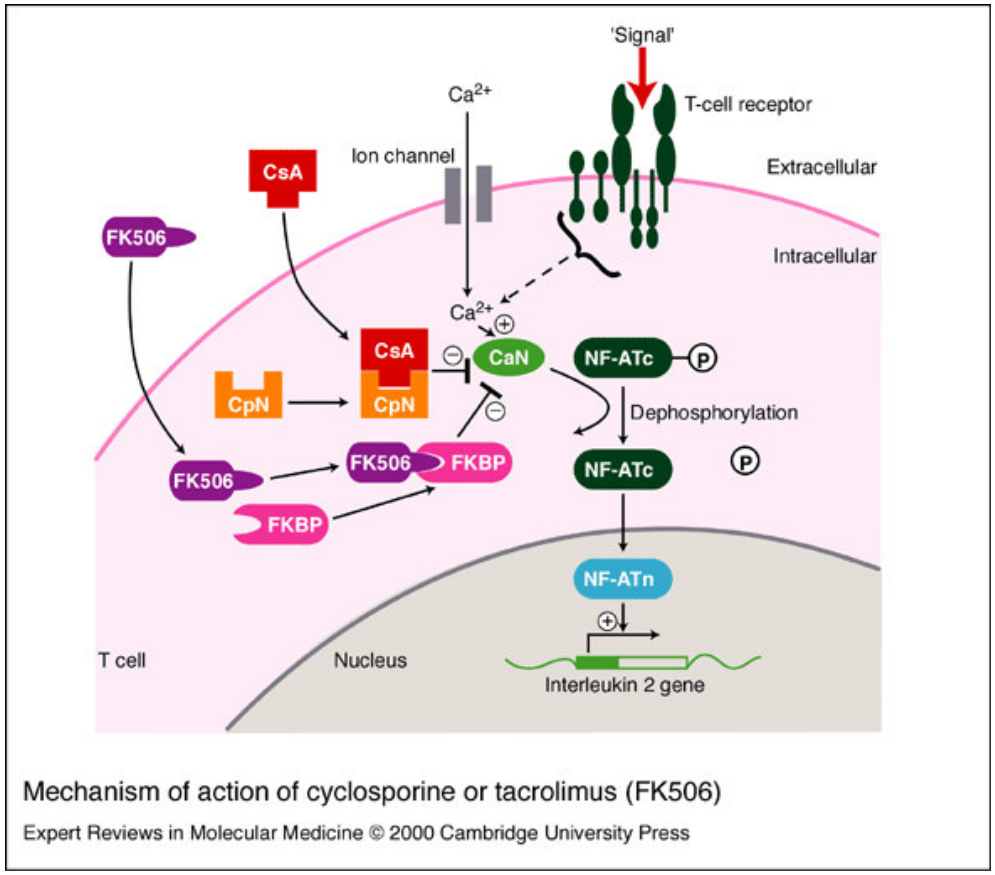
Anti-calcineurínicos no

Josep M Grinyó
Hospital Universitari de Bellvitge.
IDIBELL
Universitat de Barcelona

Calcineurin Inhibitors: Mechanism of Action



Mechanism of action of cyclosporine or tacrolimus (FK506)

CsA: Cyclosporine

FK506: Tacrolimus

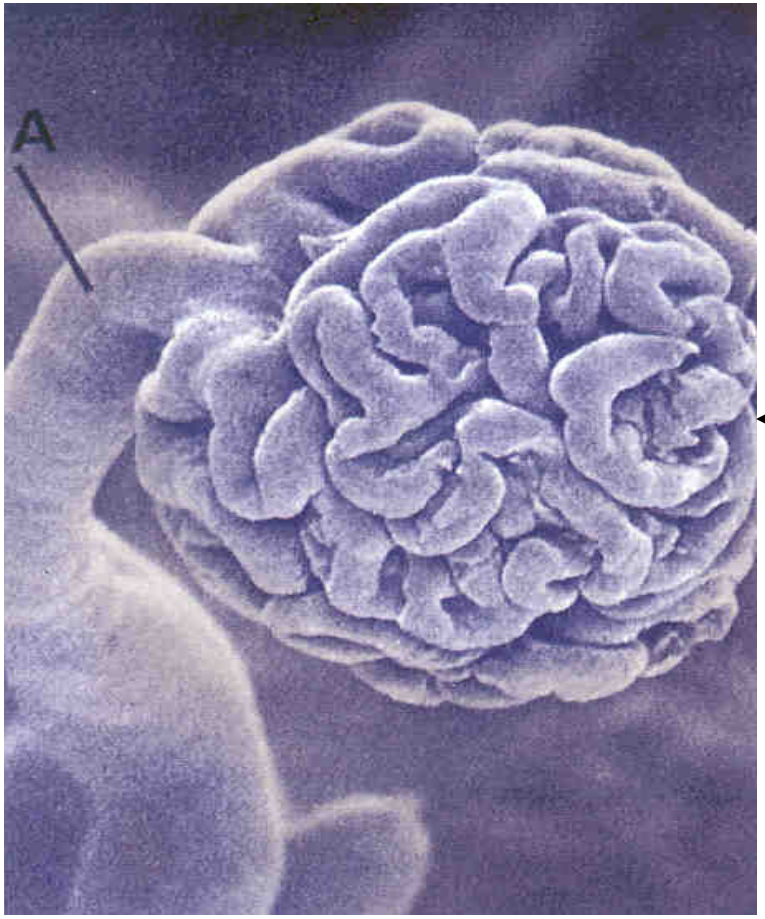
FKBP: FK Binding Protein

CpN: Cyclophilin

NF-AT: Nuclear Factor of Activated T-cells (c-cytosolic component; n-nuclear component).

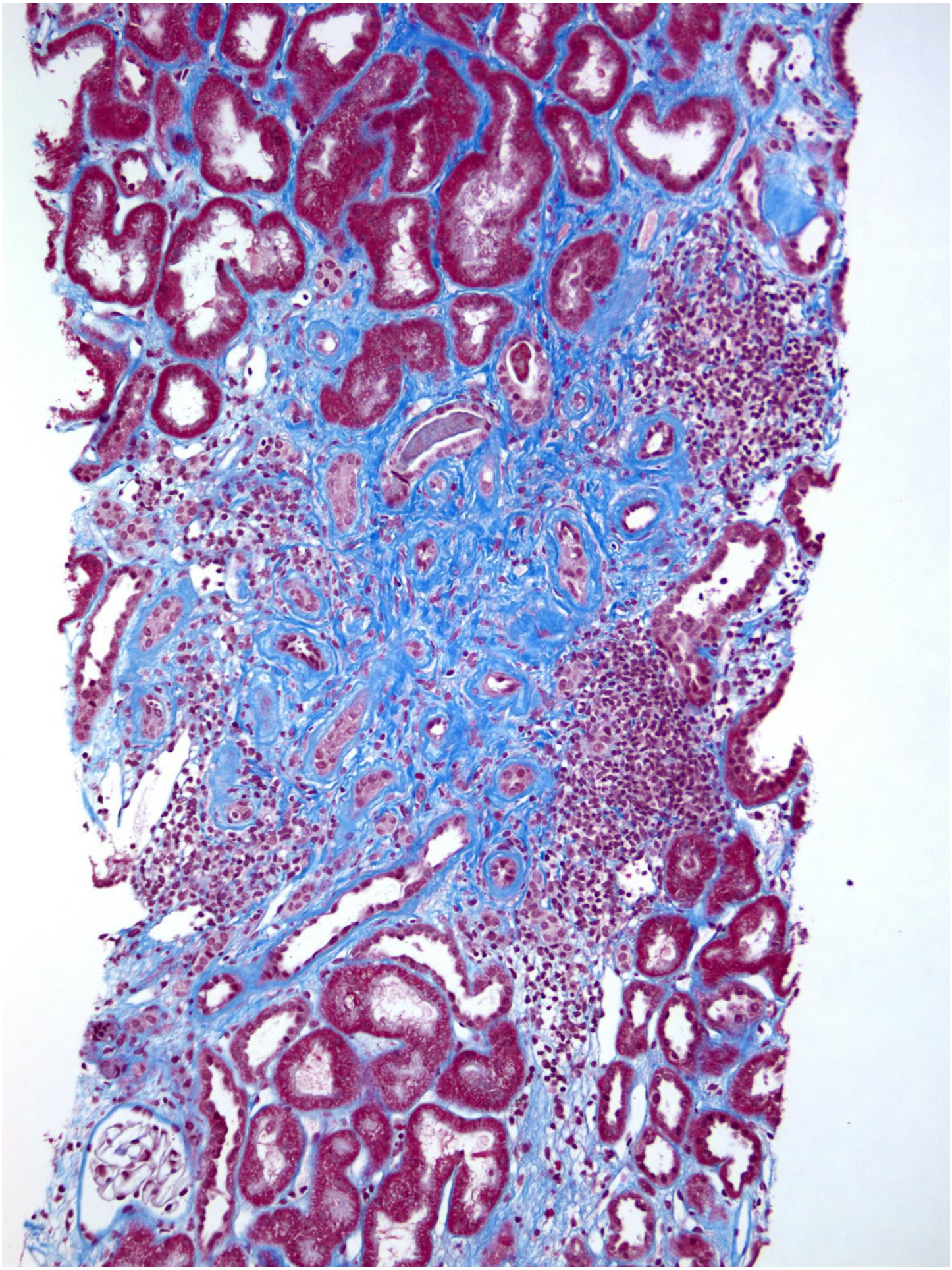
Stepkowski, *Expert Rev Mol Med*, 2000;2(4):1

CALCINEURIN INHIBITORS



Afferent arteriole of glomerulus without CsA or FK

AA with CyA or FK present

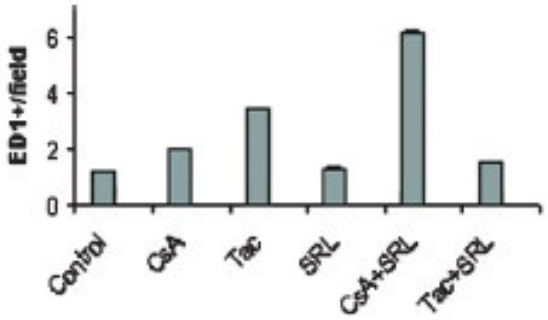


CNI Toxicity Scoring

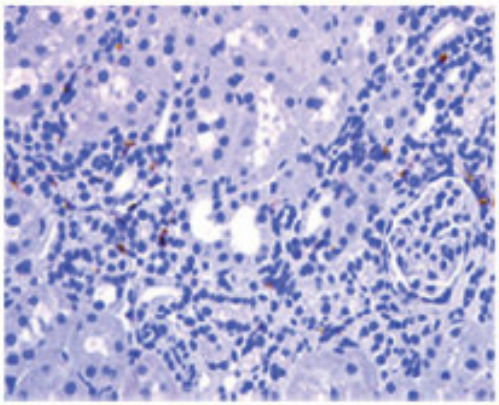
Histological feature	Criteria	Score
% Glomerulosclerosis	0; 1-25%, 26-50%; >50%	0-3
Mesangial matrix expansion	0; 1-25%, 26-50%; >50%	0-3
Isometric tubular vacuolization	0; 1-25%, 26-50%; >50%	0-3
Tubular atrophy	0; 1-25%, 26-50%; >50%	0-3
Interstitial fibrosis	0-5%; 6-25%, 26-50%; >50%	0-3
Arteriolar hyaline	0; mild-moderate (1 arteriole); moderate-severe (1-2 arteriole); severe (many arterioles)	0-3
Total score		18

Experimental nephrotoxicity

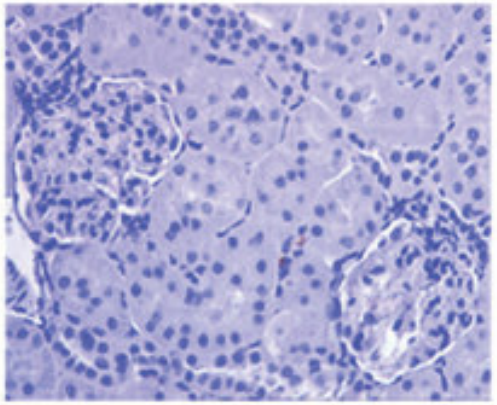
Different renal toxicity profiles



ED1

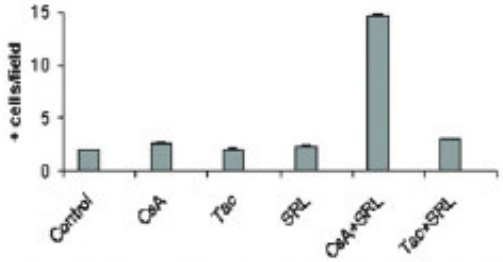


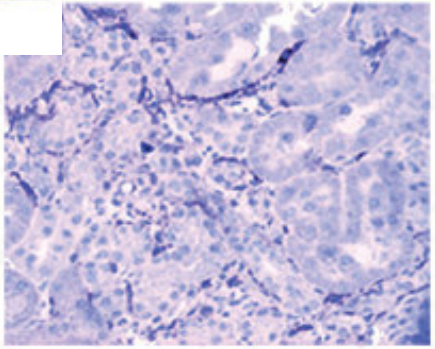
CsA+SRL



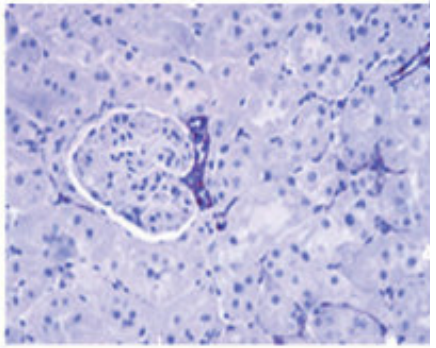
Tac+SRL

alfa-SMA





CsA+SRL

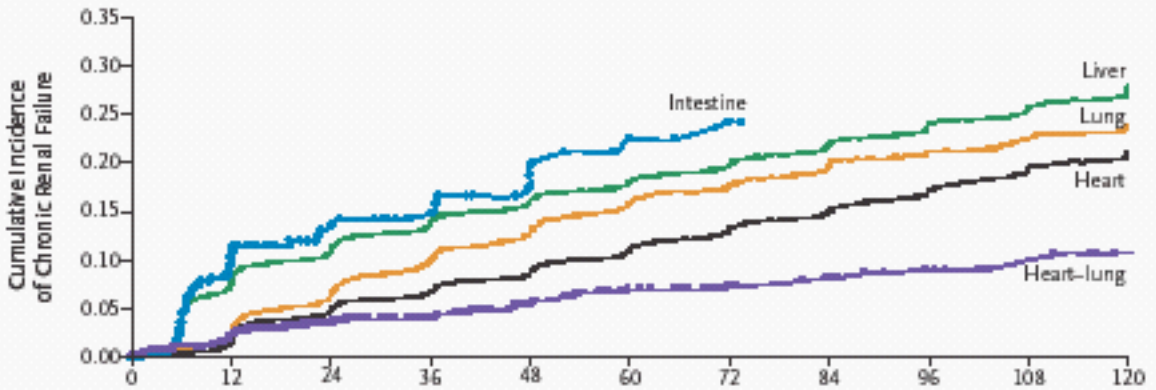


Tac+SRL

The NEW ENGLAND JOURNAL of MEDICINE

Chronic Renal Failure after Transplantation of a Nonrenal Organ

Ojo A, et al. NEJM 349:931-940, 2003.



No. at Risk											
Heart–lung	576	375	295	219	194	156	133	107	72	46	30
Heart	24,024	19,885	17,238	14,687	12,341	10,022	7997	6104	4526	3096	1991
Intestine	228	152	110	84	57	33	23	13	8	5	5
Liver	36,849	28,495	24,041	19,508	15,724	12,564	9844	7345	5292	3614	2261
Lung	7,643	5,633	4,316	3,184	2,327	1,629	1136	745	468	258	133

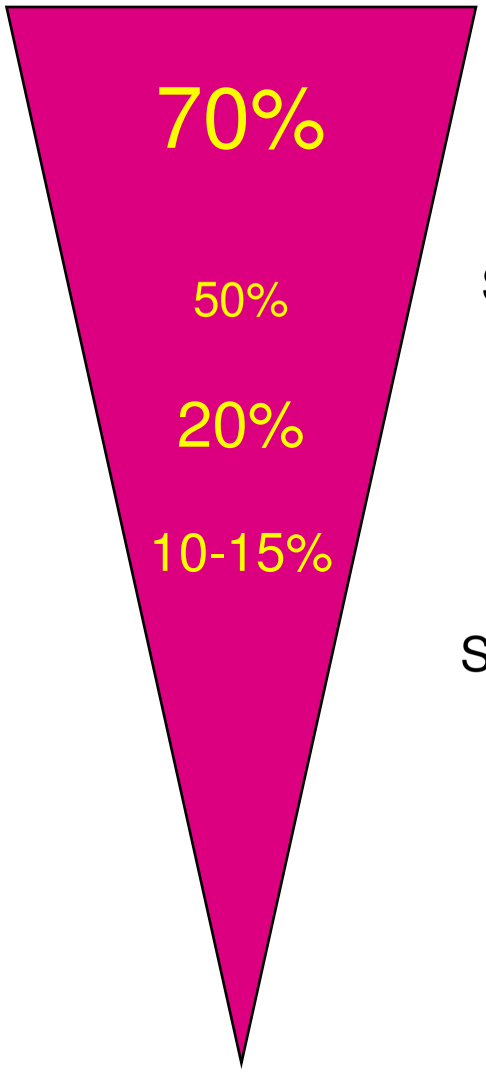
Figure 1. Cumulative Incidence of Chronic Renal Failure among 69,321 Persons Who Received Nonrenal Organ Transplants in the United States between January 1, 1990, and December 31, 2000.

The risk of chronic renal failure was estimated with a noncompeting-risk model. Measurements of renal function were obtained at six-month intervals during the first year and annually thereafter.

Table 3. Risk Factors Associated with Chronic Renal Failure in Recipients of Nonrenal Organ Transplants.*

Variable	Overall Relative Risk (95% CI)	P Value	Relative Risks in Subgroups of Recipients		
			Liver Transplants	Heart and Heart–Lung Transplants	Lung Transplants
Age (per 10-year increment)	1.36 (1.34–1.38)	<0.001	1.29	1.56	1.40
Pretransplantation glomerular filtration rate					
≥90 ml/min/1.73 m²	1.00 (reference group)		1.00	1.00	1.00
60–89 ml/min/1.73 m²	1.38 (1.30–1.46)	<0.001	1.54	1.16†	1.00†
30–59 ml/min/1.73 m²	2.25 (2.12–2.39)	<0.001	2.54	1.92	1.00†
≤29 ml/min/1.73 m²	3.41 (3.15–3.70)	<0.001	3.78	2.82	1.42†
Missing or unknown	1.33 (1.21–1.46)	<0.001	1.25	1.29	1.13†
Postoperative acute renal failure‡	2.13 (1.99–2.27)	<0.001	2.11	3.03	4.56
Dialysis treatment before transplantation	1.46 (1.27–1.68)	<0.001	1.45	1.25†	—§
Male sex	0.74 (0.71–0.77)	<0.001	0.71	0.78	0.68
Race					
White	1.00 (reference group)		1.00	1.00	1.00
Black	1.02 (0.95–1.10)	0.57	1.01†	1.05†	0.91†
Asian	0.77 (0.66–0.89)	<0.001	0.79	0.86†	0.32†
Other	0.73 (0.63–0.85)	<0.001	0.76	0.58	1.34†
Calcineurin-inhibitor treatment during initial hospitalization					
Tacrolimus	1.00 (reference group)		1.00	1.00	1.00
Cyclosporine	1.24 (1.17–1.30)	<0.001	1.25	0.98†	1.09†
Missing or unknown	0.87 (0.80–0.95)	<0.001	0.63	1.04†	1.10†
Sirolimus treatment during initial hospitalization					
No	1.00 (reference group)		1.00	1.00	1.00
Yes	1.19 (0.94–1.52)	0.16	1.21†	1.82†	0.36†
Hepatitis B	1.06 (0.96–1.18)	0.25	1.04†	1.41†	0.66†
Hepatitis C	1.15 (1.08–1.23)	<0.001	1.22	1.34	1.07†
Hypertension before transplantation	1.18 (1.10–1.26)	<0.001	1.04†	1.24	1.26
Diabetes mellitus before transplantation	1.42 (1.33–1.51)	<0.001	1.39	1.51	1.53
Year of transplantation					
1998–2000	1.00 (reference group)		1.00	1.00	1.00
1994–1997	1.08 (1.02–1.14)	0.008	1.23	0.80	0.84
1990–1993	1.31 (1.15–1.48)	<0.001	1.52	0.92†	0.62

Incidence of acute rejection



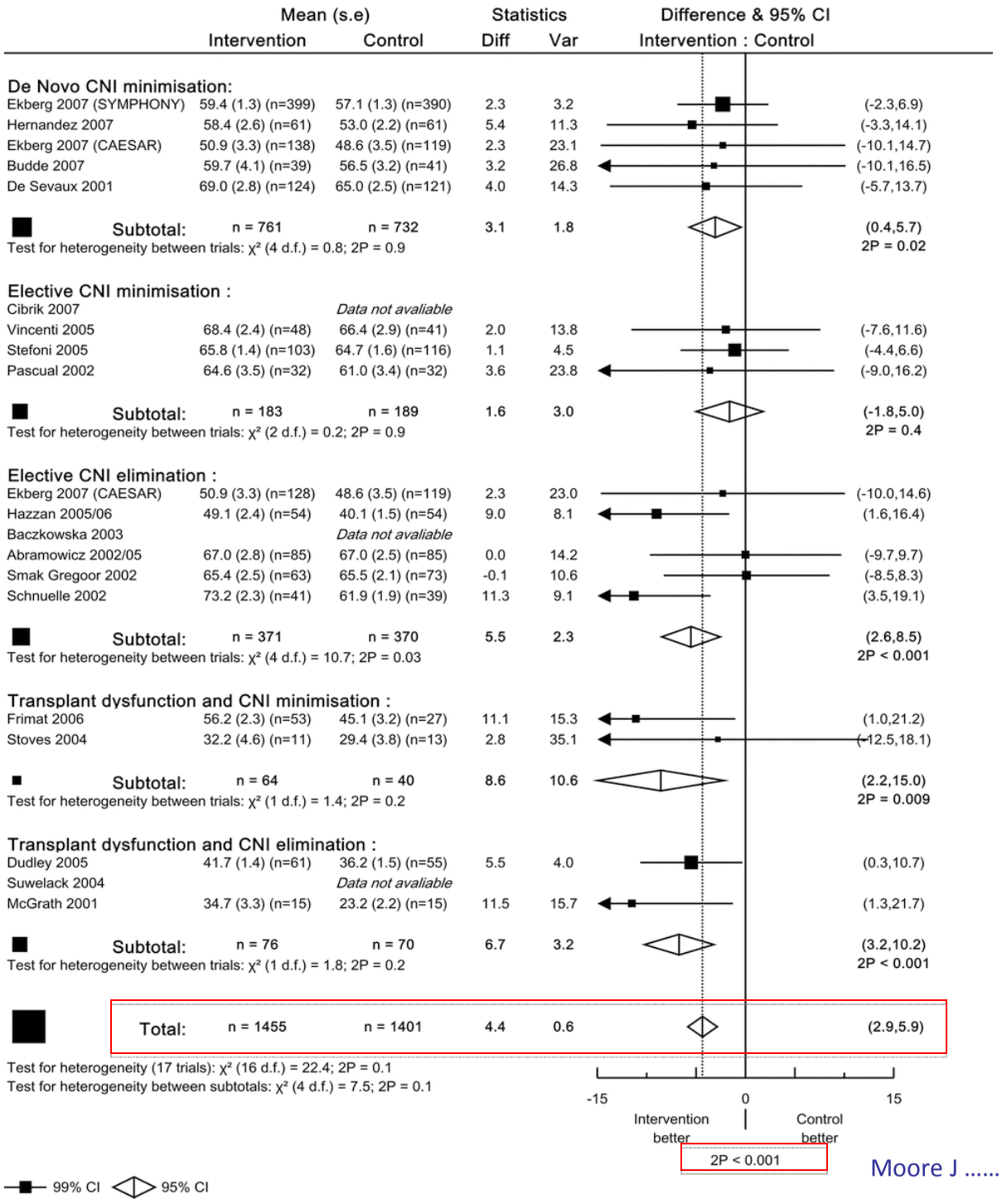
Immurel- PD

Sandimmun/Prograf-PD

Sandimmun/Prograf-PD
CellCept

Sadimmun/Prograf
Rapamune

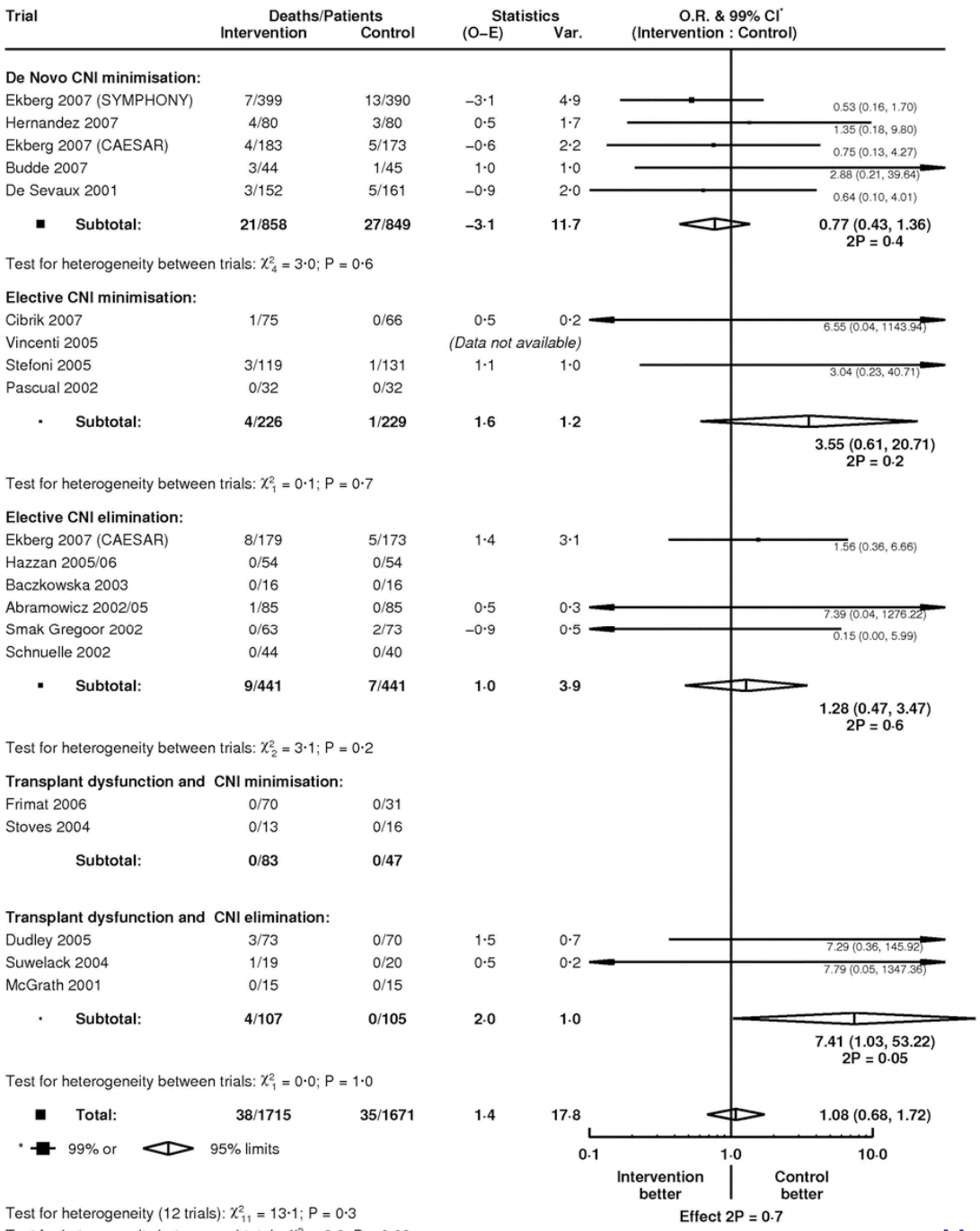
Help



Meta-analysis on CNI sparing with MMF in KTx:

Renal function

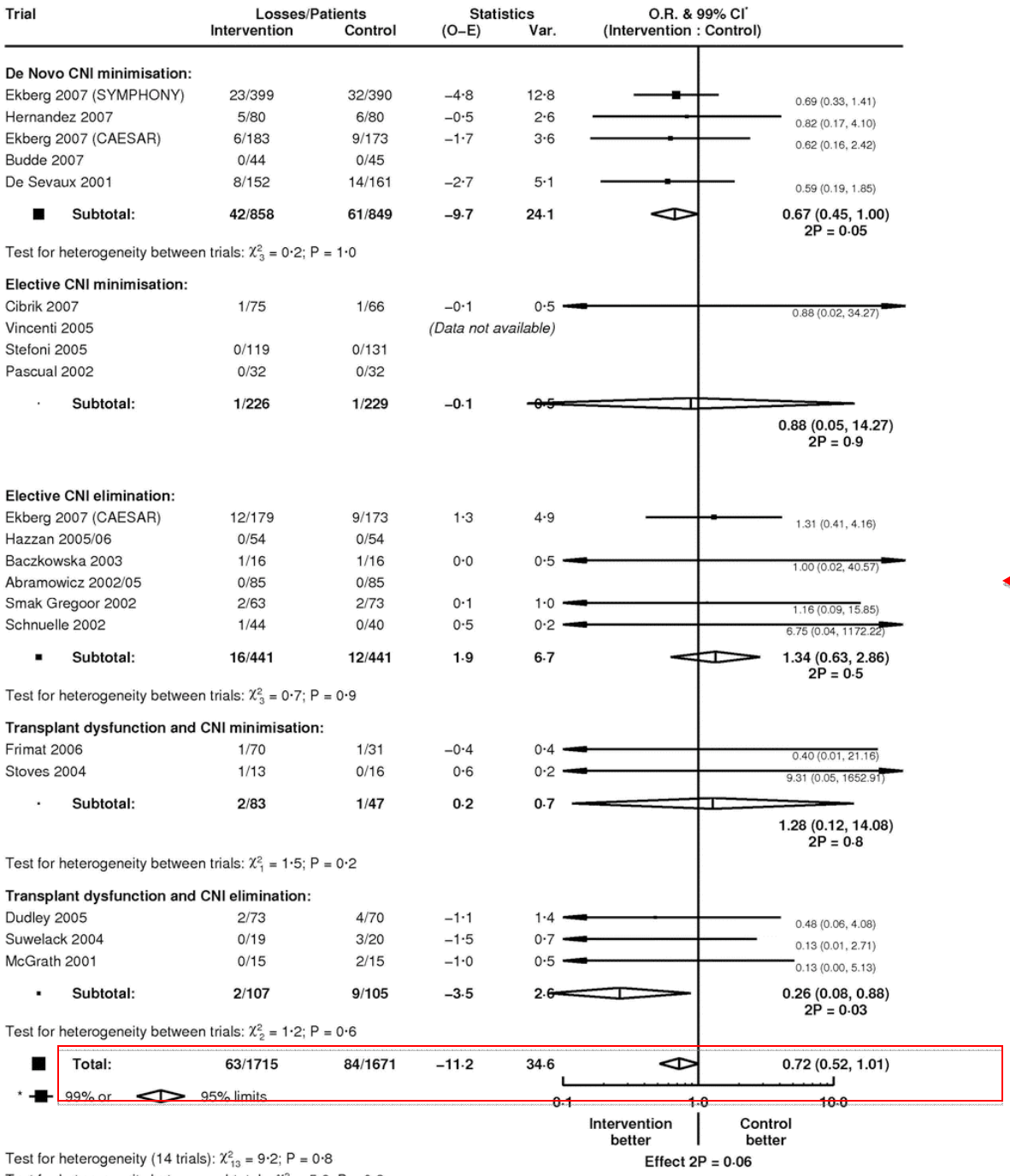
Moore J ……Borrows R, Transplantation 2009; 87: 591-605.



Meta-analysis on CNI sparing with MMF in KTx:

Mortality

Moore J ……Borrows R, Transplantation 2009; 87: 591-605.

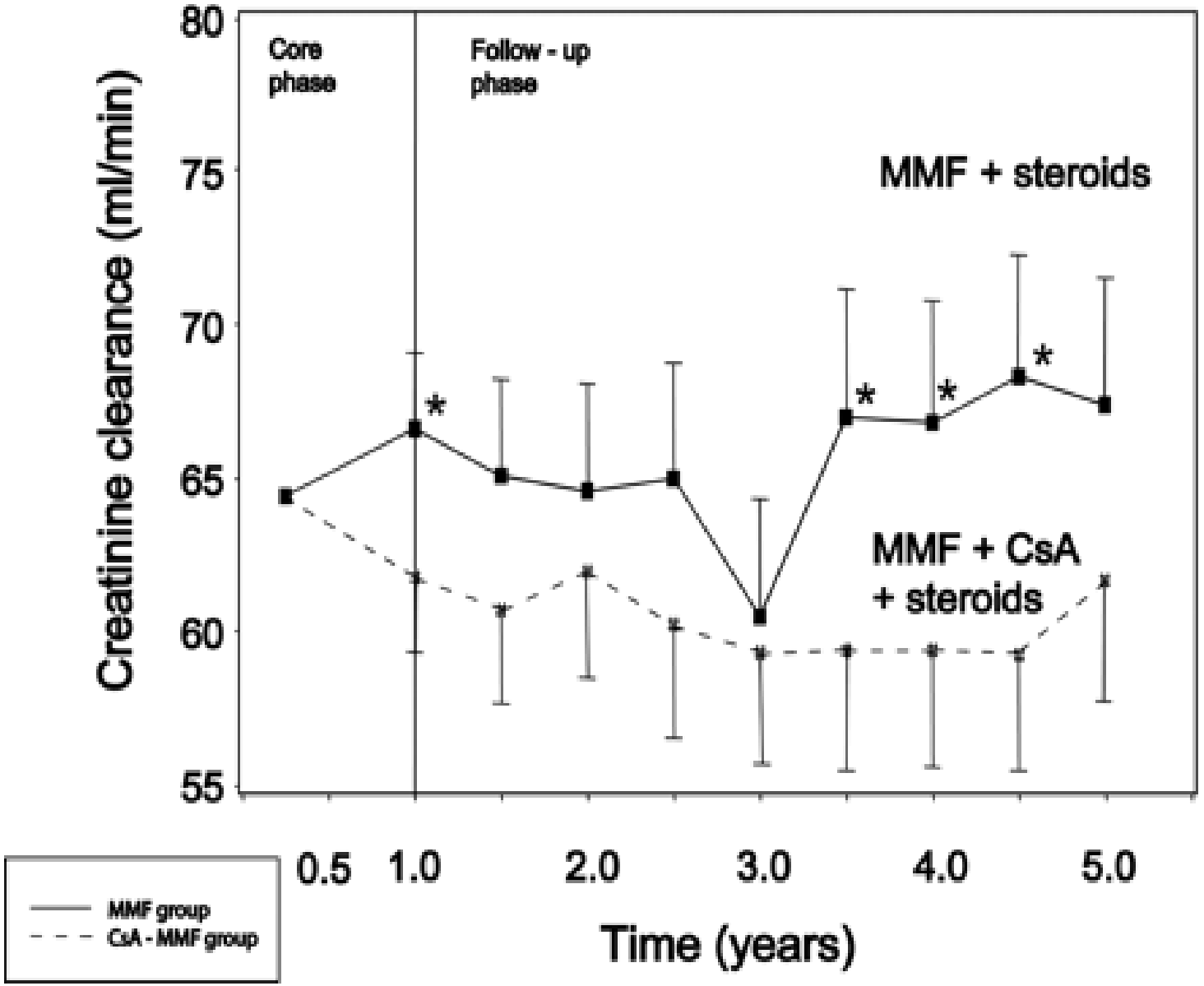


Meta-analysis on CNI sparing with MMF in KTx:

Incidence of graft loss

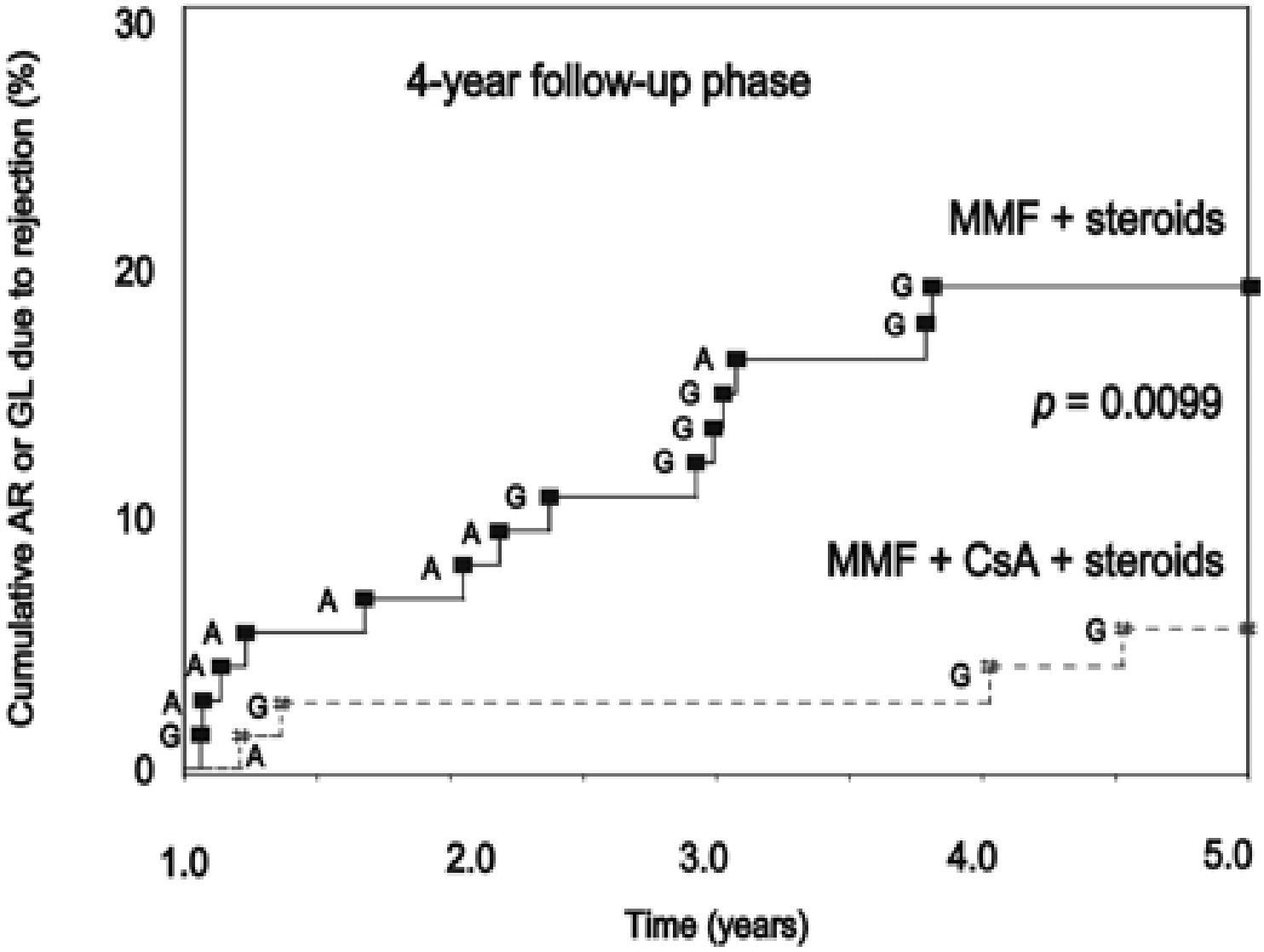
Moore J ……Borrows R, Transplantation 2009; 87: 591-605.

Renal function



Abramowicz et al JASN 2005; 16:2234-40

Rejection Episodes



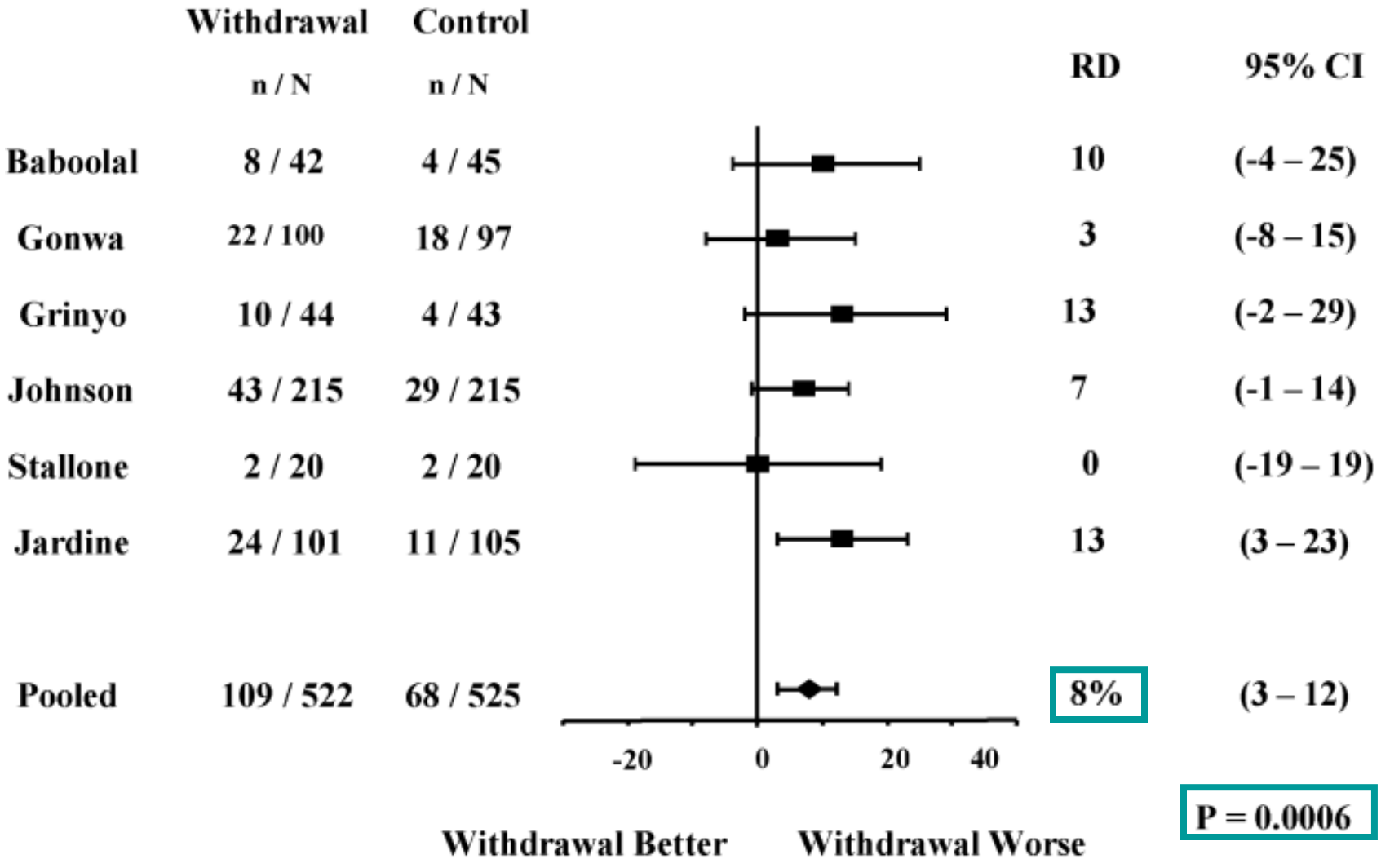
Graft loss-CR

n=9

n=3

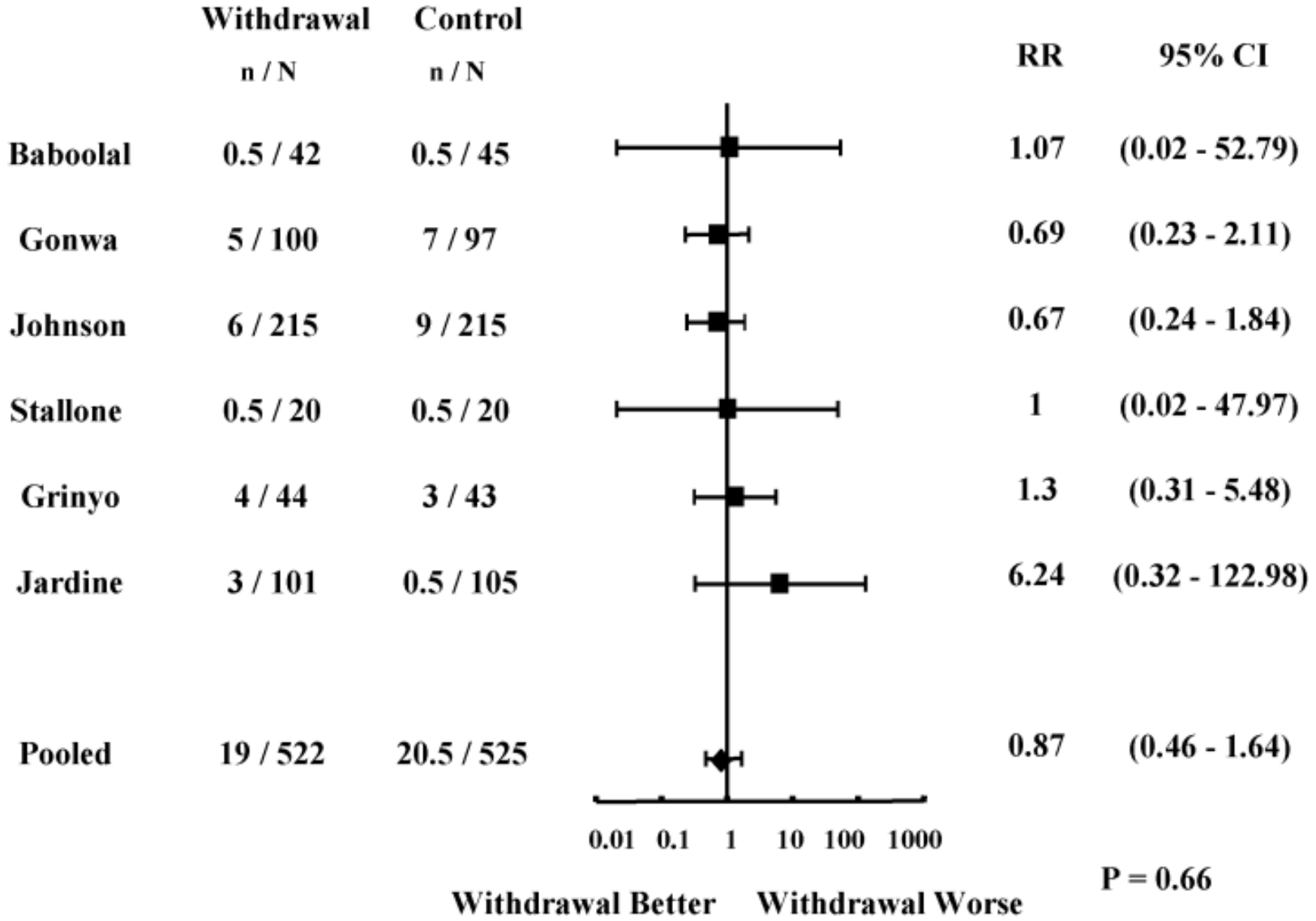
Abramowicz et al JASN 2005; 16:2234-40

CNI withdrawal from sirolimus immunosuppression (absolute risk difference of acute rejection)



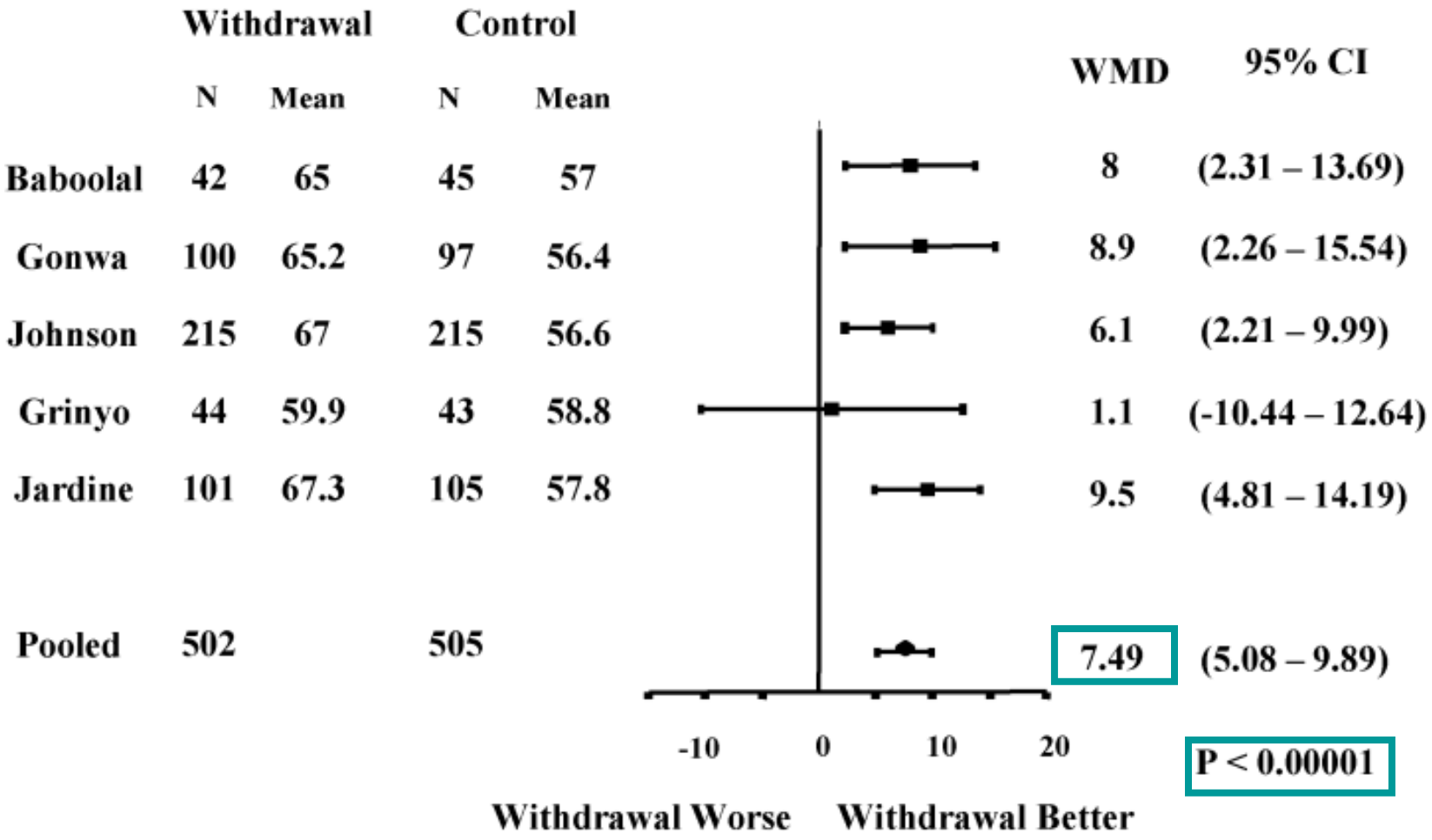
Mulay et al. AJT 2005; 5: 1748.

CNI withdrawal from sirolimus immunosuppression (RR of graft loss)



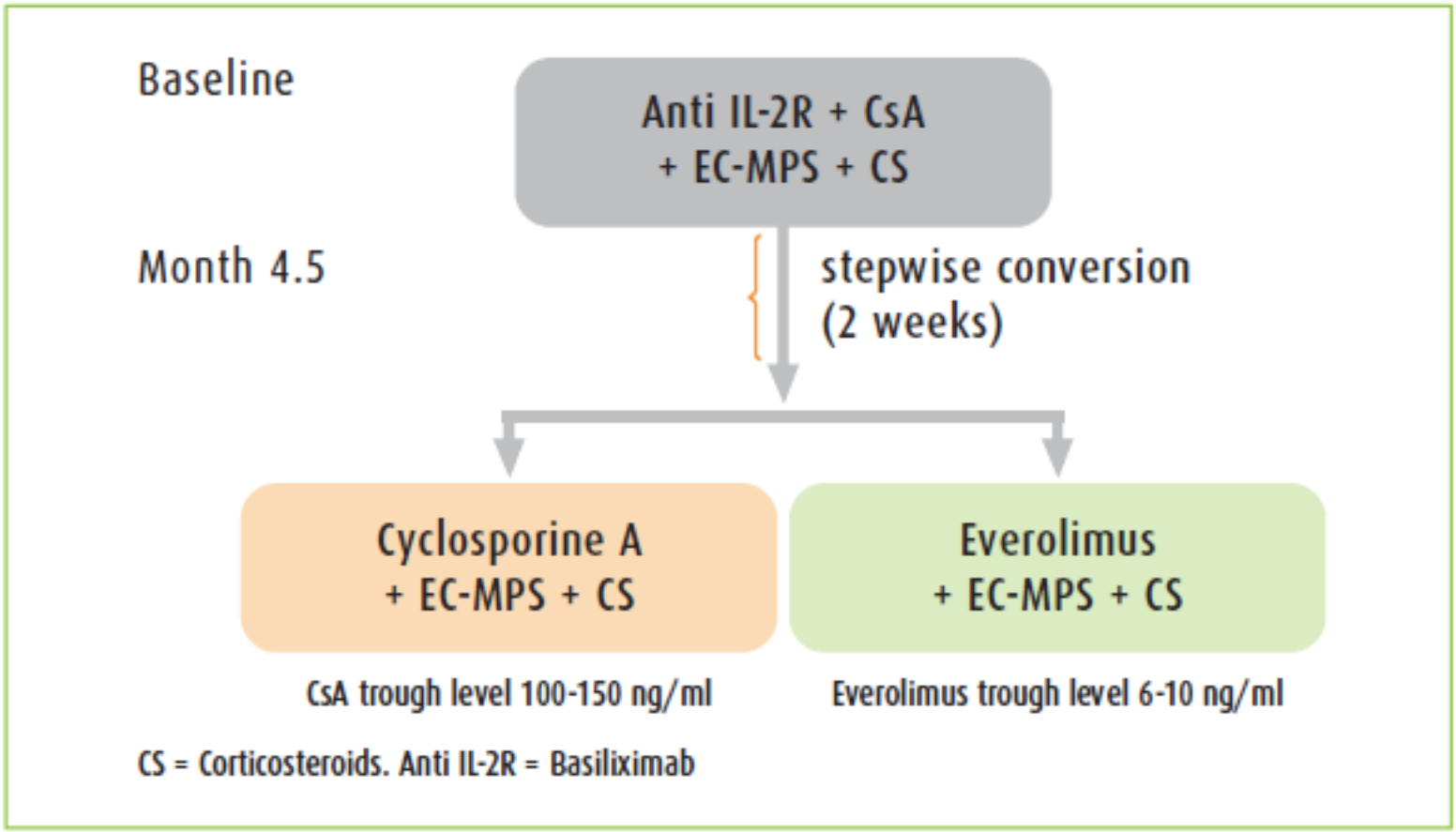
Mulay et al. AJT 2005; 5: 1748.

Creatinine clearance



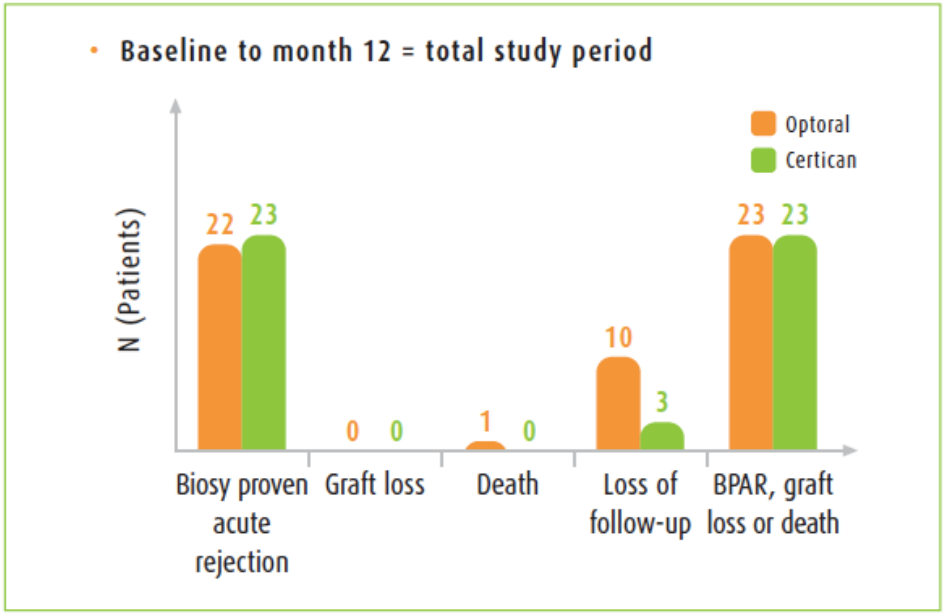
Mulay et al. AJT 2005; 5: 1748.

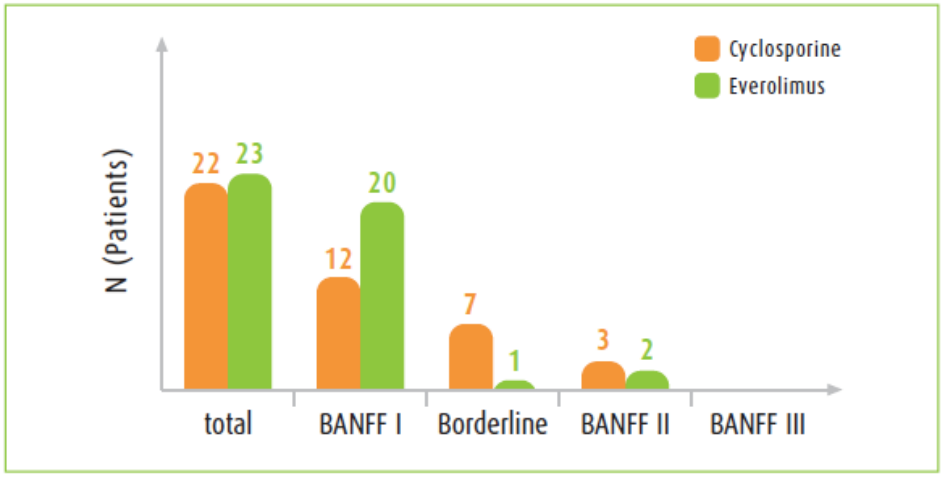
Efficacy and safety of an everolimus/enteric-coated mycophenolate sodium regimen after calcineurin inhibitor withdrawal in the novo renal transplant recipients: Results of the Zeus trial



Budde et al. Lancet 2011.

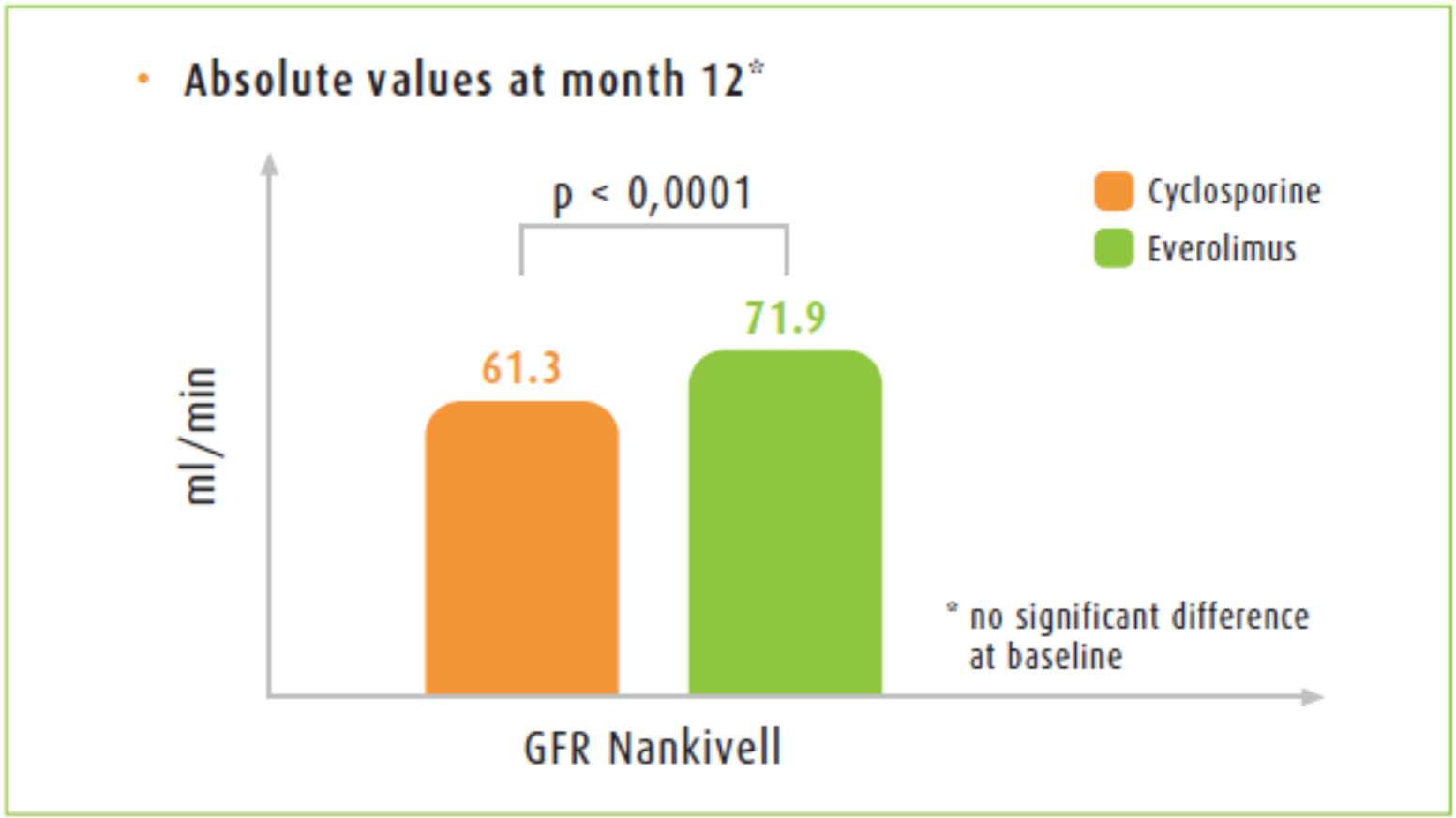
The Zeus trial: acute rejection





Budde et al. Lancet 2011.

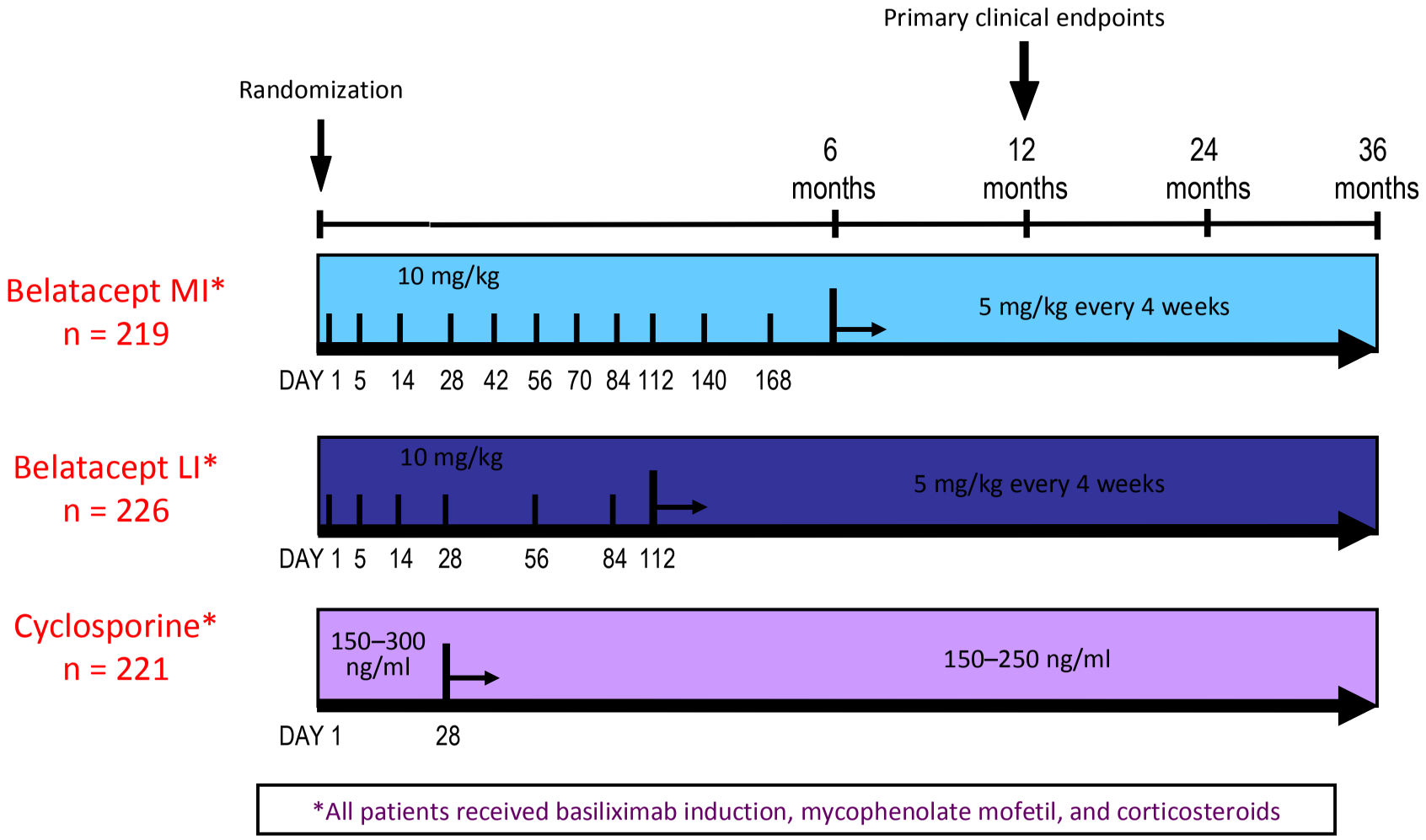
The Zeus trial: Renal function



Budde et al. Lancet 2011.

Belatacept in renal transplantation

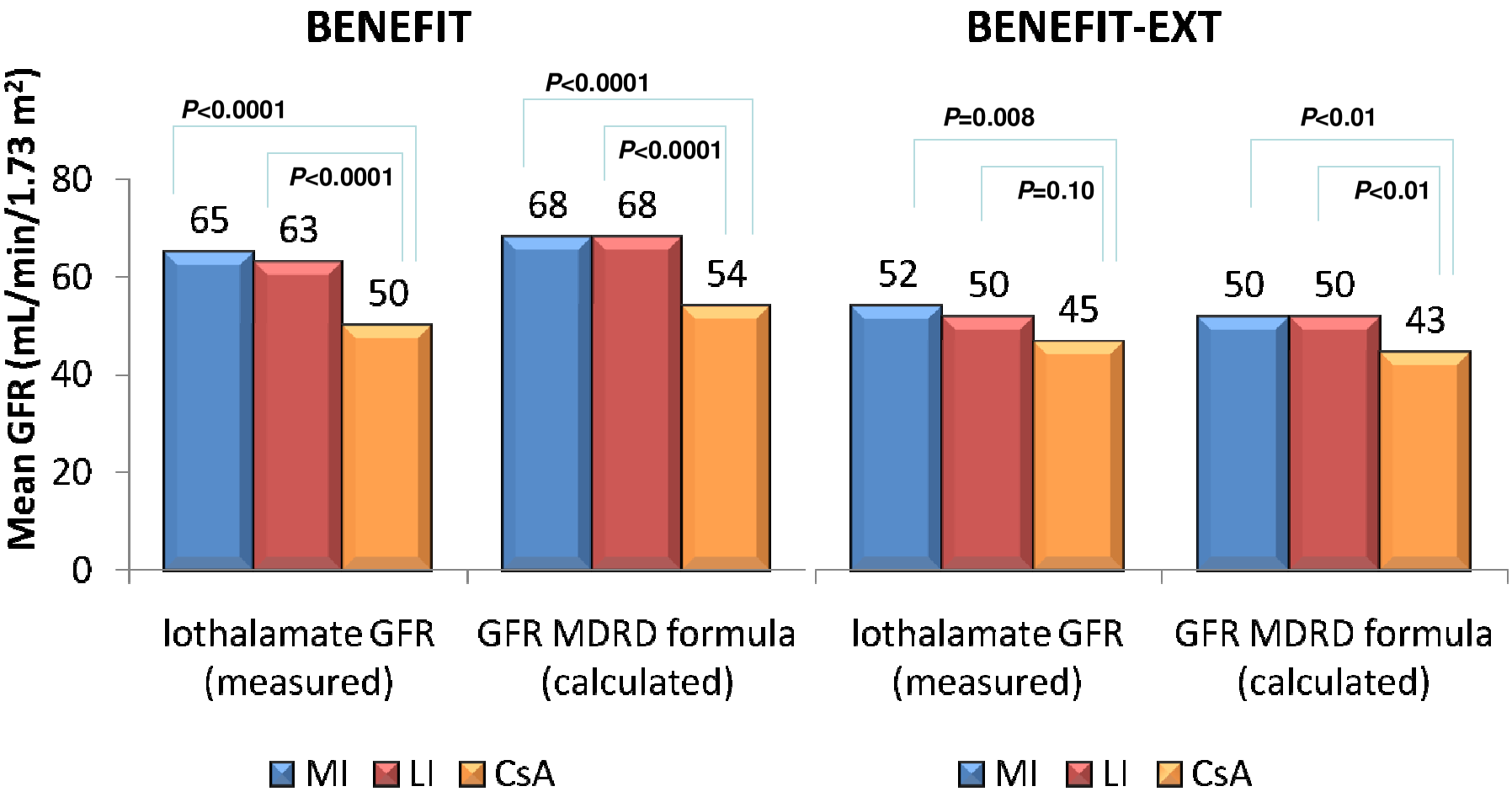
BENEFIT and Benefit-EXT Study Designs. Phase III



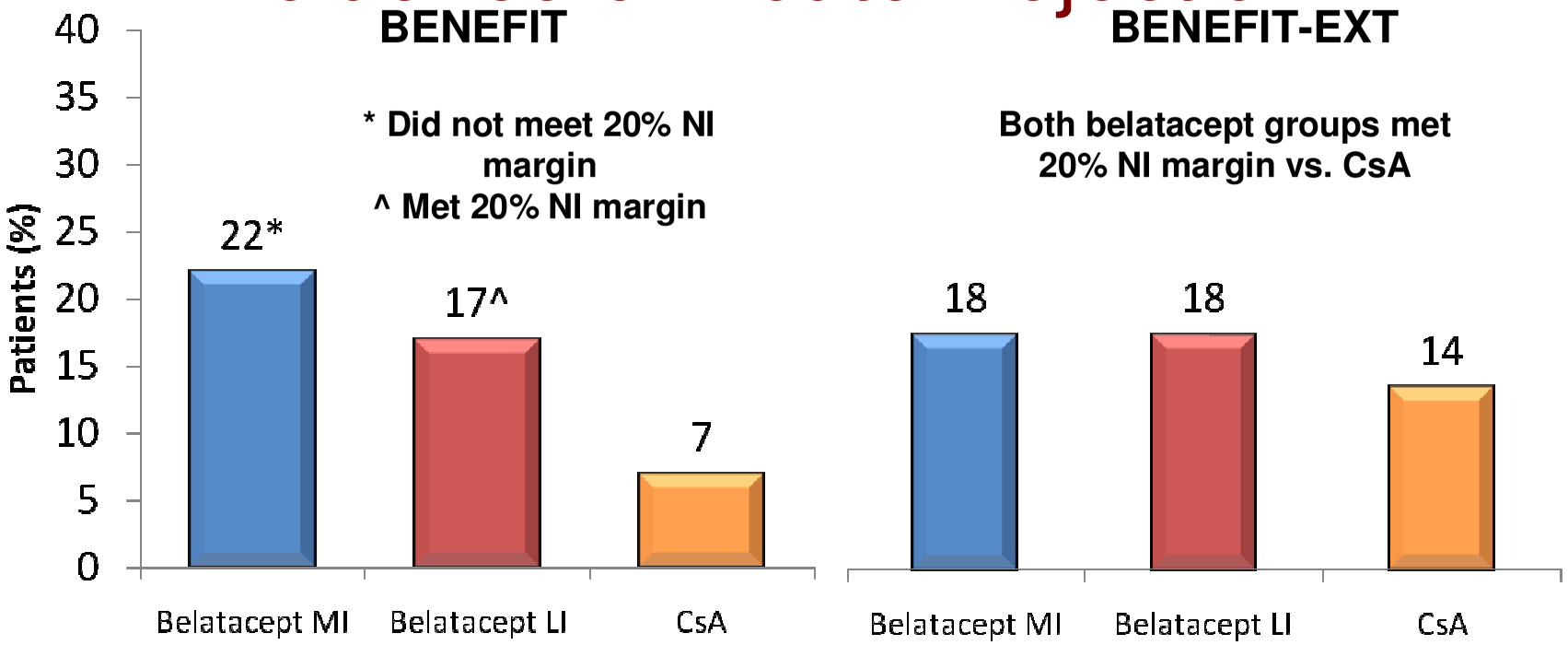
LI = less intensive; MI = more intensive.

Vincenti et al. Am J Transpl 2010; 10: 535-46.
Durrbach et al. Am J Transpl 2010; 10: 547-57

Belatacept Phase 3 Clinical Trial Results: Measured and Calculated GFR



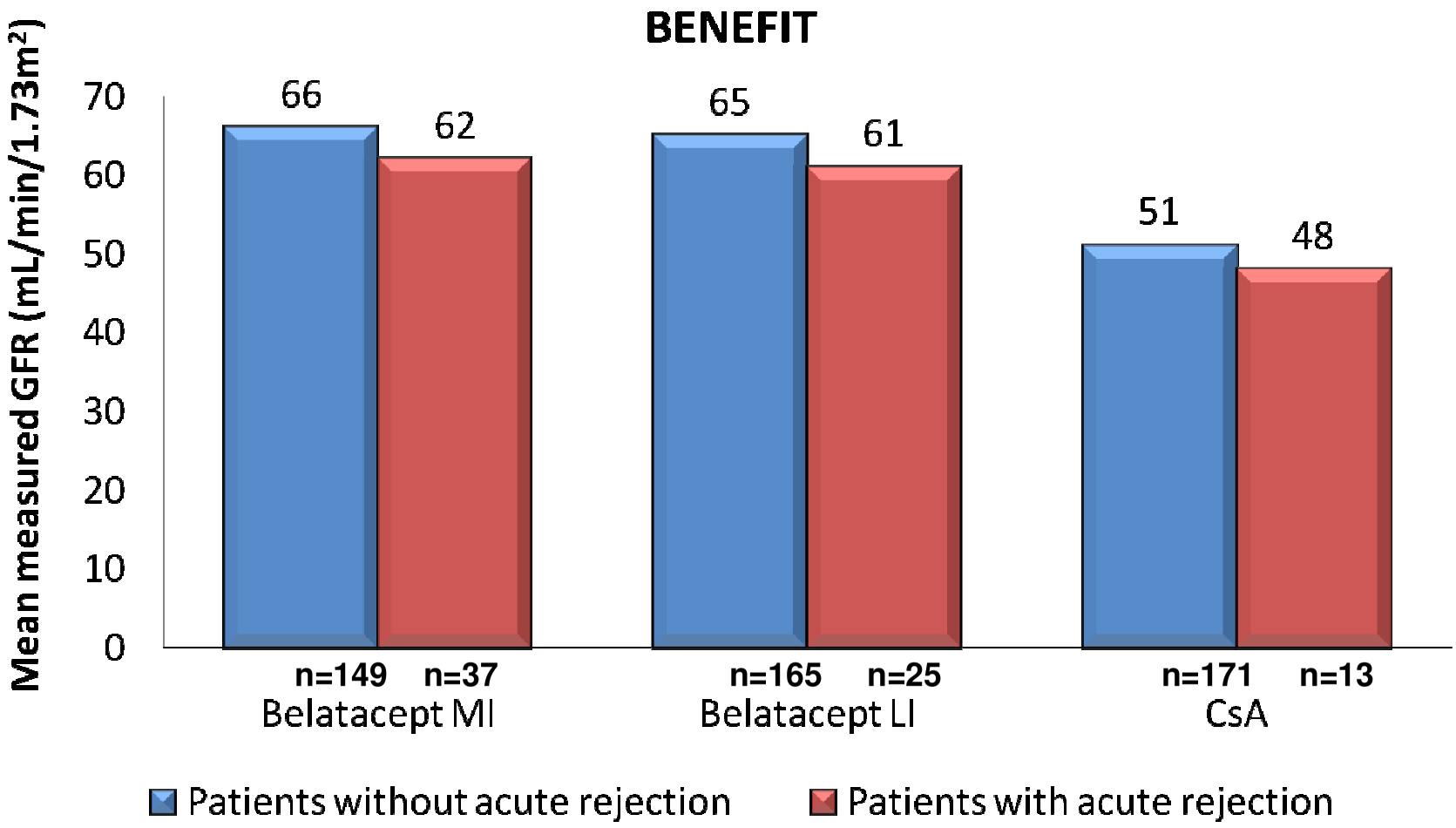
Belatacept Phase 3 Clinical Trial Results: Incidence of Acute Rejection



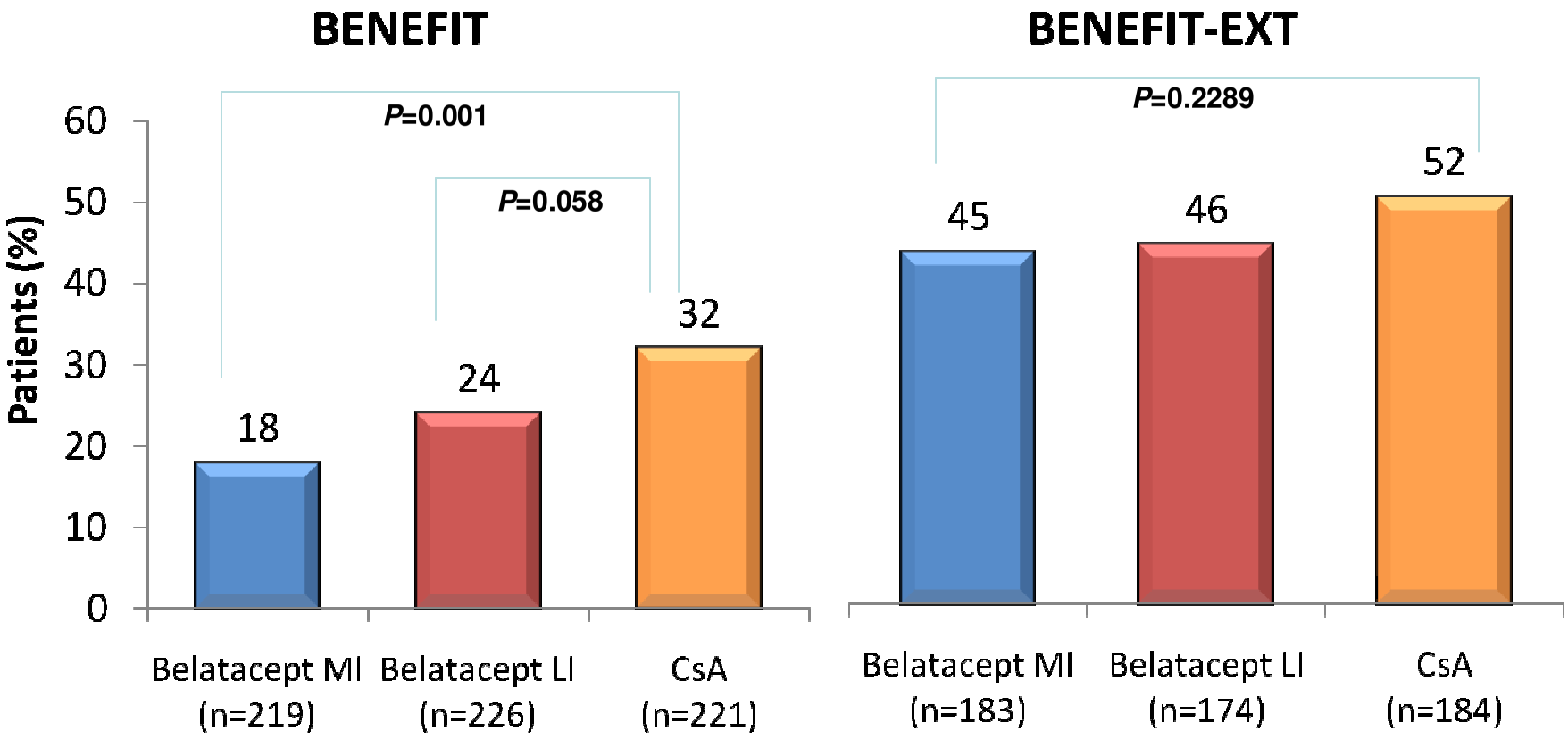
Banff Grade			
Mild acute (IA)	7(3)	4(2)	3(1)
Mild acute (IB)	3(1)	8(4)	5(2)
Moderate acute (IIA)	17(8)	16(7)	6(3)
Moderate acute (IIB)	20(9)	10(4)	2(1)
Severe Acute (III)	2(1)	1(<1)	0

IA	0	4(2)	2(1)
IB	7(4)	2(1)	2(1)
IIA	10(5)	17(10)	17(9)
IIB	16(9)	8(5)	5(3)
III	0	0	0

Belatacept Phase 3 Clinical Trial Results: Renal Function Maintained in Patients with Acute Rejection



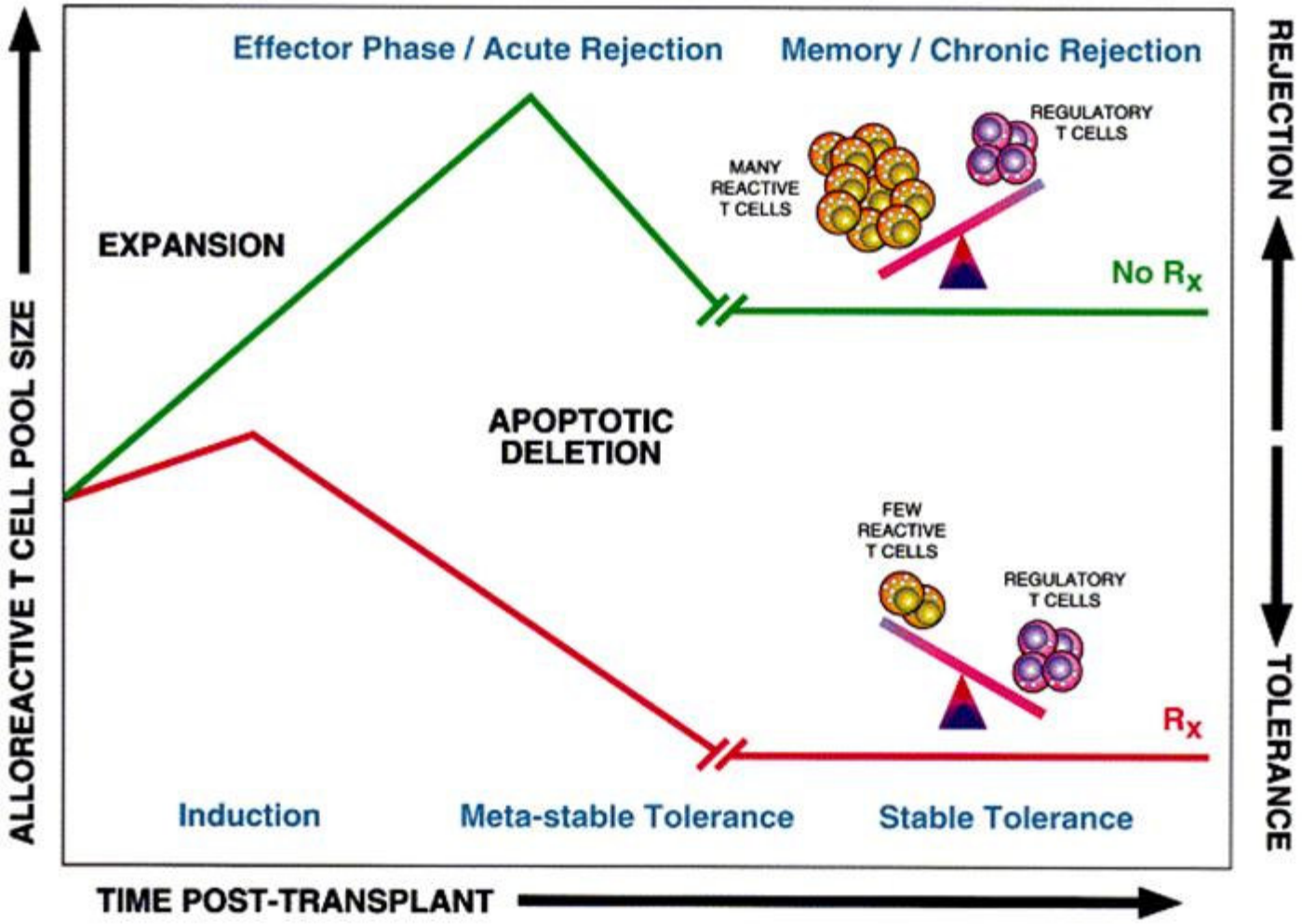
Belatacept Phase 3 Clinical Trial Results: Reduced Prevalence of Chronic Allograft Nephropathy



Criticisms to CNI sparing/avoidance strategies

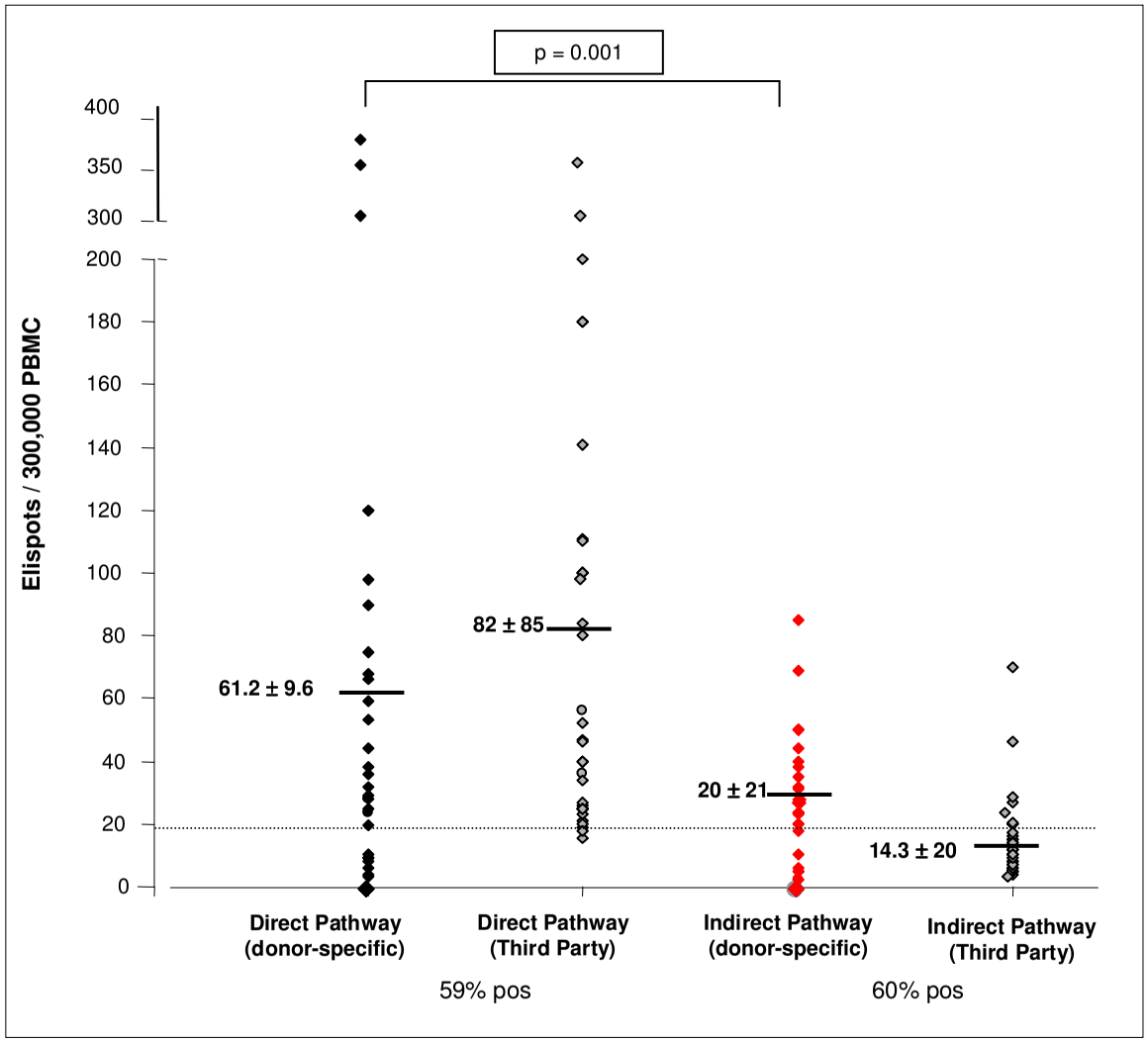
- Without fully rational basis.
- Missing MOAs differences of IS
- Hierarchy, timing?
- Lack of assessment of T and B cell responses.
- Correlation between immune responses and graft damage/function?
- Biomarkers
- Indiscriminate strategies

The balance of Teff/T regs determines outcome



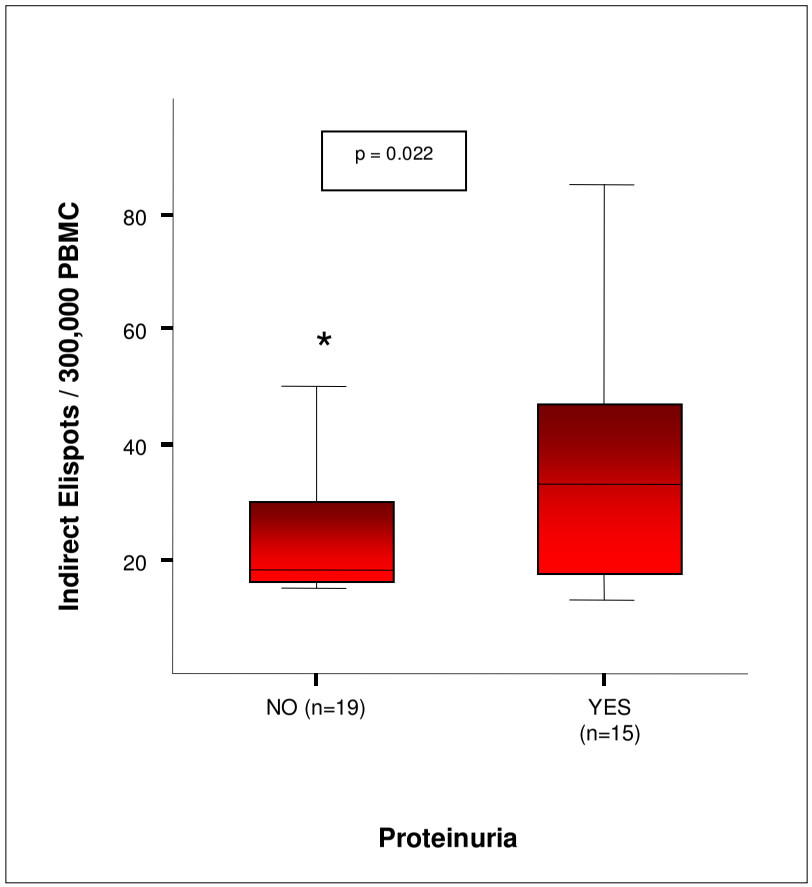
Turka/Strom/Sayegh 2007

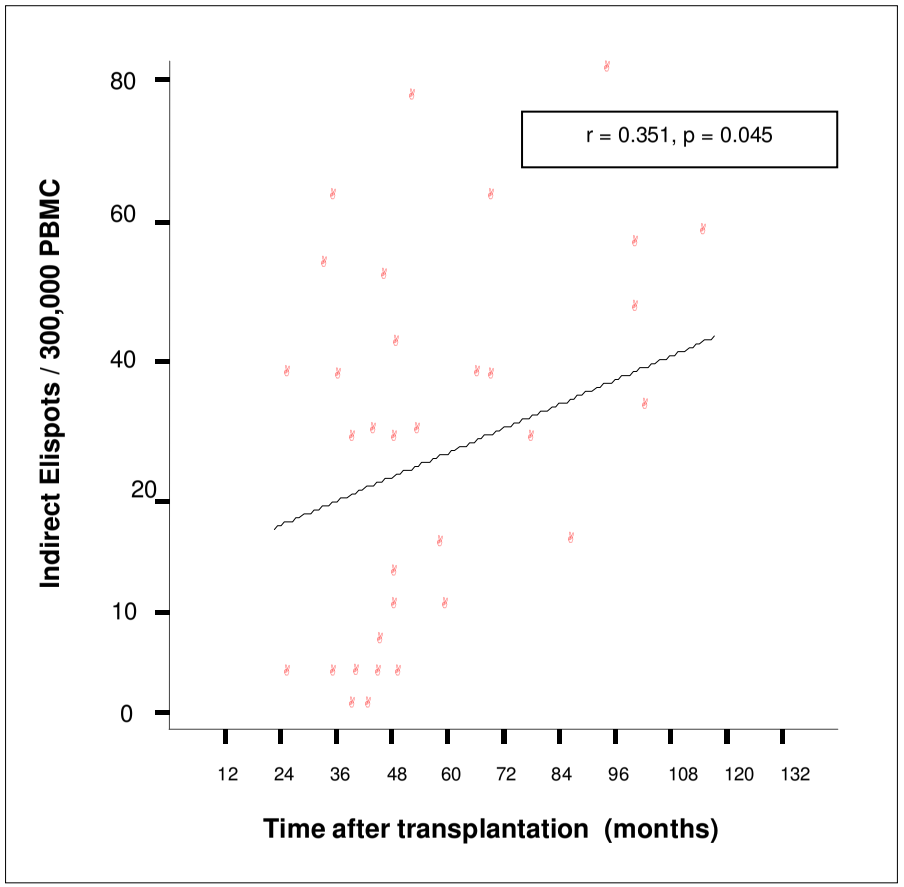
Direct pathway 3 times higher than indirect responses and increased compared to early post-Tx



Bestard et al.J Am Soc Nephrol, 2008; 19: 1419-29

Indirect pathway T-cell alloresponse is related to proteinuria and time after transplantation

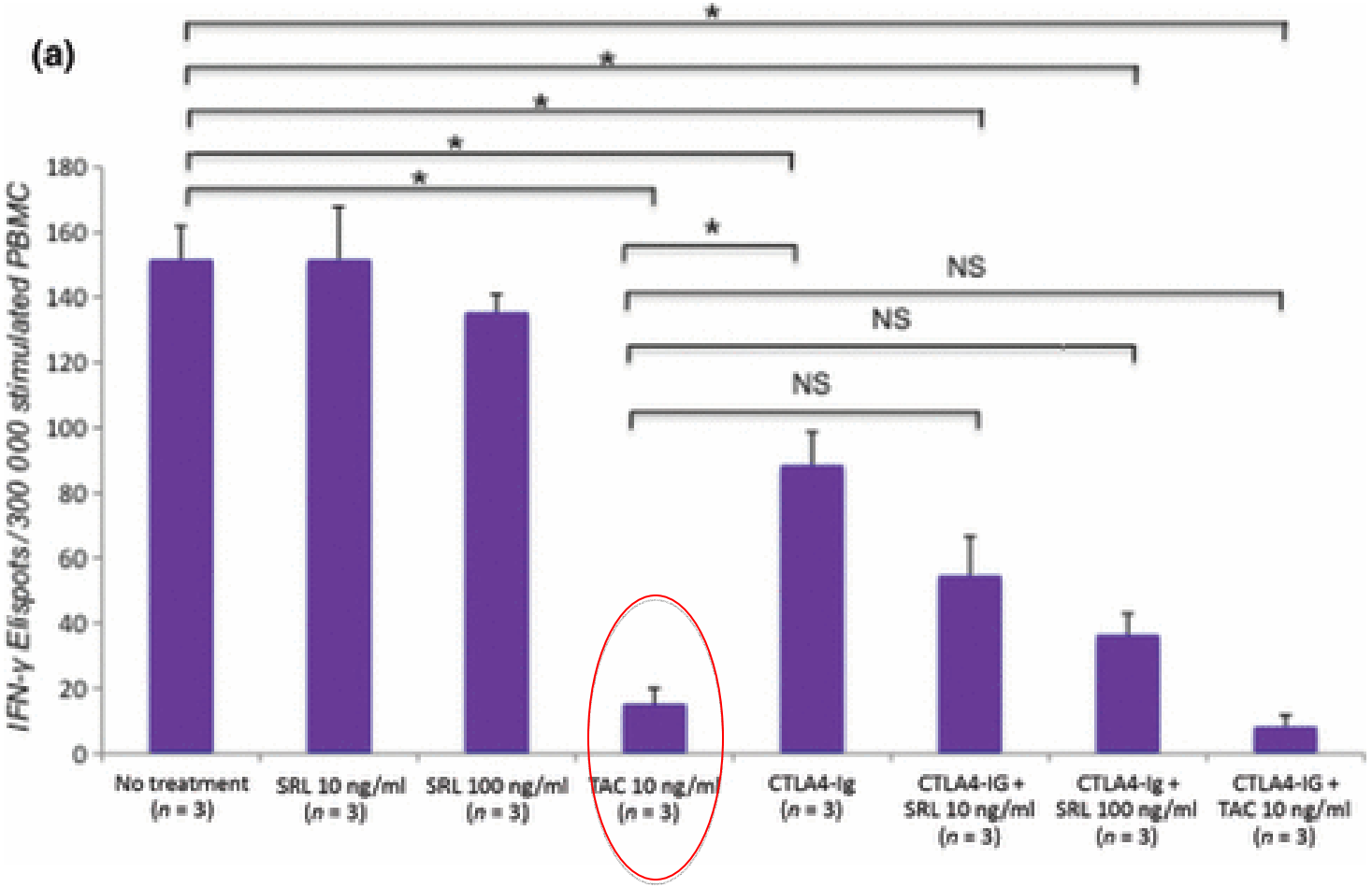




Only one out of 33 screened patients had circulating DSA after transplantation. This patient had a positive indirect but a negative direct pathway Elispot

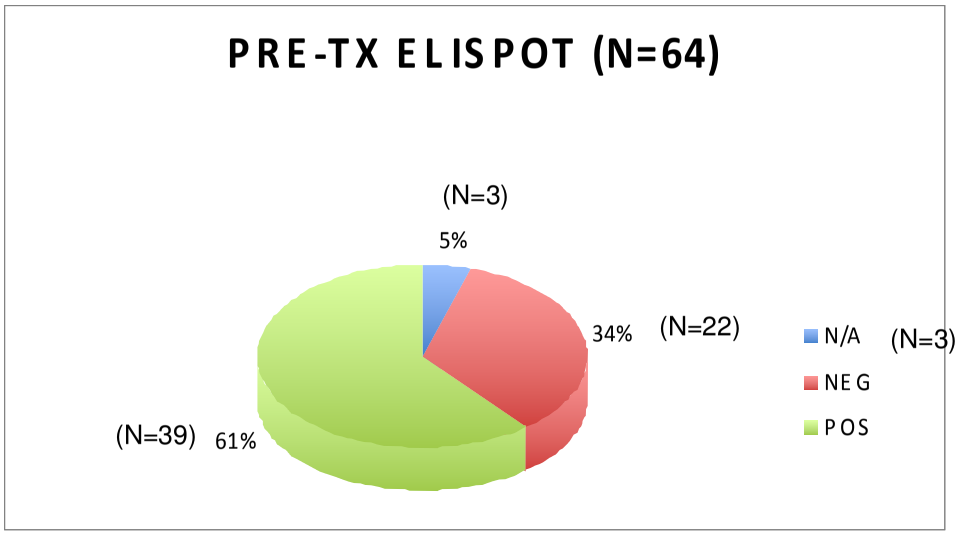
Bestard et al.J Am Soc Nephrol, 2008; 19: 1419-29

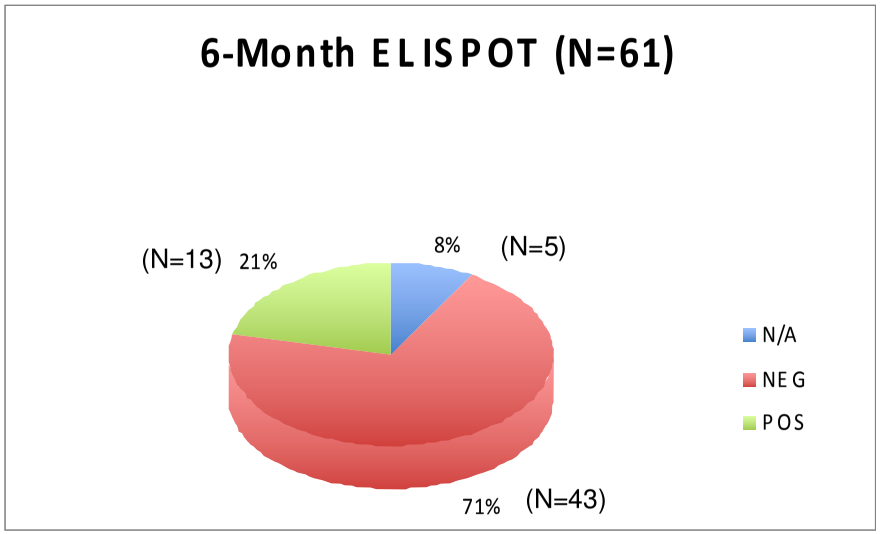
In vitro evaluation immunosuppressivion on circulating memory/effector T cells

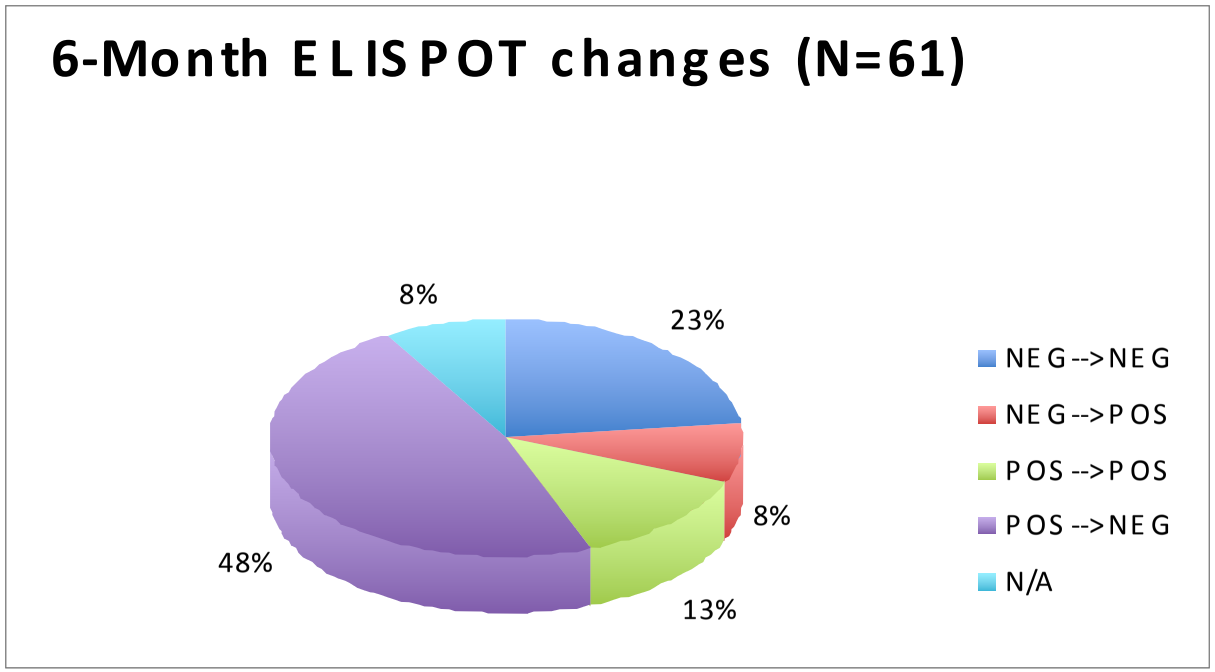


Bestard O et al Transpl Int 2011

Distribution of d-s celullar immune response

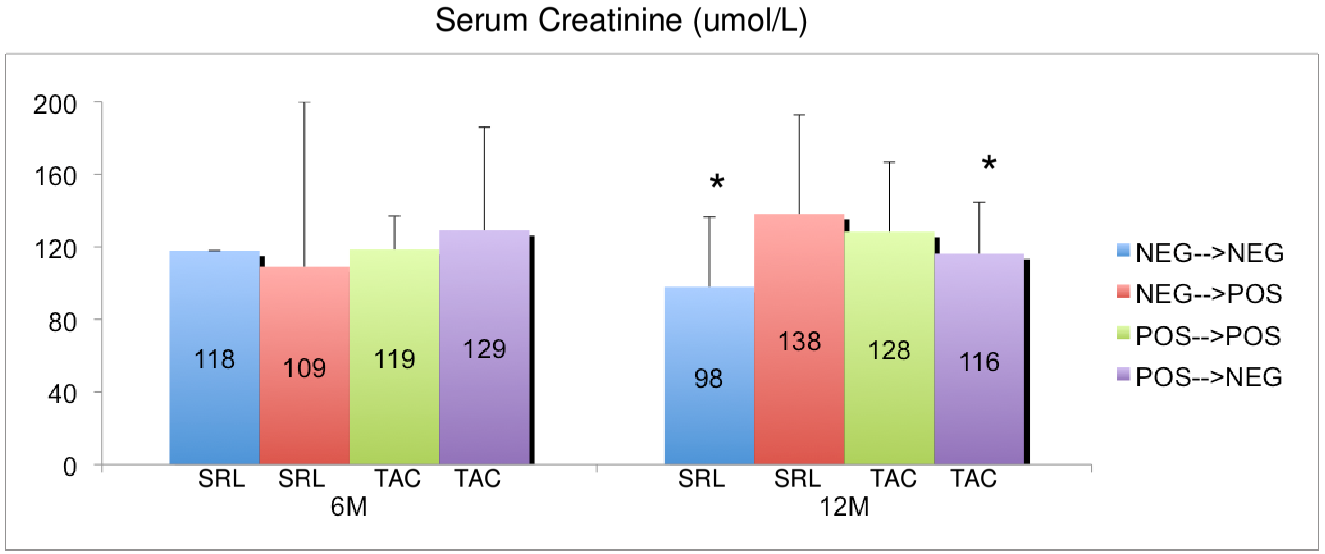


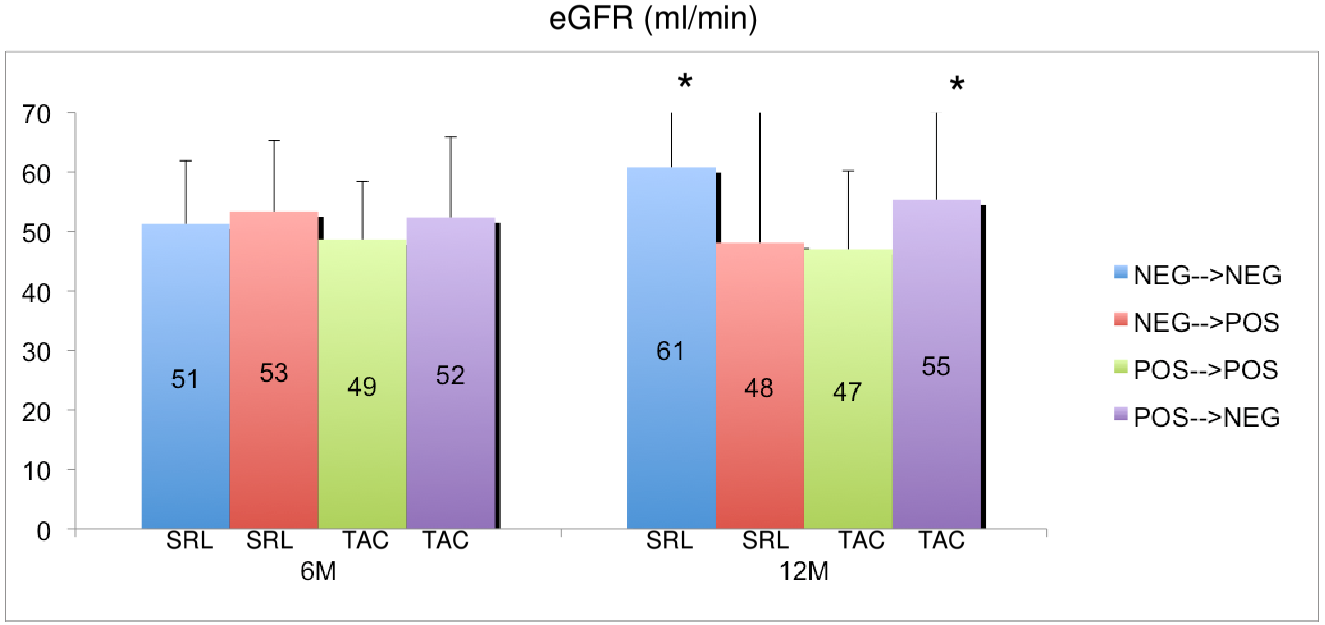




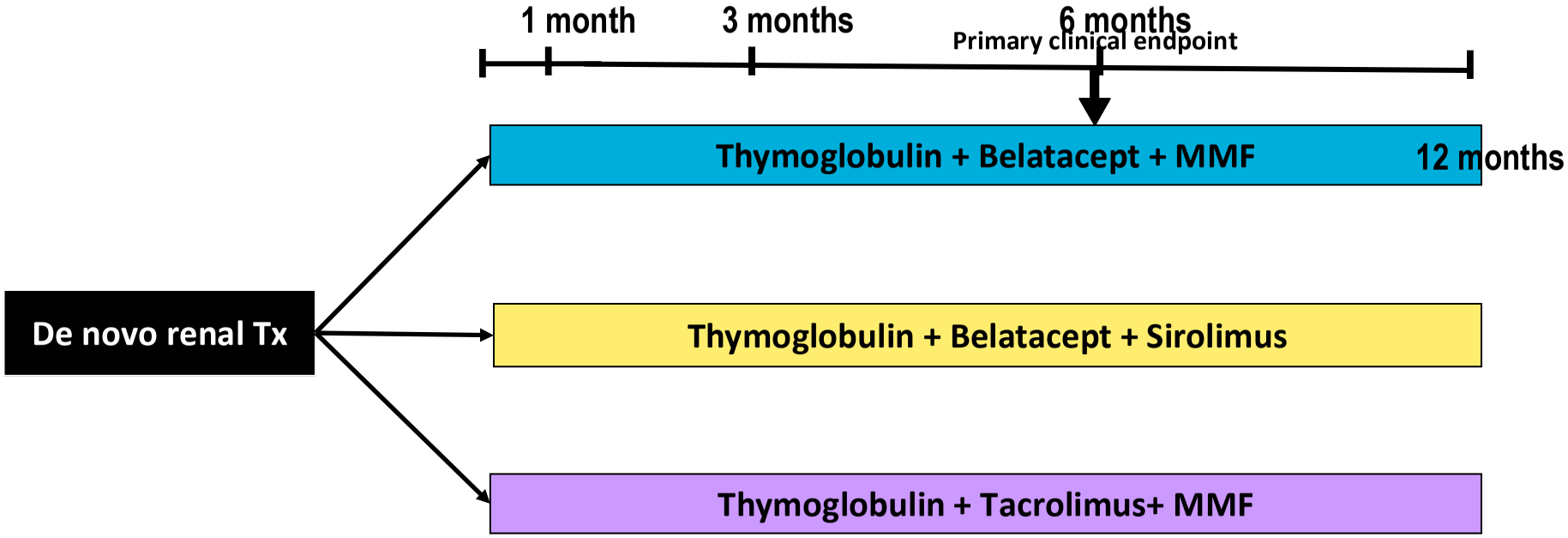
Number of Patients
NEG (22) → NEG: 14
NEG (22) → POS: 5
POS (39) → POS: → 8
POS (39) → NEG: 29
NA : (3 NEG, 2 POS) 5

6-M donor-specific Elispot changes and Graft function evolution





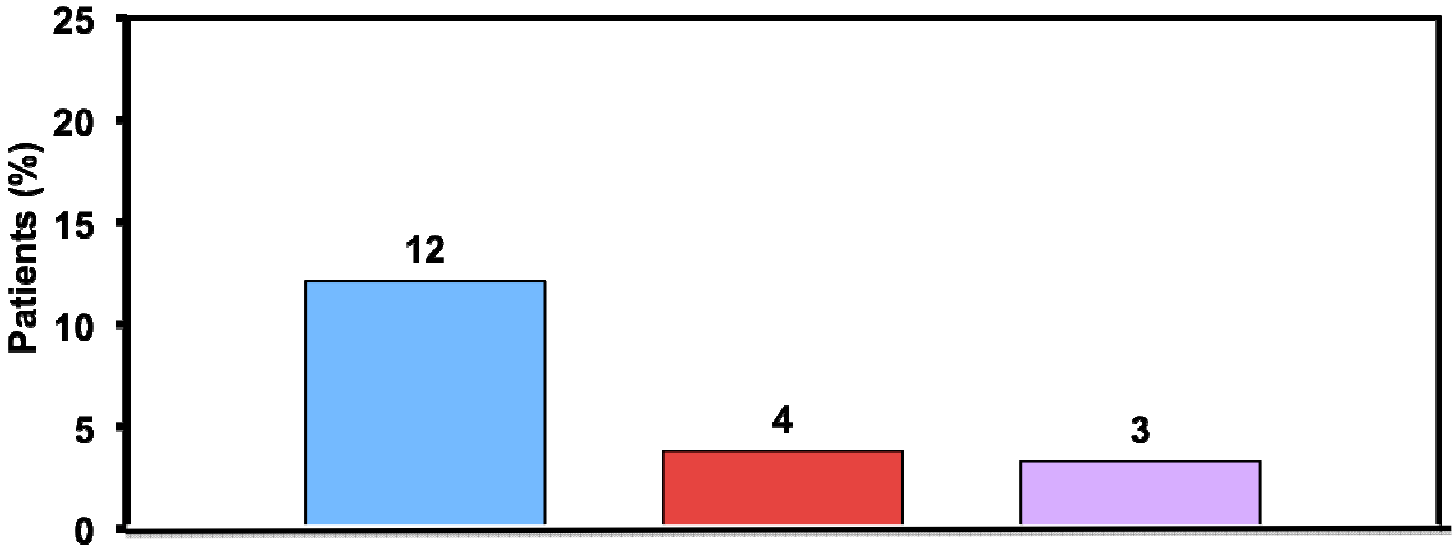
Belatacept-based CNI and steroid-free regimen (exploratory phase IIA trial)



All patients received thymoglobulin (1.5 mg/kg iv on Days 1–4 to max total dose of 6 mg/kg)
All patients received iv steroids on Days 1 (500 mg), 2 (250 mg), 3 (125 mg) and 4 (60 mg)
Belatacept: MI regimen
Conventional levels of Tac and SRL

Ferguson, Grinyo et al. Am J Transplant. 2011;11:66-76

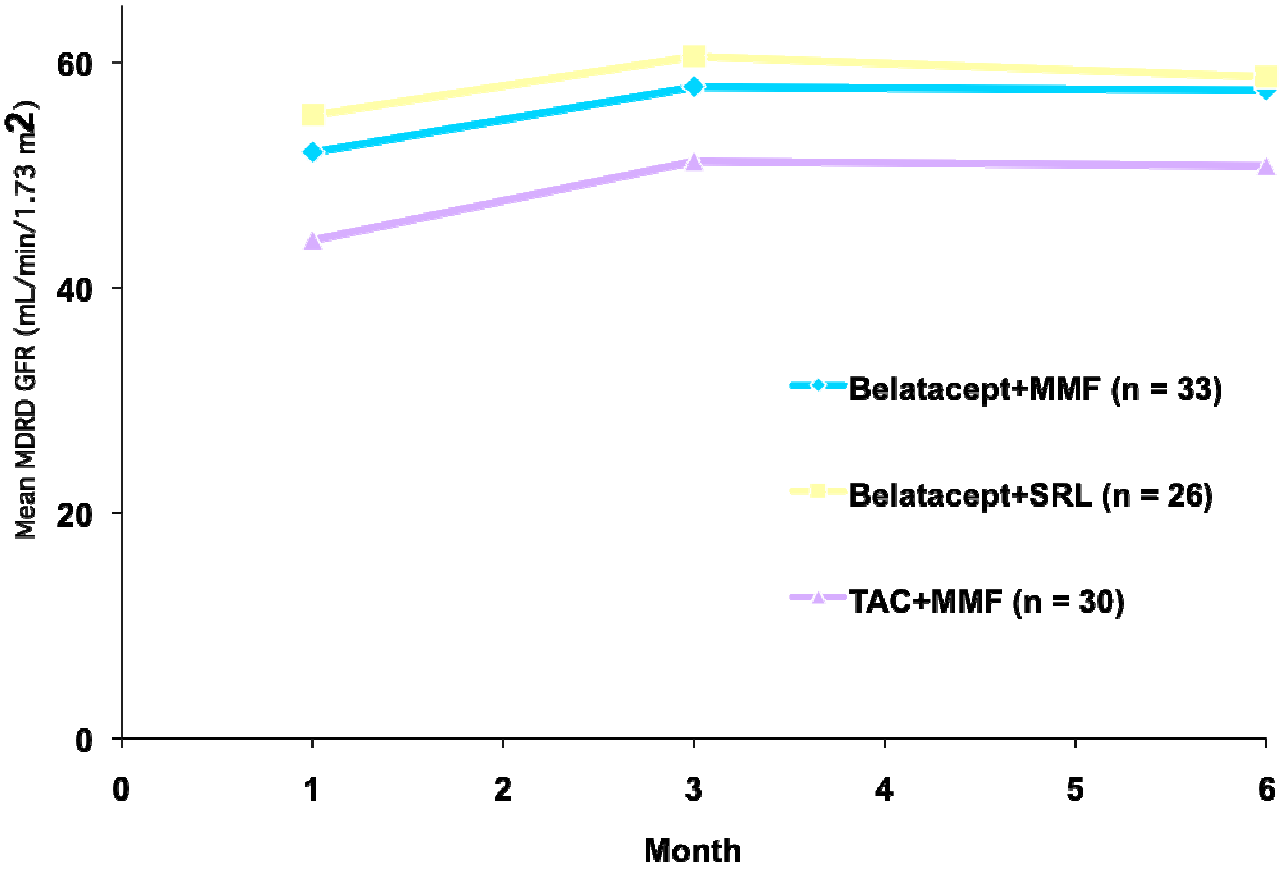
Acute Rejection by Month 6



Banff grade, n (%)	Belatacept + MMF	Belatacept + SRL	TAC + MMF
Mild acute (IA)	0	0	0
Mild acute (IB)	0	0	0
Moderate acute (IIA)	2 (6)	0	1 (3)
Moderate acute (IIB)	1 (3)	1 (4)	0
Severe acute (III)	1 (3)	0	0

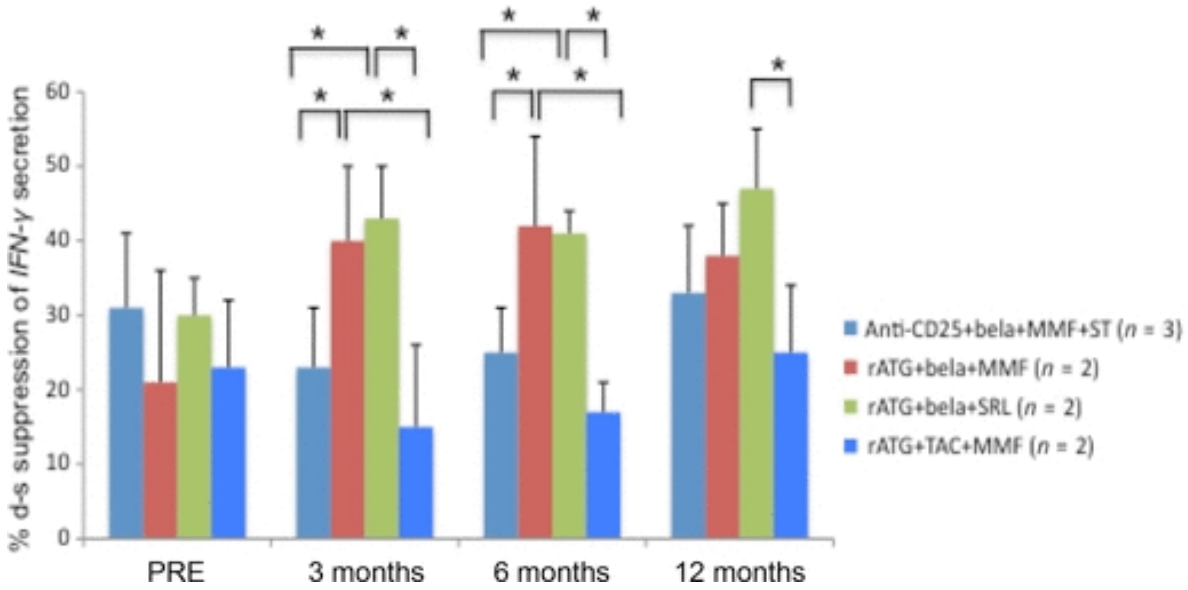
Ferguson, Grinyo et al. Am J Transplant. 2011;11:66-76

Mean Calculated GFR (MDRD Formula) Over Time



Ferguson, Grinyo et al. Am J Transplant. 2011;11:66-76

Anti-donor suppressive activity of Tregs from different IS regimens in allogeneics co-culture at different time-points.



Bestard et al. Transplant Int 2011.