FDA Public Workshop:

Antibody-mediated Rejection in Kidney Transplantation

The Choice of Induction / Maintenance Immunosuppression and their Impact on Preexisting and De Novo Antibodies

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Disclosures

- I have nothing to disclose in relation to this presentation:
- Following drugs used “off label” will be discussed:
  - Thymoglobulin
  - Campath
  - IVIg
  - Belatacept
  - Rituximab
  - Eculizumab
  - C1q Inhibitors

TABLE 1

Therapy	Action	Evidence supporting the treatment[a]
Plasmapheresis (PP)[b]	Decrease the titer and block the effect of DSA	Low, benefit not consistently demonstrated
Immunoadsorption (column)	Decrease the titer of DSA	Low, seems beneficial
IVIG	Decrease the titer and block the effect of DSA	Very low
Bortezomib	Decrease production of DSA	Very low
Corticosteroids	Decrease inflammation caused by DSA in graft and decrease production of DSA, suppression of T cells	Very low
Anti-thymocyte preparations	Reduce production of DSA by decreasing Helper T cells, suppression of T cells	Very low
Eculizumab	Block complement activation resulting from DSA activation	Very low
Mycophenolate	Block the effect and decrease production of DSA, suppression of T cells	Very low
Rituximab	Decrease production of DSA	Very low
Cyclophosphamide	Decrease production of DSA	Very low
Deoxyspergualin	Decrease production of DSA, suppression of T cells	Very low
Splenectomy	Decrease production of DSA	Very low
Tacrolimus	Decrease production of DSA, Suppression of T cells	Very low

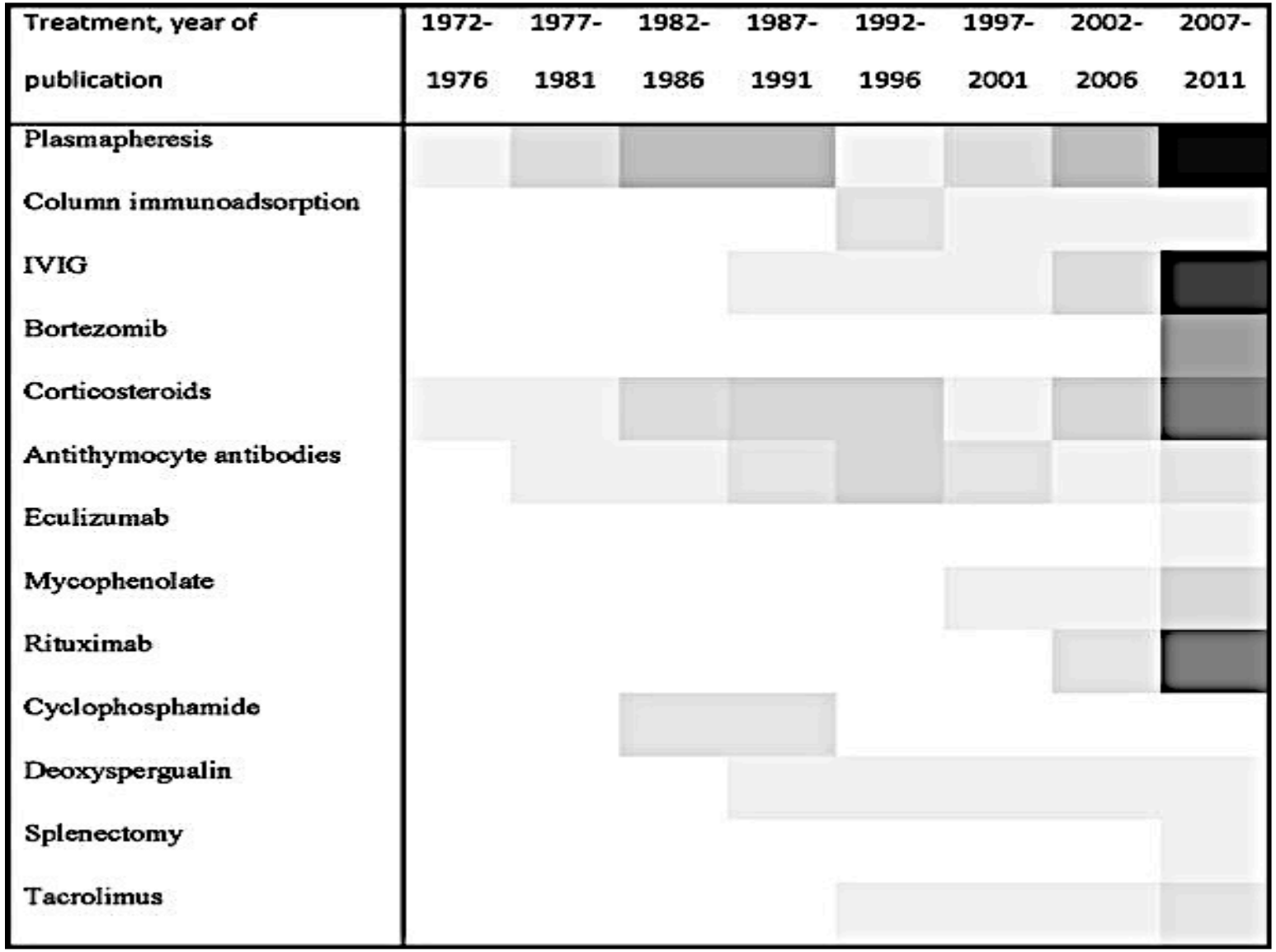
[a] According to the GRADE system, as described in the *Materials and Methods* section.
[b] Plasmapheresis may have other effects, which block the effect of DSA, including removal of other circulating factors such as complement (28, 62–65).

The Treatment of Acute Antibody-Mediated Rejection in Kidney Transplant Recipients-A Systematic Review.
Roberts, Darren; Jiang, Simon; Chadban, Steven

Transplantation. 94(8):775-783, October 27, 2012.
DOI: 10.1097/TP.0b013e31825d1587

TABLE 1 Therapeutic agents used against DSAs in the treatment of antibody-mediated rejection and the evidence supporting their role

FIGURE 2



The Treatment of Acute Antibody-Mediated Rejection in Kidney Transplant Recipients-A Systematic Review.
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FIGURE 2 . Trends in the use of treatments for AMR over time on the basis of all publications identified in the systematic review. Using a gray scale, black represents the most commonly used (in the case of PP, approximately 700 patients were treated between 2007 and 2011), whereas no color (white) means that it was not used. This includes patients from any observational, treatment, or epidemiology-based study identified in the systematic review. The use of tacrolimus and mycophenolate in patients with AMR is likely to be underrepresented in this figure because in recent years, these treatments are commonly used as baseline immunosuppression for high-risk KTRs, whereas the data included here only included new treatments administered to patients in response to a diagnosis of AMR/vascular rejection.

ABMR Protocols

- Suppression of the T-cell response
- Elimination of pre-formed antibody
- Inhibition of residual antibody and the complement system cascade
  - IVIg
  - Eculizumab
  - C1q inhibitors
- Depletion of antibody producing cells and/or their precursors
  - Rituximab

ABMR Protocols

- Suppression of the T-cell response
  - Depletional Agents
    - Polyclonal: rATG
    - Humanized antibodies: Alemtuzumab
  - Non-depletional Agents
    - Belatacept

Antithymocyte Globulin is Associated with a Lower Incidence of De Novo Donor-Specific Antibodies in Moderately Sensitized Renal Transplant Recipients

Marissa M. Brokhof, PharmD, BCPS[1], Hans W. Sollinger, MD, PhD, FACS[3], David R. Hager, PharmD, BCPS, CNSC[1], Brenda L. Muth, RN, MS, ACNP[2], John D. Pirsch, MD[2], Luis A. Fernandez, MD[3], Janet M. Bellingham, MD[3], Joshua D. Mezrich, MD[3], David P. Foley, MD[3], Anthony M. D'Alessandro, MD[3], Jon S. Odorico, MD[3], Maha A. Mohamed, MD[2], Vijay Vidyasagar, MD[2], Thomas M. Ellis, PhD[4], Dixon B. Kaufman, MD, PhD, FACS[3], and Arjang Djamali, MD, MS, FASN[2]

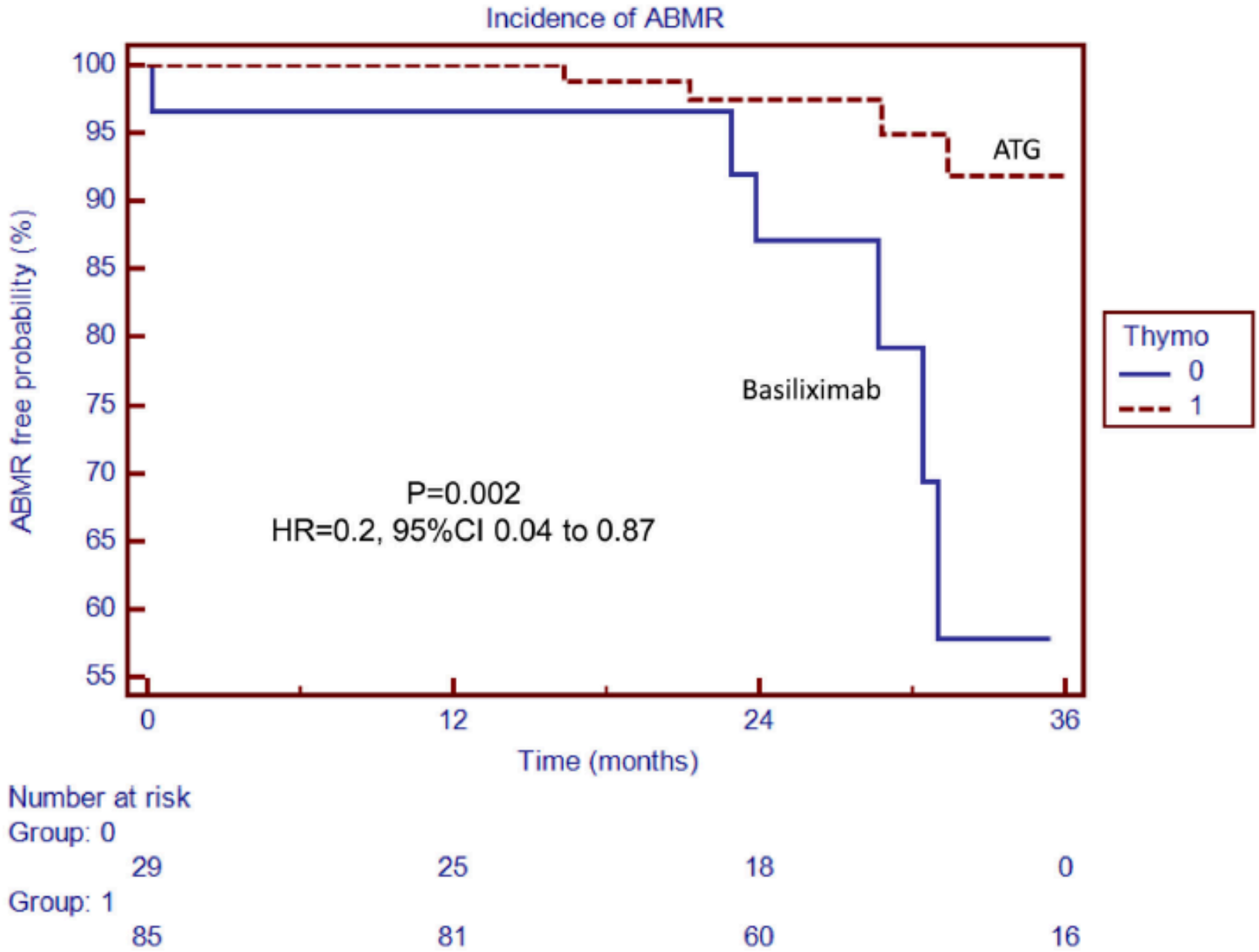
Transplantation 97 (6) March 2014

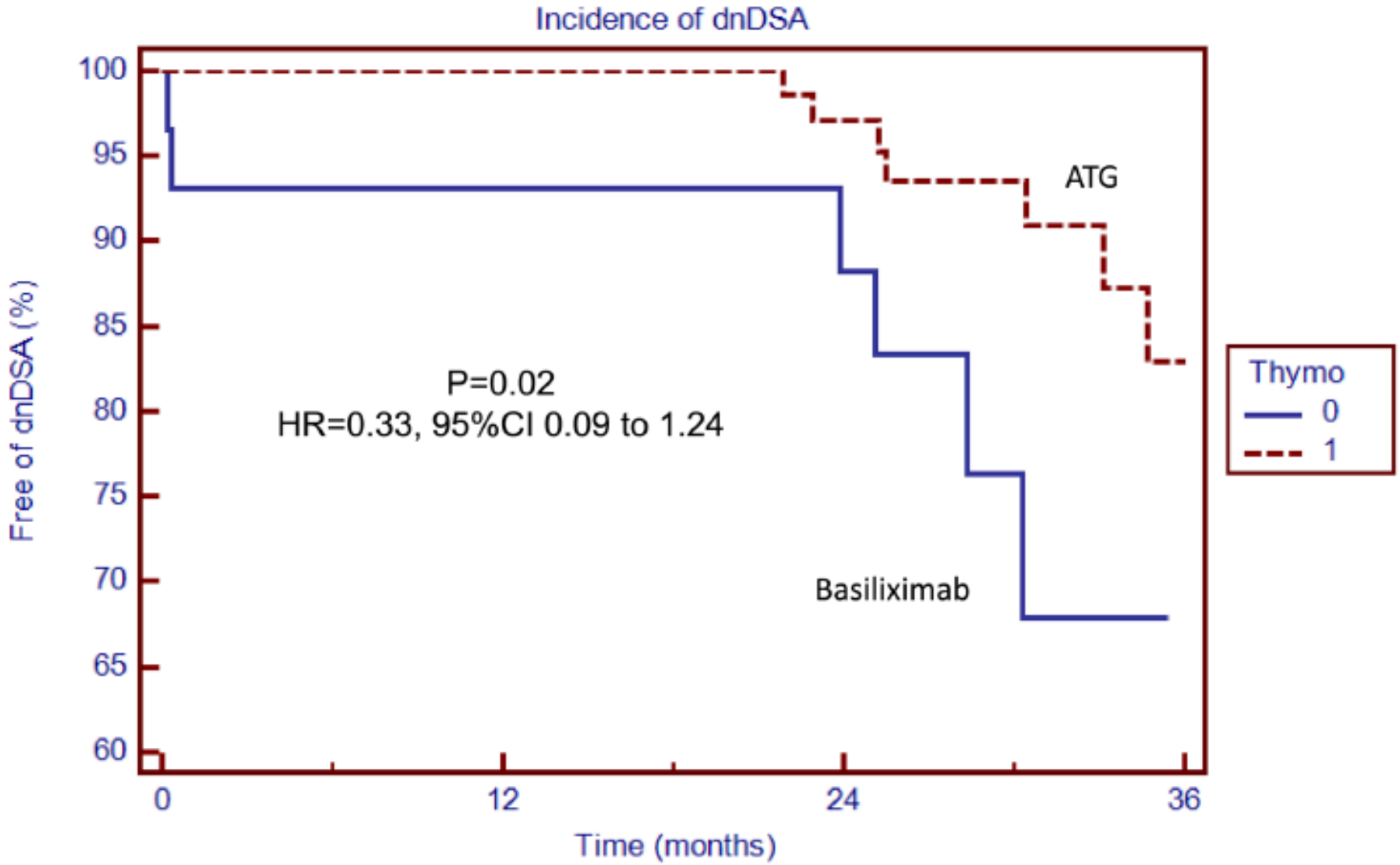
Methods

- 114 moderately sensitized deceased donor renal transplant recipients between December 2009 and November 2011
  - Positive DSA (MFI max 500-4,000 by SAB Luminex)
  - Negative flow crossmatch
  - Induction: ATG or basiliximab based on provider preference
  - Maintenance: TAC/MPA/Pred
  - Followed for 36 months
- De novo DSA
  - Defined as the absence of pre-transplant DSA (MFI less than 300) increasing at least three-fold (greater than 900 MFI)

    post-transplant
  - Assessed blindly by HLA lab director (TE)

Figure 1. (b) ATG was associated with a lower incidence of Acute ABMR





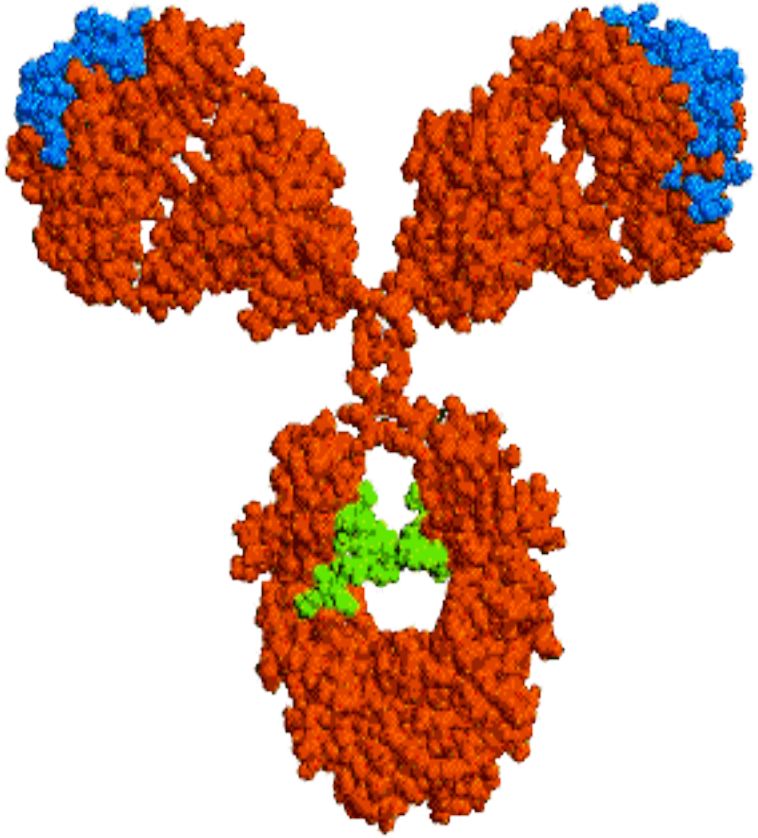
Number at risk

Group: 0				
	29	25	18	0
Group: 1				
	85	81	60	16

Summary and Conclusion

- Induction with ATG (thymoglobulin) is associated with a reduction in the incidence of dnDSA and ABMR without a significant change in the incidence of CMV infection or BK nephropathy when compared with basiliximab in moderately sensitized deceased donor renal transplant recipients
- Randomized clinical trials are required to specifically address the role of induction immunosuppression on dnDSA and ABMR

ALEMTUZUMAB (CAMPATH-1H)



- A recombinant DNA-derived humanized monoclonal antibody directed against CD52
  - IgG1 kappa with human variable framework and constant regions with murine CDR regions

Uses of Alemtuzumab in Kidney Transplantation

- Antibody-Induction Agent:
  - CNI avoidance
  - Steroid-free protocols
    - CNI monotherapy
    - "Prope" tolerance induction
    - Induction of HIV patients undergoing KTx
  - Induction in desensitization protocols
- Treatment of Acute Rejection:
  - Four studies encompassing an N=62
    - Two studies used Campath-1H and one Campath-1G
    - Two published in a peer-reviewed journal

De Novo α-HLA Antibodies in Alemtuzumab Induction

- Cai J et al: Transplantation 2004; 78:919-924
  - 42% (n=10) of the patients enrolled in the pilot study of alemtuzumab induction for CNI avoidance have developed Class I and Class II α-HLA antibodies
    - **60% DSA**
    - **40% non-DSA**
  - At 24 mos of F/U:
    - **Of 10 Pts developing α-HLA antibodies, 4 (40%) have had BPAMR**
      - **Of these:**
        - **3 patients had DSA α-HLA antibodies**
        - **1 patient had non-DSA α-HLA antibodies**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rituximab and Intravenous Immune Globulin for Desensitization during Renal Transplantation

Ashley A. Vo, Pharm.D., Marina Lukovsky, Pharm.D., Mieko Toyoda, Ph.D., Jennifer Wang, M.D., Nancy L. Reinsmoen, Ph.D., Chih-Hung Lai, Ph.D., Alice Peng, M.D., Rafael Villicana, M.D., and Stanley C. Jordan, M.D.

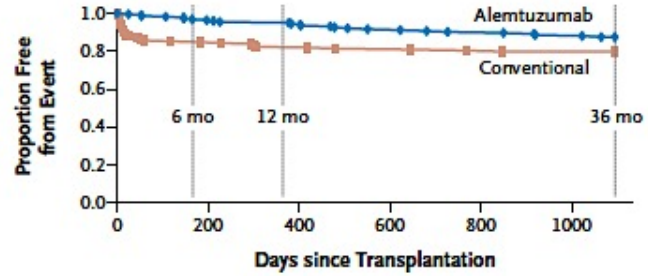
N Engl J Med July 17, 2008

Alemtuzumab Induction in Renal Transplantation

Michael J. Hanaway, M.D., E. Steve Woodle, M.D., Shamkant Mulgaonkar, M.D., V. Ram Peddi, M.D., Dixon B. Kaufman, M.D., Ph.D., M. Roy First, M.D., Richard Croy, M.A., John Holman, M.D., for the INTAC Study Group

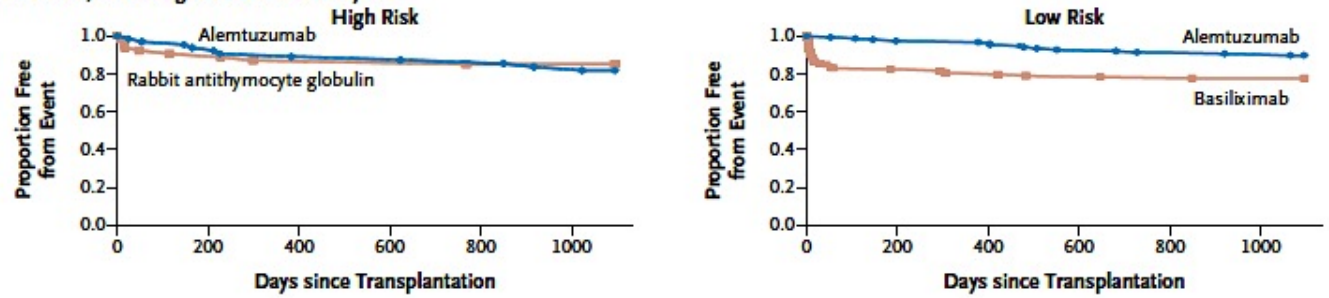
N Engl J Med
Volume 364(20):1909-1919
May 19, 2011

A BCAR

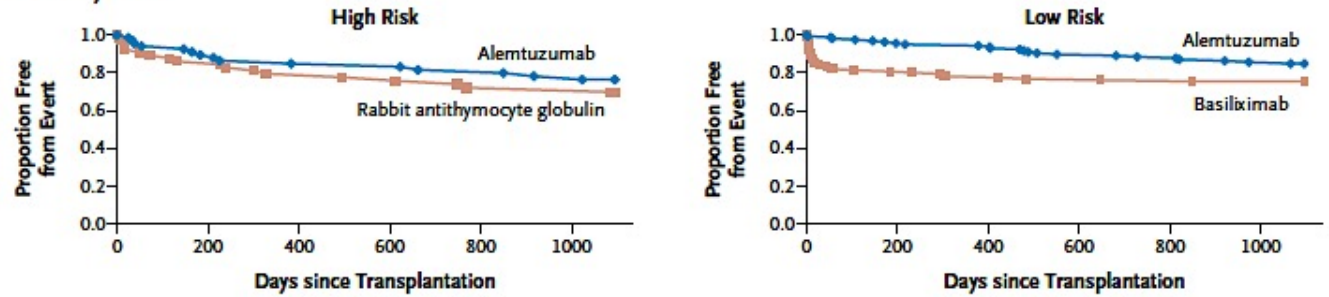


Months	% of Patients with BCAR		P Value
	Alemtuzumab	Conventional therapy	
6	3	15	<0.001
12	5	17	<0.001
36	13	20	0.03

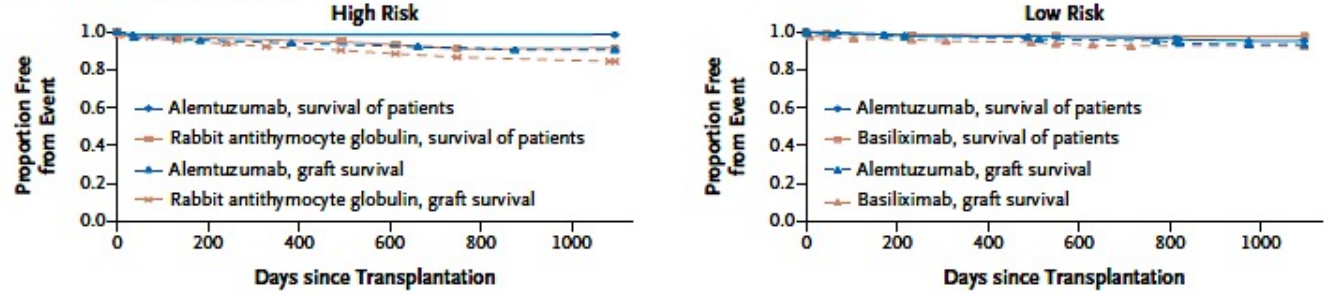
B BCAR, According to Risk of Graft Rejection



C Efficacy Failure

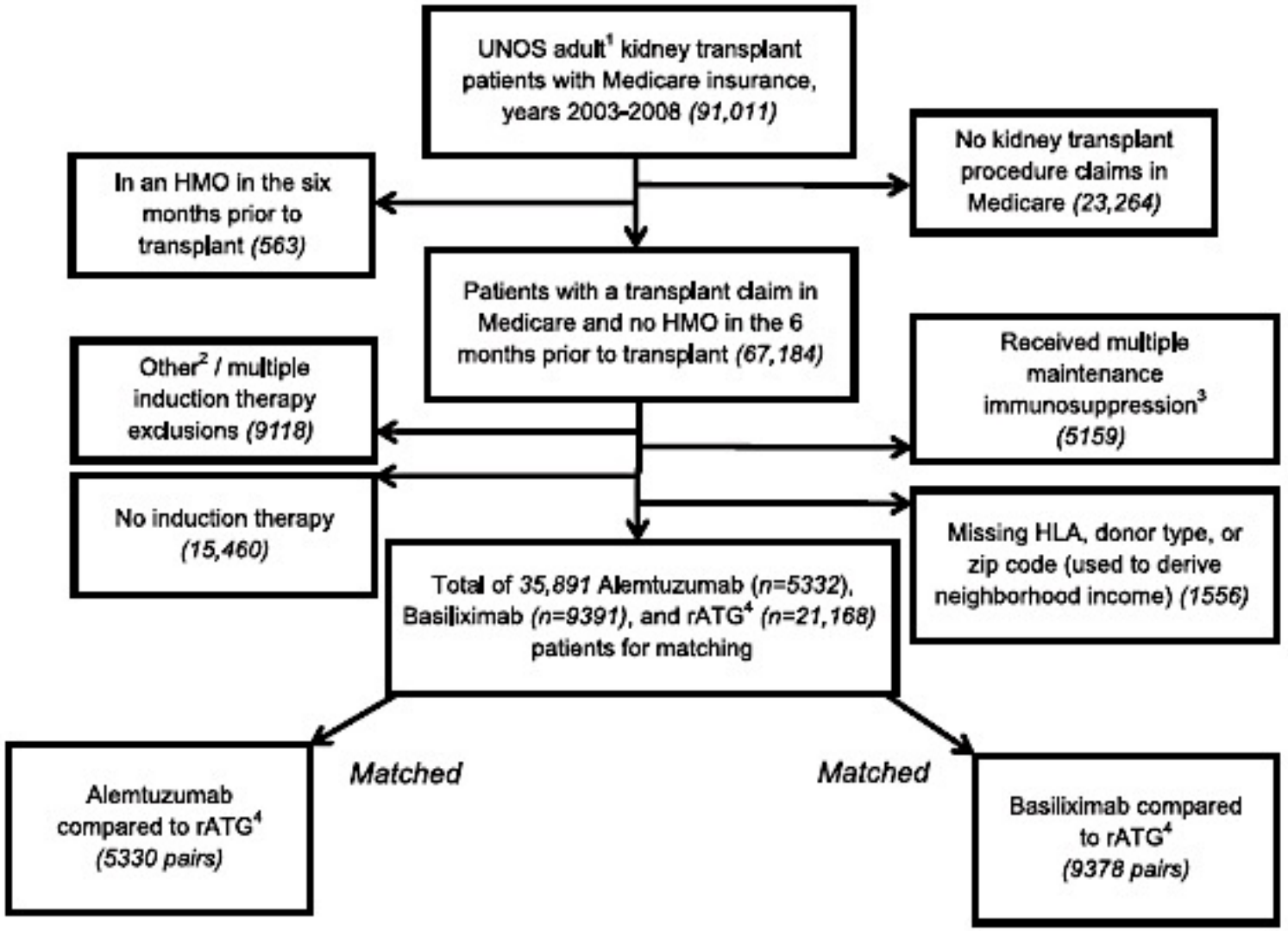


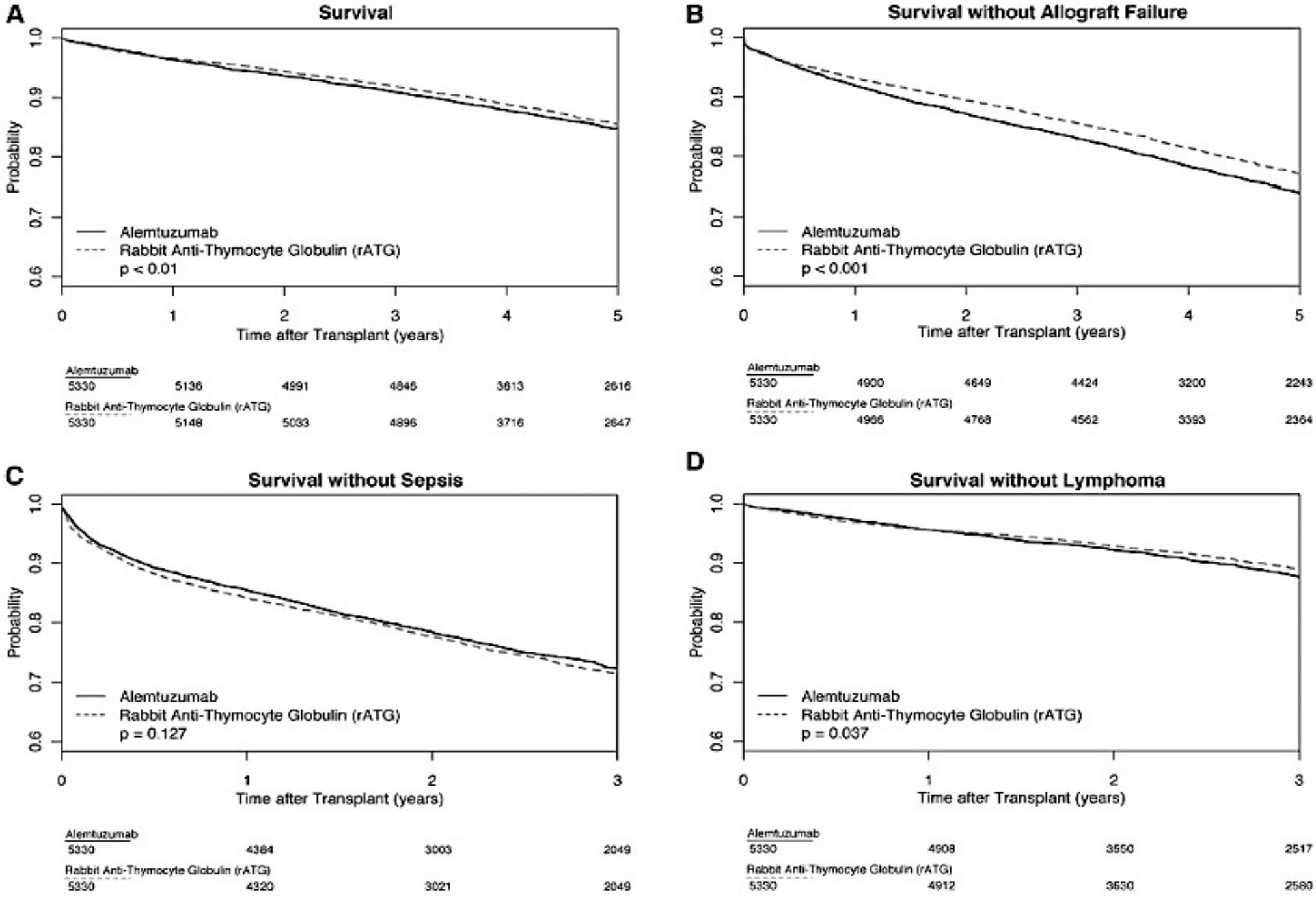
D Survival of Patients and Grafts

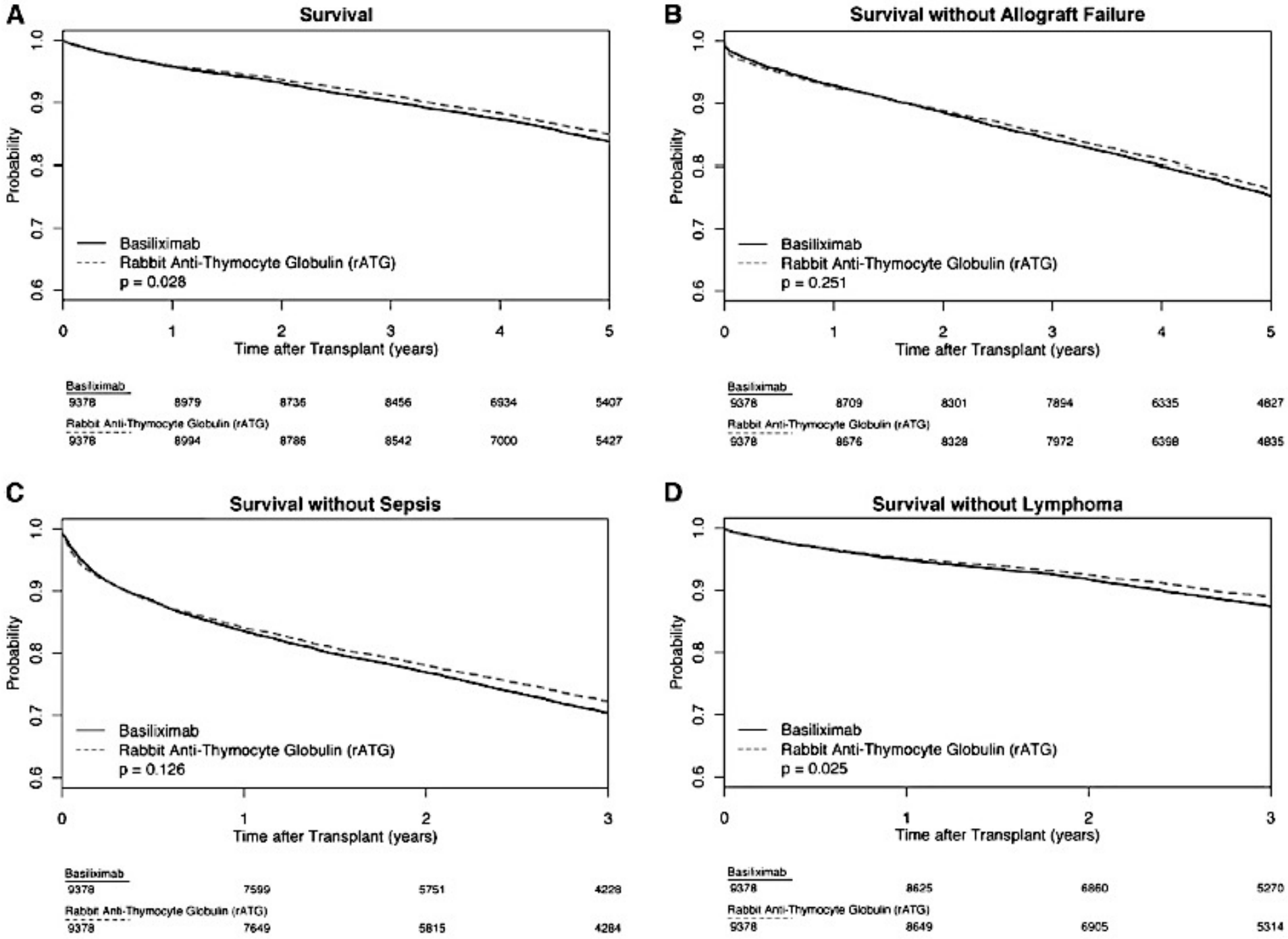


Com ion
The

Neel K S. Hill,[†]
Josep Sawinski,[‖]
Susan d
Peter

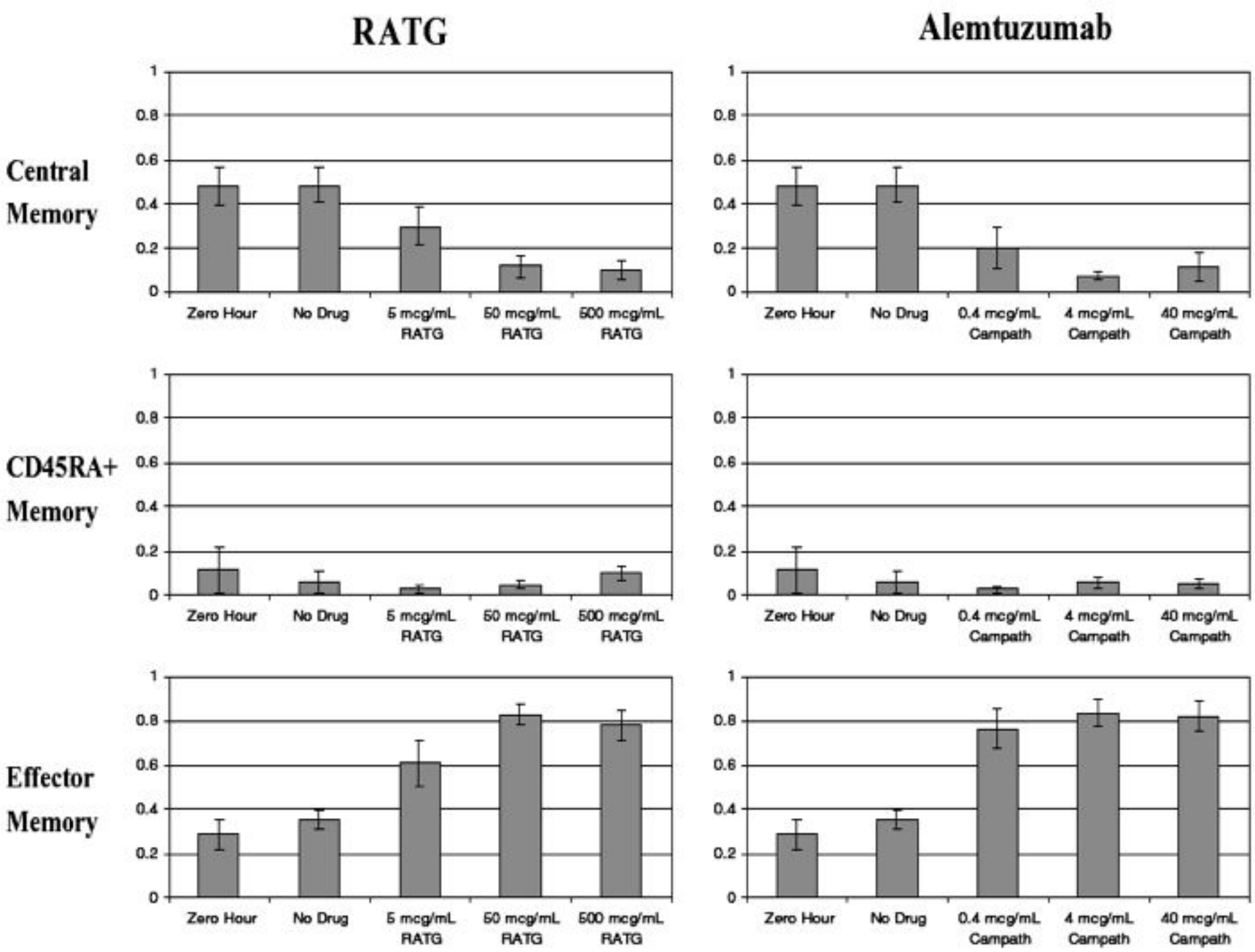



A
Survival
Probability
1.0
0.9
0.8
0.7
0.6
Alemtuzumab
Rabbit Anti-Thymocyte Globulin (rATG)
p < 0.01
0
1
2
3
4
5
Time after Transplant (years)
Alemtuzumab
5330 5136 4991 4846 3613 2616
Rabbit Anti-Thymocyte Globulin (rATG)
5330 5148 5033 4896 3716 2647
B
Survival without Allograft Failure
Probability
1.0
0.9
0.8
0.7
0.6
Alemtuzumab
Rabbit Anti-Thymocyte Globulin (rATG)
p < 0.001
0
1
2
3
4
5
Time after Transplant (years)
Alemtuzumab
5330 4900 4649 4424 3200 2243
Rabbit Anti-Thymocyte Globulin (rATG)
5330 4966 4768 4562 3393 2364
C
Survival without Sepsis
Probability
1.0
0.9
0.8
0.7
0.6
Alemtuzumab
Rabbit Anti-Thymocyte Globulin (rATG)
p = 0.127
0
1
2
3
Time after Transplant (years)
Alemtuzumab
5330 4384 3003 2049
Rabbit Anti-Thymocyte Globulin (rATG)
5330 4320 3021 2049
D
Survival without Lymphoma
Probability
1.0
0.9
0.8
0.7
0.6
Alemtuzumab
Rabbit Anti-Thymocyte Globulin (rATG)
p = 0.037
0
1
2
3
Time after Transplant (years)
Alemtuzumab
5330 4908 3550 2517
Rabbit Anti-Thymocyte Globulin (rATG)
5330 4912 3530 2580


A
Survival
Probability
1.0
0.9
0.8
0.7
0.6
Basiliximab
Rabbit Anti-Thymocyte Globulin (rATG)
p = 0.028
0
1
2
3
4
5
Time after Transplant (years)
Basiliximab
9378 8979 8735 8456 6934 5407
Rabbit Anti-Thymocyte Globulin (rATG)
9378 8994 8785 8542 7000 5427
B
Survival without Allograft Failure
Probability
1.0
0.9
0.8
0.7
0.6
Basiliximab
Rabbit Anti-Thymocyte Globulin (rATG)
p = 0.251
0
1
2
3
4
5
Time after Transplant (years)
Basiliximab
9378 8709 8301 7894 6335 4827
Rabbit Anti-Thymocyte Globulin (rATG)
9378 8676 8328 7972 6398 4835
C
Survival without Sepsis
Probability
1.0
0.9
0.8
0.7
0.6
Basiliximab
Rabbit Anti-Thymocyte Globulin (rATG)
p = 0.126
0
1
2
3
Time after Transplant (years)
Basiliximab
9378 7599 5751 4228
Rabbit Anti-Thymocyte Globulin (rATG)
9378 7649 5815 4284
D
Survival without Lymphoma
Probability
1.0
0.9
0.8
0.7
0.6
Basiliximab
Rabbit Anti-Thymocyte Globulin (rATG)
p = 0.025
0
1
2
3
Time after Transplant (years)
Basiliximab
9378 8625 6860 5270
Rabbit Anti-Thymocyte Globulin (rATG)
9378 8649 6905 5314

Immunocompetent T-Cells with a Memory-Like Phenotype are the Dominant Cell Type Following Antibody-Mediated T-Cell Depletion

Pearl JP et al: Am J Transplant 2005; 5:465-474


RATG
Alemtuzumab
Central Memory
CD45RA+ Memory
Effector Memory
1
0.8
0.6
0.4
0.2
0
Zero Hour
No Drug
5 mcg/mL RATG
50 mcg/mL RATG
500 mcg/mL RATG
0.4 mcg/mL Campath
4 mcg/mL Campath
40 mcg/mL Campath

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rituximab and Intravenous Immune Globulin for Desensitization during Renal Transplantation

Ashley A. Vo, Pharm.D., Marina Lukovsky, Pharm.D., Mieko Toyoda, Ph.D., Jennifer Wang, M.D., Nancy L. Reinsmoen, Ph.D., Chih-Hung Lai, Ph.D., Alice Peng, M.D., Rafael Villicana, M.D., and Stanley C. Jordan, M.D.

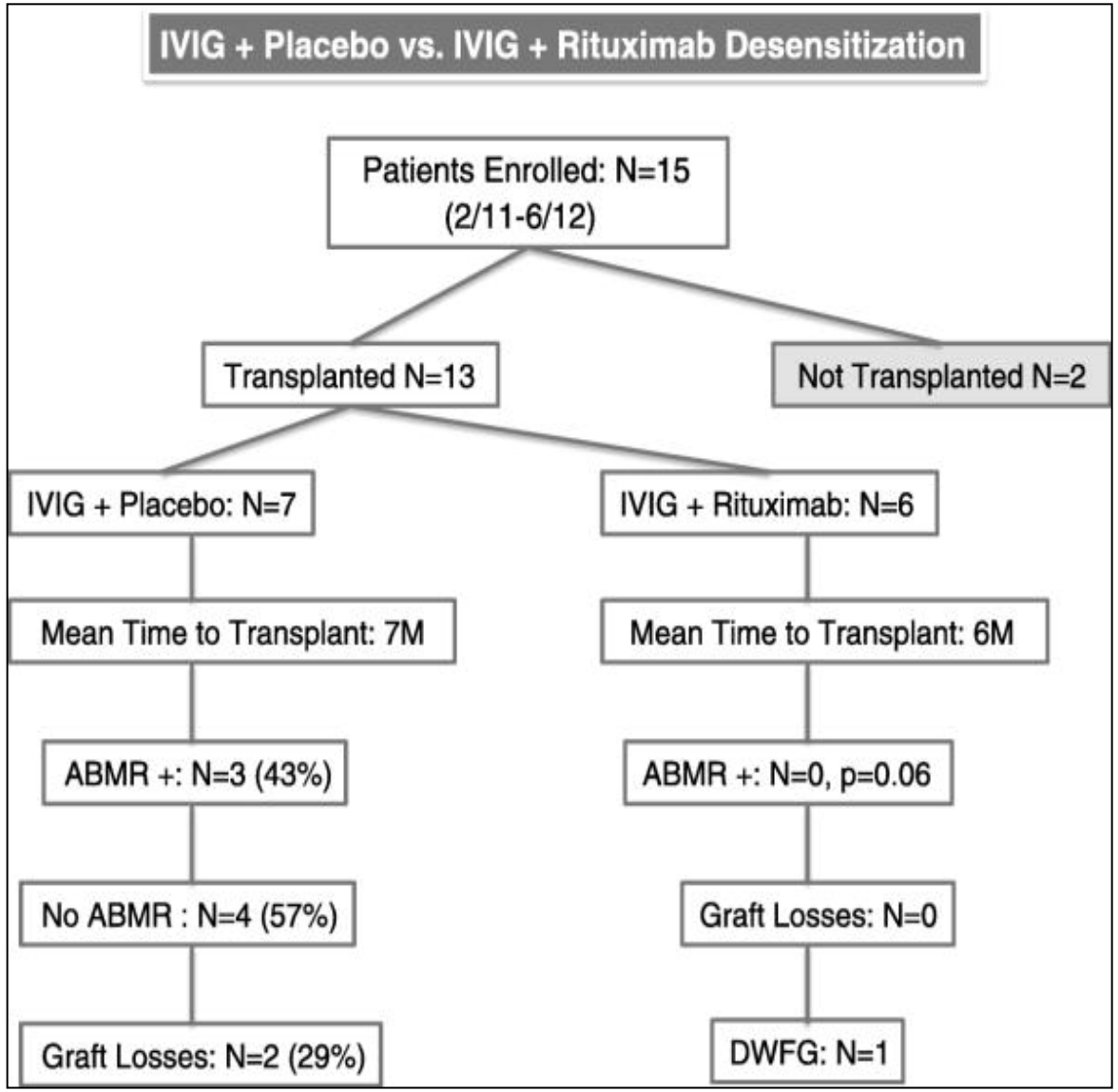
N Engl J Med July 17, 2008

Rituximab+IVIg: Final Verdict?

- 2/11-6/12:
  - Randomized to IVIg+Placebo or IVIg+Ritux
- Total enrollment goal = 90 patients
- End-points:
  - Rates of Transplantation
  - ABMR
  - Protocol biopsies at 1 year
  - Scr, DSA monitoring
  - Patient and Graft survival

Transplantation. 98(3):312-319, August 15, 2014.
DOI: 10.1097/TP.0000000000000064

FIGURE 1



Benefits of Rituximab Combined With Intravenous Immunoglobulin for Desensitization in Kidney Transplant Recipients.
Vo, Ashley; Choi, Jua; Cisneros, Kristen; Reinsmoen, Nancy; Haas, Mark; Ge, Shili; Toyoda, Mieko; Kahwaji, Joseph; Peng, Alice; Villicana, Rafael; Jordan, Stanley

Transplantation. 98(3):312-319, August 15, 2014.
DOI: 10.1097/TP.0000000000000064

FIGURE 1 . Study design. Patients were randomized in a 1:1 ratio to receive IVIG+placebo versus IVIG+rituximab. Treatment is as described in the text. The attribution to study groups is shown. Briefly, 15 patients were enrolled. Of those, 87% underwent transplantation. Seven patients were randomized to IVIG+placebo group; six patients were randomized to IVIG+rituximab group. Outcomes are described in the text.

Transplantation. 98(3):312-319, August 15, 2014.
DOI: 10.1097/TP.0000000000000064

Outcomes

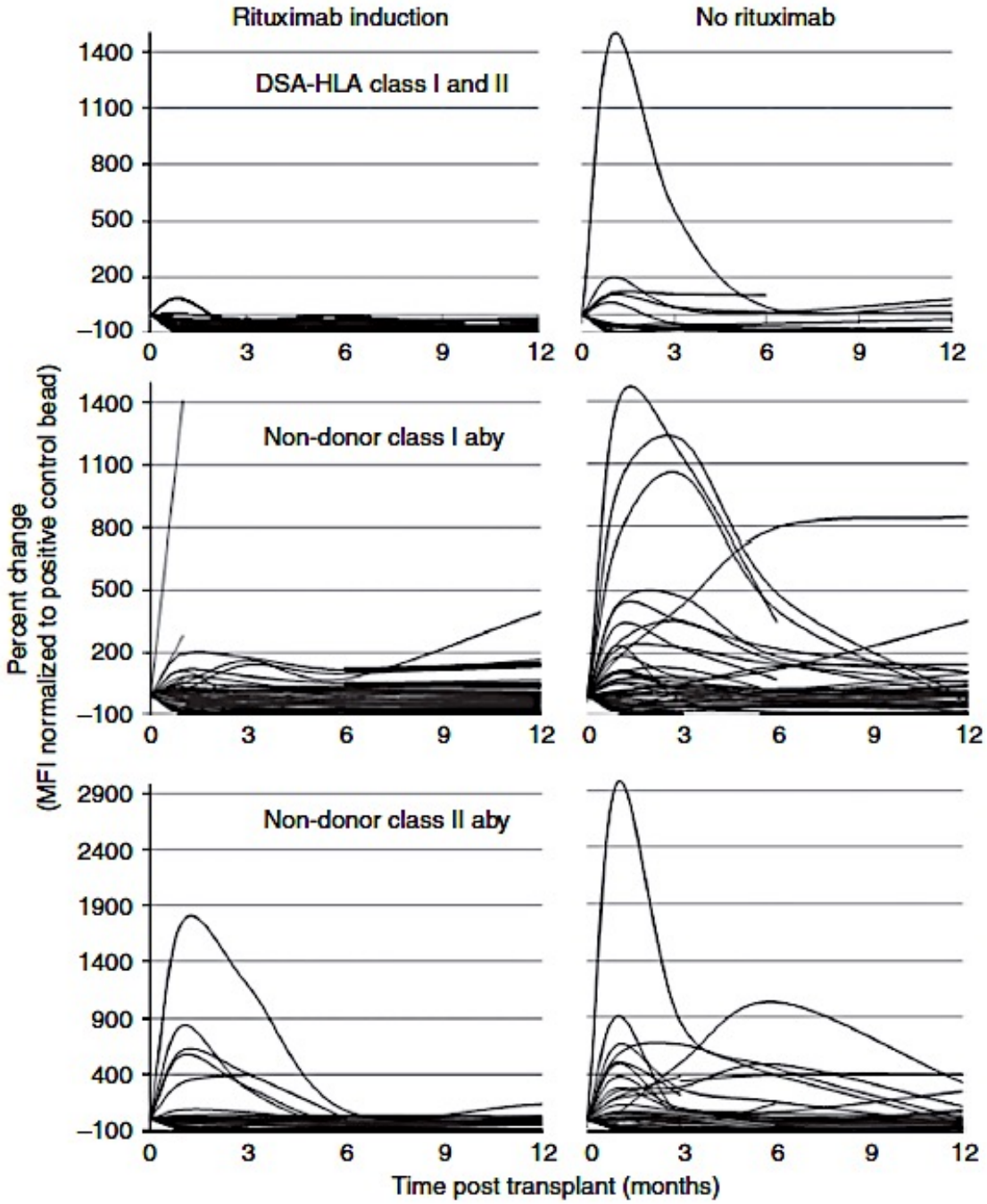
End-points	Blinded study	IVIg	IVIg+Ritux
Enrollment	15		
Transplant Rate	11 (73%)	5	6
ABMR	3	3 (43%)	0
Graft loss	2	2	0
Cause of GL		ABMR, BKVN	0

Rx of ABMR required PLEX+Ritux+Eculizumab
Efficacy similar in enabling transplantation by reduction of DSA
DSA monitoring showed rebound at 6 mo in the IVIg placebo group associated with 60% severe AMBR (3/6)
IVIg+Ritux patients (50%; 3/6) had no ABMR in protocol Bx

A closer look at rituximab induction on HLA antibody rebound following HLA-incompatible kidney transplantation

Annette M. Jackson[1], Edward S. Kraus[1], Babak J. Orandi[2], Dorry L. Segev[2], Robert A. Montgomery[2] and Andrea A. Zachary[1]

[1]Department of Medicine, Johns Hopkins University, Baltimore, Maryland, USA and [2]Department of Surgery, Johns Hopkins University, Baltimore, Maryland, USA



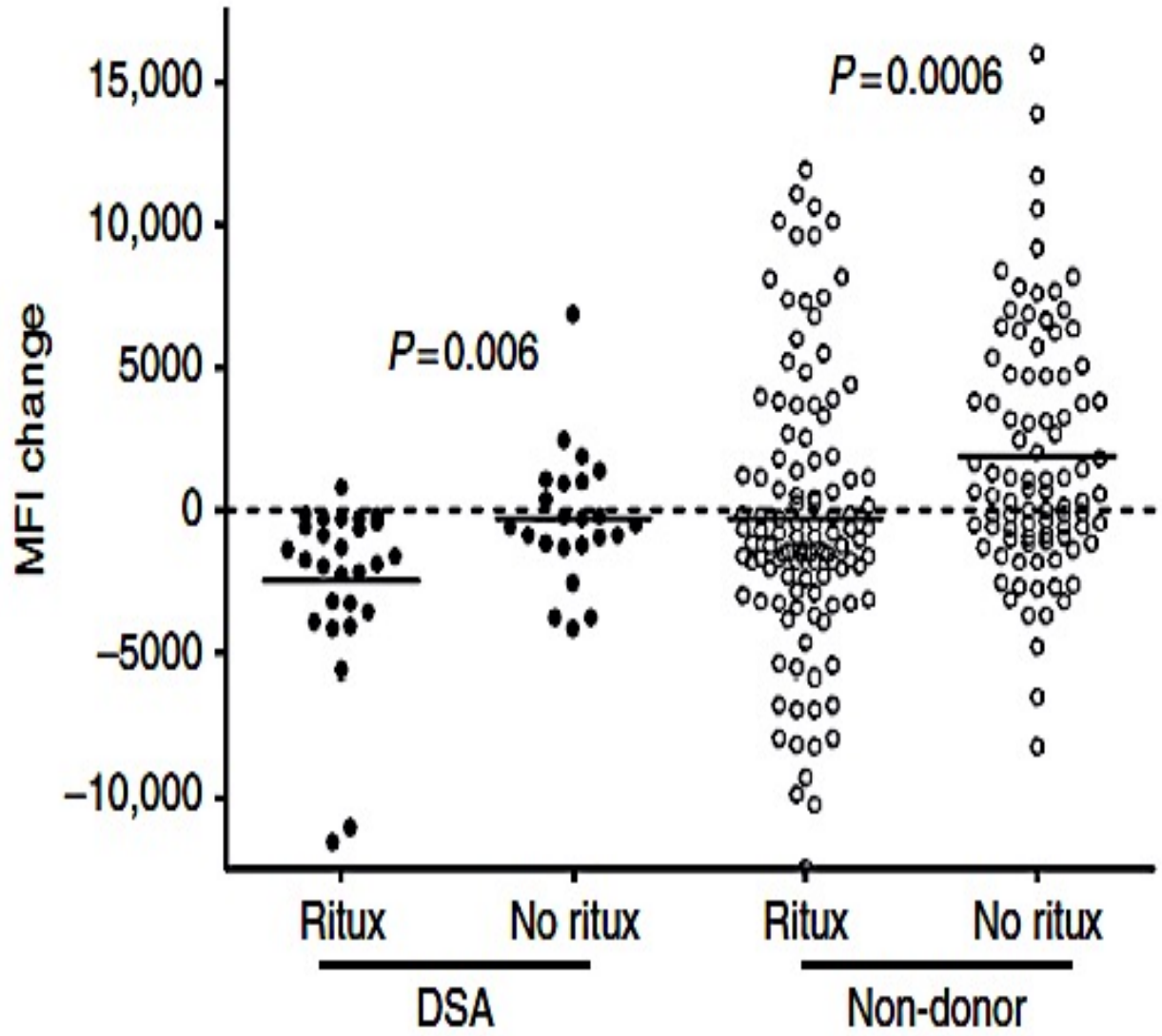


Figure 2 | Rituximab induction reduces donor-specific (DSA) and non-DSA human leukocyte antigen (HLA) antibody strength and incidence of rebound post transplantation. The change in

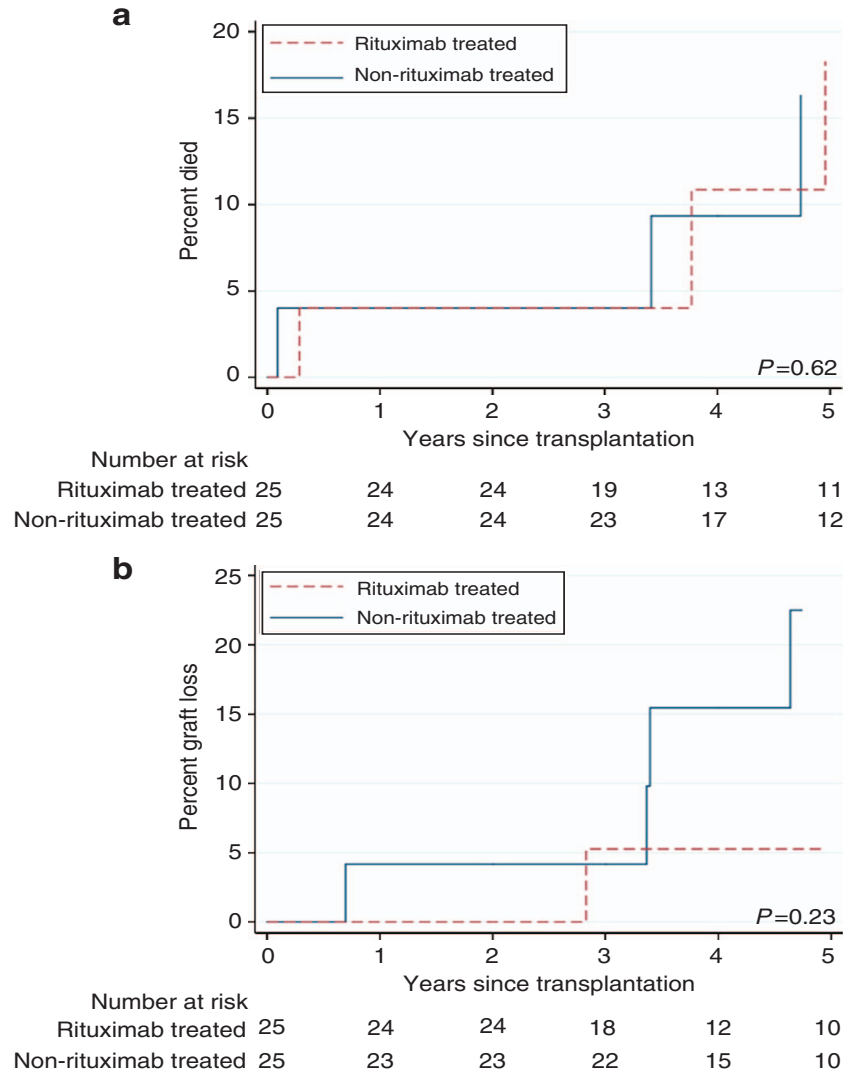


Figure 4 | Mortality and death-censored graft loss in the rituximab-treated versus non-rituximab–treated cohorts. Kaplan–Meier estimates of (**a**) the patients' 1- and 5-year survival were 96.0% (95% CI: 74.8–99.4%) and 81.7% (95% CI: 51.9–94.0%) in the rituximab-treated group and 96.0% (95% CI: 74.8–99.4%) and 83.7% (95% CI: 56.3–94.6%) in the non-rituximab-treated group ($P = 0.6$); (**b**) graft 1 and 5-year death-censored survival were 100.0 and 94.7% (95% CI: 68.0–99.0%) in the rituximab-treated group and 95.8% (95% CI: 73.9–99.4%) and 77.5% (95% CI: 49.7–91.1%) in the non-rituximab-treated group ($P = 0.23$). CI, confidence interval.

Table 1 | Patient demographics

	Rituximab $N=25$	No rituximab $N=25$	P-value
Recipient age (mean, s.d.)	41 ± 15	48 ± 13	0.08
Male gender (no. of patients, %)	8 (32%)	7 (28%)	1.0
Previous Txn (no. of patients, %)	19 (76%)	7 (28%)	0.002
Previous Txn ⩾3	5 (20%)	0	0.06
HLA-A;B;DR;DQ mismatch (mean)	4.8	5.0	0.61
Repeat HLA mismatch (No. of patients, %)	20 (80%)	0	0.0001
CDC CPRA[a] (mean, median)	48, 50	26, 3	0.02
FCXM CPRA (mean, median)	80, 89	60, 60	0.02
Crossmatch strength (no. of patients)			
CDC+	2	1	1.0
FCXM+	9	11	0.77
FCXM−, DSA+	14	13	1.0
Number of DSAs[b] (mean, median)	2.0, 2.0	1.7, 1.0	0.59
Donor age (mean, s.d.)	38 ± 12	46 ± 11	0.03
No. of pre-transplant plasmapheresis (mean)	3.7	2.3	0.08
No. of post-transplant plasmapheresis (mean)	4.1	3.9	0.81
Anti-CD25 induction (no. of patients, %)	10 (40%)	12 (48%)	0.78
Thymoglobulin induction (no. of patients, %)	15 (60%)	13 (52%)	0.78

Abbreviations: CDC, complement-dependent cytotoxicity; CPRA, calculated panel reactive antibody; DSA, donor-specific antibodies; FCXM, flow cytometric crossmatch; HLA, human leukocyte antigen; Txn, transplantation.

[a]CPRA was determined for HLA-specific antibodies of sufficient strength to yield a positive cytotoxicity (CDC) or FCXM.

[b]Number of DSAs before desensitization.

American Journal of Transplantation 2006; 6: 346–351
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2005.01178.x

A Comparison of Plasmapheresis Versus High-Dose IVIG Desensitization in Renal Allograft Recipients with High Levels of Donor Specific Alloantibody

Stegall MD et al Am J Transplant 2006; 6: 346-351

Table 1: Desensitization protocols in sensitized renal allograft patients

Protocol	N = 61	Pre-conditioning therapy
PP/IVIG/anti-CD20 from April 2000 to July 2003	32	PP/IVIG (100 mg/kg) daily Rituximab 375 mg/m^2 Splenectomy 19/32 patients
High-dose IVIG from August 2003 to July 2004	13	IVIG 2 gm/kg × 1 prior to Tx (3 gm/kg in 2 patients)
PP/IVIG/anti-CD20/monitoring form August 2004 to May 2005	16 (2*)	PP/IVIG (100 mg/kg) daily Rituximab 375 mg/m^2 × 1 Intensive post-transplant DSA monitoring

*2 patients resistant to desensitization protocol, not transplanted.

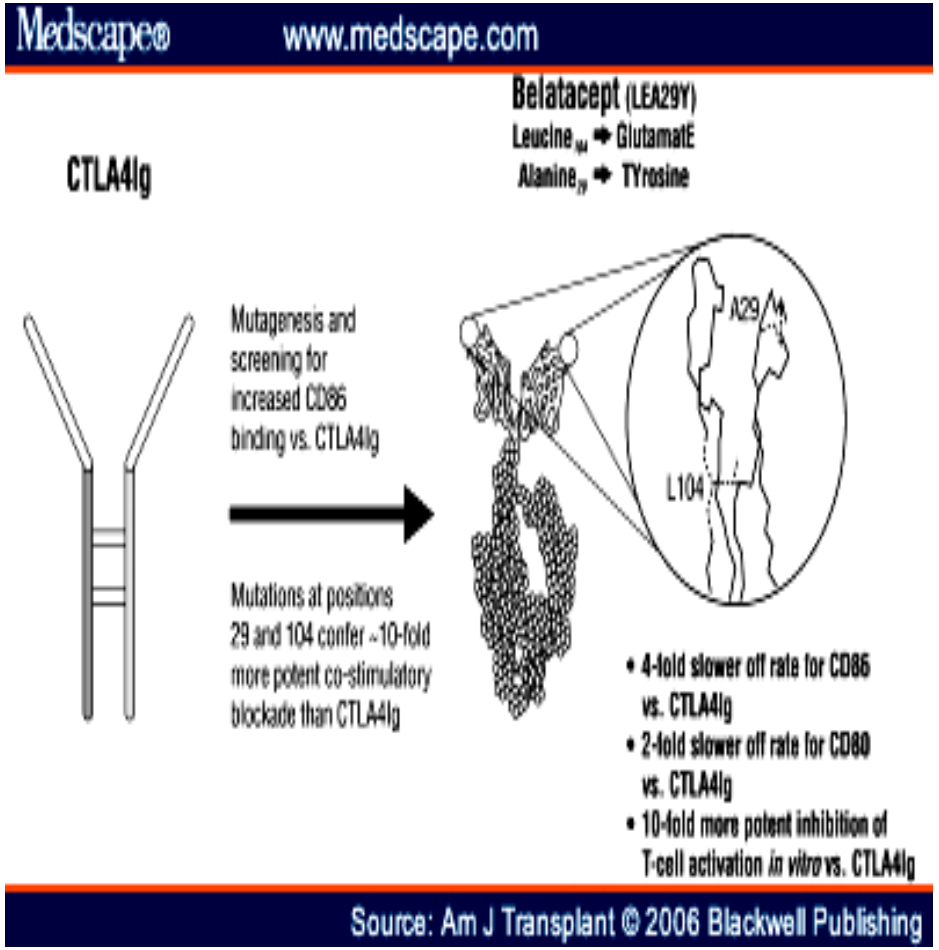
Humoral Rejection Rates

		N	AMR
Negative X-match @ Tx			
	High dose IVIG	5	4/5 (80%)
	PP/IVIg/anti-CD20	30	11/30 (37%)
	PP/IVIg/monitoring	14	4/14 (29%)
Positive X-match @ Tx	High dose IVIg PP/IVIg/anti-CD20	10	7/1- (70%) 5/10 (50% GL)

Stegall et al: Am J Transplant 2006

2nd Generation CTLA4-Ig (LEA29Y)

- Fusion-Receptor Protein including the extracellular region of human CTLA4 and Fc domain of IgG_1
- Increased binding avidity to CD80 (B7.1) and CD86 (B7.2)
- 10-fold increase in "in vitro" effectiveness in inhibiting T cell effector function than CTLA4-Ig



Acute Rejection: Incidence and Banff Grade

	Belatacept MI (n = 219)	Belatacept LI (n = 226)	CsA (n = 221)
Acute rejection, %	22%	17%	7%
Banff 97 grade, %			
Mild acute (IA)	3	2	1
Mild acute (IB)	1	4	2
Moderate acute (IIA)	8	7	3
Moderate acute (IIB)	9	4	1
Severe acute (III)	1	<1	0

Anti-Donor Antibodies by Month 12

	Belatacept MI (n = 219)	Belatacept LI (n = 226)	CsA (n = 221)
No AR			
Patients with anti-donor HLA positive, n/N (%)	4 / 164 (2%)	3 / 179 (2%)	13 / 184 (7%)
With AR			
Patients with anti-donor HLA positive, n/N (%)	2 / 44 (5%)	0 / 37 (0)	1 / 14 (7%)

Terminal Complement Inhibition Decreases Antibody-Mediated Rejection in Sensitized Renal Transplant Recipients

Stegall MD et al Am J Transplant 2011; 11

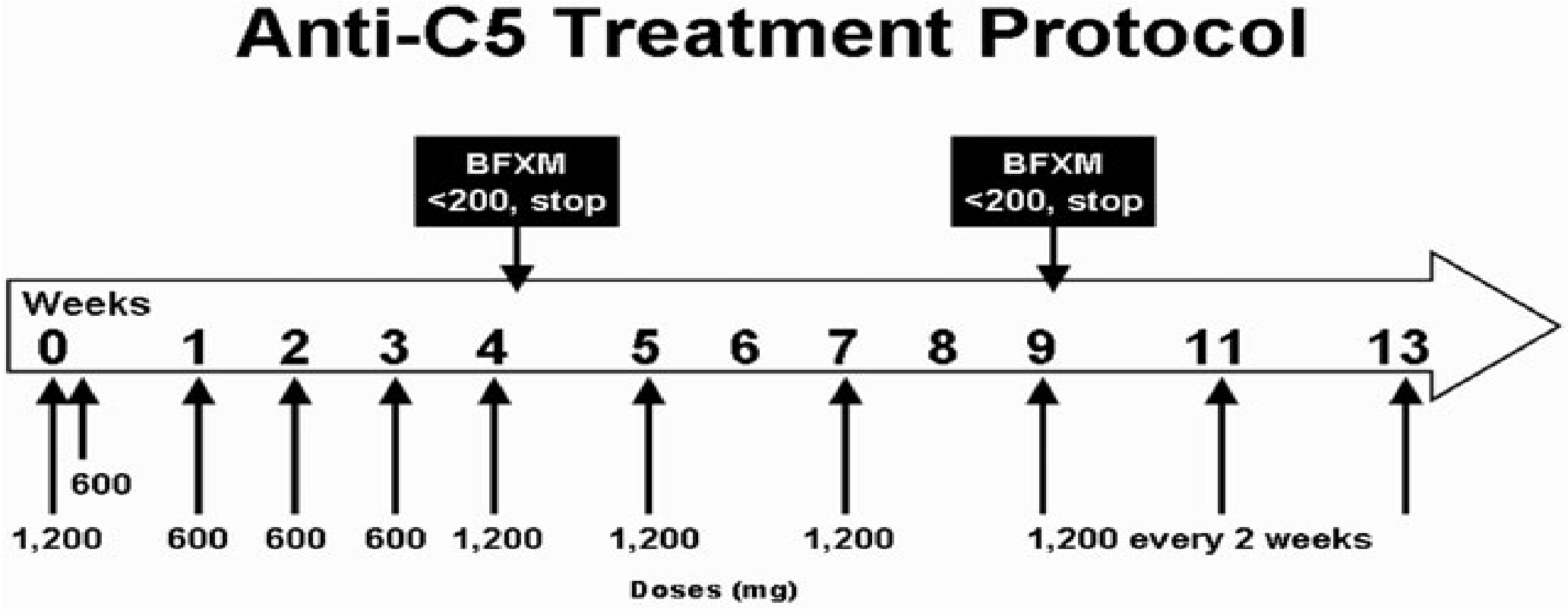
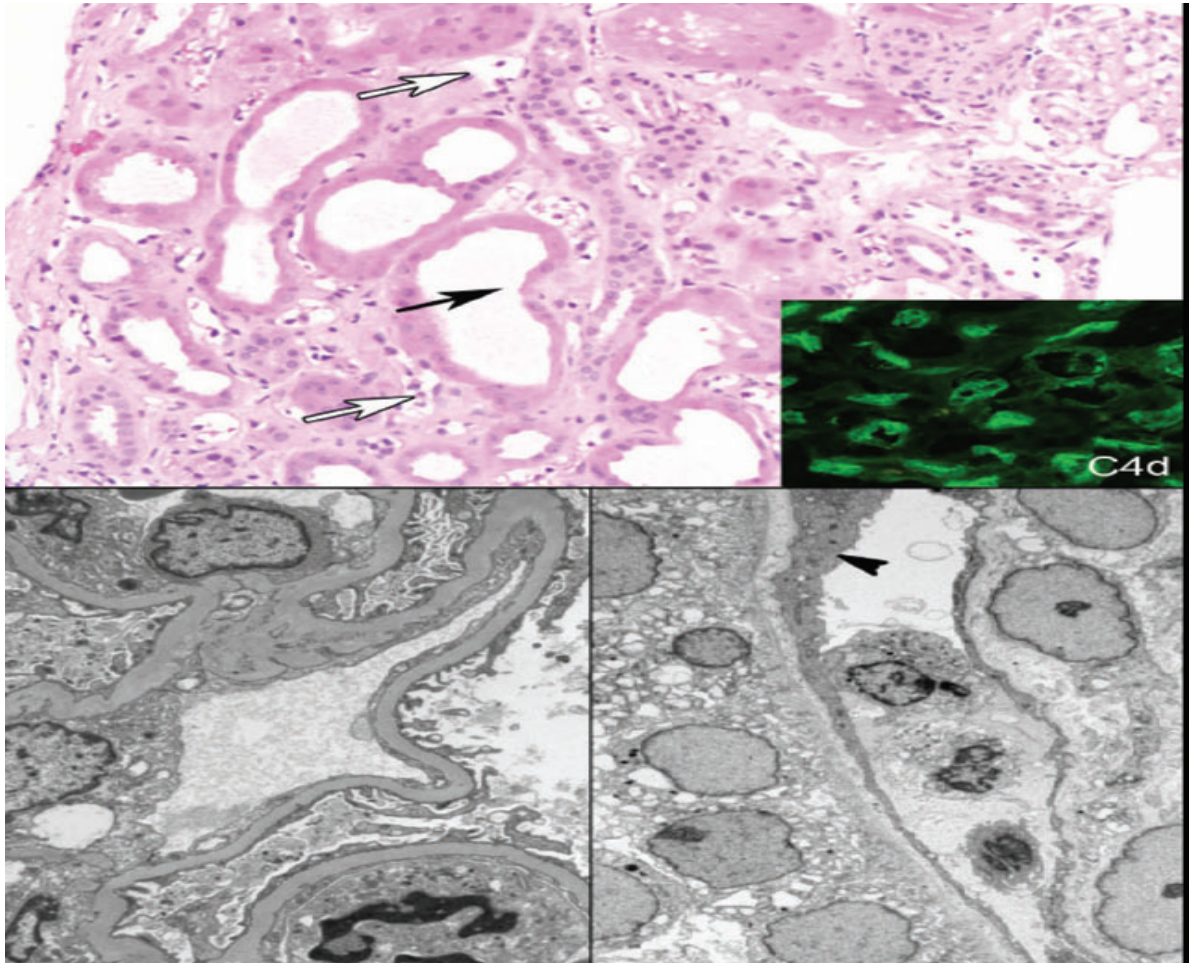


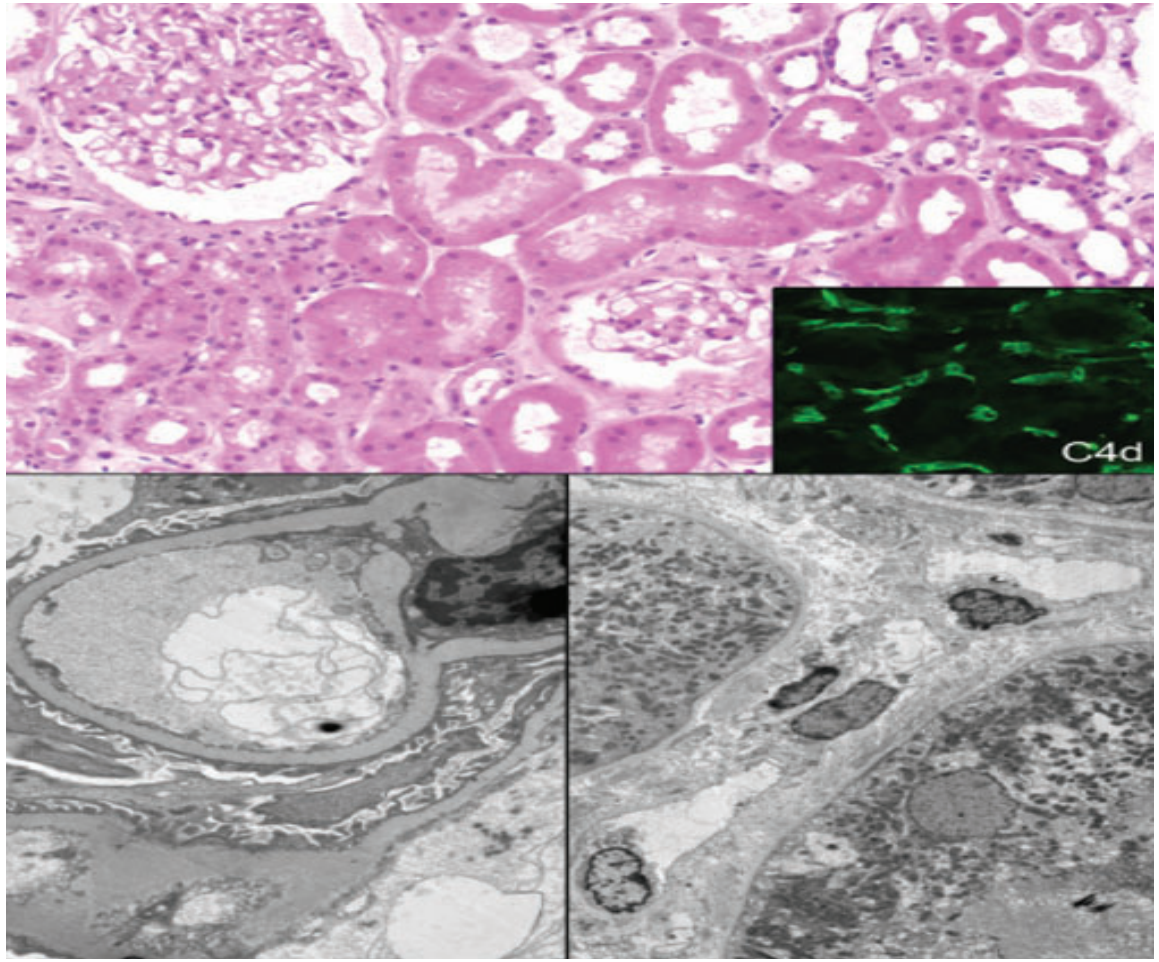
Table 2: Posttransplant outcomes in the eculizumab-treated and control groups

Category	Eculizumab group (n = 26)	Control group (n = 51)	p-Value
Follow-up (mean months ± SD, range)	11.8 ± 6.3 (3.0–27.5)	48.8 ± 14.1 (7.8–69.8)	
Graft survival at 1 year (n, %)	16/16 (100%)	49/51 (96%)	1.00
Antibody-mediated rejection ≤ 3months (n, %)	2 (7.7%)	21 (41%)	0.0031
Patients developing high DSA levels ≤ 3 months[1]	13 (50%)	22 (43%)	0.63
High DSA biopsies C4d+ (n, %)	13 (100%)	20 (91%)	0.52
High DSA and C4d+ biopsies showing AMR (n, %)	2 (15%)	20 (100%)	<0.0001
Cellular rejection ≤3 months (n, %)	1 (6.2%)	1 (2%)	0.42
Plasma exchange posttransplant			
Patients receiving PE (n, %)	3 (12%)	39 (76%)	<0.0001
Number of PE treatments (mean ± SD)	0.35 ± 1.1	7.9 ± 7.5	<0.0001
Splenectomy (n, %)	0 (0%)	9 (18%)	0.025
Graft dysfunction in first month (mg/dL) (maximum serum creatinine – nadir serum creatinine)	0.45 ± 0.37	0.93 ± 1.15	0.05
Histology at 1 year			
Transplant glomerulopathy incidence (n, %)	1/15 (6.7%)	15/42 (36%)	0.044
Cg score (mean ± SD)	0.20 ± 0.78	0.74 ± 1.13	0.17
Ci score (mean ± SD)	1.00 ± 0.76	0.79 ± 0.80	0.31
Ct score (mean ± SD)	1.13 ± 0.74	0.91 ± 0.80	0.33
Cv score (mean ± SD)	0.80 ± 0.68	0.59 ± 0.74	0.23

[1] B flow crossmatch channel shift >350 at any time point in the first 3 months.

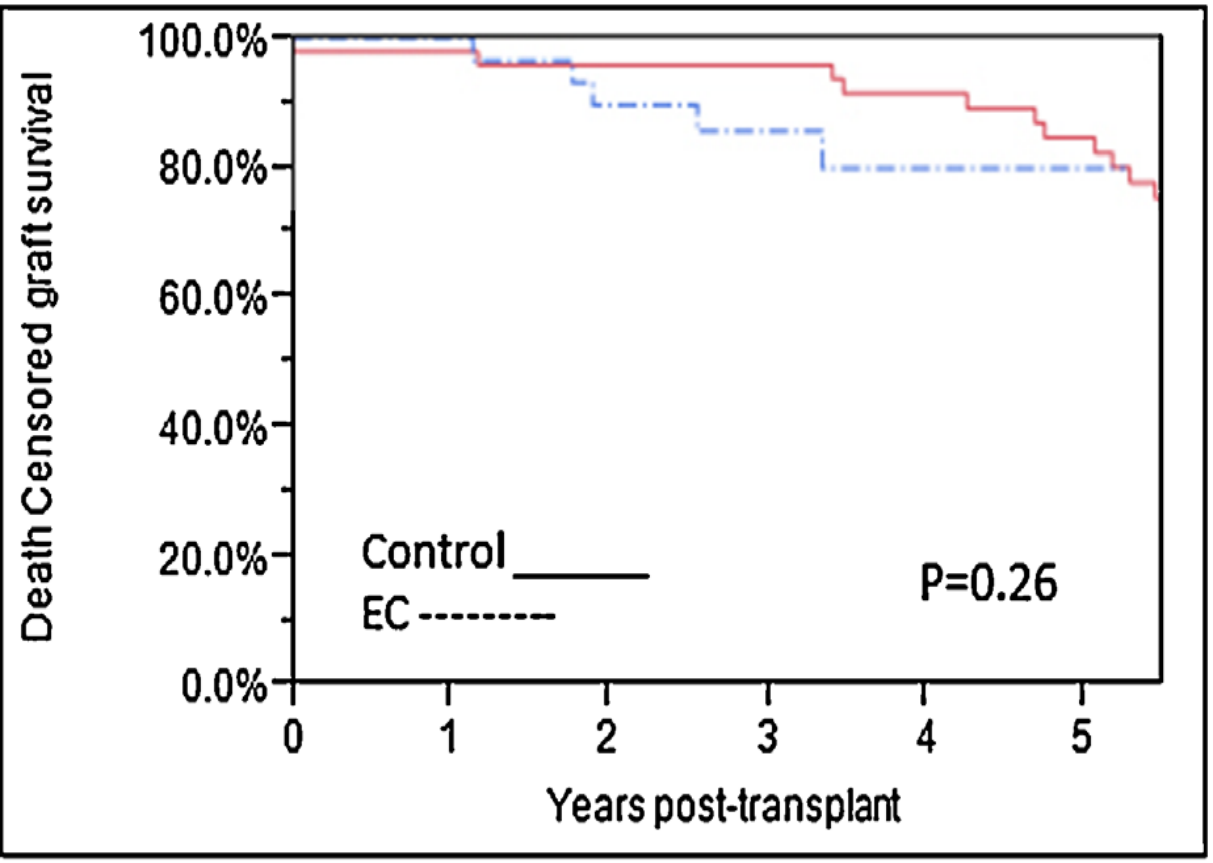
Histological Injury Is Ameliorated By Eculizumab





Long-term Outcomes in Patients Treated with Eculizumab
Cornell et al: Am J Transplant 2015:15

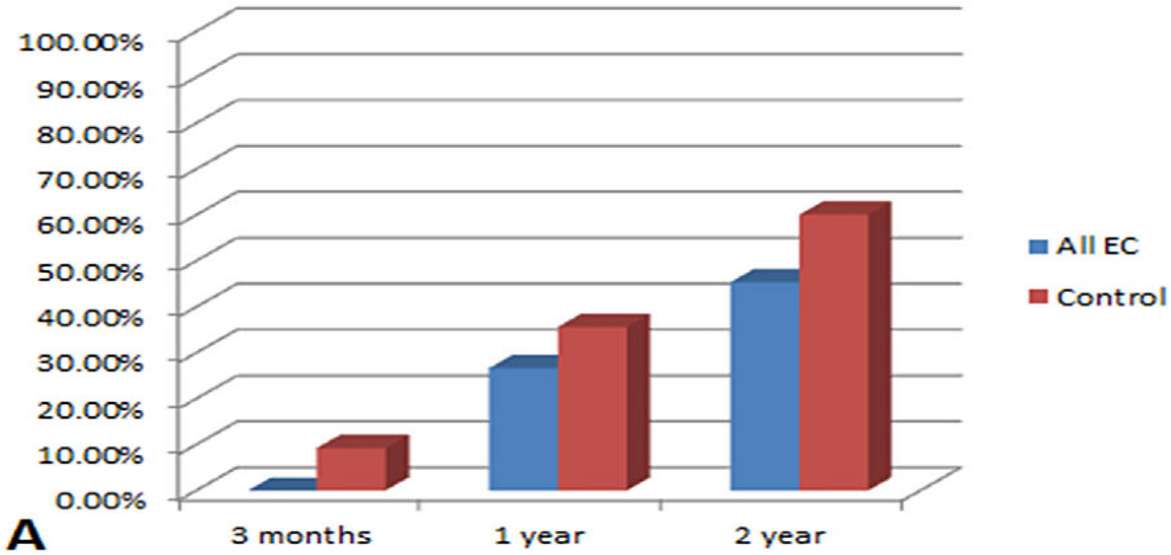
A.



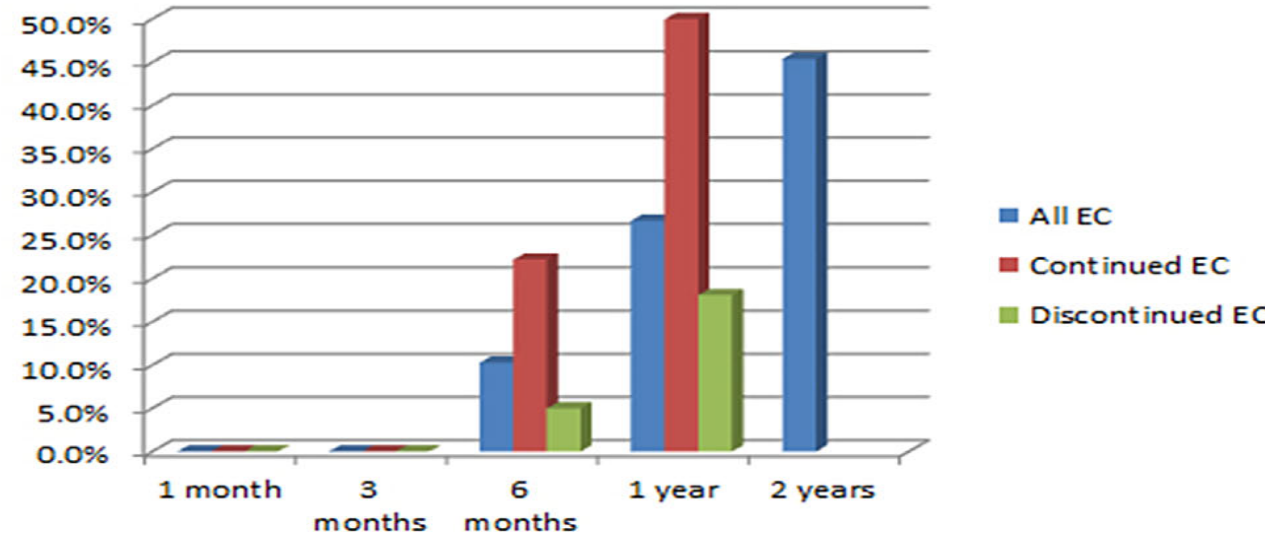
At risk	0	1	2	3	4	5
Control	48	46	46	45	40	37
EC	30	30	26	21	8	2

B.

	Eculizumab n=6	Control n=17	p-value
Transplant glomerulopathy	5(83.3%)	10 (58.8%)	P=0.37
Death with Function	1 (16.7%)	3 (17.6%)	P=1.0
Recurrent Focal Segmental Glomerulosclerosis	0 (0%)	1 (5.9%)	P=1.0
Recurrent IgA Nephropathy	0 (0%)	1 (5.9%)	P=1.0
Late Combined Cellular & Antibody Mediated Rejection	0 (0%)	1 (5.9%)	P=1.0
Unknown	0 (0%)	1 (5.9%)	P=1.0

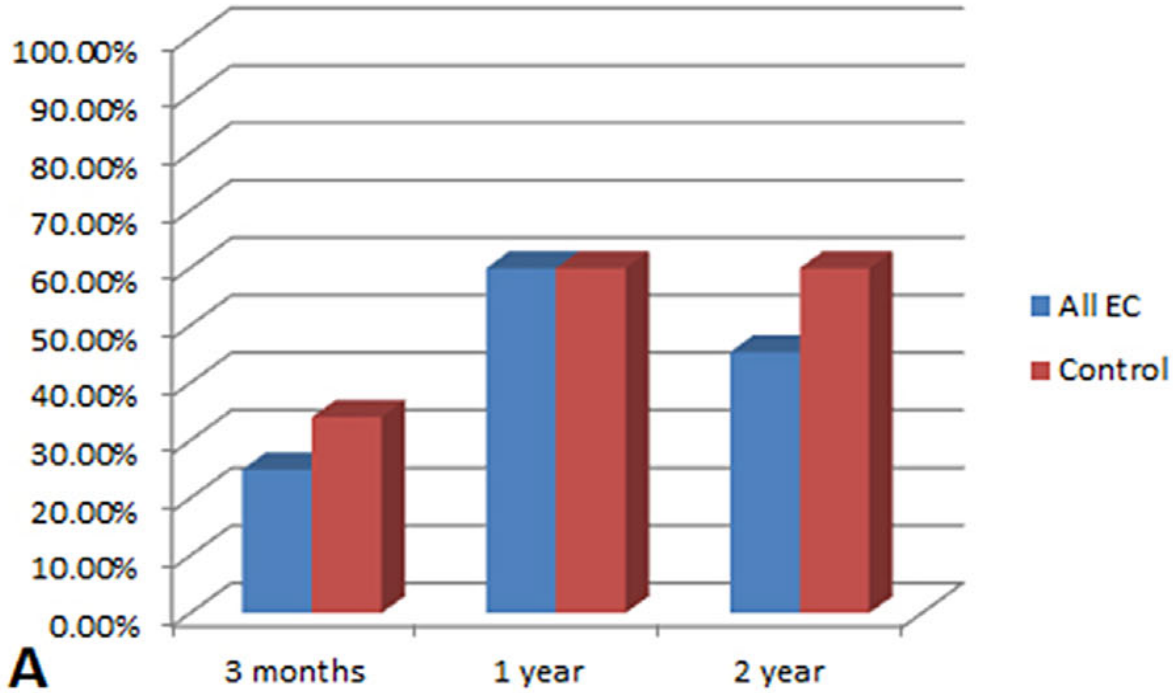


A

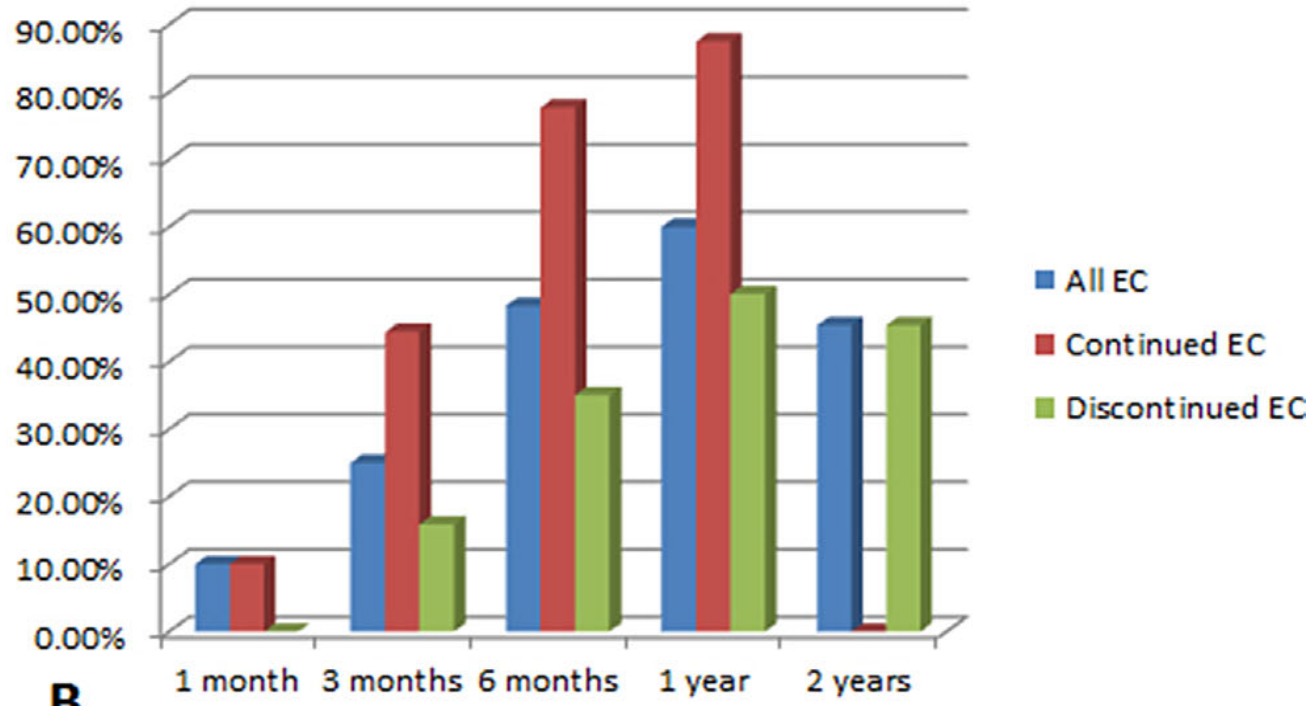


Transplant Glomerulopathy in Controls vs. Eculizumab			
	3-4 months	1 year	2 year
All EC	0% (0/28)	26.7% (8/30)	45.4% (10/22)
Control	9.3% (4/43)	39.5% (15/38)	63.6% (21/33)
p-value (EC vs. control)	P=0.15	P=0.31	P=0.27

Transplant glomerulopathy over time in Eculizumab group					
	1 month	3-4 months	6 months	1 year	2 years
All EC	0% (0/30)	0% (0/28)	10.3% (3/29)	26.7% (8/30)	45.4% (10/22)
Continued EC	0% (0/30)	0% (0/9)	22.2% (2/9)	50.0% (4/8)	NA
Discontinued EC	NA	0% (0/19)	5.0% (1/20)	18.1% (4/22)	NA
p-value	NA	P=1.0	P=0.22	P=0.16	NA



A



B

Moderate-to-Severe Peritubular capillaritis in Controls vs. Eculizumab			
	3-4 months	1 year	2 year
All EC	25.0% (7/28)	60.0% (18/30)	45.4% (10/22)
Control	34.1% (14/41)	60.0% (21/35)	60.0% (15/25)
p-value (control vs. EC)	P= 0.59	P=1.00	P=0.39

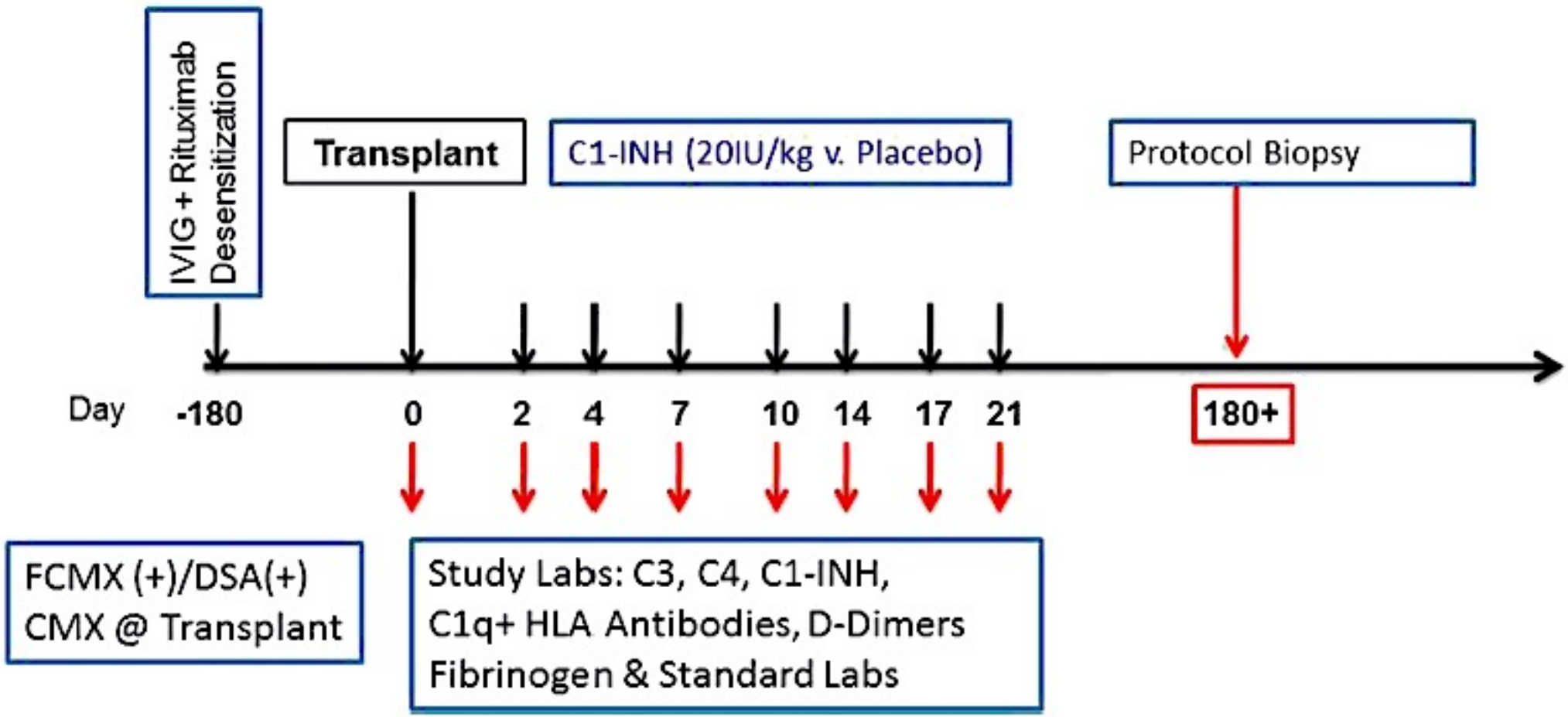
Moderate-to-Severe Peritubular capillaritis over time in Eculizumab group					
	1 month	3-4 months	6 months	1 year	2 years
All EC	10% (3/30)	25.0% (7/28)	48.3% (14/29)	60% (18/30)	45.4% (10/22)
Continued EC	10% (3/30)	44.4% (4/9)	77.7% (7/9)	87.5% (7/8)	NA
Discontinued EC	NA	15.9% (3/19)	35.0% (7/20)	50.0% (11/22)	NA
p-value	NA	P=0.17	P=0.05	P=0.10	NA

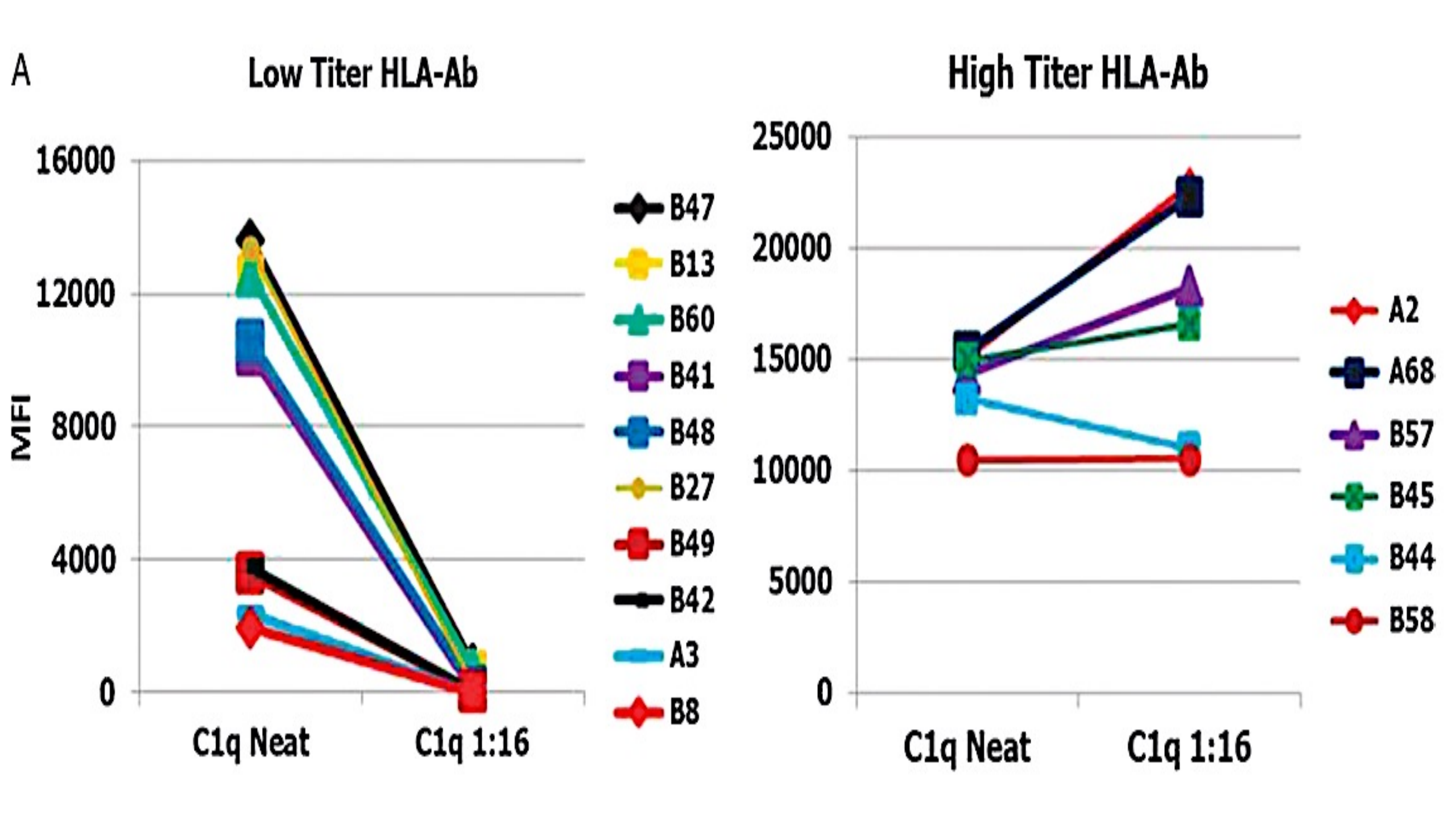
Original Clinical Science

A Phase I/II Placebo-Controlled Trial of C1-Inhibitor for Prevention of Antibody-Mediated Rejection in HLA Sensitized Patients

Ashley A. Vo,[1] Adriana Zeevi,[2] Jua Choi,[1] Kristen Cisneros,[1] Mieko Toyoda,[3] Joseph Kahwaji,[1] Alice Peng,[1] Rafael Villicana,[1] Dechu Puliyanda,[1] Nancy Reinsmoen,[4] Mark Haas,[5] and Stanley C. Jordan[1]

C1-INH Study Format




A
Low Titer HLA-Ab
16000
12000
8000
4000
0
MFI
C1q Neat
C1q 1:16
B47
B13
B60
B41
B48
B27
B49
B42
A3
B8
High Titer HLA-Ab
25000
20000
15000
10000
5000
0
C1q Neat
C1q 1:16
A2
A68
B57
B45
B44
B58

Assessment of Tocilizumab (Anti–Interleukin-6 Receptor Monoclonal) as a Potential Treatment for Chronic Antibody-Mediated Rejection and Transplant Glomerulopathy in HLA-Sensitized Renal Allograft Recipients

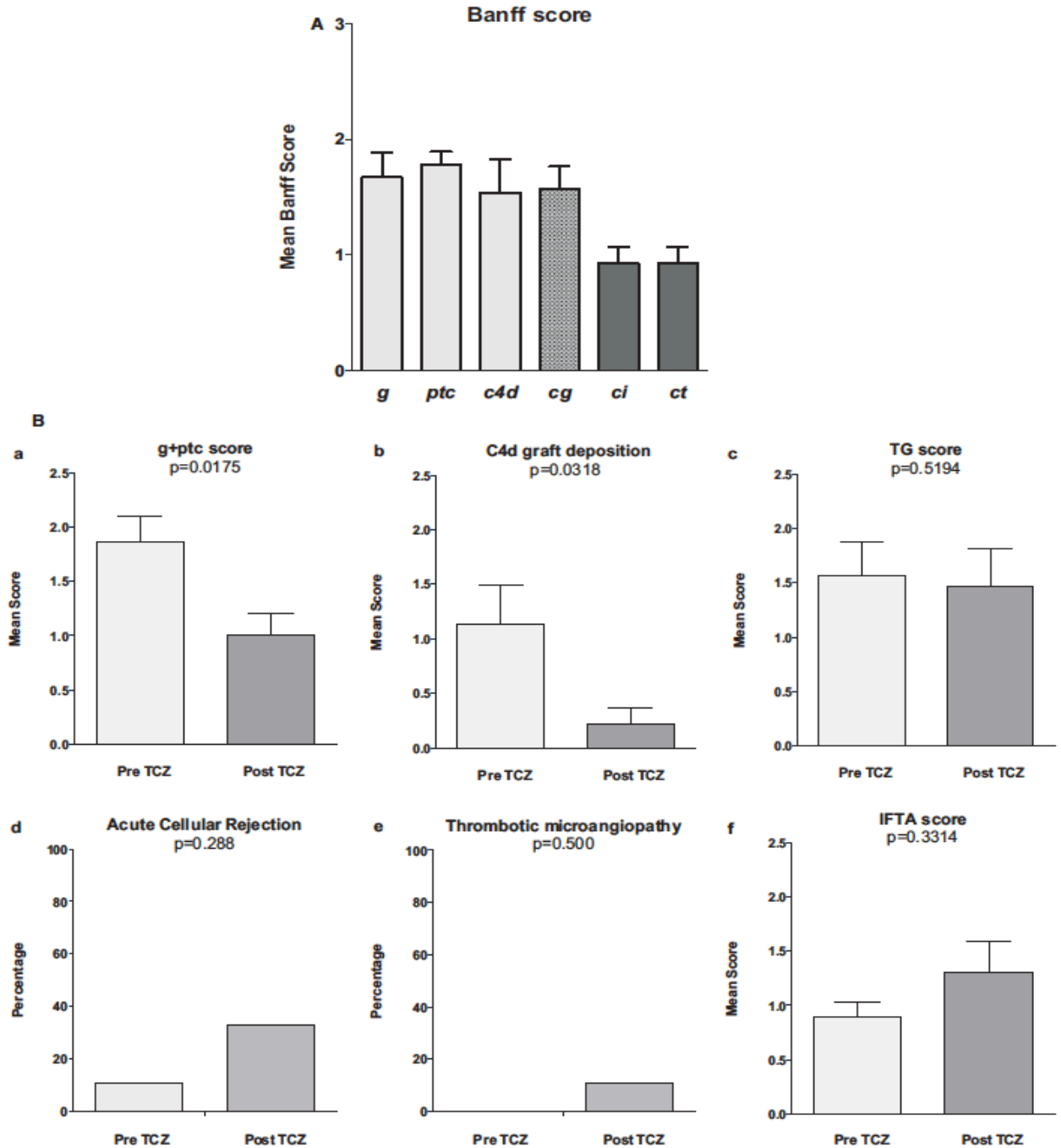
J. Choi[1,*], O. Aubert[2], A. Vo[1], A. Loupy[2], M. Haas[3], D. Puliyanda[1], I. Kim[1], S. Louie[1], A. Kang[1], A. Peng[1], J. Kahwaji[1], N. Reinsmoen[3], M. Toyoda[4] and S. C. Jordan[1]

From 2011-2016: 36 patients received tocilizumab 8 mg/Kg monthly for 6-25 mo

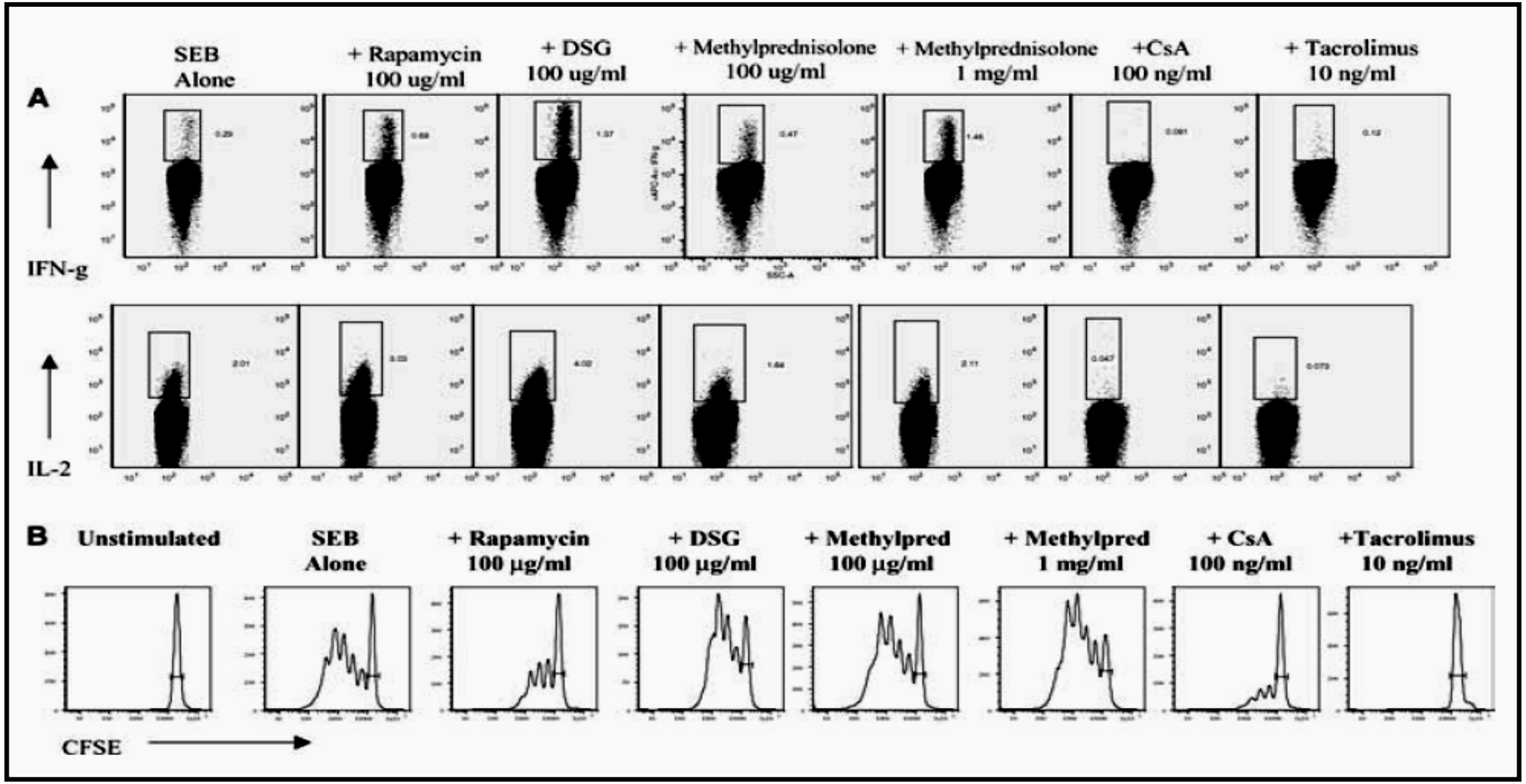
Maximal dose of 800 mg

As ‘rescue therapy’ for cAMR with or without TG

Am J Transpl 2017; XX:1-9


A
Banff score
Mean Banff Score
3
2
1
0
g
ptc
c4d
cg
ci
ct
B
a
g+ptc score
p=0.0175
Mean Score
2.5
2.0
1.5
1.0
0.5
0.0
Pre TCZ
Post TCZ
b
C4d graft deposition
p=0.0318
Mean Score
Pre TCZ
Post TCZ
c
TG score
p=0.5194
Mean Score
Pre TCZ
Post TCZ
d
Acute Cellular Rejection
p=0.288
Percentage
100
80
60
40
20
0
Pre TCZ
Post TCZ
e
Thrombotic microangiopathy
p=0.500
Percentage
Pre TCZ
Post TCZ
f
IFTA score
p=0.3314
Mean Score
Pre TCZ
Post TCZ

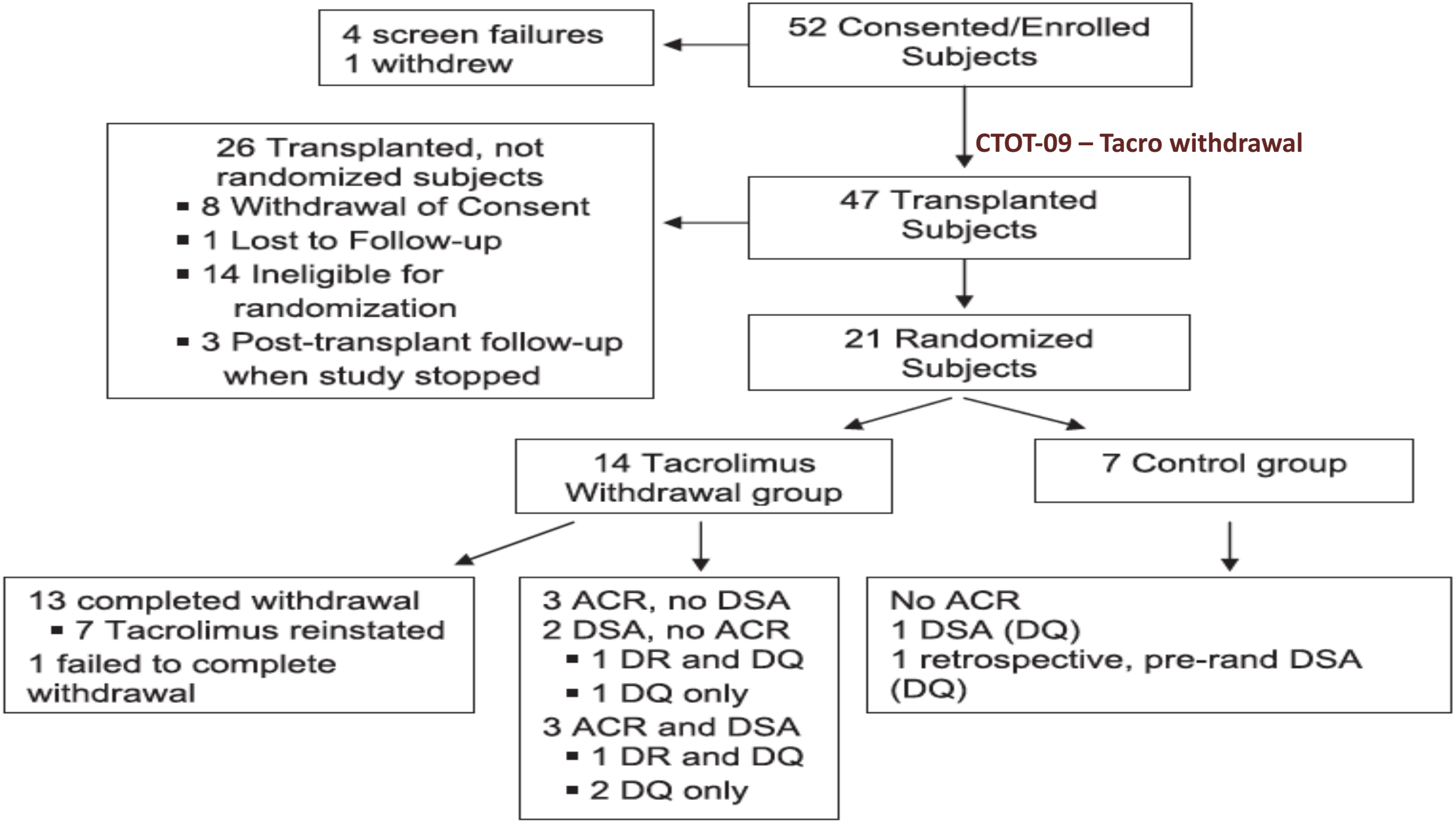
CNIs Uniquely Inhibit the Function of $CD4^+$ Memory Cells

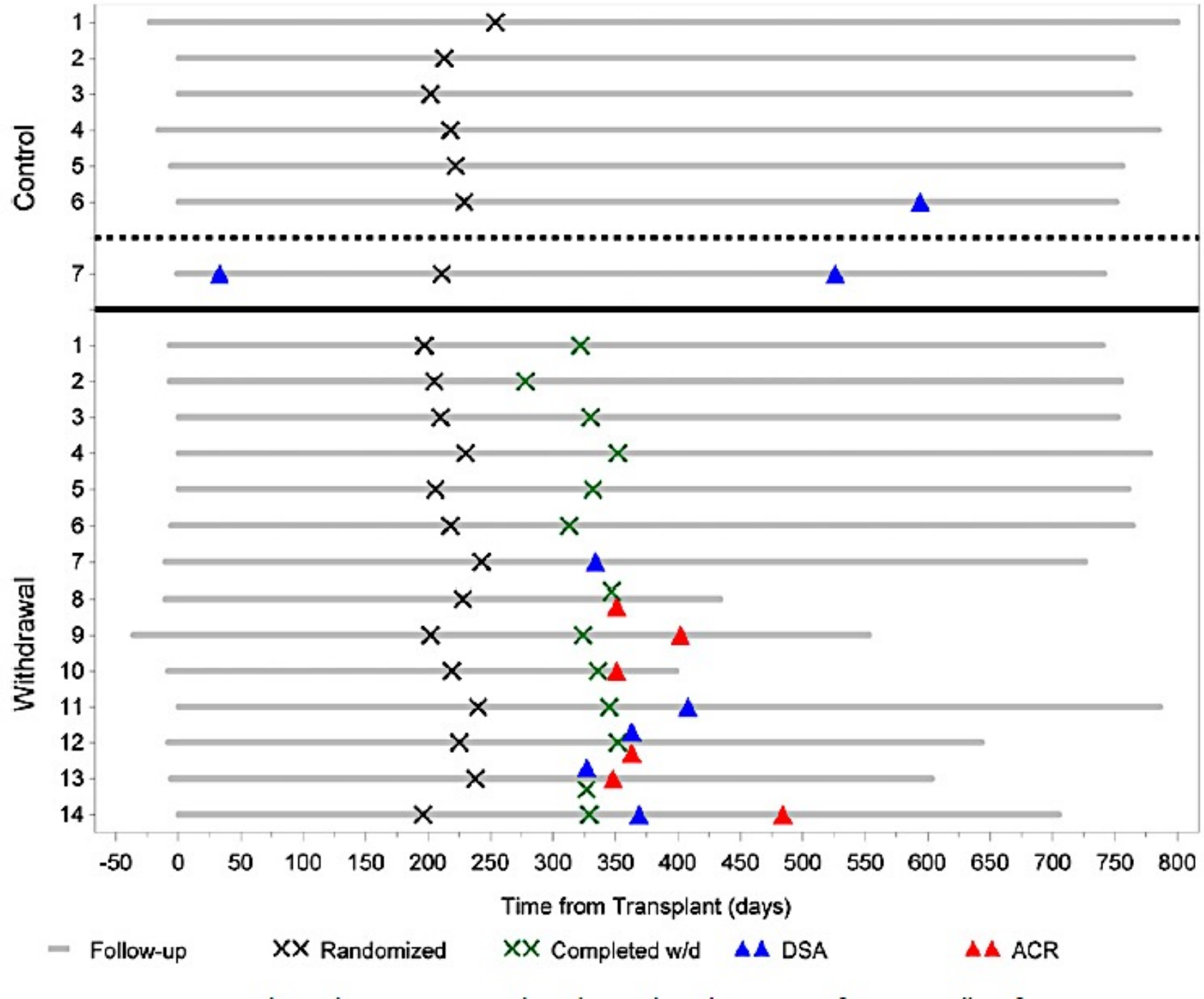


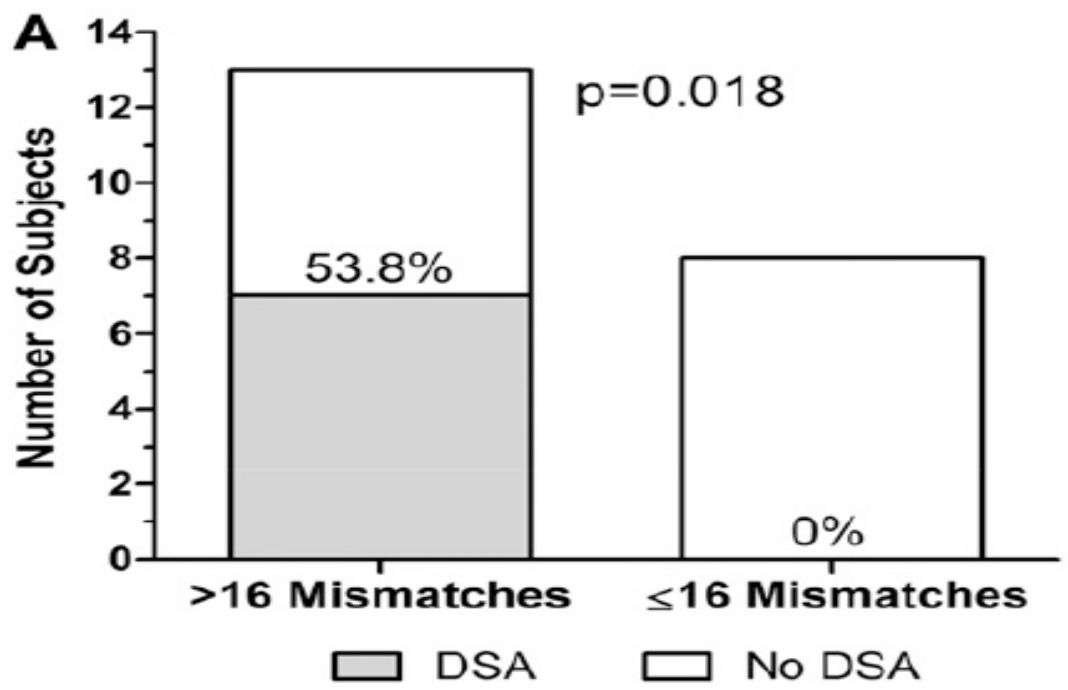
Adverse Outcomes of Tacrolimus Withdrawal in Immune–Quiescent Kidney Transplant Recipients

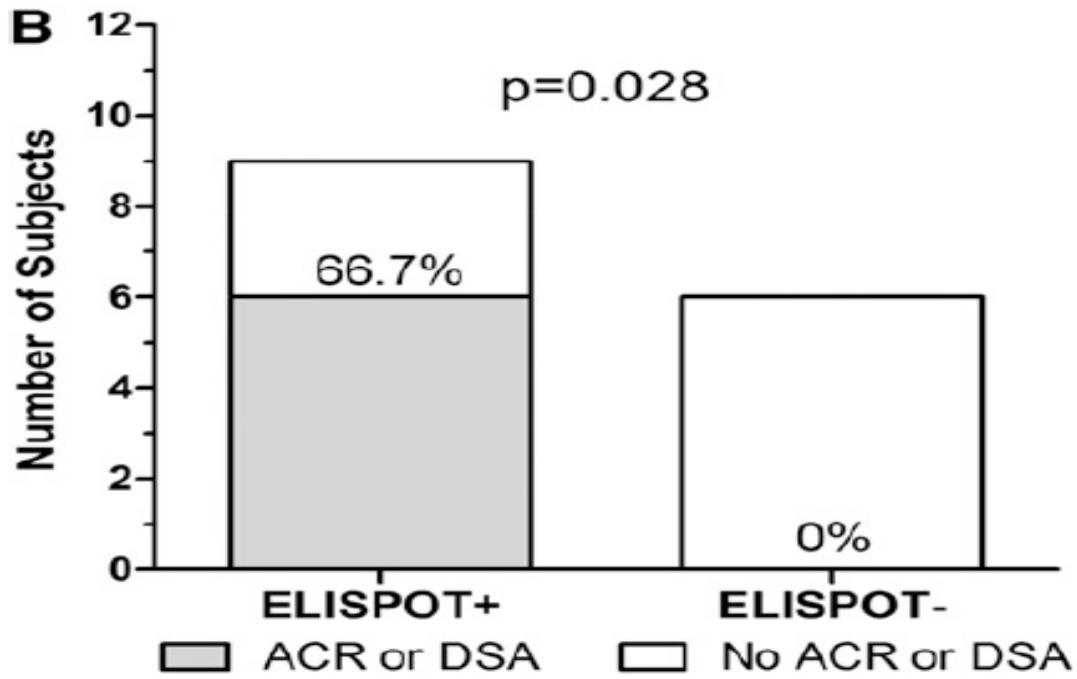
Donald E. Hricik,* Richard N. Formica,† Peter Nickerson,‡ David Rush,‡ Robert L. Fairchild,§ Emilio D. Poggio,§ Ian W. Gibson,‡ Chris Wiebe,‡ Kathryn Tinckam,‖ Suphamai Bunnapradist,¶ Milagros Samaniego-Picota,** Daniel C. Brennan,†† Bernd Schröppel,‡‡ Osama Gaber,§§‖‖ Brian Armstrong,¶¶ David Ikle,¶¶ Helena Diop,*** Nancy D. Bridges,*** and Peter S. Heeger,‡‡ for the Clinical Trials in Organ Transplantation-09 Consortium

Low immunological risk population:
1ary living donor Tx recipients
rATG induction; tacro, MMF, pred
>70% Caucasian recipients
Median HLA MM 4


52 Consented/Enrolled Subjects
4 screen failures
1 withdrew
CTOT-09 – Tacro withdrawal
47 Transplanted Subjects
26 Transplanted, not randomized subjects
8 Withdrawal of Consent
1 Lost to Follow-up
14 Ineligible for randomization
3 Post-transplant follow-up when study stopped
21 Randomized Subjects
14 Tacrolimus Withdrawal group
7 Control group
13 completed withdrawal
7 Tacrolimus reinstated
1 failed to complete withdrawal
3 ACR, no DSA
2 DSA, no ACR
1 DR and DQ
1 DQ only
3 ACR and DSA
1 DR and DQ
2 DQ only
No ACR
1 DSA (DQ)
1 retrospective, pre-rand DSA (DQ)

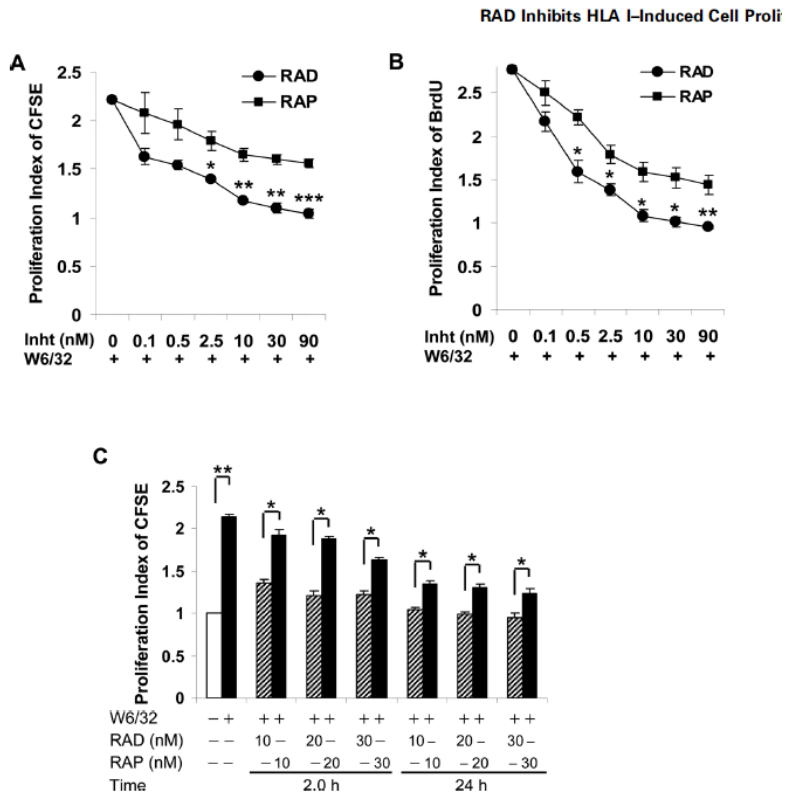

Control
1
2
3
4
5
6
7
Withdrawal
1
2
3
4
5
6
7
8
9
10
11
12
13
14
-50
0
50
100
150
200
250
300
350
400
450
500
550
600
650
700
750
800
Time from Transplant (days)
Follow-up
Randomized
Completed w/d
DSA
ACR


A
Number of Subjects
14
12
10
8
6
4
2
0
p=0.018
53.8%
0%
>16 Mismatches
≤16 Mismatches
DSA
No DSA


B
Number of Subjects
12
10
8
6
4
2
0
p=0.028
66.7%
0%
ELISPOT+
ELISPOT-
ACR or DSA
No ACR or DSA

Everolimus Inhibits Anti-HLA I Antibody-Mediated Endothelial Cell Signaling, Migration and Proliferation More Potently Than Sirolimus

Y.-P. Jin[1], N. M. Valenzuela[1], M. E. Ziegler[1], E. Rozengurt[2] and E. F. Reed[1,*]



Donor-Specific HLA Antibodies in a Cohort Comparing Everolimus With Cyclosporine After Kidney Transplantation

L. Liefeldt[a,†,*], S. Brakemeier[a,†], P. Glander[a], J. Waiser[a], N. Lachmann[b], C. Schönemann[b], B. Zukunft[a], P. Illigens[a], D. Schmidt[a], K. Wu[a,c], B. Rudolph[c], H.-H. Neumayer[a] and K. Budde[a]

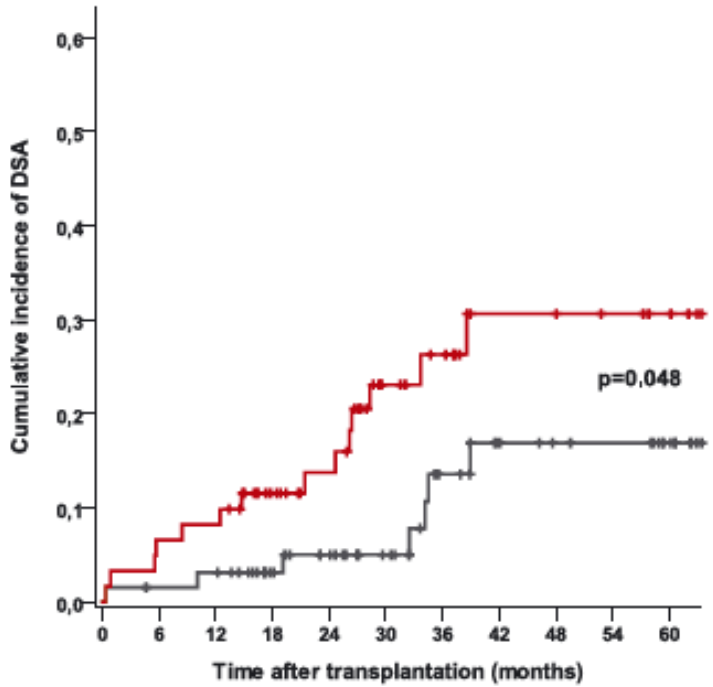


Figure 1: Cumulative incidence plot of DSA-detection in 61 patients (red) with everolimus-based immunosuppression compared to 66 patients (black) with cyclosporine-treatment (log-rank: $p = 0.048$).

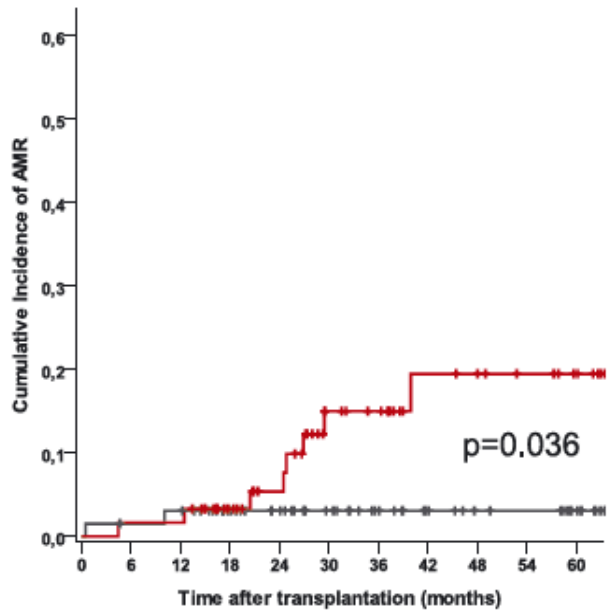
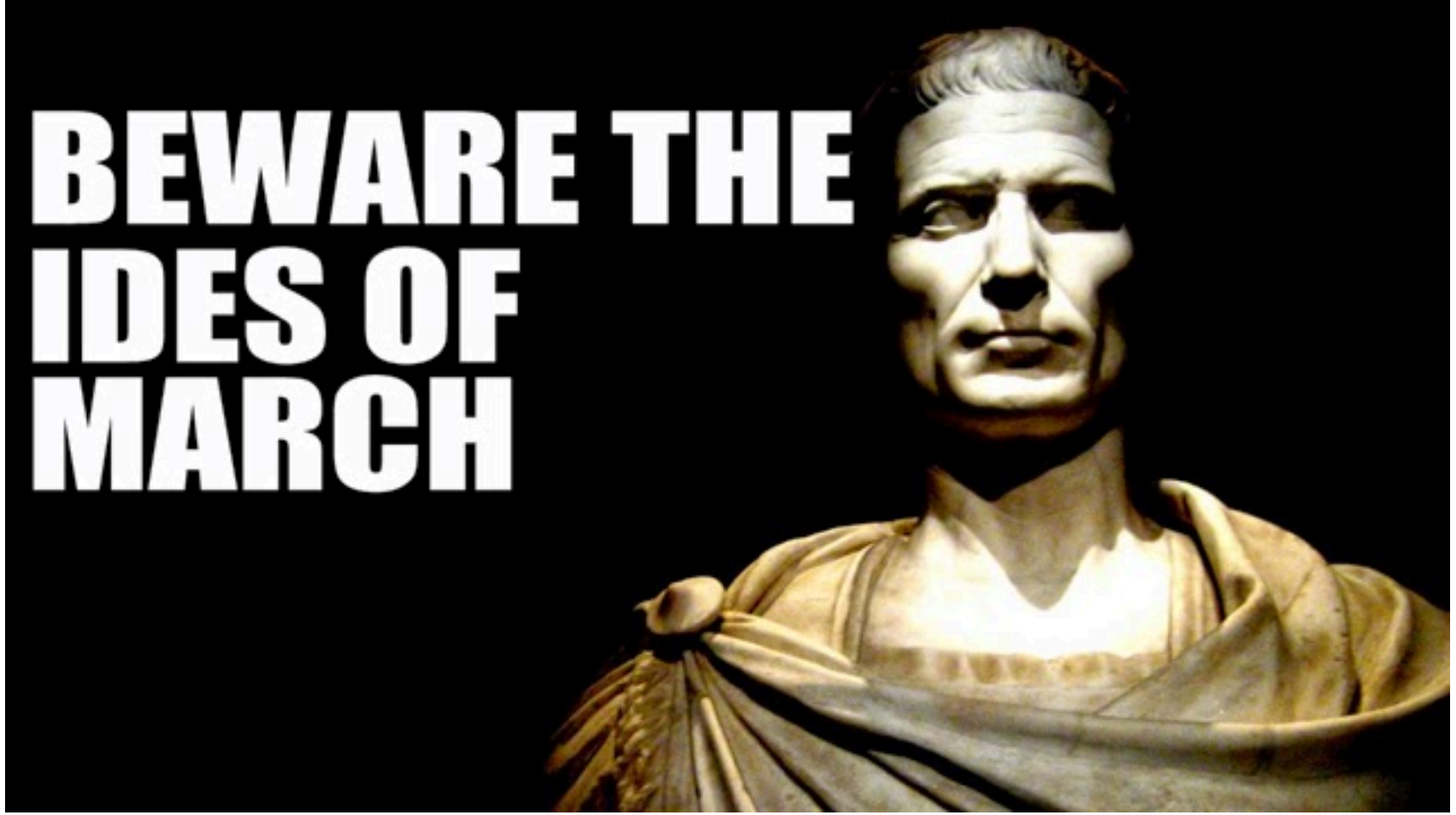


Figure 2: Cumulative incidence plot of first antibody-mediated rejection in 61 patients (red) with everolimus-based immunosuppression compared to 66 patients (black) with cyclosporine-treatment (log-rank: $p = 0.036$).

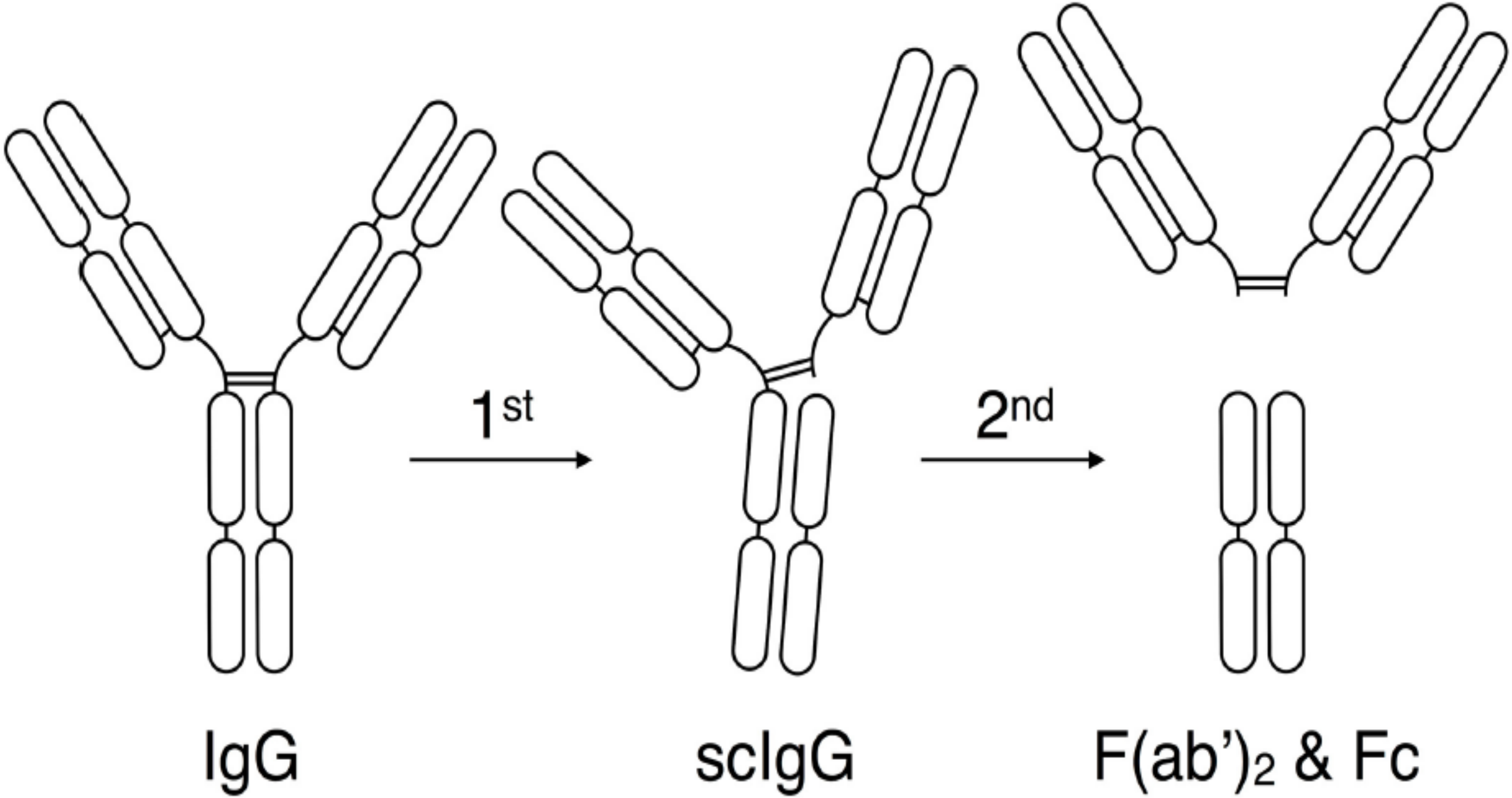
Table 3: Outcome after KTX in patients randomized to receive cyclosporine- or everolimus-based immunosuppression

Parameter		Cyclosporine (n = 66)	Everolimus (n = 61)
Patient survival number (%)	Month 12	65 (98.5%)	61 (100.0%)
	Month 24	64 (97.0%)	60 (98.4%)
	Last observation[1]	63 (95.4%)	60 (98.4%)
Death censored graft survival number (%)	Month 12	65/65 (100.0%)	60/61 (98.4%)
	Month 24	63/64 (98.4%)	57/60 (95.0%)
	Last observation[2]	61/63 (96.8%)	55/60 (91.7%)
Creatinine (mg/dL) median ± interquartile range	Month 12	1.46 ± 0.61 (n = 65)	1.21 ± 0.57 (n = 60)***
	Month 24	1.69 ± 0.57 (n = 49)	1.31 ± 0.84 (n = 44)*
	>24 Months	1.73 ± 0.70 (n = 40)	1.45 ± 1.06 (n = 36)#
Proteinuria (mg/day) median±interquartile range	Month 12	179 ± 172 (n = 60)	258 ± 183 (n = 46)**
		Proteinuria >1 g/day: n = 0	Proteinuria >1 g/day: n = 2
	Month 24	150 ± 97 (n = 39)	380 ± 608 (n = 34)***
		Proteinuria >1 g/day: n = 0	Proteinuria >1 g/day: n = 6
	>24 Months	132 ± 185 (n = 35)	278 ± 608 (n = 33)**
		Proteinuria >1 g/day: n = 1	Proteinuria >1 g/day: n = 7

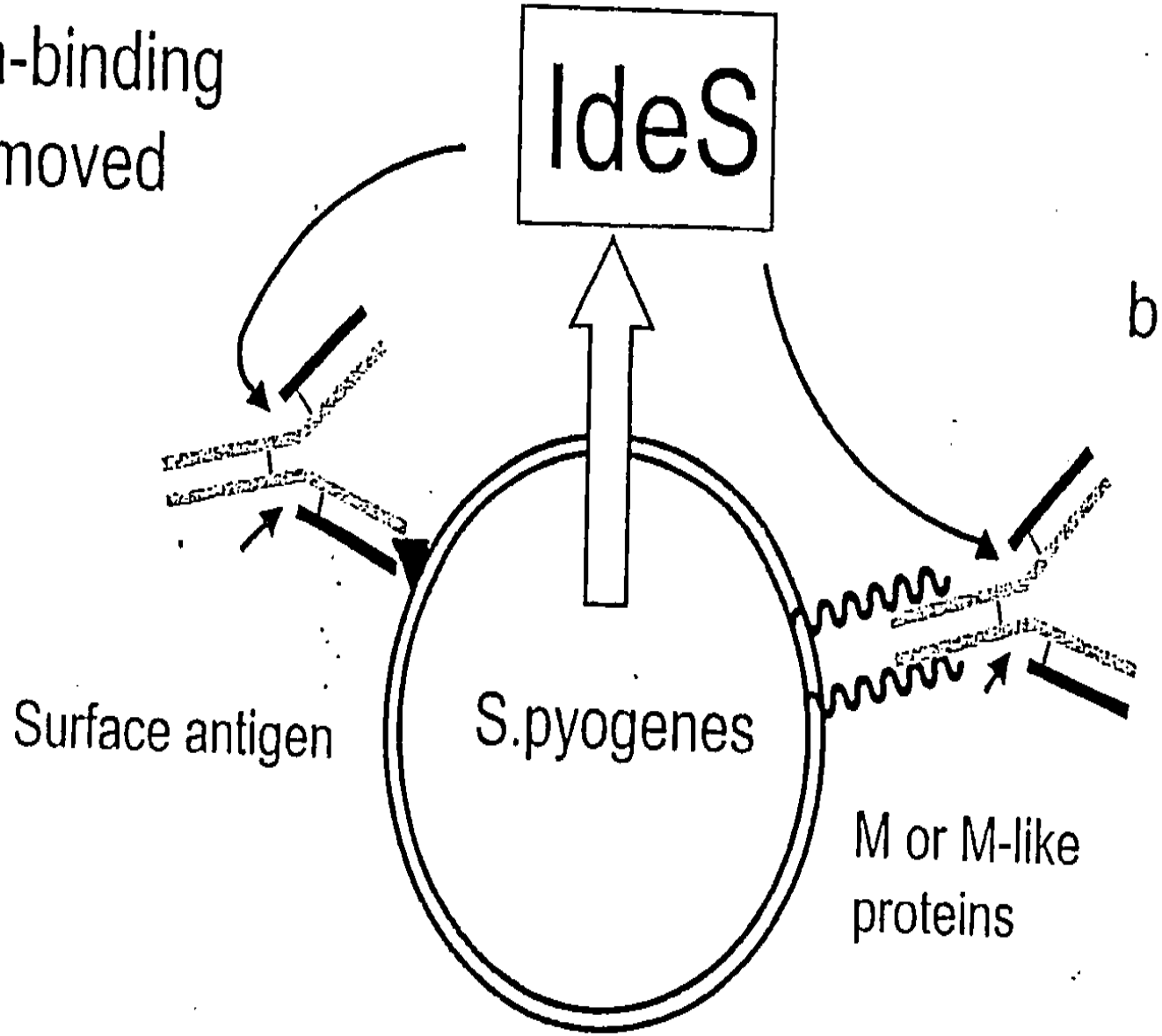
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, #$p = 0.075$ (Wilcoxon–Mann–Whitney test).
[1]median follow-up: 1094 (372–2107) days, [2]median follow-up: 1108 (372–2107) days



IdeS: IgG-degrading enzyme of S. pyogenes
Cysteine proteinase that cleaves extracellular IgG with unique specificity in the hinge region

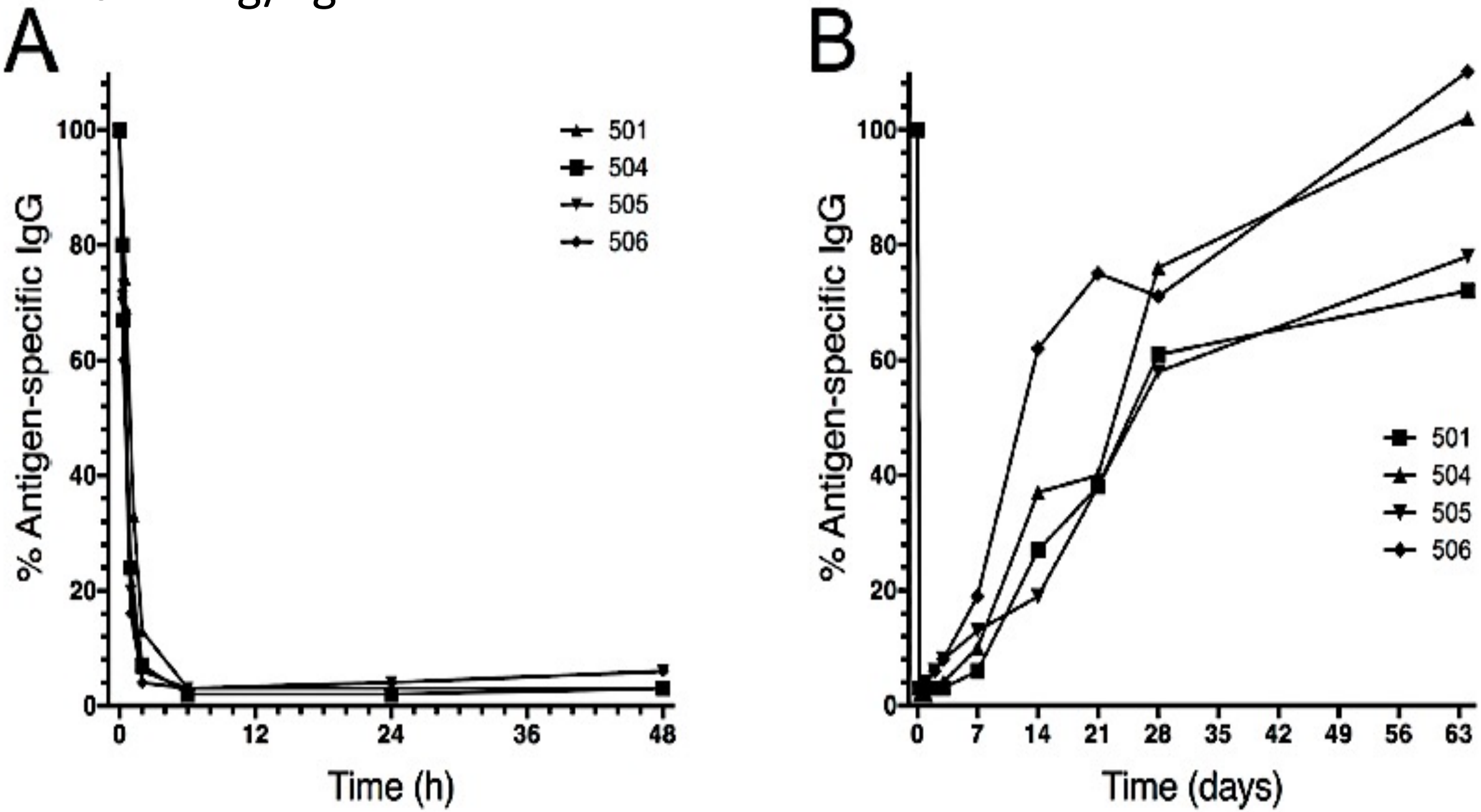

1st
2nd
IgG
scIgG
F(ab')2 & Fc

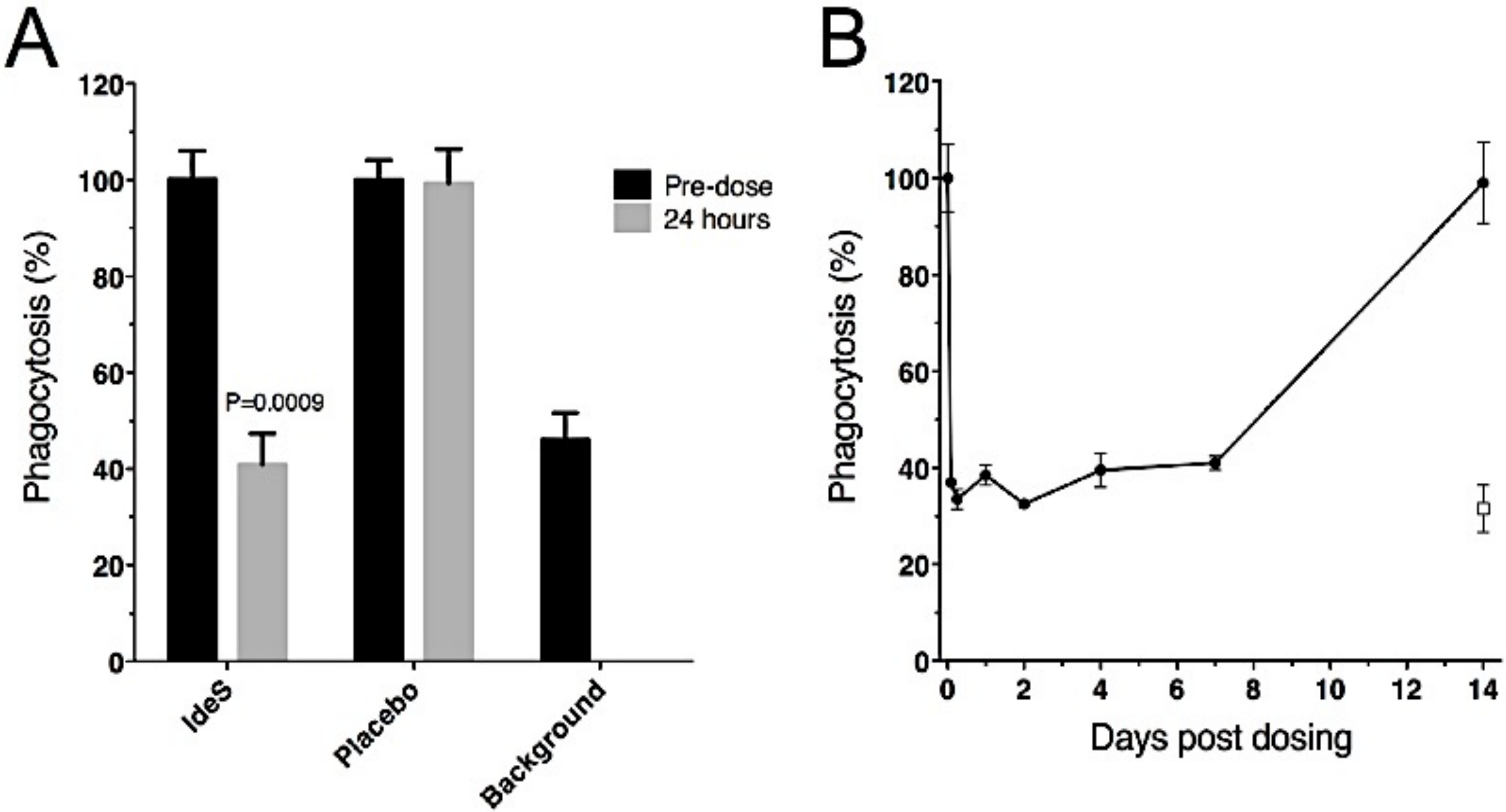
a) Fc and non-binding Fab are removed

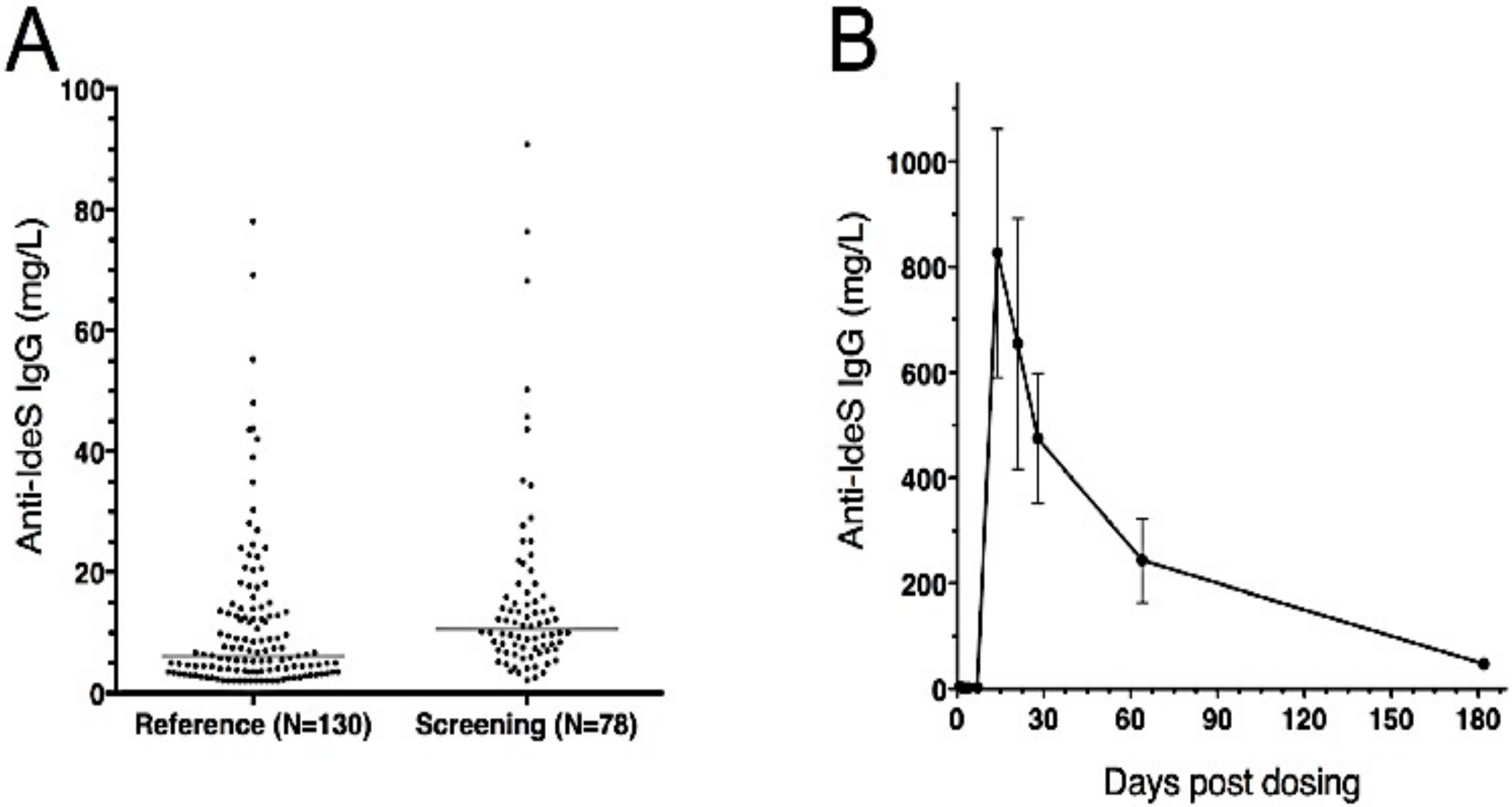


b) Fab's are removed and Fc is blocked

0.24 mg/Kg IBW


A
% Antigen-specific IgG
100
80
60
40
20
0
0
12
24
36
48
Time (h)
501
504
505
506
B
% Antigen-specific IgG
100
80
60
40
20
0
0
7
14
21
28
35
42
49
56
63
Time (days)
501
504
505
506


A
Phagocytosis (%)
120
100
80
60
40
20
0
P=0.0009
Pre-dose
24 hours
IdeS
Placebo
Background
B
Phagocytosis (%)
120
100
80
60
40
20
0
0
2
4
6
8
10
12
14
Days post dosing


A
Anti-IdeS IgG (mg/L)
100
80
60
40
20
0
Reference (N=130)
Screening (N=78)
B
Anti-IdeS IgG (mg/L)
1000
800
600
400
200
0
0
30
60
90
120
150
180
Days post dosing