NUHS Liver Transplant Symposium : 23 Sep 2023

Systemic (Chemo)therapy for HCC recurrence Post -liver transplantation

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Disclosures

- **Lecture/ Speaker fees:** AstraZeneca, Bristol-Myers Squibb, Eisai, Amgen, Roche, Merck, MSD
- **Consultancy / advisory role:** AstraZeneca, Eisai, Ipsen, Merck Sharp & Dohme, Roche, Guardant, Astellas
- Travel: Taiho, AZ, BMS

Case study

- 65y Chinese male with Hep B
- Stage 2 HCC in June 2013 s/p Resection
- Sep 2013: Recurrence in liver – s/p TACE then Y90-RE
- s/p liver transplant in China Jan 2014

==========

June 2014: Multiple HCC in both lobes of liver : largest lesion 1.6cm > 6 lesions

s/p TACE x 2- progression of cancer in liver

CP A5 , Creatinine normal

ECOG 0

Recent OGD: no oesophageal varices

What would you do next?

1) Y90 radioembolization
2) Start atezolizumab + bevacizumab
3) Start lenvatinb or sorafenib
4) Start cytotoxic chemotherapy

HCC Recurrence after Liver Transplant

- Recurrences are systemic (“mets from liver”) even when confined to liver
- Patients are in an immuno-compromised state (immunosuppressive therapy)
- Liver graft needs to be maintained (enough immunosuppression to avoid graft rejection)
- Survival of post-LT HCC recurrence is dismal and significantly worse than relapse after resection (median OS around 12 mo *vs* nearly 2 years in transplanted and resected patients, respectively), and immunosuppression is a potential driver of such a difference

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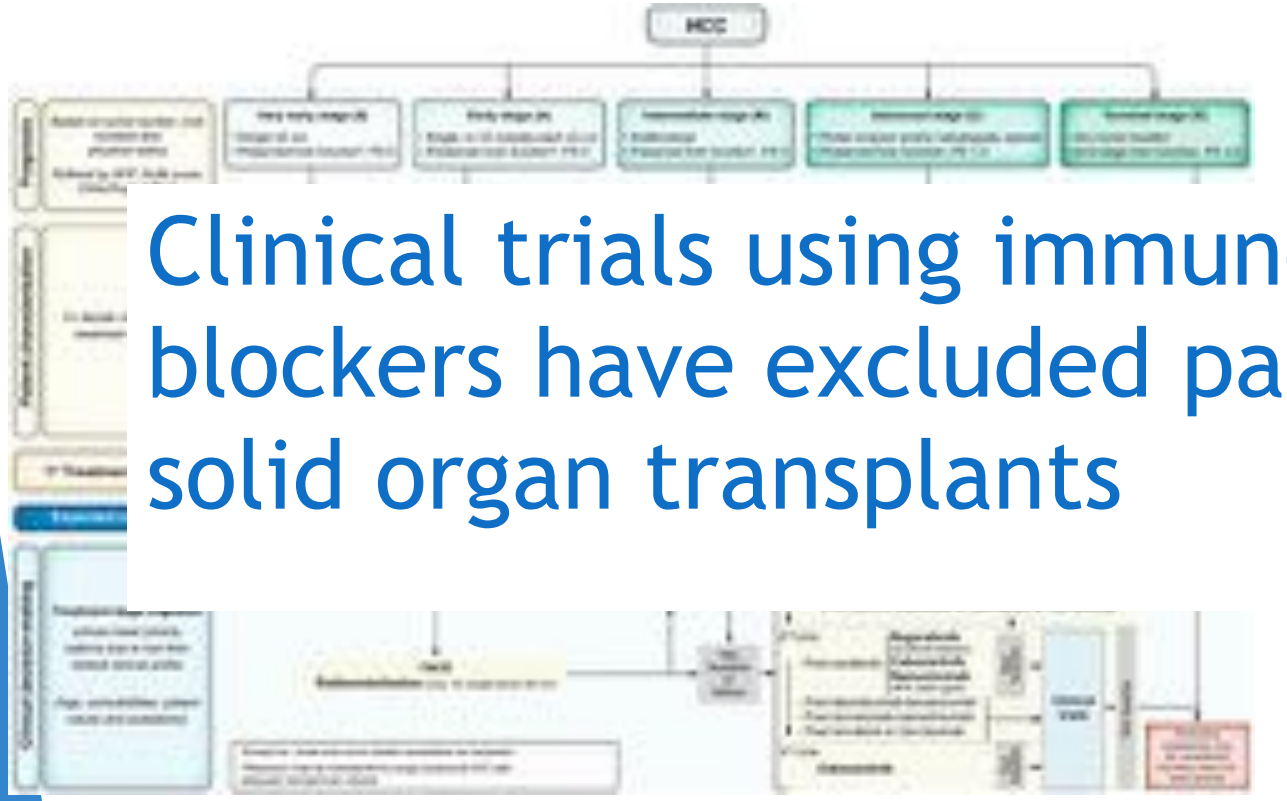
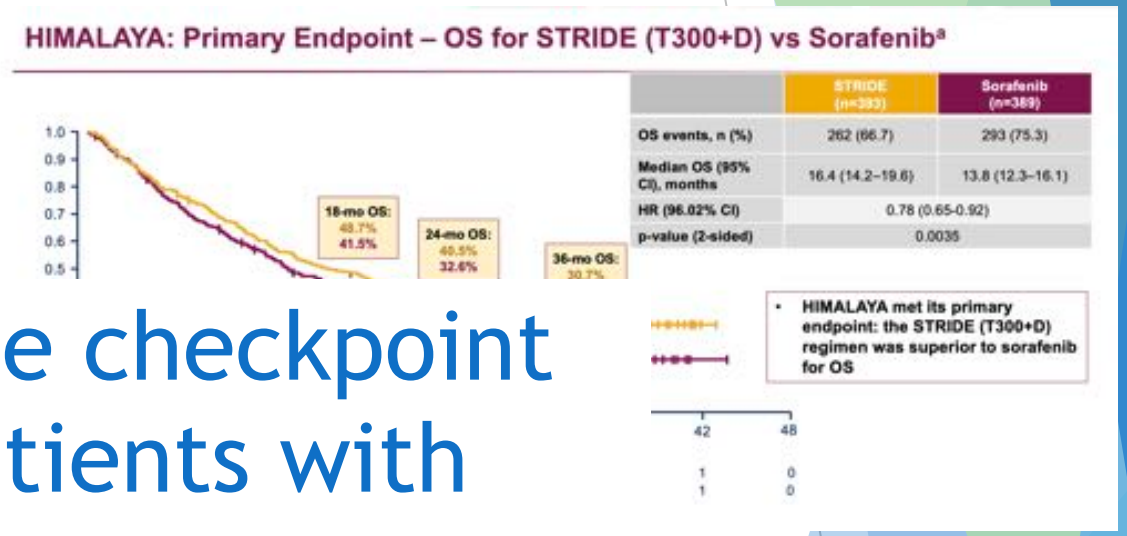
Immune checkpoint blockade has been a game changer for the treatment of HCC

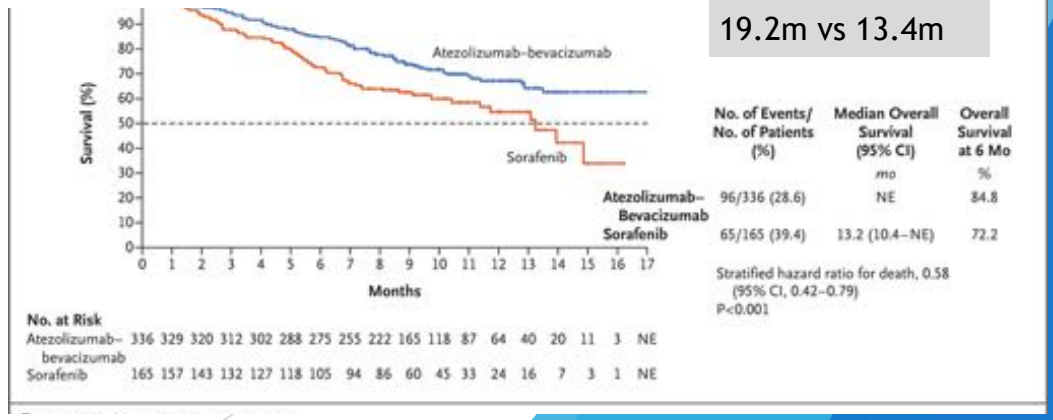


BCLC M Reig et al Jhep 2022



Clinical trials using immune checkpoint blockers have excluded patients with solid organ transplants

bevacizumab vs sorafenib



19.2m vs 13.4m

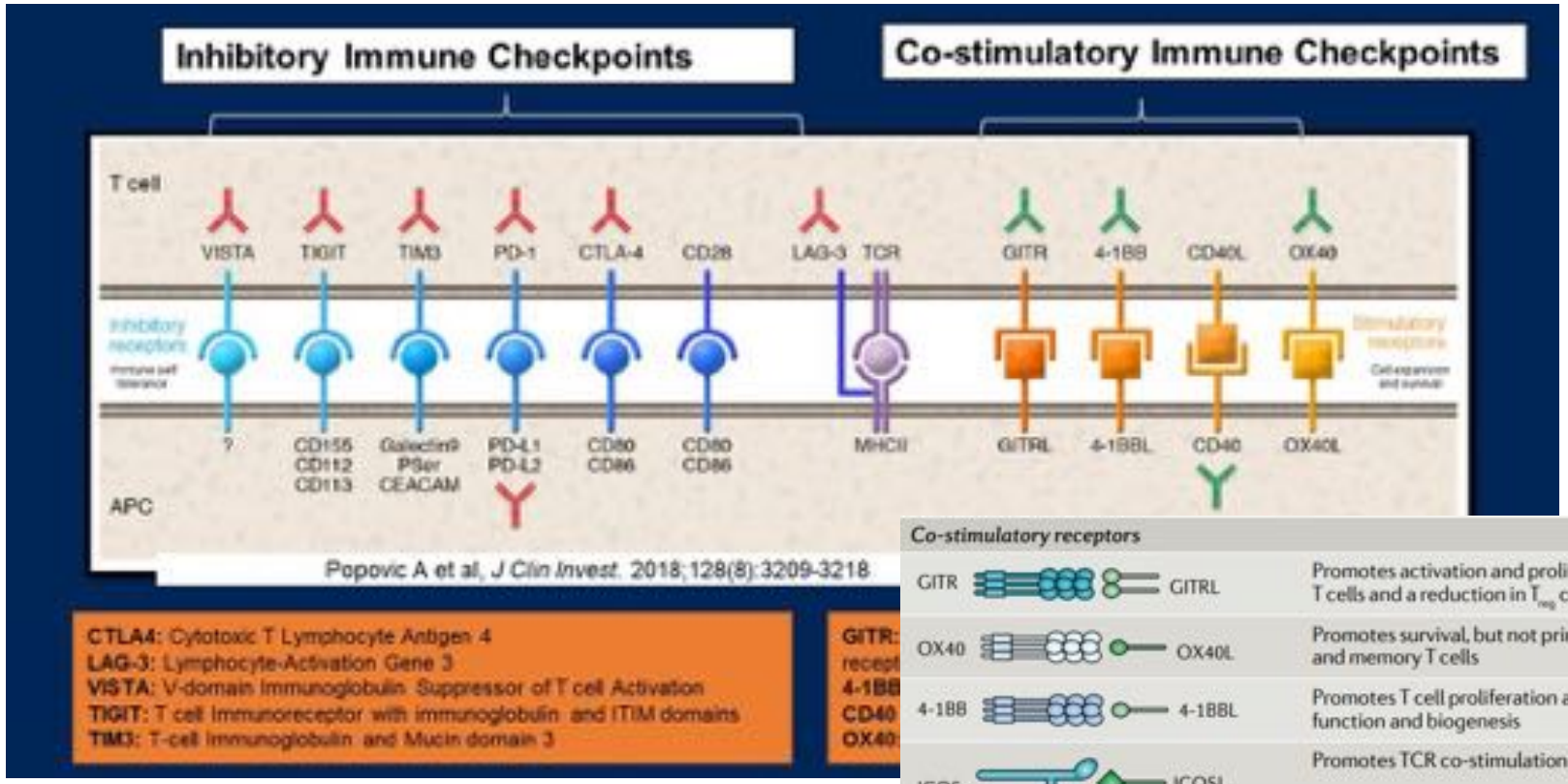
1st Line Combination therapies for advanced HCC- outcomes

	HIMALAYA: T300 + durvalumab vs sorafenib (vs durvalumab)	*Atezolizumab + bevacizumab vs sorafenib	Sintilimab + biosimilar bevacizumab vs sorafenib	Camrelizumab + rivoceranib vs sorafenib
Median OS	**16.4m vs 13.8m HR 0.85 , p 0.035**	19.2m vs 13.2m HR 0.66 p0.0009	NR vs 10.4m HR 0.56	22.1 vs 15.2m HR0.62 , p<0.001
Median PFS	3.78m vs 4.07m HR 0.9	**6.9m (vs 4.3m) HR 0.65 p0.0001**	4.5m vs 2.8m HR0.56	5.6m vs 3.7m HR 0.57 p<0.0001
ORR (RECIST)	**20% vs 5.1%**	**30% vs 11%**	20.3% vs 4.1 %	25.4% vs 5.9%
DCR	60% vs 60%	74 vs 55%	-	78 vs 54%
Median Duration of Rx	22.3m vs 18.4m	**18.1m vs 14.9m**	NR vs 9.8m	14.8m vs 9.2m

- ORR up to 30%; mOS 20months

1. Llovet J, *et al. N Engl J Med* 2008;359:378–390.
2. Cheng A, *et al. Lancet Oncol* 2009;10:25–34.
3. Kudo M, *et al. Lancet* 2018;391:1163–1173
4. Finn R, *et al. N Engl J Med 2020;382:1894-1905.*
5. *Cheng A, et al. ESMO Asia 2019 (Abstract LBA3)*
6. *Qin S ESMO 2022.*

Immune Checkpoint Inhibitors- many in development in HCC

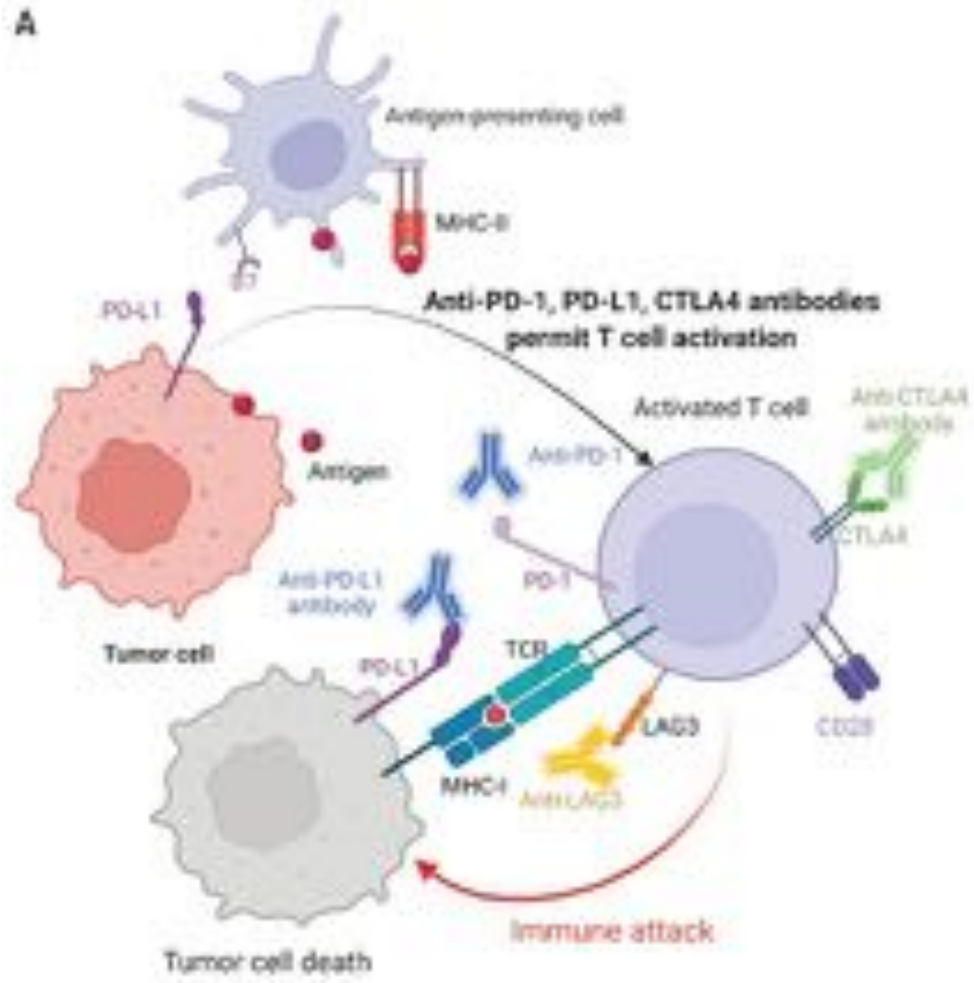


Co-stimulatory receptors				
GITR	GITRL	Promotes activation and proliferation of effector T cells and a reduction in T_{reg} cells	Phase II trials ongoing	TRX518, BMS-986156
OX40	OX40L	Promotes survival, but not priming, of both effector and memory T cells	Phase II trials ongoing	GSK3174998, MEDI6469, PF-04518600
4-1BB	4-1BBL	Promotes T cell proliferation and mitochondrial function and biogenesis	Phase I trials ongoing	Utomilumab, urelumab
ICOS	ICOSL	Promotes TCR co-stimulation and T_{reg} cell stimulation	Phase I trials ongoing	Vopratelimab, KY1044, GSK3359609

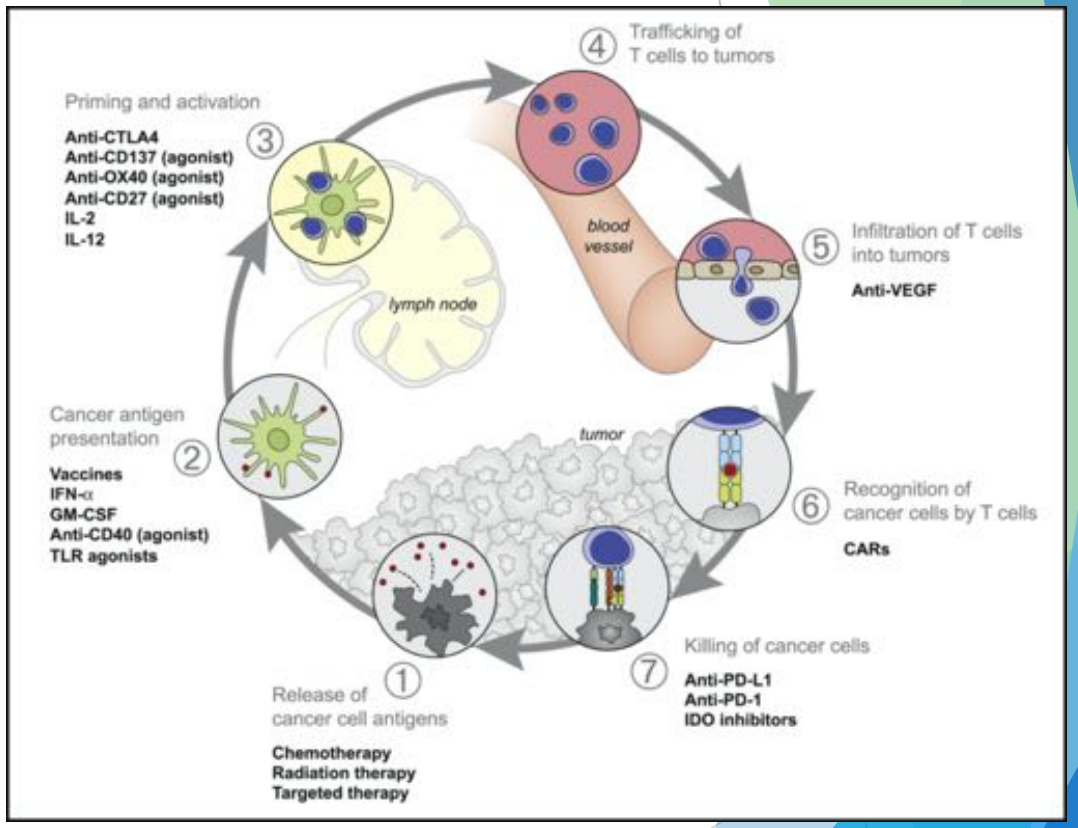
- Other co-inhibitory immune checkpoints like LAG3, VISTA, TIGIT, TIM3 can potentially enhance T cell effects of anti-PD1/CTLA4/PDL-1
- Activation of co-stimulatory receptors : tumor necrosis factor receptor super family (GITR, OXO40, 4-1BBL) and immunoglobulin superfamily (CD28, ICOS) most common- cell expansion and survival
- Intercellular pathways also play a role – amino acids like IDO etc

M Amin ASCO GI 2023 ; Krahenbuehl 2022

How PD-1, PD-L1 and CTLA4 inhibitors activate the T cell response



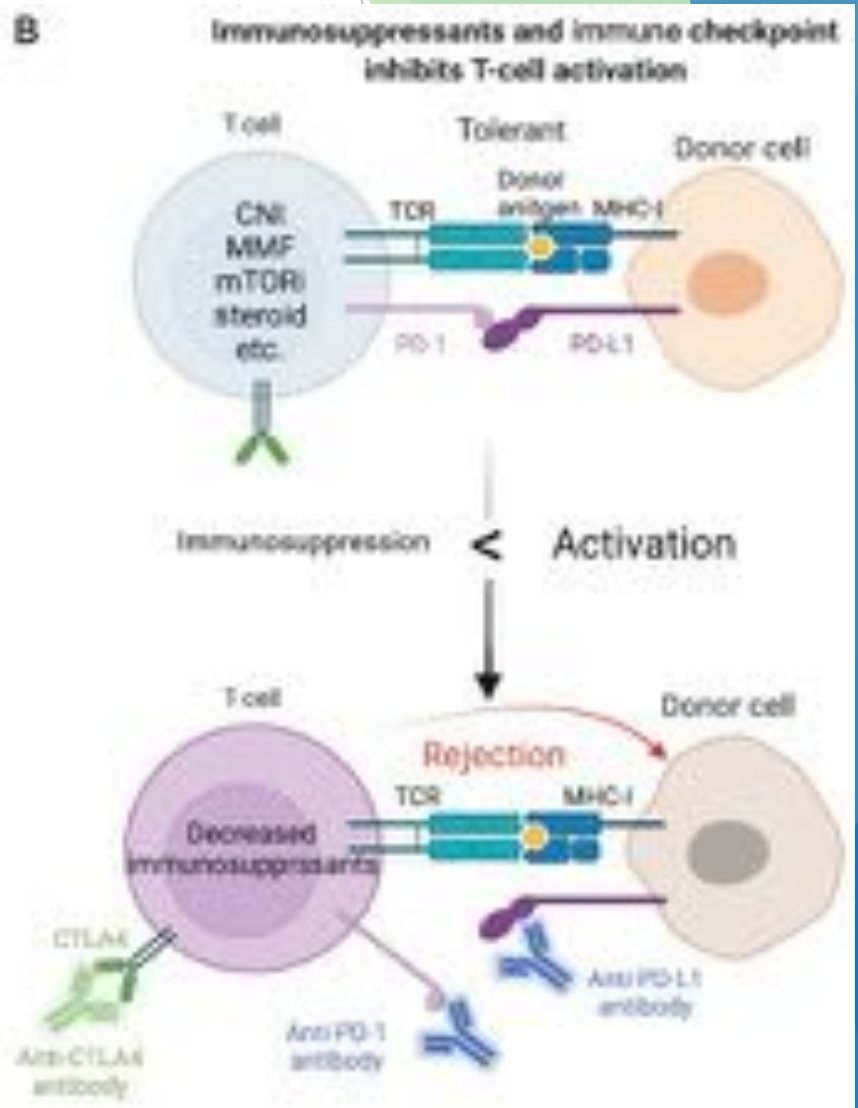
Kawashima J 2022



I Mellman, DS Chen 2013

Donor organ rejection caused by ICIs

- After transplant, donor cells release donor antigens and provoke alloantigen-directed IR
- Immunosuppressants like calcineurin inhibitors (CNIs), mycophenolate mofetil (MMF), mammalian target of rapamycin (mTOR) inhibitors, and steroids are the mainstay for suppressing T cell activation and regulating immunological tolerance.
- 1) In post transplant cancer patients, dose of immunosuppressants often reduced to avoid overimmunosuppression and to recover adequate tumor immunity.
- 2) ICIs have the potential to disrupt this equilibrium of immunological tolerance and lead to acute rejection
- Post-rejection biopsies: largely T cell mediated (Acute cellular rejections), about 21 % antibody mediated rejections
- Donor derived cell free DNA can be used to monitor for rejection

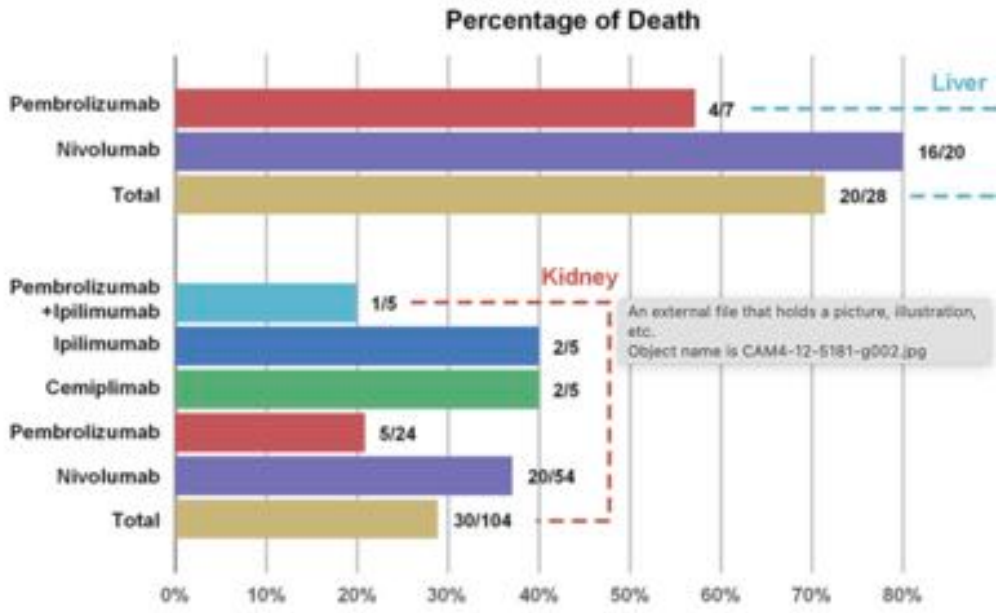


Kawashima J 2022; Nguyen L 2020

ICI use in solid tumor transplant recipients (SOTR)

- Mainly retrospective reports (since excluded from trials) and in skin cancers

	Vigibase Nguyen LS et al 2021	FAERS (FDA ADR) Cui X et al 2022
Number of Transplant patients	96 (65 kidney; 23 liver; 5 heart; 2 cornea)	168
Cancer types	43.8% melanoma; 14.6% HCC	43.5% melanoma; 13.7% HCC
ICI given	89.6% monotherapy (93% antiPD1/PDL-1) ; 10.4% combination	89.1% monotherapy (96% antiPD1/PDL-1); 10.1% combination
Time from ICI initiation to graft rejection	21 days (irregardless of transplant organ, ICI type)	23 days (irregardless of transplant organ)
Overall mortality following graft rejection	36.5%	32.1%
Mortality highest in LT	73.9% LT vs 24.7% for other organs ,$p<0.0001$	71.4% LT vs 28.9% kidney transplant , $p<0.001$



Fatality proportion of liver or kidney transplant rejection following different ICI regimens.

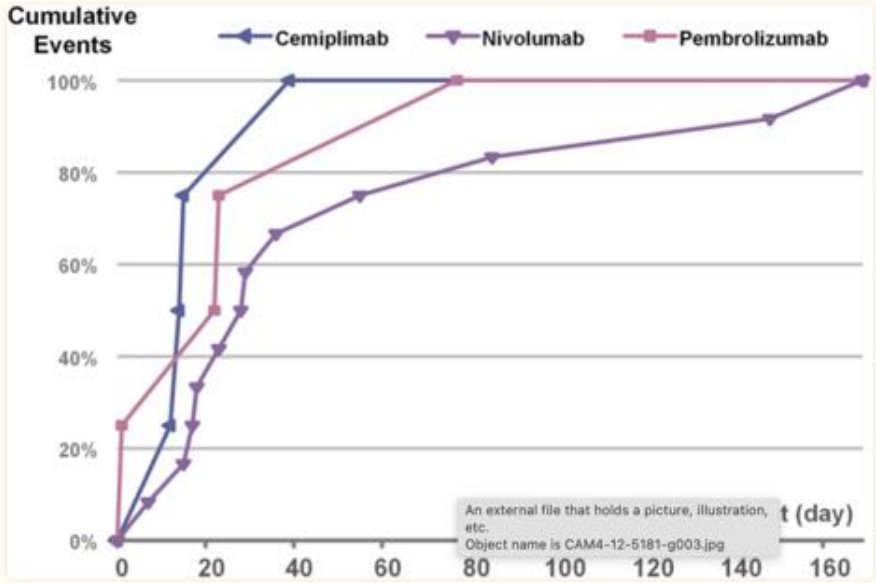


FIGURE 3

Time (days) to event onset of transplant rejection following different anti-PD-1 regimens.

Cui X et al Cancer Med 2022

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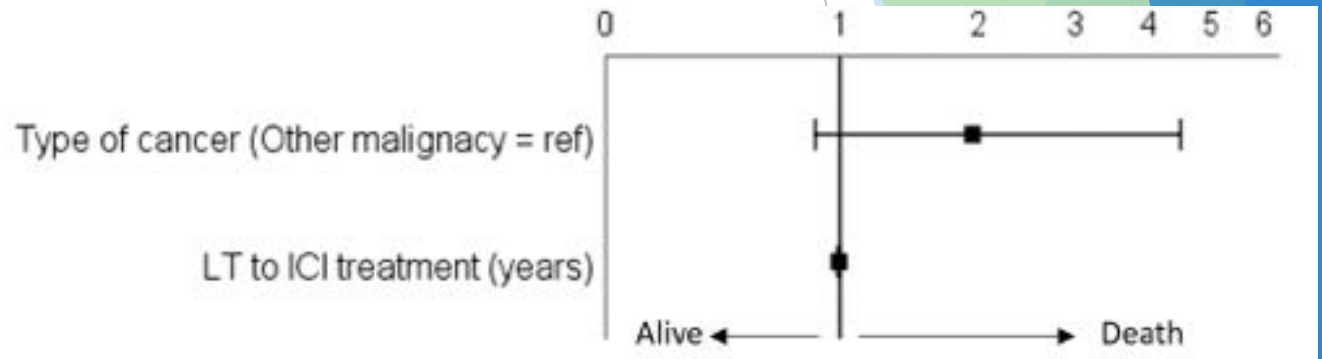
Immune checkpoint inhibitors in malignancies **after** liver transplantation: A systematic review and pooled analysis

- 31 publications : total of 52 patients treated with ICIs after LT (71% for HCC), median age 62 years (IQR, 53–66 years); male gender 76.9%
- **Acute graft rejection 28.8%; death from graft loss 13.4%**
- Rejection associated with shorter overall survival (OS) (3.5 mths, vs. 17.2mths, $p < 0.001$)
  - Disease control rate was 44.2% ($n = 23$), and in these patients,
  - OS was longer in ICI responders (26.4 mths, vs. 3.4 mths, $p < 0.001$)
- 9 patients underwent graft biopsy : All 4 with PDL-1 positive experienced graft rejection, 5 with negative PD-L1 had no bouts of rejection ($p = 0.008$).
- Suggestive that patients treated with ICI at least 4y after LT were better responders



Variables	Univariate analysis		
	HR	95% CI	P
Age (years)	0.986	0.958 – 1.0151	0.342
Gender (female = ref)	1.319	0.546 - 3.189	0.539
LT to ICI treatment (years)	**0.914**	**0.838 – 0.996**	**0.041**
Time from cancer diagnosis to ICI (months)	1.012	0.970 – 1.055	0.591
Type of cancer (Other malignancy = ref)	1.973	0.973 – 4.001	0.060

Duration between LT and initiation of ICI did not correlate clearly with graft rejection

Liver International, Volume: 43, Issue: 1, Pages: 8-17, First published: 14 September 2022, DOI: (10.1111/liv.15419)Kayali S et al

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ICI use **prior** to transplantation

- **Literature review of 24 publications :**
  - **n=45 patients 67**% male, Mean age 57y; HCV 29%; HBV 22%
  - 46.7% within Milan criteria.
  - All received anti-PD1 therapy except for 3 who received anti PDL-1 therapy
- Rate of rejection: 24% (11 out of 45) acute graft rejection
- Higher risk of rejection with shorter interval from ICI to LT
  - Treatment with nivolumab within 27 days (1 half-life) of liver transplant : acute rejection in three out of four (75%) of cases.
  - Within 81 days: 32% acute rejections; Beyond 81 days: 14% acute rejections
- Timing of graft rejection : majority 6-14 days after transplantation
- PDL-1 positive in donor organ associated with rejection (?biomarker)
- Treatment of rejection variable

- What is optimal timing of ICI?
- What is optimal immunosuppression after LT?
- What is risk of recurrence after LT?

SM Woo et al 2022 Curr Oncol; Yin Hepatoma Res 2021

Factors for/against ICI-associated rejection

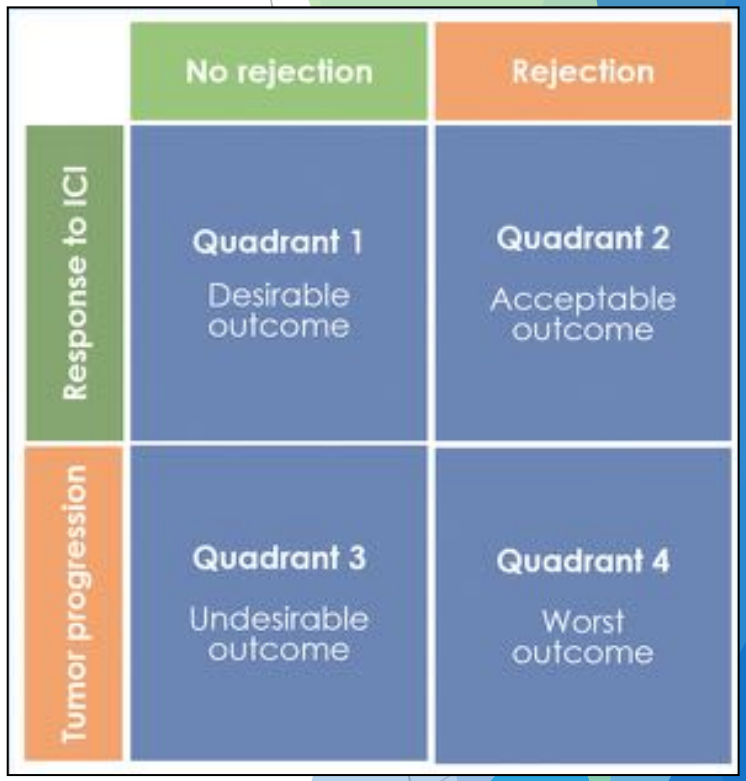
Protective factors

- Use of higher number of immunosuppressants (Murakami KI 2021, d'Izarny-Gargas, AJT 2020)
- ?Peri-infusion steroid mini-pulses (Barnett NEJM 2017, Danesh, CII 2020)
- mTOR inhibitors (Murakami KI 2021, Barnett NEJM 2017, Esfahani, Nat Comm 2019)
- Long-term transplant recipients (d'Izarny-Gargas, AJT 2020)

Risk factors

- Previous history of rejection (d'Izarny-Gargas, AJT 2020)

Kawashima 2022 KJT



Ferrandiz-Pulido C et al Transplantation 2023

Courtesy of Dr Joycelyn Lee;

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EASL CONGRESS Vienna, Austria 2023

Neoadjuvant PD-1 blockade with Pembrolizumab combined with Lenvatinib therapy in patients with hepatocellular carcinoma beyond Milan criteria before liver transplantation (PLENTY): a single-site pilot randomized controlled trial

Z. J. ZHANG [1], Z. C. LV [1], Z. Y. QIAO [1], L. XIA [1], Y. TONG [1], Z. G. ZHUANG [1], Z. B. LIU [1], Q. XIA [1] and H. FENG [1]

1 Department of Liver Surgery, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, 200127, China; 2 Institut Gustave Roussy, Bâtiment de médecine moléculaire, 94800 Villejuif, France; 3 Department of Radiology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, 200127, China; 4 Department of Pathology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, 200127, China

Take-home message

Neoadjuvant Pembrolizumab and Lenvatinib for HCC patients is safe, well tolerated, and yielded favorable ORR as well as significantly improved RFS after liver transplant.

1 Introduction

Liver transplantation (LT) has become the most effective treatment for hepatocellular carcinoma (HCC); however, the high recurrent rate after LT remains a clinical challenge, especially for those exceeding the Milan criteria (MC). Recently, there have been no approved standardized neoadjuvant therapies for hepatocellular carcinoma before LT.

2 Aim

To investigate whether programmed death receptor 1 (PD-1) blockade plus Lenvatinib as a neoadjuvant therapy before LT allows safely administered and effectively reduces post-LT recurrence for those patients with HCC beyond MC.

3 Method

In this prospective, randomized, open-label, pilot study, patients with HCC exceeding the MC before LT were randomly assigned (1:1) to:

- PLENTY group: 200 mg of Pembrolizumab every 3 weeks until approximately 6 weeks before LT and combined with Lenvatinib 8 mg orally once daily until 1 week before LT.
- Control group: routine treatments.

The primary endpoint of the study was the recurrence-free survival after LT.
The secondary endpoints were objective response rate, overall survival, adverse events.

4 Results

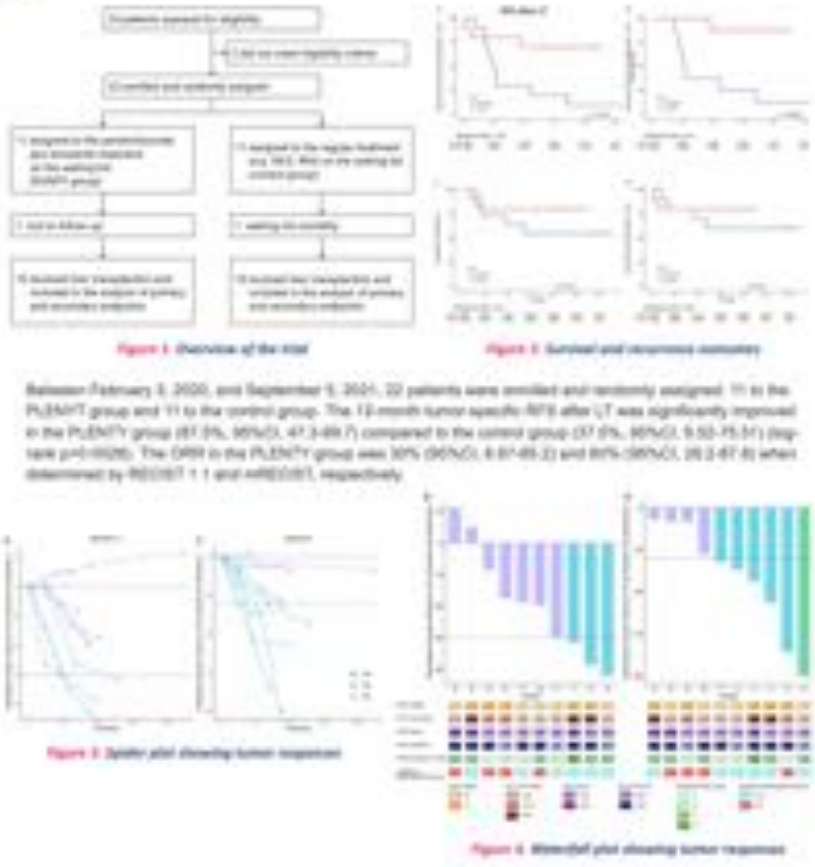


Figure 1: Overview of the trial

Figure 2: Survival and recurrence outcomes

Between February 3, 2020, and September 9, 2021, 22 patients were enrolled and randomly assigned 1:1 to the PLENTY group and 11 to the control group. The 12-month tumor-specific RFS after LT was significantly improved in the PLENTY group (87.5%, 95%CI, 47.3-69.7) compared to the control group (37.5%, 95%CI, 9.53-75.51) (log-rank p=0.0026). The ORR in the PLENTY group was 50% (95%CI, 8.87-69.2) and 80% (95%CI, 28.2-87.8) when determined by RECIST 1.1 and mRECIST, respectively.

Figure 3: Spider plot showing tumor responses

Figure 4: Waterfall plot showing tumor responses

5 Conclusions

Neoadjuvant Pembrolizumab plus Lenvatinib before LT appears to be safe and feasible. It would be a potential therapeutic option for patients exceeding the MC, associated with significantly better RFS. Our findings support further studies of neoadjuvant immunotherapy in combination with TKIs in the bridging treatment for HCC.

6 Acknowledgements

This study was funded by Shanghai Science and Technology Development Foundation (Hf. 20Y11908600, 23XD1422100), Major research projects of National Natural Science Foundation, China (XG: 82085098), and Innovative research team of high-level local universities in Shanghai (Hf. SHSMU-ZLCX20211602). The Renji Clinical Research Unit supported the study set-up, site identification, and delivery of this study.

7 References

- Finn RS, Ikeda M, Zhu AX, et al. Phase Ib Study of Lenvatinib Plus Pembrolizumab in Patients With Unresectable Hepatocellular Carcinoma. J Clin Oncol. 2020 Sep 10;38(26):2960-2970. 9.
- Qiao JY, Zhang ZJ, Lv ZC, et al. Neoadjuvant Programmed Cell Death 1 (PD-1) Inhibitor Treatment in Patients With Hepatocellular Carcinoma Before Liver Transplant: A Cohort Study and Literature Review. Front Immunol. 2021 Jun 30;12:685210.

Trials exploring ICI use prior to LT

Recruiting	Durvalumab (MEDI4736) and Tremelimumab for **Hepatocellular Carcinoma** in Patients Listed for a **Liver Transplant**	• **Hepatocellular Carcinoma** • Cirrhosis • Portal Hypertension	• Drug: Durvalumab • Drug: Tremelimumab • Procedure: **Liver Transplant**	• Washington University School of Medicine Saint Louis, Missouri, United States • University of Cincinnati Cincinnati, Ohio, United States
Recruiting	Downstaging Protocol Containing **Immunotherapy** for HCC Beyond the Milan Criteria Before **Liver Transplantation**	• **Liver Transplantation** • **Hepatocellular Carcinoma**	• Procedure: Downstaging procedures containing **immunotherapy** • Procedure: **Liver transplantation**	• Sun Yat-sen Memorial Hospital, Sun Yat-sen University Guangzhou, Guangdong, China
Recruiting	Effect of PD-1 /PD-L1 Inhibitor Therapy Before **Liver Transplantation** on Acute Rejection After **Liver Transplantation** in Patients With **Hepatocellular Carcinoma**	• **Hepatocellular Carcinoma** • Acute Rejection		• Beijing Tsinghua Changgung Hospital Beijing, Beijing, China
Recruiting	**Durvalumab** and Lenvatinib in Participants With Locally Advanced and Metastatic **Hepatocellular Carcinoma** (Dulect2020-1)	• **Liver Carcinoma** • **Liver Transplant**; Complications	• Drug: **Durvalumab** Injection • Drug: Lenvatinib 4 MG	• Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University Shanghai, China

Management of SOTR patient before, during ICI and if acute graft rejection

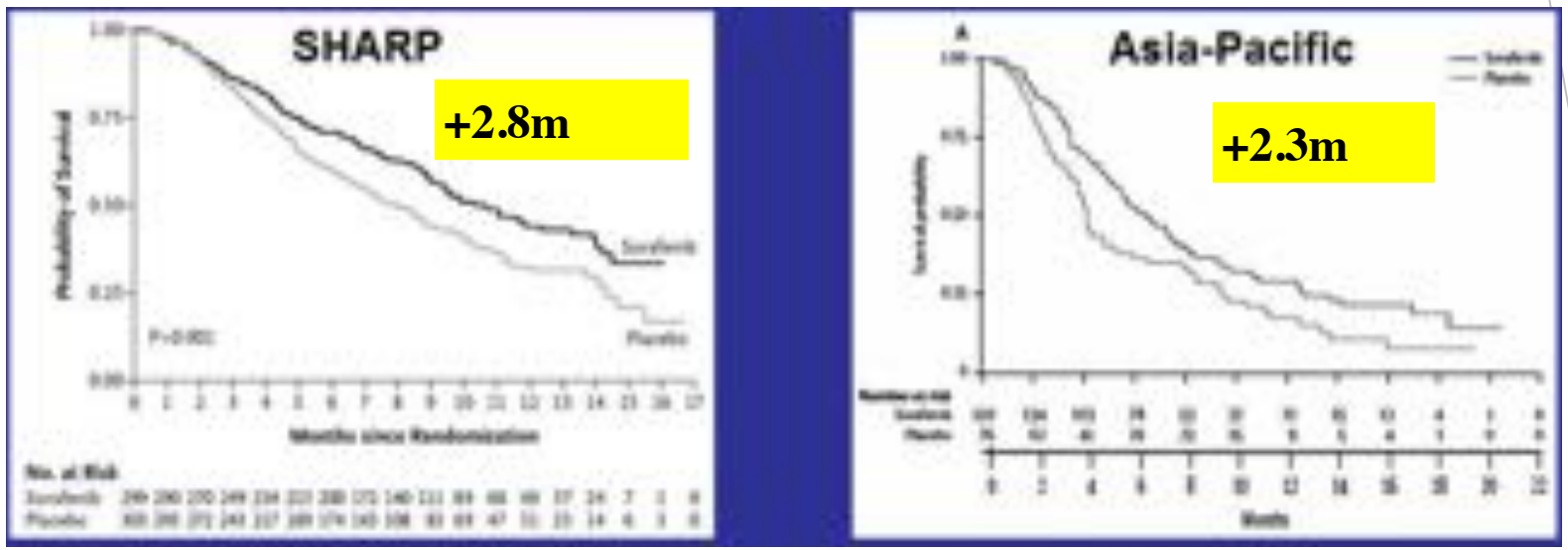
Ferrandiz-Pulido C et al Transplantation 2023

1st Line treatment of advanced HCC- outcomes of TKIs vs IO

	Sorafenib vs placebo	Lenvantinib vs sorafenib	*Atezolizumab + bevacizumab vs sorafenib	Nivolumab (CM459) vs sorafenib
Median OS	10.7 vs 7.9m (SHARP) 6.5 vs 4.2m (AP)	13.6m vs 12.3m	**19.2m** vs 13.2m HR 0.66	16.4 vs 14.7m HR 0.85
Median PFS	TTP 5.5m	7.3m (vs 3.7m)	6.9m (vs 4.3m) HR 0.65	3.7m (vs 3.8m)
ORR	2-3% (RECIST)	18.8 vs 6.5% (RECIST)	**30%** vs 11% (RECIST)	15% vs 7% (RECIST)
DCR	43 vs 32%	75.5 vs 60.5%	74 vs 55%	55% vs 58%
Duration of Rx	5.3m vs 4.3m	5.7 vs 3.7m	**18.1m vs 14.9m** (median FU 8.6m)	23.3m vs 23.4m
Common toxicities	HFS. Diarrhea, Hypt, fatigue, alopecia	Hypt, HypoT4, weight loss	Hypt, Proteinuria, Fever, ALT rise	Fatigue, pruritus, rash, AST increase, diarrhea
Discontinuation due to toxicities	38% ; 26% dose reduced	9% ; 53% had dose reduction	7% : 16% withdrew 1 drug	9% vs 11%

1. Llovet J, *et al. N Engl J Med* 2008;359:378-390.
2. Cheng A, *et al. Lancet Oncol* 2009;10:25-34.
3. Kudo M, *et al. Lancet* 2018;391:1163-1173
4. Finn R, *et al. N Engl J Med 2020;382:1894-1905.*
5. *Cheng A, et al. ESMO Asia 2019 (Abstract LBA3)*
6. T Yau Annals Oncol Oct 2019.

Two Phase III trials established sorafenib as a standard of care



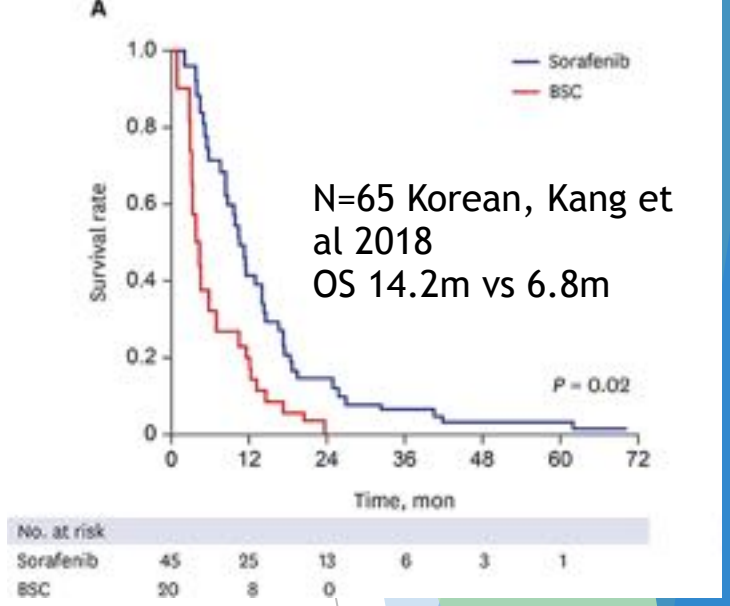
	Response rates		Time To Treatment Progression		Overall Survival		HR
	Sorafenib	Placebo	Sorafenib	Placebo	Sorafenib	Placebo	
SHARP	2%	1%	5.5m	2.8m	10.7m	7.9m	0.69 (0.55-0.87)
Asia-Pac	3.3%	1.3%	2.8m	1.4m	6.5m	4.2m	0.68 (0.5-0.93)

Llovet NEJM July 2008

Cheng et al. Lancet Oncol 09

Sorafenib for HCC recurrence after LT

- Review of 17 retrospective studies (2 from Asia-Pacific), n=200
  - Median OS 10.5m (range 5-21.3m)
  - Most common cause of death- disease progression followed by GI bleeding (only those on mTORinhibition)
  - Common AEs: fatigue, GI, skin, cardiovascular
- Meta-analysis and regression analysis on 8 studies with survival data:
  - Pooled estimate of 1-year survival was 63%
  - Significant heterogeneity among studies ($P < 0.0001$)
  - Among 34 variables assessed by univariate meta-regression, 5 were associated with an increase in the 1-year survival rate: (1) male gender ($P = 0.001$); (2) Time to progression ($P = 0.038$); and adverse drug events, divided in (3) gastrointestinal ($P = 0.038$), (4) cardiovascular ($P = 0.029$), and (5) dermatological ($P = 0.014$).



N=65 Korean, Kang et al 2018
OS 14.2m vs 6.8m

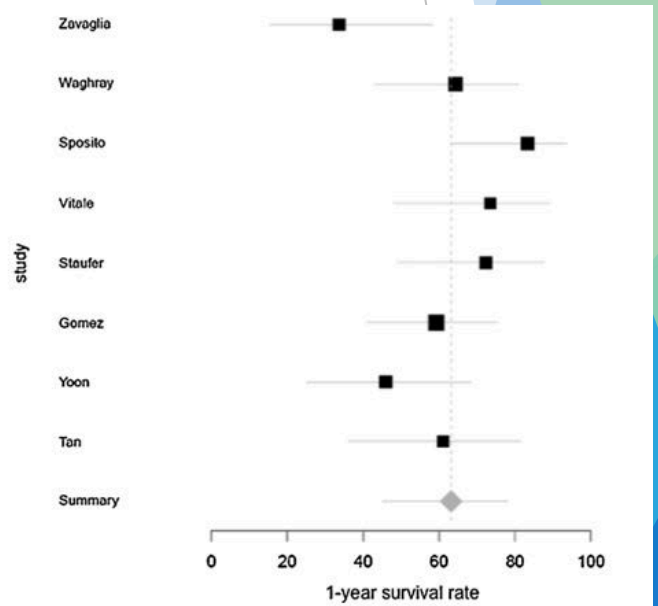


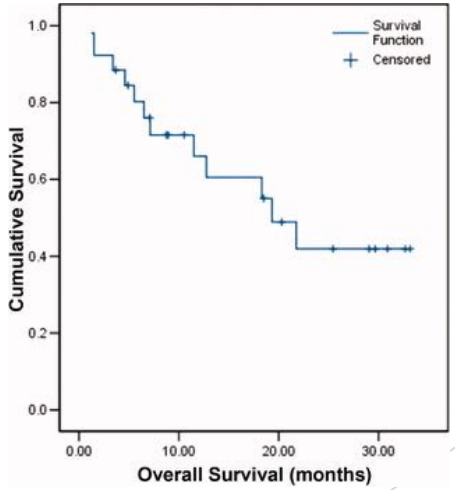
Fig. 2. Forest plot of 1-year survival rates of patients treated with sorafenib for hepatocellular carcinoma recurrence after liver transplant in 8 studies using random-effects model. Studies are arranged by publication year.

Mancuso A et al, Dig Liv D 2015

Safety and efficacy of sorafenib with mTOR inhibition in HCC recurrence after LT

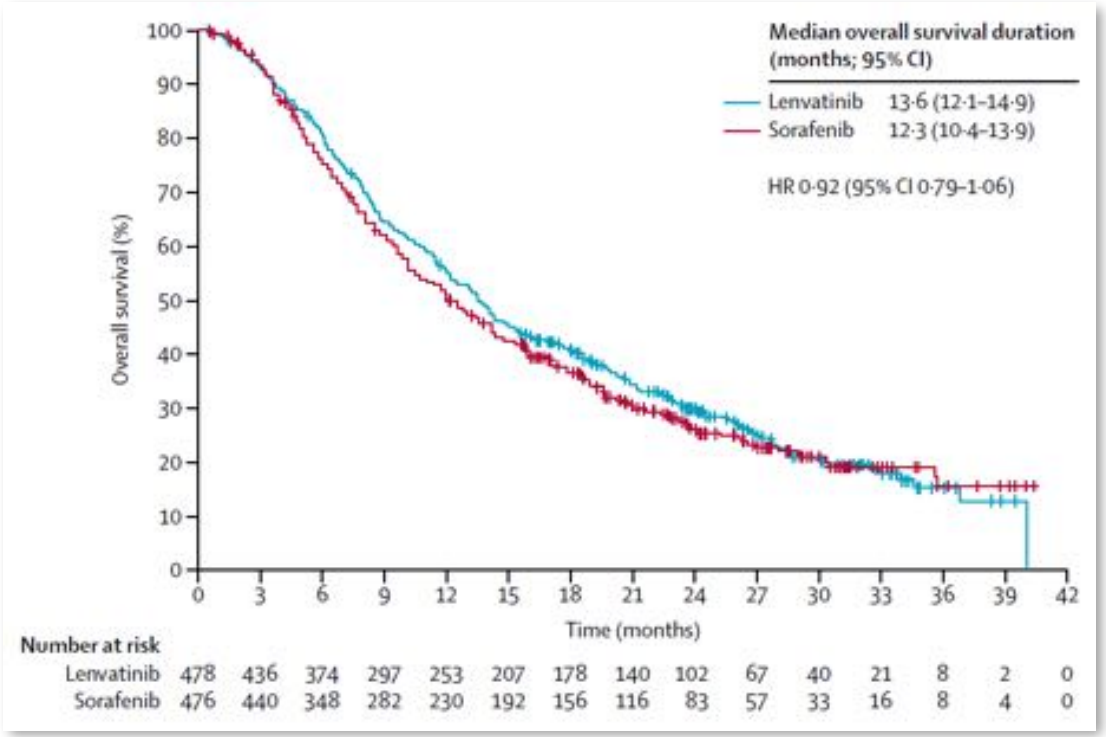
- Open label, multicentre retrospective, uncontrolled cohort study
- n=31 Post LT HCC recurrence patients, switched to mTOR inhibitor and started on sorafenib
- Median OS 19.3m
- TTP 6.77m
- Grade ≥ 3 hypoglycemia =2; Gr≥ 3 mucositis=1
- Diarrhea most common 12.9%

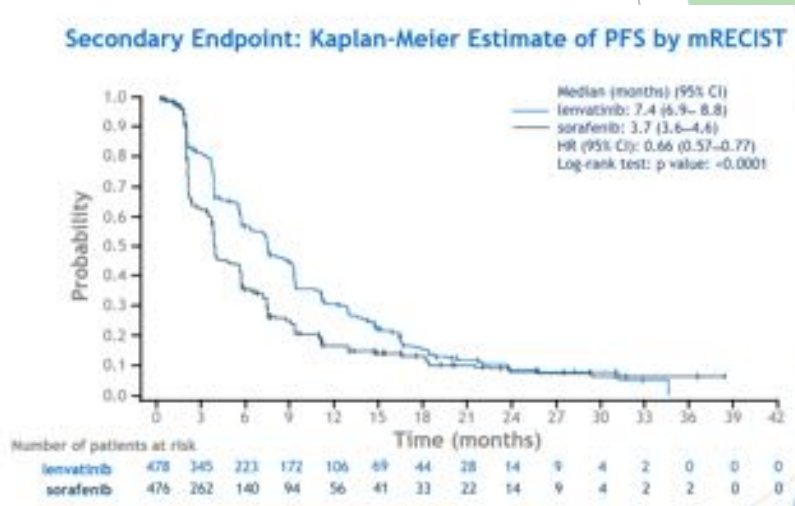
Complete response	0 (0.0)
Partial response	1 (3.8)
Stable disease	13 (50.0)
Progressive disease	10 (38.5)
Not assessable *	2 (7.7)
Overall clinical benefit rate	14 (53.8)



C Gomes Martin 2011

REFLECT: 1L Lenvatinib was not inferior to sorafenib in OS





Median OS 13.6m vs 12.3m

Better PFS (lenvatinib vs sorafenib):
7.4 mo vs 3.7 mo; HR 0.66

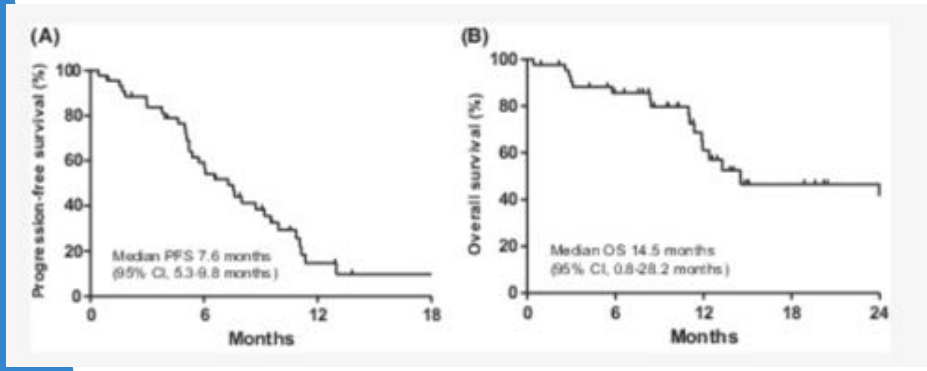
Better ORR (lenvatinib vs sorafenib):
24.1% vs 9.2%; P < 0.0001

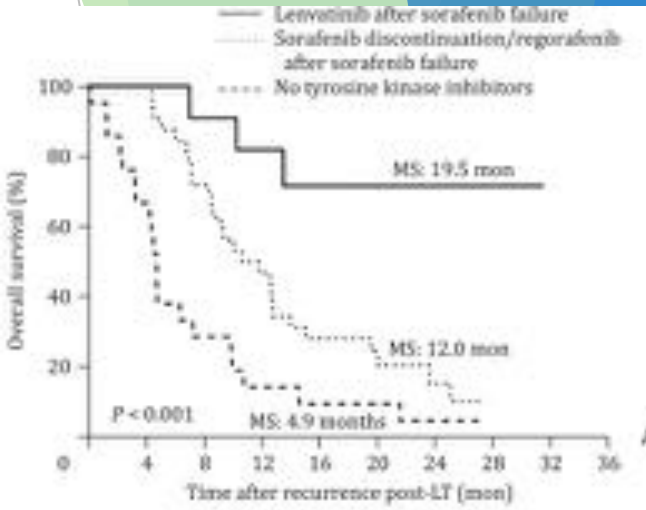
CI, confidence interval; HR, hazard ratio; mo, months; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Kudo M, *et al. Lancet* 2018;391:1163-1173.

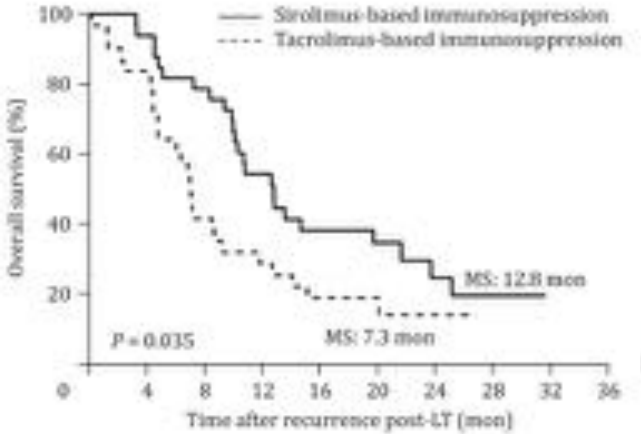
Lenvatinib for HCC recurrence after LT

			ORR	PFS	OS
Bang K et 2023	N=45, Korea, HK, Italy	95.6% CP A 77.8% ALBI 1	20%	7.6m	14.5m
Chen YY et al 2021	N=10 Taiwan		20% DCR 70%	3.7m	16.4m
Yang Z et al 2020	N=11 Lenvatinib Vs n=32 regorafenib China	48% tacrolimus 51.6% sirolimus	NR		19.5m with Lenvatinib Vs 12m with rego





OS after recurrence	1-year	2-year
Lenvatinib after sorafenib failure (n = 11)	81.8%	71.6%
Sorafenib discontinuation/regorafenib after sorafenib failure (n = 32)	46.9%	15.4%
No tyrosine kinase inhibitors (n = 21)	14.3%	4.8%



OS after recurrence	1-year	2-year
Sirolimus-based immunosuppression (n = 33)	54.5%	25.0%
Tacrolimus-based immunosuppression (n = 31)	29.0%	14.5%

EACH study design

- Phase III, randomized, open-label study in mainland China, Taiwan, Korea and Thailand

Randomization (N = 371)

Stratification
- Country or area
- Disease status
- BCLC stage

N = 184

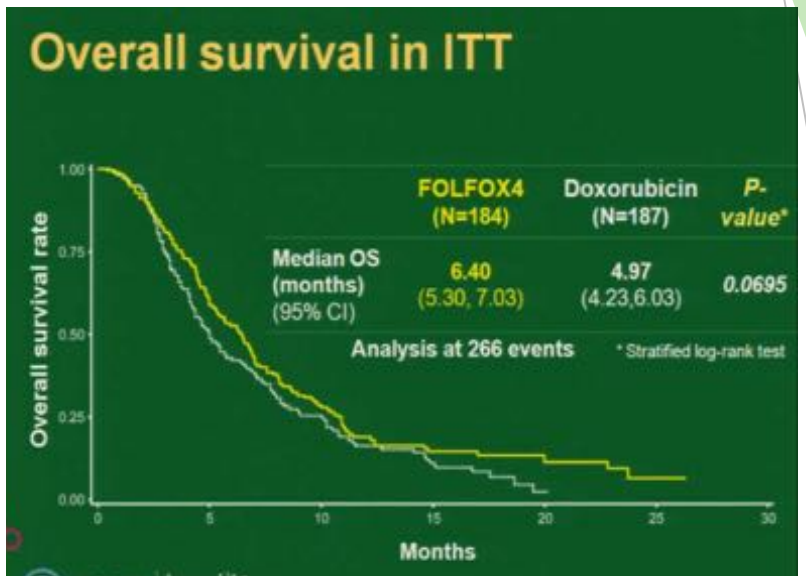
Arm A (FOLFOX4)
- OXA 85mg/m² i.v. h0 – h2 Day 1
- LV 200mg/m² i.v. h0 – h2 Day 1
- 5FU 400mg/m² i.v. bolus Day 1, then 600 mg/m² over 22 hours in Day 1 & 2 , every 2 weeks

N = 187

Arm B (Doxorubicin)
- Doxorubicin 50 mg/m² i.v. on Day 1, every 3 weeks

- Treatment to be continued until progression, toxicity, death or eligibility for resection

Overall survival in ITT



	FOLFOX4	Doxorubicin	
OS	6.40	4.37	P=0.0695
PFS	2.93	1.77	P =0.002
ORR	8%	3%	P=0.023
DCR	52%	32%	P<0.001

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Data with 2L systemic therapy using targeted therapies in advanced HCC

	RESORCE[1]		CELESTIAL[2]		APATINIB[3]		REACH-2[4]	
	Regorafenib	Placebo	Cabozantinib	Placebo	Apatinib	Placebo	Ramucirumab	Placebo
Phase	Phase III		Phase III		Phase III		Phase III	
Patient population	Child-Pugh A HCC that progressed on sorafenib		Child-Pugh A advanced HCC that progressed on sorafenib		BCLC stage B/C that progressed on sorafenib		BCLC stage B/C that progressed on sorafenib; AFP ≥ 400 ng/mL	
OS, months	10.6	7.8	10.2	8.0	8.7	6.8	8.5	7.3
	HR = 0.63		HR = 0.76		HR = 0.79		HR = 0.71	
PFS, months								
ORR, %	11	4	4	0.4	11	2	5	1
Grade 3/4 AEs, %	50[a]	17[a]	68	37	77a	19a	NA	NA
Median DOR, months	3.6	1.9	3.8	2.0	6.5	NA	3.5	2.6

Must tolerate and progress on sorafenib

Included 3L patients

Mainly HBV+ Chinese patients

AFP must be ≥ 400 ng/mL

2/3L, second-/third-line; AE, adverse event; AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; DOR, duration of response; HBV+, hepatitis B virus-positive; HCC hepatocellular carcinoma; HR, hazard ratio; NA, not applicable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
[a] Treatment-related.

1. Bruix J, *et al. Lancet*. 2017 Jan 7;389(10064):56-66.
2. Abou-Alfa, *et al N Engl J Med* 2018;379:54-63.
3. Qiu Li, *et al.* ASCO 2020 (Abstract 4507).
4. Zhu A, *et al. Lancet Oncol* 2019; 20:282-296.

Regorafenib in 2L in post LT HCC patients

Study	Type	Treatment	Median OS	Duration
Massimo I et al 2021	Observational multicentre retrospective	Grp 1:36 on **regorafenib** Grp 2: 45 on BSC	13.1 vs 5.5m , p<0.01 mOS from sorafenib start 28.8m vs 15.3m	Rego was independent predictor of outcome 61% dose reductions
Ivarone M et al 2019	Retrospective , multicentre	N=28 post LT who had progressed on sorafenib 54% on mTORi	12.9m mOS from sorafenib start: 38.4m	Main toxicities involved skin(25%) and fatigue (Gr18%)

NCT04204850 Cabozantinib in HCC recurrence post LT: phase 2 single arm –trial- PMH Toronto

Case study

- 65y Chinese male with Hep B
- Stage 2 HCC in June 2013 s/p Resection
- Sep 2013: Recurrence in liver – s/p TACE then Y90-RE
- s/p liver transplant in China Jan 2014

==========

June 2014: Multiple HCC in both lobes of liver

s/p TACE x 2– progressed

s/p Lenvatinib –from 2015 till 2021- good PR and SD =s/p SBRT in Aug 2021
Surveillance
Early 2022 : PD: s/p regorafenib for 1 month- PD
Cabozantinib for 7 weeks – initial SD then PD
Restarted on Lenvatinib– till Aug 2022- stopped coz of proteinuria
s/p Xeloda + oxaliplatin from Sep 2022 till March 2023 – PD and worsening of liver function- eventually passed away from liver failure May 2023

From recurrence, survival was >9 years

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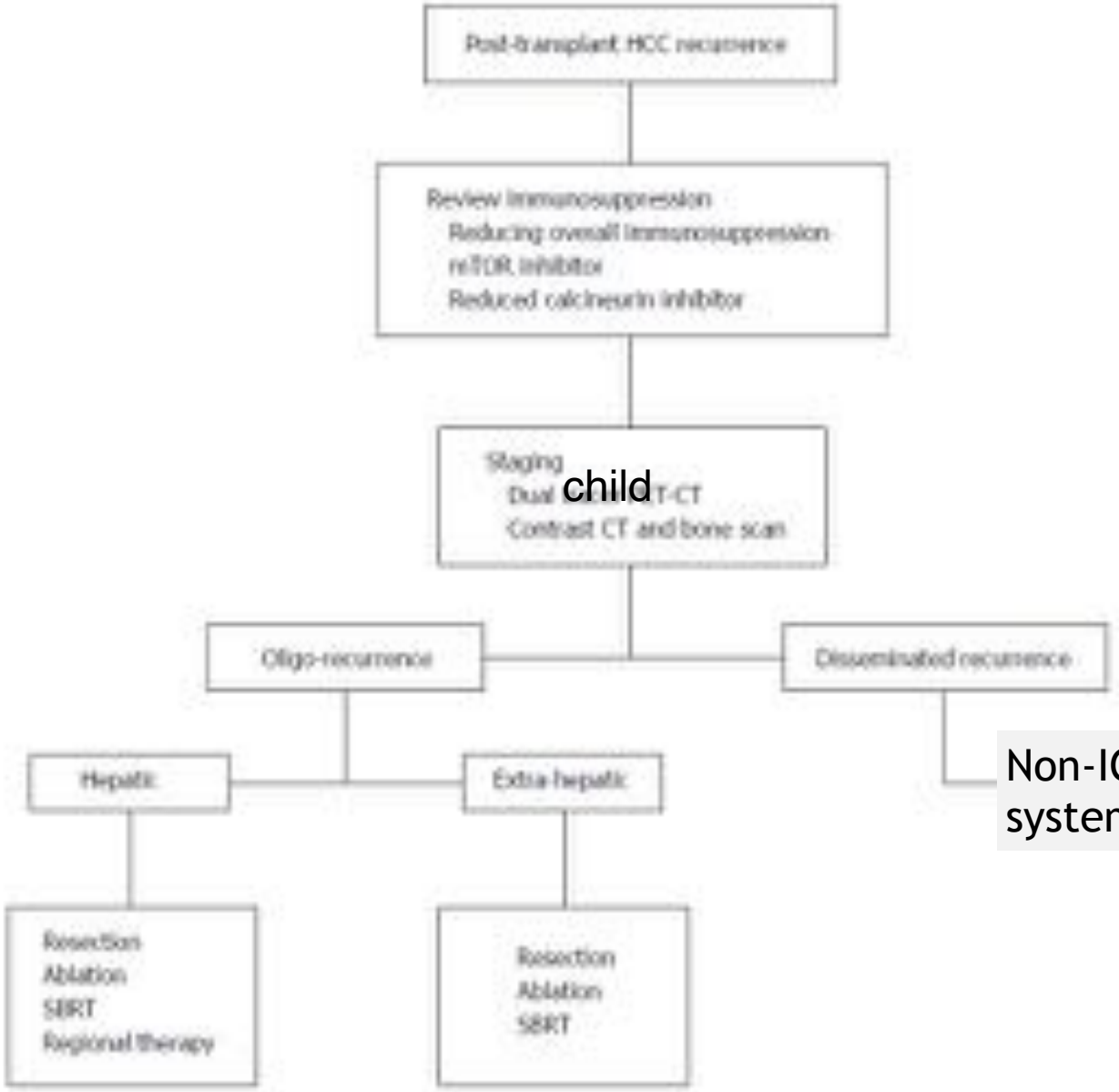
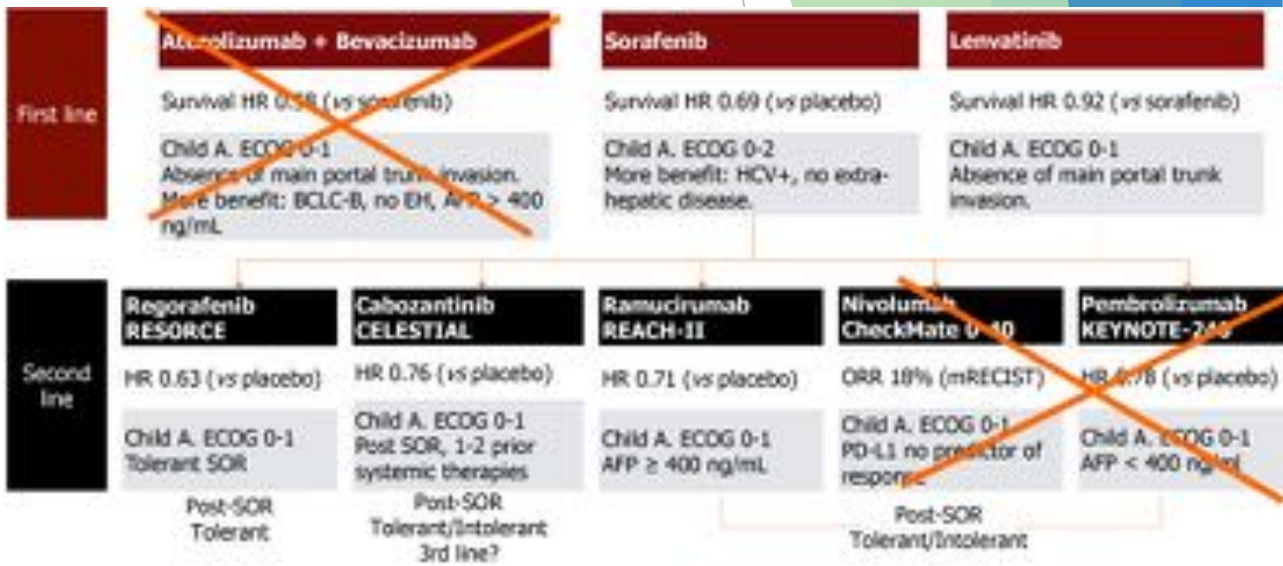
Proposed algorithm for treatment of HCC recurrence after LT





Non-ICI systemic tx

Au KP 2018; Pnero F 2020

Summary

- Use of ICI in post-LT HCC recurrence is associated with increased risk of graft rejection (up to 32%) with high mortality rates (best immunosuppressive agents ?)
- ICIs can still be efficacious in post LT HCC
- Use of ICI in post-LT patients needs to be individualized, discussed with a multidisciplinary team and risk-benefit ratio needs to be weighed
- For now, tyrosine kinase inhibitors are recommended for patients with HCC recurrence post LT and have shown comparable efficacy in these patients
- Role of ICI in post LT patients needs to be further evaluated prospectively and strategies of immune monitoring needs to be investigated

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Thank you

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Locations:
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Farrer Park Hospital
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