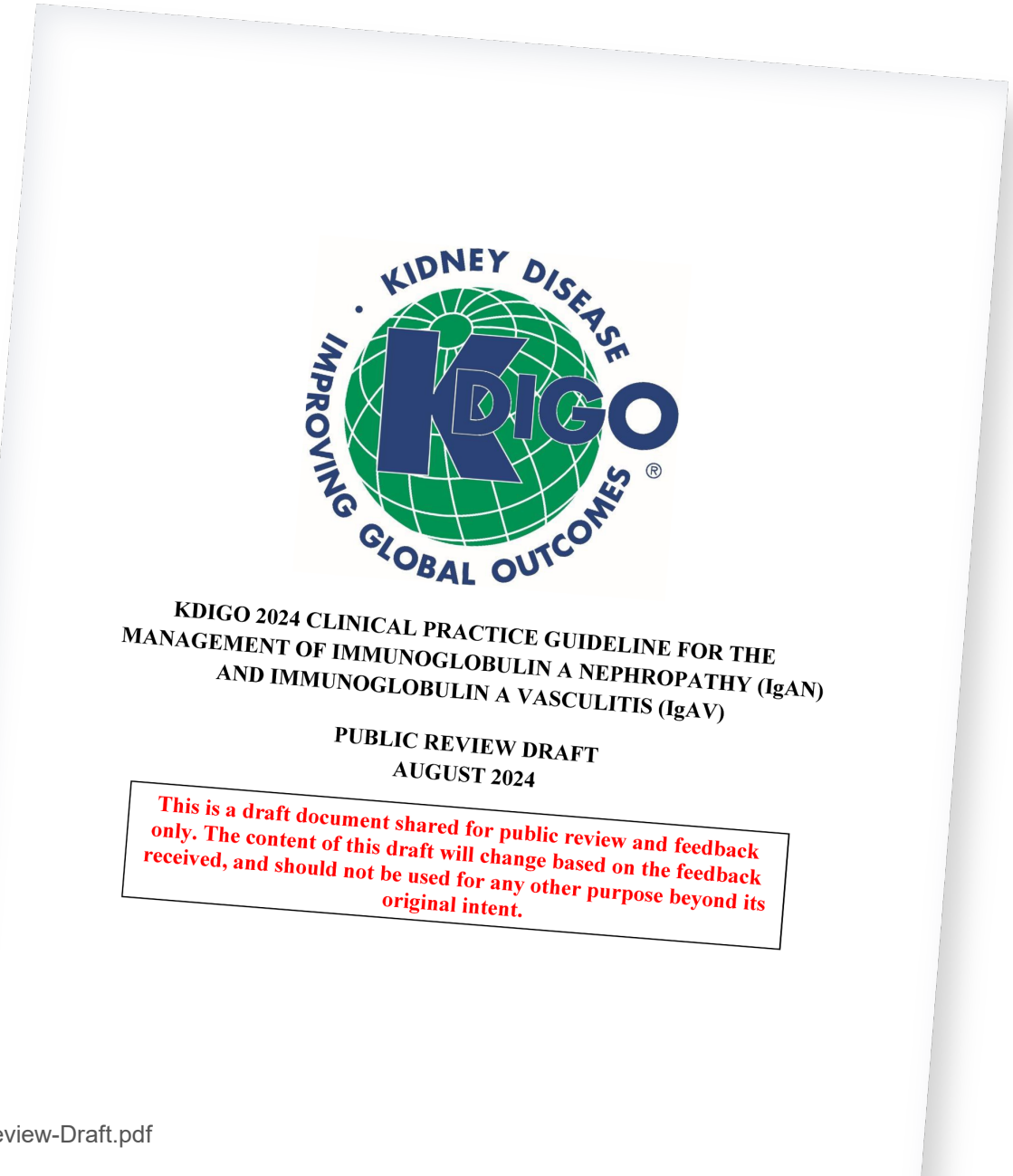
DRAFT KDIGO 2024 CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF IMMUNOGLOBULIN A NEPHROPATHY (IgAN) AND IMMUNOGLOBULIN A VASCULITIS (IgAV)


KDIGO 2024 CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF IMMUNOGLOBULIN A NEPHROPATHY (IgAN) AND IMMUNOGLOBULIN A VASCULITIS (IgAV)

PUBLIC REVIEW DRAFT
AUGUST 2024

This is a draft document shared for public review and feedback only. The content of this draft will change based on the feedback received, and should not be used for any other purpose beyond its original intent.

KDIGO Glomerular Diseases Work Group. Public review draft.
https://kdigo.org/wp-content/uploads/2024/08/KDIGO-2024-IgAN-IgAV-Guideline-Public-Review-Draft.pdf

CLINICAL CASE

20-YEAR-OLD MAN

Case Description:

- Blood and protein in the urine
- UPCR revealed proteinuria of 2.5 g/g
- Hematuria
- eGFR of 68 mL/min/1.73 m^2/year
- Kidney biopsy confirmed IgA nephropathy
- No hypertension

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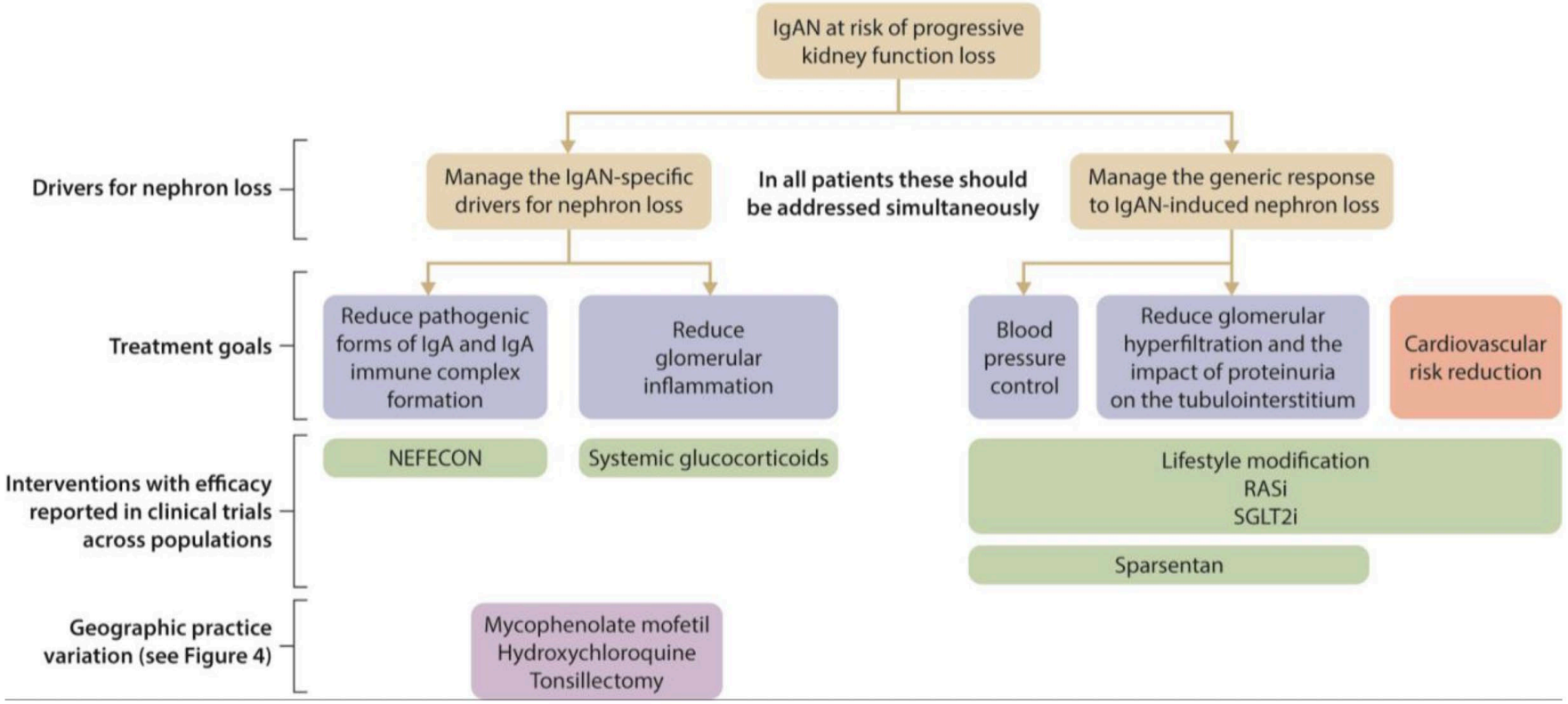


Figure 3 | Treatment targets in immunoglobulin A nephropathy (IgAN) and available to-date approved treatment options. *Measures to reduce glomerular hyperfiltration and the impact of proteinuria on the tubulointerstitium, using singly or in combination, renin-angiotensin system (RAS) blockade sparsentan, and sodium-glucose cotransporter-2 inhibition (SGLT2i). RASi, renin-angiotensin system inhibitors.

KDIGO Glomerular Diseases Work Group. Public review draft.
https://kdigo.org/wp-content/uploads/2024/08/KDIGO-2024-IgAN-IgAV-Guideline-Public-Review-Draft.pdf

Quote by Jürgen Floege, MD

“But we become rheumatologists, hit hard and early before the joint is damaged, now replace joint with nephron before a nephron is lost because it won't come back.”

Quote by Jonathan Barratt, MD

“I'm not going to make a decision on one treatment over another simply on the basis of the MEST-C score.”

Treatment Options

Sparsentan

- Single molecule
- Dual endothelin and angiotensin II receptor antagonist

Nefecon

- Targeted-release formulation of budesonide designed to act at the gut mucosal level

Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group

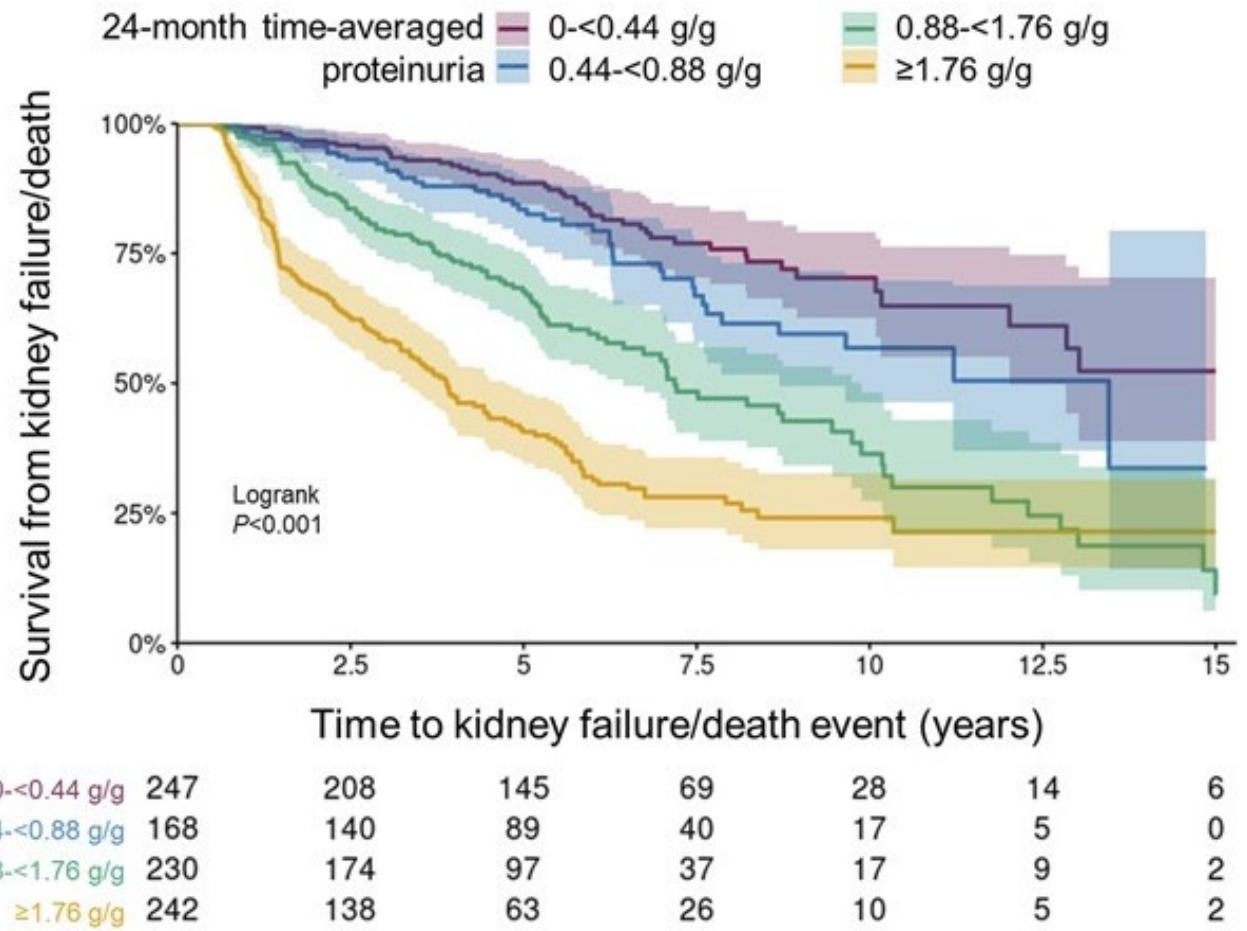
2021 Clinical Practice Guideline for the Management of Glomerular Diseases

- Recommendation 2.3.1 Patients with IgAN who are at high risk of progressive CKD despite maximal supportive care
  - Practice Point 2.3.1.2 Proteinuria reduction to under 1 g/d is a surrogate marker of improved kidney outcomes in IgAN, and reduction to under 1 g/d is a reasonable target.

KDIGO Glomerular Diseases Work Group. *Kidney Int*. 2021;100(4S):S1-S276.

There Is No “Safe” Proteinuria Threshold: An Analysis of the UK National RaDaR IgA Nephropathy Cohort

Development of kidney failure and mortality by severity of proteinuria*



*Kaplan-Meier curves for patients categorized by TA-PU. TA-PU, time-averaged proteinuria.

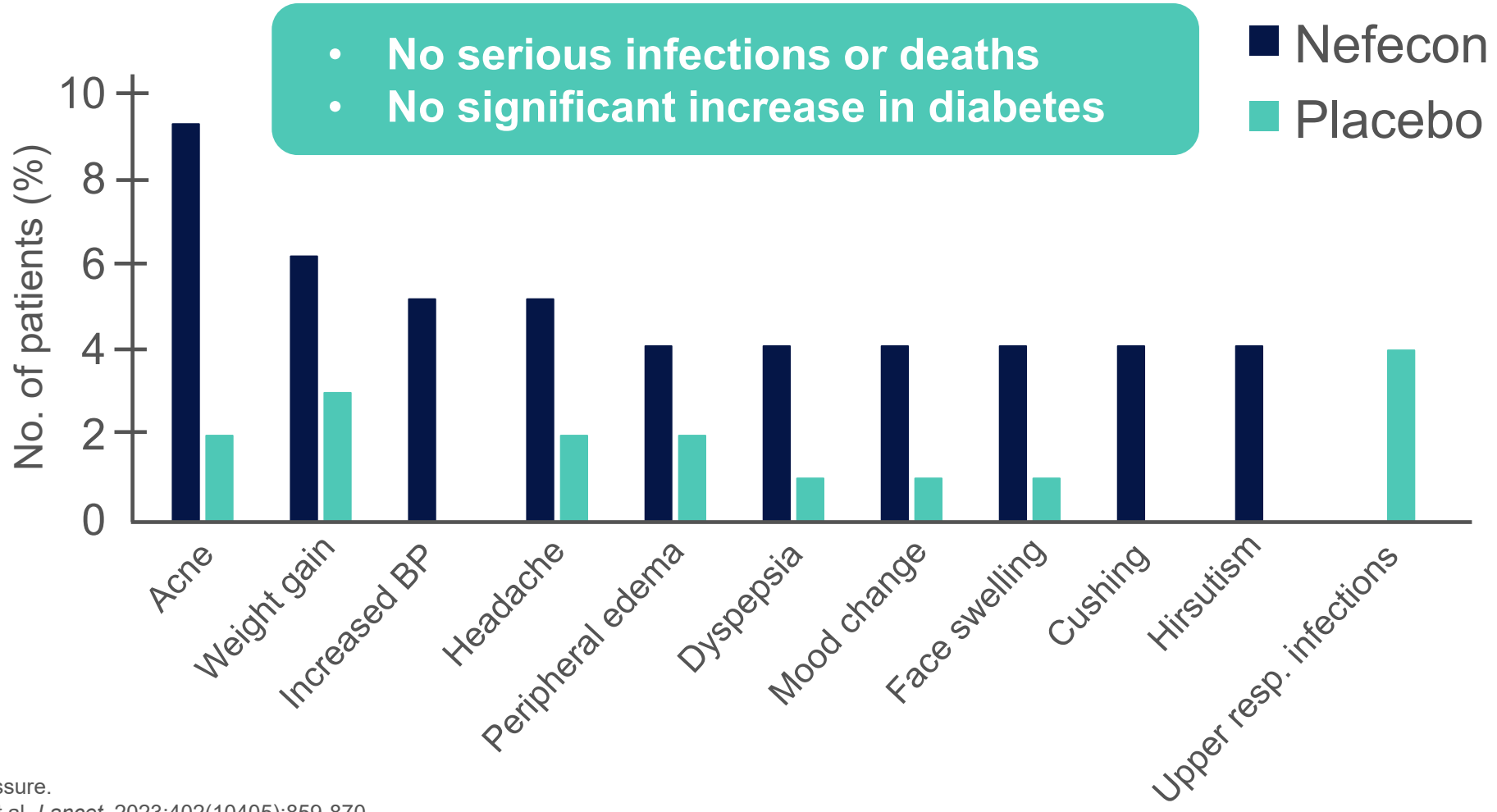
Pitcher D, et al. *Clin J Am Soc Nephrol.* 2023;18(6):727-738.

Quote by Jürgen Floege, MD

"Full remission defined as **proteinuria of ideally 0.3 or less**, but 0.5 is something that would already make me happy."

Neflgard Phase 3 Trial: Adverse Events

- Treatment-emergent adverse events in >4% patients (full analysis set, n = 197)

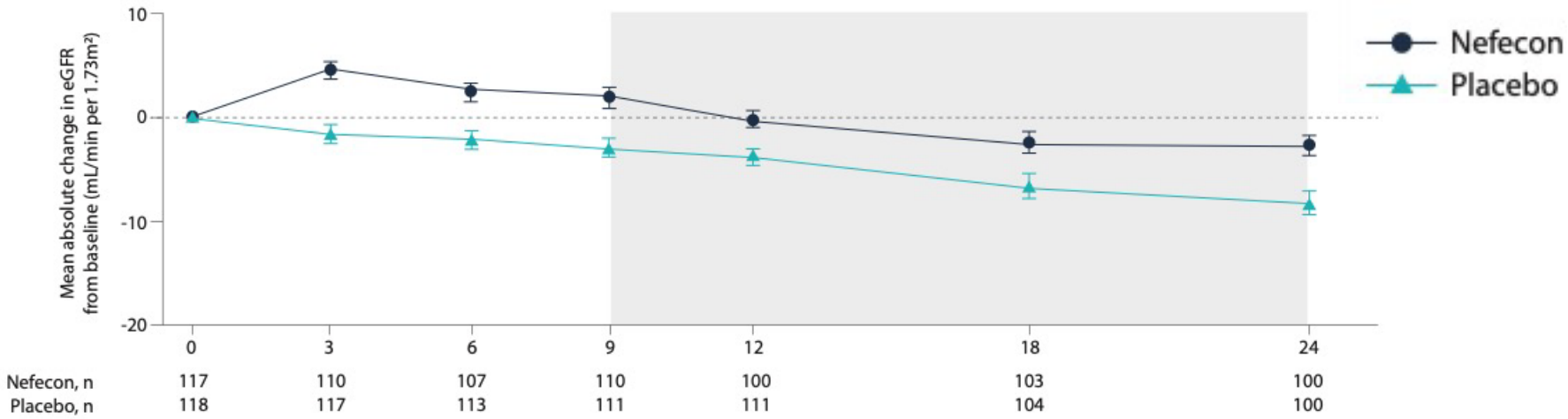


BP, blood pressure.

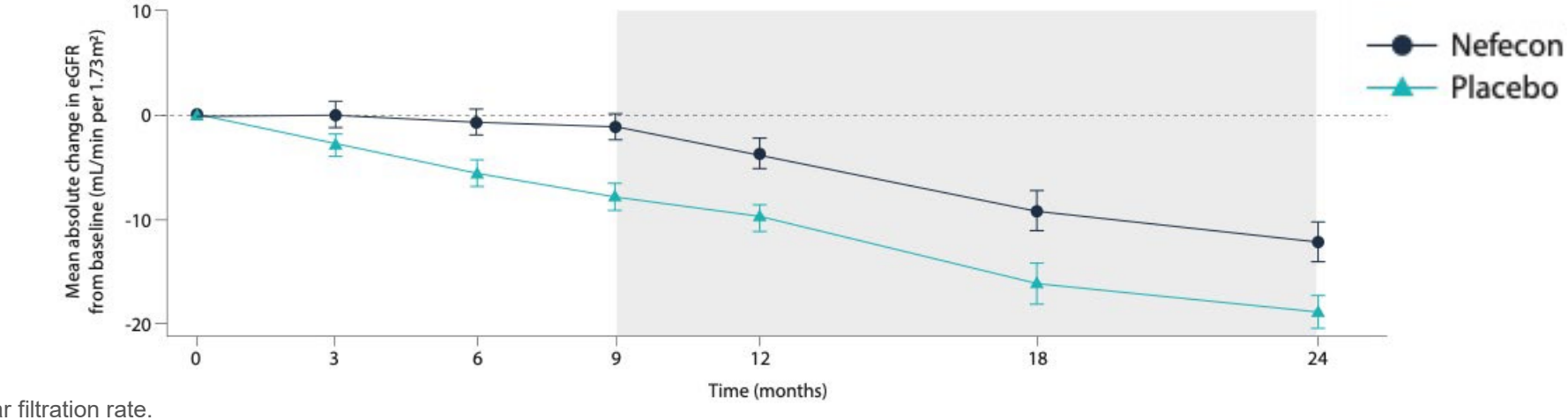
Lafayette R, et al. *Lancet*. 2023;402(10405):859-870.

Targeted-Release Budesonide (Nefecon) in IgAN: Neflgard Phase 3 Trial

eGFR: Baseline proteinuria <1.5 g/g



eGFR: Baseline proteinuria ≥1.5 g/g



eGFR, estimated glomerular filtration rate.

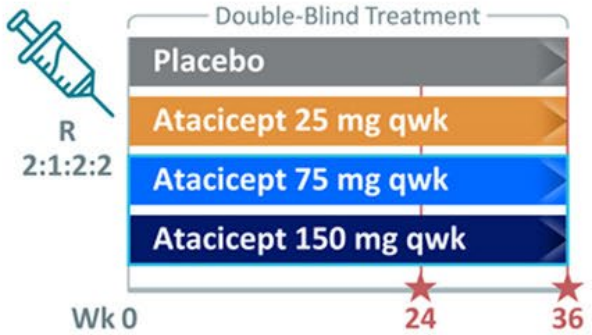
Lafayette R, et al. *Lancet*. 2023;402(10405):859-870.

Quote by Jonathan Barratt, MD

“Nefecon at 9 months does not cure IgA nephropathy.”

A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Clinical Trial of Atacicept for Treatment of IgAN

Methods and population

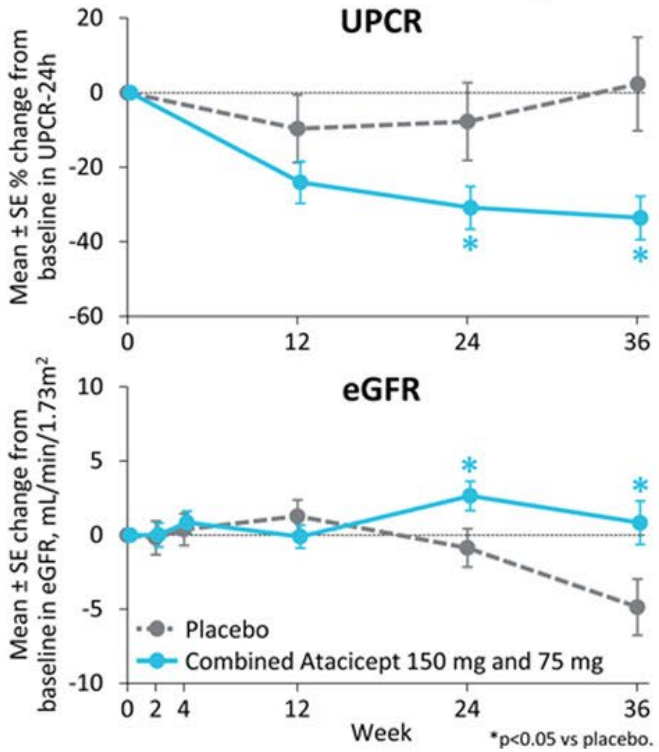


- 116 adults from 13 countries
- Biopsy-proven IgAN within 10 years prior to screening
- ≥12 weeks on maximally tolerated, stable dose of RAASi
- SGLT2i use was allowed

Key baseline characteristics

- Mean UPCR-24h **1.6** g/g
- Mean eGFR **63** mL/min/1.73m²

Outcomes with combined 75 mg and 150 mg group vs placebo



1° endpoint met at 24 weeks:

UPCR reduction **Δ25%** **p=0.037**

Key 2° endpoints at 36 weeks

UPCR reduction **Δ35%** **p=0.004**

eGFR difference **11%** **p=0.022** **5.7** **mL/min/1.73m²**

Gd-IgA1 reduction **Δ60%** **p<0.0001**

Safety profile of all atacicept doses similar to placebo

- Treatment with atacicept, a dual BAFF/APRIL inhibitor, in addition to current standard of care, resulted in clinically and statistically significant UPCR reductions at weeks 24 and 36 and eGFR stabilization at week 36, supporting a pivotal phase 3 trial

eGFR, estimated glomerular filtration rate; RAASi, renin-angiotensin-aldosterone system inhibitor; SGLT2i, sodium-glucose cotransporter 2 inhibitor; UPCR, urine protein-creatinine ratio.

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

Sparsentan Targets Glomerular Injury and Slows Kidney Funtion Decline[1,2]

Sparsentan (SPAR) is a non-immunosuppressive, single-molecule, dual endothelin angiotensin receptor antagonist (DEARA)[1] approved in the US and EU for adults with IgAN[2,3]

Effects

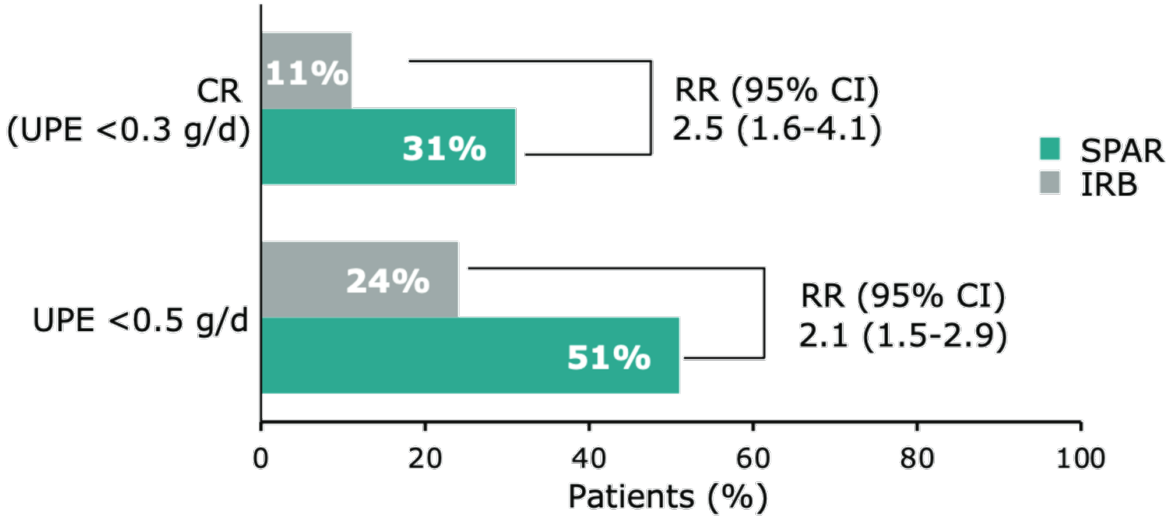
- Anti-inflammatory[4-7]*
- Anti-proliferative[4,5,7]*
- Anti-fibrotic[6,7]*
- Anti-proteinuric[8]

*These effects are based on pre-clinical animal modeling data. Ang II, angiotensin II; AT_1R, angiotensin II type 1 receptor; DEARA, dual endothelin angiotensin receptor antagonist; ET-1, endothelin 1; ET_AR, endothelin-1 type A receptor; IgAN, immunoglobulin A nephropathy; SPAR, sparsentan.

1. Kohan DE, et al. *Clin Sci (Lond)*. 2024;138(11):645-662. 2. Sparsentan. Prescribing information. Travere Therapeutics, Inc.; 2024. 3. Sparsentan. SmPC. CSL Vifor; 2024. 4. Jenkinson C, et al. Poster presented at: ISN World Congress of Nephrology; Melbourne, Australia; April 12-15, 2019. SAT-010. 5. Reily C, et al. *Am J Physiol Renal Physiol*. 2024;326:F862-F875. 6. Nagasawa H, et al. *Nephrol Dial Transplant*. 2024;39:1494-1503. 7. Jenkinson C, et al. Presentation at: International Symposium on IgANephropathy; Buenos Aires, Argentina; September 27-29, 2018. 8. Rovin BH, et al. *Lancet*. 2023;402(10417):2077-2090.

Implications of Proteinuria Remission on Estimated Glomerular Filtration Rate Trajectory in Patients With IgA Nephropathy in PROTECT

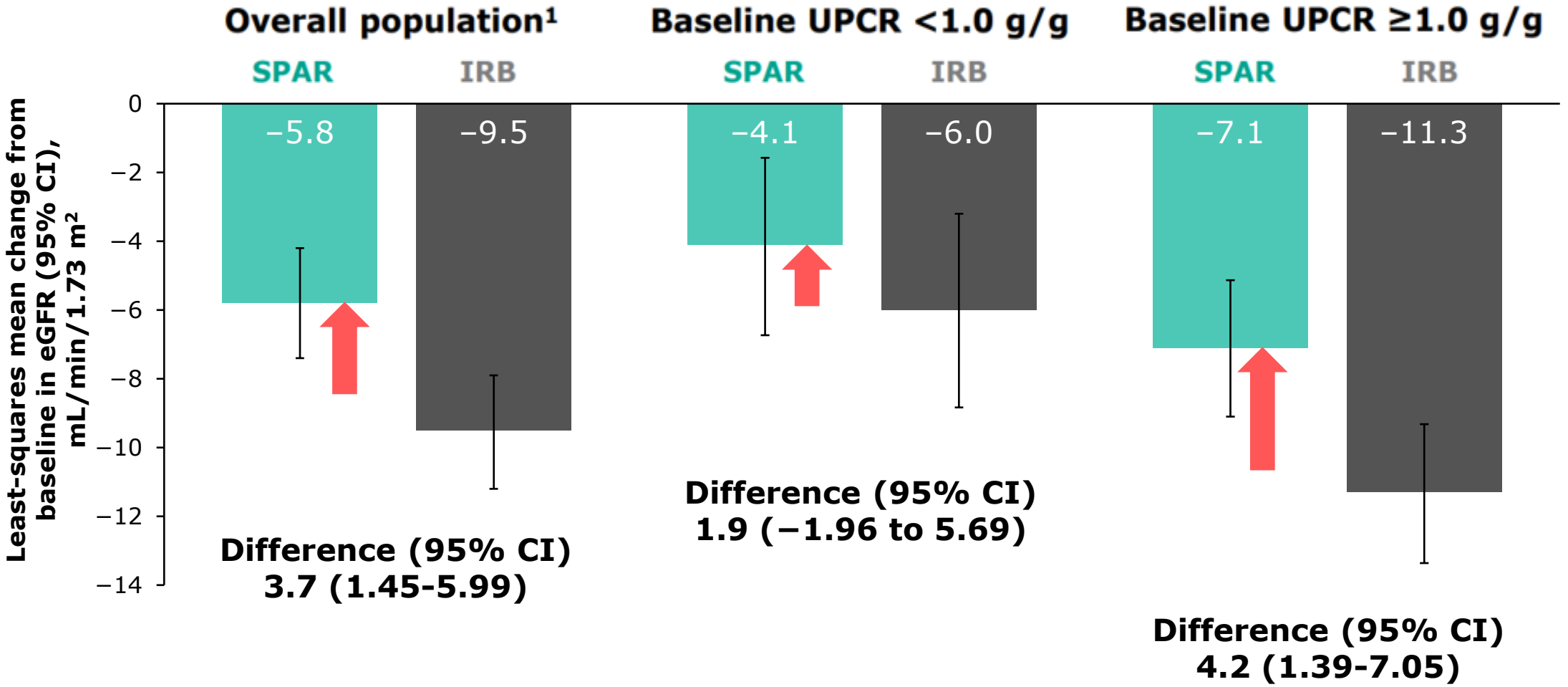
Figure 1. Patients Achieving CR or UPE <0.5 g/d in PROTECT[3]



- eGFR preservation was more evident in patients who achieved low proteinuria vs those who did not. Notably, in patients who achieved CR, the mean rate of kidney function decline (eGFR chronic slope) was below the therapeutic goal of <1.0 mL/min/1.73 m^2/y
- As sparsentan-treated patients achieved proteinuria remission more frequently vs maximum labeled dose irbesartan in the PROTECT trial, this analysis further supports the interplay between proteinuria and kidney function decline, and the benefit of sparsentan for long-term preservation of kidney function

Heerspink HJL, et al. ASN Kidney Week 2024. Abstract FR-PO872.

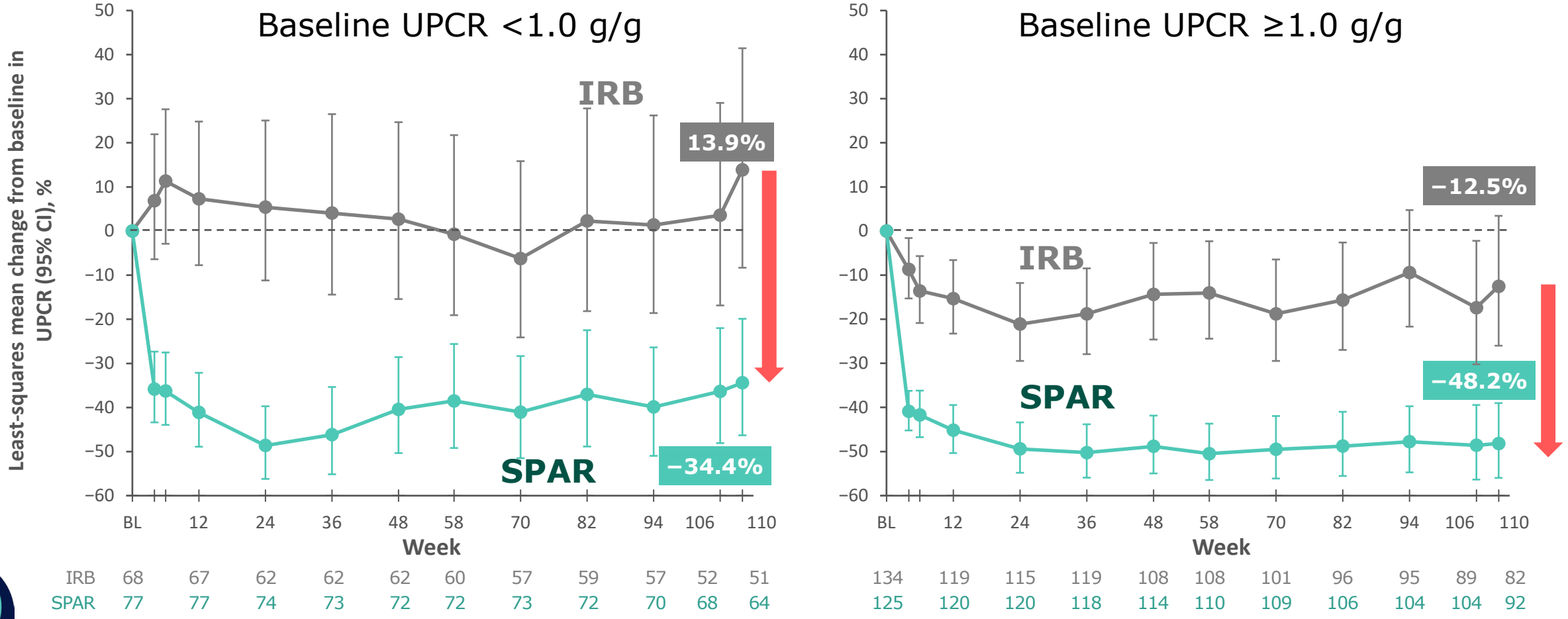
Absolute Change in eGFR From Baseline to Week 110 Was Lower With SPAR vs Maximum Labeled Dose IRB, Regardless of Baseline UPCR Level



eGFR, estimated glomerular filtration rate; IRB, irbesartan; SPAR, sparsentan; UPCR, urine protein-to-creatinine ratio.

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

SPAR Showed Rapid and Sustained Reductions in Proteinuria Through Week 110, Superior to Maximum Labeled Dose IRB, Regardless of Baseline UPCR Level

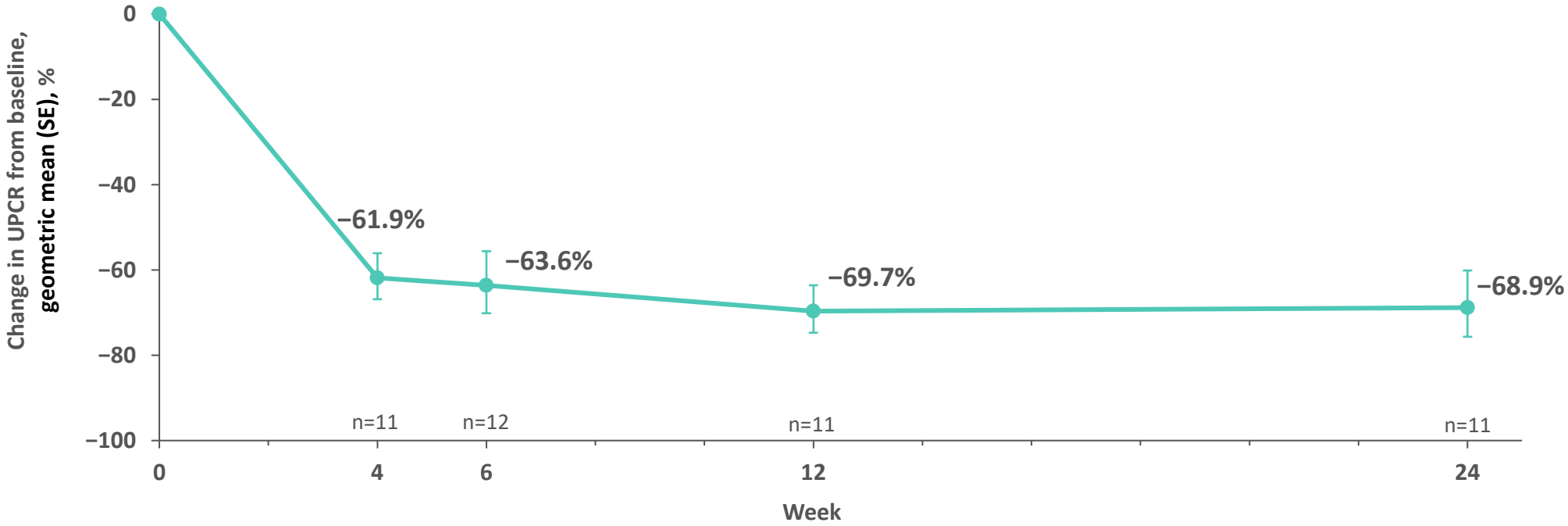


IRB, irbesartan; SPAR, sparsentan; UPCR, urine protein-to-creatinine ratio.

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

Sparsentan as First-Line Treatment of Incident Patients With IgA Nephropathy (IgAN): Interim Analysis of the SPARTAN Trial

- Proteinuria change (UPCR) from baseline*
- Proteinuria reductions were rapid (~60% from baseline at week 4) and sustained over 24 weeks of sparsentan treatment



*On-treatment analysis; 1 patient discontinued after week 6.

Cheung CK, et al. ASN Kidney Week 2024. Abstract FR-OR63.

Quote by Jürgen Floege, MD

"So in terms of CKD therapy with SGLT2 inhibitors having this really nice effect on kidney protection, can we combine it with these newer drugs like…sparsentan?"

Concomitant Sparsentan and Sodium-Glucose Cotransporter-2 Inhibitors in Adults With IgA Nephropathy in the Ongoing Phase 2 SPARTACUS Trial

Figure 3. Change in UACR at Each Visit

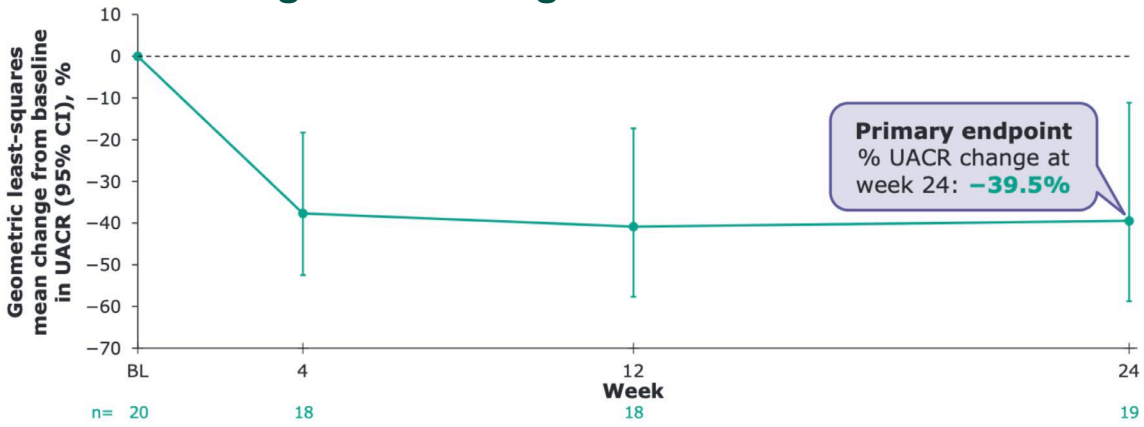
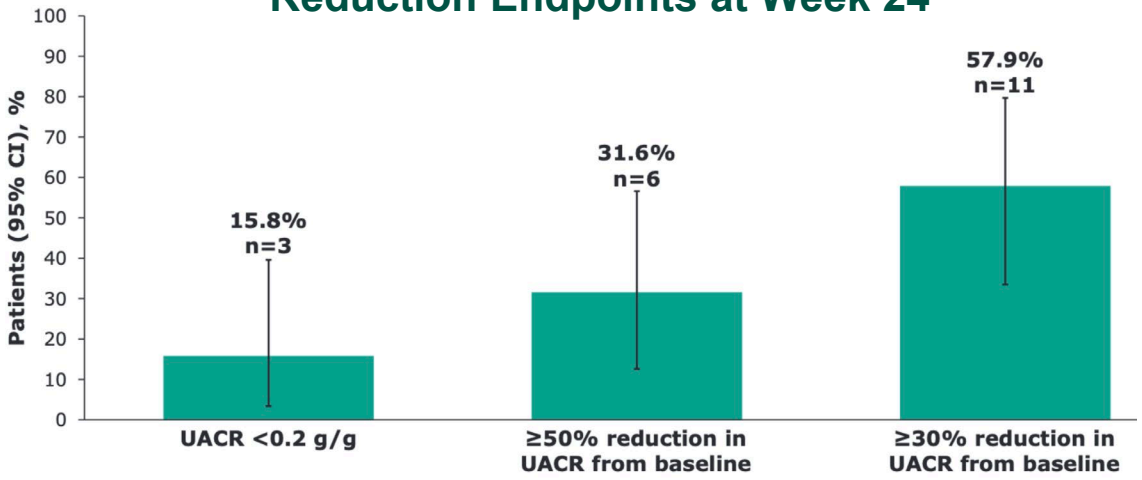


Figure 4. Percent of Patients Achieving UACR Reduction Endpoints at Week 24



Ayoub I, et al. ASN Kidney Week 2024. Abstract FR-PO849.

PROTEINURIA
REMAINS **THE BEST**
PROGNOSTICATOR

Quote by Jonathan Barratt, MD

“And the guideline is a guideline. It's there to help guide, but it's not meant to be a rigid bar upon which clinicians should base every single decision.”

Key Takeaway

- Diagnose patients early
- Proteinuria > 0.5 g/d
  - Consider IgAN
  - Kidney biopsy
  - Significant risk of progressive kidney disease
- Treat to lowest possible proteinuria
  - Below 0.5 g/d
- Treat both sides of IgAN
  - Immunology
  - CKD

Key Takeaway

- Treat early and aggressively to preserve kidney function