FIRST REPORT MANAGED CARE

OPTIMIZING IGA NEPHROPATHY OUTCOMES

Managed Care Considerations for Novel Dual BAFF/APRIL Disease-Modifying Therapies

Faculty

Russell Spjut, PharmD

Clinical Strategy Director
SmithRx

Matthew R. Weir, MD

Professor and Director
Division of Nephrology
University of Maryland School of Medicine

Disclosures

- **Russell Spjut, PharmD** has nothing to disclose
- **Matthew R. Weir, MD:** Advisory board – AstraZeneca, Bayer, CSL Vifor, Boehringer-Ingelheim, NovoNordisk, Mineralys, Vera

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References

Learning Objectives

- Evaluate the clinical and economic burden of IgAN, including the limitations of symptom-directed/conventional therapies on patients, healthcare systems, and payers
- Analyze the efficacy, safety, and mechanisms of action of novel dual BAFF/APRIL B-cell–directed therapies for the treatment of IgAN
- Develop strategies to enhance multidisciplinary care coordination and improve timely access to novel IgAN therapies

IgAN = IgA nephropathy; BAFF = B-cell activating factor; APRIL = a proliferation-inducing ligand.

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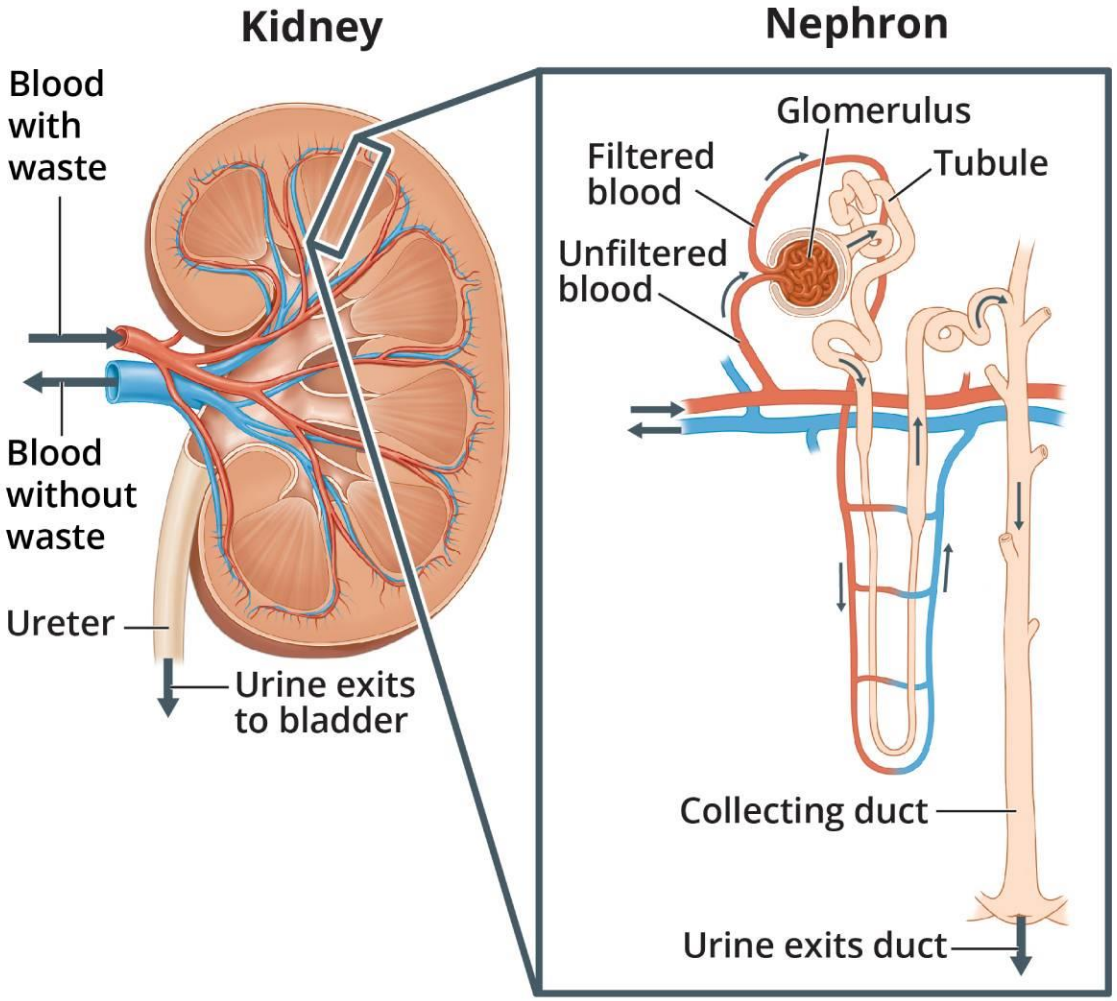
Managed Care Introduction

Russell Spjut, PharmD

What Is IgA Nephropathy?



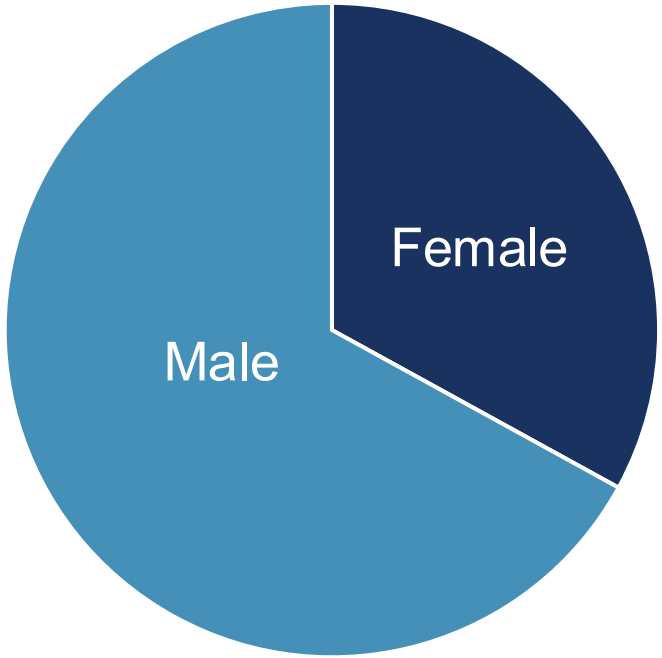
- An immune-mediated kidney disease in which IgA-containing immune complexes deposit in the glomeruli
- These deposits lead to damage of the glomeruli causing leakage of blood and proteins into the urine
- Damage progresses including scaring, progressive loss of kidney function, and eventual end stage renal disease

Rovin BH, et al. *Kidney Int.* 2025;108(4):S1-S71. Image: National Institute of Health (NIH). https://www.niddk.nih.gov/-/media/Images/Health-Information/Kidney/Kidney_Nephron_FINAL-NEW-SIZE_W-MOD.jpg

Burden of IgA Nephropathy: Epidemiology

- IgAN is considered the most common primary glomerular disease worldwide
- Current data gives an estimate of 200,000 patients in the US living with IgAN
- Annual incidence has been reported between 1.3 to 2.2 per 100,000 people
  - Enough that most managed care organizations will see members diagnosed in a given year
  - Just low enough that it is unlikely to be a regular topic for review
- Average age of diagnosis lands in the late 30s to early 40s

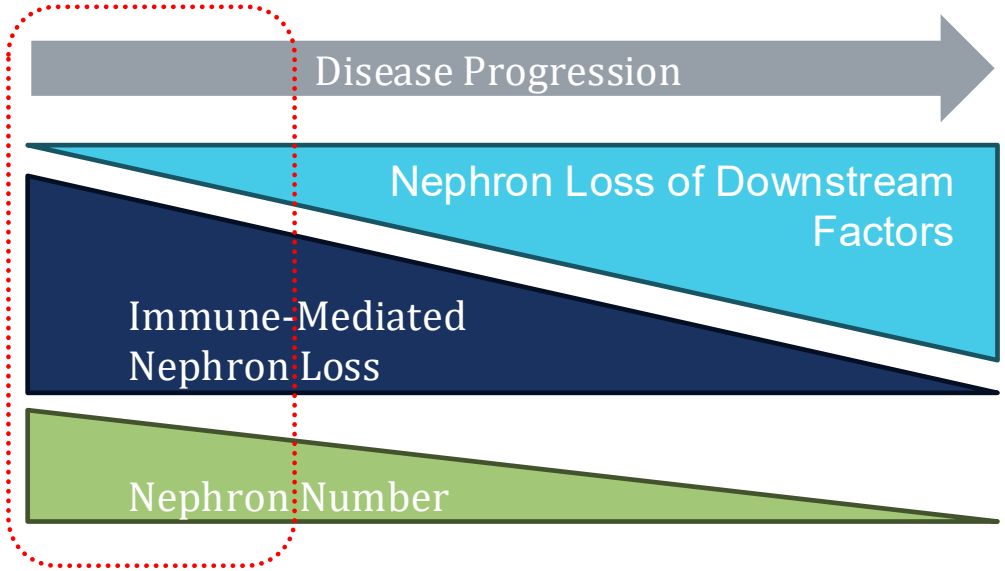
Proportion of Patients by Sex



About more than twice as common among males than females

DeCongelio M, et al. *Clin Nephrol*. 2025;103(1):19-25. Rovin BH, et al. *Kidney Int*. 2025;108(4):S1-S71. Institute for Clinical and Economical Review (ICER). Accessed April 15, 2026. https://icer.org/assessment/iga-nephropathy-2025/

Burden of IgA Nephropathy: Progression

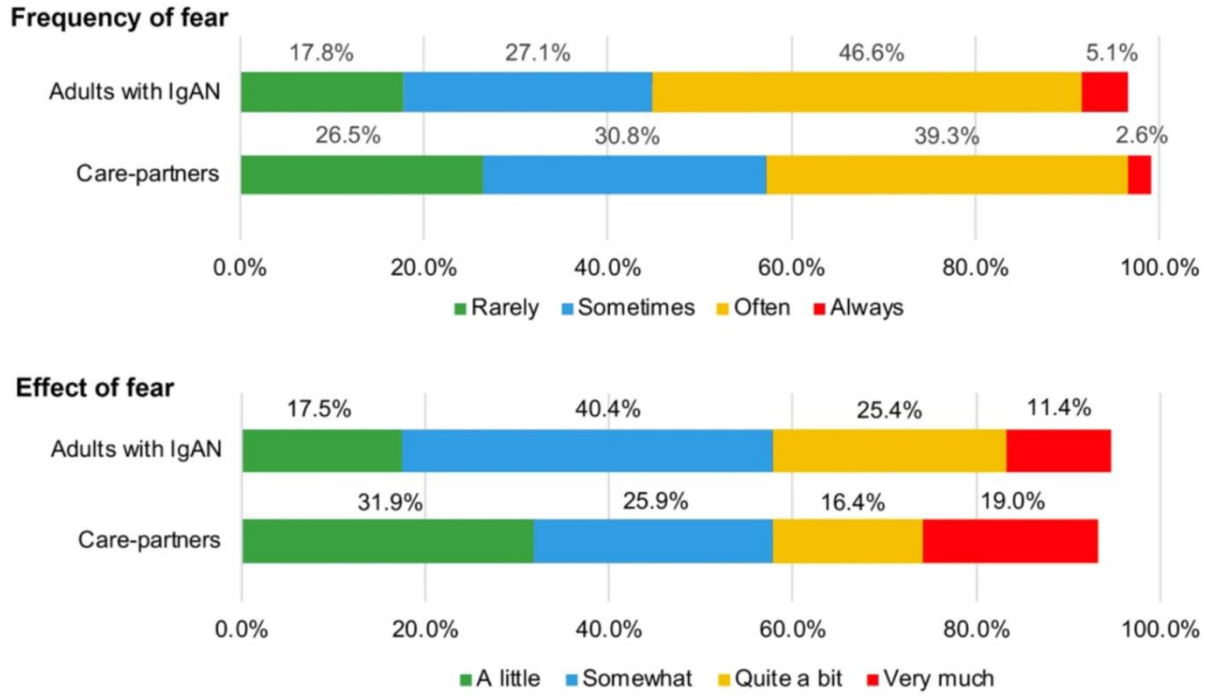


- Data shows that approximately 30-40% of patients with IgAN reach end stage renal disease (ESRD) or death within 6-10 years of diagnosis
- A majority of diagnoses occur after a decline in kidney function with average eGFR between 50-60 mL/min
- A treatment goal of slowing the decline of eGFR to < 1 mL/min/year helps avoid lifetime ESRD
  - This has often been unachievable within traditional treatment options

Szklarzewicz J, et al. *Qual Life Res*. 2025;34(2):353-363. Wheeler DC, et al. *Kidney Int.* 2021;100(1):215-224. Cheung CK, Barratt J. *Semin Nephrol*. 2024;44(5):151573. Pitcher D, et al. *Clin J Am Soc Nephrol*. 2023;18(6):727-738.

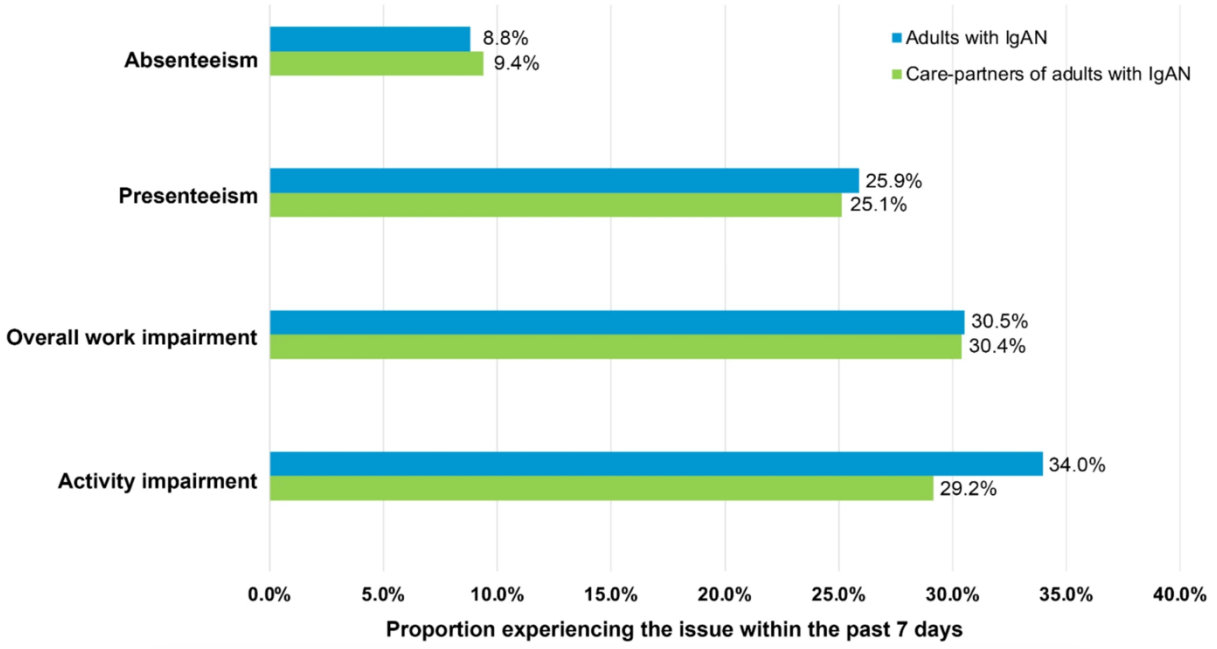
Burden of IgA Nephropathy: Patient Experience

- Very few symptoms in early disease often leads to delayed diagnosis
- Many patients experience burdensome symptoms like joint pain, facial or abdominal swelling, fatigue, and restless leg syndrome
- Mental health also a large consideration
  - Fear of diseases progression and the unknown future
  - Moderate to severe depression found in 49% of patients
  - Moderate to severe anxiety found in 27% of patients
- Burden of caregivers also found to include higher rates of depression and anxiety



Szklarzewicz J, et al. *Qual Life Res*. 2025;34(2):353-363. Rovin BH, et al. *Kidney Int*. 2025;108(4):S1-S71. Jhaveri KD, et al. Pharmacoecon Open. 2023;7(5):709-722.

Burden of IgA Nephropathy: Economic



- ICER estimates heath care costs of ESRD in patients with IgAN costs $1.3 billion annually in the US
- Avoidance of ESRD is a key factor in reducing lifetime costs by avoiding dialysis and/or kidney transplant
- With the early age of diagnosis, large impacts seen for employers
  - Directly in work related costs
  - Increased claim liability

ICER. Accessed April 15, 2026. https://icer.org/assessment/iga-nephropathy-2025/.

Key Learning Points

- IgAN is a disease of early to mid adulthood often diagnosed late as symptoms are minimal in early-stage disease
- Progression can occur rapidly with estimated 30%-40% of patients progressing to ESRD or death within 6-10 years of diagnosis
- High burden on patients and caregivers including physical and mental health related symptoms
- Large economic impact driven by both direct health care costs as well as impacts on productivity

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IgA Nephropathy: The Evolving Landscape for Treatment

Matthew R. Weir, MD

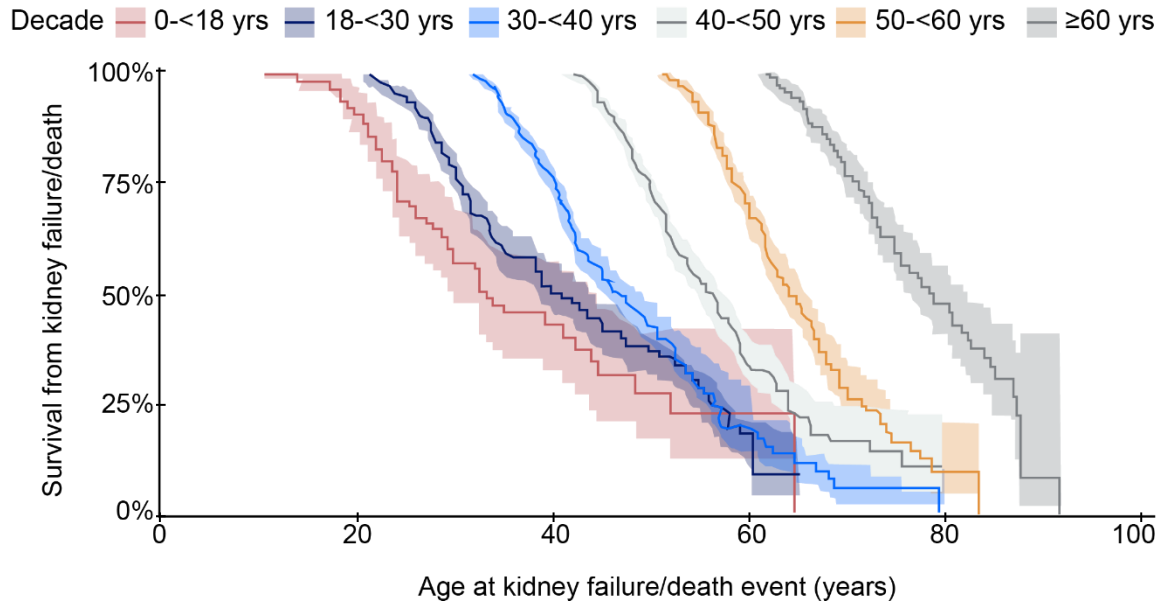
IgAN: High Unmet Need for Disease-Modifying Therapies

- IgAN is a serious B-cell-mediated autoimmune disease and is most commonly diagnosed in people aged 20-40 years
- Up to 50% of patients with IgAN progress to ESKD within 20 years of disease presentation, requiring dialysis or kidney transplant; in a UK cohort with progressive disease, most progressed to kidney failure within 10-15 years
- Current standards of care are primarily supportive CKD therapies, including ACEi and ARB, which provide limited benefit and fail to stop an unrelenting decline in kidney function
- There is a high unmet medical need for new safe and effective disease-modifying treatments that target the source of disease and can stabilize eGFR over the long term

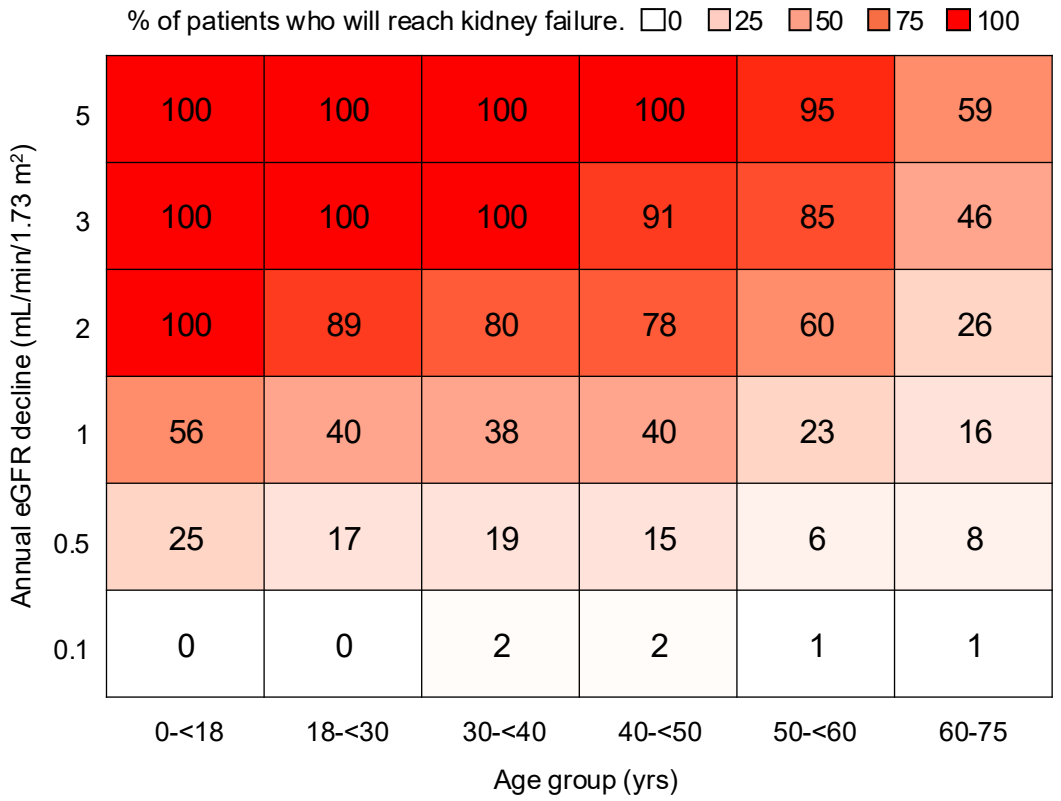
ESKD = end-stage kidney disease; CKD = chronic kidney disease; ACEi = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers; eGFR = estimated glomerular filtration rate.

Rajasekaran A, et al. *Am J Med Sci*. 2021;361:176-194. Pattrapornpisut P, et al. *Am J Kidney Dis*. 2021;78(3):429-441. Salim SA. *Medscape*. Updated February 9, 2026. Accessed April 6, 2026. https://emedicine.medscape.com/article/239927-overview#showall. Pitcher D, et al. *Clin J Am Soc Nephrol*. 2023;18:727-738.

Most Patients with IgAN Progress to ESKD within 10 to 15 Years of Diagnosis



0-<18 yrs	140	95	16	2	0	0
18-<30 yrs	521	520	99	8	0	0
30-<40 yrs	576	576	350	21	0	0
40-<50 yrs	532	532	532	60	0	0
50-<60 yrs	388	388	388	206	2	0
≥60 yrs	282	282	282	282	41	0



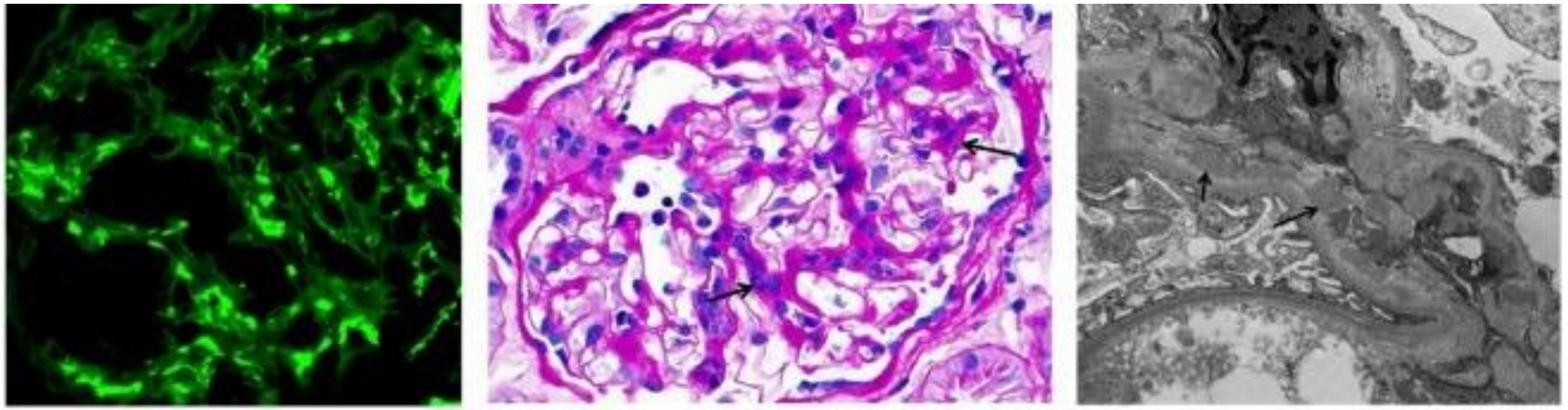
Emerging treatment goal for IgAN: Reduce rate of loss of kidney function to <1 mL/min/yr for the rest of the patient's life

Pitcher D, et al. *Clin J Am Soc Nephrol*. 2023;18:727-738.

Renal Biopsy Findings in IgAN Are Characterized by Mesangial IgA-Containing Immune Complexes

- IgAN, also referred to as Berger disease, was first described in 1968 by Jean Berger (pathologist, France) and Nicole Hinglais (electron microscopist, France)

Examples of Microscopy Features of Renal Biopsy Specimens From Patients With IgAN



Berger J, et al. *J Urol Nephrol*. 1968;74(9);694-695. Rout P, Afzal M. In: StatPearls [Internet]. StatPearls Publishing; 2024. Accessed April 6, 2026. https://www.ncbi.nlm.nih.gov/books/NBK538214/. Feehally J, et al. *Kidney Int*. 2011;80:437-438. Rajasekaran A, et al. *Am J Med Sci*. 2021;361:176-194. Knoppova B, et al. *Front Immunol*. 2016;7(117):1-25.

IgAN: Histopathology (MEST-C)

Mesangial hypercellularity ≥4 mesangial cells in any mesangial area of a glomerulus	**Endocapillary hypercellularity** An increased number of cells in glomerular capillary lumen	**Segmental glomerulosclerosis** Adhesion or sclerosis not involving the entire glomerulus	**Tubular atrophy/ interstitial fibrosis** The percentage of tubular atrophy/interstitial fibrosis of cortical area	**Cellular/ fibrocellular crescents** Extracapillary cell proliferation >2 cell layers thick and <50% matrix
M0 ≤50% of glomeruli	**E0** Absence	**S0** Absence	**T0** 0-25%	**C0** Absence
M1 >50% of glomeruli	**E1** Any presence	**S1** Any presence	**T1** 26-50%	**C1** <25% of glomeruli
			T2 ≥50%	**C2** >25% of glomeruli

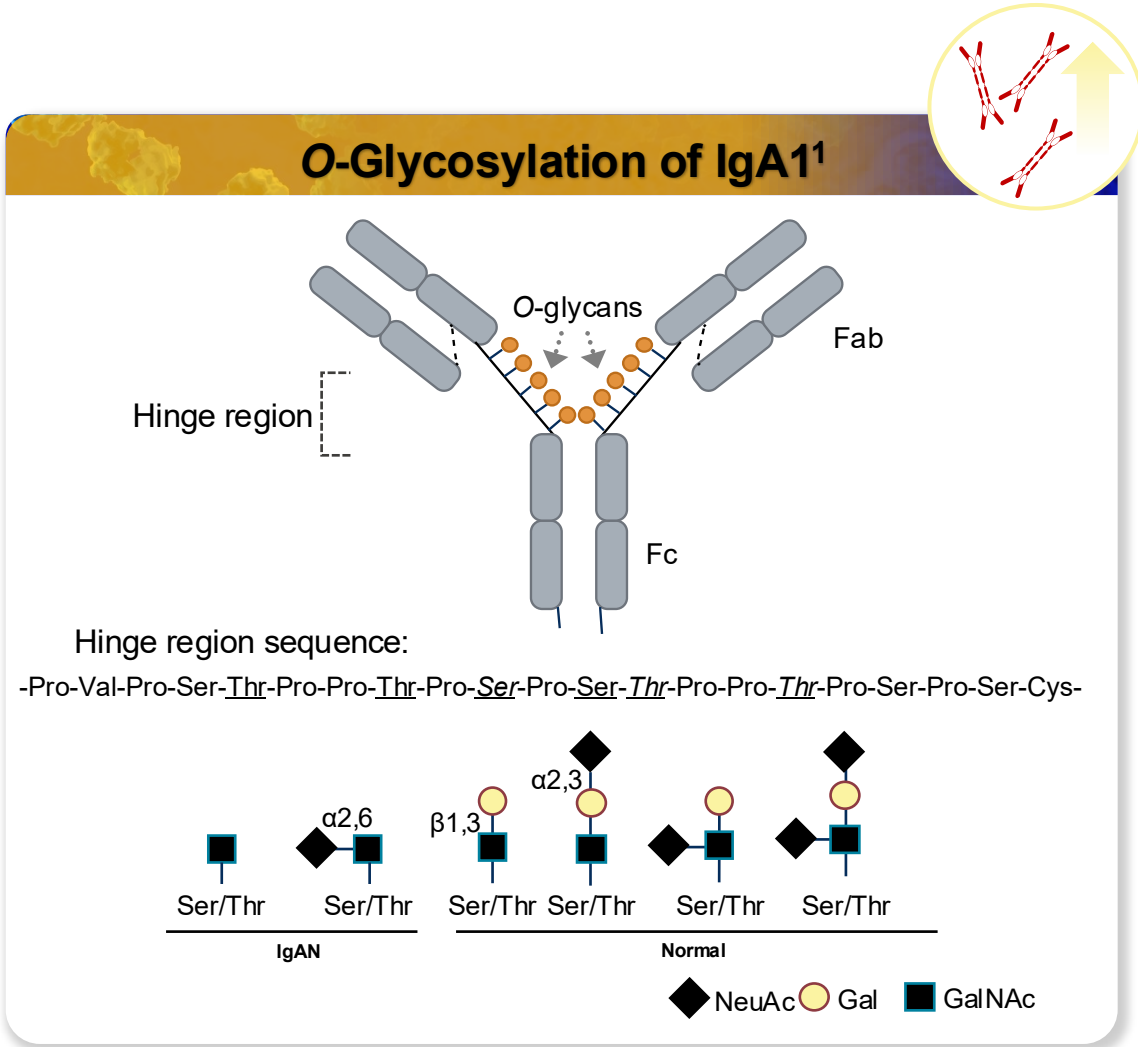
The MEST-C score offers valuable insight, serving to evaluate the risk of progression to kidney failure

MEST-C = mesangial hypercellularity, endocapillary hypercellularity, segmental glomerulosclerosis, tubular atrophy/interstitial fibrosis, and cellular/fibrocellular crescents.

Pattrapornpisut P, et al. *Am J Kidney Dis*. 2021;78(3):429-441. Cattran DC, et al. *Kidney Int Rep*. 2023;8(12):2515-2528. AJKDblog. Accessed March 30, 2026. https://ajkdblog.org/2023/03/01/nephmadness-2023-iga-nephropathy-region/#prettyPhoto.

Gd-IgA1 and Its Autoantibody Are Required for IgAN Disease

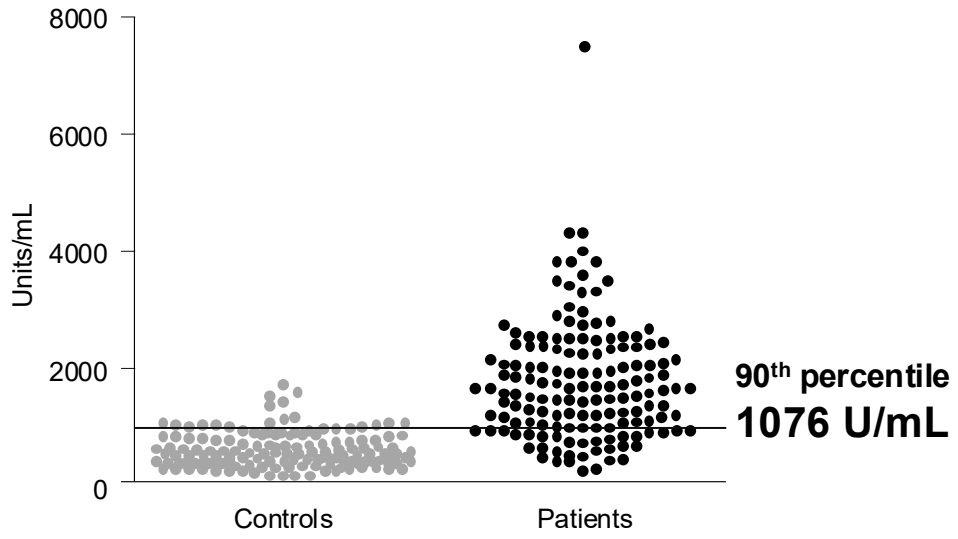
- Gd-IgA1 is a pathogenic form of IgA1 produced by plasma cells
- Gd-IgA1 is characterized by altered glycosylation at the hinge region
- The proportion of Gd-IgA1 compared to total IgA is increased in patients with IgAN
- Recognition of Gd-IgA1 by IgG autoantibodies results in the formation of nephritogenic immune complexes
  - Circulating and mesangial immune complexes contain predominantly polymeric Gd-IgA1 as well as IgG autoantibodies and C3



Ohyama Y, et al. *J Clin Med*. 2021;10(16):3467. Lai KN, et al. *Nat Rev Dis Primers*. 2016;2:16001.

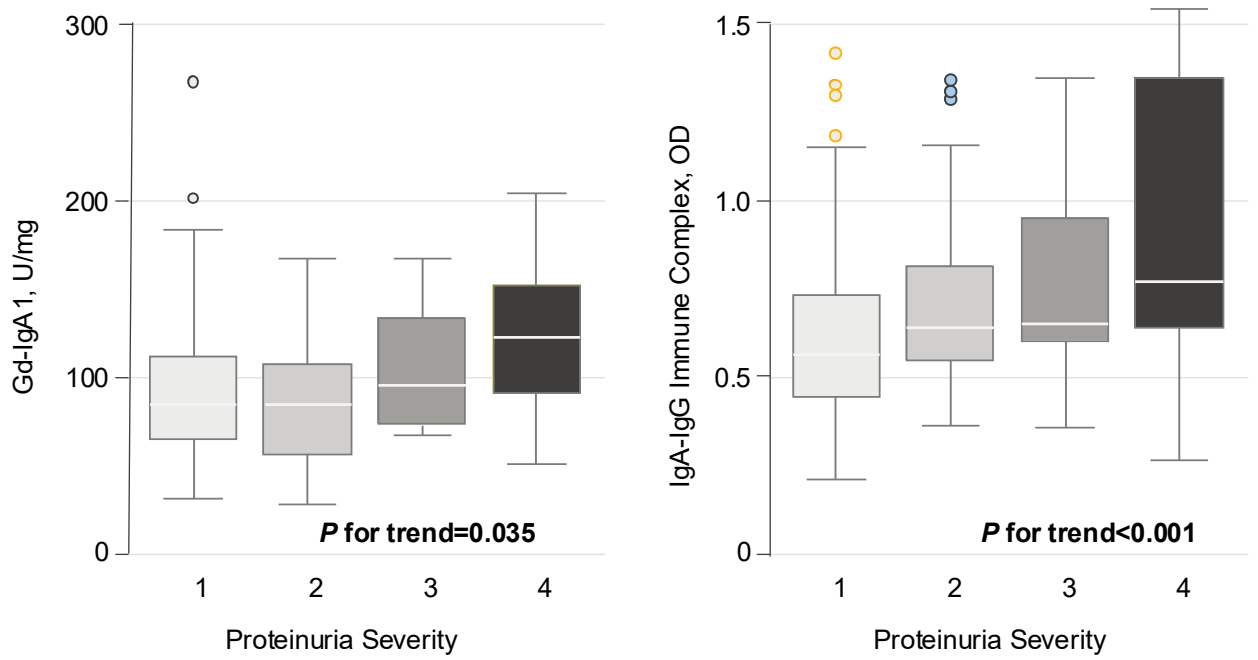
Gd-IgA1 and Related Immune Complexes Are Associated with Clinical Disease Activity in Patients with IgAN

Serum Levels of Gd-IgA1 in Patients With IgAN and Healthy Controls



HAA-IgA1 >1076 U/mL has PPV 88.6% and NPV 78.9%

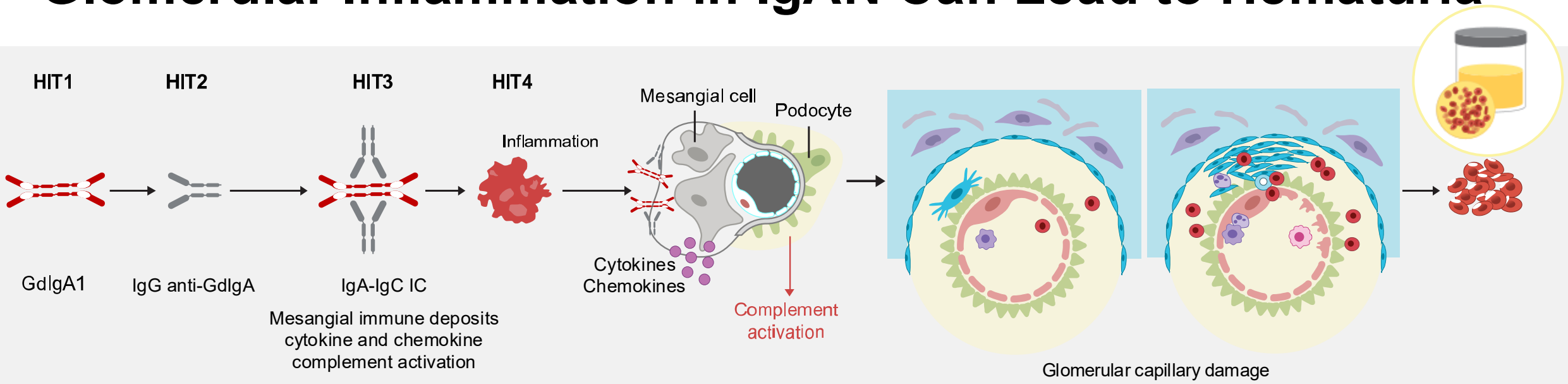
Correlation Between Proteinuria Severity and Serum Gd-IgA1 or IgA/IgG-Immune Complex Levels



NPV = negative predictive value; PPV = positive predictive value; OD = optical density.

Moldoveanu Z, et al. *Kidney Int*. 2007;71(11):1148-1154. Suzuki Y, et al. *Clin Exp Nephrol*. 2014;18:770-777.

Glomerular Inflammation in IgAN Can Lead to Hematuria



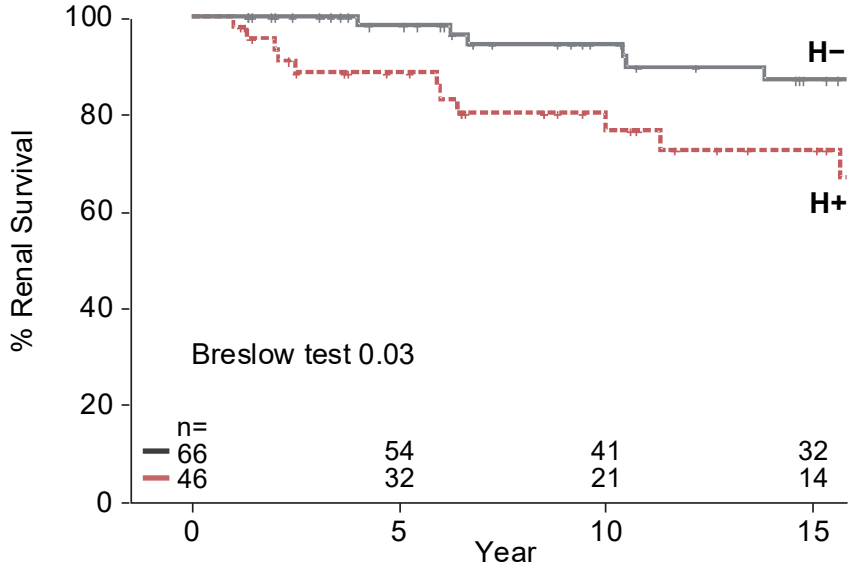
- Immune complexes are deposited in the kidney, leading to inflammation and glomerular injury, due to the release of cytokines, chemokines, and activation of the complement cascade
- This results in damage to the glomerular filtration barrier, passage of RBCs into the urinary space, and development of hematuria

RBC = red blood cell.

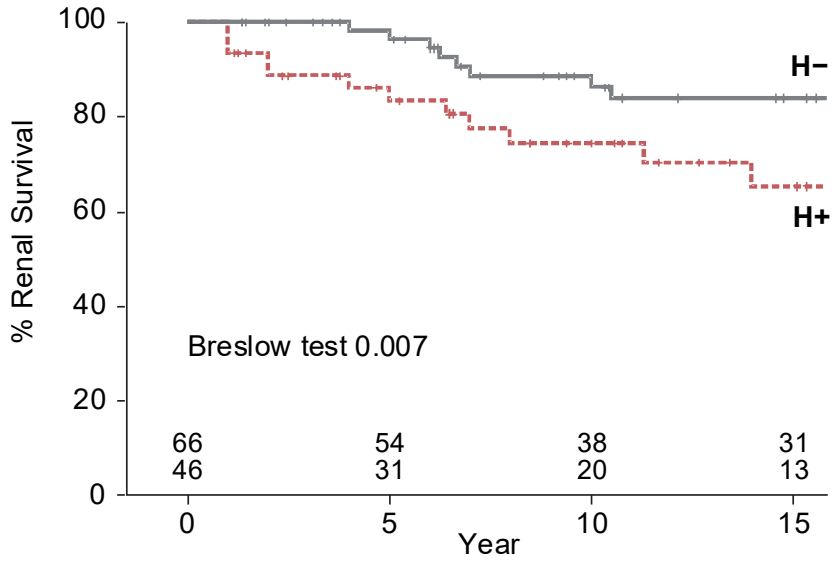
Zand L, et al. *Clin Kidney J.* 2023;16(suppl 2):ii19-ii27.

Persistent Hematuria Predicted Worse Clinical Renal Outcomes

Renal Survival Free of ESRD



Renal Survival Free of 50% Reduction of Renal Function



	All Patients n=112	H− n=66	H+ n=46	*P*-value
ESRD, n (%)	21 (17)	7 (11)	14 (30)	0.01
50% reduction in renal function, n (%)	27 (22)	10 (15)	17 (37)	0.01
Rate of renal function decline, mL/min/1.73 m^2 per year	-2.34 ± 5	-1.54 ± 3.92	-3.34 ± 6.12	0.06

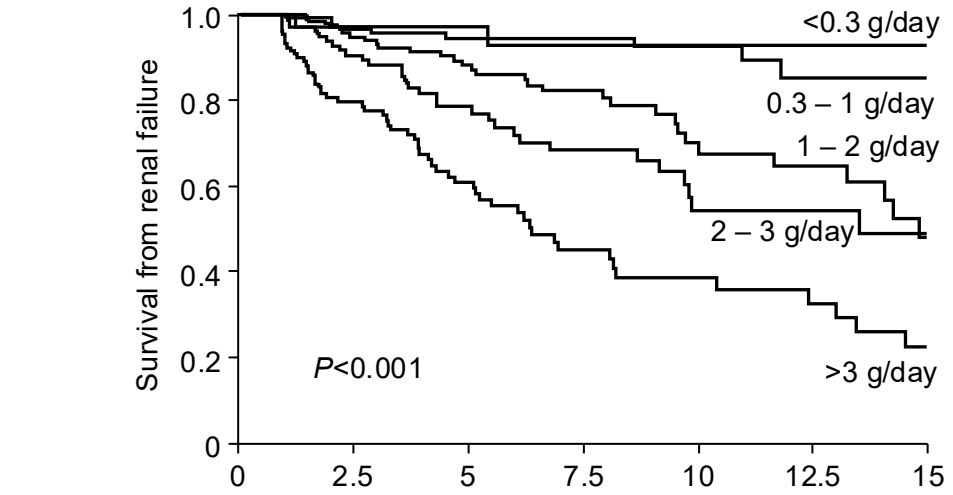
The percentage of patients reaching ESRD or a 50% reduction of renal function was significantly greater among those with persistent hematuria than those with minimal or negative hematuria

H− = patients with minimal or negative hematuria during follow-up (time-averaged hematuria ≤5 RBC x hpf); H+ = patients with persistent hematuria during follow-up (time-averaged hematuria >5 RBC x hpf); hpf = high-power field.

Sevillano AM, et al. *J Am Soc Nephrol.* 2017;28:3089-3099.

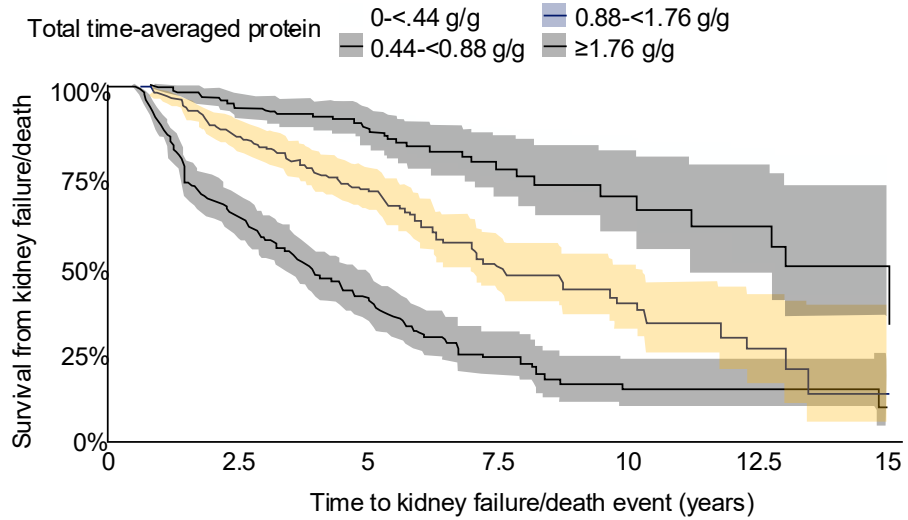
Proteinuria Is Associated with Decreased Renal Survival

Renal Survival by Category of TA Proteinuria Among Patients in the Toronto Glomerulonephritis Registry



<0.3 g/day	37	22	8	1		
0.3 – 1 g/day	134	79	35	11		
1 – 2 g/day	145	79	28	10		
2 – 3 g/day	105	50	18	4		
>3 g/day	120	44	13	6		

Time to Kidney Failure/Death Event among Patients in the RaDaR IgA Nephropathy Cohort



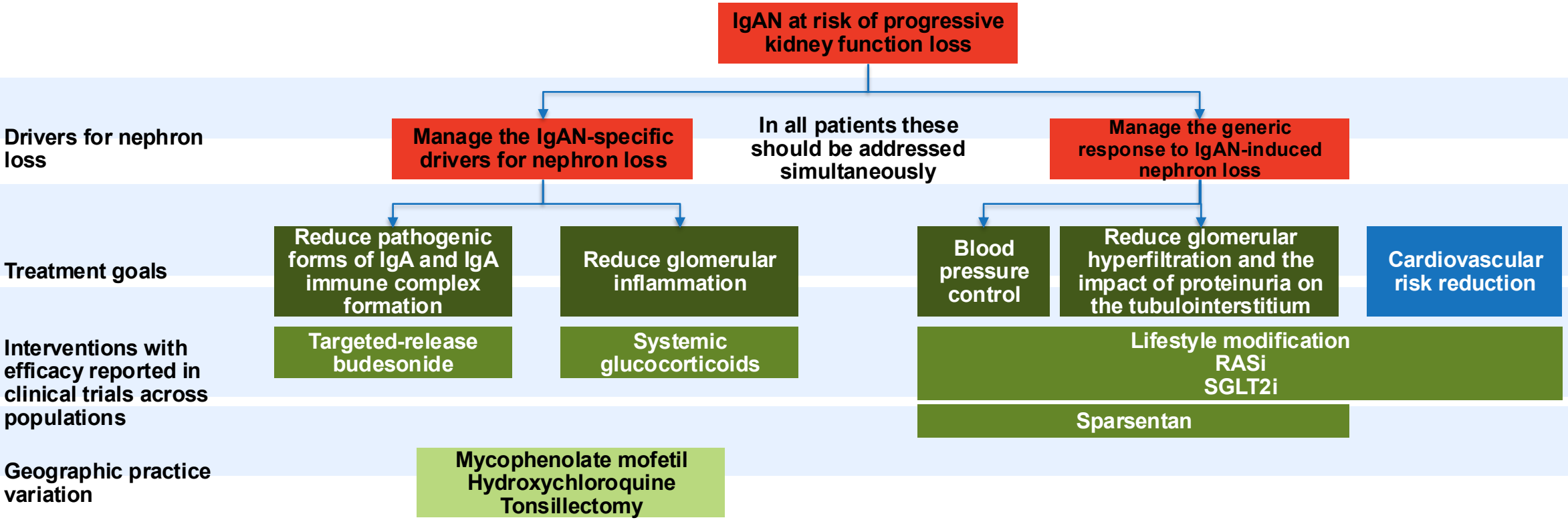
0-<0.44 g/g	215	176	114	57	22	10	6
0.44-<0.88 g/g	175	147	94	40	20	11	1
0.88-<1.76 g/g	251	195	120	51	20	7	1
≥1.76 g/g	246	142	66	24	10	5	2

Recent data have shown that even lower levels of proteinuria are associated with a significant lifetime risk of renal failure

RaDaR = UK National Registry of Rare Kidney Diseases; TA = time-averaged.

Reich HN, et al. *J Am Soc Nephrol*. 2007;18:3177-3183. Pitcher D, et al. *Clin J Am Soc Nephrol*. 2023;18:727-738.

Draft Clinical Practice Guideline for IgAN



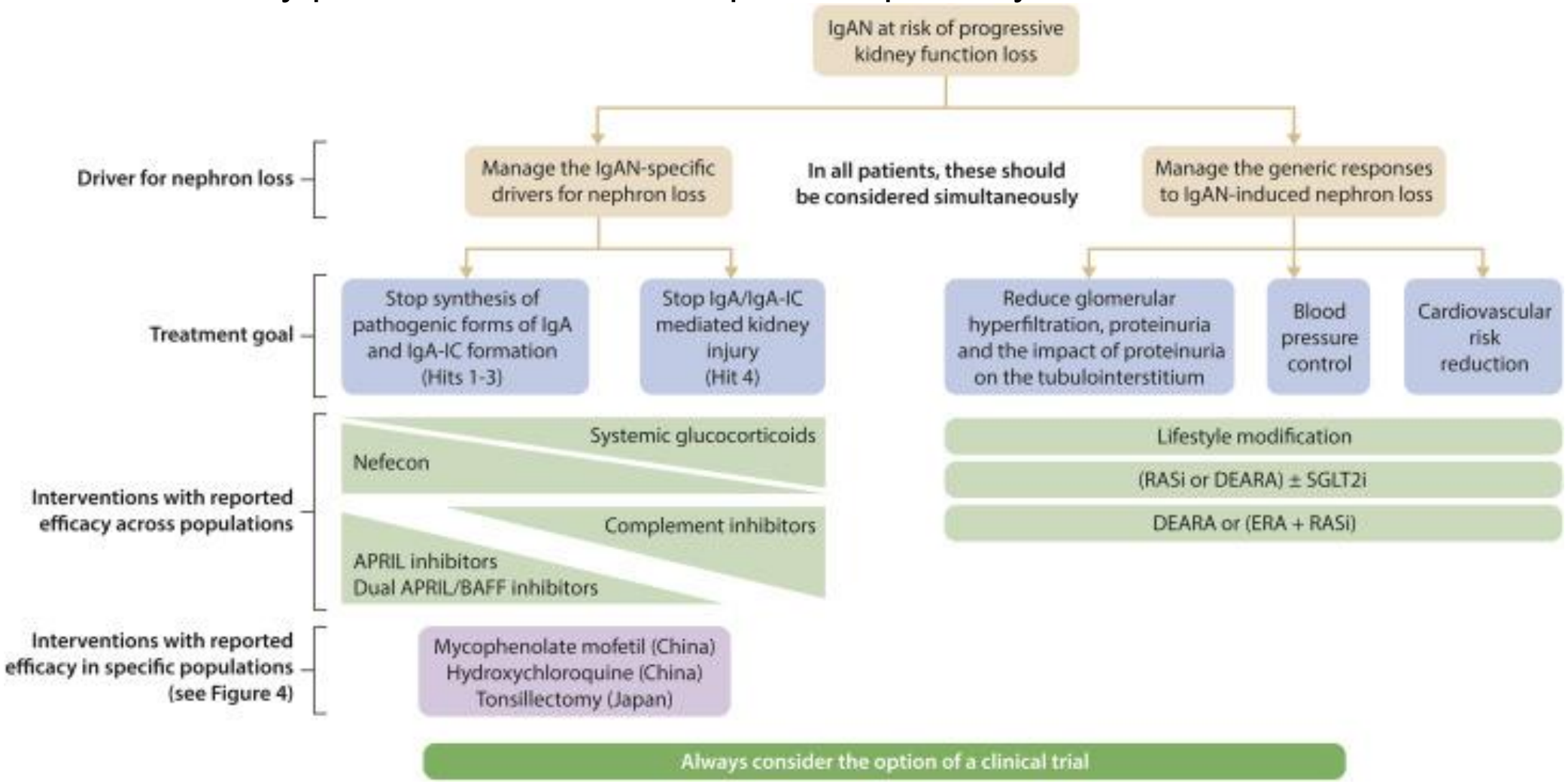
With the development and recent approval of new therapies for IgAN, draft KDIGO guidelines recommend therapies that

1. Prevent/reduce IgA immune complex formation and subsequent glomerular injury
2. Manage the consequences of existing IgAN-induced nephron loss

RASi = renin-angiotensin system inhibitor.

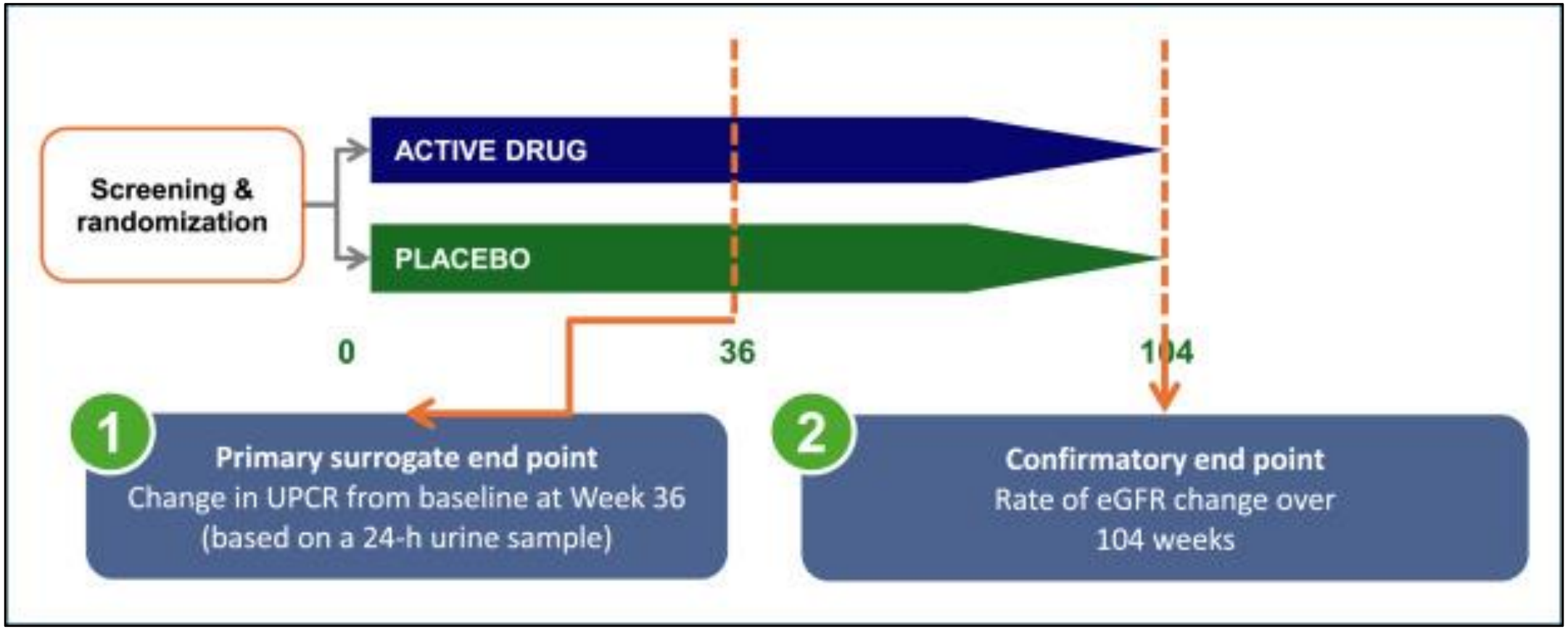
Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. *KDIGO 2024 Clinical Practice Guideline for the Management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A Vasculitis (IgAV) Public Review Draft*. 2024.

- The newly released KDIGO commentary (2026) highlights a shift toward disease-modifying therapies in IgAN, particularly those targeting upstream immune mechanisms such as B-cell activation/antibody production and the complement pathway



DEARA = dual endothelin angiotensin receptor antagonist; ERA = endothelin type A receptor antagonist.
Rovin BH, et al. *Kidney Int*. 2028:S0085-2538(26)00213-9. [Epub ahead of print.]

Newer Clinical Trial Designs IgAN



Treatment Goal

- Renal protective strategies
- Targeting the immune mechanisms in IgA nephropathy

Renal Protective Strategies/Reducing Nephron Loss

- RAAS blockade
- SGLT2 inhibitors
- Endothelin receptor antagonists (ETA)
- Corticosteroids

- RAASi, SGLT2i, and ETA offer hemodynamic and non hemodynamic benefits, but not immunologic effects

Grabe DW. *Am J Manag Care*. 2023;29(3 Suppl):S31-S43.

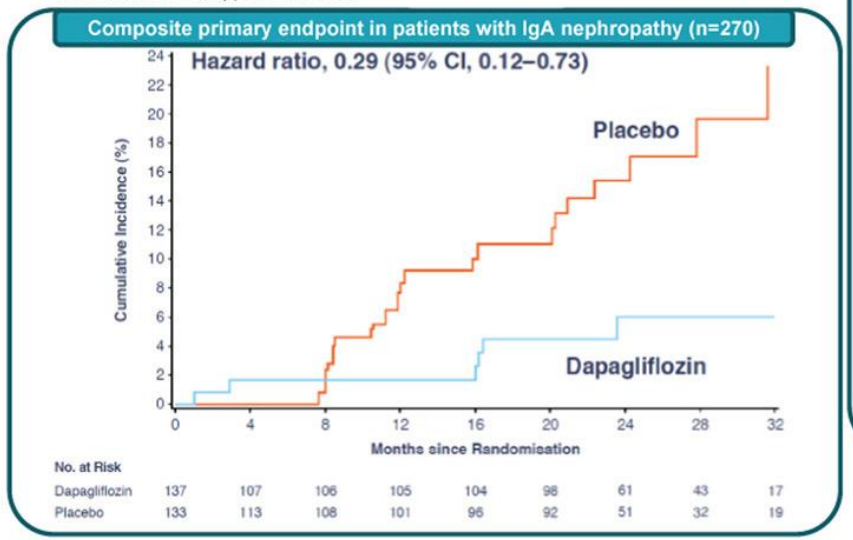
SGLT2 Inhibitors-DAPA CKD Trial

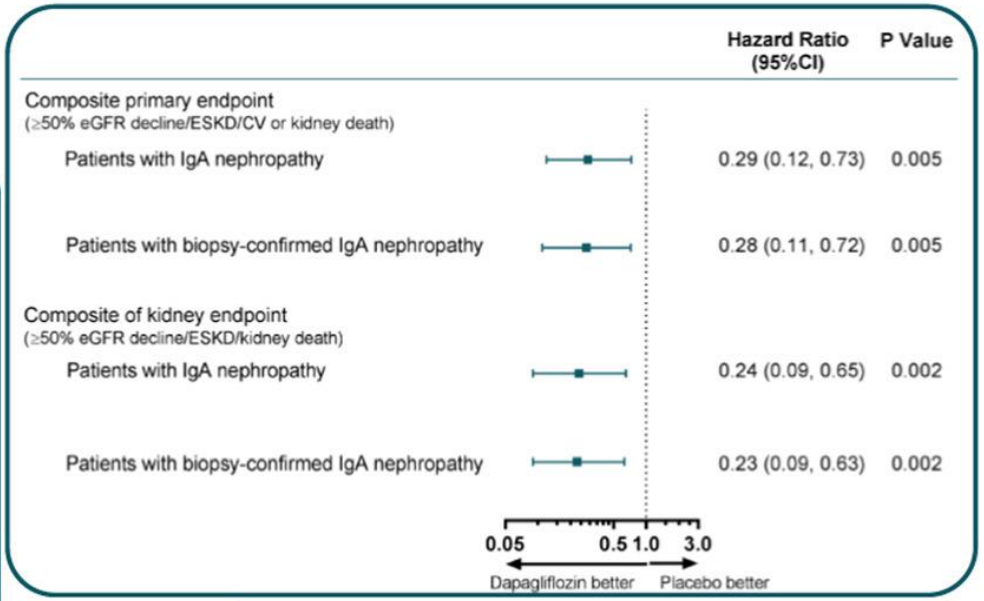
A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy.

DAPA-CKD population:

- eGFR 25-75 mL/min/1.73m^2
- UACR 200-5000 mg/g
- Receiving a stable, maximally tolerable ACEi/ARB dose
- With and without type 2 diabetes

⇨ **270 participants with IgA nephropathy** ⇨ **254 participants with biopsy-confirmed IgA nephropathy**





IgA, immunoglobulin A; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CKD, chronic kidney disease; ESKD, end-stage kidney disease

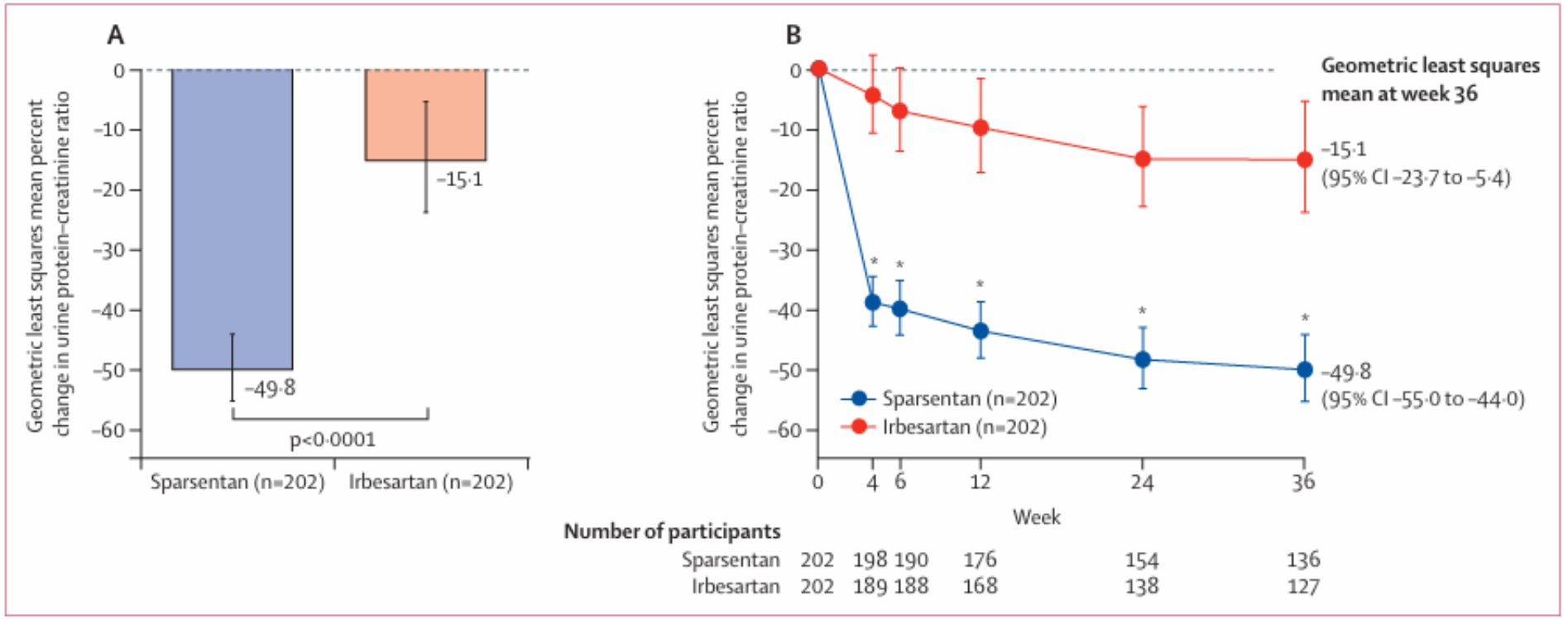
CONCLUSION:

In patients with IgA nephropathy, when added to ACEi/ARB therapy, dapagliflozin significantly and substantially reduced the risk of CKD progression

Wheeler DC, et al. *Kidney Int*. 2021;100(1):215-224.

ET_AR Antagonists (ERA)

Dual ERA/AngII Antagonist-***Sparsentan*-PROTECT Trial**



- Phase 3, double-blind, randomized, placebo-controlled trial
- Sparsentan 400/d or irbesartan 300/d
- eGFR ≥30 ml/min/1.73m2, 24-hour urine protein ≥1 g despite max RAAS blockade
- 41% relative reduction in uPCR
- No episode of heart failure. More hypotension and dizziness in the sparsentan group

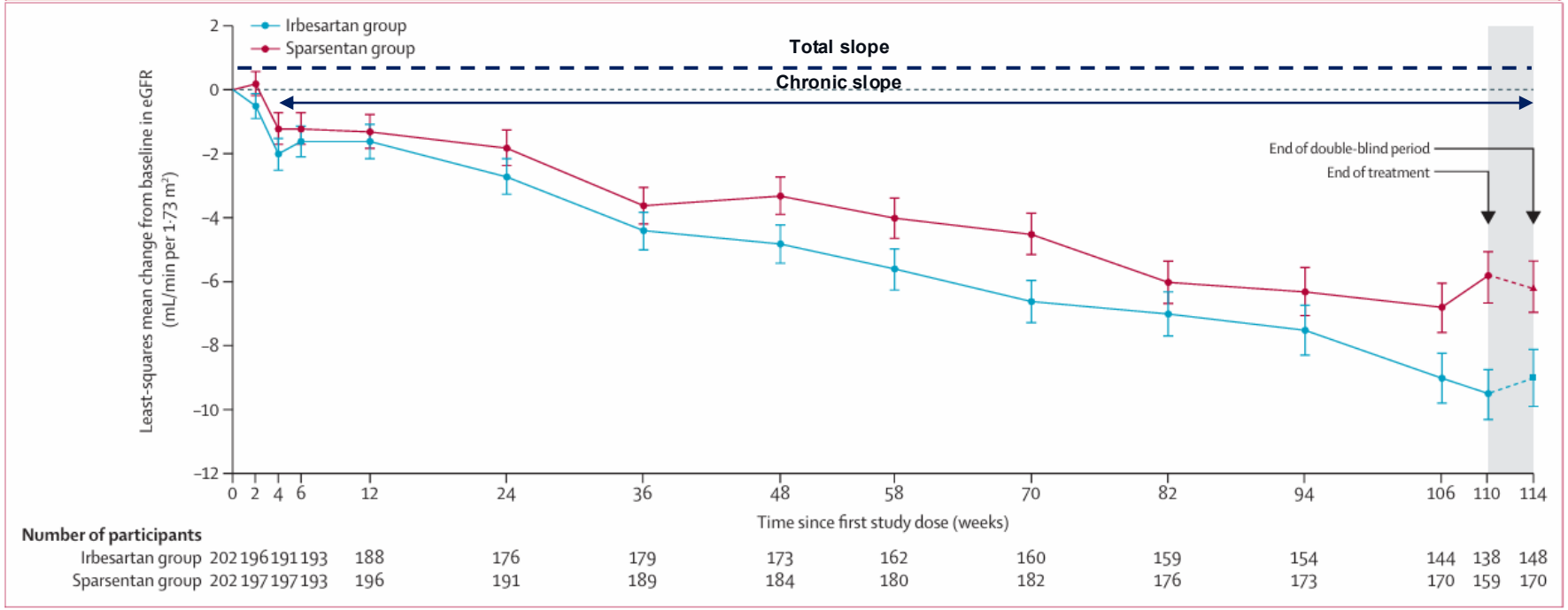
uPCR = urine protein creatinine ratio.

Heerspink HJL, et al. *Lancet*. 2023;401(10388):1584-1594.

Dual ERA/AngII Antagonist-***Sparsentan*-PROTECT Trial**

	Sparsentan group (n=202)	Irbesartan group (n=202)	Between-group difference (95% CI)	p value
Key secondary efficacy endpoints*				
Chronic slope from week 6 to week 110, mL/min per 1·73 m² per year	−2·7 (−3·4 to −2·1)	−3·8 (−4·6 to −3·1)	1·1 (0·1 to 2·1)	0·037
Total slope from day 1 to week 110, mL/min per 1·73 m² per year	−2·9 (−3·6 to −2·2)	−3·9 (−4·6 to −3·1)	1·0 (−0·03 to 1·94)	0·058
Other secondary efficacy endpoint*				
Absolute change from baseline to week 110, mL/min per 1·73 m²	−5·8 (−7·4 to −4·2)	−9·5 (−11·2 to −7·9)	3·7 (1·5 to 6·0)	..
Prespecified exploratory endpoint†				
Absolute change from baseline to week 114, mL/min per 1·73 m²	−6·1 (−7·7 to −4·5)	−9·0 (−10·7 to −7·2)	2·9 (0·5 to 5·3)	..

Data are least-squares mean change (95% CI) in eGFR unless otherwise stated. eGFR=estimated glomerular filtration rate. *Assessed in the full analysis set. †Assessed in patients in the full analysis set who completed the study treatment.

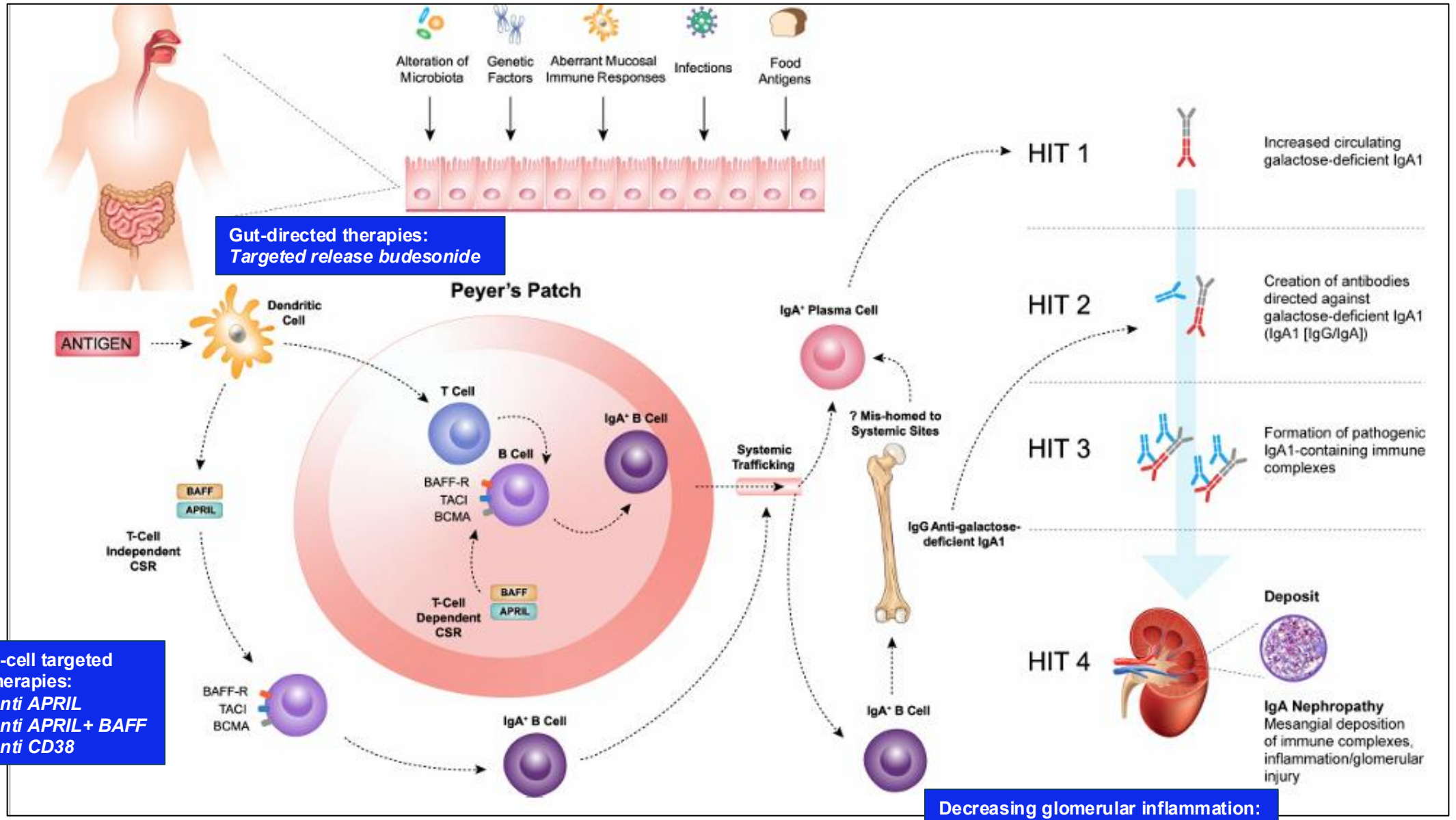


Change in eGFR

Rovin BH, et al. *Lancet*. 2023;402(10417):2077-2090.

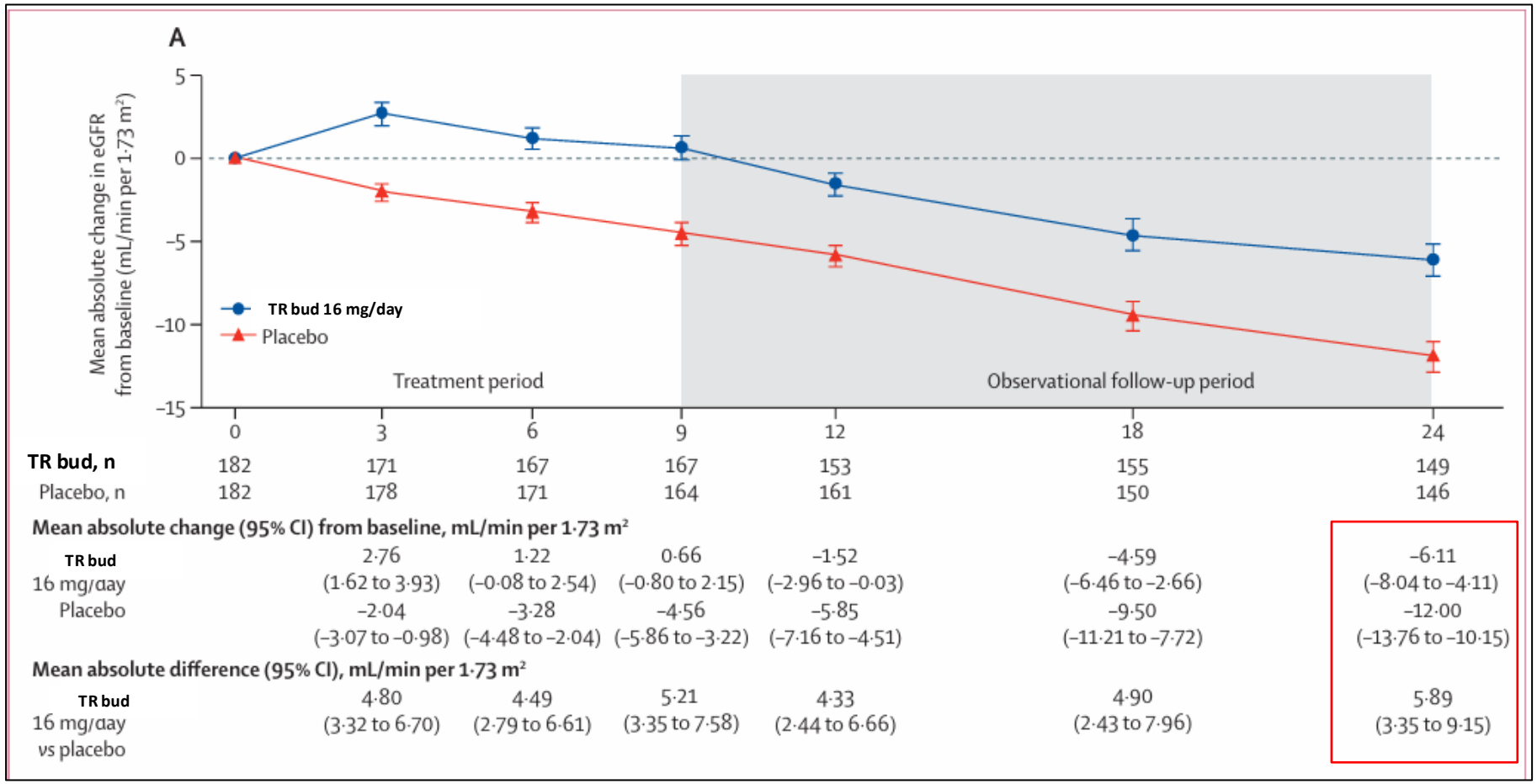
Targeting the Immune Mechanisms in IgA Nephropathy

- Enterically active steroids
- Anti B-cell therapies
- Complement inhibitors



Cheung CK, et al. *Front Nephrol*. 2024;3:1346769.

Targeted Release Budesonide: NeflgArd-Phase 3, Part B



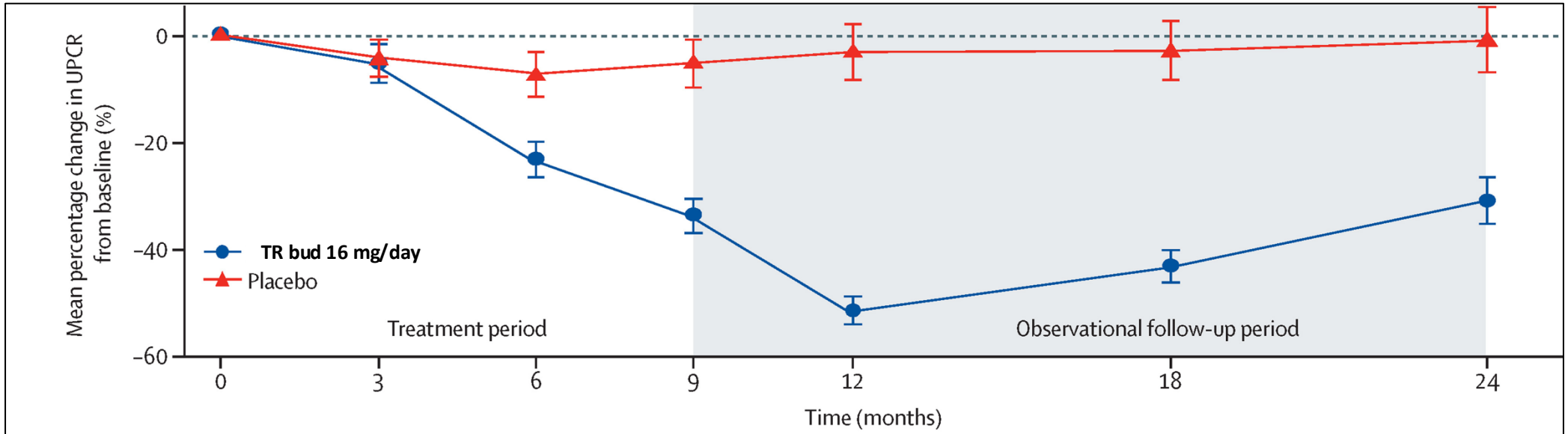
TR bud, n	182	171	167	167	153	155	149
Placebo, n	182	178	171	164	161	150	146
Mean absolute change (95% CI) from baseline, mL/min per 1·73 m²							
TR bud 16 mg/day		2·76 (1·62 to 3·93)	1·22 (−0·08 to 2·54)	0·66 (−0·80 to 2·15)	−1·52 (−2·96 to −0·03)	−4·59 (−6·46 to −2·66)	−6·11 (−8·04 to −4·11)
Placebo		−2·04 (−3·07 to −0·98)	−3·28 (−4·48 to −2·04)	−4·56 (−5·86 to −3·22)	−5·85 (−7·16 to −4·51)	−9·50 (−11·21 to −7·72)	−12·00 (−13·76 to −10·15)
Mean absolute difference (95% CI), mL/min per 1·73 m²							
TR bud 16 mg/day vs placebo		4·80 (3·32 to 6·70)	4·49 (2·79 to 6·61)	5·21 (3·35 to 7·58)	4·33 (2·44 to 6·66)	4·90 (2·43 to 7·96)	5·89 (3·35 to 9·15)

Mean absolute change in eGFR from baseline over 24 months

- Over 2 years, time weighted average of eGFR with significant benefit of targeted-release oral budesonide (TR bud) vs placebo (difference 5 ml/min/1.73m2)
- eGFR total slope over 2 years- difference of 2.95ml/min/1.73m2/year

Lafayette R, et al. *Lancet*. 2023;402(10405):859-870.

Targeted Release Budesonide: NeflgArd-Phase 3, Part B



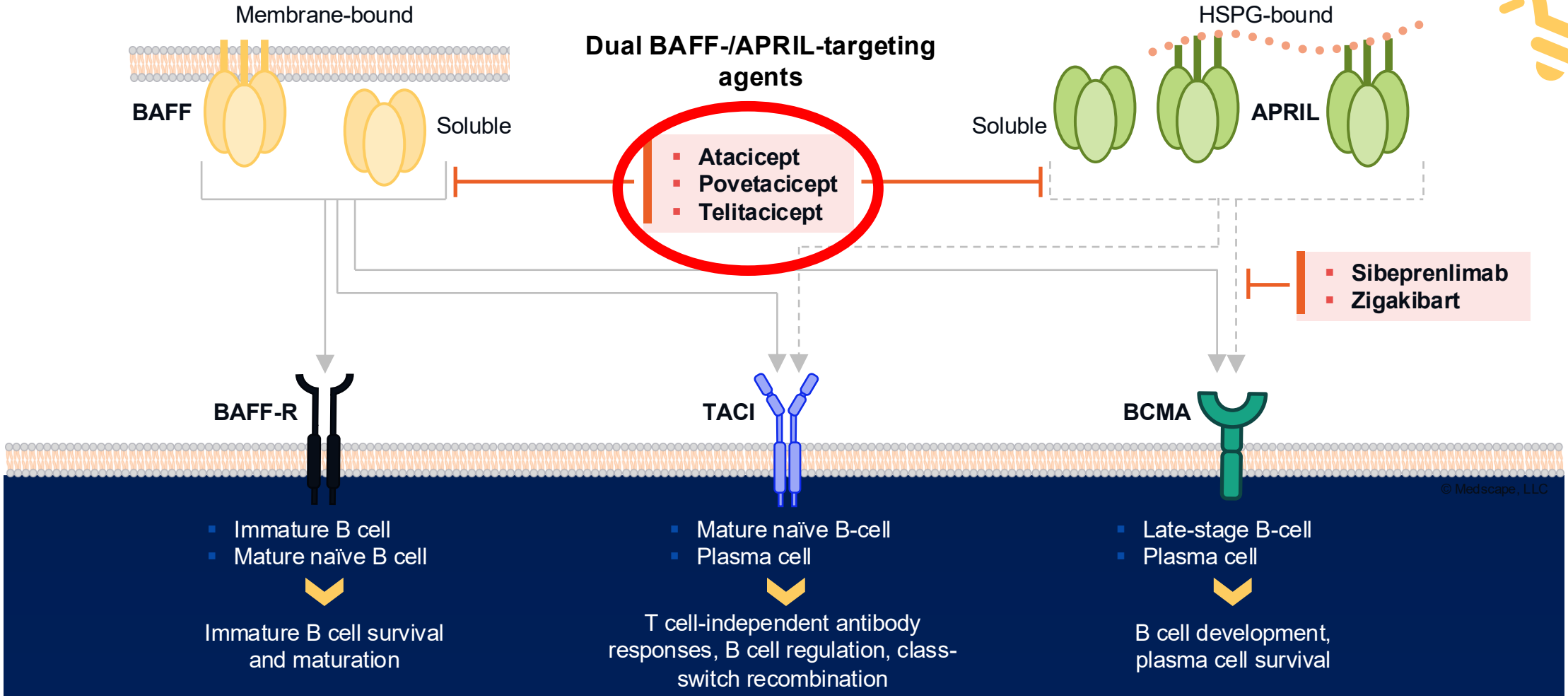
TR bud, n	182	173	169	166	157	155	145
Placebo, n	182	176	169	164	160	151	142
Mean percentage change (95% CI) from baseline, %							
TR bud 16 mg/day		-5·2 (-11·8 to 1·9)	-23·1 (-29·5 to -16·1)	-33·6 (-39·6 to -27·0)	-51·3 (-56·2 to -45·9)	-43·1 (-49·0 to -36·6)	-30·7 (-38·9 to -21·5)
Placebo		-4·3 (-10·9 to 2·9)	-7·3 (-15·0 to 1·2)	-5·2 (-13·8 to 4·3)	-3·2 (-12·8 to 7·5)	-2·9 (-13·0 to 8·3)	-1·0 (-12·8 to 12·4)
Percentage reduction (95% CI), %							
TR bud 16 mg/day vs placebo		1·0 (-9·6 to 10·5)	17·1 (6·1 to 26·7)	30·0 (19·9 to 38·8)	49·7 (41·6 to 56·6)	41·4 (31·7 to 49·8)	30·1 (16·4 to 41·5)

Lafayette R, et al. *Lancet*. 2023;402(10405):859-870.

Mechanisms of Emerging Agents Targeting B-Cells

- **Monoclonal antibodies**
  - Sibeprenlimab
  - Zigakibart
- **Fusion protein**
  - Atacicept
  - Povetacicept
  - Telitacicept

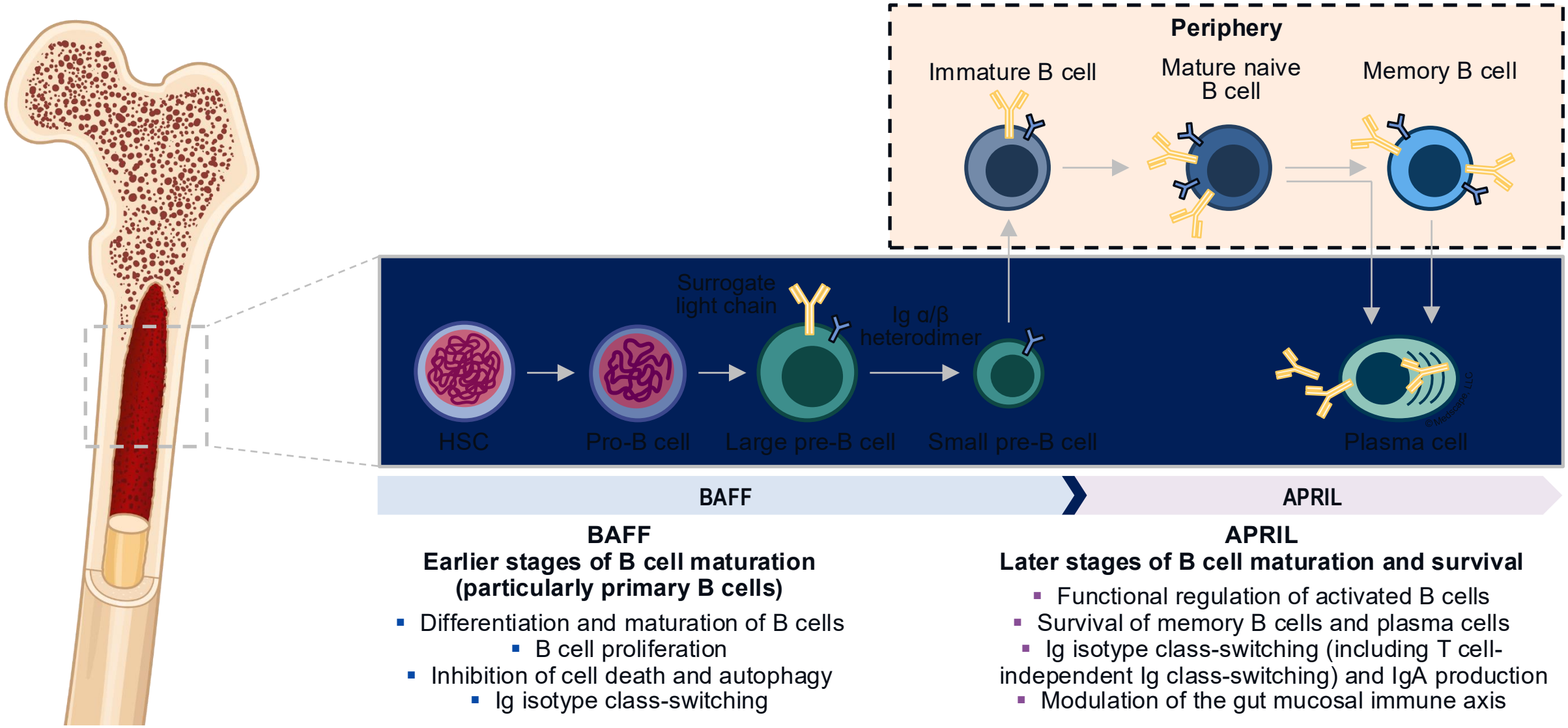
B-Cell and Plasma Cell Targets and the Consequences of Disease-Modulating Therapies



GSPG = heparan sulfate proteoglycan.

Hengeveld PJ, Kersten MJ. *Blood Cancer J.* 2015;5(2):e282.

Roles of BAFF and APRIL in the Normal Physiology of B-Cell Maturation and Survival



BAFF
Earlier stages of B cell maturation (particularly primary B cells)

- Differentiation and maturation of B cells
- B cell proliferation
- Inhibition of cell death and autophagy
- Ig isotype class-switching

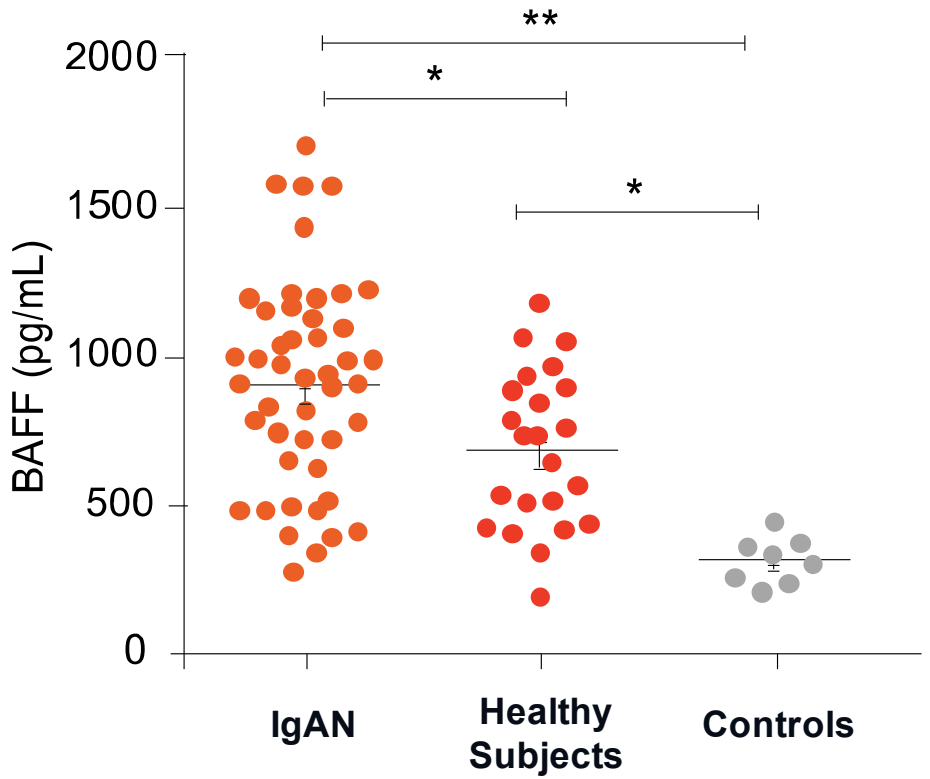
APRIL
Later stages of B cell maturation and survival

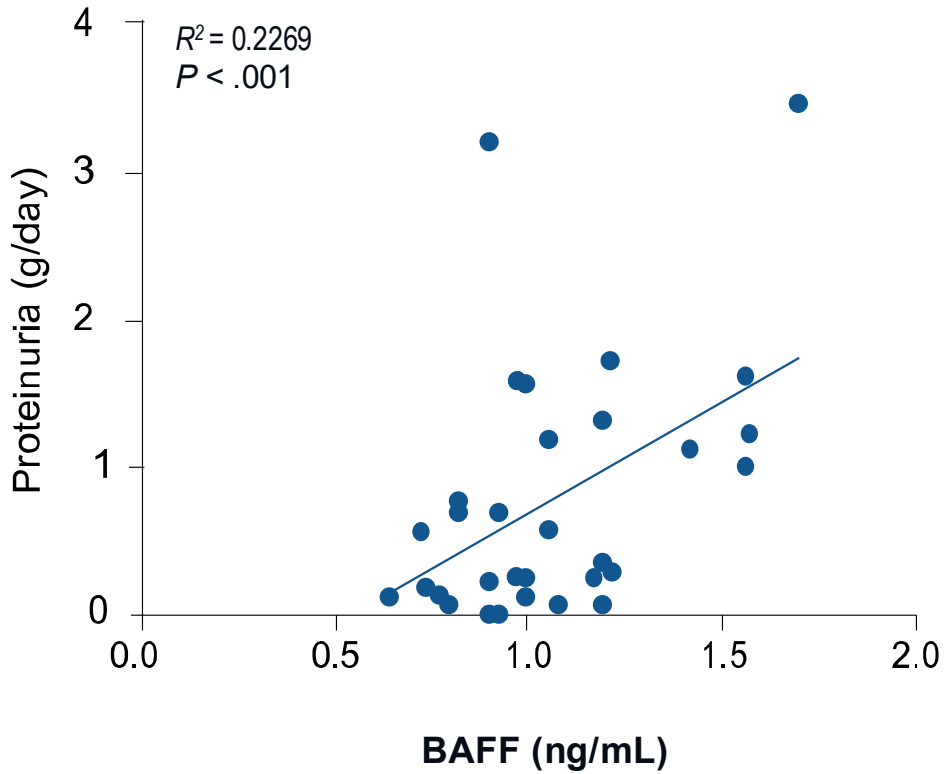
- Functional regulation of activated B cells
- Survival of memory B cells and plasma cells
- Ig isotype class-switching (including T cell-independent Ig class-switching) and IgA production
- Modulation of the gut mucosal immune axis

HSC = hematopoietic stem cell.

Chacko B, et al. *ASN Kidney News*. 2024;16:11-12.

BAFF Levels Correlate with Proteinuria in Patients with IgAN



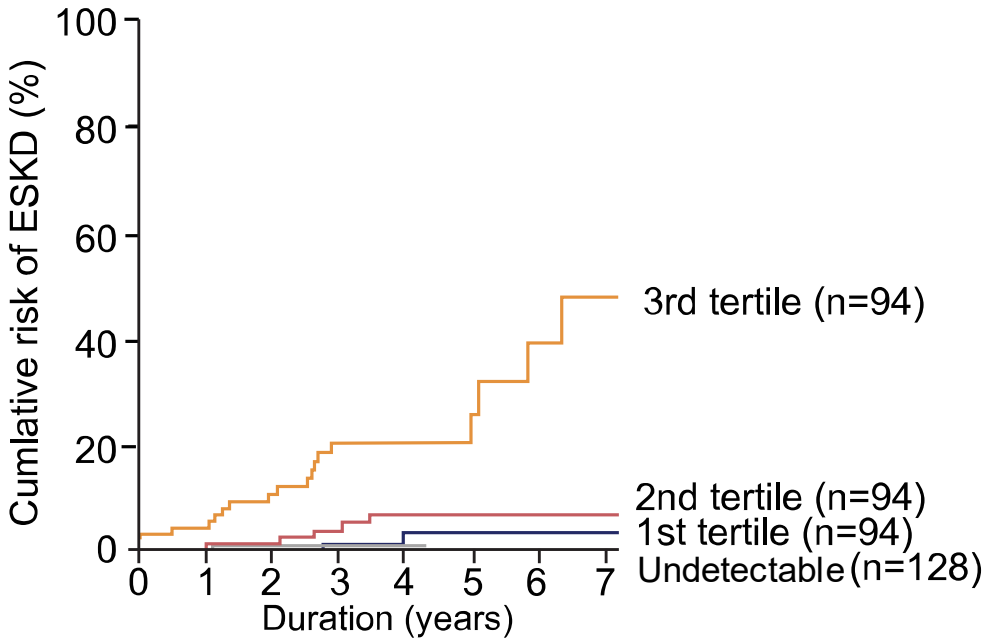


*$P \leq .05$; **$P \leq .005$.

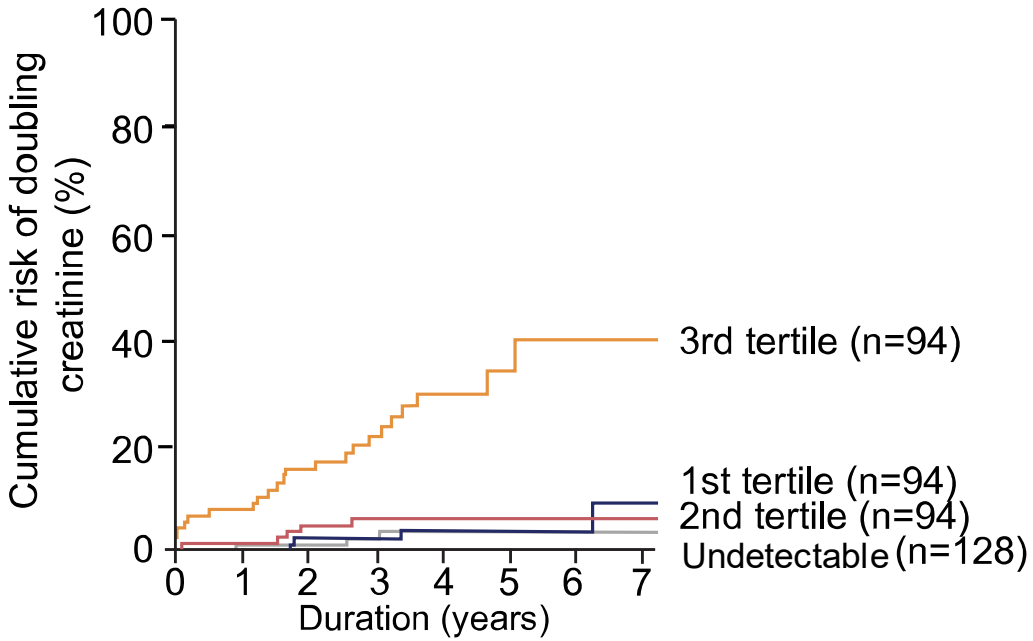
Sallustio F, et al. *Nephrol Dial Transplant*. 2021;36(9):1765.

High APRIL Levels Are Associated with Increased Risk of ESKD in Patients with IgAN

Cumulative Risk of ESKD (%)
by APRIL Level Tertiles



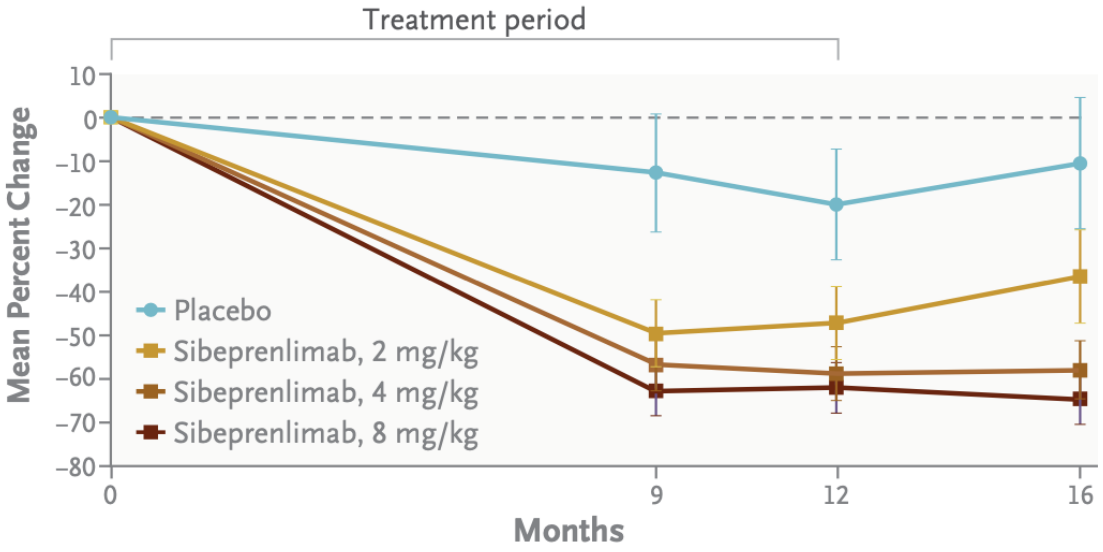
Cumulative Risk of Doubling Creatinine (%)
by APRIL Level Tertiles



Han SS, et al. *J Am Soc Nephrol*. 2016;27:3430-3439.

ENVISION Trial: Primary Outcome and Biomarker Reductions

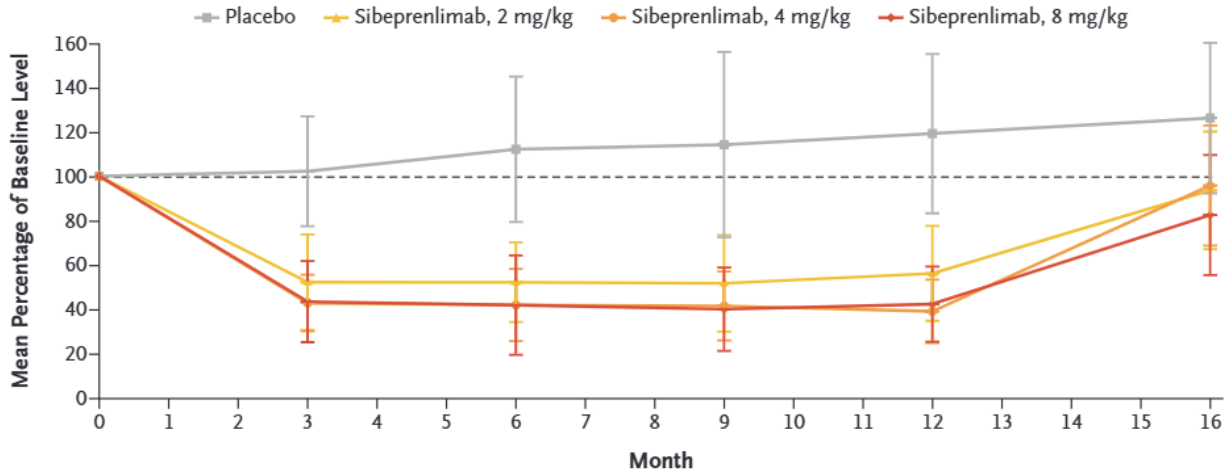
Change in 24-Hr Urinary Protein-to-Creatinine Ratio



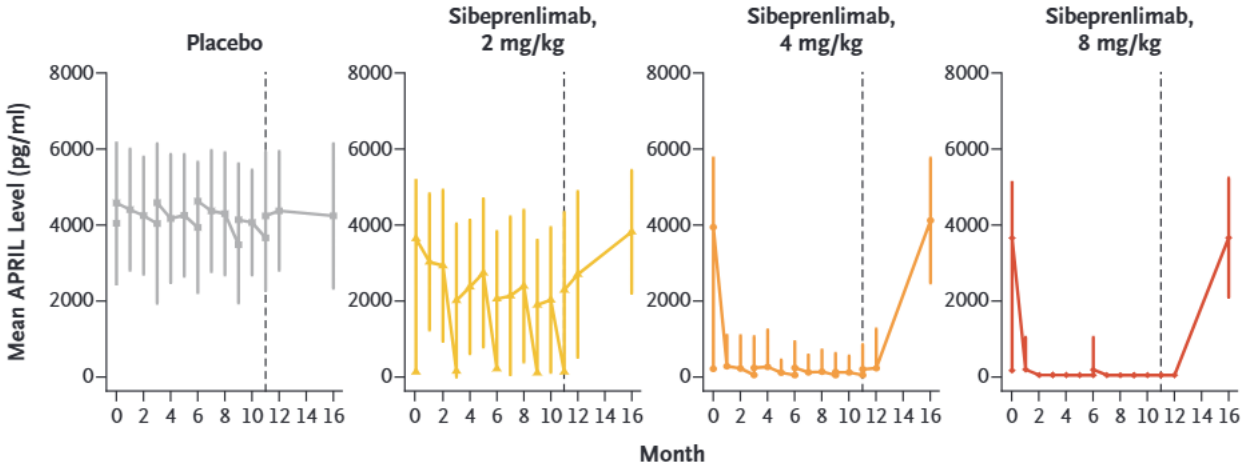
Geometric Mean Percent Reduction in 24-Hr Urinary Protein-to-Creatinine Ratio

End Point	Sibeprenlimab 2 mg/kg (N=38)	Sibeprenlimab 4 mg/kg (N=41)	Sibeprenlimab 8 mg/kg (N=38)	Placebo (N=38)
Month 9	49.6±7.7	56.7±6.2	62.8±5.5	12.7±13.4
Month 12	**47.2±8.2**	**58.8±6.1**	**62.0±5.7**	**20.0±12.6**
Month 16	36.5±10.6	58.0±6.6	64.6±5.7	10.6±15.0

Change in Gd-IgA1 Level Over Time



Change in APRIL Level Over Time



Mathur M, et al. *N Engl J Med*. 2024;390(1):20-31.

ENVISION Trial: Secondary Endpoint: eGFR

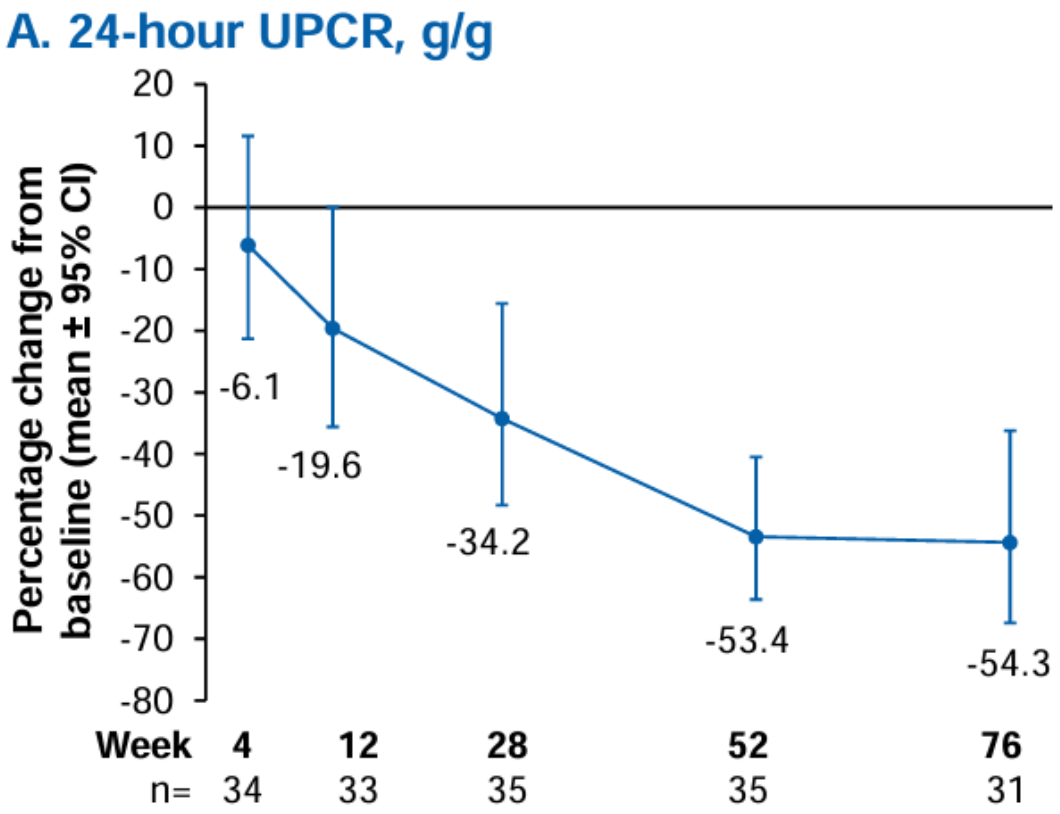
End Point	Sibeprenlimab, 2 mg/kg (N=38)	Sibeprenlimab, 4 mg/kg (N=41)	Sibeprenlimab, 8 mg/kg (N=38)	Placebo (N=38)
Least-squares mean change from baseline in eGFR at month 12 — ml/min/1.73 m^2§	−2.7±1.8	0.2±1.7	−1.5±1.8	−7.4±1.8
Least-squares mean difference in eGFR relative to placebo from baseline to month 12 (95% CI) — ml/min/1.73 m^2	4.6 (−0.3 to 9.5)	7.6 (2.8 to 12.3)	5.8 (0.9 to 10.7)	—
Annualized eGFR slope estimate from baseline to month 12 — ml/min/1.73 m^2¶	−4.1±1.7	0.1±1.6	−0.8±1.6	−5.9±1.7
Treatment difference in eGFR slope relative to placebo (95% CI) — ml/min/1.73 m^2	1.81 (−2.8 to 6.4)	5.96 (1.5 to 10.4)	5.08 (0.5 to 9.6)	—

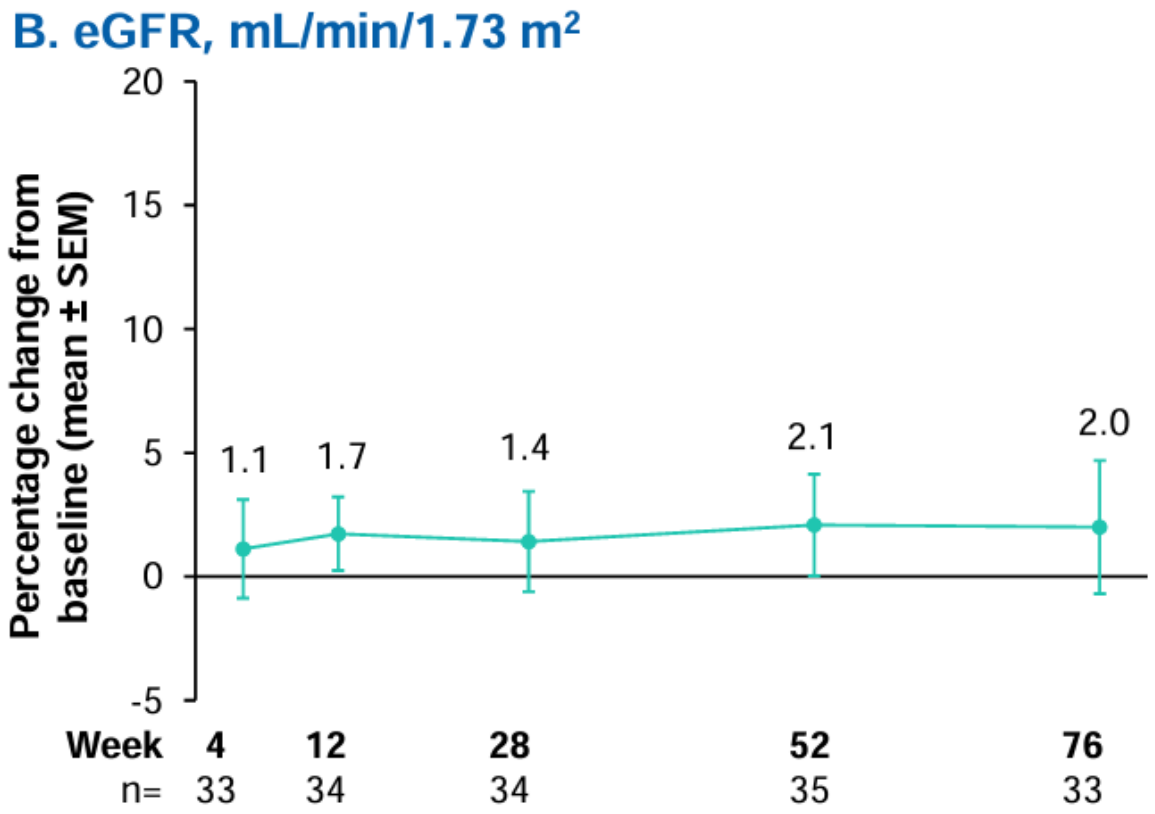
All sibeprenlimab groups had an attenuated decline in eGFR compared with placebo

§A regression model for repeated measures was used for this analysis. ¶A linear mixed-effects model was used for this analysis.

Mathur M, et al. *N Engl J Med*. 2024;390(1):20-31.

Phase 2 Trial of Zigakibart: Efficacy to Week 76 (Combined Cohorts 1 and 2)

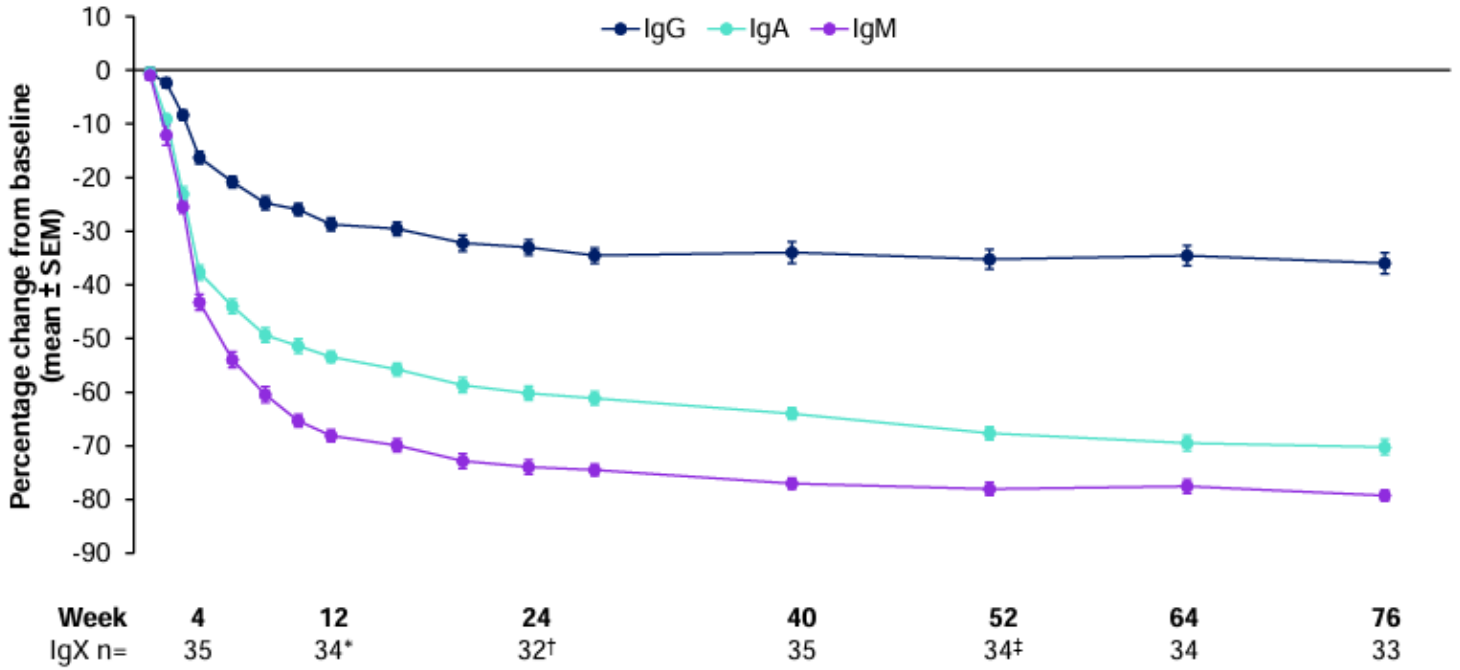




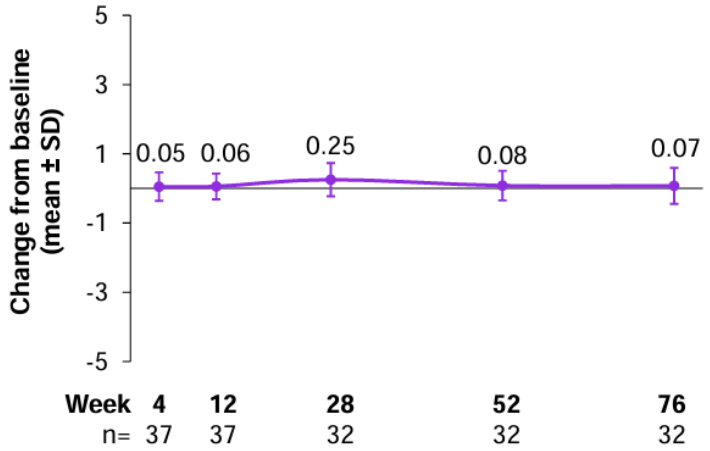
Barratt J, et al. Presented at the American Society of Nephrology (ASN) Kidney Week; October 23-27, 2024; San Diego, CA. FR-PO856.

Phase 2 Trial of Zigakibart: Biomarkers to Week 76 (Combined Cohorts 1 and 2)

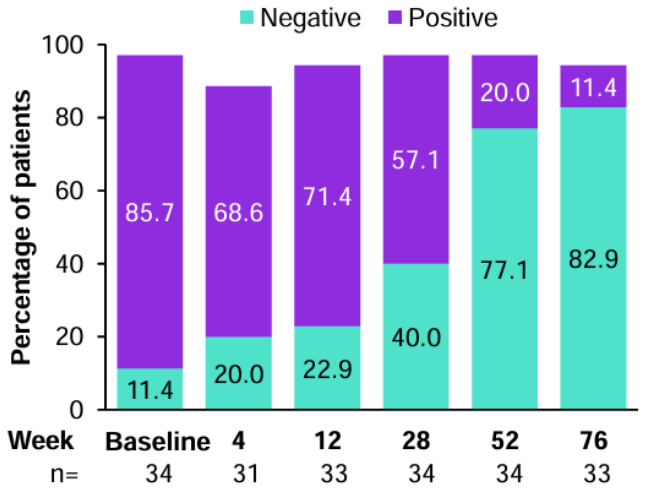
A. Serum immunoglobulins



B. Mean change from baseline in total lymphocyte count, 10^9/L



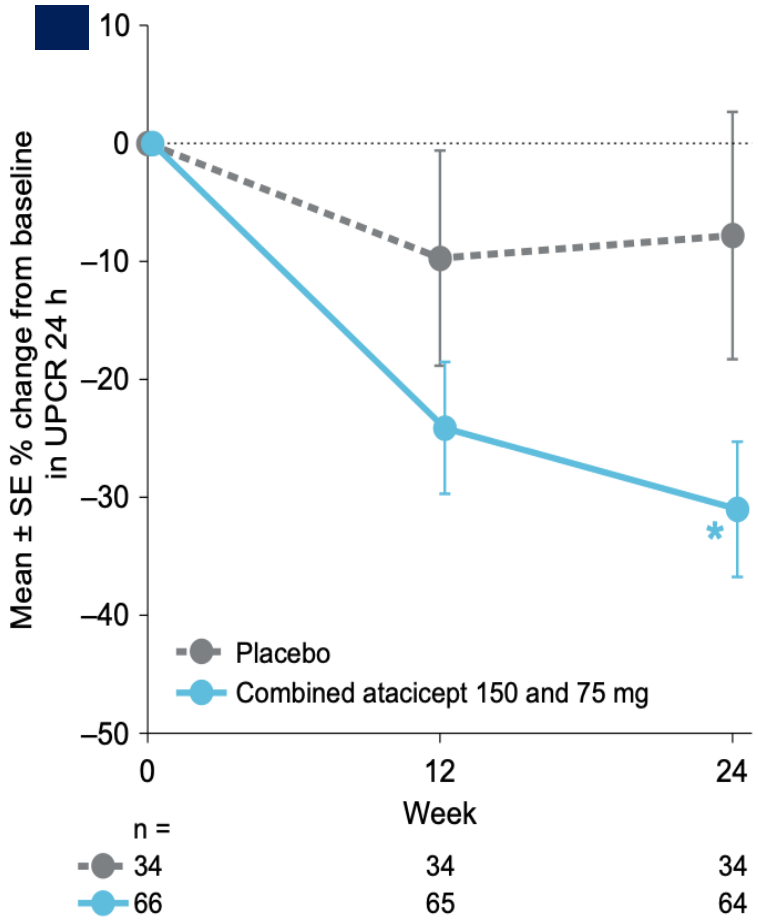
C. Resolution in hematuria§



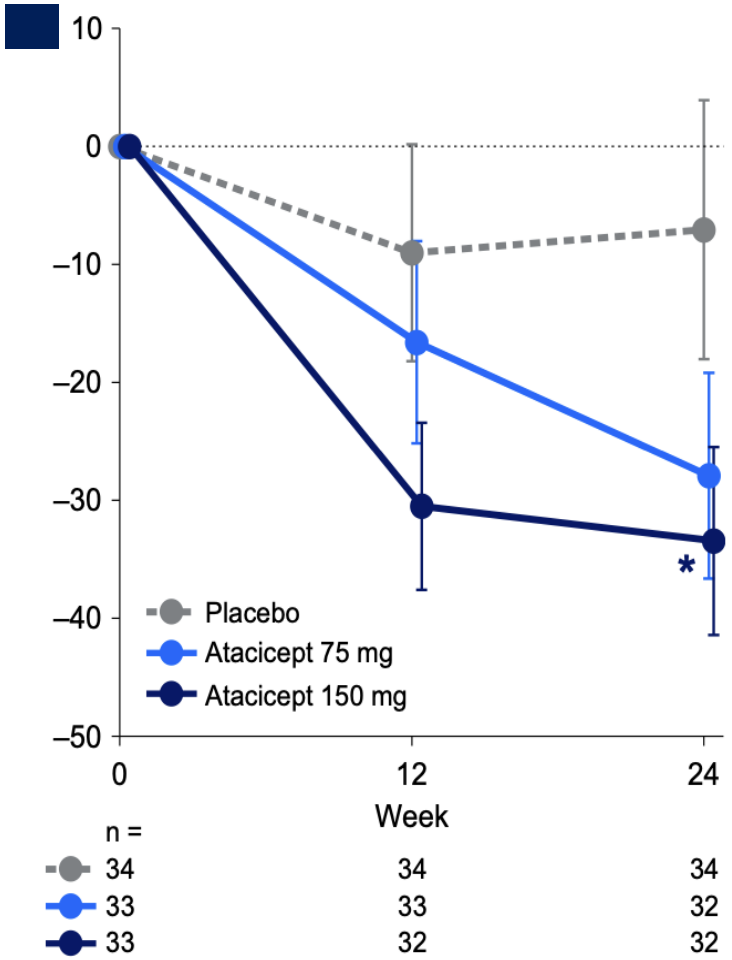
Barratt J, et al. Presented at the ASN Kidney Week; October 23-27, 2024; San Diego, CA. FR-PO856.

ORIGIN: Primary Endpoint: Change in 24-h UPCR at 24 Wks

Combined Atacicept 150-mg and 75-mg Group vs Placebo



Individual Atacicept 150-mg and 75-mg Groups vs Placebo

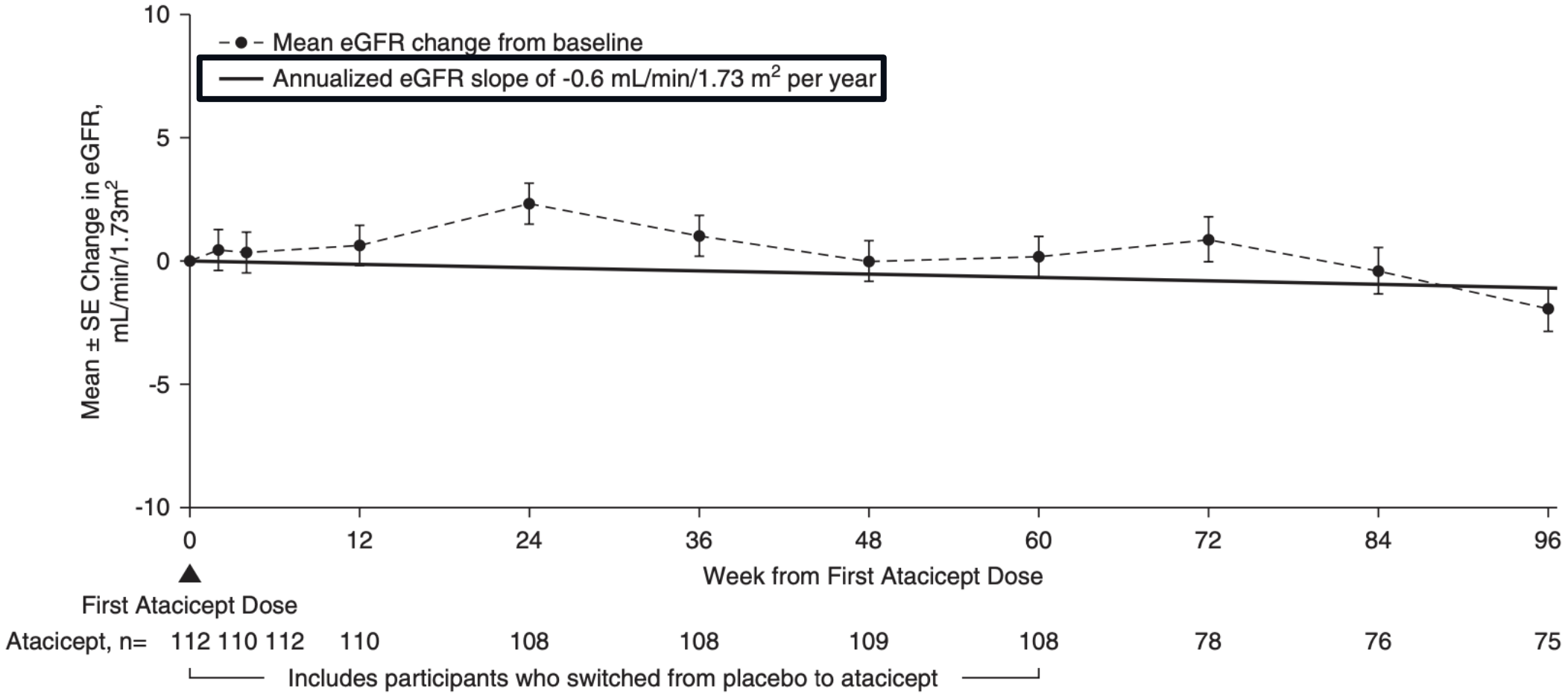


Lafayette R, et al. *Kidney Int*. 2024;105(6):1306-1315.

ORIGIN: Open-Label Extension: Change in eGFR at 96 Wks

(150 mg atacicept)

Change in eGFR through 96 Wk

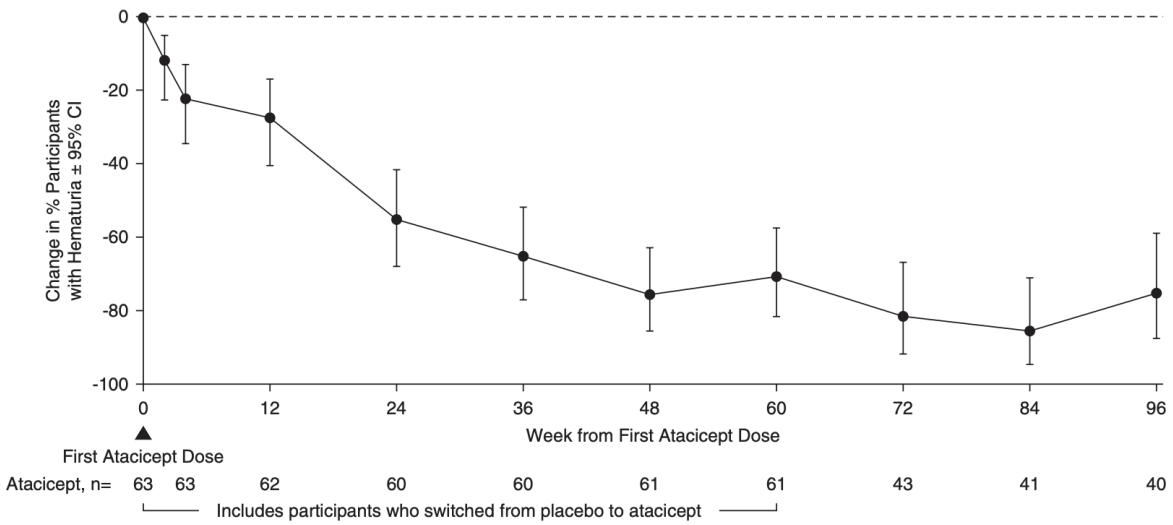


Barratt J, et al. *J Am Soc Nephrol*. 2025;36(4):679-687.

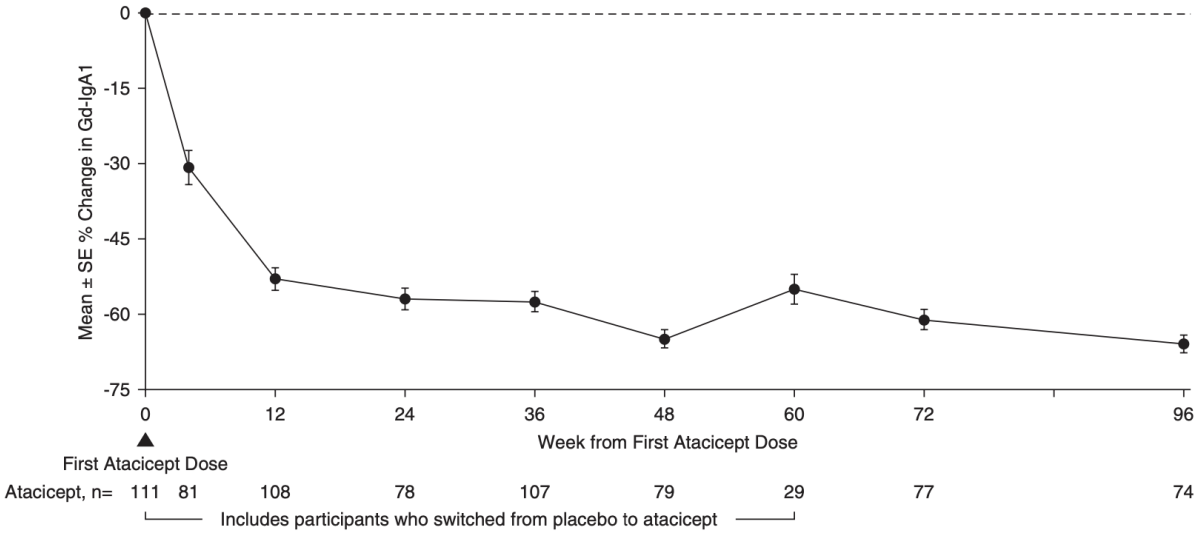
ORIGIN: Open-Label Extension: Effect on Hematuria and Gd-IgA1

(150 mg atacicept)

Change in Percentage of Patients With Hematuria through 96 Weeks



Gd-IgA1 Percentage Change through 96 Wk



Barratt J, et al. *J Am Soc Nephrol*. 2025;36(4):679-687.

ORIGIN 3

- Atacicept 150 mg
  - The safety and efficacy of atacicept is being evaluated for the treatment of IgAN in an ongoing global, randomized, double-blind, placebo-controlled Phase 3 clinical trial

- A total of 203 patients were included in the prespecified interim analysis

Lafayette R, et al. *N Engl J Med*. 2026;394(7):647-657.

ORIGIN 3

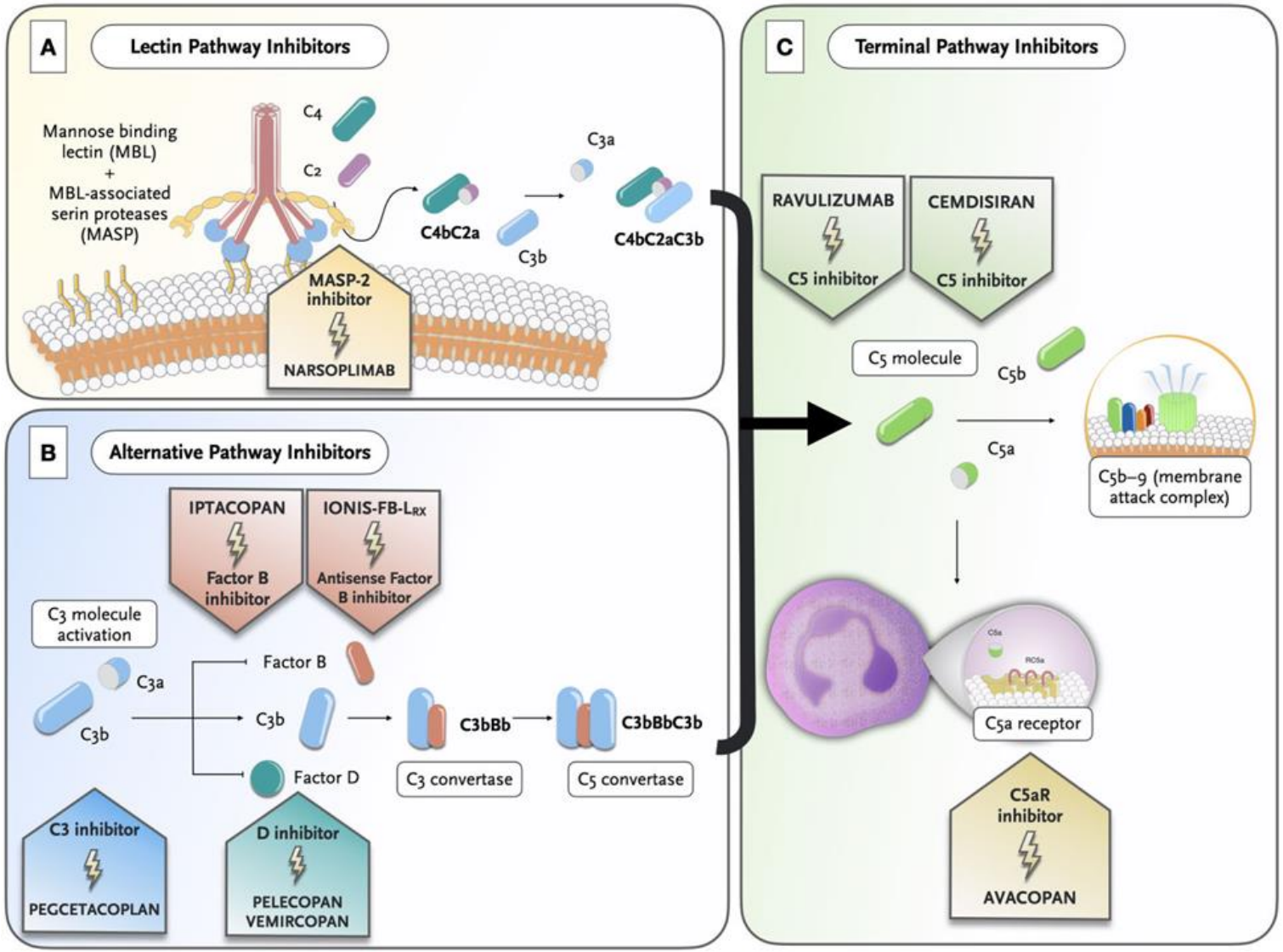
- **Primary endpoint**
  - Atacicept achieved a 46% reduction from baseline in 24-hour uPCR vs 7% with placebo, with decreases observed as early as Week 12 at first assessment, and maintained through Week 36

- **Secondary endpoints**
  - At week 36, the reduction from baseline in the galactose-deficient IgA1 level was 68.3% in the atacicept group and 2.9% in the placebo group

  - At week 36, among the 122 patients (60.1% of the 203 patients included in the interim analysis) with baseline hematuria (≥1+) determined on the basis of dipstick testing, resolution of hematuria (defined as a reduction to negative or trace dipstick findings) had occurred in 51 of 63 patients (81.0%) in the atacicept group and in 12 of 58 (20.7%) in the placebo group

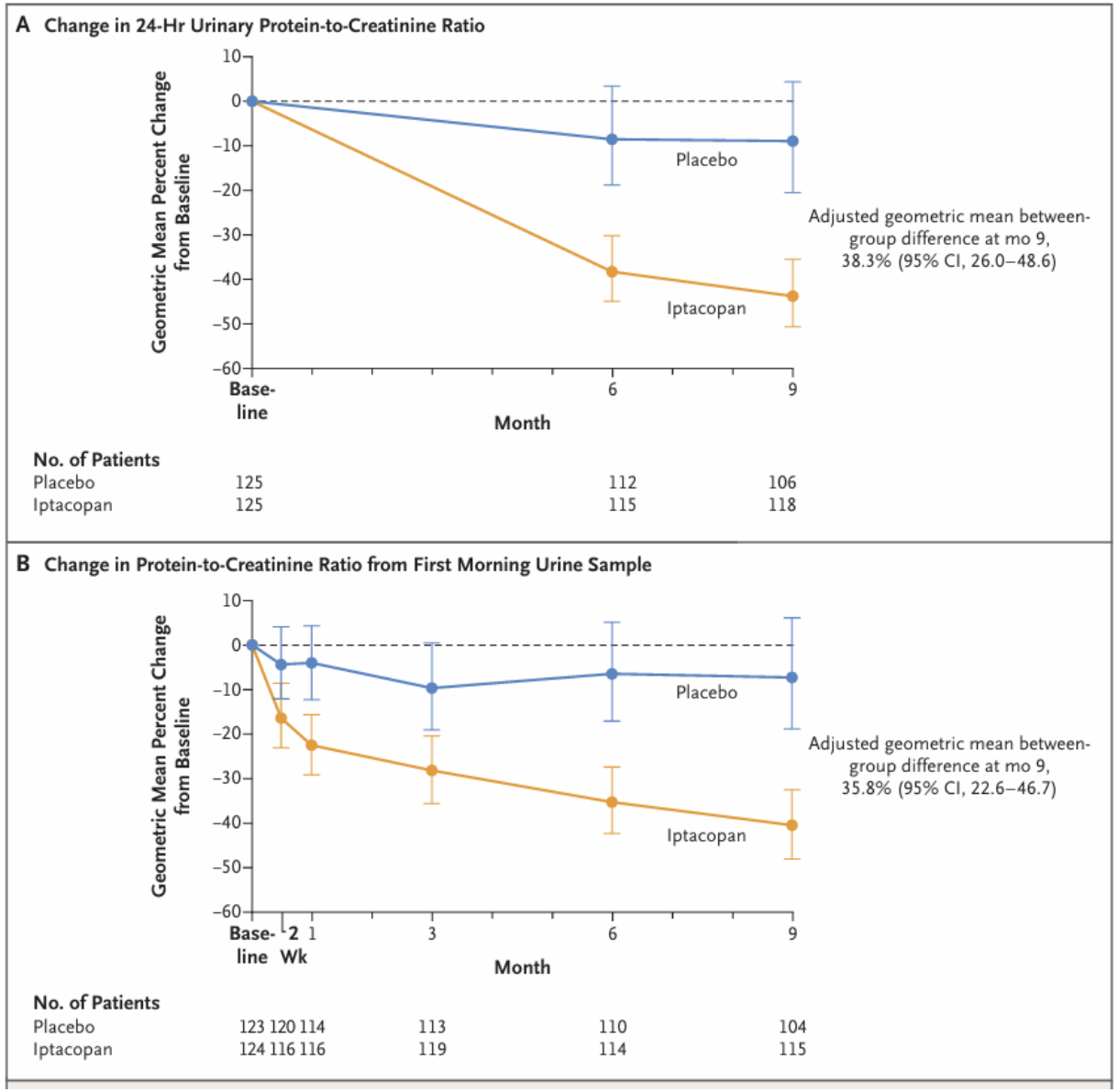
Lafayette R, et al. *N Engl J Med*. 2026;394(7):647-657.

Complement Pathways (Active in IgAN)



Caravaca-Fontán F, et al. *Clin Kidney J.* 2023;16(Suppl 2):ii28-ii39.

Complement Inhibition-*Iptacopan*, APPLAUSE-IgAN



Changes in urine protein creatinine ratio

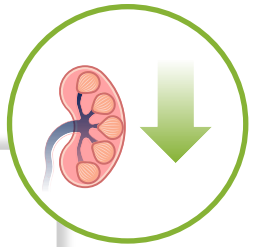
- Iptacopan (LNP023) is an oral FB inhibitor
- Phase 3 study, 443 patients from 34 countries, 24-hour UPCR ≥ 1 g/g, eGFR ≥ 30 ml/min/1.73m2
- Iptacopan 200 mg or placebo twice daily for 24 months
- 250 patients included for interim analysis at 9 months
- 51% patients from Asia
- Mean 24-hour UPCR reduced by 38.3% in iptacopan vs placebo

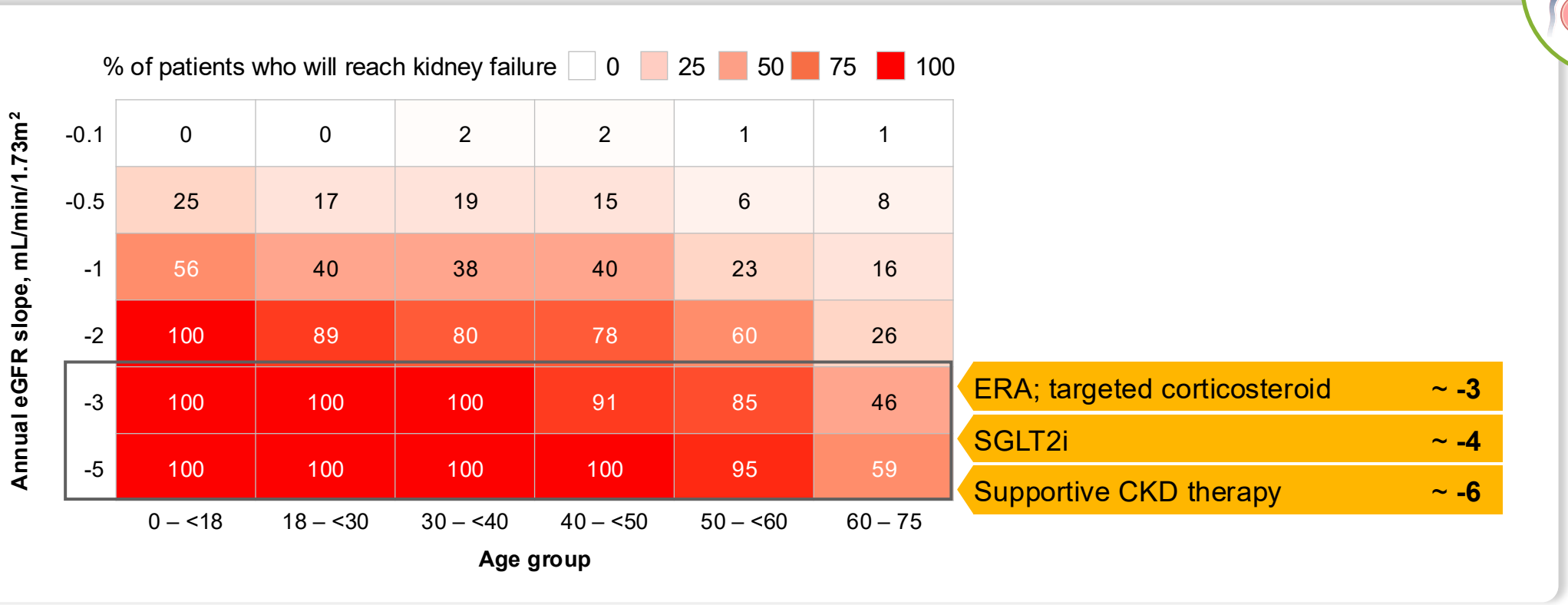
Perkovic V, et al. *N Engl J Med*. 2025;392(6):531-543.

Historical Treatments

- Fish oil
- RAAS inhibition
- Lower blood pressure / proteinuria
- Systemic corticosteroids

The Draft Clinical Practice Guideline for IgAN Calls for a Target eGFR Slope ≤ -1 mL/min/year





Current IgAN therapies do not meet the goal of reducing eGFR decline to ≤ 1 mL/min/year

Pitcher D, et al. *Clin J Am Soc Nephrol*. 2023;18:727-738. Rovin BH, et al. *Lance*t. 2023;402:2077-2090. Lafayette R, et al. *Lancet*. 2023;402:859-870. Wheeler DC, et al. *Kidney Int*. 2021;100:215-224. Li PK-T, et al. *Am J Kidney Dis*. 2006;47(5):751-760. Manno C, et al. *Nephrol Dial Transplant*. 2009;24:3694-3701. Lv J, et al. *JAMA*. 2017;318(5):432-442. Lv J, et al. *JAMA*. 2022;327(19):1888-1898. Zhang H, et al. Presented at ASN Kidney Week; November 1-5, 2023; Philadelphia, PA. Mathur M, et al. *N Engl J Med*. 2024;390(1):20-31. KDIGO Glomerular Diseases Work Group. *KDIGO 2024 Clinical Practice Guideline for the Management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A Vasculitis (IgAV) Public Review Draft*. 2024.

- Need long-term data with new therapies or combinations
- Rely on surrogate measures now

Key Learning Points

Reduce the production of pathogenic IgA and IgA immune complexes	Reduce glomerular inflammation	Address the consequences of ongoing nephron loss
• TRF-budesonide • APRIL inhibitors • APRIL+BAFF inhibitors • Anti-CD38 mAbs	• Corticosteroids • Complement inhibitors	• RAS inhibitors • SGLT2 inhibitors • Endothelin receptor antagonists
Optimize supportive care Control blood pressure to ≤120/70 mm Hg and, address cardiovascular risk factors Lifestyle advice, including dietary sodium restriction, smoking cessation, weight reduction, and exercise as appropriate		

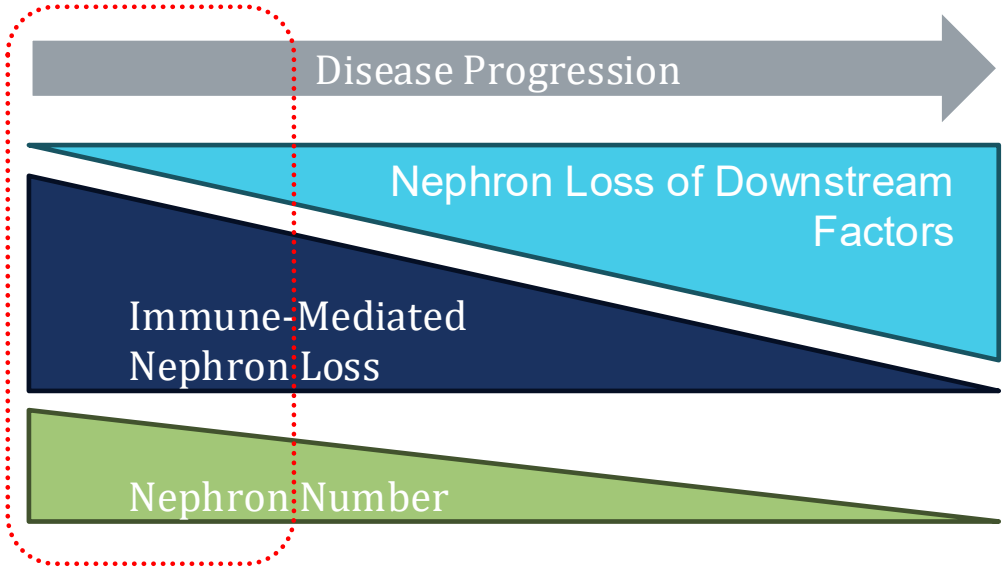
- We need to do both
  - ***Preserve renal function***
    - RAAS blockade in all patients
    - SGLT2 inhibitors
      - DAPA CKD, EMPA CKD-no requirements for patients to be on 3 month of RAAS blockade before SGLT2 inhibitor addition.
      - Appropriate if proteinuria> 0.5 g/d despite RAAS blockade and disease modifying therapy in patients with eGFR< 60 ml/min/1.73m2.
        - Consider above eGFR> 60 ml/min/1.73m2, but do not use in lieu of disease modifying therapy (KDIGO draft 2024)
    - Endothelin antagonists-DEARA, ERA alone
    - ? MRA
    - Atacicept, povetacicept, and telitacicept are dual BAFF-/APRIL-targeting agents
  - ***Stop the immunological drivers of disease/decrease renal inflammation-disease modifying therapy***
    - Proteinuria reduction to as low as possible ideally < 0.3 grams per day
    - ? Role of repeat renal biopsy to determine inflammatory vs chronic changes
    - ? Combination of treatments/multitarget treatment
    - Need biomarkers to help guide treatment response, need for retreatment/ongoing treatment

FIRST REPORT MANAGED CARE

Managed Care Presentation

Russell Spjut, PharmD

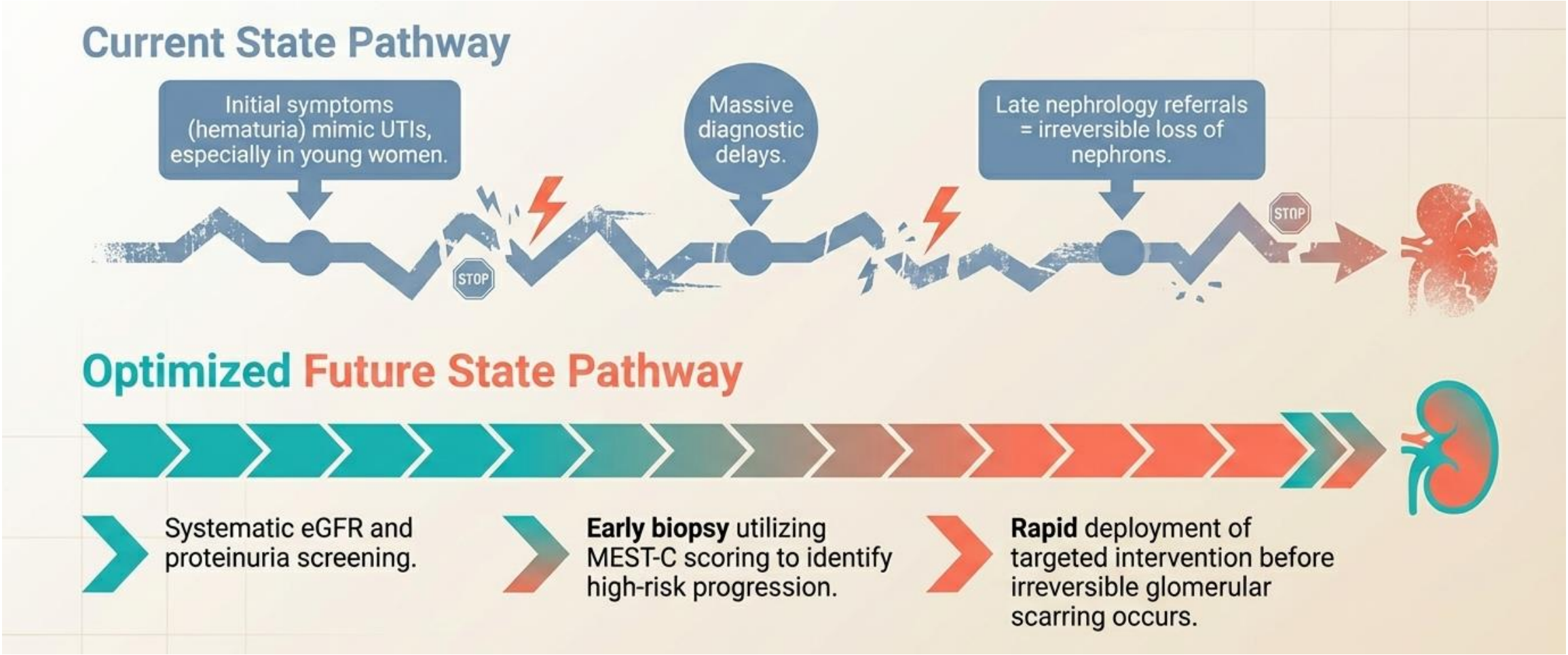
The Promise of Immune-Process Targeting



- In just the short span since the last KDIGO guidelines in 2021, we are moving from supportive care + corticosteroid consideration to targeting the upstream cause of the disease
- As always, we will be asking for long-term outcomes data, but even the short-term outcomes seem to point to a better lifelong journey
- Avoiding reliance on corticosteroids has the potential to increase adherence and improve quality of life

KDIGO Glomerular Diseases Work Group. *KDIGO 2024 Clinical Practice Guideline for the Management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A Vasculitis (IgAV) Public Review Draft*. 2024.

Optimizing the Patient Journey



KDIGO Glomerular Diseases Work Group. *KDIGO 2024 Clinical Practice Guideline for the Management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A Vasculitis (IgAV) Public Review Draft*. 2024.

Coordinating Care Pathways: Managed Care Considerations

- Aligning policies and pathways throughout the patient journey from diagnosis to treatment
- Encourage, and make available, early urinalysis in high-risk populations
- Ensure access to nephrologists if early markers point toward IgAN
  - Best to have access to specialists with expertise in glomerulopathies
  - In areas direct access may be unavailable, create pathways for consults and telemedicine
- In a rapidly expanding and shifting treatment landscape, ensure that coverage policies are regularly reviewed and aligned with the best data available

Rovin BH, et al. *Kidney Int*. 2025;108(4):S1-S71. Cheung CK, et al. *Nat Rev Nephrol*. 2025;21(1):9-23. ICER. Accessed April 15, 2026. https://icer.org/assessment/iga-nephropathy-2025/

Access Considerations

- Patient selection criteria considerations
  - The use of uPCR and eGFR as inclusion criteria and progress markers, while surrogates toward long-term outcomes, are well understood generally in nephrology to have high correlation with slowing progression of kidney dysfunction
  - Drug coverage policies aligning with clinical trial markers likely a good base for coverage policies while also coupling with the goal of a streamlined patient journey
- ICER and a value-based framework
  - ICER found that current prices for some novel B-cell therapies are significantly higher than value-based price benchmarks
  - Those benchmarks will be refined as longer-term data becomes available
  - As new products launch, experts recommend against stepping through systemic corticosteroids or budesonide to get to B-cell inhibitors if pricing aligns with value targets

Rovin BH, et al. *Kidney Int*. 2025;108(4):S1-S71. ICER. Accessed April 15, 2026. https://icer.org/assessment/iga-nephropathy-2025/

Value Targets: Costs vs Long-Term Savings

- High acquisition vs long-term offsets
  - The wholesale acquisition cost of novel biologics is high with currently published estimates of ~$292k/year
  - Transitioning a patient through CKD stages costs payers a lot, potentially setting the stage for long-term cost offset realization
    - Stage 5/ESRD costs are estimated at ~$11,882 per patient per month though higher in the first 33 months before Medicare coverage begins.
    - Mean cost for kidney transplant is $446,800 with an ongoing $4,614 per month in support of the transplant
- Managed care considerations today
  - Aggressive early management to delay ESRD can lead to substantial long-term medical care savings, potentially justifying the cost of disease-modifying therapies depending on pricing
  - Staying on top of what looks like a landscape set to evolve rapidly for the foreseeable future, especially long-term outcomes data, will help us laser into the best value coverage policies

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Key Learning Points

- Early detection, and therapy that targets the underlying cause of the disease, will likely contribute to saving glomerular function
- Optimal outcomes will require a smoothing of the patient journey and access to both diagnosis and treatment
- Access criteria for new therapies should be baselined off the markers of uPCR and eGFR as found in clinical studies
- This is a rapidly evolving area where it will be important for managed care organizations to stay on top of new data to optimize value

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Q&A