ICIs Application Before and After Liver Transplant: Where Are We?

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The Liver Transplant Symposium 2023

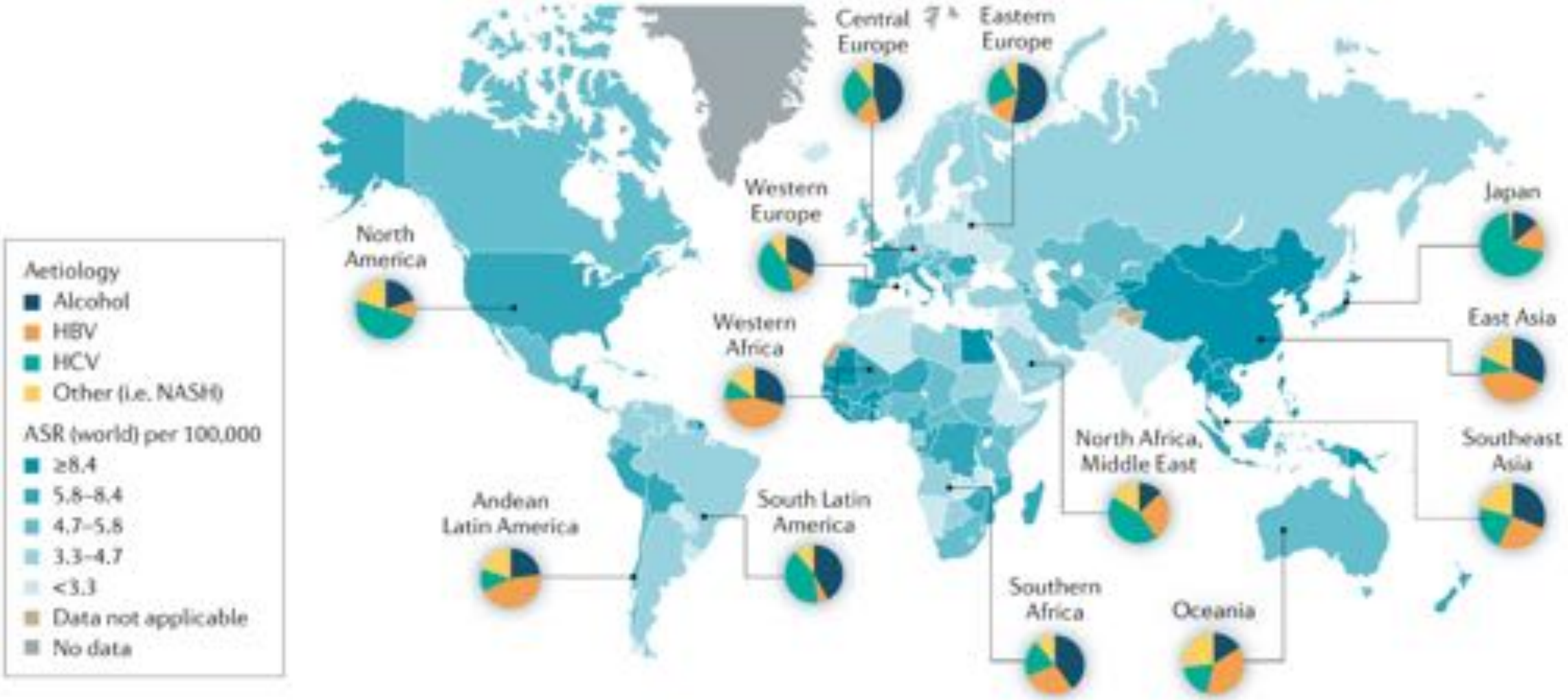
Contents

Section 1

Introduction to ICIs for HCC

Overview of HCC

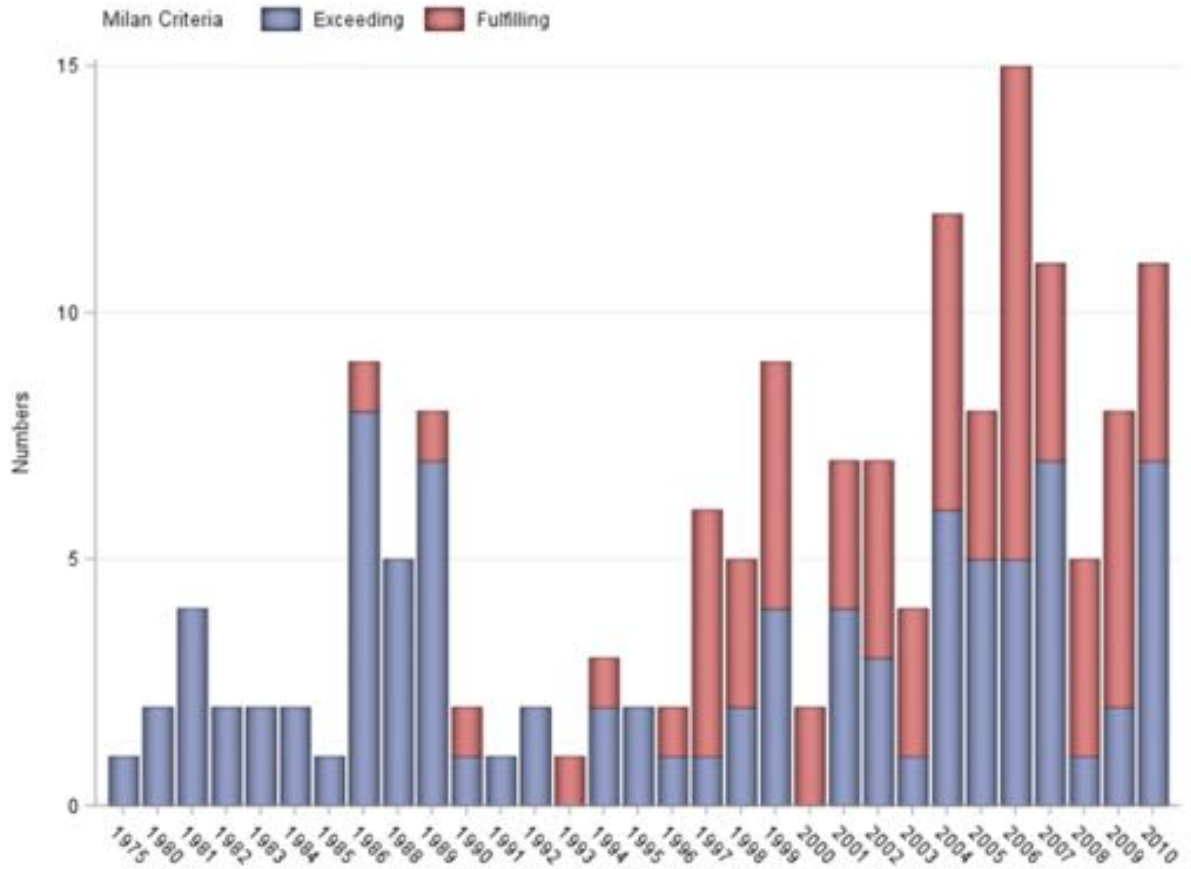
By 2025, hepatocellular carcinoma will affect > 1,000,000 individuals annually

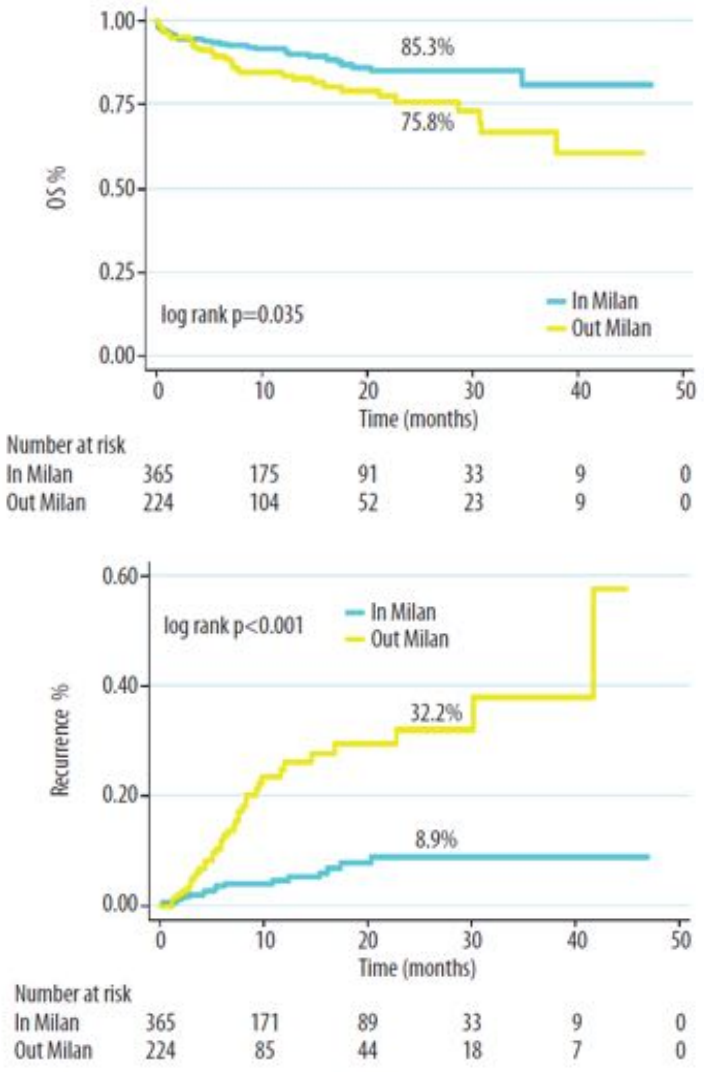


Llovet et al., *Nat Rev Dis Primers,* **2021**, *7*, 6

Overview of HCC

Half of HCC patients exceeded Milan Criteria, leading to poorer LT outcomes.

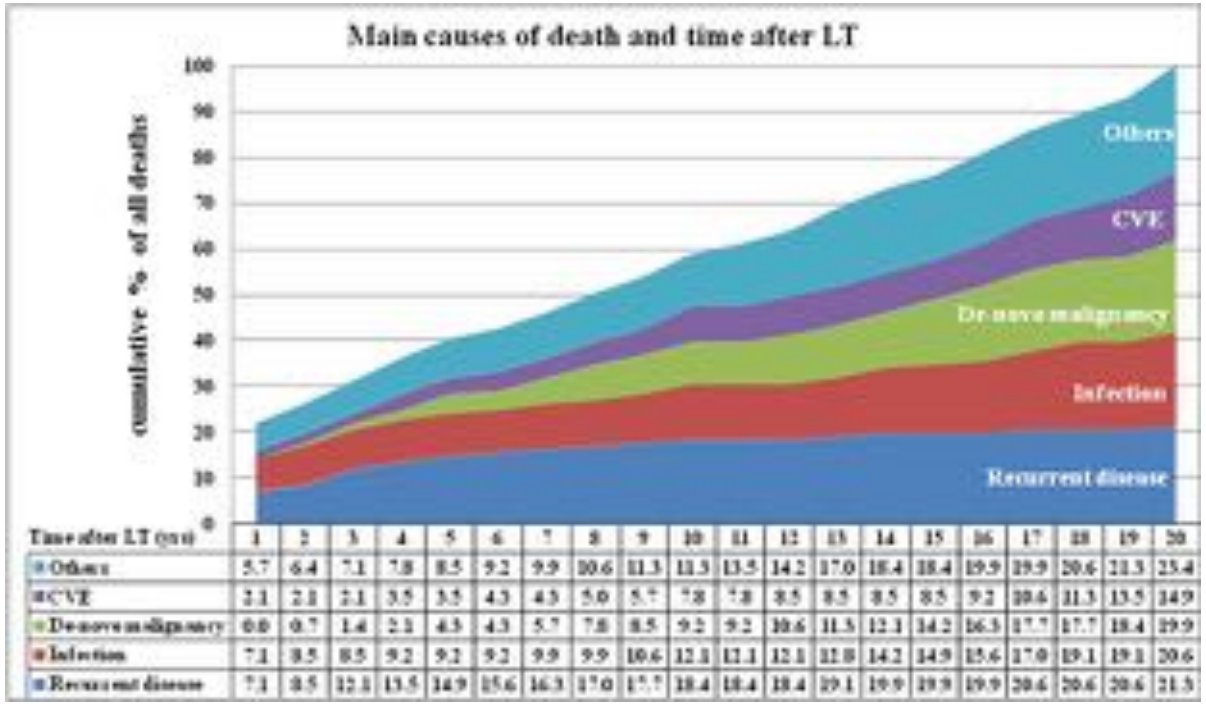


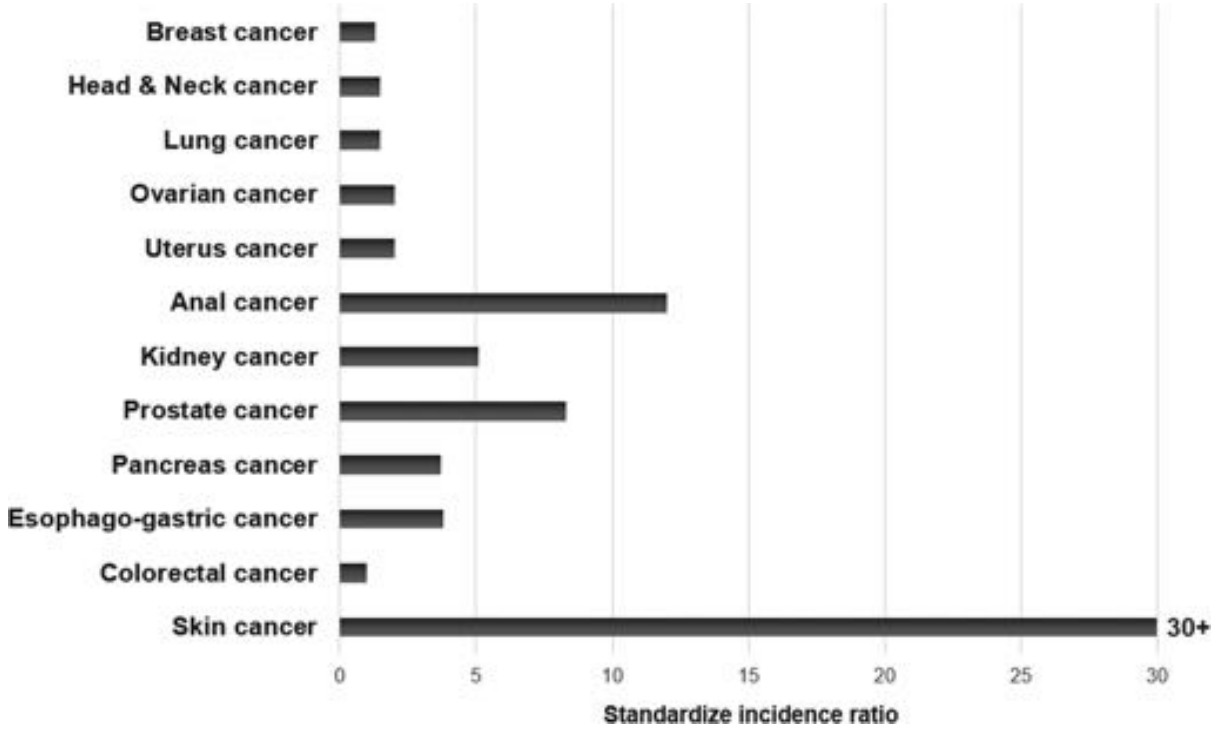


Qu et al., *Langenbecks Arch Surg*, **2018**, *403*, 643
Schoening et al., *Am J Transplant.*, **2013**, *13*, 2384

Overview of HCC

Patients also suffer from HCC recurrence and/or *de novo* malignancies after LT

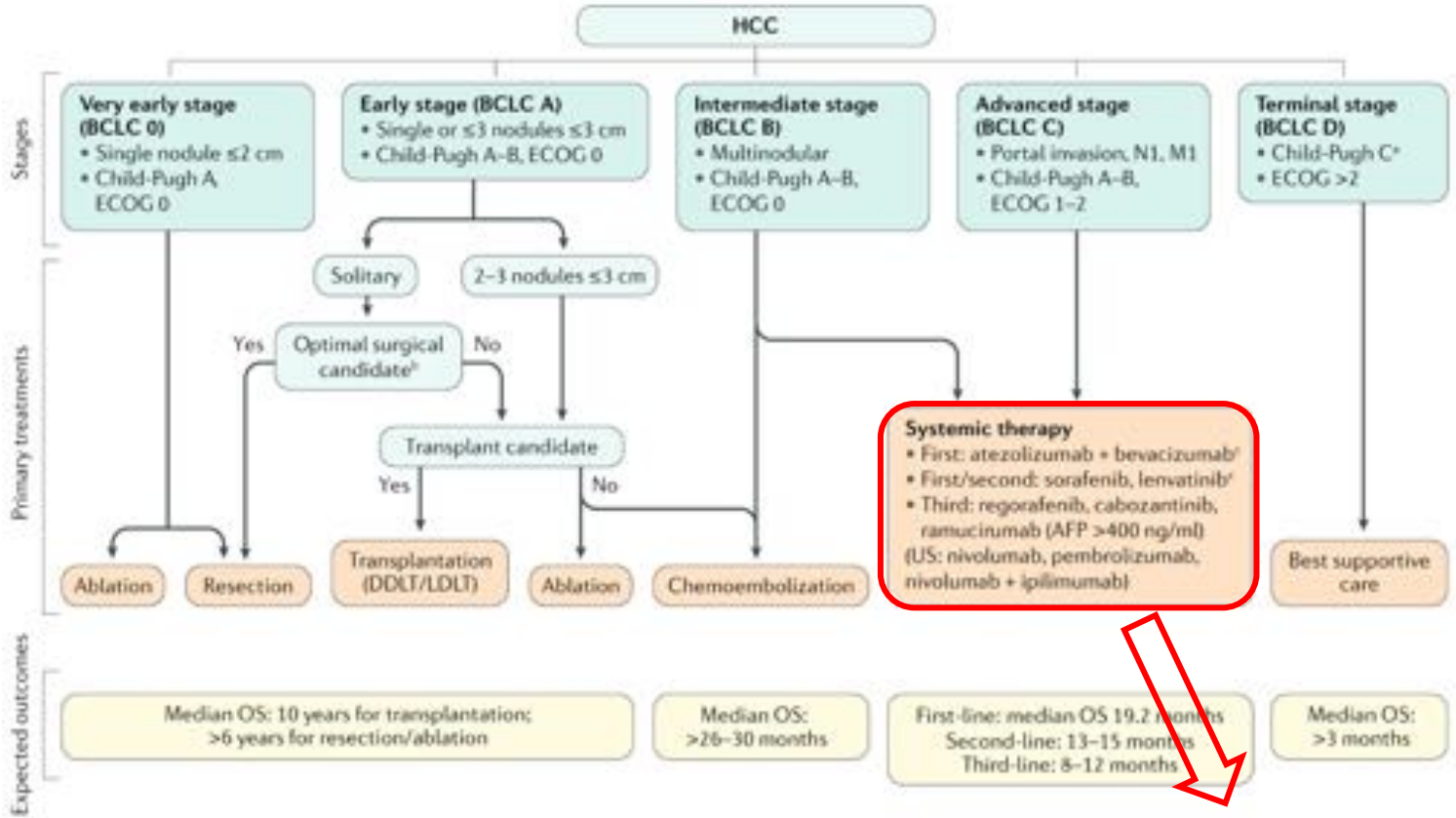




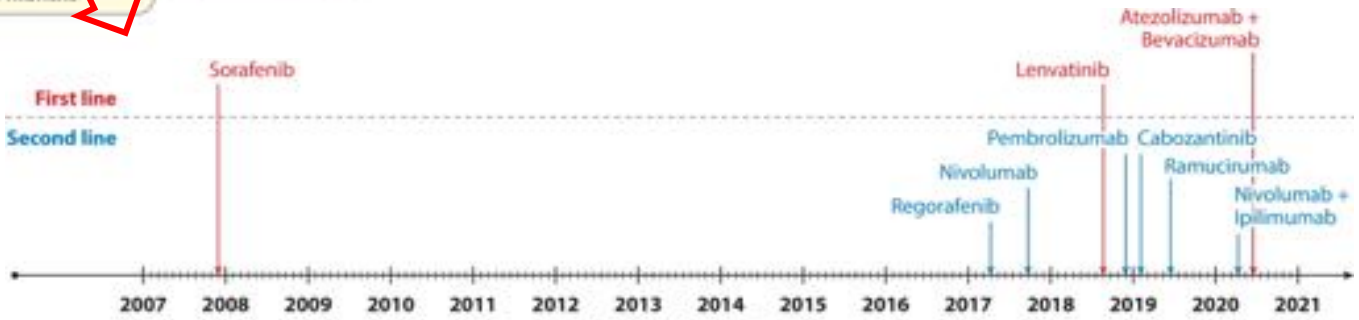
Peri-transplant management of HCC as well as other malignancies are necessary

Colmenero et al., *Transplantation.*, **2022**, 106,30

Systemic Treatment of HCC



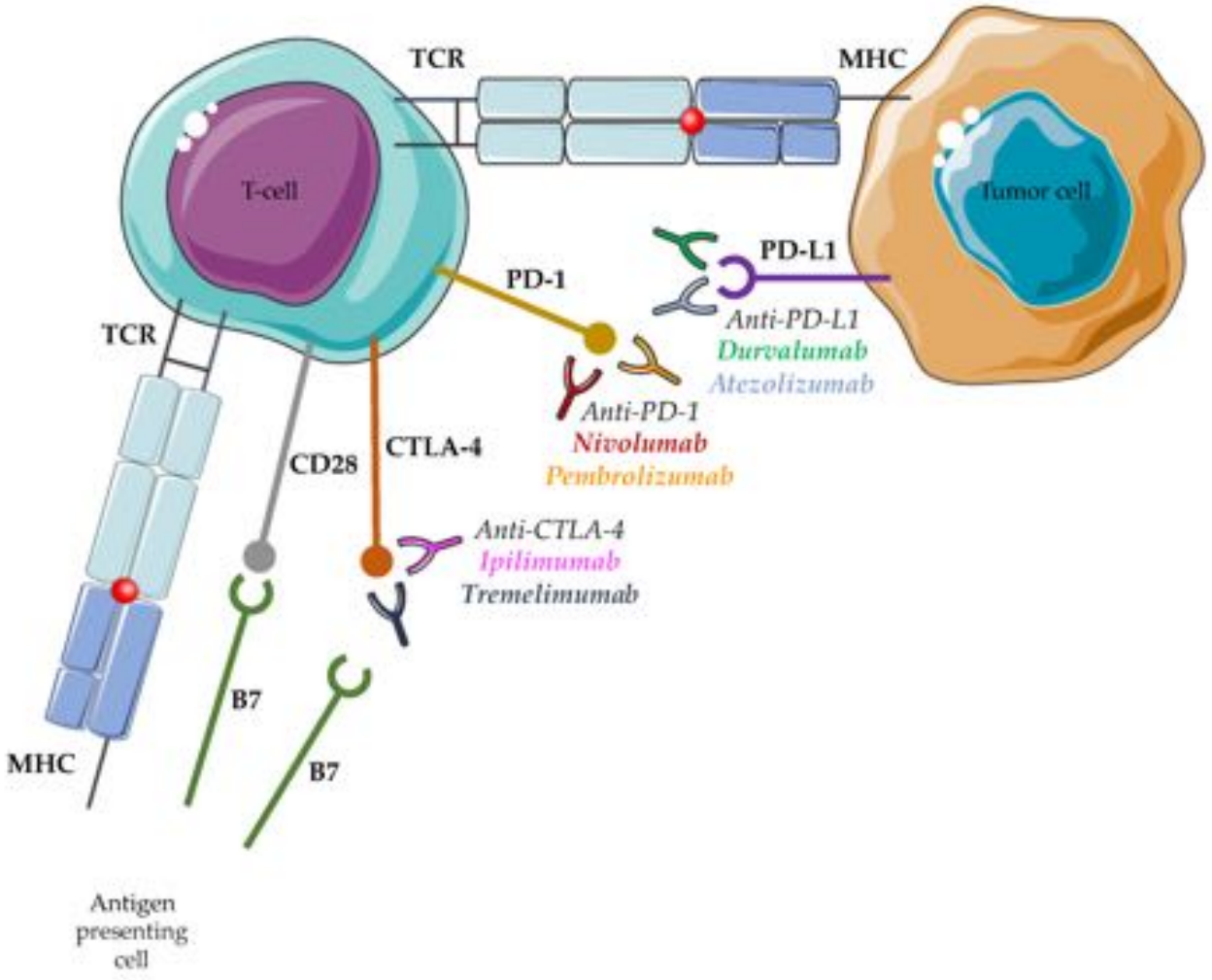
Treatment strategy of HCC



Timeline of FDA-approved HCC systematic treatment

Llovet et al., *Nat Rev Dis Primers*, **2021**, *7*, 6
Sperandio et al., *Annu. Rev. Med.*, **2022**, *73*, 267

Mechanisms of ICIs



Up-to-date FDA Approved ICIs in HCC

Drug	Target	Apv. Dat.	Usage
Nivolumab	PD-1	2017	2nd line
Pembrolizumab	PD-1	2018	2nd line
Ipilimumab	CTLA-4	2020	2nd line (combo. Nivolumab)
Atezolizumab	PD-L1	2020	1st line (combo. Bevacizumab)
Tremelimumab	CTLA-4	2022	2nd line
Durvalumab	PD-L1		

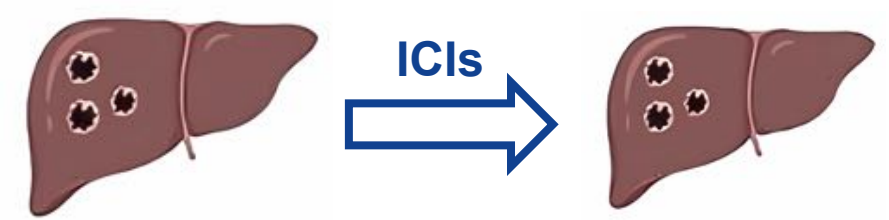
Psilopatis et al., *Int. J. Mol. Sci.*, **2023**, *24*, 2685.

Combining Liver Transplant with ICIs

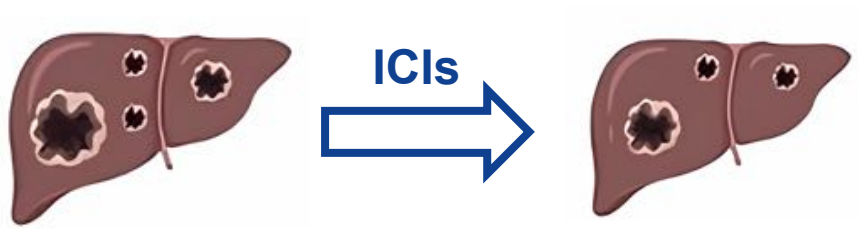
ICIs exhibited promising prospects in the peri-transplant management of HCC

☐ Scheme 1:

Pre-operative use of ICIs to help HCC patients meet the Milan Criteria



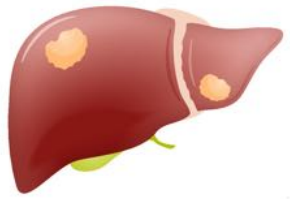
Bridging Therapy



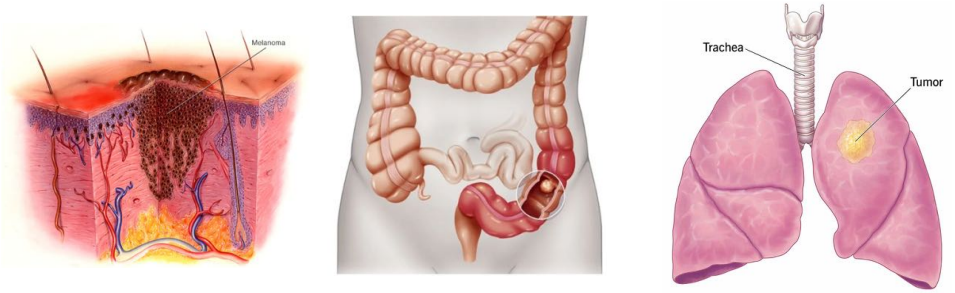
Downstage Therapy

☐ Scheme 2:

Post-operative use of ICIs to manage recurrent and/or *de novo* malignancies



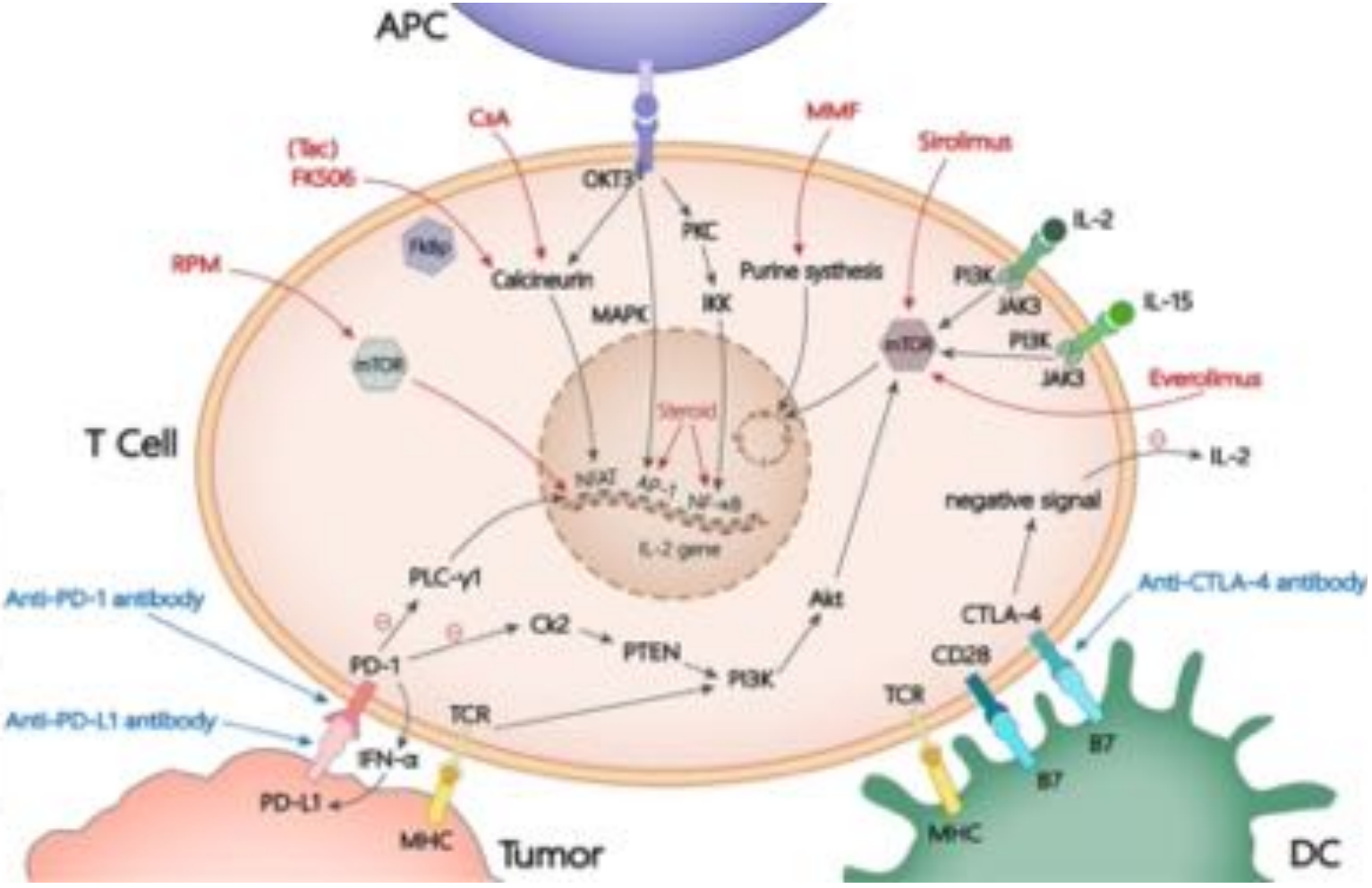
HCC Recurrence



***De novo* Malignancies**

Combining Liver Transplant with ICIs

Safety and **Efficacy** needs to be evaluated for the peri-transplant use of ICIs



Immunosuppressants
to protect from rejection

ICIs
for anti-tumor immunotherapy

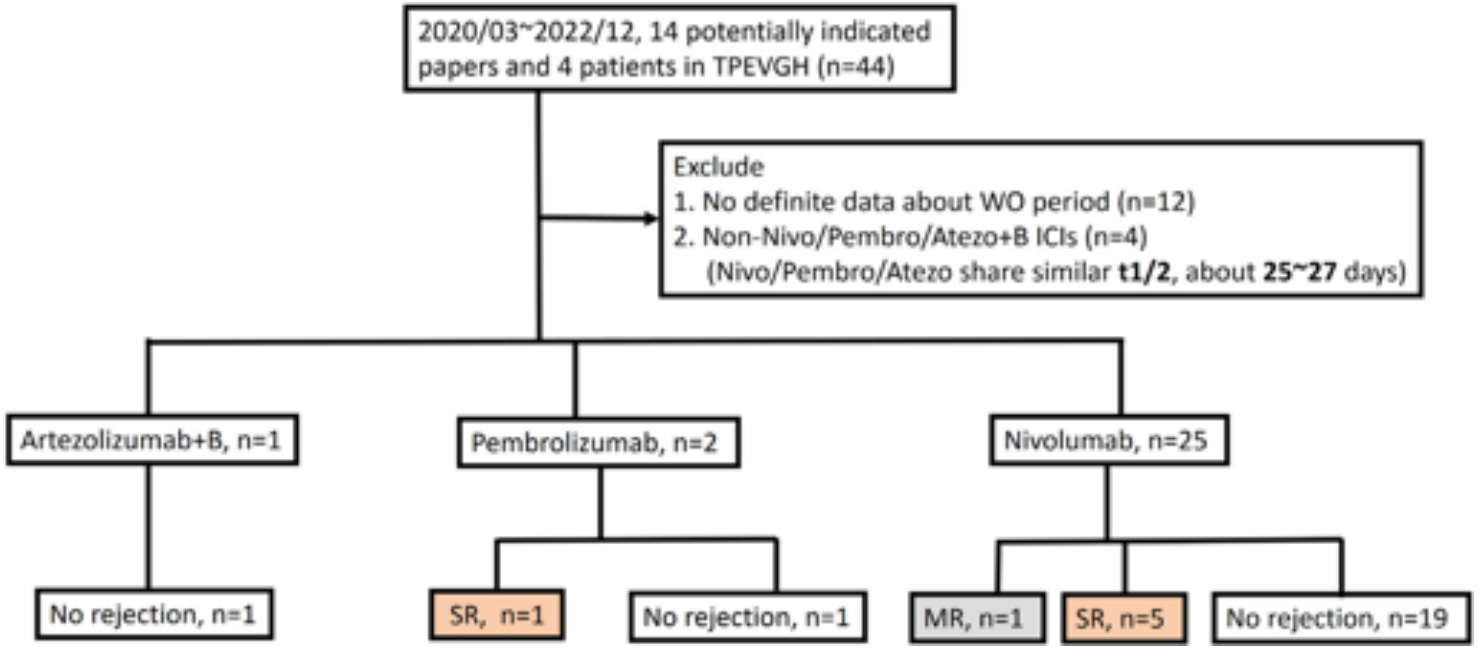
Gu et al., *Chin J Cancer Res*, **2023**, *35*, 92

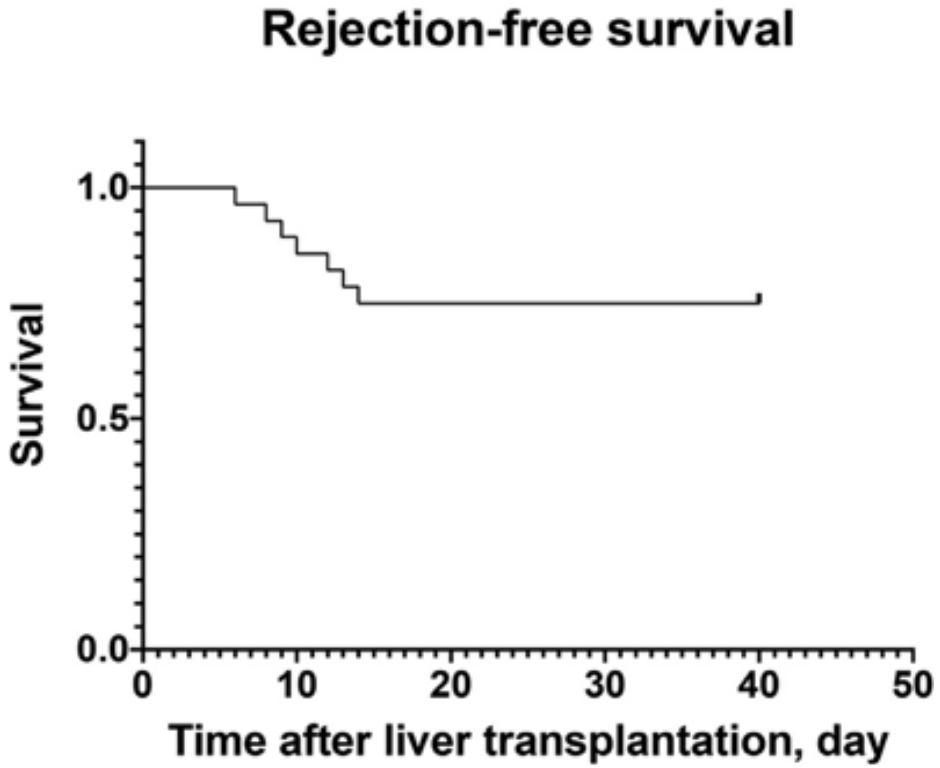
Section 2

ICIs as Neoadjuvant Therapy of HCC *Before* Liver Transplantation

Safety: Allograft Rejection (AR)

7 out of 44 (15.9%) patients who received pre-LT ICIs had AR





Kuo et al., *Transplantation Proceedings*, **2023**, *55*, 878

Safety: Allograft Rejection (AR)

Most of the rejection patients (6/7) can be rescued by adjusting immunosuppressant regimens and/or re-transplantation

	Status	Induction	Regimen	WO tme	BPAR time	Management	Result	Reference
1	SR	MTP 500 mg	Nivolumab	8 d	6 d	MTP/rATG	Death	Am J Transplant. 2020;20:879–883
2	MR	MTP 500 mg	Nivolumab	22 d	NA	Increase Tacrolimus level	Alive	Am J Transplant. 2021;21:1979–1980
3	SR × 2	MTP (NA)	Nivolumab	35 d	12/16 d	1. MTP/rATG/PE/IVIG 2. MTP	Re-Tx, alive	Clin J Gastroenterol. 2021;14:1718–1724
4	SR	MTP 1000 mg	Nivolumab	35 d	12 d	MTP/rATG/PE/IVIG	Re-Tx, alive	Am J Transplant. 2022;22:1699–1704
5	SR	MTP 1000 mg, rATG 3 mg/kg	Nivolumab	10 d	14 d	MTP/rATG/ Rituximab/IVIG	Alive	Am J Transplant. 2022;22:1699–1704
6	SR	MTP (NA)	Nivolumab	16 d	9 d	MTP/rATG	Alive	Transplant Direct. 2022;8:e1304
7	SR	MTP 500 mg	Pembrolizumab	30 d	13 d	MTP/PE	Alive	TPEVGH

BPAR, biopsy-proven acute rejection; IVIG, intravenous immunoglobulin; MR, mild rejection; MTP, methylprednisolone; PE, plasma exchange; rATG, rabbit antithymocyte globulin; SR, severe rejection; TPEVGH, taipei veterans general hospital; Tx, transplant; WO, washout.

Kuo et al., *Transplantation Proceedings*, **2023**, *55*, 878

Efficacy: Response Rate and Recurrence

- **67%~71% patients had at least partial remission (PR) to neoadjuvant PD-1 blockade**
- **8.3% patients had tumor recurrence after LT**

Reference	*n*	ICIs	Recurrence
Schwacha-Eipper et al., 2020	1	Nivolumab	No
Chen et al., 2021	5	Nivolumab	2/5, Yes
Kang et al., 2021	1	Pembrolizumab	No
Sogbe et al., 2021	1	Durvalumab	No
Tabrizian et al., 2021	9	Nivolumab	No
Lizaola-Mayo et al., 2021	1	Ipilimumab+ Nivolumab	No
Abdelrahim et al., 2022	1	Atezolizumab	No
Schnickel et al., 2022	5	Nivolumab	No

On-going Trial:NCT04425226

Title	Safety and Efficacy Study of Pembrolizumab in Combination With LENvatinib in Participants With Hepatocellular Carcinoma (HCC) Before Liver Transplant as Neoadjuvant TherapY--PLENTY Randomized Clinical Trial
Outcome	Recurrence-Free Survival (RFS) Objective Response Rate (ORR) Disease Control Rate (DCR) Adverse Event (AE)
Status	Done Recruiting
Sponsor	Renji Hospital

Qiao et al., *Front. Immunol*, **2021**, *12*, 653437

Efficacy: Response Rate and Recurrence

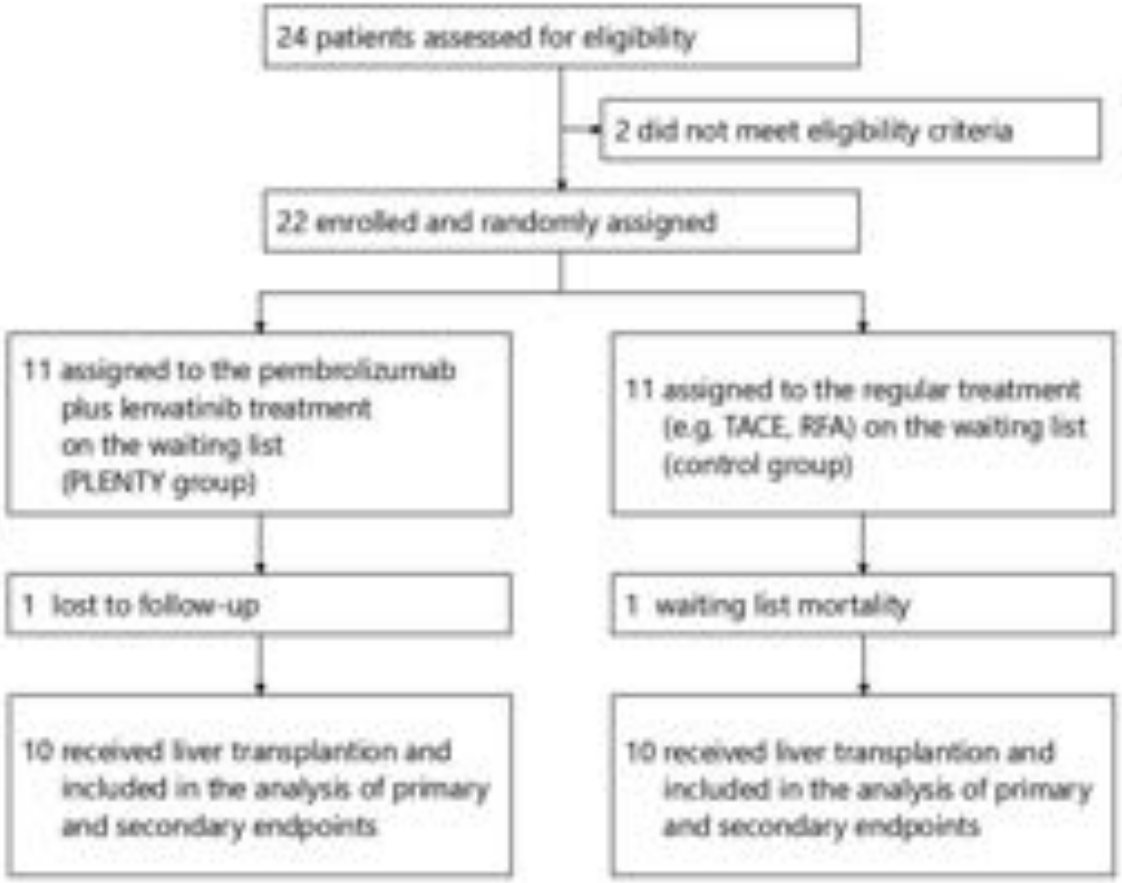


Figure 1. Overview of the trial

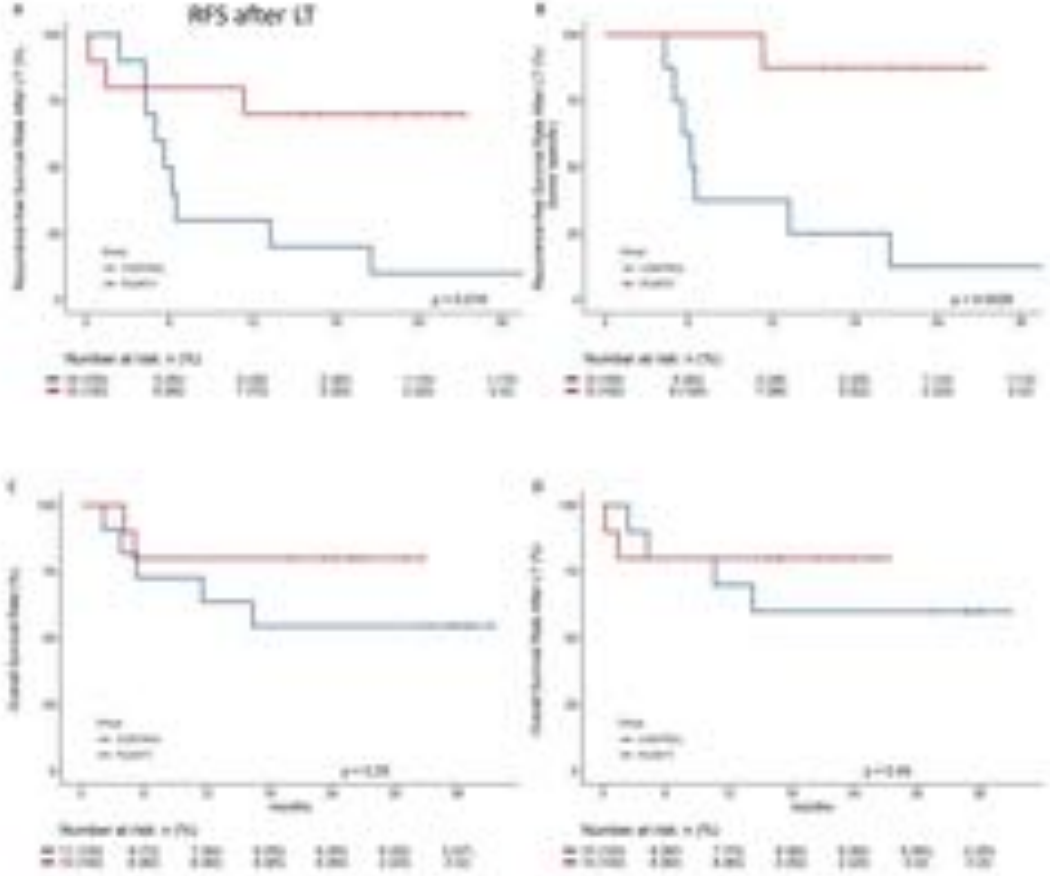


Figure 2. Survival and recurrence outcomes

Feb. 3rd, 2020-Sep. 5th, 2021

EASL 2023,
Poster, TOP-051

Efficacy: Response Rate and Recurrence

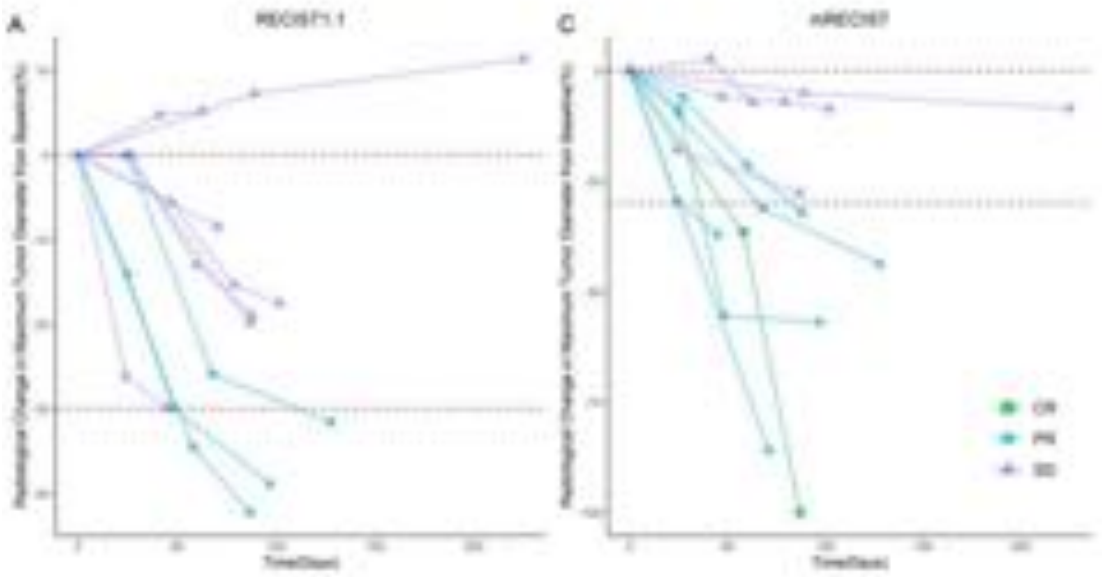


Figure 3. Spider plot showing tumor responses

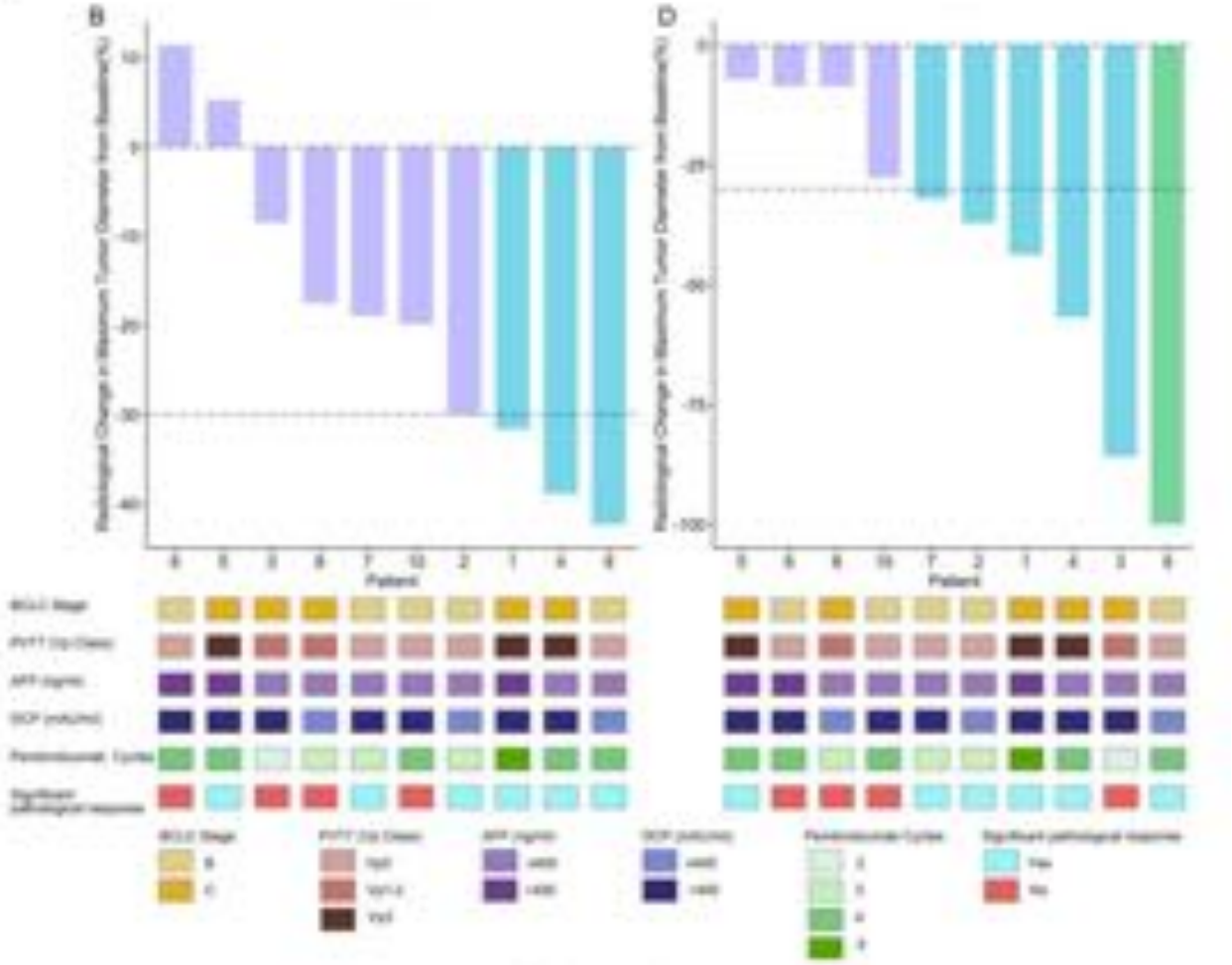


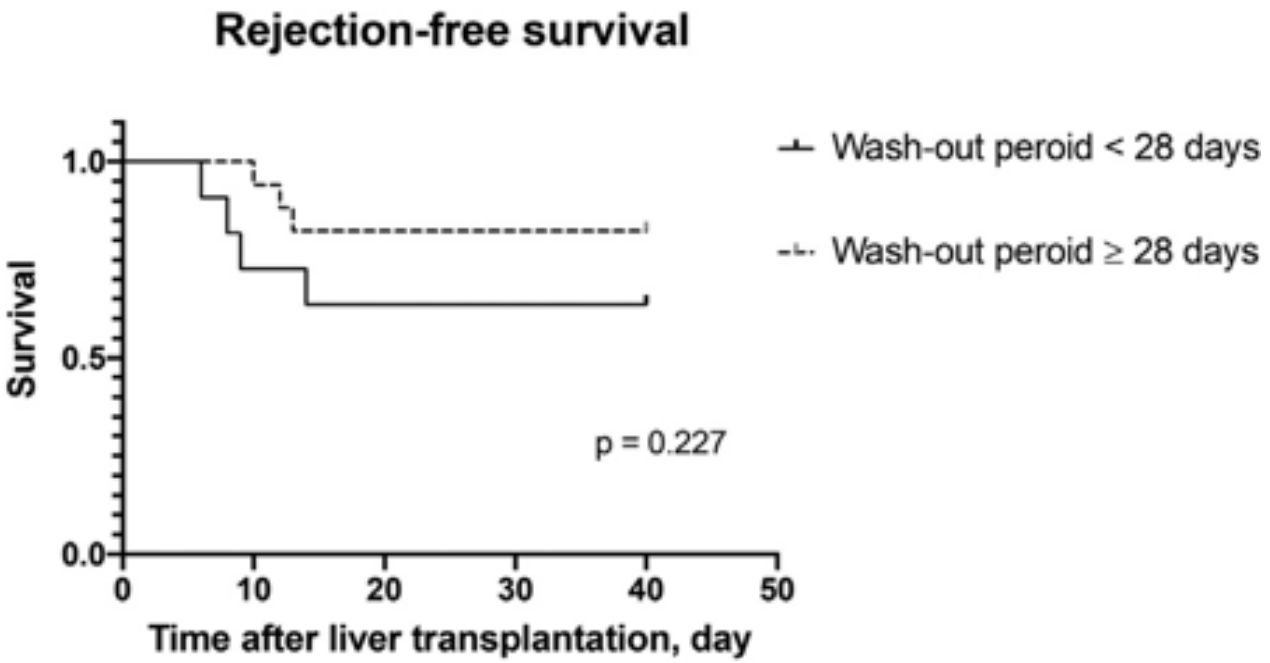
Figure 4. Waterfall plot showing tumor responses

- No AR occurred in either group
- No grade 4 or 5 AE
- Grade 3 AE: 30%

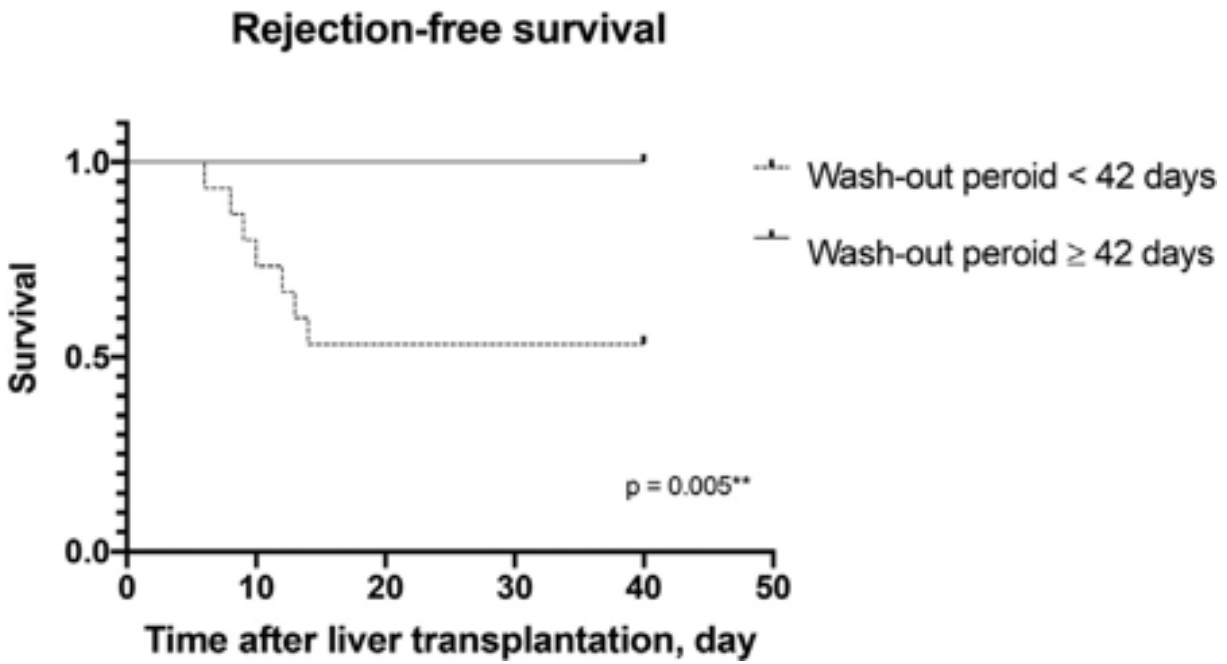
EASL 2023,
Poster, TOP-051

Peri-Transplantation Management

- **Prolonged interval between last ICI and LT decreased the risk of rejection**



RFS showed **no difference** for an interval of 28 d



RFS showed **significant difference** for an interval of 42 d

We suggest the interval between last ICI dose and LT more than 42 days (1.5 × half-life of ICIs)

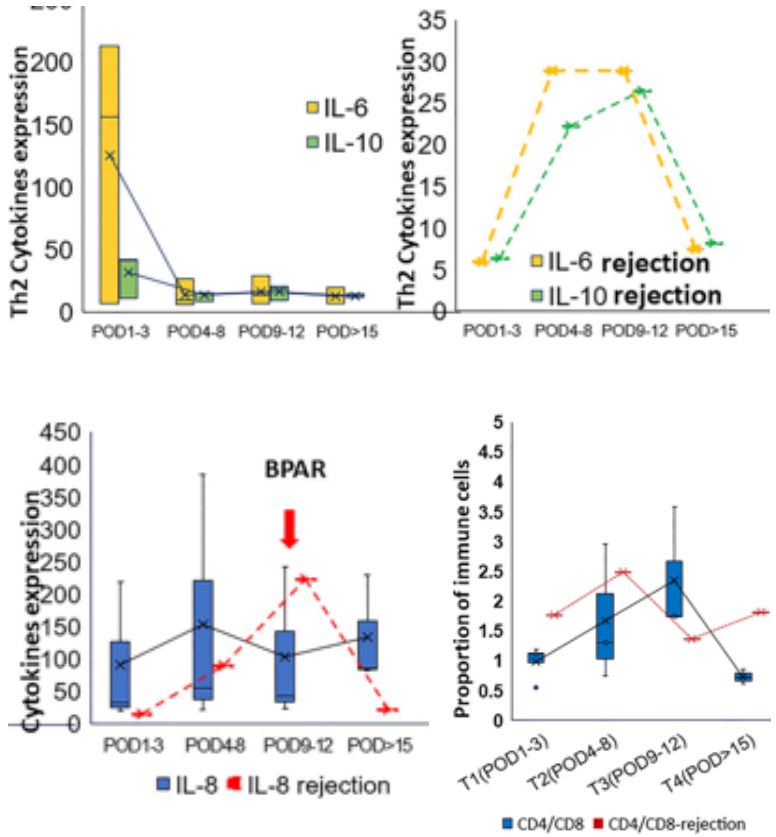
Kuo et al., *Transplantation Proceedings*, **2023**, *55*, 878

Peri-Transplantation Management

- **Early detection** of allograft rejection improves treatment outcome

- Allograft PD-L1 expression (biopsy)
- CD4/CD8 ratio in lymph node
- IL-6
- IL-8
- IL-10
- etc.

May be the immunological biomarkers for predicting rejection



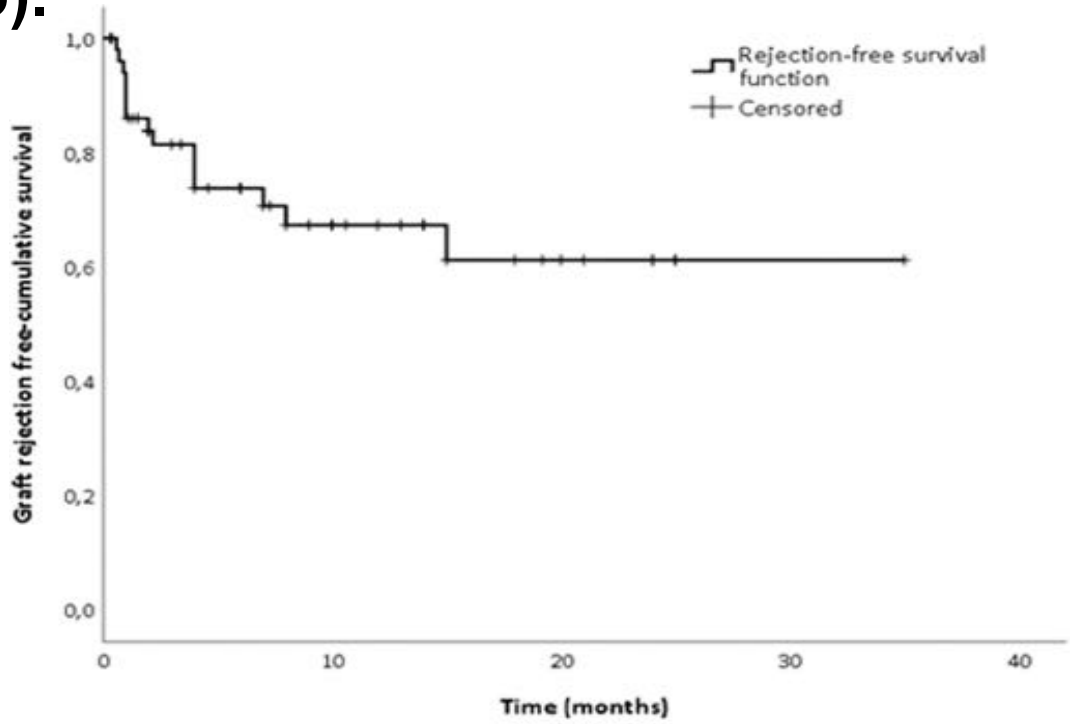
Qiao et al., *Front. Immunol*, **2021**, *12*, 653437

Section 3

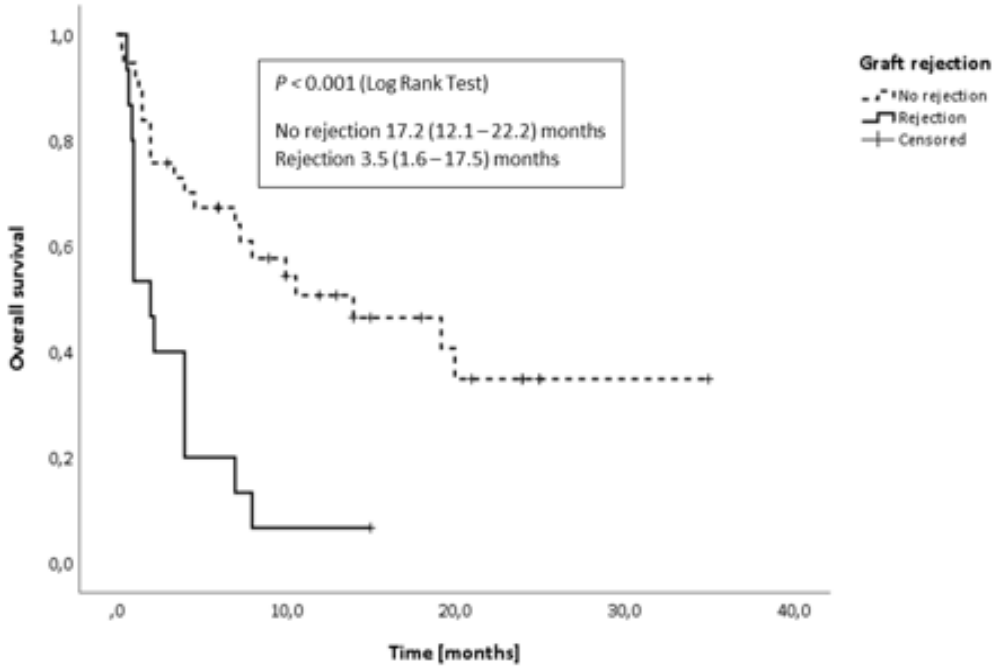
ICIs for Malignancies *After* Liver Transplantation

Safety: Allograft Rejection (AR)

Acute graft rejection occurred in 15 out of 52 (28.8%) patients who received post-LT ICIs, resulting in poorer OS (3.5 (1.6–17.5) mo *vs* 17.2 (12.1–22.2) mo).



Time (Month)	0	5	10	15	20	25	30	35
N° at Risk	52	27	17	10	6	2	2	0



Time (Month)	0	5	10	15	20	25	30	35
Non-responder (n = 37)								
N° at Risk	37	24	16	9	6	2	1	0
Responder (n = 15)								
N° at Risk	15	3	1	0	0	0	0	0

Kayali et al., *Liver Int.*, **2022**, *43*, 8

Safety: Allograft Rejection (AR)

ICIs-related allograft rejection can be fatal

Overall ICIs	Organ of transplant rejection No		No of death	Percentage
Nivolumab ($n = 96$)	Kidney	54	20	37.74%
	Liver	20	16	80.00%**
	Heart	5	1	20.00%
	Lung	1	1	100.00%
	NA	16	2	12.50%
	Total	96	40	41.67%*
Pembrolizumab ($n = 41$)	Kidney	24	5	21.74%
	Liver	7	4	57.14%**
	Heart	1	0	0.00%
	NA	9	0	0.00%
	Total	41	9	21.95%*
Cemiplimab ($n = 7$)	Kidney	5	2	40%
	NA	2	0	0.00%
	Total	7	2	28.57%
Avelumab ($n = 1$)	Kidney	1	0	0.00%
	Kidney	5	2	40.00%
Ipilimumab ($n = 6$)	Liver	1	0	0.00%
	Total	6	2	33.33%
Nivolumab + Ipilimumab ($n = 8$)	kidney	8	0	0.00%
Pembrolizumab + Ipilimumab ($n = 7$)	Kidney	5	1	20%
	NA	2	0	0.00%
	Total	7	1	14.29%
Pembrolizumab + Nivolumab ($n = 2$)	Kidney	2	0	0.00%
	Total	168	54	32.14%

*$p < 0.05$, the total percentage of death of Nivolumab is higher than that of Pembrolizumab.; **$p < 0.05$, the percentage of death of liver transplant rejection is higher than that of kidney transplant rejection.

- **71.4%** of patients who had ICI-related AR were caused **death**, according to Cui et al. through the search of FAERS database.
- Median time **from ICI initiation to AR** was 12 (5–45) days, according to Luo et al.

Cui et al., *Cancer Medicine*, **2023**, *12*, 5181
Luo et al., *World J Gastrointest Oncol*, **2022**, *14*, 163

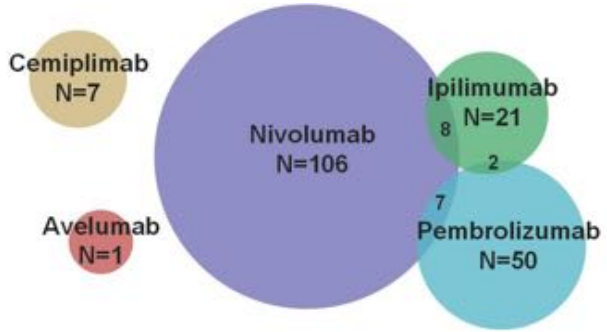
Risk Factors of ICIs-Related AR

- **With limited evidences, PD-1 inhibitors exhibited higher rejections risks**

Target Category	Drug	No. of Patients	No. of Rejections	Rejection Rate
PD-1	Nivolumab	20	7	8/28
	Pembrolizumab	6	1	
	Camrelizumab	1	0	
	Toripalimab	5	0	
PD-L1	Atezolizumab	2	0	0/2
CTLA-4	Ipilimumab	5	1	1/5

Jiang et al., *Front. Immunol.*, **2023**, *14*, 1092401
Abboud et al., *Cancers*, **2023**, *15*, 1433

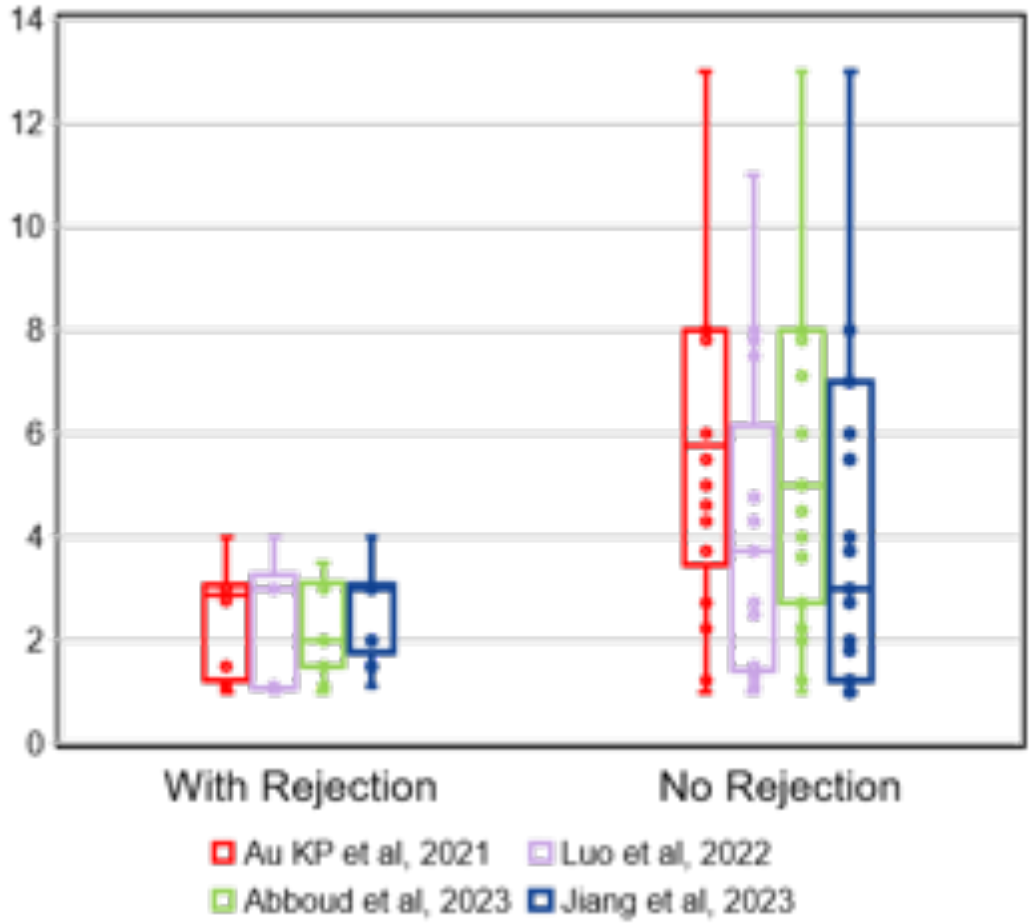
Similar conclusion was drawn by Cui et al in the study of SOTRs.



Cui et al., *Cancer Medicine*, **2023**, *12*, 5181

Risk Factors of ICIs-Related AR

- **Longer interval since LT is probably associated with lower risks of AR**



Ref.	*n*	LT–ICI interval (Rejection) (yrs)	LT–ICI interval (No Rejection) (yrs)	*p*
Au KP *et al*	28	2.9 (1.2–3.1)	5.3 (2.7–8.0)	0.02
Luo *et al*	29	2.5 ± 1.2	4.0 ± 2.5	0.191
Abboud *et al*	35	2 (1.4–3.2)	4.55 (2.33–7.95)	*
Jiang *et al*	41	2.52	4.65	*

Au KP et al., *World J Gastrointest Surg*, **2021**, *13*, 1267
Luo et al., *World J Gastrointest Oncol*, **2022**, *14*, 163
Abboud et al., *Cancers*, **2023**, *15*, 1433
Jiang et al., *Front. Immunol.*, **2023**, *14*, 1092401

Risk Factors of ICIs-Related AR

- **Higher allograft PD-L1 expression level indicated higher risk of rejection**

No	Graft PD-L1 Status	Rejection	Time to Rejection
1	+	Yes	2.5 weeks
2	+	Yes	1 week
3	0%	No	-
4	0%	No	-
5	30%	Yes	0.9 months
6	0%	No	-
7	25%	Yes	0.7 months

All the 4 **PD-L1 (+) recipients** occurred ICIs-related rejection, while the **PD-L1 (-)** recipients did **not**.

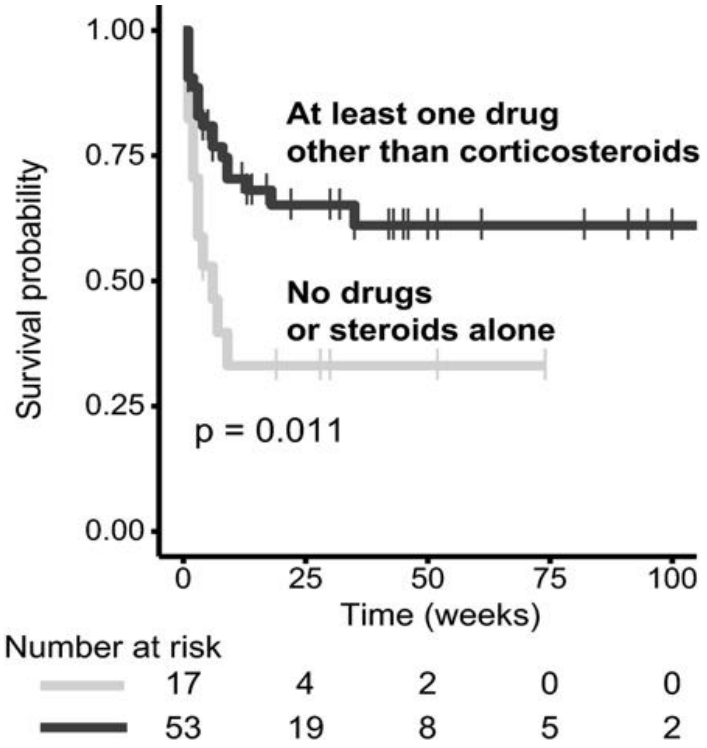
Abboud et al., *Cancers*, **2023**, *15*, 1433

Risk Factors of ICIs-Related AR

☐ Immunosuppressant regimens may affect the occurrence of AR

Baseline regimes before ICI initiation

Immunosuppressant	Allograft Rejection (%)	Tumor Response (%)	Median OS (months)
All patients	*15/38 (40%)*	*15/32 (47%)*	
Prednisone (≤10 mg/d)	7/9 (78%)	5/8 (63%)	5.8 (0.75–19)
mTOR inhibitors	2/3 (67%)	1/2 (50%)	**7.3 (1.3–10.0)**
Calcineurin inhibitors	**1/9 (11%)**	2/8 (25%)	3.8 (1–26.7)
Combination therapy	**5/17 (29%)**	**7/14 (50%)**	3.2 (1–17.0)



Abdel-Wahab et al., *Journal for ImmunoTherapy of Cancer*, **2019**, *7*, 106
Gargas et al., *Am J Transplant.*, **2020**, *20*, 2457

Safety: Other Side Events

Patients reporting at least 1 irAE—n (%)	15 (18.1)	
Dermatitis	4	
Pneumonitis	3	
Colitis	3	
Hepatitis	3	
Constitutional symptoms	2	
Autoimmune hemolytic anemia	1	
Arthralgia	1	
Diarrhea	1	
Infusion reaction	1	
Pruritus	1	
Thyroiditis	1	
Frequency of irAE depending on CPI regimen—n (%)		
Anti–PD-1/PD-L1	10/61 (16.4)	
Anti–CTLA-4	4/13 (30.8)	$P = .460$
Combination	1/9 (11.1)	
Frequency of irAE depending on immunosuppression—n (%)		
Corticosteroids	10/50 (20.0)	$P = .772$
Calcineurin inhibitors	4/34 (11.8)	$P = .257$
mTOR inhibitors	8/30 (26.7)	$P = .146$
Antimetabolites	4/21 (19.0)	$P = 1$
At least 1 drug other than corticosteroids	12/64 (18.8)	$P = 1$
Modification of immunosuppressive regimen before CPI use	8/36 (28.6)	$P = .730$

Other immune-related adverse events (**irAEs**), such as:

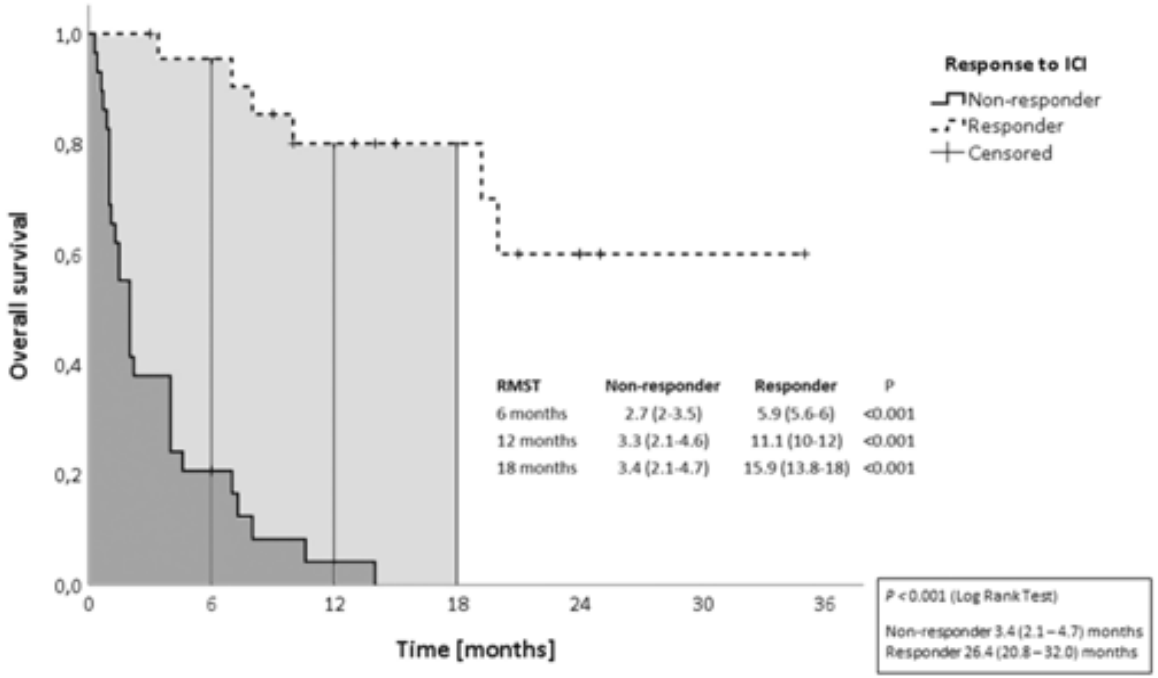
- biliary stricture,
- grade 1/2 transaminitis,
- chills,
- fatigue,
- fever,
- etc.

may occur, but are **neither ICI-specific nor immunosuppressant-specific.**

Gargas et al., *Am J Transplant.*, **2020**, *20*, 2457

Efficacy: Tumor Response and Survival

23/52 (DCR: 44.2%) patients responded to ICIs, resulting in better outcomes



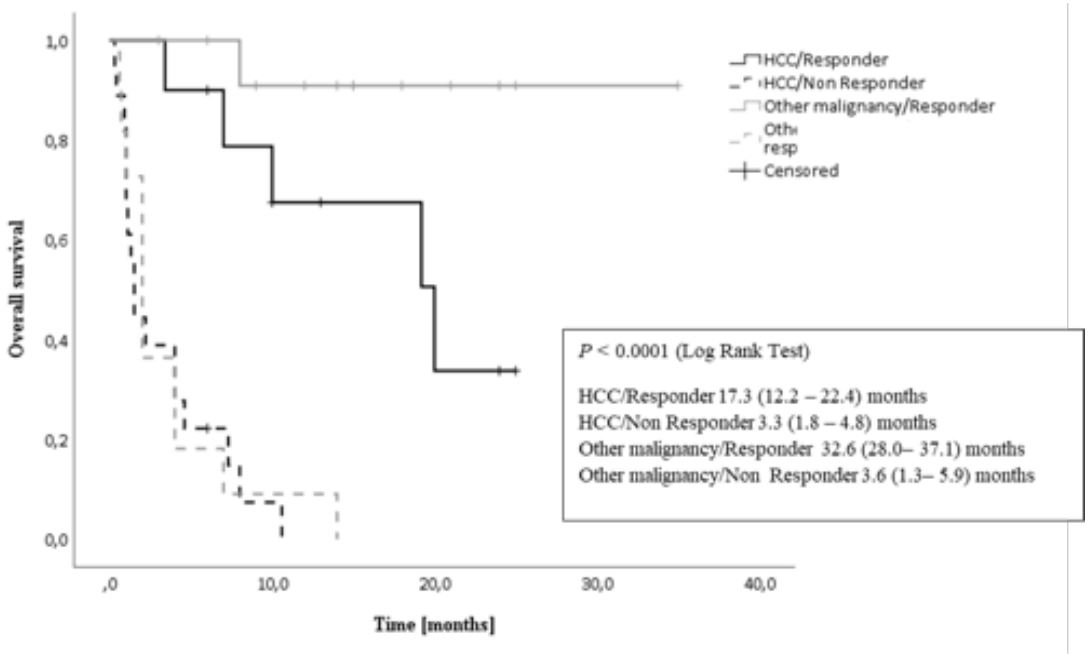
Time (Month)	0	5	10	15	20	25	30	35
Non-responder (n = 29)								
N° at Risk	29	6	2	0	0	0	0	0
Responder (n = 23)								
N° at Risk	23	21	15	10	6	2	1	0

Outcome	Non-responders (*n*=29)	Responders (*n*=23)	*p*
OS (months)	2.0 (1.0–4.0)	14.0 (8.0–21.0)	<0.0001
PFS (months)	0 (0–0)	11.0 (4.0–18.0)	<0.0001
Early Mortality	9 (31.0%)	0	0.006
Death	28 (96.6%)	6 (26.1%)	<0.0001

Kayali et al., *Liver Int.*, **2022**, *43*, 8

Influence Factors of ICI Efficacy

- The efficacy of ICIs showed **no significant difference** between the treatment of recurrent HCC and *de novo*/other malignancies



Parameters	Non-responders n = 29	Responders n = 23	p
Gender (male)	22 (75.9)	18 (78.3)	.838
Age (years)	63 (53–66)	59 (54–65)	.599
Therapeutic approach (n)	3 (2–4)	3 (2–4)	.674
LT to ICI treatment (years)	3 (1–5)	6 (4–11)	.003
Time from cancer diagnosis to ICI (months)	15.0 (5.0–20.0)	8.5 (4.0–18.0)	.584
Death	28 (96.6)	6 (26.1)	<.0001
Early mortality	9 (31.0)	0 (0)	.006
Overall survival (months)	2.0 (1.0–4.0)	14.0 (8.0–21.0)	<.0001
Progression-free survival (months)	0 (0–0)	11.0 (4.0–18.0)	<.0001
Graft rejection (present)	14 (48.3)	1 (4.3)	.001

- **Longer interval between LT and ICI initiation** resulted in higher response rate

Kayali et al., *Liver Int.*, **2022**, *43*, 8

Influence Factors of ICI Efficacy

☐ **The efficacy showed no difference between 3 types of ICIs**

	PD-L1 inhibitors	CTLA-4 inhibitors	PD-1 inhibitors				*p*	
	Atezolizumab/ Bevacizumab	Ipilimumab	Cemiplimab	Pembrolizumab	Nivolumab	Total	*p*	
n	1	5	2	15	29	46		
Response	1 (100%)	4 (80%)	1 (50%)	9 (60%)	8 (28%)	18 (39%)	0.070	0.114
OS (months)	10.0	13.0 (9.0–14.0)	5.0 (2.0–8.0)	8.0 (3.0–19.2)	3.4 (1.3–7.3)	4.3 (1.5–12.0)	0.214	0.216
PFS (months)	6.0	4.0 (3.0–5.0)	0 (0–0)	7.2 (0–12.4)	0 (0–3.0)	0 (0–9.2)	0.207	0.475
Death	1 (100%)	1 (20%)	2 (100%)	7 (47%)	23 (79%)	32 (70%)	**0.027**	0.066

Kayali et al., *Liver Int.*, **2022**, *43*, 8

Decision on Post-LT Use of ICIs

Risks and benefits of ICIs should be carefully evaluated for post-LT patients

		Immunological risk: High	Immunological risk: Low
		LT performed <12 months ago. Young women, autoimmune disease, preformed or *de novo* DSA, previous episodes of rejection, baseline altered transaminases, elevated transient elastography or subclinical rejection in the liver biopsy.	LT performed >12 months ago. Older patients without DSA and persistently normal transaminases. Absence of fibrosis in trasient elastrography and/or liver biopsy.
Oncological benefit: High	Advanced stage unresectable tumours in which ICIs are the first-line systemic agents showing a meaningful benefit in survival and quality of life in well-designed RCT. Absence of a second therapeutic line with acceptable efficacy and safety.	**Prescription of ICI with extreme caution** Strict surveillance of liver tests and early withdrawal of ICI even with mild alterations, followed by liver biopsy and steroids.	**Prescription of ICI allowed** Regular follow-up including frequent transaminases testing. Management of liver side effects according to the algorithm provided.
Oncological benefit: Low	ICIs have not demostrated superiority in terms of survival and quality of life compared with other therapeutic options in well-designed RCT. Second line therapy available with comparable efficacy. Patients with poor performance status (ECOG ≥2) or severe comorbitties.	**Prescription of ICI strongly discouraged** Consider alternative therapies or palliative care as appropriate.	**Consider alternative therapies or palliative care as appropriate**

Decision table suggested by Montano-Loza *et al.*

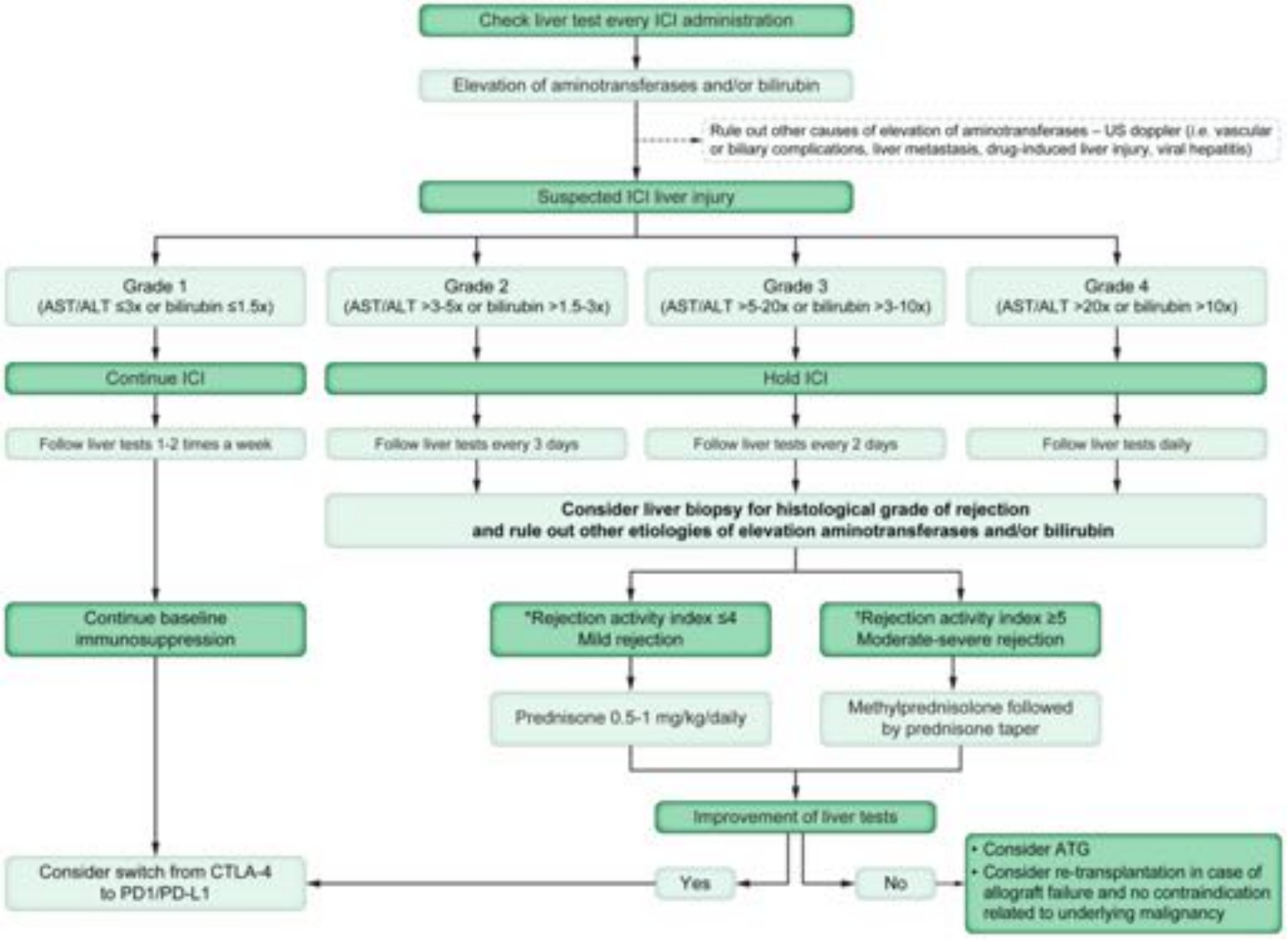
We suggest:

- ➢ **Assessment of allograft biopsy**
- ➢ **Longer interval since LT is favored**
- ➢ **A rational and dynamic combination of ICIs and immunosuppressants**

Montano-Loza et al., *J Hepatol.*, **2023**, *78*, 1199

Management of Post-LT Use of ICIs

Diagnosis and treatment algorithm for liver toxicity secondary to ICIs, suggested by Montano-Loza et al.



Despite most of the ICI-related AR were cellular mediated,

- ➢ **High dose of steroids**
- ➢ **Plasmapheresis**
- ➢ **Antithymocyte globulin**
- ➢ **Infliximab**

may also help the treatment.

Luo et al., *World J Gastrointest Oncol*, **2022**, *14*, 163
Montano-Loza et al., *J Hepatol.*, **2023**, *78*, 1199

On-going Clinical Trials

Further research are in urgent need for the better evaluation and guidance of the use of ICIs for malignancies after LT.

NCT03966209	
Title	Evaluation of PD-1 Inhibition in Patients With Recurrent Hepatocellular Carcinoma After Liver Transplantations
Design	Single Group Assignment
Status	Recruiting
Sponsor	Shanghai Zhongshan Hospital

NCT04564313	
Title	Clinical Study of Anti-PD-1 Antibody Camrelizumab in the Treatment of Recurrent Hepatocellular Carcinoma After Liver Transplantation
Design	Single Group Assignment
Status	Recruiting
Sponsor	Third Affiliated Hospital, Sun Yat-Sen University

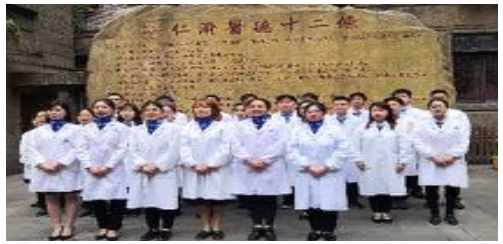
NCT04425226	
Title	Pembrolizumab and LENvatinib in Participants With Hepatocellular Carcinoma (HCC) Before Liver Transplant
Design	Parallel Assignment
Status	Done Recruiting
Sponsor	RenJi Hospital

Sum-Up

1. ICIs are promising neoadjuvant therapy in patients undergo LT.

2. Safety and efficacy of ICI should be carefully evaluated in LT patients, balancing tumor response and allograft rejection.

3. Larger scale of clinical trials are in urgent need for better explicit of risk factors, predictive biomarkers and management strategies for the ICI use in peri-LT patients.



Thank You