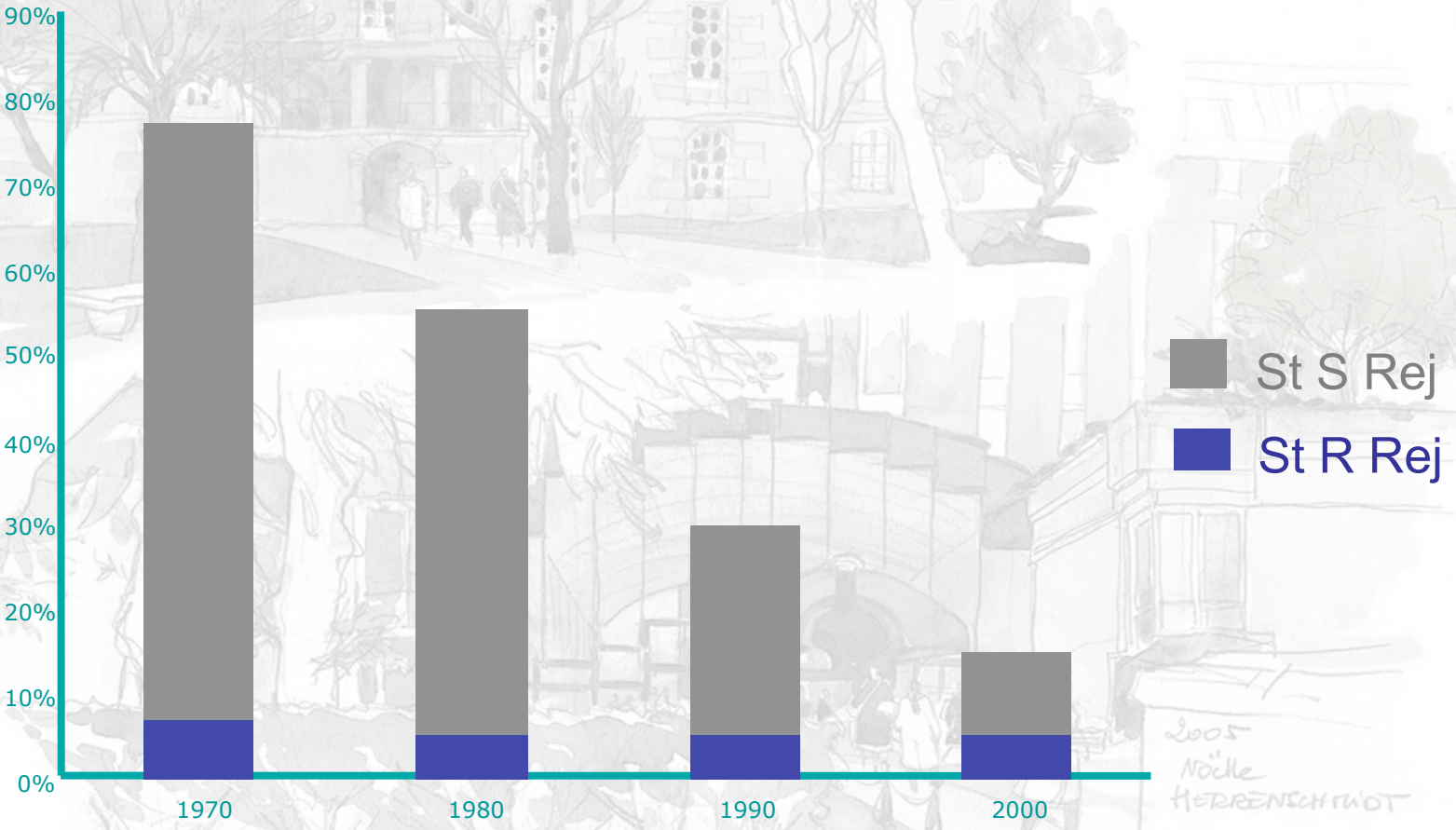
Update on the treatment of Antibody-Mediated Rejections

11 CONGRESO Societat Catalana de Trasplantament
Barcelona
16 - 18 marzo 2011

D. Glotz

The changing picture of Rejections



Antibody Mediated Rejection

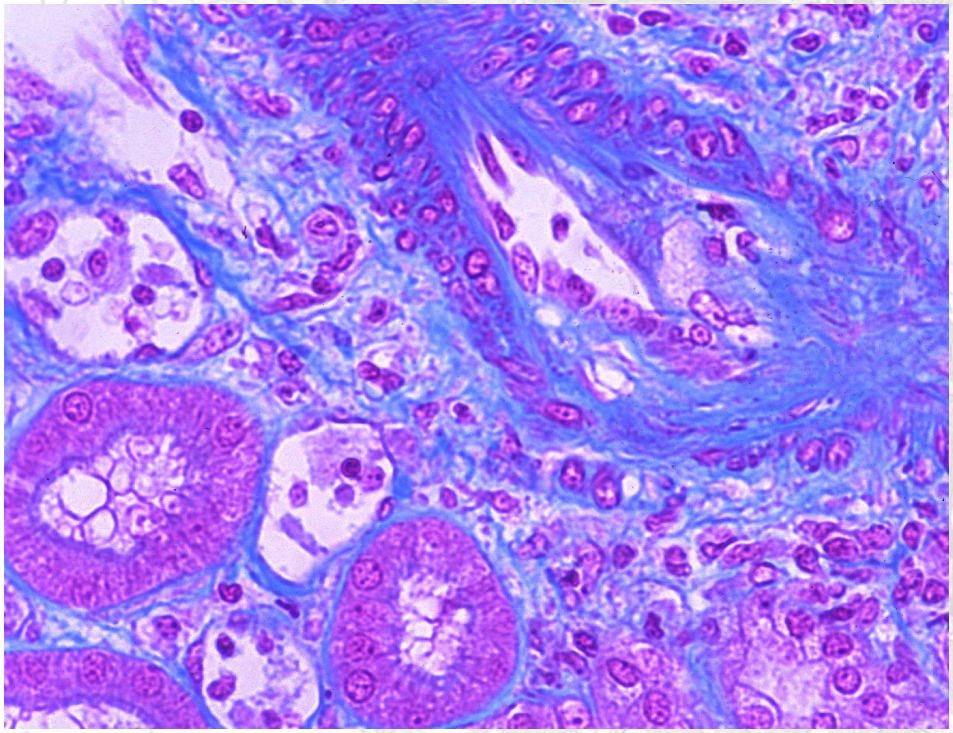
Kidney

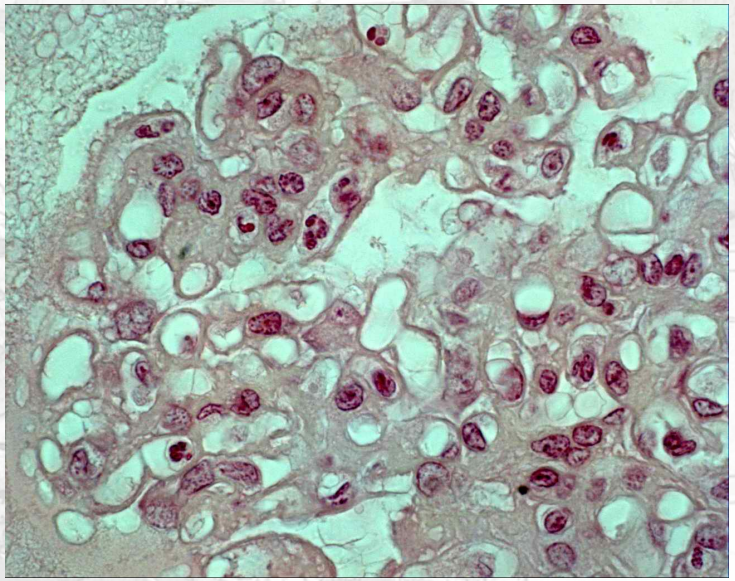
- Histological Lesions
  - ATN
  - CPT, glom, thromboses
  - Arteritis
- C4d positive
- Donor specific Antibodies

Racusen AJT 2003

Antibody Mediated Rejection

Kidney



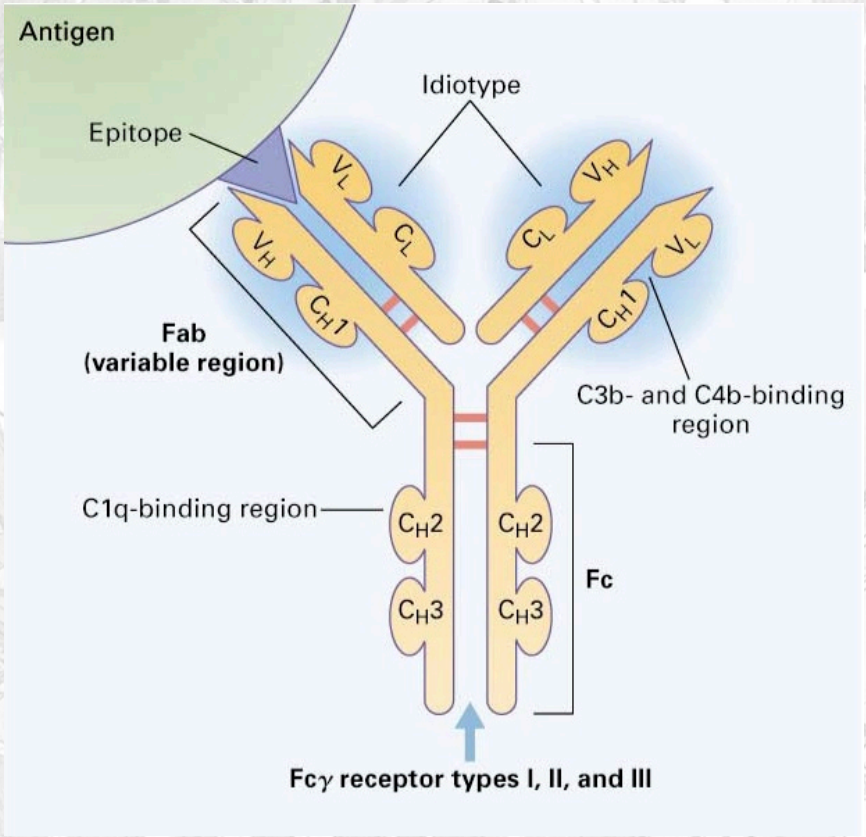


D. Nochy

C4d positivity in various Tx centers

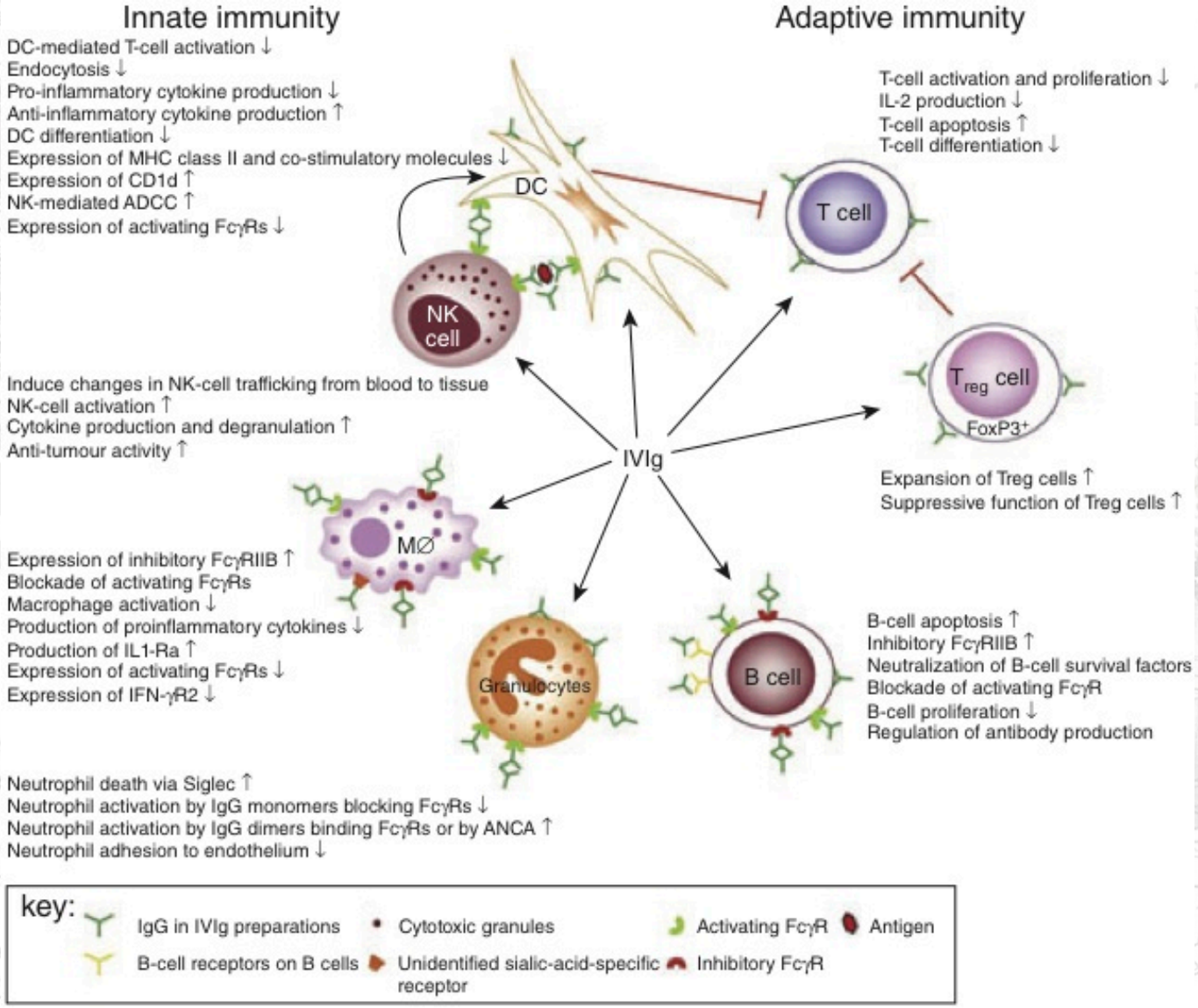
Authors	Biopsies/Pts	indication	C4d+ (% Pt)
Feucht 1993	93/93	Renal failure	46%
Lederer 2001	310/218	Renal failure	46%-72%
Regele 2001	102/61	Renal failure	51%
Bohmig 2002	113/58	Renal failure	28%
Nickeleit 2002	398/265	Renal failure	35%
Herzenberg 02	126/93	Rejection	37%
Mauiyyedi 02	67/67	Renal failure	30%
Regele 2002	213/213	Renal failure	34%
Sund 2003	37/37	Protocol	30%
Koo 2004	96/48	Protocol	13%

Prophylaxis of AMR: IVIg



Kazatchkine NEJM 2001

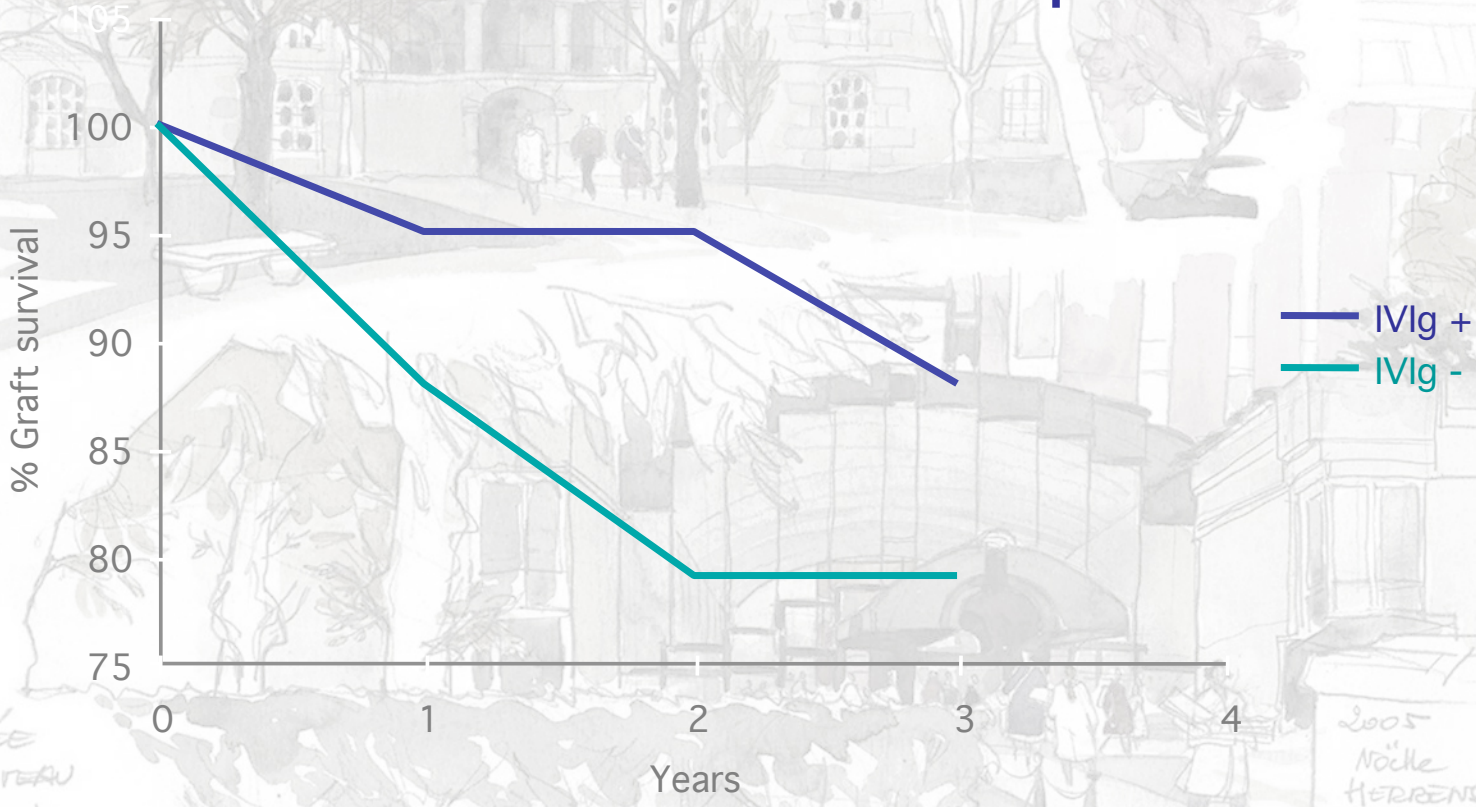
Mechanisms of action of IVIg



Durandy Clin Exp Immunol 2009

IVIg at the time of Transplantation

Pediatric CMV recipients



Bunchman Clin Transpl 1997

IVIg at the time of Transplantation

Cadaveric re-transplants

- 41 patients
- Immunized or not
- Quadruple IS
- IVIg 0,4 gr/Kg for 5 days

Peraldi Transpl 1996

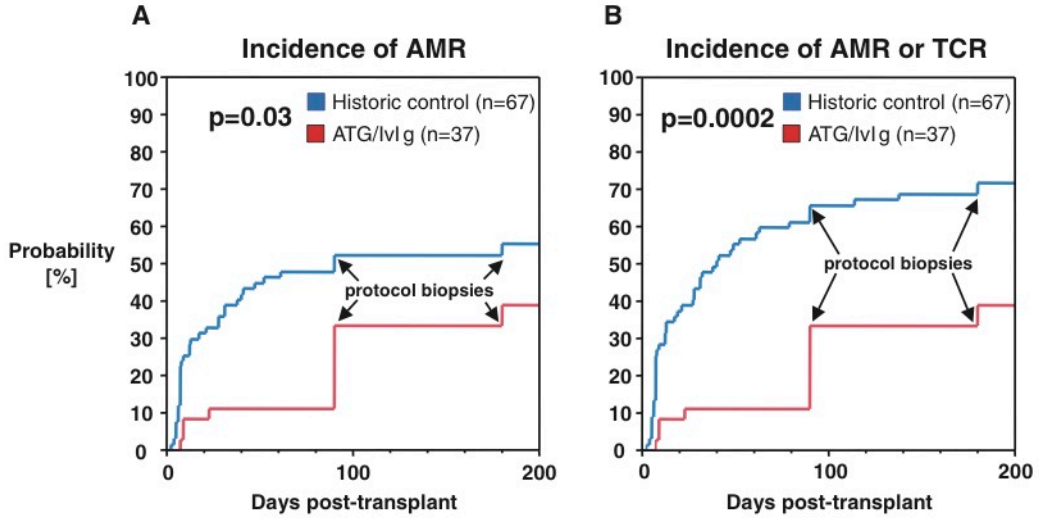
IVIg at the time of Transplantation

Cadaveric re-transplants

Peraldi Transpl 1996

Prophylaxis of AMR

ATG/IVIg in DSA +, XM - pts

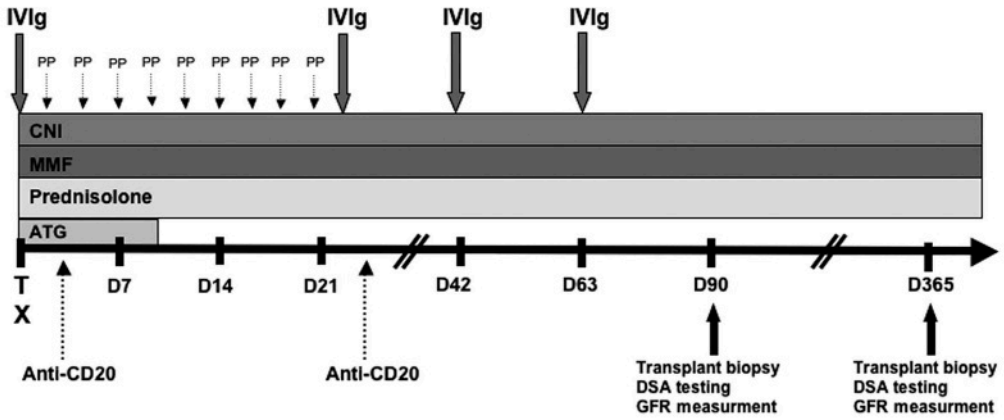


Cumulative strength of DSA [MFI]*			
Median (range)	6494 (524–36 715)	2287 (543–26 537)	<0.0001
Cumulative strength of DSA, grouped			
<2000 MFI, n (%)	10 (15)	16 (43)	
2000–5000 MFI, n (%)	15 (22)	12 32)	0.001
5000–10 000 MFI, n (%)	16 (24)	4 (11)	
>10 000 MFI, n (%)	26 (39)	5 (14)	
Known presensitizing events**			
Prior transplants, n (%)	30 (45)	18 (49)	0.84
Blood transfusions, n (%)	22 (33)	21 (57)	0.02
Pregnancies, n (%)	25 (37)	17 (46)	0.41
Induction therapy			
None, n (%)	35 (52)	n/a	
Basiliximab, n (%)	26 (39)	n/a	
Daclizumab, n (%)	6 (9)	n/a	
ATG/Ivlg, n (%)	n/a	37 (100)	

Bächler AJT 2010

Prophylaxis of AMR

ATG/IVIg vs ATG/IVIg/Ritux/PP



Peak serum DSA MFI			NS
Class I or II DSA_{max} MFI	8747±779	8837±1198	NS
Class I MFI_{max} DSA	5314±782	8427±1052	0.04
Class II MFI_{max} DSA	4591±1018	3002±1557	NS
% positive class I or II DSA	36/36 (100)	18/18 (100)	NS
Day 0 serum DSA MFI			
Class I or II DSA_{max} MFI	5314±807	5150±1477	NS
Class I MFI_{max} DSA	2457±634	4936±1233	0.04
Class II MFI_{max} DSA	3286±824	2831±1216	NS
% Positive class I or II DSA	26/27 (96.2)	14/14 (100)	NS
Outcome			
Acute humoral rejection	7 (19.6)	3 (16.6)	NS
Patient death at last follow-up	1 (2.7)	1 (5.5)	—
Graft lost at last follow-up	4 (11.1)	2 (11.1)	—
Mean follow-up	35.4±16.7	19.5±9.3	0.0005

Loupy Transpl 2010

After transplantation

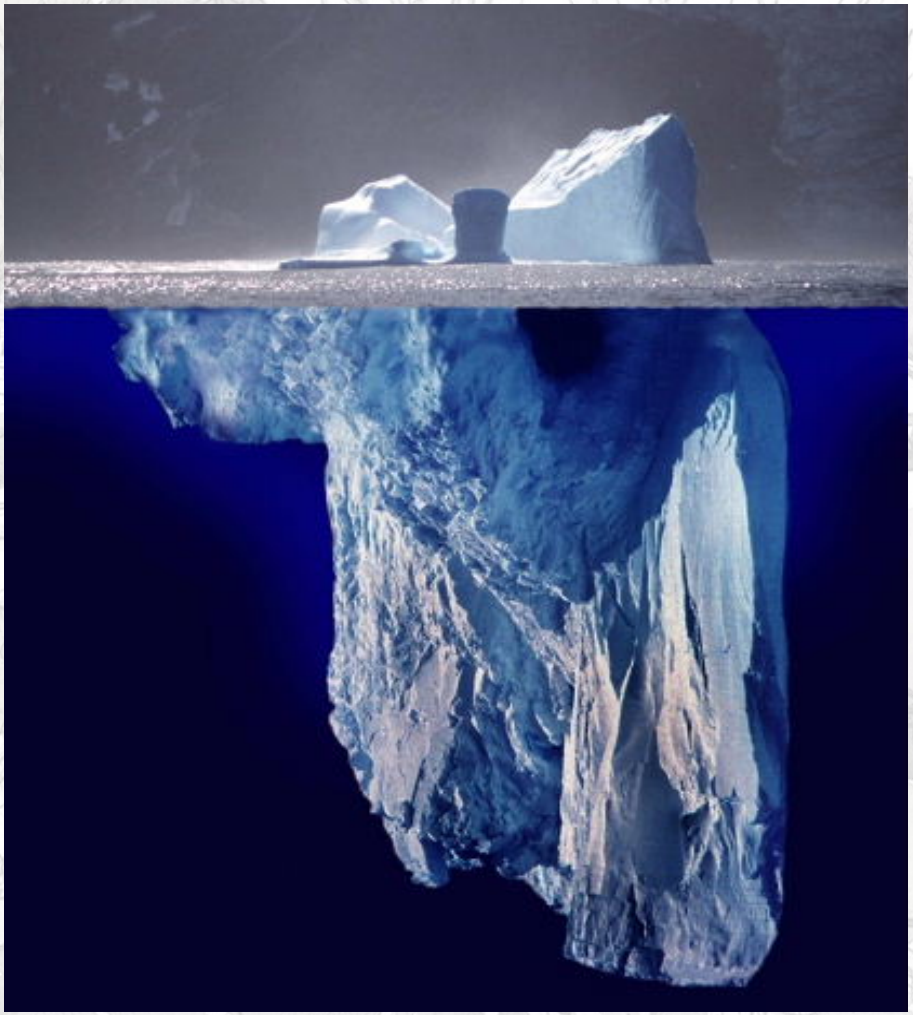
Treatment of established rejection

- Acute AbMR
- Sub-clinical AbMR
- Chronic AbMR

Subclinical-AMR

Function

Pathology

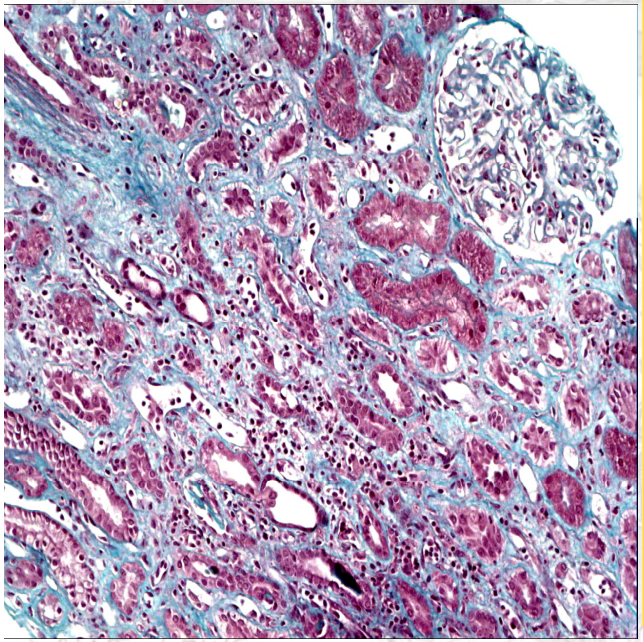


Usefulness of Abs/screening biopsies+++

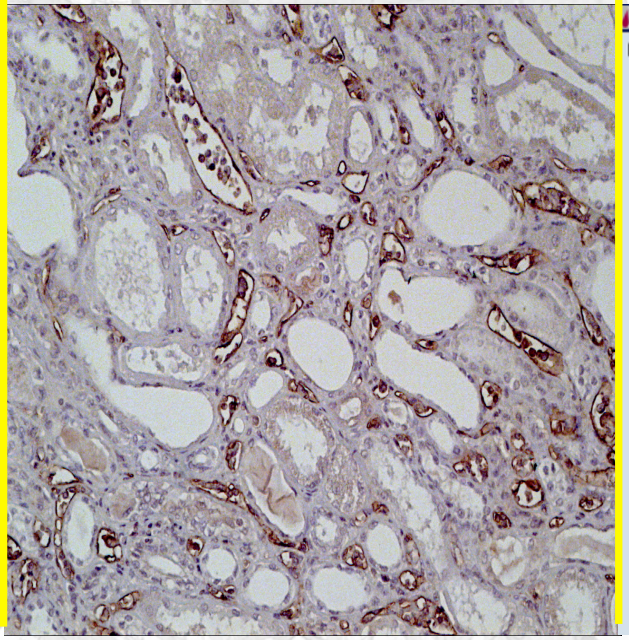
Subclinical-AMR definition

Patient in a steady state: **Stable GFR**

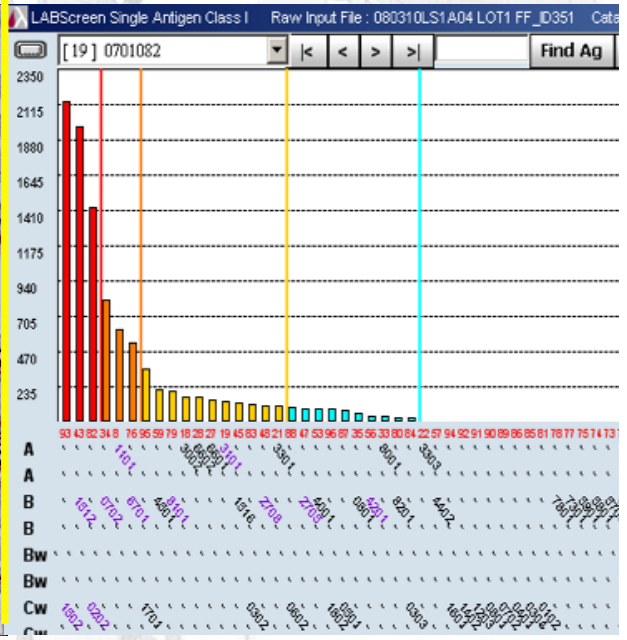
Evidence for Ab injury **glomerulitis + / PTC+**



Evidence for Ab action in PTC: **C4d+**



Evidence for serologic Ab: **DSA+**



Gloor et al; Haas et al; Lerut et al

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

High dose IVIg

→ *Jordan SC et al., Transplantation 1998*

- 10 patients with severe AR / 4 DSA+
- 100% response short term
- fall of anti-HLA Abs titers

→ *Luke PP et al., Transplantation 2001*

- 17 patients
- AR aux steroid- resistant / anti-lymphocyte Abs
- Patients Survival 18 months : 94%
- Graft Survival 18 months : 71%

→ *H.E.G.P./Saint-Louis Lefaucheur AJT 2007*

- 71,5% success, 1 death
- Mean Follow-up : 30 ± 20 months
- SCr end of FU : 187 µmol/L

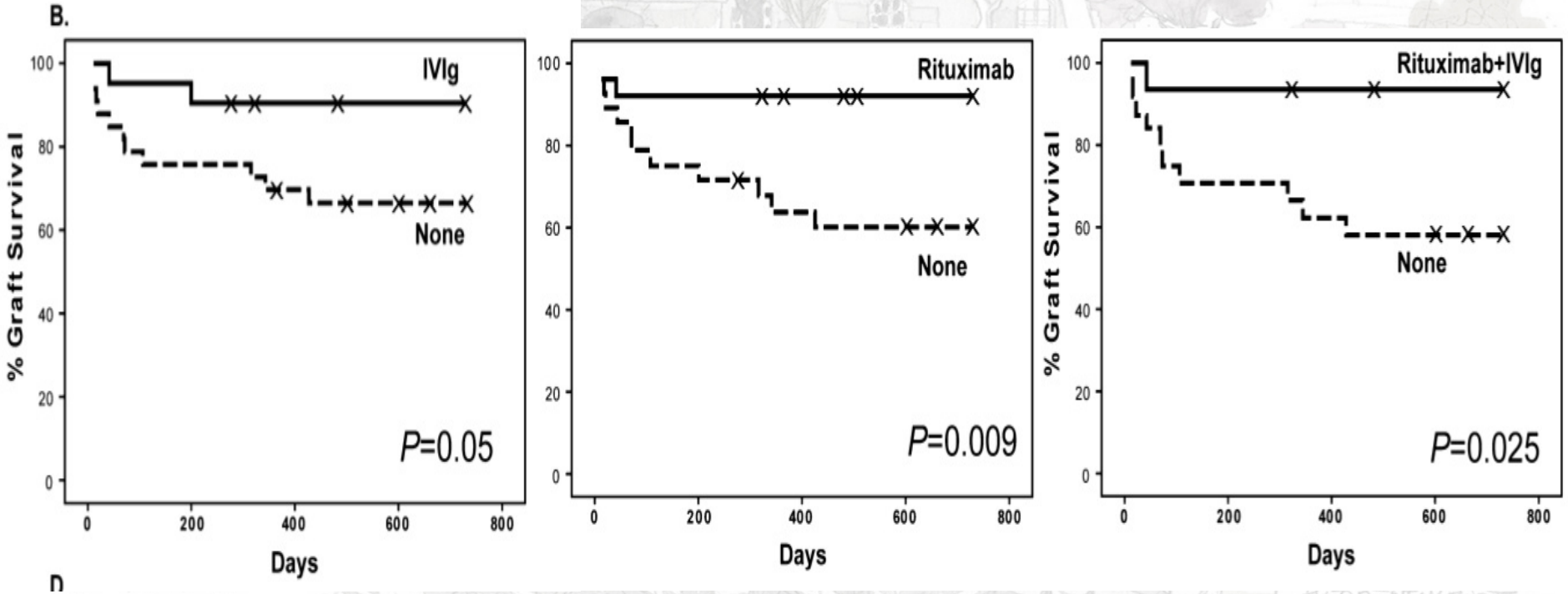
Antibody Mediated Rejection Treatment

IVIg/PP treatment

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

Rocha, Transpl 2003

Impact of a single agent difficult to juge..



Kapotzas, Clin Tx 2008

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

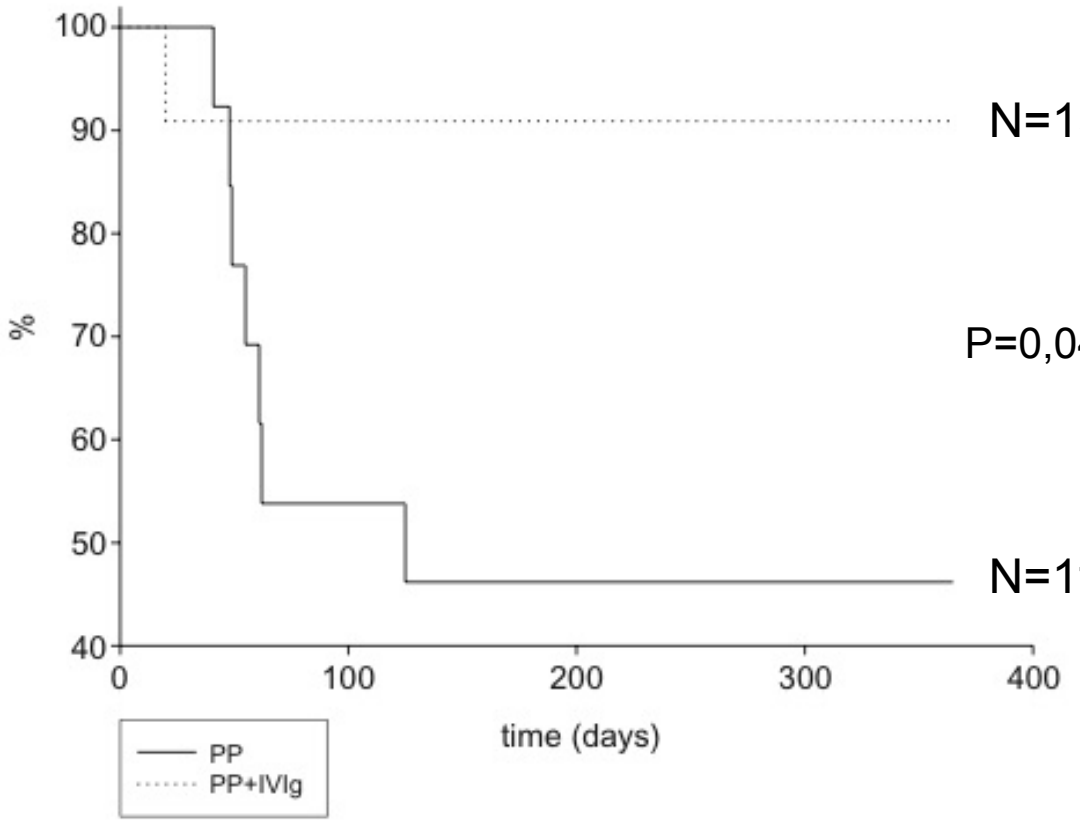
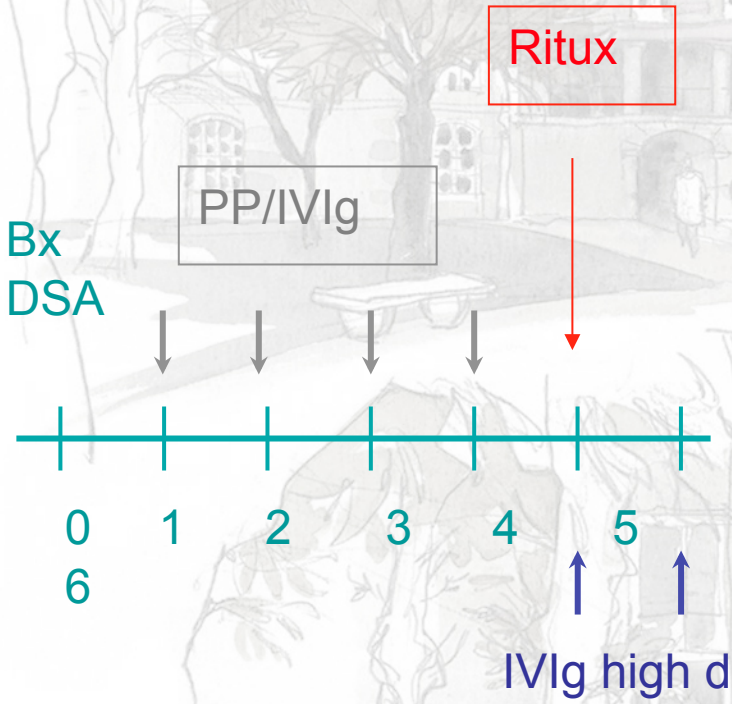


FIG. 1. Graft survival. Patients receiving the plasmapheresis (PP) and intravenous immunoglobulin (IVIg) combination had better one-year graft survival than those treated using only PP. $P = 0.044$.

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

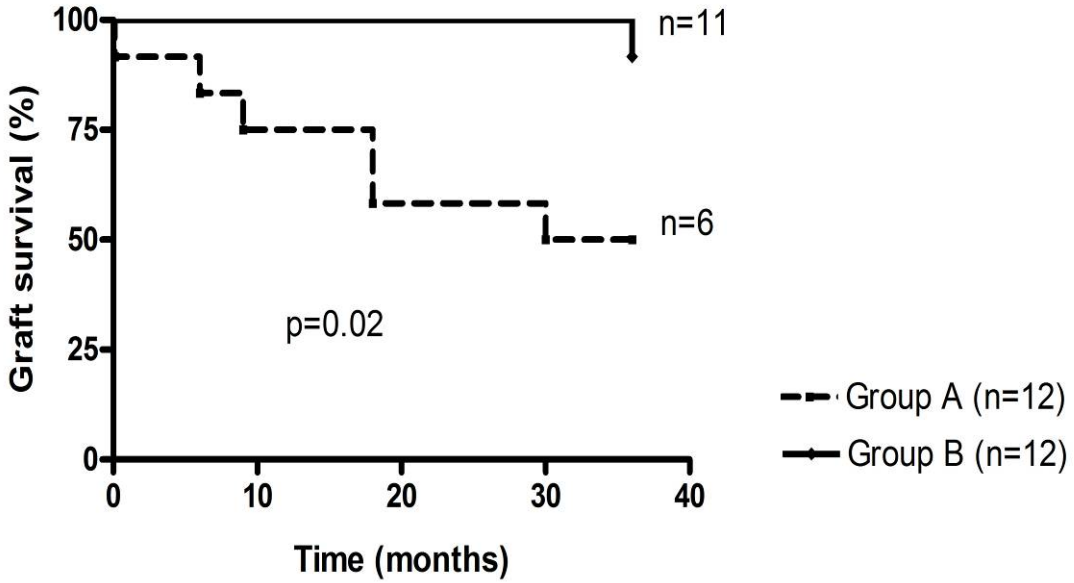
Comparison of Combination Plasmapheresis/IVIg/anti-CD20 versus High-Dose IVIg in the Treatment of AMR

- **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

Kaplan Meier plot of graft survival in patients with AMR according to treatment type

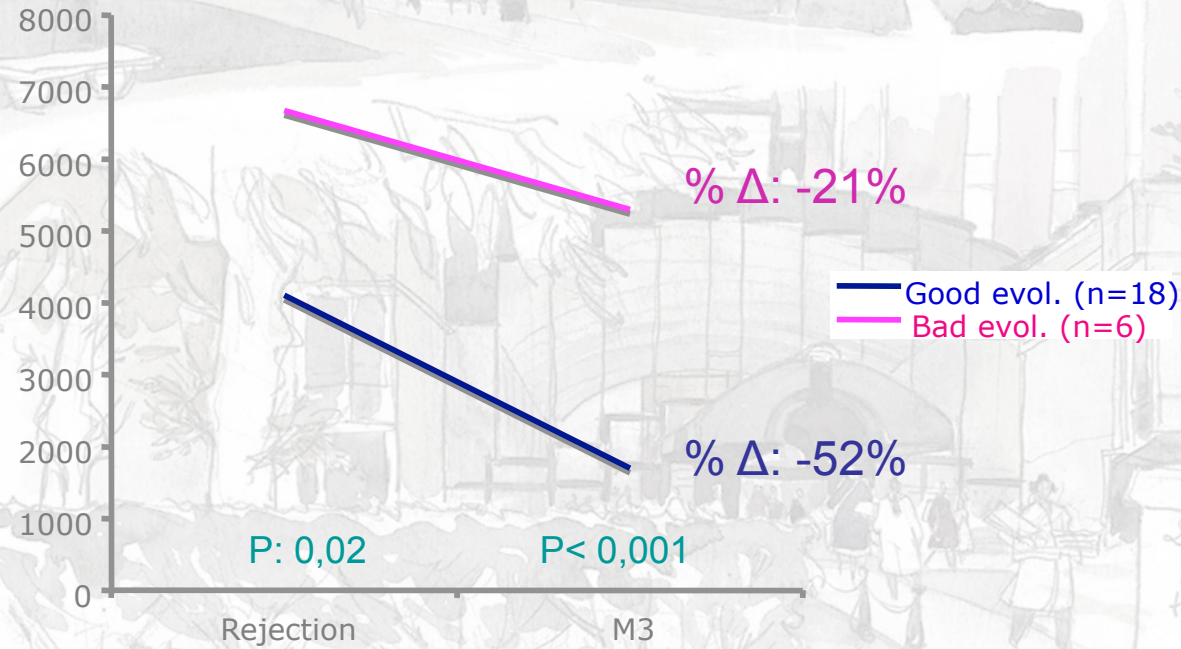


Lefaucheur, A.J.T. 2009

DSA Monitoring is key

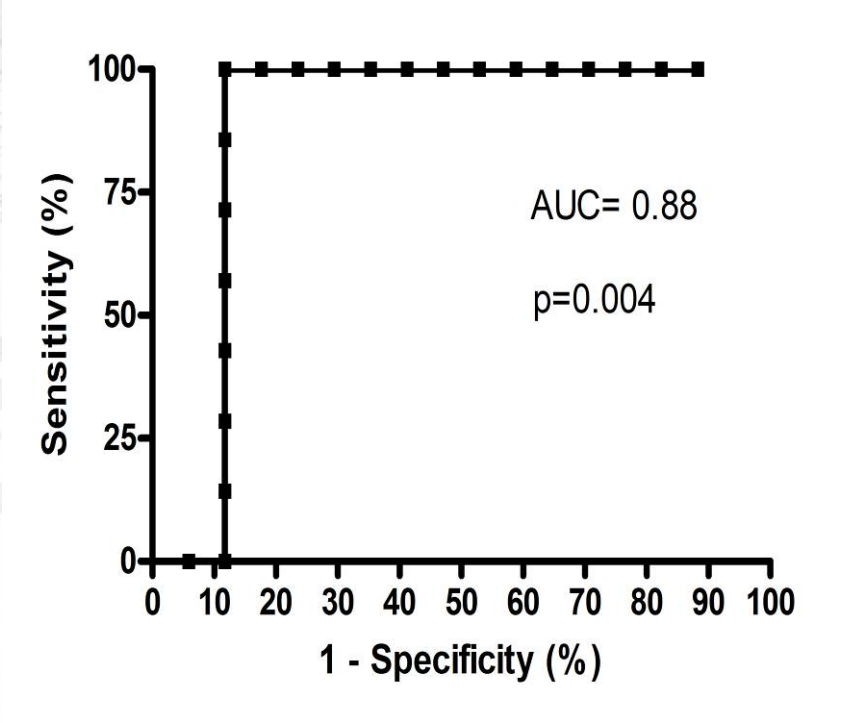
The absence of decrease of DSA post-treatment is associated with poor prognosis

24 patients, DSA at rejection and 3 months post TT



Lefaucheur, A.J.T. 2009

High levels of DSA post-treatment are associated with a higher risk of graft loss



MFI max > 5000
Se 100%
Sp 77.8%

Receiver operating characteristic (ROC) curve for the MFImax of DSAs detected 3 mo post-AMR associated with GFR ≤ 15 mL/min/1.73m2 at 36 months post-AMR.

DSA Monitoring is key

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

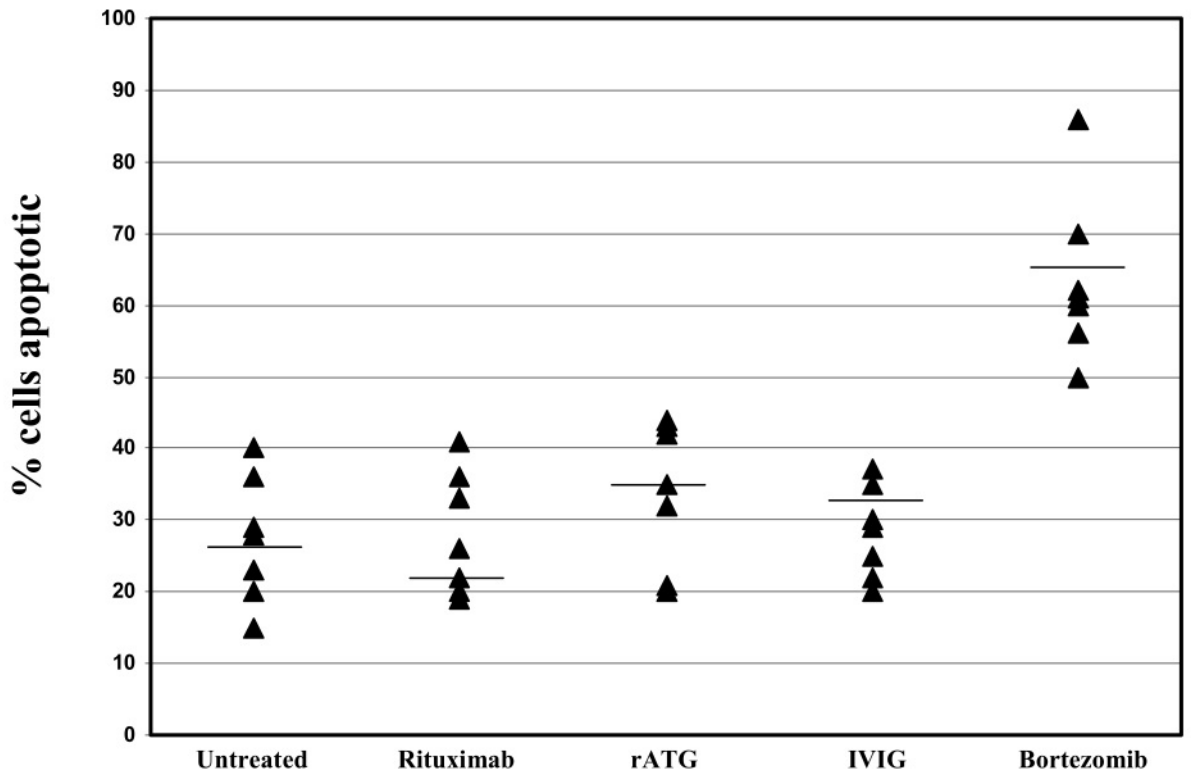
16 patients, DSA 14 days post diagnostic biopsy

	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%

Everly WTC 2008

Bortezomid

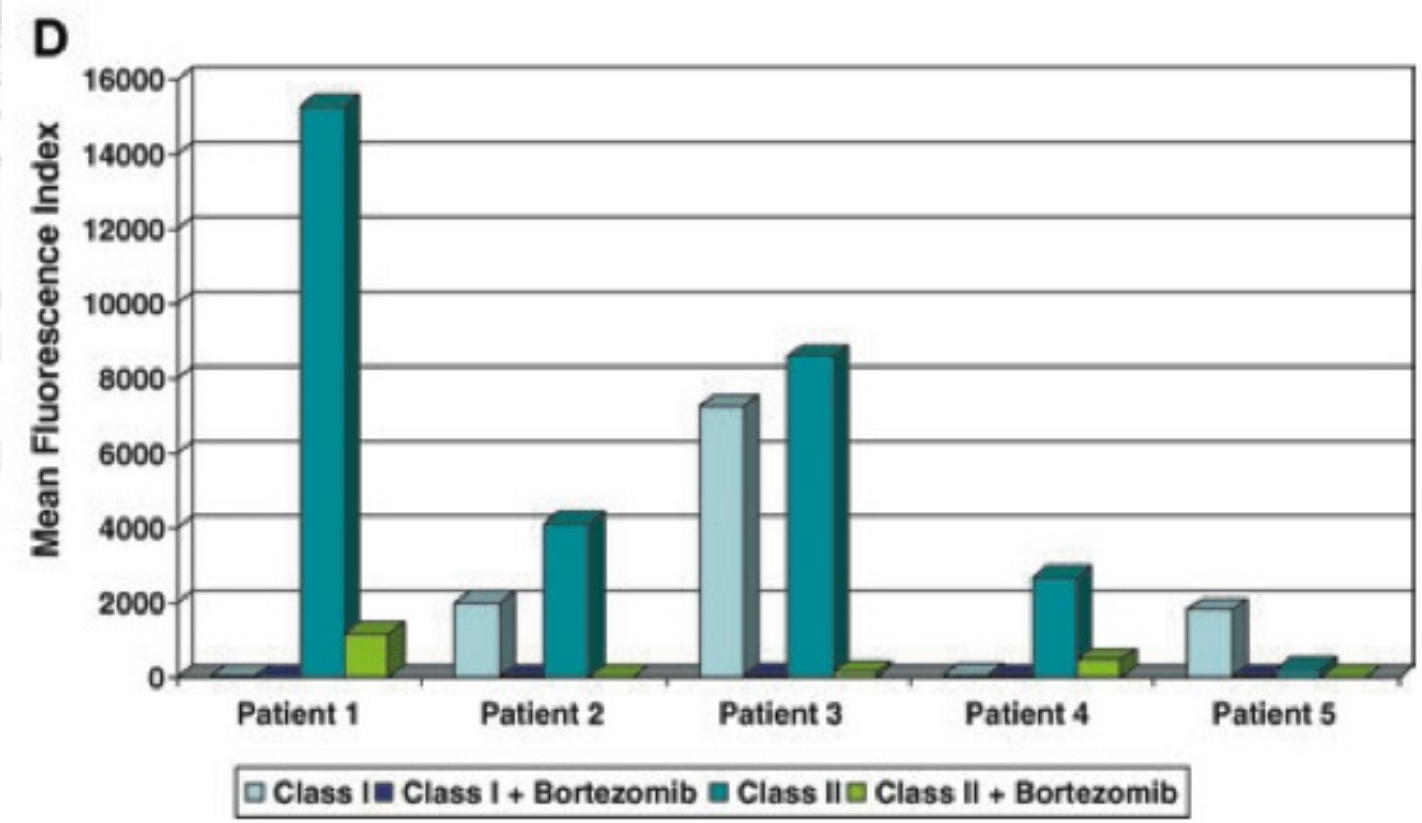
In vitro….



Perry, AJT 2009

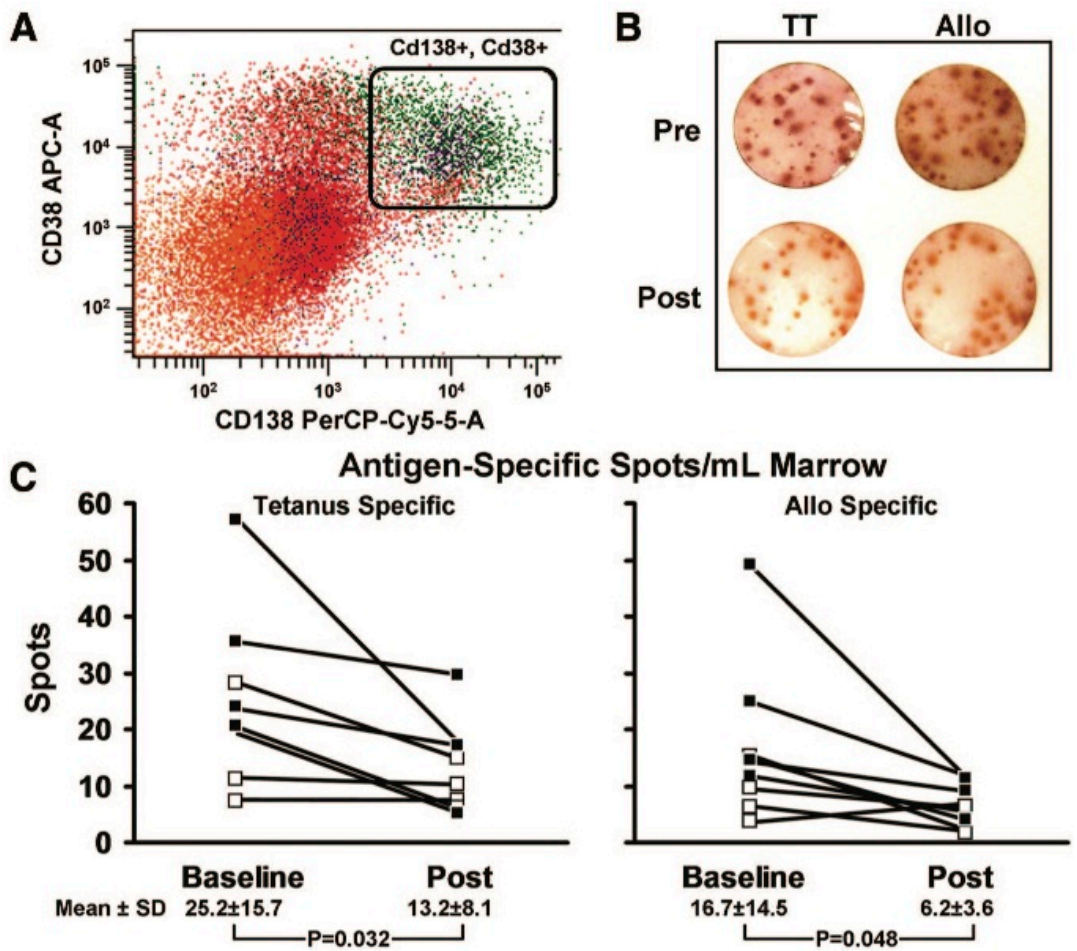
Bortezomid

In vitro….



Bortezomid

In vitro….



Diwan, transpl 2011

Bortezomid

In vivo....

	Bortezomib						Control			
Sl no	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

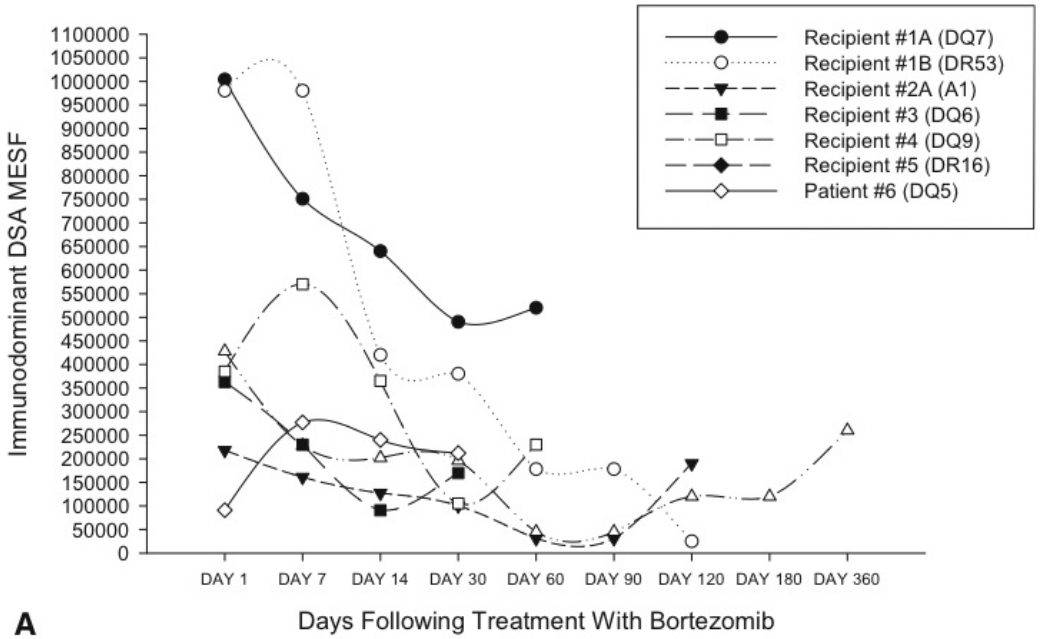
(a) Similar numbers of plasma exchanges were performed in the bortezomib-treated patients compared with the control group, $P=0.9$. (b) Bortezomib treatment before plasma exchange resulted in a greater reduction in serum donor-specific alloantibody compared with untreated controls ($P=0.008$). (c) The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

HLA, human leukocyte antigen; SD, standard deviation.

Diwan, transpl 2011

Bortezomid

Treatment of rejection



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

Everly, Transpl. 2008

Bortezomid

Treatment of rejection

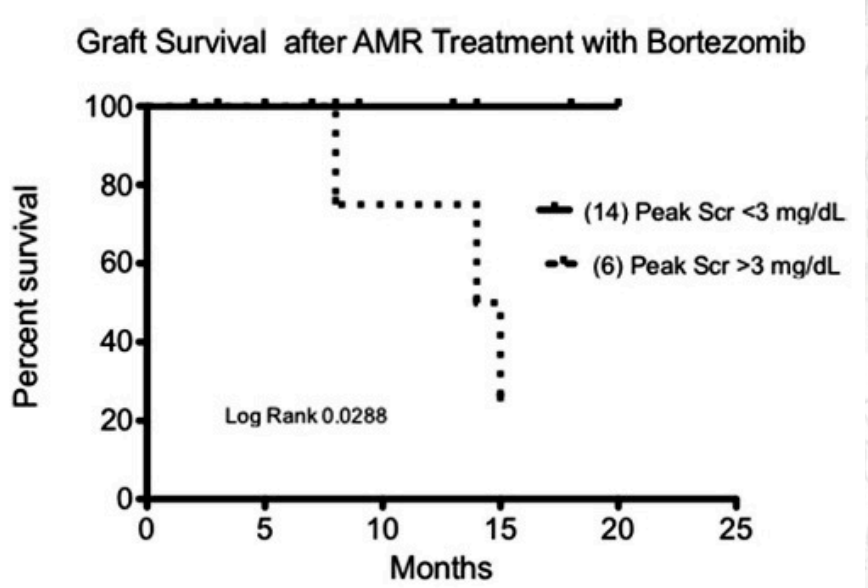
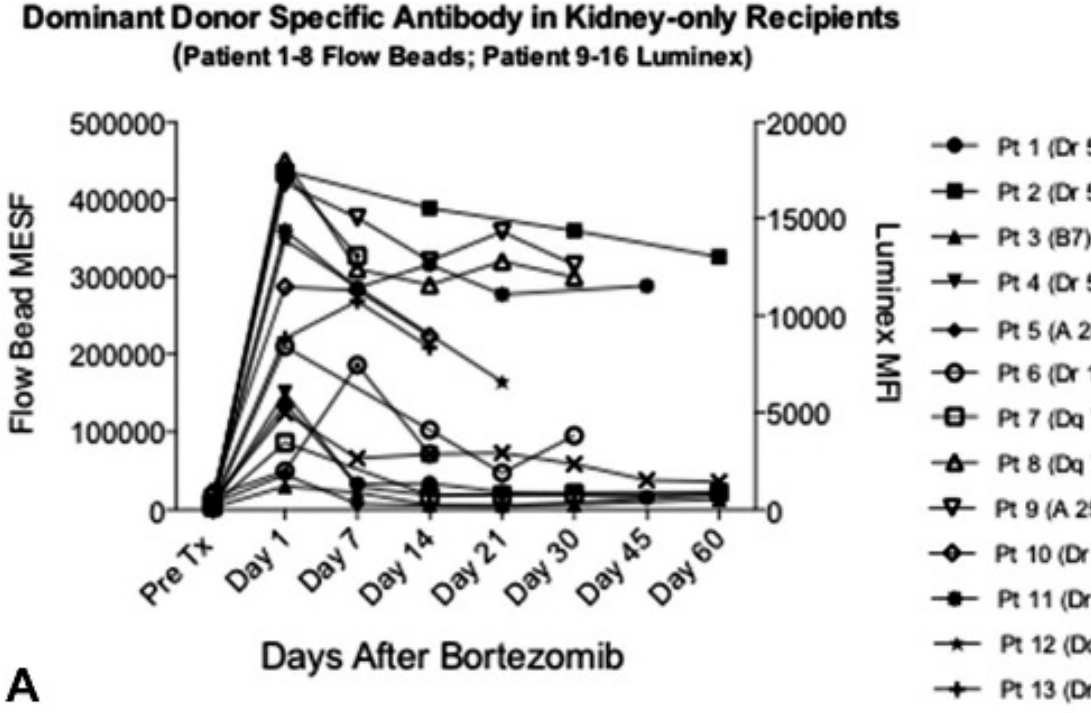


FIGURE 1. Actuarial graft survival for 20 bortezomib-treated recipients according to a peak serum creatinine (SCr) greater than or less than 3 mg/dL during treatment of antibody- mediated rejection (AMR). At 15 months difference was 100% versus 32%, $P=0.0288$ by log-rank test.

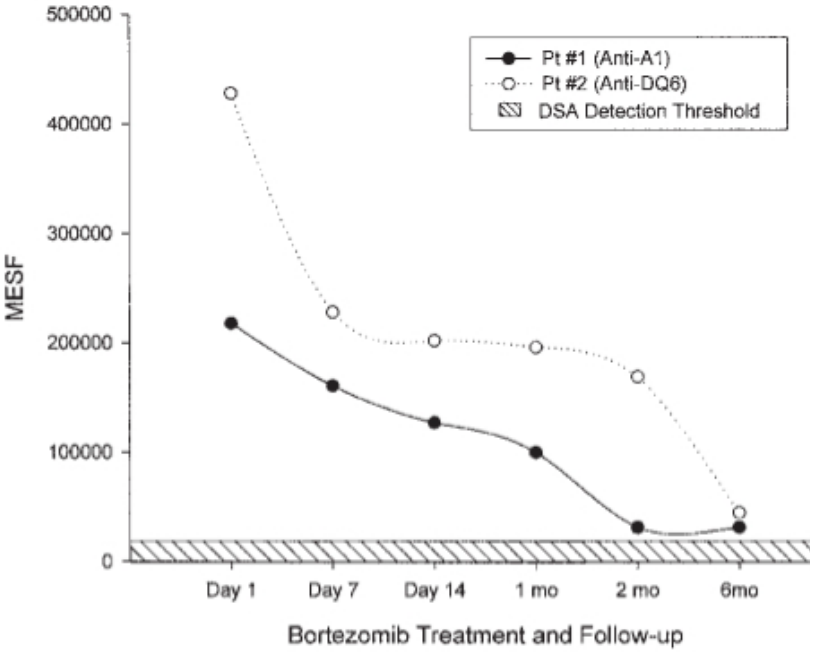


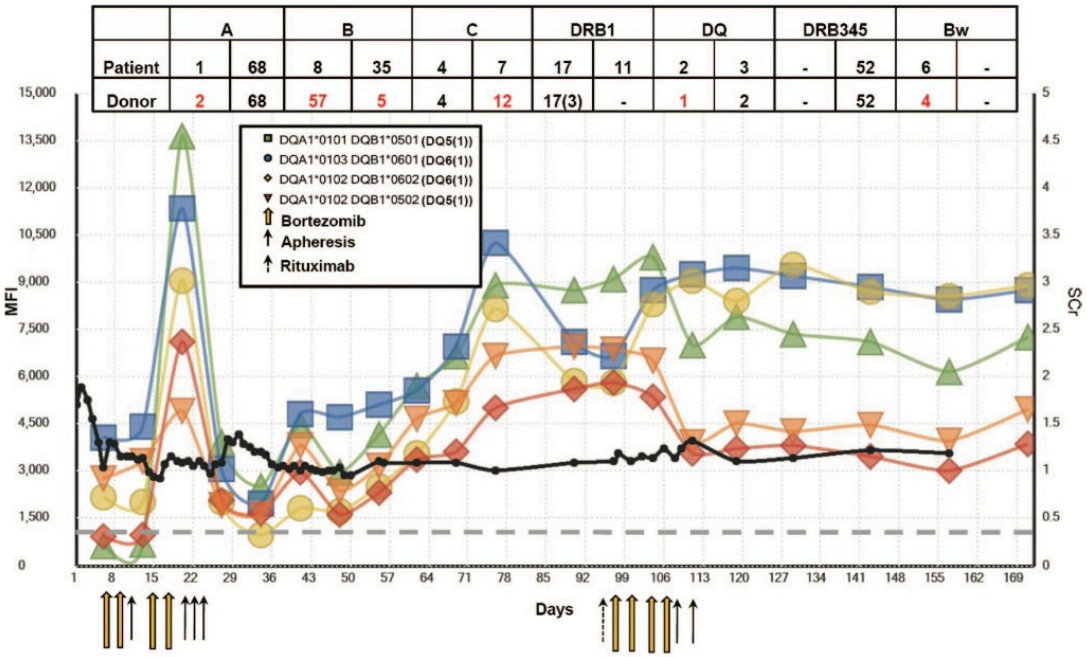
- 1,3 mg/m^2 x4
- 20 patients, GS 9,5 months 85%…..

Flechner, Transpl. 2010

Bortezomid

In vivo…. ????





5 pts with AMR/ACR

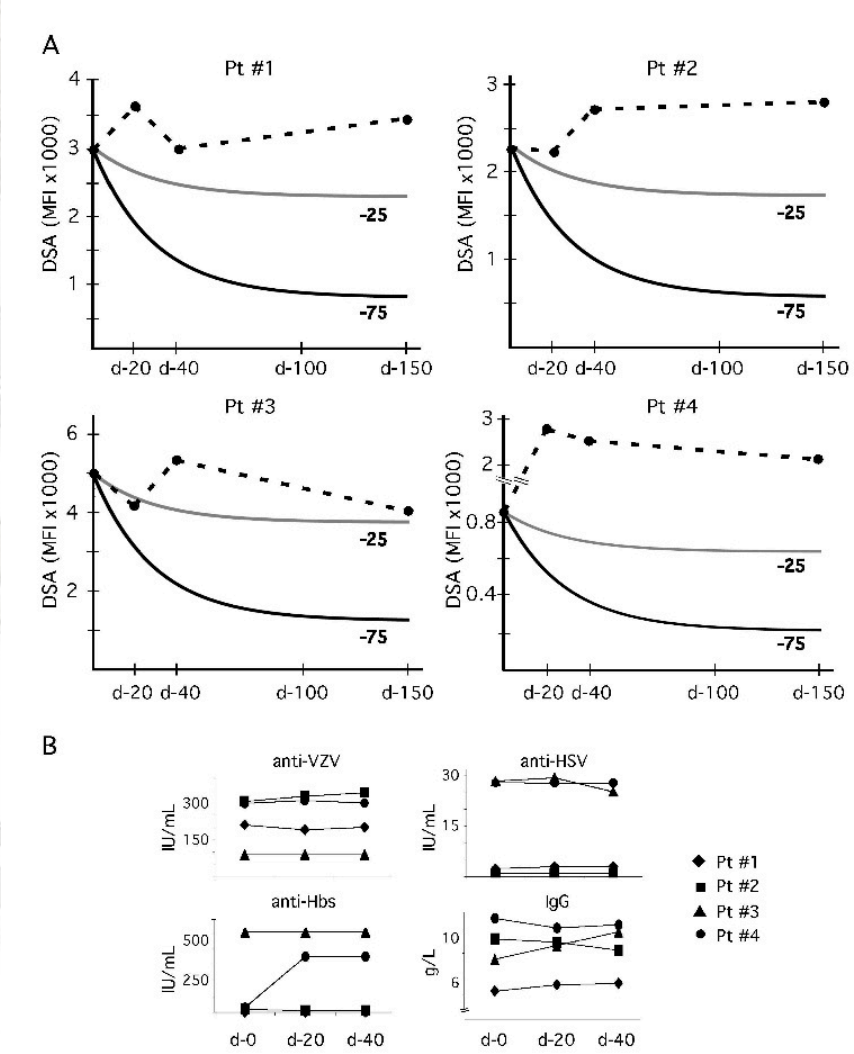
Everly Trans Proc 2009

11 pts without AMR/ACR, 8 DSA

Trivedi Transpl 2009

Bortezomid

In vivo....????



Legendre AJT 2010

C5 inhibition

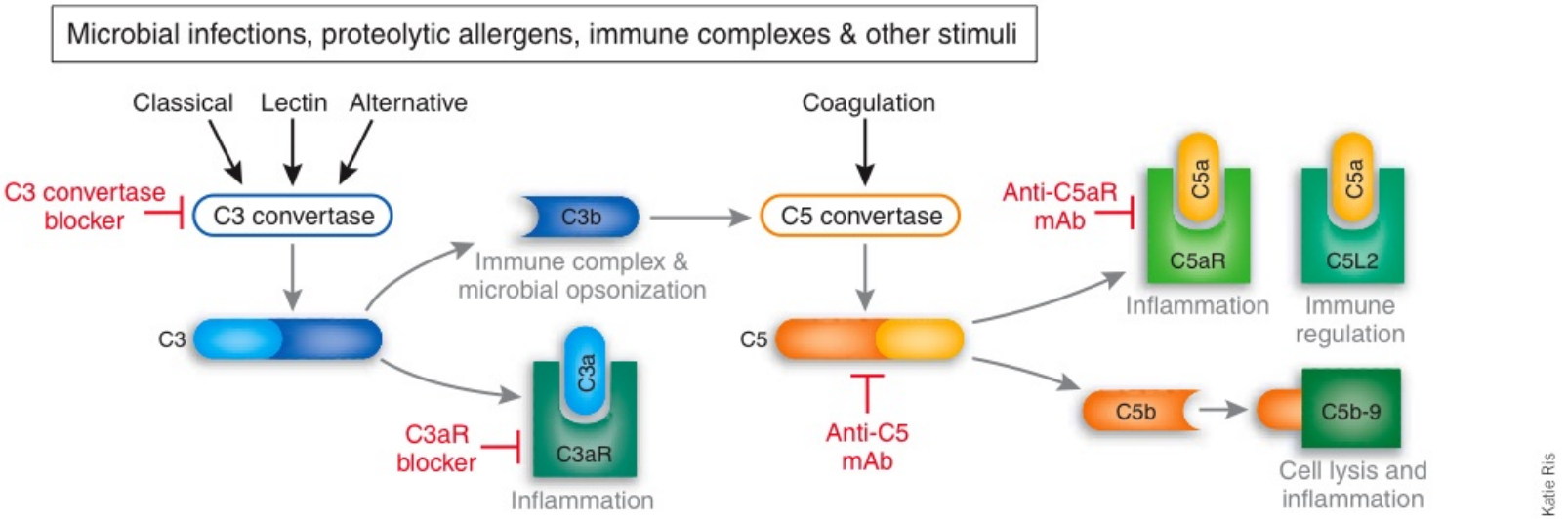


Figure 1 A simplified scheme of the complement activation cascade shows that C3 and C5 are critical convergence points of four activation pathways and indicates potential targets of anti-inflammatory drugs. Inhibitors targeting C5 may impact activation of all four pathways and offer advantages over C3 inhibitors, most notably the generation of C3b, a key component of the innate immune response. Inhibitors of C5aR signaling seem to have a different mechanism of action and associated risk-benefit profile compared with those that block cleavage of C5 to generate C5a and C5b-9.

C5 inhibition

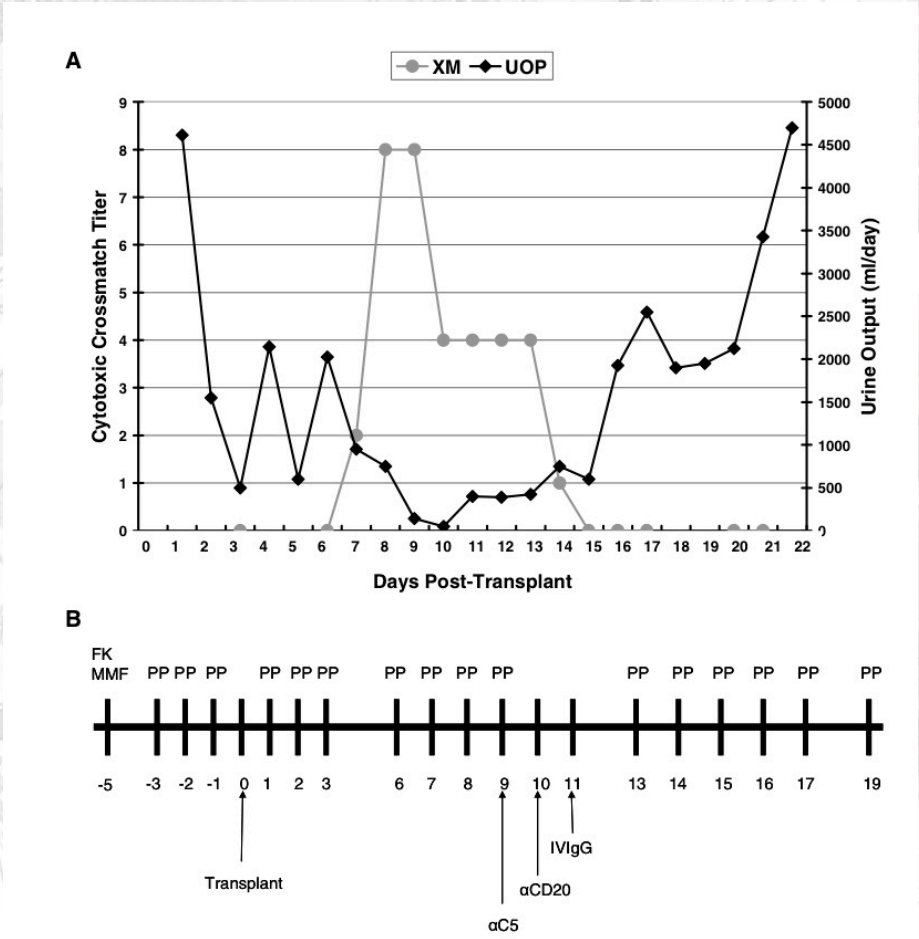
Monoclonal anti C5 Ab: Eculizumab

- 26 patients
- Inclusion: positive B cell flow XM
- Success: diminution of B cell flow XM
- PP pre-Tx if B cell flow XM > 300
- Eculizumab: D0, weeks 1, 2, 3, 4…. and more
- Only 2 rejections

Historical control group (n=51): 41% AMR

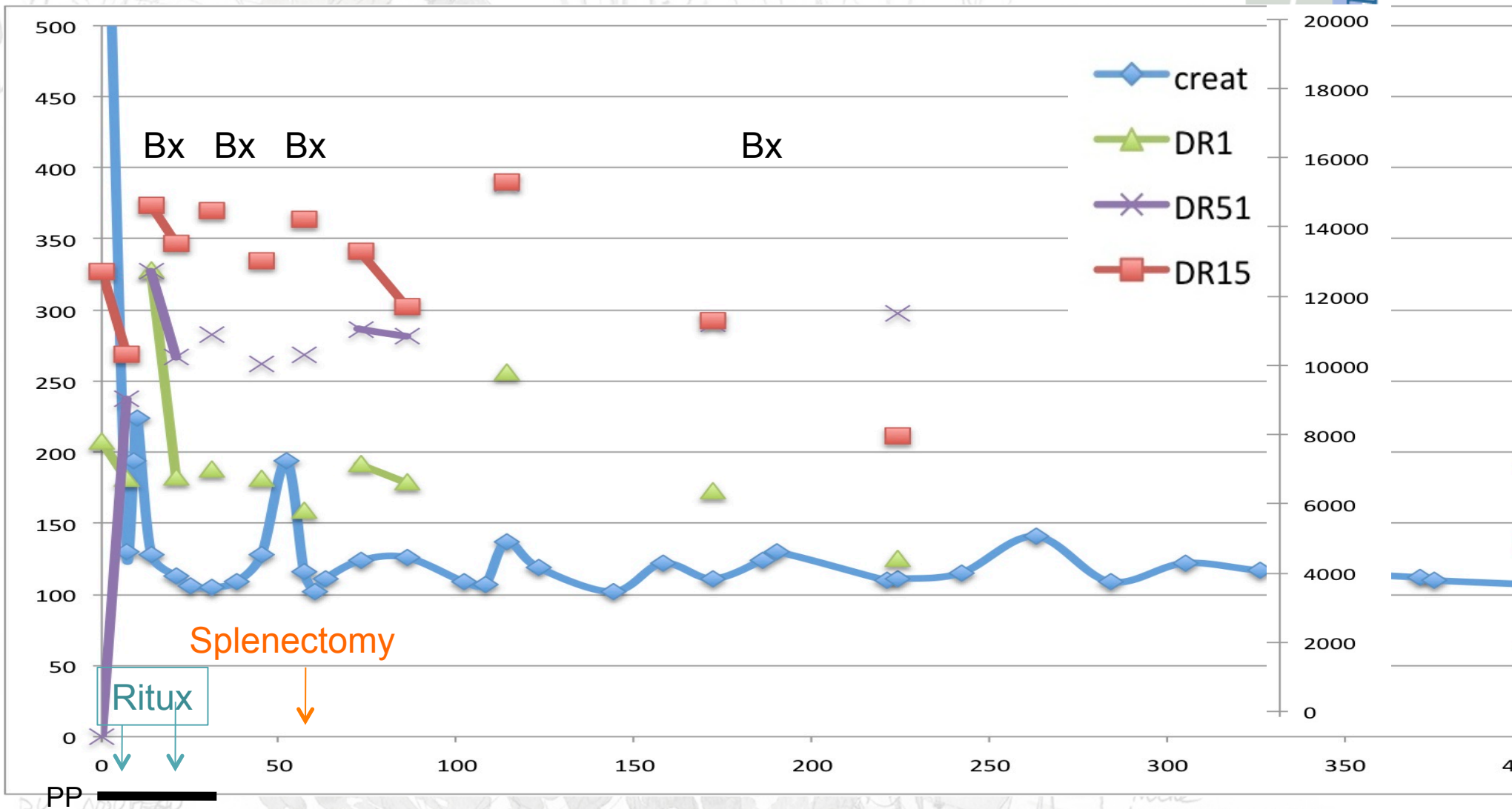
Stegall, Gloor

C5 inhibition

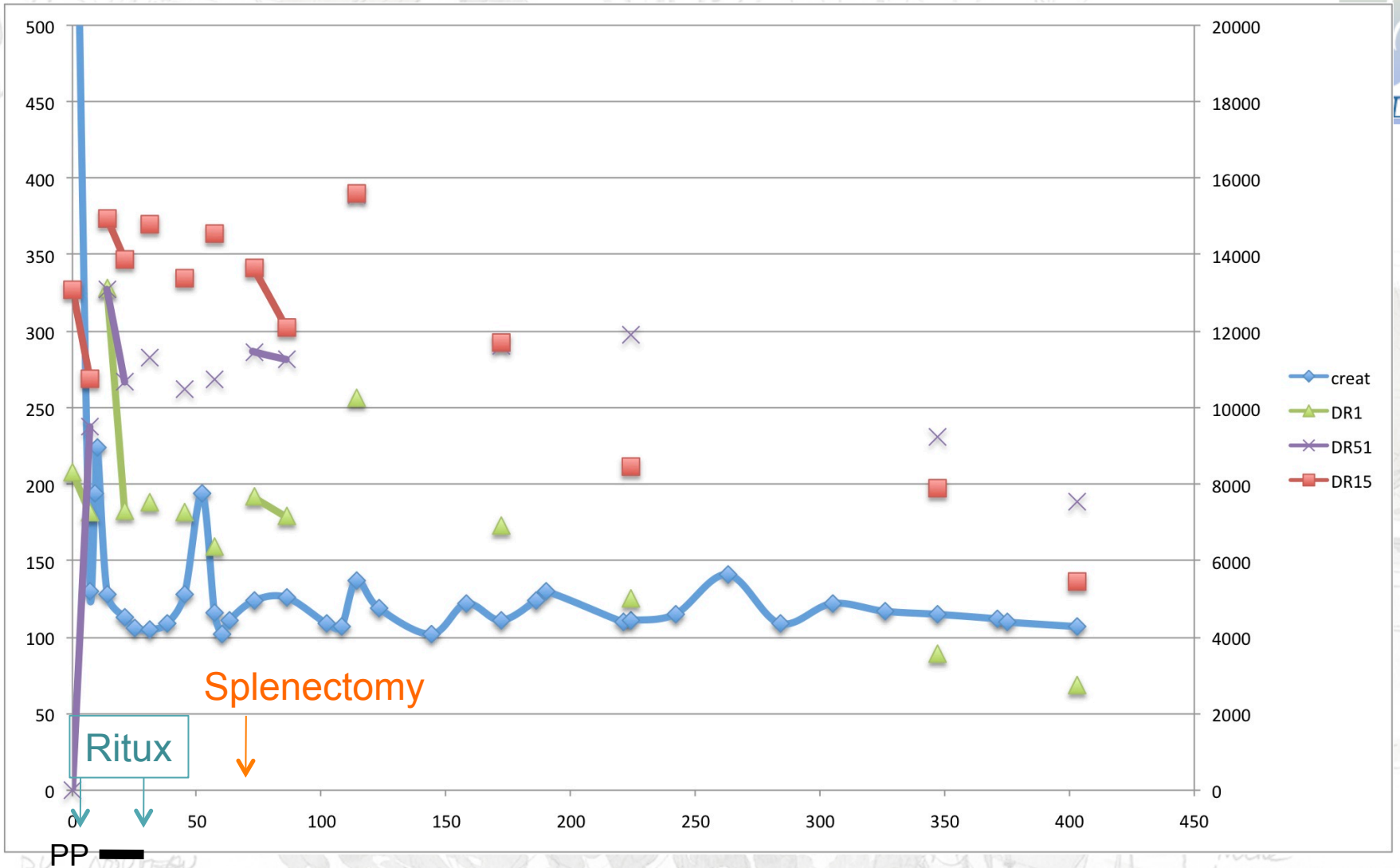


Locke AJT 2009

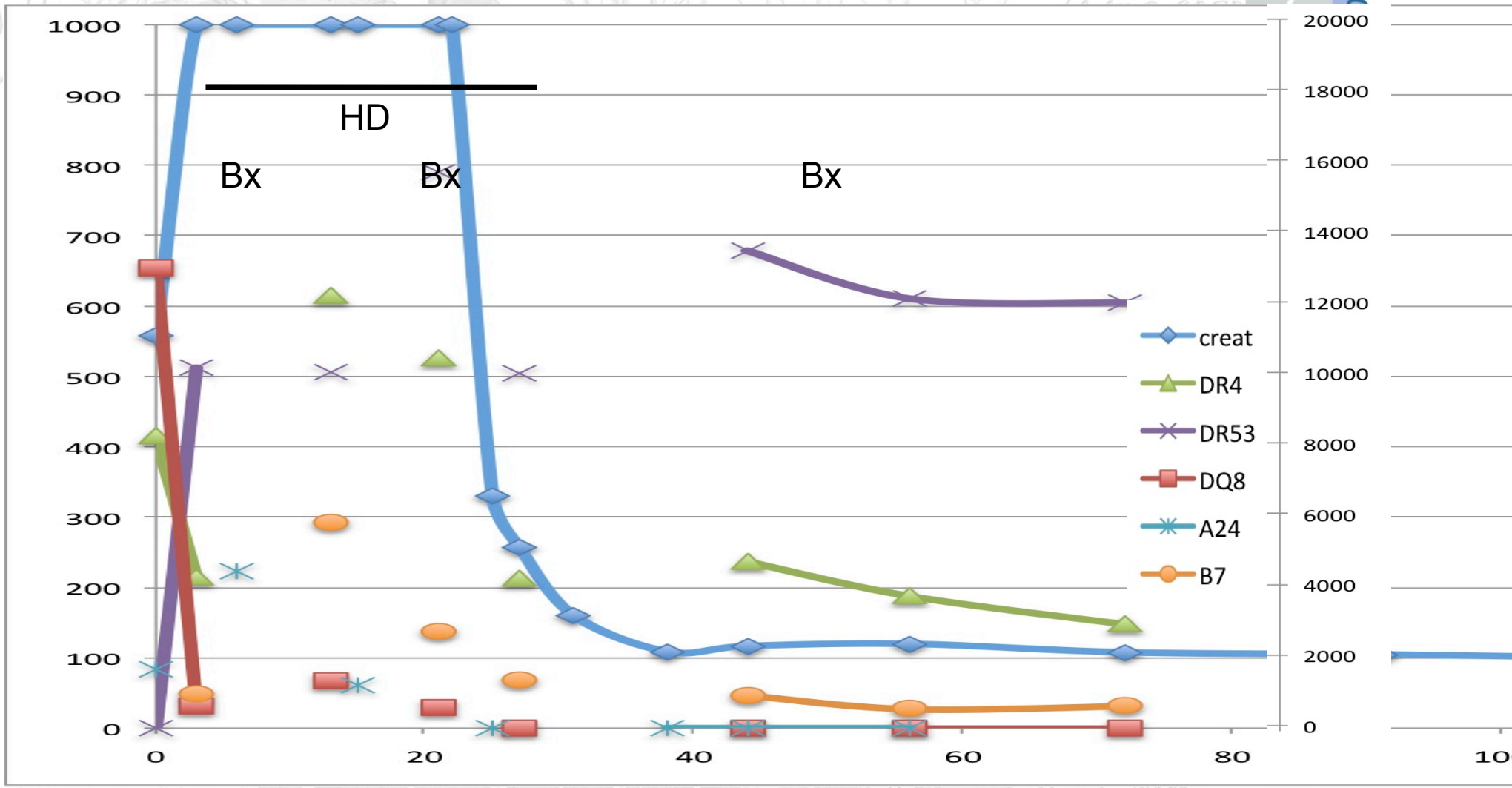
C5 inhibition: CAD Tx



C5 inhibition: CAD Tx



C5 inhibition: LD Tx



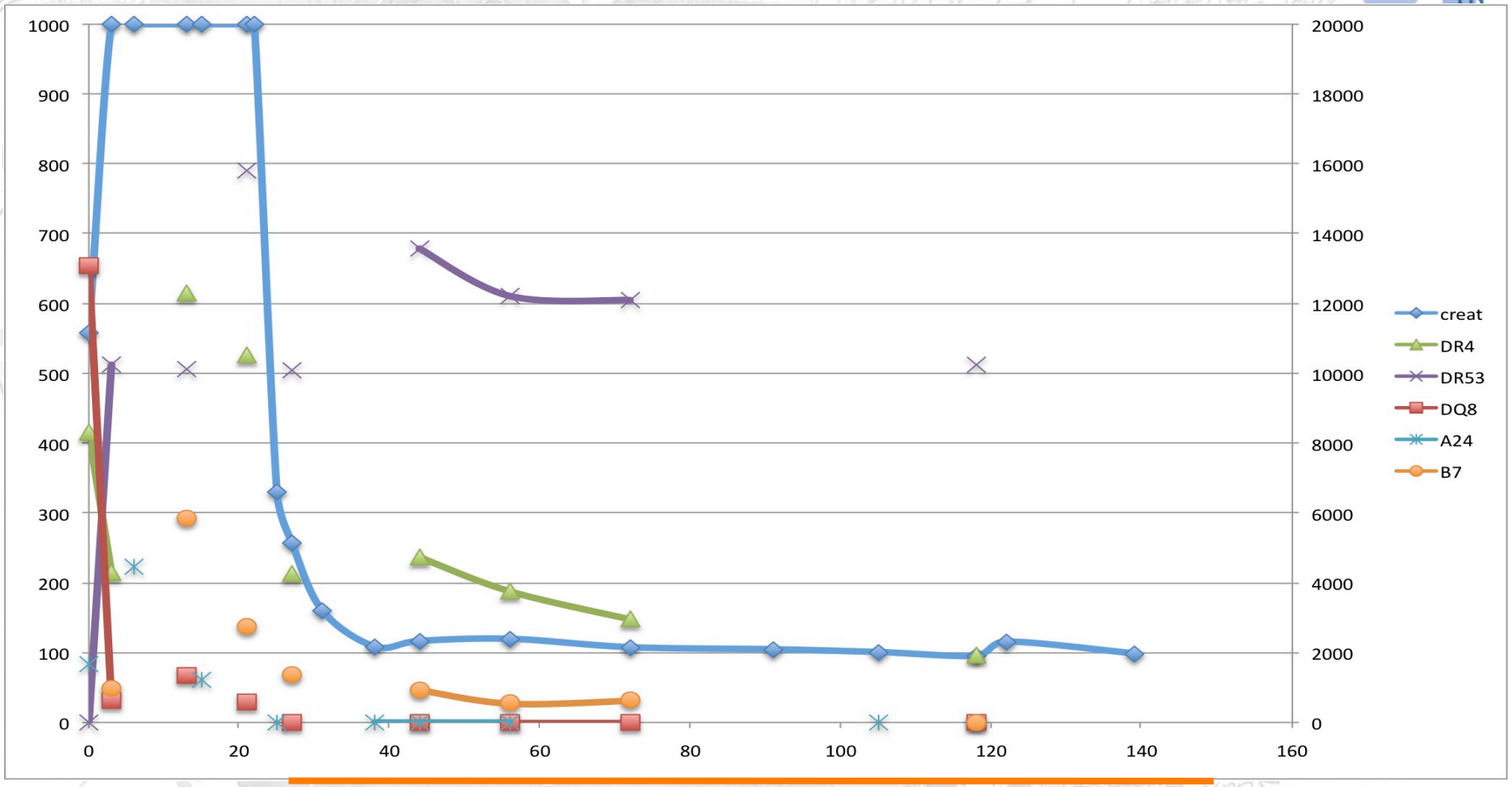
PP

IVIg

Cy

Soliris

C5 inhibition: LD Tx



Soliris

BAFF, APRIL, TACI and co…