Centre Hospitalier Régional
Universitaire de Lille

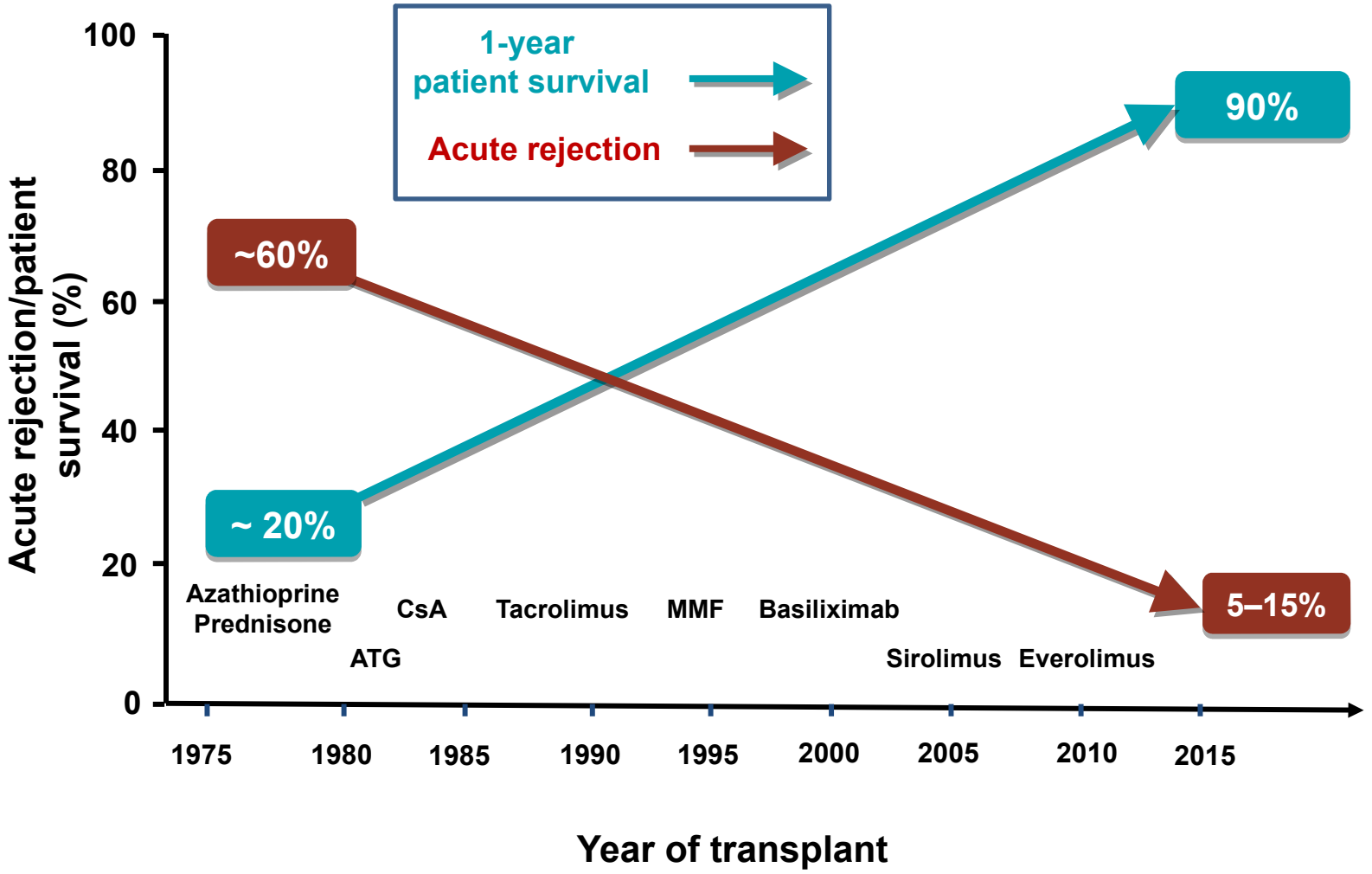
Liver transplantation issues in 2018

Minimisation of immunosuppression in the long term : what is it for ?

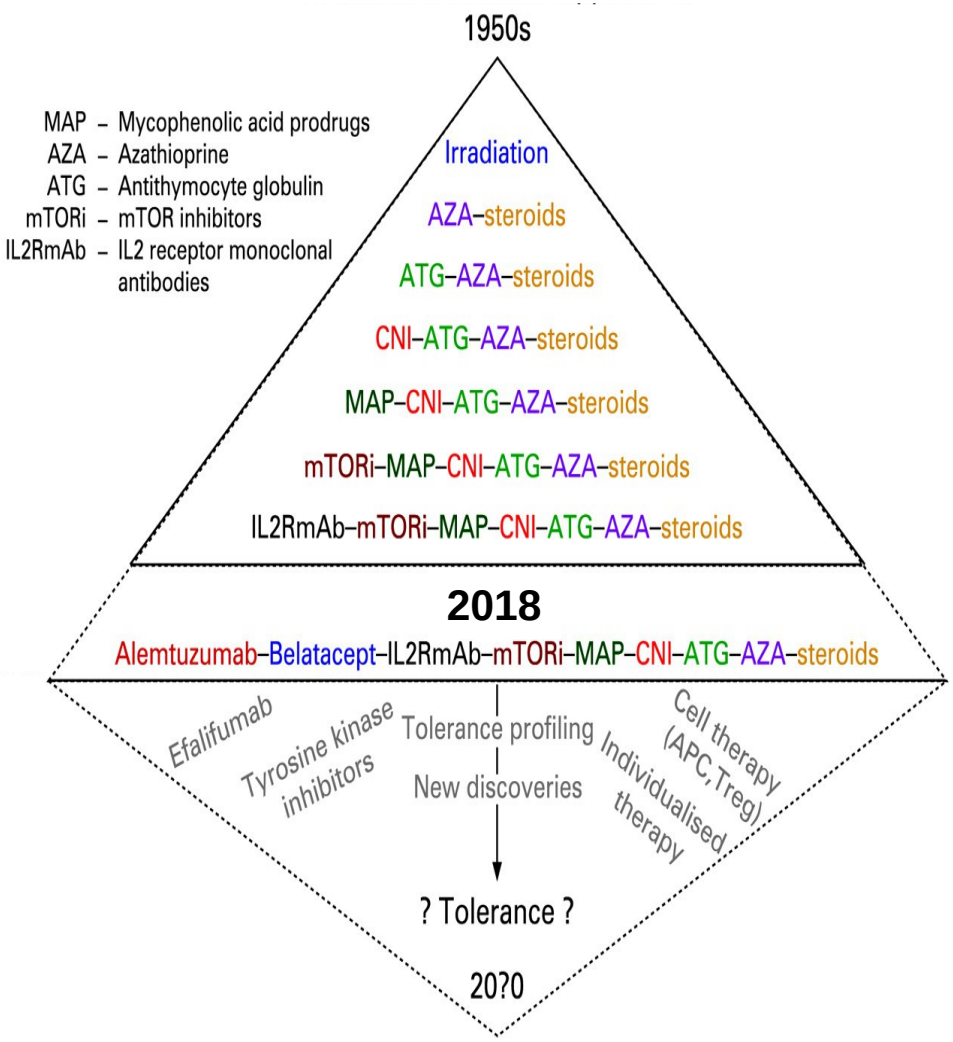
Chairs: Didier SAMUEL (France) Pierre-Alain CLAVIEN (Switzerland)
Speakers: Dominique THABUT (France) Sébastien DHARANCY (France)

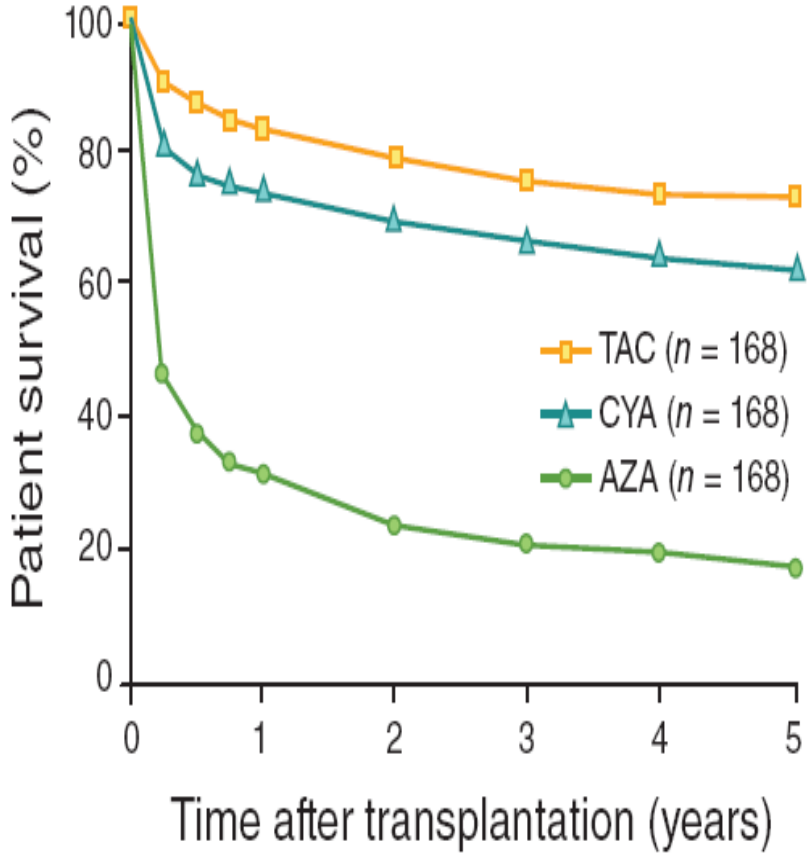
2018 11th Paris Hepatology Conference
Organised by Pr Patrick Marcellin, APHC
15 & 16 January 2018
Palais des Congrès Paris

Considerable improvements have been made in acute rejection and short-term patient/graft survival

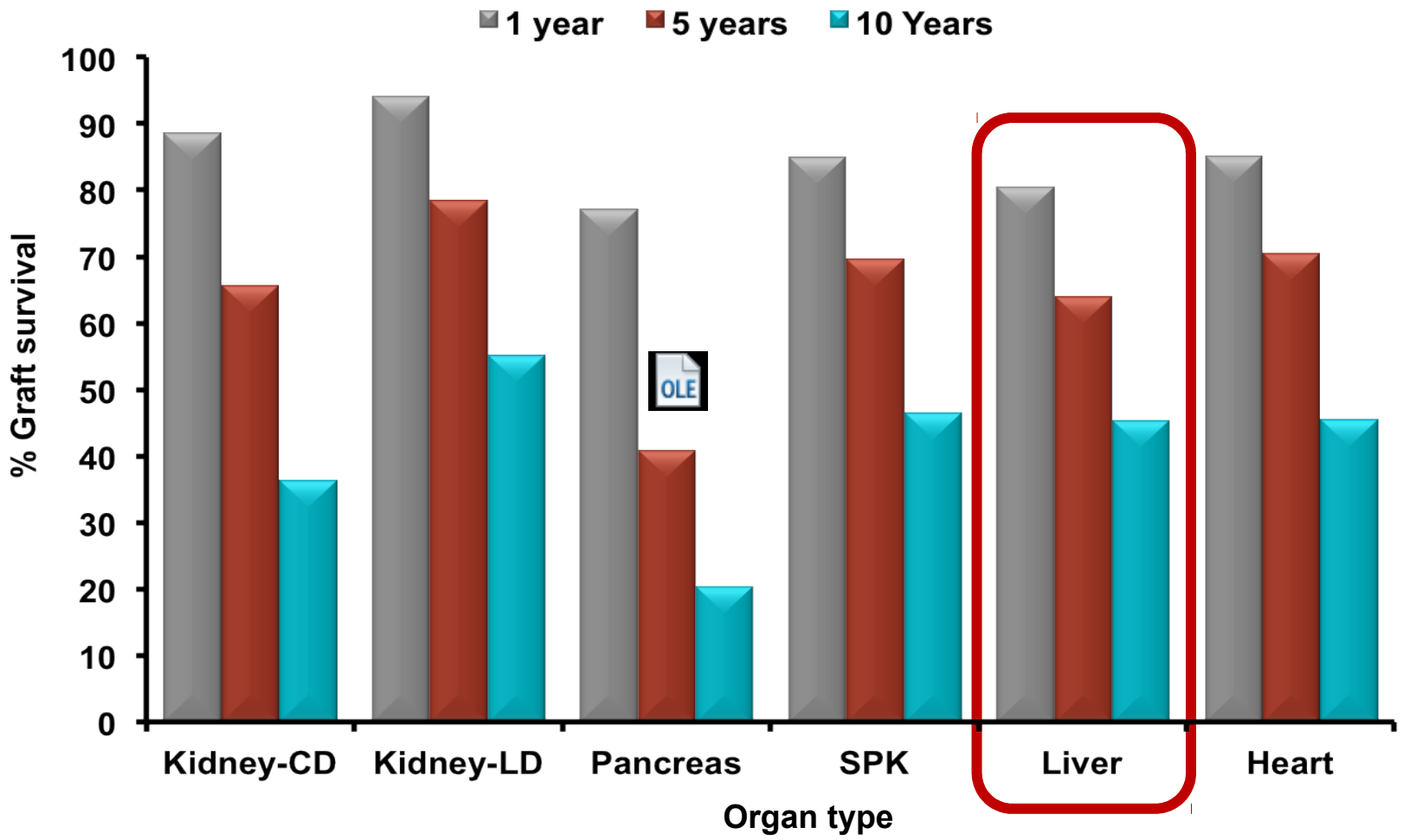


Progressive enrichment in drugs leading to a stepwise improvement in survival, but…





Weak improvements have been made in long-term patient survival



Levy GA, et al . Current Trends in Transplantation: Drug Therapy and Monitoring 2009

What are the exact statements regarding long-term complications after Liver Transplantation ?

A / Cardiovascular diseases are the leading cause of non-hepatic mortality after LT

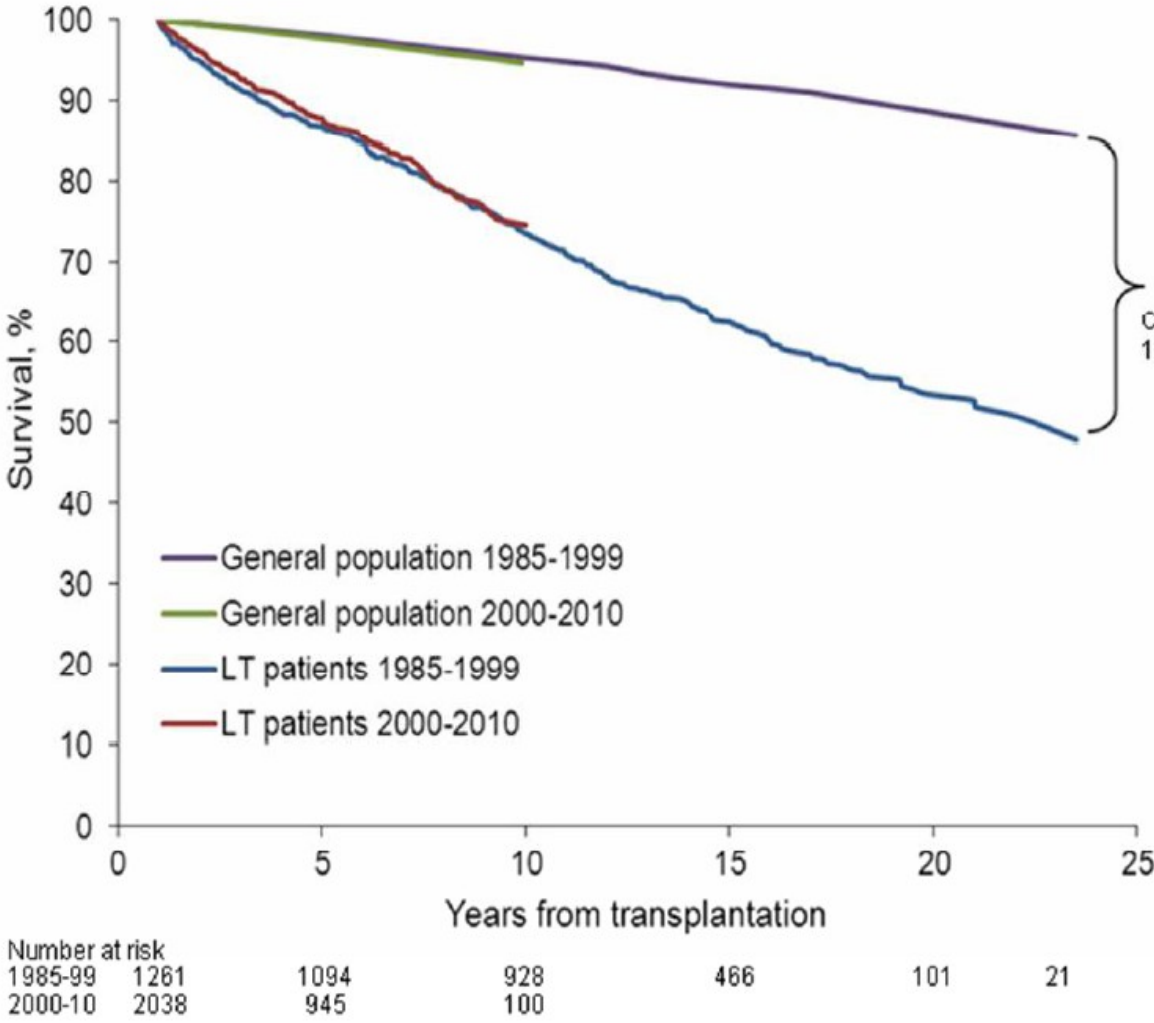
B / *De novo* cancers are the leading cause of non-hepatic mortality after LT

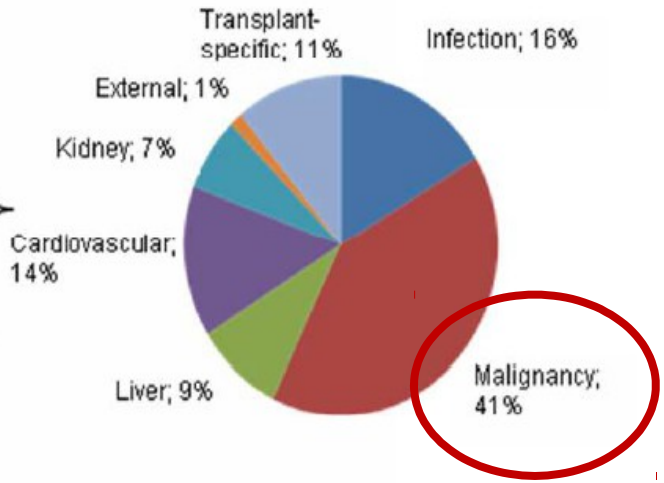
C / The RR to develop *de novo* cancer is 2 to 15 fold higher in transplant patients than in the general population

D / Life expectancy after LT is similar than general population

Life expectancy after LT

Stable « survival deficit » as compared with general population

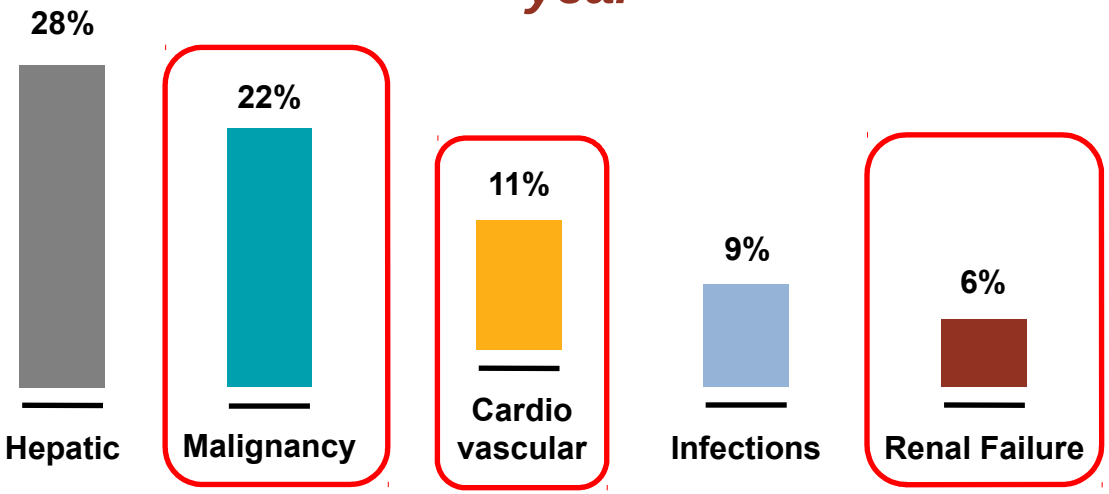




Aberg F et al. Hepatology 2014

The evolving mortality in liver transplantation

Causes of death among LTx recipients > 1 year



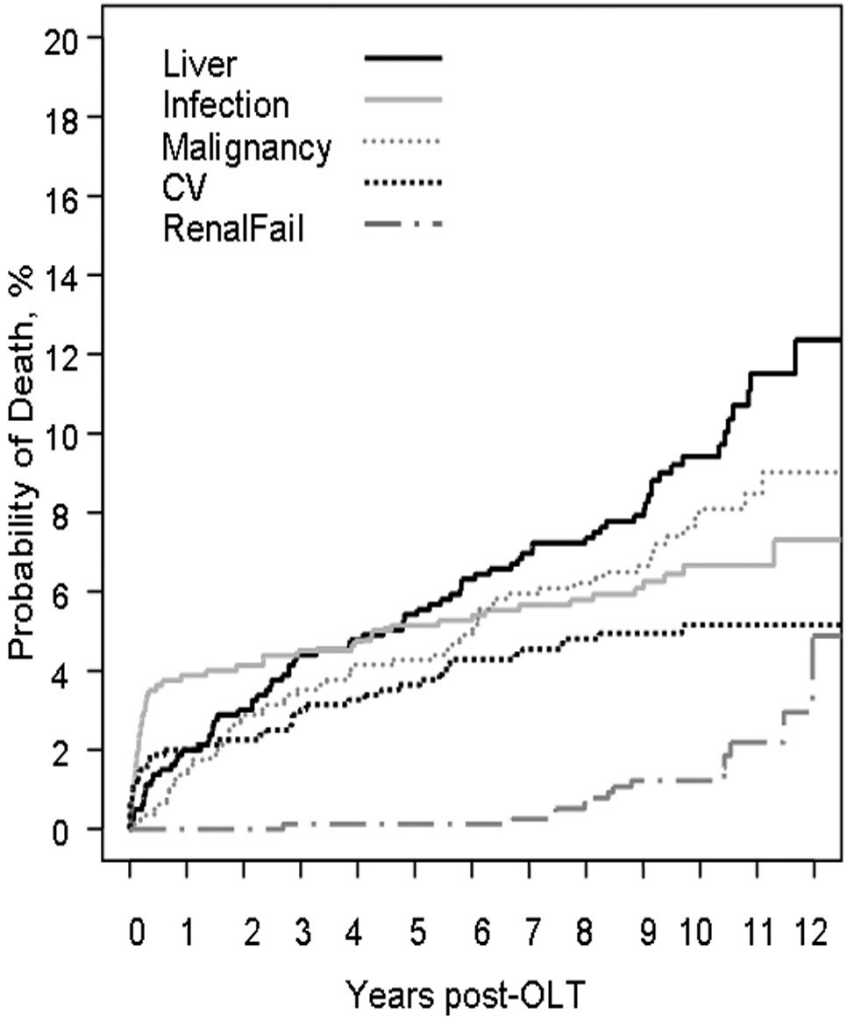
Renal-related mortality increased dramatically over time

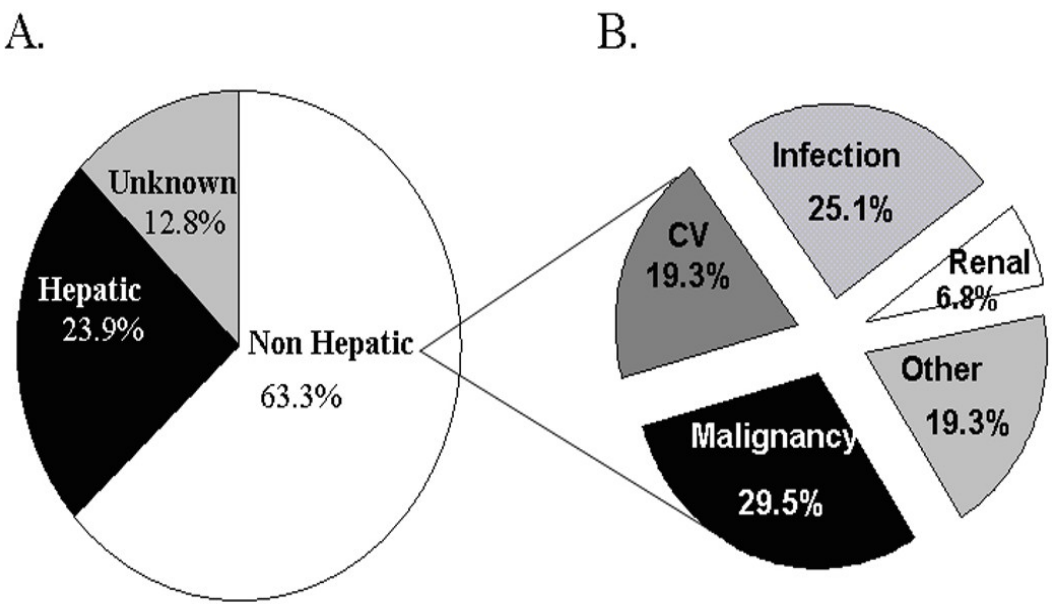
- **10.2% of deaths after 5 years | greatest increase among the major causes**
- **Increased probability after 8 years**
- **Sharp rise after 10 years**

- Renal insufficiency/failure was present in 17% of pre-LT, 47% of post-LT by 1 year, and 64% of post-LT patients overall
- Post-transplant renal insufficiency was strongly associated with increased overall mortality beyond 1 year (HR: 4.10, 95%CI: 2.87–5.86; P<0.001)

Watt KDS, et al. Am J Transplant. 2010

The evolving mortality in liver transplantation





Watt KDS, et al. Am J Transplant. 2010

Causes of mortality after LT in "real life"

The Montpellier LT team center

Indications	ALD	HCV	HCC	HBV	Other	Total
Causes of death	n = 206	n = 74	n = 57	n = 25	n = 79	
Recurrence	13/55 23.6%	6/21 28.6%	11/19 57.9%	1/4 25%	10/19 52.6%	41/118 34.7%
Non-hepatic cancer	18/55 32.7%	5/21 23.8%	4/19 21%	2/4 50%	3/19 15.8%	32/118 27.1%
Cardiovascular	8/55 14.5%	2/21 4.7%	1/19 5.3%	1/4 25%	2/19 10.5%	14/118 11.9%
Infection	6/55 10.9%	4/21 9.5%	1/19 5.3%	0	1/19 5.3%	12/118 10.2%
Rejection	2/55 3.6%	2/21 4.7%	0	0	1/19 5.3%	5/118 4.2%
Others	8/55 14.5%	2/21 4.7%	2/19 10.5%	0	2/19 10.5%	14/118 11.9%
Total	55	21	19	4	19	118

Faure S et al. J Hepatol 2012

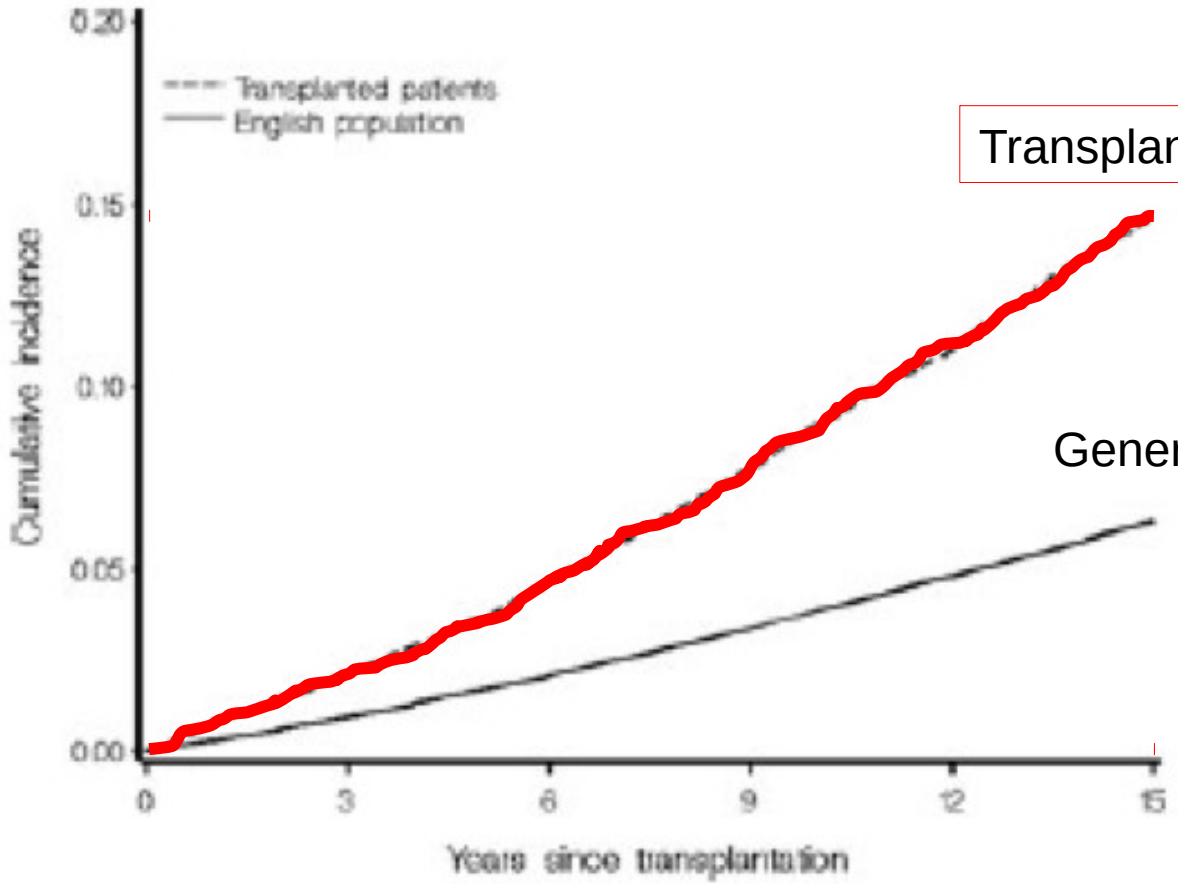
De novo cancer after LT

TABLE 1. Relative Risks of Neoplasia in Liver Transplant Recipients in Comparison with a Sex-Matched and Age-Matched Population

Type of Neoplasia	Relative Risk
Overall	2–4
Squamous and basal cell skin cancer	20–70
Lymphoma	10–30
Head and neck cancer	4–7
In alcoholic liver disease	25
Lung cancer	1.7–2.5
Colorectal cancer	3–12
In ulcerative colitis	25–30
Prostate cancer	Not increased
Breast cancer	Not increased
Kidney cancer	5–30
Kaposi's sarcoma	100
Hepatocellular carcinoma	3.4

Herrero Jl et al, Liver Transplant 2005

De novo cancer after LT



Transplanted patients

General population

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

Collett D, Am J Transplant 2010

De novo cancer after LT in France

Table 1. Comparison of the solid cancer incidences post-LT and in the general population. Incidences expressed per 100,000 persons and per annum

	Solid cancer	Oral cancer	Lung cancer	Digestive cancer	Colorectal cancer	Oesophageal cancer
Hérault registry						
Gross incidence	339.8	26.9	49.0	70.1	59.1	6.7
95% CI lower limit	337.2	26.1	48.0	68.9	58.0	6.3
95% CI upper limit	342.5	27.6	50.0	71.3	60.2	7.1
Standardized incidence	203.4	17.8	29.5	39.9	33.3	4.0
95% CI lower limit	199.4	17.7	29.3	39.6	33.1	4.0
95% CI upper limit	207.4	17.9	29.7	40.2	33.5	4.0
LT population						
Gross incidence	1310.8	352.9	302.5	327.7	176.5	100.8
95% CI lower limit	998.8	209.0	171.8	190.3	84.1	37.8
95% CI upper limit	1720.2	595.9	532.7	564.4	370.1	268.7
Standardized incidence	760.0	281.4	150.5	145.3	88.8	41.8
95% CI lower limit	721.7	268.2	148.9	143.7	88.1	41.6
95% CI upper limit	800.3	295.3	152.1	147.0	89.6	42.1
Relative risk	3.7	15.8	5.1	4.6	2.7	10.5
95% CI lower limit	2.8	9.4	2.9	2.6	1.3	3.9
95% CI upper limit	4.9	26.7	9.0	7.8	5.6	27.9
P value	<0.001	<0.001	<0.001	<0.001	0.007	<0.001

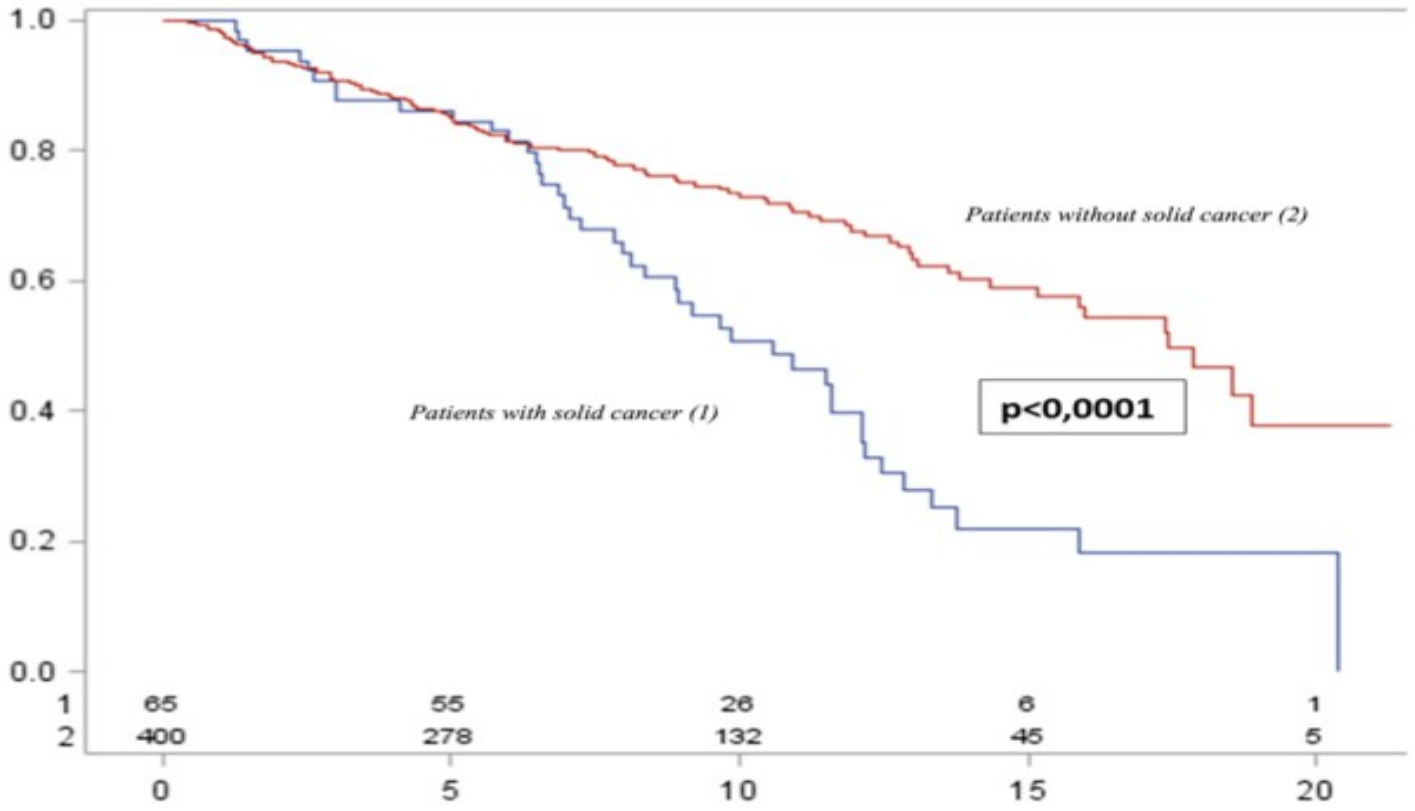
95% CI = 95% confidence interval

Study including 322 recipients

Carenco C, Liver Int 2015

Survival is impaired in case of *de novo* cancer after Liver Transplantation

Overall survival of patients who developed solid cancers or not



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Carenco C, Liver Int 2015

What are the exact statements regarding long-term complication after Liver Transplantation ?

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Immunosuppression after LT:
good intentions, accelerating life countdown…

What's CNI minimization?

A / Tac C0 Levels 10-15 ng/mL

B / Tacrolimus withdrawal

C / Target Tac C0 levels at 5 ng/mL

D / Tac C0 levels 5-8 ng/mL

E / Immunosuppresion withdrawal

Immunosuppression withdrawal because liver is a « tolerogenic organ » !

TABLE 2. Elective Withdrawal Studies

Center (No. of Patients)	Adult or Pediatric	DDLT or LDLT	Baseline IS	Years from LT to Tapering	Tolerant	Failure*
Pittsburgh (n = 95)	Both	DDLT	TAC or CyA + AZA	Mean, 8.4 ± 4.7	18 (18.9%)	40 (42.1%)
London (n = 18)	Adult	DDLT	CyA, AZA, prednisolone	Median, 7 (5-11)	5 (27.7%)	13 (72.2%)
Kyoto (n = 115)	Pediatric	LDLT	TAC	>2	49 (42.6%)	20 (17.4%)
Murcia (n= 9)	Adult	DDLT	CyA	Median, 5.1 (2-9)	3 (33.3%)	6 (66.6%)
Rome (n = 34, only HCV)	Adult	DDLT	CyA	Mean, 5.3 ± 1.7	8 (23.5%)	26 (76.5%)
New Orleans (n = 18)	Adult	DDLT	TAC	>0.5	1 (5.6%)	17 (94.4%)
Winnipeg (n = 26)†	Adult	DDLT	CyA + AZA or prednisolone	Mean, 4.3 ± 1.1	8 (30.8%)	18 (69.2%)
Miami (n = 104)‡	Adult	DDLT	TAC or CyA	Median, 4 (3.6-4.6)	23 (22.1%)	81 (61.5%)
Barcelona (n = 102)	Adult	DDLT	TAC or CyA	Median, 7.9	40 (77.9%)	62 (60.0%)

*Either due to rejection, immune-mediated hepatitis, noncompliance, resumption of immunosuppression, disease recurrence, or other. The remaining patients were deemed "weaning in progress" in all studies.
†Randomized controlled trial of ursodeoxycholic acid given at 15 mg/kg/day versus placebo in withdrawing patients; 3 patients developed autoimmune hepatitis recurrence after withdrawal.
‡45 received donor bone marrow cell infusions; 59 did not.

Letvisky J et al Liver Transplant 2011

The liver as a tolerogenic organ
More or less !

Lucky !

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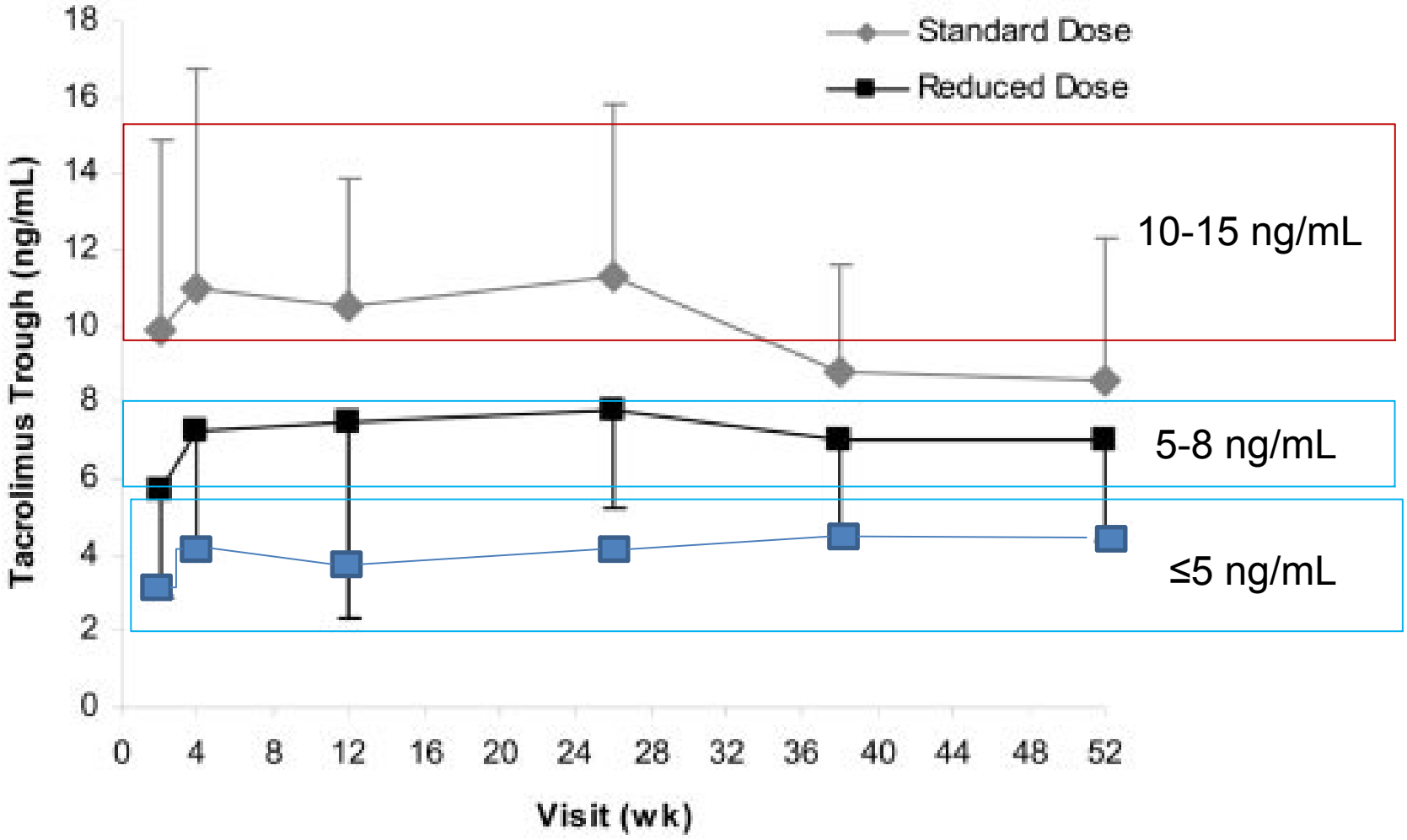
Unlucky…

IS withdrawal = russian roulette so far…

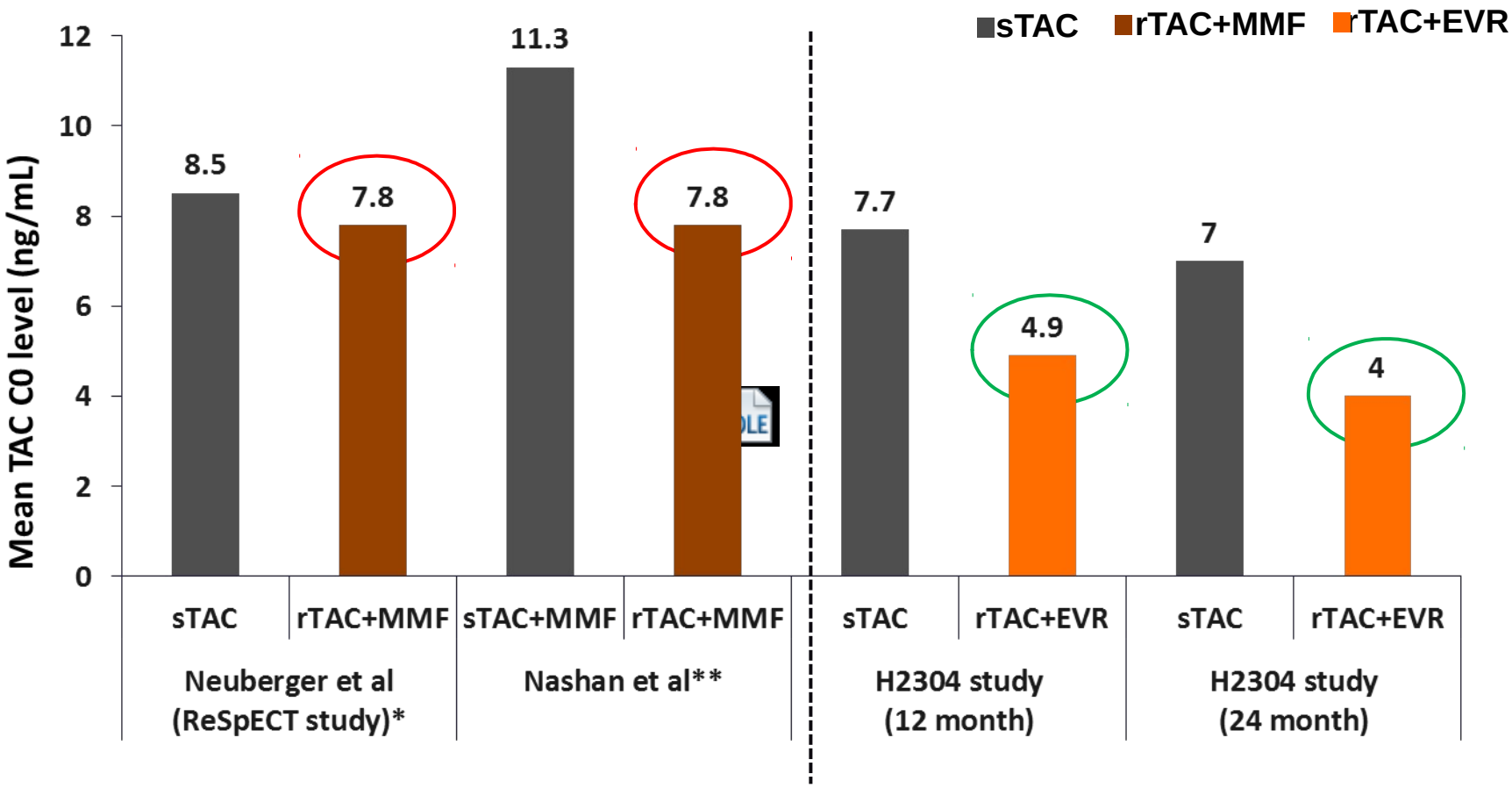
Letvisky J et al Liver Transplant 2011

Current concept of CNI minimization



Nashan B, et al. Liver Transpl 2009

Reduction in Tacrolimus Trough Levels Achieved in Different Studies



Neuberger JM et al. Am J Transplant 2009;9:327–336
Nashan B et al. Liver Transplant 2009;15:136–147

What's CNI minimization?

A / Tac C0 Levels 10-15 ng/mL

B / Tacrolimus withdrawal

C / Target Tac C0 levels at 5 ng/mL

D / Tac C0 levels 5-8 ng/mL

E / Immunosuppresion withdrawal

Clinical observation (1)

- 58 years old woman
- Past medical history: diabetes, dyslipidemia, smoking 30 pack/year, COPD, appendectomy
- Weight 55 kg, Size 1m68, BMI 19
- LT on October 30 2007 for decompensated alcoholic cirrhosis with hepatorenal syndrome (Child Pugh C10, MELD 24)
- Native liver without HCC
- Immunosuppressive regimen:
  - Solupred withdrawn in May 2008
  - Tacrolimus 6 mg x2 /d (C0: 10 ng/mL)
  - MMF (Cellcept) 1 g × 2/day

What are the *de novo* cancer risk factors identified in this patient ?

A / Age > 50 years

B / History of alcoholic liver disease

C / Gender

D / Smoking

E / Exposure to CNI

F / Weight

Environmental risk factors

Table 3. Risk Factors for Solid Organ Malignancy: Multivariate Analysis

Risk factor	HR (95% CI)	*P* value
Age by decade	1.33 (1.05–1.66)	.014
Smoking history	1.72 (1.06–2.79)	.029
ALD	2.14 (1.22–3.73)	.007
PSC	2.62 (1.50–4.56)	.001

ALD, alcohol-related liver disease; CI, confidence interval; HR, hazard ratio; PSC, primary sclerosing cholangitis.

Study including 798 recipients

Watt KD, Gastroenterology 2009

Table 2. Risk factors for developing *de novo* solid cancer post-LT, univariate and multivariate analyses

Univariate analysis of solid cancer risk factors (n = 465)

Variable	No solid cancer (N = 400) n/N (%)	Solid cancer (N = 65) n/N (%)	*P* value	OR	95% CI
Age at LT > 50 years	222/400 (55.5)	40/65 (61.5)	0.36		
Male	296/400 (74)	50/65 (76.9)	0.62		
Excessive OH before LT	241/371 (65)	53/63 (84.1)	0.003	2.9	(1.4; 5.8)
Excessive OH after LT	44/383 (11.5)	12/64 (18.8)	0.10		
Diabetes	142/391 (36.3)	26/64 (40.6)	0.51		
Smoking before LT	200/372 (53.8)	54/64 (84.4)1	<0.0001	4.6	(2.3; 9.4)
Smoking after LT	119/370 (37.2)	36/64 (56.3)	0.0002	2.7	(1.6; 4.6)
Obesity	60/381 (15.8)	17/62 (27.4)	0.02	2	(1.1; 3.8)

Patients included in the study (N = 465): multivariate analysis of solid cancer risk factors

Variable	*P* value	OR	Wald 95% CI
Smoking before LT	<0.0001	5.5	(2.5; 12)
Obesity	0.0184	2.2	(1.1; 4.3)

Table 3. Univariate and multivariate analysis of risks factors for *de novo* solid cancers post-LT with tacrolimus

Risks factors for *de novo* solid cancer after LT with tacrolimus

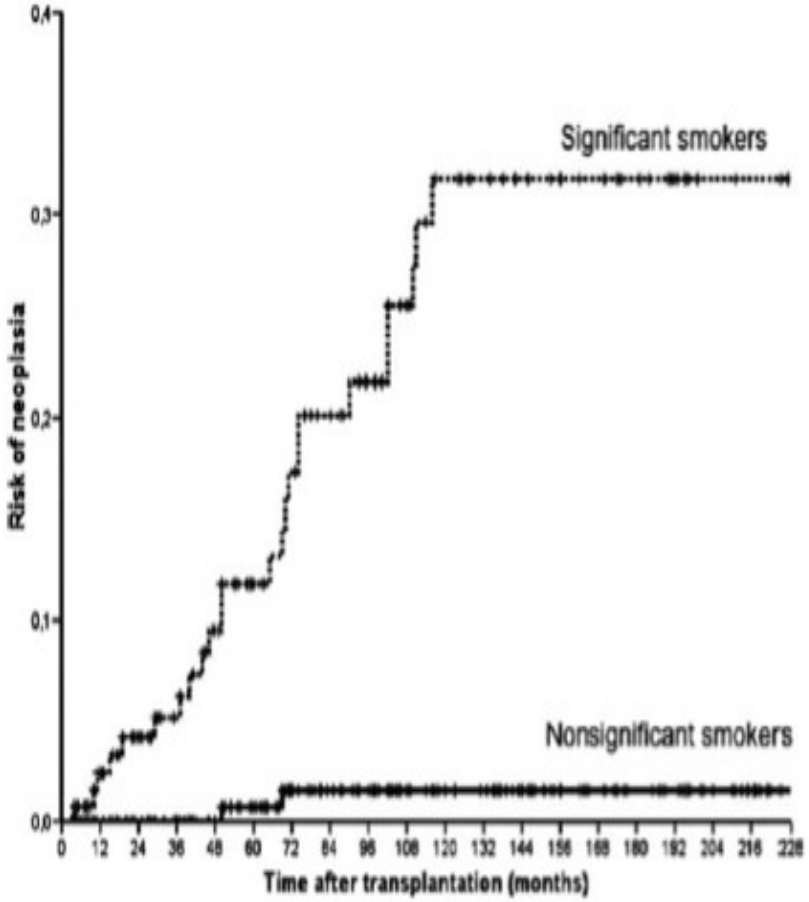
	Tacrolimus 1 year (43 with C & 204 without C)					
	Univariate analysis			Multivariate analysis		
Variable	*P* value	OR	95% CI	*P* value	OR	95% CI
Age >50	0.37	NS				
Male	0.7	NS				
Alcohol pre-LT	0.07	NS				
Alcohol post-LT	0.27	NS				
Diabetes mellitus	0.56	NS				
Tobacco pre-LT	0.0001	5.1	(2.1–12.6)	0.002	4.54	(1.74–11.8)
Tobacco post-LT	0.002	2.8	(1.4–5.5)			
Obesity	0.12	NS				
CNI level exposure*	<0.0001	11.2	(3.9–32.5)	<0.0001	15.3	(4.5–52.2)

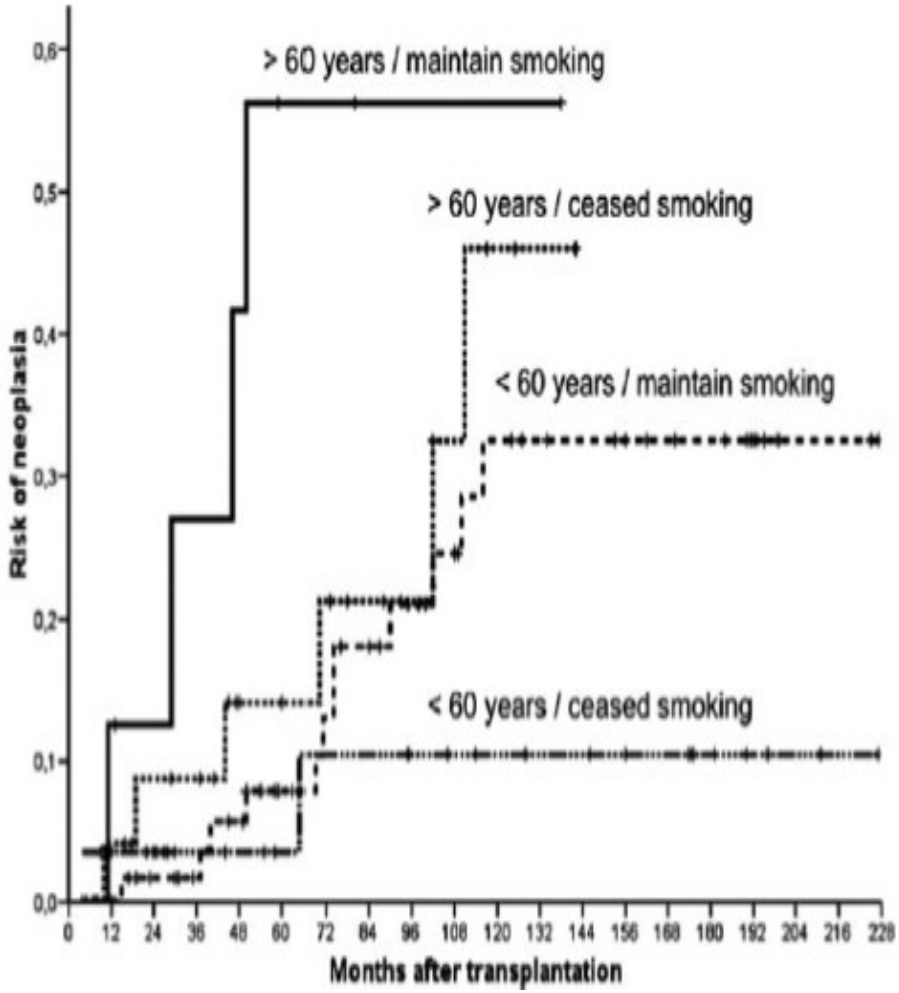
*Mean annual tacrolimus blood trough concentration > 8 ng/ml during the first year after LT and > 7 ng/ml during the 3 years after LT.

LT, liver transplantation; NS, non-significant; C, cancer. CNI, calcineurin inhibitors.

Carenco C, Liver Int

Smoking and *de novo* cancer

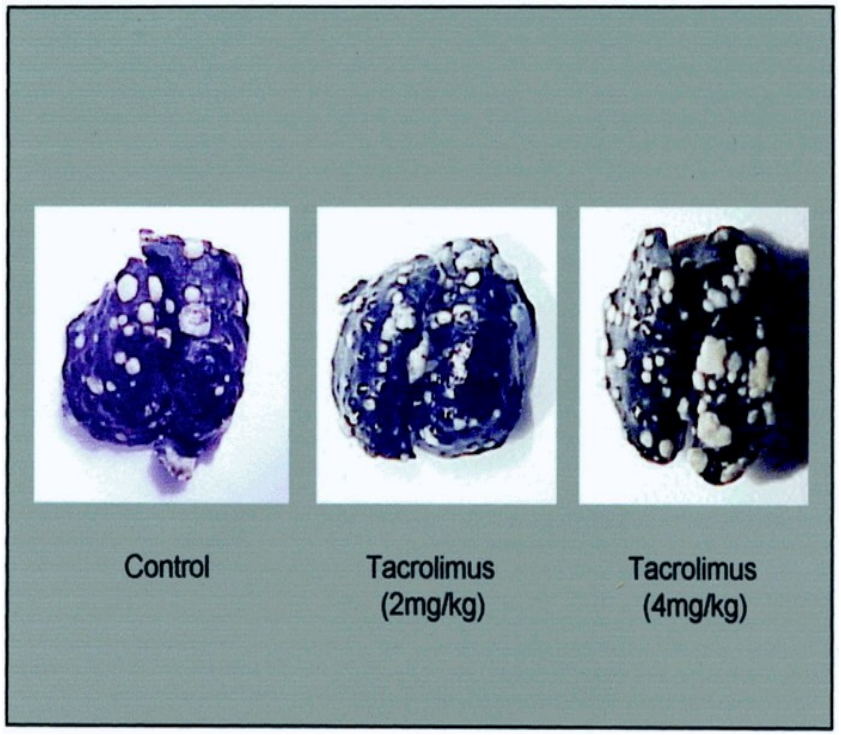


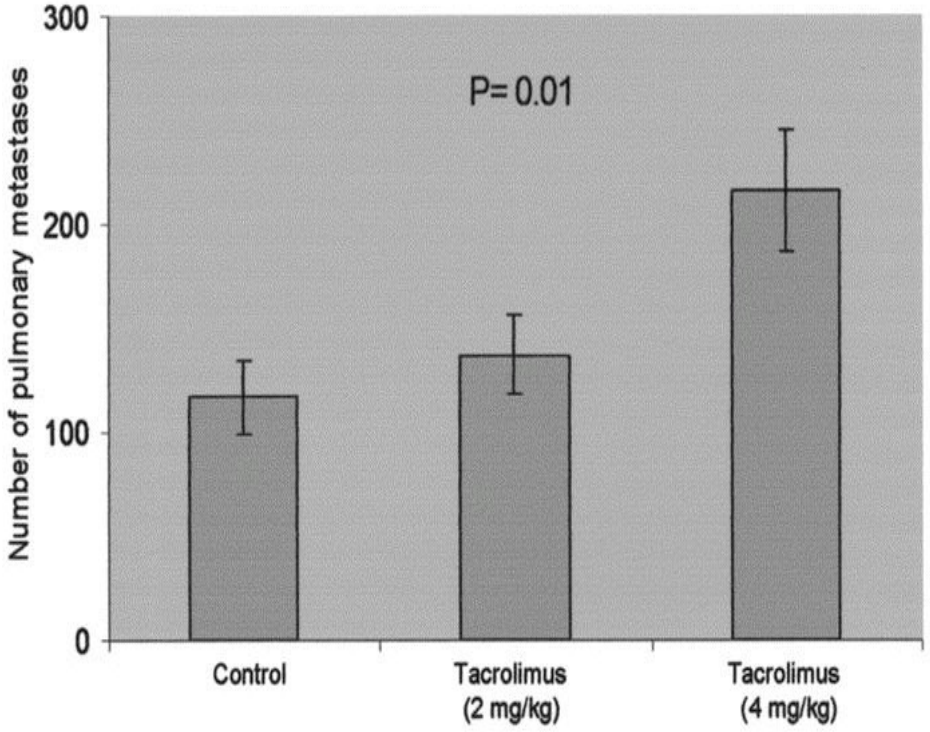


Herroro JI, Liver Transpl 2011

Experimental arguments in favor the linkage between CNI and cancer

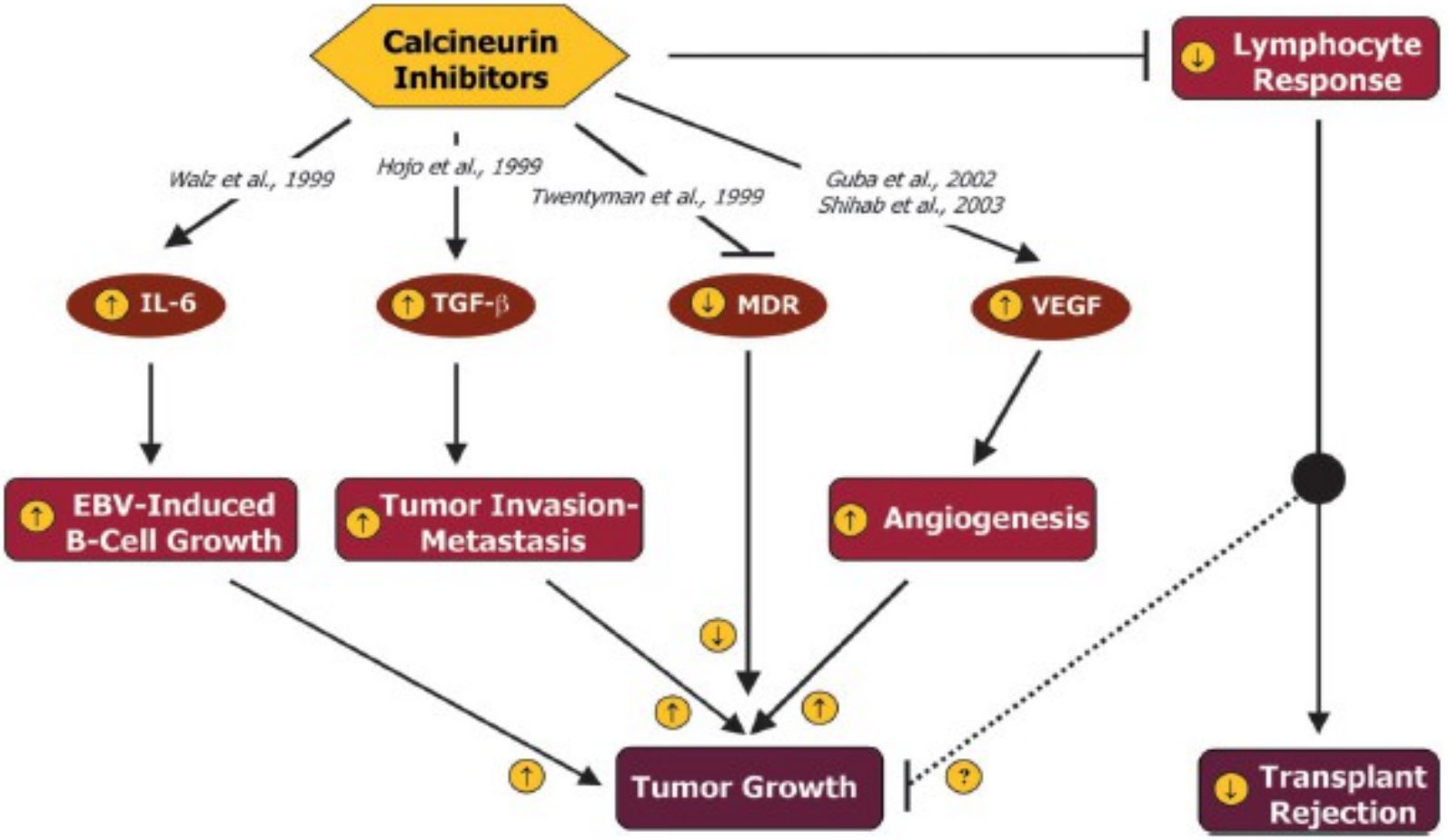
Number of lung metastases in a model
of renal cancer metastases in SCID mice





Maluccio et al. Transplantation 2003

CNI promotes tumor growth, metastasis and angiogenesis



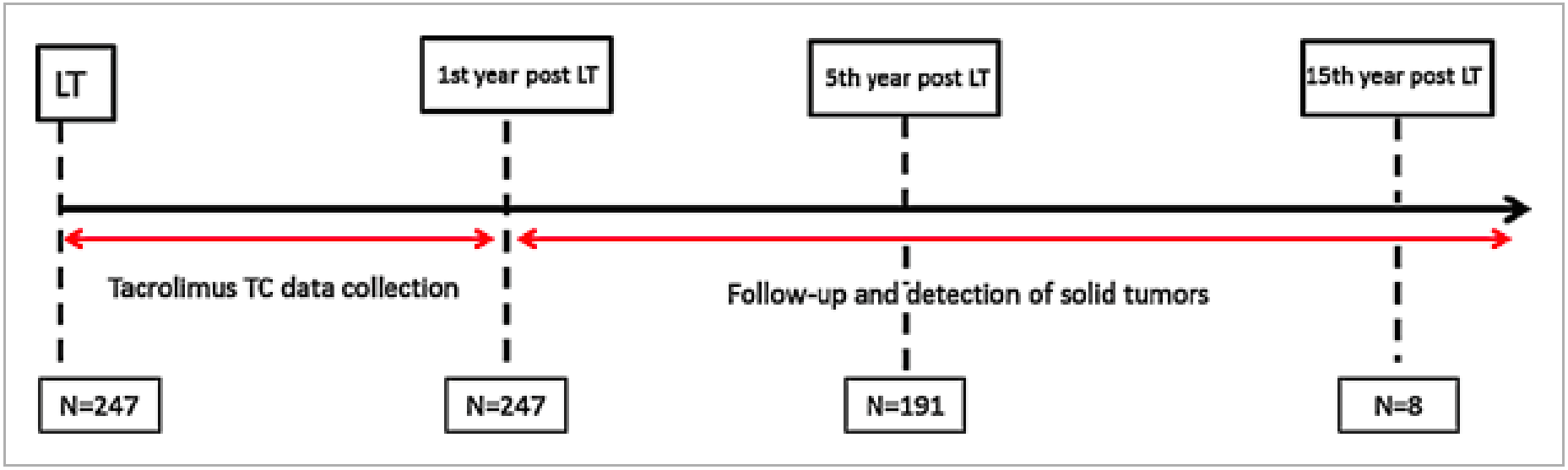
Guba et al. Transplantation 2004

American Journal of Transplantation
AST AMERICAN SOCIETY OF TRANSPLANTATION ASTS

Tacrolimus and the Risk of Solid Cancers After Liver Transplant: A Dose Effect Relationship

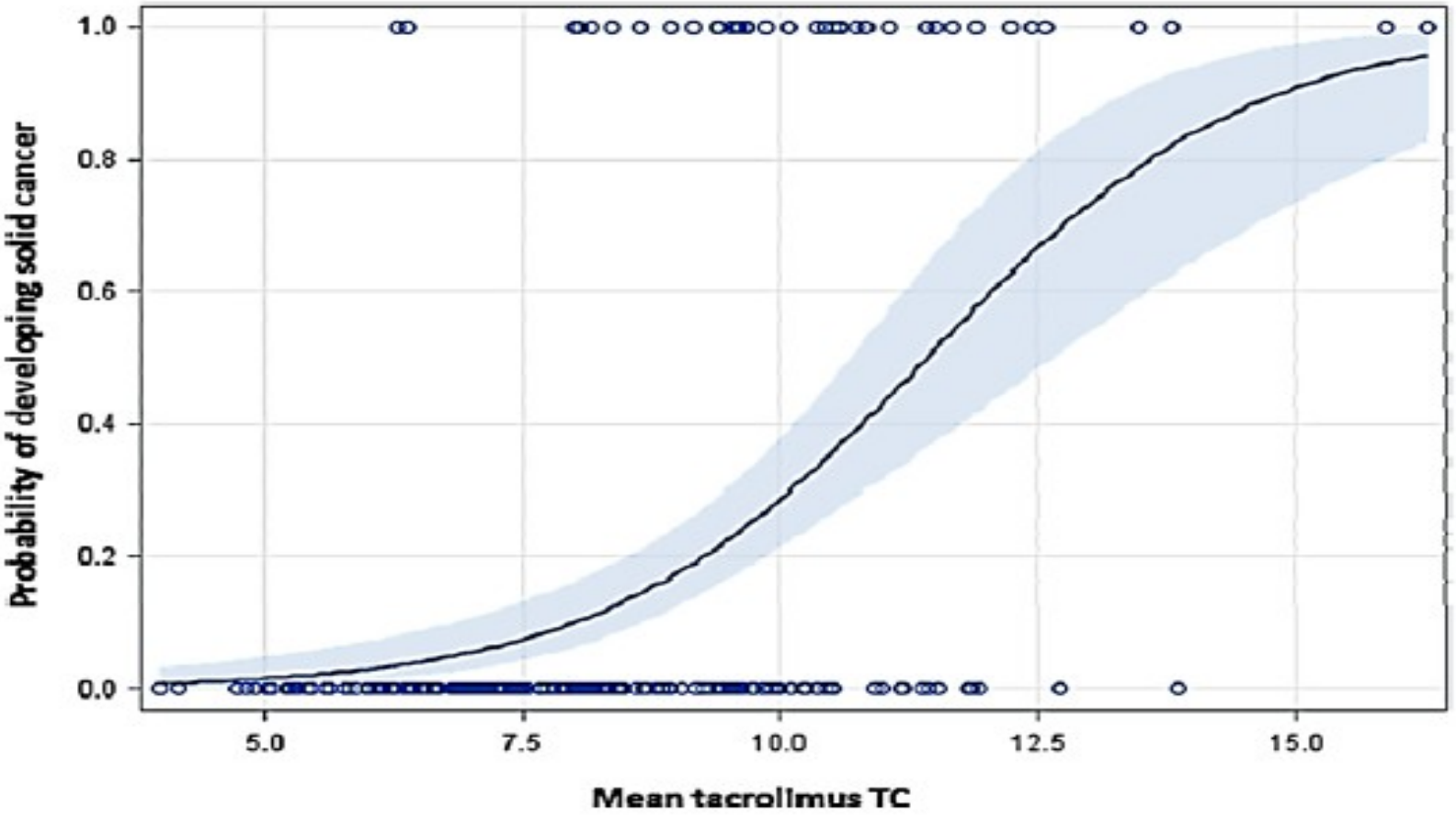
C. Carenco, E. Assenat, S. Faure, Y. Duny, G. Danan, M. Bismuth, A. Herrero, B. Jung, J. Ursic-Bedoya, S. Jaber, D. Larrey, F. Navarro, G.-P. Pageaux

First published: 3 February 2015 Full publication history



CNI exposure and the risk of solid cancers after LT
A dose effect relationship

Relationship between mean TC during the first year and occurrence of solid cancers



Carenco C, et al. Am J Transplant 2015

What are the *de novo* cancer risk factors identified in this patient?

A / Age > 50 years

B / History of alcoholic liver disease

C / Gender

D / Smoking

C / Exposure to CNI

D / Weight

Clinical observation (2)

- October 2012 (5 years post LT)
- Gradual development of chronic renal dysfunction
  - eGFR at 40 mL/min/kg
  - Proteinurea 0.2 g/L
- Arterial hypertension despite bitherapy
- Liver function tests : normal values

What are you proposing?

A / Tac whithdrawal and monotherapy with mycophenolate

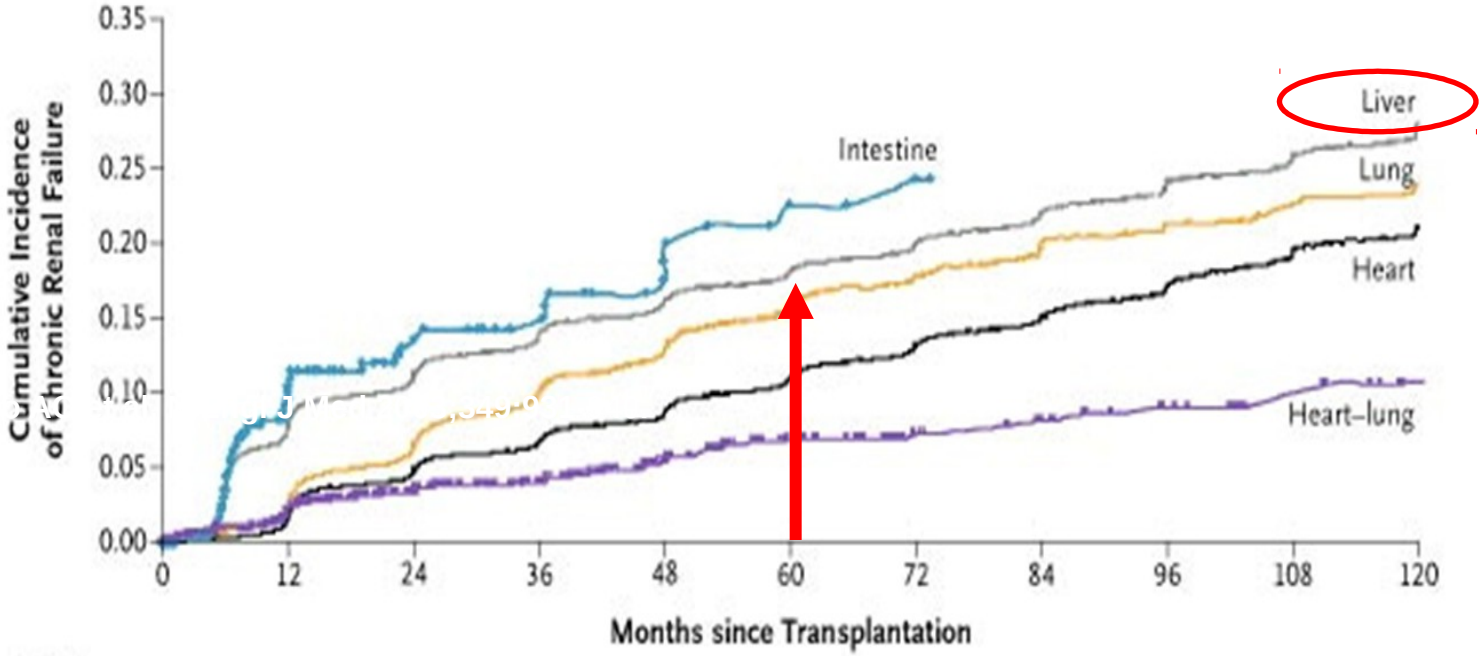
B / Dual therapy mycophenolate + everolimus

C / Switch from Tac to everolimus monotherapy

D / No change for now…

E / Low dose of Tac (target C0 3-5 ng/mL) + everolimus start

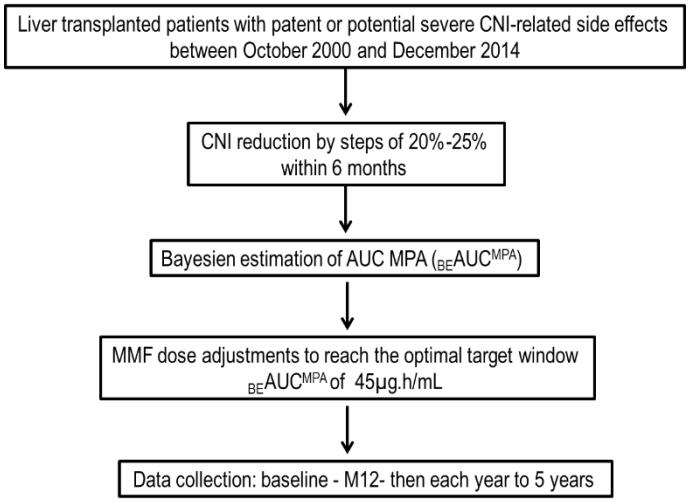
CRD after LT



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

Ojo AO. et al, New Engl J Med 2003

CNI withdrawal and monotherapy MMF for serious CNI-induced side effects



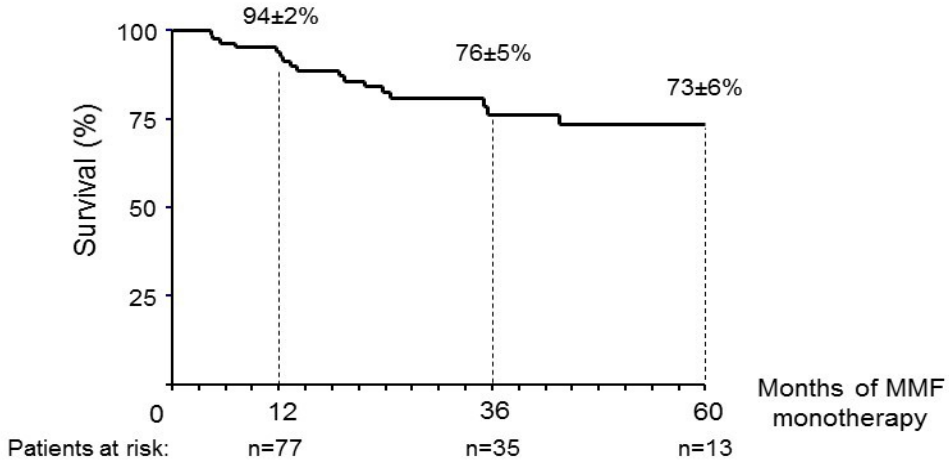
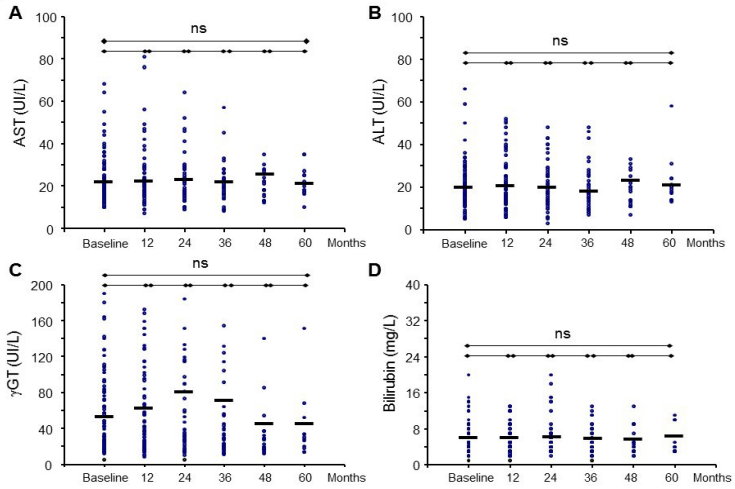
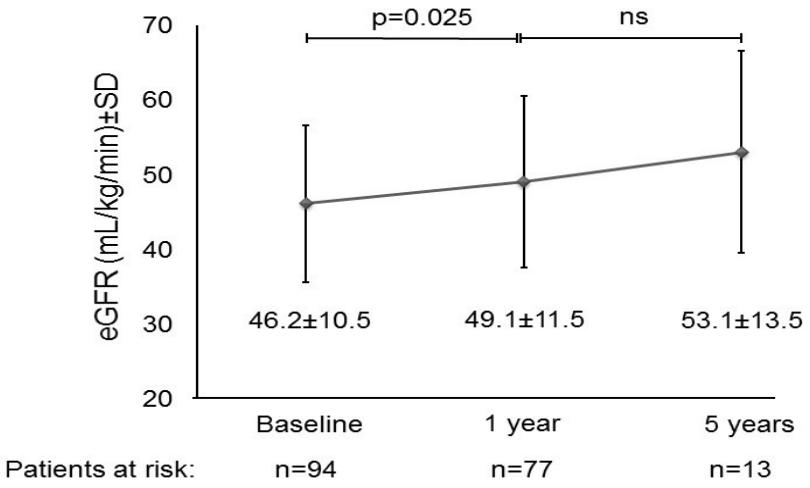


Figure 3





Lassaily G, et al. Submitted

CNI minimization with antimetabolites/induction agents in de novo liver transplantation

Author	Design	IS	AR	Renal function (eGFR*), mean	F-UP (mo)	Comments
Boudjema et al 2011	Randomized controlled	CNI+S (#100) rCNI+MMF+S (#95)	46% vs. 30% (p=0.024)	78 ± 26 vs. 90 ± 30 (p = 0.004**)	12	rCNI+MMF+S: superior outcome of renal function and rejection rates
Benitez et al 2010	Randomized controlled	TAC+S (#16) vs. ATG+rTAC→ weaning 3 mo. (#21)	31.2% vs. 66.7% (p=0.03)	NA	12	Study stopped prematurely due to ↑rejection in very-low TAC arm (<5ng/mL)
Neuberger et al 2009	Randomized controlled	(A)TAC-C+S vs. (B)rTAC+MMF+S vs. (C) anti-CD25+ +drTAC+MMF+S	27.6% vs. 29.2% vs. 19.0%	eGFR decrease by 23.61 vs. 21.22 vs. 13.63 mL/min at M12 (A vs C, p=0.012; A vs. B, p=0.199)	12	Superior renal function for anti-CD25+drTAC+MMF vs. TAC-C. Non superiority of rTAC+MMF vs. TAC due to overlapping blood levels
Nashan et al 2009	Randomized controlled	sTAC+MMF+S + (#28) vs. rTAC+MMF+S (#27)	17.8% vs. 18.5%	CrCl 66.3 (17.6-110.2) 78.6 (49.6-172.8)	6	Comparable efficacy

AR: acute rejection; ATG: anti-thymocyte globulin; CNI: calcineurin inhibitor; CNI-C: CNI control; CsA: cyclosporin; dCNI: delayed CNI; drCNI: delayed-reduced CNI; dTAC: delayed TAC; EVR: everolimus; F-UP: follow-up; IS: immunosuppression; MMF: mycophenolate mofetil; rCNI: reduced CNI; rTAC: reduced TAC; sTAC: standard TAC; S: steroids; SRL: sirolimus; TAC: tacrolimus; TAC-C: TAC control

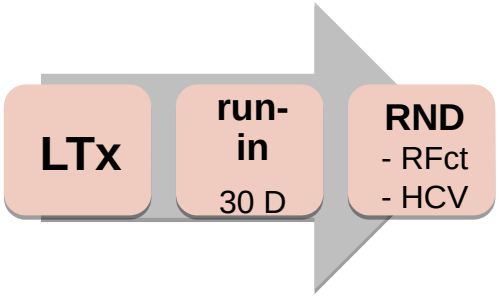
CNI minimization with antimetabolites/induction agents in de novo liver transplantation

Author	Design	IS	AR	Renal function (eGFR*), mean	F-UP (mo)	Comments
Otero A et al 2009	Randomized controlled	TAC+S (#79) vs. antiCD25+TAC+ MMF+S (#78)	26.6% vs. 11.5% (p=0.017)	sCr (mg/dL) 1.2 vs. 1.0	6	Overlapping between arms for TAC levels
Bajjoka et al 2008	Retrospective cohort	CNI+MMF+S (#80) vs. ATG+dCNI+ +MMF+S	26% vs. 16% (p=0.08)	43.7 vs. 57.4 (p< 0.001)	12	ATG induction with delayed CNI: lower incidence of early acute rejection and superior renal function
Lin et al 2005	Non-randomized controlled	TAC+S (#18) vs. BAX+rTAC+S (#27)	27.8% vs. 11.1 (p=ns)	Median CrCl at M3 57 vs. 72 mL/min (p=0.04)	6	Comparable efficacy of BAX+rTAC+S vs. TAC+S
Yoshida et al 2005	Randomized controlled	CNI+MMF+S (#76) vs. anti-CD25+drCNI+M MF+ S (#72)	27.7% vs. 23.2% (p=0.68)	69.5 vs. 75.4 (p=0.038) at 6 mo. 73.2 vs. 71.7 (p=0.587) at 12 mo.	12	Superior renal function under delayed rCNI only in the early post-transplant period

AR: acute rejection; ATG: anti-thymocyte globulin; BAX: basiliximab; CNI: calcineurin inhibitor; CNI-C: CNI control; CsA: cyclosporin; dCNI: delayed CNI; drCNI: delayed-reduced CNI; dTAC: delayed TAC; EVR: everolimus; F-UP: follow-up; IS: immunosuppression; MMF: mycophenolate mofetil; rCNI: reduced CNI; rTAC: reduced TAC; S: steroids; SRL: sirolimus; TAC: tacrolimus; TAC-C: TAC control.

EVR + rTAC after liver transplantation: the H2304 study design

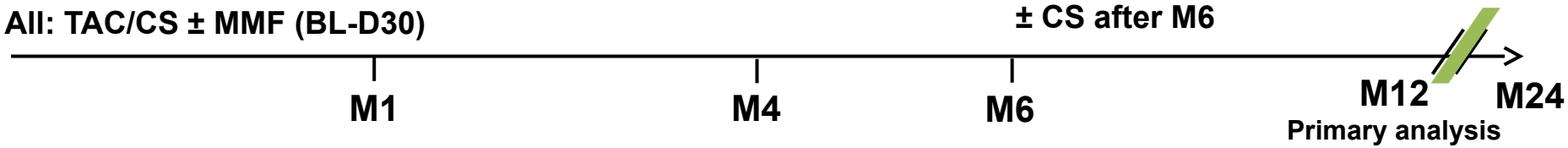
A multicenter, open-label, randomized, controlled study to evaluate the efficacy and safety of EVR to eliminate or reduce TAC in *de novo* liver transplant recipients



TAC Elimination halted early due to high AR rate

EVR + Reduced TAC — EVR C0 3–8 ng/mL; TAC C0 3–5 ng/mL

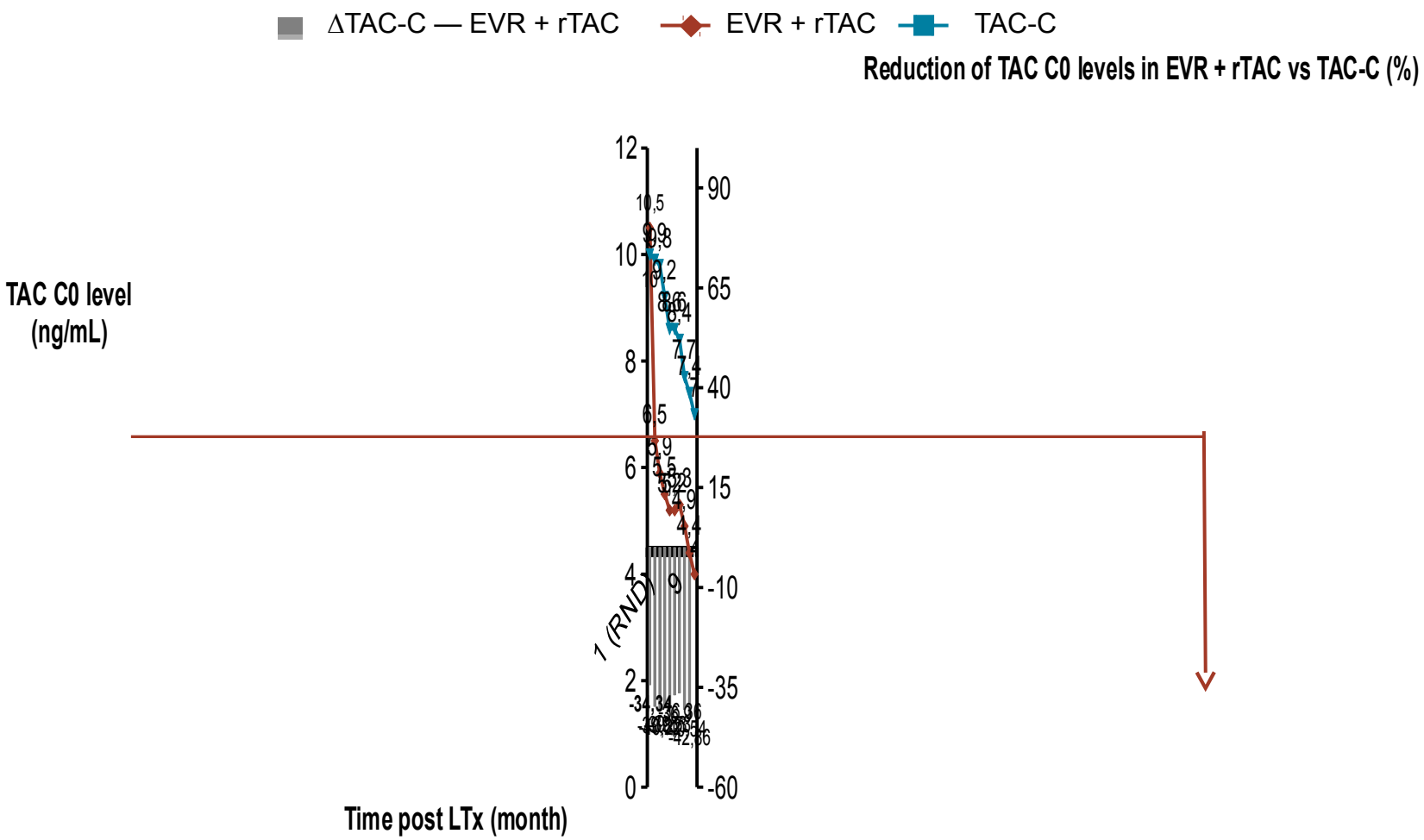
TAC Control — TAC C0 8–12 → ↓ 6–10 ng/mL (M4)



Enrollment into TAC-WD arm was stopped due to higher rejection rates and protocol was amended based on DMC recommendation (Apr 2010)

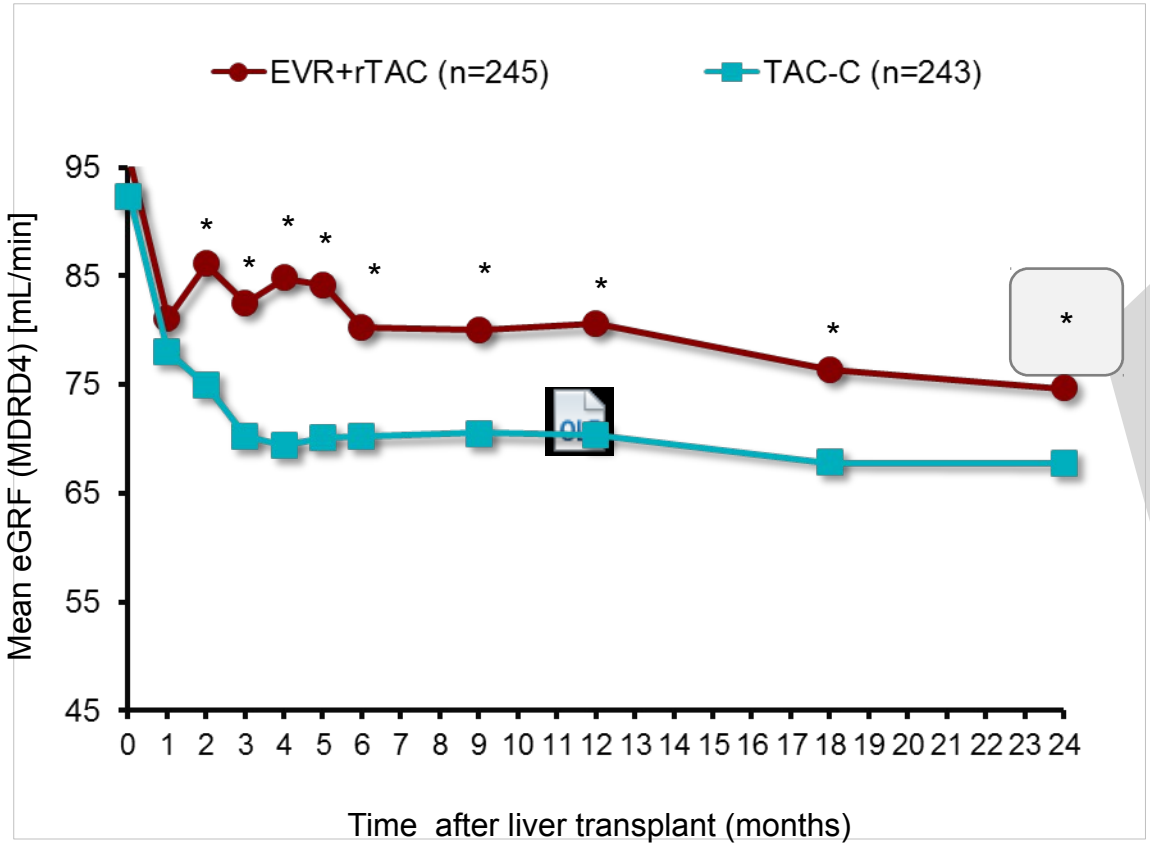
De Simone P, et al. Am J Transplant .2012;12:3008–20;

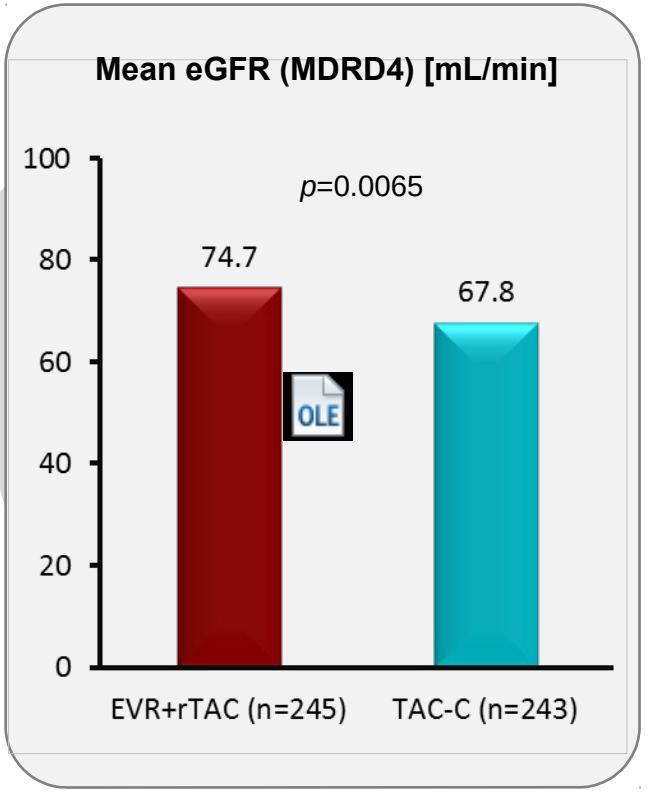
Clear separation and clinically relevant reduction in TAC exposure in EVR + rTAC arm



Saliba F, et al. Am J Transplant. 2013;13:1734–1745.

Renal function in patients on EVR + reduced TAC





Saliba F, et al. Am J Transplant. 2013;13:1734–1745.

What are you proposing?

A / Tac whithdrawal and monotherapy with mycophenolate

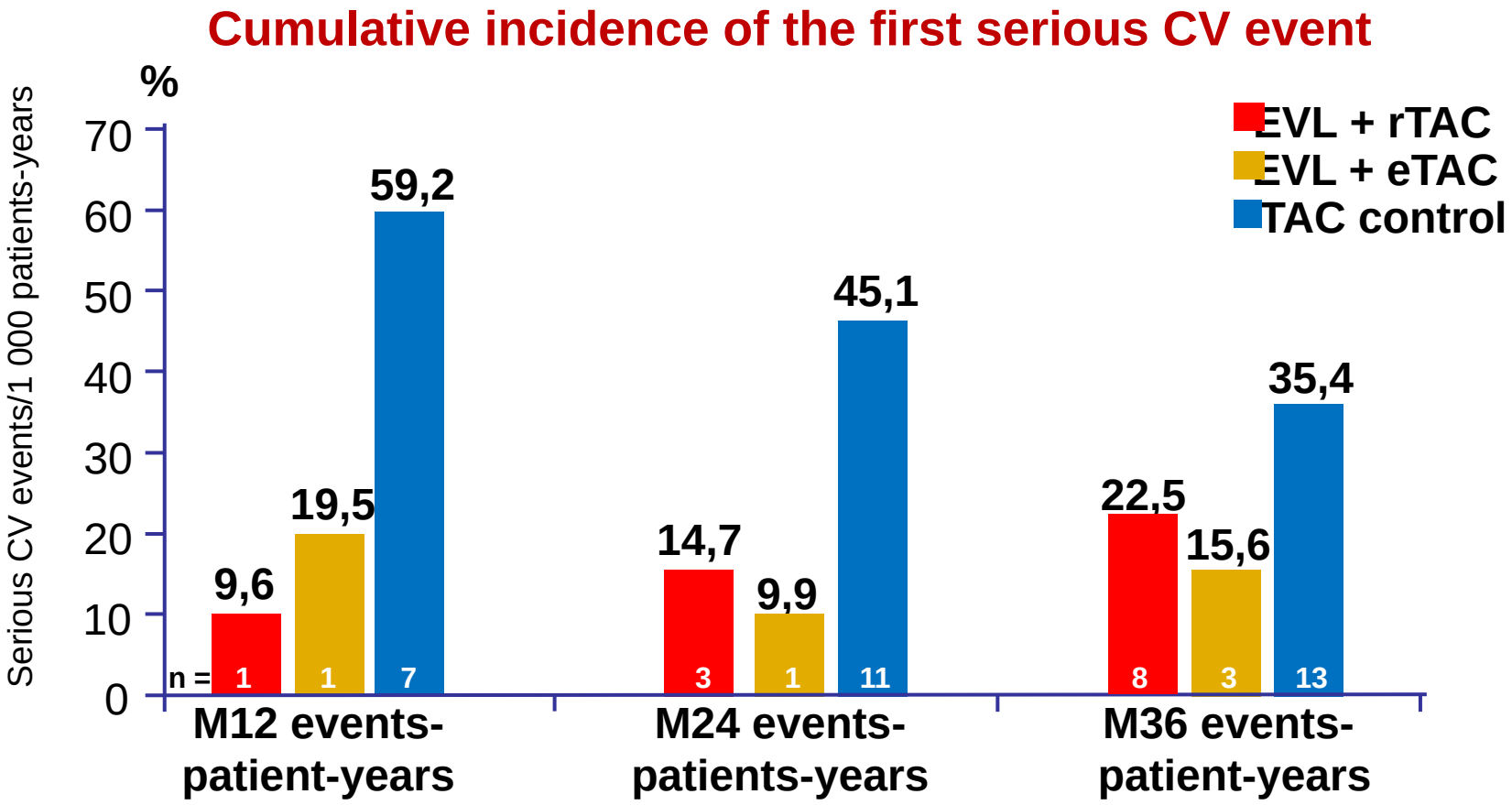
B / Dual therapy mycophenolate + everolimus

C / Switch from Tac to everolimus monotherapy

D / No change for now…

E / Low dose of Tac (target C0 3-5 ng/mL) + everolimus start

Lower risk of serious cardio-vascular events on EVR + reduced TAC



Bernhardt P, Suisse, ILTS 2016, Abs. O-07

Clinical observation (3)

- In February 2014: mandibular pain
- Oto-rhino-laryngology assessment: Endobuccal epidermoid carcinoma reaching the mandibular region
- Head - Neck Oncology comittee:
  - Surgery (pelvimandibulectomy with lymphadenectomy under temporary tracheostomy)
  - Adjuvant radiotherapy.
- IS : Tac and MMF…

What is your management with IS ?

A / Tac whithdrawal and monotherapy with mycophenolate

B / Dual therapy mycophenolate + everolimus

C / Switch from Tac to everolimus now

D / Switch to everolimus one month after surgery

E / No change for now…

F / Sparing strategy with Tac to target C0 5-8 ng/mL

My management would be…

A / Tac whithdrawal and monotherapy with mycophenolate

B / Dual therapy mycophenolate + everolimus

C / Switch from Tac to everolimus now

D / Switch to everolimus one month after surgery

E / No change for now…

F / Sparing strategy with Tac to target C0 5-8 ng/mL

Why not ?

A / Tac whithdrawal and monotherapy with mycophenolate

B / Dual therapy mycophenolate + everolimus

C / Switch from Tac to everolimus now

D / Switch to everolimus one month after surgery

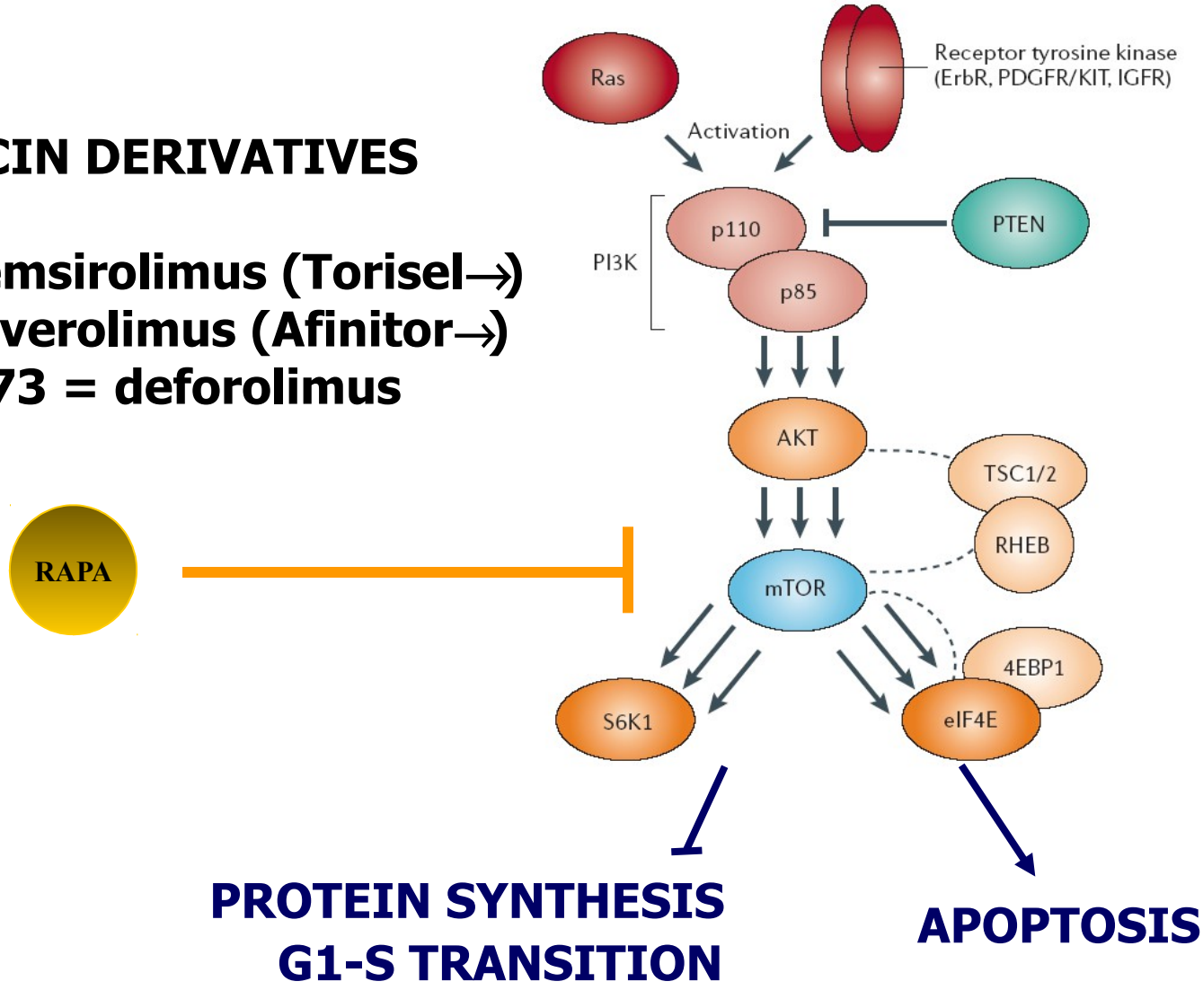
E / No change for now…

F / Sparing strategy with Tac to target C0 5-8 ng/mL

Blocking mTOR inhibits protein synthesis, cell cycle transition and restores apoptosis

RAPAMYCIN DERIVATIVES

CCI779 = temsirolimus (Torisel→)
RAD001 = everolimus (Afinitor→)
AP23573 = deforolimus



mTOR Inhibitors in recipients with de novo cancer

Use of Everolimus as a Rescue Immunosuppressive Therapy in Liver Transplant Patients With Neoplasms

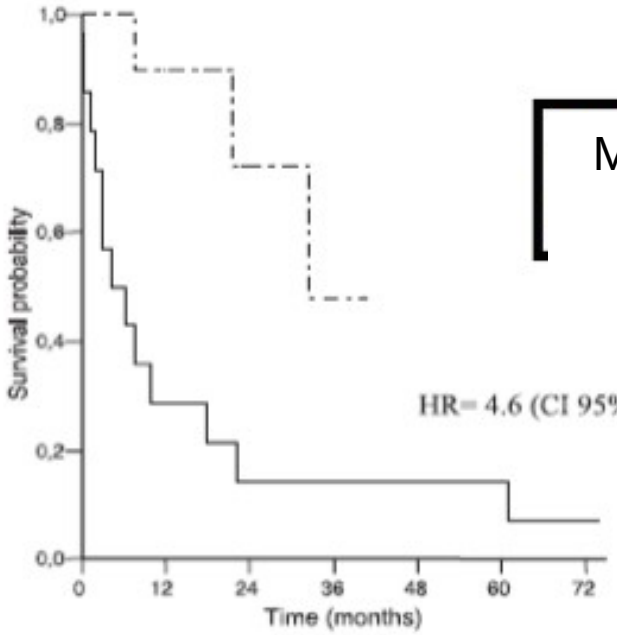
Judith Gomez-Camarero, Magdalena Salcedo, Diego Rincon, Oreste Lo Iacono, Cristina Ripoll, Ana Hernando, Cecilia Sanz, Gerardo Clemente, and Rafael Bañares

Transplantation 2007

- 10 patients with SOT after LT

VS

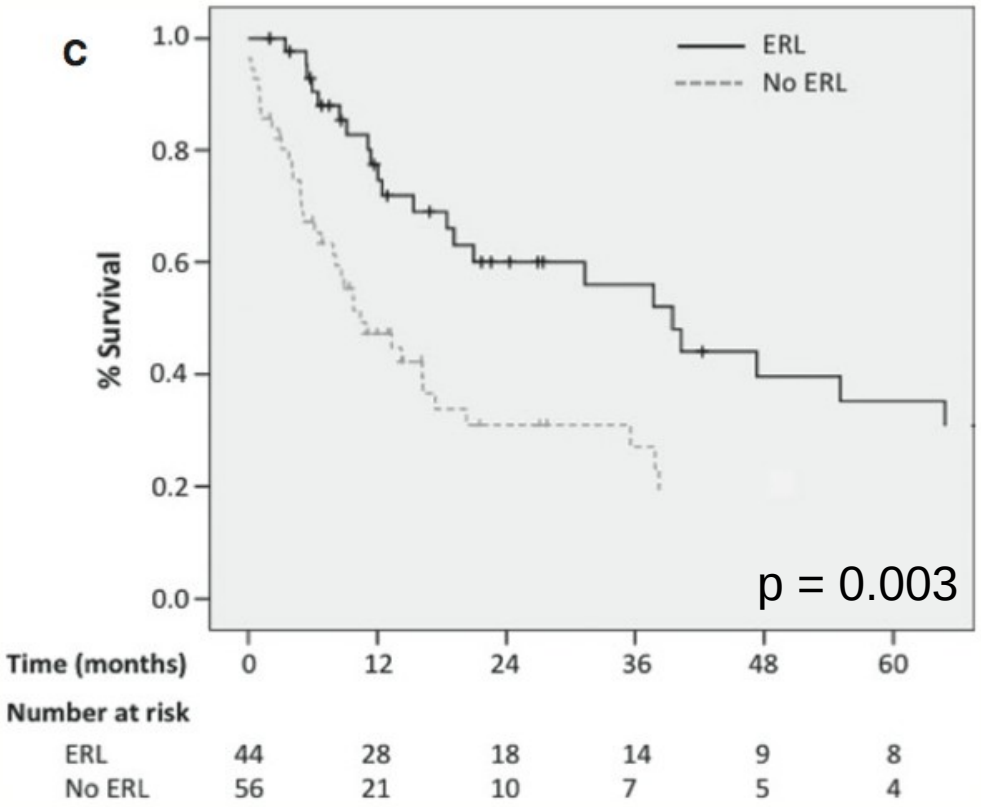
- Historical control without EVL



Median survival 21.3 vs 5.3 months

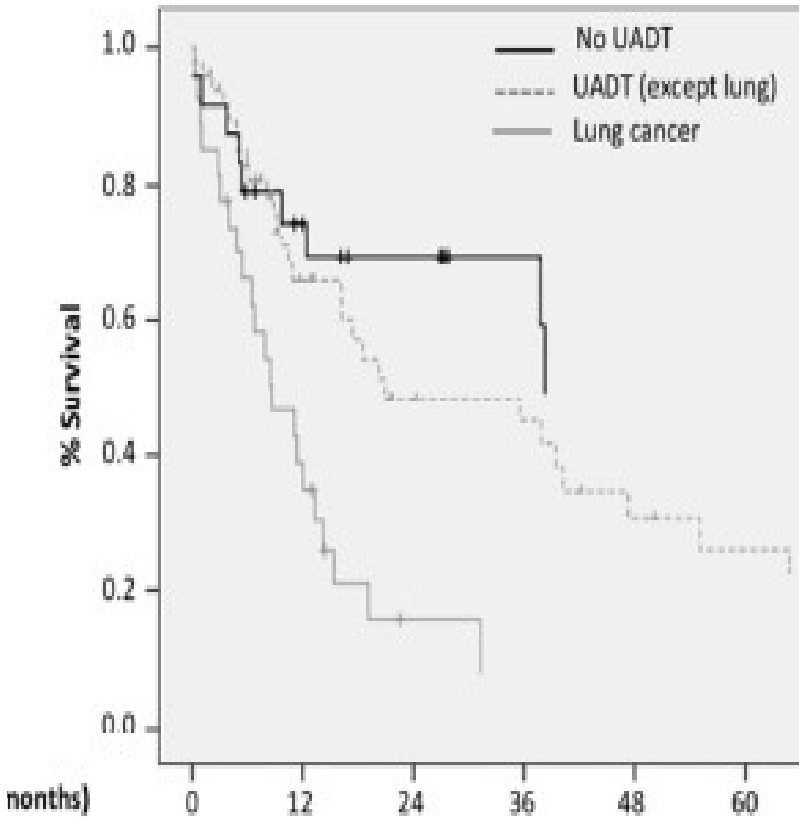
Conversion to everolimus dramatically improves the prognosis of de novo malignancies after liver transplantation for alcoholic liver disease

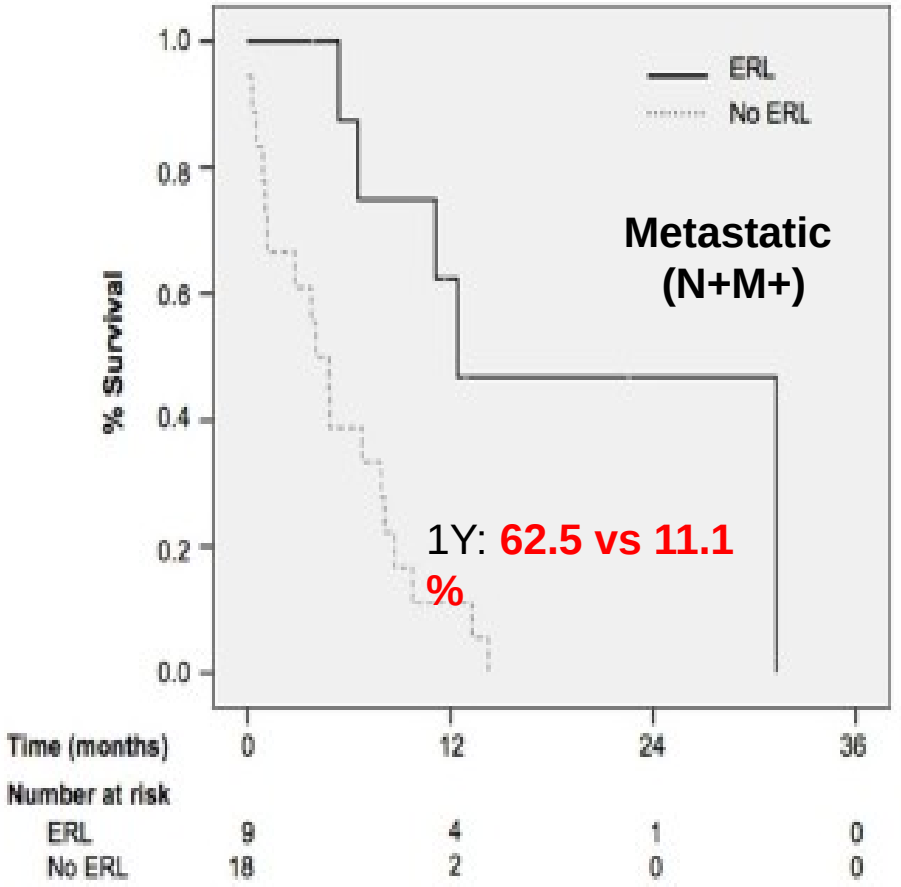
- Retrospective study
- De novo SOT after LT for ALD
- 83 patients : 38 pts EVR
- EVR :
  - One year survival 77, 4 % vs 47,2 %
  - 5 years survival35,2% vs 19,4 %
  - p = 0,003
  - RR 0,447



Thimonier E, Clin Transpl 2014

Conversion to everolimus dramatically improves the prognosis of de novo malignancies after liver transplantation for alcoholic liver disease

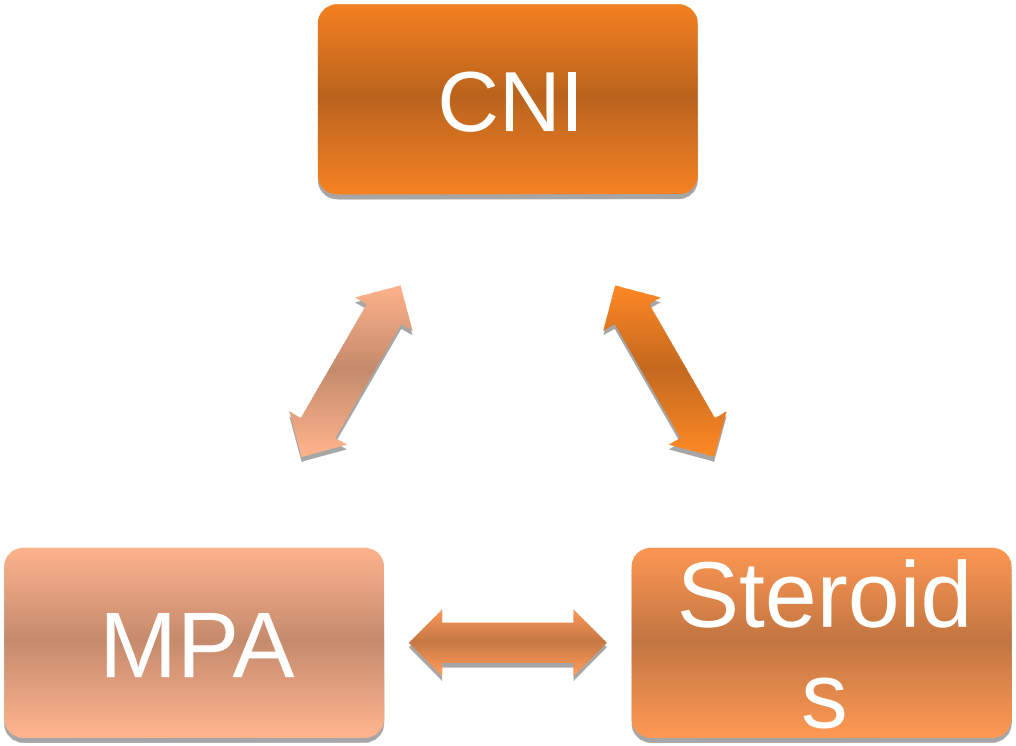




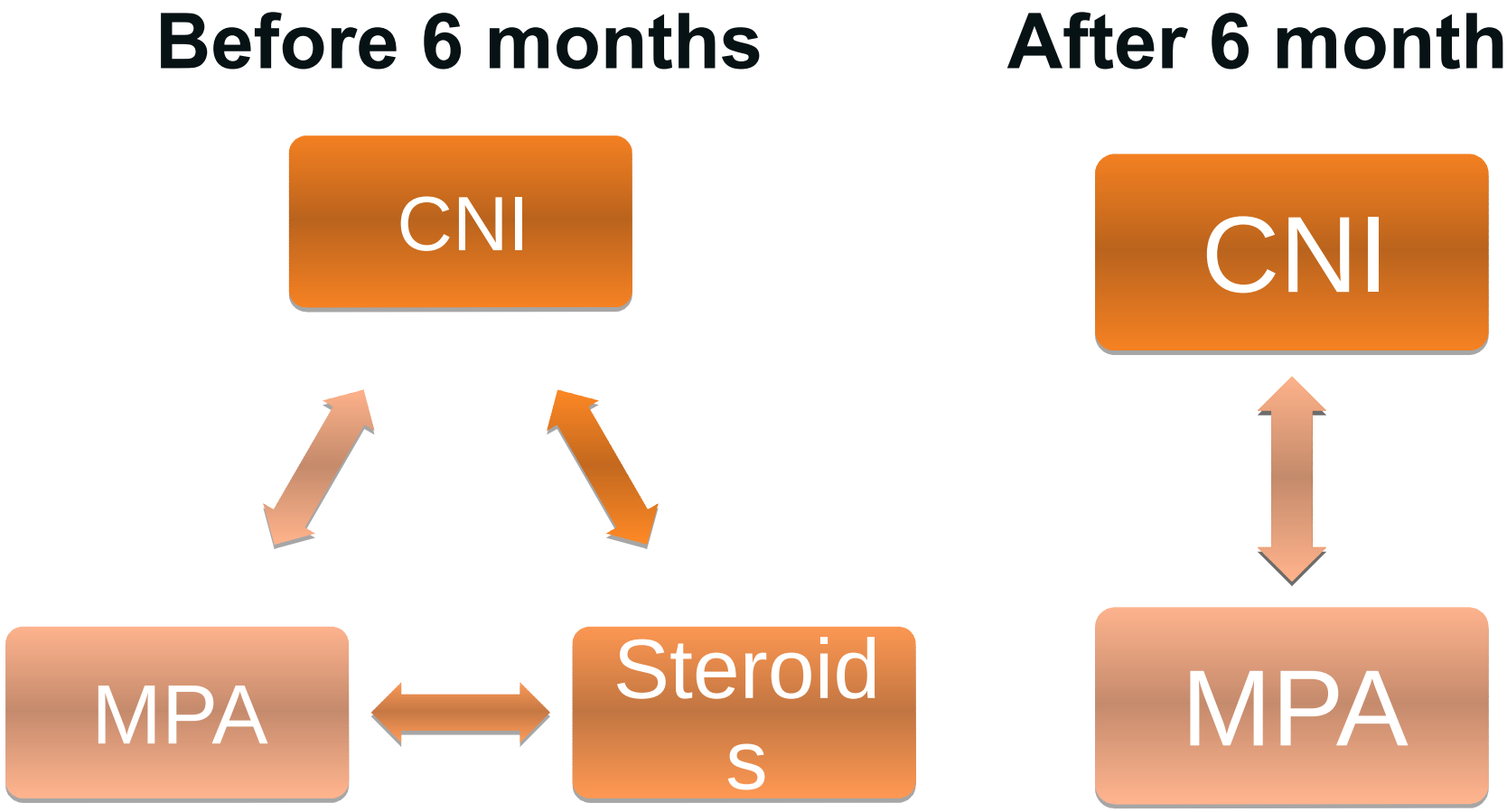
Thimonier E, Clin Transpl 2014

Basical-Pivotal IS regimen for ALD
Synergistic action

Before 6 months

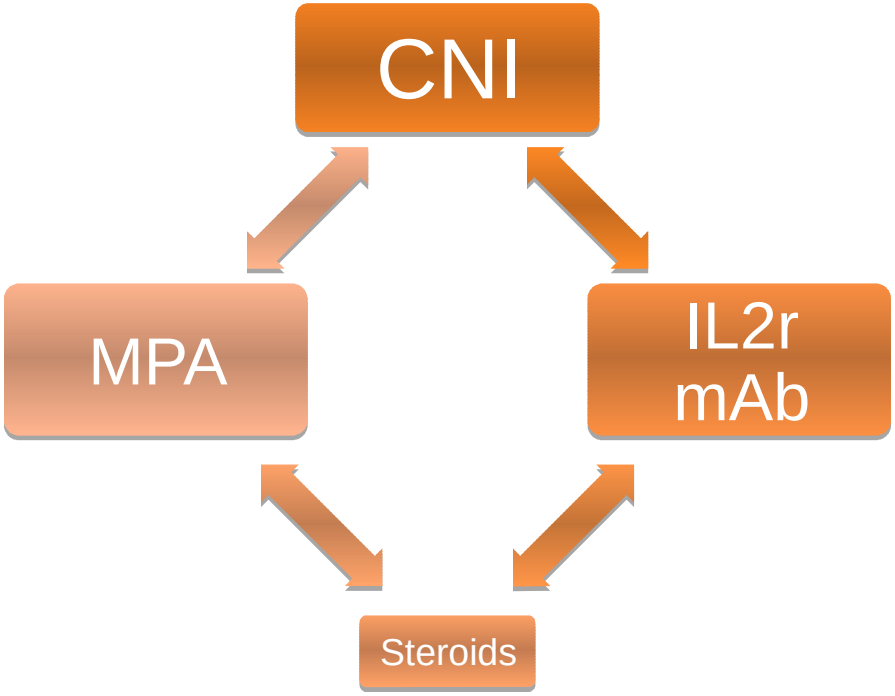


Basical-Pivotal IS regimen for ALD
Synergistic action



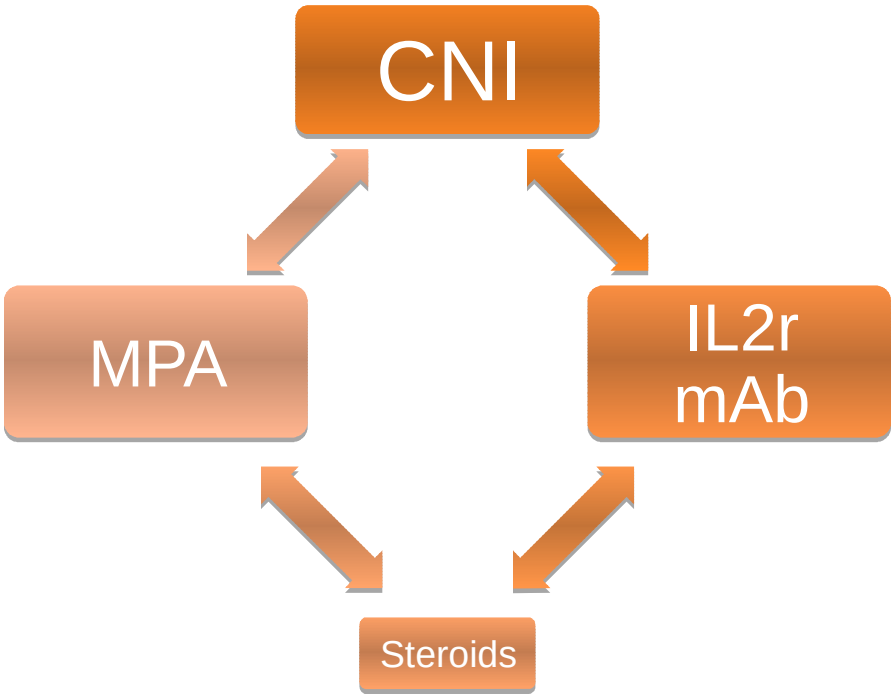
The modern trend in high risk *de novo* SOT

During 1st months

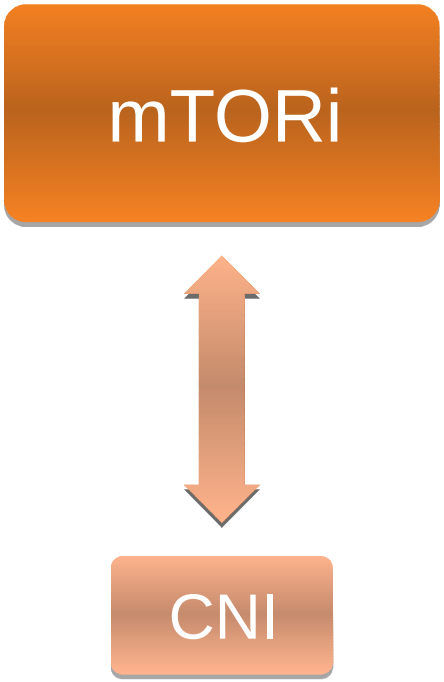


The modern trend in high risk *de novo* SOT

During 1st months



After x months



Clinical observation (4)

- EVL initiation after surgery 0.75 mg x 2/jr
- Mycophenolate withdrawal
- Tapering use of Tac
- At the end 2016 : metastatic lung progression
- Systemic chemotherapy by ERBITUX and TAXOL
- Reduced EVL C0 level < 5
- Death in october 2017

Conclusions

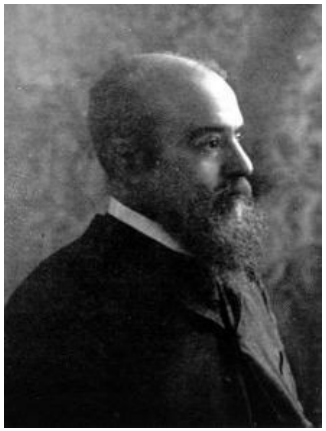
1) Patients take benefit from CNI sparing strategies reducing :

- *De novo* solid cancers
- HCC recurrence
- Serious cardio vascular events
- Chronic renal dysfonction

2) However few patients may develop humoral rejection (AMR)

3) Interest to develop new tools to individualize management of IS minimization and to identify « High risk patients »

Management of liver recipients



Vilfredo Pareto (1848– 1923)

Italian sociologist, economist and philosopher.

He made several important contributions to economics, particularly in the study of income distribution and in the analysis of individuals' choices

Pareto principle

« 80% of effects are the products of 20% of causes »

Most of the concerns are concentrated in few patients !

BACK UP

What about Donor-specific antibody (DSA) after minimization?

The Need for precision

- *Preformed* (retransplantation, female recipient, transfusion, biliary or autoimmune disease)
- *De novo*

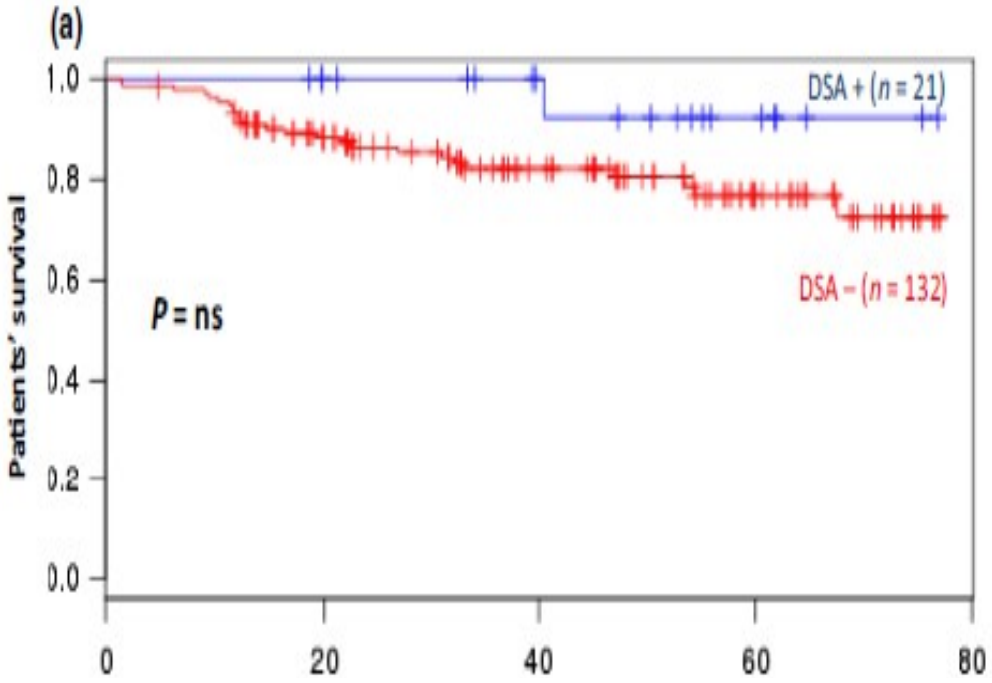
- Yes
- No

- Quantified by Luminex +++ (Mean fluorescence intensity – MFI) - positive > 300-500
- Considered high when ≥ 10 000
- Class II : mostly de novo, persisting DSA (impact of DQ +++)
- Class I : mostly preformed

De novo DSA after liver transplantation Controversial impact

De novo donor-specific anti-HLA antibodies mediated rejection in liver-transplant patients

Arnaud Del Bello,[1,2] Nicolas Congy-Jolivet,[2,3,4] Marie Danjoux,[5] Fabrice Muscari,[2,6] Laurence Lavayssière,[1] Laure Esposito,[1] Isabelle Cardeau-Desangles,[1] Joëlle Guitard,[1] Gaëlle Dörr,[1,2] David Milongo,[1] Bertrand Suc,[2,6] Jean Pierre Duffas,[6] Laurent Alric,[2,7] Christophe Bureau,[2,8] Céline Guilbeau-Frugier,[2,5] Lionel Rostaing[1,2,9] and Nassim Kamar[1,2,9]

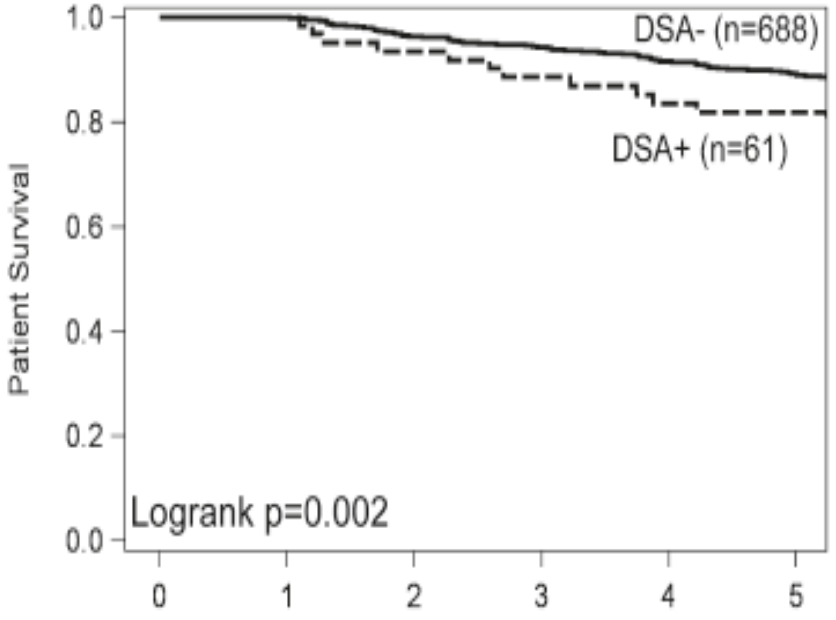


De Novo Donor-Specific HLA Antibodies Decrease Patient and Graft Survival in Liver Transplant Recipients

H. Kaneku[1,*], J. G. O'Leary[2], N. Banuelos[3], L. W. Jennings[2], B. M. Susskind[2], G. B. Klintmalm[2] and P. I. Terasaki[1,3]

Received 02 November 2012, revised 16 Janu and accepted 04 February 2013

De novo DSA HR 1,99



Low CNI level
Impact on *de novo* DSA development

O'Leary, AJT,

		DSA−	DSA+	p-value
Immunosuppression	Induction	24%	60%	0.001
	Tacrolimus[1]	73%	42%	<0.001
	Mycophenolate[1]	62%	60%	0.50
	Rapamycin[1]	16%	29%	0.20
	Steroids[1]	40%	18%	0.04
HLA mismatches (total)		6 (5–7)	7 (6–8)	0.07
2 DQ HLA mismatches		27%	51%	0.047
Antibody characteristics	Class II preformed that was also present at the protocol biopsy	0%	22%	0.001
	Class II *de novo*	0%	82%	<0.001

	Univariate analysis			Multivariable analysis		
Variables	Odds ratio	95% CI	p Value	Odds ratio	95% CI	p Value
Cyclosporine (compared to tacrolimus) at 1 year[1]	2.61	1.48–4.62	<0.001	2.5	1.35–4.63	0.004
Sirolimus at 1 year[1]	1.83	0.99–3.4	0.055	0.63	0.23–1.7	0.359
Steroids at 1 year[1]	0.51	0.28–0.9	0.021	0.67	0.35–1.28	0.229
Mycophenolate vs Azathioprine/none at 1 year[1]	1.07	0.63–1.81	0.805	1	0.54–1.86	0.998
Low level of calcineurin inhibitor in the first year[1]	2.3	1.14–4.66	0.02	2.66	1.21–5.84	0.015

<3ng/ml

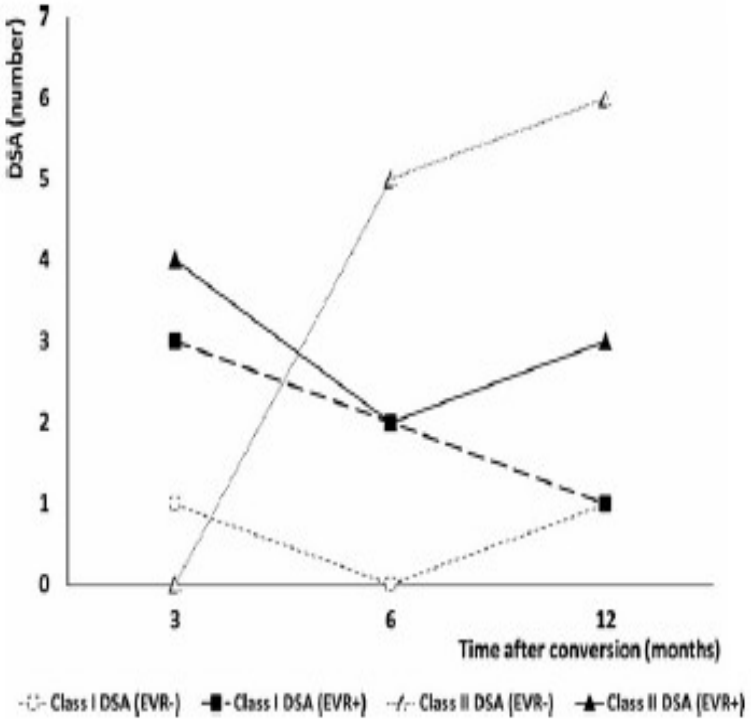
Kaneku, AJT, 2013

mTOR inhibitors and DSA

Evolution of donor-specific antibodies (DSA) and incidence of *de novo* DSA in solid organ transplant recipients after switch to everolimus alone or associated with low dose of calcineurin inhibitors

Clin Transplant, 2014

	EVR+ n = 59 (45%)	EVR− n = 72 (55%)	p (<0.05)
ABMR (%)	2 (3.3)	4 (5.5)	NS
ACR (%)	6 (10.1)	7 (9.7)	NS
Time from switch to ACR (months)	1–3–8–10–18	Not relevant	
Time from switch to ABMR (months)	1–2	Not relevant	
Pre-transplantation anti-HLA antibodies (%)	8 (13.5)	13 (18)	NS
DSA before transplantation (%)	2 (3.3)	7 (9.7)	NS
DSA before conversion to EVR (%)	9 (15.2)	15 (20.8)	NS
Number of *de novo* DSA after switch (%)	4 (6.7)	8 (11.1)	NS
Class I *de novo* DSA			
Patients (number)	2	2	NS
DSA (number)	4	2	NS
MFI immunodominant (median)	3180 ± 1006.8	2214 ± 1350.37	NS
Class II *de novo* DSA			
Patients (number)	2	6	NS
DSA (number)	2	12	NS
MFI immunodominant (median)	3274 ± 1103.2	1380 ± 3351.6	NS
Progression of *de novo* DSA MFI sum from M3 to M12			
Class I	NS	NS	
Class II	NS	0.026	
Mean delay from switch to DSA *de novo* detection (months)	9 ± 3.8	8.6 ± 4	NS
Median (range) of DSA number after switch	2 (1–6)	2 (1–4)	NS



Antibody-mediated rejection
Take home messages

- **AMR is a reality**
  - Acute AMR: high sensitized recipients
  - Chronic AMR: IS minimization

- **Crossmatch T/B, HLA DSA monitoring**
- **Liver graft biopsy protocol**
- **To define therapeutic protocol**