Refractory INS in adults and children : where to place rituximab, obinutuzumab, daratumumab ?

Actualités Néphrologiques Jean Hamburger 2026

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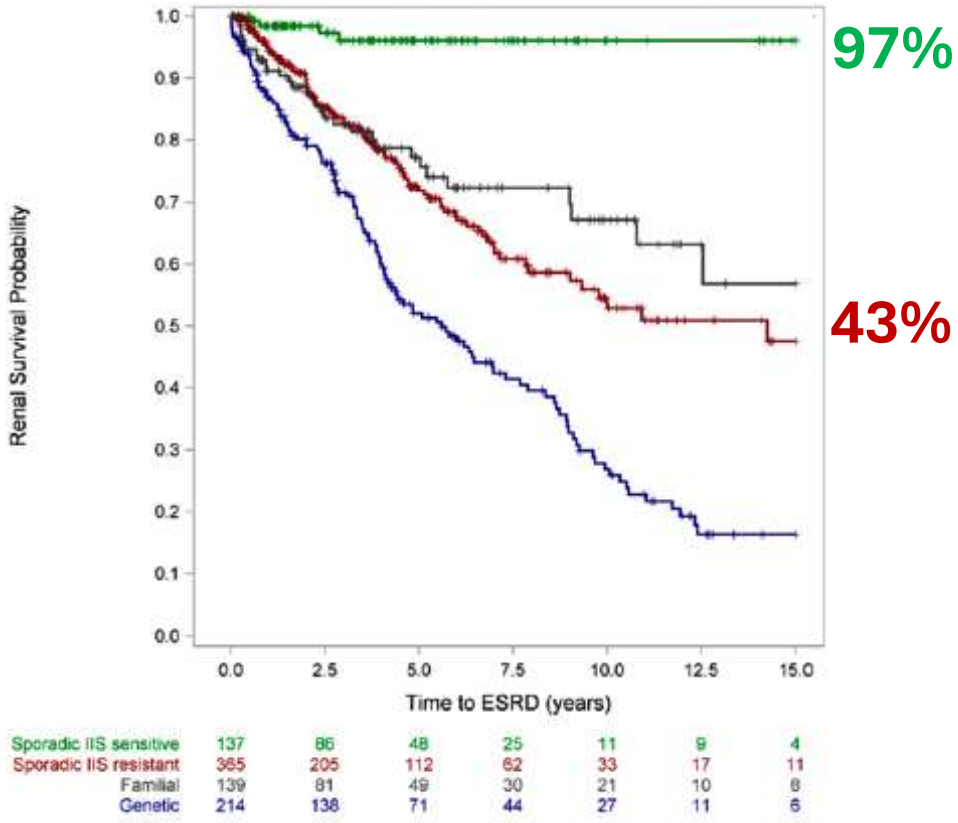
CRMR Syndrome Néphrotique Idiopathique de l'enfant et de l'adulte

Menu

- What is refratory INS ?
- Overview of B-cell Targeting Therapies
- **Rituximab** in refractory NS on native kidneys/recurrence
- **Obinutuzumab** in refractory NS on native kidneys/recurrence
- **Daratumumab** in refractory NS on native kidneys/recurrence

- Where to place these BcTT ?
- PIANO initiative
- Future directions ?

Outcomes in refractory INS

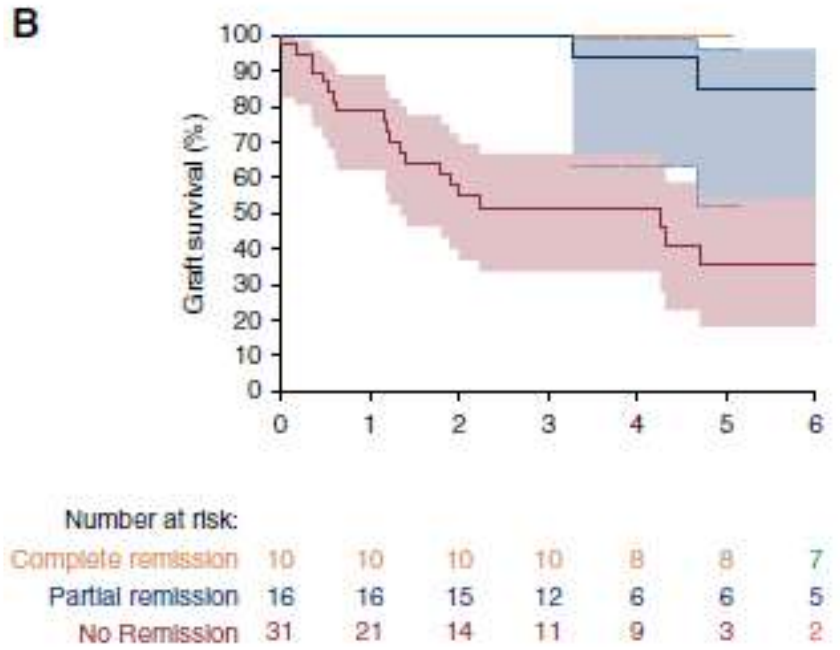


97%

43%

Trautmann, JASN 2017

- SRNS accounts for 10-12% children with ESKD
- Recurrence risk : 1st Tx : **50 %-** 2nd Tx: **90 %**
- Recurrence impacts graft function



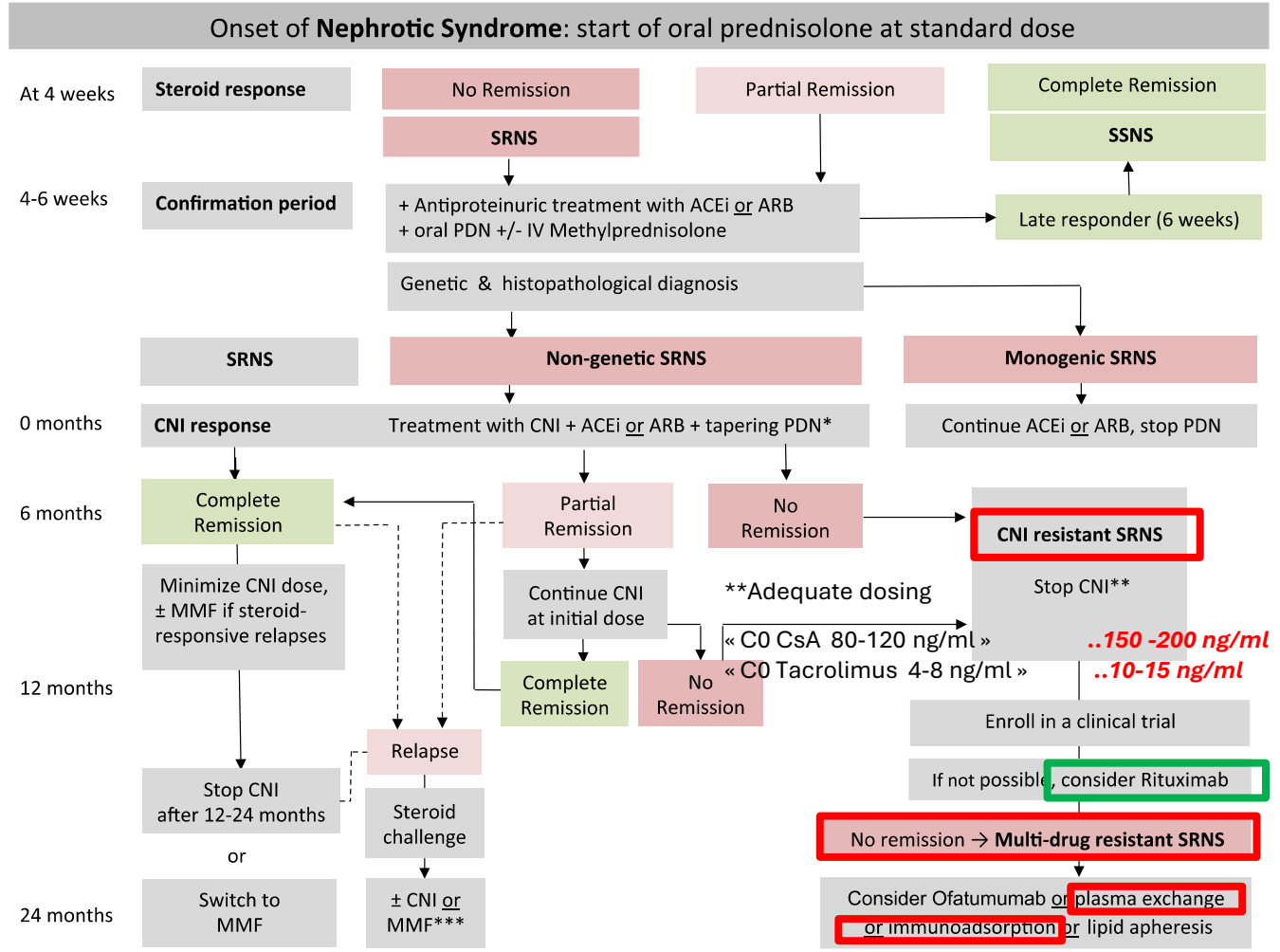
Uffing CJASN 2020, TANGO project

What is refractory INS ?

Children

- **SSNS:** Complete remission after 4 weeks of prednisone or prednisolone at standard dose
- **Infrequent relapsing NS:** <2 relapses per 6 months within 6 months of disease onset or <4 relapses per 12 months in any subsequent 12-month period
- **Frequent relapsing NS:** ≥2 relapses per 6 months within 6 months of disease onset or ≥4 relapses per 12 months in any subsequent 12-month period
- **Steroid-dependent NS:** Two consecutive relapses during therapy with prednisone or prednisolone (either at full dose or during tapering) or within 15 days of prednisone or prednisolone discontinuation
- **SRNS:** Lack of complete remission at 4 weeks of therapy with daily prednisone or prednisolone at standard dose
- **Late responder:** Complete remission at 6 weeks.
- **Calcineurin inhibitor-responsive SRNS:** Partial remission after 6 months of treatment and/or complete remission after 12 months of treatment with a calcineurin inhibitor at adequate doses and/or levels
- **Calcineurin inhibitor-resistant SRNS:** Absence of partial remission after at least 6 months of treatment with a calcineurin inhibitor at adequate doses and/or levels
- **Multi-drug resistant SRNS:** Absence of complete remission after 12 months of treatment with 2 mechanistically distinct glucocorticoid-sparing agents at standard doses (see below)
- **Secondary SRNS:** A SSNS patient at disease onset who at a subsequent relapse fails to achieve remission after 4 weeks of therapy with daily prednisone or prednisolone at standard dose

KDIGO 2021



IPNA recommendations, Ped Nephrol 2020

What is refractory INS ?

Adults MCD

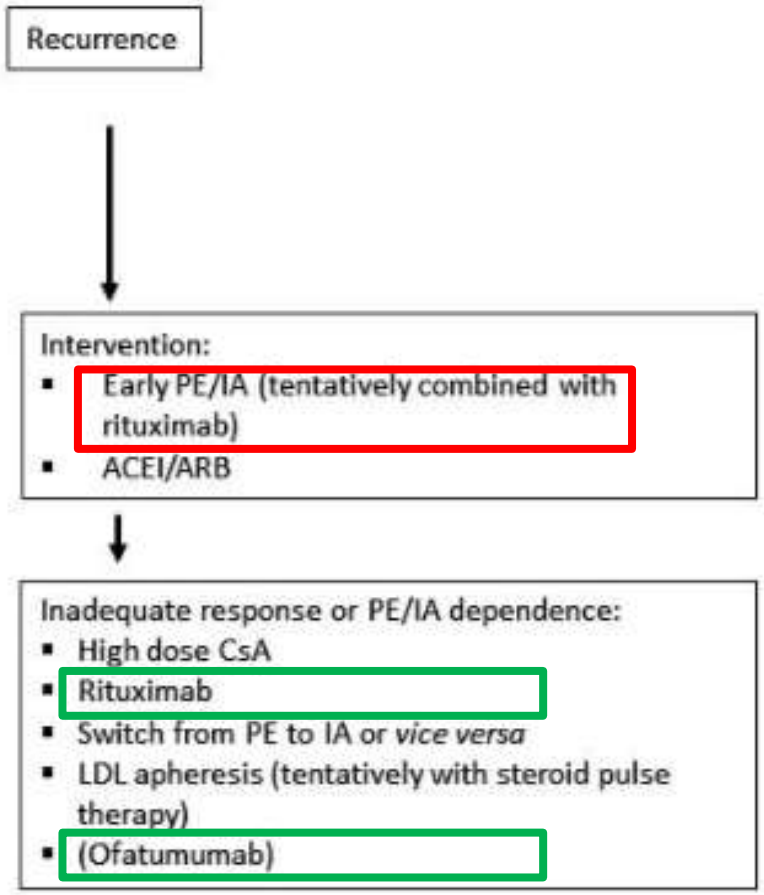
Complete remission
Reduction of proteinuria to <0.3 g/d or PCR <300 mg/g (or <30 mg/mmol), stable serum creatinine and serum albumin >3.5 g/dl (or 35 g/l)
Partial remission
Reduction of proteinuria to 0.3–3.5 g/d or PCR 300–3500 mg/g (or 30–350 mg/mmol) and a decrease >50% from baseline
Relapse
Proteinuria >3.5 g/d or PCR >3500 mg/g (or 350 mg/mmol) after complete remission has been achieved
Steroid-resistant MCD
Persistence of proteinuria >3.5 g/d or PCR >3500 mg/g (or 350 mg/mmol) with <50% reduction from baseline despite prednisone 1 mg/kg/d or 2 mg/kg every other day for >16 weeks
Frequently relapsing MCD
Two or more relapses per 6 months (or four or more relapses per 12 months)
Steroid-dependent MCD
Relapse occurring during, or within 2 weeks of completing glucocorticoid therapy

Adults Steroid-Resistant FSGS

Treatment	Dose and duration
Calcineurin inhibitors*	**Starting dose:** • Cyclosporine 3–5 mg/kg/d in 2 divided doses OR tacrolimus 0.05–0.1 mg/kg/d in 2 divided doses • Target trough levels could be measured to minimize nephrotoxicity • Cyclosporine target trough level: 100–175 ng/ml (83–146 nmol/l) • Tacrolimus target trough level: 5–10 ng/ml (6–12 nmol/l)
	Treatment duration for determining CNI efficacy: • Cyclosporine or tacrolimus should be continued at doses achieving target trough level for at least 6 months, before considering the patient to be resistant to CNI treatment
	Total CNI treatment duration: • In patients with partial or complete remissions, cyclosporine or tacrolimus should be continued at doses achieving target trough level for at least 12 months to minimize relapses • The dose of cyclosporine or tacrolimus can be slowly tapered over a course of 6–12 months as tolerated • Consider discontinuing cyclosporine or tacrolimus if the eGFR continues to decline to <30 ml/min per 1.73 m^2
Inability to tolerate or contraindications to calcineurin inhibitors	• Lack of quality evidence for any specific alternative agents • Mycophenolate mofetil and high-dose dexamethasone, rituximab, and ACTH have been considered • Treatment will need to be personalized and is dependent on availability of drugs and resources, as well as the benefits of further treatment and risks of adverse effects of immunosuppression • Patients should be referred to specialized centers with the appropriate expertise, and should be evaluated on the appropriate use of alternative treatment agents or to discontinue further immunosuppression

KDIGO 2021

Post-transplant recurrence



Weber & CERTAIN group, Ped transplant 2021

meeting report www.kidney-international.org

Post-transplant recurrence of focal segmental glomerular sclerosis: consensus statements

Rupesh Raina[1,2,31], Swathi Jothi[1,31], Dieter Haffner[3], Michael Somers[4], Guido Filler[5,6,7], Prabhav Vasistha[1],

We conducted a meta-analysis of 58 patients across 23 studies and found a total remission rate of 63.8%, a complete remission rate of 48.3%, and a partial remission rate of 15.5%. On performing a subgroup analysis, we noted that age ($P = 0.24$) and rituximab ($P = 0.70$) were not significantly associated with remission. The various doses used in these 23

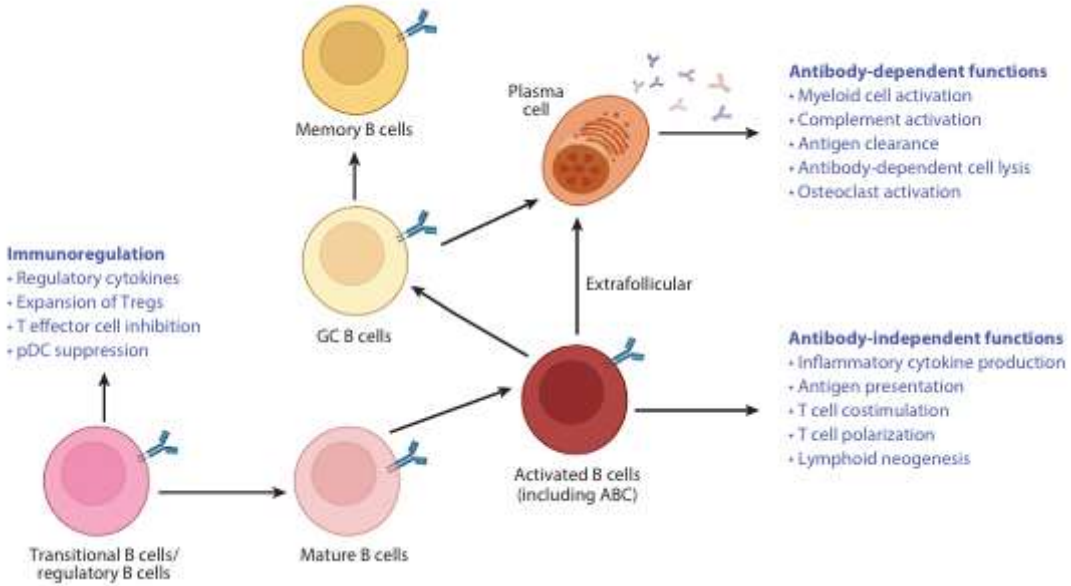
Clinical practice guidelines

- Therapy with rituximab should be considered in patients with rFSGS who have contraindications to plasmapheresis, or who fail to improve despite treatment with plasmapheresis or immunoadsorption. Rituximab doses ranged from 75 to 3375 mg (median dose, 1500 mg/m^2) (2B).

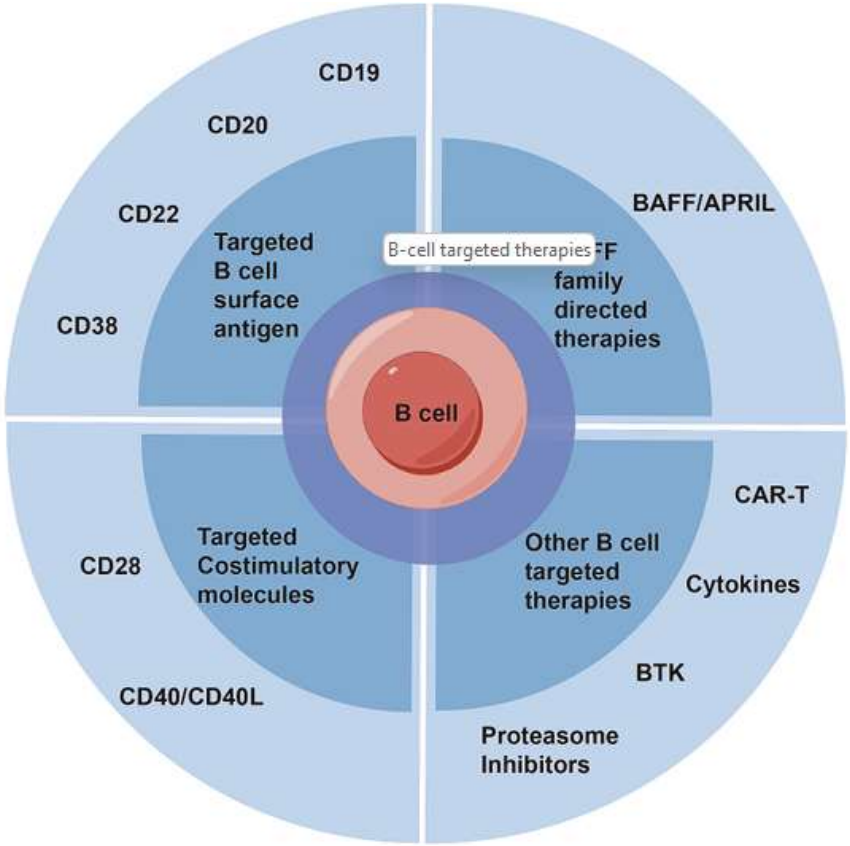
KI 2023

B-cell targeting therapies

- B-cell functions in auto-immunity



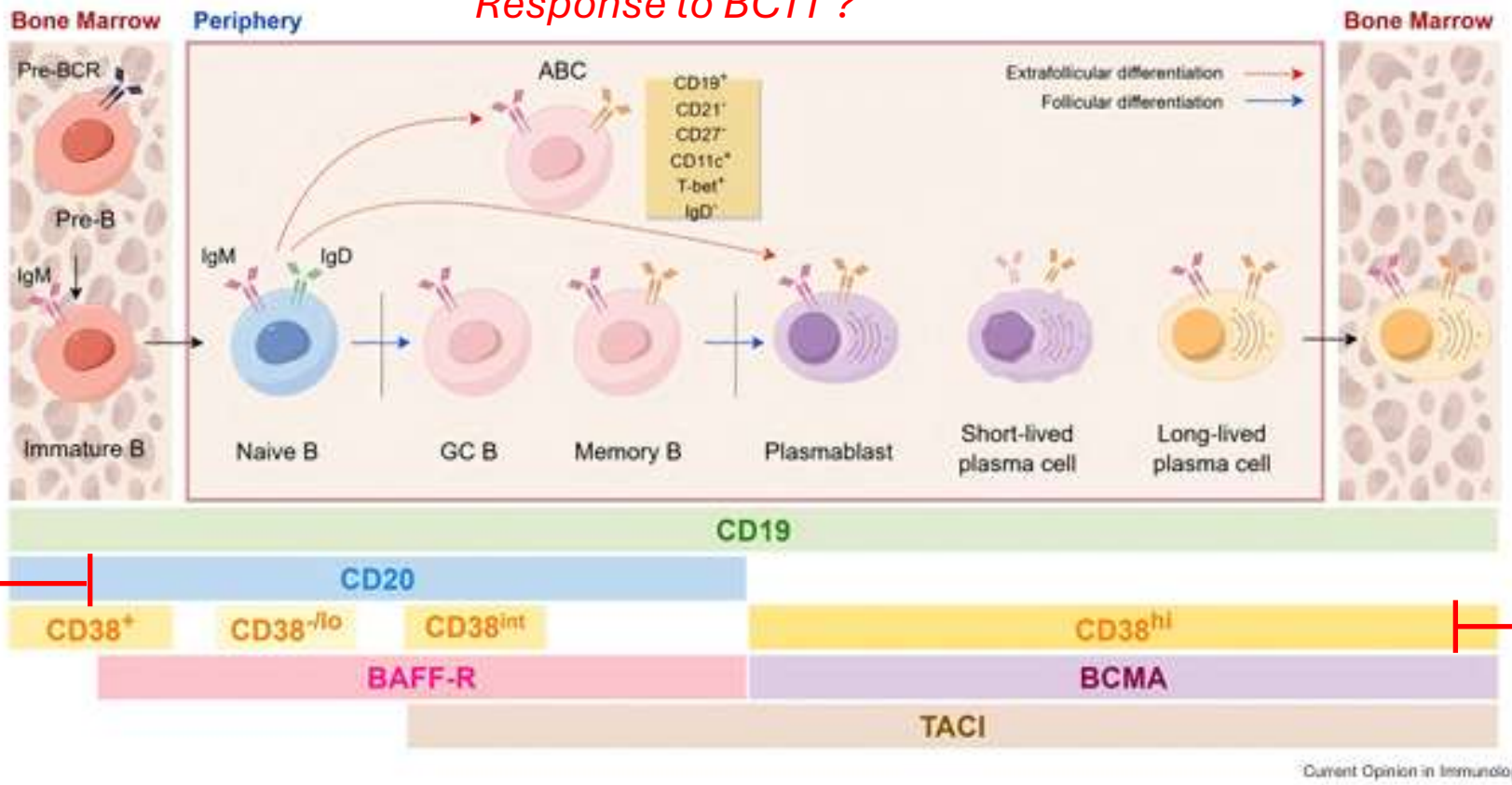
Abeles Annul Rev Immunol 2024



Chen Bio Pharmacol 2025

B-cell targeting therapies

Atypical B-cells
Response to BCTT ?



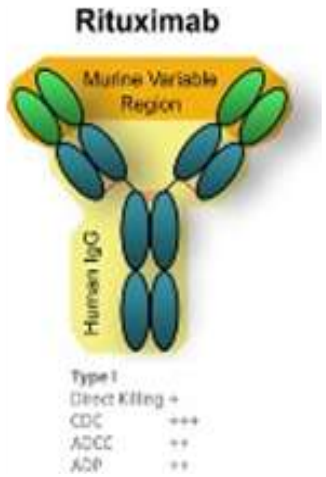
Rituximab
Obinutuzumab
Ofatumumab
Ocrelizumab
Ublituximab

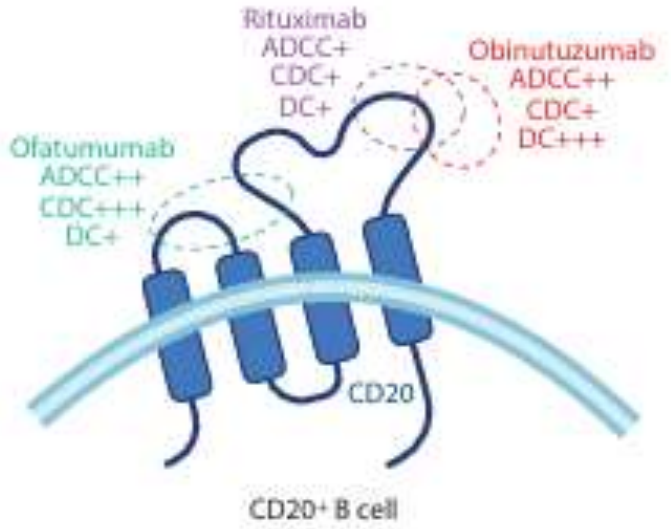
Daratumumab
Felzartamab

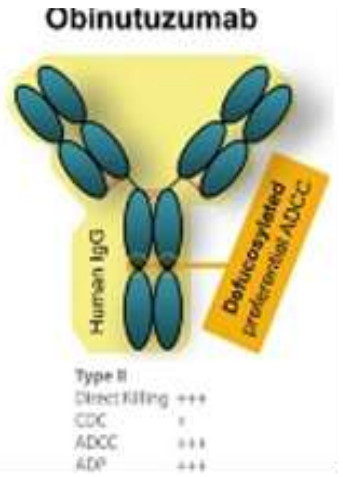
B-cell targeting therapies - Safety

- **Infusion related-reactions**
- **Infectious risk**
  - Bacterial/viral/fungal infections
  - HBV reactivation
  - VZV/HSV reactivation
  - Progressive multifocal leukoencephalopathy (rare)
- **Hematologic risk**
  - Late onset neutropenia
- **Transient hypogammaglobuinemia**
- **Persistent hypogammaglobulinemia**

B-cell targeting therapies : anti CD20







Benz Ped Neph 2004

Deschênes Ped Neph 2020

Rituximab in SRNS

- **CNI-R > 6m**
- **4 RTX 375 mg/m²**
- CR in 4/5, within 2-8 weeks after 4th RTX

Table 1. Characteristics of the Five Patients and Their Response to Treatment with Rituximab.

Patient No.	Age		Previous Treatment*	Ratio of Urinary Protein to Creatinine		Serum Albumin		Status at Follow-up and Subsequent Treatment†
	At Onset of Disease	At Study Inclusion		Baseline	Follow-up	Baseline	Follow-up	
	yr					g/dl		
1	2.3	10.3	Intravenous corticosteroids, oral and intravenous cyclophosphamide, cyclosporine, tacrolimus	17.5	1.8	1.5	2.2	Partial remission (duration, 58 wk); tacrolimus (0.1 mg/kg/day), prednisolone (0.6 mg/kg/alternate day)
2	3.3	8.6	Intravenous cyclophosphamide, cyclosporine, mycophenolate mofetil	3.6	0.1	1.1	3.6	Complete remission (duration, 38 wk); prednisolone (1 mg/kg/alternate day)
3	2.8	15.0	Intravenous corticosteroids, oral and intravenous cyclophosphamide, azathioprine, cyclosporine	6.0	0.1	1.2	4.4	Complete remission (duration, 30 wk); cyclosporine (3 mg/kg/day), prednisolone (0.3 mg/kg/alternate day)
4	1.8	16.0	Oral cyclophosphamide, intravenous corticosteroids, mycophenolate mofetil, cyclosporine, chlorambucil, vincristine, tacrolimus	10.0	2.0	1.7	2.7	Partial remission (duration, 14 wk); tacrolimus (0.04 mg/kg/day), prednisolone (0.2 mg/kg/alternate day)
5	1.0	2.8	Cyclosporine	4.3	0.2	1.7	4.3	Complete remission (duration, 14 wk); cyclosporine (2.5 mg/kg/day), prednisolone (0.3 mg/kg/alternate day)

Bagga NEJM 2004

Characteristic	SRNS[a] (n = 33)
Age at onset (years)	6.3 ± 4.8 (1 to 41)
Age at rituximab therapy (years)	12.7 ± 9.1 (2 to 41)
Boys	17
Type of resistance (initial/late)	24/9
Renal histology	n = 33
MCD	17
FSGS	16
mesangial hypercellularity	—
Previous immunosuppressive therapy	33
long-term alternate day prednisolone	33
intravenous methylprednisolone	9
levamisole	2
mycophenolate mofetil	3
cyclophosphamide	20 (23 courses)
calcineurin inhibitor	24
vincristine	2
Duration of CNI therapy (months)	22.7 ± 17.1 (4 to 56)

Table 2. Response rates at 6 months in patients with SRNS according to type of resistance and renal histology

	IR (n = 24)	LR (n = 9)	MCD (n = 17)	FSGS (n = 16)	Total (n = 33)
Complete remission (%)	5[a] (20.8)	4 (44.5)	7 (41.2)	2 (12.5)	9 (27.2)
Partial remission (%)	6[a] (25)	1 (11.1)	4 (23.5)	3 (18.7)	7 (21.2)
Non response (%)	13 (54.1)	4 (44.5)	6 (35.2)	11 (68.7)	17 (51.5)
P	0.7		0.08		

IR, initial resistance; LR, late resistance.

Gulati CJASN 2010

Rituximab in SRNS

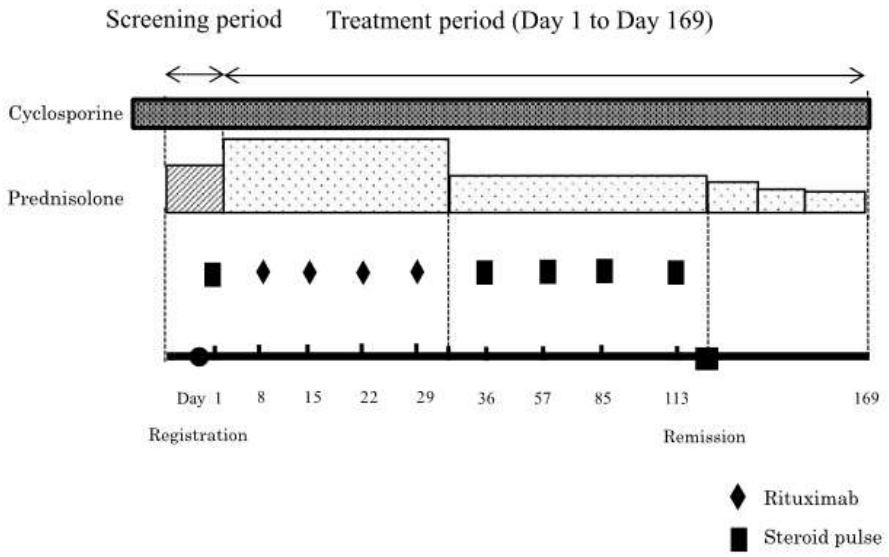
- **RCT** : 2 RTX 375 mg/m2 vs SOC
- N=31
- Under CsA (50-100 ng/ml) or FK (5-10 ng/ml)
- At least 6 months
- Age 7.9 yrs
- **Outcome : change Pu at M3**

	Early-Resistant Patients				Delayed-Resistant Patients			
	Rituximab Group (*n*=9)		Control Group (*n*=7)		Rituximab Group (*n*=7)		Control Group (*n*=8)	
	T0	T3	T0	T3	T0	T3	T0	T3
Proteinuria (g/day per m^2)	2.9 (1.2, 6.6)	2.7 (1.6, 7.8)	6 (1.5, 8.8)	3.9 (1.2, 7.1)	1.3 (0.8, 6.3)	0.8 (0.1, 1.7)	2.4 (0.8, 4.8)	0.8 (0.1, 4.6)
Serum albumin (g/L)	2.1±0.5	2.1±0.6	2.2±0.7	2.1±0.9	2.6±0.6	3.3±0.3	2.4±0.4	2.9±0.8
Serum creatinine (mg/dl)	0.6±0.2	0.7±0.3	0.7±0.4	0.7±0.4	0.5±0.4	0.6±0.4	0.5±0.3	0.5±0.3
Remission (*n*)	0		0		3		3	

✓ **No benefit on adding RTX**

Magnasco JASN 2012

Rituximab in SRNS



- Multicenter single arm study in Japan
- Under CNI + steroid for > 2m
- **4 RTX 375 mg/m2** (max 500mg)
- MP 30 mg/kg (max 1g)
- N=6 children

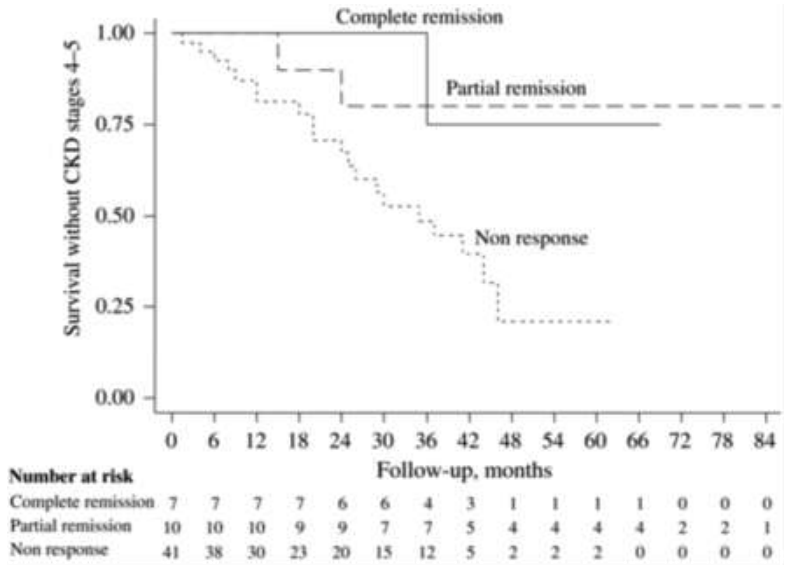
Table 2 Proportions of the primary endpoint, remission, nephrotic status, and chronic renal failure development

	Numbers in analysis set	Achieved number	Proportion (%)	95% confidence interval [%]
(Primary endpoint) 50% reduction of the Up/Uc at Day 169	6	5	83.3	[43.6, 97.0]
(1) More than 50% reduction of the Up/Uc and the Up/Uc is 0.2 to 2.0 g/gCr at Day 169	6	2	33.3	[9.7, 70.0]
(2) Complete remission at Day 169	6	2	33.3	[9.7, 70.0]
(3) Incomplete remission at Day 169	6	2	33.3	[9.7, 70.0]
(4) Either incomplete or complete remission at Day 169	6	4	66.7	[30.0, 90.3]
(5) Nephrotic status at Day 169	6	2	33.3	[9.7, 70.0]
(6) Chronic renal failure development during the treatment period	6	0	0.0	[0.0, 39.0]

Ir outcome : reduction of 50% of UPCR at D169
Iir outcomes : **2/6 CR + 2/6 PR**
Safety : 6 infections requiring ttt in n=3

Nozu, Clin Exp Neph 2023

Rituximab in SRNS



- Monocentric retro 2006-2013
- N= 193 from India
- N=58 CNI-R > 6mths

- ✓ **7 complete remission (12%)**
- ✓ **10 partial remission (17%)**
- ✓ **No response 70%**
- ✓ Predictor of no response : FSFG OR 11 (95% IC 1.3-99.8; p=0.028)

Table 4. Outcomes in patients with steroid- and CNI-resistant nephrotic syndrome, in relation to response to rituximab

Status	At 12 months[a]		Last effective follow-up[b]		Last follow-up[c]	
	Responders ($n=17$)	Non-response ($n=41$)	Responders ($n=17$)	Non-response ($n=41$)	Responders ($n=17$)	Non-response ($n=41$)
Remission (complete/partial)	12 (6/6)	6 (2/4)	1 (1/0)	0	8 (7/1)	6 (2/4)
Infrequent relapses	1	0	1	0	4	1
Frequent relapses, dependence	1	0	8	0	1	1
Steroid resistance, non-response	3	30	7	28	1	13
CKD 4–5 (transplant)	0	5	0	13	3 (1)	20 (6)

2015 NDT Sinha

Rituximab in SRNS

- **Retrospective multiethnic stduy**
- N=246 children from 19 countries
- including **146 CNI > 6 months**
- Ethinicity : 64% South Asia, 23 % White, 7% East Asia, 5% others
- Age NS onset 5 yrs ± 3.8, 53 % primary SRNS
- Histology : 27 % MCD, 57% FSGS
- Age RTX : 8.8 ± 41

Table 6 | Secondary outcomes at 3, 6, and 12 months and last follow-up in those who received CNIs ≥6 months before rituximab (CNI-resistant SRNS)

CNIs ≥6 months before rituximab (CNI-resistant SRNS)	At rituximab (n = 146)	3 mo (n = 146)	6 mo (n = 146)	12 mo (n = 133)	Last follow-up (n = 146)
Laboratory findings					
UPCR, mg/mg	3 (2.9–6.2)	3 (1–3)	2.4 (0.8–3)	2.6 (0.7–3)	2 (0.4–3)
erum albumin, g/L	21 (17–26)	28 (20–36.3)	27.7 (20–36.7)	32 (22–38)	32.2 (24–40)
Serum creatinine, µmol/L	51.9 (35.4–70.7)	48 (33.1–70.6)	55.1 (35.4–85.4)	54.4 (36.4–85.4)	72 (52.8–188.9)
eGFR, ml/min per 1.73 m^2	89 (66–120)	96 (68–128.5)	86 (60.8–114)	92 (56.3–119.8)	78 (29.3–107.8)

Table 4 | Remission status following rituximab therapy in children who received ≥6 months (CNI resistant) and <6 months of CNIs before rituximab administration

Variable	3 mo	6 mo	12 mo	24 mo
≥6 mo of CNIs (CNI-resistant SRNS)				
All patients, n	146	146	134	92
Complete or partial remission	38 (26; 19.3–34.1)	52 (35.6; 28.0–44.0)	47 (35.1; 27.2–43.8)	36 (39.1; 29.2–49.9)
Complete remission	24 (16.4; 11.0–23.7)	26 (17.8; 12.2–25.2)	22 (16.4; 10.8–24.0)	22 (23.9; 15.9–34.1)
Partial remission	14 (9.6; 5.5–15.8)	26 (17.8; 12.2–25.2)	25 (18.7; 12.7–26.5)	14 (15.2; 8.9–24.6)

Chan KI 2024

Rituximab in SRNS

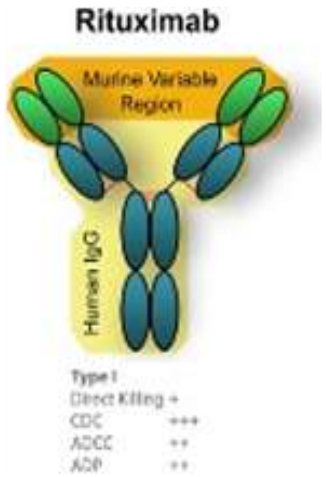
TABLE 2 OVERVIEW THE STUDIES INCLUDED ABOUT FOCAL SEGMENTAL GLOMERULOSCLEROSIS AND = MINIMAL CHANGE DISEASE

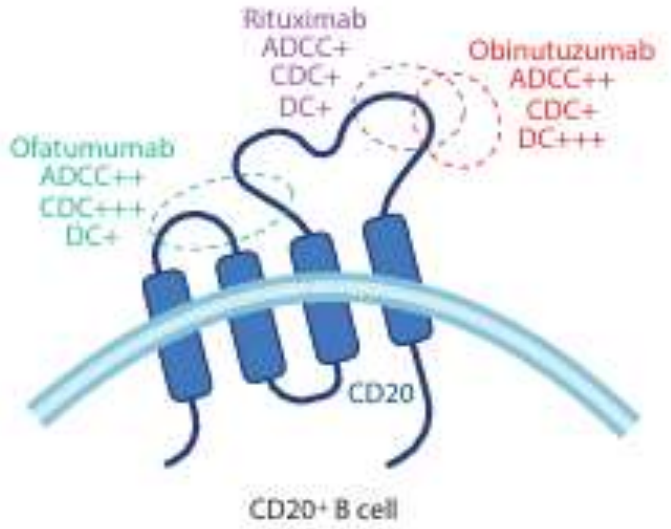
Reference	Disease	Patients (n)	Treatment before RXT	Prot. prior RTX g/dia	Cr before RTX, mg/dL	Relapses before RTX	RTX dose	Follow-up (mo)	Remission (definition per study)	Cr after RTX, mg/dL	Relapses after RTX	Treatment after RTX	Study design
Fernandez-Fresnedo et al, 2009[49]	FSGS (SRNS)	8	TAC (3), MMF (7), CyA (2), Csa (7) Steroids (8)	14.0 ± 4.4	1.4 ± 0.5	ND	4 weekly doses of 375mg/m² (5) 4 weekly doses of 375mg/m² followed by the same scheme at 12 mo (1) 4 weekly doses of 375mg/m² followed by the same scheme at 6 mo (1) 8 weekly doses of 375mg/m² (5)	12-24	PR (1) NR (7)	2.2 ± 1.8	ND	ND	Retro
Kong W.Y. et al, 2013[50]	FSGS	4	CyA (2), Csa (2), Aza (1) MMF (1), steroids (3)	ND	ND	12 relapses (1) 0 relapses (3)	375mg/m², single dose	11-51	CR (2), PR (1), NR (1)	ND	1 relapses (1) 0 relapses (3)	Steroids(2)	Retro
Ochi A. et al. 2012[51]	FSGS (2SRNS, 2SDNS)	4	Csa (2), MZ (1), CyA (1), MMF (1), steroids (4),	3.6-13.0	0.5-2.1	2 patients relapses more than 3 times	375mg/m², single dose	variable	CR(2) NR (2)	DN	2 patients relapse	Steroids (2)	Retro
Rocatello D. et al, 2017[52]	FSGS	8	Supportive treatment	5.3 ± 1.9	2.6 ± 1.2	NA	8 weekly doses of 375mg/m²	29.1 ± 8.8	NR (7) PR (1)	3.5 ± 2.5	ND	Only supportive treatment	Prosp
Munyentwali et al, 2013[48]	MCD steroid-dependent (15); MCD steroid-resistant (2)	17	TAC(2), MMF (12), Csa (13), CyA (4), LEV (7) mechlorethamina (3), chlorambucil (1), pefloxacin (1), basiliximab (1), steroids (17)	0.05-6.2	ND	All patients had at least 2 relapses	375mg/m², single dose (1) 2 weekly doses of 375mg/m² (7) 3 weekly doses of 375mg/m² (4) 4 weekly doses 375mg/m² (3) 1000mg on day 1 and 15 (2)	5.1-82.2	CR (15), NR (2)	NA	6 patients with at least 1 relapse each	CyA (1); Steroids (4); TAC (1)	Retro
Takei T. et al, 2013[47]	MCD steroid-dependent and frequently relapse	25	MMF (3), CyA (20), MZ (5), steroids (25)	2.5 ± 3.5	0.7 ± 0.2	62 relapses (patients experienced at least 1)	Single dose of 375mg/m², 6 months apart, during 1 year (25)	12	CR (25)	0.6 ± 0.1	4 patients with 1 relapse each	CyA (6), steroids (4)	Prosp
Iwabuchi Y. et al, 2014[46]	MCD steroid-dependent and frequently relapse	25	MMF(1), CyA(20), MZ(6), TAC(1) steroids (28)	2.5 ± 4.9	0.7 ± 0.2	108 relapses (patients experienced at least 1)	Single dose of 375mg/m², 6 months apart, during 2 years	24	CR (25)	0.7 ± 0.1	8 patients with 1 relapse each	CyA (5), Steroids (4)	Prosp
Papakrivopoulou E. et al, 2016[53]	MCD steroid-dependent and frequently relapse	15	MMF(3), CyA(5), LEV (3),Csa (6), TAC (4)	ND	0.95 ± 0.3	39 relapses (patients experienced at least 1)	Single dose of 375mg/m², 6 months apart, during 1 year (15)	43	ND	ND	7 patients with 1 relapse each	Dose reduction of TAC and Csa; steroids (0)	Prosp
Fenoglio R. et al, 2018[45]	MCD	6	RTX as first line therapy	11.75 ± 7.8	1.95 ± 1.5	NA	4 weekly doses of 375mg/m²	8-36 months	CR (5)	0.86 ± 0.18	0 relapses	None	Case series

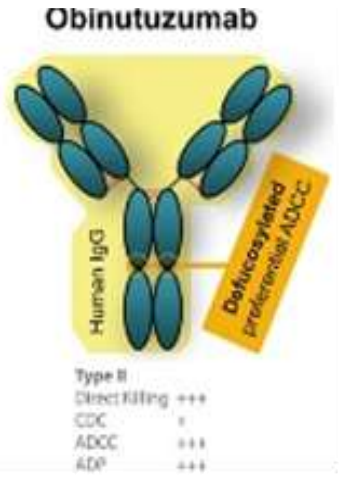
Glauckler JASN 2025 *MCD FSGS* *183 (40 SRNS)* *CR 45% M12 CR 36% M36* *Retro*

After Rituximab 20-30 % CR In SRNS

B-cell targeting therapies : anti CD20



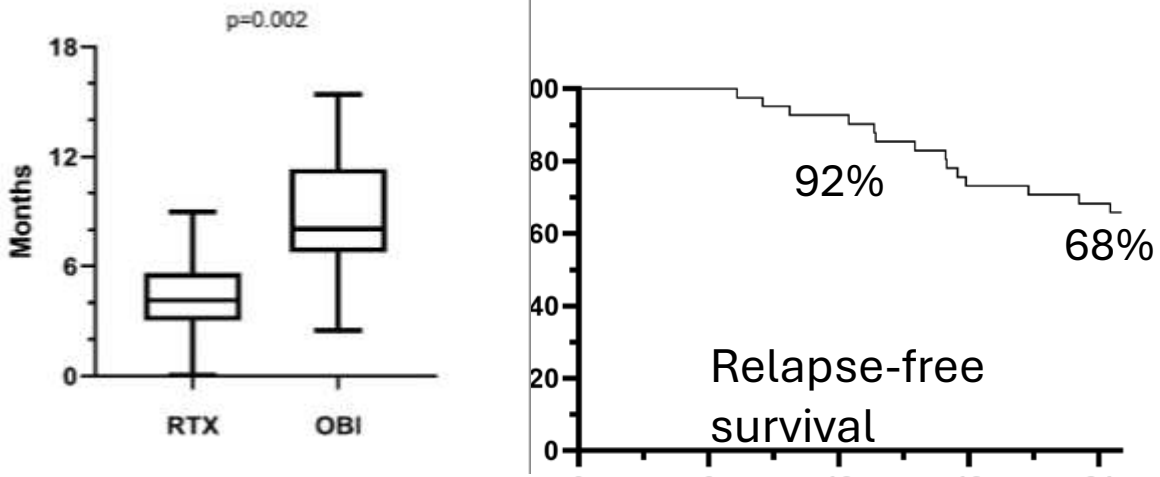




Benz Ped Neph 2004

Deschênes Ped Neph 2020

Obinutuzumab in difficult-to-treat SDNS

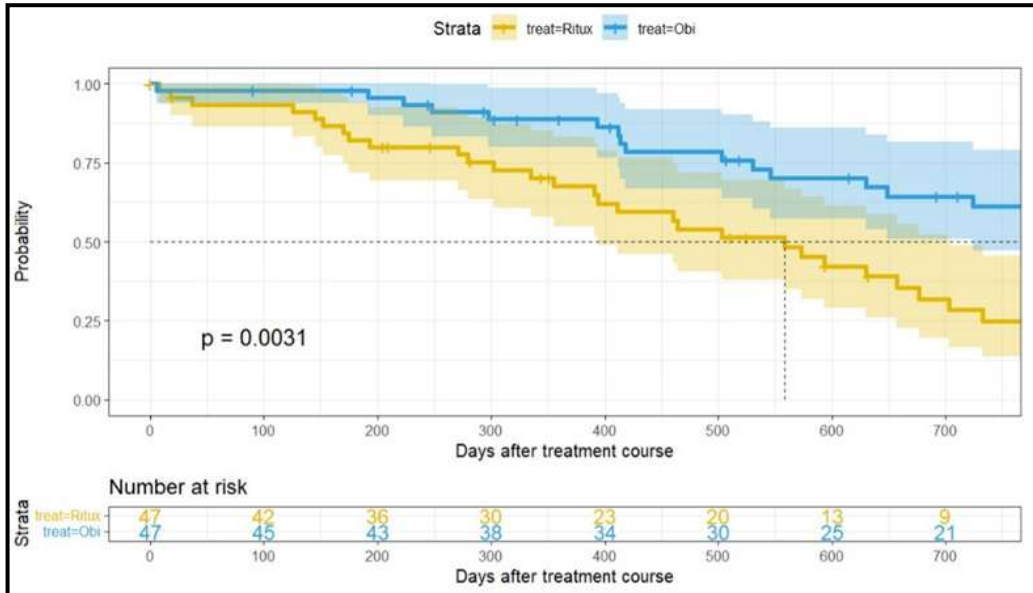


Duration of B-cell depletion

Dossier, CJASN 2023

RCT: OBIRINS in 88 FR/SDNS
RTX 375mg/m^2 vs OBI 300mg/1.73m^2

Dossier, BMJ 2025



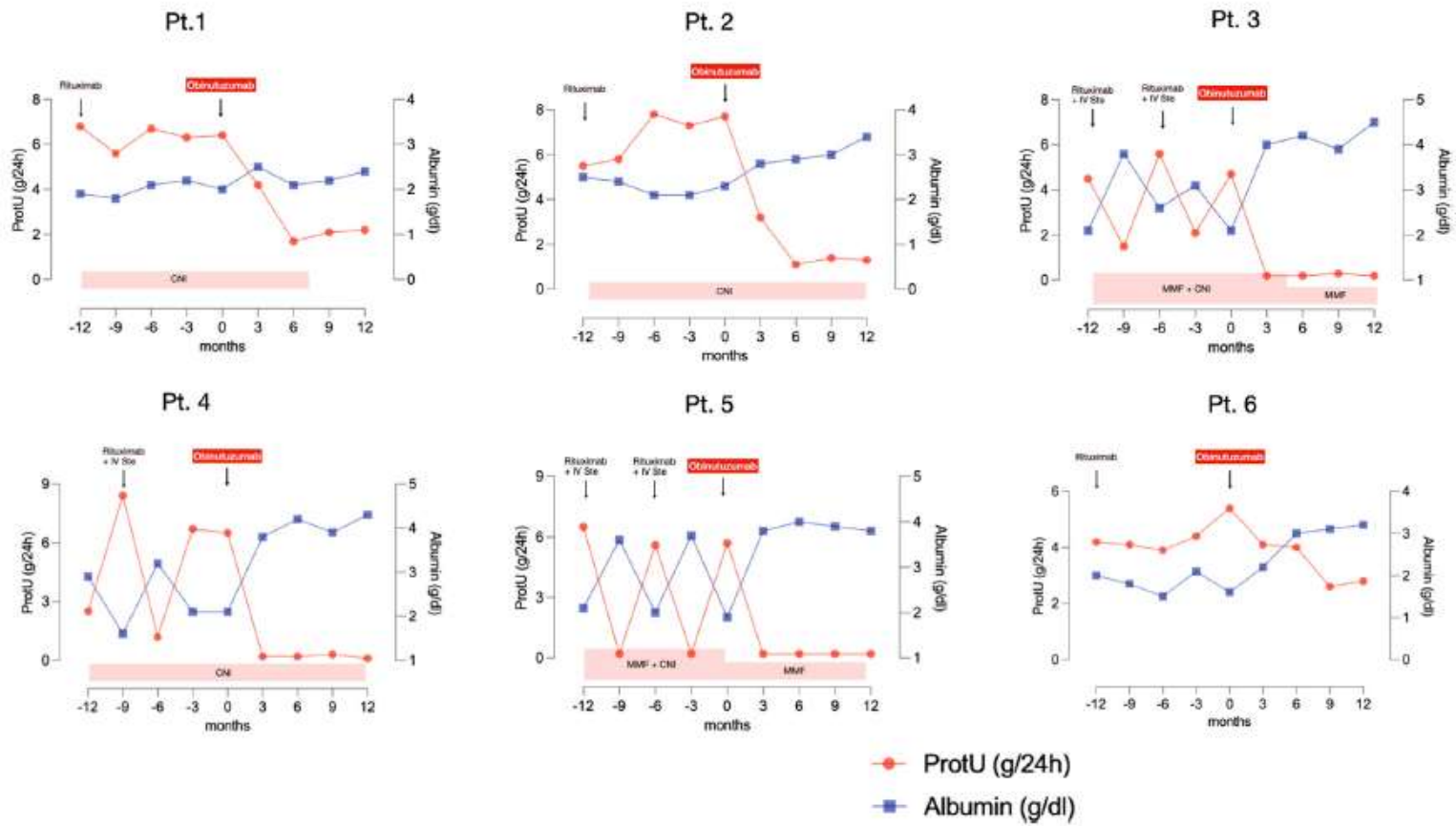
Propensity score Matching
47 **OBI** et 47 **RITUX**

Badea - Hogan, unpublished

Obinutuzumab in SRNS

- ✓National study – Italy
- ✓N=6 , Resistant to CNI-MMF-RTX
- ✓OBI D0-D15 375mg/1.73m^2
- ✓Outcome : CR < 0.3 g/d, PR 0.3-3.5g/d

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age, sex, race	16y, male, caucasian	13y, male, caucasian	17y, female, caucasian	7y, male, caucasian	12y, male, caucasian	24y, female, caucasian
Proteinuria (g/day)	7.8	4.2	6.1	5.7	5.1	6.3
Serum Albumin (g/dl)	2.2	2.0	1.9	2.0	1.7	2.1
Serum Creatinine (mg/dl)	0.9	0.6	0.7	0.5	0.7	0.8
eGFR* (ml/min/ 1.73m²)	112	108	124	132	121	115
Anti-Nephrin Antibodies	Neg	Neg	Neg	Neg	Neg	Neg
N' of previous rituximab courses	1	2	1	2	1	1
Months since last rituximab	11	6	9	6	12	12
Immunosuppressive Regimen	CNI	CNI	CNI, MMF	CNI	CNI, MMF	None
Kidney Biopsy	FSGS	MCD	MCD	NA	NA	MCD

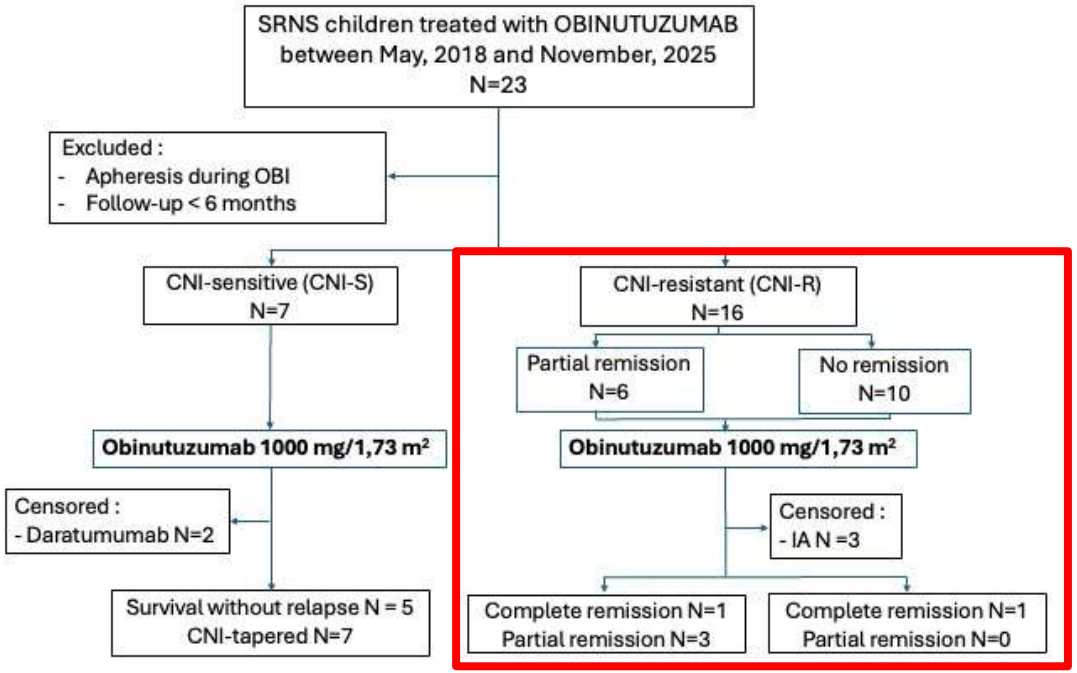


All 6 responded within 3 months : 3 CR and 3 PR, sustained at M12

2025 KIR Angeletti

Obinutuzumab in SRNS

- ✓National Retrospective study – France
- ✓N=16 children,
- ✓1-4 weekly OBI infusion 1g/1.73m
- ✓Outcome : CR, PR, Pu reduction %



Baseline characteristics	CNI-R (N = 16)
Male (N, %)	11 (69%)
Subsaharian/Caribbean (N, %)	11 (69%)
Age at diagnosis, years (median, IQR)	13,51 (10,39-15,06)
Biological parameters at diagnosis	
Albumin, g/L (median, IQR)	15,5 (11,5-26,5)
UPCR, g/mmol (median, IQR)	1,02 (0,57-1,2)
eGFR , ml/min/1.73 m^2 (median, IQR)	84,96 (68-107)
Serum creatinine, µmol/L (median, IQR)	73 (54,75-92)
Renal histology	
MCD (N, %)	4 (25%)
FSGS (N, %)	12 (75%)
Genetics	
APOL1 risk variants (N, %)	8 (50%)
Prior therapies	
Calcineurin inhibitor (N, %)	16 (100%)
Rituximab (N, %)	6 (37%)
Ofatumumab (N, %)	1 (6%)
Daratumumab (N, %)	1 (6%)
Immunoadsorption (N, %)	3 (18%)

All were primary SRNS

3/16 had a prior CR after 10, 16, 19m CNI

Age at obinutuzumab, years (median,	
Duration of CNI for this flare, months	9.8 (5.1-12)

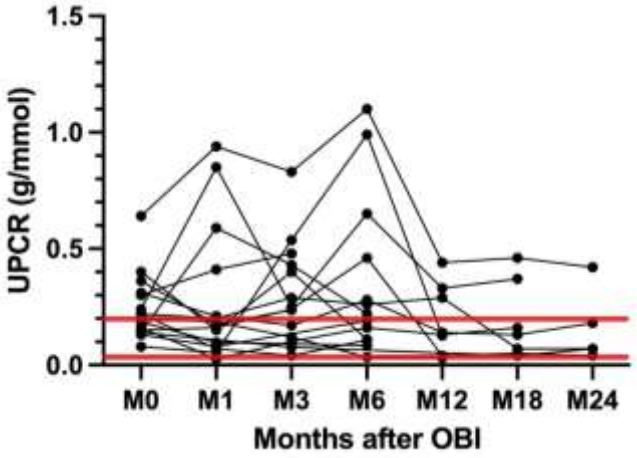
S. Damou, unpublished

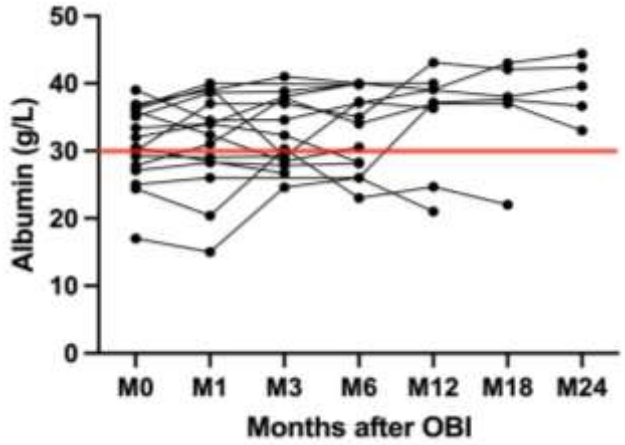
Obinutuzumab in SRNS

- ✓National Retrospective study – France
- ✓N=16 children,
- ✓1-4 weekly OBI infusion 1g/1.73m
- ✓Outcome : CR, PR, Pu reduction %

Biology (median, IQR)	At OBI (16)	M3 (16)	M6 (16)	M12 (14)
eGFR ml/min/1.73m	80 (64-97)	77 (65-88)	90 (74-103)	74 (65-88)
Serum Albumin g/l	31 (28-36)	31 (28-38)	34 (28-37)	37 (33-39)
UPCR g/mmol	0.21 (0.15-0.30)	0.25 (0.13-0.42)	0.22 (0.11-0.46)	0.13 (0.10-0.30)

Outcome	N=6 PR at baseline	N=10 No response
Complete Remission	1/6 at M15	1/10 at M6
Partial Remission		0





Outcome	M3	M6
UPCR reduction > 30%	5/16	6/16
UPCR reduction > 50%	1/16	2/16

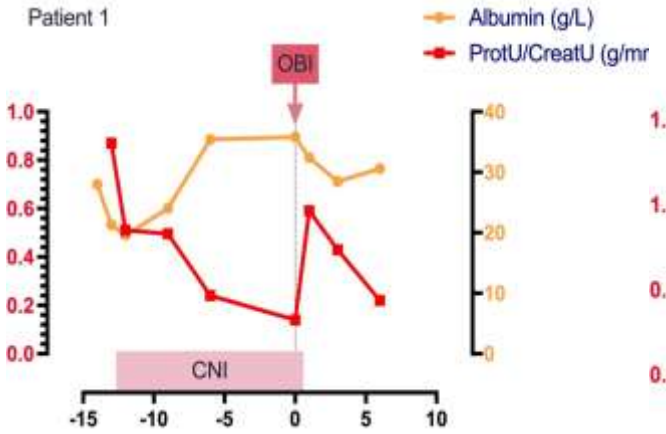
2/16 **(12.5%) complete remission**

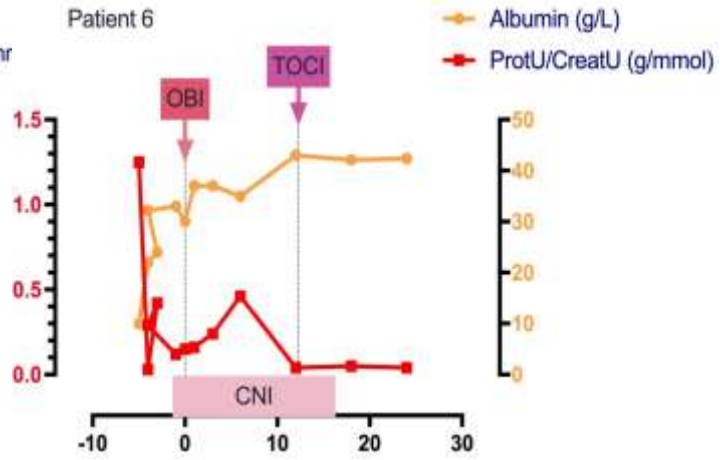
No response on UPCR in 10/16 **at M6 (62.5%)**

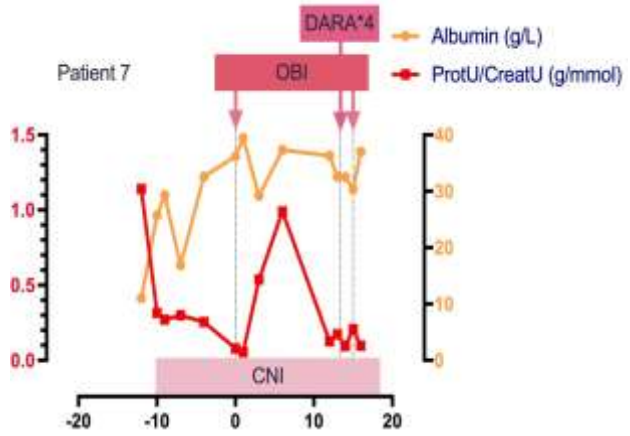
S. Damou, unpublished

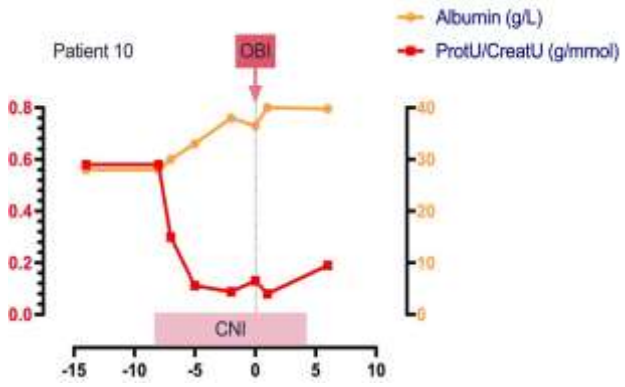
Obinutuzumab in SRNS

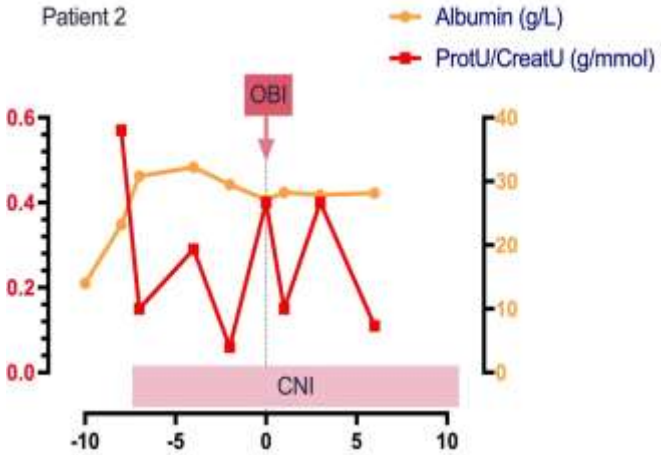
✓N=16 children,
✓1-4 weekly OBI infusion 1g/1.73m
✓Outcome : CR, PR, Pu reduction %

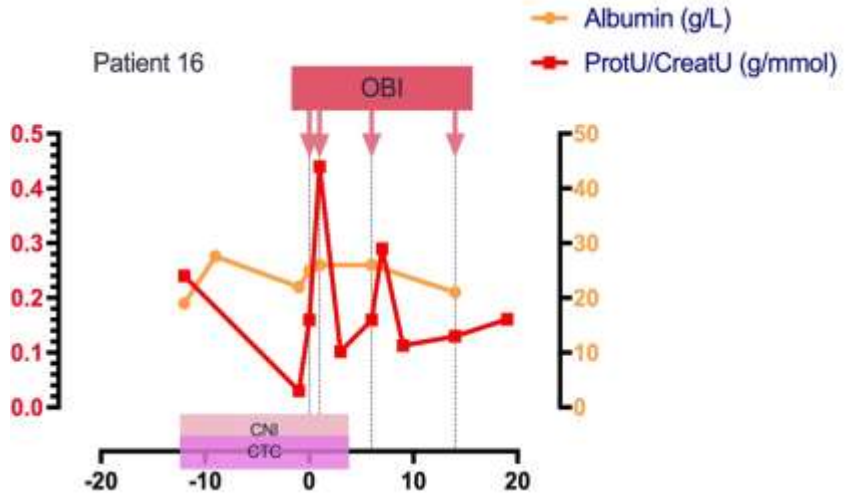












S. Damou, unpublished

Ofatumumab in SRNS

✓**RCT -** NCT02394106
✓Resistant to > 6m CNI-MMF +/- RTX
✓ OFA 1x 1500mg/1.73m² vs placebo
✓Outcomes : CR < 0.2g/g at M3
PR < 2g/g or %change UPCR > 50%

Table 2 Study follow-up. Clinical parameters relative to primary and secondary end points of the study. *CsA*, cyclosporine A; *FK*, tacrolimus; *MMF*, mycophenolate mofetil; *CP*, cyclophosphamide; *RTX*, rituximab; *PEX*, plasmapheresis; *MSC*, mesenchymal stem cells; *MCD*, minimal change disease; *FSGS*, focal-segmental glomerulosclerosis; *IgM Mes*, mesangial proliferative glomerulonephritis with IgM deposition; *PD*, peritoneal dialysis; *ESRF*, end-stage renal failure; *Tx*, renal transplant; *GFR*, glomerular filtration rate calculated by the revised Shwartz formula (JASN March 2009)

Pat ID	Age		Glucocorticoid-sparing agent used previously	Renal biopsy	Urinary protein-to-creatinine ratio (mg/g)				GFR (ml/min per 1.73 m²)		Serum albumin (g/dl)		CD19 (%)		Status of disease
	At onset	At enroll			T_0	3 months	6 months	12 months	T_0	12 months	T_0	6 months	T_0	3 months	36 months
Ofatumumab group															
1	1.9	3.8	*CsA, FK, MMF, CP, PEX*	*MCD*	*10.250*	*11.200*	*12.451*	*8.891*	82	143	1.61	1.28	13.2	1.1	Dead[ff]
2	16.6	18.1	*CsA, MMF*	*MCD*	*10.212*	*10.500*	*10.212*	*20.961*	49	12	1.62	1.93	NA	6.9	ESRF
3	7.5	17.6	*FK*	*FSGS*	*9.488*	*7.380*	*6.267*	*5.841*	103	100	3.13	3.05	9.1	1.3	Active
4	4.7	8.6	*CsA, FK, RTX*	*FSGS*	*7.559*	*7.150*	*6.132*	*4.326*	65	47	1.98	2.13	17.6	6.4	Active
5	7.7	16.3	*CsA, FK, RTX*	*FSGS*	*1.661*	*2.200*	*2.925*	*2.925*	37	6	3.3	3.14	13.0	3.1	PD
6	4.6	5.0	*CsA, FK*	*FSGS*	*3.797*	*3.500*	*3.515*	*3.540*	19	21	3.66	3.7	17.1	3.2	Active
7	5.4	9.6	*CsA, FK, MMF, Cycloph.*	*FSGS*	*3.455*	*3.600*	*4.705*	*3.483*	80	86	2.60	2.60	18.0	2.1	Active
								*ns***		*ns**		*ns**		***P = 0.03****	
Placebo group															
8	10.8	18.0	*CsA, FK*	*IgM Mes*	*9.930*	*8.100*	*5.167*	*5.509*	102	63	2.56	1.96	17.0	19.9	Tx
9	15.5	16.3	*CsA, FK*	*MCD*	*34.016*	*32.340*	*36.661*	*31.541*	39	22	1.83	1.60	9.8	NA	Tx
10	14.8	15.9	*CsA, FK*	*IgM Mes*	*11.931*	*12.010*	*14.048*	*12.672*	137	157	2.19	2.36	6.7	NA	Active
11	12.1	13.2	*FK, MMF, MSC*	*FSGS*	*7.977*	*8.200*	*15.276*	*11.200*	41	17	1.98	1.80	17.2	NA	PD
12	4.9	7.8	*FK*	*FSGS*	*4.879*	*4.950*	*4.270*	*8.515*	155	168	1.85	1.72	10.1	14	Active
13	2.4	5.1	*CsA, FK, MMF, RTX*	*MCD*	*7.172*	*6.850*	*5.174*	*7.361*	146	117	1.58	1.01	9.6	12	Active
								*ns***		*ns**		*ns**		*ns**	

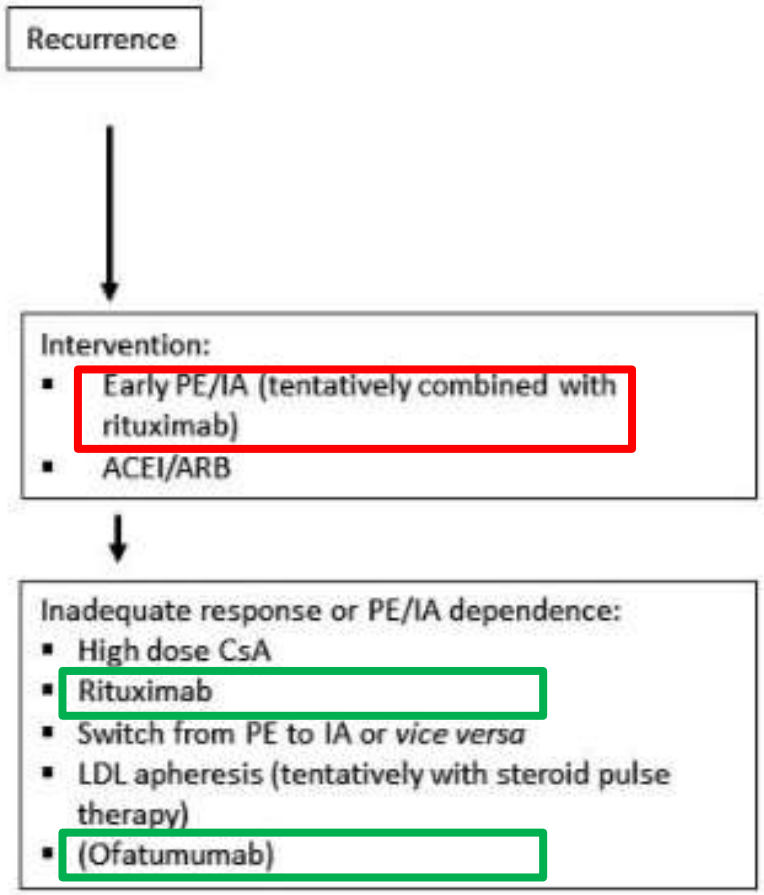
Interrupted after 13/50 inclusions : All 13 children remained nephrotic. ESKD in 5 children.

Ravani Ped Neph 2020

Summary on anti CD20

- Rituximab and Obinutuzumab **may be** effective in refractory NS
- OBI offers a **higher degree of B-cell depletion**
- Need for larger multiethnic **prospective studies**
- Need for **biomarkers** to better understand **patient heterogeneity** and predict treatment response
- Role and **contribution** to the disease of **different subsets** of B-cells
- Issues :
  - depletion in tissue ?
  - Depletion of Atypical B cells ?
  - How to achieve sustained remission / immune recovery without remergence of autoreactivity ?

Post-transplant recurrence



Weber & CERTAIN group, Ped transplant 2021

meeting report www.kidney-international.org

Post-transplant recurrence of focal segmental glomerular sclerosis: consensus statements

Rupesh Raina[1,2,31], Swathi Jothi[1,31], Dieter Haffner[3], Michael Somers[4], Guido Filler[5,6,7], Prabhav Vasistha[1],

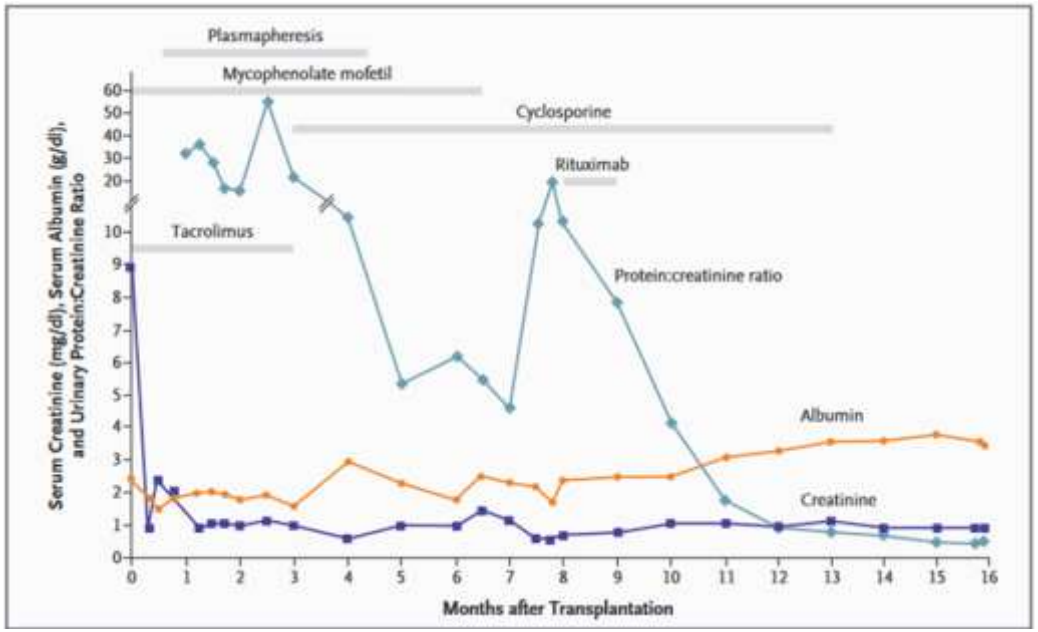
We conducted a meta-analysis of 58 patients across 23 studies and found a total remission rate of 63.8%, a complete remission rate of 48.3%, and a partial remission rate of 15.5%. On performing a subgroup analysis, we noted that age ($P = 0.24$) and rituximab ($P = 0.70$) were not significantly associated with remission. The various doses used in these 23

Clinical practice guidelines

- Therapy with rituximab should be considered in patients with rFSGS who have contraindications to plasmapheresis, or who fail to improve despite treatment with plasmapheresis or immunoadsorption. Rituximab doses ranged from 75 to 3375 mg (median dose, 1500 mg/m^2) (2B).

KI 2023

Rituximab in NS recurrence



Pescovitz NEJM 2006

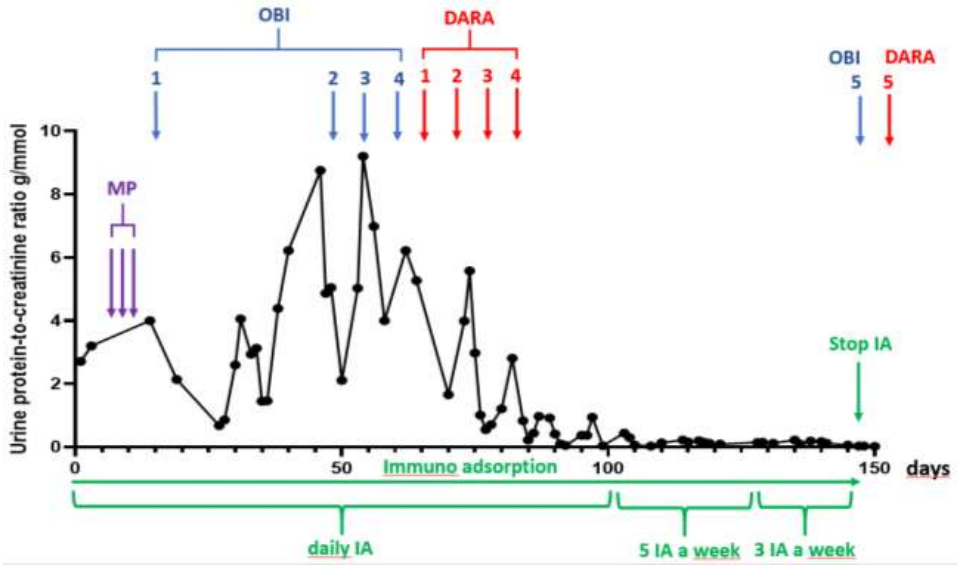
- Multicenter retrospective study, France
- N=19 adults
  - N=6 immediately at recurrence
  - N=10 after failure of initial tt IV-CsA –steroids-PE
  - N=3 relapse at weaning of PE
- **Complete remission 47 % + Partial Rem 16%**
- 50% response in N=10+3 resistant cases
- Sev

Infections	Patient (no. flares)
Bacterial infection, N	
Pyelonephritis	7 (13)
Escherichia coli	6 (11)
Pseudomonas aeruginosa	2 (2)
Febrile neutropenia	2
Sigmoiditis	1
Virus infection, N	
CMV enteritis	1
Chronic viral hepatitis E	1
HSV with cutaneous lesion	1
BK viremia	1
Fungal infection, N	
Extensive dermatophytosis	1

Garrouste Transplantation 2017

Obinutuzumab in NS recurrence

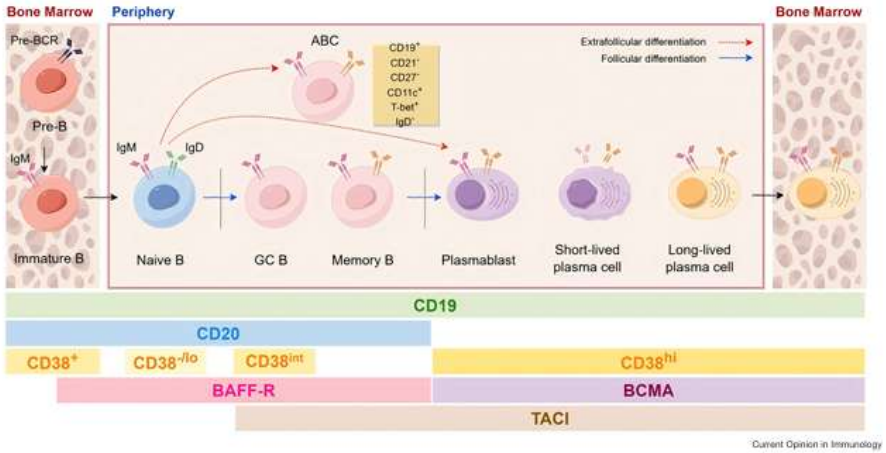
- Always associated to apheresis
- Success **for maintainaing remission after apheresis**
- Less successful to induce remission in non responders



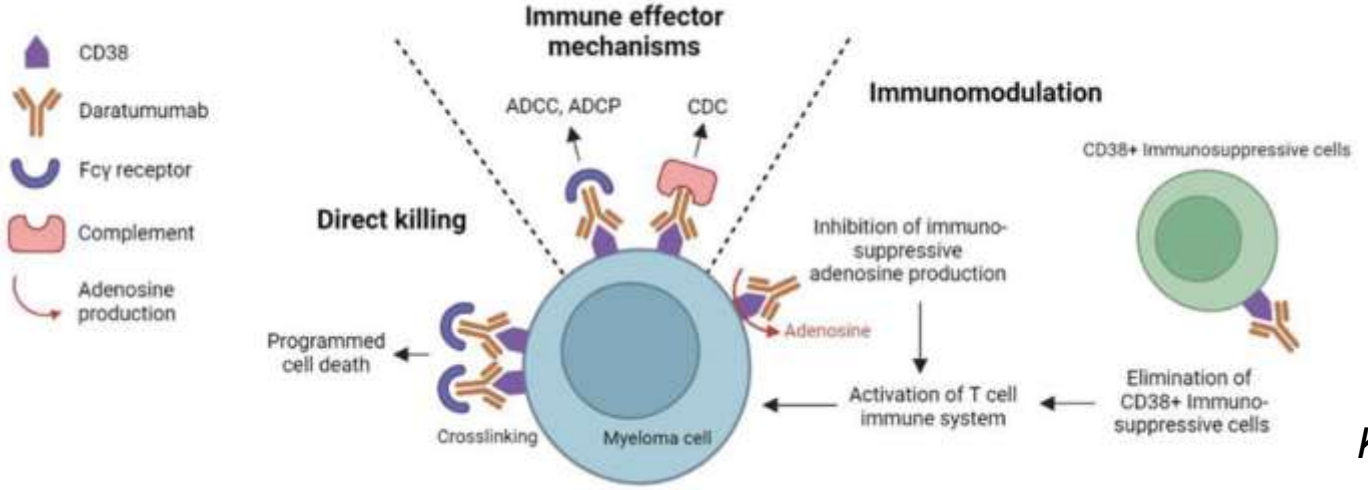
Delbet Ped Transpl 2023

Daratumumab in SRNS

- Humanized anti-CD38 mAb
- CD38 expressed on
  - B lymphocytes and plasma cells
    >> T cells, NK, monocytes-macrophages, dendritic cells
  - other cellules (neurones ..)



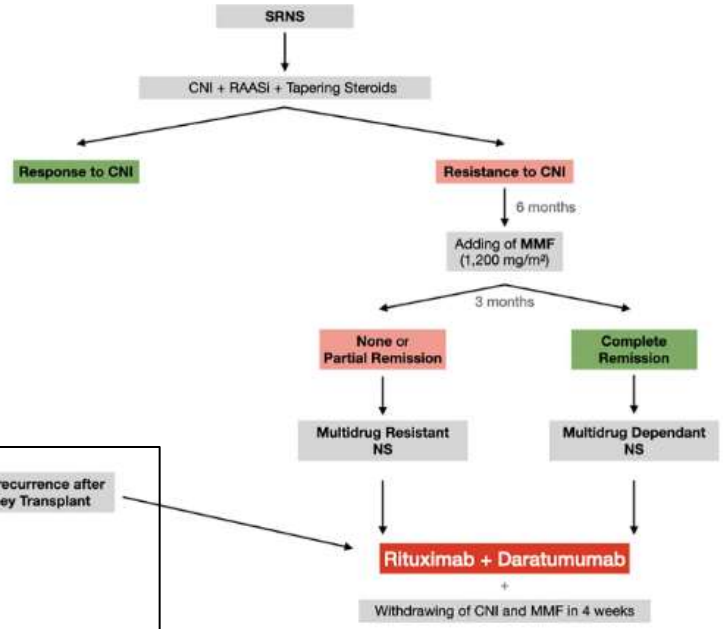
- Mechanisms of action of anti-CD38



Kim, Clin PK, 2023

Daratumumab in SRNS

- **Single group**, phase II Proof of concept, **Dual 1**
- a **before-after clinical trial** testing the superiority of **rituximab plus daratumumab (16 mg/kg**) in **maintaining drug free remission** in patients with **multi-drug dependent** nephrotic syndrome
- NCT05704400



Inclusion criteria
- ✓ 3-24 yrs
- ✓ MD dependant or resistant for at least 6 months
  - > 2 relapses under double ttt (pred, MMF, CNI)
  - Resistance to pred + CNI or MMF
- ✓ Post transplant Recurrence

Main Exclusion criteria
- ✓ RTX or CYC in past 6 months
- ✓ CD20 B < 2.5%
- ✓ eGFR < 60 ml/min/1.73m^2

2023 Front Immunol Ghiggeri

2023 AJT Angeletti
- 5 early NS recurrence
- Resistant to PE & RTX
- Complete remission in 5
- Well tolerated

Daratumumab in SRNS

Multidrug Resistant Nephrotic Syndrome	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age, sex, race	22y, male, caucasian	24y, female, caucasian	21y, female, caucasian	3y, female, caucasian	14y, male, caucasian	17y, male, caucasian	12y, male, caucasian
Proteinuria (g/24H)	4.2	4.5	11	3.1	3.4	3.9	3.7
Serum Albumin (g/dl)	2.2	2.8	1.6	2.7	2.1	2.4	3.1
Serum Creatinine (mg/dl)	1.2	0.7	0.5	0.5	0.7	0.7	0.4
eGFR* (ml/min/1.73m²)	74	92	111	98	102	99	118
N° of previous rituximab courses	2	3	3	0	0	5	0
Months since last rituximab dose	23	19	28	N/A	N/A	24	N/A
Current Immunosuppressive Regimen	CNI, MMF	CNI, MMF	N/A	CNI, MMF	Ste, CNI,	Ste, CNI,	Ste, CNI,
Duration of Current Immunosuppressive Regimen (months)	9	32	15		11	18	6
Age at Disease Onset	10y	12y	11y	18m	12y	8y	4y
Kidney Biopsy	MCD	FSGS	FSGS	N/A	MCD	MCD	FSGS

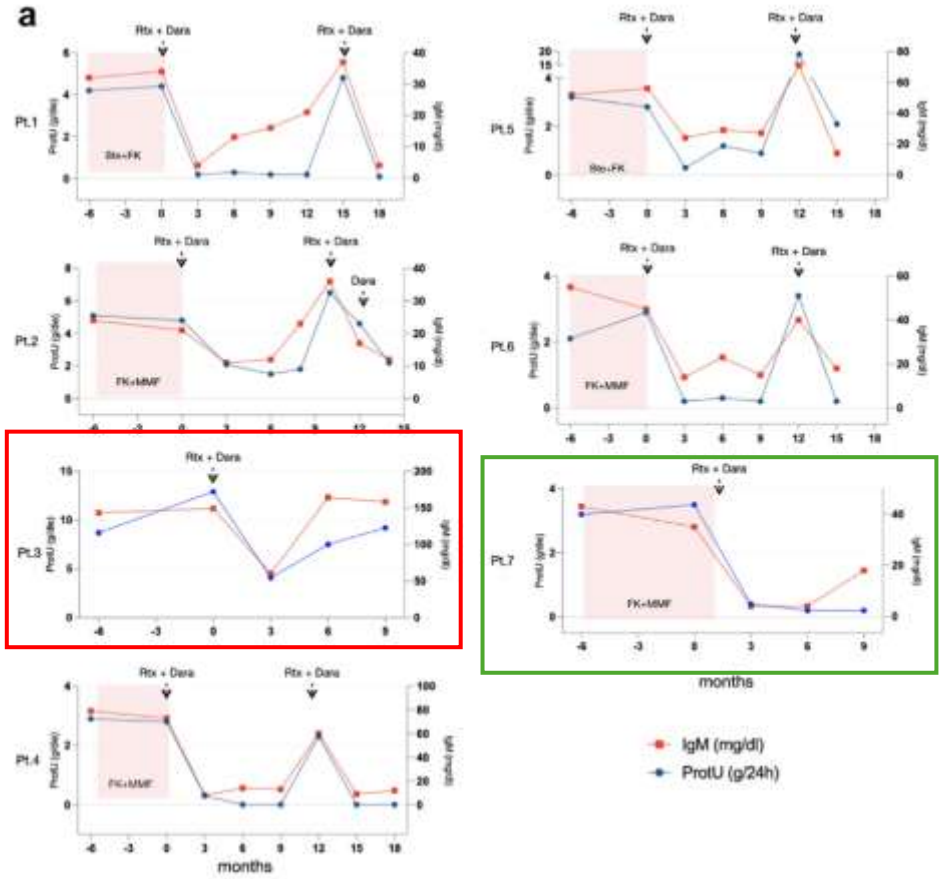
Rituximab + Daratumumab

D0:375 mg/m² D15:16 mg/kg IV

Withdrawing of CNI and MMF in 4 weeks

- N=7
- **4 CR**
- **2 PR**

- F-up 14 m (9-18)
- 5 relapses
- successfully retreated



2024 KIR Angeletti

Aderse events with Daratumumab

- Infusion-related Reaction : **31 %** (mild to moderate)

	Daratumumab	Rituximab
Adverse events infusion related	no. (%)	no. (%)
SAEs (Grade≥3)	0	0
Not SAEs (Grade<3)	0	0
Pruritus	1 (3)	0
Erythema	5 (15)	0
Glottis edema	1 (3)	0
Dyspnea	3 (9)	0
Fever	6 (22)	0
Cough	3 (9)	0
Adverse events within 6 months		
SAEs (Grade≥3)	0	0
Not SAEs (Grade<3)	0	0
Severe low IgG (<300mg/dl) at 6 months	6 (22)	

Prémédication
With Salbutamol

long term follow up

2024 KIR Angeletti

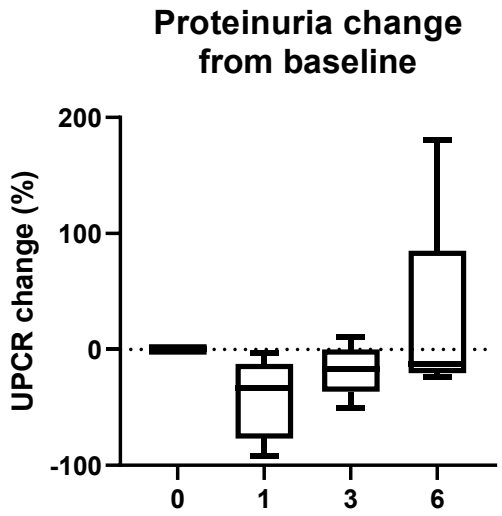
Daratumumab in SRNS

- ✓Monocentric Retrospective study – Robert-Debré
- ✓N=5
- ✓4 weekly OBI infusion 1g/1.73m
- ✓Outcome : CR, PR, Pu reduction %

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age at onset, sex	10.9, male	17.8, male	5.7, male	7.1, male	6.4, male
Ethnicity	caucasian	african	african	caribbean	african
Type of MRNS	primary	primary	primary	primary	secondary
Kidney biopsy	FSGS	FSGS	FSGS	FSGS	nd
Genetics APOL1	negative nd	negative G1G1	negative negative	negative G1G1	nd negative
Prior treatments	Ciclosporin Tacrolimus Rituximab Tocilizumab	Tacrolimus	Ciclosporin MMF Rituximab Ofatumumab	Tacrolimus Rituximab Obinutuzumab Tocilizumab	Tacrolimus Rituximab Obinutuzumab
Prior complete rem	yes IA	no	yes IA	yes tacrolimus	yes tacrolimus

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age at DARA	18.4	18.6	9.9	18.2	13.5
UPCR g/mmol	0.94	0.27	0.65	0.12	0.09
S. albumin g/l	15	27	23	42	33
S. creatinin µmol/l	94	114	72	112	38
eGFR ml/min/1.73m2	67	55	73	59	145
Nb of DARA	4 + 11	4	4 + 4	4	4
CNI	no	tacrolimus	ciclosporin	tacrolimus	tacrolimus
anti CD20	OBI	OBI at M+1	OBI	no	OBI at M+1
Ig supplementation	yes	no	yes	no	yes
other treatment	RAASb	RAASb SGLT2i	RAASb	RAASb	RAASb
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Outcome after M6	No response to Belimumab	PR under IA	CR under IA	PR no IS	PR tacrolimus

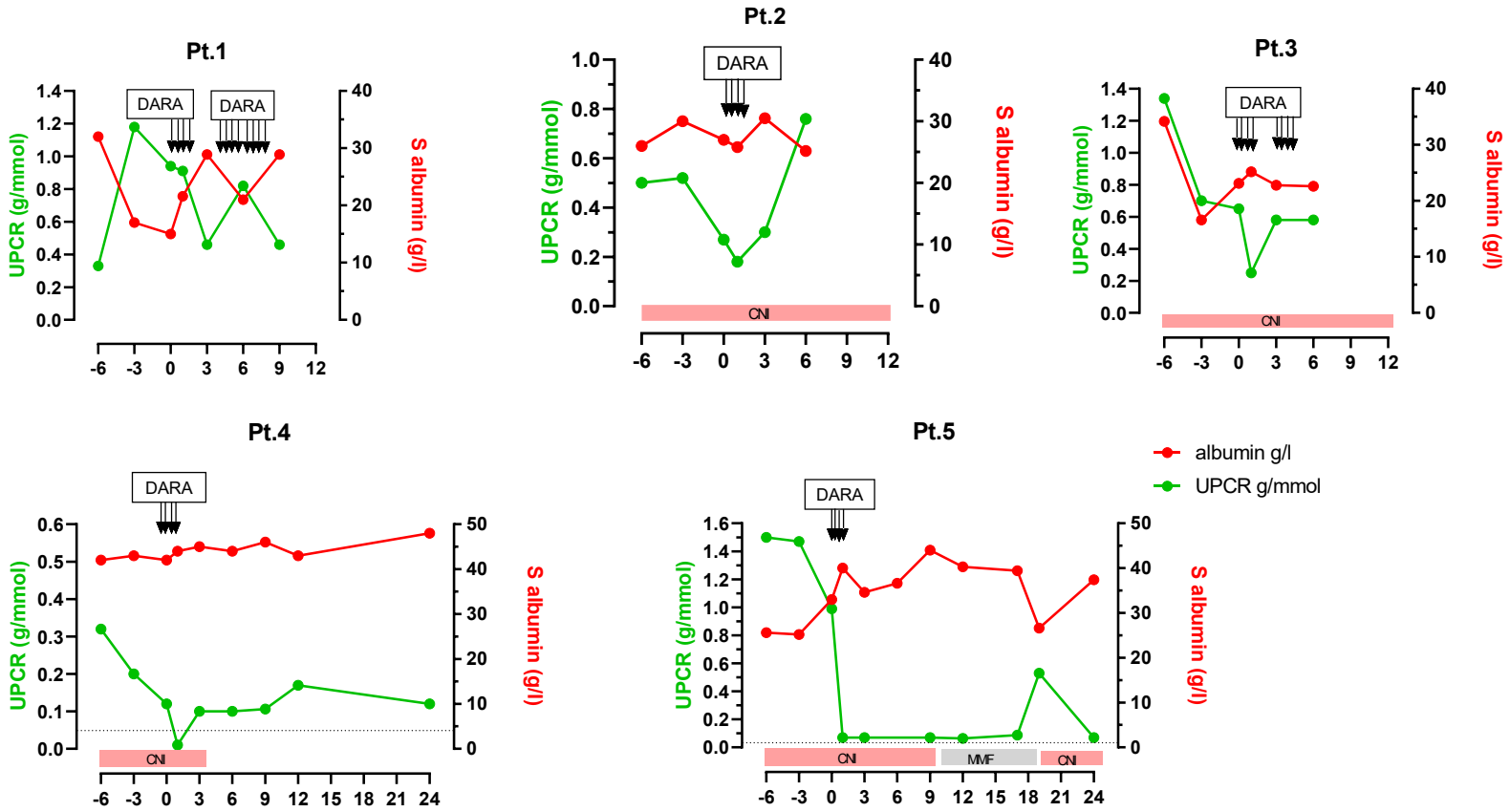
Biology mean ± SD	DARA	M1	M3	M6
eGFR ml/min/1.73m	91	77 (65-88)	90 (74-103)	74 (65-88)
Serum Albumin g/l	28	31 (28-38)	34 (28-37)	37 (33-39)
UPCR g/mmol	0.41	0.25 (0.13-0.42)	0.22 (0.11-0.46)	0.13 (0.10-0.30)



unpublished

Daratumumab in SRNS

✓Monocentric Retrospective study – Robert-Debré
✓N=5
✓4 weekly OBI infusion 1g/1.73m
✓Outcome : CR. PR. Pu reduction %



	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Outcome at last Fup	No response to Belimumab	PR under IA	CR under IA	PR no IS	PR tacrolimus

Unpublished, ongoing national retrospective study

Daratumumab **to maintain remission after apheresis** in MRSN

- Multicenter retrospective, France
- N=7
- **Complete remission under PE/IA, but relapse when spacing out apheresis**

Patient	Sex	INS onset age (yrs)	Renal Histology	CNI-R	Multi-R	Transient Remission	Time to 1st IA since NS onset (months)	N IA sessions to remission	B-cell depletion at 1st IA attempt	cumulated Adverse Events
1	M	5,7	FSGS IgM+	CsA, Tac	MMF, RTX, OFA TCZ, IFN, LVM	yes	47,6	6	OBI	Tacro-diabetes AKI CVC sepsis neutropenia
2	M	6,4	MCD	Tac	MMF	no	10,3	63	OBI	AKI severe HTA CVC-sepsis
3	F	7,9	MCD	CsA, Tac	MMF, RTX	yes	67,4	3	OBI	growth retardation HTA
4	F	5,5	FSGS	Tac, IV CsA	0	no	5,7	6	RTX	
5	M	6,5	MCD	CsA, Tac	0	no	13,5	na	RTX	CVC-sepsis
6	M	5,8	FSGS	Tac	MMF, RTX	yes	10,3	2	RTX	hypoCa - cardiac arrest

- Intensive IA 1-4 DARA 1g/1.73m^2

- Age NS onset 6 yrs
- Time to 1st IA 12 months
- Time to DARA 29 months
- Delay to IA discontinuation : 23d

	PROCEDURE with DARATUMUMAB							OUTCOME at last Follow-up					
Patient	Age at disease onset	Age at DARA	Type of Apheresis	Concomittant Oral IS	Concomittant anti CD20	N weekly DARA	Days to end of apheresis	Months after DARA	Years after NS onset	Treatment	eGFR	S-Alb (g/l)	UPCR (g/mmol)
1	5,7	12,43	IA	Csa	OBI	4	107	27,9	9,0	ACEi OBI-DARA	70	38	0,05
2	6,4	7,81	IA	Pred, Tacro MMF	OBI	4	23	27,1	3,7	Pred, Tacro MMF, LVM	100	40	0,01
3	7,9	14,08	IA	Pred, Tacro MMF	OBI	4	13	24,6	8,3	ACEi OBI	90	33	0,01
4	5,5	6,54	IA	Tacro	OBI	4	18	35,0	3,9	ACEi OBI-DARA	97	43	0,02
5	6,5	9,95	IA	CsA	OBI	4	62	22,0	5,3	ACEi OBI-DARA	104	35	0,04
6	5,8	6,89	IA	Tacro	OBI	1	41	24,1	3,1	ACEi	101	41,6	0,02
7	10,8	12,1	IA	Tacro	OBI	4	94	13,7	2,4	ACEi	118	38,5	0,06

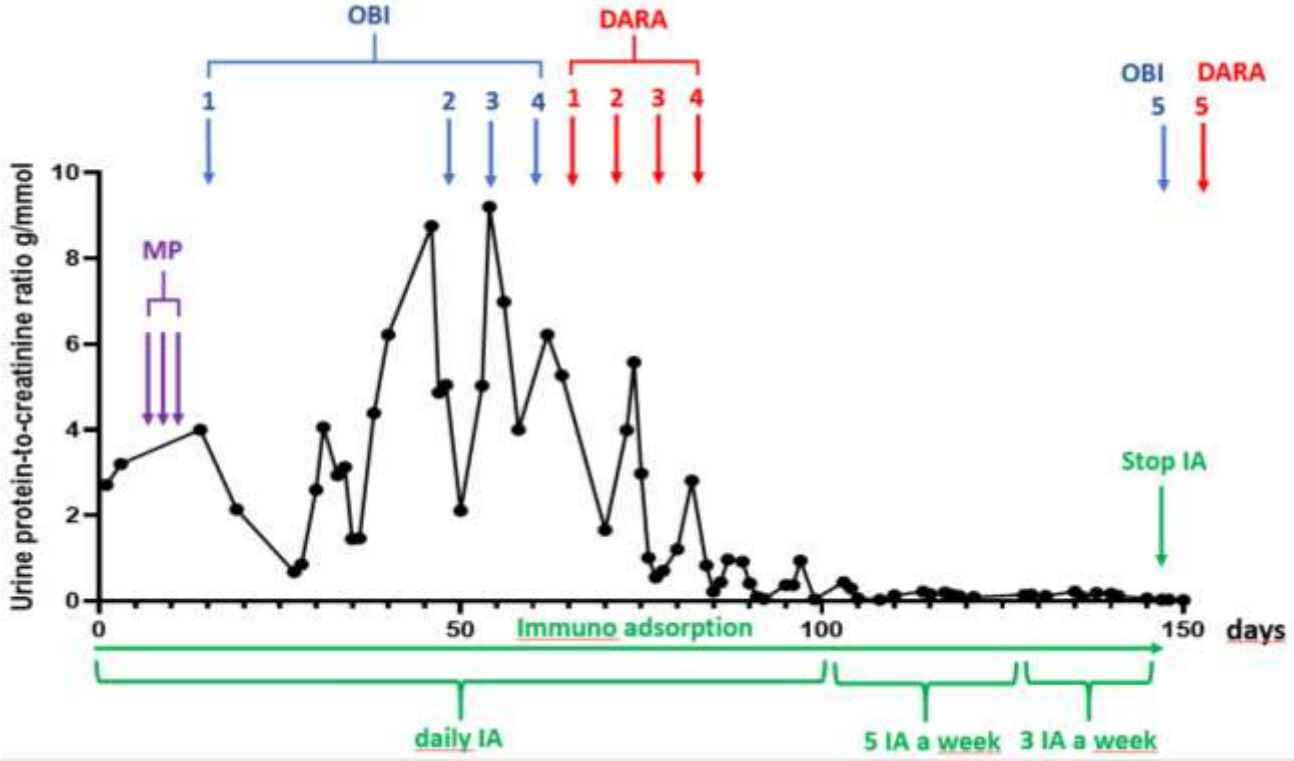
ESPN 2022-OP

Daratumumab **to induce remission** in NS recurrence

- 2-yr girl, African ancestry
- MRNS : MP pulse, IV-CsA, 30 PE
- ESKD, binephrectomy M4

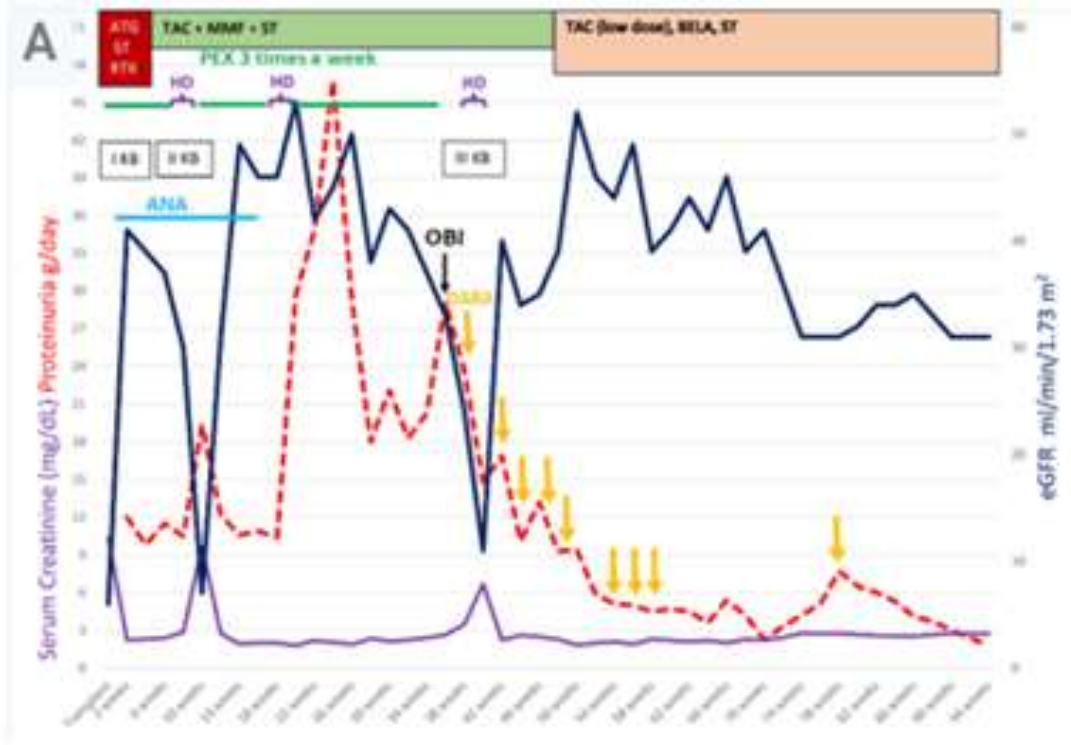
- DD – kidney transplant at 4yrs

- Relapse at H2
- IV-MP, tacro 10-15 ng/ml
- daily IA until D99
- OBI x 4
- Complete Remission with DARA 1g/1.73m^2 x4 weekly

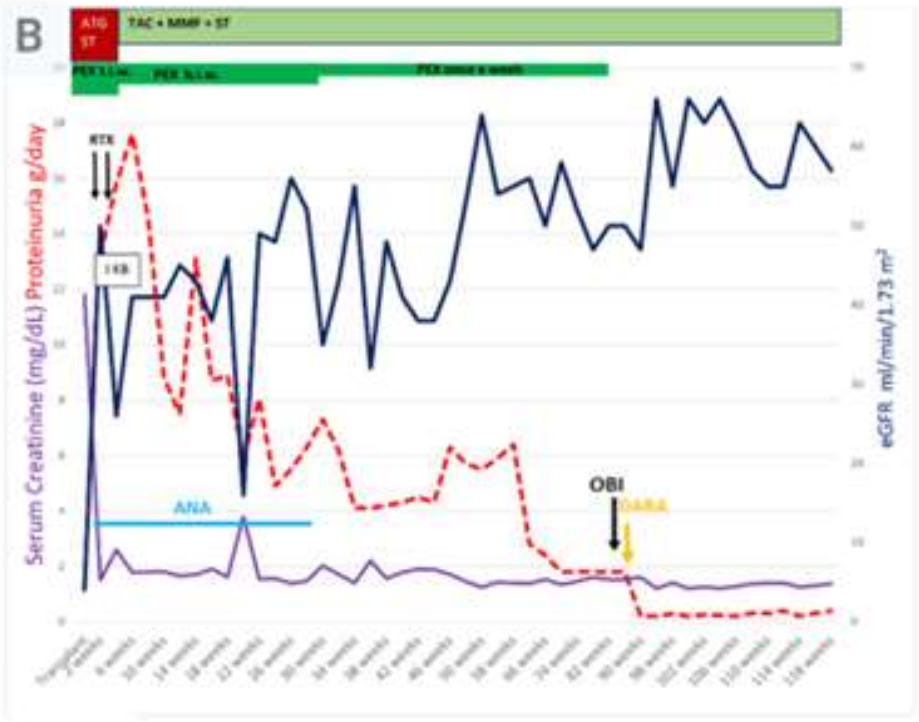


Delbet Ped Transpl 2023

Daratumumab **to induce remission** in NS recurrence



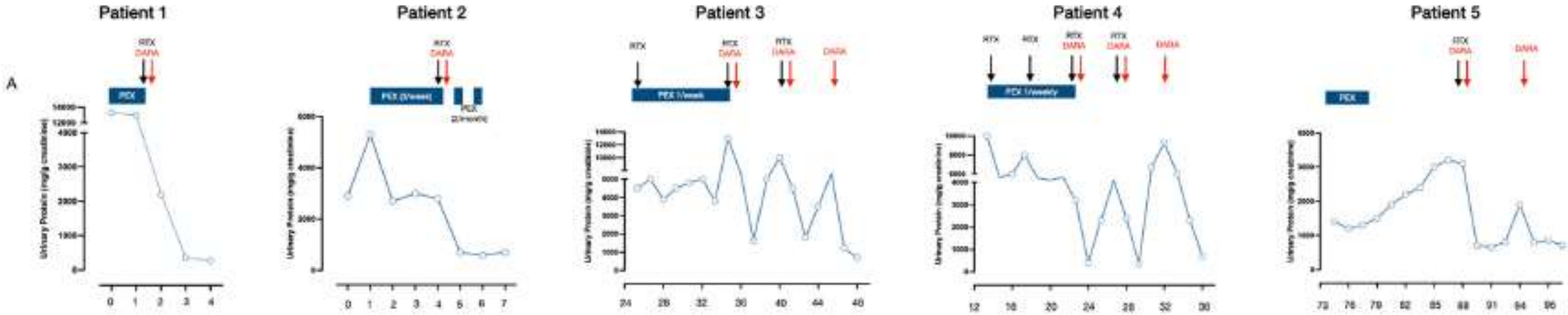
Male, SRNS at 17yrs
Deceased Donor Tx at 21



Female, SRNS at 10yrs
Living Donor Tx at 14

Randone AJT 2024

Daratumumab **to induce remission** in NS recurrence



	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age, sex, race	18 y, female, Caucasian	18 y, female, Caucasian	24 y, male, Caucasian	16 y, male, Caucasian	21 y, male, Caucasian
Time at FSGS recurrence after KT	23 d	3 d	11 d	18 d	21 d
Time of treatment after KT	5 wk	11 wk	3 y	2 y	7 y

Angeletti AJT 2023

Daratumumab **to maintain remission after apheresis** in NS recurrence

- Multicenter retrospective, Fr
- n=4
- Age NS onset 5.9 yrs
- Delay to ESKD 1.4 yrs
- **Complete remission under PE/IA, but relapse when spacing out apheresis**

- Intensive IA/PE
- 1-4 DARA 1g/1.73m^2

	Age		Procedure with DARA					
#	At disease onset	At Kidney Tx (range)	Mths after Tx	Type of Apheresis	Concomittant oral IS	Anti CD20 mAb	N DARA	Days to end of apheresis
1	13,6	16,2 (1)	2,5	IA	Tacro-MMF-Pred	OBI	2	50
2	5,9	12,0 (1)	76,3	IA	Tacro-MMF-Pred	OBI	1	46
3	8,6	12,3 (1)	17,0	EP	CsA-MMF-Pred	OBI	4	41
4	5,1	20,0 (2)	1,7	IA	CsA-MMF-Pred	RTX	4	33

	Outcome at last Follow-up					
#	Months after DARA	Months after NS onset	Treatment	eGFR	S-Alb g/l	UPCR g/mmol
1	20,5	23	Tacro-MMF-Pred- OBI-DARA	78	45	0,02
2	11,4	87,7	Tacro-MMF-Pred- OBI-DARA	39	42	0,03
3	19,7	36,7	CsA-MMF-Pred	52	45	0,01
4	19,5	21,1	Tacro-MMF-Pred-RTX	ESRD*	28	1

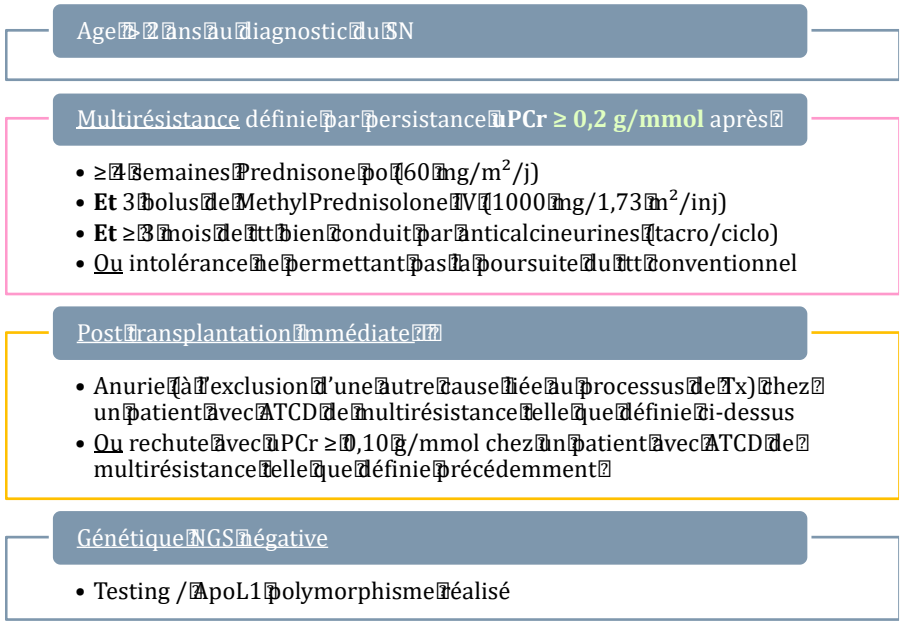
* Graft loss on Acute T-cell Mediated Rejection because of non observance

ESPN 2023-OP

PIANO

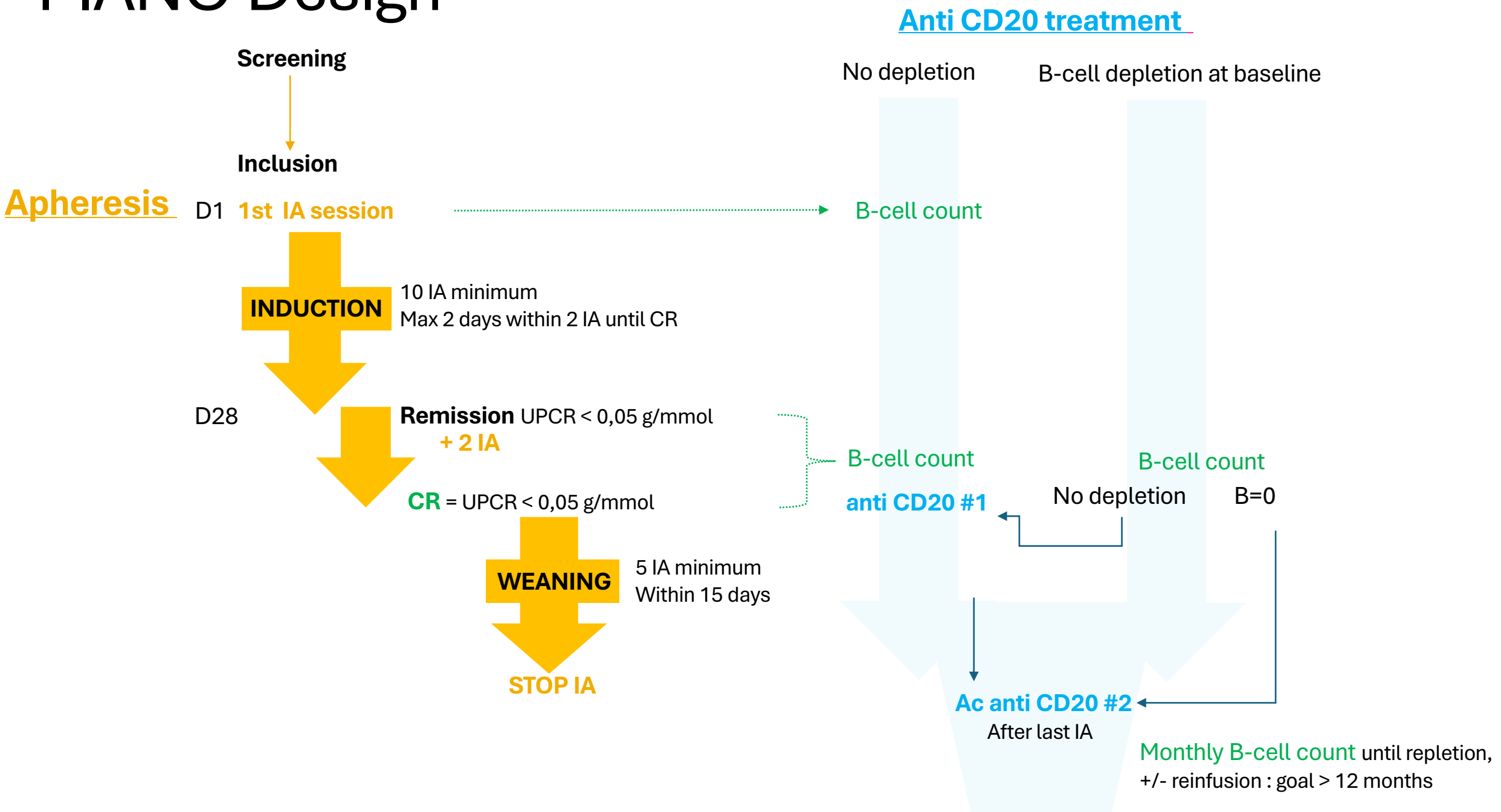
Protocole with **I**mmuno**A**dsorption in multiResistant **N**S combined to **O**binutuzumab or rituximab and daratumumab

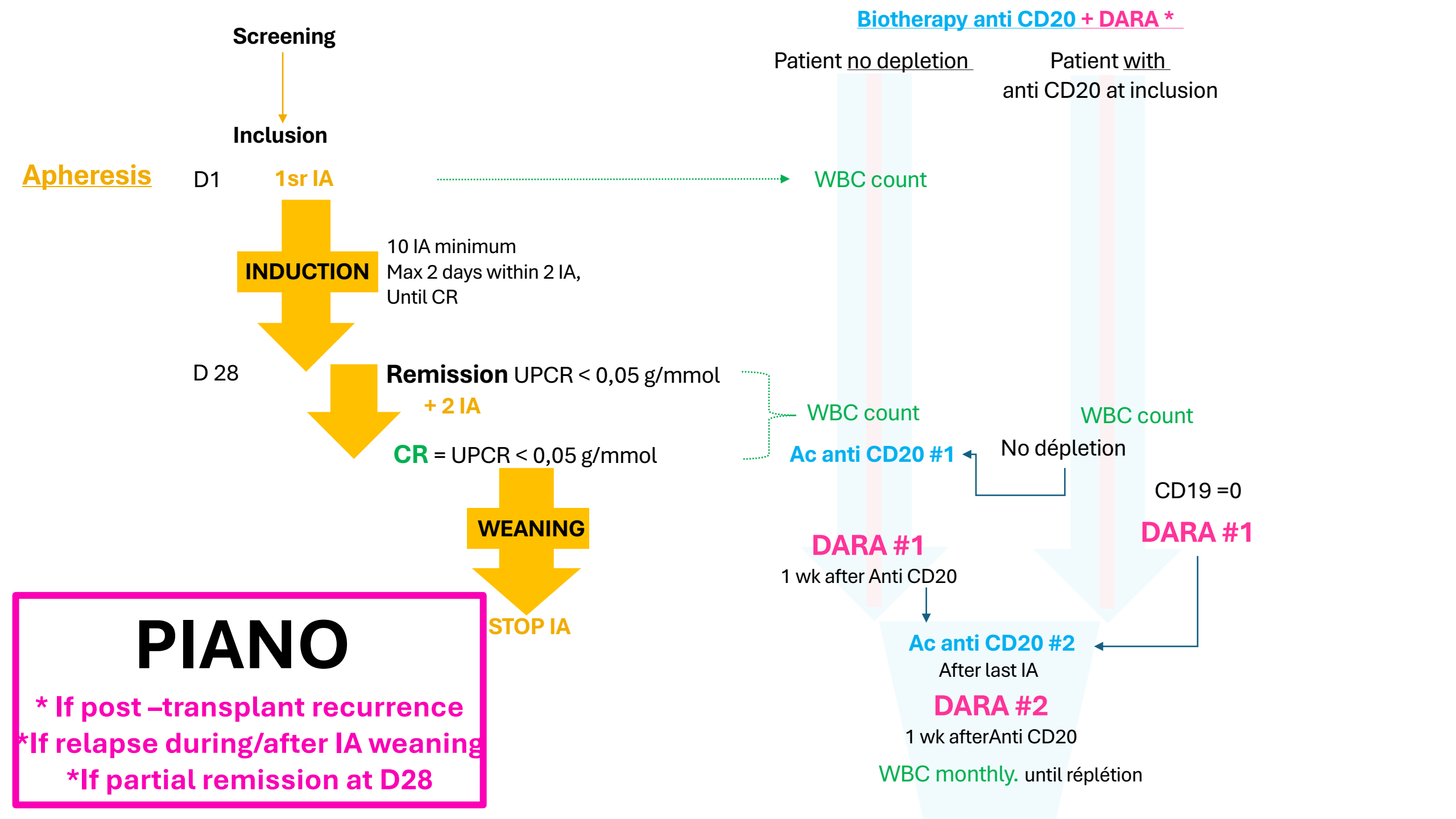
- Multicentric prospective cohort study
- Inclusion criteria



- Primary Objective
  - Rate of complete & partial remission at D28
- Secondary Objectives
  - Tolerance of IA
  - Rate of sustained remission after IA discontinuation / anti CD20
  - Rate of sustained remission after IA discontinuation /Anti CD20 & CD38
  - Biobanking

PIANO Design

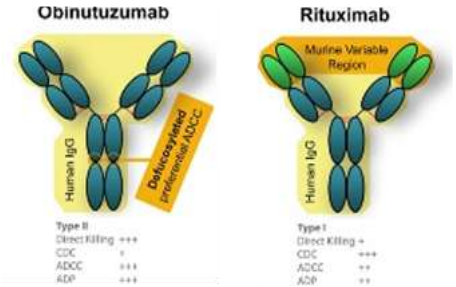



Screening
Inclusion
Apheresis
D1
1sr IA
INDUCTION
10 IA minimum
Max 2 days within 2 IA,
Until CR
D 28
Remission UPCR < 0,05 g/mmol
+ 2 IA
CR = UPCR < 0,05 g/mmol
WEANING
STOP IA
Biotherapy anti CD20 + DARA *
Patient no depletion
Patient with
anti CD20 at inclusion
WBC count
WBC count
Ac anti CD20 #1
No dépletion
WBC count
CD19 =0
DARA #1
1 wk after Anti CD20
DARA #1
Ac anti CD20 #2
After last IA
DARA #2
1 wk afterAnti CD20
WBC monthly. until réplétion
PIANO
* If post –transplant recurrence
*If relapse during/after IA weaning
*If partial remission at D28

B-cell targeted biotherapy

Anti CD20 mAb = systematic

- At CR (UPCR < 0.05 g/mmol + 2 IA)



- Rituximab or Obinutuzumab 1g/1.73m^2
- Delay of 24h before next IA
- Duration of B-cell depletion > 12m
- Monthly monitoring of B-cell count
- Oral IS withdrawal within 3-6 m (except transplant patient)

Anti CD38 mAb = if :

- If Partial remission at D28 (0.05-0.20 g/mmol)
- If relapse during / after IA weaning
- If post-transplant recurrence in a patient treated with IA –antiCD20 on native kidney

- Daratumumab 1g/1.73m^2

When to use Daratumumab ?

- ✓ Post-transplant recurrence with no response to apheresis
- ✓ Post-transplant recurrence responsive but dependent on apheresis
- ✓ MRNS with partial response to apheresis
- ✓ MRNS responsive but dependent on apheresis

But still a lot of questions

- ✓Preventing post-transplant recurrence ?
- ✓in CNI-R on native kidneys
  - Before apheresis ?
  - Alone or only combined to anti CD20 ?
- ✓Which regimen ? IV ou SC , 1 -4 – 8 injections ? +/- maintenance ttt ?
- ✓hypoIgM, prolonged (definitive ?) hypoIgG in children

When to use RTX/OBI ?

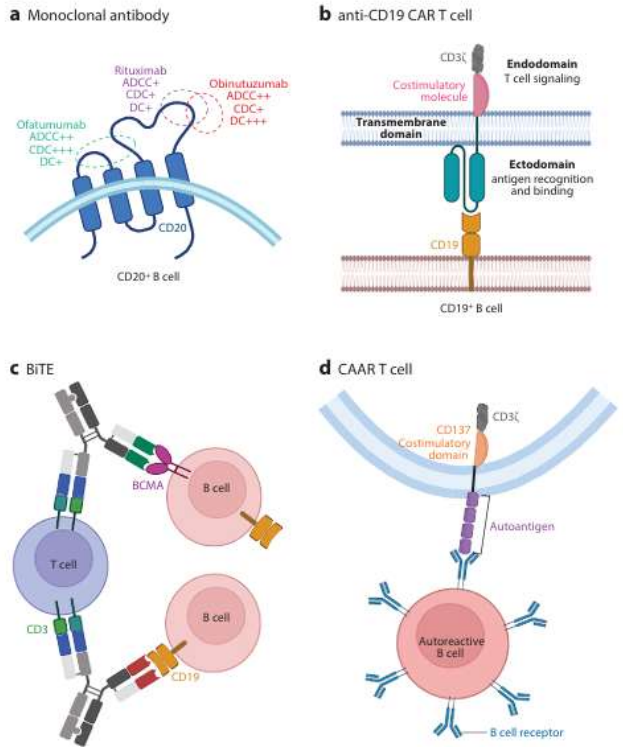
Obinutuzumab Approval in SD/FRNS in 2026

- Consider in **refractory NS after 6 months CNI** :
- **Partial response** (albuminemia > 30 g/l, UPCR > 2g/g)
  - ✓ OBI
  - +/- DARA

- **No response** or albuminemia < 30g/l)
  - Central line for intensive apheresis, maintain high dose CNI
  - ✓OBI at remission
  - ✓If no response at D28 or relapse after remission : DARA
  - ✓Reinfusion of OBI + DARA after apheresis discontinuation, and for 12-18 months

Future perspectives : emerging B-cell targeted ttt

- Bispecific T cell engagers targeting B cells and plasma cells
- Selective depletion of the autoreactive B-cells



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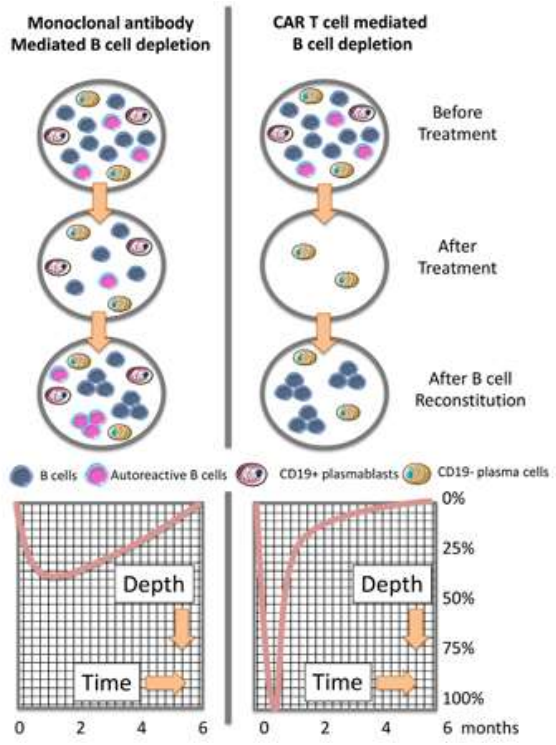

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Hôpital universitaire
mère-enfant
Robert-Debré

Thank you for your attention

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claire.dossier@aphp.fr

Les RDV du SNI

Les RCP SNI pédiatrique : 1er Jeudi / 2 mois à 14h

adulte : mercredi /mois à 14h30

Journée scientifique CRMR SNI : mardi 9 juin 2026