Towards an immunosuppressive regimen for indigenous Australians

Graeme Russ

South Australian Renal Transplant Service

Characteristics of renal transplantation in Aboriginal Australians

- Less matching with donors
- More comorbidities
  - Diabetes, obesity, vascular disease
- More delayed graft function
- More rejection
  - Early and late
  - Compliance
- More infection
- Death
  - Infection in first 12 months
  - CV disease after 12 months

DGF/ Rejection rates

- DGF more common among Aboriginal recipients
  - Crude OR 1.70 [1.33-2.18]
  - Adjusted OR 1.49 [1.14-1.96]
- Rejection (in first 6 months) also more common
  - Crude OR 1.55 [1.19-2.02]
  - Adjusted OR 1.54 [1.16-2.07]

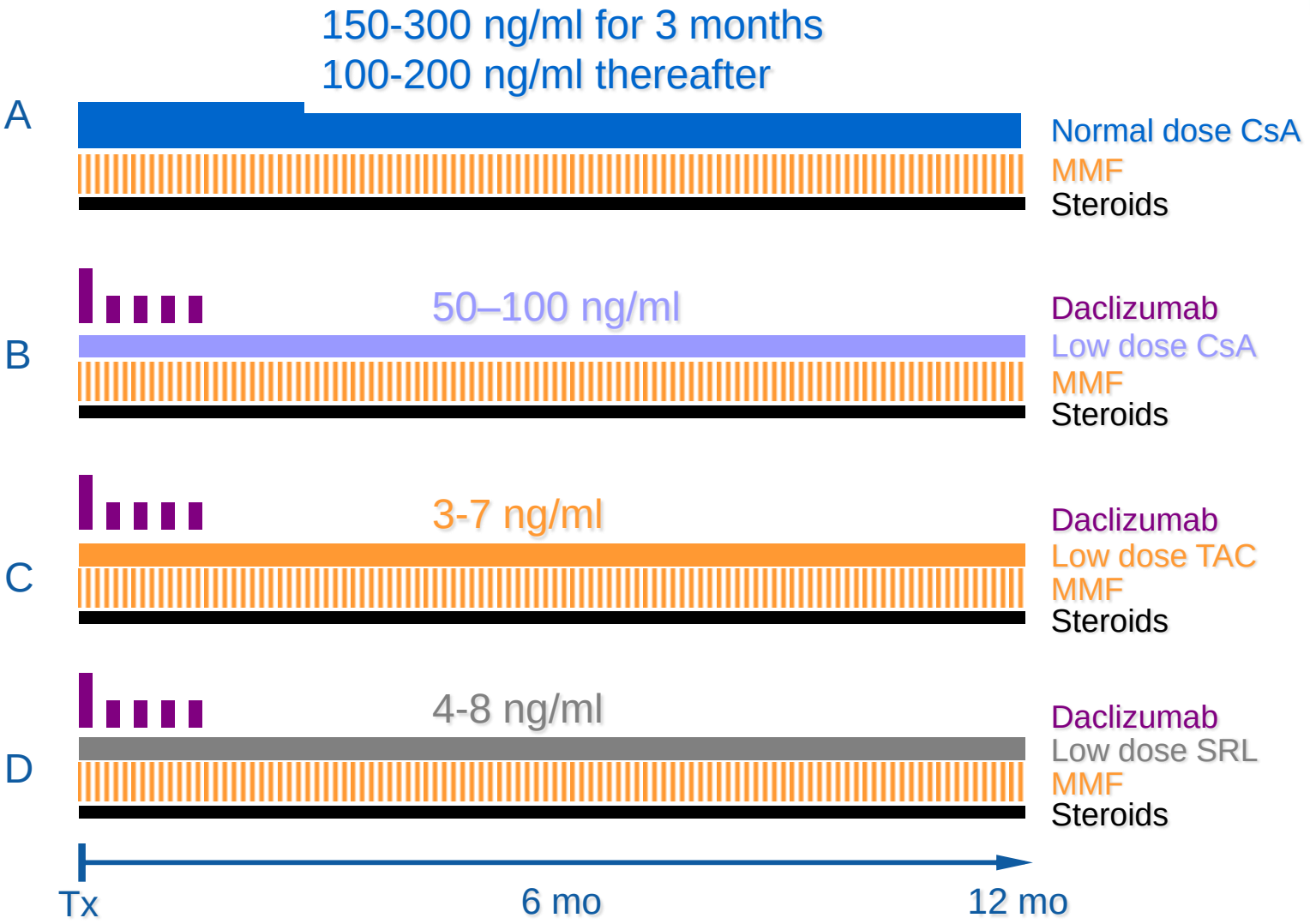
Characteristics of renal transplantation in Aboriginal Australians

- Less matching with donors
- More comorbidities
  - Diabetes, obesity, vascular disease
- More delayed graft function
- More rejection
  - Early and late
  - Compliance
- More infection
- Death
  - Infection in first 12 months
  - CV disease after 12 months

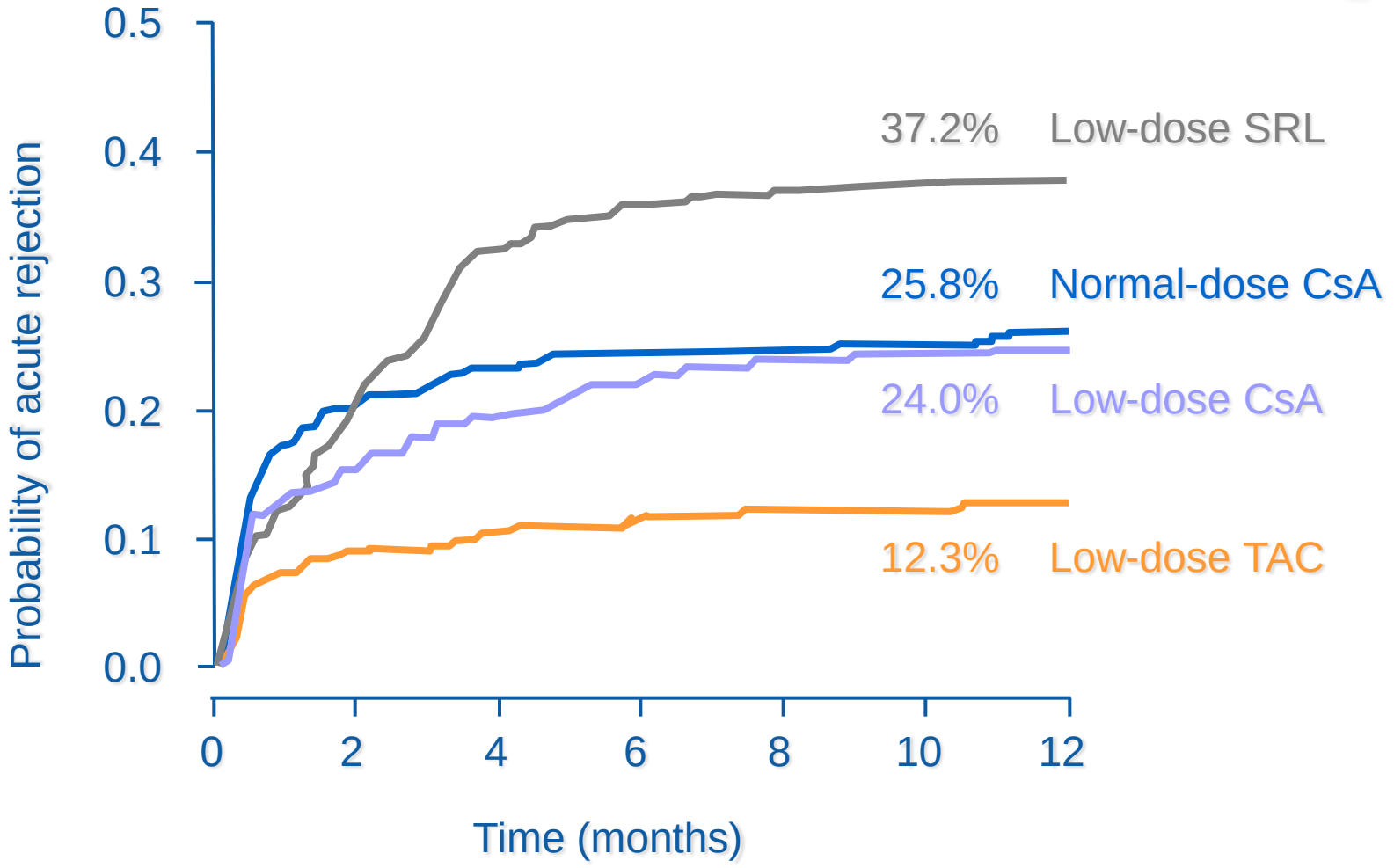
The issues

- Current immunosuppressive regimens
  - do not provide an adequate level of rejection prophylaxis
    - Immunological high risk
  - The high rate of infection suggest over-immunosuppression at least in some individuals
    - How do we identify these
  - Contribute to worsening risk factors for CV disease
    - Especially diabetes

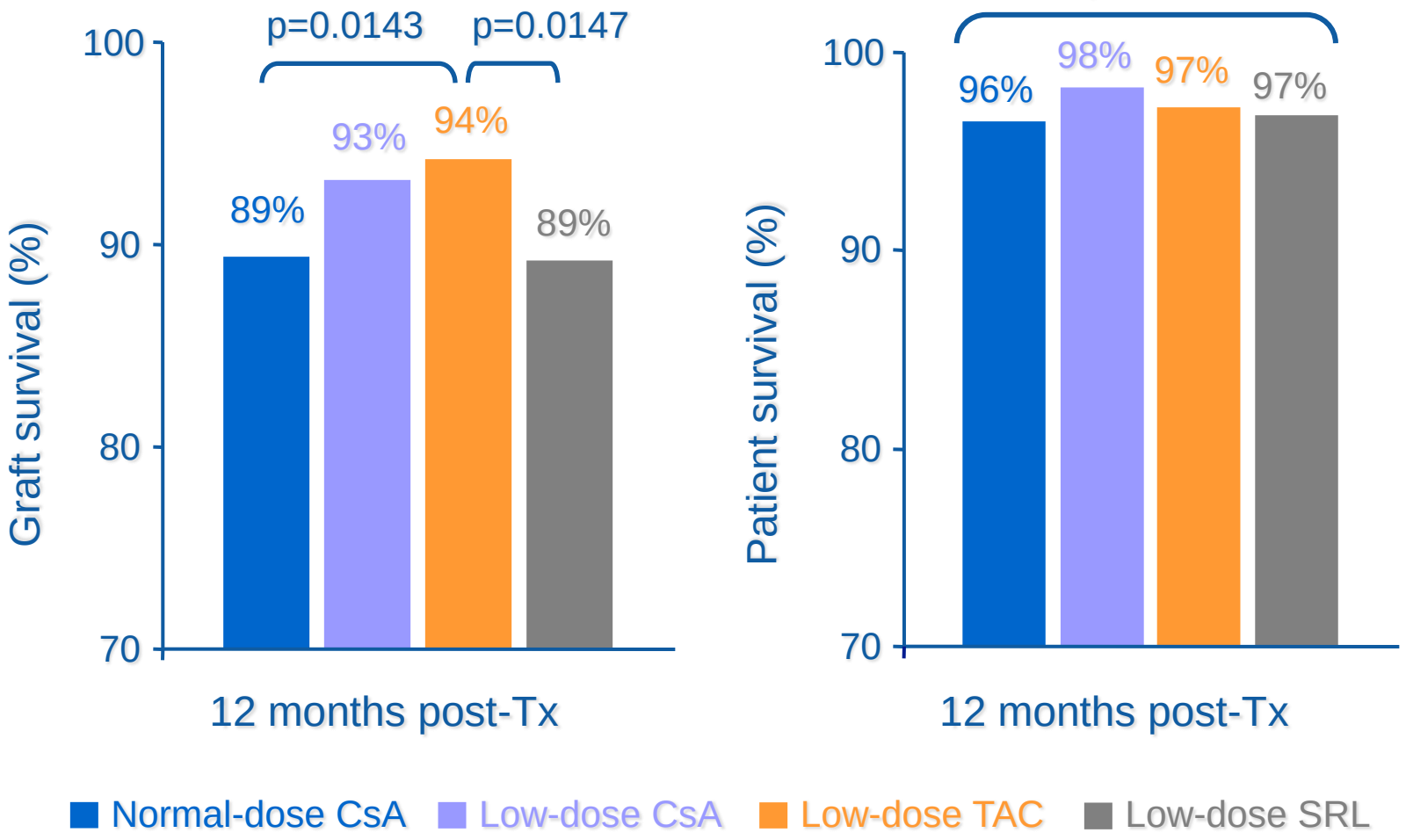
SYMPHONY Study Design



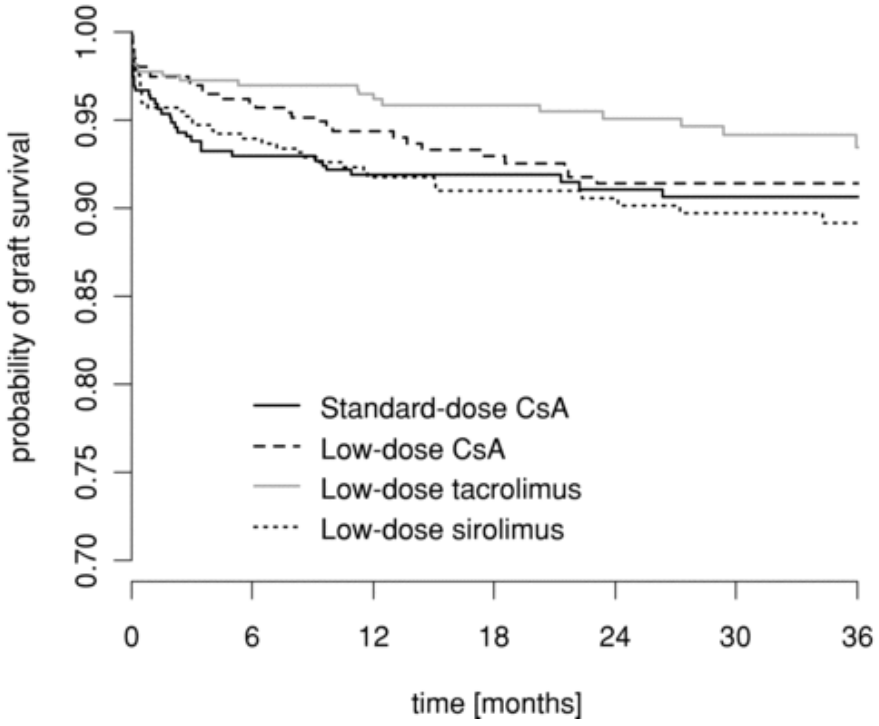
Biopsy Proven Acute Rejection
(ITT, Excluding Borderline)



Graft and Patient Survival

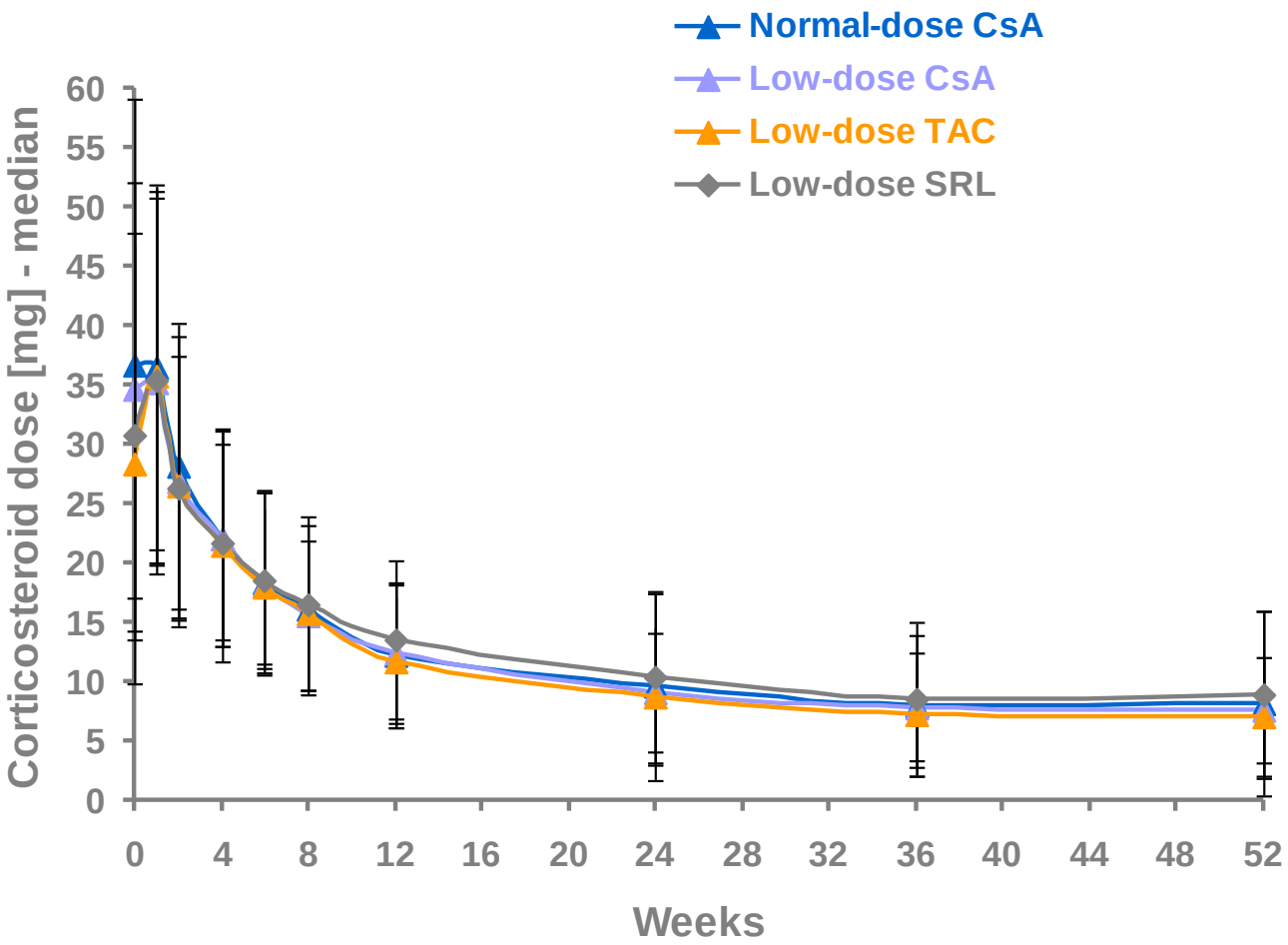


Calcineurin Inhibitor Minimization in the Symphony Study: Observational Results 3 Years after Transplantation



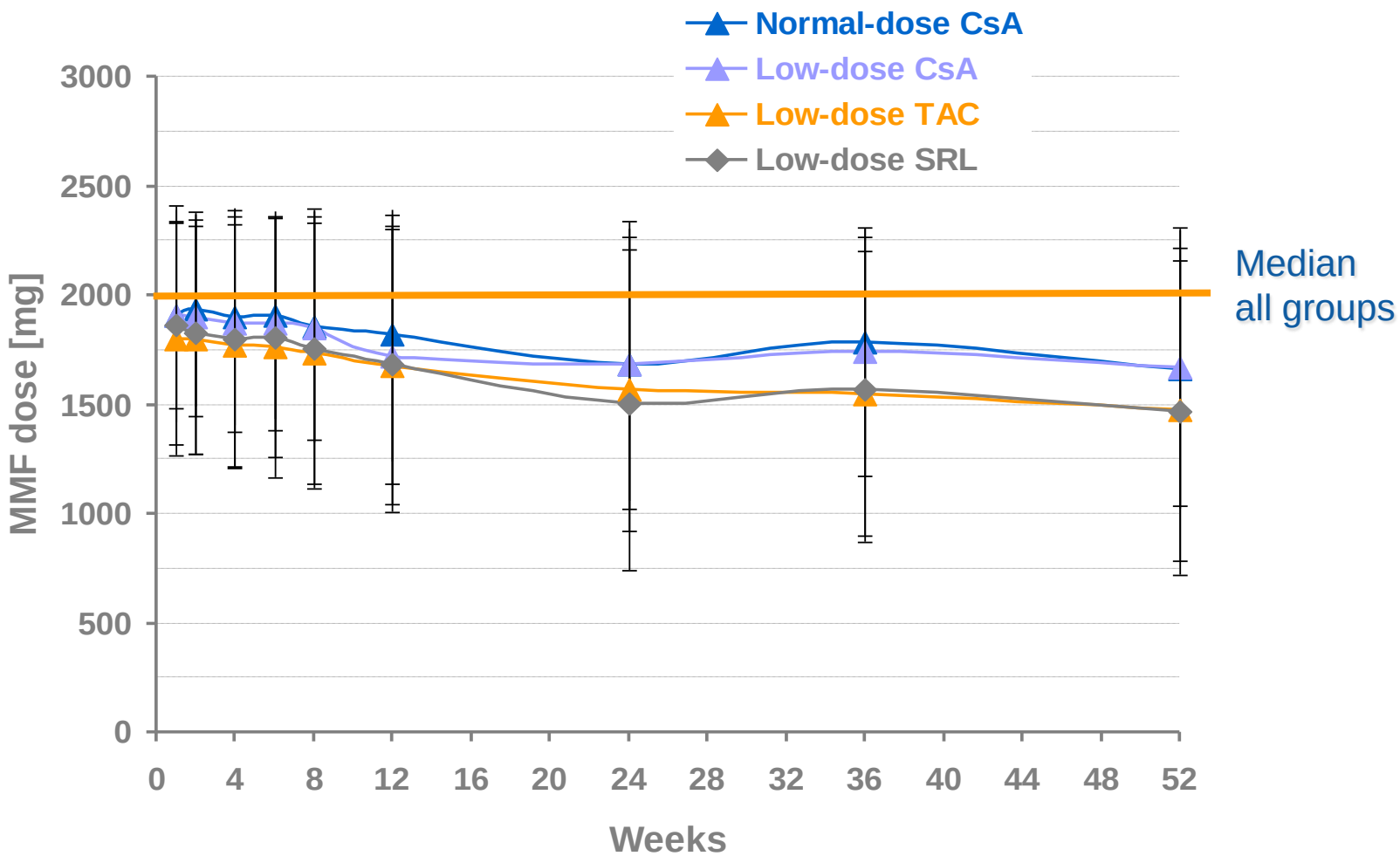
American Journal of Transplantation
Volume 9, Issue 8, pages 1876-1885, 26 JUN 2009 DOI: 10.1111/j.1600-6143.2009.02726.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1600-6143.2009.02726.x/full#f3

Corticosteroid Doses



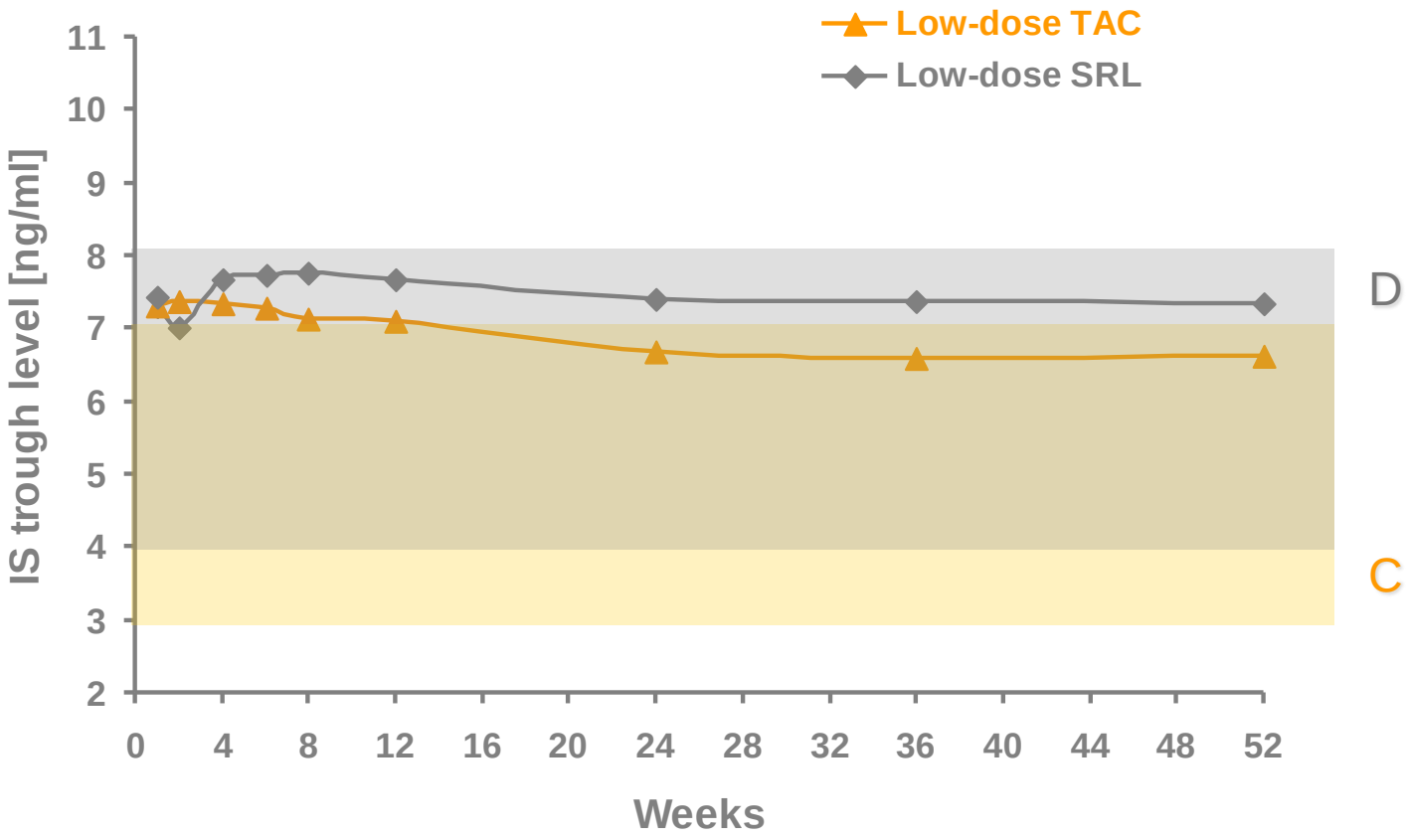
ITT population, means±SD, excluding pulse steroids and outliers <0 and >75 mg

MMF Doses



ITT population, means±SD

Trough Levels TAC and SRL



ITT population, means – trimmed means (C: <2.2 or >18.4; D: <2.2 or >24.3)

Features of the current regimen

- Uses induction with anti-IL2r antibody
- Minimizes but still uses a CNI
  - ? Contributes/prolongs DGF
  - Contributes to CV risk, worsens diabetes
  - Nephrotoxicity in long term
- Maintains corticosteroids
  - Contributes to CV risk, worsens diabetes/obesity
- Uses an anti-proliferative known to promote viral infection
  - Maintains dosage out to 12 months

The current regimen

- Do any of the agents contribute specifically to any particular infections?
- Do any of the agents contribute to poorer compliance?
- Do any of the agents contribute to poorer CV outcomes?

Issue

- Avoidance of rejection – is it important?
- Rejection equates with an increase in immunosuppression
  - Steroids first
  - ATG after
- Increases risk of infection

Issue

- Do we need an induction agent?
- Choice of induction agent
  - Basiliximab v ATG

ATG v Basiliximab
Brennan et al 2006

- Recipients at high risk of DGF or rejection (n=278)
- All got CsA/MMF/steroids out to 12 months
- No difference in DGF, death, graft loss
- Less rejection (15% v 25%) with ATG
- Less severe rejection (1.4% v 8%) with ATG
- More infection (85% v 75%) with ATG
  - More UTI with ATG (39% v 27%)
  - Less CMV with ATG (8% v 18%)
  - More other viral with ATG (21% v 12%)
  - PTLD 3 with ATG, 0 with Bas

Issue

- Choice of CNI
  - Tacrolimus v Cyclosporin A
- Should we aim for CNI withdrawal?

Safety

	Overall infections *	CMV infections *	Lympho-celes *	Diarrhoea *	Diabetes mellitus* (post-Tx)	Wound not healed ¥	Malig-nancy **
Normal-dose CsA	65.6%	15.3%	6.9%	17.5%	6.3%	10.9%	1.3%
Low-dose CsA	57.7%	11.5%	7.0%	14.2%	4.8%	11.0%	1.0%
Low-dose TAC	58.3%	10.2%	3.7%	27.3%	10.6%	9.4%	2.0%
Low-dose SRL	62.5%	6.5%	15.3%	23.9%	7.3%	16.6%	2.4%

* Kaplan-Meier estimates ¥ at week 2 ** diagnosed within first 12 months post-Tx

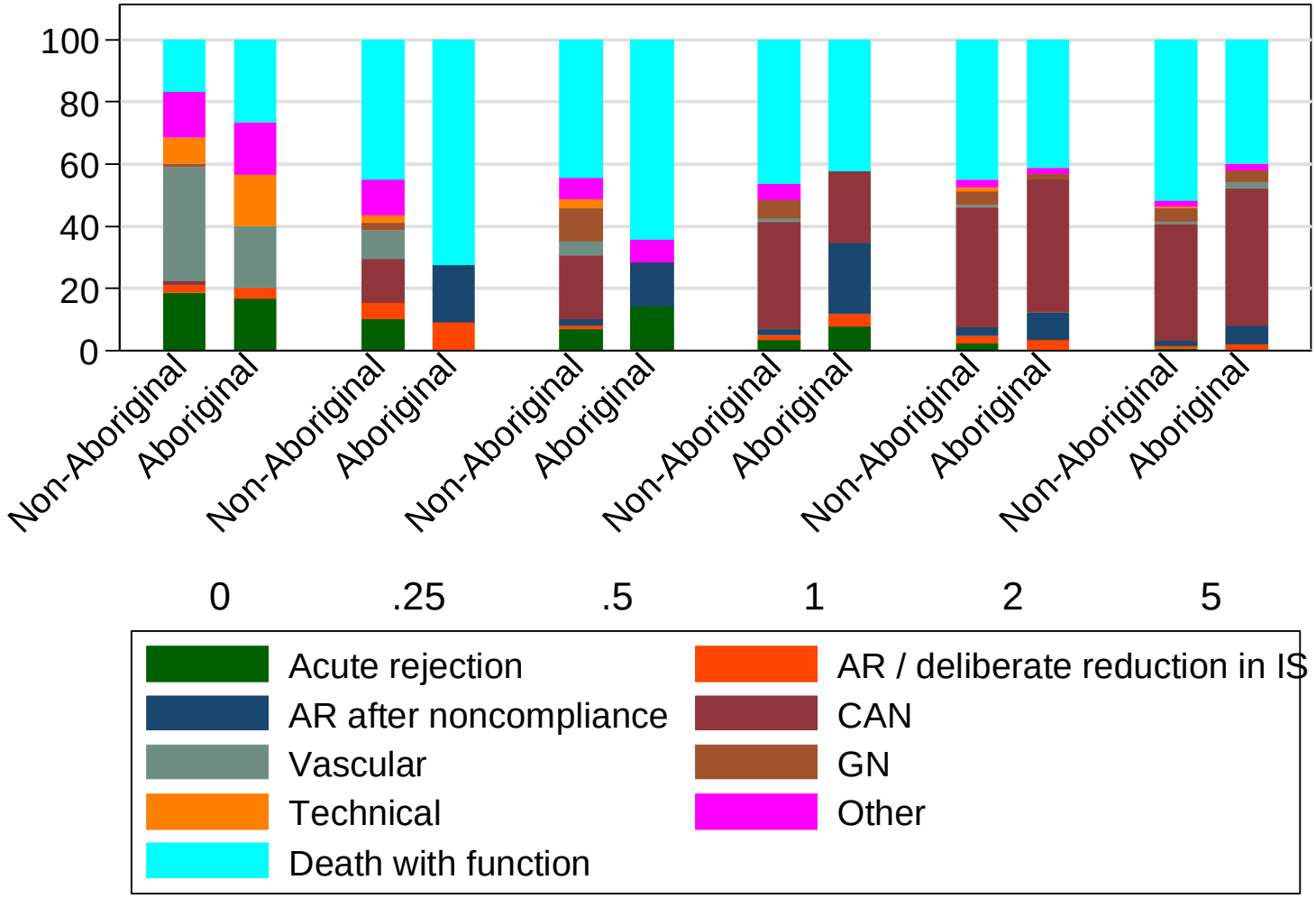
Issue

- Choice of CNI
  - Tacrolimus v Cyclosporin A
- Should we aim for CNI withdrawal?
  - In virtually all studies associated with increased rejection

Issue
Steroid withdrawal or avoidance

- Desirable in these patients because of infection and diabetes
- Multiple studies have demonstrated an increased rejection rate (with both CNI, anti-IL2r Ab)
  - Not recommended particularly for high immune risk recipients
- The only studies which have demonstrated safe CS withdrawal (ie without rejection) are after induction with ATG

Causes of graft failure



Causes of graft loss, Australian tx, 1991-2011

Simplifying the regimen

- Use single day dosage of immunosuppressive agents
  - Extended release tacrolimus once daily– Tacrolimus XL
  - Use sirolimus rather than BD dosage of CNI
  - Use azathioprine rather than BD dosage of mycophenolic acid

Depot agents

- An agent where a single or few doses have a prolonged effect
- Advantage where efficacy of other agents is variable or unreliable
  - Variation in absorption
  - Non-compliance is an issue
- Disadvantage of not being able to reverse effect in cases of toxicity

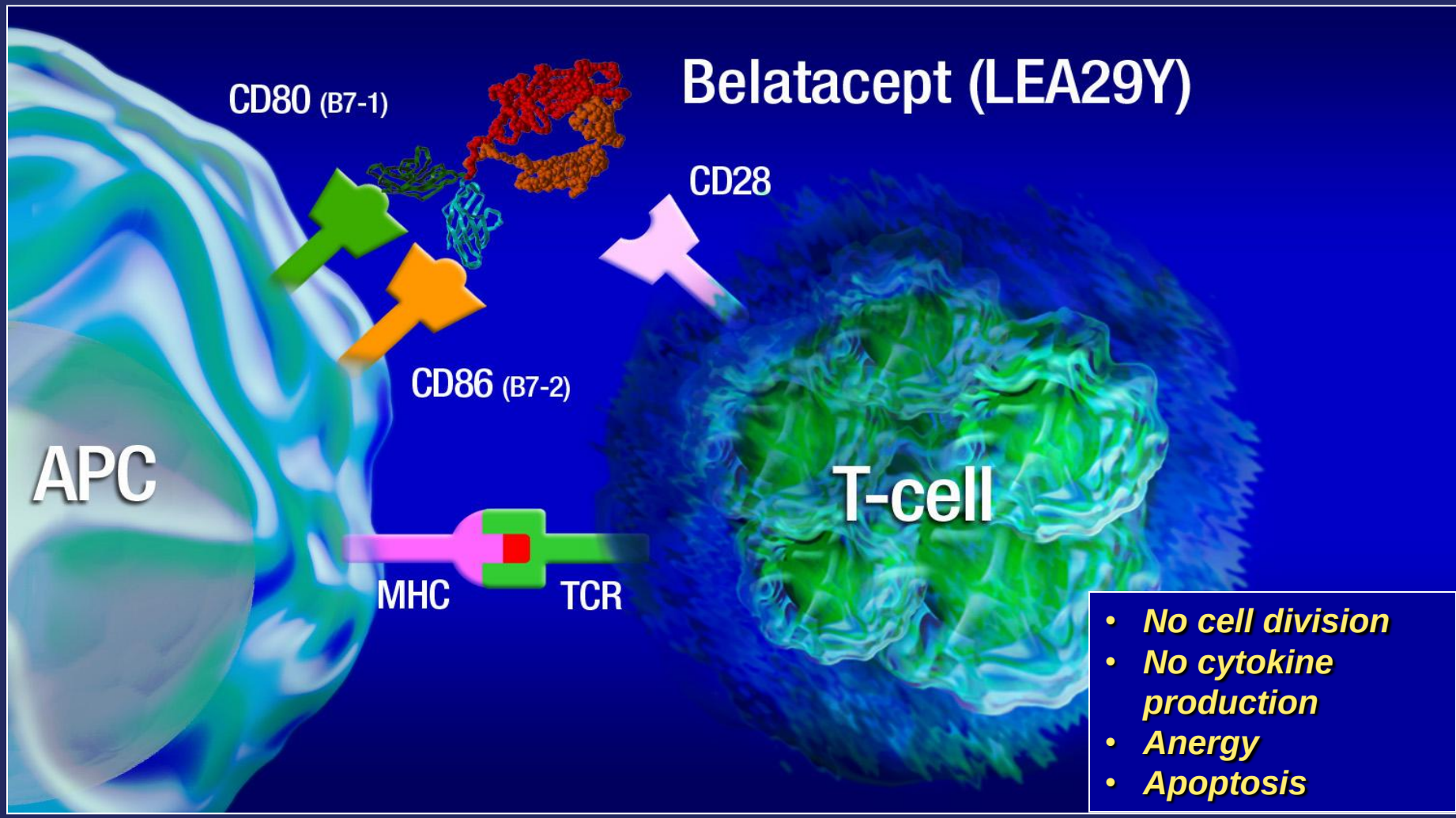
What agents provide a depot effect?

- Thymoglobulin
  - >3 mg/kg has 3-6 months
- Basiliximab
  - 2 doses of 20mg has 6 weeks
- Alemtuzumab
  - Single dose has 6-12 months
- Belatacept
  - Single dose has 1 month

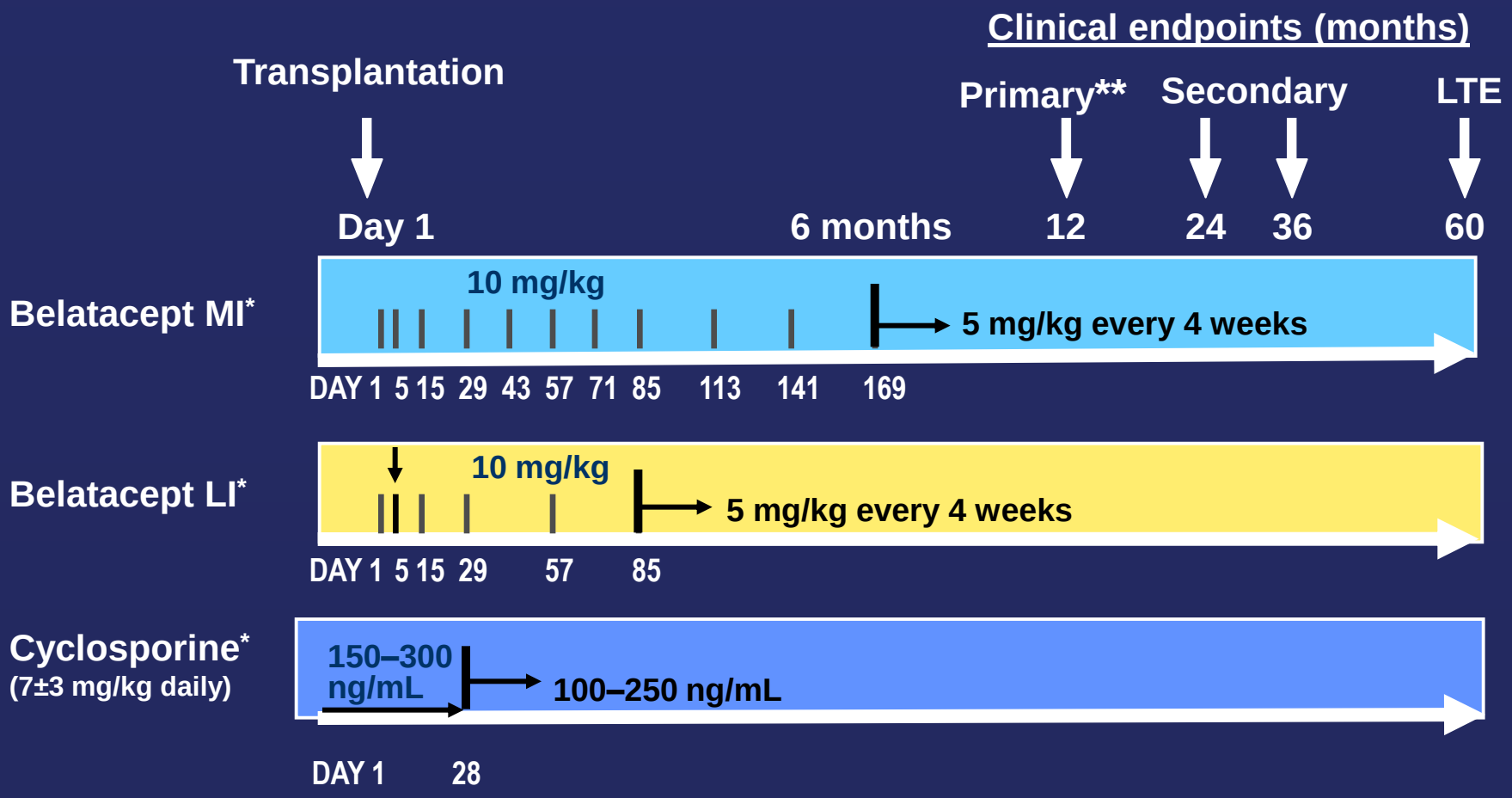
What about belatacept?

- Pivotal studies show increased rejection, but improved renal function when used in a CNI-free regimen
- But higher rate of PTLD especially with EBV-naïve recipients who have received ATG
- Higher rate of tuberculosis (in endemic areas)

Belatacept Selectively Blocks T-cell Activation



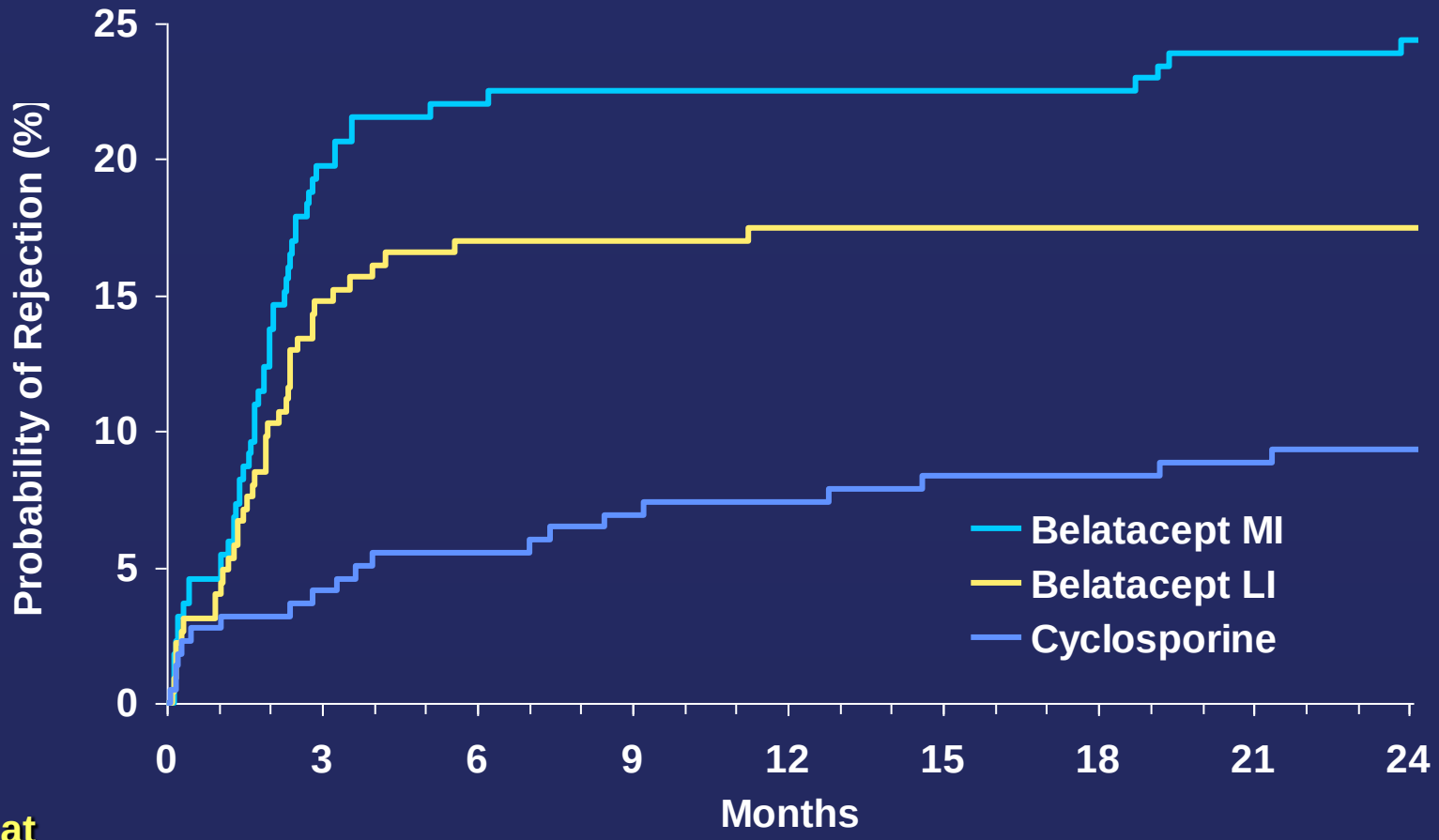
BENEFIT and BENEFIT-EXT Treatment Regimen



*All patients received basiliximab induction, mycophenolate mofetil, and corticosteroid-taper;

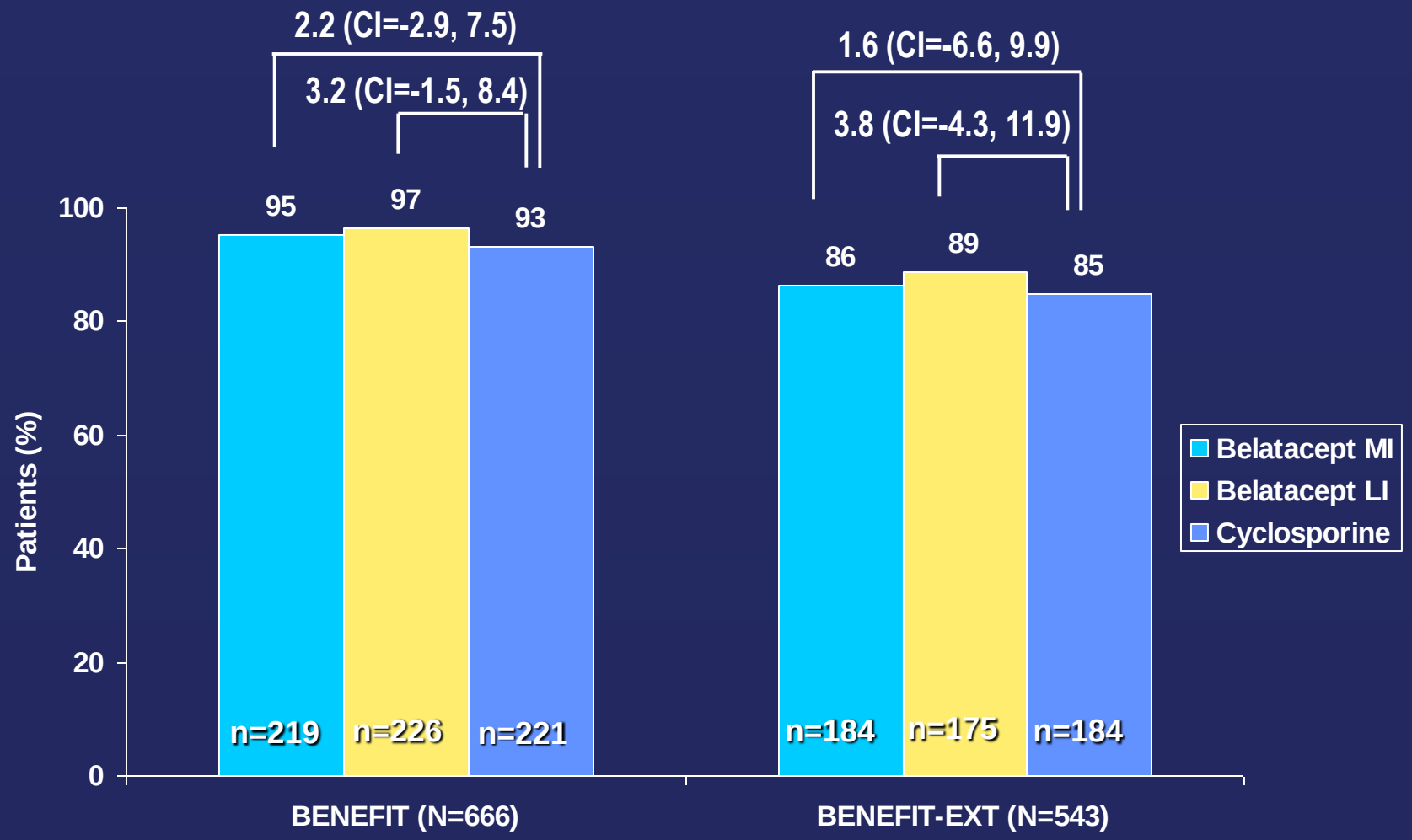
**Belatacept arms unblinded at 12 months; LTE=Long-term extension; LI=less intensive; MI=more intensive

BENEFIT
Time to Acute Rejection



Patients at Risk									
Belatacept MI	219	174	168	166	165	164	164	161	154
Belatacept LI	226	190	185	184	183	182	182	181	178
Cyclosporine	221	207	201	197	195	190	188	186	169

BENEFIT and BENEFIT-EXT
Patients Surviving with a Functional Graft by Month 12*



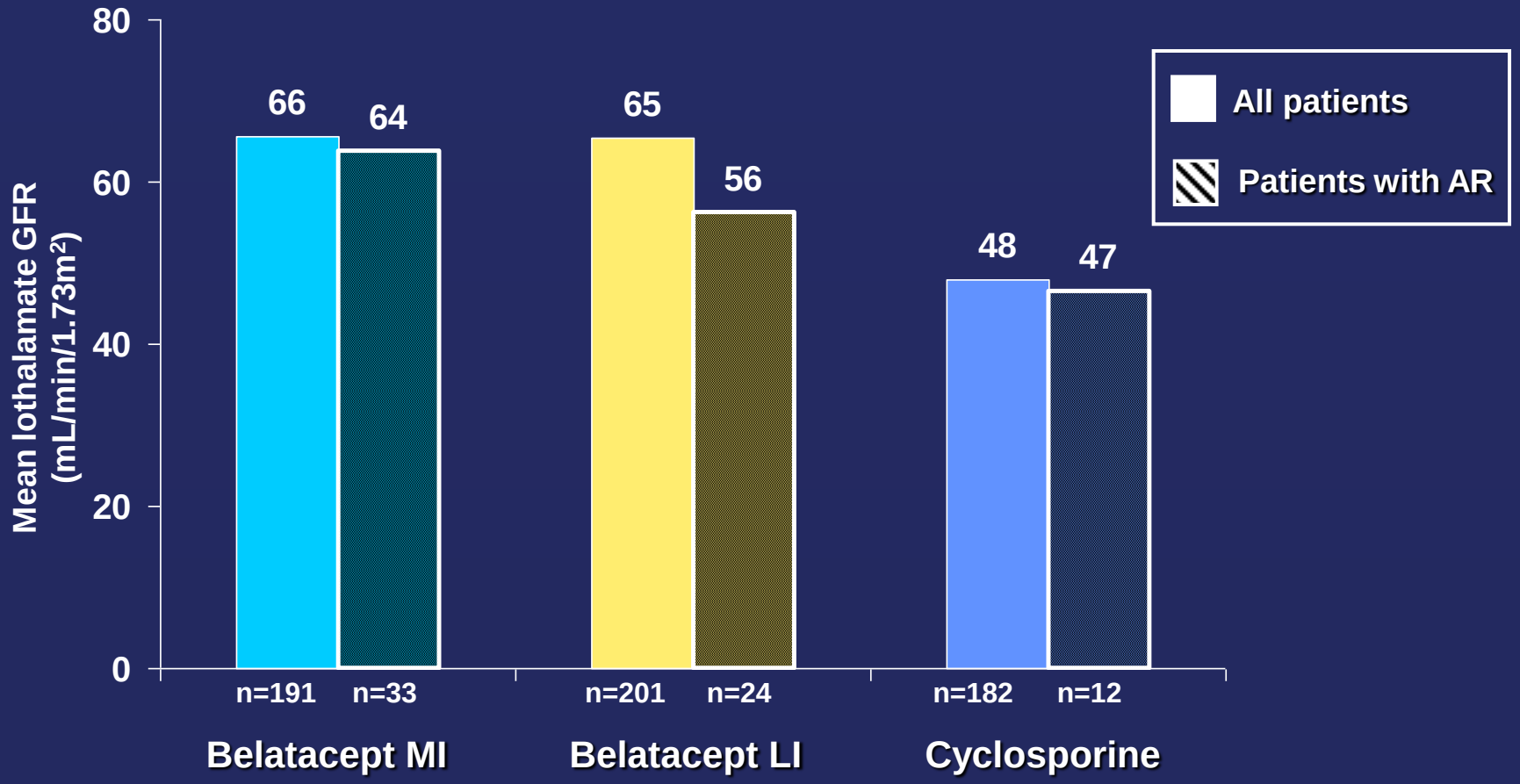
*Intent-to-treat population (ITT); All belatacept arms met 10% non-inferiority margin vs cyclosporine; CI=97.3% confidence interval

BENEFIT
Acute Rejection by Month 24*

	Belatacept MI (n=219)	Belatacept LI (n=226)	CyA (n=221)
Acute rejection, n (%)	53 (24)	39 (17)	20 (9)
Months 12–24	4 (2)	0	4 (2)
Banff 97 grade			
Mild acute (IA)	7 (3)	4 (2)	4 (2)
Mild acute (IB)	3 (1)	8 (4)	7 (3)
Moderate acute (IIA)	18 (8)	16 (7)	6 (3)
Moderate acute (IIB)	22 (10)	10 (4)	3 (1)
Severe acute (III)	3 (1)	1 (<1)	0

*Intent-to-treat population (ITT)

BENEFIT
Measured GFR at Month 24 by Acute Rejection Status



GFR=glomerular filtration rate

-008
24 month

BENEFIT
Infections by Month 24*

Category	Belatacept MI (n=219)	Belatacept LI (n=226)	Cyclosporine (n=221)
All infections	77%	77%	78%
Serious infections	24%	27%	29%
Fungal infections	18%	20%	18%
Viral infections – total	34%	32%	35%
BK polyomavirus**	8%	4%	8%
Herpes viruses			
Cytomegalovirus	10%	11%	11%
Herpes (simplex, zoster)	11%	9%	7%
Tuberculosis	3	0	1

*Intent-to-treat population (ITT)

PTLD Cases

PTLD cases, n	Belatacept MI (n=477)	Belatacept LI (n=472)	Cyclosporine (n=476)
Total	8	6*	2
Phase II study	3	0	1
BENEFIT study	3	2	1
BENEFIT-EXT	2	4	0

*Includes one case reported after June/July 2009

Multivariate Risk Factor Assessment for PTLD in Belatacept-Treated Patients*

Risk factors	All belatacept PTLD		Belatacept CNS PTLD	
	Hazard ratio	95% CI	Hazard ratio	95% CI
Recipient EBV status (negative vs positive)	14.03	4.36, 45.15	19.49	4.39, 86.52
LDT (yes vs no)	3.82	1.13, 12.84	5.20	1.18, 22.98
CMV infection post-transplant (yes vs no)	3.19	0.95, 10.68	7.54	1.77, 32.21
Recipient CMV status (negative vs positive)	1.80	0.59, 5.51	1.71	0.43, 6.76

*Up to database lock; LDT=Lymphocyte-depleting therapy; CMV=Cytomegalovirus

Belatacept conversion studies

- Successful conversion from CNI to belatacept at 6 months post-transplant without significant rejection or adverse event
- Better renal function and CV risk factors

Long term follow up of belatacept trials to 5 years

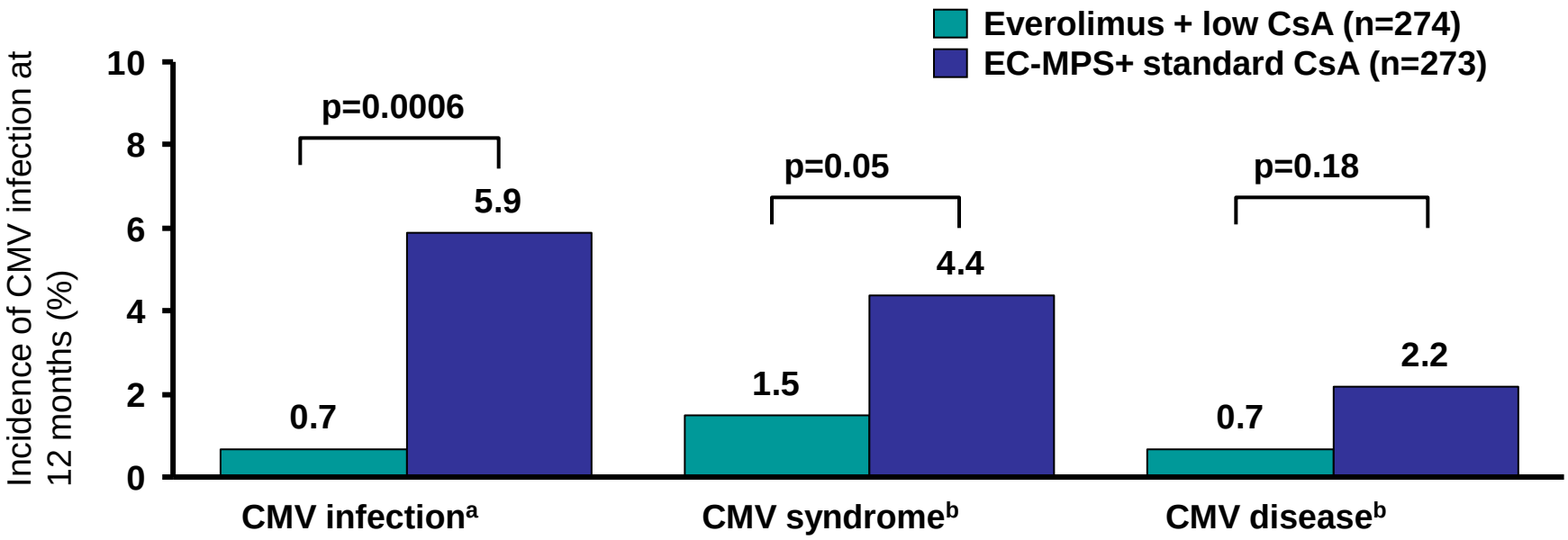
- Over 650 patients
- No difference
  - Acute rejection (low)
  - Infections
  - Graft loss
  - Patient death
  - PTLD (3/400 Belat, 0/200 CsA)
- Difference in renal function maintained

What about TOR inhibitors? Sirolimus and Everolimus

- Advantages
  - Potential for single day dosage (sirolimus)
  - Very low rate of viral (CMV and BKV) infection
    - May allow shorter period of valcyte prophylaxis
- Disadvantages
  - Unlikely to allow steroid withdrawal
  - Adverse effect on wound healing if used early
  - No better for diabetes than tacrolimus
  - ? More resp infection

Everolimus was associated with a lower incidence of CMV syndrome and disease

Prospective analysis of CMV infection incidence in A2309



Tedesco Silva H Jr *et al*. *Am J Transplant* 2010;10:1401–13

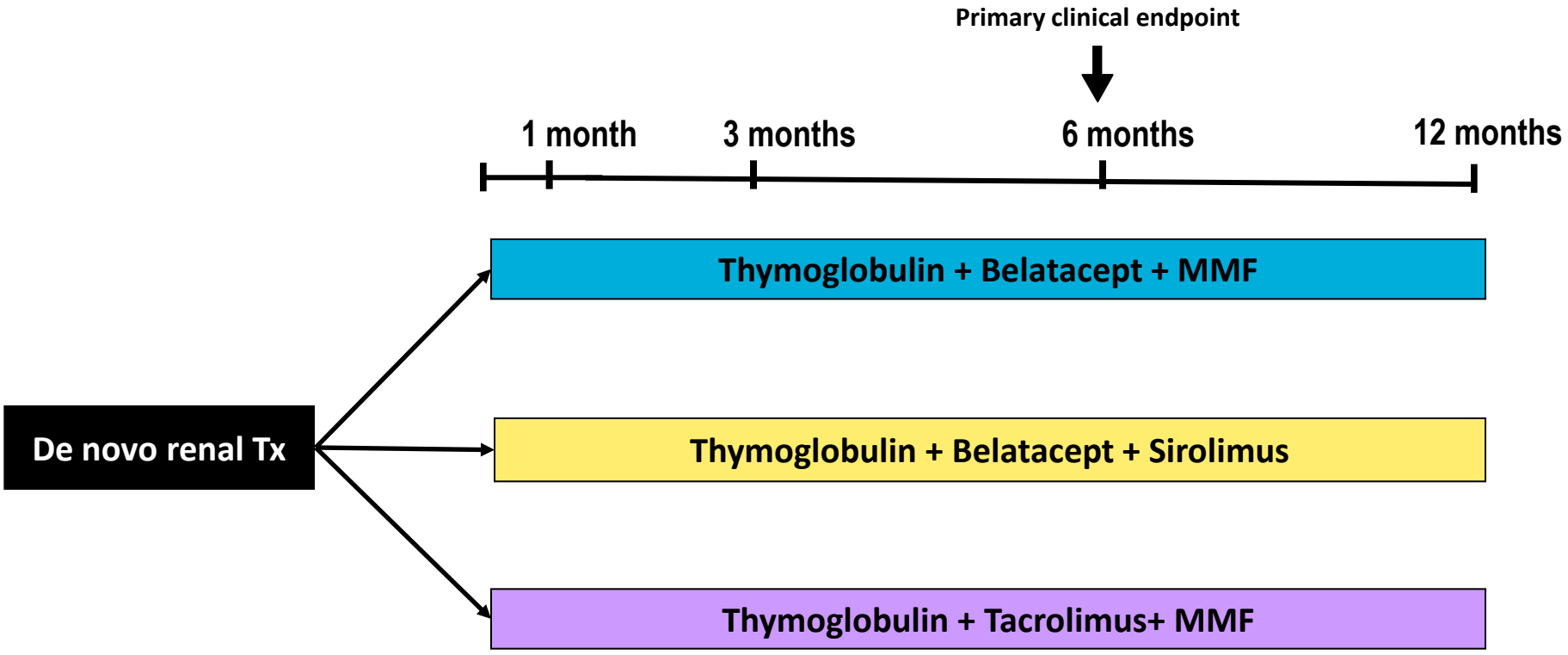
An immunosuppressive regimen for renal transplantation in the indigenous

- Bold innovative approach
- Increased early efficacy to prevent rejection
  - With maximal infective prophylaxis
- Lower baseline immunosuppressive burden later to reduce infection
  - Steroid withdrawal
  - CNI withdrawal
- Strategies to promote compliance
  - Depot (long acting) agents

How do I think things stack up

- ATG rather than Basiliximab
- Steroid avoidance/early withdrawal
- Possible CNI withdrawal/avoidance
- To reduce viral infection
  - Avoid anti-proliferatives
  - Use TORi
- Use belatacept to reduce complexity later

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

Outcomes

	Bela-MMF (n=33)	Bela-SRL (n= 26)	TAC-MMF (n=30)
Acute Rejection at Month 6, n (%)	4 (12)	1 (4)	1 (3)
Difference from TAC (95% CI)	8.8 (−6.6, 24.9)	0.5 (−14.5, 16.7)	–
Banff Grade, n (%)			
Mild acute (IA or IB)	0	0	0
Moderate acute (IIA)	2 (6)	0	1 (3)
Moderate acute (IIB)	2 (6)	1 (4)	0
Severe acute (III)	0	0	0
Acute rejection at Month 12, n (%)	5 (15)	1 (4)	1 (3)
Difference from TAC (95% CI)	11.8 (−4.1, 28.7)	0.5 (−14.5, 16.7)	–
Subject and graft survival at Mo 12, n (%)	30 (91)	24 (92)	30 (100)
Difference from TAC (95% CI)	−9.1 (−23.6, 2.8)	−7.7 (−24.1, 4.1)	–
Graft loss	2 (6)	2 (8)	0
Death	1 (3)1	0	0
Death with functioning graft	1 (3)1	0	0
Proportion steroid-free at Month 12, n (%)	24 (73)	20 (77)	28 (93)
Prop steroid and CNI-free at Mo 12, n (%)	24 (73)	18 (69)	1 (3)

Infection at 12 months

- Bela/MMF v Bela/Sir v Tac/MMF
  - Any infection 79 v 77 v 67
  - Serious infection 21 v 15 v 17
  - Fungal 15 v 4 v 7
  - Viral 12 v 8 v 20