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Integrating Systemic Therapy for Hepatocellular Carcinoma

Neil Mehta, MD

University of California San Francisco (UCSF) Division of GI/Hepatology

Director, HCC Multidisciplinary Clinic

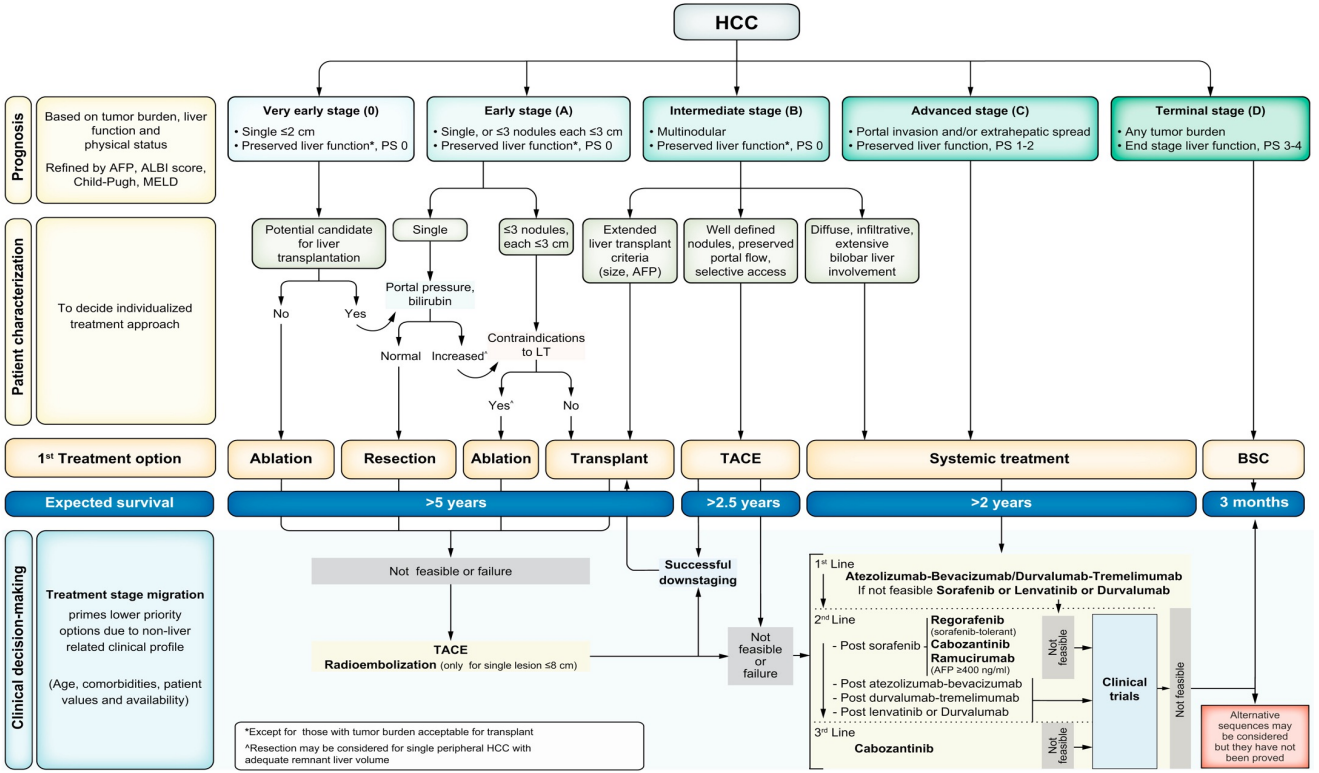
Disclosures

- I have served on advisory boards or as a consultant for FujiFilm WAKO Diagnostics, Sirtex, Merck and Genentech
- I have received institutional research funding from FujiFilm Wako Diagnostics, Genentech, Glycotest, Exact Sciences, and Target Pharmasolutions

Overview

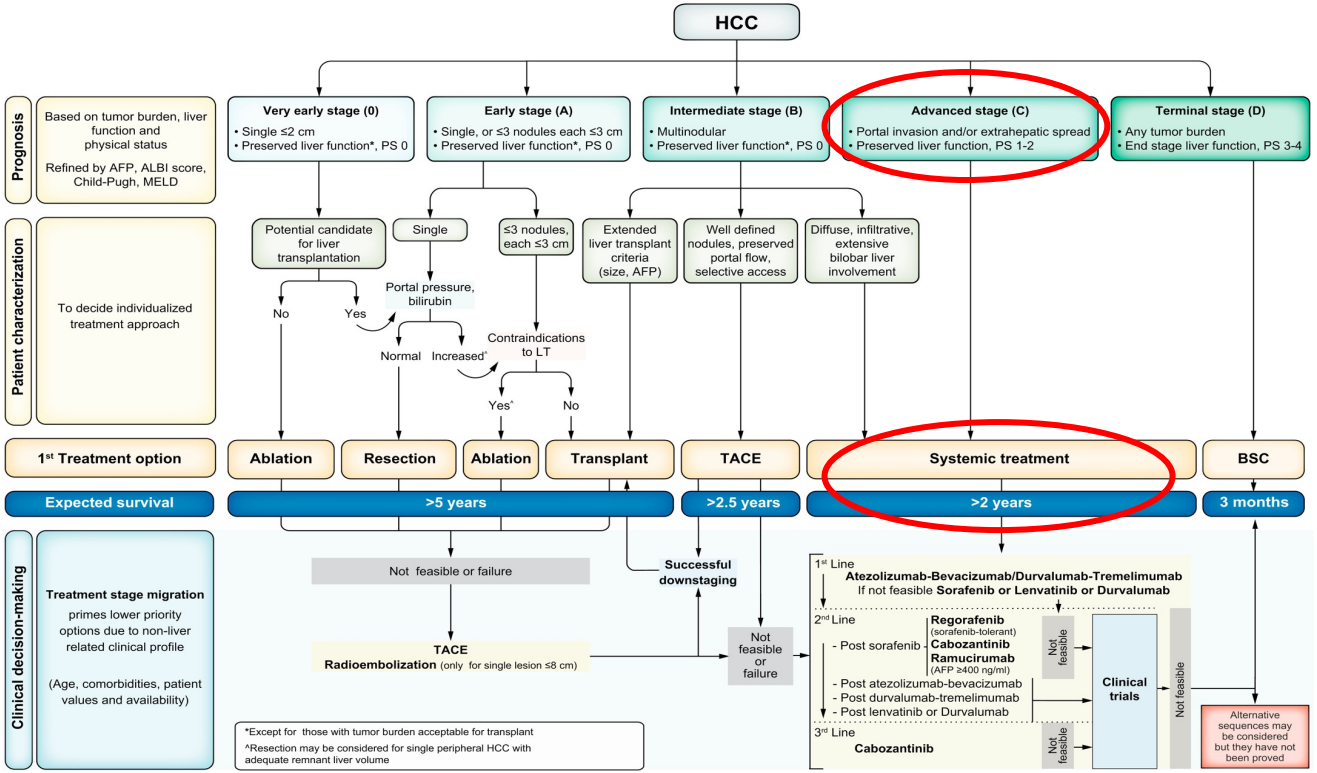
- Role of systemic therapy for:
  - Advanced stage HCC
  - Adjuvant therapy after resection/ablation
- Updates in down-staging and “all-comers” outcomes
  - Combining systemic therapy with down-staging prior to LT?
  - Ongoing combination clinical trials for intermediate stage HCC

BCLC Staging Classification



Reig M et al. *Journal of Hepatology*. 2022.

BCLC Staging Classification

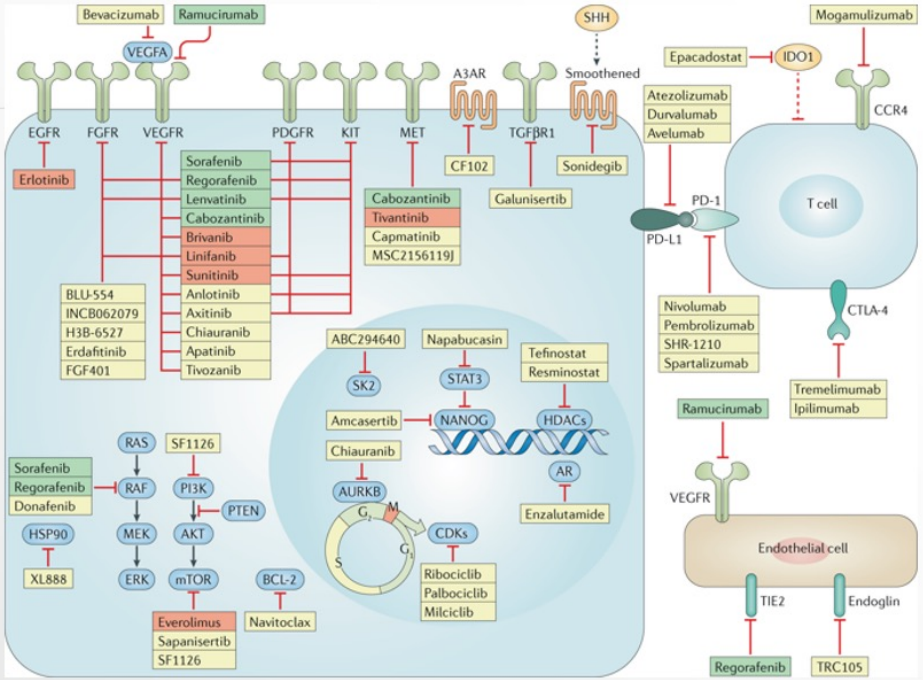


Reig M et al. *Journal of Hepatology*. 2022.

Targeted Therapy for HCC Tyrosine Kinase Inhibitors

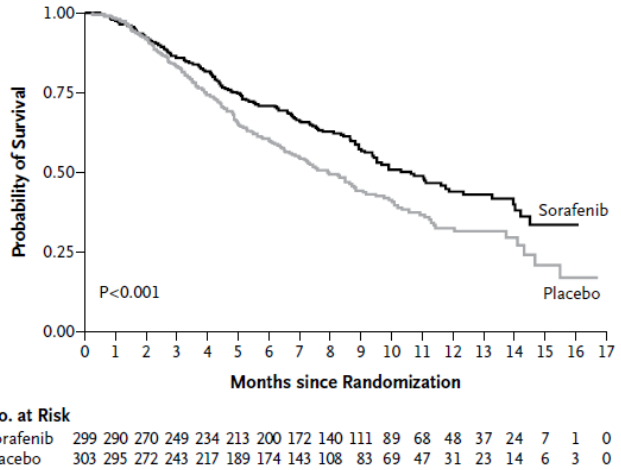
Therapeutic Targets in HCC

- Receptor tyrosine kinases (RTK) or ligands
  - Angiogenesis
  - Other growth factor pathways
    - e.g., MET, FGFR, PDGFR
- Intracellular kinases
  - e.g., RAF, PI3K, mTOR
- Cell cycle
- Epigenetics
- Immune response



Targeted Therapy for HCC
Sorafenib

- SHARP trial - 602 patients with advanced HCC (1/2 with vascular invasion or metastases) and Child's A cirrhosis randomized to oral sorafenib 400 mg bid versus placebo, showing a modest but significant survival benefit with sorafenib
  - Median survival 3 months longer (10.7 vs 7.9 mo)



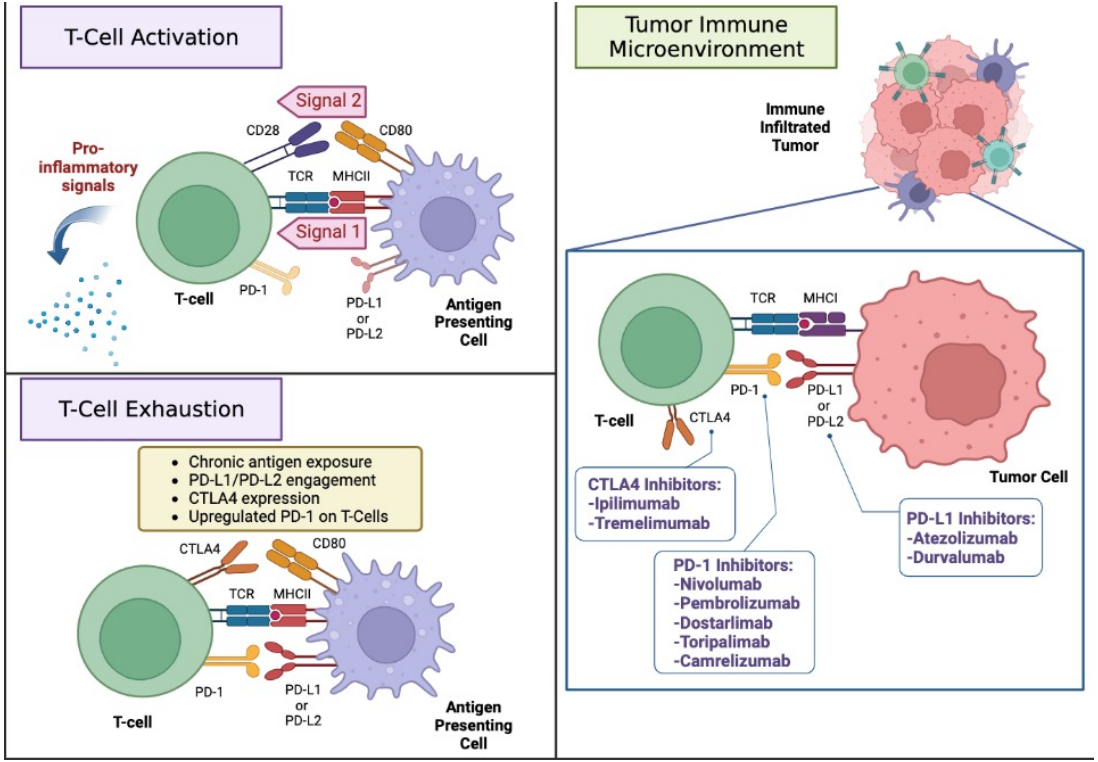
Llovet JM et al. *NEJM.* 2008; 359:378-390.

Targeted Therapy for HCC
Lenvatinib

- Open label phase-3 study REFLECT compared 1st line lenvatinib vs sorafenib
- Lenvatinib was non-inferior to sorafenib
  - Median OS 13.6 vs 12.3 mo (HR 0.92)
- Lenvatinib had improvement in secondary endpts
  - PFS, TTP, and ORR all better w/ lenvatinib
- Discontinuation rate due to AEs fairly similar (9% vs 7%)
- In 2018, lenvatinib approved in US, Europe, and Japan

Kudo M et al. *Lancet.* 2018;391:1163-73.

Immunotherapy for HCC



Martin S, Mehta N, Emamaullee J. *Liver Txp.* 2023.

Targeted Therapy for HCC
Atezolizumab/Bevacizumab

The NEW ENGLAND JOURNAL of MEDICINE

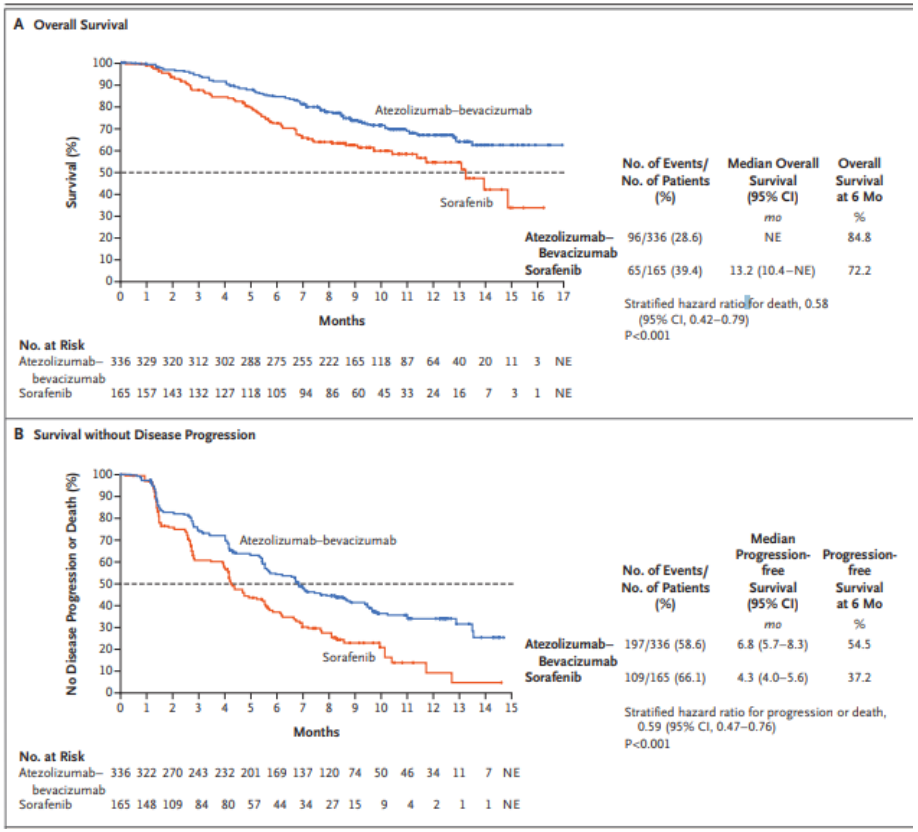
ORIGINAL ARTICLE

Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma

- Global, open label phase 3 trial
- 336 pts randomized to Atezolizumab (immunotherapy) plus Bevacizumab (VEGF-inhibitor) vs 165 pts in Sorafenib arm
- Pts with untreated varices were excluded

Finn R et al. *NEJM*. 2020.

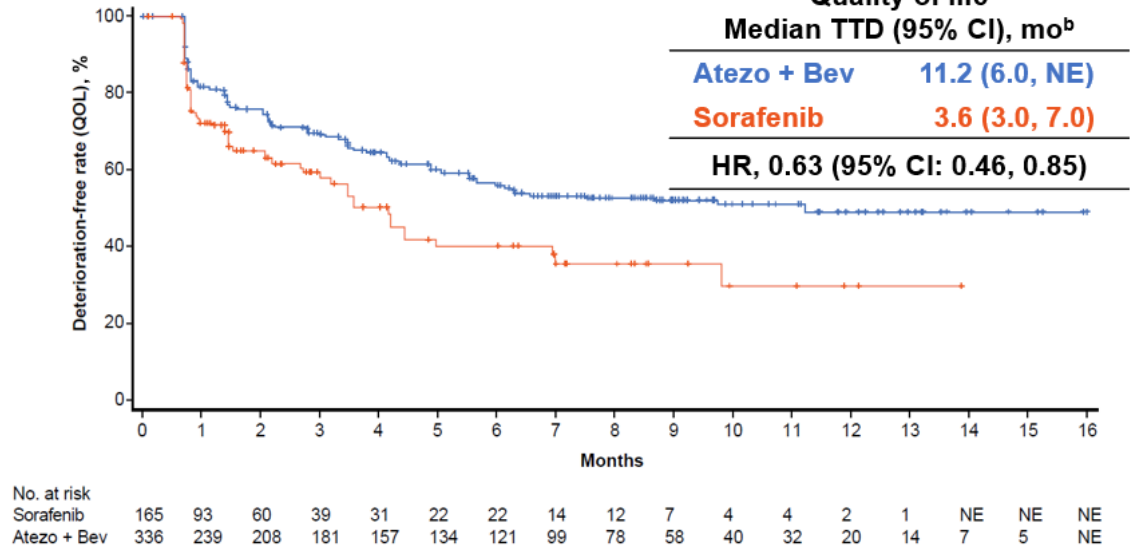
Targeted Therapy for HCC
Atezolizumab/Bevacizumab



Finn R et al. *NEJM*. 2020.

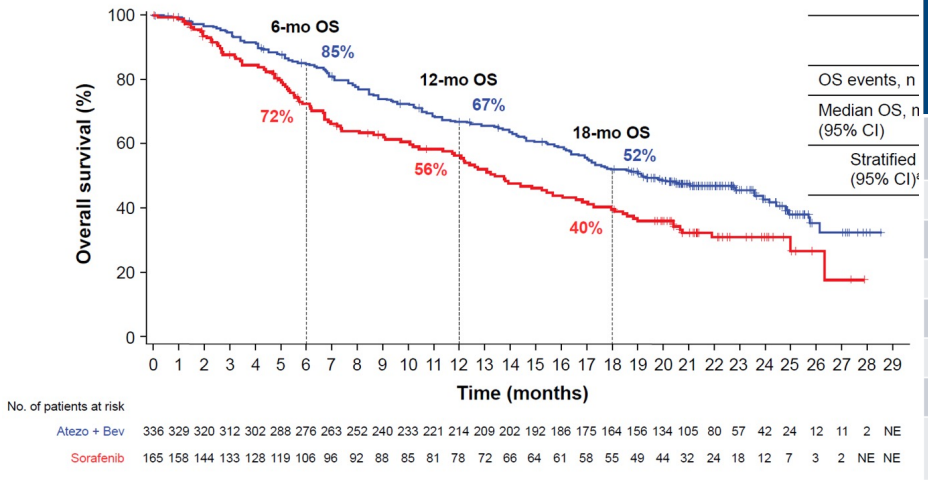
Targeted Therapy for HCC
Atezolizumab/Bevacizumab

Atezolizumab + bevacizumab delayed the time to deterioration of patient-reported quality of life compared with sorafenib



Finn R et al. *NEJM*. 2020.

Targeted Therapy for HCC
Atezo/Bev Updated Results

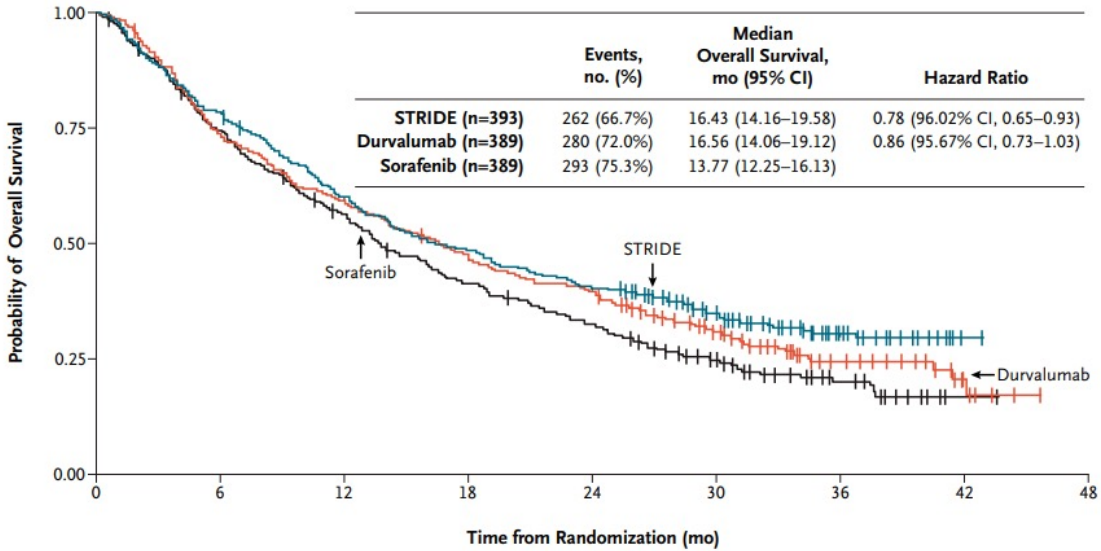


	Updated analysis[a] RECIST 1.1	
	Atezo + Bev (n = 326)	Sorafenib (n = 159)
Confirmed ORR (95% CI), %	**30 (25, 35)**	**11 (7, 17)**
CR, n (%)	25 (8)	1 (< 1)
PR, n (%)	72 (22)	17 (11)
SD, n (%)	144 (44)	69 (43)
DCR, n (%)	241 (74)	87 (55)
PD, n (%)	63 (19)	40 (25)
Ongoing response, n (%)	54 (56)	5 (28)
Median DOR (95% CI), mo[b]	**18.1 (14.6, NE)**	**14.9 (4.9, 17.0)**

Median OS 19.2 vs 13.4 mos, HR 0.66
Median PFS 6.9 vs 4.3 mos, HR 0.65

Cheng A et al. *J Hep.* 2022.

Targeted Therapy for HCC
Durvalumab/Tremelimumab



	Events, no. (%)	Median Overall Survival, mo (95% CI)	Hazard Ratio
STRIDE (n=393)	262 (66.7%)	16.43 (14.16–19.58)	0.78 (96.02% CI, 0.65–0.93)
Durvalumab (n=389)	280 (72.0%)	16.56 (14.06–19.12)	0.86 (95.67% CI, 0.73–1.03)
Sorafenib (n=389)	293 (75.3%)	13.77 (12.25–16.13)	

No. at Risk									
STRIDE	393	308	235	190	158	98	32	1	0
Durvalumab	389	286	230	183	153	87	27	6	0
Sorafenib	389	283	211	155	121	62	21	1	0

Abou-Alfa G et al. *NEJM Evidence.* 2022.

Targeted Therapy for HCC

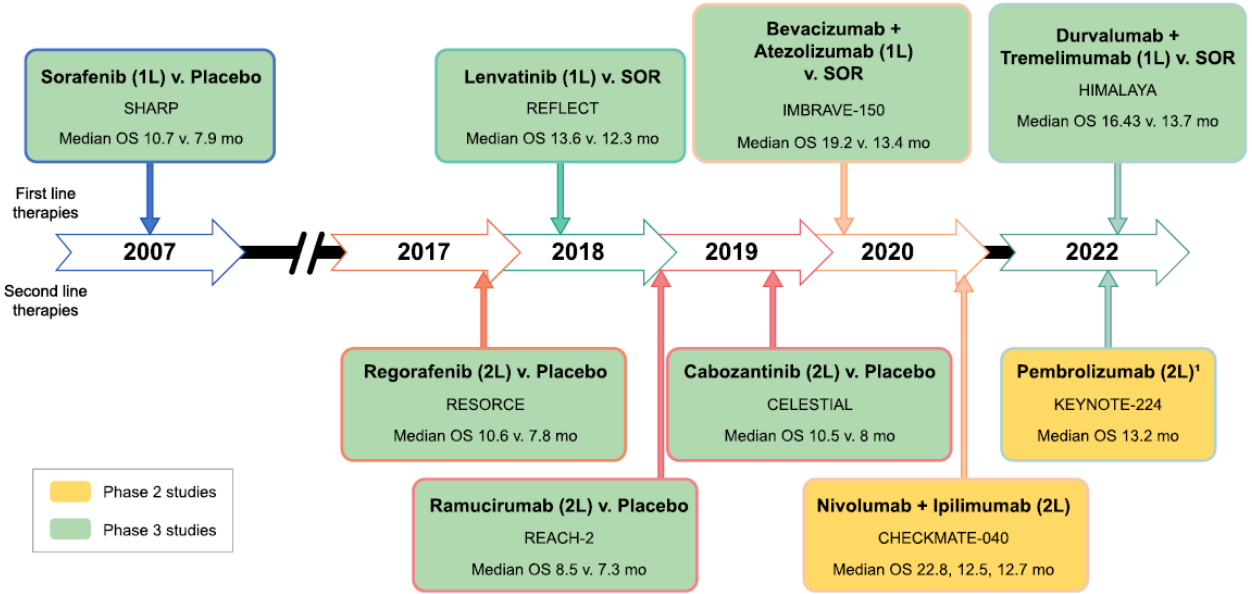
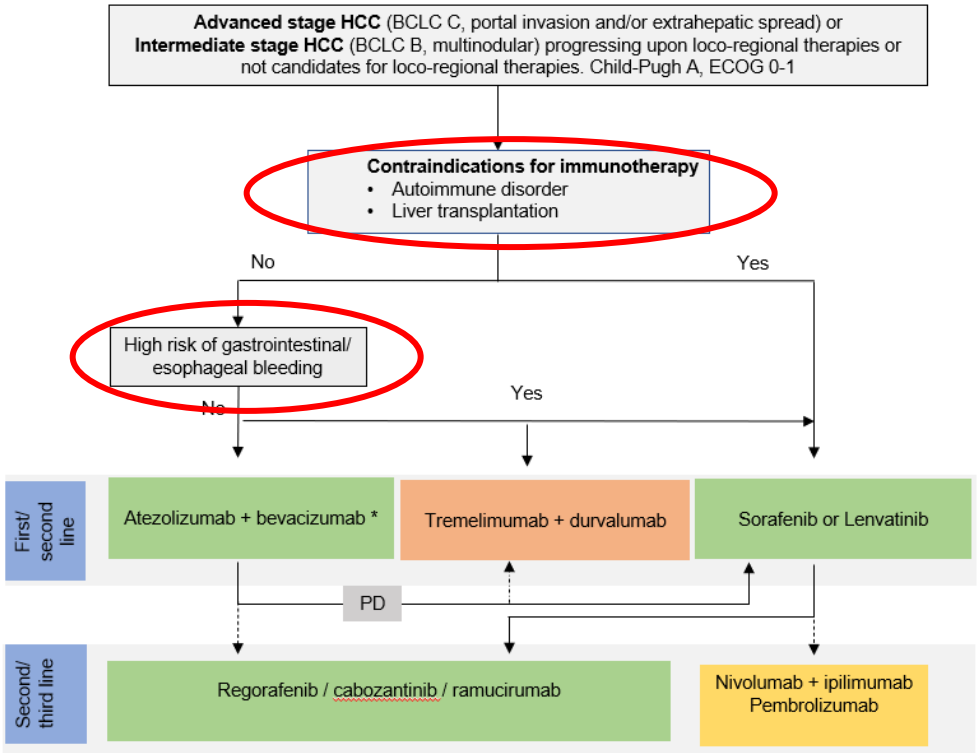


FIGURE 15 Timeline of systemic therapies for hepatocellular carcinoma (HCC) and resultant survival. (First line therapies are above the timeline; second line therapies are below the timeline.) [1]KEYNOTE 224 was a non-randomized phase 2 trial. Phase 3 studies of pembrolizumab versus sorafenib have had conflicting results, with improved median OS noted in an Asian population.

Singal A et al. AASLD HCC Practice Guidance. 2023.

Targeted Therapy for HCC

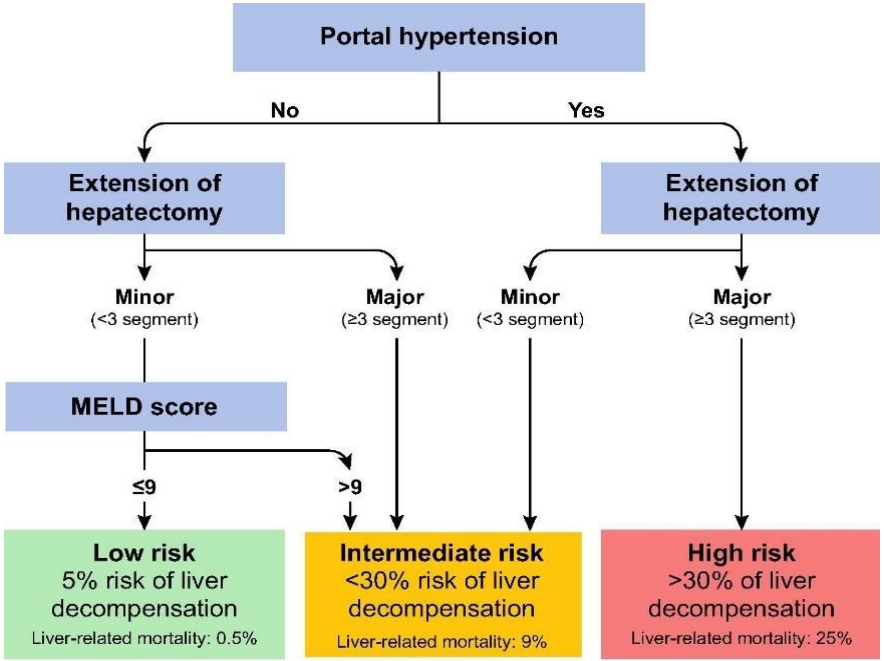


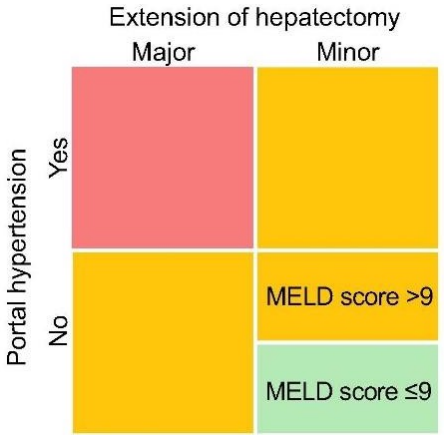
Singal A et al. AASLD HCC Practice Guidance. 2023.

Patient Case

- 65 y/o patient with compensated MASH cirrhosis
- Found to have single 4 cm LR-5 HCC on quad phase CT scan in segment 2, no metastatic spread, no portal vein invasion, normal spleen size
- Excellent functional status
- Bili 0.8 mg/dL, albumin 3.7 g/dL, INR 1.1, AST/ALT 40s, Platelets 120K; Child-Pugh A5, MELD-Na 8
- AFP 35 ng/mL, AFP-L3 17%, DCP 1.8 ng/mL

BCLC Optimal Surgical Candidate



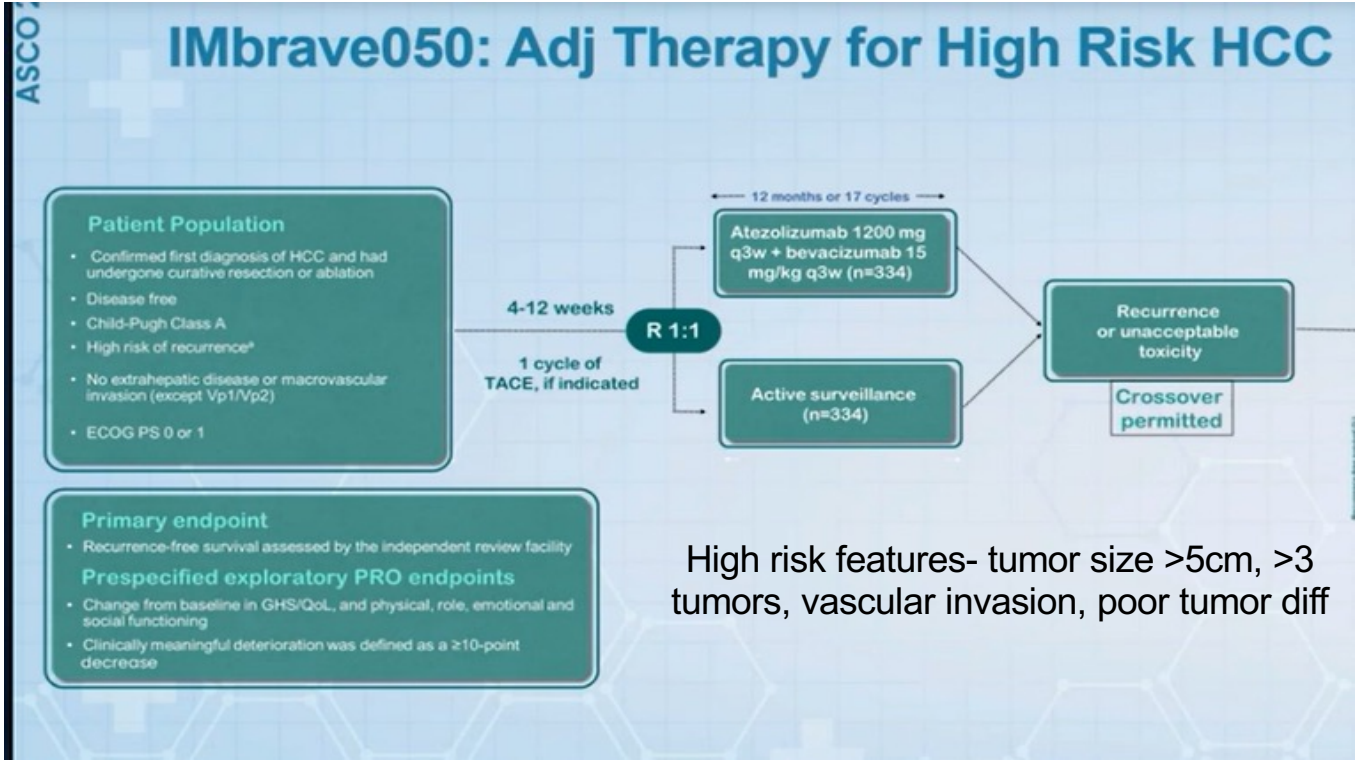


EASL Clinical Practice Guidelines. 2018.

Patient Case

- 65 y/o patient with compensated MASH cirrhosis and 4 cm LR-5 lesion, undergoes resection
- Resection specimen shows 4.3 cm HCC, moderate differentiation, and microvascular invasion
- Any role for adjuvant therapy?

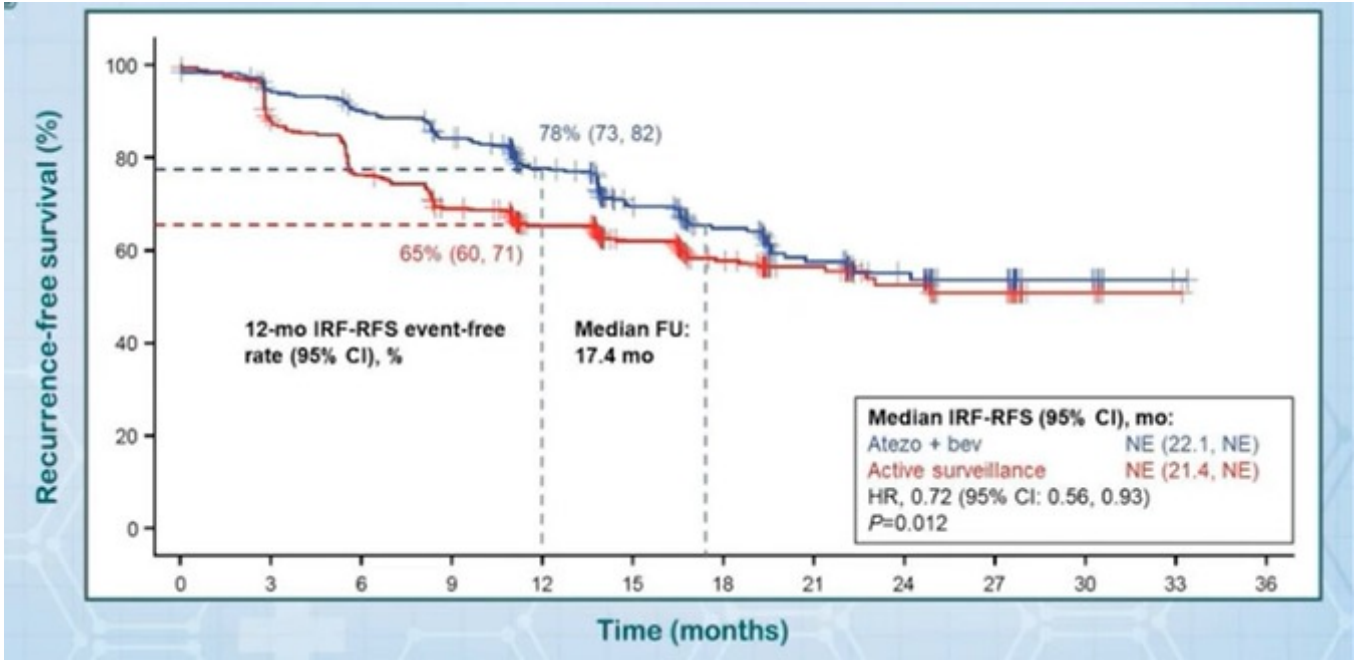
Role for Adjuvant Therapy?



High risk features- tumor size >5cm, >3 tumors, vascular invasion, poor tumor diff

ASCO GI 2023. IMbrave050.

Role for Adjuvant Therapy?



ASCO GI 2023. IMbrave050.

Role for Adjuvant Therapy

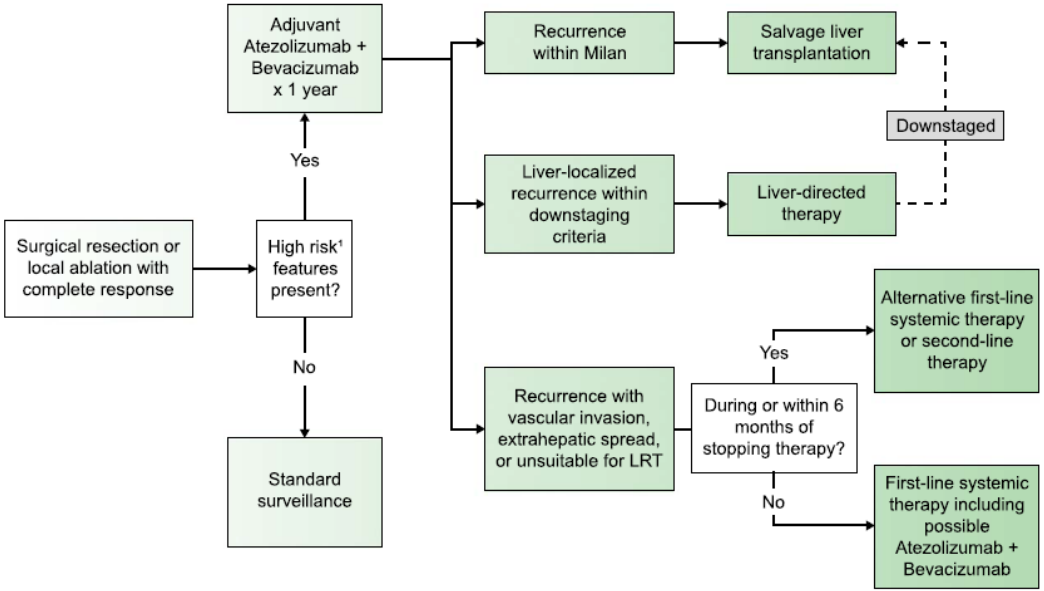


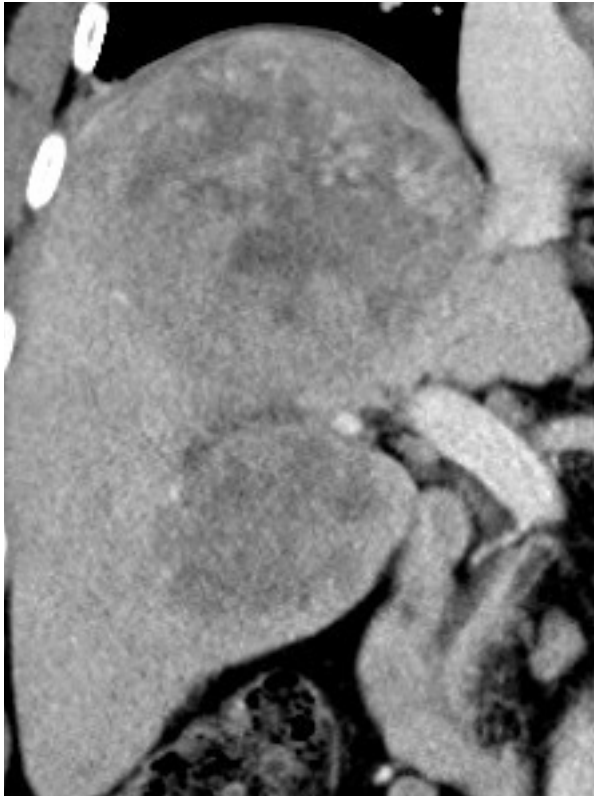
FIGURE 11 Management of patients with recurrence during or after adjuvant therapy. [1]High-risk features include tumor size >5 cm, more than 3 tumors, microvascular or macrovascular invasion, and poor tumor differentiation.

Singal A et al. AASLD HCC Practice Guidance. 2023.

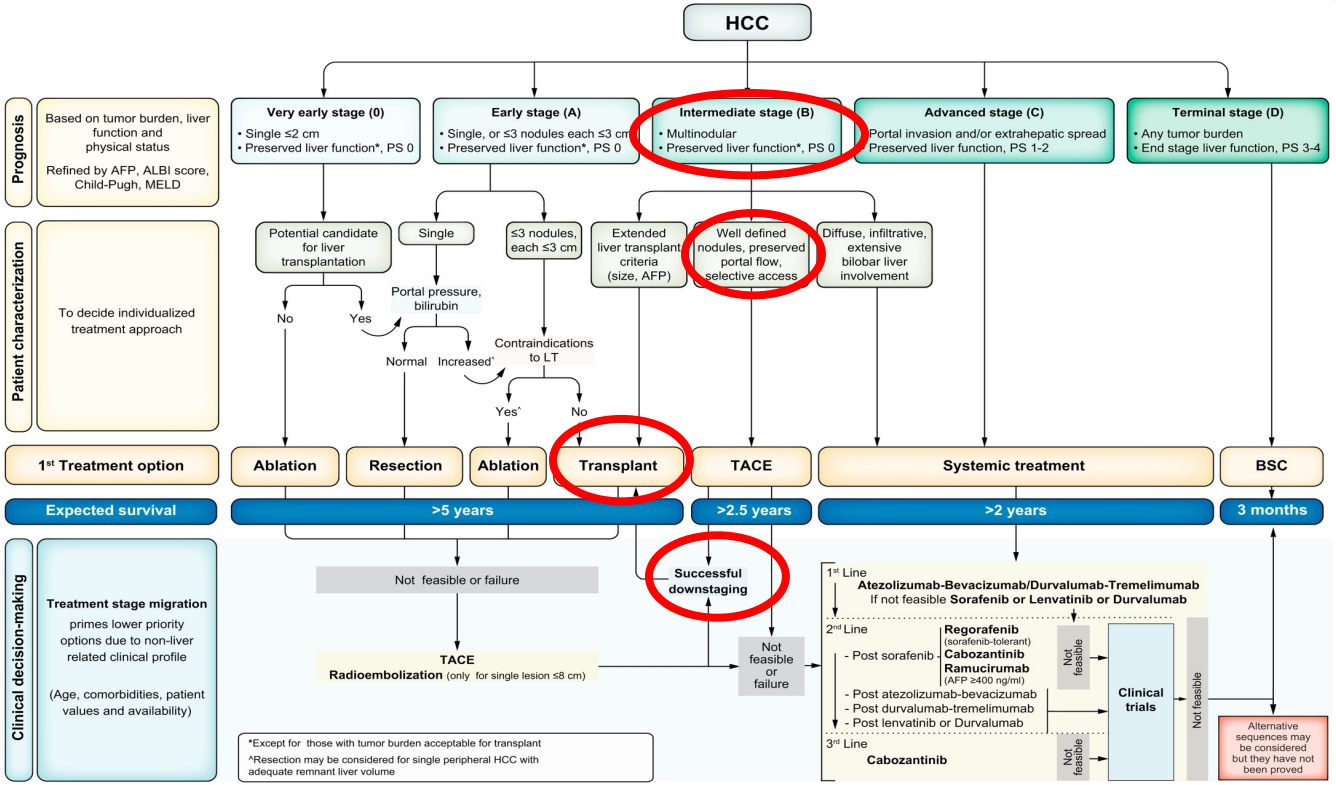
Patient Case (Revised)

- 65 y/o patient with compensated MASH cirrhosis
- Found to have multifocal unilobar HCC, two large LR-5 lesions 9 cm and 5 cm (total diameter of 14 cm); no metastatic spread, no portal vein invasion, mild splenomegaly
- Excellent functional status
- Bili 1.5 mg/dL, albumin 3.4 g/dL, INR 1.3, AST/ALT 40s, Platelets 100K; Child-Pugh A6, MELD-Na 12
- AFP 35 ng/mL, AFP-L3 17%, DCP 3.8 ng/mL

65 yo With MASH and Large HCC



BCLC Staging Classification



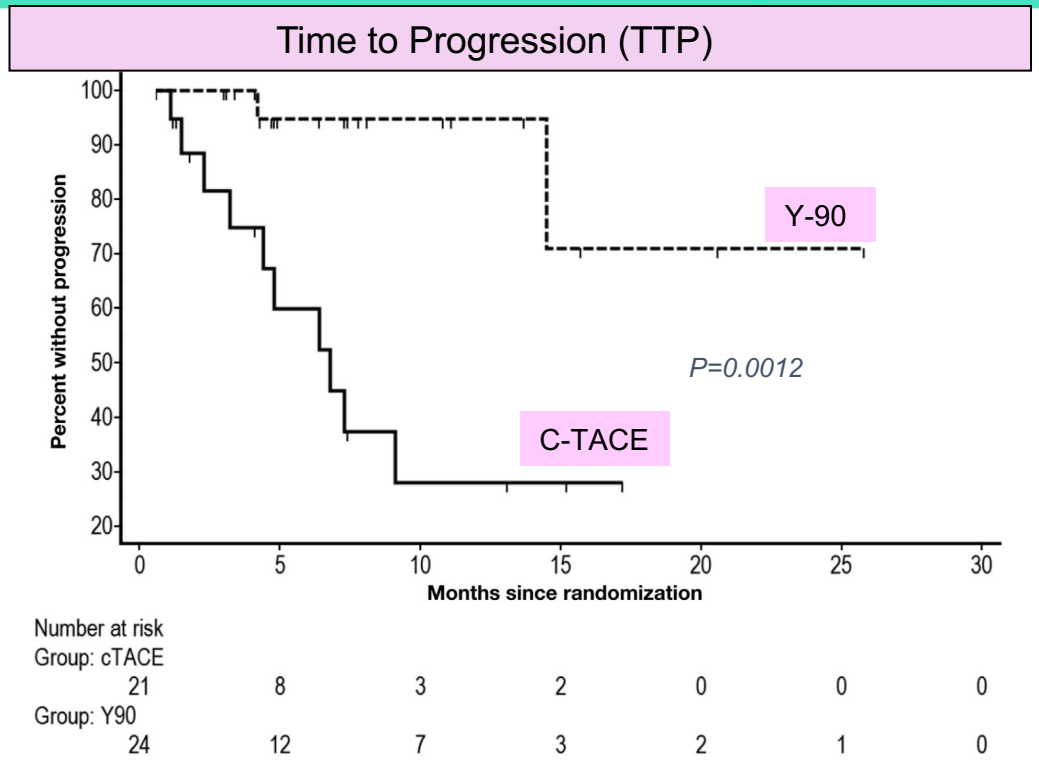
Reig M et al. *Journal of Hepatology*. 2022.

Down-Staging of HCC for Transplant

- Definition: Reduction in the size of tumor using local regional therapy to meet acceptable criteria for liver transplant[1]
- Tumor response: Based on radiographic measurement of the size of all viable tumors, not including the area of necrosis from local regional therapy[2]
- A selection tool for tumors with more favorable biology that respond to down-staging treatment and also do well after liver transplant[1]

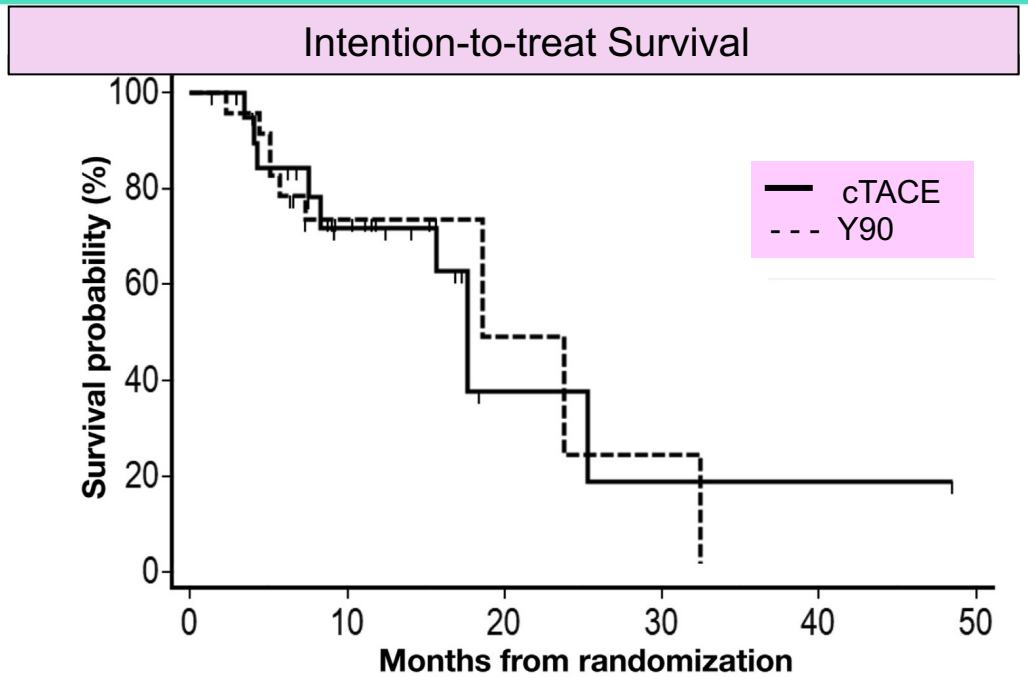
1. Yao & Fidelman. *Hepatology.* 2016;63:1014-1025; 2. EASL Guidelines - Briux J et al. *J Hepatol.* 2001;35: 421–430.

SIRT (Y-90) Versus TACE (PREMIERE)



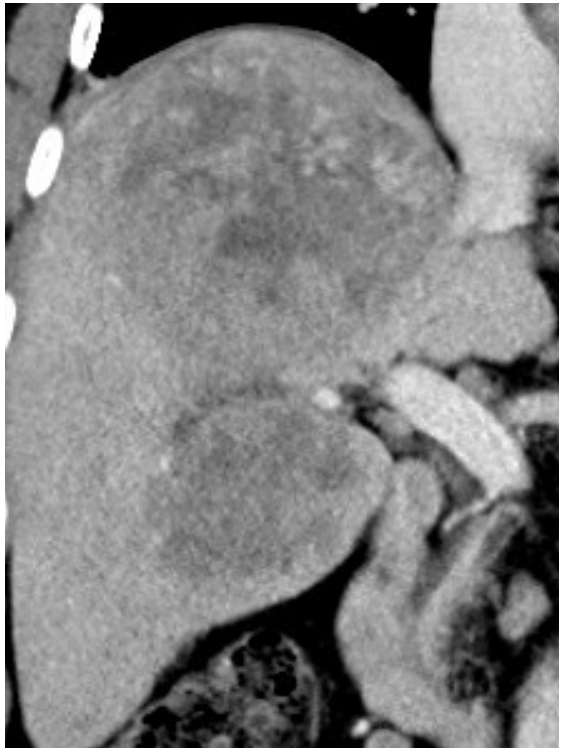
Salem R et al. *Gastroenterology.* 2016;151:1155-1163.

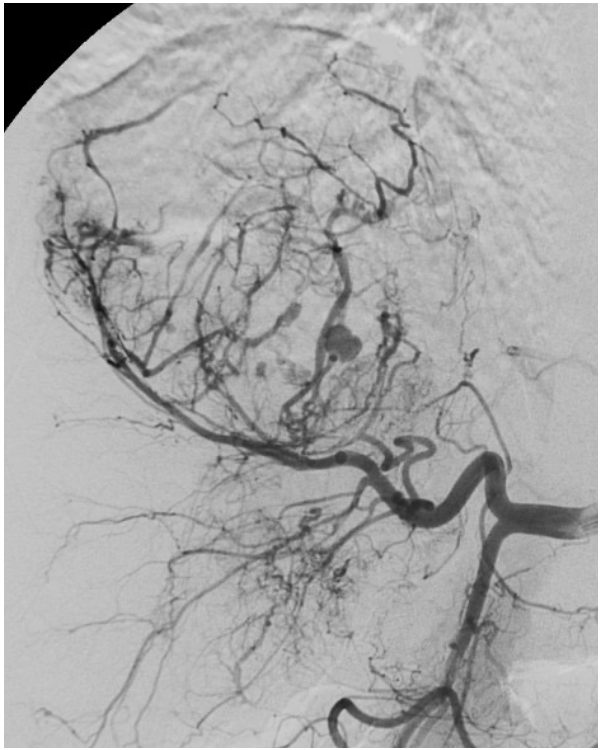
SIRT (Y-90) Versus TACE (PREMIERE)



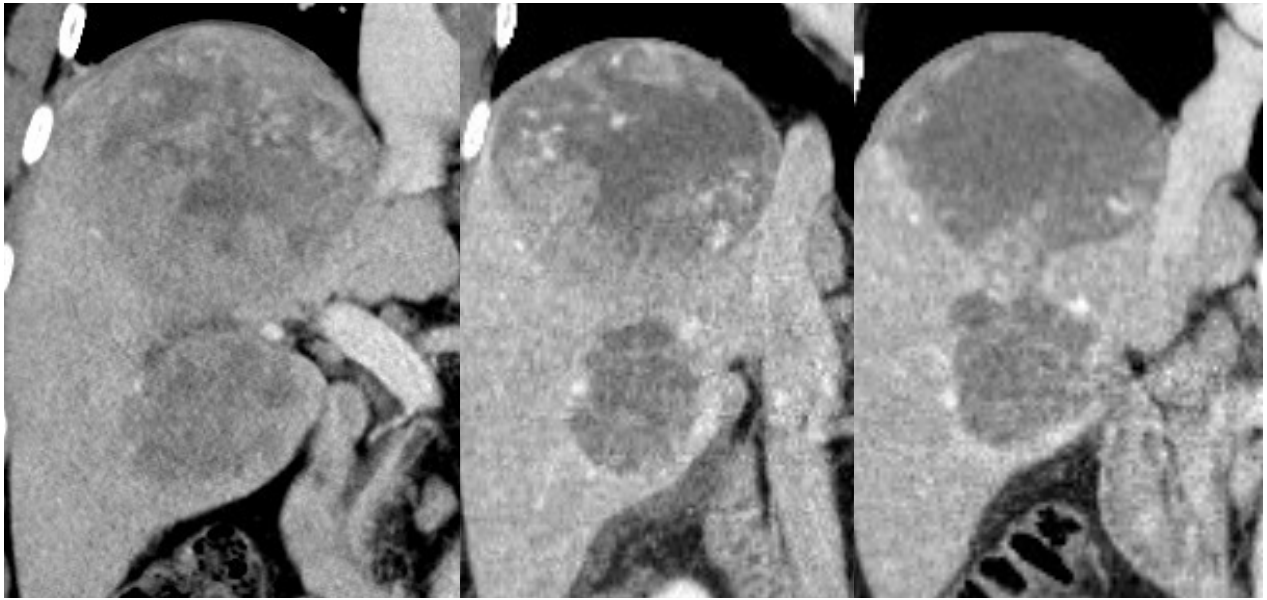
Salem R et al. *Gastroenterology.* 2016;151:1155-1163.

65 yo With MASH and Large HCC





65 yo With MASH and Large HCC



Pre-treatment

1 mo after Y-90 #1

1 mo after Y-90 #2
4 mo after Y-90 #1

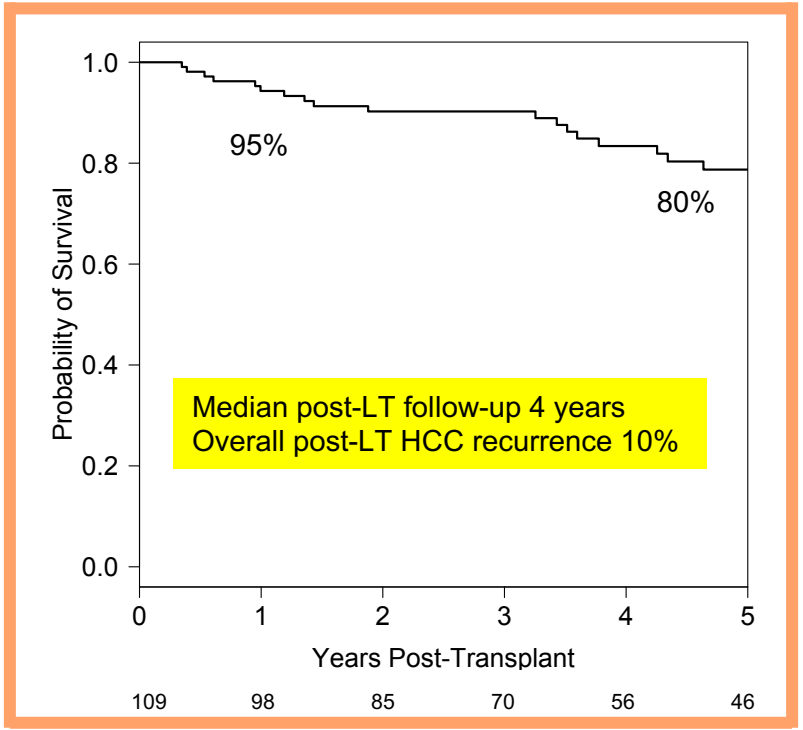
UNOS Down-Staging Protocol

- Inclusion criteria
  - 1 lesion > 5 cm and ≤ 8 cm
  - 2 or 3 lesions ≤ 5 cm w/ total tumor diameter ≤ 8 cm
  - 4 or 5 lesions ≤ 3 cm w/ total tumor diameter ≤ 8 cm
  - No vascular invasion or extrahepatic disease on imaging

- Minimum 3 month observation period after successful down-staging into Milan before LT can be undertaken

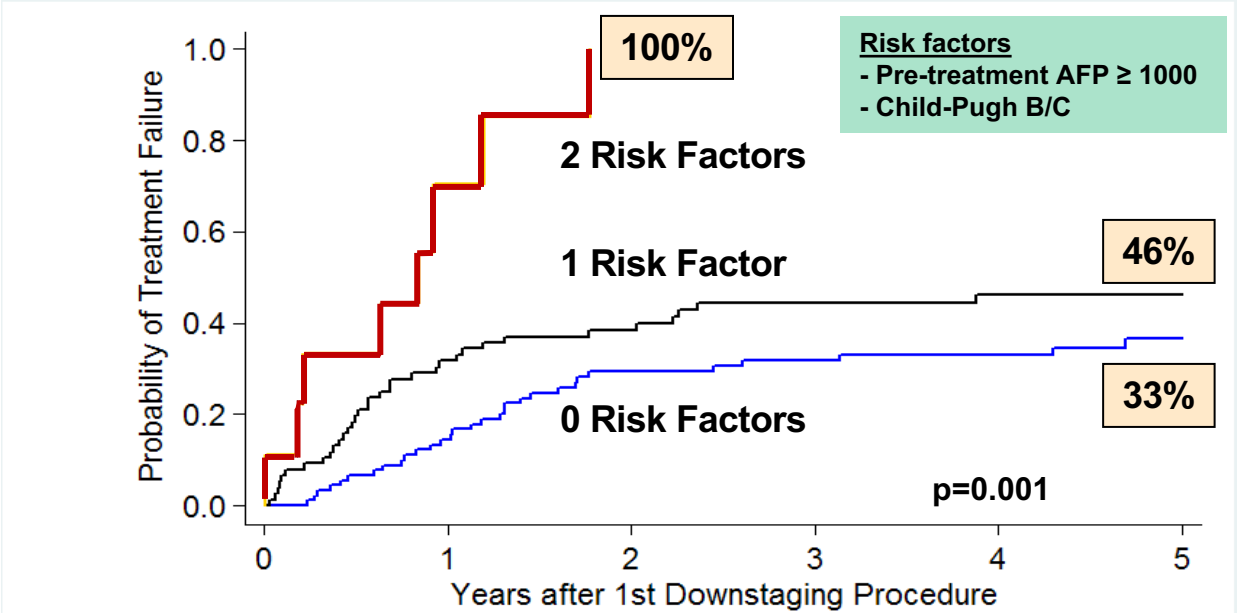
Yao et al. *Hepatology.* 2008;48:819-827.

Multicenter Down-Staging: Region 5



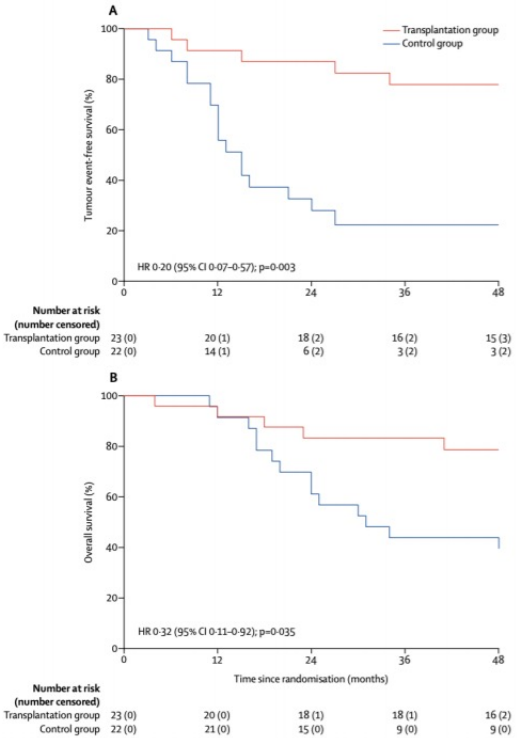
Mehta N et al. *Clin Gastroenterol Hepatol.* 2018;16:955-964.

Treatment Failure: AFP and Child's Class



Mehta N et al. *Clin Gastroenterol Hepatol.* 2018;16:955-964.

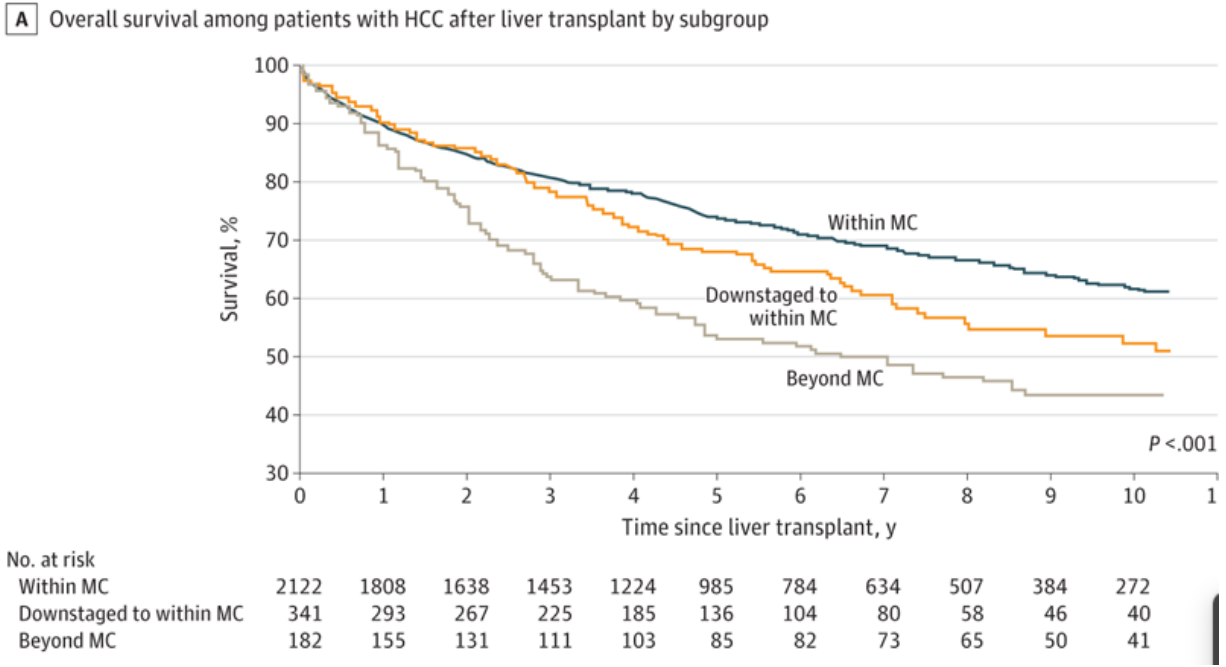
Multicenter Down-Staging RCT: Italy



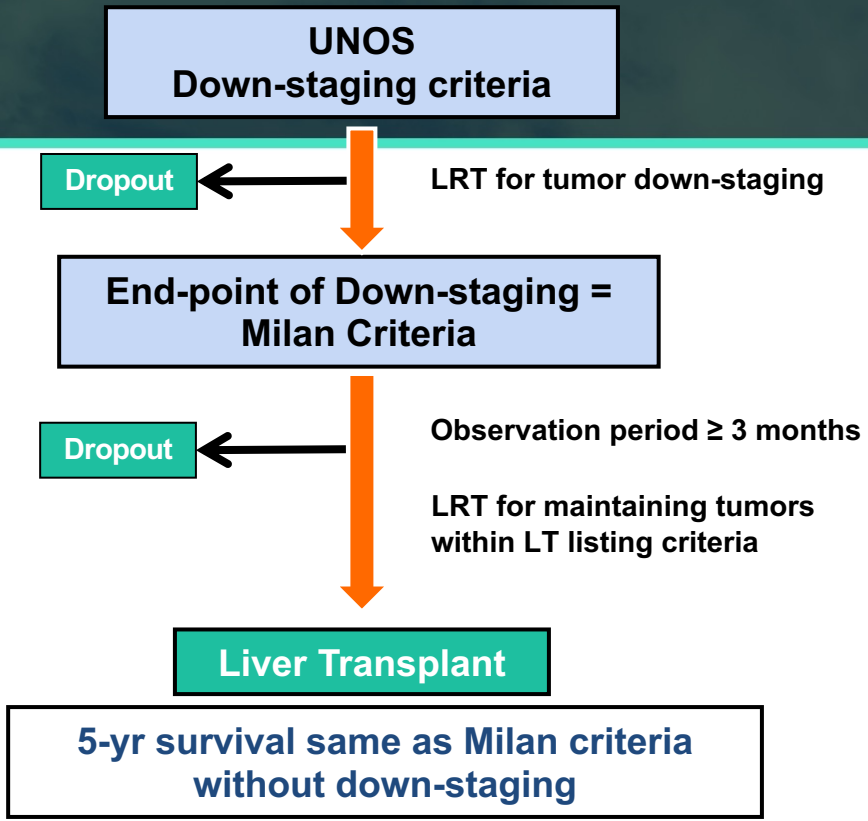
- From 2011-15, pts initially beyond Milan criteria with partial or complete response (mRECIST) randomly assigned to LT or non-transplantation therapies

Mazzaferro et al. *Lancet Oncology*. 2020.

Multicenter Down-Staging Study



P Tabrizian et al. *JAMA Surgery*. 2022.



Automatic MELD exception for UNOS-DS after down-staging now national policy

Multicenter Evaluation of Reduction In Tumor Size before Liver Transplantation (MERITS-LT) Consortium

UCSF
USC
UCSD
CPMC
Scripps Clinic
Stanford
U Michigan
Mt. Sinai
U Pennsylvania

Prospective Down-Staging Multi-Regional Study: MERITS-LT

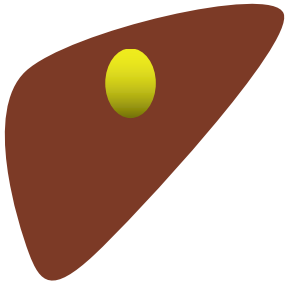
- Among 209 HCC pts meeting UNOS-DS criteria, 2-yr probability of successful down-staging 88%
- No difference in probability of successful down-staging or liver transplant between TACE (n=132) and Y-90 (n=62)
- Tumor under-staging (explant > Milan) in 43%, and sum of the number of viable tumors + largest tumor diameter on last imaging only significant predictor of under-staging

Mehta N et al on behalf of MERITS-LT Consortium. *Gastroenterology.* 2021.

Patient Case (Reminder)

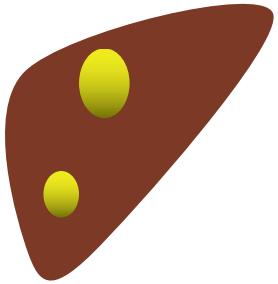
- 65 y/o patient with compensated MASH cirrhosis
- Found to have multifocal unilobar HCC, **two large LR-5 lesions 9 cm and 5 cm (total diameter of 14 cm);** no metastatic spread, no portal vein invasion, mild splenomegaly
- Excellent functional status
- Bili 1.5 mg/dL, albumin 3.4 g/dL, INR 1.3, AST/ALT 40s, Platelets 100K; Child-Pugh A6, MELD-Na 12
- AFP 35 ng/mL, AFP-L3 17%, DCP 3.8 ng/mL

HCC Transplant Criteria



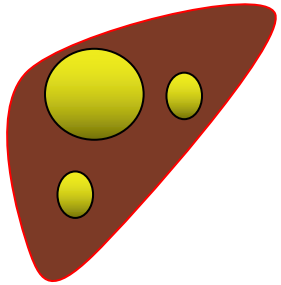
MILAN CRITERIA

- 1 lesion ≤ 5 cm
- 2-3 lesions ≤ 3 cm
- No extra-hepatic dz



UNOS DOWNSTAGING CRITERIA

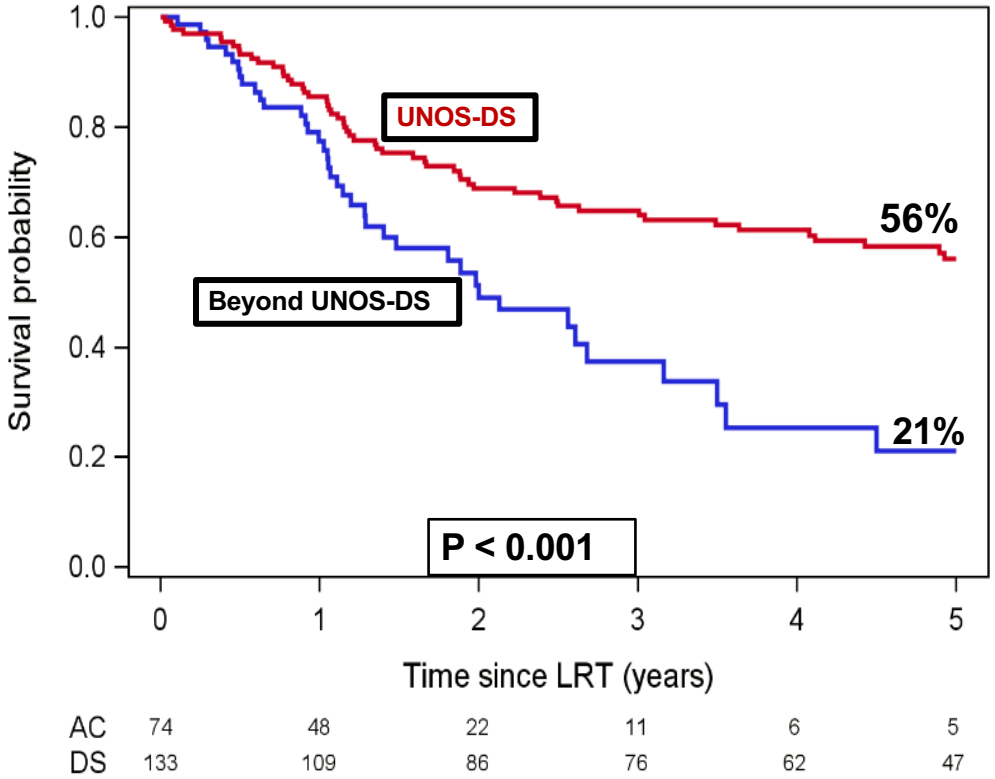
- 1 lesion 5.1-8cm
- 2-3 lesions ≤ 5 cm
- 4-5 lesions ≤ 3 cm
- TTD ≤ 8 cm
- No extra-hepatic dz



"BEYOND UNOS-DS" CRITERIA

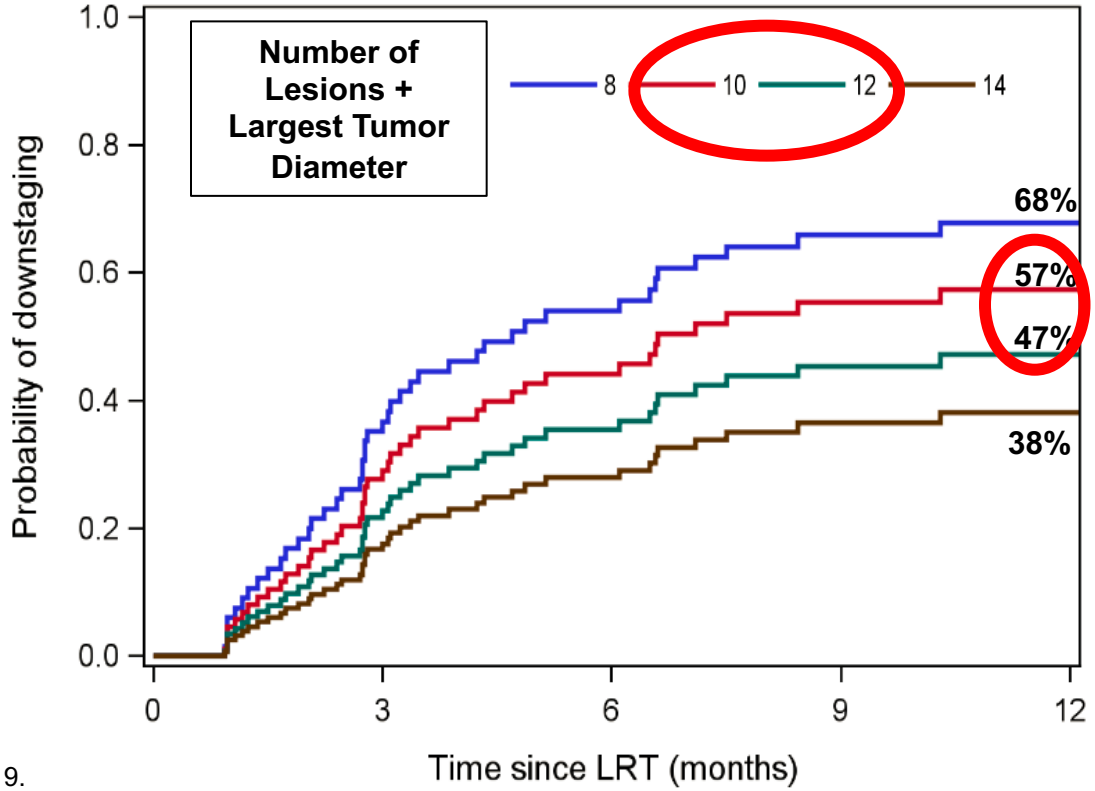
- Any number of tumors
- TTD > 8cm
- No extra-hepatic dz

UNOS-DS vs Beyond UNOS-DS: Intention-to-Treat Survival



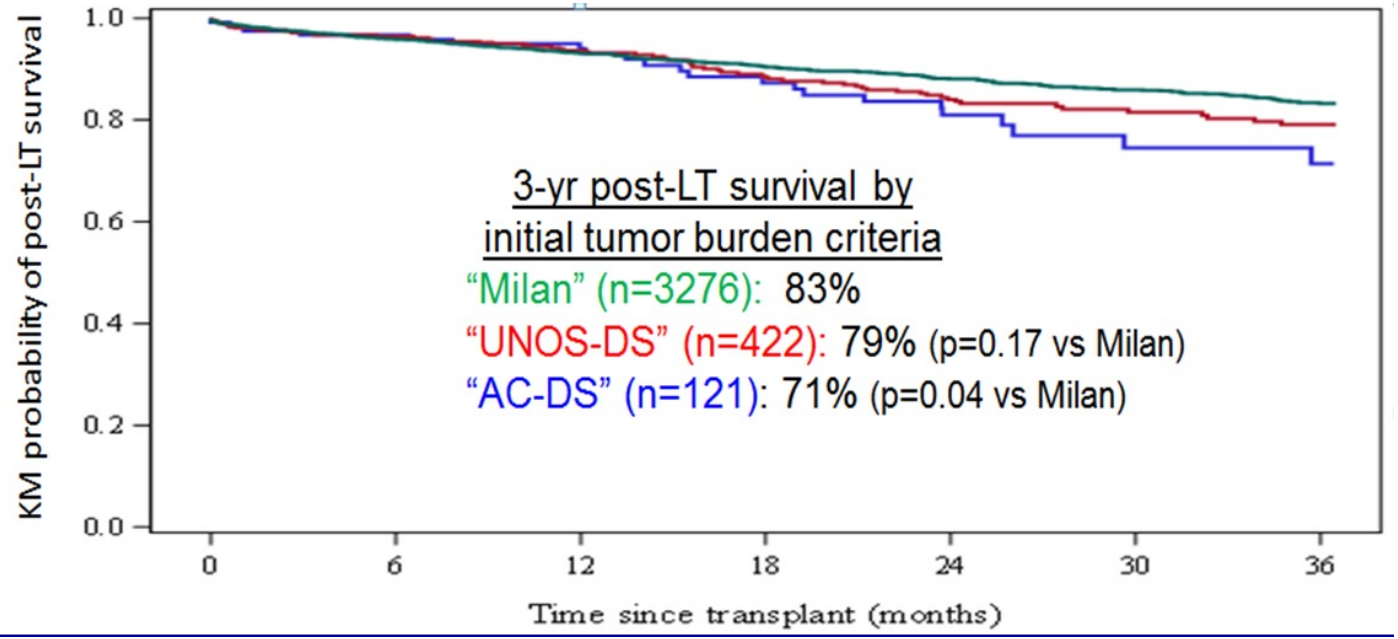
Sinha J. *Hepatology*. 2019.

Probability of Downstaging by Initial Tumor Burden



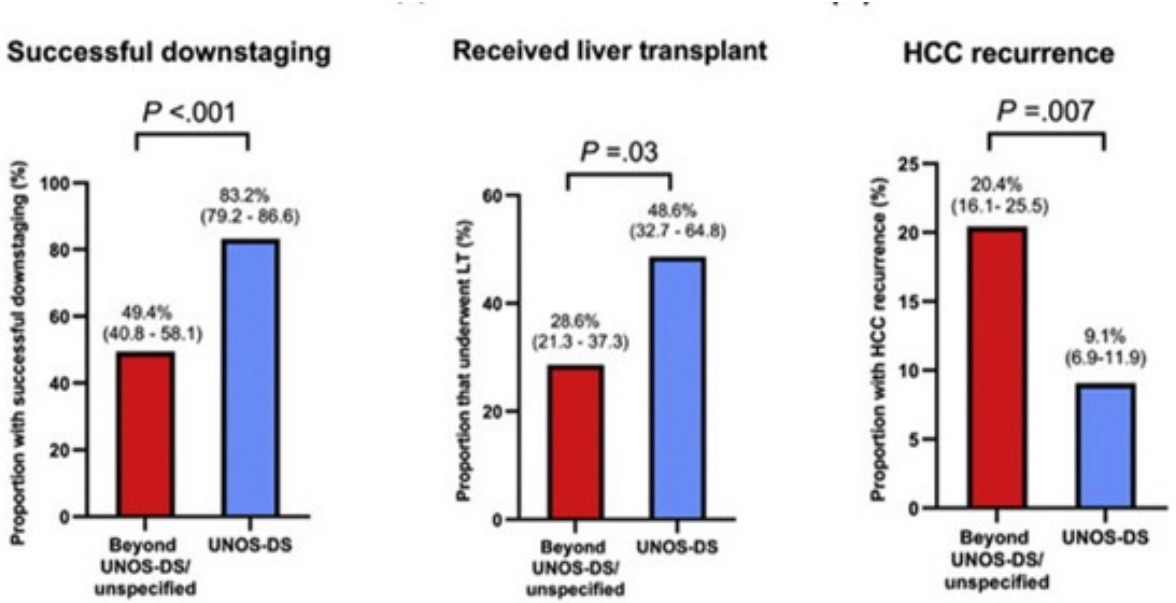
Sinha J. *Hepatology*. 2019.

UNOS Down-Staging Cohorts



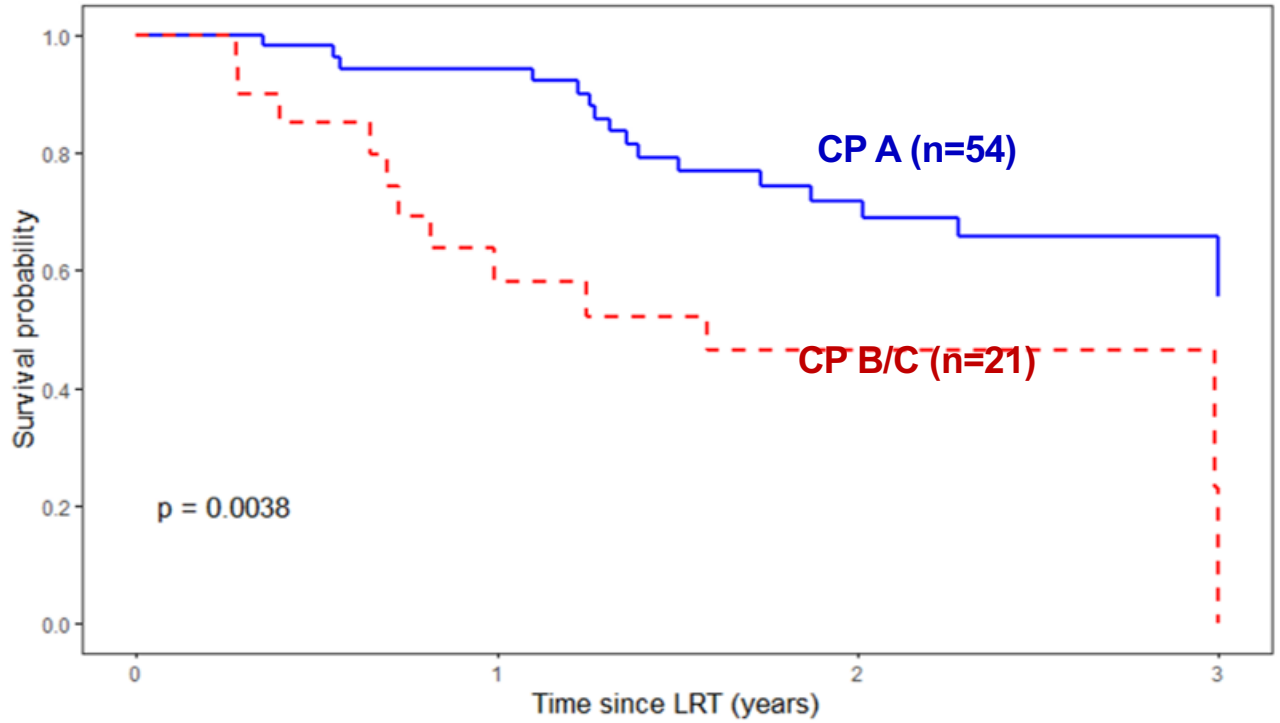
Mehta et al. *Hepatology.* 2020;71(3):943-54.

Within Vs Beyond UNOS-DS Systematic Review + Meta-Analysis



Tan et al. *CGH*. 2022.

ITT Survival From 1st DS Procedure in All-Comers by CP Score



Natarajan B et al on behalf of the MERITS-LT Consortium. *AJT*. 2023.

Inferior Outcomes Beyond UNOS-DS

- An upper limit in tumor burden probably exists beyond which successful LT after down-staging becomes an unlikely goal
  - Significantly worse rates of down-staging, ITT survival, waitlist dropout, and post-LT survival for HCC pts initially beyond UNOS-DS compared to Milan and UNOS-DS patients

- Could adding systemic therapy in this population be helpful to improve outcomes??

EMERALD-1 Press Release

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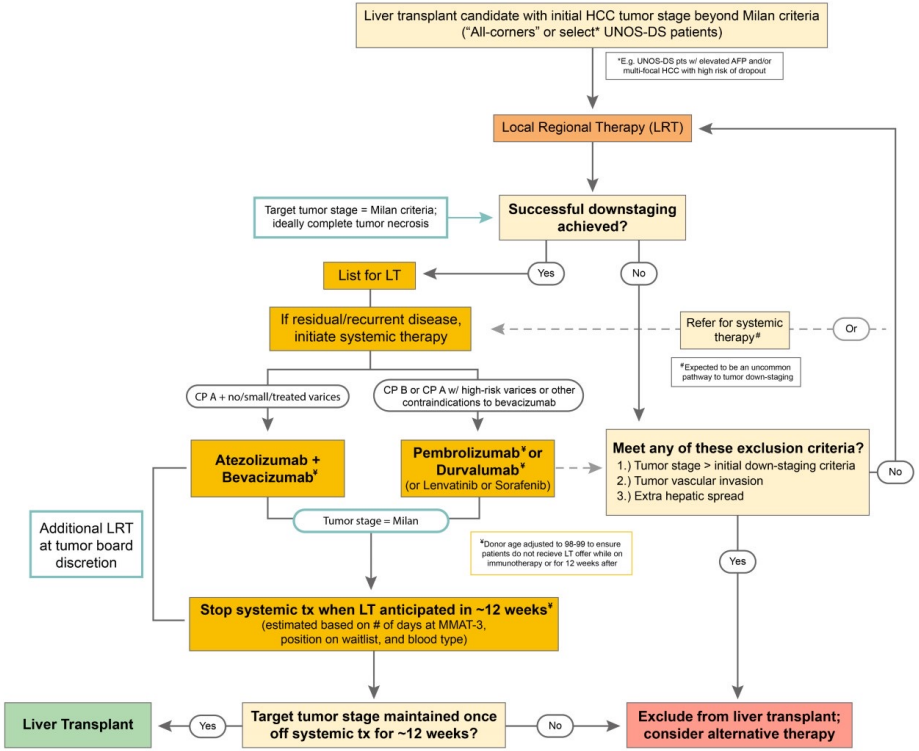
- Could adding systemic therapy in this population be helpful to improve outcomes??

Ongoing HCC Immunotherapy Trials

Study	Phase	Trial ID	Brief Summary
Transplantable Disease			
Durvalumab and Tremelimumab for Hepatocellular Carcinoma In Patients Listed for Liver Transplant	II	NCT05027425	Evaluate immunotherapy as a strategy to downstage patients and achieve a durable systemic disease control in HCC patients undergoing liver transplant
Resectable Disease			
MORPHEUS-NEO HCC: A Study Evaluating the Efficacy and Safety of Neoadjuvant Immunotherapy Combinations in Patients with Surgically Resectable Hepatocellular Carincoma	Ib/II	NCT05908786	Multicenter, randomized platform study to evaluate neoadjuvant immunotherapy combinations in participants with resectable HCC
Feasibility and Efficacy of Perioperative Nivolumab With and Without Relatlimab for Patients With Potentially Resectable Hepatocelluar Carcinoma	I	NCT04658147	Safety and tolerability of neoadjuvant/adjuvant Nivolumab or Nivolumab plus Relatlimab in patients with HCC
KEYNOTE-937: Safety and Efficacy of Pembrolizumab Versus Placebo as Adjuvant Therapy in Participants with Hepatocellular Carcinoma and Complete Radiological Response After Surgical Resection or Local Ablation	III	NCT03867084	Randomized, double-blind, phase III trial designed to investigate the safety and efficacy of adjuvant pembrolizumab versus placebo in patients with HCC who have had a complete radiologic response after resection or local ablation
Unresectable/Non-Transplantable Disease			
ROWAN: TheraSphere with Durvalumab and Tremelimumab for HCC	II	NCT05063565	Efficacy and saftey of TheraSphere Followed by durvalumab and tremelimumab
CTLA-4/PD-L1 Blockade Following Transarterial Chemoembolization (DEB-TACE) in Patients with Intermediate Stage of HCC Using Durvalumab and Tremelimumab	II	NCT03638141	Determine the safety and efficacy of immunotherapy durvalumab and tremelimumab combined with DEB-TACE in patients with HCC
Combined Treatment of Durvalumab, Bevacizumab, Tremelimumab and Transarterial Chemoembolization in Subjects with Hepatocellular Carcinoma or Biliary Tract Cancers	II	NCT03937830	Evaluate 6-month progression free survival in people with advanced HCC treated with bevacizumab. Durvalumab and TACE
A Study of Durvalumab or Trememlimumab Monotherapy or Durvalumab in Combination With Tremelimumab or Bevacizumab in Advanced Hepatocelluar Carcinoma	II	NCT02519348	Multicenter, open-label, stratified, randomized study to evaluate the safety, tolerability, antitumor activity, pharmacokinetics, pharmacodynamics, and immunogenicity of durvalumab or tremelimumab monotherapy, or durvalumab in combination with tremelimumab or bevacizumab in advanced hepatocellular carcinoma
Trial of Atezolizumab and Bevacizumab with SRF388 or Placebo in Patients with Hepatocellular Carcinoma	II	NCT05359861	efficacy and safety of SRF388 in combination with atezolizumab plus bevacizumab compared to placebo

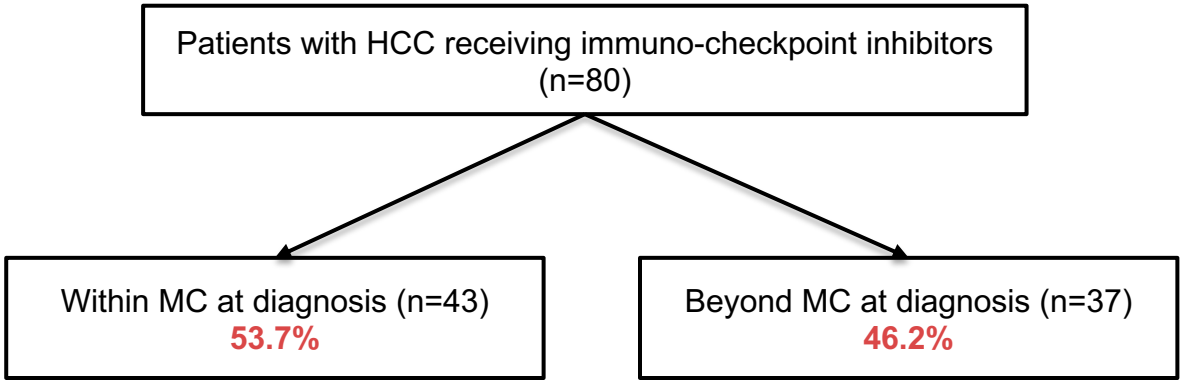
Martin S, Mehta N, Emamaullee J. *Liver Txp*. 2023.

Planned Clinical Workflow Within MERITS-LT Consortium

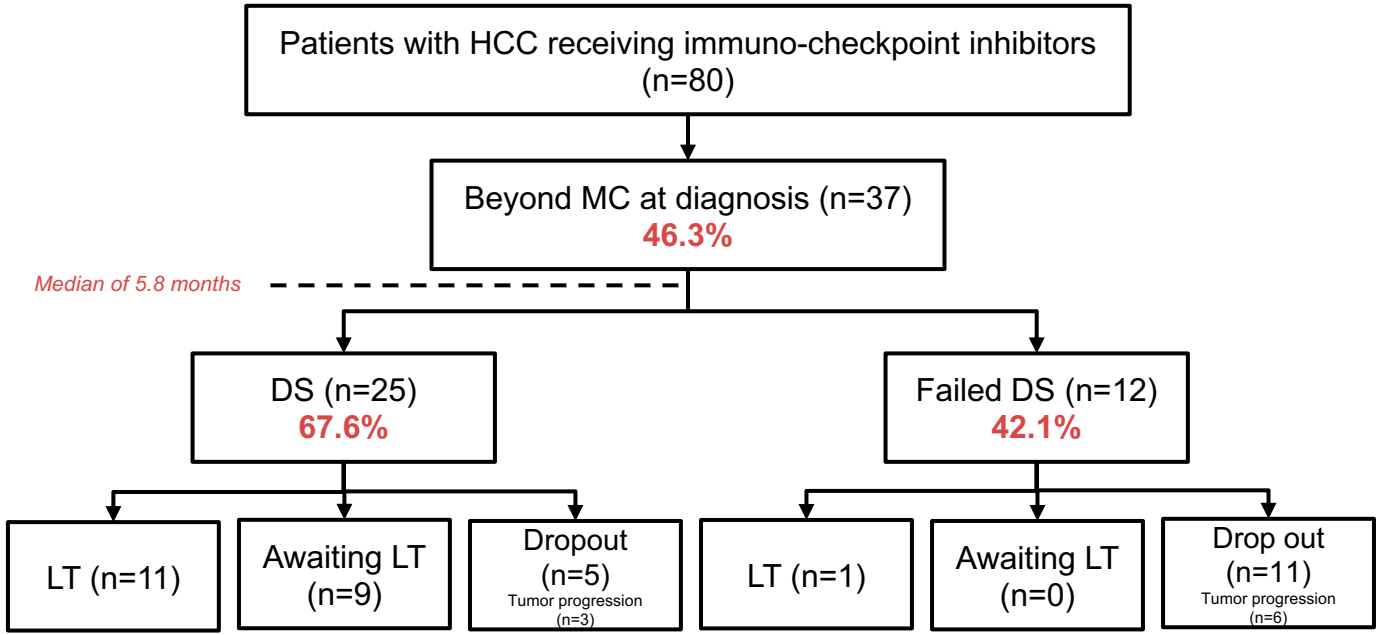


Mehta N, Yao FY, Kelley RK. *Hepatology*. 2023.

MERITS-LT Consortium



Tabrizian P et al. ILTS and AASLD 2023.



The 3-year cumulative probability of dropout
53.7% in beyond MC cohort

Rejection Post LT

- Post-LT rejection rate was 16.6%

  n=2 severe, 1 graft loss and re-LT

  n=3 mild secondary to low immunosuppression

- ICI dose < 3 months pre-LT was associated with increased rejection (p=0.04)

  → Type, duration, ULD not significant

HCC Systemic Therapy Summary

- Atezo/Bev and STRIDE (Durva/Treme) regimen are excellent 1st line treatment options for advanced HCC
  - Need EGD before (or right after) starting Atezo/Bev to exclude high bleeding risk

- Very early immature data but Atezo/Bev (IMbrave050) first ever positive adjuvant tx trial for HCC after resection or ablation w/ high risk for recurrence

HCC Systemic Therapy Summary

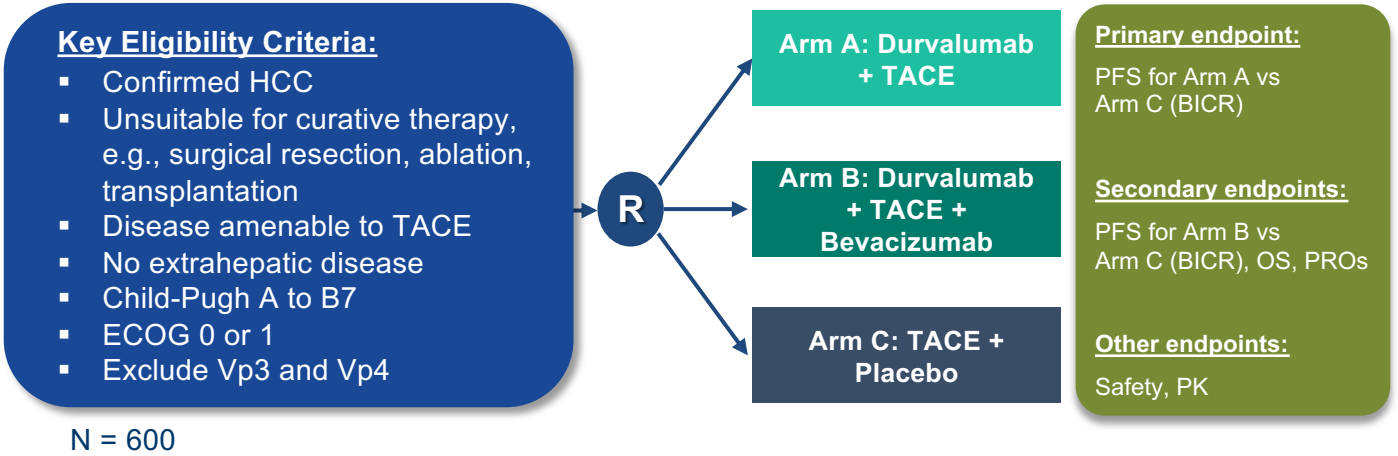
- Several ongoing trials combining systemic therapy with LRT for intermediate stage HCC with recent press release for positive results with EMERALD-1 regimen
- Patients with tumor burden exceeding UNOS-DS criteria must be very carefully selected for LT
  - Consider additional LRT, minimum observation period before LT, and more stringent AFP cutoffs
  - With improved systemic therapy, interest in combining w/ LRT to improve ITT outcome
    - Need washout period of ~3 months with immunotherapy prior to LT

Thank You!

neil.mehta@ucsf.edu

ICI + TACE: Phase 3 Trial EMERALD-1

- A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study



N = 600

www.Clinicaltrials.gov, NCT03778957.

Immunotherapy for HCC

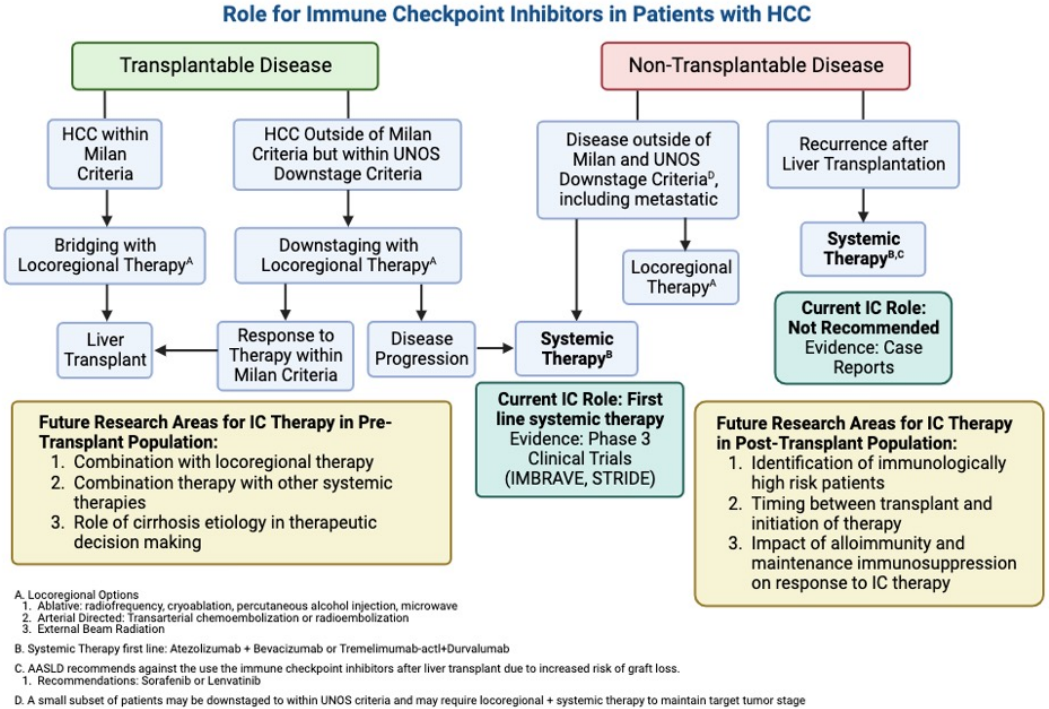


Figure 3: Overview of clinical use of immune checkpoints in patients with HCC.
HCC: Hepatocellular Carcinoma, IC: Immune Checkpoint Therapy, UNOS: United Network for Organ Sharing

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Targeted Therapy for HCC

- From 2008-2017, multiple agents failed to show superiority over sorafenib in randomized trials in 1st line advanced, unresectable HCC
  - Brivanib
  - Sunitinib
  - Linifanib
  - Sorafenib+erlotinib; Sorafenib+doxorubicin
  - Bevacizumab+erlotinib

- Multiple negative studies in 2nd line after sorafenib
  - Everolimus, ramucirumab, brivanib, tivantinib, others

TABLE 7 Summary efficacy data for selected first line phase III randomized controlled trials compared with sorafenib

Aspect	IMbrave150[312]		HIMALAYA[323]			REFLECT[313]	
Study drugs	Atezolizumab + bevacizumab	Sorafenib	Durvalumab + tremelimumab	Durvalumab	Sorafenib	Lenvatinib	Sorafenib
Median OS, months (95% CI)	19.2 (17.0–23.7)	13.4 (11.4–16.9)	16.4 (14.2–19.6)	16.6 (14.1–19.1)	13.8 (12.3–16.1)	13.6 (12.1–14.9)	12.3 (10.4–13.9)
HR for death (95% CI)	0.66 (0.52–0.85)		Durvalumab + tremelimumab vs. sorafenib: 0.78 (0.65–0.92) Durvalumab vs. sorafenib: 0.86 (0.73–1.03)			0.92 (0.79–1.06)	
Median PFS, months (95% CI)	6.8 (5.7–8.3)	4.3 (4.0–5.6)	3.8 (3.7–5.3)	3.7 (3.2–3.8)	4.1 (3.8–5.5)	7.3 (5.6–7.5)	3.6 (3.6–3.9)
ORR by RECIST 1.1	29.8	11.3	20.1	17.0	5.1	18.8	6.5
Common AEs[a]	Hypertension (30%), fatigue (20%), proteinuria (20%), AST increase (20%), pruritis (20%), diarrhea (19%)	Diarrhea (49%), PPE (48%), hypertension (24%), decreased appetite (24%), fatigue (19%), AST increase (17%)	Diarrhea (27%), pruritis (23%), rash (22%), decreased appetite (17%), fatigue (17%)	Diarrhea (15%), pruritis (14%), constipation (11%), AST increased (14%), decreased appetite (14%)	PPE (47%), diarrhea (45%), fatigue (19%), hypertension (18%), decreased appetite (18%)	Hypertension (42%), diarrhea (39%), decreased appetite (34%), decreased weight (31%), fatigue (30%), PPE (27%), proteinuria (25%), hypothyroidism (16%)	PPE (52%), diarrhea (46%), hypertension (30%), decreased appetite (27%), fatigue (25%), decreased weight (22%)

Abbreviations: AE, adverse event; AST, aspartate aminotransferase; CI, confidence interval; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PPE, palmar plantar erythrodysesthesia.

[a]AEs and frequencies for HIMALAYA and REFLECT are treatment-emergent AEs.

TABLE 8 Summary efficacy data for selected second line studies after prior sorafenib therapy

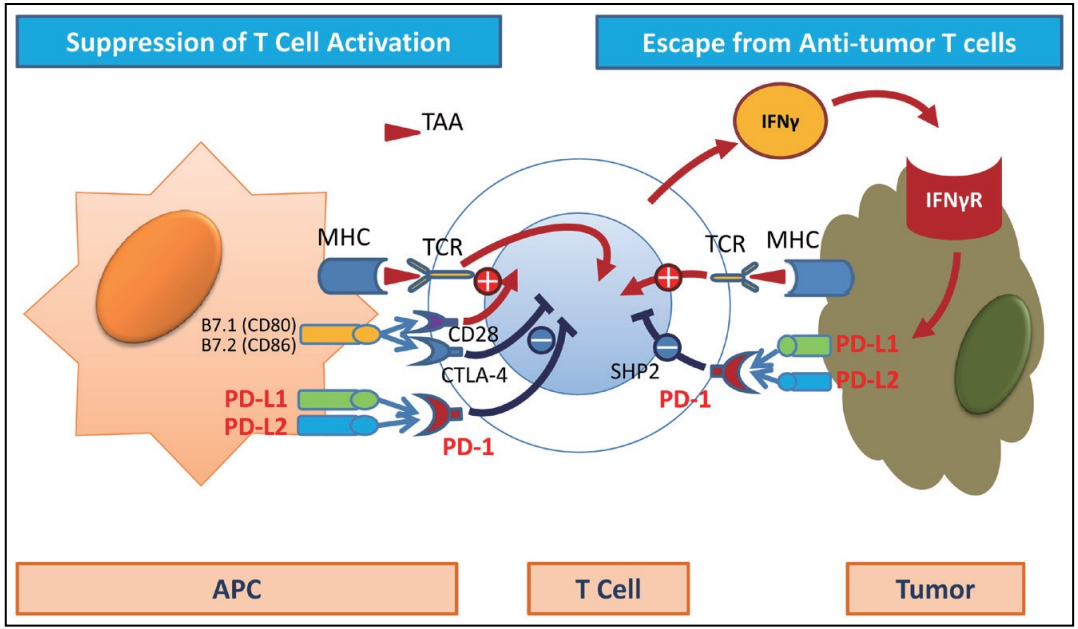
Aspect	CELESTIAL[314]	RESORCE[315]	REACH-2[127]	KEYNOTE-240[316]	KEYNOTE-394[317]	CheckMate 040[318]
Study design	Phase III: cabozantinib vs. placebo	Phase III: regorafenib vs. placebo	Phase III: ramucirumab vs. placebo	Phase III: pembrolizumab vs. placebo	Phase III: pembrolizumab vs. placebo	Phase II: ipilimumab + nivolumab
Population	Prior sorafenib, second or third line	Tolerated and progressed on sorafenib, second line	Prior sorafenib, second line, AFP > 400 only	Prior sorafenib, second line	Prior sorafenib, second line, Asia only	Prior sorafenib, multiple prior lines allowed
Median OS	10.2 vs. 8.0 m	10.6 vs. 7.8 m	8.5 vs. 7.3 m	13.9 vs. 10.6 m	14.6 vs. 13.0 m	22.8 m
OS HR	0.76 (0.63 to 0.92)	0.63 (0.50 to 0.79)	0.71 (0.53 to 0.95)	0.78 (0.61 to 0.998)	0.79 (0.63 to 0.99)	N/A
PFS	5.2 vs. 1.9 m	3.1 vs. 1.5 m	2.8 vs. 1.6 m	3.0 vs. 2.8 m	2.6 vs. 2.3 m	Not reported
ORR	4% vs. 1%	10% vs. 4%	5% vs. 1%	18.3% vs. 4.4%	12.7% vs. 1.3%	32%
Common AEs[a]	Diarrhea (54%), decreased appetite (48%), PPE (46%), fatigue (45%), nausea (31%), hypertension (29%), vomiting (26%)	PPE (53%), diarrhea (41%), fatigue (40%), hypertension (31%), anorexia (31%), increased blood bilirubin (29%), abdominal pain (28%), increased AST (25%)	Fatigue (24%), peripheral edema (24%), decreased appetite (22%), liver injury or failure (21%), nausea (19%), bleeding (19%), proteinuria (18%), hypertension (12%)	AST increased (23%), blood bilirubin increased (19%), fatigue (19%), pruritis (18%), ALT increased (18%), decreased appetite (17%), diarrhea (17%)	Immune-related AEs (18.1%), severe grade 3–5 immune-related AEs (3%)	Pruritis (45%), rash (29%), diarrhea (24%), AST increased (20%), hypothyroidism (20%), fatigue (18%), ALT increase (16%), lipase increased (14%), adrenal insufficiency (14%), rash maculopapular (14%)

Abbreviations: AE, adverse event; AFP, alpha fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PPE, palmar plantar erythrodysesthesia.

[a]AEs and frequencies for RESORCE, REACH2 are treatment-emergent AEs; AEs and frequencies for CHECKMATE 040 are treatment-related AEs.

Immune Checkpoint Blockade in HCC

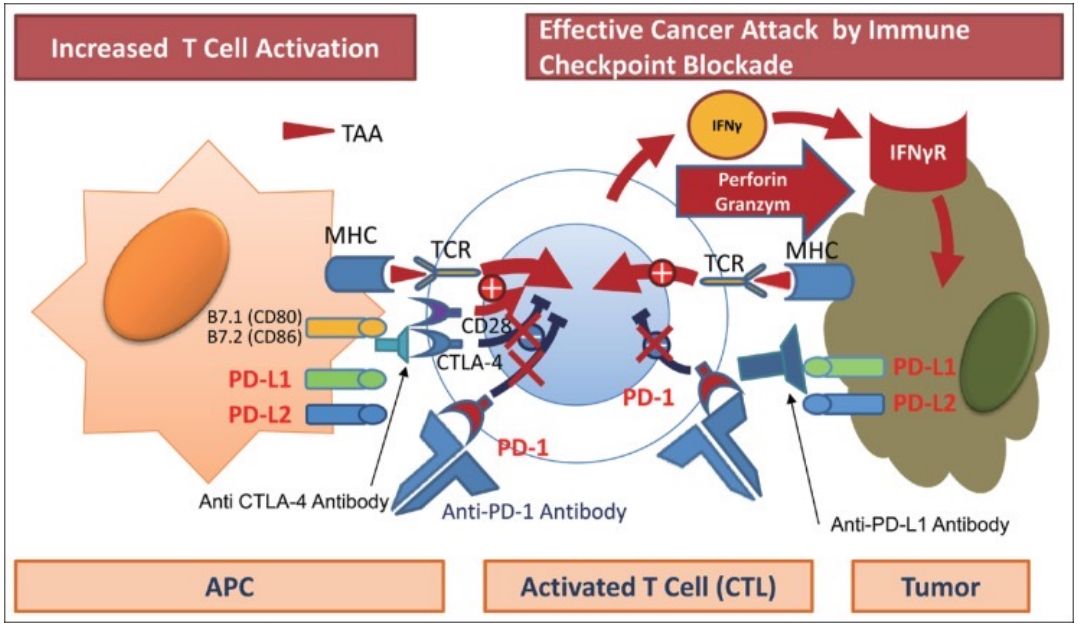
- “Immune escape” of tumor cells from activated CD8(+) T-cells Expression of PD-L1/PD-L2 that binds to PD-1



Kudo M. *Liver Cancer*. 2015;6:1-12.

Immune Checkpoint Blockade in HCC

- Immune checkpoint blockade: anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies restore cytotoxic T-cell activity



Kudo M. *Liver Cancer*. 2015;6:1-12.

Immunotherapy (n=30)

- Types: Nivolumab (80%)
  Pembrolizumab (10%)
  Atezo/Bev (10%)

- ICI cycles: 7.5 (IQR 4-13.5)

- 13 (43.3%) receiving their last ICI dose < 30 days pre-LT

- No grade 3-5 adverse events were reported on the wait list

Overall Survival (ITT and Post LT)