

Immunotherapy Before & After Liver Transplantation

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Disclosures

- ▶ None relevant to this presentation

Managing Pre LT Malignancy With ICI

ICI use in HCC

Keynote (n=413)- almost 20% of pembrolizumab arm remained free from progression >1 year compared to <7% of controls

Checkmate (n=743) (median survival 16.4 versus 14.7 months, HR 0.85; P=0.07)
1-year and 2-year survival rates were 60% and 37% for nivolumab compared with 55% and 33% for sorafenib, respectively

Imbrave (n=501) stopped at interim analysis 8.6m -- improved OS (HR 0.58, 95% CI 0.42-0.79; P = 0.0006) and improved PFS (HR 0.59, 95% CI 0.47-0.76; P<0.0001). 52% and 40% of patients surviving at 18 months, respectively.

Table 2 | Results from randomized controlled trials involving ICIs as systemic therapy for HCC

Agent (dose)	Number of patients	MVI	EHD	AFP >400 ng/ml	ORR (CR)	mPFS	mOS (95% CI)	HR	Ref.
KEYNOTE-240 (second-line setting)									
Pembrolizumab (200mg every 3 weeks)	278	13	70	46 ^a	18 (2)	3.0	13.9 (11.6–16.0)	0.78	¹¹⁰
Placebo	135	12	69	43 ^a	4 (0)	2.8	10.6 (8.3–13.5)		
CheckMate 459 (first-line setting)									
Nivolumab (240mg every 2 weeks)	371	75 ^b	75 ^b	33	15 (4)	3.7	16.4 (14.0-18.5)	0.85	¹¹²
Sorafenib (400mg twice a day)	372	70 ^b	70 ^b	38	7 (1)	3.8	14.8 (12.1-17.3)		
IMbrave150 (first-line setting)									
Atezolizumab (1,200mg every 3 weeks plus bevacizumab 15mg/kg every 3 weeks)	336	38	63	38	27 (6)	6.8	NE	0.58	¹¹⁹
Sorafenib (400mg twice a day)	165	43	56	37	12 (0)	4.3	13.2 (10.4–NE)		

NEW standard of care

ICI use in HCC - Adverse events

Table 3 | Safety profiles of ICIs for HCC

PD1/PDL1 agent (dose)	Other agents (dose)	TRAE (%)				AST (%)	
		Total	Grade ≥3	Leading to discontinuation	Serious	Any grade	Grade ≥3
Monotherapies							
Nivolumab (various doses)	No	83	25	6	6	21	10
Pembrolizumab (200 mg every 3 weeks)	No	73	26	17	15	7	7
Camrelizumab (3 mg/kg every 2 or 3 weeks)	No	NR	22	4	11	21	5
Durvalumab (1,500 mg every 4 weeks)	No	60	20	8	11	8	3
Atezolizumab (1,200 mg every 3 weeks)	No	41	5	2	3	14	3
Tremelimumab (750 mg every 4 weeks)	No	84	43	13	25	10	4
Combinations of two immune checkpoint inhibitors							
Durvalumab (1,500 mg every 4 weeks)	Tremelimumab (300 mg single dose on day 1)	82	35	11	16	16	12
Durvalumab (1,500 mg every 4 weeks)	Tremelimumab (75 mg every 4 weeks x4)	69	24	6	14	15	8
Nivolumab (3 mg/kg every 3 weeks) ^a	Ipilimumab (1 mg/kg every 3 weeks) ^b	71	29	6	18	20	8
Nivolumab (1 mg/kg every 3 weeks) ^a	Ipilimumab (3 mg/kg every 3 weeks) ^b	94	53	22	22	20	16
Combinations of an immune checkpoint inhibitor and a tyrosine-kinase inhibitor							
Pembrolizumab (200 mg every 3 weeks)	Lenvatinib (8 or 12 mg per day)	94	80	10	59	31	18
Nivolumab (240 mg every 2 weeks)	Cabozantinib (40 mg per day)	89	47	NR (6 ^c)	NR	14	8
Nivolumab (240 mg every 2 weeks)	Ipilimumab (1 mg/kg every 6 weeks plus cabozantinib 40 mg per day)	94	71	15.5 (7 ^b)	NA	29	23
Combinations of an immune checkpoint inhibitor and a VEGF inhibitor							
Atezolizumab (1,200 mg every 3 weeks)	Bevacizumab (15 mg/kg every 3 weeks)	88	39	NR (10 ^c)	24	15	5
Atezolizumab (1,200 mg every 3 weeks)	Bevacizumab (15 mg/kg every 3 weeks)	84	38	15 (7 ^c)	17	19.5	7

Triple therapy.

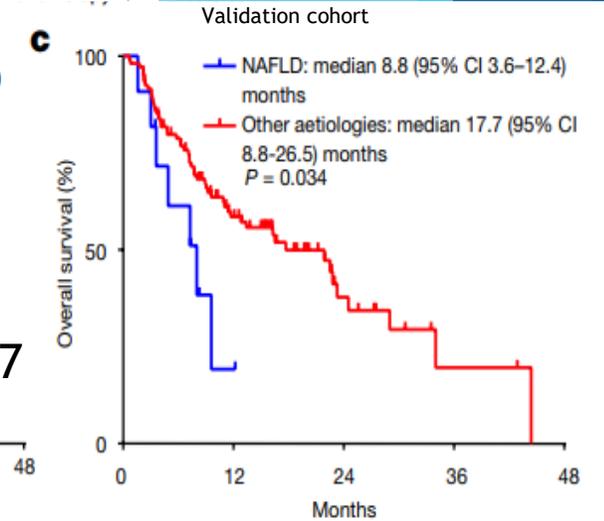
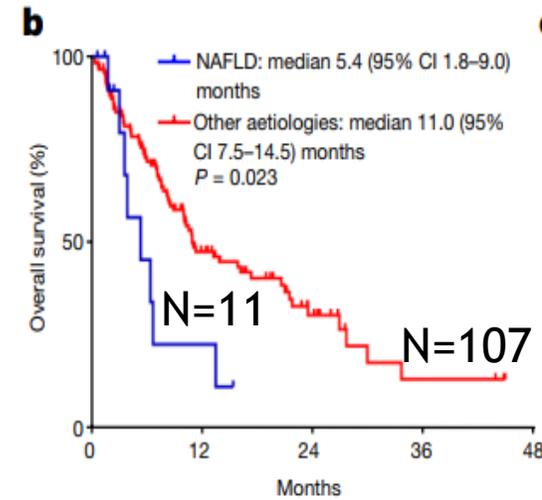
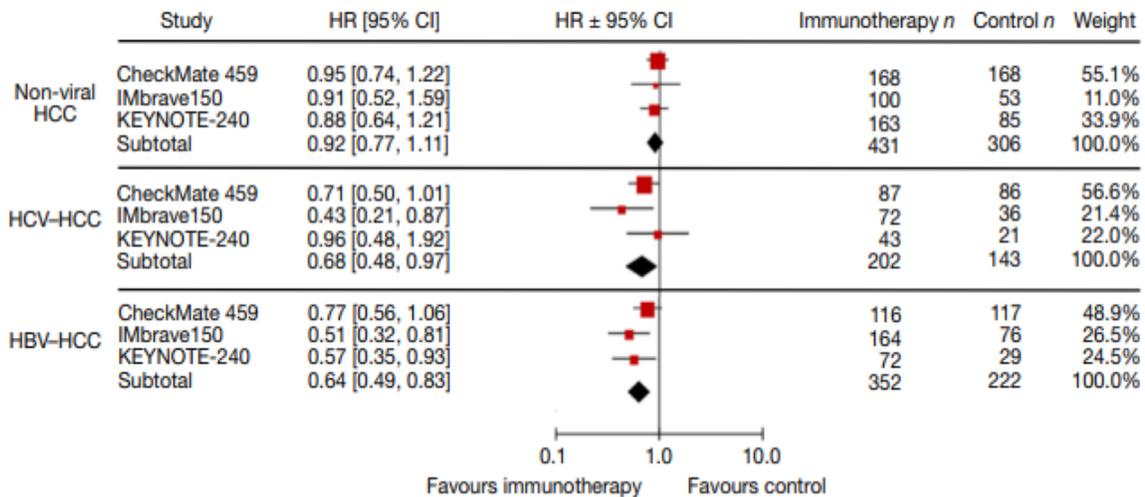
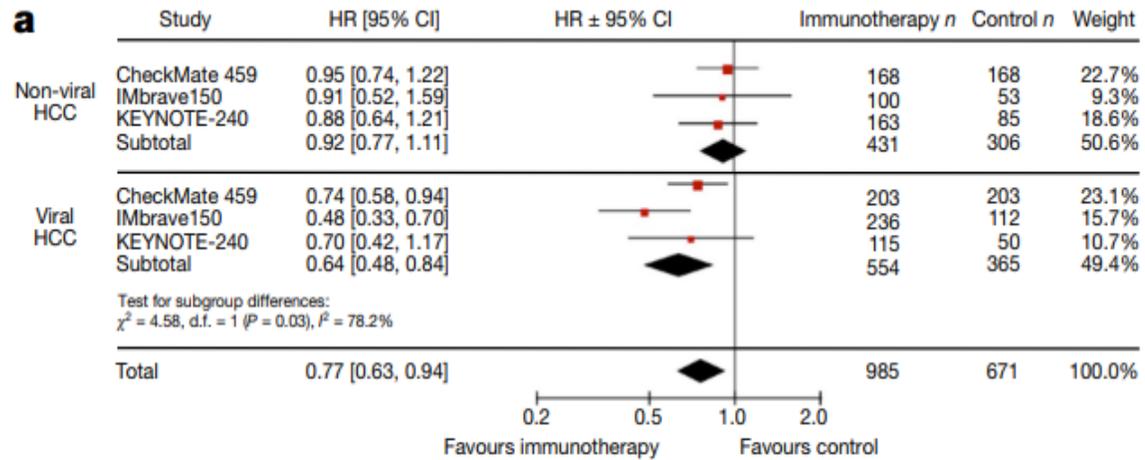
Median PFS was 5.5 months for NIVO (240mg/day) + CABO (40mg/day) and 6.8 months for the NIVO (3mg/kg) + IPI (1mg/kg)+ CABO (40mg/day), median OS was not reached in either arm.

Grade 3-4 treatment-related adverse events were reported in 15 pts (42%) in the NIVO + CABO arm and 25 pts (71%) in the NIVO + IPI + CABO arm and led to discontinuation in 1 (3%) and 7 (20%) patients, respectively

Chronic Liver Disease May Matter

- ▶ Peri tumoral regions of HCC and possibly liver mets themselves have massive increase lymphocyte infiltration and thus stain positive for PD1 or PDL1
- ▶ PDL1 expression may be more associated with HBV compared to non viral hepatitis
- ▶ PDL1 expression can be stimulated by viral infection and interferon this
- ▶ PDL1 expression can change post LT (a donor bx at procurement will not represent PDL1 status at time of ICI)
- ▶ Patients with chronic liver disease have higher PD 1 expressing lymphocytes than normal control.
- ▶ PD-1 expression was higher in AIH patients than VH patients. PDL-1 was statistically similar (AIH 32.3%, HCV 13.3%. P=0.07), but higher PDL-1 in AIH responders than non responders, so PD1-PDL1 ratio higher in non responders). Neither related to the degree of fibrosis or grade of inflammation
- ▶ PDL1 expression in liver tissues similar in AIH and HCV whereas healthy controls had no expression.

Cancer type and CLD etiology may affect Outcomes



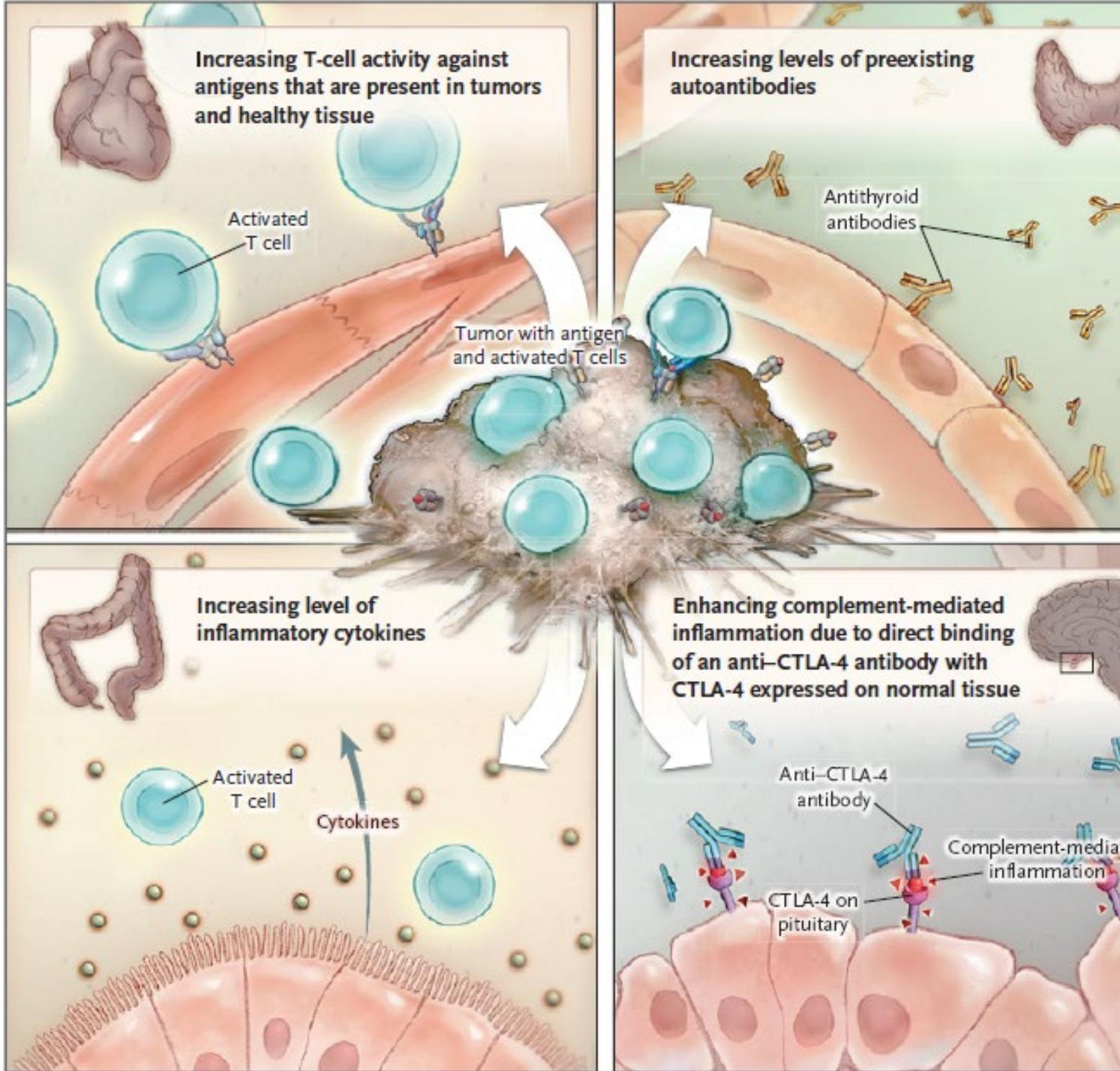
- ▶ HCC in NASH reduced benefit from ICI
- ▶ Possibly worse outcome from ICI
- ▶ Possibly worse CLD outcomes as well ?

Decision making Tidbits

Severe cardiovascular disease and thrombotic or bleeding events (including diabetic & ischemic ulcers) are contraindications to TKIs and anti-angiogenics including bevacizumab

Anti-Drug Antibodies to ICI in HCC is low at 0-12.7% but impacts response and OSS

PD-1 mAbs have a half life of 14-27 days and take 12-18 weeks to reach steady state.
PD-L1 mAbs have a half life of 21-27 days and 6-16 weeks to reach steady state.
CTLA-4 mAbs have a half life of 15-22 days and 9 weeks to reach steady state.



ICI Effects

Hepatitis virus impact

Cohorts (N)	ORR ^a N (%)	Any Grade irAEs N (%)	Grade ≥ 3 irAEs N (%)
HIV (21)	2 CR/3 PR (28)	5 (24)	3 (14)
HBV/HCV (34)	6 PR (18)	15 (44)	10 (29) ^b

HIV: NS change in VL or CD4 count

HCV: 9 SVR, 9 active HCV (and did not receive DAA), 5?

HBV: 8 s Ag + (5 w VL detectable 10-25IU), 7 cAb+, 1?

NO Viral reactivation

**Transitioning to
Transplant
w ICI??**

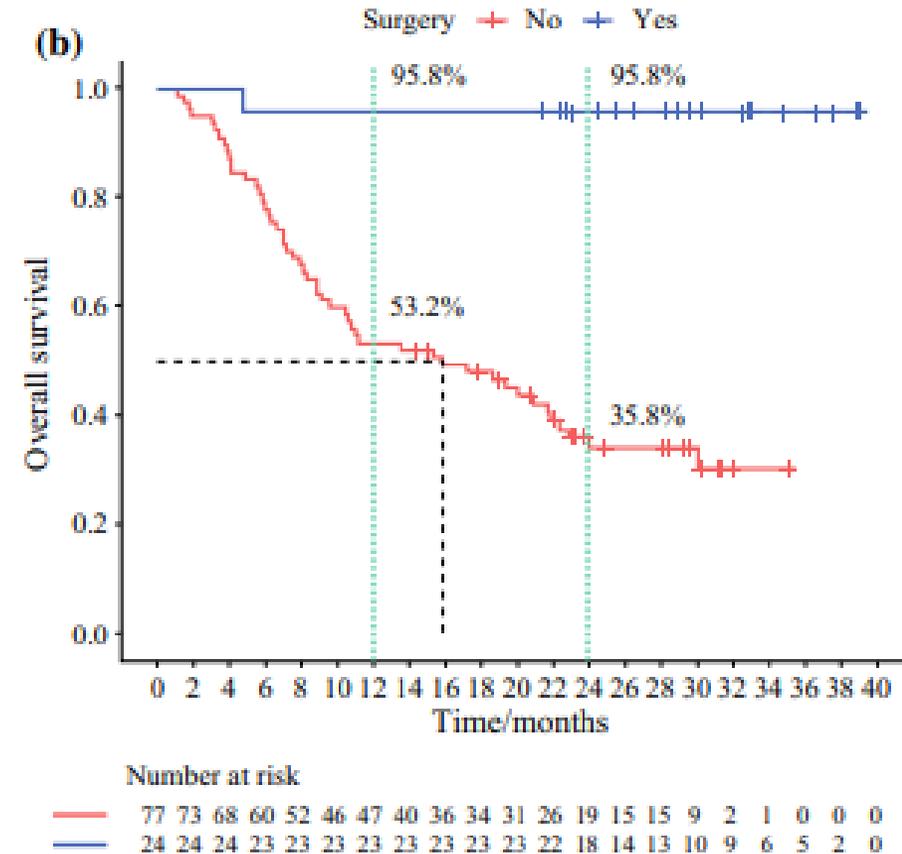
Who gets ICI?

When to transition to ICI

- ▶ RCT patients = Childs A 97-100% ECOG 0-1
 - ▶ BCLC C 80-90%, 44-87% failed prev Tx
 - ▶ 13-38% vasc invasion, 53-80% extra hep dis
- ▶ Technical or other contraindication to LRT
- ▶ Progressive disease/ lack of response to LRT (at least twice)

Downstaging with ICI

- ▶ Consecutive N=101 unresectable/adv HCC, received TKI with anti-PD-1inh, followed by resection (retrospective)
 - ▶ 93% Childs A, 56% with vasc tumor thrombus, 29% Xhep spread
- ▶ mRECIST 50% ORR, (10 CR, 40 PR, 30 stable, 15 progress) within 4 months Rx 24% underwent resection (54% MVI and 17% Xhep spread initially)
- ▶ 10/24 (41%) path CR
- ▶ 5/10 - post resection liver failure, 5/10 post complications IIIa-V, one death from immune related complication
- ▶ Of resections (80% 1 year rec free survival)
- ▶ 51 died by 21 months



Longer outcomes of resection candidates

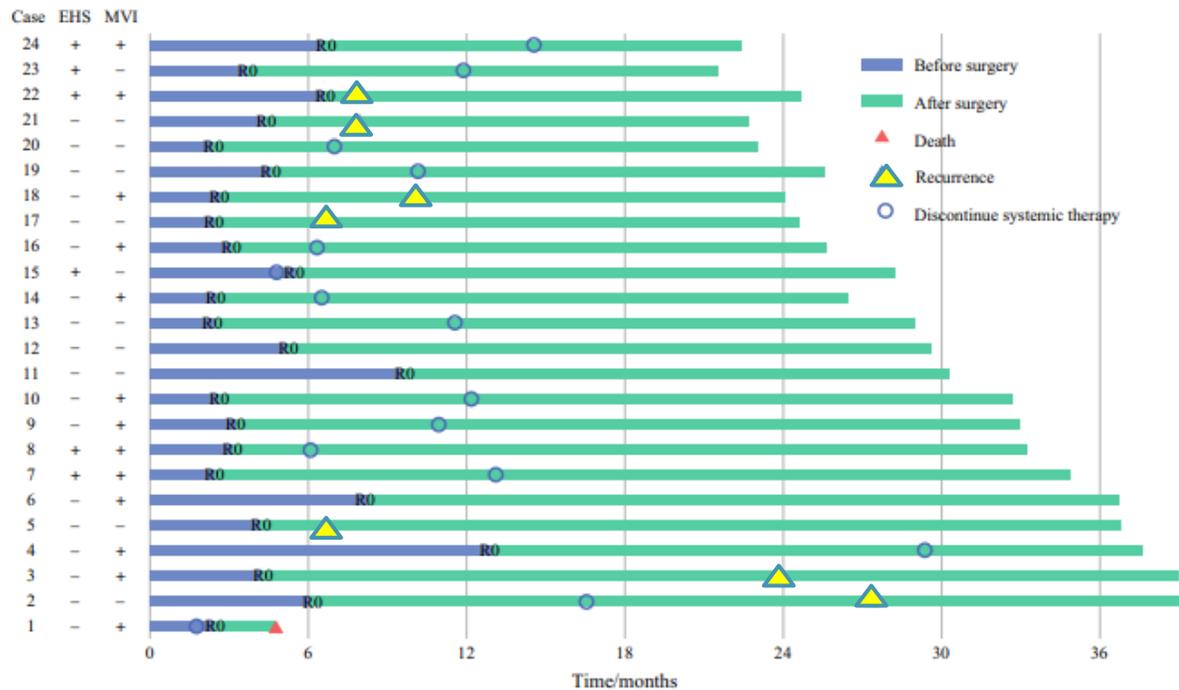
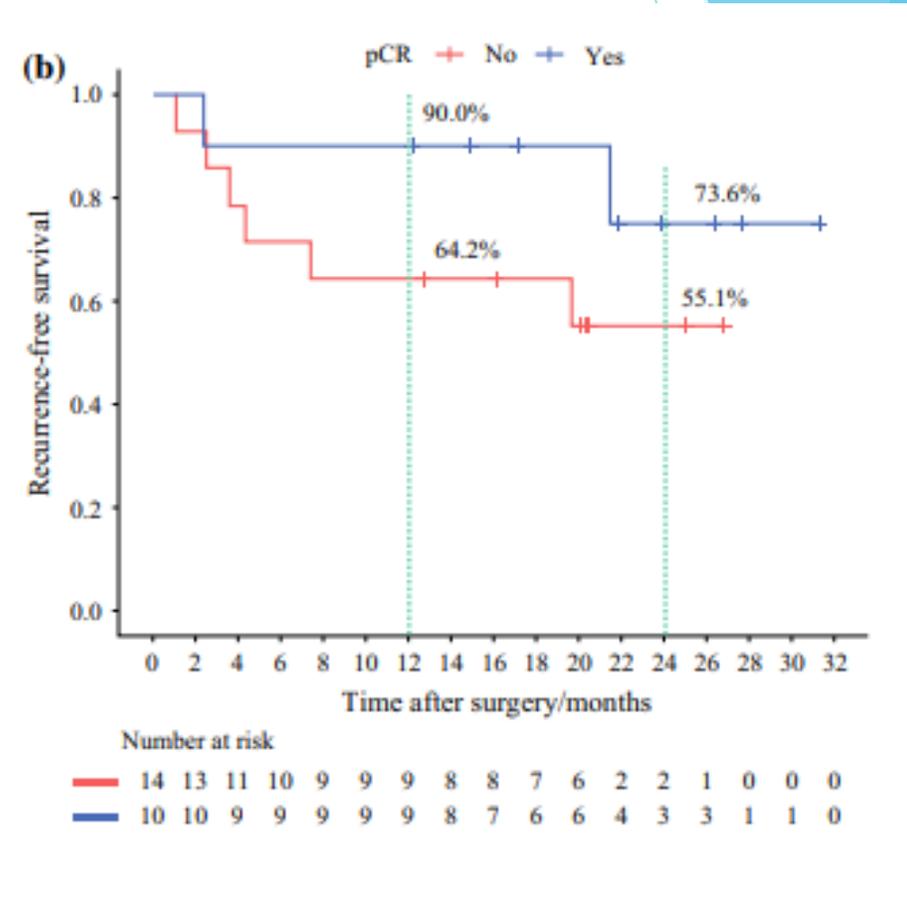


FIG. 2 Swimmer plots of the 24 patients who underwent conversion resection. EHS, extrahepatic spread; MVI, macrovascular invasion; R0, R0 resection



22/24 continue TKI/PD1 post op, 14/23 stopped

Downstaging with ICI to LT

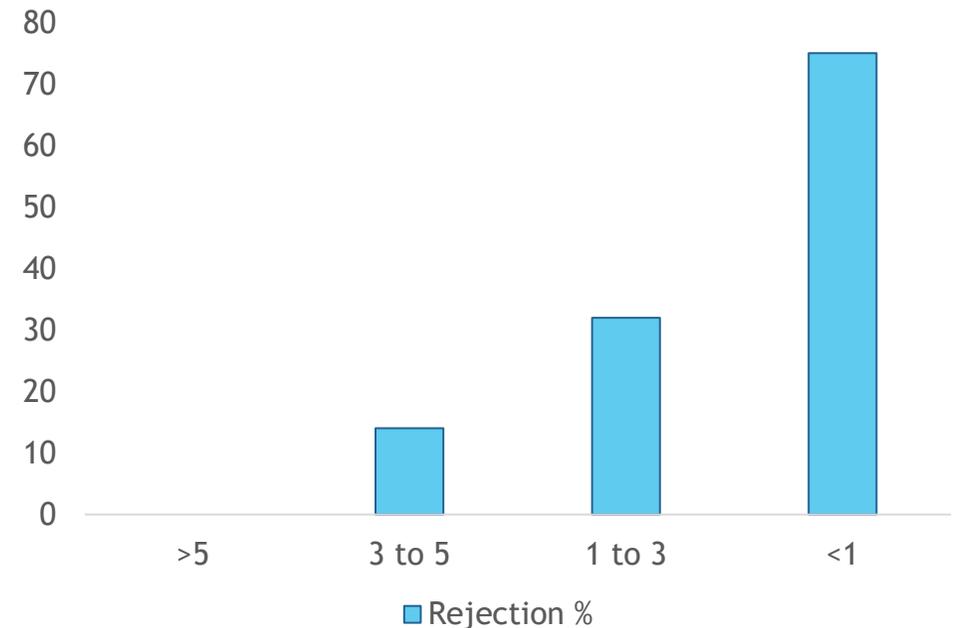
Sys Rev. 24 'studies', 45 patients (30 males), 14-68yrs, 16/21 with Milan detail in criteria, 1/2 that was outside Milan → downstaged within Milan

42/45 PD-1i, 3/45 PD-L1i, receiving 1-34 'cycles of Rx, 33/45 received LRT/other treatment

- ▶ T $\frac{1}{2}$:15-27 days
- ▶ 11/45 (24%) rejection, (2 AMR)
 - ▶ 3 death (2 within 36 h), 4 graft loss, 4 resolved
- ▶ LTx within 1x $\frac{1}{2}$ life - $\frac{3}{4}$ (75%) rejection
 - ▶ 8-24 months of ICI in 3 rejections (1 dose- non rejection)
- ▶ May need to consider PLEX or IVIG in refr rejection
- ▶ Induction with ATG/IL2r not definitive

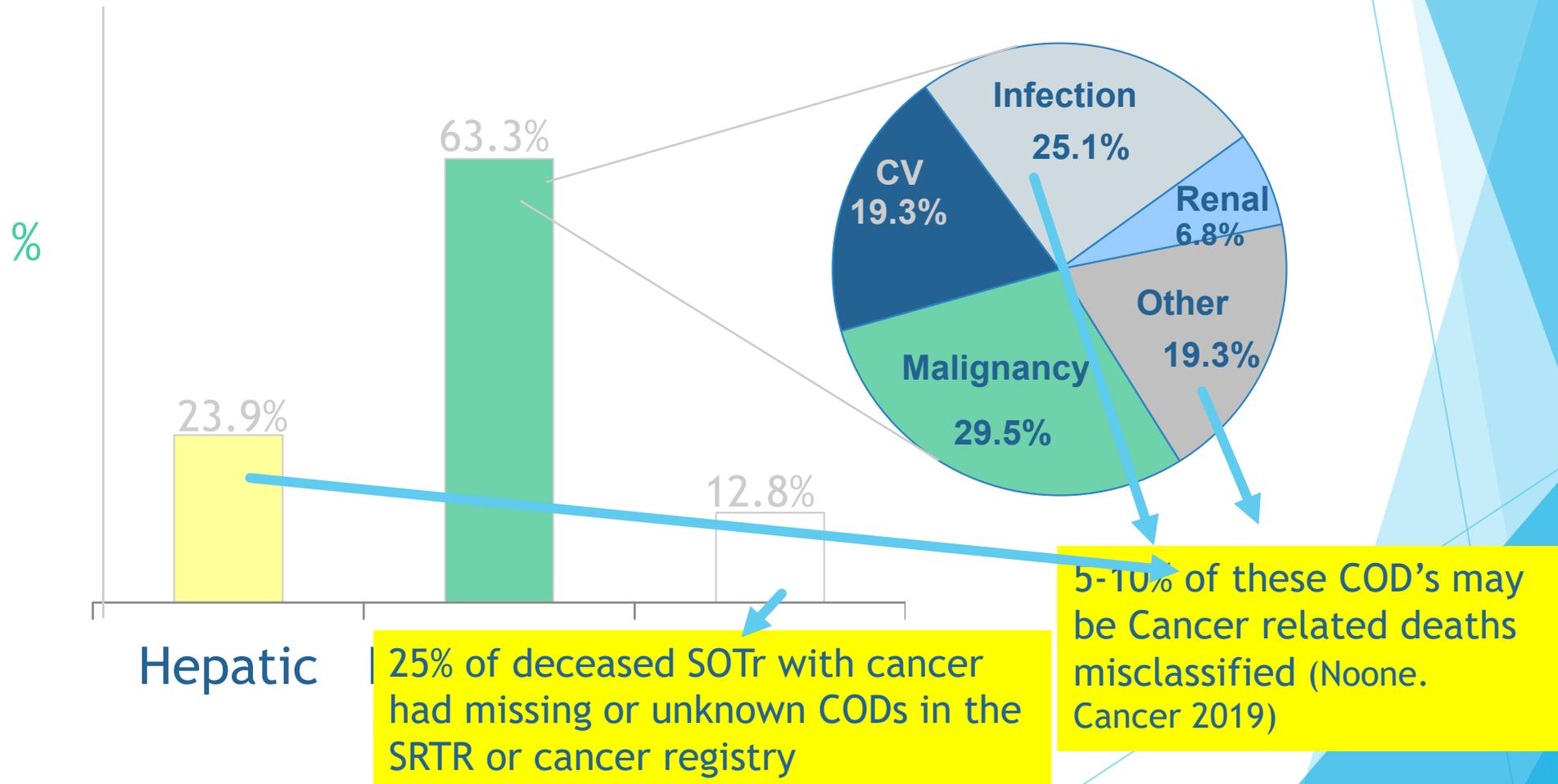
Remember: No true denominator

Rejection post LT within ICI $\frac{1}{2}$ life



POST Liver Transplant

Causes of Death After LT Beyond 1 year



Age specific rate

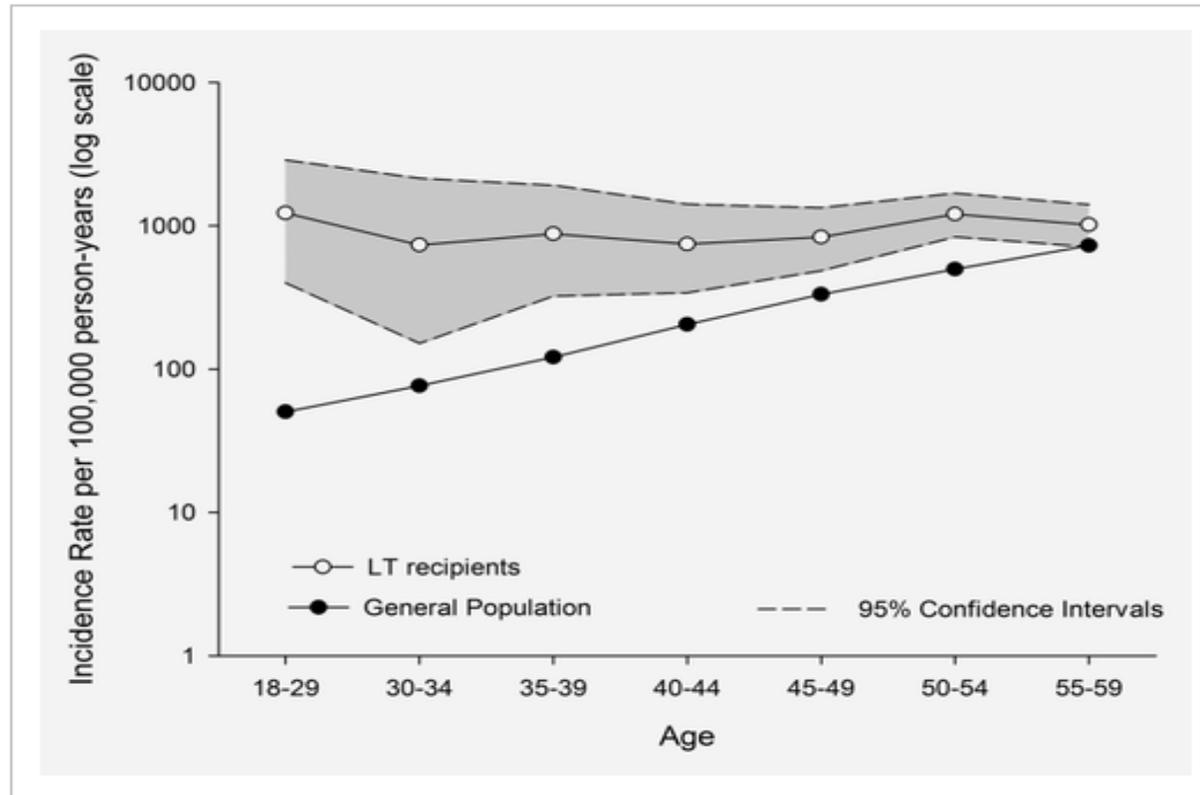


Figure 2

[Open in figure viewer](#) | [PowerPoint](#)

Age-specific incidence rates for *de novo* malignancies observed in liver transplant (LT) recipients and in the Italian general population.

Probability of Death after Cancer Diagnosis

	1yr (%)	3 yr (%)	5 yr (%)
ALL	40	48	54
CDC	21	32	36

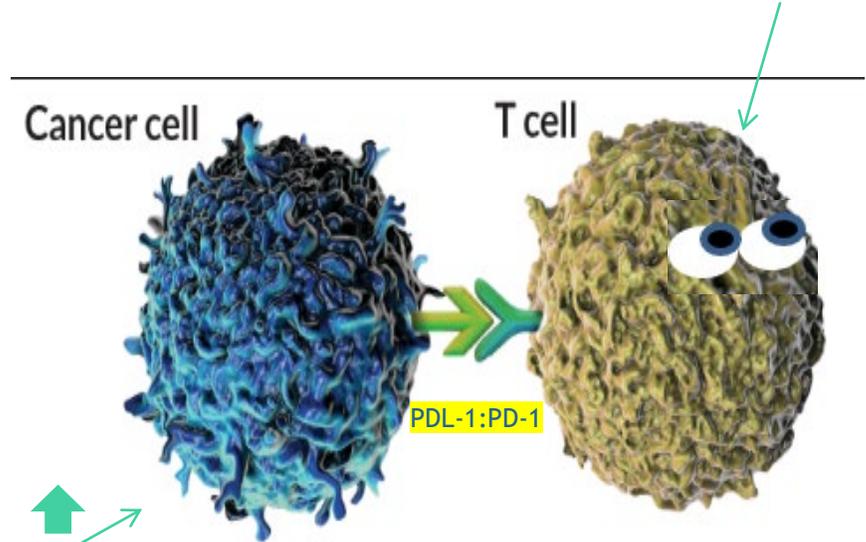
Malignancy as cause of death:

Hematologic: 9/15 (60%), Infection (27%)

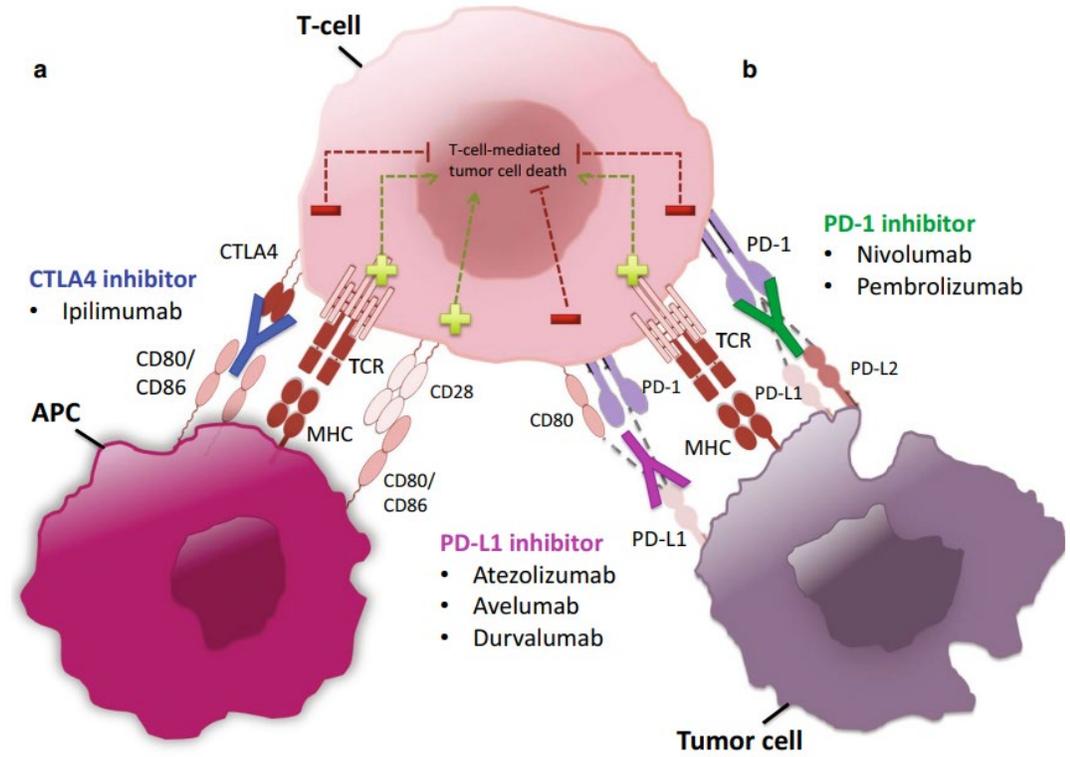
Solid organ CA: 36/45 (80%)

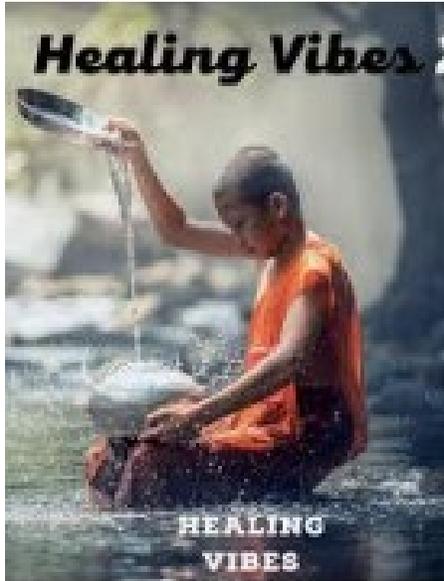
Immunosuppression Effects

Hyperglycemia,
 HyperInsulinemia
 Low adiponectin,
 Hi Leptin, TNF α ,
 IL-6
 Obesity

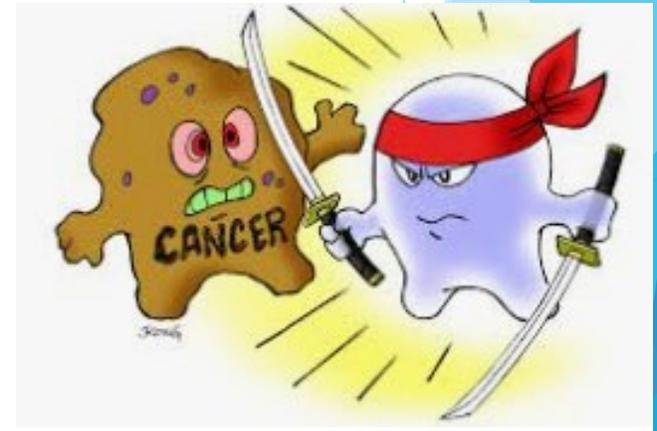


- Dose dependent decrease surveillance
- Decrease doubling time
- Increased risk of recurrent CA or Denovo CA.



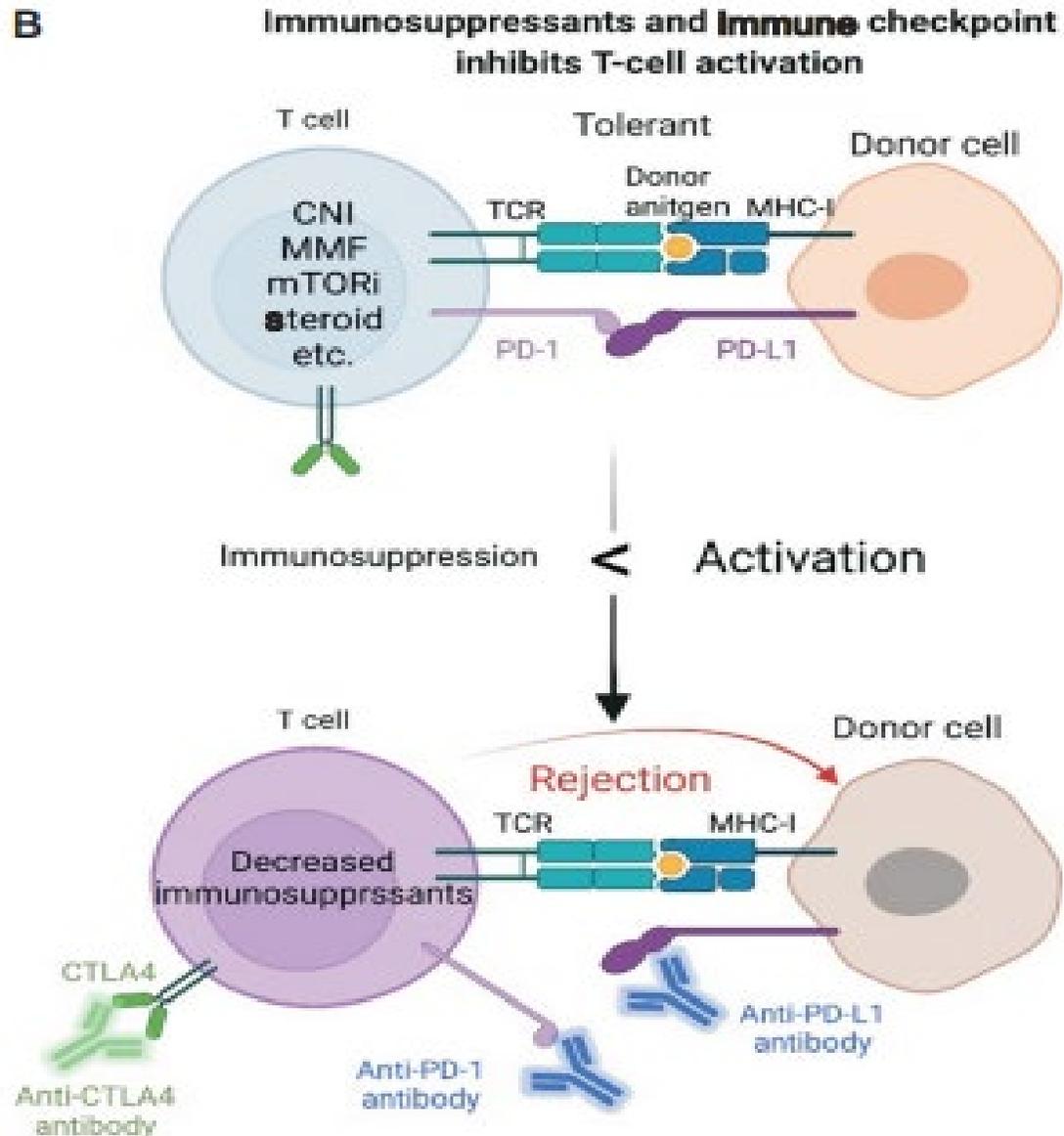


Managing POST LT Malignancy W ICI



ICI & the LIVER

- ▶ PD-1 and CTLA4 pathways facilitate immune tolerance of the graft
- ▶ PD-L1 is expressed in 20-80% of hepatocytes and cholangiocytes and is critical in tolerance
- ▶ PD-1 is heavily expressed on graft-infiltrating T-cells



Rejection

Systematic Review 24/83 SOT pt w LT

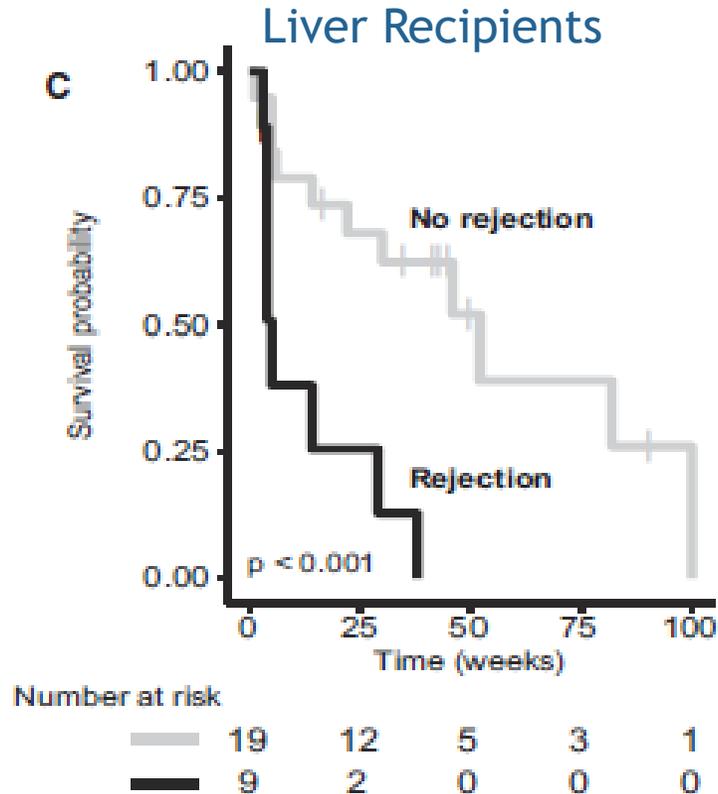
- ▶ Ranges 15-38% (fair # ‘historic’ data included)
- ▶ First few weeks of ICI, highest risk



TABLE 2 Rejections

Patients experiencing allograft rejection—n (%)	33 (39.8)
Kidney recipients	23/53 (43.4)
Liver recipients	9/24 (37.5)
Heart recipients	1/6 (16.7)
Time (weeks) to graft rejection from first CPI use—mean (SD)	5.6 (7.0)
Kidney recipients	7.3 (7.9)
Liver recipients	2.1 (1.0)
Heart recipients	1 (NA)

Causes of Death are still Cancer Dominant



ALL SOT Recipients

Reported causes of death—n (%)	n = 48
Cancer	38 (79.1)
Rejection	9 (18.8)
Sudden cardiac death	2 (4.2)
Multiorgan failure, not otherwise specified	1 (2.1)
Sepsis	1 (2.1)
Not reported	1 (2.1)

Rejection assoc. w increase risk death.
 Partly due to organ failure
Mostly due to stopping immunotherapy and disease progression

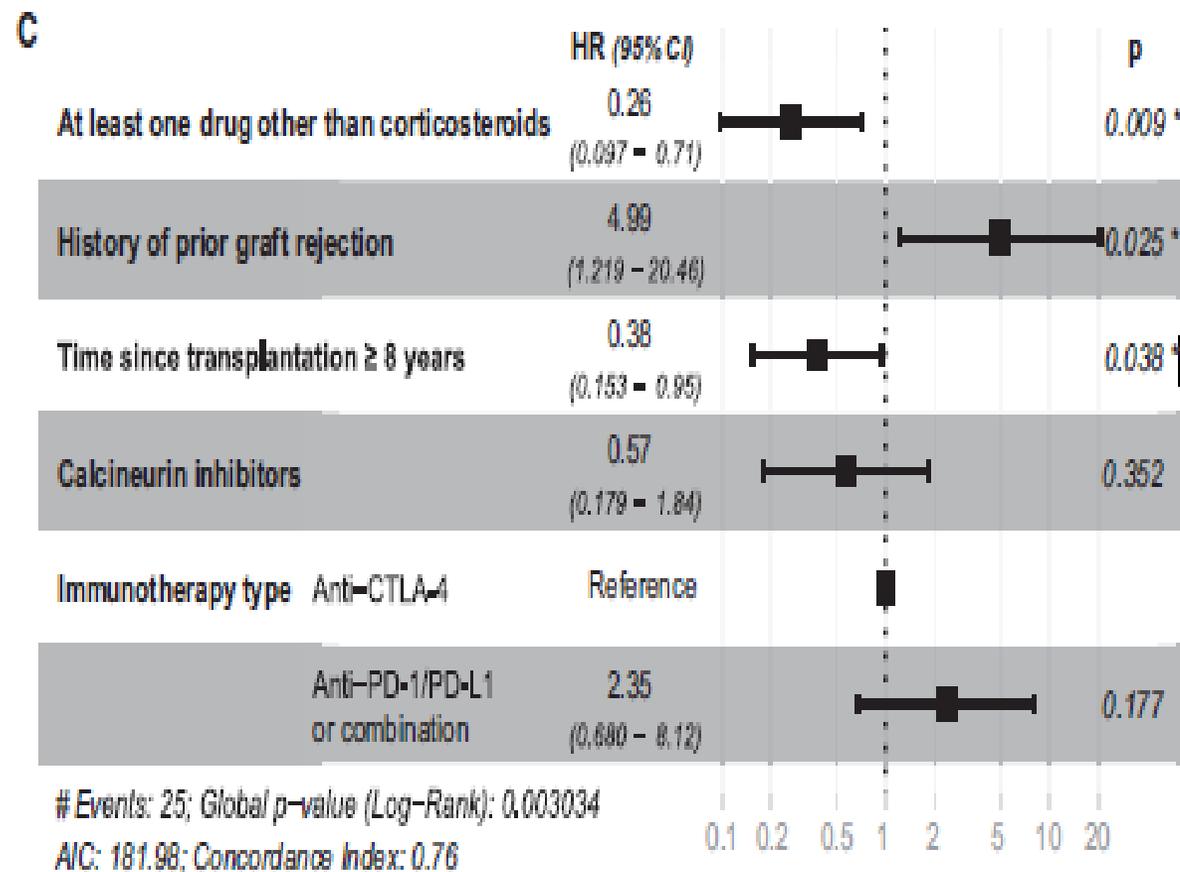
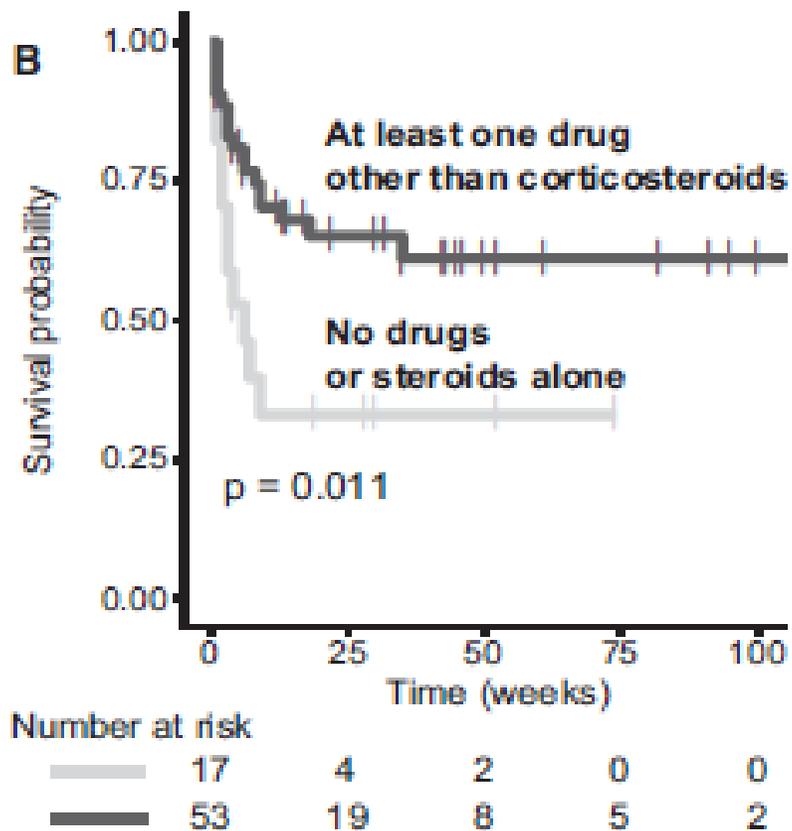
Rejection

- ▶ T cell mediated > B cell mediated
- ▶ Increase risk if :
 - ▶ Only on steroids
 - ▶ If <60 years
 - ▶ If < 3 years from LT
 - ▶ Hx prior Rejection
- ▶ Other impacting factors (applicable to preLT pop'n):
 - ▶ The duration of ICI treatment prior to transplant,
 - ▶ allograft PD-L1 receptor activity (? at time of ICI)
 - ▶ blood replacement during transplant (diluting remaining ICI)

Study	Type of cancer	Before/ after	Allograft outcome	Checkpoint inhibitor	Year from tx to ICI	IS regimen
Tsung et al. (2021) [24]	cSCC	After	No rejection	Cemiplimab x2	NA	Tac 1 mg
	cSCC	After	No rejection	Cemiplimab x12	NA	Tac 0.5 mg
Qiu et al. (2020) [55]	HCC Rec	After	No rejection	Camrelizumab	4	Tac → sirolimus
Zhuang et al. (2020) [56]	HCC Rec	After	No rejection	Nivolumab	2.7	Tac
Biondani et al. (2018) [57]	LUSC	After	No rejection	Nivolumab	13	Tac+MMF+Pred → Tac+everolimus+Pred
DeLeon et al. (2018) [58]	HCC Rec	After	No rejection	Nivolumab x3	2.7	Tac
	Melanoma	After	No rejection	Pembrolizumab x2	5.5	Everolimus, MMF
	HCC Rec	After	No rejection	Nivolumab x4	7.8	Sirolimus, MMF
	HCC Rec	After	No rejection	Nivolumab x5	3.7	Tac
	HCC Rec	After	No rejection	Nivolumab x2	1.2	Tac
Gassmann et al. (2018) [59]	Melanoma	After	Acute rejection	Nivolumab x2	1.1	Sirolimus
	HCC Rec	After	Acute rejection	Pembrolizumab x2	3.1	MMF, Pred
	HCC	After	Cellular rejection	Nivolumab	3	Everolimus
Kuo et al. (2018) [60]	Melanoma	After	No rejection	Ipilimumab then pembrolizumab	5	Tac+MMF+Pred → sirolimus+MMF
Rammohan et al. (2018) [61]	HCC	After	No rejection	Pembrolizumab	3	Tac/sirolimus
De Toni et al. (2017) [62]	HCC Rec	After	No rejection	Nivolumab x15	1	Tac
Friend et al. (2017) [63]	HCC Rec	After	Cellular rejection	Nivolumab	4	Sirolimus 2 mg
	HCC Rec	After	Cellular rejection	Nivolumab	3	Tac 4 mg
Schwartzman et al. (2017) [64]	Melanoma	After	No rejection	Pembrolizumab	20	Tac
Varkaris et al. (2017) [65]	HCC Rec	After	No rejection	Pembrolizumab	8	Tac → 50% reduction dose
Morales et al. (2015) [66]	Melanoma	After	No rejection	Ipilimumab x4	8	Sirolimus 3 mg → 1 mg, MMF → off
Ranganath et al. (2015) [67]	Melanoma	After	No rejection	Ipilimumab	8	Tac

HCC, hepatocellular carcinoma; Rec, recurrence; PR, partial response; OS, overall survival; LUSC, lung squamous cell carcinoma; MMF, mycophenolate mofetil; Pred, prednisone; CR, complete response; POD, postoperative day.

Rejection Risk & Immunosuppression (MV)

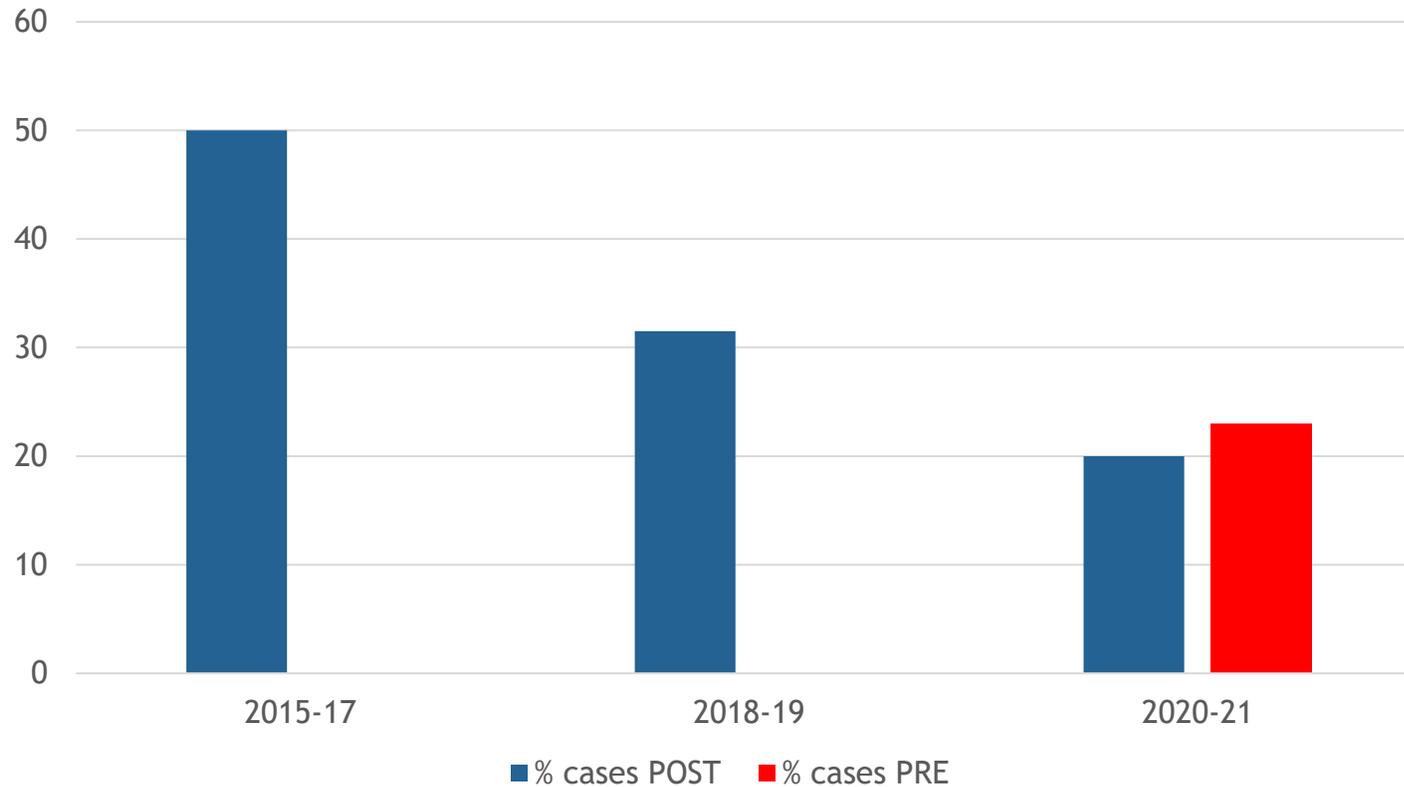


MC KTpl data N=69. mTOR based IS \rightarrow reduced risk ACR
Murakamy N. Kid Int 2021.

Rejection rates over time



% cases reporting rejection



KTp single center 18 patient prospective study: 12% rejection
Carroll R. Lancet 2022

Morales 2015	0/1	
Ranganath 2015	0/1	
Wang 2016	1/1	
Gomez 2016	1/1	
Friend 2017	2/2	
Schwatsman 2017	0/1	
Dueland 2017	1/1	
DeToni 2017	0/1	
Vankaris 2017	0/1	
		5/10 (50%)
Deleon 2018	2/7	
Tio 2018	1/1	
Rammahon 2018	0/1	
Ashwin 2018	0/1	
Gassman 2018	1/1	
Kuo 2018	0/1	
Chen 2019	0/1	
Lee 2019	1/1	
Kondo 2019	0/1	
Dai 2019	0/2	
Bittner 2019	1/1	
Amjad 2019	0/1	
		6/19 26%
Zuang 2020	0/1	
Qui 2020	0/1	
Abdel Wahab 2020	1/1	
Anugwen 2020	0/1	
Braun 2020	1/1	
Owoyemi 2020	2/8	
Pandey 2020	0/1	
Shi 2020	0/5	
AlJamoudi 2020	1/3	
Dengahn 2021	1/1	
Tsung 2021	0/1	
Jin 2022	0/1	
		5/25 (20%)
Tabrizian 2021	1/9	
Chen 2021	1/1	
Qiao 2021	1/7	
Aby 2022	1/1	
Lizao-mayo 2022	0/1	
Schwachal-Epper 2020	0/1	
Nordness 2020	1/1	
Biondani 2018	0/1	
		5/22 23%

Rejection rates Improving over time, Death is still CA

- ▶ N=43/119 liver recipients (same first 24 patients)
- ▶ ACR: 30.2% (13/43) of LTRs (9/24 (37%) in prev review, 4/19 (21%) more recent
- ▶ 2 cases immune hepatitis in all SOT
- ▶ Allograft failure: 9/43, 21% (6/24, 25% previous rev)

Suggests we try to late?

- ▶ probability of rejection decreased as the number of immunosuppressive agents increased (OR, 0.60; 95% CI, 0.36-1.00; P =.05,
- ▶ LTRs, less rejection was seen only with tacrolimus use (17.4% vs 47.4%; OR, 0.23; 95% CI, 0.06-0.95; P=.04)

- N= 47 patients (Chinese and Eng sys rev)
 - median survival time after treatment → 6.5 (0.3~48) mo
 - overall remission rate after ICIs 29.8% (14/47), and case fatality rate 61.7% (29/47).

rejection total, 2021 data -20% reject,

Death largely due to CA.

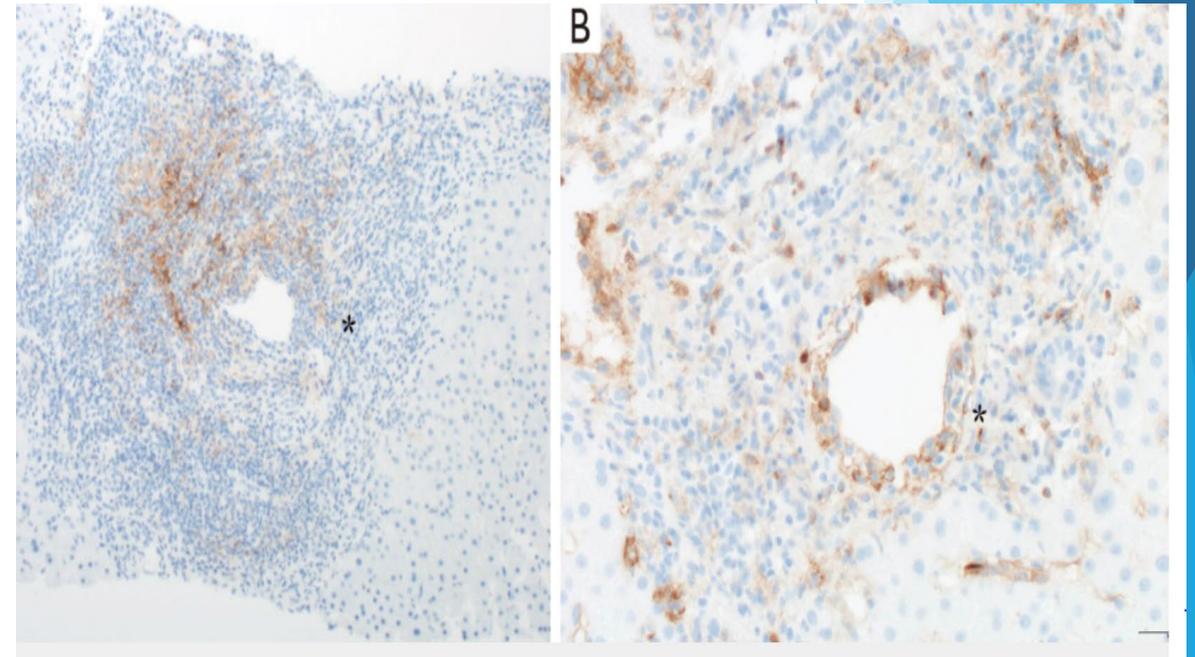
Rejection & PDL-1 Allograft staining

Table 2 Immunotherapy outcomes

ID	Immunotherapy	Line of therapy	RECISTv1.1 response	DOT (months)	PFS (months)	OS (months)	Reason for stopping therapy	Graft rejection	Allograft PD-L1 staining	PD-L1 tumor staining	TILs	Prior sorafenib therapy	Immunosuppressive agent(s) used
1	Nivolumab	3	PD	1.2	2.2	1.2	Progression	No	-	10%	10%	Yes	Tacrolimus
2	Pembrolizumab	2	CR	9.5	21.1*	21.1	Complete response	No	0%	5%	50%	No	Everolimus, mycophenolate mofetil
3	Nivolumab	4	PD	1.1	0.7	1.1	Progression	No	0%	-	-	Yes	Mycophenolate mofetil, sirolimus
4	Nivolumab	5	PD	1.3	1.3	1.3	Progression	No	0%	0%	5-10%	Yes	Tacrolimus
5	Nivolumab	2	-	0.3	-	0.3	Multi-organ failure	No	-	0%	10%	Yes	Tacrolimus
6	Nivolumab	2	-	0.9	-	0.9	Graft rejection	Yes	30%	0%	-	Yes	Sirolimus
7	Pembrolizumab	2	-	0.7	-	0.7	Graft rejection	Yes	25%	-	-	No	Mycophenolate mofetil, prednisone
Median	N/A	2	N/A	1.1	1.8	1.1	N/A	N/A	0%	0%	10%	N/A	N/A

Shi. Liver Transpl 2020:

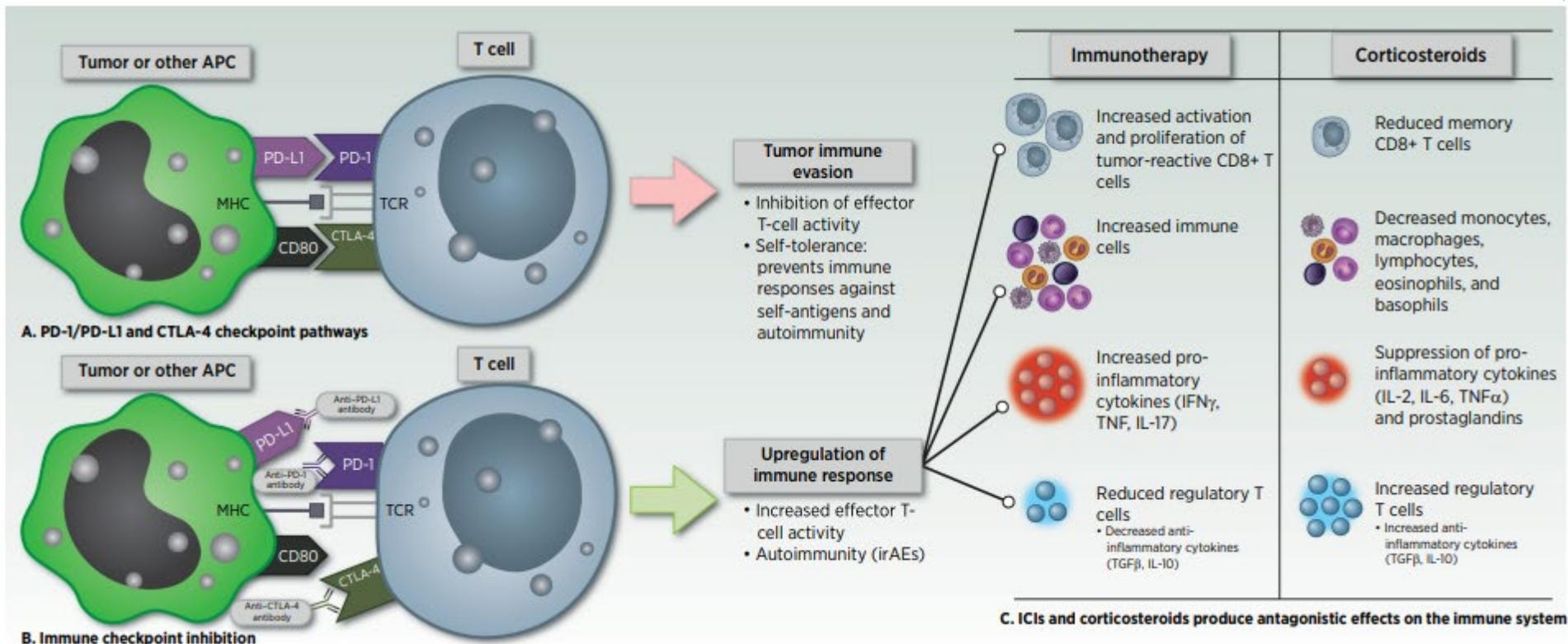
9/18 recHCC patients had no PDL-1 staining on biopsy
5 received ICI - no rejection (by 2 months)



Hepatotoxicity DDx

- ▶ AIH - like (technically DILI)
- ▶ 2-10% within 4-9 weeks
- ▶ ↑ with combo therapy, CTLA-4

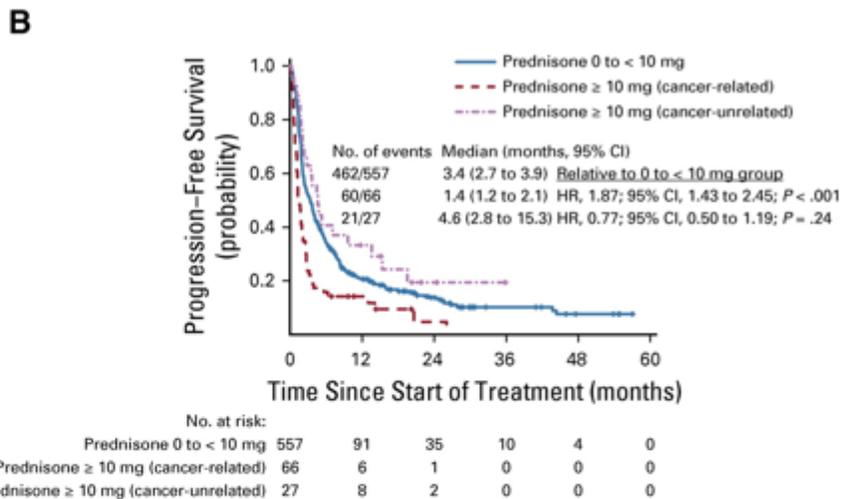
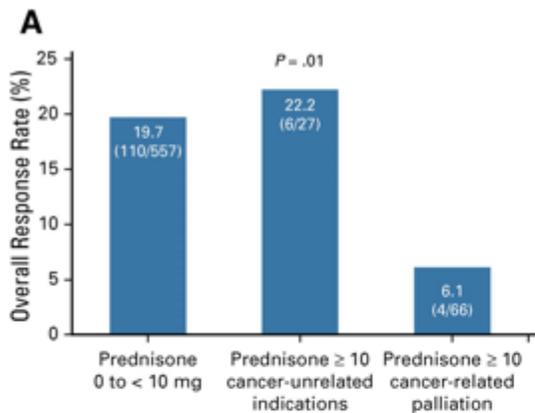
Steroid effects



baseline corticosteroid use (≤ 14 days prior to, and up to 30 days after start ICI) was associated a 23%-47% increased risk of death compared with no use.

low-dose steroids (10 mg/d) at baseline may not

glucocorticoid can enhance PD1 expression and dose dependent manner



Steroid for AE

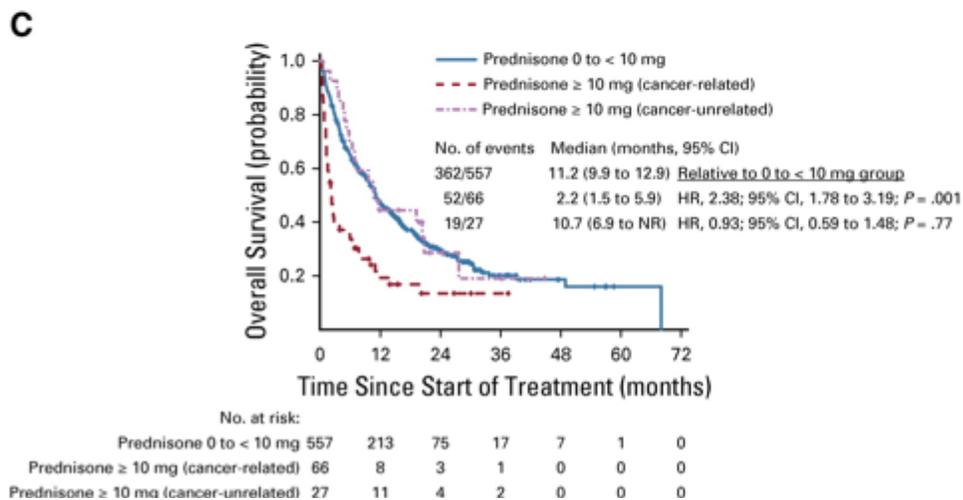


Table 2. Subgroup analysis for overall survival.

Subgroup Analysis	N of Studies/pts	HR (95% CI)	<i>p</i>	I ²	Type of Analysis
Reason for steroid use					
• BSC	3/836	2.5 (1.41–4.43)	<0.01	76%	Random effect model
• BMs	3/1164	1.51 (1.22–1.87)	<0.01	49%	Random effect model
• AEs	9/926	1.08 (0.79–1.49)	0.62	48%	Random effect model

Cancer Response Rates

Table 2. Outcomes of ICI Treatment for the Overall Cohort and Most Common Cancer Types

MV analysis

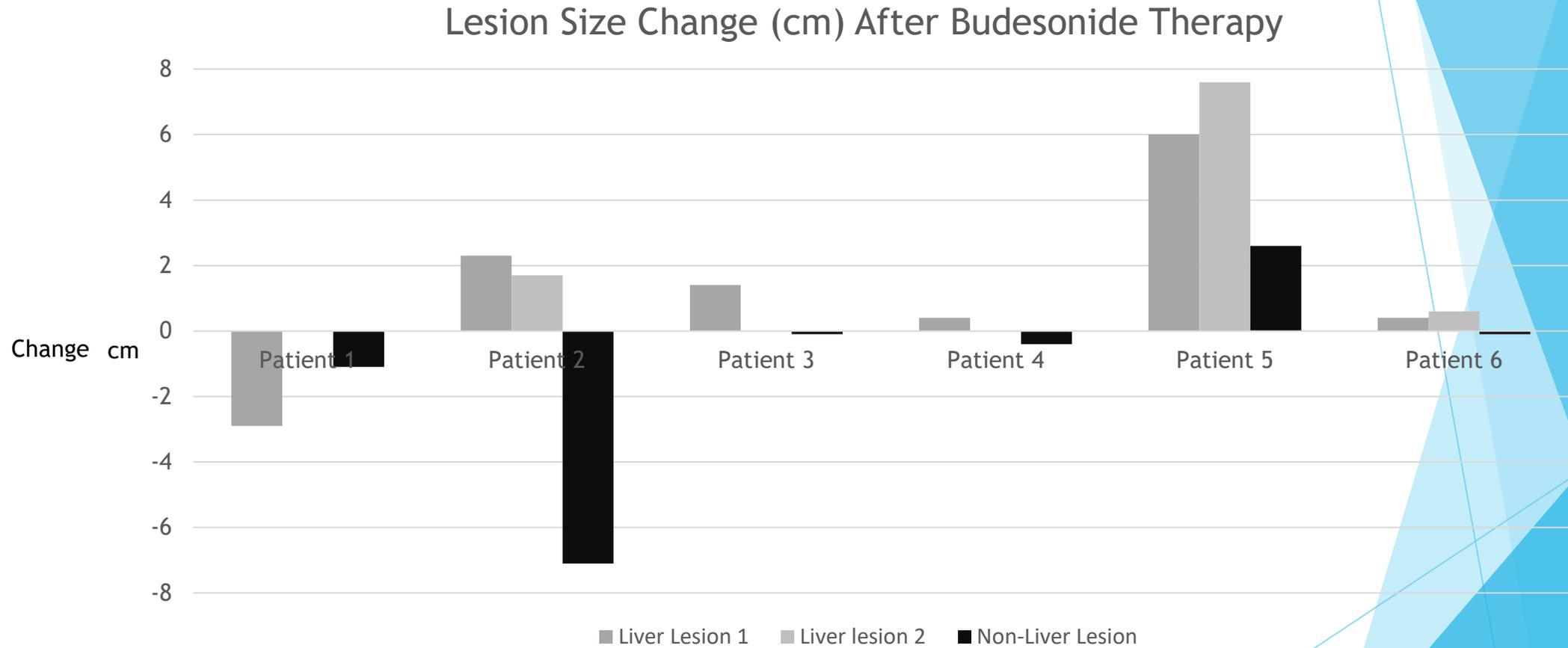
		Overall Cohort n (%)	cMEL n (%)	HCC n (%)	cSCC n (%)
Cancer					
Non-cSCC	97	26 (26.8%)		Ref	
cSCC	22	15 (68.2%)		5.85 (2.15–15.96)	.0006
cMEL	42	15 (35.7%)			
HCC	27	5 (18.5%)			
NSCLC	7	0 (0.0%)			
Tumor PD-L1					
Negative	3	0 (0.0%)		Ref	
Positive	5	4 (80.0%)		Infinite	.14 ^c
History of rejection					
No	79	29 (36.7%)		Ref	
Yes	12	3 (25.0%)		0.57 (0.14–2.30)	.43
Time from txp to ICI, y ^a	92			1.09 (1.02–1.16)	.008

Striking The Balance..

Table 5. Immunosuppressive regimen, graft rejection, and tumor response.

Immunosuppressive regimen	Rate of rejection in %	Median survival time (months)	Rate of disease remission in %	Mortality in %
Single-agent immunosuppressive therapy	38 (7/18)	3 (0.3–48)	17 (3/18)	72 (13/18)
Steroid	100 (2/2)	4 (2–4)	0 (0/2)	100 (2/2)
Sirolimus	60 (3/5)	1.95 (0.9–9)	20 (1/5)	60 (3/5)
Tacrolimus	10 (1/10)	3 (0.3–48)	20 (2/10)	70 (7/10)
Cyclosporine	100 (1/1)	0.6	0 (0/1)	100 (1/1)
Combined immunosuppressive regimen	31 (4/13)	11 (0.7–24)	38 (5/13)	69 (9/13)
2-drug combination	40 (4/10)	8 (0.7–24)	40 (4/10)	70 (7/10)
3-drug combination	0 (0/2)	15	0 (0/2)	100 (2/2)
4-drug combination	0 (0/1)	10	100 (1/1)	0 (0/1)
Total	35 (11/31)	6 (0.3–48)	26 (8/31)	71 (22/31)

Budesonide Role in IS?



SUMMARY

- ▶ All data is retrospective and missing elements
- ▶ IS regimens known in some but not all... but not levels
 - ▶ No data on specific cancer and mTOR vs CNI
- ▶ Publication Bias
- ▶ ALL systematic reviews include the early learning curve which skews the overall rejection rate estimates.

- ▶ **THERE IS NO TRUE DENOMINATOR!**

- ▶ Most
more

REALISTICALLY WEIGH RISK:BENEFIT

DO NOT Exclude ICI option in LTR if best chance to survive



THANK YOU!

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