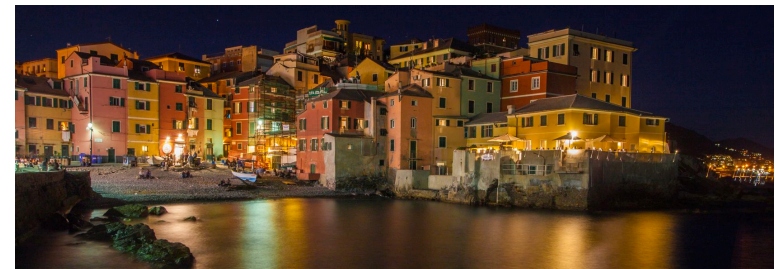
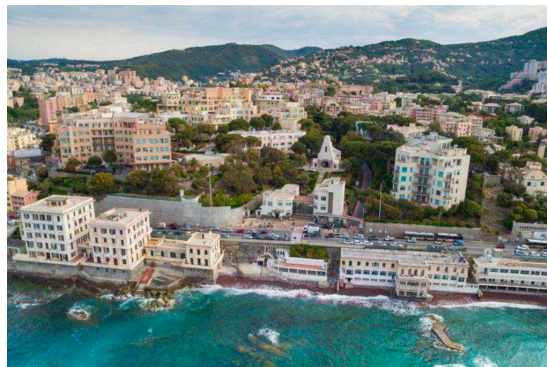


# Monoclonal Antibodies in Nephrotic Syndrome

Gian Marco Ghiggeri

Andrea Angeletti

*Istituto Giannina Gaslini, Genova*



# Monoclonal Antibodies (-MAB)

**Mono - clonal Antibody**



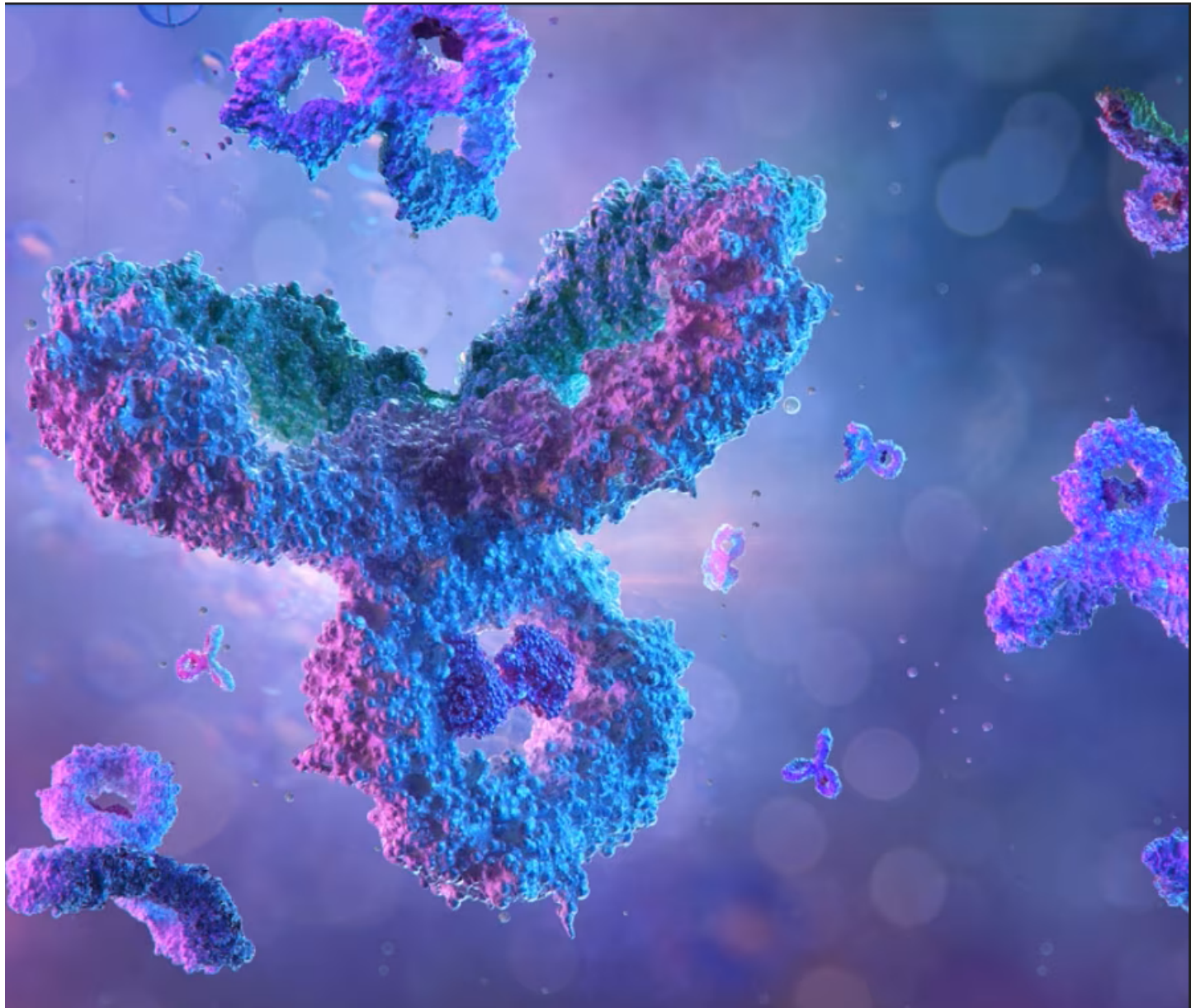
**SINGLE  
Or  
ONE**



**IDENTICAL/SAME  
GROUP OF CELLS  
DERIVED FROM SINGLE  
PARENT CELLS**

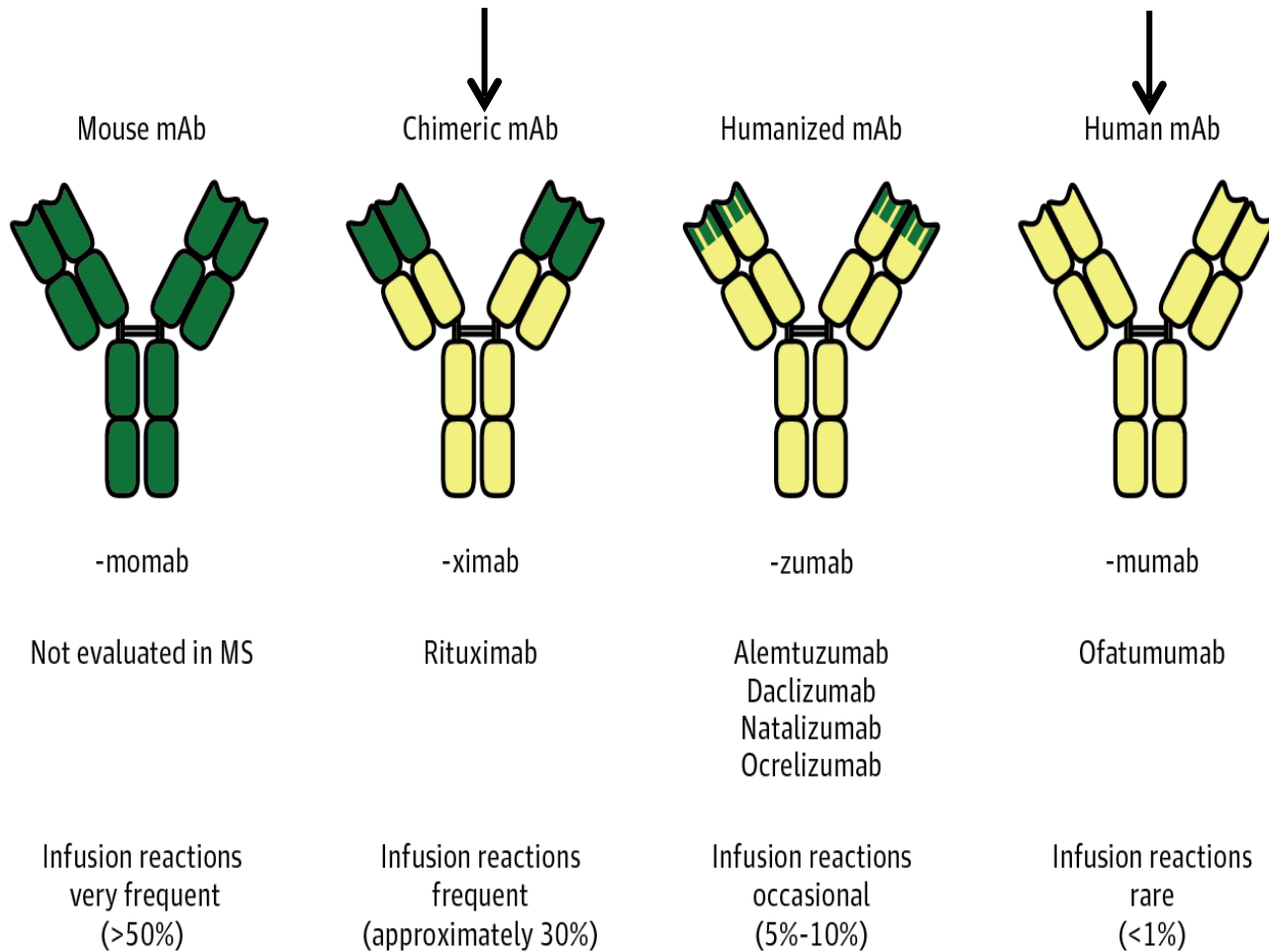
**ANTIBODY PRODUCED BY  
ONE  
TYPE OF IMMUNE CELLS**

- ANTIBODY BINDS TO SINGLE SPECIFIC ANTIGENS (TARGET)
- HIGHLY SPECIFIC
- UNIFORM
- LARGE QUANTITIES



(Chinese hamster ovary)

(murine myeloma)



Alta

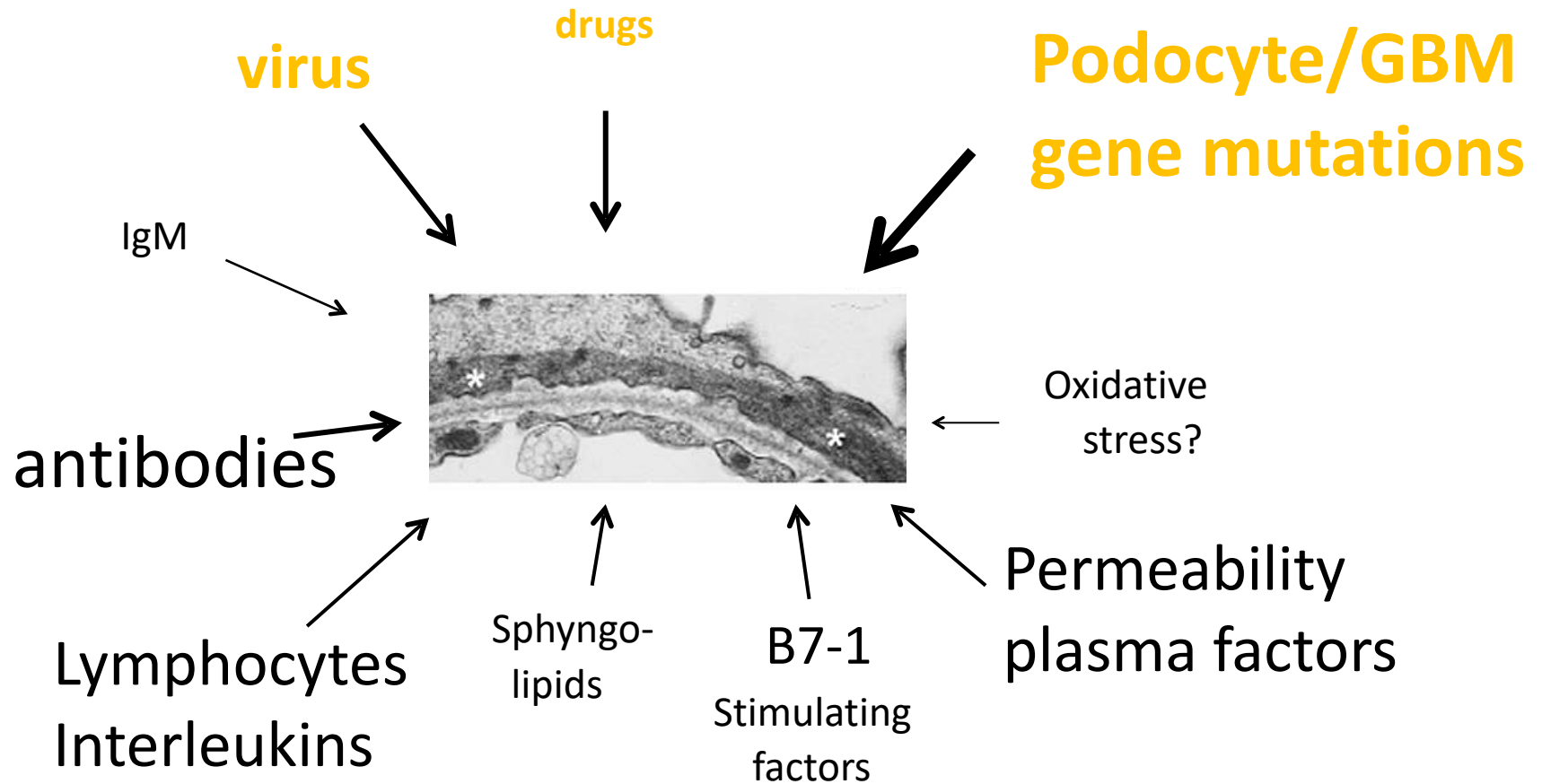
IMMUNOGENICITÀ

Bassa

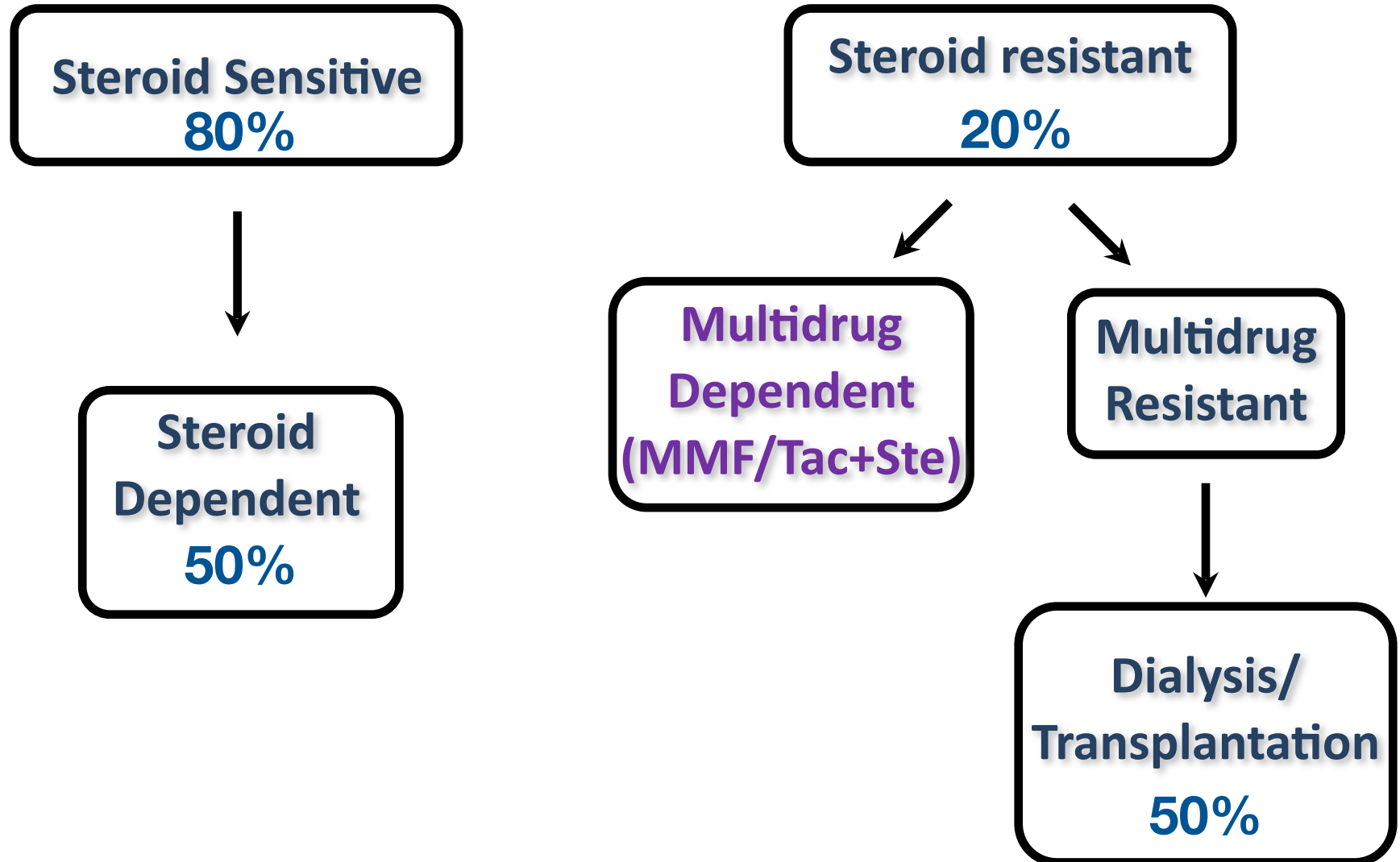


**Primary  
NS**

**Secondary  
NS**



# Nephrotic Syndrome: Definition

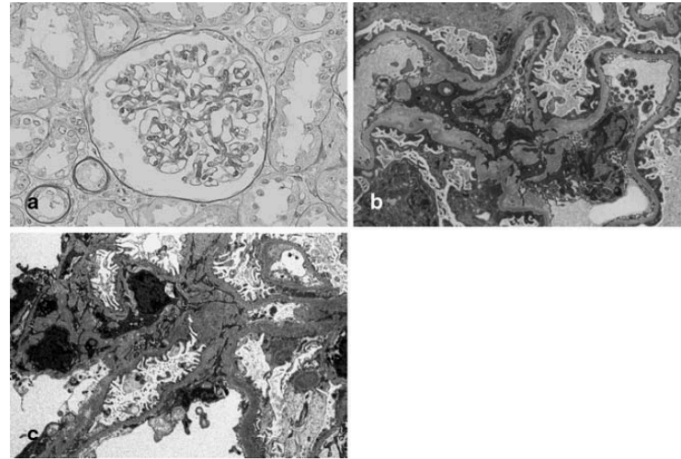


# Historical use of Anti-CD20

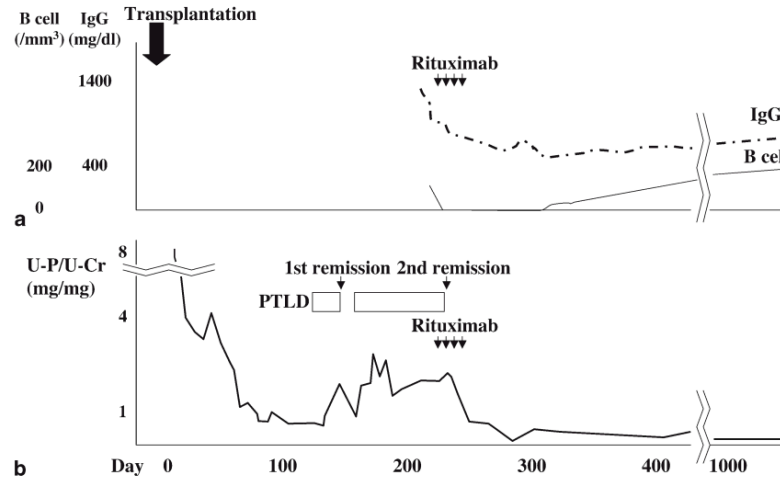
- Introduced in the late '90s to treat NH lymphoma
- Used to treat autoimmune disease with predominant humoral component / pathogenetic auto-ab
- *Found to reduce proteinuria in children with nephrotic syndrome secondary to PTLN (Nozu, Pediatric Nephrol 2005; Pescovitz, NEJM 2006)*

# Historical use of Anti-CD20

**Fig. 1** Renal biopsy 2 months after transplantation (a, b) and 3 years after transplantation (c). **a** PAS staining shows minor glomerular abnormalities. **b** Electron microscopy indicates 60% foot process fusion. **c** No foot process fusion is detectable



**Fig. 2** Clinical course in terms of peripheral B cell counts, serum IgG levels, and ratio of urinary protein to urinary creatinine (U-P/U-Cr). **a** Peripheral B cells disappeared immediately after the rituximab treatment, while serum IgG levels decreased gradually. **b** Urinary protein decreased immediately after the rituximab administration





# Nephrotic Syndrome: Most Relevant RCTs for RITUXIMAB

**Table 1**

**Major published clinical studies testing biologics in pediatric MCD and FSGS**

Reference	Disease	N	F/U (mo) <sup>a</sup>	Study design	Dose	CR (%)	Comments
Rituximab Ravani <i>et al.</i> [40]	SDNS	30	22 (1–60)	RCT	375 mg/m <sup>2</sup> (1–4 doses) vs. no therapy	N/A	Add-on RTX did not significantly increase the rate of remission after steroid tapering
Iijima <i>et al.</i> [32]	FRNS/SDNS	48	12	RCT	375 mg/m <sup>2</sup> (4 doses) vs. placebo	81	Mean daily steroid dose after randomization was significantly lower in the RTX group than in the placebo group
Ruggenenti <i>et al.</i> [39]	SDNS	30	12	Off-on trial	375 mg/m <sup>2</sup> (1–2 doses)	100	Patients were in remission at treatment start. During the 24 mo after RTX administration, patients experienced fewer recurrences than in the 24 mo prior
Ravani <i>et al.</i> [42]	multidrug dependent NS	46	6	Off-on trial	375 mg/m <sup>2</sup> (1–5 doses)	48	At 18 mo, 20% of children were still in prednisone and CNI-free remission
Sinha <i>et al.</i> (2015)	multidrug dependent NS	19 5	12	Prospective cohort	375 mg/m <sup>2</sup> (2–4 doses)	38	Remission rate was 57.6% in steroid dependent, 33% in CNI-dependent and 12% in steroid + CNI-resistant patients at 12 months
Sellier-Lecler <i>et al.</i> [33]	SDNS	30	38 (25–51)	Prospective cohort	375 mg/m <sup>2</sup> (1–4 doses)	63	19 patients underwent remission without steroids. 11 patients relapsed, ten of them received RTX re-treatment
Fujinaga <i>et al.</i> [31]	SDNS	10	17 (13–21)	Prospective cohort	375 mg/m <sup>2</sup> (1 dose)	N/A	All patients had MCD
Kamei <i>et al.</i> [37]	SDNS	12	12	Prospective cohort	375 mg/m <sup>2</sup> (1 dose)	25	After steroid withdrawal, 9 patients relapsed, but 3 remained in remission without steroids for >1 year

# Nephrotic Syndrome: Most Relevant RCTs for RITUXIMAB

**TRY RESCUE 2**

Ghiggeri, cJASN 2011,  
Ghiggeri, JASN 2015

**RCRNS**

Iijima, Lancet 2014

**RITURNS**

Basu, JAMAP 2018

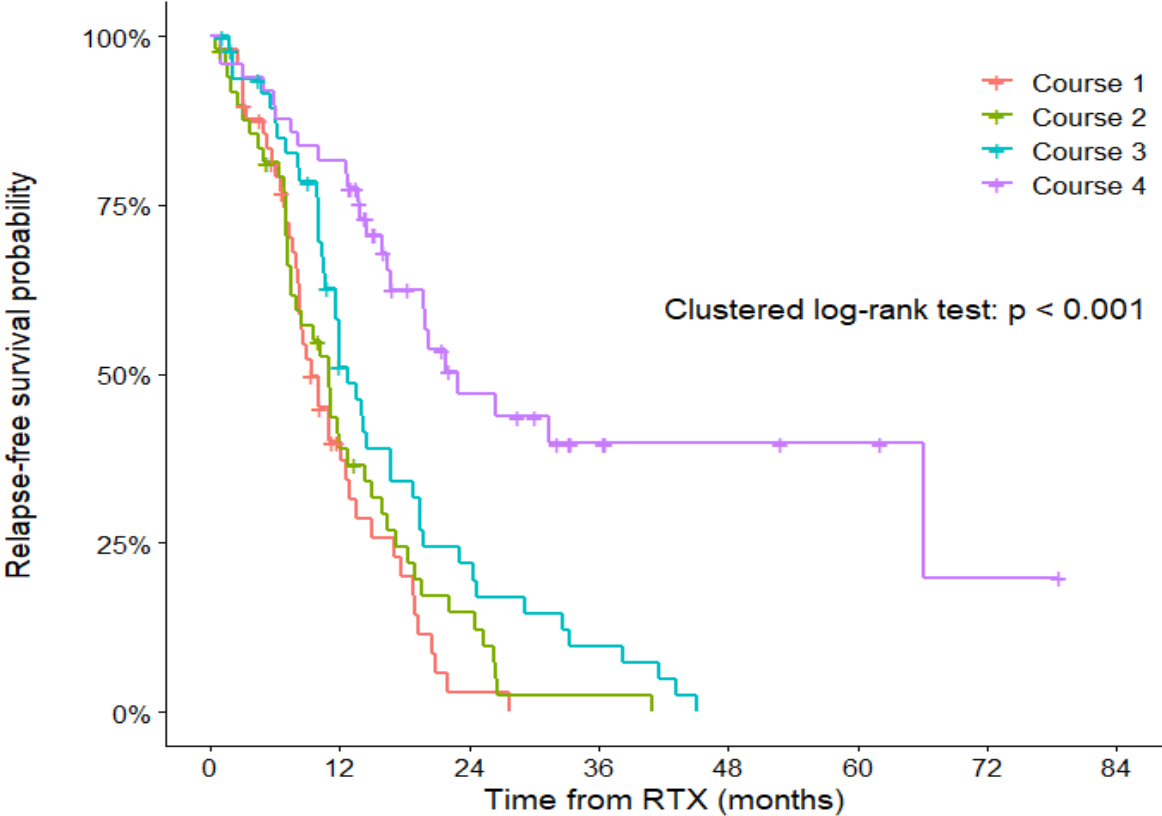
**OFA 2**

Ghiggeri, JASN 2021

**RTX 4**

Ghiggeri, end of recruitment

# Long-Term Efficacy and Safety of Repeated Rituximab to Maintain Remission in Idiopathic Childhood Nephrotic Syndrome: An International Study

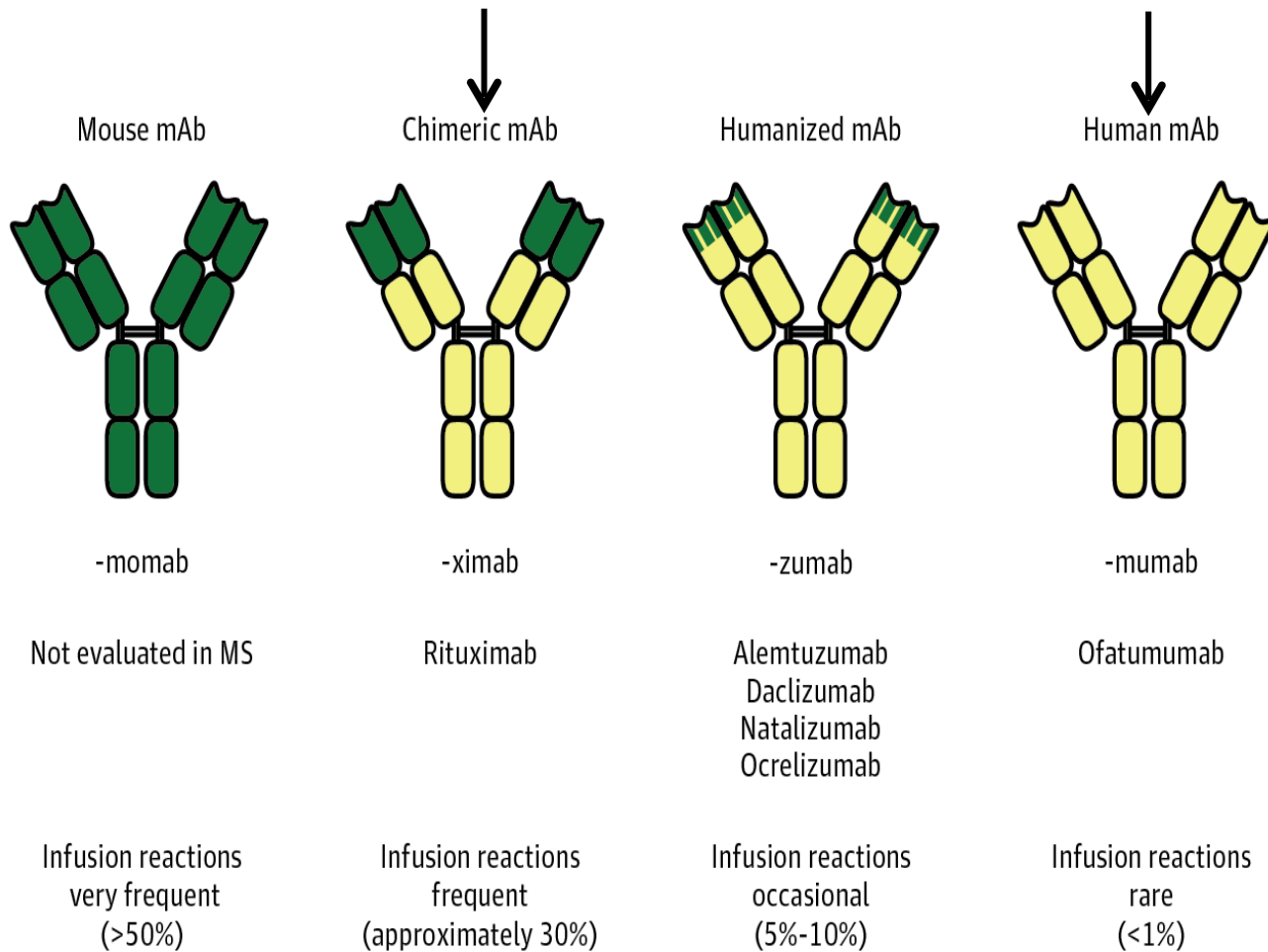


Children receiving repeated courses of rituximab for FRSDNS experience an improving clinical response. Side effects appear acceptable

Number at risk								
Course 1	49	14	1	0	0	0	0	0
Course 2	49	18	6	1	0	0	0	0
Course 3	49	24	9	4	0	0	0	0
Course 4	49	40	14	6	4	3	1	0
	0	12	24	36	48	60	72	84
Time from RTX (months)								

(Chinese hamster ovary)

(murine myeloma)



**Alta**

**IMMUNOGENICITÀ**

**Bassa**



# RTX vs. OFA

## Human or Chimeric Monoclonal Anti-CD20 Antibodies for Children with Nephrotic Syndrome: A Superiority Randomized Controlled Trial

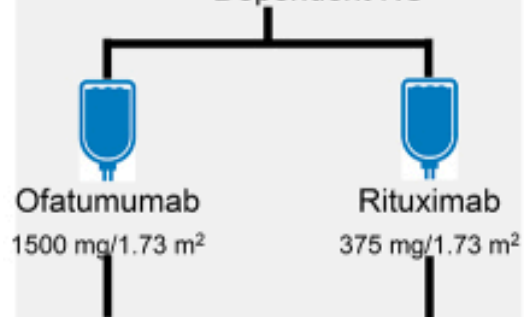
**JASN**  
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

### METHODS

Open-label, two-parallel-arm, randomized controlled trial



140 patients (2-24yrs)  
with Steroid  
Dependent NS



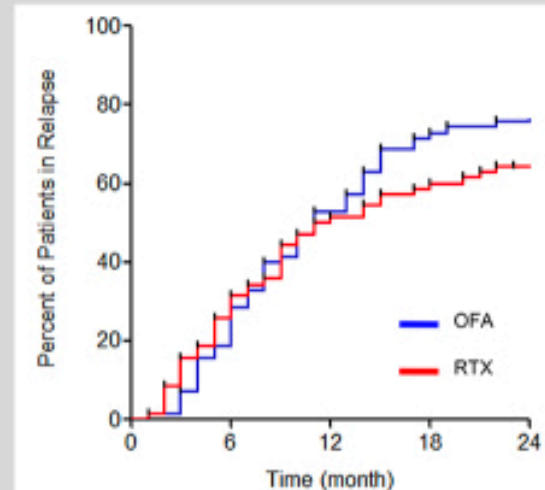
### Endpoints

Relapse at 12 and 24 months

### OUTCOME

#### Relapse

	OFA	RTX
12 months	37/70	36/70
24 months	53/70	46/70



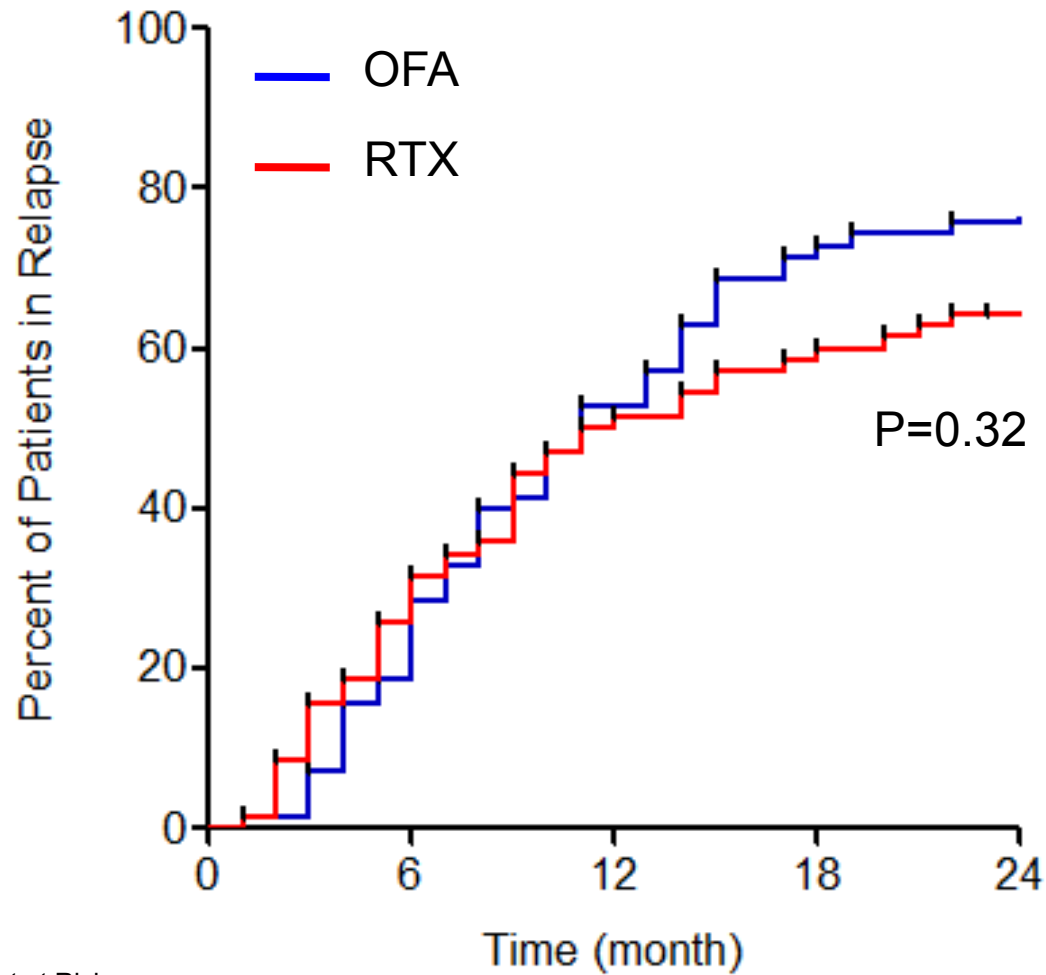
#### Safety

No relevant AEs

### Conclusion

Ofatumumab was not superior to rituximab in maintaining remission in children and young adults with steroid- and calcineurin inhibitor-dependent nephrotic syndrome.

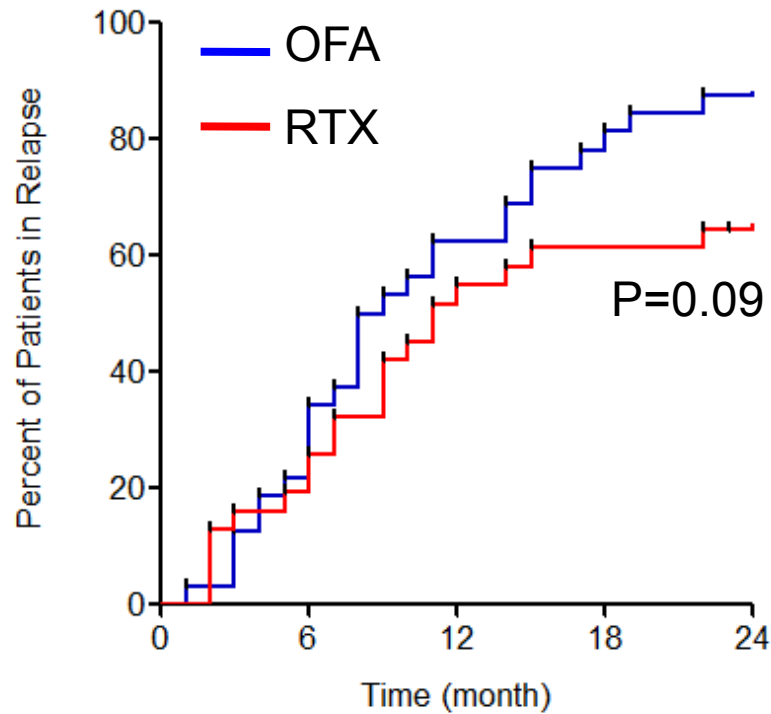
doi: 10.1681/ASN.2021040561



Subject at Risk

Months	0	6	12	18	24
OFA	70	57	33	20	17
RTX	70	52	34	29	24

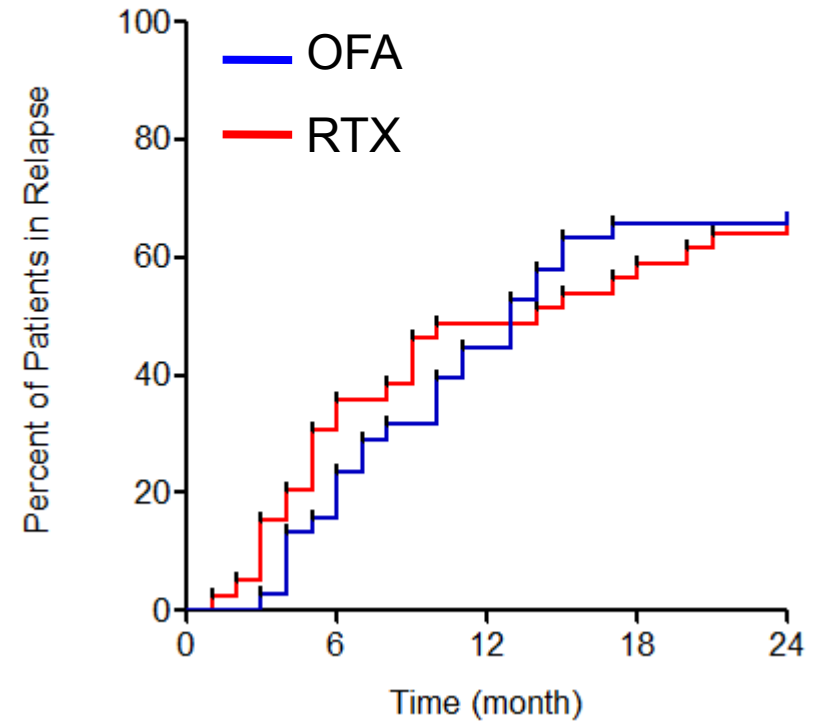
≤9 years



Subjects at Risk

Months	0	6	12	18	24
OFA ≤9 yrs	32	25	12	8	5
RTX ≤9 yrs	31	25	14	13	11

>9 years



Subjects at Risk

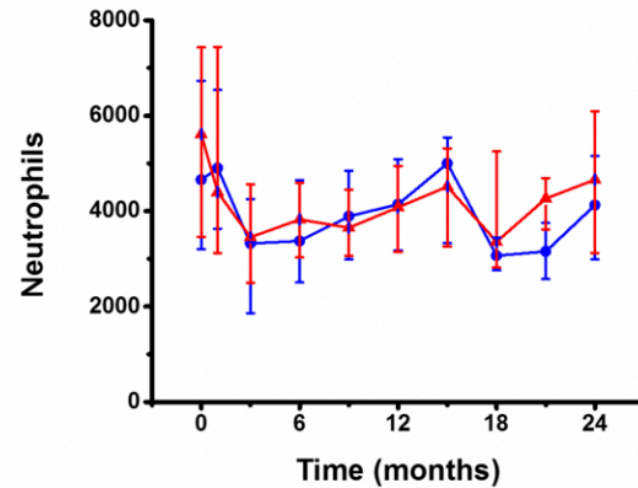
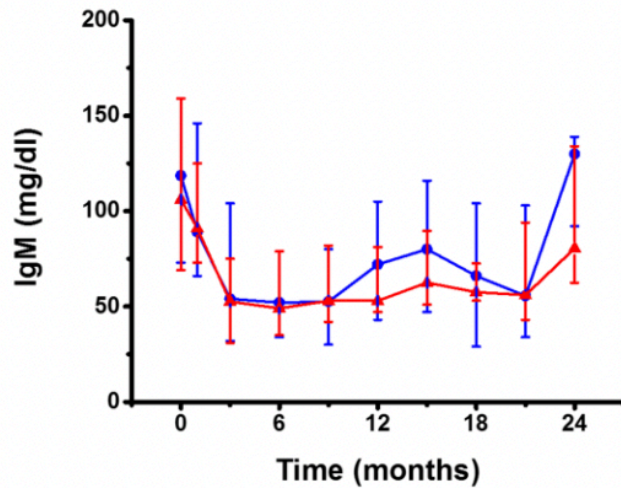
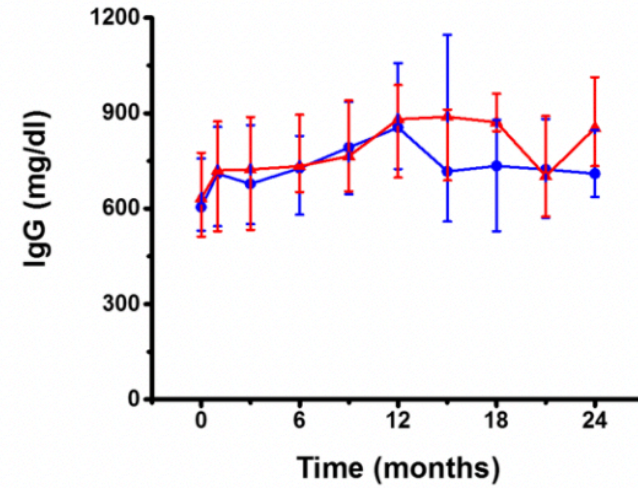
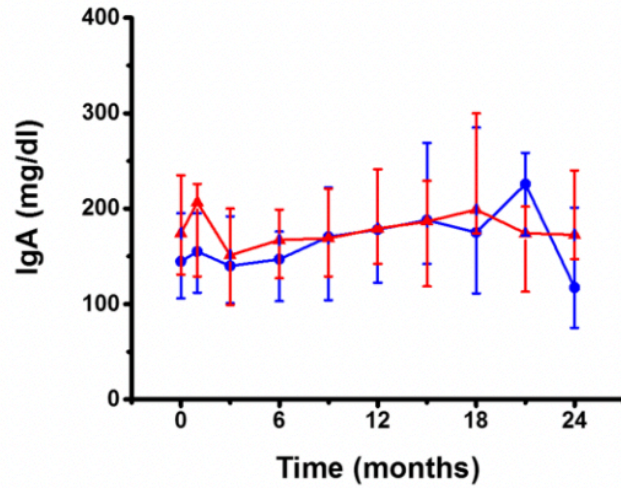
Months	0	6	12	18	24
OFA >9 yrs.	38	32	21	12	12
RTX >9 yrs	39	27	20	17	13

# Safety

- Used in one million of patients with hematologic malignancies (first line / maintenance)
- First **infusion adverse reactions** (bronchospasm, cough, chills, rash, fever, headache); mild / absent thereafter
- Systematic review in RCTs of RA treated with biologic therapy (N = 29,423): **no increased risk of malignancies** (Lopez-Olivo JAMA 2012)
- 23 cases of **PML** in > 500,000 patients; had either B-cell cancer (20) or lupus (3); all taking chemotherapy - **no cases in NS**

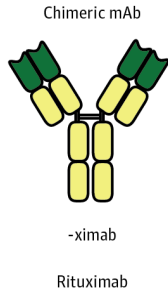


# Safety

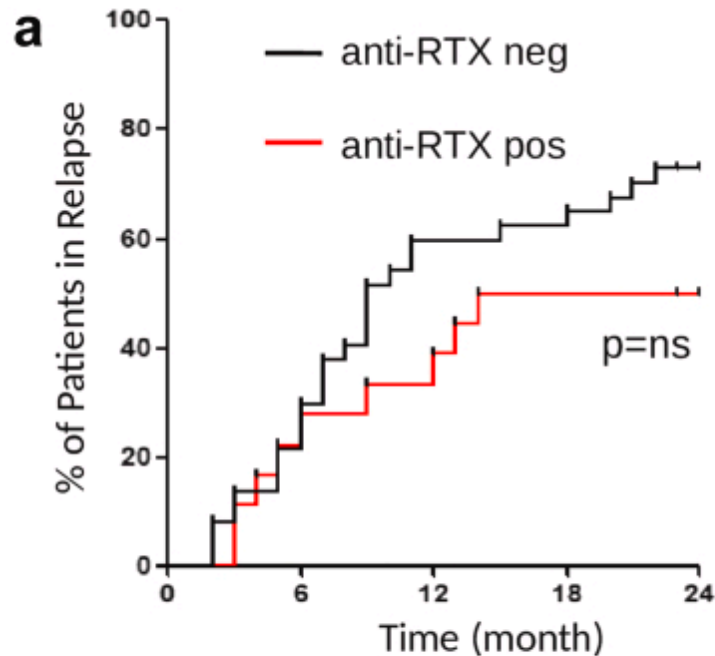


—●— Ofatumumab —▲— Rituximab

# Safety



## Circulating Anti-Rituximab Antibodies Do Not Affect Response to Rituximab in Steroid-Dependent Nephrotic Syndrome



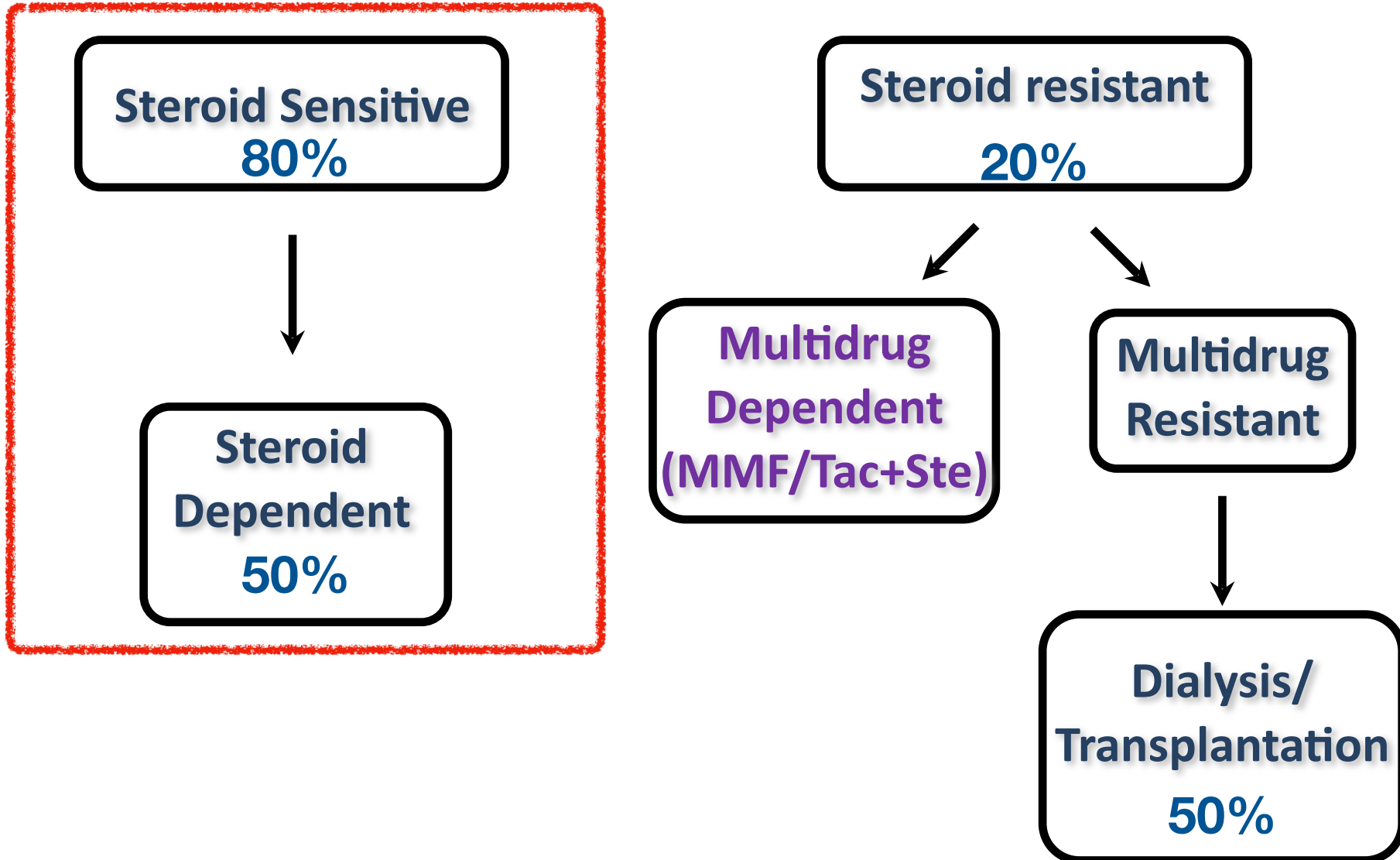
Subjects at Risk

Months	0	6	12	18	24
anti-RTXpos	14	11	10	9	8
anti-RTX neg	40	36	30	27	22

# Key points

- RTX is useful in the treatment of some forms of INS in children (combined steroid/CNI dependent forms)
- RTX high superior to PDN on pure dependent forms
- OFatumumab is equal to Rituximab
- RTX ineffective in multidrug-resistant INS

# Nephrotic Syndrome: Definition





# Nephrotic Syndrome: Definition

**Steroid Sensitive**  
**80%**



**Steroid Dependent**  
**50%**

**Steroid resistant**  
**20%**



**Multidrug Dependent**  
**(MMF/Tac+Ste)**

**Multidrug Resistant**



**Dialysis/  
Transplantation**  
**50%**

# STEROID/MULTIDRUG RESISTANT NS

Reference	Disease	N	Study	Dose	CR (%)
<b>Rituximab</b>					
Bagga A, <i>et al.</i> , 2007 (20)	SRNS	5	Case series	375mg/m <sup>2</sup> (4 doses)	60
Gulati A, <i>et al.</i> , 2010 (21)	SRNS	33	Multicentric Cohort Study	375mg/m <sup>2</sup> (4 doses)	27
Magnasco A, <i>et al.</i> , 2012 (22)	SRNS	31	RCT	375mg/m <sup>2</sup> (2 doses) vs 375mg/m <sup>2</sup> + Cyc	30
<b>Ofatumumab</b>					
Basu B, <i>et al.</i> , 2014 (49)	multidrug resistant NS	5	Case series	300mg/m <sup>2</sup> followed by 5 weekly infusions (2g/m <sup>2</sup> )	80
Bonanni A, (50) <i>et al.</i> , 2015	multidrug resistant NS	4	Case series	375-700 mg/m <sup>2</sup> (1 dose)	25
Wang CS, <i>et al.</i> , 2017 (52)	SRNS	4	Case series	300mg/m <sup>2</sup> followed by 5 weekly infusions (2g/m <sup>2</sup> )	75
Ravani P, <i>et al.</i> , 2020 (53)	multidrug resistant NS	7	RCT	1,500mg/m <sup>2</sup> (1 dose)	0

# STEROID/MULTIDRUG RESISTANT NS

- **Obinutuzumab** (lesson from Lupus nephritis)
- **Anti-CD38 Abs +Rituximab** (trial in development)
- Finerenone
- SGLT2i

## **A Study to Evaluate the Efficacy and Safety of Obinutuzumab Versus MMF in Participants With Childhood Onset Idiopathic Nephrotic Syndrome (INShore)**

### **A Phase 3 study**

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	80 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	None (Open Label)
Primary Purpose:	Treatment
Actual Study Start Date :	March 29, 2023
Estimated Primary Completion Date :	December 1, 2025
Estimated Study Completion Date :	August 15, 2026

1) Title

**Efficacy and tolerance of the association between chimeric monoclonal anti-CD20 (Rituximab Biosimilar) and monoclonal anti-CD38 (Daratumumab) antibodies in the treatment of childhood multidrug dependent and resistant and in post transplant recurrence of nephrotic syndrome.**

**A Phase 2 study (the DUAL1)**

2) Trial Registration

NCT05704400

Eudract: 2022-001769-11

**ENROLLING PHASE**

# BIOMARKERS-PATHOGENESIS

- CD20
- Memory/IgM CD20 (in progress)
- Antibodies (in developement)
- Serum/Urinary proteins (in progress)

# MOMA\* Project

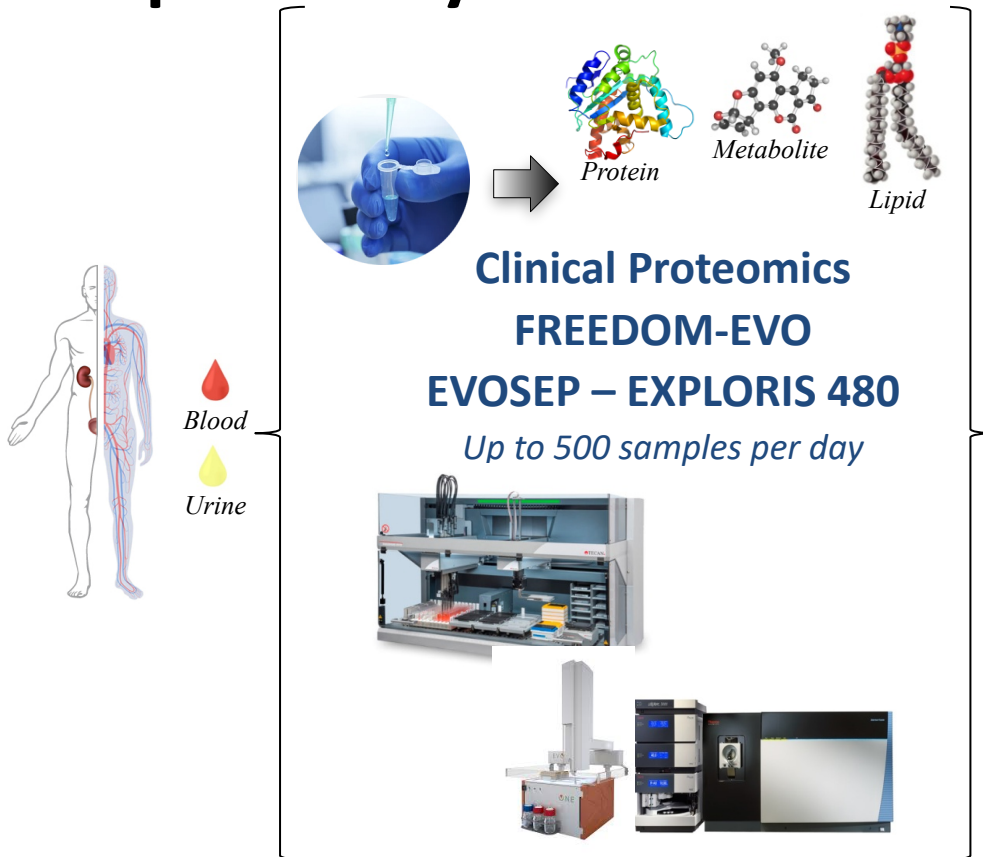
\* Multi

Omics

Molecular

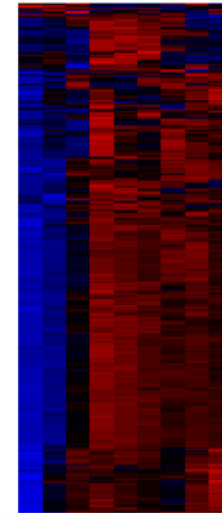
Analysis

## Nephrotic Syndrome



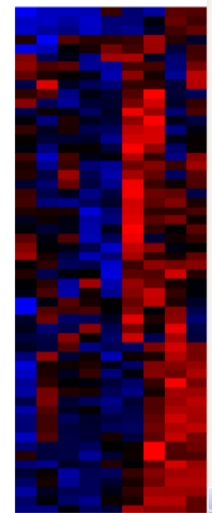
### PLASMA

Name	Total
Lipid_C18_Pos_plasma_D_014	970
Lipid_C18_Pos_plasma_D_015	971
Lipid_C18_Pos_plasma_D_021	968
Lipid_C18_Pos_plasma_IPA_017	965
Lipid_C18_Pos_plasma_IPA_020	960
Lipid_C18_Pos_plasma_IPA_024	963
Lipid_C18_Pos_plasma_MANN_016	959
Lipid_C18_Pos_plasma_MANN_019	960
Lipid_C18_Pos_plasma_MANN_022	959

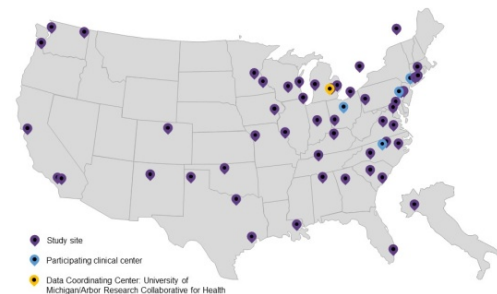
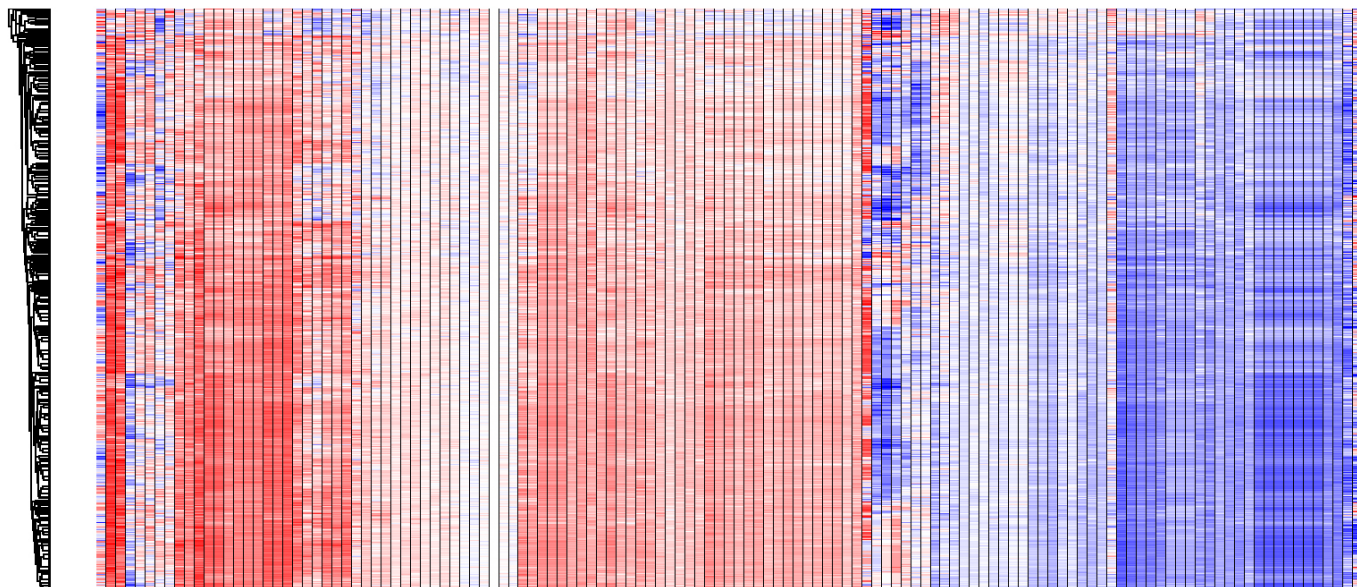


### URINE

Name	Total
Lipid_C18_Pos_urine_D_044	248
Lipid_C18_Pos_urine_D_051	248
Lipid_C18_Pos_urine_D_053	248
Lipid_C18_Pos_urine_IPA_045	241
Lipid_C18_Pos_urine_IPA_048	243
Lipid_C18_Pos_urine_IPA_050	243
Lipid_C18_Pos_urine_MANN_...	245
Lipid_C18_Pos_urine_MANN_...	245
Lipid_C18_Pos_urine_MANN_...	246

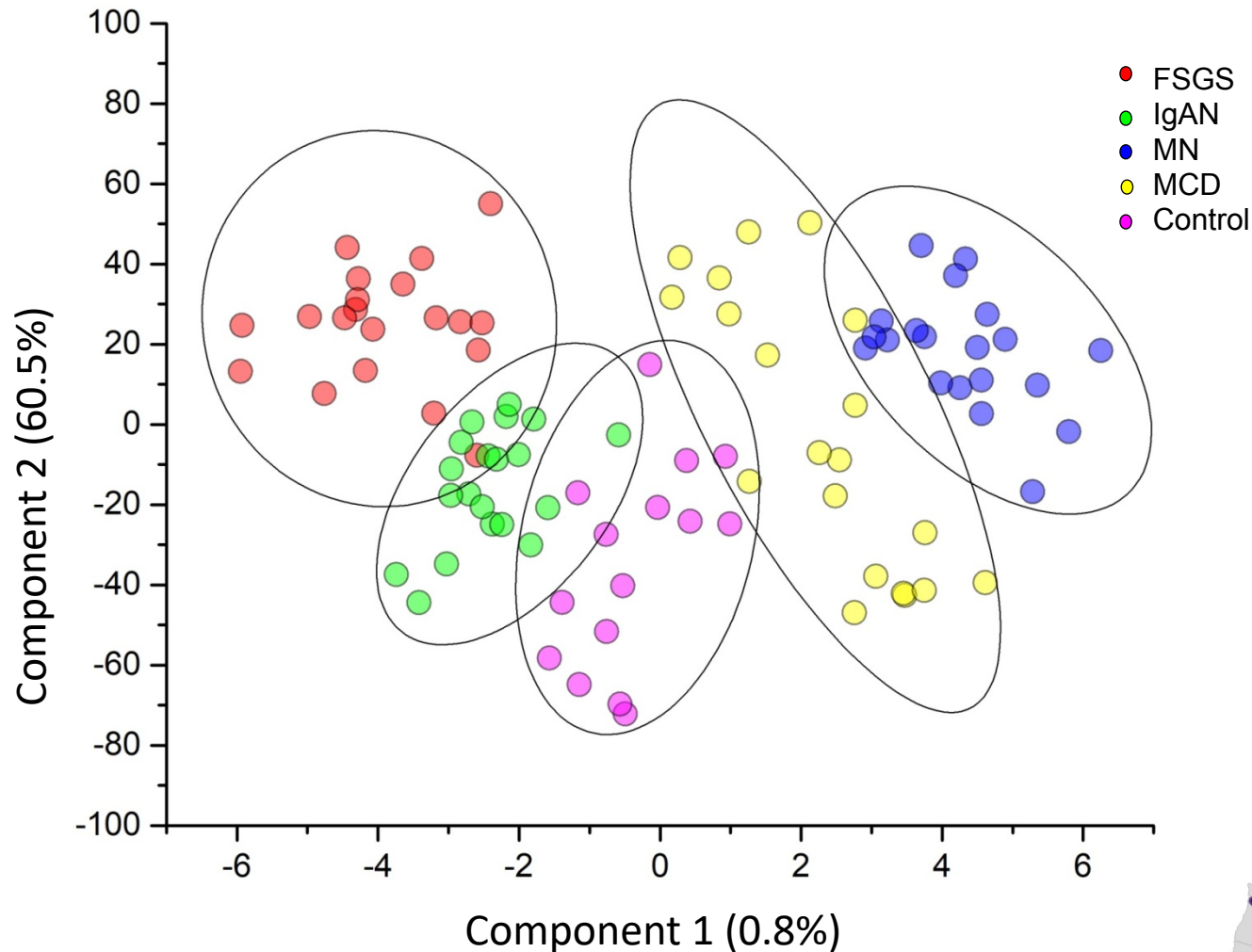


(Langfelder P and Horvath S, BMC Bioinformatics, 2008)





## Machine learning and supervised cluster analysis



unpublished data

# Lab Crew

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Maurizio Bruschi

Gianluca Caridi

Giovanni Candiano

Khuliana Kasana

Sonia Spinelli

Andrea Garbarino



Dr. Enrico Verrina

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In memory of Prof R Gusmano

Thanks to Dr G Ghiggeri