Changing the therapeutic landscape in IgA nephropathy.

The value of targeted release budesonide

Maria Stangou

Associate Professor in Nephrology,

Aristotle University of Thessaloniki,

1st Department of Nephrology,

Hippokration Hospital Thessaloniki, Greece

Immune abnormalities in IgA nephropathy

IgA1 mucosal surfaces
systemic circulation

IgA2 mucosal surfaces

Differences IgA1/IgA2

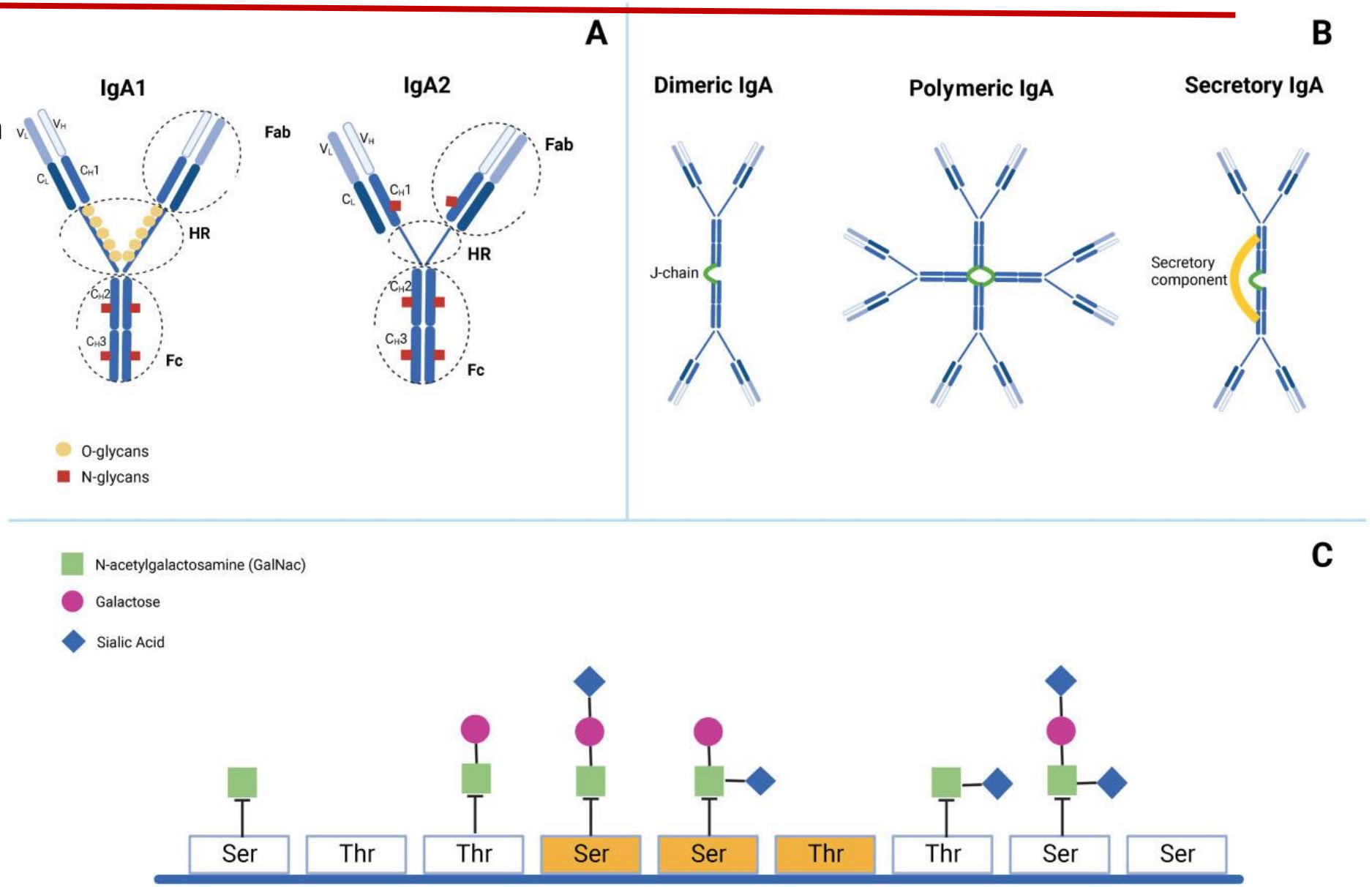
1. Numbers of N-linked

carbohydrates

in the heavy chain

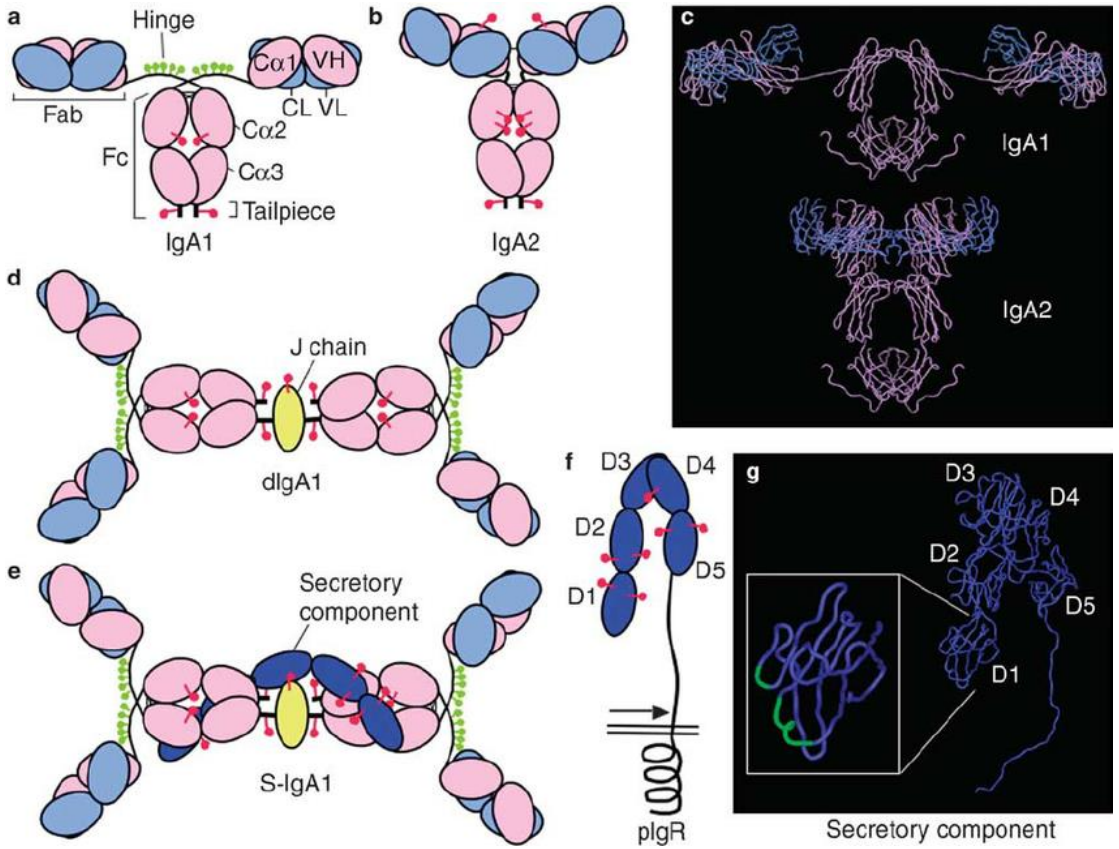
2. Hinge Region (HR)

9 serine and threonine
3-6 O-linked glycans
[GalNac +*β*1,3-linked galactose +sialic acid]



Clinical Kidney Journal, 2023

Secretory IgA *N*- and *O*-Glycans Provide a Link between the Innate and Adaptive Immune Systems



Schematic representations of human dimeric IgA1 and secretory IgA1

J Chain:
Two IgA monomers are depicted tail-to-tail, with a **J chain** covalently linking together the heavy chain tails from each monomer.

The Secretory Component:
five immunoglobulin-like domains
covalently linked to domain V and domain C2, C3, domain I and the J chain.

SIgA2 has one more *N*-glycan on the C2 domain and one or two more on the C1 domain than SIgA1.
SIgA1 has four of the five possible sites are shown on the hinge region occupied by O-glycans.
There are no *O*-glycans on the hinge region of SIgA2.

Secretory IgA *N*- and *O*-Glycans Provide a Link between the Innate and Adaptive Immune Systems

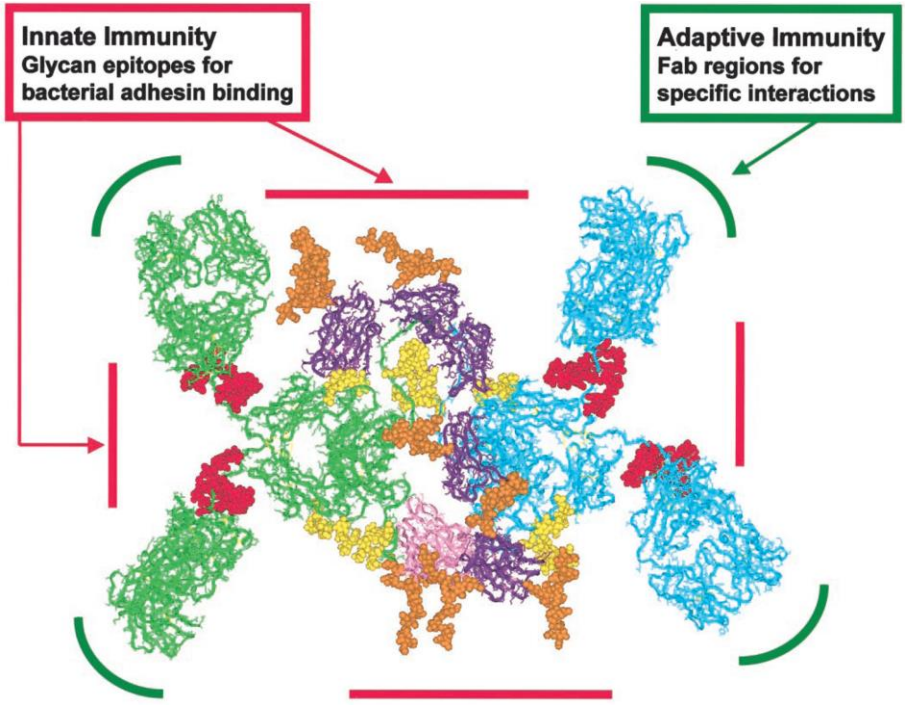
Innate immunity

- interaction with bacterials

Adaptive immunity

- Fab antibody-binding sites

  interaction with Ags



J chain

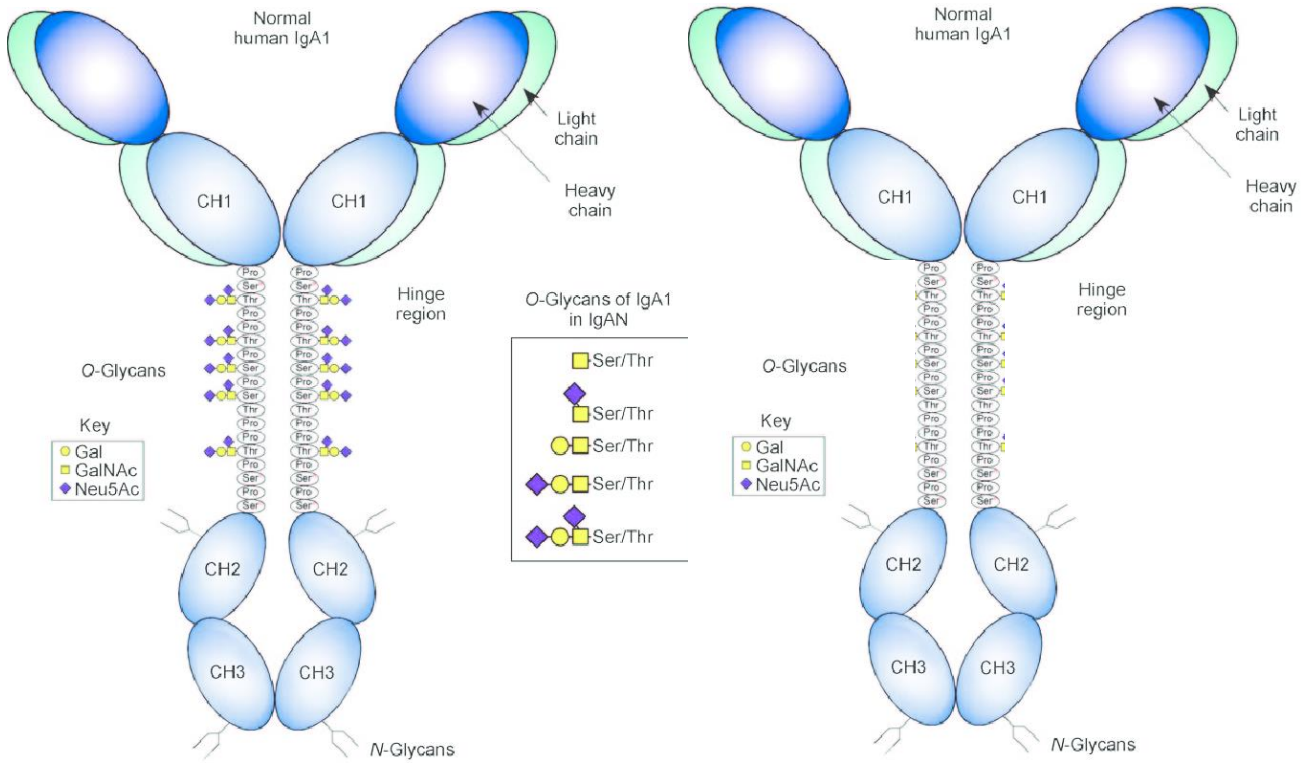
Secretory component

***O*-glycans** (on the hinge region)

***N*-glycans on the H chains**

***N*-glycans on the SC and J chain**

Molecular model of SIgA1 with *N*- and *O*-glycans

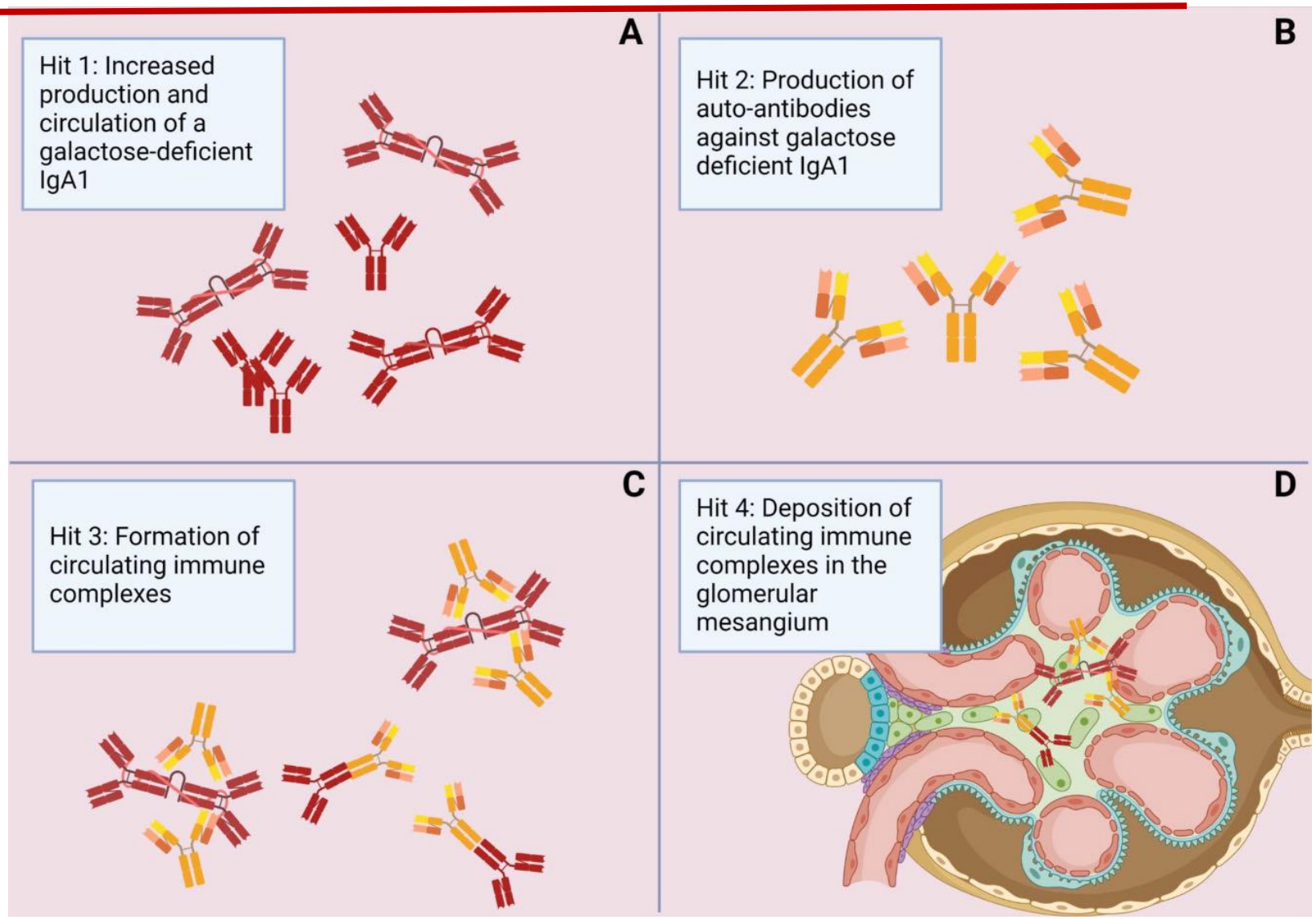


Immune abnormalities in IgA nephropathy

IgA1 mucosal surfaces
systemic circulation

IgA2 mucosal surfaces

1. ↑Circulating levels of Gd-IgA1
2. Antiglycan autoantibodies against Gd-IgA1
3. Circulating immune complexes contain Gd-IgA
4. The Gd-IgA1-antiglycan IgG immune complexes deposit in the mesangium



Clinical Kidney Journal, 2023

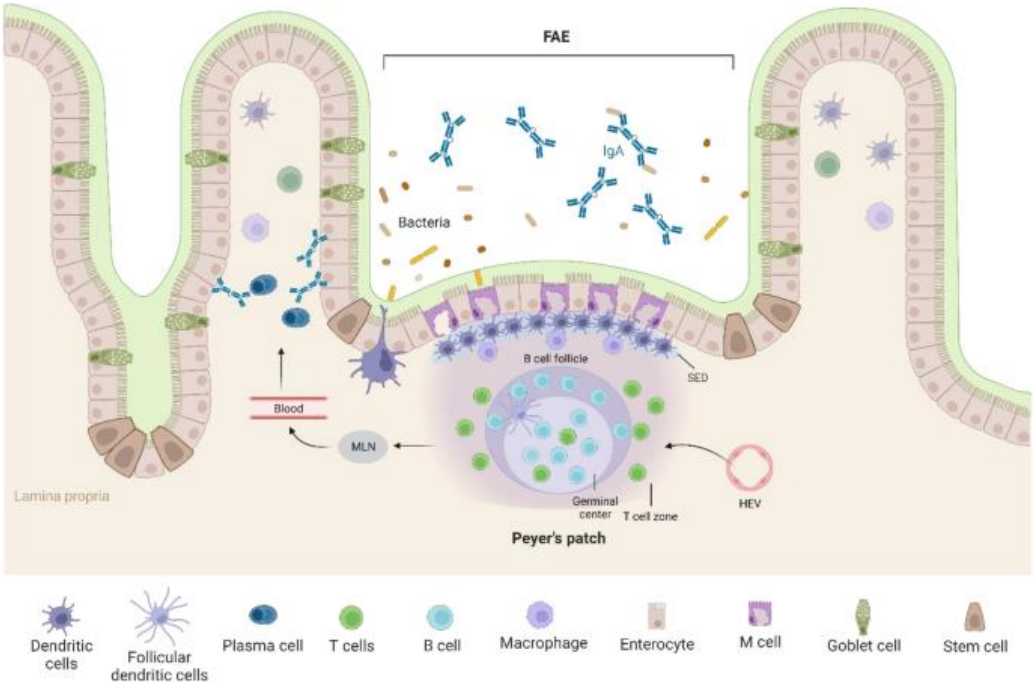
Where does the responsible IgA come from?

The site of gd-IgA1 production is still unclear, **evidence on the involvement of Peyer's patches and mesenteric lymph nodes**

↑Serum levels of gd-IgA1 directed against mucosal pathogens

Is Gd-IgA molecule pathogenic?

1. ↑Circulating levels of SIgA
2. Positive correlation between SIgA and disease activity
3. Mesangial deposits of Gd-IgA



Peyer's patches (PPs) follicles are enclosed by follicle-associated endothelium (FAE)

Expansion and differentiation of B cells is stimulated by interactions between B cells and T cells at FAE

Tissue Eng Reg Med 2023

Where does the responsible IgA come from?

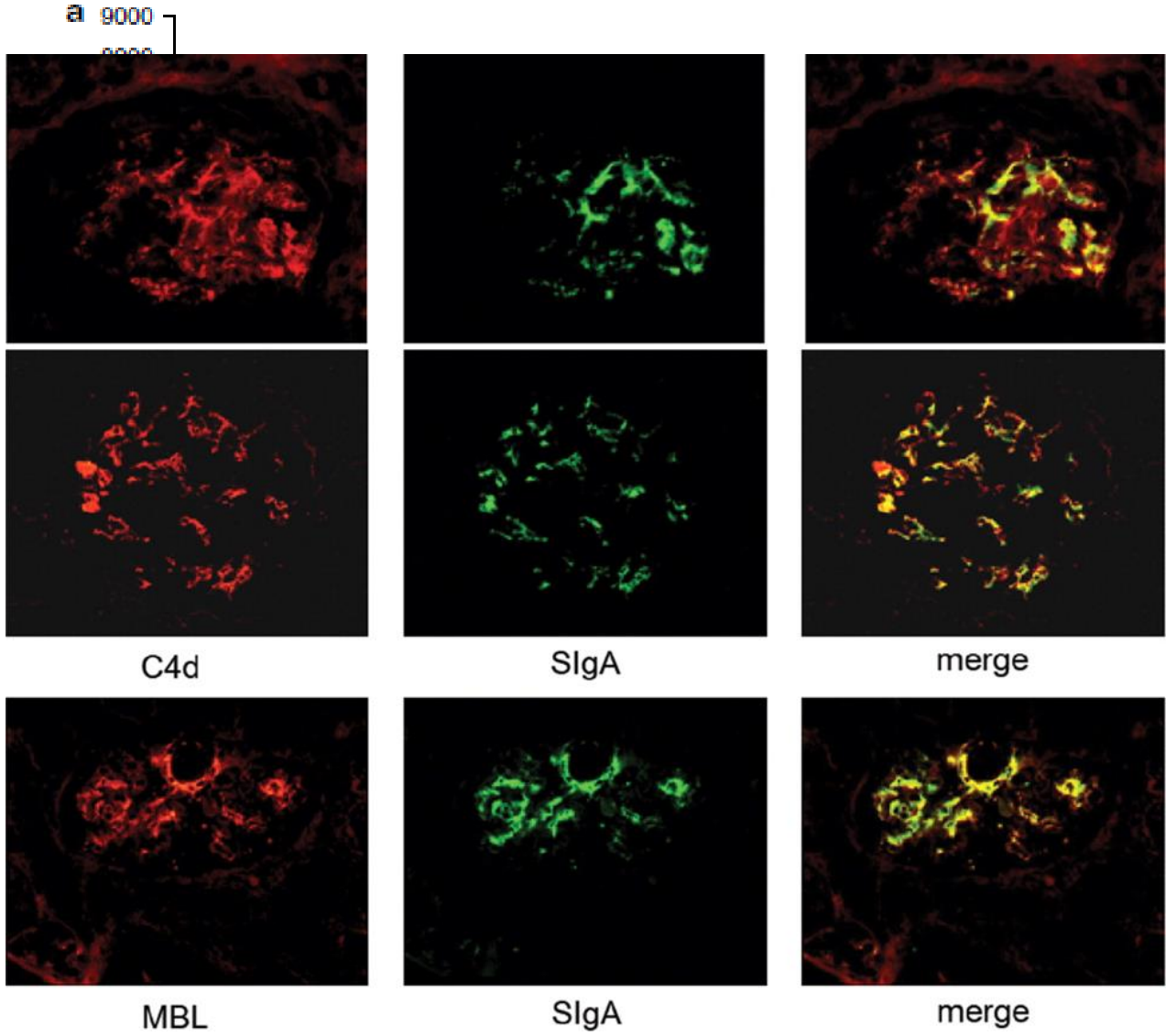
Nephrol Dial Transplant (2007) 22: 3191–3195

The site of gd-IgA1 production is still unclear, **evidence on the involvement of Peyer's patches and mesenteric lymph nodes**

↑Serum levels of Gd-IgA1 directed against mucosal pathogens in IgAN patients

Is Gd-IgA molecule pathogenic?

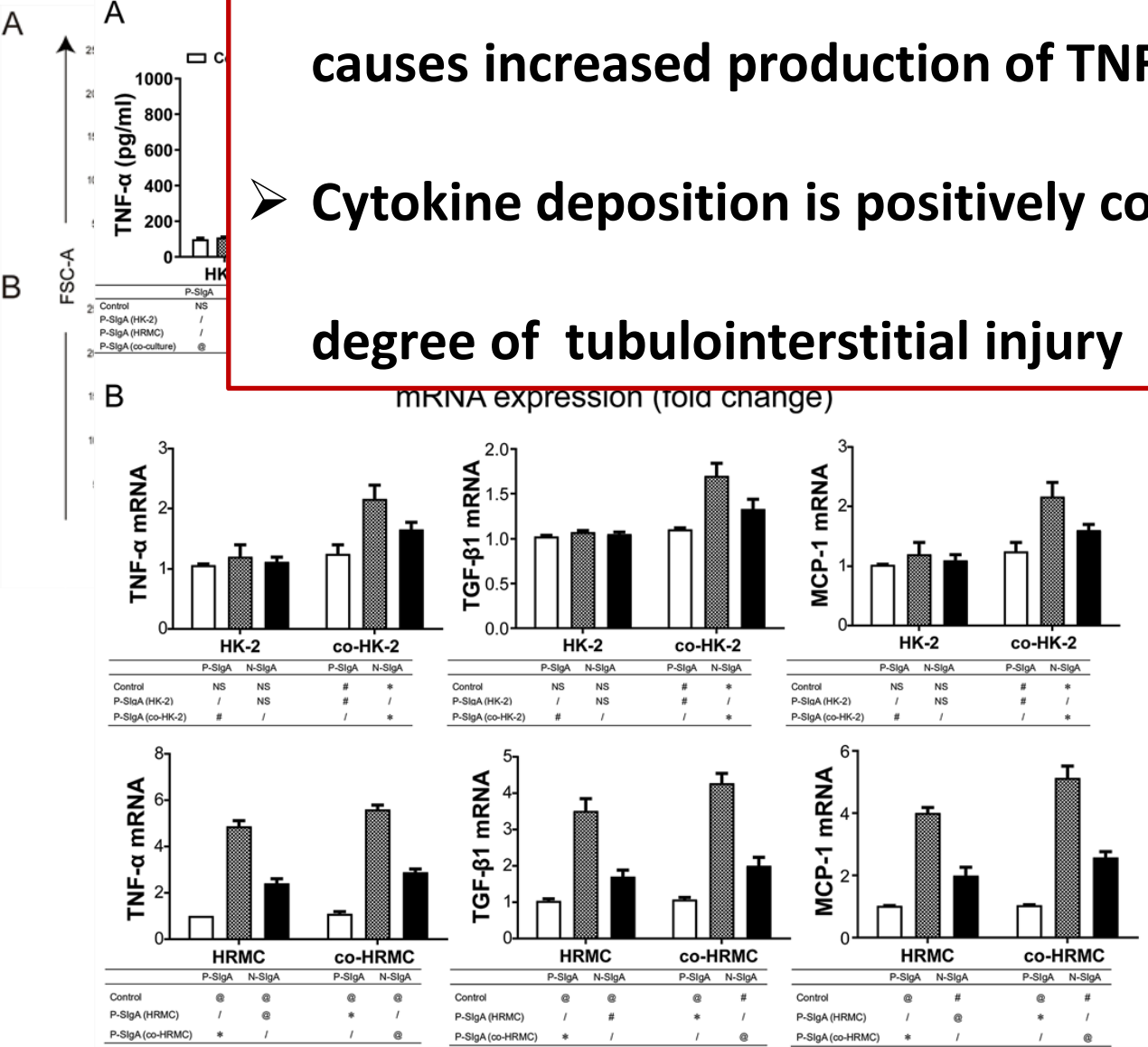
1. ↑Circulating levels of SIgA
2. Positive correlation between SIgA and disease activity
3. Mesangial deposits of Gd-IgA

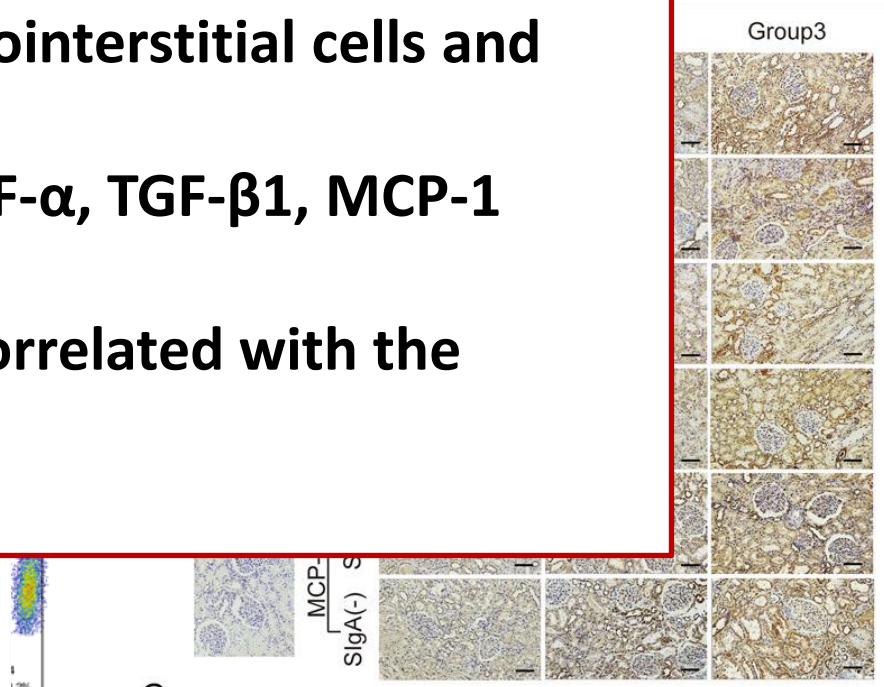


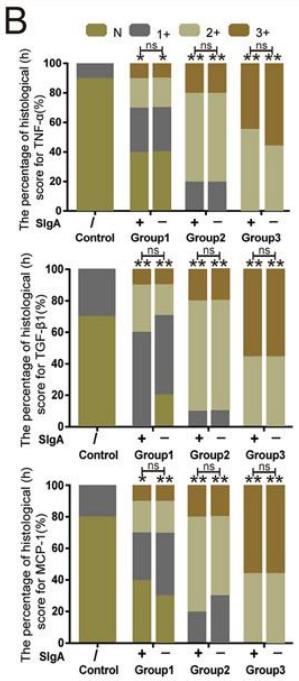
Kidney Blood Press Res 2021;46:286–297

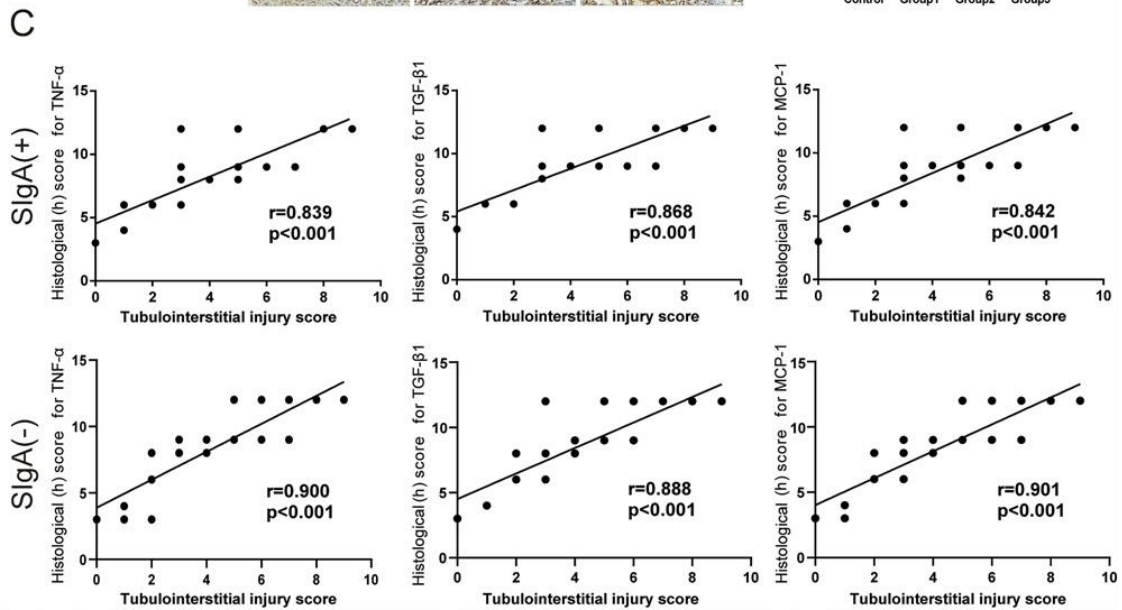
- **SIgA binds to Mesangial and Tubulointerstitial cells and causes increased production of TNF-α, TGF-β1, MCP-1**
- **Cytokine deposition is positively correlated with the degree of tubulointerstitial injury**

Binding

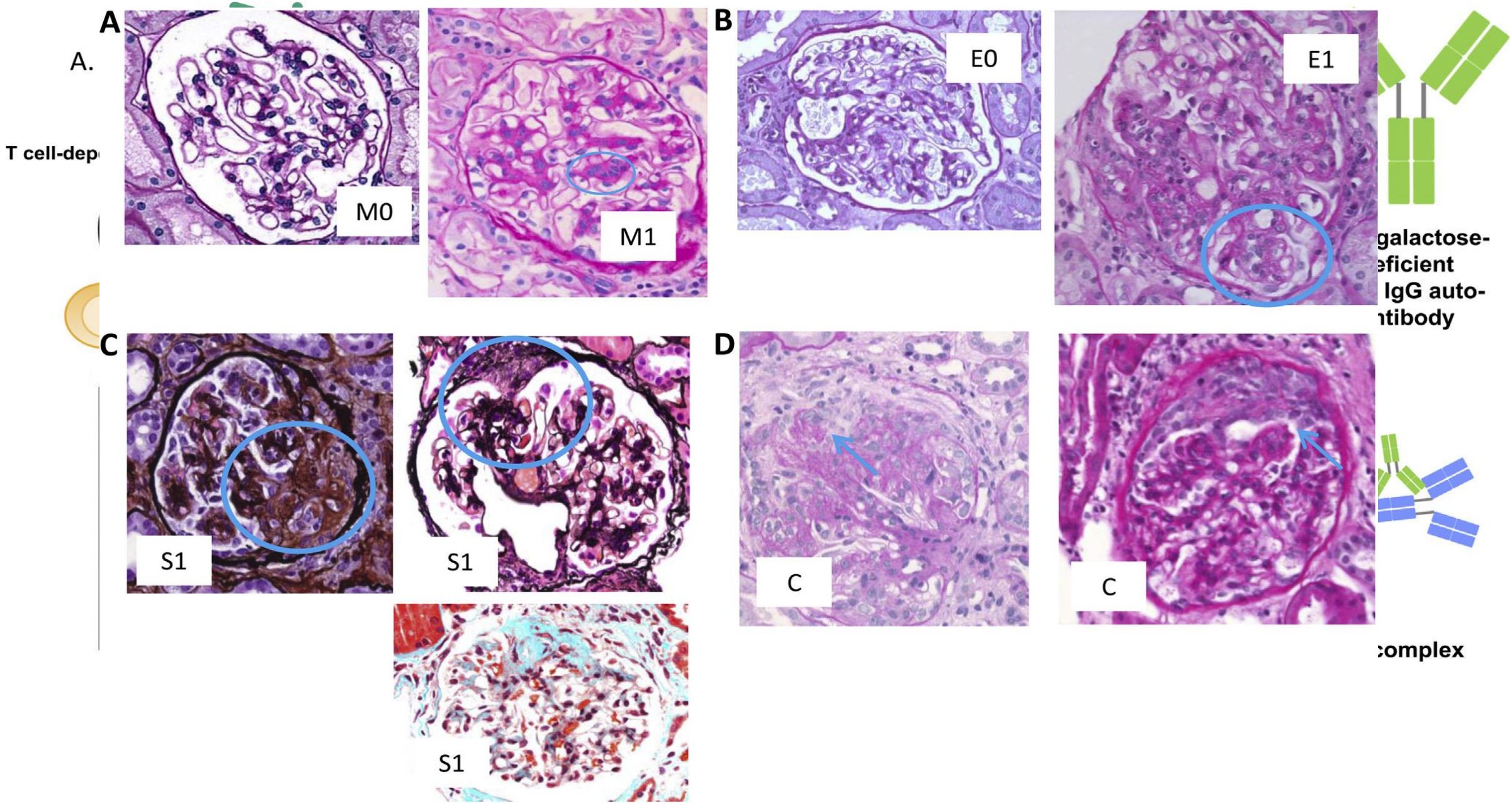






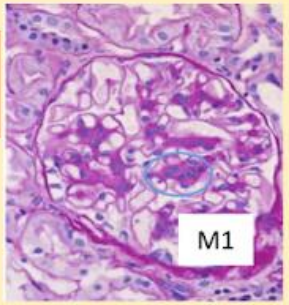


IgA Nephropathy – from pathogenesis to histology



IgA Nephropathy: Histopathology (MEST-C)

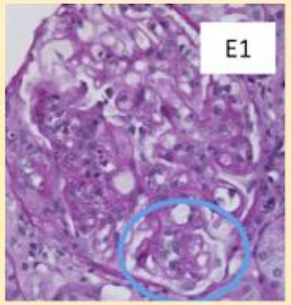
M



Mesangial hypercellularity

≥4 mesangial cells in any mesangial area of a glomerulus

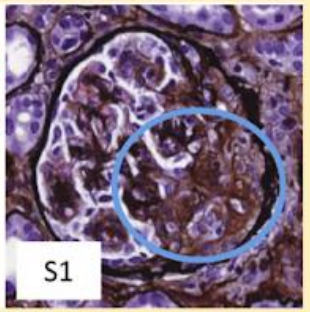
E



Endocapillary hypercellularity

An increased number of cells in glomerular capillary lumen

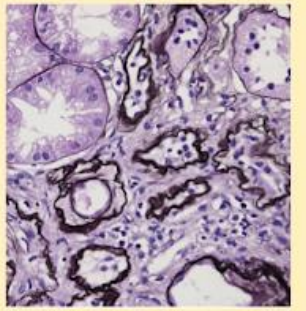
S



Segmental glomerulosclerosis

Adhesion or sclerosis that not involving the entire glomerulus

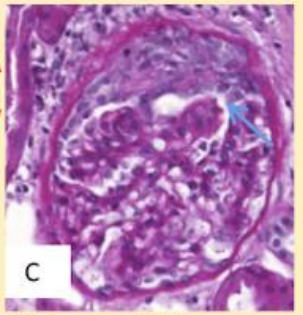
T



Tubular atrophy/ interstitial fibrosis

The percentage of tubular atrophy/ interstitial fibrosis of cortical area

C



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

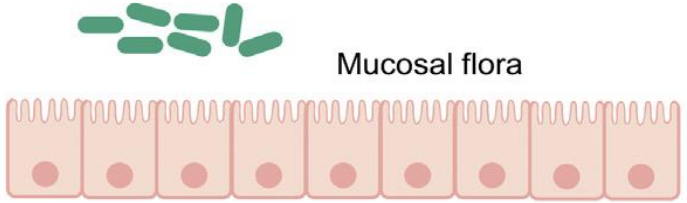
Conclusion:
IgAN pathogenesis, clinical manifestations, histology, prediction tools, and treatment are reviewed, and case examples are presented to illustrate the approach to the management of patients with IgAN.

Pattrapornpisut P, Avila-Casado C, Reich HN. IgA Nephropathy: Core Curriculum 2021. Am J Kidney Dis. 2021 Sep;78(3):429-441. doi: 10.1053/j.ajkd.2021.01.024. Epub 2021 Jul 9. PMID: 34247883.

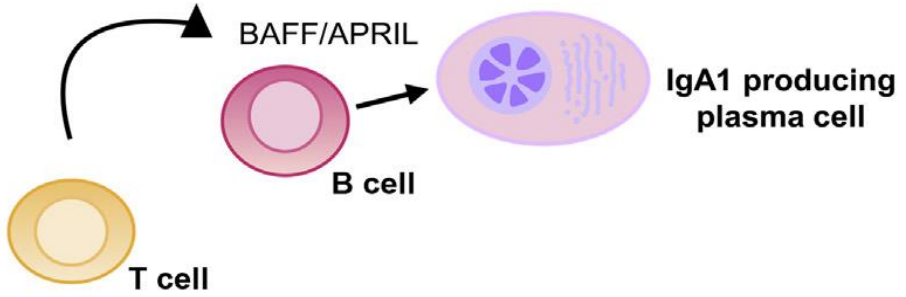
VA by @Dilushiwijay MD MRCP

IgA Nephropathy – from pathogenesis to histology

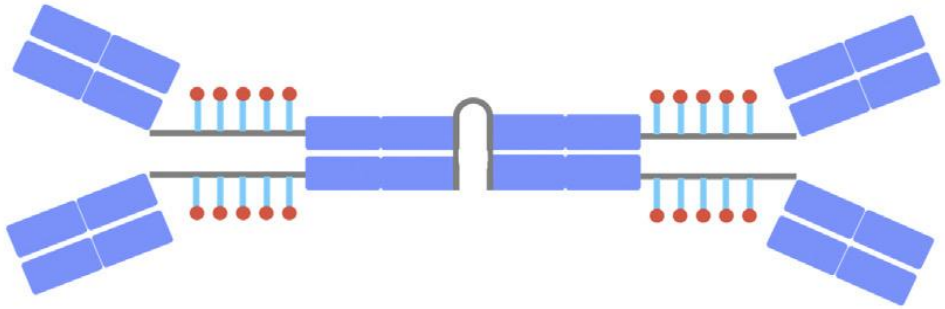
A.



T cell-dependent and independent B cell activation and class switch

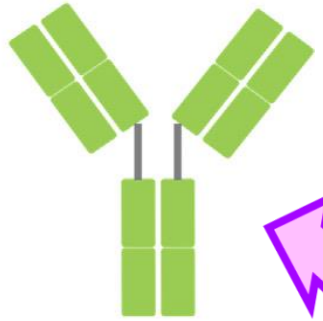


B.



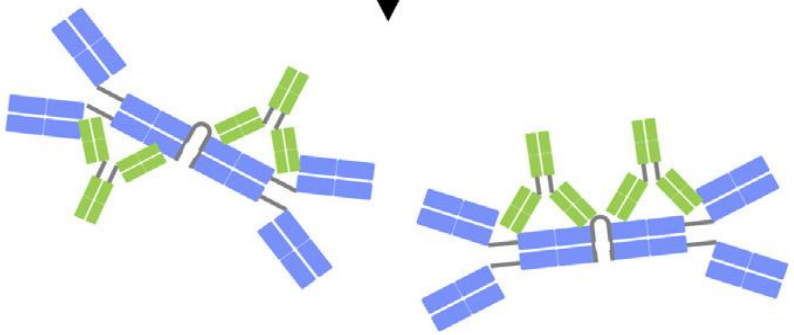
Polymeric galactose-deficient IgA1

C.



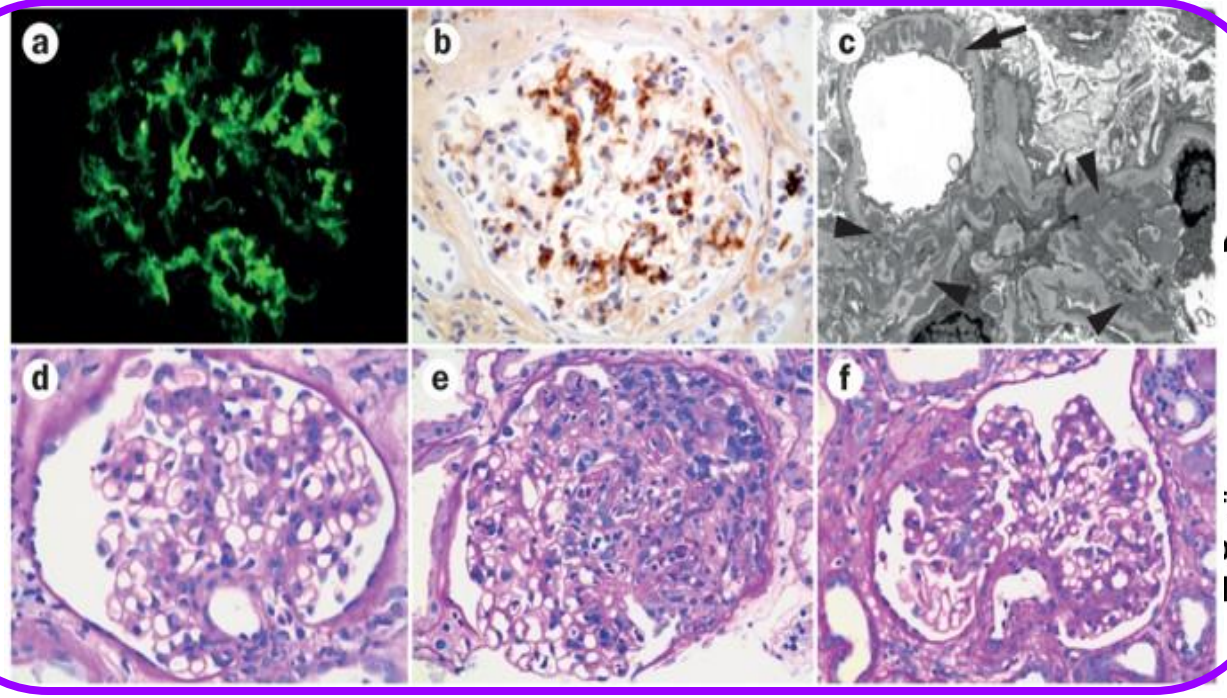
Anti-galactose-deficient IgA1 IgG auto-antibody

D.



Formation of circulating immune complex

E



lexes
lement

Supportive Care in IgA Nephropathy

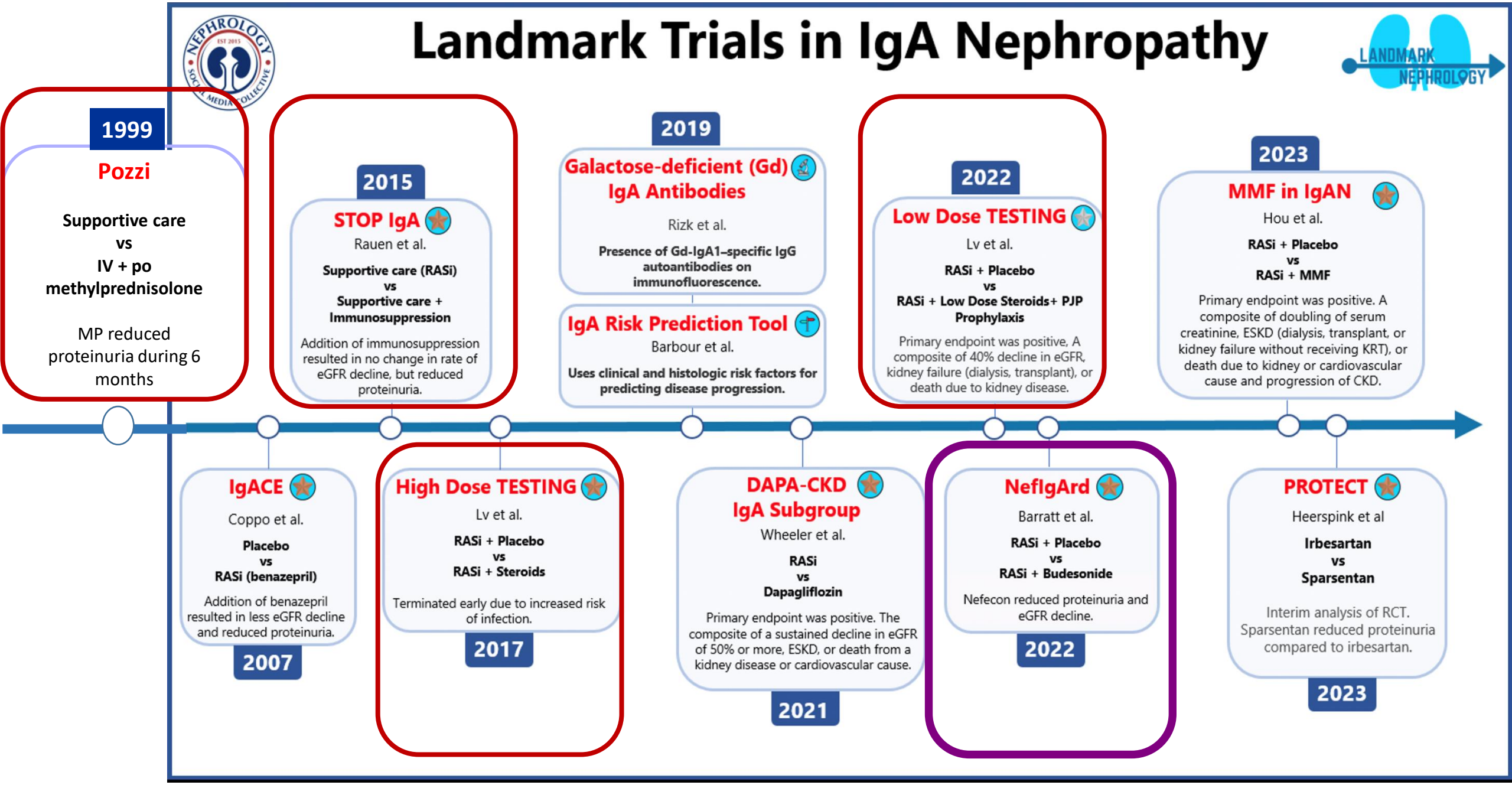
neph madness 2023

	BP reduction	RAAS Blockade ACEi & ARB	SGLT2i dapa & empa	ETAB/ARB sparsentan	Weight loss	Smoking Cessation	Dyslipidemia	Fish oil	Tonsillectomy
Goal	Slow kidney disease progression								
	< 125 -130 < 75 - 80	Proteinuria < 1 g/d or < 0.5 g/d	↓ Albuminuria	Start for UPCR >1.5 g/g ↓ Proteinuria	↓ Proteinuria		↓ Proteinuria	♥ Cardio-vascular benefits	Immuno-modulatory
Mechanism of Action	↓ intraglom pressure ↓ proteinuria & ↓ secondary glom injury	↓ intraglom pressure ↓ proteinuria	↓ Na reabsorption in proximal convoluted tubule ↓ Intraglom pressure -other effects	↓ intraglom pressure ↓ proteinuria Anti-inflammatory	↓ obesity-related hyperfiltration glom & segmental sclerosis	Improves general health	Proposed glomerular & mesangial protective effects	Kidney protection is not proven. Conflicting data.	Removal of source of abnormal IgA ↓ circulating immune complexes & glom deposits
Mentions	Hypertension = most potent predictor of outcome	ACEi + ARB combo hyperkalemia No benefit	Dapaglifozin ↓ Primary composite endpoint eGFR decline 50%, ESKD, death from kidney or CV cause	FDA conditional approval based on proteinuria outcomes *NOT PUBLISHED REMS AST/ALT monitoring	↓ Proteinuria in low calorie diet *no RCTs	Cigarette smoking = dose-dependent predictor in IgAN progression	↓ Proteinuria (from 800 mg/d to 500 mg/d) in statin arm *Small study (n=21), short follow up	Requires high doses (3-12 g/d) *do not use alone	Japanese cohort ↓ hematuria reduction /clinical remission *marginal improvement in proteinuria

Best Evidence in IgAN | RCT Ongoing | IgAN specific studies backing but important therapy | Conflicting evidence

@Nephroseeker

Landmark Trials in IgA Nephropathy



Glucocorticoid

Full dose cohort

Methylprednisolone	Conversion to Prednisolone/prednisone
0.6 - 0.8mg/kg/day for 2 months with maximum 48mg/day, tapering by 8mg/day each month for a total of 6-8 months.	0.8 - 1mg/kg/day for 2 months with maximum 60mg/day, tapering by 10mg/day each month for a total of 6-8 months.

Reduce dose cohort

Methylprednisolone	Conversion to Prednisolone/Prednisone
0.4mg/kg/day for two months with a maximum 32mg/day, tapering by 4mg/day each month for 6-9 months. + addition of trimethoprim/ sulfamethoxazole as prophylaxis for pneumocystis pneumonia during the first 12 weeks of therapy.	0.5mg/kg/day for two months with a maximum 40mg/day tapering by 5mg/day each month for 6-9 months. + addition of trimethoprim/ sulfamethoxazole as prophylaxis for pneumocystis pneumonia during the first 12 weeks of therapy.

VS

Matching Placebo

Issues arise from treatment with Systemic Steroids

1. **Steroids reduce glomerular inflammation but do not act in the disease pathogenesis**

   no change in Gd-IgA1 circulating levels

   temporary beneficial effect – relapse of proteinuria early after withdrawal

   need to repeat steroid course

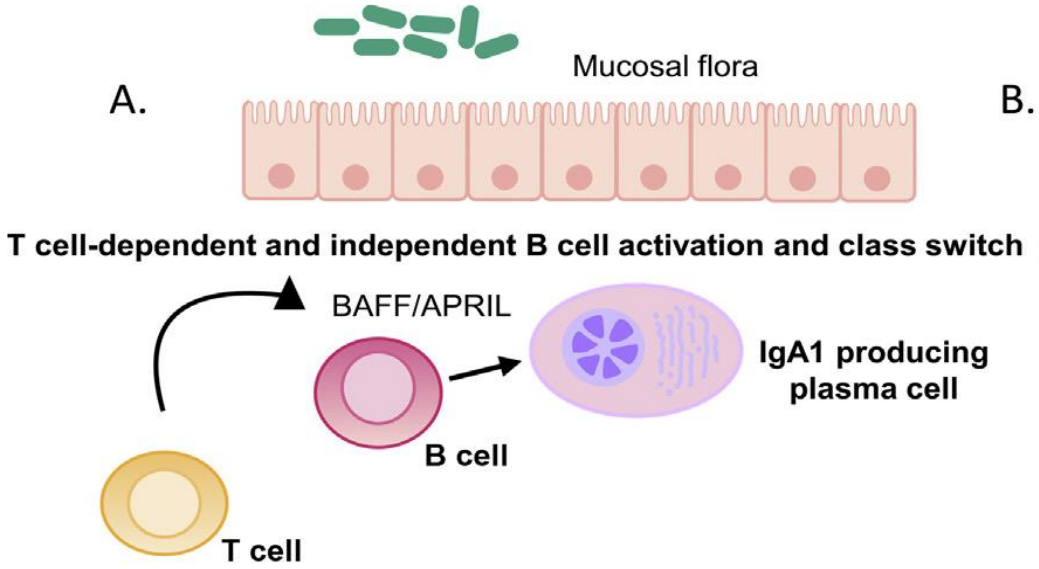
2. **Steroid toxicity (reported only in newer clinical studies)**

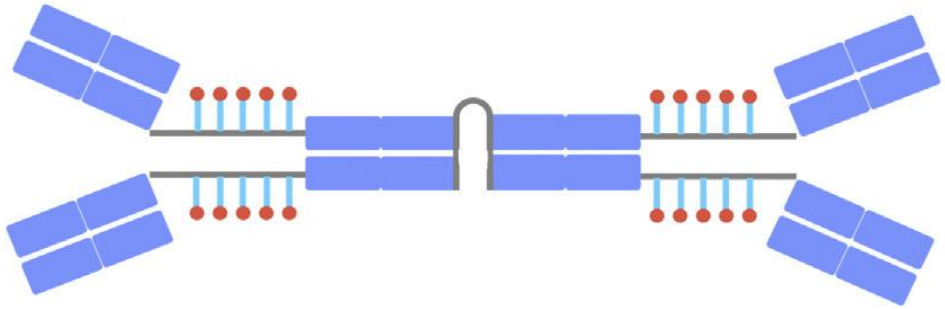
   infections (*Pneumocystis jirovecii*, *Nocardia* and *Cryptococcus) – need for Pneumocystis* prophylaxis

   diabetes melitus

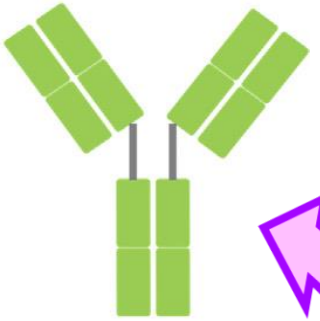
   death due to sepsis

IgA Nephropathy – from pathogenesis to histology

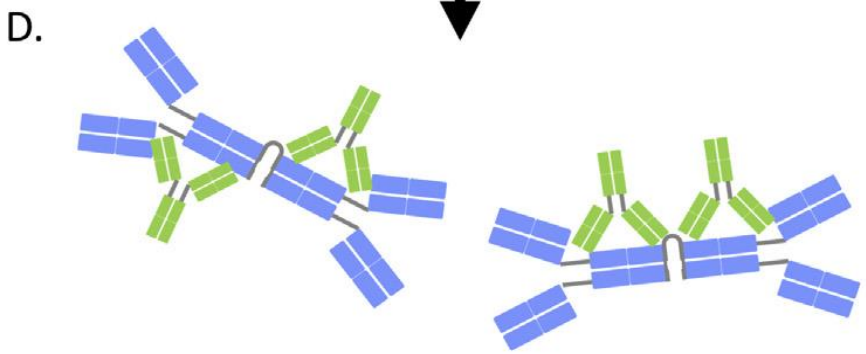


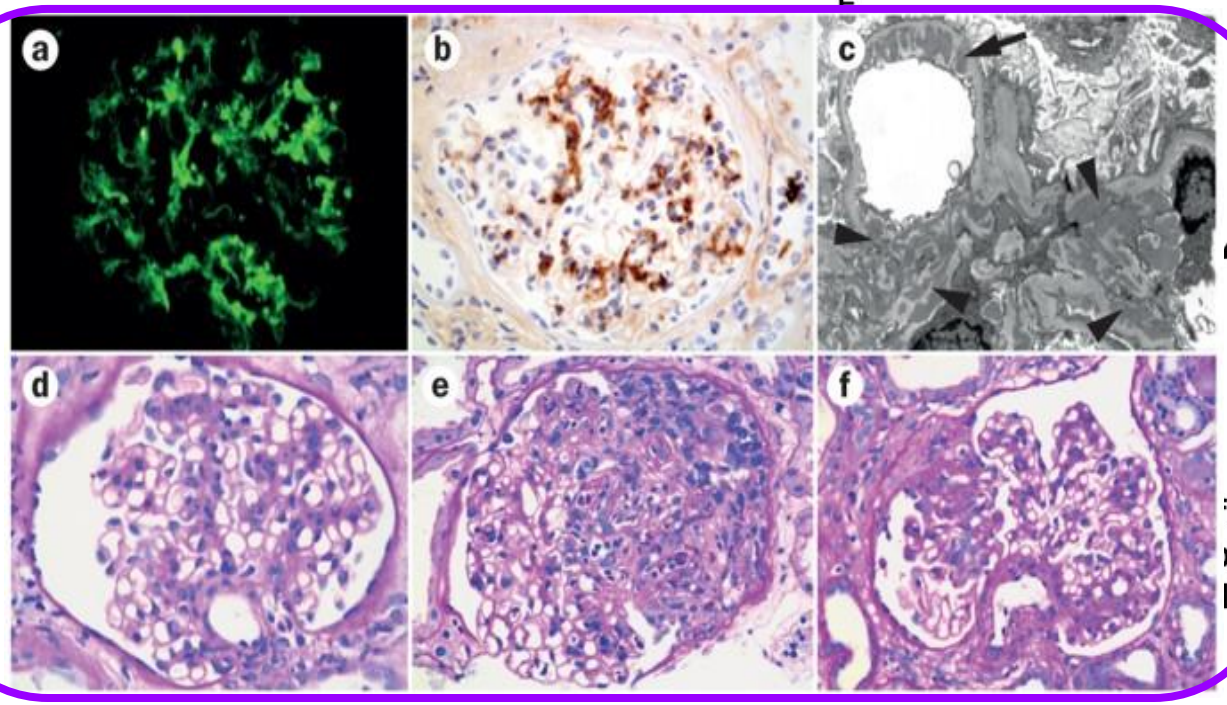


Polymeric galactose-deficient IgA1



Anti-galactose-deficient IgA1 IgG auto-antibody





Therapies that target Gd-IgA1

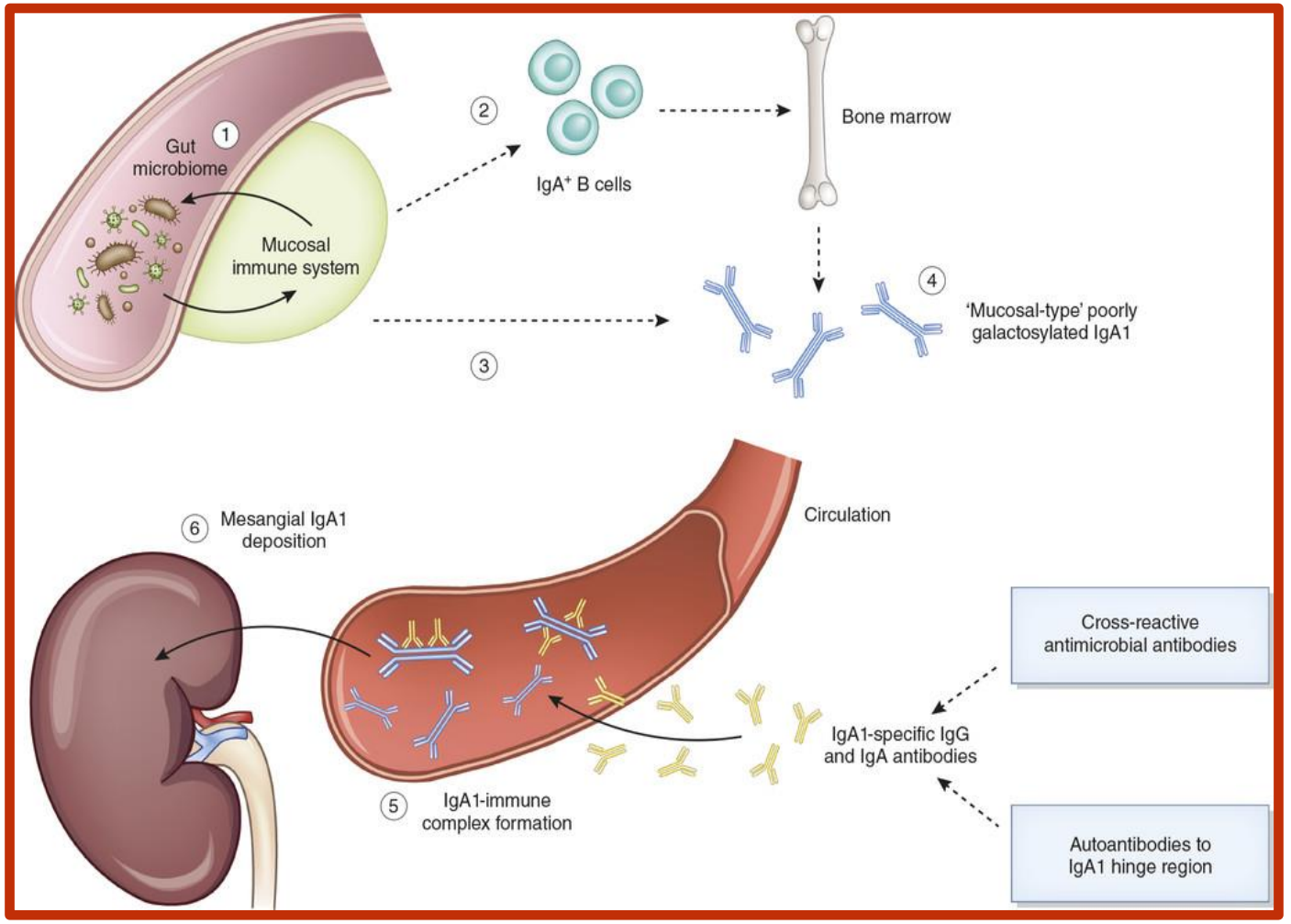
Targeted-release budesonide

B cell and plasma cell targeted treatment

Nefecon: Targeted-Release Budesonide

pH dependent and time delayed release

- Nefecon is designed to achieve a **high dose delivery of budesonide to the distal ileum** where Peyer's patches are highly concentrated.
- Approximately **46% of all Peyer's patches** are located in the **final 25cm segment of the distal ileum**
- **90% first pass effect** reduces systemic exposure and the risk of AEs typically associated with the systemic administration of corticosteroids.



Nefecon: Targeted-Release Budesonide

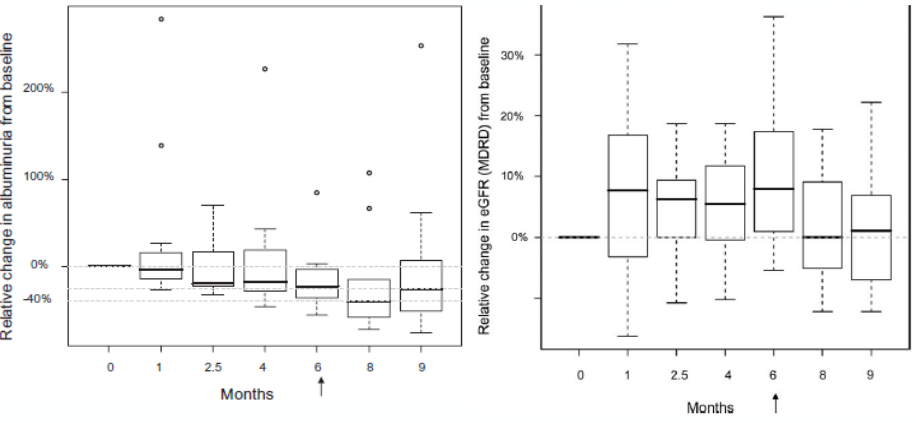
Trials overview

2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 | 2023 | 2024

Phase 2A Pilot Study

N=16 IgAN

↓Uprot 23%



◇ NDT 2011

NEFIGAN
Phase 2B Study

◇ Lancet 2017

NEFIGARD
Phase 3A

◇ Kidney Int 2022

Phase 3B

◇ Lancet 2023

Phase 3 OLE

Last patient out: Q1 2024

◇ Publication

Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial

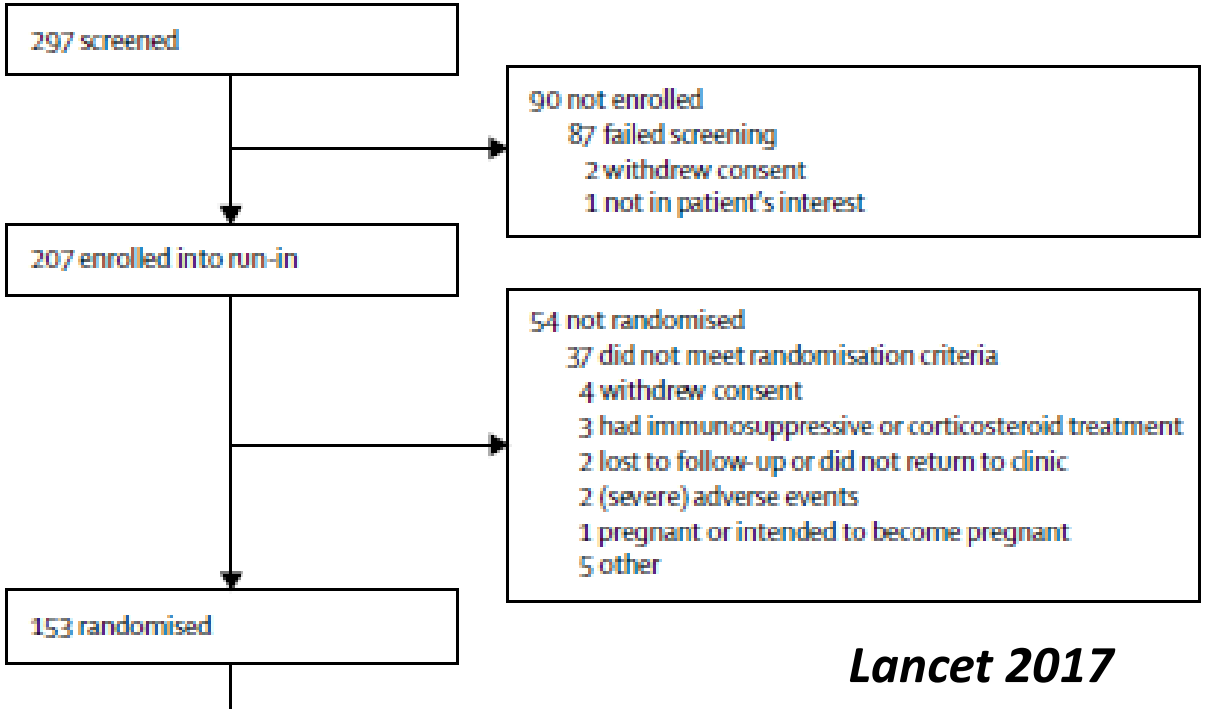
NEFIGAN
Phase 2B Study

Double-blind, placebo-controlled phase 2b trial, 6-month run-in,
9-month treatment,
3-month follow-up (62 nephrology clinics across 10 European countries)

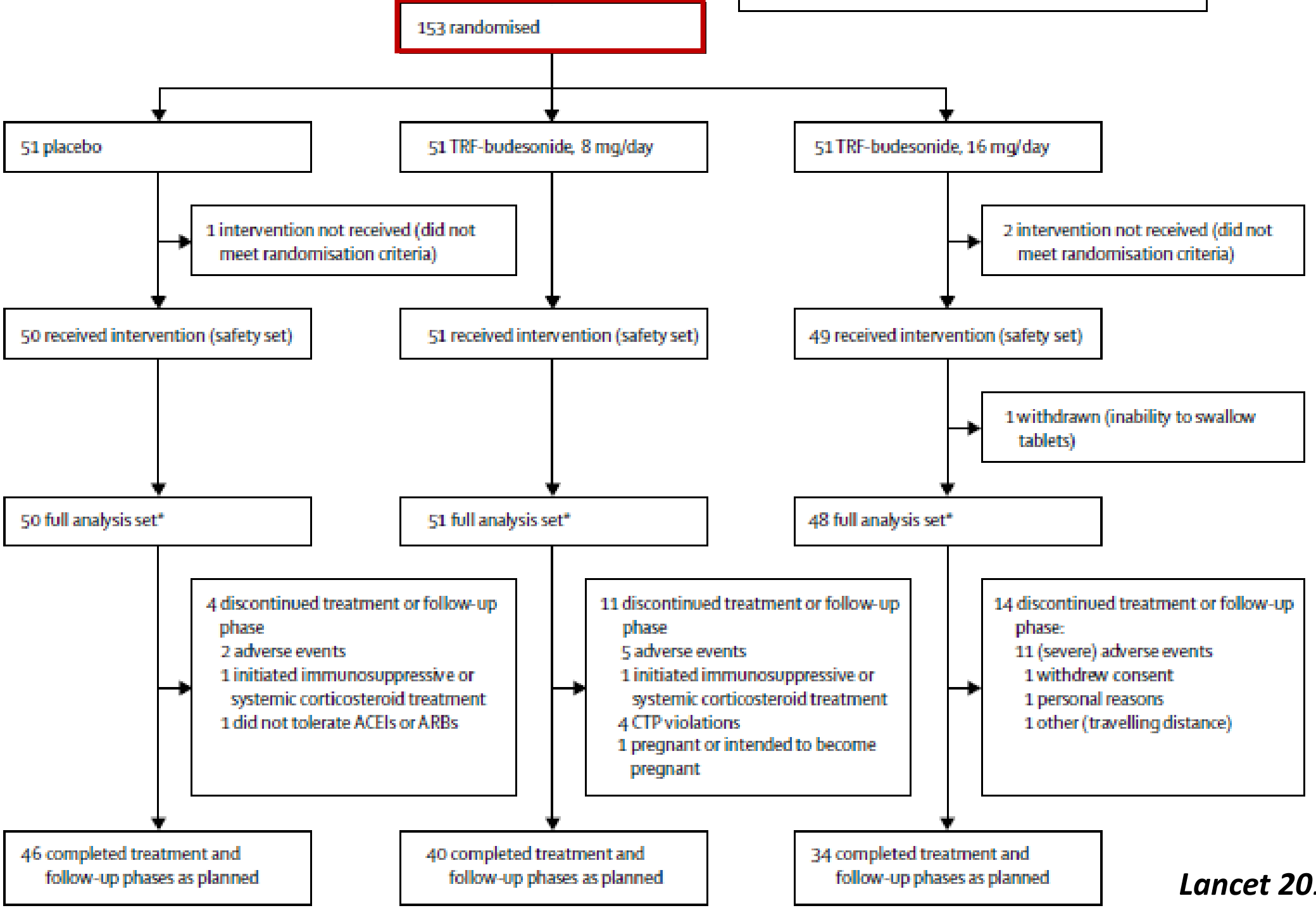
Randomised **1:1:1 ratio to 16 mg/day TRF-budesonide, 8 mg/day TRF-budesonide, or placebo**

Inclusion criteria

- GFR (eGFR) ≥ 45 mL/min/1.73m²
- UPCR≥0.5 g/g or Uprot ≥ 0.75 g/day
- Target blood pressure <130/80mmHg (ACEIs or ARBs to a maximum recommended dose or maximum tolerated dose)



Lancet 2017


153 randomised
51 placebo
51 TRF-budesonide, 8 mg/day
51 TRF-budesonide, 16 mg/day
1 intervention not received (did not meet randomisation criteria)
2 intervention not received (did not meet randomisation criteria)
50 received intervention (safety set)
51 received intervention (safety set)
49 received intervention (safety set)
1 withdrawn (inability to swallow tablets)
50 full analysis set*
51 full analysis set*
48 full analysis set*
4 discontinued treatment or follow-up phase
2 adverse events
1 initiated immunosuppressive or systemic corticosteroid treatment
1 did not tolerate ACEIs or ARBs
11 discontinued treatment or follow-up phase
5 adverse events
1 initiated immunosuppressive or systemic corticosteroid treatment
4 CTP violations
1 pregnant or intended to become pregnant
14 discontinued treatment or follow-up phase:
11 (severe) adverse events
1 withdrew consent
1 personal reasons
1 other (travelling distance)
46 completed treatment and follow-up phases as planned
40 completed treatment and follow-up phases as planned
34 completed treatment and follow-up phases as planned

Lancet 2017

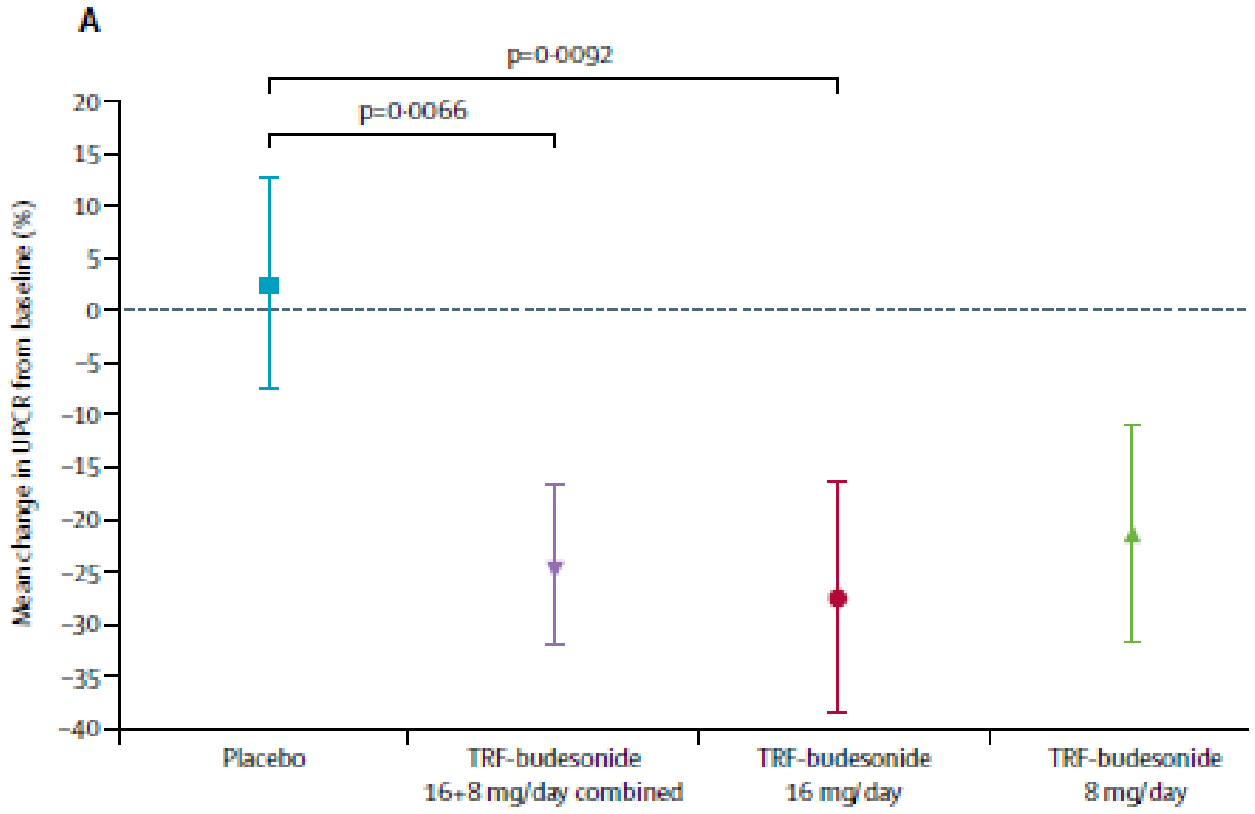
Outcomes

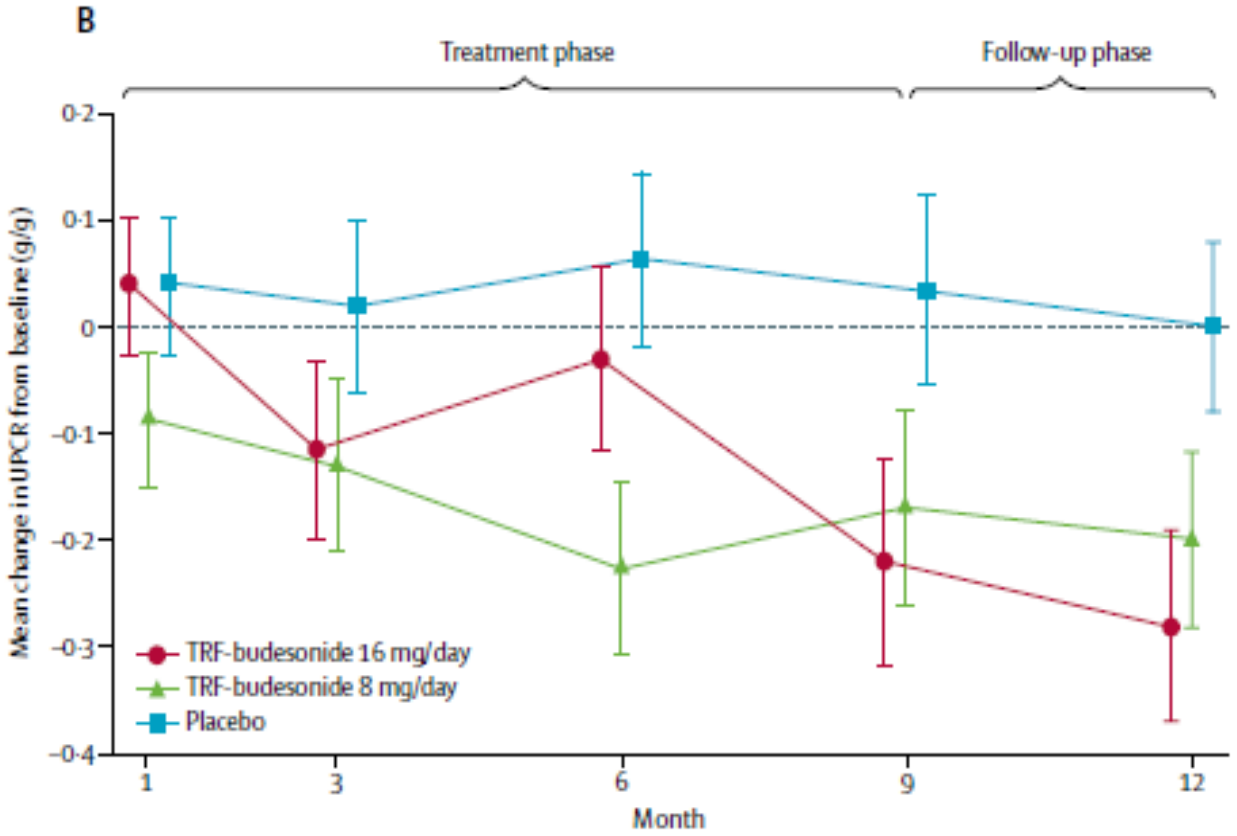
Primary outcome

9-months: Mean change in UPCR

Secondary outcomes

12 months: Mean changes from baseline in eGFR, UPCR, Uprot (g/24hr), UACR, Ualb (g/24hr)





Lancet 2017

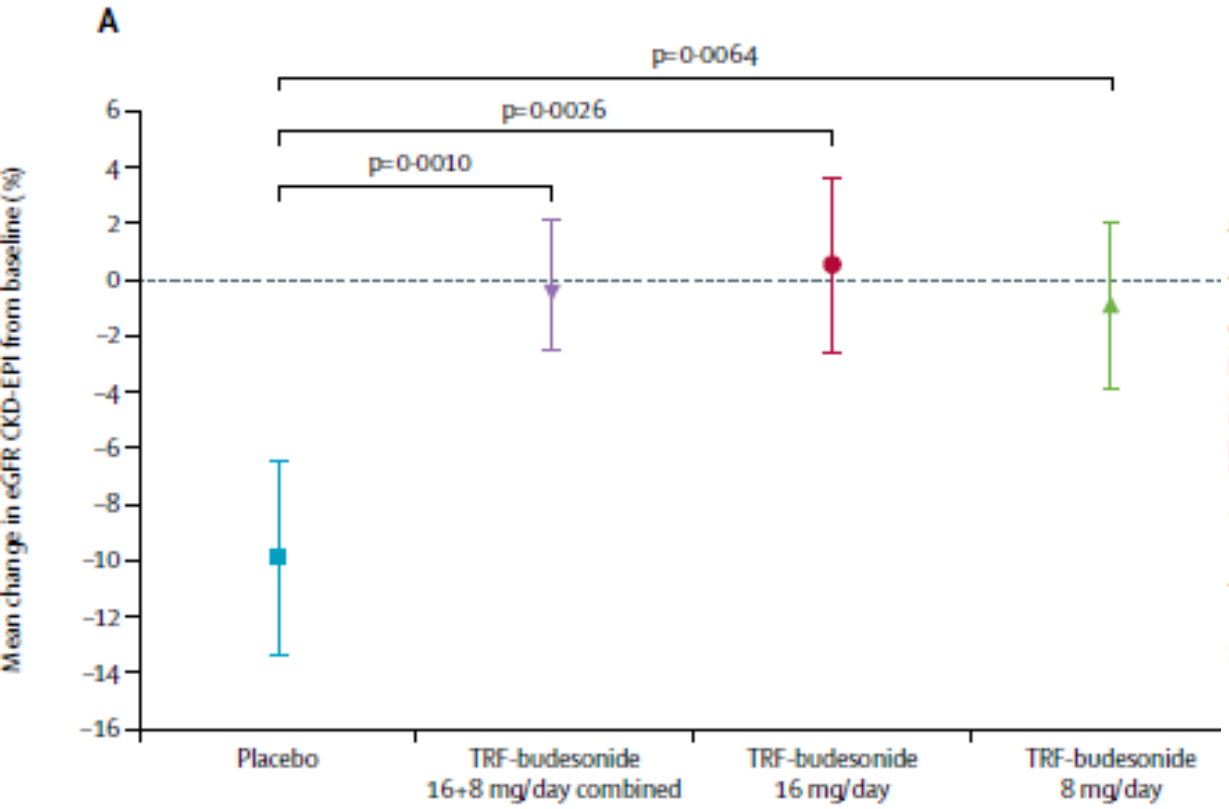
Outcomes

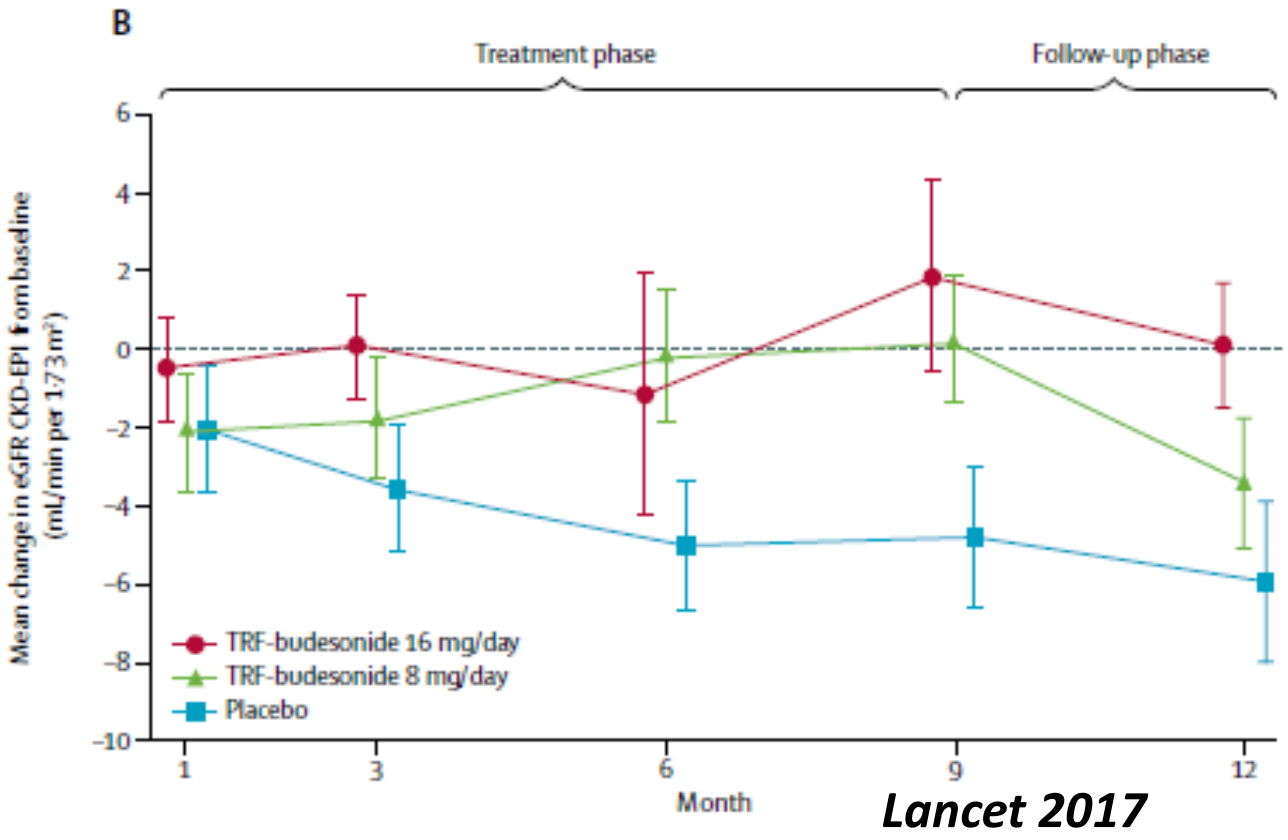
Primary outcome

9-months: Mean change in UPCR

Secondary outcomes

12 months: Mean changes from baseline in eGFR, UPCR, Uprot (g/24hr), UACR, Ualb (g/24hr)

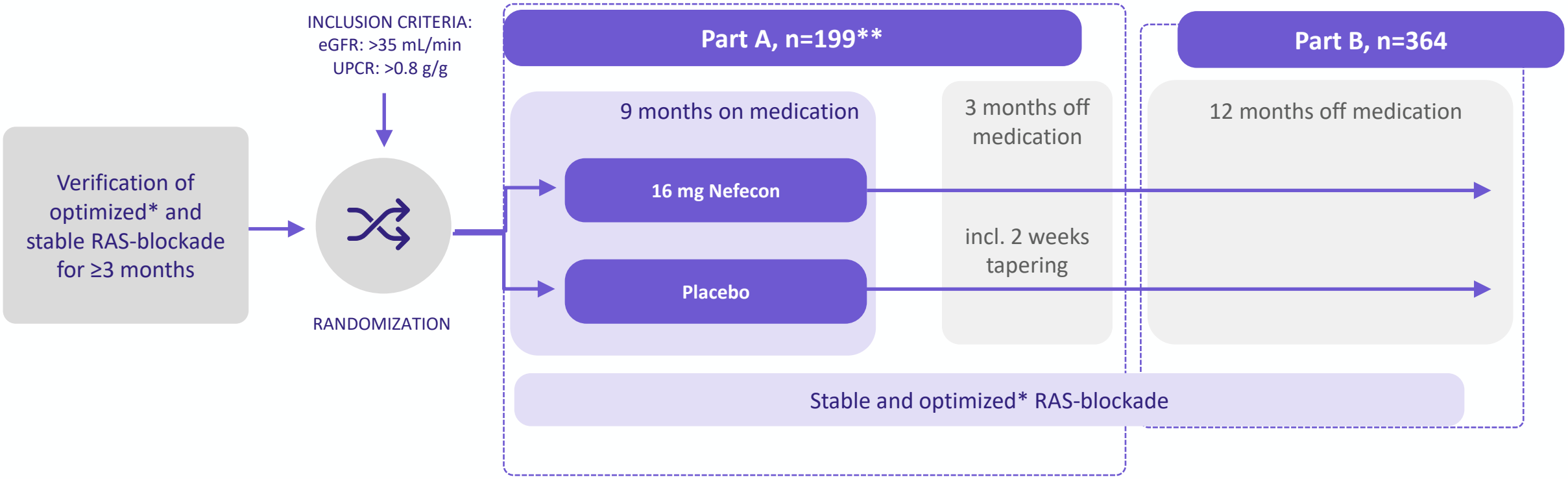




Lancet 2017

NeflgArd: Study Design

Efficacy and safety of Nefecon in patients with primary IgA Nephropathy



Kidney Int 2022

NEFIGARD
Phase 3A

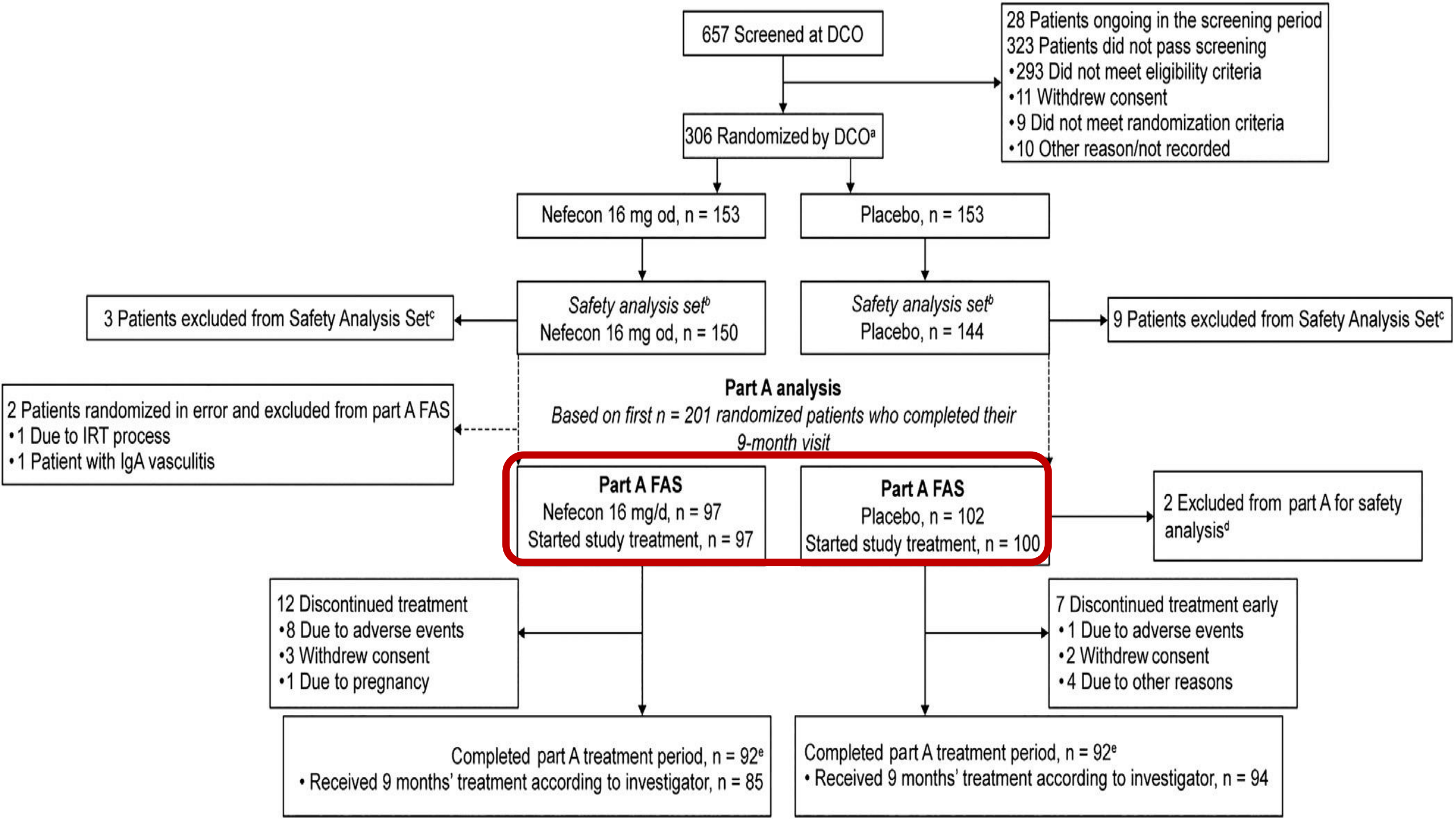
Results from part A of the multi-center, double-blind, randomized, placebo-controlled NefIgArd trial, which evaluated targeted-release formulation of budesonide for the treatment of primary immunoglobulin A nephropathy

Inclusion criteria

- Persistent proteinuria (UPCR >0.8 g/g or Uprot >1 g/24 h)
- eGFR 35 - 90 ml/min/1.73 m2 using CKD-EPI.
- Maximum tolerated or maximum allowed of an RAASinhibitors for at least 3 months
- Patients with type 1 or type 2 diabetes were eligible provided their diabetes was adequately controlled,

Exclusion criteria

- All secondary forms of IgAN or any non-IgAN glomerulonephritis
- Inadequately controlled BP>140/90 mm Hg,
- Kidney transplant,
- Treatment with systemic glucocorticoids or immunosuppressants in the 12 months

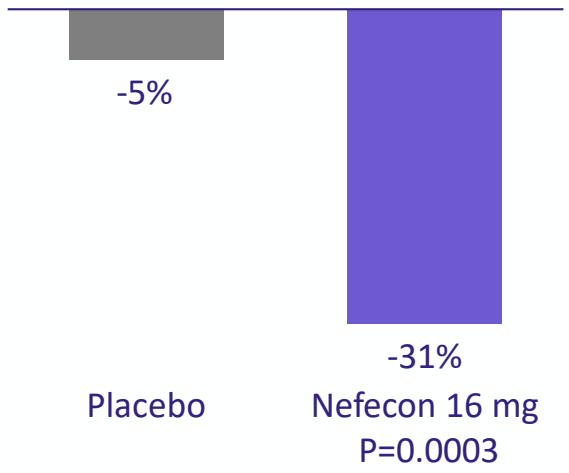

657 Screened at DCO
28 Patients ongoing in the screening period
323 Patients did not pass screening
•293 Did not meet eligibility criteria
•11 Withdrew consent
•9 Did not meet randomization criteria
•10 Other reason/not recorded
306 Randomized by DCO[a]
Nefecon 16 mg od, n = 153
Placebo, n = 153
3 Patients excluded from Safety Analysis Set[c]
Safety analysis set[b]
Nefecon 16 mg od, n = 150
Safety analysis set[b]
Placebo, n = 144
9 Patients excluded from Safety Analysis Set[c]
2 Patients randomized in error and excluded from part A FAS
•1 Due to IRT process
•1 Patient with IgA vasculitis
Part A analysis
Based on first n = 201 randomized patients who completed their 9-month visit
Part A FAS
Nefecon 16 mg/d, n = 97
Started study treatment, n = 97
Part A FAS
Placebo, n = 102
Started study treatment, n = 100
2 Excluded from part A for safety analysis[d]
12 Discontinued treatment
•8 Due to adverse events
•3 Withdrew consent
•1 Due to pregnancy
7 Discontinued treatment early
•1 Due to adverse events
•2 Withdrew consent
•4 Due to other reasons
Completed part A treatment period, n = 92[e]
• Received 9 months' treatment according to investigator, n = 85
Completed part A treatment period, n = 92[e]
• Received 9 months' treatment according to investigator, n = 94

NEFIGARD
Phase 3A

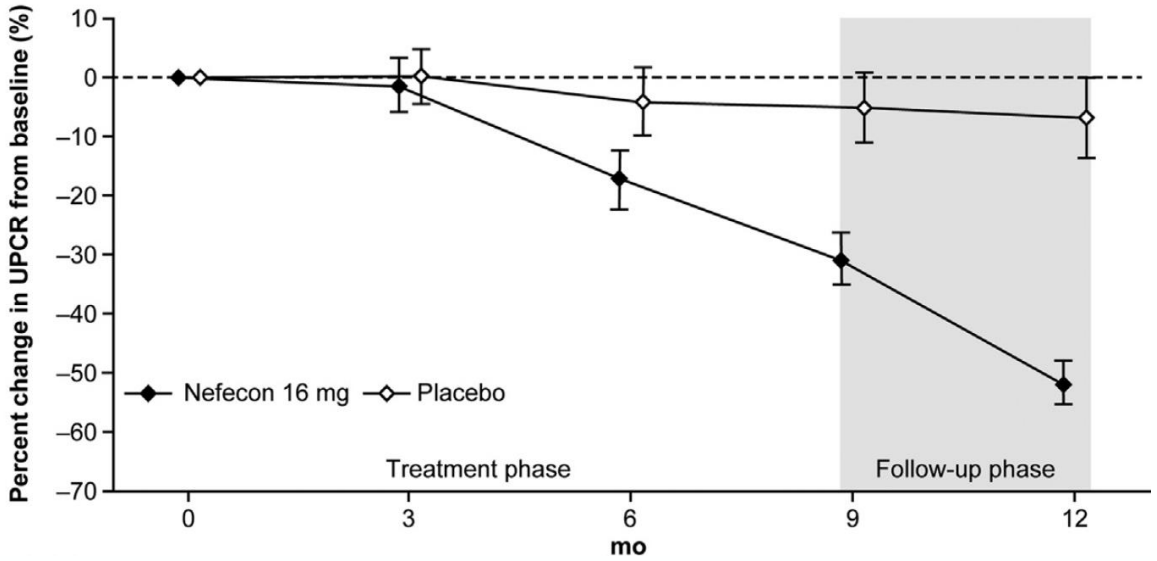
NefIgArd Part A: Results

Change in UPCR at 9 and 12 months vs. baseline

Primary endpoint: change in UPCR from baseline at 9 months



Change in UPCR from baseline over 12 months



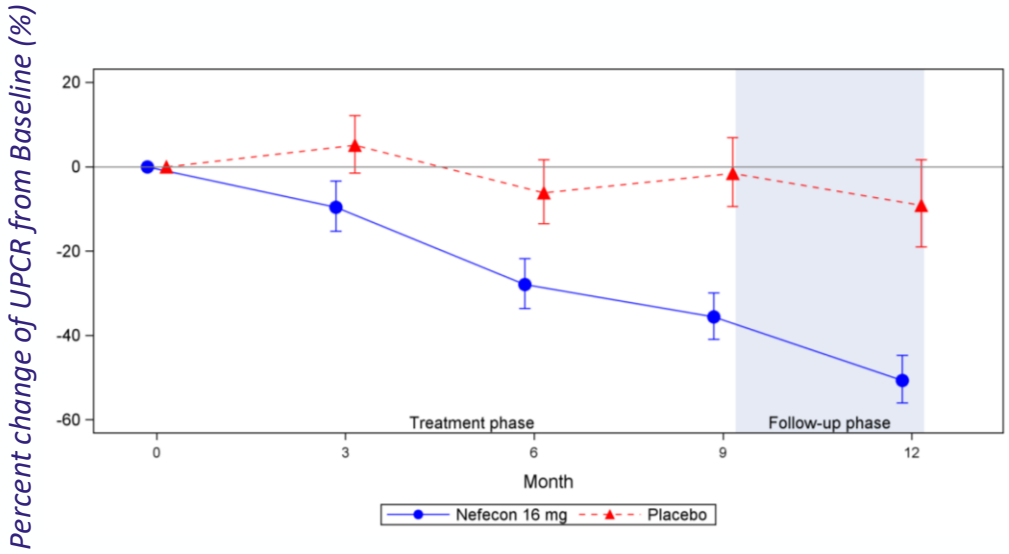
Barratt J et al. (2023) Kidney Int. 103(2):391-402

NEFIGARD
Phase 3A

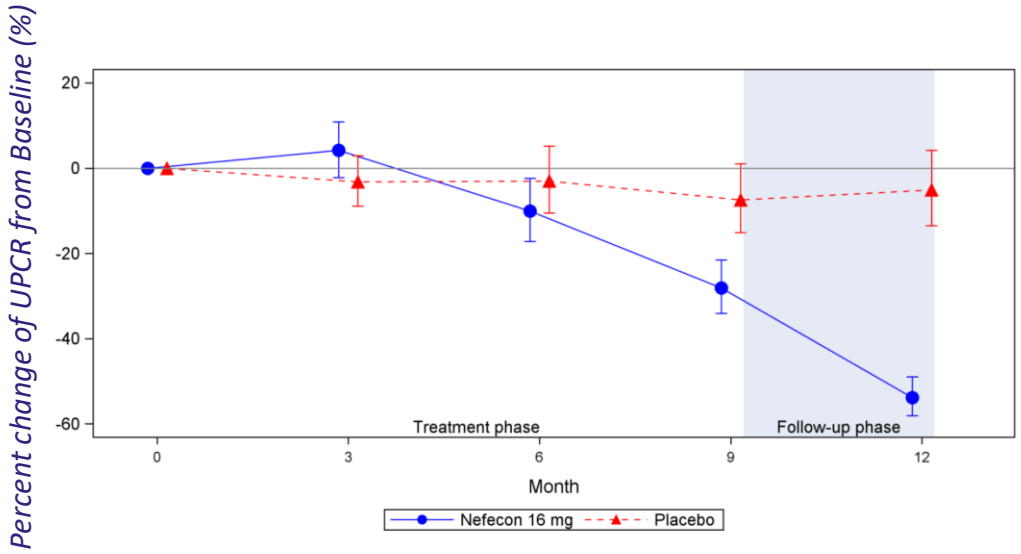
NefIgArd Part A: Results

Subgroup analysis: UPCR change in patients based on baseline UPCR

Baseline UPCR subgroup ≥1.5 g/g



Baseline UPCR subgroup <1.5 g/g

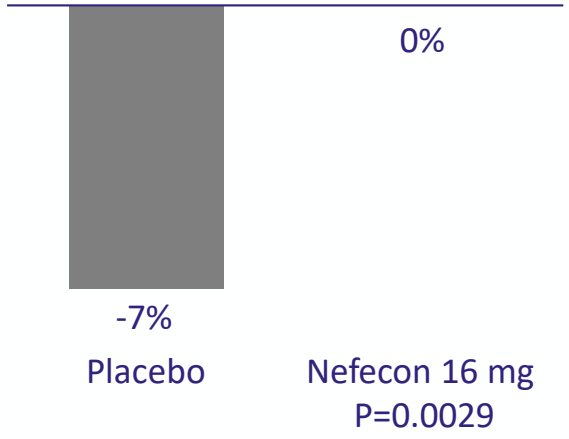


NEFIGARD
Phase 3A

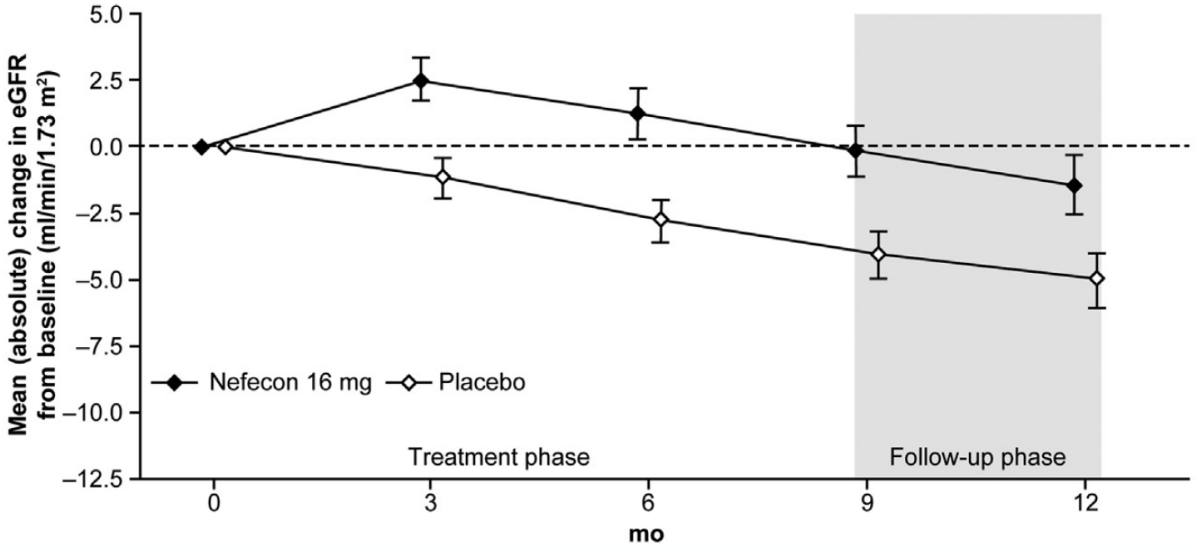
NefIgArd Part A: Results

Change in eGFR at 9 months vs. baseline

Secondary endpoint: change in eGFR from baseline at 9 months



Change in eGFR from baseline over 12 months



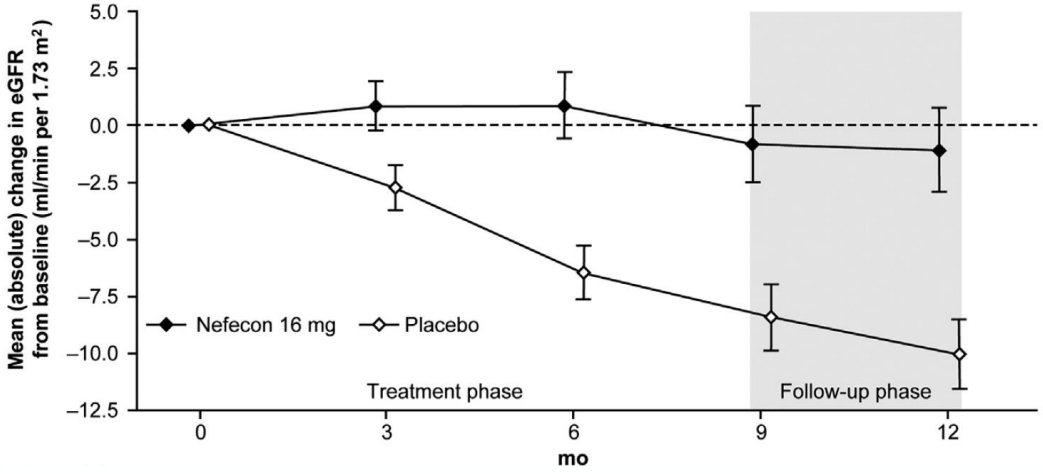
Barratt J et al. (2023) Kidney Int. 103(2):391-402; eGFR: estimated glomerular filtration rate

NEFIGARD
Phase 3A

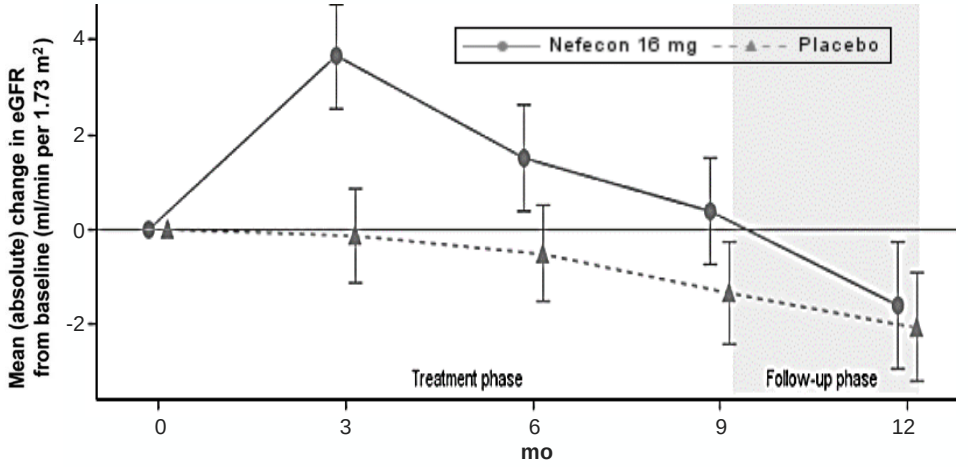
NefIgArd Part A: Results

Subgroup analysis: eGFR change in patients based on baseline UPCR

Baseline UPCR subgroup ≥1.5 g/g



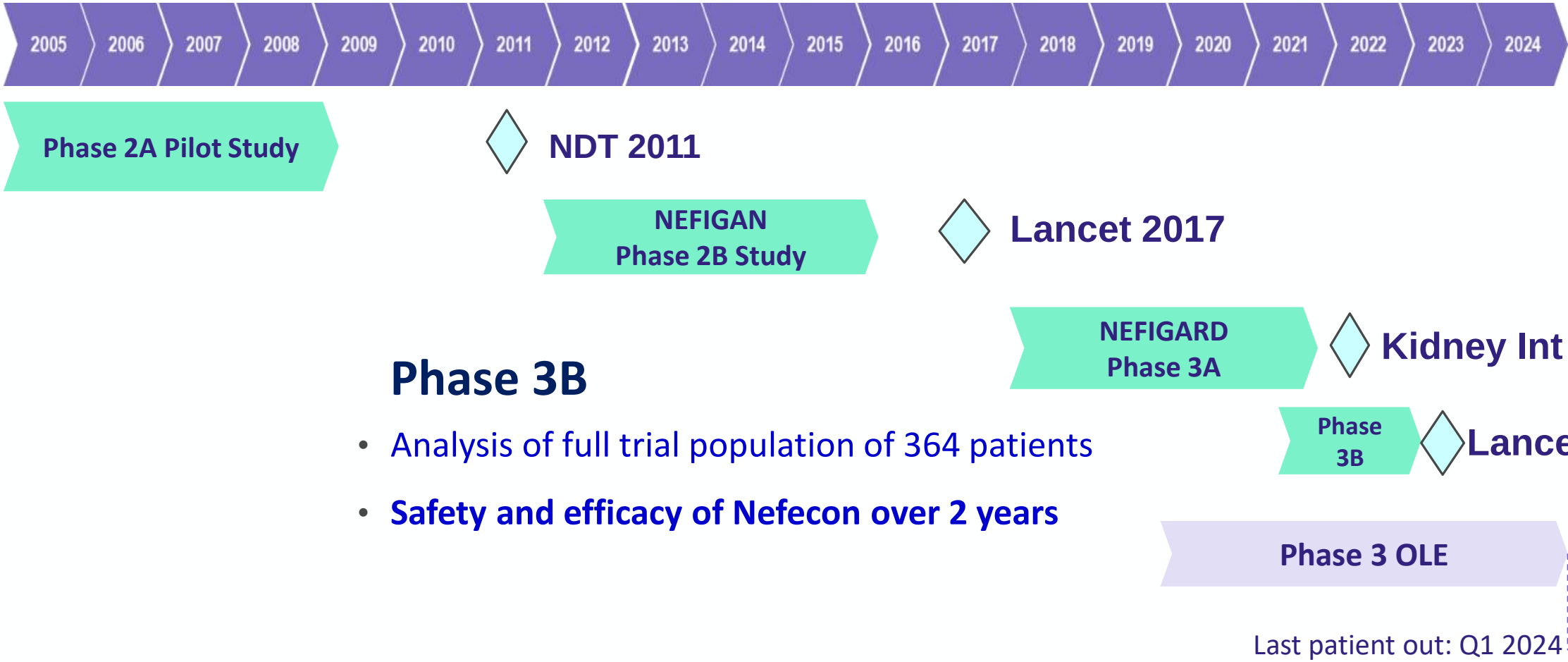
Baseline UPCR subgroup <1.5 g/g



Barratt J et al. (2023) Kidney Int. 103(2):391-402; UPCR: urine protein-creatinine ratio; eGFR: estimated glomerular filtration rate

Nefecon: Targeted-Release Budesonide

Trials overview



Phase 3B

- Analysis of full trial population of 364 patients
- **Safety and efficacy of Nefecon over 2 years**

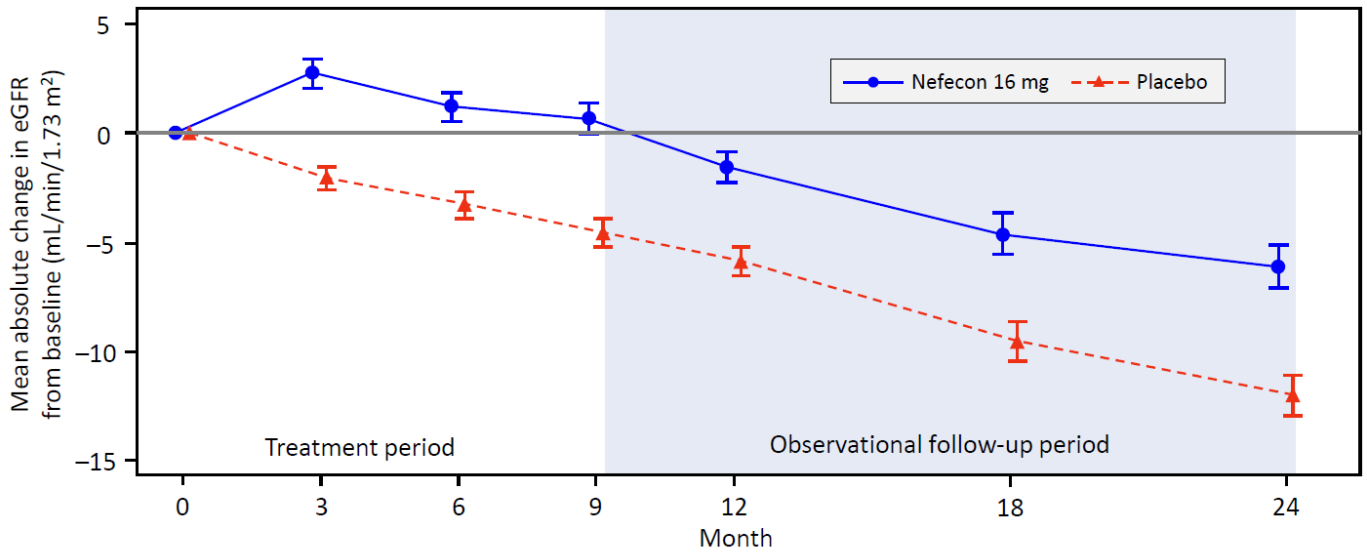
Phase 3B

NefIgArd Part B: Results

Time-weighted average of eGFR over 2 years

- **Primary endpoint:** time-weighted average of eGFR over 2 years showed a statistically **significant benefit with Nefecon vs. Placebo of 5.05 mL/min/1.73 m²** (p<0.0001).
- The eGFR **benefit** at the end of the 9-month treatment period with Nefecon **was maintained** during the 15-month of observational follow-up.

Mean absolute change in eGFR from baseline to 24 months in the overall study population

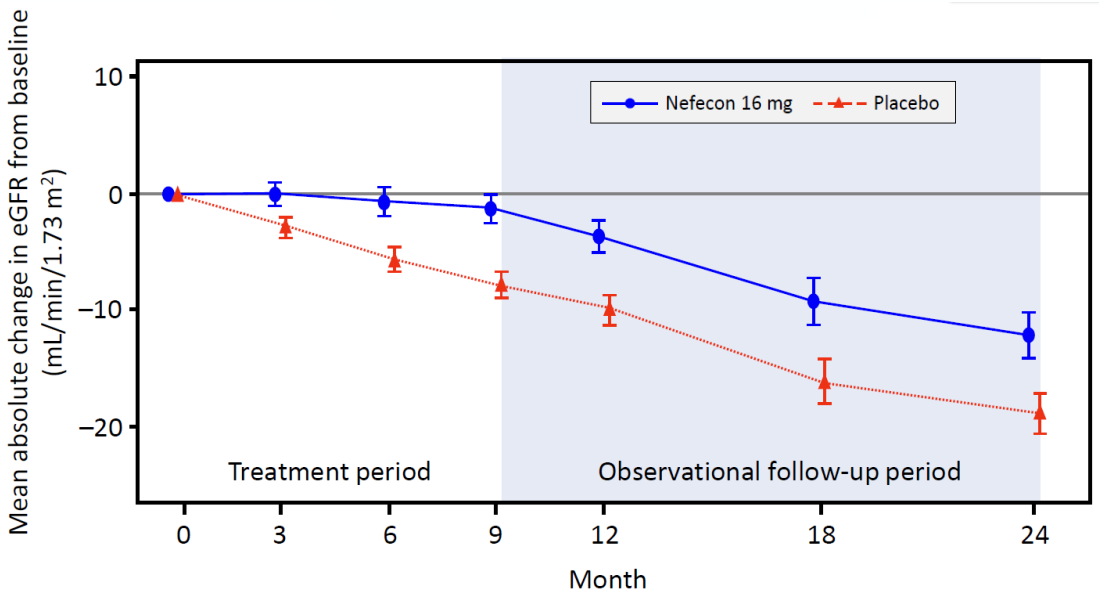


Phase 3B

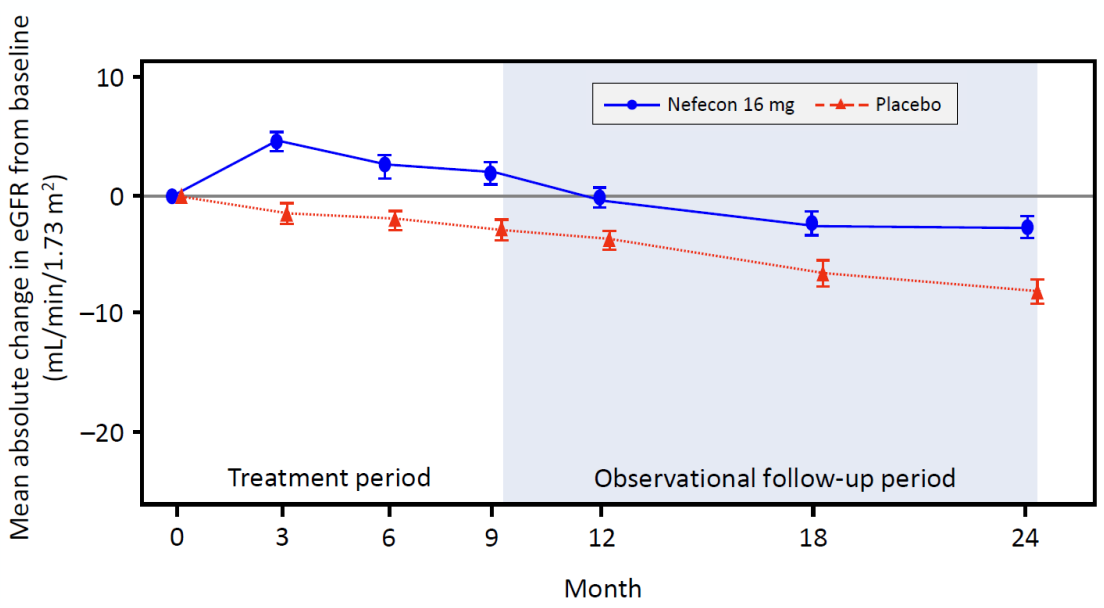
NefIgArd Part B: Results

Subgroup analysis: eGFR change in patients based on baseline UPCR

Baseline UPCR subgroup ≥1.5 g/g



Baseline UPCR subgroup <1.5 g/g



Richard Lafayette, presented at ERA-EDTA 2023 in Milano; https://www.calliditas.se/en/wp-content/uploads/sites/2/2023/06/Presentation-European-Renal-Association-ERA-Congress-2023.pdf; UPCR: urine protein-creatinine ratio; eGFR: estimated glomerular filtration rate

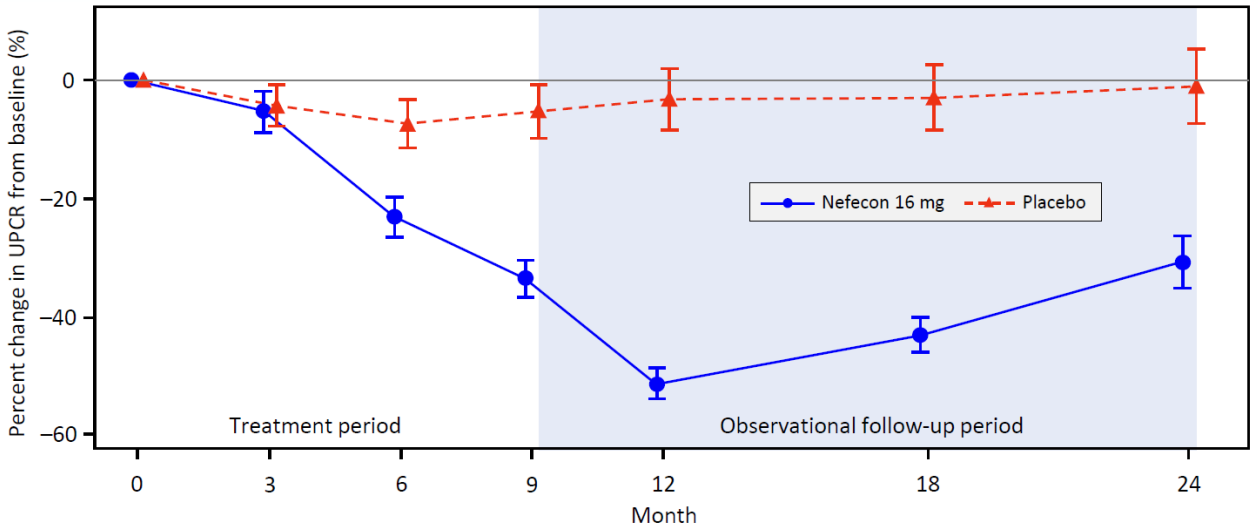
Phase 3B

NefIgArd Part B: Results

UPCR change over 24 months

- Mean relative **change in UPCR at 24 months was -30.7%** with Nefecon vs. -1.0 % with Placebo
- **At 24 months**, the percentage reduction in UPCR in the Nefecon vs placebo arm was **similar to the end of the 9-month treatment period**

Mean relative change in UPCR from baseline to 24 months in the overall study population



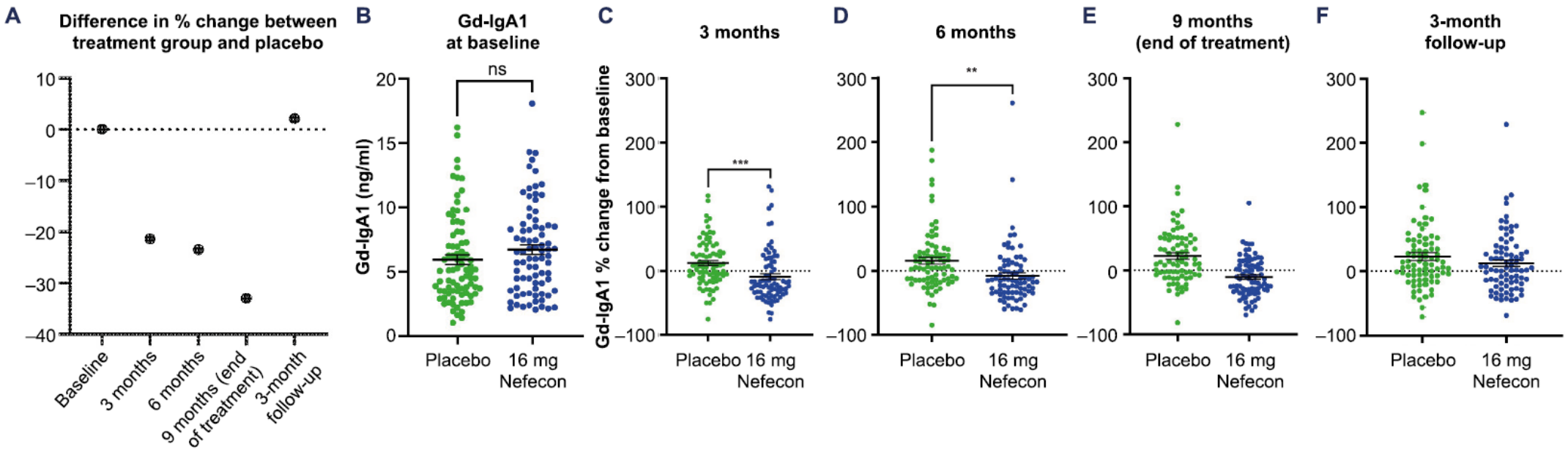
Phase 3B

NefIgArd Part B

Summary

- The NefIgArd study **met its 2-year primary endpoint**, demonstrating that 9 months of treatment with Nefecon on top of optimized standard of care provided a **statistically significant and clinically relevant preservation of eGFR** compared with optimized standard of care alone.
- The size of the **eGFR benefit was maintained over the 15-month off-drug** observational follow-up period.
- The observed eGFR benefit was **independent of baseline UPCR.**
- Nefecon 16 mg was generally **well tolerated**, and the AE profile was consistent with that reported in the previous interim analysis.

Treatment with Nefecon reduces circulating levels of gd-IgA1



	3 months	6 months	9 months
Mean reduction in gd-IgA1 vs. placebo	-21.4%	-23.5%	-34%
P-value	<0.0005	<0.0017	<0.0001

Molyneux et al., ASN 2022 Orlando, poster SA-PO654

HELLENIC SOCIETY OF NEPHROLOGY
MEETING & SEMINAR
Combined with:
18th BANTAO CONGRESS
October 19-22, 2023
Makedonia Palace Hotel THESSALONIKI, GREECE

Serum Gd-IgA1 and proteomic analysis of plasma and urine in patients with IgAN, schedule of the study evaluating changes after deactivating intestinal-renal axis

Christodoulos Keskinis[1,2], Eleni Moysidou[1,3], Jerome Zoidakis[4], Vasileios Vaios[1,5], Eleni Kapsia[6], Maria Trivyza[7], Panagiotis Pateinakis[2], Marios Papasotiriou[7], Smaragdi Marinaki[6], Pantelis Sarafidis[1,3], Vassilios Liakopoulos[1,5], Vladimir Tesar[8], Maria Stangou[1,3]

[1]*School of Medicinie, Aristotle University of Thessaloniki (AUTH), Greece*

[2]*Department of Nephrology, Papageorgiou Hospital, Thessaloniki, Greece*

[3]*1st Department of Nephrology AUTH, Hippokration Hospital, Thessaloniki, Greece*

[4]*Center of Systems Biology, Biomedical Research Foundation of the Academy of Athens, Greece*

[5]*2nd Department of Nephrology AUTH, AHEPA Hospital, Thessaloniki, Greece*

[6]*National and Kapodistrian University of Athens, Medical School, Nephrology Department and Renal Transplantation Unit, Laiko Hospital Athens, Athens, Greece*

[7]*Department of Nephrology and Renal Transplantation, University Hospital of Patras, Patras, Greece*

[8]*Department of Nephrology, 1st Faculty of Medicine, Charles University, Prague, Czech*

Introduction

Aim of the study will be to evaluate Gd-IgA1 serum levels and inflammatory mediators in plasma and urine of patients with IgAN during deactivation of intestinal-renal axis.

Material & Methods

Adult patients,
eGFR>30ml/min/1.73m^2
Uprotein>750mg/24hr
Renal biopsies will be revaluated, and classified according to MEST-C score. Serum levels of Gd-IgA1 and plasma and urine proteomics will be estimated and analyzed by performing machine learning algorithms at the beginning of treatment (T0), and accordingly at 3, 6, 9 and 12months

Results

Between 05/2023 and 09/2023 N=24, M/F:17/7,

Mean age: 47.21±13.4years

Started on budesonide treatment.

At time of diagnosis,

41.46 ±37.79 months ago,

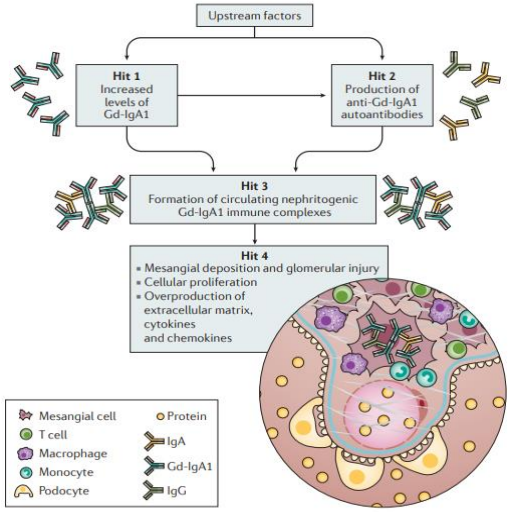
Mean age 43.29±14.48years, eGFR 68.7±25.3ml/min/1.73 m2 Uprot 2.993±2.07gr/24hrs.

At time of inclusion,

10/24 patients had already received steroids and 1/24 cyclophosphamide.

At time starting budesonide treatment,

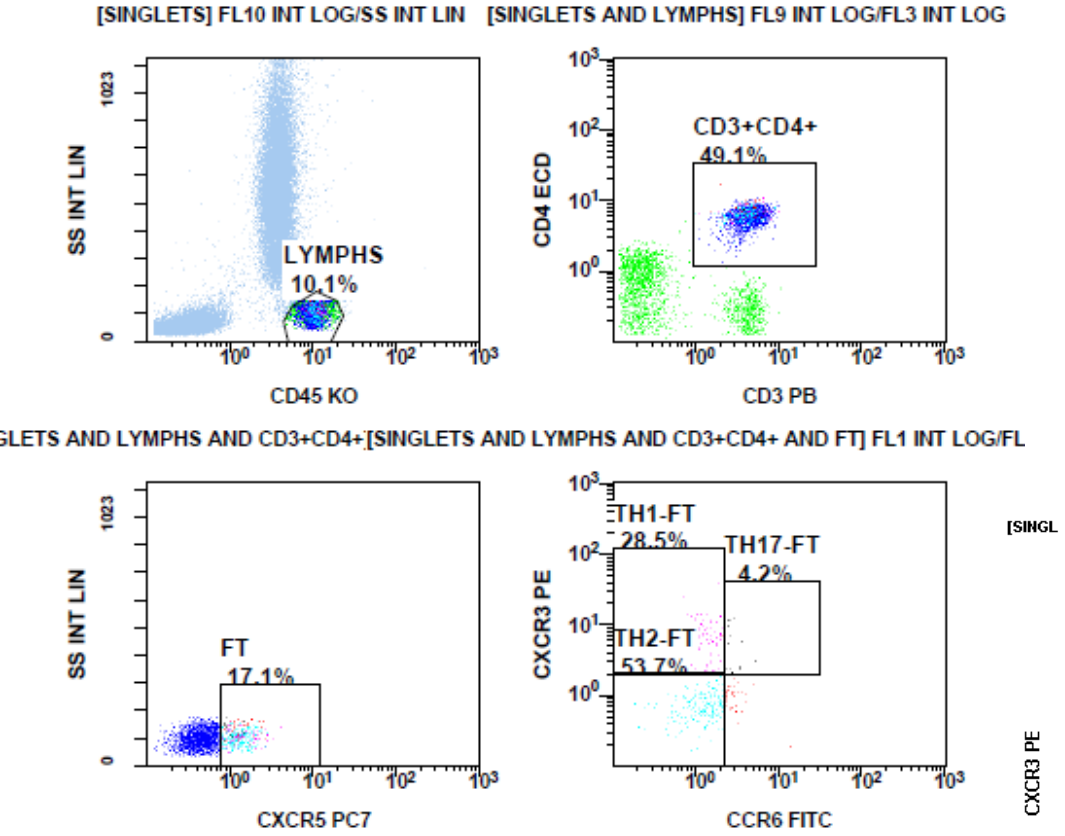
eGFR58.82±25.83ml/min/1.73m^2
Uprot= 2.821±2.08gr/24hrs.



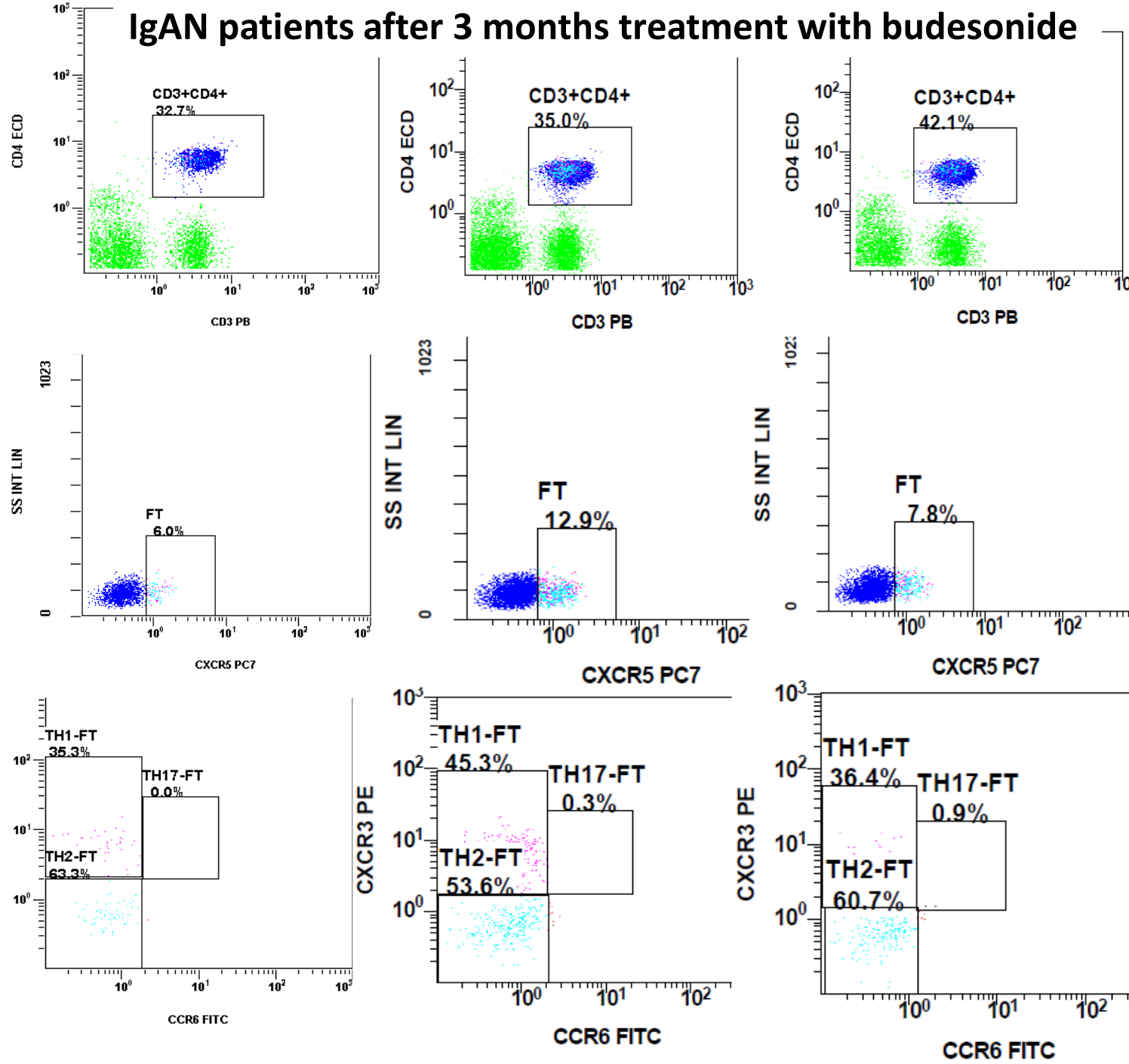
Conclusion

Levels of Gd-IgA1 and disease biomarkers at time of disease activity and during follow up will give important information about disease pathogenesis and also, reveal predictive markers of disease activity and outcome.

IgAN patient at diagnosis



IgAN patients after 3 months treatment with budesonide



Conclusions

1. The gut-kidney axis is implicated in the pathogenesis and progression of IgAN
2. Increased levels of Gd-IgA1 lead to immune-complex formation and deposition into the mesangium leading to active and chronic renal lesions
3. Steroid treatment reduces inflammation, but it is not specific and followed by frequent relapses and side-effects
4. Budesonide aims to reduce production of Gd-IgA1
5. It is proved safe and efficient to reduce proteinuria and improve renal function

Time has come to change the aspect of our therapeutic approach

– from symptomatic treatment to precise medicine

Thank you for your attention!