Advancing Kidney Health
Through Optimal Medication Management

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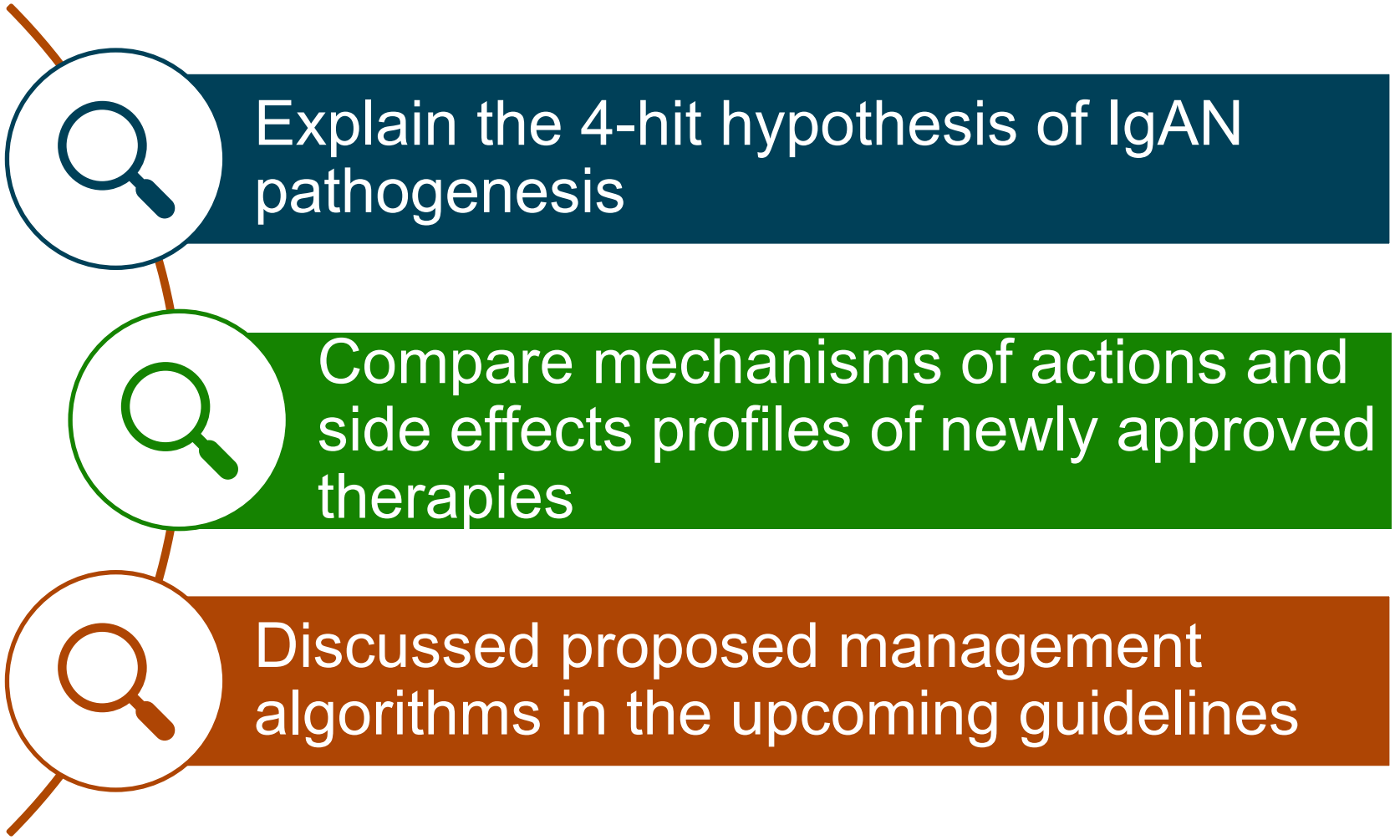
Targeting IgA Nephropathy: Insights into Pathogenesis, Novel Therapies, and Clinical Application

What We're Going to Cover



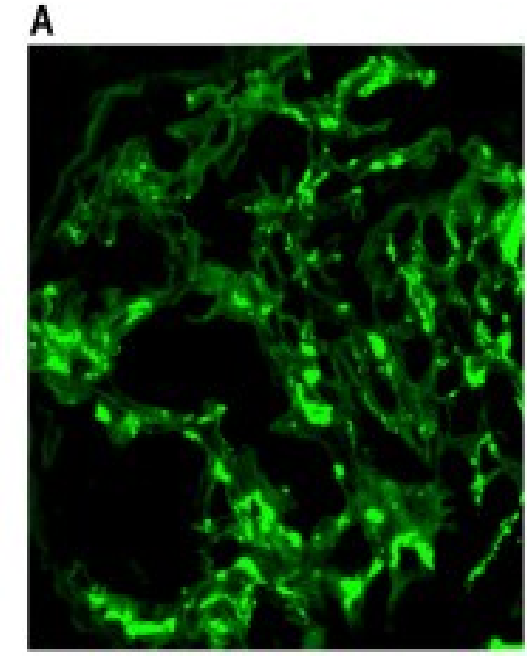
Glossary of Terms

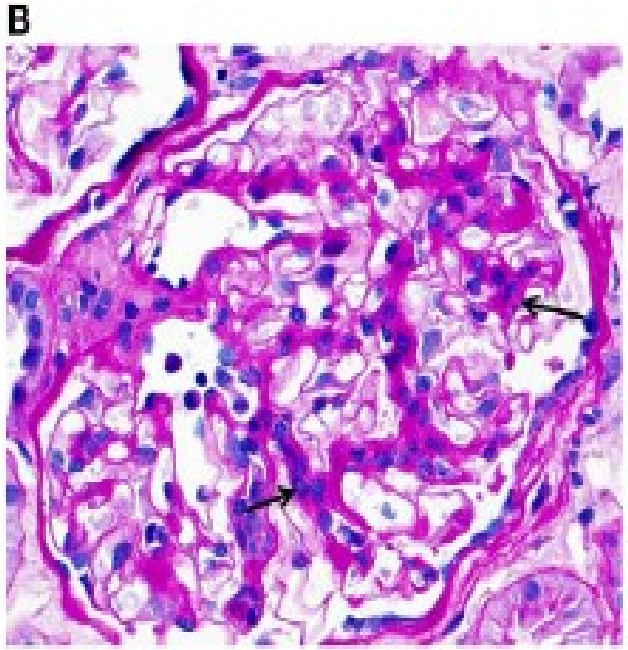
- **AT1** = Angiotensin II receptor type
- **CKD** = Chronic Kidney Disease
- **DEARA** = Dual Endothelin Angiotensin Receptor Antagonist
- **eGFR** = estimated glomerular filtration rate
- **ERA** = Endothelin Receptor Antagonist
- **ESKD** = End Stage Kidney Disease
- **IFTA** = Interstitial Fibrosis and Tubular Atrophy
- **IgAN** = Immunoglobulin A Nephropathy
- **KDIGO** = Kidney Disease: Improving Global Outcomes
- **LFT** = Liver Function Test
- **MEST-C** = Mesangial hypercellularity, Endocapillary hypercellularity, Segmental glomerulosclerosis, Tubular atrophy/interstitial fibrosis, and Crescents
- **MRA** = mineralocorticoid receptor antagonist
- **PAS** = Periodic Acid-Schiff
- **RASi** = Renin-Angiotensin System inhibitors
- **REMS** = Risk Evaluation and Mitigation Strategy
- **SCr** = Serum Creatinine
- **SGLT2i** = Sodium-Glucose Cotransporter-2 inhibitors
- **UACR** = Urine Albumin-to-Creatinine Ratio
- **UPCR** = Urine Protein-Creatinine Ratio

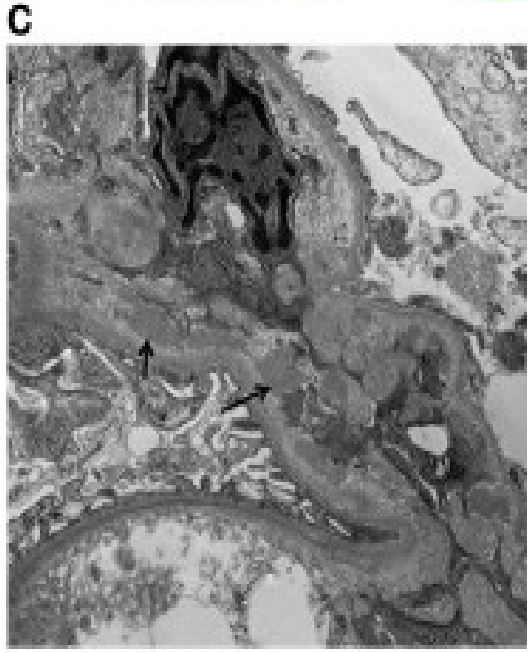
Pathology: Berger's Disease

- IgA mesangial deposits are dominant or co-dominant immunoglobulin (usually with C3, often IgG and sometimes IgM)
- Mesangial expansion and proliferation noted on PAS stain
- Electron-dense deposits

Images: First described in 1968 by Jean Berger (Pathologist, France) and Nicole Hinglais (Electron microscopist, France)







Berger J, Hinglais N J Urol Nephrol. 1968
Knoppova B et al. Frontiers in Immunology 2016

Epidemiology: IgA nephropathy (IgAN)

Most frequent primary glomerulonephritis in USA and the world

Annual incidence in USA estimated at 1/100,000 persons

Peak incidence in the second to third decade of life

M:F ratio 2-3:1 in USA and 1:1 in East Asia

Frequent cause of kidney failure

Rare familial cases

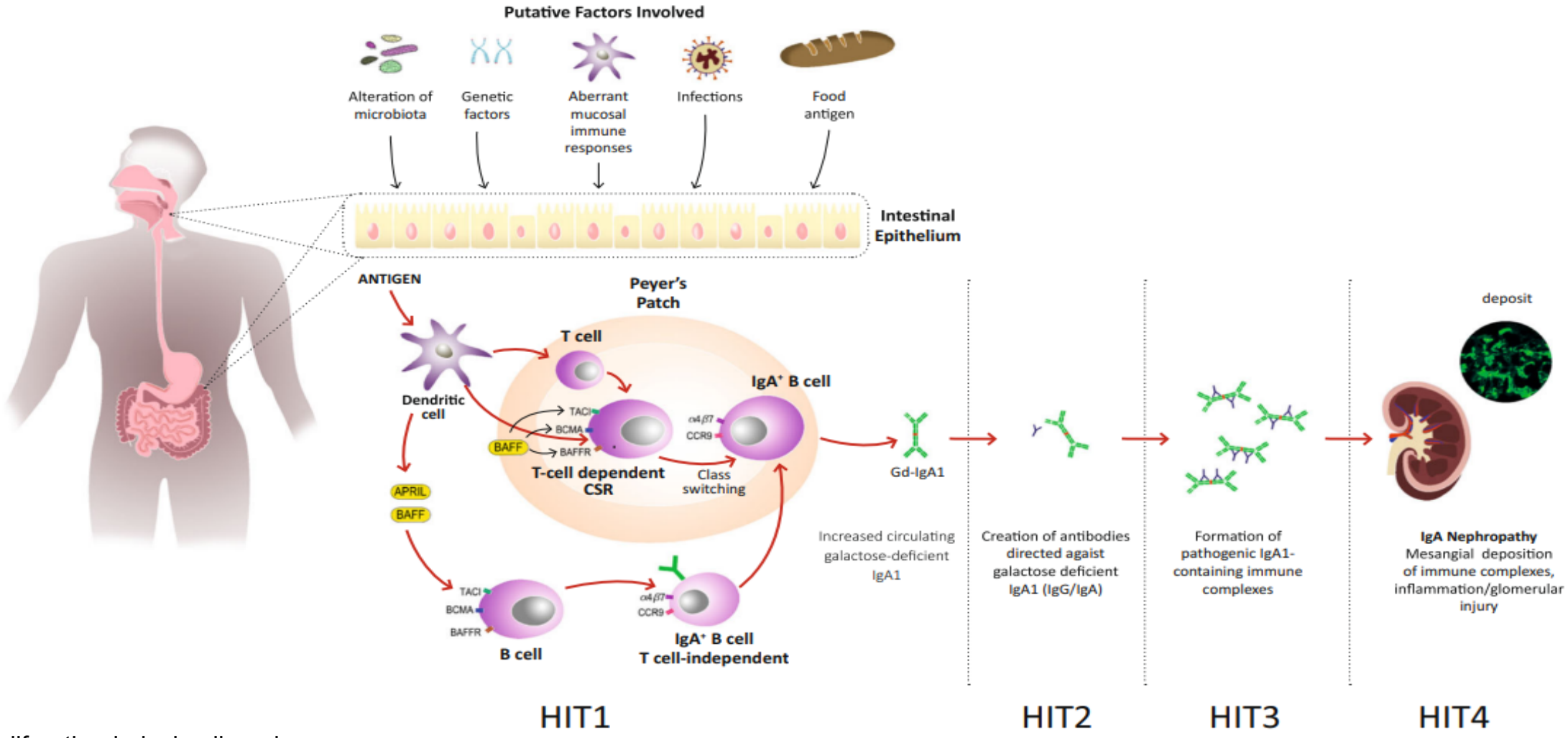
IgAN Prevalence

True prevalence of the disease is unknown:

- Screening practices
- Threshold to perform biopsies
- Renal IgA deposits also seen in ~ 5-15% of kidney biopsies from individuals with no evidence of nephritis (kidney donors, autopsy series)

Rajasekaran A et al. AJMS 2020; Suzuki K et al. KI 2003
Waldherr R et al. Nephrol Dial Transplant. 1989

Current Understanding of IgAN: Multi-Hit Hypothesis for Pathogenesis



APRIL: A proliferation-inducing ligand
BAFF: B-cell activating factor
CSR: Class switching recombination

Gesualdo L et al. Seminars in Immunopathology 2021

Mortality and Risk of Kidney Failure

IgAN increases the mortality risk and correlates with shortening of life expectancy by 6-10 years

Increased mortality risk mediated primarily by kidney failure

It is estimated that 20-50% of patients progress to kidney failure within 20 years from the time of biopsy diagnosis

Jarrick S et al. JASN 2019; Hastings et al. KI Rep 2018; Knoop et al. AJKD 2013

Risk Factors for IgAN Progression

Non- Modifiable Risk Factors	Modifiable Risk Factors
Male gender	Hypertension
Race/ Ethnicity (Asians vs. Caucasians)	Proteinuria
Age at diagnosis	Lifestyle (maintaining normal weight, exercise, smoking etc.)
eGFR at diagnosis	Hyperlipidemia
Pathologic findings (Oxford MEST-C score)	--

MEST-C: Mesangial hypercellularity, Endocapillary hypercellularity, Segmental glomerulosclerosis, Tubular atrophy/interstitial fibrosis, and Crescents

Predicting Risk of Progression: Oxford Classification (MEST-C Score)

MEST-C Score:

- Histology findings used to predict renal outcome independent of proteinuria, BP, eGFR
- M1, S1 and T1/2 are associated with poor renal outcomes
- E1 and crescents may predict response to treatment
- C2 associated with increased risk of poor renal outcomes even in those treated with immunosuppression.

M0 Mesangial hypercellularity in ≤ 50% of glomeruli
M1 Mesangial hypercellularity in > 50% of glomeruli

E0 Endocapillary hypercellularity absent
E1 Endocapillary hypercellularity present

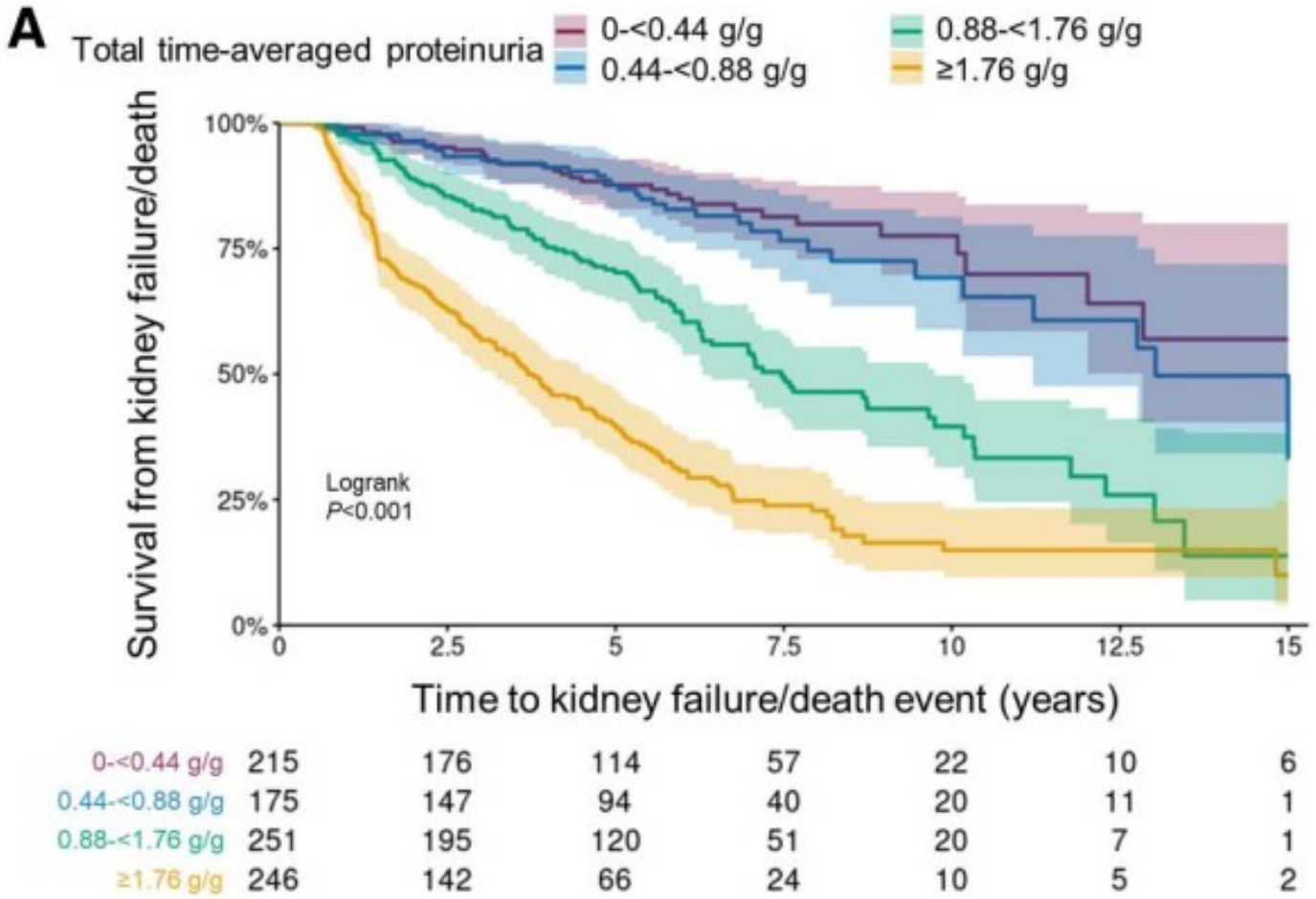
S0 Segmental sclerosis absent
S1 Segmental sclerosis present

T0 0-25% IFTA
T1 26-50% IFTA
T2 > 50% IFTA

C0 no glomerulus with a crescent
C1 < 25% glomeruli with a crescent
C2 ≥ 25% glomeruli with a crescent

Floege J et al. Kidney Int. 2019
Trimarchi H et al. Kidney Int. 2017
Cattran DC et al. Kidney Int. 2009

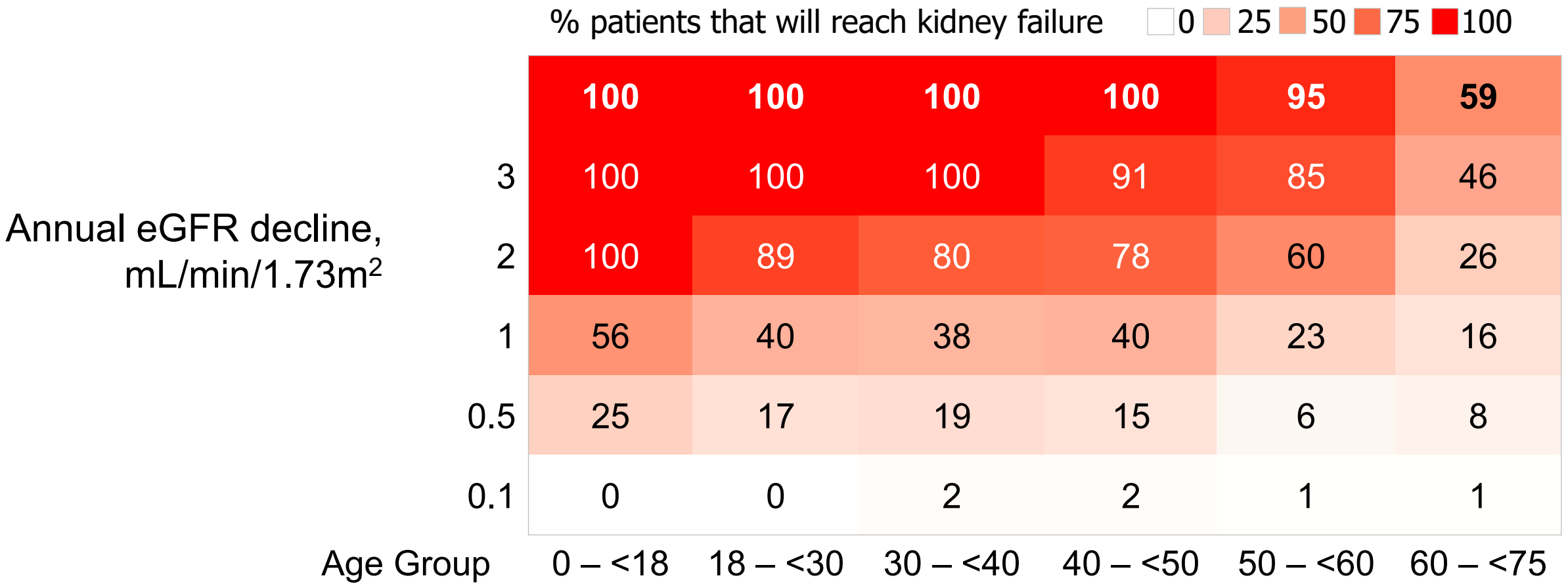
How About Longer Term Outlook? UK RaDaR



20% of patients with time-averaged proteinuria <0.44 g/g and 30% with time-averaged proteinuria 0.44 to <0.88 g/g progressed to kidney failure within 10 years of diagnosis.

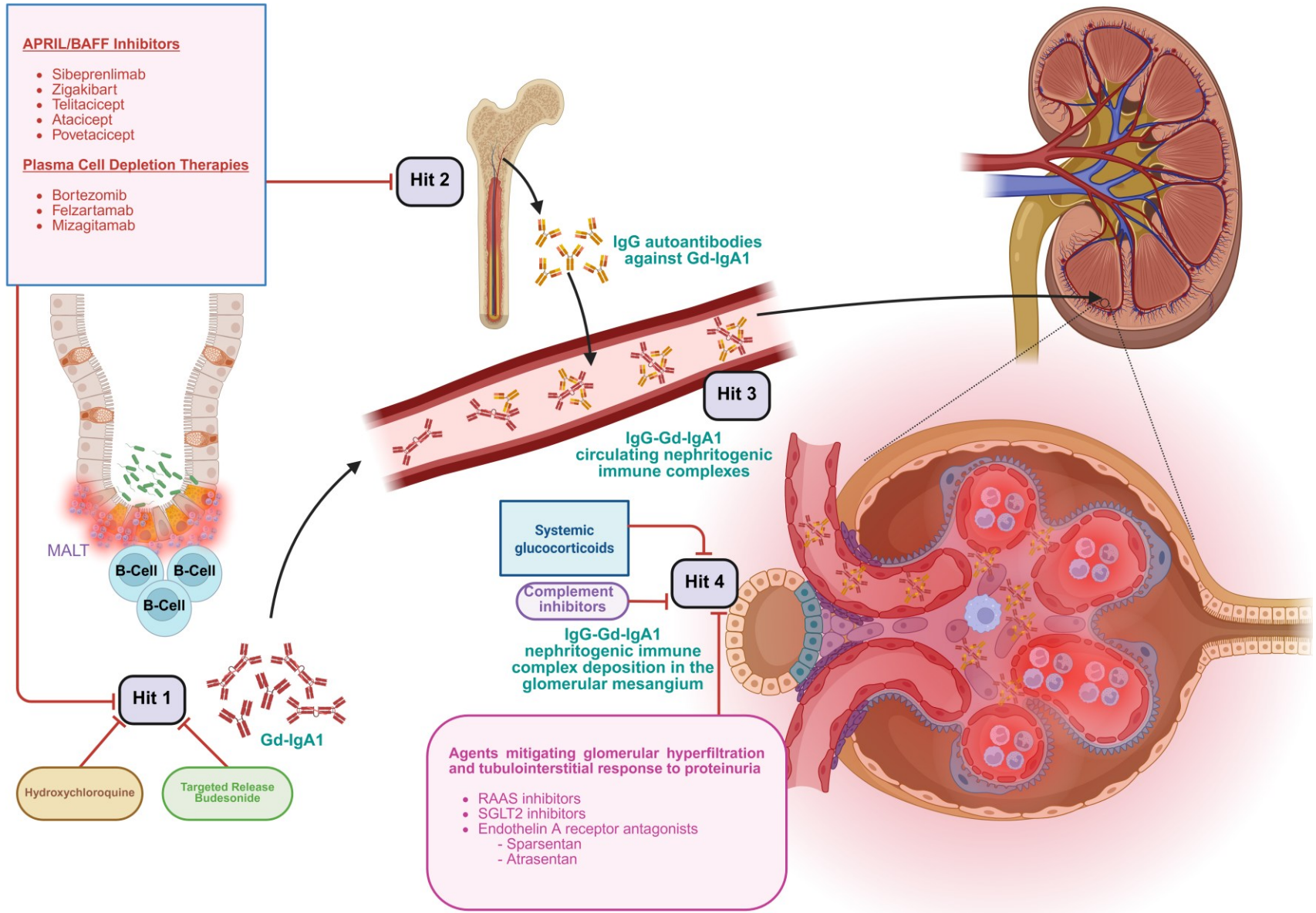
Pitcher D et al. CJASN 2023

The Majority of Patients With IgAN Are at High Risk for ESKD in Their Lifetime Unless eGFR Loss Can be Minimized



Pitcher D, et al. CJASN 2023

Pathogenesis of IgAN and Emerging Targets

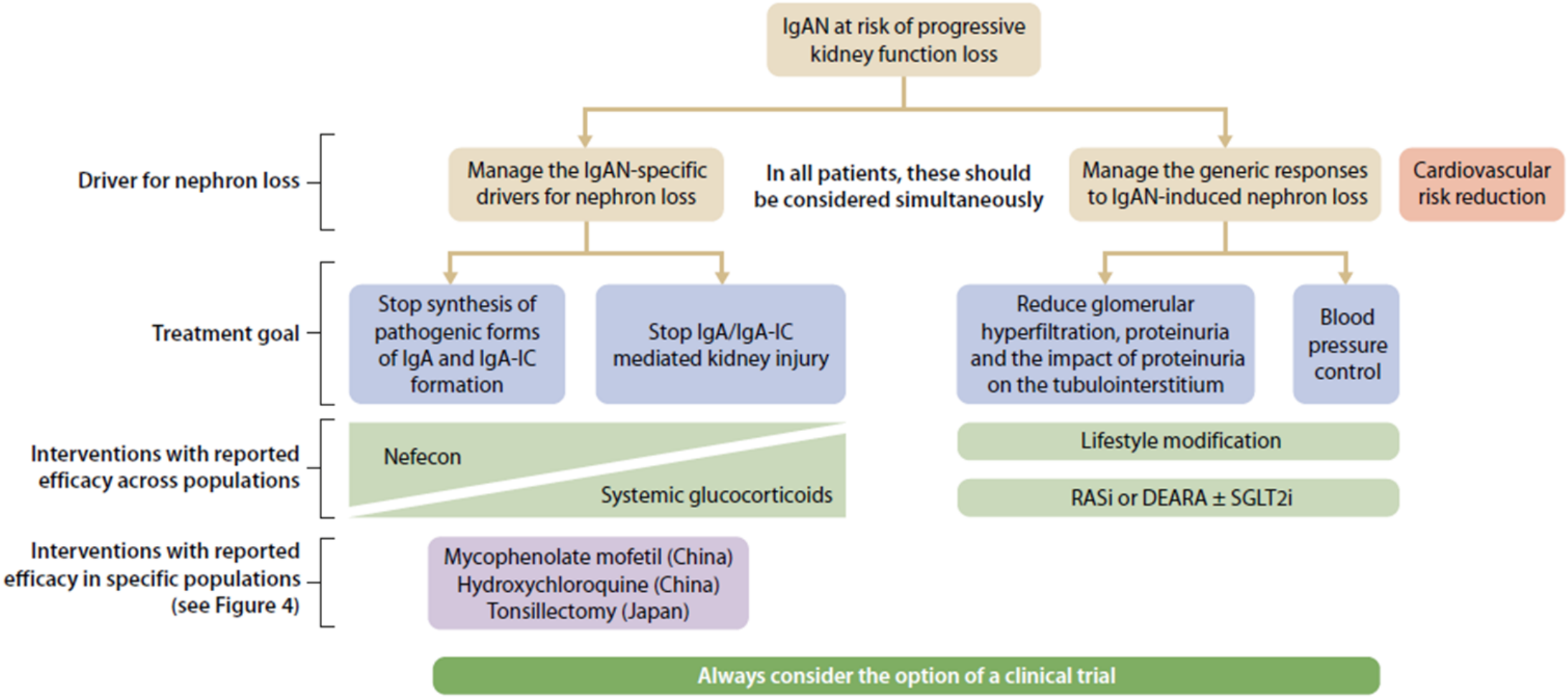


Konda R et al. NDT 2025

Medication Options

Drug	Mechanism of Action	Key Side Effects	Targeted Hit in Pathogenesis per KDIGO	Approval
Dapagliflozin	SGLT2 inhibitor	Urogenital infections, volume depletion, DKA (if diabetic), hypoglycemia (if on other anti-glycemic)	Hit 4	Full
Empagliflozin	SGLT2 inhibitor	Urogenital infections, volume depletion, DKA (if diabetic), hypoglycemia (if on other anti-glycemic)	Hit 4	Full
Sparsentan	Dual ETA/AT1 receptor blocker	Hypotension, fluid retention, hyperkalemia Of note: LFT elevation 3.5%	Hit 4	Full REMS (LFT)
Atrasentan	Selective ETA receptor blocker	Fluid retention, anemia	Hit 4	Accelerated
Iptacopan	Factor B inhibitor (alternative complement pathway)	GI, headache, possible hyperlipidemia (based on C3G trials)	Hit 4 (?only)	Accelerated REMS (vaccination)
Systemic steroids	Anti-inflammatory but also immunosuppressant	Infections, GI bleeding, fracture (with high dose)	Hit 4 (?only)	No
Targeted release budesonide	Targeted steroid delivery to the GALT	GI, hypertension, steroid- related but mild to moderate	Hit 1 (?only)	Full

KDIGO 2025 Guidelines



Kidney Disease: Improving Global Outcomes (KDIGO) IgAN and IgAV Work Group. KDIGO 2025 Clinical Practice Guideline for the Management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A Vasculitis (IgAV). Kidney Int. 2025;108(4S):S1–S71.

Evidence Review: Surrogate Endpoints for Clinical Trials

Traditional approval relied on clinical endpoints

- Progression to ESRD
- Death

Alternative approval pathway allows for surrogate markers

- Proteinuria
- eGFR slope

Significant impact on drug development in nephrology rare diseases

- Smaller sample size
- Shorter duration

Levey AS, et al. Am J Kidney Dis 2020;75(1):84-104.

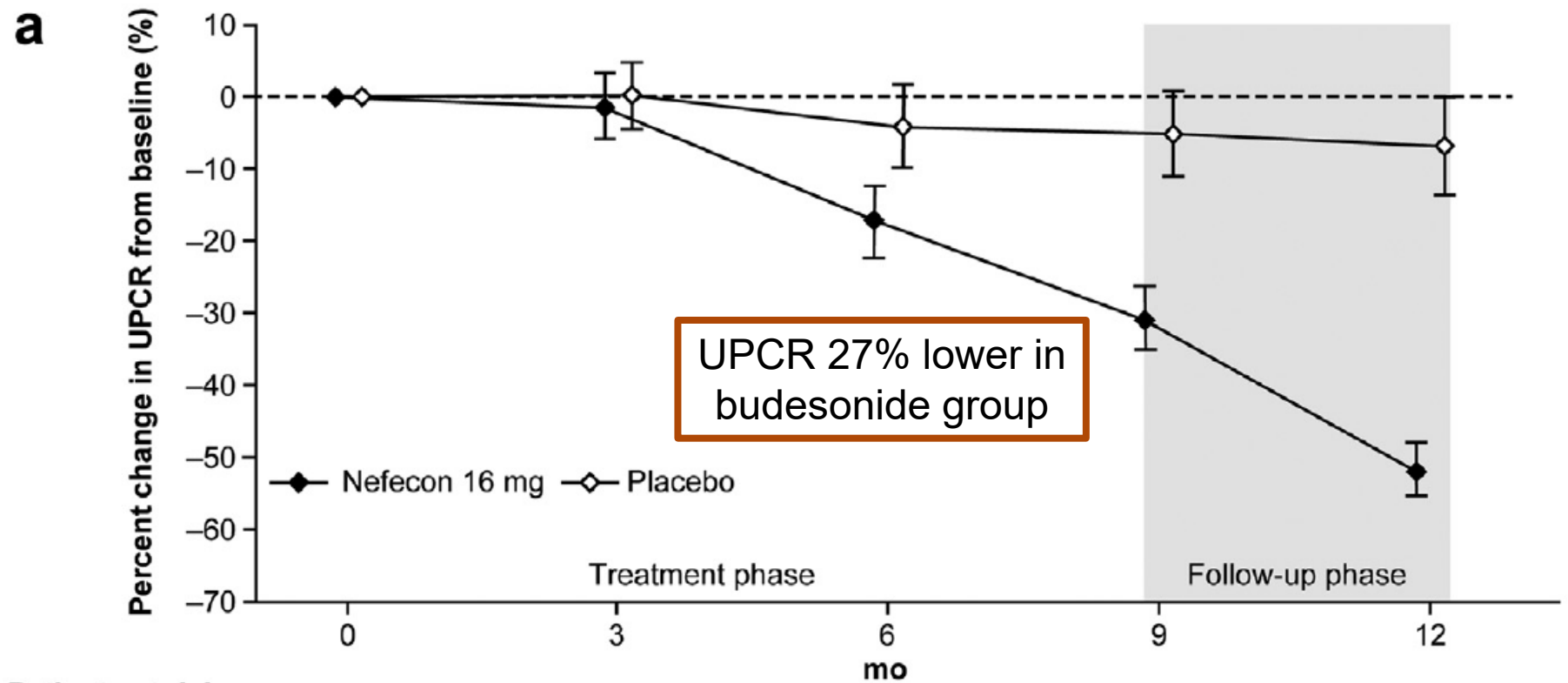
NeflgArd Trial 2023: Budesonide Delayed Release

- Patients with biopsy-proven IgAN
  - stable maximized RASi therapy
  - persistent proteinuria (UPCR >0.8 g/g or >1 g/24 h)
  - eGFR 35-90 ml/min/1.73 m^2
- Budesonide delayed release capsules 16 mg daily for 9 months→ 8 mg daily for 2 weeks → stop, compared to placebo

Part A	Part B
UPCR at 9 months	eGFR slope at 2 years

Barratt J , et al. Kidney Int 2023;103(2):391-402.

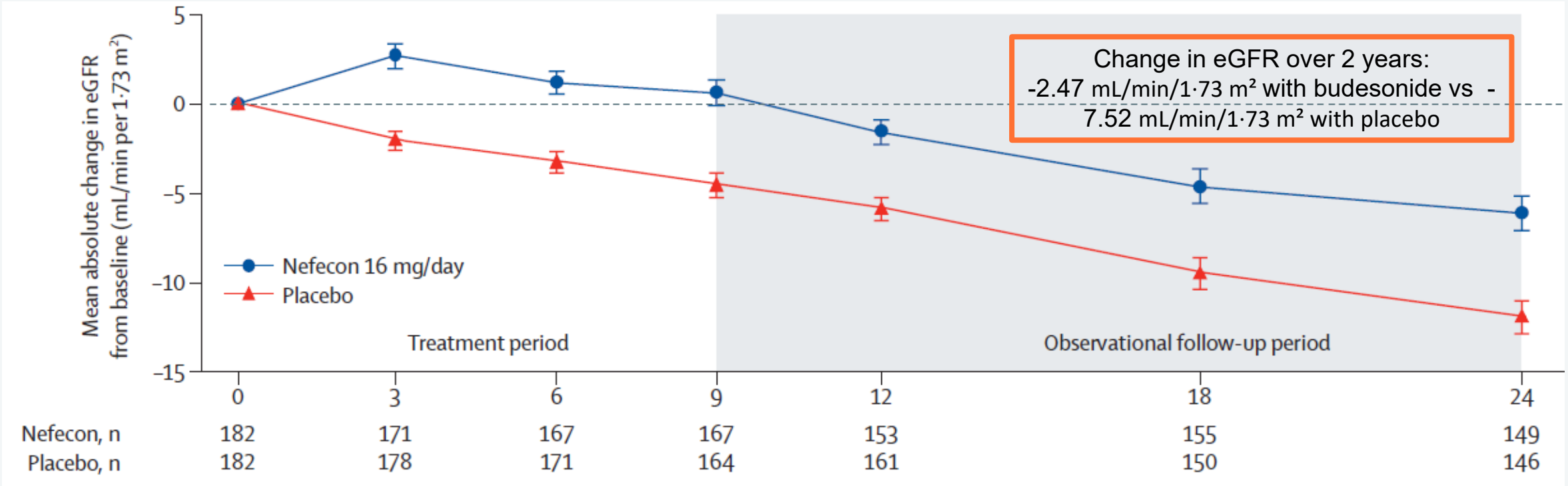
NeflgArd Trial 2023: Part A, UPCR Data



Patients at risk, n					
Placebo	102	98	94	90	66[a]
Nefecon 16 mg	97	93	90	89	59[a]

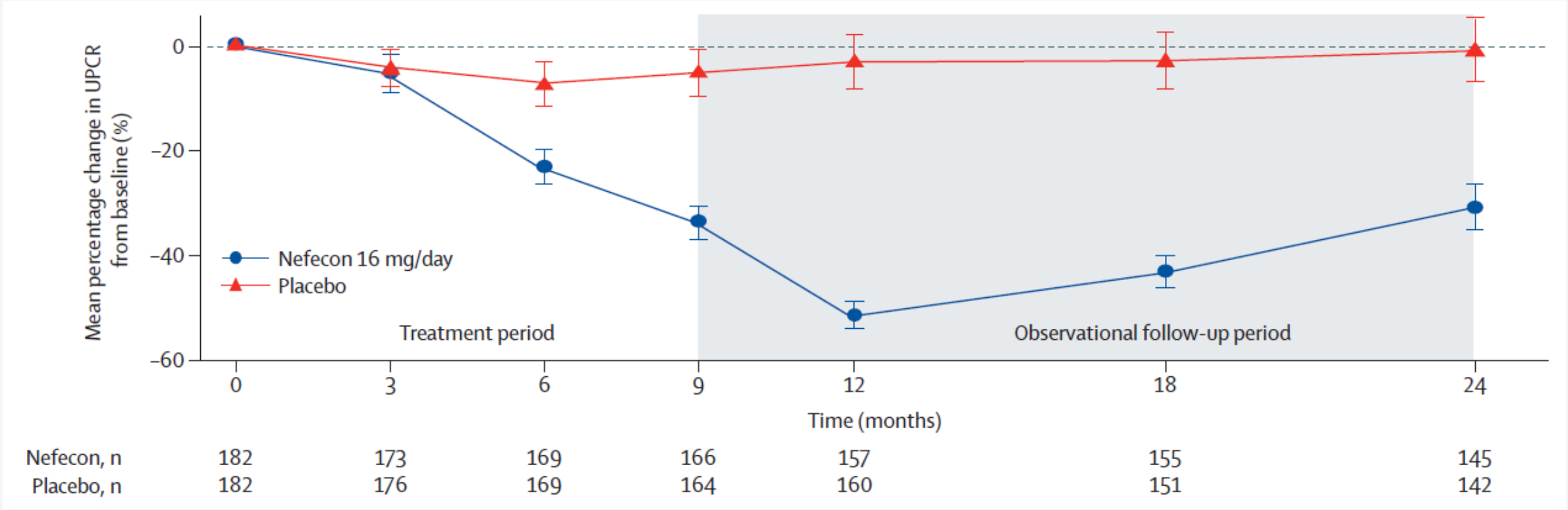
Barratt J , et al. Kidney Int 2023;103(2):391-402.

NeflgArd Trial 2023: Part B, eGFR Data



Lafayette R , et al. Lancet 2023; 402(10405):859-70.

NeflgArd Trial 2023: Part B, UPCR Data



Nefecon, n	182	173	169	166	157	155	145
Placebo, n	182	176	169	164	160	151	142

Lafayette R , et al. Lancet 2023; 402(10405):859-70.

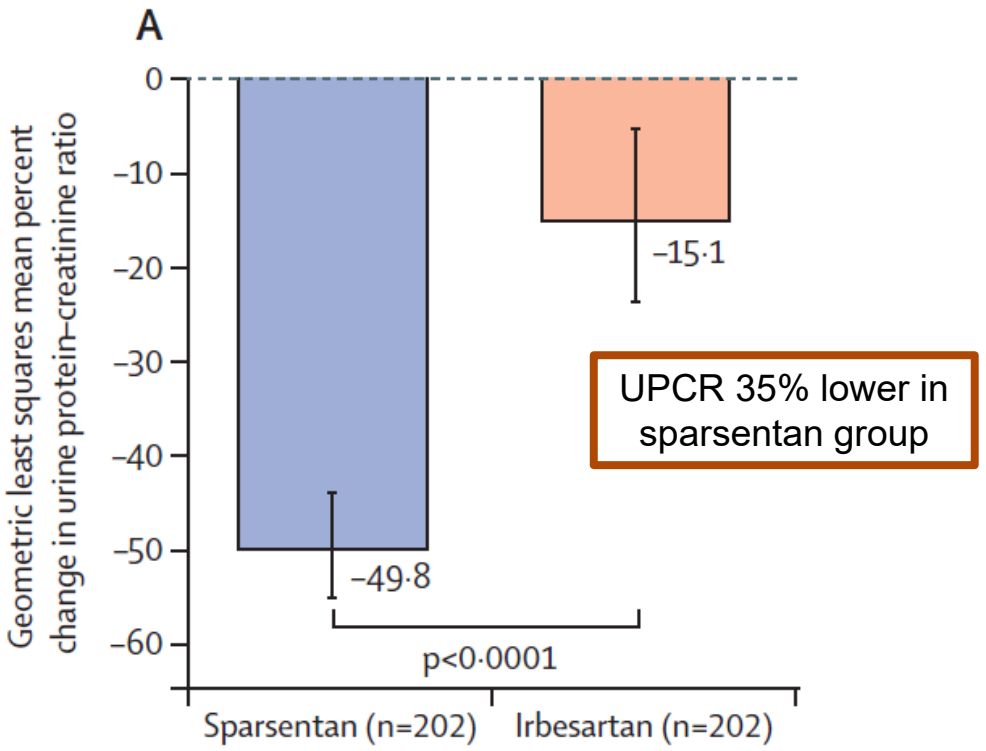
PROTECT Trial 2023: Sparsentan

- Patients with biopsy-proven IgAN
  - stable maximized RASi therapy
  - persistent proteinuria (UPCR >1 g/24 h)
  - eGFR ≥ 30 ml/min/1.73 m^2
- Sparsentan 200 mg daily for 2 weeks then 400 mg daily vs irbesartan 150 mg daily for 2 weeks then 300 mg daily

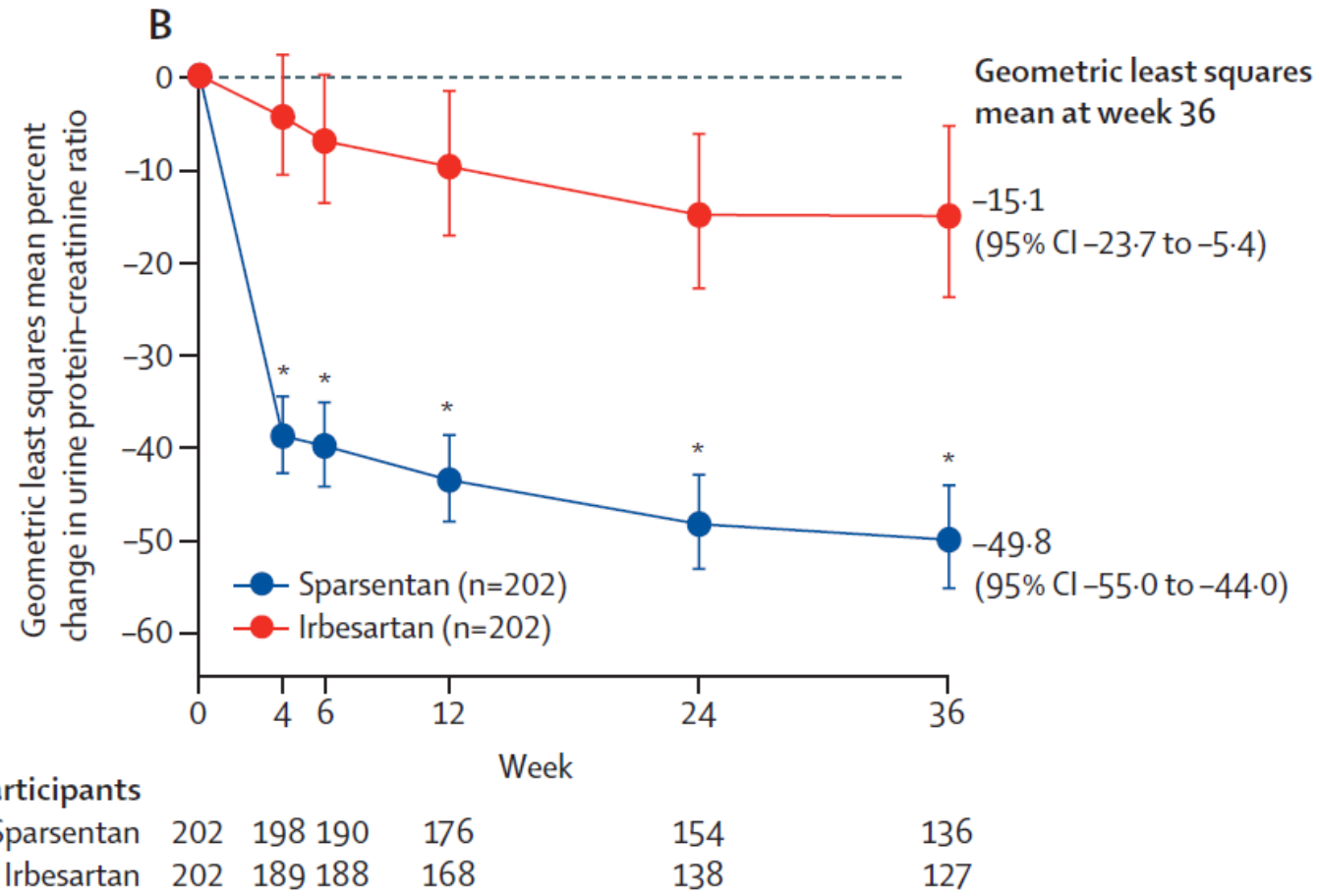
Part A	Part B
UPCR at 9 months	eGFR slope at 2 years

Heerspink H , et al. Lancet 2023; 401(10388):1584-94.

PROTECT Trial 2023: Part A, UPCR Data

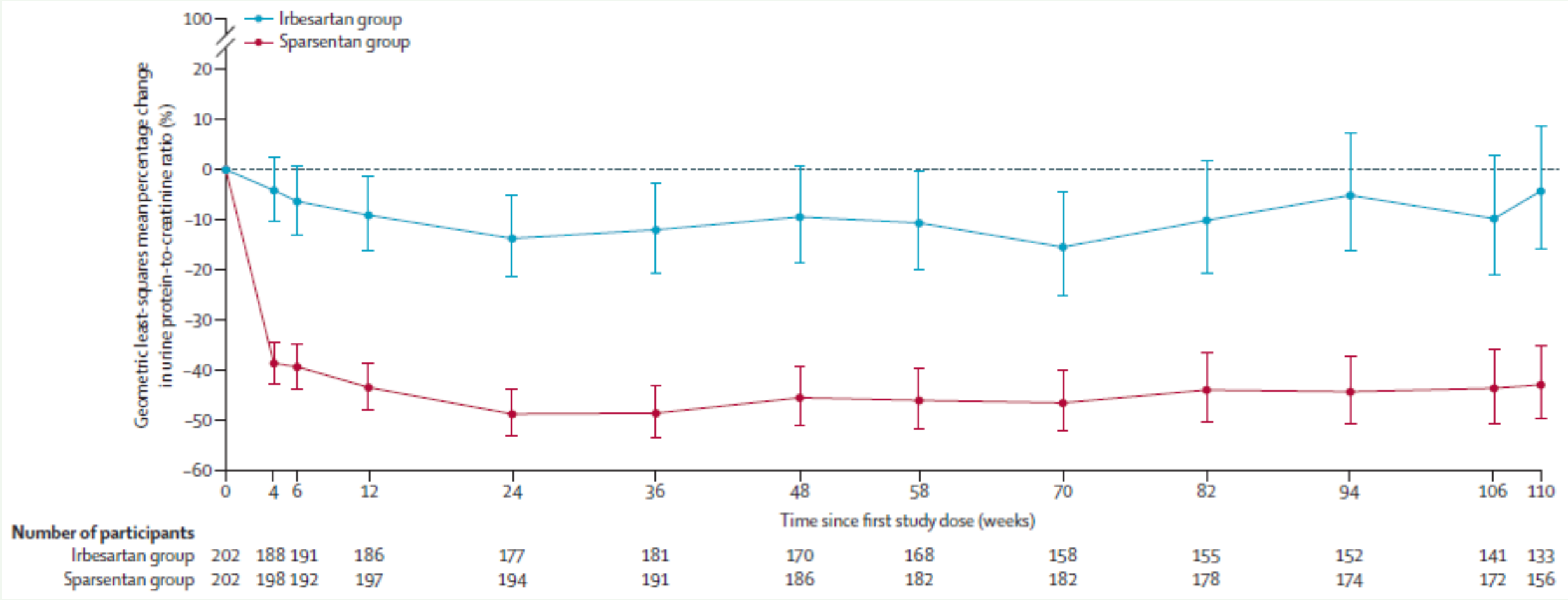


UPCR 35% lower in sparsentan group



Heerspink H , et al. Lancet 2023; 401(10388):1584-94.

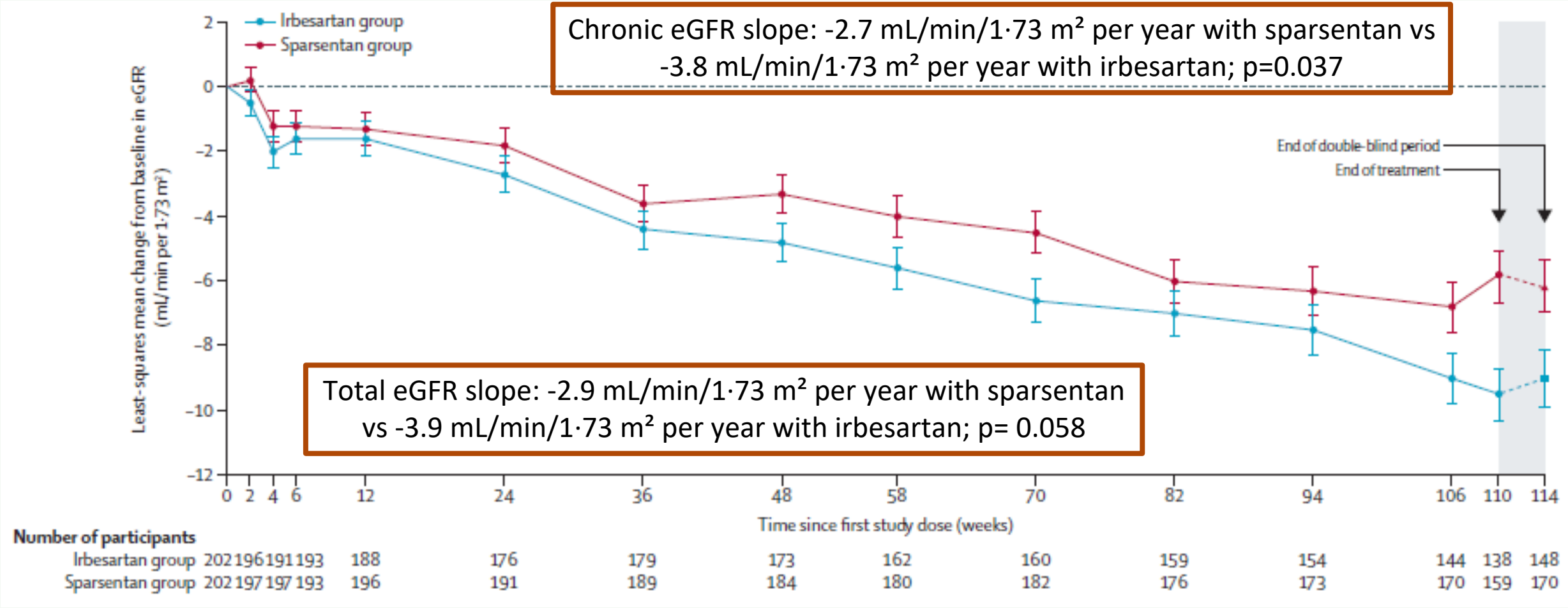
PROTECT Trial 2023: Part B, UPCR Data



Number of participants												
Irbesartan group	202	188	191	186	177	181	170	168	158	155	152	141	133
Sparsentan group	202	198	192	197	194	191	186	182	182	178	174	172	156

Rovin B, et al. Lancet 2023; 402(10417):2077-90.

PROTECT Trial 2023: Part B, eGFR Data

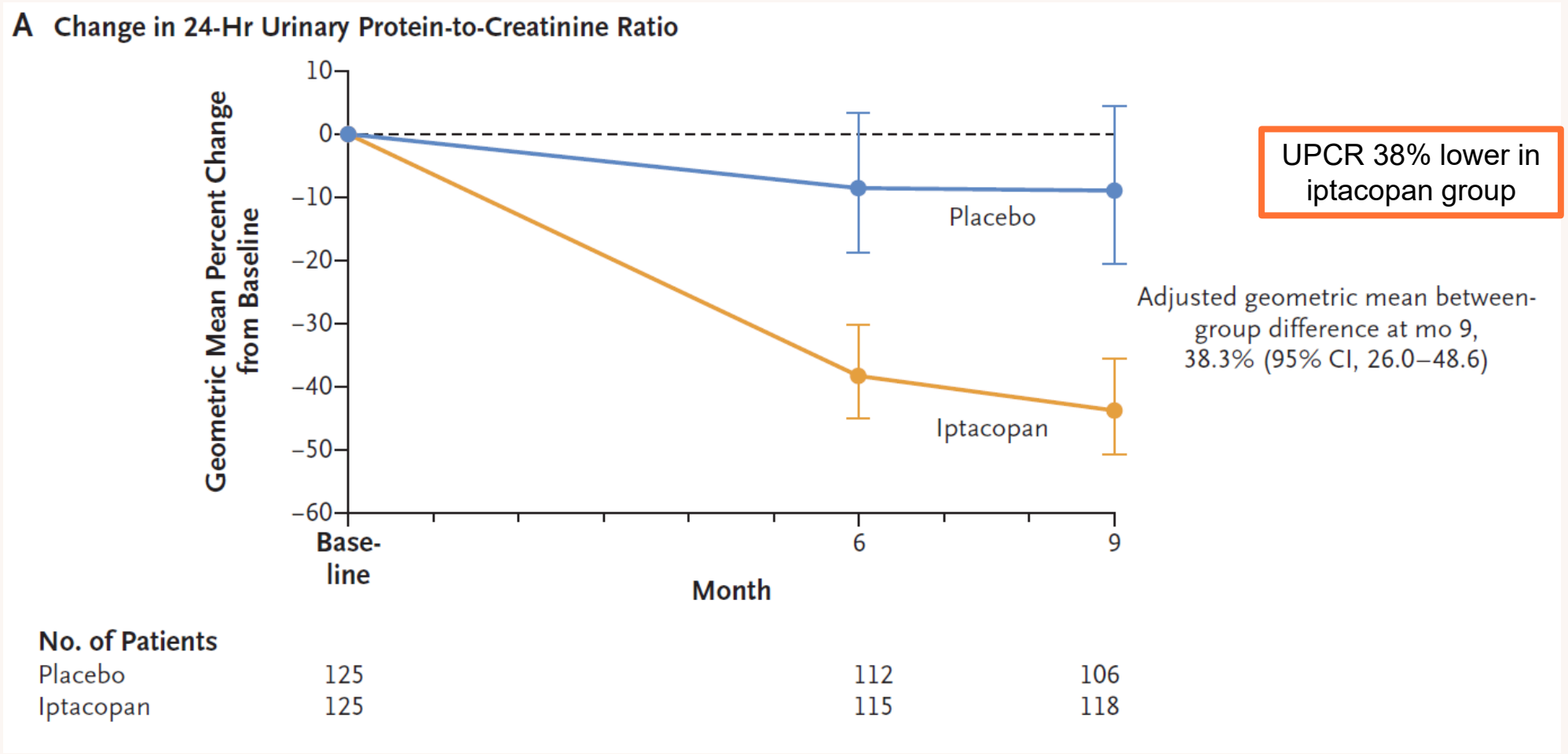


Chronic eGFR slope: -2.7 mL/min/1·73 m² per year with sparsentan vs -3.8 mL/min/1·73 m² per year with irbesartan; p=0.037

Total eGFR slope: -2.9 mL/min/1·73 m² per year with sparsentan vs -3.9 mL/min/1·73 m² per year with irbesartan; p= 0.058

Rovin B, et al. Lancet 2023; 402(10417):2077-90.

APPLAUSE-IgAN Trial 2024: Part A, UPCR Data



UPCR 38% lower in iptacopan group

Perkovic V, et al. NEJM 2025; 392(6):531-43.

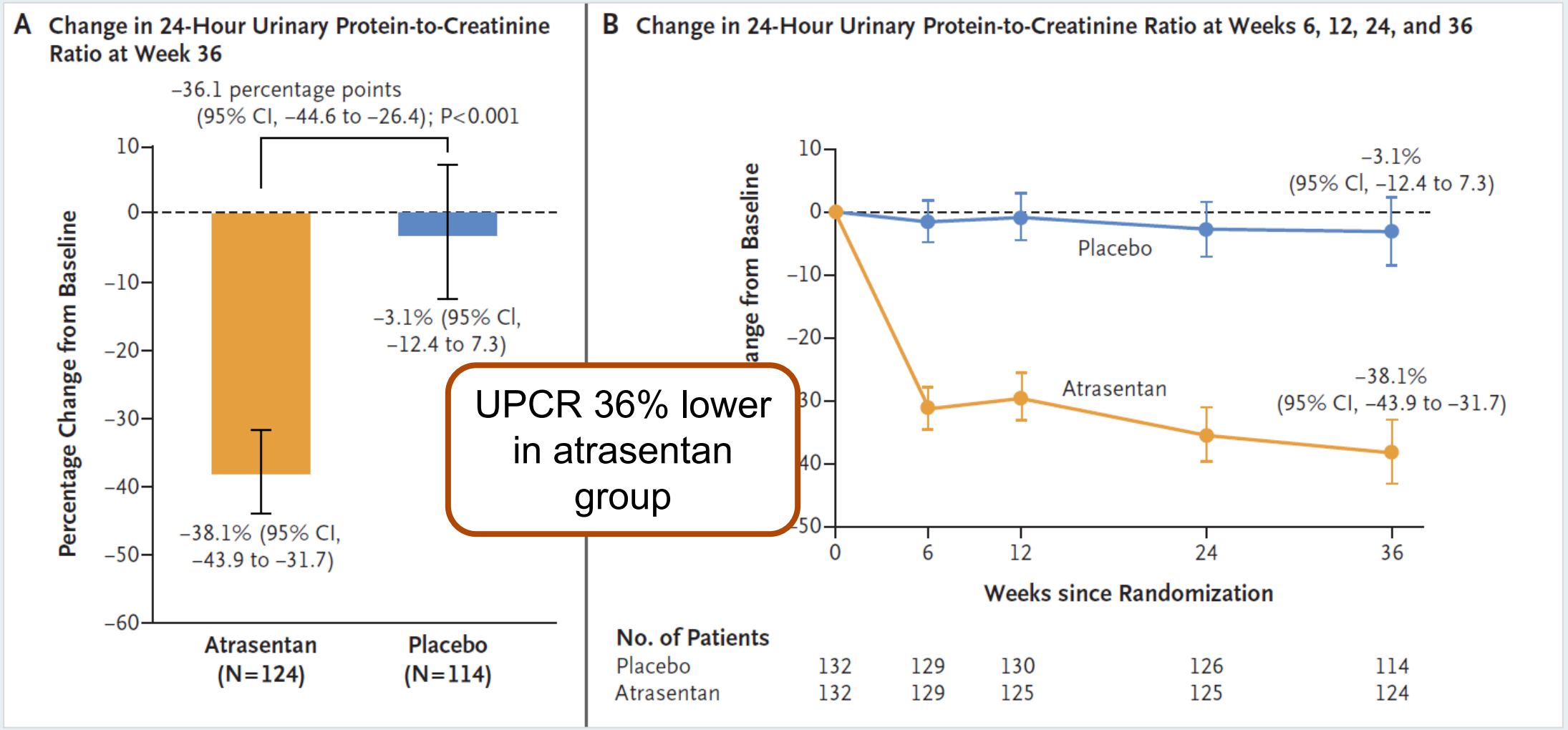
ALIGN Trial 2025: Atrasentan

- Patients with biopsy-proven IgAN
  - stable maximized RASi therapy
  - persistent proteinuria (UPCR >1 g/24 h)
  - eGFR ≥ 30 ml/min/1.73 m^{2*}
- Atrasentan 0.75 mg once daily vs placebo

Part A:	Part B
UPCR at 9 months	eGFR slope at 2.6 years, *ONGOING*

Heerspink H, et al. NEJM 2025; 392(6):544-54.

ALIGN Trial 2025: Part A, UPCR Data



UPCR 36% lower in atrasentan group

Heerspink H, et al. NEJM 2025; 392(6):544-54.

Case Study: Patient & Quiz

Patient
28-year-old woman with biopsy-confirmed IgAN M1E0S1T0C0 per biopsy report 7/2022

PMH	
CKD G2 A3	HTN

Medications
Amlodipine 5 mg daily
Atorvastatin 20 mg daily
Dapagliflozin 10 mg daily
Losartan 100 mg daily

Vital	Today	3 mo ago	6 mo ago
BP	125/84	126/86	132/90
Weight (lbs)	167	166	168
Lab	**Today**	**3 mo ago**	**6 mo ago**
SCr (mg/dL)	1.25	1.16	1.21
eGFRcr (mL/min/1.73 m^2)	60	66	63
UACR (mg/g)	2221	2450	2185

Note: Patient has expressed desire to become pregnant in the future.

What is the Goal in Treating IgAN?

Slow Decline in GFR → Goal: <1 ml/min/year

Reduction in Proteinuria → Goal: <0.5 g/d

KDIGO 2025 Clinical Practice Guideline for IgAN/IgAV

How Should We Approach Treatment?

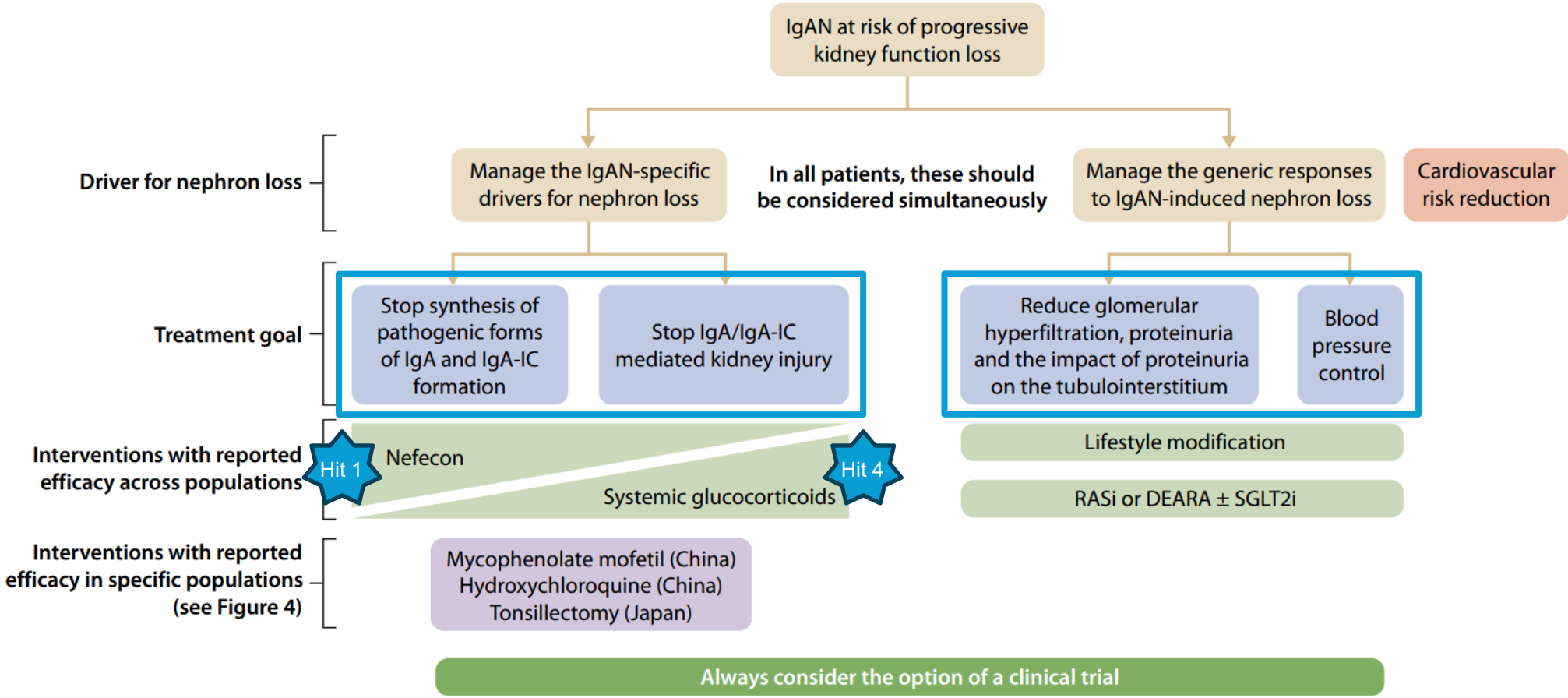
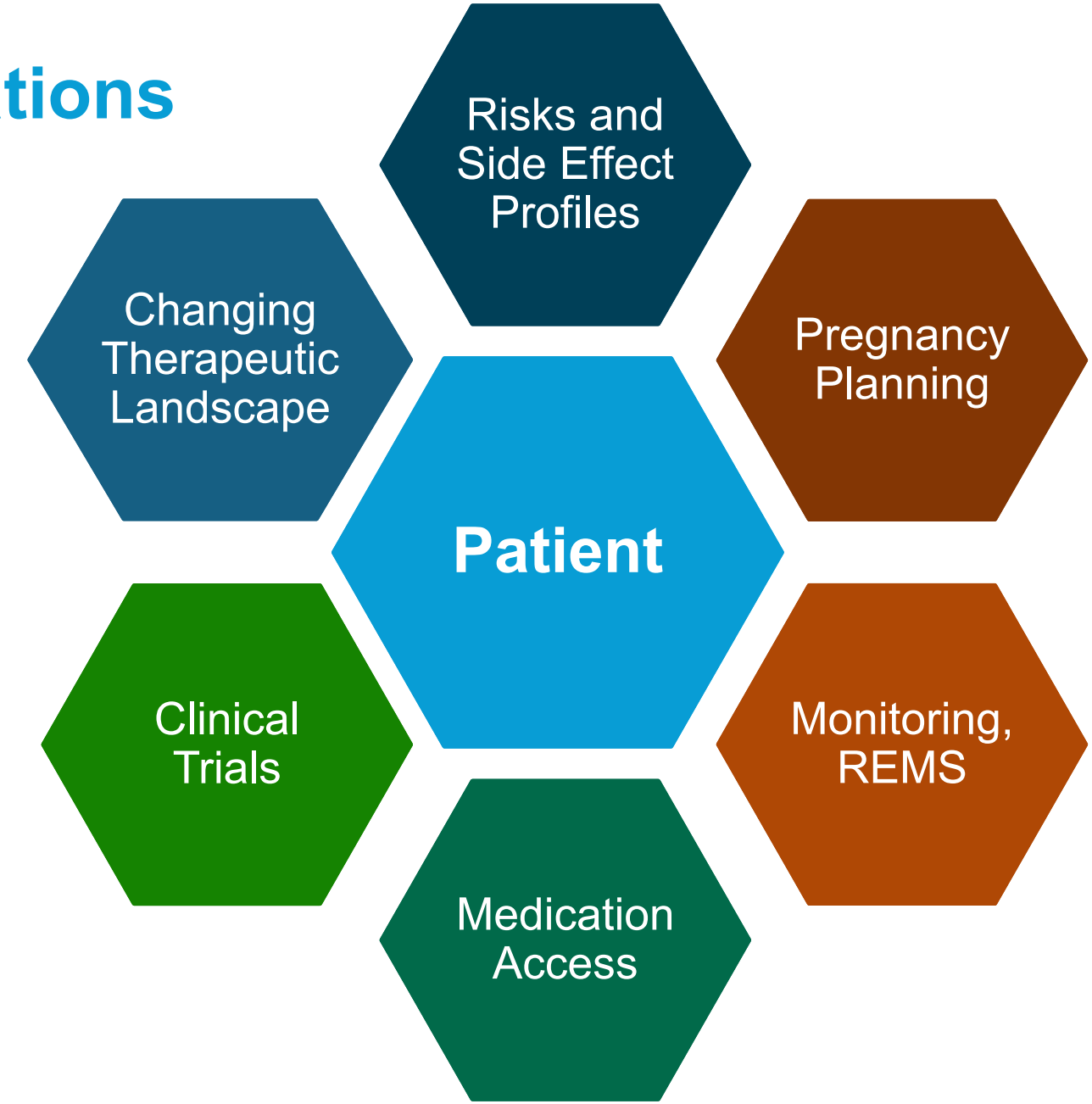


Figure 3 | Treatment targets in immunoglobulin A nephropathy (IgAN) and the positioning of drugs included in this guideline.

Considerations



Embryo/fetal toxicity

- Avoid atrasentan, sparsentan, RASi, and SGLT2i
- Unknown risk with budesonide and iptacopan

REMS

- Sparsentan: LFTs
- Iptacopan: vaccines +/- antibiotic prophylaxis, infection risk

Case Study: Patient

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eGFRcr (mL/min/1.73 m^2)	60	66	63
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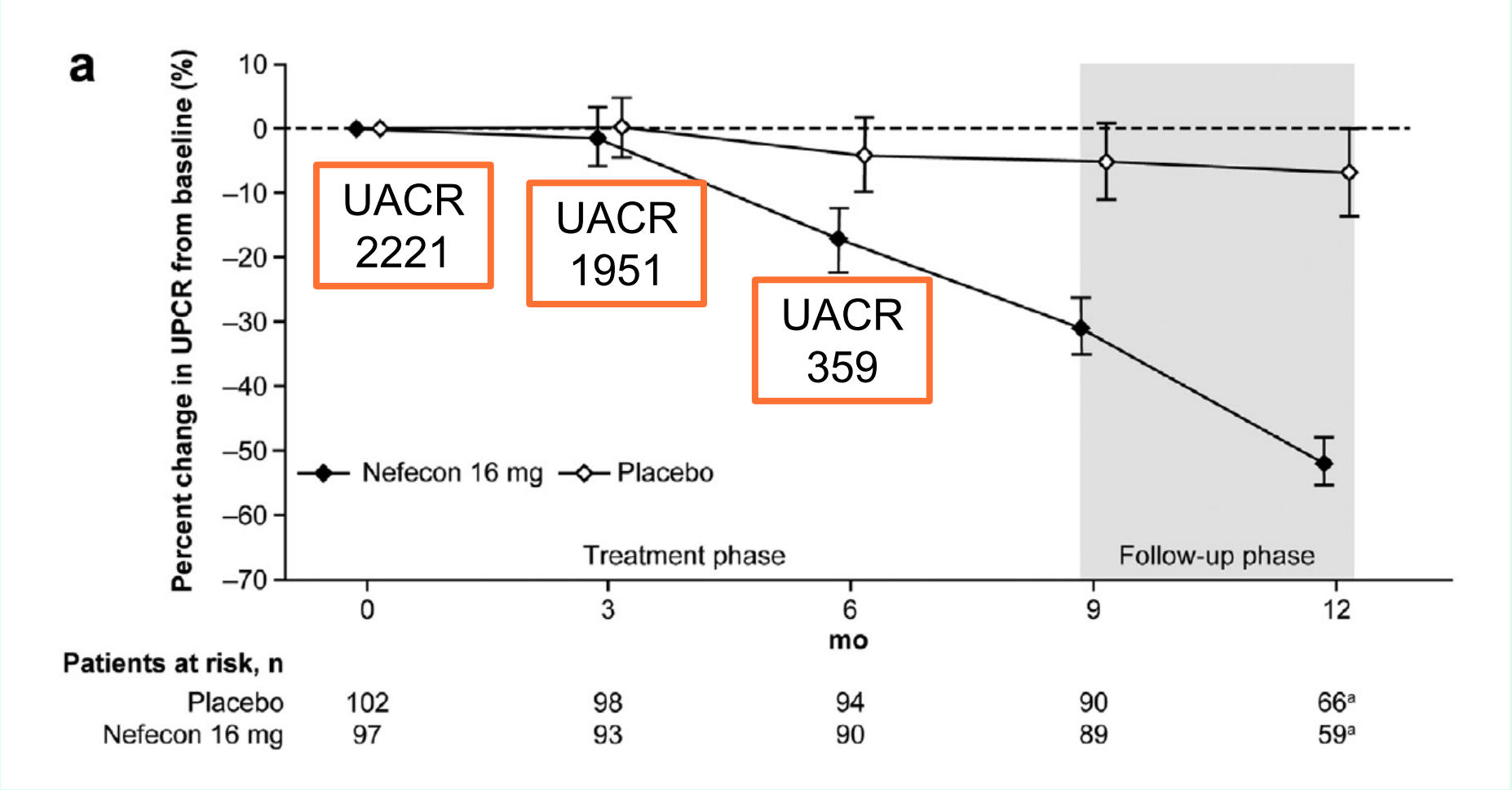
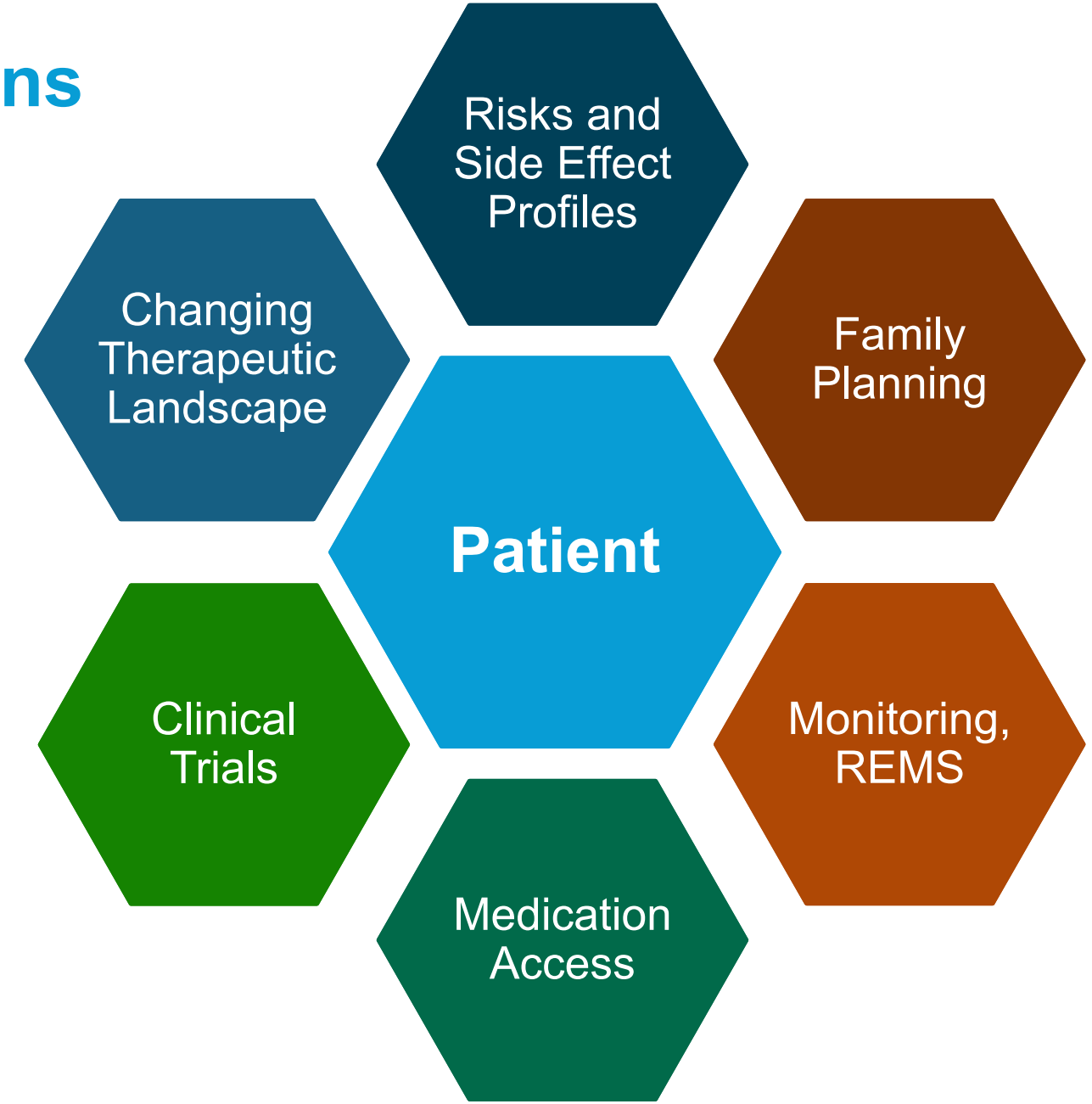
Note: Patient has expressed desire to become pregnant in the future.

Expected Change in Proteinuria



Barratt J , et al. Kidney Int 2023;103(2):391-402.

Considerations



Pipeline Therapies

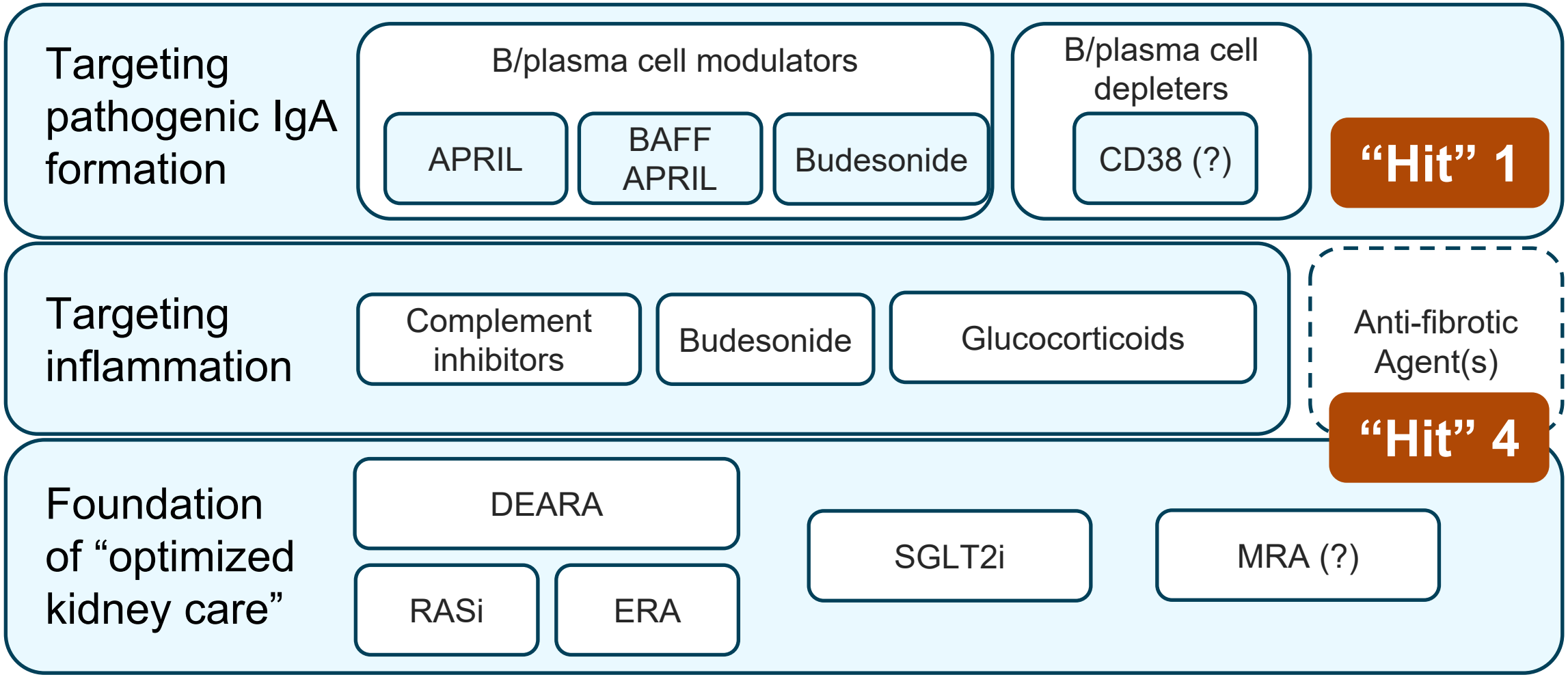
Table 1. Newly Approved and New Treatments in Clinical Development for IgAN

Agent	Target	Type	Clinical Trial Phase	ClinicalTrials.gov Identifier	Status/Author
Mucosal B-cell priming					
Nefecon	GALT	Targeted-release budesonide	Approved		Lafayette et al[26]
B-cell-directed therapies					
Mezagitamab	CD38	mAb	2	NCT05174221	Active, not recruiting
Felzartamab	CD38	mAb	2 (IGNAZ)	NCT05065970	Active, not recruiting
Sibeprenlimab (VIS649)	APRIL	mAb	3 (VISIONARY)	NCT05248646	Active, not recruiting
Zigakibart (BION-1301)	APRIL	mAb	3 (BEYOND)	NCT05852938	Recruiting
Atacicept	APRIL+BAFF	TACI-Fc fusion protein	3 (ORIGIN 3)	NCT04716231	Recruiting
Telitacicept	APRIL+BAFF	TACI-Fc fusion protein	3	NCT05799287	Recruiting
Povetacicept	APRIL+BAFF	TACI-Fc fusion protein	2 (RUBY-3)	NCT05732402	Recruiting
Complement inhibitors					
Iptacopan (LNP023)	Factor B	Small molecule	3 (APPLAUSE-IgAN)	NCT04578834	Active, not recruiting
RO7434656	Factor B	Antisense oligonucleotide	3 (IMAGINATION)	NCT05797610	Recruiting
Ravulizumab	C5	mAb	3 (ICAN)	NCT06291376	Recruiting
ARO-C3	C3	RNA interference	1/2	NCT05083364	Recruiting
Cemdisiran	C5	Small interfering RNA	2	NCT03841448	Completed; Barratt et al[87]
Avacopan (CCX168)	C5aR1	Small molecule	2	NCT02384317	Completed; Bruchfeld et al[88]
ERAs					
Sparsentan	DEARA	Small molecule	Approved		Lambers Rovin et al[102]
Atrasentan	ERA	Small molecule	3 (ALIGN)	NCT04573478	Active, not recruiting

NOTE. Data from www.clinicaltrials.gov (accessed August 29, 2024). Abbreviations: APRIL, a proliferation-inducing ligand; BAFF, B-cell-activating factor; DEARA, dual endothelin angiotensin receptor antagonist; ERA, endothelin receptor antagonist; Fc, Fragment crystallizable; GALT, gut-associated lymphoid tissue; IgAN, IgA nephropathy; mAb, monoclonal antibody; TACI, Transmembrane Activator and Calcium modulator and cyclophilin ligand Interactor.

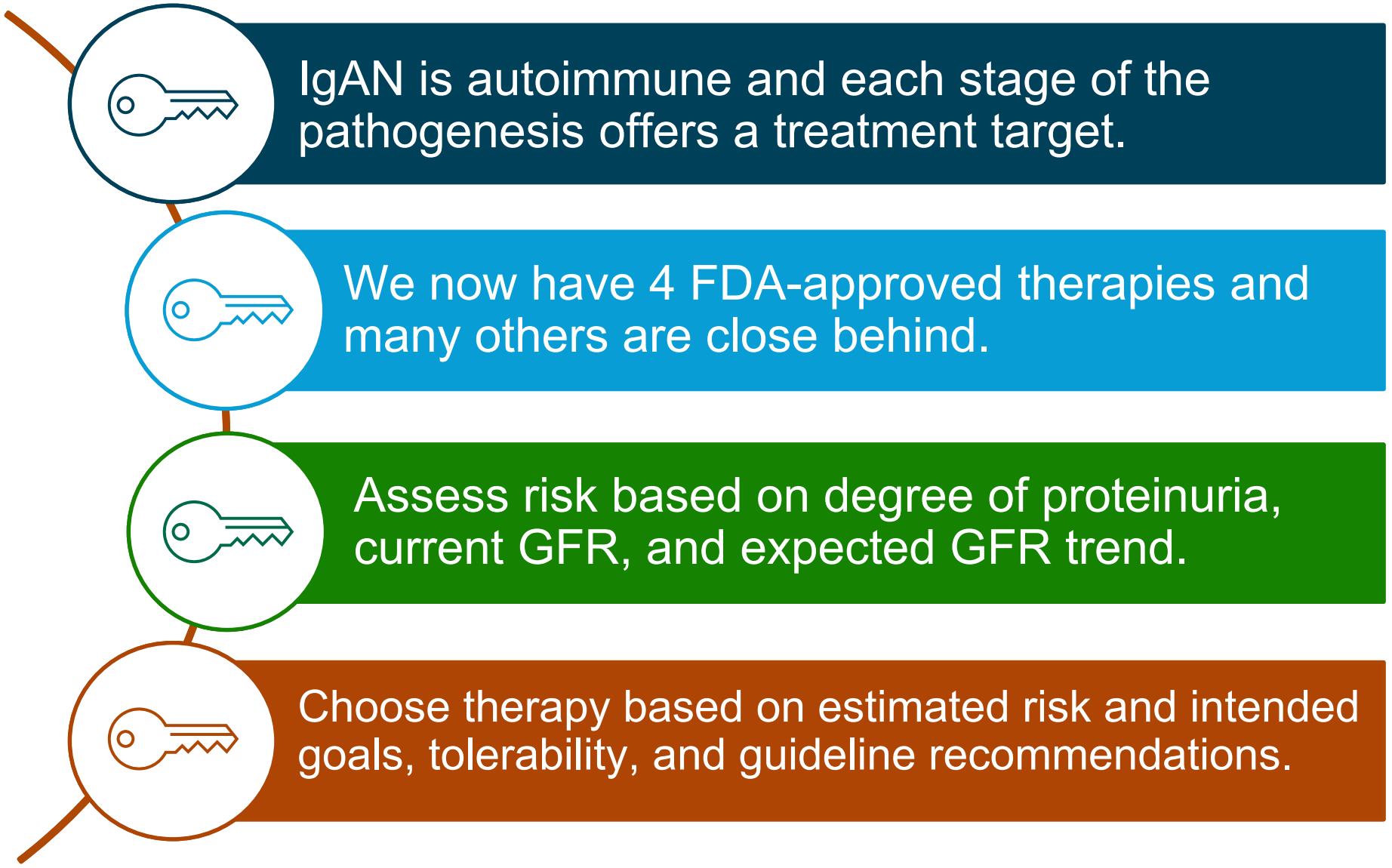
Cheung CK, Barratt J. Semin Nephrol 2024;44(5), 151573.

Pillars of IgAN Treatment



Barratt J, et al. Front Med 2024;11:1461879.

Key Takeaways



Additional Resources

- KDIGO 2025 Clinical Practice Guideline for the Management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A Vasculitis (IgAV)
- International IgAN Prediction Tool at biopsy - Adults | QxMD
- International IgAN Prediction Tool post-biopsy - Adults | QxMD
- IgA Nephropathy Foundation: www.igan.org
- NephCure: www.nephcure.org

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Thank you!