Treating Membranous Nephropathy 2019

St Petersburg
Russia
June 1,2019

Daniel Cattran

Professor of Medicine
Senior Scientist
Toronto General Research Institute
University Health Network
University of Toronto

TORONTO Glomerulonephritis REGISTRY

MN remains a serious issue

Table 1 | Trends in Toronto Glomerulonephritis Registry: 1975–2015[a]

	1975–1979	1980–1984	1985–1989	1990–1994	1995–1999	2000–2004	2005–2011	2012–2015[a]	Total
MN	134	172	171	164	129	138	230	168	1306
MPGN	99	67	33	46	37	22	34	N/A	329
FSGS	141	164	163	239	311	318	338	288	1962
IGA	129	215	227	262	309	299	349	286	2076
LUPUS	170	191	143	174	136	130	262	N/A	1206
Vasculitis	29	66	76	93	76	87	152	N/A	579

Доклад Даниеля Каттрана
Дни нефрологии в
Санкт-Петербурге
30 мая- 01 июня 2019 г.

Cattran ,Brenchley KI 2017

First thing in MN

Comprehensive supportive care

1. **includes RAS blockade,**
2. **blood pressure management targeting <125/75 mmHg,**
3. **dietary sodium restriction to <4g/day and**
4. **dietary protein restriction to 0.8-1g protein/kg/day.**
5. **R/O secondary causes and potential serious secondary complications eg RVT**
6. **Only the algorithms… Immunosuppresion options**

So,how should we select the "ideal" IS for MN treatment

- **S**afety
- **P**atient related outcomes
- **E**fficacy
- **E**conomics
- **D**urability of response

then PLUS specific patient factors

Efficacy (clinical vs regulatory)
Proteinuria outcome measures used

CLINICAL

Complete remission, ESRD, mortality

(acceptable but often limited due to known slow natural progression and by ,in contrast short duration of RCT's)

Partial Remission

(decrease in initial proteinuria by >50% and <3.5 g/l)

<u>FDA</u>

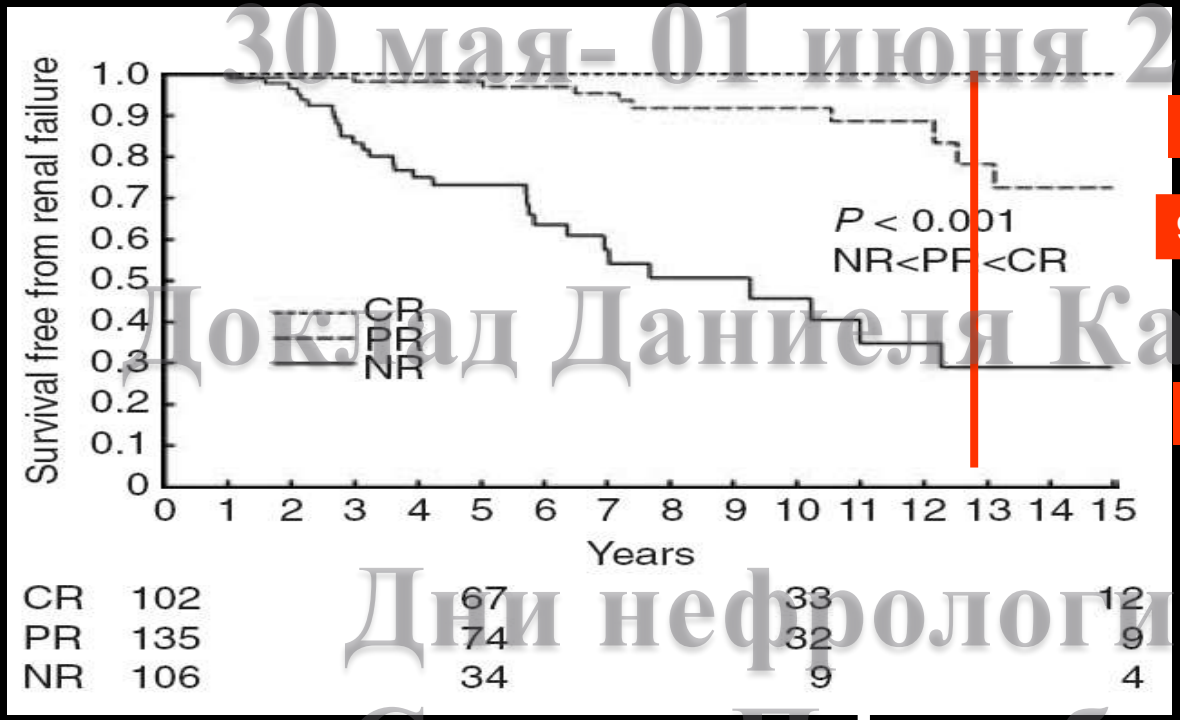
Efficacy measured by preserved eGFR

(fewer with decline from baseline =>40%)

or

CR (PR with accelerated approval)

Efficacy ; helped by capacity to quantitate the value of CR, PR and no remission on hard outcomes



100%

90%

50%

Troyanov …Cattran KI 2004

(PR = 50% in proteinuria and <3.5g/d

EFFICACY OF CURRENT TREATMENTS

1Classic

Alkylating agent /steroids

Calcineurin inhibitors

Rituximab

2 New (sort of)

ACTH

MMF

3 Newer

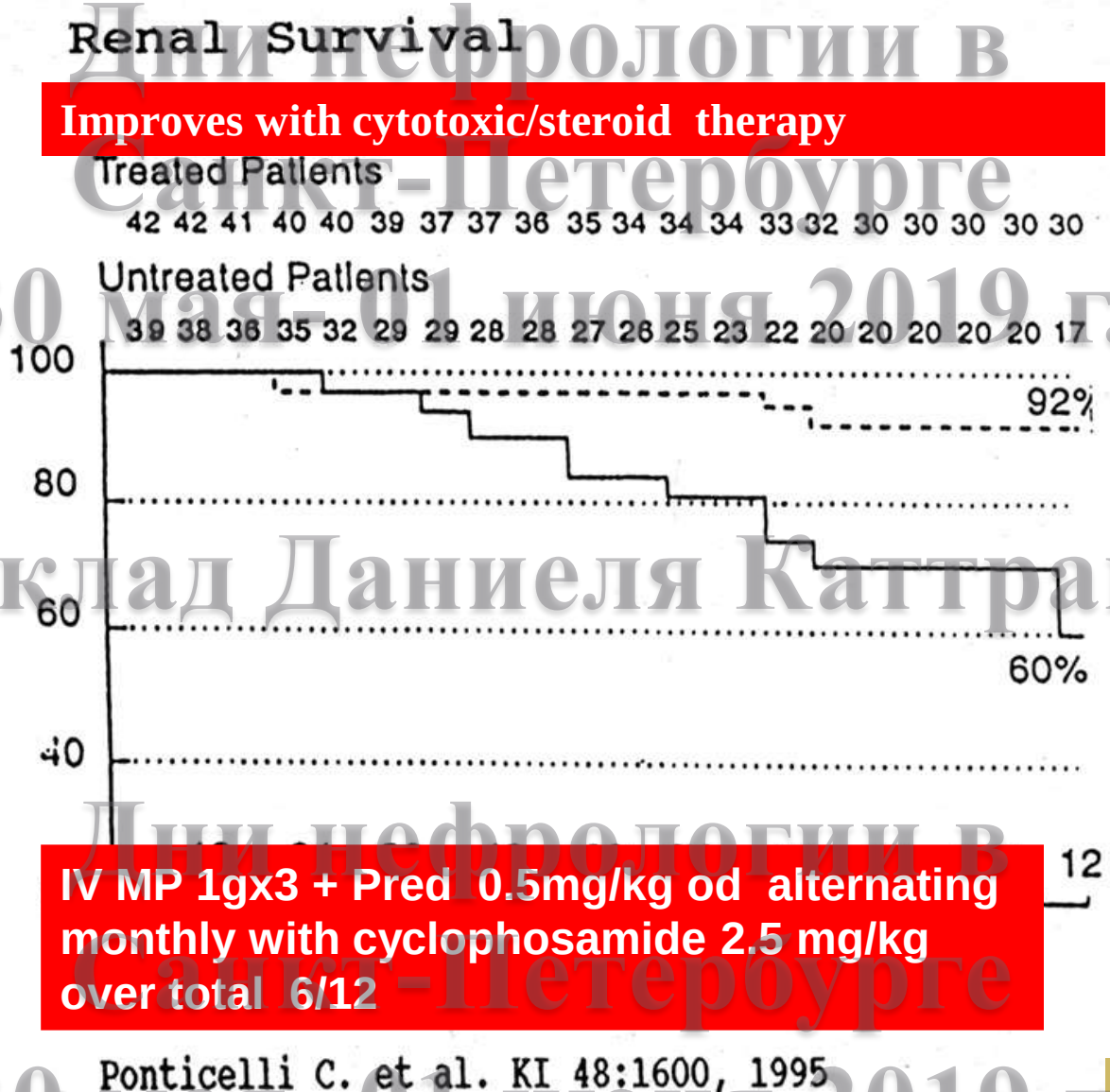
Direct comparison(no placebo)

4 Combinations of above

5 Novel

New approaches but little evidence

Classic alkylating agent/corticosteroids

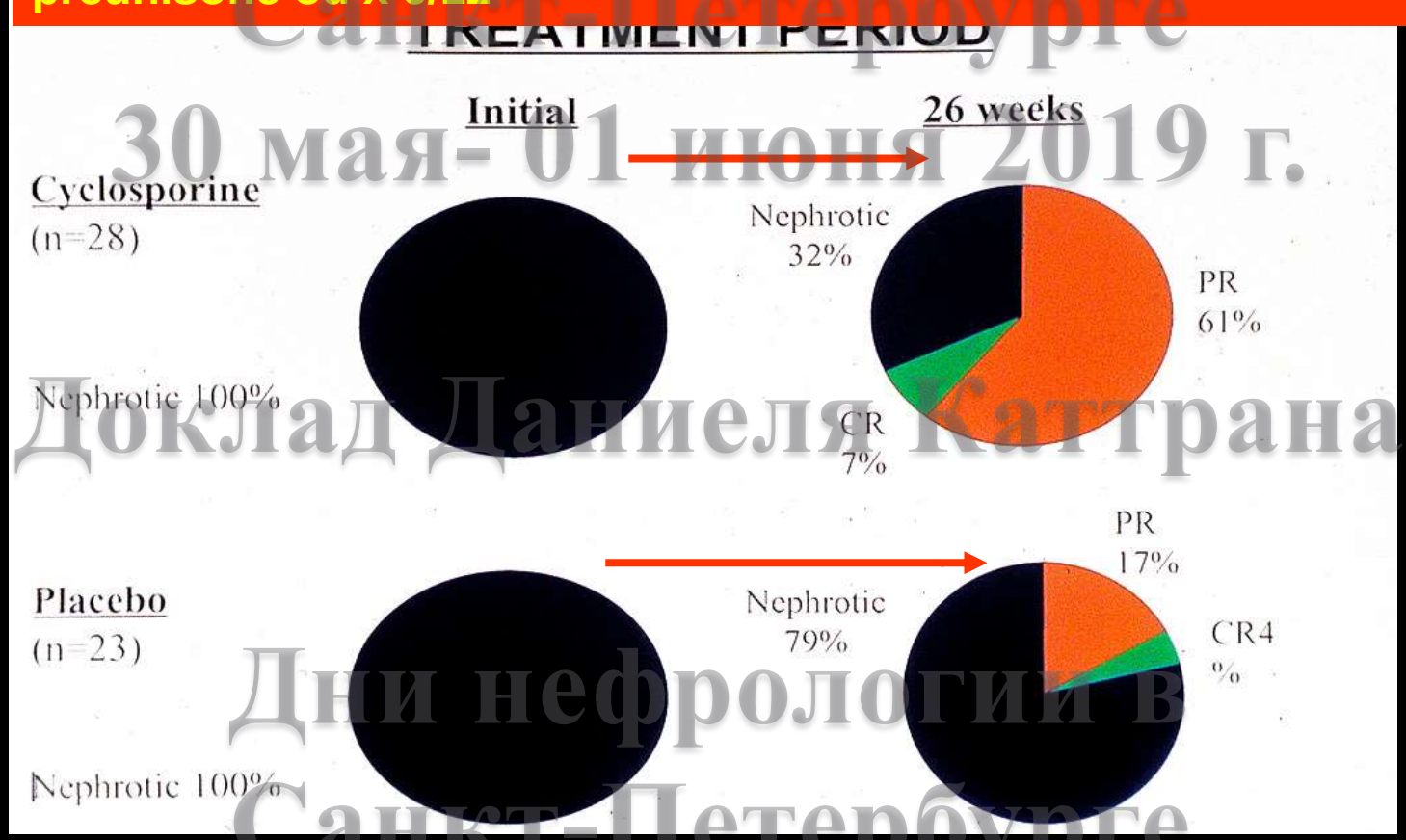


Jha JASN 2007

Calcineurin inhibitors versus placebo in MN

RCT Calcinurin inhibitors

Nephrotic syndrome improved with CSA 3-4mg/kg + 10 mg prednisone od x 6/12



Plus Praga JASN 2007

Cattran et al K. I.2001

Rituximab versus Placebo Gemritux RCT

Compared conservative therapy to rituximab dosed at 375 /m2 on day 1 and 8 in 75 patients with nephrotic range IMN

Primary endpoint : remission rates

at 6

- control 22% (8/38)
- versus treatment 35%(13/37); p=ns

NB Post Hoc +(observation period mean 17 months)

- control to 34%
- vs treatment 65% (p<0.01) .

PLUS

No differences were seen in SAE's between the groups

Changes in PLA2R level paralleled responsiveness

Dahan et al JASN 2016

Delayed effect of Ritux(ad hoc)

Table 3. Results of efficacy analysis at last follow-up

End Point	NIAT-Rituximab Group, n=37	NIAT Group, n=38	P Value
Remission, complete and partial[a]	24 (64.9; 48.5 to 80.2)	13 (34.2; 19.1 to 49.3)	<0.01
Protein-to-creatinine ratio, mg/g	2194.8 (1309.8–5310.0)	4701.1 (2027.8–8265.3)	0.02
Serum albumin, g/L	32 (26–35)	27 (20–30)	0.03
Serum creatinine, μmol/L	101 (87–135)	97.2 (78.5–133.5)	0.50
eGFR, ml/min per 1.73 m^2	61.1 (48.7–83.4)	73.1 (50.4–90.5)	0.48

Jury out

Forth Option:Synthetic ACTH

RCT : response after one year of injections equal to Cyto/Pred routine in MGN

ACTH Synactin Cohort

Ponticelli…AJKD19:2006

Доклад Даниеля Каттрана
Дни нефрологии в Санкт-Петербурге
30 мая- 01 июня 2019 г.

Доклад Даниеля Каттрана
Дни нефрологии в Санкт-Петербурге
30 мая- 01 июня 2019 г.

- Safety

Доклад Даниеля Каттрана
Дни нефрологии в Санкт-Петербурге
30 мая- 01 июня 2019 г.

Adverse events across the spectrum of immunosuppressive drugs from 36 randomized controlled trials in MN: Network meta-analysis

Table 1. The adverse reaction of 11 kinds of treatments for IMN.

Treatments (N)	Infection	Bone marrow suppression	Abnormal liver function	Incidence of hypertension	Incidence of DM	Relapse
CTX (n = 448)	68	10	18	2	19	4
Control (n = 497)	6	0	0	1	2	8
Chlorambucil (n = 244)	19	19	1	1	1	40
Tacrolimus (n = 177)	38	0	10	8	30	2
CsA (n = 137)	8	0	0	12	0	29
MMF (n = 71)	14	6	2	1	1	2
Steroids (n = 309)	5	0	0	6	1	32
Azathioprine (n = 34)	2	5	1	3	0	5
Mizoribine (n = 62)	0	0	0	0	0	0
ACTH (n = 15)	0	0	0	0	0	0
LEF (n = 24)	0	0	0	0	0	0

CTX: cyclophosphamide; CsA: cyclosporine; MMF: mycophenolate mofetil; LEF: leflunomide

N 2

N 1

N 3

N 4

N ?

Ren et al PLOS ONE 2017

Synthetic ACTH Adverse Events

	N Events	(%)	N patients	(%)
Mood disorders/agitation	8		8	(40%)
Increasing oedema	12		12	(60%)
Myalgia/arthralgia	7		7	(35%)
Sleeping disturbances	10		10	(50%)
Fever/infection	9		8	(40%)
Flushing	7		7	(35%)
Hyperpigmentation skin	8		8	(40%)
Hypokalemia	7		3	(15%)
Erythema/local reaction	6		6	(30%)
Hypertension	5		5	(25%)
Weigth gain	6		6	(30%)
Acne	4		4	(20%)
Hyperglycemia	4		4	(20%)
Hair growth/hirsutism	4		4	(20%)
Cushingoid face	4		4	(20%)
Leukopenia	1		1	(5%)
Other	43		16	(80%)
Overall				

No. of patients with 1 or more AE 19 (95%)

No. of patients needing dose decrease 2 (10%)

No. of SAE (hospitalizations) 5 (25%)

Same routine
Wetzels et al PLOS ONE 2016

AE's time and frequency rituximab vs CYC/steroids

	Hazard Ratio (95% Confidence Interval)	Events per group		
			Rituximab	*Cyclophos-phamide*
Crude				
First adverse event		0.26 (0.16 - 0.41)	25	67
Serious adverse event		0.31 (0.15 - 0.66)	9	30
Non-serious adverse event		0.23 (0.14 - 0.39)	18	58
Adjusted				
First adverse event		0.27 (0.16 - 0.44)	25	67
Serious adverse event		0.32 (0.15 - 0.68)	9	30
Non-serious adverse event		0.23 (0.13 - 0.41)	18	58

1.0

Van den Brand et al JASN 2017

HEALTH ECONOMICS

Direct Cost Least to Most Costs

Alkylating agents plus steroid

Mycophenolate mofetil

Calcineurin inhibitor

Rituximab

ACTH

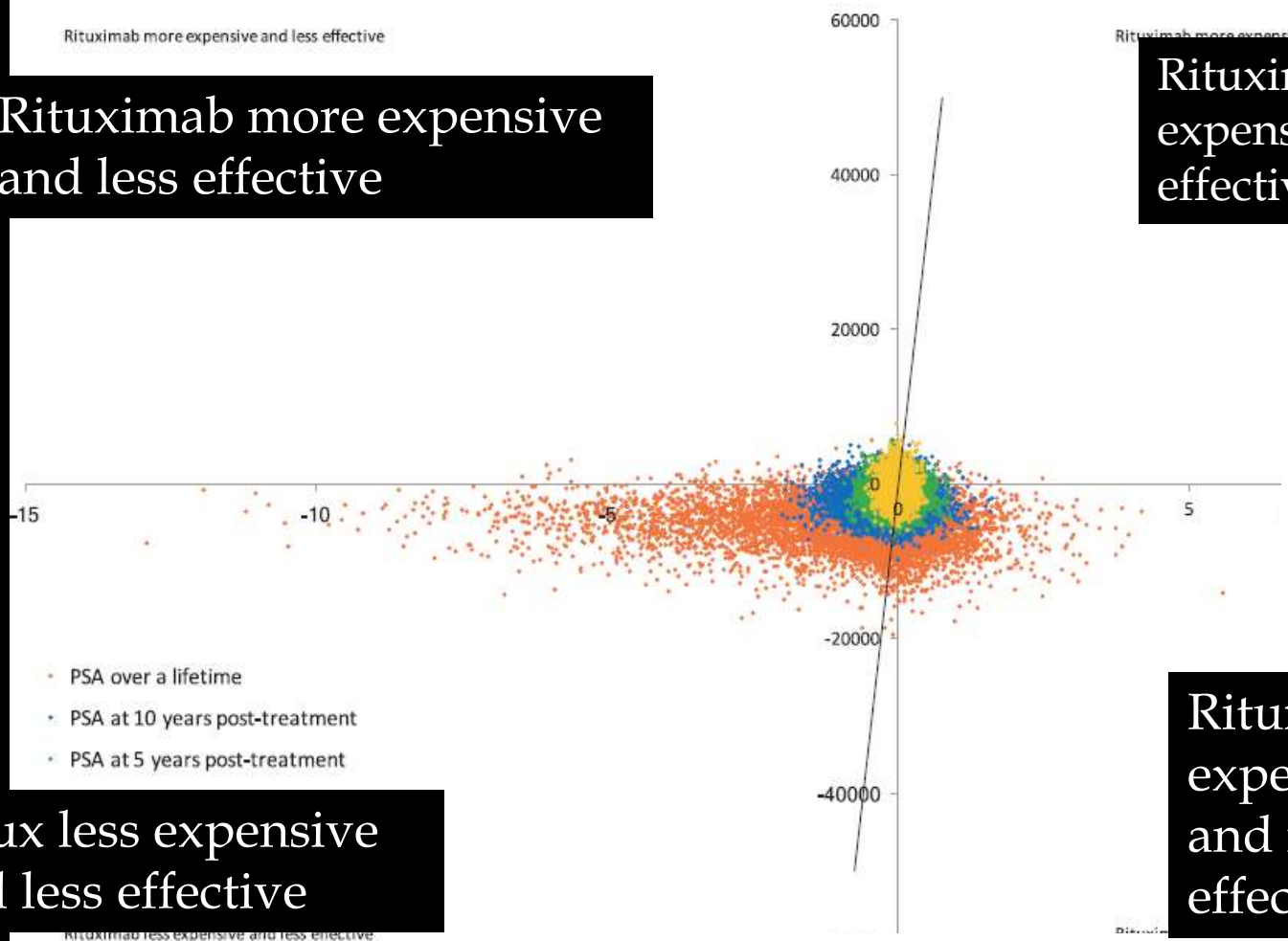
(total direct costs varies dramatically across geographic and health care systems and duration of therapy but the order and magnitude of differences remains)

Cost effectiveness rituximab versus
modified Ponticelli routine
Primary outcome at 5 years

Secondary at 1 and 10 years

Hamilton et al NDT 2018

Economic Modeling of Rituximab versus mPR in MN



Rituximab more expensive and less effective

Rituximab more expensive and more effective

Horizontal axis Quality-of-life years gained

Ritux less expensive and less effective

Ritux less expensive and more effective

Vertical axis incremental costs

probabilistic sensitivity analysis (PSA)

Hamilton et al NDT 2018

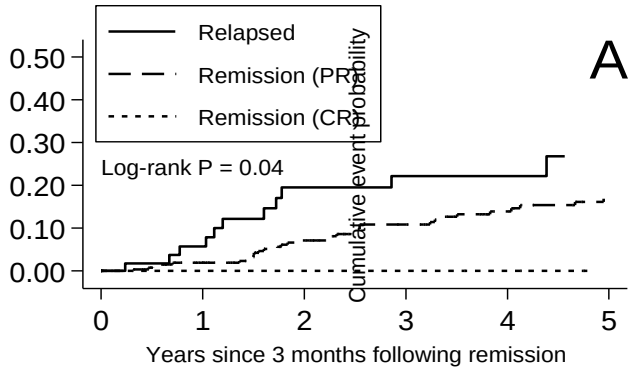
Patient related outcomes
Why study Quality of life in MN?

- Important individual outcome,
- Allows for identification of response to treatment in a variety of domains,
- Helps identify areas of impact in order to intervene
- May be importantly related to other outcomes (e.g. morbidity and mortality).
- Can be included in studies of treatment effectiveness.

Durability of Response

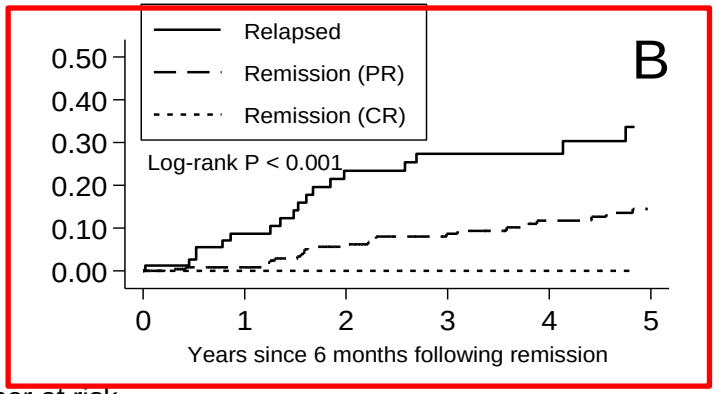
Predictive value of remission duration on hard outcome at

(A)3 months, (B) 6 months, (C) 12 months, (D) 24 months after Complete or partial remission



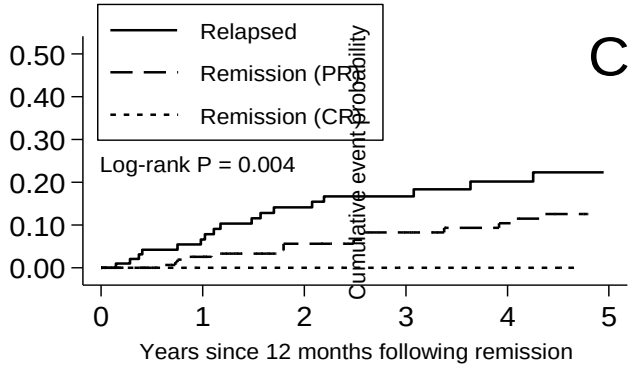
Number at risk

Relapsed	60	44	33	29	21	14
Remission(PR)	273	231	186	155	122	107
Remission(CR)	14	13	12	11	10	7



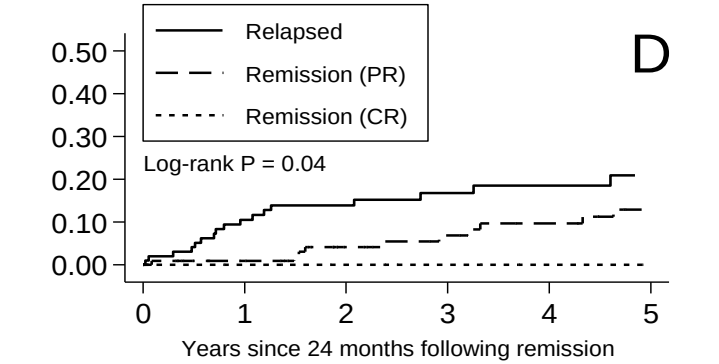
Number at risk

Relapsed	80	56	40	35	25	17
Remission(PR)	240	201	161	134	106	93
Remission(CR)	19	17	16	14	12	9



Number at risk

Relapsed	100	77	65	56	37	29
Remission(PR)	171	146	117	95	83	74
Remission(CR)	31	25	24	19	15	11

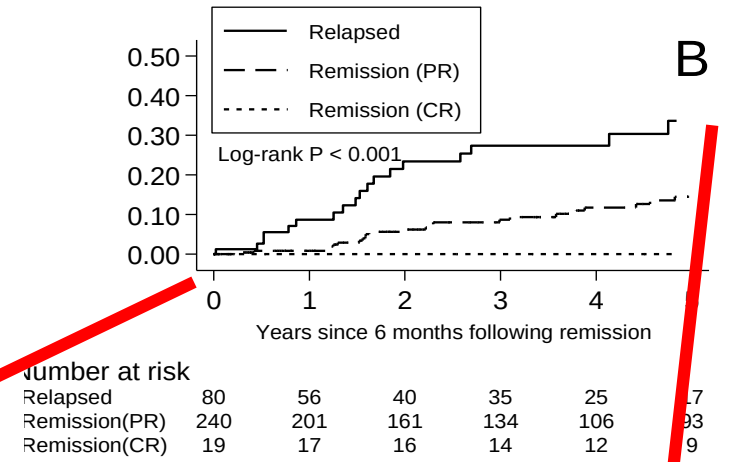


Number at risk

Relapsed	101	79	68	48	39	31
Remission(PR)	115	96	78	68	61	49
Remission(CR)	39	36	28	23	17	12

Cattran 2017

Long Term Value of 6 mos of initial Remission



Entered remission from -6 months

Hard outcome at 5yrs and 6 mos post remission (after only 6mos remission)

Cattran et al JASN 2017

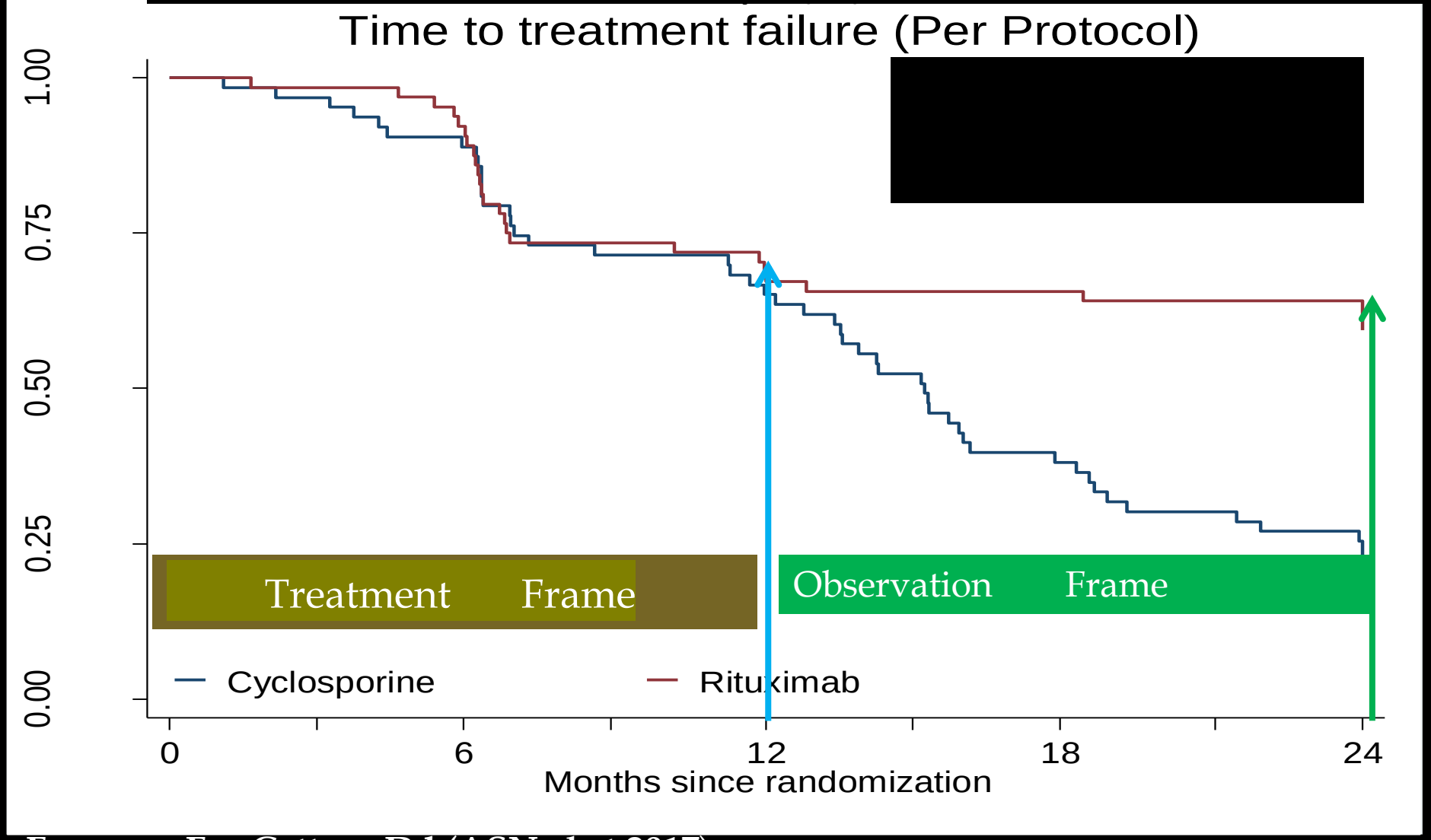
Recent Study Variables in MN Trials

- **Head to Head IS**
- **Sequential/Combination IS routines**

Patient characteristics at baseline

Baseline Characteristics	Rituximab (n=65)	Cyclosporine (n=65)
Age - yr	51.9 (12.6)	52.2 (12.4)
Male - no.(%)	47 (72.3)	53 (81.5)
Systolic blood pressure - mmHg	125.7 (14.8)	123.3 (13.4)
Diastolic blood pressure - mmHg	74.7 (10.1)	76.5 (9.8)
Height - m	1.7 (.1)	1.7 (.1)
Weight - kg	96 (22.9)	90 (20.1)
BMI - kg/m^2	31.8 (6.3)	29.3 (5.6)
History of immunosuppressive therapy - no.(%)	19 (29.2)	20 (30.8)
Lipid – LDL cholesterol (mg/dL)	114.1 (57.7)	122.3 (63)
Lipid – total cholesterol (mg/dL)	145.1 (61.6)	144.8 (69.8)
Anti-PLA2R, median (IQR) - (u/mL)	409 (163 to 834)	413 (206 to 961)
Anti-PLA2R positive (>40u/mL) - no.(%)	50 (76.9)	46 (70.8)
Serum Albumin, median(IQR) - g/dL	2.5 (2.1,2.9)	2.5 (2.1,2.9)
Serum Creatinine - mg/dL	1.3 (.4)	1.3 (.4)
Urine Protein, median(IQR) - g/24h	8.9 (6.8,12.3)	8.9 (6.7,12.9)
Creatinine Clearance - mL/min/1.73m^2	84.9 (29.8)	87.4 (34.4)

Head to Head …… MENTOR
Ritux vs CSA



Fervenza F …Cattran D l (ASN abst 2017)

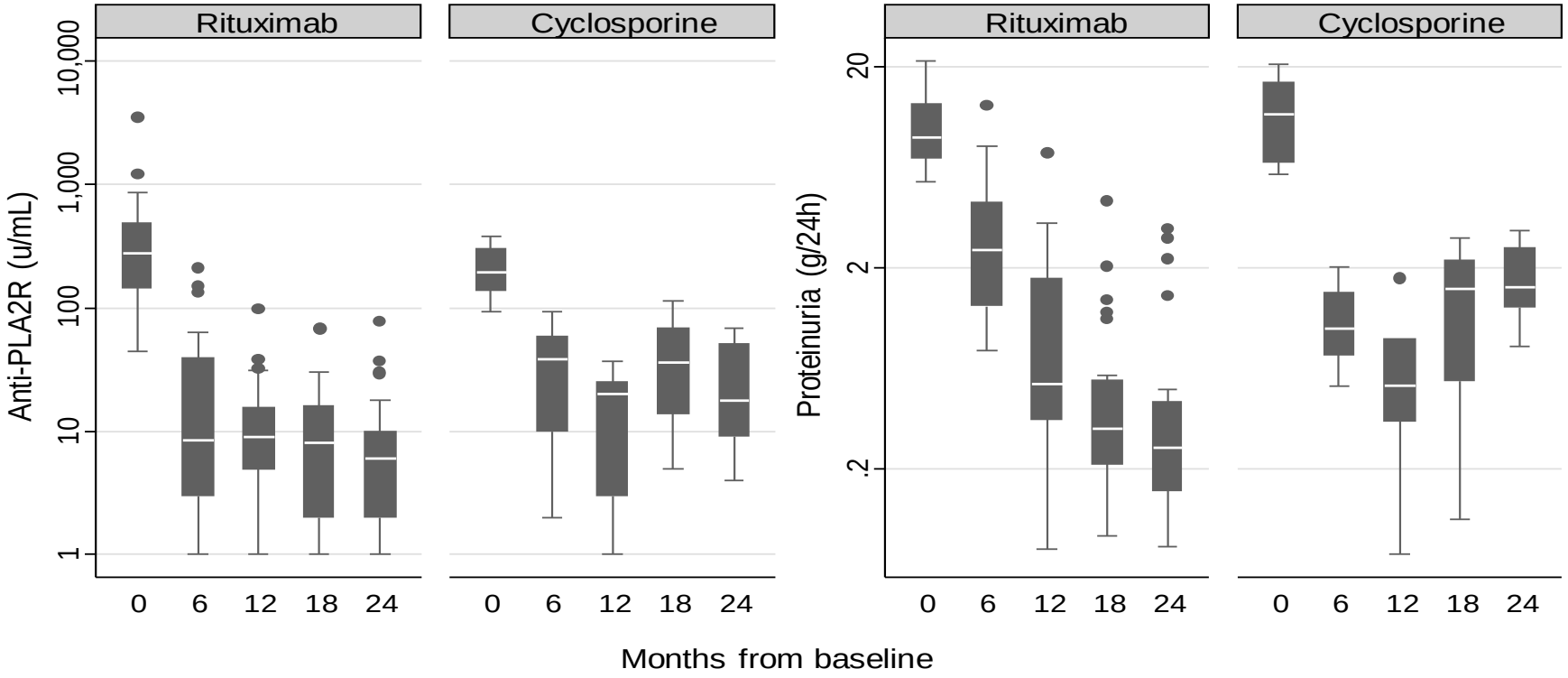
Number of patients with complete or partial remission

Time from randomization	Rituximab		Cyclosporine		Risk difference (95% CI)	P-value*
	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)	0.11
12 months	**65**	**39 (60.0)**	**65**	**34 (52.3)**	**7.7 (-9.3 to 24.7)**	**0.38**
18 months	65	40 (61.5)	65	15 (23.1)	38.5 (22.8 to 54.1)	<0.001
24 months	**65**	**39 (60.0)**	**65**	**13 (20.0)**	**40.0 (24.6 to 55.4)**	**<0.001**
PP population						
6 months	63	22 (34.9)	63	32 (50.8)	-15.9 (-32.9 to 1.2)	0.068
12 months	63	38 (60.3)	63	33 (52.4)	7.9 (-9.3 to 25.2)	0.37
18 months	63	39 (61.9)	63	15 (23.8)	38.1 (22.1 to 54.0)	<0.001
24 months	63	39 (61.9)	63	13 (20.6)	41.3 (25.7 to 56.9)	<0.001

Adverse events Mentor trial

	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
Grade ≥3	34 (52.3)	76 (116.9)	44 (67.7)	109 (167.7)	0.073
Grade <3	36 (55.4)	99 (152.3)	34 (52.3)	104 (160.0)	0.73
Serious adverse event	11 (16.9)	13 (20.0)	20 (30.8)	22 (33.8)	0.064
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.00
Non-fatal	11 (16.9)	13 (20.0)	20 (30.8)	22 (33.8)	0.064

Outcome by PLA 2R + status at baseline



TORONTO Glomerulonephritis REGISTRY

CRCl and Upro by group and time in CR and PR patients

	Rituximab		Cyclosporine	
Proteinuria (g/24h)	n	Median (IQR)	n	Median (IQR)
Anti-PLA2R+				
Baseline	28	8.92 (7.06 to 13.11)	6	11.70 (6.75 to 16.74)
6 months	28	2.47 (1.28 to 4.22)	6	1.01 (0.74 to 1.51)
12 months	28	0.53 (0.35 to 1.76)	6	0.52 (0.35 to 0.88)
18 months	27	0.32 (0.21 to 0.55)	6	1.58 (0.55 to 2.18)
24 months	28	0.25 (0.16 to 0.43)	6	1.62 (1.27 to 2.50)
Anti-PLA2R-				
Baseline	11	6.62 (5.72 to 8.47)	7	7.72 (6.45 to 9.50)
6 months	11	2.67 (1.01 to 4.21)	7	1.23 (1.13 to 2.25)
12 months	11	1.00 (0.24 to 1.65)	7	0.52 (0.43 to 1.67)
18 months	11	0.30 (0.13 to 1.96)	7	0.82 (0.46 to 1.52)
24 months	11	0.32 (0.10 to 0.63)	7	0.47 (0.39 to 1.35)

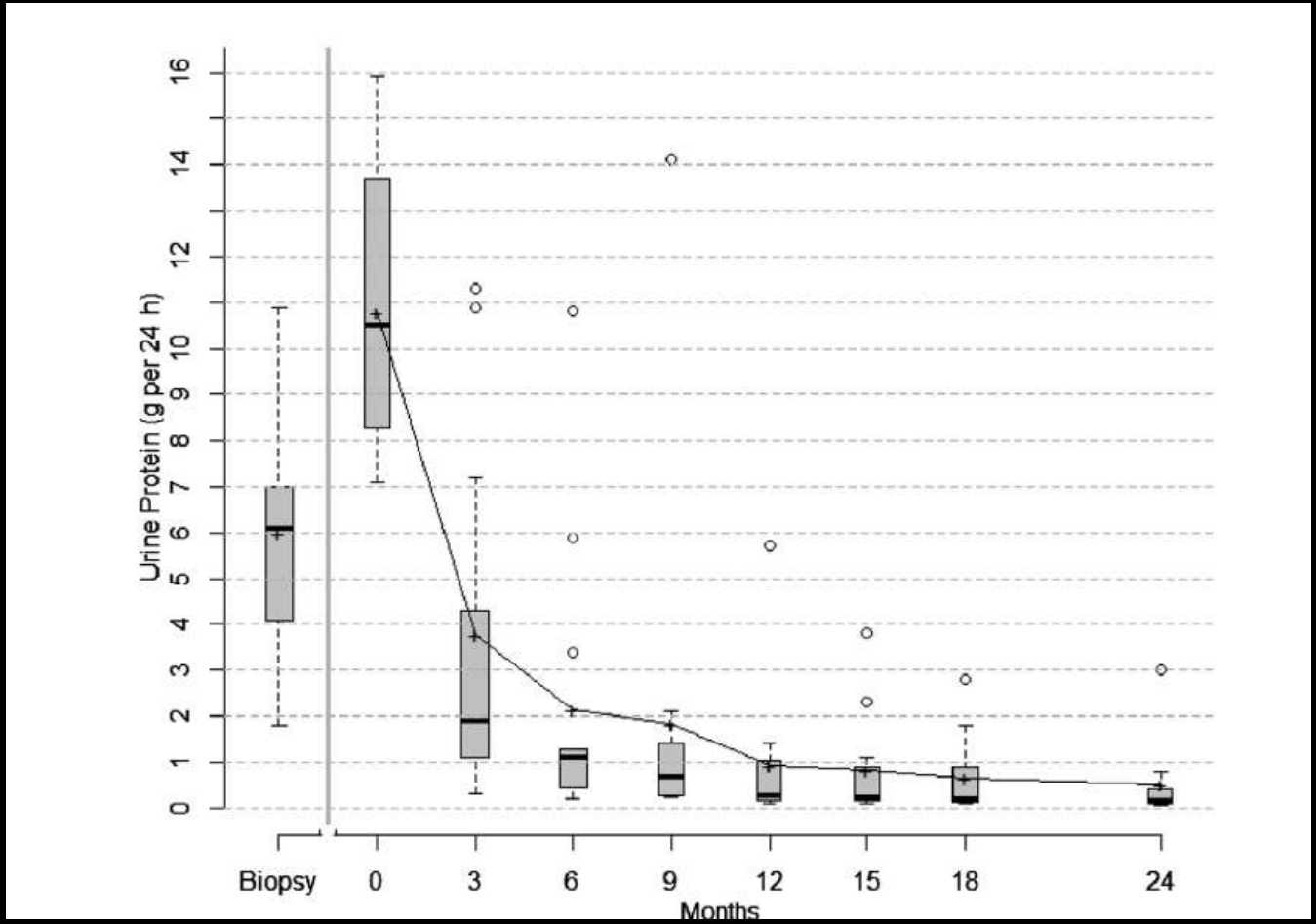
Creatinine Clearance (mL/min/BSA)	n	Mean (SD)	n	Mean (SD)
Anti-PLA2R+				
Baseline	28	87 (29)	6	94 (26)
6 months	28	91 (29)	6	75 (17)
12 months	28	93 (26)	6	74 (18)
18 months	27	100 (30)	6	87 (23)
24 months	28	99 (31)	6	90 (21)
Anti-PLA2R-				
Baseline	11	107 (36)	7	105 (56)
6 months	11	97 (33)	7	83 (38)
12 months	11	103 (28)	7	76 (37)
18 months	11	99 (25)	7	84 (35)
24 months	11	102 (26)	7	85 (42)

NIDDK Study sequential design

MN patients high risk of progression (10.8g/d)(N=13) given 1 course (2 doses) Ritux plus CSA for 6 mos …

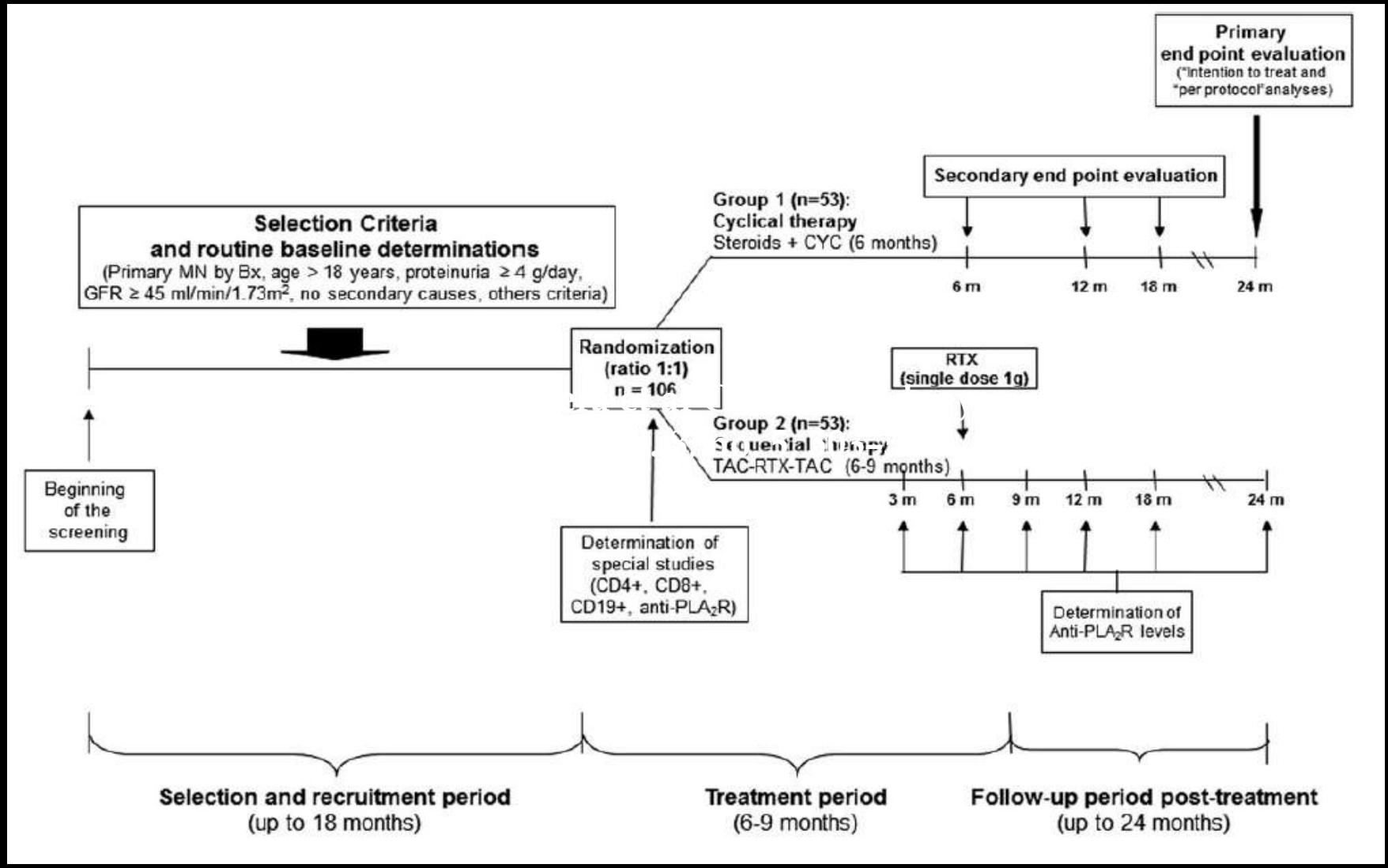
then tapering CSA(50mg/d/3weeks) plus repeat Ritux in all when B cells replete

Proteinuria rate of reduction accelerated



Waldman et al KIR 2017

COMING SOON…RCT CYCLIC CYC/GC VS TAC/RITUX/TAC



J Rojas -Rivera et al Clinical Kidney Journal, 2015, 8, 5,

Consider(beyond the guidelines) + employ judgement/acumen

- **Comorbidities DM,obesity,young femles,… not steroids**
- **Renal function,extensive TA/IF…., not CNI**
- **Immediate start, low PLA2R but sick,secondary investigations not complete … not Rituimab**
- **Availability…. Most expensive Rituximab consider Geographic/socioeconomics factors**
- **Costs …. Cheapest cyc/pred**
- **Adherence issues .. Rituximab best**
- **….etc**

NEW APPROACHES/THERAPIES

1 utilization of PLA2r monitoring/treatment

2 control(induction/maintenance) vs cure

3 combination therapy

4 complement inhibition +

5 antibody removal (immune suppression vs Immunoadsorption) (epitope spreading story)

6 use of stable soluble peptides (downregulate PLA2R response)

WHAT ? REMAINS

30-40% unresponsive

May be no over lap by Rx and response

Ethnicity may play a part in response

Consider Rx in early phase to prevent kidney damage

Different approach(early versus late Rx) risk/benefit

Numerous new/novel therapies on the horizon

WHAT IS CURRENT IDEAL BASED ON DRUG CHARACTERISTICS

Rituximab

Short term equally effective
Long-term lower cost
Less SAEs
Adherence better
PRO's better*
Longer remission *

*** To CNI's**

MGN TREATMENT ALGORITHM

Mild UPro
<4g/day
RFT's normal
Low PLA2R

↓

BP ≤125/75
ACE_i /ARB,Diet
Monitor

Moderate UPro
(≥4 <8 g/day)
RFT's normal
Mid PLA2R level

↓

BP ≤125/75
ACE_i. /ARB , Diet
Monitor 6/12

↓

*** Persistent**
≥4g/day

↓

Rituximab
or
Cytotoxic +steroids
OR
CNI

Heavy UPro
≥ 8 g/day
± ↓ RFT's
High PLA2R

↓

BP ≤125/75
ACE_i/ARB,Diet
Monitor < 3/12

↓

*** Persistent ≥ 8 g/day ± ↓ RFT's**

↓

Rituximab
or
****Cytotoxic + steroids**
or
****CNI**

****** **ACTH**
OTHERS

***risk reduction strategies/patient characteristics**
**** consider risk/benefit of IS**

SPASIBA
THANK YOU