A l'aube d'un nouvel espoir thérapeutique pour les patients GC3 : discussion autour de cas cliniques

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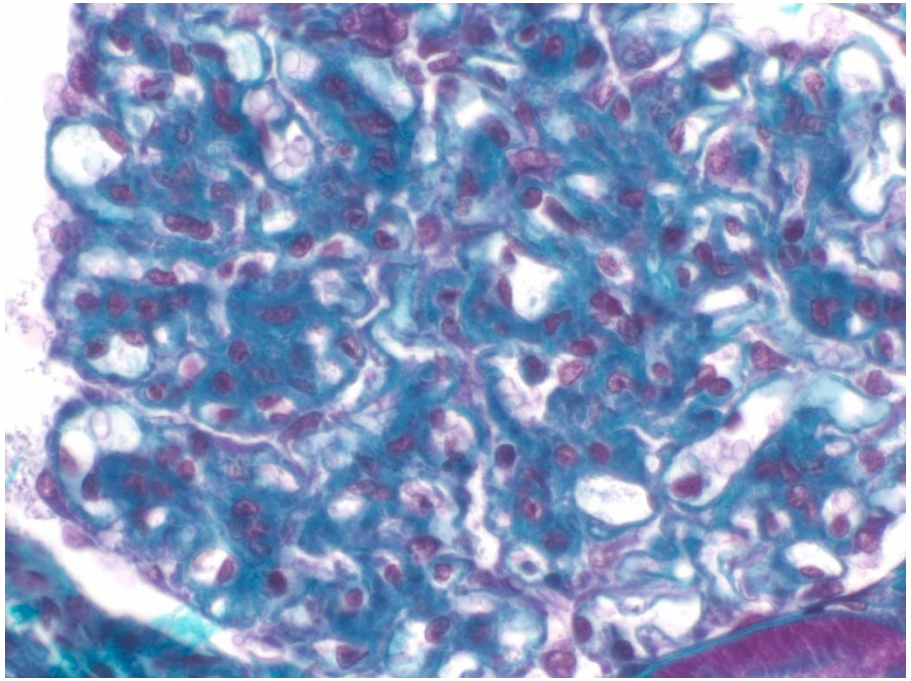
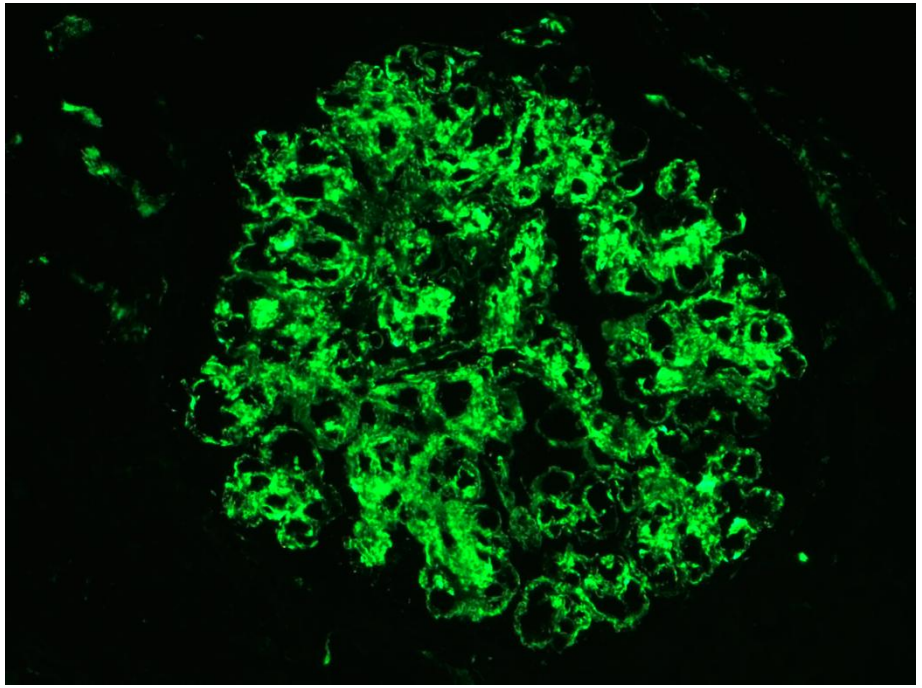
Liens d’intérêt

- Novartis: speaker fees

Case report

- 15 yrs: nephrotic syndrome+microscopic hematuria
- Creatininemia 70 µmol/L, albuminemia 13 g/L, proteinuria 3.2 g/g
- C3 121 mg/L, C4 normal, C3 Nef positive





Case report: treatment

- ACEi and Steroids
- Albuminemia 24 g/L, proteinuria 2 to 4 g/g
- M2 +MMF
- Partial remission: albuminemia 32 g/L, proteinuria 1.1 g/g

Dense Deposit Disease: Clinicopathologic Study of 32 Patients

- 14 children and 18 adults including 7 (39%) > 60 yrs of age
- IS: steroids in all 18 patients and 5 received a 2nd agent
- Combined therapy (IS with RAS blockade) was more efficacious than IS or RAS blockade therapy alone (P=0.03)
- Predictors of ESRD were adult age at biopsy, absence of combined IS/RAS blockade

Table 8. Predictors of ESRD by Kaplan and Meier survival estimates

Factor		Mean Time from Biopsy to ESRD in Months ± SEM	*P*
Age	Pediatric	244.8 ± 38.6	0.033
	Adult	62.0 ± 17.7	
IS therapy (with or without RAS blockade)	Yes	239.6 ± 31.4	0.002
	No	27.9 ± 8.1	
Any therapy	RAS blockade	29.5 ± 9.7	0.007
	IS	90.6 ± 19.7	
	Combined	No endpoints	
Subepithelial humps	Yes	109.1 ± 48.6	0.017
	No	124.5 ± 16.4	
Presence of arteriosclerosis (any degree)	Yes	49.9 ± 18.8	0.006
	No	252.0 ± 32.9	

Nasr et al, CJASN, 2009

When and which immunosuppressive drug?

- KDIGO:
  - IS si PU> 1-2 g/d adult or 0.5 g/d children
    especially if increase/active lesions on biopsy
- MMF and steroids
- FH, FH gene therapy
- Eculizumab
- Complement inhibitors

Vivarelli et al, KI, 2024

Mycophenolate mofetil

60 patients, median follow up: 47 months
22 MMF+CS
18 CS or CS+cyclophosphamide
20 not treated

Table 1 | Characteristics of patients at baseline and clinical presentation

	All patients ($n=60$)	Non-IST ($n=20$)	IST ($n=40$)	P-value[a]	MMF-IST ($n=22$)	Other-IST ($n=18$)	P-value[b]
Age (years)[c]	27 (13–57)	29 (18–49)	24 (12–62)	0.594	35 (13–66)	18 (10–41)	0.109
Gender, no. (%), male	34 (57)	14 (70)	20 (50)	0.174	14 (64)	6 (33)	0.111
Hypertension, no. (%)	27 (45)	11 (55)	16 (40)	0.288	9 (41)	7 (39)	1.0
Clinical presentation, no. (%)				<0.001			0.126
Nephrotic syndrome	31 (52)	4 (20)	27 (67)		17 (77)	10 (55)	
Nephritic syndrome	19 (32)	7 (35)	12 (30)		4 (18)	8 (44)	
Asymptomatic urinary abnormalities	10 (17)	9 (45)	1 (2)		1 (4)	0 (0.0)	
SCr (mg/dl)[c]	1.4 (0.7–2.8)	1.3 (0.8–2.0)	1.4 (0.7–2.9)	0.772	1.3 (0.6–2.9)	1.6 (0.8–2.9)	0.838
eGFR (ml/min per 1.73 m^2)[c]	66 (25–104)	65 (34–96)	66 (24–113)	0.963	67 (23–119)	66 (26–112)	0.870
Proteinuria (g/24 h)[c]	3.8 (1.4–7.0)	1.4 (0.9–3.1)	5.2 (3.4–7.4)	0.001	6.5 (3.9–8.6)	4.3 (1.5–5.6)	0.099
Serum albumin (g/dl)[c]	3 (2.6–3.5)	3.6 (2.9–4.3)	2.8 (2.4–3.1)	<0.001	2.8 (2.1–3.1)	2.9 (2.5–3.1)	0.340
Hypocomplementemia C3, no. (%)	38 (63)	8 (40)	29 (72)	0.024	15 (68)	14 (78)	0.723
Follow-up (months)[c]	47 (16–93)	38 (11–136)	50 (20–77)	0.605	44 (22–66)	54 (13–78)	0.744

Rabasco et al, KI, 2015

Outcomes

Table 3 | Outcomes

	All patients ($n=60$)	Non-IST ($n=20$)	IST ($n=40$)	*P*-value[a]	MMF-IST ($n=22$)	Other-IST ($n=18$)	*P*-value[b]
Primary outcome							
ESRD, no. (%)	10 (17)	7 (35)	3 (7)	0.012	0 (0)	3 (16)	0.083
Secondary outcomes							
Clinical remission, no. (%)	33 (55)	5 (25)	28 (70)	0.002	19 (86)	9 (50)	0.018
CR	13 (39)	2 (40)	11 (39)		6 (32)	5 (56)	
PR	20 (61)	3 (60)	17 (61)		13 (68)	4 (44)	
Doubling SCr, no. (%)	14 (23)	7 (35)	7 (17)	0.195	0 (0)	7 (39)	0.002

Clinical remission in 28 of the patients who had immune-based therapy, 19 of whom had MMF

Rabasco et al, KI, 2015

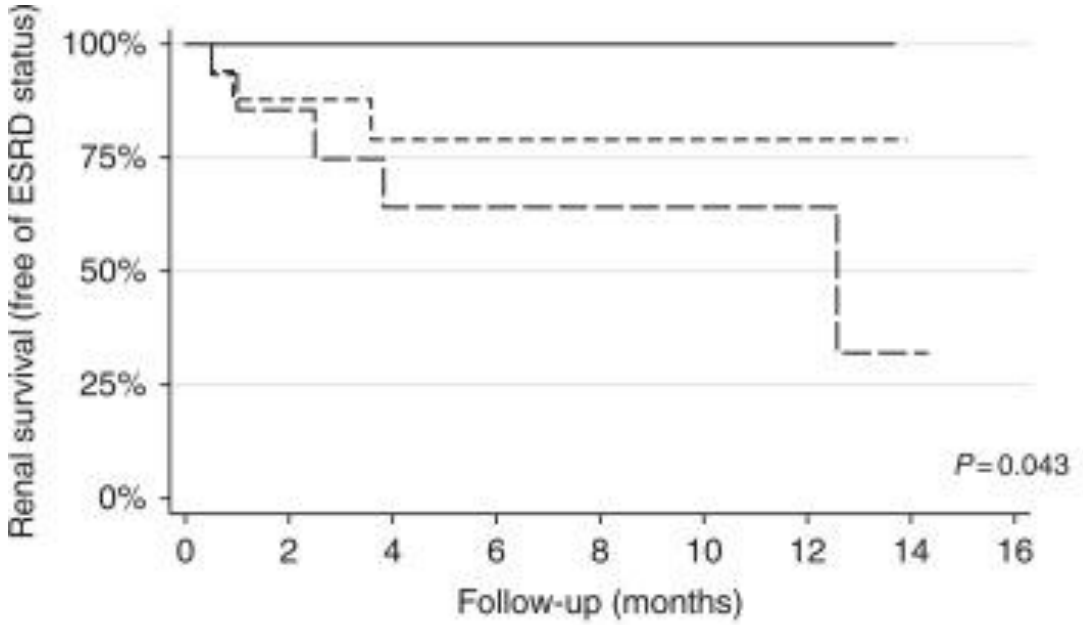
Renal survival

60 patients

22 MMF+CS
18 CS or CS+cyclophosphamide
20 not treated

Remission:
85, 50, 25%

Renal survival:
100, 80, 72%



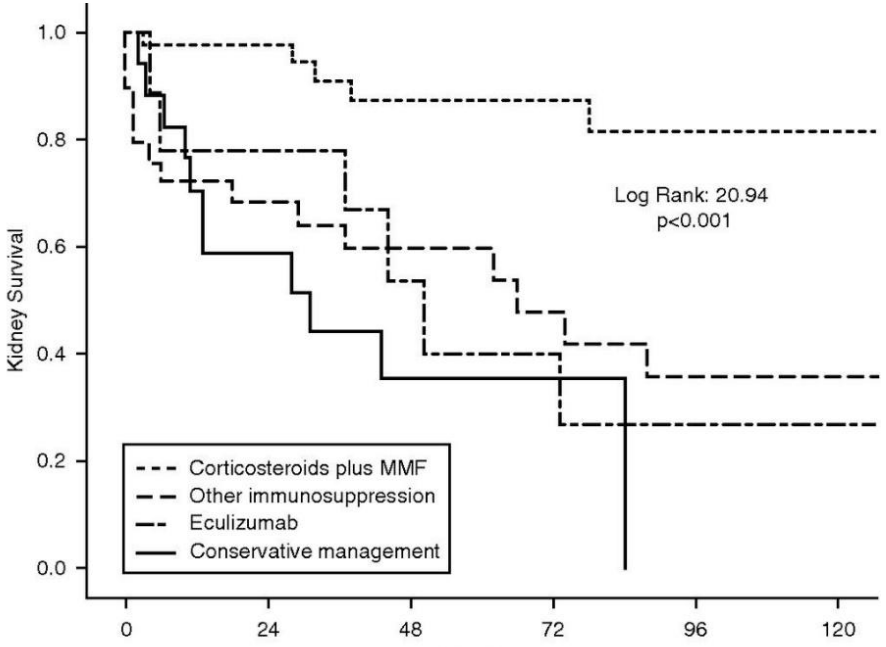
Patients at risk according to months of follow-up

Group of treatment	0	2	4	6	8	10	12	14	16
MMF-IST	22	15	10	5	4	4	2	1	1
Other-IST	18	13	10	6	4	2	2	1	1
No IST	20	14	11	7	6	6	5	4	3

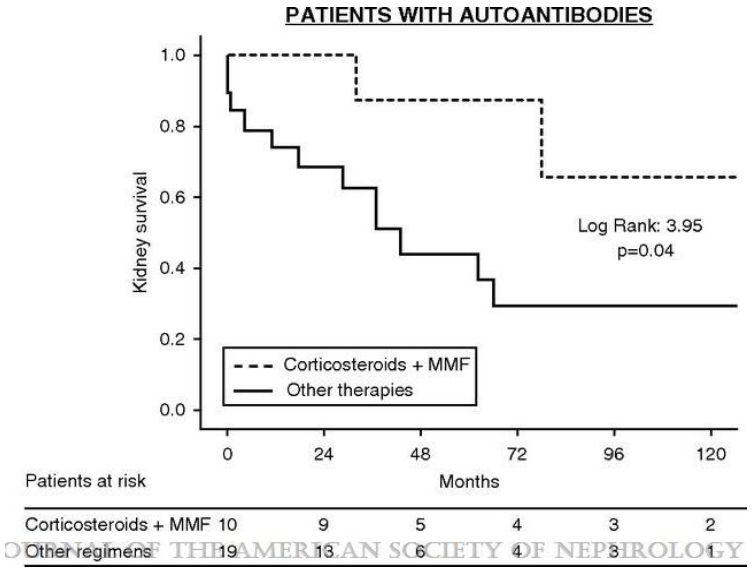
Rabasco et al, KI, 2015

Kidney survival according to therapeutic regimen

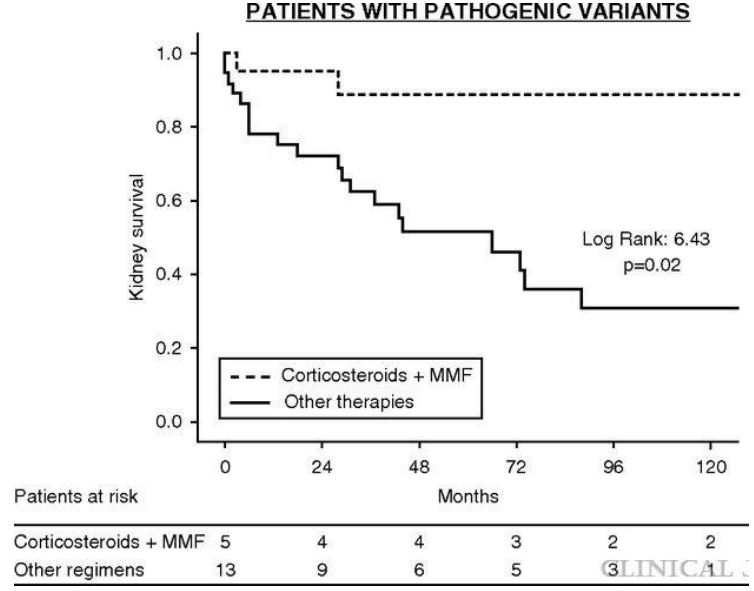
97 patients



Patients at risk						
Corticosteroids plus MMF	42	32	20	16	10	5
Other immunosuppression	29	17	11	8	6	5
Eculizumab	9	7	4	3	2	1
Conservative management	17	8	4	1		



Patients at risk						
Corticosteroids + MMF	10	9	5	4	3	2
Other regimens	19	13	6	4	3	1



Patients at risk						
Corticosteroids + MMF	5	4	4	3	2	2
Other regimens	13	9	6	5	3	1

Caravaca-Fontán et al, CJASN, 2020

Follow up

- Only 36% of patients achieving a complete remission
- Optimal duration of treatment?
- 30%–50% of patients relapsed when treatment was stopped

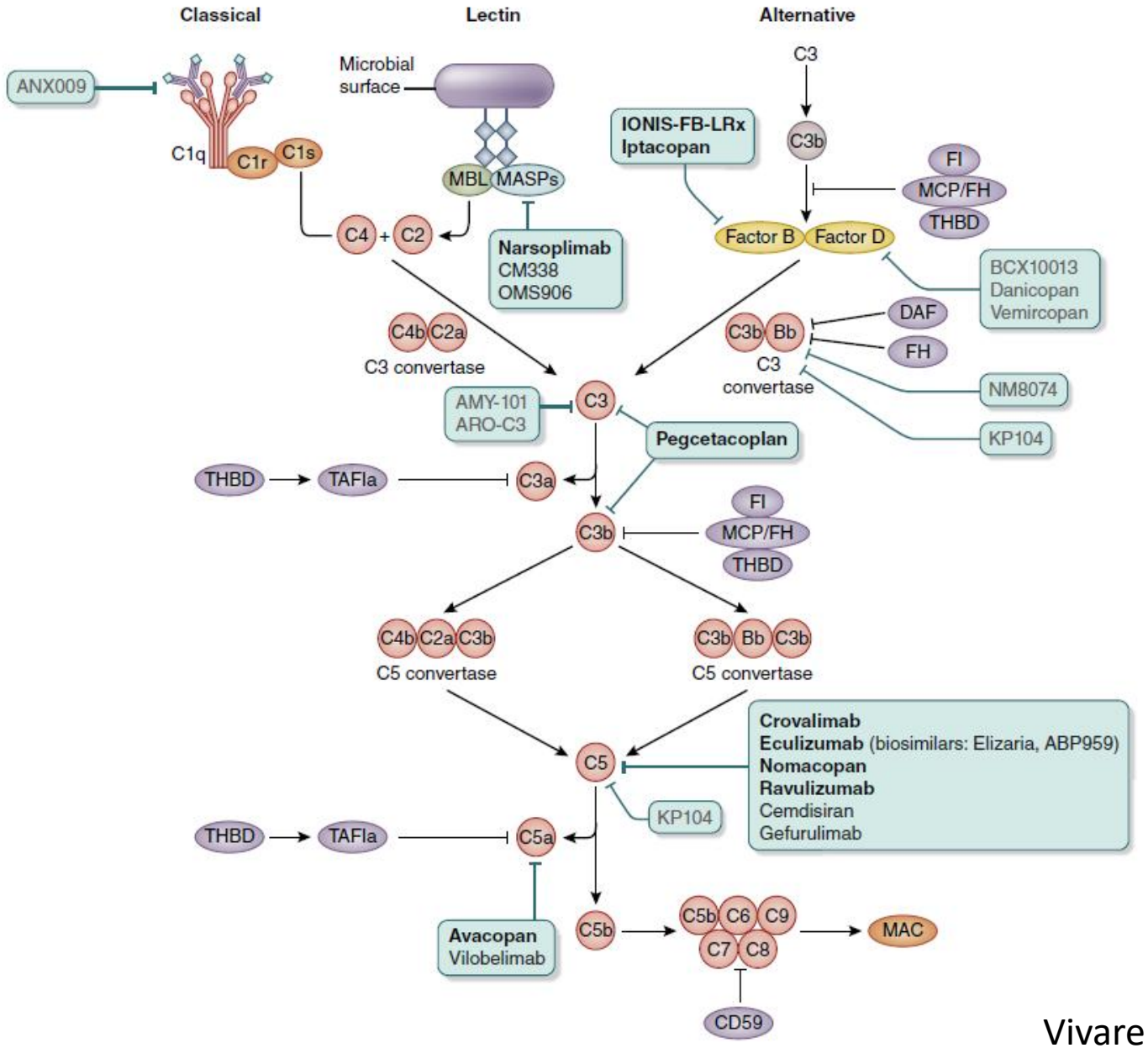
Case report: follow up

- Nephrotic proteinuria and albuminemia 12 g/L
- Kidney biopsy: C3 deposits and endocapillary proliferation, IF <5%
- MMF +CS 5 mg/d
- ECULIZUMAB?

Alternative pathway of complement activation

- Central and early role in disease pathophysiology
- Frequency and functional effect of NeFs
- Presence of variants in complement genes
- For autoimmune (C3NeF)-driven C3G, therapies targeting the autoantibody not effective
- Therapy targeting the alternative pathway

Therapeutic inhibitors of complement



Vivarelli et al, KI 2024

Eculizumab

Publication	Type of study	Diagnosis	Age	Follow up (months)	Effect
Daina 2012	Case report	DDD	22	11	+
Vivarelli 2012	Case report	DDD	17	18+9	+
Radhakrishnan 2012	Case report	C3GN	16	1,5	+
McCaughan 2012	Case report	DDD (RT)	29	2,5	+
Bomback 2012	Prospective non controled	DDD DDD DDD (RT) C3GN C3GN (RT) C3GN (RT)	22 42 32 25 22 20	12 9 12 12 12 12	+ - + - - +
Gurkan 2013	Case report	C3GN (RT)	21	12	+
Besbas 2013	Case report	C3GN	16	10	-
Kerns 2013	Case report	C3GN	16	3,5	+

Publication	Type of study	Diagnosis	Age	Follow up (months)	Effect
Ozkaya 2014	Case report	DDD	14	7	+
Rousset-Rouvière 2014	Case report	DDD	10	6,5	+
Berthe-Aucejo 2014	Case report	DDD	17	3,5	-
Sanchez-Moreno 2014	Case report	DDD (RT)	14	30	+
Iman 2015	Case report	C3GN	38	11	+
Oosterveld 2015	Case series	DDD	13	6,5	+
		DDD	6	6, 2 cures	+
		DDD	7		+
		DDD	6,5	3, 2 cures	+
		DDD	2		+
Haffner 2015	Case report	C3GN	15	multimodal	+
Payette 2015	Case report	C3GN	5	36	+
Le Quintrec 2015	Case series	C3GN	3 adults	6-32	+
Lebreton 2017	Case series	C3GN	4 children	8-22	+ 3/4
Tran Pediatr Nephrol 2016	Case report	C3GN	13	9	+

Patterns of Clinical Response to Eculizumab

- 26 patients
- 13/26 pediatric
- Mean duration of eculizumab 14 months
- 6 (23%) complete response
- 6 (23%) partial
- 14 (54%) no response
- Correlated with rapidely progressive disease and extra capillary proliferation

Lequintrec et al, AJKD, 2018

EAGLE study

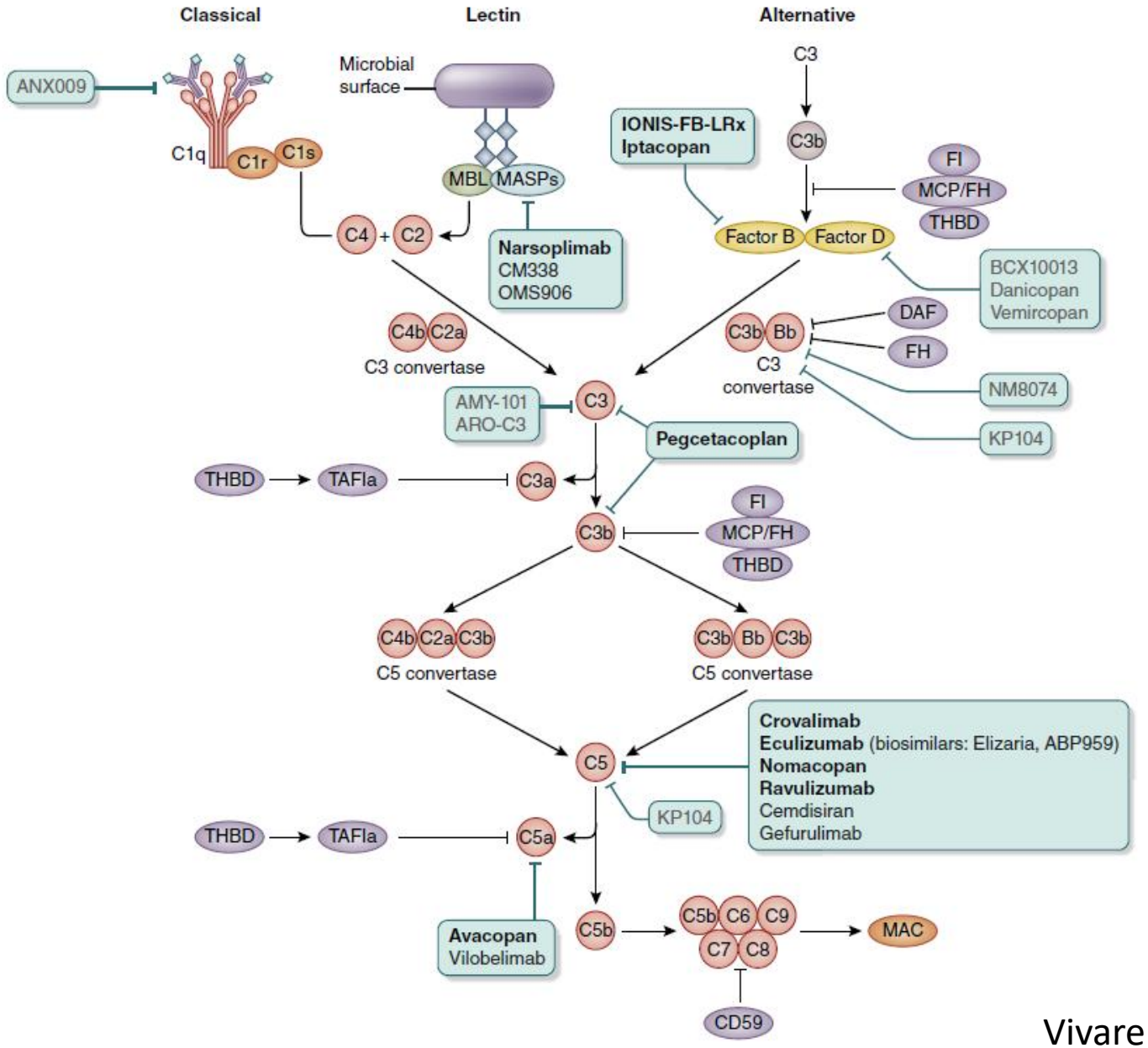
- A single-arm clinical trial
- 10 patients
- 6 IC MPGN or 4 C3GN
- High PU (>3.5 g/d) and high C5b9
- Eculizumab:
  - 48 weeks,
  - followed by 12 weeks of wash out,
  - another 48 weeks of eculizumab
- Only 3 achieved partial remission, no complete remission
- 7 were non-responders
- During the washout period all patients had a rise in proteinuria and serum C5b9 levels

Ruggenenti et al, AJKD, 2019

Case report: follow up

- Partial improvement with Eculizumab:
  - albuminemia 29 g/l but then 22 g/l
  - proteinuria negative and then increased to 2.7 g/g
- Kidney biopsy: 4/9 sclerotic glomeruli, segmental endocapillary proliferation, IF 30%, C3 +++

Therapeutic inhibitors of complement



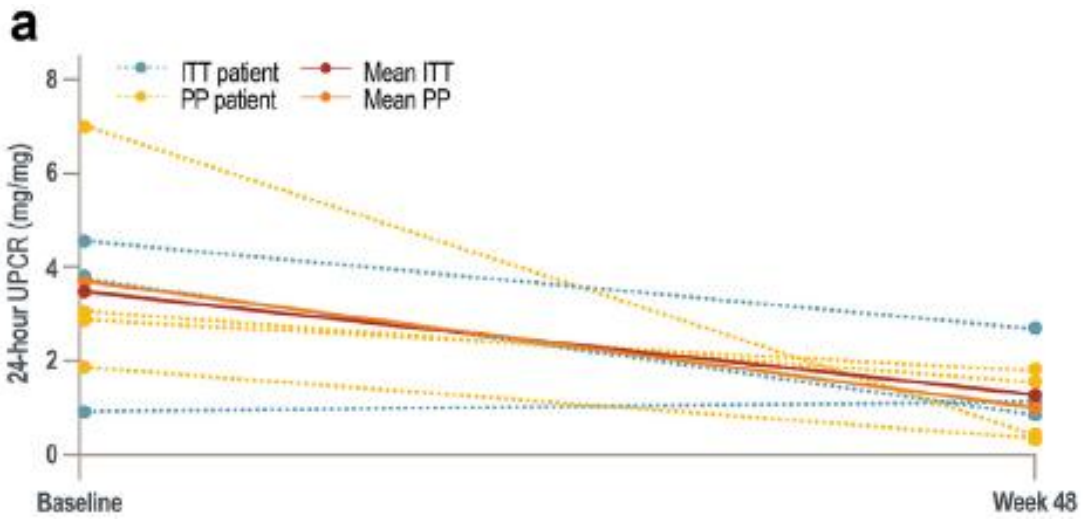
Vivarelli et al, KI 2024

Pegcetacoplan

- Phase 2, open-label, 48-week study
- C3G n=8
- Mean proteinuria reduction: 50,9%

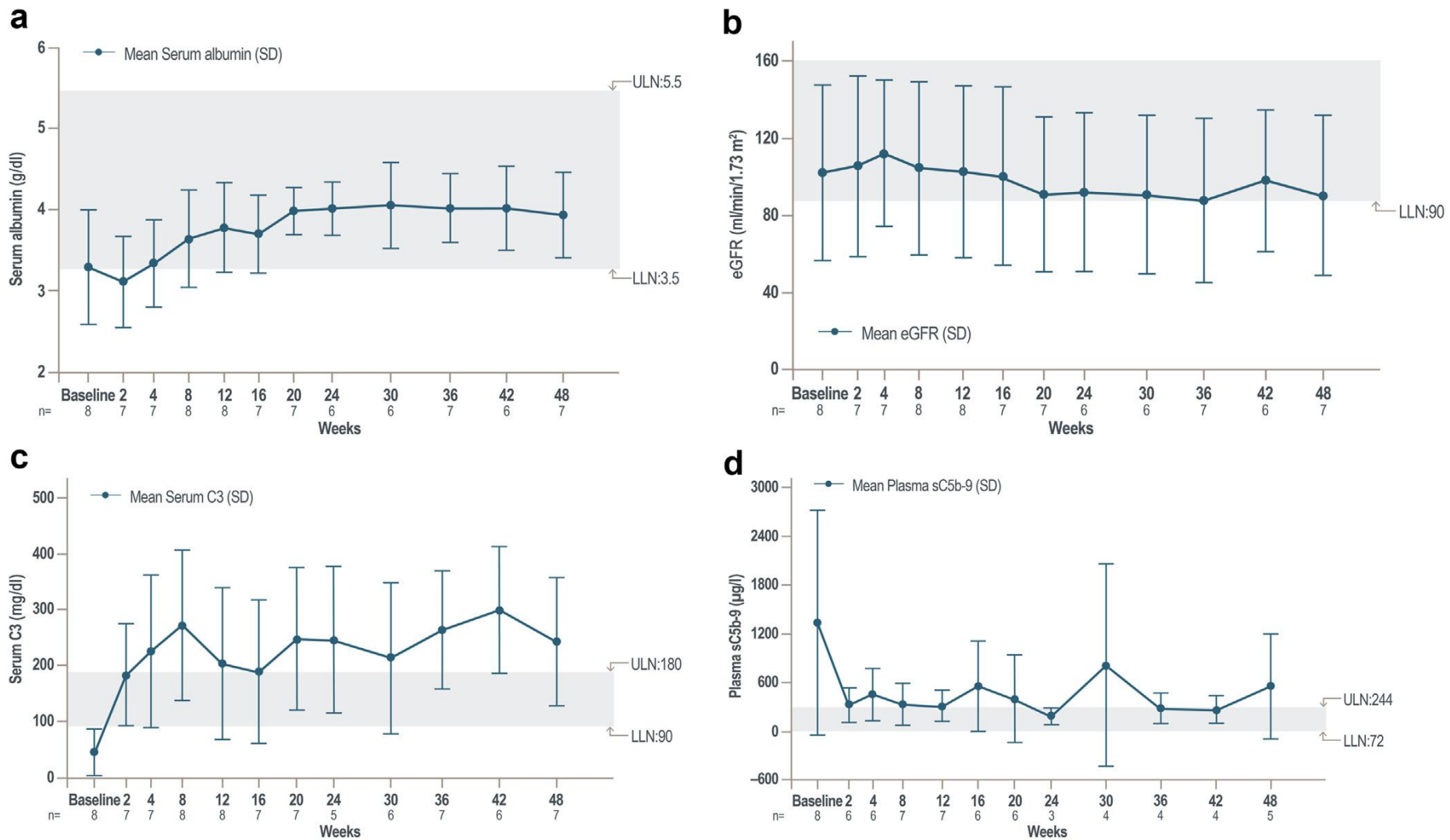
Table 2. Primary end points at baseline and week 48 for patients with C3G (ITT and PP populations)

Parameter, mean (SD)	ITT	PP
Baseline[a]		
Number of patients	8	4
24-hour UPCR, mg/mg	3.3 (1.7)	3.5 (2.1)
Week 48		
Number of patients	7	4
24-hour UPCR, mg/mg	1.2 (0.8)	1.0 (0.7)
Individual CFB (SD) in 24-hour UPCR, mg/mg[b]	−2.0 (2.0)	−2.5 (2.5)
Individual %CFB (SD) in 24-hour UPCR[b,c]	−50.9 (39.1)	−65.4 (26.4)



Dixon et al, KI Rep, 2023

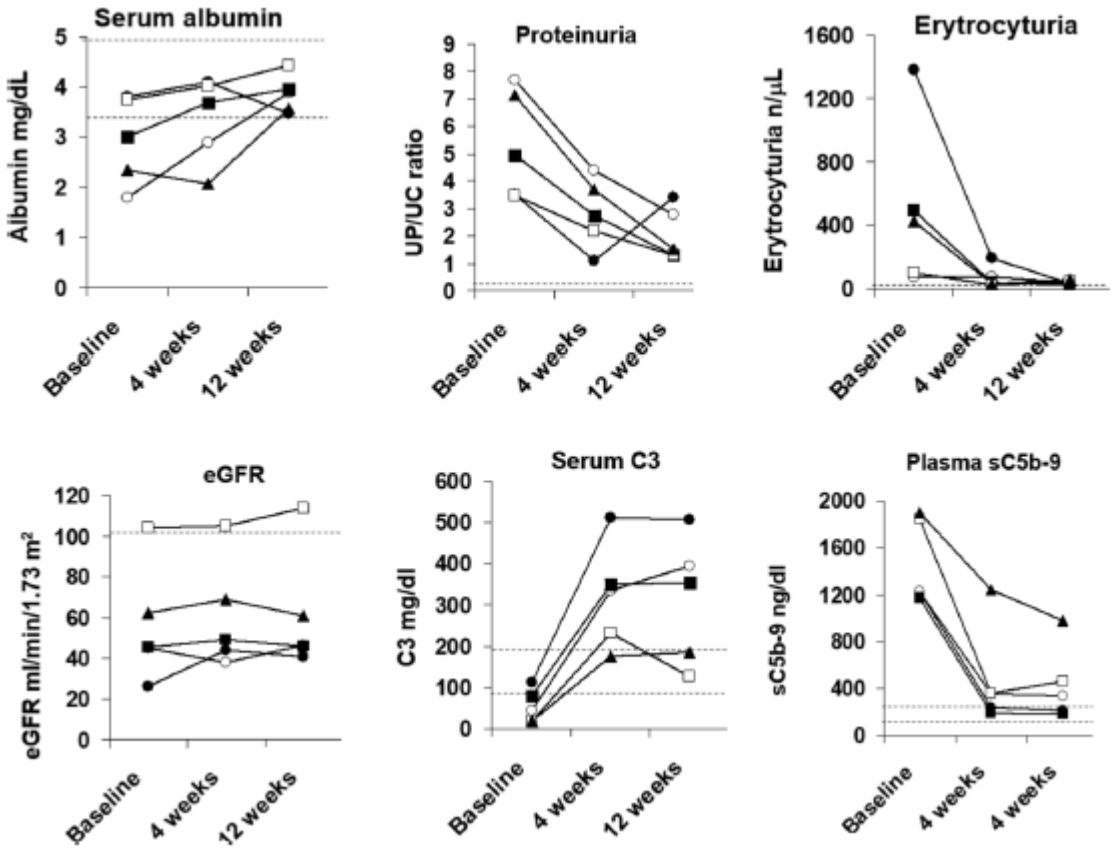
Results



Dixon et al, KI Rep, 2023

Pegcetacoplan in children

- Retrospective, observational study
- 5 pediatric patients, 12-week treatment period
- 3 of 4 patients with impaired kidney function showed an improvement in eGFR



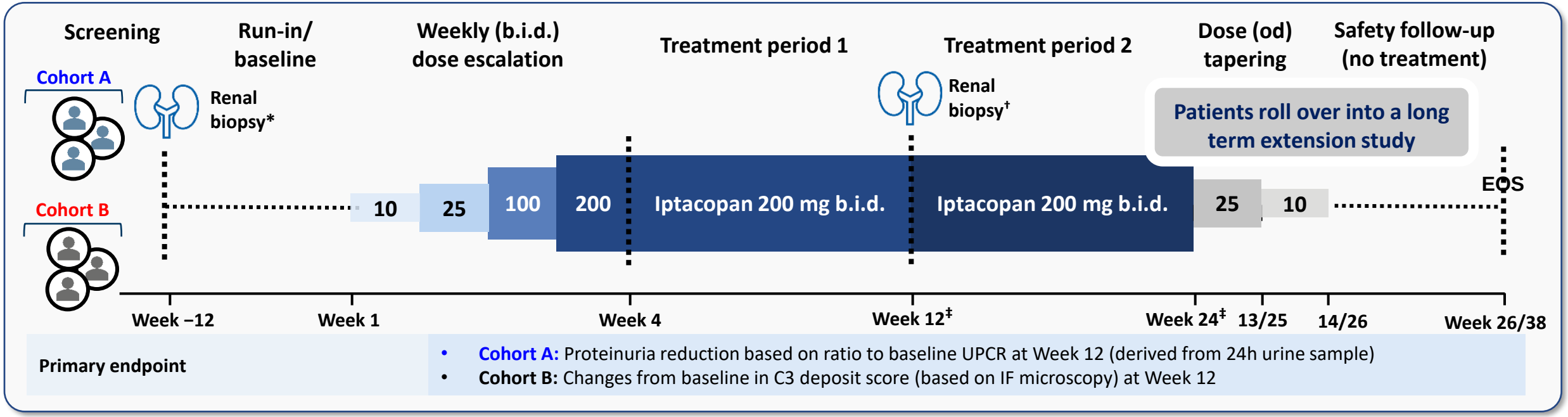
Mancuso et al, Pediatr Nephrol, 2025

Iptacopan in C3G: Phase 2 Study

Proximal complement inhibitor: specifically binds factor B and inhibits the AP

Key inclusion criteria:

- **Cohort A**: Biopsy confirmed C3G patients aged ≥18 years, with native kidneys and reduced serum C3 levels
- **Cohort B**: Adult (≥18 years) patients with C3G recurrence following kidney transplantation



*Not required for Cohort A unless most recent biopsy material >12 months old; †Optional for Cohort A;

Wong et al, KI Rep, 2023

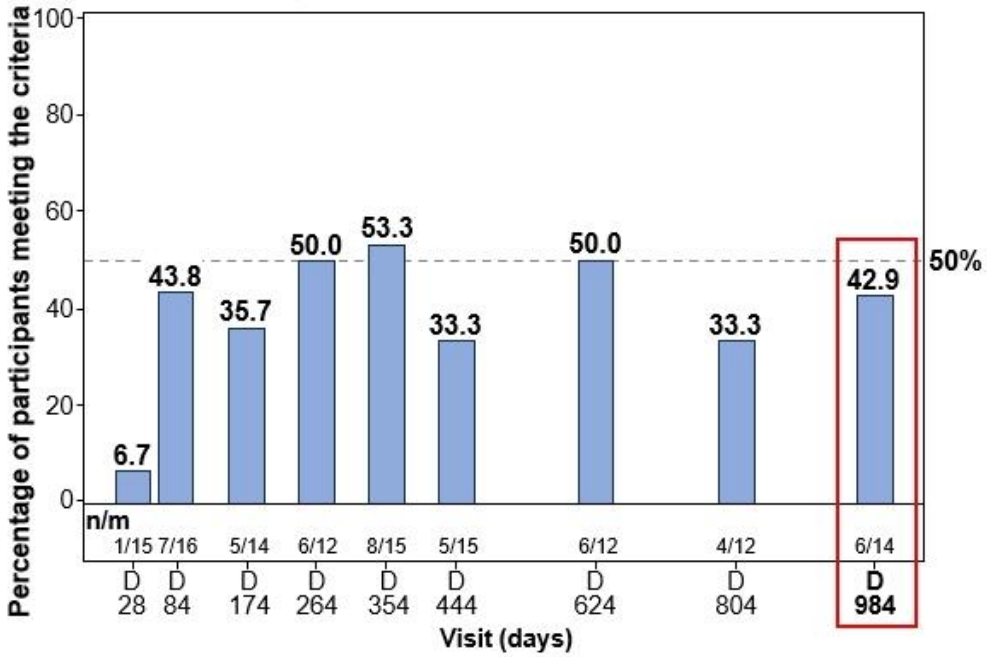
Extension study

- Of 27 patients completing the Ph2 study (NCT03832114)
  - ➢26 (16 Cohort A, 10 Cohort B) entered the extension study
  - ➢**22 patients** (14 Cohort A, 8 Cohort B) **completed 33M of follow-up**
- At baseline, median UPCR was within the normal range for transplanted Cohort B with C3G recurrence, but not for Cohort A with native kidney C3G

Baseline characteristics (NCT03955445)		Cohort A N=16	Cohort B N=10
Age (years)	Mean (SD)	26.1 (10.57)	35.9 (18.72)
	Median (Range)	22.0 (18–59)	32.5 (18–70)
Gender, n (%)	Male (%)	10 (62.5)	8 (80.0)
Race, n (%)	Caucasian (%)	16 (100)	9 (90.0)
	American Indian or Alaska Native (%)	–	1 (10.0)
eGFR (mL/min/1.73m²)*	Mean (SD)	70.0 (35.05)	53.9 (17.14)
	Median (Range)	64.6 (28–134)	59.5 (27–74)
24 h UPCR (g/g)†	Mean (SD)	4.018 (2.143)	1.071 (1.6663)
	Median (Range)	3.457 (1.76–9.01)	0.162 (0.08–3.94)
FMV UPCR (g/g)†	Mean (SD)	3.613 (2.6934)	0.868 (1.6155)
	Median (Range)	2.863 (0.73–8.75)	0.079 (0.04–4.36)
Serum C3 (g/L)‡	Mean (SD)	0.312 (0.2224)	0.588 (0.2610)
	Median (Range)	0.238 (0.02–0.69)	0.550 (0.17–1.00)

*Normal eGFR: ≥60 mL/min/1.73 m²; †Normal UPCR: <200 mg/g; ‡Normal serum C3: 0.9–1.8 g/L

42.9% (6/14) of patients (Cohort A) met the 2-component composite renal endpoint criteria i.e., eGFR stability [≤10% reduction] and ≥50% proteinuria reduction – at 33M

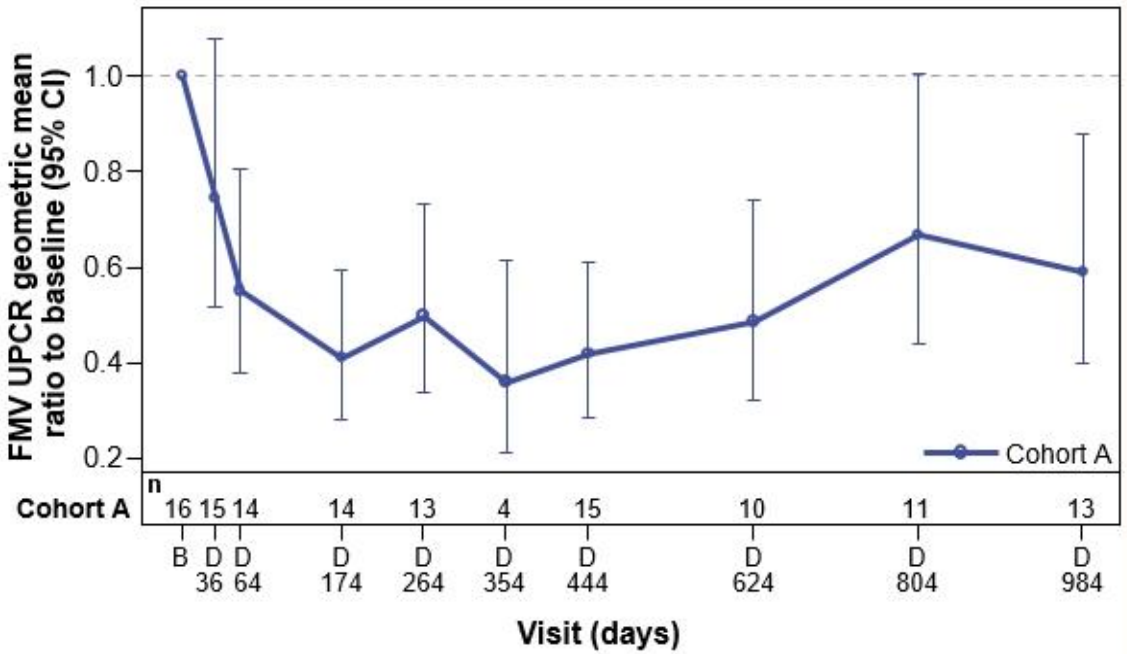


- Given the normal range of the baseline UPCR in Cohort B, this composite endpoint was not assessed as this would be clinically meaningless

Nester et al, ERA congress 2024, Nephrology Dialysis Transplantation, 2024

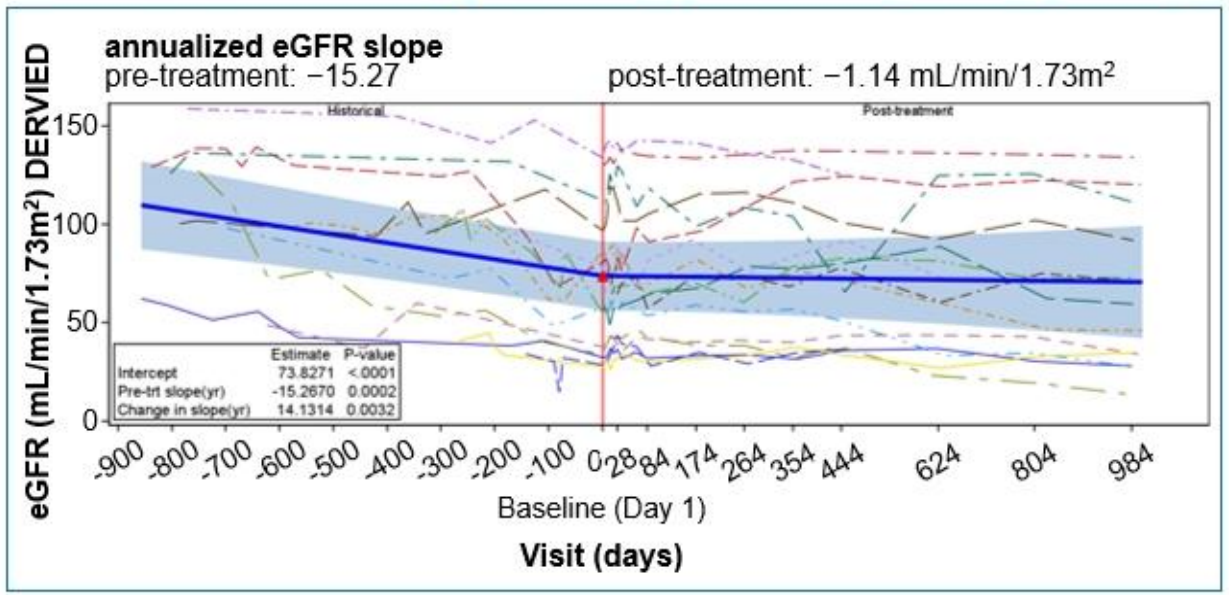
Results

Proteinuria was reduced by 41% (p=0.0097) following 33M of iptacopan treatment in Cohort A



- Baseline proteinuria values (FMV UPCR) were within the normal range for most participants in Cohort B and remained so during iptacopan treatment

In Cohort A, the annualized eGFR slope (N=16) upon initiation of iptacopan was improved to −1.14 mL/min/1.73 m², representing a change in the eGFR trajectory of +14.13 mL/min/1.73m² in annualized eGFR compared to the pre-treatment period (p=0.0032)

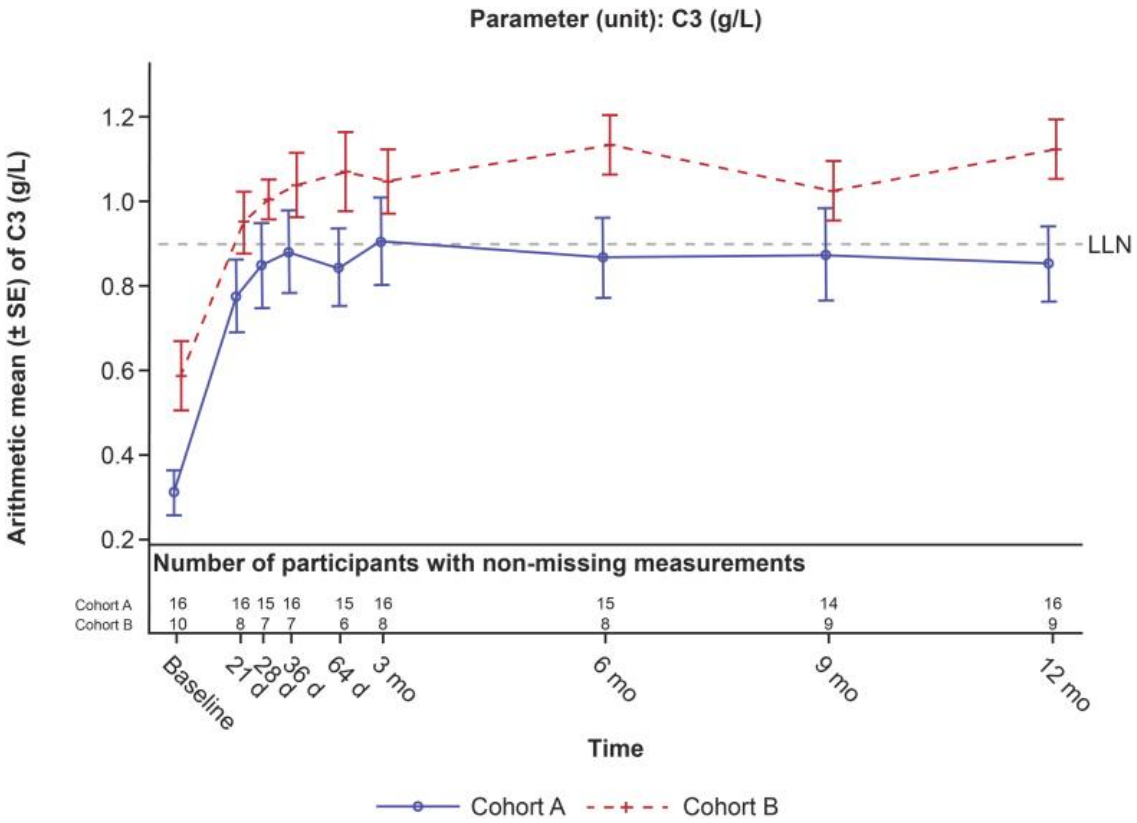


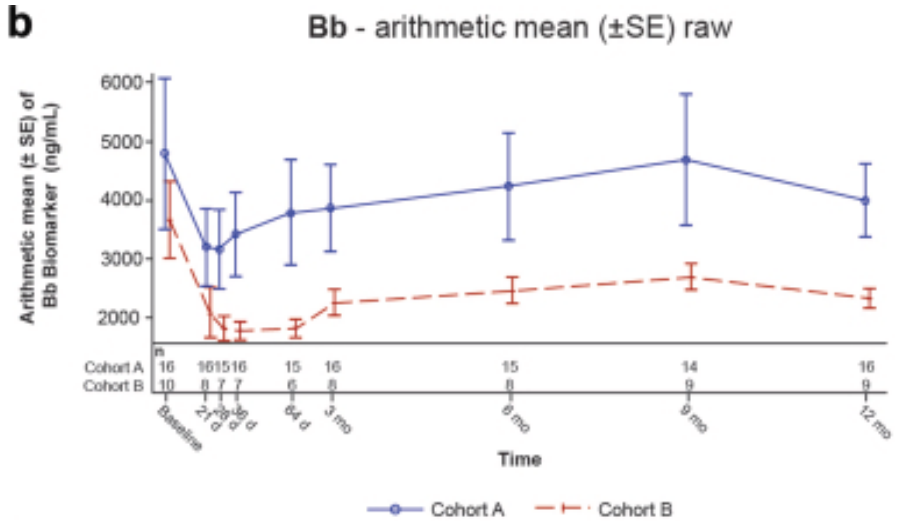
eGFR change from baseline at 33M

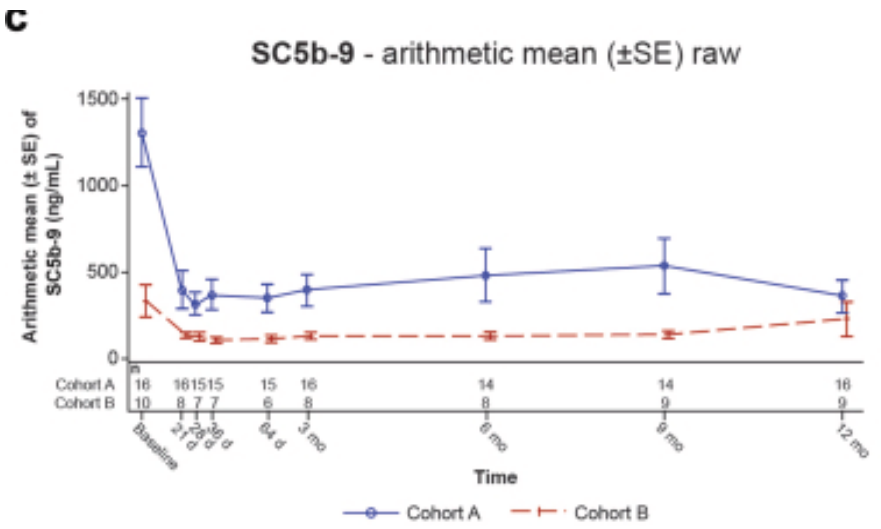
- **Cohort A**: eGFR stabilized or improved in most patients (10/14) over time and change (adjusted arithmetic mean) from baseline at the 33M time-point was -3.18 mL/min/1.73 m²
- **Cohort B**: eGFR change (adjusted arithmetic mean) from baseline at the 33M follow-up was -6.34 mL/min/1.73 m²

Nester et al, ERA congress 2024, Nephrology Dialysis Transplantation, 2024

Serum C3 and biomarkers



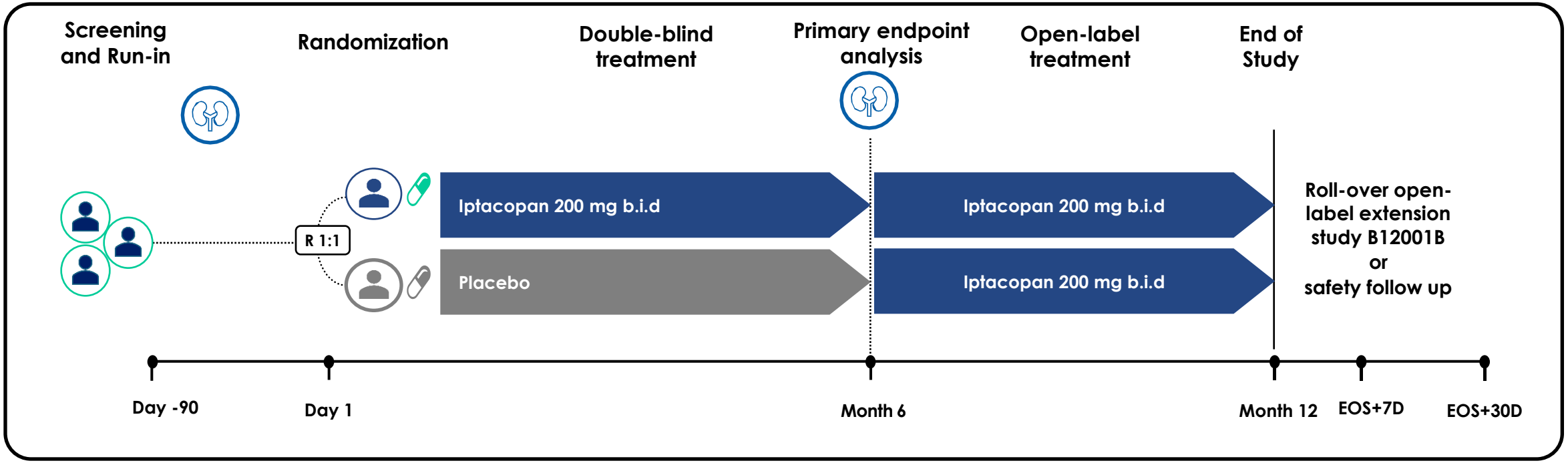




Nester et al, KI Rep, 2025

APPEAR Phase 3 study

APPEAR-C3G is a randomized, double-blind, multicenter, placebo-controlled Phase 3 study



Inclusion criteria:

- Biopsy proven
- Low C3
- PU>1g/g
- eGFR>30 ml/min/1.73m²

Bomback et al. KI Reports. 2022

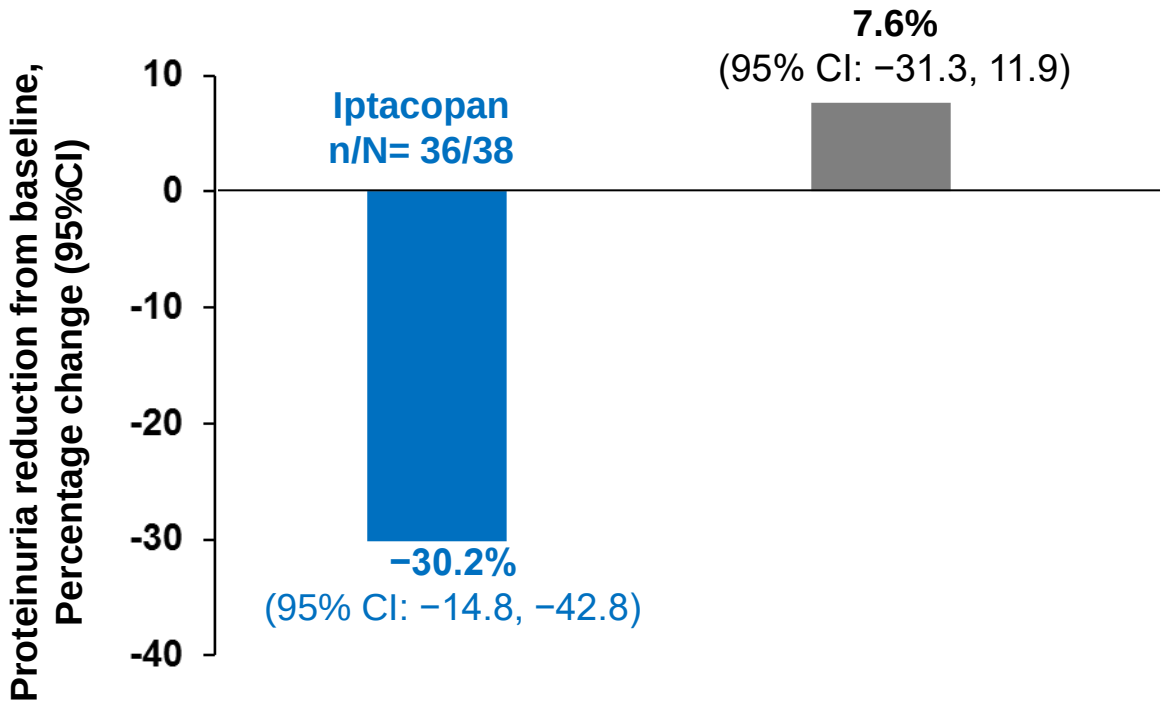
Baseline demographics & disease characteristics

Characteristic		Iptacopan (N = 38) n (%)	Placebo (N = 36) n (%)
Age (years), Mean (SD)		26.1 (10.39)	29.8 (10.79)
Gender, n (%)	Male	27 (71.1)	20 (55.6)
	Female	11 (28.9)	16 (44.4)
Race, n (%)	White	27 (71.1)	24 (66.7)
	Black or African American	1 (2.6)	1 (2.8)
	Asian	9 (23.7)	9 (25.0)
	American Indian or Alaska Native	0	1 (2.8)
	Multiple or unknown	1 (2.6)	1 (2.8)
Baseline UPCR 24h [g/g] Geometric mean (95%CI)		3.33 (2.79–3.97)	2.58 (2.18–3.05)
Baseline total urinary protein (24h), n (%)	<3 g/day	11 (28.9)	15 (41.7)
	≥3 g/day	27 (71.1)	21 (58.3)
Baseline UPCR (24h), n (%)	<3 g/g	17 (44.7)	25 (69.4)
	≥3 g/g	21 (55.3)	11 (30.6)
Baseline eGFR [mL/min/1.73m^2] Mean (SD)		89.3 (35.2)	99.2 (26.9)
Age at C3G diagnosis, n (%)	<18 years	15 (39.5)	6 (16.7)
	≥18 years	23 (60.5)	30 (83.3)
C3G subtype at diagnosis, n (%)	C3GN	26 (68.4)	32 (88.9)
	DDD	9 (23.7)	1 (2.8)
	Mixed C3GN/DDD	2 (5.3)	2 (5.6)

The iptacopan arm exhibited a more severe disease phenotype at baseline

Kavanagh D et al. Oral. Presented at ERA, 2024

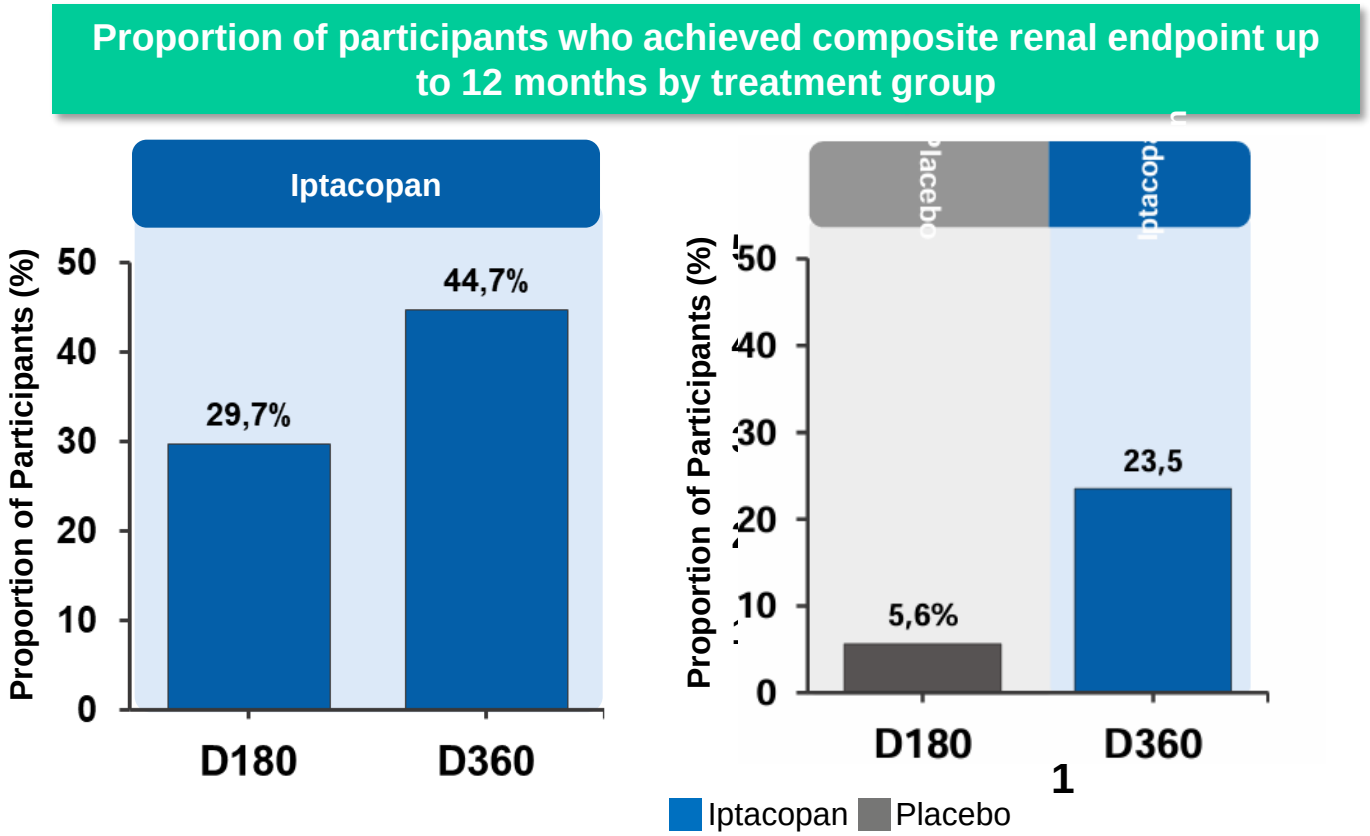
Proteinuria at Month 6



Relative percent reduction between iptacopan and placebo at Month 6 (95% CI):
35.1%; 1-sided p-value: **0.0014**

Kavanagh D et al. Oral. Presented at ERA, 2024

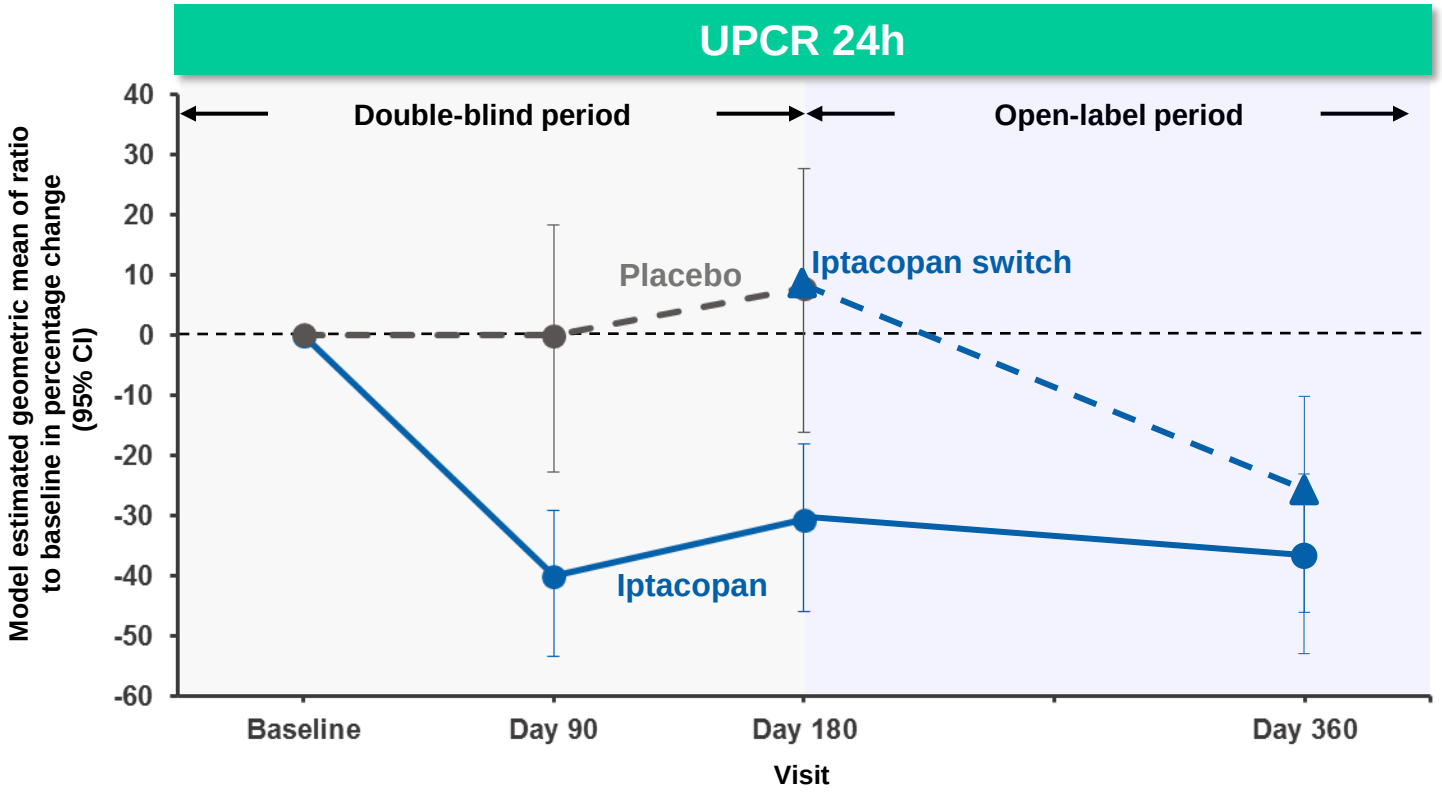
Composite renal endpoint at 12 months



Composite renal endpoint:
≥50% reduction UPCR +
≤15% reduction in eGFR

Smith R, et al. ASN 2024, San Diego, CA, 2024

Proteinuria at 12 months



Proteinuria reduction between iptacopan and placebo at Month 6
35.1%
(1-sided p-value: 0.0014)

Proteinuria reduction following switch from placebo to iptacopan
(-31% from Month 6 to 12)*

Sustained proteinuria reduction to 12 months in iptacopan arm
(-37% from baseline)

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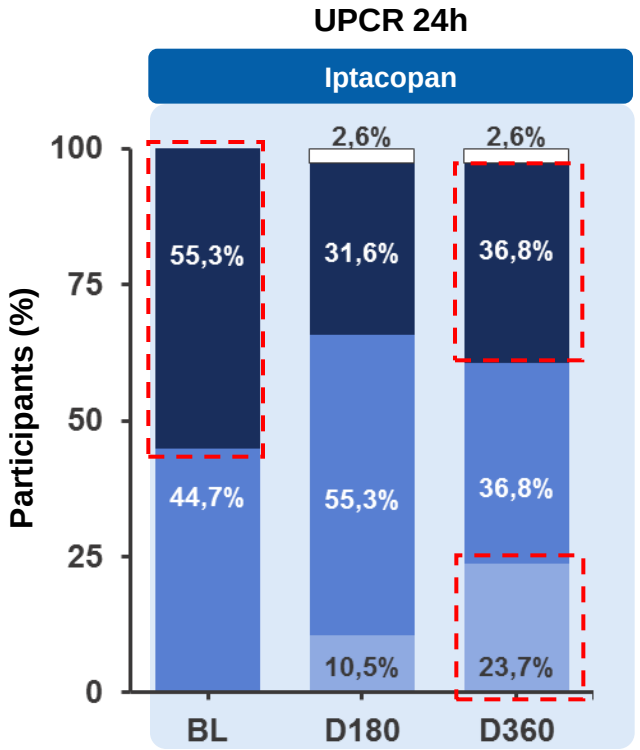
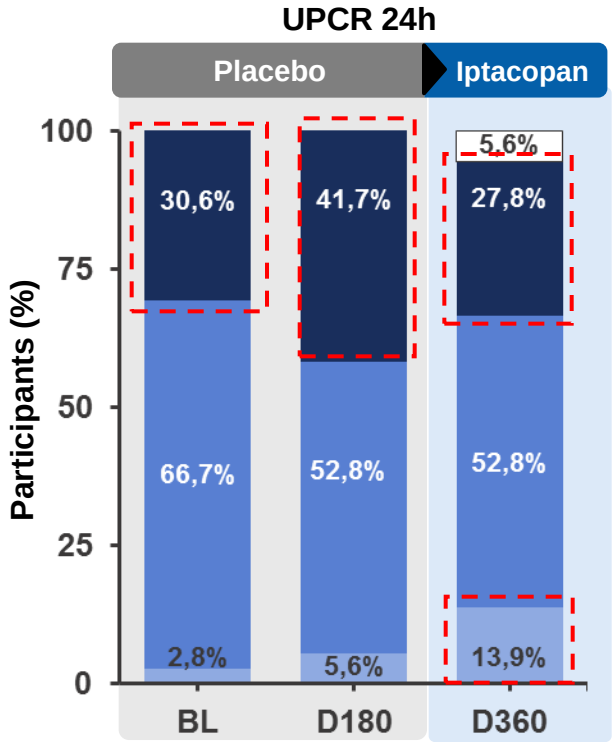
Nephrotic-range proteinuria at Month 12



- **Decrease** in participants with nephrotic range proteinuria **(UPCR ≥3 g/g)** at Month 12 (-18%)
- **Increase** in participants achieving **UPCR <1 g/g** after 12 months (+24%)



- **Increase** in participants with nephrotic range proteinuria **(UPCR ≥3 g/g)** with placebo during double-blind (+11%) with subsequent **reduction** following switch to Iptacopan in the open-label period (-14%)
- **Increase** in participants achieving **UPCR <1 g/g** after switching to Iptacopan in the open-label period (+14%)

Improvement in all UPCR categories upon initiation of iptacopan

At Day 360: decreased percentage of participants with nephrotic range proteinuria and more participants PU <1 g/g

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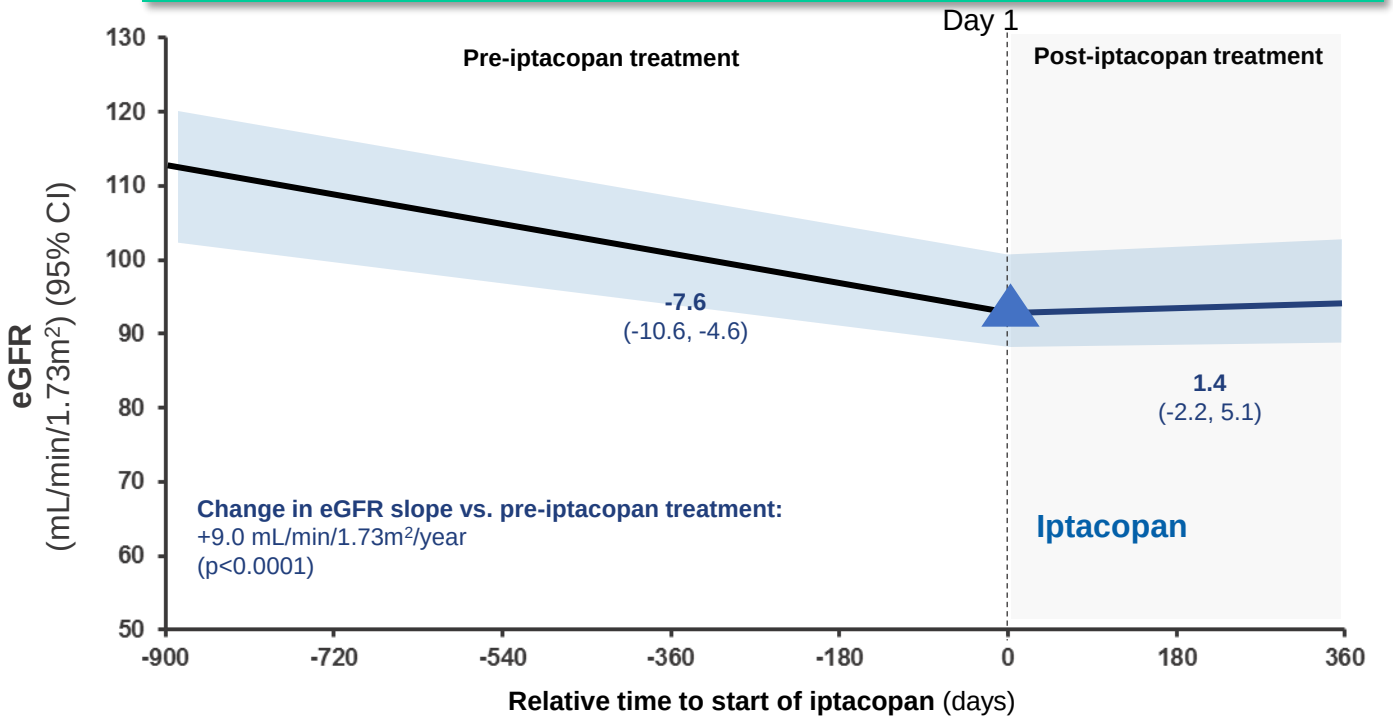
Annualized eGFR slope

eGFR slope by treatment group pre- and post-iptacopan treatment initiation up to 6 months: Overall population (N=74)



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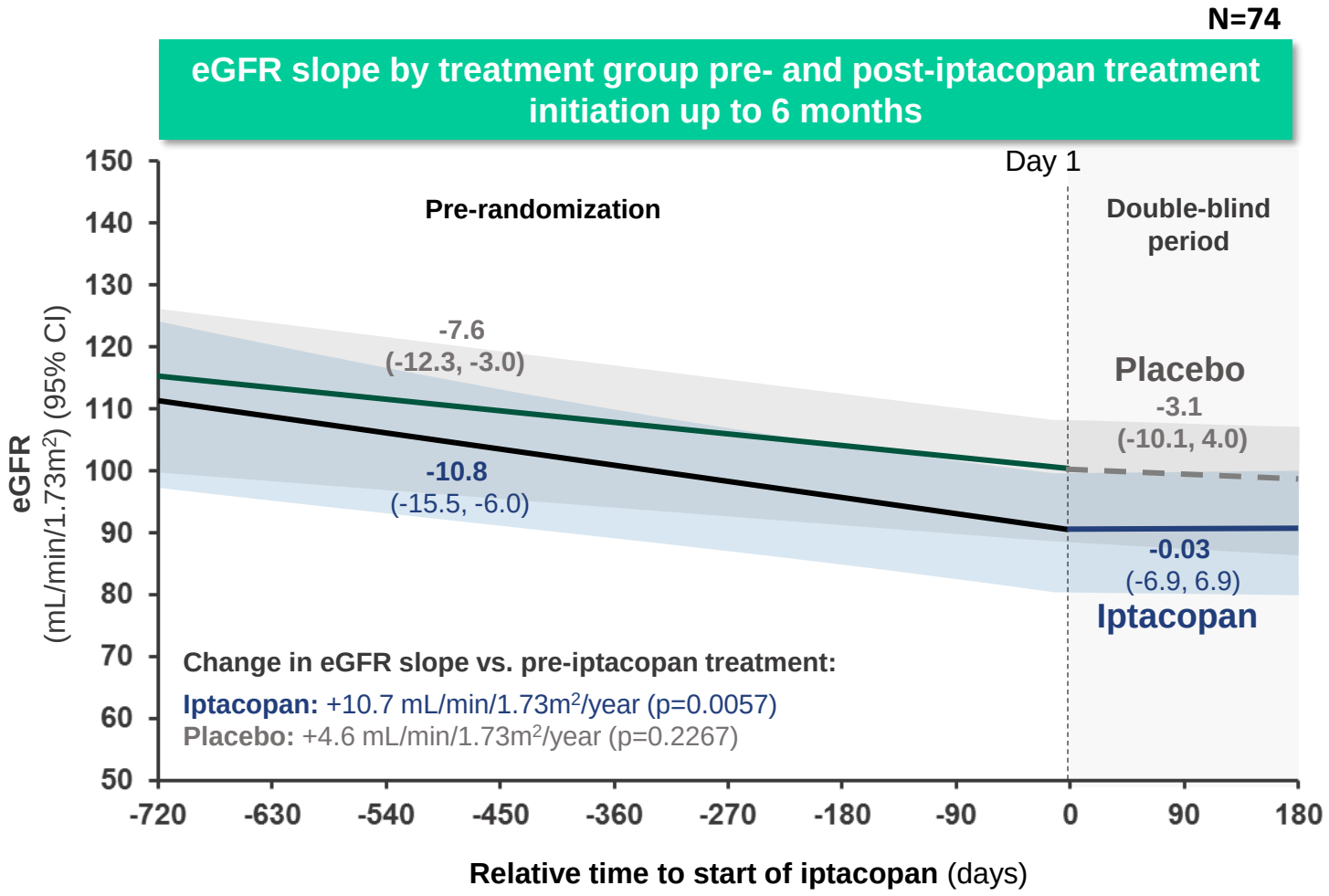
Conclusion

- Mycophenolate and steroids 1st line
- Eculizumab as a rescue therapy if acute/proliferative
- New complement inhibitors: Iptacopan and Pegcetacoplan
- Iptacopan:
  - statistically significant reduction in 24h UPCR at 6 months vs. placebo, sustained up to 12 months
  - eGFR stabilized
  - improvements in eGFR slopes up to 12 months compared to the pre-iptacopan treatment eGFR slope

Thank you for your attention !

aude.servais@aphp.fr

Annualized eGFR slope change



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