



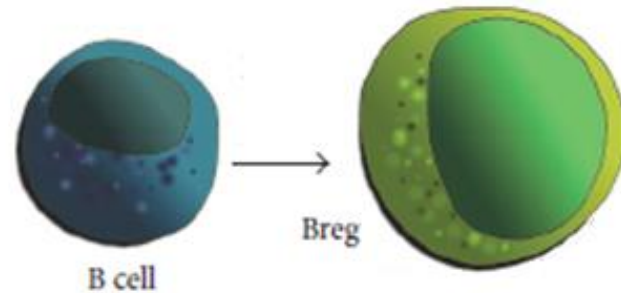
EL INMUNOFENOTIPADO DIRECTO DE CÉLULAS B REGULADORAS A LOS 3 MESES TIENE UN VALOR PREDICTIVO DE MEJOR EVOLUCIÓN RENAL Y RIESGO DE RECHAZO EN EL TRASPLANTE RENAL.

Inés Perezpayá, Sergio G. Garcia, Marta Clos-Sansalvador , Marta Sanroque-Muñoz, Maria Molina, Rosana Gelpi¹, Miriam Font-Morón, Ángela Casas ,Omar Taco, Mónica Bolufer, Anna Vila-Santandreu, Jordi Bover, Francesc E. Borràs.Laura Cañas. Marcella Franquesa

REMAR-IGTP Group, Germans Trias i Pujol Research Institute (IGTP) & Nephrology Department, University Hospital Germans Trias i Pujol (HUGTiP), Can Ruti Campus, Badalona (Barcelona), Catalonia, Spain

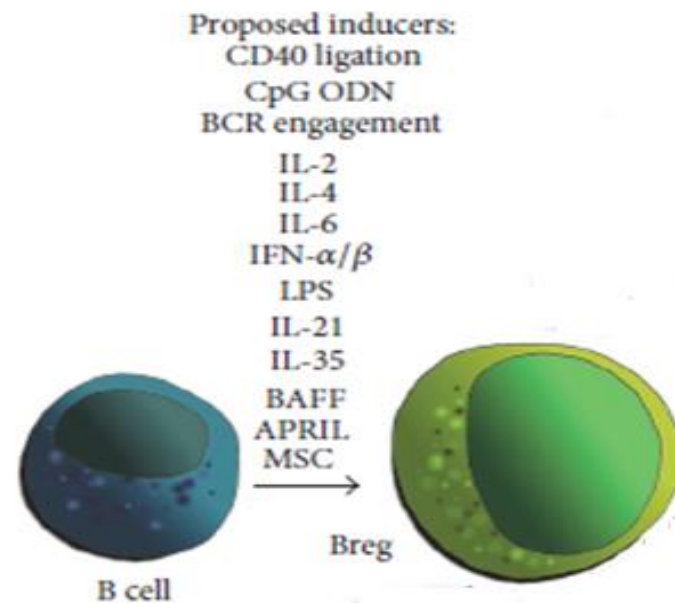
Células B Regulatoras

- Subgrupo de células B con **capacidad de regular** la respuesta inmune.



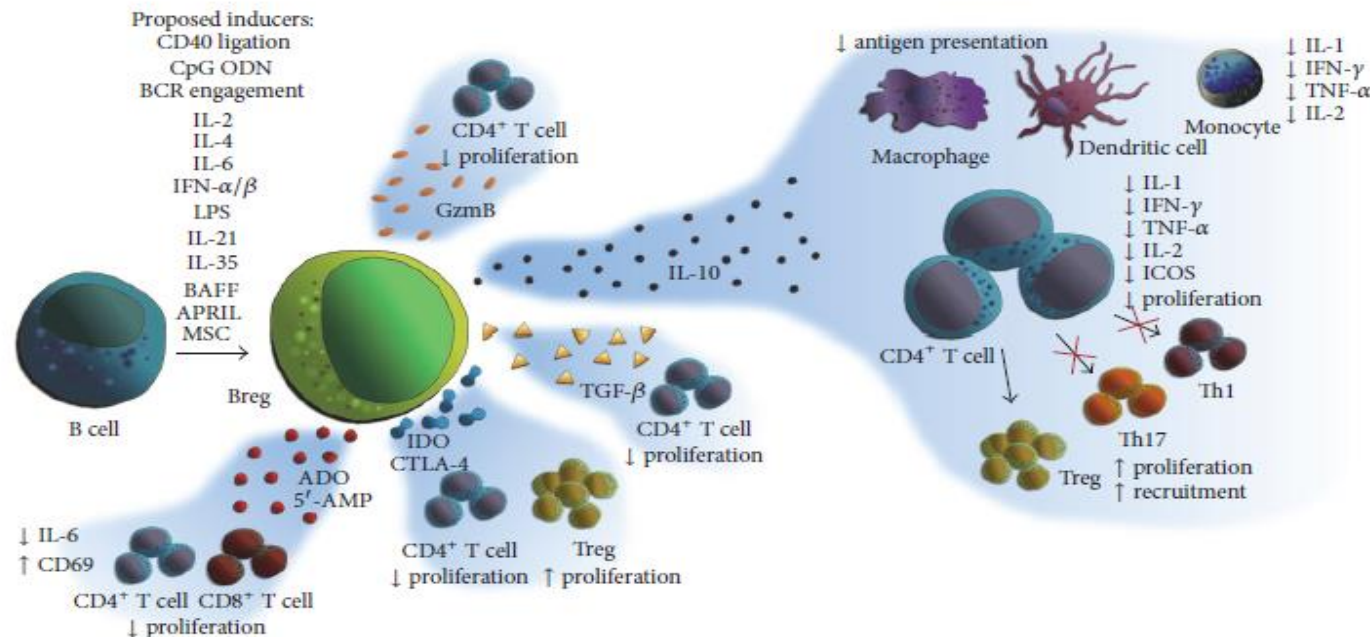
Células B Regulatoras

- Subgrupo de células B con **capacidad de regular** la respuesta inmune.
- Distintos mecanismos de **inducción** y activación—**Ambiente inflamatorio**



Células B Reguladoras

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- Distintos mecanismos de **inducción** y activación – **Ambiente inflamatorio**.
- **Mecanismo de acción:** citoquinas supresoras: **IL-10**, pero no la única.



Células B Regulatoras

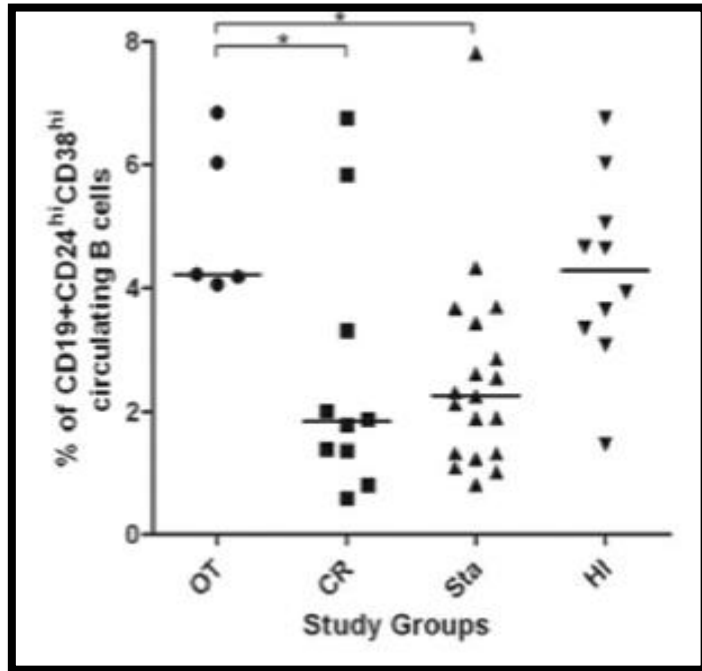
- Subgrupo de células B con capacidad de regular la respuesta inmune.
- Distintos mecanismos de **inducción** y activación – **Ambiente inflamatorio.**
- **Mecanismo de acción:** citoquinas supresoras: **IL-10**, pero no la única.
- Principal fenotipo: **CD19⁺CD24^{hi}CD38^{hi}**

J Am Soc Nephrol 25: 1575-1585, 2014. doi: 10.1681/ASN.2013080837

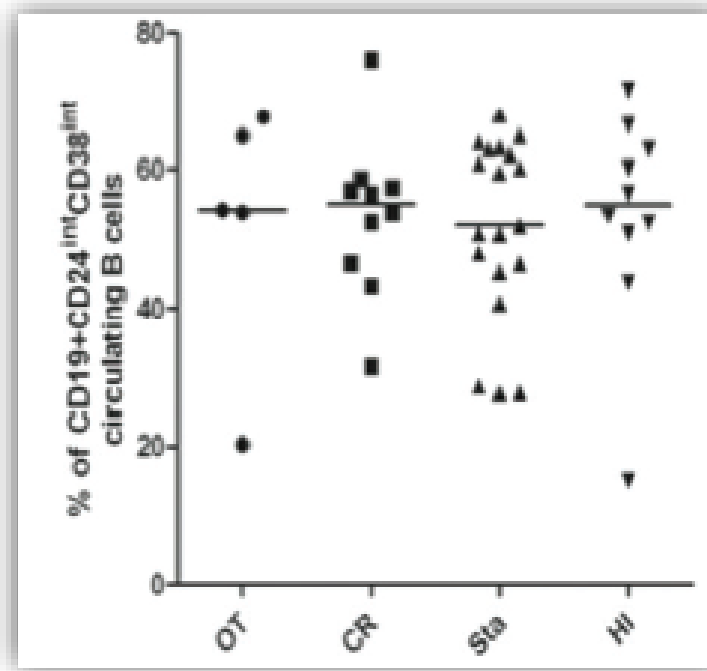
Transplant International 2016; 29: 540-548. doi: 10.1111/tri.12571

American Journal of Transplantation 2015; 15: 1384-1391. doi: 10.1111/ajt.13122

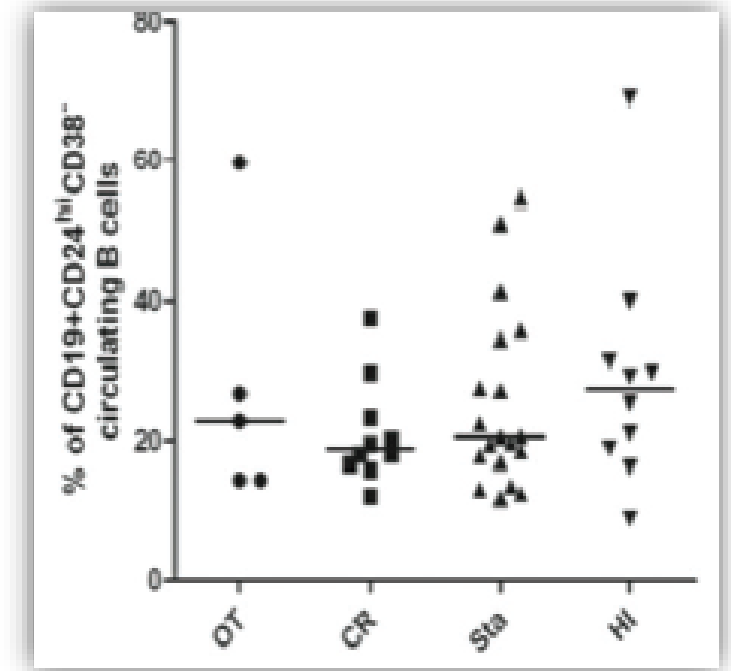
Células B Reguladoras – Trasplante Renal



Células Bregs (CD19+CD24^{hi}CD38^{hi})



Células B Naive (CD19+CD24^{int}CD38^{int})



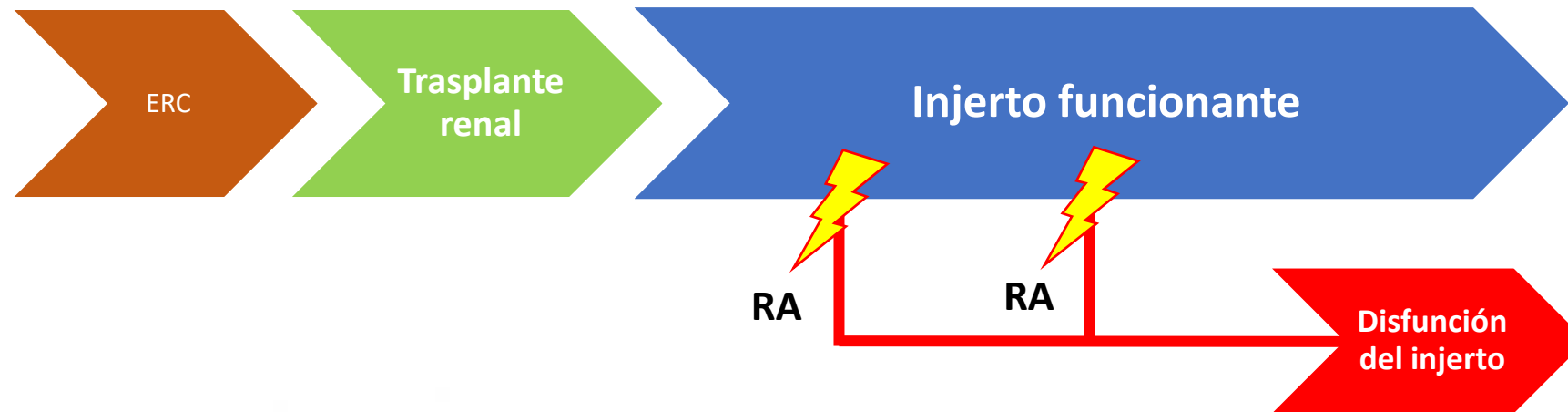
Células B Memoria (CD19+CD24^{hi}CD38⁻)

J Clin Invest. 2010; 120(6):1836-1847. doi:10.1172/JCI39933

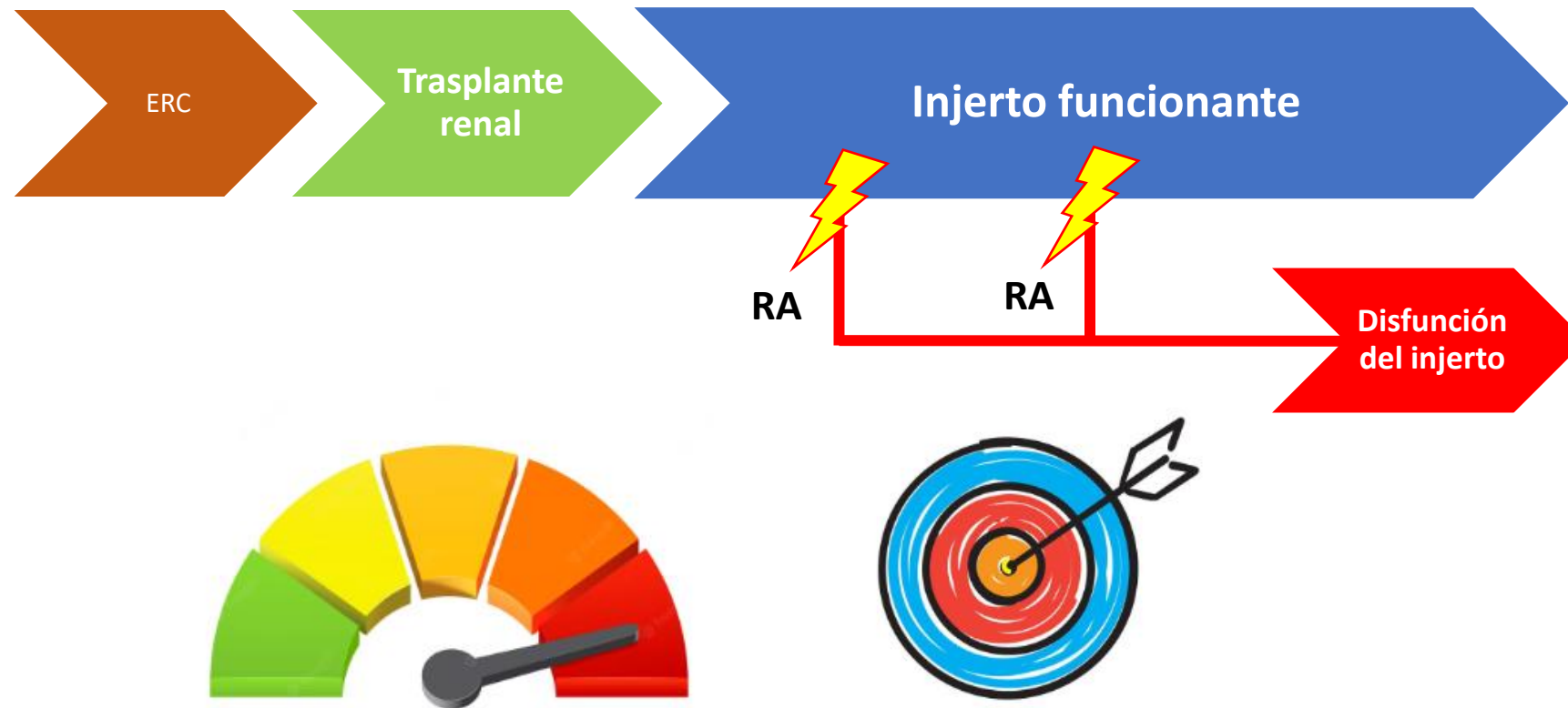
J Clin Invest. 2010; 129(6):1848-1861. doi:10.1172/JCI39922

Mol Med. 2012 Jul 18;18(1):733-43. doi: 10.2119/molmed.2011.00281

Células B Reguladoras – Trasplante Renal



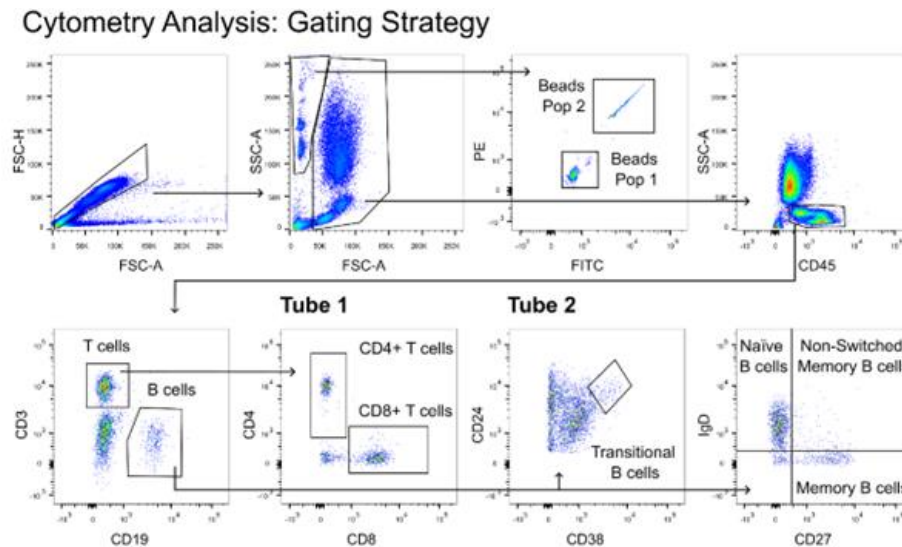
Células B Reguladoras – Trasplante Renal



MONITORIZACIÓN DE BREGS EN PACIENTES TRASPLANTADOS RENALES

- **Prospectivo** unicéntrico
- Seguimiento a **12 meses**
- Recolección de muestras:

Pre trasplante --- +7d --- +3m --- +6m --- + 12m



Células T (CD3+)
Células T CD4+
Células T CD8+

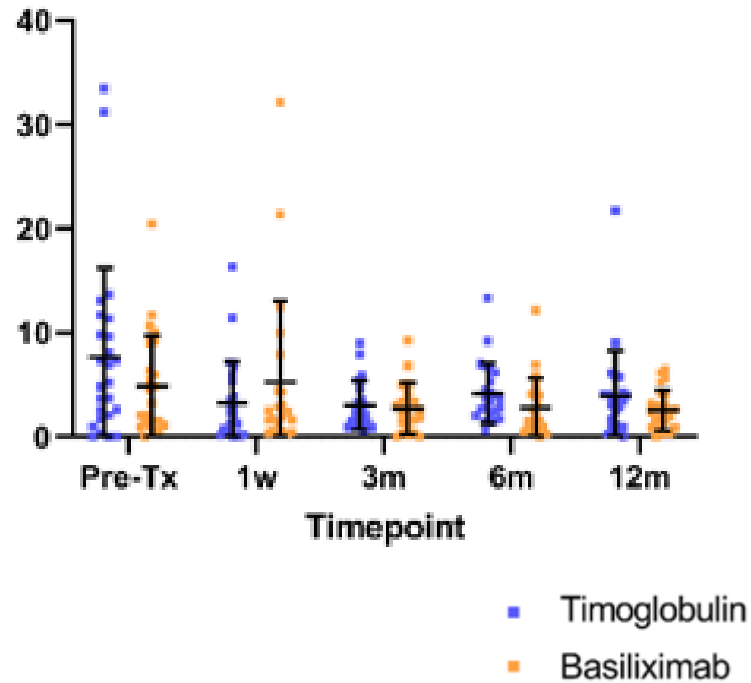
Células B (CD19+)
B Naive (CD19+CD27-IgD+)
B Memoria (CD19+ CD27+IgD-)
B Reguladoras (CD19+ CD24hi CD38hi)

VARIABLES CLÍNICAS	TOTAL (n=51)
Age	60 (35-80)
Sex (male)	24 (47%)
IS treatment Pre-KTx	10 (19.6%)
Previous KTx	6 (11.8%)
CKD Etiology	
Unknown	20 (39.2%)
PKD	13 (35.5%)
Glomerulonephritis	7 (13.7%)
DN	4 (7.8%)
Others	7 (13.7%)
Dialysis	35 (68.6%)
Months in dialysis	8 (0-280)
Type of donor	
After brain death	24 (47%)
After circulatory death	20 (39%)
Live donor	7 (13.7%)
CIT (min)	860 (81-1605)
HLA mismatches	
0-3	10 (19.6%)
4-6	41 (80.4%)
Anti-HLA Abs pre-KTx	26 (51%)
DSA pre-KTx	3 (6%)

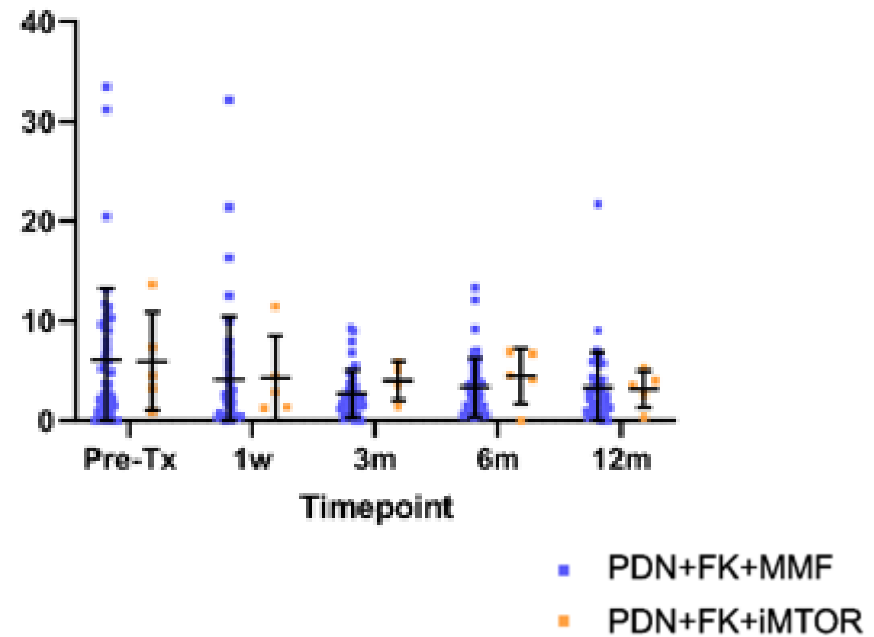
VARIABLES CLÍNICAS	TOTAL (n=51)
Induction therapy	
rATG	25 (49%)
Basiliximab	24 (47%)
None	2 (3.9%)
Maintenance therapy	
PDN+FK+MMF	46 (90.2%)
PDN+FK+ i-mTOR	5 (9.8%)
Delay graft function	11 (21.6%)
CMV infection	10 (19.6%)
SARS CoV2 infection	6 (11.8%)

Bregs-Tratamiento inmunosupresor

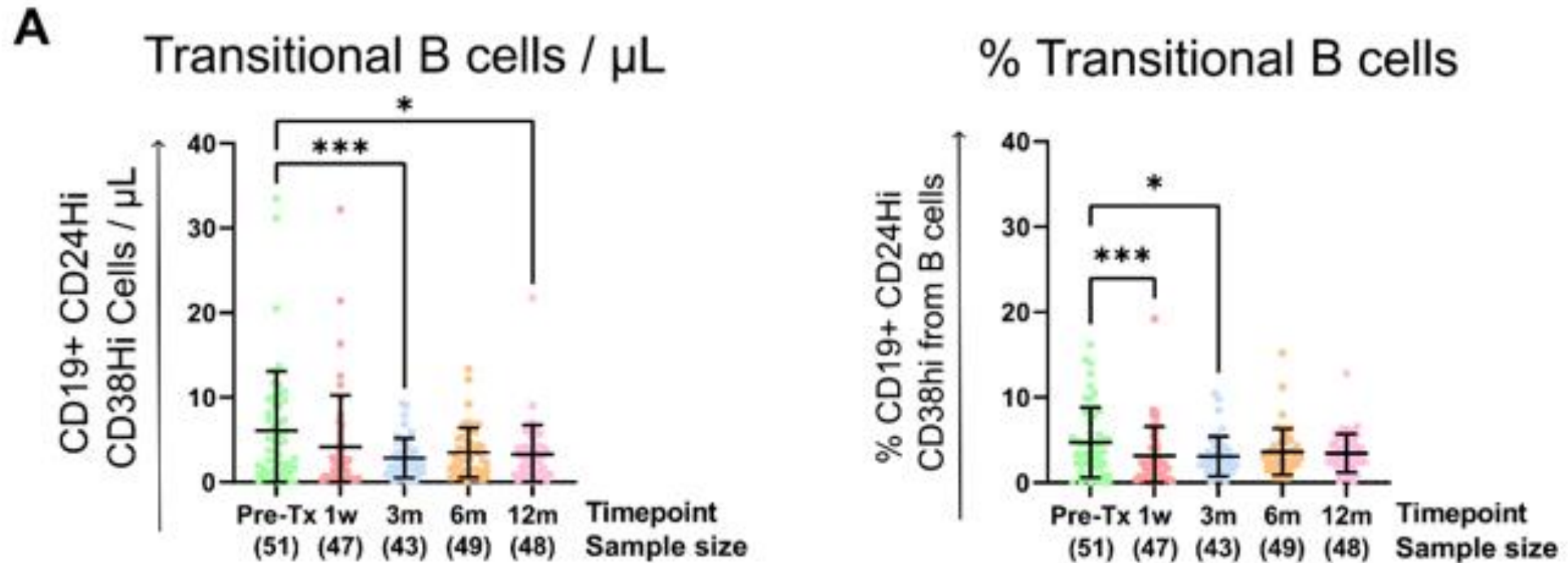
Transitional B cells



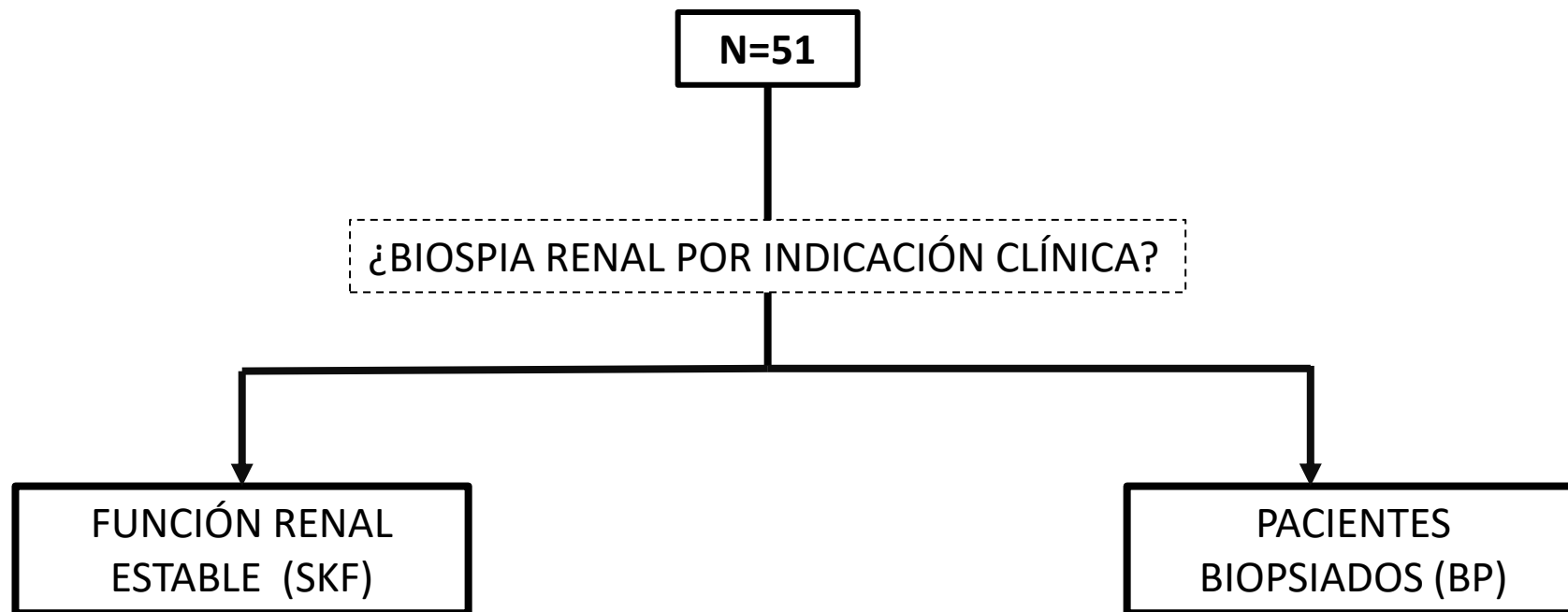
Transitional B cells



Evolución de Bregs durante el seguimiento:



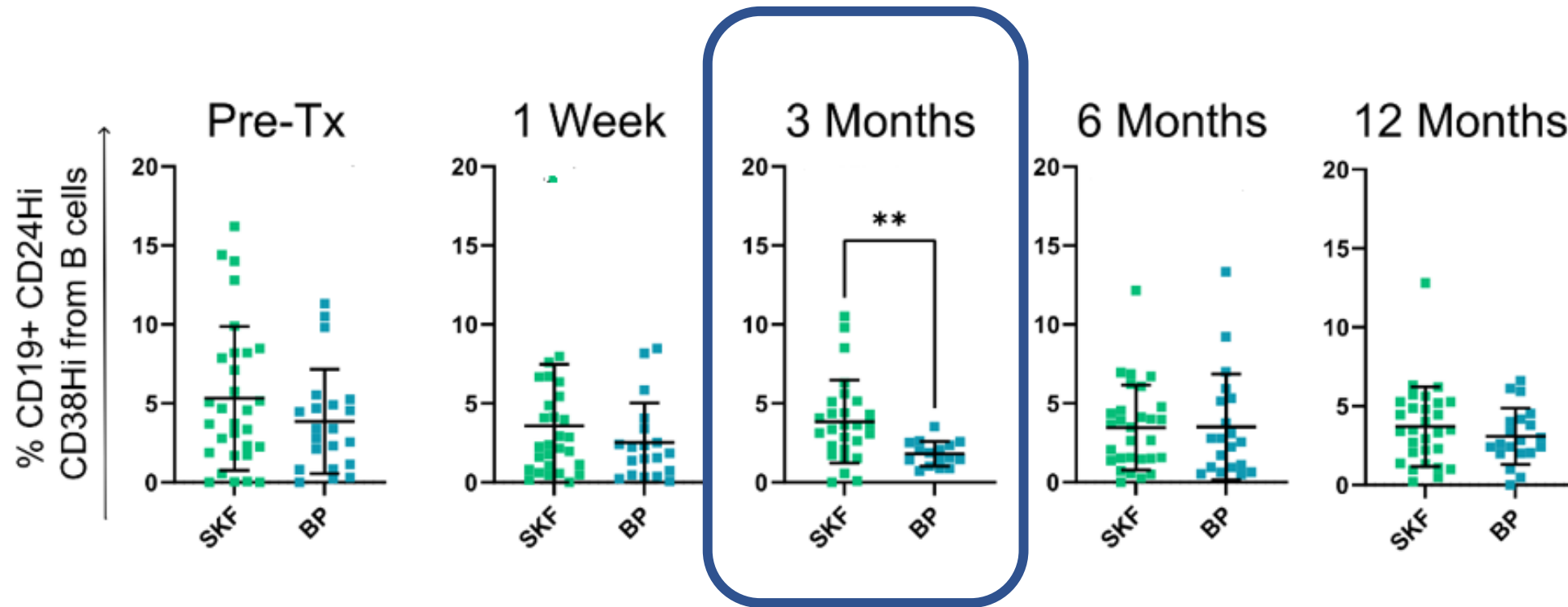
Relación Bregs con la evolución del injerto renal



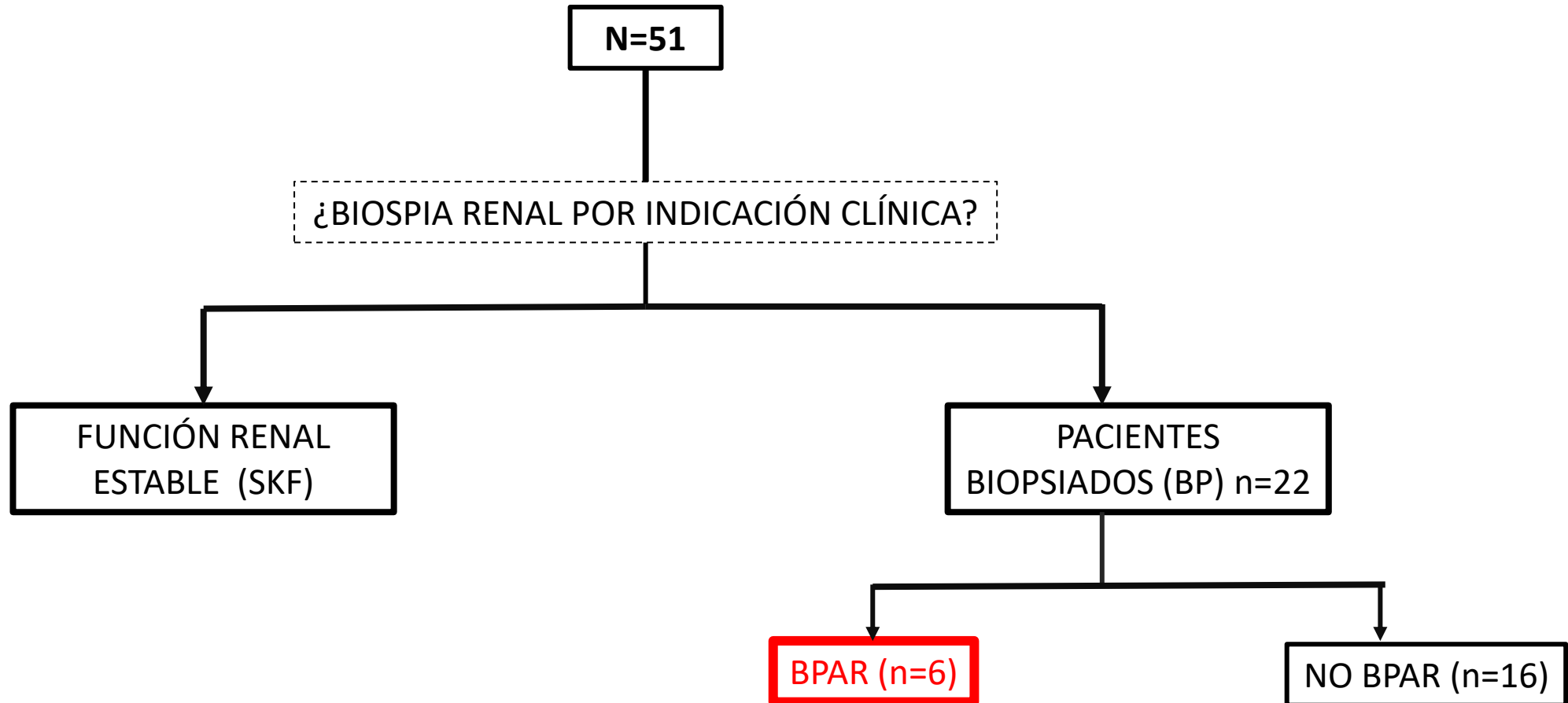
	Stable Kidney Function (SKF) (n=29)	For Cause biopsy (BP) (n=22)	p Value
Age	61 (36-80)	58 (35-74)	NS
Sex (male)	16 (55%)	11 (40.7%)	NS
IS treatment Pre-KTx	6 (20.7%)	4 (18.2%)	NS
Previous KTx	3 (10.3%)	3 (13.6%)	NS
CKD Etiology			
Unknown	14 (48%)	6 (27%)	
PKD	7 (24%)	6 (27%)	
Glomerulonephritis	2 (6.8%)	5 (22.5%)	
DN	1 (3%)	3 (13%)	
Others	5 (17%)	2 (9%)	
Dialysis	21 (72.4%)	14 (63.6%)	NS
Months in dialysis	22 (0-240)	12.6 (0-72)	NS
Type of donor			NS
After brain death	13 (44.8%)	11 (50%)	
After circulatory death	12 (41%)	8 (36.4%)	
Live donor	4 (13.7%)	3 (13%)	
CIT (min)	832 (81-1605)	735 (140-1500)	NS
HLA mismatches			NS
0-3	4 (13.8%)	6 (27.3%)	
4-6	25 (86%)	16 (72.7%)	
Anti-HLA Abs pre-KTx	14 (48%)	12 (54%)	NS
DSA pre-KTx	1 (3.4%)	2 (9.1%)	NS

	Stable Kidney Function (SKF) (n=29)	For Cause biopsy (BP) (n=22)	p Value
Induction therapy			NS
rATG	12 (41%)	13 (59%)	
Basiliximab	17 (58%)	7 (31.8%)	
None	0	2 (9%)	
Maintenance therapy			NS
PDN+FK+MMF	25 (86%)	21 (95.5%)	
PDN+FK+ i-mTOR	4 (13.8%)	1 (4.5%)	
Delay graft function	6 (20.7%)	5 (22.7%)	NS
CMV infection	4 (13.8%)	6 (27.3%)	NS
SARS CoV2 infection	3 (10.3%)	3 (13.6%)	NS
Creatinine (mg/dL)			
1 week	2.8 (0.74-12)	3.4 (0.6-12)	NS
3m	1.33 (0.71-2.4)	2.05 (0.9-8.7)	0.02
6m	1.39 (0.7-2.7)	1.81 (0.9-3.5)	0.01
12m	1.35 (0.6-2.7)	1.79 (1-3.2)	0.005
Proteinuria (mg/g)			
3m	225 (21-710)	710 (108-3085)	0.07
6m	192 (15-928)	582 (75-3521)	0.015
12m	210 (13-682)	424 (95-2972)	NS

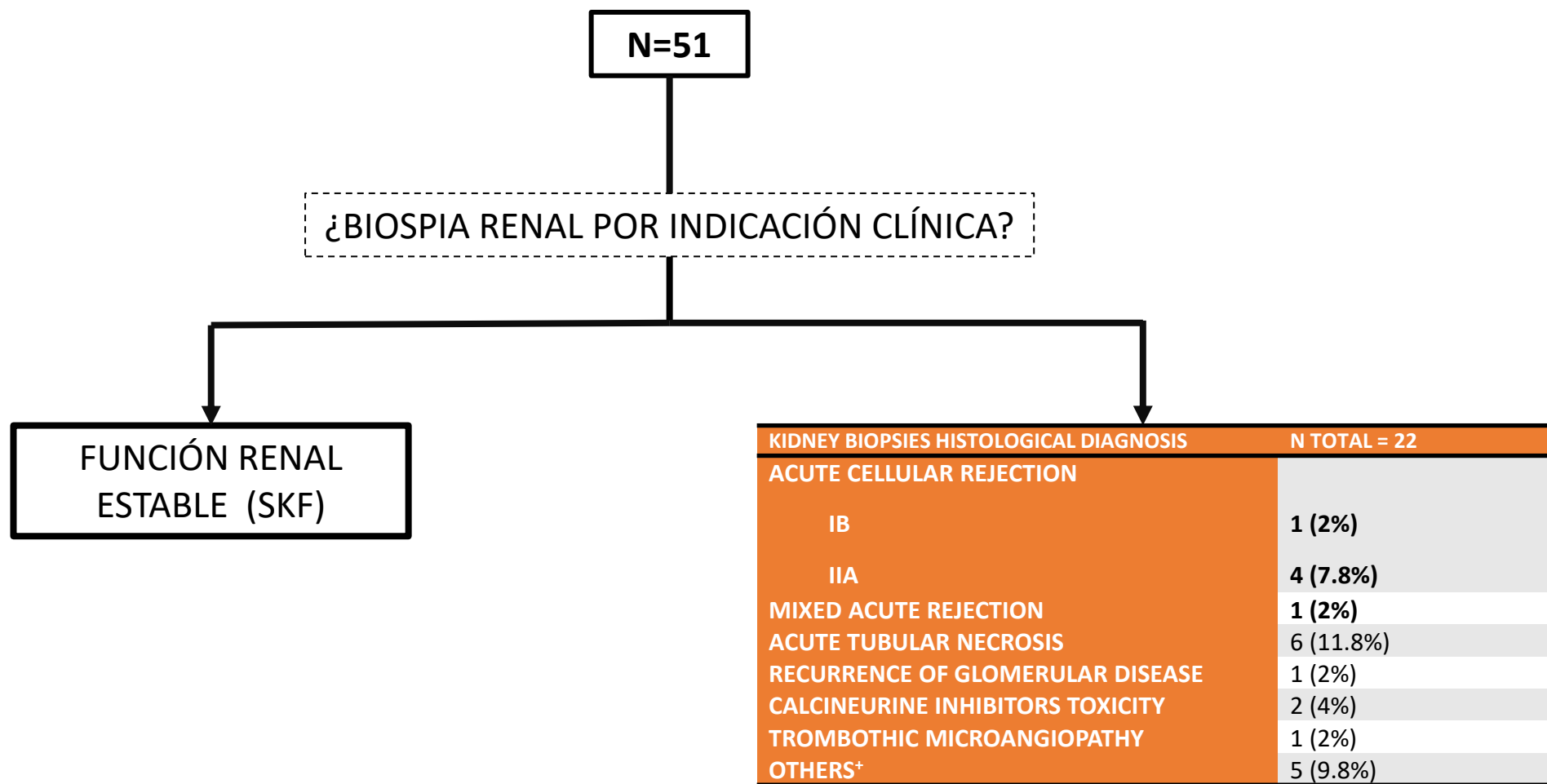
Mayor % Bregs a 3m en pacientes con función renal estable.



Relación de Bregs con el rechazo agudo



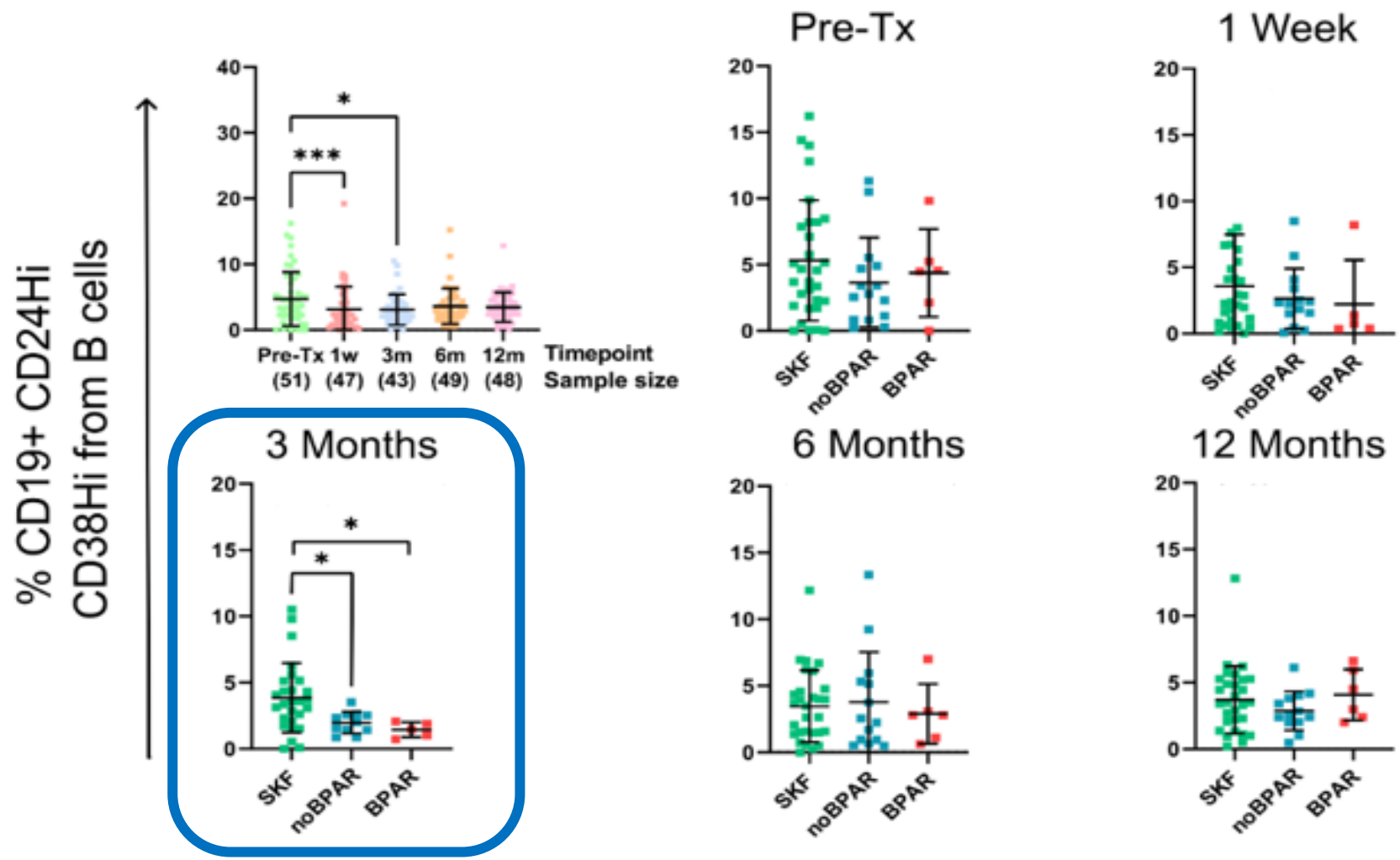
Relación de Bregs con el rechazo agudo



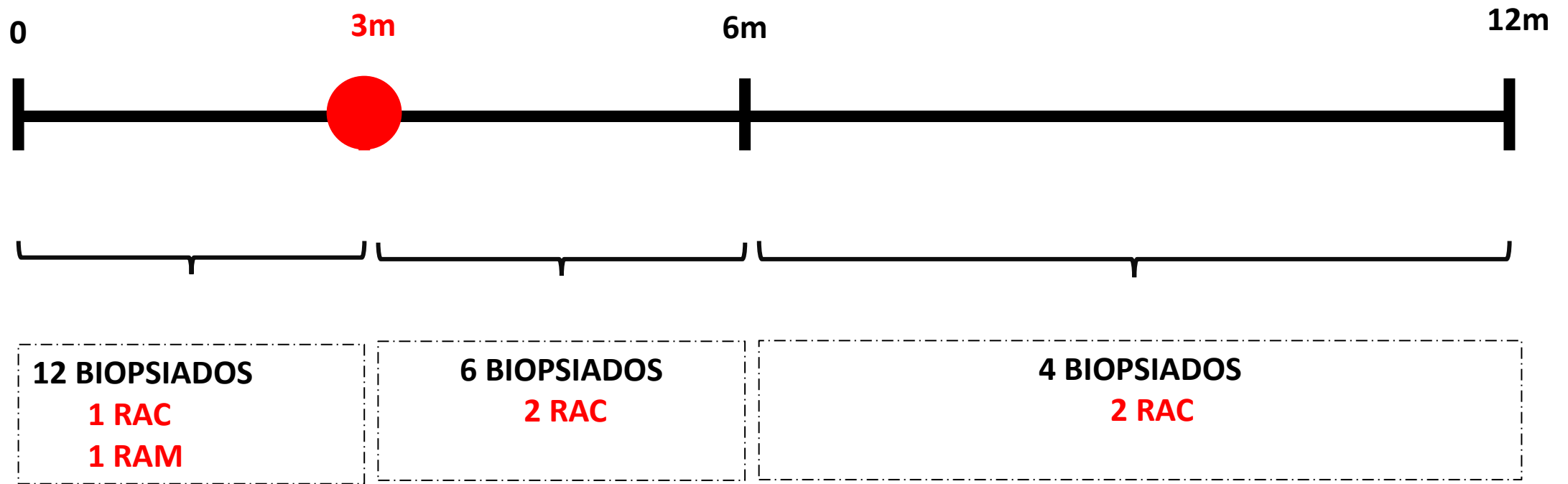
	BPAR (n =6)	No BPAR (n= 16)	p value
Age	59 (55-63)	58 (35-74)	NS
Sex (male)	2 (33%)	9 (56.3%)	NS
IS treatment Pre-KTx	0	4 (25%)	NS
Previous KTx	0	3 (18.8%)	NS
CKD Etiology			NS
Unknown	1 (16.7%)	5 (31.3%)	
PKD	3 (50%)	3 (18.8%)	
Glomerulonephritis	0	3 (18.8%)	
DN	1 (16.7%)	2 (12.5%)	
Others	1 (16.7%)	3 (18.8%)	
Dialysis	4 (66.7)	10 (62.5)	NS
Months in dialysis	2 (0-72)	9.6 (0-64)	NS
Type of donor			
After brain death	2 (33%)	8 (50%)	
After circulatory death	3 (50%)	5 (31.3%)	
Live donor	1 (16.7%)	3 (18.8%)	
CIT (min)	720 (210-1125)	752 (140-1500)	NS
HLA mismatches			
0-3	2 (33%)	4 (25%)	
4-6	4 (66.7%)	12 (75%)	
Anti-HLA Abs pre-KTx	6 (100%)	6 (37.5%)	0.001
DSA pre-KTx	2 (33.3%)	0	0.01

	BPAR (n=6)	No BPAR (n=16)	p value
Induction therapy			NS
rATG	4 (66.7)	9 (56.3)	
Basiliximab	1 (16.7)	6 (37.5)	
None	1 (16.7)	1 (6.3)	
Maintenance therapy			NS
PDN+FK+MMF	6 (100%)	15 (93.8%)	
PDN+FK+ i-mTOR	0	1 (6.3%)	
Delay graft function	1 (16.7%)	4 (25%)	NS
CMV infection	1 (16.7%)	5 (31.3%)	NS
SARS CoV2 infection	2 (33%)	1 (6.3%)	NS
Creatinine (mg/dL)			NS
1 week	2.7 (1-12)	2.2 (0.68-9.16)	
3m	1.62 (1-2.6)	1.79 (0.8-8.7)	
6m	1.6 (1-3.47)	1.59 (0.8-3.2)	
12m	2.07 (1.1-3.1)	1.64 (1-2.9)	
Proteinuria (mg/g)			NS
3m	292 (108-1227)	316 (145-3085)	
6m	436 (98-949)	210 (75-3521)	
12m	183 (98-459)	177 (95-2972)	

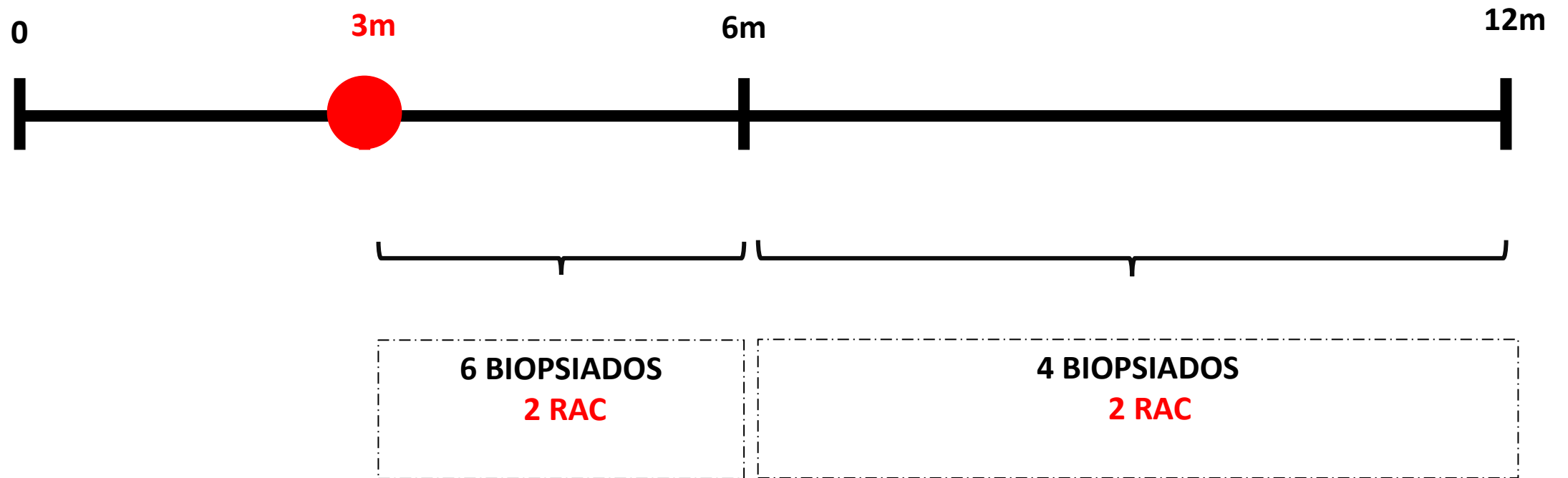
Menor % Bregs 3m en pacientes con BPAR.



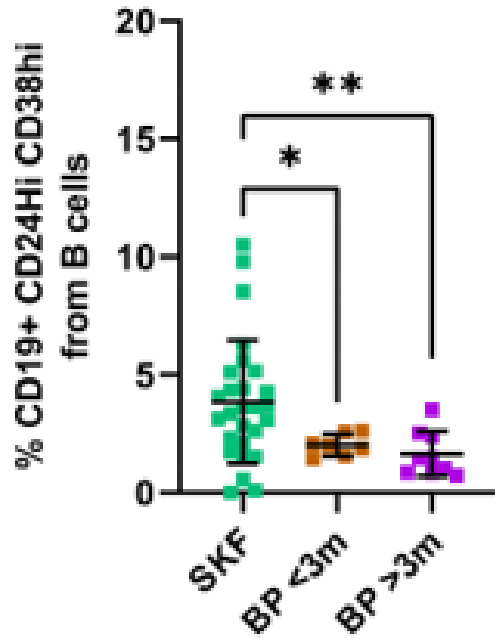
Pacientes biopsiados durante el seguimiento



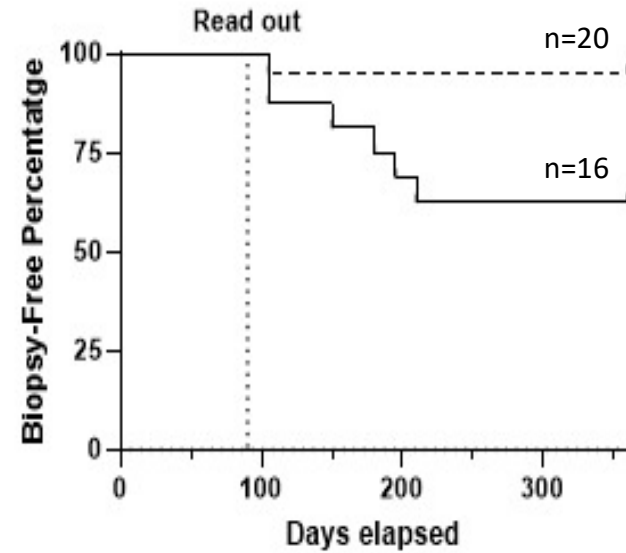
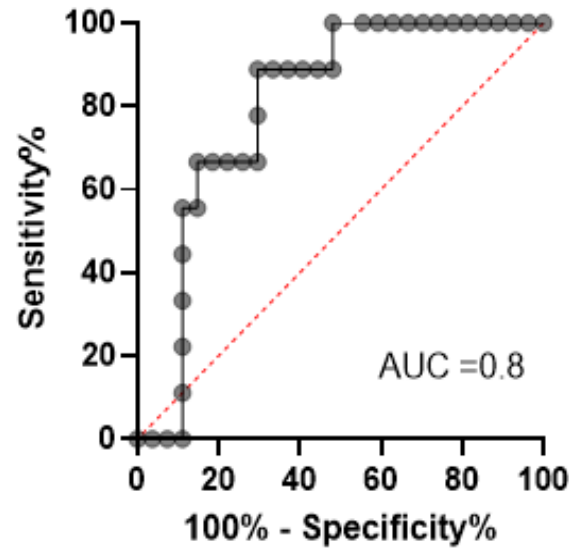
Pacientes biopsiados durante el seguimiento



Valor predictivo de %Bregs3m de mejor función renal



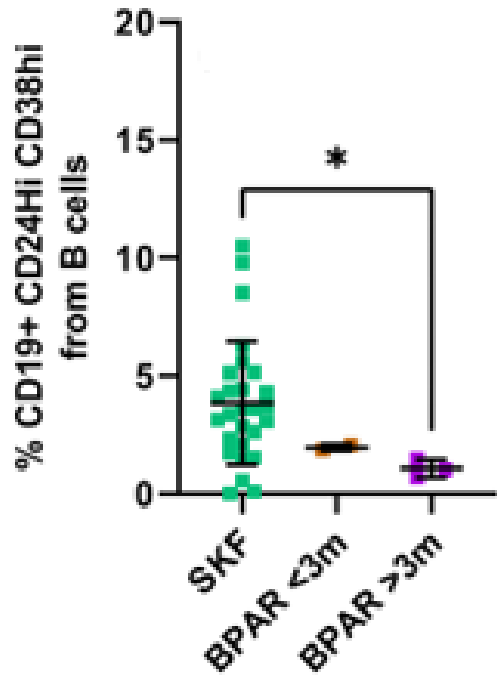
BP >3m ROC curve of % TR 3 Months



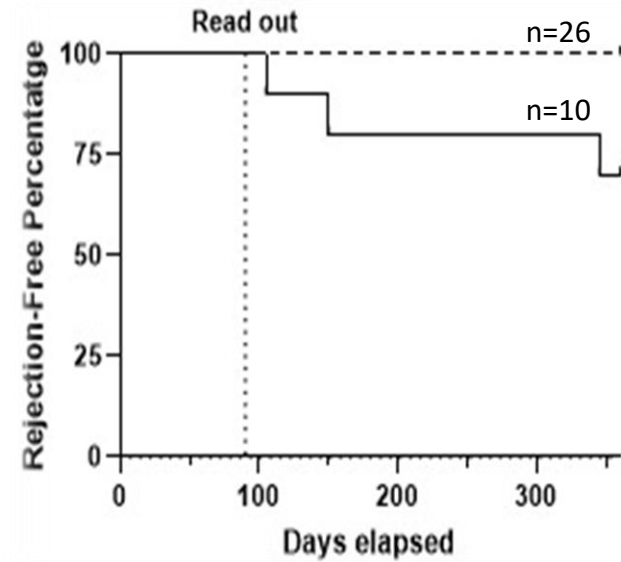
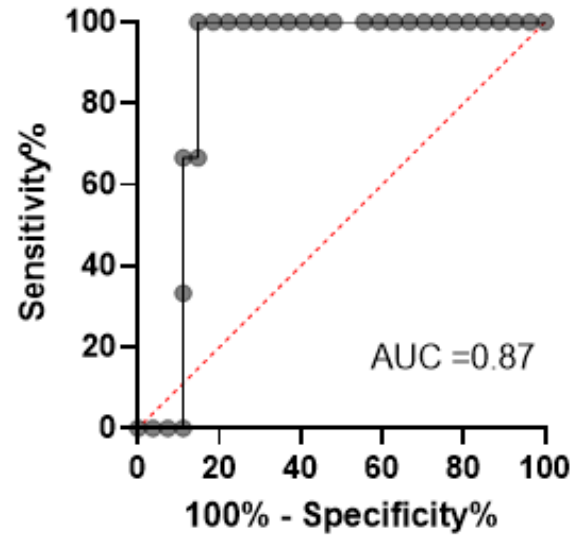
--- % 3m TR B cells > 2.575
— % 3m TR B cells < 2.575

Se 88.89%
Sp 85.19%

Valor predictivo de %Bregs3m de riesgo de rechazo



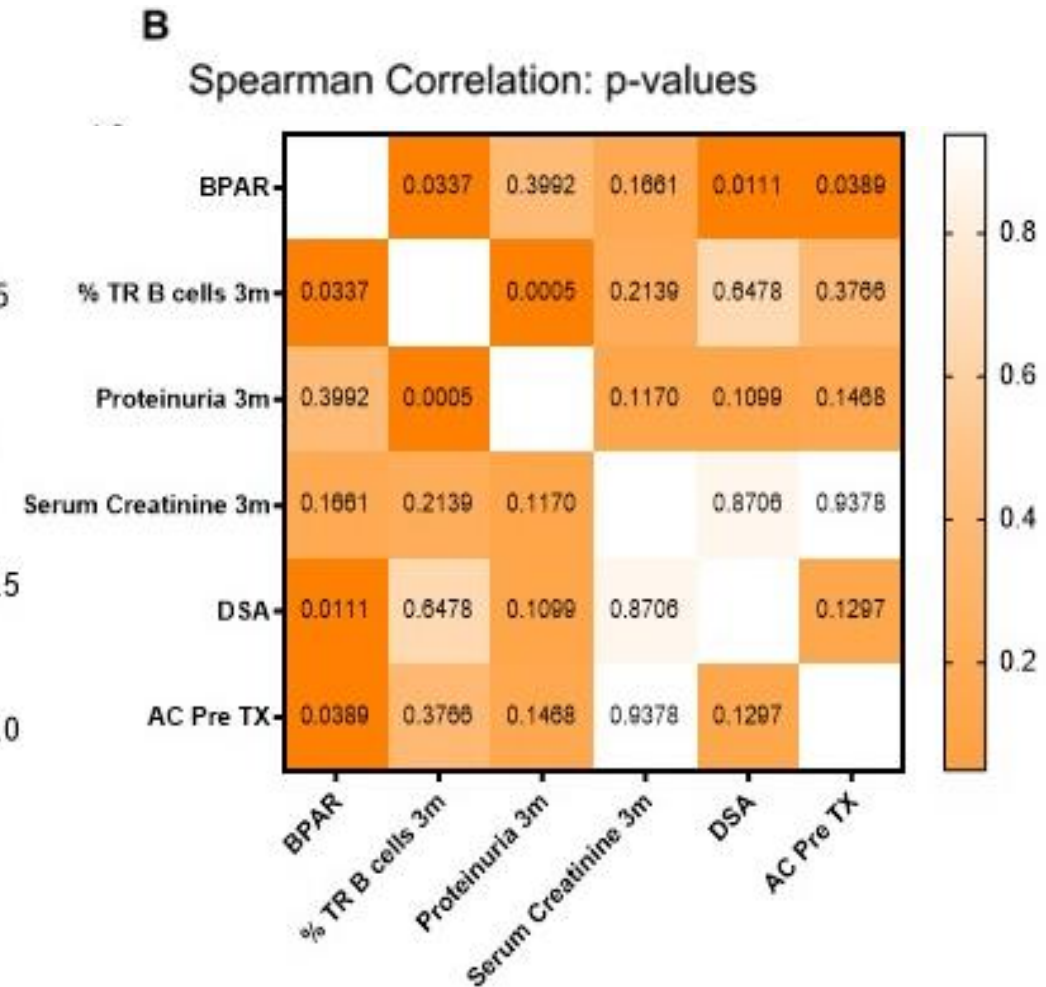
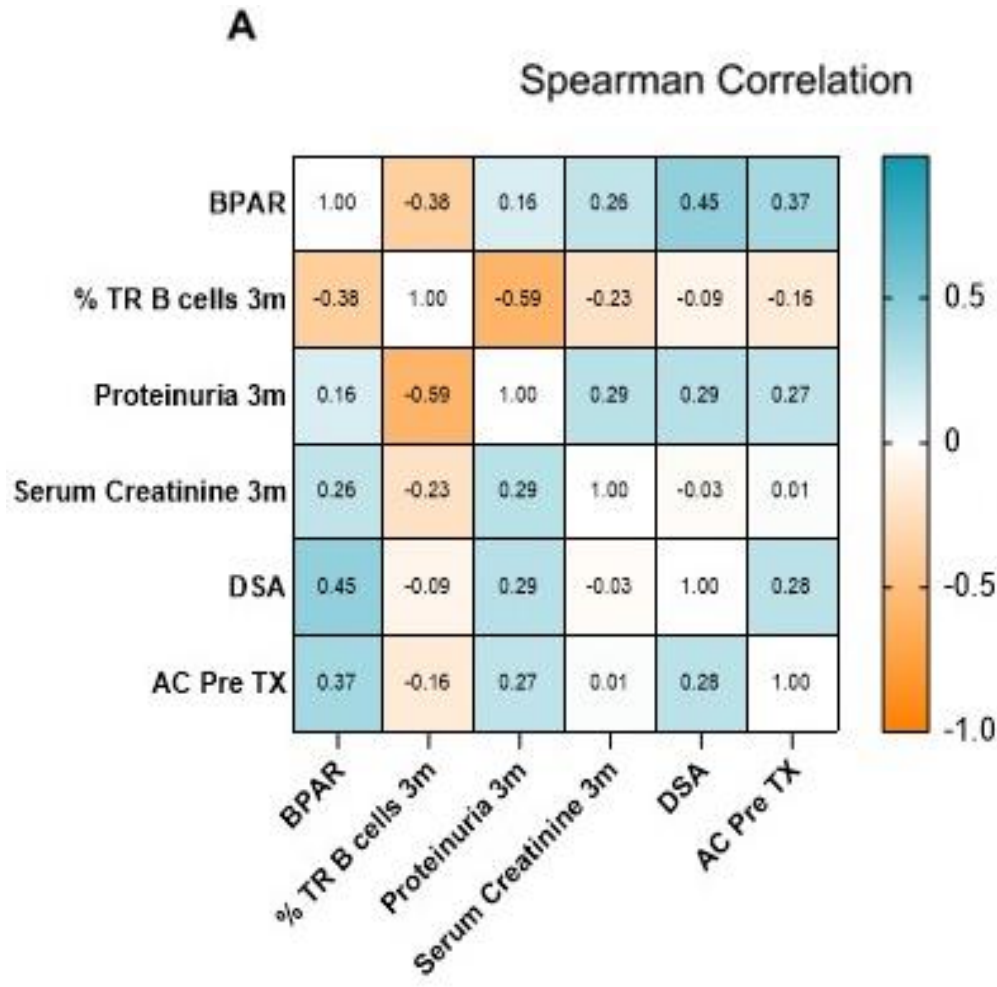
BPAR >3m ROC curve of % TR 3 Months



--- % 3m TR B cells > 1.5
— % 3m TR B cells < 1.5

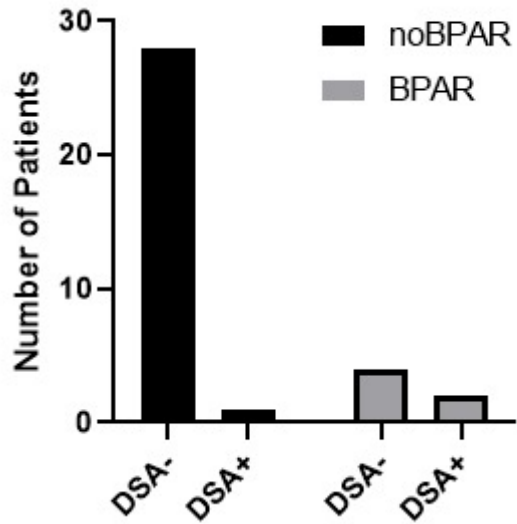
Se 100%
Sp 85%

Valor predictivo de %Bregs3m de riesgo de rechazo



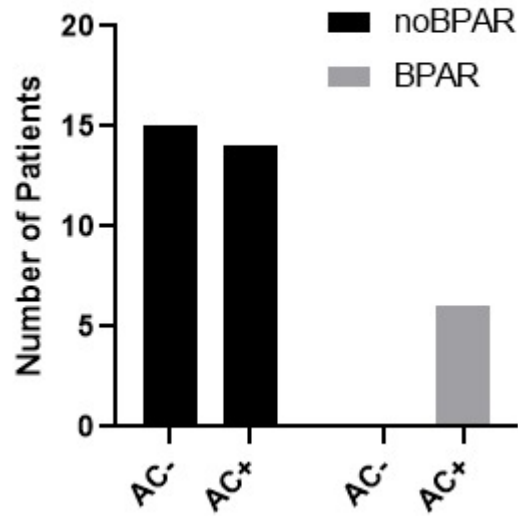
%Bregs3m tiene mejor Se/Sp para predecir BPAR

SKF vs BPAR DSA



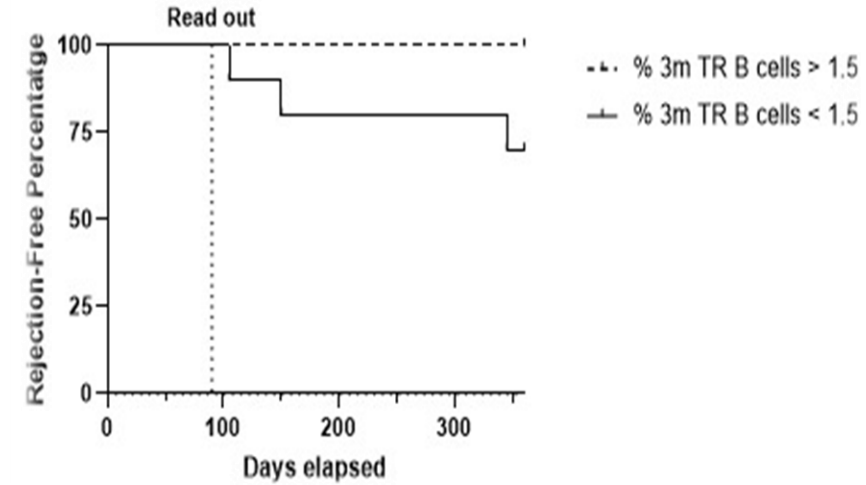
Effect size	Value
Sensitivity	0.9655
Specificity	0.3333

SKF vs BPAR AC +/- Pre TX



Effect size	Value
Sensitivity	0.5172
Specificity	1.000

SKF vs BPAR Bregs>1.5%



Effect size	Value
Sensitivity	1.000
Specificity	0.850

CONCLUSIONES

- Bregs tienen una implicación en la **tolerancia del injerto**
- **Mayor nºBregs a los 3 meses** se relacionan con **mejor evolución** del injerto renal y **menor riesgo de rechazo** con una alta sensibilidad y especificidad en el primer año.
- **Biomarcador** de evolución de función renal.
- **Estratificar** pacientes **en función del riesgo** de rechazo
 - $\%Bregs_{3m} > 2.5 =$ Bajo riesgo
 - $\% Bregs_{3m} < 1.5 =$ Alto riesgo
- **Individualizar inmunosupresión.**

AGRADECIMIENTOS

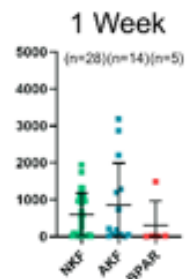
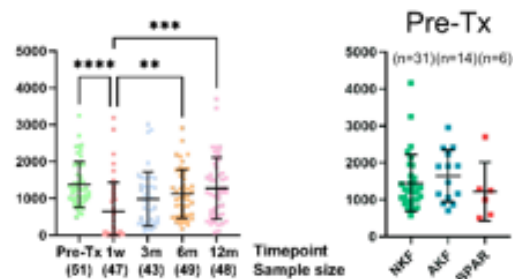


Marcella Franquesa PhD
Sergio García García PhD student
Francesc E Borrás PhD
Marta Closs PhD student

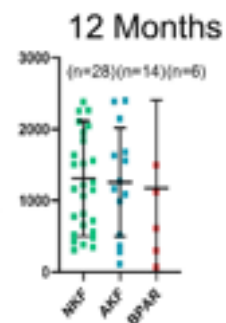
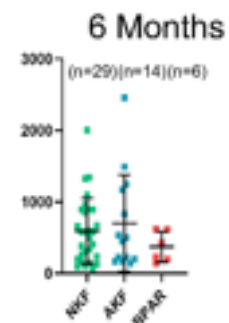
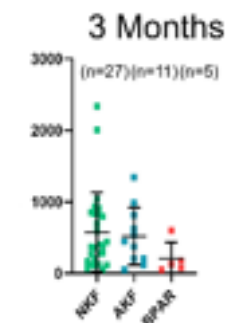
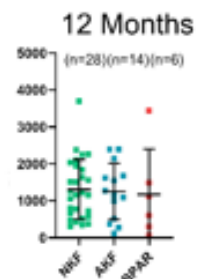
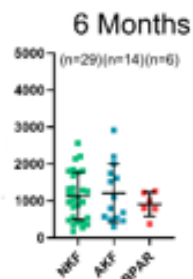
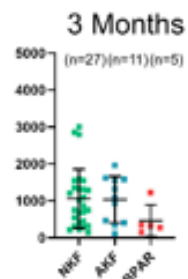
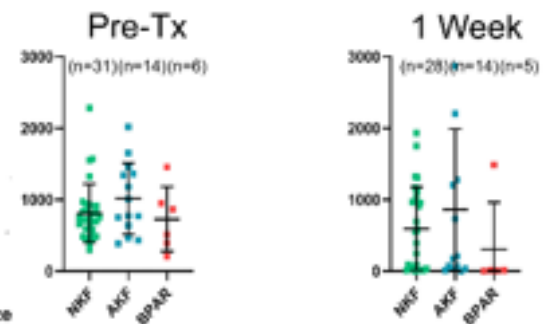
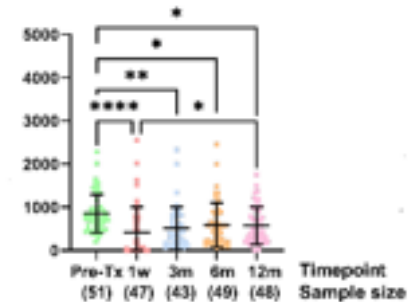


Laura Cañas MD PhD
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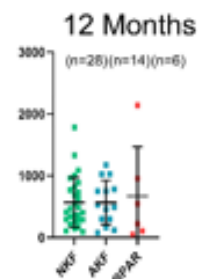
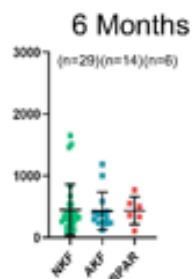
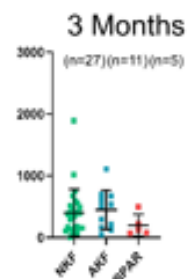
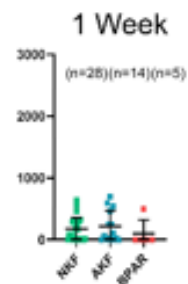
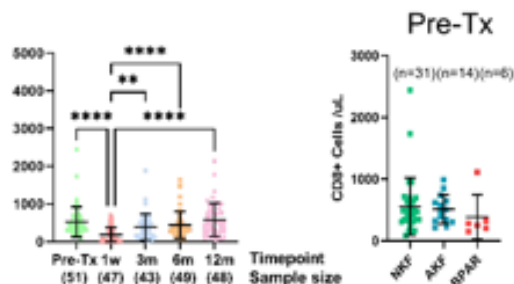
Number of T cells: CD3+ Cells / μ L



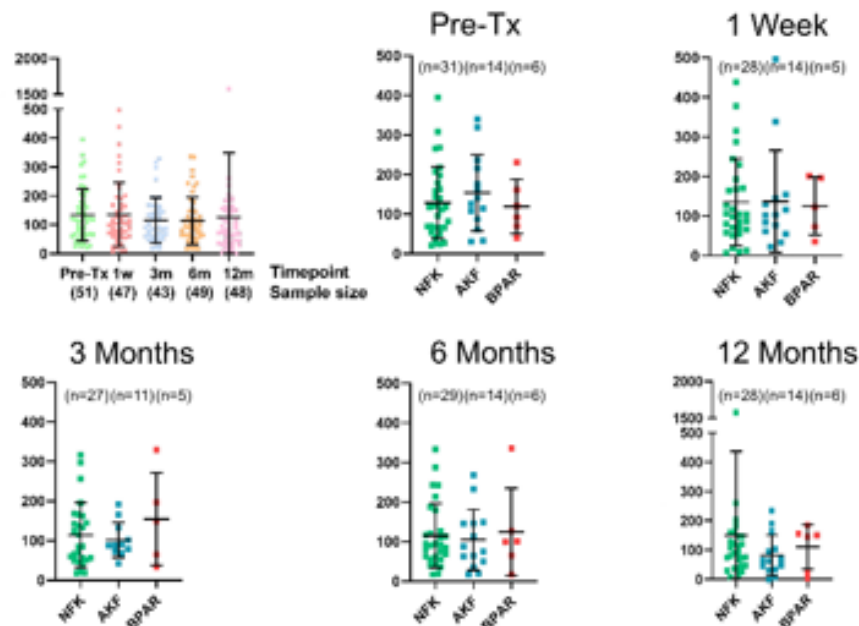
Number of CD3+ CD4+ Cells / μ L



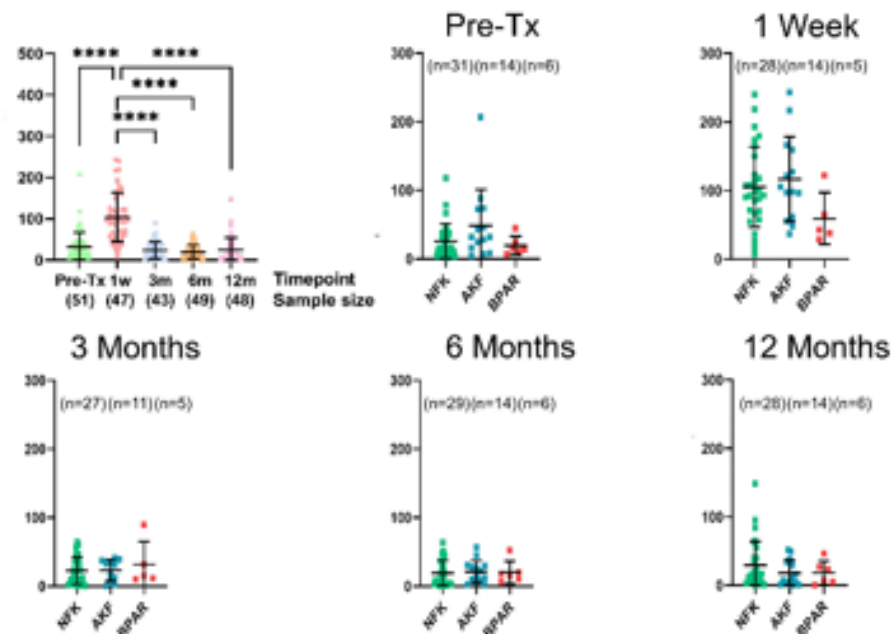
Number of CD3+ CD8+ Cells / μ L



Number of B cells: CD19+ Cells / μ L



CD19+ CD27+ IgD- Cells / μ L



CD19+ CD27- IgD+ Cells / μ L

