Immunosuppression Strategies for HCC

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HCC Patients with Liver Transplantation

- Despite careful selection criteria, HCC recurs in ~5-20% of HCC recipients after LT
- Recurrence of HCC after LT is associated with limited curative options and high rate of mortality (mean survival ~ 1 year after diagnosis)
- The risk of recurrence is primarily related to tumour factors – size, number, differentiation, invasion, AFP, and the presence of micro-metastasis at the time of transplant

Potential Effects of Immunosuppression on HCC Liver Transplant Recipients

- Immune system has important role in modulating the development of malignancy and in disease progression, including the recurrence of HCC after LT
- Recurrence of HCC may be secondary to small populations of residual tumour cells where immunosuppression can affect its survival
- Immunosuppression may theoretically drive tumour growth, as seen with the accelerated rate of disease progression in LT recipients with HCC recurrence compared to non-transplant HCC patients

Influence of Immunosuppressive on HCC Recurrence after LT

- Steroids
  - Inhibits apoptosis via weakening of immune-inflammatory response and contributes to HCC recurrence
- CNI
  - Promotes tumour growth. Increase TGF-β
  - Dose-dependent increase in HCC recurrence
- MMF
  - Antiproliferative drug with VCAM-1 suppression and IMPDH suppression
  - Unclear risk on HCC recurrence
- mTOR-I
  - Antiproliferative effect
  - May be beneficial in reducing HCC recurrence and progression

Oncogenic Influence Amongst Different IS on (de novo) Tumour Development

Property	Anti-oncogenic	Pro-oncogenic
CNI	–	+
mTORi	+	–
MPA	+ (in vitro)	–
AZA	–	+
STER	–	±
Anti-IL-2Rα antibodies	–	–
rATG	–	+
rATLG	–	+

J Lerut et al. Transl Gastroenterol Hepatol 2017

Use of ATG/OKT3 Associated with Increase HCC Recurrence after LT

Four hundred and twelve patients transplanted for HCC between 1988 and 1998 in 14 French centers

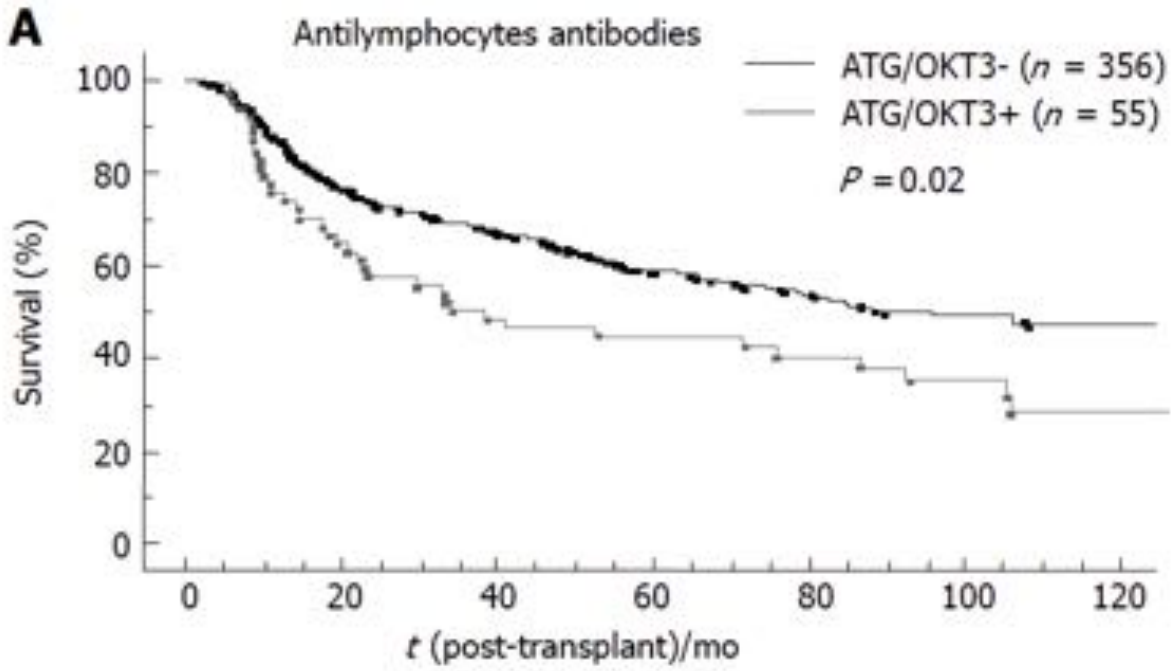


Table 3 Factors associated with recurrence-free survival (Multivariate analysis)

	Relative risk	95% CI	P
Use of anti-lymphocyte antibodies	1.8	1.2-2.6	0.005
Tumor differentiation	1.6	1.24-2.06	0.0006
Maximum diameter of the largest nodule	1.12	1.08-1.17	< 0.0001
Portal/hepatic vein obstruction	1.6	1.01-2.72	0.06
Number of nodules	1.13	1-1.28	0.06
Recent period of transplantation	0.66	0.54-0.82	0.0001

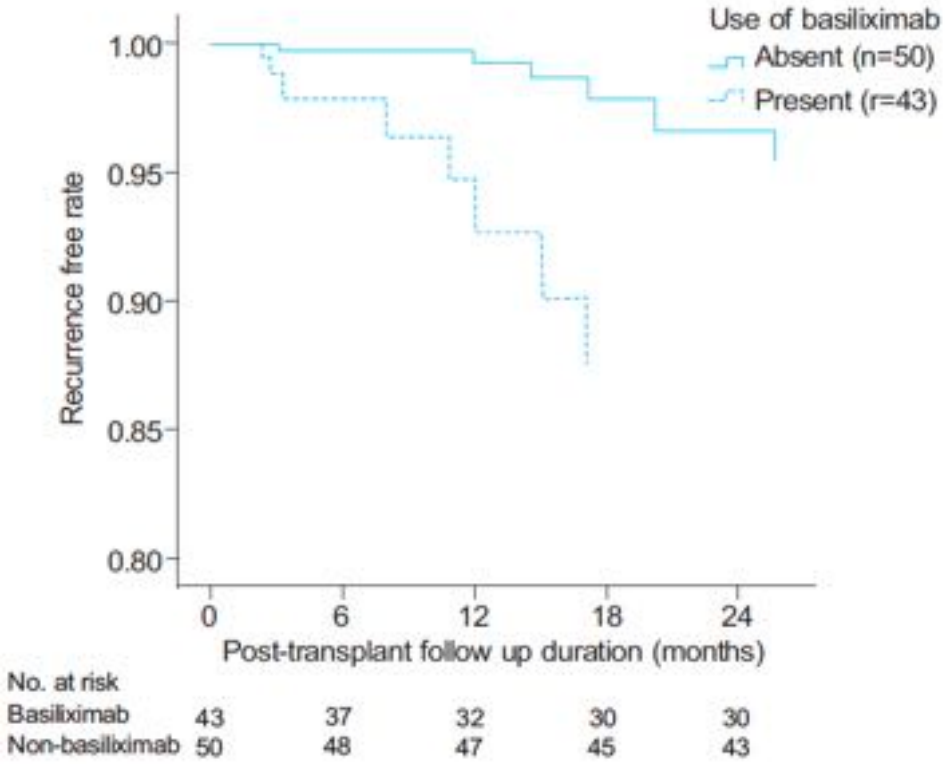
* On univariate analysis – initial type of CNI and rejection episodes were associated with HCC recurrence, but not after multivariate analysis

Use of antilymphocyte antibodies is a predictive factor of tumor recurrence after LT for HCC

T Decaens et al. World J Gastroenterol 2006

Impact of Basiliximab Induction on Early HCC Recurrence after LT

93 LT with HCC (2005-2009, SNUH)
Retrospective Study

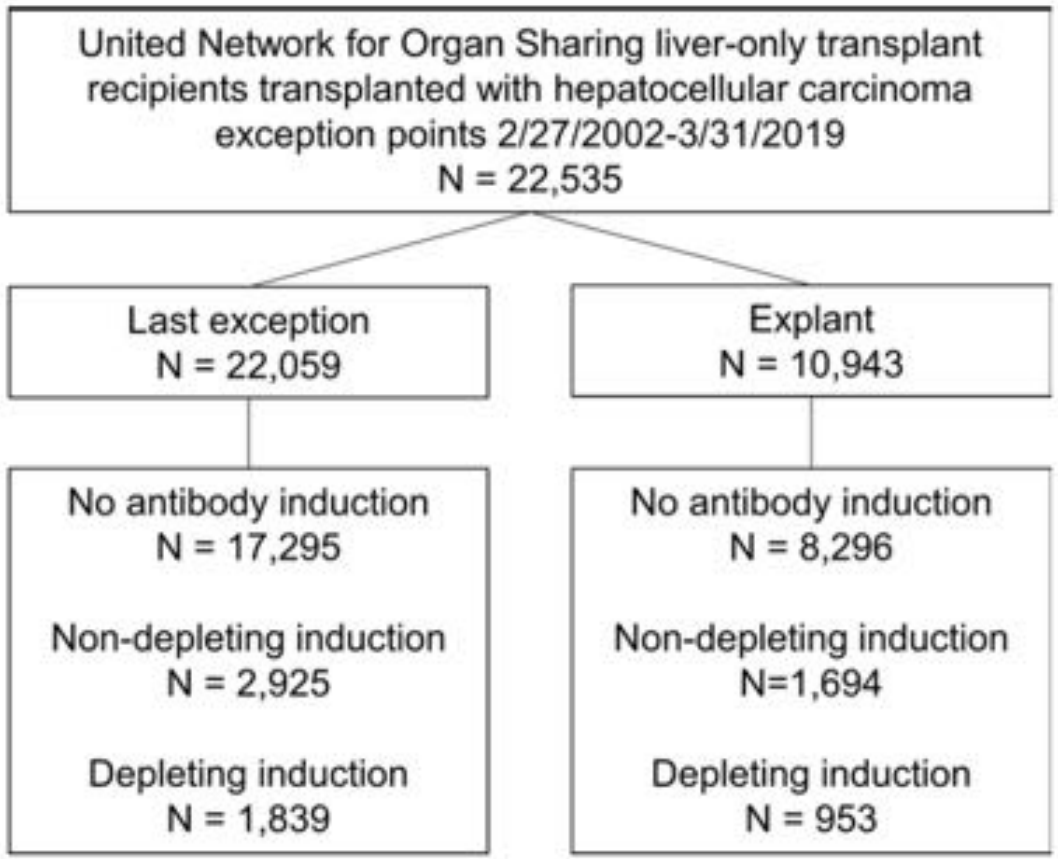


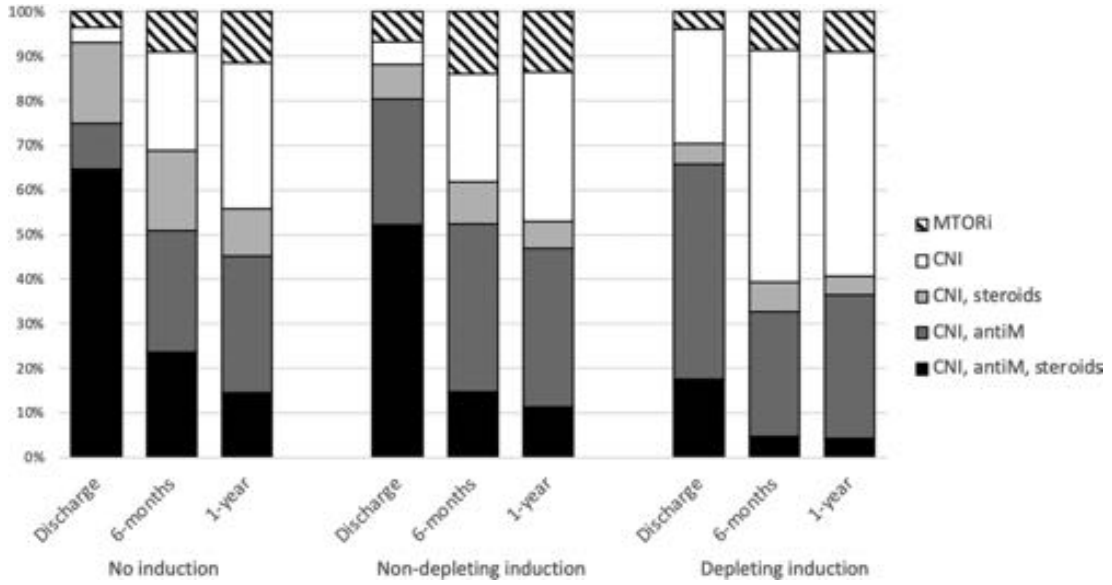
1-year recurrence

Variables (n)	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
AFP level >400 ng/mL	24.11	6.47-89.91	<0.001	87.24	9.25-822.64	<0.001
PIVKA-II level >100 mAU/mL	6.00	1.90-18.94	0.002	11.42	2.04-63.83	0.006
Presence of preoperative treatment	2.17	0.7-6.73	0.18	–	–	–
Number of tumors ≥3	2.77	0.89-8.58	0.078	–	–	–
Maximum tumor diameter > 5 cm	4.84	1.31-17.89	0.018	–	–	–
Tumor differentiation G3-G4	5.70	1.25-26.00	0.025	–	–	–
Presence of microvascular invasion	10.57	3.16-35.40	<0.001	6.06	1.23-29.91	0.027
Presence of serosal invasion	3.9	1.17-12.96	0.026	–	–	–
Presence of intrahepatic metastasis	3.06	0.79-11.83	0.106	–	–	–
Pathologic tumor stage, pT2-pT3	6.51	1.43-29.72	0.016	–	–	–
Milan criteria unfulfilled	5.12	1.62-16.13	0.005	–	–	–
Presence of rejection episode	0.89	0.20-4.08	0.884	–	–	–
Immunosuppression						
Use of MMF	2.36	0.76-7.32	0.125	–	–	–
Use of basiliximab	3.87	1.05-14.29	0.043	19.73	2.78-134.00	0.003
High tacrolimus exposure*	3.00	0.94-9.98	0.073			
1-year cumulative steroid dosage (mg)	1.00	0.10-1.00	0.351	–	–	–
1-year cumulative MMF dosage (g)	1.00	1.00-1.00	0.128	–	–	–

JY Lee et al. Clin Mol Hepatol 2014

Induction IS Does Not Worsen HCC Recurrence after Liver Transplantation





Cohort	Discharge induction regimen	HCC recurrence HR (95% CI)	HCC recurrence *P*
Last exception cohort[a,b] (N = 22 033)	None	Reference	–
	NDI	0.92 (0.76-1.12)	0.43
	DI	1.05 (0.80-1.38)	0.74
Explant cohort[a,c] (N = 10 915)	None	Reference	–
	NDI	0.80 (0.55-1.18)	0.27
	DI	0.92 (0.54-1.60)	0.78

C Durkin et al. Transplantation 2023

HCC Recurrence by Induction and Maintenance Immunosuppression Regimens at Discharge

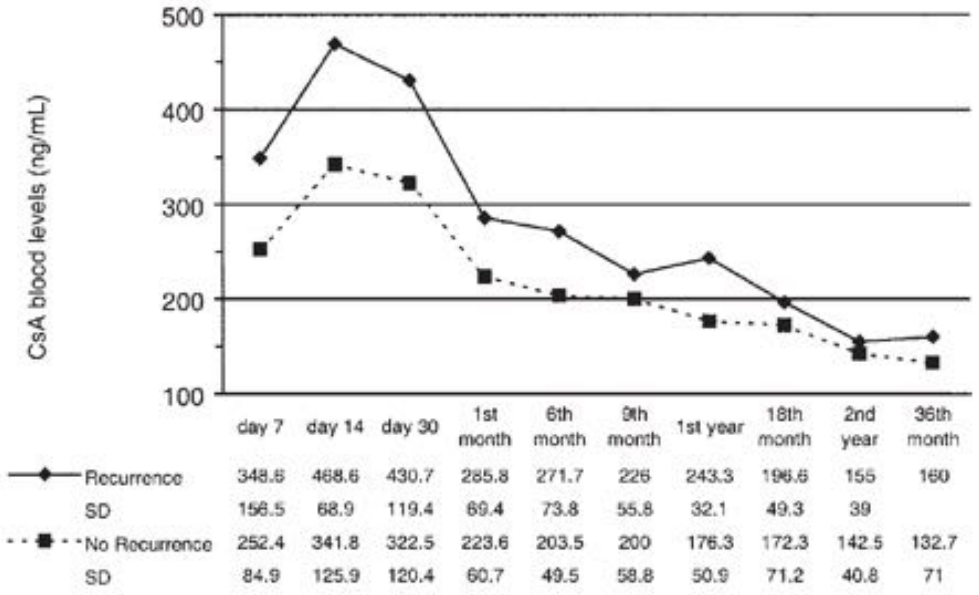
		Maintenance regimen at discharge				
		CNI + antiM + steroid	CNI + antiM	CNI + steroid	CNI alone	mTORi-based
Last exception cohort[a,b] (N = 22 033)	None	Reference	1.04 (0.82-1.31)	1.18 (0.99-1.42)	**1.47 (1.07-2.04)**	1.37 (0.96-1.95)
	NDI	0.90 (0.69-1.17)	0.89 (0.57-1.30)	1.15 (0.66-2.01)	1.54 (0.82-2.91)	1.51 (0.87-2.60)
	DI	1.05 (0.64-1.72)	1.38 (0.92-2.06)	1.58 (0.72-3.46)	1.14 (0.64-2.03)	1.04 (0.62-1.73)
Explant cohort[a,c] (N = 10 915)	None	Reference	1.26 (0.82-1.92)	1.02 (0.62-1.67)	1.32 (0.51-3.41)	0.60 (0.29-1.23)
	NDI	0.88 (0.56-1.39)	0.85 (0.47-1.54)	0.46 (0.10-2.06)	–	1.91 (0.35-10.26)
	DI	0.82 (0.33-2.04)	1.05 (0.47-2.36)	3.81 (0.73-19.95)	1.13 (0.29-4.42)	0.45 (0.06-3.56)

Combination of no antibody induction with CNI monotherapy at discharge may lead to an increased risk of HCC recurrence, which could highlight the potential benefit of CNI dose reduction

C Durkin et al. Transplantation 2023

Effects of CNI on HCC Recurrence after LT

Comparison between mean CsA levels in patients with and without HCC recurrence



M Vivarelli et al. Liver Transpl 2005

139 HCC patients with LT (60 TAC, 79 CSA) with 21 HCC recurrence

Optimal cut-off values of exposure (AUROC) for recurrence risk:
FK 10 ng/mL (AUC 0.913), CSA 220 ng/mL (AUC 0.752)

	Univariate Analysis			Multivariate Analysis		
Variable	Exp (B)	95% C.I.	*P*	Exp (B)	95% C.I.	*P*
Higher drug exposure *	6.44	2.59–15.99	<0.001	4.01	1.33–12.09	0.014
Age (yrs)	1.05	0.98–1.12	0.159	—	—	—
Female gender	1.56	0.53–4.64	0.424	—	—	—
Viral cirrhosis	1.65	0.38–7.09	0.501	—	—	—
AFP levels >50 ng/mL	4.99	2.11–11.78	<0.001	4.77	1.99–11.48	0.001
Non-incidental tumor	32.7	0.50–92.08	0.102	—	—	—
Histological Milan criteria unfulfilled	2.23	0.86–5.78	0.100	—	—	—
Diameter of largest tumor (cm)	1.31	0.93–1.85	0.121	—	—	—
Tumor grading G3–G4	4.08	1.49–11.19	0.006	4.05	1.41–11.61	0.009
Presence of MVI	4.80	1.76–13.12	0.002	2.96	1.05–8.32	0.040
pT Stage 2–3	1.12	1.04–1.23	0.013	1.10	0.98–1.20	0.118

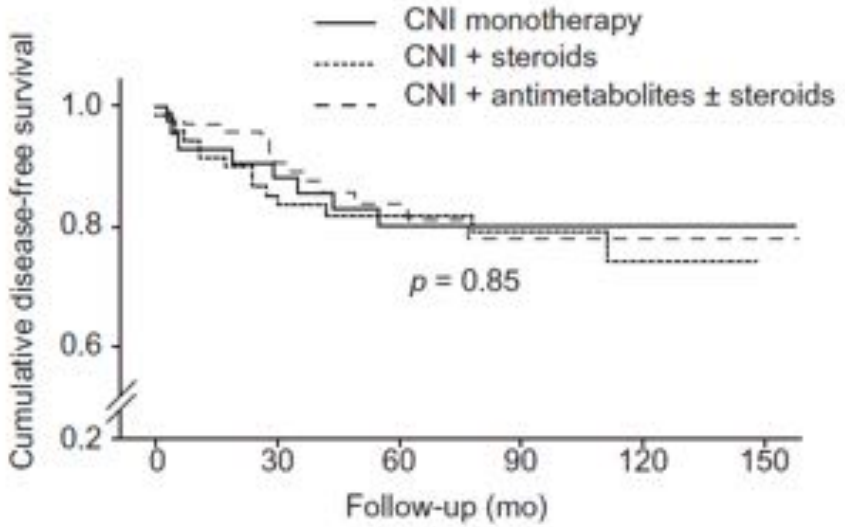
AFP indicates alpha-fetoprotein; MVI, microvascular invasion.
*Tacrolimus exposure equal to or above 10 ng/mL or cyclosporine exposure equal to or above 220 ng/mL.

M Vivarelli et al. Ann Surg 2008

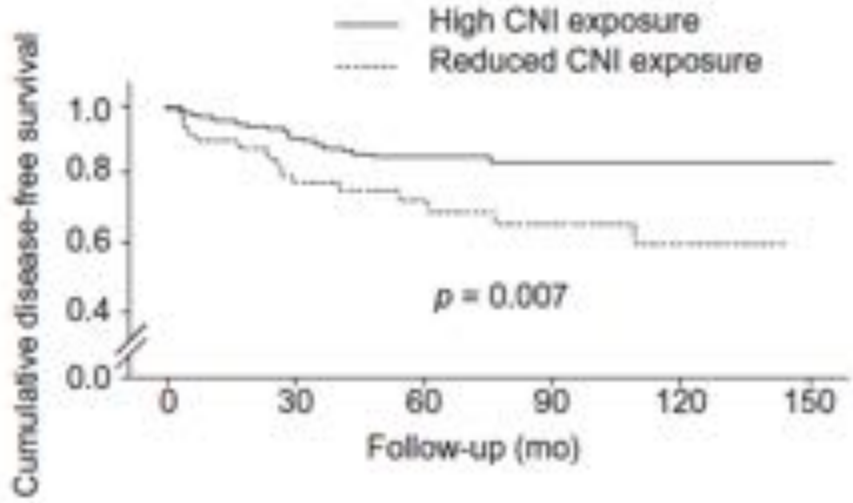
Early Exposure to CNI and HCC Recurrence after Liver Transplantation

219 HCC consecutive patients with LT at 2 European Centers 2000-2010. Median FU 51 months

RFS and HCC risk According to Immunosuppression Protocol within the first month after LT



HCC recurrence % (No. at risk)	1 year	3 years	5 years
CNI monotherapy	6.9 (39)	14.3 (33)	19.9 (26)
CNI + steroids	8.5 (61)	16.3 (48)	19.2 (37)
CNI + antimetabolites ± steroids	3 (92)	10.8 (58)	16.2 (32)



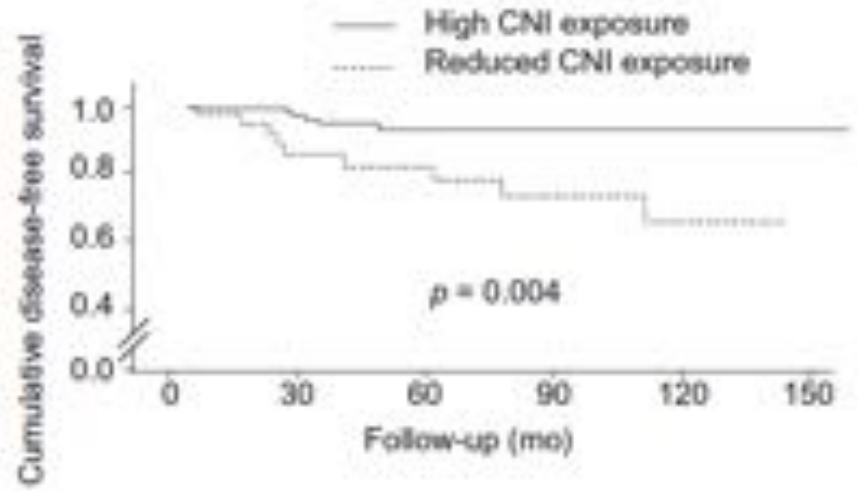
HCC recurrence % (No. at risk)	1 year	3 years	5 years
High CNI exposure (n = 48)	9.4 (40)	22.1 (30)	27.7 (24)
Reduced CNI exposure (n = 171)	4.3 (150)	10.9 (108)	14.7 (69)

*Mean TAC >10ng/ml or CSA >300 ng/ml within the first month

M Ropdriguez-Peralvarez. J Hepatol 2013

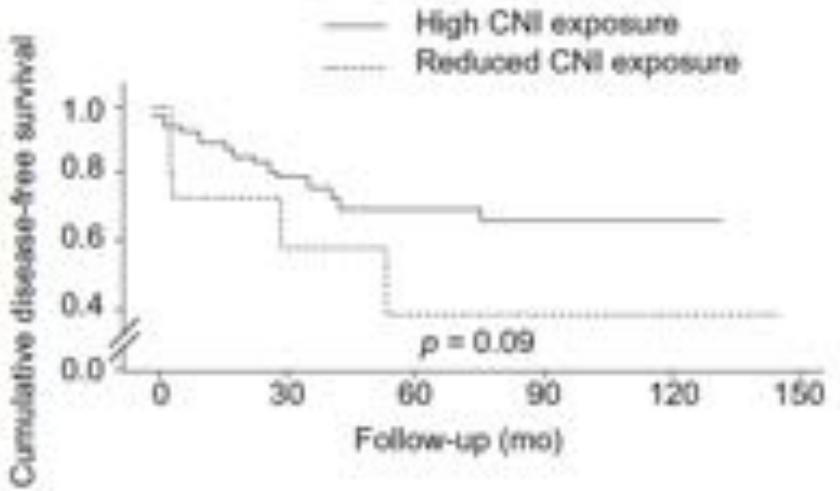
Early CNI Exposure and Disease-free Survival & HCC Recurrence according to Milan Criteria

Within MILAN criteria



HCC recurrence % (No. at risk)	1 year	3 years	5 years
High CNI exposure (n = 36)	5.7 (32)	14.7 (27)	22 (21)
Reduced CNI exposure (n = 106)	1 (99)	5.5 (79)	7 (48)

Outside MILAN criteria



HCC recurrence % (No. at risk)	1 year	3 years	5 years
High CNI exposure (n = 11)	28 (8)	42 (4)	61 (2)
Reduced CNI exposure (n = 61)	10.1 (51)	21 (28)	29.9 (21)

M Ropdriguez-Peralvarez. J Hepatol 2013

Multivariate Analysis for Independent Associations with Recurrent HCC after LT

Variables	RR	95% CI	*p* value
High exposure to calcineurin inhibitors*	2.82	1.4-5.8	0.005
Diameter of the main nodule	1.31	1.2-1.4	<0.001
Microvascular invasion	2.98	1.4-6.1	0.003
Incidental macrovascular invasion	4.57	1.7-12.3	0.003

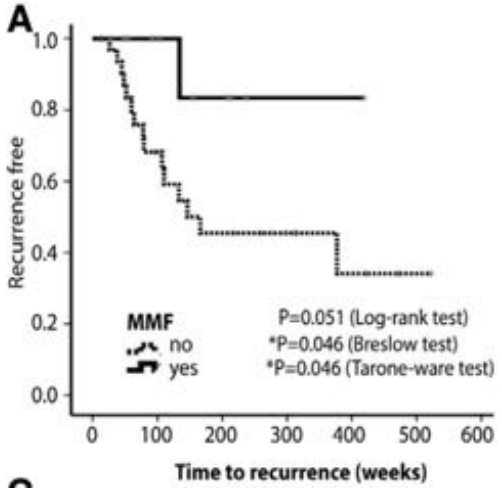
Variables controlled as possible confounding factors: centre of transplantation ($p = 0.61$), number of nodules ($p = 0.16$) and mTOR inhibitors ($p = 0.87$).
Variables eliminated from the model: viral cirrhosis ($p = 0.96$), pre-transplant α-fetoprotein ($p = 0.85$), pre-transplant local treatment of hepatocellular carcinoma ($p = 0.76$), capsular invasion ($p = 0.75$), lymphatic permeation ($p = 0.33$), and concomitant immunosuppressants: boluses of steroids to treat rejection ($p = 0.64$), antimetabolites ($p = 0.39$), dose of mycophenolate ($p = 0.87$), maintenance steroids ($p = 0.37$).
*Defined as mean trough concentrations of tacrolimus >10 ng/ml or cyclosporine >300 ng/ml within the first month after liver transplantation.

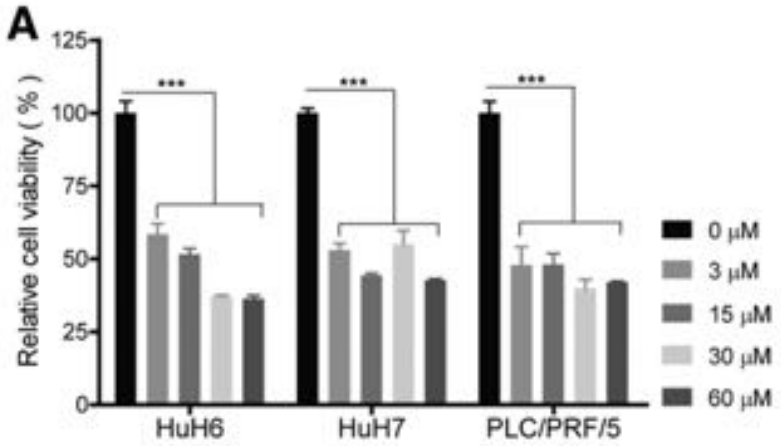
An increased risk of HCC recurrence occurs with a higher early exposure to CNI. The first month after LT is particularly relevant as higher levels (tacrolimus TC >10 ng/ml or cyclosporine TC >300 ng/ml) often occur and are associated with a tripled risk of HCC recurrence when taking into account other known factors able to increase tumour recurrence.

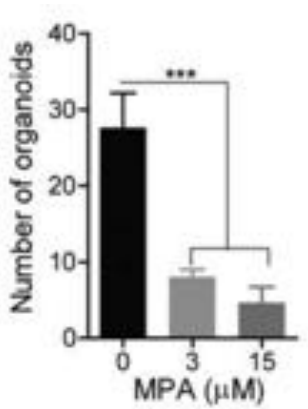
M Ropdriguez-Peralvarez. J Hepatol 2013

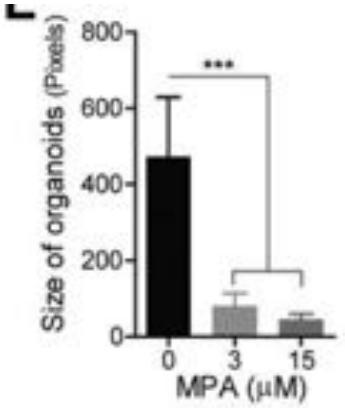
Effects of Mycophenolic Acid on HCC in Patients & Experimental Models

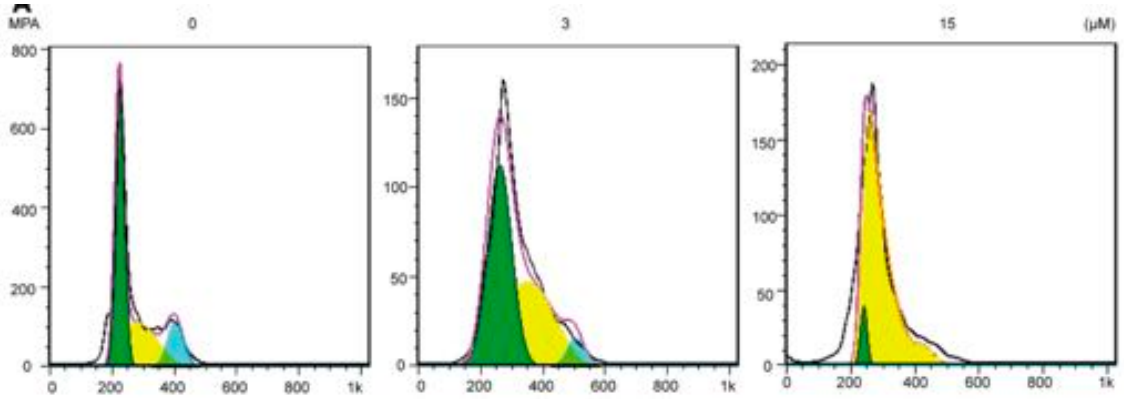
Three human HCC cell lines and organoids from mouse primary liver tumor

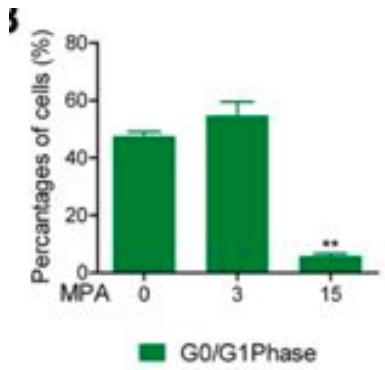


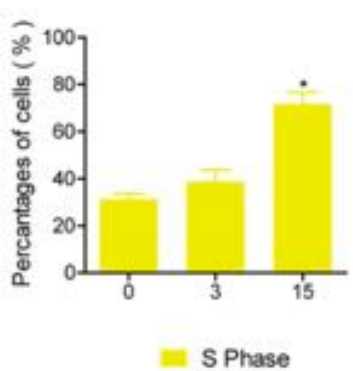


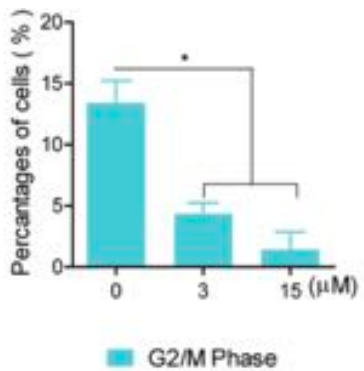












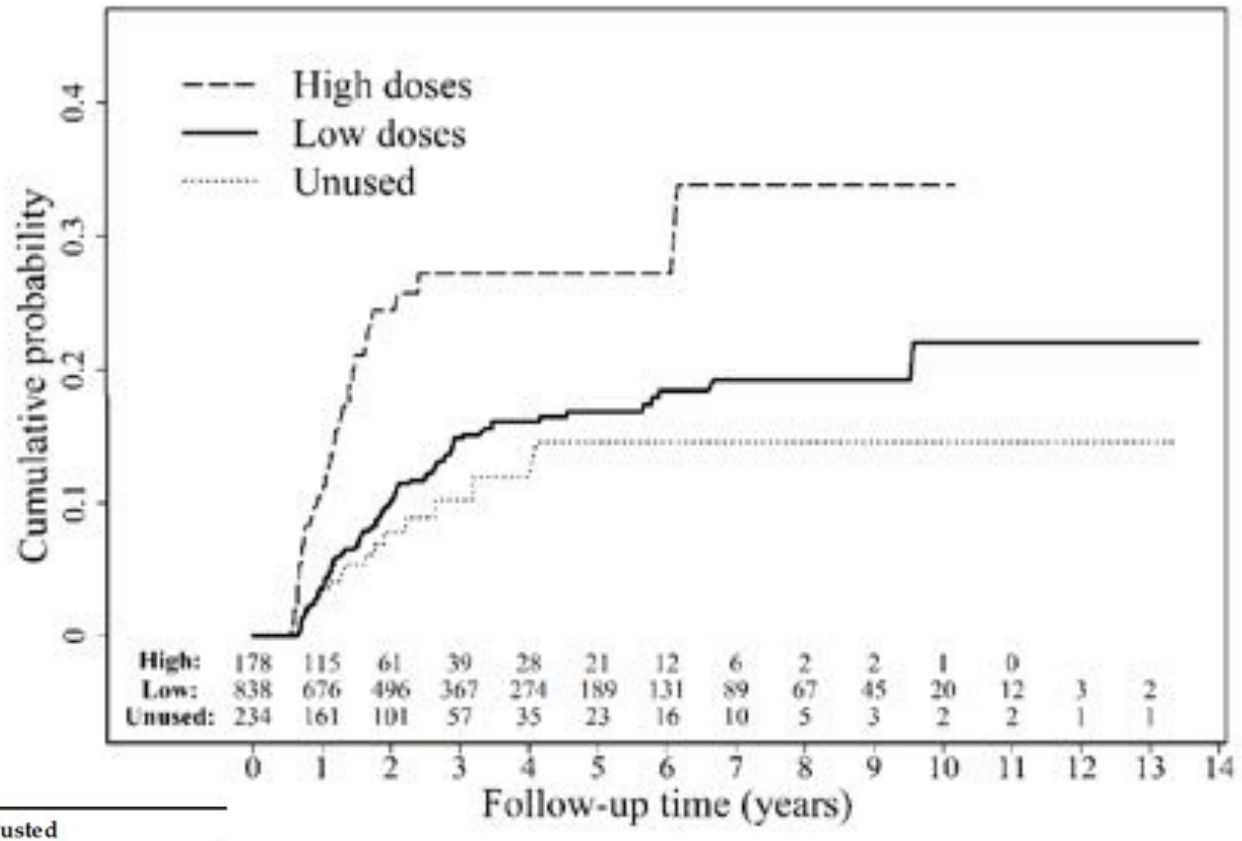
K Chen et al. Transplantation 2019

Effects of MMF on HCC Recurrence after LT

National Health Insurance Research Database of Taiwan

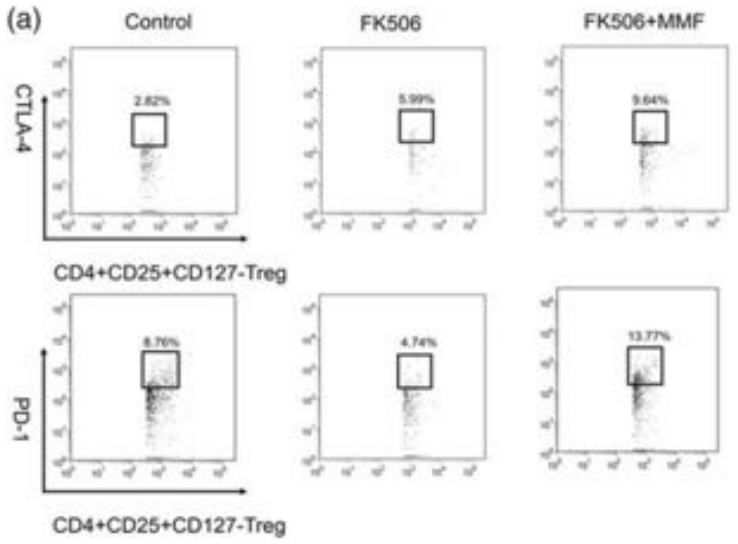
- N=1250 LT recipients with HCC
  - 96% tacrolimus
  - 81% MMF
  - 26% sirolimus
  - 12% cyclosporine
- 151 with HCC recurrence

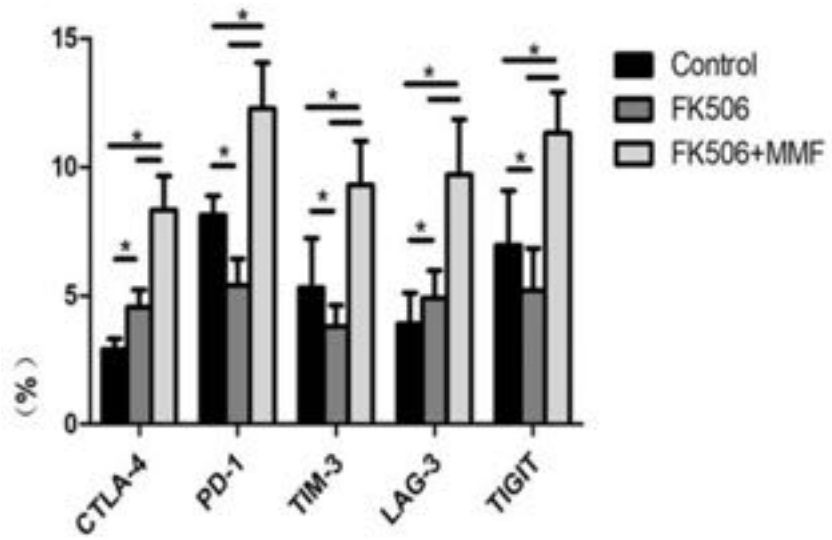
	Recurrence (n = 151)		Non-Recurrence (n = 1099)		p
	N or Mean	% or SD	N or Mean	% or SD	
Cyclosporine	14	9.27	139	12.65	0.0936
Tacrolimus	147	97.35	1054	95.91	0.2458
MMF	135	89.40	881	80.16	0.0316 *
Sirolimus	33	21.85	301	27.39	0.1218



	Non-Recurrence (n = 1099)	Recurrence (n = 151)	Unadjusted			Adjusted		
			Crud HR	95% CI	p	Crude HR	95% CI	p
High doses	145 (13.19%)	33 (21.85%)	2.265	(1.527, 3.360)	<0.0001	2.234	(1.503, 3.319)	<0.0001
Low doses	736 (66.97%)	102 (67.55%)	-	-	-	-	-	-
Unused	218 (19.84%)	16 (10.60%)	0.742	(0.438, 1.259)	0.2690	0.717	(0.420, 1.226)	0.2240

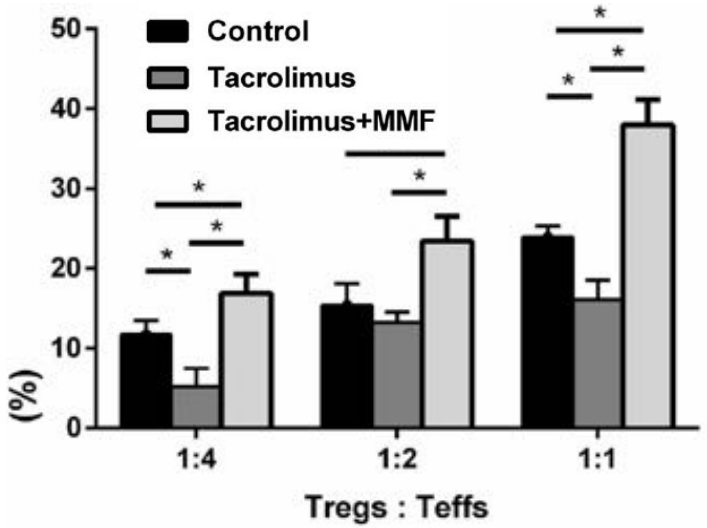
Synergistic Effect of TAC+MMF on Inhibitory Function of Tregs after LT





Expressions of co-inhibitory receptors (CTLA-4, PD-1, Tim-3, LAG-3 and TIGIT) on Tregs in FK506+MMF group were significant higher than those in the FK506 group and control group

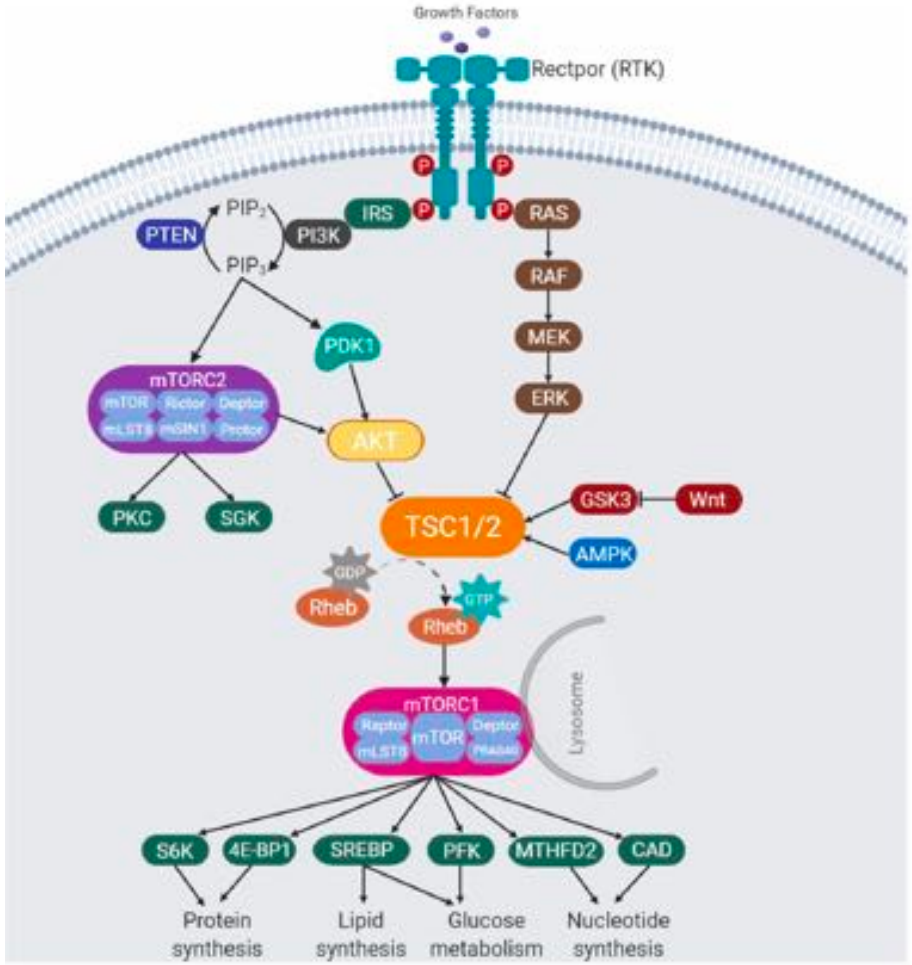
Q Zeng et al. Immunopharmacol Immunotoxicol 2019

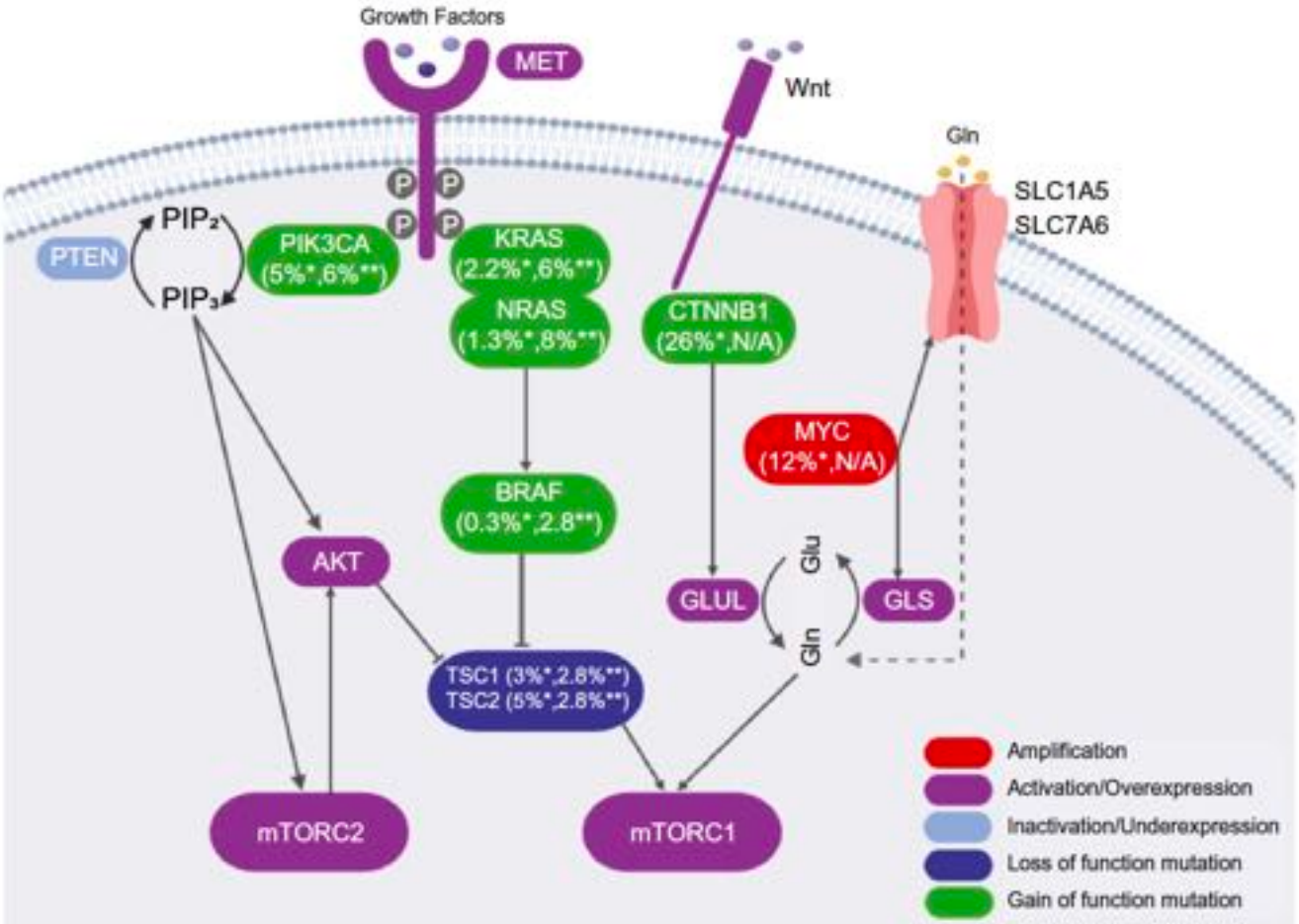


At each mixture ratio, Tac+MMF had the highest Tregs inhibition rate compared to Tac and control

Q Zeng et al. Immunopharmacol Immunotoxicol 2021

mTOR Signaling Pathway & Common Gene Mutations in Liver Cancer





mTOR 1-2 pathways upregulated in ~50% of HCC → associated with less differentiated tumours/poorer biology

Lu XJ et al. Hepatology 2021

Randomized Trials of Everolimus in HCC Patients after Liver Transplantation

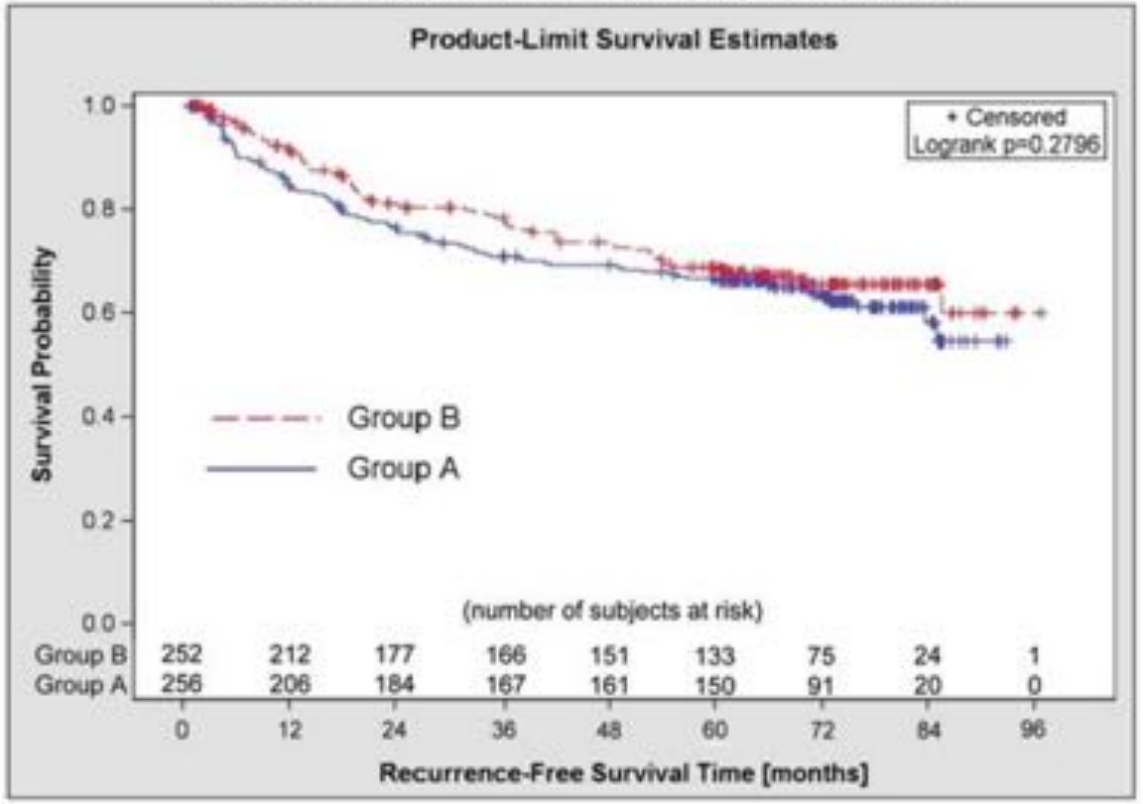
- 3 randomized trials with mTORi from first month after LT vs standard CNI therapy reported on HCC outcomes, although the primary endpoint was to look at renal function

Reference	Design	n	Within Milan criteria at time of tx	mTORi/CNI	Follow-up	HCC recurrence	P value
Masetti et al 2010 [76]	Randomized	44	Not stated	EVR/CNI-free from day 30	1 year	7.1% (2/28)	0.37
	Open-label Single center			Standard CsA		28.8% (3/16)	
De Simone et al 2013 [77]	Randomized Open-label	203	89.2%	EVR + reduced TAC (from day 30) (n = 67) or EVR + TAC withdrawal (n = 69)	3 years	3.7% (5/136)	-
Fischer 2014 [78]	Multicenter			Standard TAC		11.9% (8/67)	-
Fischer et al 2012 [79]	Randomized	37	Not stated	EVR/CNI-free from week 4	1 year	0% (0/14)	-
	Open-label Multicenter			Standard CsA		4.3% (1/23)	-

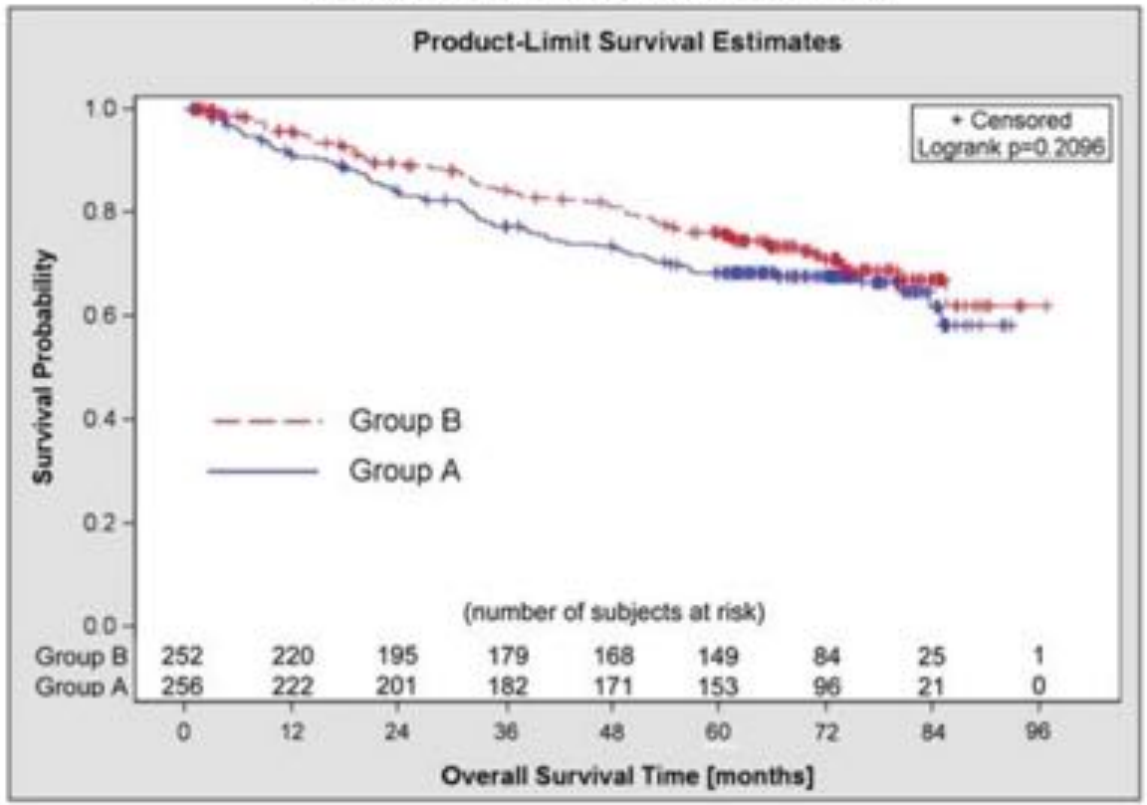
mTOR-Inhibitors and Recurrence of Hepatocellular Carcinoma (SiLVER study)

Prospective randomized open label international trial. 525 LT patients with HCC
Grp A: mTORi-free regimen vs Grp B: sirolimus-containing regimen

HCC recurrence-free survival (primary endpoint)

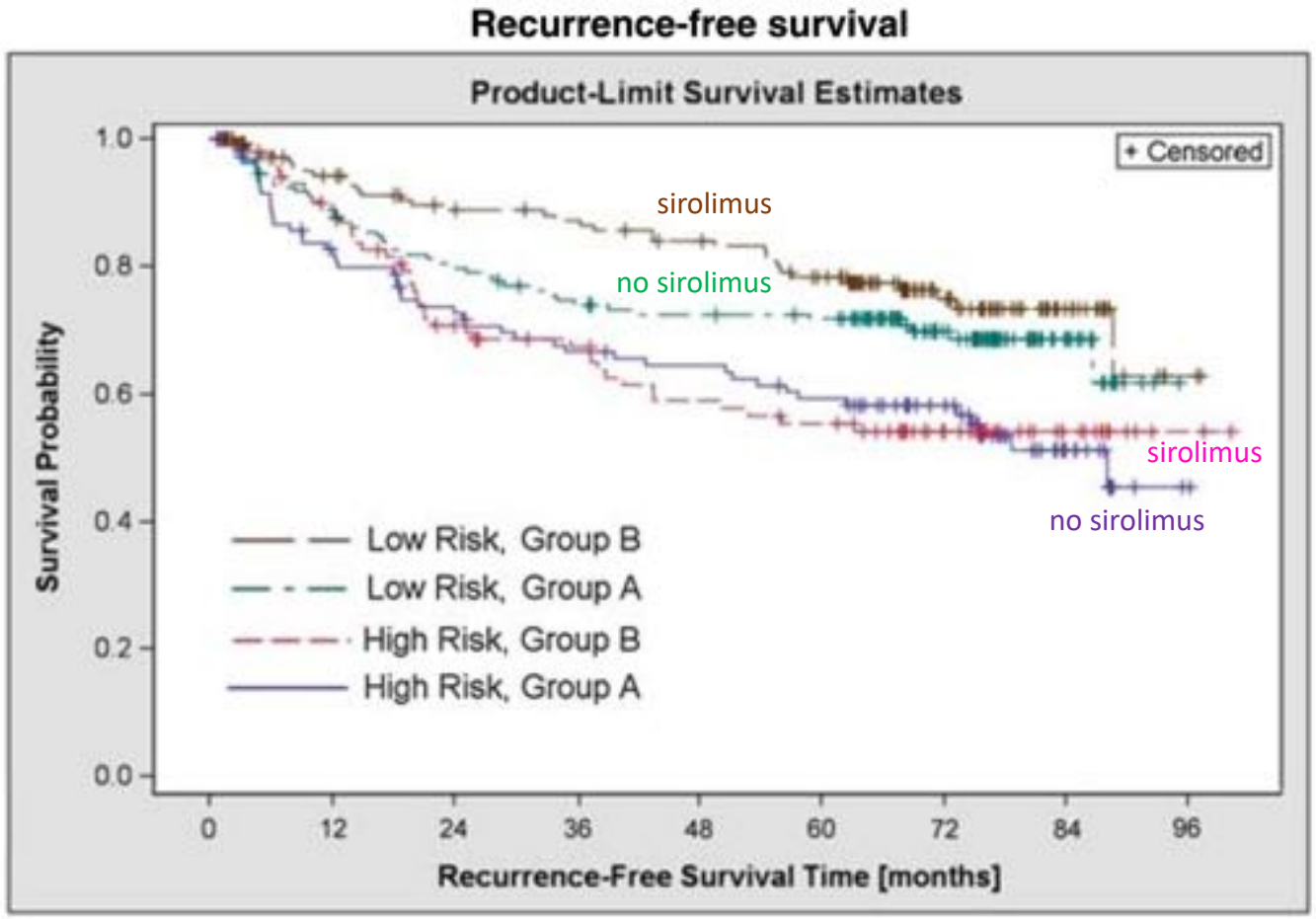


Overall survival (secondary endpoint)



Geissler EK et al. Transplantation 2016

mTOR-Inhibitors and Recurrence of Hepatocellular Carcinoma (SiLVER study)



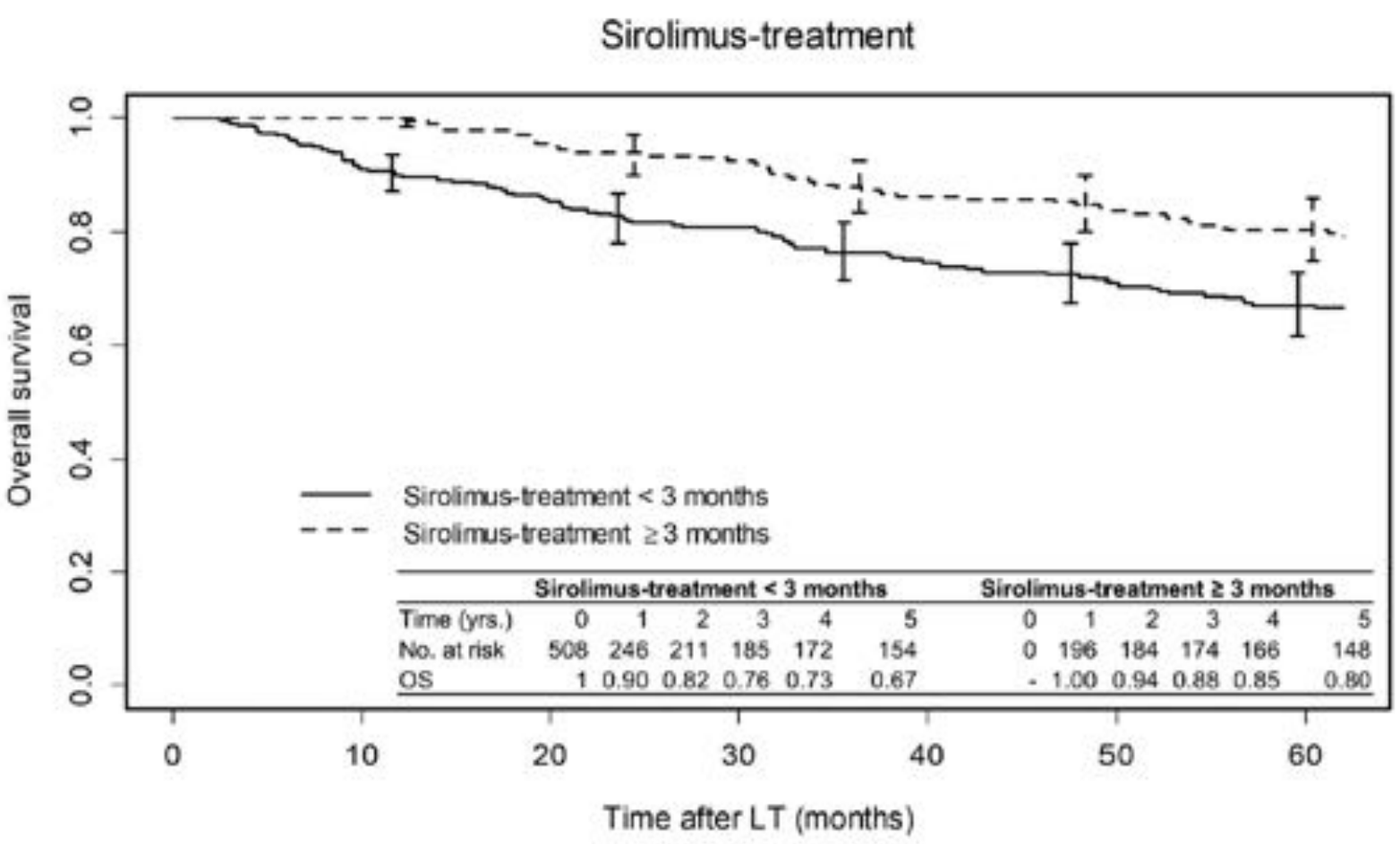
Recurrence-free survival over years (ITT population) - low risk

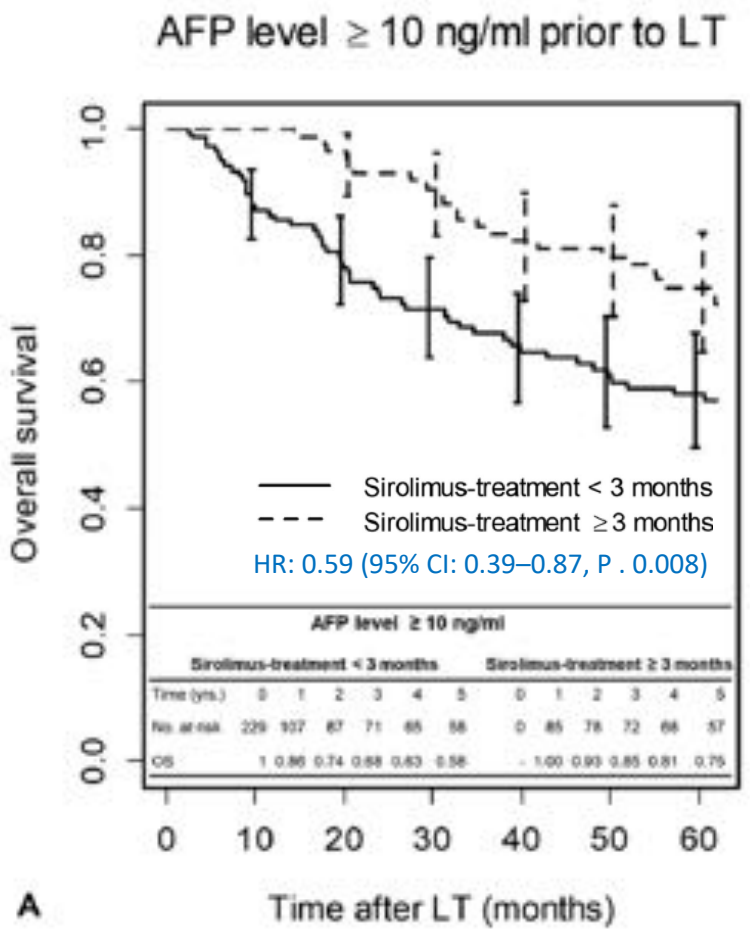
Time point after LTx	Group A (N=146)	Group B (N=146)	P-value (log-rank test)
1 year	128 (87.7%)	138 (94.5%)	0.0566
2 years	117 (80.1%)	131 (89.7%)	0.0383
3 years	109 (74.7%)	128 (87.7%)	0.0106
4 years	107 (73.3%)	124 (84.9%)	0.0280
5 years	106 (72.6%)	118 (80.8%)	0.1393
6 years	103 (70.5%)	114 (78.1%)	0.2103
7 years	102 (69.9%)	114 (78.1%)	0.1668
8 years	102 (69.9%)	113 (77.4%)	0.2047

Recurrence-free survival over years (ITT population) - high risk

Time point after LTx	Group A (N=110)	Group B (N=106)	P-value (log-rank test)
1 year	90 (81.8%)	95 (89.6%)	0.0970
2 years	81 (73.6%)	78 (73.6%)	0.9017
3 years	76 (69.1%)	75 (70.8%)	0.7606
4 years	74 (67.3%)	68 (64.2%)	0.6918
5 years	69 (62.7%)	65 (61.3%)	0.7939
6 years	67 (60.9%)	64 (60.4%)	0.8495
7 years	64 (58.2%)	64 (60.4%)	0.9257
8 years	63 (57.3%)	64 (60.4%)	0.8527

Survival Benefit of Sirolimus Use ≥3 Months from the SiLVER Study



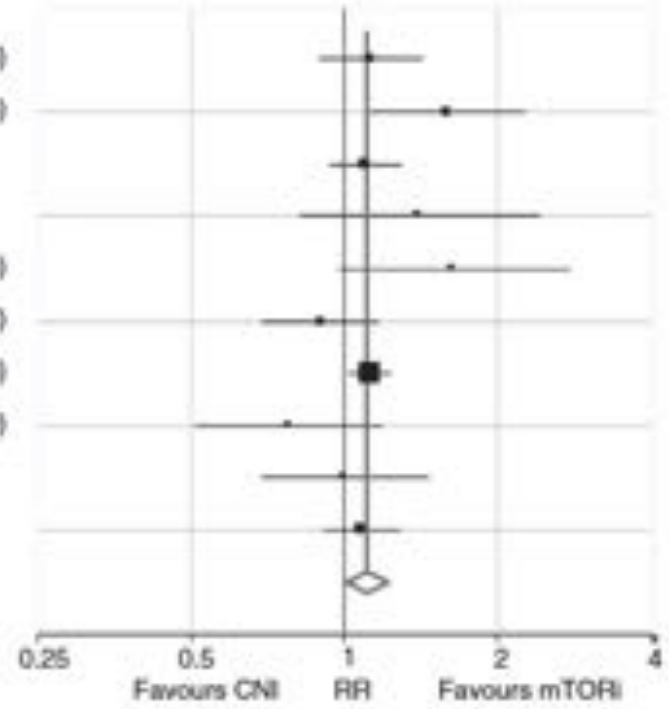


Systemic Review/Meta-analysis of mTORi in LT for HCC

3-year recurrence free survival

Author (year)	mTORi	mTORi based: events (total)	CNI based: events (total)	Weight%	RR (95% CI)
Zimmerman (2008)	SRL	35 (45)	36 (52)	10.53%	1.12 (0.88; 1.43)
Vivarelli (2010)	SRL	27 (31)	17 (31)	5.83%	1.59 (1.12; 2.25)
Zhao (2014)	SRL	77 (94)	53 (71)	17.03%	1.1 (0.93; 1.29)
Bhangui (2016)	SRL	14 (21)	10 (21)	2.63%	1.4 (0.82; 2.4)
Shen (2016)	SRL	17 (26)	12 (30)	2.83%	1.63 (0.97; 2.75)
Xu (2016)	SRL	36 (62)	52 (80)	8.99%	0.89 (0.68; 1.17)
Geissler (2016)	SRL	203 (252)	185 (256)	27.09%	1.11 (1.01; 1.23)
Lee (2017)	SRL	12 (20)	17 (22)	4.11%	0.78 (0.51; 1.19)
Houssel (2013)	EVR	12 (16)	15 (20)	4.99%	1 (0.68; 1.46)
Rodriguez-Peralvarez (2018)	EVR	49 (64)	91 (128)	15.98%	1.08 (0.9; 1.28)
Synthesis		482 (631)	488 (711)	100%	1.1 (1.01; 1.21)

Heterogeneity: Q = 12.64 (Q-df = 1.64, P = 0.18), I^2 = 29% (95% CI 0 - 66), T^2 = 0.01 (95% CI = 0 - 0.03)



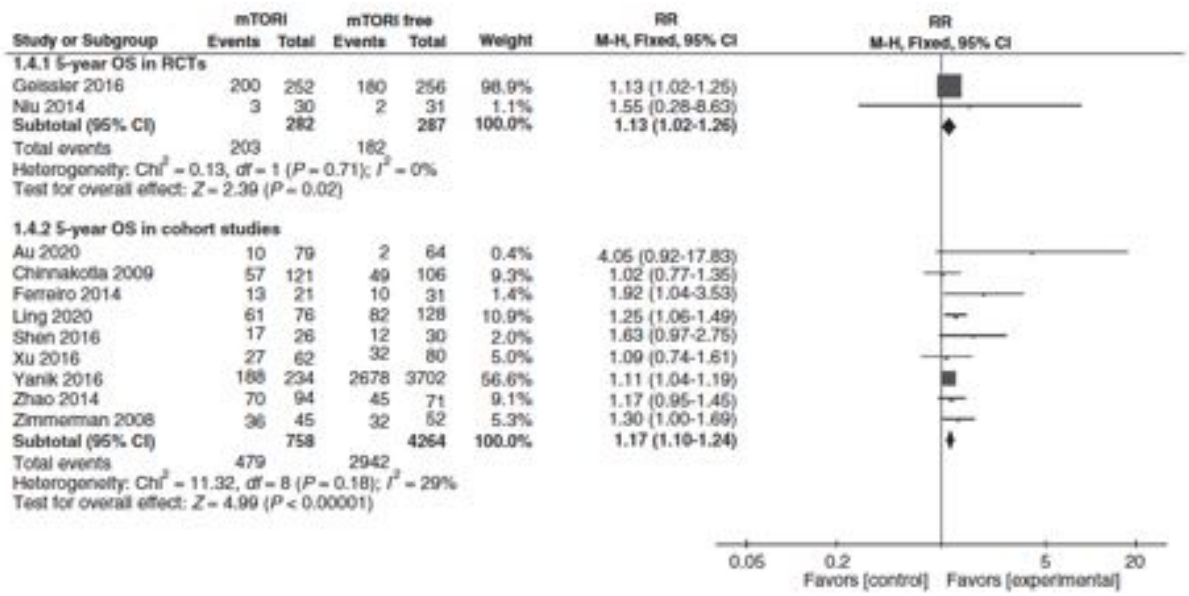
Significant survival advantage with mTOR-I at 1-year, 3-years and 5-years (RR: 1.18, 95% CI: 1.08-1.29 @ 5 years)
Recurrence-rate was lower in the mTOR-inhibitor arm (RR: 0.67, 95% CI: 0.56-0.82)
Significant reduction in recurrence related mortality in mTOR-I treated patients (RR 0.5; 95%CI, 0.31-0.81)
No significant increase in acute rejection (RR: 1.1, 95% CI: 0.94-1.28).

Grigg SE et al. Aliment Pharmacol Ther 2019

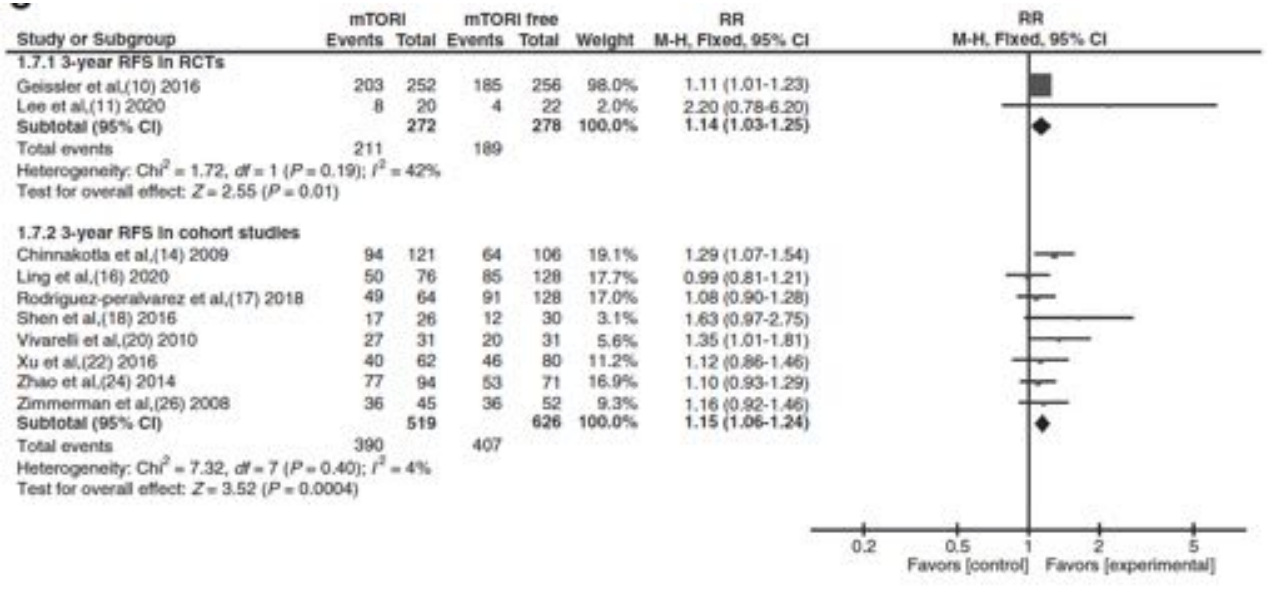
Systemic Review & Meta-analysis of mTOR-inhibitors in Survival after LT

17 studies: 3 RCTs + 14 cohort studies

Overall survival for Patients with LT for HCC at 5 years



Recurrence-Free survival for Patients with LT for HCC at 3 years

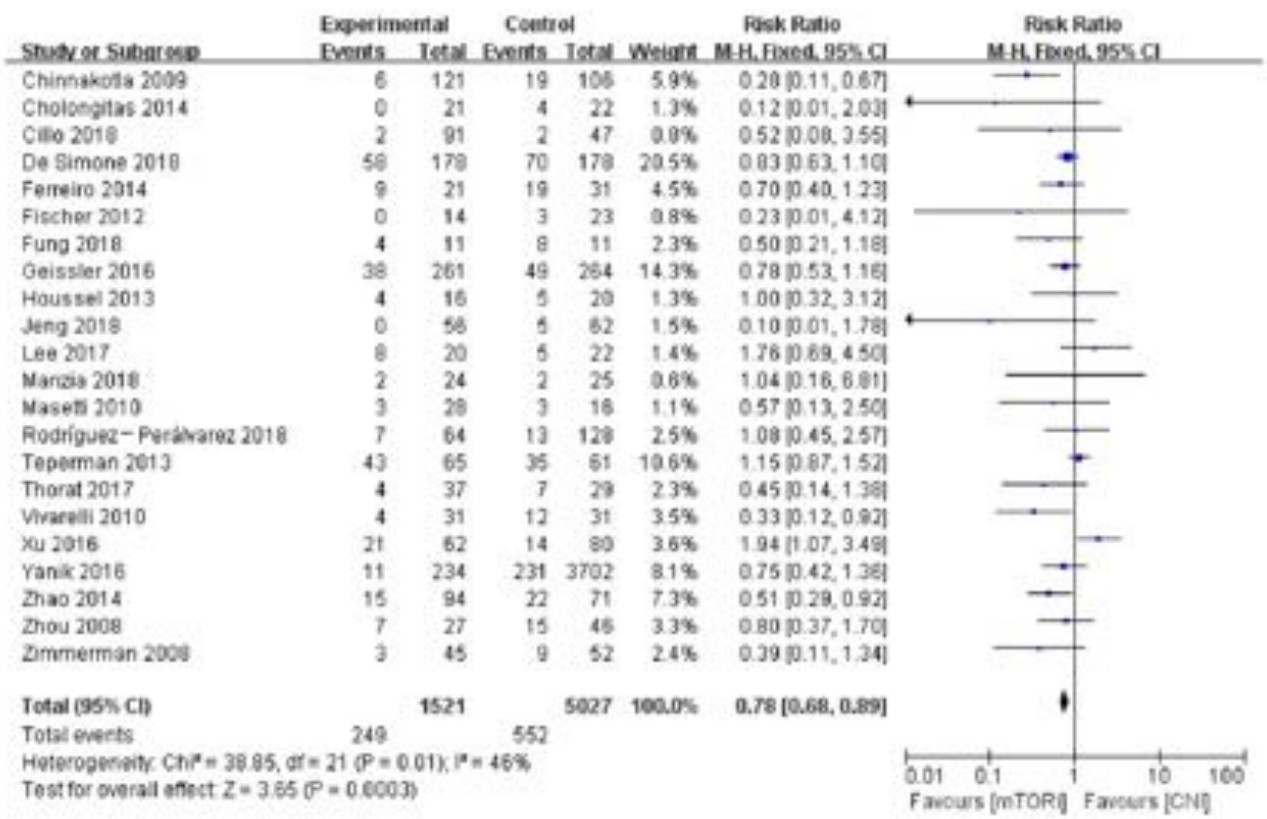


Five year OS improved in the RCTs (RR 1.13; 95%CI 1.02-1.26) and in the cohort studies (RR 1.17; 95%CI 1.10-1.24)
Three year RFS improved in the RCTs with RR of 1.14 (95%CI, 1.03-1.25) and cohort studies (RR 1.15; 95%CI, 1.06-1.24)

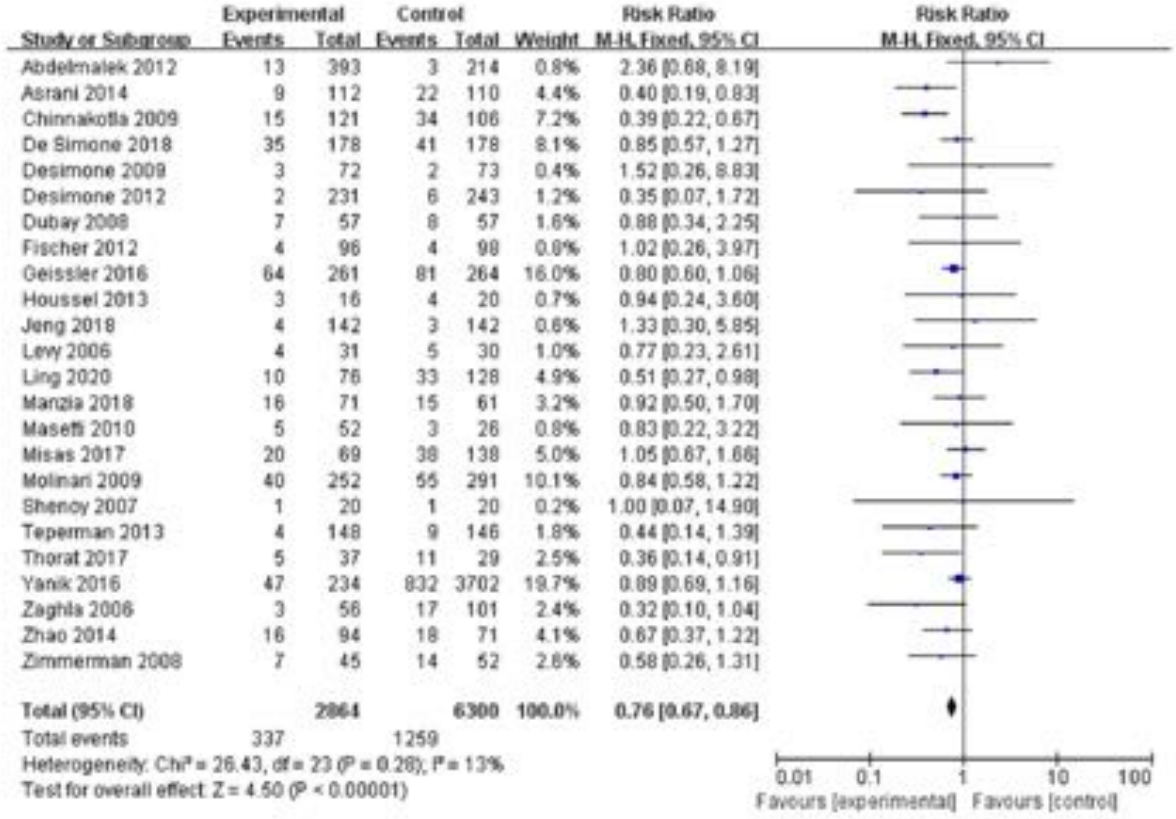
Systematic Review & Meta-Analysis of mTOR-I in HCC Recurrence & Survival

A total of 38 trials involving 10,607 participants included in the analysis

Recurrence Rates



Overall Mortalities



incidence of recurrence & overall mortality was significantly lower in mTORi than CNI group (RR:.78, 95%CI: .68–.89 and RR: .76, 95%CI:.67–86, respectively)

Recurrence of HCC after Liver Transplantation

- Direct treatment options is determined by tumour, graft, and functional status of patient
  - Local resection, locoregional therapies, systemic chemotherapy, best supportive care

- Modification of immunosuppressive regimen
  - Inconclusive data on survival benefits
  - 2 major approaches
    - **Adding switching to mTOR-I**
    - **IS minimization**

Recent Studies on IS Modification with mTOR-I after Post-Transplant HCC Recurrence

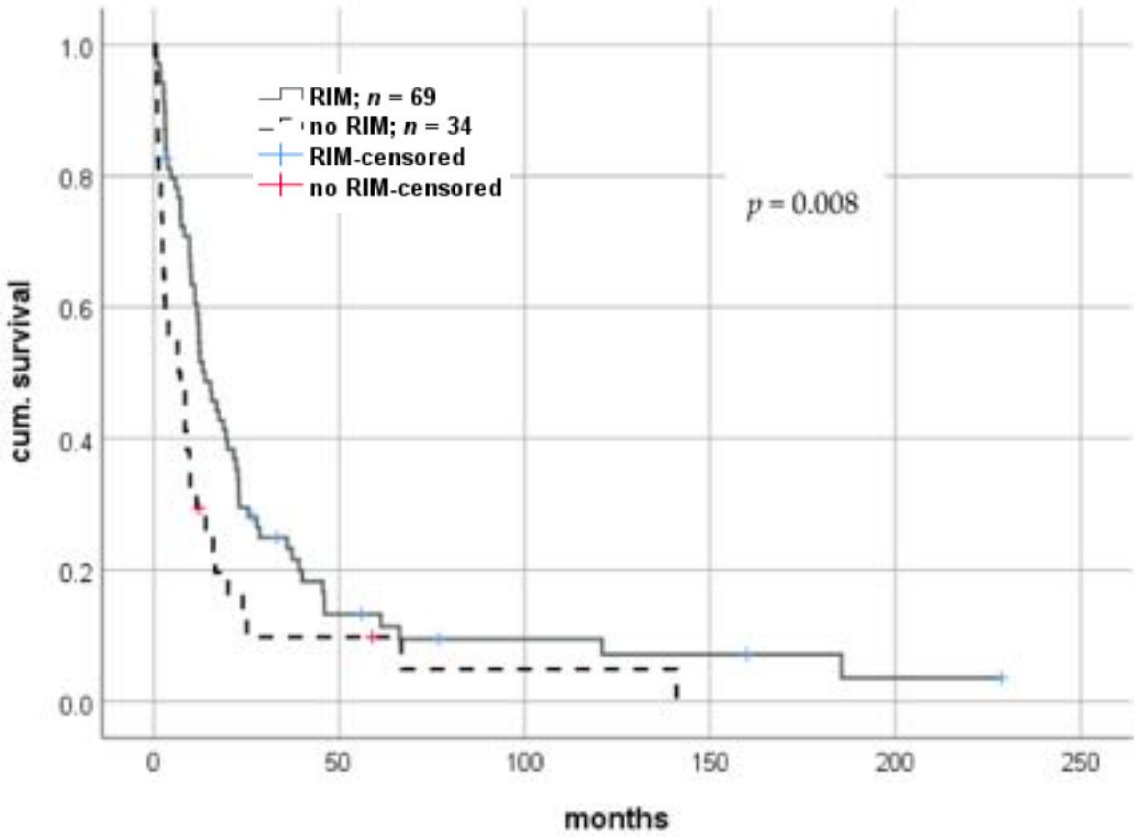
Author, year	Method	*n*	mTORi	mTORi + sorafenib	Survival, median	*p*
Lee KW et al. [24]	RCT	42	SRL vs. others	-	21.1 vs. 14.1 months	0.001
Ekpanyapong S et al. [29]	Retrospective	96	SRL vs. others	-	15.7 vs. 5.2 months	< 0.0001
Au Kp et al. [30]	Retrospective	143	mTORi vs. others	59% combined with sorafenib	21 vs. 11.2 months	0.04
Invernizzi F et al. [27]	Retrospective	50	-	(SRL/Eve) + sorafenib vs. others	5-year OS %18 vs. < 2 years (median 12 months survival benefit with mTORi + sorafenib)	0.03
Jung DH et al. [28]	Retrospective	232	-	(SRL/Eve) + sorafenib vs. others	39.2 vs. 14 months	< 0.0001
Nitta H et al. (25)	Retrospective	43	-	Eve + Sorafenib vs. others	19.9 vs. 14 months	0.0006
mTORi vs. non-mTORi IS modifications					21 vs. 14 months	

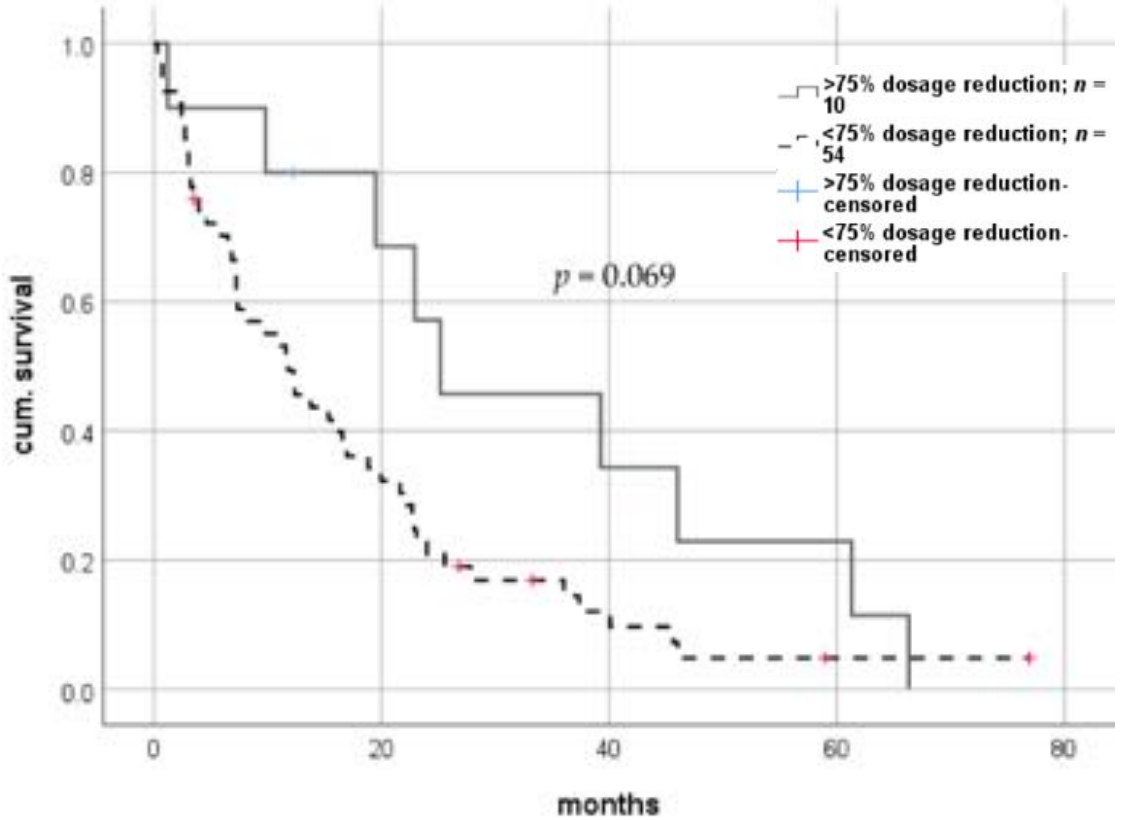
mTORi mammalian target of rapamycin inhibitors, *OS* overall survival, *RCT* randomized clinical study, *SRL* sirolimus

Restrictive Immunosuppression after Recurrence of HCC after Liver Transplantation

484 HCC LT with 112 patients (23.1%) recurrent HCC – diagnosed at median 16 months, with median survival of 10.6 months

Restrictive immunosuppressive management (RIM) approach, ie, discontinuation or significant dose reduction after diagnosis of rHCC





Median survival of 13.2 months in patients with RIM versus 7.0 in patients without RIM with a mean prolongation of survival of 5.5 months

Restrictive immunosuppression; HR 0.55 (95% CI 0.32-0.93, p=0.026)

Recommendations on Post-transplant HCC Recurrence

Asian Liver Transplant Network Clinical Guidelines on Immunosuppression in Liver Transplantation

- Addition of an mTOR inhibitor and CNI minimization is recommended
- Combination for mTOR-I with sorafenib is associated with serious adverse events and should only be administered by experienced physicians

Posttransplant Management of Recipients Undergoing Liver Transplantation for Hepatocellular Carcinoma. Working Group Report From the ILTS Transplant Oncology Consensus Conference

- In case of recurrence, dosing and regimen of IS could be reconsidered, although no clinical studies support this approach
- The same holds true for switching to an mTORi

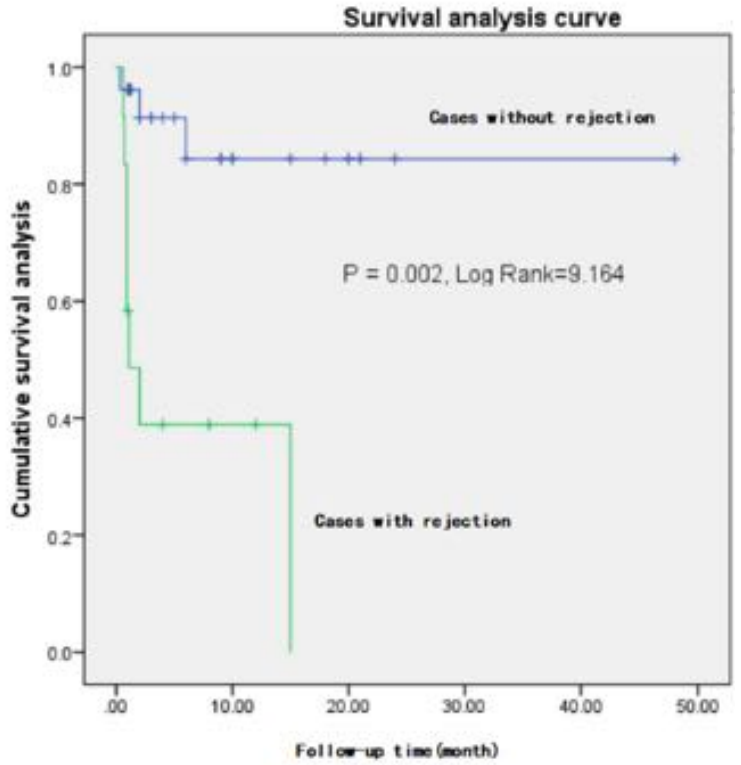
Systemic Analysis of Immune Checkpoint Inhibitors After Liver Transplantation

28 articles with 47 recipients on ICIs after LT (59.6% HCC)

31.9% (15/47) had rejection.

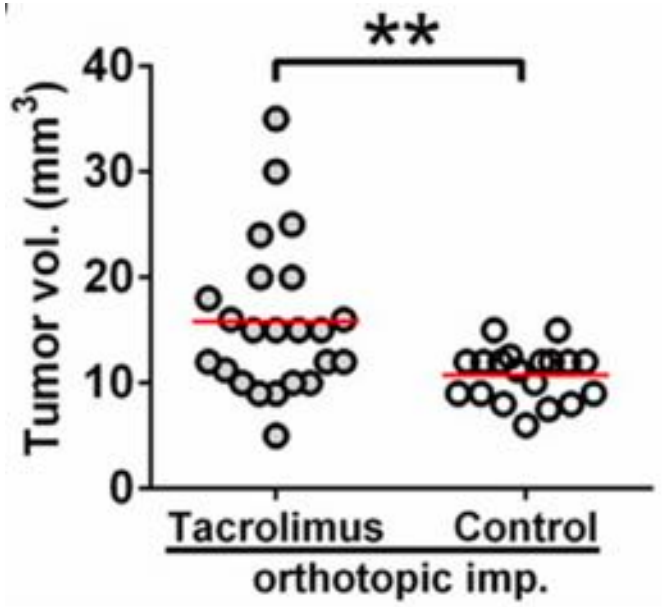
ICIs	Rate of rejection in %
PD-1/PD-L1	32 (14/42)
Nivolumab	35 (8/23)
Pembrolizumab	54 (6/11)
Camrelizumab	0 (0/3)
Toripalimab	0 (0/5)
CTLA-4	
Ipilimumab	33 (1/3)
Combined regimen	
Pembrolizumab + ipilimumab	0 (0/2)
Total	32 (15/47)

Immunosuppressive regimen	Rate of rejection in %
Single-agent immunosuppressive therapy	38 (7/18)
Steroid	100 (2/2)
Sirolimus	60 (3/5)
Tacrolimus	10 (1/10)
Cyclosporine	100 (1/1)
Combined immunosuppressive regimen	31 (4/13)
2-drug combination	40 (4/10)
3-drug combination	0 (0/2)
4-drug combination	0 (0/1)
Total	35 (11/31)

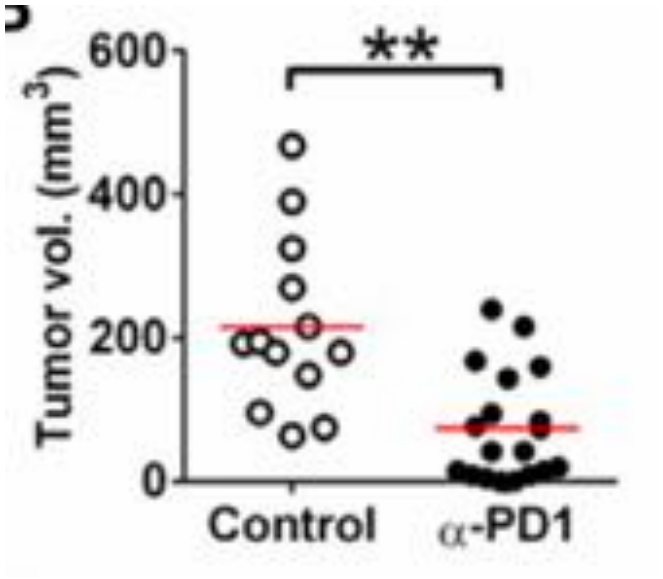


Effects of Anti-PD1 Therapy on HCC Under TAC Treatment

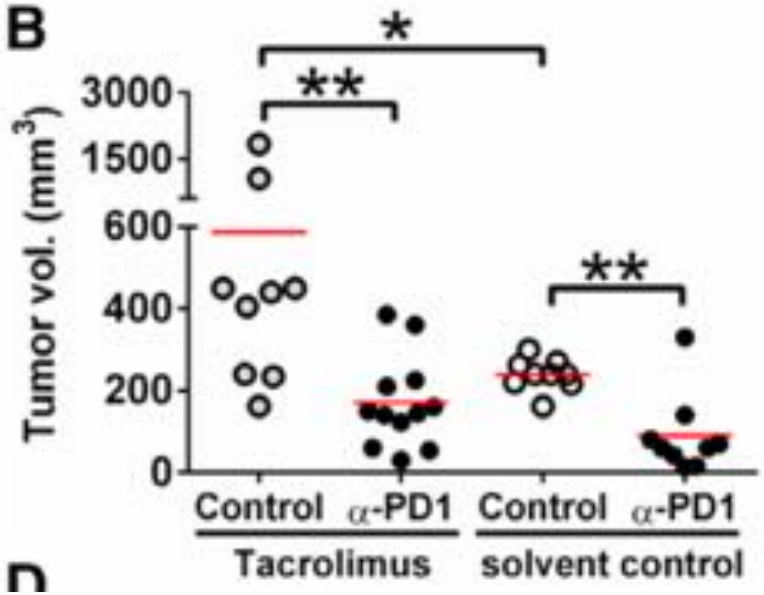
Murine Allogeneic Skin Transplantation Model and Murine Syngeneic Subcutaneous & Orthotopic HCC Models



Administration of high-dose tacrolimus increases tumor volume



Treatment with PD1 blockade inhibits orthotopic HCC tumor progression and lung metastasis

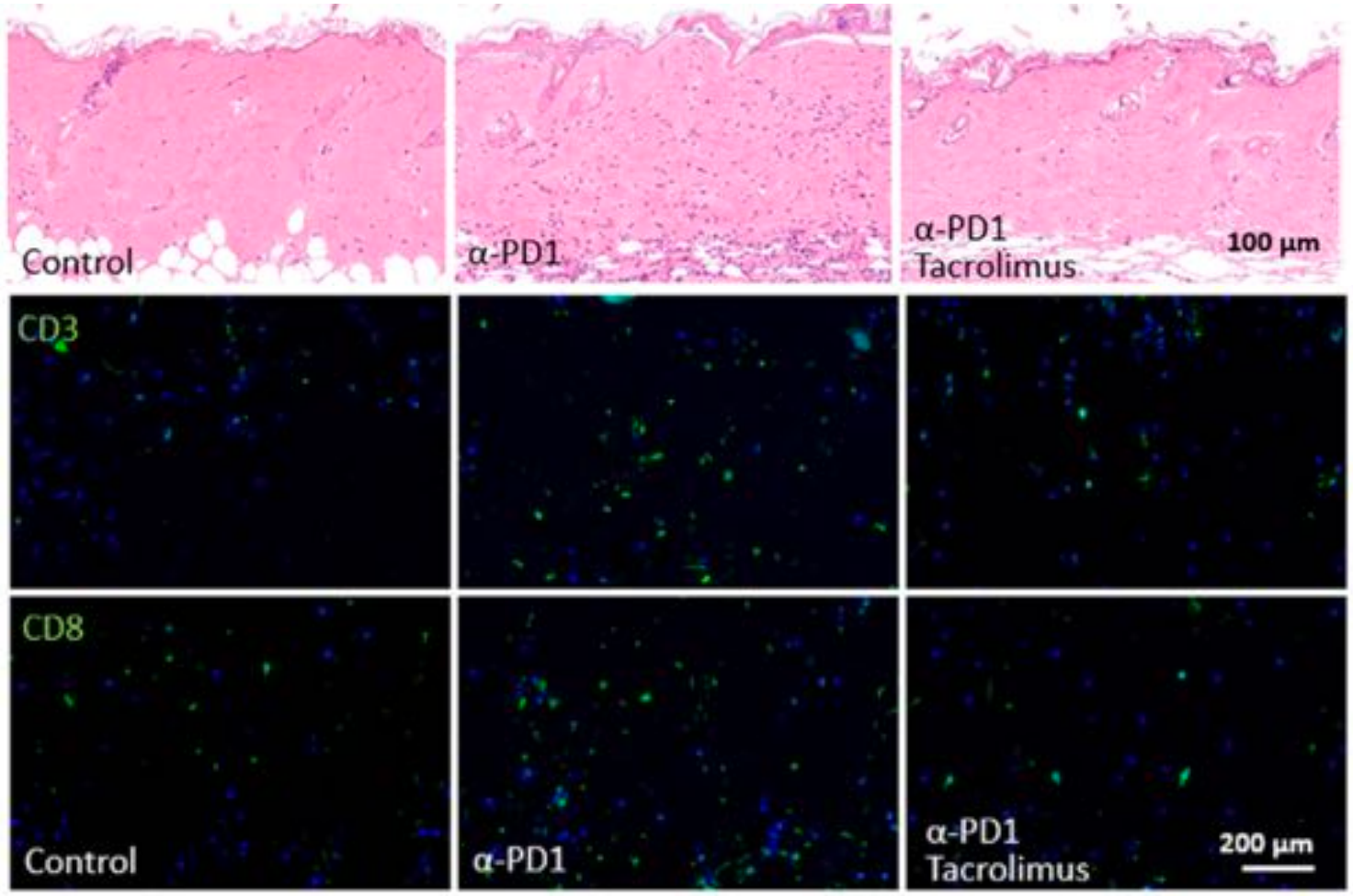


Anti-PD1 inhibits tumor progression and incidence of lung with long-term administration of high-dose tacrolimus

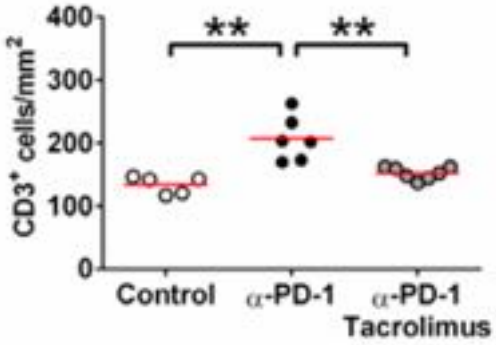
Administration of High Dose TAC Rescued Acceleration of Transplant Rejection Induced by PD-1 Blockade

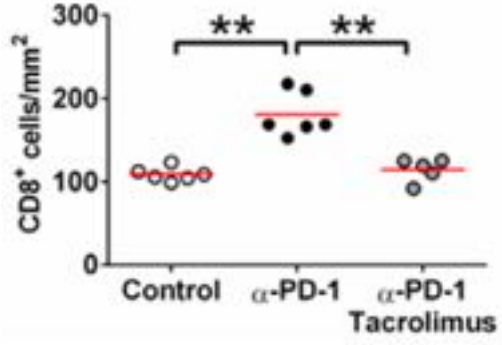
Histology

IHC for CD3+ and CD8+ T cells



Number of skin-infiltrating CD3+ & CD8+ T cells of transplanted skin grafts





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Summary (I)

- There is no current optimal immunosuppressive regimen for HCC patients in preventing recurrence and for disease progression after recurrence
  - Treatment must be individualized
    - Tumour biology, rejection risk, renal function, metabolic disorders

- The available data to date would suggest that
  - Induction IS does not appear to increase the risk of HCC recurrence
  - TAC and steroid minimization may be beneficial
  - Use of MMF may augment the effect of TAC
  - mTORi may be beneficial

Summary (II)

- Once HCC recurs, again, there is no general consensus as to the most optimal IS approach should be, although the general approach would be similar to HCC prevention
  - Minimize CNI and steroid
  - Using mTOR-I

- Use of ICI associated with increased risk of rejection and graft loss
  - Possible lower risk with adequate dosing of TAC in combination with other IS agents, without reducing the effect of ICI

Thank You Very Much For Your Attention

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