Immunomonitoring du Rituximab

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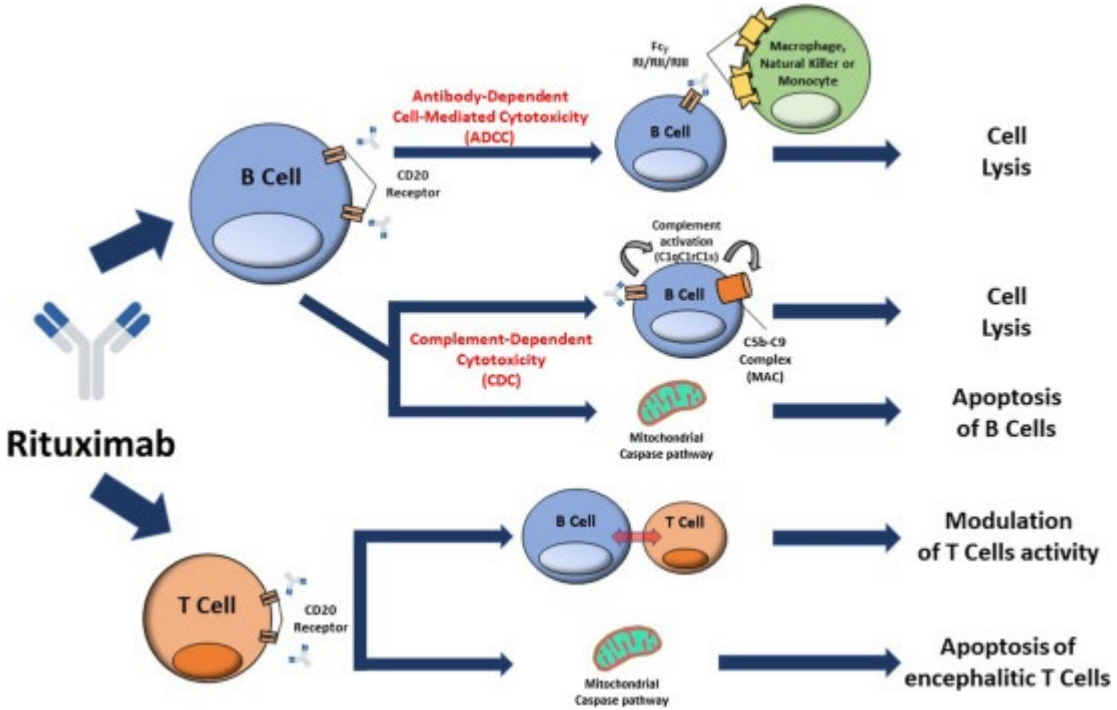
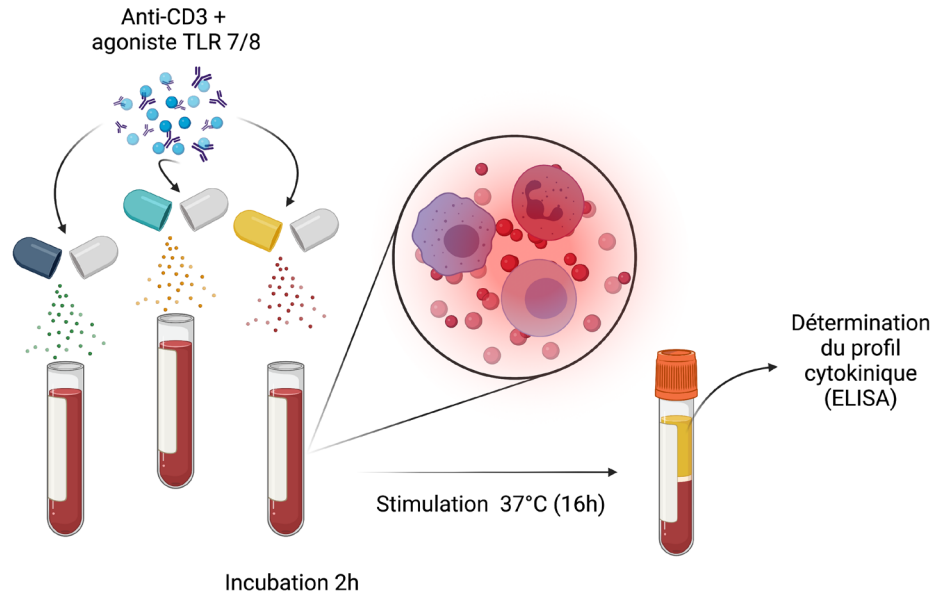
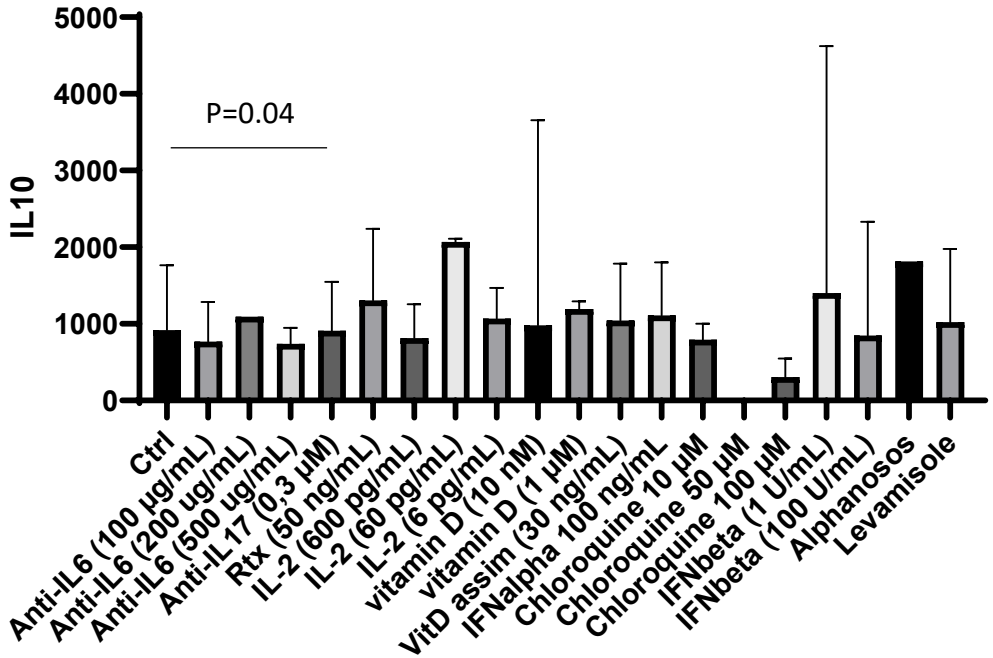
CRMR Syndrome Néphrotique Idiopathique
LBMR Exploration des Syndrome Néphrotiques

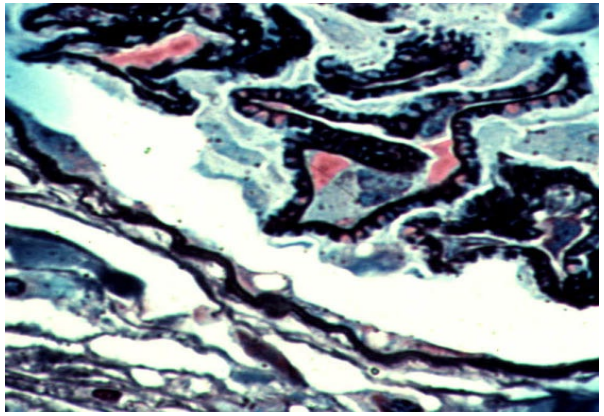
Rituximab


Rituximab
B Cell
CD20 Receptor
Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC)
Macrophage, Natural Killer or Monocyte
Cell Lysis
Complement-Dependent Cytotoxicity (CDC)
Complement activation (C1qC1rC1s)
C5b-C9 Complex (MAC)
Cell Lysis
Mitochondrial Caspase pathway
Apoptosis of B Cells
T Cell
Modulation of T Cells activity
Apoptosis of encephalitic T Cells

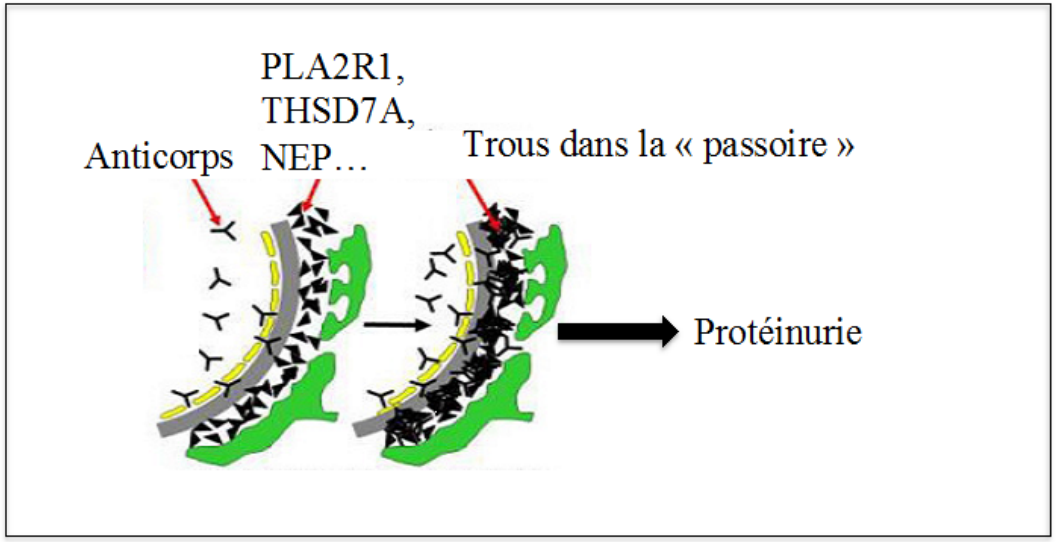

Anti-CD3 + agoniste TLR 7/8
Incubation 2h
Stimulation 37°C (16h)
Détermination du profil cytokinique (ELISA)


IL10
5000
4000
3000
2000
1000
0
P=0.04
Ctrl
Anti-IL6 (100 µg/mL)
Anti-IL6 (200 ug/mL)
Anti-IL6 (500 ug/mL)
Anti-IL17 (0,3 µM)
Rtx (50 ng/mL)
IL-2 (600 pg/mL)
IL-2 (60 pg/mL)
IL-2 (6 pg/mL)
vitamin D (10 nM)
vitamin D (1 µM)
VitD assim (30 ng/mL)
IFNalpha 100 ng/mL
Chloroquine 10 µM
Chloroquine 50 µM
Chloroquine 100 µM
IFNbeta (1 U/mL)
IFNbeta (100 U/mL)
Alphanosos
Levamisole

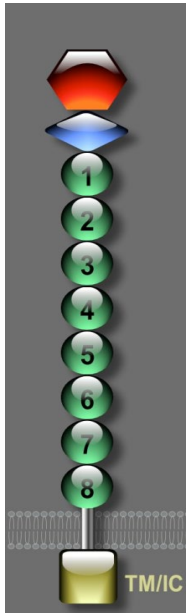
Immunopathologie des GEM



- Maladie auto-immune rare :
  1,3 cas pour 100 000
- H>F après 50 ans
- 1ère cause de syndrome néphrotique de l'adulte

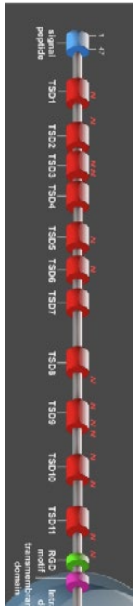


PLA2R1 70%



Beck et al., NEJM 2009

THSD7A 2-5%



Thomas et al., NEJM 2014

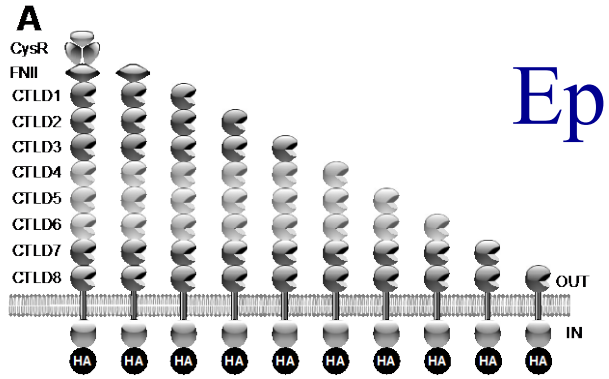
1/3 Rémission spontanée

1/3 Syndrome Néphrotique persistant

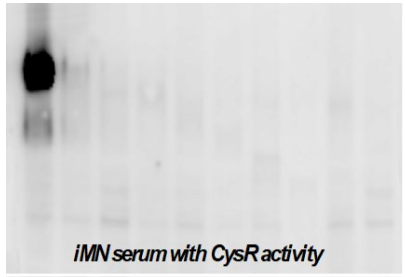
1/3 IRCT

Recommandations KDIGO: 6 mois de traitement symptomatique avant débuter un traitement immunosuppresseur

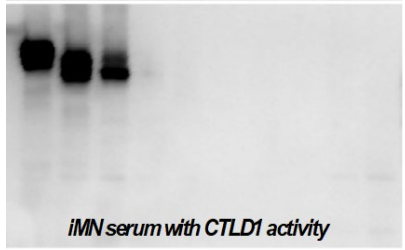
Epitope Spreading : Marqueur Pronostique



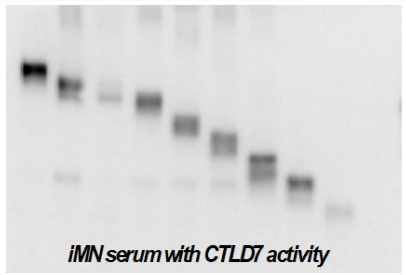
CysR 12/50

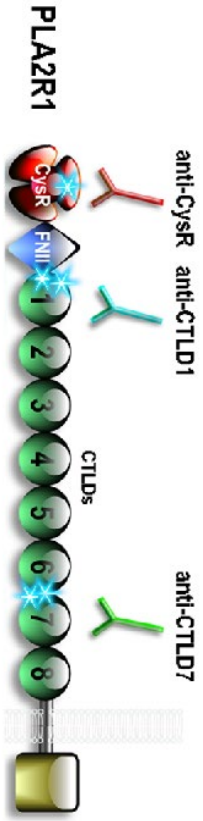


CTLD1 11/50



CTLD7 27/50





Screening of 50 sera

33%

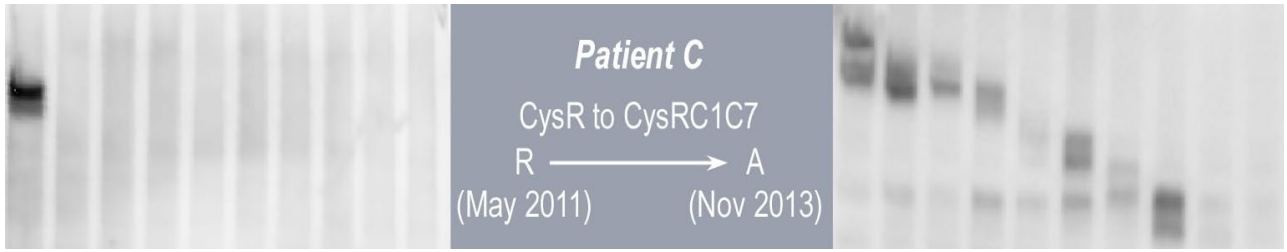
20%

47%

	CysR	CysRC1	CysRC1C7	p value
Age	48±12	54±16	61±15	0.008
Sex	19M/4F	10M/4F	25M/7F	ns
Ac anti-PLA2R1 titer	1369 (273-6717)	3873 (448-8237)	4732 (148-7766)	ns
Proteinuria	3.0* (0.3-7.8)	3.0* (0.8-12.0)	5.5* (0.3-24.0)	0.018
sCreatininemia	92 (45-120)	109 (43-329)	106 (59-600)	ns
Follow-up	36 (12-190)	44 (18-120)	33 (12-216)	ns
Treatment	12/23 (25%)	8/14 (18%)	21/32 (4%)	ns
Spontaneous remission	10/23* (43%)	4/14 (29%)	4/32* (12%)	0.03
Poor prognosis	3/23*	7/14	21/32*	0.001
Hemodialysis	0/23	2/14	10/32	0.01

***Seitz-Polski** et al., JASN 2016 IF:14.978*

Epitope Spreading et Histoire naturelle



1er évènement:
anti-CysR activité

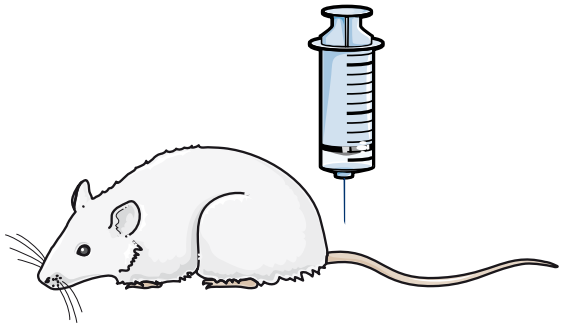
2ème évènement:
Intramolecular epitope spreading

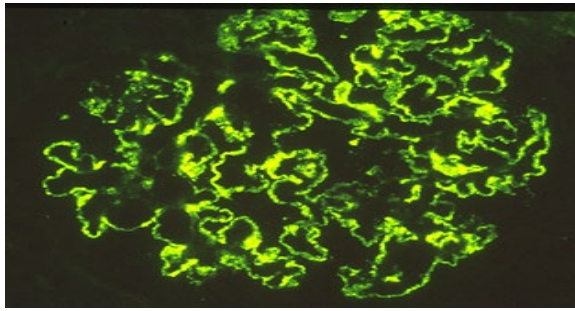
Mild disease Spontaneous remission

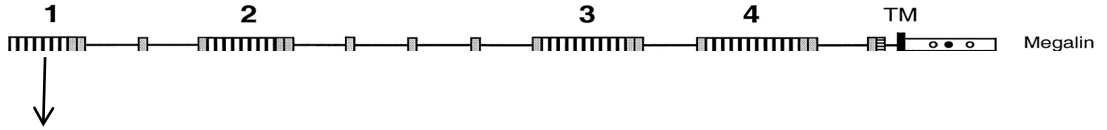
Severe disease

Seitz-Polski *et al., JASN 2015*

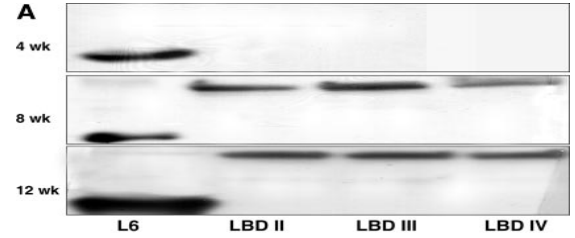
Dépôts IgG

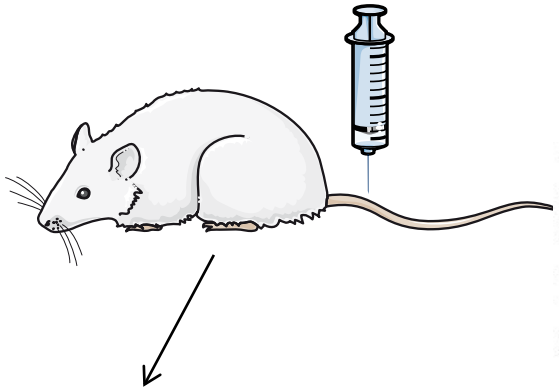




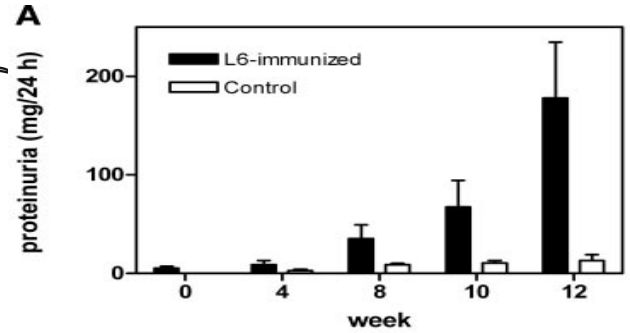


Peptide L6





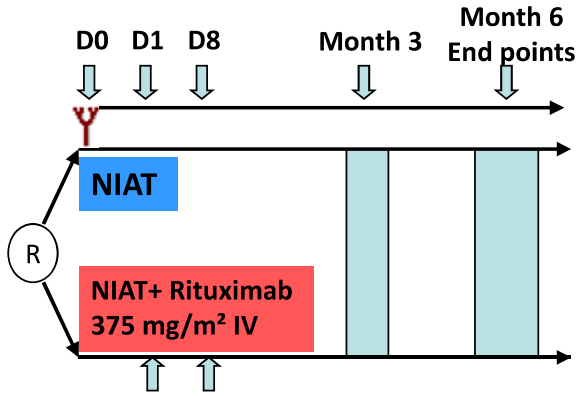
Ab + Actice disease



Shah et al., JASN 2007

Rémission spontanée et Epitope Spreading

Anti-PLA2R-Ab



M6	Remission (n=15)	No Remission (n=43)	P value
NIAT - NO spread M0	5 (33.33)	6 (13.95)	0.0374
NIAT - Spread M0	1 (6.67)	17 (39.53)	
RITUX - NO spread M0	4 (26.67)	5 (11.63)	
RITUX - Spread M0	5 (33.33)	15 (34.88)	

Last follow-up	Remission (n=32)	No Remission (n=26)	P value
NIAT - NO spread M0	8 (25.00)	3 (11.54)	0.0118
NIAT - Spread M0	5 (15.63)	13 (50.00)	
RITUX - NO spread M0	8 (25.00)	1 (3.85)	
RITUX - Spread M0	11 (34.38)	9 (34.62)	

***Seitz-Polski** et al. JASN 2018 IF: 14.978*

Rate of spontaneous remission Spread- à M6 : 45%

Rate of spontaneous remission Spread+ à M6: 0.05%

Table 2. Unadjusted and adjusted odd ratios for clinical remission at M6 and last follow-up of baseline indicators (M0)

Effect	Unadjusted				Adjusted			
	Odds Ratio	95% Wald Confidence Limits		Type 3 Analysis *P* Value	Odds Ratio	95% Wald Confidence Limits		Type 3 Analysis *P* Value
M6								
Age, yr	1.02	0.98	1.07	0.38	1.02	0.97	1.07	0.37
Sex				0.93				0.96
Men	1				1			
Women	0.94	0.25	3.53		1.04	0.24	4.54	
PLA2R1-Ab at M0, RU/ml	1.00	0.99	1.00	0.67	1.00	0.99	1.00	0.44
Treatment				0.37				0.21
NIAT	1				1			
NIAT and RITUX	1.73	0.52	5.69		2.37	0.62	9.06	
Spreading M0				0.02				0.02
No	1				1			
Yes	0.23	0.07	0.79		0.16	0.04	0.72	
Last follow-up								
Age, yr	1.01	0.98	1.05	0.51	1.02	0.98	1.07	0.38
Sex								
Men	1			0.92	1			0.54
Women	1.06	0.33	3.39		1.54	0.4	5.99	
PLA2R1-Ab at M0, RU/ml	1.00	0.99	1.00	0.22	1.00	0.99	1.00	0.86
Treatment								
NIAT	1			0.12	1			0.04
NIAT and RITUX	2.34	0.81	6.74		3.72	1.05	13.2	
Spreading M0								
No	1			0.01	1			0.01
Yes	0.18	0.05	0.65		0.15	0.03	0.64	

Note that spreading at baseline is the only predictor of remission at M6, and it also predicts remission at last follow-up before any treatment modification, independently from PLA2R1-Ab titer.

Epitope Spreading et Dose de Rituximab

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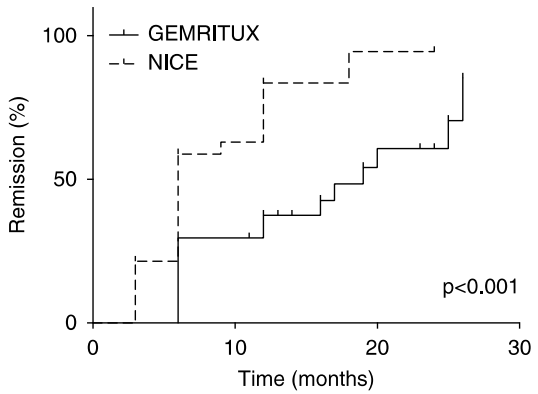
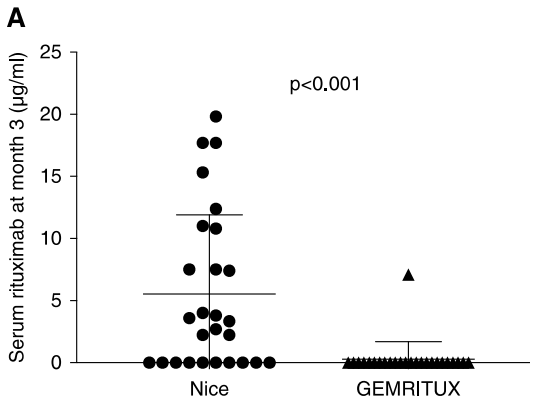
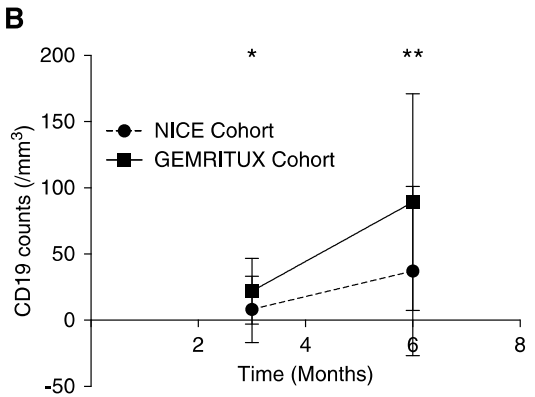
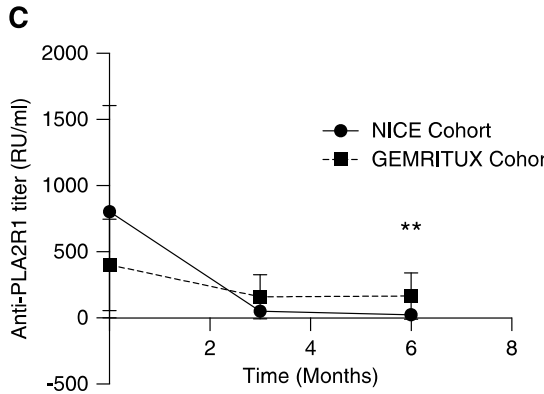
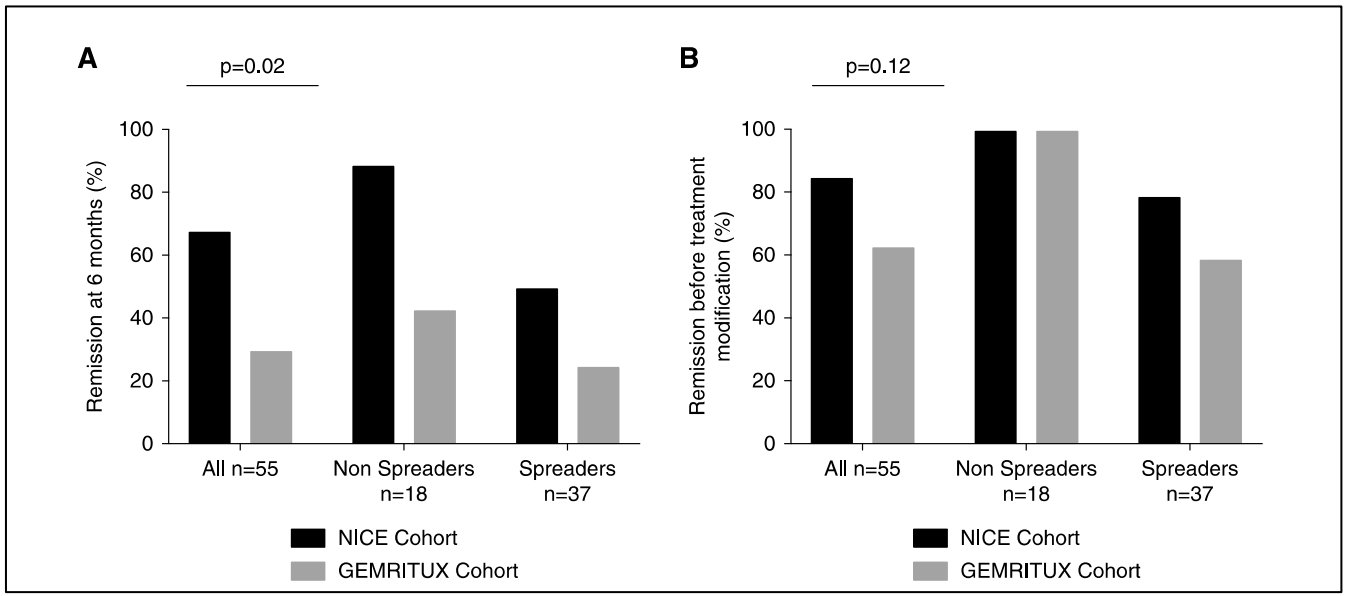
GEMRITUX: 375 mg/m^2 J0 J7 (1,4 g) vs NICE: 1g J0 J15 (2g)











Conclusions:

- Pas de spontaneous remission S+ (0.05% vs 45%)
- S+ nécessitent de fortes doses au diagnostic → 1gx2 au diagnosis
- Obtenir une remission immunologique pour obtenir une remission clinique→ Retraiter en cas de persistence d'une activité immunologique

Seitz-Polski *et al. CJASN 2019 IF: 10.614*

Personalized Medicine in MN

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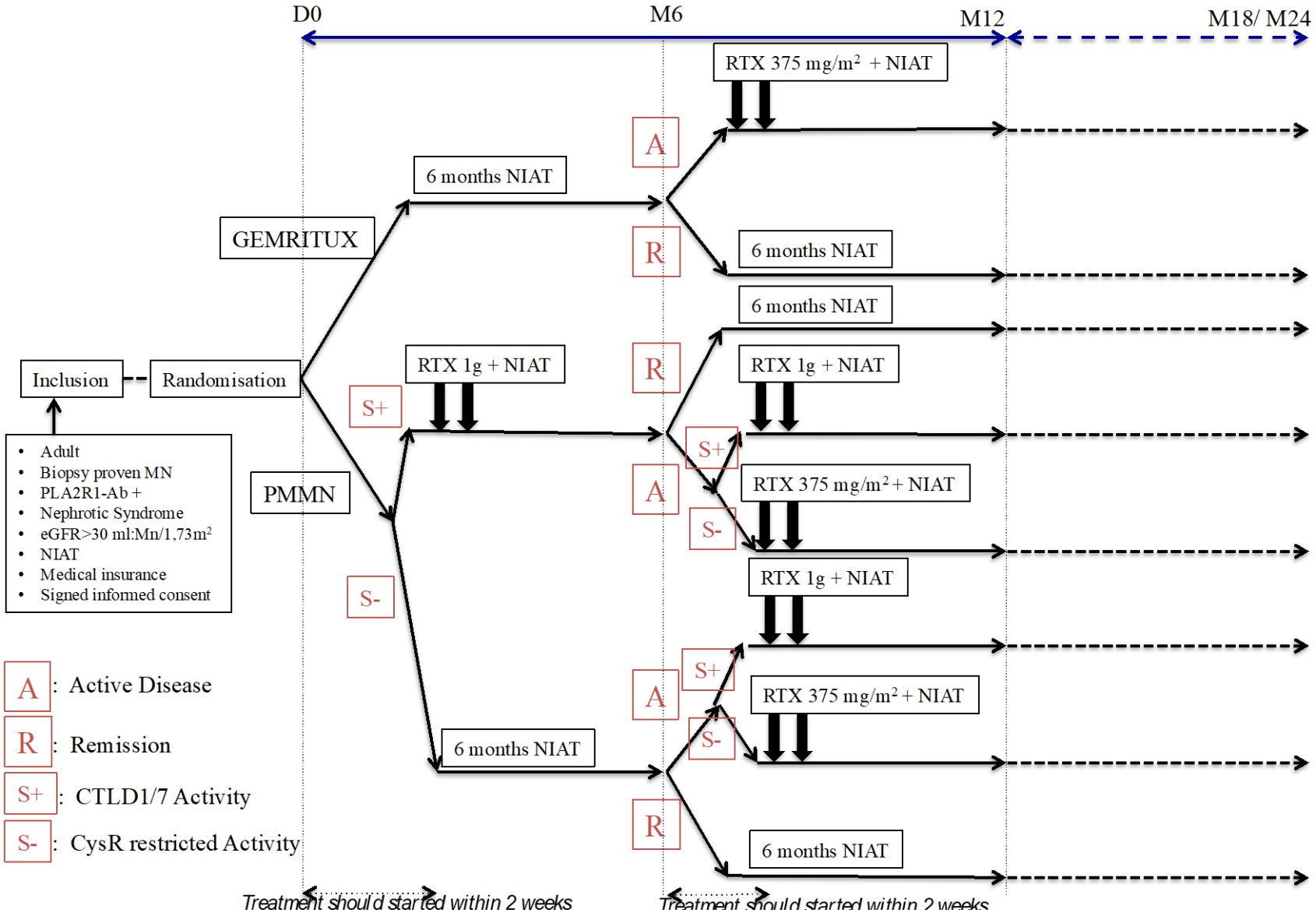
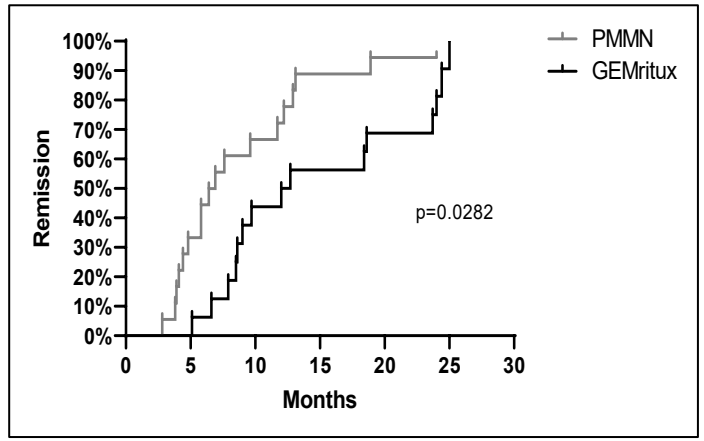


Expected remission rate at M12: 40%

Expected remission rate at M12: 80%



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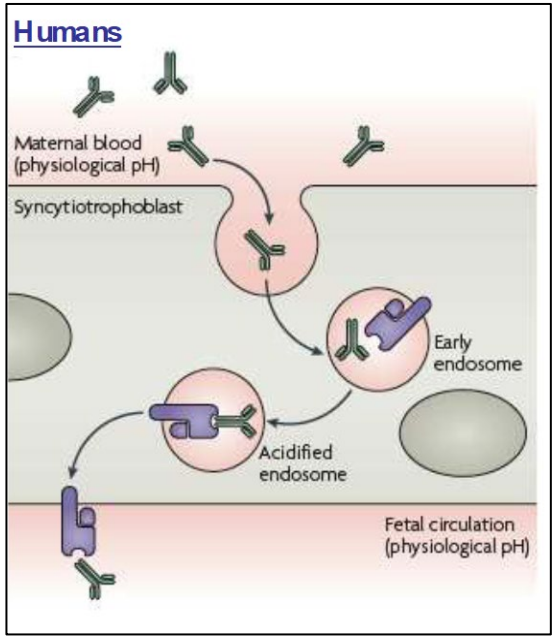
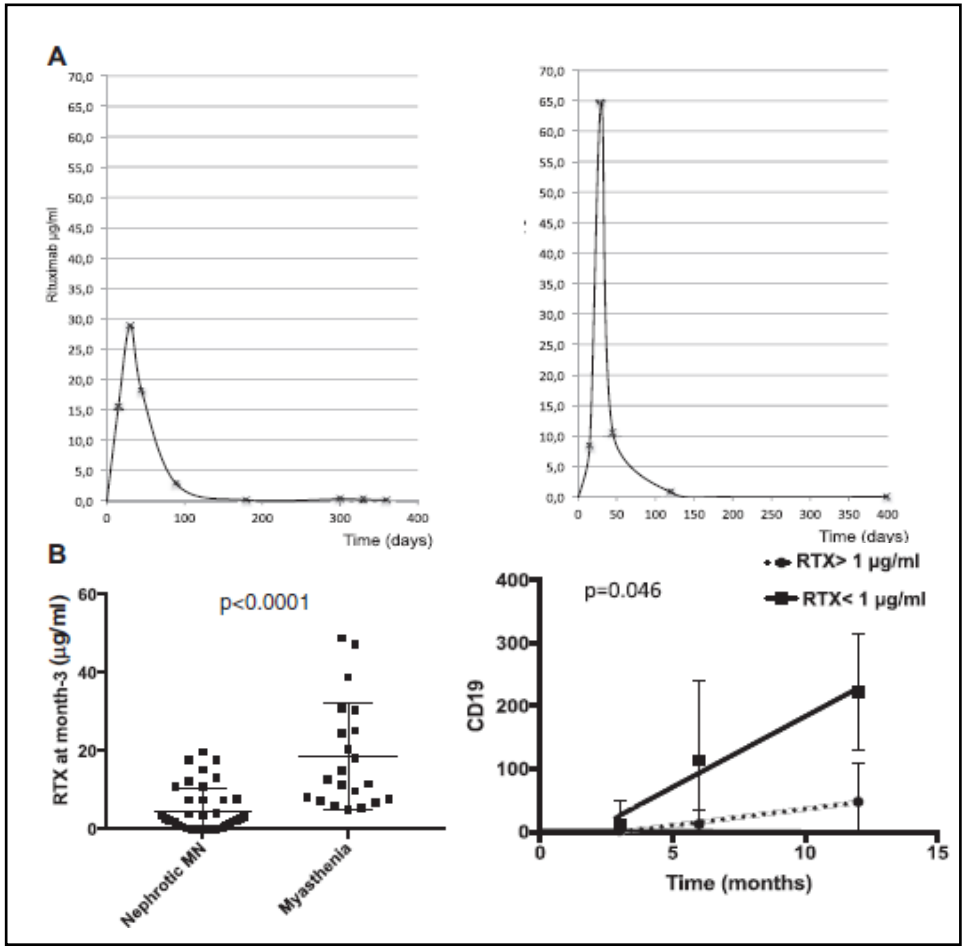
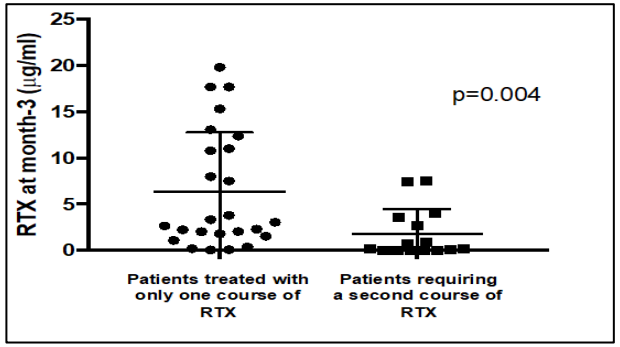
Monitoring du RTX







Boyer-Suavet et al. ***NDT 2019 IF: 7.186***

1. *Boyer-Suavet et al.* ***NDT 2019 IF: 7.186***
2. *Boyer-Suavet et al.* ***Front Immunol IF: 8.786***
3. *Teisseyre et al.* ***Front Immunol. 2021 IF: 8.786***
4. *Teisseyre et al.* ***Kidney International Report IF: 6.234***
5. *Teisseyre et al.* ***CJASN IF: 10.614***
6. *Destere*, Teisseyre** ***CJASN soumis***

Rituximab Monitoring

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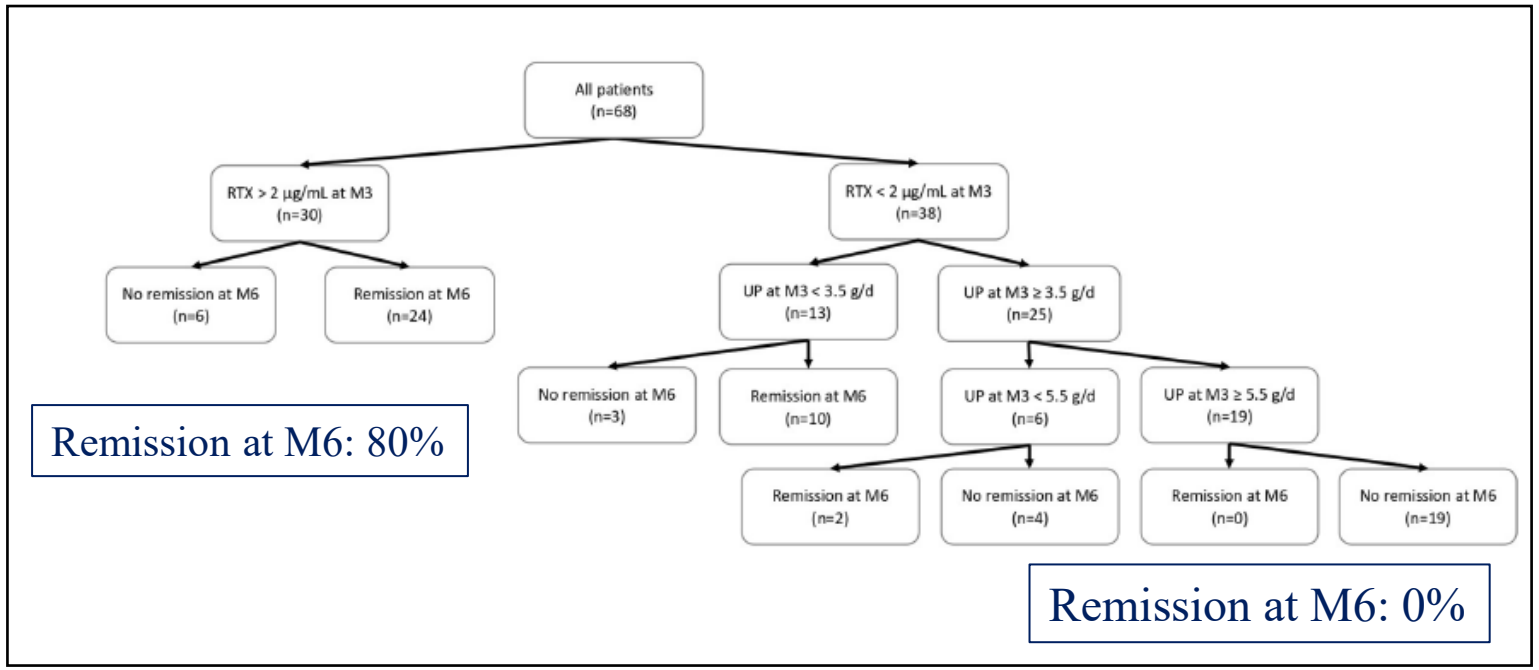
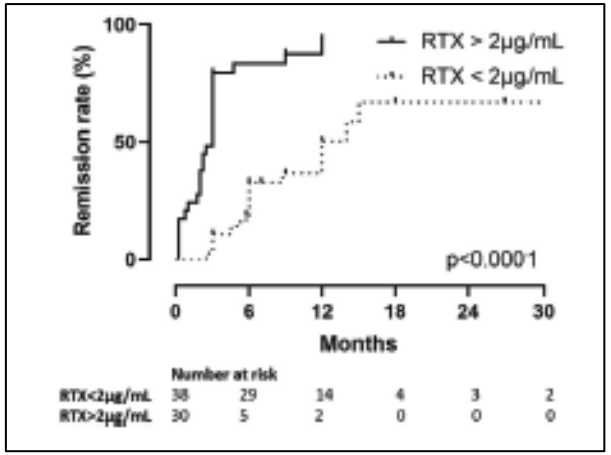


Remission at M6: 80%

Remission at M6: 0%



Variables	Remission at month-12 (n=41)	No remission at month-12 (n=27)	Univariate *P*-value	Multivariate *P*-value
Age (years)	60.0 [50.0–68.0]	56.0 [42.0–67.0]	0.3	
Gender (Female/Male)	11/30	8/19	1	
Weight (kg) at baseline*	71.5 [66.0–82.0]	78.0 [74.0–89.2]	0.06	0.02
UP (g/d) at baseline*	5.2 [4.0–7.1]	7.4 [5.6–11.9]	0.005	0.2
Serum creatinine (µmol/L) at baseline	118 [87–149]	123 [87–184]	0.4	
Serum albumin (g/L) at baseline*	24.8 [20.2–29.4]	16.0 [13.0–22.1]	0.001	0.7
$CD19^+$ count (cell/µL) at baseline	186.0 [125.0–285.0]	185.0 [88.7–263.8]	0.9	
$CD19^+$ count (cell/µL) at month-3*	0.0 [0.0–2.7]	3.0 [1.0–16.0]	0.005	0.9
Etiology			0.8	
Anti-PLA2R1-associated pMN	37 (90%)	25 (93%)		
Anti-THSD7A-associated pMN	1 (2%)	1 (3%)		
Double negative patients	3 (8%)	1 (3%)		
Anti-PLA2R1 Ab titer (RU/mL) at baseline*	86 [21–188]	226 [110–561]	0.001	0.5
Patient with RTX <2µg/mL at month-3*	16 (26%)	22 (85%)	0.001	0.01

Variables	Patients with serum rituximab level < 2µg/mL at month-3 (n = 38)	Patients with serum rituximab level > 2µg/mL at month-3 (n = 30)	Univariate *P*-value	Multivariate *P*-value
Characteristics at baseline				
Age (years)	57.5 [44.0–67.5]	60.5 [50.5–68.0]	0.3	
Gender (Female/Male)*	14/24	5/25	0.1	0.3
Weight (kg)	76.3 [66.6-83.6]	77.0 [67.9-86.0]	1	
UP (g/d)*	7.0 [4.9–10.1]	5.5 [3.9–7.1]	0.07	0.2
Serum creatinine (µmol/L)*	119 [83–138]	137 [90–183]	0.1	0.3
Serum albumin (g/L)*	20.2 [14.1–24.6]	26.6 [22.0–31.7]	0.001	0.005
$CD19^+$ count (cell/µL)	208.0 [138.0–280.0]	142.5 [77.2–215.5]	0.2	
Etiology			0.2	
Anti-PLA2R1-associated pMN	35 (92.%)	27 (90%)		
Anti-THSD7A-associated pMN	0 (0%)	2 (7%)		
Double negative patients	3 (8%)	1 (3%)		
Anti-PLA2R1 Ab titer (RU/mL)*	184 [71–489]	89 [20–173]	0.01	0.5

***Teisseyre** et al. Front Immunol 2019 IF: 8.786*

PHRC i-Ritux

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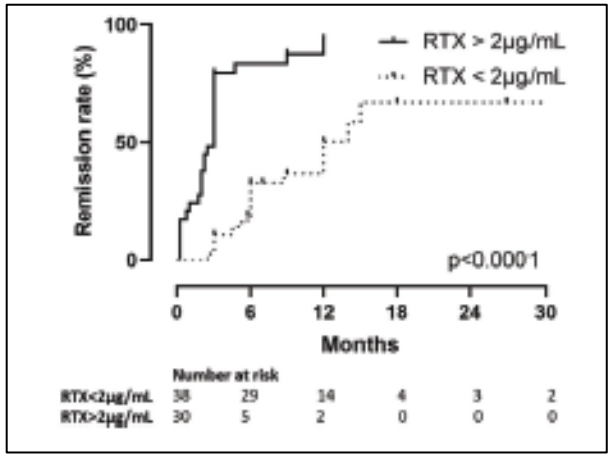
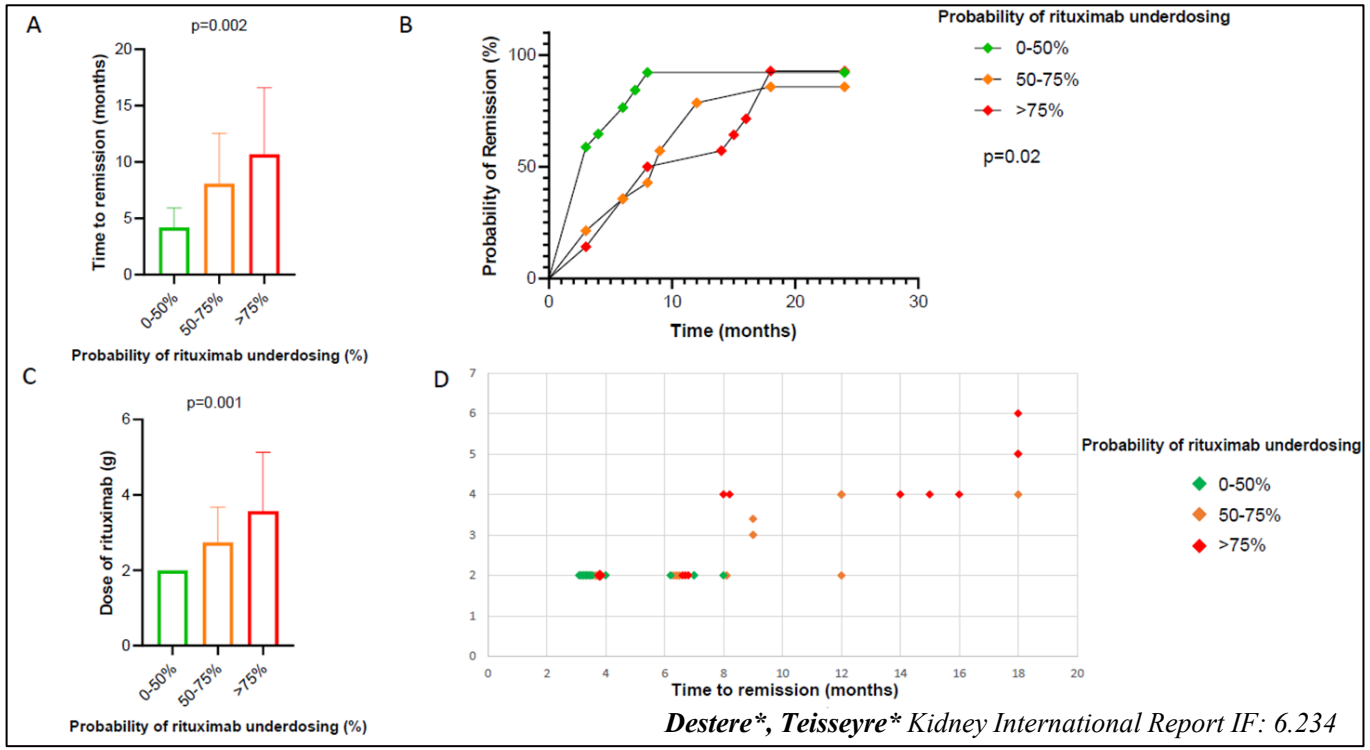
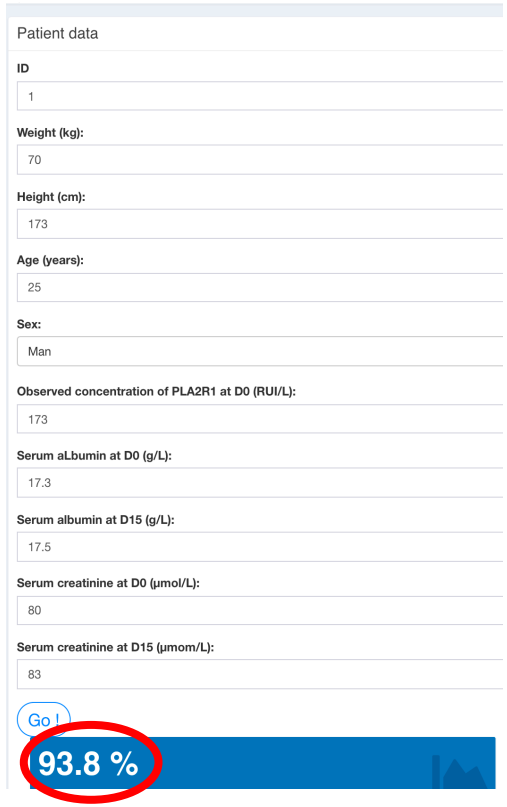
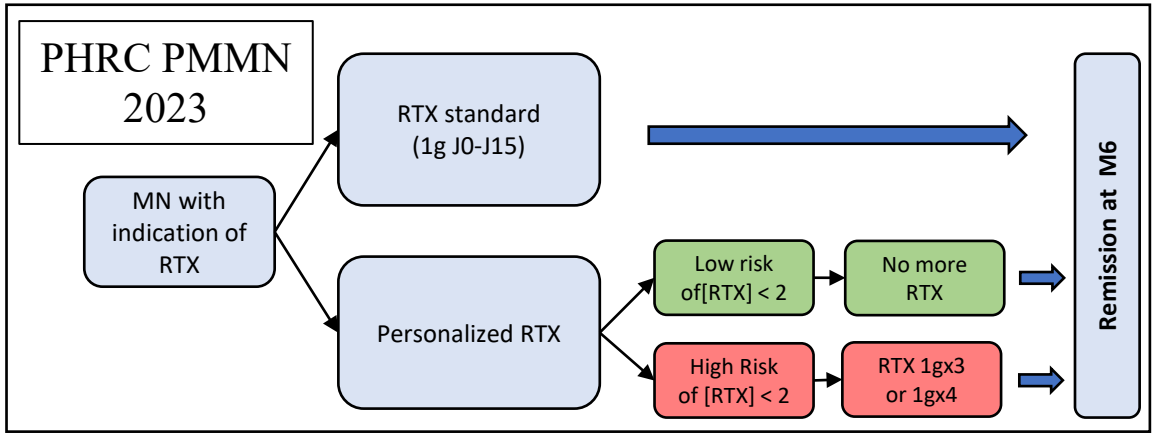




Destere*, Teisseyre* *Kidney International Report IF: 6.234*

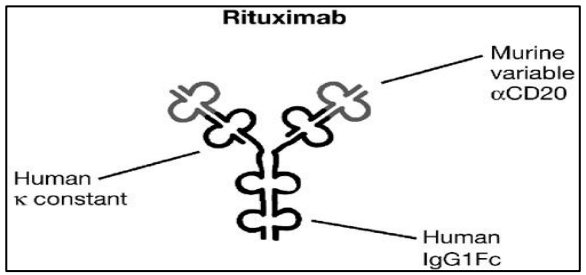


accuracy	sensitivity	specificity
79.4%	78.7%	81%



EXACTCURE

Immunisation contre le Médicament



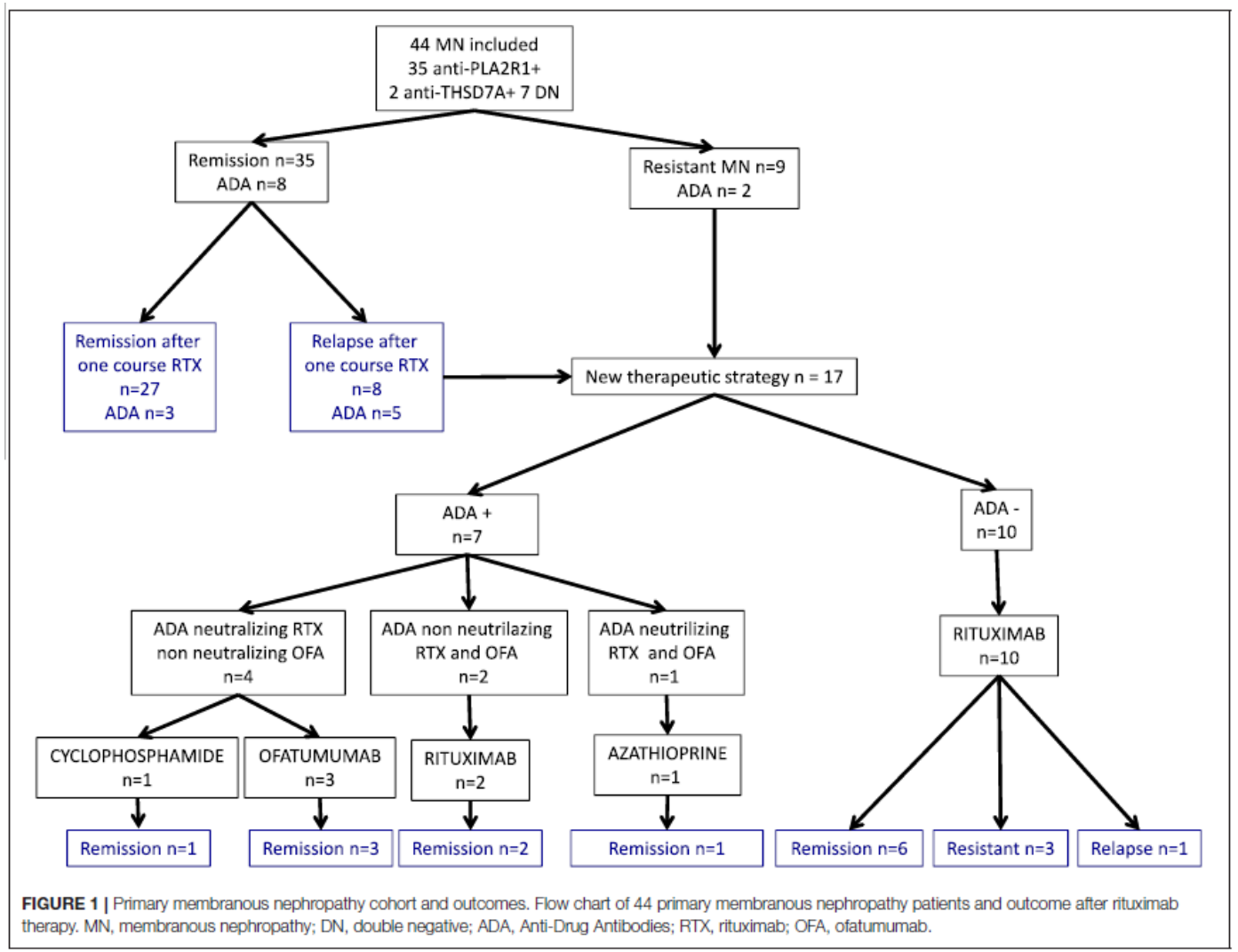
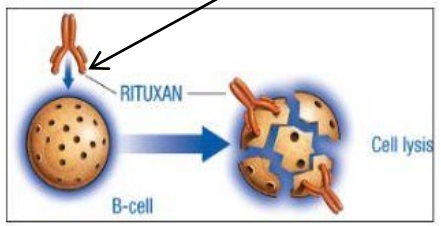


FIGURE 1 | Primary membranous nephropathy cohort and outcomes. Flow chart of 44 primary membranous nephropathy patients and outcome after rituximab therapy. MN, membranous nephropathy; DN, double negative; ADA, Anti-Drug Antibodies; RTX, rituximab; OFA, ofatumumab.

Neutralisation des ADA

Cross-match anti-B

+ Sérum +/- Ac anti-Ritux

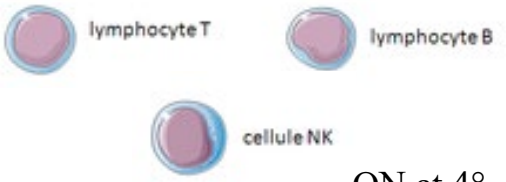


+ Complément de Lapin

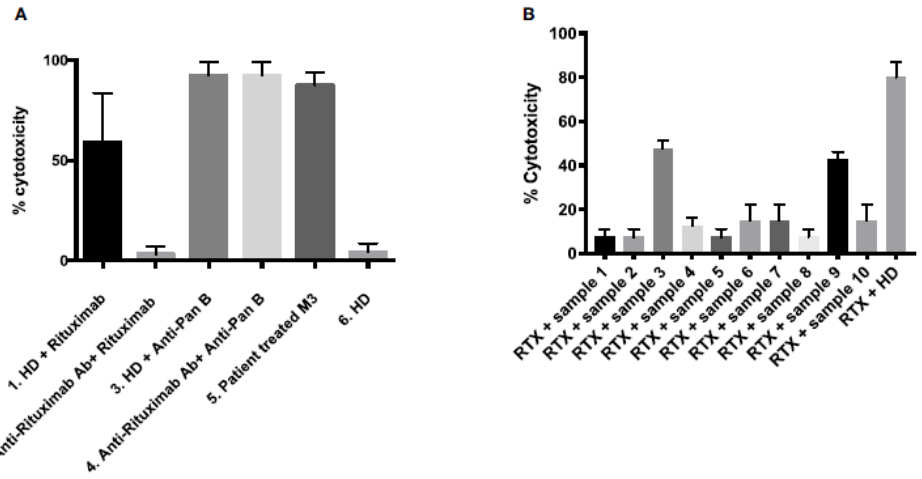
Peripheral Bloob

Ficoll

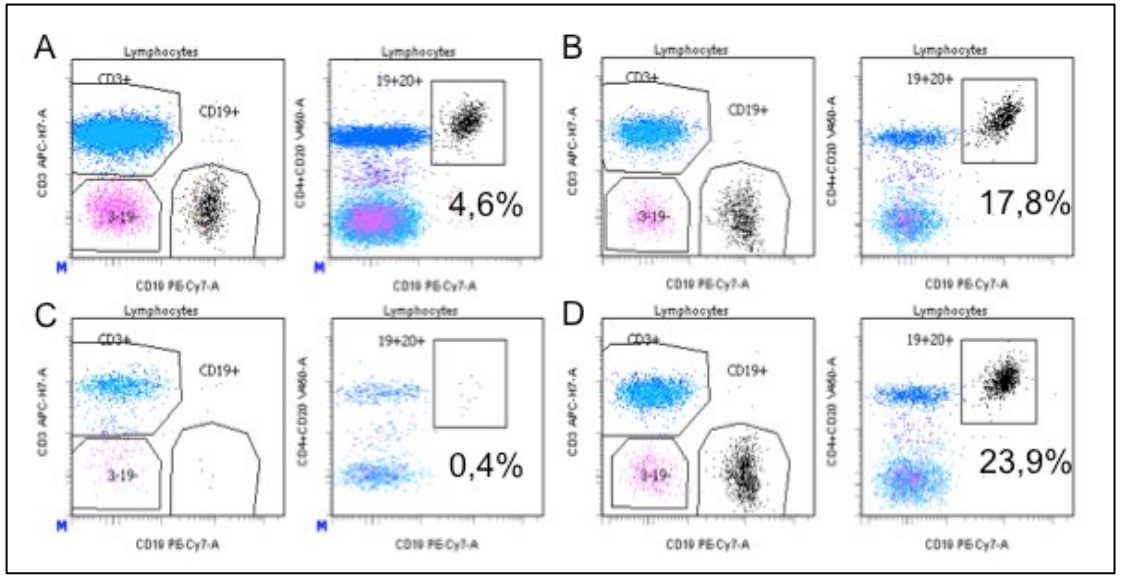
PBMC



ON at 4°

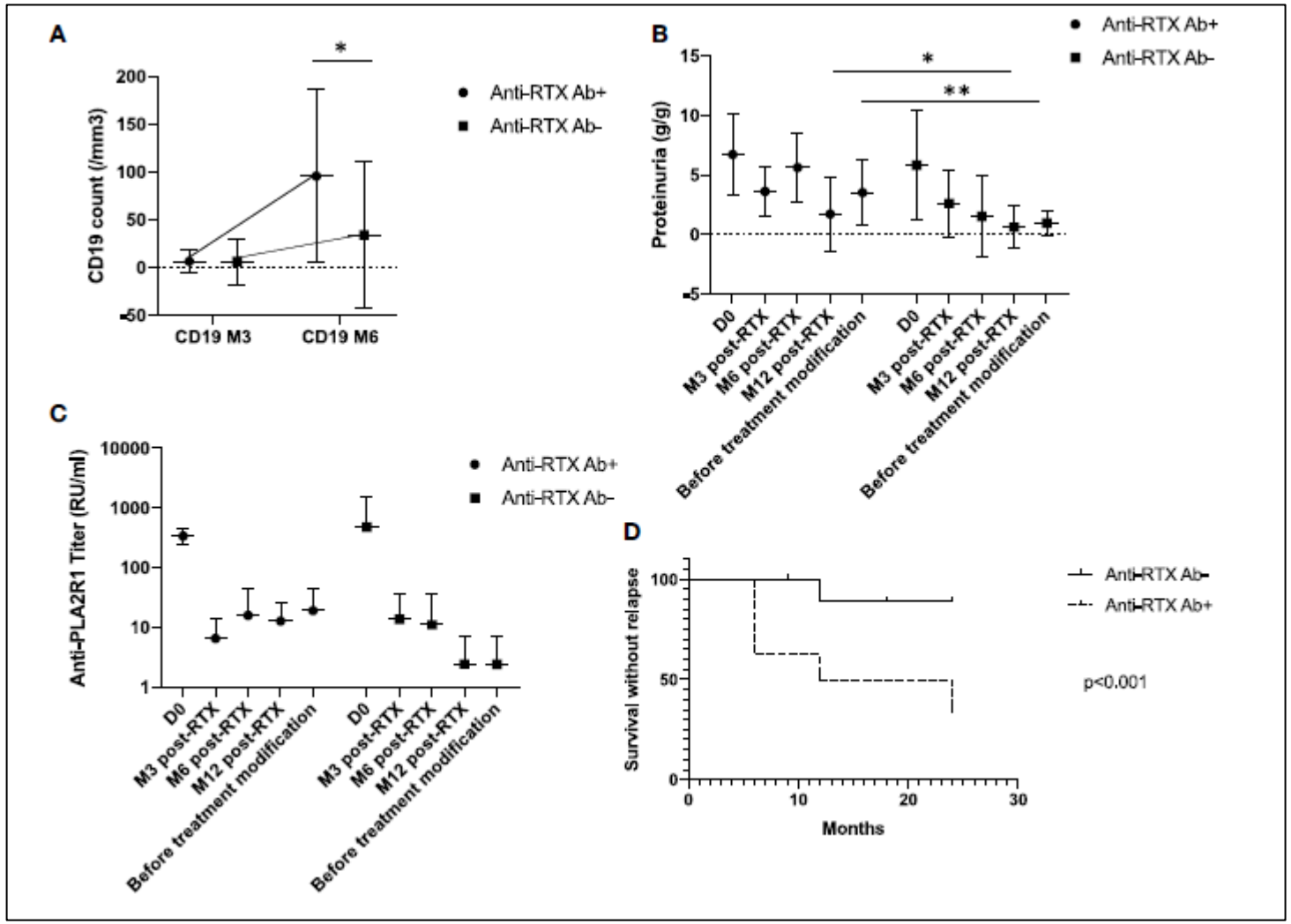


Patients	1	2	3	4	5	6	7	8	9	10
Antul-rituximab antibodies titer (ng/ml)	40	130	47	17	4400	87	55	26	13	17

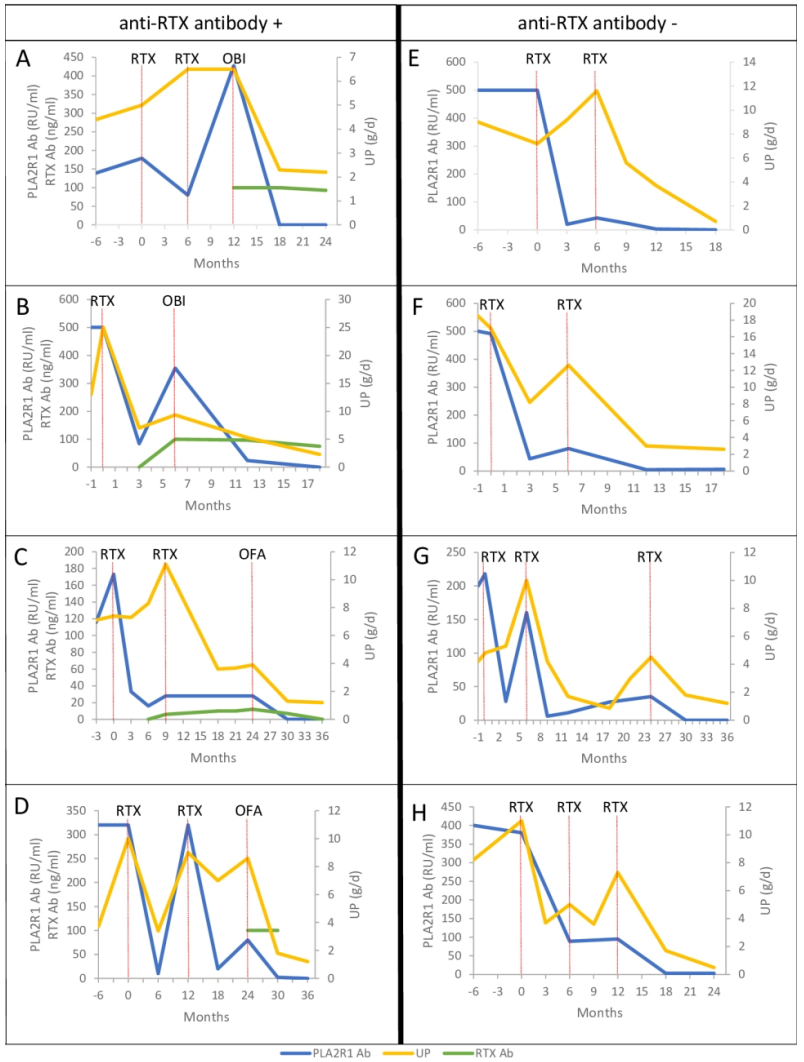


Boyer-Suavet et al. FI

Impact clinique des ADA

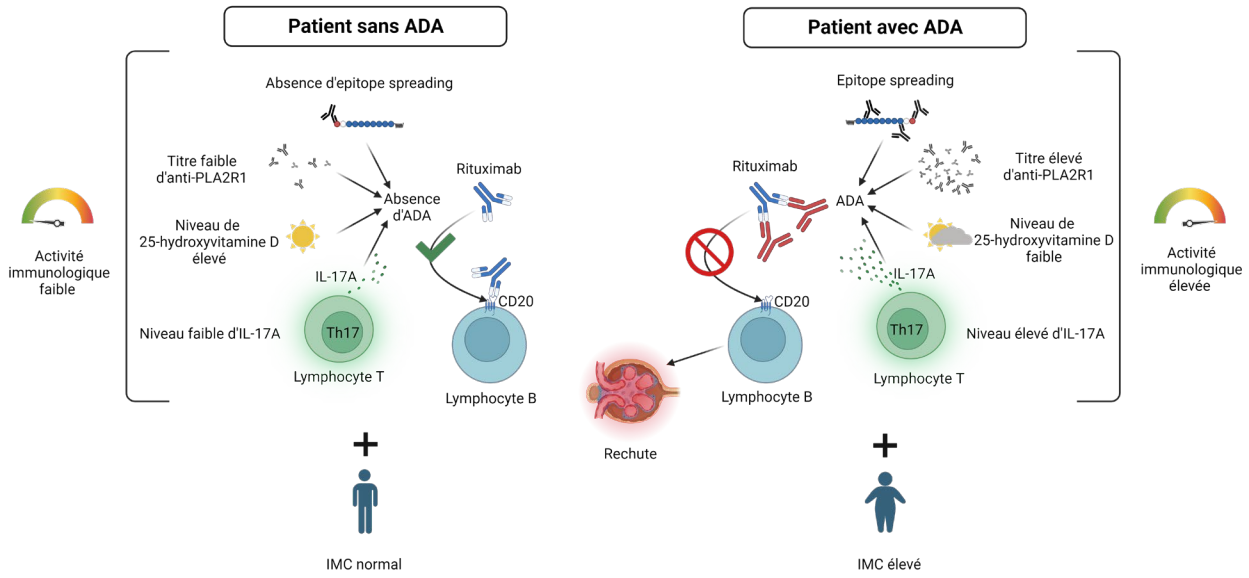


Boyer-Suavet et al. FI



Teisseyre et al. KIR 2021

Facteurs de risque de développer des ADA



Variables	n	All patients (n=55)	Patients with ADA (n=21)	Patients without ADA (n=34)	p-value
Characteristics at first rituximab infusion					
Age (years)	55	58 [45-68]	65 [47-71]	58 [44-67]	0.4
BMI (kg/m2)	55	26.2 [23.7-28.2]	26.9 [24.7-30.0]	24.8 [23.2-27.7]	0.06
Serum albumin (g/L)	55	22.1 [18.5-27.9]	20.0 [18.0-25.5]	24.7 [19.7-28.4]	0.2
UPCR (g/g)	55	6.0 [4.1-8.2]	5.5 [4.1-7.9]	6.3 [4.1-9.3]	0.5
eGFR (mL/min/1.73m2)	55	56 [41-87]	54 [45-87]	56 [39-87]	0.9
25-hydroxyvitamin D (ng/mL)	51	20.1 [8.8-32.1]	10.7 [7.0-17.4]	23.2 [15.3-35.0]	0.006
Etiology	55				
Anti-PLA2R1-associated pMN		47 (85%)	18 (86%)	29 (85%)	0.7
Anti-THSD7A-associated pMN		1 (2%)	0	1 (3%)	
Double negative pMN		7 (13%)	3 (14%)	4 (12%)	
Anti-PLA2R1 titer (RU/mL)	47	87 [31-275]	195 [73-386]	70 [25-160]	0.03
PLA2R1 epitope spreading	44				
Yes		26/44 (59%)	14/17 (82%)	12/27 (44%)	0.01
No		18/44 (41%)	3/17 (18%)	15/27 (56%)	
Cytokine Profile	31				
IL-17A level (pg/mL)		75.5 [19.4-120.0]	181.0 [76.8-382.8]	54.6 [11.5-94.4]	0.002
IL-12p70 level (pg/mL)		14.3 [6.4-34.1]	18.6 [10.0-37.1]	7.6 [5.2-43.9]	0.4
IL-4 level (pg/mL)		5.4 [1.1-9.9]	6.7 [3.6-12.0]	1.6 [0.7-9.3]	0.1
IL-5 level (pg/mL)		7.6 [2.0-13.5]	7.9 [4.7-10.6]	7.4 [1.4-14.9]	0.8
Prior immunosupprive treatment	55	10 (18%)	3 (14%)	7 (21%)	0.6

Teisseyre et al. CJASN IF=10.641

Protocole National de Diagnostic et de Soins (PNDS)
Glomérulonéphrite Extra-Membraneuse

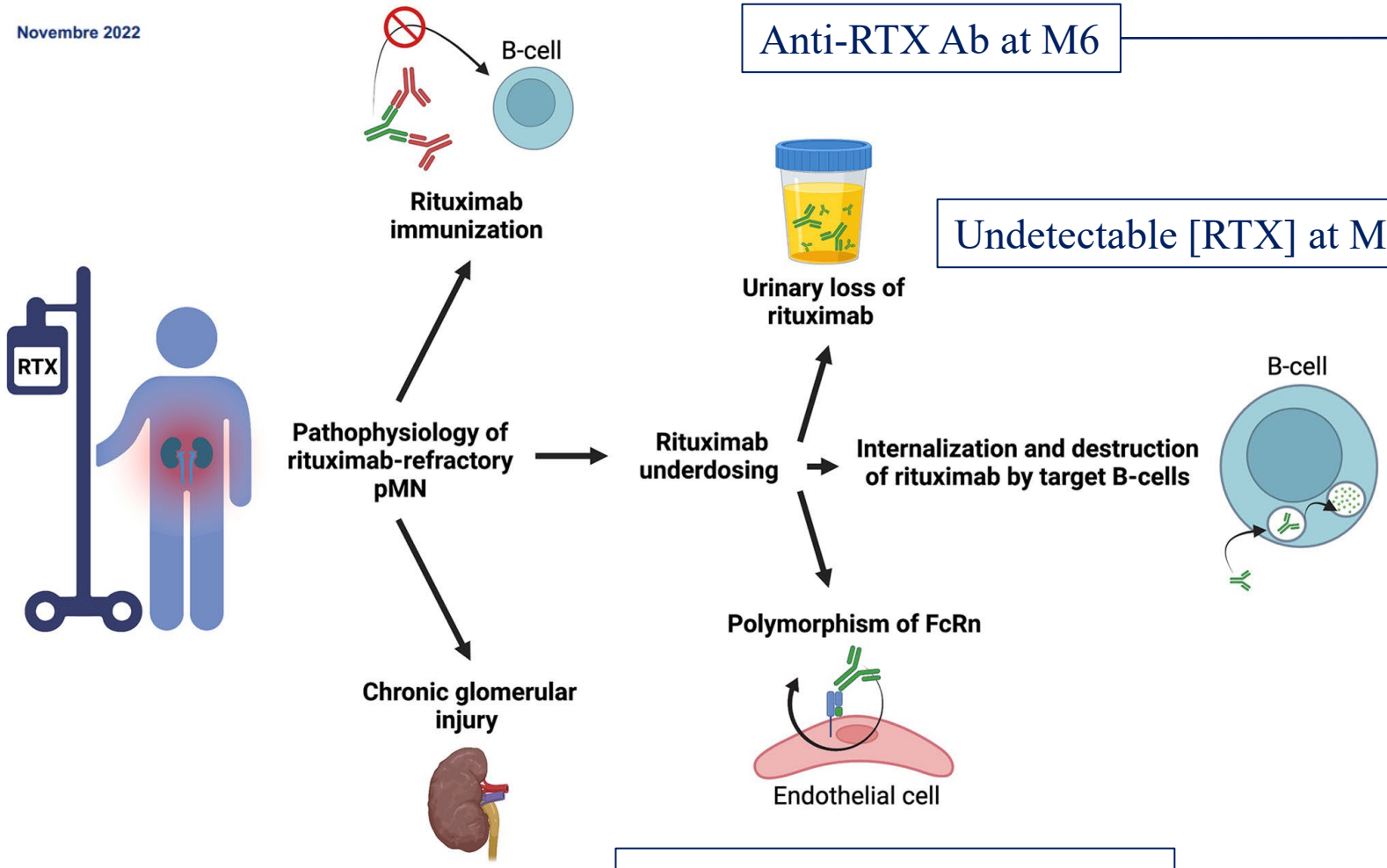
Texte du PNDS

Centre de Référence Maladies Rares du Syndrome Néphrotique Idiopathique

Novembre 2022

Prise en charge des GEM

HAS
HAUTE AUTORITÉ DE SANTÉ



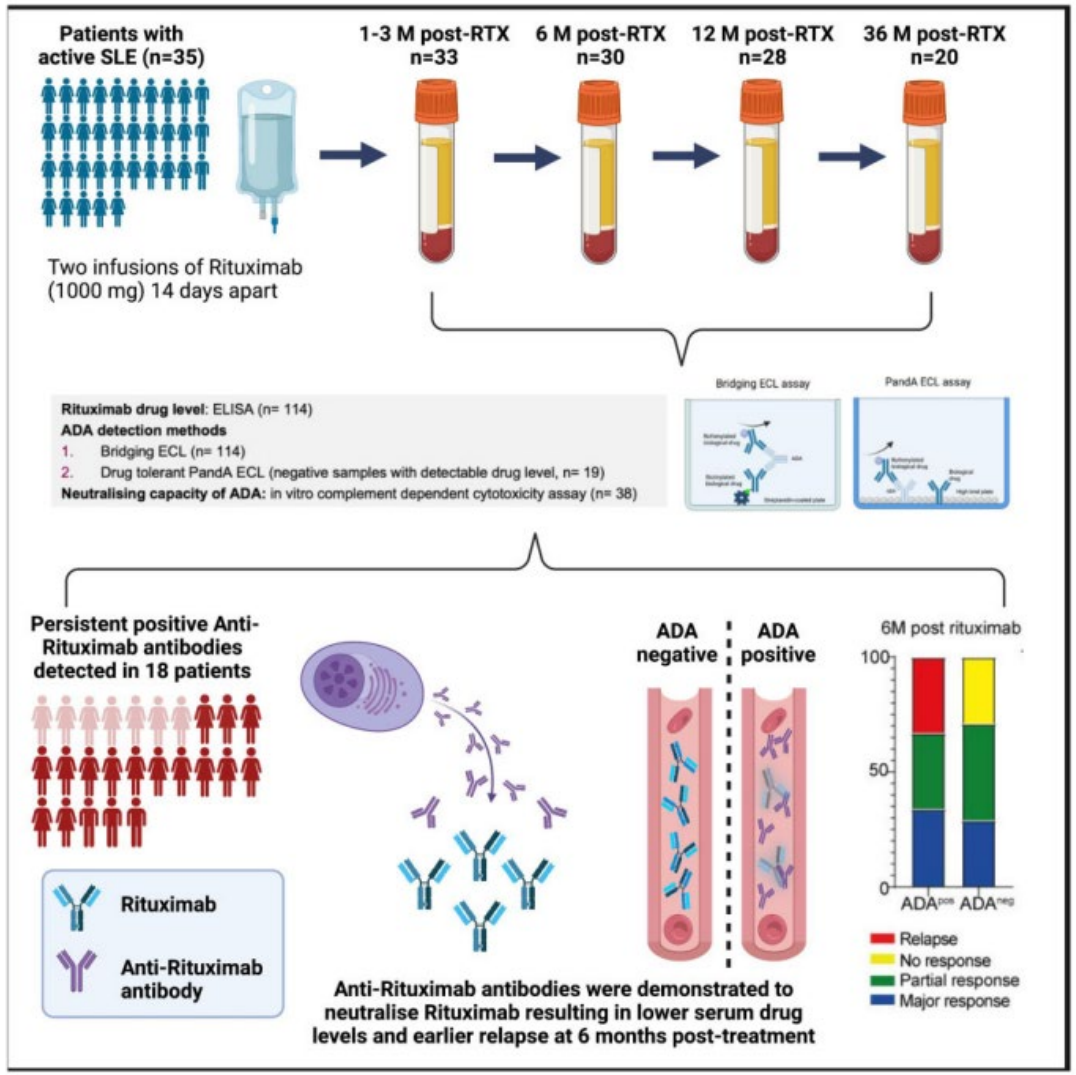
Anti-RTX Ab at M6 → Humanized Anti-CD20

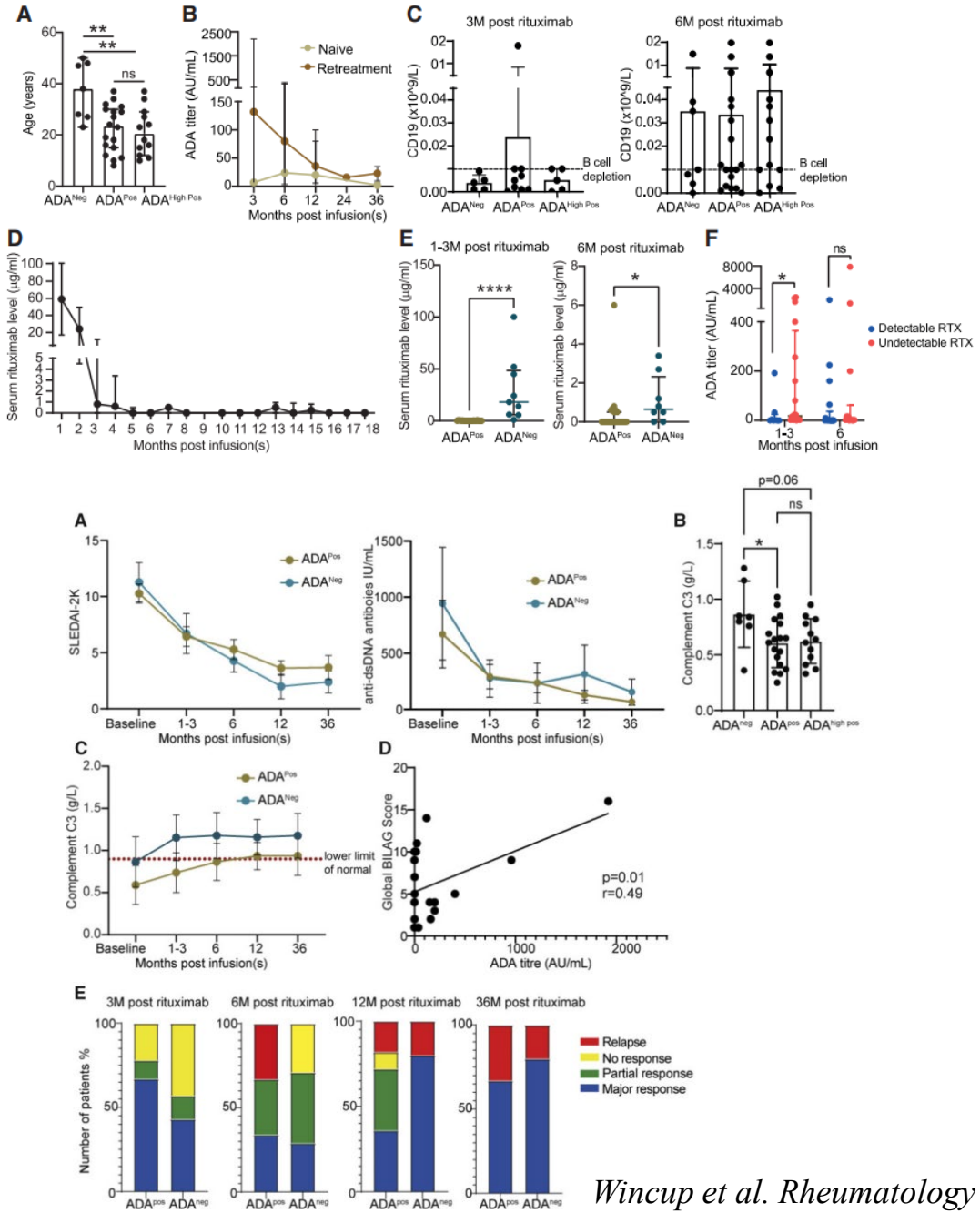
Undetectable [RTX] at M3 → RTX

Increase symptomatic Therapy → iSGLT2, Sparsentan

Teisseyre *et al. Front Immunol. 2022 IF: 8.786*

Lupus: Impact des ADA





Wincup et al. Rheumatology 2023

Conclusions

- Monitoring des taux résiduels de RTX :

→Etablir les objectifs de taux résiduels à M3

- ADA :

→Plus de rechutes

→Mauvaise déplétion B

→Switch vers anti-CD20 humanisé

chu de Nice

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