2017 BANFF-SCT
Joint Scientific Meeting
BARCELONA
27-31 March 2017

Societat Catalana de Trasplantament and
BANFF Foundation for Allograft Pathology
are pleased to co-host the
2017 Banff-SCT Joint Scientific Meeting

2017 BANFF-SCT Joint Scientific Meeting

Personalized Medicine in Liver Transplantation

Miquel Navasa
Liver Transplant Unit.
Hospital Clínic. Barcelona.

Barcelona, March 2017

CLÍNIC BARCELONA Hospital Universitari
IDIBAPS Institut d'Investigacions Biomèdiques August Pi i Sunyer
ciberehd isciii
MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD
Instituto de Salud Carlos III
Universitat de Barcelona

Disclosures

Consultant for

-Astellas

-Novartis

GOALS

To evaluate complications of immunosuppression.

To apply different immunosuppressive regimes according to the problems of the patients.

To personalize medicine according to the profile of the patient.

IMMUNOSUPPRESSION IN LIVER TRANSPLANT

"*Tailored" immunosuppression*: adapted to each patient according with:

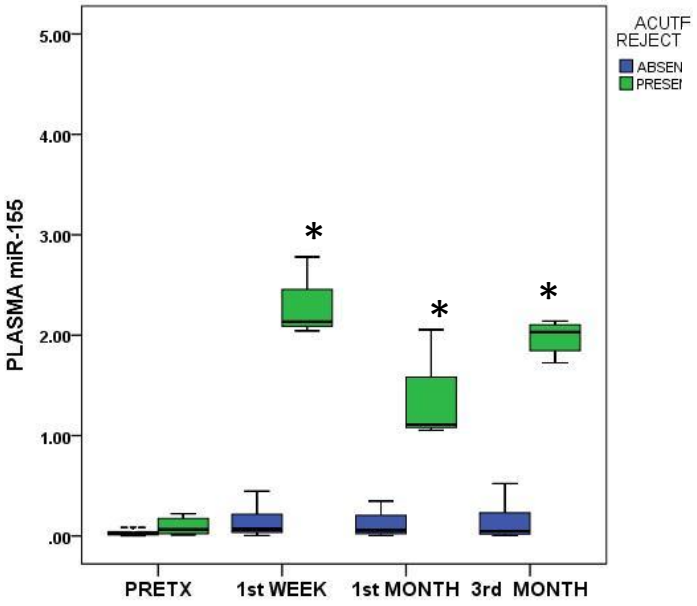
- Risk of rejection
- Risk or presence of adverse effects
- Primary disease

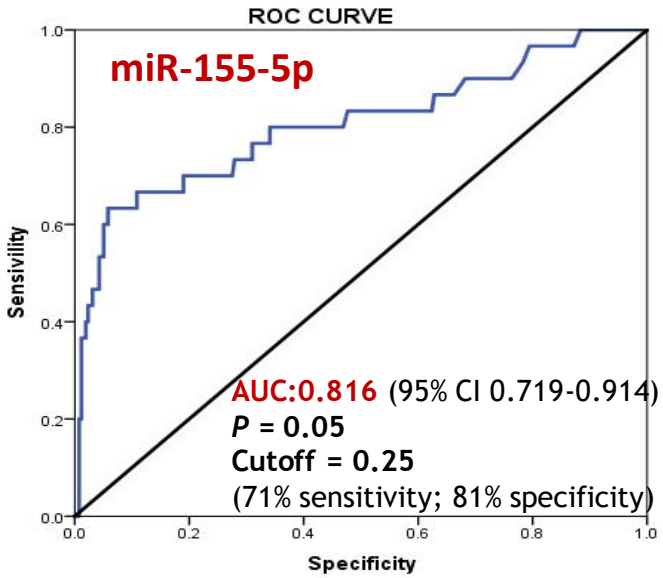
Adapted in relation to:

- Immunosuppressor efficacy
- Type of immunosuppressor

2017 BANFF-SCT
Joint Scientific Meeting
BARCELONA
27-31 March 2017
Societat Catalana de Trasplantament and
BANFF Foundation for Allograft Pathology
are pleased to co-host the
2017 Banff-SCT Joint Scientific Meeting

Monitoring miRNA-155-5p expression as biomarker of prognosis and diagnosis of acute rejection in liver transplant recipients





PPV=80%
NPV=100%

Millán O, Aliart I, Budde K, Bardaji B, Crespo G, Guirado L, Navasa M, Orts L, Ruiz P, Sommerer C, Brunet M.

Oral Session 1: Experimental & Immunology Aspects

Barcelona, March 29th 2017

CLÍNIC BARCELONA Hospital Universitari

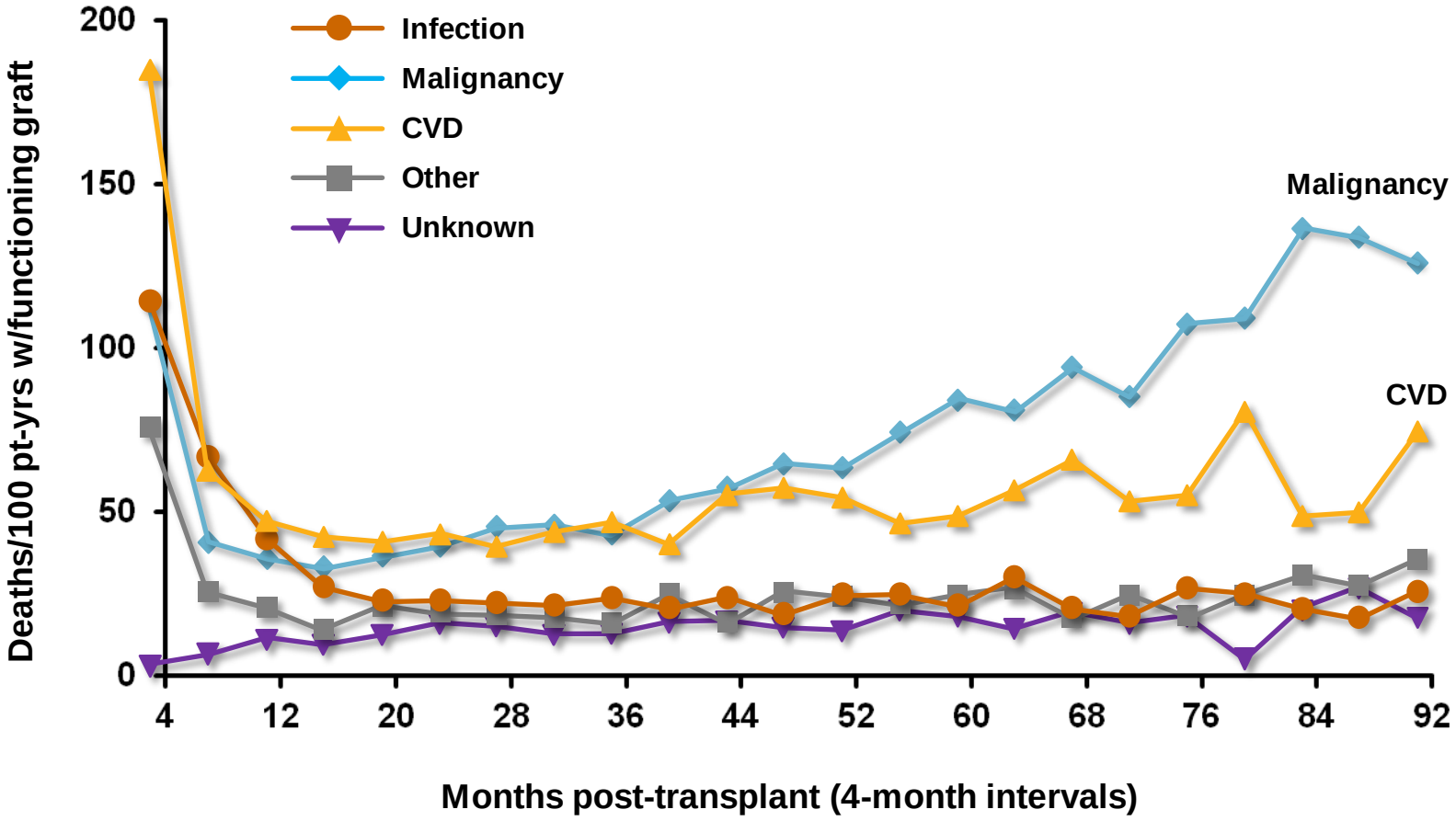
ciberehd

IMMUNOSUPPRESSION AND SIDE EFFECTS

Prevalent side effects with negative impact on survival:

- Infections
- *De novo* tumors
- Metabolic disorders
- Cardiovascular Disease
- Kidney dysfunction
- **Particularly related to CNI and steroids.**

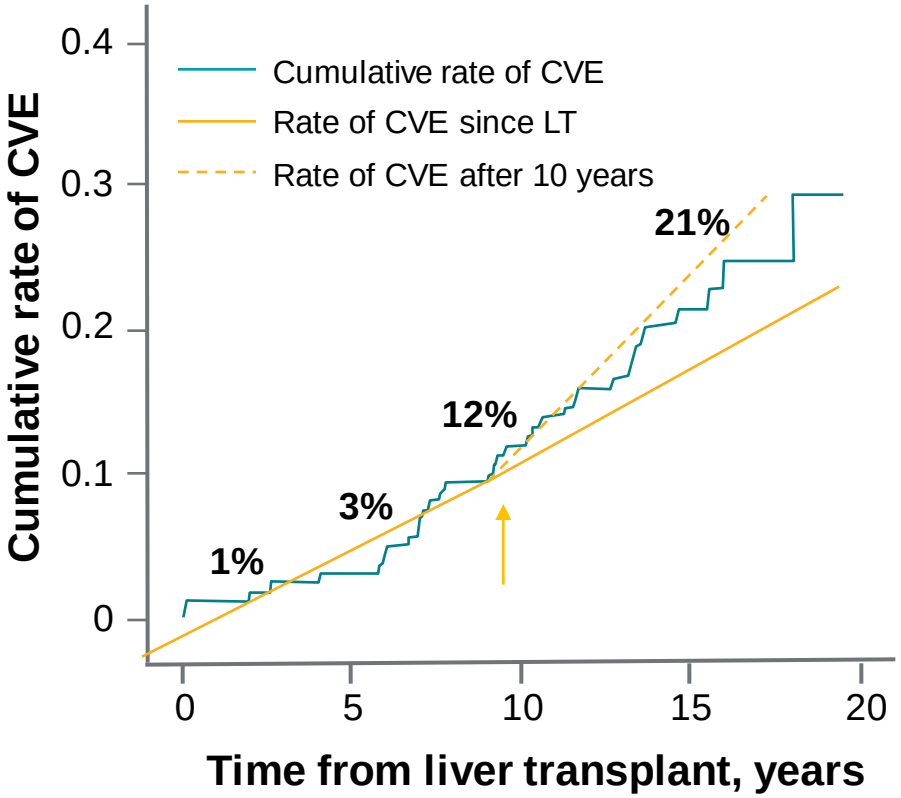
Mortality rates, by cause



CVD, cardiovascular disease; pt-yrs, patient-years

US Organ Procurement and Transplantation Network and Scientific Registry of Transplant Recipients Annual Report 2008; Available at: http://optn.transplant.hrsa.gov/ar2008/Preface_Contributors.htm?cp=1, accessed 28 September 2012

Risk of cardiovascular events after liver transplantation



Risk factors of CVE, since baseline (10 years from LT)

- Family history of cardiomyopathy
- Indication for LT: alcohol-related cirrhosis
- **Renal insufficiency at any time point post-LT**

*Cardiovascular events were defined as ischemic cardiomyopathy (myocardial infarction or angina with pathological coronary angiography), cerebrovascular disease (thrombosis or hemorrhagic stroke demonstrated on computed tomography or magnetic resonance imaging) and peripheral vascular disease (occlusive or sub-occlusive arterial disease). CVE in patients with sepsis or hemorrhage were excluded.
CVE, cardiovascular event, LT, liver transplant.
Rubin A, et al. *Transpl Int.* 2013; 26:740−750.

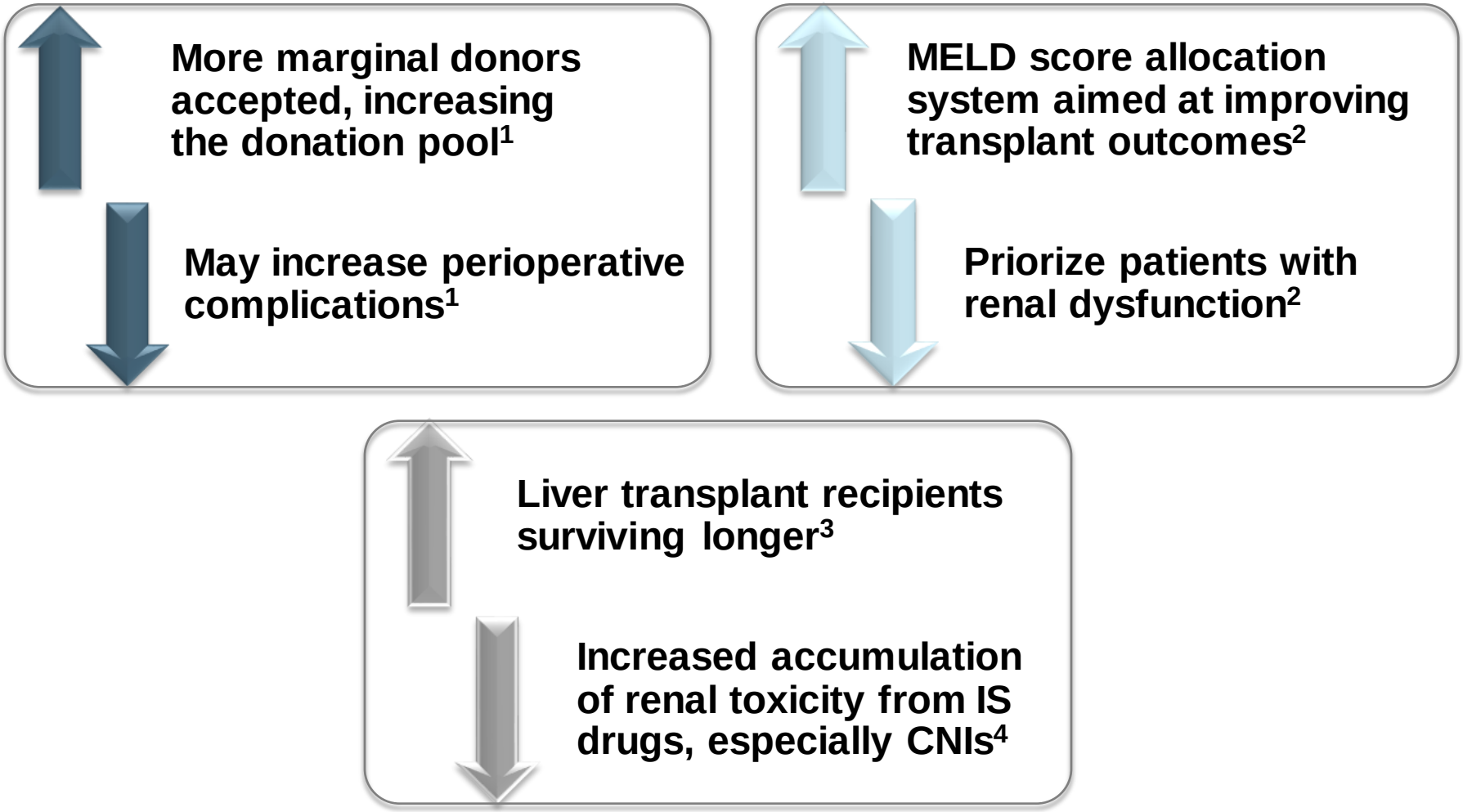
Incidence of kidney dysfunction after Liver Transplantation

Severe renal dysfunction at 5 years, 2006-2012

	No. of patients	GFR <30 mL/min/1.73m2	Dialysis, kidney tx
Ojo 2002, Cohen 2003	**36,849**	**18%**	**5 - 10%**
O'Riordan, 2006	230	9%	3%
Aberg, 2008	396	10%	2%
Sharma, 2009	221	22%	4%
Burra, 2009	233	3%	-
Karie-Guigues, 2009	1508	5%	1%
Ramachandran, 2010	130	8%	-
Martinez-Saldivar, 2012	921	5%	1%
Average, 2006-2012	**3,639**	**7%**	**2%**

O'Riordan, Nephrol Dial Transplant 2006. Burra, Dig Liver Dis 2009. Karie-Guigues, Liver Transpl 2009. Ramachandran, Transplant Proc 2010. Aberg, Clin Transplant 2008. Sharma, Liver Transpl 2009. Martinez-Saldivar, Transplantation 2012.

Increased Renal Toxicity in Liver Transplantation



CNI, calcineurin inhibitor; HCV, hepatitis C virus; IS, immunosuppressive; MELD , Model for End-stage Liver Disease.

1. Busuttil RW, et al. *Liver Transplant* 2003:9:651–662; 2. Sharma P, et al. *Liver Transpl* 2009;15:1142–1148; 3.US Organ Procurement and Transplantation Network and Scientific Registry of Transplant Recipients Annual Report 2011; Available at: http://srtr.transplant.hrsa.gov/annual_reports/2011/default.aspx, accessed Mar 2014; 4. Fabrizi F, et al. *Int J Artif Organs.* 2010;33:803–811.

Protecting kidney function at the time of transplant: Immunosuppression.

-**Optimize treatment at the time of transplant (Hemodynamic stability)**

-**Avoid nephrotoxic drugs**

-**Immunosuppression:**

- **Diminish**
- **Delay**
- **Stop**
- **Avoid**

} **Calcineurine Inhibitors**

- **Diminish, delay, stop or avoid CNIs may protect kidney function.**
- **Substitution options:**

  Mycophenolate

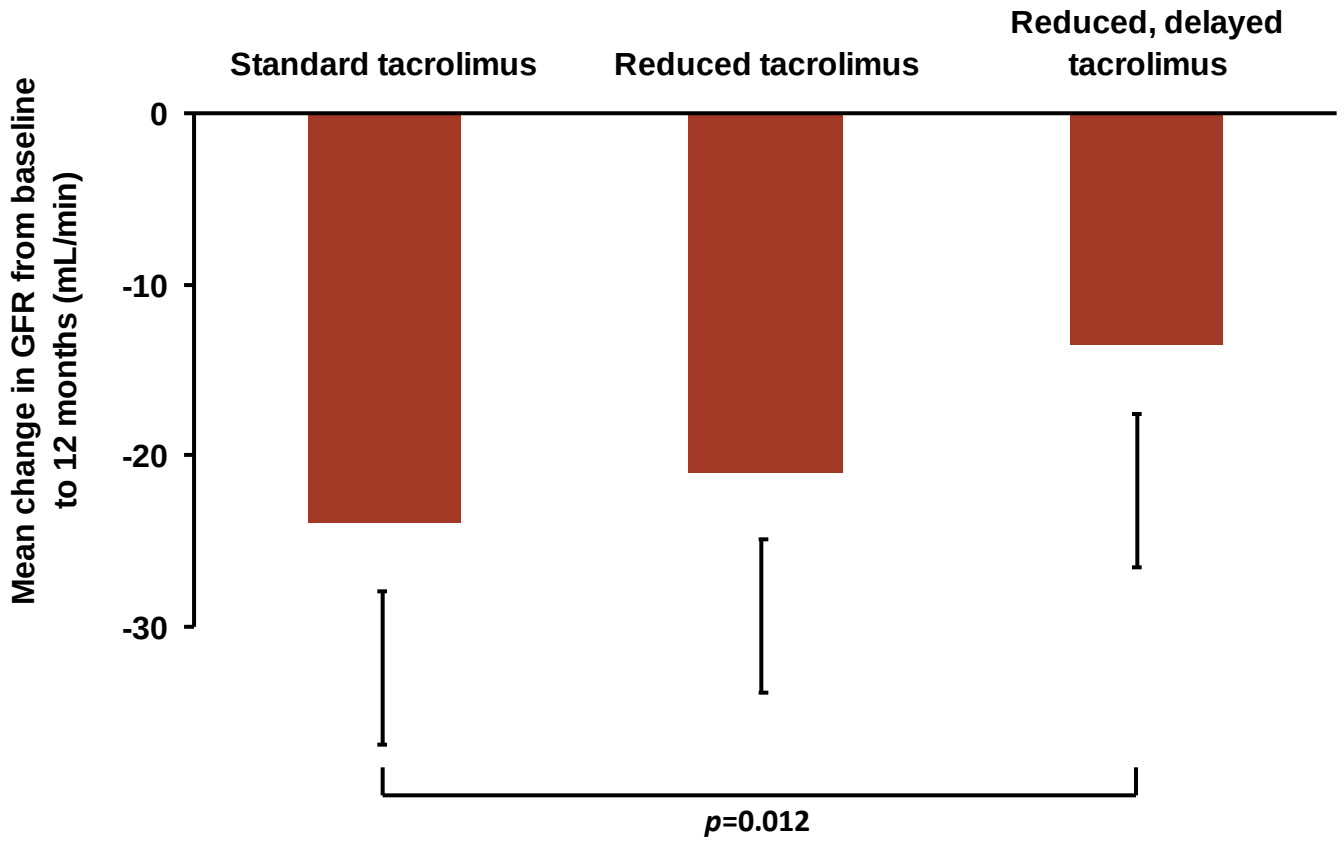
  mTOR inhibitors

  Everolimus*, sirolimus*

  Biologic agents for induction or maintenance:

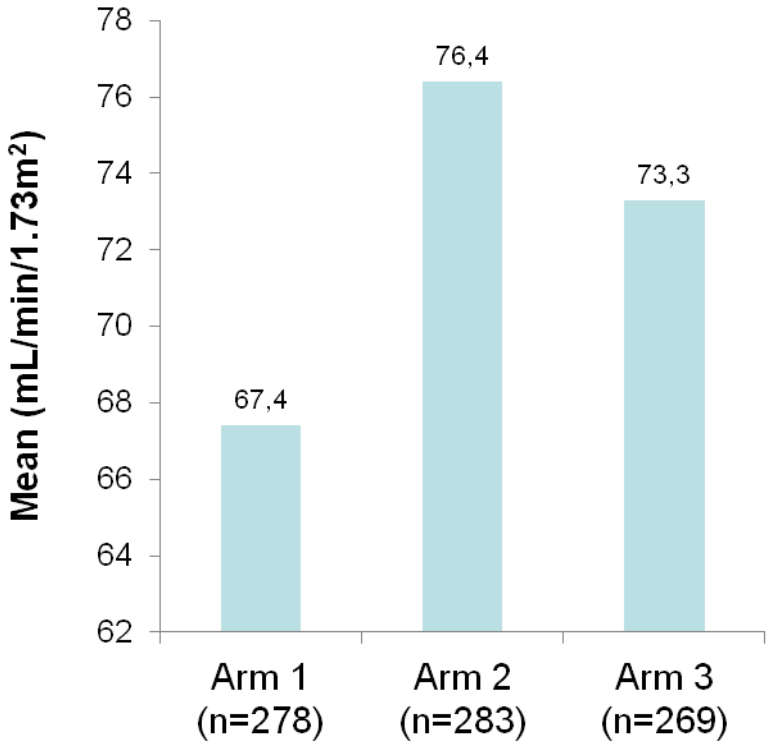
  ATG, basiliximab*

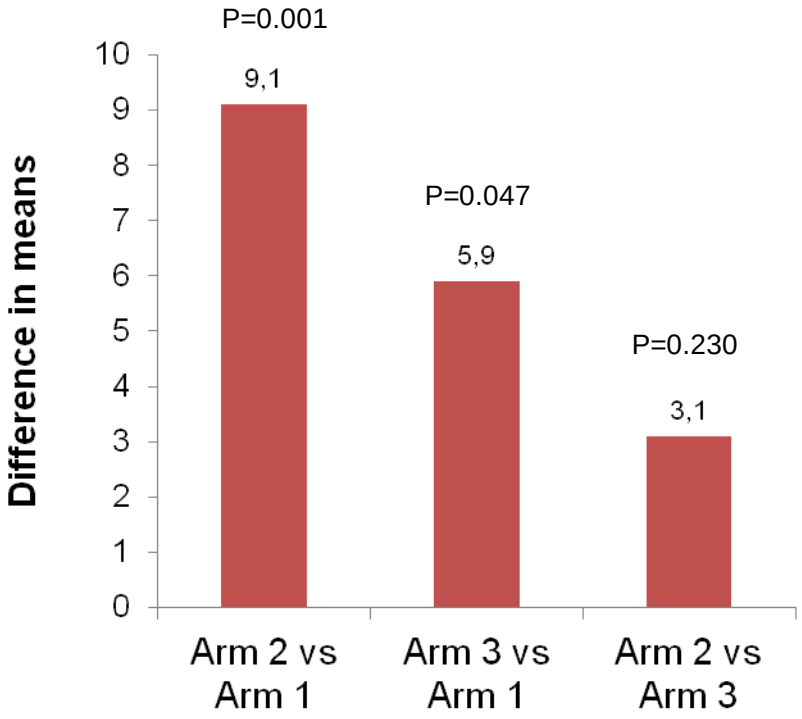
ReSpECT study: prospective randomized trial of tacrolimus and/or MMF regimens in 517 de novo liver transplant recipients



Neuberger JM, *Am J Transplant.* 2009;9:327–36

DIAMOND study
Primary variable: eGFR (MDRD4) at Week 24



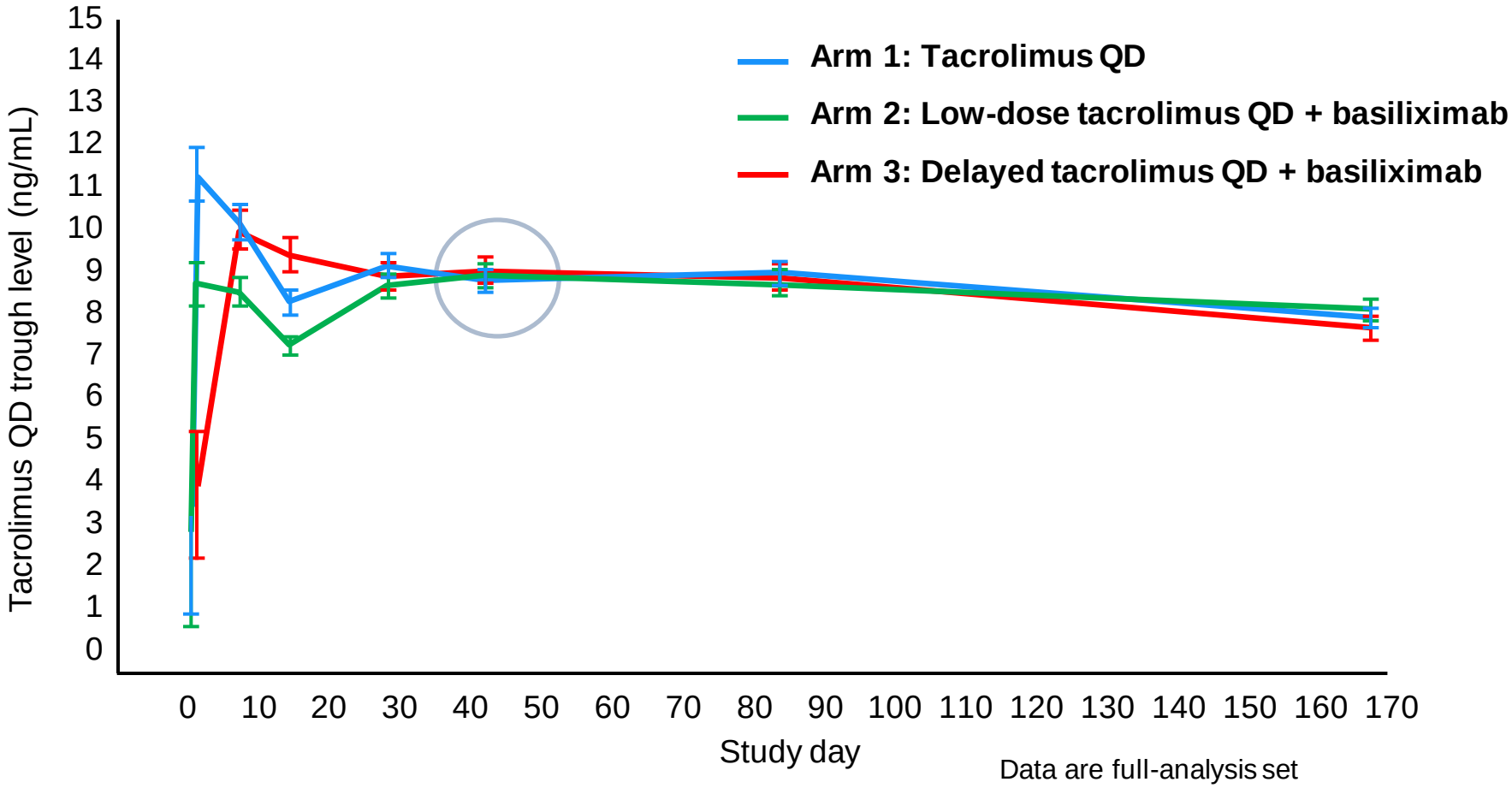


Arms 2 and 3 were associated with significantly improved renal function at Week 24 compared with Arm 1

Data are full-analysis set; P-value (ANOVA)

Tunecka P et al. Am J Tx 2015

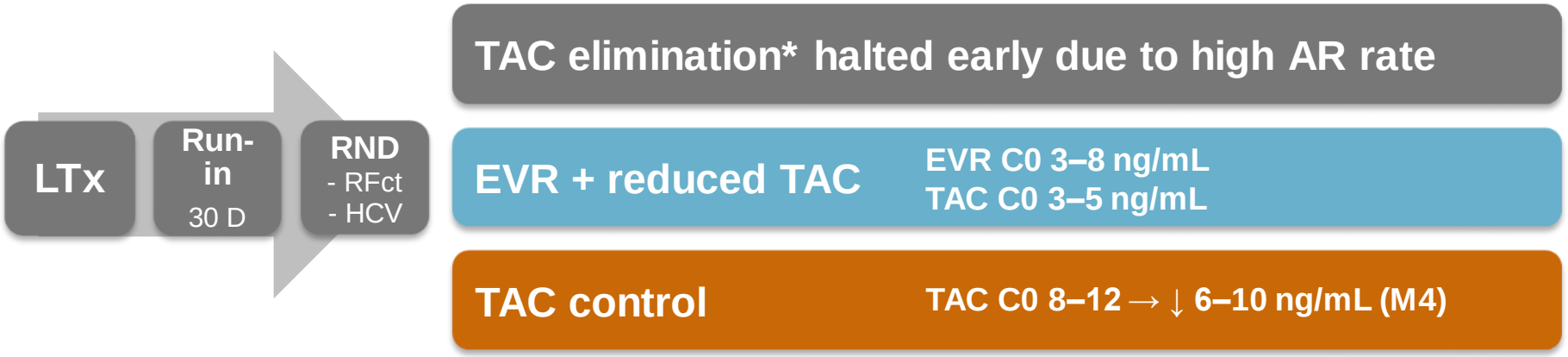
DIAMOND study
Tacrolimus QD exposure over 24 weeks of treatment



Tunecka P et al. Am J Tx 2015

H2304: Pivotal trial - Study design

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



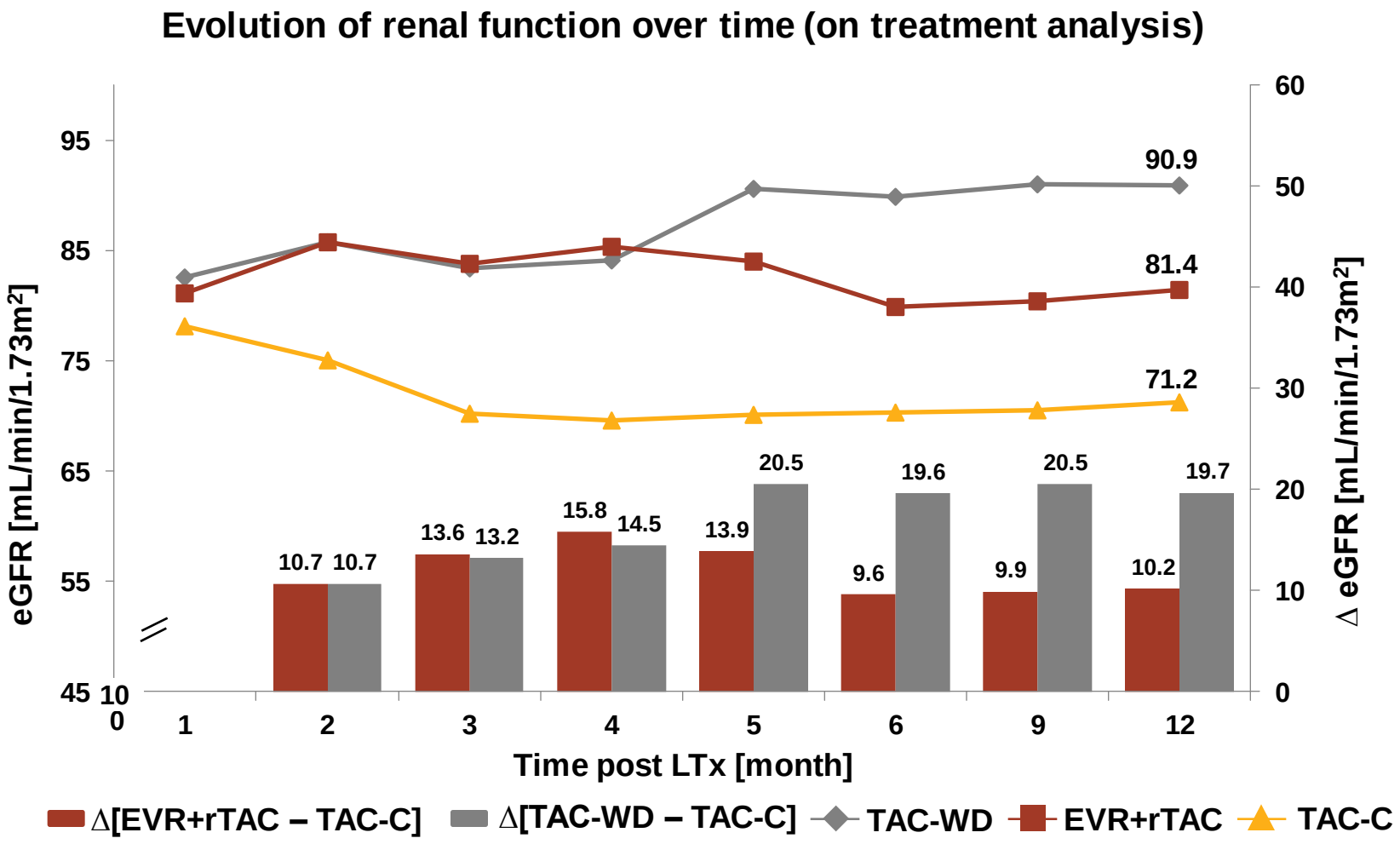
- Enrollment into TAC-WD arm was stopped due to higher rejection rates, and protocol was amended based on DMC recommendation (Apr-2010)

* Off-label use

AR, acute rejection; BL, baseline; C0, concentration; CS, corticosteroids; D, day; DMC, data monitoring Committee; EVR, everolimus; HCV, hepatitis C virus; LTx, liver transplantation; M, month; MMF, mycophenolate mofetil; RFct, renal function; RND, randomization; TAC, tacrolimus; tacrolimus withdrawal.

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

RAD 2304 Study: TAC vs TACr + Evero vs Evero



eGFR = estimated glomerular filtration rate; RND = randomization

P. De Simone et al. Am J Transpl 2012 ; 12: 3008–3020,

Steroid-free regimes: A meta-analysis of outcomes

	Effect estimated	p value	Favors group
Rejection:			
- ST not replaced	RR=0.75 [0.58, 0.98]	<0.05	Steroid
- ST replaced	RR=1.31 [1.09, 1.58]	<0.01	Non-steroid
CMV infection	RR=1.47 [0.99, 2.17]	<0.05	Non-steroid
***De novo* diabetes**	RR=1.86 [1.43, 2.41]	<0.001	Non-steroid
Cholesterol levels	WMD=19.71 [13.7, 25.7]	<0.001	Non-steroid
HCV recurrence	RR=1.15 [1.01, 1.13]	<0.05	Non-steroid

No significant difference in:

- Infection, hypertension, renal dysfunction, neurologic complications, survival

Sgourakis et al, Transpl Int 2009; 22: 892-905

IMMUNOSUPPRESSION AND HCV RECURRENCE

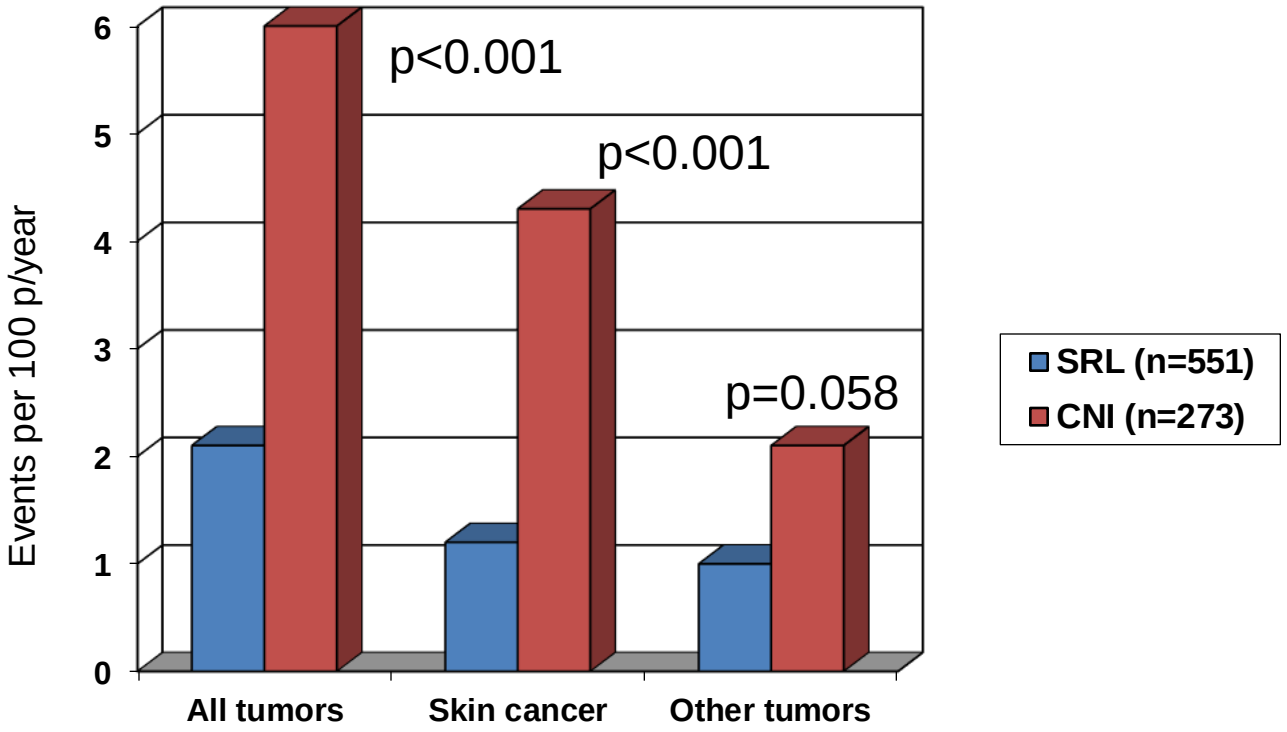
The role of steroids:

- Boluses *(Wiesner, Liver Tr 2003)*
- Maintenance: controversial, Fast *vs* Slow

(Brillanti, Liver Tr 2002. Klintmalm, Liver Tr 2011. Neuhaus, J Transpl 2012)

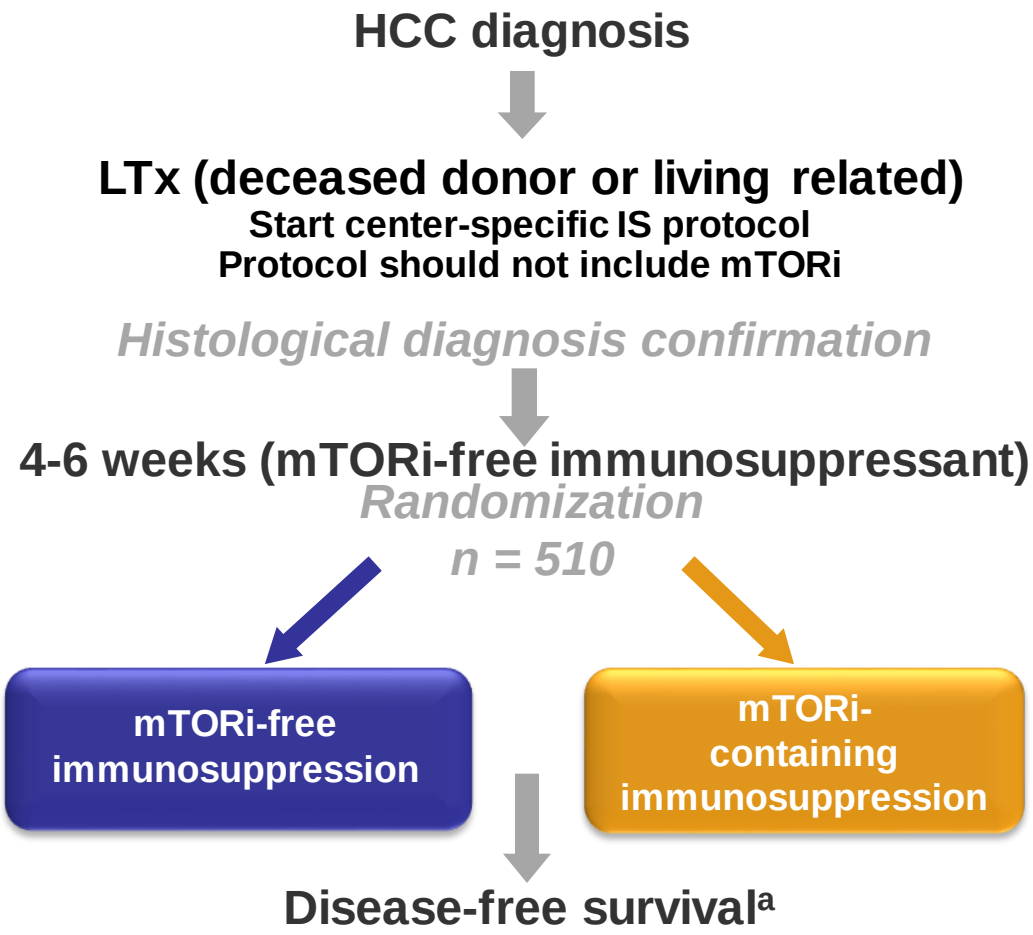
- **Ciclosporine vs. tacrolimus** *(Berenguer, Liver Tr 2011)*:
  - Progression of HCV recurrence.
  - Efficacy of classic antiviral treatment
- **mTOR inhibitors, antifibrogenic effect.** *(Asthana, Can J Gastro 2011. McKenna, AJT 2011)*
- **New DAAs "The End"**

CONVERT STUDY: *DE NOVO* TUMORS IN KIDNEY TRANSPLANTATION



Alberú et al, Transplantation 2011

SiLVER: Trial Investigated SRL in Patients With HCC After LTx



Investigational protocol; ClinicalTrials.gov identifier: NCT00355862

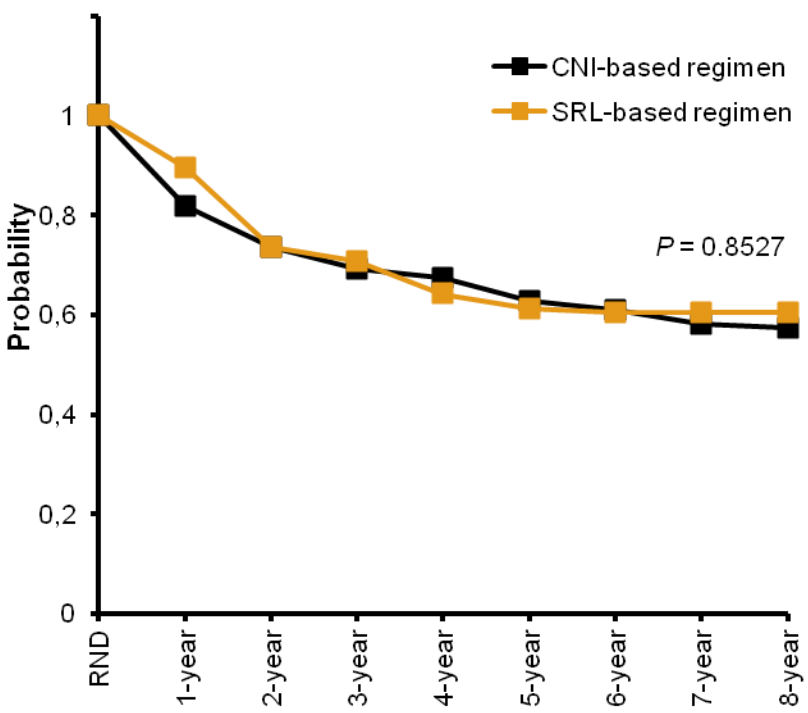
[a]End-point analysis will be performed 5 years after all patients are enrolled (with yearly interim analyses)

HCC, hepatocellular carcinoma; IS, immunosuppressive; LTx, liver transplantation; mTORi, mammalian target of rapamycin inhibitor; SRL, sirolimus

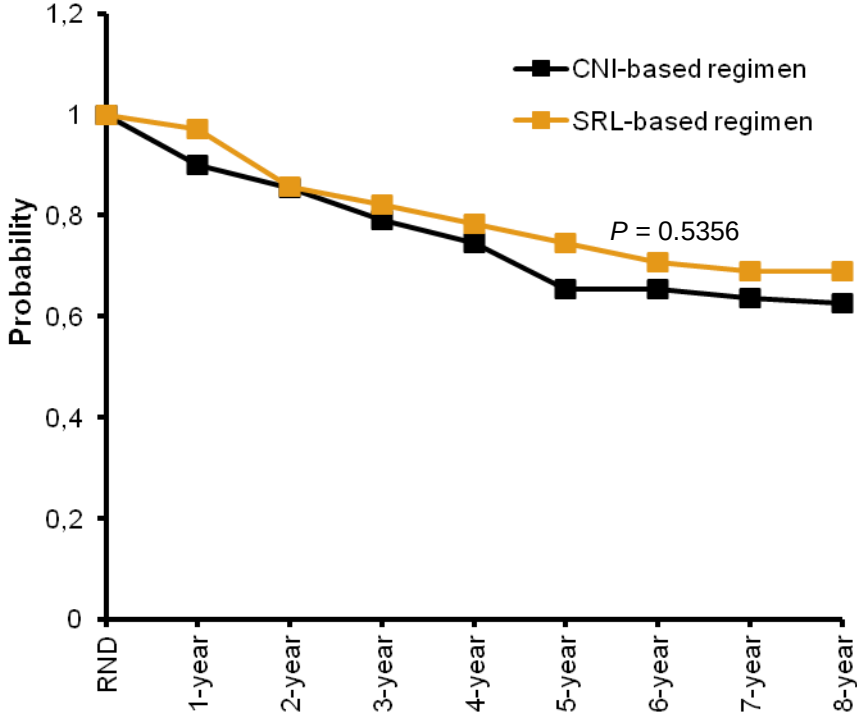
Geissler EK et al. Transplantation. 2016:100(1):116-25

Improvement in survival with SRL was not observed in high-risk patients*

Recurrence-free survival



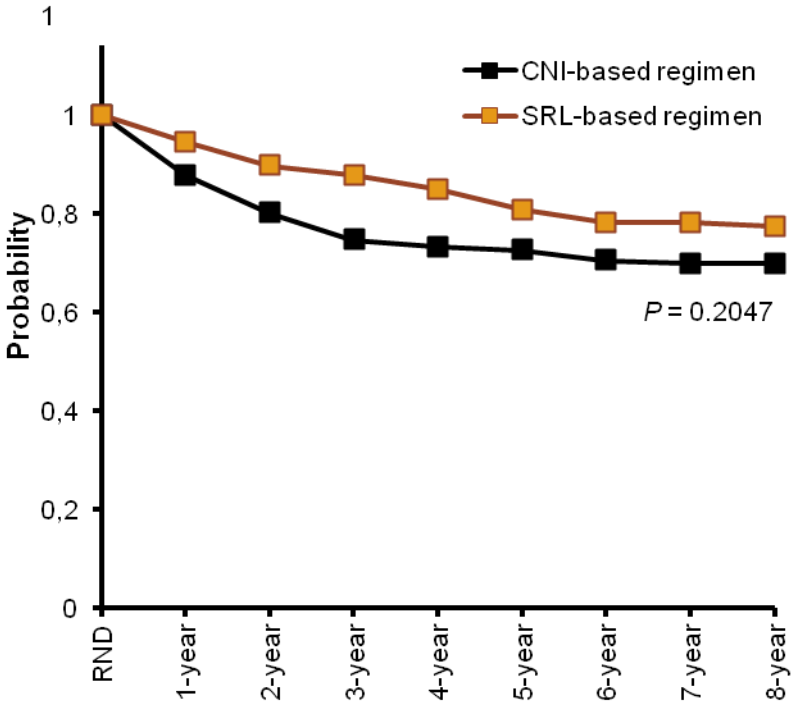
Overall survival



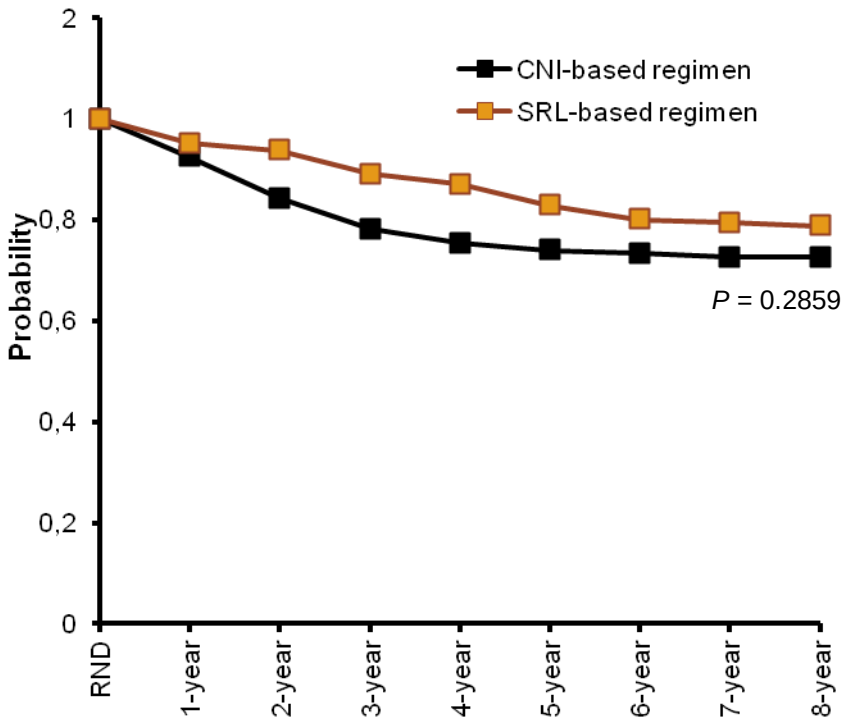
*patients outside Milan criteria, without liver cirrhosis, or undergoing salvage LT
CNI, calcineurin inhibitor; LT, liver transplantation; RND, randomization; SRL, sirolimus
Geissler EK et al. *Transplantation* 2016:100:116-25

Survival rates were numerically higher with SRL in low-risk patients

Recurrence-free survival



Overall survival



CNI, calcineurin inhibitor; RND, randomization; SRL, sirolimus

Geissler EK et al. *Transplantation* 2016;100:116-25

IMMUNOSUPPRESSION AND RISK OF RECURRENCE OF PRIMARY DISEASE

Primary Biliary Cirrhosis:

- CyA vs. Tacrolimus.

  Selective immunosuppression with ciclosporin and preventive ursodeoxycholic acid?

Autoimmune Hepatitis:

- Protector role of steroids.

Primary Sclerosing Cholangitis:

Improved control of inflammatory bowel disease or even colectomy.

Neuberger, Liver Transplant 2004; Tripathi, Sem Liver Dis 2009; Montano-Loza AJ, Aliment Pharmacol Ther 2017 Feb;45(4):485-500

CONCLUSIONS

Malignancy and cardiovascular events as a consequence of the increase in the cardiovascular risk factors and kidney dysfunction, are the major long-term complications in liver transplantation.

It is possible to apply different immunosuppressive regimes aimed at reducing kidney dysfunction and some cardiovascular risk factors (steroids and diabetes).

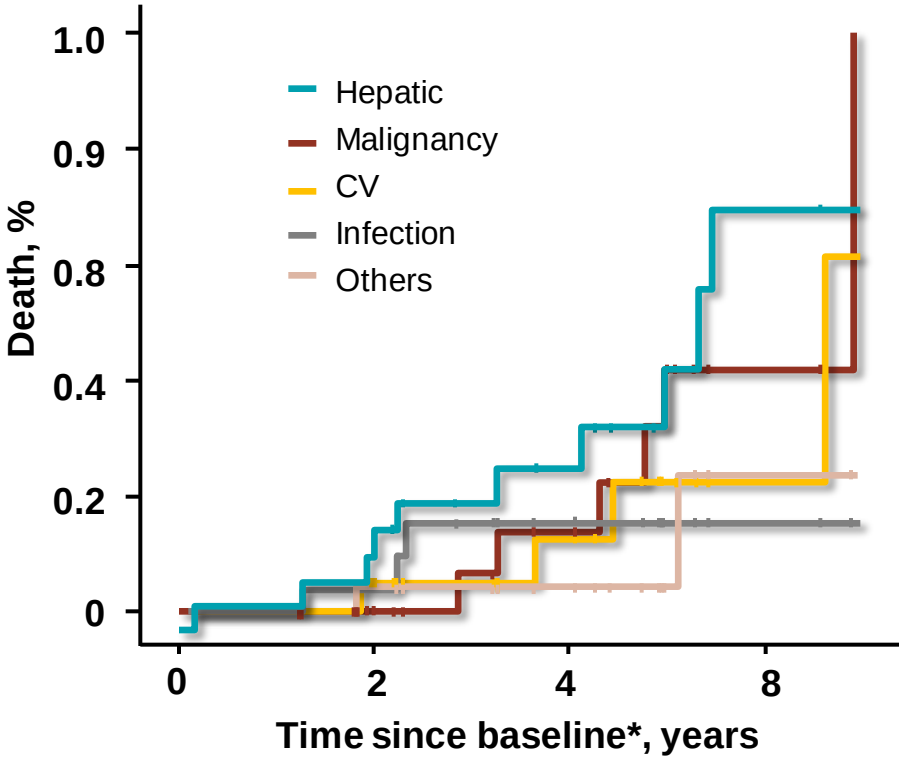
We do not have specific indications of immunosuppression for malignancy in liver transplantation.

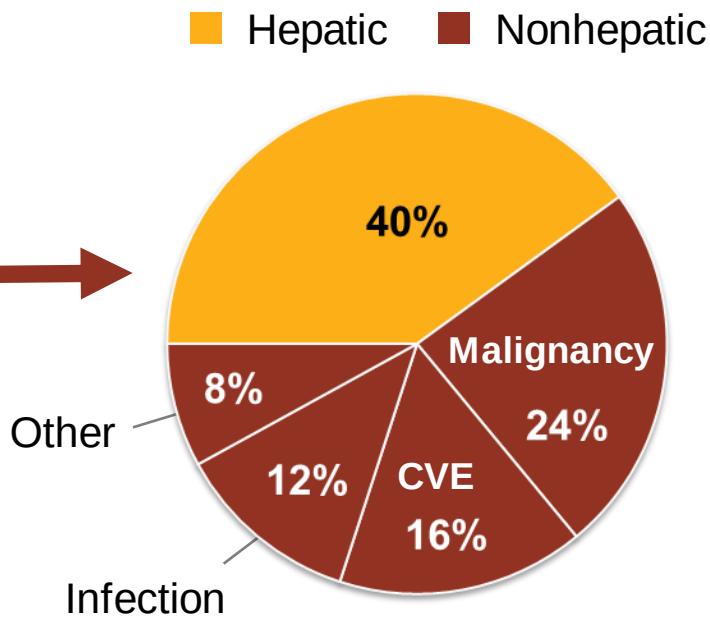
Maintenance of steroids is recommended in transplanted patients with autoimmune hepatitis.

Causes of death in long-term liver transplant survivors

- 10 years post-transplant:167 (52%) alive

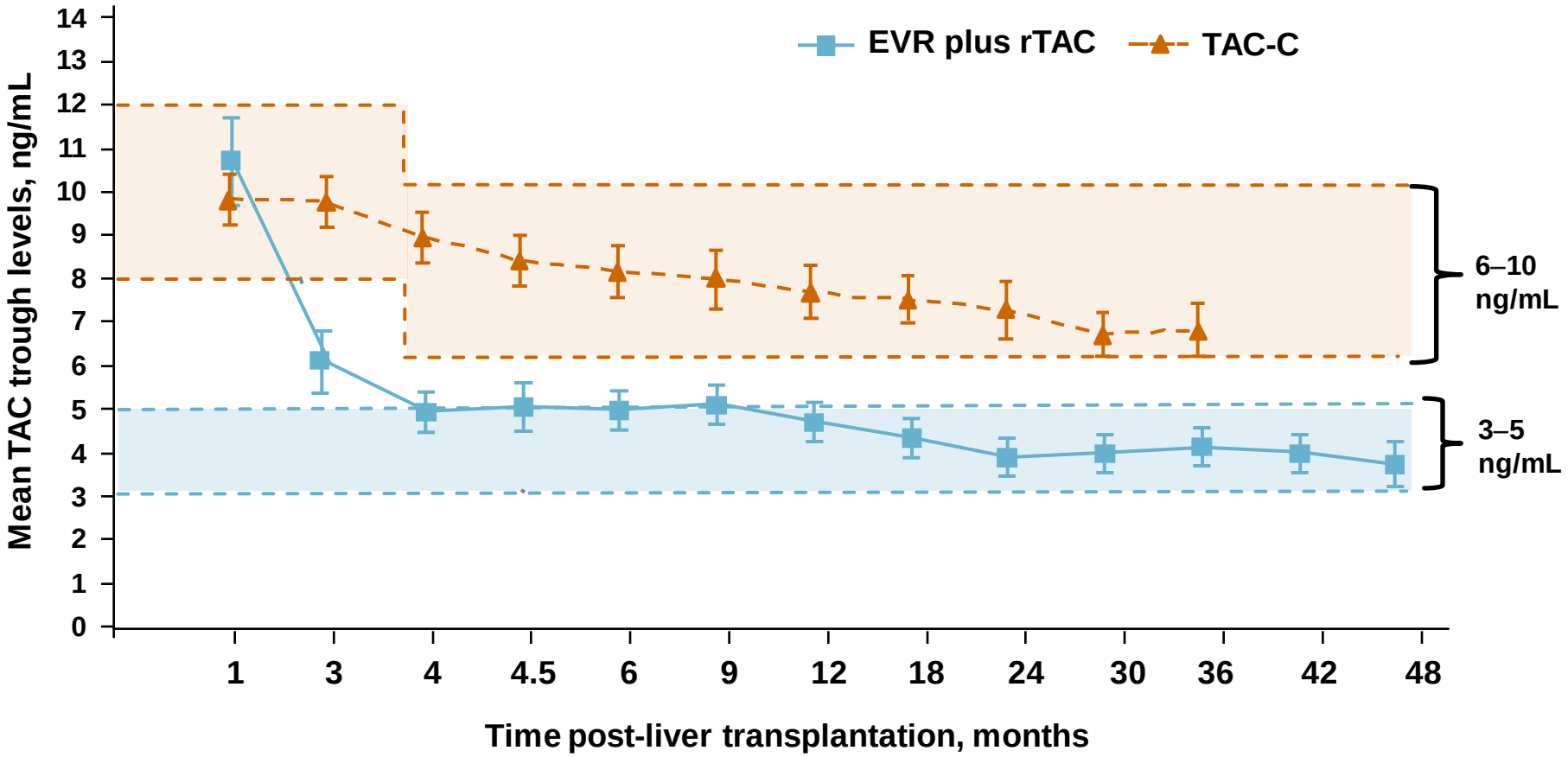
Causes of late mortality (10 years after LT)





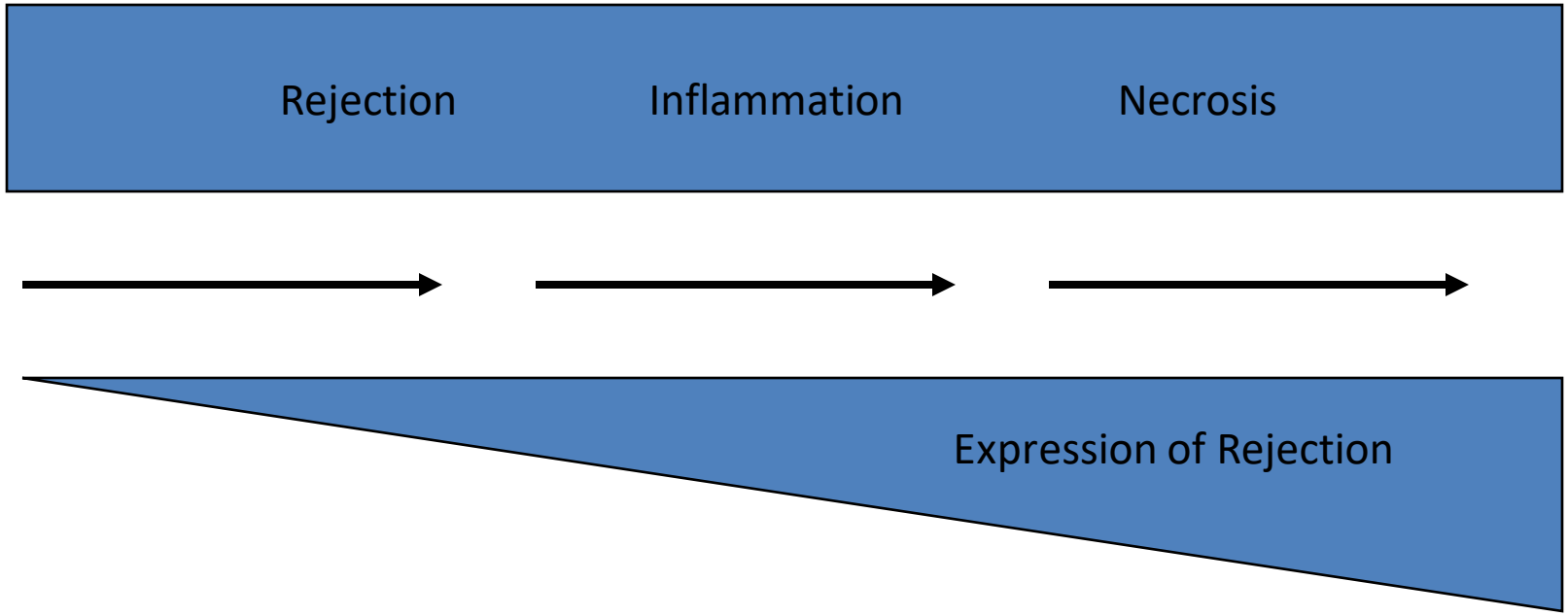
*Patients surviving 10 years post-LT (n=158). Of the 167patients with a minimum survival of 10 years, nine additional cases were excluded because of lack of data (lost to follow-up), so that the final cohort comprised 158 LT recipients surviving beyond 10 years from transplantation.
CV, cardiovascular; CVE, cardiovascular event; LT, liver transplantation.
Rubin A, et al. *Transpl Int*. 2013;26:740−750.

Target TAC trough levels throughout extension phase



Baseline extension to M48; Vertical lines indicate 95% CI at each time point
EVR, everolimus; rTAC, reduced tacrolimus; TAC-C, tacrolimus control.
Data on file. Basel, Switzerland: Novartis Pharma AG; 2013.

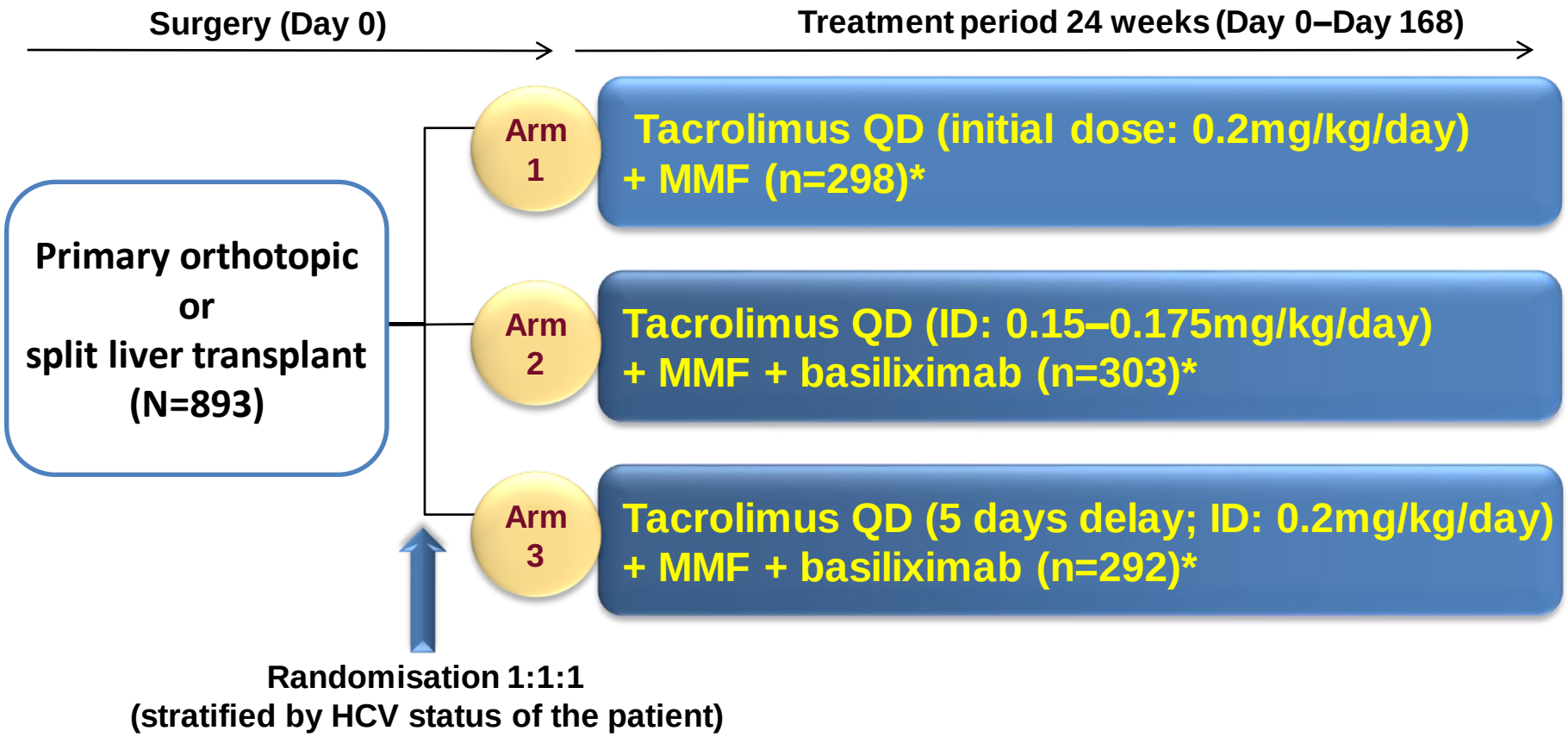
Diagnosis of Rejection



Immune Biomarkers
Serum/Urine Biomarkers
Imaging Biomarkers
Clinical Biomarkers
Biopsy

DIAMOND study design

Multicentre, randomised, open-label, parallel-group comparative Phase IIIb study



- *0mg to 1000mg IV bolus corticosteroid (pre-, intra-, or post-op) on Day 0

- **Tunecka P et al. Am J T 2015**