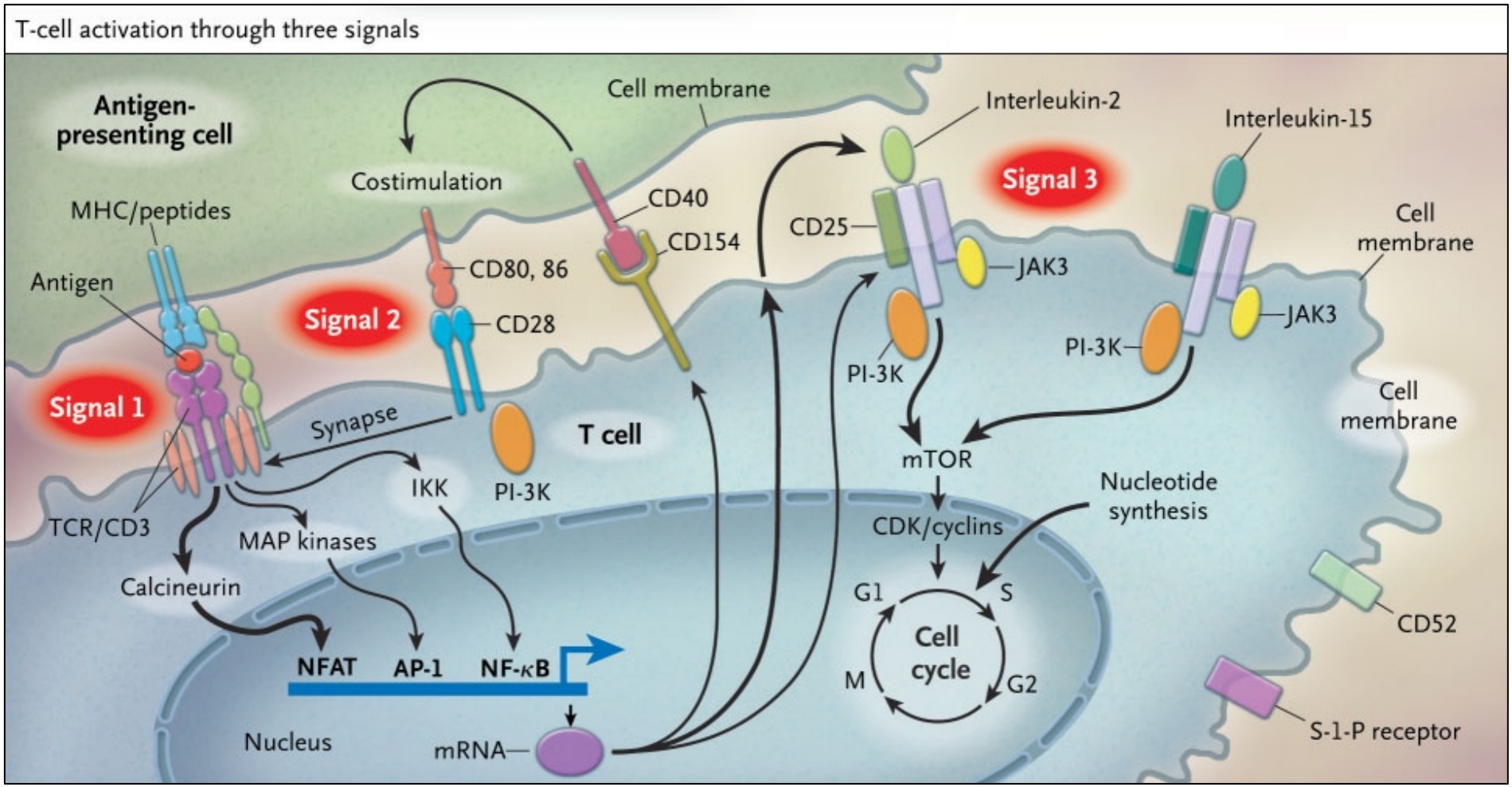
Nouveaux Traitements Immunosuppresseurs en Transplantation Rénale

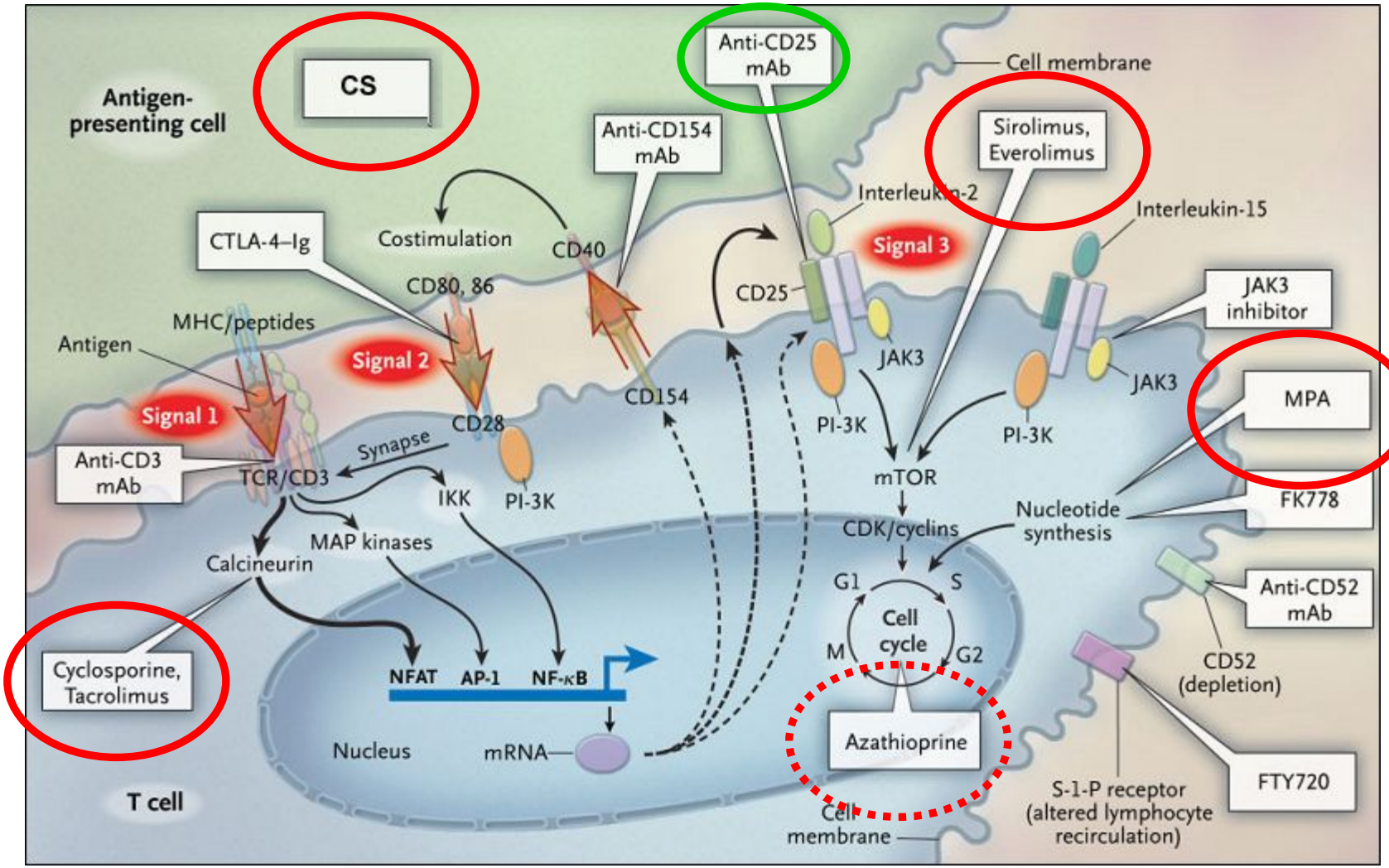
Jacques DANTAL
Institut ITUN. CHU Nantes

Sites d'action des immunosuppresseurs



Halloran P. N Engl J Med. 2004.

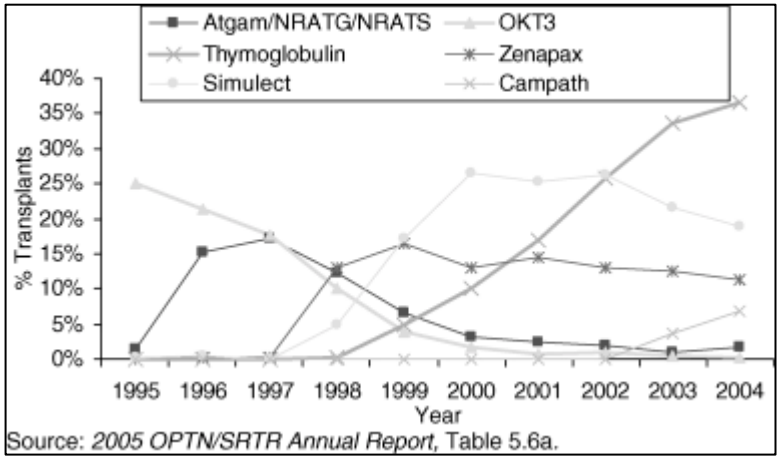
Sites d'action des immunosuppresseurs



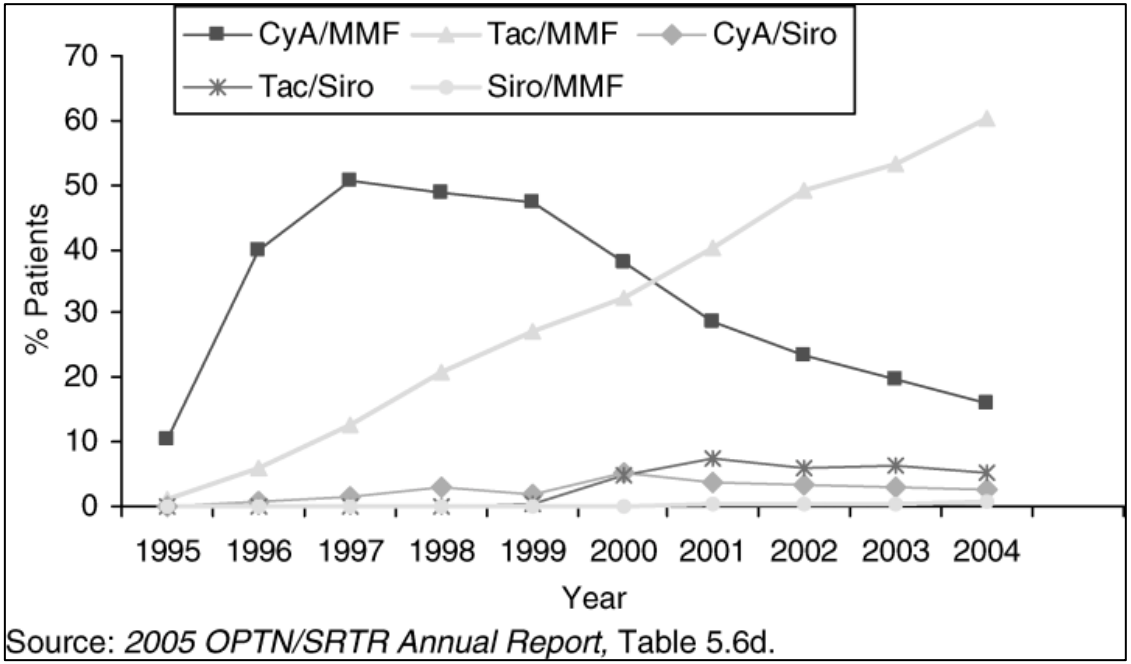
- ✓ AntiCD25
- ✓ ATG

Halloran P. N Engl J Med. 2004.

L’association la plus utilisée aujourd’hui est CNI-MMF



Source: *2005 OPTN/SRTR Annual Report*, Table 5.6a.

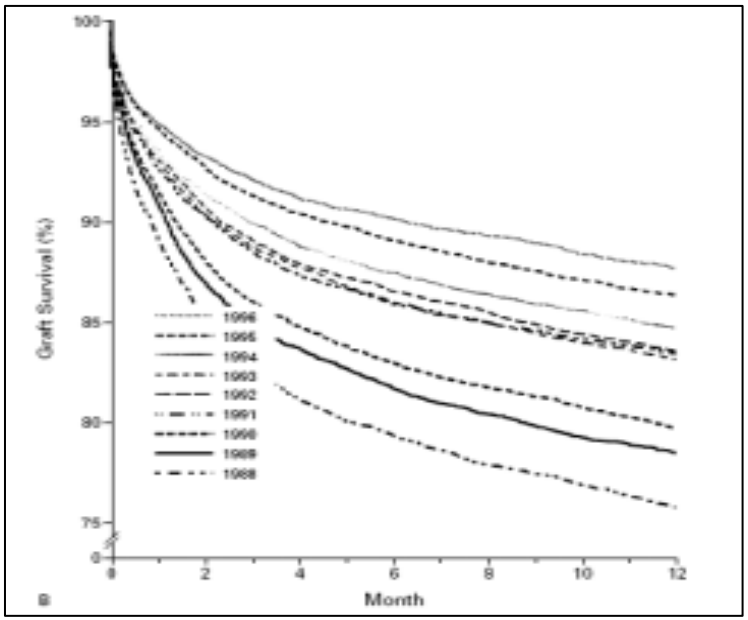


Source: *2005 OPTN/SRTR Annual Report*, Table 5.6d.

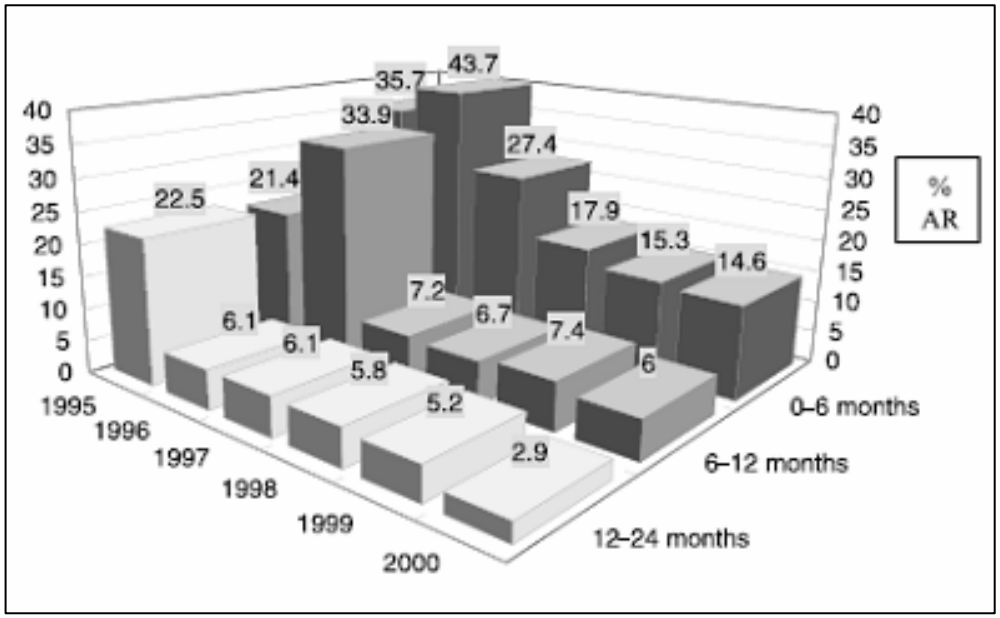
Meier-Kriesche et al. Am J Transplant. 2006.

L'association CNI-MMF a permis une amélioration des résultats

- ✓ Diminution de l'incidence des rejets aigus
- ✓ Augmentation de la survie à un an
- ✓ Augmentation de la survie du pt et greffon
- ✓ Malgré l'augmentation d'âge des D et R



Hariharan S et al, N Engl J Med, 2000.



Meier-Kriesche et al. Am J Transplant. 2004.

Oui mais… la satisfaction n'est que partielle car:

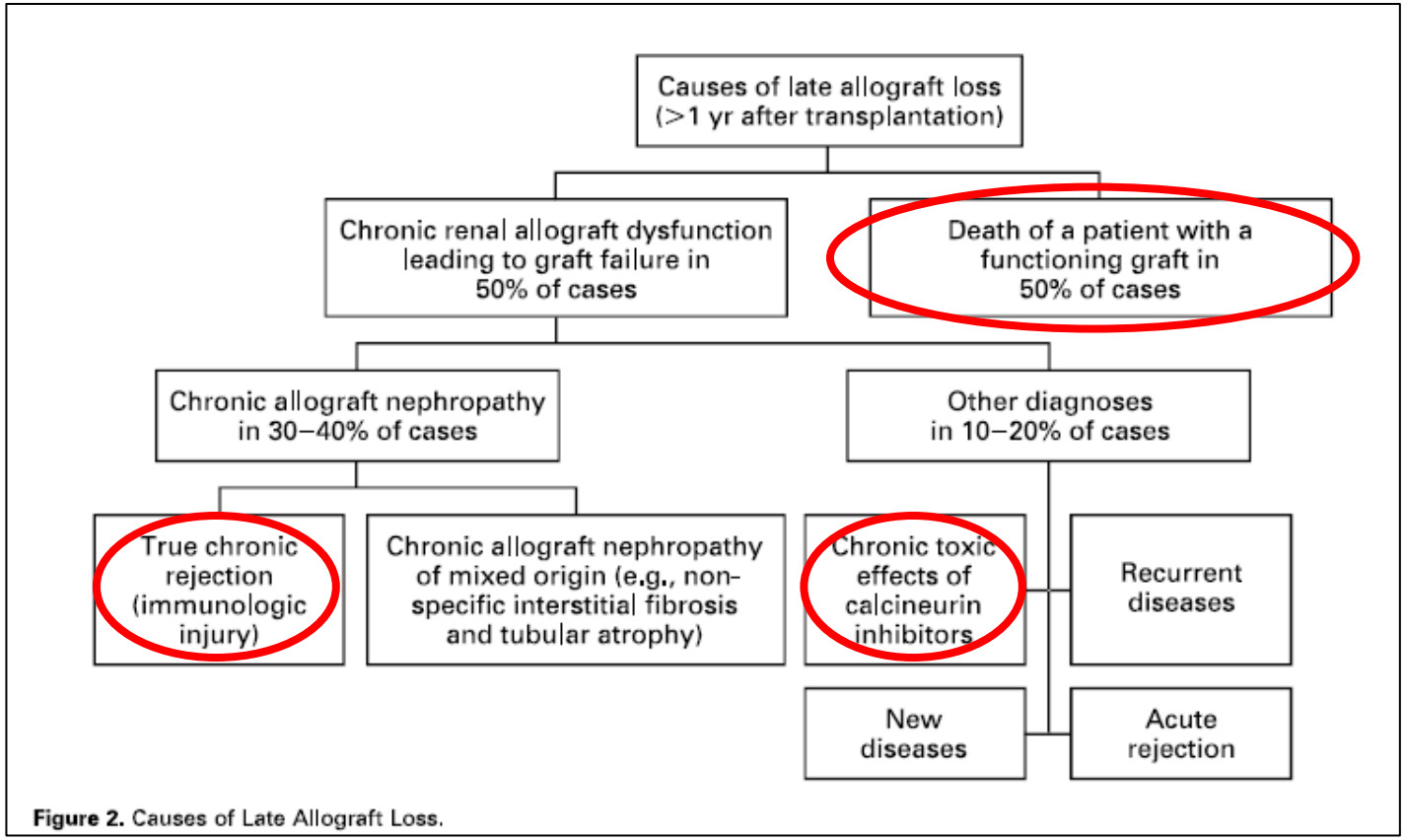
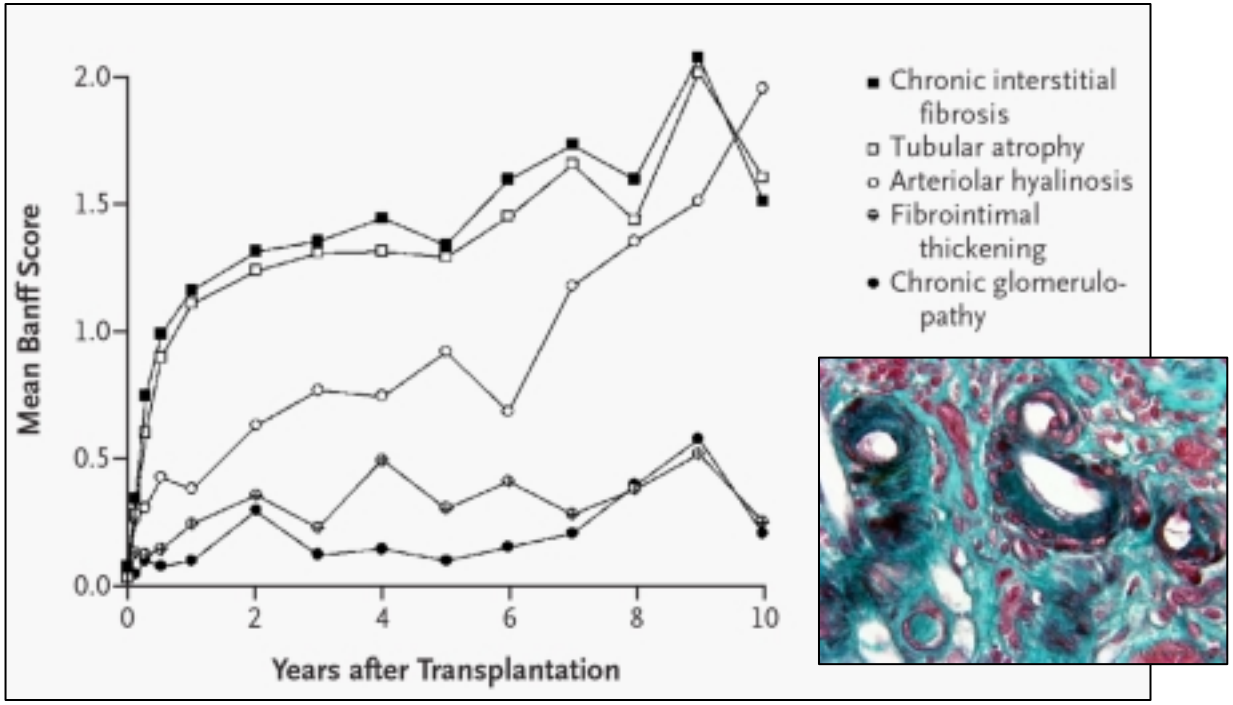
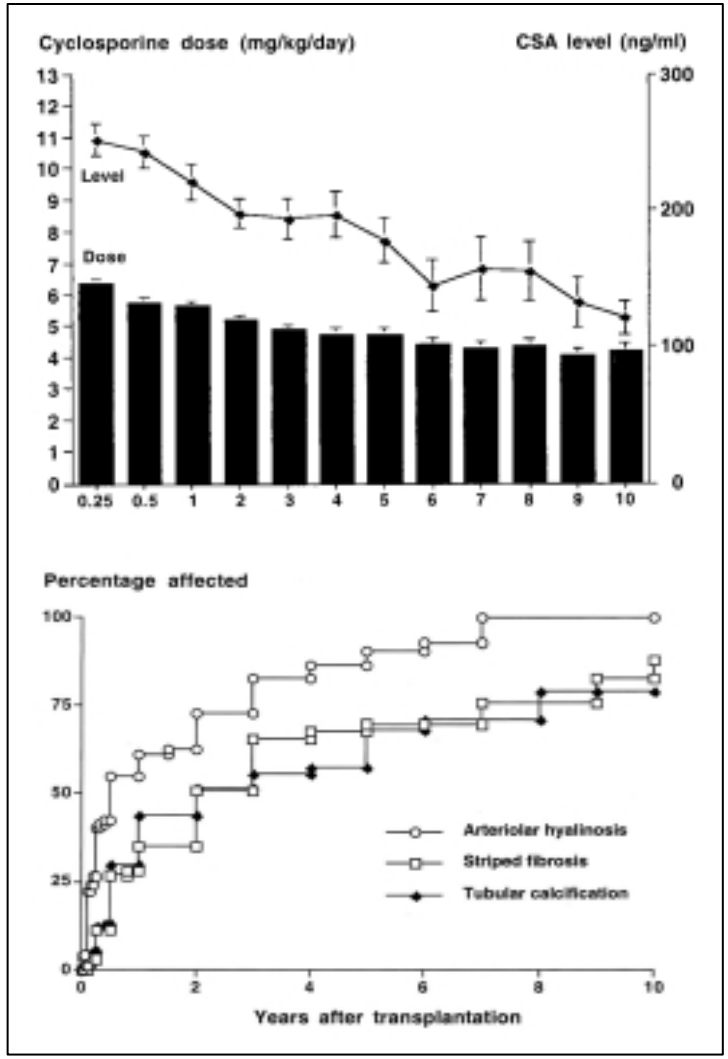


Figure 2. Causes of Late Allograft Loss.

Mazuecos et al. Transplant Int. 2009.

1) Les CNI sont néphrotoxiques

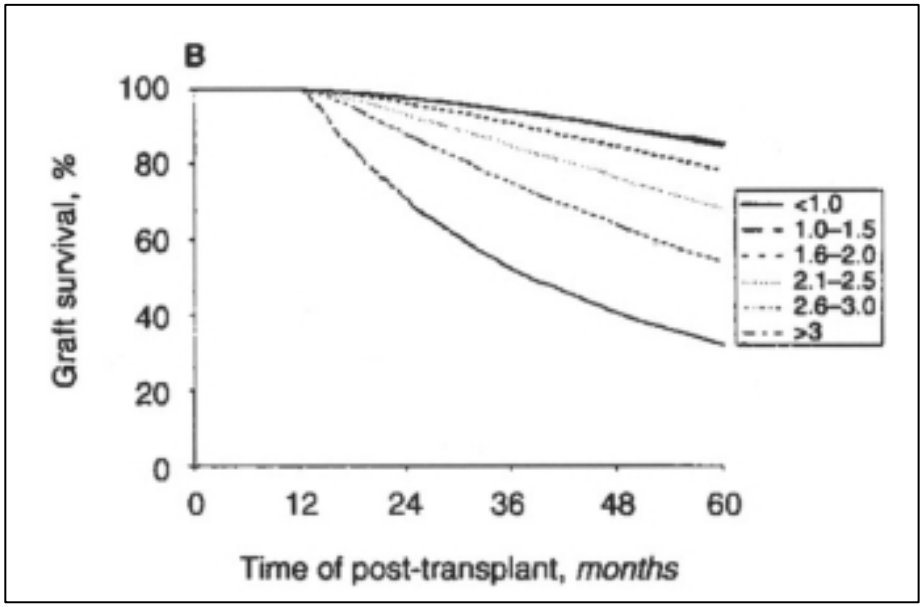




Mais aussi HTA,
Dyslipidémie,
Diabète

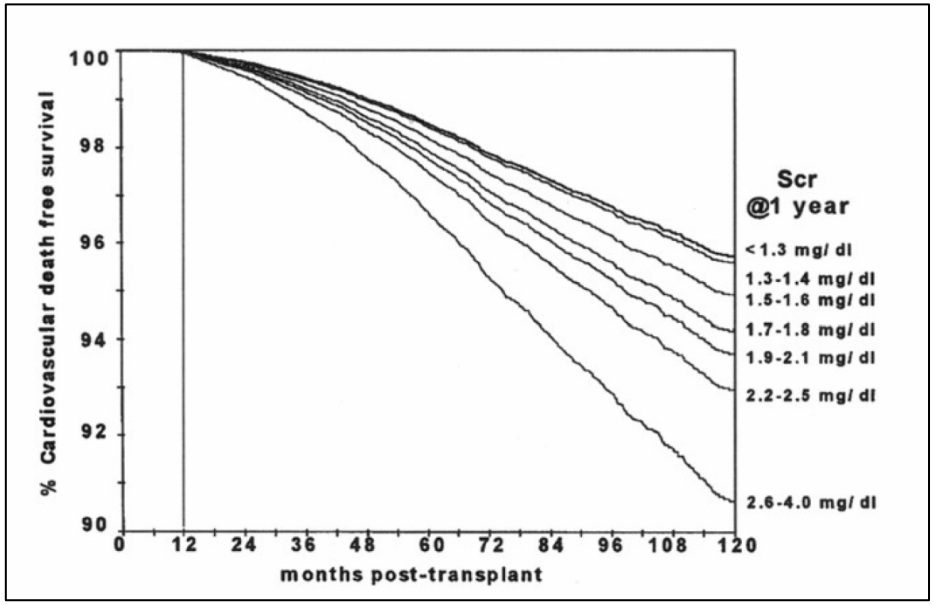
Nankivell B et al. N Engl J Med. 2003; Nankivell B et al. Transplantation. 2004.

1) La fonction rénale à un an est un facteur de survie du patient et du greffon



Survie du greffon

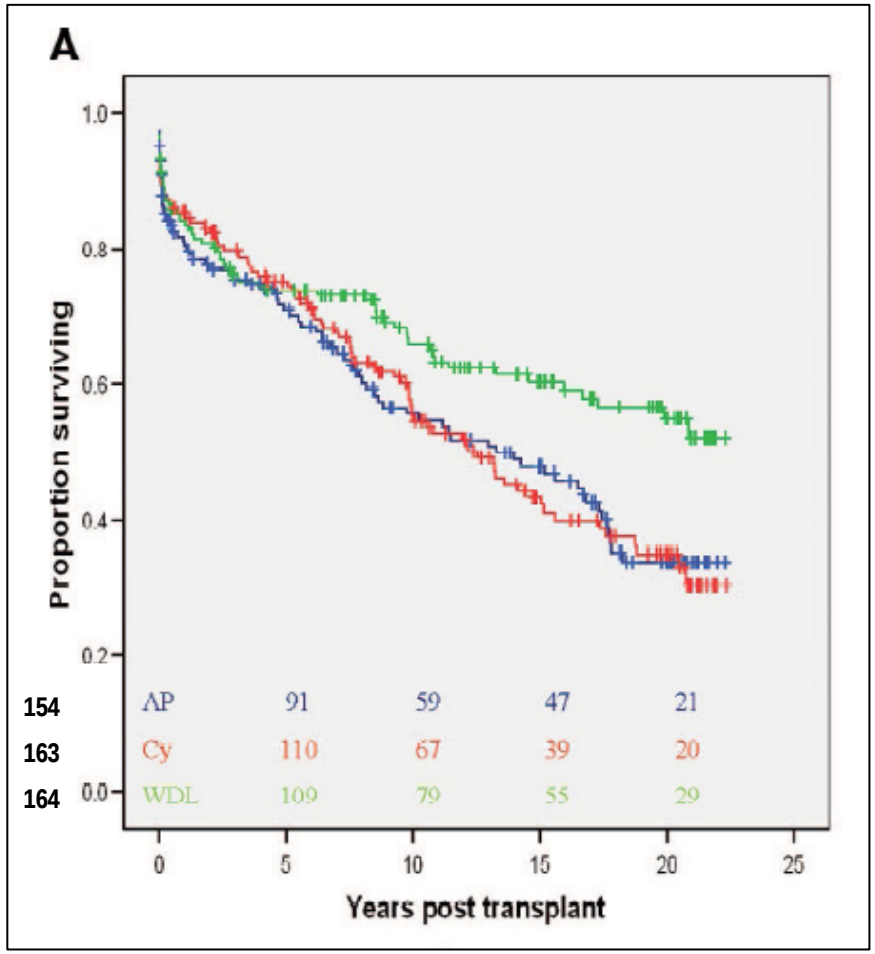
Hariharan S et al. Kidney Int. 2002.

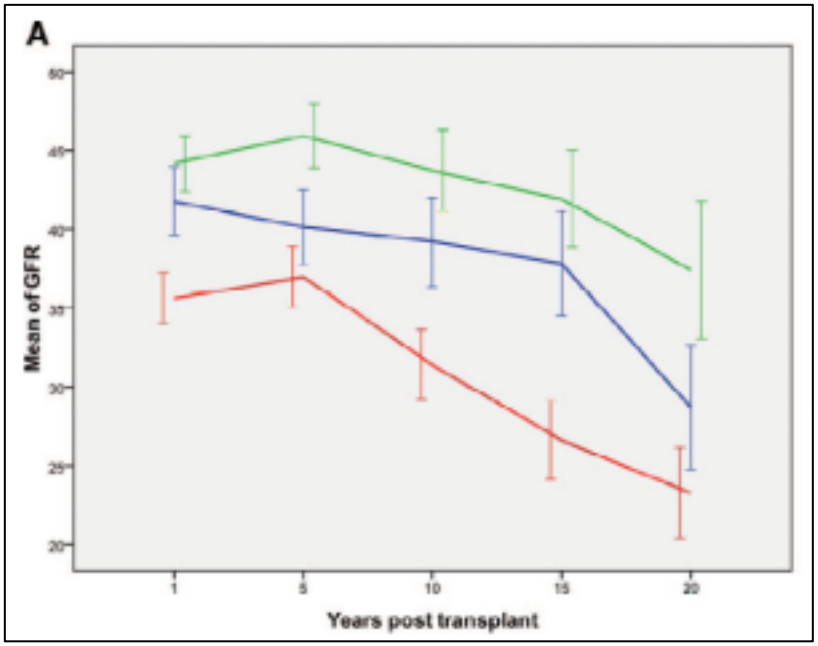


Mortalité secondaire à des événements cardio-vasculaire

Meier Kriesche H et al. Am J Transplant.2004.

2) Les CNI sont ne permettent pas d'amélioration de la survie du greffon au long terme (1)

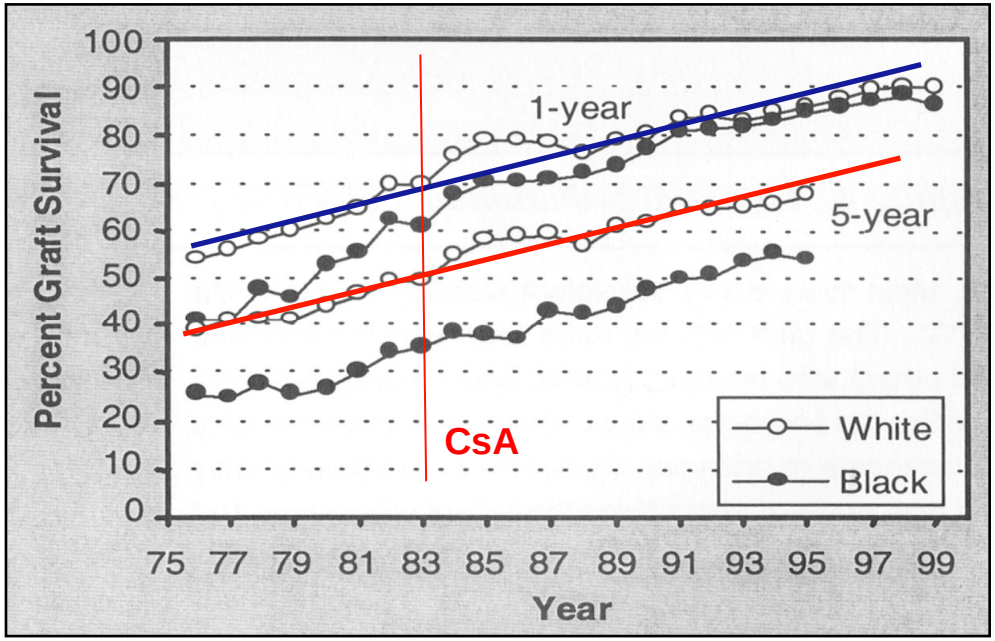


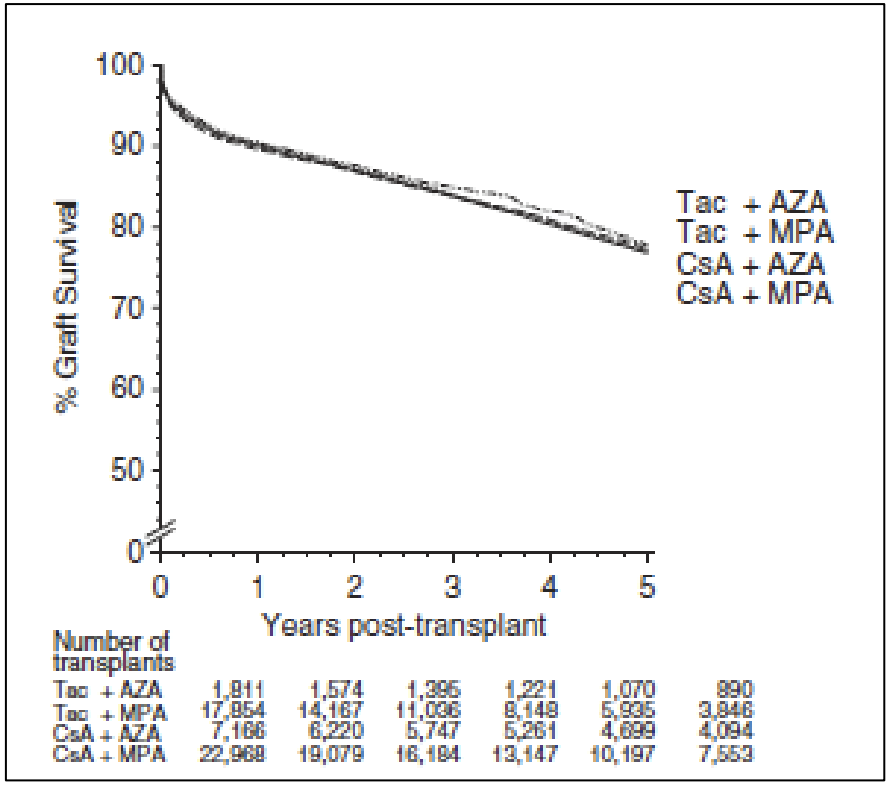


- ✓ Etude randomisée entre 1983 et 1986
- ✓ CS-AZA vs CsA vs arrêt CsA à 3mois
- ✓ Résultats en ITT
- ✓ Censure pour les décès

Gallagher M et al. Transplantation. 2009.

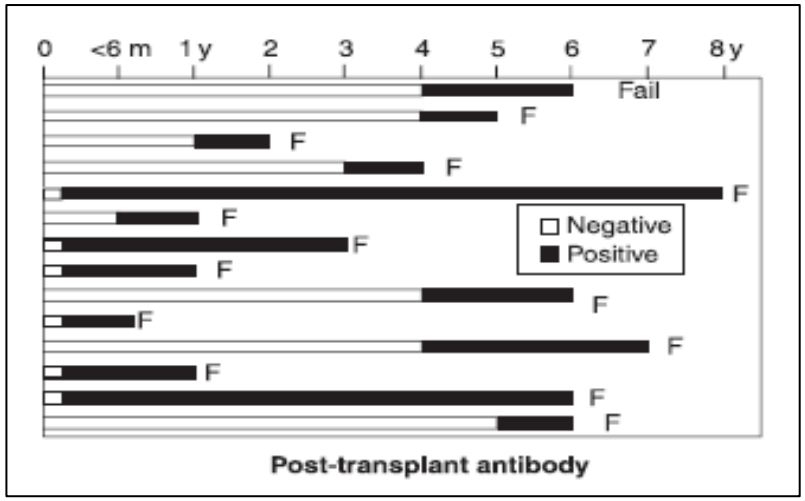
2) Les CNI sont ne permettent pas d'amélioration de la survie du greffon au long terme (2)



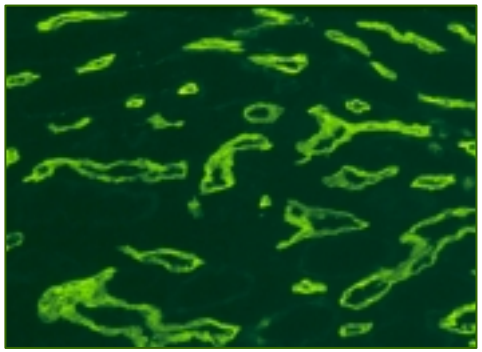


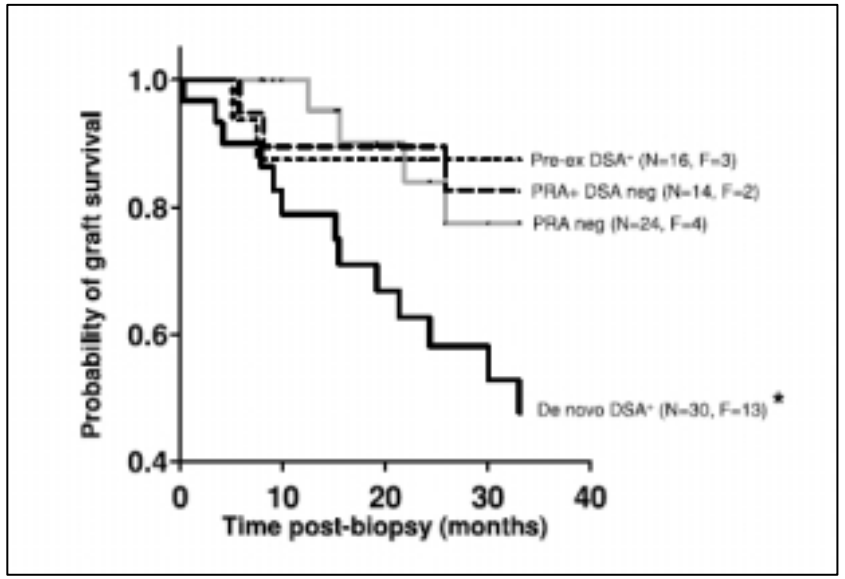
Opelz G et al. Transplantation. 2009.

3) Les stratégies immunosuppressives actuelles ne ciblent pas suffisamment la production d'anticorps anti-donneur

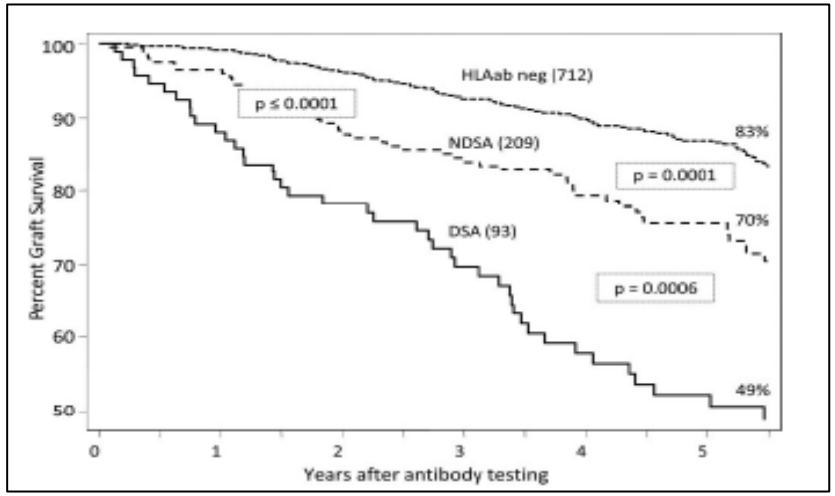


Terasaki P et al. Am J Transplant. 2003.





Hidalgo L et al. Am J Transplant. 2009.



Lachmann N et al. Transplantation. 2009.

4) Les stratégies immunosuppressives actuelles favorisent le développement des néoplasies

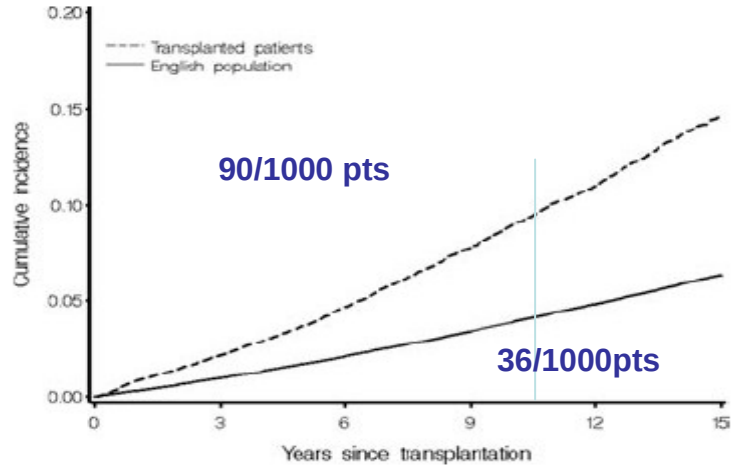


Figure 1: Overall cumulative incidence of any *de novo* cancer (excluding nonmelanoma skin cancer) in the transplanted and general populations.

Cause of Death	Early Deaths (≤1 Year)* 1984–1995 (n = 74)	Early Deaths (≤1 Year)* 1996–2007 (n = 109)	Late Deaths (>1 Year)† 1984–1995 (n = 235)	Late Deaths (>1 Year)† 1996–2007 (n = 165)
Cardiovascular	20.3	22.9	35.3	24.8
Infection	40.5	40.4	14	17
Malignancy	2.7	6.4	20	29.7
Hepatic	2.7	1.8	11.1	3
Other	25.7	20.2	10.2	12.7
Unknown	8.1	8.3	9.4	12.7

Data are presented as percentages.
*No significant difference.
†$P = .004$.

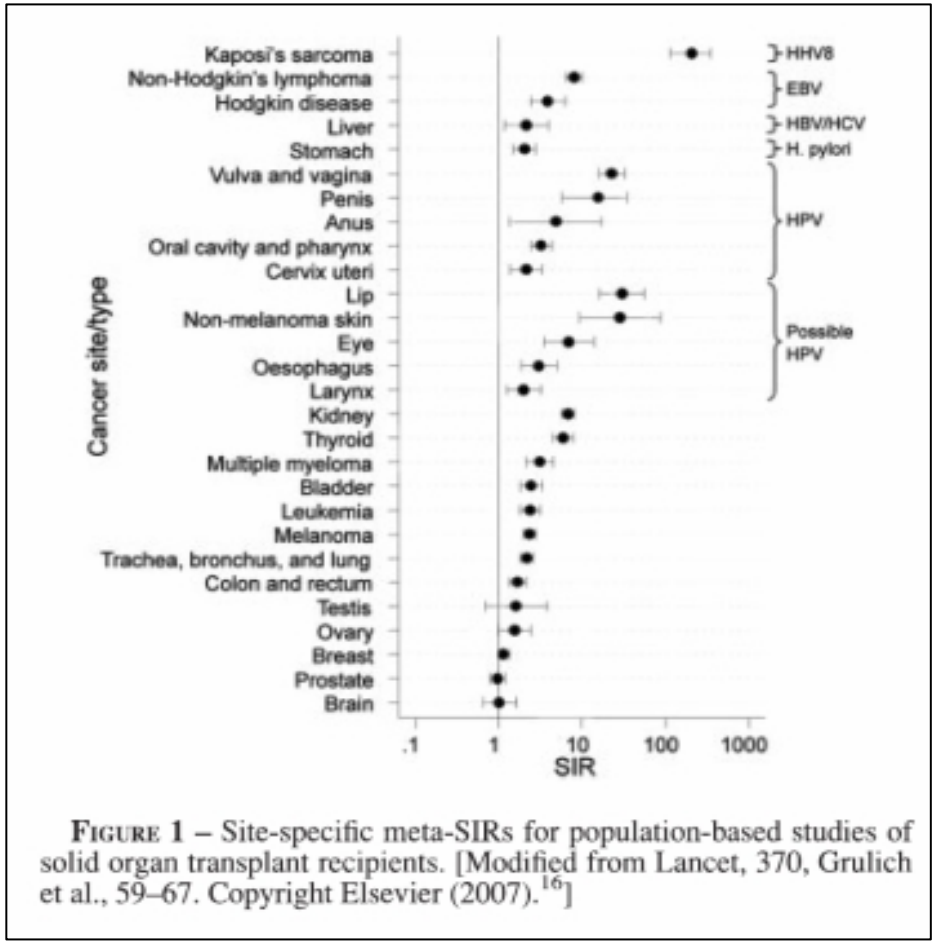
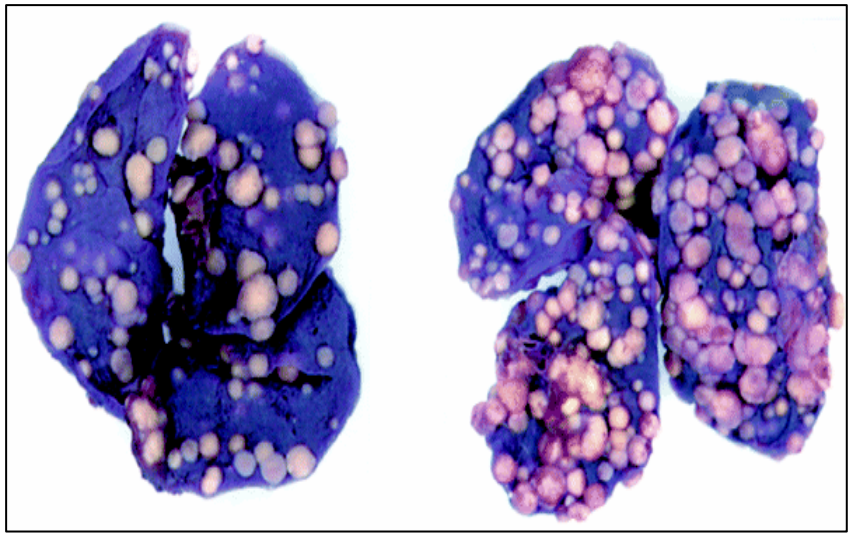


FIGURE 1 – Site-specific meta-SIRs for population-based studies of solid organ transplant recipients. [Modified from Lancet, 370, Grulich et al., 59–67. Copyright Elsevier (2007).[16]]

Mazuecos et al, Transplant Int, 2009
Collett D et al. Am J Transplant. 2010.
Vajdic C et al. Int J Cancer, 2009

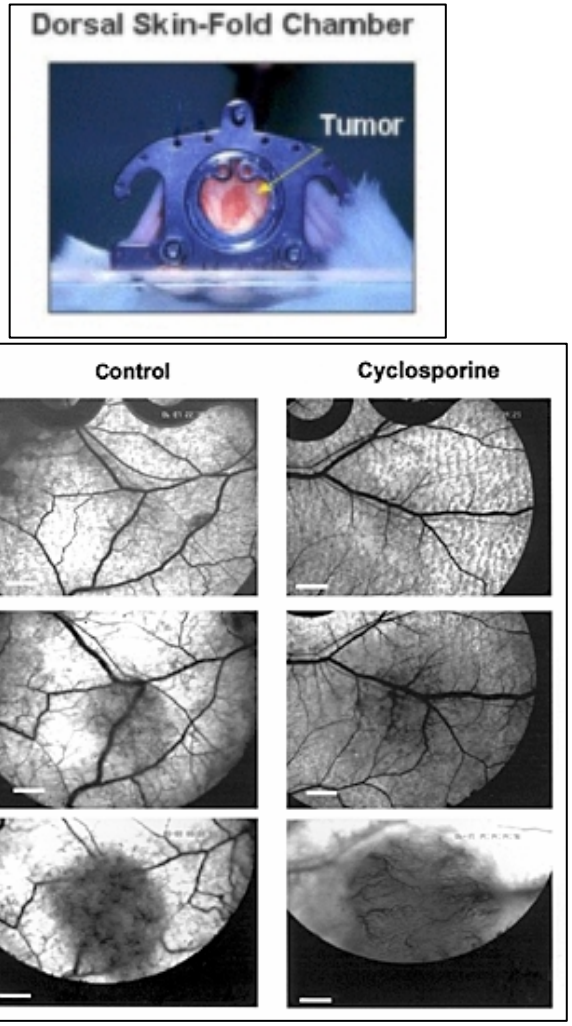
4) Les CNI sont fortement impliquées dans le développement des cancers post transplantation (1)

Souris SCID-Beige,
Injection IV de cellules néoplasiques
Sacrifice J19-23.



Augmentation dissémination métastatique

Hojo M et al. Nature. 1999.



Guba M et al. Nature Med. 2002.

4) Les CNI sont fortement impliquées dans le développement des cancers post transplantation (2)

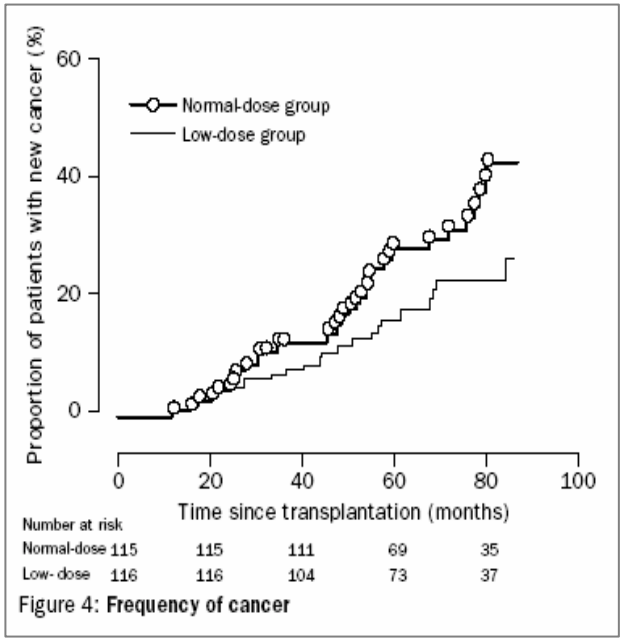
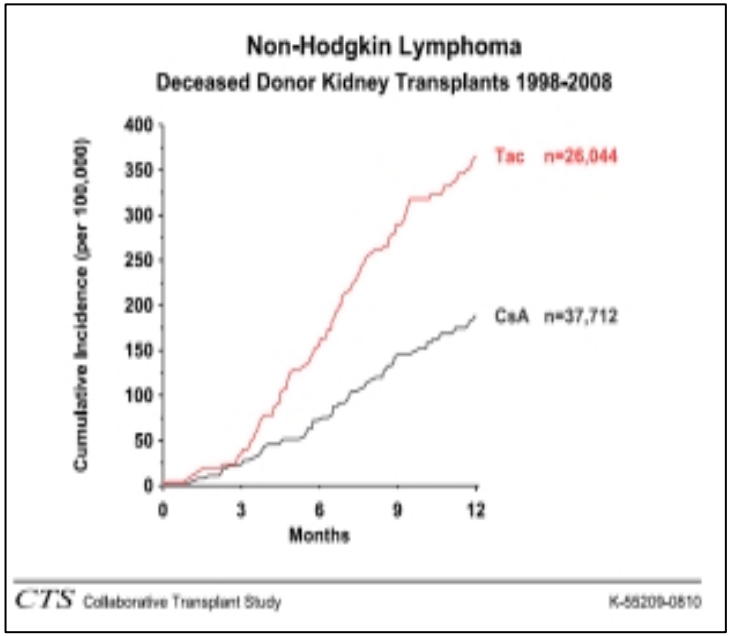
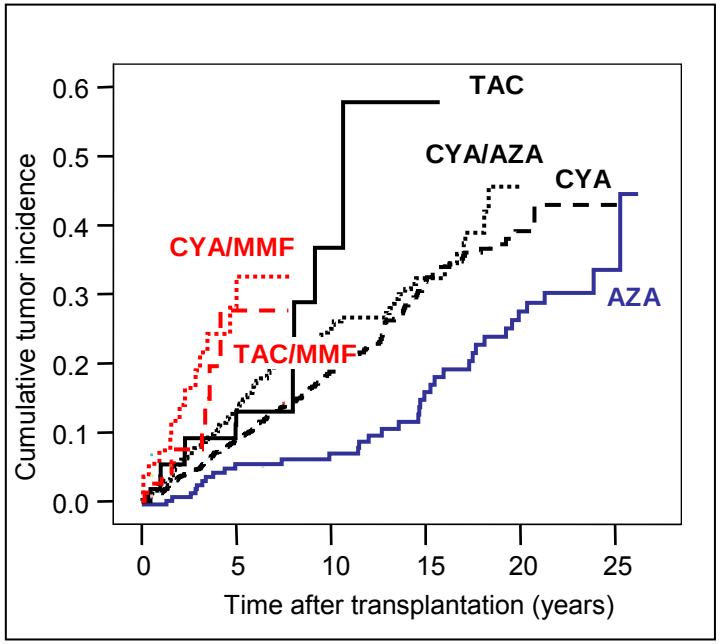


Figure 4: **Frequency of cancer**

Dantal J et al. Lancet. 1998.



Opelz G et al, CTS registry
http://www.ctstransplant.org/

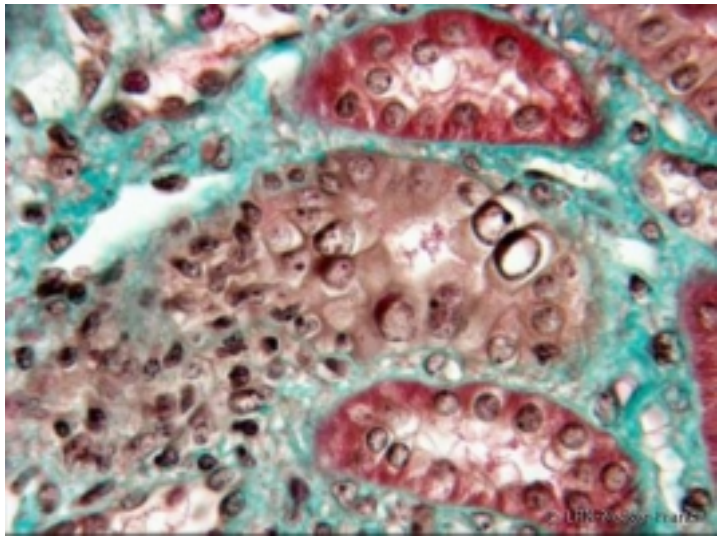


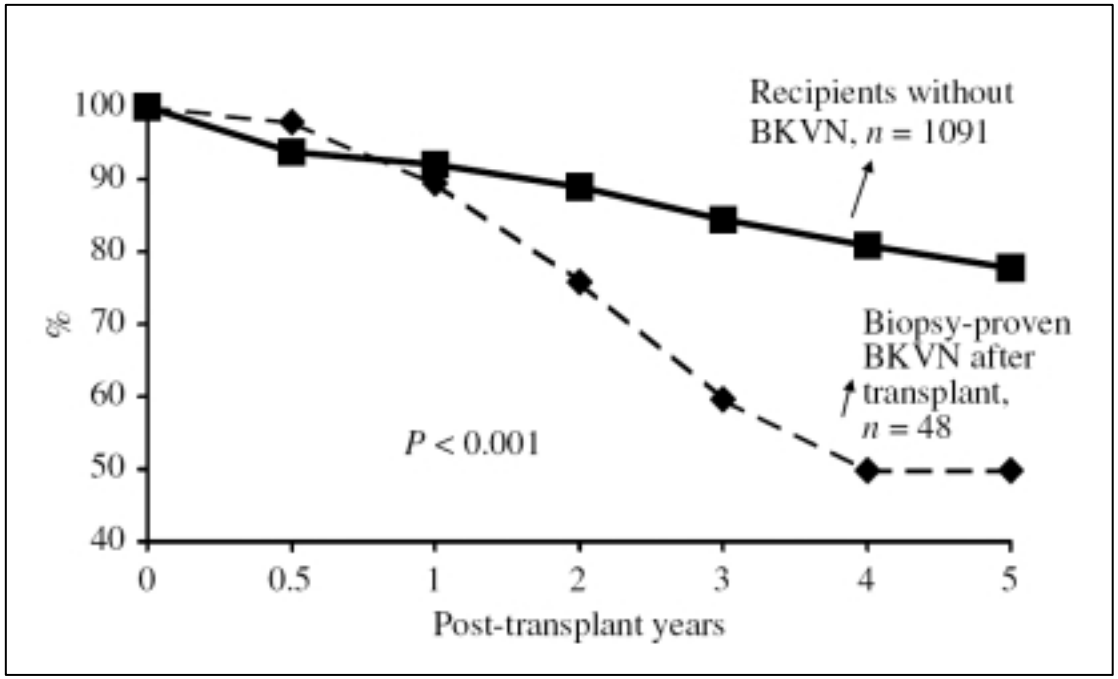
Wimmer et al. Kidney Int. 2007

5) L'immunosuppression est limitée par des complications infectieuses

- ✓ Prophylaxie: CMV…pneumocystose…

- ✓ Infection à BKV (polyomaV.)
- ✓ Virémie 12% à un an
- ✓ Diminution du TTT IS

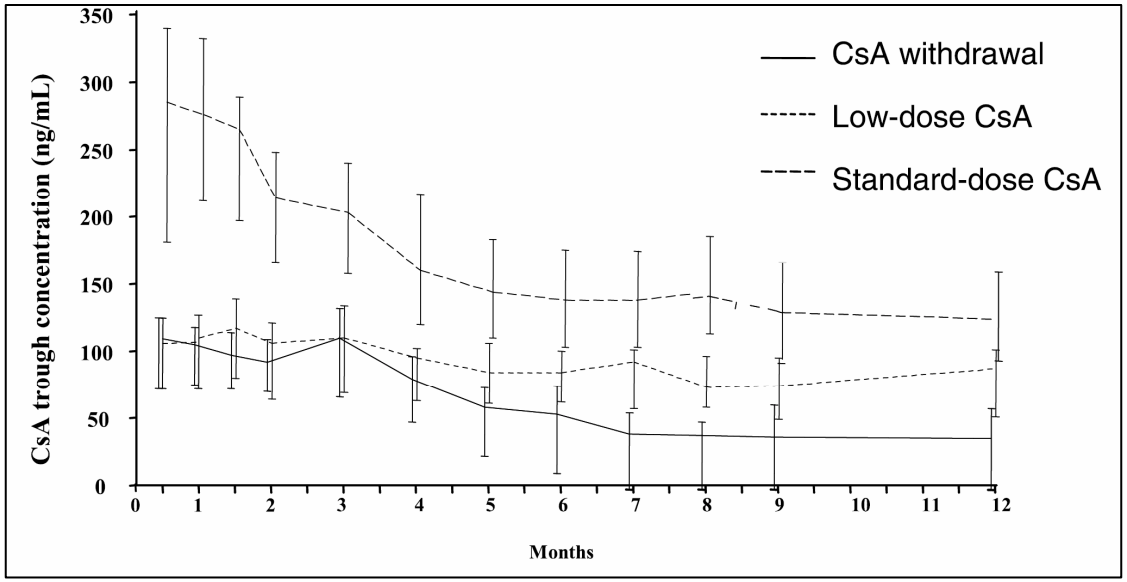


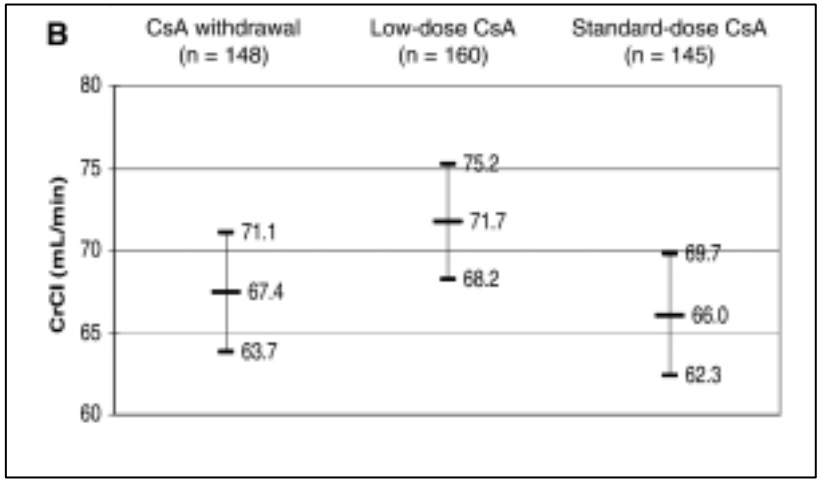


Hariharan S. Kidney int. 2006

6) Les études récentes avec arrêt des CNI montrent des résultats non satisfaisants

- ✓ Etude Caesar
- ✓ Recevant tous Dac, MMF et CS
- ✓ 3 groupes
  - ✓CsA diminuée à 4M arrêt 6M
  - ✓CsA low dose
  - ✓CsA std



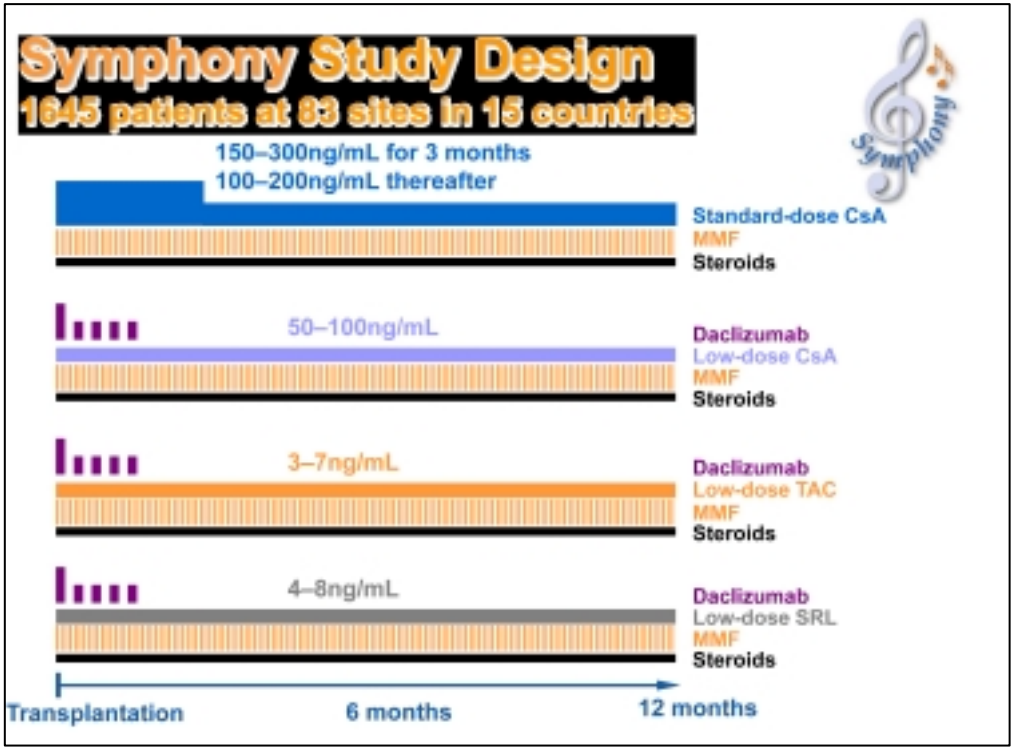


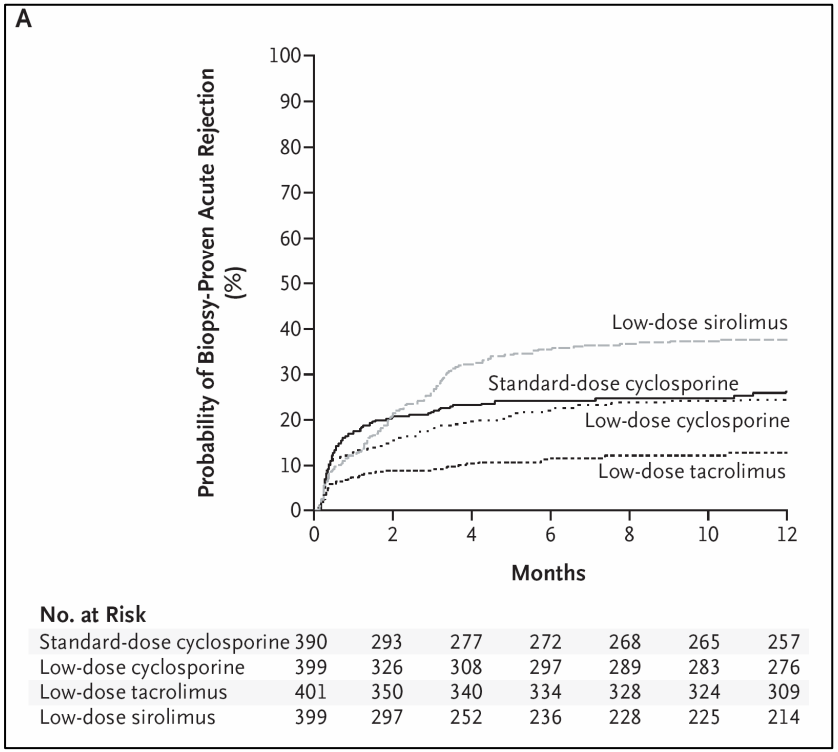
	CsA withdrawal (n = 179)	Low-dose CsA (n = 183)	Standard-dose CsA (n = 173)	p-value
Patient survival (%)	95.5	97.8	97.1	NS[1]
Graft survival censored for patient death (%)	93.3	96.7	94.8	NS[1]
Graft survival not censored for patient death (%)	89.3	94.5	92.4	NS[1]
Delayed graft function (%)[2]	16.8	20.2	22.5	ND
BPAR (%)				
6 months	24.7	24.2	26.2	NS
12 months	38	25.4	27.5	Withdrawal vs. low-dose 0.027 vs. standard-dose 0.04

= en faveur d'un traitement « CsA low dose »

Ekberg H et al. Am J Transplant. 2007

7) La minimisation des CNI reste l'option de préférence



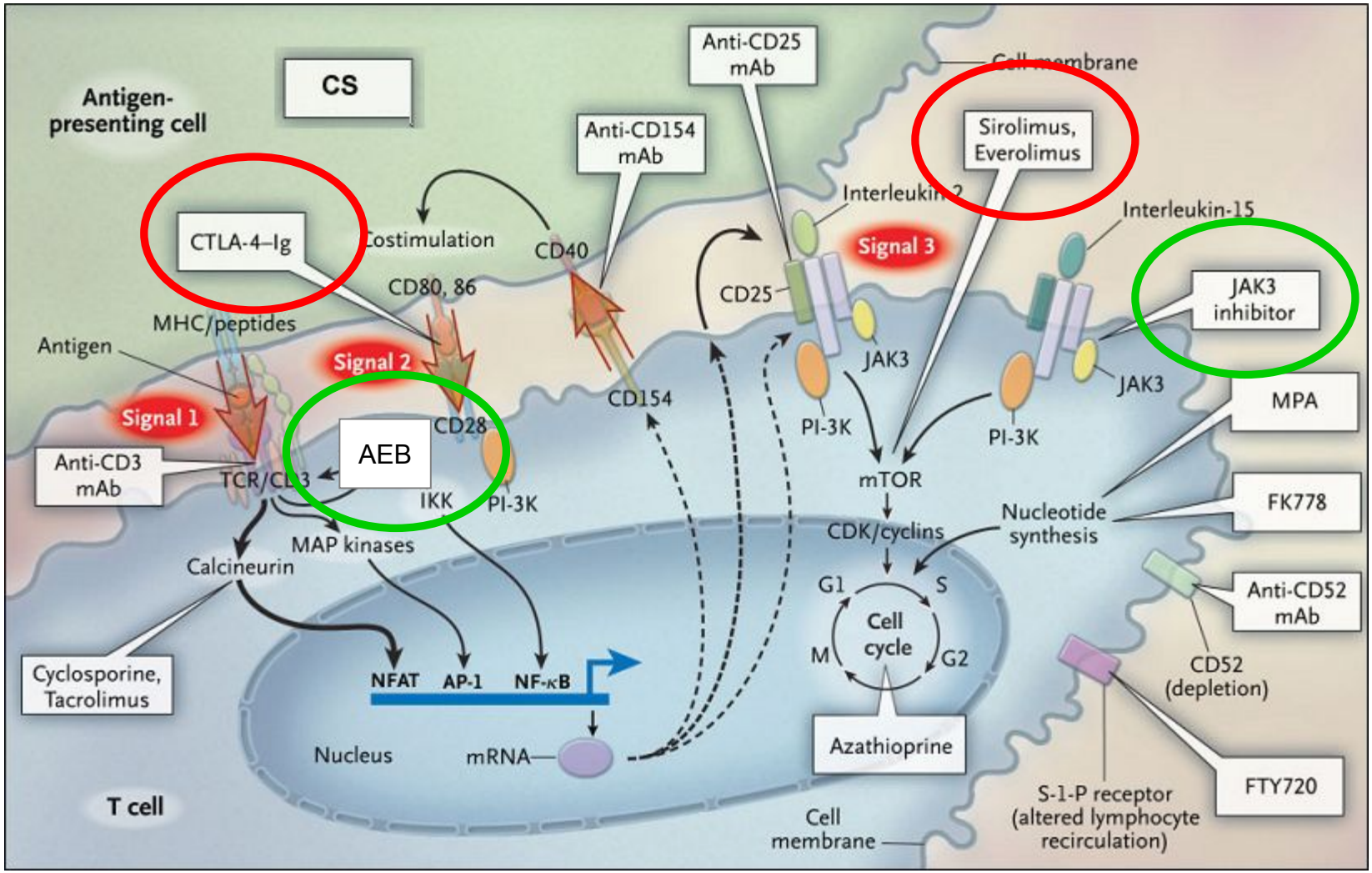


End Point	Standard-Dose Cyclosporine (N=390)	Low-Dose Cyclosporine (N=399)	Low-Dose Tacrolimus (N=401)	Low-Dose Sirolimus (N=399)	P Value†
Primary end point					
Mean calculated GFR — ml/min‡	57.1±25.1	59.4±25.1	65.4±27.0	56.7±26.9	<0.001
P value for comparison with tacrolimus	<0.001	0.001	Reference	<0.001	
Secondary end points					
Mean calculated GFR — ml/min¶	46.2±23.1	50.2±23.1	54.3±23.9	47.5±26.1	<0.001
Allograft survival‖					
Censored for death of patients with functioning allograft — %	91.9	94.3	96.4	91.7	0.02

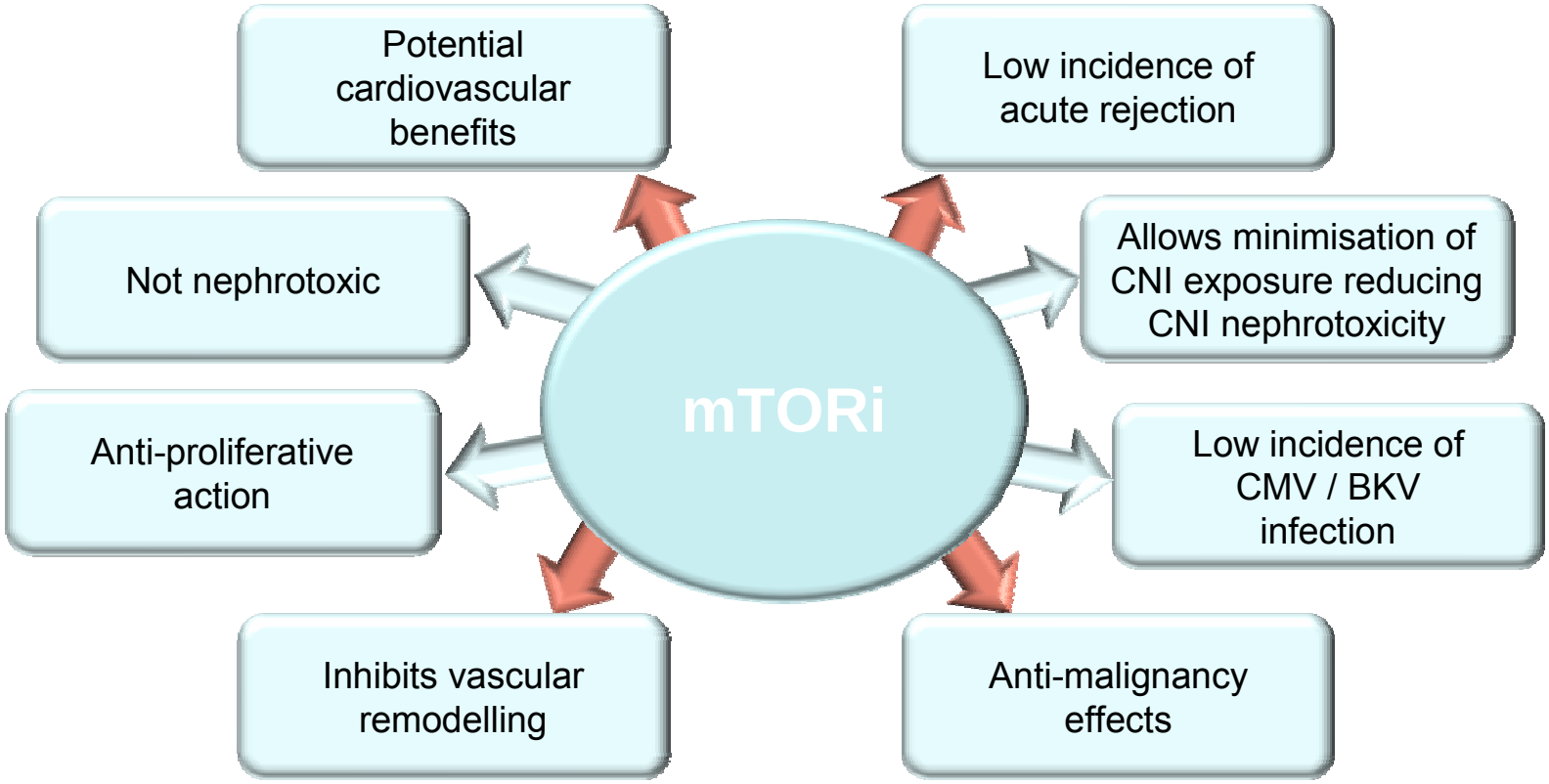
En faveur du « Low Tac-MMF »
Quelque soit les sous-groupes
Maintien des résultats à 3 ans
Plus de NODAT (<3% de TTT)

Ekberg H et al. N Engl J Med. 2007
Ekberg H et al. Am J Transplant. 2009

Les nouveaux immunosuppresseurs peuvent-ils améliorer les résultats de la transplantation?



Les intérêts des inhibiteurs de mTOR



La minimisation des CNI avec les ImTOR

- ✓ Garder une immunosuppression efficace (synergie) et évitant la néphrotoxicité
- ✓ Inhibiteurs mTOR : Sirolimus (Rapamune®) Everolimus (Certican®)

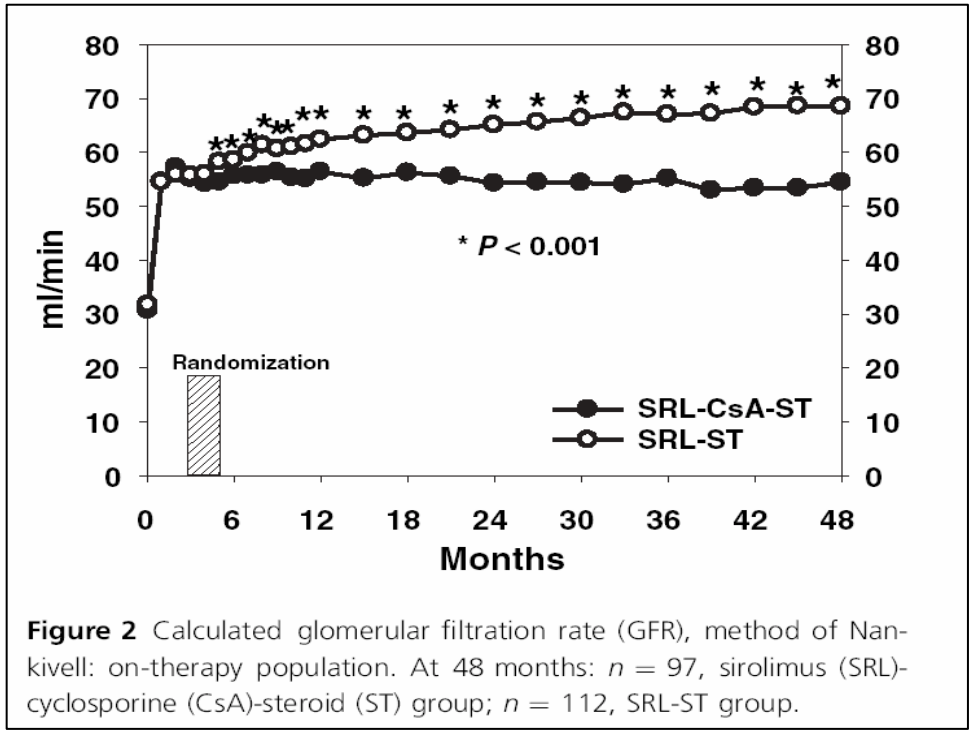


Figure 2 Calculated glomerular filtration rate (GFR), method of Nankivell: on-therapy population. At 48 months: $n = 97$, sirolimus (SRL)-cyclosporine (CsA)-steroid (ST) group; $n = 112$, SRL-ST group.

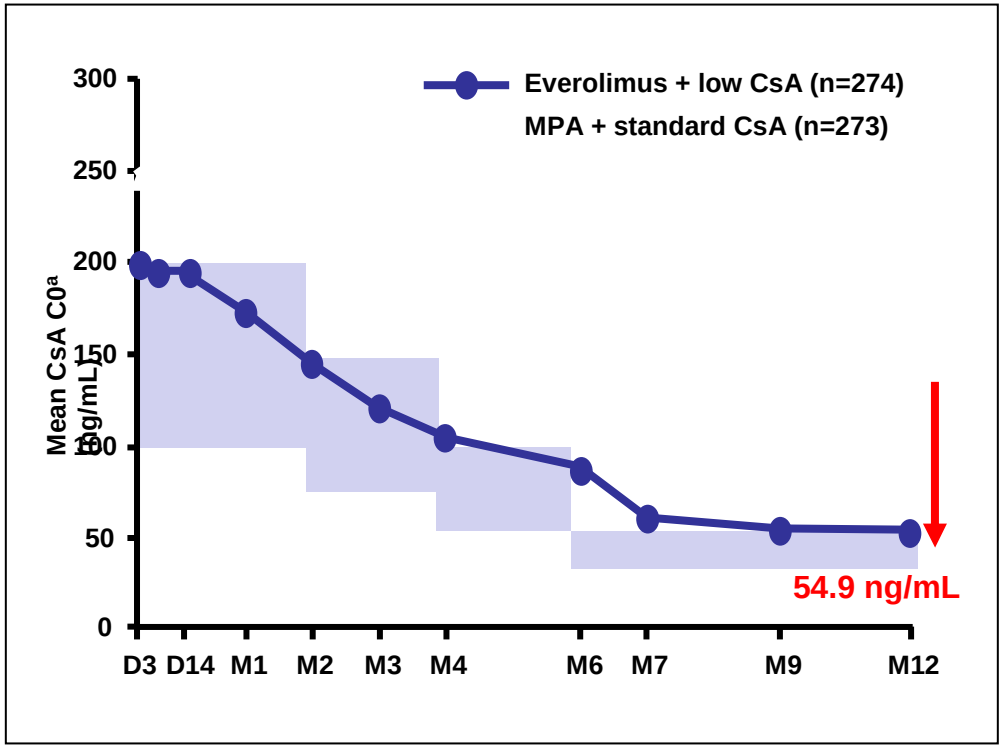
Oberbauer R et al. Transplantation Int. 2005,

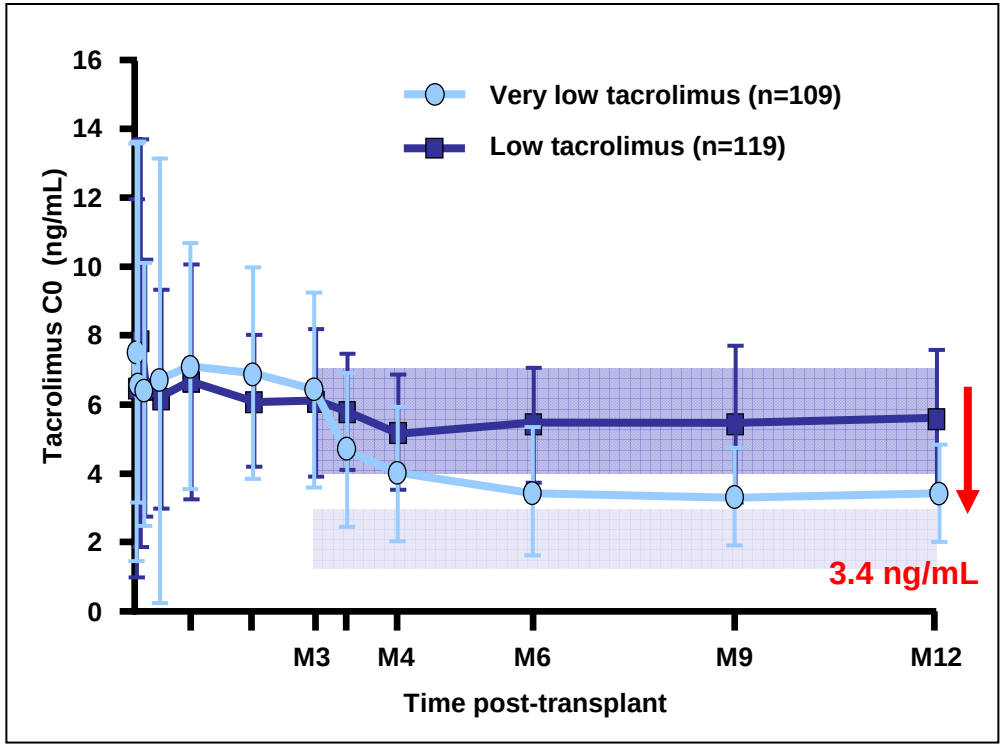
Outcomes	Total	MMF	SRL	p-value
Composite endpoint, n (%)	17 (17)	9 (18)	8 (16)	1.000
First treated acute rejection, n (%)	20 (20)	10 (20)	10 (20)	1.000
First treated biopsy-confirmed acute rejection, n (%)	13 (13)	6 (12)	7 (14)	1.000
Banff IA, n (%)	4 (4)	2 (4)	2 (4)	
Banff IB, n (%)	2 (2)	0 (0)	2 (4)	
Banff IIA, n (%)	6 (6)	3 (6)	3 (6)	
Banff IIB, n (%)	1 (1)	1 (2)	0 (0)	
	Total	MMF	SRL	p-value
Creatinine (mg/dL)	1.5 ± 0.4	1.4 ± 0.3	1.6 ± 0.5	0.007
Creatinine clearance (mL/min)	65.4 ± 16.8	67.6 ± 16.4	63.4 ± 17.1	0.234
Proteinuria (g/L)	0.2 ± 0.4	0.1 ± 0.2	0.3 ± 0.5	0.012
Patients with proteinuria, n (%)	16 (30.2)	3 (10.7)	13 (52.0)	0.041
Patients without proteinuria, n (%)	37 (69.8)	25 (89.3)	12 (48.0)	
Time to first biopsy-confirmed acute rejection (days)	38.5 ± 79.1	12.3 ± 19.4	60.9 ± 104.5	0.287
Death, n (%)	4 (4)	3 (6)	1 (2)	0.617
Graft loss, n (%)	1 (1)	1 (2)	0	1.000
Patient survival (%)	96	94	98	0.308
Graft survival (%)	95	92	98	0.168
Death censored graft survival (%)	99	98	100	0.317

Sampaio E et al. Clin Transplantation. 2008.

La minimisation des CNI avec les ImTOR (2)

✓ Inhibiteurs mTOR : Everolimus (Certican®)

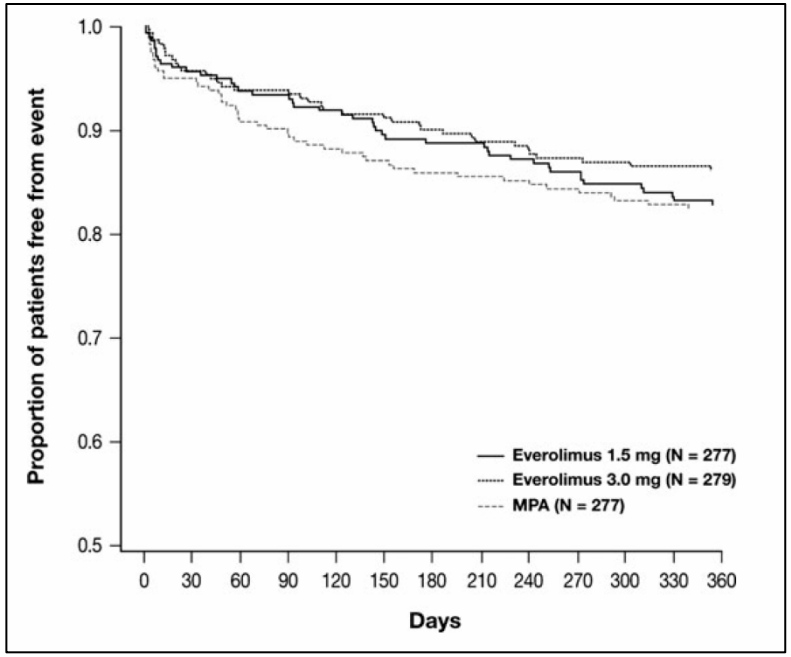


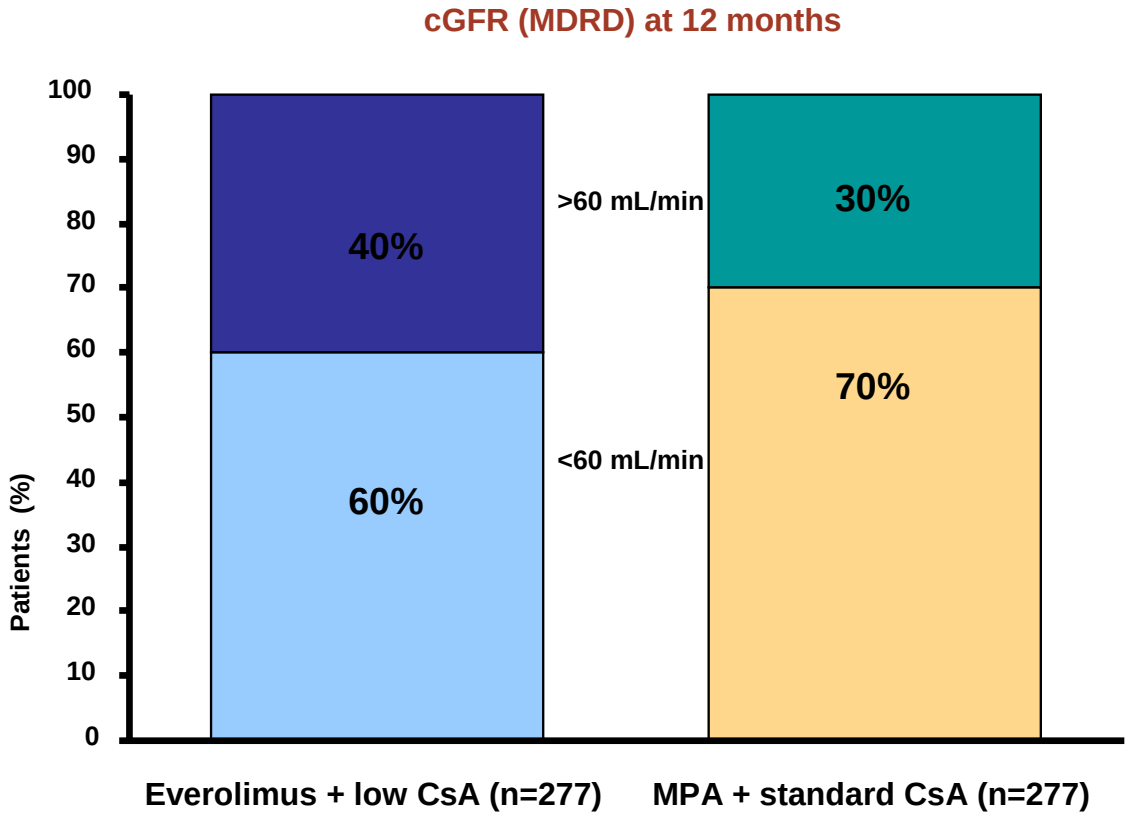


Tedesco-Silva J et al. Am J Transplant. 2010.

Vitko S et al. Oral presentation at ESOT 2009

La minimisation des CNI avec les ImTOR (3)





Etude ASSET

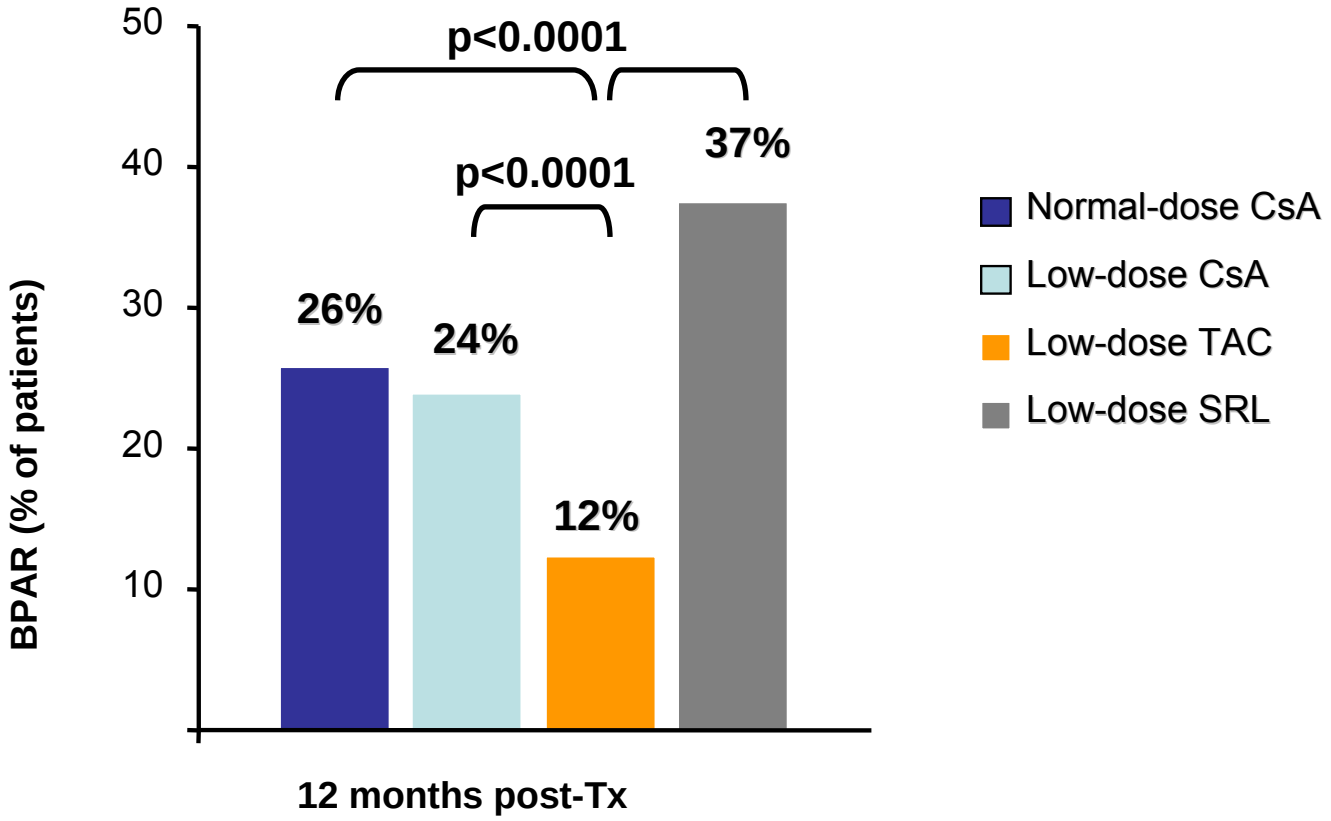
Etude Everest…

Tedesco-Silva J et al. Am J Transplant. 2010.

L'initiation de novo d' ImTOR sans CNI n'est pas efficace en phase initiale de transplantation.

- ✓ SRL de novo avec MMF, CS et anti-IL2R = Augmentation d'incidence des rejets

- ✓ **ORION = 29.6%**
- ✓ **SYMPHONY = 37%**



L'initiation de novo d' ImTOR sans CNI peut être efficace en phase initiale de transplantation si le traitement est renforcé.

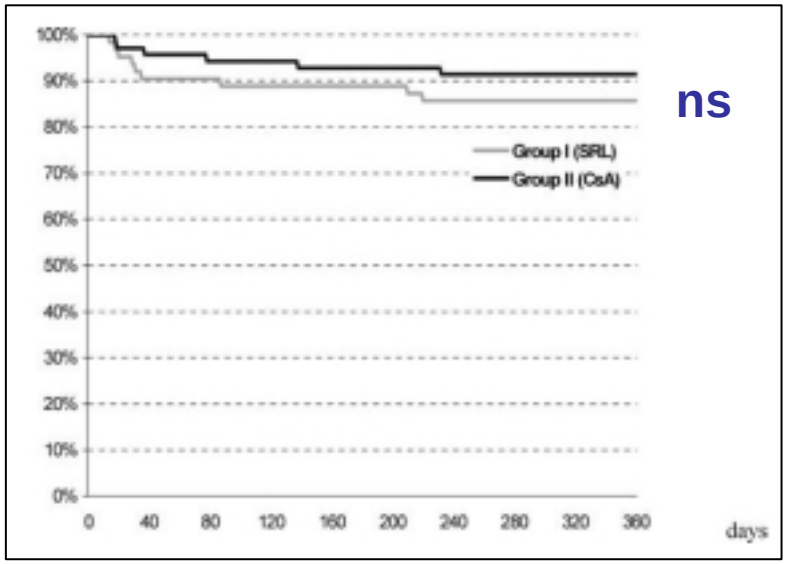
145 pts

ATG 5 jours

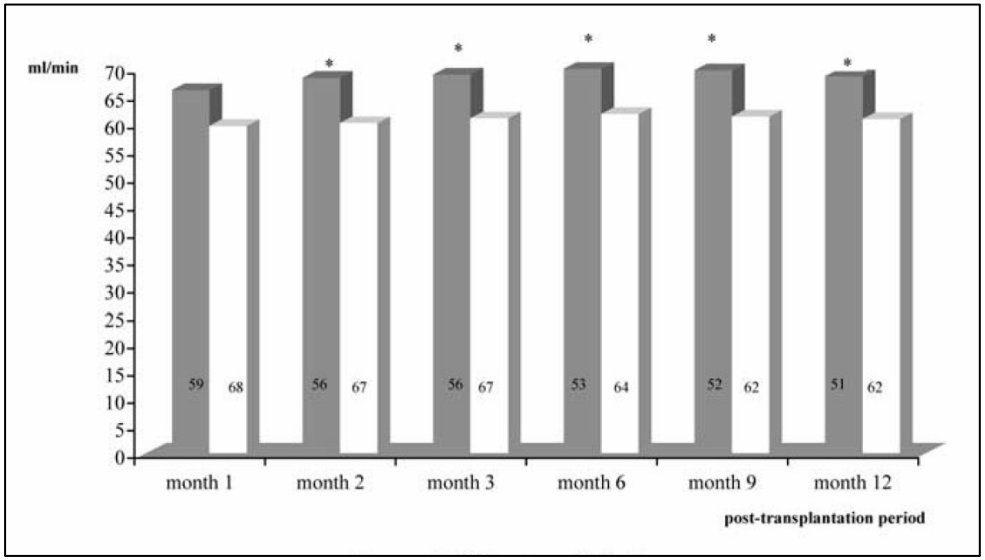
MMF
CS

Group 1: Sirolimus
MMF + CsA + corticosteroids
Dose de charge 15 mgx2 puis taux entre 10 – 15 ng/ml

Group 2: CsA
150 – 300 ng/ml pdt 3 mois puis 75-125 ng/ml



ns



Buchler M et al. Am J Transplant. 2007

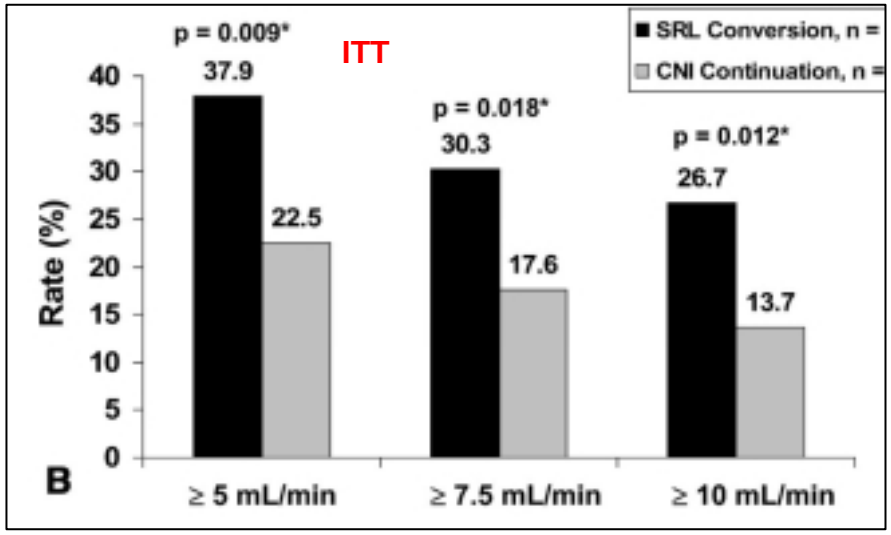
Le relai des CNI par un ImTOR après la première année de Tx apporte un gain modéré sur la fonction (CONVERT).

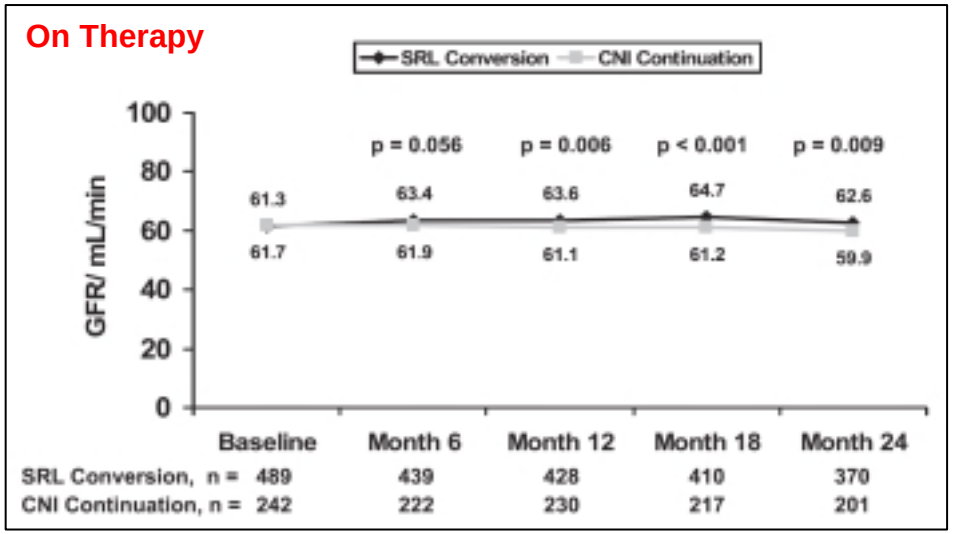
830 pts
CAN
6 – 120 mois
CsA ou FK

Random 2/1

Group 1: CNI
MMF ou AZA + CsA ou FK +/- corticosteroids

Group 2: Sirolimus
Day 1: Stop CNI + SRL (12-20 mg/day)
Day 2: SRL (4 - 8 mg/day)
Step 5-7: SRL adujst (8–20 ng/mL)





Schena F et al. Transplantation. 2009

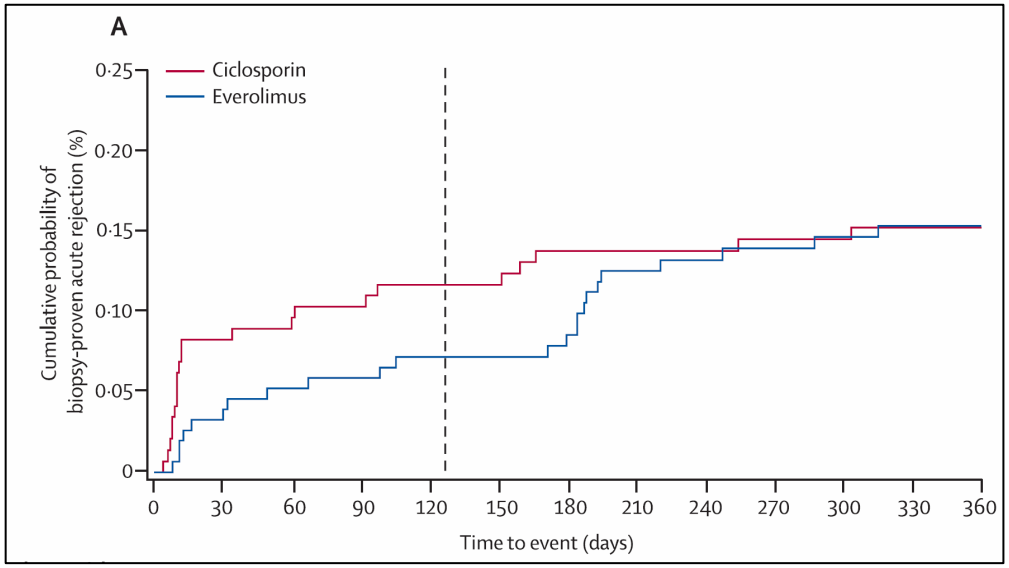
Les ImTOR semblent pouvoir être proposés en relai précoce après une phase initiale de TTT par CNI (ZEUS).

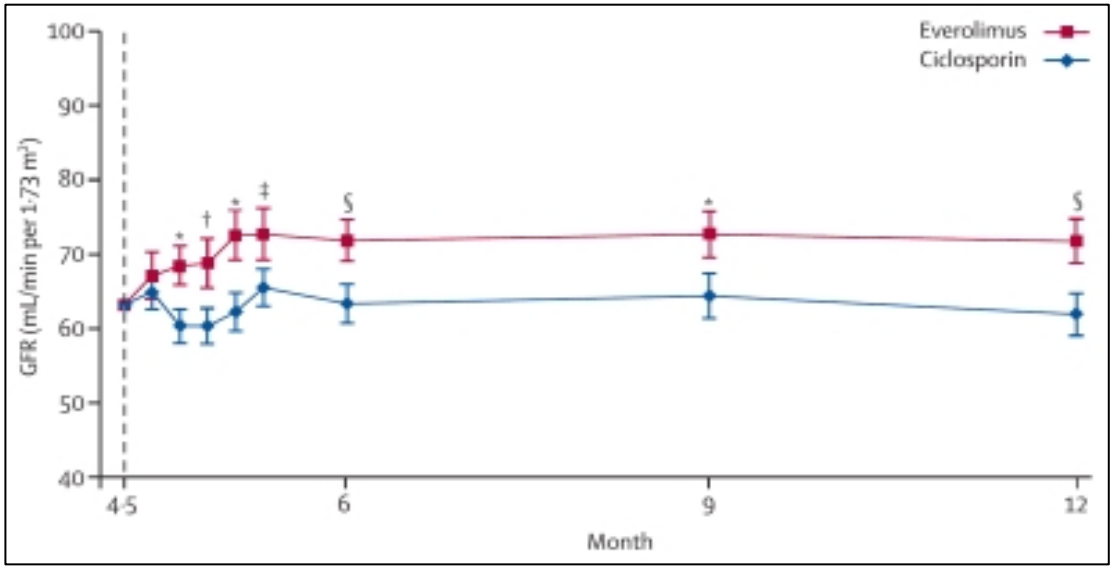
Basiliximab
EC-MPS
CsA
Corticosteroids

4.5 months post-transplantation

Group 1: CsA
EC-MPS + CsA + corticosteroids

Group 2: everolimus
Step 1: EC-MPS + EVR (1.5 mg/day) + CsA (50%) + CS
Step 2: EC-MPS + EVR (6–10 ng/mL) + CsA (25%) + CS
Step 3: EC-MPS + EVR (6–10 ng/mL) + CS





Budde K et al. Lancet. 2011

Les ImTOR semblent pouvoir être proposés en relai précoce après une phase initiale de TTT par CNI (Spare the Nephron).

Basiliximab
MMF
CsA ou FK
Corticosteroids

30 – 180 days post-transplantation

Group 1a: CNI, Group 1b: FK
MMF (1g BID) + corticosteroids

Group 2a:CNI → SRL, Group 2b: FK → SRL
MMF (1 g BID) + Corticostéroïdes
Loading dose then adaptated to trough levels (5-10 ng/ml)

Overall population	MMF/SRL (*N*=148)	MMF/CNI (*N*=151)	MMF/SRL (TAC withdrawal) (*N*=122)	MMF/TAC (*N*=120)	MMF/SRL vs MMF/CNI*	TAC withdrawal vs MMF/TAC*
Calculated GFR, ml/min						
Baseline, mean ± s.d.	71.3 ± 13.8	72.7 ± 16.2	71.2 ± 14.1[a]	74.1 ± 16.6		
Month 12, mean ± s.d.	74.6 ± 17.9	71.5 ± 21.2	74.1 ± 17.8	72.7 ± 21.2		
% Change, baseline to month 12 (*n*)	5.2 ± 25.3 (123)	−0.9 ± 23.4 (123)	4.9 ± 26.2 (103)	−2.0 ± 22.3 (96)	0.06	0.09
Month 24, mean ± s.d.	75.5 ± 19.2	71.2 ± 23.5	74.8 ± 19.7	72.6 ± 23.5		
% Change, baseline to month 24 (*n*)	6.5 ± 28.4 (120)	−1.8 ± 27.3 (116)	6.3 ± 29.5 (102)	−2.4 ± 26.0 (92)	0.04	0.08
Serum creatinine, µmol/l						
Baseline, mean ± s.d.	121.1 ± 30.0	124.4 ± 37.9	121.3 ± 30.5	121.6 ± 38.7		
Month 12, mean ± s.d.	126.2 ± 82.8	145.0 ± 96.5	128.8 ± 89.4	142.7 ± 96.2		
% Change, baseline to month 12 (*n*)	6.0 ± 57.8 (124)	20.4 ± 92.8 (123)	7.7 ± 62.3 (103)	20.4 ± 89.4 (96)	0.11	0.23
Month 24, mean ± s.d.	127.1 ± 83.9	151.8 ± 117.0	130.0 ± 90.3	146.1 ± 110.0		
% Change, baseline to month 24 (*n*)	6.1 ± 59.8 (120)	30.8 ± 114.2 (116)	7.5 ± 64.1 (102)	28.6 ± 108.6 (92)	0.04	0.12

Weir M et al. Kidney Int. 2010.

Les ImTOR semblent pouvoir être proposés en relai précoce après une phase initiale de traitement par CNI.

- ✓ ↑ retard de reprise de fonction
- ✓ ↑ complications de paroi et lymphocèle

  = Introduction retardée

- ✓ ↑ des rejets aigus
- ✓ ↑ des arrêts pour effets secondaires
- ✓ ↑ des lipides
- ✓ ↑ protéinurie

MAIS

- ✓ Meilleure fonction rénale
- ✓ Moins d'HTA
- ✓ Moins d'infections à CMV et à BKV

Relai < 1 an

Patients à faible risque immunologique

Protéinurie < 0,8 g/24h

Clairance de la créatinine > 40 ml/min

Résultats à 1-2 ans

Etude CONCEPT… 4 ans

Lebranchu Y et al. Am J Transplant. 2009.

Long terme?

Survie du greffon

Survie du patient

Décès de cause cardioVx

Les schémas de traitements comportant un ImTOR sont associés à une incidence réduite de cancer de novo après Tx

✓Nombreux arguments pour espérer une interférence avec les mécanismes de l'oncogénèse

Guba M et al Nat Med 2002

Ferte C et al. Nat Rev Clin Oncol. 2010

Koehl G et Al. Oncogene 2010

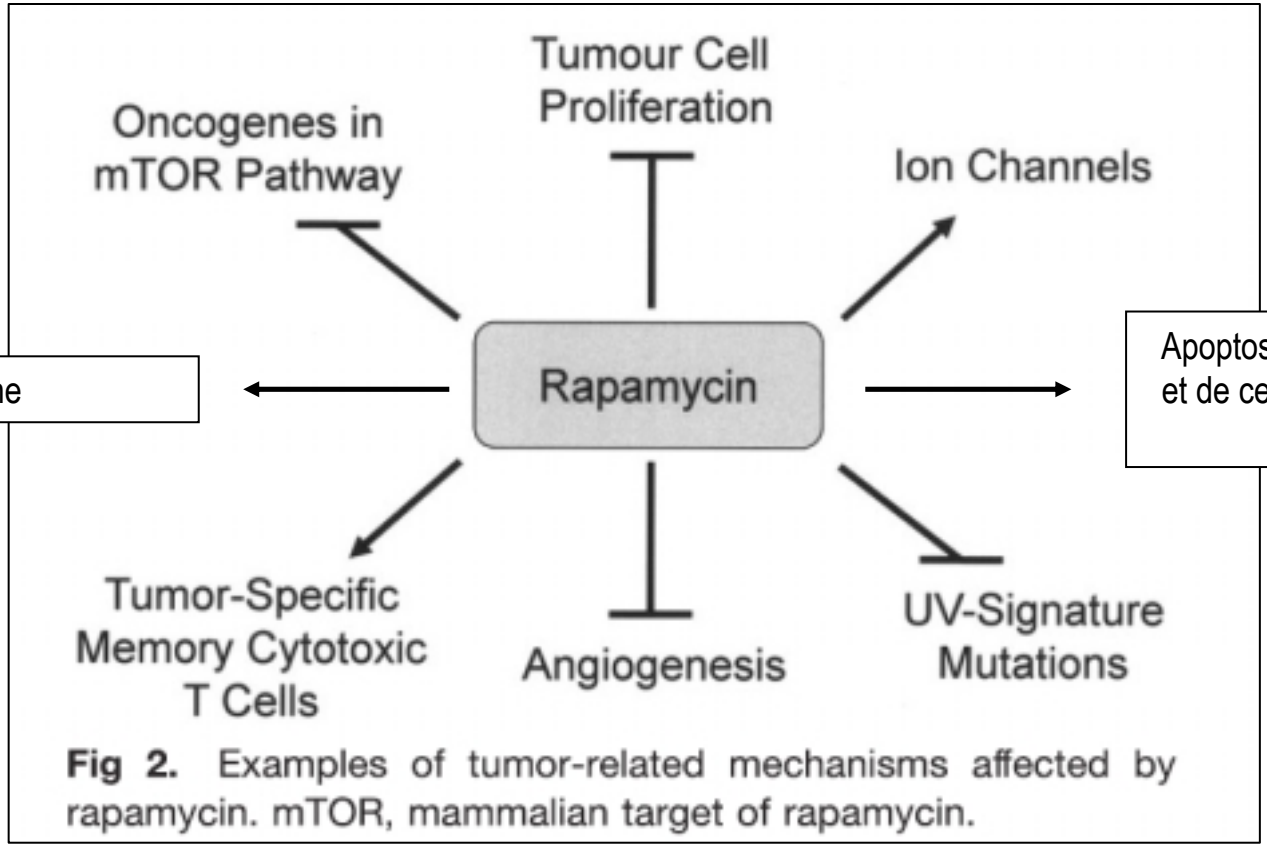


Fig 2. Examples of tumor-related mechanisms affected by rapamycin. mTOR, mammalian target of rapamycin.

E Caderine

Luang F et al Transplantation. 2002

Apoptose des lignées tumorales et de celle induite par la DXM et le Cisplatine

Shi Y et al Cancer Res, 1995
Majewski M et al PNAS 2000

Rao R et al. Immunity 2010
Gattinoni L et al. Nat Med 2009

De Gruijl F et al. Int J Cancer 2009

Geissler E et al. Transplant Proc.2010.

Les schémas de traitements comportant un ImTOR sont associés à une incidence réduite de cancer de novo après Tx

- ✓Données des registres
  Kauffman H et al, Transplantation. 2005.
- ✓ Etudes en cours (TUMORAPA…)
- ✓Tx hépatique (Etude SILVER)

- ✓Etude Multicentrique CONVERT, 830 patients
- ✓Conversion CNI/SRL, Randomisation ratio 1 / 2
- ✓Résultats en ITT à 24 mois

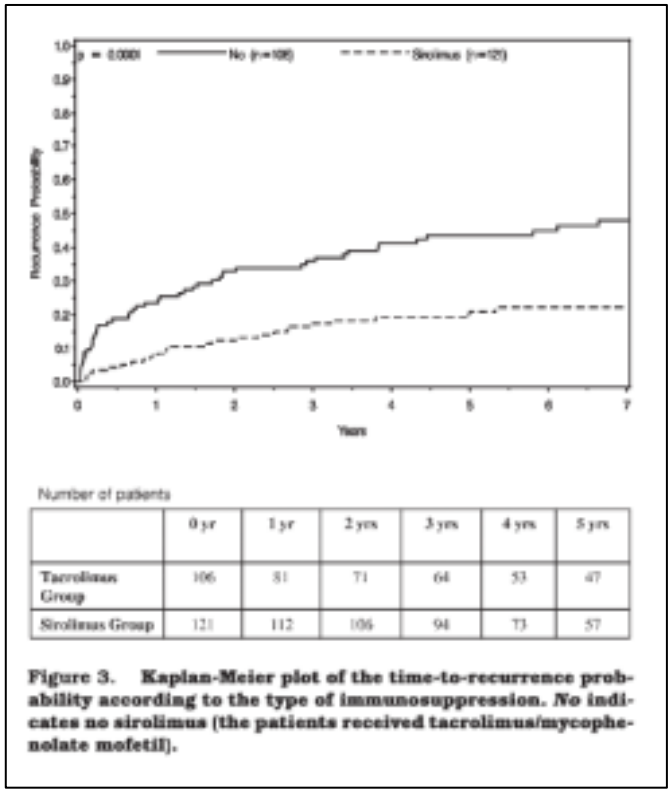
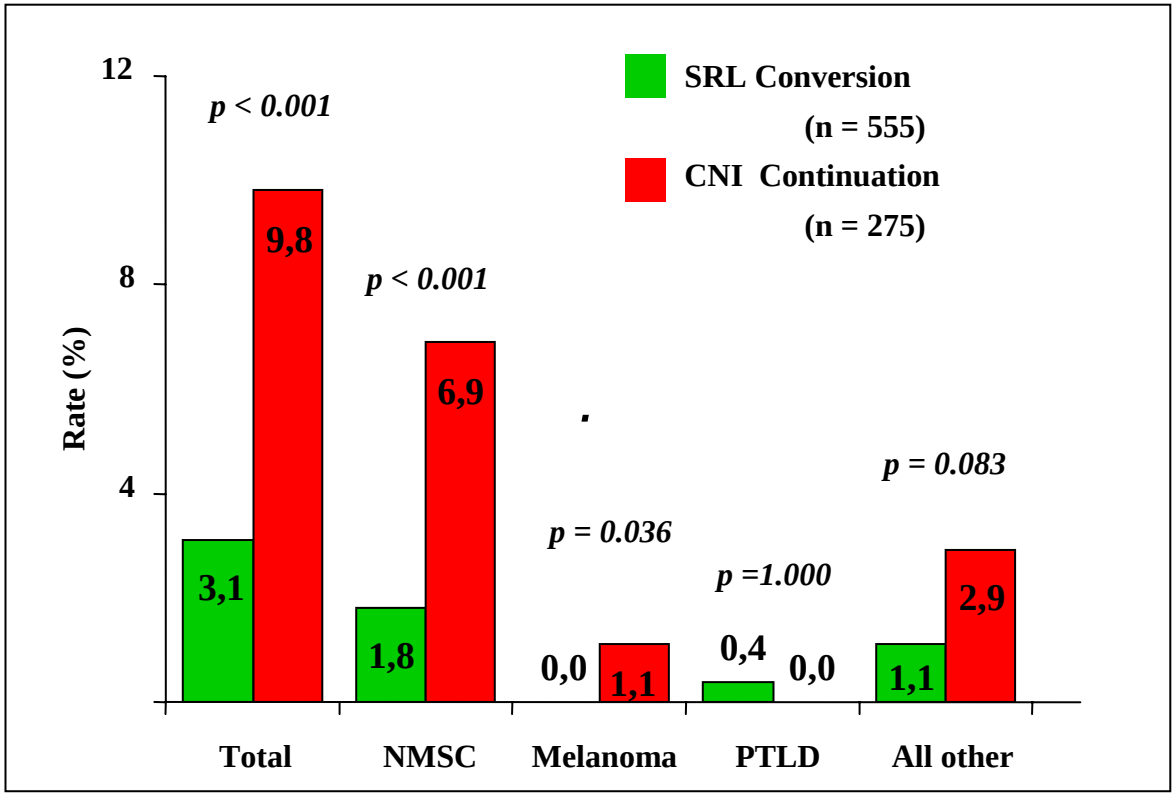


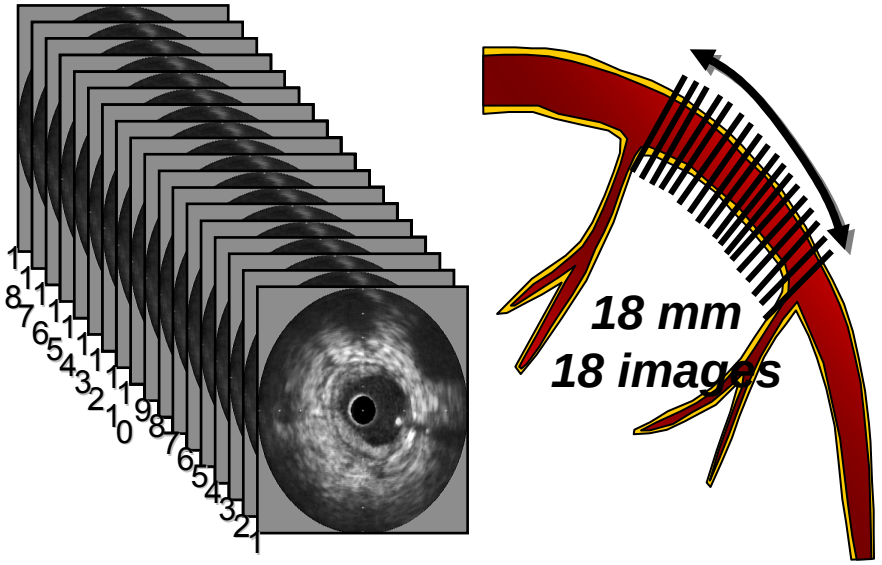
Figure 3. Kaplan-Meier plot of the time-to-recurrence probability according to the type of immunosuppression. *No* indicates no sirolimus (the patients received tacrolimus/mycophenolate mofetil).

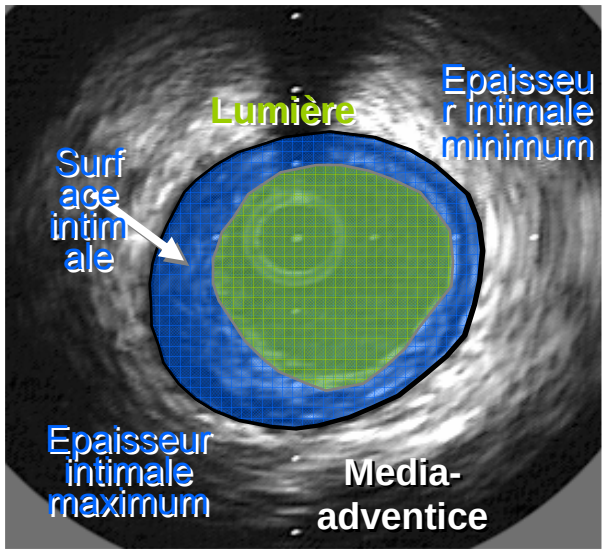
Chinnakotla S et al. Liver Transplant. 2009

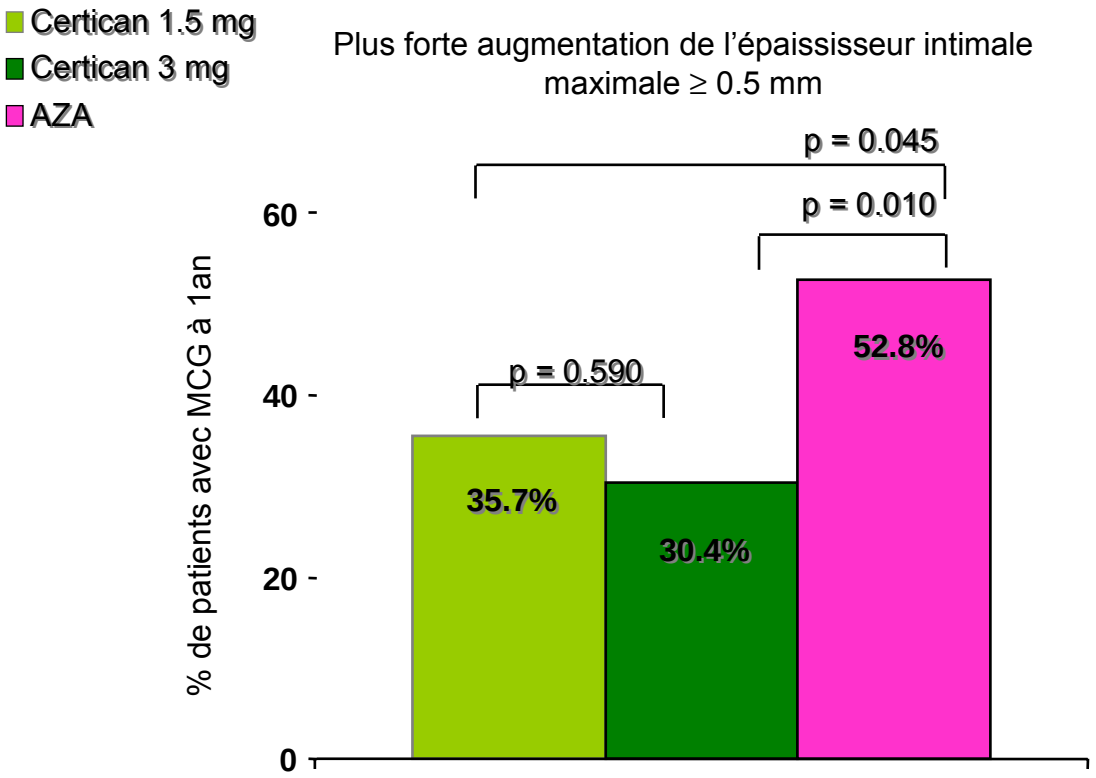


Schena F et al. Transplantation. 2009

Les ImTOR préviennent l'apparition de la vasculopathie du transplant cardiaque







Diminution de la maladie coronaire du greffon cardiaque

Eisen H et al. New Engl J Med. 2003.

La mauvaise tolérance clinique des ImTOR est un obstacle à une large utilisation de ces molécules

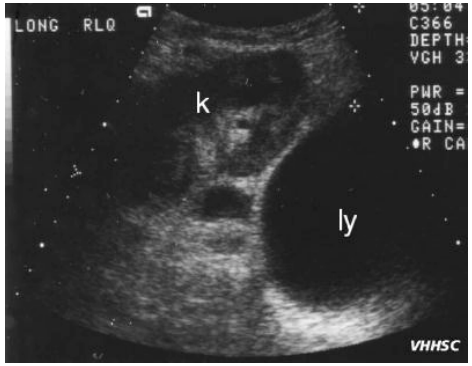
✓30 à 50 % d'arrêt dans études initiales.

✓Meilleure connaissance d'utilisation en fonction des associations avec autres immunosuppresseurs, suppression des doses de charge, diminution des taux…

✓Amélioration de la gestion des effets secondaires.

Lymphocèle – retard de cicatrisation

30 – 40%



Patients obèse, post op. immédiat

Age, diabète et dose de CS

Hypoalbuminémie

Dose de charge SRL

Dyslipidémie

>60%

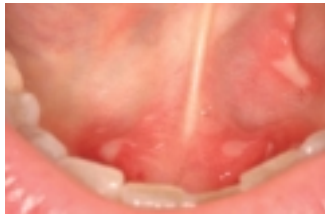
Dose dépendant

Statine

Effets long terme?

Cutanéo-muqueux

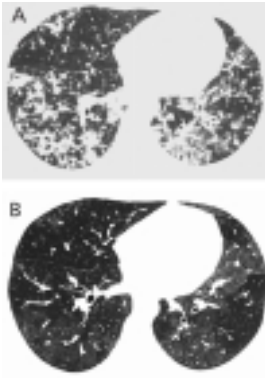
>60%



Initialement

Effet des CS

Pneumopathie



Pas de période

Taux élévés

Autres

Protéinurie

DGF

Anémie

Thrombopénie

Stérilité

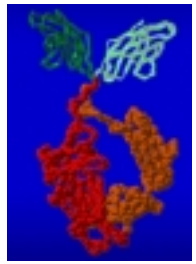
Un concept sans CNI avec blocage de la costimulation

B7-1 (CD80)

- Low abundance, inducible on APC
- Sustains immune response
- Ongoing signaling via B7-1 may contribute to chronic rejection

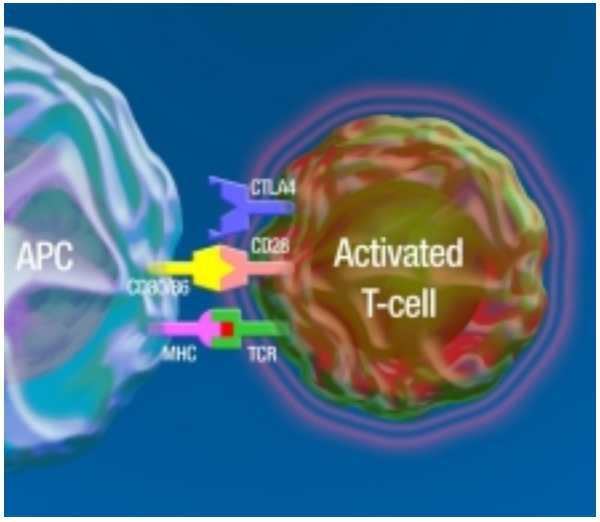
CD28

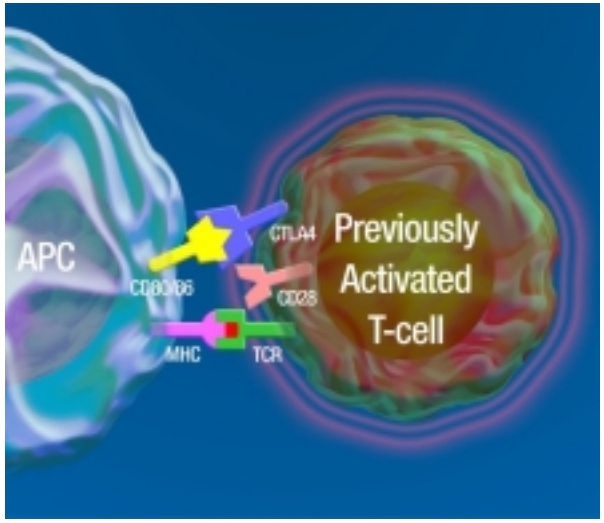
- Constitutive on most CD4+ and CD8+ T-cells.
- Critical for T-cell activation

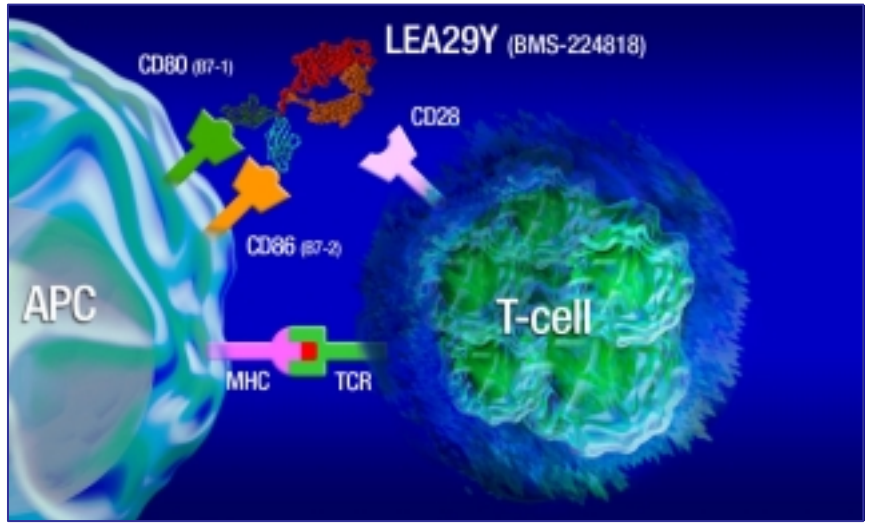


Belatacept (LEA29Y)

- 4 fold slower off rate from CD86 and 2-fold from CD80 vs CTLA4Ig
- ~10-fold more potent inhibition of T cell activation







B7-2 (CD86)

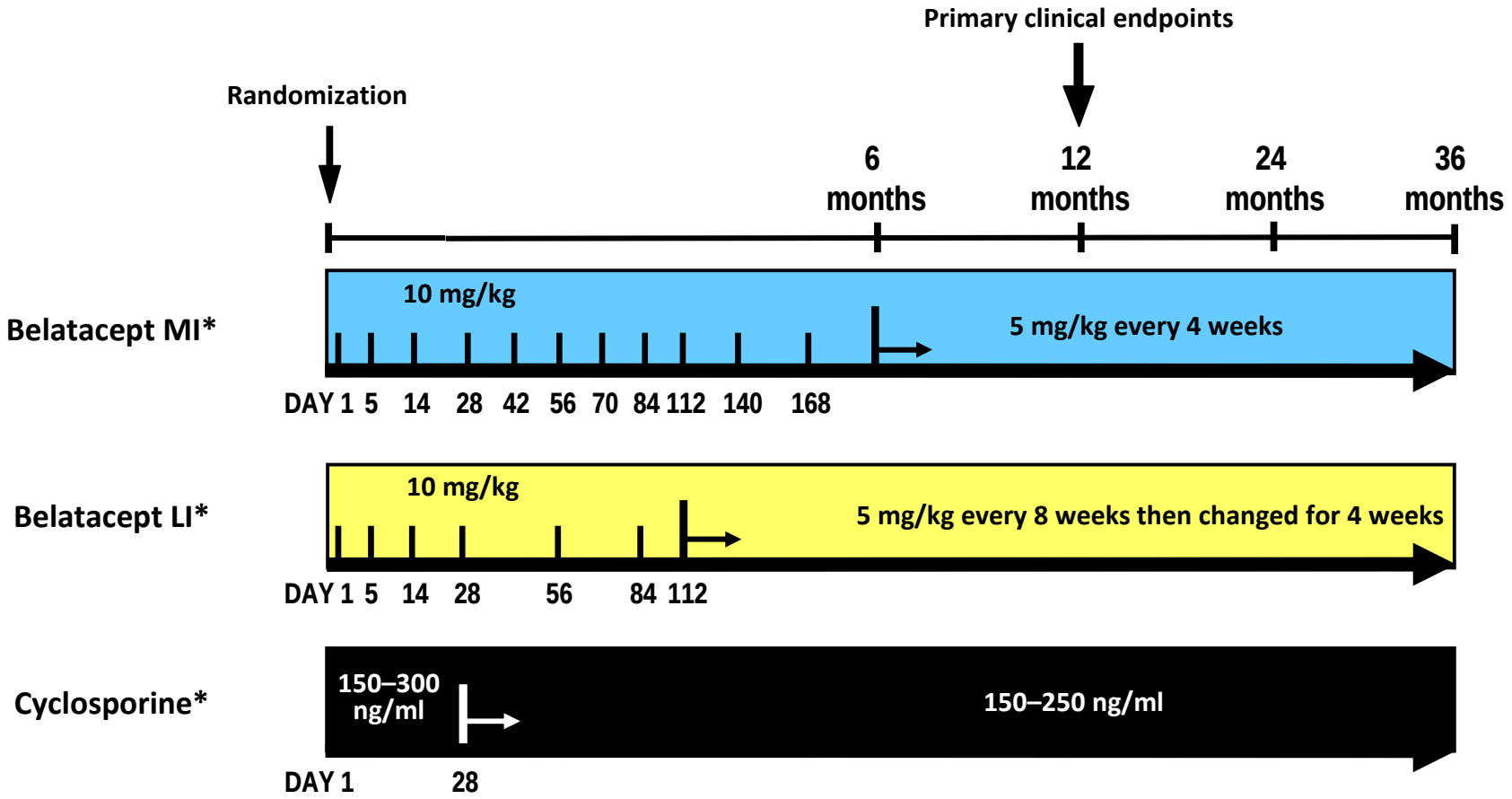
- Higher abundance, constitutive, and inducible on APC
- Initiates immune response
- Signaling via B7-2 may play an important role in acute rejection

CTLA4 (CD152)

- Rapidly induced upon T-cell activation
- Structurally similar to CD28
- Binds CD80 and CD86 more avidly than CD28
- CTLA4 negatively regulates T-cell activation

- *No cytokine production*
- *No cell division*
- *Becomes anergic*
- *Undergoes apoptosis*

Un mode d'administration différent par rapport aux autres traitements d'entretien



*All patients received basiliximab induction, mycophenolate mofetil, and corticosteroids

Le Belatacept sans CNI améliore significativement la fonction du greffon rénal à 1 an et 5 ans

Phase II

Effective immunosuppression well tolerated

Better GFR and less CAN than CsA

Improved CV risk factors

3 PTLD in MI regimen (1 CsA)

Table 2. Incidence of Primary and Secondary Efficacy End Points.

End Point	Intensive Belatacept (N=74)	Less-Intensive Belatacept (N=71)	Cyclosporine (N=73)
Primary efficacy end point			
Clinically suspected and biopsy-proven acute rejection at 6 mo — no. (%)	5 (7)	4 (6)	6 (8)
Absolute difference in rate from cyclosporine group — percentage points (exact 95% CI)*	−1.5 (−11.3 to 8.3)	−2.6 (−12.3 to 6.7)	—
Secondary efficacy end points			
Mild acute rejection (grade IA) — no. (%)	2 (3)	0	1 (1)
Mild acute rejection (grade IB) — no. (%)	0	0	1 (1)
Moderate acute rejection (grade IIA) — no. (%)	2 (3)	3 (4)	2 (3)
Moderate acute rejection (grade IIB) — no. (%)	1 (1)	1 (1)	2 (3)

5 years:

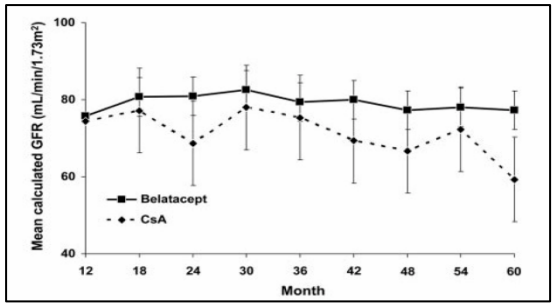


Table 3. Renal Function and Histologic Findings.*

End Point	Intensive Belatacept	Less-Intensive Belatacept	Cyclosporine
Measured GFR			
No. of patients	32	37	27
Mean GFR — ml/min/1.73 m²†	66.3±20.7	62.1±15.9	53.5±16.4
Difference from cyclosporine group — ml/min/1.73 m² (95% CI)	12.8 (2.9 to 22.7)	8.6 (0.4 to 16.8)	—
Chronic allograft nephropathy			
No. of patients	52	54	45
CAN at 12 mo — no. (% [95% CI])‡	15 (29 [16.5 to 41.2])	11 (20 [9.6 to 31.1])	20 (44 [29.0 to 59.0])
Mild CAN (stage I) — no. (%)	11 (21)	6 (11)	16 (36)
Moderate CAN (stage II) — no. (%)	4 (8)	1 (2)	3 (7)
Severe CAN (stage III) — no. (%)	0	4 (7)	1 (2)
Absolute difference in rate from cyclosporine group — percentage points (asymptotic exact 95% CI)	−15.6 (−34.6 to 3.4)	−24.1 (−42.1 to 6.0)	—
Calculated GFR			
No. of patients	60	59	50
Mean GFR — ml/min/1.73 m²	72.4±22.5	73.2±22.5	68.0±28.1
Difference from cyclosporine group — ml/min/1.73 m² (95% CI)	4.4 (−5.2 to 14.0)	5.2 (−4.4 to 14.8)	—
No. of patients without CAN	49	50	37
Mean GFR — ml/min/1.73 m²	75.9±21.3	73.2±19.8	76.6±24.4
Difference from cyclosporine group — ml/min/1.73 m² (95% CI)	−0.7 (−10.5 to 9.1)	−3.4 (−12.8 to 6.0)	—
No. of patients with CAN	11	9	13
Mean GFR — ml/min/1.73 m²	56.9±22.2	73.1±35.9	43.6±23.5
Difference from cyclosporine group — ml/min/1.73 m² (95% CI)	13.3 (−6.2 to 32.8)	29.5 (3.2 to 55.8)	—

Vincenti F et al. N Engl J Med. 2005.
Vincenti F et al. J Am Soc Nephrol. 2010

Les résultats des études de phase III, BENEFIT et BENEFIT-EXT confirment les résultats de l'étude de phase II

Survie patients et greffon similaires

Meilleure fonction rénale (même si rejet)

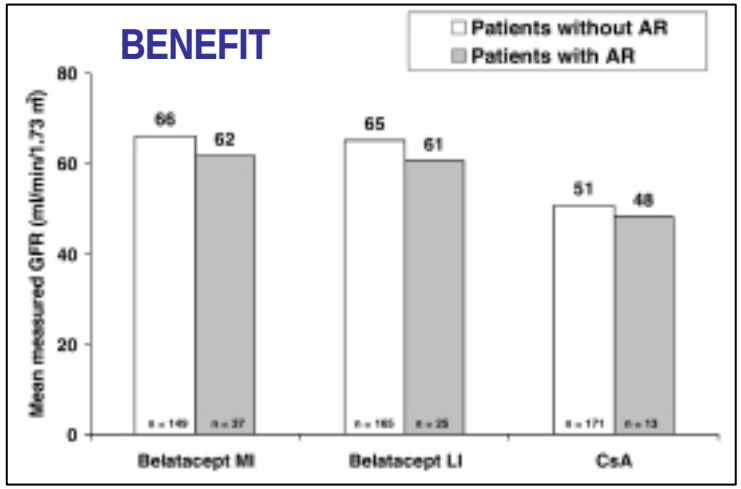
Vincenti F et al. Am J Transplant 2010.
Durrbach A et al. Am J Transplant 2010.

BENEFIT

CAN, n (% [95% CI])	40 (18 [13.1–23.4])	54 (24 [18.3–29.5])	71 (32 [26.2–38.6])
Difference from CsA (97.3% CI)	−14.2 (−23.2, −5.0)	−8.5 (−17.9, 0.9)	–
Mild CAN (stage I), n (%)	21 (10)	29 (13)	41 (19)
Moderate CAN (stage II), n (%)	5 (2)	6 (3)	9 (4)
Severe CAN (stage III), n (%)	4 (2)	6 (3)	6 (3)
Acute rejection			
Acute rejection, n (%)	49 (22)	39 (17)	16 (7)

BENEFIT-EXT

CAN, n (% [95% CI])	82 (45 [37.6–52.0])	80 (46 [38.6–53.4])	95 (52 [44.4–58.9])
Difference from cyclosporine (97.3% CI)	−6.8 (−18.2, 4.7)	−5.7 (−17.2, 6.0)	–
Mild CAN (Stage I), n (%)	45 (25)	40 (23)	49 (27)
Moderate CAN (Stage II), n (%)	10 (6)	14 (8)	13 (7)
Severe CAN (Stage III), n (%)	8 (4)	7 (4)	12 (7)
Acute rejection			
Acute rejection, n (%)	33 (17.9)	31 (17.7)	26 (14.1)



Moins d'immunisation anti-HLA

Moins de NODAT et moins de dyslipidémie

Plus de PTLD et de LEMP

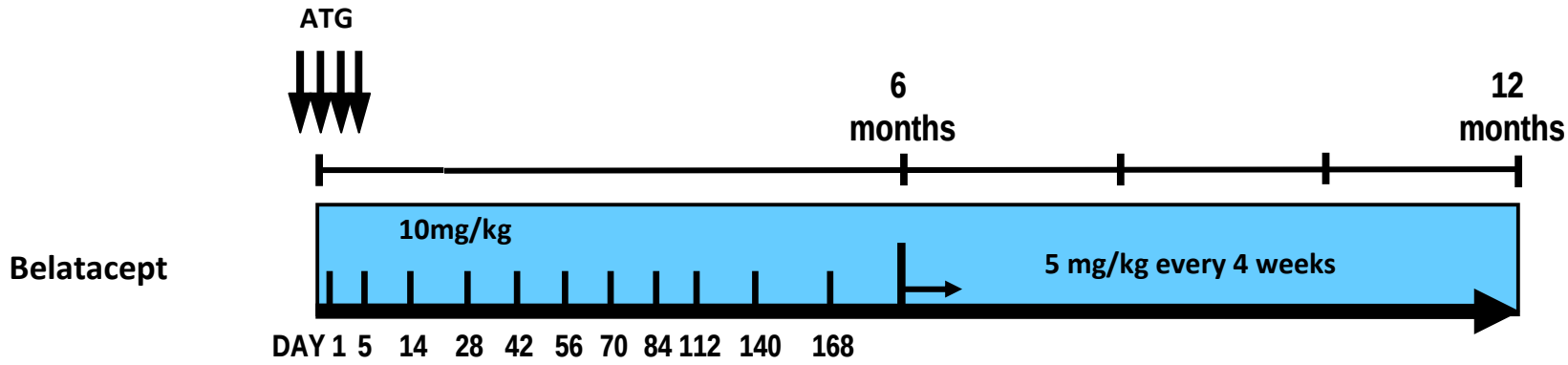
	Belatacept	CsA
Cases	13/949 (1.4%)	2/476 (0.
CNS	8/13	

Hazard Ratios for Developing PTLD (95% CI)

- EBV negative recipient — **15.3** (50.4, 4.7)
- T cell depleting antibody therapy — **5.0** (17.8, 1.4)
- CMV disease — **3.8** (13.3, 1.1)

Larsen C et al Am J Transplant. 2009.

Le Belatacept peut être utilisé dans d'autres schémas d'associations immunosuppressives



G1 (33pts)= MMF 1 gramme/jour

G2 (26pts)= SRL 5 mg/j J0, Taux cibles 7-12 ng/ml jusqu'à M6 puis 5-10 ng/ml

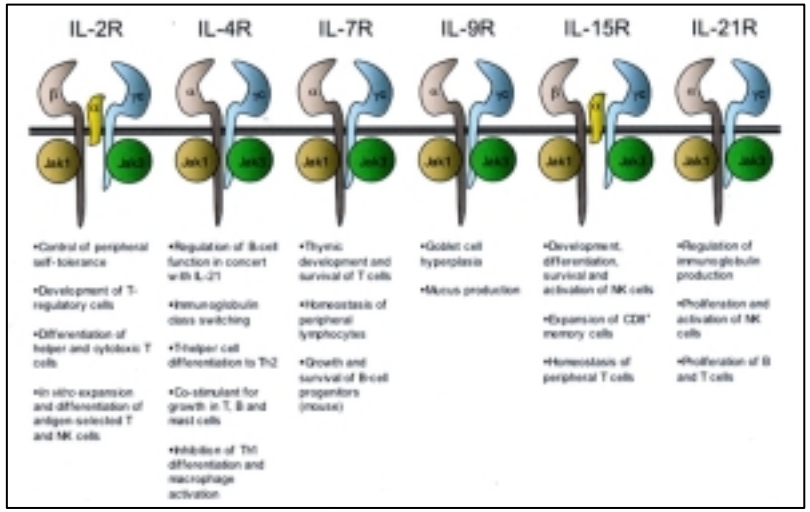
G3 (30pts)= TAC 0,1 mg/kg, Taux cibles 8-12 ng/ml jusqu'à M1 puis 5-10 ng/ml

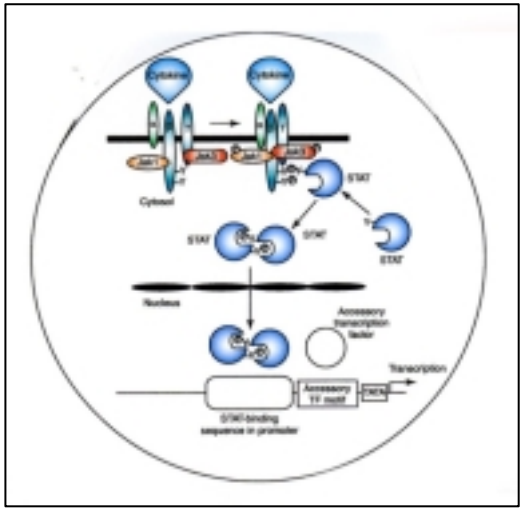
	Belatacept-MMF (n = 33)	Belatacept-SRL (n = 26)	TAC-MMF (n = 30)
Acute Rejection at Month 6, n (%)	4 (12)	1 (4)	1 (3)
Difference from TAC (95% CI)	8.8 (−6.6, 24.9)	0.5 (−14.5, 16.7)	–
Subject and graft survival at Month 12, n (%)	30 (91)	24 (92)	30 (100)
Mean (SD) calculated GFR at Month 12, mL/min/1.73m^2	63.6 (27.27)	61.8 (30.66)	54.0 (14.95)
Proportion steroid-free at Month 12, n (%)[2]	24 (73)	20 (77)	28 (93)
Proportion steroid-free and [3]CNI-free at Month 12, n (%)[2]	24 (73)	18 (69)	1 (3)

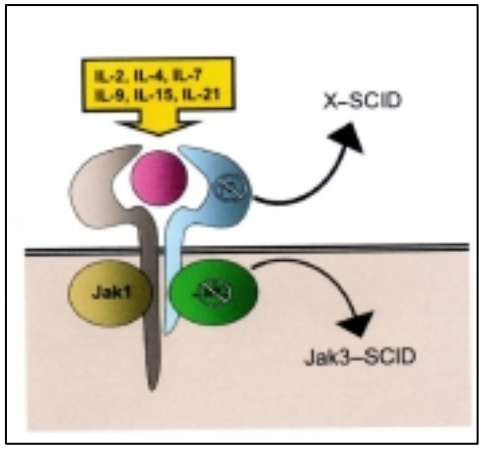
Ferguson R et al. Am J Transplant. 2011

Un autre concept sans CNI : Inhibiteur de JAK3

Jak/Stat deficiency	Overall development	Lymphoid tissue development	Lymphoid apoptosis	Risk of infections	Risk of autoimmunity
Jak 1	Embryonic death	↓↓ T cells	↑↑↑ in T cells	↑↑	↑↑
		↓↓↓ pro/pre-B cells SCID phenotype			
Jak2	Embryonic death	No impact	No impact	ND	ND
Jak3	Immune compromised	↓↓↓↓ T, B, NK cells SCID phenotype	↑↑↑ in T cells	↑↑	ND
Tyk2	No impact	↓↓ response to IFN-α/β, IFN-γ and IL-12	No Impact	↑↑	↑↑↑

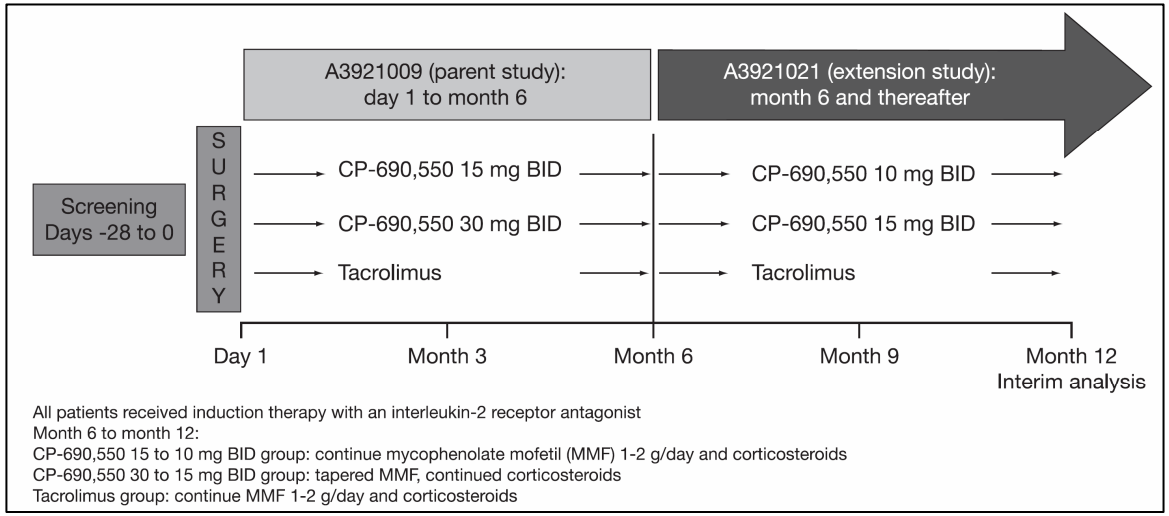




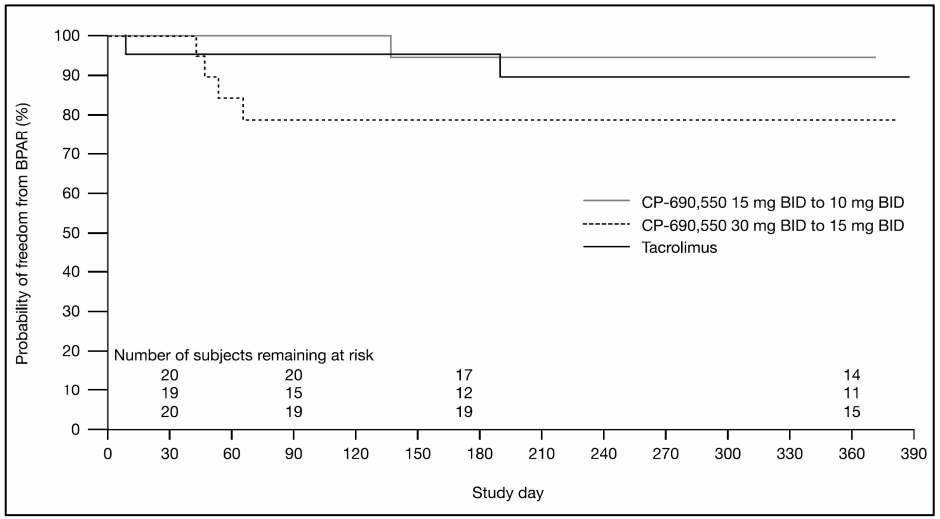


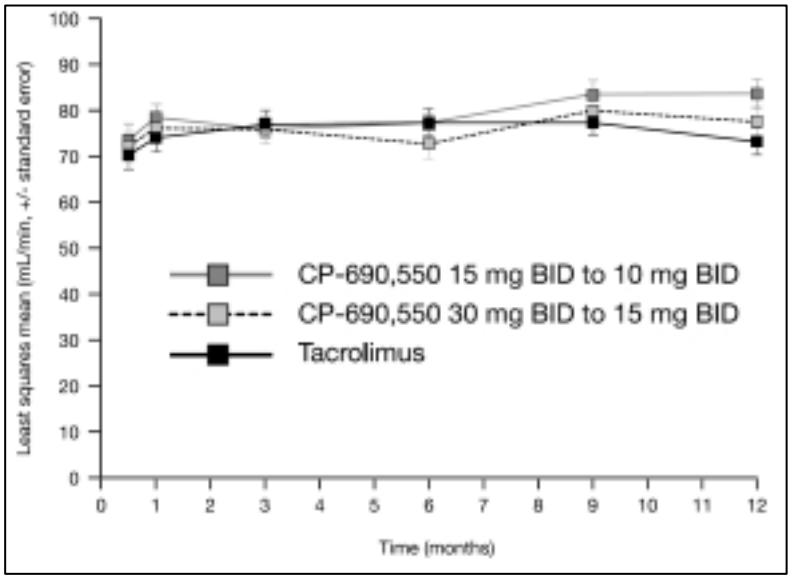
Borie DC, et al. Trends in Molecular Med. 2004.
Pesu M, et al. Immunological Reviews 2005.

Les premiers résultats avec le Tofacinitib (inhibiteur de JAK3)



All patients received induction therapy with an interleukin-2 receptor antagonist
Month 6 to month 12:
CP-690,550 15 to 10 mg BID group: continue mycophenolate mofetil (MMF) 1-2 g/day and corticosteroids
CP-690,550 30 to 15 mg BID group: tapered MMF, continued corticosteroids
Tacrolimus group: continue MMF 1-2 g/day and corticosteroids





	CP15	CP30	FK
Significant infections at M6 n (%)	6 (30)	11 (59.3)	5 (24.4)
Significant infections at M12 n (%)	9 (47.5)	11 (59.3)	7 (35.2)
CMV disease at 6 months, n (%)	2 (10.3)	4 (21.1)	0 (0)
CMV disease at 12 months, n (%)	3 (16.3)	4 (21.1)	0 (0)
BK virus nephropathy	0	4	0
HZV infections	4	0	1

Busque S et al. Am J Transplant 2009.

Les premiers résultats avec le Tofacinitib (inhibiteur de JAK3)

✓ Résultats de la phase IIb (Basiliximab, MMF et CS)

CP1 = CP-690,550 15 mg BID until M6 then 10

CP2 = CP-690,550 15 mg BID until M3 then 10

Results at Month 12, unless stated otherwise	CsA (n=109)	CP1 (n=106)	CP2 (n=107)
BPAR rate at Month 6, %	17.7	16.1#	12.4#
BPAR rate at Month 12, %	18.8	17.4#	15.4#
Graft survival, %	97.1	97.0	97.1
Mean measured GFR, mL/min	53.9	64.6*	64.7*
CAN in protocol biopsy, %	48.3	25.0*	23.9*
NODAT, %	20.8	9.9	9.3
Serious infection, %	25.3	44.5*	37.0*
CMV disease including CMV syndrome, %	4.5	19.5*	13.3*
BKV nephritis, %	1.1%	2.6%	3.9%
Number of patients with PTLD	0	2	1
# Statistically non-inferior to CsA; * p<0.05 vs. CsA; 2 additional cases of PTLD occurred in CP1 after Month 12			

Abstract 4

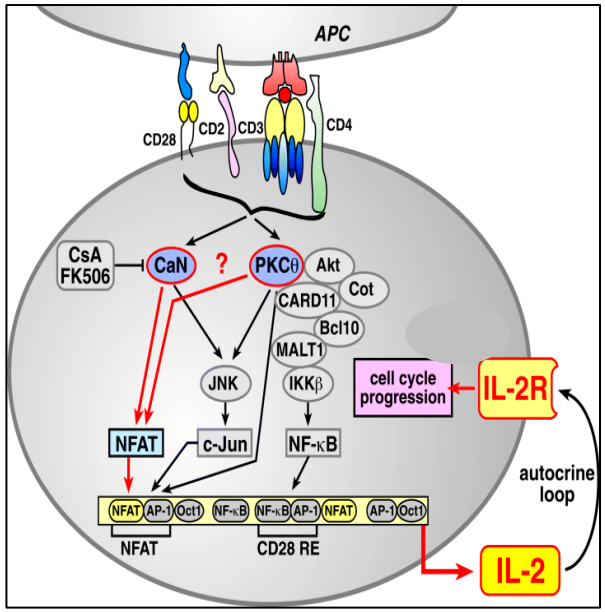
% patients with increase in Banff ci score#	45.8	26.1*	23.3*
% patients with increase in Banff ct score#	45.8	28.3	23.3*
% deceased donor recipients with DGF	14.9	18.5	15.4

Abstract 225

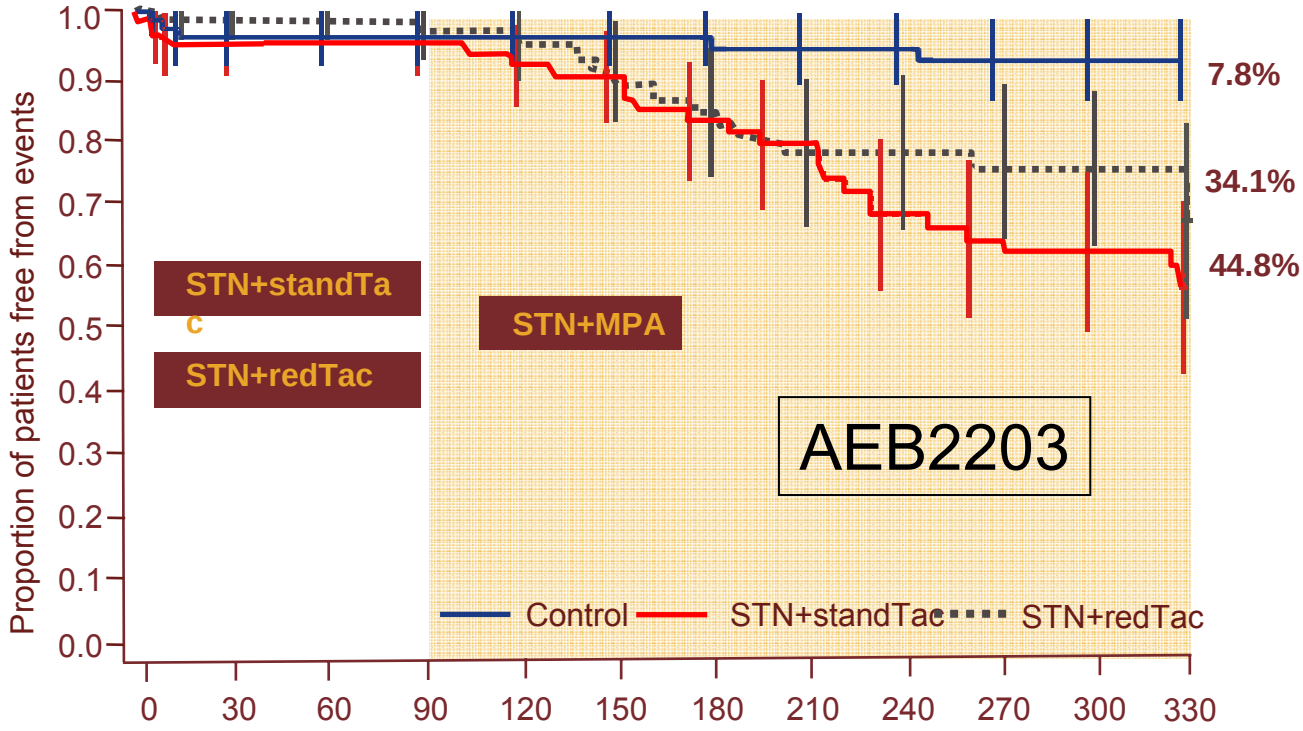
Vincenti F et al. ATC. 2011.

Autres immunosuppresseurs en développement

✓ Sotrastaurine (AEB)



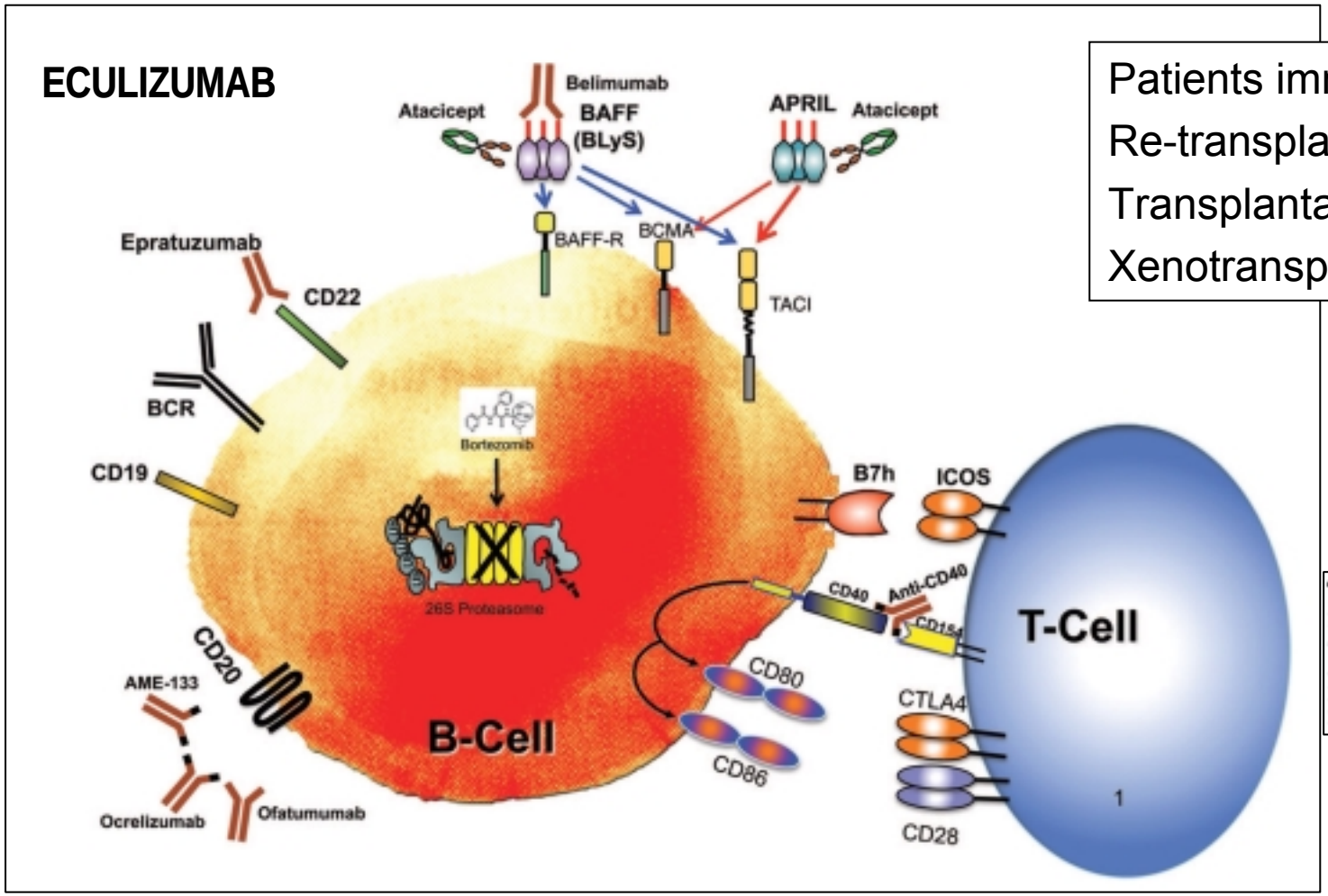
G. Baier. Immunol Reviews. 2003.



✓ Sotrastaurine (AEB) et Certican en cours d'étude

Autres développements en immunosuppression

✓ Cibler la formation/présence des anticorps anti-donneur



Patients immunisés
Re-transplantations
Transplantations ABO incompatibles
Xenotransplantation

TABLE 2. Monoclonal antibodies targeting CD40

Lucatumumab, fully human (Novartis, Basel, Switzerland)
CHI220, chimeric (Bristol-Myers Squibb, New York, NY)
ASKP1240, fully human (Astellas Pharma, Deerfield, IL)[a]
PG102, deimmunized chimeric (PanGenetics, Utrecht, Netherlands)
PRO64553, humanized (Genentech, South SF, CA)

Conclusions

- ✓ Pour des patients à faible risque, les nouveaux schémas d'immunosuppression semblent aussi efficaces que ceux utilisant des CNI
  - non néphrotoxiques
  - avec un moindre impact cardio-vasculaire et/ou néoplasique
  - avec un profil d'effet secondaires différents

Etudes
À
long terme…

- ✓ Le patient à fort risque immunologique reste, pour le moment, avec les traitements les plus classiques (déplétion lymphocytaire, CNI, MMF, CS)

- ✓ Nombreuses voies de recherche sur la réponse B (désensibilisation → rejet chronique)

- ✓ Espoir de protocoles d'induction de tolérance ou de médecine régénérative