Nouveaux traitements disponibles pour la néphropathie à IgA en 2025 ?

Société de Néphrologie Pédiatrique
Reims, 20/11/2025

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Liens d’intérêt

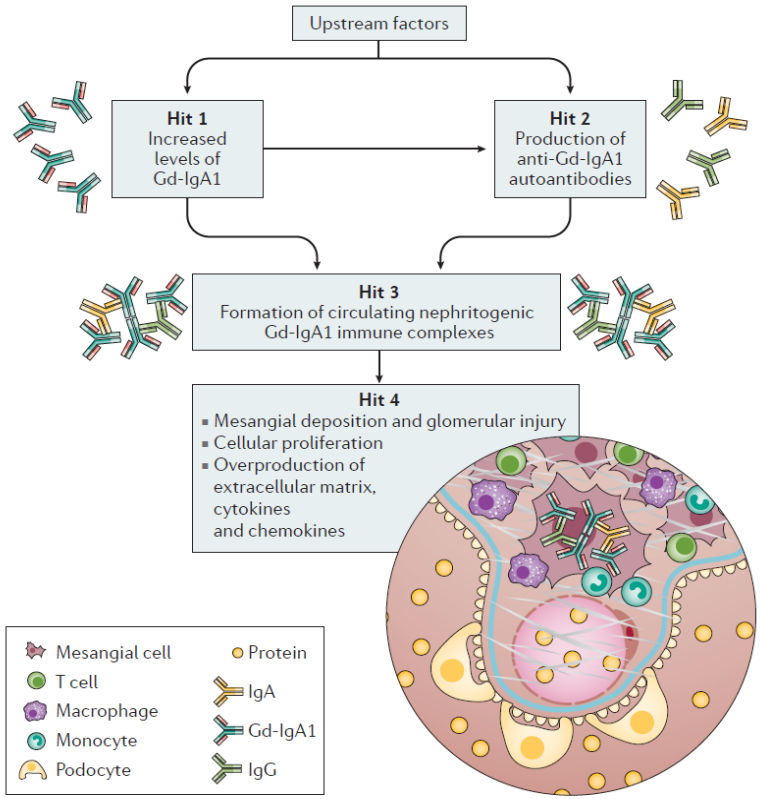
- CSL Vifor: financement de congrès, consulting
- Novartis: financement de congrès, consulting

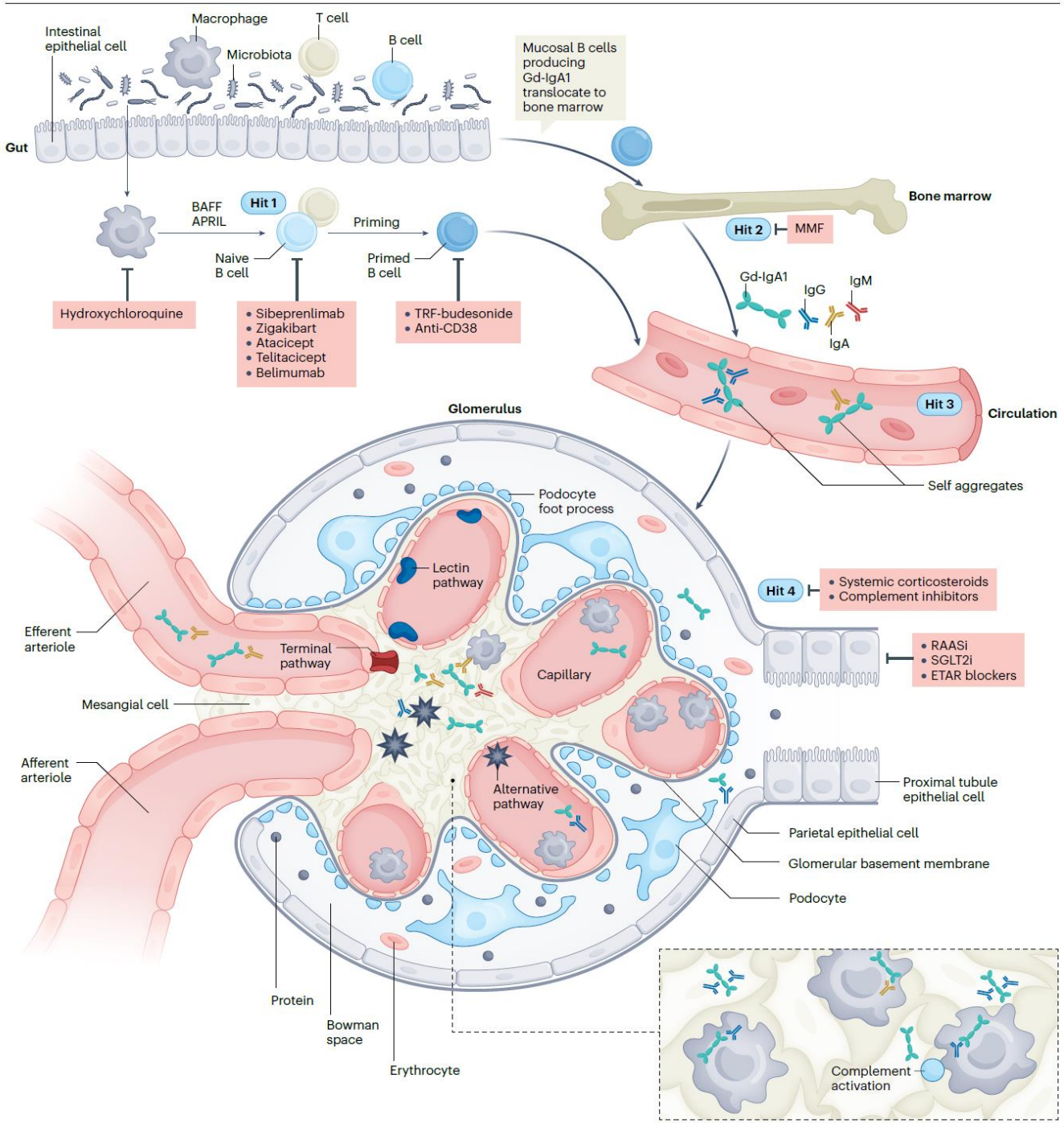
Nouveaux traitements ***disponibles ?***

Anciens traitements ***disponibles***

Nouveaux traitements *(non)****disponibles***

Physiopathiology (briefly !): 4 hits hypothesis

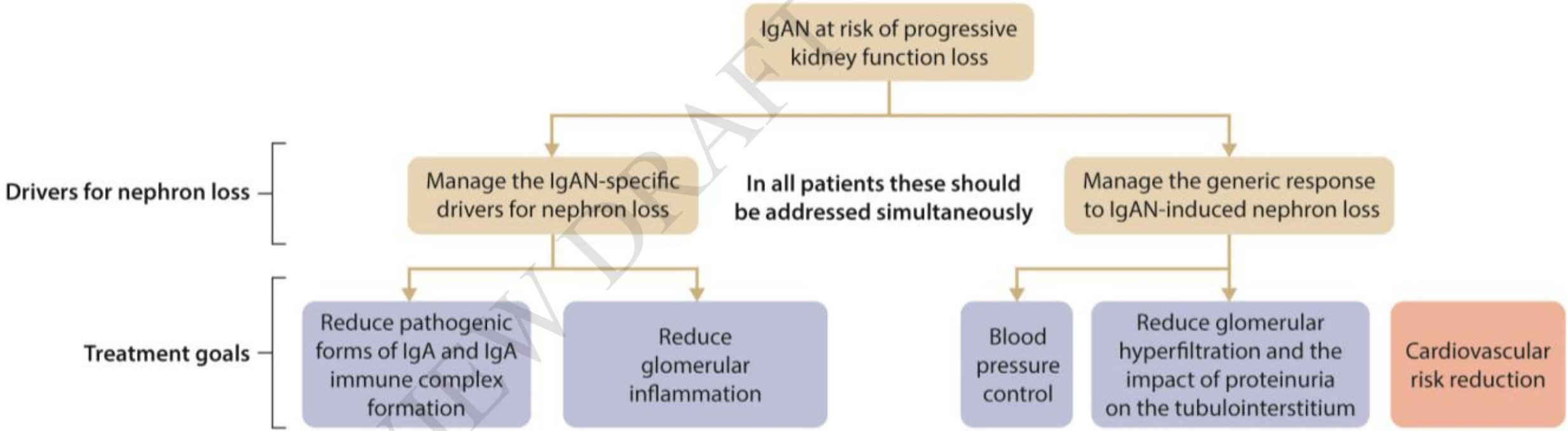




Lai, Nat Rev Dis Prim, 2018
Stamellou, Nat Rev dis Prim, 2023

New paradigm

- **The focus of management in most patients should be to *simultaneously*:**
  - **Prevent or reduce IgA immune complex formation and immune complex-mediated glomerular injury.**
  - **In parallel, manage the consequences of existing IgAN-induced nephron loss.**



KDIGO, 2024

JAMA | Original Investigation

Effect of Oral Methylprednisolone on Decline in Kidney Function or Kidney Failure in Patients With IgA Nephropathy
The TESTING Randomized Clinical Trial

2022

Lv, JAMA, 2022

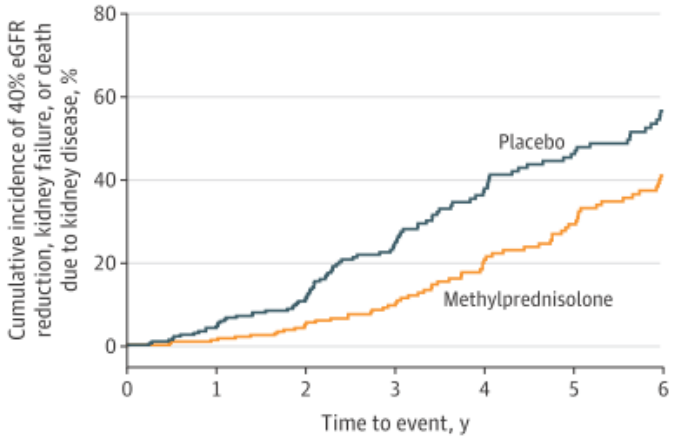
2012-2019, 503p, **China++,** 35,6y, eGFR 61,5$_{ml/mn/1,73m^2}$, Pu 2,4g/j, M1 60%, S1 70%, E1 20-30%, T2 10-15%

MethylP 0,4mg/kg (max 32mg), tapering 6-9m, Trimet/Sulf

Iry outcome (40% GFR or ESRD or death), Mean FU 4,2y

74 (steroids) vs 106 (placebo), HR 0,53 !

A Primary outcome in all patients

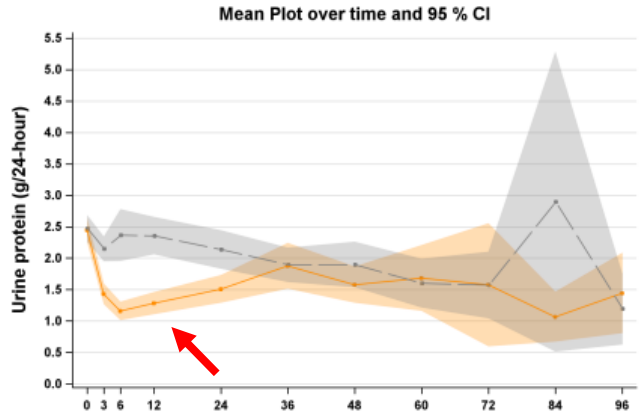


No. of patients at risk

Methylprednisolone	257	250	215	161	105	92	66
Placebo	246	234	188	127	76	66	44

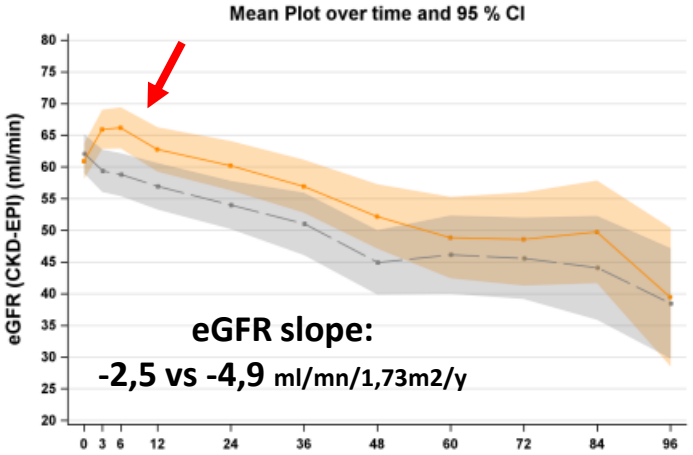
Pu

A) Mean 24 hour protein excretion by randomized group over time



eGFR

B) Mean eGFR over time



Serious adverse events: low dose steroids:
6 vs 3 patients, 1 death

TRF-Budesonide

364 patients, FU 24months

TRF-Budesonide: 16mg/d, 9months; Iry outcome: time-weighted eGFR over 2y

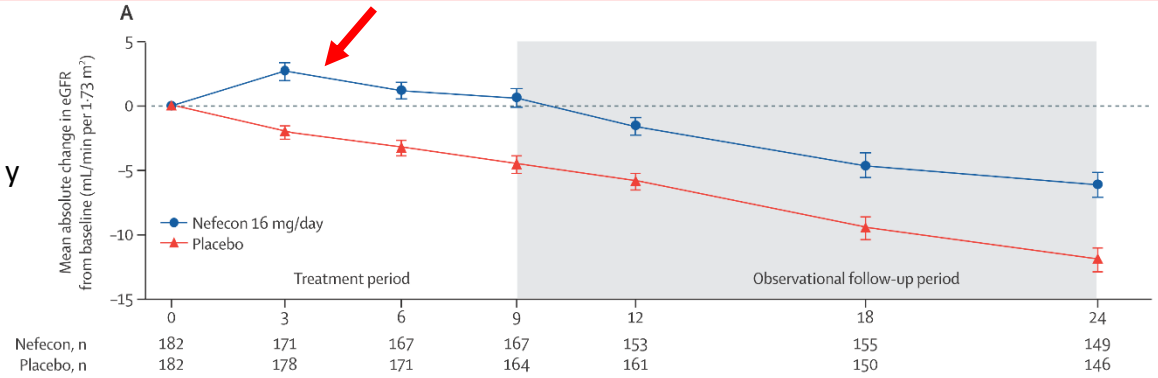
43y, 76% caucasian, Median UPCR 1,48g/g, median eGFR 55$_{ml/mn/1,73m^2}$, Hu 70%

RB~2,5y

eGFR

-6,11 vs -12 $_{ml/mn/1,73m2}$ /2 y

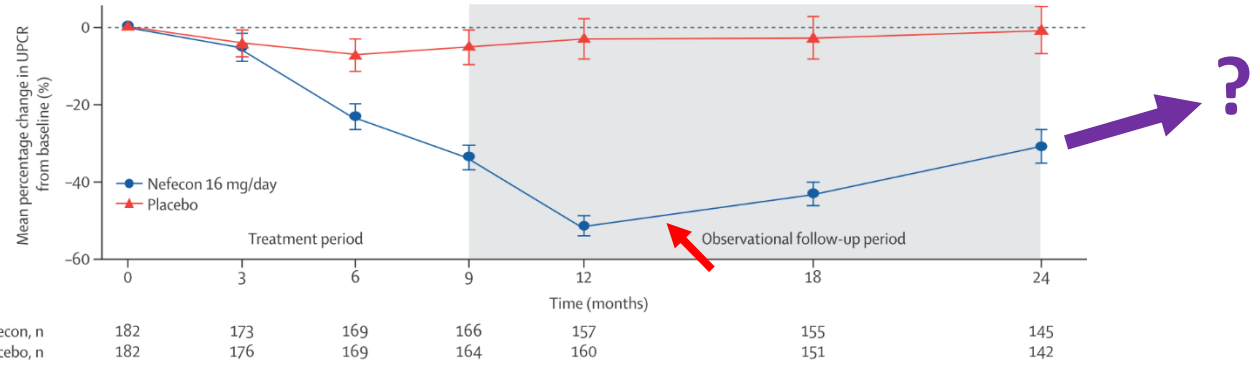
Δ=5,9 $_{ml/mn/1,73m2}$



uPCR

40% reduction/baseline

No Haematuria:
59% vs 34%



Lafayette, Lancet, 2023

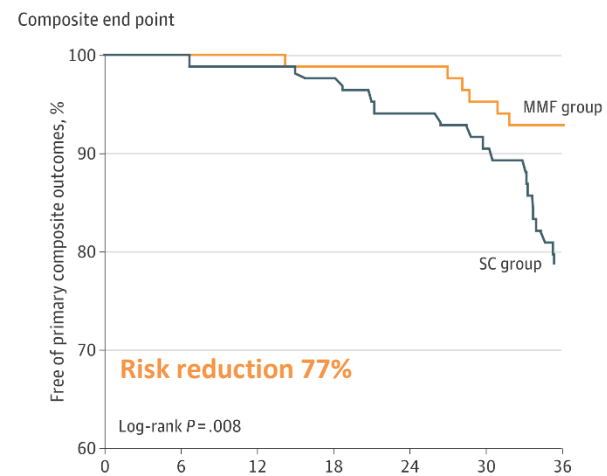
Original Investigation | Nephrology

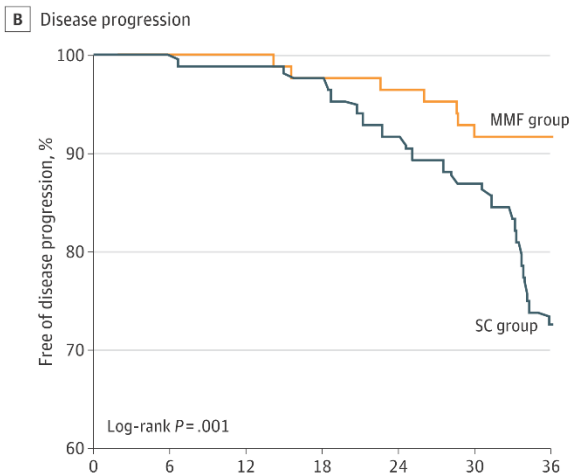
Effectiveness of Mycophenolate Mofetil Among Patients With Progressive IgA Nephropathy

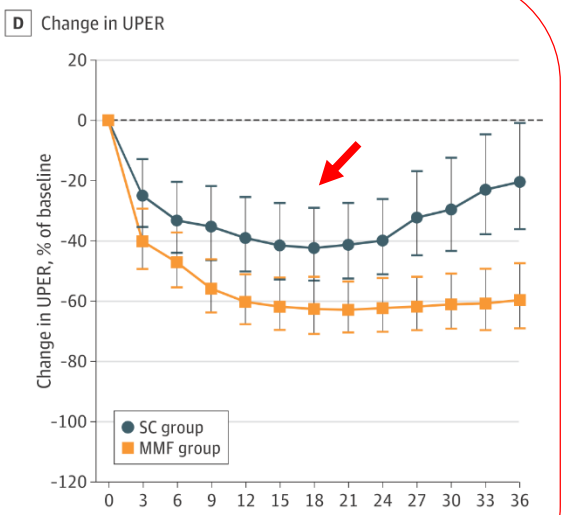
170p, 36y, chinese, UPCR 1,9g/d, eGFR 50ml/mn/1,73m², Hu 100%, RB<1y (90%); M1 100%, E1 10%, S1 83%, T2 54%, C1 40%

MMF: 1,5g 12m then 1g at least 6 m (mean 30m)

Iry outcome: doubling sCreat, ESRD, CKD progression







eGFR slope/y: -1,2 vs -3,8 ml/mn/1,73m2

Infections: 16% vs 10% (ns)

Post trial: 60 months

80 MMF, 77 SC; **mean eGFR loss/y: 6,1 (MMF discontinuation) vs 7,1 ml/mn/1,73m2**

Hou, JAMA Netw Op, 2023

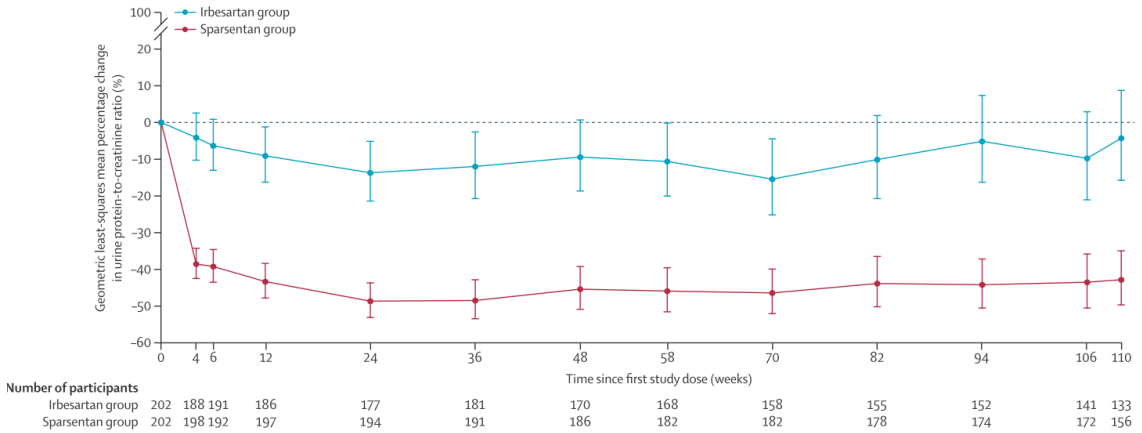
Nephroprotection: Sparsentan

404 IgAN, RAS blockers and Pu >1g/d; 69% male, 64% caucasian, Proteinuria >1,7g/d and eGFR 57ml/mn; RB ~6y

Sparsentan 400mg <u>vs Irbesartan 300mg</u>, FU 2y (data at 36w, prespecified), No SGLT2i

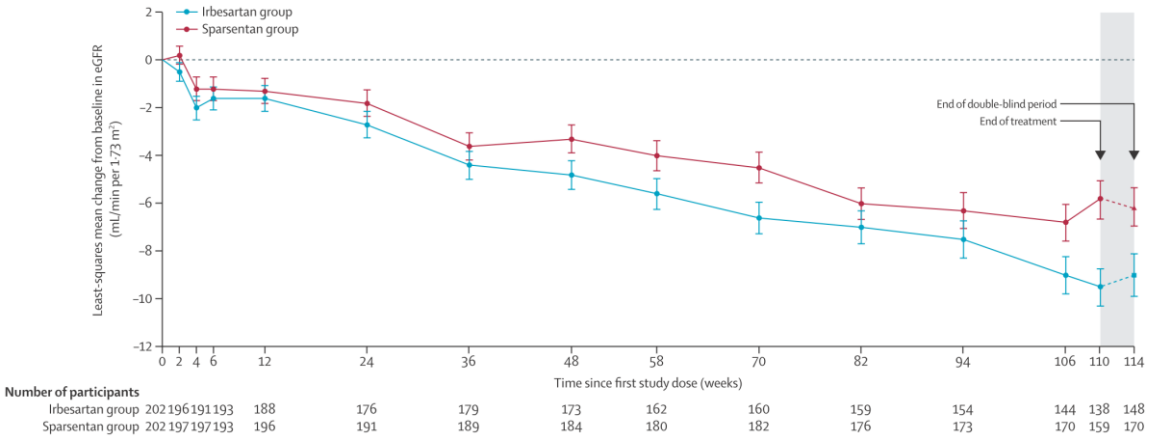
Iry Outcome: proteinuria at W36

uPCR



Pu: -49,8% vs -15,1%
Similar control of BP
No excess in TEAE

eGFR



eGFR slope:
-2,7 vs -3,8 ml/mn/1,73m2/y

Heerspink, Lancet, 2023

Emerging therapies ?

Endothelin Receptor Antag

B and plasma cell

Complement: B, C3, C5

Table 1. Molecules in clinical development for the treatment of IgA nephropathy

Treatment		Target	Phase	Identifier	Outcome	Estimated Study Completion Date
Supportive care						
SGLT2i	CLIgAN	SGLT2		NCT04662723	UPE	December 26
Sparsentan	SPARTAN	ERA+ARB		NCT04663204	24 h-UPCR and eGFR	November 23
Sparsentan	SPARTACUS	ERA+ARB	II	NCT05856760	UACR (sample)	December 24
Sparsentan	PROTECT	ERA+ARB	III	NCT03762850	24 h-UPCR	July 26
Sparsentan (pediatrics)	EPPIK	ERA+ARB	II	NCT05003986	UPCR	June 25
Atrasentan	ALIGN	ERA		NCT04573478	UPCR	December 25
Atrasentan	ASSIST	ERA		NCT05834738	UPCR	October 25
Atrasentan	AFFINITY	ERA	II	NCT04573920	UPCR	February 26
SC 0062		ERA	II	NCT05687890	UACR	April 25
Steroids						
Steroids		Systemic	III	NCT03468972	eGFR	May 23
Steroids	CLIgAN	Systemic	III	NCT04662723	UPE	December 26
Steroids	TIGER	Systemic	III	NCT03188887	UPCR (sample)+eGFR	January 24
Steroids		Systemic	III	NCT04833374	24 h-UPE	December 23
B and plasma cell						
Rituximab		CD20	IV	NCT05824390	UPE	October 23
Rituximab	RITA	CD20	IV	NCT04525729	UPE	December 23
Feltarzamab	IGNAZ	CD38	II	NCT05065970	UPE	May 24
Belimumab	BELIGA	BAFF	II	EudraCT: 2017–004366-10	UPE	
Sibeprenlimab	enVISion	APRIL	II	NCT04287985	24 h-UPCR	June 23
Sibeprenlimab	VISIONARY	APRIL	III	NCT05248646	24 h-UPCR	December 26
Ataticept	ORIGIN-3	BAFF+APRIL	II/III	NCT04716231	24 h-UPCR	July 2028
Telitaticept		BAFF+APRIL	II	NCT04905212	24 h-UPE	January 24
Bortezomib		Proteasome	II	NCT05383547	24 h-UPE	December 23
AT-1501		CD40 L	II	NCT05125068	24 h-UPCR	August 25
Complement						
Iptacopan	APPLAUSE-IgA nephropathy	CF B		NCT04578834	24 h-UPCR+eGFR	October 25
Narsoplimab		MASP-2	III	NCT03608033	24 h-UPE	April 23
Vermicopan		CF D	II	NCT05097989	24 h-UPE	August 26
Pegcetacoplan		C3	II	NCT03453619	UPCR	December 23
Ravulizumab	SANCTUARY	C5	II	NCT04564339	24 h-UPE	June 25
Cemdisiran		C5 RNA	II	NCT03841448	24 h-UPCR	February 25
IONIS-FB-LRx		CF B RNA	II	NCT04014335	24 h-UPE	December 23
RO7434656	IMAGINATION	CF B RNA	III	NCT05797610	24 h-UPCR	September 30
KP 104		C3 convertase+C5	II	NCT05517980	24 h-UPCR	September 25
Microbiome						
Enterobacteriaceae capsules		Microbiome	II	NCT05182775	24 h-UPE	December 23

Emerging therapies: Endoth Rec antogonism ?

Phase 3

Interim analysis (270patitents/group):

9 months: evolution of proteinuria (repeated measures model)

2021-2023, 45y, 41% female, 57% Asian, eGFR 58,9ml/mn/1,73m^{2,} Pu 1,4g/d, Hu ?

7-16% discontinuation

99% RASi

Diagnosis: 5,6y before inclusion

ORIGINAL ARTICLE

Atrasentan in Patients with IgA Nephropathy

Table 1. Demographic and Clinical Characteristics of the First 270 Patients in the Main Stratum.*

Characteristic	Atrasentan (N = 135)	Placebo (N = 135)
Duration of disease — yr	5.14±5.41	6.14±6.04
Blood pressure — mm Hg		
Systolic	125.4±13.3	122.9±12.3
Diastolic	79.6±9.8	78.7±9.0
Median total urinary protein excretion (IQR) — mg/day	1847.4 (1314.0–2775.9)	1851.0 (1328.9–2550.0)
24-Hour urinary protein-to-creatinine ratio§		
Median (IQR)	1435.7 (1006.7–1988.6)	1429.2 (1100.9–1918.3)
Distribution — no. (%)		
<1500	72 (53.3)	76 (56.3)
≥1500	63 (46.7)	59 (43.7)
Median 24-hour urinary albumin-to-creatinine ratio (IQR)¶	1051.3 (769.2–1485.8)	1059.3 (770.2–1480.8)
Estimated glomerular filtration rate		
Mean — ml/min/1.73 m²	58.28±23.75	59.49±24.42
Distribution — no. (%)		
≤45 ml/min/1.73 m²	54 (40.0)	53 (39.3)
>45–60 ml/min/1.73 m²	25 (18.5)	28 (20.7)
>60 ml/min/1.73 m²	56 (41.5)	54 (40.0)
Hemoglobin level — g/dl	13.58±1.73	13.70±1.74
Use of RAS inhibitor at baseline — no. (%)		
ARB only	97 (71.9)	95 (70.4)
ACE inhibitor only	37 (27.4)	37 (27.4)
Use of diuretic at baseline — no./total no. (%)	21/134 (15.7)‖	16/135 (11.9)

Heerspink, NEJM, 2024

Emerging therapies: Endoth Rec antogonism ?

ORIGINAL ARTICLE

Atrasentan in Patients with IgA Nephropathy

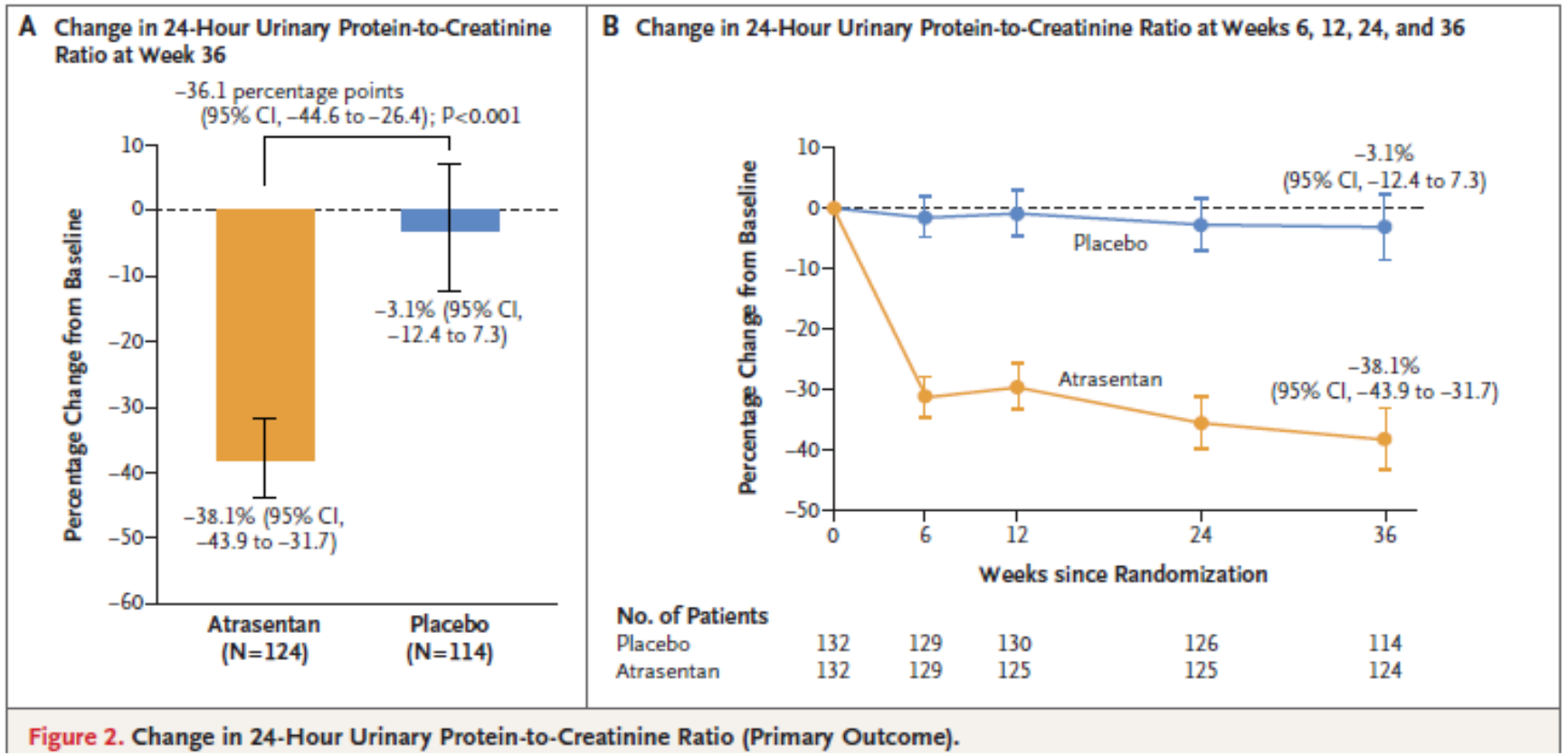


Figure 2. Change in 24-Hour Urinary Protein-to-Creatinine Ratio (Primary Outcome).

p<0,001

Idem in 29 patients with SGLT2i, no difference in weight gain, blood pressure, or adverse events (anemia ?)

Heerspink, NEJM, 2024

Emerging therapies: complement ?

ORIGINAL ARTICLE

Alternative Complement Pathway Inhibition with Iptacopan in IgA Nephropathy

Phase 3

Interim analysis (125 patitents/group): 9 months: evolution of proteinuria (repeated measures model)

3 months run-in of supportive care, then iptacopan or placebo
« eGFR >45ml/mn/1,73m^2 » or « eGFR> 30 and RB <2y with <T2 »

2021-2023, 39y, 48% female, 51% Asian, eGFR 62-65ml/mn/1,73m^2
Pu 1,8g/d, Hu 70-78%

13%SGLT2i, 99% RASi

RB: 0,8y-1,3y before inclusion

HIGH RISK OF PROGRESSION

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Iptacopan (N=125)	Placebo (N=125)
Time since kidney biopsy — yr		
Mean	1.7±1.4	1.6±1.7
Median (IQR)	1.3 (0.5–2.8)	0.8 (0.3–2.6)
Oxford Classification MEST-C score — %‡		
M score		
M1	60.8	64.0
M0	32.0	31.2
E score		
E1	28.8	28.8
E0	63.2	64.8
S score		
S1	69.6	71.2
S0	22.4	23.2
T score		
T1 or T2	38.4	42.4
T0	54.4	53.6
C score		
C1	26.4	16.0
C2	1.6	1.6
C0	60.8	68.0
24-Hour urinary protein-to-creatinine ratio — g of protein/g of creatinine		
Median (IQR)	1.8 (1.4–2.7)	1.9 (1.5–2.8)
<2 — no. (%)	71 (56.8)	67 (53.6)
≥2 — no. (%)	54 (43.2)	58 (46.4)

Perkovic, NEJM, 2024

Alternative Complement Pathway Inhibition with Iptacopan in IgA Nephropathy

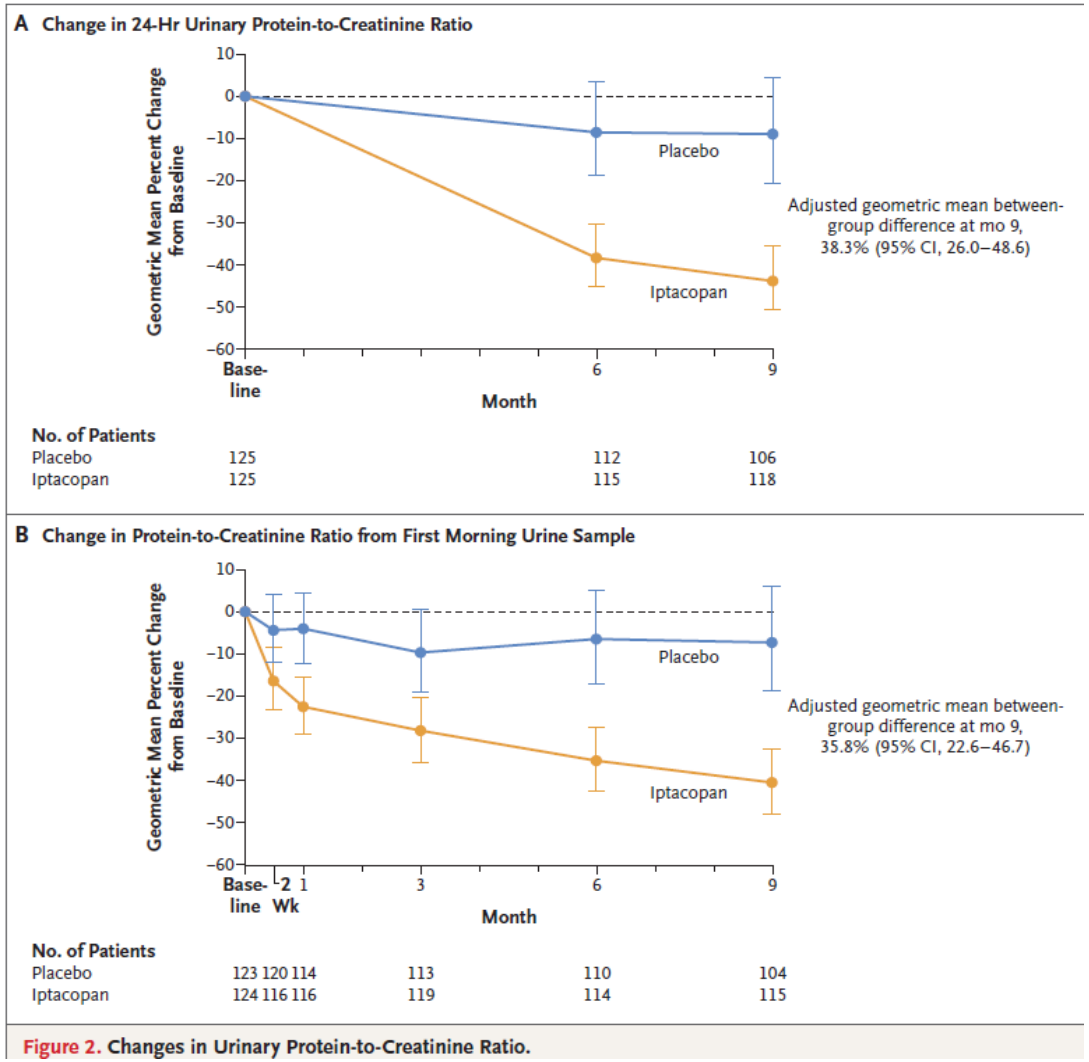
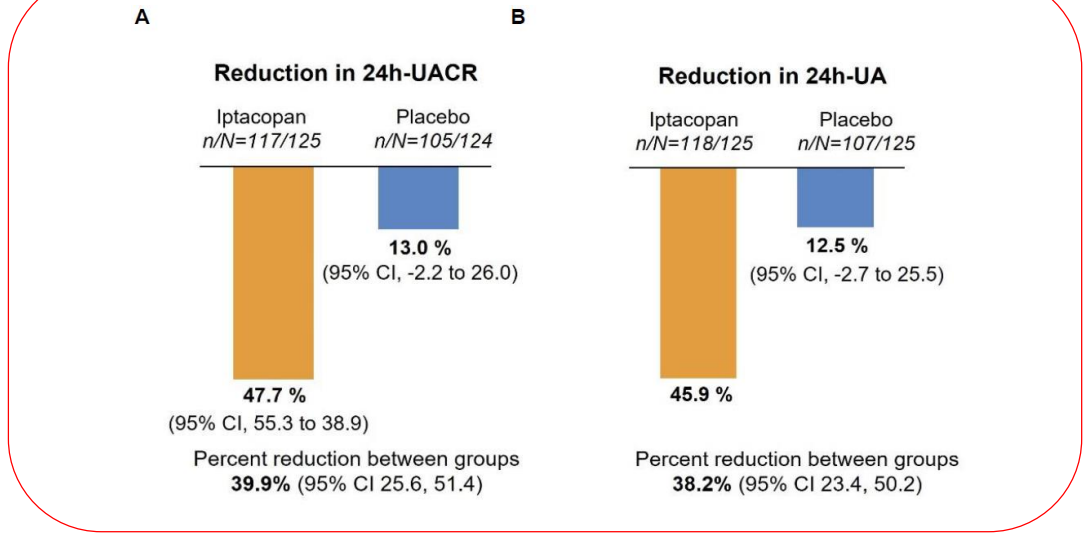
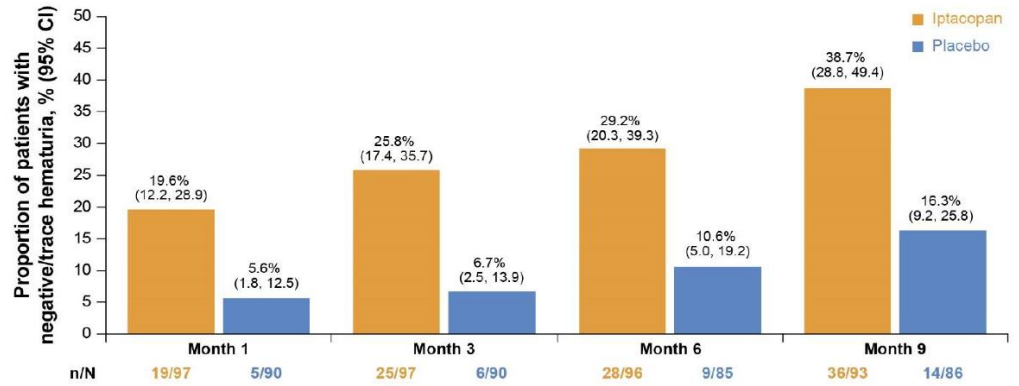


Figure 2. Changes in Urinary Protein-to-Creatinine Ratio.

<1g/g: 54/119 (ipta)vs 24/110 (plcb)

< 0,5g/g: 18/119 (ipta)vs 7/110 (plcb)





Hematuria disappearence: 38% vs 16%

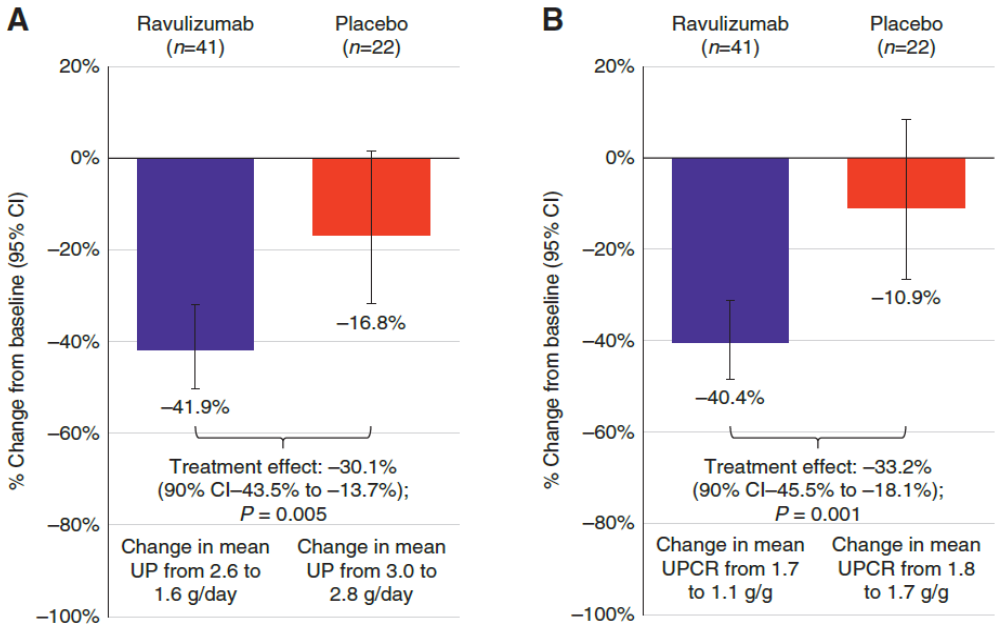
Perkovic, NEJM, 2024

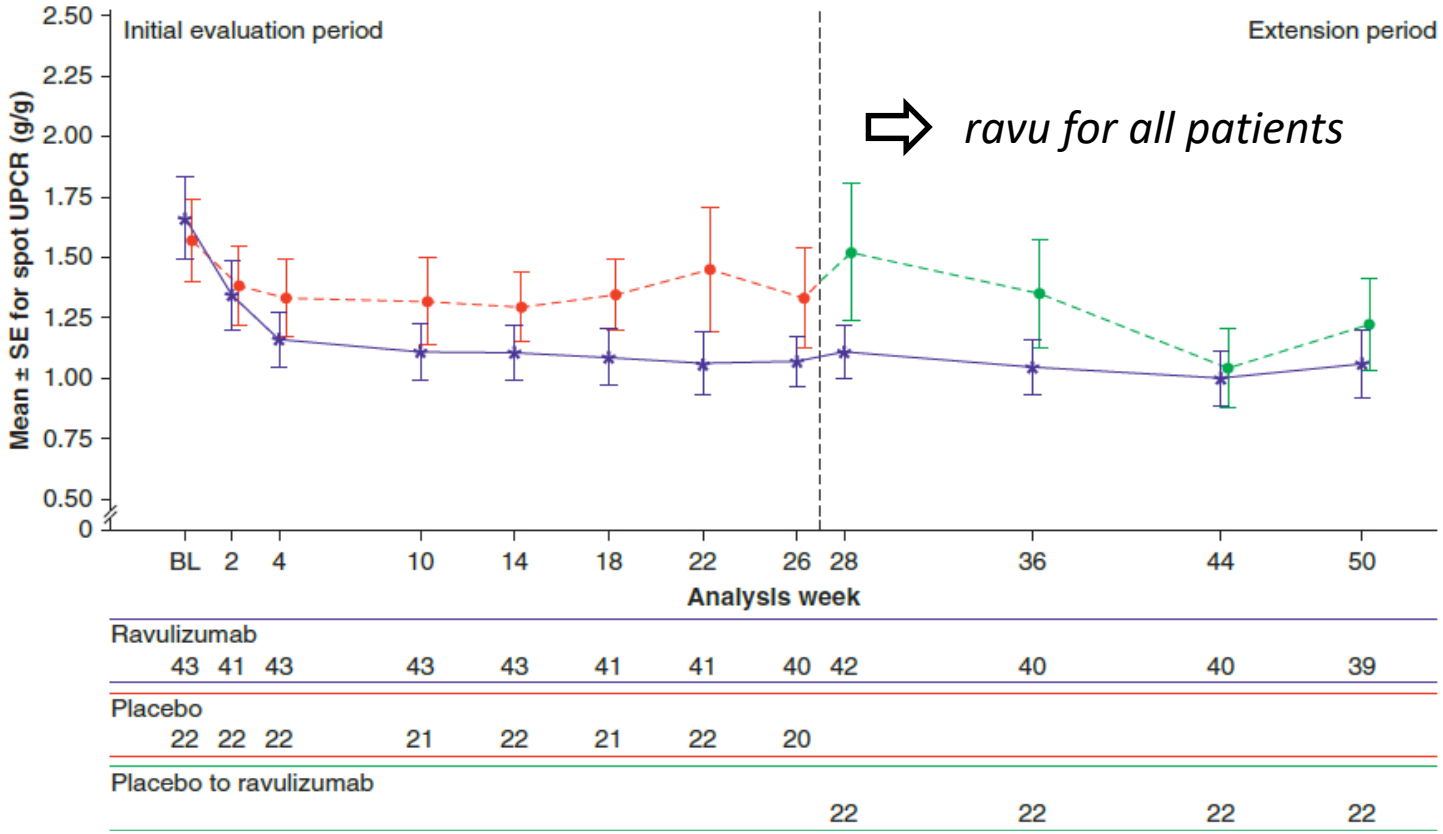
Efficacy and Safety of Ravulizumab in IgA Nephropathy

A Phase 2 Randomized Double-Blind Placebo-Controlled Trial

Phase 2 study. Pu > 1g/g despite RASi, eGFR >30
66 patients, 46% female, 21% Asian, UPCR 1,67, eGFR 74ml/mn/1,73m^2 , 17-21% SGLT2i

W36: UPCR: 42% reduction vs 17% (placebo); Favourable safety profile





Lafayette, JASN , 2024

Emerging therapies: B cells ?

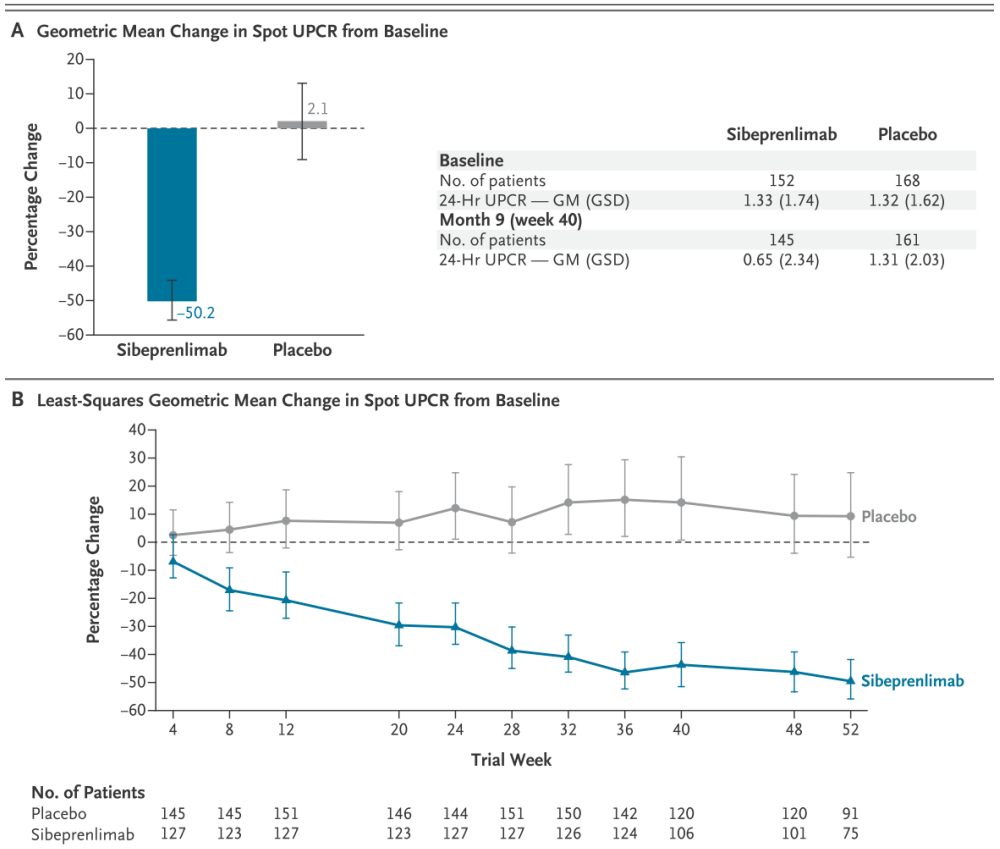
Sibeprenlimab: anti-APRIL

320 patients, 62% men, 59% Asian, 0,75g/g, ACE/ARB, iSGLT2 40%, no T2/C2

Median: 42y, 63,4ml/mn/1,73m2, P/C 1,25g/g

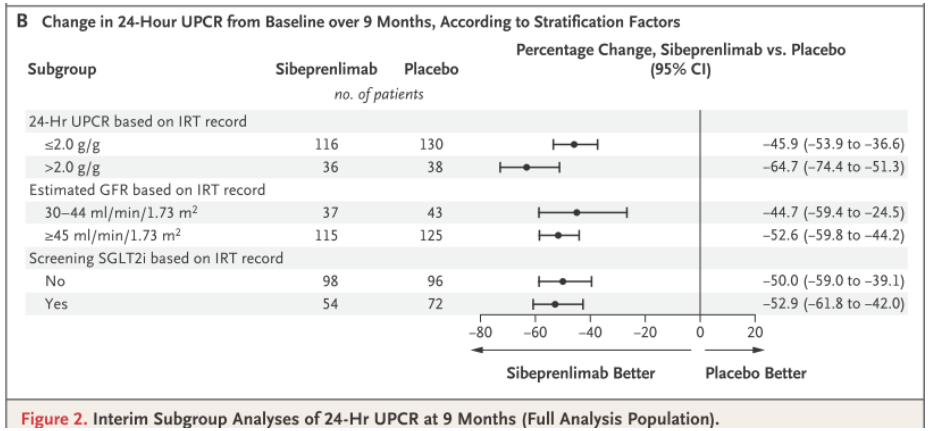
Sibeprenlimab: 400mg sub cutaneous /week (ongoing phase 3)

Interim analysis W40



	Sibeprenlimab	Placebo
Baseline		
No. of patients	152	168
24-Hr UPCR — GM (GSD)	1.33 (1.74)	1.32 (1.62)
Month 9 (week 40)		
No. of patients	145	161
24-Hr UPCR — GM (GSD)	0.65 (2.34)	1.31 (2.03)

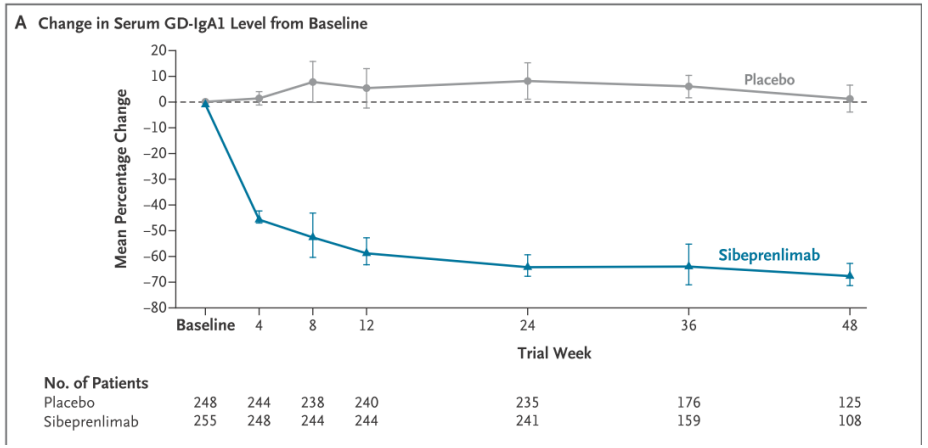
Figure 1. Change from Baseline in Urinary Protein-to-Creatinine Ratio.



B Change in 24-Hour UPCR from Baseline over 9 Months, According to Stratification Factors

Subgroup	Sibeprenlimab	Placebo	Percentage Change, Sibeprenlimab vs. Placebo (95% CI)
	no. of patients		
24-Hr UPCR based on IRT record			
≤2.0 g/g	116	130	−45.9 (−53.9 to −36.6)
>2.0 g/g	36	38	−64.7 (−74.4 to −51.3)
Estimated GFR based on IRT record			
30–44 ml/min/1.73 m²	37	43	−44.7 (−59.4 to −24.5)
≥45 ml/min/1.73 m²	115	125	−52.6 (−59.8 to −44.2)
Screening SGLT2i based on IRT record			
No	98	96	−50.0 (−59.0 to −39.1)
Yes	54	72	−52.9 (−61.8 to −42.0)

Figure 2. Interim Subgroup Analyses of 24-Hr UPCR at 9 Months (Full Analysis Population).



<0,5g/g: 34/99, 34% vs 15/118, 12%

Perkovic, NEJM, 2025

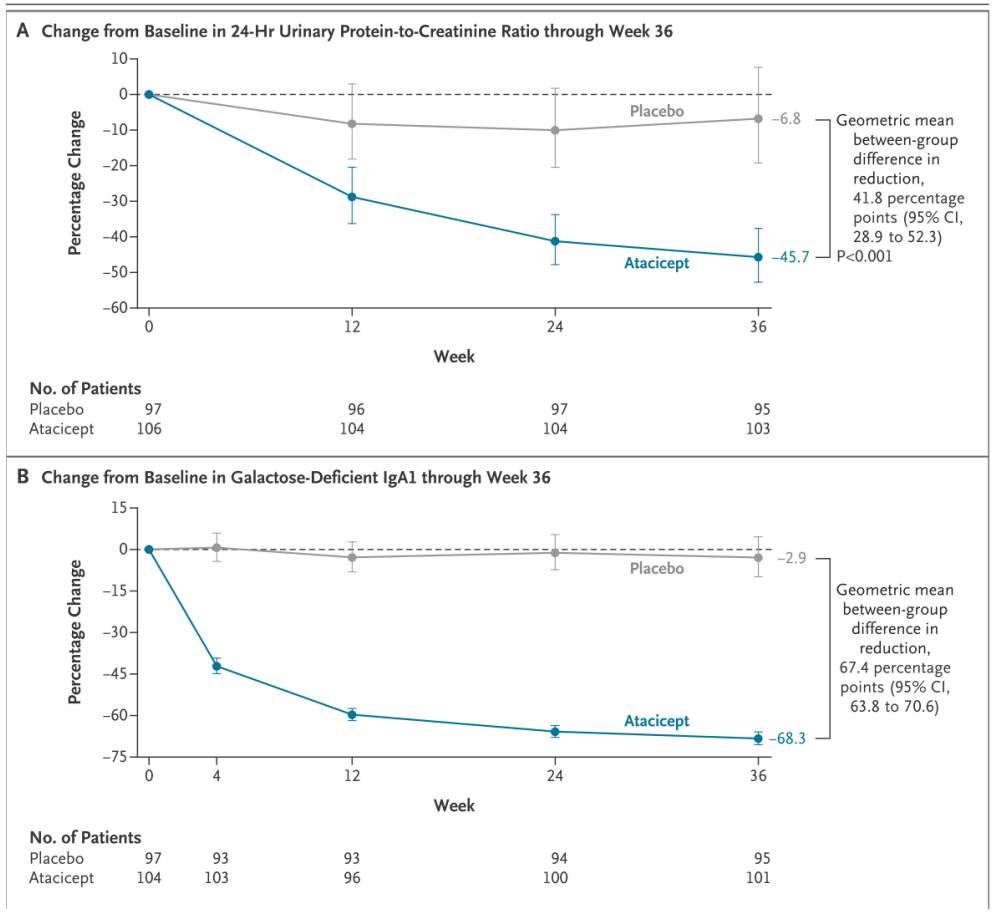
Emerging therapies: anti B cell: atacicept ?

203 patients, 57% men, 55% Asian, 99% ACE/ARB, iSGLT2 53%

Median: 40y, 65ml/mn/1,73m2, Proteinuria 2,2g/d

Atacicept: 150mg sub cutaneous /week (ongoing phase 3)

W36 proteinuria



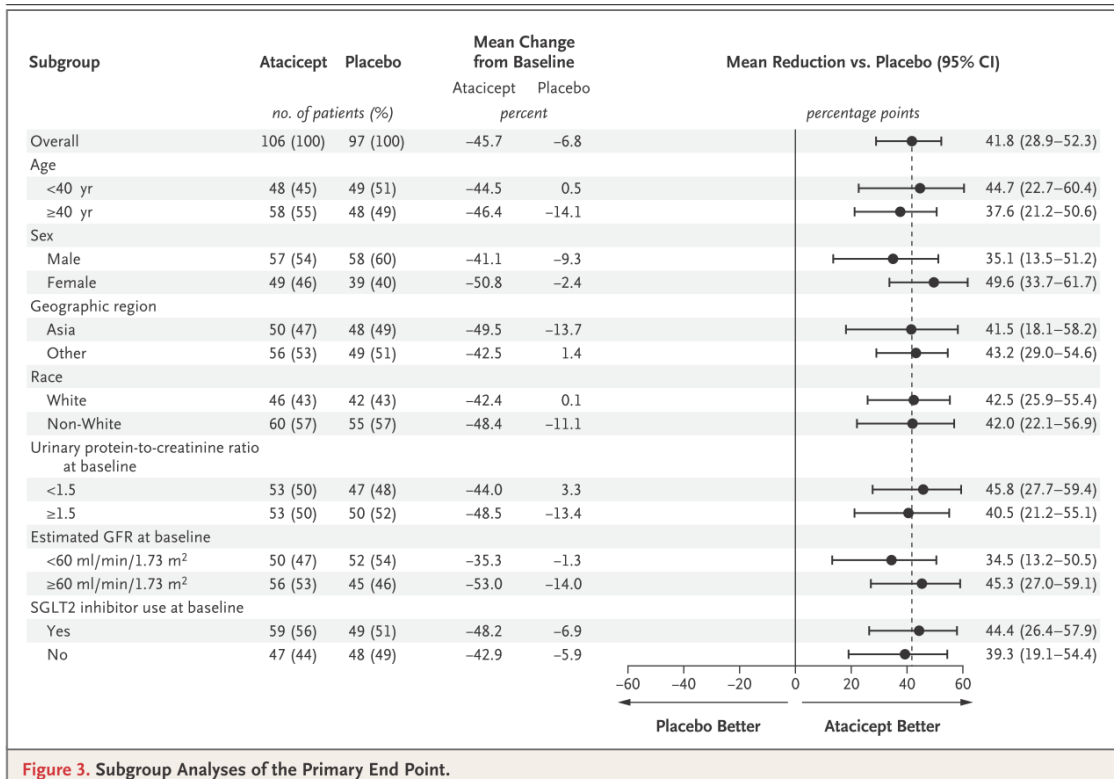


Figure 3. Subgroup Analyses of the Primary End Point.

Hu resolution: 81% vs 12%

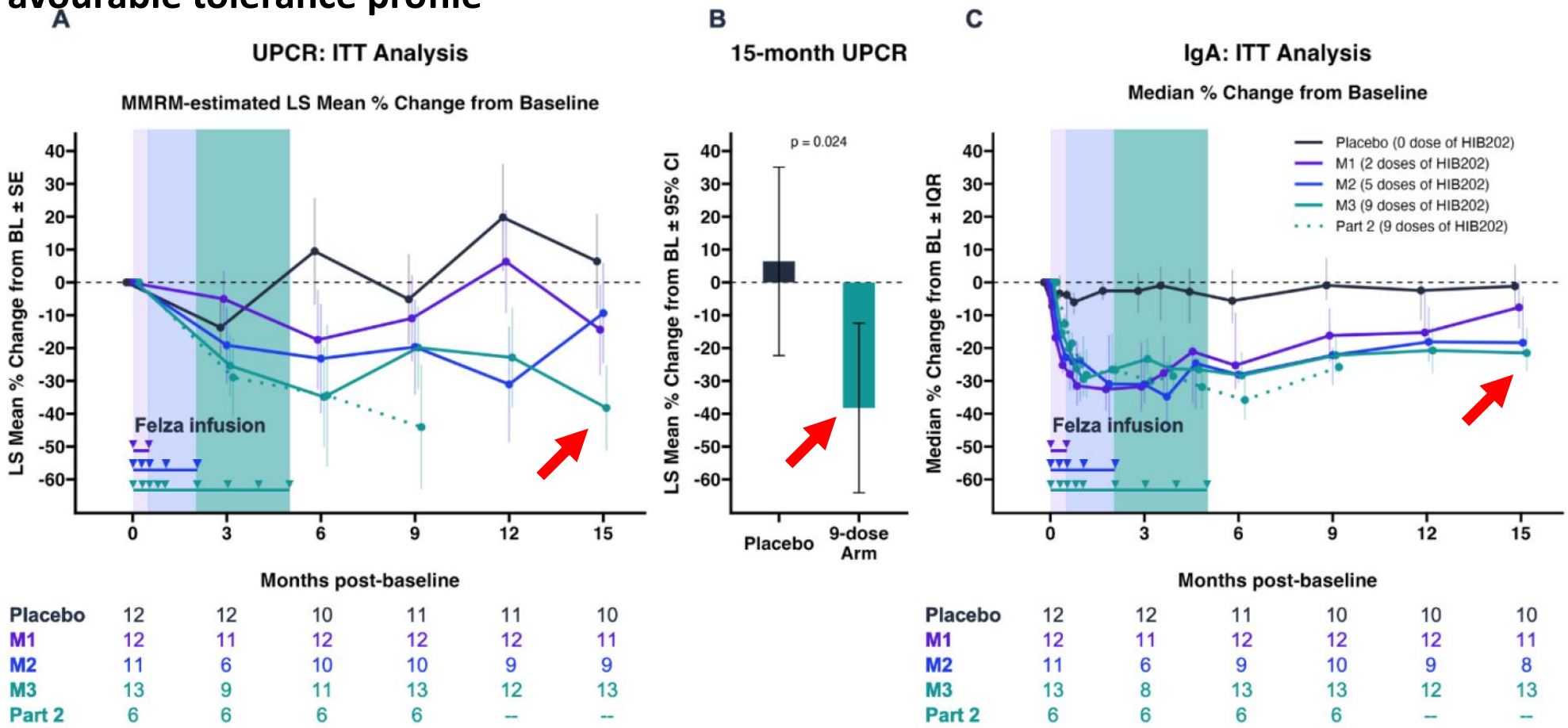
No safety alert

Lafayette, NEJM, 2025

Emerging therapies: anti B cells ?

Felzartamab: **anti-CD38;** phase 2 study, different doses (max 9d in 5 months)
48 patients, UPCR 1,67, eGFR 74ml/mn/1,73m^2

UPCR: 38% reduction at m15 (9 doses regimen); reduction in circulating IgA
Favourable tolerance profile



Placebo	12	12	10	11	11	10
M1	12	11	12	12	12	11
M2	11	6	10	10	9	9
M3	13	9	11	13	12	13
Part 2	6	6	6	6	–	–

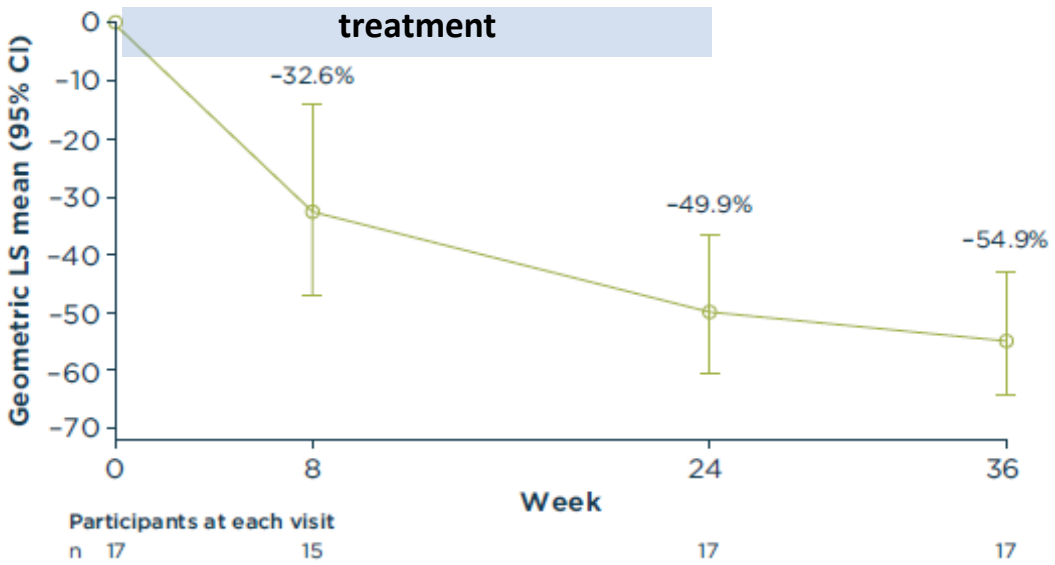
Placebo	12	12	11	10	10	10
M1	12	11	12	12	12	11
M2	11	6	9	10	9	8
M3	13	8	13	13	12	13
Part 2	6	6	6	6	–	–

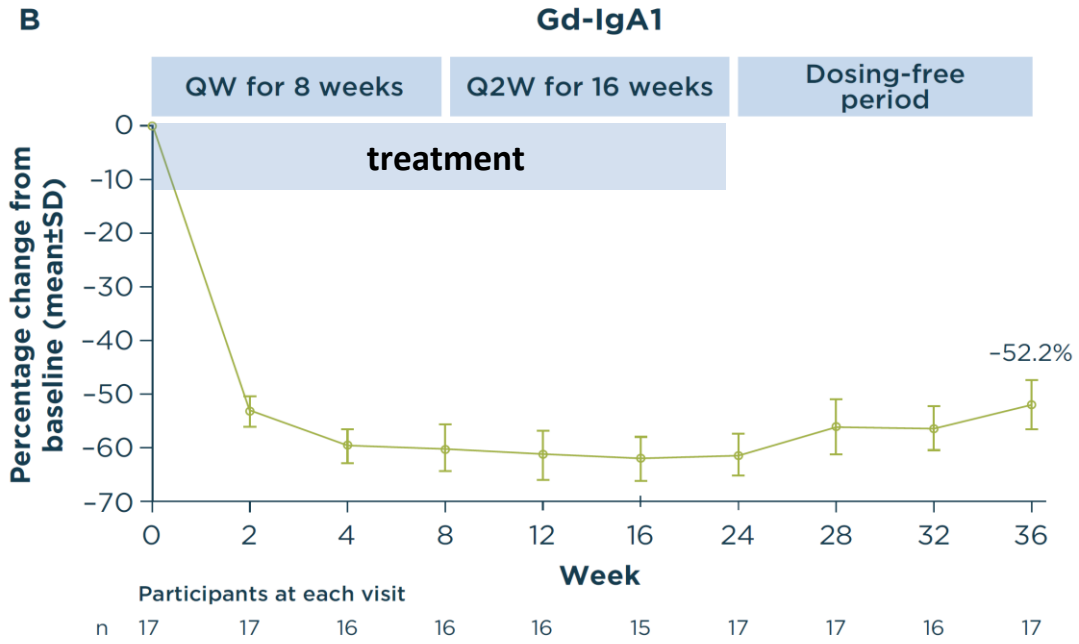
Floege, ERA 2024

Emerging therapies: anti B cells ?

Mezagitamab: **anti-CD38;** phase 1b study, 24w treatment
17 patients, 40y, UPCR 1,5, eGFR 74ml/mn/1,73m^2
UPCR: 54% reduction at m9; reduction in circulating IgA; Favourable tolerance profile

Figure 3. Percentage change from baseline in proteinuria based on 24-h UPCR over time



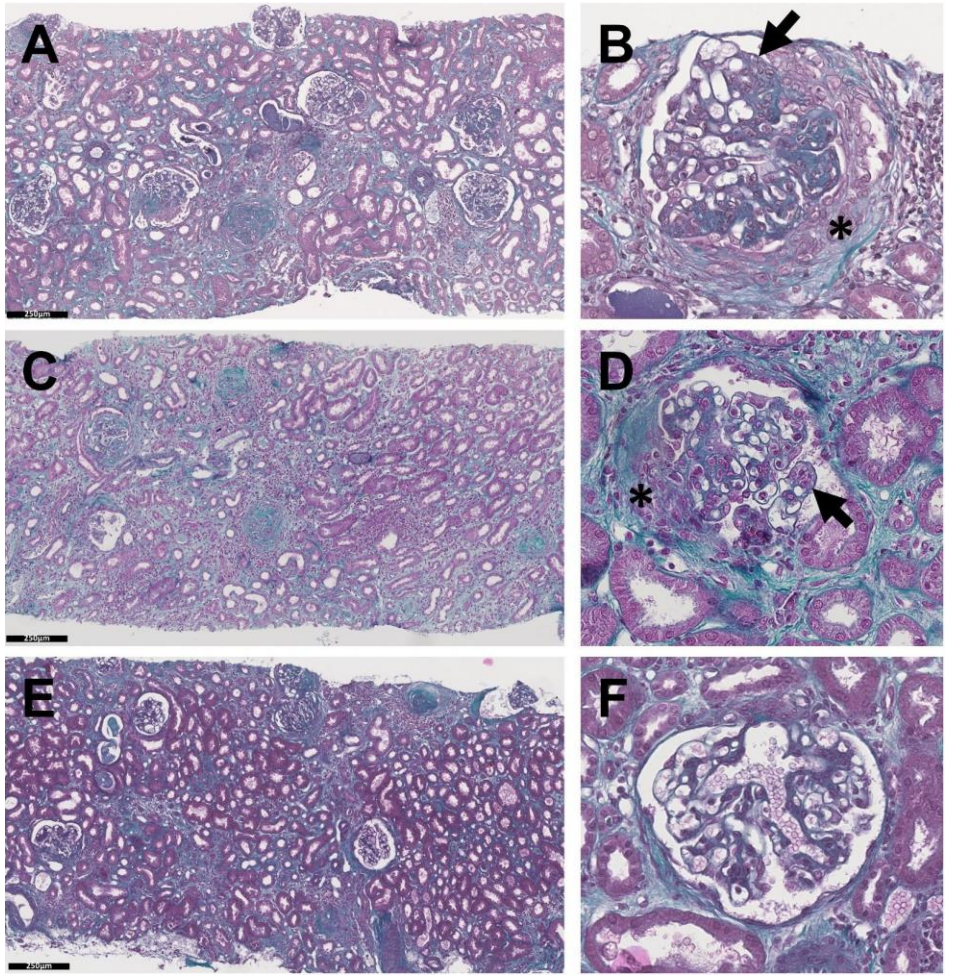


Barratt, ASN, 2024

Emerging therapies: anti B cells ?
Daratumumab (routinely available anti-CD38 antibody)

Daratumumab in high risk IgAN patients (n=4…)

Presentation at dara initiation						Last follow-up from dara initiation					
eGFR	Alb	PCR	UHem	Last IgAN KB (delay/dara initiation)	Protocol	FU	eGFR	Alb	PCR	UHem	Repeat KB (delay/dara initiation)
58	NA	1,5	100000	M0E1S0T0C1 (3m)	Dara Bor Dex, 9m	21m	51	48	0,1	1000	M1E1S0T0 C0 (3 m)
26	32,8	4,1	15000	M1E1S1T1 C1 (2m)	Dara Dex, 9m	11m	59	42	0,5	<1000	M1E0S1T1 C0 (4m)
17	36	0,73	100000	M1E0S1T0 C1 (35m)	Dara Dex, 6m	16m	23,2	NA	0,1	4000	NA
25	27	4.47	90000	M1E1S1T0 C1 (29m)	Dara Dex, 12m	13m	32	42	0,9	7000	NA

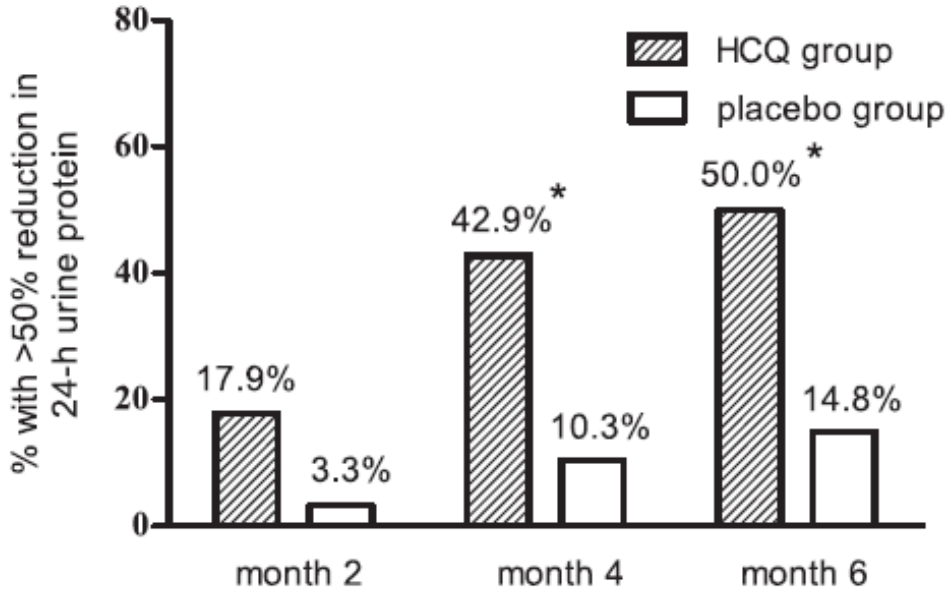


Poux, Submitted

Emerging therapies: anti-B cell ?

Hydroxychloroquine

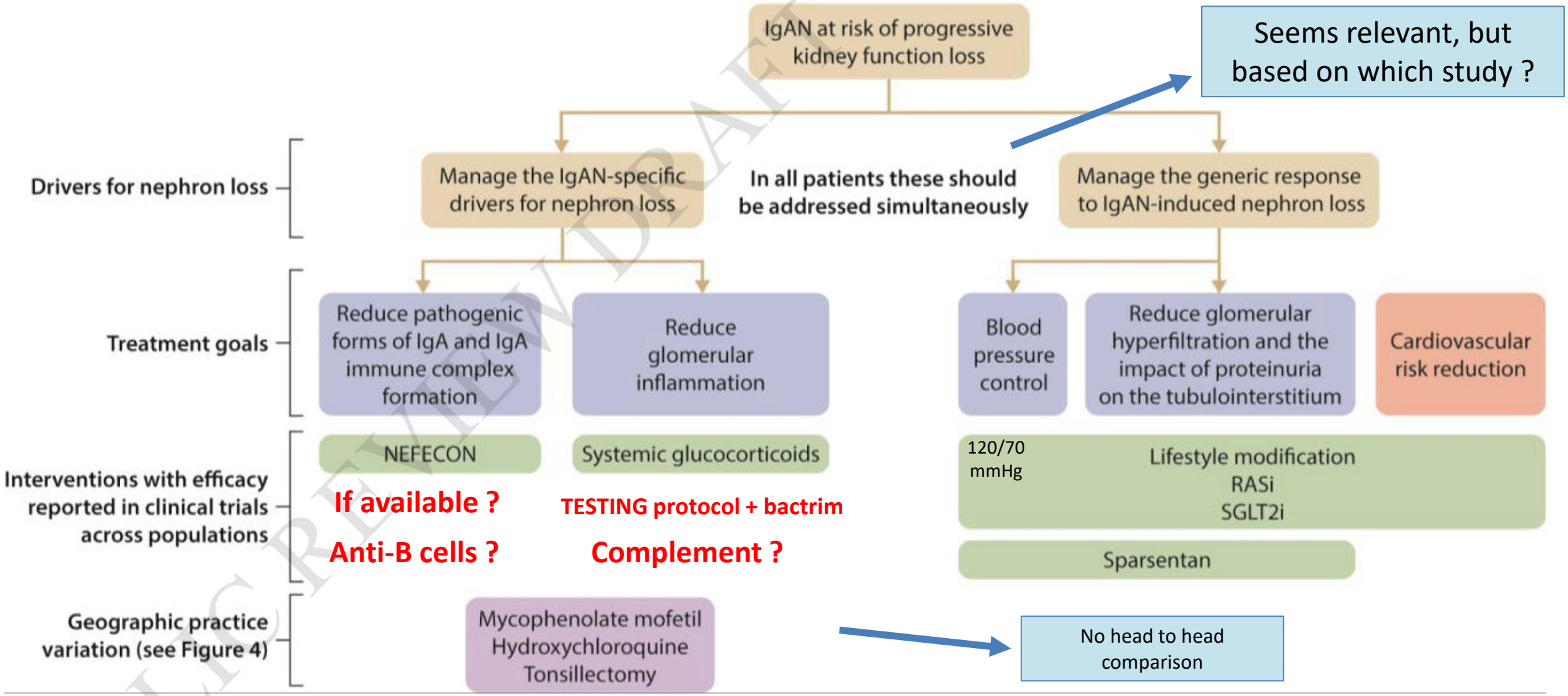
60 chinese patients, Pu 1,6g/d despite RASi,; HCQ: 50% Pu reduction M6



PHRC 2021
N. Maillard (St Etienne)

Liu, AJKD, 2019

New paradigm ?



Which criteria to stratify these treatments ?

CONCLUSIONS: new available treatments ?

When ?

Nephroprotection and immunomodulation **simultaneously**

How ?

Various protocols (no pozzi…)

Low-dose steroids (Testing) for Asian? +/- MMF ?

TRF-budesonide or available enteric budesonide ?

The next: numerous new tools

Nephroprotection (Endoth Recept antagonism)

Timing, selection criteria

Anti-B cell treatments (BAFF-APRIL/ CD38) ? Complement ? Long term HCQ ?

Patrapornpisut, AJKD 2021; Ghaddar, Curr op nephrol Hypert, 2023; El Karoui, JASN, 2023; KDIGO 2024

Individualized treatment approach: proposition

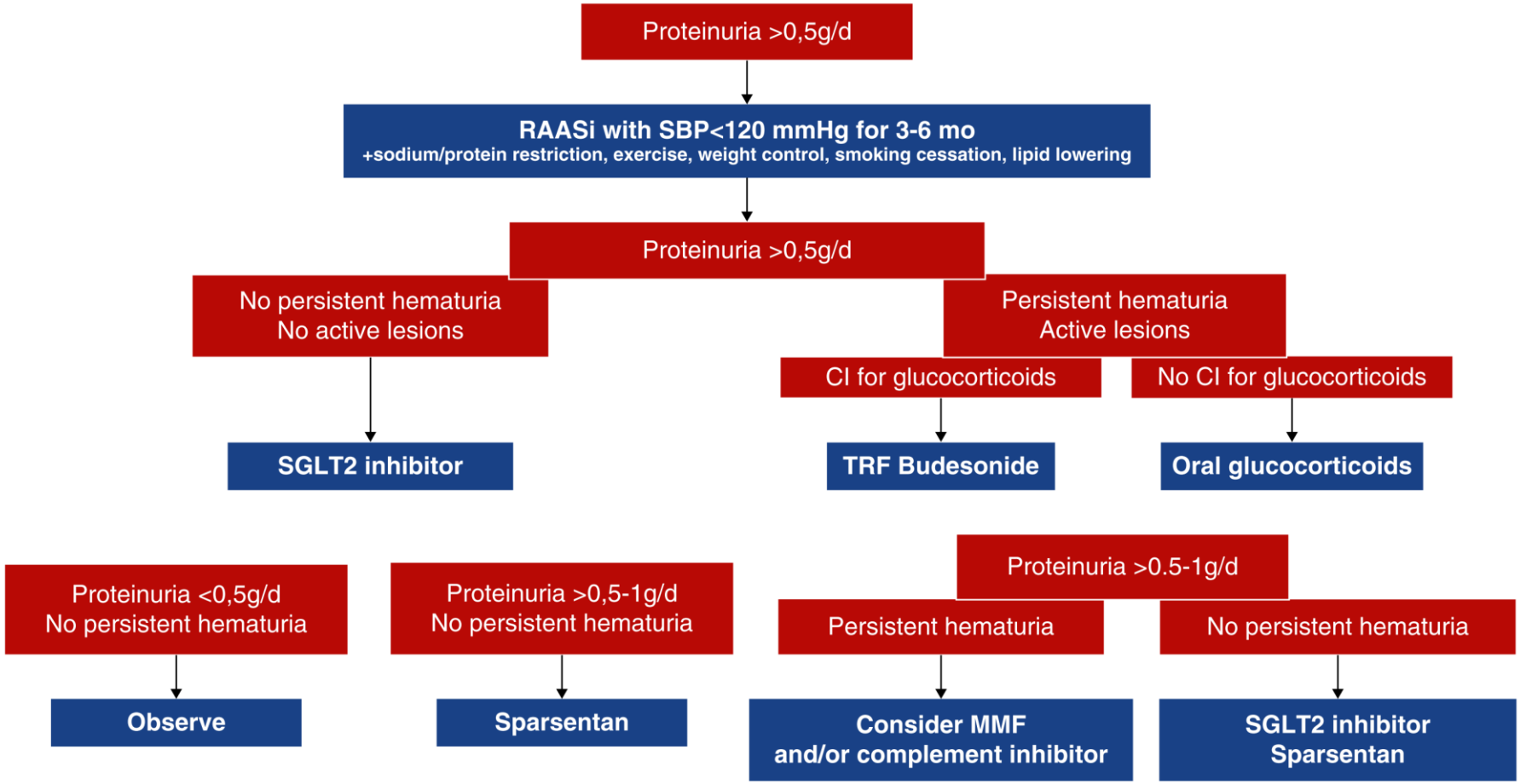
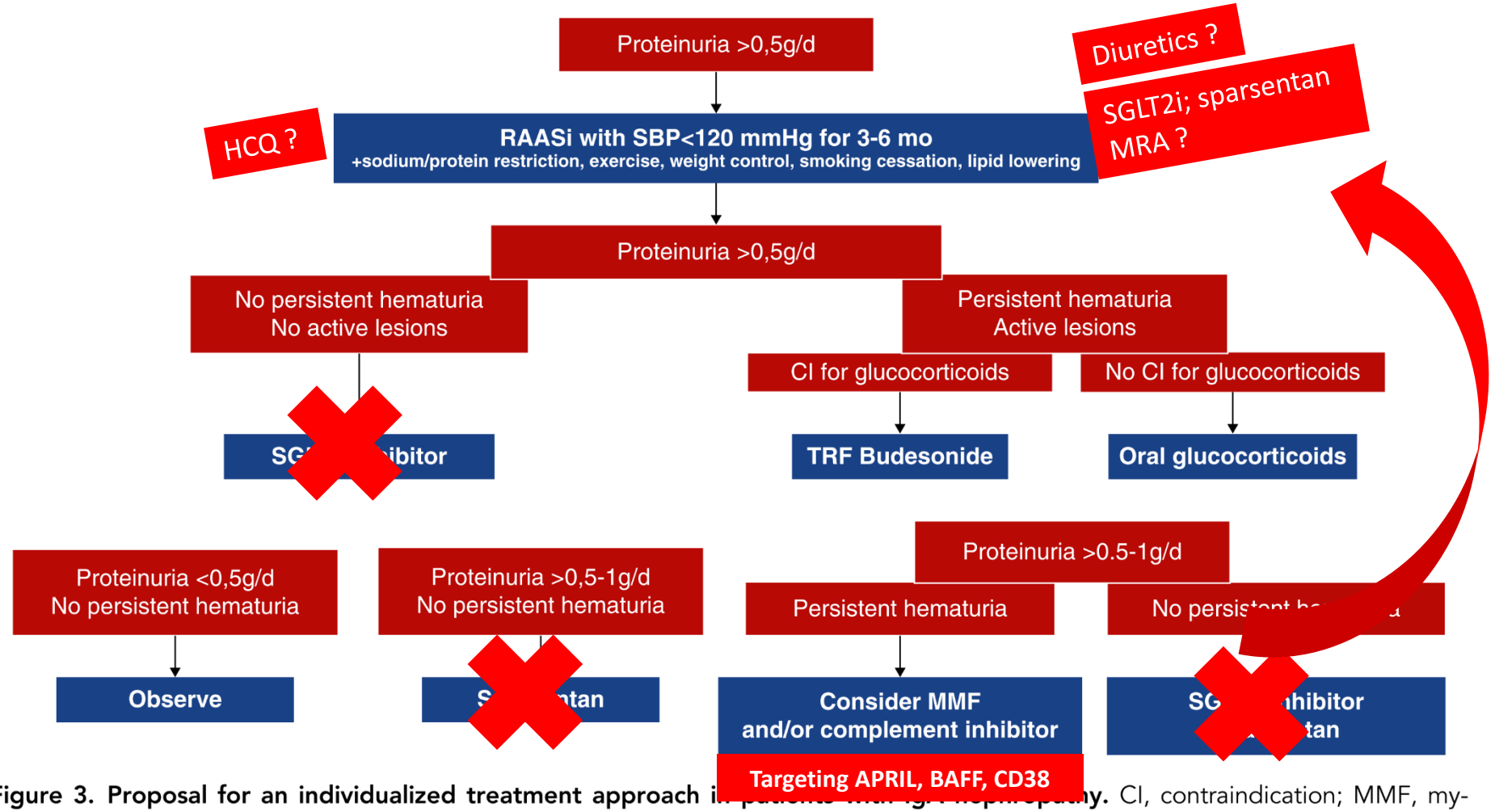


Figure 3. Proposal for an individualized treatment approach in patients with IgA nephropathy. CI, contraindication; MMF, mycophenolate mofetil; TRF, targeted-release formulation; SGLT2, sodium–glucose transporter 2.

El Karoui, Fervenza, De Vriese, JASN, 2023

Individualized treatment : just a proposition



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El Karoui, Fervenza, De Vriese, JASN, 2023

Subgroup	Iptacopan	Placebo	Iptacopan vs. Placebo, Percent Difference (95% CI)	P Value
	no. of patients/total no.			
Overall	118/125	106/125	38.3 (26.0 to 48.6)	<0.001
Sex				
Male	68/71	49/60	35.5 (17.4 to 49.7)	
Female	50/54	57/65	42.6 (24.5 to 56.4)	
Geographic region				
Asia	63/64	55/64	31.6 (13.4 to 46.0)	
All other regions	55/61	51/61	45.5 (28.3 to 58.5)	
24-Hr urinary protein-to-creatinine ratio at baseline				
<1.5	45/45	30/34	27.3 (2.4 to 45.9)	
≥1.5	73/80	76/91	41.2 (26.0 to 53.2)	
<2	71/71	59/67	35.0 (18.8 to 48.0)	
≥2	47/54	47/58	41.2 (20.9 to 56.4)	
eGFR at baseline				
30 to <45 ml/min/1.73 m^2	32/36	27/34	45.4 (25.3 to 60.1)	
≥45 ml/min/1.73 m^2	86/89	79/91	35.1 (19.0 to 48.0)	
SGLT2 inhibitor use at baseline				
Yes	16/18	12/14	36.7 (4.4 to 58.1)	
No	102/107	94/111	38.1 (24.4 to 49.2)	
Hematuria at baseline				
≥1	93/97	74/90	35.4 (21.8 to 46.7)	
Negative or trace	20/23	28/30	42.8 (6.1 to 65.2)	
M score				
M1	69/76	66/80	44.3 (28.7 to 56.5)	
M0	40/40	35/39	20.8 (−6.1 to 40.9)	
E score				
E1	32/36	30/36	39.2 (19.1 to 54.3)	
E0	76/79	69/81	37.4 (20.1 to 50.9)	
S score				
S1	81/87	81/89	35.3 (19.2 to 48.2)	
S0	27/28	19/29	39.4 (13.2 to 57.7)	
T score				
T1 or T2	46/48	44/53	34.4 (15.0 to 49.4)	
T0	63/68	58/67	40.3 (21.8 to 54.5)	
C score				
C1 or C2	32/35	17/22	45.5 (15.0 to 65.0)	
C0	72/76	72/85	32.5 (15.2 to 46.2)	

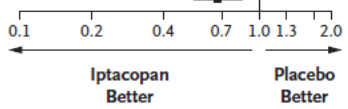
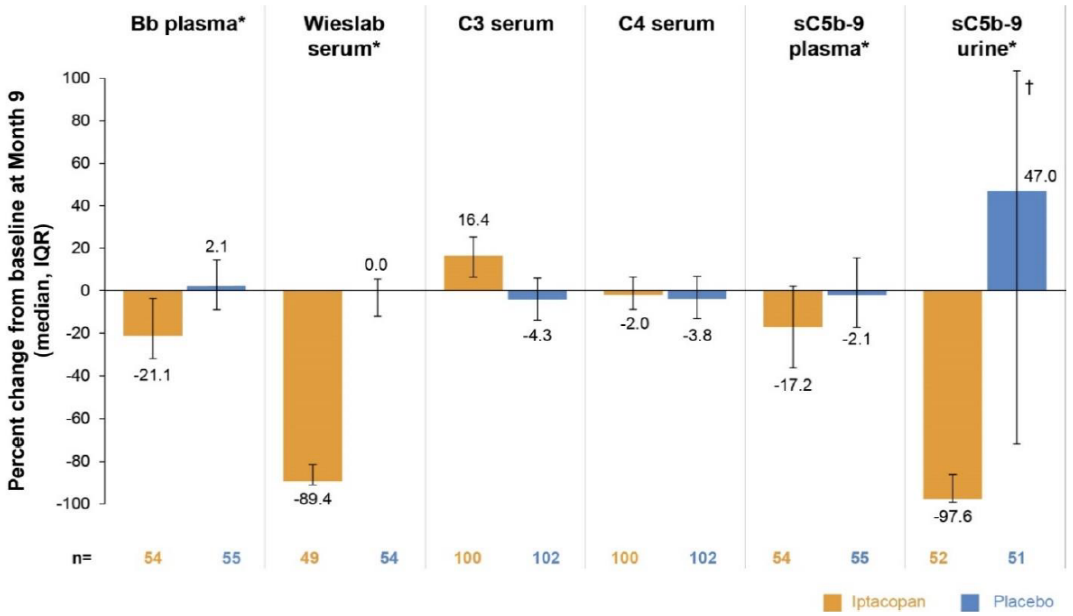


Figure 3. Subgroup Analyses.

Benefit of iptacopan in subgroup analysis

Supplementary Figure S6: Change from Baseline to Month 9 in Complement Pathway Biomarkers



Reduction in C biomarkers (uC5b9: proteinuria ??)

Perkovic, NEJM, 2024