Contemporary Issues in Liver Transplantation Immunosuppression

3rd GCC Organ Transplantation and Nephrology Congress

January 19, 2017

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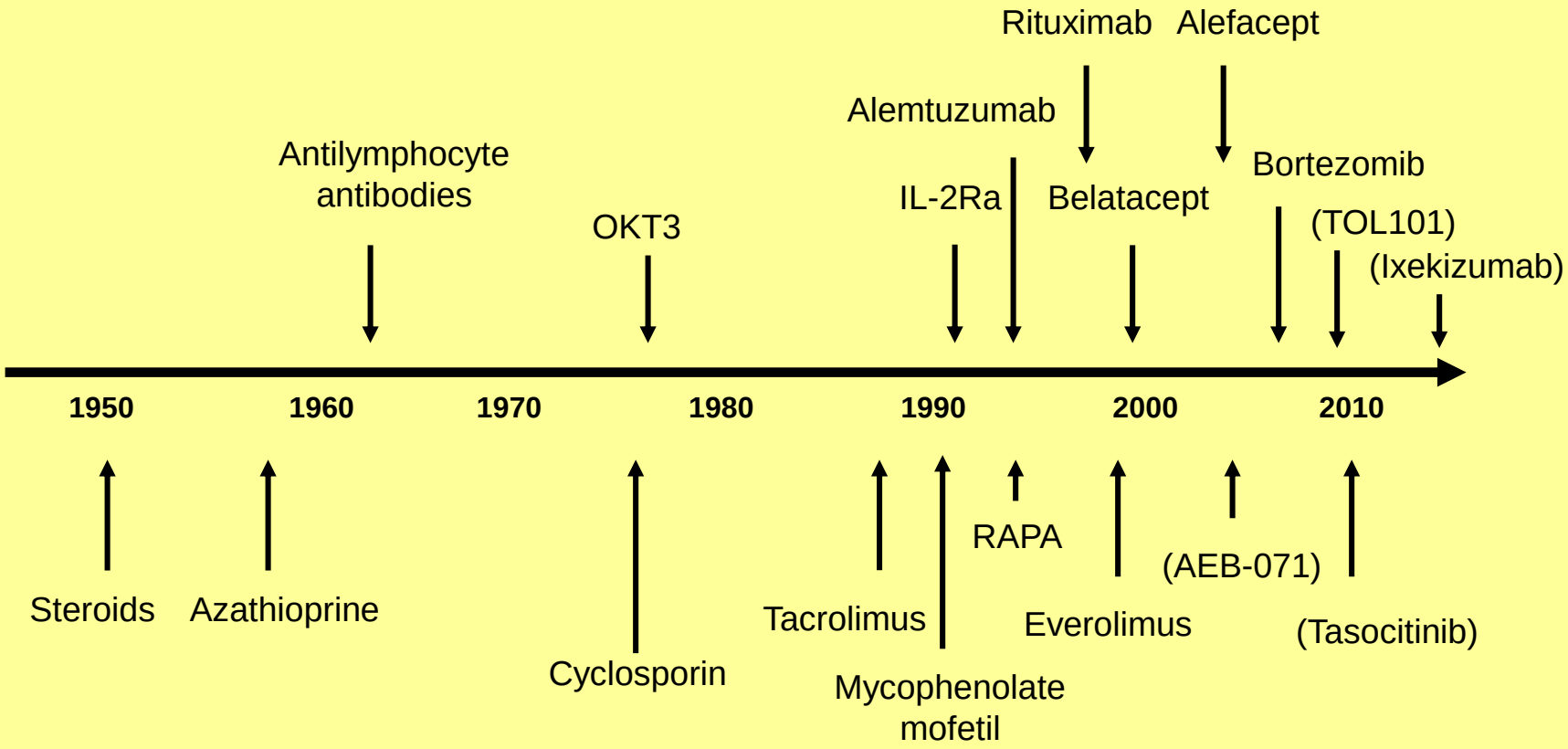
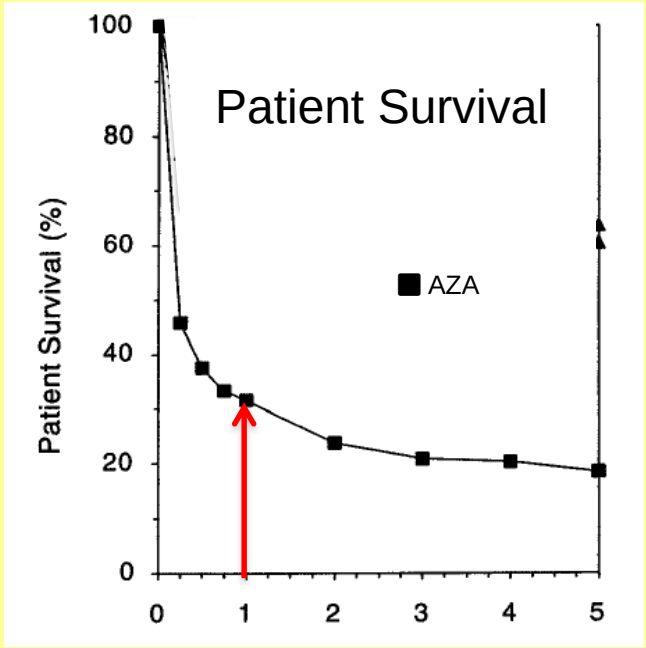
University of Chicago

Immunosuppressive Drug Development Timeline



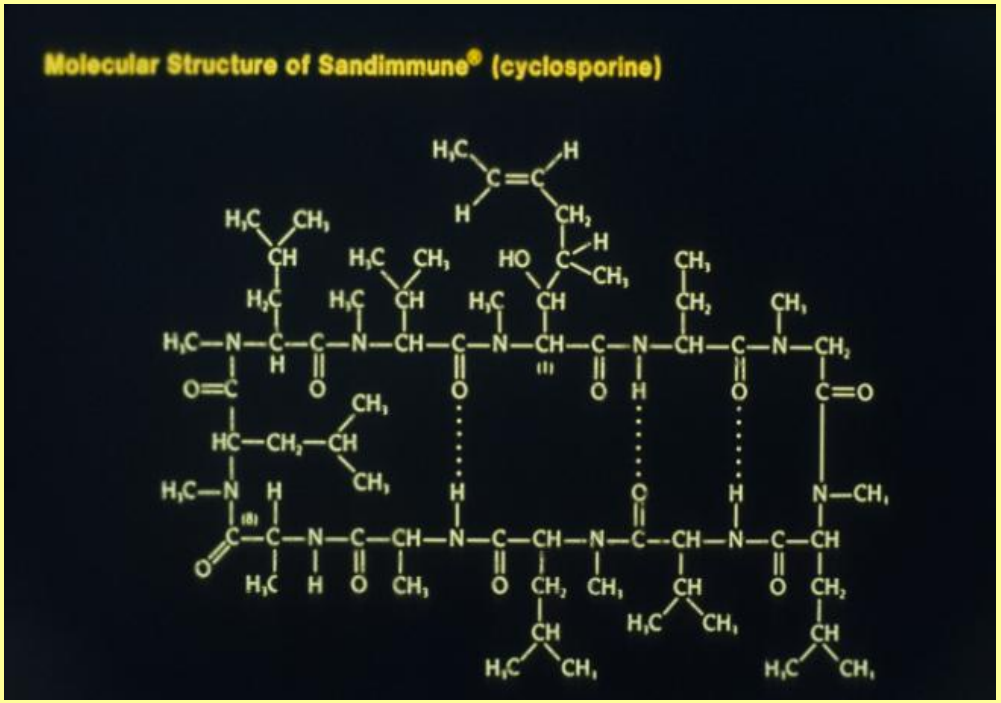
1963-1980

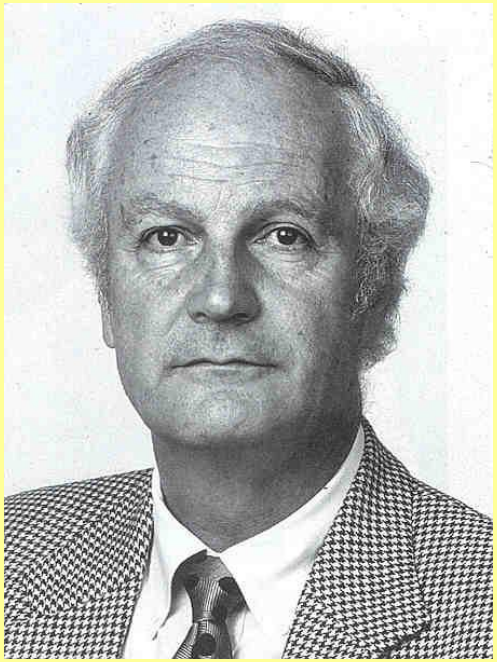
University of Colorado utilizes azathioprine with corticosteroids in clinical transplantation – with and without ALG.



1972

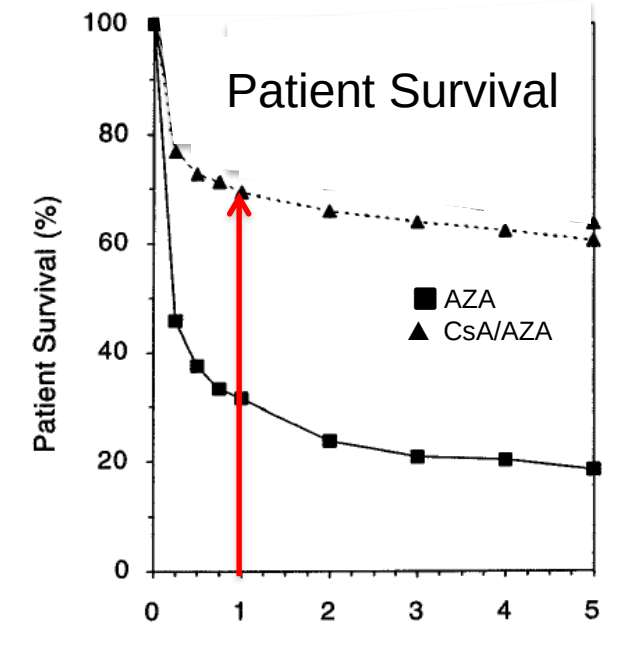
Jean Borel identifies immunosuppressive properties of cyclosporine isolated from the fungus *Beauveria nive*

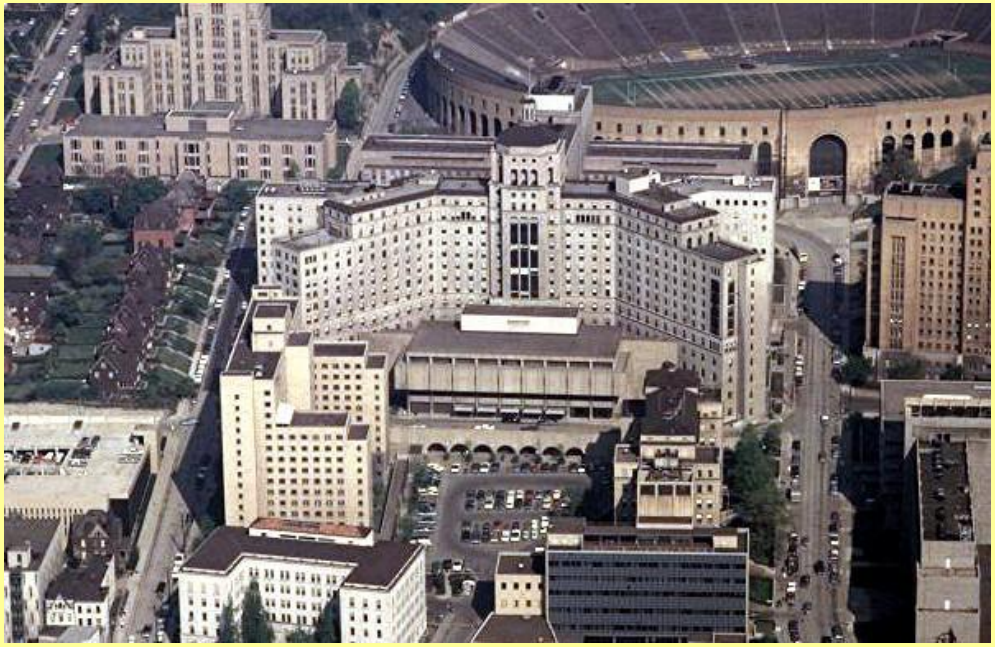




1981

Cyclosporine, in combination with AZA and corticosteroids, found to be effective immunosuppressive agent in clinical liver, kidney and heart transplantation in trials at the University of Colorado and then the University of Pittsburgh - approved by FDA in 1983

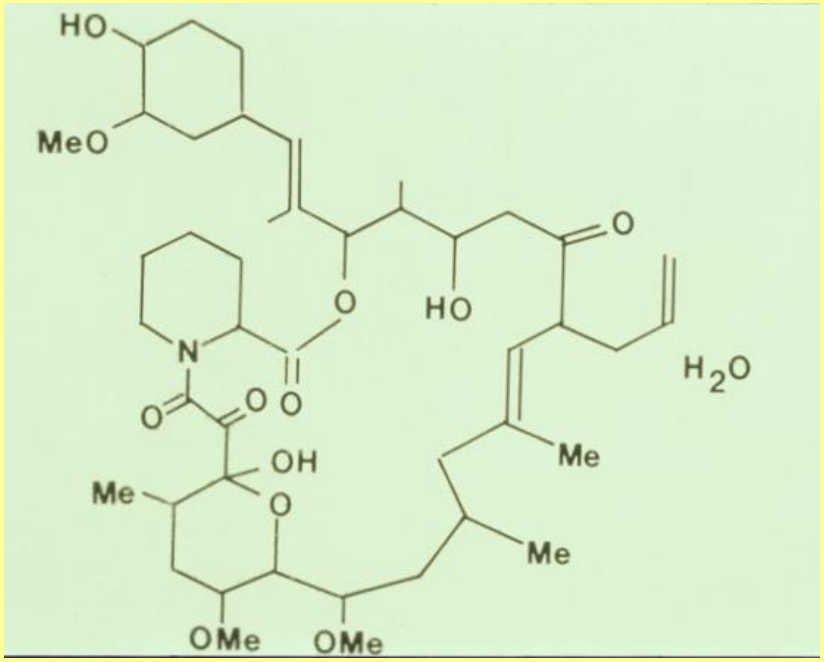




1987

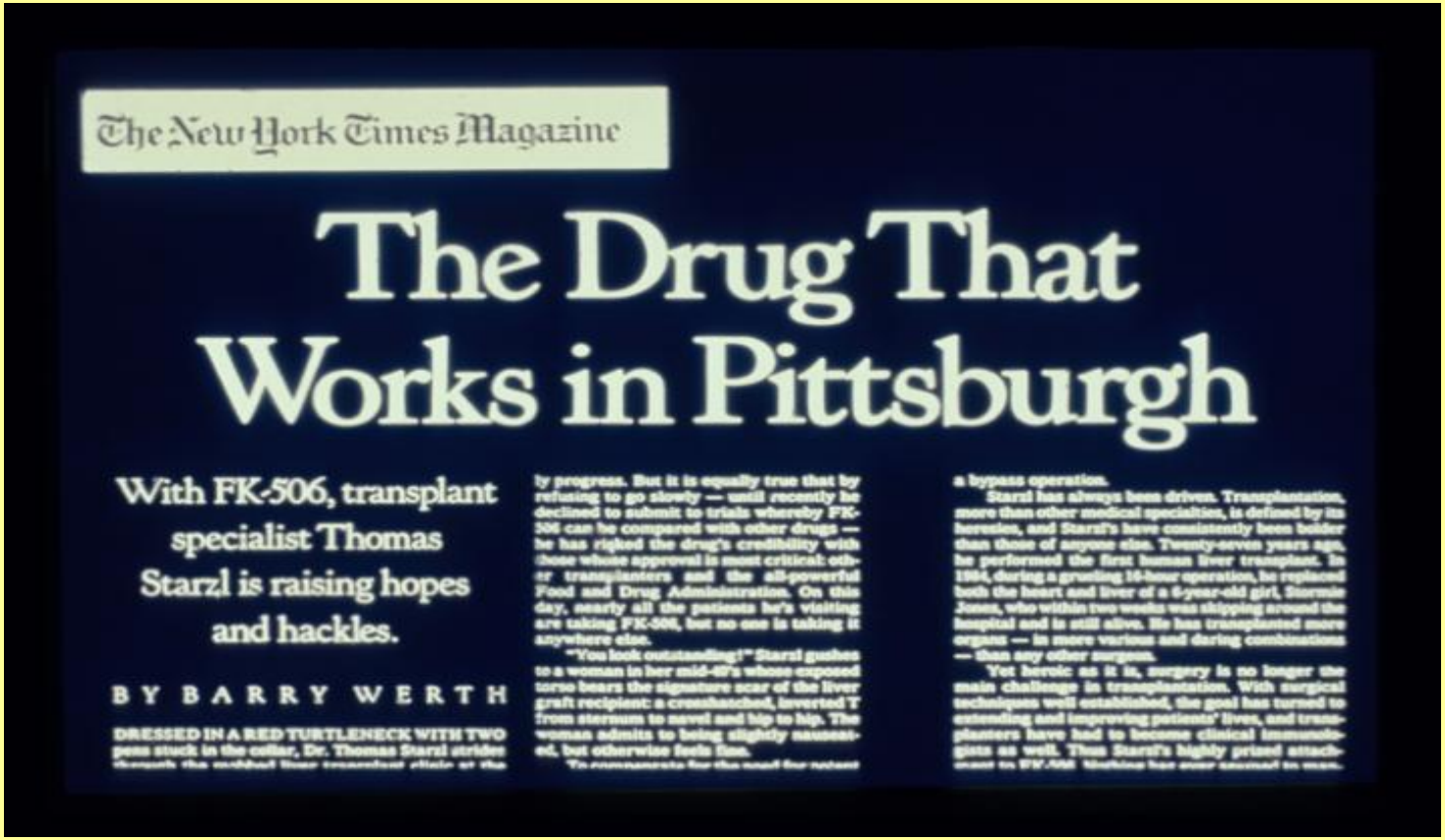
Kino and Goto isolate FK506 from *Streptomyces tsukabensis*

Ochiai describes the immunosuppressive qualities in animal models



1991

Successful University of Pittsburgh experiences in multiple organ transplants leads to multiple solid organ transplant registration trials - FDA approval in 1994



The New York Times Magazine

The Drug That Works in Pittsburgh

With FK-506, transplant specialist Thomas Starzl is raising hopes and hackles.

BY BARRY WERTH

DRESSED IN A RED TURTLENECK WITH TWO pens stuck in the collar, Dr. Thomas Starzl strides

ly progress. But it is equally true that by refusing to go slowly — until recently he declined to submit to trials whereby FK-506 can be compared with other drugs — he has risked the drug's credibility with those whose approval is most critical: other transplanters and the all-powerful Food and Drug Administration. On this day, nearly all the patients he's visiting are taking FK-506, but no one is taking it anywhere else.

"You look outstanding!" Starzl gushes to a woman in her mid-40's whose exposed torso bears the signature scar of the liver graft recipient: a cross-hatched, inverted T from sternum to navel and hip to hip. The woman admits to being slightly nauseated, but otherwise feels fine.

a bypass operation.

Starzl has always been driven. Transplantation, more than other medical specialties, is defined by its heroines, and Starzl's have consistently been bolder than those of anyone else. Twenty-seven years ago, he performed the first human liver transplant. In 1984, during a grueling 16-hour operation, he replaced both the heart and liver of a 6-year-old girl, Stormie Jones, who within two weeks was skipping around the hospital and is still alive. He has transplanted more organs — in more various and daring combinations — than any other surgeon.

Yet heroic as it is, surgery is no longer the main challenge in transplantation. With surgical techniques well established, the goal has turned to extending and improving patients' lives, and transplanters have had to become clinical immunologists as well. Thus Starzl's highly prized attach-

IMMUNOSUPPRESSION IN LIVER TRANSPLANTATION

J Am Coll Surg. 1996 August ; 183(2): 117–125.

The Pittsburgh Randomized Trial of Tacrolimus Compared to Cyclosporine for Hepatic Transplantation

John J. Fung, MD, PhD[*], Michael Eliasziw, PhD[†], Satoru Todo, MD, FACS[*], Ashok Jain, MD[*], Anthony J. Demetris, MD[*], John P. McMichael, BSC[*], Thomas E. Starzl, MD, FACS, PhD[*], Paul Meier, PhD[‡], and Allan Donner, PhD[†]

THE NEW ENGLAND JOURNAL OF MEDICINE Oct. 27, 1994

A COMPARISON OF TACROLIMUS (FK 506) AND CYCLOSPORINE FOR IMMUNOSUPPRESSION IN LIVER TRANSPLANTATION

THE U.S. MULTICENTER FK506 LIVER STUDY GROUP*

Randomised trial comparing tacrolimus (FK506) and cyclosporin in prevention of liver allograft rejection ☆

European FK506 Multicentre Liver Study Group[1]

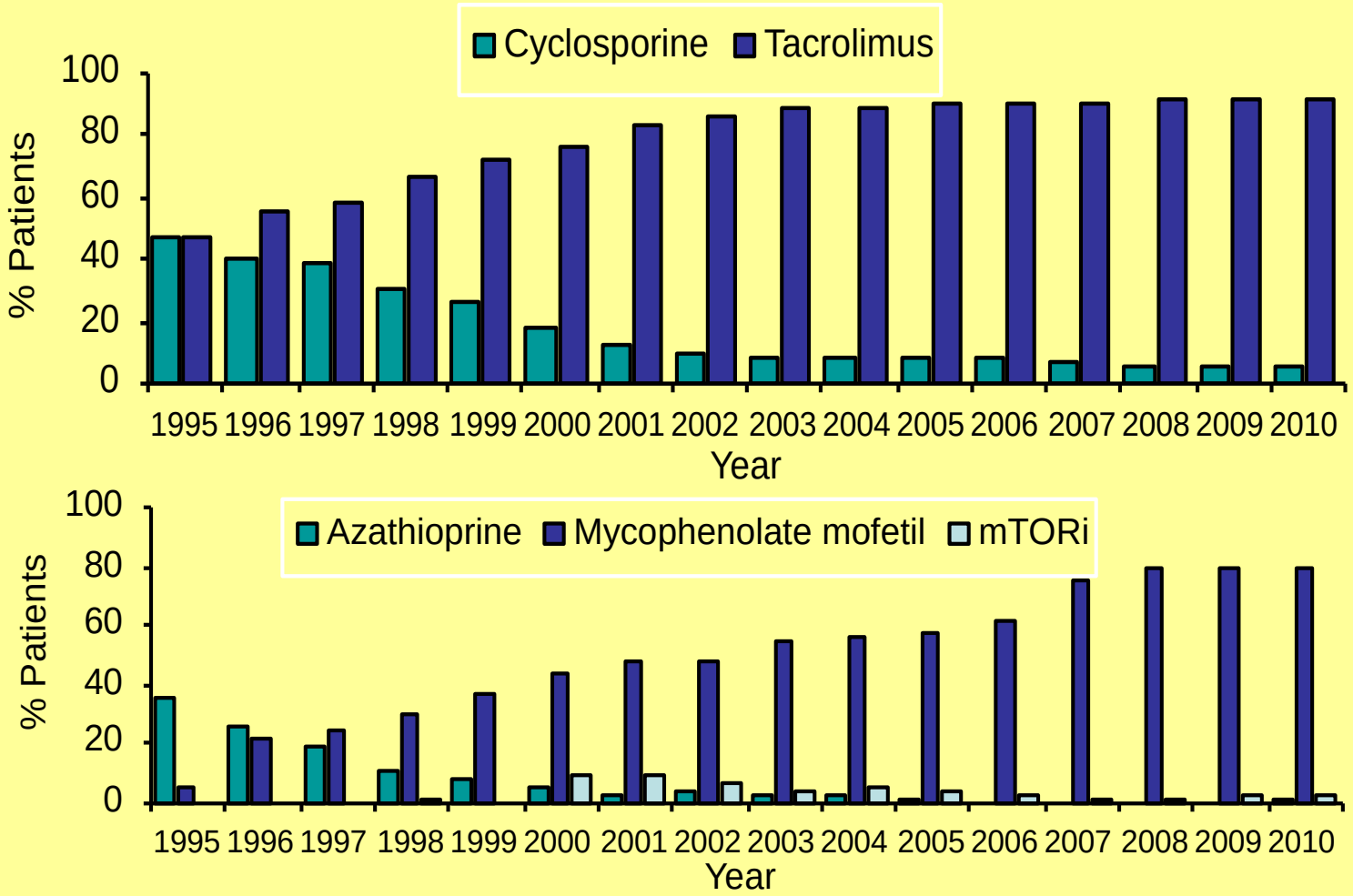
THE LANCET
Volume 344, Issue 8920, 13 August 1994, Pages 423–428

Tac vs CsA: Meta-Analysis

	RR	P-value
Patient Death	0.85	<0.03
Graft Loss	0.73	<0.001
Acute Rejection	0.81	<0.001
SRR	0.54	<0.003
Diabetes	1.38	<0.04

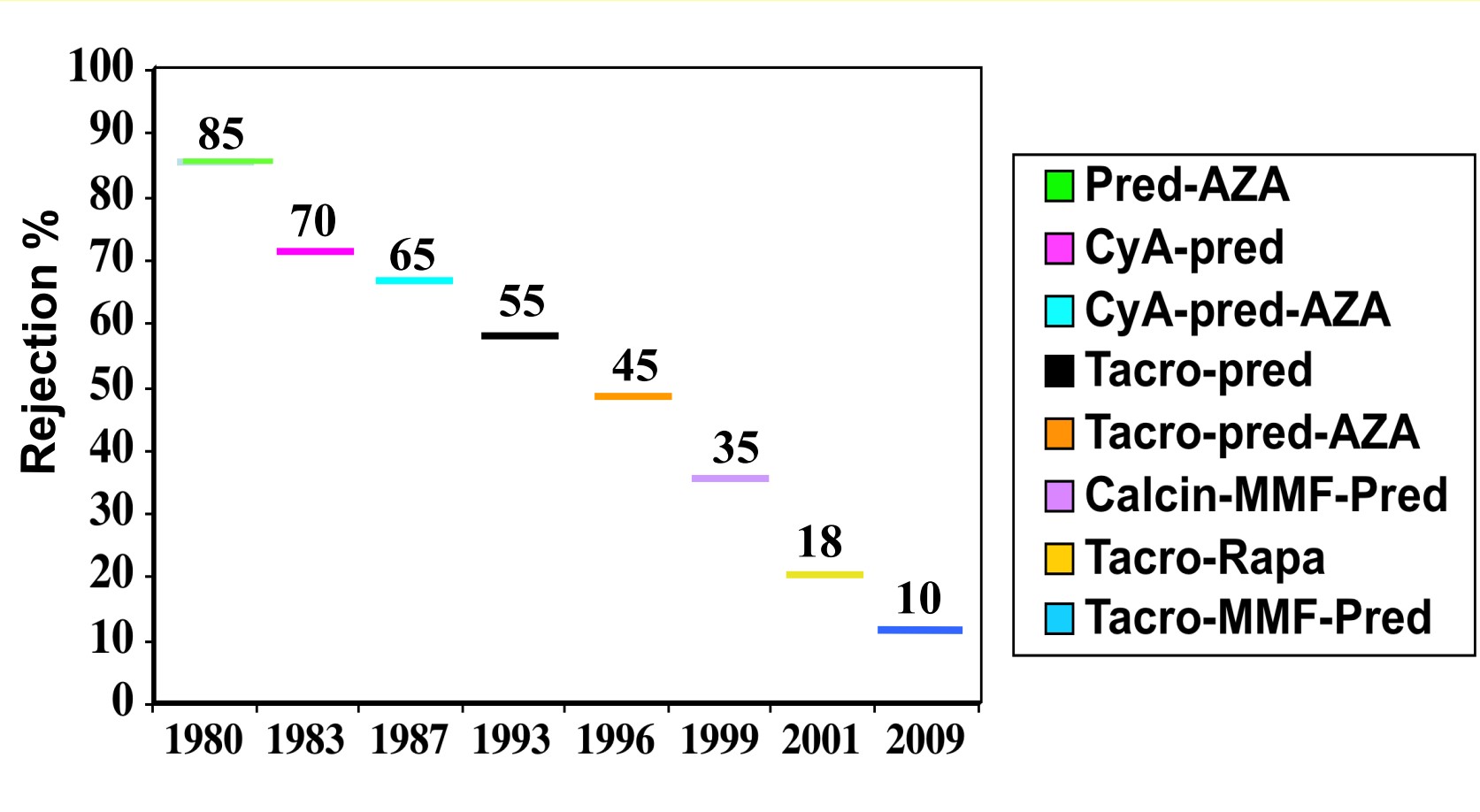
McAlister et al. Am J of Transpl 2006, 6:1578

Trends in Immunosuppression At Discharge for LTX: 1995-2010

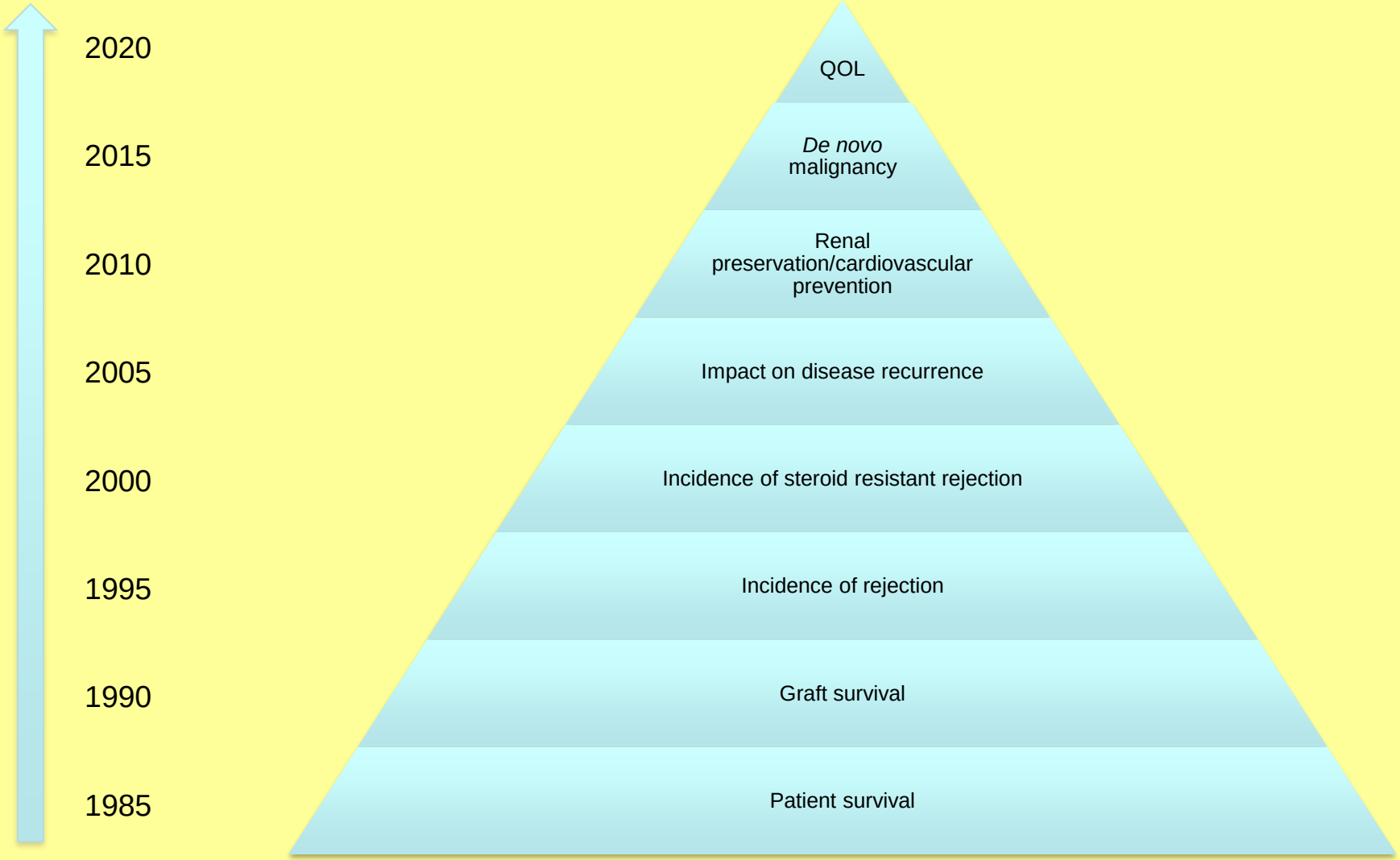


Health Resources and Services Administration 2011 SRTR and OPTN Annual Report
http://srtr.transplant.hrsa.gov/annual_reports/2011/flash/03_liver/index.html.
Accessed March 7, 2014

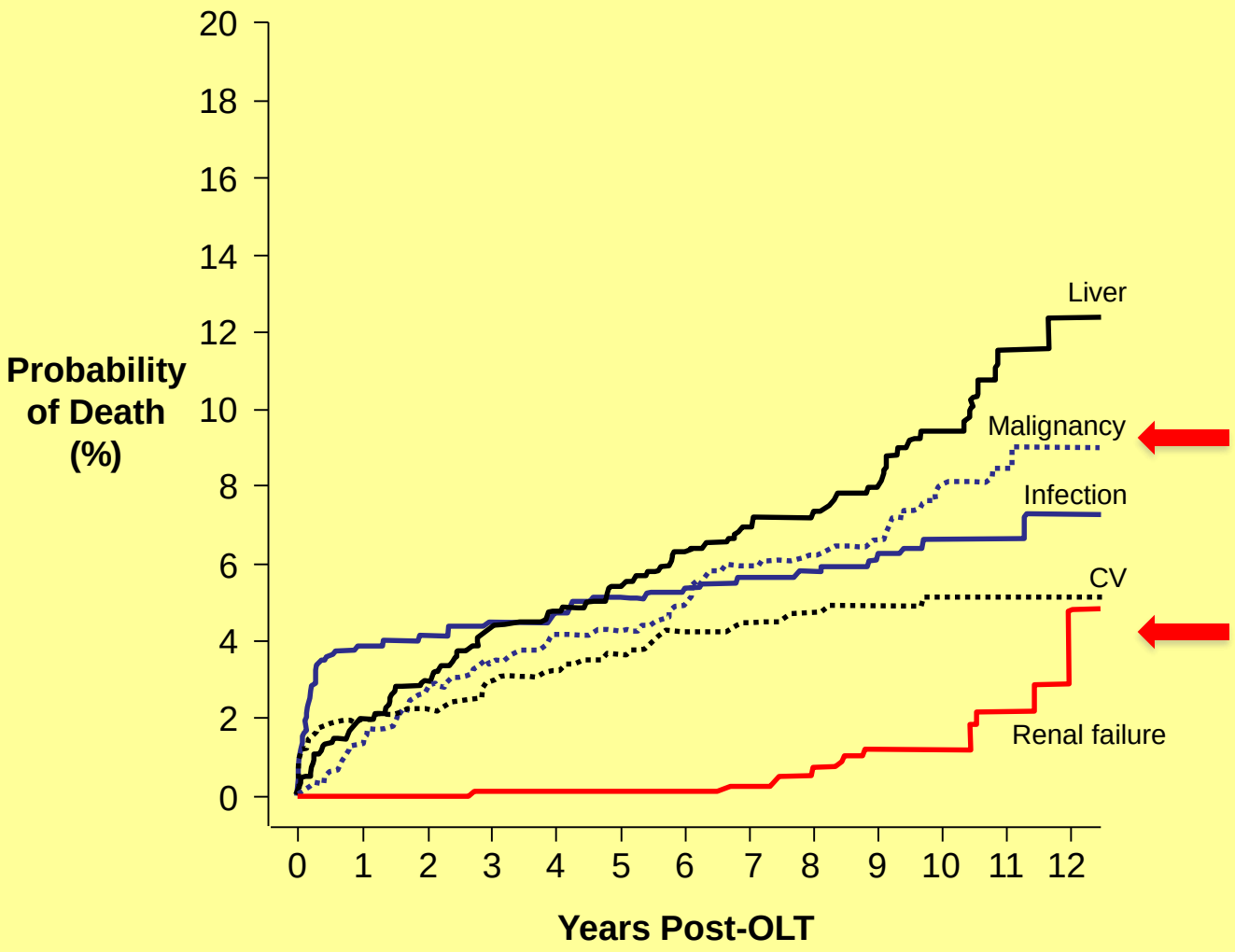
Incidence of Acute Rejection by Immunosuppressive Regimen



Evolution of Endpoints in Liver Transplantation



Probability of Post-LTX Death By Cause

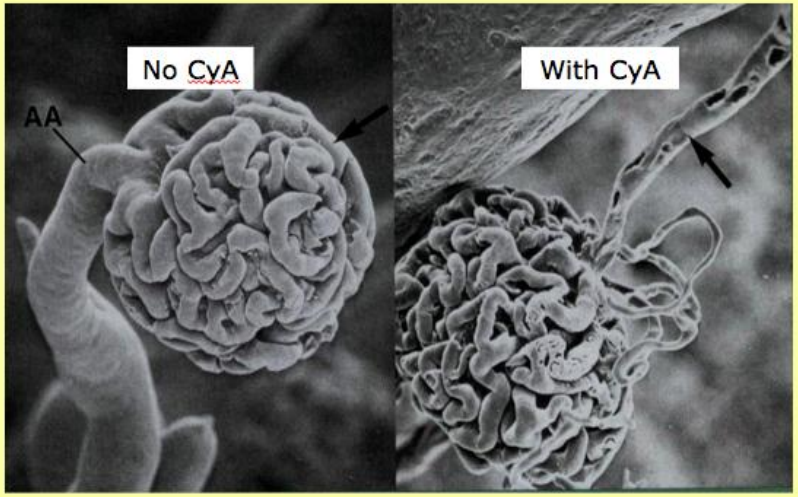


- Renal-related deaths increased in probability after 8 years of follow-up, with a sharp rise after 10 years
- Renal-related mortality increased to 10.2% of deaths after 5 years

Watt KDS et al. *Am J Transpl.* 2010;10:1420-1427.

Renal Failure Is An Increasing Problem In LTX

- **MELD score allocation pre-transplantation[1]**
  - Selects for patients with renal dysfunction
- **More marginal donors accepted[1]**
  - Associated with perioperative complications
- **More liver transplant recipients are surviving long-term[1]**
  - Accumulating renal toxicity of long-term CNI use



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

1. Sharma P *et al. Liver Transpl* 2009;15:1142-8; 2) **English J, et al. Transplantation; 44: 135-141.**

Chronic CNI Therapy Decreases Renal Function After LTX

Shift table of renal function by stage of kidney disease in LTX patients

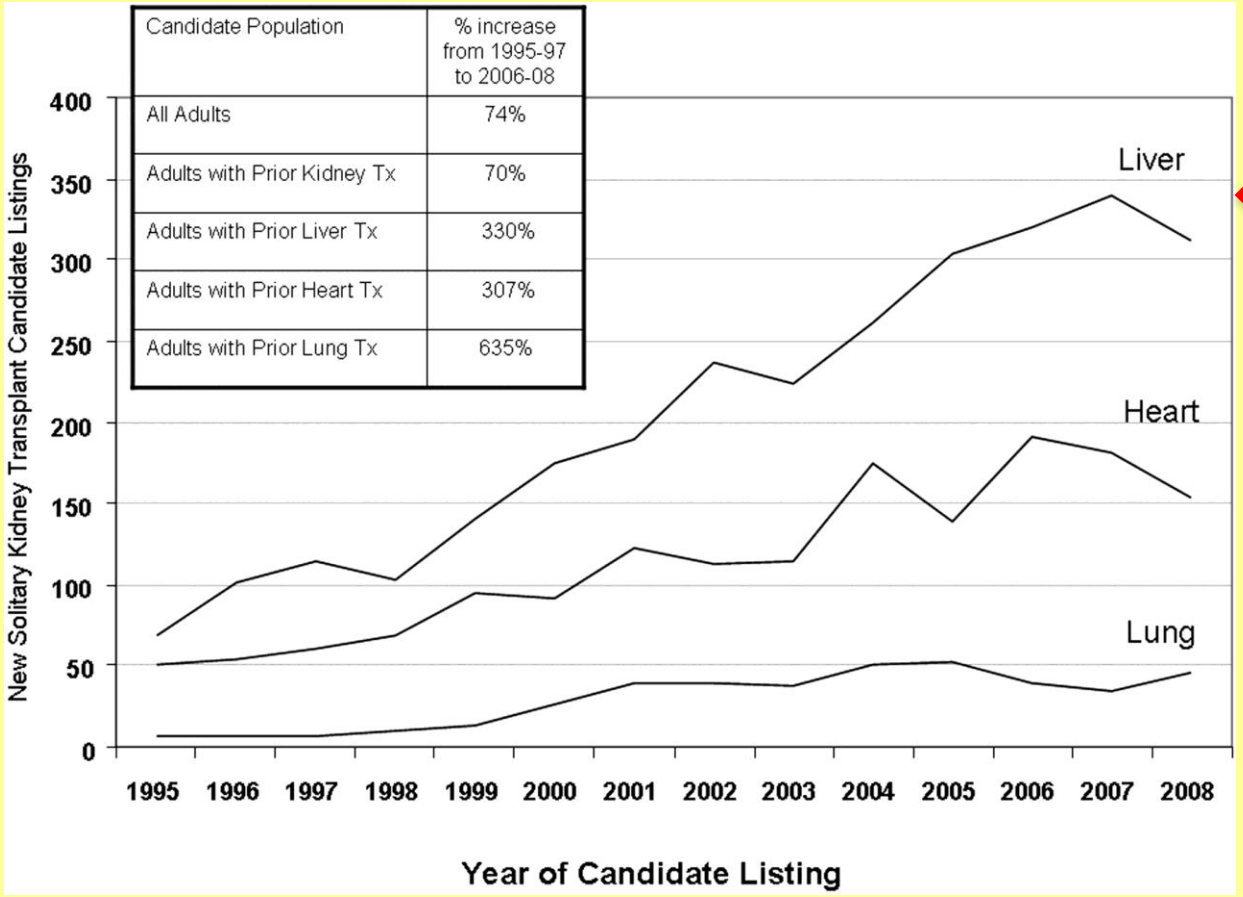
Stage of Kidney Disease	GFR (mL/min/1.73 m^2)	Before Liver Transplantation [%(n)]	After Liver Transplantation [%(n)]		
			1 Month	12 Months	60 Months
1	≥90	54.3 (819)	15.9 (240)	7.7 (117)	5.7 (86)
2	60-89	34.9 (526)	36.4 (549)	41.1 (619)	36.6 (552)
3	30-59	9.5 (143)	43.9 (662)	48.7 (734)	52.7 (795)
4	15-29	1.1 (17)	3.5 (53)	2.4 (36)	3.7 (56)
5	<15 and HD	0.2 (3)	0.3 (4)	0.13 (2)	1.3 (19)

CNI, calcineurin inhibitor; GFR, glomerular filtration rate; HD, hemodialysis

Karie-Guigues S *et al. Liver Transpl* 2009;15:1083–91

An Emerging Population: Kidney Transplant Candidates after Liver Transplantation

Candidate Population	% increase from 1995-97 to 2006-08
All Adults	74%
Adults with Prior Kidney Tx	70%
Adults with Prior Liver Tx	330%
Adults with Prior Heart Tx	307%
Adults with Prior Lung Tx	635%



Srinivas T R et al., *Clinical J American Society of Nephrology* 2010

Protecting Renal Function Requires A Multifactorial Approach

- **Optimized perioperative management including fluid management**
- **Avoiding nephrotoxic drugs**
- **Immunosuppressive regimens**
  - reducing
  - delaying
  - withdrawing
  - avoiding

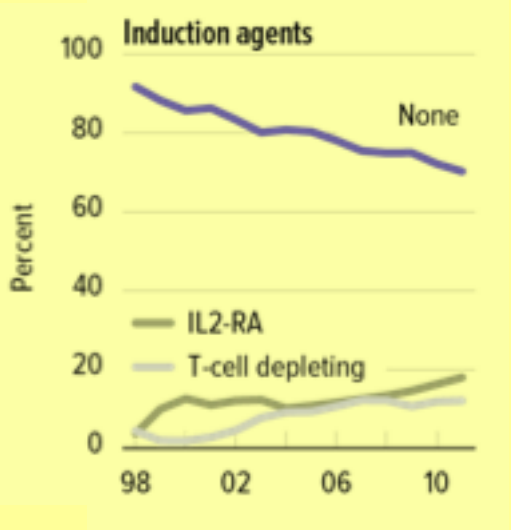
  } **calcineurin inhibitors**

- **Reducing, delaying, withdrawing or avoiding CNIs can lead to better protection of renal function**
  - Biological agents for induction or maintenance
    - ATG, basiliximab
  - Replacement options:
    - Mycophenolate
    - mTOR inhibitors
      - Everolimus, sirolimus*
  - New drugs
    - Belatacept*

*Not approved for liver transplantation
CNI, calcineurin inhibitor; mTOR, mammalian target of rapamycin; ATC, anti-thymocyte globulin

Strategies to Reduce Development of CNI Nephrotoxicity

Minimizing use of CNI in the early post-transplant period - use of induction antibody preparations and delay of CNI



Study Design

3-arm, randomized, controlled Phase II investigator initiated trial

Control: Tac by post-op day 2, MMF, Steroid taper in 3 weeks

r-ATG 2-dose: 3 mg/kg (1.5 mg/kg/dose), MMF, Steroid taper in 3 weeks, Tac start on post-op day 10

r-ATG 3-dose: 4.5 mg/Kg (1.5 mg/kg/dose), MMF, Steroid taper in 3 weeks, Tac start on post-op day 10

Eghtesad B et al: ILTS 2014

Biopsy Proven Acute Rejection

Subject	Group	POD	Rejection Classification (activity index)	Treatment
010	STD CNI	POD 63	Moderate (6/9)	Solumedrol
002	r-ATG 3 mg/kg	POD 7	Mild	Solumedrol/FK
014	r-ATG 3 mg/kg	POD 8	Mild (5/9)	FK started
017	r-ATG 3 mg/kg	POD 10	Mild	FK started
011	r-ATG 3 mg/kg	POD 70 *	Very Mild (3/9)	FK increased
030	r-ATG 4.5 mg/kg	POD 8	Moderate / Severe (8/9)	Solumedrol

BPAR was greatest in the 3 mg/kg group and less in the Control and 4.5 mg/kg groups

Results – Serum Creatinine

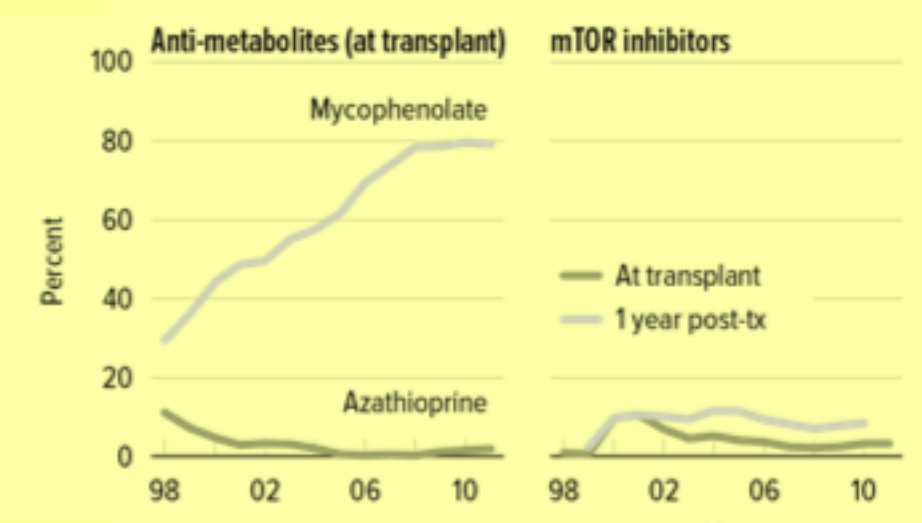
	STANDARD CNI (*)		r-ATG 3 mg/ kg (&)		r-ATG 4.5 mg/kg (#)	
	Serum Creatinine mg/dL	Δ Creatinine	Serum Creatinine mg/dL	Δ Creatinine	Serum Creatinine mg/dL	Δ Creatinine
BASELINE (30)	0.97 +/- 0.32		0.98 +/- 0.47		0.93 +/- 0.39	
MONTH 1 (29)	1.15 +/- 0.21	0.18 +/- 0.26	1.11 +/- 0.35	0.12 +/- 0.24	1.07 +/- 0.23	0.14 +/- 0.43
MONTH 3 (28)	1.23 +/- 0.27*	0.27 +/- 0.31	1.15 +/- 0.41	0.17 +/- 0.23	0.99 +/- 0.16	0.06 +/- 0.39
MONTH 6 (27)	1.33 +/- 0.47*	0.37 +/- 0.44	1.18 +/- 0.35	0.17 +/- 0.24	1.04 +/- 0.21	0.11 +/- 0.17
MONTH 9 (27)	1.25 +/- 0.34*	0.33 +/- 0.28	1.13 +/- 0.30	0.01 +/- 0.25	1.02 +/- 0.22	0.09 +/- 0.11
MONTH 12 (14)	1.50 +/- 0.59*^	0.64 +/- 0.51	1.04 +/- 0.23	-0.01 +/- 0.30	1.02 +/- 0.30	0.09 +/- 0.12

(*) Serum creatinine difference for STD CNI versus Baseline significant with 90% confidence

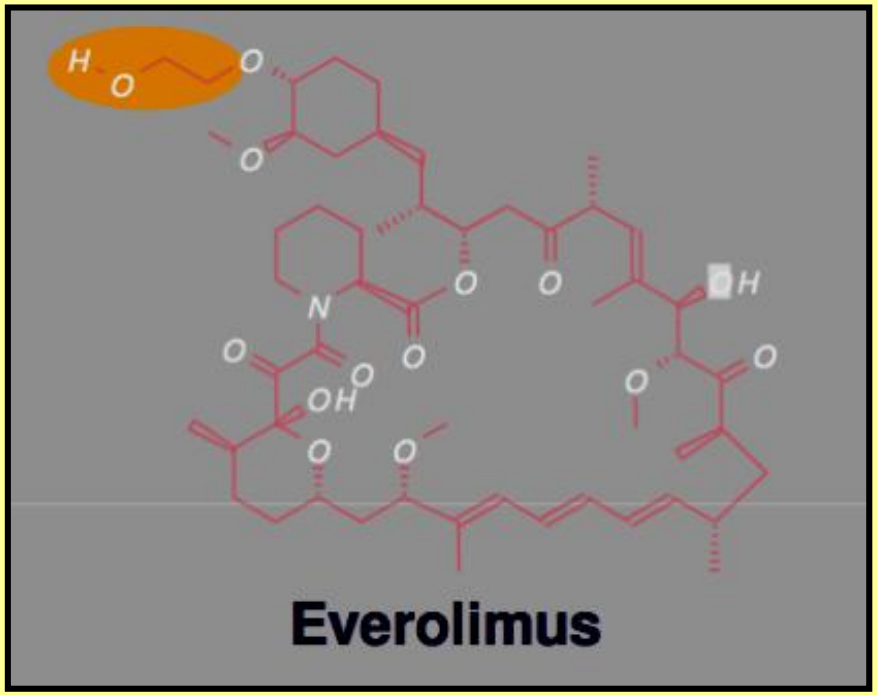
(^) STD CNI vs. combined r-ATG at Month 12 significantly different ($p = 0.05$)

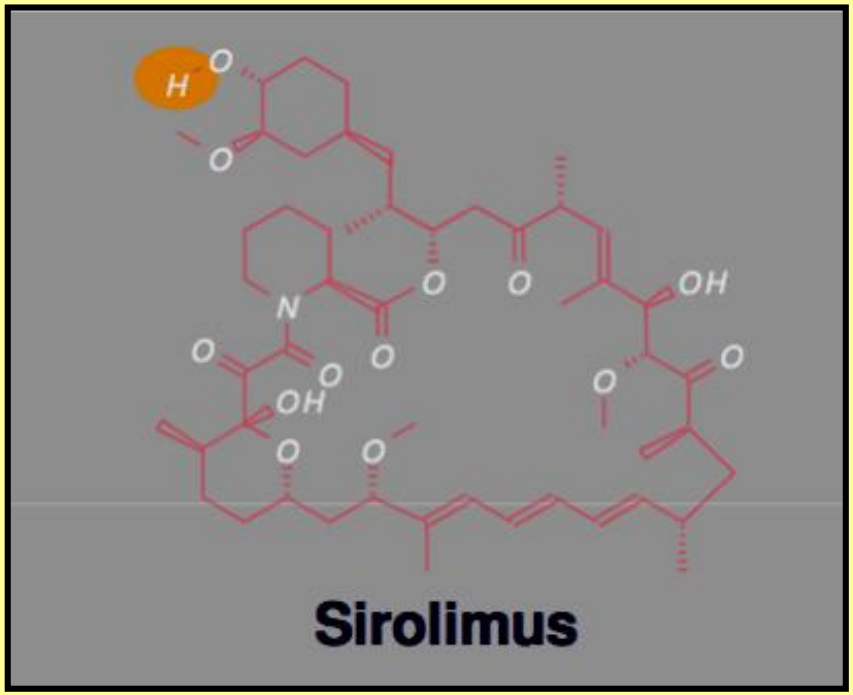
Strategies to Reduce Development of CNI Nephrotoxicity

Employing use of adjunctive immunosuppressive agents - conversion from CNI to non-nephrotoxic immunosuppressive agents



IMMUNOSUPPRESSION IN LIVER TRANSPLANTATION

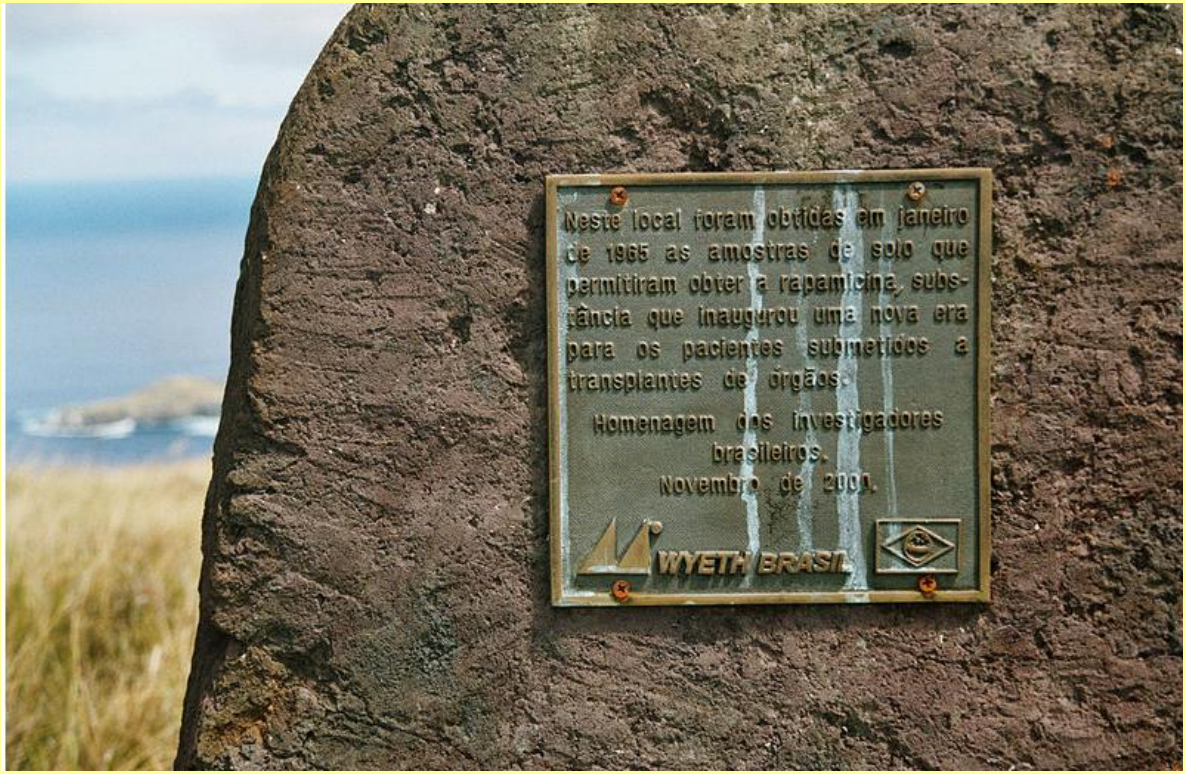




Sirolimus = Rapamycin

Isolated from fungus from Easter Island, aka, Rapa Nui

IMMUNOSUPPRESSION IN LIVER TRANSPLANTATION




Dr. Suren Sehgal

"In this-area, samples of soil were obtained in January 1965 from which rapamycin was derived to inaugurate a new era for transplant patients"

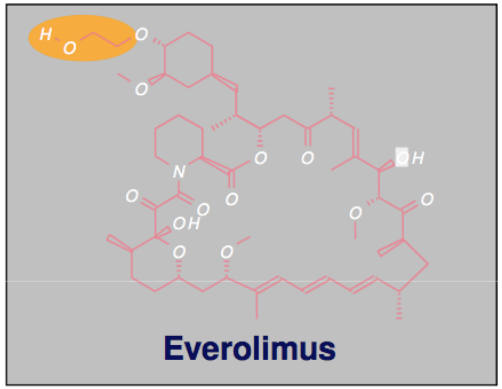
International Rapamycin and Tacrolimus Study

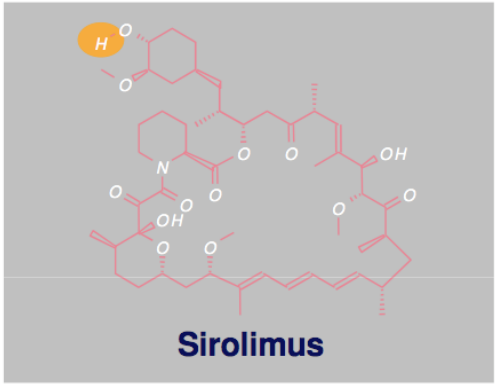
	Rapa/Tacro n=110	Tacro n=112	p value
Graft loss (%)	22.7	8.9	<0.006
Death (%)	14.5	5.4	<0.025
AR (%)	20	22	ns
HAT (%)	5.4	0.9	0.06
Septic death (%)	9.1	0.9	<0.05

* Stopped Prematurely

Asrani SK et al. Am J Transpl 2014; 14:356

mTOR/PSI





	Everolimus[1]	Sirolimus[2]
Oral bioavailability	20%	14%
Time to T_{max}	1–2 hours	1–2 hours
Half-life	28 hours	62 hours
Loading dose	NO	6.0 mg
Time to steady state	4 days	5–7 days
Plasma protein binding	74%	92%
Dosing interval	Twice daily	Once daily
Target trough levels	**3–8 ng/mL**	**4–12 ng/mL**
Tablet options	0.25, 0.5, 0.75 and 1 mg	1 and 2 mg

RAD001H2304: A 24 month, multi-center, open-label, randomized, controlled study to evaluate the efficacy and safety of concentration-controlled everolimus to eliminate or to reduce tacrolimus compared to tacrolimus in *de novo* liver transplant recipients

Test drug/investigational product: everolimus/RAD001

Indication studied: Liver transplantation

Study design: See title.

Sponsor: Novartis

Protocol identification: **Protocol no.** CRAD001H2304, **Eudract no.** 2007-001821-85

Development phase of study: III

Study initiation date: 28-Jan-2008 (first patient first visit)

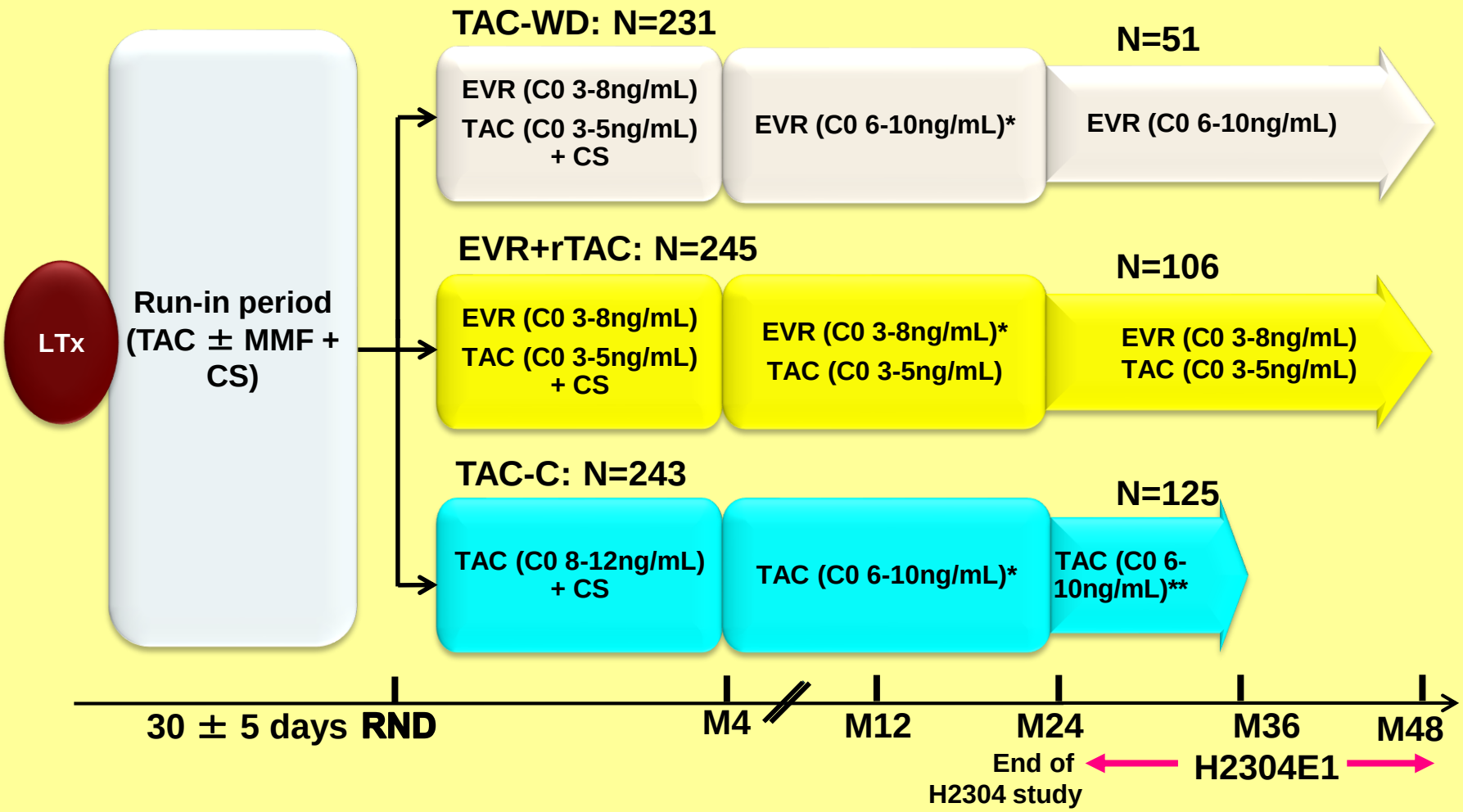
Early termination date: Not applicable

Study completion date: 12-Apr-2012 (last patient last visit)

Principal or Coordinating Investigator(s): Dr. John J. Fung

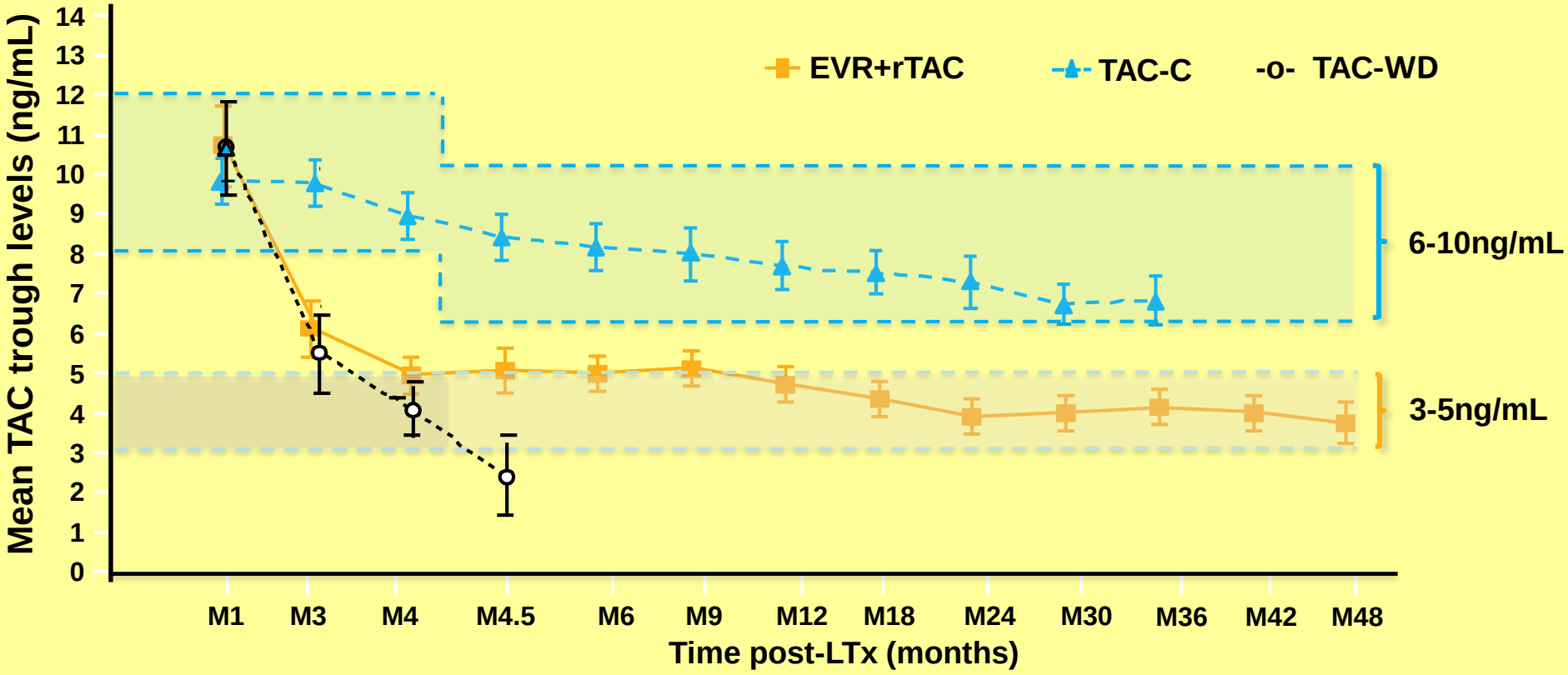
Company/Sponsor signatory: Novartis Pharmaceuticals Corporation

H2304 and H2304E1: Study design



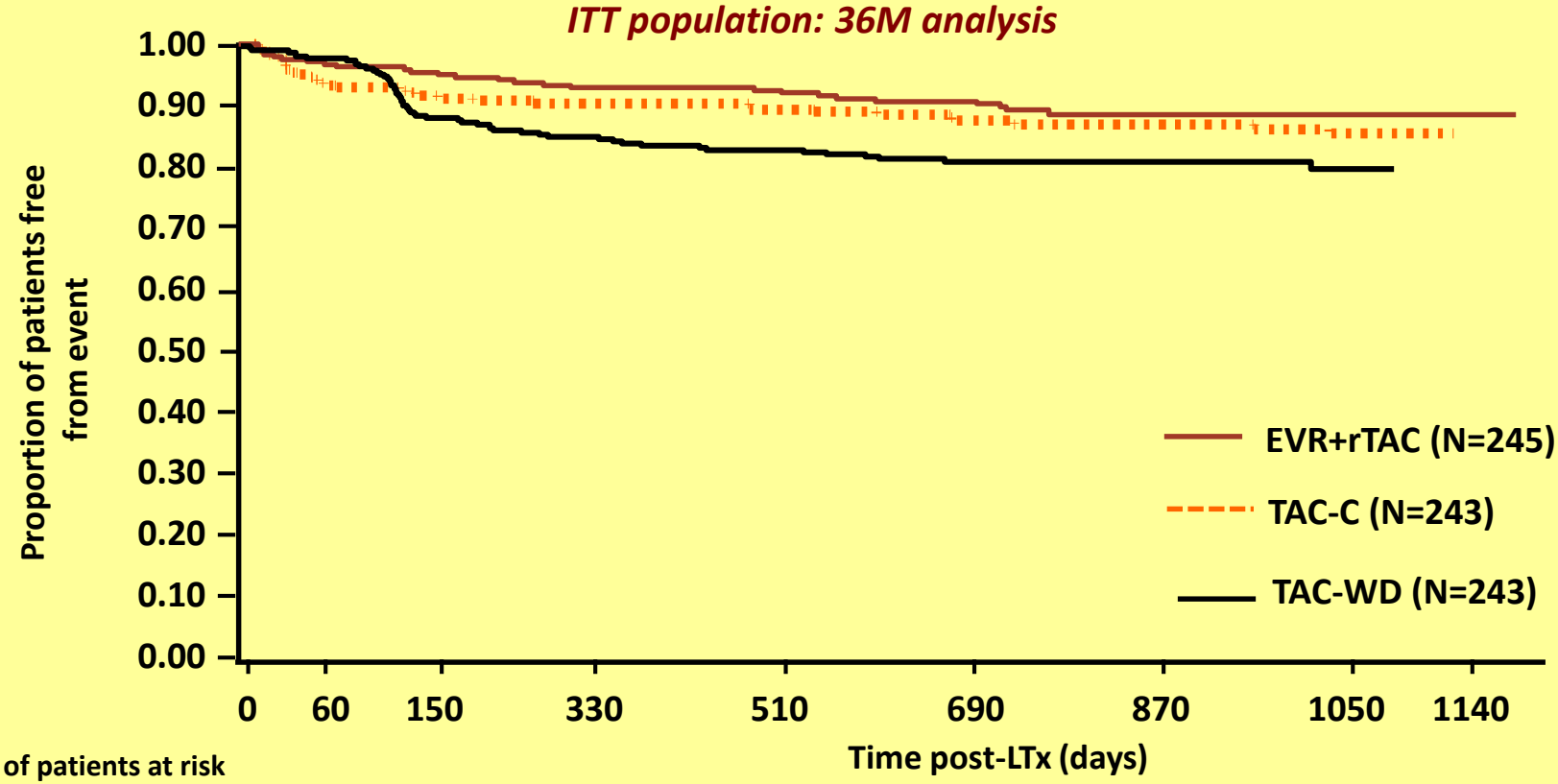
CS, corticosteroids; eGFR, estimated glomerular filtration rate; EVR, everolimus; HCV, hepatitis C virus; LTx, liver transplantation; MMF, mycophenolate mofetil; M, month; RND, randomization; rTAC, reduced tacrolimus; TAC-C, tacrolimus control; TAC-WD, tacrolimus withdrawal.

Clear Separation in TAC Exposure



Vertical lines indicate 95% CI at each time point

Freedom From Composite Efficacy Failure (RND to M36)

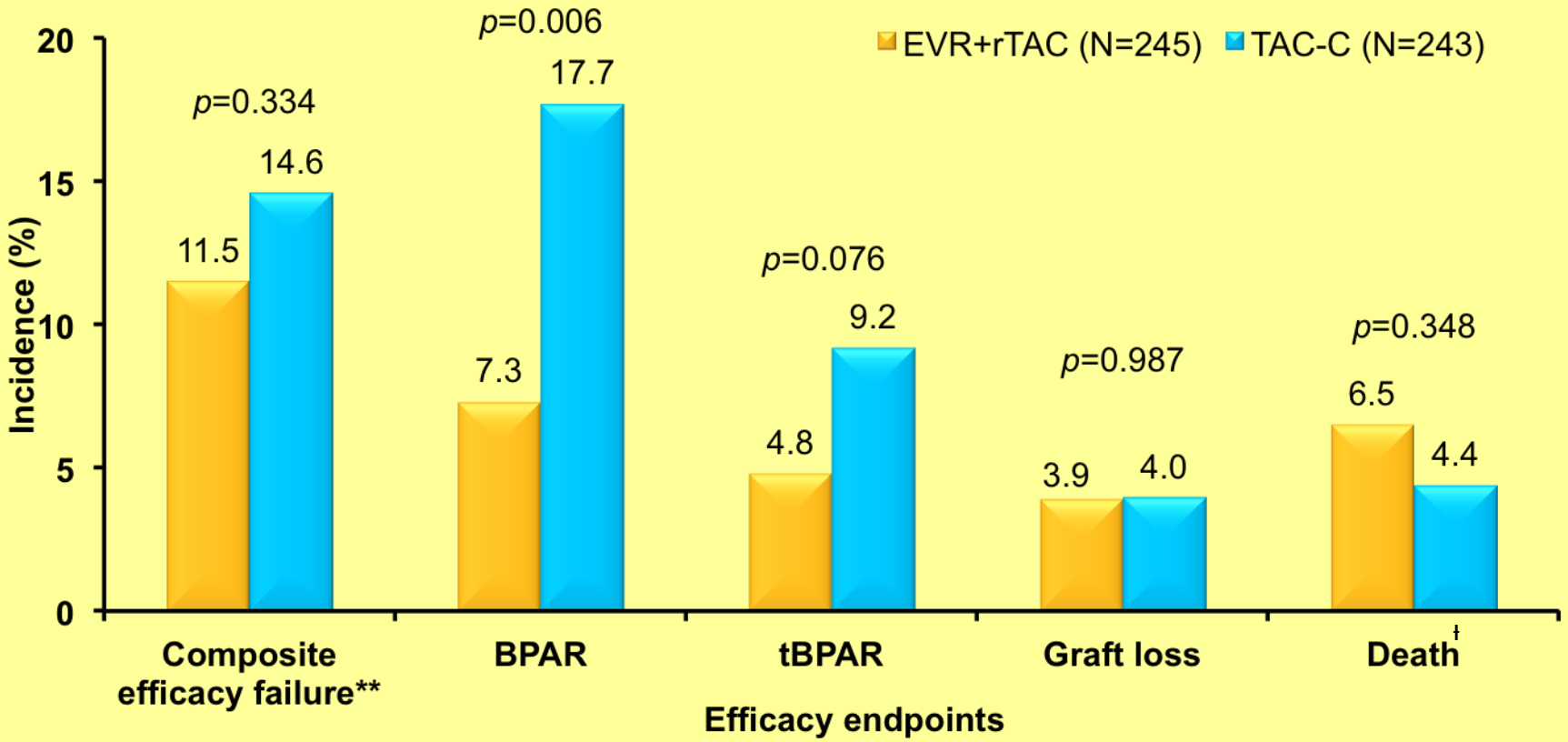


Number of patients at risk

EVR+rTAC	245	234	227	218	209	176	101	92	69
TAC-C	243	221	214	202	196	160	120	96	10
TAC-WD	231	219	197	167	155	123	47	46	

EVR, everolimus; ITT, intent-to-treat; LTx, liver transplantation; M, month; rTAC, reduced tacrolimus; TAC-C, tacrolimus control; TAC-WD, tacrolimus withdrawal

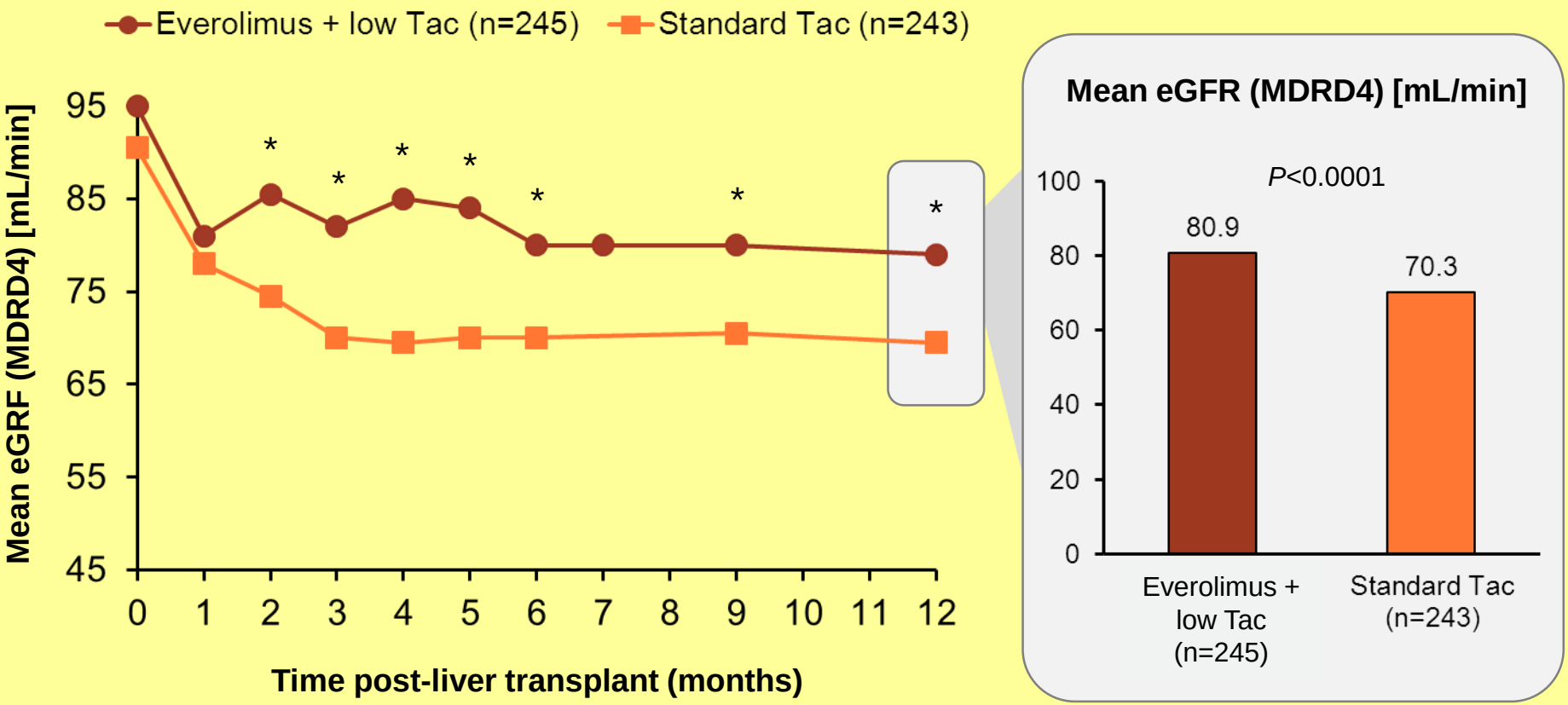
Efficacy Endpoints from RND to M36



Composite efficacy failure is defined as tBPAR, graft loss or death. *ITT population consisted of all patients randomised in the 24-month core study; **Includes two patients who never received everolimus. †One case of hypoglycemia and one sudden death; both considered unrelated to study drug

BPAR, biopsy proven acute rejection; EVR, everolimus; ITT, intent-to-treat; M, month; rTAC, reduced tacrolimus; TAC-C, tacrolimus control; tBPAR, treated BPAR

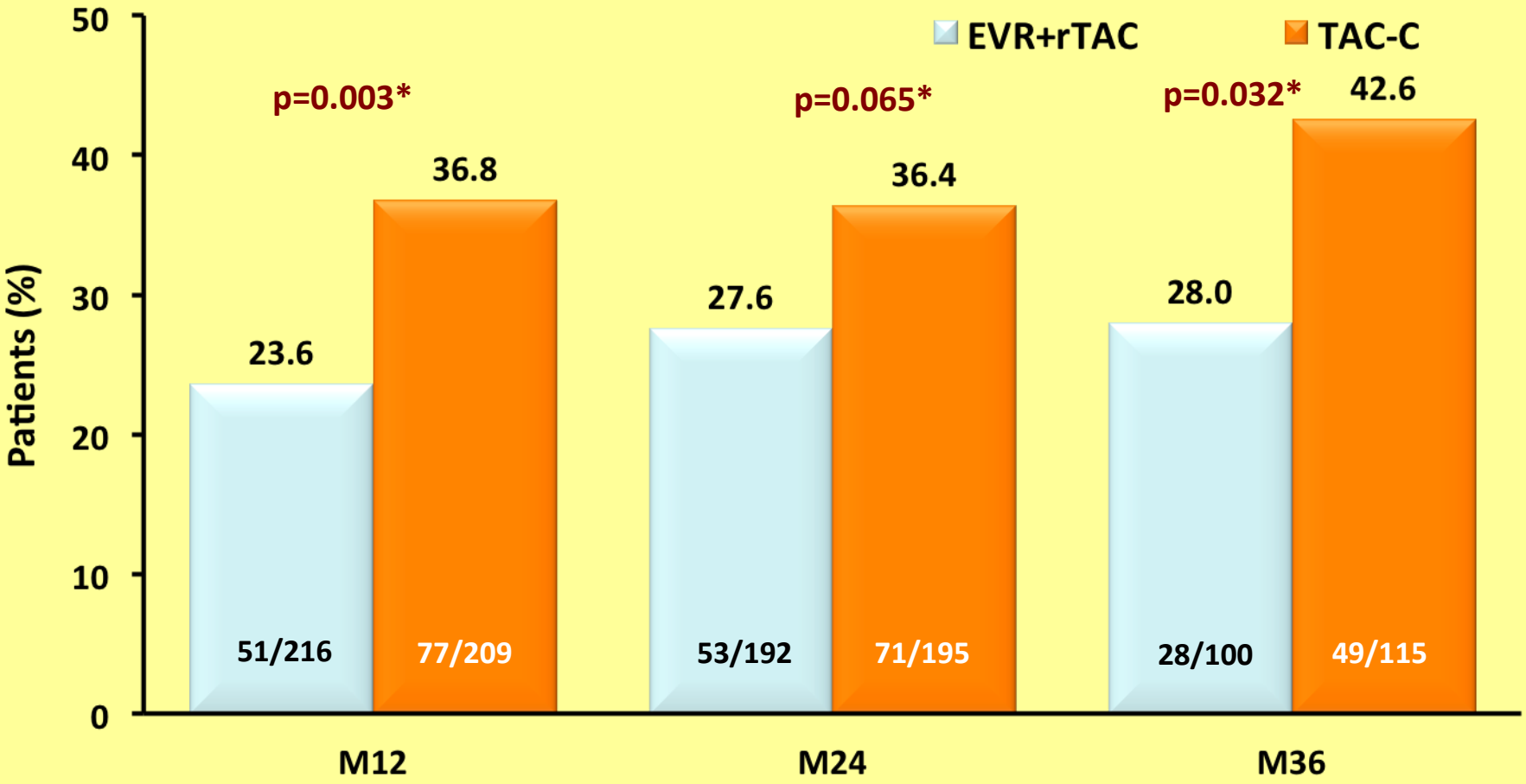
Improvements In Renal Function With Everolimus + Low Tac Were Immediate And Sustained



Tac, tacrolimus; eGFR, estimated glomerular filtration rate; MDRD, modified of diet in renal disease
Data on file, Novartis

Patients with eGFR <60mL/min

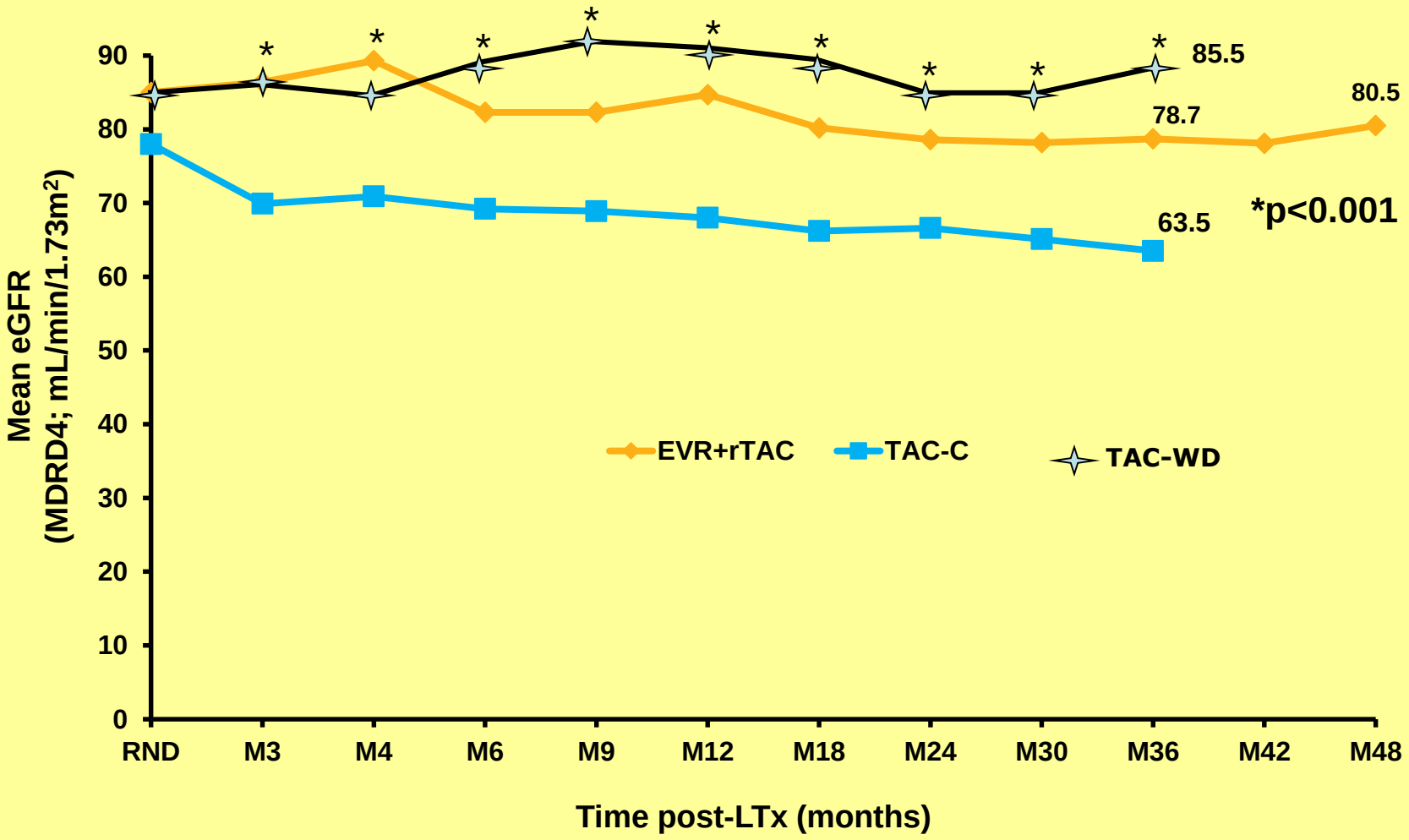
ITT population



*Indicates Fischer's exact test p value

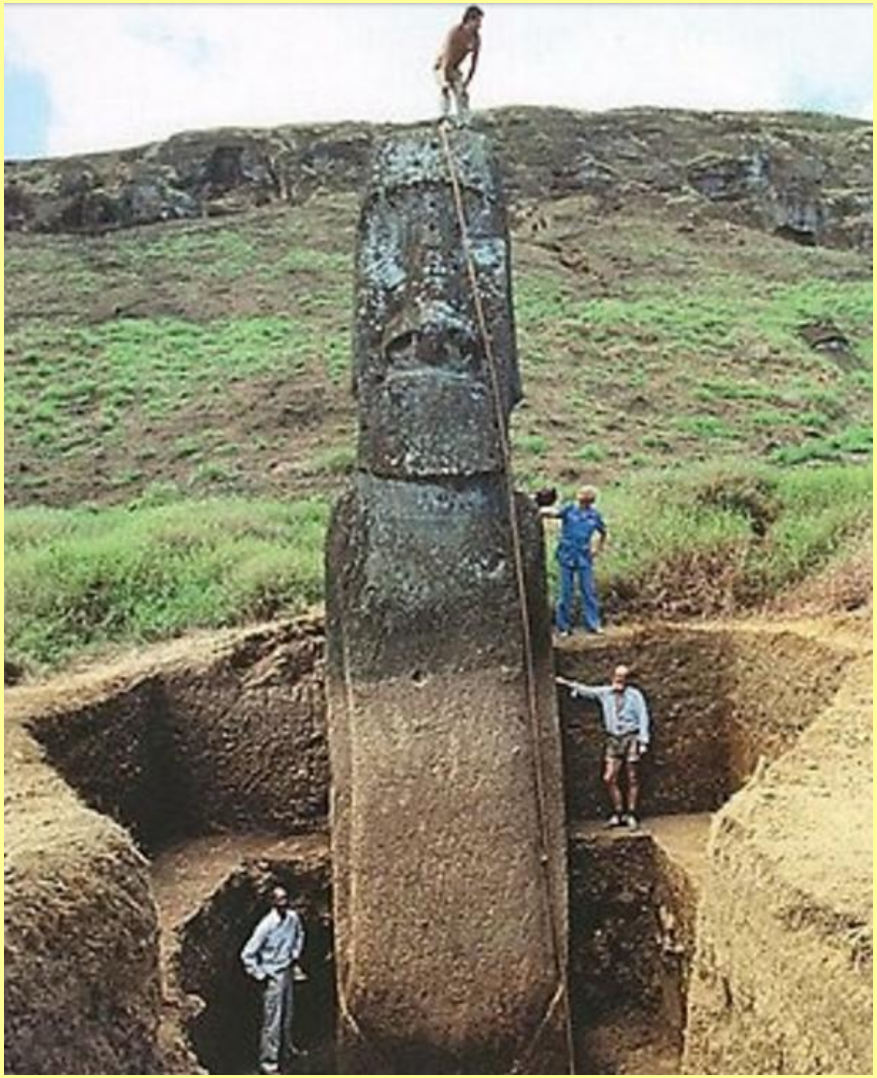
eGFR, estimated glomerular filtration rate; EVR, everolimus; ITT, intent-to-treat; M, month; MDRD, modification of diet in renal disease; rTAC, reduced tacrolimus; TAC, tacrolimus; TAC-C, tacrolimus control; TAC-WD, tacrolimus withdrawal

Renal Function

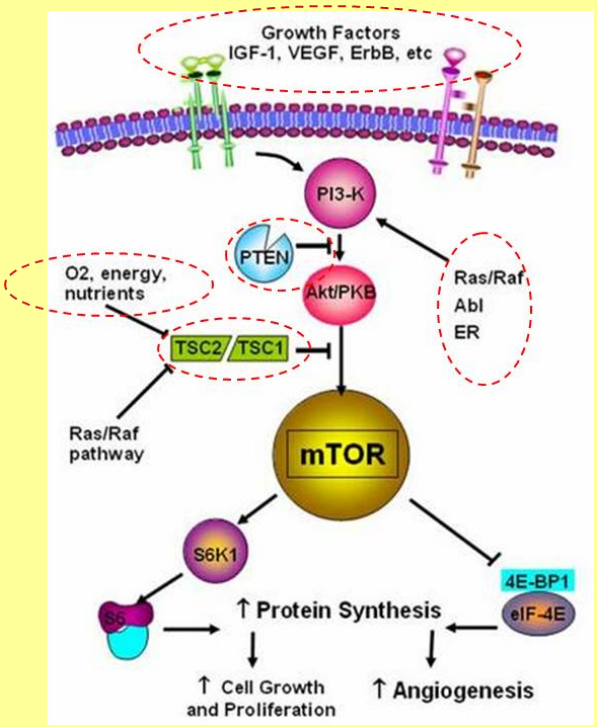


Complexity of mTOR Inhibitors

Complexity of mTOR Inhibitors



mTOR Has A Central Role In Cancer Development



Sites of Action

- Angiogenesis
- Growth/proliferation
- Oncogenes/tumor suppressors
- Immunity

Indications

- Renal cell cancer
- Neuroendocrine tumors
- Breast cancer
- Prostate cancer

mTOR, mammalian target of rapamycin; PI3-K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homologue; VEGF, vascular endothelial growth factor.

Guba M, et al. *Nat Med.* 2002;8:128–135; Lang SA, et al. *Int J Cancer.* 2007;120:1803–1810; Lang SA, et al. *Hepatology.* 2009;49:523–532; Cohen A, Hall MN. *Cell.* 2009;136:399–400; Nicklin P, et al. *Cell* 2009;136:521–534; Rao RR, et al. *Immunity.* 2010;32:67–78.

First Use of Rapamycin for Treatment of Recurrent Liver Cancer After LTX - 1991

Tom Landry: “We really do credit Dr. Starzl with keeping Lisa alive for four additional years”

RAPA for Post-LTX HCC Recurrence Prevention

[Schnitzbauer A, BMC 2010]

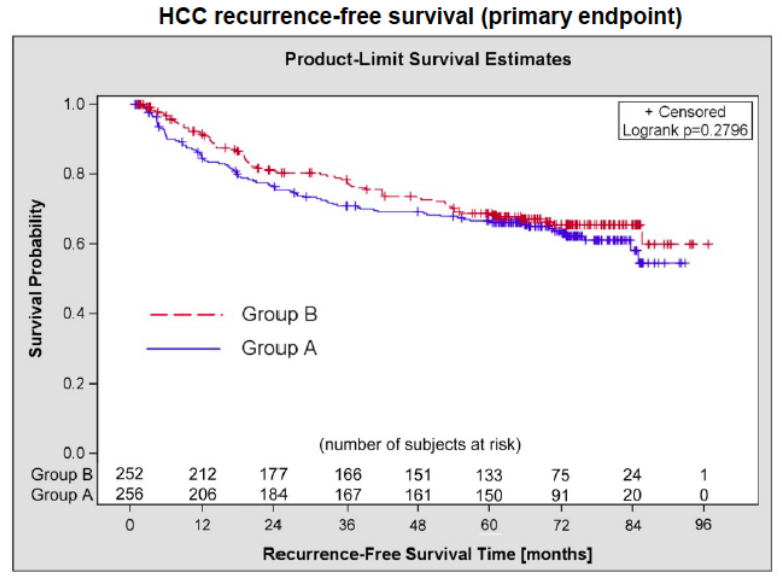
BMC Cancer

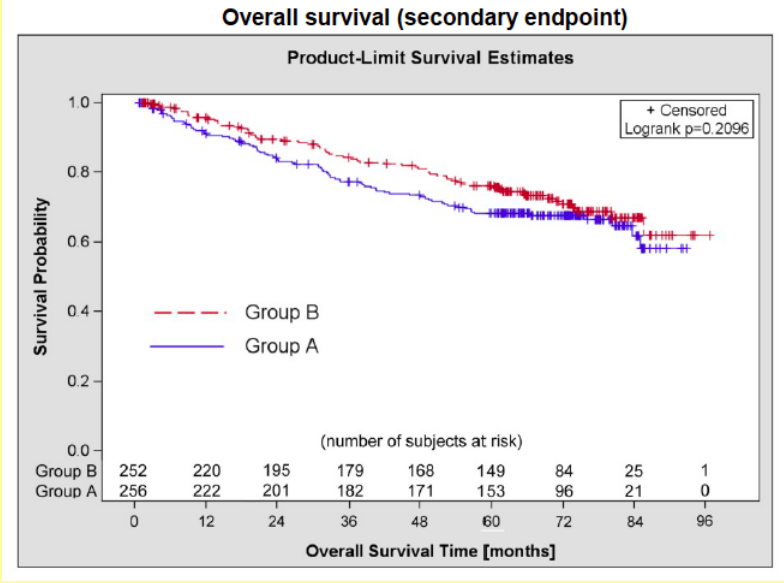
STUDY PROTOCOL Open Access

A prospective randomised, open-labeled, trial comparing sirolimus-containing versus mTOR-inhibitor-free immunosuppression in patients undergoing liver transplantation for hepatocellular carcinoma

Phase III trial – SILVER

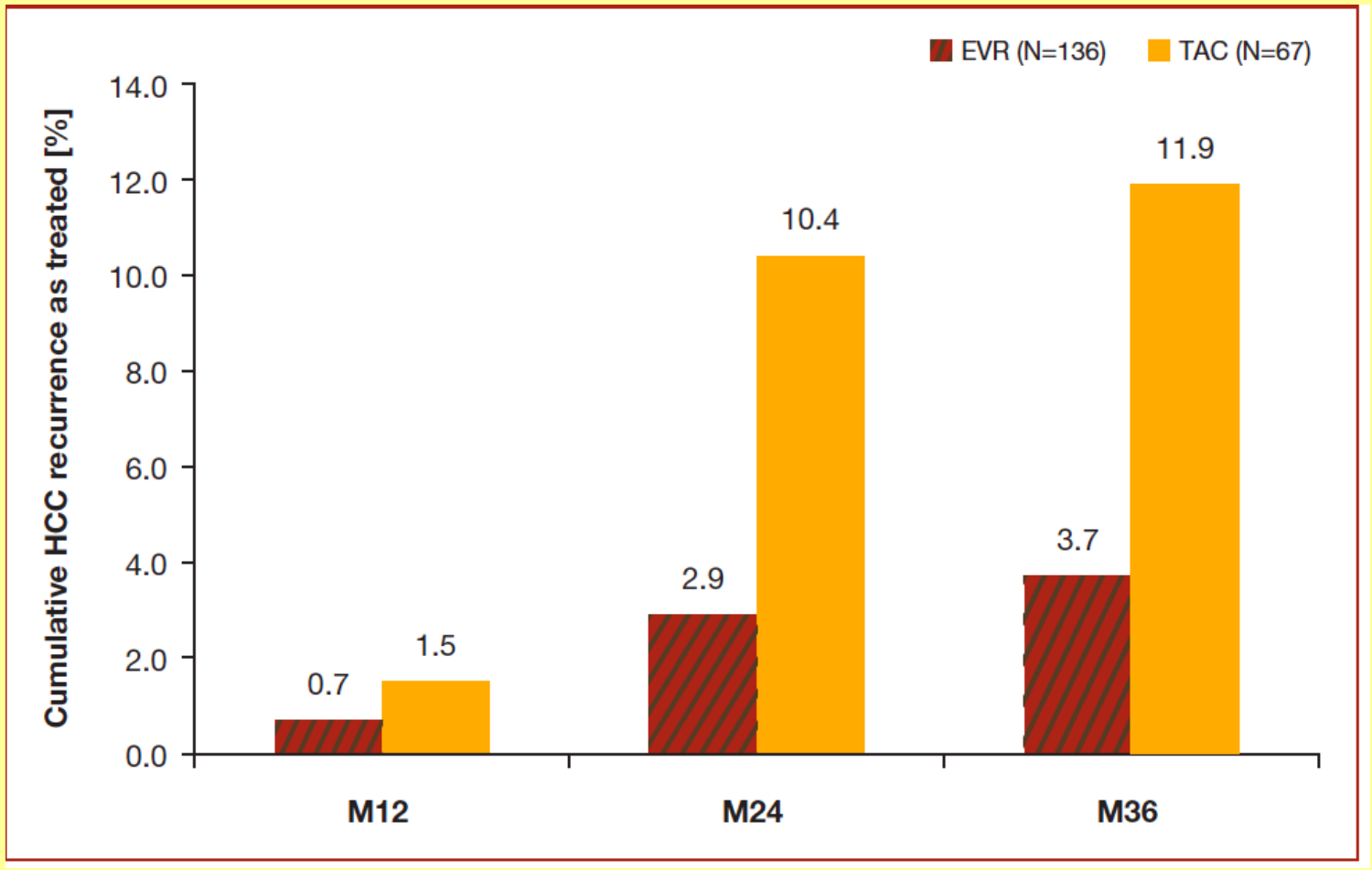
- 510 patients enrolled with histologically proven HCC
- ***Stratified HCC within and exceeding Milan***
- Randomized in two groups according to inclusion of mTOR inhibitor regimen vs Center Specific immunosuppression regimen
- 1º endpoint: recurrence free HCC survival at 5 yrs





Edward Geissler, unpublished data

H2304 Trial with Everolimus in LTX: Cumulative HCC Recurrence



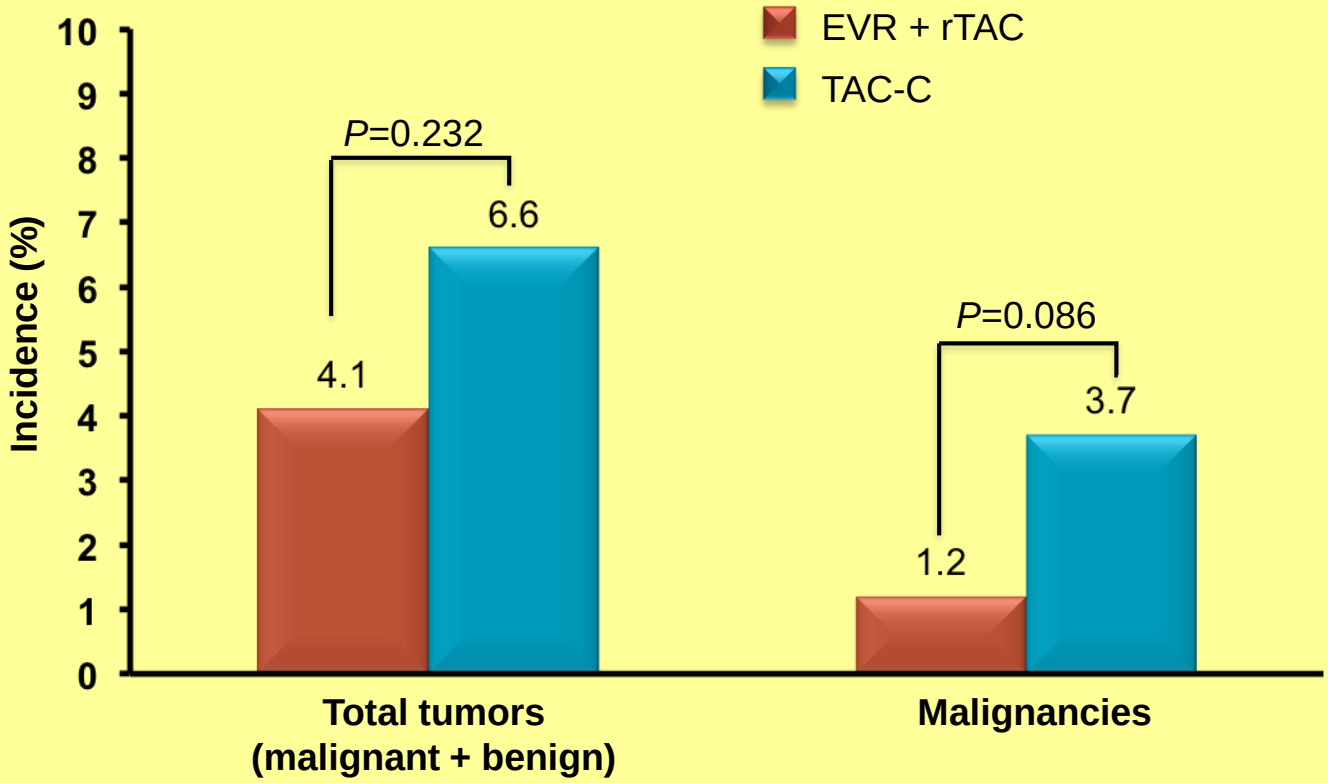
mTOR Inhibitors Lower the Risk of *de novo* Cancer

	Total IRR (95% CI)	Kaposi IRR (95% CI)	NHL IRR (95% CI)	Solid IRR (95% CI)
Gender				
Men	1	1	1	1
Women	0.7 (0.6–0.9) [a]	0.9 (0.5–1.4)	0.6 (0.3–1.2)	0.7 (0.5–0.9) [a]
Age				
<40	1	1	1	1
40–59	2.5 (1.8–3.7) [a]	3.6 (1.4–9.2) [a]	0.7 (0.3–1.5)	3.9 (2.2–6.8) [a]
60+	4.9 (3.4–7.2) [a]	5.0 (1.9–13.0) [a]	0.9 (0.4–2.2)	8.8 (5.0–15.2) [a]
Use of CNIs				
No	1	1	1	1
Yes	1.1 (0.6–2.0)	1.6 (0.4–6.4)	1.0 (0.1–7.3)	1.0 (0.5–2.0)
Use of mTORis				
No	**1**	**1**	**1**	**1**
Yes	**0.5 (0.4–0.7)** [a]	**0.5 (0.2–0.9)** [a]	**0.3 (0.1–1.1)** [b]	**0.6 (0.4–0.9)** [a]

[a] *P*<0.05; [b] *P*<0.10 CNI, calcineurin inhibitor; IRR, incidence rate ratio; mTORi, mammalian target of rapamycin inhibitor; NHL, non-Hodgkin's lymphoma.

Piselli P, et al. *Eur J Cancer* 2013;49:336–344.

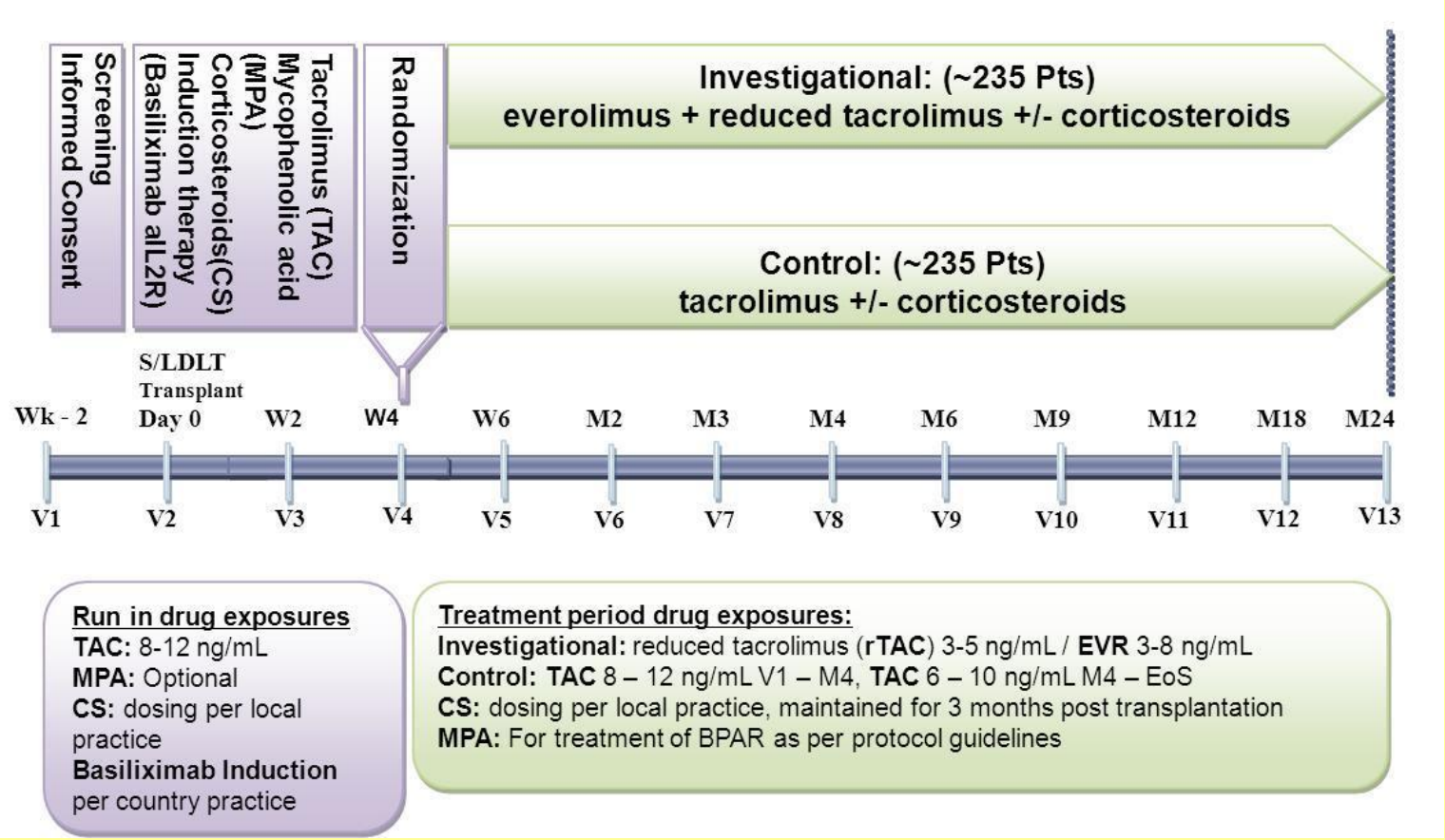
Everolimus With Early CNI Minimization Is Associated With Fewer *de novo* Cancers: H2304



C, control; CNI; calcineurin inhibitor; EVR, everolimus; rTAC, reduced tacrolimus; TAC, tacrolimus.
De Simone P, et al. *Am J Transplant*. 2012;12:3008-3020.

Current Trial with EVR in LTX

Novartis – CRAD001H2307 – Everolimus in Living Donor Liver Transplantation

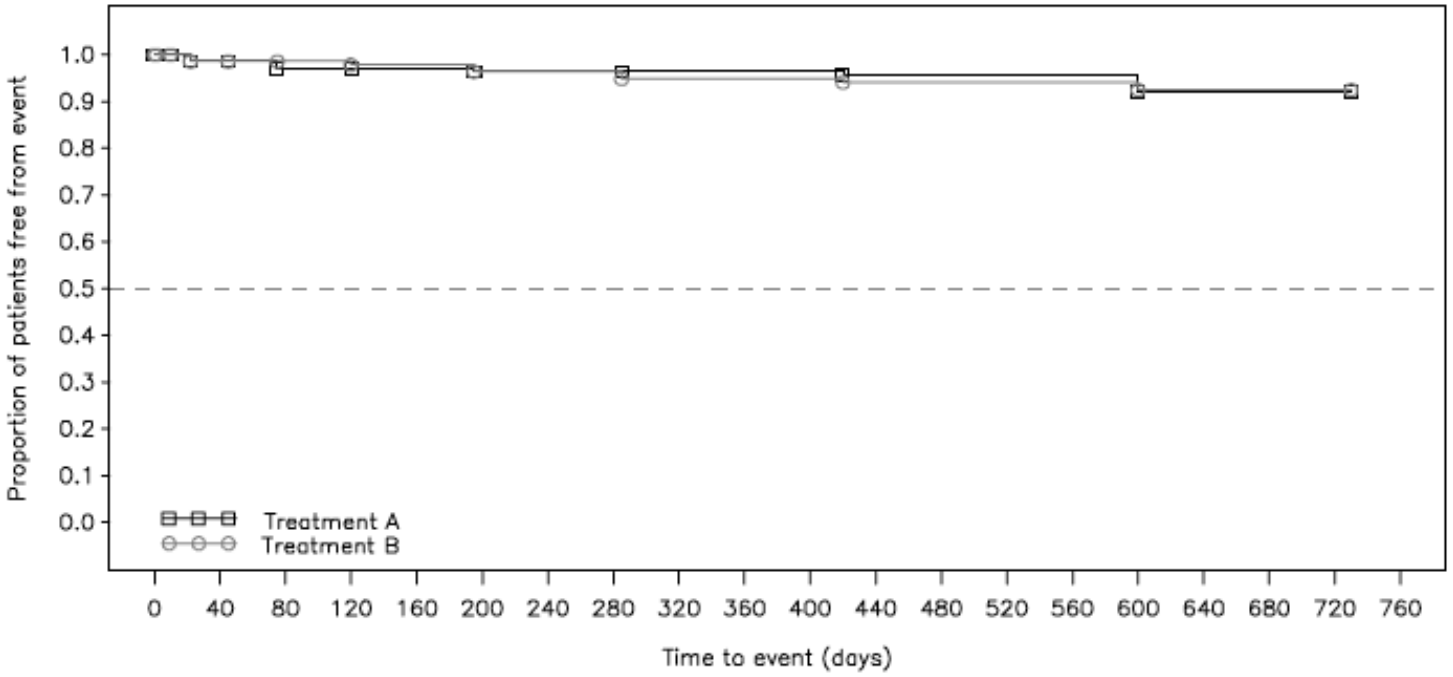


H2307 – Primary Endpoint – BPAR/Death/Graft Loss

CRAD001H2307 Data Cut-off Date: 16AUG2016

Figure 1-3 (Page 1 of 1)

Kaplan-Meier Plot of Proportion of Patients Free from Composite Efficacy Failure Event (Treated BPAR/Graft Loss/Death)
(DMC FAS Population)

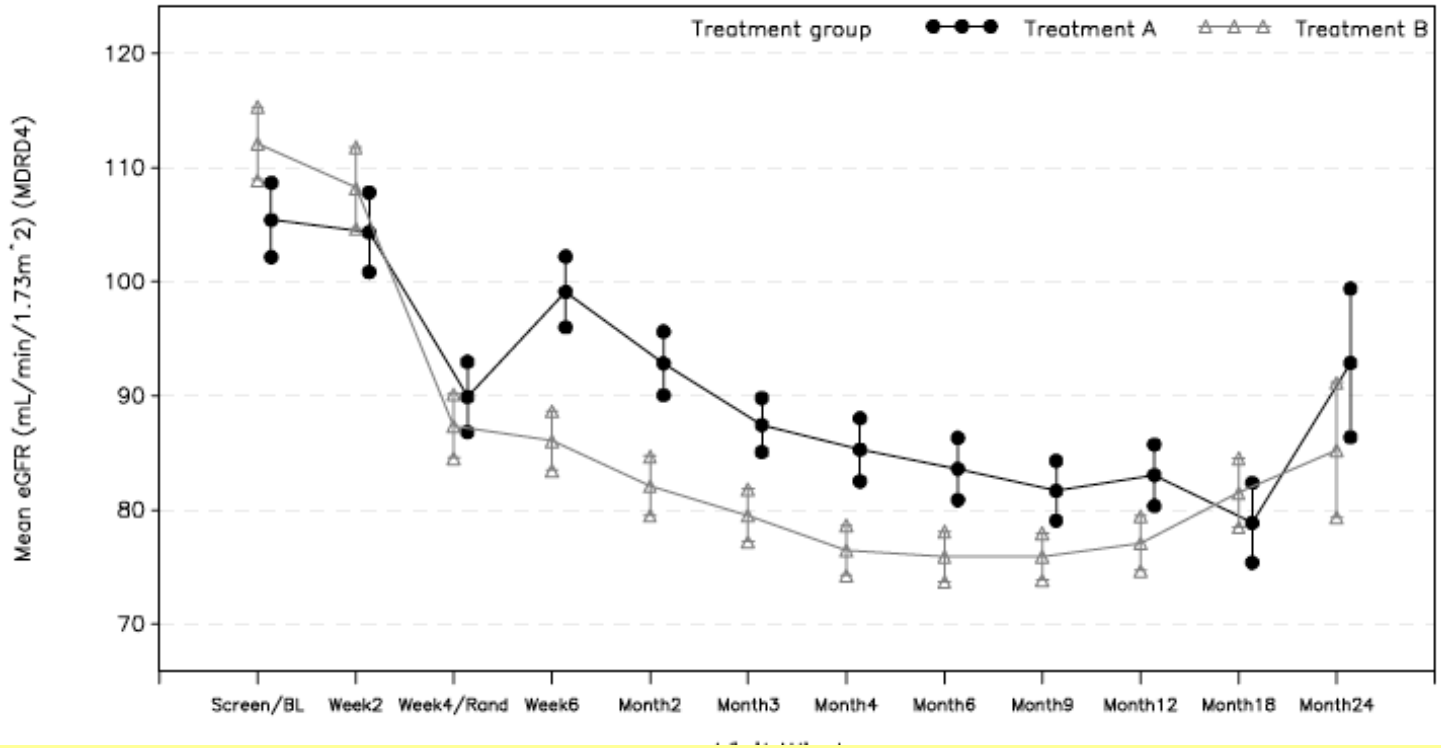


H2307 – eGFR by Treatment

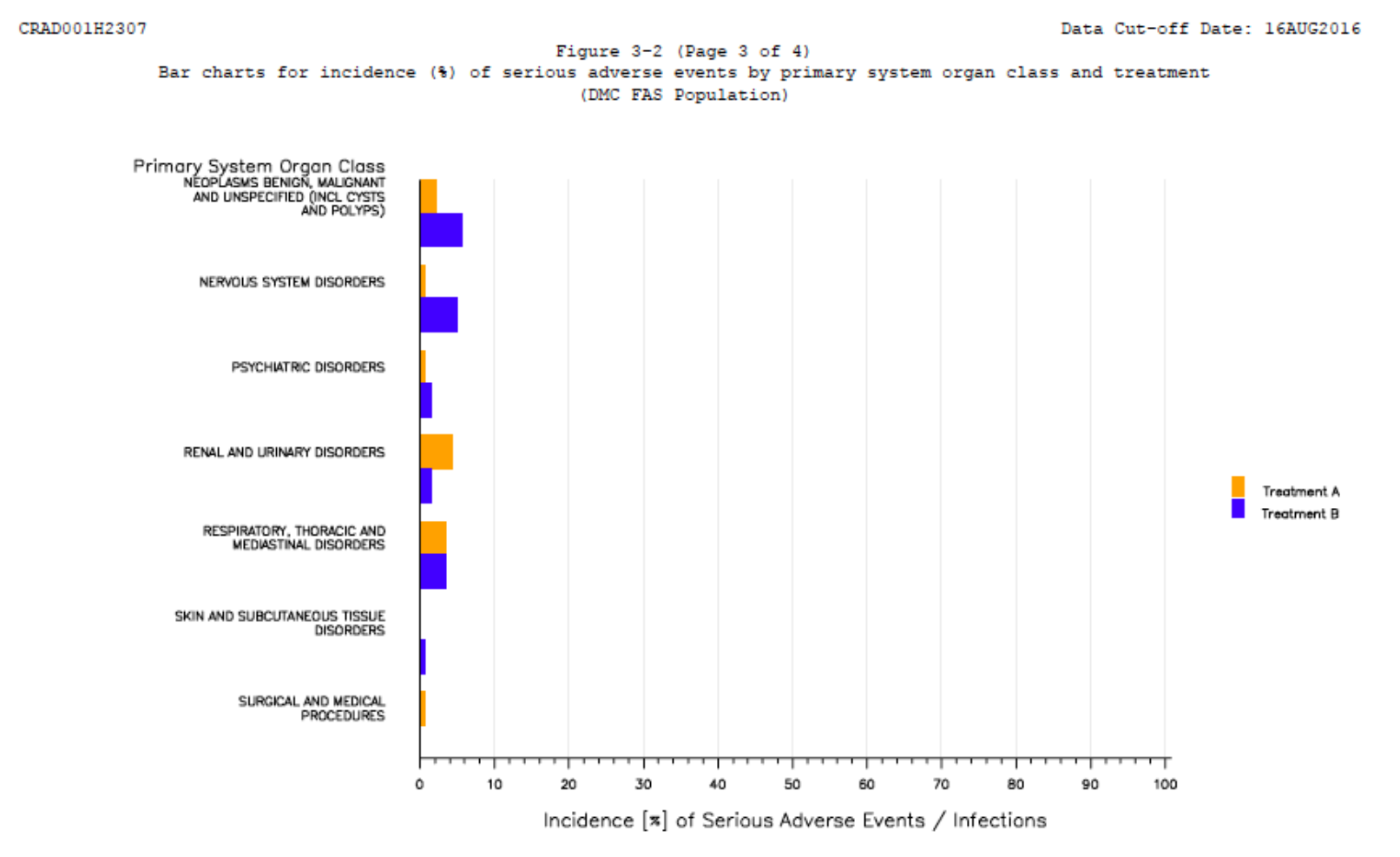
CRAD001H2307

Data Cut-off Date: 16AUG2016

Figure 2-3 (Page 1 of 1)
Estimated GFR (MDRD4 formula) [mL/min/1.73m^2]: Mean +/- standard error plots over Time
(DMC FAS Population)

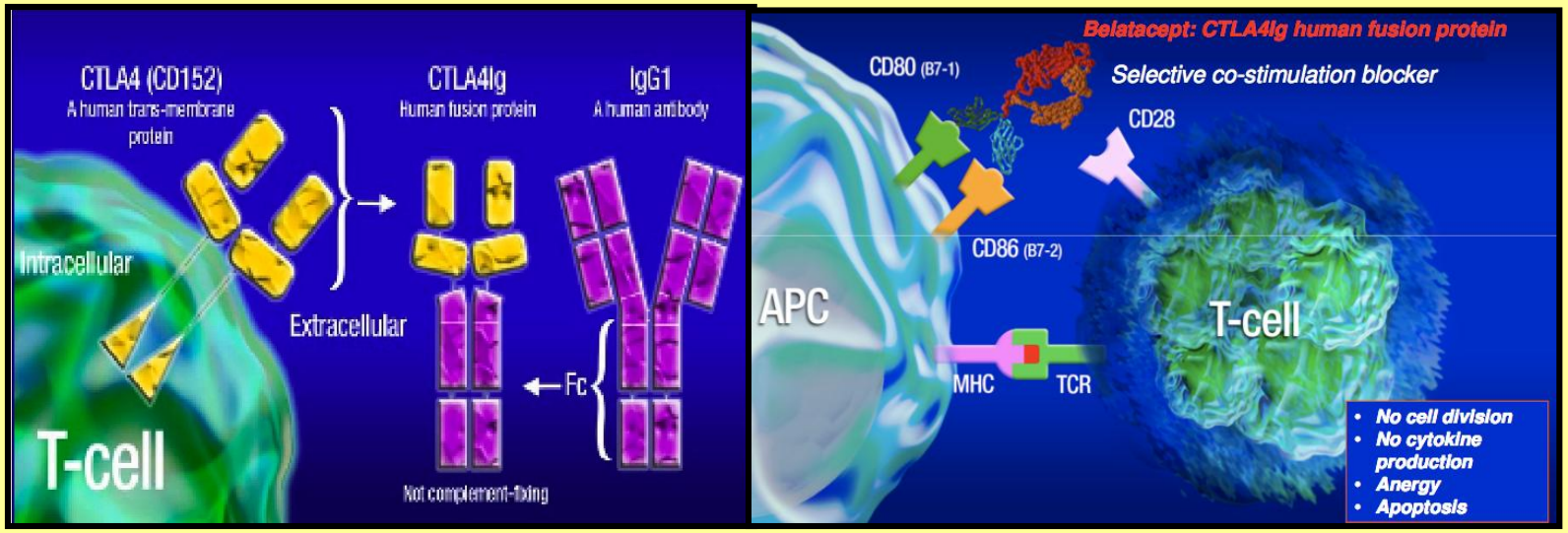


H2307 - Serious Adverse Events by Treatment



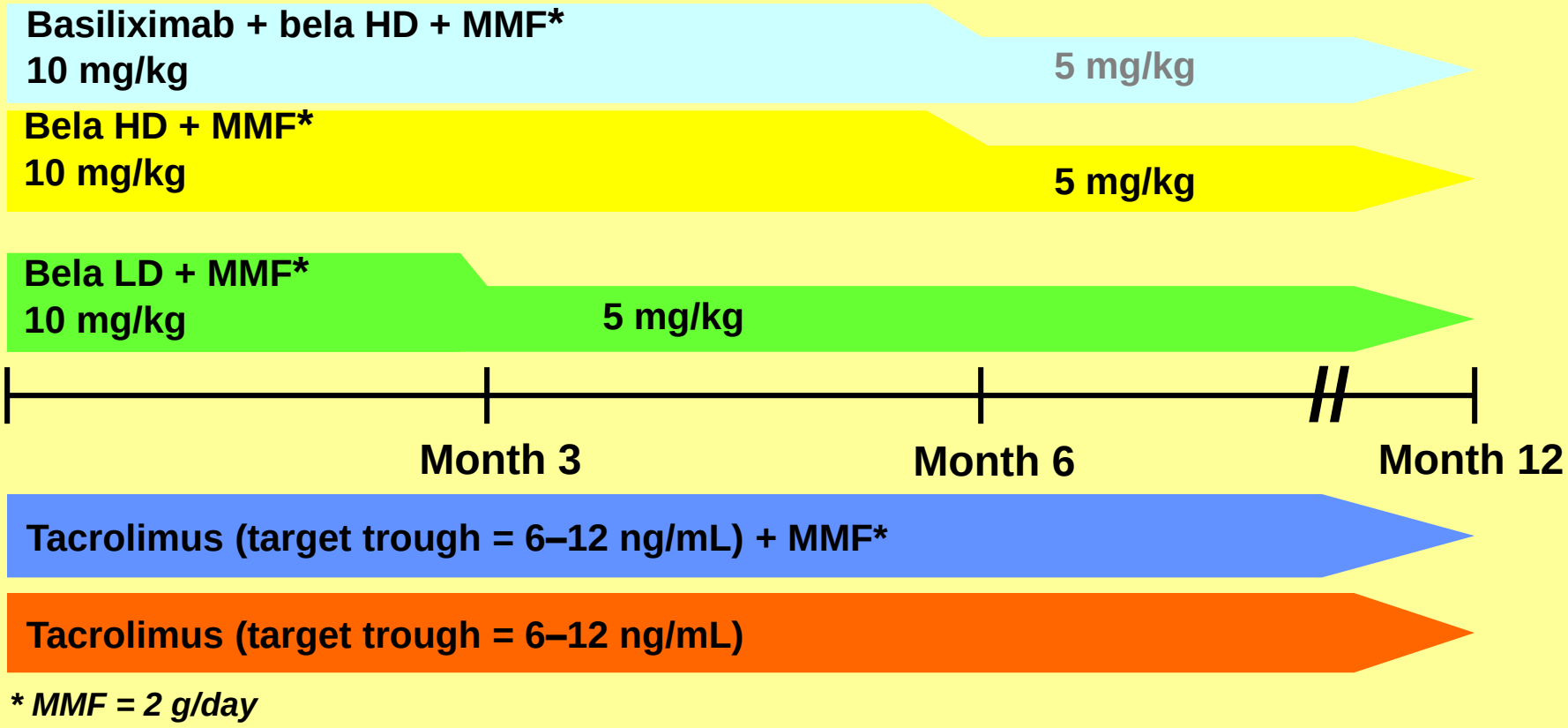
Strategies to Reduce Development of CNI Nephrotoxicity

Avoidance of CNI altogether



CTLA4Ig/LEA29Y are novel fusion proteins that interferes with T-cell co-stimulation by inhibiting the CD28-B7 interaction

Treatment Regimens

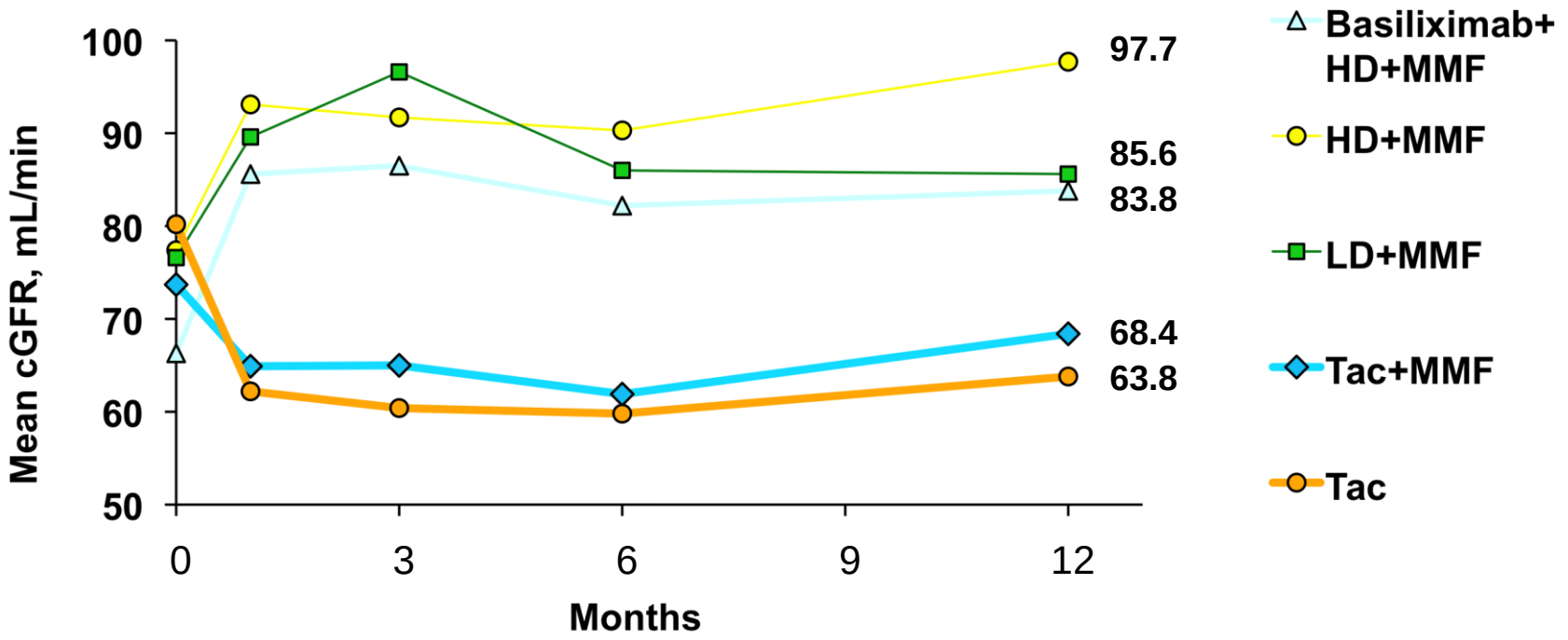


** MMF = 2 g/day*

Belatacept dosing for liver differed from dosing in renal studies:

- **1 additional dose on Day 3 in all belatacept arms**
- **1 additional dose allowed for excessive bleeding (>3L) and ascites (>4L)**

Mean Calculated GFR (MDRD)



Composite End Point at Month 12

	Number of Patients				
	Basiliximab + Bela HD + MMF (n=50)	Bela HD + MMF (n=48)	Bela LD* + MMF (n=49)	Tac + MMF (n=53)	Tac (n=50)
Composite end point, 12-mo	26	23	26	10	20
Acute rejection	22	16	16	7	15
Death	4	7	10	1	4
Graft loss	2	2	8	4	4

Conclusions

Although CNI-based IS is still considered a critical element for successful transplant outcomes, the impact on long-term outcomes drives the investigation to alternative IS strategies

The availability of novel immunosuppressive agents may facilitate the ability to reduce or eliminate CNI and reducing the long-term complications of chronic immunosuppression