腎兒知癒實驗室 KIDS' CURE LAB

APCN x TSN 2025

# Childhood Nephrotic Syndrome

## *An update on management*


Eugene Yu-hin Chan

Clinical Associate Professor

MBBS (HK), MD (HKU), FRCPCH (UK), FISN

Department of Paediatrics, The Chinese University of Hong Kong

Hong Kong Children's Hospital


CU Medicine HONG KONG

香港中文大學醫學院

Faculty of Medicine

The Chinese University of Hong Kong

***APCN x TSN x 2025***

香港兒童醫院

Hong Kong Children's Hospital

# Disclosures

- No relevant financial relationships with ineligible companies

# Natural History of NS

First presentation of nephrotic syndrome

Prednisolone or prednisone (PDN) 60 mg/m²/d

80-90%

SSNS

SRNS

CNI-resistance

50% in 5-10 years

25% No relapse

25% Infrequent relapser

>50% FRSDNS

FRNS

SDNS

Levamisole

Alternate-day low-dose PDN

MMF

CNIs

Rituximab

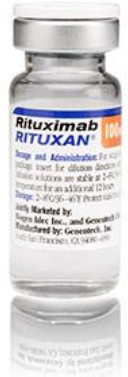
Sustained remission
Limited treatment-associated toxicities
Good quality of life

Levamisole

MMF

CNI

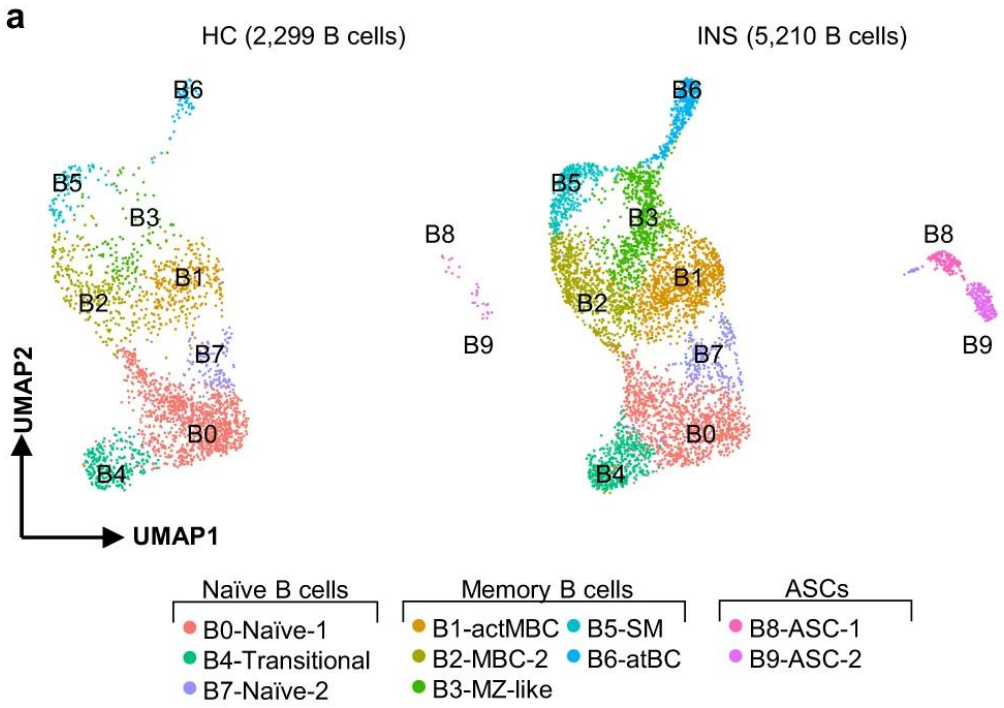
CYC



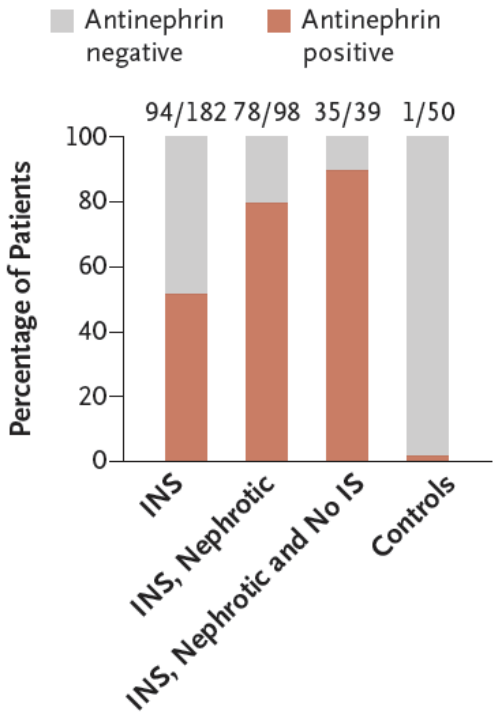

Chan & Boyer. KI, 2024; Photo use consented

# B-cells and anti-nephrin antibodies: Towards personalized medicine?

## SSNS

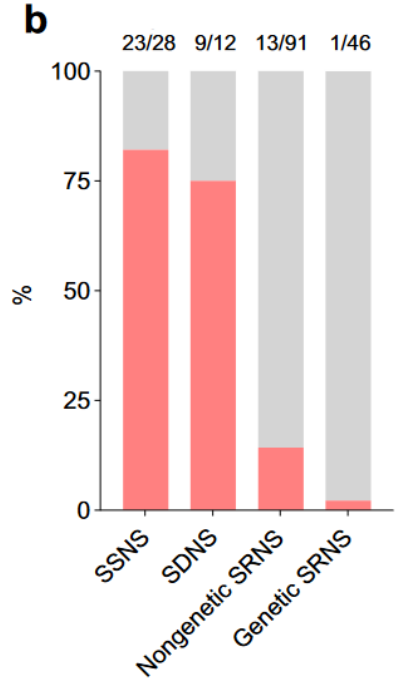



**Extra-follicular B cell response**




**80-90% children with SSNS had anti-nephrin Abs**

## SRNS




**~20% SRNS has anti-nephrin Abs**

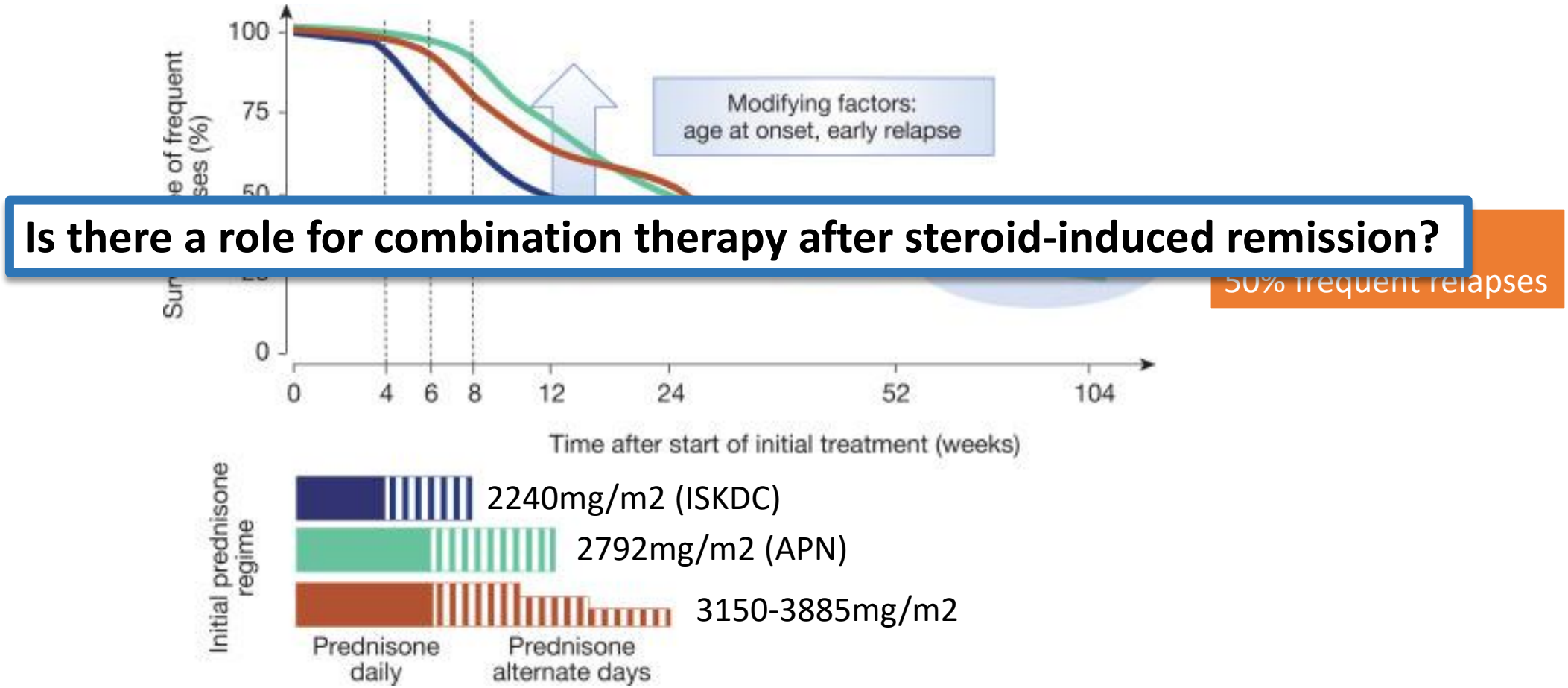
Al-aubdoah, Nat Comm 2023; Hengel, NEJM 2024; Hengel, KI 2025

# Outlines

- Initial management
- Anti-CD20 monoclonal antibodies in FRSDNS
- Management of immune-mediated SRNS

# *Initial treatment*

# Initial steroid treatment does not alter long-term disease behavior

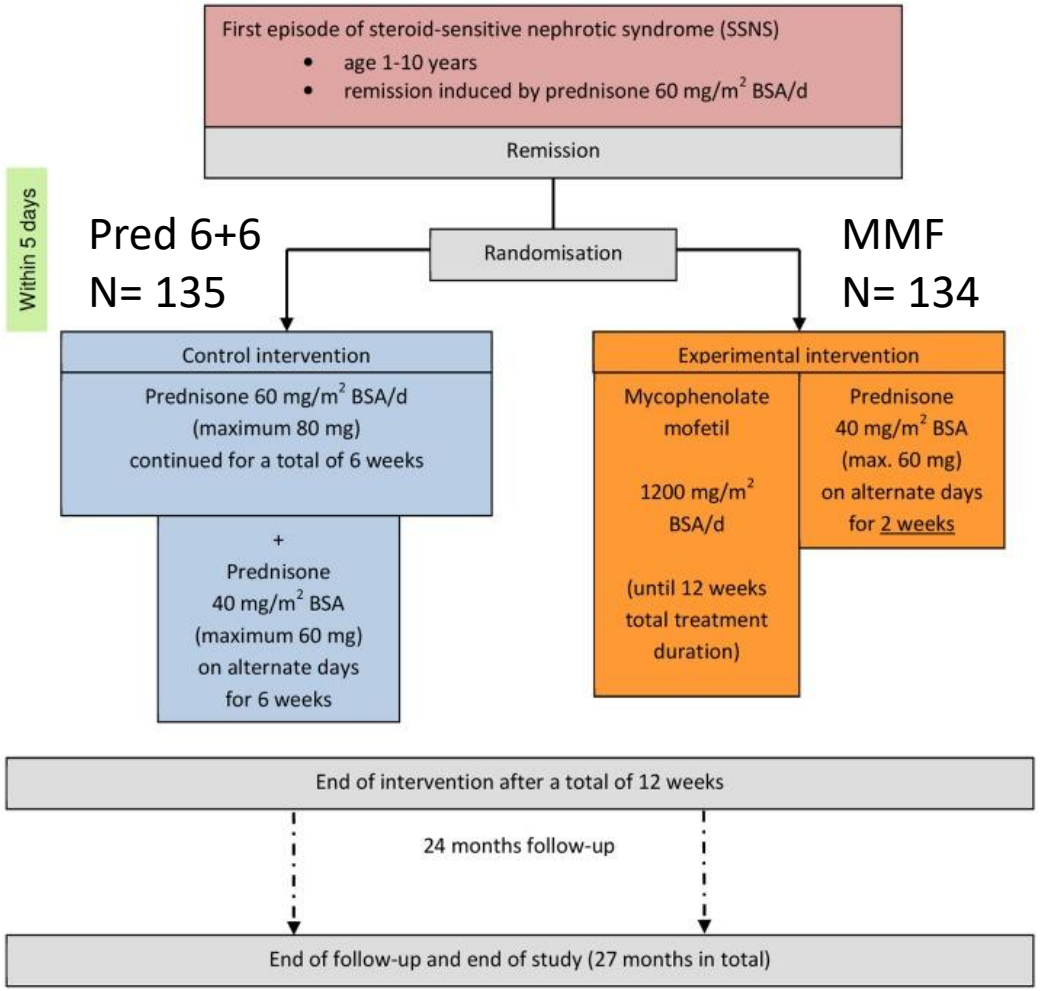



**Is there a role for combination therapy after steroid-induced remission?**

50% frequent relapses

Hoyer et al. KI 2015
Webb et al. BMJ 2019

# MMF (Phase 3, open-label, non-inferiority INTENT Trial)




**Primary outcome: Relapse**

N= 269 First NS
Median Age 4 years
MMF not inferior to prednisolone
(79.1% vs 74.8%);
Difference 4.3%, 95% CI -4.2 to 12.7%
FRNS rates similar between two groups

Less steroid S/E with MMF group
More infections and GI disorder

Preprint:
http://dx.doi.org/10.2139/ssrn.5306078

# Levamisole

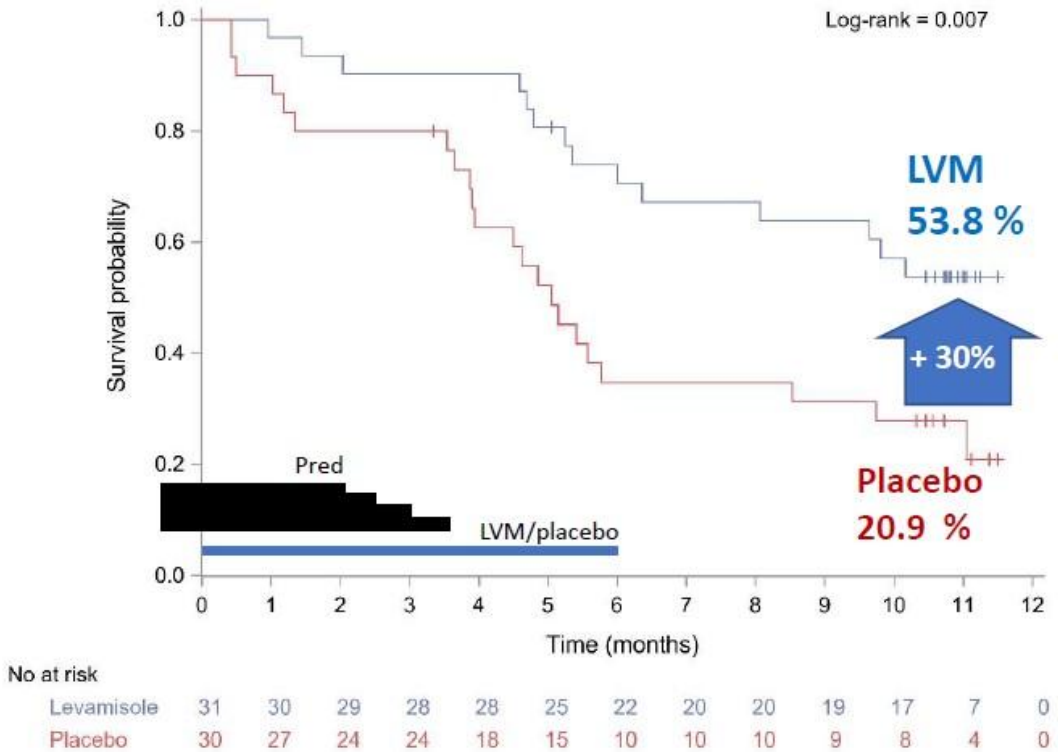
## LEVAMISOLE, NEPHROVIR-3 study

- A placebo-controlled, double-blind, superiority, randomized (1:1) trial

✓ *Primary Objective* : Assess the efficacy of **levamisole**, given at the posology of **2.5 mg/kg/48h, during 6 months**, in addition to a **18 weeks-steroid** therapy in children at first flare of steroid sensitive nephrotic syndrome.

✓ *Primary Endpoint* : Relapse-free survival at M12

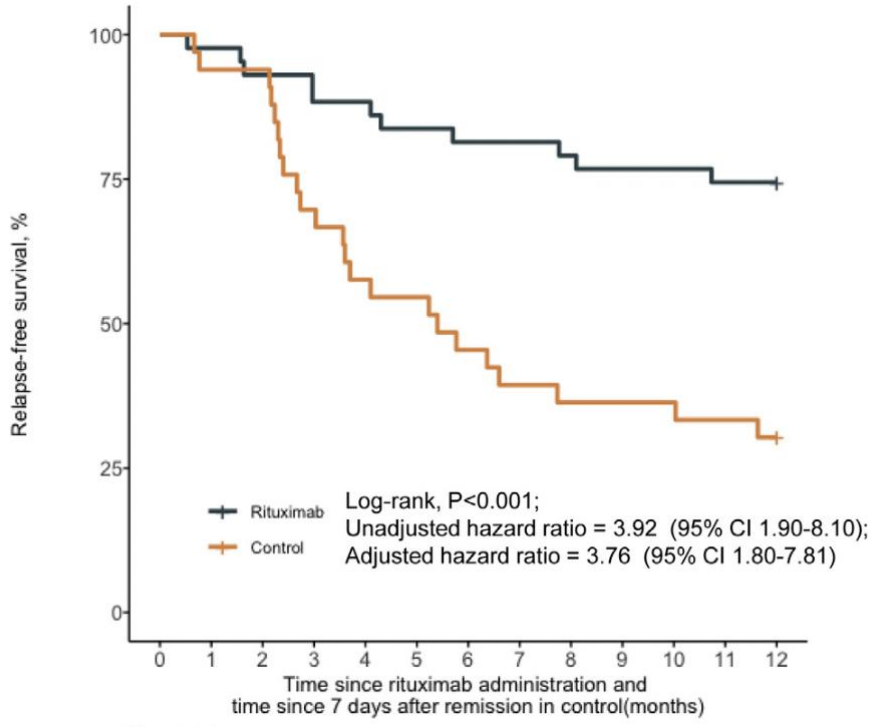
- 38 centers (NEPHROVIR network / Paris area)
- 2-16 yrs
- N= 86 inclusions
- N= 63 randomisations (SS after 4 wks of oral pred)




N° EUDRACT 2016-002324-92, NCT02818738

Courtesy of Claire Dossier

# Rituximab - Moving more upfront?




**Complete protocol:**
- IV rituximab × 4
- 1-week intervals

**N=17**

Complete remission in **12** cases **(70%)**
- 11 maintained
- 1 relapsed after 85 weeks

Partial remission or no response in **5** cases

**Add rituximab therapy after steroid-induced remission**

**Anti-CD20 monotherapy as induction for new-onset NS**

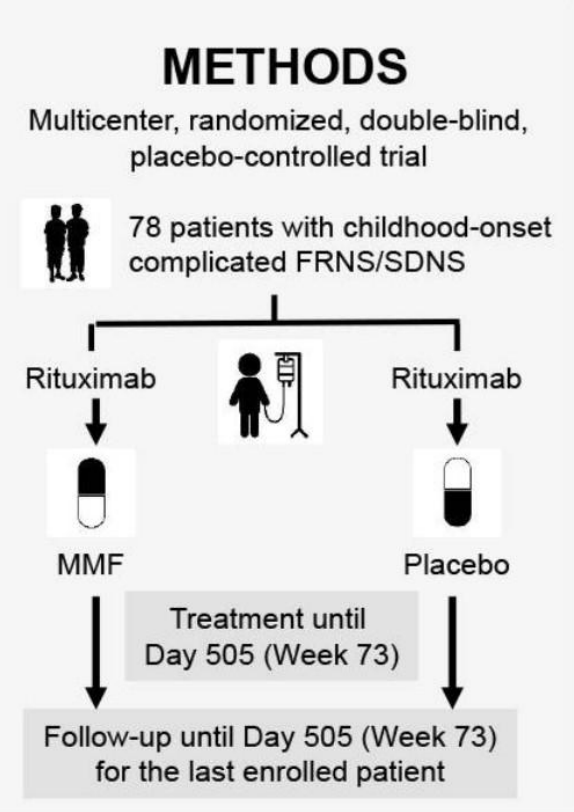
Liu et al. KI Report 2024; Zhang et al. CKJ 2024

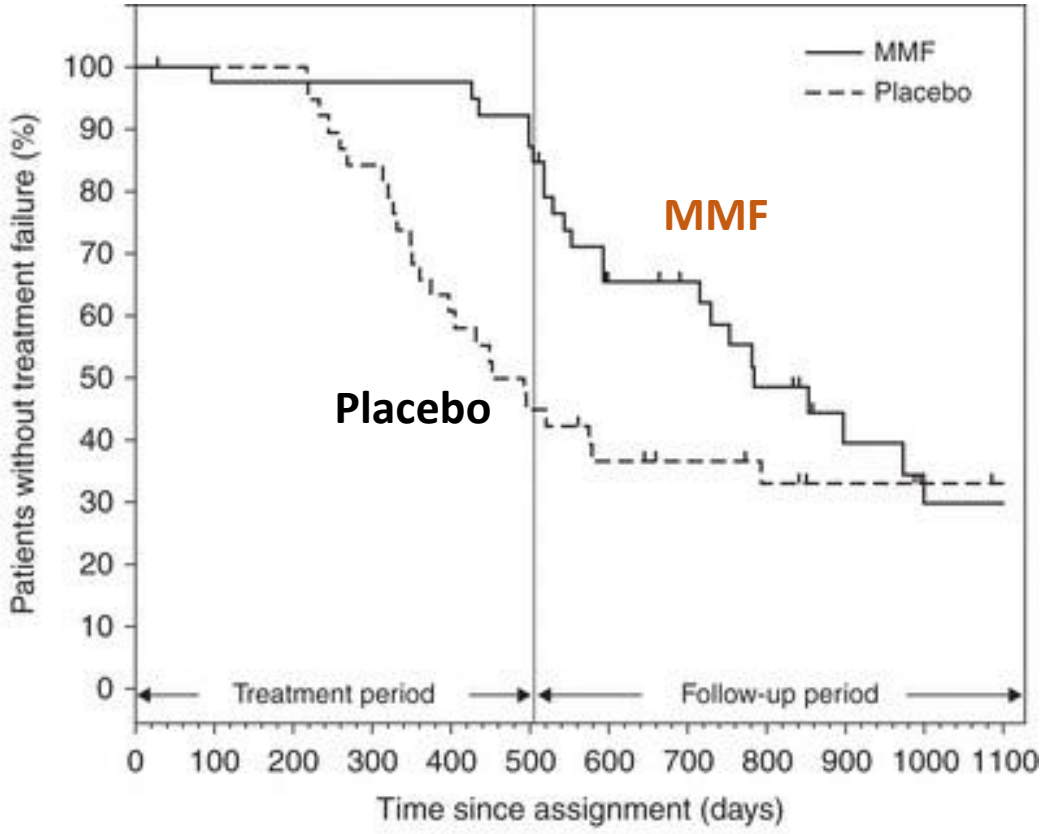
# *Anti-CD20 therapy in FRSDNS*

# MMF reduces relapse but effect wean after discontinuation

**Mycophenolate Mofetil after Rituximab for Childhood-Onset Complicated Frequently-Relapsing or Steroid-Dependent Nephrotic Syndrome**

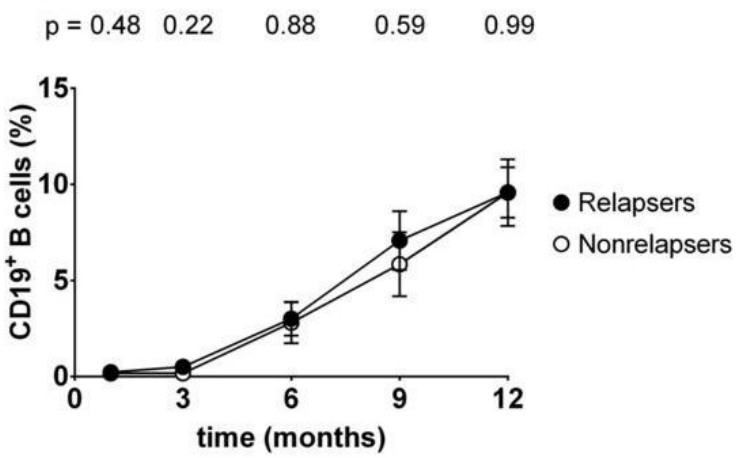
JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

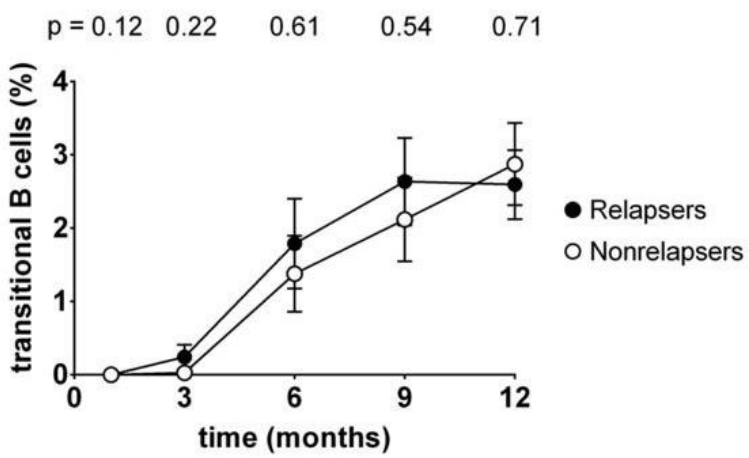


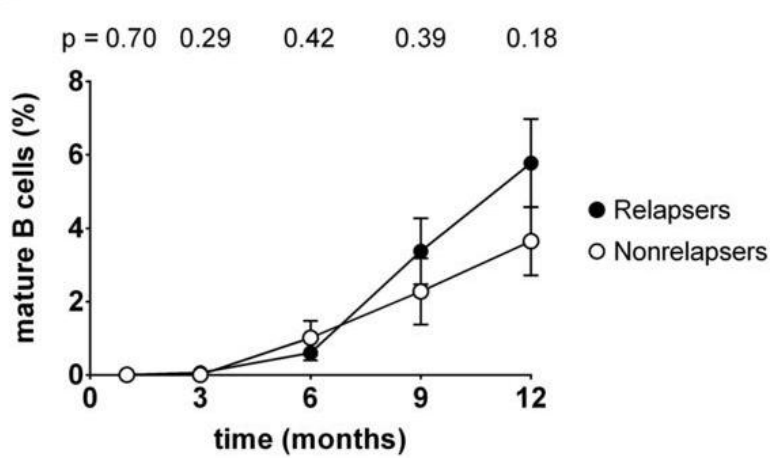




Iljima et al. JASN 2022

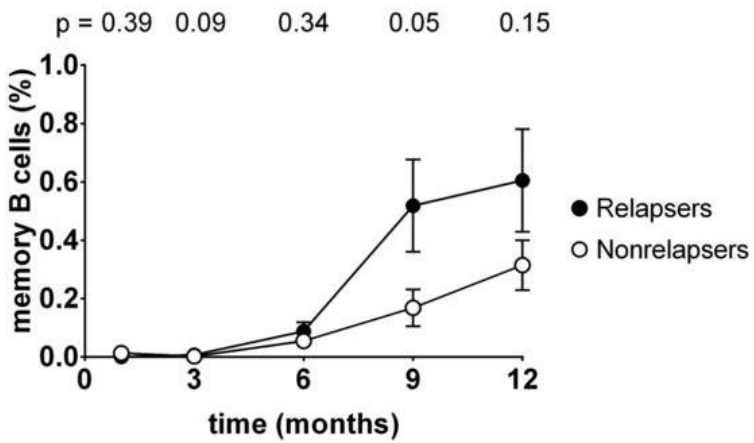
# Memory B cells as a promising biomarker

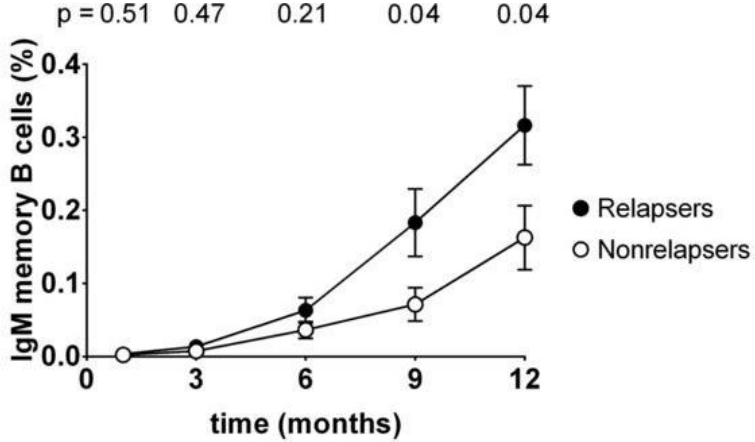


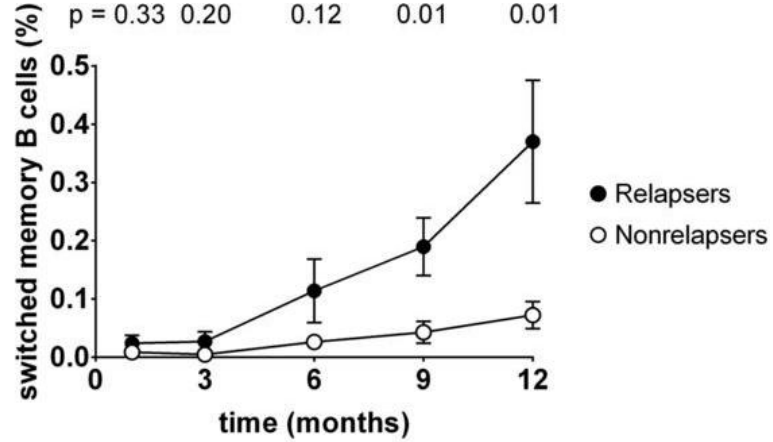




**Total**, transitional and mature B cells: No difference between relapser and non relapser




**Memory B cells & subsets reconstitution are associated with NS relapse**

Vivarelli et al. JASN 2016

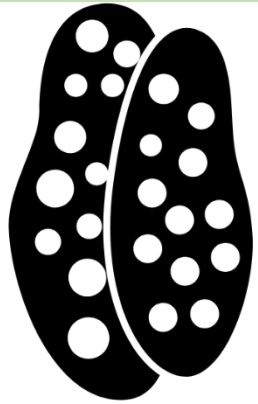
# Long-term safety profiles (346 children, 1149 infusions)

Infectio

1%

**Similar incidence with increasing courses and cumulative dose of RTX**

Neutropenia, 4%



Neoplasia, n=1/1149

Chan et al. JASN 2022

# Sequential rituximab therapy sustains remission of nephrotic syndrome but carries high risk of adverse effects

## Background

Rituximab induced remission of nephrotic syndrome lasts 6–18 months; repeat therapy is often required. Significant adverse events have been reported following multiple rituximab doses.

## Methods

**Nephrotic syndrome**
- 72% boys
- Median age 10yrs
- Steroid dependence (SSNS) n = 127
- Steroid resistance (SRNS) n = 123

+++

**Therapy**
≥ 2 sequential courses of IV rituximab

**Screened for adverse events (AE)**

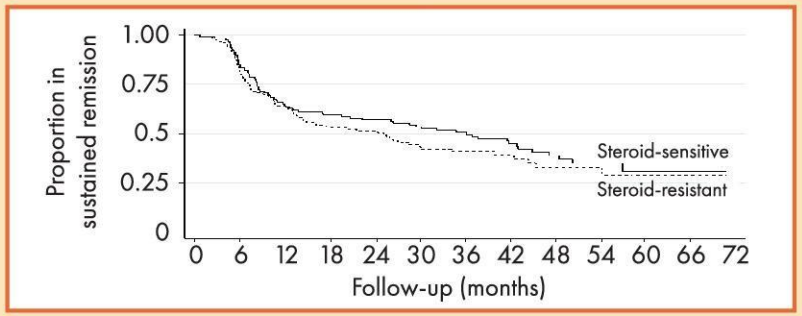
## Results

### Efficacy

**Relapses**
2.0 (95% CI 1.8–2.2) per person-year

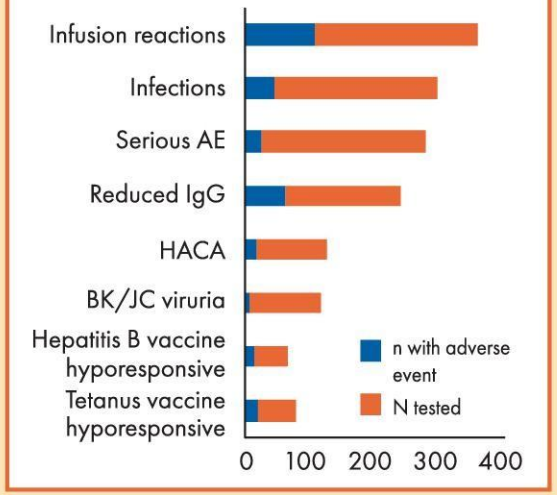
### Sustained remission

SSNS: 41%
Median time 3 yrs
SRNS: 40%
Median time 2 yrs




### Adverse events

**0.20** (95% CI 0.17–0.23) **per person-years**




## Conclusion

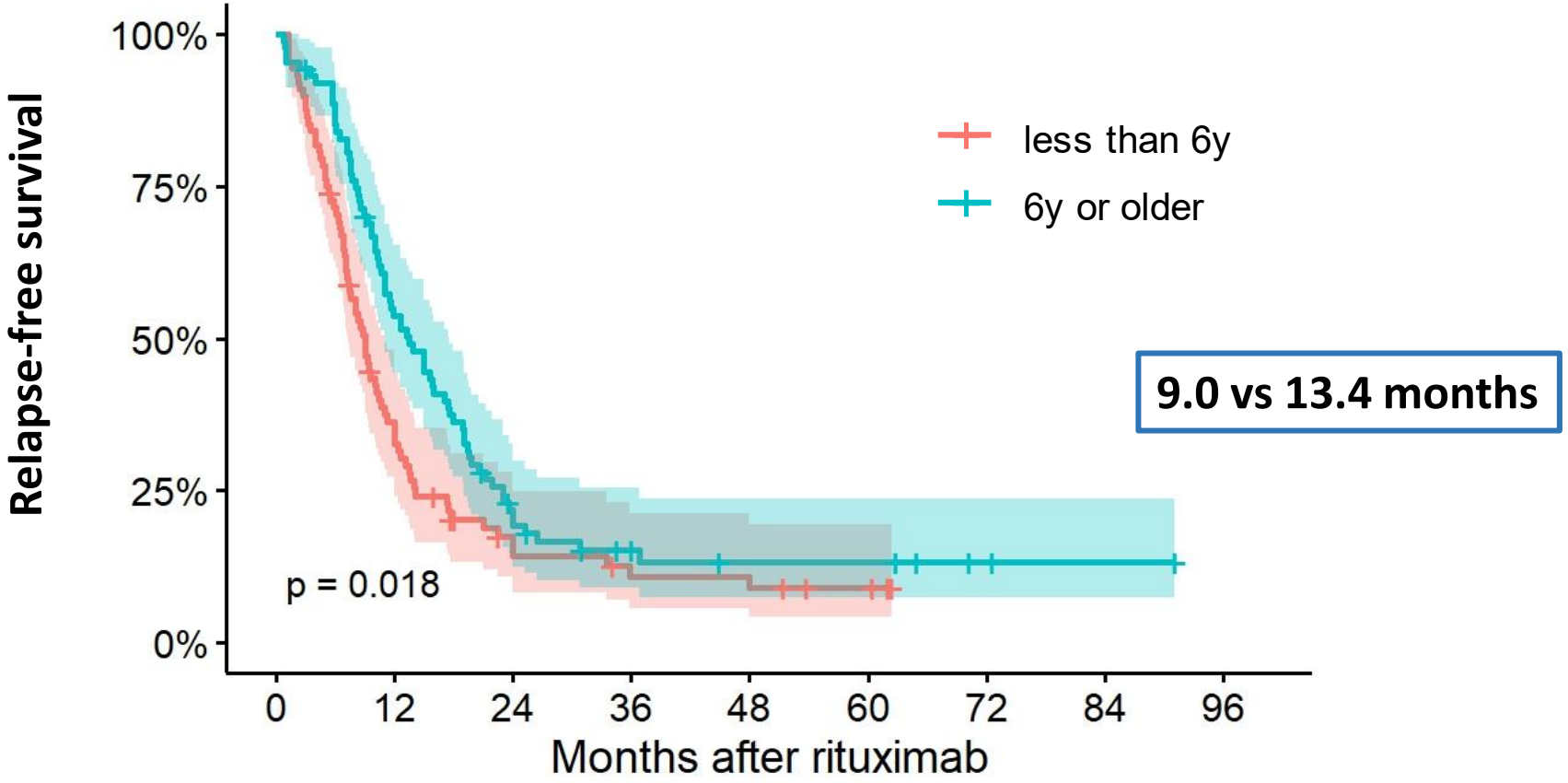
**Sequential rituximab therapy enables sustained remission in difficult-to-treat SSNS and SRNS. Therapy carries significant risk of infusion reactions, infections, development of human antichimeric antibodies and low levels of IgG.**


ERA ndt NEPHROLOGY DIALYSIS TRANSPLANTATION

Sinha, A., et al. NDT (2022)
@NDTSocial

# Matched 88 young children (<6 years) with older children (>6 years) at first RTX:

Shorter relapse-free survival in young children



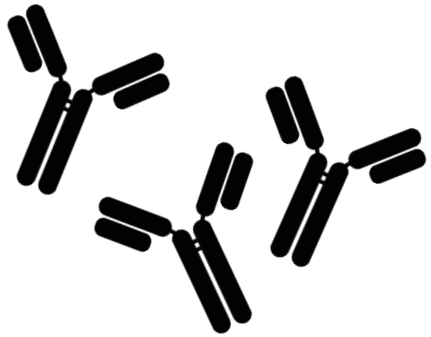

**9.0 vs 13.4 months**

BEGINS
B cell therapy Exploration Group for Idiopathic Nephrotic Syndrome

Under review

# Safety profiles (younger vs older children)

**Severe infusion reaction – minimal**



**Hypo IgG, 53% vs 39%**

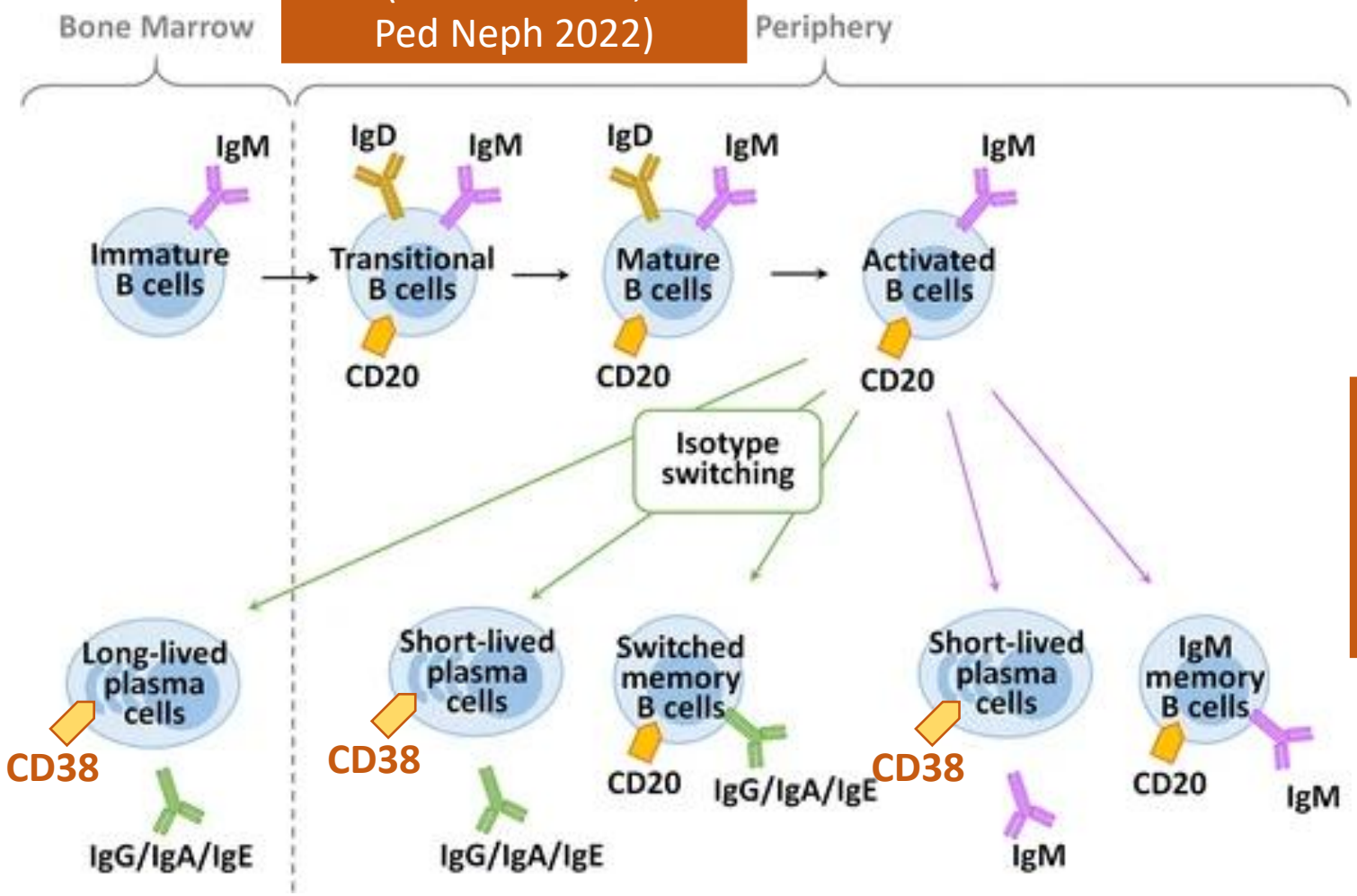
**Agranulocytosis, 6% vs 1.2%**

**Infection, 7% vs 3%**

**Under review**

# New therapeutic targets/ approaches on B cell

B-cell Activating Factor (BAFF) - Belimumab (Vivarelli et al., Ped Neph 2022)




CD20 -ve short and long lived plasma cells (CD38+)

Add-on daratumumab (Dossier, Pediatr Nephrol 2021; Angeletti et al., KIR 2024)

B-cells in tissue (e.g. lymph nodes) - Obinutuzumab (Dossier et al., CJASN 2024)

CJASN
Clinical Journal of the American Society of Nephrology


ORIGINAL ARTICLE: GLOMERULAR AND TUBULOINTERSTITIAL DISEASES

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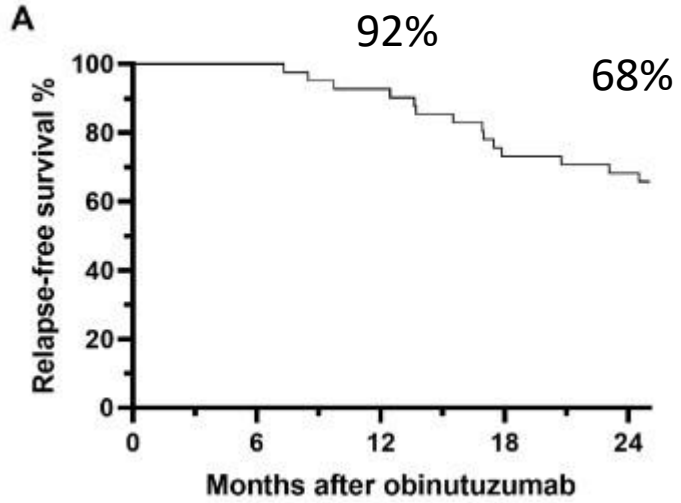
Cite

# Obinutuzumab in Frequently Relapsing and Steroid-Dependent Nephrotic Syndrome in Children

Dossier, Claire[1]; Bonneric, Stéphanie[1]; Baudouin, Veronique[1]; Kwon, Theresa[1]; Prim, Benjamin[1]; Cambier, Alexandra[1]; Couderc, Anne[1]; Moreau, Christelle[2]; Deschenes, Georges[1]; Hogan, Julien[1,3,a]

- Single centre, n=41
- Resistance or relapse after ritux
- 1 single infusion of Obi 300mg/1.73m$^2$
- Cessation of IS within 2 months

- B cell depletion 8.3m, longer than ritux
- Infusion reaction 12%, neutropenia 21%
- HypoIgM (83%)

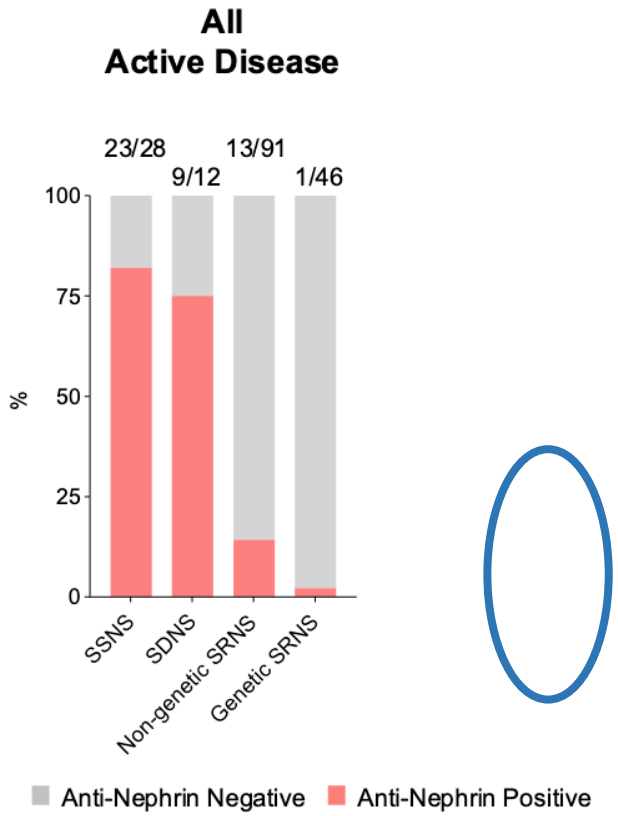



Dossier et al. CJASN 2023

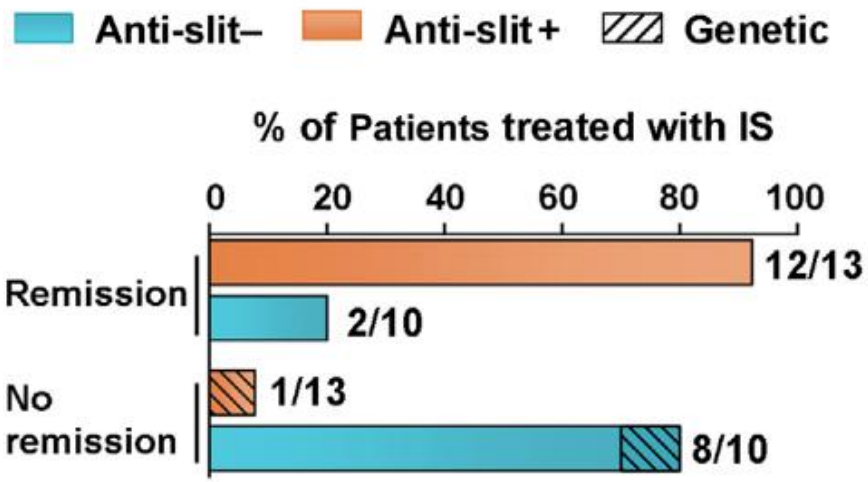
# *Immune-mediated SRNS*

# Anti-nephrin/ slit Ab uncommon in SRNS but indicate immune dysregulation and predict response to IS

Non-genetic SRNS (n=103)
- IIS-responsive (n=86)
- MDR-SRNS (n=17)




## SRNS, n=45




**Higher response to IS: 93% vs 20%**

Hengel et al., KI 2025; Riaglianti et al. KI 2024

# Rituximab enhances remission in CNI-resistant SRNS

***Rituximab therapy in childhood steroid-resistant nephrotic syndrome (SRNS): an international, multi-centre study***

kidney INTERNATIONAL

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

***Methods and cohort***

Retrospective cohort study

28 paediatric nephrology centres in 19 countries

246 children with SRNS
Age 6.9±4.2; 55% boys

FSGS 57%; MCD 33%

Follow-up 32.4 months

***Intervention***

CNIs treatment before rituximab

**≥ 6 months (CNI-resistant)**

***N=146***

**< 6 months**

***N=100***

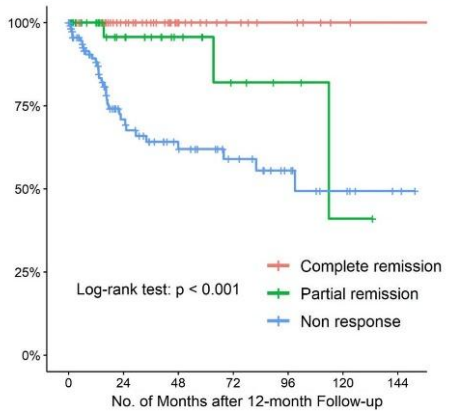
**Rituximab**
**750mg/m2 (46.3%)**
**1500mg/m2 (40.7%)**

***Findings***

Complete/ partial remission

| | 3m | 6m | 12m |
|---|---|---|---|
| ≥ 6 months (CNI-resistant) | 26% | 36% | 35% |
| < 6 months | 42% | 52% | 55% |

***Worse kidney survival with non-response at 12-months***



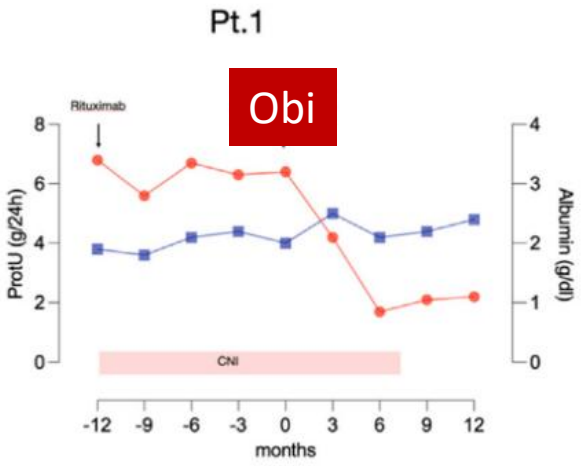

**Adverse events (35%)** | **Hypo-IgG (12.6%)** | **Infusion reaction (11.8%)** | **Infection (5.7%)** | **Neutropenia (1.6%)**

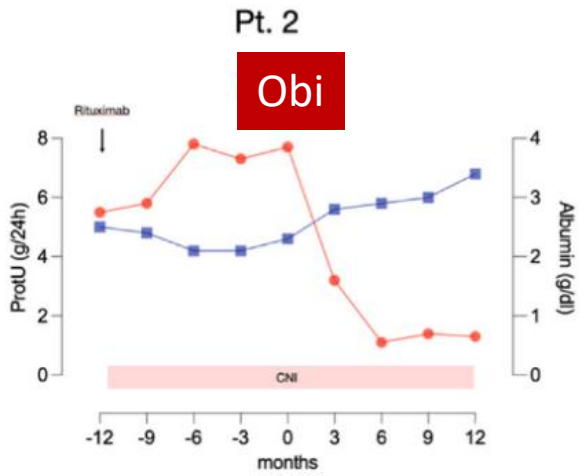
***Chan et al. 2024***

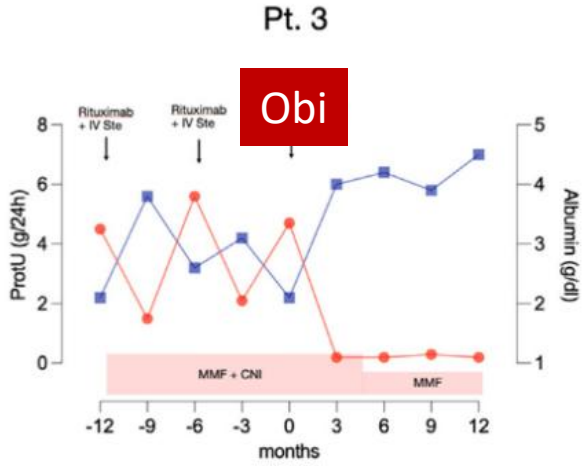
**CONCLUSION** *Rituximab enhances remission in a subset of children with SRNS, and is generally safe. Complete remission following rituximab is associated with favourable kidney outcome.*

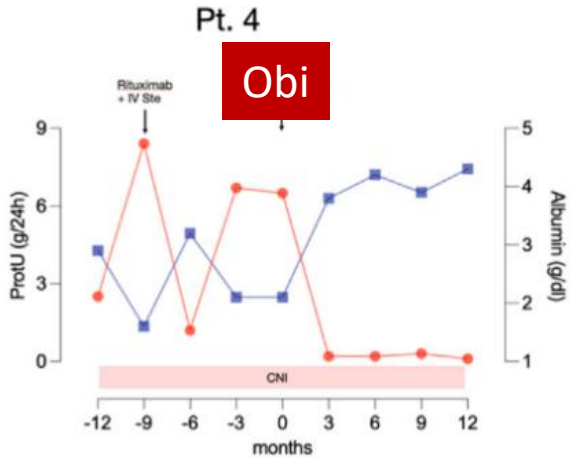
**Chan et al. KI 2024**

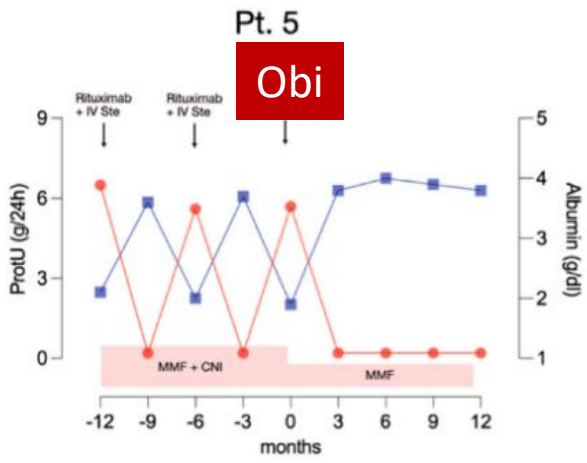
# Obinutuzumab in SRNS

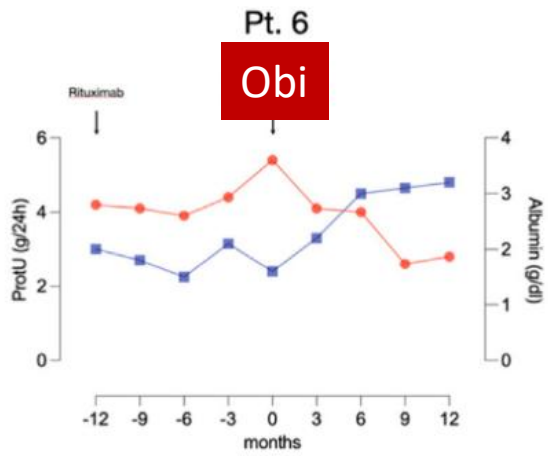


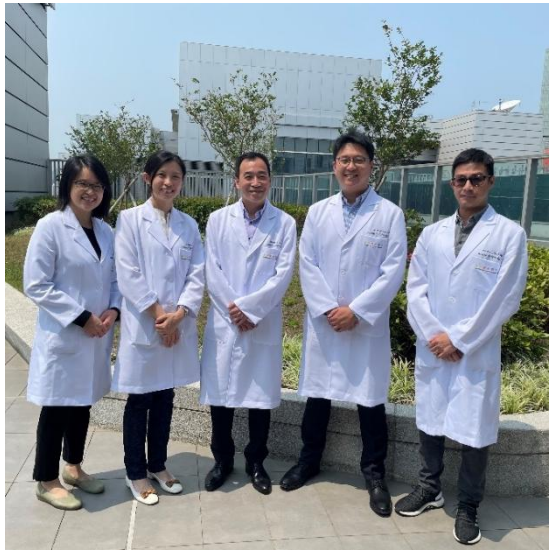




**Obi, N=6**
**RTX & CNI R MRNS**
CR 3/6, PR 3/6

Angeletti et al. KI Report 2024 & 2025

# Summary

- Rapidly evolving therapeutic landscape - precision and personalised medicine
- Combination therapy in high risk patients at disease onset
- Using anti-CD20 as second or third line IS in FRSDNS and SRNS
- B cell depletion (? and deeper) in selected patients
- ? Prognostic value of anti-nephrin antibodies

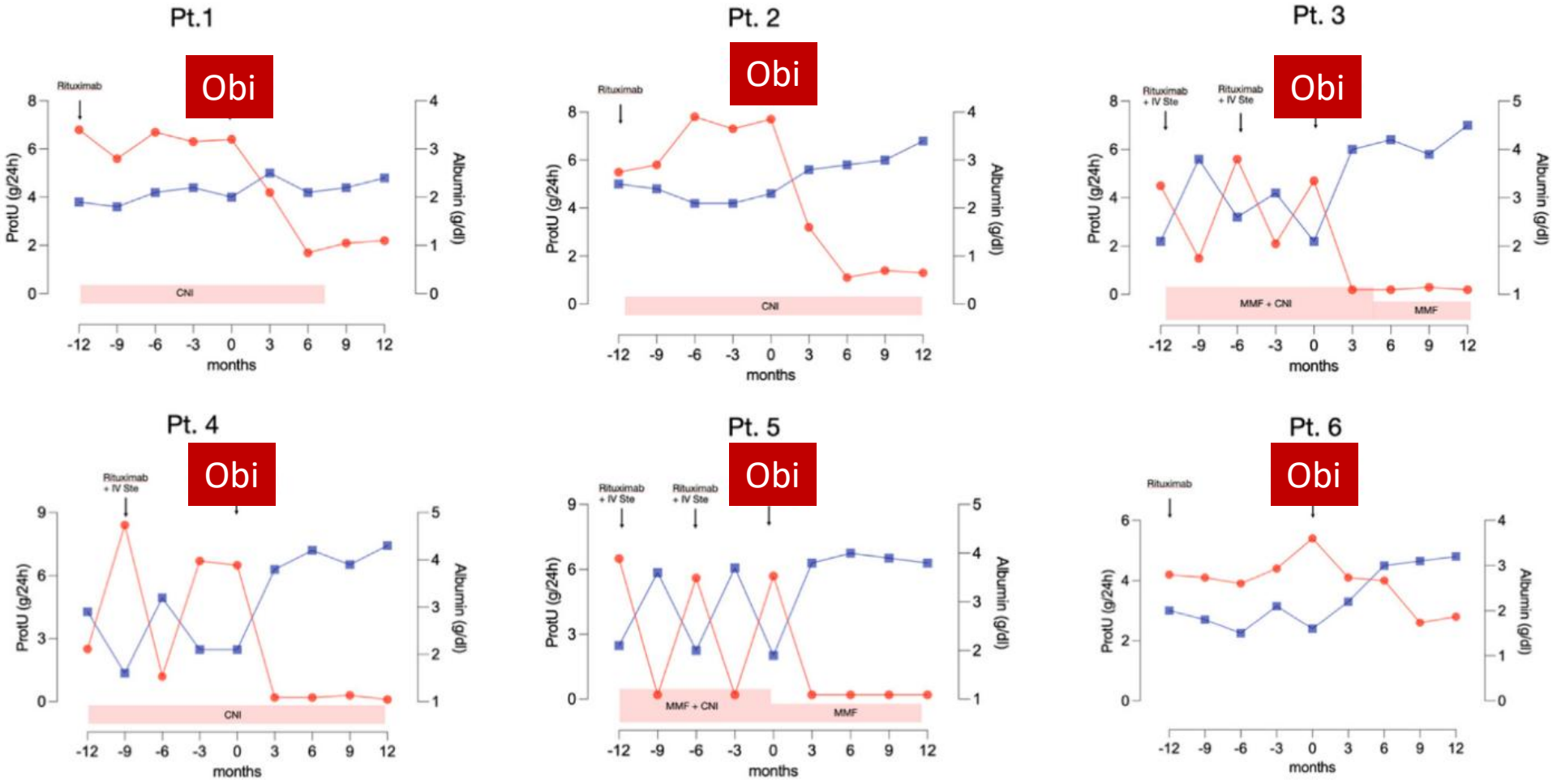

# *多謝哂！Many thanks!*

*Email: Eugene.chan@cuhk.edu.hk*

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

腎兒知癒實驗室
KIDS'CURE LAB

# Obinutuzumab in SRNS

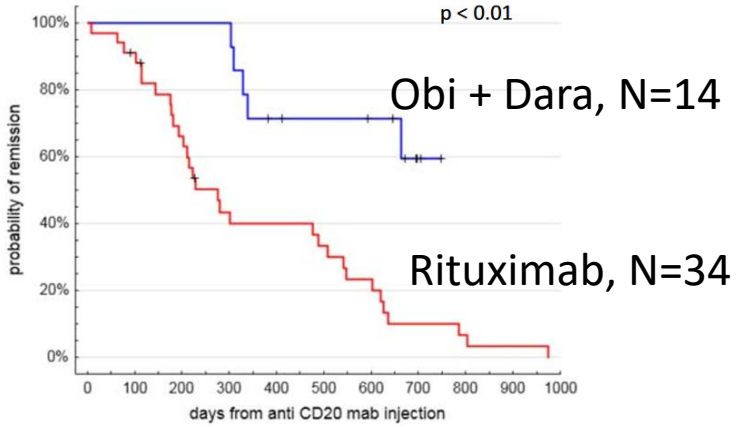



**Obi, N=6**
**RTX & CNI R MRNS**
CR 3/7, PR 3/7

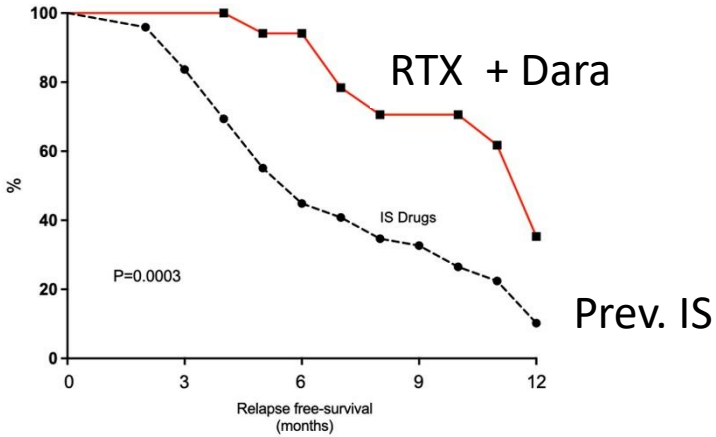
Angeletti et al. KI Report 2024 & 2025

# Anti-CD38 Daratumumab w/ anti-CD20

- Dossier et al. N=14, refractory to rituximab
  - Obi + Daratumumab
  - ? Obi effect
  - Mild Infusion reaction, neutropenia
  - Low IgG 12/14, Low IgA 8/14 and IgM 14/14

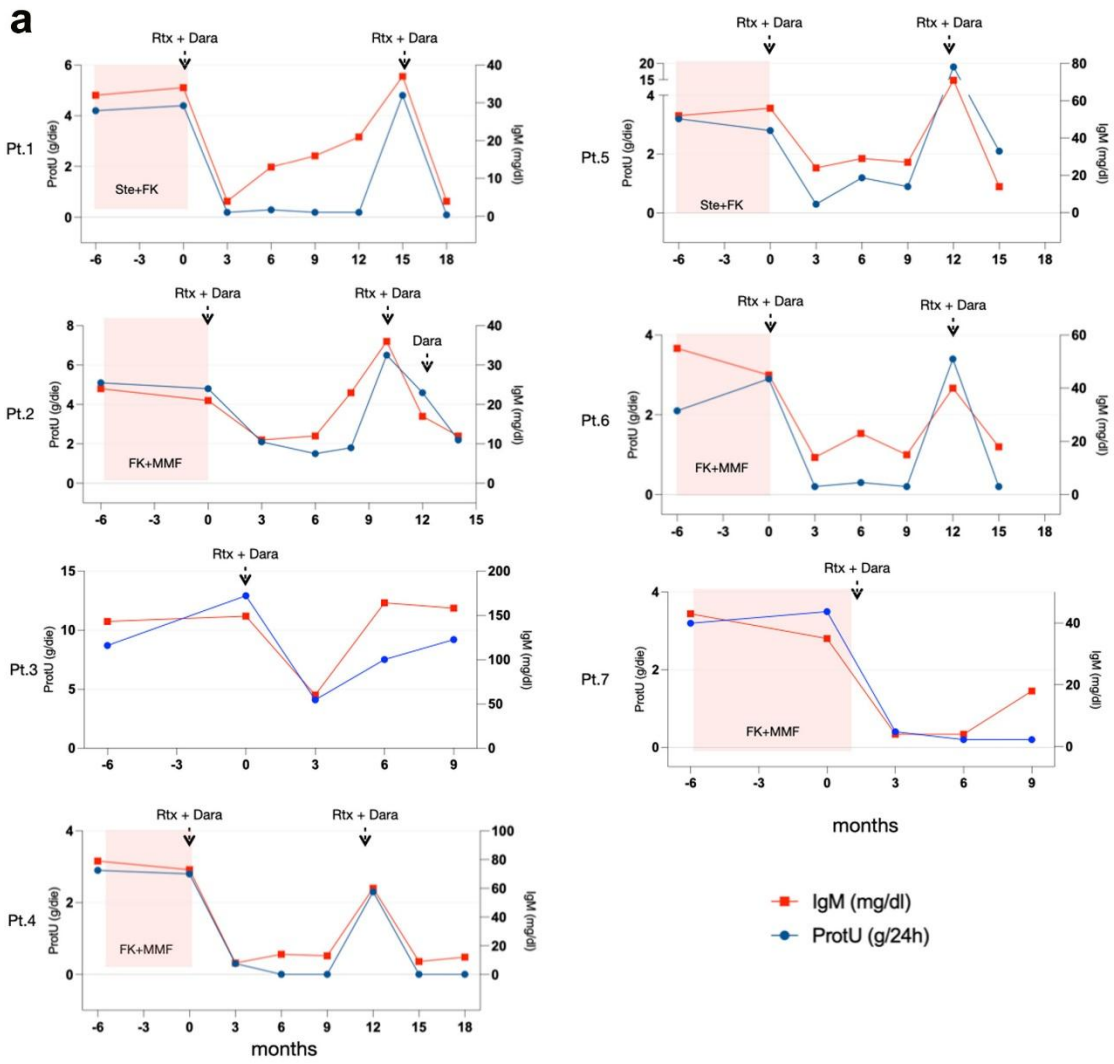



- Angeletti et al. MDNS, n=16
  - IS drugs Prev. Ritux, N=12 (75%)
  - RTX + Dara, tail IS




Dossier et al. Pediatr Nephrol 2021; Angeletti et al. KI Report 2024

# RTX + Dara in SRNS




**RTX + Dara, N=7 MRNS**
CR 4/7, PR 2/7

Angeletti et al. KI Report 2024 & 2025