >75% of the readings will be eligible).

OR

If patient is intolerant to even a very low dose of either ACEi or ARB therapy, approval for participation in the trial has been obtained from the study PI(s) prior to randomization.

Patients with documented evidence of ≥3 months treatment with maximal angiotensin II blockade, on an HMG-CoA reductase inhibitor, and BP control (BP <140/80 mm Hg in >75% of the readings) who remain with proteinuria ≥5g/24h and meet the other eligibility criteria (as confirmed at the Time 0 visit by the central lab results) may enter the treatment phase of the study and be randomized to RTX/CSA without the need of the run-in/conservative phase of the study. However, in addition these patients must have a documented <50% reduction in proteinuria compared to previous 24 hr proteinuria or Uprot/Ucrea ratio estimates during this period of ACEi and/or ARB treatment otherwise

they must fulfill the run-in requirement (Please refer to manual of operation for clarification of tests mandated for patients who are randomized without the run-in period).

- Proteinuria $\geq 5\text{g}/24\text{h}$ using the average from two 24-hour urine collections collected within 14 days of each other despite Ang II blockade for ≥ 3 months as described above.
- Estimated GFR ≥ 40 ml/min/ 1.73m^2 while taking ACEi/ARB therapy OR quantified endogenous creatinine clearance ≥ 40 ml/min based on a 24-hour urine collection. The GFR will be estimated using the 4 variable MDRD equation as published in the NKF-CKD guidelines. This approach is adopted, rather than the much more expensive and more invasive techniques (e.g. inulin or iothalamate clearance) since the likelihood of detecting significant changes in GFR in this short term study is remote regardless of which method is chosen. At entry into the study and at set time points thereafter patients will also have a 24h urine collection for calculation of CrCl and proteinuria.

Exclusion Criteria

- Patients with presence of active infection or a secondary cause of IMN (e.g. hepatitis B, SLE, medications, malignancies). Testing for HIV, Hepatitis B and C should have occurred < 2 years prior to enrolment into the study. Screening for malignancy should be carried out according to standard guideline recommendations.
- Type 1 or 2 diabetes mellitus: to exclude proteinuria secondary to diabetic nephropathy. Patients who have recent history of steroid induced diabetes but no evidence on renal biopsy performed within 6 months of entry into the study are eligible for enrolment.
- Pregnancy or breast feeding (for safety reasons).
- History of resistance to CSA (or other calcineurin inhibitors, e.g. tacrolimus), RTX or alkylating agents (e.g. Cytoxan). Patients who previously responded to CSA/CNI, RTX or alkylating agents with either a CR or PR but relapsed off CSA/CNI after 3 months, or relapsed off RTX or alkylating agent after 6 months, are eligible.

B. Primary outcome

The primary outcome of the MENTOR trial was defined as a composite of CR or PR of proteinuria at 24 months after randomization. The primary endpoint was assessed in an intention to treat (ITT) analysis.

- CR: proteinuria ≤ 0.3 g/24h and serum albumin $\geq 3.5\text{g/dl}$

- PR: Reduction in baseline proteinuria of $\geq 50\%$ plus final proteinuria ≤ 3.5 g/24h but >0.3 g/24h

CR and PR were therefore defined irrespective of eGFR, PR was defined irrespective of serum albumin.

Patients who reached less than 25% reduction of proteinuria from baseline at 6 months, patients who relapsed, patients who had a premature termination of the protocol-specified treatment schedule before 12 months due to disease activity or adverse event, patients who used an immunosuppressive medication other than the study medication for the treatment of membranous nephropathy before 12 months, patients who used any immunosuppressive medication for the treatment of membranous nephropathy after 12 months and before 24 months and patients who did not meet criteria of CR or PR at 24 months were considered failures. Patients who were lost to follow-up at 24 months were considered failures unless they were found to have achieved CR or PR at their 18 month visit.

C. Secondary outcomes

The pre-specified secondary outcomes and the populations and timepoints analysed for these outcomes were as follows:

- Composite of CR or PR
 - ITT population, at 6, 12 and 18 months

CR was defined as proteinuria ≤ 0.3 g/24h and serum albumin ≥ 3.5 g/dl; PR was defined as a reduction in baseline proteinuria of $\geq 50\%$ plus final proteinuria ≤ 3.5 g/24h but >0.3 g/24h.
- Time to composite of CR or PR
 - ITT population, up to 12 months
- CR
 - ITT population, at 6, 12 and 18 months
- Proteinuria
 - Patients with complete or partial remission at each time point, at months 6, 12, 18 and 24
 - Anti-PLA2R+ patients with complete or partial remission at each time point, at months 6, 12, 18 and 24
- Relapse
 - Patients with CR or PR at end of 12-month treatment period, at 24 months

Relapse was defined as development of nephrotic range proteinuria of >3.5 g/24h.

- Treatment failure
 - ITT population, at 6, 12, 18 and 24 months

Treatment failure was defined as less than 25% reduction of proteinuria from baseline at 6 months, relapse (see above for definition), premature termination of the protocol-specified treatment schedule before 12 months due to disease activity or adverse event, use of an immunosuppressive medication other than the study medication for the treatment of membranous nephropathy before 12 months, use of any immunosuppressive medication for the treatment of membranous nephropathy after 12 months and before 24 months, loss to follow-up before 24 months, or not meeting criteria of CR or PR at 24 months (see section 3.3. for definition).

- Time to treatment failure
 - ITT population
 - Subgroup of patients with CR or PR at the end of treatment period, from 12 to 24 months
- Anti-PLA2R levels
 - Anti-PLA2R+ patients with complete or partial remission at each time point, at months 6, 12, 18 and 24
 - Patients with complete or partial remission at each time point, at months 6, 12, 18 and 24
- Quality of life as assessed by the Kidney Disease Quality of Life Short Form (KDQOL-SF), Version 1.3
 - Patients with complete or partial remission at each time point, at months 6, 12 and 24

The KDQOL-SF includes the SF-36 as a generic core plus various subscales related to kidney disease.

The following subscales were given precedence: physical health composite and mental health composite of SF-36; burden of kidney disease; symptom/problems; effects of kidney disease on daily life.

- $\geq 50\%$ decrease in creatinine clearance from baseline
 - ITT population, at 24 months
- End stage renal disease
 - ITT population, at 24 months

End stage renal disease was defined as stage 5 chronic kidney disease with an estimated or measured GFR <15 mL/min or initiation of permanent renal replacement therapy (dialysis or transplant).

- Creatinine Clearance
 - Patients with complete or partial remission at each time point, at months 6, 12, 18 and 24

The safety outcomes, which were also considered secondary outcomes, and the populations and timepoints analysed for these outcomes were as follows:

- All adverse events
 - Safety population, up to 24 months
- Adverse events were defined as any untoward medical occurrence and their severity graded as follows:
- Grade 1: mild
 - Grade 2: moderate
 - Grade 3: severe or medically significant
 - Grade 4: life-threatening
 - Grade 5: fatal
- Adverse events grade ≥ 3
 - Safety population, up to 24 months
 - Adverse events grade < 3
 - Safety population, up to 24 months
 - Serious adverse events
 - Safety population, up to 24 months

Serious adverse events were defined as any untoward medical occurrence that results in death, is life-threatening requires inpatient hospitalization or causes prolongation of an existing hospitalization, results in disability or permanent damage, or in a congenital anomaly/birth defect in the offspring.

D. Sample size considerations

The primary objective of this trial was to determine whether Rituximab is non-inferior to Cyclosporine in inducing long-term CR or PR of proteinuria in patients with idiopathic membranous nephropathy at 24 months after randomization. Assuming that 55% of patients on Rituximab, and 45% on Cyclosporine have a CR or PR of proteinuria at 24

months after randomization, 63 patients per group would result in 80% power to detect non-inferiority at a one-sided alpha of 0.025 (corresponding to a two-sided alpha of 0.05) and a non-inferiority margin of 15% on an absolute risk difference scale.

As previously described,¹ preliminary data indicated that cyclosporine is effective in inducing a CR or PR of proteinuria in between 60 and 75% of MN cases.^{2,3} However, nephrotic syndrome relapses may be as high as 50% once cyclosporine is discontinued.⁴ Thus, we estimated a percentage of the composite of CR or PR in patients treated with cyclosporine of approximately 45% at 24 months after randomization. Similar remission and relapse rates with the use of tacrolimus were reported by Praga et al.⁵ In this latter study, almost half of the MN patients had a relapse of the nephrotic syndrome after tacrolimus was discontinued. On the other hand, based on the long term follow up on 35 patients treated with RTX from our own 2 studies, we estimate the relapse rate to be <10% at 24 months.^{6,7} A subsequent study by Ruggenenti et al. showed similarly low relapse rates.⁸

The decision to use a 15% non-inferiority margin was made by consensus among the investigators on the premise that even if the lower limit of the two-sided 95% confidence interval of the risk difference of the composite of CR or PR was compatible with rituximab being inferior to cyclosporine by 15%, rituximab would have other advantages, including tolerability, greater ease of administration (no need to take medications on a daily basis), certainty of compliance, no need to have frequent monitoring of drug and potassium levels, fewer side effects including lack of nephrotoxicity, lack of worsening hypertension and the need to take or increase anti-hypertensive medications, and potentially reduced cost since the relapse rate was expected to be lower after tapering of treatment in patients treated with rituximab when compared to patients treated with cyclosporine, who would become cyclosporine dependent and require this form of treatment long-term.¹ As such, the cumulative cost of cyclosporine over the years would be higher than the total cost of rituximab. This assumption has been confirmed by independent investigators comparing cost for rituximab versus the modified Ponticelli.⁹

The non-inferiority margin of 15% corresponded to half of the risk difference in the composite of CR or PR of approximately 30% that would be expected 12 months after the initiation of tapering of cyclosporine (composite of CR or PR expected in approximately 45% of patients) as compared with placebo or non-intervention control (composite of CR or PR expected in approximately 15%).²

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E. Extended description of statistical methods

Primary stepwise analysis of primary outcome

The primary analysis of the primary outcome of the composite of CR or PR at 24 months was performed in the ITT population using a stepwise approach for testing. First, we performed a confirmatory test of non-inferiority of Rituximab as compared with Cyclosporine. Using the non-inferiority test as a gatekeeper to control the family-wise type I error (the probability of making one or more type I errors when performing multiple tests), we only continued to perform a confirmatory test of superiority of Rituximab if the non-inferiority test was significant. Non-inferiority was pre-defined as a lower limit of the two-sided 95% confidence interval of the absolute risk difference of CR or PR (risk of CR or PR in the Rituximab group minus the risk of CR or PR in the Cyclosporine group) larger than -15% at 24 months. One-sided p values for non-inferiority were calculated from Z tests comparing differences between groups with the non-inferiority margin, calculating the standard error for the Z test for the primary outcome using a generalized linear model with a binomial distribution and identity link function. The test was considered significant if the one-sided p value was <0.025 (corresponding to a two-sided p-value of <0.05). As predefined, a confirmatory test of superiority of Rituximab at a two-sided p<0.05 was to be performed if the one-sided p-value of non-inferiority was significant at p<0.025. Rituximab was considered superior if a two-sided p value was <0.05. Model fit was assessed using a likelihood ratio test based on the deviance statistic D^2 , comparing the values predicted by the fitted model to those predicted by a hypothetical saturated model assumed to have a perfect fit. A negative likelihood ratio test suggested satisfactory model fit.

Secondary non-inferiority analyses

A secondary non-inferiority analysis of the primary outcome in the PP population at 24 months, and a non-inferiority analysis in the ITT population at 12 months, were performed. Since the composite of CR or PR at 12 months was a secondary outcome, we adopted a pre-specified Bonferroni correction, which allowed for this outcome to be tested in addition

to the primary outcome at a one-sided alpha level of 0.0125 (0.025/2). The test was therefore considered significant if the one-sided p value was <0.0125.

Analyses of secondary outcomes

All other comparison of outcomes between randomized groups were done using two-sided 95% confidence intervals. Binary outcomes were compared between groups based on risk differences with 95% confidence intervals. Time-to-event outcomes were analyzed using Kaplan Meier curves and hazard ratios from Cox regression models with 95% confidence intervals. Continuous outcomes were analyzed using analysis of covariance adjusted for baseline values of the analyzed continuous outcome. If data were strongly positively skewed, data were log transformed, geometric means with 95% confidence intervals calculated per group, and ratios of geometric means were derived using analysis of covariance adjusted for log transformed baseline values; to achieve better interpretability, differences in geometric means were estimated from the difference between geometric mean in control group and product of geometric mean in control group and geometric mean ratio, with appropriate 95% confidence intervals estimated from the difference between geometric mean in control group and product of geometric mean in control group and upper and lower limits of the geometric mean ratio. By design, patients did not undergo systematic assessment of continuous outcomes once they satisfied criteria for treatment failure. Therefore, continuous outcomes were analyzed in a cross-sectional manner at each time point only in patients with complete or partial remission to allow exploratory comparisons of the quality of remission between groups at each time point; this approach does not allow longitudinal comparisons between time points. No adjustment for multiple comparisons was done for secondary outcomes, as all comparisons were considered exploratory. Because the widths of 95% confidence intervals were not adjusted for multiple comparisons, these intervals should not be used for inference about treatment effects. Box and Whisker plots of proteinuria and anti-PLA2R levels were done after log transformation of the data.

Analyses of safety outcomes

Safety outcomes were tabulated by investigator-assessed relationship to study drug, by body system. In addition, safety outcomes were listed by type of adverse event if a type of event occurred in at least 4 patients during the trial. Comparisons between groups were done for both, the number of patients experiencing an event and for the number of events. The number of patients were compared between groups with a two-sided chi-squared test, or a two-sided Fisher's exact test if the number of expected events per group was below 5. Because p-values were not adjusted for multiple comparisons, they should not be used for inference about treatment effects.

Subgroup analyses

We undertook prespecified subgroup analyses of the primary outcome to determine whether the difference between rituximab and cyclosporine on the primary outcome varied according to prespecified subgroups of baseline characteristics: sex, age (≤ 50 versus > 50 years of age), proteinuria ($< 8\text{g}/24\text{h}$ vs $\geq 8\text{g}/24\text{h}$), anti-PLA2R status (positive, defined as $>$

40 U/mL, versus negative), previous immunosuppressive therapy (naïve versus history of previous immunosuppressive therapy). In addition, we performed exploratory subgroup analyses of the composite of CR or PR at 12 months that were only specified post-hoc. Subgroup analyses were accompanied by two-sided P-values derived from z-tests for interaction between treatment and subgroup.

Sensitivity analyses

Pre-specified sensitivity analyses were conducted to investigate whether different approaches for statistical analysis would reach similar results. Sensitivity analyses of the primary outcome of CR or PR at 24 months and secondary outcomes of CR or PR at 6, 12 and 18 months included the following: generalized estimating equation (GEE) to derive risk differences with two-sided 95% confidence intervals; logistic regression, crude and adjusted for center and proteinuria at baseline (<8g/24h vs ≥8g/24h), to derive odds ratios with two-sided 95% confidence intervals; ordinal logistic regression to compare the ordered outcome of CR, PR or no response, crude and adjusted for center and proteinuria at baseline (<8g/24h vs ≥8g/24h). Pre-specified sensitivity analyses of continuous outcomes at 6, 12, 18 and 24 months included the following: mixed repeated measures linear regression with random intercepts for patients to derive differences in arithmetic means with two-sided 95% confidence intervals; mixed repeated measures linear regression with random intercepts for patients and random slopes for centers to derive differences in arithmetic means with two-sided 95% confidence intervals; analysis of covariance of log transformed outcome data adjusted for log transformed baseline values of the outcome to derive ratios of geometric means with two-sided 95% confidence intervals in case of strongly positively skewed data, such as proteinuria or anti-PLA2R data.

F. PLA2R ELISA test

The extracellular PLA2R protein sequence (NC8; 180 kDa) was used to coat ELISA plates at 0.125 µg/mL in sodium bicarbonate buffer (pH 9.6) for 18 hours. The PLA2R protein construct was the full extracellular sequence (amino acids 21–1397; containing N-terminal cysteine-rich domain, Fibronectin Type II domain, and C-type lectin domain 1–8) devoid of the transmembrane domain (amino acids 1398–1418) and cytoplasmic domain (amino acids 1419–1463). Plates were blocked for 1 hour with SuperBlock (Thermosystems) and kept at 4°C until use (within 3 days). Patient serum diluted 1:100 in superblock containing 0.1% Tween 20 was added in duplicate 100-µl aliquots to the ELISA plate, which also contained a six-point dilution series of Standards covering the range of 12.3u/mL to 3000u/ml and quality control sample in duplicate wells (between-plate quality control sample). After 2 hours incubation at room temperature on a plate shaker, the plates were washed thoroughly (eight times) with PBS plus 0.1% Tween 20. Anti-human IgG–horseradish peroxidase conjugate (HRP; Jackson Laboratories) diluted 1:25,000 in

Superblock was added (100 µl per well) and incubated for 2 hours as before. After washing as before, enzyme substrate tetramethylbenzidine (Sigma) was added and developed for 10 minutes, and the reaction was stopped with 0.5 M H₂SO₄. The plates were read at 450 nm, standard curves were plotted using Softmax software, and values were assigned to samples. Samples that were off scale were diluted 1:1000 to 1:10,000 and reanalyzed. The Standard was a pool of high-titer samples (n=10) that had been microfuged and filtered through 0.22-µm membrane, aliquoted, and stored in individual aliquots at -80°C until use.

Seventy-three serum samples from healthy individuals (mean age=41±10 years) were used to define the normal range. Using mean + 3 SD of the normal range, we report a threshold above 40 U/mL as positive. Results from 22 different plate batches show a coefficient of variation of 17.8%. Samples applied to the same plate report less than 8% variation.¹

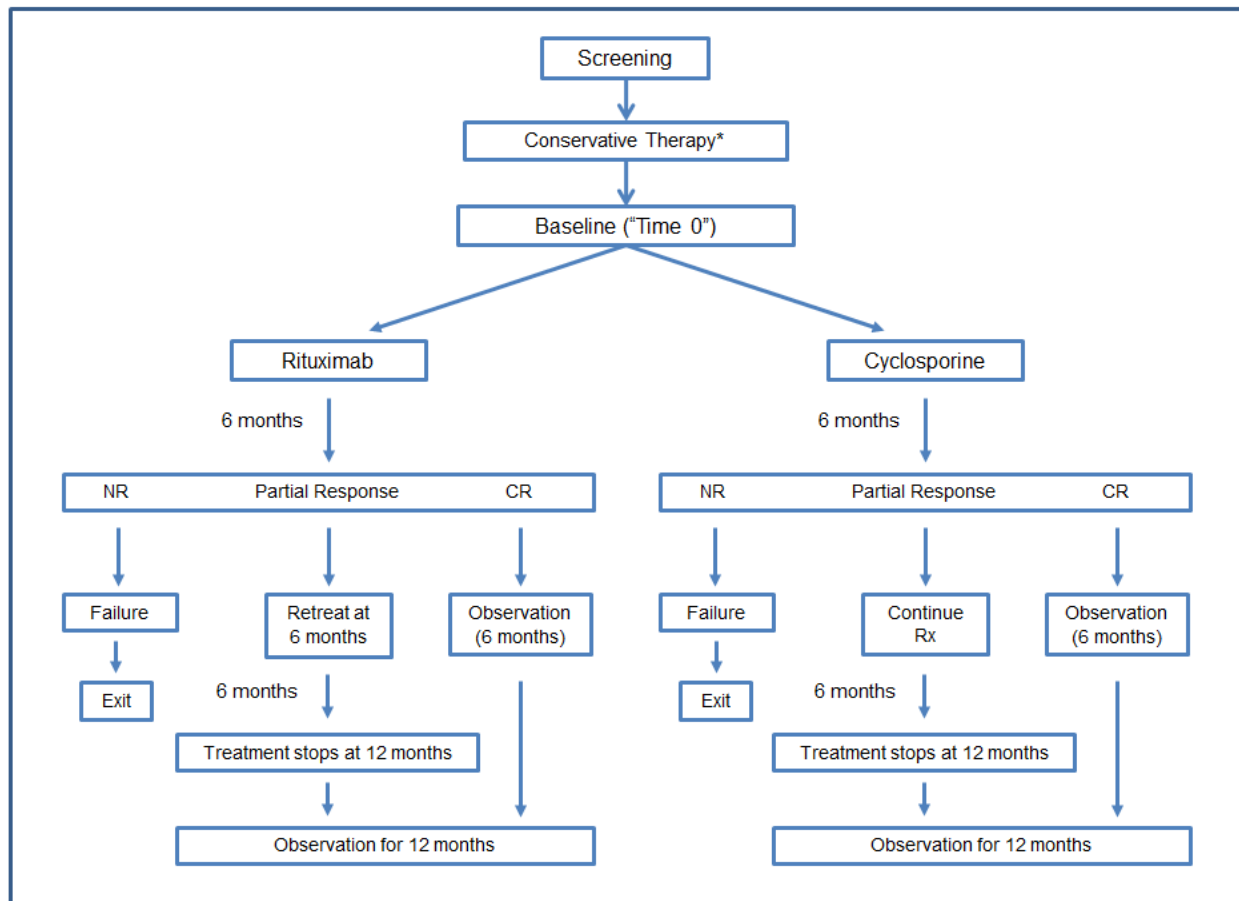
1. Kanigicherla D, Gummadova J, McKenzie EA, Roberts SA, Harris S, Nikam M, et al. Anti-PLA2R antibodies measured by ELISA predict long-term outcome in a prevalent population of patients with idiopathic membranous nephropathy. *Kidney Int.* 2013 May;83(5):940–8.

G. Data and safety monitoring board

The Data and Safety Monitoring Board (DSMB) acted in an advisory capacity to the PIs to monitor participant safety, data quality and evaluate the progress of the study. The DSMB convened meetings on a semiannual basis and provided recommendation to continue or to terminate the study. The recommendation was made by a formal majority vote based on safety concerns as evidenced by statistical and clinical judgment, progress of the trial including data quality and accrual/retention and new scientific or therapeutic developments that may have an impact on the safety. The Data Management and Coordination Center (DMCC) was responsible for the data analysis and the DMCC statistician provided the interface with DSMB members. The DSMB received semi-annual reports of enrollment and events, including events as reported by the site and had full access to the data.

III. Supplementary figures and tables referred to in main text

Figure S1: MENTOR study design



*See protocol for conservative therapy exemption criteria; NR, non-response defined as <25% reduction from baseline proteinuria; Partial Response at 6 months was defined as ≥25% reduction from baseline proteinuria but not a complete remission; CR, complete remission defined as proteinuria ≤0.3 g/24h and serum albumin ≥3.5g/dL.

Figure S2: CONSORT diagram

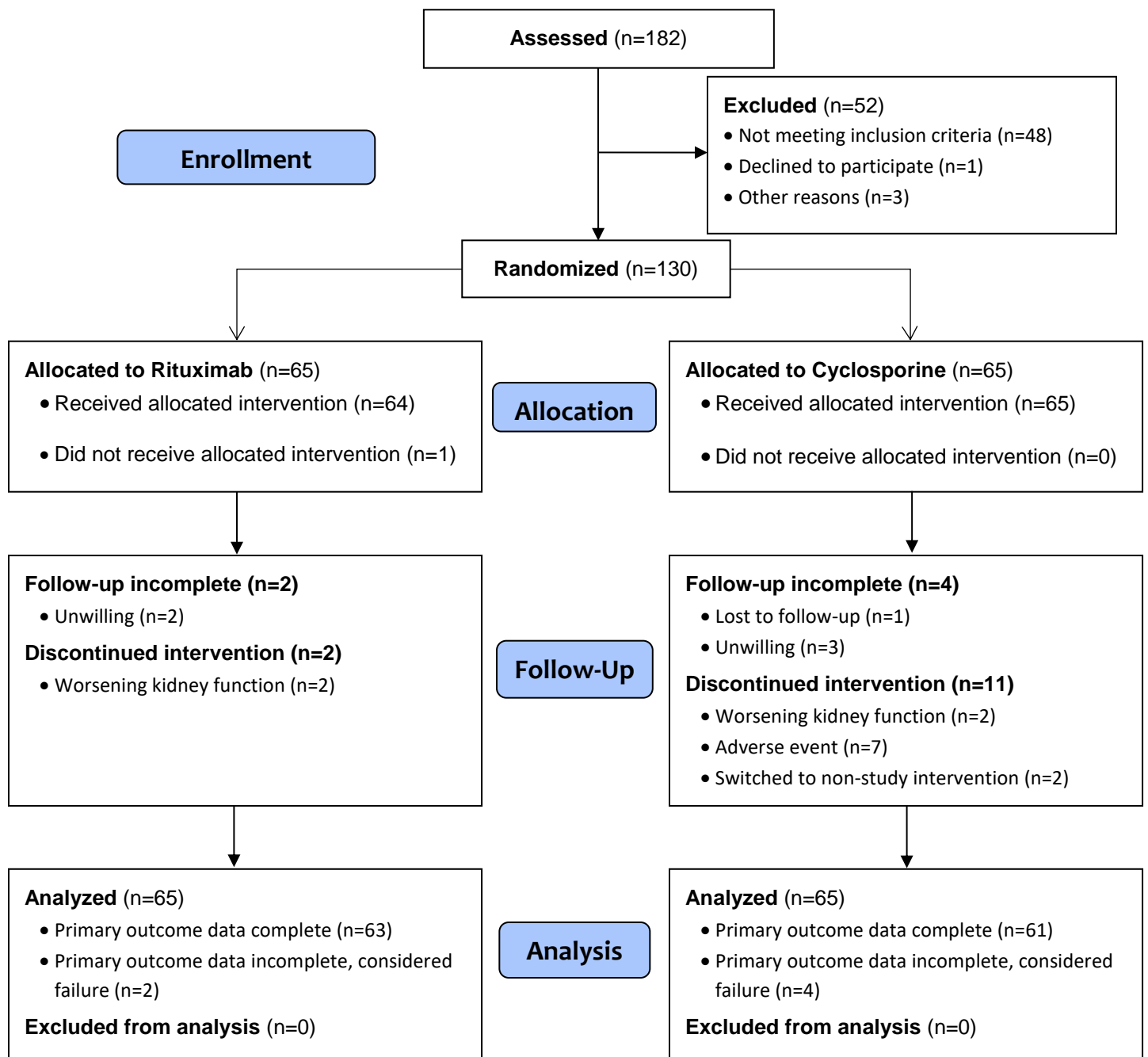


Table S1: Anti-PLA2R levels of anti-PLA2R positive patients with a decrease in proteinuria of $\geq 25\%$ and patients with a decrease in proteinuria of $< 25\%$ at 6 months

Anti-PLA2R – geometric mean (95% CI)	Decrease in proteinuria from baseline at 6 months			
	Rituximab		Cyclosporine	
	$< 25\%$	$\geq 25\%$	$< 25\%$	$\geq 25\%$
n	11	37	8	32
Baseline (u/mL)	587.4 (275.6 to 1251.7)	358.1 (237.2 to 540.7)	812.8 (228.3 to 2893.9)	410.9 (258.5 to 653.2)
Follow-up (u/mL)	208.9 (51.2 to 852.4)	16.0 (8.9 to 28.9)	156.1 (43.6 to 558.9)	53.9 (30.7 to 94.6)
Difference (95% CI)	148.1 (31.5 to 551.8)		59.6 (-19.1 to 315.9)	

48 and 40 anti-PLA2R positive patients underwent assessments at 6 months, of these 11 and 8 patients had a $< 25\%$ decrease in proteinuria from baseline, with rituximab and cyclosporine, respectively. Among anti-PLA2R positive patients, 48 and 40 patients underwent assessments at 6 months, of these 11 and 8 patients had a $< 25\%$ decrease in proteinuria from baseline. Because the widths of 95% confidence intervals of secondary outcomes were not adjusted for multiple comparisons, these intervals should not be used for inference about treatment effects; Anti-PLA2R, anti-phospholipase A2 receptor autoantibody; n, number of patients analyzed; CI, confidence interval.

Table S2: Immunological response of anti-PLA2R positive patients with a decrease in proteinuria of $\geq 25\%$ and patients with a decrease in proteinuria of $< 25\%$ at 6 months

Immunological response	Decrease in proteinuria from baseline at 6 months			
	Rituximab		Cyclosporine	
	$< 25\%$	$\geq 25\%$	$< 25\%$	$\geq 25\%$
n	11	37	8	32
No. events (%)	1 (9.1)	25 (67.6)	1 (12.5)	12 (37.5)
Difference (95% CI)	-58.5 (-81.2 to -35.8)		-25.0 (-53.4 to 3.4)	

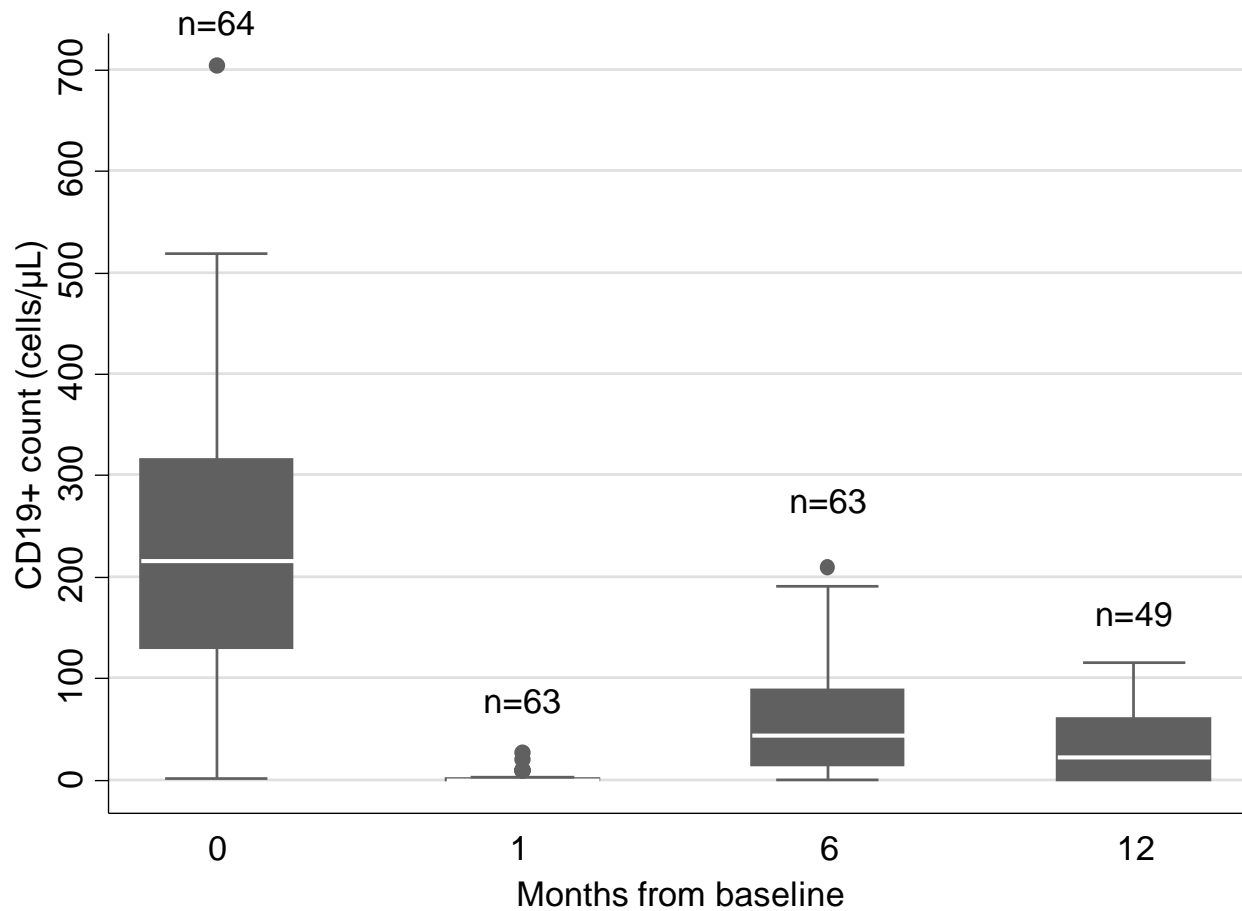
48 and 40 anti-PLA2R positive patients underwent assessments at 6 months, of these 11 and 8 patients had a $< 25\%$ decrease in proteinuria from baseline, with rituximab and cyclosporine, respectively. Because the widths of 95% confidence intervals of secondary outcomes were not adjusted for multiple comparisons, these intervals should not be used for inference about treatment effects; Anti-PLA2R, anti-phospholipase A2 receptor autoantibody; n, number of patients analyzed; CI, confidence interval.

Table S3: Serum albumin of patients with a decrease in proteinuria of $\geq 25\%$ and patients with a decrease in proteinuria of $< 25\%$ at 6 months

Serum Albumin – mean (95% CI)	Decrease in proteinuria from baseline at 6 months			
	Rituximab		Cyclosporine	
	$< 25\%$	$\geq 25\%$	$< 25\%$	$\geq 25\%$
All patients				
n	14	49	9	49
Baseline (g/dL)	2.7 (2.4 to 3.0)	2.6 (2.5 to 2.8)	2.4 (2.1 to 2.7)	2.7 (2.5 to 2.8)
Follow-up (g/dL)	2.8 (2.4 to 3.2)	3.5 (3.3 to 3.7)	2.6 (2.2 to 3.0)	3.5 (3.3 to 3.8)
Difference (95% CI)	-0.8 (-1.1 to -0.4)		-0.8 (-1.2 to -0.4)	
Anti-PLA2R positive patients				
n	11	37	8	32
Baseline (g/dL)	2.6 (2.2 to 2.9)	2.6 (2.4 to 2.7)	2.5 (2.1 to 2.8)	2.5 (2.3 to 2.7)
Follow-up (g/dL)	2.7 (2.2 to 3.1)	3.5 (3.2 to 3.7)	2.6 (2.1 to 3.1)	3.5 (3.2 to 3.8)
Difference (95% CI)	-0.8 (-1.2 to -0.4)		-0.9 (-1.3 to -0.4)	

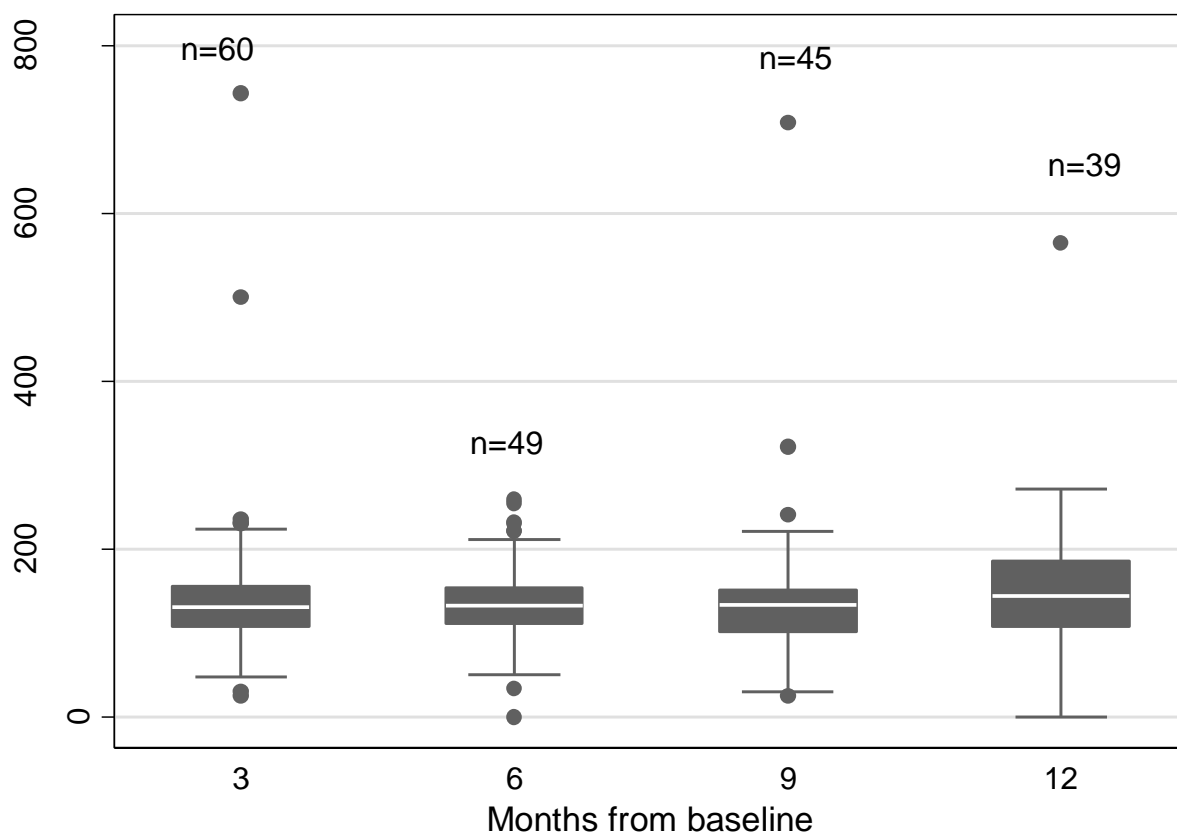
63 and 58 patients underwent assessments at 6 months, of these 14 and 9 patients had a $< 25\%$ decrease in proteinuria from baseline, with rituximab and cyclosporine, respectively. Among anti-PLA2R positive patients, 48 and 40 patients underwent assessments at 6 months, of these 11 and 8 patients had a $< 25\%$ decrease in proteinuria from baseline. Because the widths of 95% confidence intervals of secondary outcomes were not adjusted for multiple comparisons, these intervals should not be used for inference about treatment effects; Anti-PLA2R, anti-phospholipase A2 receptor autoantibody; n, number of patients analyzed; CI, confidence interval.

Figure S3: CD19+ Counts in patients randomized to rituximab



All patients randomized to rituximab with available data included for analysis of each time point; n, number of patients at each time point; Displayed are medians (white horizontal line), interquartile ranges (boxes), adjacent values (whiskers), and outliers (dots).

Figure S4: Cyclosporine serum trough levels in patients randomized to cyclosporine



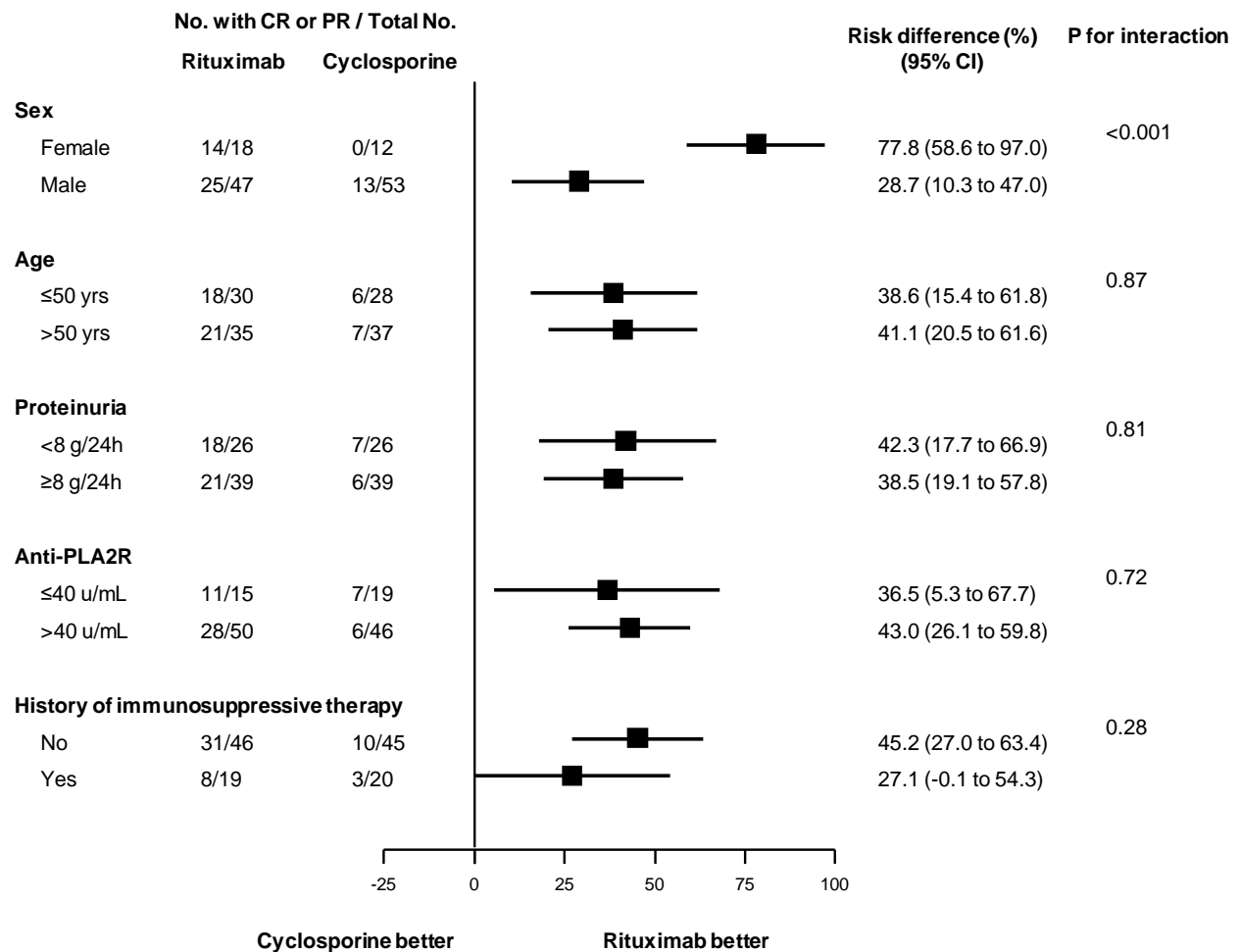
All patients randomized to rituximab with available data included for analysis of each time point; n, number of patients at each time point; Displayed are medians (white horizontal line), interquartile ranges (boxes), adjacent values (whiskers), and outliers (dots).

Table S4: Non-inferiority analyses of composite outcome of complete or partial remission at 12 and 24 months

Time from randomization	Rituximab		Cyclosporine		Risk difference (95% CI)	P-value*
	n	CR/PR (%)	n	CR/PR (%)		
ITT population						
12 months	65	39 (60.0)	65	34 (52.3)	7.7 (-9.3 to 24.7)	0.004
24 months**	65	39 (60.0)	65	13 (20.0)	40.0 (24.6 to 55.4)	<0.001
PP population						
24 months***	63	39 (61.9)	63	13 (20.6)	41.3 (25.7 to 56.9)	<0.001

n, number of patients analyzed; CR, complete remission; PR, partial remission; CI, confidence interval; *P-value is one-sided, for non-inferiority; ITT, intention to treat population consisting of 65 patients randomized to rituximab and 65 patients randomized to cyclosporine; PP, per-protocol population consisting of 63 patients randomized to rituximab and 63 patients randomized to cyclosporine. **Primary analysis of primary outcome. ***Secondary analysis of primary outcome.

Figure S5: Pre-specified subgroup analysis of the primary composite outcome of complete or partial remission at 24 months follow-up



Subgroup analyses of the primary composite outcome of complete or partial remission at 24 months by pre-specified characteristics of patients at baseline; Because the widths of 95% confidence intervals were not adjusted for multiple comparisons, these intervals should not be used for inference about treatment effects; 95% CI, two-sided 95% confidence interval; Two-sided P-values for interaction derived from z-tests.

Table S5: Selected baseline characteristics by group allocation and sex

	Rituximab		Cyclosporine	
	n		n	
Age, mean (SD) - yr				
Females	18	52.9 (13.3)	12	53.3 (12.5)
Males	47	51.5 (12.5)	53	52 (12.5)
Anti-PLA2R, median (IQR) - u/mL				
Females	18	179 (32 to 377)	12	535 (266 to 933.5)
Males	47	382 (48 to 764)	53	167 (23 to 552)
Anti-PLA2R positive (>40u/mL) - no. (%)				
Females	18	13 (72.2)	12	10 (83.3)
Males	47	37 (78.7)	53	36 (67.9)
Urine Protein, median (IQR) - g/24h				
Females	18	6.9 (6.1 to 8.7)	12	8.9 (6.5 to 14.8)
Males	47	10.4 (7.4 to 14.3)	53	8.9 (6.7 to 12.8)

Numbers displayed are mean and SD unless otherwise specified; SD, standard deviation; n, number of patients analyzed; Anti-PLA2R, anti-phospholipase A2 receptor autoantibody; IQR, interquartile range. The treatment by sex interaction (Figure S5) appears confounded by anti-PLA2R levels, with a tendency towards higher values in the cyclosporine arm among women, and a tendency towards lower values in the cyclosporine arm among men.

Table S6: Crude and adjusted treatment by sex interaction for primary outcome of complete or partial remission at 24 months

Time from randomization	Rituximab		Cyclosporine		Risk difference (95% CI)	P for interaction
	n	CR/PR (%)	n	CR/PR (%)		
Crude						<0.001
Females	18	14 (77.8)	12	0 (0)	77.8 (58.6 to 97.0)	
Males	47	25 (53.2)	53	13 (24.5)	28.7 (10.3 to 47.0)	
Adjusted						0.93
Females	18	-	12	-	33.3 (-20.0 to 86.7)	
Males	47	-	53	-	30.8 (5.7 to 55.9)	

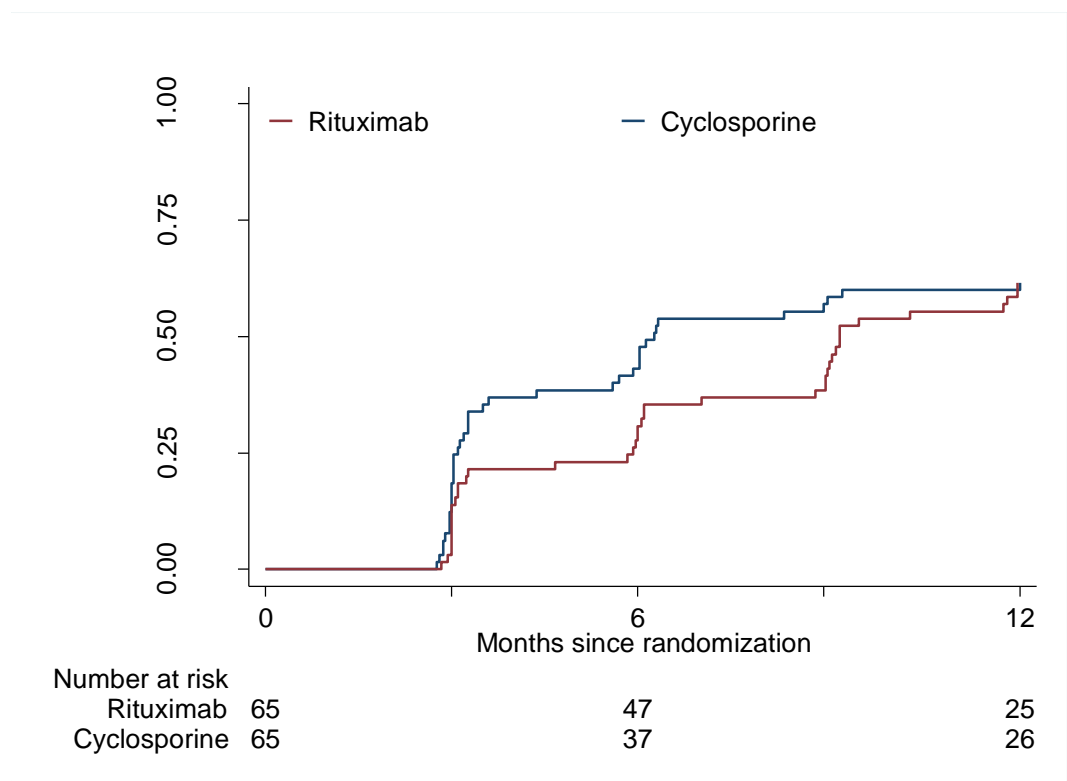
Adjusted risk differences and p-value for interaction calculated from analyses stratified by anti-PLA2R status and tertiles of anti-PLA2R levels in anti-PLA2R positive patients (anti-PLA2R negative versus lowest, mid and highest tertile in anti-PLA2R positive patients) to adjust for differences in anti-PLA2R levels at baseline. When analyses were stratified by anti-PLA2R status and tertiles of anti-PLA2R levels in anti-PLA2R positive patients to adjust for differences in anti-PLA2R levels at baseline, the interaction with sex disappeared entirely.

Table S7: Complete remission at 6 to 24 months

Time from randomization	Rituximab		Cyclosporine		Risk difference (95% CI)
	n	CR (%)	n	CR (%)	
ITT population					
6 months	65	0 (0.0)	65	1 (1.5)	-1.5 (-4.5 to 1.5)
12 months	65	9 (13.8)	65	3 (4.6)	9.2 (-0.6 to 19.1)
18 months	65	18 (27.7)	65	1 (1.5)	26.2 (14.9 to 37.4)
24 months	65	23 (35.4)	65	0 (0.0)	35.4 (23.8 to 47.0)
PP population					
6 months	63	0 (0.0)	63	1 (1.6)	-1.6 (-4.7 to 1.5)
12 months	63	9 (14.3)	63	3 (4.8)	9.5 (-0.6 to 19.6)
18 months	63	18 (28.6)	63	1 (1.6)	27.0 (15.4 to 38.6)
24 months	63	23 (36.5)	63	0 (0.0)	36.5 (24.6 to 48.4)

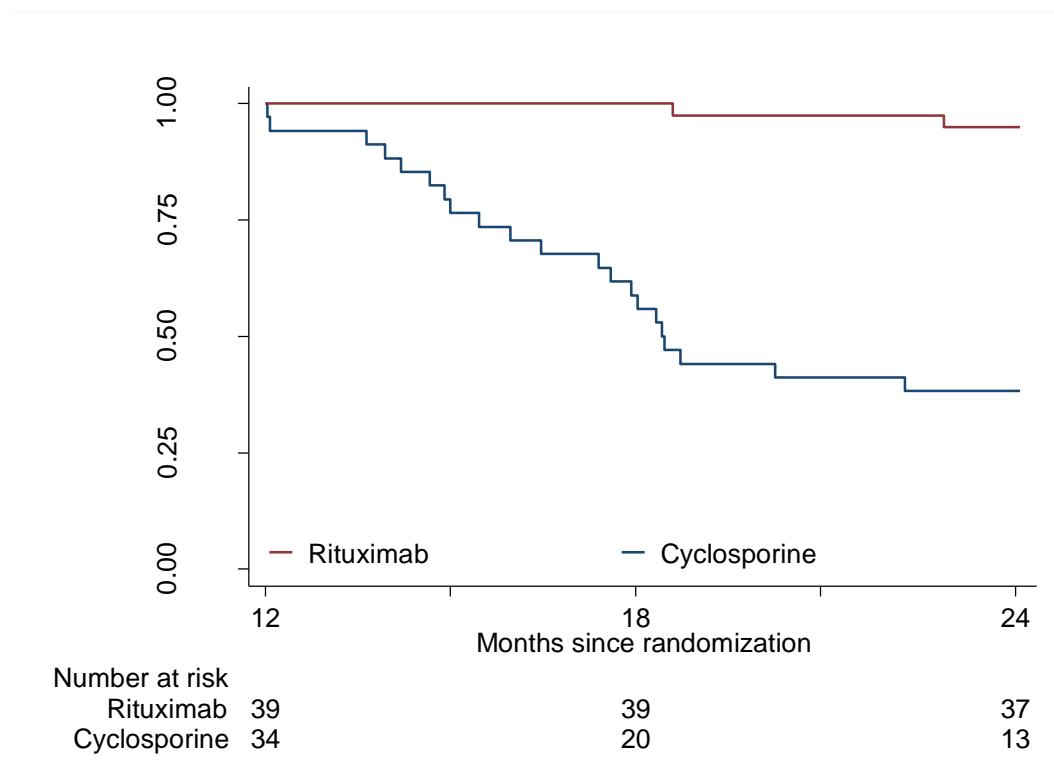
Because the widths of 95% confidence intervals of secondary outcomes were not adjusted for multiple comparisons, these intervals should not be used for inference about treatment effects; n, number of patients analyzed; CR, complete remission; CI, confidence interval; ITT, intention-to-treat population consisting of 65 patients randomized to rituximab and 65 patients randomized to cyclosporine at baseline; PP, per-protocol population consisting of 63 patients randomized to rituximab and 63 patients randomized to cyclosporine at baseline.

Figure S6: Time to composite of complete or partial remission during the 12-month treatment period



Complete remission defined as proteinuria ≤ 0.3 g/24h and serum albumin ≥ 3.5 g/dL; partial remission defined as reduction in baseline proteinuria of $\geq 50\%$ plus final proteinuria ≤ 3.5 g/24h but >0.3 g/24h.

Figure S7: Time to treatment failure during the observation period of 13 to 24 months in patients with complete or partial remission at the end of 12-month treatment period



Patients with complete or partial remission at the end of treatment period consisted of 39 patients randomized to rituximab and 34 patients randomized to cyclosporine at baseline who received the allocated study medication at least once.

Table S8: Cumulative number of patients with treatment failures

Time from randomization	Rituximab		Cyclosporine		Risk difference (95% CI)
	n	Failure (%)	n	Failure (%)	
6 months	65	17 (26.2)	65	19 (29.2)	-3.1 (-18.5 to 12.3)
12 months	65	17 (26.2)	65	21 (32.3)	-6.2 (-21.8 to 9.4)
18 months	65	18 (27.7)	65	48 (73.8)	-46.2 (-61.4 to -30.9)
24 months	65	26 (40.0)	65	52 (80.0)	-40.0 (-55.4 to -24.6)

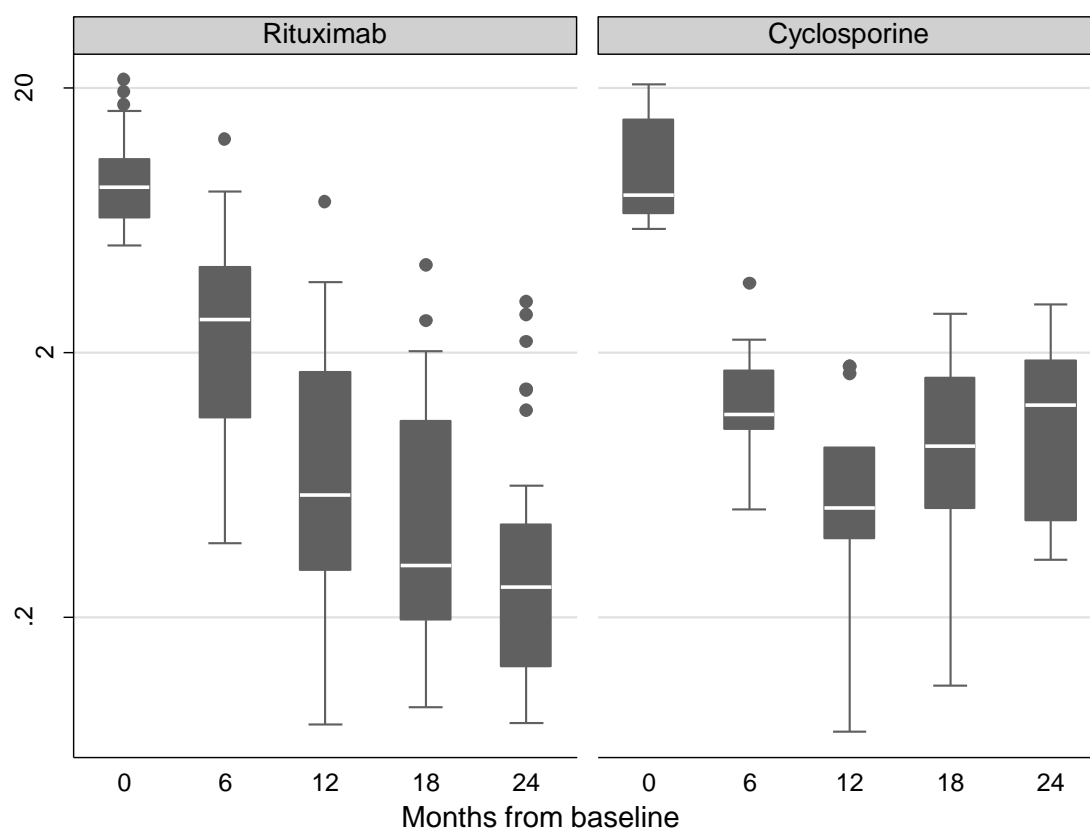
Because the widths of 95% confidence intervals of secondary outcomes were not adjusted for multiple comparisons, these intervals should not be used for inference about treatment effects; n, number of patients analyzed; CI, confidence interval. Intention-to-treat population consisting of 65 patients randomized to rituximab and 65 patients randomized to cyclosporine.

Table S9: Laboratory outcomes in patients with complete or partial remission at months 6, 12, 18 and 24

	6 months		12 months		18 months		24 months	
	Rituximab	Cyclosporine	Rituximab	Cyclosporine	Rituximab	Cyclosporine	Rituximab	Cyclosporine
Proteinuria – geometric mean (95% CI)								
n	23	32	39	34	40	15	39	13
Baseline (g/24h)	7.83 (6.84-8.97)	8.81 (7.60-10.21)	8.74 (7.70-9.93)	9.47 (8.21-10.92)	8.47 (7.58-9.46)	10.01 (7.90-12.67)	8.79 (7.78-9.93)	9.46 (7.30-12.25)
Follow-up (g/24h)	1.40 (1.11-1.77)	1.26 (1.02-1.56)	0.63 (0.45-0.88)	0.93 (0.69-1.27)	0.43 (0.31-0.60)	1.02 (0.61-1.71)	0.30 (0.22-0.41)	1.02 (0.64-1.64)
Difference (95% CI)	0.12 (-0.25 to 0.63)		-0.27 (-0.50 to 0.10)		-0.56 (-0.77 to -0.16)		-0.72 (-0.86 to -0.47)	
Creatinine clearance–mean (SD)								
n	23	32	39	34	40	15	39	13
Baseline (mL/min/1.73m ²)	99 (30)	102 (30)	93 (31)	96 (35)	93 (31)	96 (42)	93 (32)	100 (43)
Follow-up (mL/min/1.73m ²)	101 (31)	75 (25)	96 (27)	72 (29)	99 (28)	83 (28)	100 (29)	87 (32)
Difference (95% CI)	28 (17 to 38)		26 (17 to 35)		17 (7 to 28)		18 (5 to 31)	

Because the widths of 95% confidence intervals of secondary outcomes were not adjusted for multiple comparisons, these intervals should not be used for inference about treatment effects; Only patients who experienced complete or partial remission at each time point (see Table 2) were included in a cross-sectional analysis of the respective time point, therefore, no longitudinal comparison between time points should be made; n, number of patients analyzed; CI, confidence interval; SD, standard deviation. Differences at follow-up estimated from analysis of covariance adjusted for baseline values.

Figure S8: Proteinuria by group and time in patients who experienced complete or partial remission at month 24



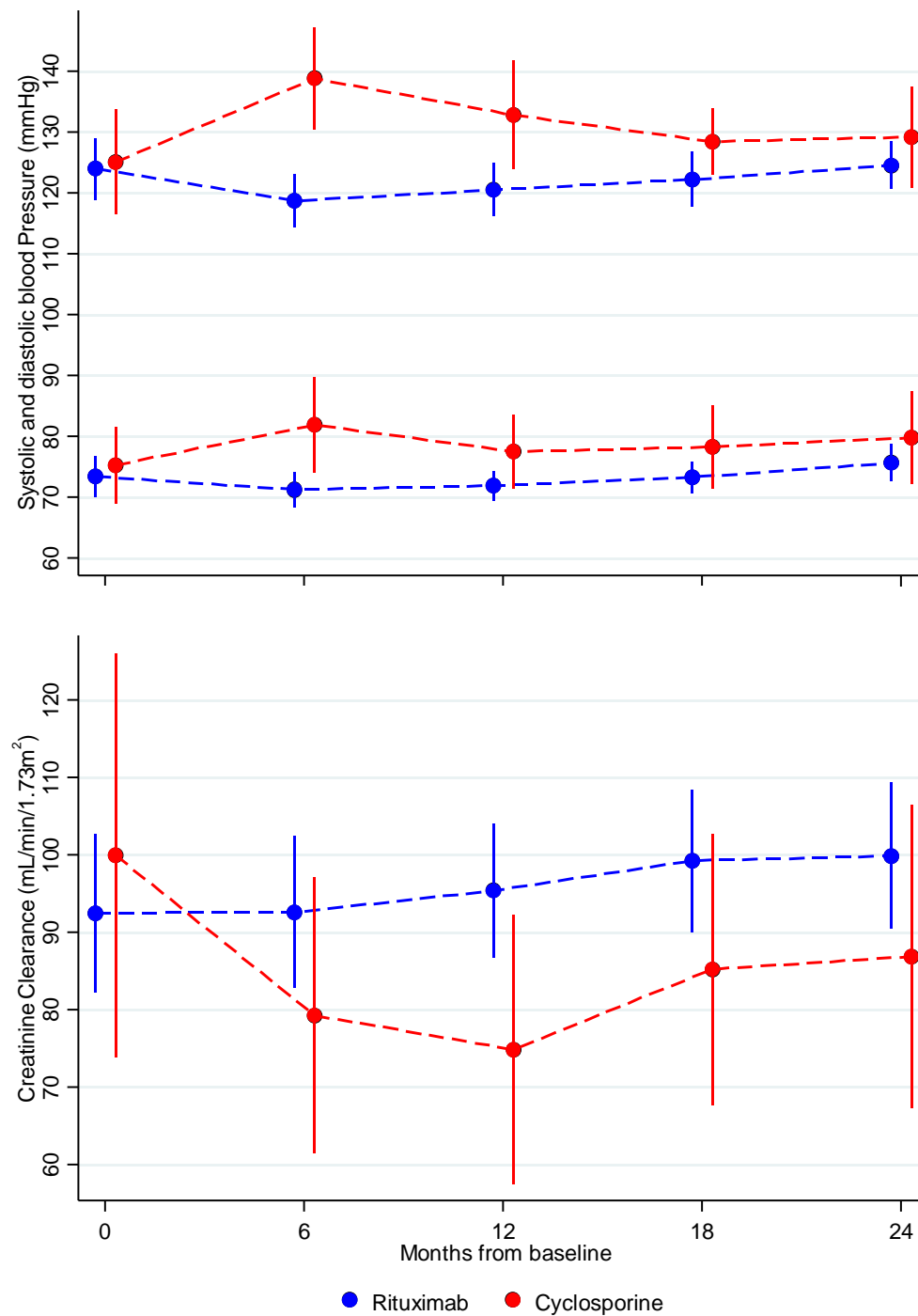
39 patients in the rituximab group and 13 in the cyclosporine group experienced complete or partial remission at month 24 and were included in the analysis; One patient in the rituximab group had missing values for proteinuria at 18 months; Therefore, 38 and 13 patients, respectively, are included in the analysis of proteinuria at 18 months; Displayed are medians (white horizontal line), interquartile ranges (boxes), adjacent values (whiskers), and outliers (dots).

Table S10: Blood pressure in patients with complete or partial remission at months 6, 12, 18 and 24

	6 months		12 months		18 months		24 months	
SBP – mean (SD)	Rituximab	Cyclosporine	Rituximab	Cyclosporine	Rituximab	Cyclosporine	Rituximab	Cyclosporine
n	23	32	39	34	40	15	39	13
Baseline (mmHg)	126.9 (15.1)	124.2 (13.4)	124.8 (14.9)	122.9 (13.1)	123.4 (15.3)	122.9 (14.5)	125.0 (15.0)	125.2 (14.3)
Follow-up (mmHg)	118.5 (13.6)	133.0 (14.0)	121.4 (12.8)	131.4 (16.5)	122.1 (13.5)	126.3 (10.4)	124.7 (11.9)	129.3 (13.7)
Difference (95% CI)	-16.0 (-22.4 to -9.5)		-10.7 (-17.2 to -4.1)		-4.4 (-11.9 to 3.2)		-4.6 (-12.3 to 3.1)	
DBP – mean (SD)								
n	23	32	39	34	40	15	39	13
Baseline (mmHg)	73.6 (10.6)	75.7 (8.9)	74.1 (10.6)	76.0 (9.7)	72.9 (9.9)	74.7 (9.9)	73.9 (10.2)	75.4 (10.4)
Follow-up (mmHg)	70.8 (9.1)	81.0 (11.0)	72.4 (7.6)	79.6 (10.2)	72.9 (7.5)	77.5 (11.0)	75.8 (9.3)	79.9 (12.6)
Difference (95% CI)	-8.8 (-13.4 to -4.2)		-6.6 (-10.4 to -2.7)		-3.9 (-8.5 to 0.7)		-3.6 (-9.8 to 2.5)	

Because the widths of 95% confidence intervals of secondary outcomes were not adjusted for multiple comparisons, these intervals should not be used for inference about treatment effects; Only patients who experienced complete or partial remission at each time point (see Table 2) were included in a cross-sectional analysis of the respective time point, therefore, no longitudinal comparison between time points should be made; SBP, systolic blood pressure; DBP, diastolic blood pressure; CI, confidence interval; SD, standard deviation. Differences at follow-up estimated from analysis of covariance adjusted for baseline values.

Figure S9: Blood pressure and creatinine clearance by group and time in patients who experienced complete or partial remission at month 24



39 patients in the rituximab group and 13 in the cyclosporine group experienced complete or partial remission at month 24 and were included in the analysis; displayed are means and 95% confidence intervals, because the widths of 95% confidence intervals of secondary outcomes were not adjusted for multiple comparisons, these intervals should not be used for inference about treatment effects.

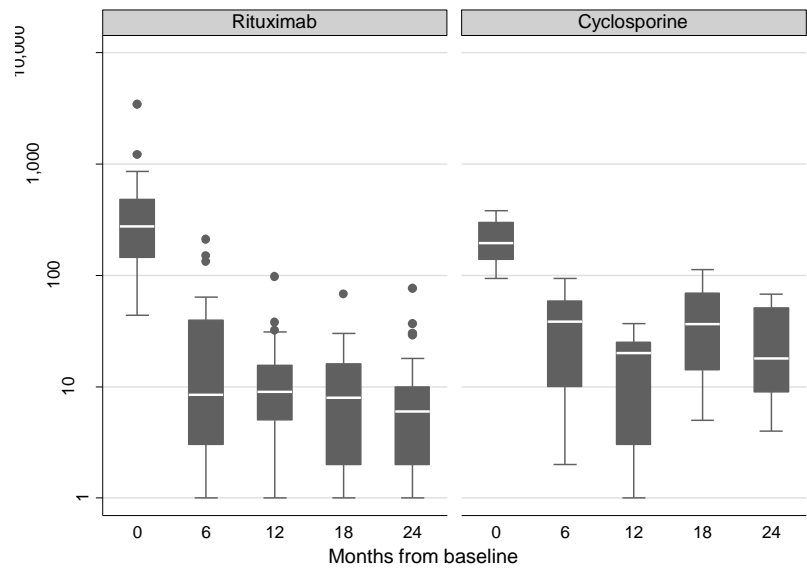
Table S11: Serum anti-PLA2R levels in anti-PLA2R positive patients with complete or partial remission at months 6, 12, 18 and 24

	6 months		12 months		18 months		24 months	
	Rituximab	Cyclosporine	Rituximab	Cyclosporine	Rituximab	Cyclosporine	Rituximab	Cyclosporine
Anti-PLA2R–geometric mean (95% CI)								
n	16	20	29	21	28	7	28	6
Baseline (u/mL)	242.5 (134.8-436.5)	302.9 (201.1-456.3)	288.2 (195.6-424.6)	256.2 (173.0-379.4)	273.4 (182.8-409.1)	163.5 (88.2-303.2)	273.5 (185.1-404.1)	195.5 (113.6-336.3)
Follow-up (u/mL)	4.6 (2.7-8.1)	29.0 (14.7-57.3)	7.3 (4.8-11.3)	23.6 (12.7-43.8)	5.6 (3.5-9.0)	26.8 (9.8-73.1)	5.4 (3.4-8.5)	18.4 (6.0-56.3)
Difference (95% CI)	-24.4 (-27.1 to -17.7)		-16.3 (-20.1 to -8.6)		-21.3 (-24.9 to -11.0)		-13.4 (-16.7 to -3.7)	

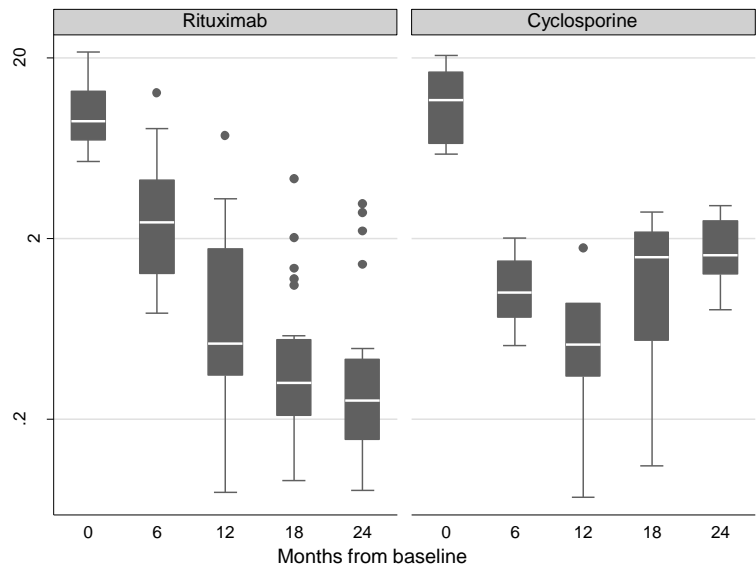
Because the widths of 95% confidence intervals of secondary outcomes were not adjusted for multiple comparisons, these intervals should not be used for inference about treatment effects; Only patients who experienced complete or partial remission at each time point (see Tables 2 and S2) were included in a cross-sectional analysis of the respective time point, therefore, no longitudinal comparison between time points should be made; Anti-PLA2R, anti-phospholipase A2 receptor autoantibody; n, number of patients analyzed; CI, confidence interval. Differences at follow-up estimated from analysis of covariance adjusted for baseline values.

Figure S10: Anti-PLA2R levels and proteinuria by group and time in anti-PLA2R positive patients with complete or partial remission at month 24

Panel A: Anti-PLA2R levels



Panel B: Proteinuria



28 Anti-PLA2R positive patients in the rituximab group and 6 in the cyclosporine group experienced complete or partial remission at month 24 and were included in the analysis of all time-points. Displayed are medians (white horizontal line), interquartile ranges (boxes), adjacent values (whiskers), and outliers (dots).

Table S12: Immunological and clinical response in anti-PLA2R positive patients

Time from randomization	Rituximab		Cyclosporine		Risk difference (95% CI)
	n	CR/PR (%)	n	CR/PR (%)	
Immunological response					
6 months	50	26 (52.0)	46	13 (28.3)	23.7 (4.7 to 42.7)
12 months	50	33 (66.0)	46	14 (30.4)	35.6 (16.9 to 54.3)
18 months	50	32 (64.0)	46	5 (10.9)	53.1 (37.1 to 69.2)
24 months	50	33 (66.0)	46	6 (13.0)	53.0 (36.6 to 69.3)
Complete or partial remission					
6 months	50	16 (32.0)	46	20 (43.5)	-11.5 (-30.8 to 7.8)
12 months	50	29 (58.0)	46	21 (45.7)	12.3 (-7.5 to 32.2)
18 months	50	28 (56.0)	46	7 (15.2)	40.8 (23.5 to 58.0)
24 months	50	28 (56.0)	46	6 (13.0)	43.0 (26.1 to 59.8)

Immunological response defined as a drop of anti-PLA2R levels to ≤ 40 u/mL; Analyses of immunological response are post hoc.

Table S13: Immunological and clinical response in anti-PLA2R positive patients by tertiles of anti-PLA2R levels

Time from randomization	Anti-PLA2R	Rituximab		Cyclosporine		Risk difference (95% CI)	P for trend
	Tertile	n	CR/PR (%)	n	CR/PR (%)		
Immunological response							
6 months	1	17	12 (70.6)	15	7 (46.7)	23.9 (-9.3 to 57.2)	0.49
	2	17	9 (52.9)	15	4 (26.7)	26.3 (-6.3 to 58.9)	
	3	16	5 (31.3)	16	2 (12.5)	18.8 (-9.2 to 46.7)	
12 months	1	17	14 (82.4)	15	7 (46.7)	35.7 (4.6 to 66.8)	0.38
	2	17	13 (76.5)	15	6 (40.0)	36.5 (4.5 to 68.4)	
	3	16	6 (37.5)	16	1 (6.3)	31.3 (4.7 to 57.8)	
18 months	1	17	14 (82.4)	15	2 (13.3)	69.0 (44.0 to 94.0)	0.041
	2	17	11 (64.7)	15	2 (13.3)	51.4 (22.9 to 79.9)	
	3	16	7 (43.8)	16	1 (6.3)	37.5 (10.5 to 64.5)	
24 months	1	17	14 (82.4)	15	3 (20.0)	62.4 (35.2 to 89.5)	0.21
	2	17	12 (70.6)	15	2 (13.3)	57.3 (29.6 to 84.9)	
	3	16	7 (43.8)	16	1 (6.3)	37.5 (10.5 to 64.5)	
Complete or partial remission							
6 months	1	17	7 (41.2)	15	8 (53.3)	-12.2 (-46.6 to 22.3)	0.29
	2	17	7 (41.2)	15	8 (53.3)	-12.2 (-46.6 to 22.3)	
	3	16	2 (12.5)	16	4 (25.0)	-12.5 (-39.2 to 14.2)	
12 months	1	17	12 (70.6)	15	11 (73.3)	-2.7 (-33.9 to 28.4)	0.30
	2	17	11 (64.7)	15	7 (46.7)	18.0 (-15.9 to 52.0)	
	3	16	6 (37.5)	16	3 (18.8)	18.8 (-11.7 to 49.2)	
18 months	1	17	12 (70.6)	15	5 (33.3)	37.3 (5.0 to 69.5)	0.91
	2	17	10 (58.8)	15	2 (13.3)	45.5 (16.5 to 74.5)	
	3	16	6 (37.5)	16	0 (0.0)	37.5 (13.8 to 61.2)	
24 months	1	17	12 (70.6)	15	4 (26.7)	43.9 (12.8 to 75.1)	0.50
	2	17	11 (64.7)	15	2 (13.3)	51.4 (22.9 to 79.9)	
	3	16	5 (31.3)	16	0 (0.0)	31.3 (8.5 to 54.0)	

Immunological response defined as a drop of anti-PLA2R levels to ≤ 40 u/mL; analyses of immunological response and subgroup analyses by anti-PLA2R tertile are post hoc; the range of anti-PLA2R levels in anti-PLA2R positive patients was 41-175 u/mL for the low tertile, 176-610 u/mL for the mid tertile and >610 u/mL for the high tertile.

Table S14: Selected subscales of Kidney Disease and Quality of Life Short Form (KDQOL-SF) in patients with complete or partial remission at months 6, 12 and 24

	Rituximab		Cyclosporine		Difference in means (95% CI)
Scale	N	Mean (SD)	N	Mean (SD)	
SF-12 Physical Health Composite					
6	20	45.1 (13)	29	45.0 (10)	2.0 (-3.5 to 7.5)
12	36	46.2 (10)	31	47.9 (9)	0.2 (-3.8 to 4.2)
24	37	47.8 (8)	11	49.9 (9)	0.2 (-4.9 to 5.3)
SF-12 Mental Health Composite					
6	20	53.2 (8)	29	51.4 (9)	3.3 (-1.4 to 7.9)
12	36	52.0 (7)	31	50.1 (11)	4.1 (0.6 to 7.6)
24	37	53.4 (7)	11	55.0 (4)	0.3 (-3.7 to 4.3)
Symptom/problem list					
6	23	84.5 (13)	32	80.9 (15)	7.4 (0.8 to 14.1)
12	38	83.5 (13)	33	85.3 (15)	2.3 (-3.2 to 7.8)
24	38	86.5 (11)	12	87.8 (16)	2.2 (-4.3 to 8.8)
Effects of kidney disease					
6	23	81.3 (20)	31	84.2 (17)	0.1 (-7.0 to 7.2)
12	38	83.8 (19)	33	83.8 (19)	3.3 (-4.0 to 10.6)
24	38	90.2 (16)	12	84.4 (14)	6.9 (-2.4 to 16.3)
Burden of kidney disease					
6	23	66.0 (24)	32	65.0 (25)	3.3 (-6.3 to 13.0)
12	38	68.6 (27)	33	73.1 (30)	-4.5 (-16.1 to 7.1)
24	38	80.8 (24)	12	80.6 (20)	1.2 (-12.5 to 14.9)

Because the widths of 95% confidence intervals of secondary outcomes were not adjusted for multiple comparisons, these intervals should not be used for inference about treatment effects; Only patients who experienced complete or partial remission at each time point (see Tables 2 and S2) were included in a cross-sectional analysis of the respective time point if they had quality of life data available, therefore, no longitudinal comparison between time points should be made; KDQOL-SF, Kidney Disease and Quality of Life™ Short Form; n, number of patients analyzed; SD, standard deviation; CI, confidence interval. Differences at follow-up estimated from analysis of covariance adjusted for baseline values.

Table S15: adverse events experienced by the 7 patients allocated to cyclosporine who discontinued the intervention at the time of discontinuation of the intervention

Patient	Description
1	AE: Severe hypertension, Flu-like symptoms, Fatigue
2	SAE: Acute cholecystitis requiring surgery and prolonged hospitalization AE: Other respiratory tract infection (Acute asthmatic bronchitis)
3	AE: Myalgia
4	SAE: Volume depletion, Hypotension, Musculoskeletal pain AE: Gastrointestinal pain, Increased serum creatinine
5	SAE: Atrial fibrillation AE: Increased serum creatinine
6	SAE: Severe hypertension AE: Increased creatine phosphokinase (CPK), Increased serum creatinine
7	AE: Headache, Severe hypertension

AE, adverse event; SAE, serious adverse event; adverse events listed, which were experienced by the patients at the time of discontinuation of the intervention; 0 (0%) versus 7 patients (10.8%) discontinued the intervention because of the adverse events listed above (2-sided p from Fisher's exact test=0.013).

VI. Additional analyses

- Tables S16 to S19 present sensitivity analyses of the composite of CR or PR, which were in line with main analyses.
- Figure S11 presents exploratory subgroup analyses of the composite of CR or PR at 12 months specified post-hoc, which suggests that the more pronounced benefit of rituximab in women was already partially apparent at the end of the treatment period (p for interaction=0.004).
- Table S20 presents exploratory subgroup analyses of the composite outcome of complete or partial remission at 6, 12 and 18 months by anti-PLA2R status.
- Table S21 presents the number of patients with relapse or failure for other reasons at 24 months in patients with complete or partial remission at end of the 12-month treatment period.
- Table S22 presents the cumulative number of patients with $\geq 50\%$ decrease in creatinine clearance from baseline.
- Tables S23 and S24 present sensitivity analyses of differences in creatinine clearance, which were in line with main analyses.
- Table S25 presents ratios of geometric means of proteinuria in patients with complete or partial remission at months 6, 12, 18 and 24.
- Tables S26 presents ratios of geometric means in anti-PLA2R positive patients with complete or partial remission at months 6, 12, 18 and 24.
- Table S27 presents differences in anti-PLA2R levels in all patients who experienced complete or partial remission at months 6, 12, 18 and 24 irrespective of their anti-PLA2R status, which were in line with the analysis of anti-PLA2R-positive patients.
- Table S28 presents ratios of geometric means of anti-PLA2R levels in anti-PLA2R-positive patients with complete or partial remission at months 6, 12, 18 and 24.
- Tables S29 and S30 present sensitivity analyses of quality of life data, which were compatible with main analyses, but slightly less conservative.
- Tables S31 and S32 present additional classifications of adverse events.

Table S16: Sensitivity analyses: comparison between groups of composite of complete or partial remission using generalized estimating equations to derive risk differences

Time from randomization	Rituximab		Cyclosporine		Risk difference (95% CI)
	n	CR/PR (%)	n	CR/PR (%)	
ITT population					
6 months	65	23 (35.4)	65	32 (49.2)	-13.8 (-30.7 to 3.0)
12 months	65	39 (60.0)	65	34 (52.3)	7.7 (-9.3 to 24.7)
18 months	65	40 (61.5)	65	15 (23.1)	38.5 (22.8 to 54.1)
24 months*	65	39 (60.0)	65	13 (20.0)	40.0 (24.6 to 55.4)
PP population					
6 months	63	22 (34.9)	63	32 (50.8)	-15.9 (-32.9 to 1.2)
12 months	63	38 (60.3)	63	33 (52.4)	7.9 (-9.3 to 25.2)
18 months	63	39 (61.9)	63	15 (23.8)	38.1 (22.1 to 54.0)
24 months*	63	39 (61.9)	63	13 (20.6)	41.3 (25.7 to 56.9)

Because the widths of 95% confidence intervals of secondary outcomes were not adjusted for multiple comparisons, these intervals should not be used for inference about treatment effects; n, number of patients analyzed; CR, complete remission; PR, partial remission; CI, confidence interval; ITT, intention-to-treat population consisting of 65 patients randomized to rituximab and 65 patients randomized to cyclosporine at baseline; PP, per-protocol population consisting of 63 patients randomized to rituximab and 63 patients randomized to cyclosporine at baseline; *Primary composite outcome.

Table S17: Sensitivity analysis: comparison between groups of composite of complete or partial remission at 24 months using multiple imputation to derive risk differences

Time from randomization	Rituximab		Cyclosporine		Risk difference (95% CI)
	n	CR/PR (%)	n	CR/PR (%)	
24 months	65	40 (61)	65	15 (23)	38 (22 to 54)

Post hoc sensitivity analysis of the primary outcome of the composite of complete or partial remission at 24 months using multiple imputation to derive the risk difference using the same model as used for the primary analysis. The multiple imputation model included age, sex, log urine protein, log anti-PLA2R, log creatinine clearance, and history of immunosuppressive therapy as variables. Twenty imputed datasets were created and combined using Rubin's rules. n, number of patients analyzed; CR, complete remission; PR, partial remission; CI, confidence interval.

Table S18: Sensitivity analyses: crude and adjusted logistic regression for the comparison between groups of composite of complete or partial remission

Time from randomization	Rituximab		Cyclosporine		Odds ratio (95% CI)
	n	CR/PR (%)	n	CR/PR (%)	
Unadjusted analysis					
ITT population					
6 months	65	23 (35.4)	65	32 (49.2)	0.6 (0.3 to 1.1)
12 months	65	39 (60.0)	65	34 (52.3)	1.6 (0.8 to 3.1)
18 months	65	40 (61.5)	65	15 (23.1)	6.2 (2.9 to 13.1)
24 months*	65	39 (60.0)	65	13 (20.0)	7.8 (3.7 to 16.8)
PP population					
6 months	63	22 (34.9)	63	32 (50.8)	0.5 (0.2 to 1.0)
12 months	63	38 (60.3)	63	33 (52.4)	1.6 (0.8 to 3.1)
18 months	63	39 (61.9)	63	15 (23.8)	6.1 (2.9 to 13.0)
24 months*	63	39 (61.9)	63	13 (20.6)	7.8 (3.6 to 16.9)
Adjusted analyses*					
ITT population					
6 months	65	23 (35.4)	65	32 (49.2)	0.5 (0.3 to 1.2)
12 months	65	39 (60.0)	65	34 (52.3)	1.3 (0.6 to 2.8)
18 months	65	40 (61.5)	65	15 (23.1)	6.2 (2.7 to 14.4)
24 months*	65	39 (60.0)	65	13 (20.0)	7.1 (2.9 to 17.1)
PP population					
6 months	63	22 (34.9)	63	32 (50.8)	0.5 (0.2 to 1.0)
12 months	63	38 (60.3)	63	33 (52.4)	1.2 (0.6 to 2.7)
18 months	63	39 (61.9)	63	15 (23.8)	5.6 (2.4 to 13.1)
24 months*	63	39 (61.9)	63	13 (20.6)	7.0 (2.9 to 16.9)

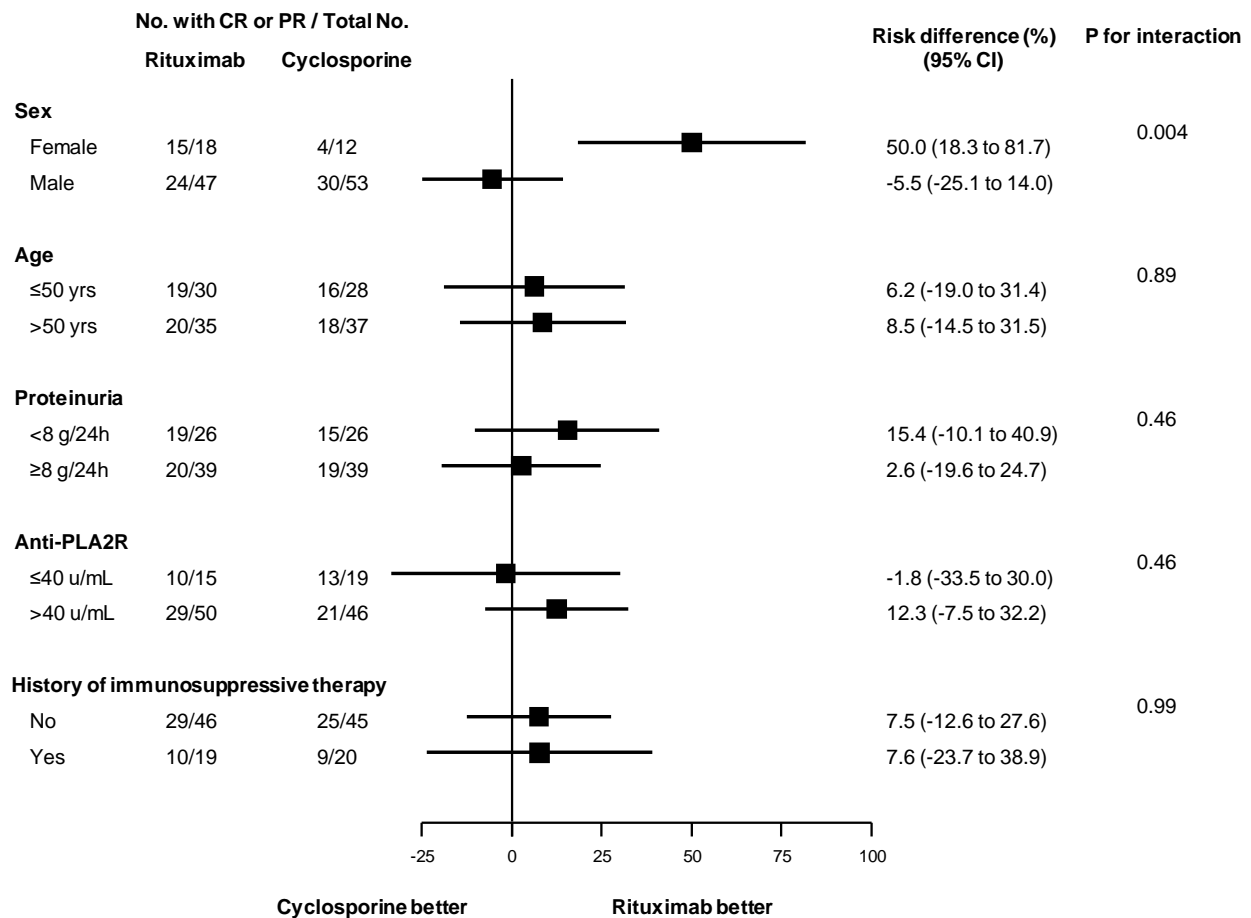
Because the widths of 95% confidence intervals of secondary outcomes were not adjusted for multiple comparisons, these intervals should not be used for inference about treatment effects; n, number of patients analyzed; CR, complete remission; PR, partial remission; CI, confidence interval; ITT, intention-to-treat population consisting of 65 patients randomized to rituximab and 65 patients randomized to cyclosporine at baseline; PP, per-protocol population consisting of 63 patients randomized to rituximab and 63 patients randomized to cyclosporine at baseline; *Primary composite outcome; **Adjusted for center and proteinuria at baseline (<8g/24h vs ≥8g/24h).

Table S19: Sensitivity analyses: crude and adjusted ordinal regression for the comparison between groups of complete and partial remission

Time from randomization	Rituximab			Cyclosporine			Odds ratio (95% CI)
	n	PR (%)	CR (%)	n	PR (%)	CR (%)	
Unadjusted analyses							
ITT population							
6 months	65	23 (35.4)	0 (0.0)	65	31 (47.7)	1 (1.5)	0.6 (0.3 to 1.1)
12 months	65	30 (46.2)	9 (13.8)	65	31 (47.7)	3 (4.6)	1.6 (0.8 to 3.1)
18 months	65	22 (33.8)	18 (27.7)	65	14 (21.5)	1 (1.5)	6.2 (2.9 to 13.1)
24 months	65	16 (24.6)	23 (35.4)	65	13 (20.0)	0 (0.0)	7.6 (3.5 to 16.5)
PP population							
6 months	63	22 (34.9)	0 (0.0)	63	31 (49.2)	1 (1.6)	0.5 (0.2 to 1.0)
12 months	63	29 (46.0)	9 (14.3)	63	30 (47.6)	3 (4.8)	1.6 (0.8 to 3.1)
18 months	63	21 (33.3)	18 (28.6)	63	14 (22.2)	1 (1.6)	6.1 (2.9 to 13.0)
24 months	63	16 (25.4)	23 (36.5)	63	13 (20.6)	0 (0.0)	8.0 (3.6 to 17.6)
Adjusted analyses*							
ITT population							
6 months	65	23 (35.4)	0 (0.0)	65	31 (47.7)	1 (1.5)	0.5 (0.2 to 1.1)
12 months	65	30 (46.2)	9 (13.8)	65	31 (47.7)	3 (4.6)	1.6 (0.8 to 3.3)
18 months	65	22 (33.8)	18 (27.7)	65	14 (21.5)	1 (1.5)	7.2 (3.2 to 16.2)
24 months	65	16 (24.6)	23 (35.4)	65	13 (20.0)	0 (0.0)	8.8 (3.8 to 20.4)
PP population							
6 months	63	22 (34.9)	0 (0.0)	63	31 (49.2)	1 (1.6)	0.5 (0.2 to 1.0)
12 months	63	29 (46.0)	9 (14.3)	63	30 (47.6)	3 (4.8)	1.5 (0.7 to 3.2)
18 months	63	21 (33.3)	18 (28.6)	63	14 (22.2)	1 (1.6)	6.8 (3.0 to 15.4)
24 months	63	16 (25.4)	23 (36.5)	63	13 (20.6)	0 (0.0)	8.8 (3.8 to 20.5)

Because the widths of 95% confidence intervals of secondary outcomes were not adjusted for multiple comparisons, these intervals should not be used for inference about treatment effects; n, number of patients analyzed; CR, complete remission; PR, partial remission; CI, confidence interval; ITT, intention-to-treat population consisting of 65 patients randomized to rituximab and 65 patients randomized to cyclosporine at baseline; PP, per-protocol population consisting of 63 patients randomized to rituximab and 63 patients randomized to cyclosporine at baseline; *adjusted for center and proteinuria at baseline (<8g/24h vs ≥8g/24h).

Figure S11: Post-hoc subgroup analyses of the primary composite outcome of complete or partial remission at end of 12-month treatment period



Subgroup analyses of the primary composite outcome of complete or partial remission at 12 months by pre-specified characteristics of patients at baseline; Because the widths of 95% confidence intervals were not adjusted for multiple comparisons, these intervals should not be used for inference about treatment effects; 95% CI, two-sided 95% confidence interval; Two-sided P-values for interaction derived from z-tests.

Table S20: Post-hoc subgroup analyses of the composite outcome of complete or partial remission at 6, 12 and 18 months by anti-PLA2R status

Time from randomization	Anti-PLA2R status	Rituximab		Cyclosporine		Risk difference (95% CI)	P for interaction
		n	CR/PR (%)	n	CR/PR (%)		
6 months	≤40 u/mL	15	7 (46.7)	18	12 (66.7)	-20.0 (-53.3 to 13.3)	0.73
	>40 u/mL	48	15 (31.3)	45	20 (44.4)	-13.2 (-32.8 to 6.4)	
12 months	≤40 u/mL	15	10 (66.7)	18	12 (66.7)	0.0 (-32.3 to 32.3)	0.55
	>40 u/mL	48	28 (58.3)	45	21 (46.7)	11.7 (-8.5 to 31.8)	
18 months	≤40 u/mL	15	12 (80.0)	18	8 (44.4)	35.6 (4.9 to 66.2)	0.78
	>40 u/mL	48	27 (56.3)	45	7 (15.6)	40.7 (23.1 to 58.3)	
24 months	≤40 u/mL	15	11 (73.3)	18	7 (38.9)	34.4 (2.7 to 66.2)	0.57
	>40 u/mL	48	28 (58.3)	45	6 (13.3)	45.0 (27.9 to 62.1)	

Subgroup analyses of the composite outcome of complete or partial remission at 6, 12, 18 months are post hoc, subgroup analysis of the primary composite outcome of complete or partial remission at 24 months is pre-specified; Because the widths of 95% confidence intervals were not adjusted for multiple comparisons, these intervals should not be used for inference about treatment effects; 95% CI, two- sided 95% confidence interval; Two-sided P-values for interaction derived from z-tests.

Table S21: Number of patients with relapse or failure for other reasons at 24 months in patients with complete or partial remission at end of 12-month treatment period

	Rituximab (n=39)	Cyclosporine (n=34)	Risk difference (95% CI)
Relapse (%)	2 (5.1)	18 (52.9)	-47.8 (-66.0 to -29.7)
Failure for other reasons (%)	0 (0.0)	3 (8.8)	-8.8 (-17.8 to 0.2)

Because the widths of 95% confidence intervals of secondary outcomes were not adjusted for multiple comparisons, these intervals should not be used for inference about treatment effects; n, number of patients analyzed; CI, confidence interval. The analyzed population consisted of 39 patients randomized to rituximab and 34 patients randomized to cyclosporine at baseline who were in CR or PR 12 months after randomization. Relapse was defined as development of nephrotic range proteinuria of >3.5g/24h.

Table S22: Cumulative number of patients with $\geq 50\%$ decrease in creatinine clearance from baseline

Time from randomization	Rituximab		Cyclosporine		Risk difference (95% CI)
	n	$\geq 50\%$ decrease (%)	n	$\geq 50\%$ decrease (%)	
6 months	65	1 (1.5)	65	4 (6.2)	-4.6 (-11.2 to 1.9)
12 months	65	1 (1.5)	65	8 (12.3)	-10.8 (-19.3 to -2.2)
18 months	65	1 (1.5)	65	8 (12.3)	-10.8 (-19.3 to -2.2)
24 months	65	1 (1.5)	65	8 (12.3)	-10.8 (-19.3 to -2.2)

Because the widths of 95% confidence intervals of secondary outcomes were not adjusted for multiple comparisons, these intervals should not be used for inference about treatment effects; n, number of patients analyzed; CI, confidence interval; Intention-to-treat population consisting of 65 patients randomized to rituximab and 65 patients randomized to cyclosporine.

Table S23: Sensitivity analysis: difference in creatinine clearance between groups from mixed repeated measures linear regression with random intercepts for patients in patients with complete or partial remission at months 6, 12, 18 and 24

Time from randomization	Rituximab n	Cyclosporine n	Difference in means (95% CI)
6 months	23	32	25 (16 to 35)
12 months	39	34	27 (18 to 35)
18 months	40	15	18 (8 to 28)
24 months	39	13	19 (8 to 29)

Because the widths of 95% confidence intervals of secondary outcomes were not adjusted for multiple comparisons, these intervals should not be used for inference about treatment effects; Only patients who experienced complete or partial remission at each time point (see Tables 2 and S2) were included, therefore, no longitudinal comparison between time points should be made; CI, confidence interval.

Table S24: Sensitivity analysis: difference in creatinine clearance between groups from mixed repeated measures linear regression with random intercept for patients and random slope for centers in patients with complete or partial remission at months 6, 12, 18 and 24

Time from randomization	Rituximab n	Cyclosporine n	Difference in means (95% CI)
6 months	23	32	25 (16 to 35)
12 months	39	34	27 (18 to 35)
18 months	40	15	18 (8 to 28)
24 months	39	13	19 (8 to 29)

Because the widths of 95% confidence intervals of secondary outcomes were not adjusted for multiple comparisons, these intervals should not be used for inference about treatment effects; Only patients who experienced complete or partial remission at each time point (see Tables 2 and S2) were included, therefore, no longitudinal comparison between time points should be made; CI, confidence interval.

Table S25: Ratios of geometric means of proteinuria in patients with complete or partial remission at months 6, 12, 18 and 24

Time from randomization	Rituximab		Cyclosporine		Ratio of geometric means (95% CI)
	n	Geometric mean (95% CI)	n	Geometric mean (95% CI)	
6 months	23	1.40 (1.11 to 1.77)	32	1.26 (1.02 to 1.56)	1.09 (0.80 to 1.50)
12 months	39	0.63 (0.45 to 0.88)	34	0.93 (0.69 to 1.27)	0.71 (0.46 to 1.11)
18 months	40	0.43 (0.31 to 0.60)	15	1.02 (0.61 to 1.71)	0.45 (0.24 to 0.85)
24 months	39	0.30 (0.22 to 0.41)	13	1.02 (0.64 to 1.64)	0.30 (0.16 to 0.54)

Because the widths of 95% confidence intervals of secondary outcomes were not adjusted for multiple comparisons, these intervals should not be used for inference about treatment effects; n, number of patients analyzed; CI, confidence interval. Ratios of geometric means estimated from analysis of covariance of log transformed data adjusted for log transformed baseline values. Group-specific geometric means are expressed in g/24h, ratios of geometric means are unitless.

Table S26: Ratios of geometric means of anti-PLA2R levels in anti-PLA2R-positive patients with complete or partial remission at months 6, 12, 18 and 24

Time from randomization	Rituximab		Cyclosporine		Ratio of geometric means (95% CI)
	n	Geometric mean (95% CI)	n	Geometric mean (95% CI)	
6 months	16	4.6 (2.7 to 8.1)	20	29.0 (14.7 to 57.3)	0.2 (0.1 to 0.4)
12 months	29	7.3 (4.8 to 11.3)	21	23.6 (12.7 to 43.8)	0.3 (0.2 to 0.6)
18 months	28	5.6 (3.5 to 9.0)	7	26.8 (9.8 to 73.1)	0.2 (0.1 to 0.6)
24 months	28	5.4 (3.4 to 8.5)	6	18.4 (6.0 to 56.3)	0.3 (0.1 to 0.8)

Because the widths of 95% confidence intervals of secondary outcomes were not adjusted for multiple comparisons, these intervals should not be used for inference about treatment effects; n, number of patients analyzed; CI, confidence interval. Ratios of geometric means estimated from analysis of covariance of log transformed data adjusted for log transformed baseline values. Group-specific geometric means are expressed in u/mL, ratios of geometric means are unitless.

Table S27: Serum anti-PLA2R levels in patients who experienced complete or partial remission at months 6, 12, 18 and 24

	6 months		12 months		18 months		24 months	
	RTX	CSA	RTX	CSA	RTX	CSA	RTX	CSA
Anti-PLA2R – geometric mean (95% CI)								
n	23	32	39	34	40	15	38	12
Baseline (u/mL)	95.3 (45.0-201.8)	99.7 (53.7-185.0)	131.2 (76.9-223.8)	80.2 (43.6-147.2)	113.5 (67.0-192.2)	41.7 (17.1-101.9)	123.6 (72.3-211.4)	58.4 (24.4-139.6)
Follow-up (u/mL)	4.4 (2.9-6.7)	19.0 (11.3-32.0)	6.8 (4.7-9.7)	15.0 (9.6-23.5)	5.3 (3.6-7.6)	17.5 (8.3-36.6)	4.5 (3.1-6.6)	12.4 (7.0-22.1)
Difference (95% CI)	-14.6 (-16.8 to -10.3)		-8.9 (-11.5 to -4.4)		-12.7 (-15.2 to -7.2)		-8.7 (-10.5 to -4.9)	

Because the widths of 95% confidence intervals of secondary outcomes were not adjusted for multiple comparisons, these intervals should not be used for inference about treatment effects; Only patients who experienced complete or partial remission at each time point (see Table 2) were included in a cross-sectional analysis of the respective time point, therefore, no longitudinal comparison between time points should be made; Anti-PLA2R, anti-phospholipase A2 receptor autoantibody; n, number of patients analyzed; IQR, interquartile range; CI, confidence interval; *95% confidence intervals are bootstrapped.

Table S28: Ratios of geometric means of anti-PLA2R levels in anti-PLA2R-positive patients with complete or partial remission at months 6, 12, 18 and 24

Time from randomization	Rituximab		Cyclosporine		Ratio of geometric means (95% CI)
	n	Geometric mean (95% CI)	n	Geometric mean (95% CI)	
6 months	16	4.6 (2.7 to 8.1)	20	29.0 (14.7 to 57.3)	0.2 (0.1 to 0.4)
12 months	29	7.3 (4.8 to 11.3)	21	23.6 (12.7 to 43.8)	0.3 (0.2 to 0.6)
18 months	28	5.6 (3.5 to 9.0)	7	26.8 (9.8 to 73.1)	0.2 (0.1 to 0.6)
24 months	28	5.4 (3.4 to 8.5)	6	18.4 (6.0 to 56.3)	0.3 (0.1 to 0.8)

Because the widths of 95% confidence intervals of secondary outcomes were not adjusted for multiple comparisons, these intervals should not be used for inference about treatment effects; n, number of patients analyzed; CI, confidence interval. Ratios of geometric means estimated from analysis of covariance of log transformed data adjusted for log transformed baseline values. Group-specific geometric means are expressed in u/mL, ratios of geometric means are unitless.

Table S29: Sensitivity analyses: comparison between groups of quality of life scores from mixed repeated measures linear regression with random intercepts for patients in patients with complete or partial remission at months 6, 12 and 24

	Rituximab	Cyclosporine	Difference in means (95% CI)
Scale	n	n	
SF-36 Physical Health Composite			
6 months	20	29	2.6 (-1.9 to 7.1)
12 months	36	31	-0.1 (-4.0 to 3.8)
24 months	37	11	1.3 (-3.9 to 6.5)
SF-36 Mental Health Composite			
6 months	20	29	3.3 (-0.4 to 7.0)
12 months	36	31	3.2 (-0.1 to 6.5)
24 months	37	11	2.9 (-1.2 to 7.1)
Symptom/problem list			
6 months	23	32	7.2 (1.7 to 12.7)
12 months	38	33	2.4 (-2.7 to 7.4)
24 months	38	12	3.7 (-2.6 to 10.0)
Effects of kidney disease			
6 months	23	31	0.5 (-7.1 to 8.0)
12 months	38	33	3.0 (-3.7 to 9.7)
24 months	38	12	9.4 (0.6 to 18.2)
Burden of kidney disease			
6 months	23	32	-0.3 (-11.0 to 10.4)
12 months	38	33	-4.6 (-14.5 to 5.3)
24 months	38	12	5.8 (-6.3 to 17.9)

Because the widths of 95% confidence intervals of secondary outcomes were not adjusted for multiple comparisons, these intervals should not be used for inference about treatment effects; Only patients who experienced complete or partial remission at each time point (see Tables 2 and S2) were included in a cross-sectional analysis of the respective time point if they had quality of life data available, therefore, no longitudinal comparison between time points should be made; KDQOL-SF, Kidney Disease and Quality of Life™ Short Form; CI, confidence interval. Differences at follow-up estimated from analysis of covariance adjusted for baseline values.

Table S30: Sensitivity analyses: comparison between groups of quality of life scores from mixed repeated measures linear regression with random intercept for patients and random slope for centers in patients with complete or partial remission at months 6, 12 and 24

	Rituximab	Cyclosporine	Difference in means (95% CI)*
Scale	n	n	
SF-36 Physical Health Composite			
6 months	20	29	2.6 (-1.9 to 7.1)
12 months	36	31	-0.1 (-4.0 to 3.8)
24 months	37	11	1.3 (-3.9 to 6.5)
SF-36 Mental Health Composite			
6 months	20	29	3.3 (-0.4 to 7.0)
12 months	36	31	3.2 (-0.1 to 6.5)
24 months	37	11	2.9 (-1.2 to 7.1)
Symptom/problem list			
6 months	23	32	7.1 (1.7 to 12.6)
12 months	38	33	2.4 (-2.6 to 7.4)
24 months	38	12	3.6 (-2.6 to 9.8)
Effects of kidney disease			
6 months	23	31	0.5 (-6.9 to 8.0)
12 months	38	33	3.1 (-3.5 to 9.7)
24 months	38	12	9.4 (0.7 to 18.2)
Burden of kidney disease			
6 months	23	32	-0.2 (-10.6 to 10.3)
12 months	38	33	-4.4 (-14.0 to 5.2)
24 months	38	12	5.8 (-6.1 to 17.7)

Because the widths of 95% confidence intervals of secondary outcomes were not adjusted for multiple comparisons, these intervals should not be used for inference about treatment effects; Only patients who experienced complete or partial remission at each time point (see Tables 2 and S2) were included in a cross-sectional analysis of the respective time point if they had quality of life data available, therefore, no longitudinal comparison between time points should be made; KDQOL-SF, Kidney Disease and Quality of Life™ Short Form; CI, confidence interval; *differences at follow-up estimated from analysis of covariance adjusted for baseline values.

Table S31: Adverse events by system organ class

	Rituximab		Cyclosporine		P-value
	Patients (%)	Events (per 100)	Patients (%)	Events (per 100)	
Any adverse event	46 (70.8)	179 (275.4)	51 (78.5)	218 (335.4)	0.31
Benign neoplasms	1 (1.5)	1 (1.5)	1 (1.5)	1 (1.5)	1.00
Blood and lymphatic system	1 (1.5)	1 (1.5)	3 (4.6)	3 (4.6)	0.62
Cardiovascular	5 (7.7)	6 (9.2)	11 (16.9)	14 (21.5)	0.11
Ear	3 (4.6)	3 (4.6)	1 (1.5)	2 (3.1)	0.62
Endocrine/metabolic	7 (10.8)	9 (13.8)	6 (9.2)	15 (23.1)	0.77
Eye	1 (1.5)	1 (1.5)	1 (1.5)	1 (1.5)	1.00
Gastrointestinal	7 (10.8)	11 (16.9)	18 (27.7)	34 (52.3)	0.014
General	25 (38.5)	42 (64.6)	15 (23.1)	24 (36.9)	0.057
Immune system	1 (1.5)	1 (1.5)	1 (1.5)	1 (1.5)	1.00
Infections	17 (26.2)	28 (43.1)	20 (30.8)	26 (40.0)	0.56
Injury	3 (4.6)	3 (4.6)	1 (1.5)	1 (1.5)	0.62
Musculoskeletal	10 (15.4)	17 (26.2)	18 (27.7)	27 (41.5)	0.088
Nervous system	11 (16.9)	15 (23.1)	16 (24.6)	26 (40.0)	0.28
Pregnancy	1 (1.5)	1 (1.5)	0 (0.0)	0 (0.0)	1.00
Psychiatric	1 (1.5)	1 (1.5)	5 (7.7)	7 (10.8)	0.21
Renal and urinary	6 (9.2)	8 (12.3)	16 (24.6)	19 (29.2)	0.019
Reproductive system and breast	3 (4.6)	4 (6.2)	1 (1.5)	1 (1.5)	0.62
Respiratory	9 (13.8)	13 (20.0)	6 (9.2)	11 (16.9)	0.41
Skin	12 (18.5)	14 (21.5)	5 (7.7)	5 (7.7)	0.069
Serious adverse event	11 (16.9)	13 (20.0)	20 (30.8)	22 (33.8)	0.064
Benign neoplasms	1 (1.5)	1 (1.5)	0 (0.0)	0 (0.0)	1.00
Blood and lymphatic system	1 (1.5)	1 (1.5)	1 (1.5)	1 (1.5)	1.00
Cardiovascular	1 (1.5)	1 (1.5)	7 (10.8)	7 (10.8)	0.062
Endocrine/metabolic	2 (3.1)	2 (3.1)	1 (1.5)	1 (1.5)	1.00
General	1 (1.5)	1 (1.5)	0 (0.0)	0 (0.0)	1.00
Infections	4 (6.2)	5 (7.7)	8 (12.3)	8 (12.3)	0.23
Musculoskeletal	0 (0.0)	0 (0.0)	1 (1.5)	2 (3.1)	1.00
Nervous system	1 (1.5)	1 (1.5)	1 (1.5)	1 (1.5)	1.00
Renal and urinary	0 (0.0)	0 (0.0)	2 (3.1)	2 (3.1)	0.50
Respiratory	1 (1.5)	1 (1.5)	0 (0.0)	0 (0.0)	1.00

Because p-values were not adjusted for multiple comparisons, they should not be used for inference about treatment effects; Reported are the numbers of patients who experienced at least 1 event (%), and the overall number of events for each type (number of events per 100 patients); P-value for the difference in proportion of patients experiencing a specific type of event from Fisher's exact test if number of expected patients with event is below 5, or from Chi-squared test.

Table S32: Adverse events with investigator-assessed probable or definite relationship to study drug

	Rituximab		Cyclosporine		P-value
	Patients (%)	Events (per 100*)	Patients (%)	Events (per 100*)	
Any adverse event	25 (38.5)	36 (55.4)	27 (41.5)	50 (76.9)	0.72
Grade ≥3	0 (0.0)	0 (0.0)	4 (6.2)	4 (6.2)	0.12
Grade <3	25 (38.5)	36 (55.4)	23 (35.4)	46 (70.8)	0.72
Serious adverse event	0 (0.0)	0 (0.0)	5 (7.7)	5 (7.7)	0.058
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.00
Non-fatal	0 (0.0)	0 (0.0)	5 (7.7)	5 (7.7)	0.058
By organ system					
Any adverse event					
Cardiovascular	0 (0.0)	0 (0.0)	5 (7.7)	6 (9.2)	0.058
Endocrine/metabolic	0 (0.0)	0 (0.0)	2 (3.1)	2 (3.1)	0.50
Gastrointestinal	1 (1.5)	2 (3.1)	9 (13.8)	14 (21.5)	0.017
General	18 (27.7)	24 (36.9)	1 (1.5)	1 (1.5)	<0.001
Infections	2 (3.1)	3 (4.6)	5 (7.7)	5 (7.7)	0.44
Musculoskeletal	2 (3.1)	3 (4.6)	4 (6.2)	6 (9.2)	0.68
Nervous system	0 (0.0)	0 (0.0)	6 (9.2)	8 (12.3)	0.028
Renal and urinary	0 (0.0)	0 (0.0)	5 (7.7)	5 (7.7)	0.058
Reproductive system and breast	0 (0.0)	0 (0.0)	1 (1.5)	1 (1.5)	1.00
Skin	4 (6.2)	4 (6.2)	2 (3.1)	2 (3.1)	0.68
Serious adverse event					
Cardiovascular	0 (0.0)	0 (0.0)	3 (4.6)	3 (4.6)	0.24
Infections	0 (0.0)	0 (0.0)	2 (3.1)	2 (3.1)	0.50

Because p-values were not adjusted for multiple comparisons, they should not be used for inference about treatment effects; *number of events per 100 patients; P-value for the difference in proportion of patients experiencing a specific type of event from Fisher's exact test if number of expected patients with event is below 5, or from Chi-squared test.