SUPPLEMENTARY APPENDIX TO:

SAFETY OF RITUXIMAB COMPARED TO CYCLOPHOSPHAMIDE FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY

Supplementary Table 1:

Results of sensitivity analysis by low or high dose cyclosphosphamide, and one or four doses of rituximab: baseline characteristics

Characteristic	Low dose ST-CP (<20g) (n=25)		High dose ST-CP (≥20g) (n=78)		Single dose RTX (n=70)		Four doses RTX (n=30)		p
Male gender	68%		78%		77%		60%		0.55
Age (years)	52.6	16.8	56.2	11.0	51.6	15.2	51.4	17.8	0.19
BMI (kg/m^2)	25.7	3.7	26.9	3.5	26.9	4.0	25.8	5.1	0.35
Disease duration (months)	13.1	(3.5-35.4)	10.8	(5.0-21.4)	10.6	(4.5-29.4)	16.2	(6.0-34.8)	0.54
Systolic blood pressure (mmHg)	135	(120-146)	130	(120-150)	131	(122-145)	132	(123-140)	0.81
Diastolic blood pressure (mmHg)	84	(70-90)	78	(70-84)	82	(74-90)	81	(76-89)	0.08
Urine protein creatinine ratio (mg/g)	10200	(5967-13734)	8620	(5649-11050)	6541	(4011-9800)	5740	(4411-7443)	<0.001
eGFR (ml/min per 1.73m2)	62.3	25.6	57.2	21.9	59.6	27.2	57.8	25.5	0.81
Serum creatinine (µmol/l)	109	(86-132)	114	(93-142)	107	(86-151)	106	(82-141)	0.80
Serum albumin (g/l)	20.9	7.9	21.8	6.1	21.8	7.2	23.5	5.7	0.53
Serum cholesterol (mmol/l)	8.0	2.7	7.6	2.6	6.9	1.8	7.0	1.7	0.08
ACEi/ARB use	80%		91%		93%		97%		0.16
Diuretic use	64%		87%		61%		80%		0.02
Statin use	52%		65%		81%		57%		0.07
Prior immunosuppressive therapy	12%		12%		39%		17%		<0.001

Data are presented as proportions (%), means and standard deviations or median and inter quartile range, respectively. The groups were compared using X^2 test for proportions and one-way ANOVA (F-test) for continuous variables. SBP: systolic blood pressure. DPB: diastolic blood pressure. UPCR: urine protein creatinine ratio. eGFR: estimated glomerular filtration rate based on the abbreviated Modification of Diet in Renal Disease (MDRD) equation for mass spectrometry calibrated serum creatinine values. ACEi: angiotensin converting enzyme inhibitors. ARB: angiotensin II receptor blockers.

Supplementary Table 2:

Result of sensitivity analysis by low or high dose cyclosphosphamide, and one or four doses of rituximab: adverse event rates and renal outcome.

Outcome	Low dose ST-CP (<20g)	High dose ST-CP (>20g)		RTX (1 dose)		RTX (4 doses)	
Crude	HR	HR	95% CI	HR	95% CI	HR	95% CI
First adverse event	1 (ref)	0.97	0.55 - 1.69	0.23	0.12 - 0.48	0.28	0.13 - 0.63
Serious adverse event	1 (ref)	0.70	0.32 - 1.54	0.25	0.08 - 0.76	0.28	0.09 - 0.93
Non-serious adverse event	1 (ref)	1.00	0.56 - 1.77	0.21	0.10 - 0.46	0.26	0.11 - 0.64
partial remission	1 (ref)	0.88	0.55 - 1.42	0.51	0.30 - 0.85	0.86	0.49 - 1.52
Complete remission	1 (ref)	1.39	0.64 - 3.03	1.10	0.46 - 2.65	1.35	0.56 - 3.26
Renal failure	1 (ref)	0.84	0.33 - 2.16	0.99	0.33 - 2.94	0.69	0.22 - 2.16
Adjusted							
First adverse event	1 (ref)	0.83	0.46 - 1.49	0.21	0.10 - 0.45	0.25	0.11 - 0.59
Serious adverse event	1 (ref)	0.70	0.32 - 1.54	0.25	0.08 - 0.77	0.28	0.09 - 0.92
Non-serious adverse event	1 (ref)	0.85	0.47 - 1.54	0.20	0.09 - 0.46	0.23	0.09 - 0.58
Partial remission	1 (ref)	0.89	0.54 - 1.46	0.51	0.30 - 0.88	0.76	0.42 - 1.40
Complete remission	1 (ref)	1.82	0.81 - 4.12	1.14	0.45 - 2.88	1.48	0.57 - 3.84
Renal failure	1 (ref)	0.91	0.33 - 2.53	1.12	0.34 - 3.62	0.85	0.24 - 3.00

HR: Hazard ratio, 95%CI: 95% confidence interval. Analyses were adjusted for the following covariates: **First adverse event:** sex, age, disease duration, urine protein creatinine ratio (UPCR), estimated GFR (by MDRD4 equation), cholesterol, ACEi/ARB, diuretics, prior immunosuppressive therapy. **Serious adverse event:** age, disease duration, prior therapy. **Non-serious adverse event:** sex, age, disease duration, UPCR, estimated GFR, cholesterol, prior immunosuppressive therapy. **Renal failure:** sex, age, disease duration, UPCR, estimated GFR. **Partial remission:** sex, age, disease duration, UPCR, estimated GFR, prior therapy. **Complete remission:** sex, age, disease duration, UPCR, estimated GFR, prior therapy.

Supplementary Table 3:

Results of sensitivity analysis: restriction to patient without prior immunosuppresion.

Outcome	Hazard Ratio	95% Confidence Interval
Crude		
First adverse event	0.27	0.16 - 0.45
Serious adverse event	0.31	0.13 - 0.75
Non-serious adverse event	0.26	0.15 - 0.47
Partial remission	0.72	0.50 - 1.04
Complete remission	0.97	0.55 - 1.72
Renal failure	0.72	0.31 - 1.68
Adjusted		
First adverse event	0.21	0.12 - 0.37
Serious adverse event	0.31	0.13 - 0.75
Non-serious adverse event	0.23	0.12 - 0.42
Partial remission	0.66	0.46 - 0.97
Complete remission	0.74	0.40 - 1.37
Renal failure	0.83	0.34 - 2.03

Analyses were adjusted for the following covariates: **First adverse event:** sex, age, disease duration, urine protein creatinine ratio (UPCR), estimated GFR (by MDRD4 equation), cholesterol, ACEi/ARB, diuretics. **Serious adverse event:** age, disease duration. **Non-serious adverse event:** sex, age, disease duration, UPCR, estimated GFR, cholesterol. **Renal failure:** sex, age, disease duration, UPCR, estimated GFR. **Partial remission:** sex, age, disease duration, UPCR, estimated GFR. **Complete remission:** sex, age, disease duration, UPCR, estimated GFR.

Supplemental Table 4.

Definitions of adverse events observed throughout the study period in patients with idiopathic membranous nephropathy and persistent nephrotic syndrome refractory to conservative therapy treated with Rituximab (n=100) or a Cyclophosphamide-based immunosuppressive regimen (n=103).

Adverse event	Definition
Leucopoenia	White blood cell count < 3.0 x 10^9/l (=3000/mm^3)
Thrombocytopenia	Platelet count < 50 x 10^9/l (=50000/mm^3)
Hemorrhagic cystitis	Non-glomerular macrohematuria confirmed by cystoscopy or necessitating withdrawal of therapy
Infertility	The inability to conceive without medical intervention such as intra uterine insemination or *in vitro* fertilization
Alopecia	Hair loss not attributed to normal ageing
Infection	Any infection or unexplained fever requiring hospital admission, use of antibiotic treatment or the interruption of therapy
Malignancy	Malignant neoplastic disease including lymphoproliferative diseases and leukaemia
Minor cardiovascular event	Stable angina pectoris, peripheral vascular disease, transient ischemic attack (without residual disability)
Major cardiovascular event	Acute myocardial infarction, stroke, unstable angina pectoris, artery revascularization, amputations, pulmonary embolism and/or deep venous thrombosis
Liver toxicity	SGTP > 90 U/l, SGOT > 80 U/l
Hyperglycemia	Initiation of glucose regulating medication (e.g. insulin, metformin) or dosage increase if pre-existing diabetes mellitus.
Osteonecrosis / pathological fractures	A-vascular necrosis, pathological fractures associated with prednisone use
Infusion reaction	Adverse reaction (e.g. fever, chills, flushing, itching, rash, altered heart rate and blood pressure, dyspnea, abdominal pain, nausea or diarrhea) following infusion of medication.

SGTP: Serum glutamic pyruvic transaminase, SGOT: Serum glutamic oxaloacetic transaminase,

Supplementary Table 5.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies.***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract ***see Abstract, page 2 – line 8***
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found ***see Abstract, page 2***
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported ***see page 3, lines 7 to 14***
Objectives	3	State specific objectives, including any prespecified hypotheses ***see page 3, lines 18 and 19.***
Methods		
Study design	4	Present key elements of study design early in the paper ***see pages 11 to 13,***
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection ***see page 11***
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up ***see page 11 lines 4 to 8, and 13 to 19***
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed ***(not applicable)***
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable ***Outcomes: page 12 (section Outcomes and definitions)*** ***Exposures: page 11 (section Patients and treatments)*** ***Potential confounders: page 12 lines 18 to 23***
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group

		see page 12, outcomes and definitions
Bias	9	Describe any efforts to address potential sources of bias ***see page 13, (statistical methods).***
Study size	10	Explain how the study size was arrived at ***see page 4 lines 4 to 13.***
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why ***see statistical methods page 13***
Statistical methods	12	*(*a) Describe all statistical methods, including those used to control for confounding ***see statistical methods page 13***
		(*b*) Describe any methods used to examine subgroups and interactions **n/a**
		(*c*) Explain how missing data were addressed **n/a**
		(*d*) If applicable, explain how loss to follow-up was addressed **See statistical methods**
		(e) Describe any sensitivity analyses ***see statistical methods***
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed ***see page 4 Patient inclusion***
		(b) Give reasons for non-participation at each stage ***see page 4 Patient inclusion***
		(c) Consider use of a flow diagram ***Flow diagrams can be found in earlier descriptions of both cohorts that are referenced in the paper (references 6 and 11)***
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders ***see Table 1***

		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount) ***see page 4, line 20***
Outcome data	15*	Report numbers of outcome events or summary measures over time ***see page 4, lines 24 to 26 and Figure 1.***
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included ***See Figure 1***
		(*b*) Report category boundaries when continuous variables were categorized ***n/a***
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses ***See page 6 lines 2 and 5, page 6 lines 23 and 25***
Discussion		
Key results	18	Summarise key results with reference to study objectives ***See page 7, lines 3 to 16***
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias ***See page 9 (limitations and strengths)***
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence ***See page 7 line 19 to page 9 line 17.***
Generalisability	21	Discuss the generalisability (external validity) of the study results ***See page 10 lines 7 to 13***
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based ***See acknowledgements***