Complement Associated Glomerular Diseases

Dr Sharon Ford
Deputy Director Nephrology, Austin Health
President, Australian & New Zealand Society of Nephrology

Austin HEALTH

Acknowledgement of Country

Disclosures

- Speaker: Abbot Laboratories, Boehringer Ingelheim, Novo Nordisk, Alexion, AstraZeneca
- Advisory Board Member: CSL Seqirus, Novartis, Novo Nordisk, Roche
- Steering Committee Member: Alexion, CSL Seqirus
- Honoraria paid to Austin Health

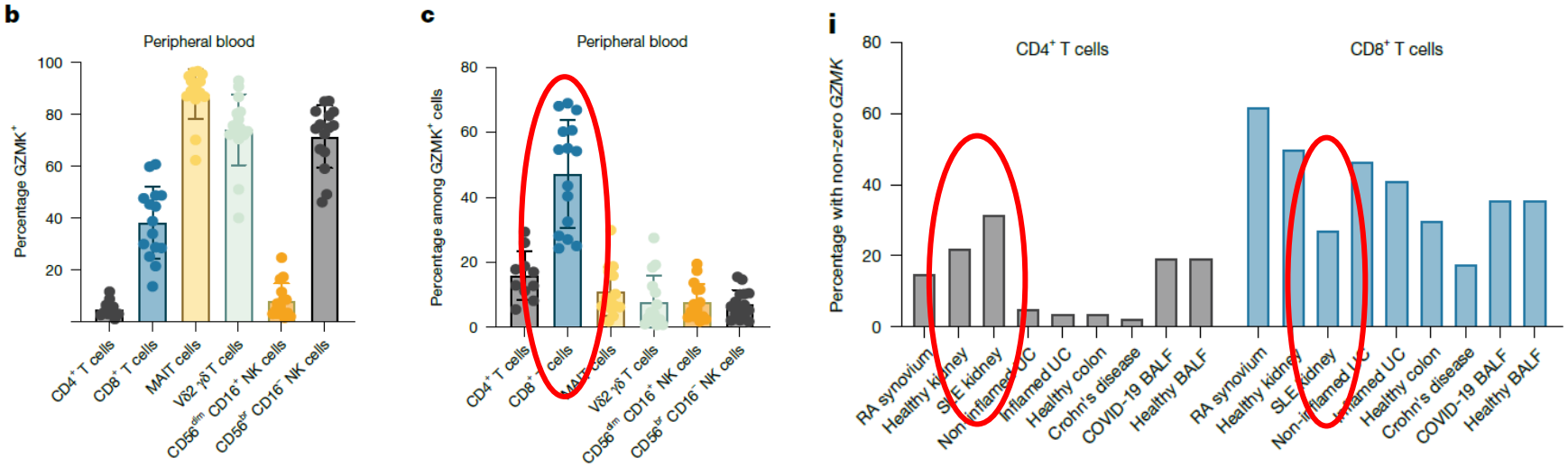
- Related to this talk:
  - Principal Investigator: Apellis Study - Pegcetacoplan in C3G & IC-MPGN
  - Advisory Board Member: Novartis - Iptacopan, APPEAR C3G Study

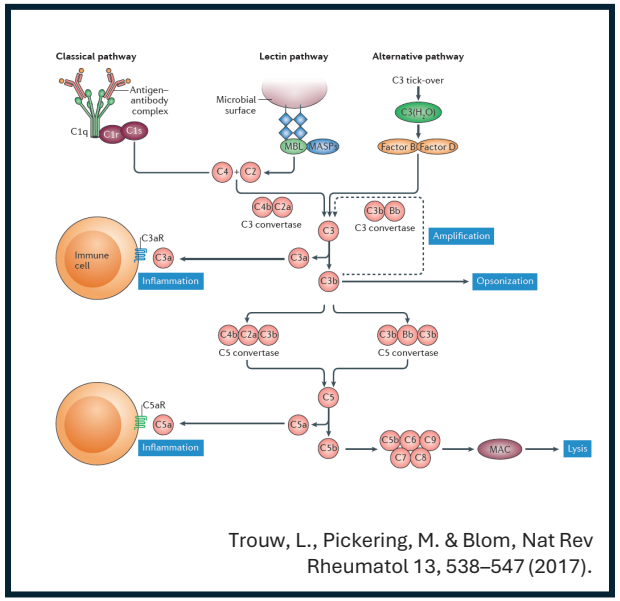
Outline

- What's new in complement biology? .... and then there were 4?
- Complement and the kidney.
- C3G & IC-MPGN – new therapies on the horizon.

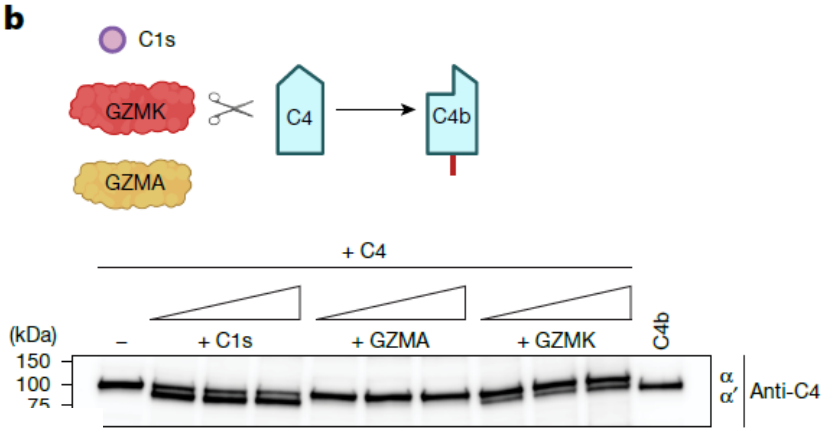
What's new in complement biology? …. and then there were 4!

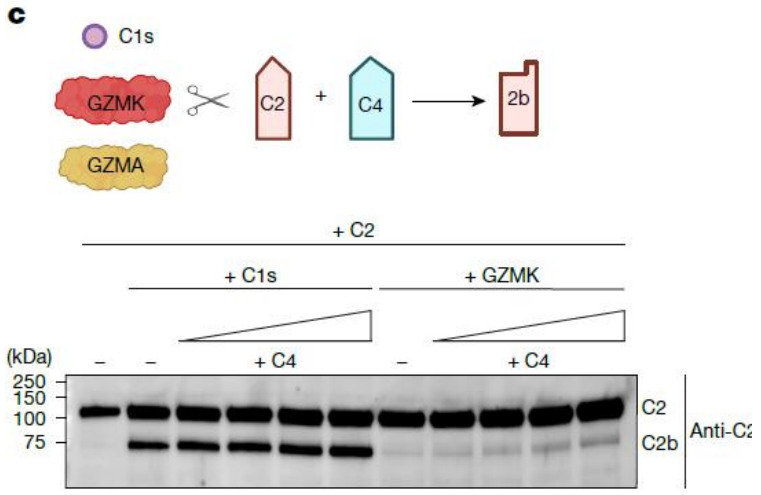
Granzyme K

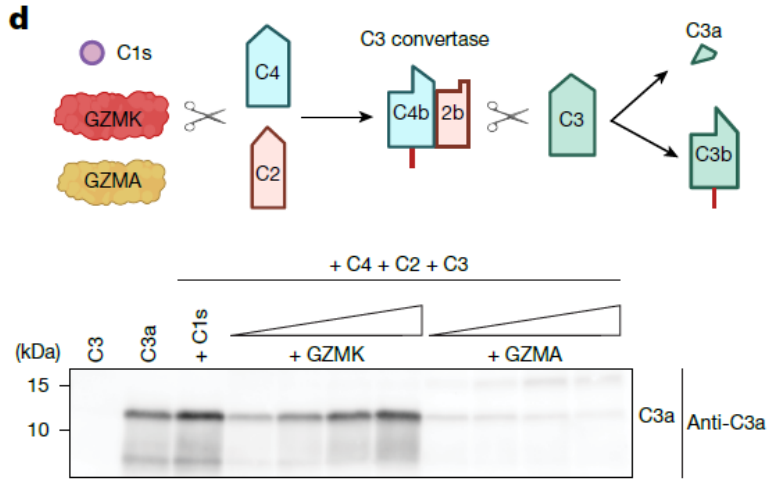




Trouw, L., Pickering, M. & Blom, Nat Rev Rheumatol 13, 538–547 (2017).

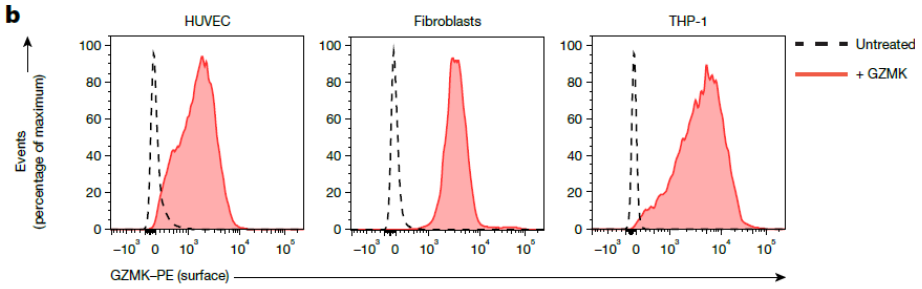


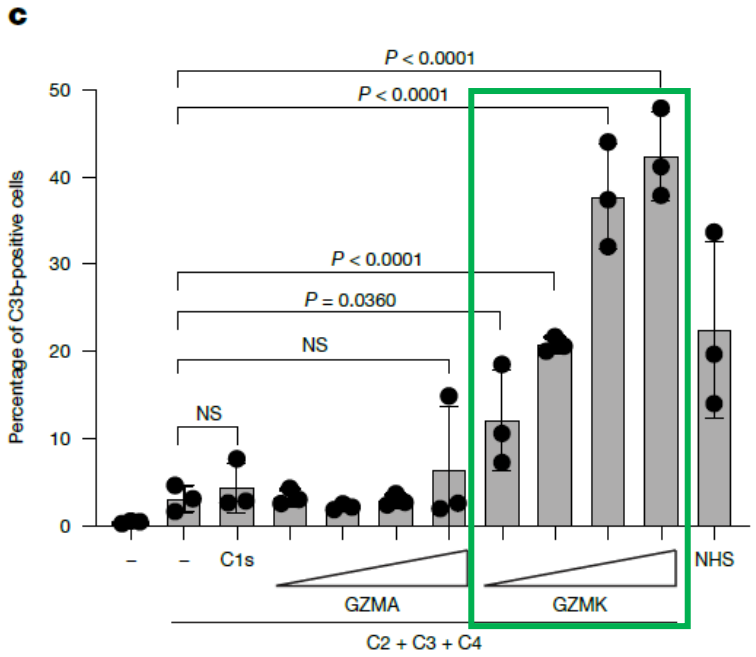


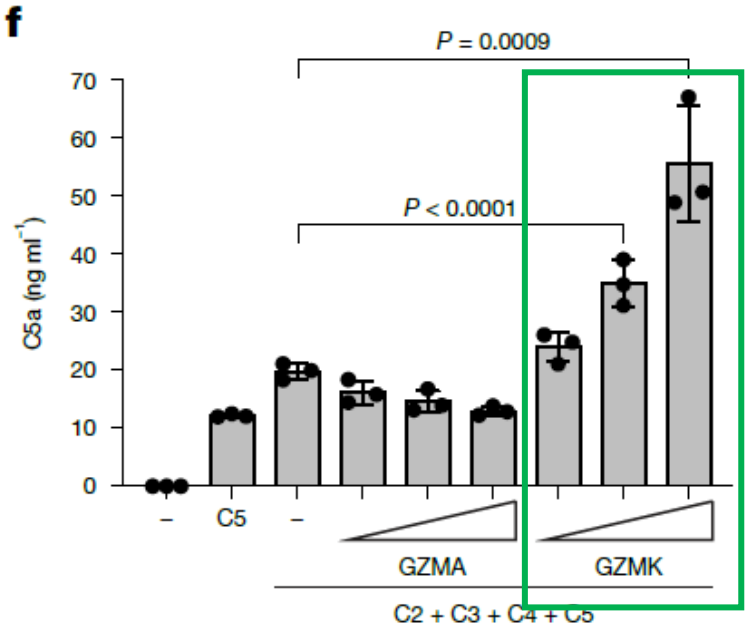


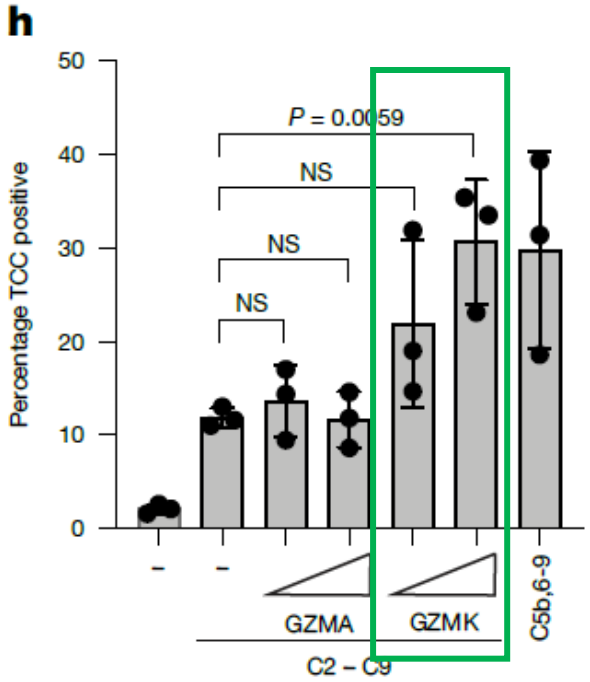
Donado, C.A. et al. Nature 641, 211–221 (2025

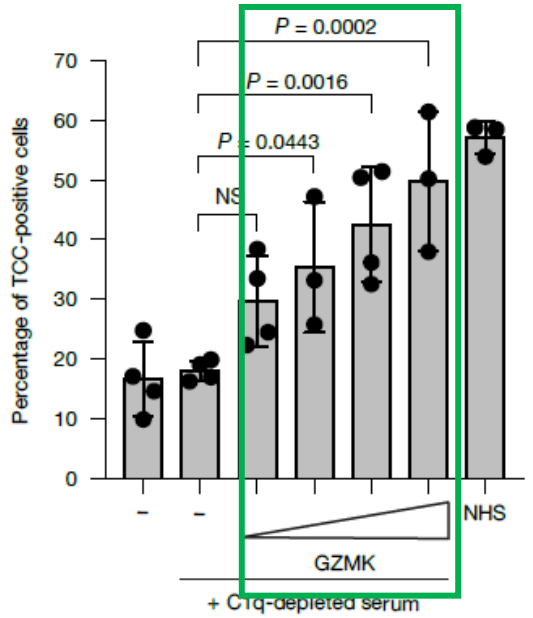
Granzyme K











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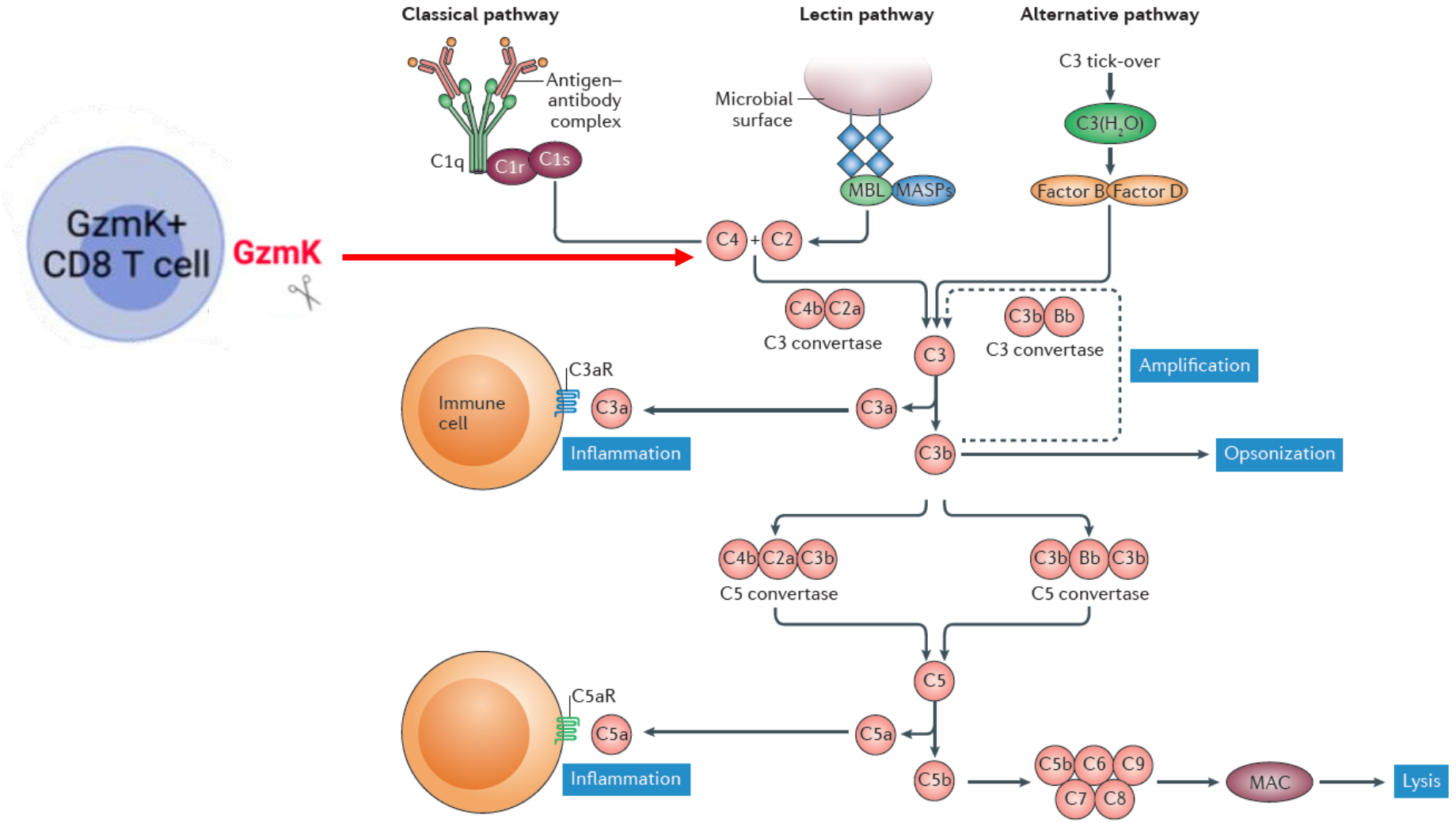
Granzyme K – and then there were 4?



Modified from
Trouw, L., Pickering, M. & Blom, Nat Rev Rheumatol 13, 538–547 (2017).

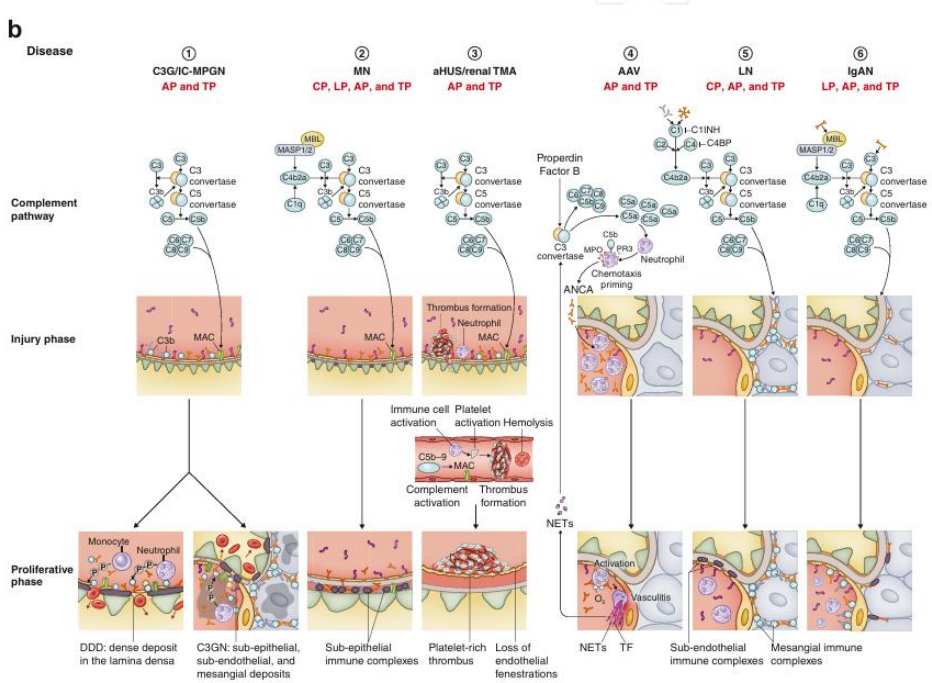
Complement and the kidney

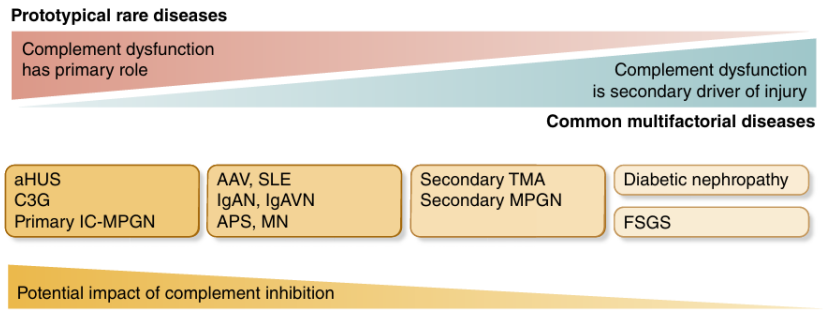
Complement and the kidney

- The kidney is a prime target for complement dysregulation
- Why?
  - High concentrations of complement proteins in close proximity to the glomerular basement membrane
  - Fenestrae in glomerular endothelial cells may increase access to the glomerular basement membrane for complement proteins
  - Glomerular basement membrane does not express intrinsic complement regulators
- Emerging evidence for the role of complement in both causation and progression of a broad range of glomerular kidney diseases

Complement in glomerular diseases

- C3G/IC-MPGN
- CM-TMA (aHUS)
- Roles for complement in:
  - Membranous Nephropathy
  - ANCA Associated Vasculitis
  - Lupus Nephritis
  - IgAN/IgAV
  - APLS
  - FSGS
  - Diabetic Kidney Disease

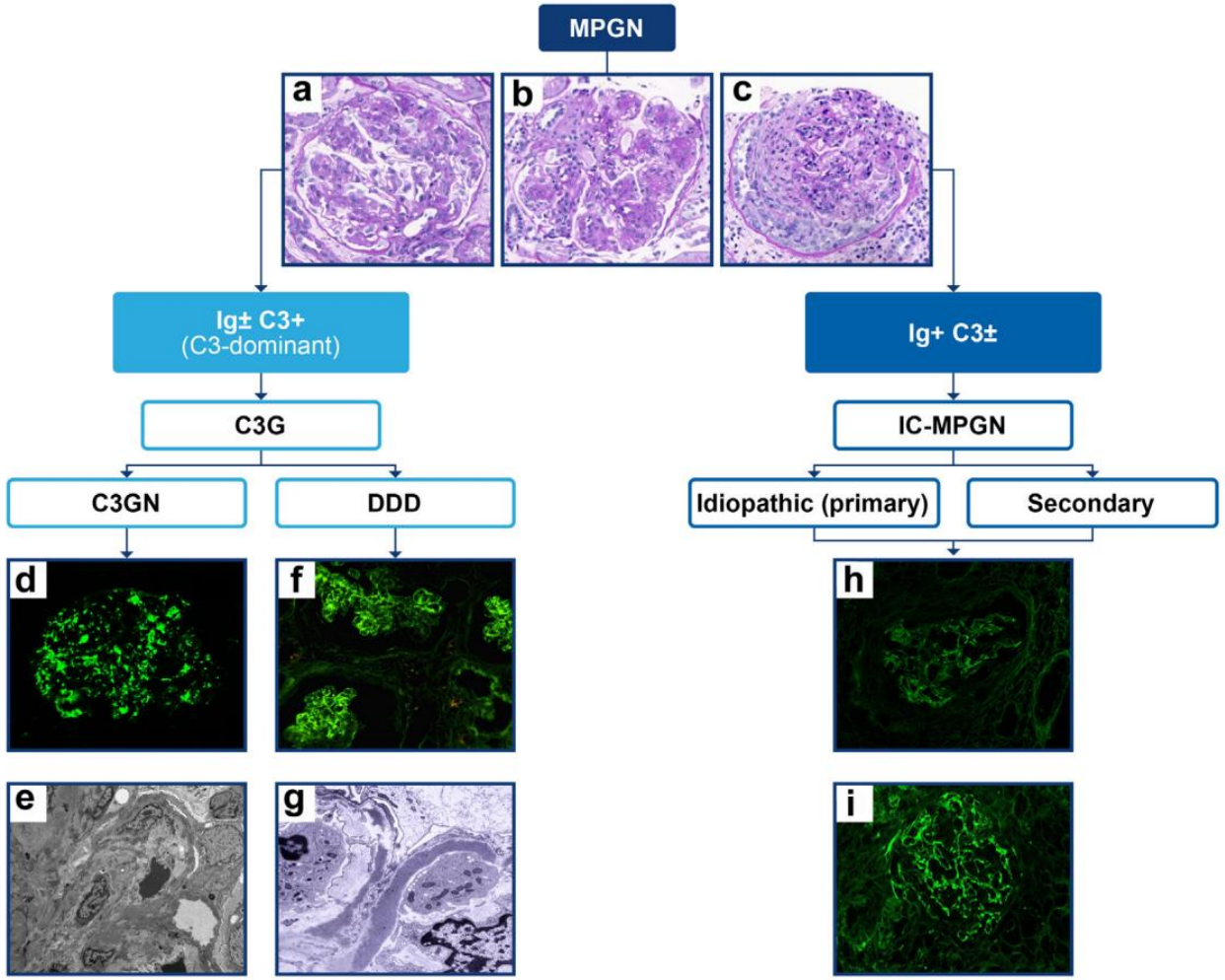




Vivarelli. et al. Kidney Int 106: 369-391 (2024)

C3G/IC-MPGN
new therapies on the horizon

C3G & IC-MPGN Histological Classification



Bomback et al. KI Reports (2024)10(1):17-18

UK RADAR Registry

Table 1 | Baseline demographics and outcomes

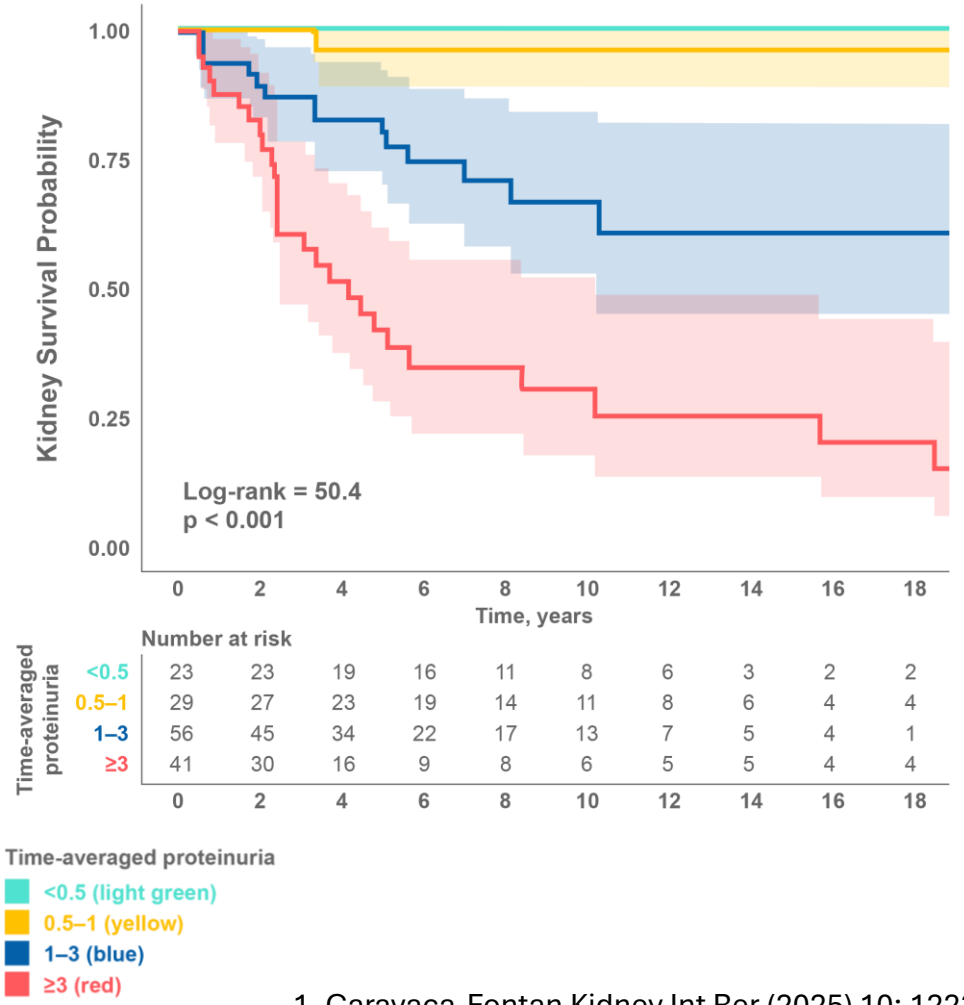
	C3G					
	C3GN		DDD		IC-MPGN	
	N = 138	(%)	N = 65	(%)	N = 168	(%)
Age at diagnosis, yr, n	138		65		168	
Median (IQR)	24 (14–46)		14 (10–34)		25 (10–54)	
Pediatric (<18 yr)	50	(36)	41	(63)	73	(43)
Sex, n	138		65		168	
Female	54	(39)	31	(48)	81	(48)
Ethnicity, n	126		58		157	
White	113	(90)	47	(81)	139	(89)
Median follow up duration, n	138		65		168	
Median (IQR), yr	10.6 (9.4–11.2)		10.6 (8.9–18.0)		12.0 (7.5–15.6)	
Serum albumin at diagnosis, n	60		38		92	
Mean (SD), g/l	32 (10)		29 (8)		28 (8)	
Complement C3 levels at diagnosis, n	48		27		45	
Median (IQR), g/l	0.41 (0.20–1.01)		0.36 (0.12–0.73)		0.64 (0.17–0.94)	
Complement C4 levels at diagnosis, n	48		26		44	
Median (IQR), g/l	0.25 (0.16–0.33)		0.22 (0.15–0.31)		0.14 (0.09–0.25)	

	eGFR and proteinuria analysis population	
	C3G (C3GN/DDD)	IC-MPGN
	N = 44	N = 47
UPCR, mg/mmol, median (IQR)		
Diagnosis	532 (301–915)	581 (310–847)
6 mo	148 (81–312)	130 (44–295)
12 mo	117 (55–321)	102 (25–360)
eGFR at diagnosis, ml/min per 1.73 m^2		
Median (IQR)	70 (40–94)	73 (41–114)

Masoud et al. Kidney Int (2025) 108(3):455-69

Sustained proteinuria >1g/d predicts eGFR decline

- Sustained proteinuria (>1 g/day) is associated with accelerated eGFR decline and an elevated risk of progression to kidney failure[1]
- While single baseline proteinuria measurements may fluctuate, **persistent or time-averaged proteinuria provides a stronger prognostic signal of ongoing disease activity and poor renal outcomes**[1,2]
- In combination with histopathological findings, longitudinal proteinuria trajectories more accurately reflect long-term risk and disease progression[1,2]



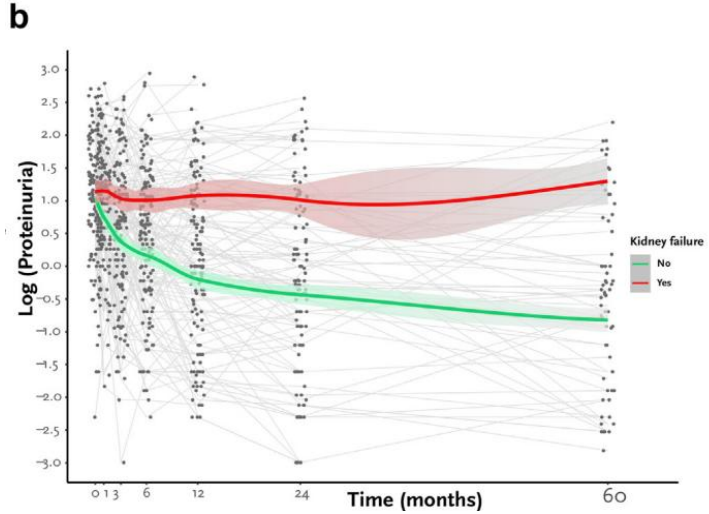
1. Caravaca-Fontan Kidney Int Rer (2025) 10: 1223-1236

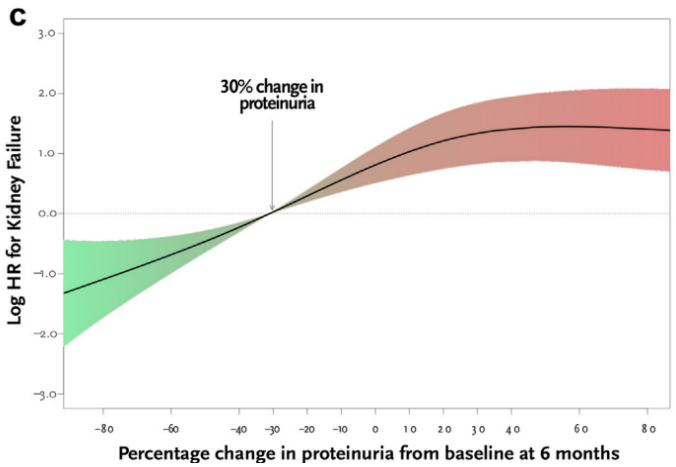
2. Masoud et al. Kidney Int (2025) 108(3):455-69

Reducing proteinuria improves kidney outcomes

- **Early reductions in proteinuria** are strongly associated with improved outcomes:
  - ≥30% fall at 6 months → slower eGFR decline[1]
  - ≥50% fall at 12 months → significantly lower kidney failure risk[1]

- **Threshold effects:**
  - uPCR <100 mg/mmol at 12 months → ~90% lower risk of kidney failure (RaDaR)[2]
  - Sustained proteinuria <1 g/day → best long-term kidney survival[1]





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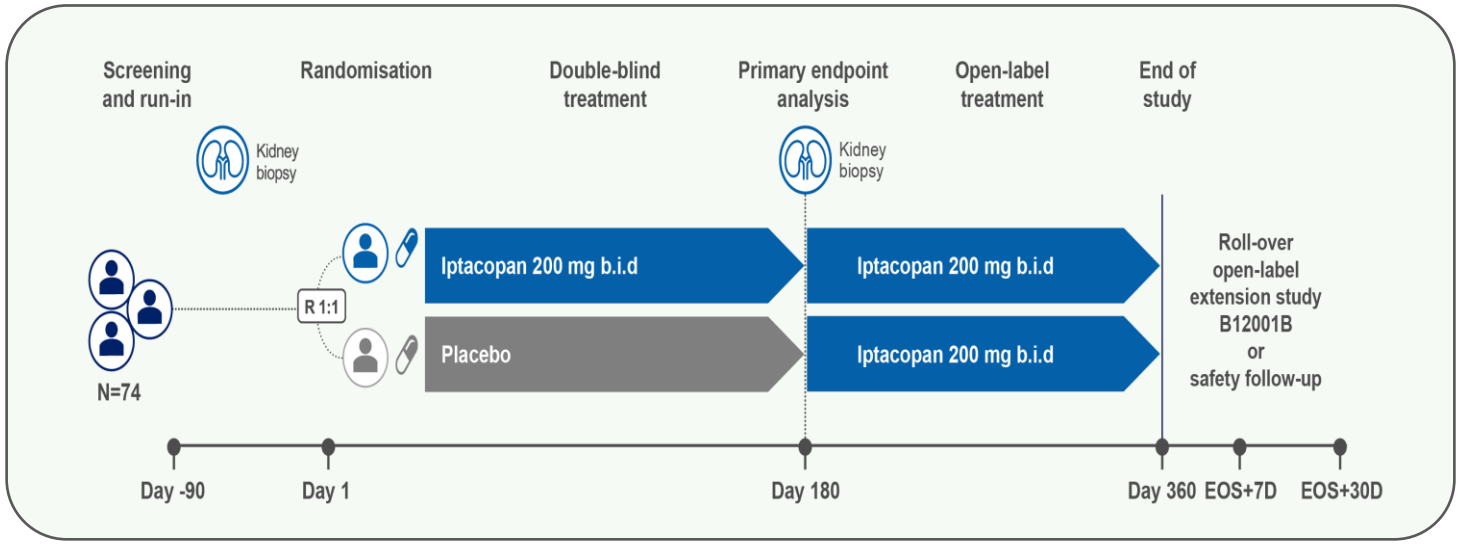
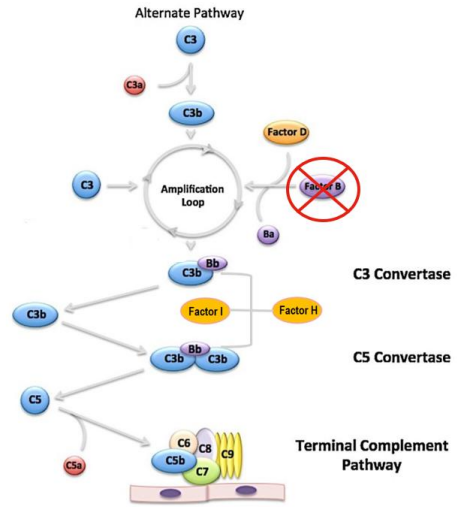
APPEAR C3G – Iptacopan



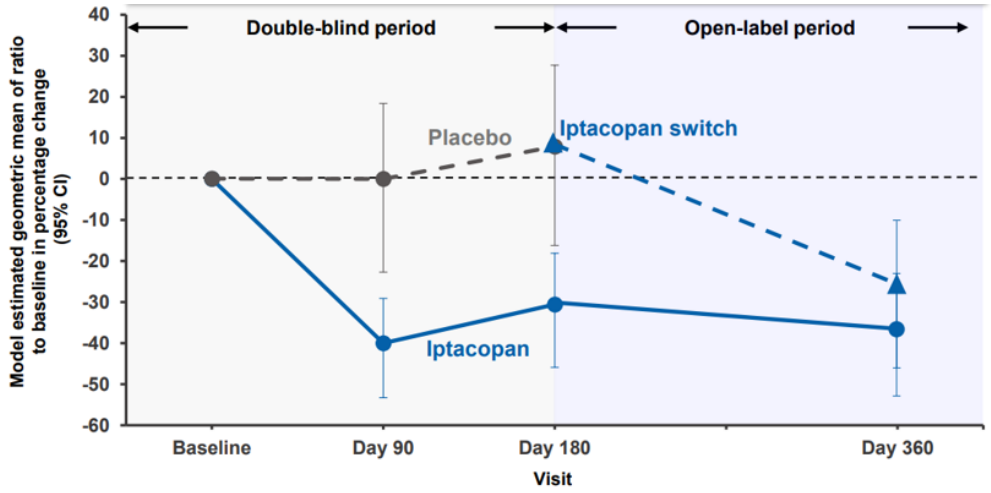


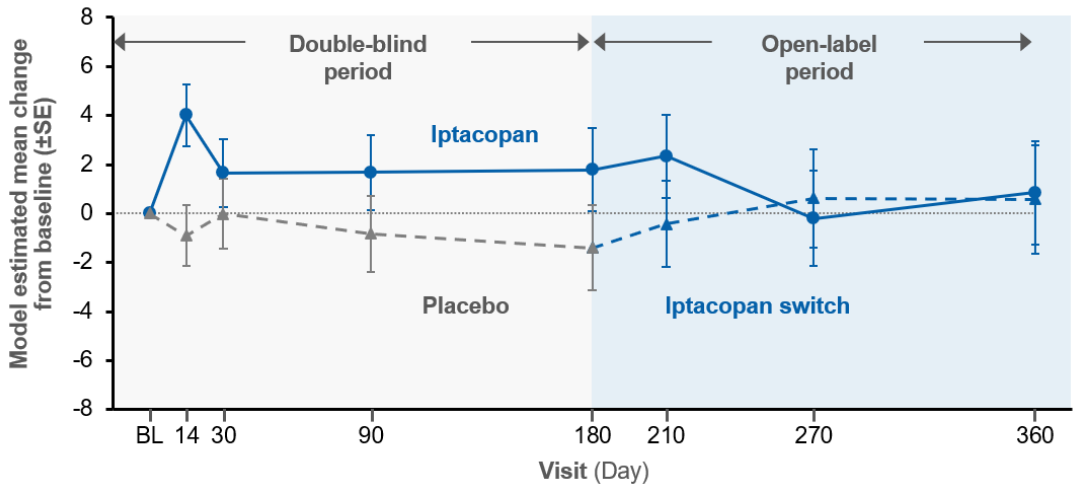
Characteristic		Iptacopan N=38, n	Placebo N=36, n
Baseline UPCR (24h) [g/g] geo-mean (95% CI)		**3.33 (2.79–3.97)**	**2.58 (2.18–3.05)**
Baseline total urinary protein (24h), n (%)	**≥3 g/day**	27 (71.1)	21 (58.3)
Baseline UPCR (24h), n (%)	**≥3 g/g (339 mg/mmol)**	21 (55.3)	11 (30.6)
Baseline eGFR [mL/min/1.73 m²], mean (SD)		**89.3 (35.2)**	**99.2 (26.9)**
Baseline eGFR, n (%)	**< 90 mL/min/1.73 m²**	19 (50.0)	12 (33.3)
Baseline eGFR, n (%)	**< 60 mL/min/1.73 m²**	10 (26.3)	4 (11.1)
Hypertension, n (%)		23 (60.5)	18 (50.0)
Age at C3G diagnosis, n (%)	**<18 years**	15 (39.5)	6 (16.7)
Time since first C3G diagnosis, n (%)	**<2 years**	15 (39.5)	15 (41.7)
Baseline RASi use, n (%)		36 (94.7)	35 (97.2)
Corticosteroid and/or mycophenolic acid treatment at randomisation	**Yes**	16 (42.1)	17 (47.2)
C3G subtype at diagnosis, n (%)	**C3GN** **DDD** **Mixed C3GN/DDD**	26 (68.4) **9 (23.7)** 2 (5.3)	32 (88.9) **1 (2.8)** 2 (5.6)

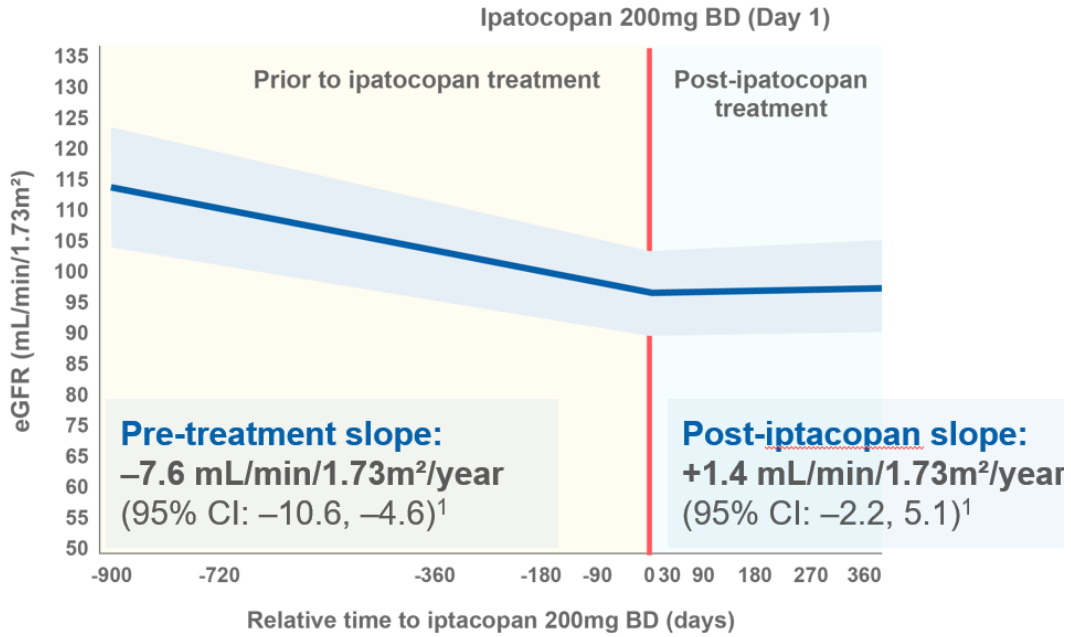
NOVARTIS | Reimagining Medicine

Reference: 1. Smith RJH et al. at The American Society of Nephrology (ASN) Kidney Week 2024; 23–27 October 2024; San Diego, CA, USA (abstract SA-OR66).

Iptacopan - sustained proteinuria reduction and improvement in eGFR slope at 52 weeks in C3G







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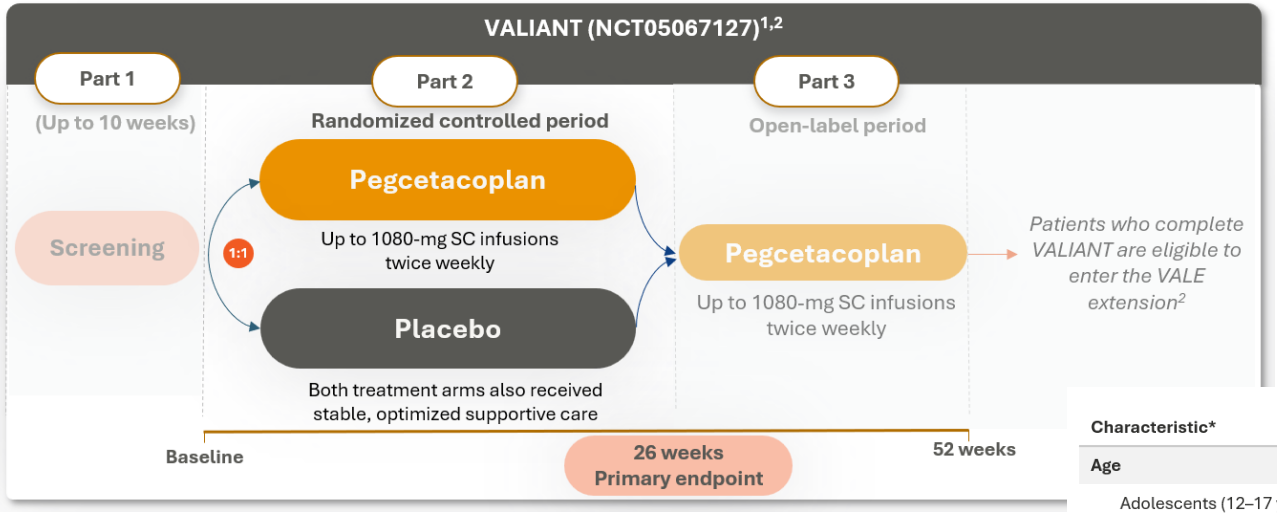
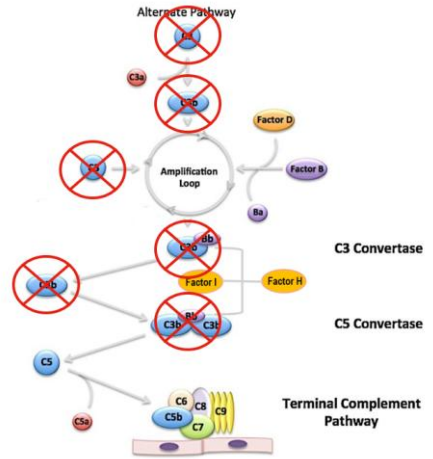
VALIANT – Pegcetacoplan





Characteristic*	Pegcetacoplan (N=63)	Placebo (N=61)
Age	28.2 (17.1)	23.6 (14.3)
Adolescents (12–17 years)/adults (≥18 years), n (%)	**28 (44.4)**/35 (55.6)	**27 (44.3)**/34 (55.7)
Age of adolescents/adults, mean (SD), years	14.6 (1.7)/39.1 (15.9)	14.8 (1.7)/30.6 (15.9)
Sex, female, n (%)	37 (58.7)	33 (54.1)
Race, white, n (%)	45 (71.4)	46 (75.4)
Baseline 24 h uPCR, mean (SD), g/g	3.95 (2.89)	3.29 (2.36)
Baseline triplicate first-morning spot uPCR, mean (SD), g/g	3.12 (2.41)	2.54 (2.01)
Baseline eGFR, mean (SD), mL/min/1.73 m²	78.5 (34.1)	87.2 (37.2)
Underlying disease based on screening biopsy, n (%)		
C3G	**51 (81.0)**	**45 (73.8)**
C3GN	45 (71.4)	41 (67.2)
DDD	4 (6.3)	4 (6.6)
Undetermined	2 (3.2)	0 (0.0)
Primary IC-MPGN	**12 (19.0)**	**16 (26.2)**
Time since diagnosis, mean (SD), years	3.6 (3.5)	3.8 (3.6)
Post-transplant recurrent disease, n (%)	**5 (7.9)**	**4 (6.6)**

*Intention-to-treat population (all randomised patients).
C3G, complement 3 glomerulopathy; C3GN, complement 3 glomerulonephritis; DDD, dense deposit disease; eGFR, estimated glomerular filtration rate; h, hour; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; SD, standard deviation; uPCR, urine protein-to-creatinine ratio.
Nester CM, *et al*. Presented at American Society of Nephrology Kidney Week 2024 (Oral SA-OR92).

Pegcetacoplan - sustained proteinuria reduction and stable eGFR at 52 weeks in C3G + IC-MPGN

VALIANT study in patients aged ≥12 years with native or post-transplant recurrent C3G/ primary IC-MPGN

Proteinuria reduction:
67% reduction in patients receiving 52 weeks of pegcetacoplan

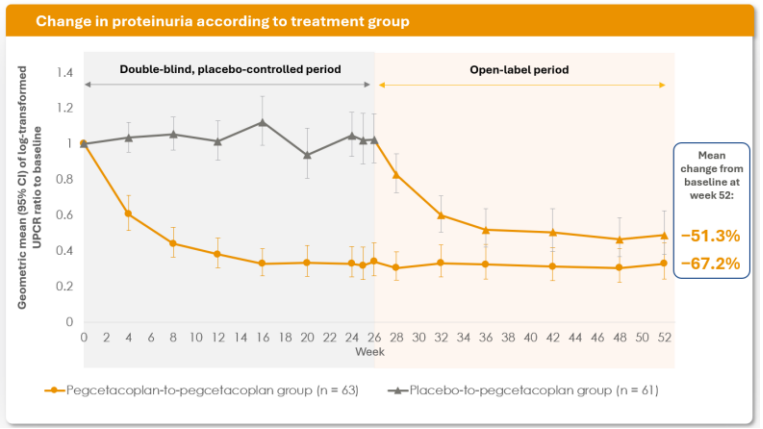
Proteinuria reduction

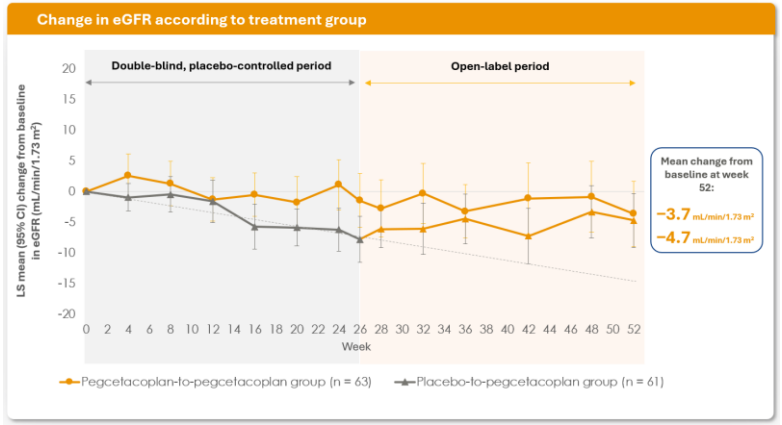
eGFR:
stabilization of eGFR
-3.7 mL/min/1.73 m² change from baseline with 52 weeks of pegcetacoplan

Histopathology improvement

eGFR stabilization/ improvement

Histopathology improvement:
glomerular C3 clearance in 71% of patients (zero staining) at week 26





Fakhouri et al at ERA, Vienna; June 2025

Summary,

- Granzyme K mediated provides a 4th pathway of complement activation.
- Complement and the kidney.
- C3G & IC-MPGN – targeted therapies on the horizon.