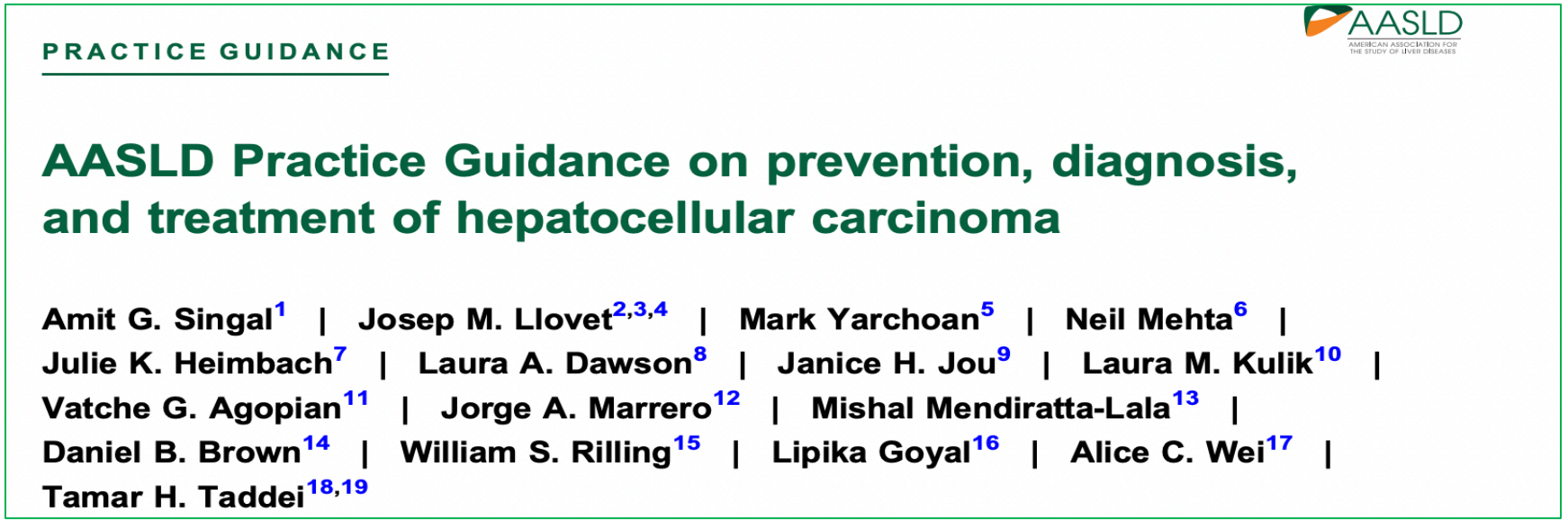
Updated AASLD HCC Practice Guidelines



PRACTICE GUIDANCE

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma

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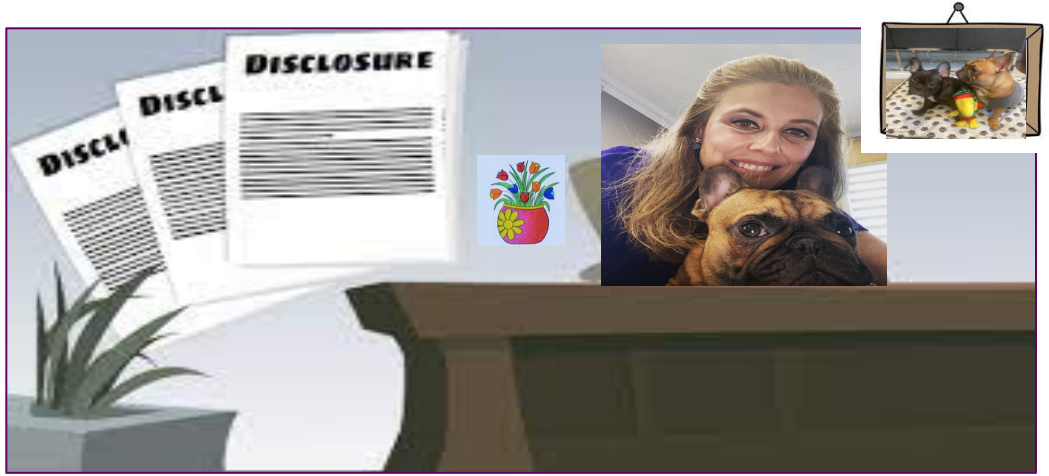
Disclosures

- **Advisory/consulting** : AstraZeneca, Eisai, Exelixis, Fujifilm, Genetech/ Roche
- **Research funding**: Glycotest, HCC Target
- **Steering committee:** AstraZeneca, Genetech/Roche

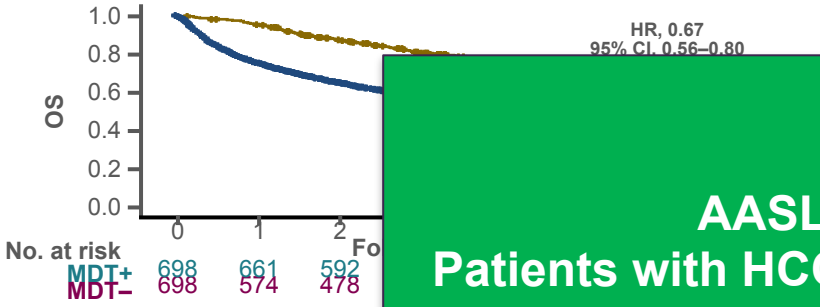


HCC Mortality

Cancer Type	Incidence	Mortality	Mortality Ratio
Breast	2,261,000	685,000	0.30
Lung	2,207,000	1,796,000	0.81
Prostate	1,414,000	375,000	0.27
Colon	1,149,000	577,000	0.50
Stomach	1,089,000	769,000	0.71
Liver	**906,000**	**830,000**	**0.92**

Roberts L AASLD 2023

Multidisciplinary Care



Matched cohort (N=1396) of pat… sin…

BCLC stage	Expected C…		
A (n=142)	>6…		
B (n=28)	2…		
C (n=100)	1…		
D (n=51)	<3		13.4

Real-world evidence shows MDT care yields OS outcomes that meet (BCLC A) or exceed (BCLC B, C and D) expectations according to BCLC stage[2]

AASLD advises:
Patients with HCC should be discussed and managed in a multidisciplinary care setting
(Level 3, Strong Recommendation).

Sinn DH, et al. *PLoS One* 2019;14:e0210730. Matsumoto MM, et al. *Cardiovasc Intervent Radiol* 2021;44:1070–1080. . Zhang J et al. Curr Oncol. 2013;20:e123–31.

HCC Surveillance

Population group	Incidence of HCC
Sufficient risk to warrant surveillance	
Child-Pugh A–B cirrhosis, any etiology Hepatitis B Hepatitis C (viremic or post-SVR) Alcohol associated cirrhosis Nonalcoholic steatohepatitis Other etiologies	≥1.0% per year
Child-Pugh C cirrhosis, transplant candidate	
Non-cirrhotic chronic hepatitis B Man from endemic country[a] age >40 y Woman from endemic country[a] age > 50 y Person from Africa at earlier age[b] Family history of HCC PAGE-B score ≥ 10[c]	≥0.2% per year
Insufficient risk and in need of risk stratification models/biomarkers	
Hepatitis C and stage 3 fibrosis	< 0.2% per year
Noncirrhotic NAFLD	*annual HCC incidence of 0.008 per 100 person-years*

NEW!

NEW!

Ultrasound + AFP

US alone *53%* (95% CI 35%-70%) sensitivity for early HCC
VS.
US + AFP *63%* (95% CI 48% - 75%) sensitivity for early HCC

Age (years)		Gender		Platelet count ($\times 10^9$/L)	
16–29	0	Female	0	>200	0
30–39	2	Male	6	100–199	6
40–49	4			<100	9
50–59	6				
60–69	8				
>70	10				

0 – 25 points: ≤ 9*, low risk; 10-17, moderate risk; and ≥ 18 high risk

* ***LIRADS NOT validated in PAGE- B < 9***

AASLD recommends against HCC surveillance in patients with life-limiting comorbid conditions that cannot be remedied by liver transplantation or other directed therapies
(Level 5, Strong Recommendation).

Tzartzeva K et al. Gastroenterology. 2018;154: 1706–718 e1701.

Biomarkers for Early HCC Surveillance

Test	Early detection research network (EDRN) phase of validation	Performance characteristics	
US plus AFP[55]	5	Sensitivity	61%
		Specificity	92%
AFP-L3%[69]	3	Sensitivity	62%
		Specificity	90%
DCP[69]	3	Sensitivity	40%
		Specificity	81%
Multitarget algorithm[70]	2	Sensitivity	82%
		Specificity	87%
GALAD[71]	2/3	Sensitivity	54–72%
		Specificity	90%
Doylestown plus[72]	2/3	Sensitivity	90%
		Specificity	95%

FDA approved: risk stratification but not HCC surveillance in USA

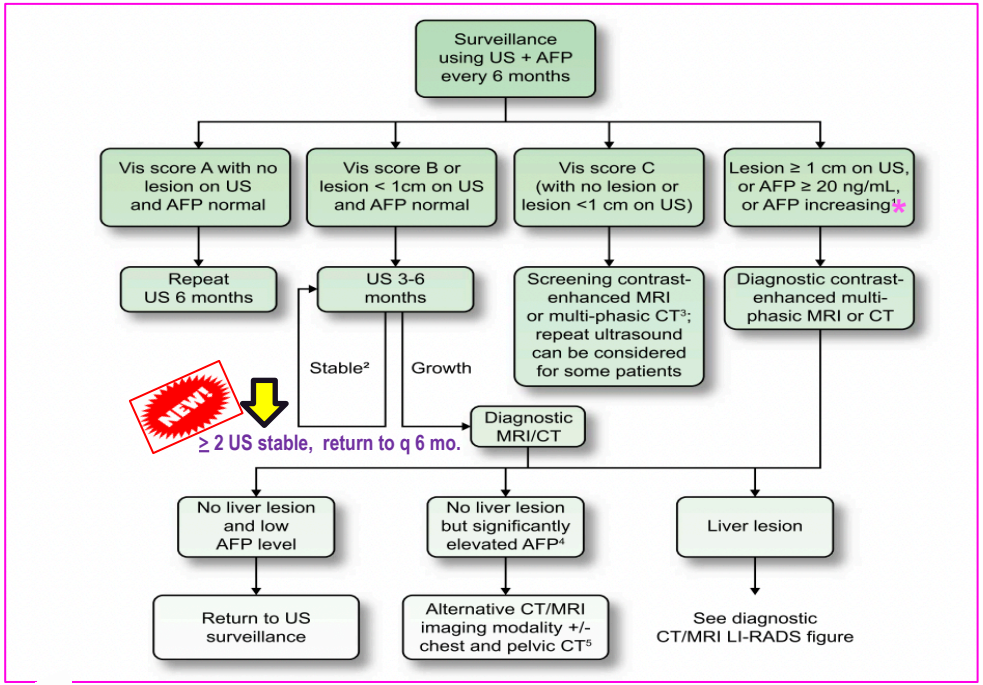
Recall Algorithm

US visualization score

A	No or minimal limitations
B	Moderate limitations
C	Severe limitations

20 %

Score	Concept	Examples
A. No or minimal limitations	Limitations if any are unlikely to meaningfully affect sensitivity	Liver homogeneous or minimally heterogeneous Minimal beam attenuation or shadowing Liver visualized in near entirety
B. Moderate limitations	Limitations may obscure small masses	Liver moderately heterogeneous Moderate beam attenuation or shadowing Some portions of liver or diaphragm not visualized
C. Severe limitations	Limitations significantly lower sensitivity for focal liver lesions	Liver severely heterogeneous Severe beam attenuation or shadowing Majority (>50%) of liver not visualized Majority (>50%) of diaphragm not visualized

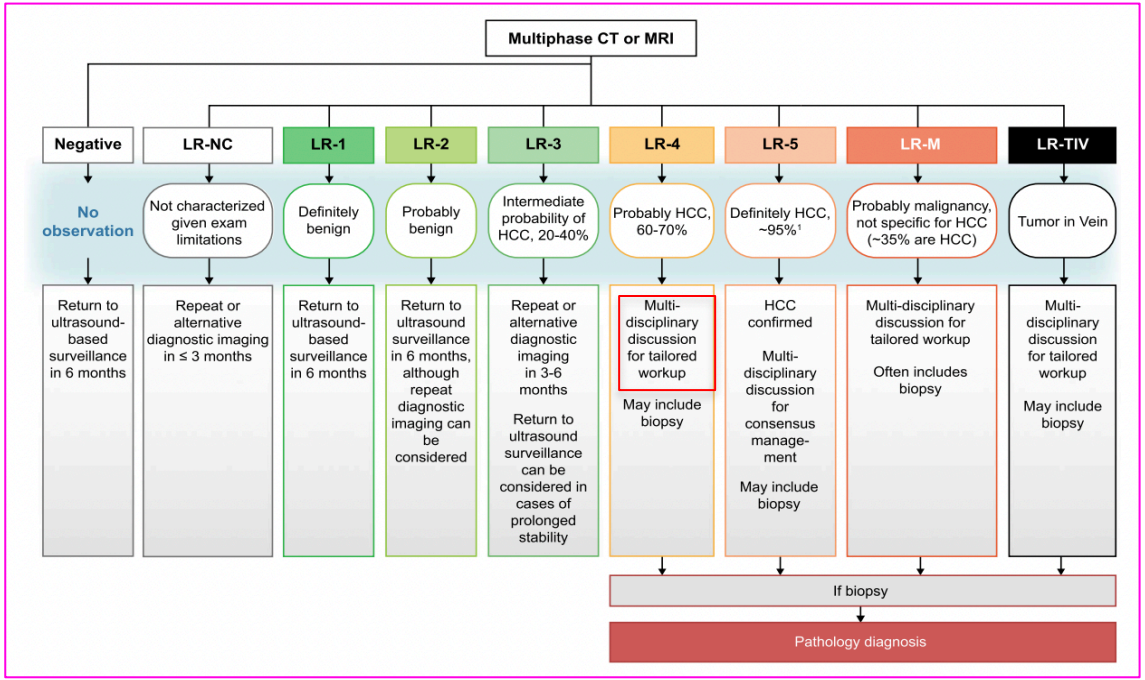


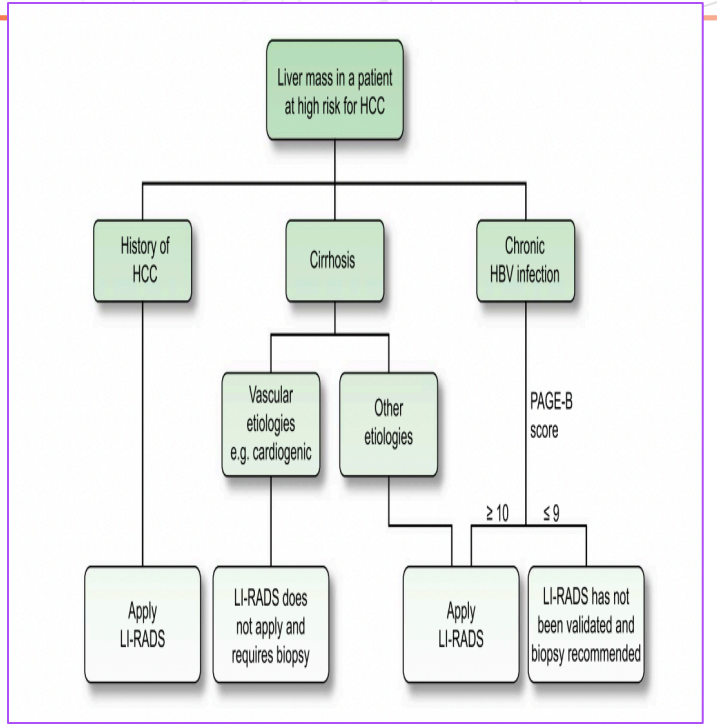
NEW!

NEW!

*Increasing AFP represents doubling of AFP, increase on two consecutive tests, or ≥20 ng/ml

Diagnosis of HCC



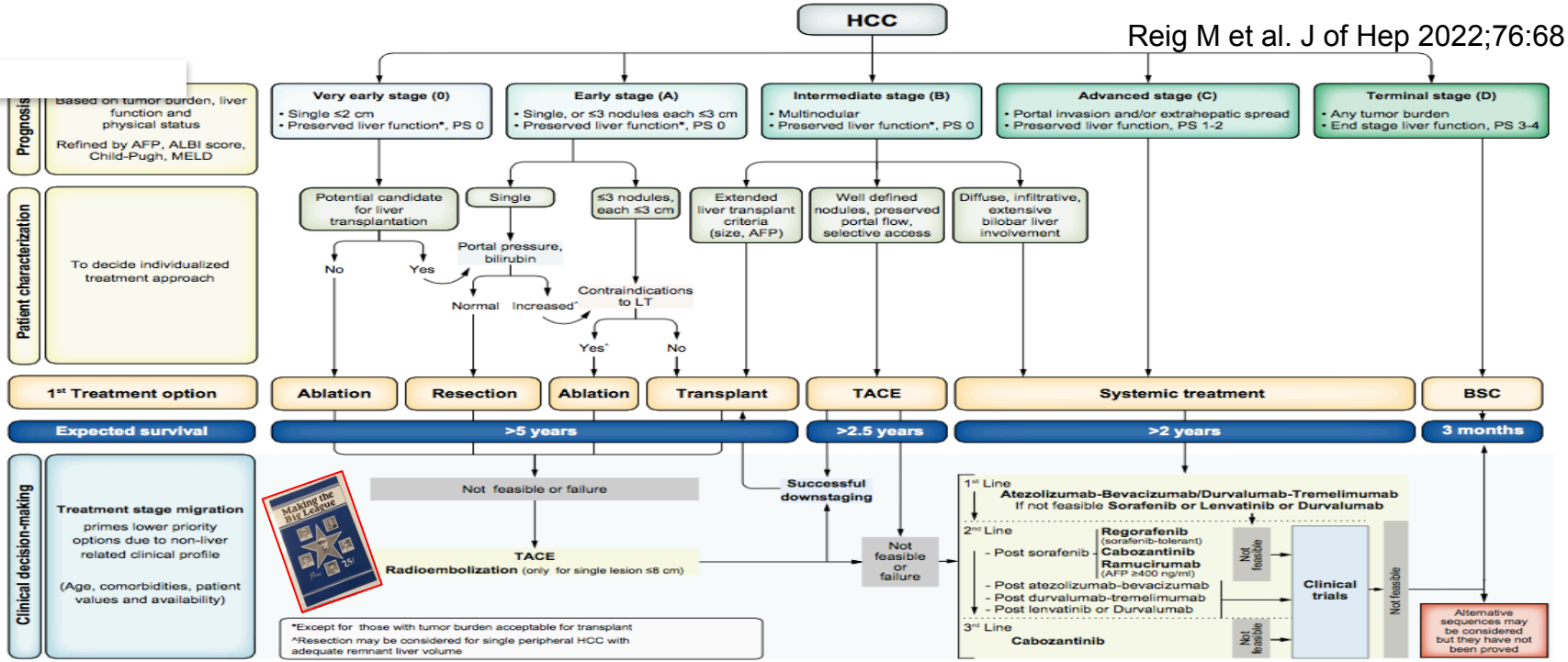


- **AASLD advises against the diagnosis of HCC based on biomarkers or liquid biopsy.**
- (Level 3, Weak Recommendation).
- **For patients in whom an immediate diagnosis would make an impact on management**

BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update ☆

Maria Reig[1,2,*,†], Alejandro Forner[1,2], Jordi Rimola[3], Joana Ferrer-Fàbrega[4], Marta Burrel[5], Ángeles Garcia-Criado[3], Robin K. Kelley[6], Peter R. Galle[7], Vincenzo Mazzaferro[8], Riad Salem[9], Bruno Sangro[2,10], Amit G. Singal[11], Arndt Vogel[12], Josep Fuster[2,4], Carmen Ayuso[2,3], Jordi Bruix[1,2,*,†]

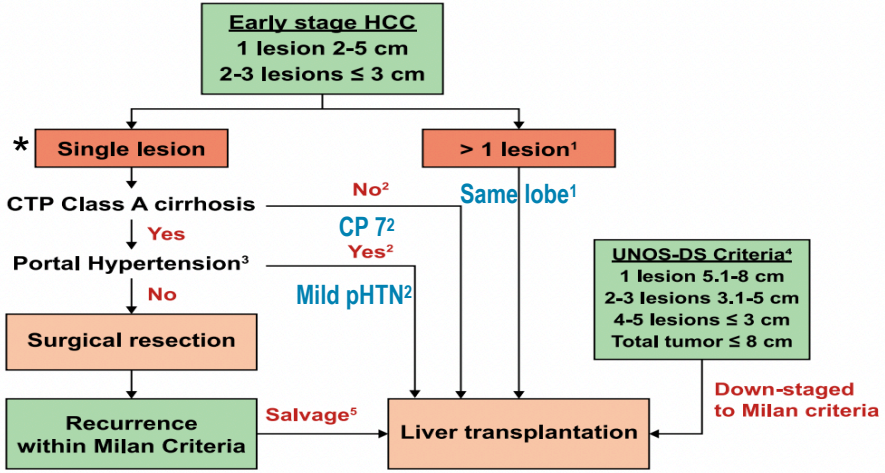
Reig M et al. J of Hep 2022;76:681



Patients with HCC beyond BCLC Stage 0 should undergo noncontrast CT of the chest to evaluate for metastatic disease
(Level 5, Strong Recommendation).
AASLD advises against routine use of PET scan and bone scan for staging given low sensitivity for HCC
(Level 3, Weak Recommendation).

Surgery in Early Stage HCC

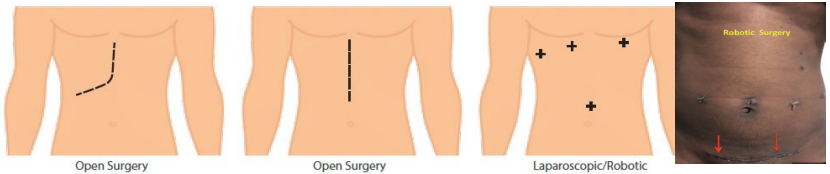
Algorithm for surgical treatment of early stage HCC



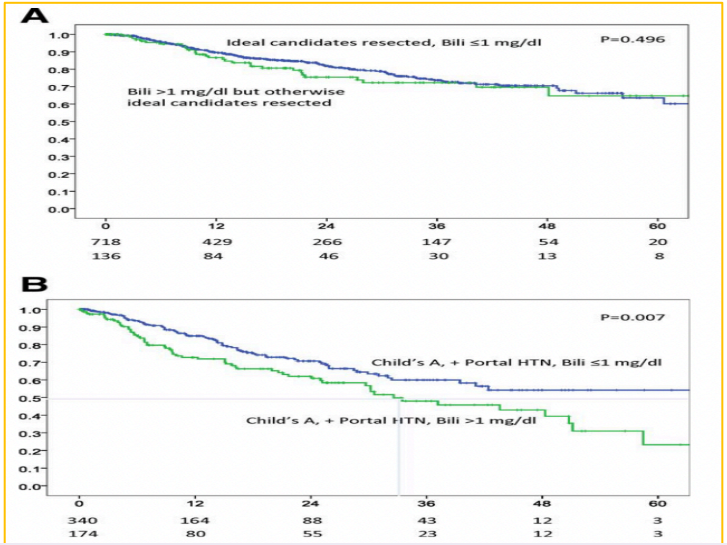
*Although larger tumor size has been associated with increased risk of recurrence, eligibility for resection is not restricted by tumor size, provided the FLR is sufficient

HCC recurrence 50-70% in 5 years!

- **Median time 20.5 mo.**
- ***7.5 mo if + mVI***



BRIDGE Study



Routine postoperative surveillance should be performed to detect recurrence using contrast-enhanced multiphasic CT or MRI every 3–6 months for all patients with HCC following liver resection (Level 3, Strong Recommendation)

Roayaie S et al. Hepatology 2015;62:440-451

Adjuvant Therapy in HCC

	EMERALD-2[1]	Checkmate 9DX[2]	KEYNOTE-937[4]	IMbrave050[5]
Phase	3	3	3	3
Patient population	N=908 • HCC and completed curative therapy (resection or ablation) • ECOG PS 0 or 1 • Child-Pugh score 5 or 6	N=545 • HCC and underwent curative resection or ablation • ECOG PS 0 or 1 • Child-Pugh score 5 or 6	N=950 • HCC with complete radiological response ≥4 weeks after surgical resection or local ablation • ECOG PS 0 or 1 within 7 days prior to Cycle 1, Day 1 • Child-Pugh score 5 or 6 within 7 days prior to Cycle 1, Day 1 • AFP <400 ng/mL within 28 days prior to Cycle 1, Day 1	N=668 • Patients with HCC who have undergone curative resection or ablation (RFA or microwave ablation only) within 4–12 weeks prior to randomisation • ECOG PS 0 or 1 • Child-Pugh score 5 or 6
Treatment	Durvalumab 1120 mg Q3W + bevacizumab 15 mg/kg Q3W Durvalumab 1120 mg Q3W	Nivolumab 480 mg Q3W[3]	Pembrolizumab 200 mg Q3W on Day 1 of each 21-day cycle for up to 17 cycles	Atezolizumab 1200 mg + bevacizumab 15 mg/kg on Day 1 of each 21-day cycle
Comparator	Placebo	Placebo	Placebo	Active surveillance
Primary endpoint(s)	RFS (for durvalumab + bevacizumab vs placebo)	RFS	RFS (BICR),† OS	RFS (IRF)
Secondary endpoint(s)	RFS (for durvalumab vs placebo), OS, RFS24 and RFS36, TTR, RFS2 / PFS2	OS, TTR	Safety; change from baseline in EORTC QLQ-C30 combined global health status / quality of life, EORTC QLQ-HCC18 and EQ-5D-5L	OS, RFS (INV), TTR, RFS24 and RFS36 (IRF), RFS24 and RFS36 (INV), OS24 and OS36, time to EHS or MVI, RFS in PD-L1-high subgroup, safety, serum concentration of atezolizumab, anti-drug antibodies to atezolizumab
Status	Ongoing	Ongoing	Ongoing	Primary completion: October 2022

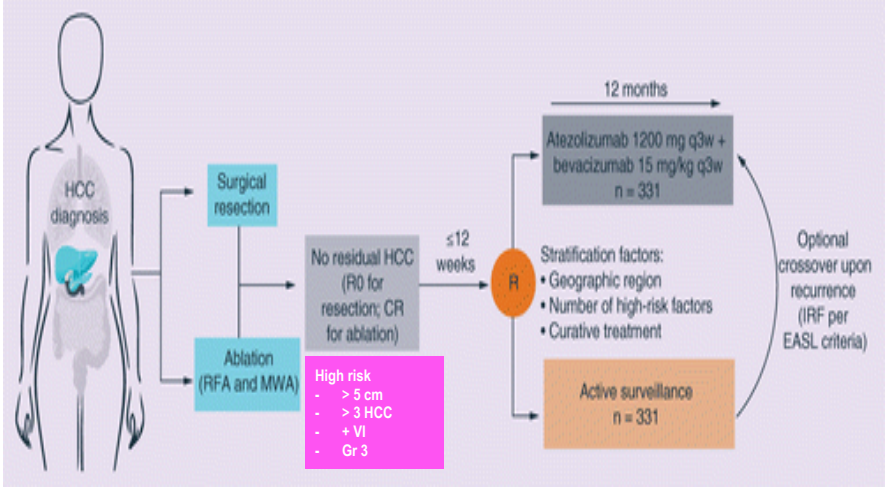
1. NCT03847428. 2. NCT03383458. 4. NCT03867084. 5. NCT04102098.

ARTICLES | ONLINE FIRST

Atezolizumab plus bevacizumab versus active surveillance in patients with resected or ablated high-risk hepatocellular carcinoma (IMbrave050): a randomised, open-label, multicentre, phase 3 trial

Shukui Qin, MD * • Minshan Chen, MD * • Ann-Lii Cheng, MD * • Ahmed O Kaseb, MD * • Prof Masatoshi Kudo, MD * • Han Chu Lee, MD * • et al. Show all authors • Show footnotes

Published: October 20, 2023 • DOI: https://doi.org/10.1016/S0140-6736(23)01796-8 • Check for updates



Panel: Criteria for high risk of hepatocellular carcinoma recurrence by curative treatment

Resection

- Up to three tumours, with largest tumour >5 cm regardless of vascular invasion (microvascular invasion or segmental portal vein invasion—Vp1 or Vp2), or poor tumour differentiation (grade 3 or 4)*
- Four or more tumours, with largest tumour ≤5 cm regardless of vascular invasion (microvascular invasion or segmental portal vein invasion—Vp1 or Vp2), or poor tumour differentiation (grade 3 or 4)*
- Up to three tumours, with largest tumour ≤5 cm with vascular invasion (microvascular invasion or segmental portal vein invasion—Vp1 or Vp2), with or without poor tumour differentiation (grade 3 or 4)*

Ablation†

- Single tumour >2 cm but ≤5 cm
- Multiple tumours (up to four tumours), all ≤5 cm

Vp1=segmental portal vein invasion. Vp2=right anterior or posterior portal vein.
*In cases in which a patient has evidence of mixed tumour differentiation, the worst differentiation status rather than the predominant differentiation status should be used to characterise high-risk criteria. †Ablation must be radiofrequency ablation or microwave ablation.

Baseline Characteristics

	Atezolizumab plus bevacizumab (n=334)	Active surveillance (n=334)
Age, years	60 (52–68)	59 (50–70)
Sex		
Male	277 (83%)	278 (83%)
Female	57 (17%)	56 (17%)
Race*		
Asian	276 (83%)	269 (81%)
White	35 (10%)	41 (12%)
Other	23 (7%)	24 (7%)
Geographical region		
Asia-Pacific, excluding Japan	237 (71%)	238 (71%)
Rest of world	97 (29%)	96 (29%)
ECOG performance status score†		
0	258 (77%)	269 (81%)
1	76 (23%)	65 (19%)
PD-L1 status‡	285	270
≥1%	154/285 (54%)	140/270 (50%)
<1%	131/285 (46%)	139/270 (50%)
Cause of hepatocellular carcinoma		
Hepatitis B	209 (63%)	207 (62%)
Hepatitis C	34 (10%)	38 (11%)
Non-viral	45 (13%)	38 (11%)
Unknown	46 (14%)	51 (15%)
Barcelona Clinic Liver Cancer stage at initial diagnosis		
0	2 (1%)	3 (1%)
A	287 (86%)	277 (83%)
B	25 (7%)	32 (10%)
C	20 (6%)	22 (7%)
D	0	0
Resection	293 (88%)	292 (87%)
Longest diameter of the largest tumour at diagnosis, cm§	5·3 (3·3–8·0)	5·9 (3·5–9·0)
Number of tumours		
1	266/293 (91%)	260/292 (89%)
2	20/293 (7%)	29/292 (10%)
3	4/293 (1%)	2/292 (1%)
≥4	3/293 (1%)	1/292 (<1%)
Adjuvant TACE following resection		
Yes	32/293 (11%)	34/292 (12%)
No	261/293 (89%)	258/292 (88%)
Any tumours >5 cm		
Yes	152/293 (52%)	175/292 (60%)
No	141/293 (48%)	117/292 (40%)
Microvascular invasion present		
Yes	178/293 (61%)	176/292 (60%)
No	115/293 (39%)	116/292 (40%)

(Table 1 continues in next column)

(Continued from previous column)

	Atezolizumab plus bevacizumab (n=334)	Active surveillance (n=334)
Segmental portal vein invasion (Vp1 or Vp2) present		
Yes	22/293 (8%)	17/292 (6%)
No	271/293 (92%)	275/292 (94%)
Poor tumour differentiation (grade 3 or 4)		
Yes	124/293 (42%)	121/292 (41%)
No	169/293 (58%)	171/292 (59%)
Ablation	41 (12%)	42 (13%)
Longest diameter of the largest tumour at diagnosis, cm	2·5 (2·3–3·0)	2·6 (2·3–3·0)
Number of tumours		
1	29/41 (71%)	31/42 (74%)
2	11/41 (27%)	8/42 (19%)
3	1/41 (2%)	3/42 (7%)

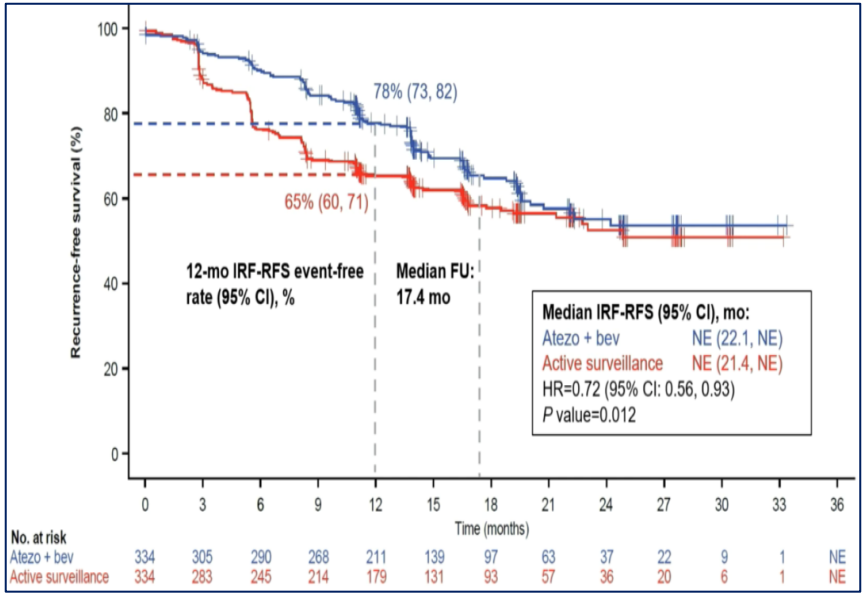
Data are median (IQR), n (%), or n/N (%). ECOG=Eastern Cooperative Oncology Group. PD-L1=programmed death-ligand 1. TACE=transarterial chemoembolisation. Vp1=segmental portal vein invasion. Vp2=right anterior or posterior portal vein. *Race was reported by the patients. †ECOG performance status scores range from 0 to 5, with higher scores indicating greater disability. ‡PD-L1 expression was determined with the use of the PD-L1 SP263 immunohistochemical assay (Ventana Medical Systems, Tucson, AZ, USA). §One patient in the atezolizumab plus bevacizumab group was excluded from the calculation due to a data entry error.

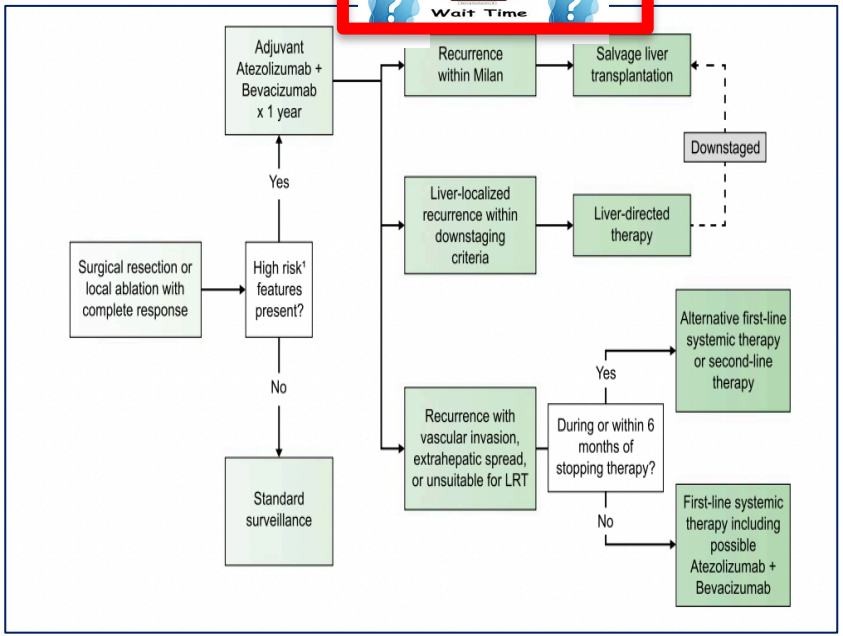
Table 1: Baseline characteristics, including curative procedures, cause, and disease characteristics, in the intention-to-treat population

81 - 83% Asian
62 - 63% HBV
87 - 88% resection vs. ablation
89 – 91% solitary lesion
52 – 60% > 5 cm
6 – 8% with PVTT V1/2

IMbrave 050

Recurrence-free survival



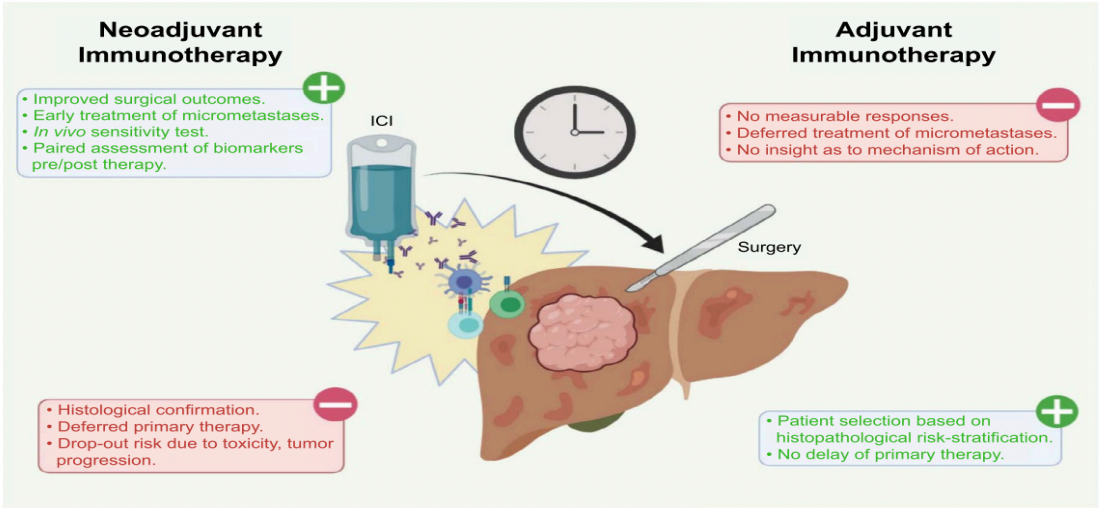


AASLD recommends use of adjuvant immune checkpoint inhibitor-based systemic therapy in patients at *high risk* of recurrence after liver resection or local ablation
(Level 2, Strong Recommendation)

Neoadjuvant vs. Adjuvant

- **CPR: 8% -25%**
- **Major pathologic response: > 70%:**
  - 20% - 42%
- **Pre-op by RECIST 1.1:**
  - CR: 0%
  - PR: 8% - 15%

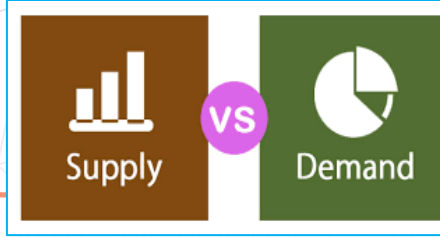
Kaseb AO at al. Lancet Gastroenterol Hepatol 2022;7(3):208-18.
Ho. WJ at al. Nat Cancer 2021;2(9):891-03.
Marron TU et al. Lancet Gastroenerol Hepatol 2022;7(3):219-29.



AASLD advises against the use of neoadjuvant systemic therapies in patients undergoing liver resection outside of a clinical trial setting.
(Level 2, Weak Recommendation)

Pinato D at al. Hepatology, VOL. 74, NO. 1, 2021

T1 HCC



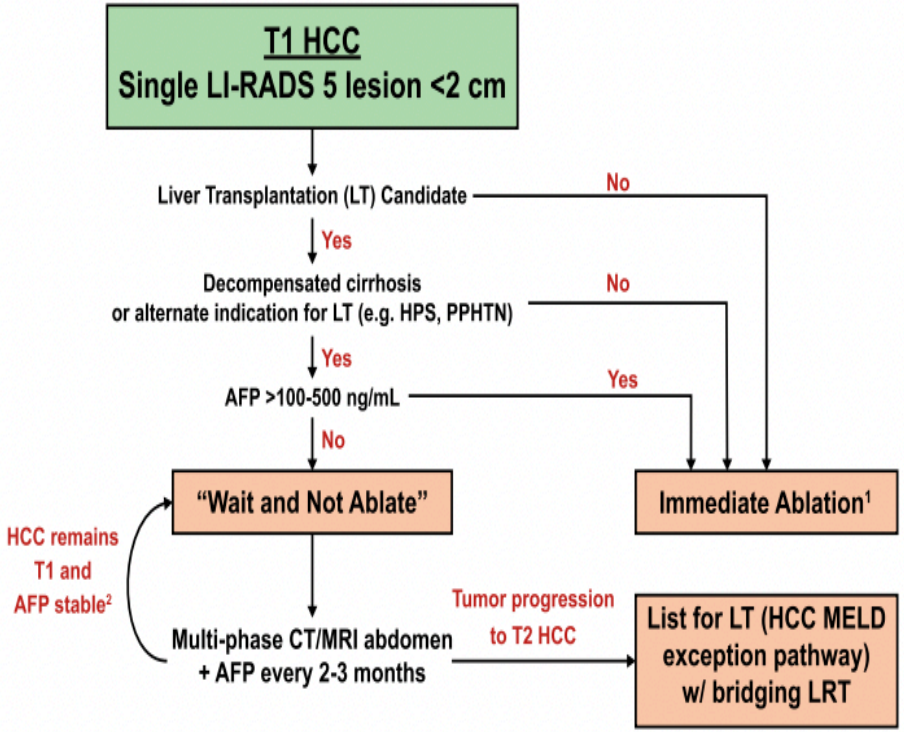
AASLD advises:

Patients with decompensated cirrhosis who develop T1 HCC and are eligible for LT be monitored with crosssectional imaging at least Q 3 months until criteria are met for MELD exception before pursuing LRT

(Level 3, Weak Recommendation).

A. Immediate LRT may be considered if AFP is significantly elevated or if the patient is not otherwise eligible for LT

(Level 3, Weak Recommendation).



BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update ☆

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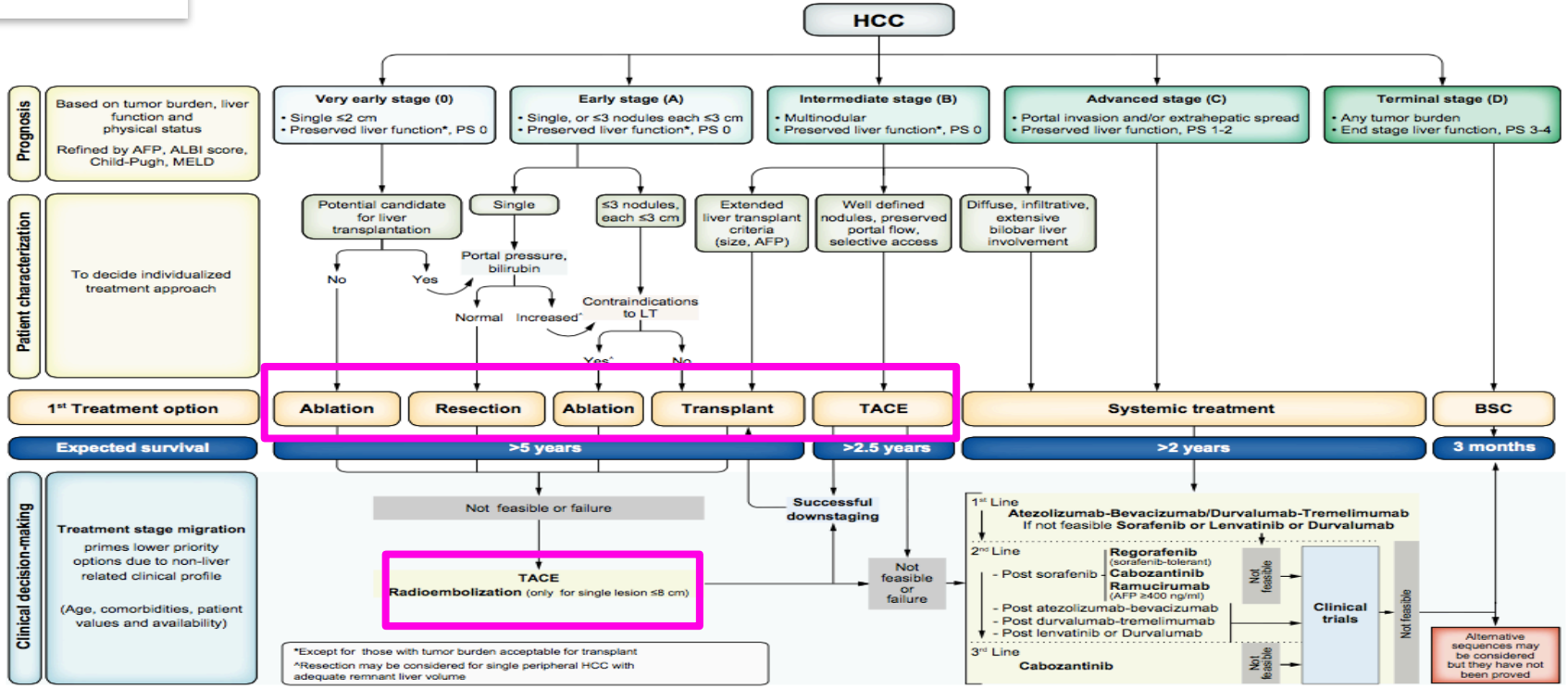


Reig M et al. J of Hep 2022;76:681

FDA Approves TheraShere Y-90 Glass Microspheres for HCC
March 18, 2021

LEGACY Study: Multi-center, single arm, **retrospective study**; N= 162

- 1° endpoints: ORR & DoR
  - Localized mRECIST : BICR
- Y90: 2014-2017: ***Ablative-level dosimetry***
- Eligibility:
  - Unresectable *solitary* HCC ≤ 8 cm
  - CP A
  - BCLC A or BCLC C (PS 1)
  - ECOG 0-1

60.5% ECOG 0	**Median age: 66**
Median tumor = 2.7 cm (1 - 8)	BCLC A: 60.5%
Neoadjuvant therapy: 21.0%: LT 6.8% resection	BCLC C: 39.5% *(due to PS 1)*
3 yr. OS 86.6% (entire cohort)	**3 yr. OS post LT/LR (n = 45) 93%**

		Localized mRECIST N (%)
Objective Response Rates, confirmed response n (%) [95% Confidence Interval]		**117 (72.2%) [64.9%, 78.5%]**
Objective Response Rates, best response n (%) [95% Confidence Interval]		**143 (88.3%) [82.4%, 92.4%]**
Best Overall Response	Complete Response (CR)	136 (84%)
	Partial Response (PR)	7 (4.3%)
	Stable Disease (SD)	0
	Progressive Disease (PD)	0
	Not evaluable	19 (11.7%)
	No imaging assessments post Day 46	5 (3.1%)
	No imaging assessments post Day 46 due to liver transplant or resection	9 (5.6%)
	Other reasons	5 (3.1%)
Duration of Response* in months, mean (SD), median		15.1 (11.2), 11.8
Duration of Response* ≥6		**80 (76.1%) [67.6%, 82.9%]**

Salem R et al. Hep

Y90 vs. TACE

PREMIERE: RCT

Y90 Radioembolization Significantly Prolongs Time to Progression Compared With Chemoembolization in Patients With Hepatocellular Carcinoma. *Gastro 2016*

- TTP (>26 months) than patients in the cTACE group (6.8 months) (*P*=.0012)

- OS ns

Segmental Y90 radioembolization versus segmental chemoembolization for localized hepatocellular carcinoma: results of a single-center, retrospective, propensity score-matched study. *J Vasc Interv Radiol 2017*

- Index CR
  - Y90 92% vs. TACE 74% P=0.001
- Overall CR
- Y90 84% vs. TACE 58% P <0.001

- Index tumor progression @ 2 yrs.
  - Y90 15% vs. TACE 42% P <0.001

OS Y90 vs. TACE
1,198 vs. 1,043 days ns

Radiation segmentectomy versus selective chemoembolization in the treatment of early-stage hepatocellular carcinoma. *J Vasc Interv Radiol 2018*

After PSM

-Overall CR
Y90 92.1% vs. 52.6%, P= 0.005

- TTST
  - Y90 812 vs. 812 days; P = 0.005

- OS ns

Bridge Therapy for HCC

- Nationwide study 2003 – 2018 with HCC upgrade
- 31,609 pts. Compared LRT vs. no LRT
- LRT increased from 42% to 92%
- TARE increased from 3% to 19%
- IPTW-adjusted analysis
  - TARE & ablation ass. w/ lower WL dropout
    - sHR, 0.85; (95% CI, 0.81–0.89), sHR, 0.95; 95% CI, 0.91–0. 99) respectively

WL Dropout	Univariable sHR (95% CI)	Multivariable sHR (95% CI)
Initial total tumor diameter, *cm*	**1.10 (1.09–1.12)**	**1.13 (1.11–1.15)**
Initial tumor number (ref: 0–1)		
2	1.01 (0.94–1.08)	0.96 (0.89–1.03)
3	**1.16 (1.04–1.28)**	0.96 (0.86–1.07)
≥4	1.51 (0.97–2.36)	1.06 (0.68–1.63)
Initial AFP level (ref: <20)		
21–40	**1.19 (1.09–1.30)**	**1.25 (1.14–1.36)**
41–500	**1.53 (1.44–1.63)**	**1.65 (1.55–1.75)**
501–1000	**1.76 (1.52–2.05)**	**2.25 (1.94–2.61)**
≥1000	**2.64 (2.32–2.99)**	**3.20 (2.81–3.64)**
Child–Pugh class (ref: A)		
B	**1.34 (1.26–1.42)**	**1.53 (1.44–1.62)**
C	**1.93 (1.80–2.08)**	**2.25 (2.08–2.42)**
Region of initial listing (ref: short)		
Medium	**1.91 (1.76–2.07)**	**2.02 (1.86–2.20)**
Long	**2.70 (2.49–2.92)**	**3.17 (2.92–3.44)**
Type of first LRT (ref: chemoembolization)		
Radioembolization	**1.26 (1.12–1.42)**	1.03 (0.91–1.17)
Thermal ablation	**0.89 (0.82–0.96)**	0.97 (0.90–1.05)
Combination	1.02 (0.88–1.18)	1.05 (0.91–1.21)
External beam radiation	1.04 (0.74–1.45)	0.88 (0.63–1.23)
Other	0.92 (0.76–1.12)	0.92 (0.76–1.12)
None	**1.07 (1.01–1.15)**	**1.37 (1.28–1.47)**
Listing era (ref: 2003–2006)		
2007–2010	**1.31 (1.19–1.44)**	**1.50 (1.36–1.65)**
2011–2014	**1.73 (1.58–1.89)**	**2.30 (2.10–2.52)**
2015–2018	**1.78 (1.63–1.95)**	**2.69 (2.44–2.96)**

Kwong A at al. Clin Gastroenterol Hepatol. 2022 May ; 20(5): 1142–1150

Results *In MMA -3 Era*

Competing risks analysis

- RE compared to CE was associated with a lower risk of waitlist dropout (sHR of 0.79)
- RE compared to CE was associated with increased time to second treatment (sHR 0.38, 95% CI 0.32-0.44)
  - Cumulative incidence of having had second LRT at 1-year from first LRT was 39% (37-42%) for CE compared to 17% (15-20%) for RE

Table 5. Univariable and multivariable competing risk analyses for time from first locoregional treatment of chemoembolization or radioembolization to waitlist dropout, with transplant considered as a competing risk.

	Univariable sHR (95% CI)	Multivariable sHR (95% CI)	p-value for multivariable analysis
Age at listing	1.02 (1.01 – 1.04)	1.03 (1.01 – 1.04)	0.001
Model for End-Stage Liver Disease at listing	1.05 (1.03 – 1.07)	1.03 (1.01 – 1.06)	0.013
Child-Pugh class (ref: A)			
B	1.49 (1.20 – 1.86)	1.37 (1.08 – 1.73)	0.009
C	1.98 (1.42 – 2.77)	1.49 (0.97 – 2.30)	0.069
Alpha fetoprotein level (ref: ≤20)			
21 – 40	1.96 (1.42 – 2.71)	2.13 (1.54 – 2.94)	<0.001
41 – 200	2.31 (1.74 – 3.07)	2.24 (1.68 – 3.00)	<0.001
> 200	2.80 (1.89 – 4.14)	2.78 (1.87 – 4.13)	<0.001
Initial aggregate tumor size, cm	1.05 (1.01 – 1.11)	1.05 (1.00 – 1.11)	0.043
Radioembolization as first treatment (ref: chemoembolization)	0.79 (0.64 – 0.99)	0.79 (0.63 – 0.98)	0.033

sHR, subdistribution hazard ratio; CI, confidence interval.

14

UCSF

Kim at al. DDW 2023 Chicago

Bridge Therapy

- AASLD ***advises the use of pre-transplant locoregional bridging therapy*** for patients being evaluated or listed for liver transplantation, if they have adequate hepatic reserve, to reduce the risk of waitlist dropout in the context of anticipated prolonged wait times for transplant (Level 3, Strong Recommendation).

- AASLD ***does NOT advise one LRT over another for bridging therapy***. The choice of locoregional modality should be based on tumor size, location, & center expertise (Level 3, Weak Recommendation).

- AASLD ***does NOT recommend the routine use of systemic therapy as bridging therapy*** for transplantation; however, its use does not preclude LT eligibility (Level 5, Weak Recommendation).
    - **If patient does receive ICI, recommend D/C for minimum of 3 months prior to OLT**

Down-staging to LT

Using (LRT) to ***biologically stage*** a tumor beyond the Milan Criteria

Inclusion criteria

HCC exceeding Milan criteria but meeting one of the following:

1. Single lesion 5.1–8 cm
2. 2–3 lesions each ≤ 5 cm with the sum of the maximal tumor diameters ≤ 8 cm
3. 4–5 lesions each ≤ 3 cm with the sum of the maximal tumor diameters ≤ 8 cm

AND absence of vascular invasion or extrahepatic disease based on cross-sectional imaging

Criteria for successful downstaging

Residual tumor size and diameter within Milan criteria (1 lesion ≤ 5 cm, 2–3 lesions ≤ 3 cm)

(a) Only viable tumor(s) are considered; tumor diameter measurements should not include the area of necrosis from tumor-directed therapy.

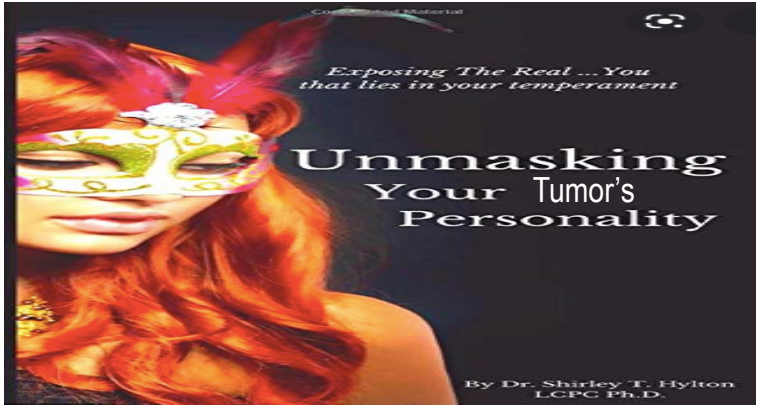
(b) If there is more than one area of residual tumor enhancement, then the diameter of the entire lesion should be counted toward the overall tumor burden.

Criteria for downstaging failure and exclusion from liver transplant

1. Progression of tumor(s) to beyond inclusion/eligibility criteria for downstaging (as defined above)
2. Tumor invasion of a major hepatic vessel based on cross-sectional imaging
3. Lymph node involvement by tumor or extrahepatic spread of tumor
4. Infiltrative tumor growth pattern
5. Persistent AFP elevations > 500 ng/ml in patients who had prior AFP ≥ 1000 ng/ml

Timing of liver transplant in relation to downstaging

1. There should be a minimum observation period of 3 mo of disease stability from successful downstaging to liver transplant
2. Per current UNOS policy, the patient must remain within Milan criteria for 6 mo after successful downstaging before receiving MELD exception points



If tumor **> UNOS DS** prior to successful DS requires a vote for exception points by NLRB

Patients who are otherwise transplant-eligible except with initial tumor burden exceeding the Milan criteria, especially those meeting UNOS downstaging criteria, should be considered for LT following successful downstaging to within Milan criteria after a 3-to-6-month period of observation (Level 2, Strong Recommendation).

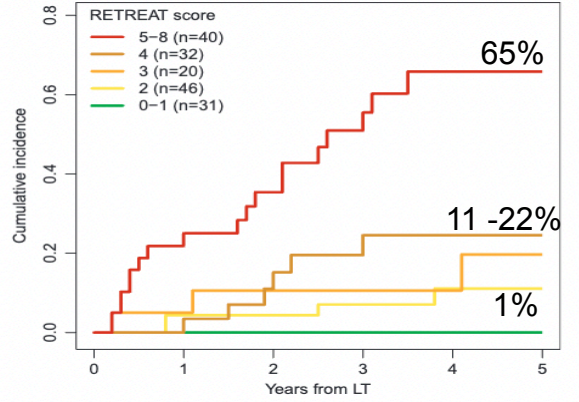
HCC Recurrence Post-LT

- HCC recurrence: leading cause of mortality post LT for HCC
  - Median OS: 1 yr. post recurrence
  - Most common site: lung (40%), liver (33%)
- Predictors of HCC recurrence:

-Tumor burden by imaging
-Response to LRT
-Explant features
-RETREAT score

Predictor	Multivariable HR (95% CI)	P value	β coefficient	RETREAT points*
AFP at LT (ng/mL)				
0 to 20	1 [reference]	NA	NA	0
21 to 99	1.80 (1.05-3.10)	0.03	0.59	1
100 to 999	2.56 (1.42-4.62)	0.002	0.94	2
≥1000	4.45 (1.98-10.00)	<0.001	1.49	3
Microvascular invasion	3.80 (2.23-6.47)	<0.001	1.34	2
Largest viable tumor diameter (cm) plus number of viable tumors¶				
0	1 [reference]	NA	NA	0
1.1 to 4.9	1.58 (0.73-3.39)	0.25	0.45	1
5.0 to 9.9	2.69 (1.24-5.83)	0.01	0.99	2
≥10	6.75 (2.55-17.88)	<0.001	1.91	3

RETREAT score	Patients	HCC Recurrence	Milan criteria In	Milan criteria Out	UCSF criteria In	UCSF criteria Out
0	2	0	2	0	2	0
1	29	0	29	0	29	0
2	46	5	30	16	38	8
3	20	3	15	5	15	5
4	32	6	14	18	19	13
5–8	40	20	14	26	20	20



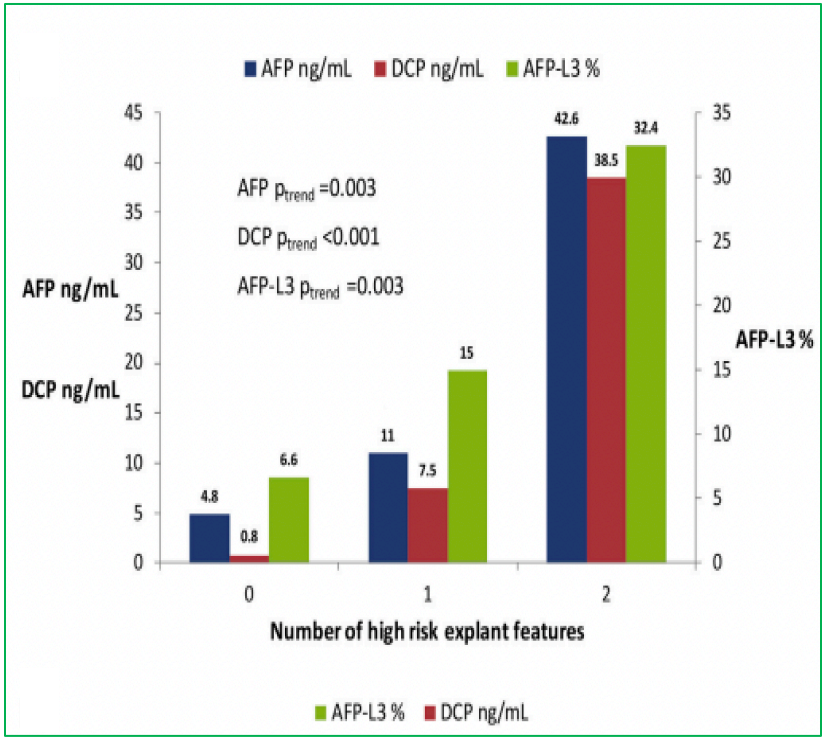
Aberg et al. Transpl International 2021

AASLD advises surveillance for detection of post-transplant HCC recurrence using multiphasic contrast-enhanced abdominal CT or MRI and chest CT scan (Level 2, Strong Recommendation).
Duration of post LT surveillance unknown

AASLD advises against the use of ICIs in patients with recurrent HCC after LT given increased risk of graft loss and death (Level 4, Strong Recommendation).
AASLD advises sorafenib or lenvatinib as first-line therapy for these patients

Tumor Markers & Explant High Risk

	Non-high-risk explant (n = 126)	High-risk explant (n = 27)
Median DCP at LT,[a] *ng/mL*	0.8 (0.2–2.3)	9.2 (1.1–60.9)
AFP-L3 ≥15% at LT[b]	19 (15.1)	15 (55.5)
DCP ≥7.5 ng/mL at LT[b]	14 (11.1)	15 (55.5)
RETREAT score[b]		
0	47 (37.3)	—
1	50 (39.7)	4 (14.8)
2	23 (18.2)	10 (37.0)
3	5 (4.0)	6 (22.2)
4	1 (0.8)	5 (18.5)
5	—	2 (7.4)



Clin Gastroenterol Hepatol 2022 Mar;20(3):701-703.e2

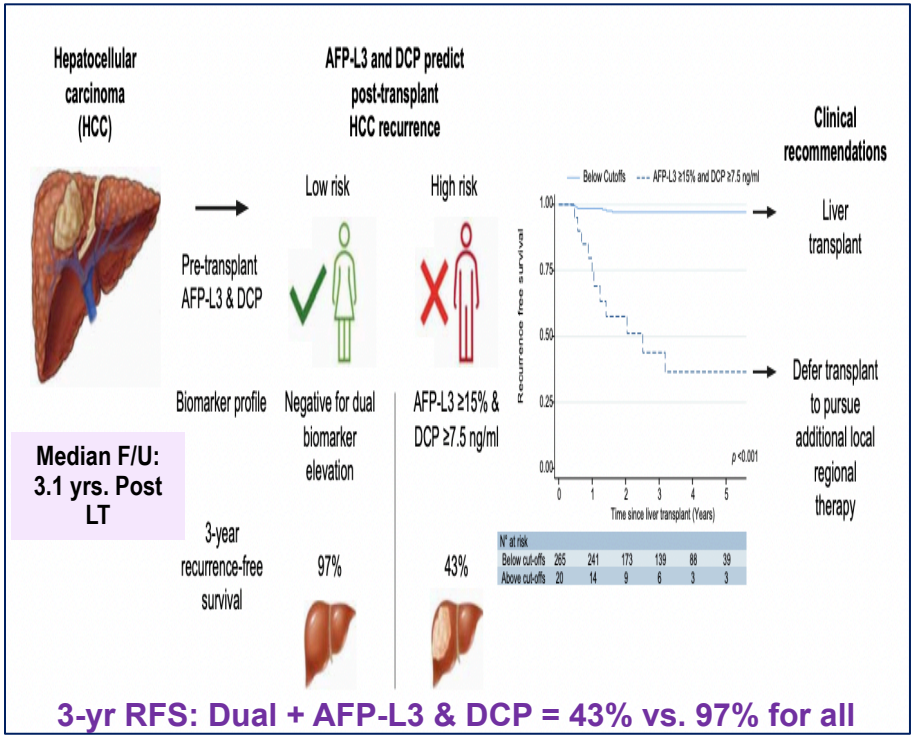
Biomarkers & RFS Post LT

- Prospective study: 285 pts with HCC
- 2017 -2022
  - all pts. within MC or DS to MC
  - AFP, AFP-L3 & DCP @ LT
  - 94.7% had LRT

	Median @ LT	C-statistic
AFP	5.0 ng/ml (IQR 3.0-12.1)	0.74
AFP-L3	6.7% (IQR 0.5-13.2)	0.81
DCP	1.0 ng/ml (0.3 – 2.8)	0.86

- HCC recurrence: 18 pts. (6.3%)

AASLD: Biomarkers require further validation



3-yr RFS: Dual + AFP-L3 & DCP = 43% vs. 97% for all others

Campion D et al J of Hep 2023 Oct 19

Y90 vs. DEB in BCLC B

TRACE TRIAL[16*]

Prospective, randomized, open label, single-center superiority study from 2011-2018
DEB-TACE vs. Glass Y-90 TARE for treatment of unresectable HCC

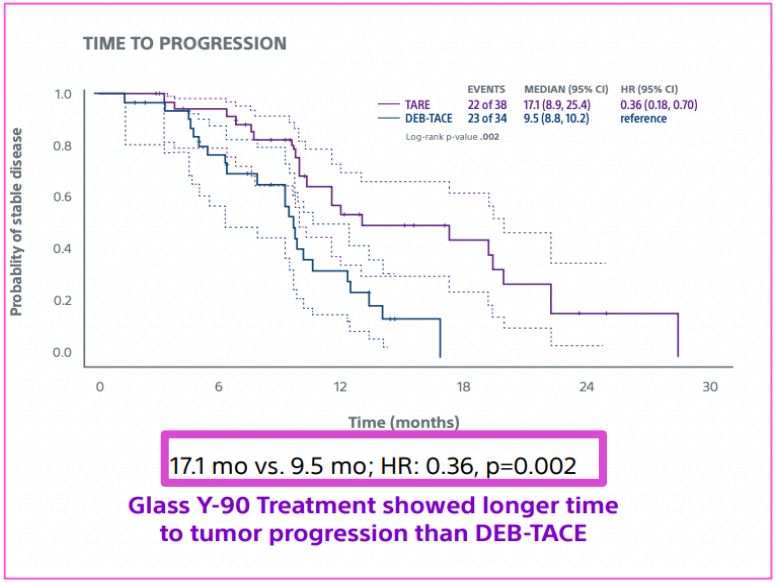
Glass Y-90 (n=38) — Randomization 1:1 — **DEB-TACE (n=34)**

120Gy absorbed dose;
Segmental approach preferred

Doxorubicin;
Max Dose 150 mg/session,
3 sessions/lesion, 5 total sessions

Primary Endpoint: TTP
Secondary Endpoint: TTP (Whole liver, Local), PFS, ORR, OS, Safety

Inclusion:
- Image/biopsy confirmed, unablatable, unresectable HCC not eligible for transplant
- BCLC B, extended to BCLC A not amendable to surgery or ablation, Child-Pugh A, ECOG 1



17.1 mo vs. 9.5 mo; HR: 0.36, p=0.002

Glass Y-90 Treatment showed longer time to tumor progression than DEB-TACE

Median OS : 30.2 months after TARE and 15.6 months after DEB-TACE (ITT group HR, 0.48; 95% CI: 0.28, 0.82; P = .006)

Digestive Disease Week

Dhondt E et al. Radiology. 2022 Jun;303(3):699-710.

BCLC B

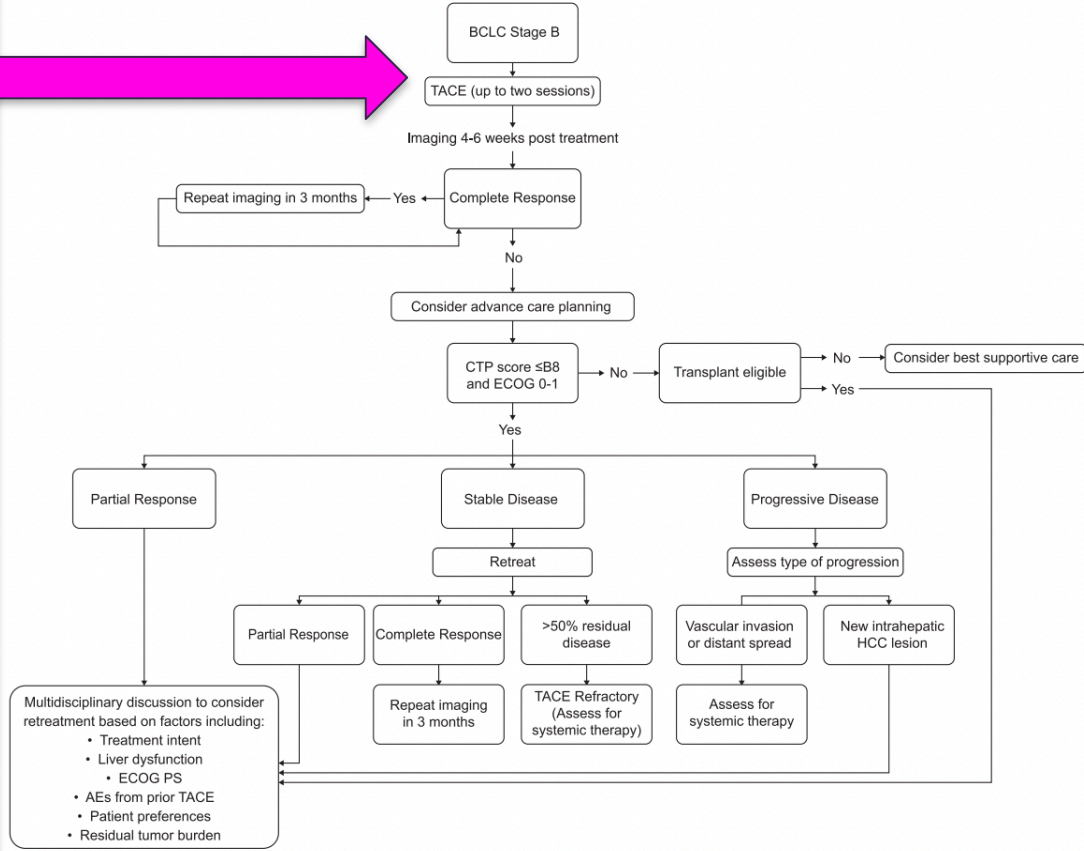
- Patients with BCLC Stage B HCC should be treated with transarterial chemoembolization (Level 1, Strong Recommendation).

- AASLD advises radioembolization as an alternative therapy to chemoembolization in patients with BCLC Stage B HCC (Level 3, Strong Recommendation).

- Transarterial therapies should be performed in a selective/segmental fashion (over lobar treatment) whenever possible given a lower risk of hepatic dysfunction (Level 5, Strong Recommendation).

- AASLD advises against the combination of systemic therapy with transarterial therapies for BCLC Stage B HCC outside of a clinical trial setting (Level 2, Strong Recommendation).

- AASLD advises systemic therapy in patients with intermediate HCC who are unsuitable for or refractory to locoregional therapies due to contraindications, worsening hepatic dysfunction, progression of HCC, or lack of objective response (Level 3, Strong Recommendation).



Systemic Therapy

Patients with advanced HCC, CP A cirrhosis should be offered atezolizumab + bevacizumab or durvalumab + tremelimumab as preferred first-line therapy options (Level 2, Strong Recommendation)

4 OS year: 25.2 vs. 15.1%

Sorafenib (1L) v. Placebo
SHARP
Median OS 10.7 v. 7.9 mo

Lenvatinib (1L) v. SOR
REFLECT
Median OS 13.6 v. 12.3 mo

Bevacizumab + Atezolizumab (1L) v. SOR
IMBRAVE-150
Median OS 19.2 v. 13.4 mo

Durvalumab + Tremelimumab (1L) v. SOR
HIMALAYA
Median OS 16.43 v. 13.7 mo

First line therapies

2007 | 2017 | 2018 | 2019 | 2020 | 2022

Second line therapies

Regorafenib (2L) v. Placebo
RESORCE
Median OS 10.6 v. 7.8 mo

Ramucirumab (2L) v. Placebo
REACH-2
Median OS 8.5 v. 7.3 mo

Cabozantinib (2L) v. Placebo
CELESTIAL
Median OS 10.5 v. 8 mo

Nivolumab + Ipilimumab (2L)
CHECKMATE-040
Median OS 22.8, 12.5, 12.7 mo

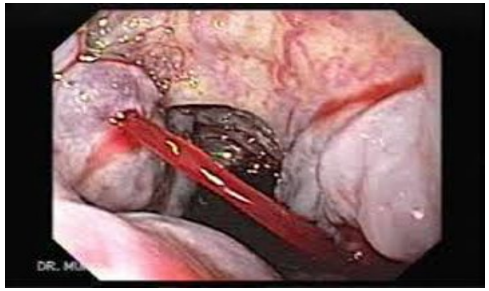
Pembrolizumab (2L)[1]
KEYNOTE-224
Median OS 13.2 mo

Phase 2 studies
Phase 3 studies

Awaiting results in 1L CheckMate 9DW

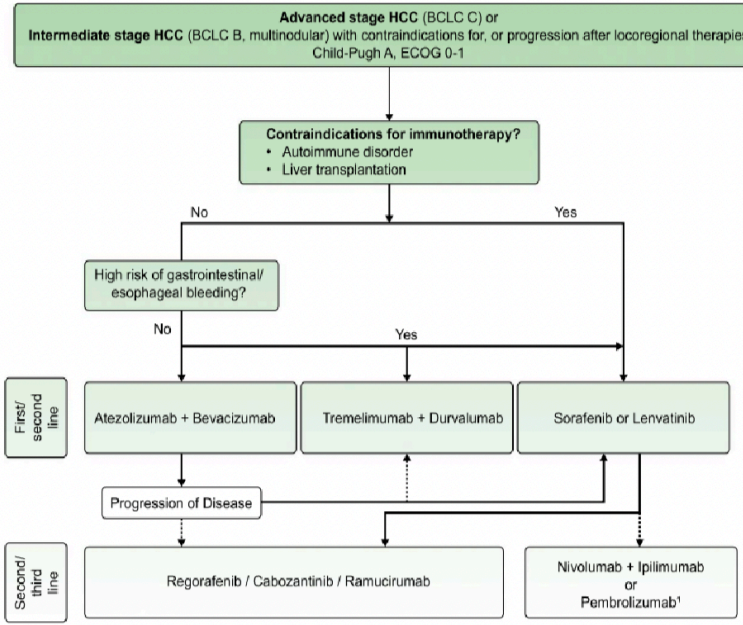
Sequencing of Systemic Therapy in HCC

The optimal treatment of large varices prior to atezolizumab plus bevacizumab initiation is unknown, although AASLD recommends at least one session of banding. Carvedilol may be considered as an alternative management of varices prior to atezolizumab plus bevacizumab (Level 5, Weak Recommendation).



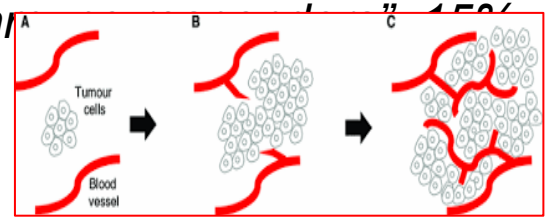
IMBRAVE 150 Trial

- EGD within 6 months of randomization required
- 26% had EV at baseline
  - 11% in Atezo/Bev treated @ baseline
  - 14% in Sor arm treated @ baseline
- 3.65% variceal bleed in atezolizumab + bevacizumab arm compared to 1.28% in the sorafenib arm



Gene Signatures as a Predictive Biomarker for Response to Atezolizumab +Bevacizumab

- 3 signatures were seen more frequently with A + B responders (30%) vs. non-responders among 401 patients
  - Tumors enriched with immune-related signatures: *"imm…*
  - 2 mechanisms were associated with A + B response:
    - Immune versus anti-angiogenic response



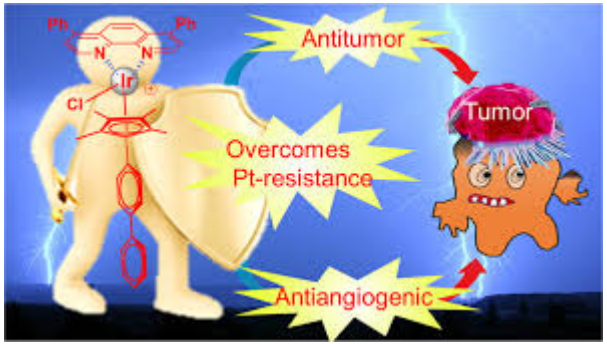
Vasudev et al. *Angiogenesis* **17**, 471–494 (2014).

If had 3 signatures present:
- 83% specificity to identify response to A + B
- Longer PFS with A + B but NOT sorafenib

Responder lacking these 3 signatures had a significant higher expression of VEGFA genes *"antiangiogenic"* responders

Findings on a biopsy of HCC prior to treatment with A + B identified patients with improved survival associated with A + B

Piqué-Gili M et al. AASLD 2023 Boston Abstract 4101



Gadre S et al. J. Med. Chem. 2023, 66, 19, 13481–13500

Advanced Care Planning

Advance care planning should be offered to all patients receiving palliative-intent therapy or best supportive care for HCC, regardless of transplant eligibility

(Level 5, Weak Recommendation).

ILTS ILCA
CONSENSUS CONFERENCE 2024
VALENCIA, SPAIN
FEBRUARY 1-2, 2024

Practice Guideline > Lancet Oncol. 2012 Jan;13(1):e11-22.
doi: 10.1016/S1470-2045(11)70175-9. Epub 2011 Oct 31.

Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report

Pierre-Alain Clavien [1], Mickael Lesurtel, Patrick M M Bossuyt, Gregory J Gores, Bernard Langer, Arnaud Perrier; OLT for HCC Consensus Group

- 60 + working group members

- New tools, treatments, approaches to liver cancer
  - **71 statements** (37 in 2012)

Approach:

- Early career investigators as the team leaders

Inclusion:

- iCCA and role of LT Advocacy groups

Thank You & Congratulations

Amit Singal MD

Tamar Taddei MD

Anjana Pillai MD.

Elizabeth Verna MD

Cynthia Levy MD

Sample Table

Text	Text	Text	Text
Text	Text	Text	Text
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Sample Chart