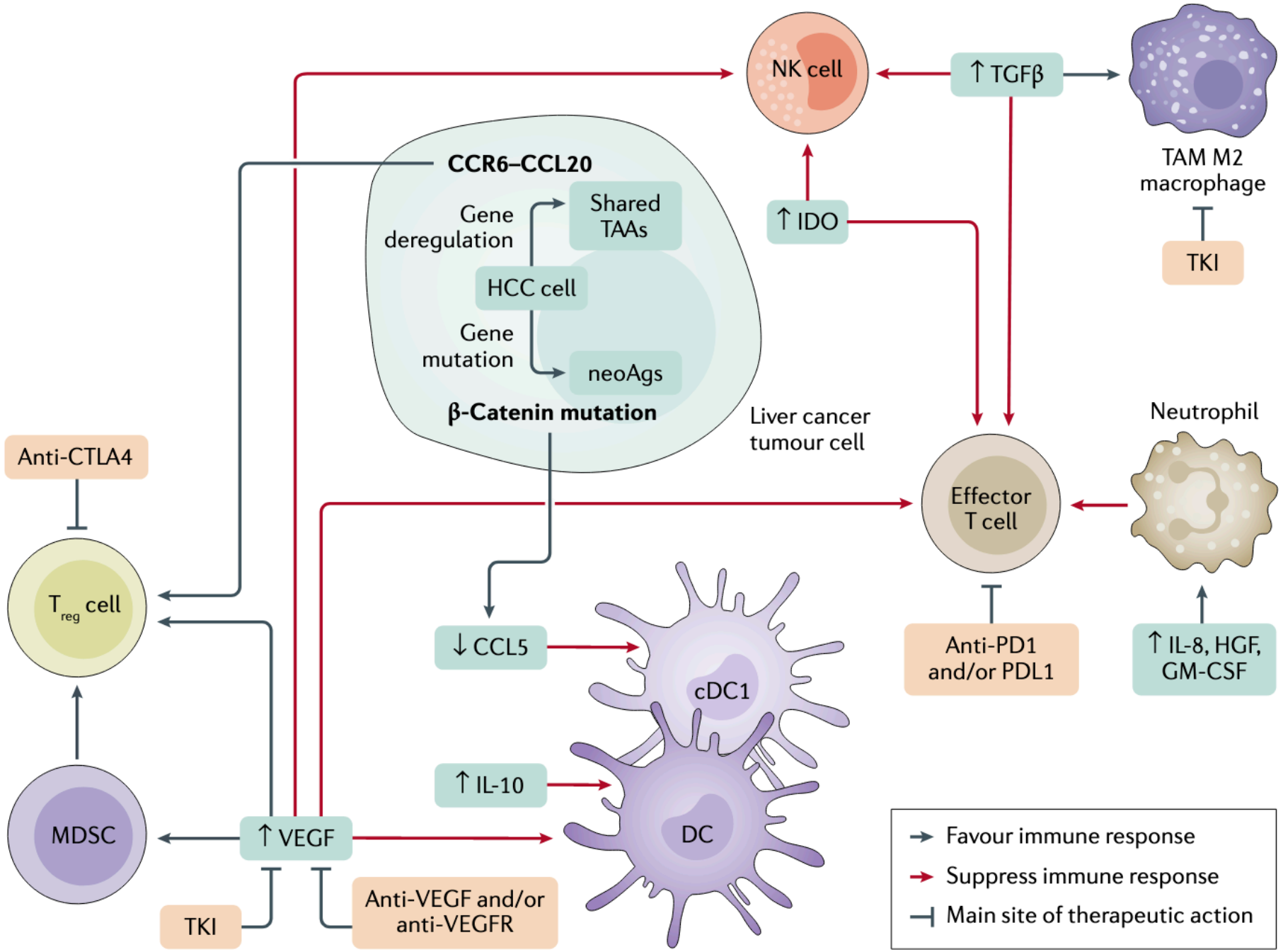
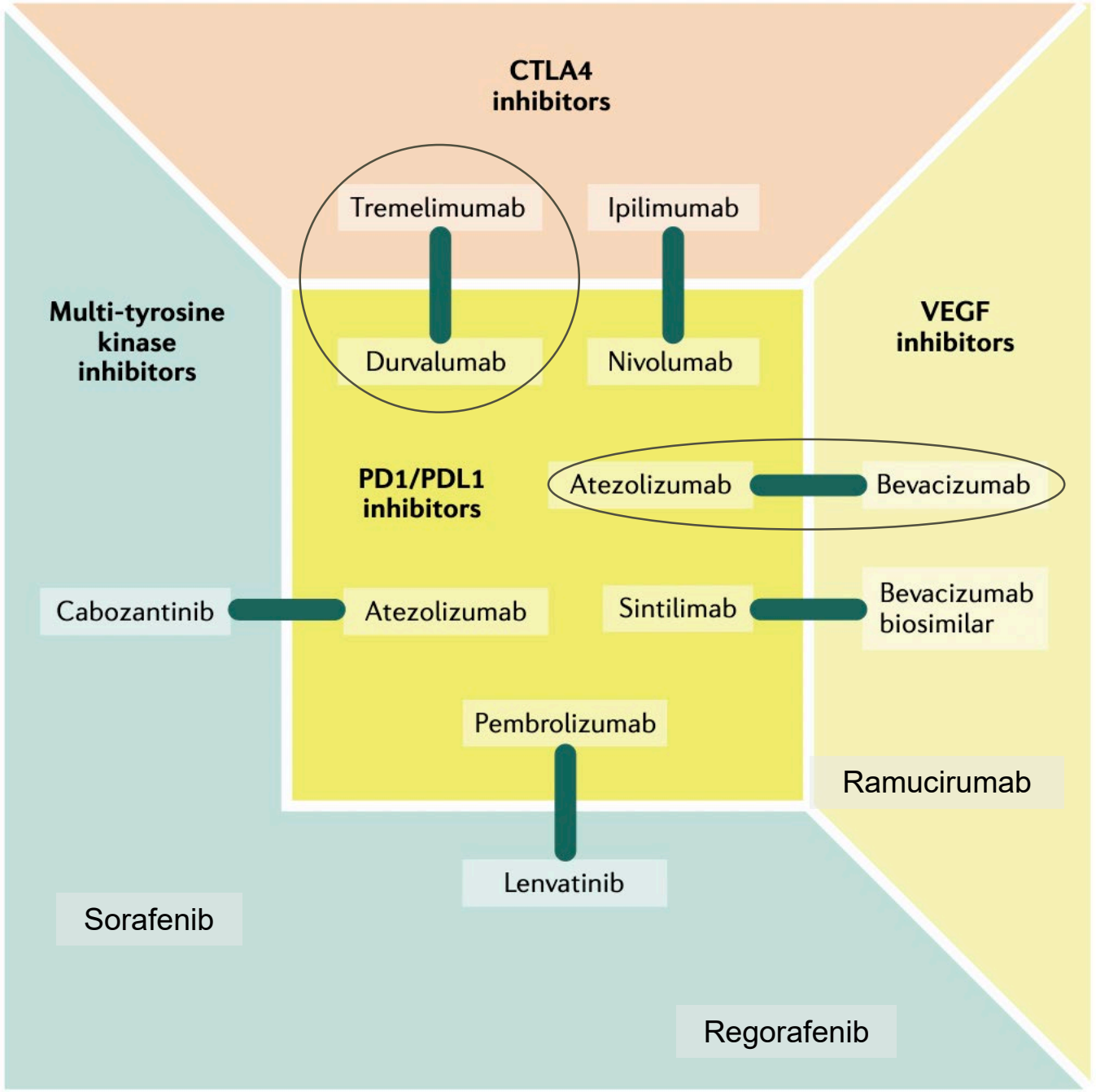
HCC
Terapie Sistemiche pre- e post-trapianto

VALENTINA BELLIA

ISTITUTO NAZIONALE DEI TUMORI, MILANO



Sangro B Nat Rev Gastro&Hepat 2021(18):525-543



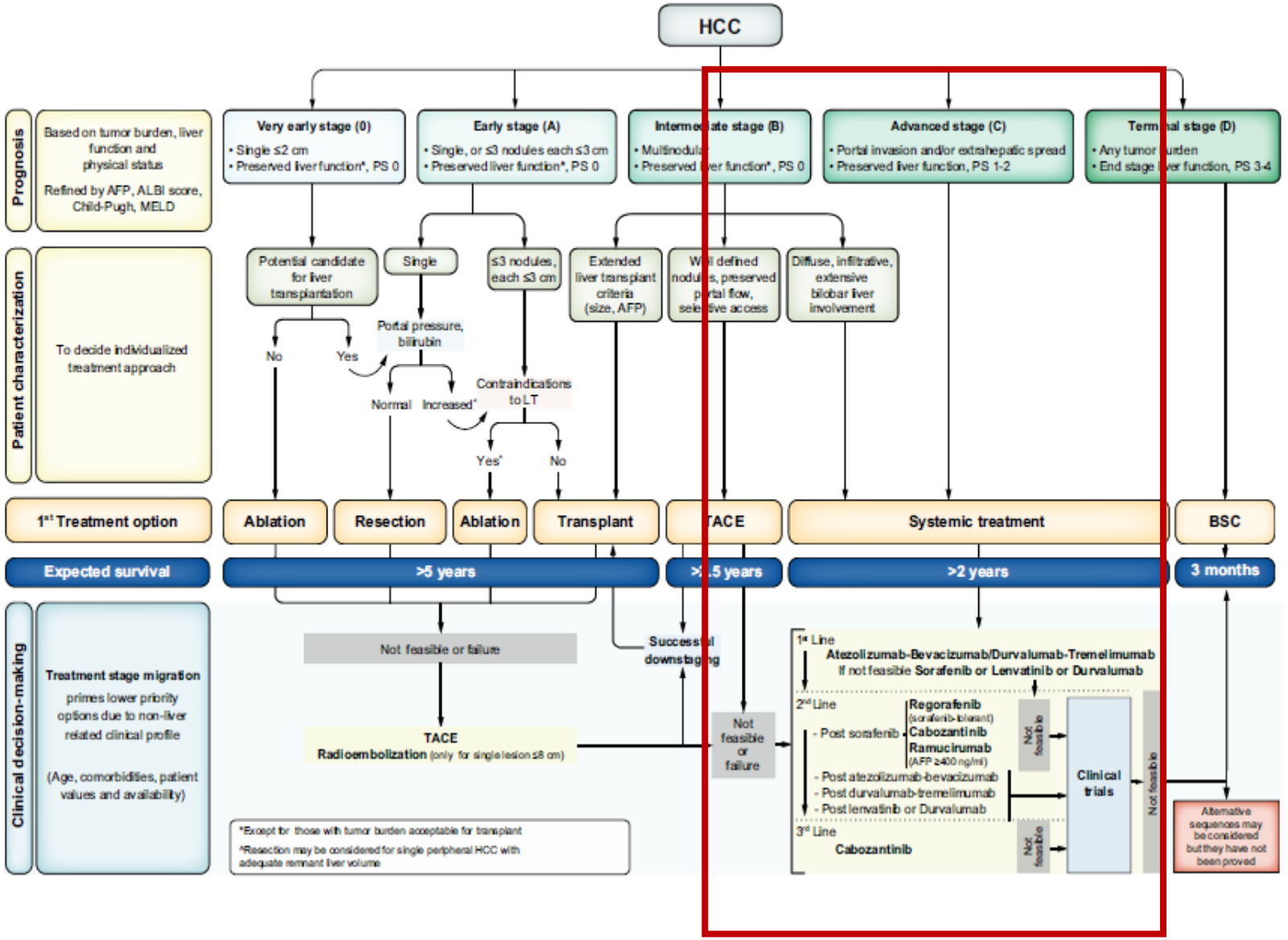
Adapted from Sangro B Nat Rev Gastro&Hepat 2021(18):525-543

Study	Arm	mOS (months) (95% CI)	HR (95% CI) *p* value	mPFS (months) (95% CI)	HR (95% CI) *p* value	ORR (%) (95% CI)	DCR(%) (95% CI)
Cheng 2013[20]	Sunitinib	7.9 (7.4–9.2)	1.30 (1.1–1.5) 0.99	3.6 (2.8–4.1)	1.13 (0.9–1.3) 0.88	6.2	50.0
	Sorafenib	10.2 (8.9–11.4)		3.0 (2.8–4.0)		5.9	51.3
Johnson 2013[21]	Brivanib	9.9 (8.5–11.5)	1.07 (0.9–1.2) 0.31	4.1 (3.1–4.2)	1.01 (0.9–1.2) 0.85	12 (9–15)	65 (61–69)
	Sorafenib	9.5 (8.3–10.6)		4.2 (4.1–4.3)		9 (7–11)	66 (61–69)
Cainap 2015[22]	Linifanib	9.1 (8.1–10.2)	1.05 (0.9–1.2)	5.4 (4.2–5.6)	0.76 (0.6–0.9) 0.001	10.1	n.a.
	Sorafenib	9.8 (8.3–11)		4.0 (2.8–4.2)		6.1	n.a.
REFLECT[2]	Lenvatinib	13.6 (12.1–14.9)	0.92 (0.8–1.1)	7.3 (5.6–7.5)	0.65 (0.6–0.8) <0.0001	18.8 (15.3–22.3)	72.8 (68.8–76.8)
	Sorafenib	12.3 (10.4–13.9)		3.6 (3.6–3.9)		6.5 (4.3–5.14)	59 (54.6–63.5)
IMbrave150[7]	Atezolizumab + bevacizumab	19.2 (17–23.7)	0.66 (0.5–0.9) <0.001	6.9 (4.7–8.6)	0.65 (0.53–0.81) <0.001	30.0 (25.0–35.0)	74
	Sorafenib	13.4 (11.4–16.9)		4.3 (4.0–5.6)		11.0 (7.0–17.0)	55
COSMIC-312[12]	Atezolizumab + cabozabtinib	15.4 (13.7–17.7)	0.90 (0.7–1.2) 0.438	6.8 (5.6–8.3)	0.63 (0.4–0.9) 0.0012	11.2 (8.1–14)	78
	Sorafenib	15.5 (12.1–NR)		4.2 (2.8–7.0)		3.7 (1.6–7.1)	65
HIMALAYA[10]	Durvalumab + tremelimumab	16.4 (14.2–19.6)	0.78 (0.7–0.9) 0.0035	3.8 (3.7–5.3)	0.90 (0.8–1.1)	20.1	60.1
	Sorafenib	13.8 (12.3–16.1)		4.2 (3.8–5.5)		5.1	60.7
CheckMate- 459[23]	Nivolumab	16.4 (13.9–18.4)	0.85 (0.7–1.0) 0.075	3.7 (3.1–3.9)	0.93 (0.8–1.1)	15 (12–19)	55
	Sorafenib	14.7 (11.9–17.2)		3.8 (3.7–4.5)		7 (5–10)	58
SHARP[18]	Sorafenib	10.7 (9.4–13.3)	0.69 (0.6–0.9) <0.001	4.1 (3.5–4.8)	1.1 (0.9–1.3) 0.77	2	43
	Placebo	7.9 (6.8–9.1)		4.9 (4.2–6.3)		1	32
Asia Pacific[19]	Sorafenib	6.5 (5.6–7.6)	0.68 (0.5–0.9) 0.014	2.8 (2.6–3.6)	0.57 (0.4–0.8) 0.0005	3.3	35.3 (27.7–43.6)
	Placebo	4.2 (3.8–5.5)		1.4 (1.3–1.6)		1.3	15.8 (8.4–26)
ORIENT-32[9]	Sintilimab + IBI305	NR	0.57 (0.4–0.8) <0.0001	4.6 (4.1–5.7)	0.56 (0.5–0.7) <0.0001	21 (17–25)	72 (67–77)
	Sorafenib	10.4 (8.5–NR)		2.8 (2.7–3.2)		4 (2–8)	64 (56–71)
Qin 2021[24]	Donafenib	12.0 (10.3–13.1)	0.84 (0.7–0.9) 0.031	3.7 (3.0–3.7)	0.91 (0.8–1.1) 0.057	4.6	30.8
	Sorafenib	10.1 (9.2–11.9)		3.6 (2.4–3.7)		2.7	28.7
LEAP-002[13]	Lenvatinib + pembrolizumab	21.2 (19.0–23.6)	0.84 (0.7–0.9) 0.0227	8.2 (6.4–8.4)	0.87 (0.7–1.0) 0.0466	26.1 (21.8–30.7)	81.3
	Lenvatinib + placebo	19.0 (17.2–21.7)		8.0 (6.3–8.2)		17.5 (13.9–21.6)	78.4
Qin 2022[11]	Camrelizumab + rivoceranib	22.1 (19.1–27.2)	0.62 (0.5–0.8) <0.0001	5.6 (5.5–6.3)	0.52 (0.4–0.7) <0.0001	25.4 (20.3–31)	78.3 (72.9–83.1)
	Sorafenib	15.2 (13.0–18.5)		3.7 (2.8–3.7)		5.9 (3.4–9.4)	53.9 (47.7–59.9)
RATIONALE-301[25]	Tislelizumab	15.9	0.85 (0.7–1.0) 0.0398	2.2	1.1 (0.9–1.3)	14.3 (10.8–18.5)	41.8
	Sorafenib	14.1		3.6		5.4 (3.2–8.4)	47.3

DCR, disease control rate; HR, hazard ratio; mOS, median overall survival; mPFS, median progression-free survival; n.a., not available; NR, not reached; ORR, objective response rate.

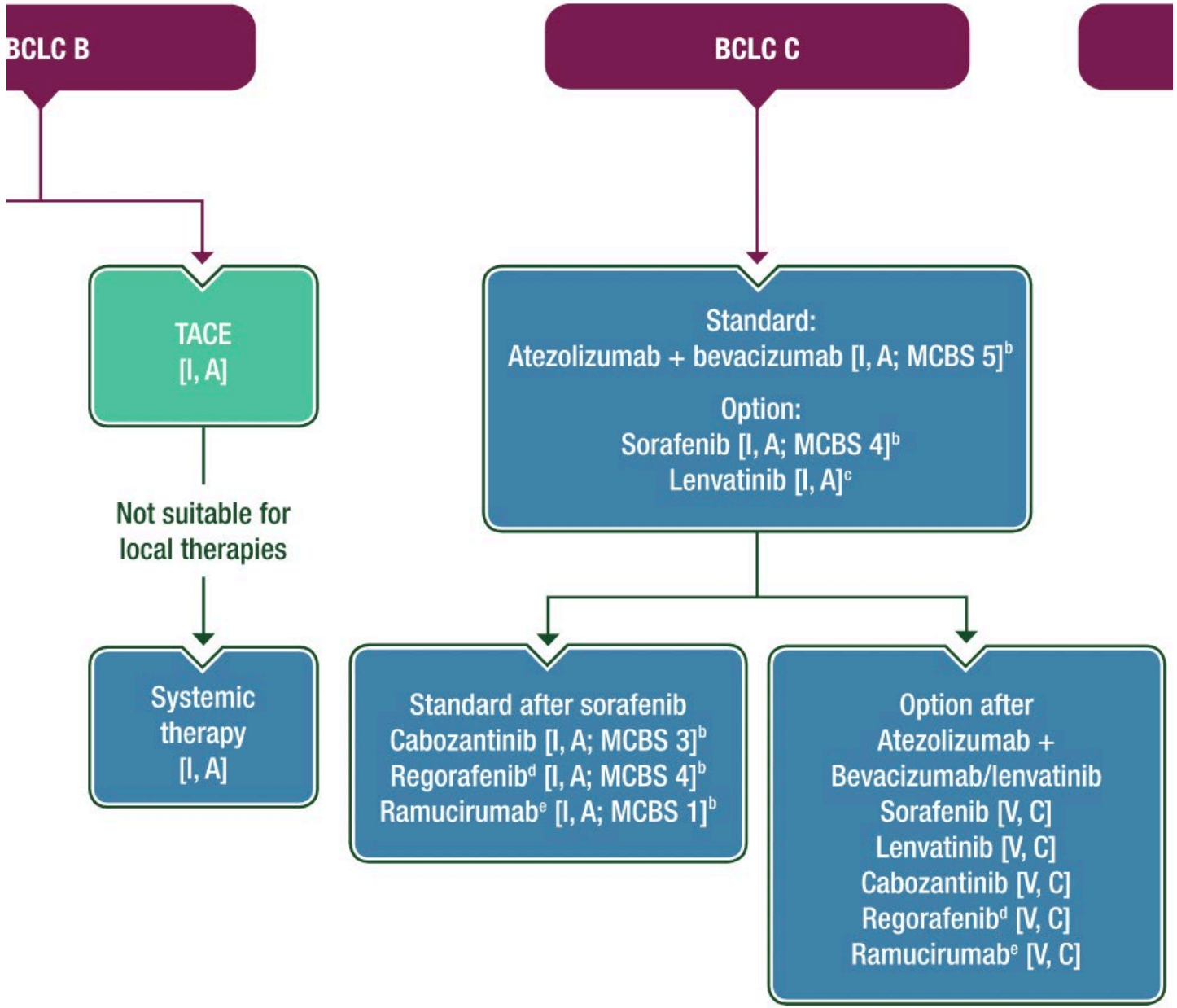
JHEP Reports 2023

EASL

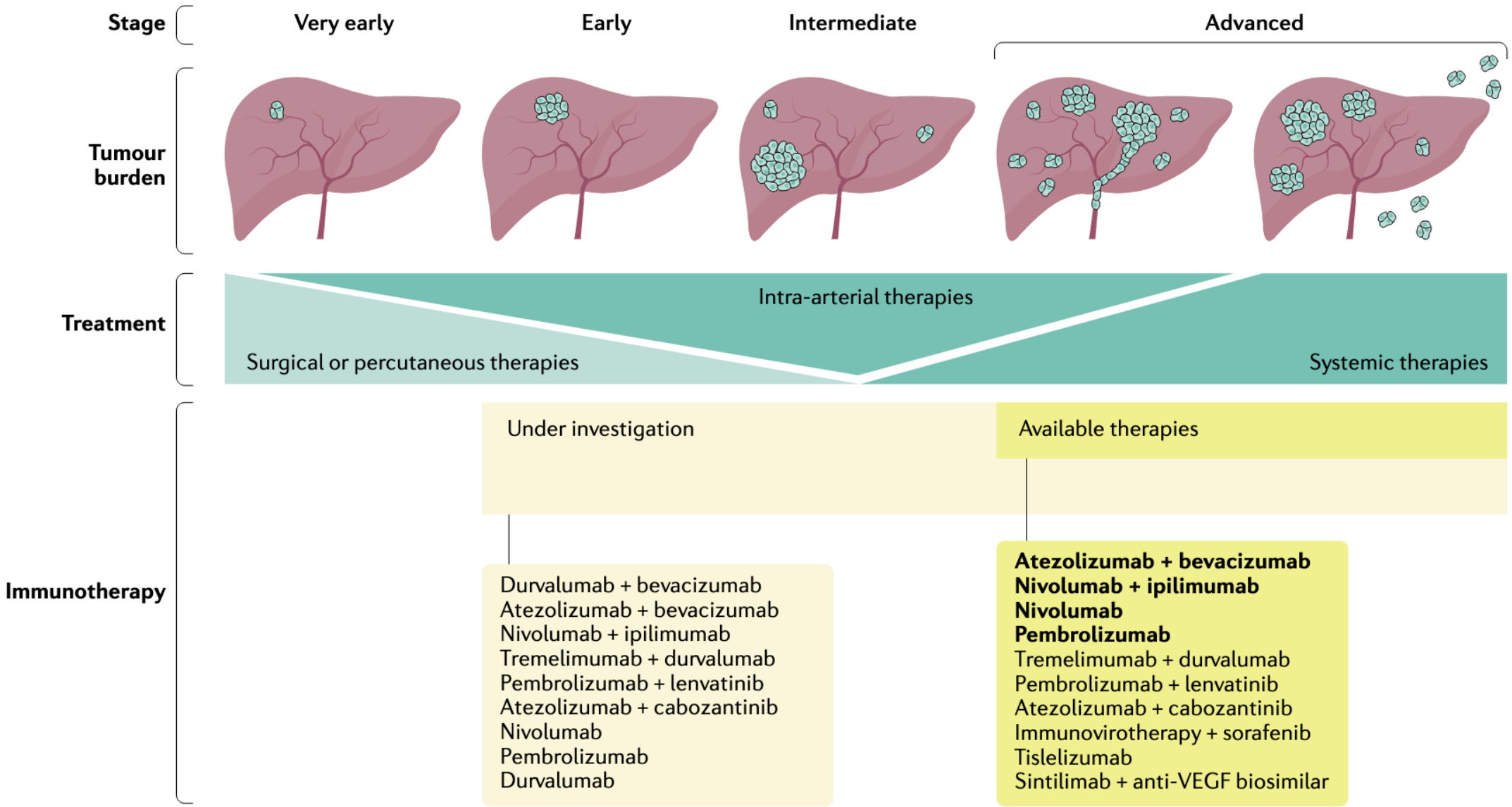


Reig M, J Hepatol 2022

ESMO Guidelines

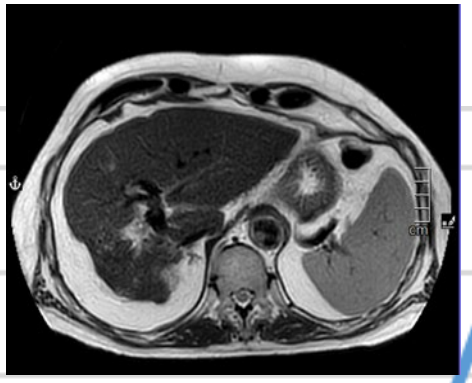


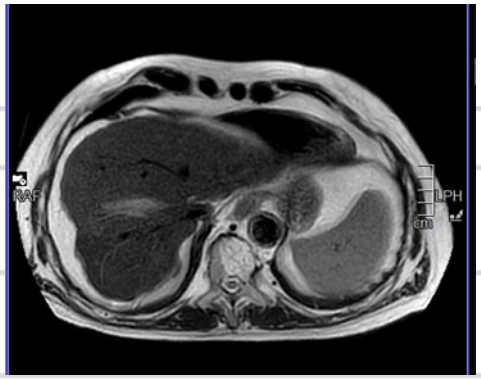
Ann Oncol 2021



Sangro B Nat Rev Gastro&Hepat 2021(18):525-543

Mr Luigi, 69 yrs old, perfumer, fit, HBV chronic liver disease, no comorbidities





1000

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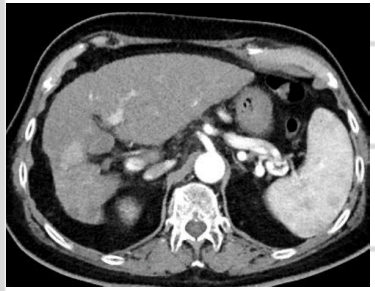
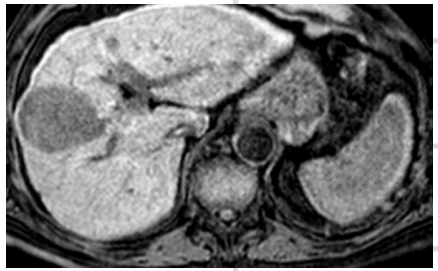
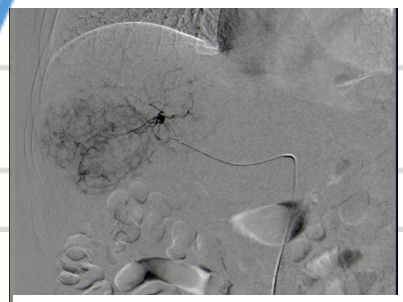
March 2022: pre-surgical evalutation; AFP 868 = 01/04/2022 AFP; I cycle atezo/beva
TVT MHV



Feb 2022: radiological PD AFP 417

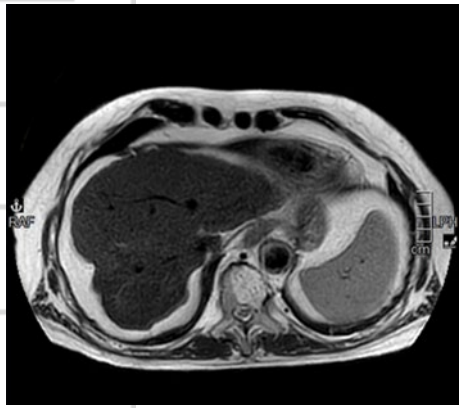


June 2021 AFP 81
July 2021 Y90 TARE



October 2021 AFP 44

22/04/2022 AFP 294; II cycle

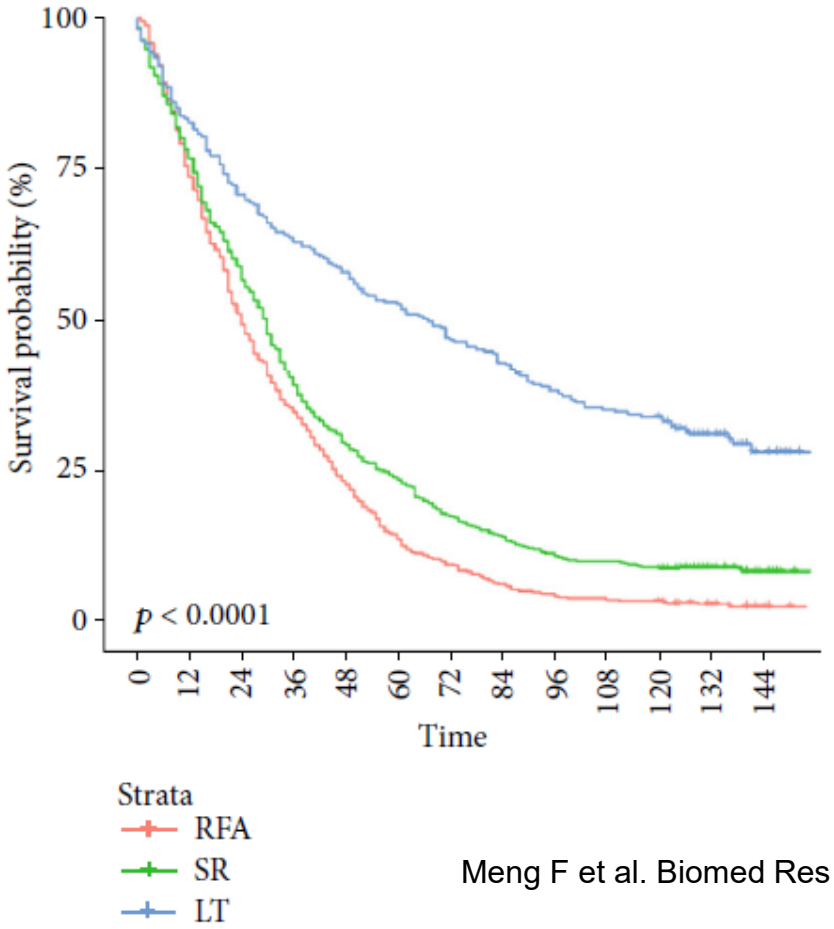


13/05/2022 AFP 38,9; III cycle

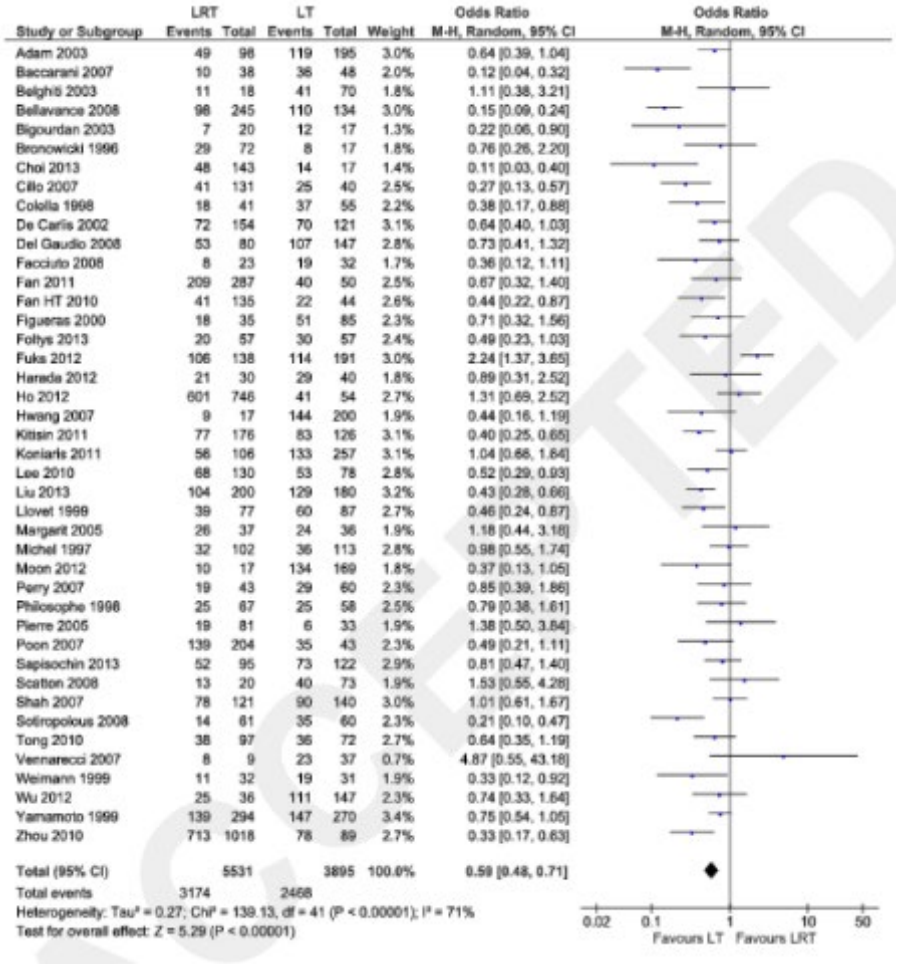
15/07/2022 AFP: 2,9; IV cycle

03/06/2022 AFP: 2,8; V cycle

In most patients Liver Transplantation is the best available treatment to cure HCC



Meng F et al. Biomed Res Int 2021



Intermediate Stage HCC

48 studies - 9835 patients

5-y OS and DFS was worse for all categories of loco-regional therapies, than for primary LT (HR): 0.59 (0.48-0.71), p<0.01

- LT has better overall survival than curative locoregional therapy **in intermediate stage HCC** and in Child-Pugh class B/C cirrhosis.

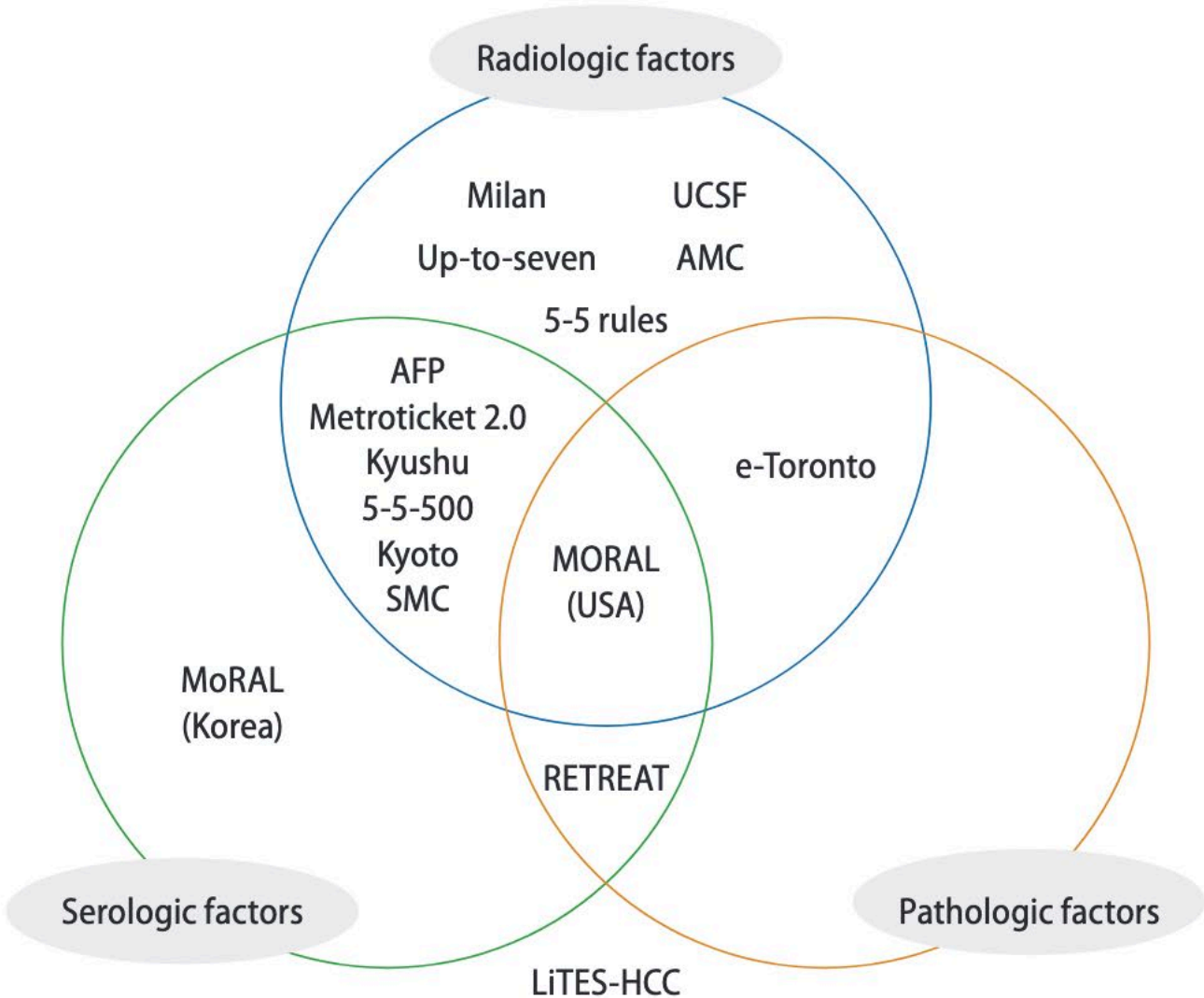


Figure 1. Prediction models based on recruited factors. UCSF, University of California, San Francisco; AMC, Asan Medical Center; AFP, alpha-fetoprotein; SMC, Samsung Medical Center; RETREAT, Risk Estimation of Tumor Recurrence After Transplant; LiTES-HCC, Liver Transplant Expected Survival-hepatocellular carcinoma.

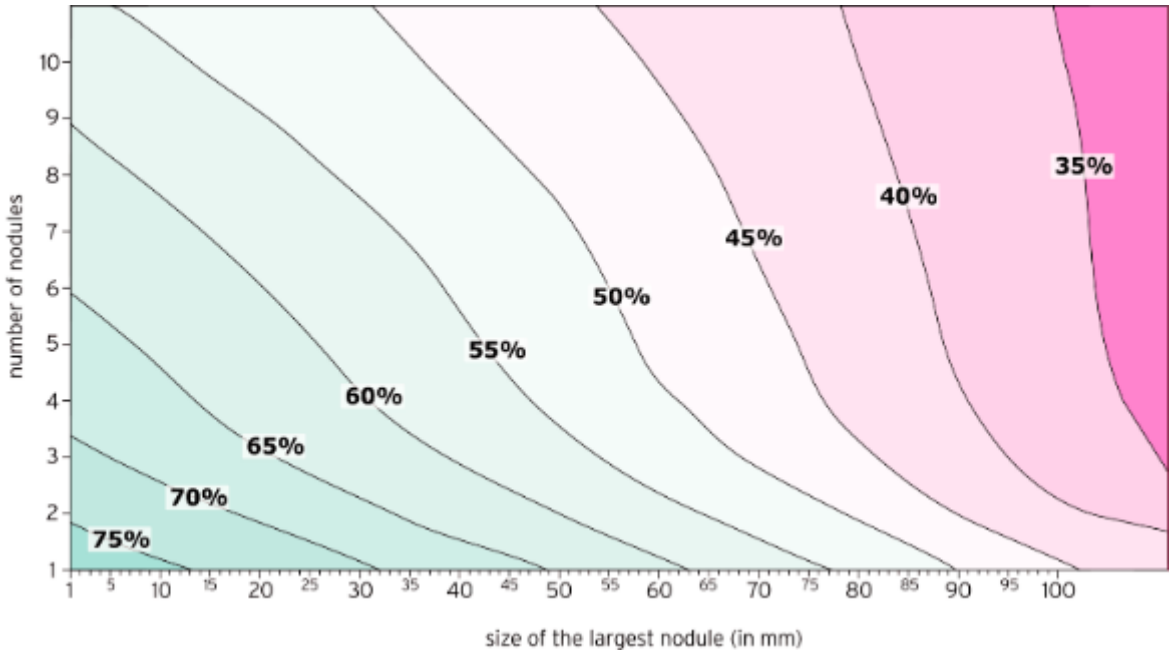
Patient selection

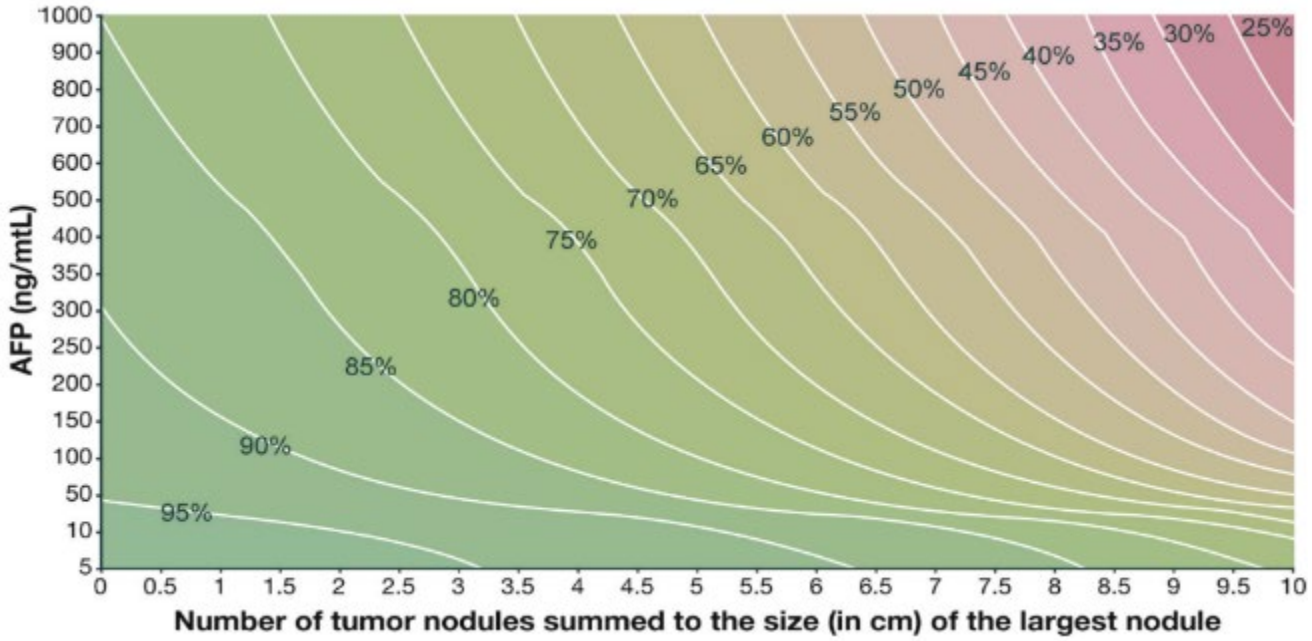
Tumor size, Tumor number and AFP as continuous variables

v. 1.0

www.hcc-olt-metroticket.org

v. 2.0





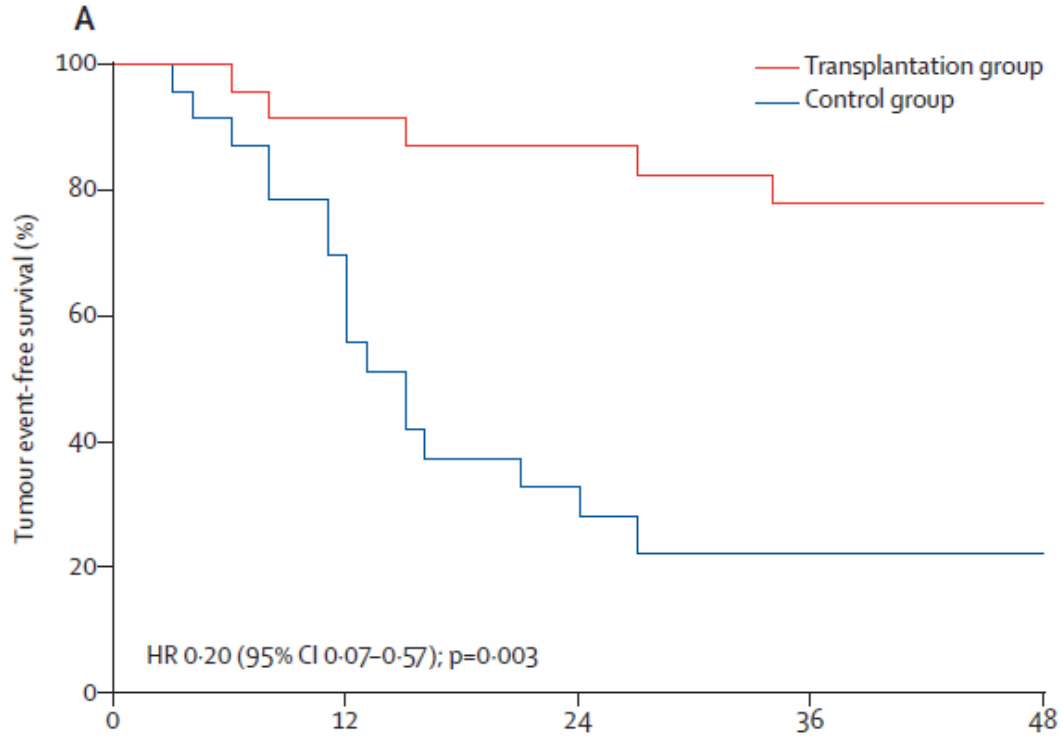
Accuracy of AFP-adjusted on tumor size criteria in predicting outcome was 0.721 (95%CI: 0.648%-0.793%), outperforming (c-statistics) Milan, UCSF, Shanghai-Fudan, Up-to-7 (P<.001), and AFP French (P=.044) models.

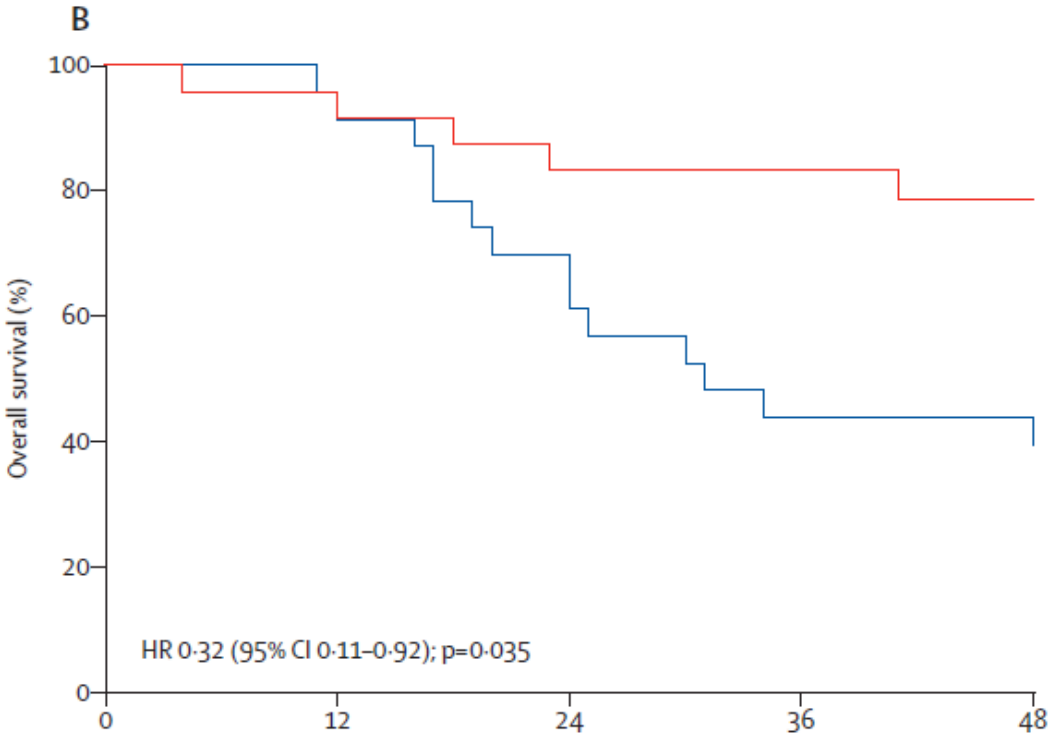
Mazzaferro V et al. Lancet Oncology 2009
Mazzaferro V, et al. Gastroenterology 2018
Lozanovski VJ et al. Br J Surg open 2022

9 Liver Transplant Centers in Italy (2011-2015)
70 months median follow-up
74 recruited pts. with HCC beyond Milan Criteria, Child A, no macrovascular invasion or extrahepatic spread
45 randomized pts after successful and sustained downstaging

XXL Trial

Expansion of conventional criteria for LT in HCC through downstaging



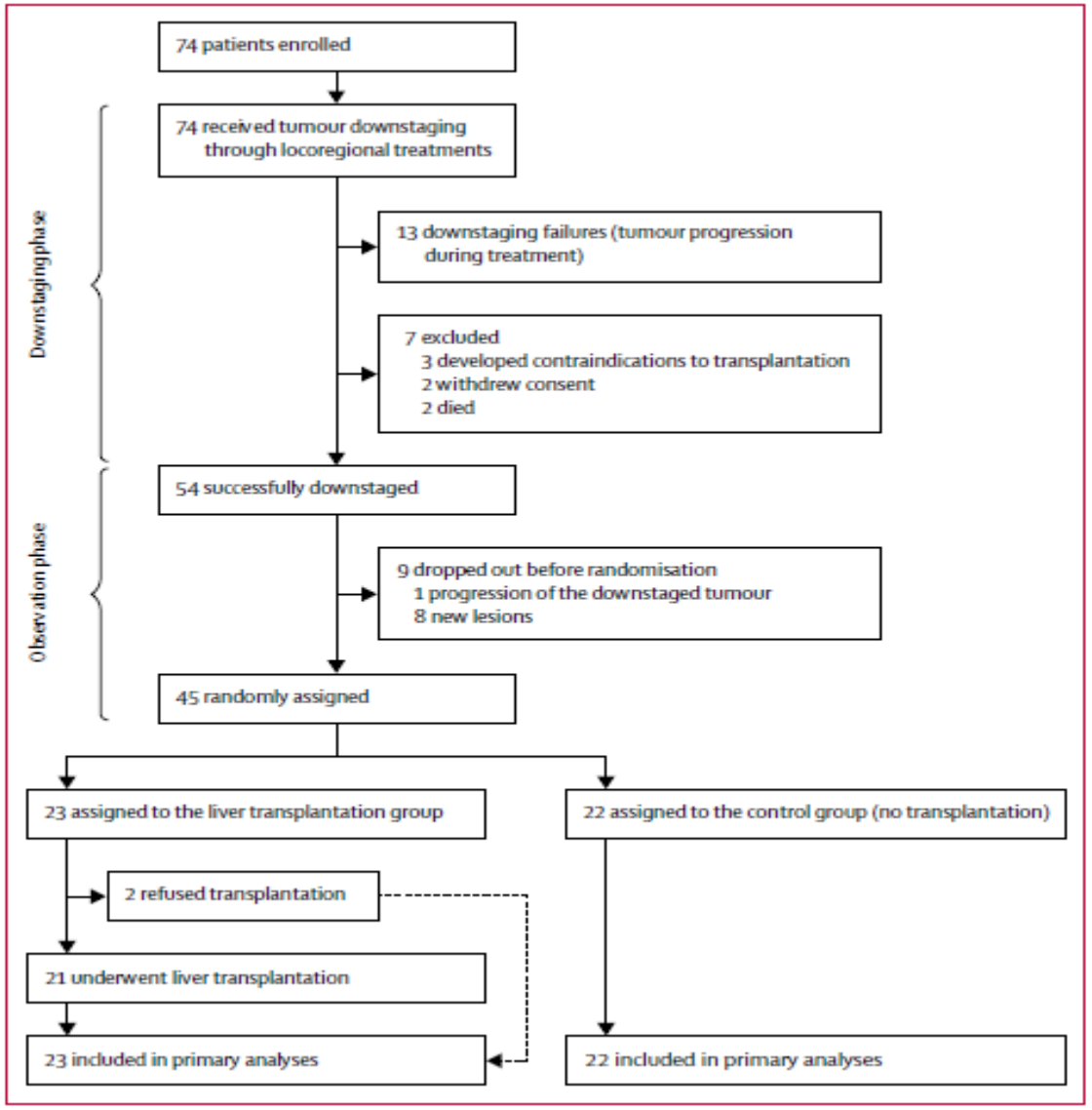


- After downstaging of eligible HCC beyond the Milan criteria, liver transplantation improves tumour event-free survival and overall survival compared with non-transplantation therapies.

- Post-downstaging tumour response could contribute to the expansion of HCC transplantation criteria.

Mazzaferro V et Al. Lancet Oncology 2020

What procedures to use for downstaging?



Trial design

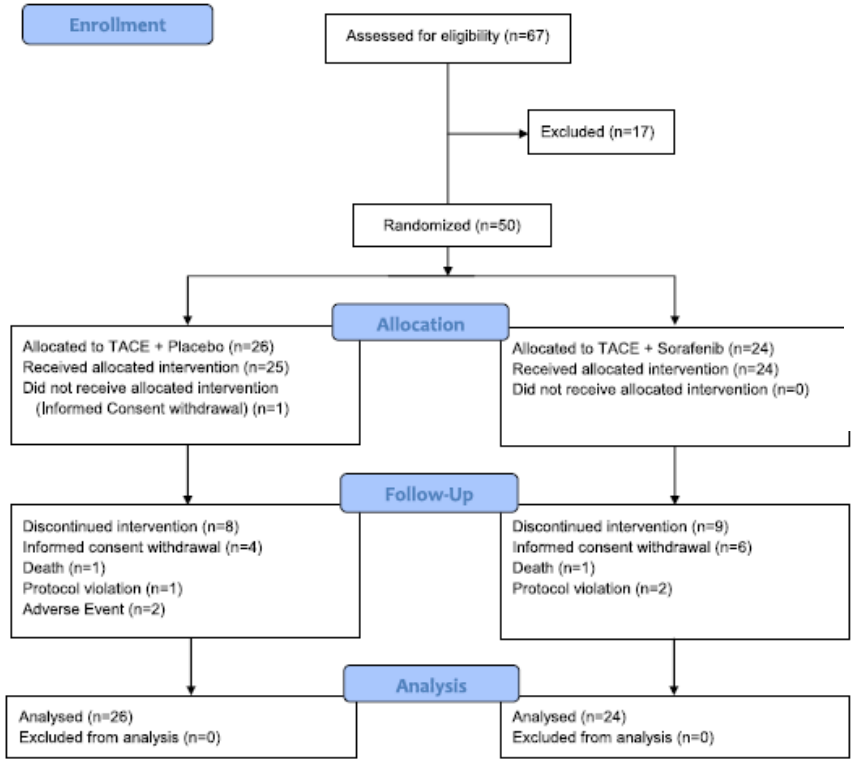
The XXL trial
(March 2011-2015)
74 pts, 45 randomized (23 LT and 22 non-LT)

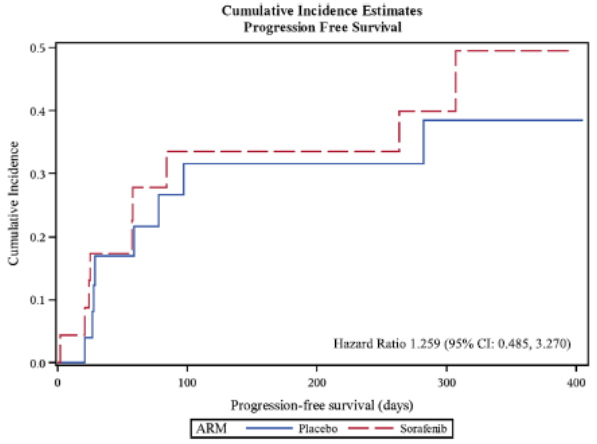
Downstaging procedures		
TACE only	12 (52%)	10 (45%)
RFA, SIRT, or surgery only	5 (22%)	3 (14%)
RFA	2 (9%)	2 (9%)
SIRT	1 (4%)	0 (0%)
Surgery*	2 (9%)	1 (5%)
Combinations of treatments	6 (26%)	9 (41%)
At least one of:		
TACE	17 (74%)	18 (82%)
RFA	8 (35%)	9 (41%)
SIRT	1 (4%)	1 (5%)
Surgical resection	4 (17%)	3 (14%)
Number of treatment sessions		
1	10 (43%)	8 (36%)
2	8 (35%)	5 (23%)
3	4 (17%)	3 (14%)
>3	1 (4%)	6 (27%)

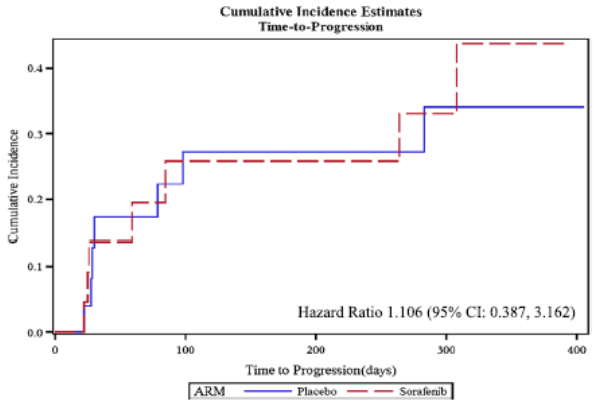
Baseline characteristics of downstaging procedures of randomized patients

Mazzaferro V et al. Lancet Oncology 2020
Tran NH, Hepatology 2022

Impact of neo-adjuvant Sorafenib treatment on liver transplantation in HCC patients – a prospective, randomized, double-blind, phase III trial







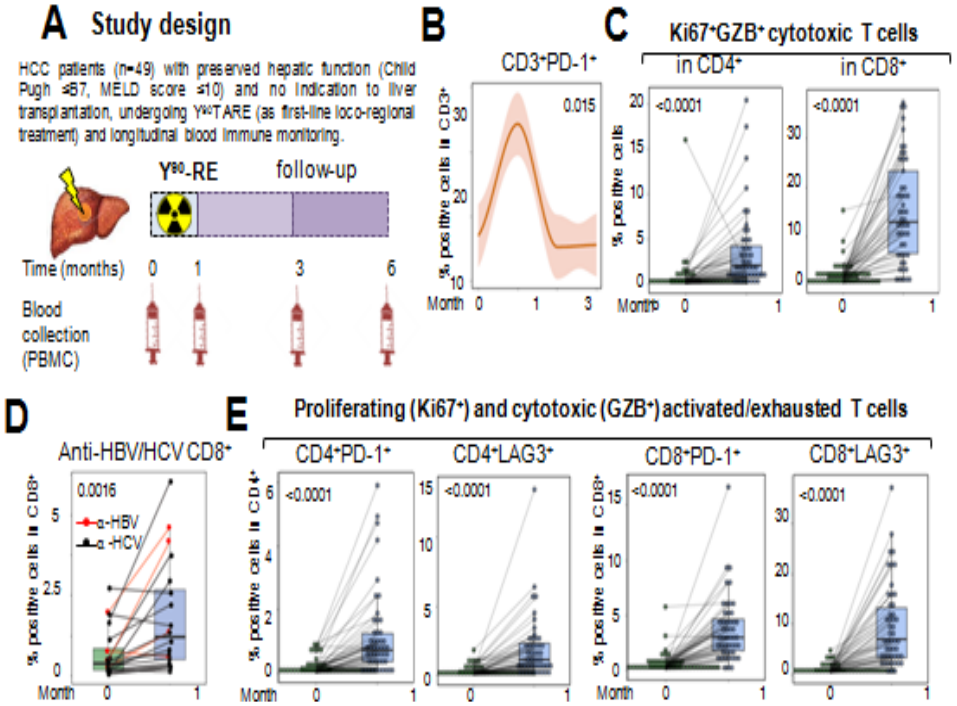
The TTP is similar after neo-adjuvant treatment with TACE and Sorafenib before LT compared to TACE and placebo.
The Tumour Response and PFS were comparable.

No usefulness in the add on of sorafenib to TACE/LRTs

Hoffmann K, BMC 2015

Combining LRTs and immunotherapy: proof of principle

Immune phenotype monitoring in the blood of 49 intermediate-advanced HCC patients undergoing Y90TARE treatment



Tumour radiation causes an immune-modulation of both adaptive and innate immune response, increasing the frequency of activated CD3+ T cells, regulatory T cells (Treg), and inflammatory (PD-L1+ and HLA-DR+) monocyte populations.

The immunomodulatory effect peaks one month after treatment indicating that Y90TARE-induced T cells are short-lived.

The increase of T cell sub-populations **is correlated with an objective response** but not with tumor control.

The add on of immunotherapy within the first month after Y90TARE could exploit the radiation-induced immune activation and convert it into a long-term immunological memory that might lead to prolonged HCC control.

Rivoltini L, Mazzaferro V, et al. Gut 2022

Downstaging with immunotherapy

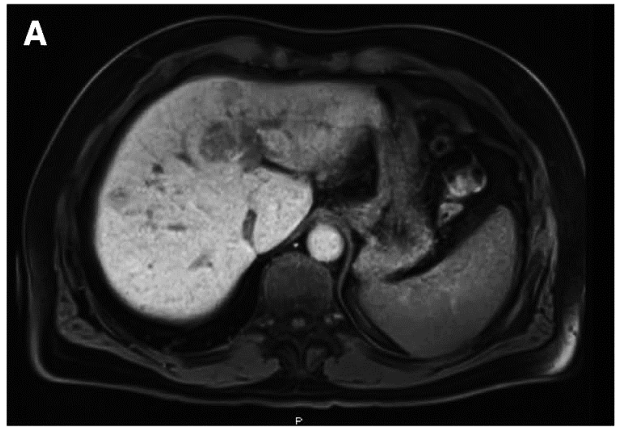
Variable	RECIST 1.1			HCC-Specific mRECIST		
	Atezolizumab–Bevacizumab (N=326)	Sorafenib (N=159)	Difference (P Value)†	Atezolizumab–Bevacizumab (N=325)	Sorafenib (N=158)	Difference (P Value)†
Confirmed objective response — no. (% [95% CI])‡	89 (27.3 [22.5–32.5])	19 (11.9 [7.4–18.0])	15.4 (<0.001)	108 (33.2 [28.1–38.6])	21 (13.3 [8.4–19.6])	19.9 (<0.001)
Complete response — no. (%)	18 (5.5)	0		33 (10.2)	3 (1.9)	
Partial response — no. (%)	71 (21.8)	19 (11.9)		75 (23.1)	18 (11.4)	
Stable disease — no. (%)	151 (46.3)	69 (43.4)		127 (39.1)	66 (41.8)	
Disease control rate — no. (%)§	240 (73.6)	88 (55.3)		235 (72.3)	87 (55.1)	
Progressive disease — no. (%)	64 (19.6)	39 (24.5)		66 (20.3)	40 (25.3)	
Could not be evaluated — no. (%)	8 (2.5)	14 (8.8)		10 (3.1)	14 (8.9)	
Data missing — no. (%)	14 (4.3)	18 (11.3)		14 (4.3)	17 (10.8)	
Ongoing objective response at data cutoff — no./total no. (%)	77/89 (86.5)	13/19 (68.4)		84/108 (77.8)	13/21 (61.9)	

Secondary Efficacy Outcomes of the Imbrave 150 trial

Finn R, et al. NEJM 2020

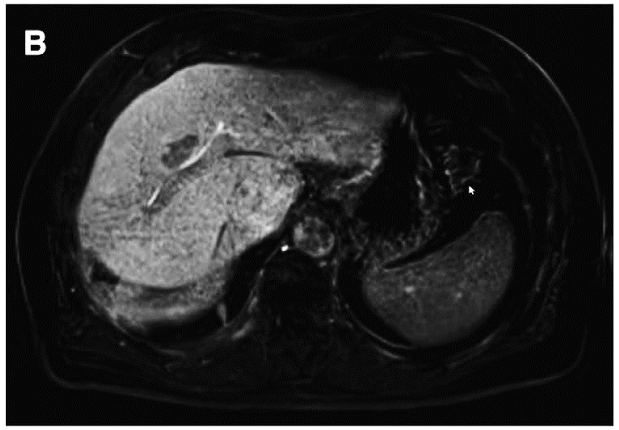
Systemic therapies before liver transplantation

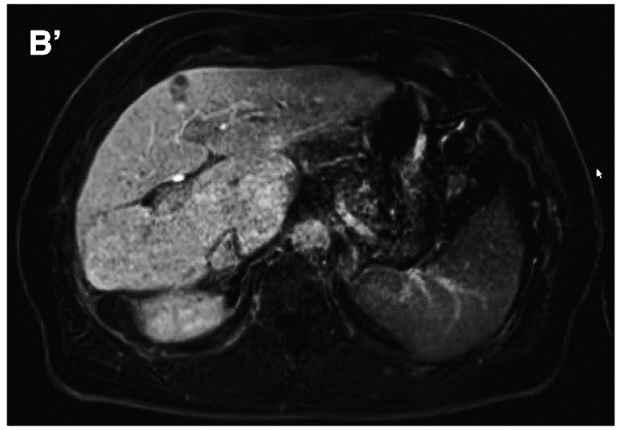
Downstaging before LT: a proof of principle



- 4 lesions before immunotherapy
- 3 lesions after nivo (1 RFA)

- Histology revealed an unifocal, poorly differentiated, 42-mm
- HCC in segment IVb/V





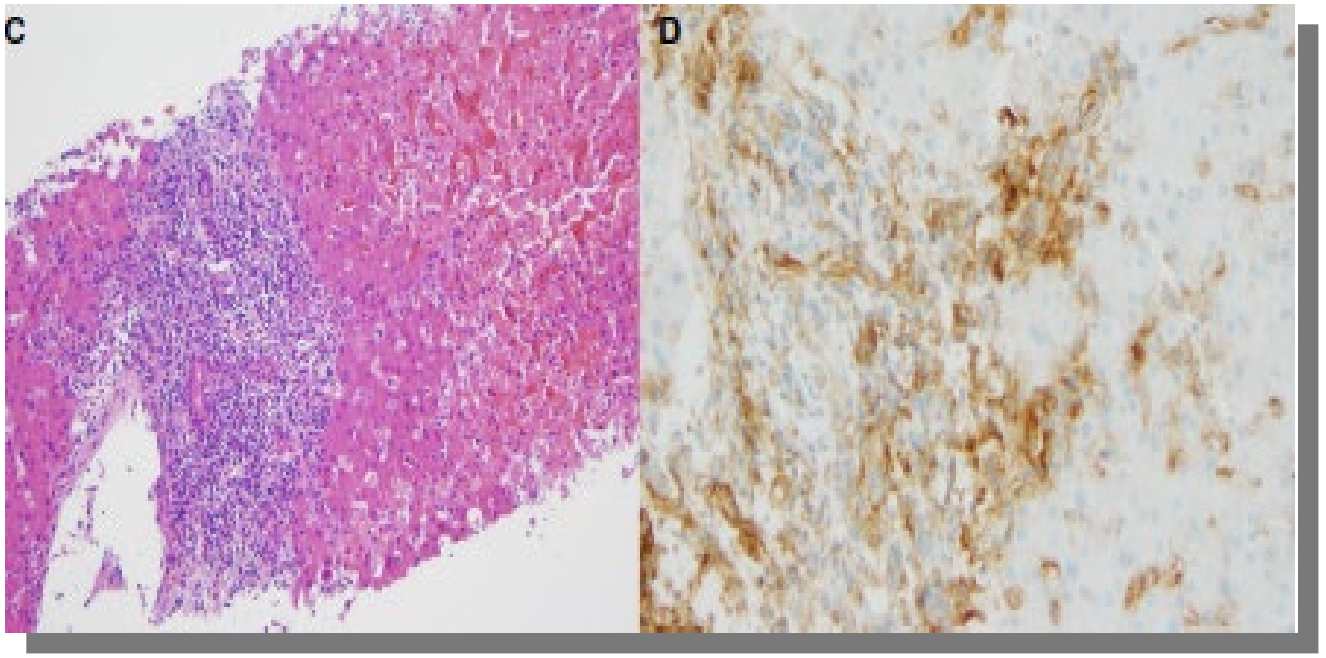
Immunotherapy (34 cycles ended **6 wks before LT**) has the potential to downstage patients with a tumor burden outside Milan criteria into Milan criteria **with no rejection and no 1 yr recurrence**

Schwacha-Eipper B, Hepatology 2020

Downstaging with immunotherapy before LT

There are several case reports in the literature addressing the use of immunotherapy as a neoadjuvant treatment before liver transplantation, **but globally its use in liver transplant candidates is conventionally considered with caution due to reports of severe allograft rejection, graft loss, and even death**

Downstaging before LT: risks related to time-to-transplant (10 days between immuno and LT)



Fatal acute hepatic necrosis in the immediate post-operative period **from a profound immune reaction likely propagated by nivolumab administered 10 days before LT**

PD-L1 staining of back-table (pre-implantation) liver biopsy was negative whereas **staining at acute event demonstrated that most inflammatory cells** in the portal tracts and lobules, including lymphocytes and macrophages/Kupffer cells, **expressed PD-L1**

Nordness MF Am J Transpl 2020

Immunotherapy combinations before LT

Reference	# of Patients	Drug(S) Used	Lines of Treatment Prior to ICI	Washout Period (Days)	Successful LT at 12 Months?	Rejection?	Tumor Regression/ Tumor Necrosis on Explant?
Qiao [62]	7	pembrolizumab or camrelizumab in combination with lenvatinib	unknown	40 (average)	In 7/7	Yes—in 1/7 (reversed with altered IS)	unknown
Tabrizian [69]	9	nivolumab	0–7	1–253	In 9/9	Yes—in 1/9 (reversed with altered IS)	In 3/9 patients
Schwacha-Eipper [70]	1	nivolumab	unknown	105	yes	No	unknown
Abdelrahim [71]	1	atezolizumab and bevacizumab	unknown	60	yes	No	unknown
Lizaola-Mayo [72]	1	nivolumab + ipilimumab	1 (TARE)	56	yes	No	unknown
Nordness [66]	1	nivolumab	4 (laparoscopic resection, sorafenib, TARE, TACE)	8	no	Yes—fatal hepatic necrosis, death on POD 10	yes
Schnickel [73]	5	nivolumab	unknown	10–183	In 4/5	Yes—in 1/5 (successful retransplant for massive hepatic necrosis)	unknown
Sogbe [76]	1	durvalumab	unknown	>90	yes	No	unknown
Chen [65]	1	toripalimab	3	93	no	Yes—fatal hepatic necrosis, death on POD 3	unknown
Aby & Lake [75]	1	nivolumab	4 (TARE, TACE, MWA, sorafenib)	16	yes	Yes—treated successfully	yes

IS: immunosuppression; POD: postop day; MWA: microwave ablation.

28 pts
6 rejections
2 death
1 retransplant

Adapted from Lominadze. Int J Mol Sci 2023

PD-1 inhibitor as bridge therapy to liver transplantation?

TABLE 1 Characteristics of the patients

No.	Age	Gender	ULD	Max tumor diameter (cm)	Max pre-LT AFP	No. of LRT	Salvage/type transplantation	Pathology Milan in/out	Cycles	Nivolumab (days pre-LT)	PRBC (U)	Duration of follow-up post LT (months)	Complication	Rejection	Recurrence
1	69	M	None	10	3	2	Yes/LDLT	Milan out within UCSF	21	18	0	23	None	None	None
2	56	F	HCV	5.4	4.4	2	No/DDLT	Milan out within UCSF	8	22	14	22	None	None	None
3	58	M	HBV	21	9.4	6	Yes/DDLT	Milan in	32	1	30	22	None	None	None
4	63	M	HCV, HIV	4.4	507	7	No/DDLT	Milan in	4	2	15	21	None	None	None
5	30	M	HBV	3.2	1493	2	Yes/DDLT	Milan in	25	22	0	16	None	Mild (low tacrolimus level)	None
6	63	M	HBV, HIV	2	158	0	No/DDLT	Milan in	4	13	1	14	Bile leak	None	None
7	66	M	HBV	2.5	479	2	Yes/DDLT	Milan in	9	253	7	14	None	None	None
8	55	F	HBV	2.8	820	3	No/DDLT	Milan in	12	7	0	8	None	None	None
9	53	F	NASH	8.7	124	1	Yes/DDLT	Milan out within UCSF	2	30	17	8	None	None	None

Tabrizian P, Am J Transpl 2021

Nivolumab was administered at a dosage of 240 mg every 2 weeks. Eight (89%) patients received their last dose **within 4 weeks of transplant**

Initial immunosuppression was with of 500 mg **methylprednisolone** tapered to prednisone 10 mg/day over 2 weeks + **MMF**, 1 g twice a day and **tacrolimus** to maintain a level of 10–12 ng/ml

At a median follow-up of 16 months (range, 8–23 months) post-LT **no severe allograft rejections/losses, tumor recurrences, or deaths occurred**

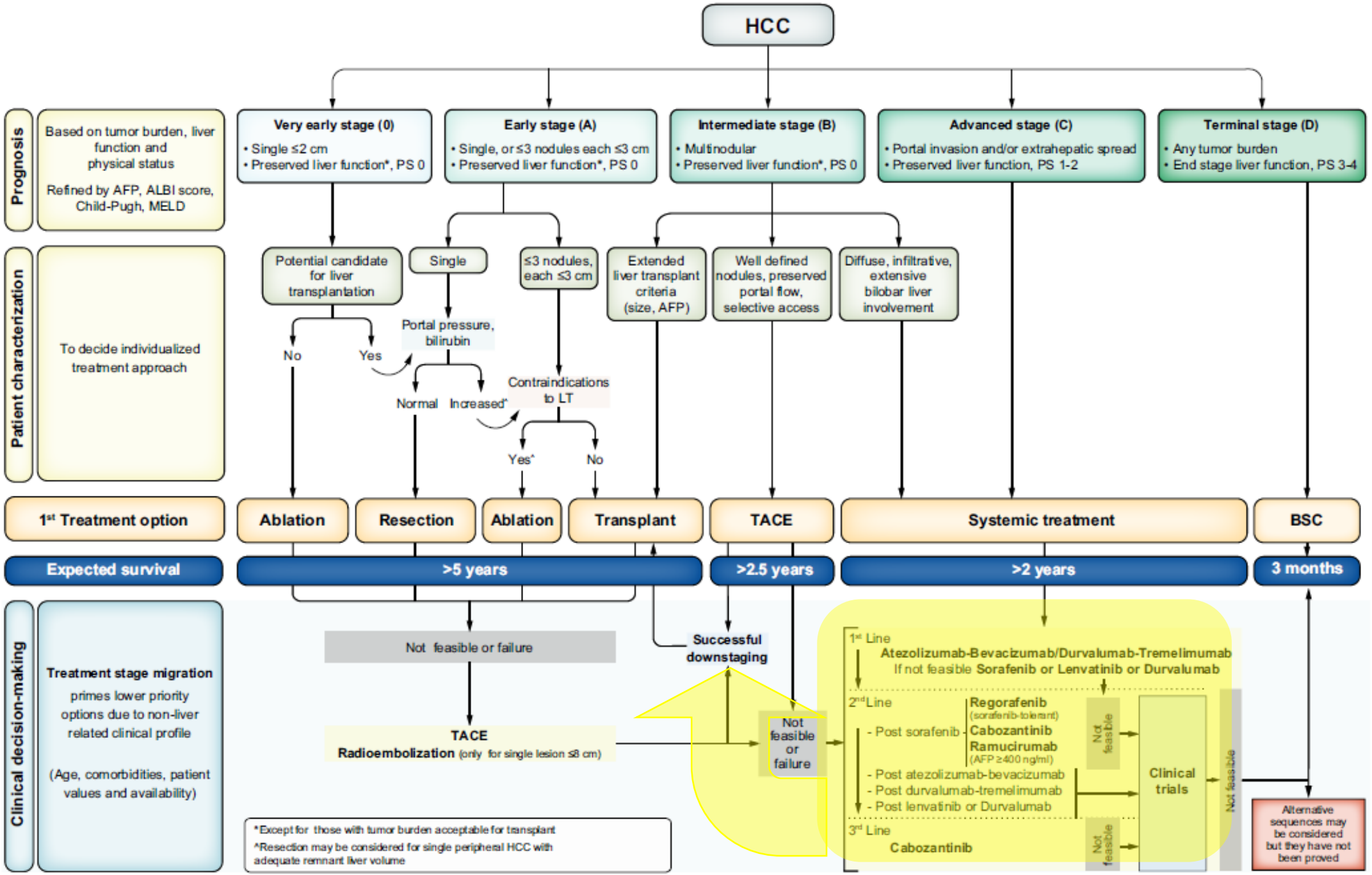
Explant pathology revealed near **complete (>90%) tumor necrosis in one third of the cases**

8 days, 4 weeks, 6 weeks…

..suggesting a very close relation between time of last administration and immunological imbalance responsible of rejection and suggesting to wait at least as long as the half time of the CPI administered

(approximately 20-28 days)

	Trade Name	Mechanism	Half-Life
Nivolumab	Opdivo	PD-1 Inhibitor	26.7 days (FDA 2014)
Pembrolizumab	Keytruda	PD-1 Inhibitor	23 days (FDA 2016)
Atezolizumab	Tecentriq	PD-L1 Inhibitor	27 days (FDA 2018)
Durvalumab	Imfinzi	PD-L1 Inhibitor	18 days (FDA 2018)
Ipilimumab	Yervoy	CTLA-4 Inhibitor	15.4 days (FDA 2015)


HCC
Prognosis
Based on tumor burden, liver function and physical status
Refined by AFP, ALBI score, Child-Pugh, MELD
Very early stage (0)
• Single ≤2 cm
• Preserved liver function*, PS 0
Early stage (A)
• Single, or ≤3 nodules each ≤3 cm
• Preserved liver function*, PS 0
Intermediate stage (B)
• Multinodular
• Preserved liver function*, PS 0
Advanced stage (C)
• Portal invasion and/or extrahepatic spread
• Preserved liver function, PS 1-2
Terminal stage (D)
• Any tumor burden
• End stage liver function, PS 3-4
Patient characterization
To decide individualized treatment approach
Potential candidate for liver transplantation
Single
≤3 nodules, each ≤3 cm
Extended liver transplant criteria (size, AFP)
Well defined nodules, preserved portal flow, selective access
Diffuse, infiltrative, extensive bilobar liver involvement
No
Yes
Portal pressure, bilirubin
Normal
Increased^
Contraindications to LT
Yes^
No
1st Treatment option
Ablation
Resection
Ablation
Transplant
TACE
Systemic treatment
BSC
Expected survival
>5 years
>2.5 years
>2 years
3 months
Clinical decision-making
Treatment stage migration
primes lower priority options due to non-liver related clinical profile
(Age, comorbidities, patient values and availability)
Not feasible or failure
Successful downstaging
TACE
Radioembolization (only for single lesion ≤8 cm)
Not feasible or failure
1st Line
Atezolizumab-Bevacizumab/Durvalumab-Tremelimumab
If not feasible Sorafenib or Lenvatinib or Durvalumab
2nd Line
- Post sorafenib
Regorafenib (sorafenib-tolerant)
Cabozantinib
Ramucirumab (AFP ≥400 ng/ml)
- Post atezolizumab-bevacizumab
- Post durvalumab-tremelimumab
- Post lenvatinib or Durvalumab
3rd Line
Cabozantinib
Not feasible
Not feasible
Clinical trials
Not feasible
Alternative sequences may be considered but they have not been proved
*Except for those with tumor burden acceptable for transplant
^Resection may be considered for single peripheral HCC with adequate remnant liver volume

P06-02

Safety and feasibility of Atezolizumab and Bevacizumab downstaging to liver transplantation of intermediate-advanced HCC: preliminary European experience on 7 patients

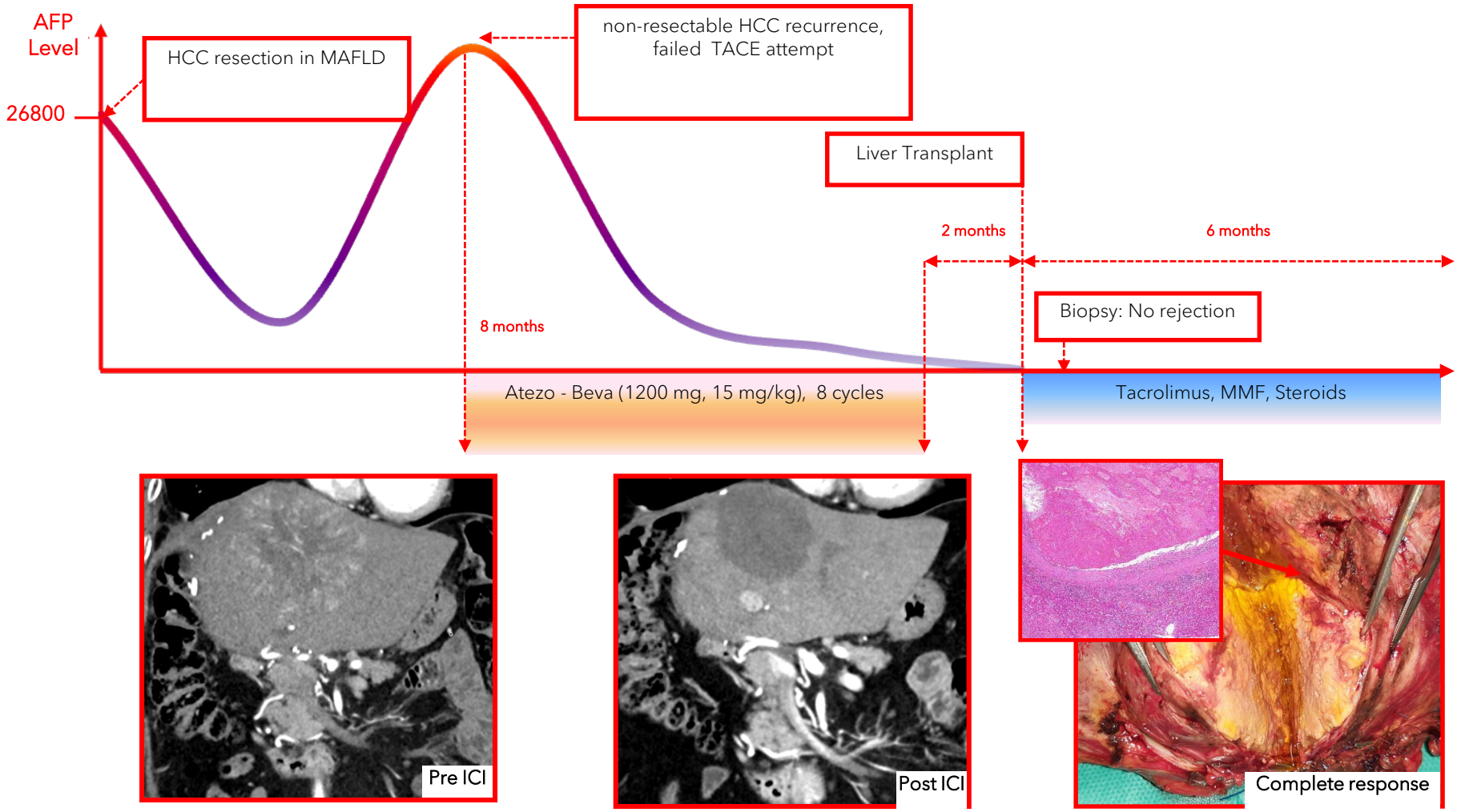
Sherrie Bhoori[1], Samuele Grandi[1], Valentina Bellia[1], Carlo Sposito[1 2], Marco Bongini[1], Banz Vanessa[3], Birgit Schwacha-Eipper[4], Maria Francesca Donato[5], Massimo Iavarone[5], Lucio Caccamo[6], Salvatore Gruttadauria[7 8], Bianca Magro[7], chiara mazzarelli[9], Luca Saverio Belli[9], Vincenzo Mazzaferro[1 2]

ESOT Survey
6/16 responding centers
11 pz receiving ICIs ahead of LT
7 atezo/beva

Results:
- No rejection
- No peripherative mortality
- 5 majors complications
  - 2 biliary
  - 3 vascular > 1 retransplant

Figure

Patients characteristics (=7 pts)	
Male (%) / Female (%)	6 (85%) / 1 (15%)
Age (median, range)	62 (58 – 72)
Underlying liver disease:	
- Viral Hepatitis	5 (71%)
- MAFLD	2 (29%)
Interventions before atezo+bev:	
- Surgery alone	1
- Multiple ablation	1
- Multiple TACE/TAE	2
- TACE/TAE + surgery	1
- TARE alone	1
- No previous loco-regional therapies	1
Tumor stage at inception of atezo+bev	
- Milan-In	0
- Milan-Out , Up7-In	2 (29%)
- Up7-Out	5 (71%)
Tumor stage at LT (radiology)	
- Milan-In	3 (43%)
- Milan-Out, Up7-In	0
- Up7-Out	4 (57%)
Tumor response at LT (explant pathology)	
- Complete necrosis	5 (71%)
- Partial necrosis	2 (29%)
Days on atezo+bev (median, range)	180 (90 – 660)
Days from last administration to LT (median, range)	82 (50 – 254)
Post-LT immunosuppression	
- CNI + mycophenolate + steroids	5 (72%)
- CNI + steroids	1 (14%)
- mTOR-i + mycophenolate	1 (14%)
Post-LT complications	
- Vascular complications	3 (43%)
- arterial thrombosis	2
- pulmonary embolism	1
- Biliary complications	2 (29%)
- Early graft rejection	0
Survival	
- Alive, tumor-free	6 (86%)
- Alive, with recurrence	1 (14%)
- Dead	0


AFP Level
26800
HCC resection in MAFLD
non-resectable HCC recurrence, failed TACE attempt
Liver Transplant
2 months
6 months
8 months
Biopsy: No rejection
Atezo - Beva (1200 mg, 15 mg/kg), 8 cycles
Tacrolimus, MMF, Steroids
Pre ICI
Post ICI
Complete response

Concerns in the use of immunotherapy before LT

- Will the add on of immunotherapy to LRT provide better outcomes?
- Will immunotherapy together with LRT be sufficient or do you have to rely on the coupling of immunotherapy plus antiangiogenic plus LRT?
- Will immunotherapy be sufficient without LRT?

  Studies with several flaws in data collection

- Is there a way of better selecting patients for neoadjuvant immunotherapy? Beyond conventional criteria? Progressing despite LRT? Post-resection recurrence?

  Urgent need for biomarkers

- Is the *test-of-time strategy* still valid? Are we suppose to stop treatments or carry on with it? Shall we prioritize rapid progressors or drop them out?

  Need of prioritization and allocation policies (cadaveric donor?)

- Will immunotherapy before LT impact on graft function and survival after LT?

  Attention on time to surgery and immunosoppressive regimens weighed against he risk of opportunist infections and tumor recurrence.

Sistemic therapies post-liver transplantation

Recurrence of HCC as the strongest predictor of post-transplant mortality in patients with HCC

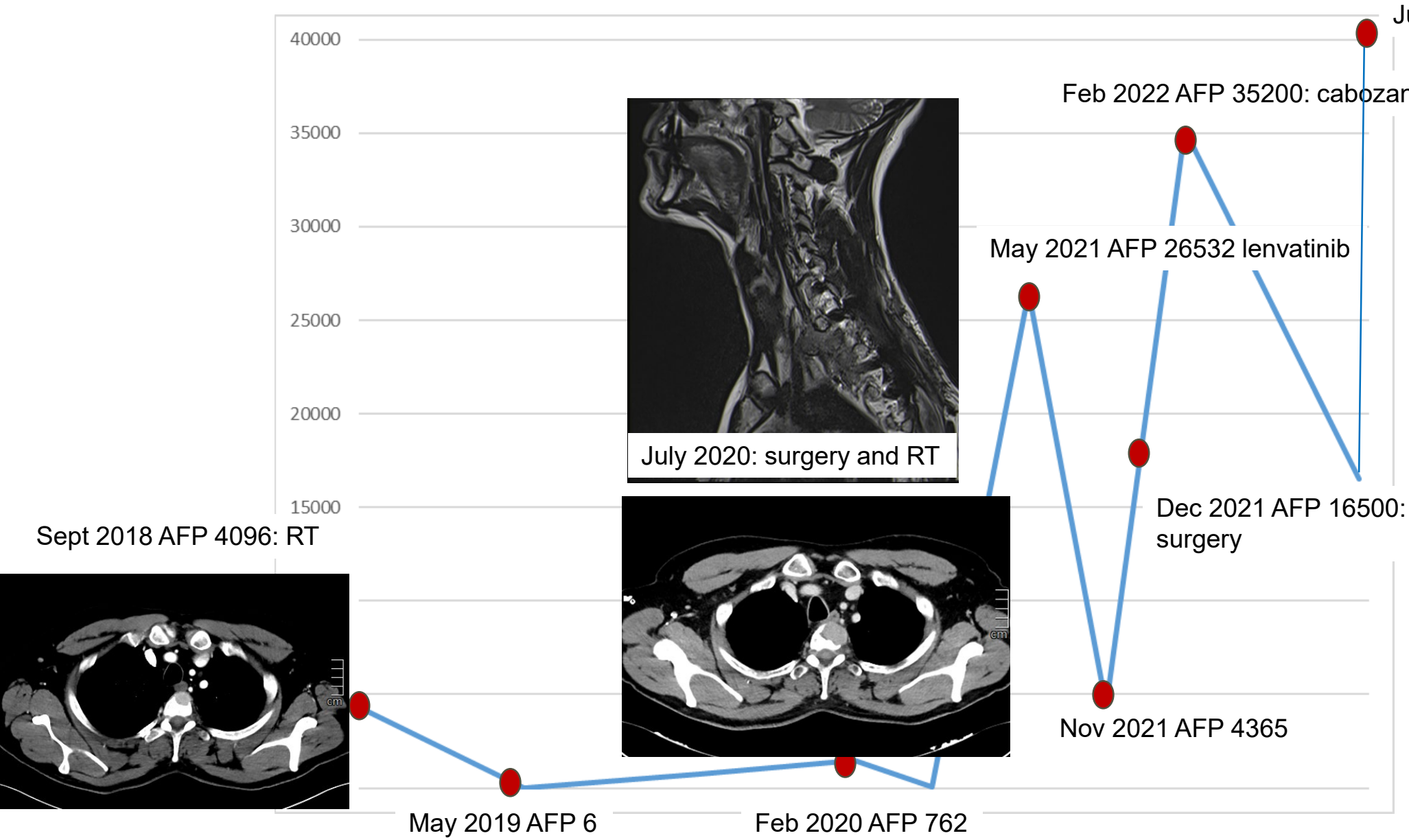
The strongest predictor of post-transplant mortality in patients with HCC is recurrence of HCC
(HR 4.17; 95% CI, 3.81–4.56)

Independent Predictors of Post-transplant Mortality in Patients With HCC ($P < .05$ Only)

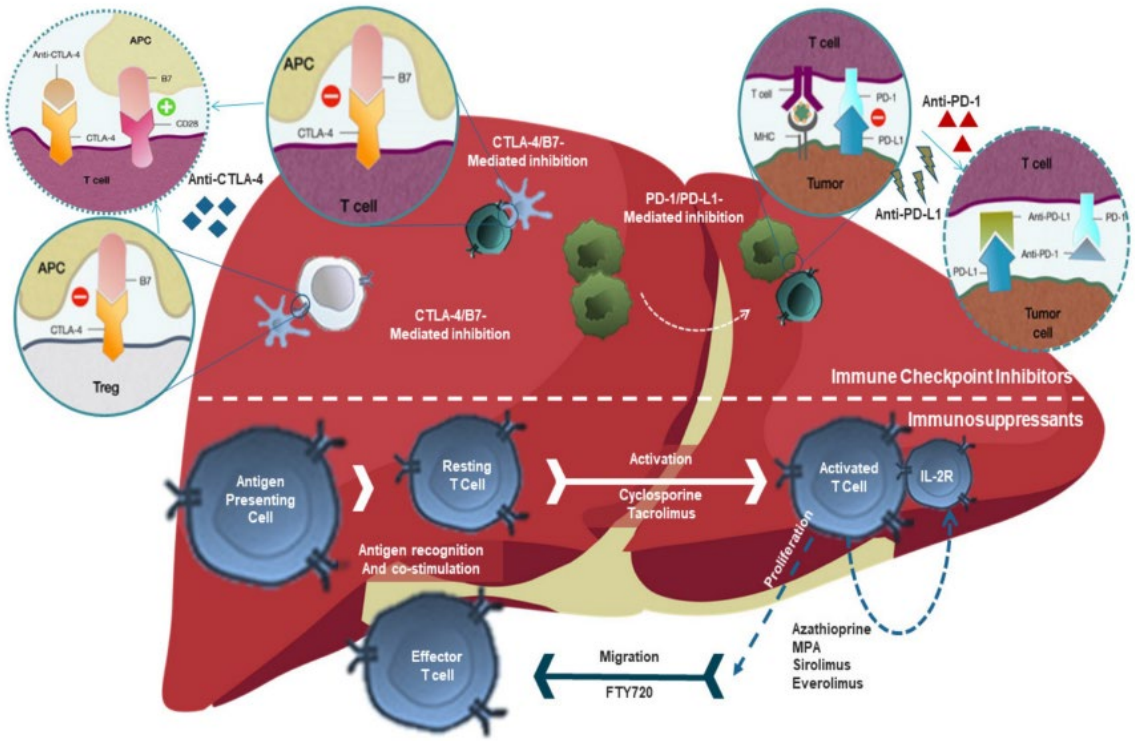
Predictor	Adjusted hazard ratio (95% CI)	*P*
Year of transplantation, per year	1.07 (1.05–1.08)	<.0001
Etiology: CHB[a]	0.67 (0.55–0.81)	<.0001
Etiology: NASH[a]	0.76 (0.65–0.89)	.0005
Age, per year	1.015 (1.009–1.022)	<.0001
Race: black	1.39 (1.23–1.57)	<.0001
Race: Asian	0.75 (0.62–0.90)	.0019
Private insurance	0.90 (0.83–0.97)	.0105
History of coronary artery disease	1.26 (1.01–1.57)	.0371
History of stroke	1.47 (1.01–2.13)	.0455
History of COPD	1.54 (1.22–1.95)	.0003
History of DM	1.21 (1.10–1.33)	<.0001
Last MELD score, per 1 point	1.010 (1.004–1.015)	.0007
Recurrence of HCC	4.17 (3.81–4.56)	<.0001

Younossi Z et al. Clin Gastroent Hepatol 2019

Mr Edoardo, 56 yrs old, aviation, HCC recurrence after LT in 2015 for HCC



Complex interplay between two opposite mechanism of action



The **effect of immunosuppression** on the native immune system (very tolerant per se) is responsible for:

- reduction of T-cell stimulation, proliferation and differentiation
- impairment of natural killer cell proliferation
- downregulated production of co-stimulatory molecules by antigen-presenting cells
- decrease in pro-inflammatory cytokines

These changes are exactly the opposite of what happens with **immunotherapy** that inhibits the “off” signals, allowing the T cells to kill cancer cells.

The risk is that the two mechanisms do not find a correct balance and fight against each other (rejection or poor tumor response)

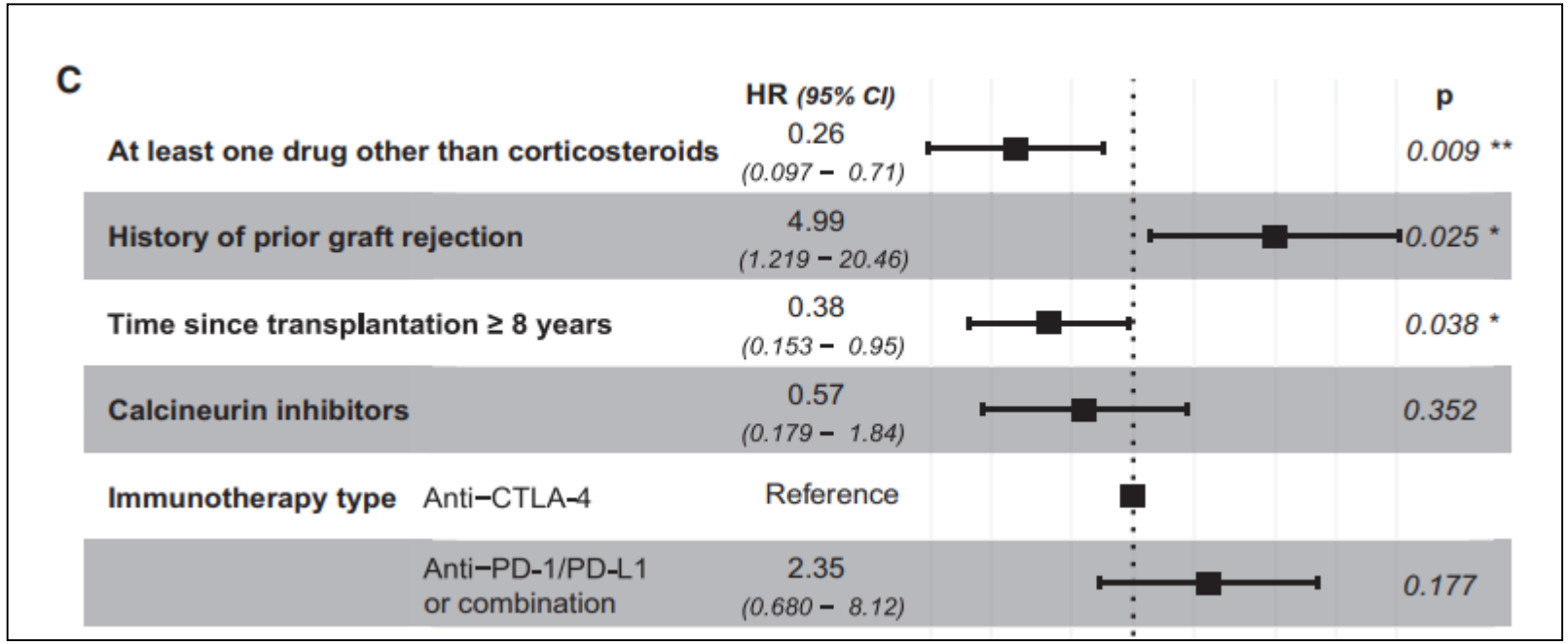
Abdelrahim M, Cancers 2022

Anugwom CM, Hepatoma Res 2022

Immunotherapy in SOT recipients (83 cases, 24 LT)

1. 83 SOT recipients, with **mean time to CPI 9,3 ± 7,6 yrs;** 24 LT 5,6 ± 4,6 (50% for HCC)
2. **39,8% rejections (33 pts); failure in 70% (only 2/33 pts had complete recovery)**
3. 2/3 changed immunosuppressive regimen at initiation of CPIs
4. **higher trend in risk with antiPD-1/PD-L1 CPIs**
5. **lower risk in steroids plus at least another drug**, but deleterious effect on cancer
6. histology of ATCR or mixed (no AMR, no C4d, no DSA reported)
7. PD: 56,6%, SD 3,6%, response: 27,7% (not reported 12%): **not reliable**

Sex—n (%)	
Male	61 (73.5)
Female	22 (26.5)
Age (y) at first CPI use—mean (SD)	61.33 (12.3)
Allograft type—n (%)	
Kidney	53 (63.9)
Liver	24 (28.9)
Heart	6 (7.2)
Follow-up duration after first CPI use—mean (SD) (n = 69)	30.9 (25.9)
Time since transplant (years) at first CPI use—mean (SD)	9.3 (7.6)
Kidney recipients	10.8 (8.4)
Liver recipients	5.6 (4.6)
Heart recipients	12.2 (4.2)
Cancer type—n (%)	
Melanoma	46 (55.4)
Hepatocellular carcinoma	12 (14.4)
Skin squamous cell carcinoma	10 (12.0)
NSCLC, squamous type	4 (4.8)
NSCLC, adenocarcinoma type	4 (4.8)
Merkel cell carcinoma	2 (2.4)
Renal cell carcinoma	2 (2.4)
Urothelial carcinoma	1 (1.2)
Duodenal adenocarcinoma	1 (1.2)
Colon adenocarcinoma	1 (1.2)
CPI regimen—n (%)	
Anti-PD-1/PD-L1	61 (73.5)
Nivolumab	31 (37.3)
Pembrolizumab	29 (34.9)
Avelumab	1 (1.2)
Anti-CTLA-4: ipilimumab	13 (15.7)
Combination	9 (10.8)
Sequential	7 (8.4)
Simultaneous	2 (2.4)
Immunosuppressive regimen at first CPI use—n (%)	
Corticosteroids	50 (60.2)
Calcineurin inhibitors	34 (41.0)
mTOR inhibitors	30 (36.1)
Antimetabolites	21 (25.3)
At least 1 drug other than corticosteroids	64 (77.1)
Modification of immunosuppressive regimen before CPI use	36/55 (65.5)



Rejections

Factors associated with graft rejection

D'Izarny-Gargas T , Am J Transpl 2020
Au KP, W J Gastrointestinal Surg 2021
Kumar V. Oncologist 2020
Kittai AS, J Immunother 2017

Immunotherapy in 28 LT recipients

	All	Rejection	No rejection	*P* value
Total (%)	28	9 (32)	19(68)	
Gender (M/F; %M)	22/6 (79)	6/3 (67)	16/3 (84)	0.29
Age	61 (53-66)	63 (34-67.5)	59 (54-64)	1.00
Year after transplant	3.9 (2.5-6.5)	2.9 (1.2-3.1)	5.3 (2.7-8.0)	0.02
Indication (%)				0.93
HCC	19 (68)	6 (67)	13 (68)	
Melanoma	8 (29)	3 (33)	5 (26)	
SCC of lung	1 (4)	0 (0)	1 (5)	
Line of systemic therapy	2 (1-3)	2 (1-3)	2 (1-4)	0.52
Immunotherapy by drug (%)				0.92
Nivolumab	15 (54)	5 (56)	10 (53)	
Pembrolizumab	10 (36)	3 (33)	7 (37)	
Ipilimumab	4 (14)	1 (11)	3 (16)	
Immunotherapy by class (%)				1.00
PD1/PD-L1	24 (86)	8 (89)	16 (84)	
CTLA-4	3 (11)	1 (11)	2 (11)	
Both	1 (4)	0 (0)	1 (5)	
PD-L1 positivity (%)				
Graft	5/7 (71)	4/4 (100)	1/3 (33)	0.053
Tumor	4/8 (50)	2/3 (67)	2/5 (40)	0.47
Immunosuppression (%)				
Single agent tacrolimus	10 (36)	2 (22)	8 (42)	0.31
Single agent mTOR-inhibitor	6 (21)	3 (33)	3 (16)	0.29
Tacrolimus with mTOR-inhibitor	5 (18)	1 (11)	4 (21)	0.52
Others	7 (25)	3 (33)	4 (21)	0.48
Acute rejection (%)	9 (32)			
Mortality in 30 d (%)	6 (21)	5 (56)	1 (5)	0.002

Descriptive characteristics of 28 pts treated with immunotherapy after LT

	All	Nivolumab	Pembrolizumab	*P* value
Total (%)	19	14 (74)	5 (26)	
Rejection (%)	6 (32)	5 (36)	1 (20)	0.52
Early mortality (%)	5 (26)	5 (36)	0 (0)	0.12
Line of systemic therapy	2 (1-3)	3 (2-4)	2 (1-2)	0.03
Tumour PD-L1 positivity (%)	3/7 (43)	3/7 (43)	0/0 (-)	
Best treatment response (%)				
Complete response	2 (11)	0 (0)	2 (40)	0.03
Partial response	0 (0)	0 (0)	0 (0)	0.64
Stable disease	2 (11)	1 (7)	1 (20)	0.58
Progressive disease	8 (42)	7 (50)	1 (20)	0.03
Progression-free survival	2.5 ± 1.0	1.3 ± 1.1	12.4	0.004
Overall survival	7.3 ± 2.7	4.0 ± 3.4	19.2	0.006

Descriptive characteristics of 19 pts treated for HCC recurrence

1. 28 SOT recipients, all LT with **median time from LT to CPI 5,5 vs 2,9 yrs (no rejection vs rejection)**
2. **32% rejections; graft failure most of patients**
3. higher risk in HCC early recurrence
4. 100% PD-L1 staining
5. need of careful immunosuppressive regimens (no increase rejection on mTOR-i)

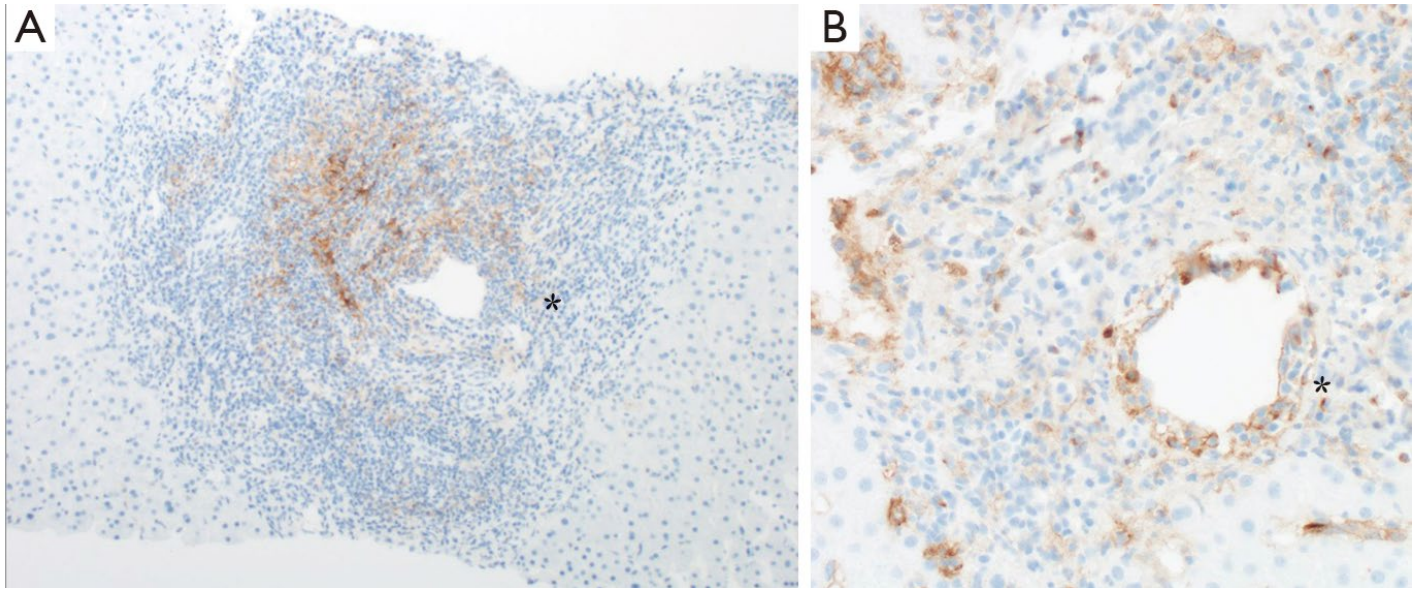
Au KP, W J Gastrointestinal Surg 2021

Allograft rejection and PD-L1 immunostaining on graft lymphocytes

DeLeon T , J Gastroint Oncol 2018

ICIs and allograft rejection in LT recipients

Immunotherapy	Graft rejection	Allograft PD-L1 staining
Nivolumab	No	–
Pembrolizumab	No	0%
Nivolumab	No	0%
Nivolumab	No	0%
Nivolumab	No	–
Nivolumab	Yes	30%
Pembrolizumab	Yes	25%



Five patients were evaluable for liver allograft lymphocyte PD-L1 expression. All three patients without allograft rejection had 0% allograft PD-L1 staining. However, both cases of allograft rejection in this cohort were found to have allograft lymphocyte PD-L1 expression with a median PD-L1 lymphocyte expression of 27.5% (range, 25–30%)

BRIEF REPORT

OPEN

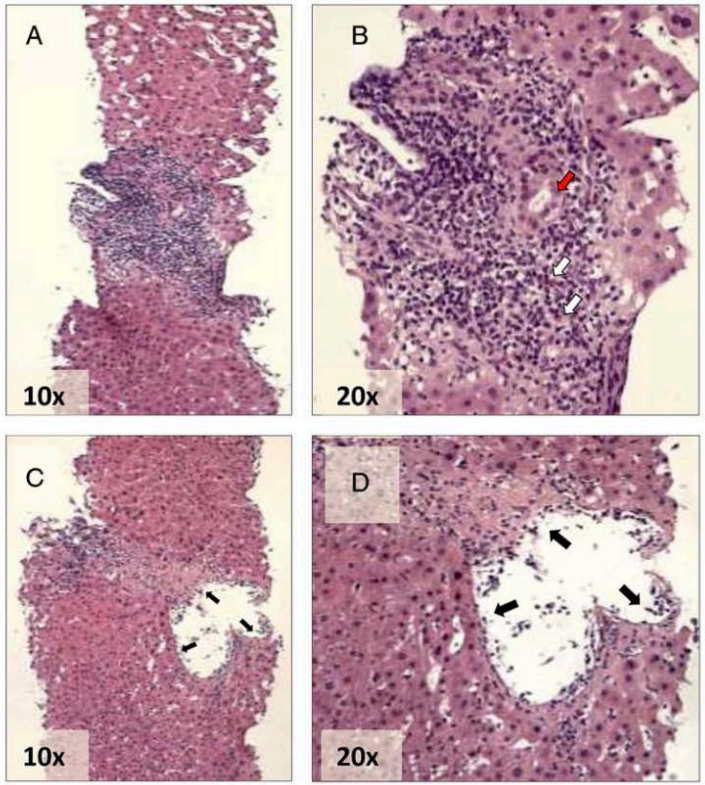
Feasibility, safety, and outcome of second-line nivolumab/ bevacizumab in liver transplant patients with recurrent hepatocellular carcinoma

OS from start sorafenib
- Nivo+beva 26.5 ± 10 m
- Regorafenib 5.8 ± 6 m
- BSC 5.5 ± 5.2 m

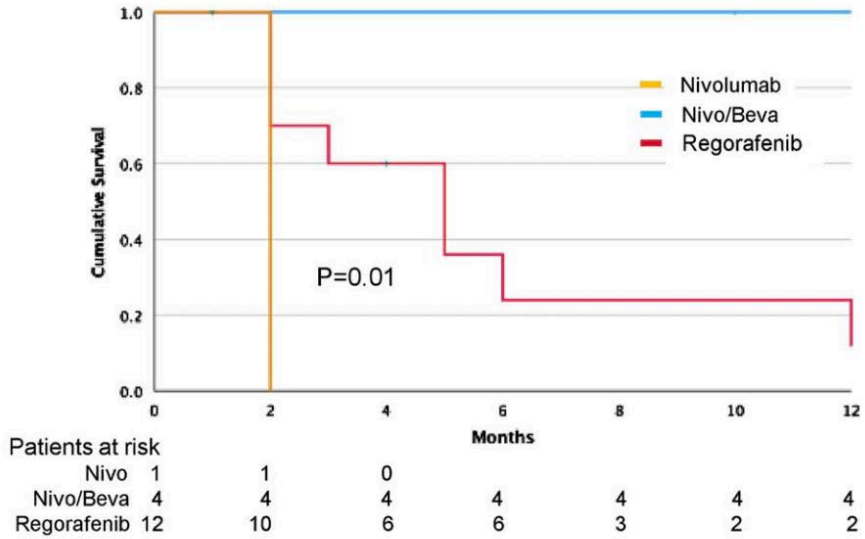
Proof of concept study

- Period 2/2018 > 9/2021
- HCC-R 14.5 m postLT (4-106)
- 22 patients
  - 4 BSC
  - 18 sorafenib
- PD 17/18 after 6 m
  - 12 regorafenib
  - 5 nivolumab
    - 4 nivo + beva

Panel (A)



Panel (B)



Di Marco L, Pivetti A, Foschi FG, d'Amico R, Schepis F, Caporali C, et al. Liver Transpl. 2023

Concerns in the use of immunotherapy after LT

- There is a very delicate balance between immunosuppresion and immunotherapy; data on this is not clear. **Severe and sometimes fatal rejections have been described but also relatively safe situations have been reported**.

- The literature (case reports, case series, single center experiences) suggests a protective effect over rejection of: time from transplantation, type of immunotherapy, immunosuppressive regimens; these, together with PD-1/PD-L1 staining **may help in choosing the best candidate after LT.**

- There is an overlap between patients experiencing rejection and those experiencing immunotherapy resistance. **ALT, fibroscan and DSA may help in identifying pts with a high risk of TCMR and resistance to immunotherapy**

- Very thorough biochemical and histological monitoring is necessary, **patients should be well counseled and provided consent on both efficacy and risks**

- Probably as things are now, we should propose immunotherapy to **long-time transplanted patients, after failure of all possibile treatments and with mTOR-i (and steroids?).**

Consider efficacy of comparator

Conclusions

- Exploring new horizons is part of the human nature and an intrinsic feature of the medical comunity. We have to make sure that what we explore **is better (and at least as safe) than the comparator**

- In the downstaging context **LRTs are the mainstay of HCC treatments** and CPIs should be added on (until we have otherwise evidence)

- Strong data helps us in this but tranplantation remains **an orphan indication** (before and expecially after)

- Preclinical studies are also needed to enhance our understanding of the **complex interactions between the immune system, cancer neoantigens, and alloantigens**

- We should do as we always have in LT: brainstorm together and **collect multicentric and prospective data** able of helping us compare areas of the world, draw indications, setting the base for future studies.

Collect multicentric data…