

# Diagnóstico y tratamiento el ABMR: evidencias clínicas

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# Disclosure

Grants from:

Astellas, Novartis, TEVA, Chiesi

Honorarium for conferences and advisory boards from :

Astellas, Novartis, TEVA, Chiesi, CSL Behring, Viateris

Humoral rejection phenotypes

Limited efficacy of classic treatments

New treatments

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Limited efficacy of classic treatments

New treatments

American Journal of Transplantation 2017  
Blackwell Munksgaard

## Meeting Report

### MEETING REPORT

The Banff 2017 Kidney Meeting Report: Revised diagnostic criteria for chronic active T cell-mediated rejection, antibody-mediated rejection, and prospects for integrative endpoints for next-generation clinical trials

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# Banff 2017 Meeting Report C4d-Negative Antibody-Mediated Rejection and Antibody-Associated Arteriosclerosis

AJT

Antibody-Mediated Rejection

Volume 19, Issue 10, October 2017  
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doi: 10.1111/ajt.12590

Antibody-Mediated Rejection and Current Prospects

Banff 2017 Meeting Report  
Graft Debridement  
of Banff Working Group

Journal of Transplantation published by  
Wiley Periodicals, Inc. on behalf of American Society of  
Transplant Surgeons  
doi: 10.1111/ajt.12590

# 2017 Banff Criteria and Humoral Rejection

## Class I

Active ABMR

Histologic evidence of injury

Microvascular injury (g+ptc)

Intimal

transmural

arteritis

Evidence of Ab interaction with vascular endothelium

Thrombotic microangiopathy

thy

Serologic evidence of DSA

## Class II

Chronic ABMR

Transplant glomerulopathy

ptc

multilayering

New onset arterial

intimal

# Humoral rejection


Active

Chronic

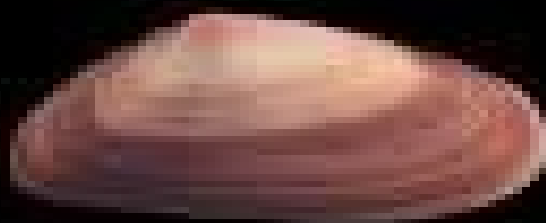
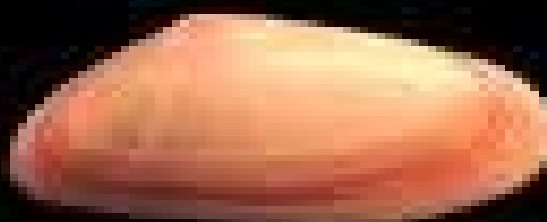
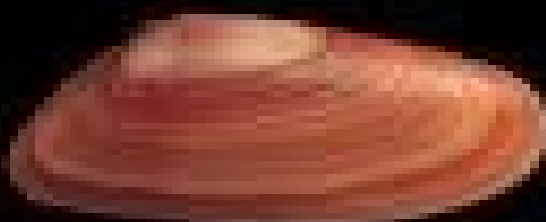
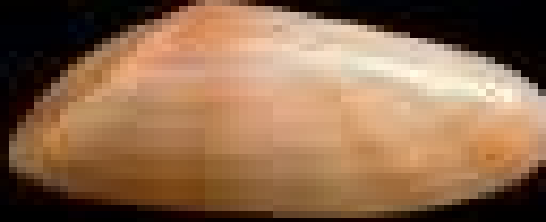
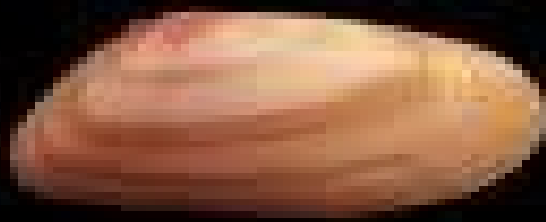
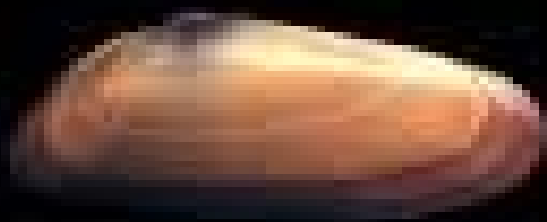
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Presentation	Acute rise SCr	Proteinuria
DSA appearance	Preexisting DSA	de novo DSA
Anti HLA Ab	Class I	Class II
IFTA	↓	↑
Cellular rejection	↓	↑
Response to treatment	Yes	No

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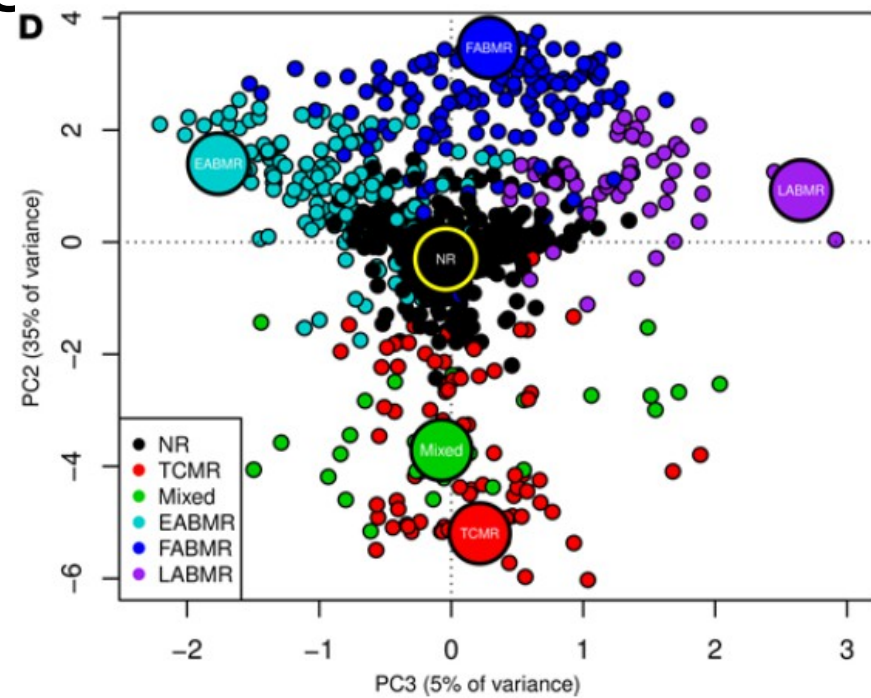
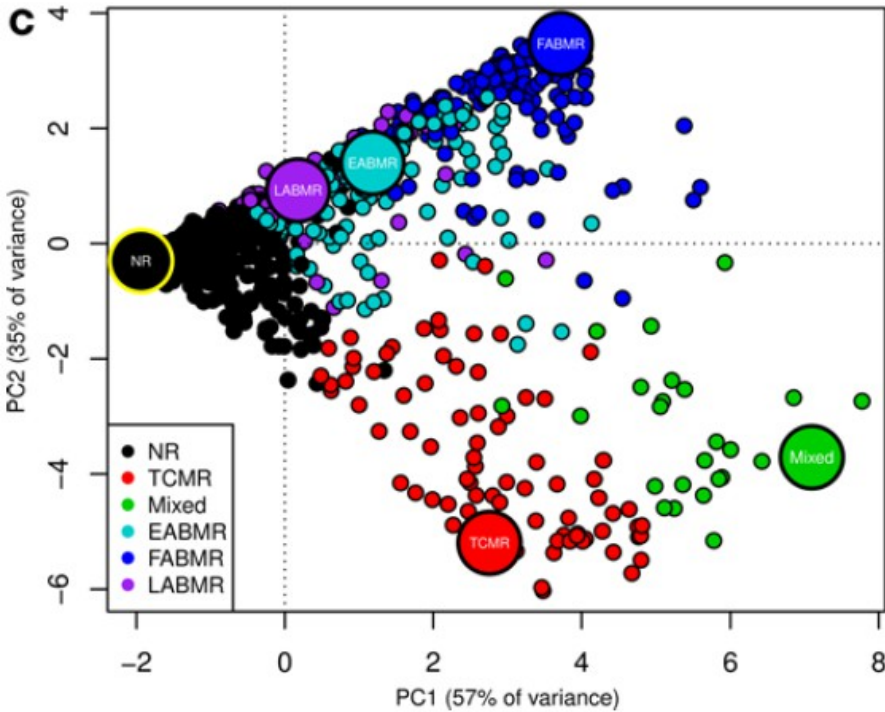


Defining the phenotype of disease



# Rejection related disease based on archetypical analysis of molecular phenotype

$r = -1.208 R_{\nu}$



NR: no rejection

EABMR: Early ABMR

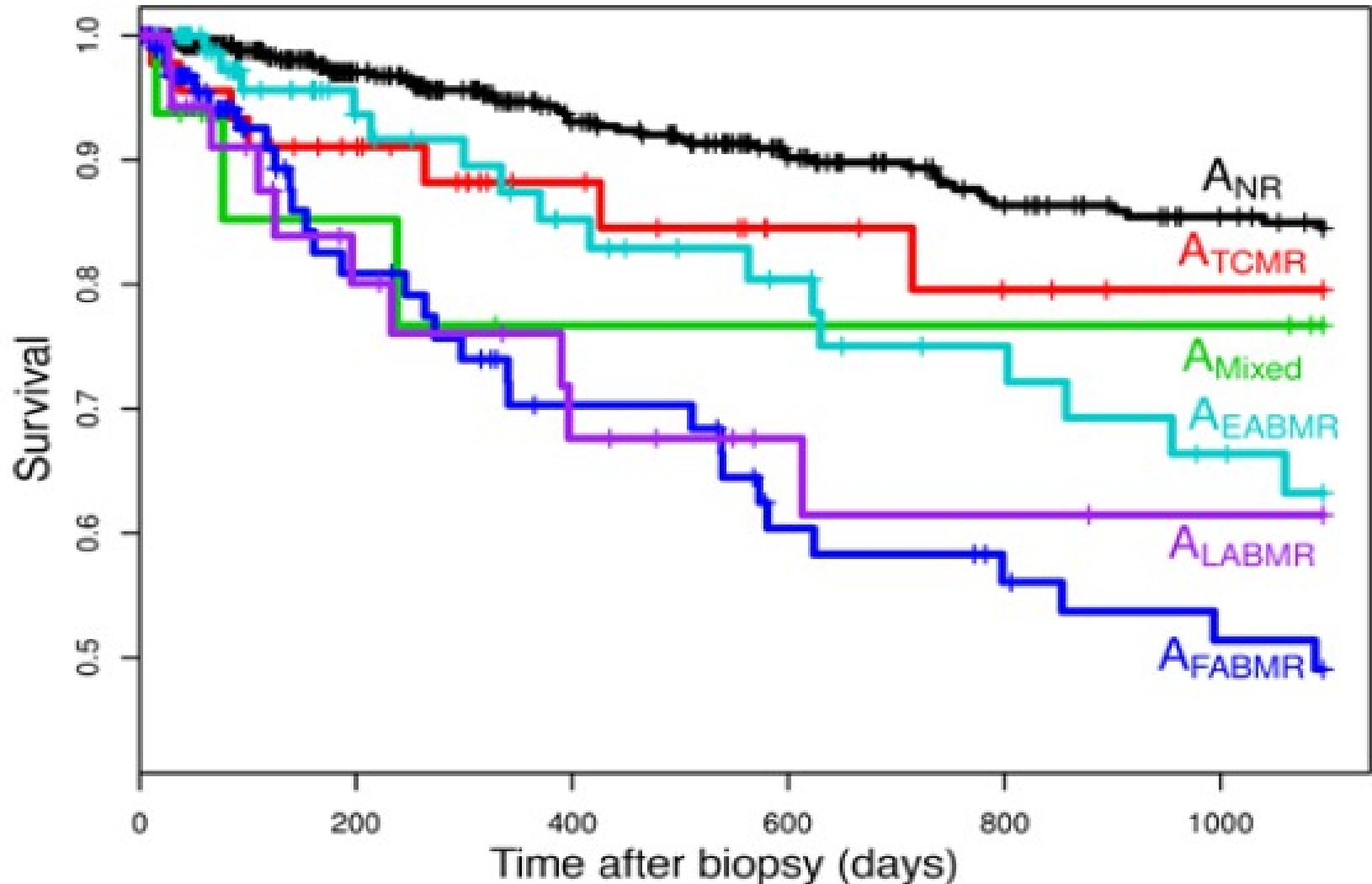
TCMR: T cell mediated rejection

FABMR: Full blown ABMR

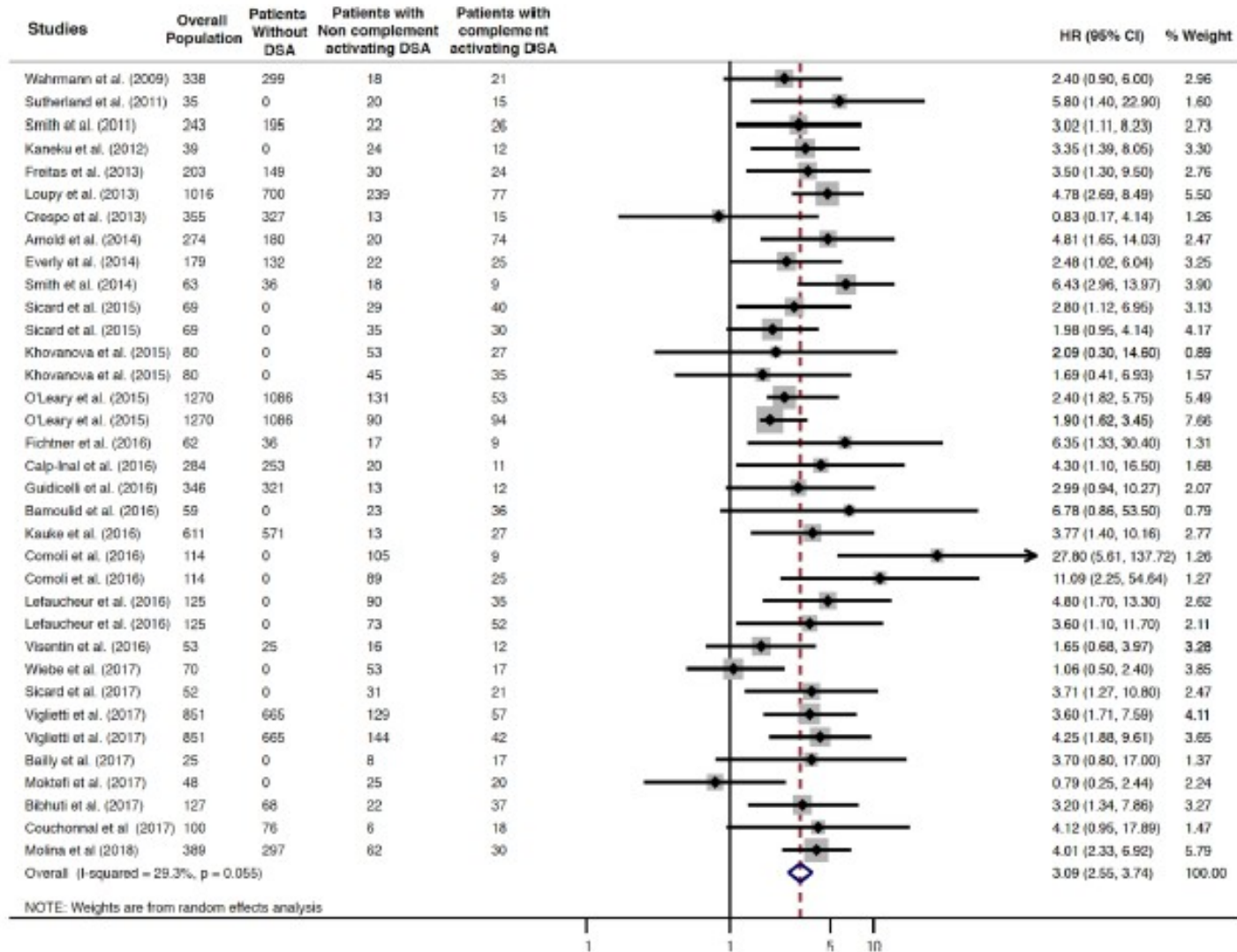
Mixed Mixed rejection

LABMR Late ABMR

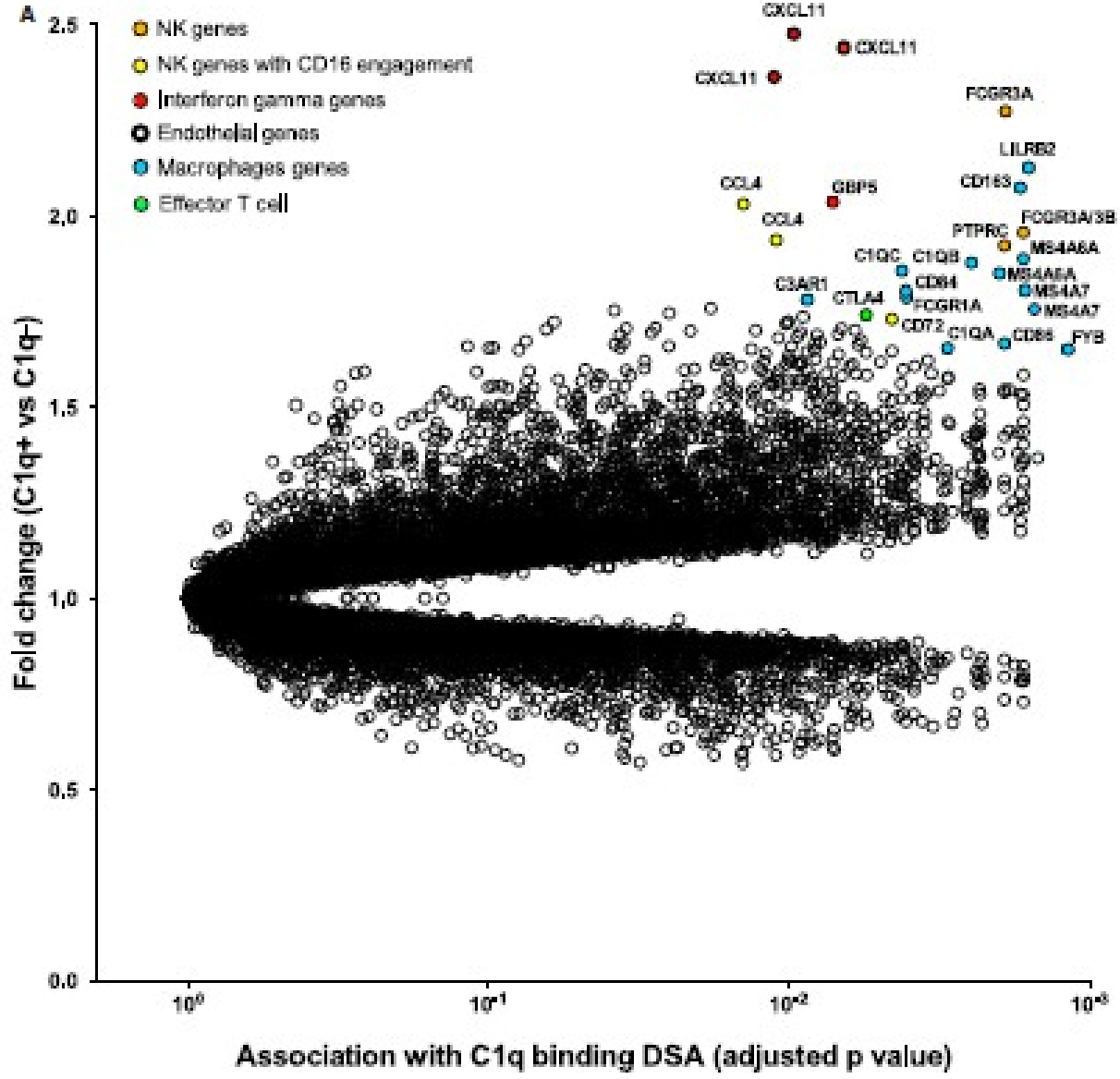
# Rejection related disease in KT biopsies based on archetypal analysis of molecular phenotype



# C fixing DSA and graft survival



# Characteristics of pts with C1q binding DSA



CXCL11  
 CCL4  
 MSA47  
 MSAA6A  
 FCGR3A



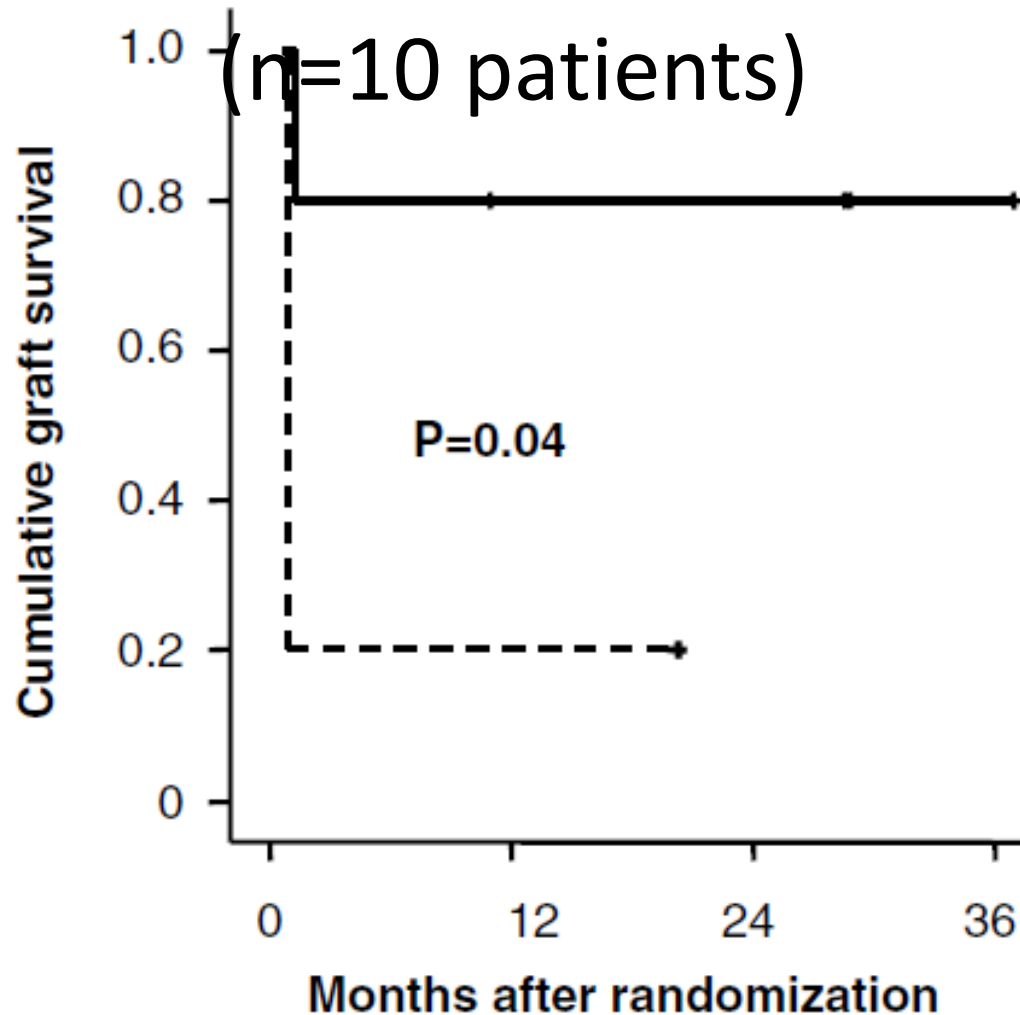
Endothelial activation  
 IFN $\gamma$  response  
 NK activation  
 Monocyte/macrophage

Humoral rejection phenotypes

Limited efficacy of classic treatments

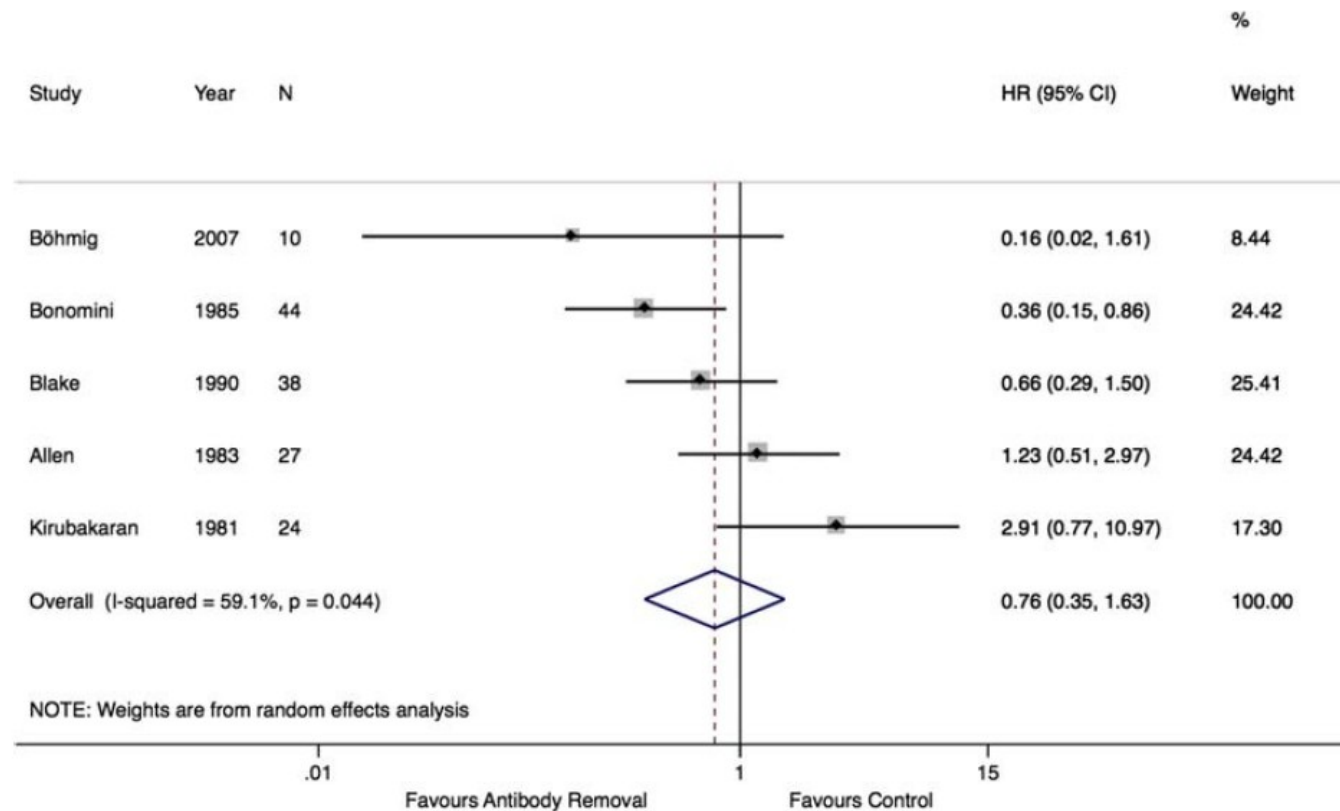
New treatments

# Immunoadsorption: a randomized controlled trial in acute AMR



# The Treatment of Antibody-Mediated Rejection in Kidney Transplantation: An Updated Systematic Review and Meta-Analysis

Susan S. Wan, MMed (Clin Epi), FRACP,<sup>1,2</sup> Tracey D. Ying, MMed (Clin Epi), FRACP,<sup>1,2</sup>  
 Kate Wyburn, FRACP, PhD,<sup>1,2</sup> Darren M. Roberts, FRACP, PhD,<sup>3,4</sup> Melanie Wyld, MBA, MPH,<sup>1,5</sup>  
 and Steven J. Chadban, FRACP, PhD<sup>1,2</sup>



PF and IVIG have become standard of care despite limited low quality evidence

# ABMR score integrating disease characteristics and response to treatment in active ABMR: n=278

At time of diagnosis Treatment PF+high IVIg, RTX+steroid boluses

Variable	Number of Patients	Number of Events	HR	95% CI	P
eGFR (per 1-ml/min per 1.73 m <sup>2</sup> increment)	278	60	0.97	(0.95 to 0.98)	<0.001
Chronic allograft glomerulopathy					
Banff score=0	228	40			
Banff score>0	50	20		(3.92)	0.004
Interstitial fibrosis/tubular atrophy					
Banff score=0	130				
Banff score>0	148			(1.62 to 5.29)	<0.001
Anti-HLA DSA status					
Performed	10		1		
De novo			2.45	(1.34 to 4.47)	0.004

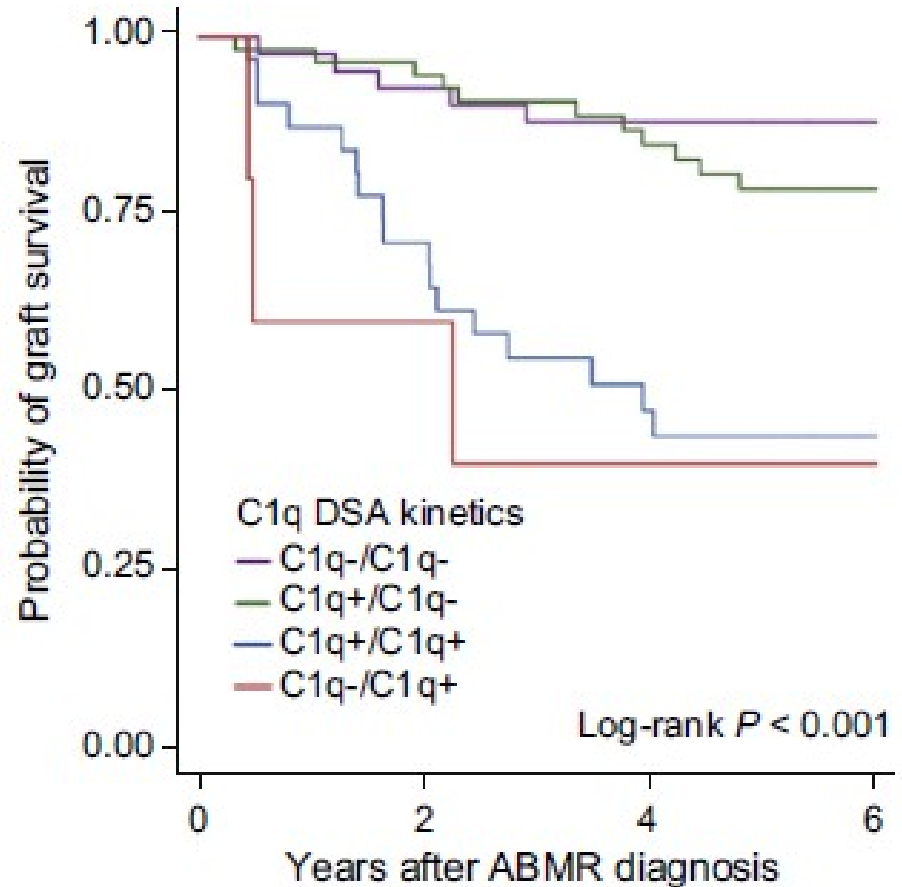
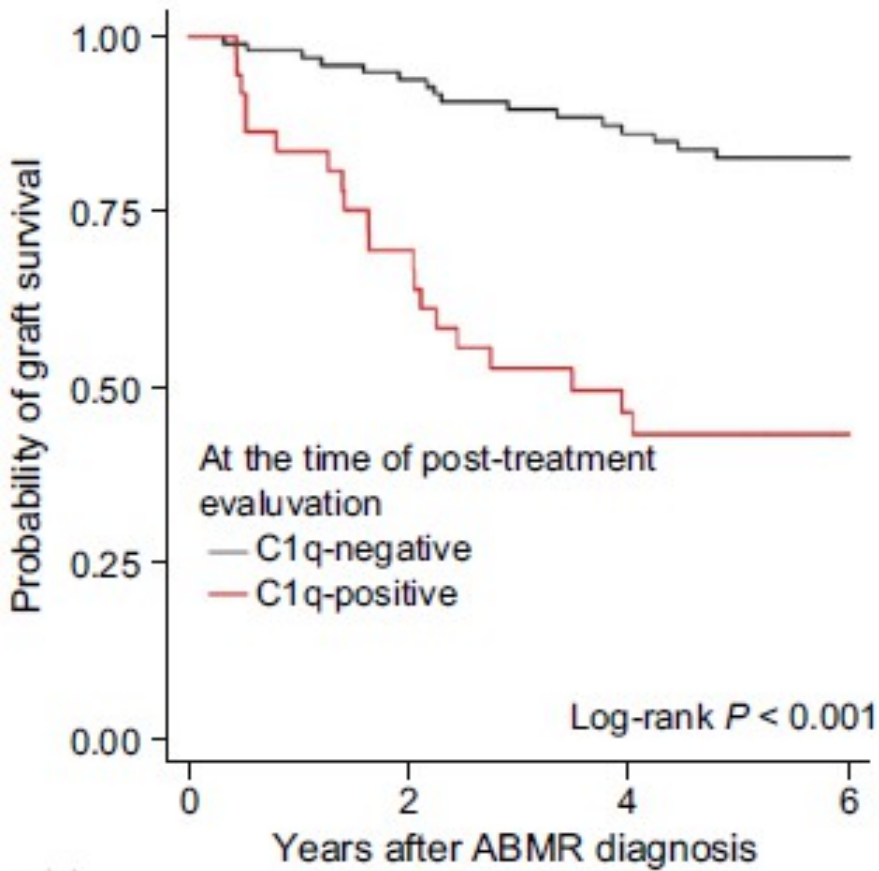
time of diagnosis and after treatment

Variable	Number of Patients	Number of Events	HR	95% CI	P
eGFR at ABMP (per 1-ml/min per 1.73 m <sup>2</sup> increment)	278	60	0.93	(0.90 to 0.95)	<0.001
Interstitial fibrosis/tubular atrophy at ABMR diagnosis					
Banff score=0	130	16	1		
Banff score>0	148	44	2.44	(1.36 to 4.37)	0.003
eGFR relative change after treatment (log <sub>10</sub> [value+0.7], continuous)	278	60	0.24	(0.16 to 0.35)	<0.001
ΔPeritubular capillaritis Banff score after treatment (continuous)	278	60	1.50	(1.16 to 1.93)	0.002
Anti-HLA DSA MFI relative change after treatment (continuous)	278	60	1.30	(1.11 to 1.52)	<0.001

↑ eGFR, ↓ PTC, ↓ MFI

# Post treatment C1q and outcome

SOC: PF+IVIG+RTX



# On top of SOC treatment strategy for acute AMR

Rituximab  
Bortezomib  
Splenectomy



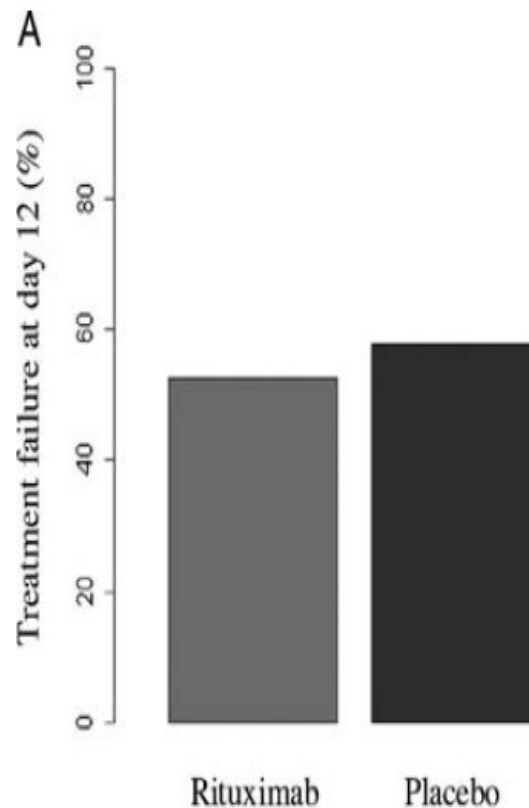
Plasma Exchange

IV Immunoglobulin

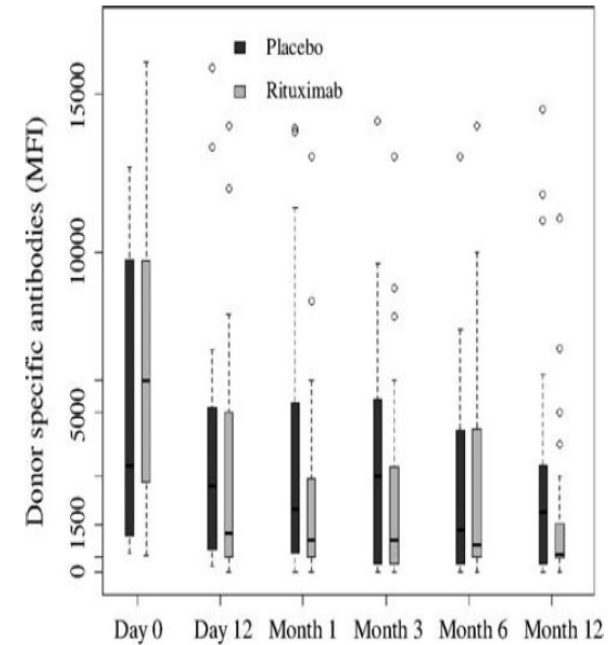
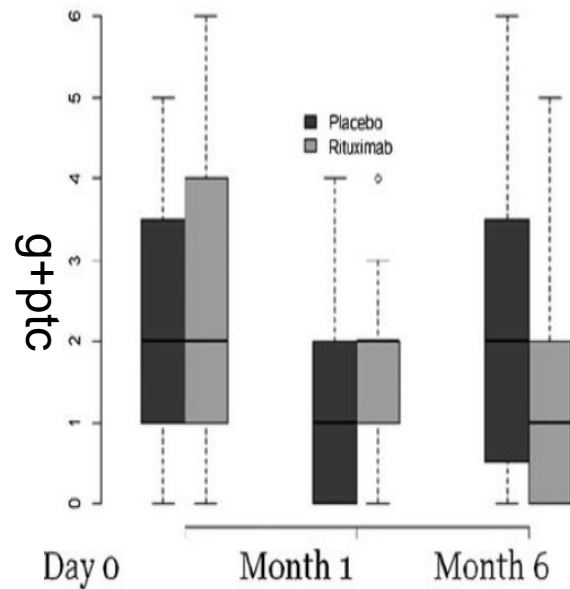
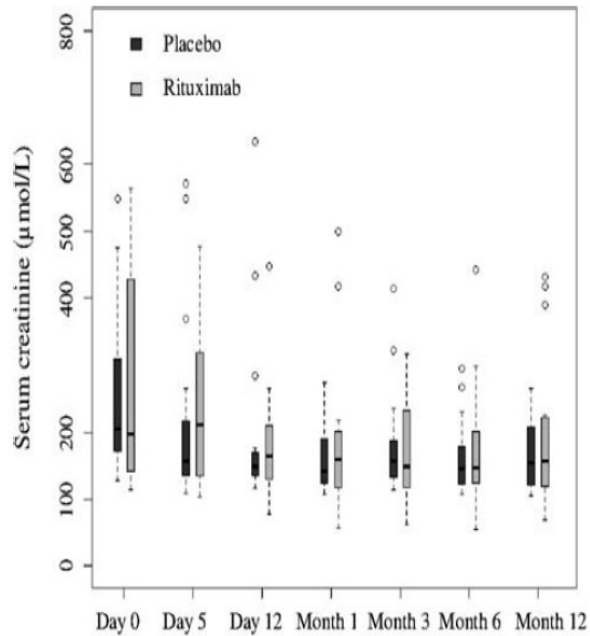
# RITUX ERAH: double blind placebo controlled trial to evaluate rituximab in acute AMR (1st year) n=38

Treatment failure: composite of graft loss and absence of GFR improvement

Acute AMR → PP+IVIG+steroids → Rituxi  
Placebo



# RITUX ERAH: results at 1 year



# Treatment of chronic AMR

Treatment



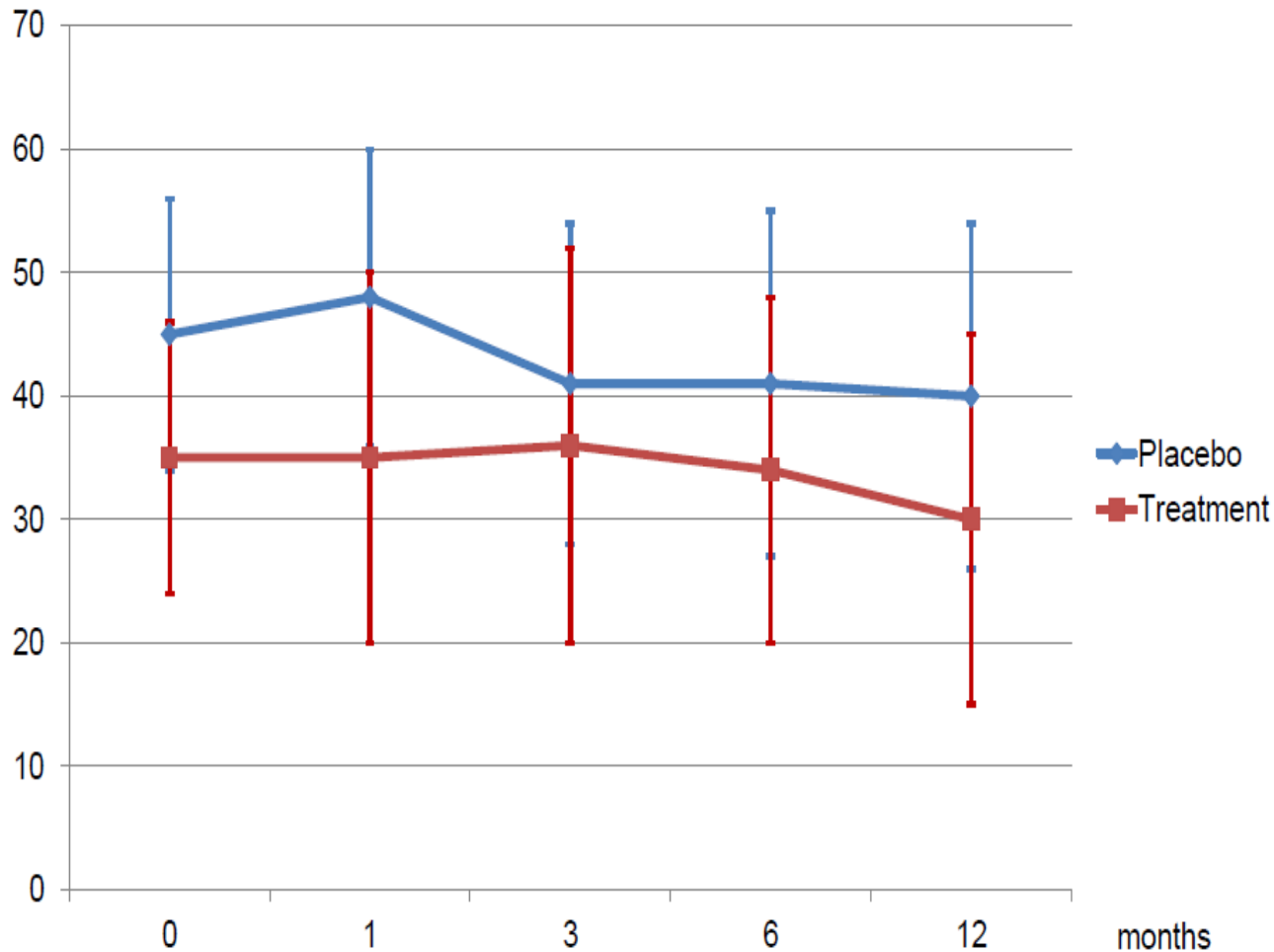
Damaging Effect of dn DSA

# Treatment of chronic ABMR with IVIG and rituximab:

a multicenter

eGFR (mL/min/1.73 m<sup>2</sup>)

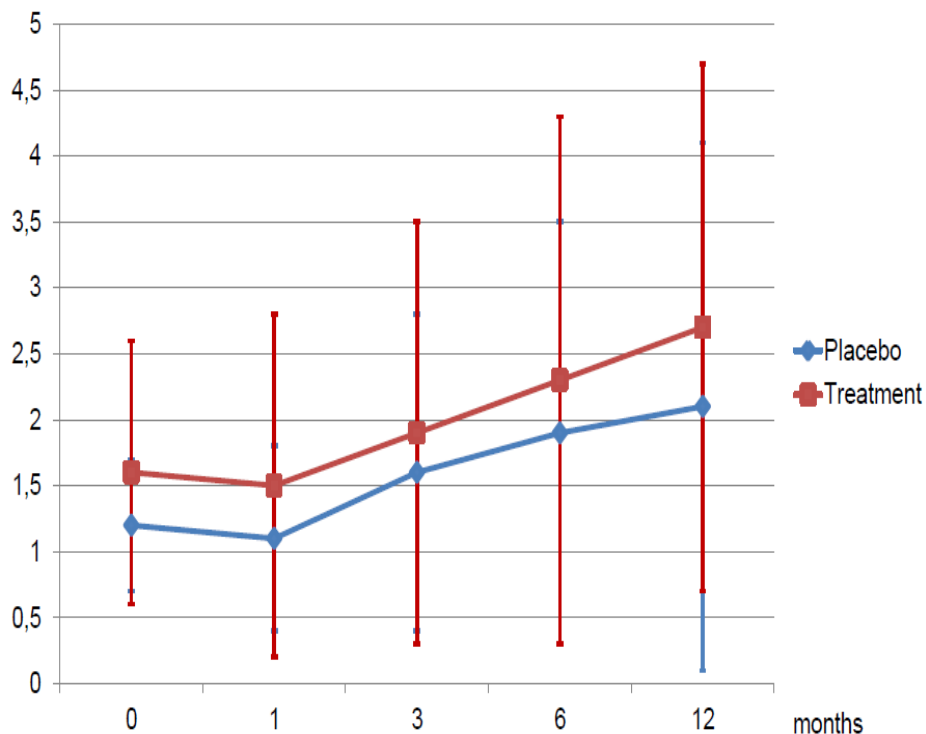
clinical



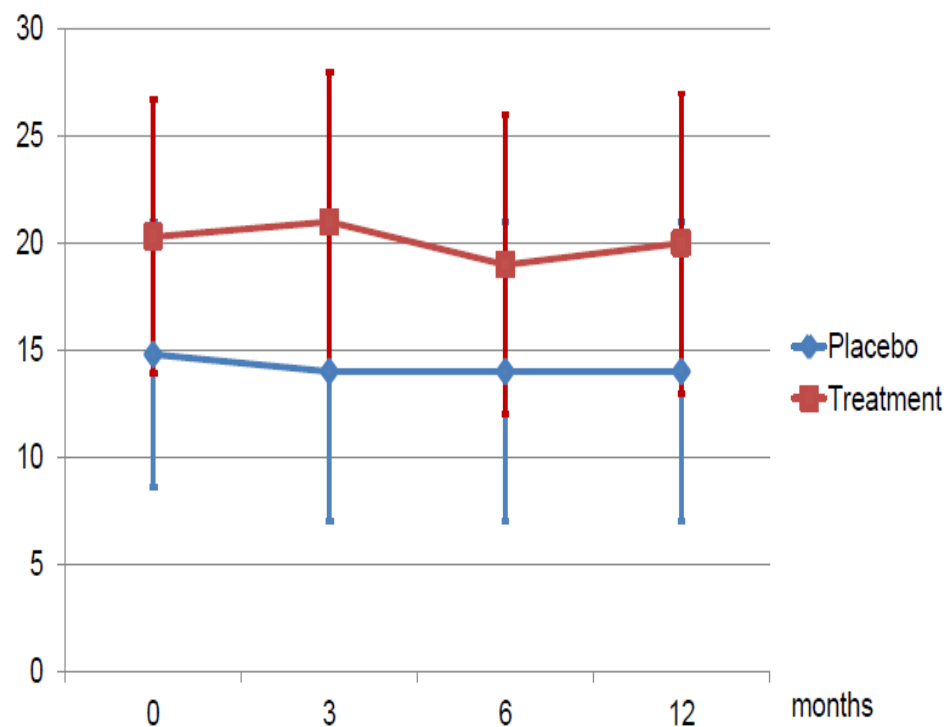
# Treatment of chronic ABMR with IVIG and rituximab:

a multicentre, prospective, randomized, double blind clinical

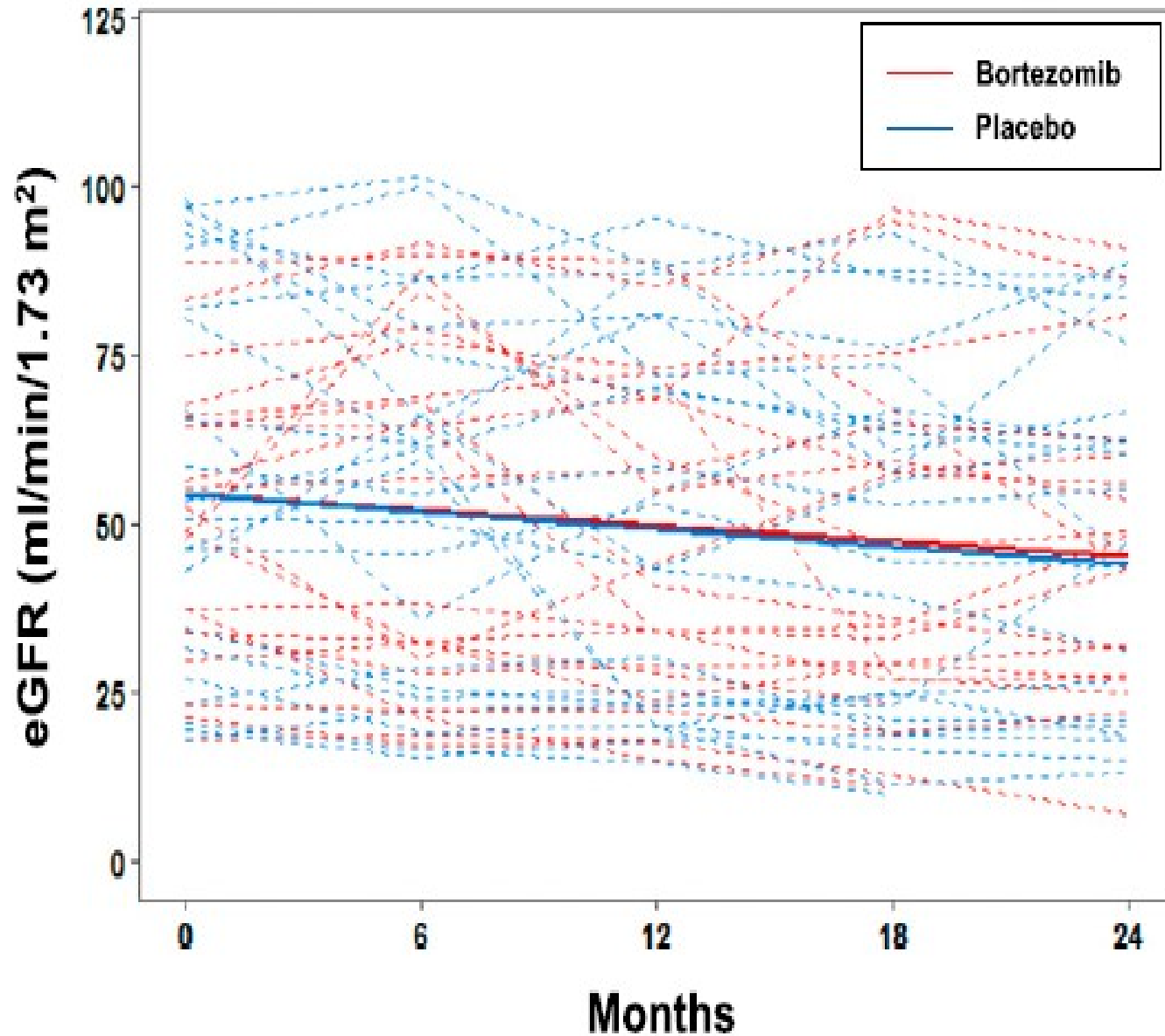
Proteinuria (g/day)



Immunodominant DSA (MFI x 1000)

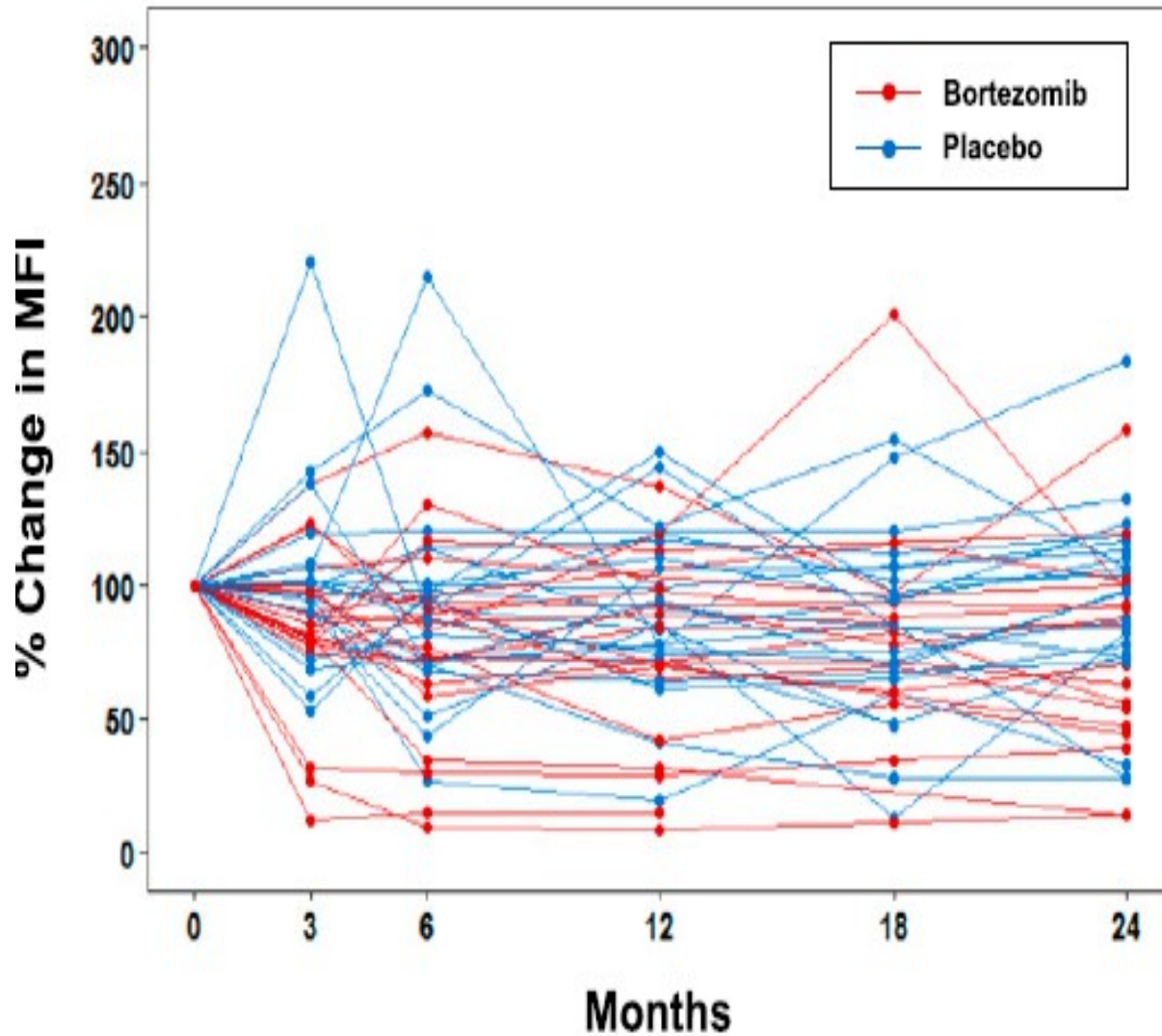


# Bortezomib trial: e-GFR



# Bortezomib trial: MFI max

DSA MFI\_max



Humoral rejection phenotypes

Limited efficacy of classic treatments

New treatments

# New treatments

Modulation of basal IS

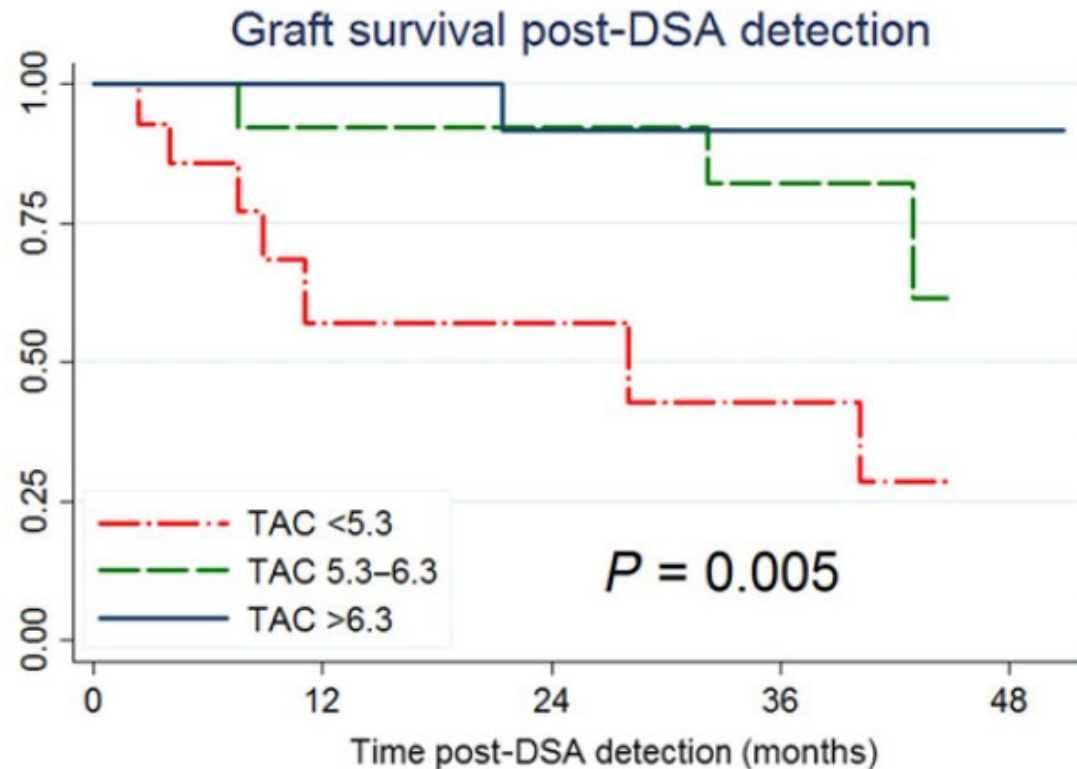
IdeS

Complement blocking/clearing

Anti IL6R/antiIL6

# Modulation of basal IS

# dnDSA and survival according to TAC exposure x 24 months (n=42)

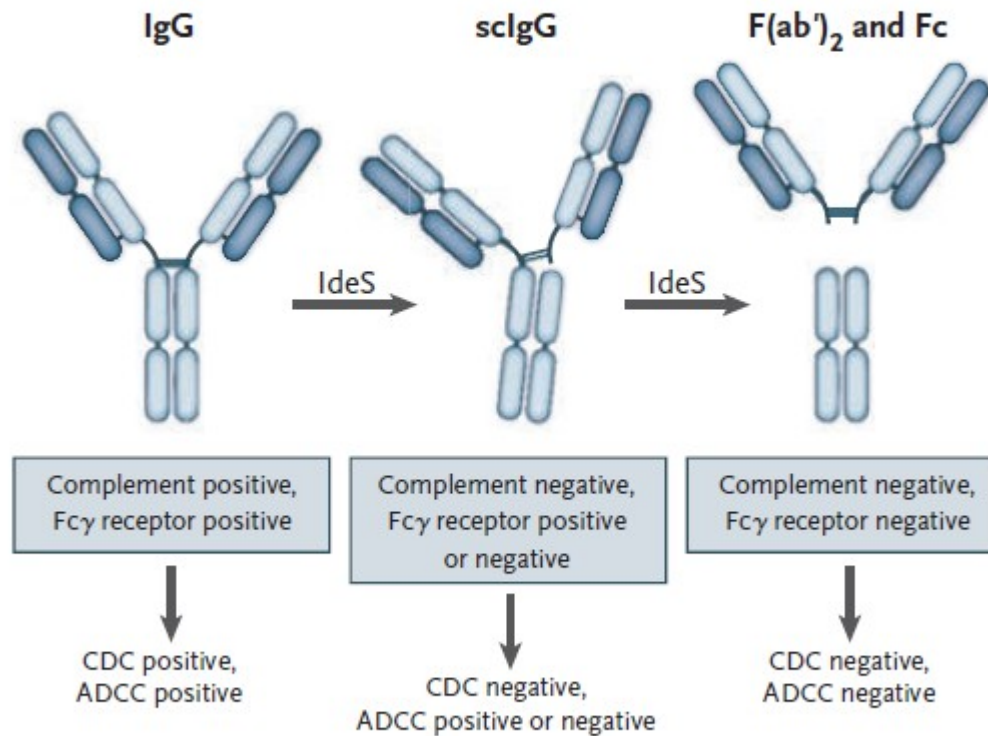


Number at risk

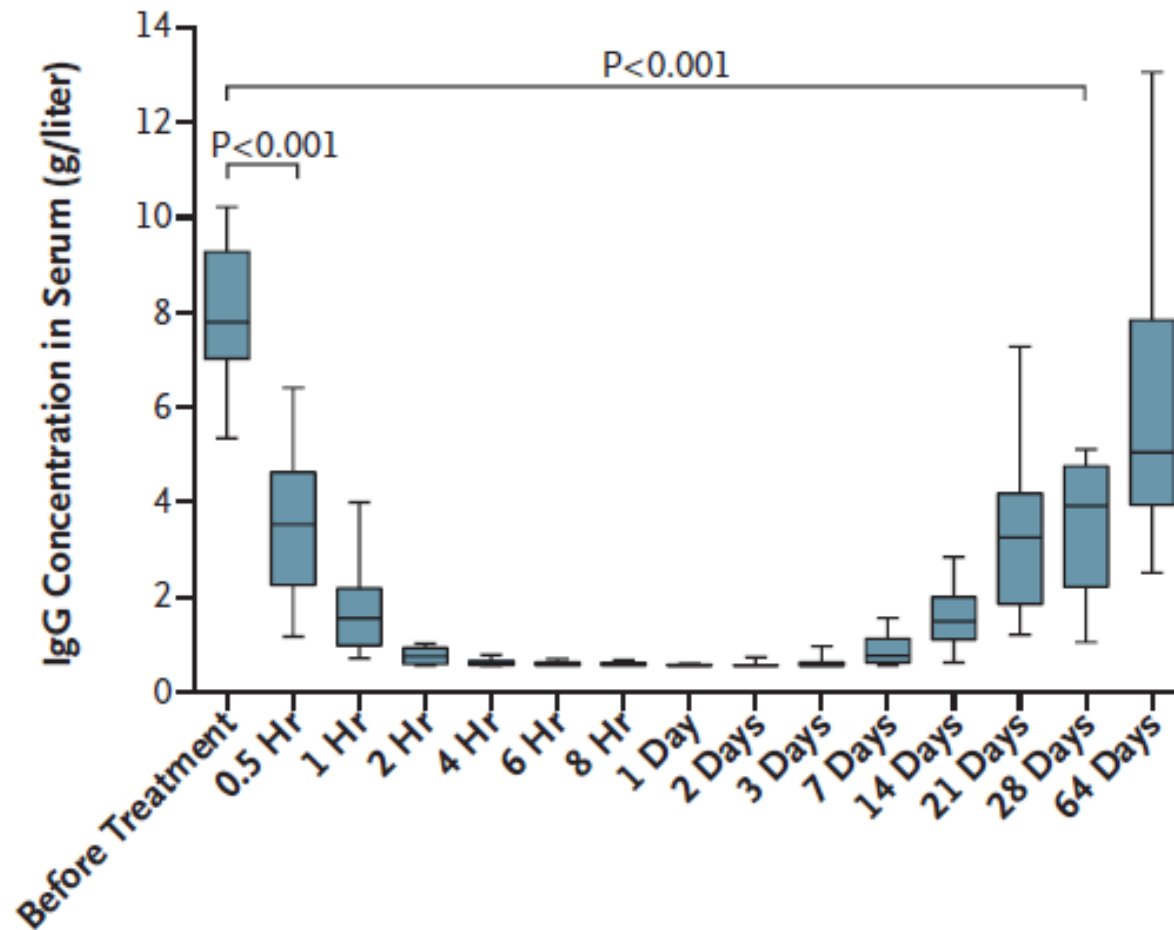
TAC <5.3	14	5	4	3	1
TAC 5.3 – 6.3	14	11	9	7	2
TAC >6.3	14	12	11	7	5

IdeS

# IgG degrading enzyme derived from *S. P. vogenes* (IdeS)

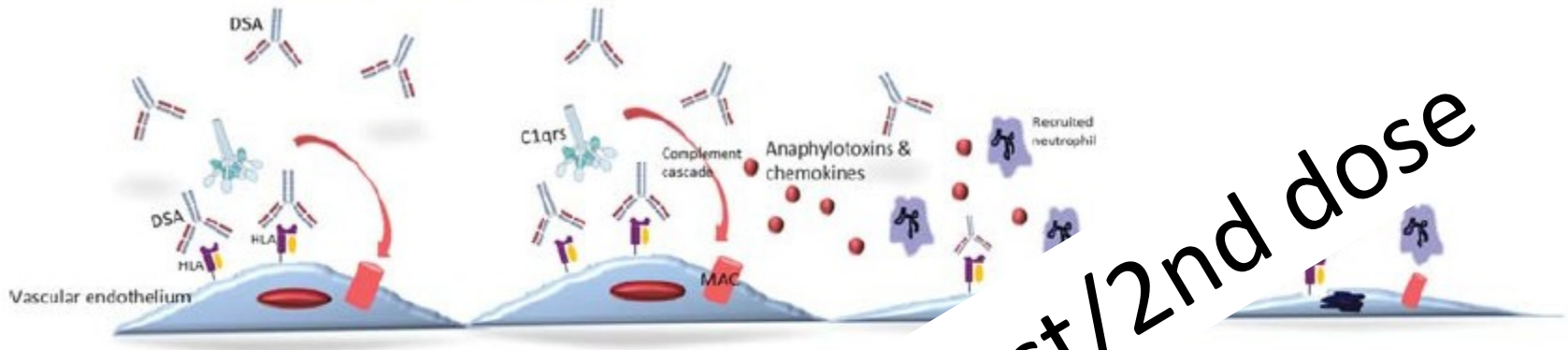


# IdeS effect on circulating IgG levels



A

*Antibody mediated rejection*



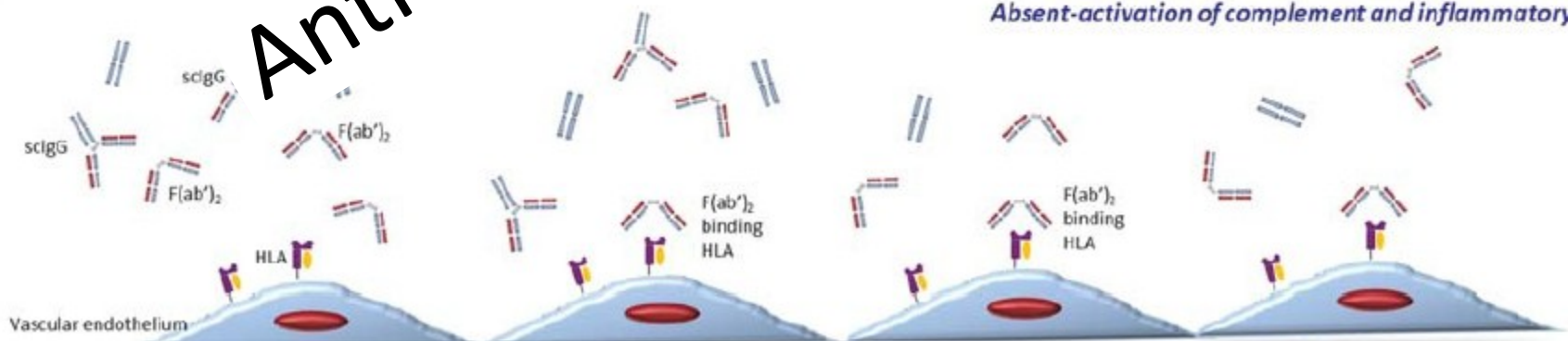
B

*IdeS - IgG degradation*



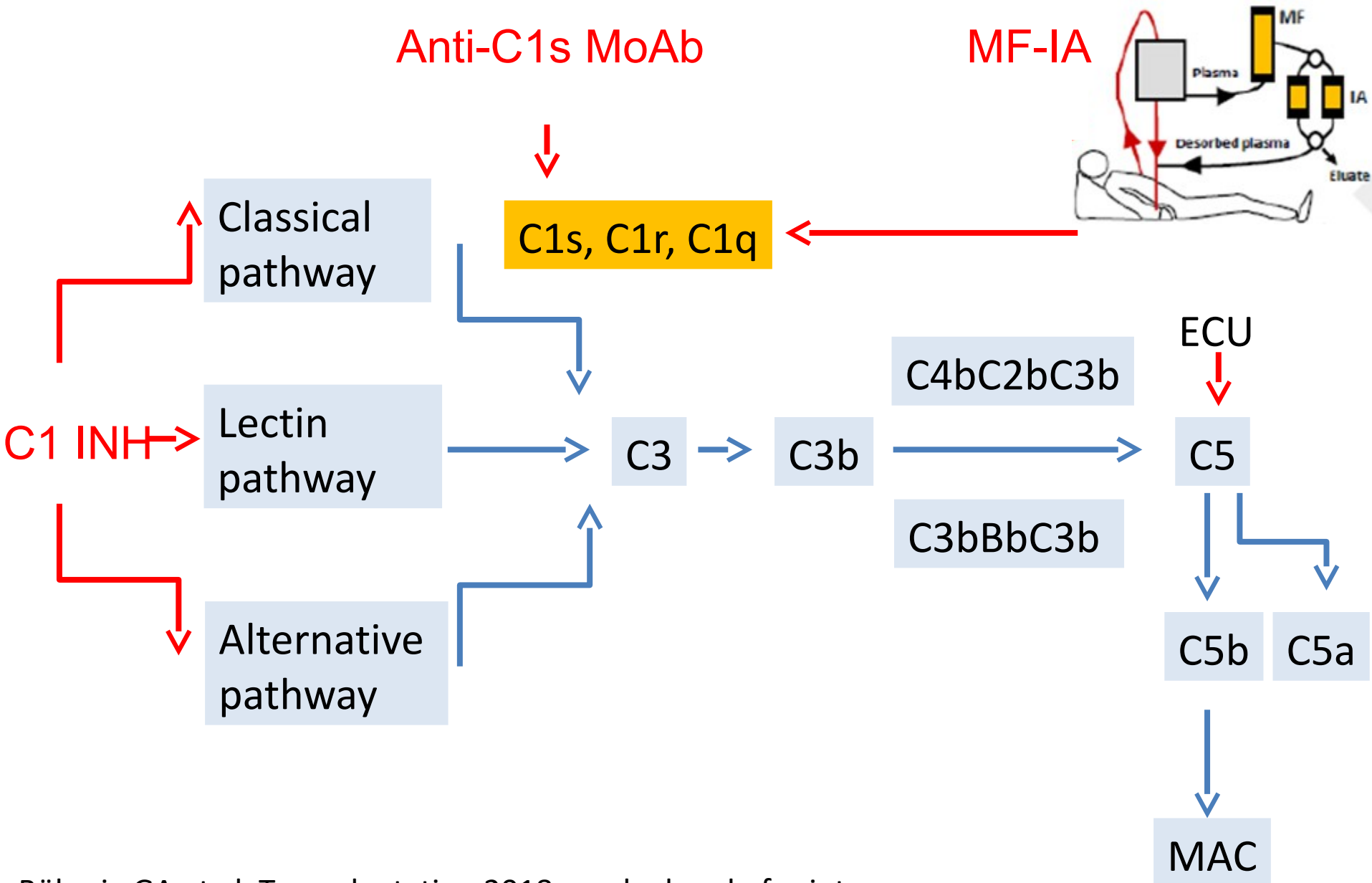
C

*IdeS prevents antibody mediated rejection  
Absent-activation of complement and inflammatory infiltrate*



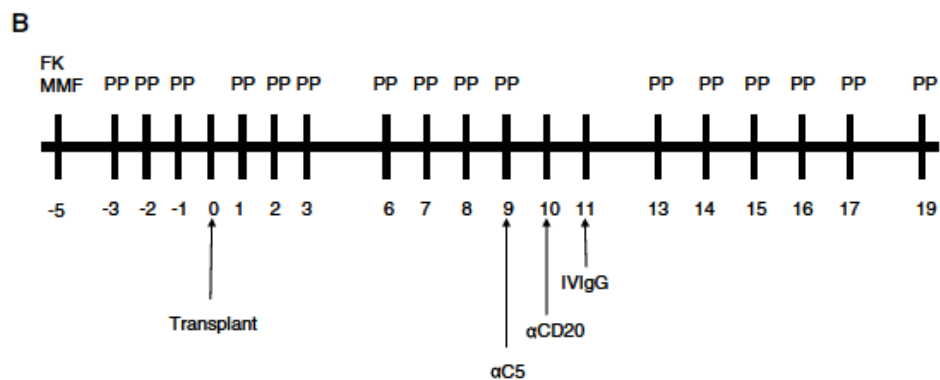
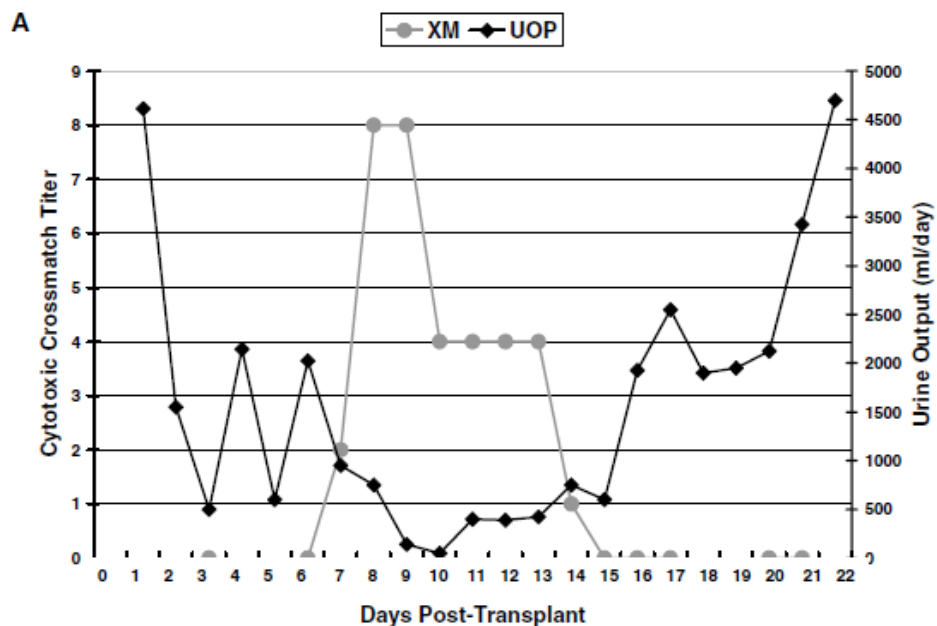
Anti-IdeS Ab after 1st/2nd dose

# Complement blocking/clearing

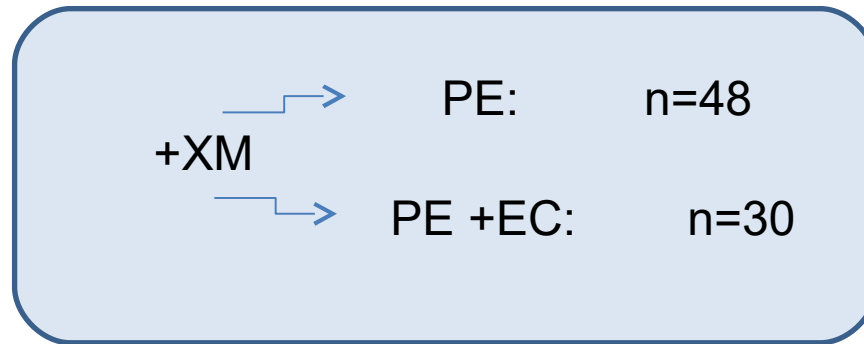


Eculizumab

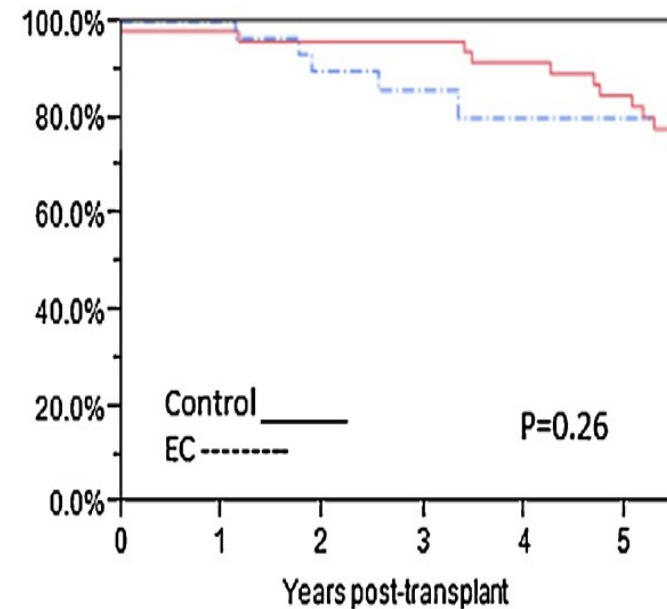
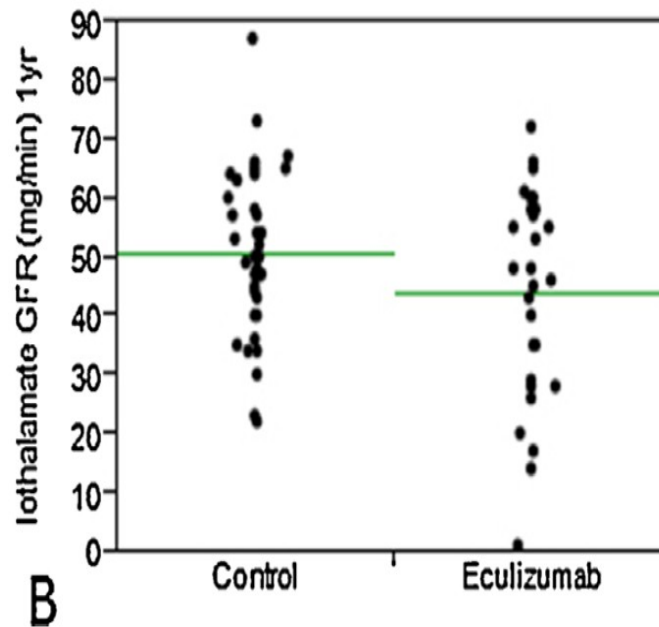
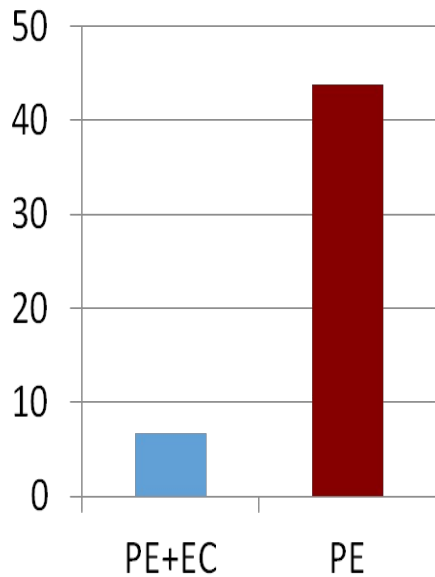
# Case report: eculizumab in severe acute ABMR



# Eculizumab for the Prevention of ABMR in +XM patients

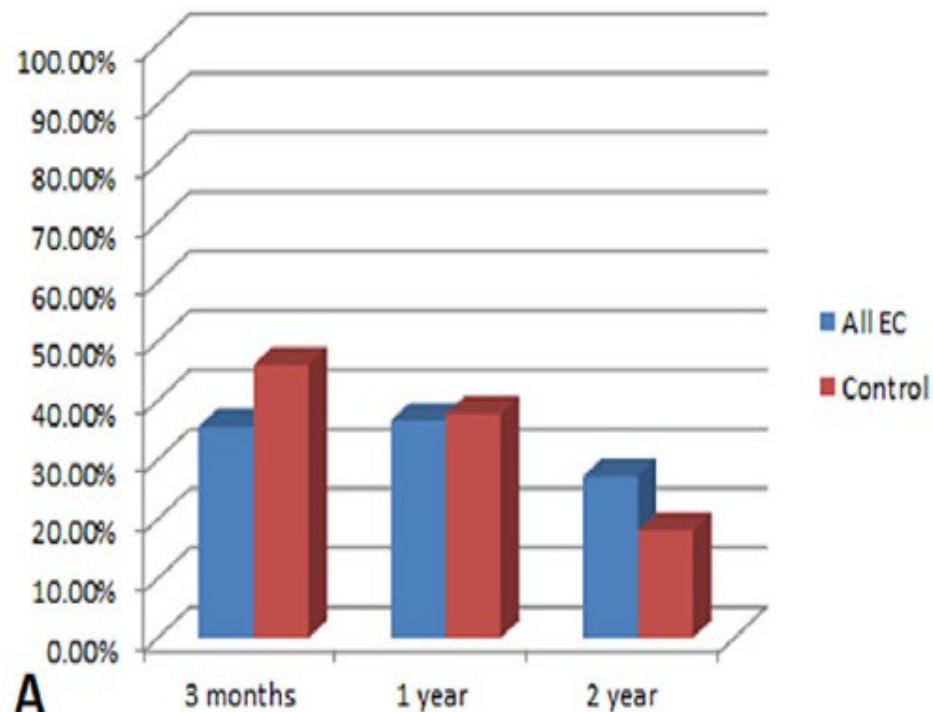


Acute AMR

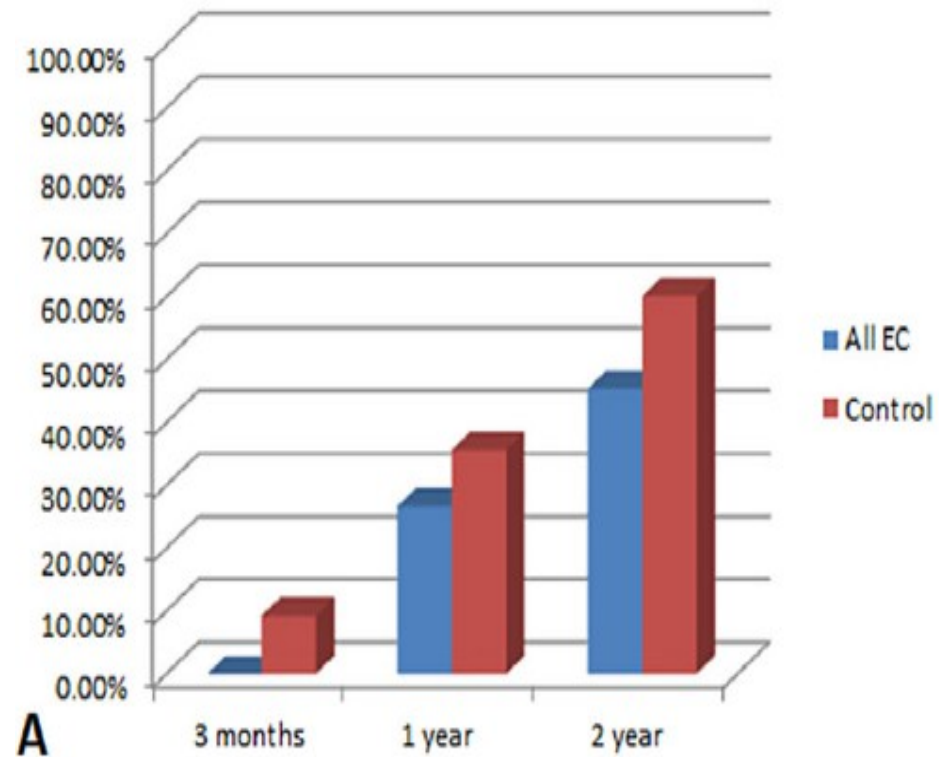


# Eculizumab and histology

## Subclinical AMR



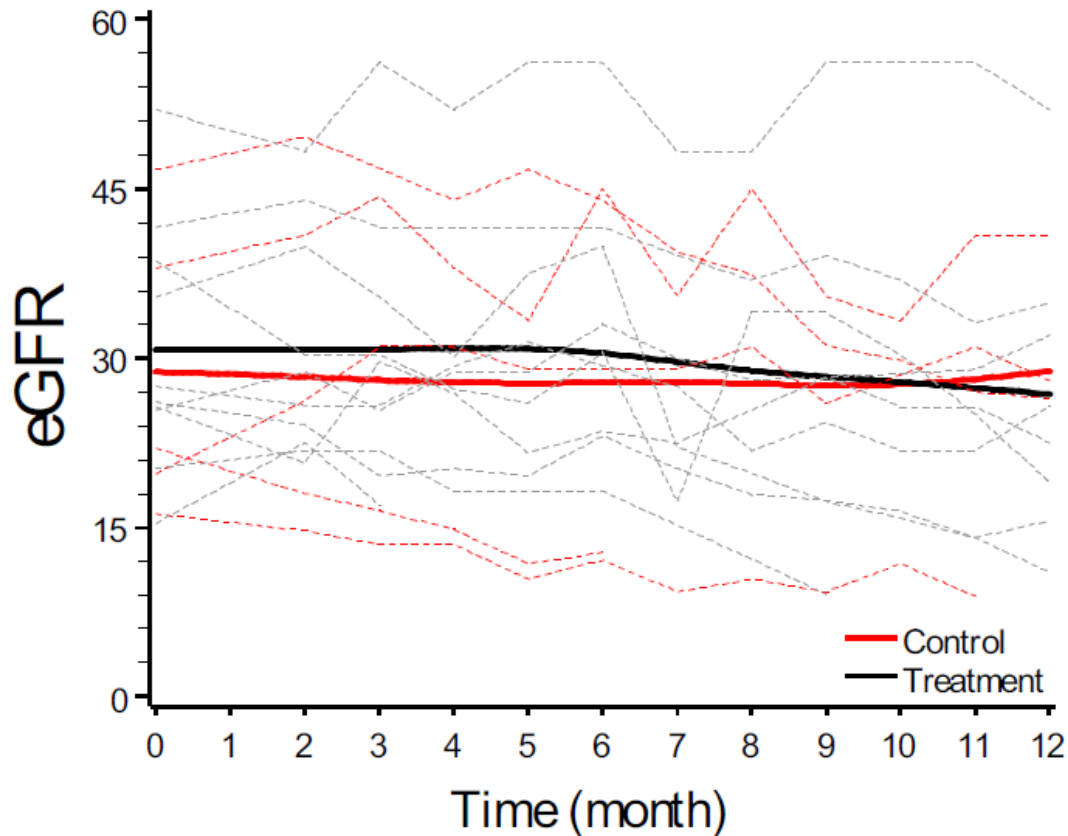
## Transplant glomerulopathy



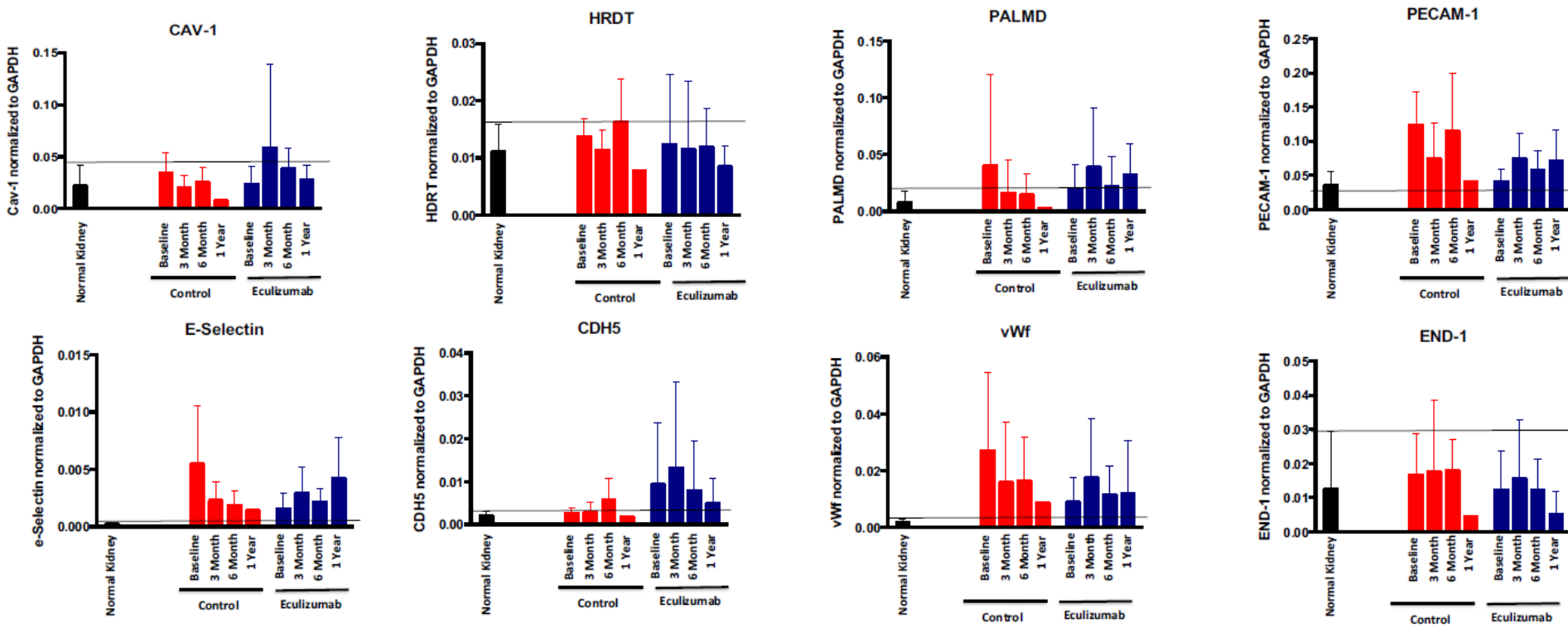
# ECU: a randomized pilot: study

(dn DSA. > 6m follow up. > 20 % eGFR decline x 12 m)

10 treatment ECU x 6m + 6m follow up  
N=15 Bx 0, 3, 6, 12 m  
5 controls no treatment, 12 follow up

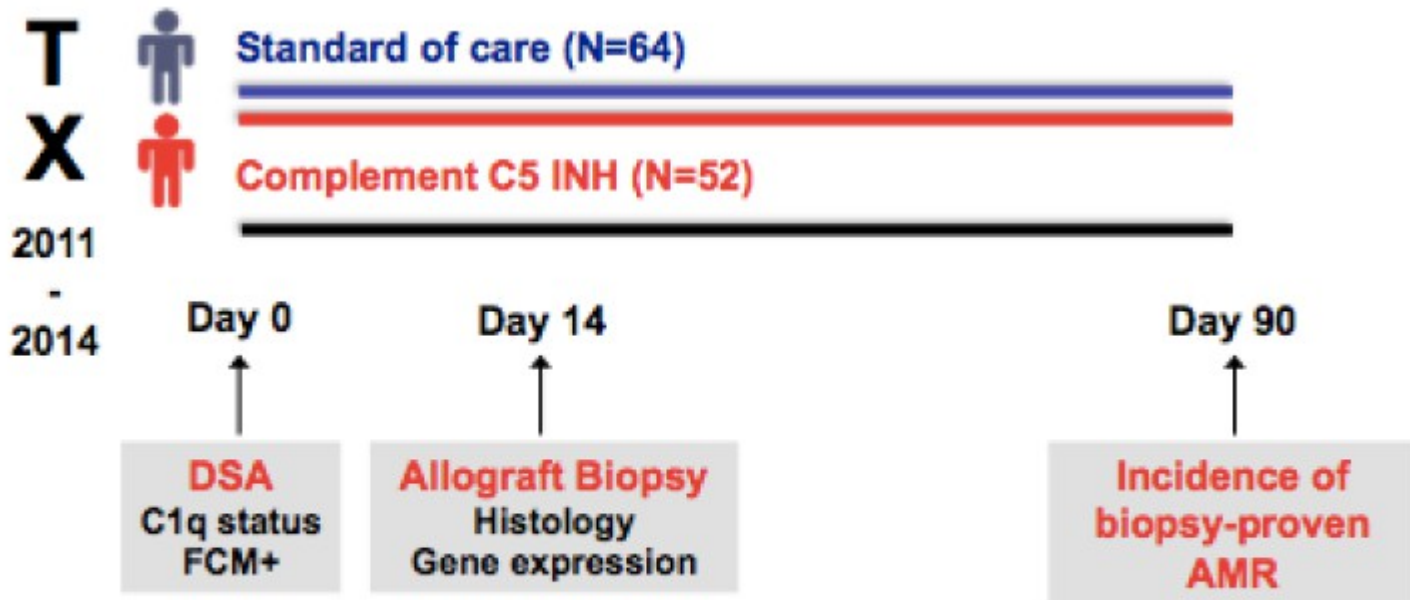


# ENDAT expression not reduced with ECU



# Eculizumab treatment (n=116) in patients with preexisting DSA

Results of 2 trials for the prevention of acute ABMR in pts receiving a kidney from cadaveric or living donor vs SOC



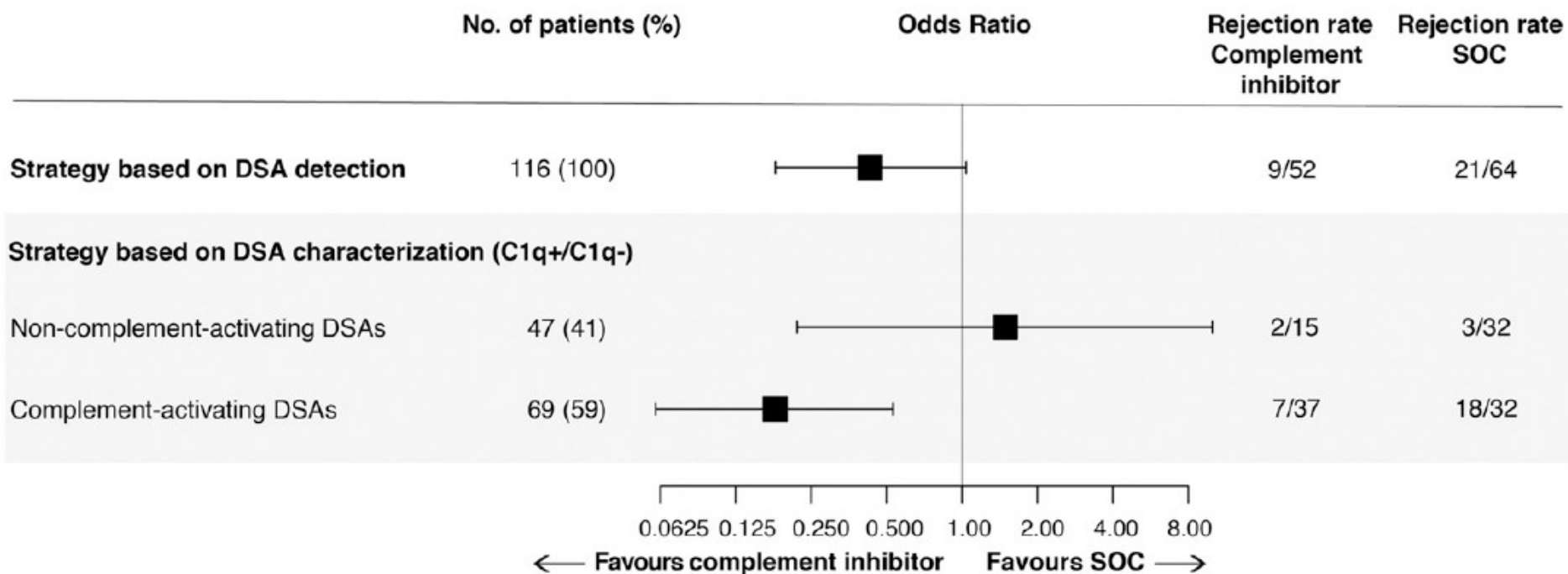
Standard of care: PE and IVIG according to local centers' protocol

C5 INH: Eculizumab 1200 mg at Tx, 900 mg/week x4 and 1200 mg at week 5, 7, 9

Lefaucheur C et al. J Am Soc Nephrol 2018; 29:620

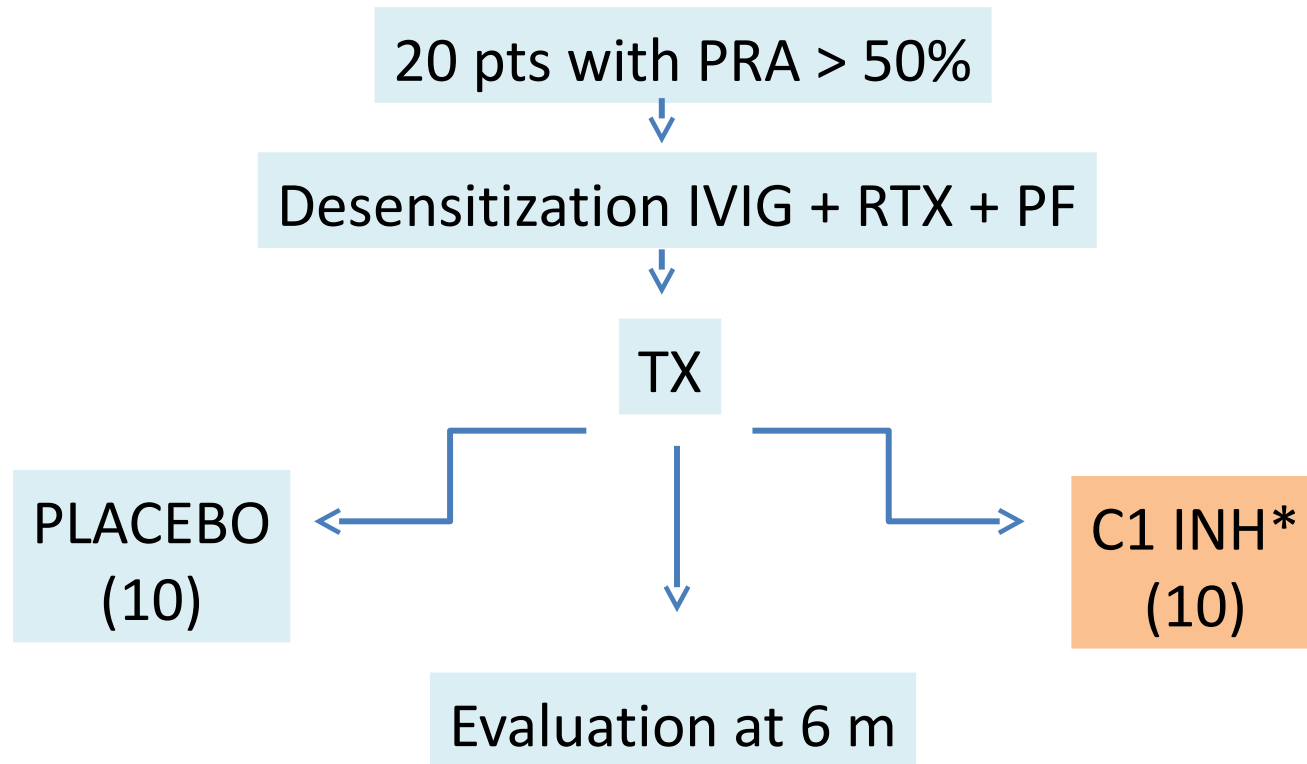
Slide, Courtesy from Christophe Legèndre

# ECU ↓ 3m ABMR in pts with preformed C1q fixing Ab

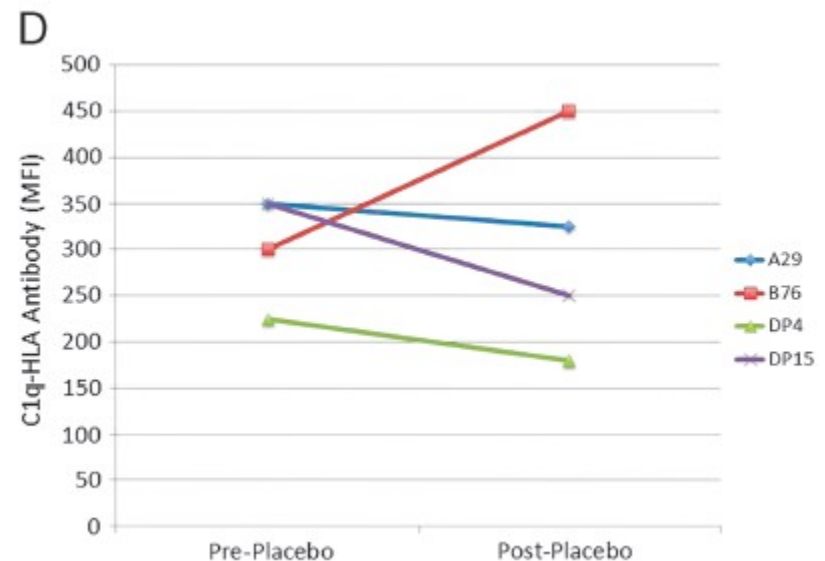
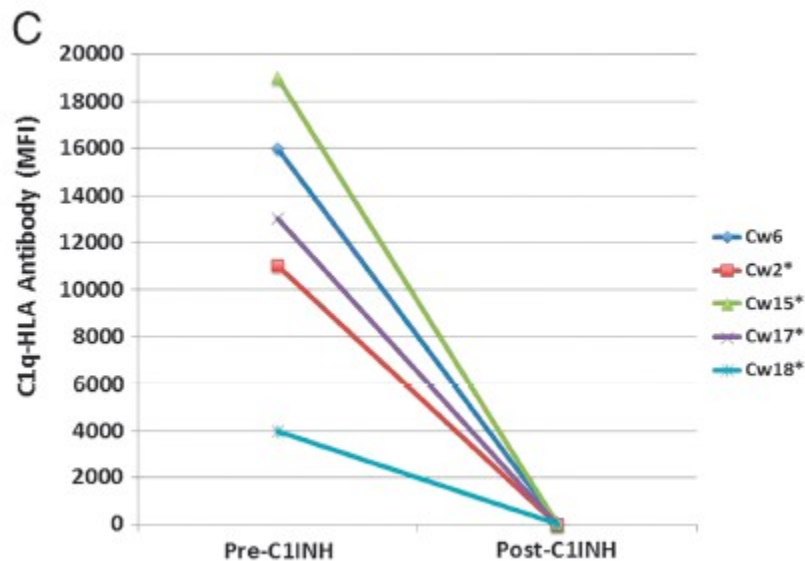
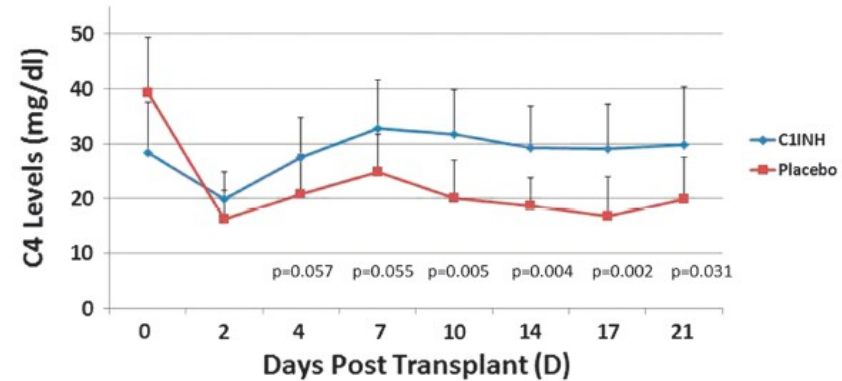
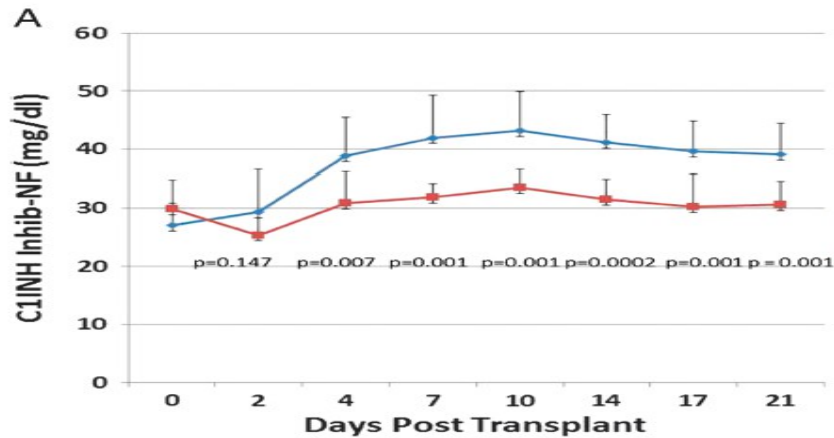


C1 INH

# C1 INH in the prevention of ABMR in sensitized pts: prospective randomized trial

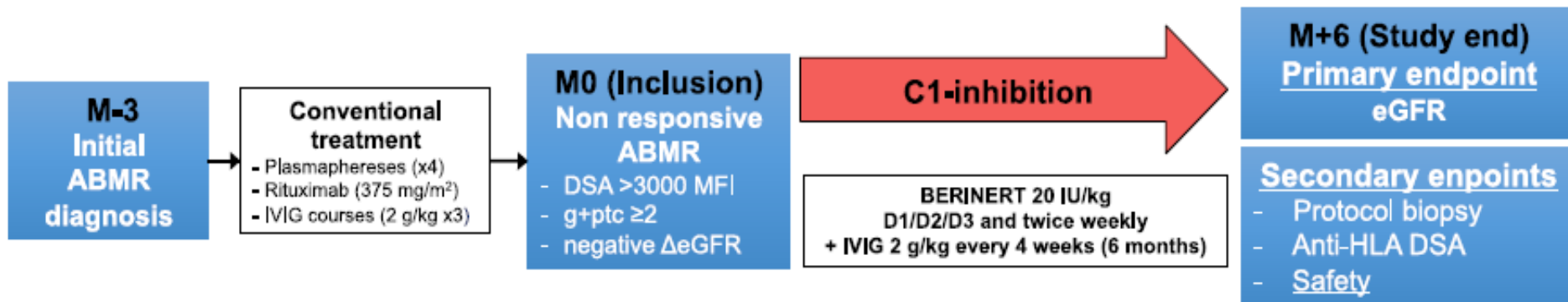


# C1inh prevents C consumption and decreases C1q fixing DSA



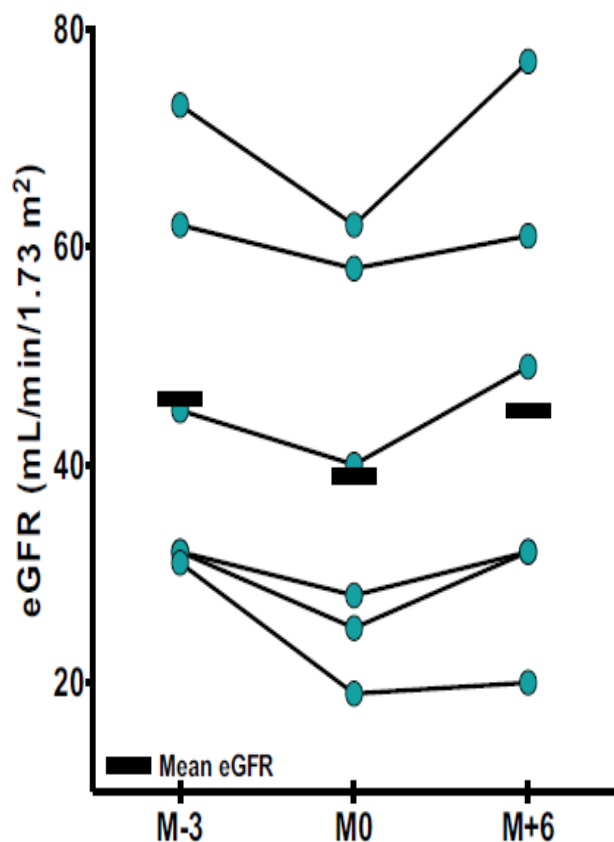
# C1 INH in acute ABMR non-responsive to conventional therapy

n=6 (Apr 2014-Jul 2016)



# C1 inhibition in acute ABMR non-responsive to conventional therapy

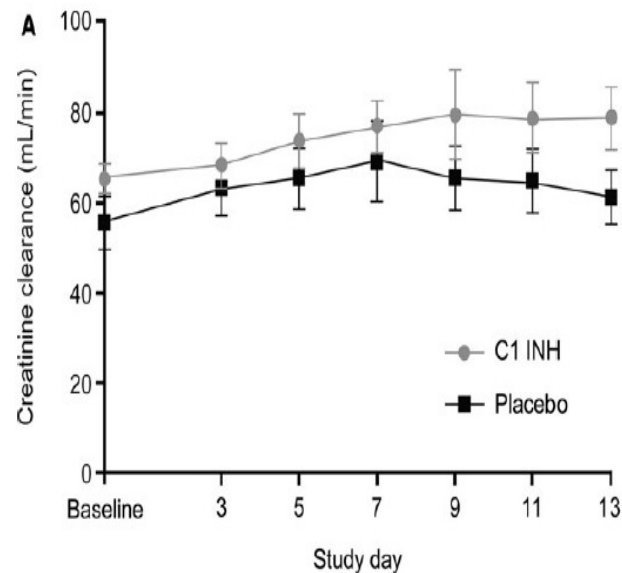
n=6 (Apr 2014-Jul 2016)



	Before	After	
eGFR	38.7±17.9	45.2±21.7	p=0.027
+ C1q DSA	6/6	1/6	p=0.025
No change in histology			

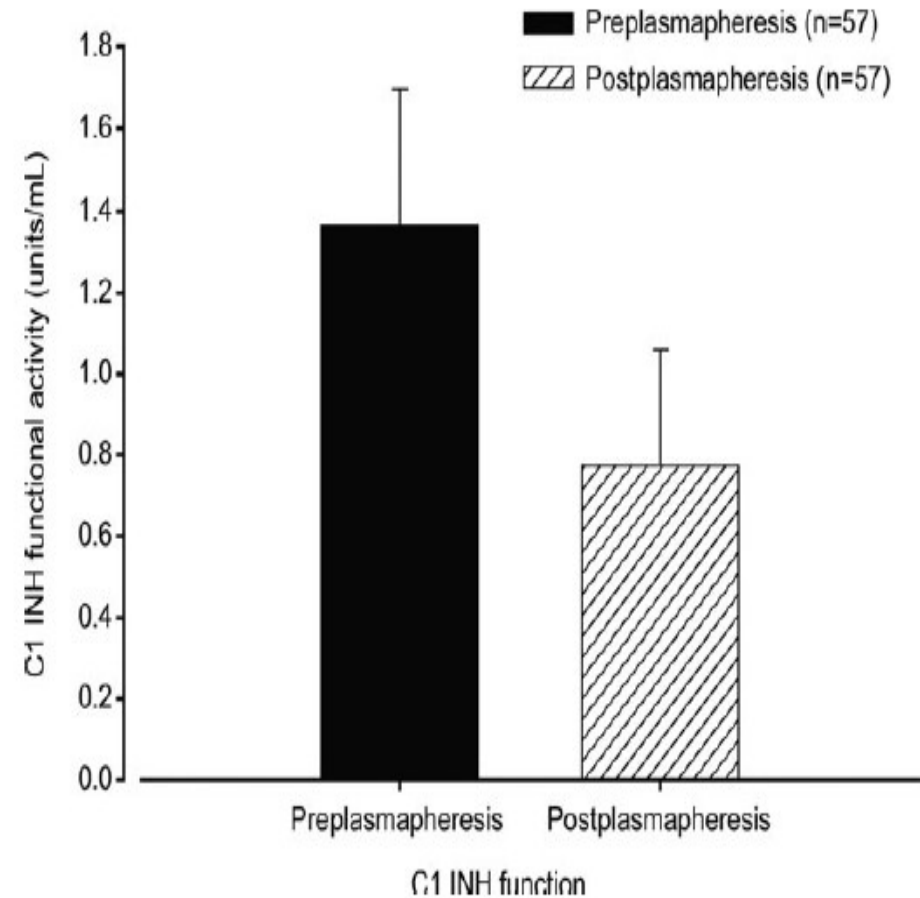
# Standard of care (9) vs standard of care + C1 INH (9): placebo controlled trial for acute ABMR Primary efficacy var: histology at 20 d

	C1INH (9)	Placebo (9)
Resolution of AMR at 20 d	7/9	6/9
TG at 6 m	0/7	3/7



# Standard of care (9) vs standard of care + C1 INH (9):

## Total number of PF



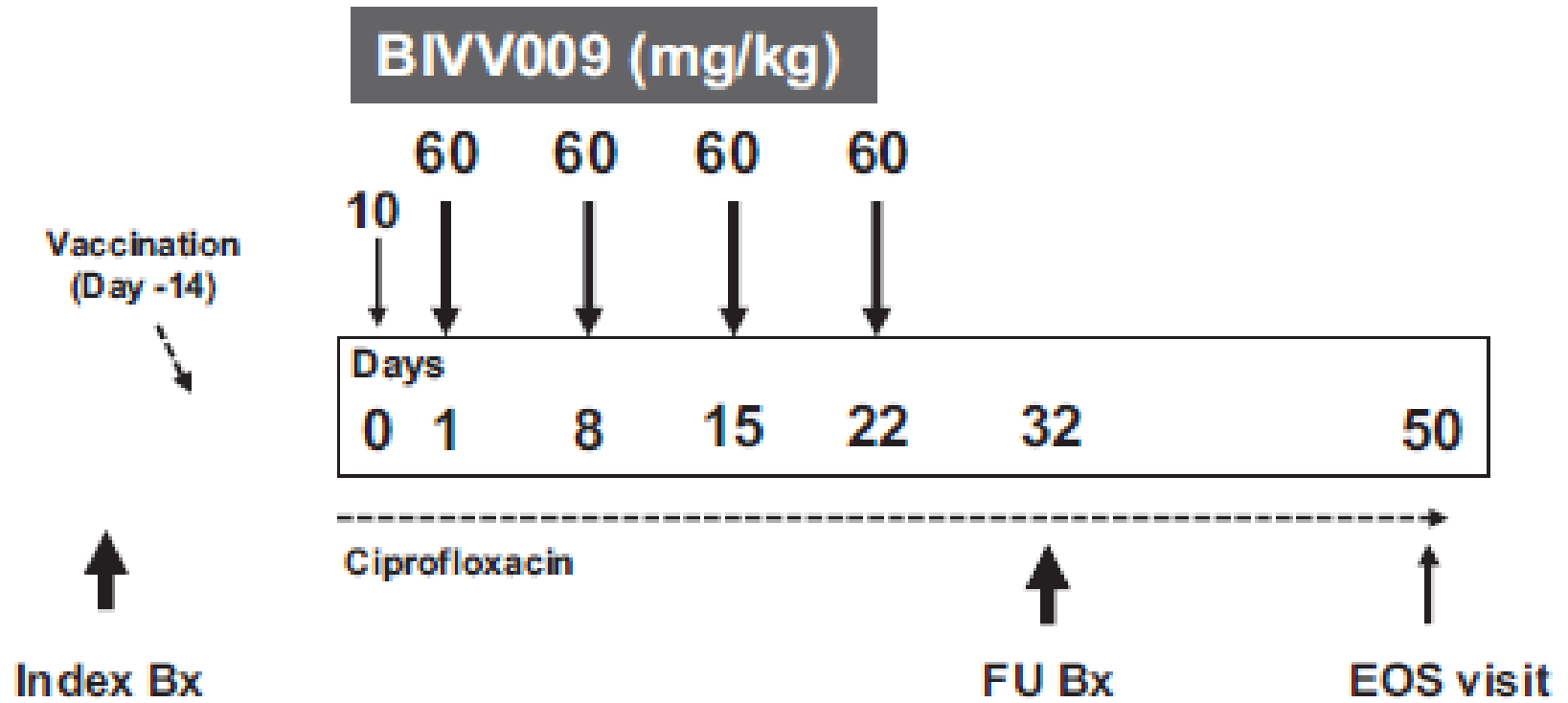
Day 1-13 C1 INH functional activity  
x 1.73 in C1 INH treated group

Anti C1s MoAb

# Anti C1s MOAB in chronic active ABMR: first in patient phase 1 trial: SAFETY and TOLERABILITY

**10 kidney transplant recipients**

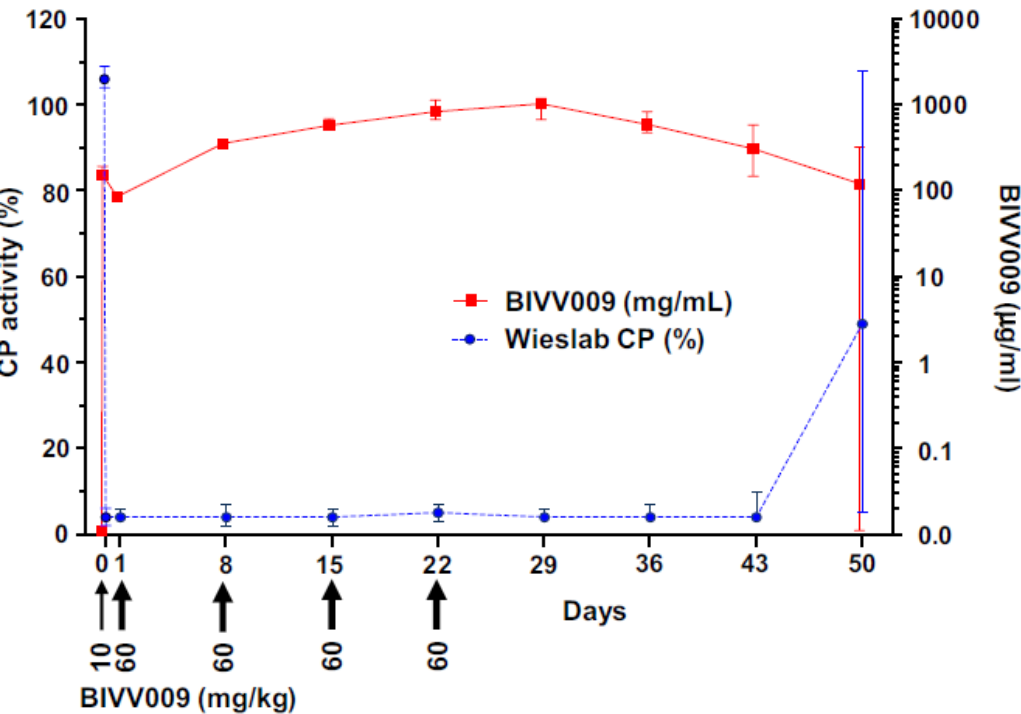
Late active ABMR with evidence of DSA-triggered CP activation



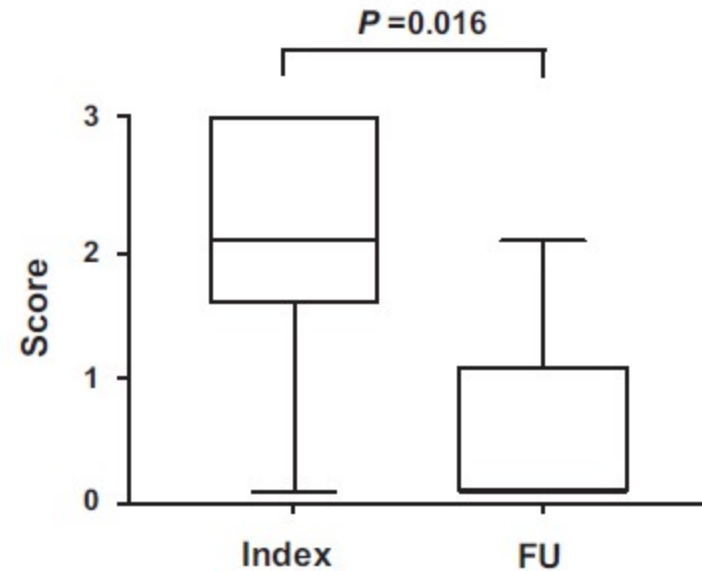
# Anti C1s MOAB in chronic active ABMR: first in patient phase 1 trial

10 KT, 4 weekly doses 4.5 y follow up

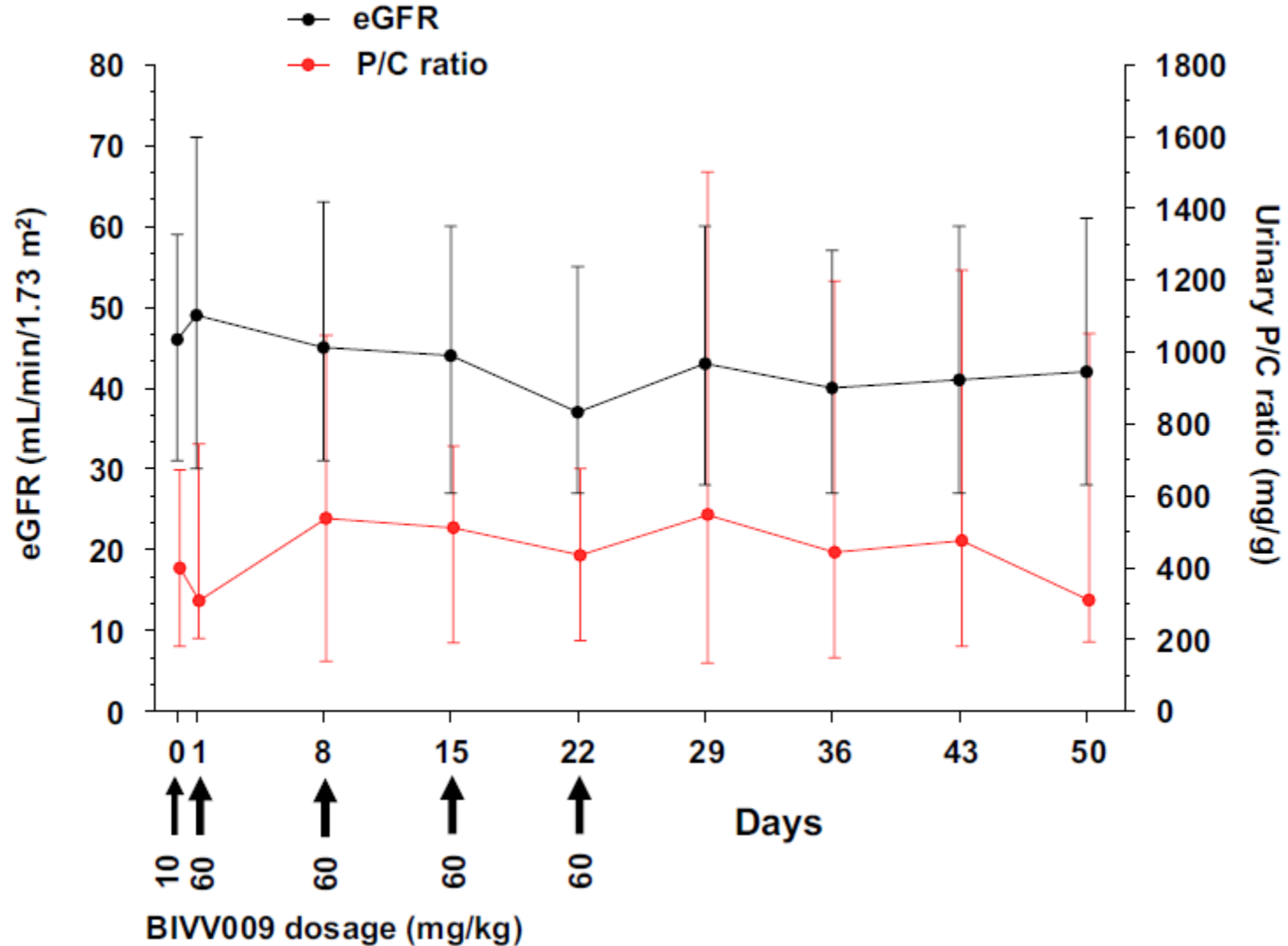
5 weeks protocol Bx



C4d score

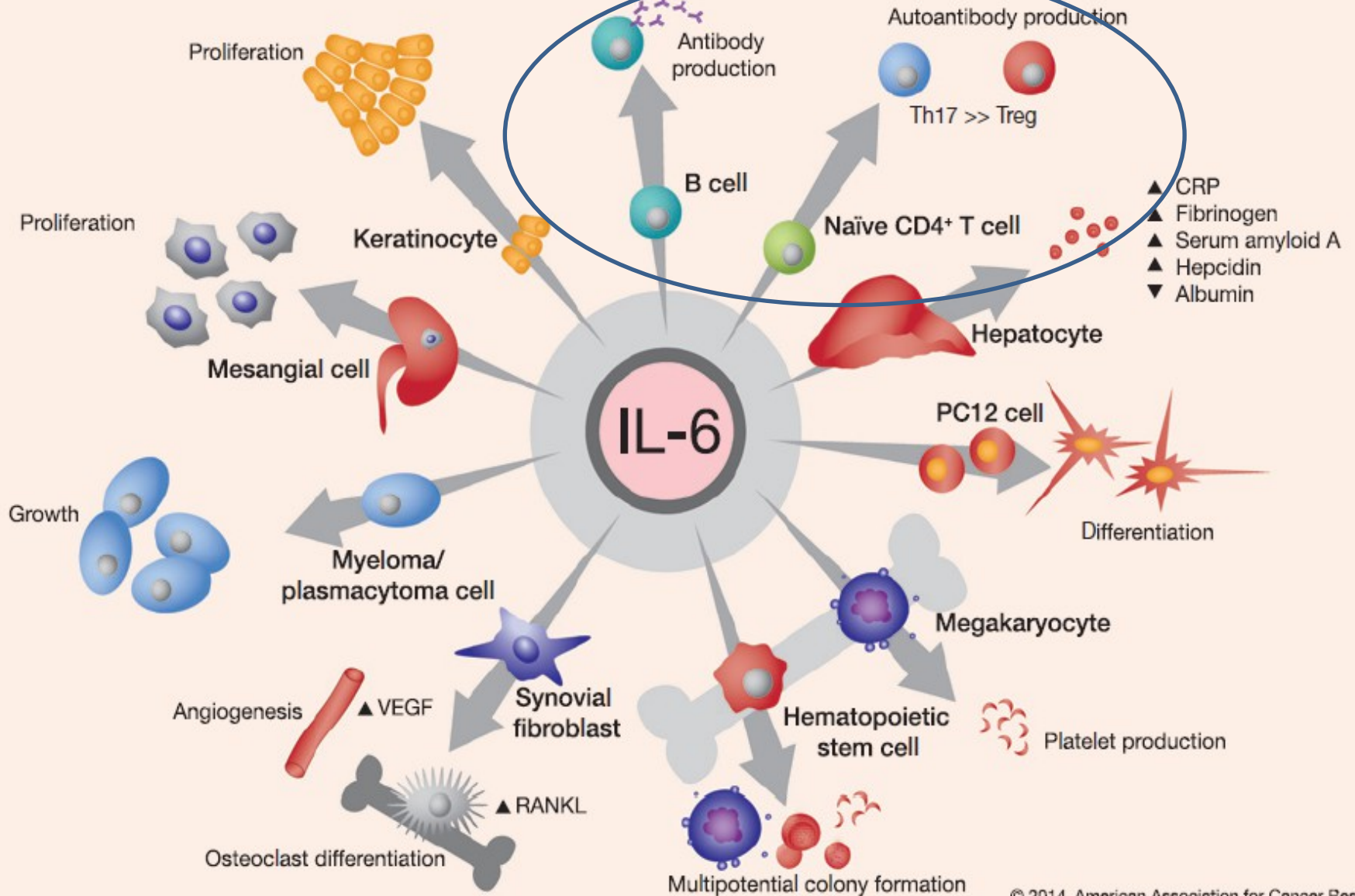


# Anti C1s MOAB in chronic active ABMR: first in patient phase 1 trial



Tocilizumab/Clazakizumab

# Biology of IL-6

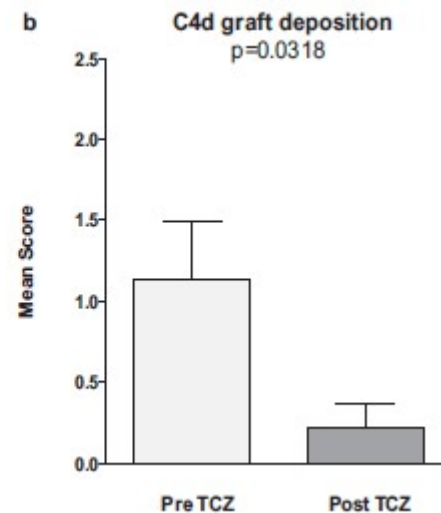
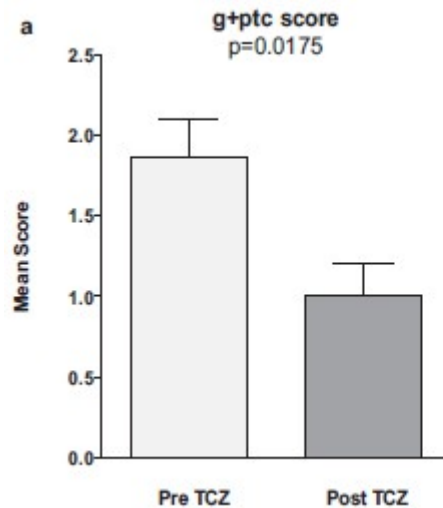
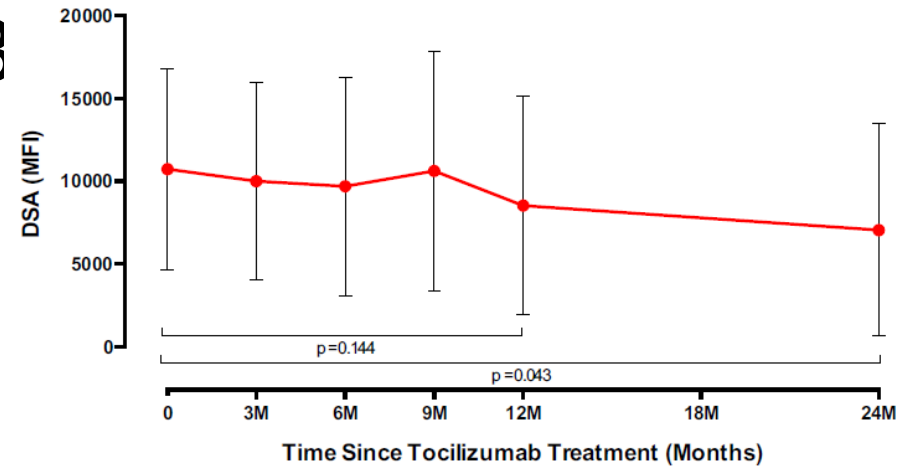
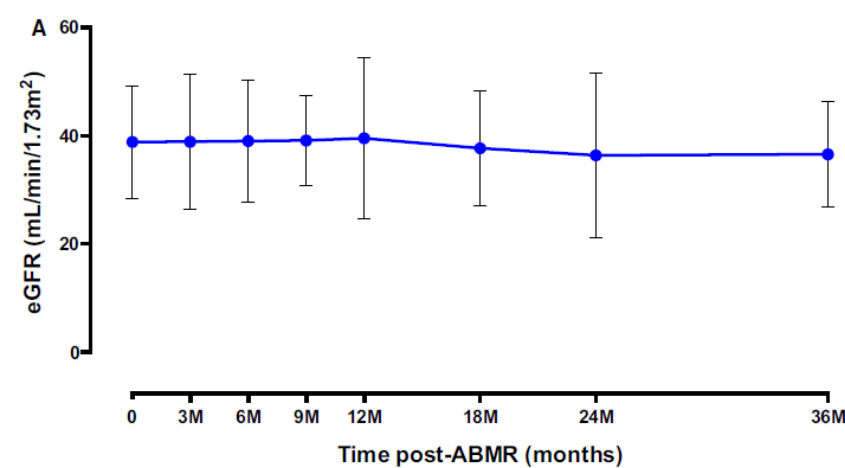


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# Tocilizumab (anti-IL-6 R) for treatment of chronic AMR

Patients with DSA and TG who failed standard care with IVIG +RTX

$n=3$



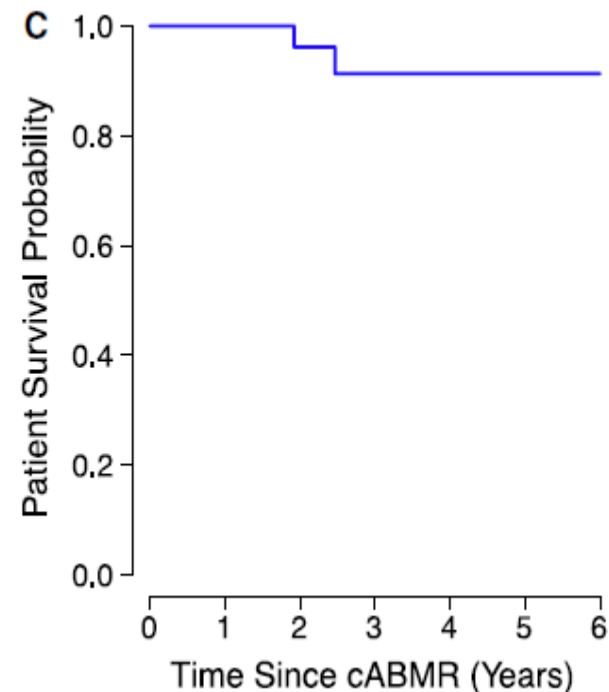
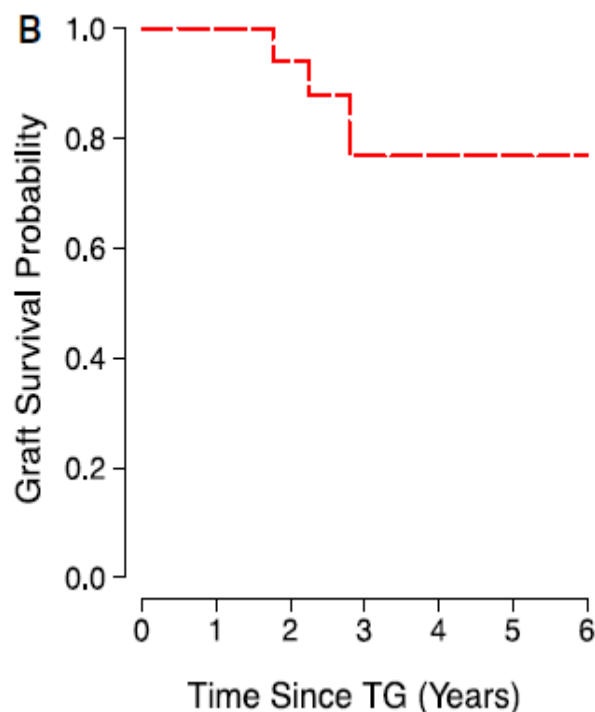
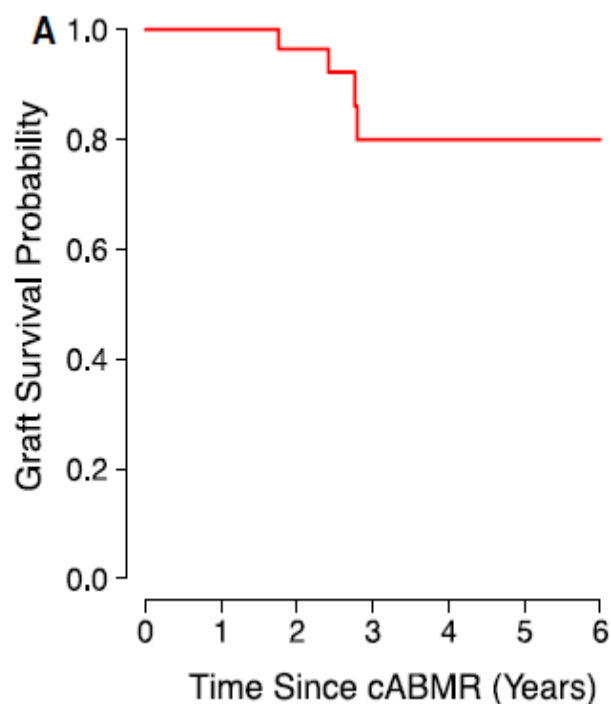
# Tocilizumab (anti-IL-6 R) in pts with cAMR & TX Glom

2011-2016, 36 pts who failed to respond to IVIG & Rituximab 8 mg(kg(m x 6-25

Graft survival (all pts)

Graft survival (pts with TG)

Patient survival



# Conclusions

Response to treatment depends on AMR phenotype

Active vs chronic

C fixing DSA vs non C fixing

PF + IVIG SOC for acute ABMR (moderate efficacy)

No efficacy of IVIG, Rituxi, Bortezomib or Ecu in chronic AMR

New strategies being explored

C1 INH, anti C1s MoAb, anti IL-6R/IL6,