Advances in the management of AbMR

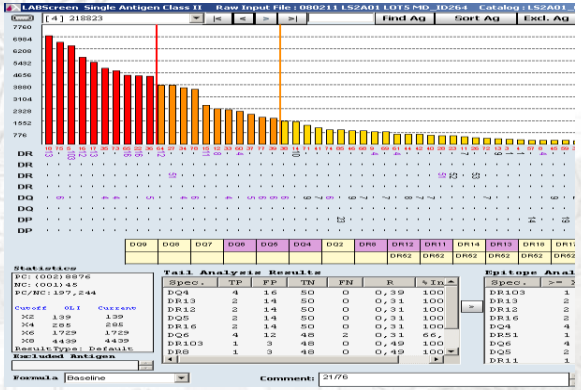
17th International Congress of Iranian Society of Nephrology

D. Glotz 2019

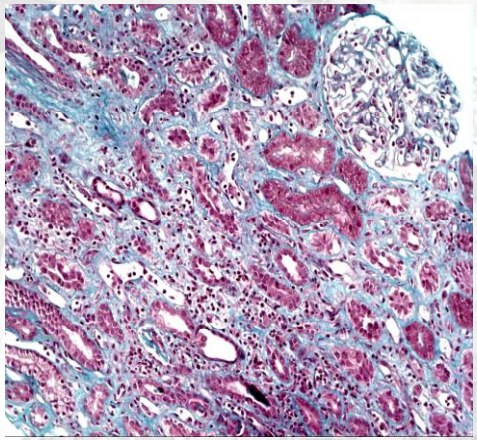
Diagnosis of AbMR

A TRIAD !

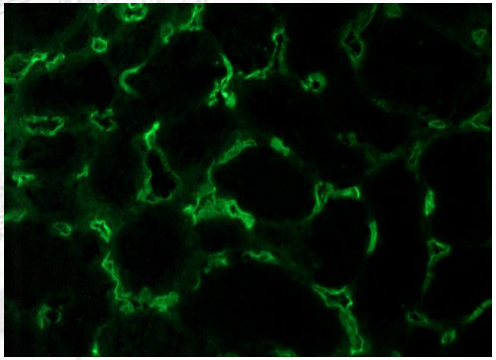
- Antibody directed against the grafted organ



- Histological lesions



- Suggestion of a causative link between Ab and lesions



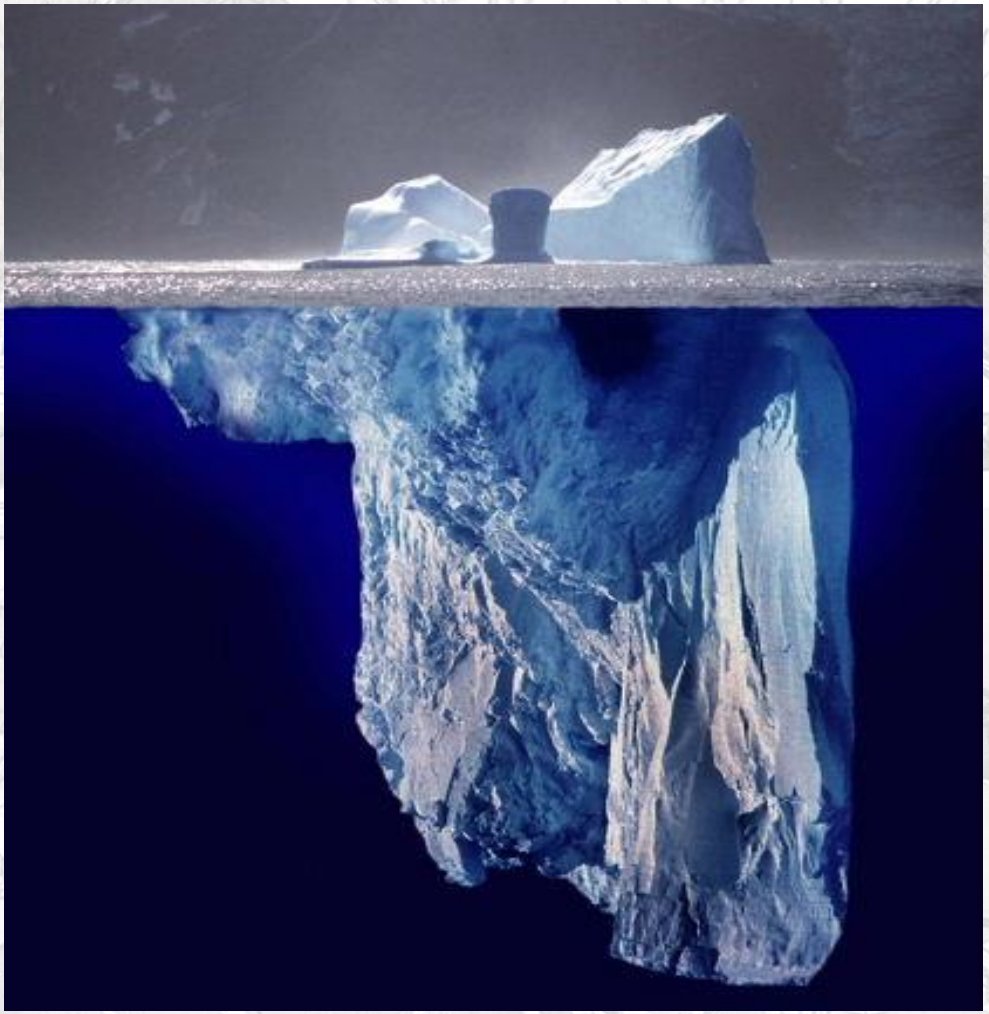
The spectrum of AbMR

- Early AbMR
- Sub-clinical AbMR
- Late AbMR
- « Chronic » AbMR (TG)

Subclinical-AMR

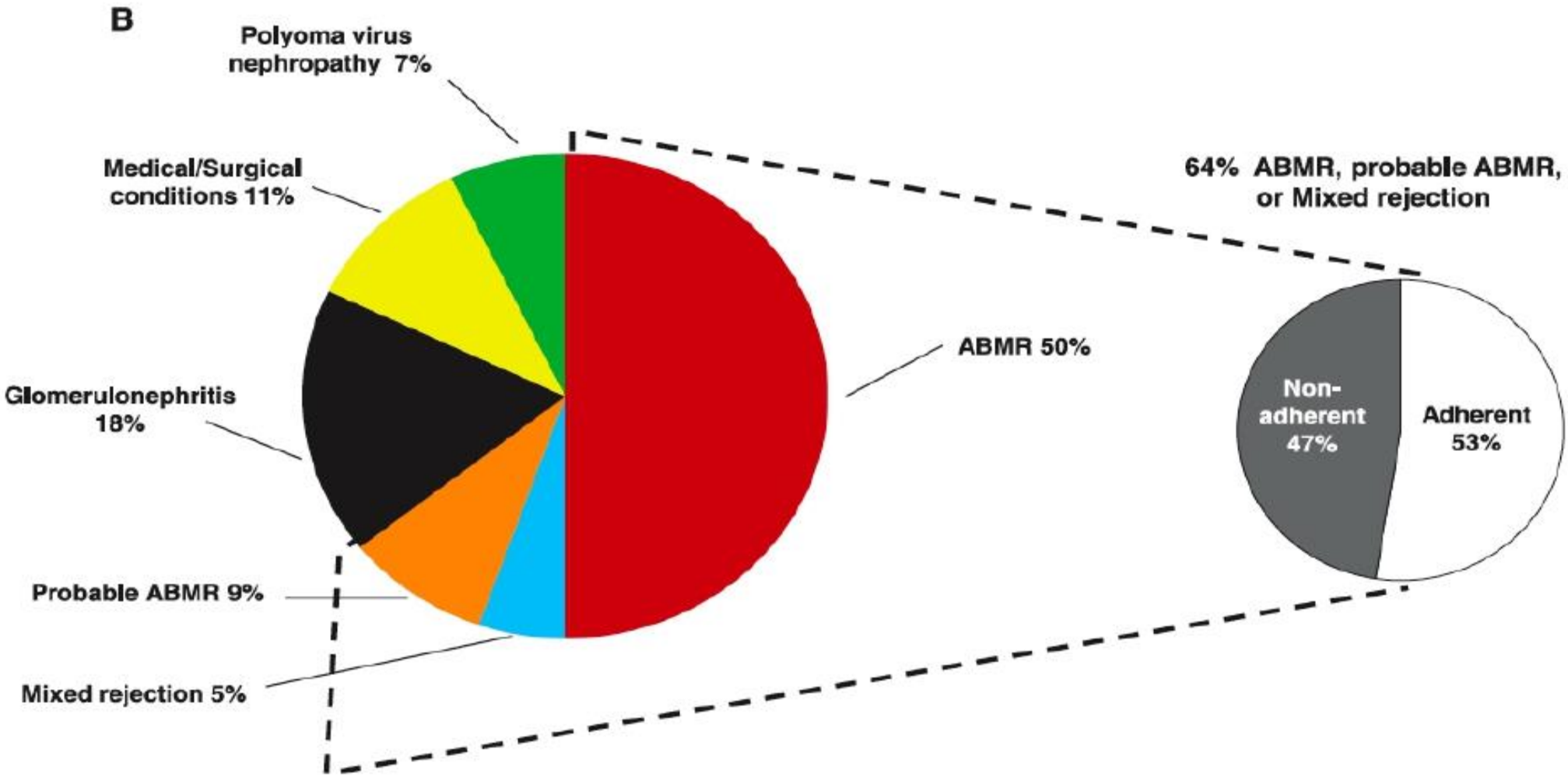
Function

Pathology



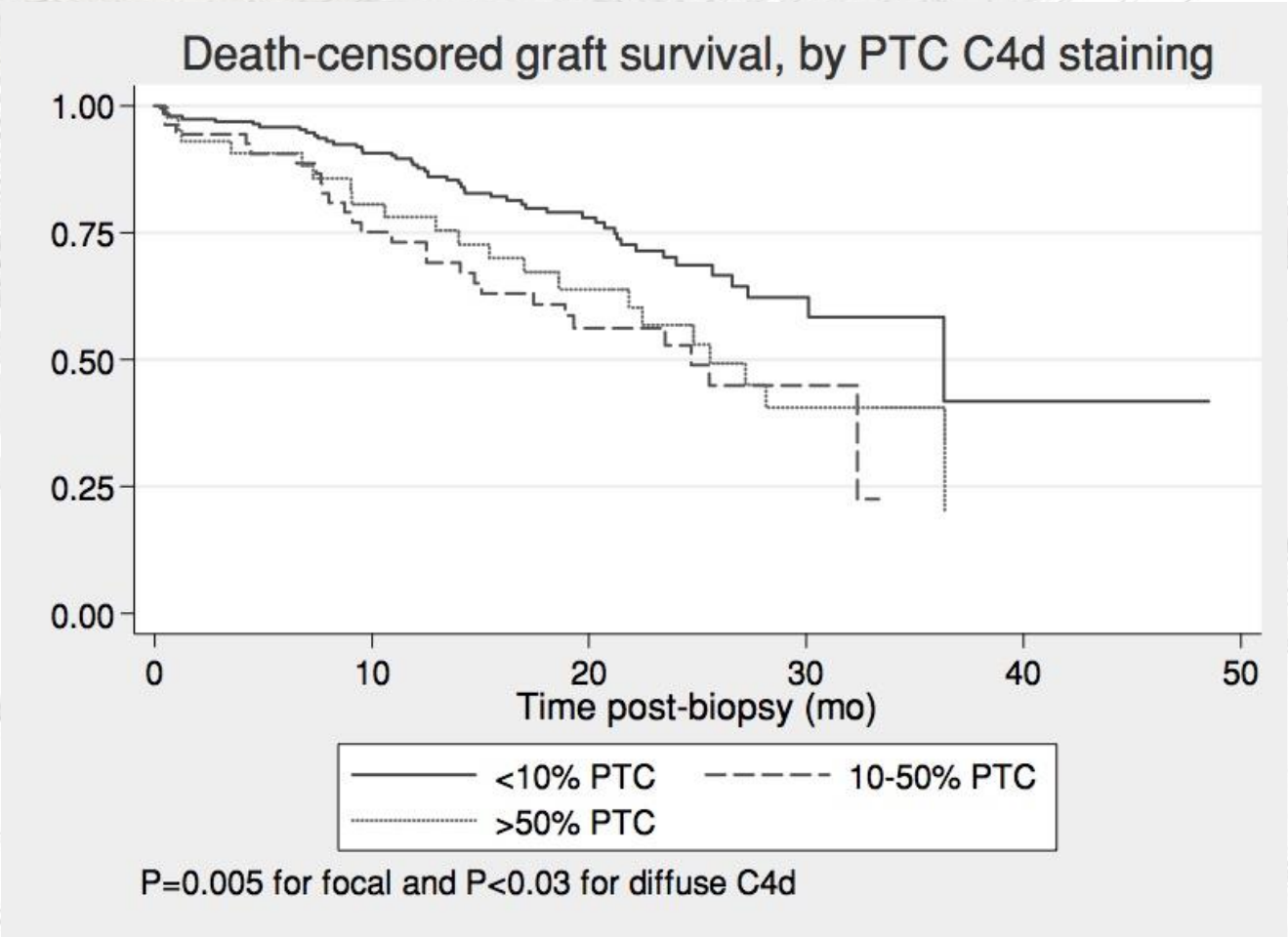
Usefulness of Abs/screening biopsies+++

ABMR is the leading cause of graft loss!



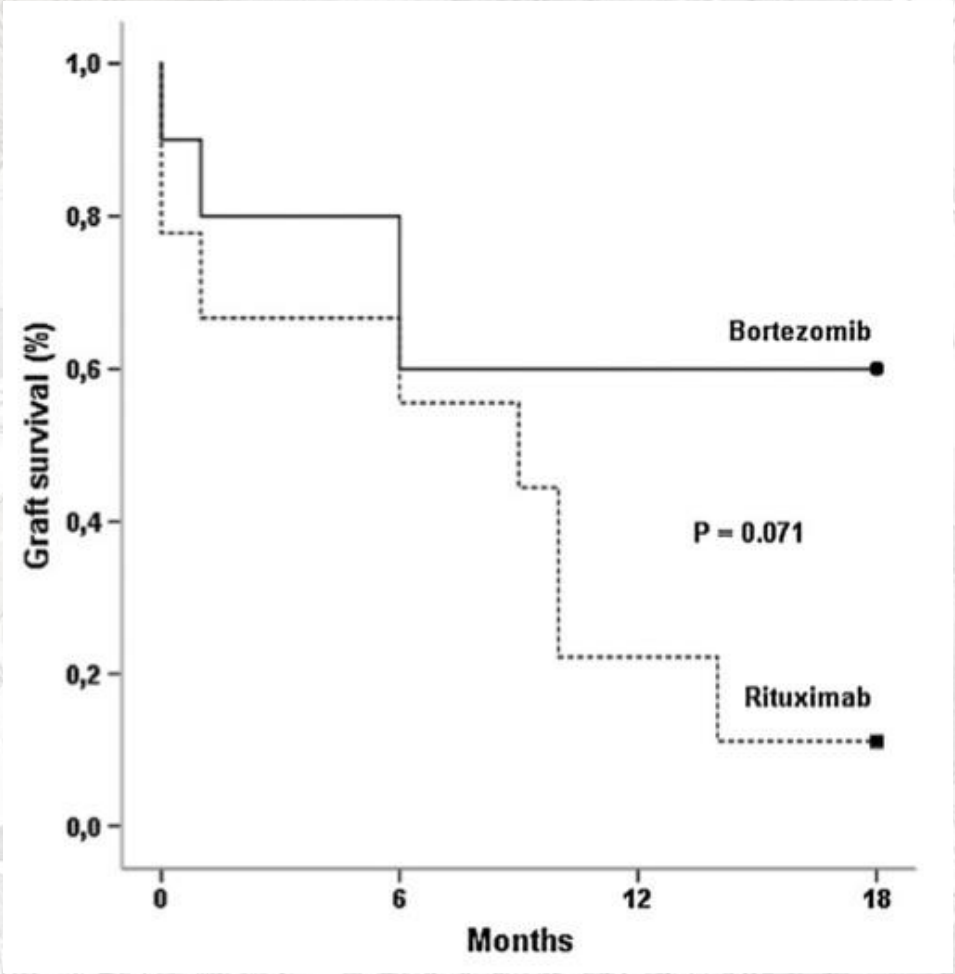
J Sellares et al, Am J Transplant 2011

Prognosis of ABMR



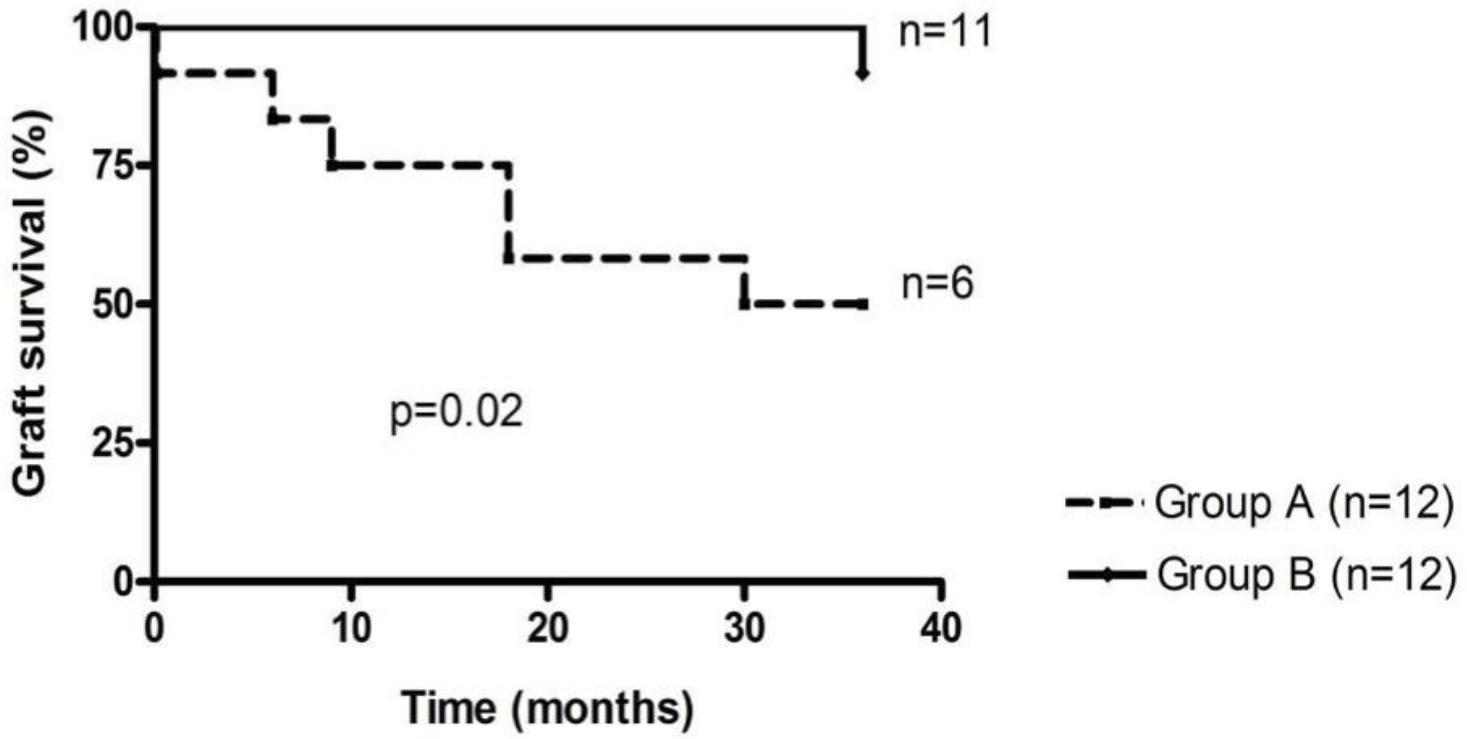
Haririan, AJT 2009

Prognosis of ABMR



Waiser, NDT 2012

Prognosis of ABMR



Lefaucheur, A.J.T. 2009

What do we know about AMR treatment?

Not much….

- Few controlled trials
- Very limited number of patients
- No well-defined endpoints

Adapted Treatment is essential

	OKT3	IVIg	PP/IVIg	Ritux/PP	PP/IVIg/ Ritux
Pts	43	21	16	8	12
Pt Surv		95%	84%	100%	100%
G Surv	57%	72%	81%	75%	92%
Author	Feucht Kidney I 1993	Lefaucheur AJT 2007	Rocha Transpl 2003	Faguer Transpl 2007	Lefaucheur AJT 2009

Antibody Mediated Rejection Treatment

IVIg/PP treatment

- 16 patients
- 100% StR, 50% AbR
- Graft survival 1 year: 81% (84%)

Rocha, Transpl 2003

Effect of PE alone on Ig synthesis

Table 3
In vitro immunoglobulin production with plasma exchange

Patient No.	Treatment			
	IgG		IgM	
	No. 1	No. 5	No. 1	No. 5
1	70 [a]	100	15 [a]	105
2	67	485	46	160
3	210	970	80	1080
4	80	230	30	160
5	0	50	45	55
6	200	355	55	120
7	180	160	65	75
8	210	210	55	80
9	110	220	65	1730
10	130	440	25	720
	126 ± 73 [b]	332 ± 267	48 ± 20 [b]	429 ± 571
	$P < 0.05$ *		$P < 0.001$ *	

Dau, J NeuroImmunol 1995

IVIg +/- Plasmapheresis

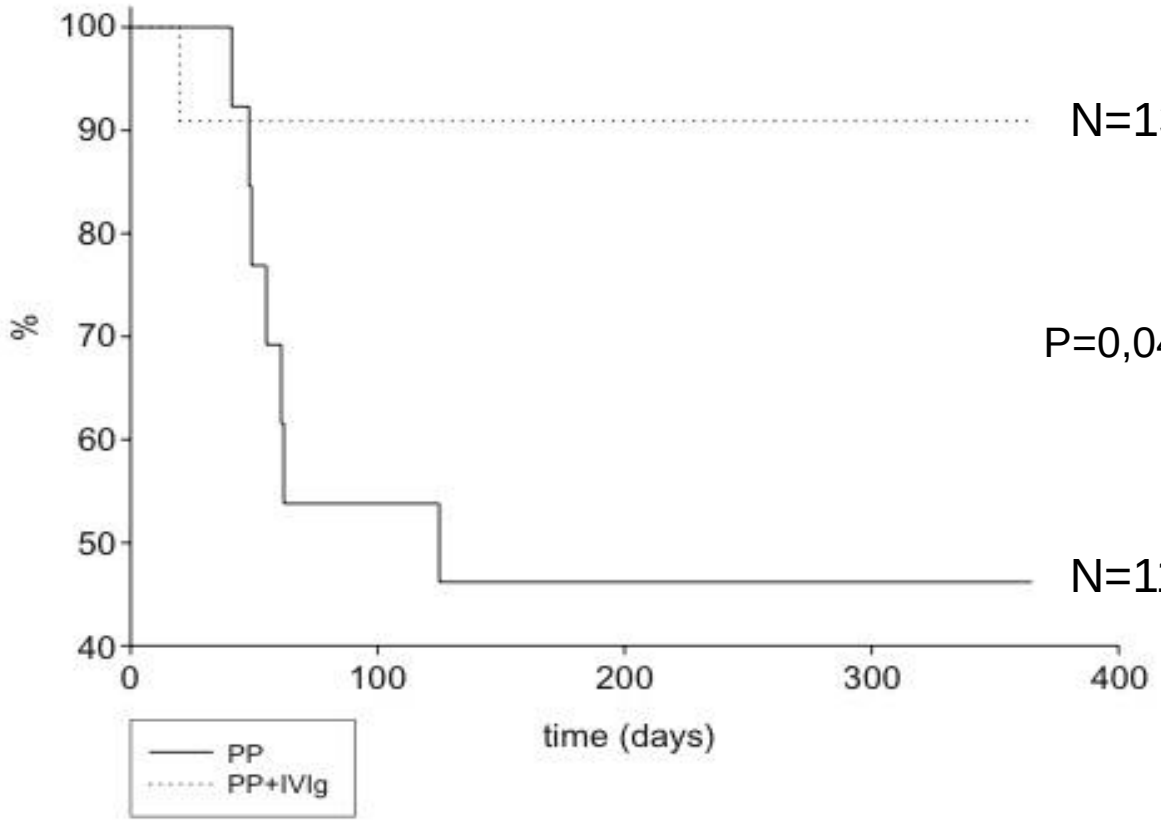
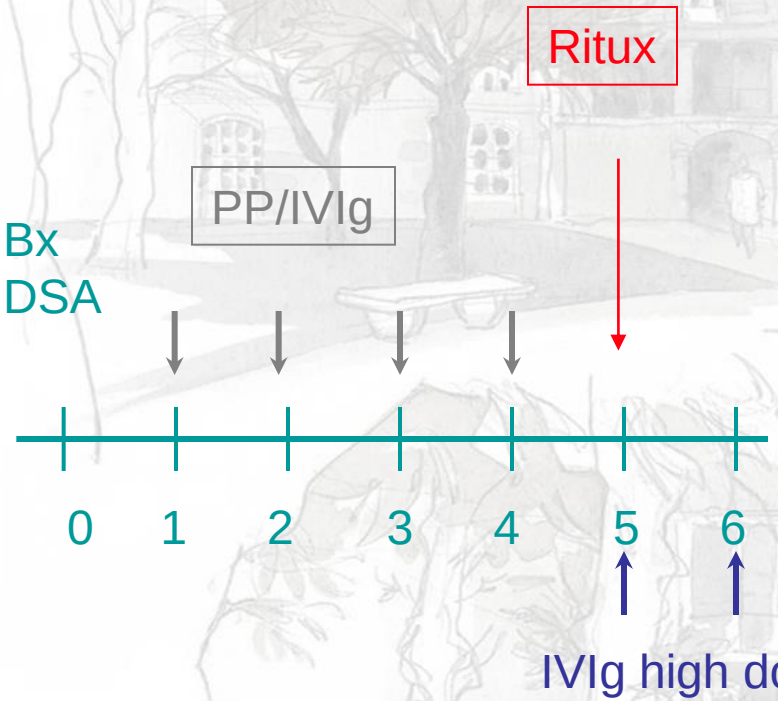


FIG. 1. Graft survival. Patients receiving the plasmapheresis (PP) and intravenous immunoglobulin (IVIg) combination had better one-year graft survival than those treated using only PP. $P = 0.044$.

Slatinska, Ther Aph Dial 2009

Antibody Mediated Rejection Treatment

The “Marrakesh” protocol



- ✓4 PP/low dose IVIg
- ✓Ritux 375 mg/m^2
- ✓IVIg 2gr/Kg

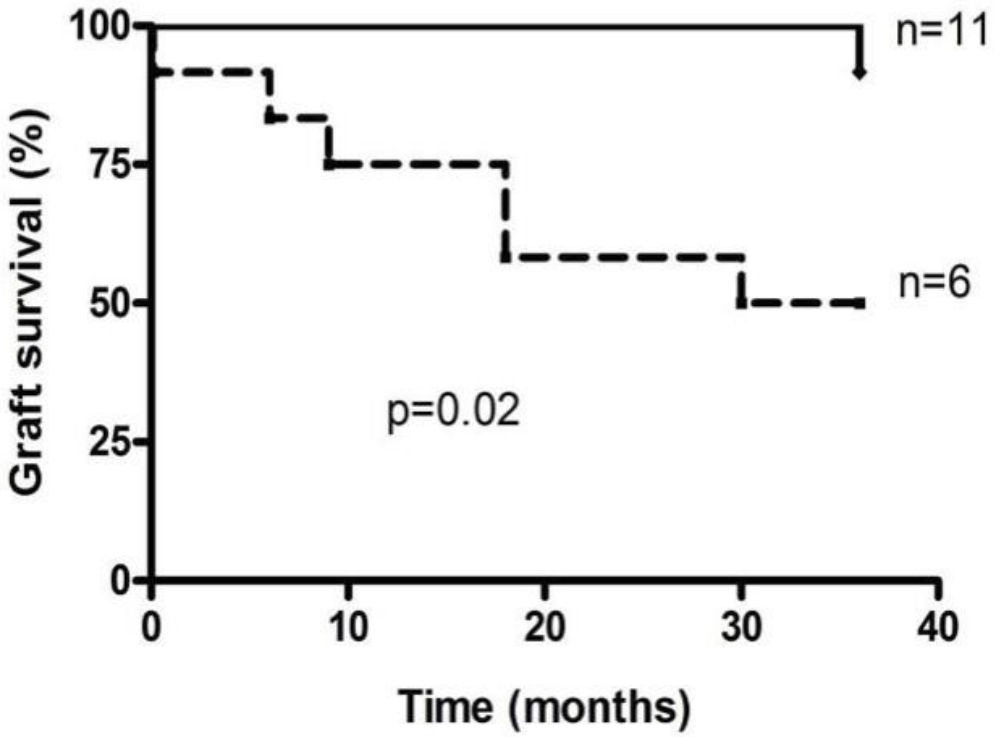
Comparison of Combination Plasmapheresis/IVIg/anti-CD20 versus High-Dose IVIg in the Treatment of AMR

- **Group A:** High-dose intravenous immunoglobulin (IVIg) regimen
  - 01/2000-12/2003
  - N=12 pts

- **Group B:** Plasmapheresis (PP) / IVIg / anti-CD20 (PP/IVIg/anti-CD20) regimen
  - 01/2004-12/2005
  - N=12 pts

Lefaucheur, A.J.T. 2009

Long term results



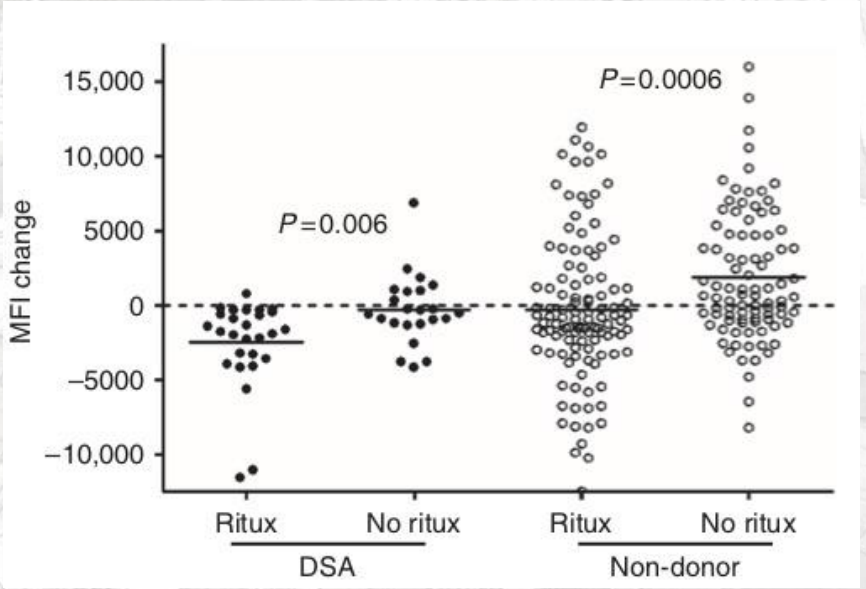
Lefaucheur, A.J.T. 2009

Any role for Rituximab?

A US retrospective study

-50 pts desensitized

-25 with ritux, 25 without Ritux



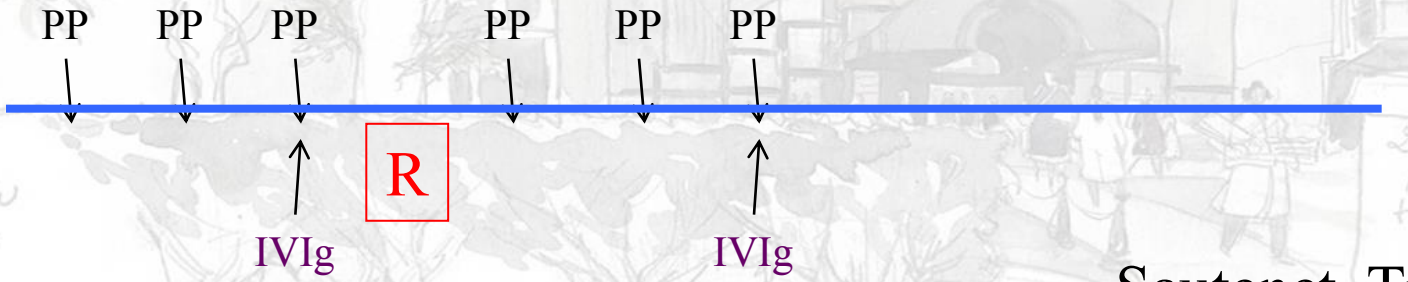
Less Antibody rebound post transplant

Jackson, KI 2014

Any role for Rituximab?

A French randomized study

-PP: 2 series of 3 (before and after R or placebo)
-IVIg 0.1 gr/Kg post each PP, then 1 gr/Kg last PP of each series
-Steroids: 500 mg x 3, then 1mg/Kg
-Tacrolimus: 0.1 mg/Kg twice daily
-Cellcept: 2 gr/day
±Ritux (375 mg/m) 1 injection after the first PP series (D5)



Sautenet, Transpl 2015

Any role for Rituximab?

A French randomized study

-Tx <1 year
-Renal failure (+20% creat)
-2 of the 3 criteria: DSA, C4d, g/v/cpt

Primary endpoint:Treatment failure D12
graft loss or lack of efficacy (<30% decrease creat)

Secondary endpoints:
Success at M1 (creat, histology), graft and patient survival D12, M1, 3, 6 and 12, active histological lesions M6….

Sautenet, Transpl 2015

Any role for Rituximab?

A French randomized study

38 pts included

Primary endpoint:Treatment failure D12
graft loss or lack of efficacy (<30% decrease creat)

R+ 52.6% (10/19) versus 57.9% (11/19) R-, p=0.744

Secondary endpoints:
Success at M1 (creat, histology), graft and patient survival D12, M1, 3, 6 and 12, active histological lesions M6….

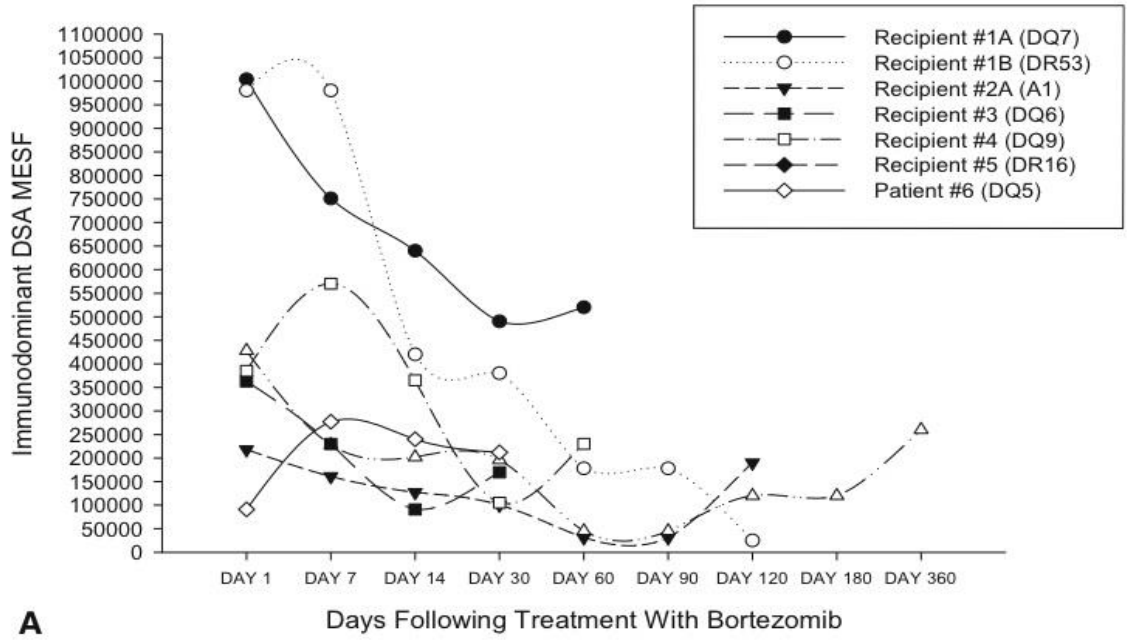
No difference at one year…

?

Sautenet, Transpl 2015

Bortezomib

Treatment of rejection



- 1,3 mg/m^2 x4
- 6 patients, 6 successes…..

Everly, Transpl. 2008

Bortezomid

Randomized trial in late AbMR

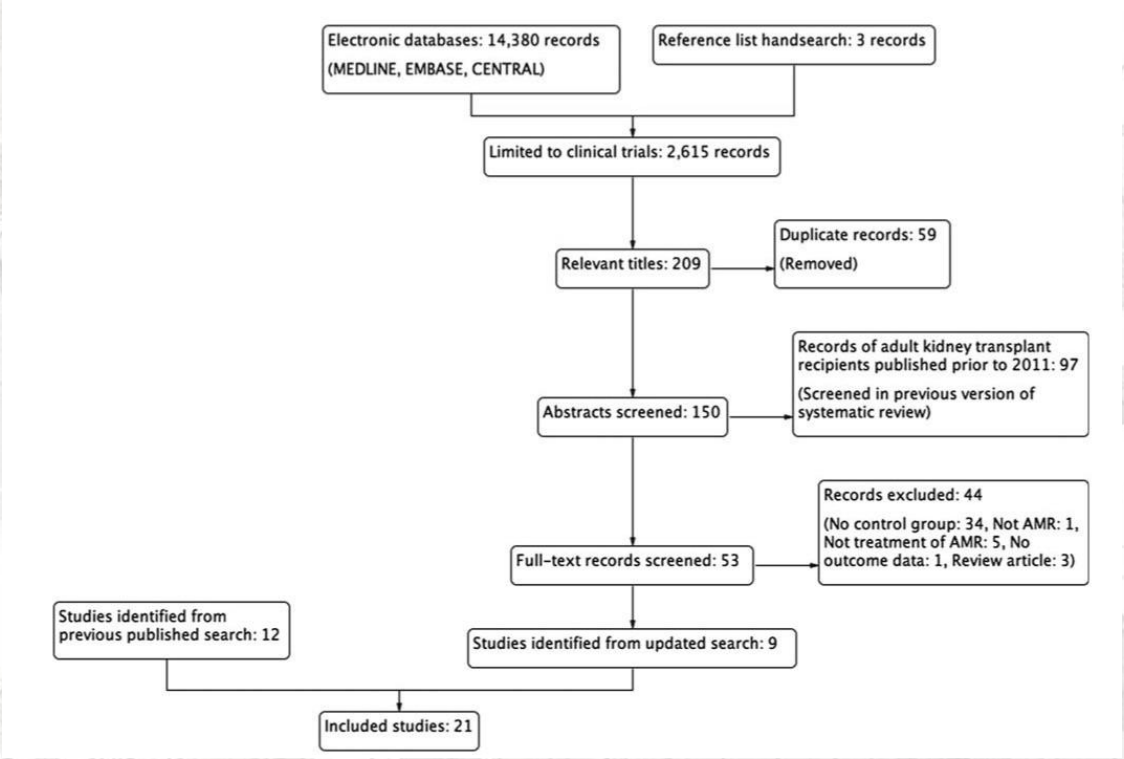
- 2 cycles of 1,3 mg/m^2 x4 vs placebo
- 44 patients, 21 B, 23 placebo
- 2 year follow-up

No efficacy on DSA, GFR, Graft survival.....

Böhmig, AJT 2017

ABMR Treatment

Meta-analysis



Despite the evidence uncertainty, plasmapheresis and IVIG have become standard-of-care for the treatment of acute AMR.

Wan, Transpl 2018

Complement inhibitors

- Block damage from DSAs
- Do not inhibit DSA synthesis

A new paradigm….

C5 inhibition

8 patients treated for ABMR
Rescue therapy with Eculizumab

2 patients with cortical necrosis: no response
3 patients with C4d negative ABMR: no response
3 patients with C4d positive ABMR: good response

Yelken Trans Proc 2015

C5 inhibition

15 patients treated for ABMR
Primary therapy with Eculizumab/PP

Early ABMR, in the first month of Tx
13 biopsy-proven patients with C4d positive ABMR
5 doses of Ec, 7 sessions of PP on average

100% graft survival at 1 year…

Tan, Transpl 2019

C1 Esterase inhibitor

American Journal of Transplantation 2016; XX: 1–11
Wiley Periodicals Inc.

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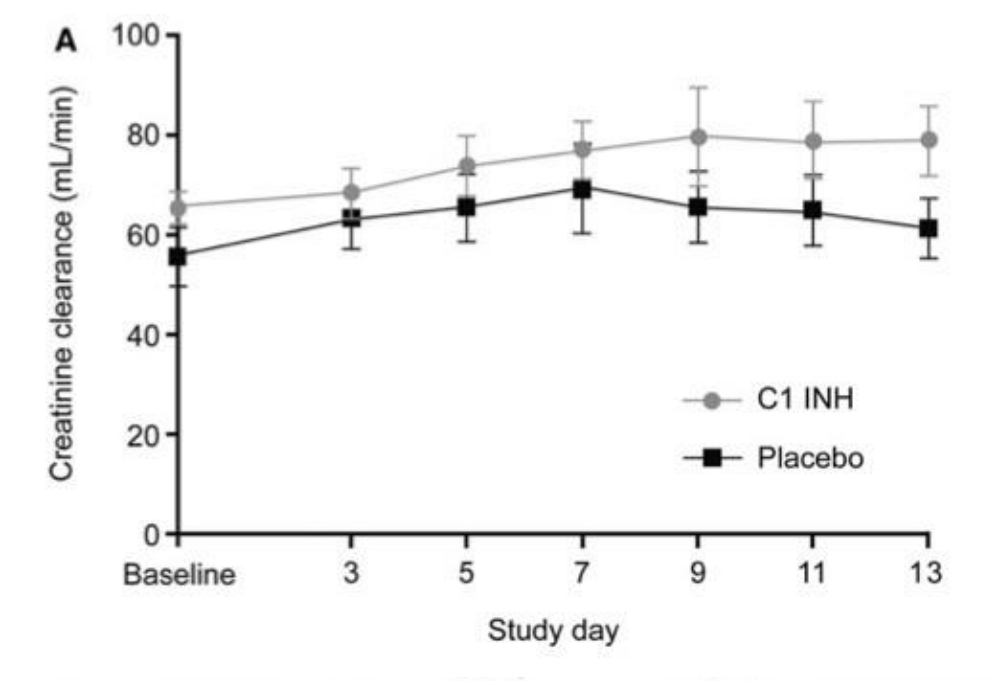
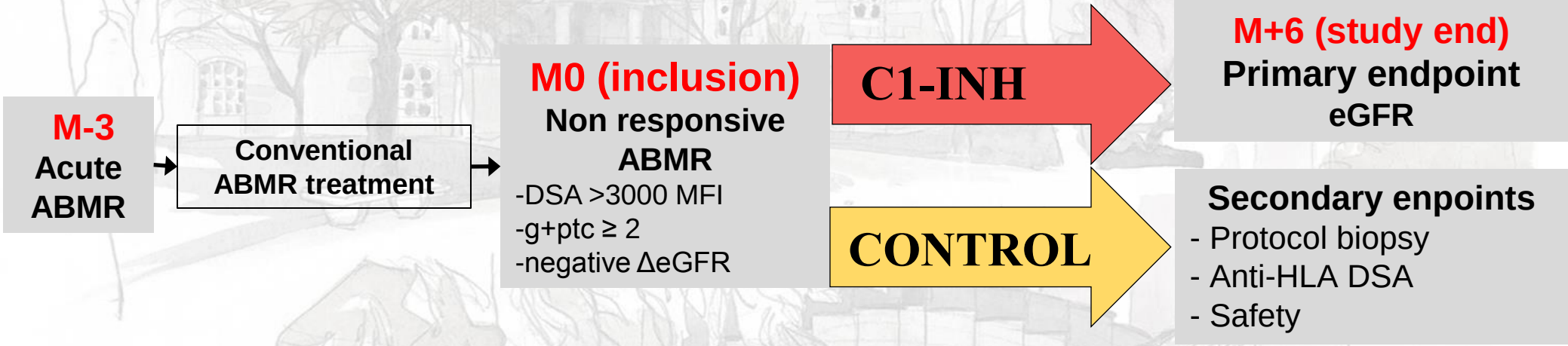
doi: 10.1111/ajt.13871

Plasma-Derived C1 Esterase Inhibitor for Acute Antibody-Mediated Rejection Following Kidney Transplantation: Results of a Randomized Double-Blind Placebo-Controlled Pilot Study



C1-Inhibitor in resistant ABMR

Prospective single-arm pilot study

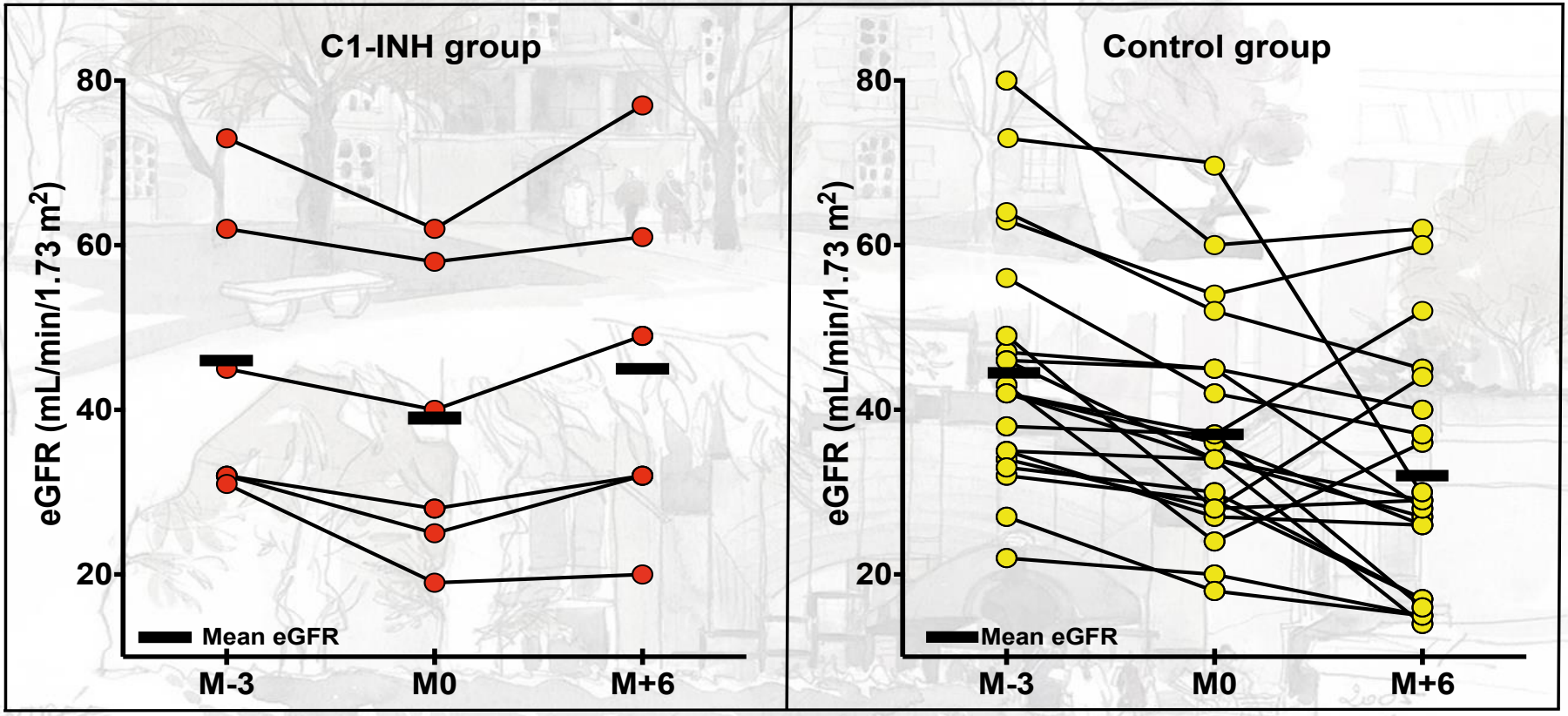


- C1-INH: BERINERT 20 IU/kg D1/D2/D3 and twice weekly + IVIG 2 g/kg every 4 weeks
- Control: IVIG 2 g/kg every 4 weeks

Viglietti, AJT 2016

C1-Inhibitor in resistant ABMR

C1-INH treated patients: increased eGFR at M+6 (P=0.03)

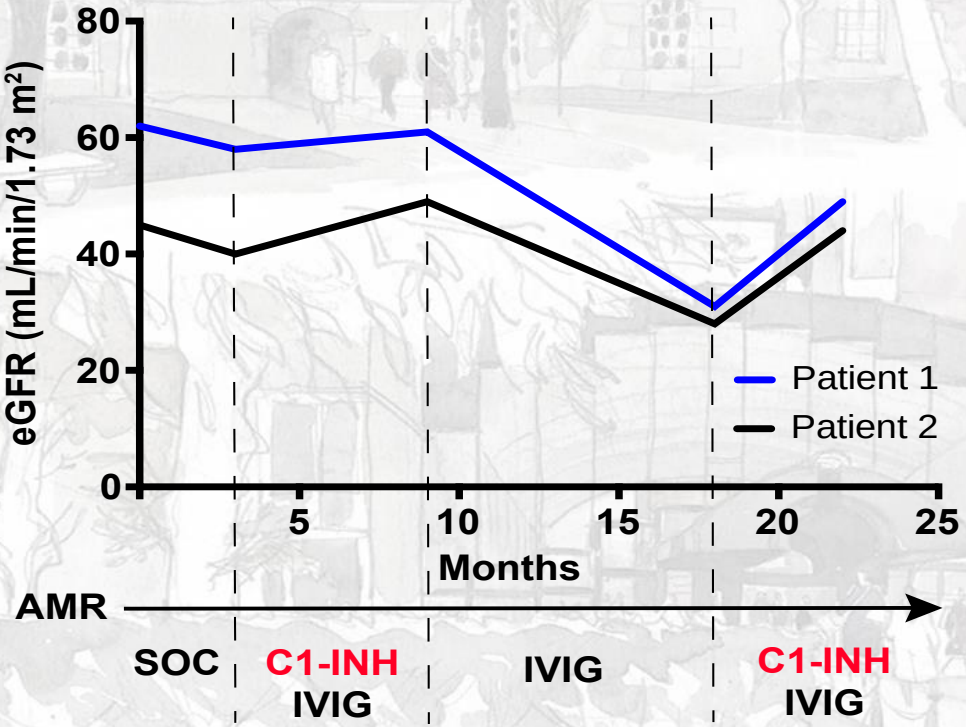


Viglietti, AJT 2016

C1-Inhibitor in resistant ABMR

- No allograft loss
- 4 patients retreated with C1-INH started between 6 and 12 mo after study end

Example of eGFR kinetics according to C1-INH treatment



Viglietti, AJT 2016

Tocilizumab

Anti-IL6

Interleukin (IL)-6 is a cytokine that has powerful stimulatory effects on B cells and plasma cells and is responsible, in conjunction with other cytokines, for normal antibody production.

-Desensitization

-Treatment of refractory AMR

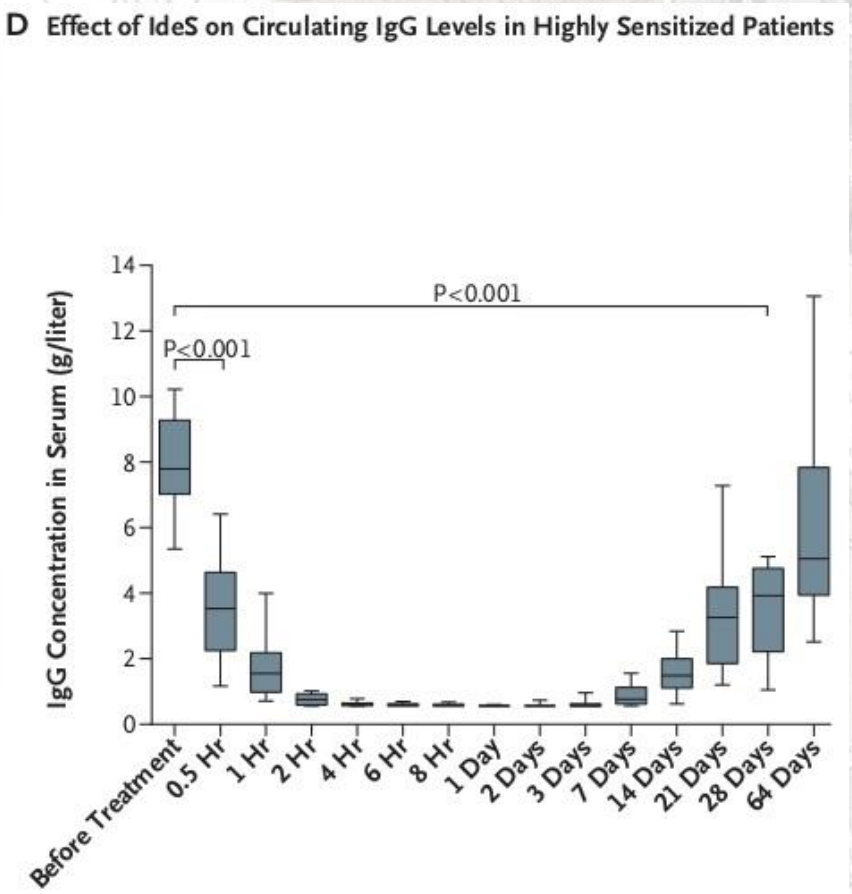
Vo, Transpl 2015

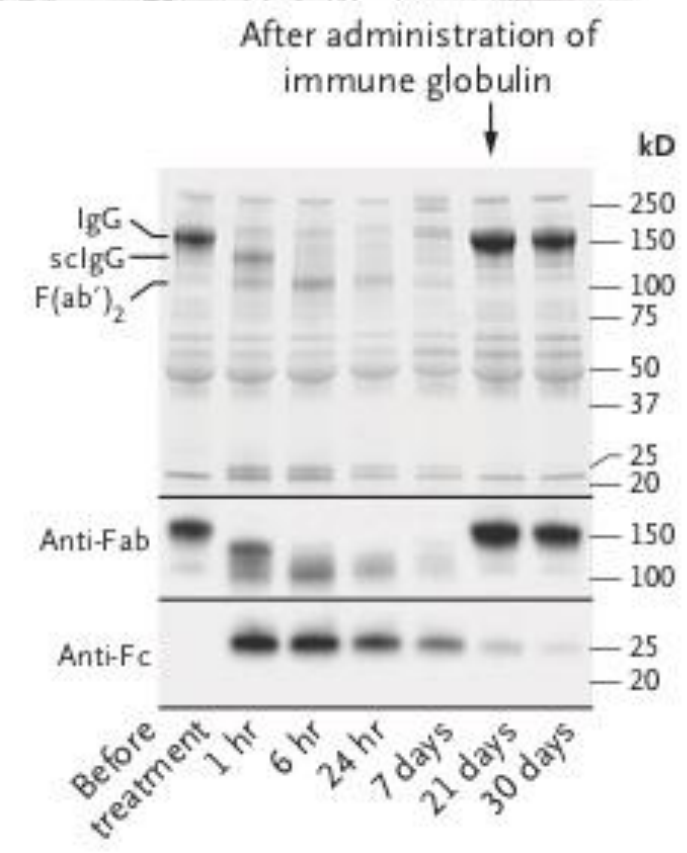
Jordan, personal comm

IdeS

The new kid in the block…

IgG degrading enzyme (from Strep pyogenes)





Jordan, NEJM 2017

IdeS

25 sensitized patients (mean cPRA 95%)
24 transplanted
10 humoral rejections

Immunologic variables	
Anti-HLA donor-specific antibody positive — no. (%)	23 (92)
No. of anti-HLA donor-specific antibodies	2.3±1.8
Mean fluorescence intensity	
Class I	5660±2364
Class II	8199±5639
Negative anti-HLA donor-specific antibodies at 1 to 6 hr after treatment — no. (%)	25 (100)
Positive cross-match at transplantation — no. (%)†	20 (80)
Estimated GFR at 1 to 6 mo after transplantation — ml/min/1.73 m^2	58±30
Follow-up — mo	4.7±1.9
Graft loss — no. (%)	1 (4)

One shot….

Jordan, NEJM 2017

IdeS

The new kid in the block…

IgG degrading enzyme (from Strep pyogenes)

On-going study on curative treament of ABMR

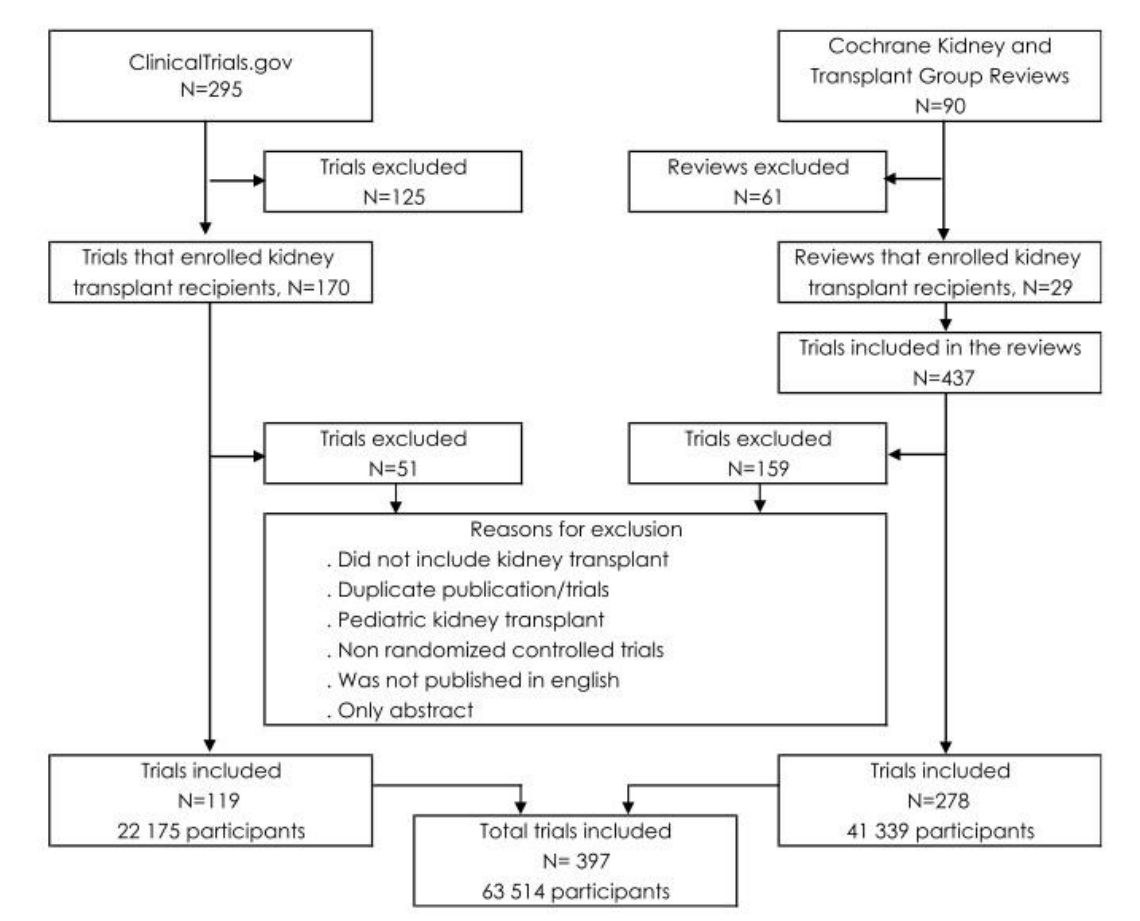
As of today…

- First line of TT: PP/IVIg
- Assess efficacy….(???)
- Then….
  - Bortezomib
  - Splenectomy
  - Anti-complement agents

How can we get better?

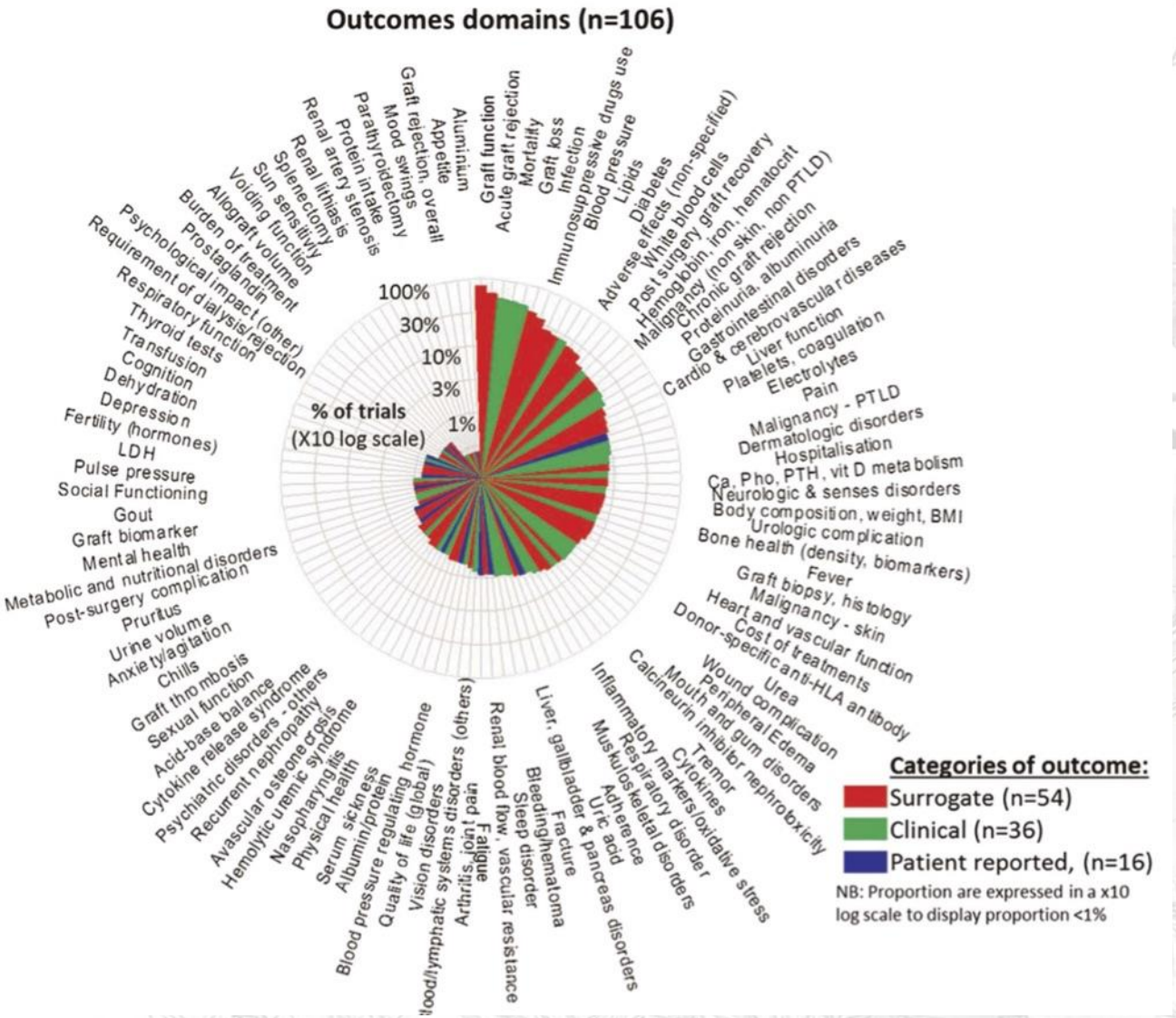
- Better trial design and endpoints
- Better selection of patients

Trial design and endpoints



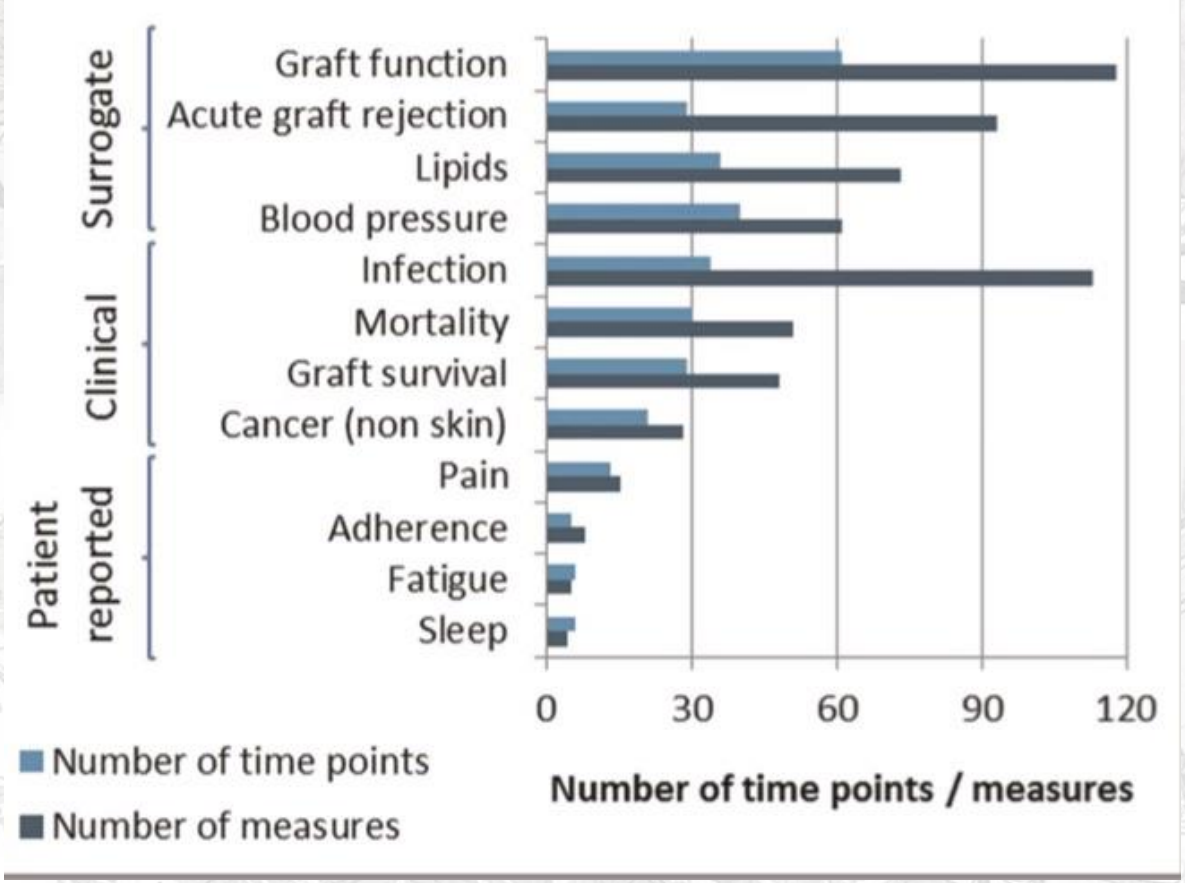
Sautenet, Transpl 2018

Trial design and endpoints



Sautenet, Transpl 2018

Trial design and endpoints



Sautenet, Transpl 2018

The spectrum of AbMR

- Early AbMR
- Sub-clinical AbMR
- Late AbMR
- « Chronic » AbMR (TG)

HETEROGENOUS!

Composite Score to Define the Risk of Allograft Loss After Standard-of-Care Treatment of ABMR in Kidney Transplantation

Paris Translational Research Center
for Organ Transplantation
paristransplantgroup.org

HYPOTHESIS

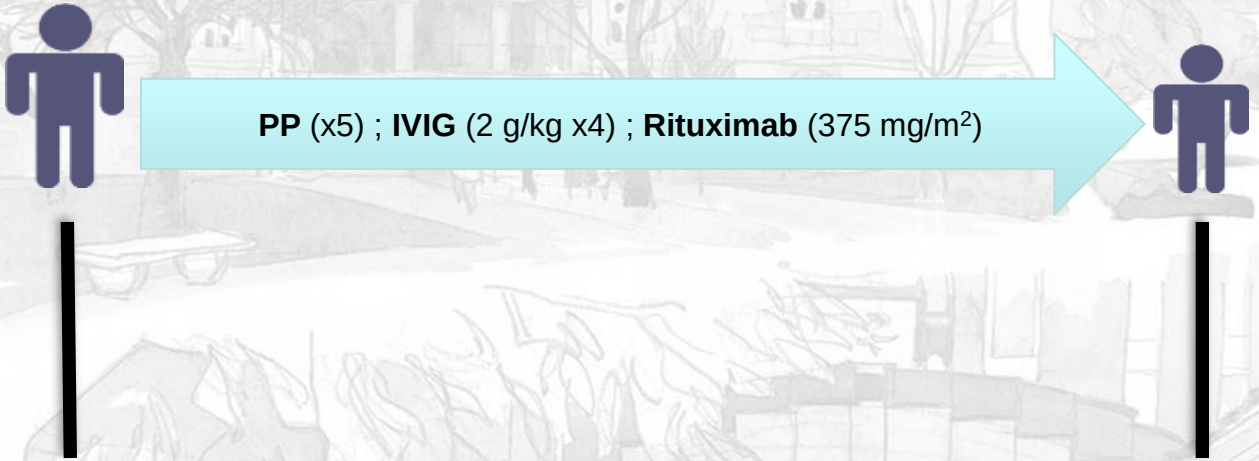
Early changes in allograft function, histology and DSA characteristics after ABMR treatment might predict kidney allograft loss

STUDY DESIGN

Prospective observational study 2008-2013

Inclusion criteria = Patients with ABMR receiving SOC (N=284)

Graft loss



01/2016

M0: ABMR diagnosis
- DSA class, specificity, MFI
- Graft biopsy
- GFR
- Prot U

M3: Response to therapy
- DSA class, specificity, MFI
- Graft biopsy
- GFR
- Prot U

Paris Transplant Group
Kidney, Heart & Lung

Viglietti, JASN 2017

INTEGRATIVE MODELING FOR RISK PREDICTION ACCORDING TO RESPONSE TO THERAPY

Model 1

At time of diagnosis

- Clinical
- Functional
- Histological
- Immunological
- Donor parameters
- Transplant parameters

Model 2

Response to therapy

- Clinical
- Functional
- Histological
- Immunological

Model 3

Integrated Model 1+2

- Clinical
- Functional
- Histological
- Immunological
- Donor parameters
- Transplant parameters

Kidney allograft loss

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Kidney, Heart & Lung

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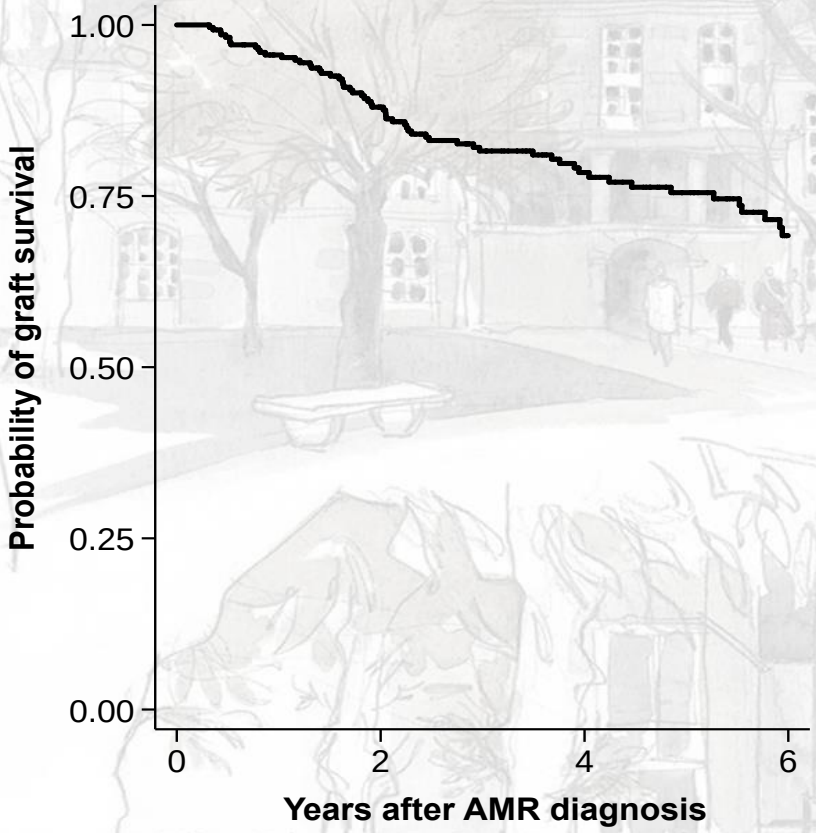
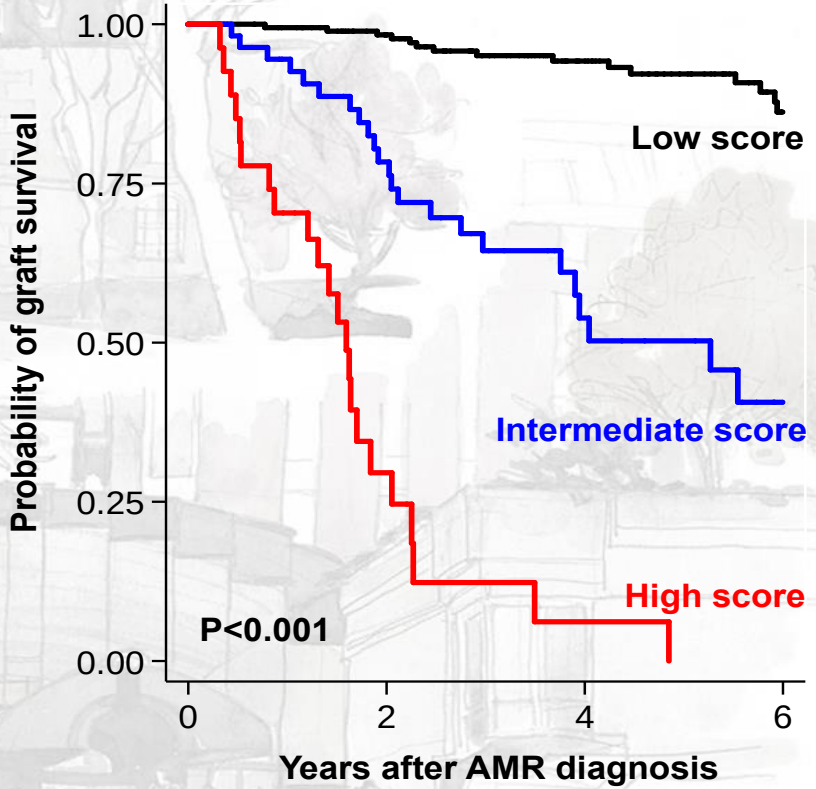
STRATIFICATION OF GRAFT SURVIVAL AFTER ABMR THERAPY BASED ON PROGNOSTIC SCORING

Overall graft survival



Number at risk				
	278	208	116	52

Score-stratified graft survival

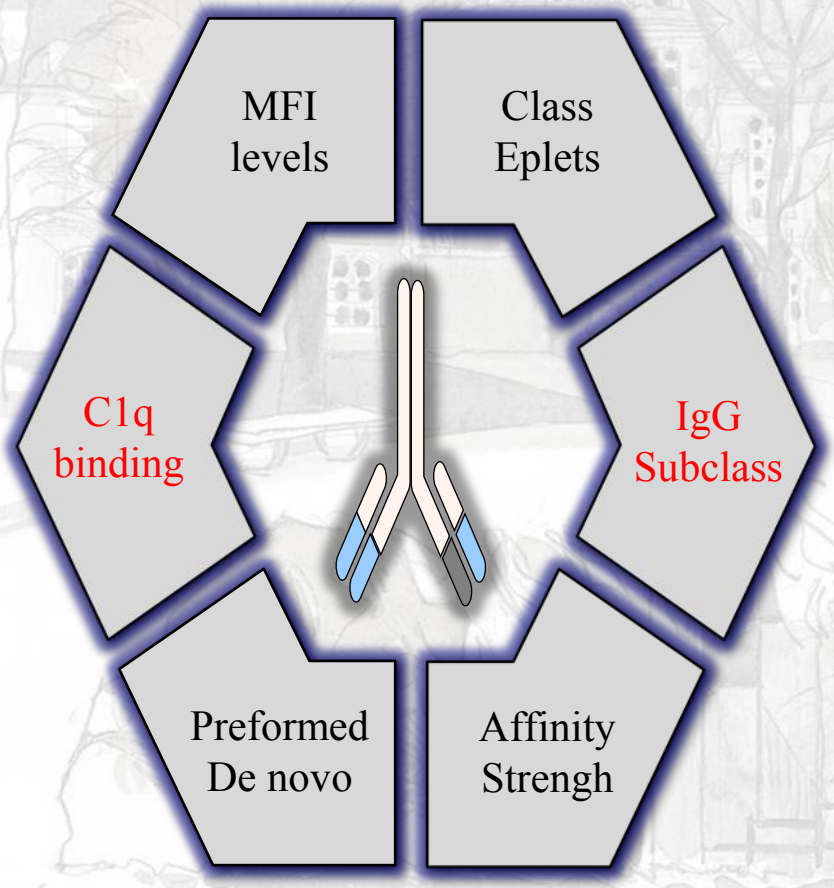


Number at risk				
Low score	194	165	100	48
Intermediate score	57	37	15	4
High score	27	6	1	0

Paris Transplant Group
Kidney, Heart & Lung

Viglietti, JASN 2017

Integrative and multiplex assessment of DSA integrated into clinical practice



Graft failures

Disease progression

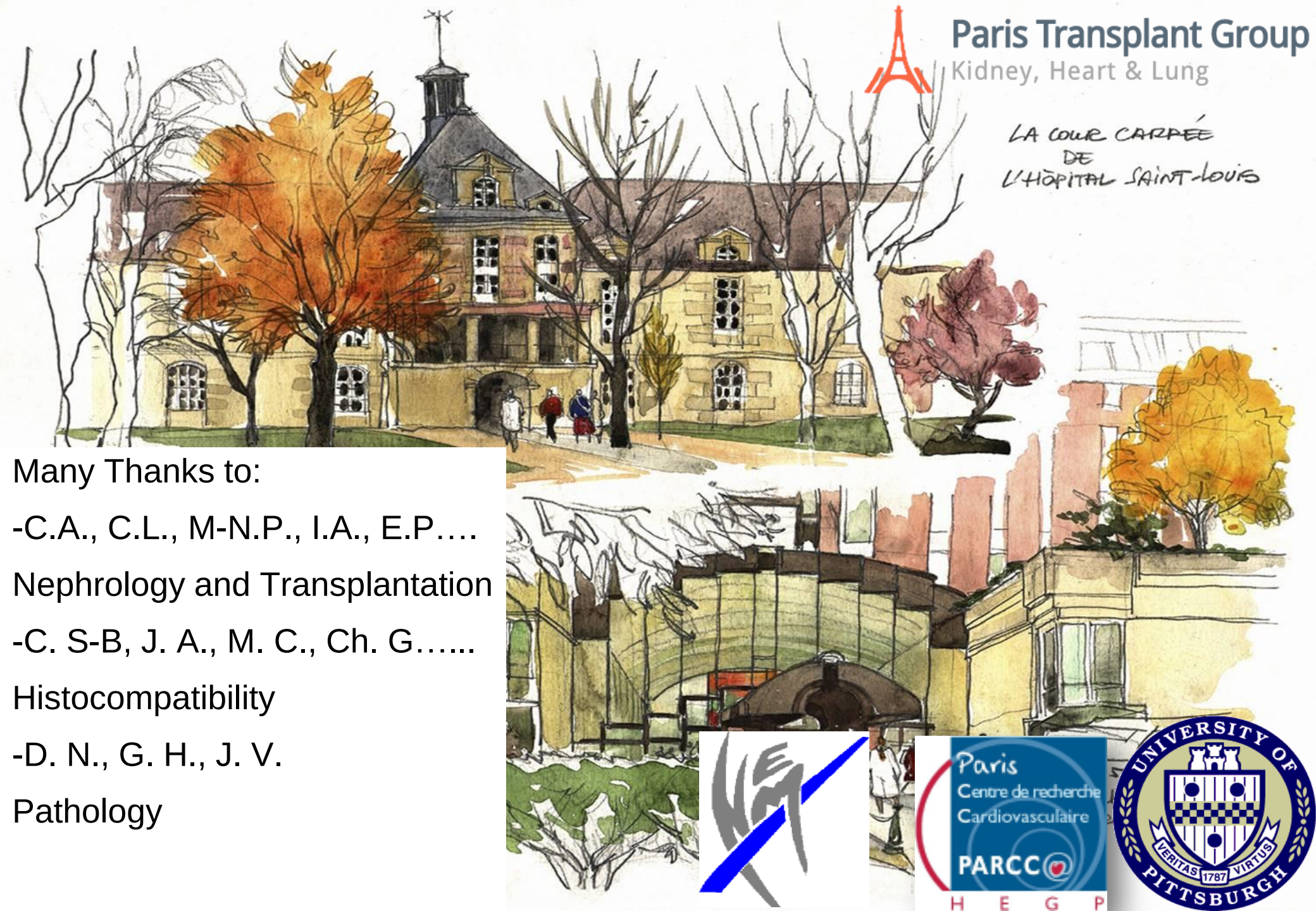
Risk prediction

Validation

Response to therapy

Personalized medicine?

- Tyan et al; Human Immunol 2011
- Loupy et; NEJM 2013
- Sicard et al; JASN 2014
- Taupin et al; JASN 2015
- Tambur et al; AJT 2015
- Viglietti et al: JASN 2015
- Akalin et al; KI 2015
- Canër et al; Transplantation 2015
- Comoli et al; AJT 2016



Many Thanks to:

-C.A., C.L., M-N.P., I.A., E.P….

Nephrology and Transplantation

-C. S-B, J. A., M. C., Ch. G…...

Histocompatibility

-D. N., G. H., J. V.

Pathology