Az mTOR inhibitorok szerepe a veseátültetés utáni immunszuppresszióban

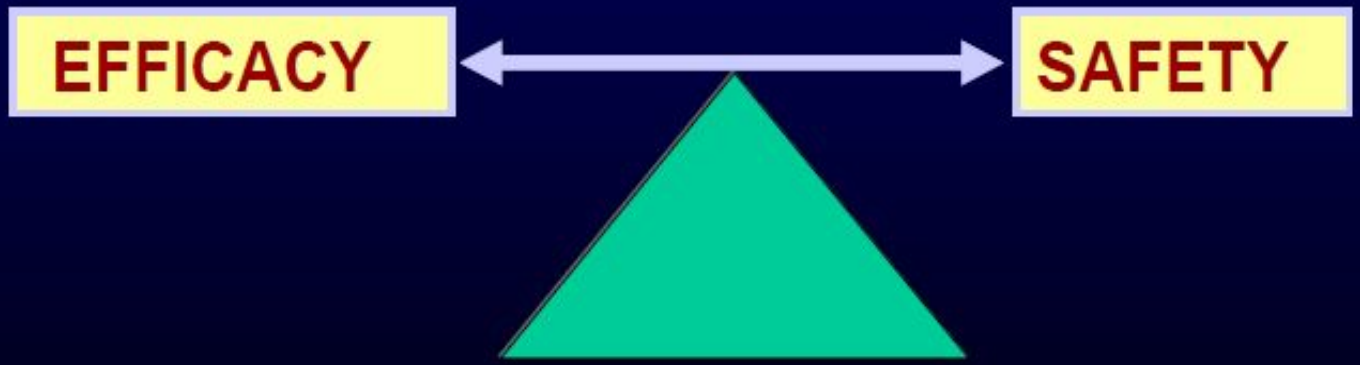
Lajos Zsom, M.D.

2014

Immunosuppressive Therapy

- Cellular response
- Humoral response

- Nephrotoxicity
- Cardiovascular RF
- Cancer
- Opportunistic Infections



LONG-TERM RESULTS ON RENAL TRANSPLANTATION

Calcineurin Inhibitors: a Price to Pay

- Cyclosporine

- vascular toxicity
- resistant hypertension
- hyperlipidemia
- diabetes mellitus
- chronic allograft nephropathy/nephrotoxicity
- hirsutism
- gingival hyperplasia

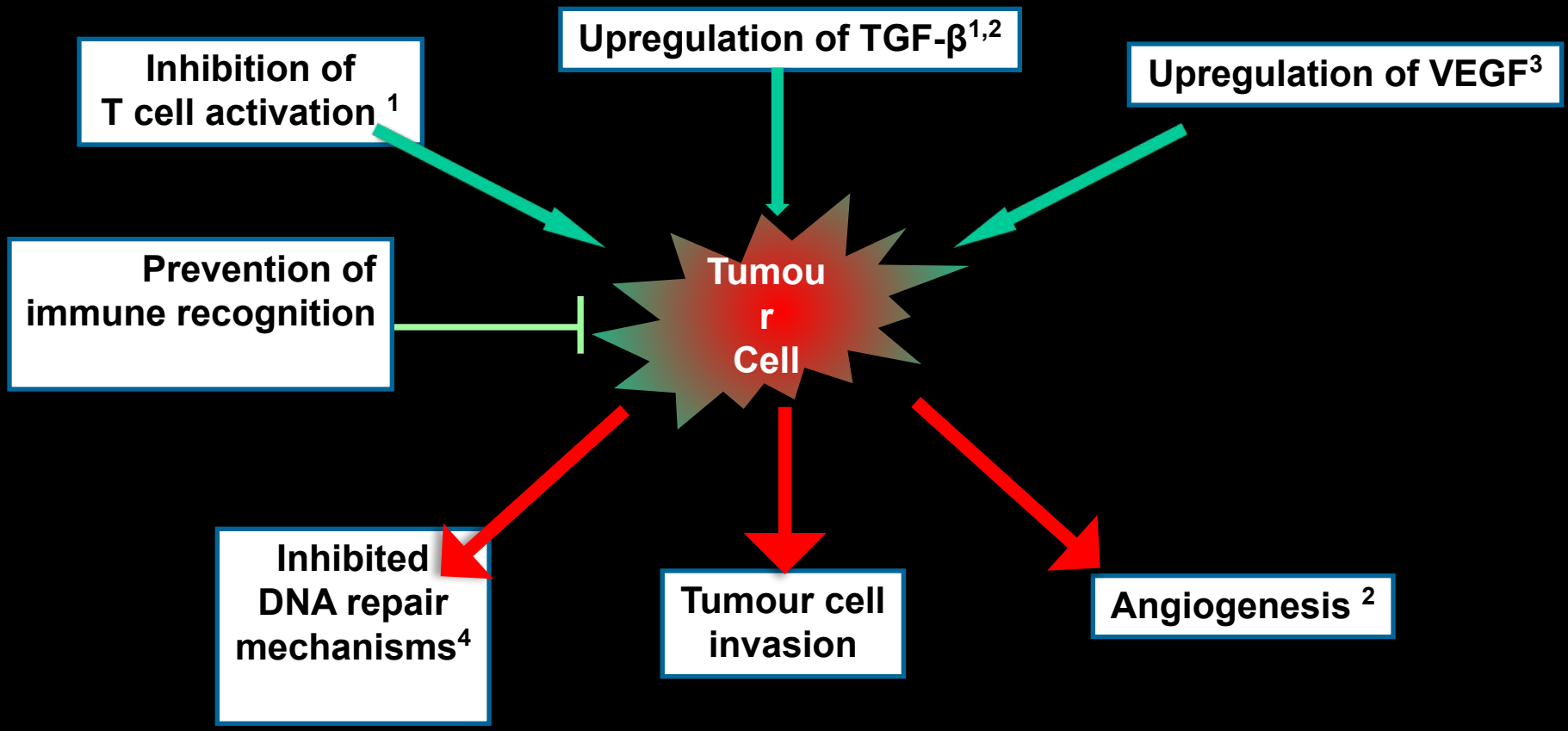
- Tacrolimus

-diabetes mellitus
-hypomagnesemia
-tremors/neuropathy
-resistant hypertension
-chronic allograft nephropathy-possibly less nephrotoxicity in therapeutic dosages

Over-immunosuppression: a New Era in Transplantation?

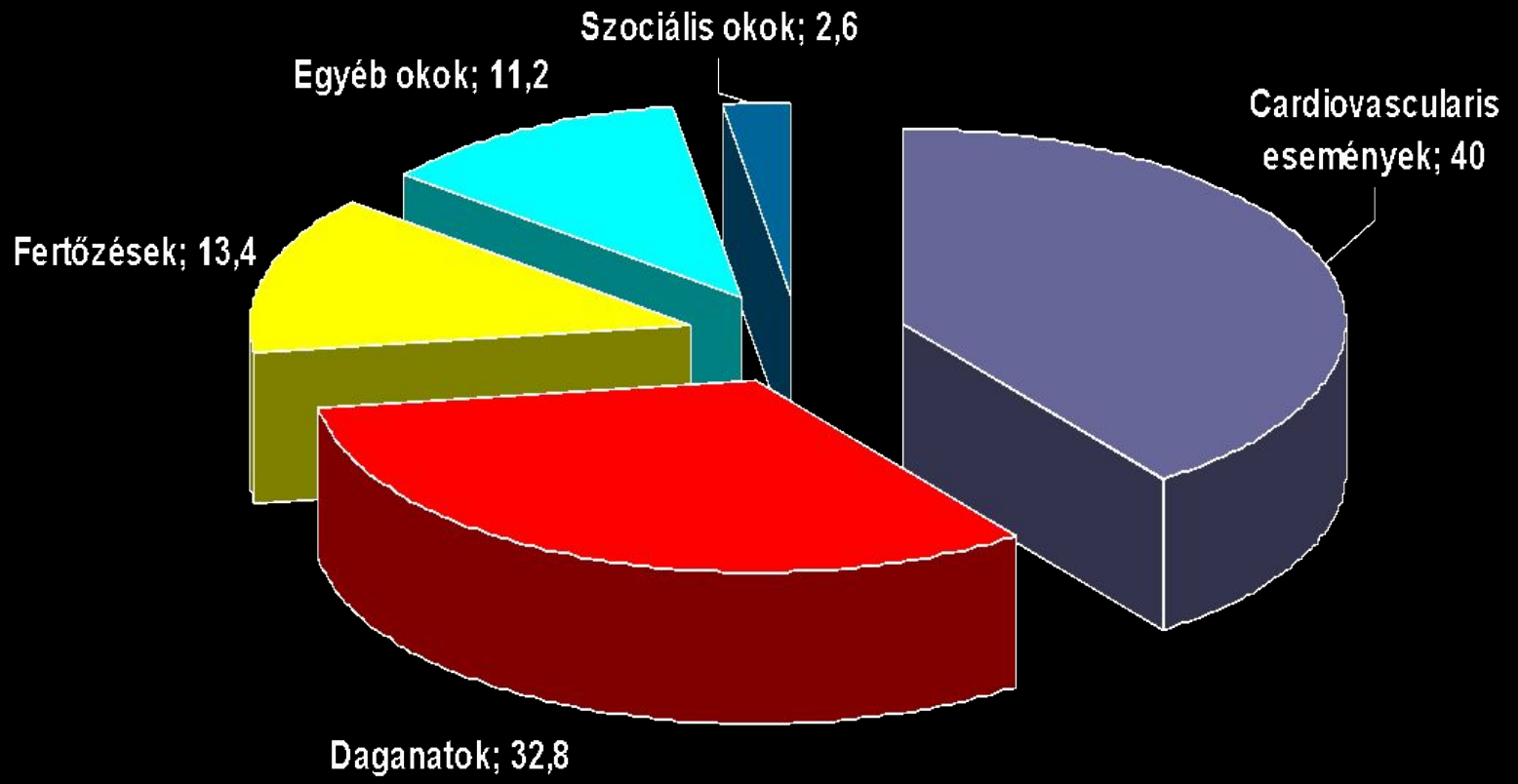
- Abundance of extremely potent new drugs: lower rejection rate but emergence of viral infections, especially CMV and polyoma BK virus
- Potential for long-term side effects such as malignancy, especially virus-induced
- Necessity to use prophylactic antibiotics, antifungal and antiviral agents
- Gancyclovir-resistant CMV-potential effect of widespread prophylactic gancyclovir use

CNIs impact on processes that promote malignancy



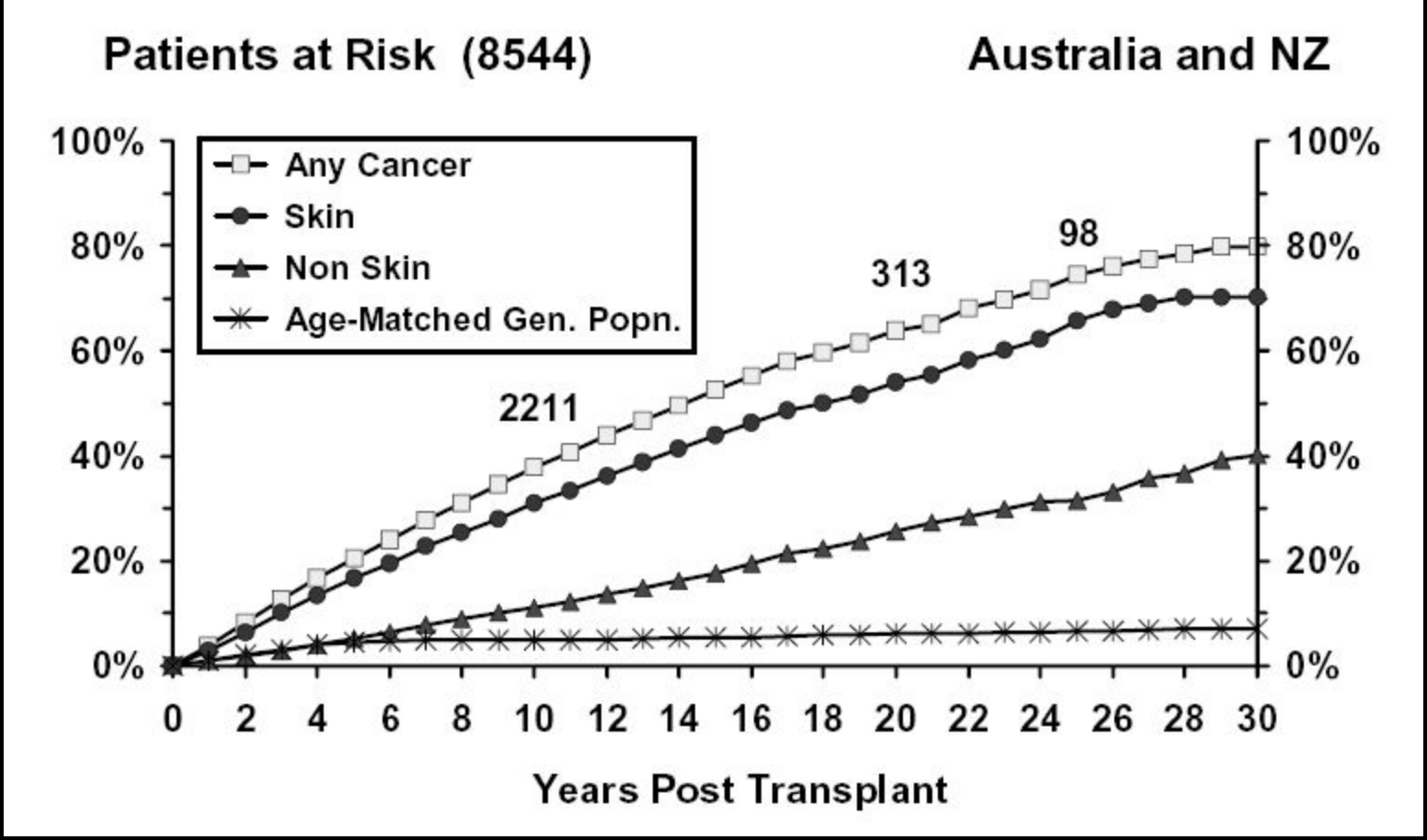
1. Hojo M, et al. *Nature* 1999;397:530–534. 2. Koehl GE, et al. *Transplantation* 2004;77:1319–1326.
3. Guba M, et al. *Nature* Med 2002;8:128–135. 4. Herman M, et al. *J Lab Clin Med* 2001;137:14–20.

Működő grafttal bekövetkező halálozás okai transzplantáció után (%)



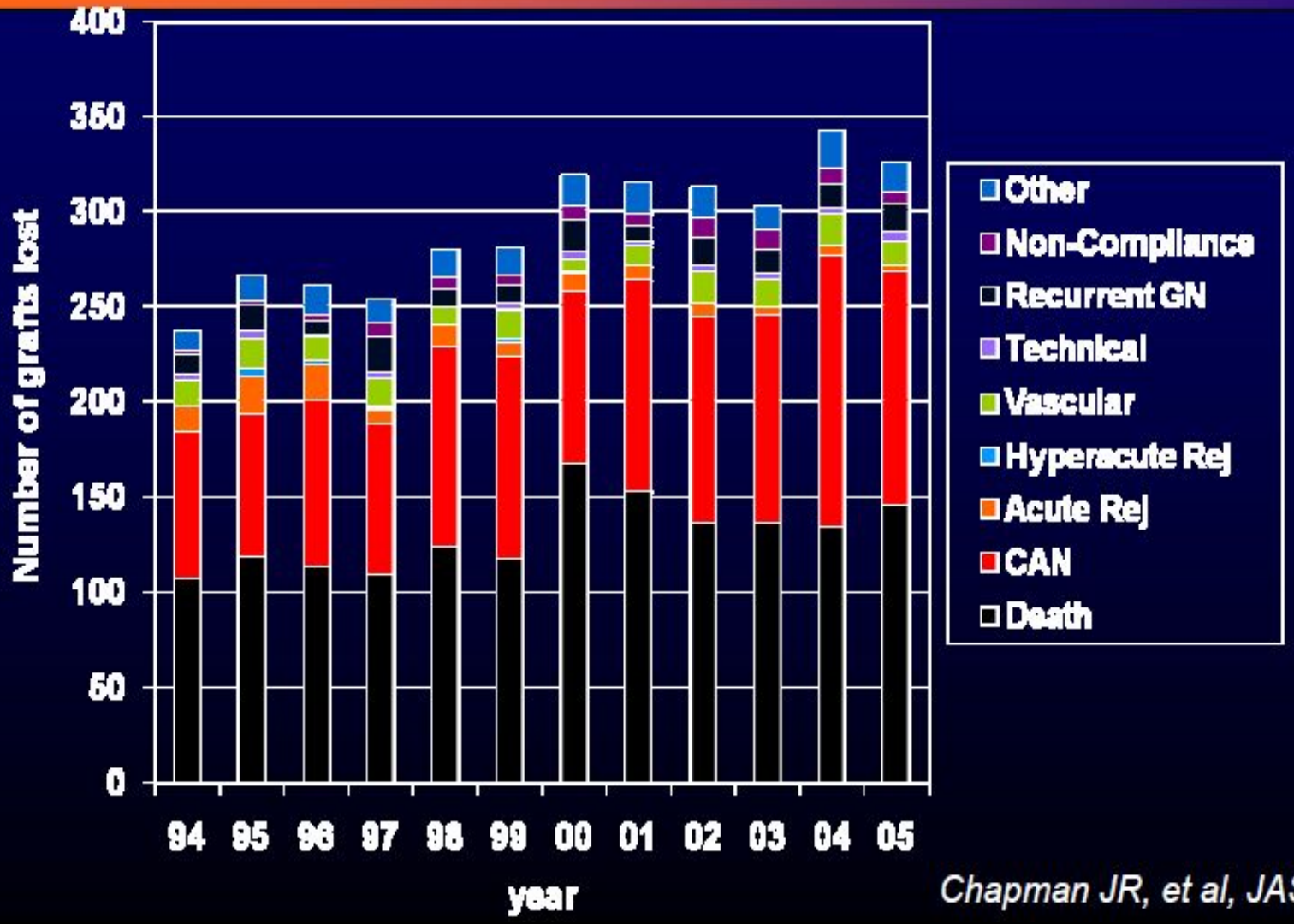
ANZDATA Registry, The 28th Annual Report 2005, Data from 2000-2004, S. 122.

Cumulative risk of cancer post-transplant in Australia and New Zealand 1965–2000



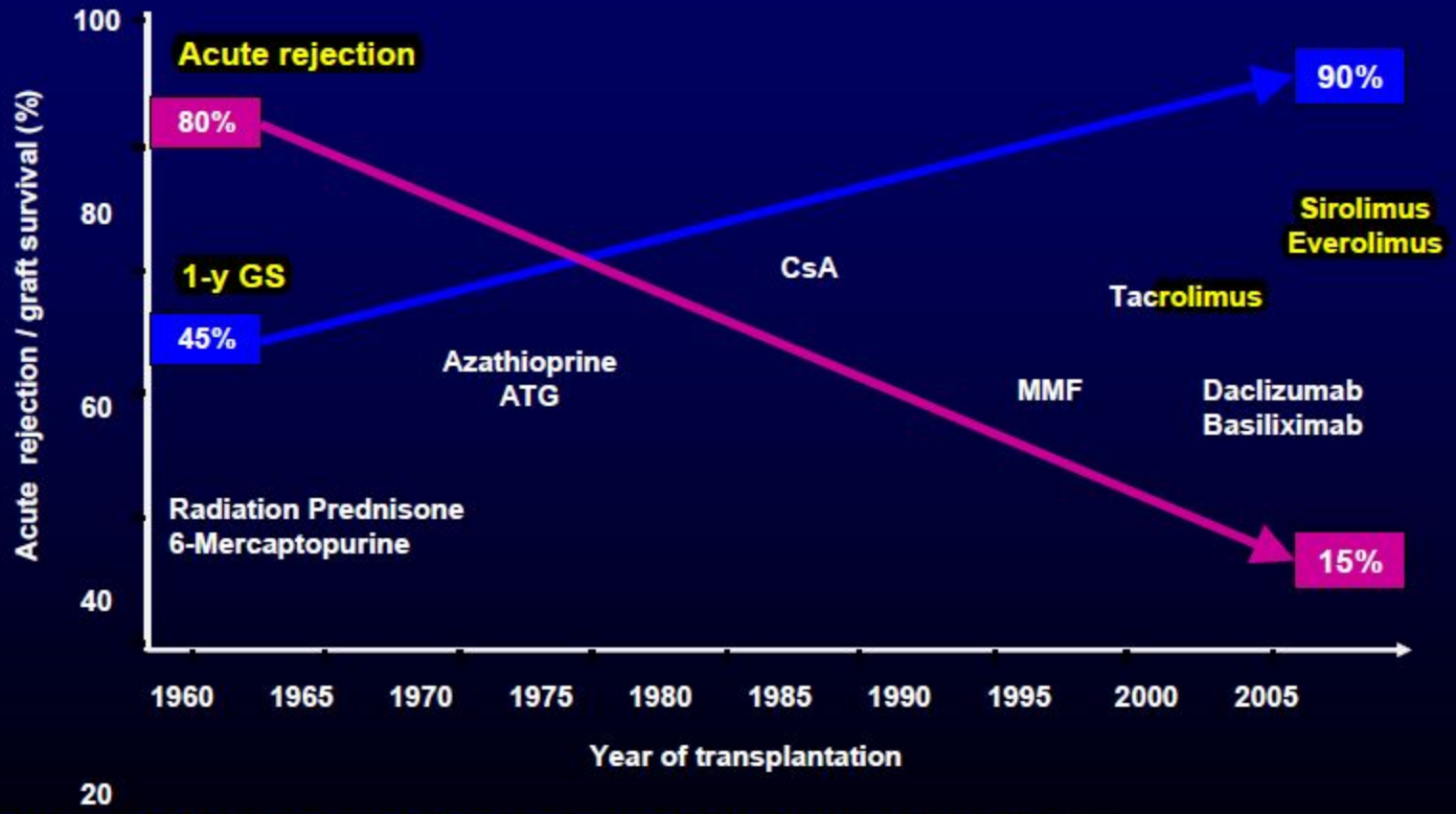
Data from Sheil AG: Cancer Report 2001. In Ross GR (ed): ANZDATA Registry Report 2004. Adelaide, South Australia, Australia and New Zealand Dialysis and Transplant Surgery, 2001, pp 84-90

Causes of kidney graft loss in Australia 1994 – 2006



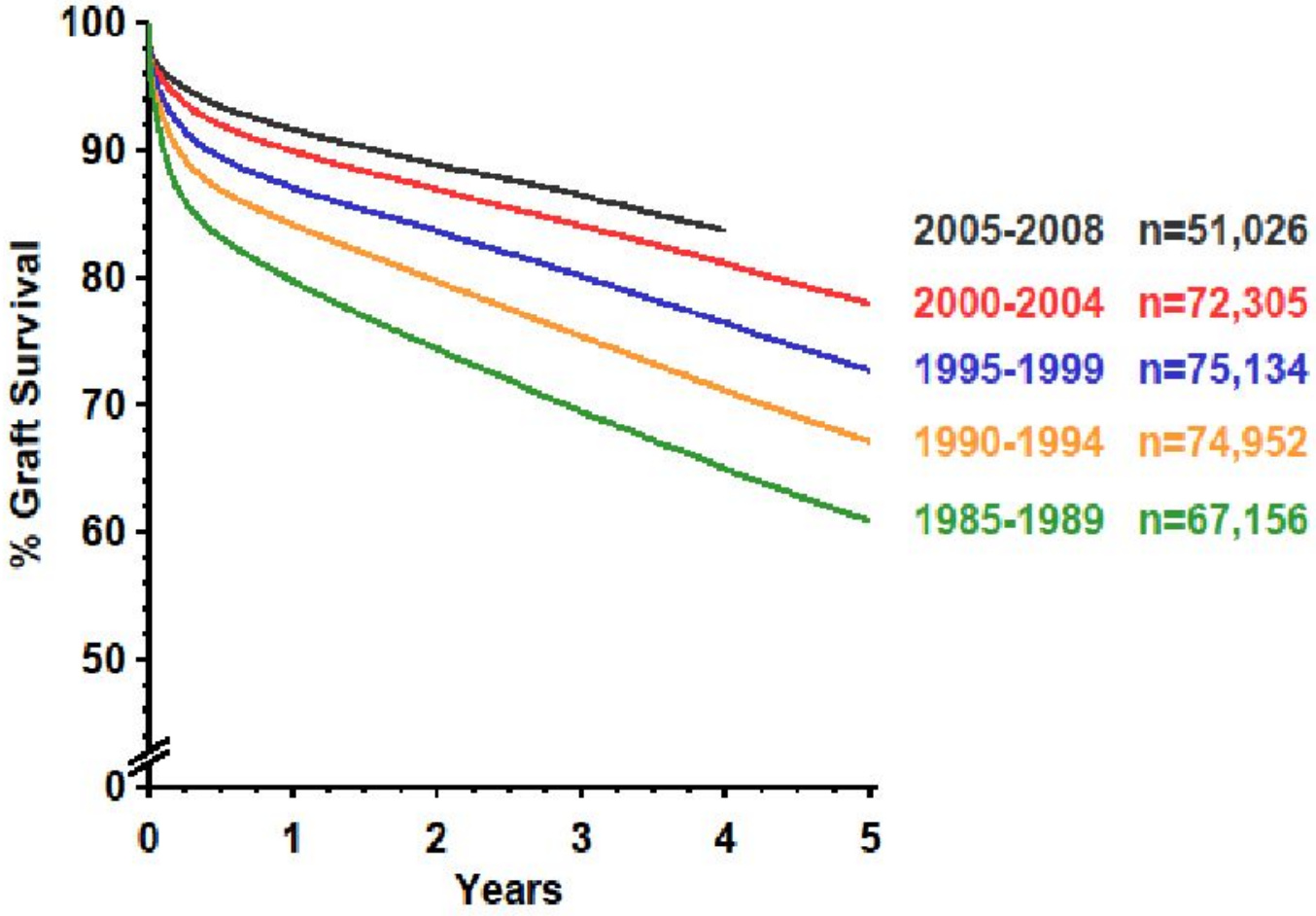
Chapman JR, et al, JASN'07

Improvement in acute rejection and short-term graft survival

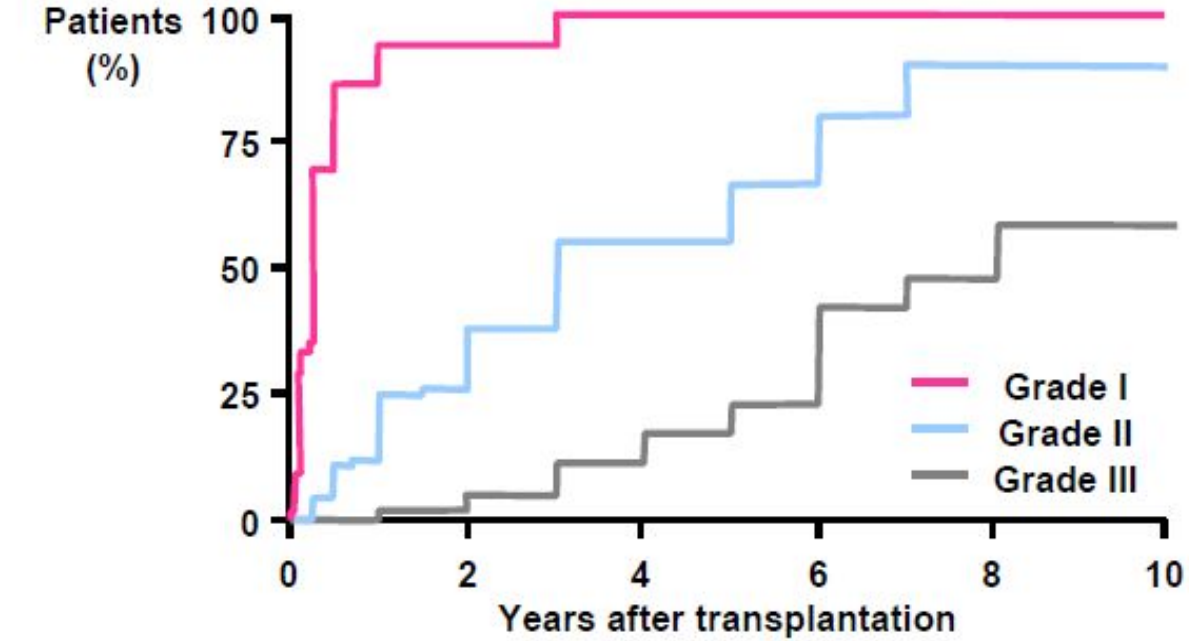


GS, graft survival; CsA, cyclosporin A; ATG, antithymocyte globulin; MMF, mycophenolate mofetil

A vesegraft túlélése: a transzplantáció évétől függően



CAN can develop early….



~ 90% of patients have CAN grade I in Year 1

CAN, chronic allograft nephropathy;
IFTA, interstitial fibrosis and tubular atrophy

Nankivell BJ *et al.*
N Engl J Med 2003;349:2326–33

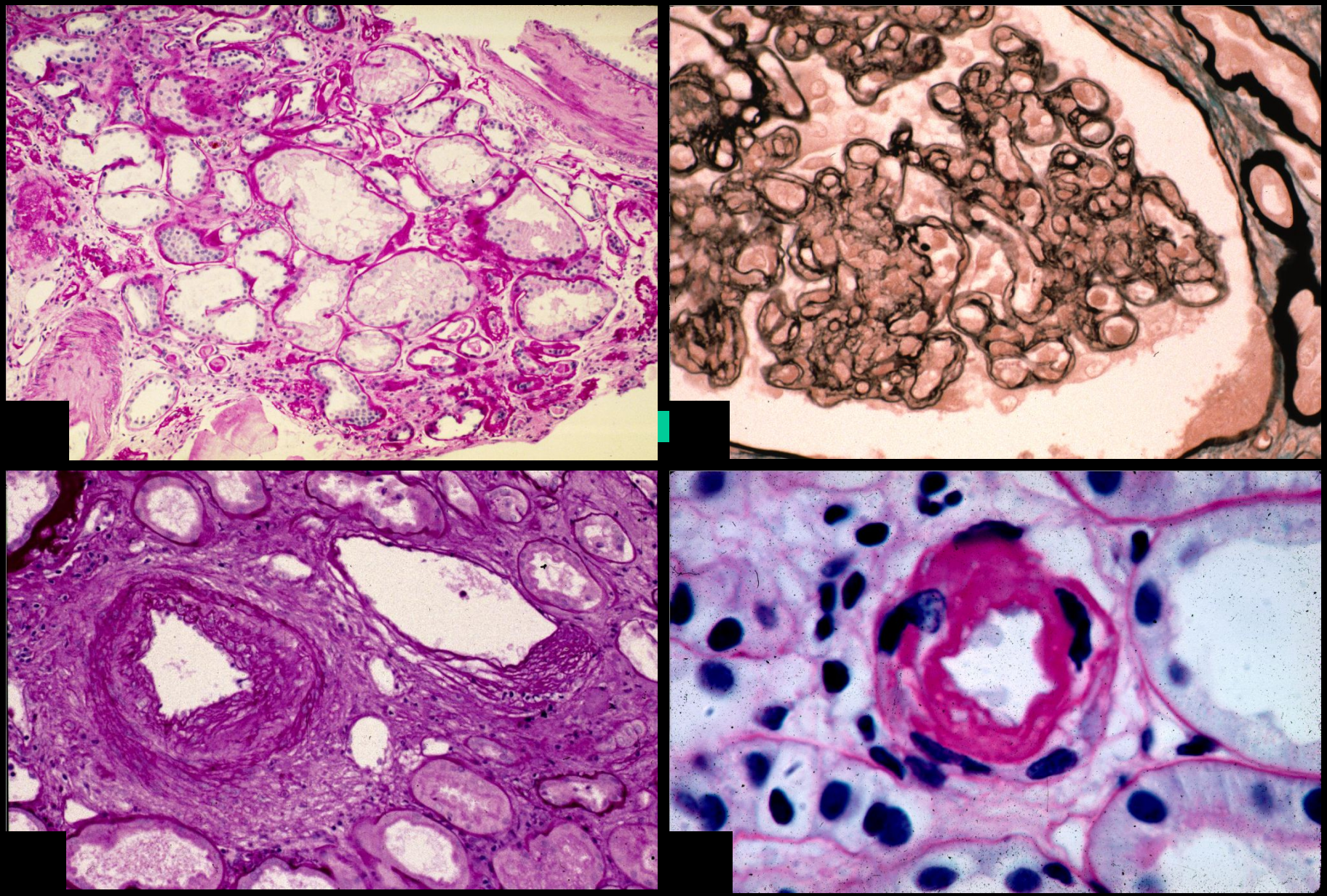
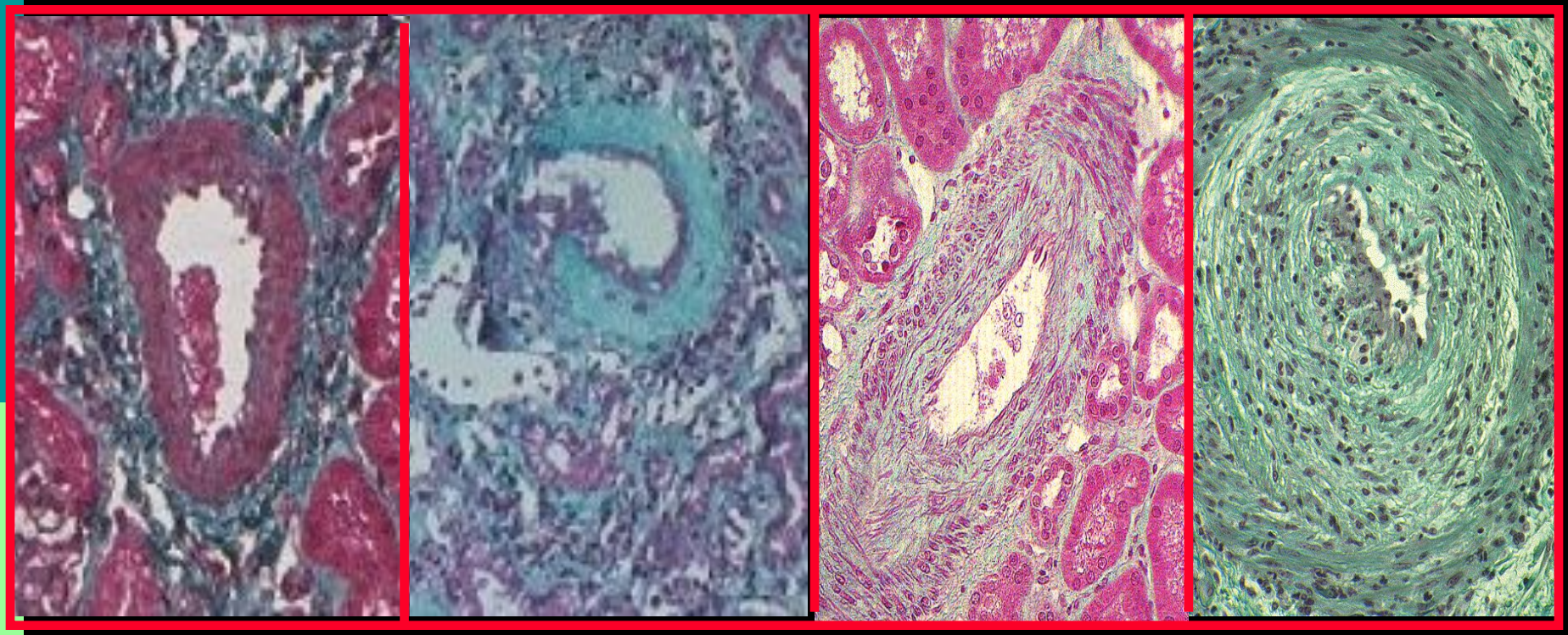
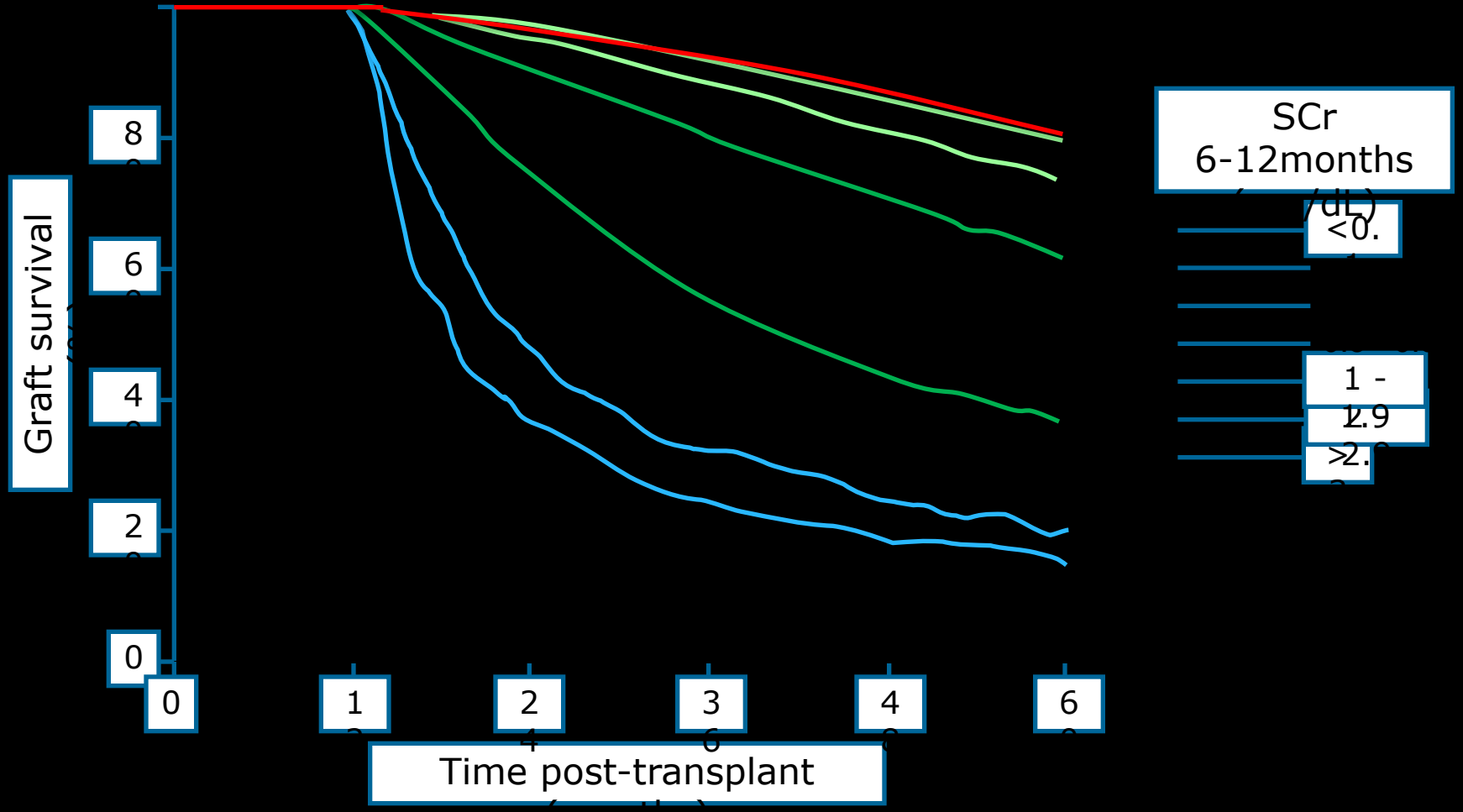


Figure 1. Characteristic histopathological findings in chronic allograft nephropathy. A. Tubular atrophy / interstitial fibrosis; B. Transplant glomerulopathy; C. Fibrous intimal thickening; D. Arteriolar hyalinosis (Womer and Sayegh 2005)

Chronic vascular changes (cv)

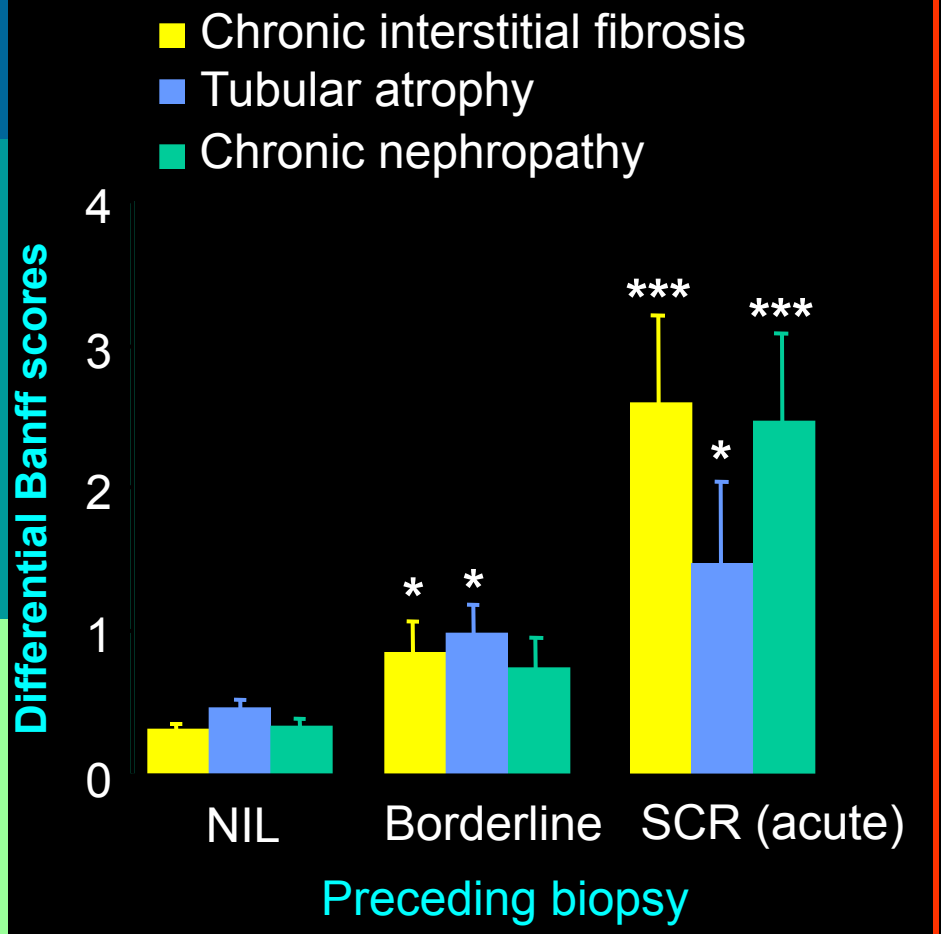
cv0	cv1	cv2	cv3
			
Nil	0–25%	26–50%	> 50%

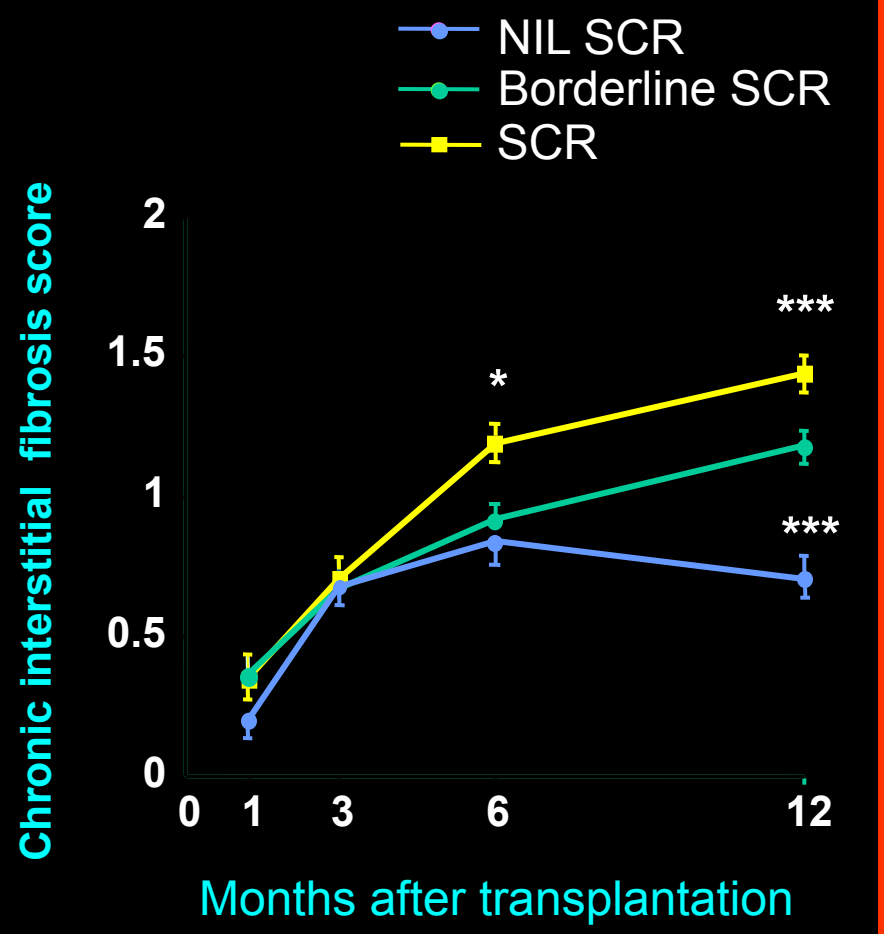
The early changes in post-transplant renal function predict long-term graft survival



Hariharan S, et al. *Kidney Int.* 2002;62:311–318.

Subclinical rejection (SCR) leads to interstitial fibrosis





Nankivell BJ et al. Transplantation 2004; 78:242-9.

Humoral alloimmunity –as a major cause of graft loss

Antibody-mediated microcirculation injury is the major cause of late kidney transplant failure

Einecke et al AJT 2009;9:2520-2531

Evidence for antibody-mediated injury as a major determinant of late kidney allograft failure

Gaston et al Transplantation 2010;90:68-74

Pathological and clinical characterization of the troubled transplant: Data from the DeKAF study

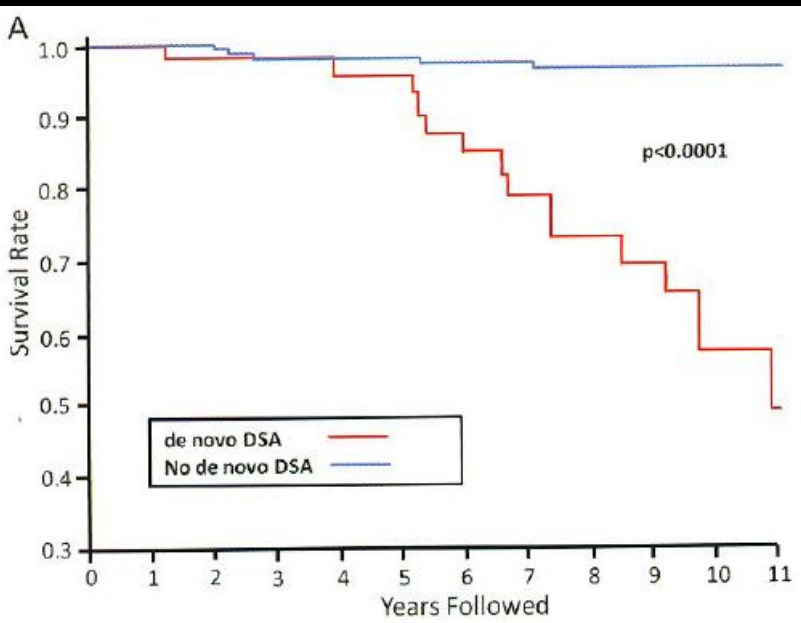
Gourishankar et al AJT 2010;10:324-330

Effect of dn DSA on renal allograft survival

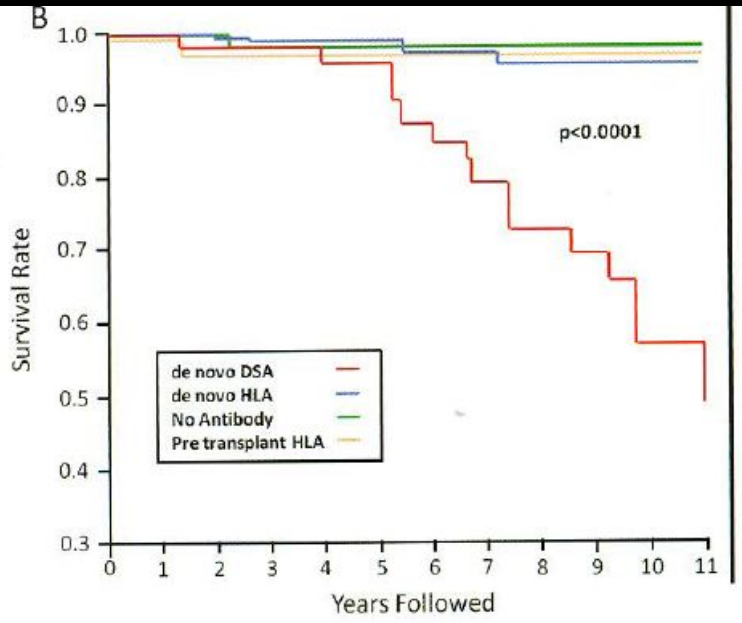
Wiebe, et al. AJT 2012;12:1157-1167

- **47/315 (15%) non-sensitized renal transplant recipients developed dn DSA at a mean follow up of 4.6 ± 3 years post-transplantation**

- ***Pathology consistent with AMR injury can occur and progress in patients with dn DSA in the absence of graft dysfunction***



(A) The graft survival of patients with *de novo* donor-specific antibodies (dnDSA) versus those without.



(B) The graft survival of pre-transplant human leukocyte antigen (HLA) antibodies, post-transplant *de novo* HLA antibodies, or no antibodies compared to patients with dnDSA.

Targeting CAN/IFTA *alias* the good the bad and the ugly

- What is the relative importance of various components of CAN: AMR, scarring (interstitial, endothelial), metabolic and hemodynamic effects?
- What is the role of CNIs-a heated, almost partisan debate….even the name is contentious…..
- If AMR is the main culprit CNIs are good…if scarring then CNIs are bad….if metabolic then CNIs are ugly….
- If we want to minimize the bad and ugly how do we proceed?

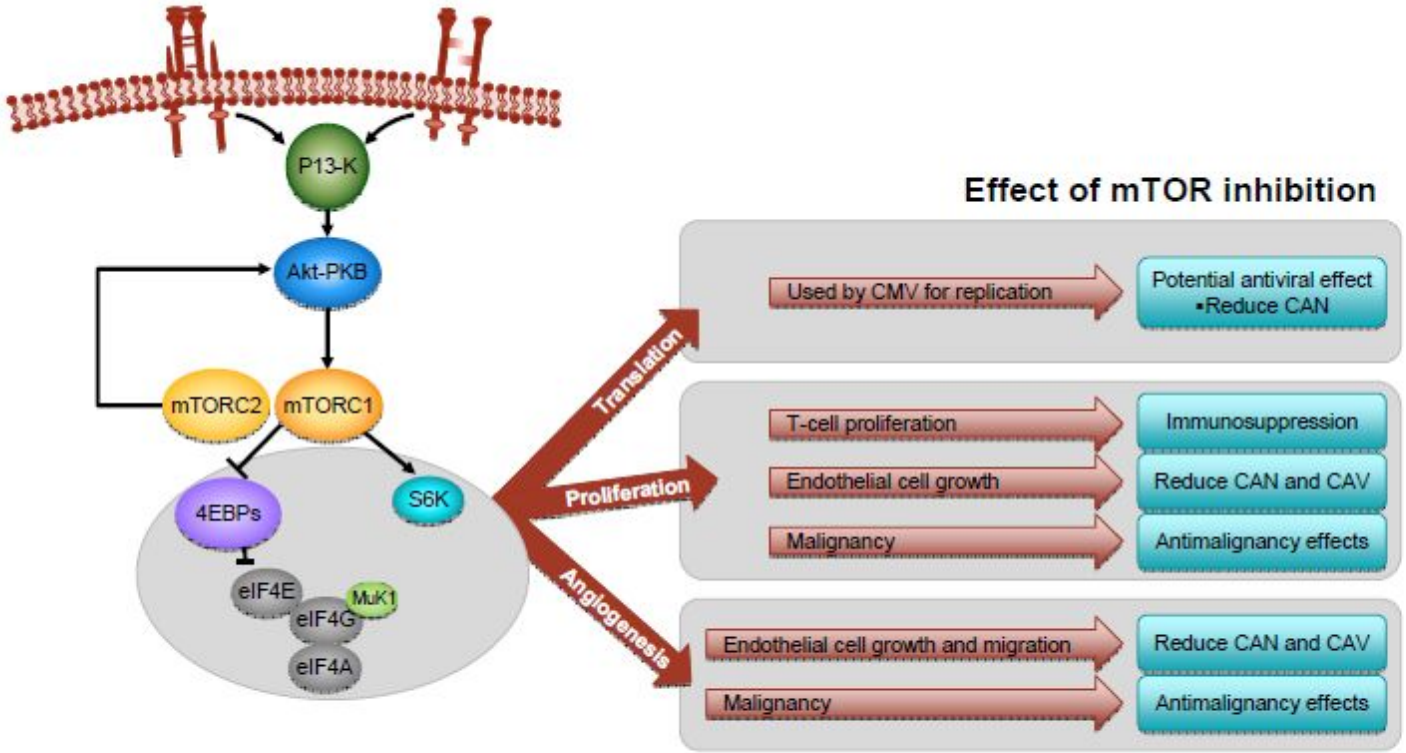
A nice fungal trip to the Easter Islands….rapa, rapa……

- Maybe we find something that works against rejection and…..
- Has antiproliferative as well as immunosuppressive effects and…..
- Maybe we can even decrease scarring and…
- Maybe we can even improve survival by nice antiviral and antitumor effects and…..
- Maybe we can even have nice cardiovascular effects and….
- Maybe we can even….oh well….REPLACE (or at least minimize) CNIs?????

Mechanism of action-overview

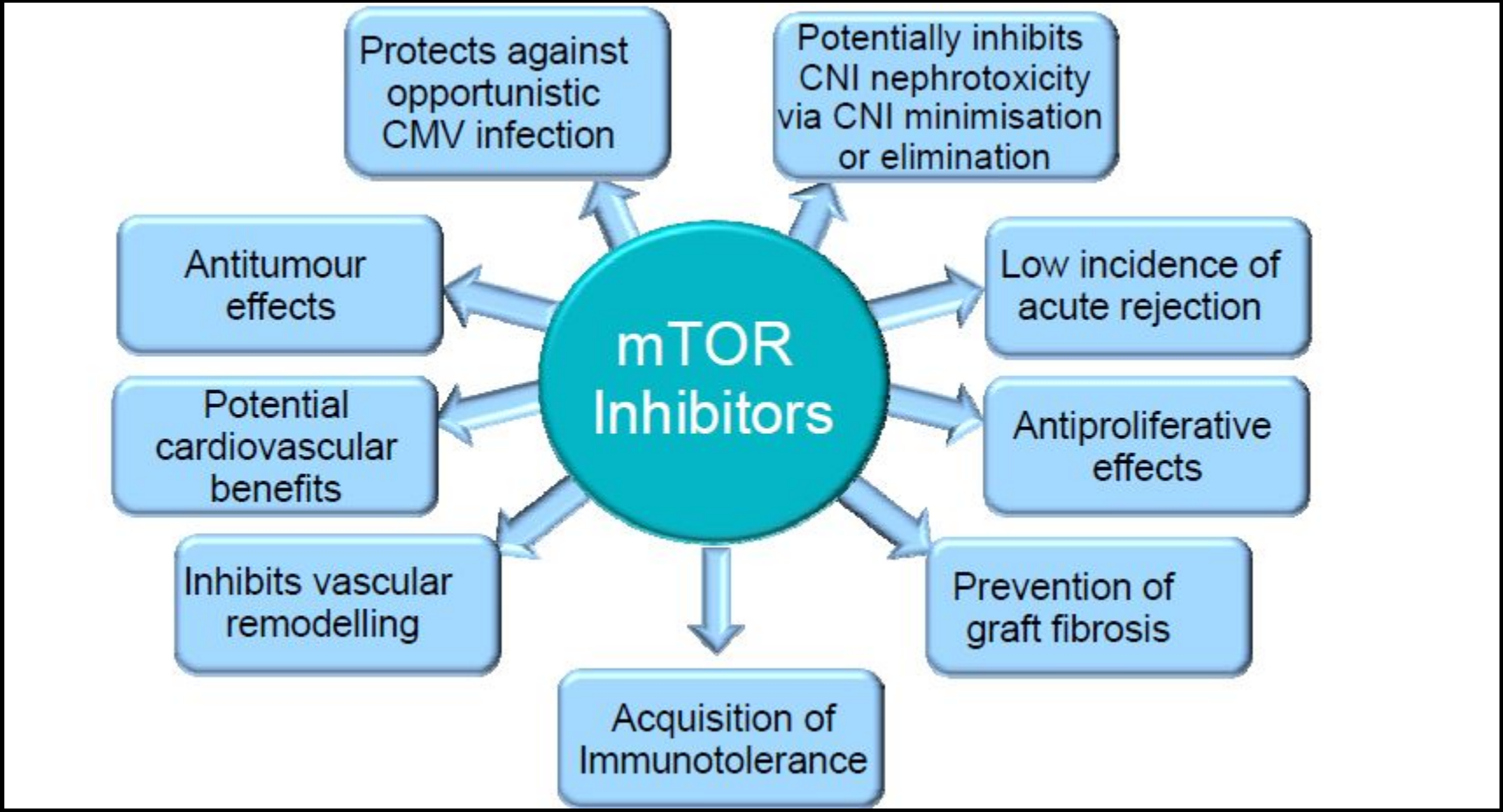
- Lymphocyte proliferation and differentiation:
  - T lymphocytes
  - B lymphocytes
- Antibody production (plasmatic cells)
- Mesenchymal-cell proliferation
  - Vascular smooth-muscle cells
  - Fibroblasts
  - Endothelial cells

Mechanism of action: pleiotropic effects

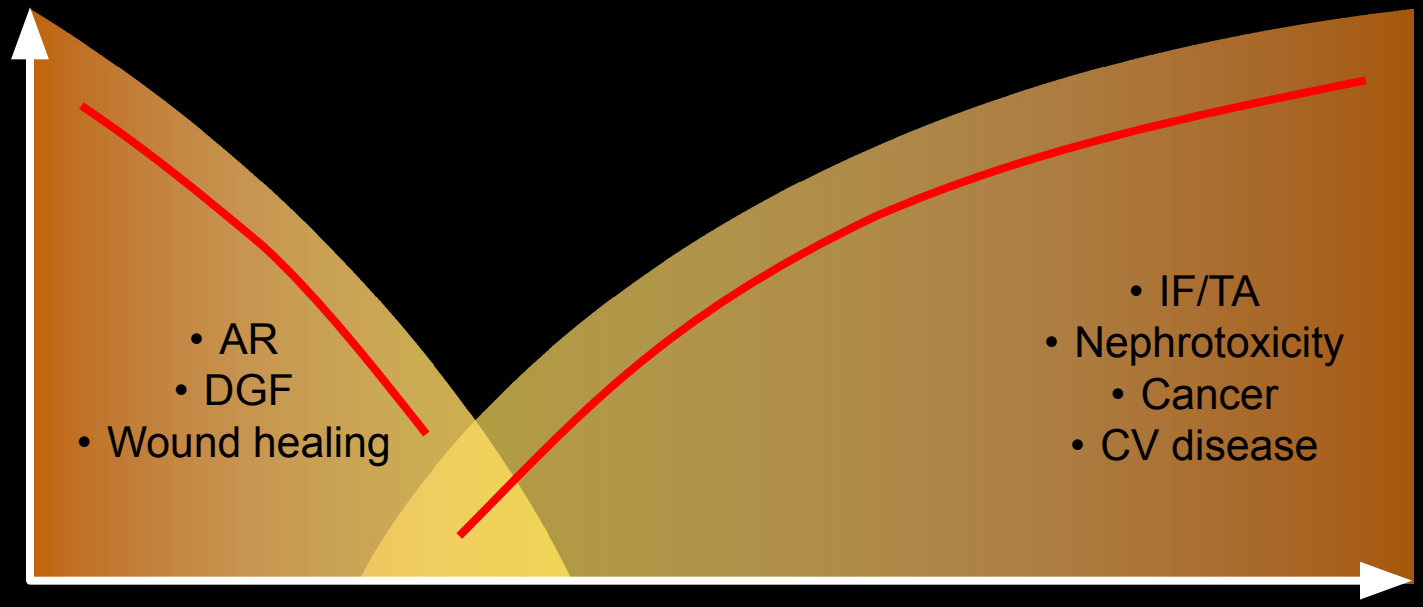


CMV, cytomegalovirus; CAN, chronic allograft nephropathy; CAV, cardiac allograft vasculopathy.

The agenda: use pleiotropic effects in a pleiotropic fashion



Considering long-term immunosuppressive strategy in kidney transplantation

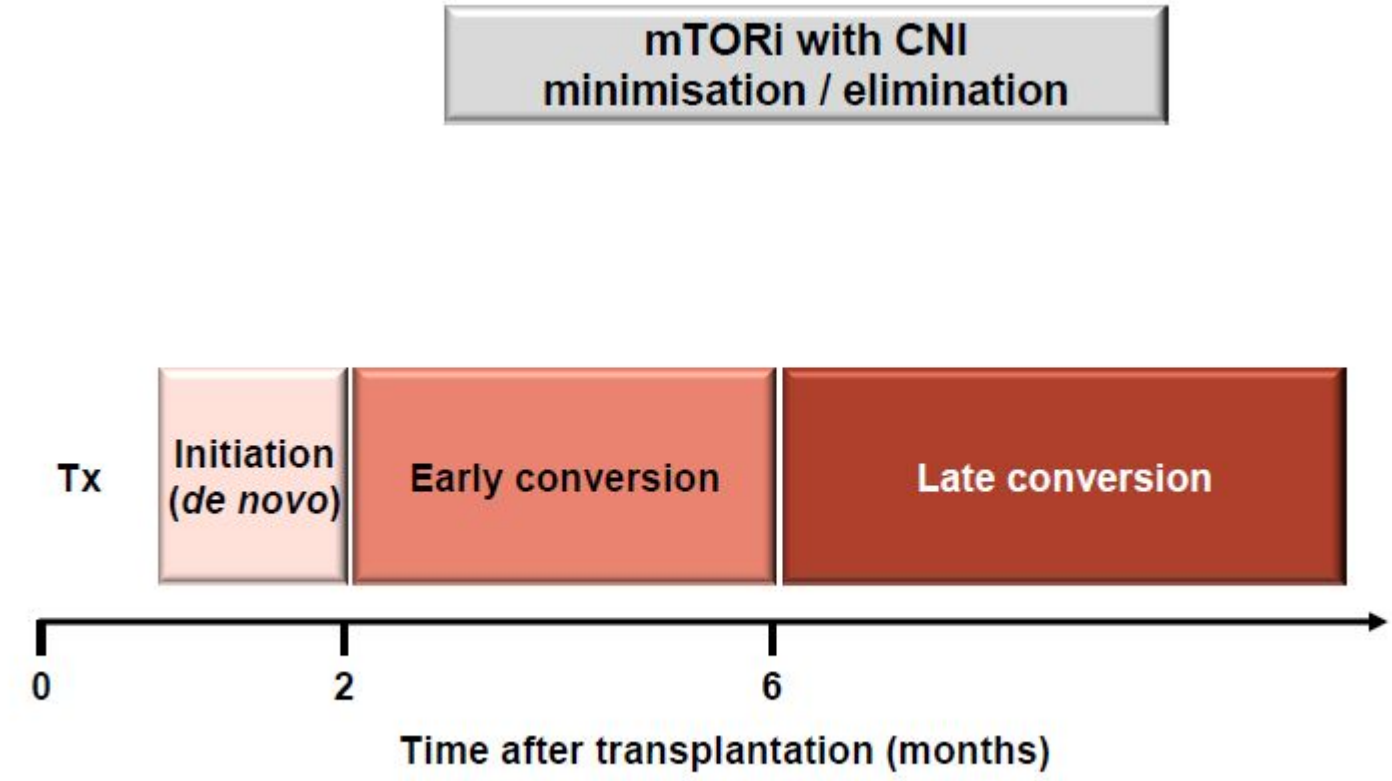


Potent combination immunosuppression incorporating a CNI

CNI-free immunosuppression with sirolimus

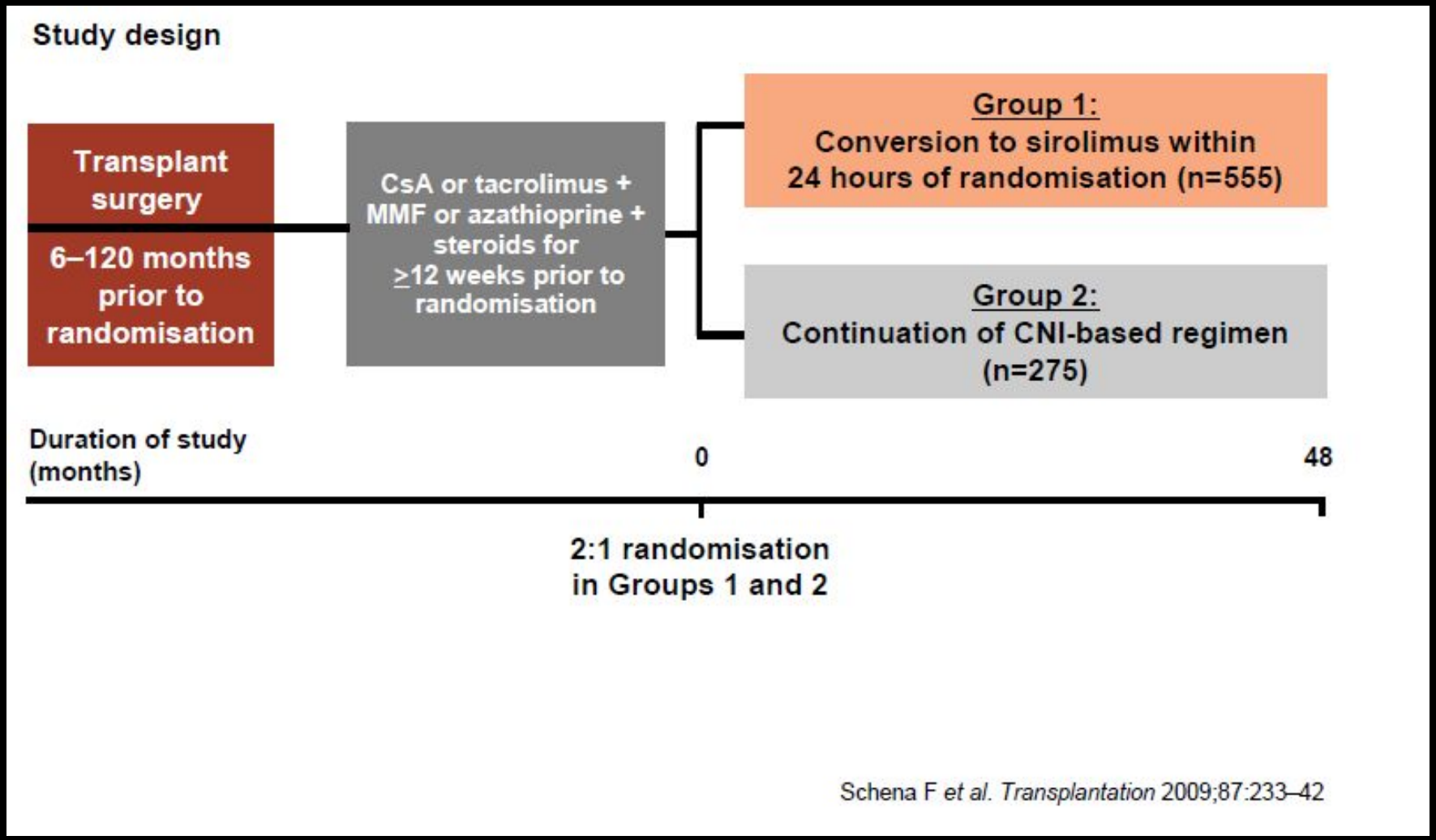
Flechner S. *Clin Transplant* 2008;22:1-15.

How to apply theory-mTor vs. CNI



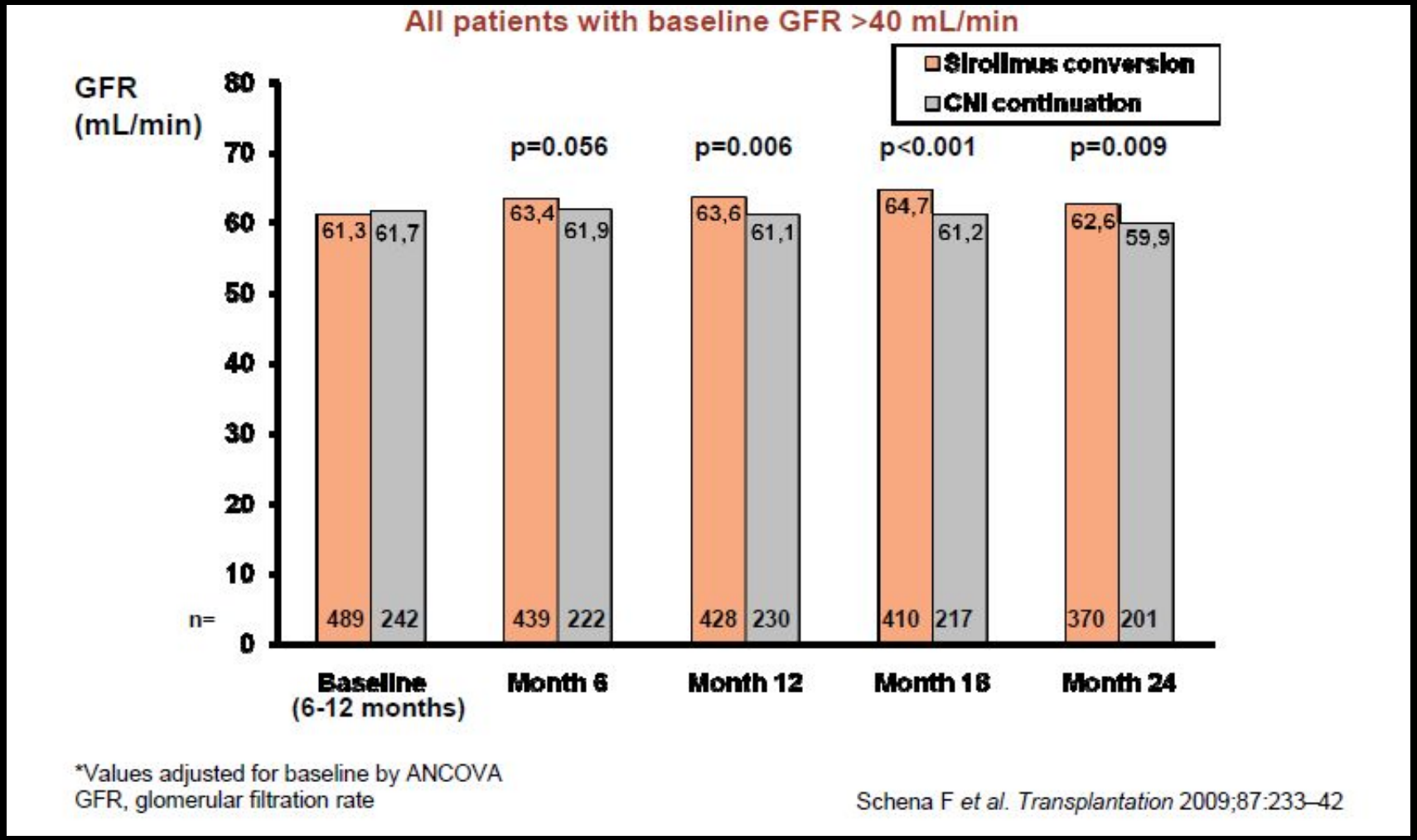
Tx, transplant

CONVERT-the first attempt



Schena F *et al. Transplantation* 2009;87:233–42

Good function-keep it….bad function lose it….



*Values adjusted for baseline by ANCOVA
GFR, glomerular filtration rate

Schena F *et al. Transplantation* 2009;87:233–42

Definition of Chronic Kidney Disease- a time to remember!!!!

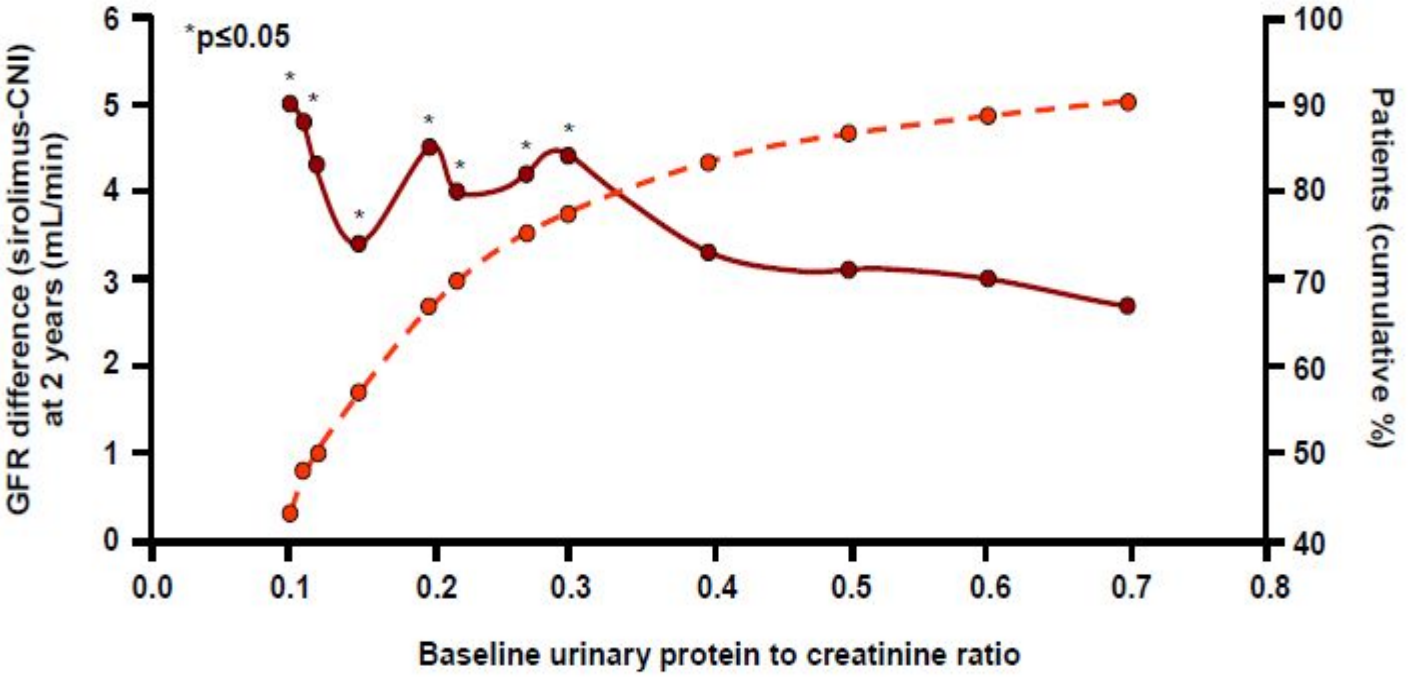
Definition of:

Chronic Kidney Disease =**GFR<60 ml/min/1.73 m^2 or persistent albuminuria***

(Definition of a nephrologist: the physician who loving numbers overestimates their importance alias we love but do not understand……)

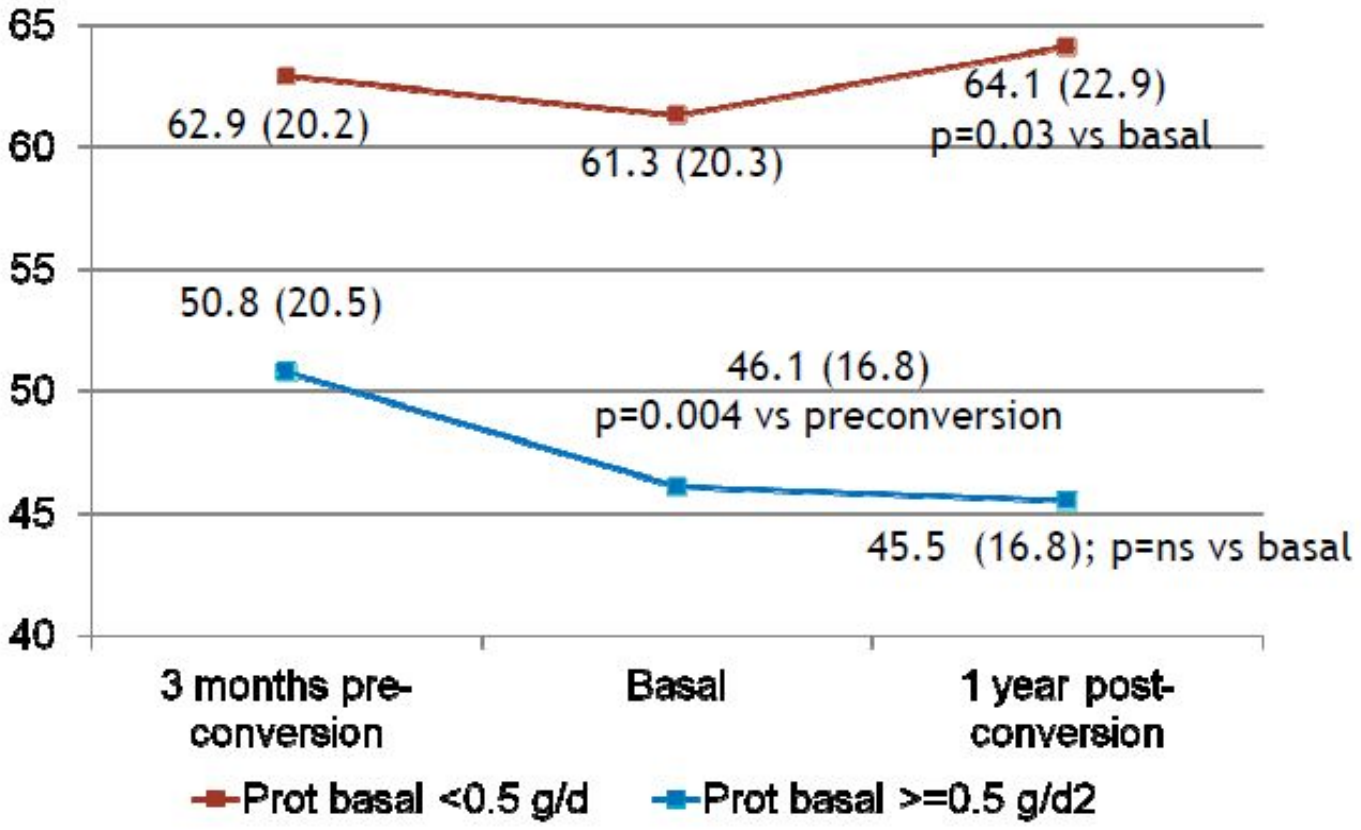
*American Journal of Kidney Diseases Vol 41, No 1, 2003: pp1-12

GFR improvement is only good if proteinuria at 2 years is minimal



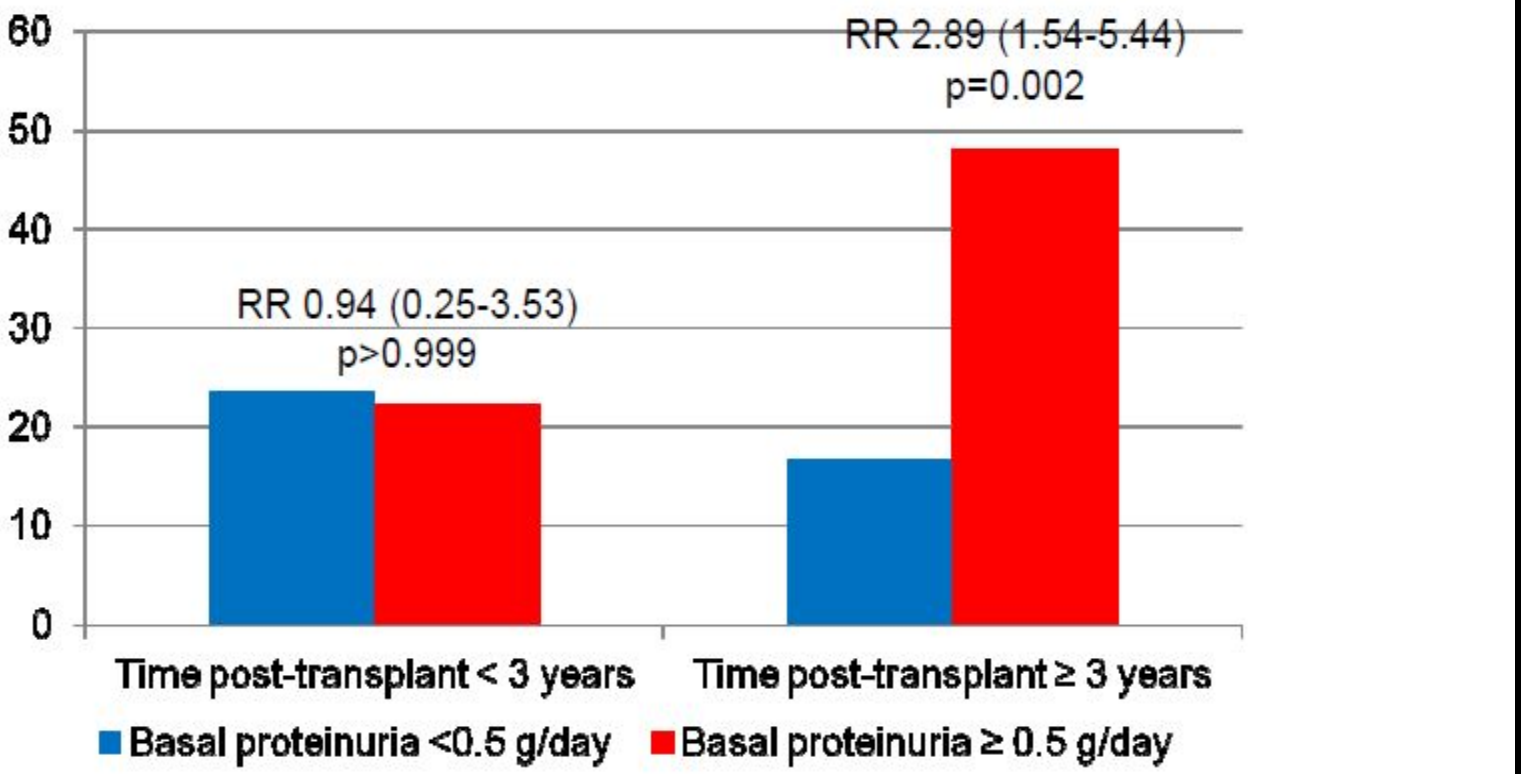
Schena F *et al. Transplantation* 2009;87:233–42

Proteinuria-it counts….



A.Sanchez – JC. Ruiz, Transplantation'12

Convert early…convert early…convert early….. (because proteinuria is a writing on the wall)

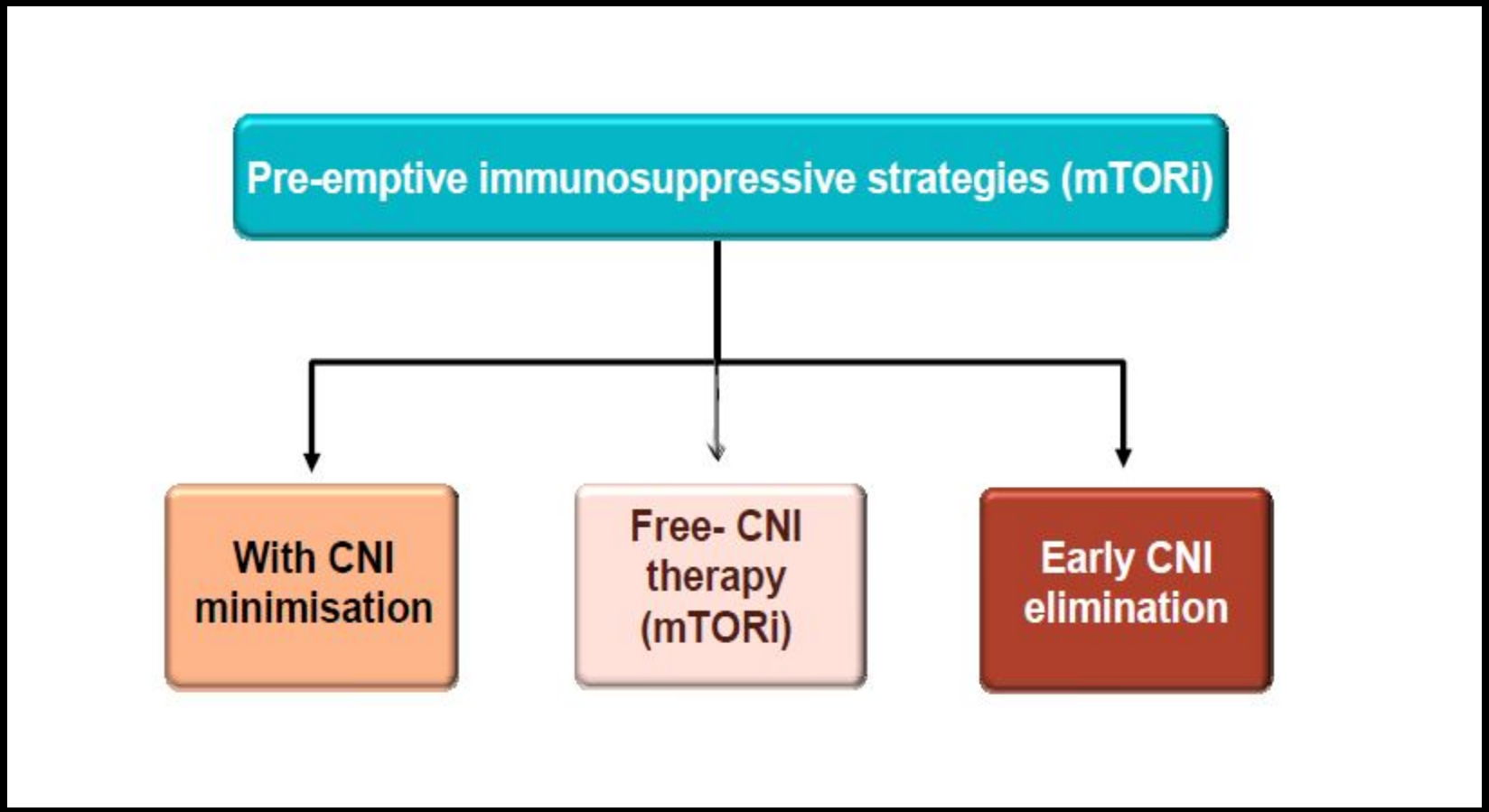


A.Sanchez – JC. Ruiz, Transplantation'12

Oops…proteinuria…..oops lipids…

- Prevention >>>> Treatment (CAN)
- As early as possible (CAN)
- Avoid loading-doses (overdosing) (TDM: 6-8 ng/mL)
- Avoid overlaping with CNI – Rapid conversion
- Renal function: sCr < 2,5 mg/dL – cGFR > 40 mL/min
- Proteinuria < 1 g/24h.
- Monitorting AE (Lipids, anemia, proteinuria)

How do we do it?

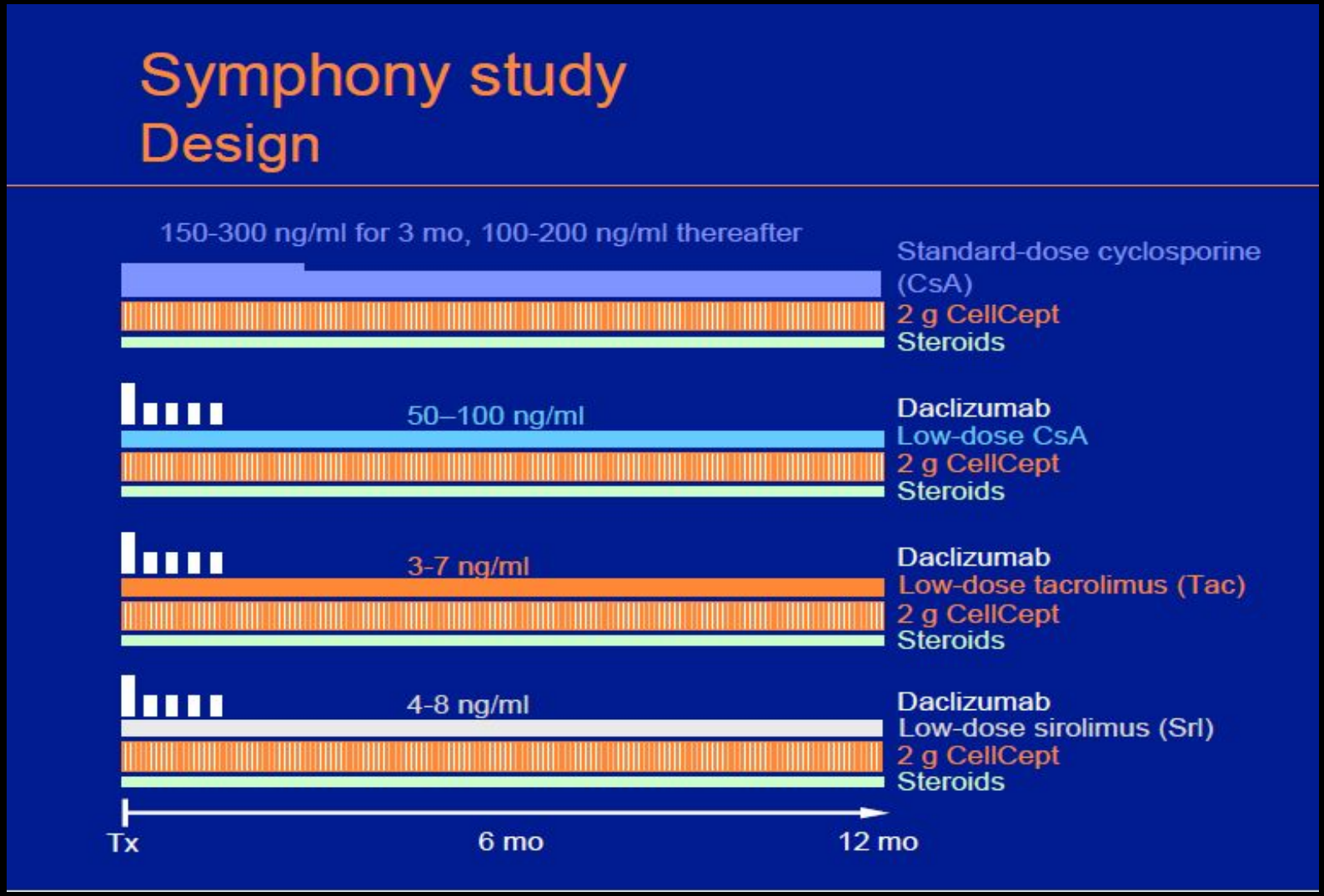


Strategy #1: CNI free

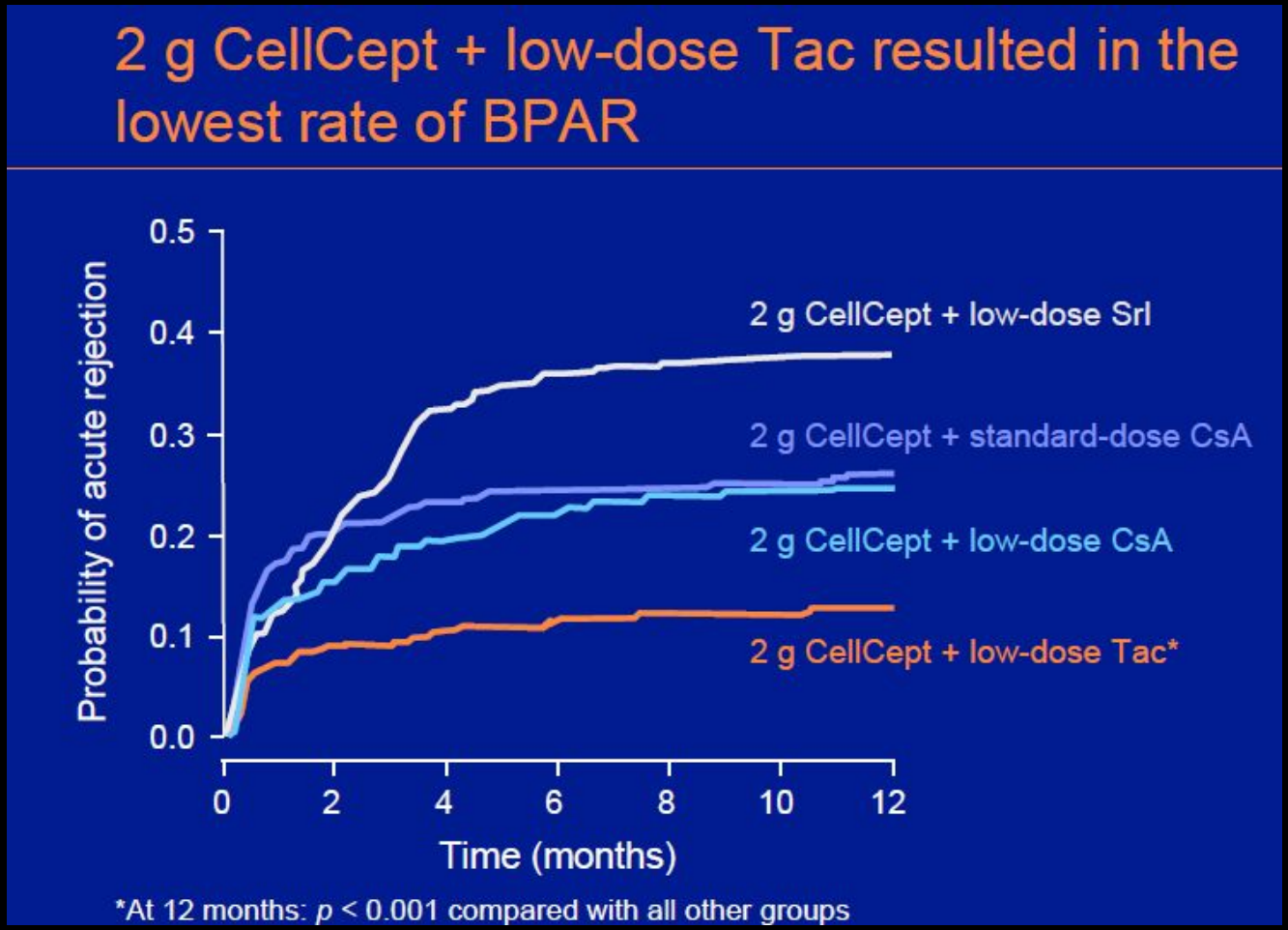
"De novo" patients: SRL + MMF (Free CNI)

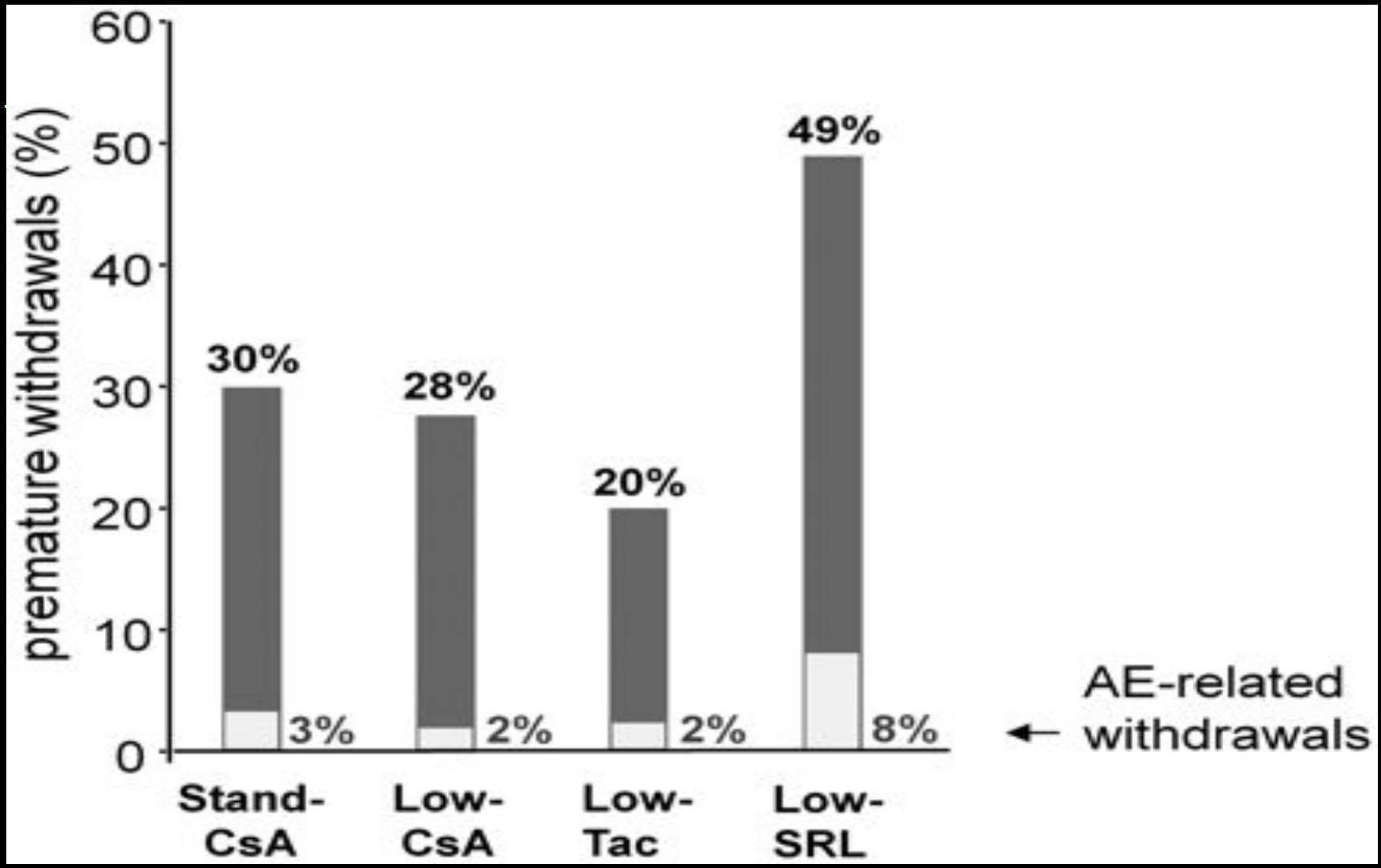
- Moderate immunosuppressive capacity
- Patients with low-mild immunological risk
- Marginal donors: NHBD – Aged donors
- Induction is necessary (ATG >> Anti-CD25)
- Excluded high risk patients SRL (obese/diabetic)
- Correct doses and blood levels (6-9 ng/mL)
- Delayed introduction of SRL (4-7 d)

Symphony-choose the best!



Symphony-results




premature withdrawals (%)
60
50
40
30
20
10
0
30%
28%
20%
49%
3%
2%
2%
8%
AE-related withdrawals
Stand-CsA
Low-CsA
Low-Tac
Low-SRL

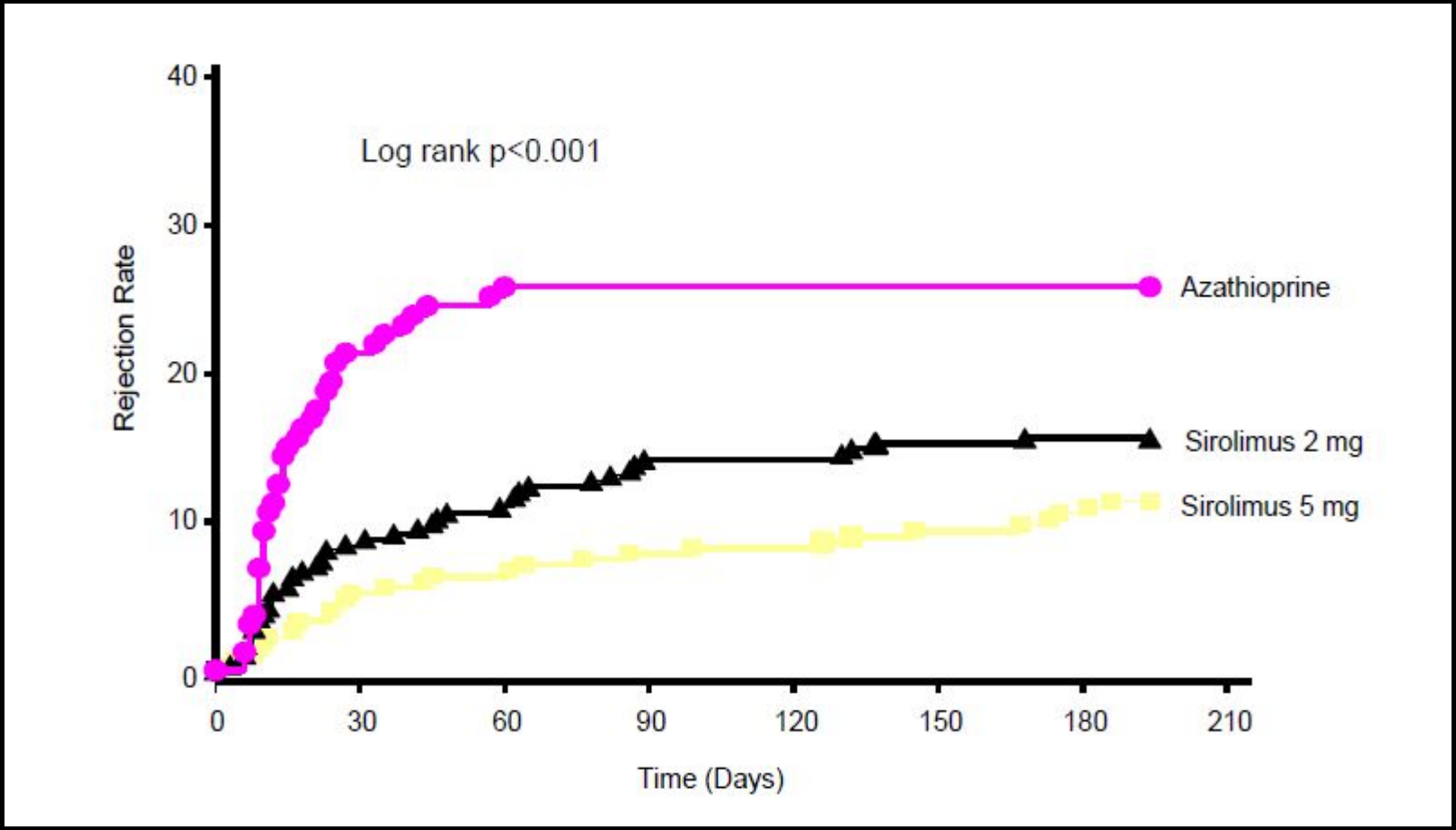
Strategy #2: if you cannot beat them join them!

- Studies 301 – 302: SRL + CsA (FDA Approval)
- Study 310 (RMR) (EMEA Approval)
- Houston Experience (B.Kahan): SRL + Csa/FK
- Nebraska Experience (B.Stevens): SRL + CsA
- Mendez R – Prograf Study Group (Transplantation'05)
- TERRA Study (Astellas): SRL + FK (Vitko – Tx'06)
- Drexel University (Kumar et al. Transplant Immunology'08)
- OA.Gaber – Houston (Transplantation'10)
- Everolimus development: EVL + CsA

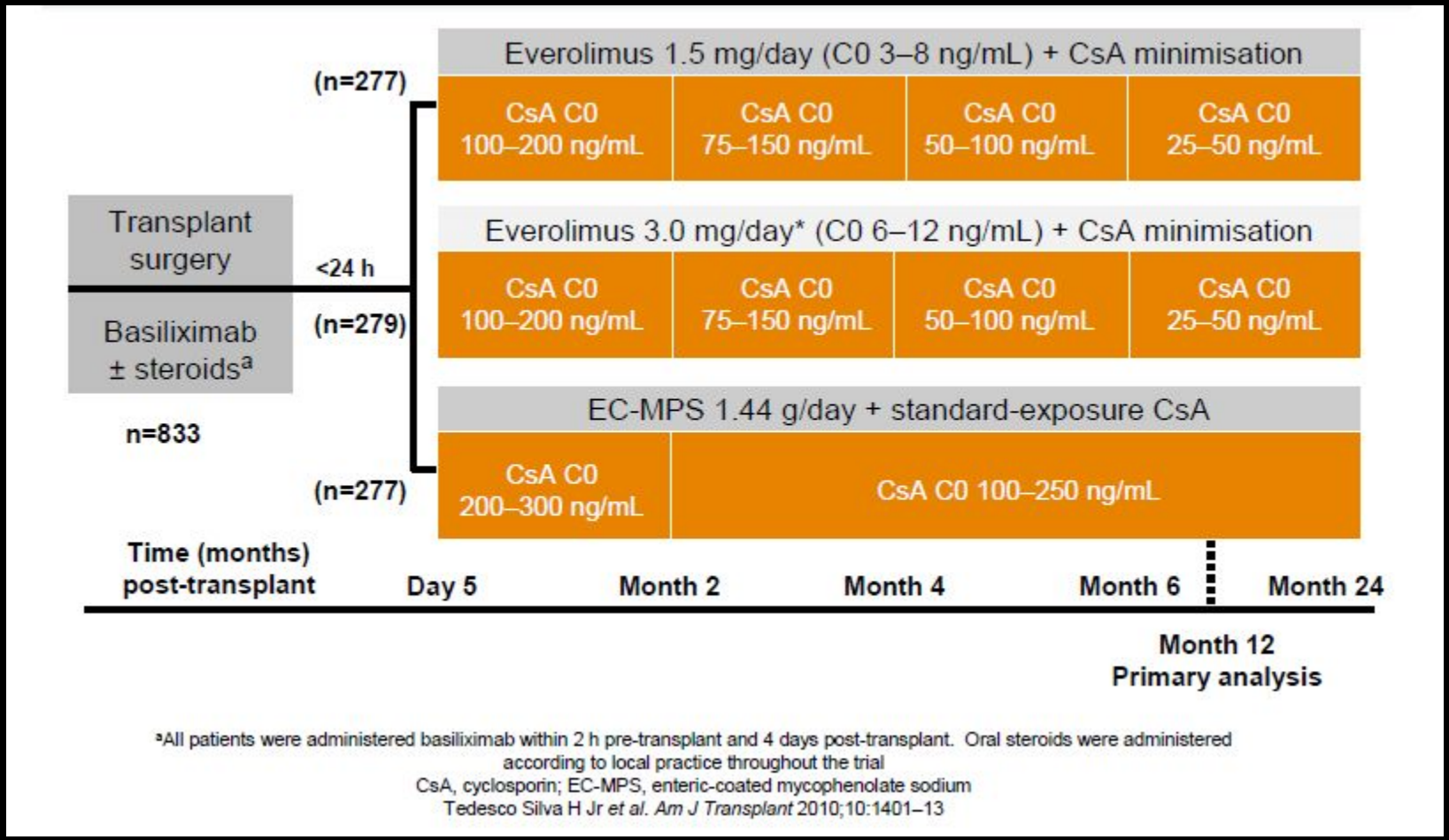
For and against…..

- **Strengths**
  - Potent and specific immunosuppressive therapy
  - High Efficacy – Prevention acute rejection
  - Low incidence of viral infections
  - Low incidence of cancer
  - Individualize Immunosuppressive therapy:
    - Withdrawal CNI
    - Withdrawal Steroids
- **Weaknesses**
  - Safety Profile: - Synergistic nephrotoxicity
    - Post-Transplant Diabetes
    - DGF / Wound Healing
  - Pharmacokinetic interaction (CsA)

In the beginning….phase III US trial



A2309-perhaps it is just a matter of right dosage….

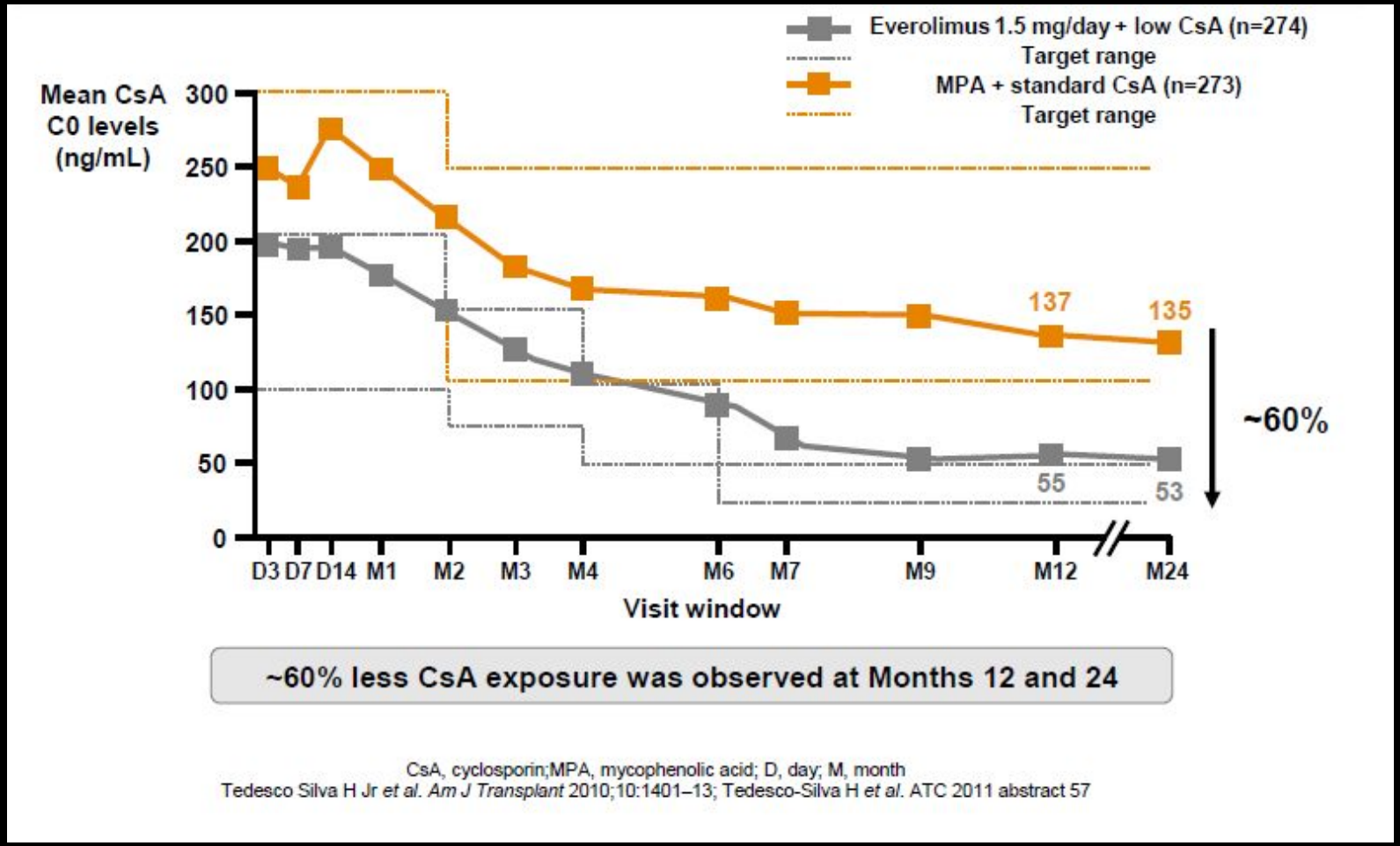


[a]All patients were administered basiliximab within 2 h pre-transplant and 4 days post-transplant. Oral steroids were administered according to local practice throughout the trial

CsA, cyclosporin; EC-MPS, enteric-coated mycophenolate sodium

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

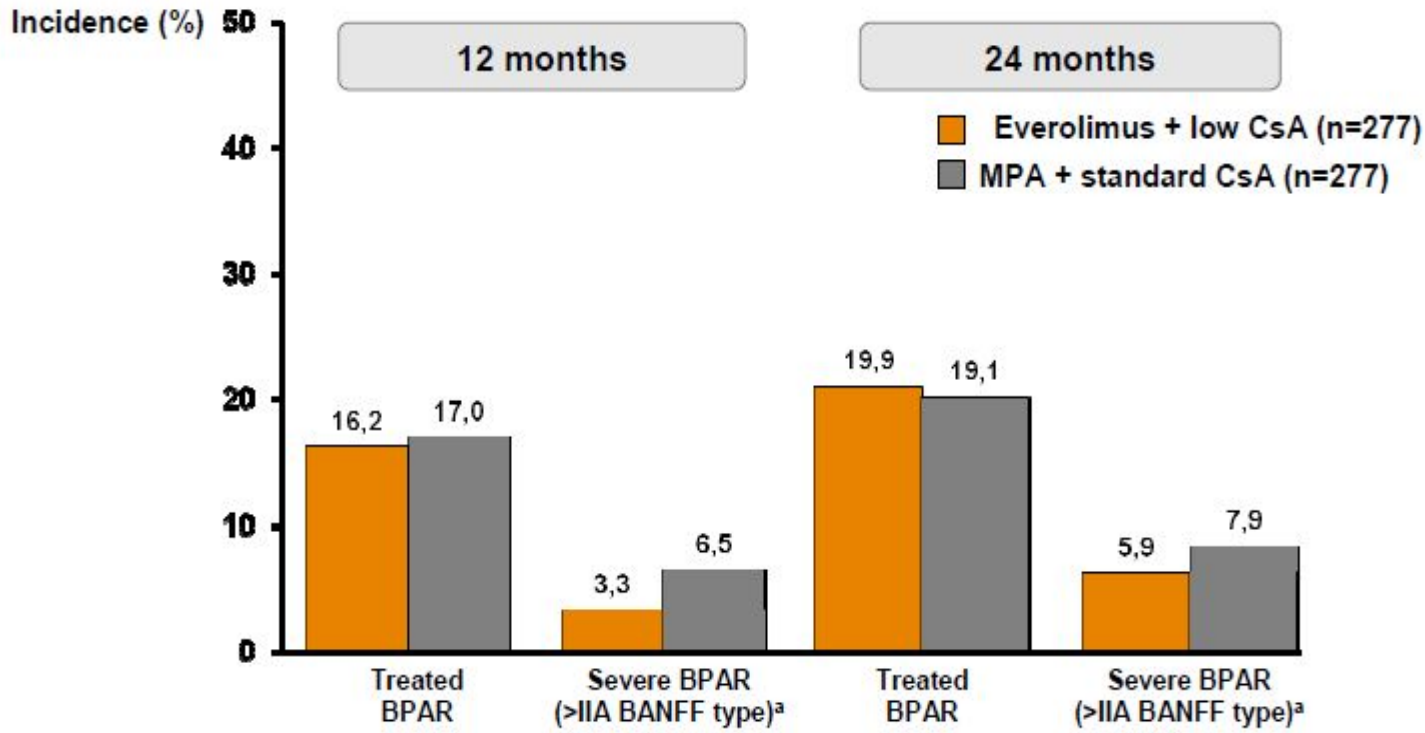
We are on to something….less CSA exposure!



CsA, cyclosporin;MPA, mycophenolic acid; D, day; M, month

Tedesco Silva H Jr *et al*. *Am J Transplant* 2010;10:1401–13; Tedesco-Silva H *et al*. ATC 2011 abstract 57

It works! Less rejections, less CSA!

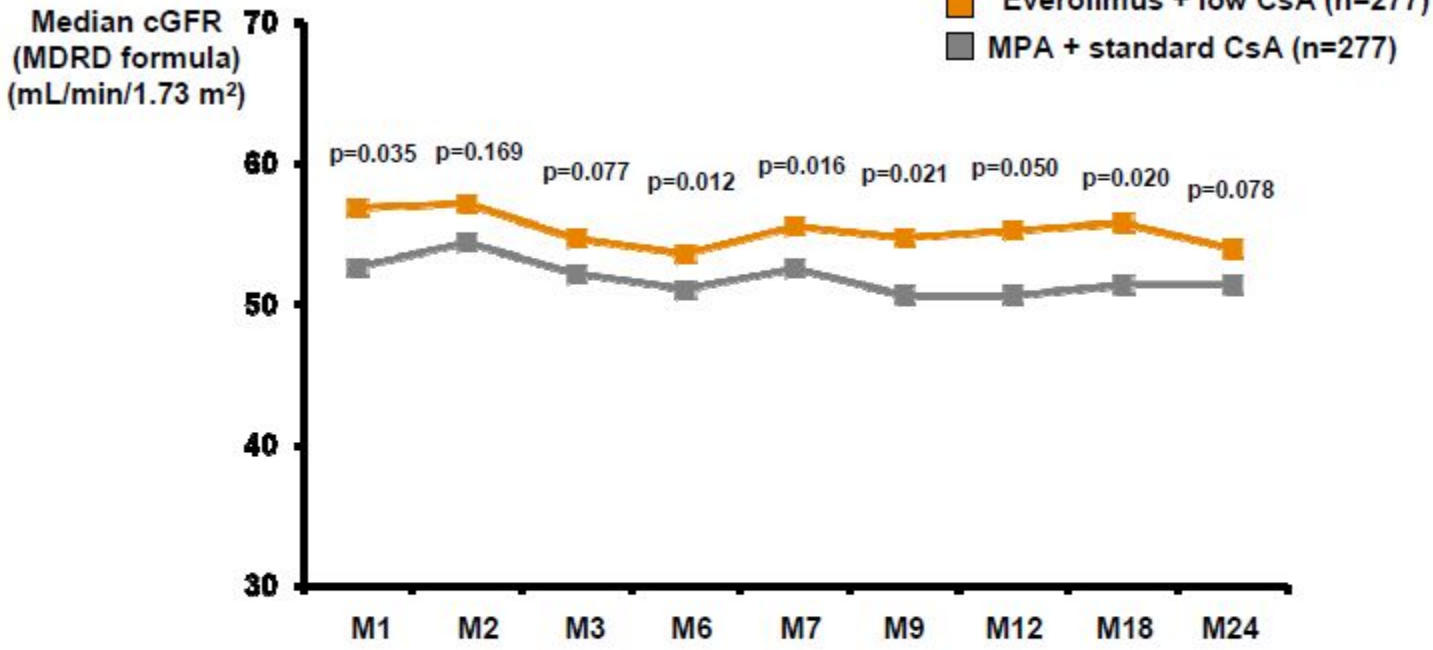


[a]Biopsy graded IIA, IIB or III

BPAR, biopsy-proven acute rejection; CNI, calcineurin inhibitor; CsA, cyclosporin; MPA, mycophenolic acid

Tedesco Silva H Jr *et al. Am J Transplant* 2010;10:1401–13; Tedesco-Silva H *et al.* ATC 2011 abstract 57

Less CSA equals more GFR



Differences in median cGFR ranged from 2.5–4.5 mL/min/1.73 m² vs MPA

cGFR, calculated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; CsA, cyclosporin; MPA, mycophenolic acid; M, month

Tedesco Silva H Jr *et al. Am J Transplant* 2010;10:1401–13; Cibrik D *et al.* ATC 2011 abstract 1293

Summary…

"De novo" patients: SRL + CNI (W/L)

- Potent immunosuppressive strategy
- Low incidence of acute rejection
- Based-immunosuppressive therapy: CNI (TAC)
- Avoid loading doses (SRL)
- Low doses of both drugs – CNIs / SRL (< 10 ng/mL)
- Consider withdrawal CNI – 3-6 m. after RT
- Consider avoid/withdrawal Steroids
- Long-term benefits (cancer & CV)

Studies to support mTOR + CNI (CsA/FK)

- Studies 301 – 302: SRL + CsA (FDA Approval)
- Study 310 (RMR) (EMEA Approval)
- Houston Experience (B.Kahan): SRL + Csa/FK
- Nebraska Experience (B.Stevens): SRL + CsA
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- Drexel University (Kumar et al. Transplant Immunology'08)
- OA.Gaber – Houston (Transplantation'10)
- Everolimus development: EVL + CsA

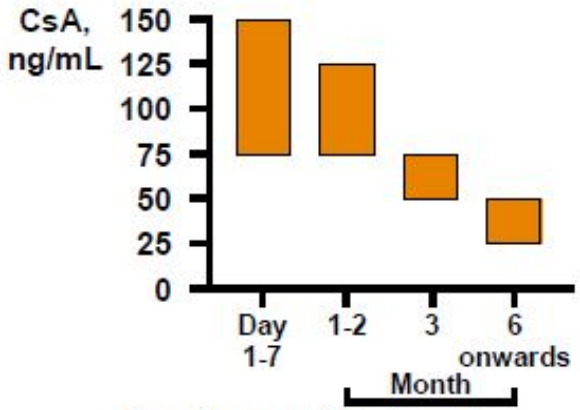
The Bacelona strategy

Everolimus: initiate at Day 1 and continue indefinitely

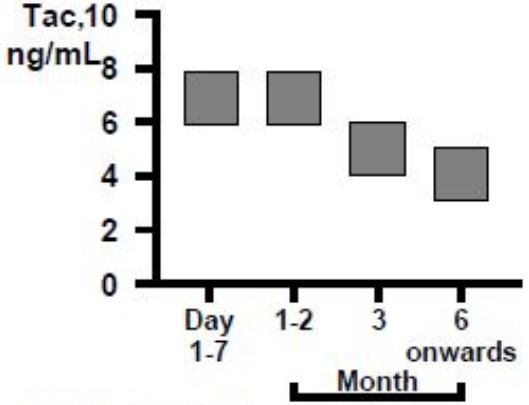
Administer everolimus orally (0.75 mg bid with CsA[1] or 1.5 mg bid with tacrolimus[2])

At Day 3–5 after 1st administration of everolimus, perform TDM to measure everolimus trough levels and maintain at 3–8 ng/mL[1]

Target CNI levels (C0)



Based on expert opinion and Studies A2307,[4] B156[5] and A2309[6]



*Based on A2426 (ASSET)[3]**

CNI, calcineurin inhibitor; CsA, cyclosporin, tac, tacrolimus; TDM, therapeutic drug monitoring

1. Certican SmPC 2007; 2. Data on file, ASSET; 3. Vitko *et al* 2009; 4. Data on file, A2307; 5. Nashan *et al* 2004; 6. Tedesco *et al* 2010

mTORi vs. MPA

Advantage

Potent/Specific Immunos. drugs
T & B Cell control
Based Immunosuppressant

Disadvantage

Side Effects
Monitoring

Advantage

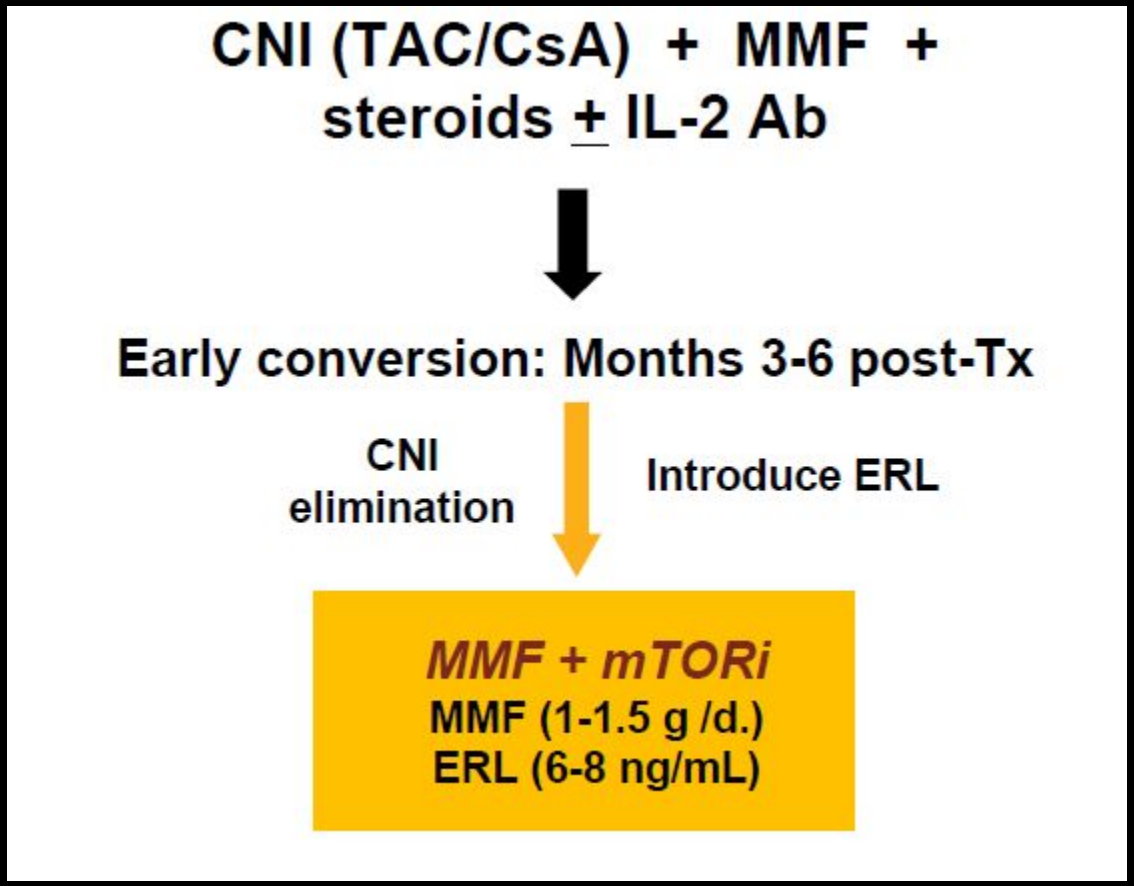
Immunosuppressive drugs
T & B Cell control
Adjuvant Immunosuppressant
le

Disadvantage

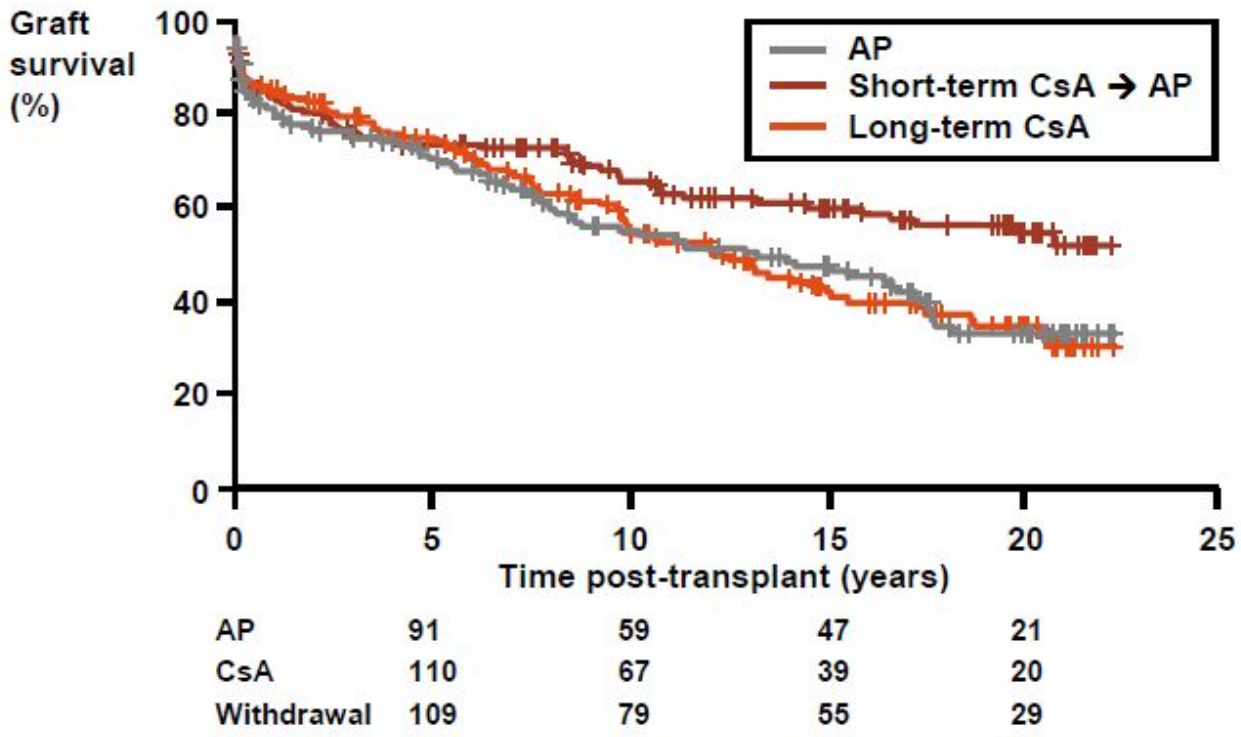
G-I tolerance
Viral infections
Cancer

mTORi >> MPA
Low Tac + Low SRL

Strategy #3: early CNI elimination



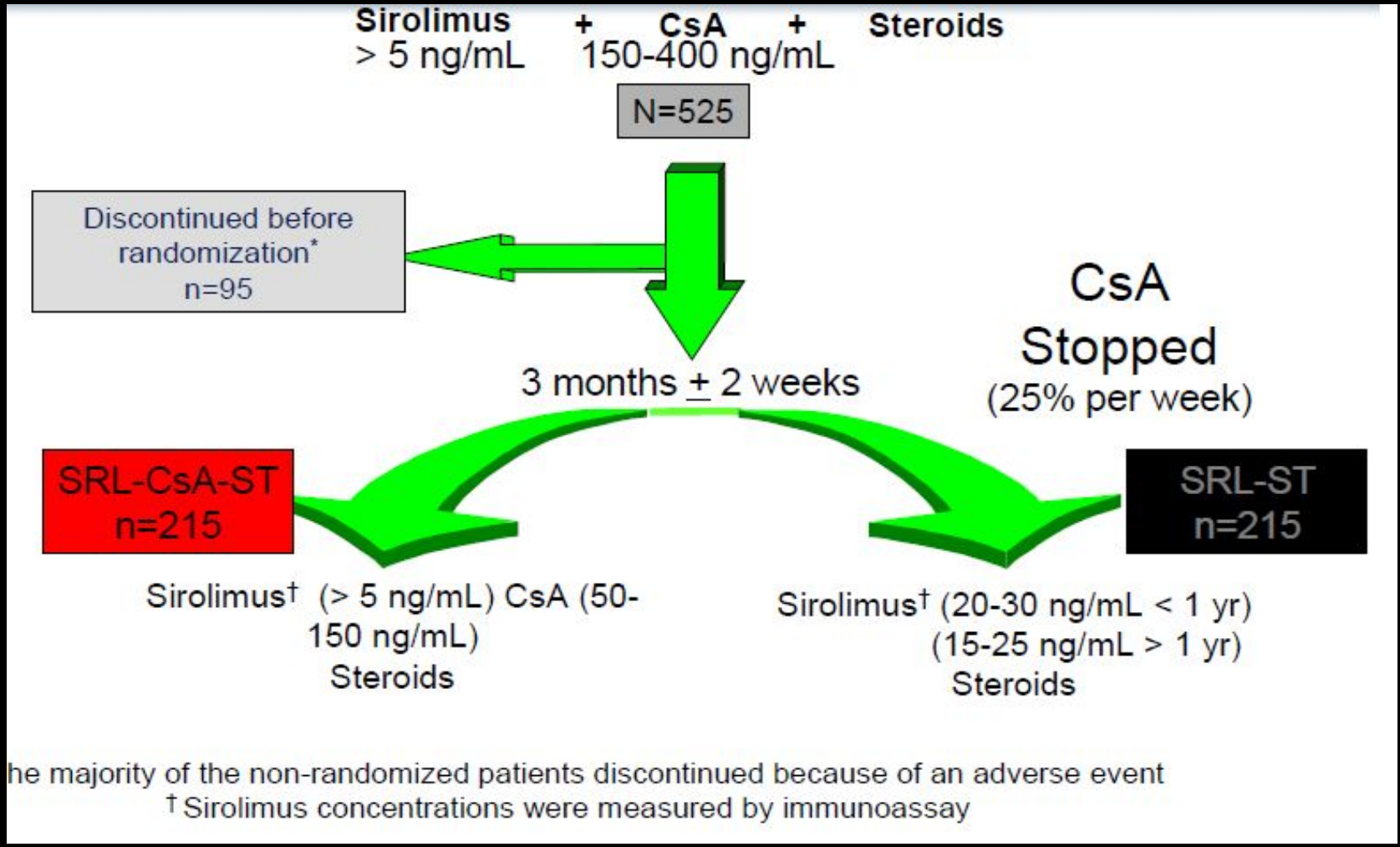
Suggestion of graft survival benefit



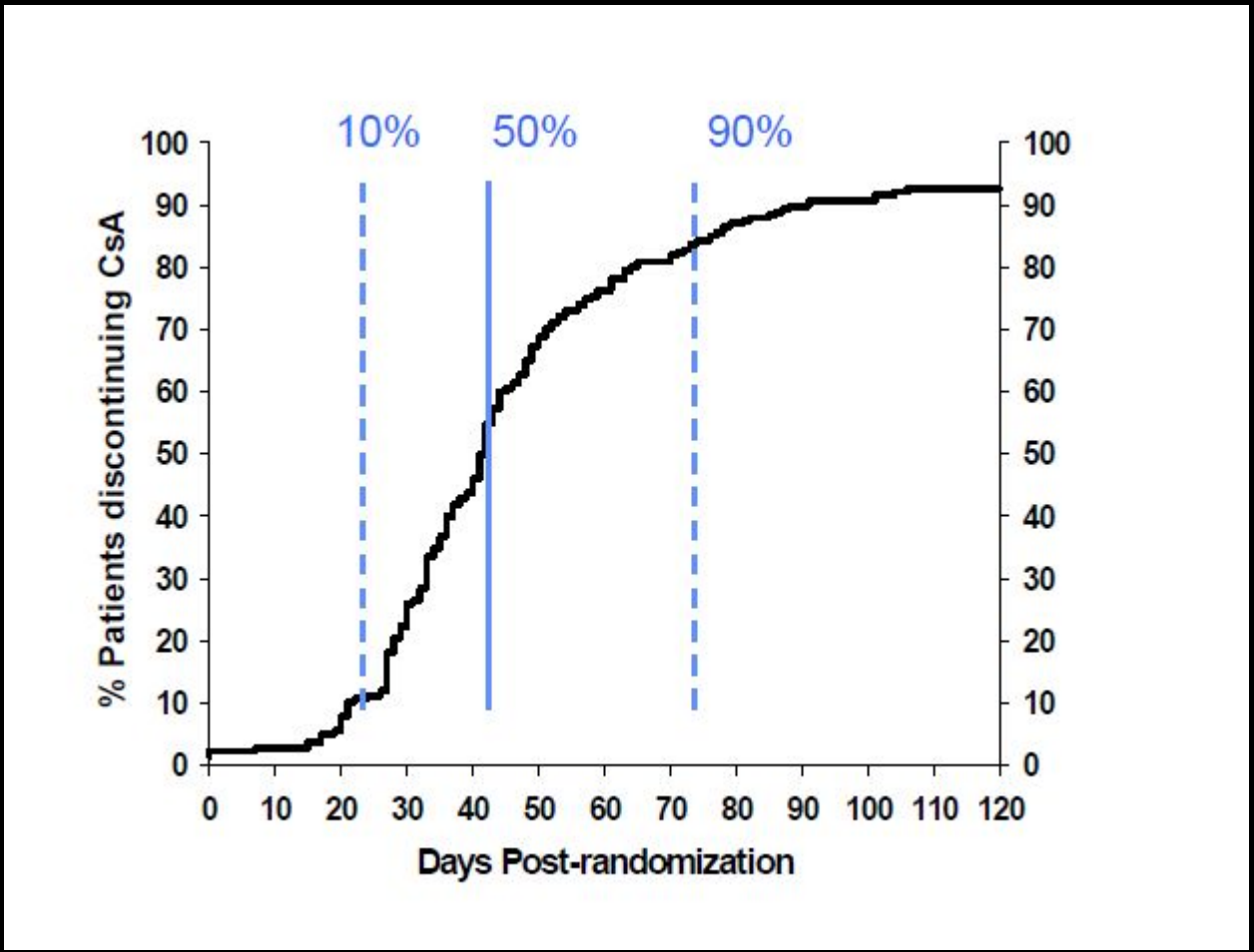
AP, azathioprine + prednisolone; CNI, calcineurin inhibitor; CsA, cyclosporin

Gallagher M *et al. Transplantation* 2009;87:1877–83

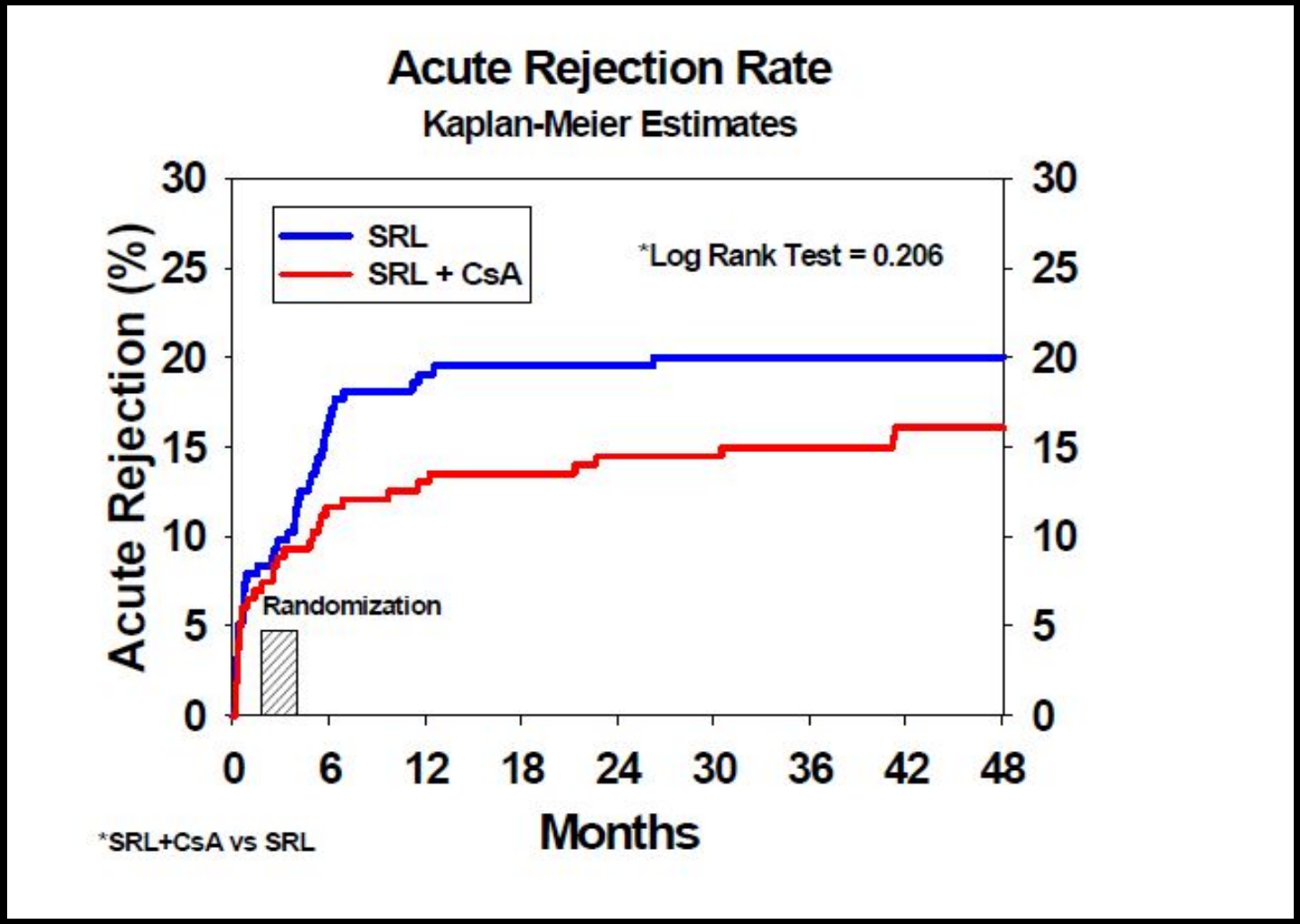
Study 310 design (RMR)



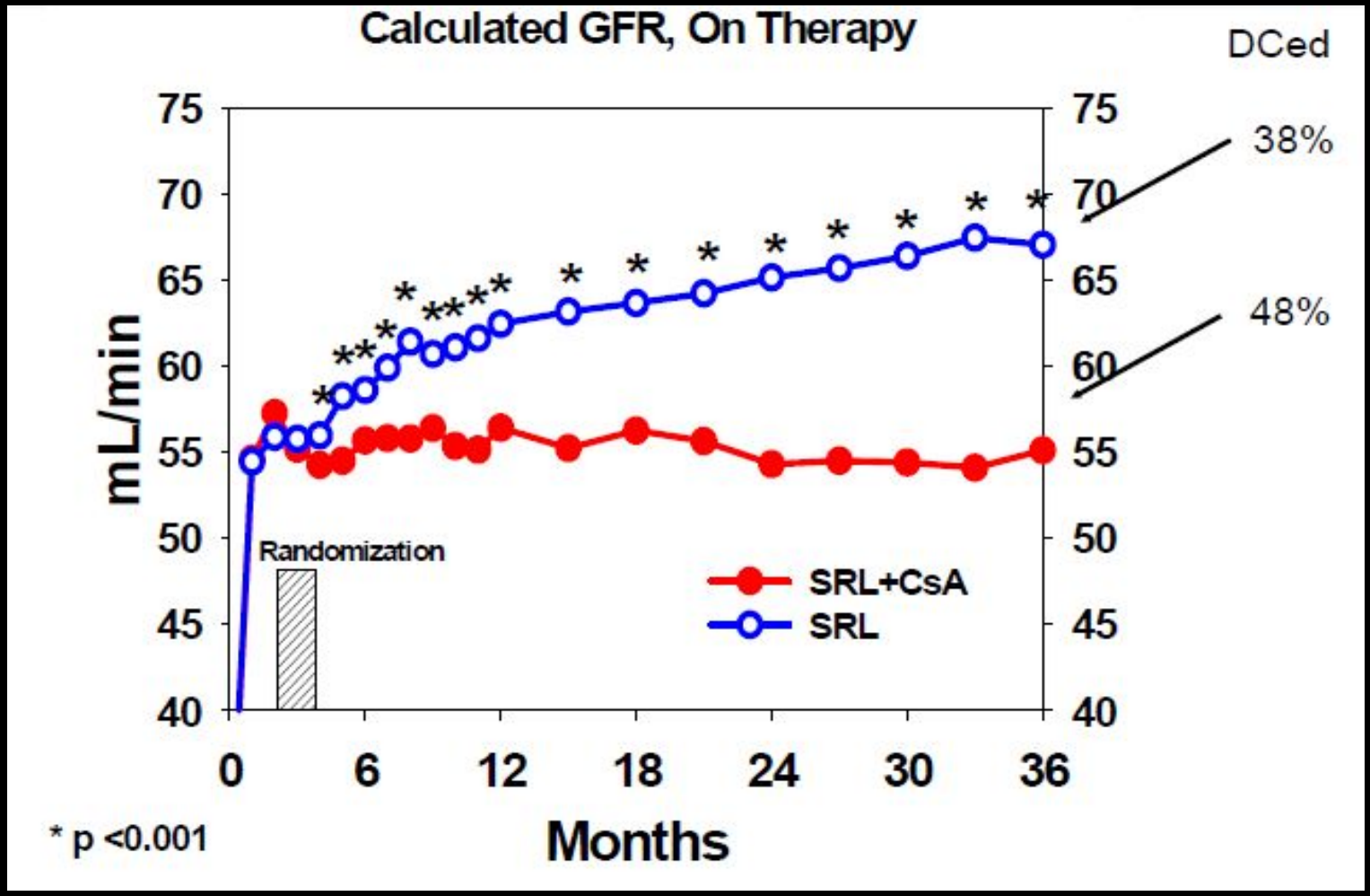
92,6 discontinued CSA



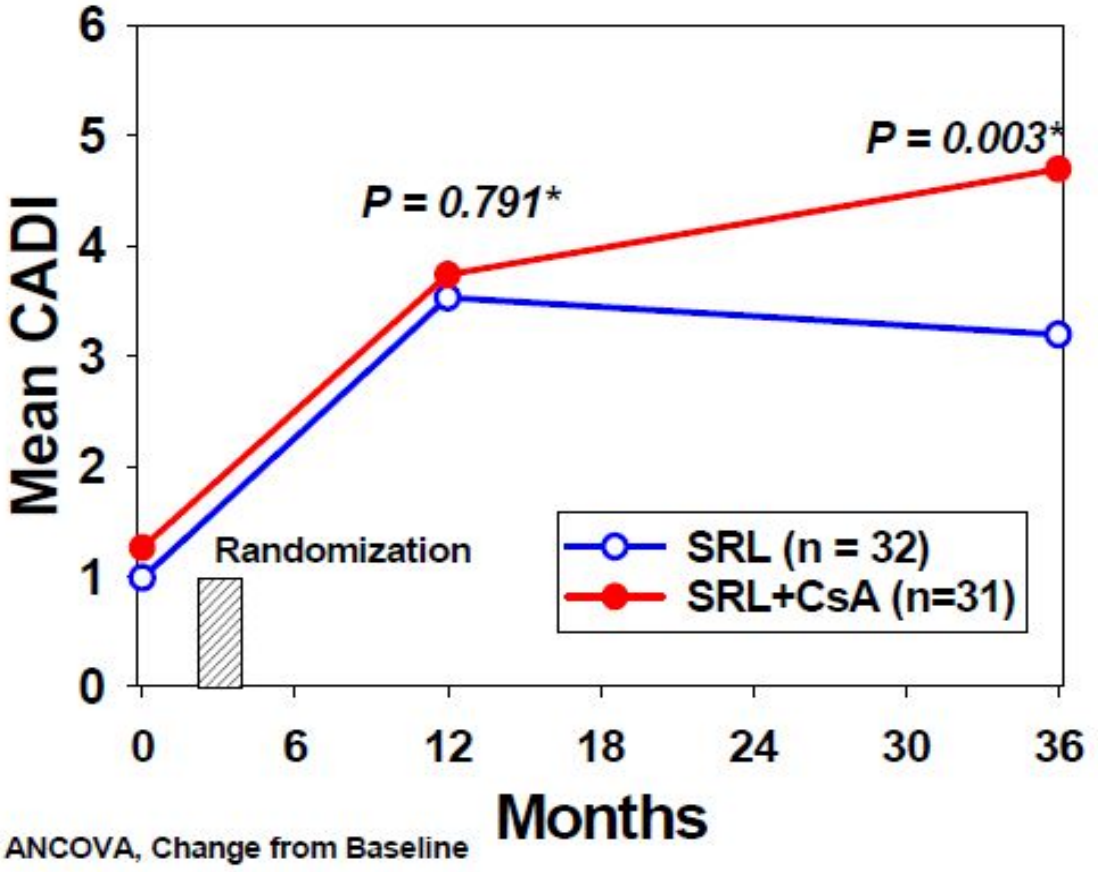
Rejection rates



Function….


Calculated GFR, On Therapy
DCed
38%
48%
mL/min
75
70
65
60
55
50
45
40
Randomization
SRL+CsA
SRL
0
6
12
18
24
30
36
Months
* p <0.001

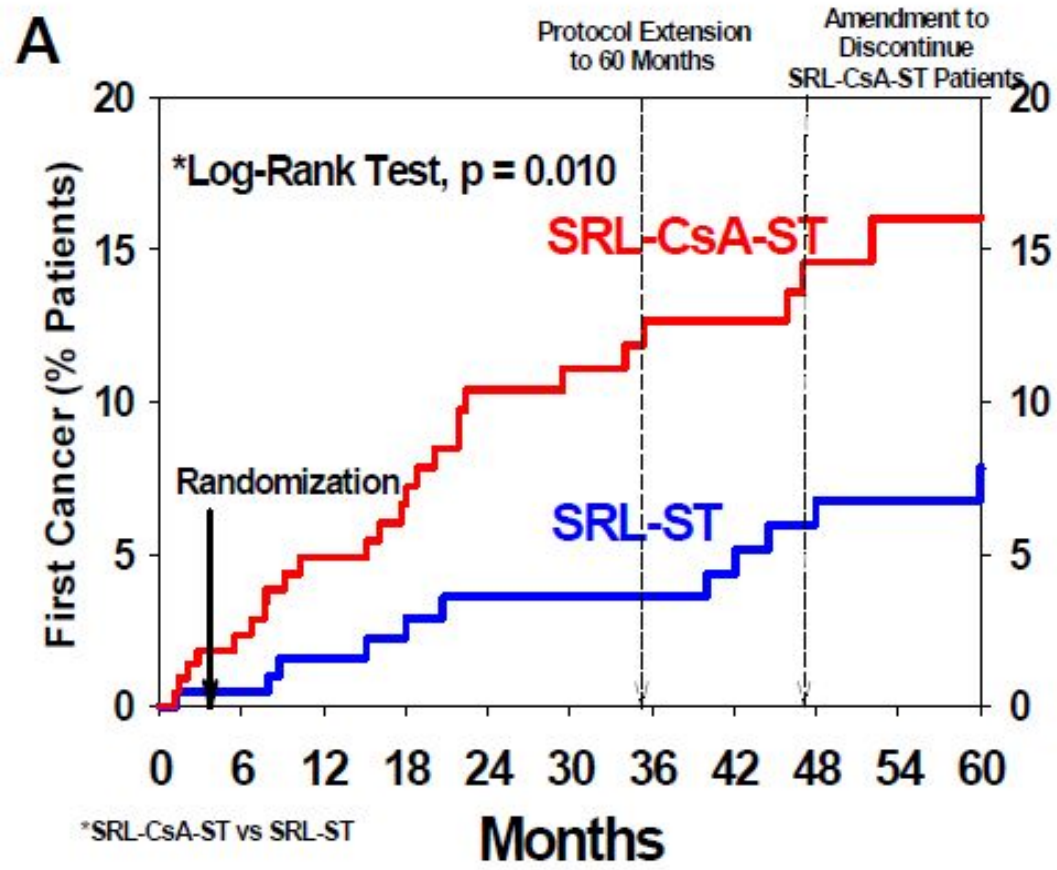
Histology…



Note: All Patients with Biopsies at Baseline, 12 and 36 Months

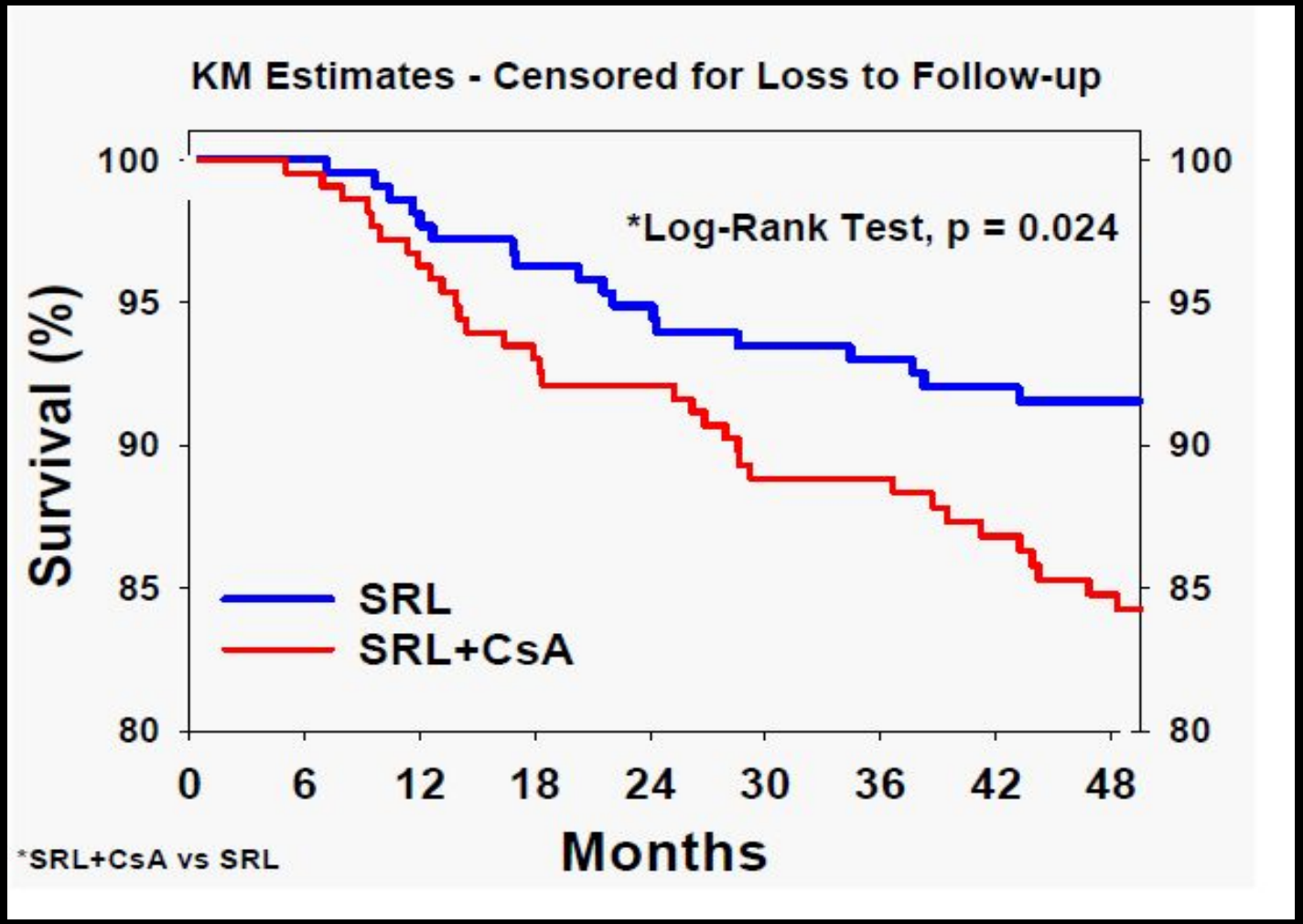
Mota et al, AJT'05

Now we are really on to something…cancer!

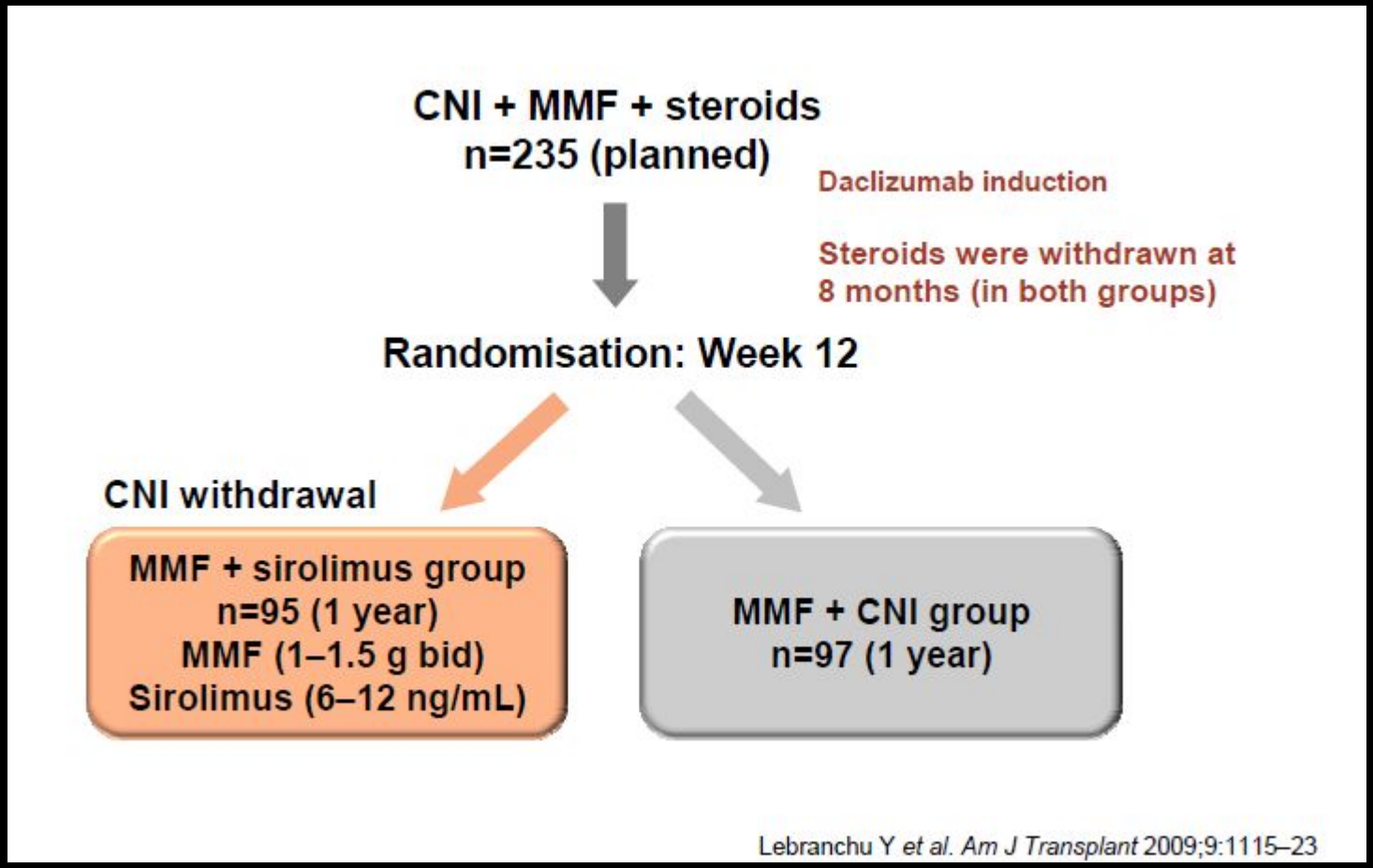


Campistol JM, et al, JASN'06

Graft survival….

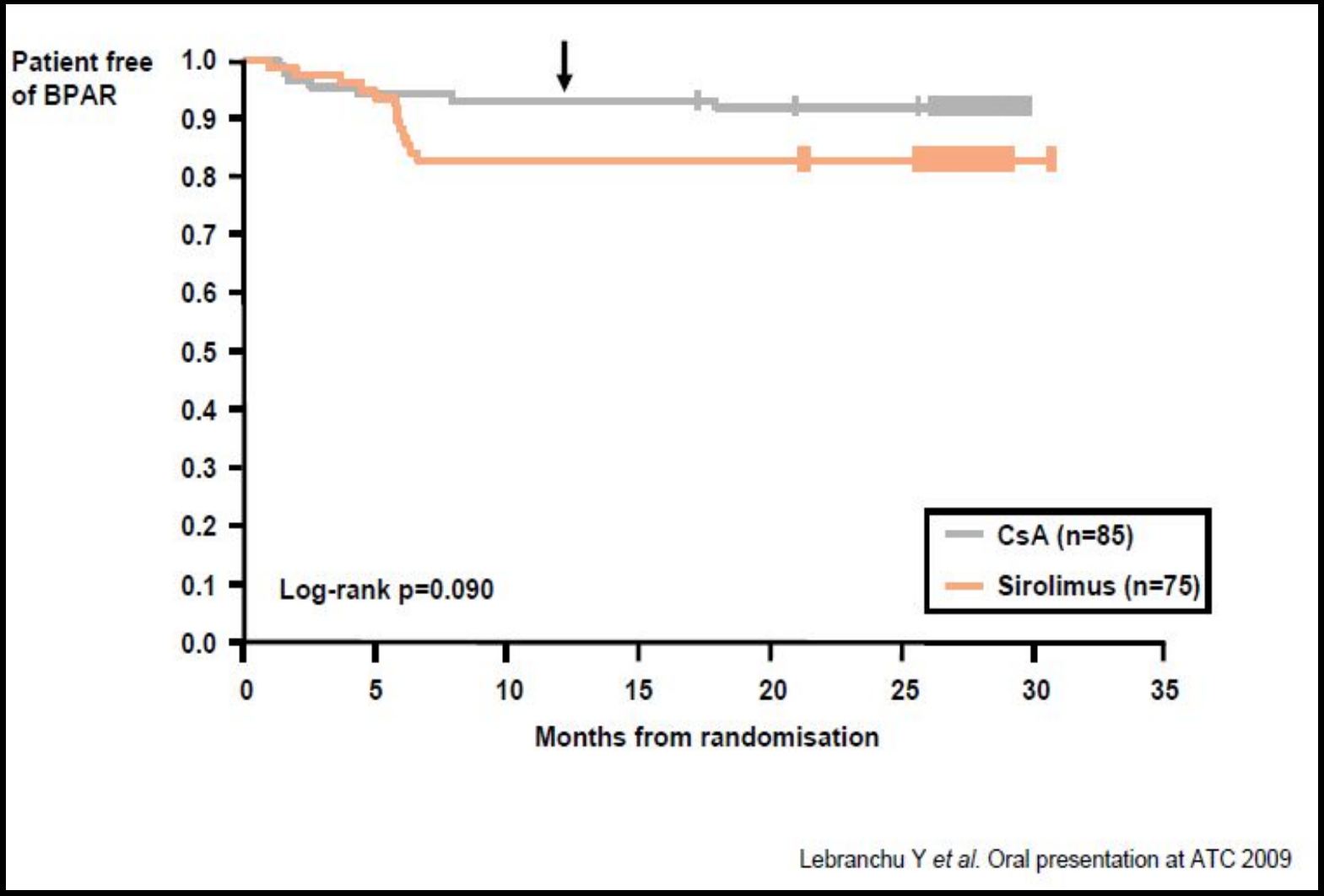


CONCEPT: design



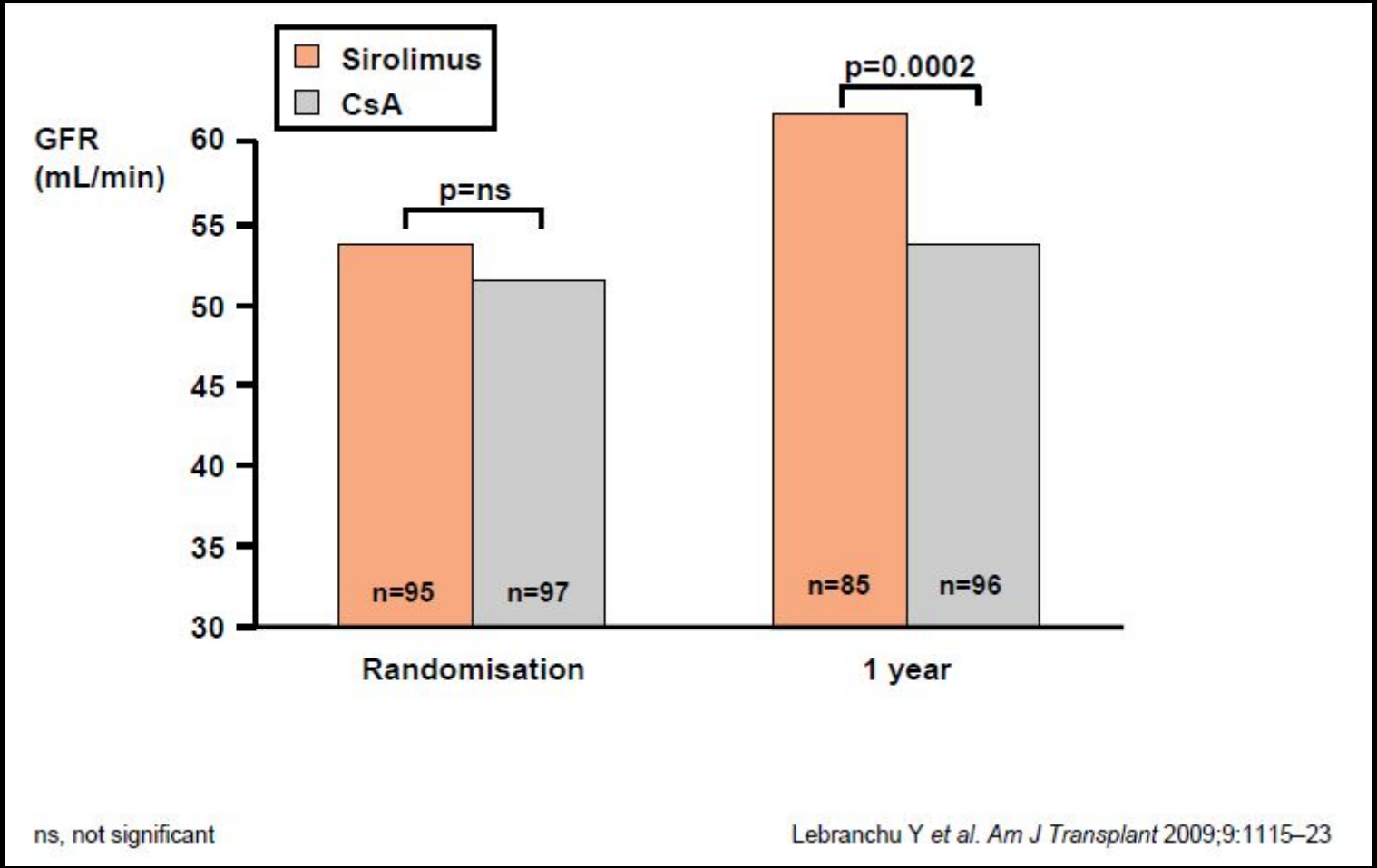
Lebranchu Y *et al. Am J Transplant* 2009;9:1115–23

CONCEPT: Rejection



Lebranchu Y *et al.* Oral presentation at ATC 2009

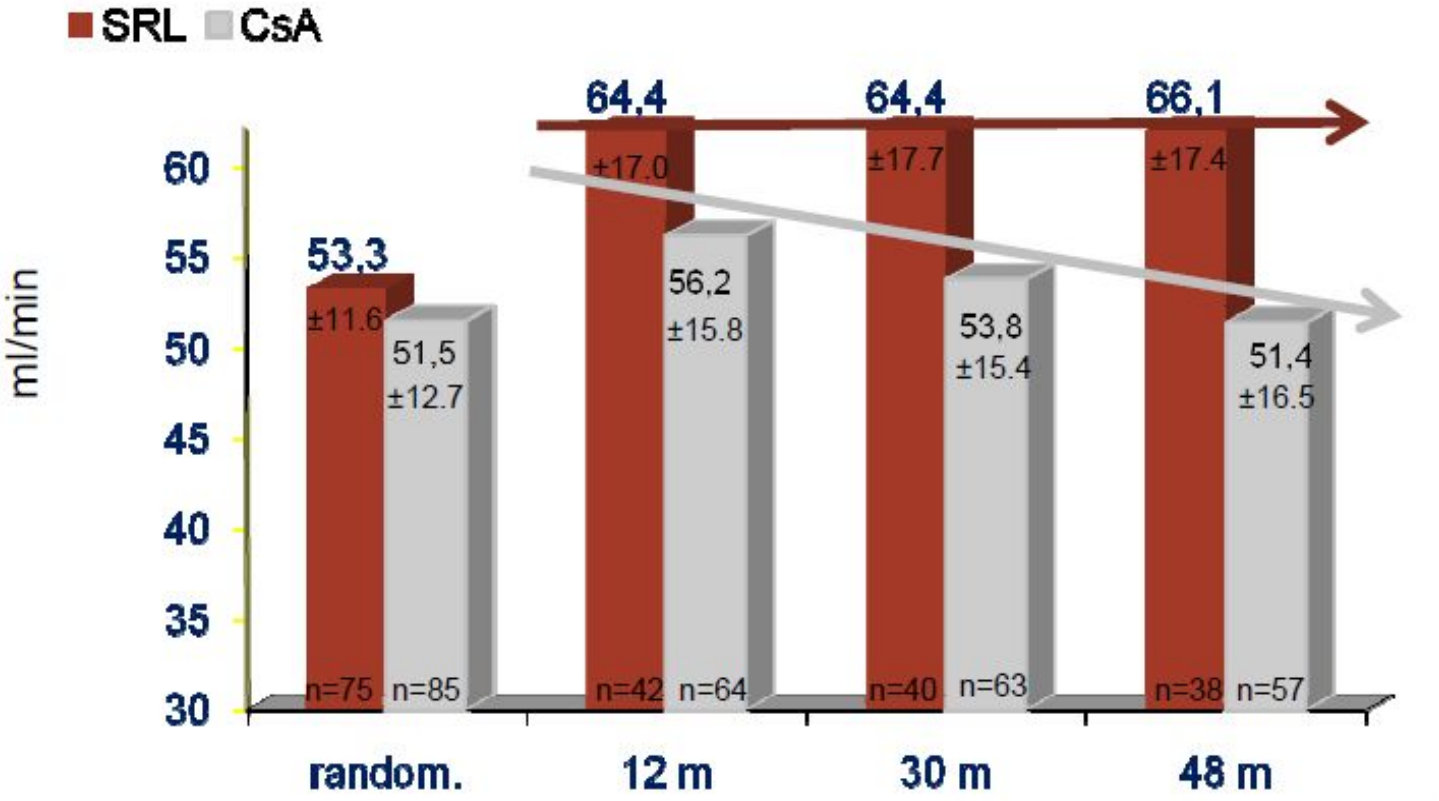
CONCEPT: Function



ns, not significant

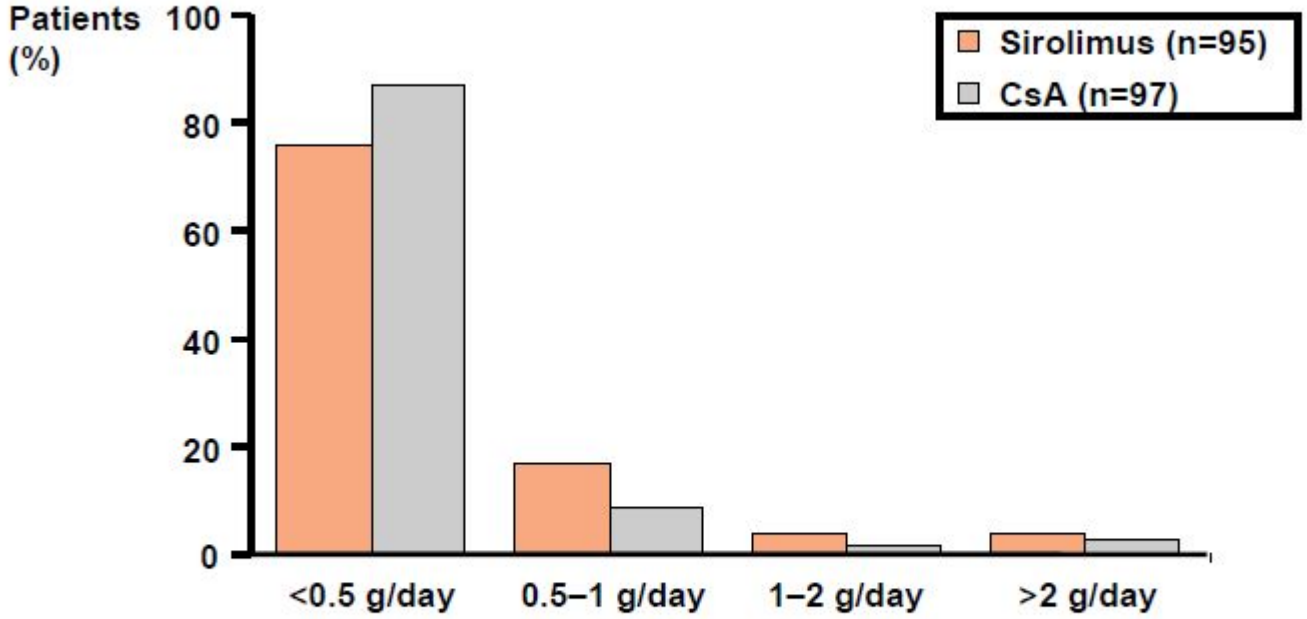
Lebranchu Y *et al. Am J Transplant* 2009;9:1115–23

CONCEPT: long term follow up



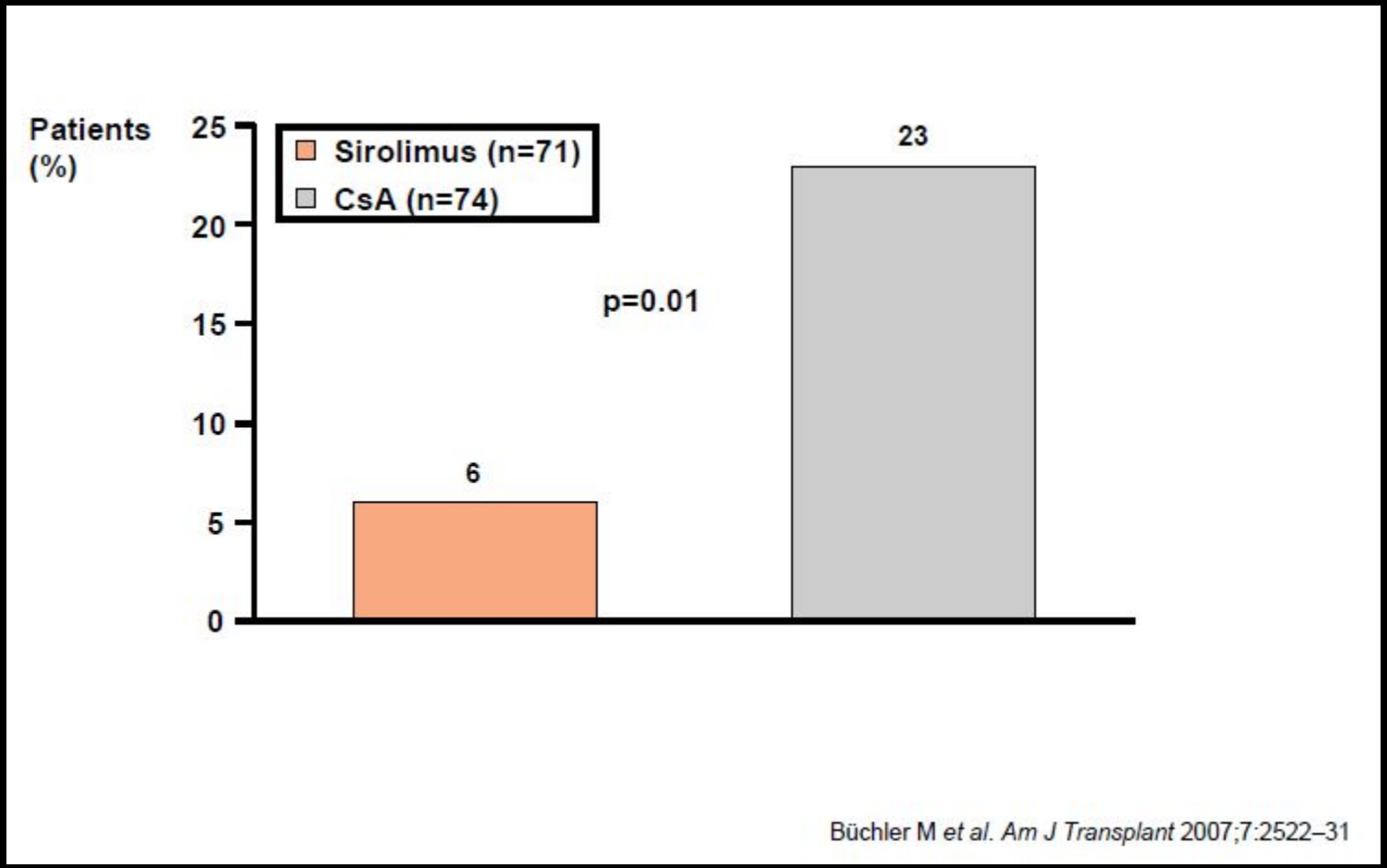
Lebranchu Y *et al. Am J Transplant* 2011

CONCEPT: proteinuria



Büchler M *et al. Am J Transplant* 2007;7:2522–31

CONCEPT: CMV



Büchler M *et al. Am J Transplant* 2007;7:2522–31

CONCEPT: malignancy

	Sirolimus + MMF	CsA + MMF
No. of patients	1	6
Type of malignancy	Metastatic bronchial carcinoma	Breast carcinoma
		MALT lymphoma
		Kaposi sarcoma
		Angiosarcoma
		Squamous cell carcinoma
		Basocellular carcinoma

MALT, mucosa-associated lymphoid tissue

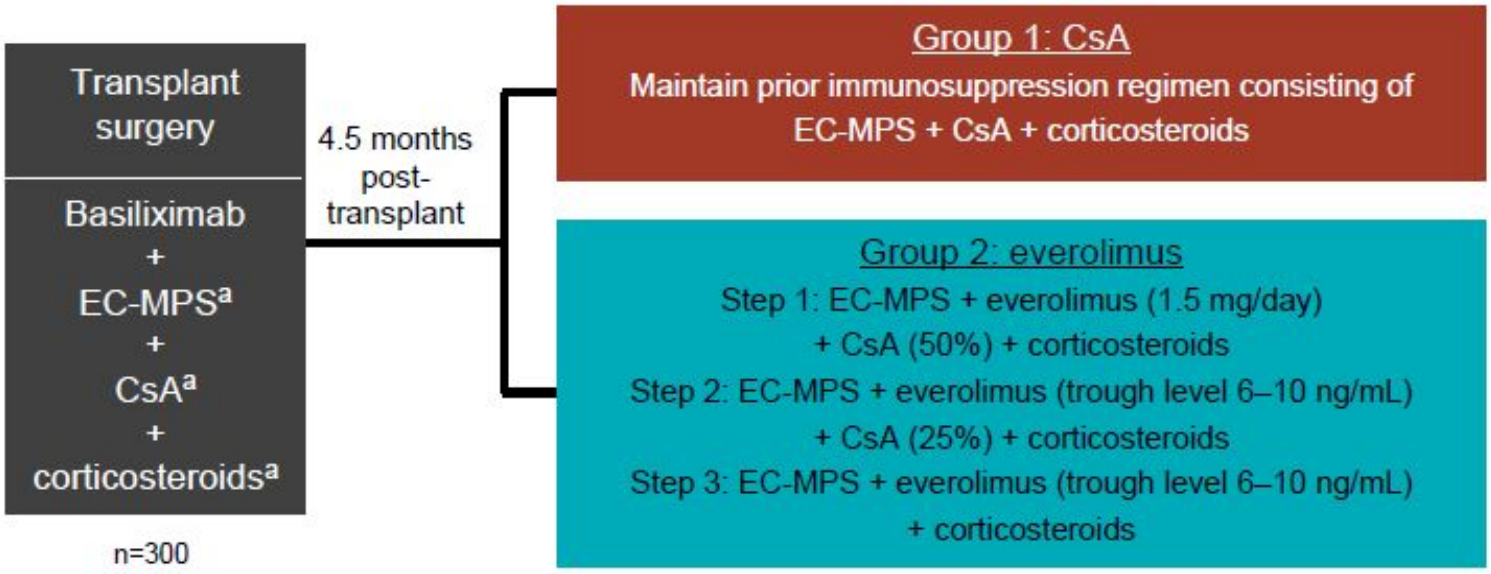
Lebranchu Y *et al. Am J Transplant* 2011

Concept: mellékhatások, szövődmények

	SRL group (n = 96)	CsA group (n = 97)	p-Value
TOTAL, nb events /nb patients	613/94	395/89	ns
Anemia	13/13	5/5	*
Leukopenia	12/10	6/6	ns
Thrombocytopenia	13/12	–	***
Aphthous stomatitis	62/44	5/5	***
Diarrhea	32/29	9/9	***
Peripheral edema	28/27	24/22	ns
CMV infection	4/4	7/6	ns
Dyslipidemia	8/8	4/4	ns
Hypercholesterolemia	5/5	1/1	ns
Diabetes (NODAT)	3	2	ns
Cutaneous carcinoma	1	–	ns
Prostate cancer	1	–	ns
Proteinuria	10/9	3/3	ns
Hematuria	5/5	3/3	ns
Acne	19/18	5/5	**

*$p < 0.01$; **$p < 0.01$; ***$p < 0.001$.

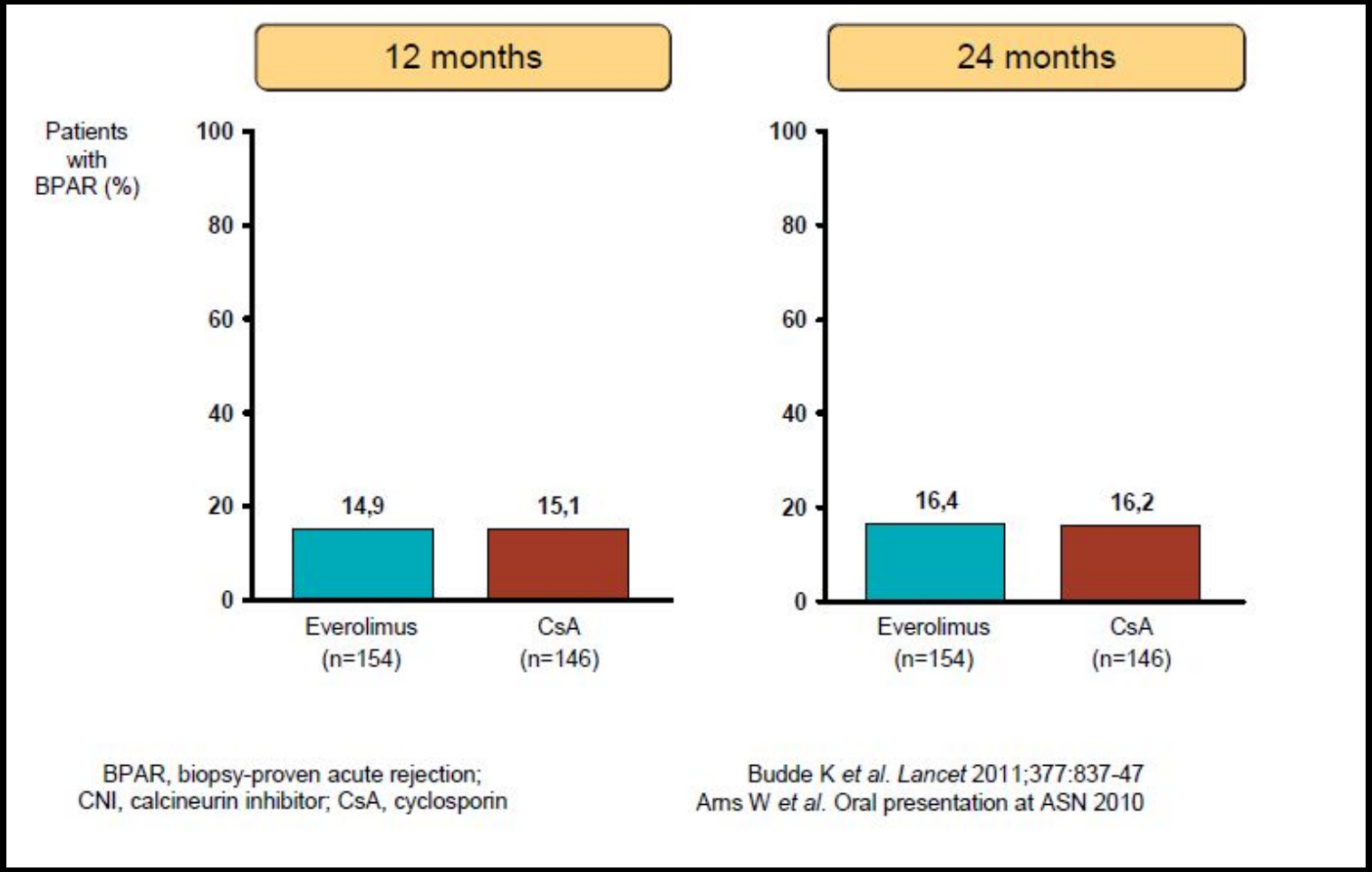
Zeus: design



[a]For the 1st 4.5 months post-transplant, all patients treated with EC-MPS, CsA and corticosteroids. Corticosteroids administered throughout the study according to local practice at a minimum dose of 5 mg
CNI, calcineurin inhibitor; EC-MPS, enteric-coated mycophenolate sodium; CsA, cyclosporin

Budde K *et al.*
Lancet 2011;377:837-47

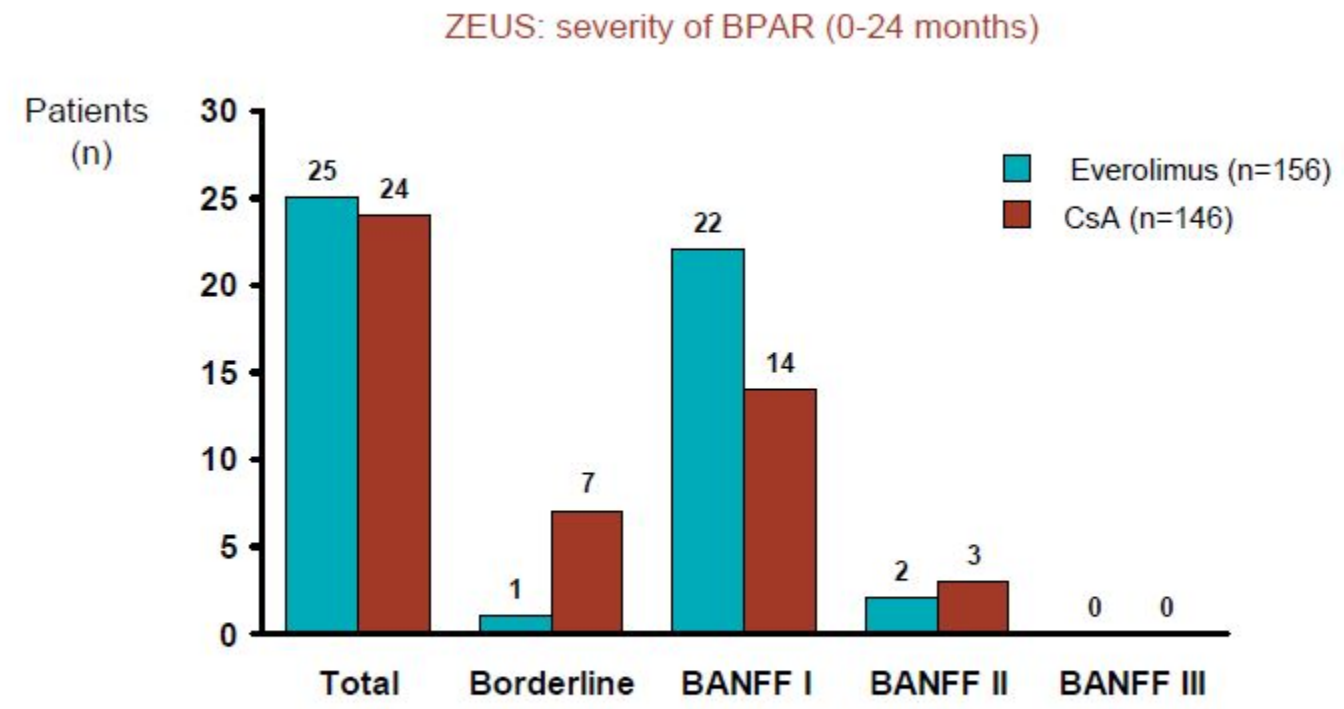
Zeus: Rejection



BPAR, biopsy-proven acute rejection; CNI, calcineurin inhibitor; CsA, cyclosporin

Budde K *et al*. *Lancet* 2011;377:837-47
Arns W *et al*. Oral presentation at ASN 2010

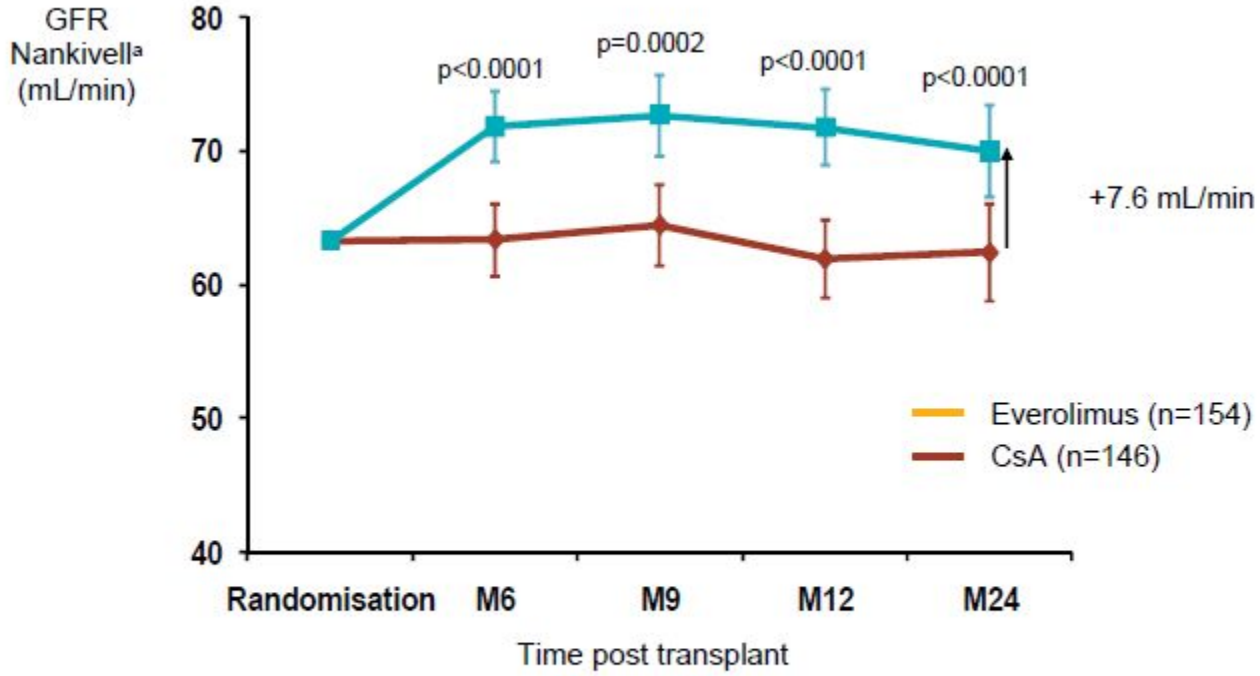
Zeus: Rejection 2



BPAR, biopsy-proven acute rejection; CsA, cyclosporin

Budde K *et al. Lancet* 2011;377:837-47
Arns W *et al.* Oral presentation at ASN 2010

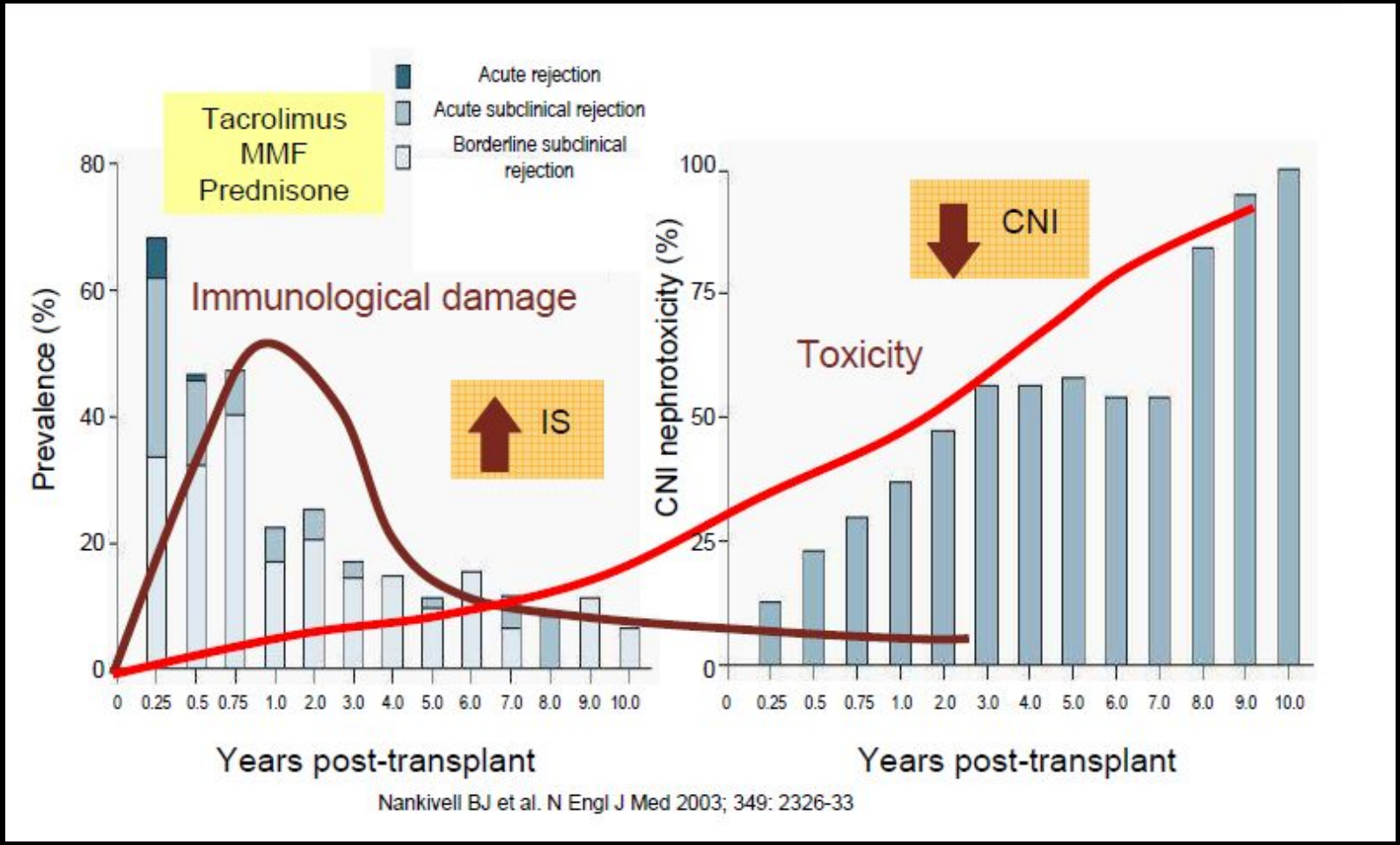
Zeus: Function



[a]Adjusted values (means from analysis of covariance model, 95% CI)
GFR, glomerular filtration rate; CsA, cyclosporin;
M, month; CI, confidence interval

Arns W *et al.*
Oral presentation at ASN 2010

If you believe CNI toxicity is a major player….



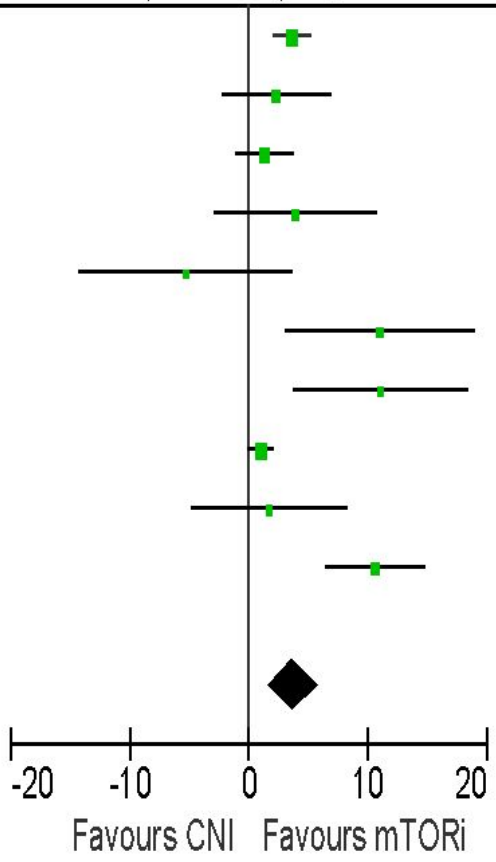
Nankivell BJ et al. N Engl J Med 2003; 349: 2326-33

Meta-analysis of mTORi conversion studies
Mean GFR 12 months after conversion (ITT)

	mTORi			CNI				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
APOLLO	62.9	3.7	46	59.3	3.69	47	16.8%	3.60 [2.10, 5.10]	
Baboolal	37.3	13.6	116	35	16.7	74	10.2%	2.30 [-2.24, 6.84]	
CONVERT	59	15.4	497	57.7	15.4	246	15.0%	1.30 [-1.05, 3.65]	
ERIC	57.3	18	54	53.4	18	54	6.6%	3.90 [-2.89, 10.69]	
Heilman	57.4	20.7	54	62.7	26.5	55	4.5%	-5.30 [-14.22, 3.62]	
MECANO	55	20	38	44	15	39	5.4%	11.00 [3.09, 18.91]	
SMART	64.5	25.2	69	53.4	18	70	6.0%	11.10 [3.81, 18.39]	
SOCRATES	72.3	2.5	49	71.3	2.5	47	17.6%	1.00 [-0.00, 2.00]	
Watson	37.8	11.1	19	36.1	9.3	19	6.9%	1.70 [-4.81, 8.21]	
ZEUS	71.8	18.5	143	61.2	16.7	137	11.0%	10.60 [6.48, 14.72]	
Total (95% CI)			**1085**			**788**	**100.0%**	**3.77 [1.59, 5.95]**	

Heterogeneity: $Tau^2 = 6.78$; $Chi^2 = 38.82$, df = 9 ($P < 0.0001$); $I^2 = 77\%$

Test for overall effect: $Z = 3.39$ ($P = 0.0007$)

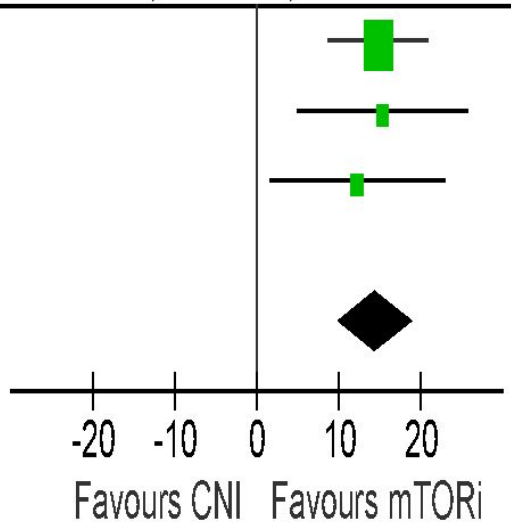


Meta-analysis of mTORi conversion studies Mean GFR between 2 and 5 years post-conversion (OT)

Study or Subgroup	mTORi Mean	mTORi SD	mTORi Total	CNI Mean	CNI SD	CNI Total	Weight	Mean Difference IV, Random, 95% CI
CONCEPT	65.1	14.1	36	50.3	14.8	55	60.1%	14.80 [8.76, 20.84]
SMART	68	23.9	28	52.7	17.4	41	20.5%	15.30 [4.97, 25.63]
Watson	43.1	13	12	30.9	13	11	19.4%	12.20 [1.56, 22.84]
Total (95% CI)			76			107	100.0%	14.40 [9.72, 19.08]

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.21$, $df = 2$ ($P = 0.90$); $I^2 = 0\%$

Test for overall effect: $Z = 6.03$ ($P < 0.00001$)

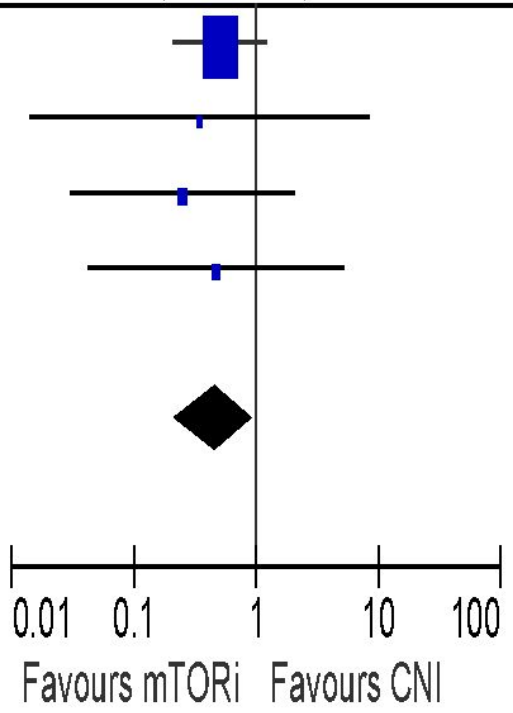


Meta-analysis of mTORi conversion trials
Graft loss up to 5 years post-conversion

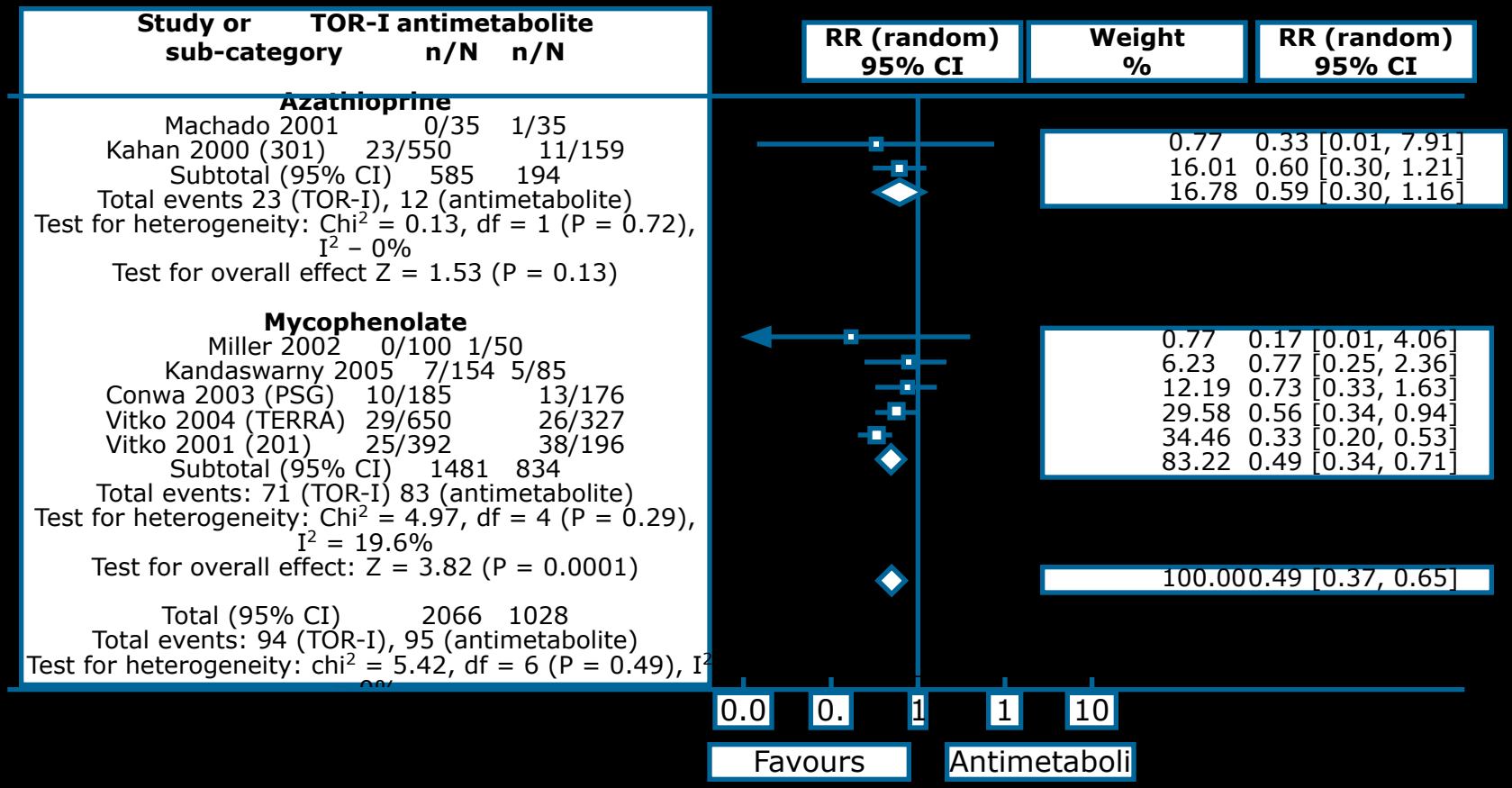
Study or Subgroup	mTORi Events	mTORi Total	CNI Events	CNI Total	Weight	Risk Ratio M-H, Random, 95% CI
Han	5	22	13	29	72.5%	0.51 [0.21, 1.21]
SMART	0	69	1	71	5.4%	0.34 [0.01, 8.27]
Watson	1	19	4	19	12.5%	0.25 [0.03, 2.04]
ZEUS	1	155	2	145	9.6%	0.47 [0.04, 5.10]
Total (95% CI)		**265**		**264**	**100.0%**	**0.45 [0.22, 0.95]**
Total events	7		20			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.41$, df = 3 (P = 0.94); $I^2 = 0\%$

Test for overall effect: Z = 2.11 (P = 0.04)

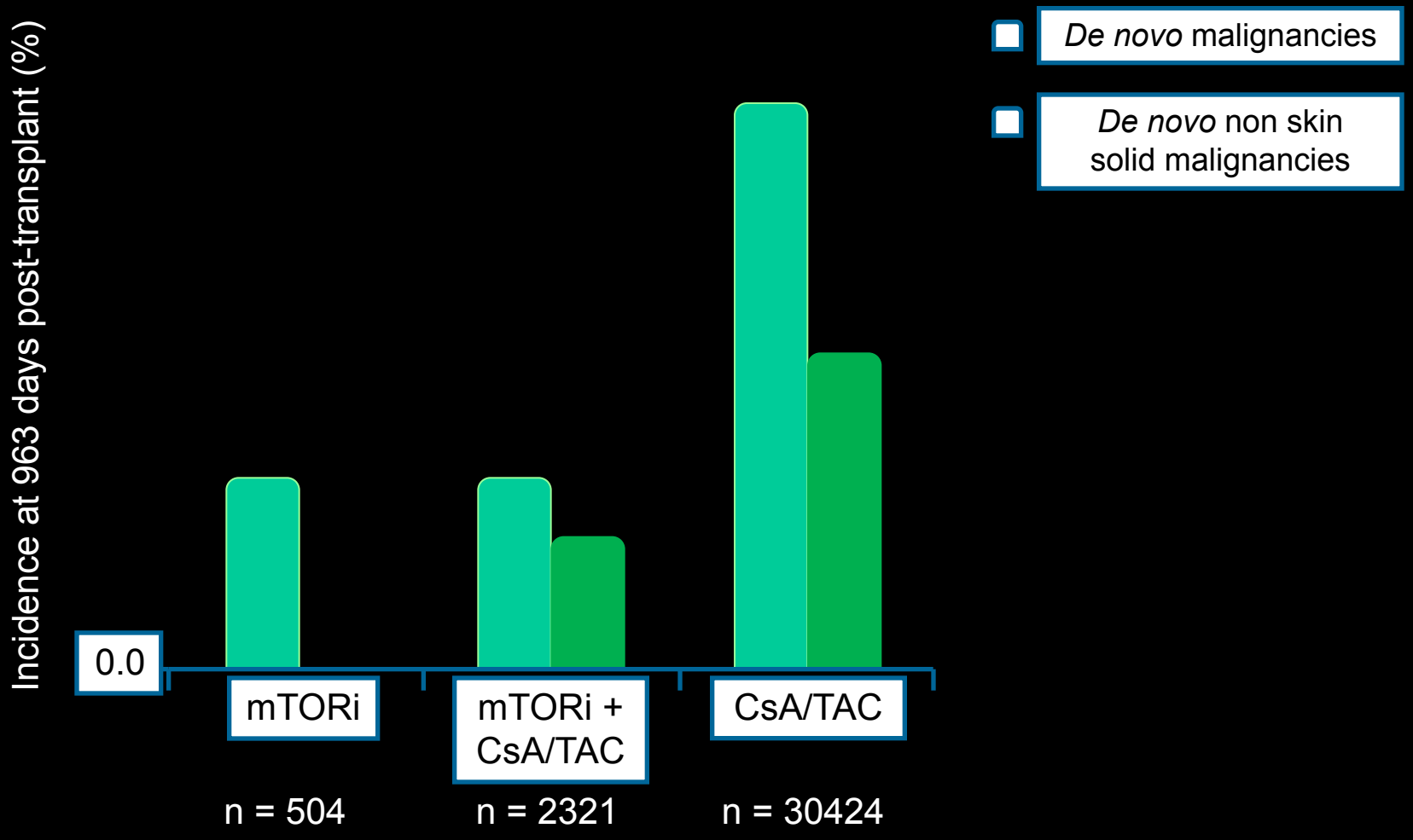


Risk of CMV infection in patients treated with mTOR-inhibitors versus anti-metabolites



Webster AC, et al. *Transplantation* 2006;81: 1234–1248.

Immunosuppression with mTOR-inhibitors reduces the incidence of post-transplant malignancy



Kauffman HM, et al. *Transplantation* 2005;80:883–889.

Common side effects

- **Short term / immediate post-surgery**
  - Surgical / wound healing
  - Lymphoceles
  - Delayed graft function / acute tubular necrosis
  - Myelotoxicity / Anemia
- **Long term / any time during follow-up**
  - Hyperlipidemia
  - Pulmonary toxicity
  - Proteinuria
  - Skin
  - Fertility
  - Diabetes

mTORi mellékhatások

Table 2. Selected frequent adverse events during the 12-month follow-up of randomized studies.

Adverse events	Rate of occurrence (%)
Surgical complications [10,57,89,94]	9–15
Acne, folliculitis [51,57,75,94]	16–25
Mouth ulcers/aphthous stomatitis [51,57,75]	8–46
Diarrhea [10,51,57,75,89]	24–39
Hypokalemia [57]	23
Peripheral edema [51,75,89]	22–32
Bronchopulmonary complications [51,57,94]	6–16

Weir et al. Transplant Int 2010; 23:447-60.

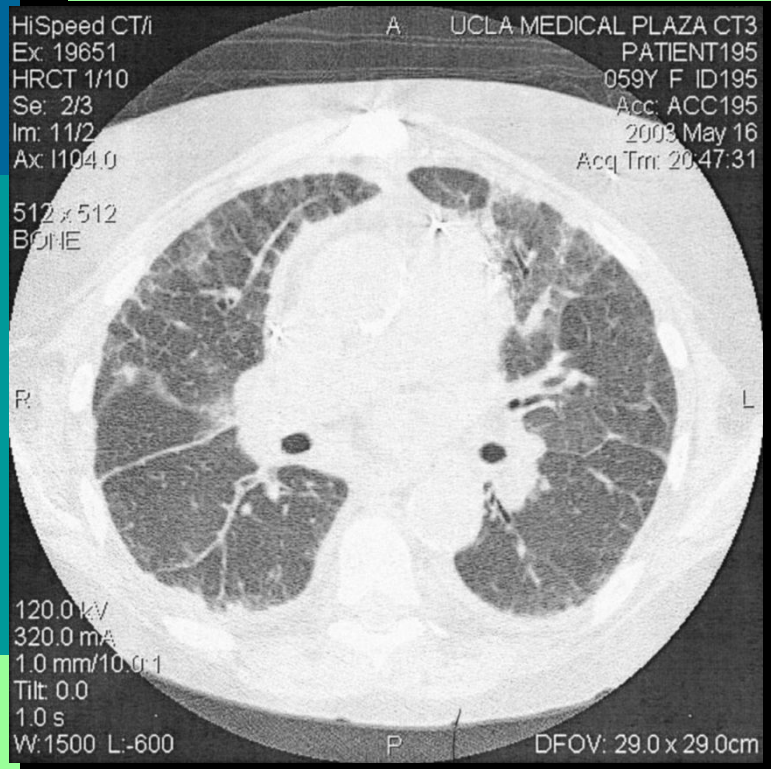
Except pulmonary toxicity

Adverse event	Intervention
Mouth ulcers	Clobetasol
Acne	Lymecycline / tetracycline
Oedema	Diuretics
Anaemia	Erythropoietin
Proteinuria	ARBs
Hyperlipidaemia	Statins

Most adverse events associated with mTORi (SRL/ERL) can be managed with adequate dose interventions

Pascual J. *Transplant Rev* 2006;20:1-18

Pneumonitis



veen 2000–2004 (including the present case)

SRL dose	Trough bld. level (ng/mL)	Lung complications and other SRL associated toxicities	Outcome
4 mg qd	n/a	Pulmonary hemorrhage, interstitial pneumonia,?organizing pneumonia; anemia, thrombocytopenia	Death
15 mg loading; 5 mg qd ×4 d; 3 mg qd thereafter	20–24	Interstitial pneumonitis: RADS - rapid and progressive infiltration of lungs bilaterally; HISTO -diffuse alveolar damage with interstitial fibrosis	Death
n/a	n/a	Interstitial pneumonitis	Death
10 mg load; 3 mg QD, then 5 mg QD, then 2 mg QD	31.9	Interstitial pneumonitis: restrictive defect, organizing pneumonia with fibrin filled air spaces, myxoid fibroblastic proliferation	Alive
n/a	n/a	Interstitial pneumonitis; pulmonary alveolar proteinosis (PAP); granulomatous lung disease	Alive
n/a	n/a	Interstitial pneumonitis; diffuse alveolar hemorrhage	Alive
n/a	11.2	Interstitial pneumonitis; BOOP	Alive
5 mg qd	9.7	Interstitial pneumonitis	Alive
n/a	8.3	Interstitial pneumonitis	Alive

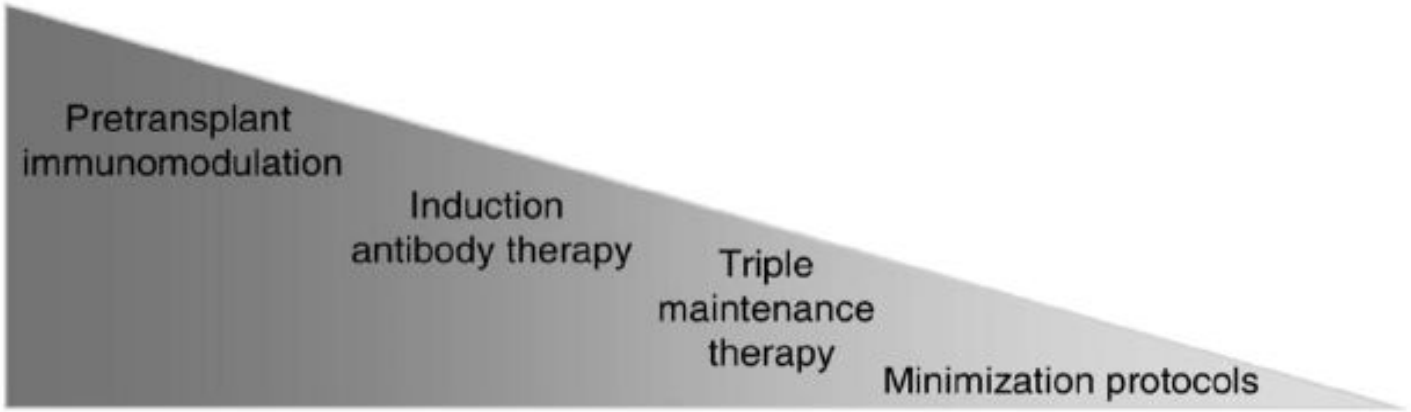
Dosage of sirolimus for adults

- No more than 2 mg/d
- No more than 8 ng/mL
- Combination use
- Further dose reduction if prolonged cough
- Patient selection:
  - Stable renal function with minimal proteinuria

Counterarguments: Ascertain and others….

- Conversion to everolimus with CNI minimization or elimination: no major benefit more Aes, discontinuation (Transplantation 92:410-418, 2011)
- Zeus: high rate of side effects, more rejection
- Higher overall DSA and AMR (AM J TR 12:1192-1198, 2012)
- US experience 1999-2010: graft loss and death markedly higher with mTor (HR=3.7) (Am J TR 13:100-110,2013)

Immunosuppression moving toward individualization based on immunologic risk



- **High Risk**
  - **Highly sensitized**
  - **Non-primary transplant**
  - **African American/Hispanic ethnicity**
  - **Deceased donor source**
  - **Poor HLA match**
- **Low Risk**
  - **Nonsensitized**
  - **Asian/Caucasian ethnicity**
  - **Elderly**
  - **Living donor source**
  - **Good HLA match**

Levy GA, Ther Drug Monit, 2010, 32, 3:246-249

Minimization vs. tailoring

Tailoring:

To modulate the amount of immunosuppression according to:

- Immunological or clinical risk factors (individualization)
- Drug exposure (TDM)
- Immune response:
  - surveillance biopsies
  - de novo DSA
  - antigen-specific or unspecific T-cell response
  - urinary biomarkers of inflammation

Transplantation: the Future

- Individualize drug combinations by assessing individual risk profile for that patient
- Withdraw or minimize immunosuppressive drugs as risk of rejection does decrease in time
- Once a major side effect develops switch to alternative agent
- Newer immunosuppressive agents with less toxicity
- Induce donor-specific immune tolerance