

LA COUR CARP  
DE  
L'HÔPITAL SAINT

# Advances in the management of AbMR



**3RD GCC ORGAN TRANSPLANTATION & NEPHROLOGY  
CONGRESS**



# AMR : an evolutive continuum

LA COUR CARP  
DE  
L'HÔPITAL SAINT



# The spectrum of AbMR

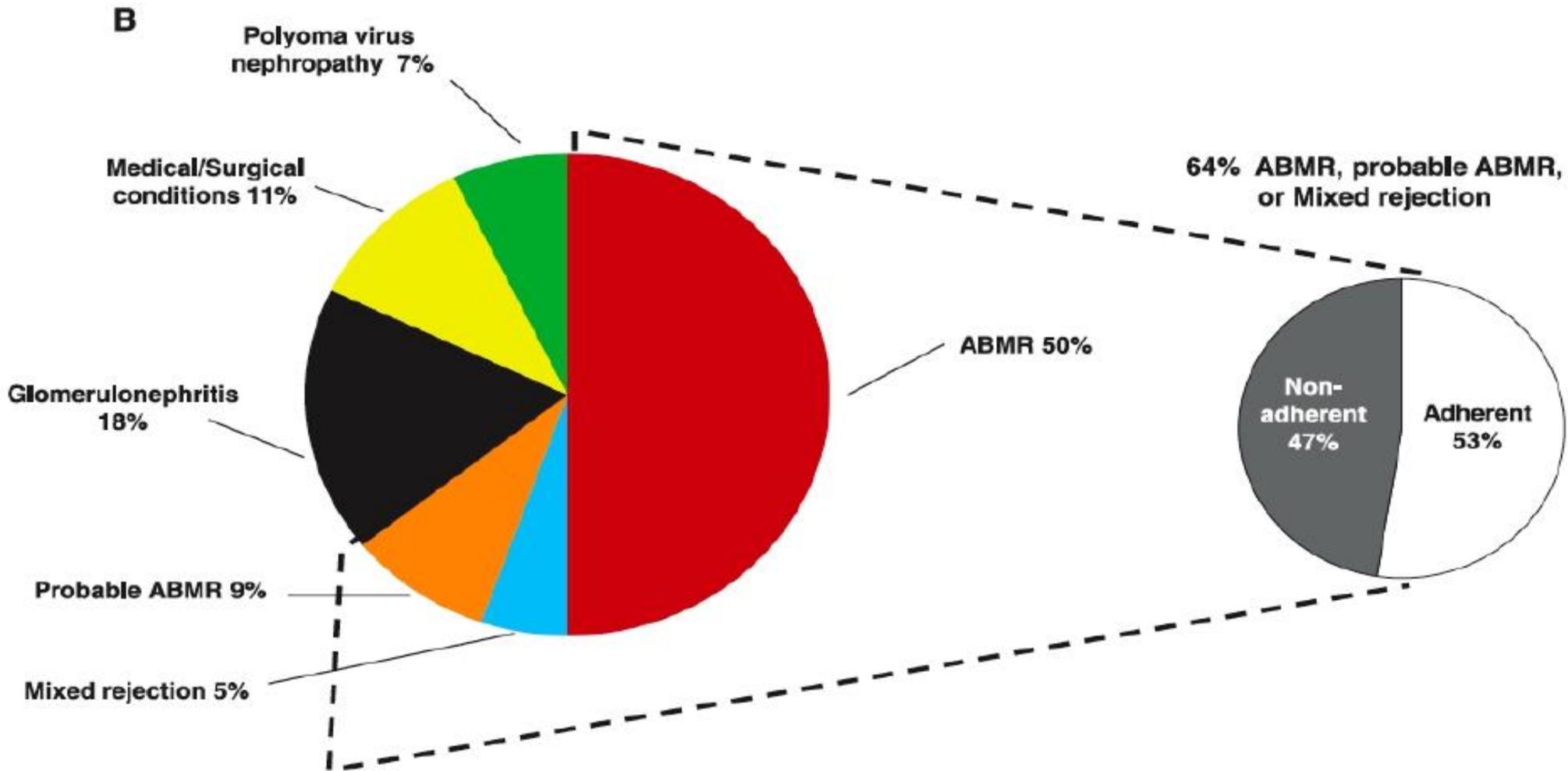
- Early AbMR
- Sub-clinical AbMR
- Late AbMR
- « Chronic » AbMR (TG)

LA COUR CARP  
DE  
L'HÔPITAL SAINT

L'ENTRÉE  
DU NOUVEAU  
SAINT-LOUIS

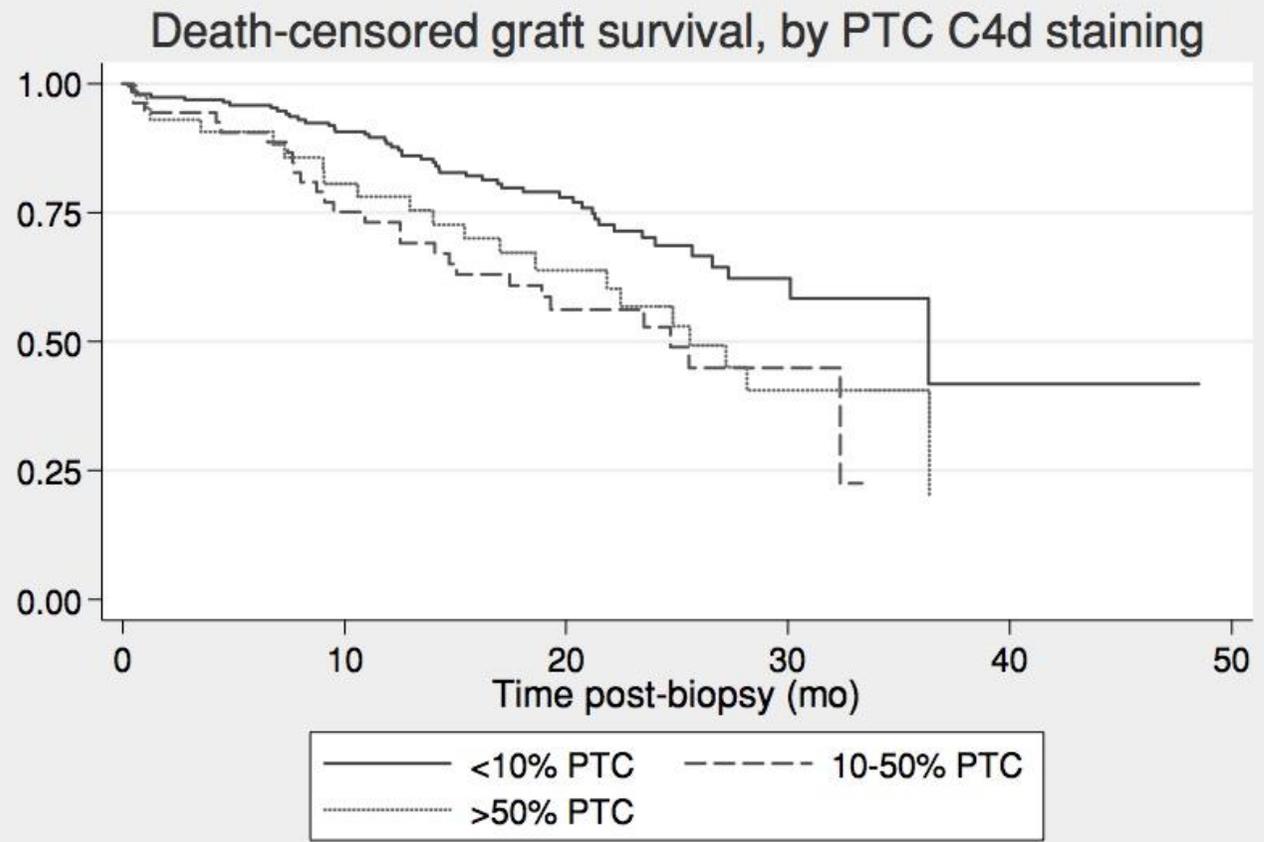
2005  
Nöcke  
HERRENSCHWOT

# ABMR is the leading cause of graft loss!



LA COUR CARP  
DE  
L'HÔPITAL SAINT

# Prognosis of ABMR



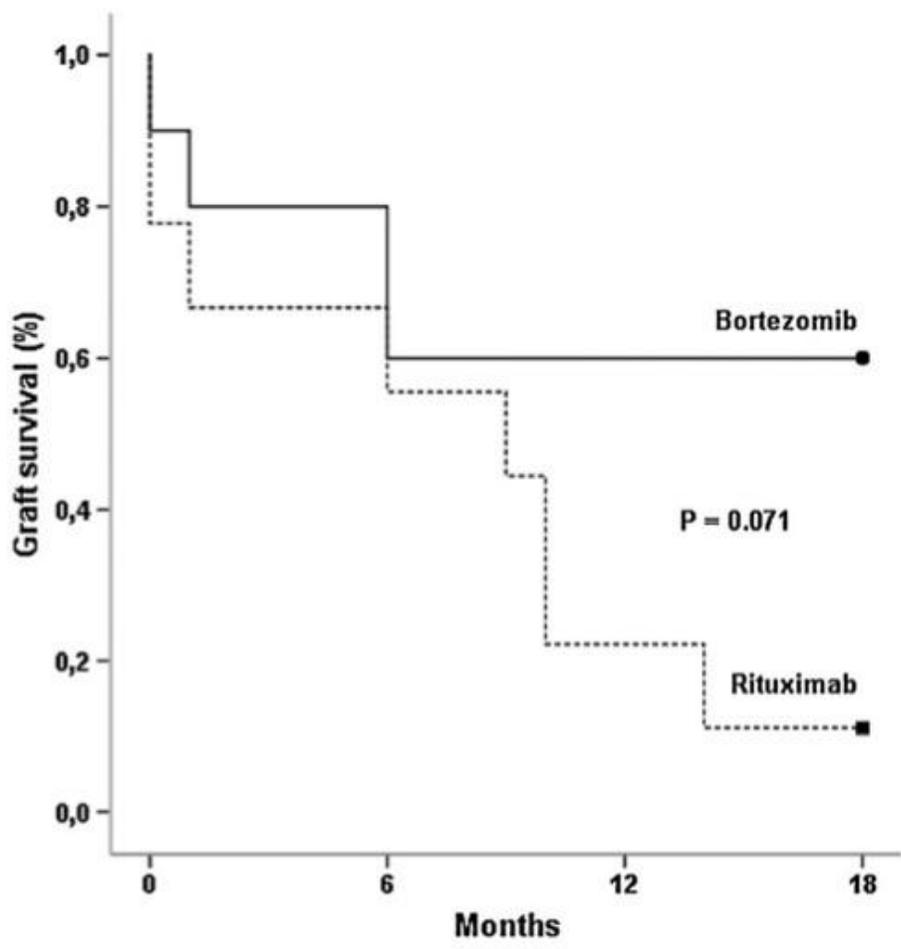
P=0.005 for focal and P<0.03 for diffuse C4d

L'ENTRÉE  
DU NOUVEAU  
SAINT-LOUIS



LA COUR CARP  
DE  
L'HÔPITAL SAINT

# Prognosis of ABMR

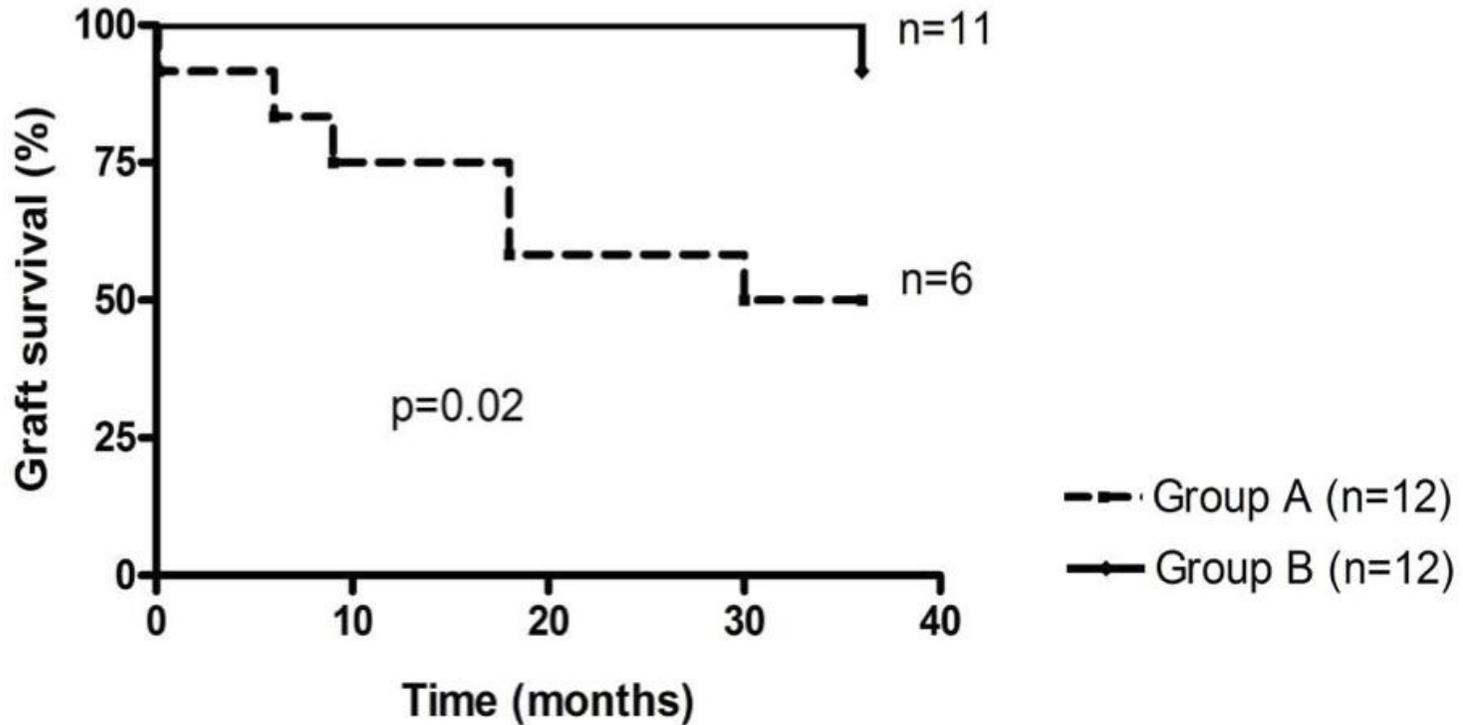


L'ENTRÉE  
DU NOUVEAU  
SAINT-LOUIS

2005  
NÖCKE  
HERRENSCHWART

# Prognosis of ABMR

LA COUR CARP  
DE  
L'HÔPITAL SAINT

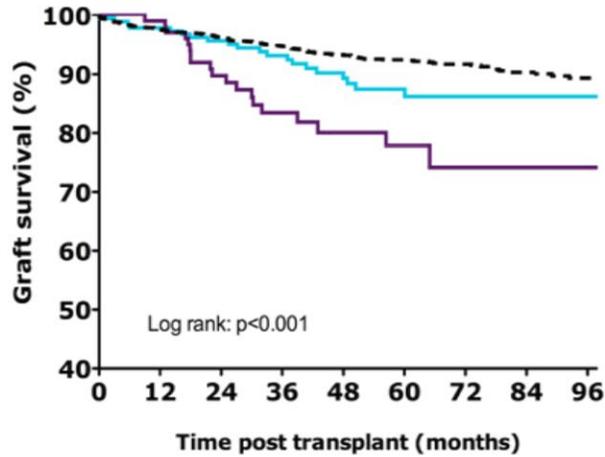


L'ENTRÉE  
DU NOUVEAU  
SAINT-LOUIS

CHAMOT

# Prognosis of ABMR

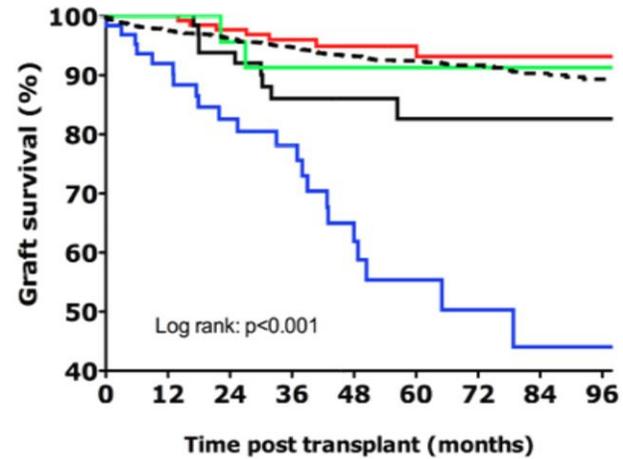
--- No Rejection (n=1777)  
 — Banff T cell mediated rejection (n=192)  
 — Banff antibody mediated rejection (n=110)



Number at risk

1777	1600	1408	1152	933	673	473	314	213
192	182	163	134	101	71	37	31	26
110	100	78	61	40	26	12	9	8

--- No Rejection (n=1777)  
 — T cell mediated rejection (n=139)  
 — Vascular rejection DSA- (n=26)  
 — Antibody mediated rejection (n=73)  
 — Vascular rejection DSA+ (n=64)



Number at risk

1777	1600	1408	1152	933	673	473	314	213
139	136	121	101	77	54	29	24	22
26	26	23	20	15	12	4	4	2
73	68	56	42	28	19	7	5	5
64	52	41	32	21	12	9	7	5

L'ENTRÉE  
DU NOUVEAU  
SAINT-LOUIS

Noche  
HERRENSCHMIDT

# What do we know about AMR treatment?

Not much....

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

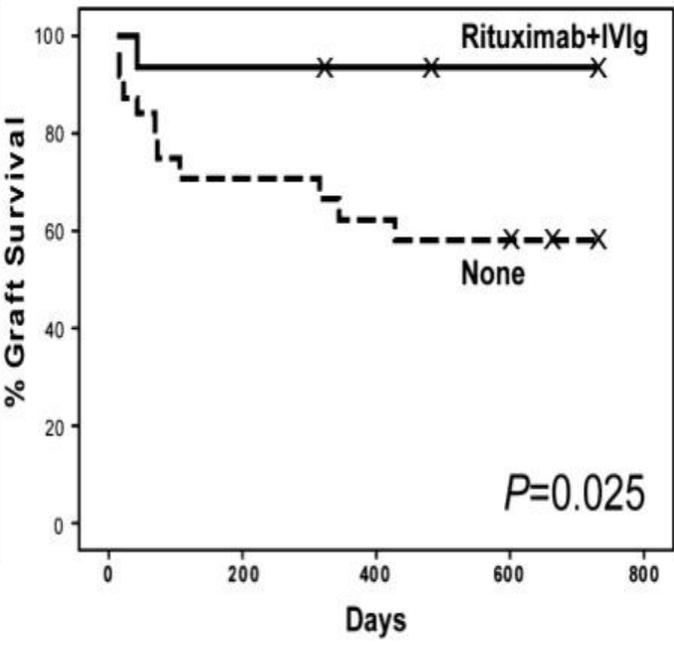
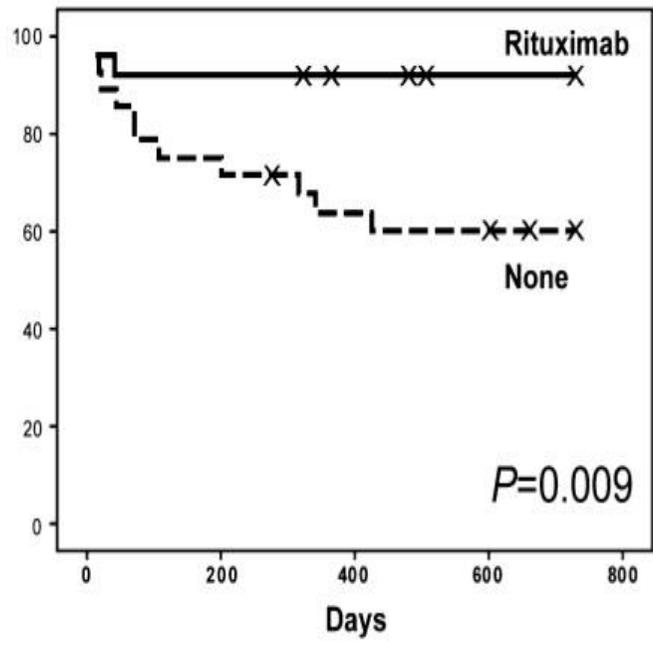
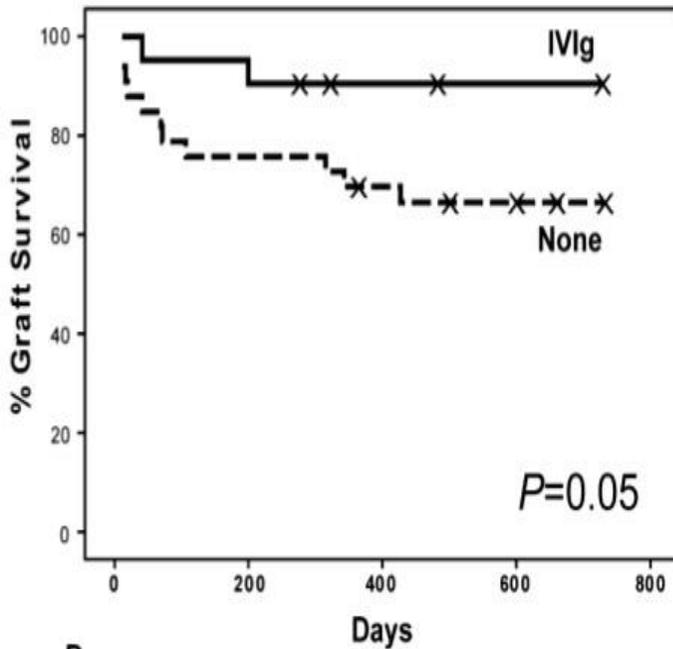
# Adapted Treatment is essential

	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

# Impact of a single agent difficult to judge..

LA COUR CARP  
DE  
L'HÔPITAL SAINT

B.



n

SAINT-LOUIS

HERRENCHWOT

# Antibody Mediated Rejection Treatment

## IVIg/PP treatment

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

L'ENTRÉE  
DU NOUVEAU  
SAINT-LOUIS

2005  
Nöcke  
HERRENSCHWART

# Effect of PE alone on Ig synthesis

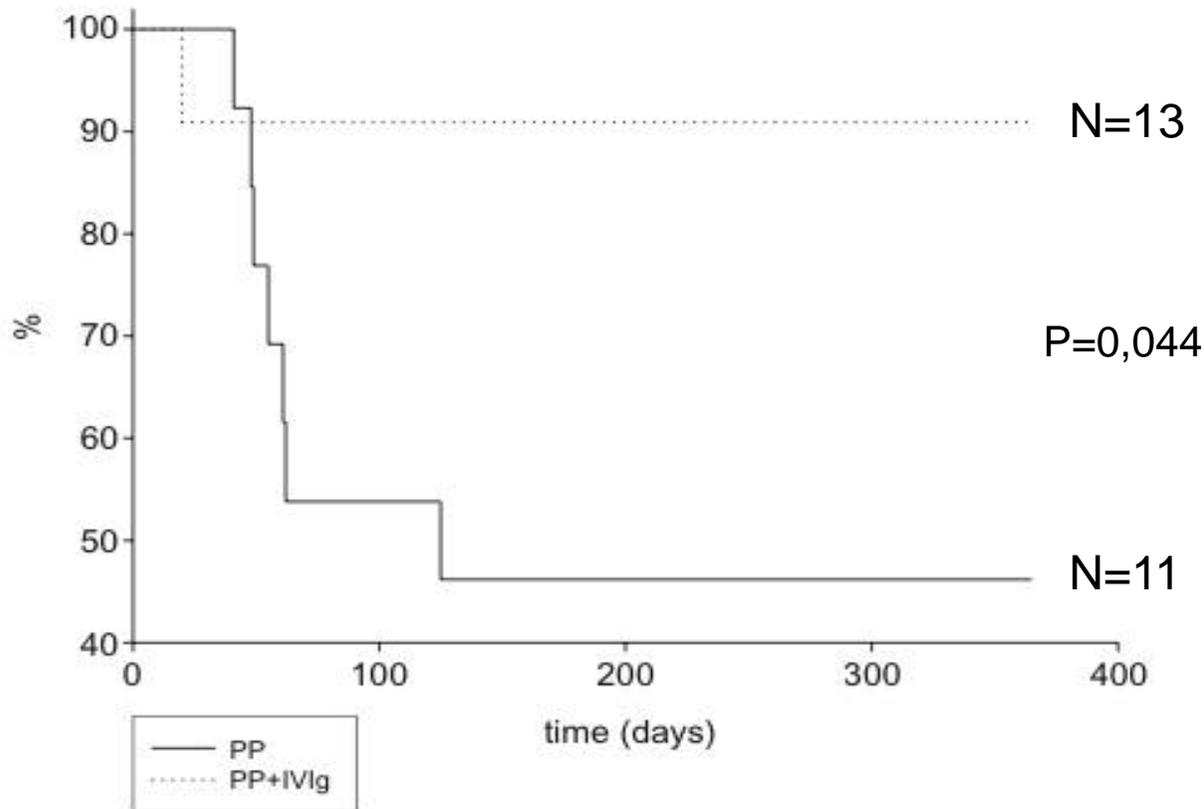
**Table 3**  
In vitro immunoglobulin production with plasma exchange

Patient No.	Treatment			
	IgG		IgM	
	No. 1	No. 5	No. 1	No. 5
1	70 <sup>a</sup>	100	15 <sup>a</sup>	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 <sup>b</sup>	332 ± 267	48 ± 20 <sup>b</sup>	429 ± 571
	P < 0.05 *		P < 0.001 *	

L'ENTRÉE  
DU NOUVEAU  
SAINT-LOUIS

2005  
Nöcke  
HERRENSCHWART

# IVIg +/- Plasmapheresis



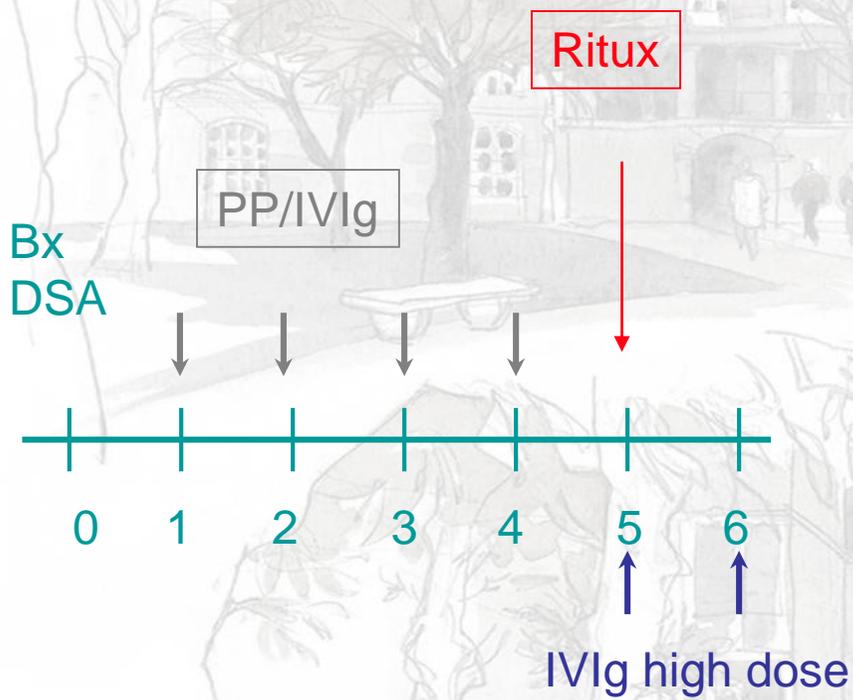
**FIG. 1.** Graft survival. Patients receiving the plasmapheresis (PP) and intravenous immunoglobulin (IVIg) combination had better one-year graft survival than those treated using only PP.  $P = 0.044$ .

L'ENTRÉE  
DU NOUVEAU  
SAINT-LOUIS



# Antibody Mediated Rejection Treatment

## The “Marrakesh” protocol



- ✓ 4 PP/low dose IVIg
- ✓ Ritux 375 mg/m<sup>2</sup>
- ✓ IVIg 2gr/Kg

L'ENTRÉE  
DU NOUVEAU  
SAINT-LOUIS

2005  
Nöcke  
HERRENSCHWART

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

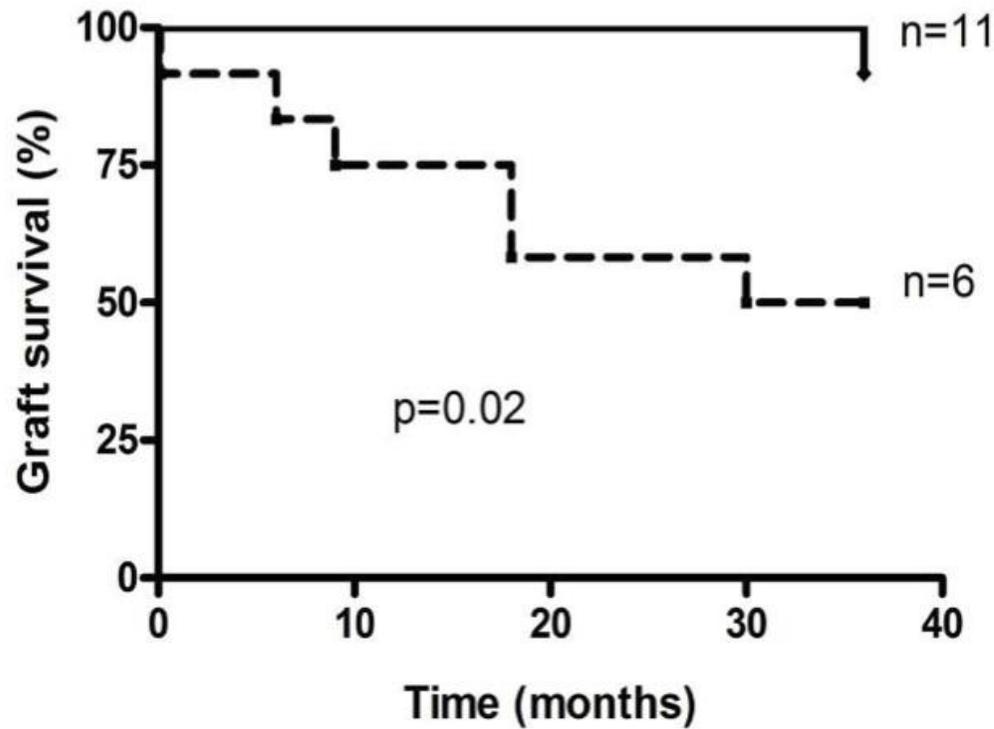
- **Group A:** High-dose intravenous immunoglobulin (IVIg) regimen  
01/2000-12/2003  
N=12 pts
- **Group B:** Plasmapheresis (PP) / IVIg / anti-CD20 (PP/IVIg/anti-CD20) regimen  
01/2004-12/2005  
N=12 pts

L'ENTRÉE  
DU NOUVEAU  
SAINT-LOUIS

2005  
Noëlle  
HERRENSCHWARTZ

# Long term results

LA COUR CARP  
DE  
L'HÔPITAL SAINT

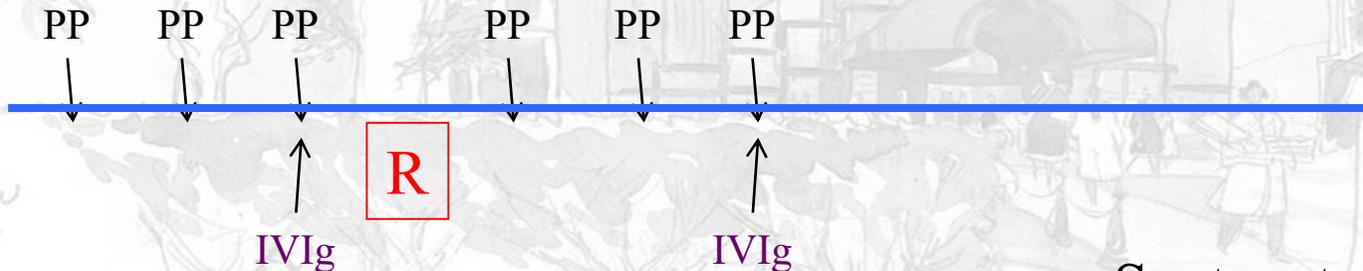


L'ENTRÉE  
DU NOUVEAU  
SAINT-LOUIS

# 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)



# 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....

# 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....

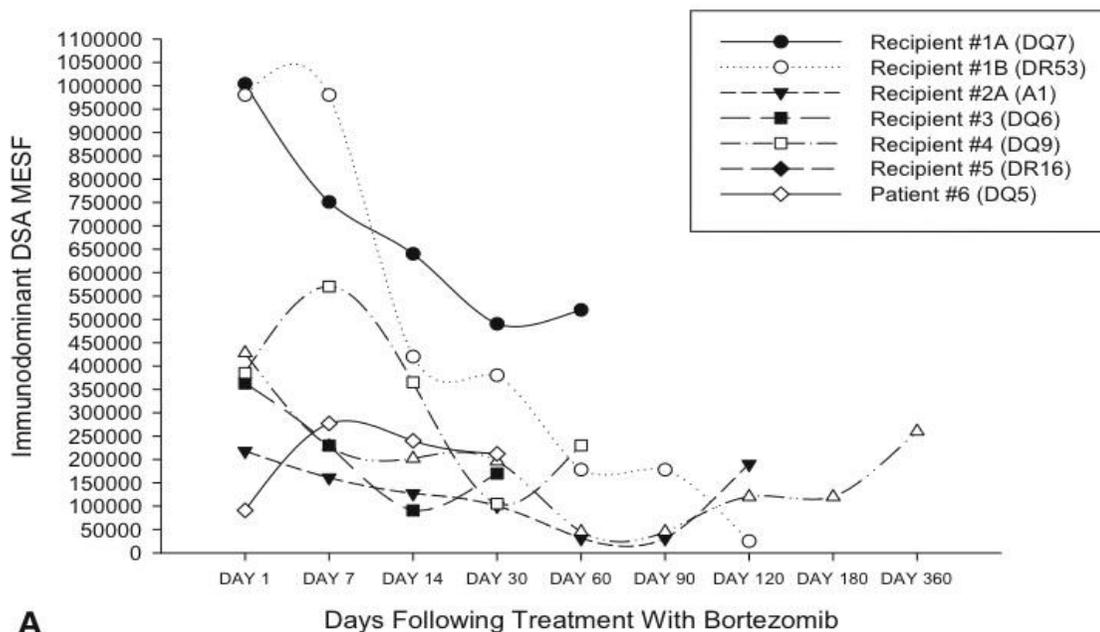
No difference at one year...



# Bortezomib

## Treatment of rejection

LA COUR CARP  
DE  
L'HÔPITAL SAINT



A

- 1,3 mg/m<sup>2</sup> x4
- 6 patients, 6 successes.....

L'ENTRÉE  
DU NOUVEAU  
SAINT-LOUIS

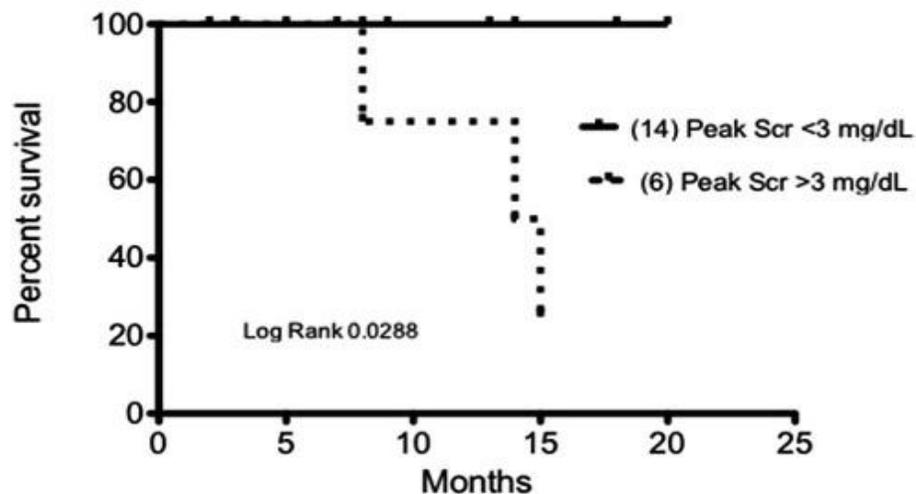
2005  
Nöcke  
HERRENSCHWART

# Bortezomid

## Treatment of rejection

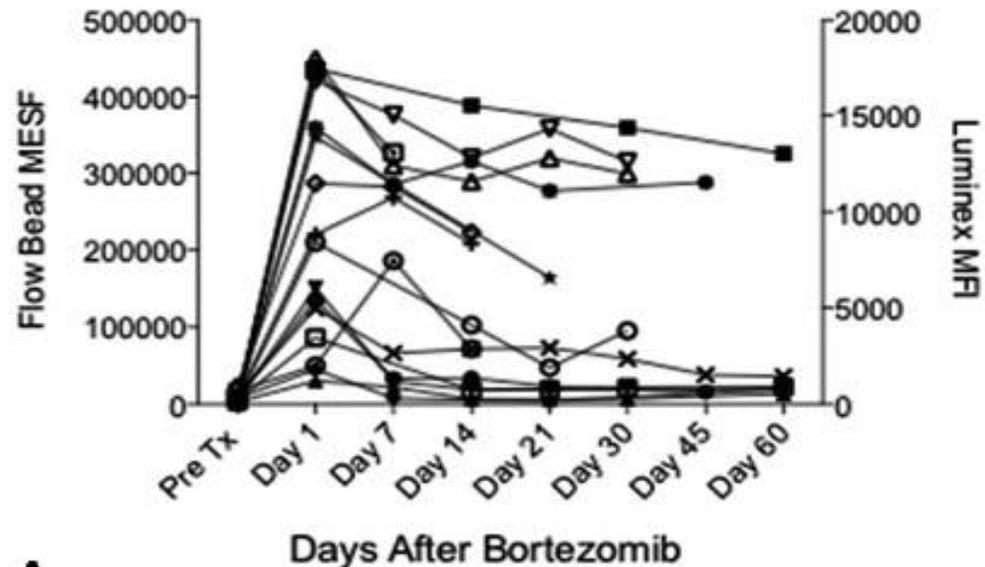
LA COUR CARP  
DE  
L'HÔPITAL SAINT

Graft Survival after AMR Treatment with Bortezomib



**FIGURE 1.** Actuarial graft survival for 20 bortezomib-treated recipients according to a peak serum creatinine (SCr) greater than or less than 3 mg/dL during treatment of antibody-mediated rejection (AMR). At 15 months difference was 100% versus 32%,  $P=0.0288$  by log-rank test.

Dominant Donor Specific Antibody in Kidney-only Recipients  
(Patient 1-8 Flow Beads; Patient 9-16 Luminex)



A

- 1,3 mg/m<sup>2</sup> x4
- 20 patients, GS 9,5 months 85%.....

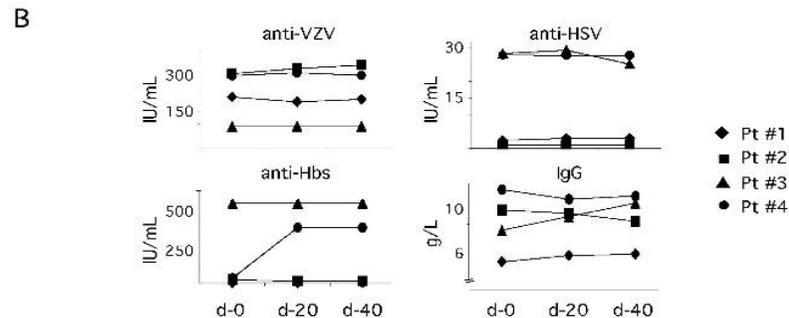
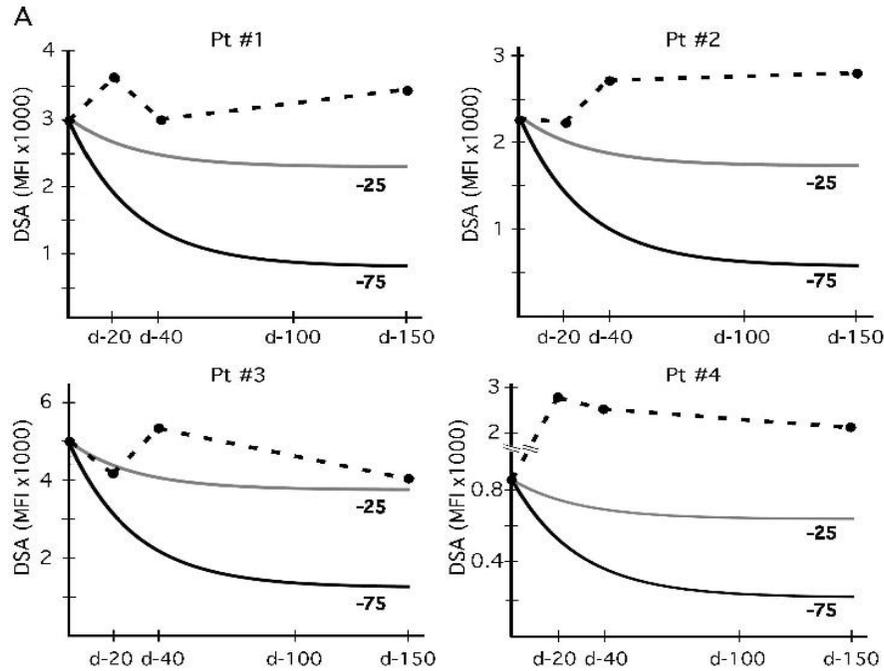
L'ENTRÉE  
DU NOUVEAU  
SAINT-LOUIS

2005  
Nöcke  
HERRENSCHWART

# Bortezomid

In vivo....????

LA COUR CARP  
DE  
L'HÔPITAL SAINT



L'ENTRÉE  
DU NOUVEAU  
SAINT-LOUIS

2005  
Nöcke  
HERRENRECHT

# Bortezomid/PP

In vivo....

LA COUR CARP  
DE  
L'HÔPITAL SAINT

SI no	Bortezomib						Control			
	BL BFXM	PT BFXM	PPE BFXM	BL MFI	PT MFI	PPE MFI	BL BFXM	PPE BFXM	BL MFI	PPE MFI
1*	556	528	-	13570	13758	-	472	347	NA	NA
2	479	493	147	10764	10280	1096	537	532	NA	NA
3*	573	622	-	8249	11931	-	528	533	NA	NA
4*	642	619	-	16157	15074	-	502	344	NA	NA
5	631	470	278	8064	11843	6492	527	446	NA	NA
6	494	316	289	9982	4522	11351	472	401	NA	NA
7	487	404	342	12622	14296	10222	525	401	NA	NA
8	672	560	344	7894	8537	8283	681	477	14258	13365
9**	515	533	-	9376	8820	-				

**TABLE 3.** Proteasome inhibition potentiates antidonor HLA antibody reduction with plasma exchange

Category	Bortezomib+PE group (n=5)	PE only group (n=8)	P
a No. PE (mean±SD)	11.4±2.7	11.6±3.9	0.9
b Baseline-post-PE BFXM (mean±SD)	272.6±92.1	95.4±72.2	0.008
c % Change in BFXM CS (mean±SD)	49.1±14.9	17.7±12.5	0.005
d Achieving a channel shift <300	3 (60%)	0 (0%)	0.035

(a) Similar numbers of plasma exchanges were performed in the bortezomib-treated patients compared with the control group,  $P=0.9$ . (b) Bortezomib treatment before plasma exchange resulted in a greater reduction in serum donor-specific alloantibody compared with untreated controls ( $P=0.008$ ). (c) The percentage change in donor-specific alloantibody also was greater ( $P=0.005$ ).

HLA, human leukocyte antigen; SD, standard deviation.

L'ENTRÉE  
DU NOUVEAU  
SAINT-LOUIS

2005  
Nöcke  
HERRENSCHWART

# Complement inhibitors

- Block damage from DSAs
- Do not inhibit DSA synthesis

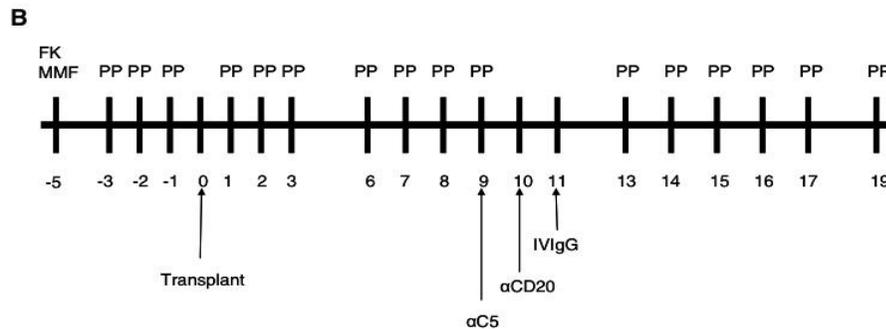
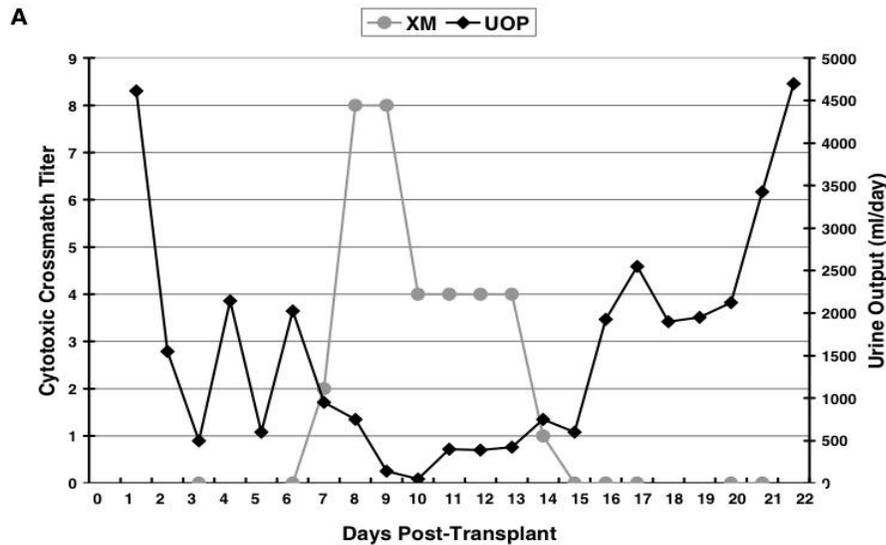
LA COUR CARP  
DE  
L'HÔPITAL SAINT

L'ENTRÉE  
DU NOUVEAU  
SAINT-LOUIS

2005  
Nöcke  
HERRENSCHWOT

# Treatment by C5 inhibition

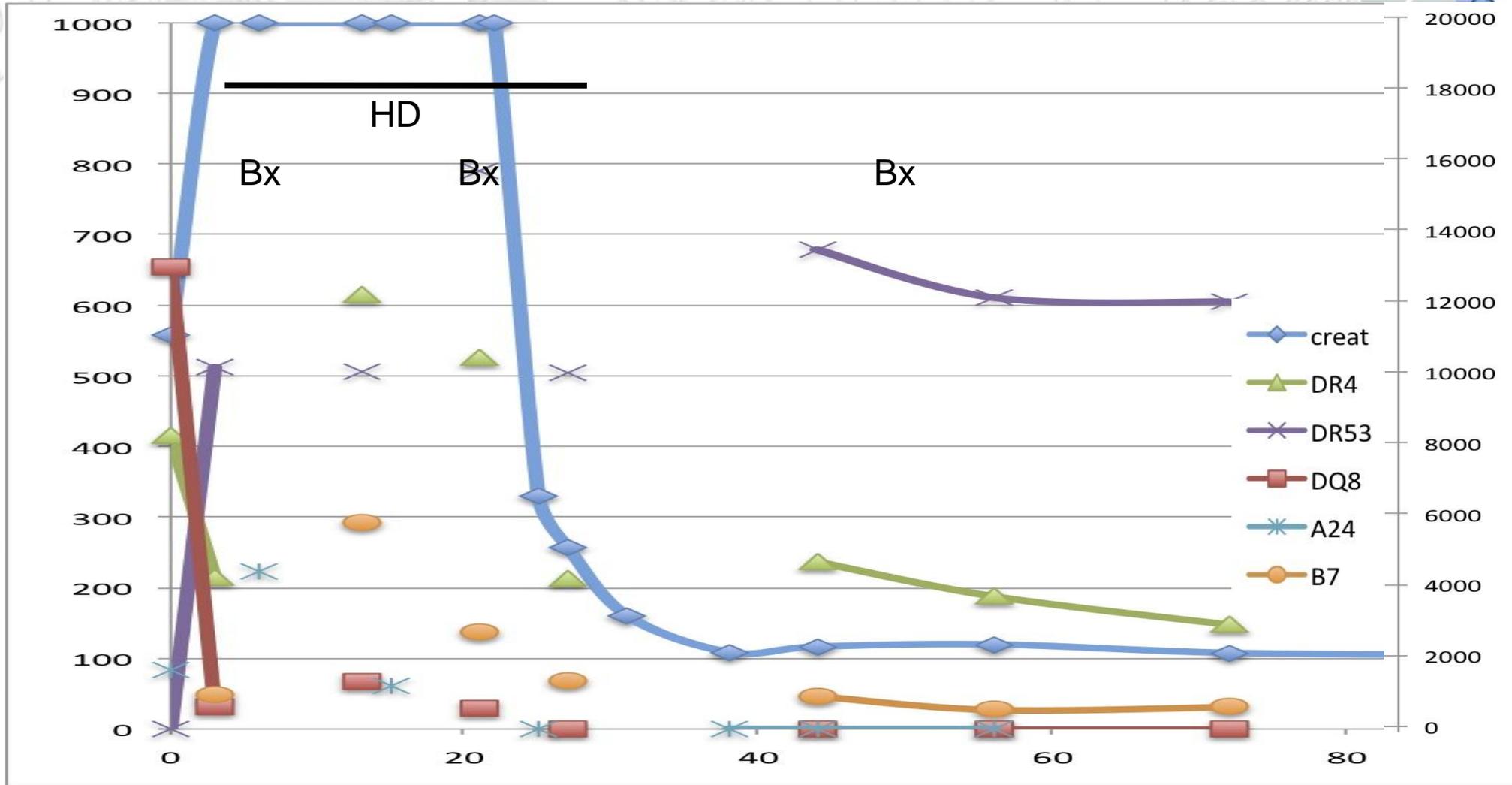
LA COUR CARP  
DE  
L'HÔPITAL SAINT



L'ENTRÉE  
DU NOUVEAU  
SAINT-LOUIS

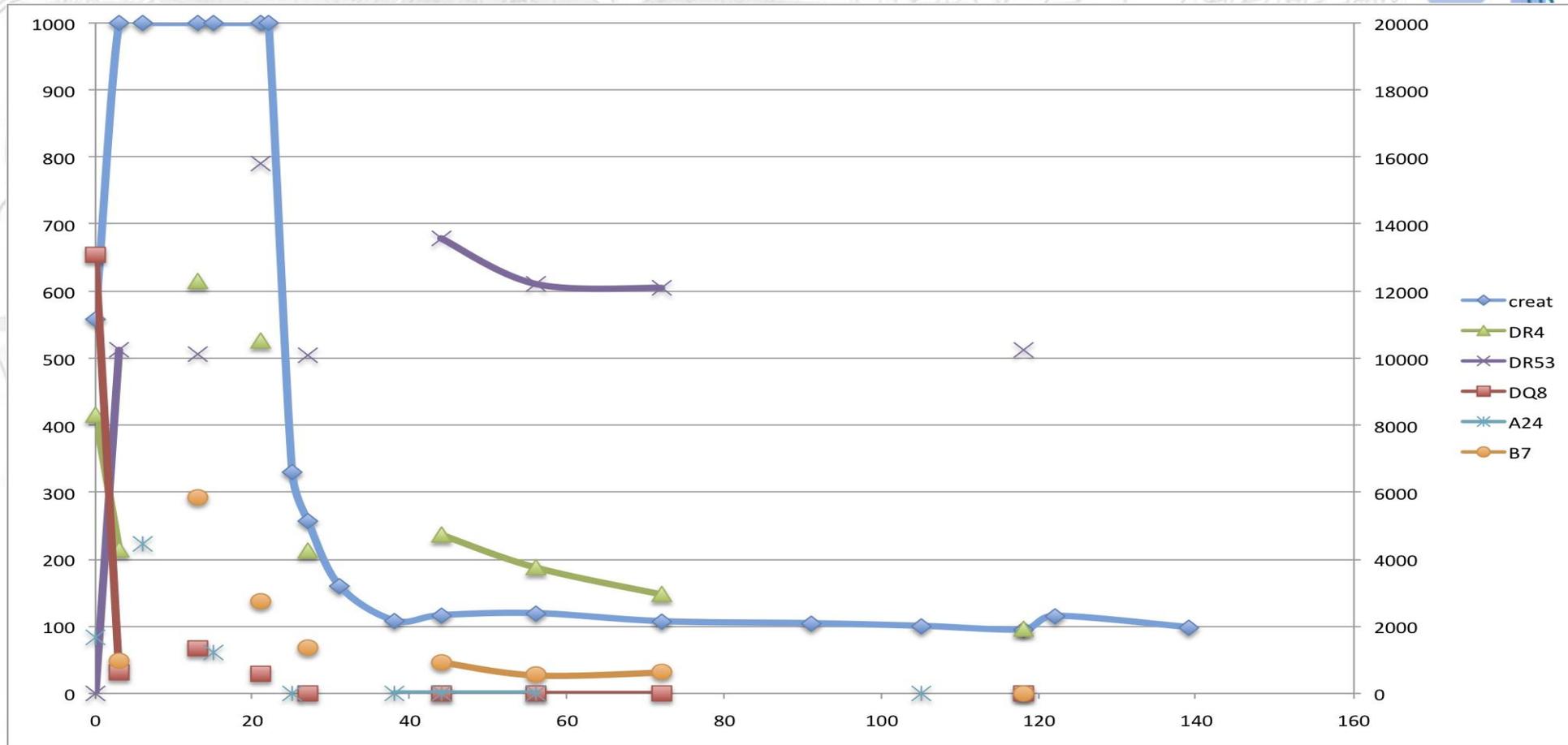


# TT by C5 inhibition: LD Tx



# TT by C5 inhibition: LD Tx

LA COUR CARP  
DE  
L'HÔPITAL SAINT



Soliris

L'ENTRÉE  
DU NOUVEAU  
SAINT-LOUIS

2005  
NÖCKE  
HERRENSCHWART

# 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

L'ENTRÉE  
DU NOUVEAU  
SAINT-LOUIS

2005  
Noëlle  
HERRENSCHWARTZ

# C1 Esterase inhibitor

LA COUR CARP  
DE  
L'HÔPITAL SAINT

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

© Copyright 2016 The American Society of Transplantation  
and the American Society of Transplant Surgeons

doi: 10.1111/ajt.13871

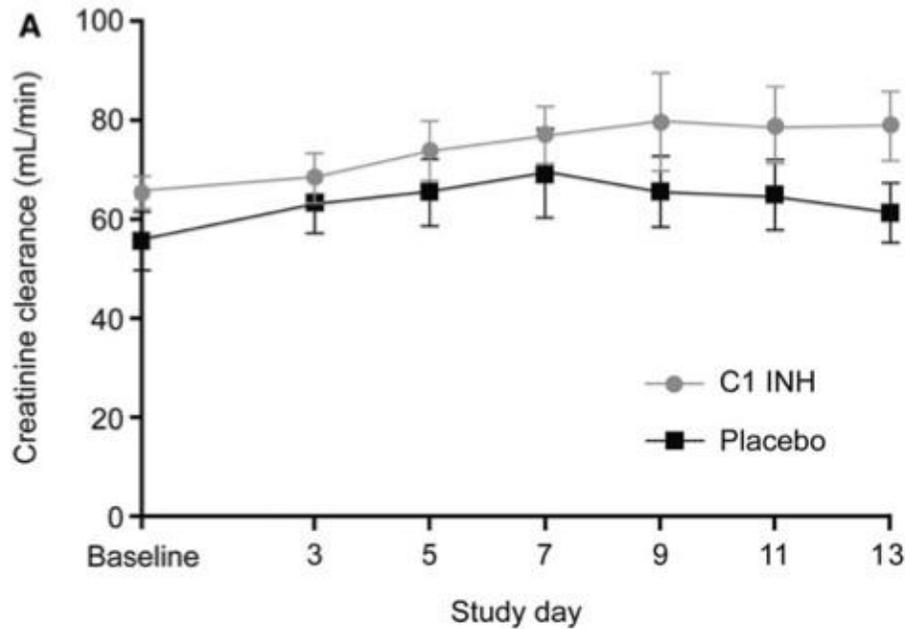
## Plasma-Derived C1 Esterase Inhibitor for Acute Antibody-Mediated Rejection Following Kidney Transplantation: Results of a Randomized Double-Blind Placebo-Controlled Pilot Study

L'ENTRÉE  
DU NOUVEAU  
SAINT-LOUIS

2005  
Nöcke  
HERRENSCHWITZ

# C1 Esterase inhibitor

LA COUR CARP  
DE  
L'HÔPITAL SAINT

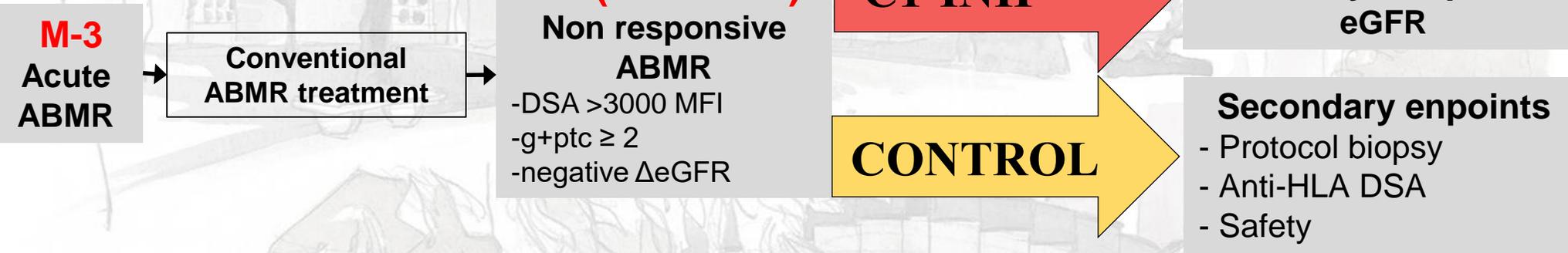


L'ENTRÉE  
DU NOUVEAU  
SAINT-LOUIS

2005  
Nöcke  
HERRENSCHWITZ

# 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

# C1-Inhibitor in resistant ABMR

A LOUË CARP  
DE  
L'HÔPITAL SAINT

**C1-INH (N=6) and control (N=21) groups similar for:**

- Donor characteristics
- Recipients demographics at the time of transplant
- HLA compatibility
- Cold ischemia time
- Immunosuppression

L'ENTRÉE  
DU NOUVEAU  
SAINT-LOUIS

2005  
Noëlle  
HERRENSCHWARTZ

# C1-Inhibitor in resistant ABMR

- No death
- No allograft loss
- 1 SAE: gastrointestinal bleeding
- 1 AE: venous thrombosis of a lower limb at 5 months after inclusion, leading to drug discontinuation

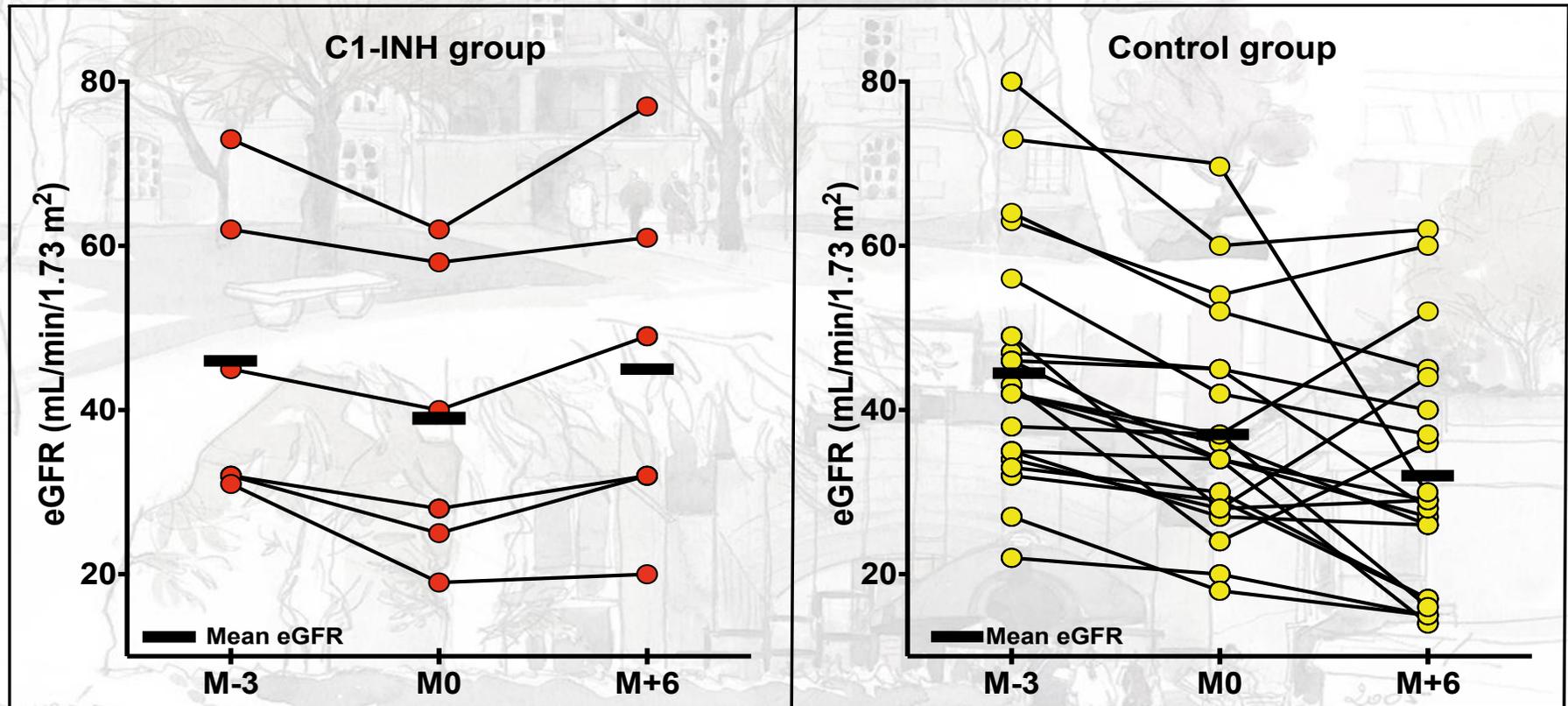
A LOUË CARP  
DE  
L'HÔPITAL SAINT

L'ENTRÉE  
DU NOUVEAU  
SAINT-LOUIS

2005  
Noëlle  
HERRENSCHWARTZ

# C1-Inhibitor in resistant ABMR

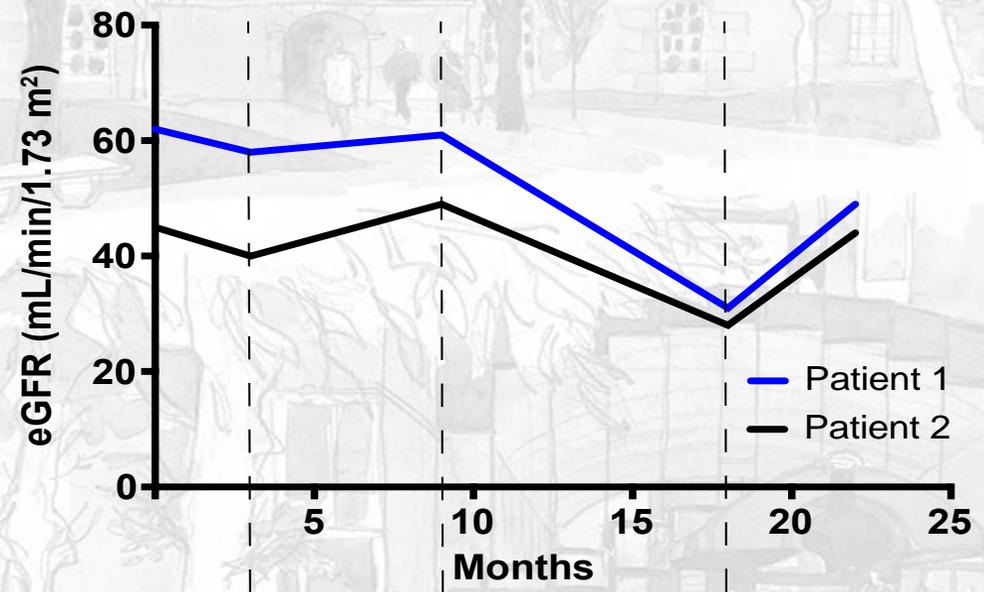
C1-INH treated patients: increased eGFR at M+6 (P=0.03)



# 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



AMR →

SOC    C1-INH  
          IVIG

          IVIG

          C1-INH  
          IVIG

L'ENTRÉE  
DU NOUVEAU  
SAINT-LOUIS

2005  
NÖLLE  
HERRENRECHT

# 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

# As of today....

LA COUR CARP  
DE  
L'HÔPITAL SAINT

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

L'ENTRÉE  
DU NOUVEAU  
SAINT-LOUIS

2005  
Nöcke  
HERRENSCHWOT

# Controlled trials are necessary

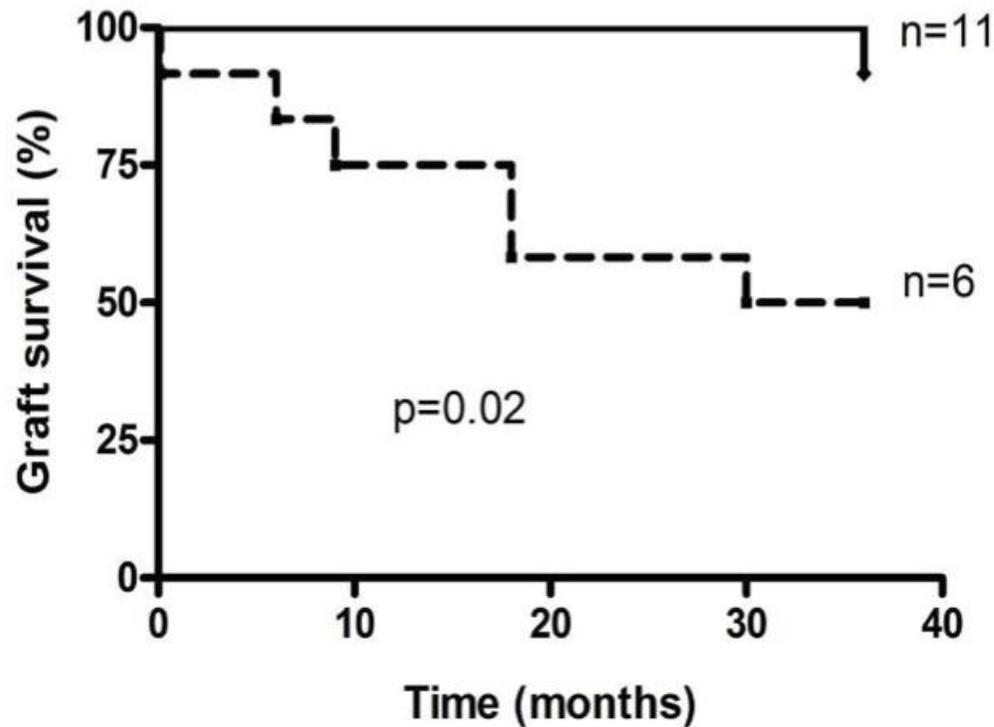
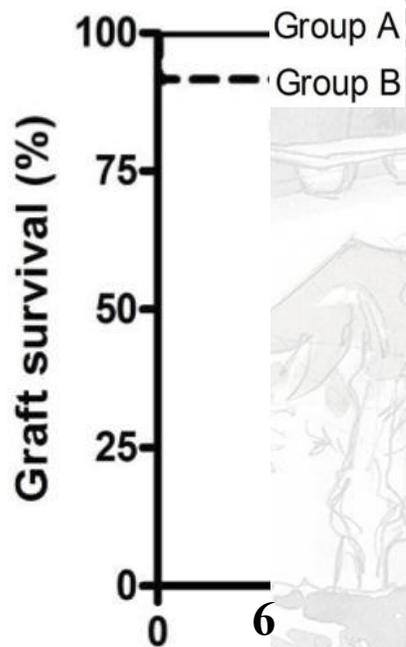
- Long follow-up is mandatory
- Surrogate markers are needed....

L'ENTRÉE  
DU NOUVEAU  
SAINT-LOUIS

2005  
Noëlle  
HERRENSCHWAB

# Long follow-up is necessary

Success or failure of a treatment need a long follow-up



# Surrogate markers

- C4d
- Endats
- DSA

LA COUR CARP  
DE  
L'HÔPITAL SAINT

L'ENTRÉE  
DU NOUVEAU  
SAINT-LOUIS

2005  
Nöcke  
HERRENSCHWOT

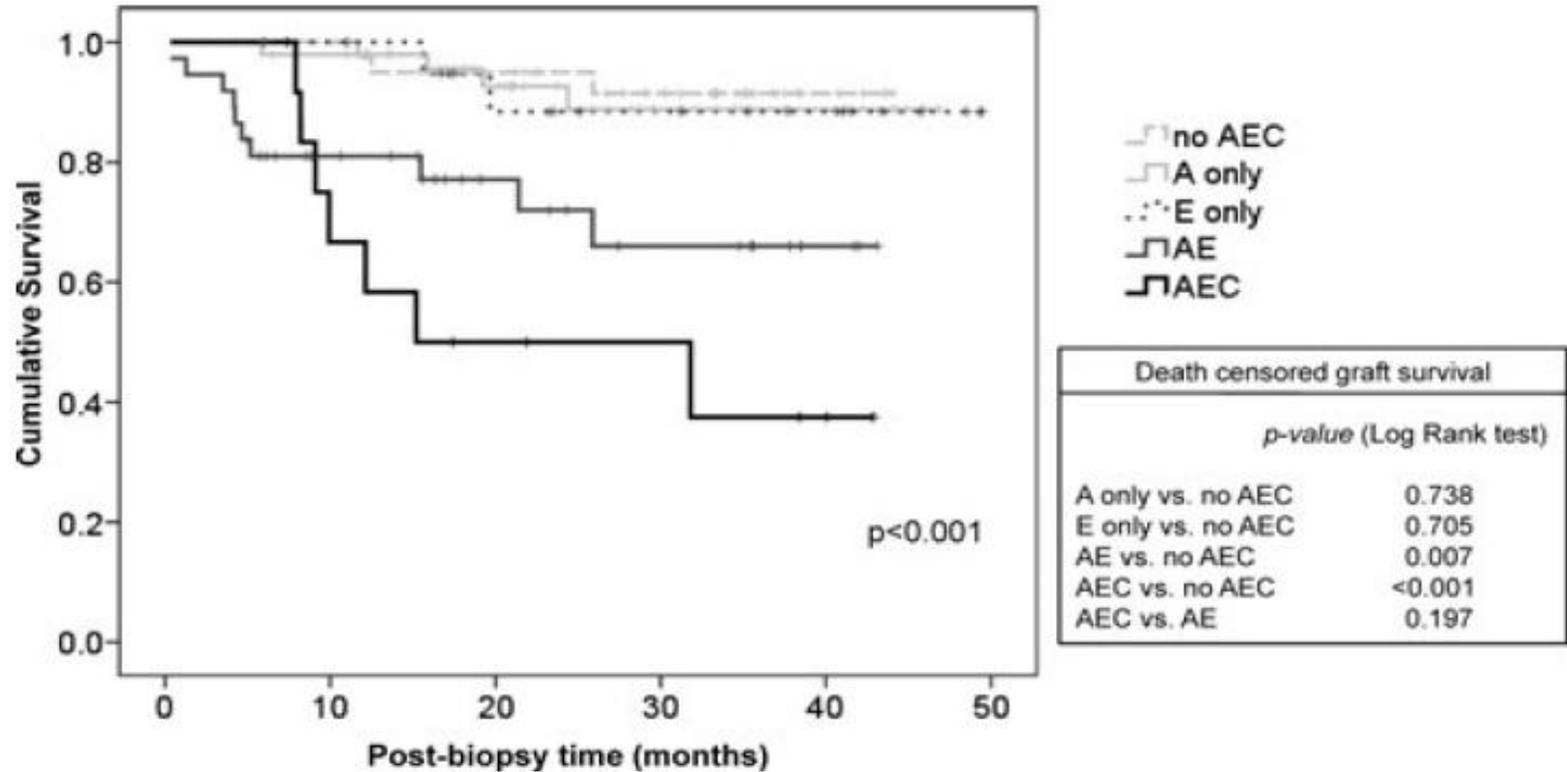
# C4d fluctuates with time in CHR

- C4d<sup>+</sup> AHR → C4d<sup>+</sup> TG (7 y)
- C4d<sup>+</sup> AHR → C4d<sup>-</sup> TG (9 m)
- C4d<sup>+</sup> AHR → C4d<sup>+</sup> TG → C4d<sup>-</sup> TG (18 m)
- C4d<sup>+</sup> TG → C4d<sup>-</sup> TG (6 m)
- C4d<sup>+</sup> TG → C4d<sup>-</sup> TG (9 y)
- C4d<sup>-</sup> TG → C4d<sup>+</sup> TG (8 m)

L'ENTRÉE  
DU NOUVEAU  
SAINT-LOUIS

2005  
Noëlle  
HERRENSCHWAB

# Sis et al, Am J Transplant 9: 2312-2323,



ENDATS + Anti-donor HLA antibody (AE) are associated with reduced graft survival, even in the absence of C4d

I HAVE NOTHING  
FURTHER TO SAY

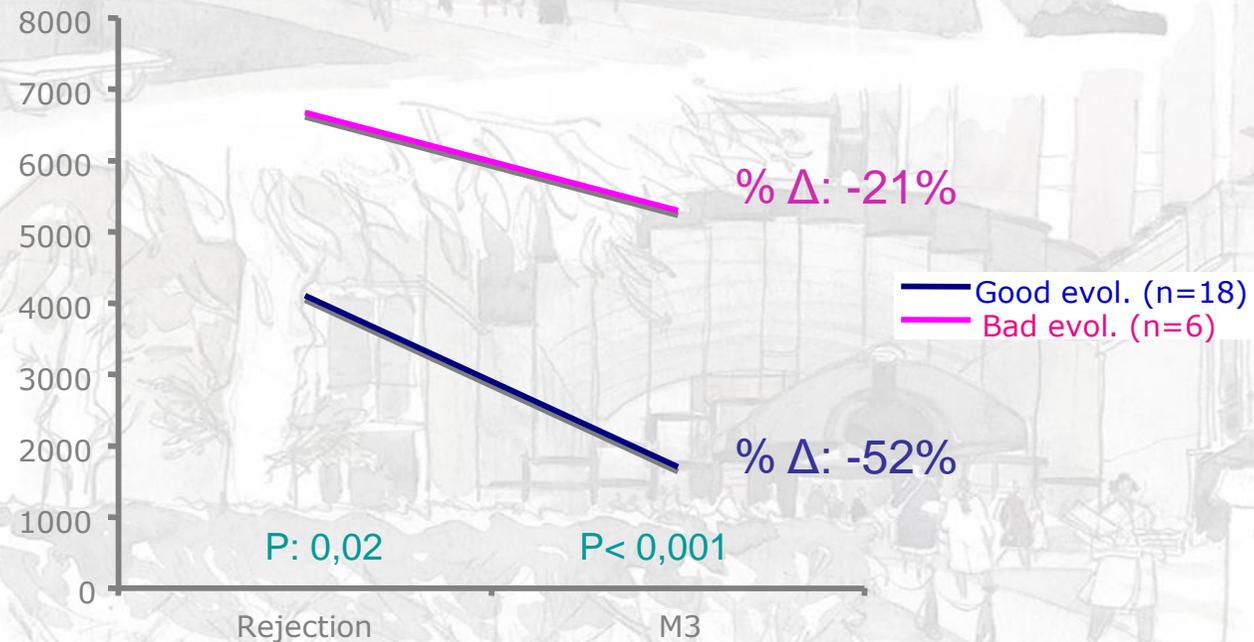
C4d

LA COUR CARP  
DE  
L'HÔPITAL SAINT

# DSA Monitoring is key

The absence of decrease of DSA post-treatment is associated with poor prognosis

24 patients, DSA at rejection and 3 months post TT



L'ENTRÉE  
DU NOUVEAU  
SAINT-LOUIS

2005  
Nöcke  
HERRENSCHWART

LA COUR CARP  
DE  
L'HÔPITAL SAINT

# DSA Monitoring is key

The absence of a fall of at least 50% of DSA post-treatment is associated with poor prognosis

16 patients, DSA 14 days post diagnostic biopsy

	More than 50% decrease of DSA	Less than 50% decrease of DSA
Rej. reversal (creat)	90%	83%
G.S. 2 years	100%	63%
G.S. 4 years	100%	20%

L'ENTRÉE  
DU NOUVEAU  
SAINT-LOUIS

2005  
Nöcke  
HERRENSCHWART

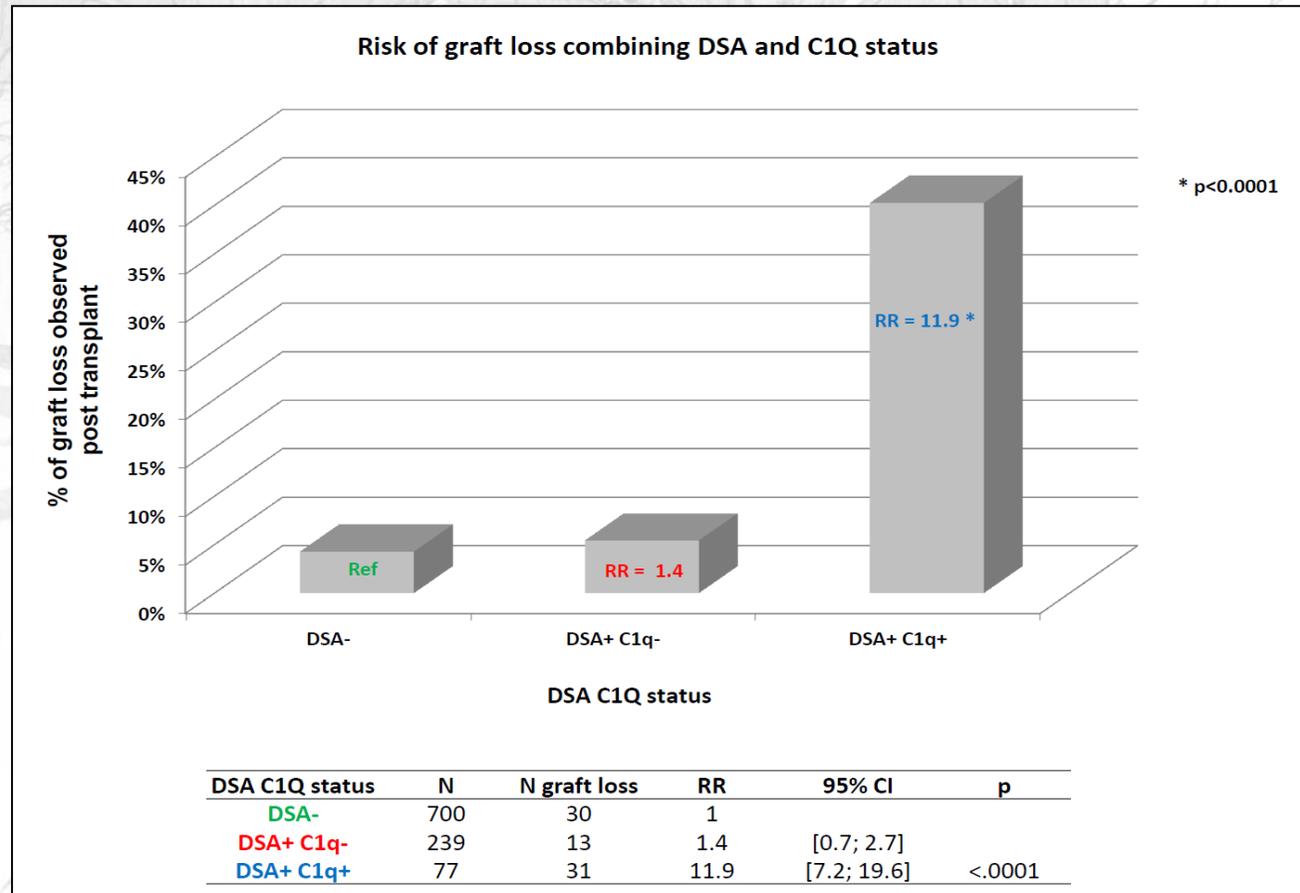
# DSA Monitoring is key

**We need better Antibody assays....**

Refining the classical Luminex assay: EDTA/Titration  
Complement binding capabilities  
Ig subclasses

# DSA Monitoring is key

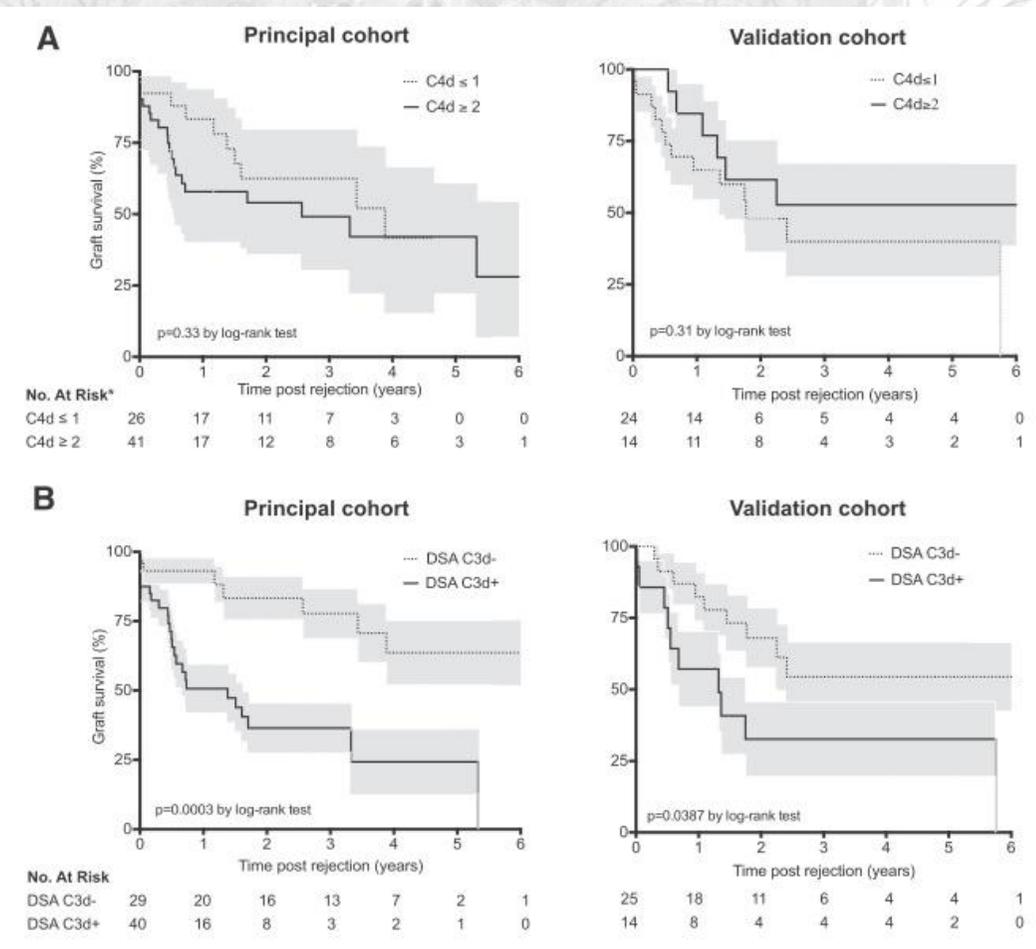
## Complement binding assays



**DSA+ / C1q+ = Higher risk of graft loss**

LA COUR CARP  
DE  
L'HÔPITAL SAINT

# C3d binding assay



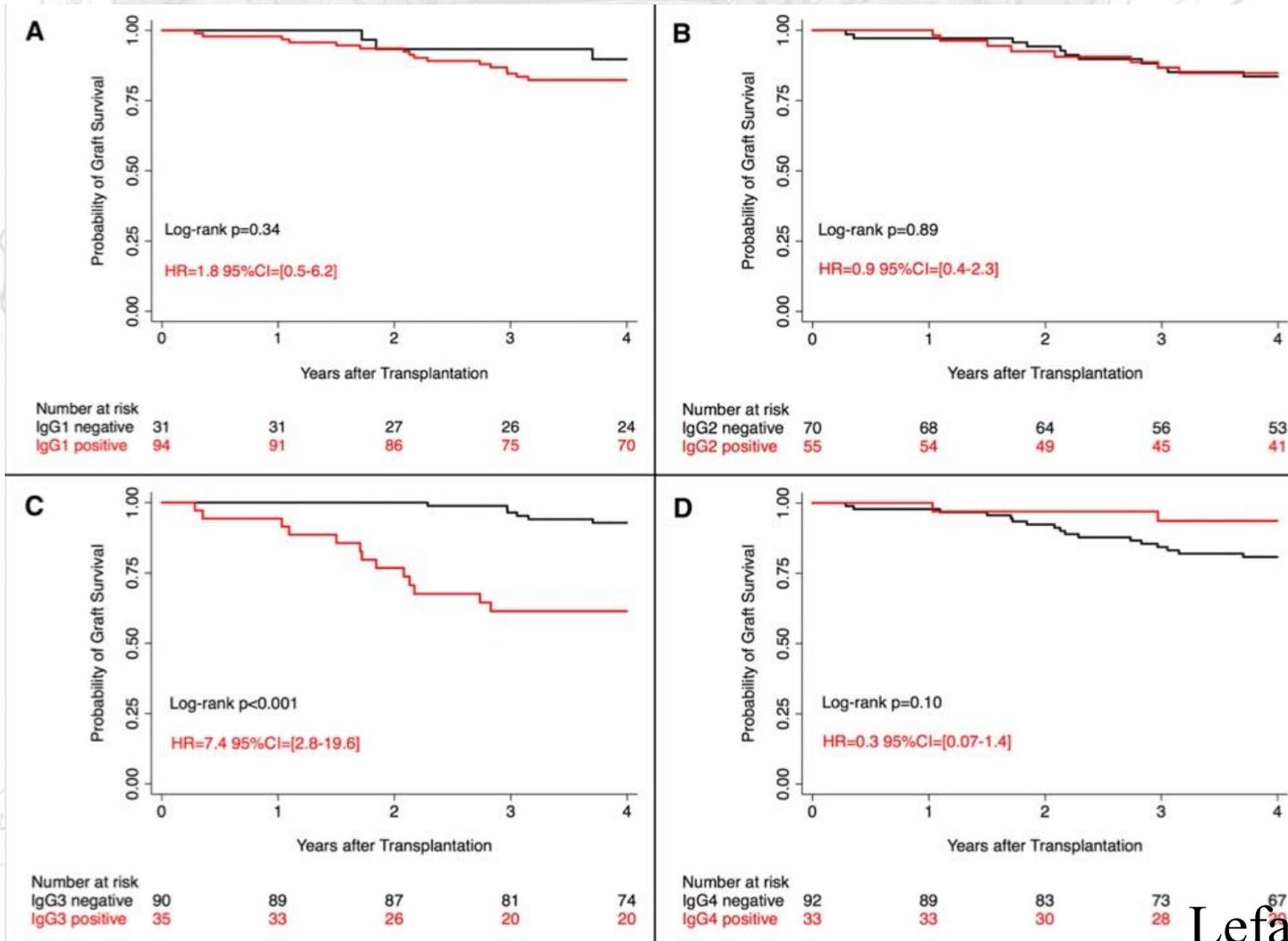
L'ENTRÉE  
DU NOUVEAU  
SAINT-LOUIS



# DSA Monitoring is key

## DSA subclass analysis

LA COUR CARP  
DE  
L'HÔPITAL SAINT



2005  
Nöcke  
HERRENSTADT

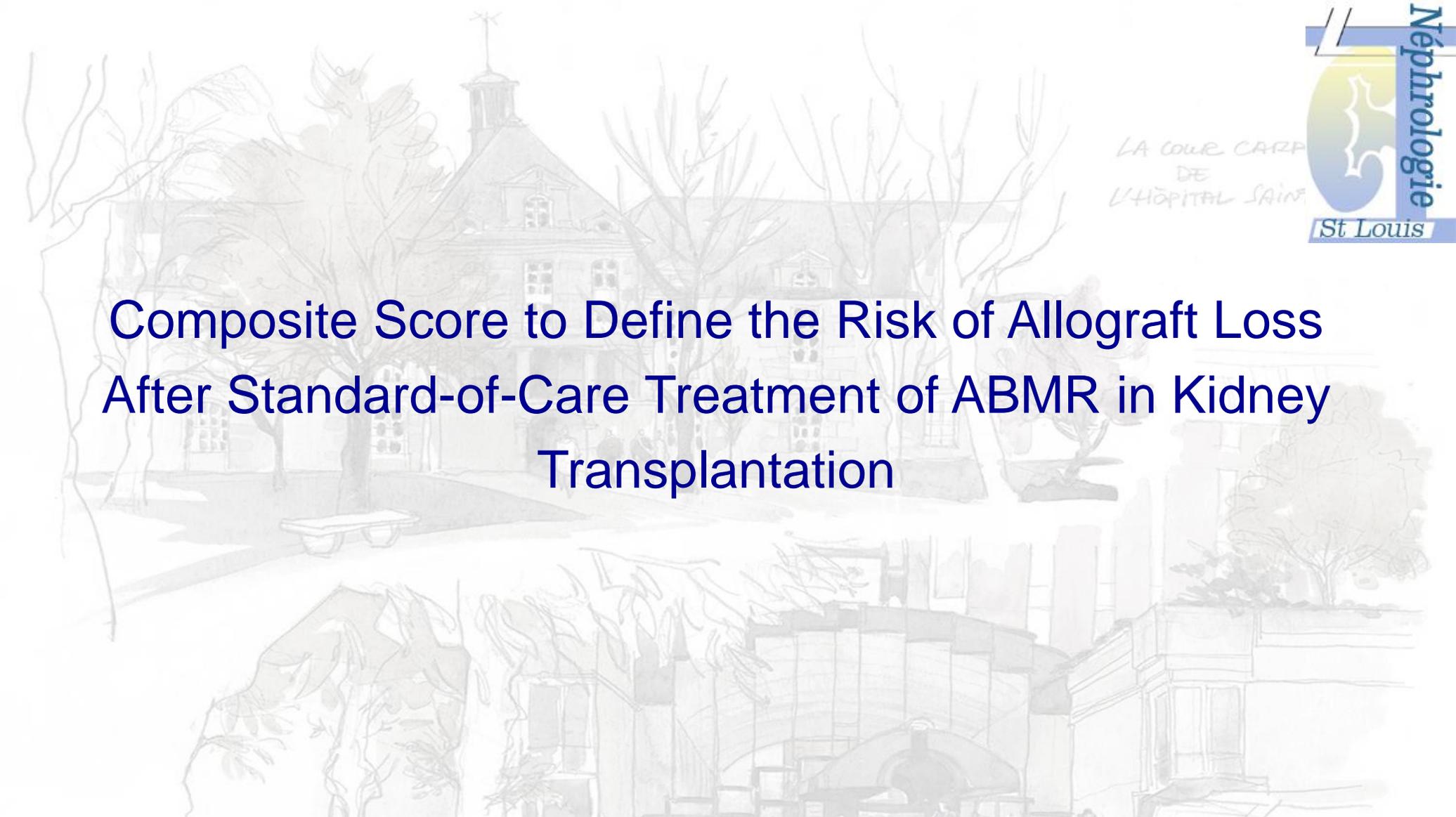
LA COUR CARP  
DE  
L'HÔPITAL SAINT

# In conclusion...

- Short term apparent success....
- We need robust biomarkers

L'ENTRÉE  
DU NOUVEAU  
SAINT-LOUIS

2005  
Nöcke  
HERRENSCHWOT



# 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](http://paristransplantgroup.org)



# HYPOTHESIS

LA COUR CARP  
DE  
L'HÔPITAL SAINT

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

L'ENTRÉE  
DU NOUVEAU  
SAINT-LOUIS



**Paris Transplant Group**  
Kidney, Heart & Lung

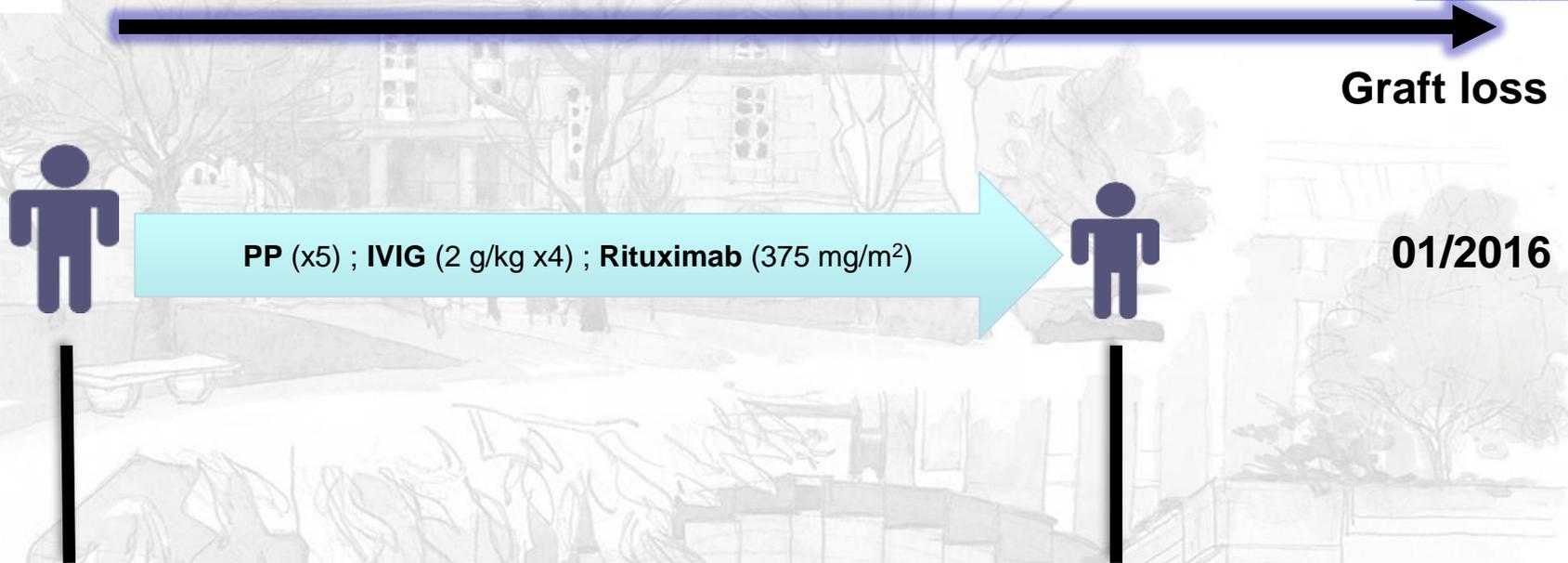
2005  
Nöcke  
HERRENSCHWART

# STUDY DESIGN

Prospective observational study 2008-2013

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

LA COUR CARP  
DE  
L'HÔPITAL SAINT



## 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

# INTEGRATIVE MODELING FOR RISK PREDICTION ACCORDING TO RESPONSE TO THERAPY

LA COUR CARP  
DE  
L'HÔPITAL SAINT

**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

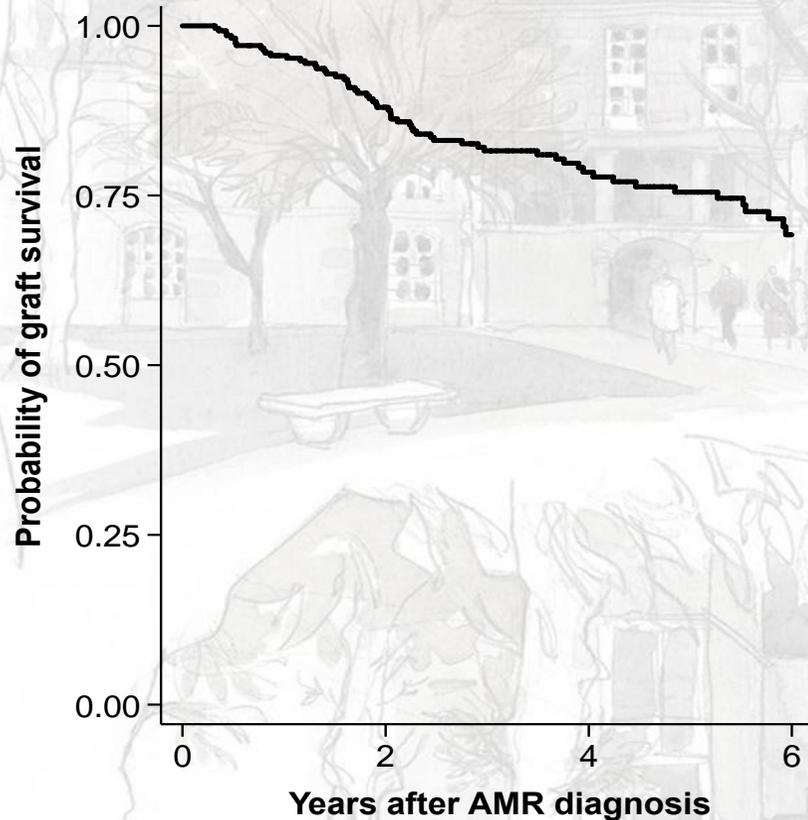
**Kidney  
allograft  
loss**



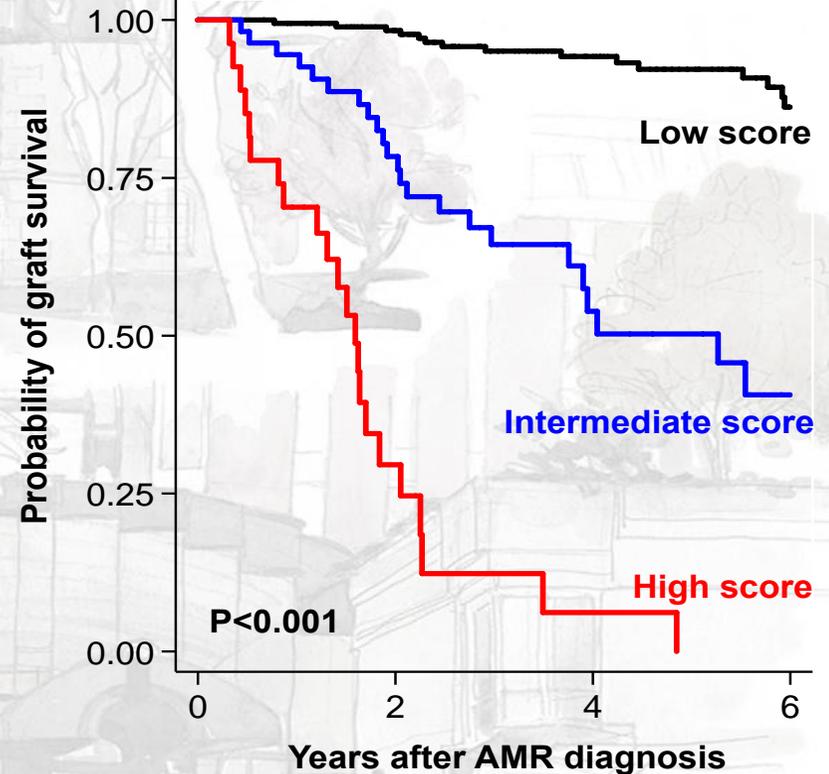
Noche  
HERRENRECHT

# STRATIFICATION OF GRAFT SURVIVAL AFTER ABMR THERAPY BASED ON PROGNOSTIC SCORING

## Overall graft survival



## Score-stratified graft survival



Number at risk 278      208      116      52

Number at risk

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



LA COUR CARRÉE  
DE  
L'HÔPITAL SAINT-LOUIS

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



H E G P