# Places des anti-plasmocytaires en transplantation rénale

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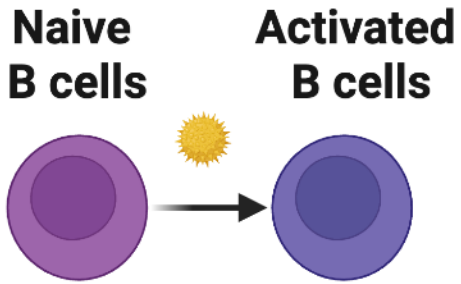
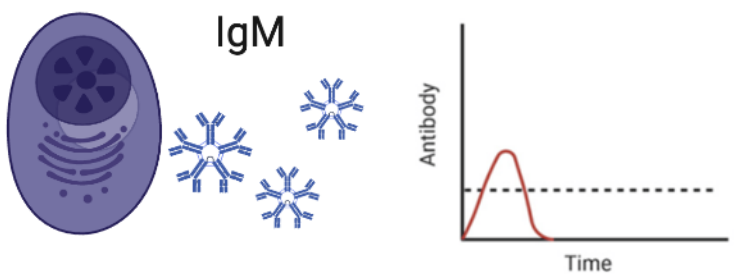

Naive
B cells
Activated
B cells

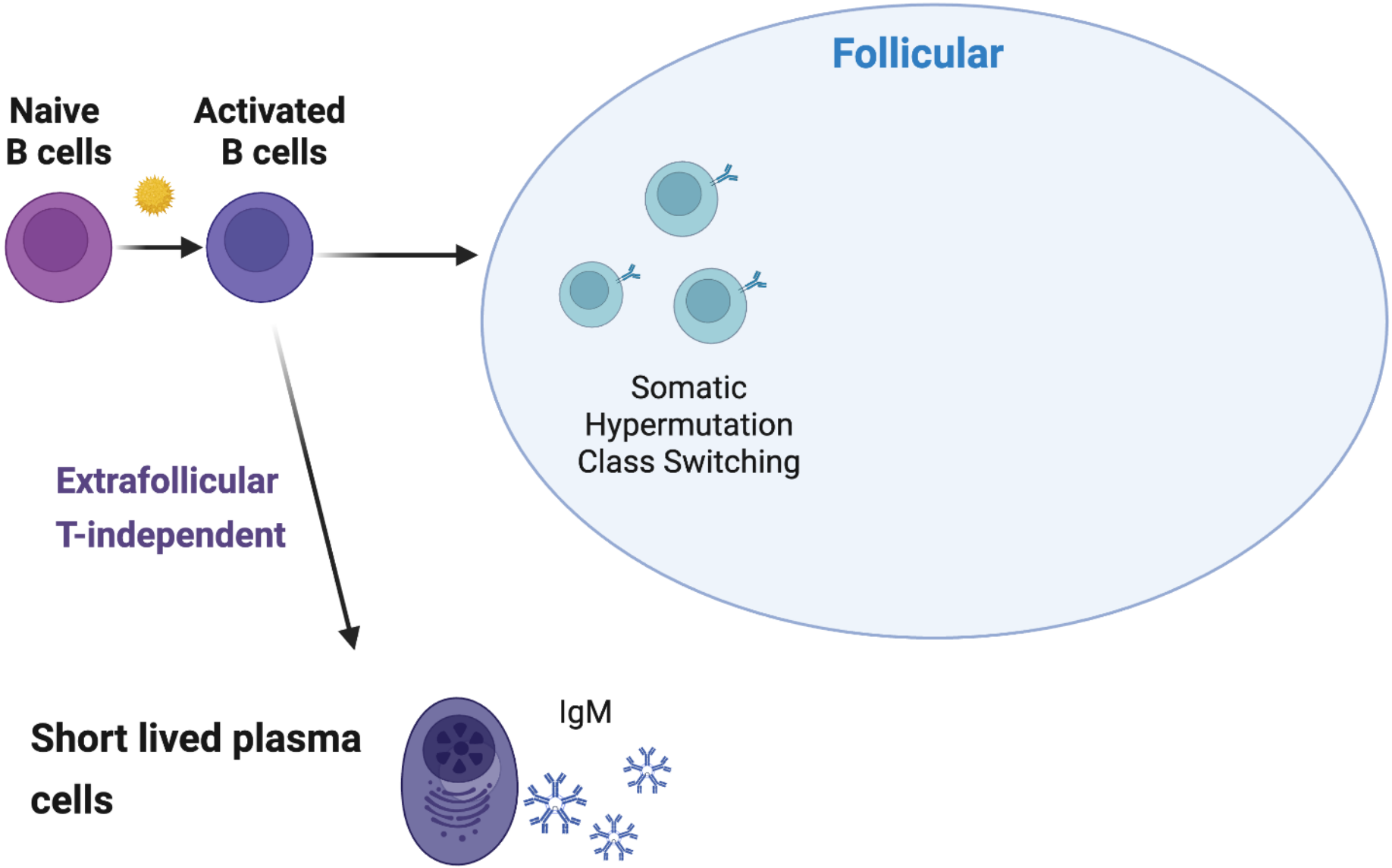
Naive B cells

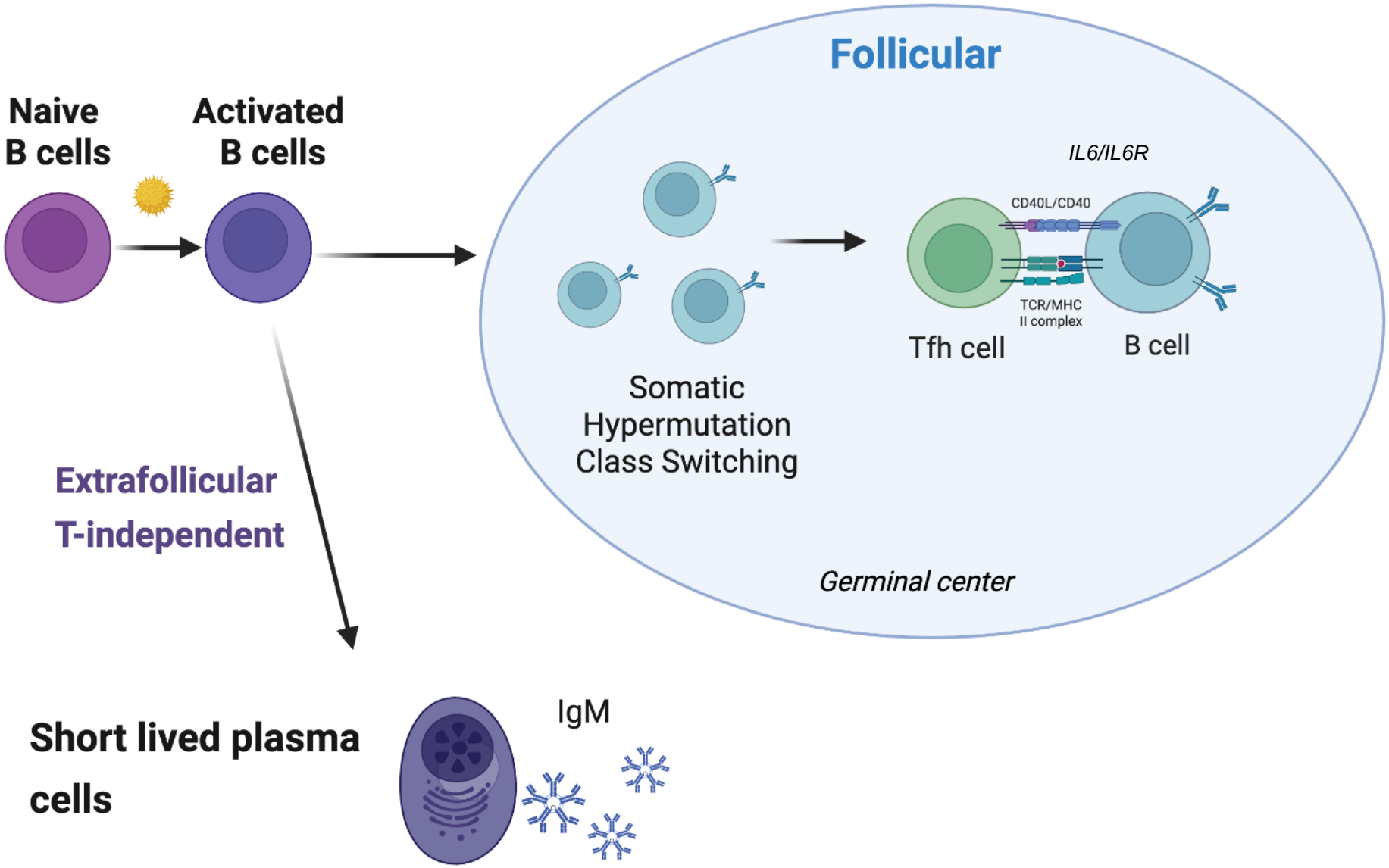
Activated B cells

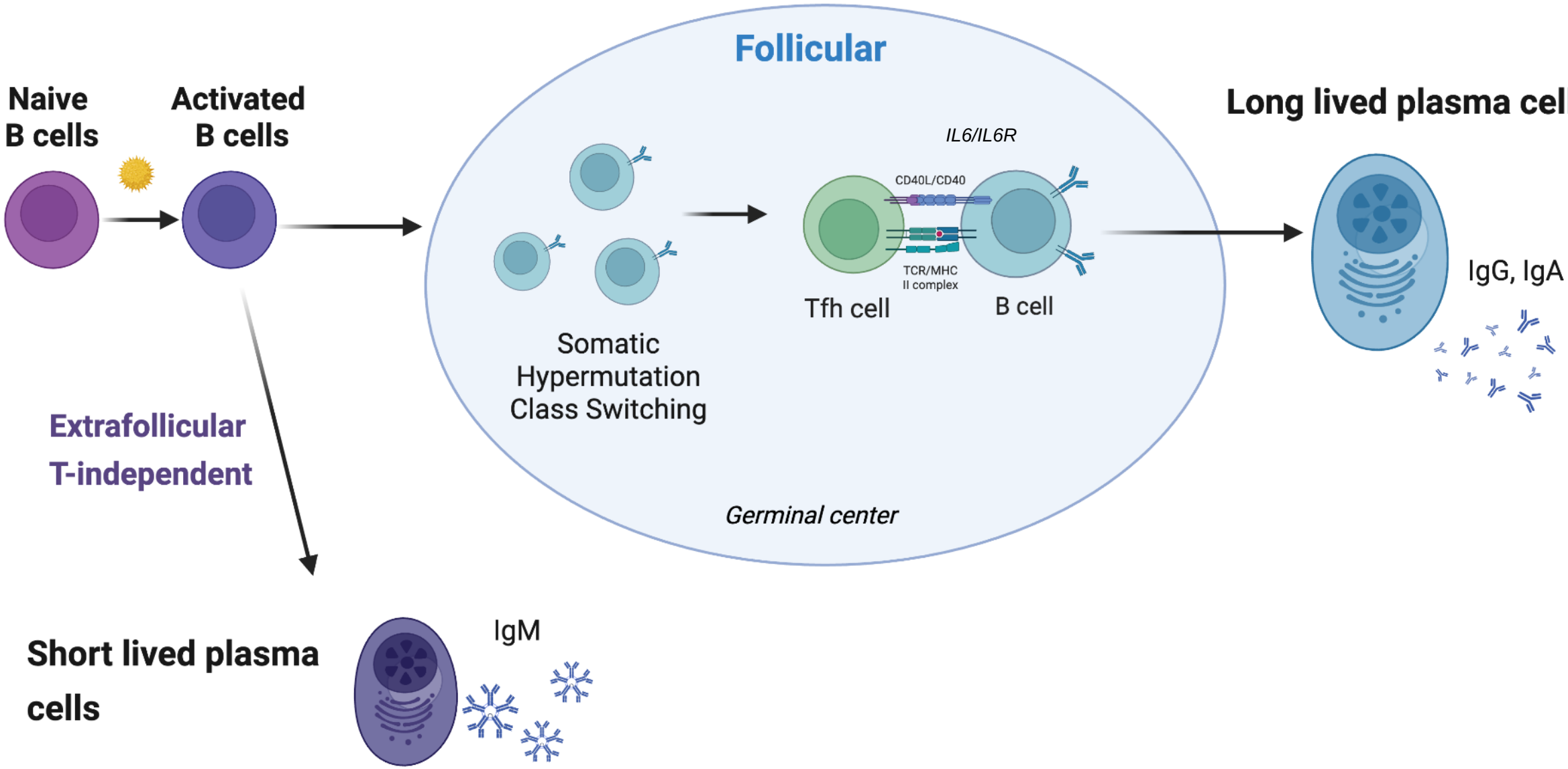
Extrafollicular T-independent

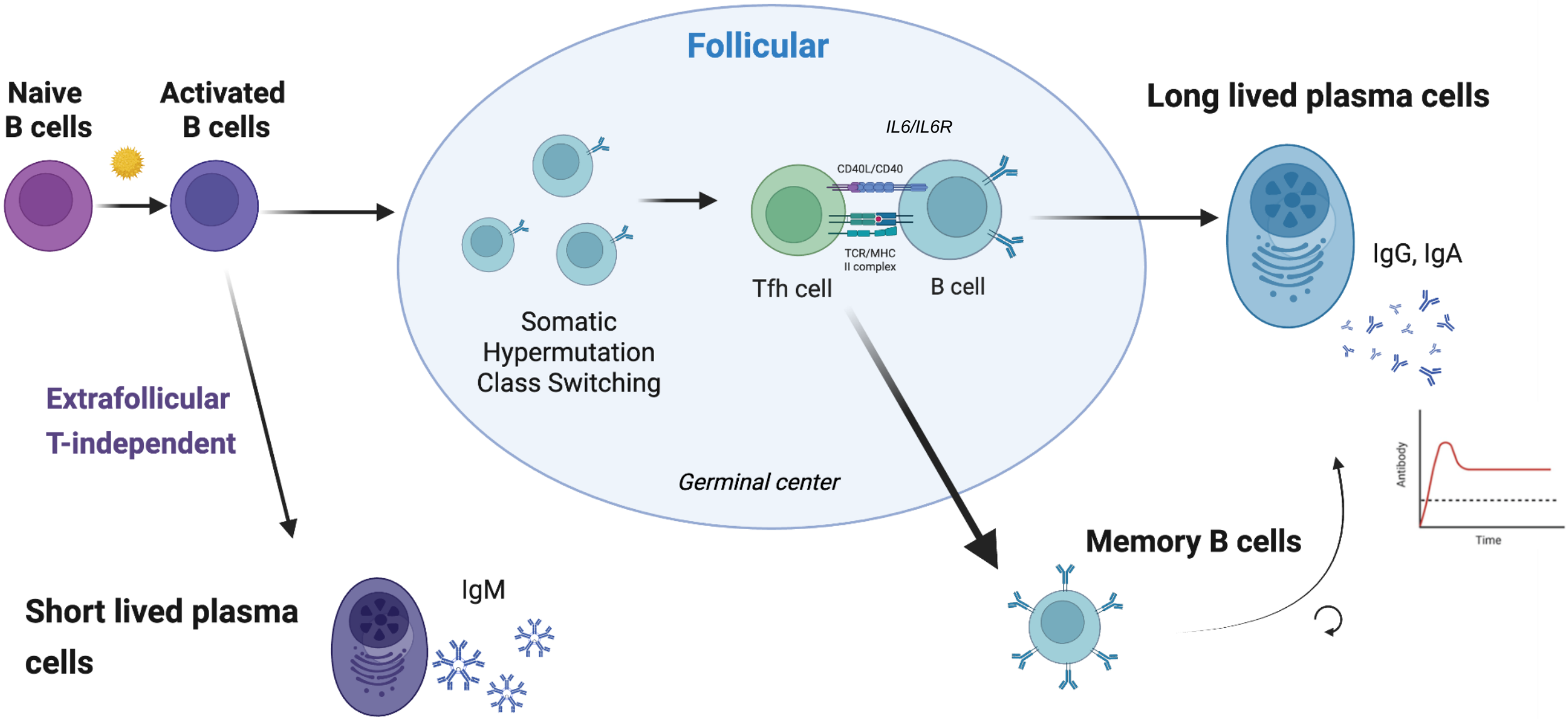
Short lived plasma cells

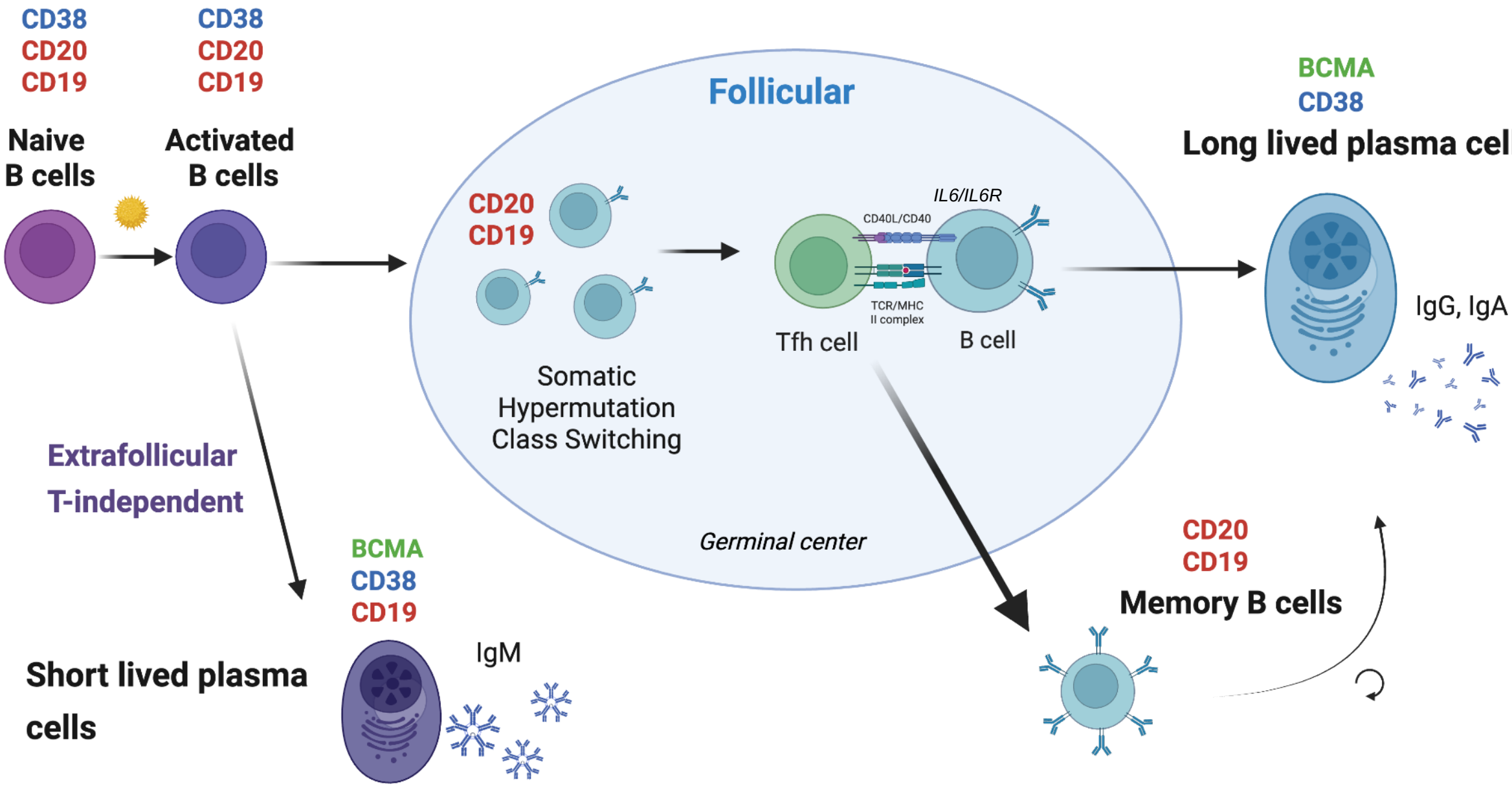



Naive
B cells
Activated
B cells
Follicular
Somatic
Hypermutation
Class Switching
Extrafollicular
T-independent
Short lived plasma
cells
IgM


Naive
B cells
Activated
B cells
Follicular
IL6/IL6R
CD40L/CD40
TCR/MHC
II complex
Tfh cell
B cell
Somatic
Hypermutation
Class Switching
Germinal center
Extrafollicular
T-independent
Short lived plasma
cells
IgM

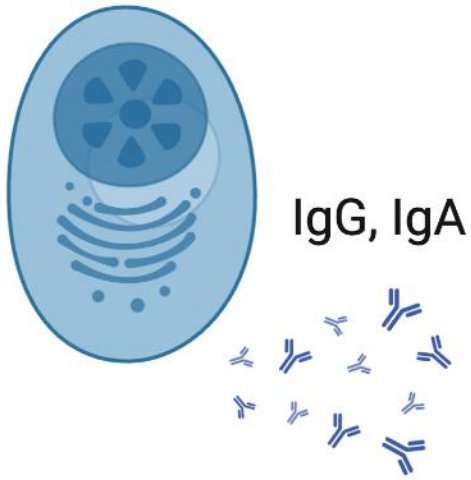

Naive
B cells
Activated
B cells
Follicular
Somatic
Hypermutation
Class Switching
IL6/IL6R
CD40L/CD40
TCR/MHC
II complex
Tfh cell
B cell
Germinal center
Long lived plasma cells
IgG, IgA
Extrafollicular
T-independent
Short lived plasma
cells
IgM

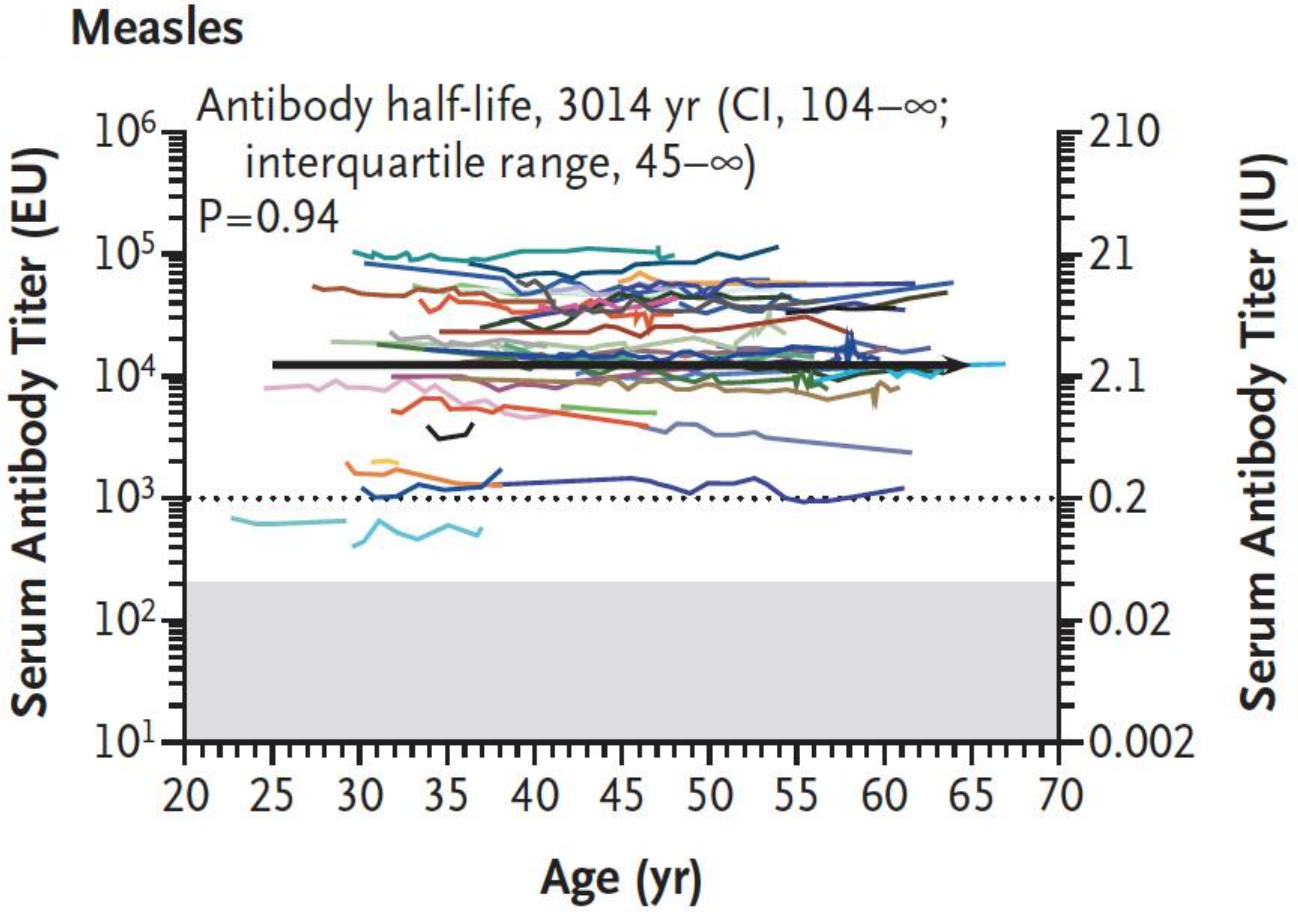

Naive
B cells
Activated
B cells
Follicular
Somatic
Hypermutation
Class Switching
IL6/IL6R
CD40L/CD40
TCR/MHC
II complex
Tfh cell
B cell
Germinal center
Long lived plasma cells
IgG, IgA
Antibody
Time
Extrafollicular
T-independent
Short lived plasma
cells
IgM
Memory B cells


CD38
CD20
CD19
Naive
B cells
CD38
CD20
CD19
Activated
B cells
Follicular
CD20
CD19
Somatic
Hypermutation
Class Switching
IL6/IL6R
CD40L/CD40
TCR/MHC
II complex
Tfh cell
B cell
Germinal center
BCMA
CD38
Long lived plasma cells
IgG, IgA
Extrafollicular
T-independent
BCMA
CD38
CD19
IgM
Short lived plasma
cells
CD20
CD19
Memory B cells

# Vaccine-induced antibody levels are stable overtime

**Long lived plasma cells**

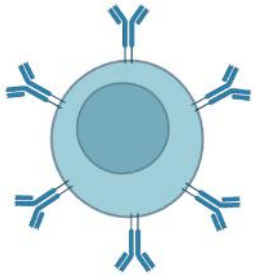


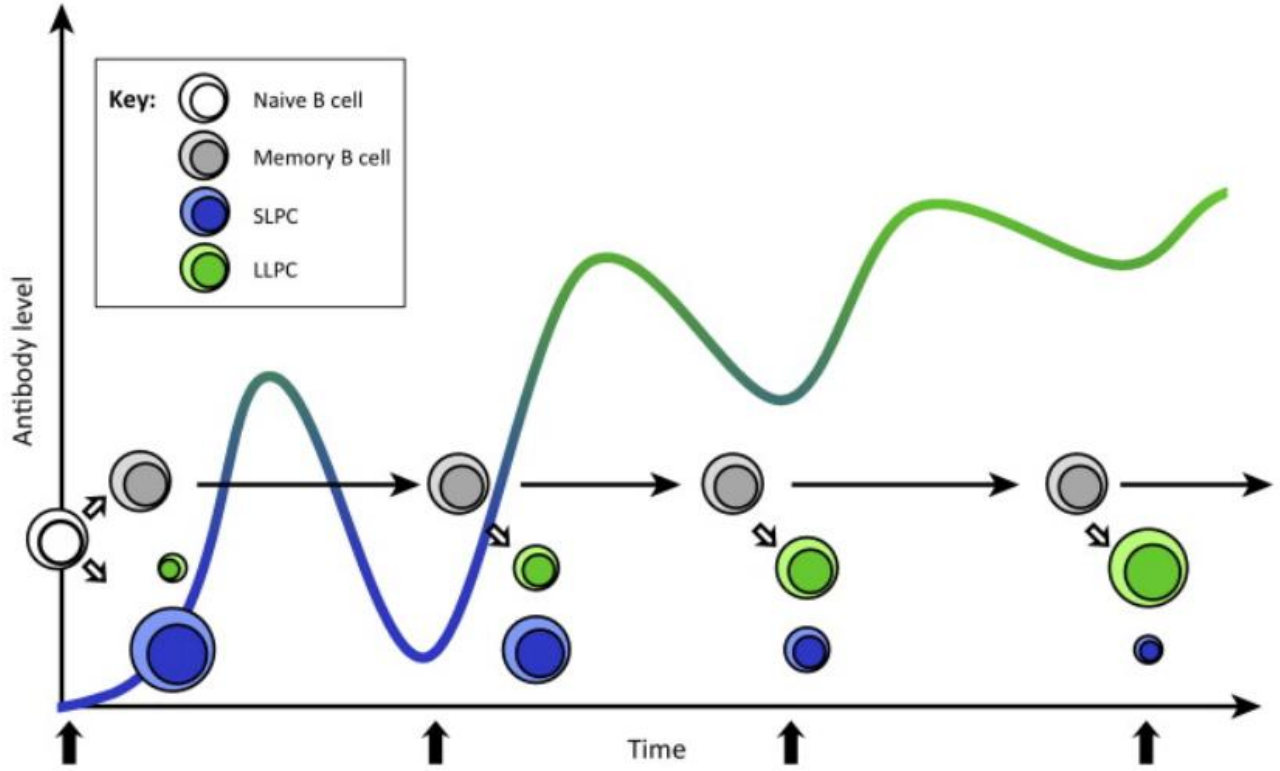




Amanna IJ et al NEJM 2007

# Increasing antibody titers upon recall stimulation

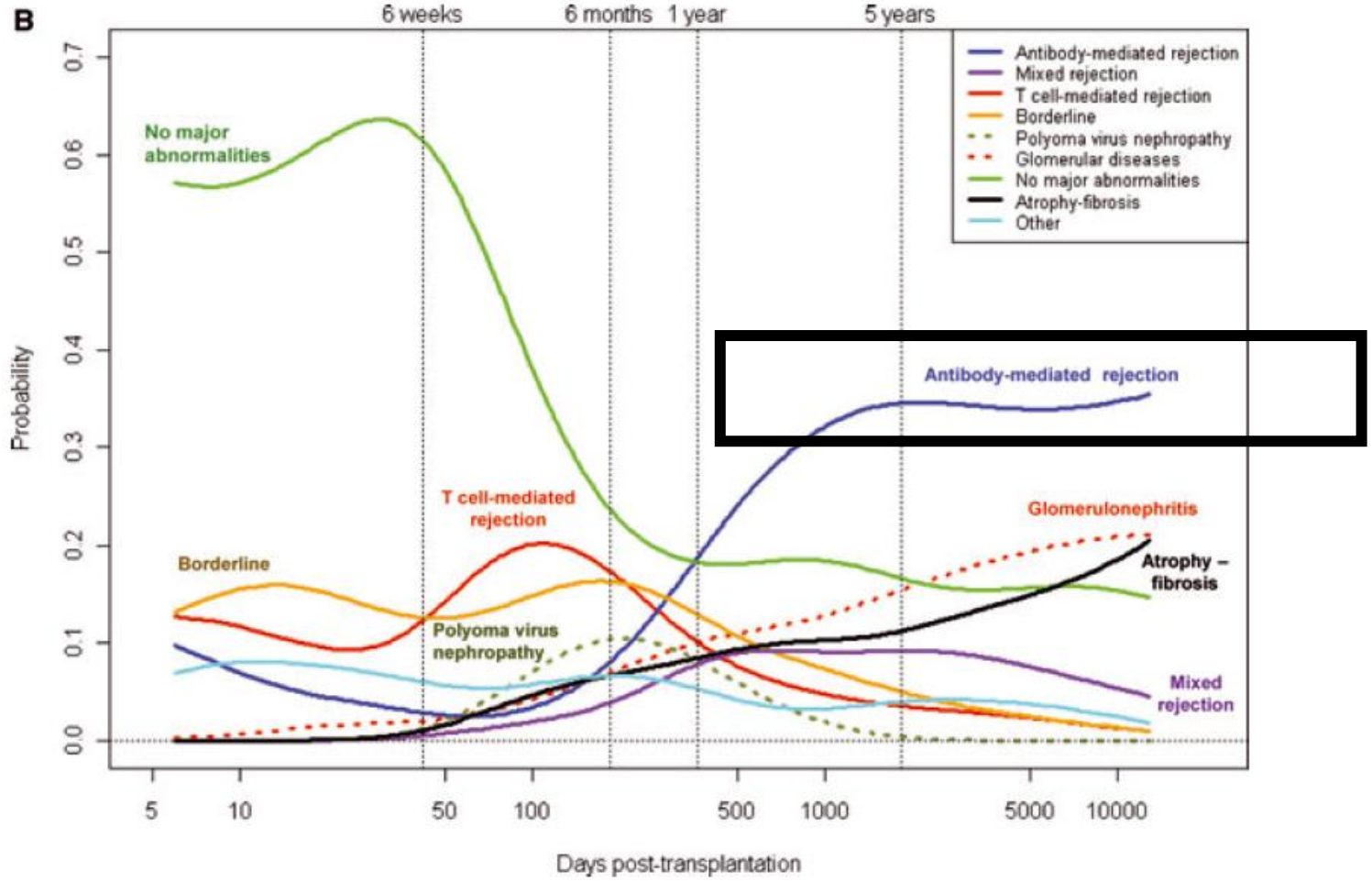
## Memory B cells





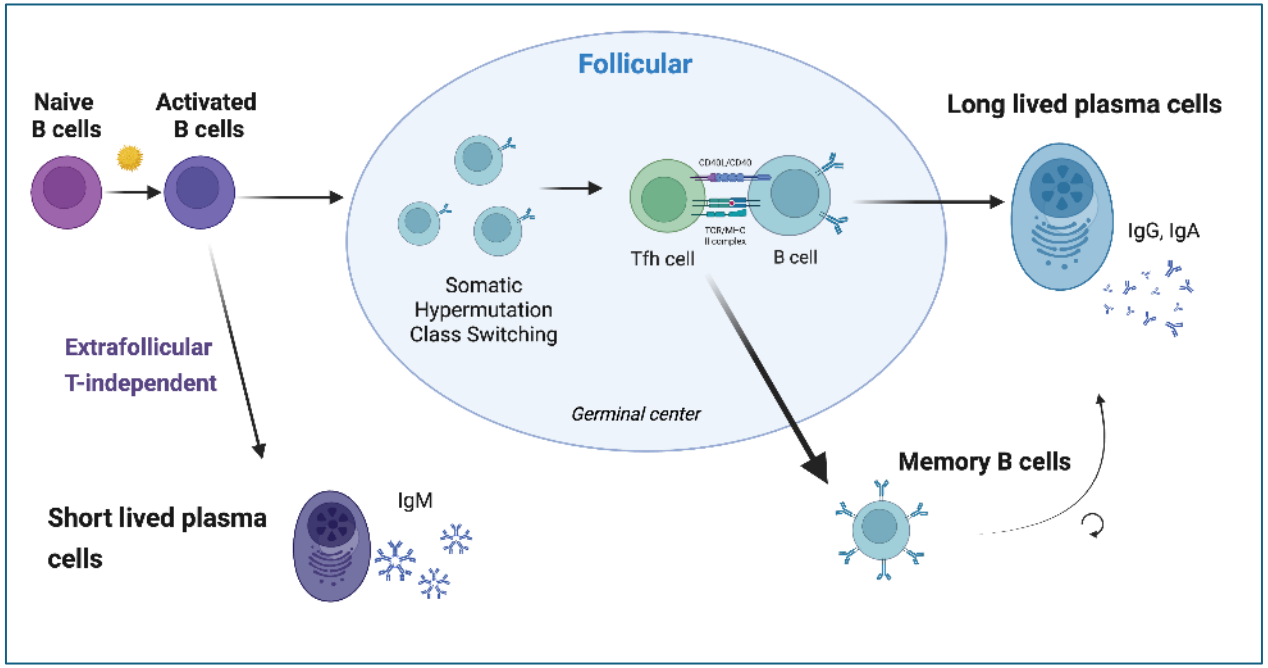

Antigen Stimulation

# Antibody-mediated rejection : main cause of late graft loss




PF Halloran et al, Kidney Int 2014

# Plasma cell targeting in kidney transplantation



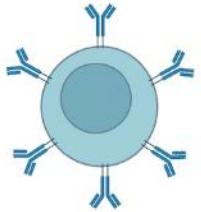

**HLA Desensitization**

**Antibody-mediated rejection**

**Antibody-mediated disease**

# HLA desensitization in transplantation: toolbox

B-cell



**Rituximab***

*Ramos AJT 2007*
*Vo NEJM 2008*

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Plasma-cell

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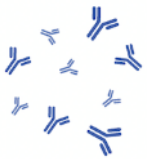

**Plasma Exchange**

*Montgomery Transplantation 2000*
*Akalin CJASN 2008*

**IVIG**

*Glotz AJT 2002*
*Jordan JASN 2004*

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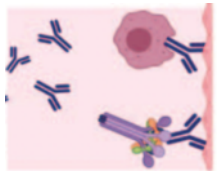


Complement

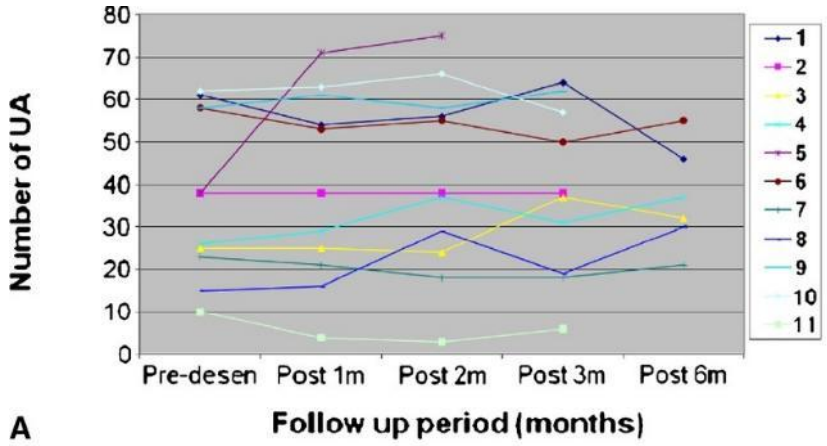
**2000** **2010** **2020** **2030**

# Rituximab as a sole desensitization agent

IVIG: 2 g/kg at day 0 and 30

Rituximab: 375 mg/m2 at day 15

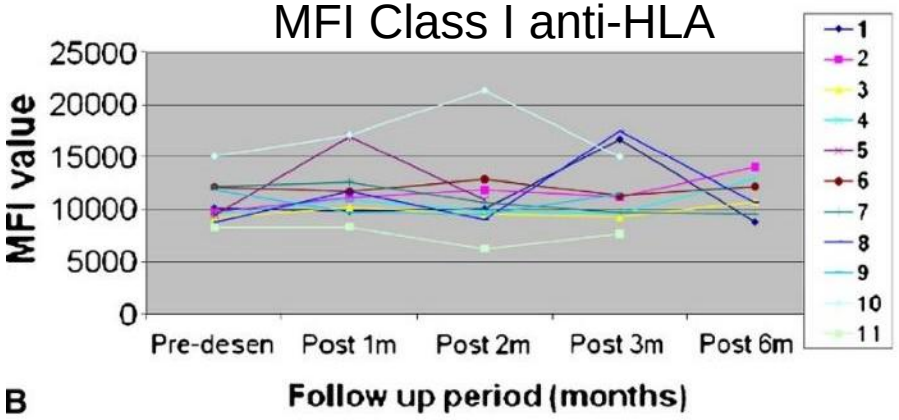
Unacceptable Antigens #



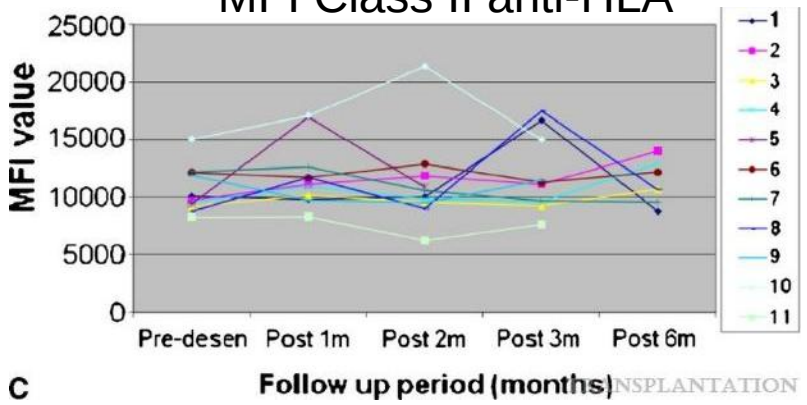

mean class I cPRA 97% ± 4% and class II cPRA of 86% ± 25%

Marfo K et al. Transplantation 2012

MFI Class I anti-HLA

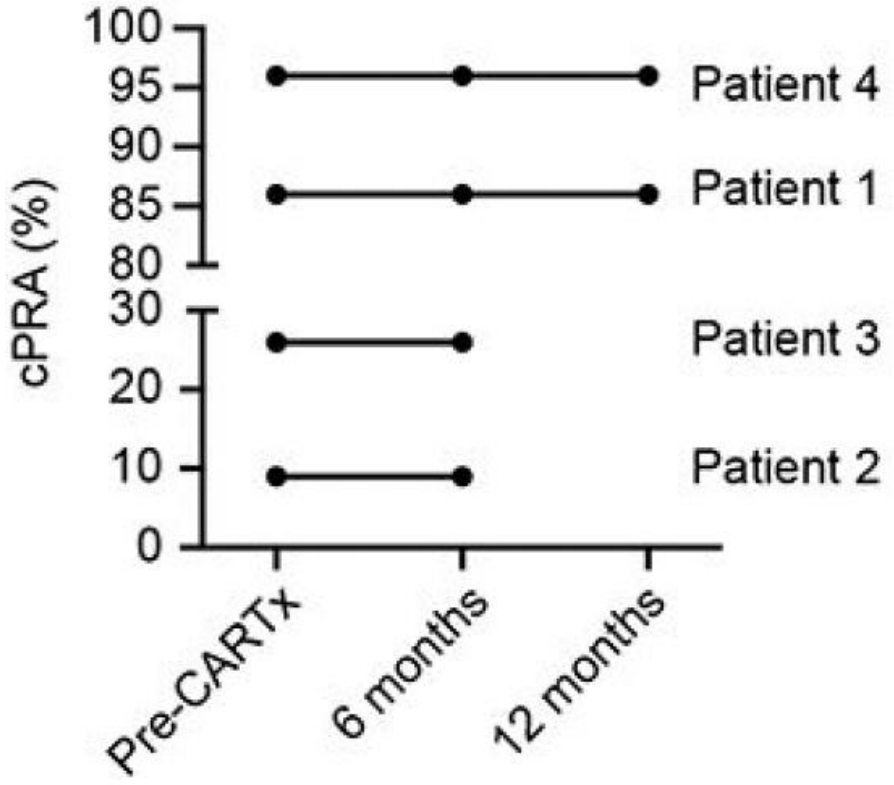



MFI Class II anti-HLA




Unmet need for HLA desensitization in highly sensitized patients

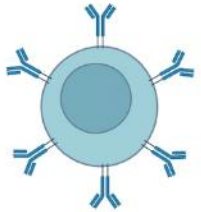
# CD19-targeted CAR T fails to decrease anti-HLA Ab levels




Hill JA et al. Am J Transplant 2023

# HLA desensitization in transplantation: toolbox

B-cell



**Rituximab***

*Ramos AJT 2007*
*Vo NEJM 2008*

**Belimumab***

*Banham Lancet 2018*
*Argawal Transp Immunol 2021*

Plasma-cell

**Bortezomib***

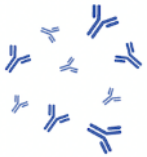
*Perry AJT 2009*
*Ejaz AJT 2013*

**Tocilizumab***

*Vo Transplantation 2015*

**Carfilzomib***

*Tremblay AJT 2020*



**Plasma Exchange**

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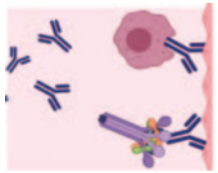
**IVIG**

*Glotz AJT 2002*
*Jordan JASN 2004*



**Eculizumab***

*Stegall AJT 2011*
*Cornell AJT 2015*

**C1-INH***

*Vo Transplantation 2015*

Complement

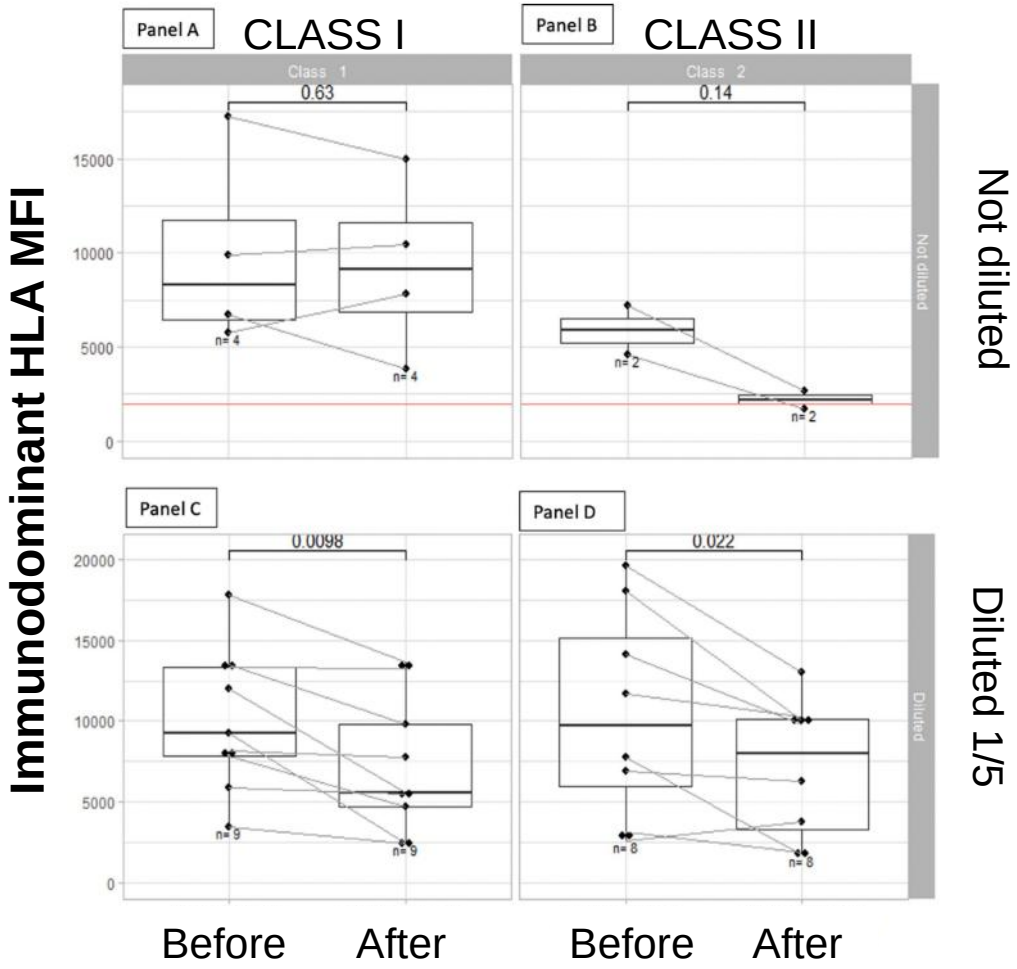
**2000** **2010** **2020** **2030**

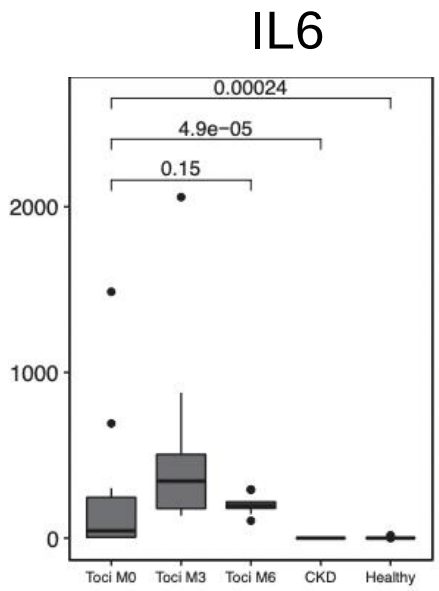
# IL6 pathway : disappointing results of anti-IL6R in monotherapy

Tocilizumab 8 mg/kg IV monthly, N=13

Decrease of plasmablasts
Increase of naive B cells

Marginal effect on anti-HLA MFI

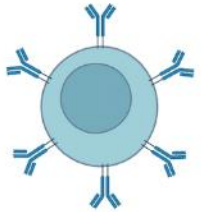



Jouve et al. AJT 2022

# HLA desensitization in transplantation: toolbox

B-cell



Rituximab*

*Ramos AJT 2007*
*Vo NEJM 2008*

Belimumab*

*Banham Lancet 2018*
*Argawal Transp Immunol 2021*

Obinutuzumab*

*Redfield AJT 2019*
*Looney Transplant direct 2023*

CD19-CAR T

HLA-Fc fusion protein

Belatacept

Plasma-cell

Bortezomib*

*Perry AJT 2009*
*Ejaz AJT 2013*

Tocilizumab*

*Vo Transplantation 2015*

Carfilzomib*

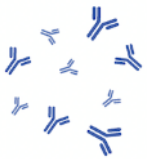
*Tremblay AJT 2019*

Anti-CD38 mAb*

*Kwun JASN 2019*
*Vincenti JASN 2024*

BCMA-CAR T

BCMA-BiTE



Plasma Exchange

*Montgomery Transplantation 2000*
*Akalin CJASN 2008*

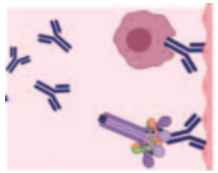
IVIG

*Glotz AJT 2002*
*Jordan JASN 2004*

Imlifidase

*Jordan NEJM 2017*

FcRn-blocker



Complement

Eculizumab*

*Stegall AJT 2011*
*Cornell AJT 2015*

C1-INH*

*Vo Transplantation 2015*

Pegcetacoplan*
Iptacopan*

2000 2010 2020 2030

# Mechanisms of action of the anti-CD38 antibodies

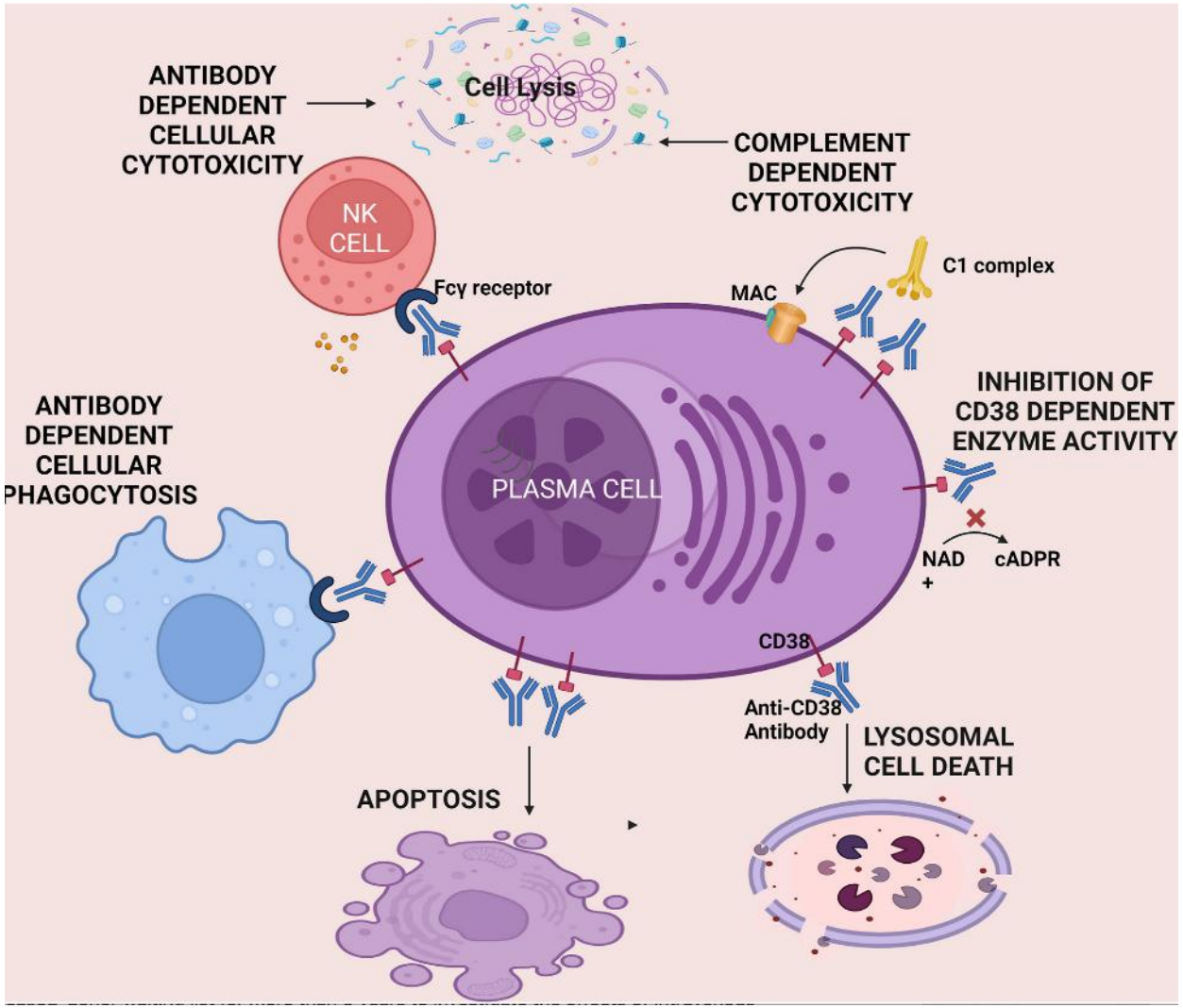
CD38 : multifonctionnal receptor and enzyme

**Daratumumab :** IgG1 kappa

**Isatuximab :** IgG1 kappa
=> direct apoptosis
=> better inhibitor of CD38 activity

**Felzartamab :** IgG1 lambda
=> no complement dependent cytoxicity

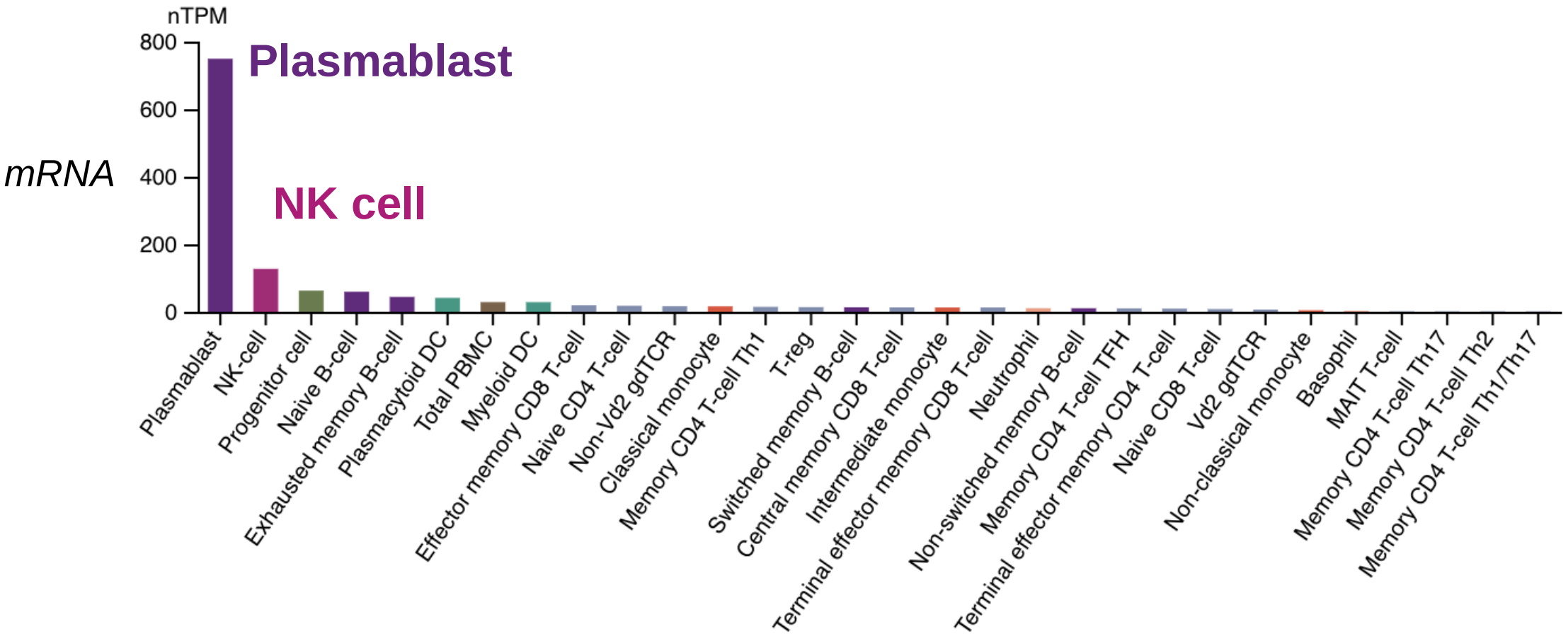
**Mezagitamab :** IgG1 lambda




Mateos NEJM 2018, Kaufman Blood 2017, Chandran et al. 2025

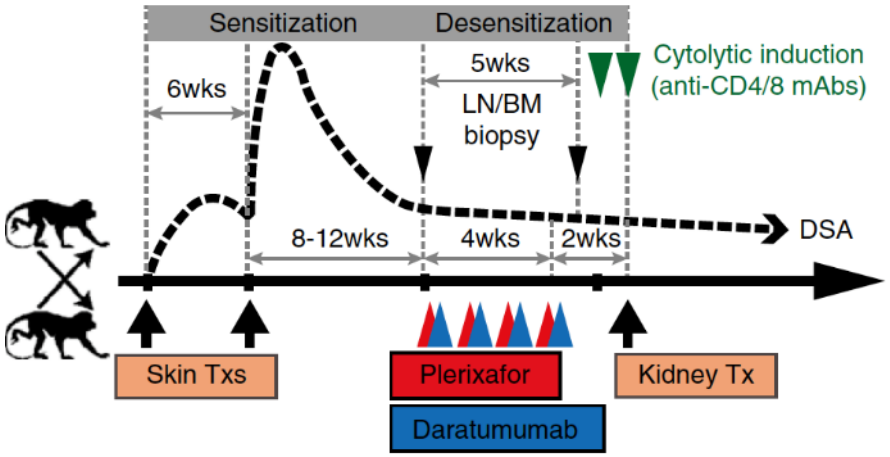
# CD38 expression

*The Human Protein Atlas*



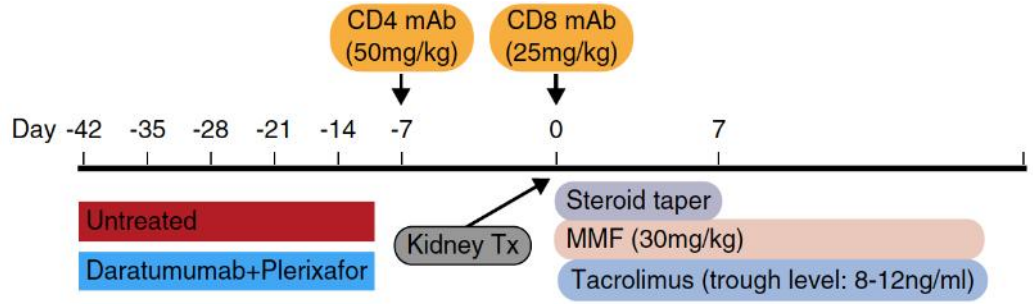

Monaco G. Cell rep 2019

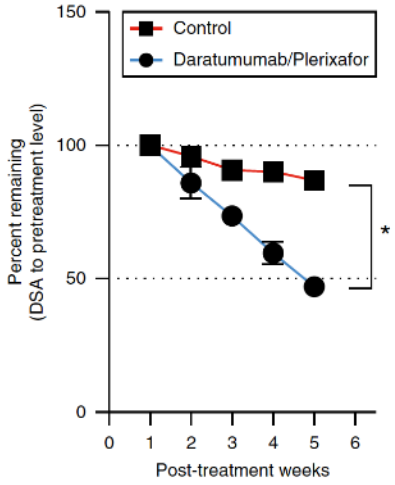
# Anti-CD38 Ab: daratunumab

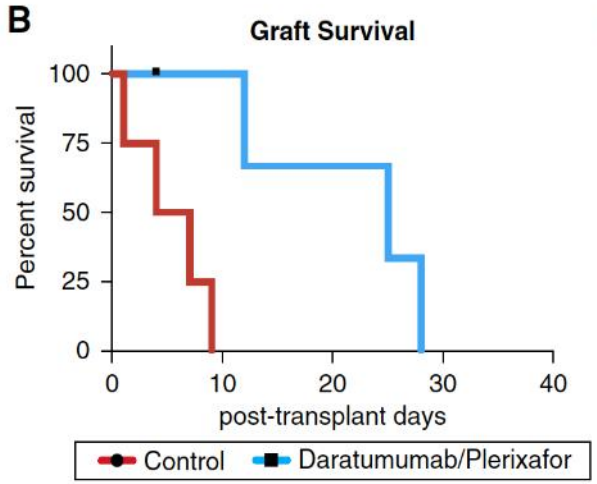


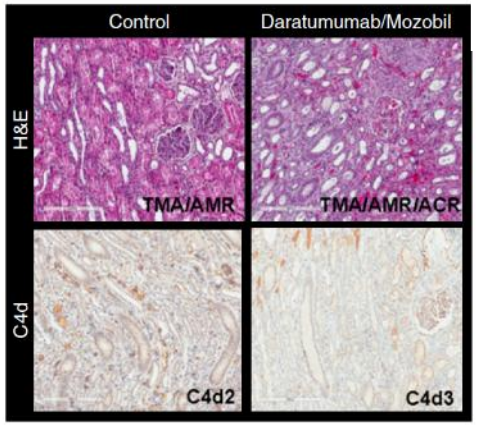

**16 mg/kg daratunumab**
**0.24 mg/kg plerixafor**

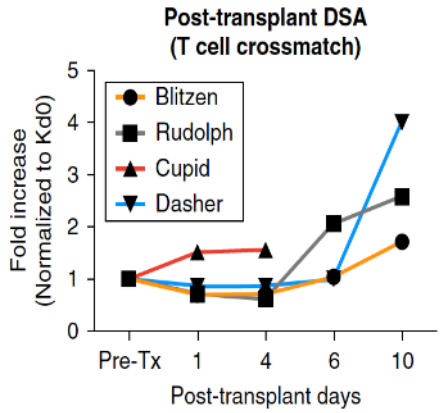
**8-12 weeks after the second skin transplantation, Once a week for 1 month**



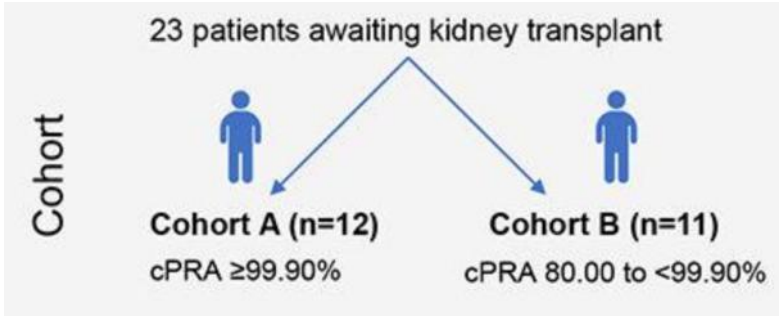




**Post-transplant DSA rebound**

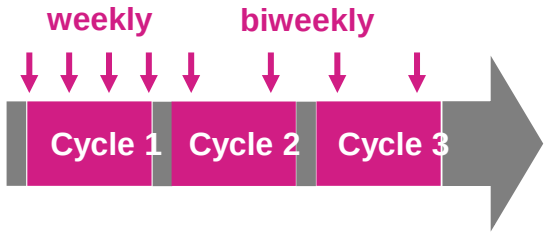
**Daratunumab depletes efficiently plasmablasts, reduces pre-Tx DSA, and delays rejection**

Kwun et al. JASN 2019

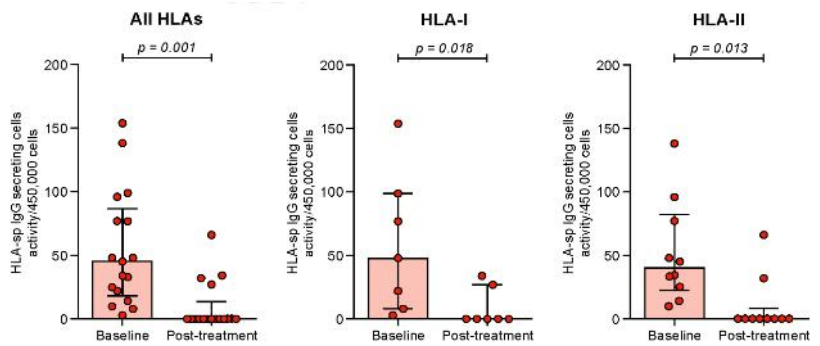
# Anti-CD38 Ab: isatuximab (Phase I/II CT)

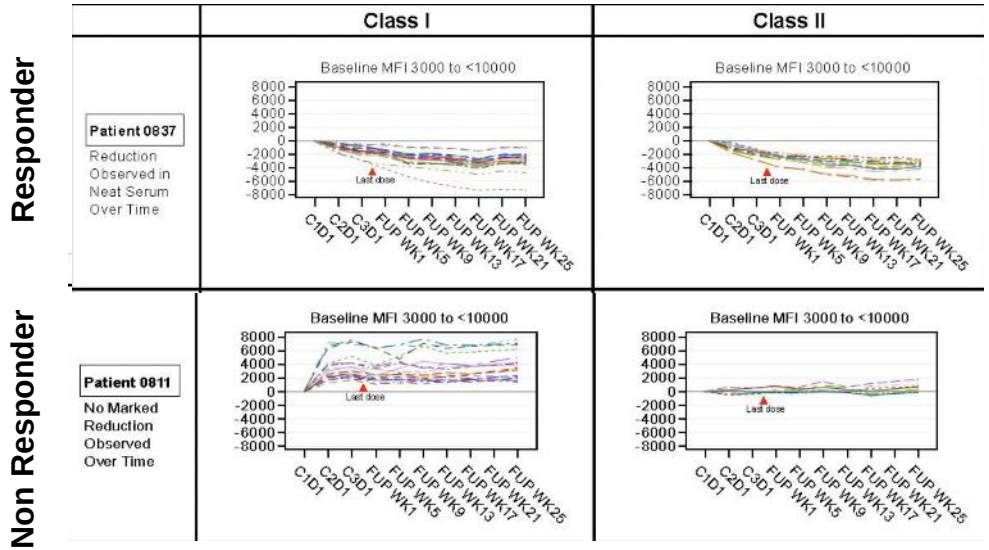



**Isatuximab (10 mg/kg) schedule**




Bone-marrow HLA-sp plasma cells




**Only 39% of patients had reached target cPRA** (i.e. resulting in at least doubling the theoretical likelihood of finding a compatible donor).

Vincenti et al. JASN 2024

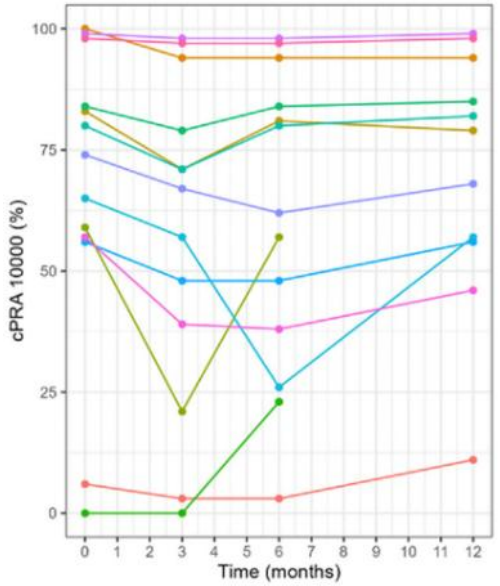
# Anti-CD38 Ab: daratumumab (Phase I/II CT)

**DARDAR study**

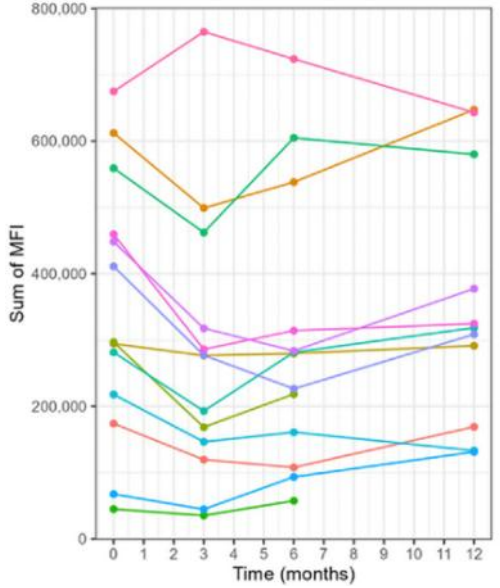
14 Patients with cPRA >95%

8 weekly infusions of
16 mg/kg of daratumumab

cPRA 10 000




MFI sum

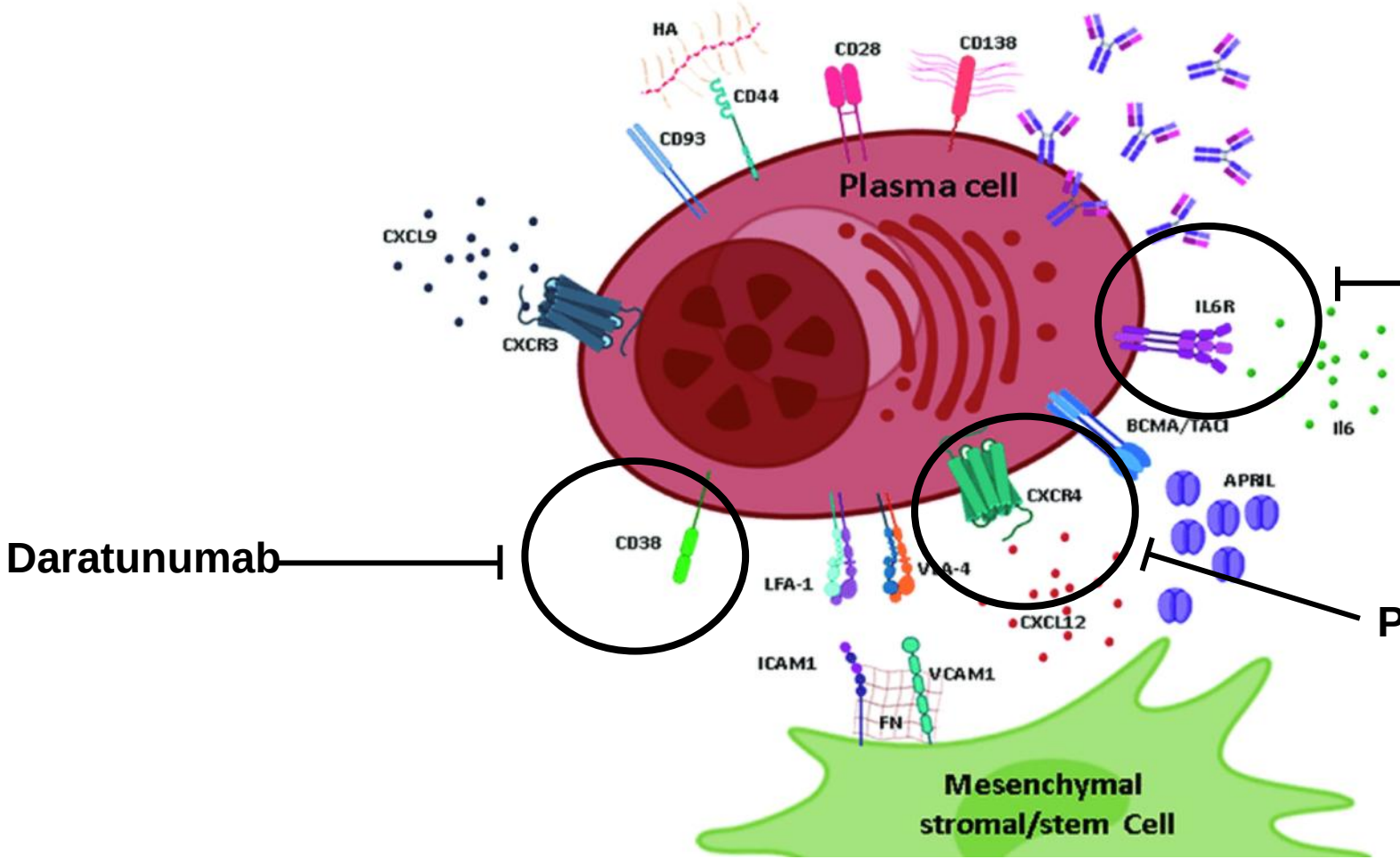



**Rapid but transient and mild reduction in anti-HLA**

Pilon et al. KI reports 2024

# Multi-hit plasma cell-targeted therapy

2 cycles of daratumumab-based regimen (a total of 8 doses)




**Tocilizumab (anti-IL6R)**

Ogiya Blood 2020, Barbick Blood 2020

**Daratunumab**

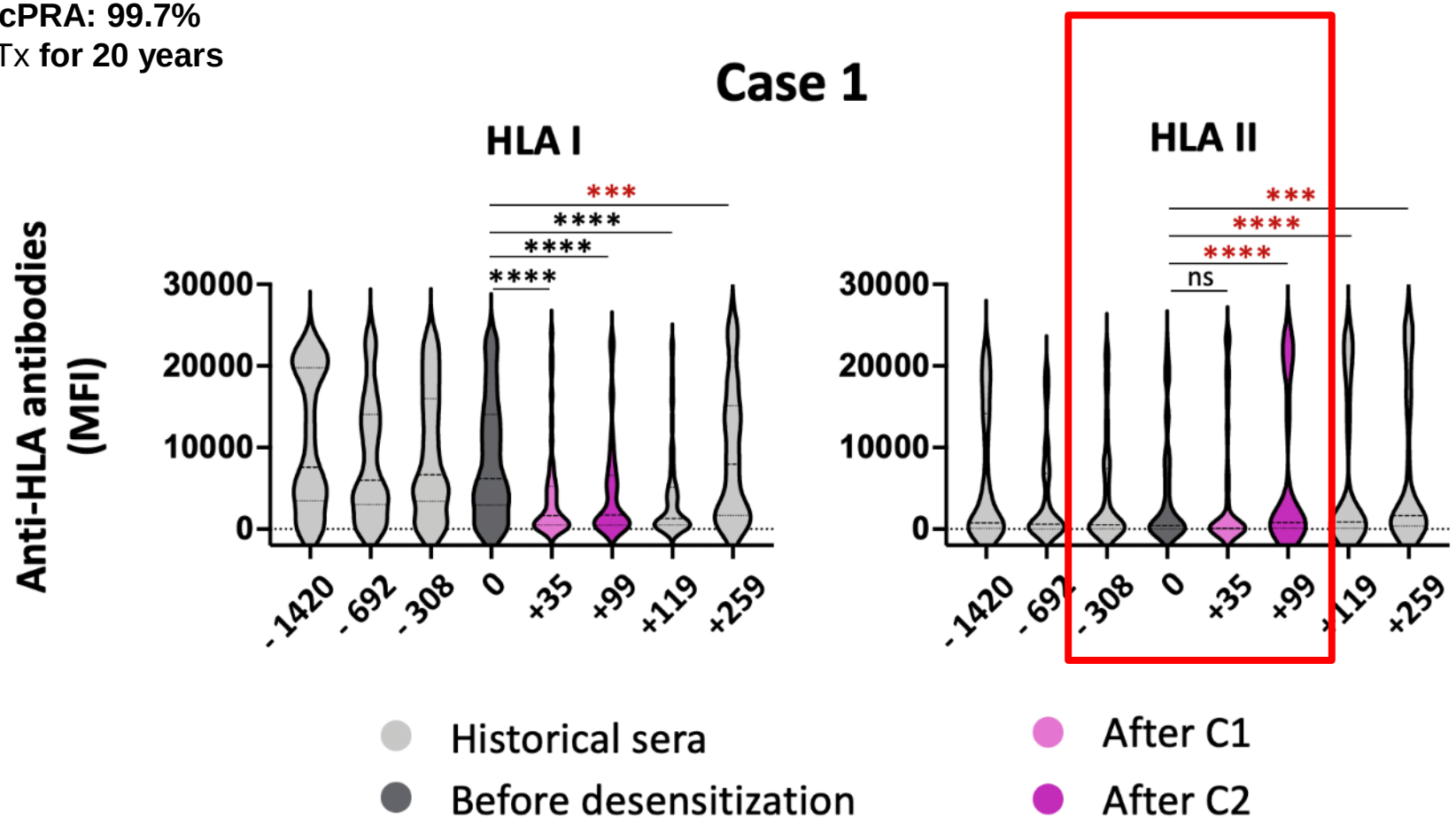
**Plerixafor – anti-CXCR4**

Leon et al. in preparation

Bonaud Front Immunol et al. 2021

# Multi-hit plasma cell-targeted therapy

37 years old
Blood type O, **cPRA: 99.7%**
Awaiting a 2st KTx **for 20 years**

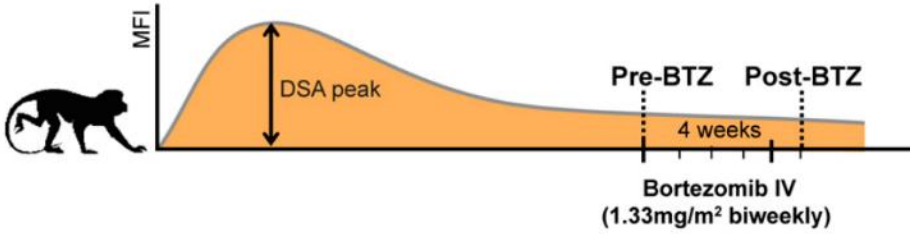


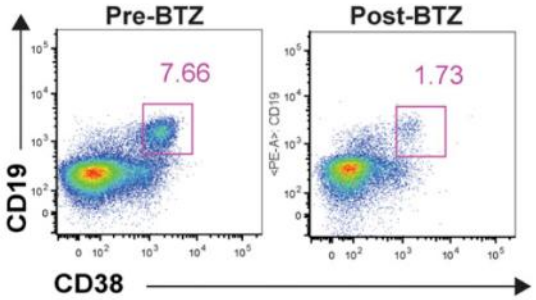

Leon et al. in preparation

# How to explain the rebound and how to face it ?

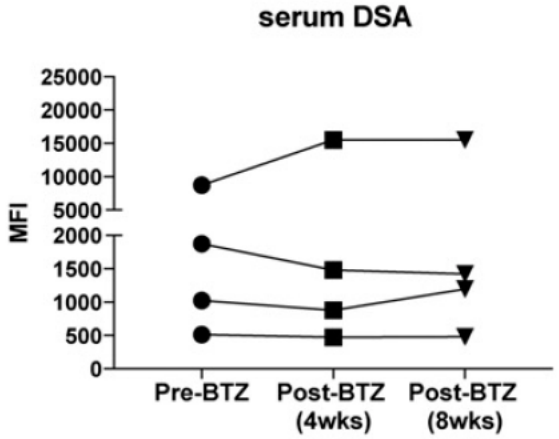
# Memory B cells can promptly refuel PC compartment following depletion

Bortezomib

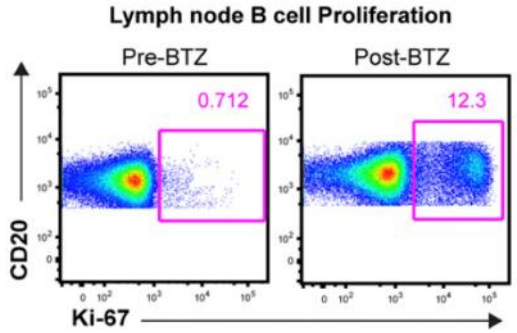


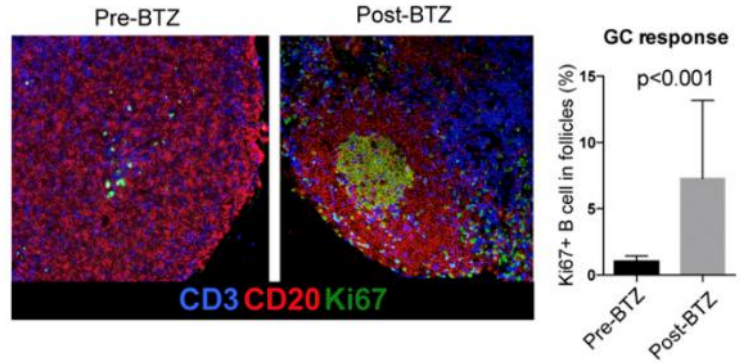




Bone marrow CD20- IgD- CD19+ CD38+ and IgG-secreting cells were significantly reduced after bortezomib




However, DSA levels did not decrease



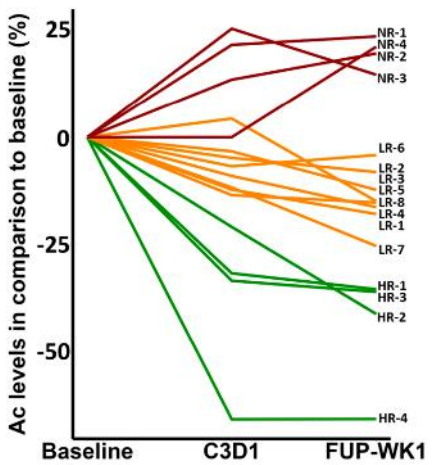



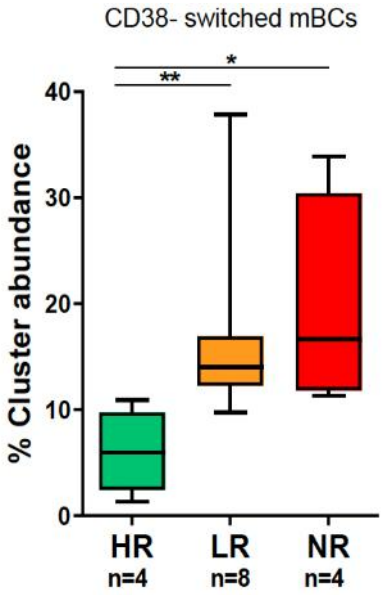

**Increased B cell activation and GC response following PC depletion**.

Kwun et al. JASN 2017
Kwun et al. JASN 2019

# Memory B cells CD38$^{-}$ pool is increased in anti-CD38 non-responders

## Anti-CD38 Ab: Isatuximab



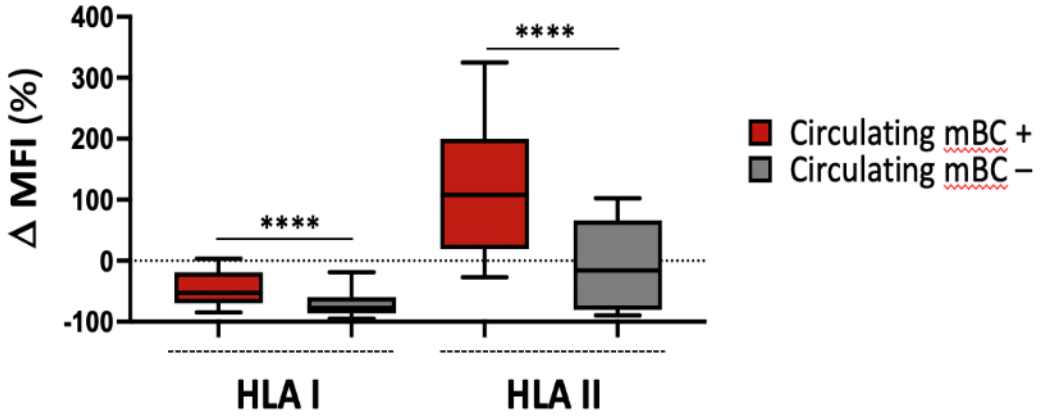




Pretreatment abundance of circulating mBC phenotypes, especially CD38neg class-switch mBCs, distinguished between high and low responders

Torija et al. Am J Transplant 2024

## Anti-CD38 Ab: Daratumumab

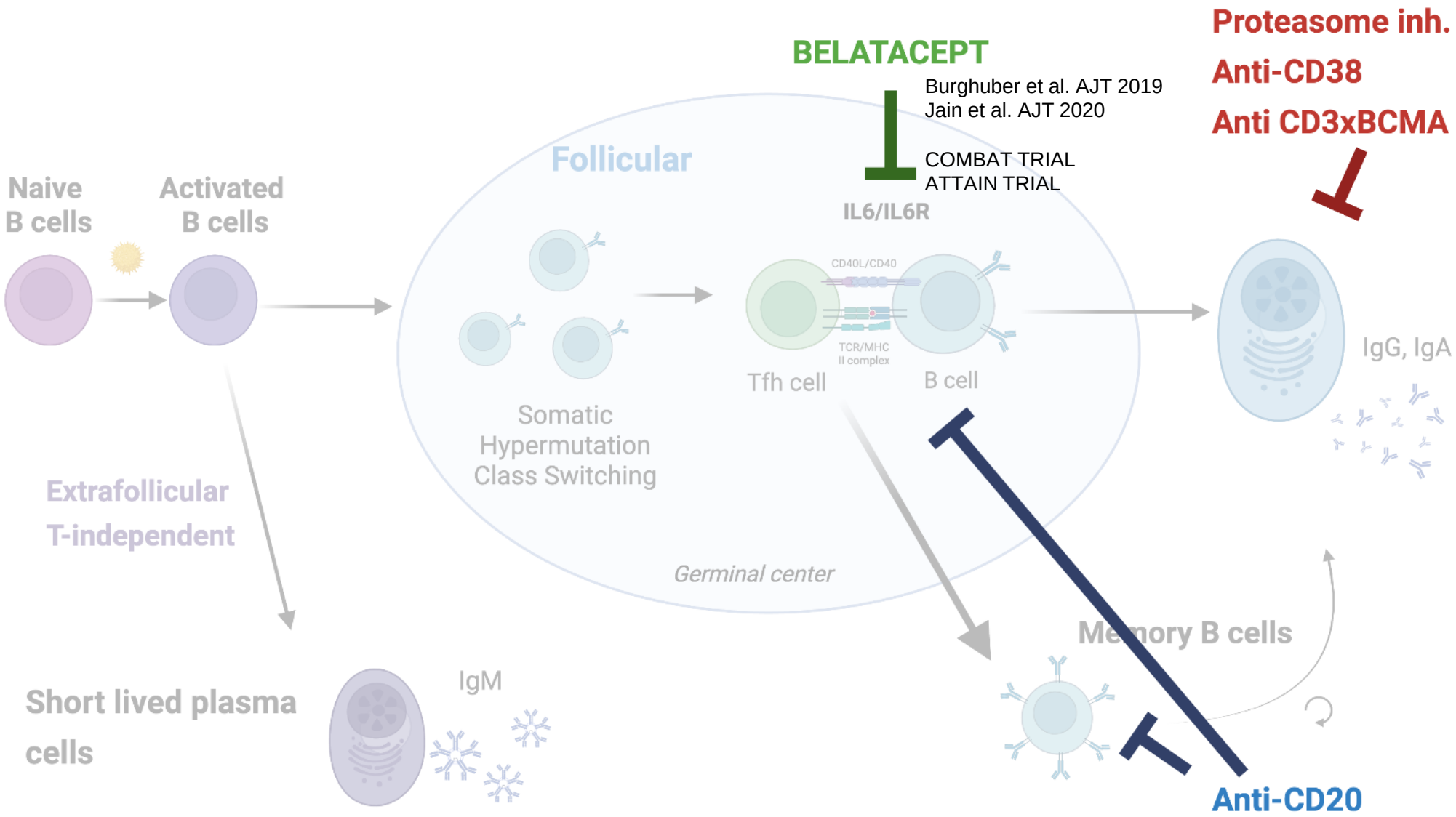
**S. Charbonnier** **M. Devriese**



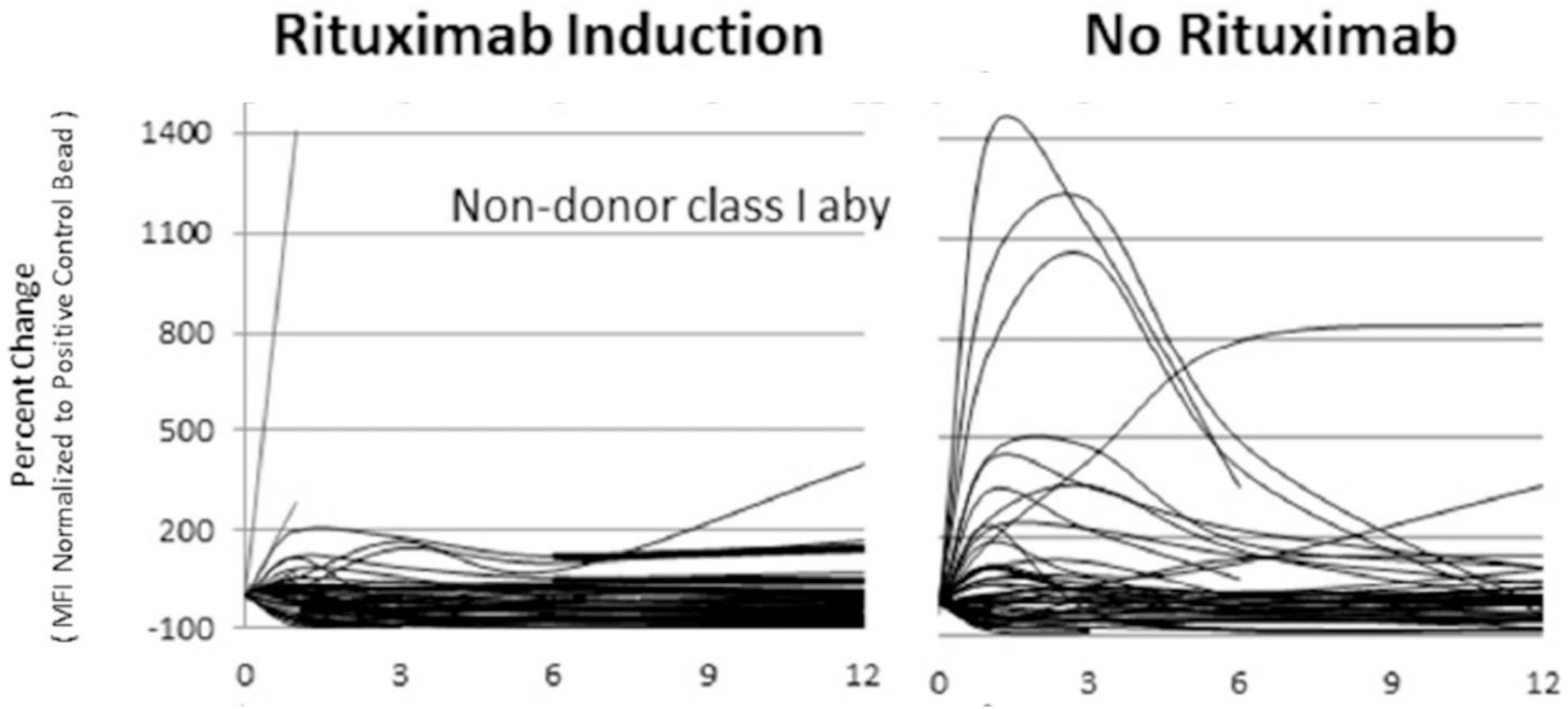

The presence of memory B cells is associated with a resistance to desensitization

Leon et al. in preparation

# Combination of plasma cell and B cell targeted therapies



# Rituximab induction and HLA Ab rebound

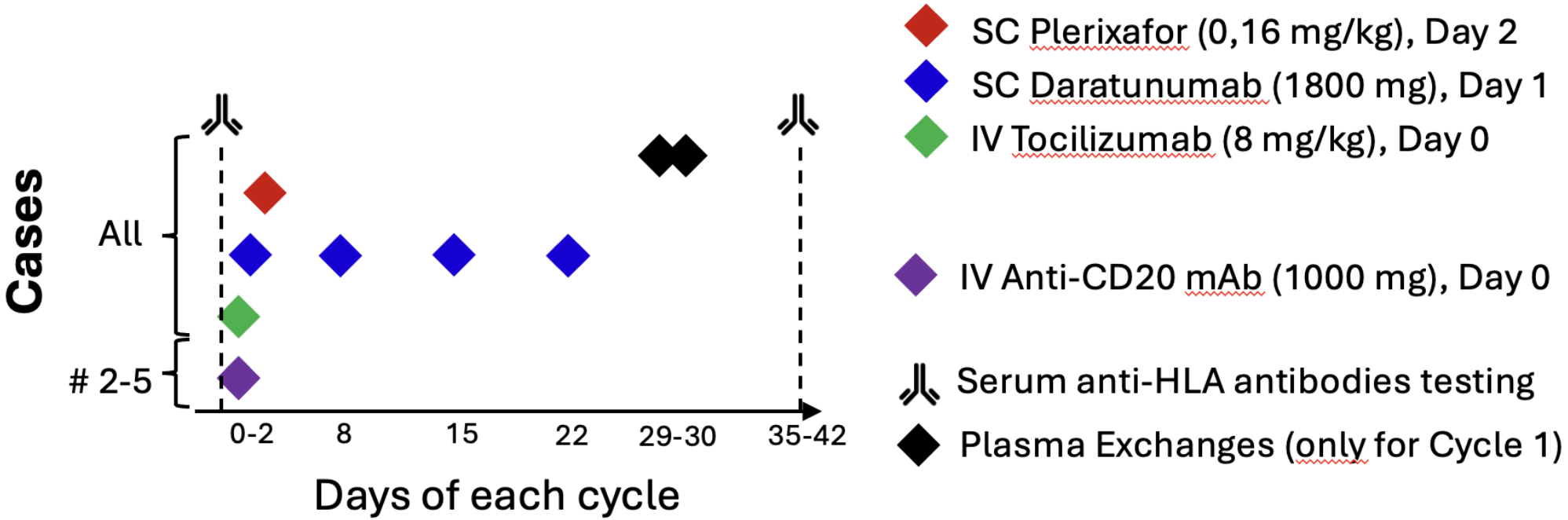



Rituximab induction reduced the incidence and magnitude of HLA Ab rebound, but did not impact DSA elimination

*Jackson A. et al. Kidney Int 2015*

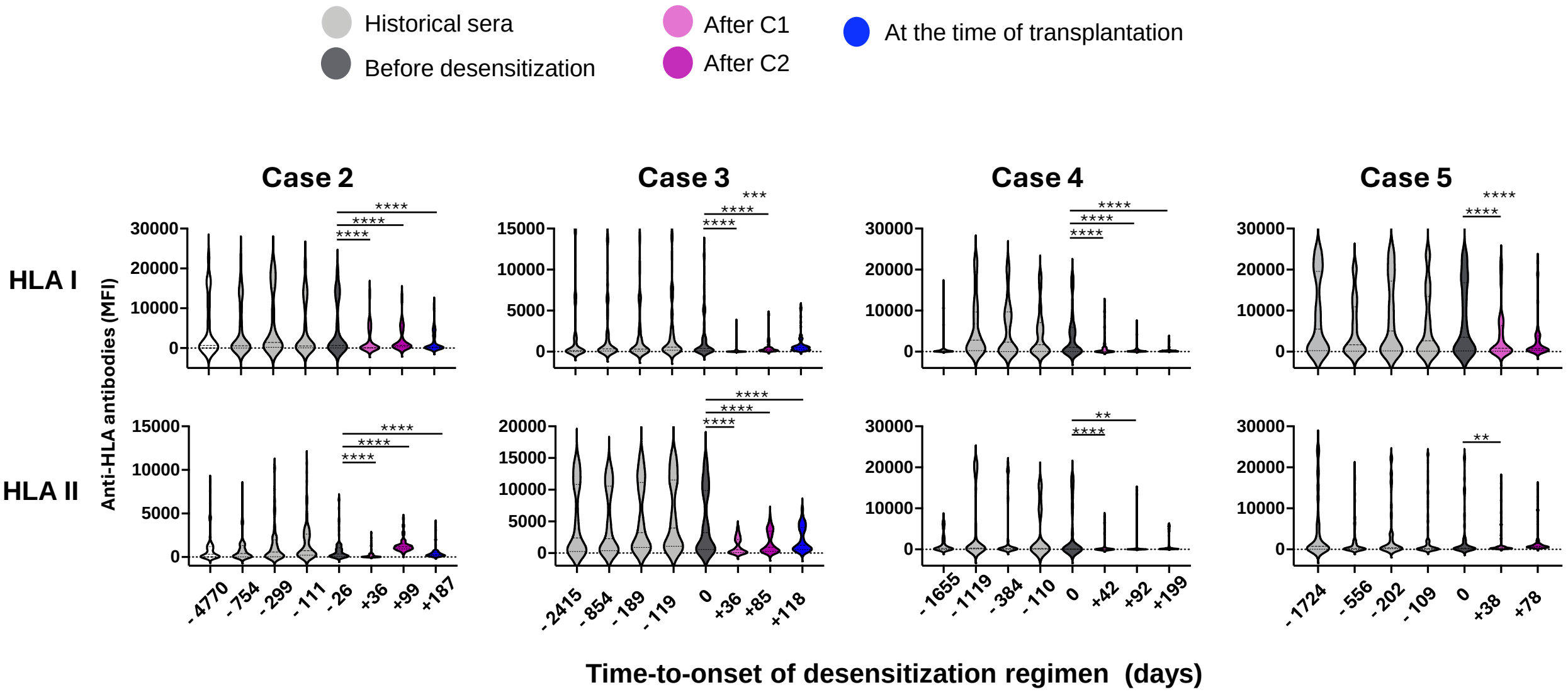
# Dual targeting of B and plasma cells : desensitization protocol

2 cycles of daratumumab-based regimen (a total of 8 doses)
**x** 2 injections d'anti-CD20



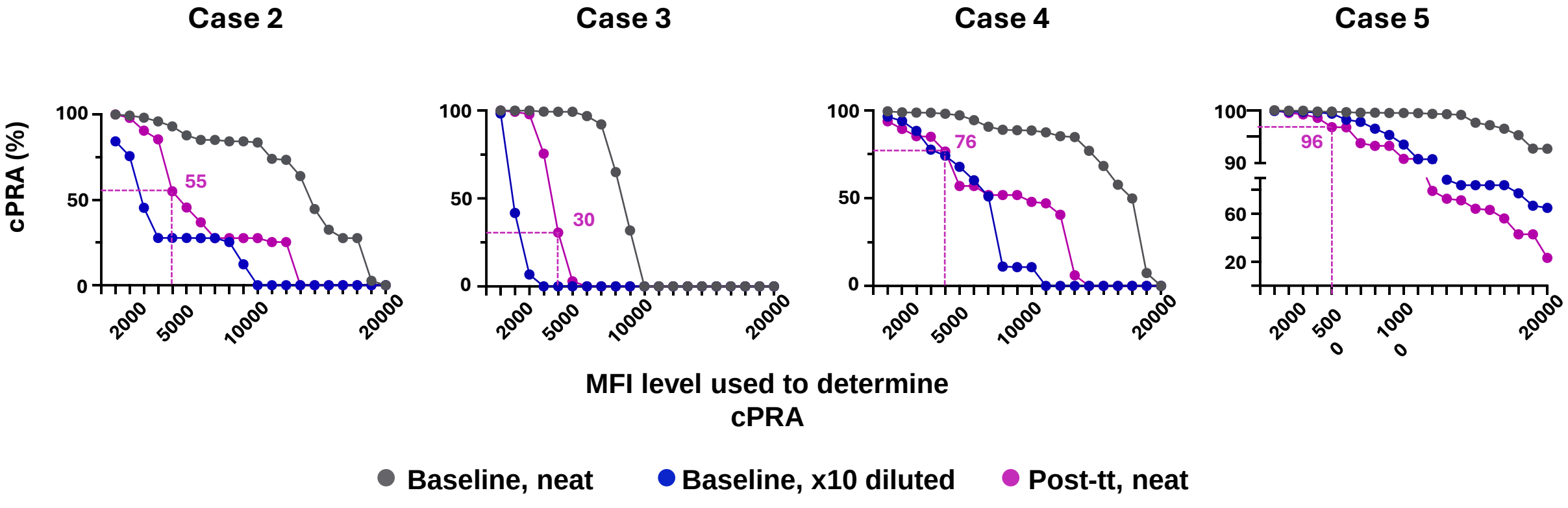
# Significant decrease in anti-HLA antibody levels

cPRA > 98%




Leon et al. en preparation

# Increased access to kidney transplantation




This protocol allows a decrease of $cPRA_{5000}$ similar to a 1:10 dilution

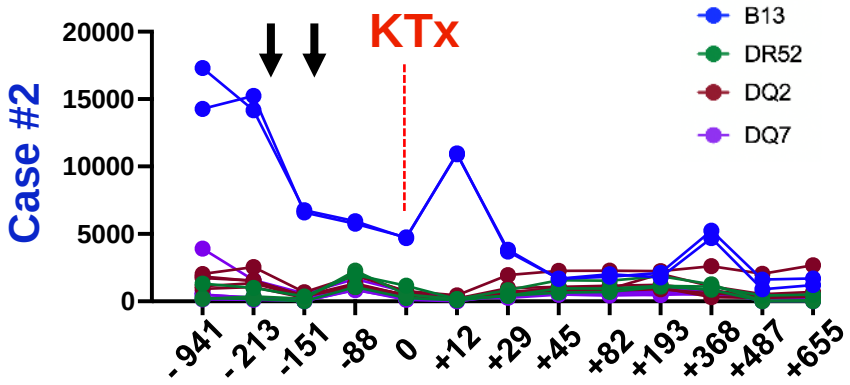
17 years

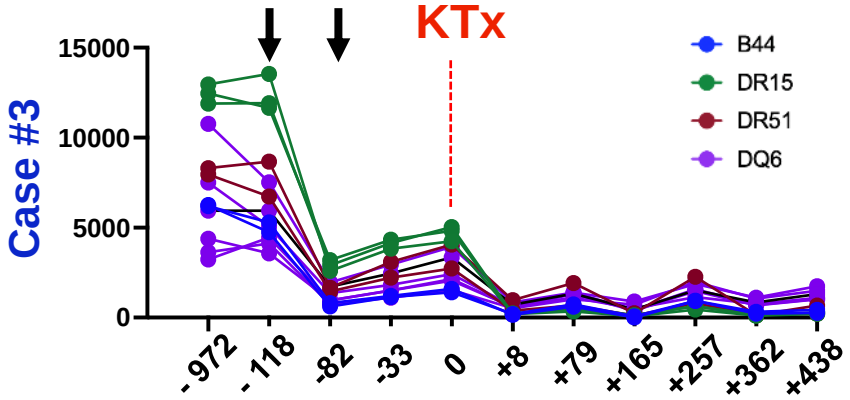
12 years

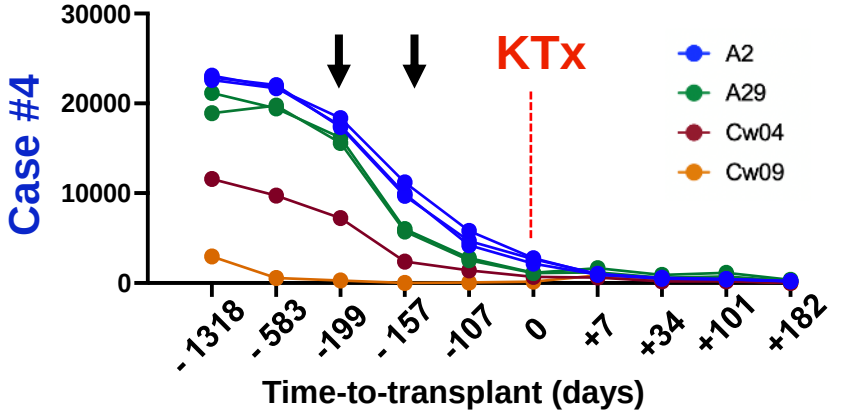
8 years

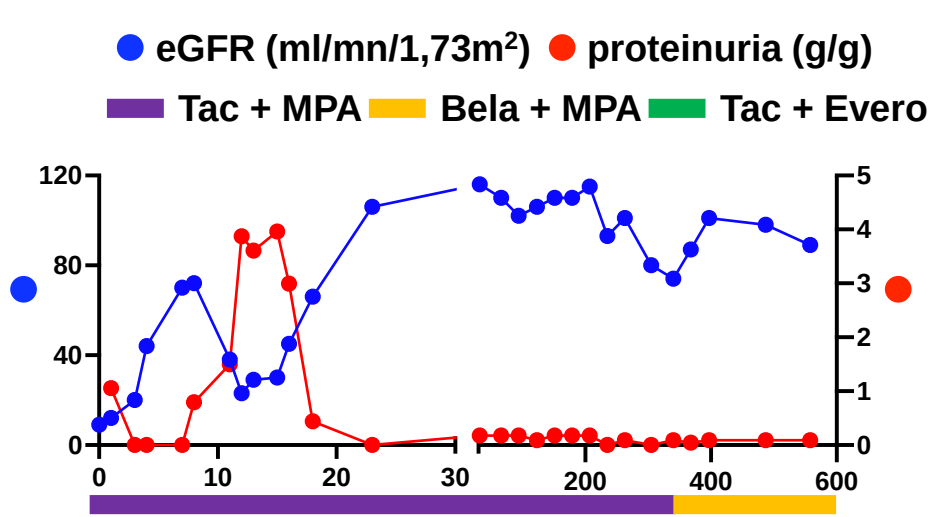
DSA (MFI)

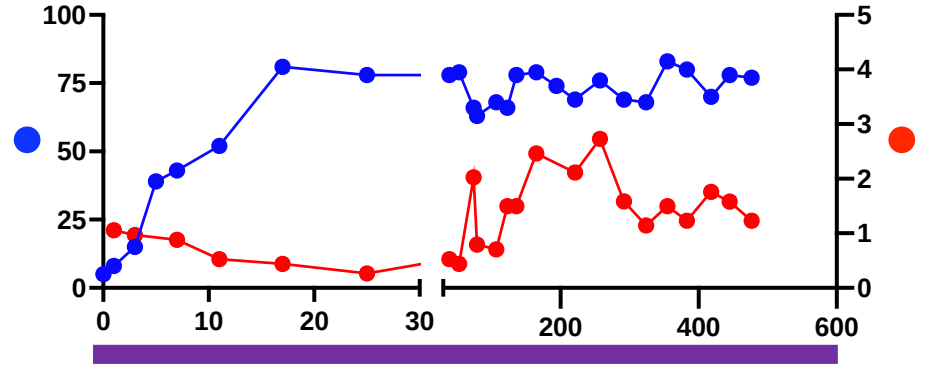
Rituximab

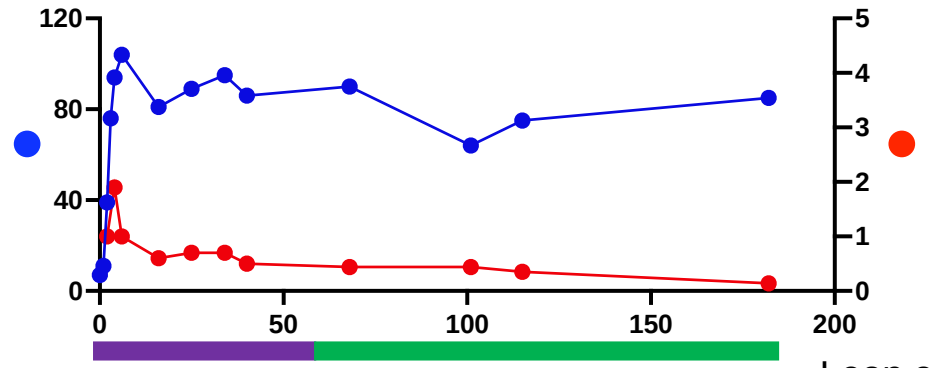


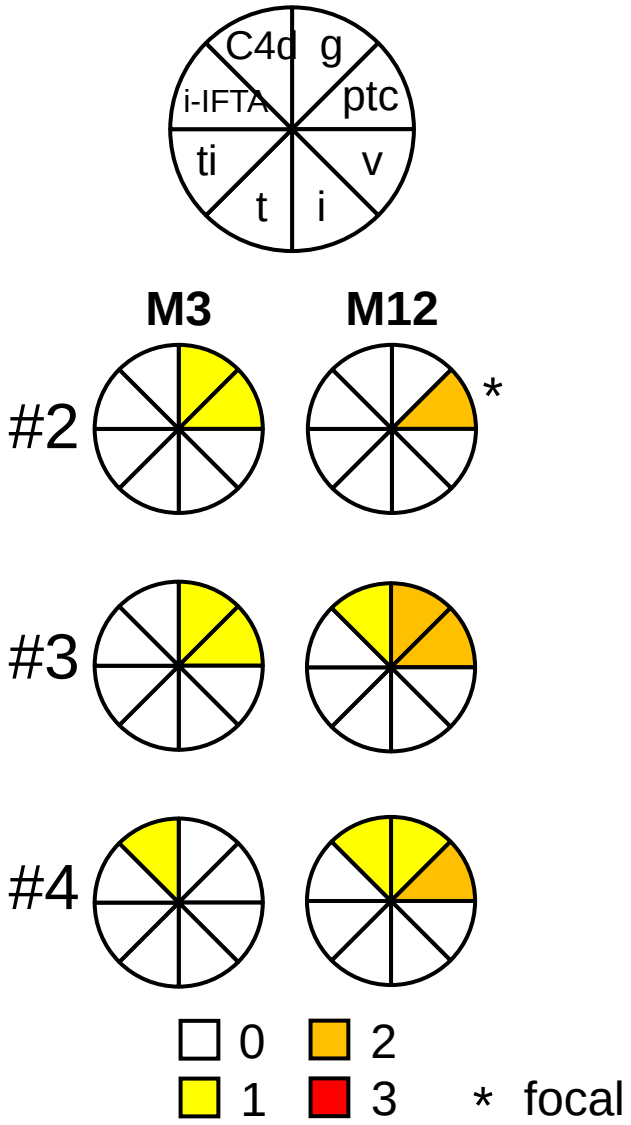

3 months

1 month

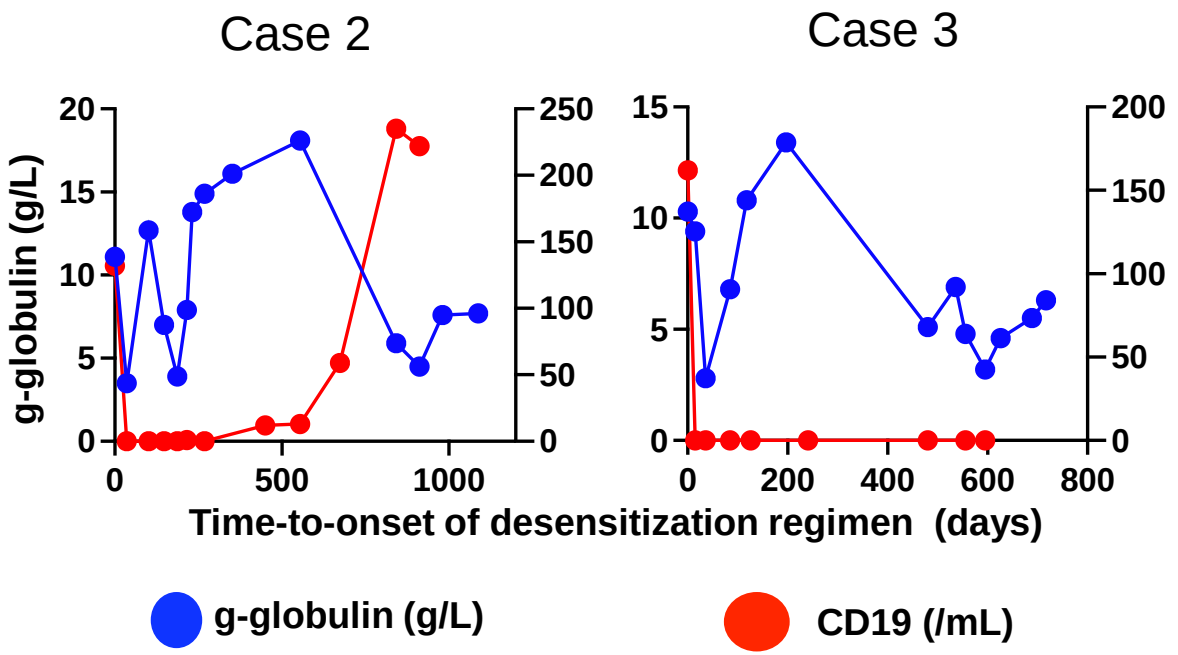
3 months

Leon et al. en preparation

# Follow-up




Presence of humoral lesions at M12

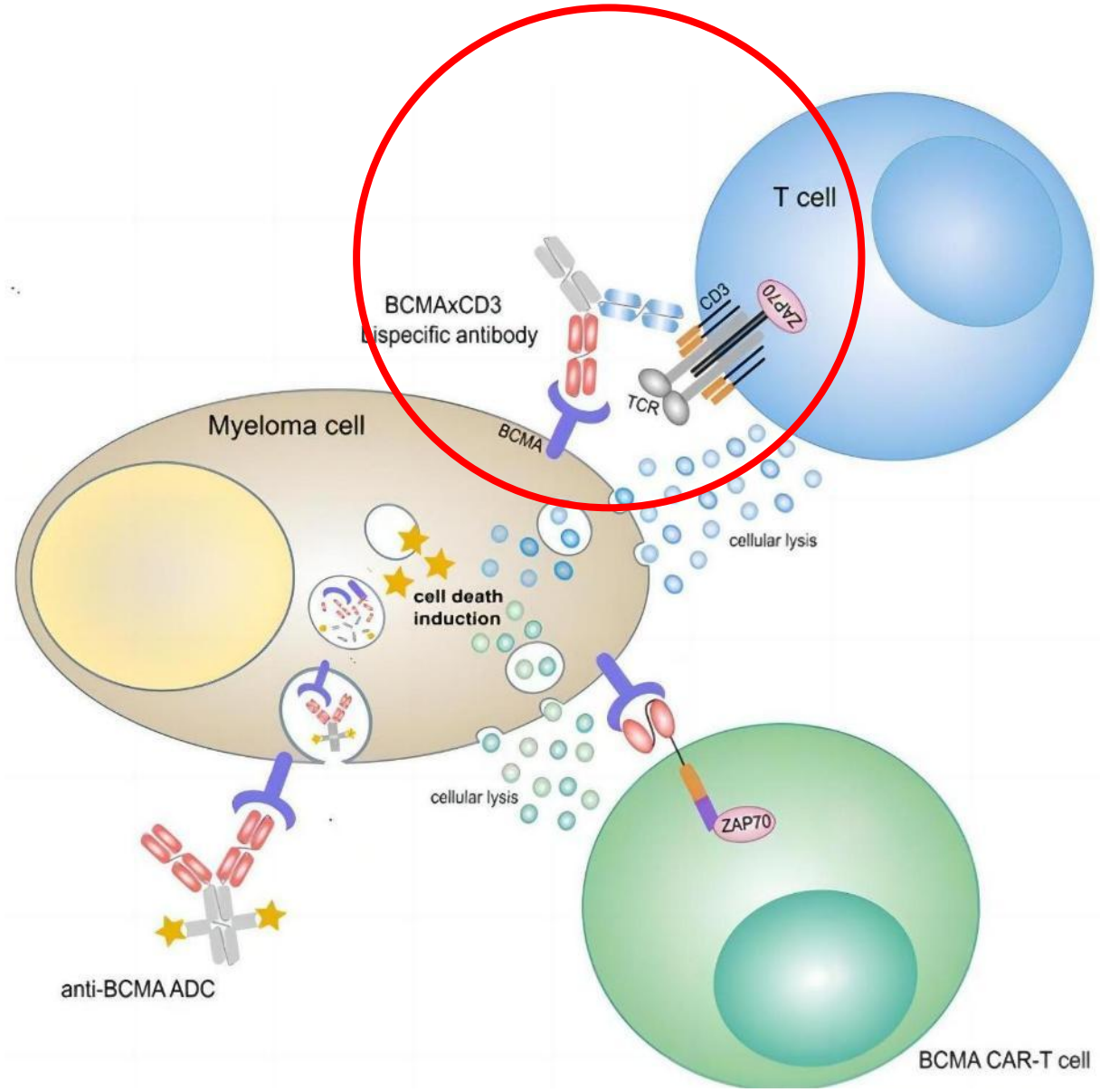



Persistant hypogammaglobulinemia

# Combination of plasma cell and B cell targeted therapies

## Future directions

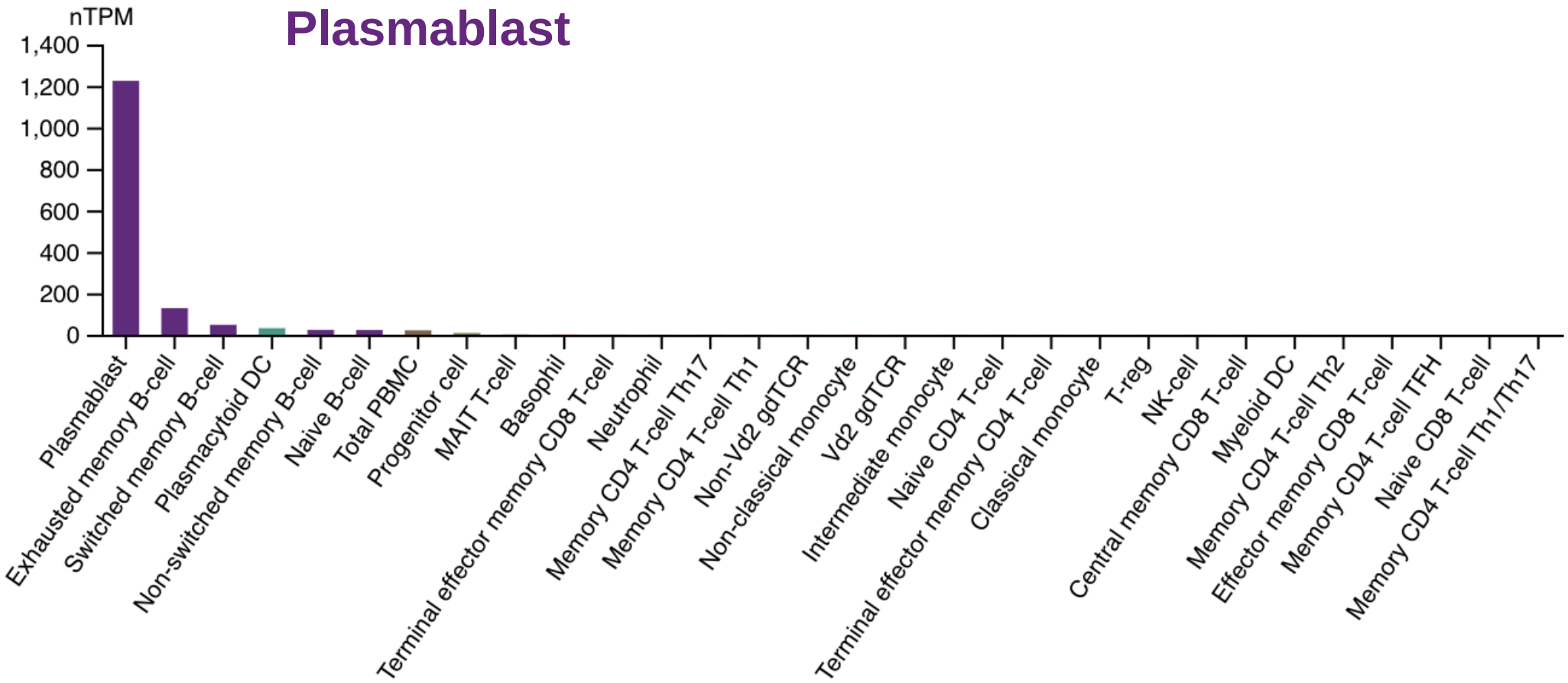
# BCMA-targeted therapy




Elranatamab

# BCMA expression

*The Human Protein Atlas*




Monaco G. Cell rep 2019

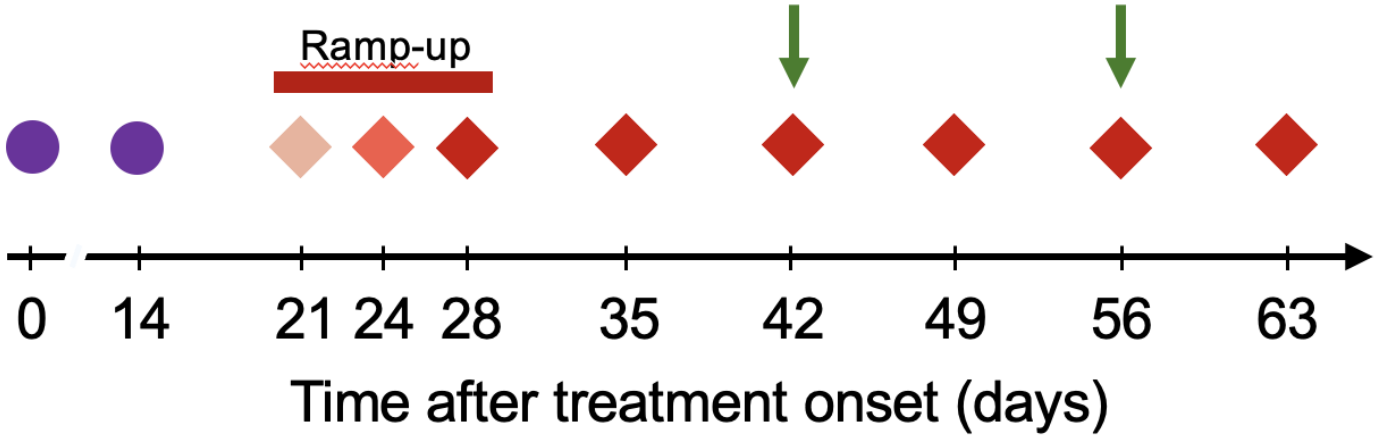
# Dual strategy combining CD3/BCMA bispecific and obinutuzumab

37 years old
Blood type O, **cPRA: 99.7%**
Awaiting a 2st KTx **for 20 years**

Obinutuzumab
1000 mg

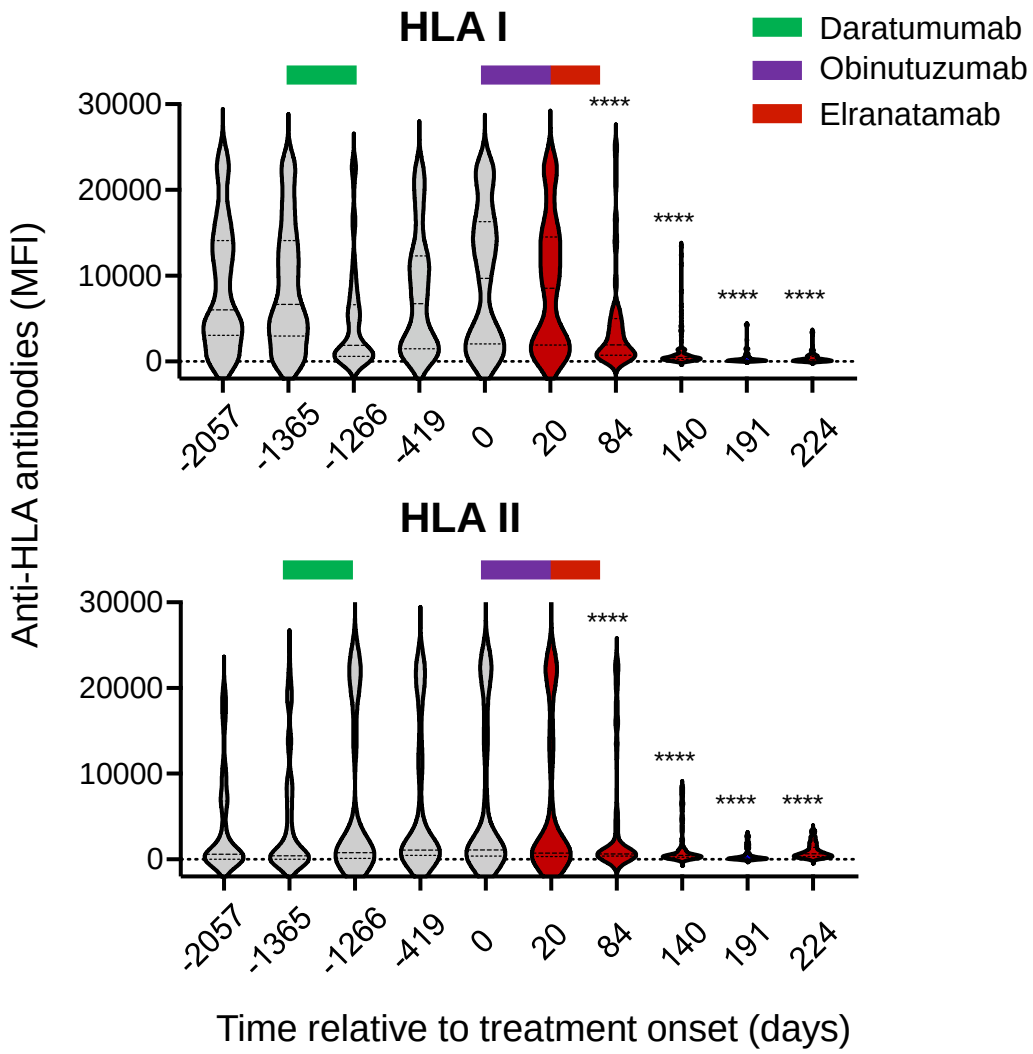
Elranatamab
12 mg 32 mg 76 mg

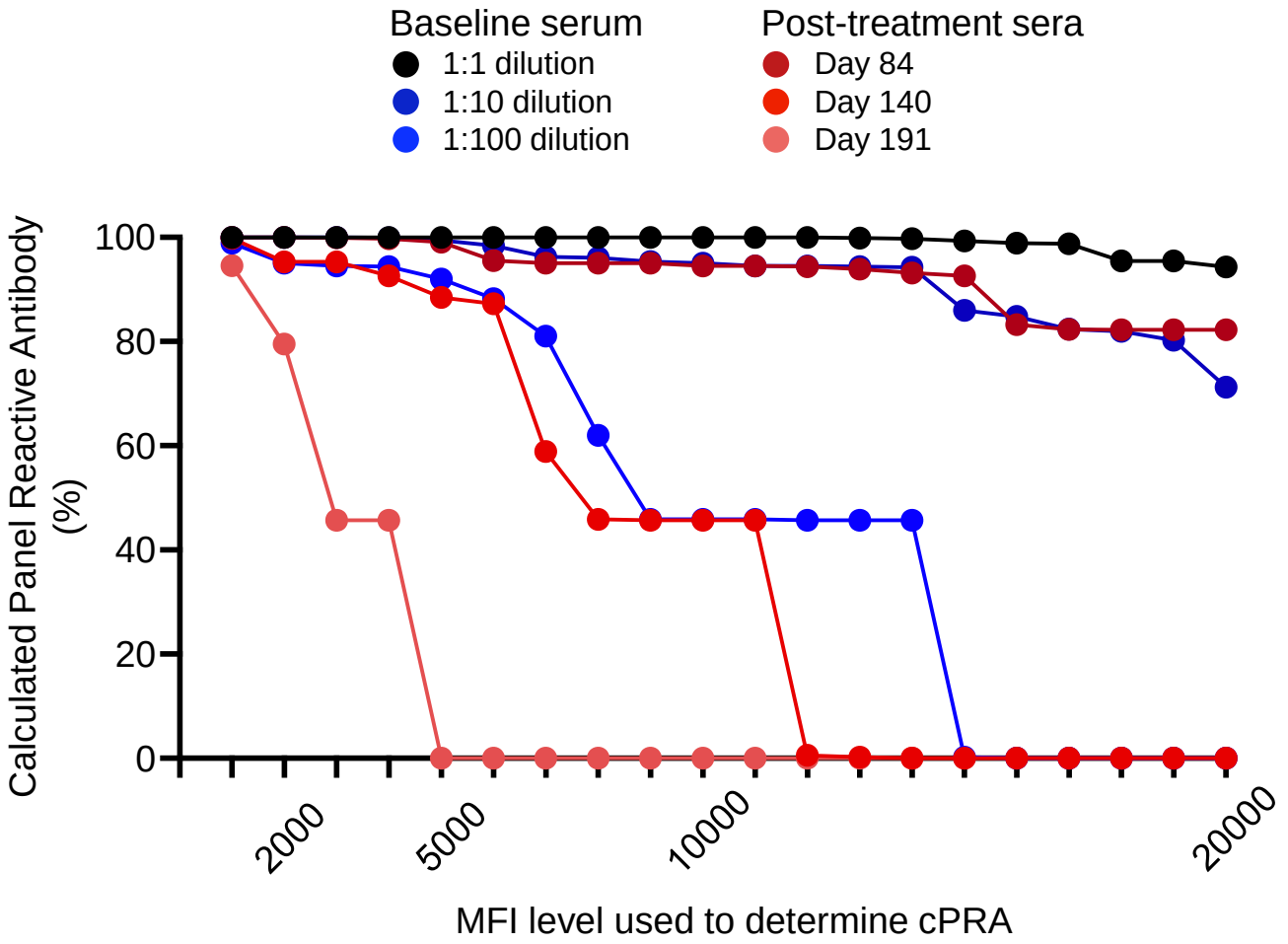
Subsitutive IgIV




Leon et al. submitted

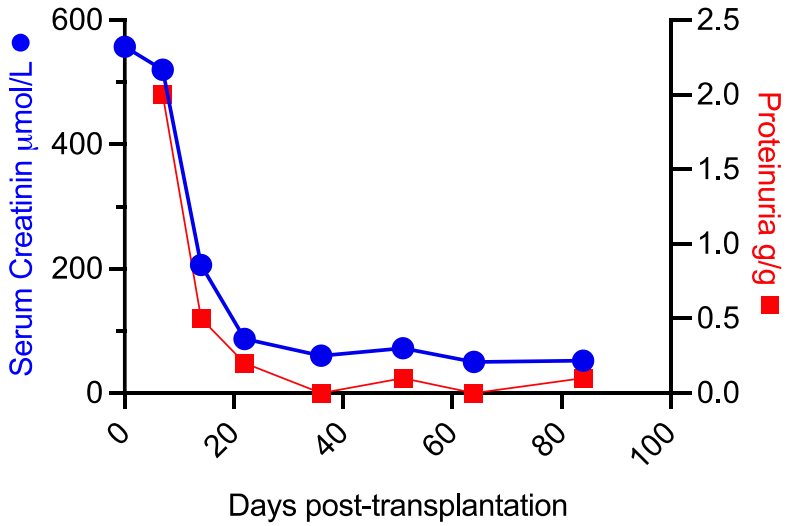
# Elranatamab + Obinutuzumab induced a strong and durable antibody depletion

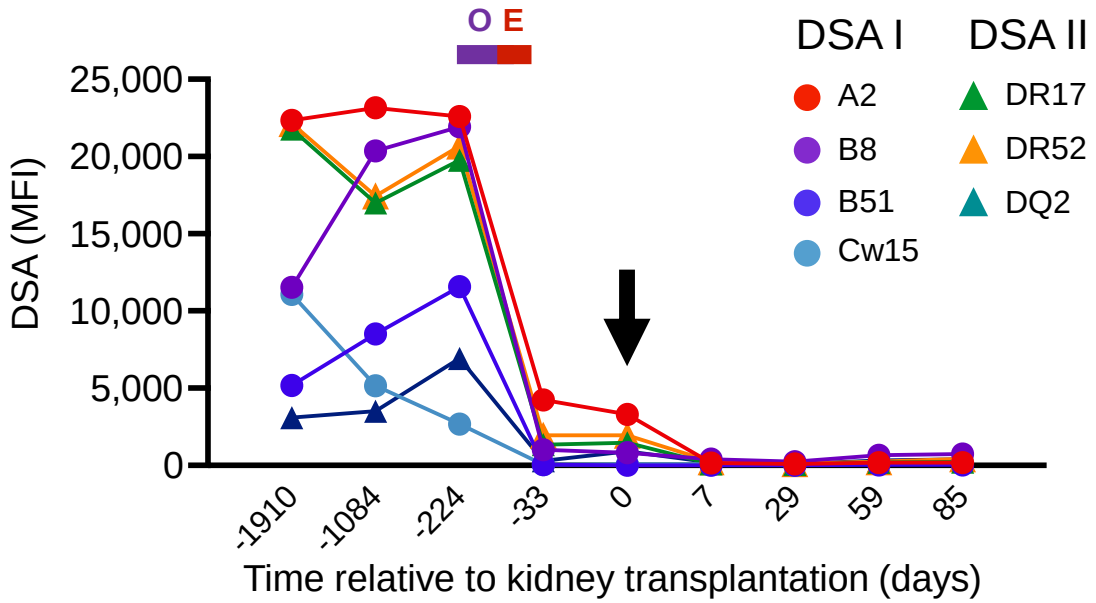


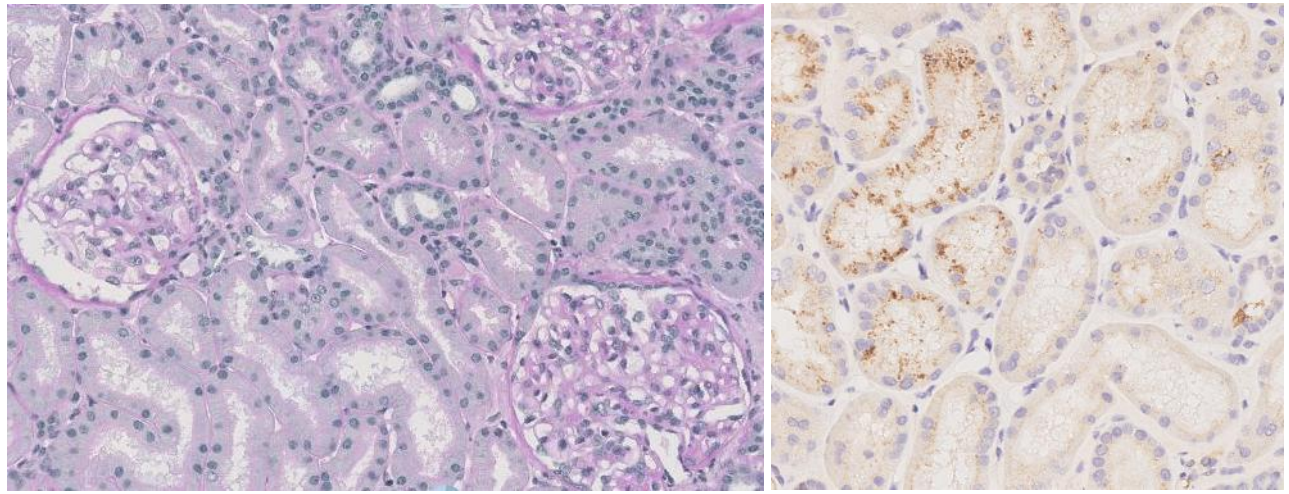

Leon et al. submitted

# ... and allowed a successful re-transplantation



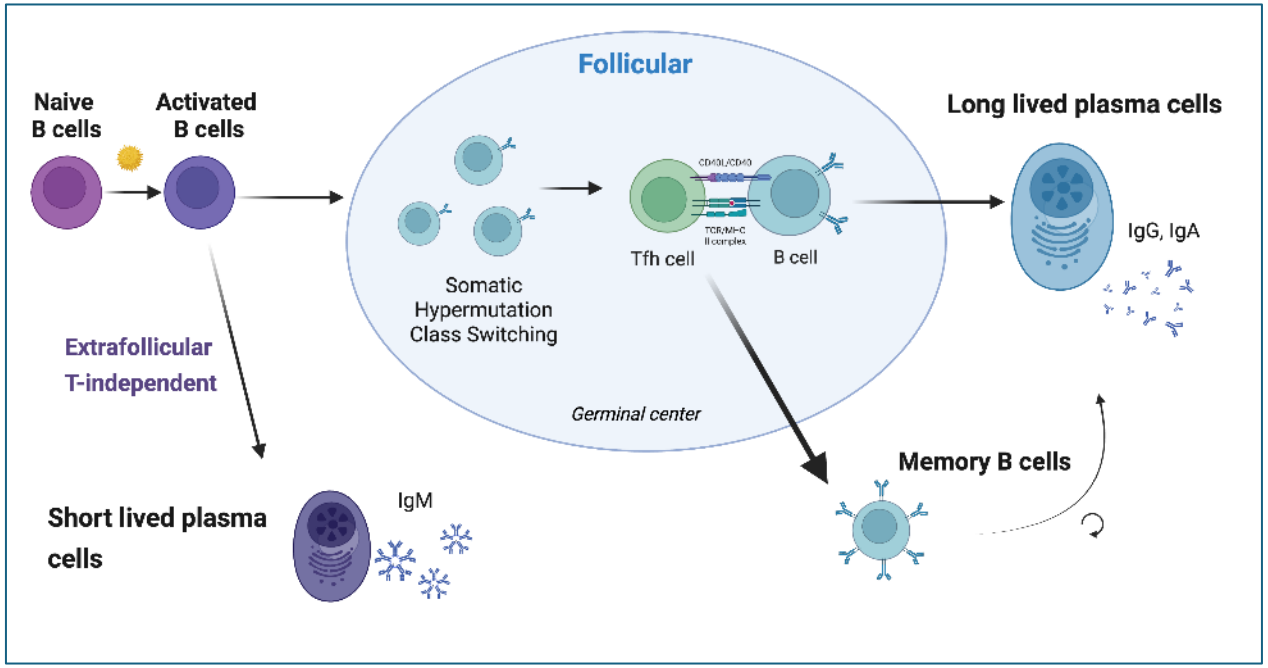

**3-month biopsy**



BANFF 0

Leon et al. submitted

# Plasma cell targeting in kidney transplantation




**HLA Desensitization**

**Antibody-mediated rejection**

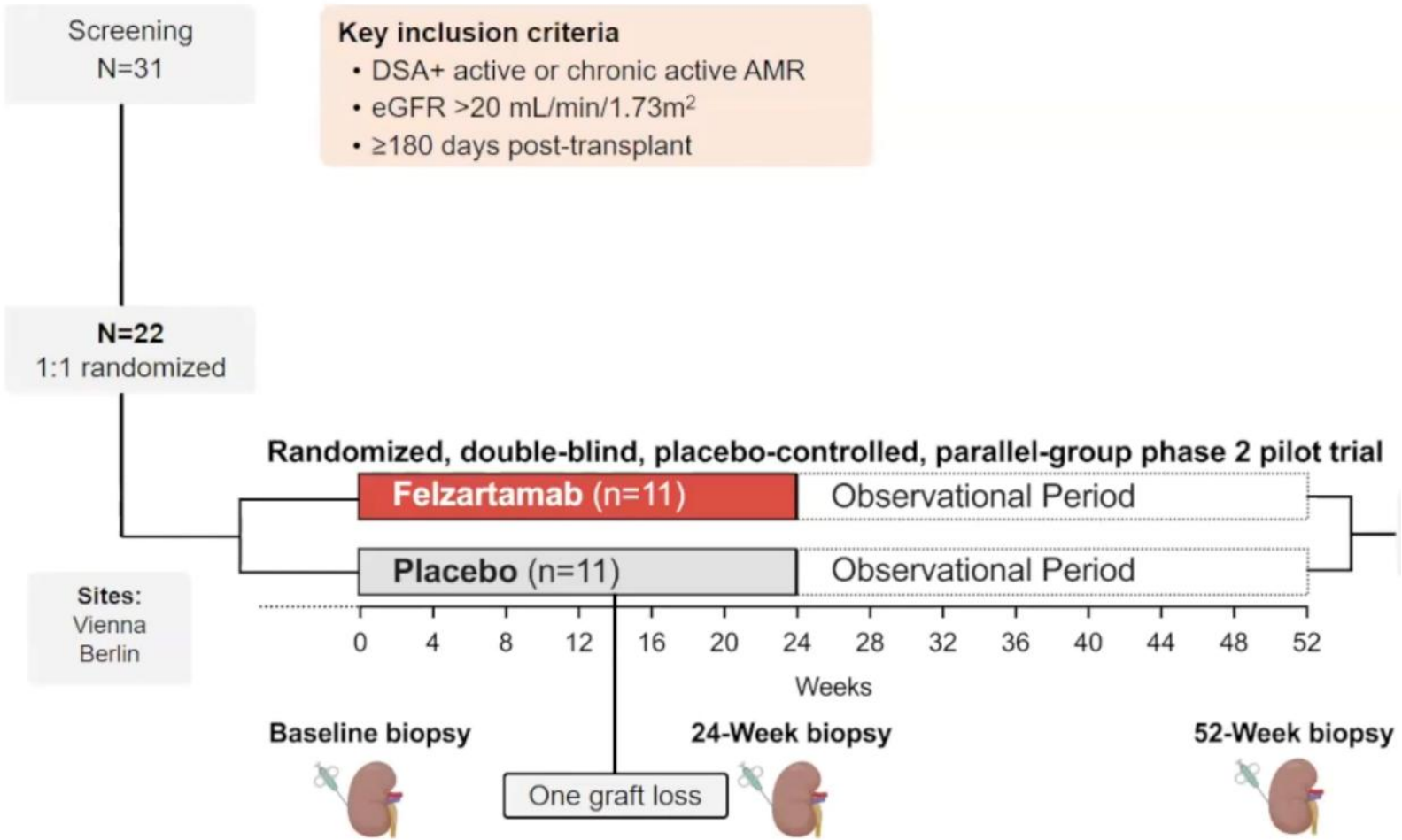
**Antibody-mediated disease**

# Targeting CD38 in AMR

| Author, year | Treatment schedule | Timing AMR | Patient, N | Associated treatment | Results | Follow-up |
|---|---|---|---|---|---|---|
| Kwun, 2019 | Daratumumab, 8 doses | late | 1 | EP + IgIV + CS<br>Anti-CD20<br>eculizumab | AMR resolution<br>DSA-MFI reduction | AMR recurrence |
| Spica, 2019 | Daratumumab, 6 doses | early, 7 days | 1 | EP + IgIV + CS<br>Anti-CD20<br>Eculizumab | ABOi AMR resolution<br>ABO Ab reduction | |
| Doberer, 2021 | Daratumumab,9 months | late | 1 | 0 | Decrease AMR activity<br>DSA-MFI reduction | Borderline lesions |
| Susal, 2023 | Daratumumab, 4 doses | early, 5 days | 1 | EP + IgIV + CS<br>Anti-CD20 | AMR resolution<br>ABO Ab & HLA Ab reduction | |
| Zhu, 2023 | Daratumumab, 12 months | late | 2 | EP + IgIV + CS<br>Anti-CD20 | Decrease AMR activity<br>DSA-MFI reduction | TCMR<br>Rebound |
| **Lemal, 2024** | **Daratumumab, 1 dose** | early | 3 | EP + IgIV + CS | AMR resolution<br>DSA-MFI reduction | |
| Osmanodja, 2024 | Daratumumab,9 months | early and late | 2 | EP + IgIV + CS<br>Anti-CD20 | Decrease AMR activity<br>DSA-MFI reduction | |

ORIGINAL ARTICLE

# A Randomized Phase 2 Trial of Felzartamab in Antibody-Mediated Rejection




Therapy : Felzartamab : 4 weekly IV for a month, and 5 IV monthly

Mayer et al. NEJM 2024

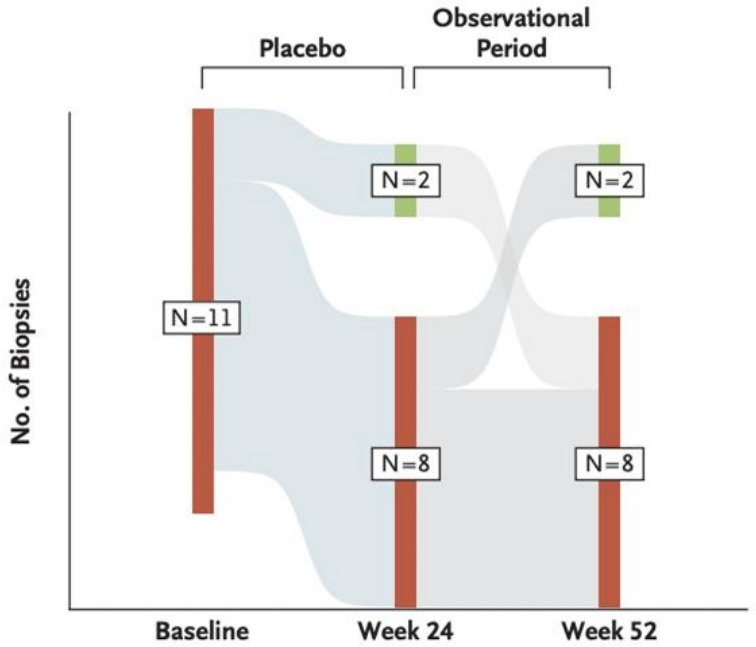
ORIGINAL ARTICLE

# A Randomized Phase 2 Trial of Felzartamab in Antibody-Mediated Rejection

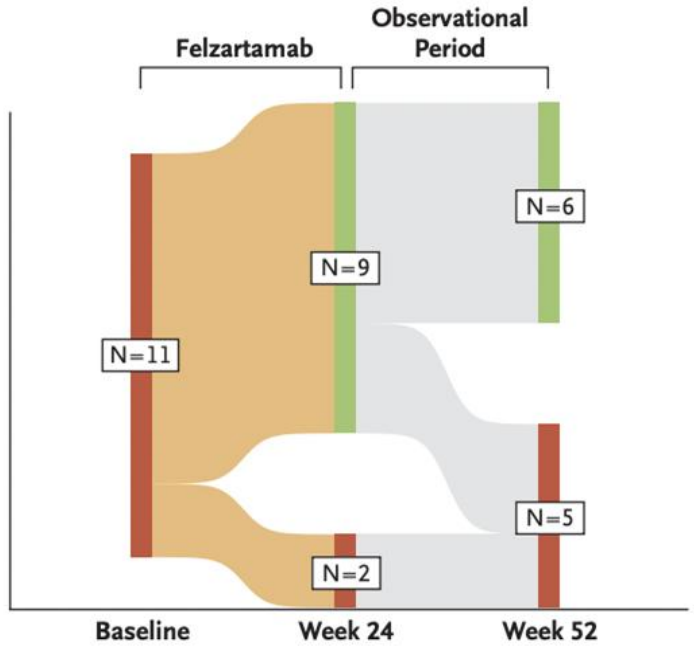
Blind, versus placebo

Population:
N= 22
ABMR with DSA+, acute or chronic
> 20 mL/min
**> 6 months post-transplantation**

PLACEBO




FELZARTAMAB




**Resolution AMR at 24 weeks** 20.0% 81.8%

**Active**

**Non active :** absence of AMR or chronic AMR without activity

Mayer et al. NEJM 2024

ORIGINAL ARTICLE

# A Randomized Phase 2 Trial of Felzartamab in Antibody-Mediated Rejection

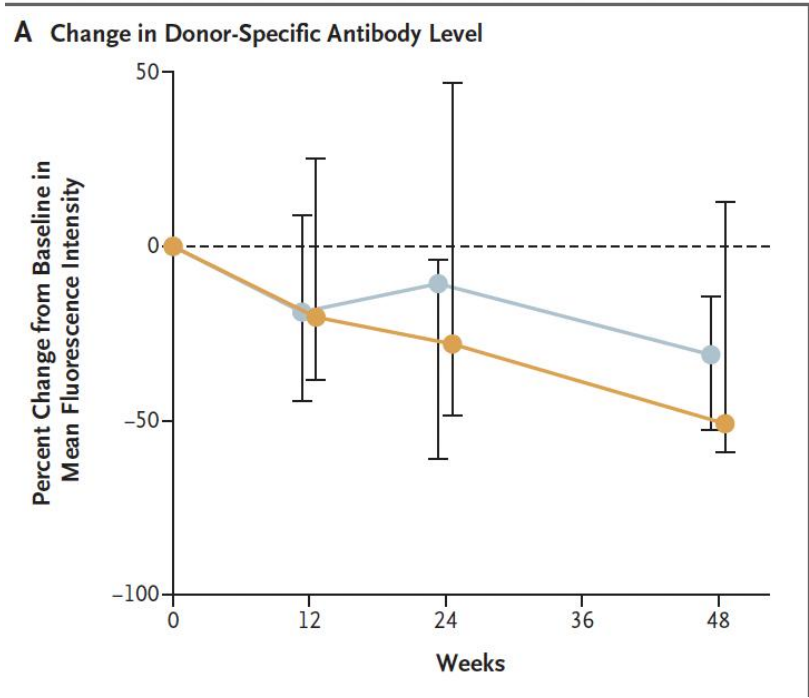
Blind, versus placebo

Population:
N= 22
ABMR with DSA+, acute or chronic
> 20 mL/min
**> 6 months post-transplantation**

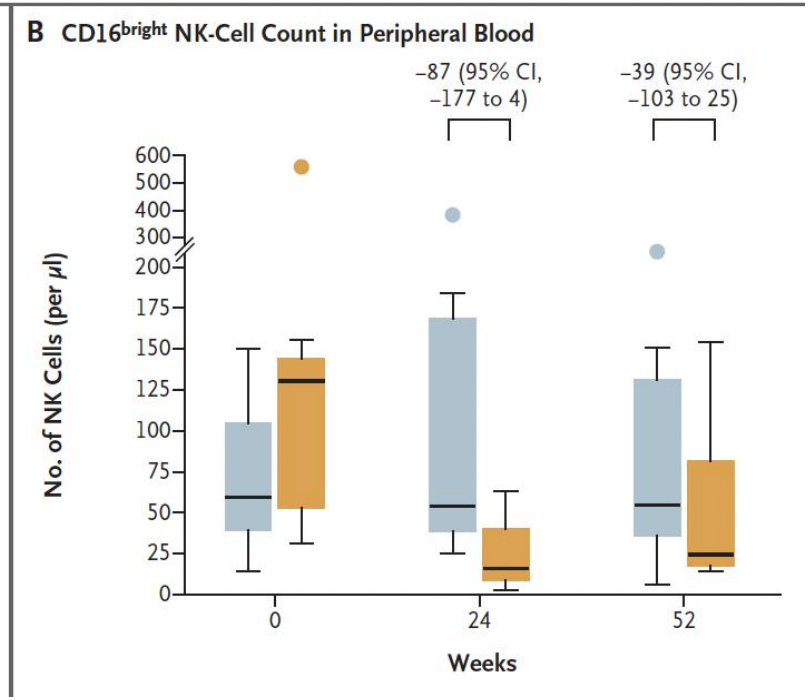
PLACEBO

FELZARTAMAB

**Change in DSA**




**CD16$^{hi}$ NK cell**

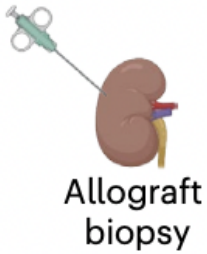


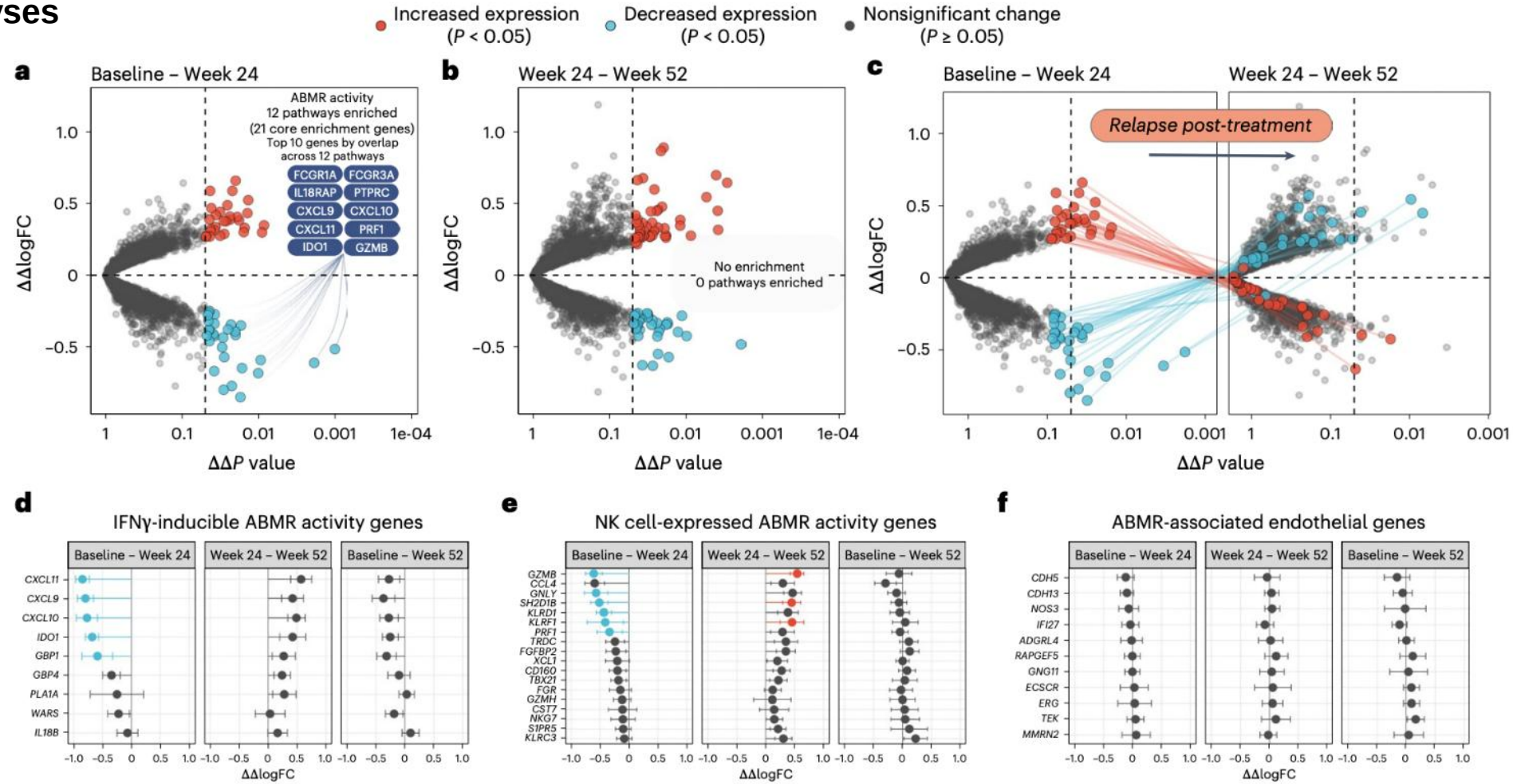

Mayer et al. NEJM 2024

# Felzartamab reduced molecular ABMR activity scores, selectively suppressing interferon gamma-inducible and NK cell transcripts

Bulk **transcriptomic analyses**

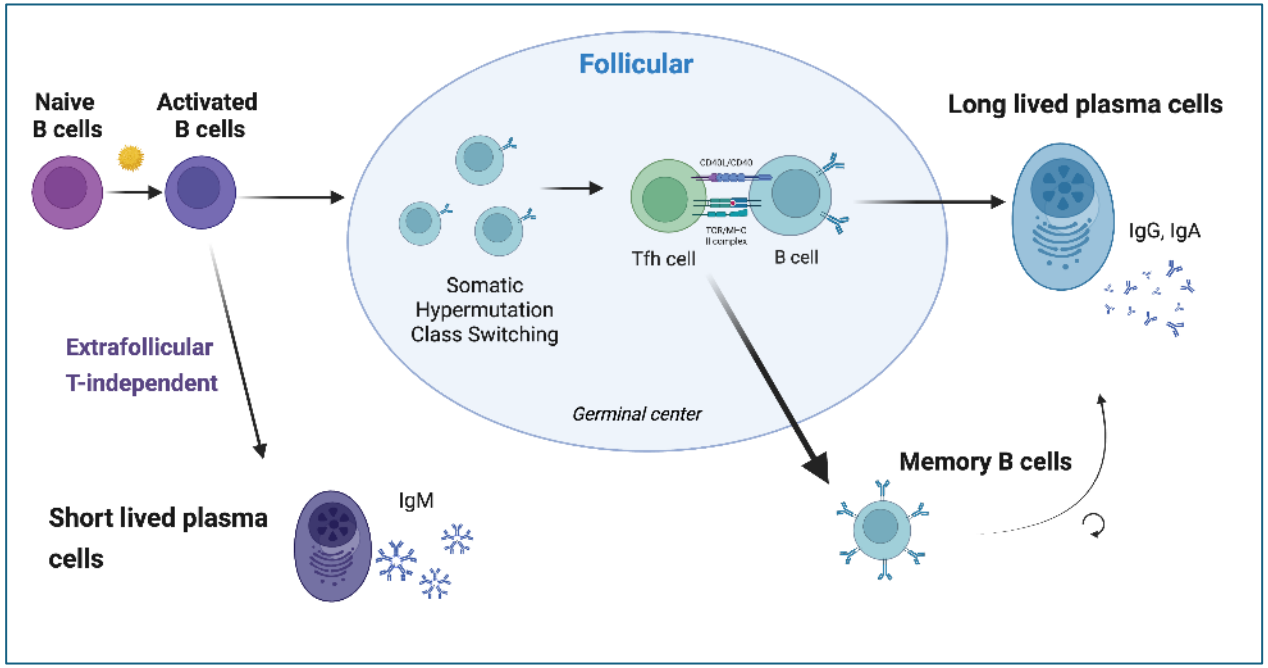
**Week 24**
**vs**
**Week 52**




Diebold et al. Nat med 2025

# Plasma cell targeting in kidney transplantation

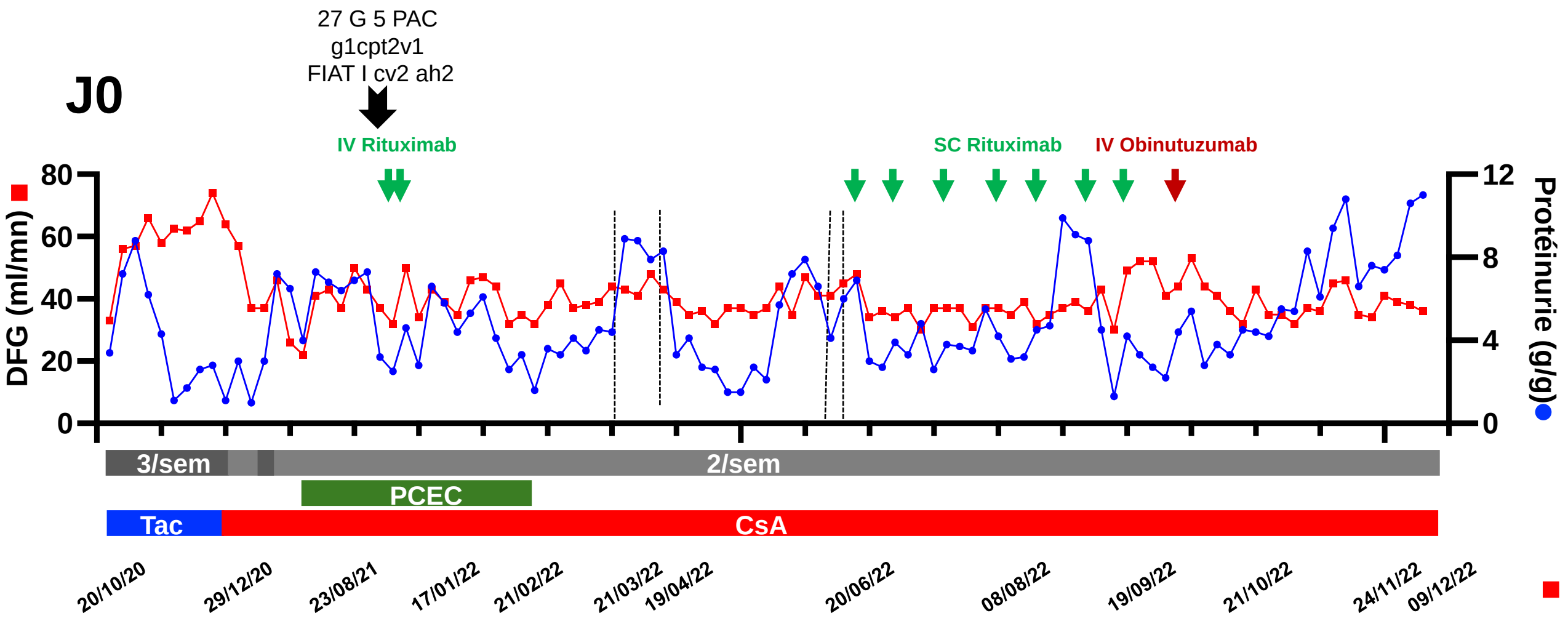



**HLA Desensitization**

**Antibody-mediated rejection**

**Antibody-mediated disease ??**

# 70 year-old, FSGS




Recurrence at day 15 post-transplant, incomplete response to Rituximab/PEX

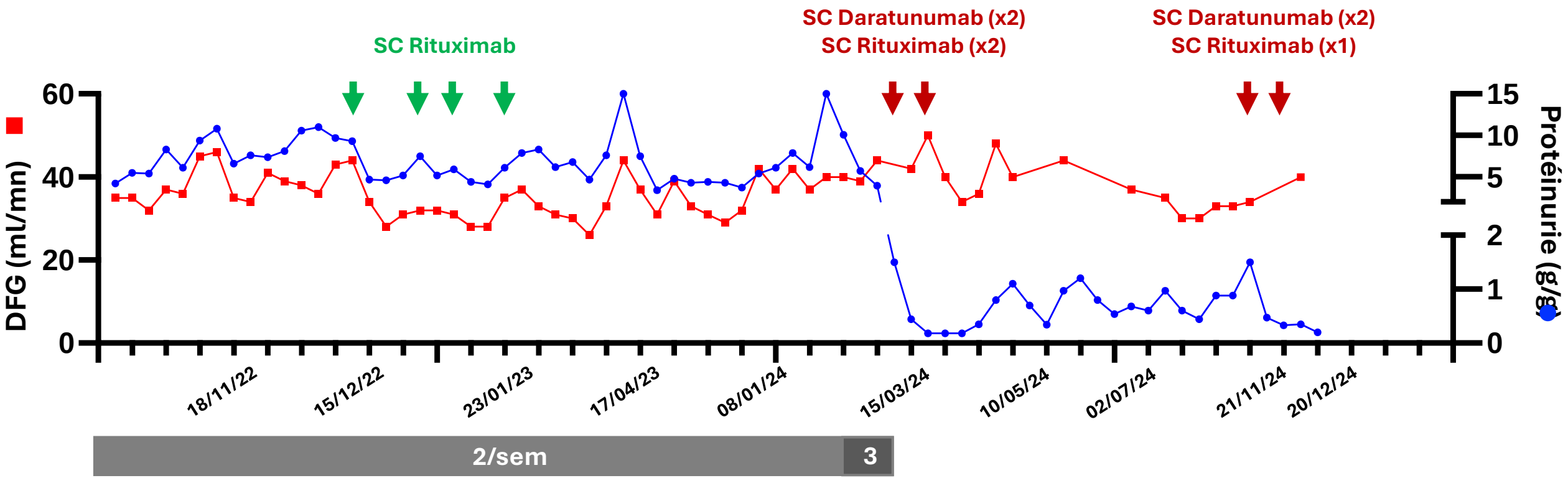
# Combined anti-CD20/anti-CD38 in FSGS recurrence

CASE REPORT · Volume 24, Issue 4, P688-692, April 2024 Download Full Issue

Efficacy of combined rituximab and daratumumab treatment in posttransplant recurrent focal segmental glomerulosclerosis

Andrea Angeletti [1] · Sofia Bin [2] · Alberto Magnasco [1] · Maurizio Bruschi [1] · Paolo Cravedi [2] · Gian Marco Ghiggeri [1]

Affiliations & Notes Article Info Linked Articles (1)




2/sem 3

# Limits of plasma-cell therapy

- Anti-CD38 : other targets and immunomodulatory effects
  - depletion of Breg, Treg = > Increase of activated cytotoxic CD8+ Tcell and reverse T cell exhaustion
  - Sur-risk of TCMR ?

- Dual therapy : increase infectious risk
  - Sustained agammaglobulinemia

# Conclusions

1- New anti-plasma cells are changing the landscape of HLA antibody treatment

2- The most efficient protocols would combine several therapeutics targeting B and plasma cells

3- New anti-plasma cell agents look very promisings : bispecific Ab /Car-T cells

4- Unanswered questions :

- how long their effect last ?
- what is the best therapeutic scheme ?
- Infectious risk management especially in dual B & plasma cells targeting

5. Missing data from larger, well-controlled trials

# Remerciements


## Transplantation rénale

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