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Management of Patients With Hepatocellular Carcinoma: 2022 Update

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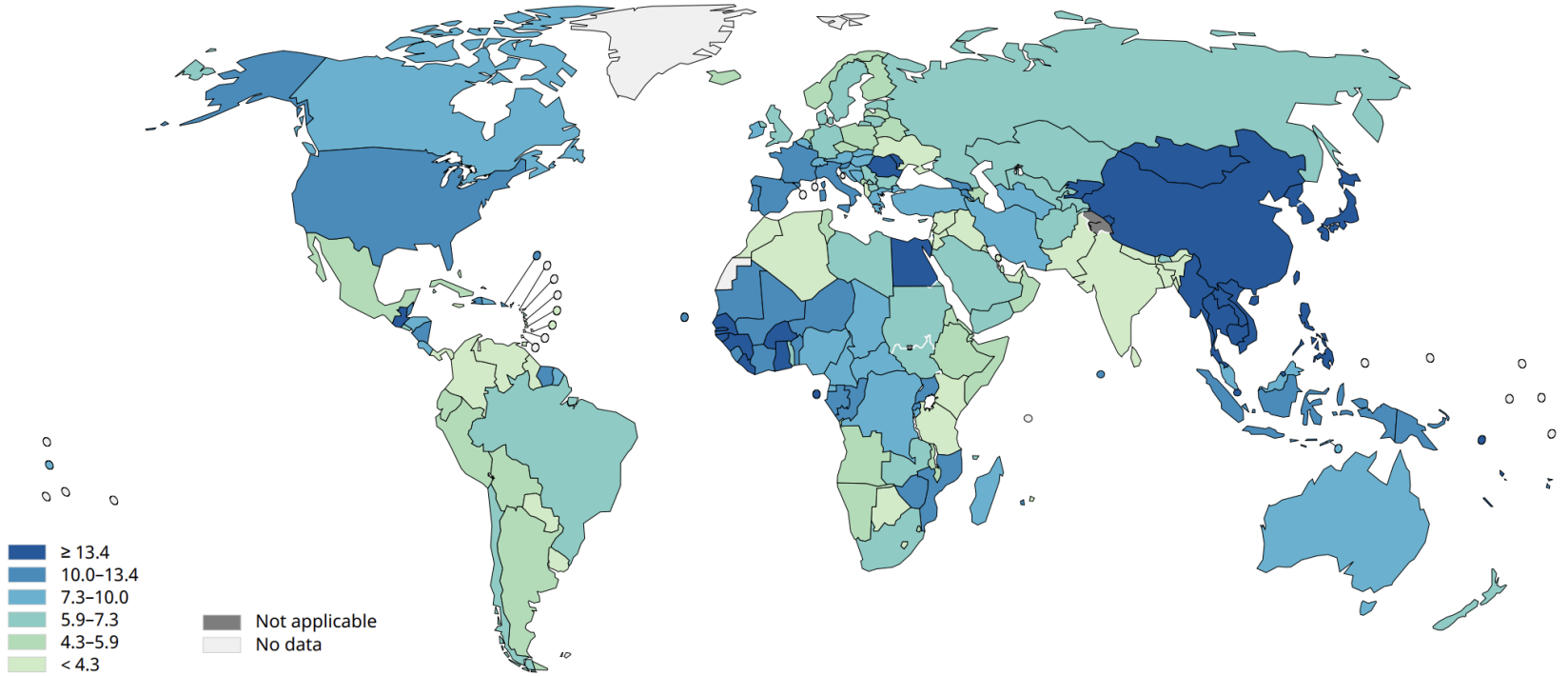
Disclosures

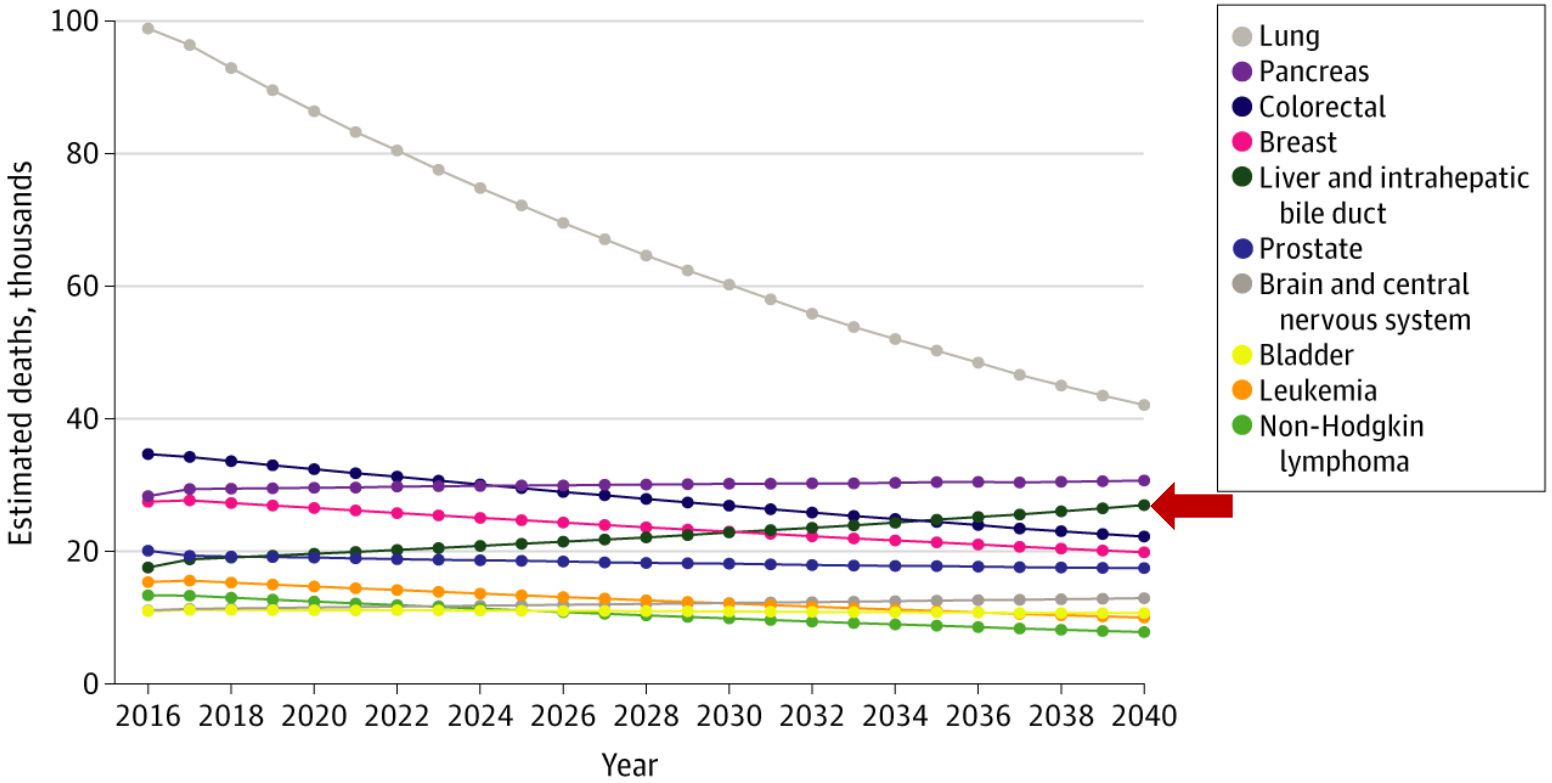
- I have served as a consultant or served on advisory boards for Genentech, AstraZeneca, Bayer, Eisai, Bristol Meyer Squibb, Exelixis, FujiFilm Medical Sciences, Glycotest, Exact Sciences, Roche, and GRAIL

Hepatocellular Carcinoma Is 3rd Leading Cause of Cancer-Related Death Worldwide



GLOBOCAN 2020.

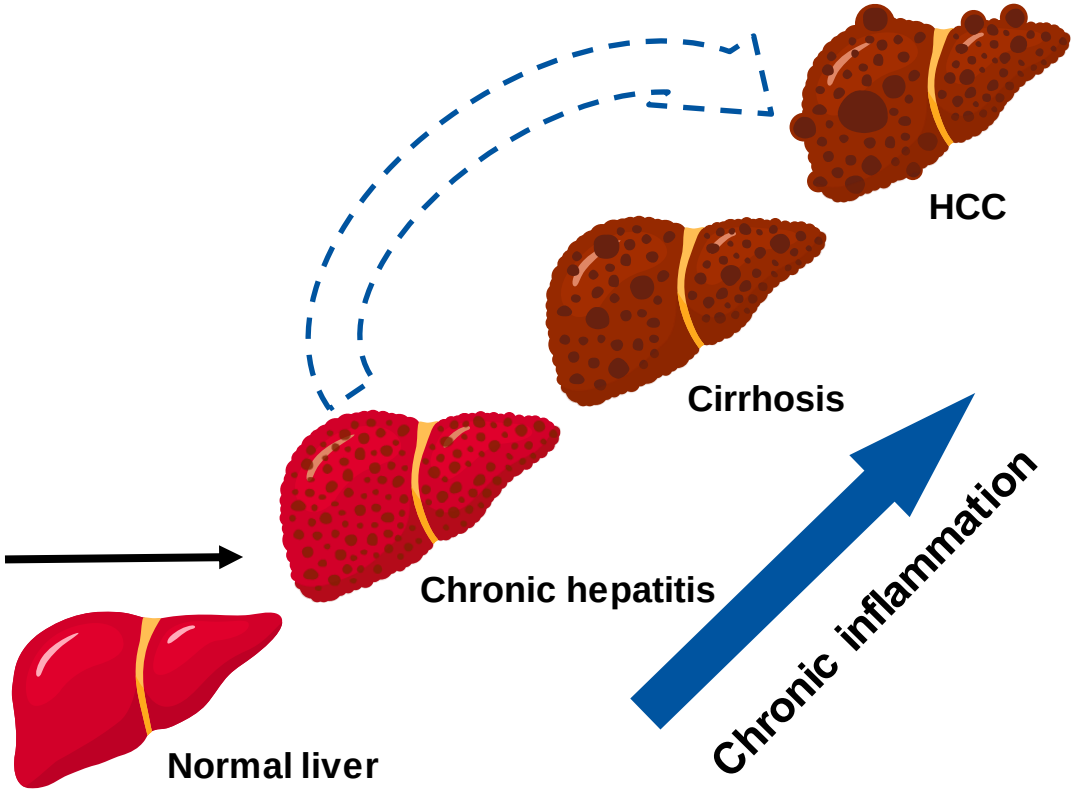
HCC Projected to Be 3rd Leading Cause of Death in US by 2035



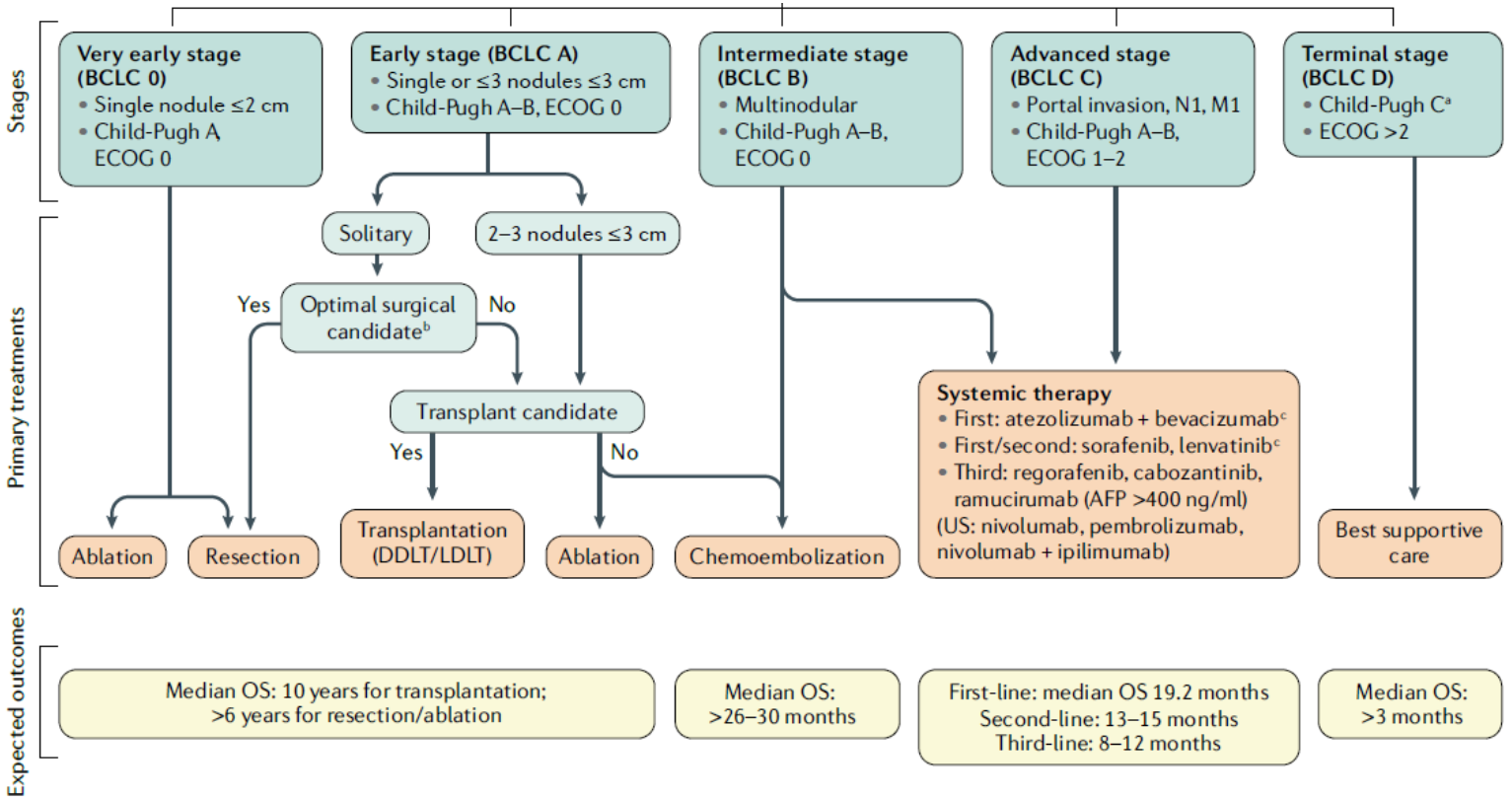
Rahib et al. *JAMA Network Open*. 2021

Most HCC Occur in the Setting of Chronic Liver Disease, if Not Cirrhosis

Hepatitis B viral infection
Hepatitis C viral infection
Alcohol-associated liver disease
Nonalcoholic steatohepatitis

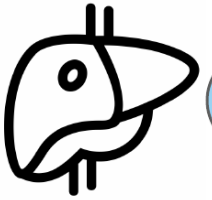


Prognosis Strongly Associated With Tumor Stage at Diagnosis



HCC Surveillance Associated With Improved Survival in Cirrhosis

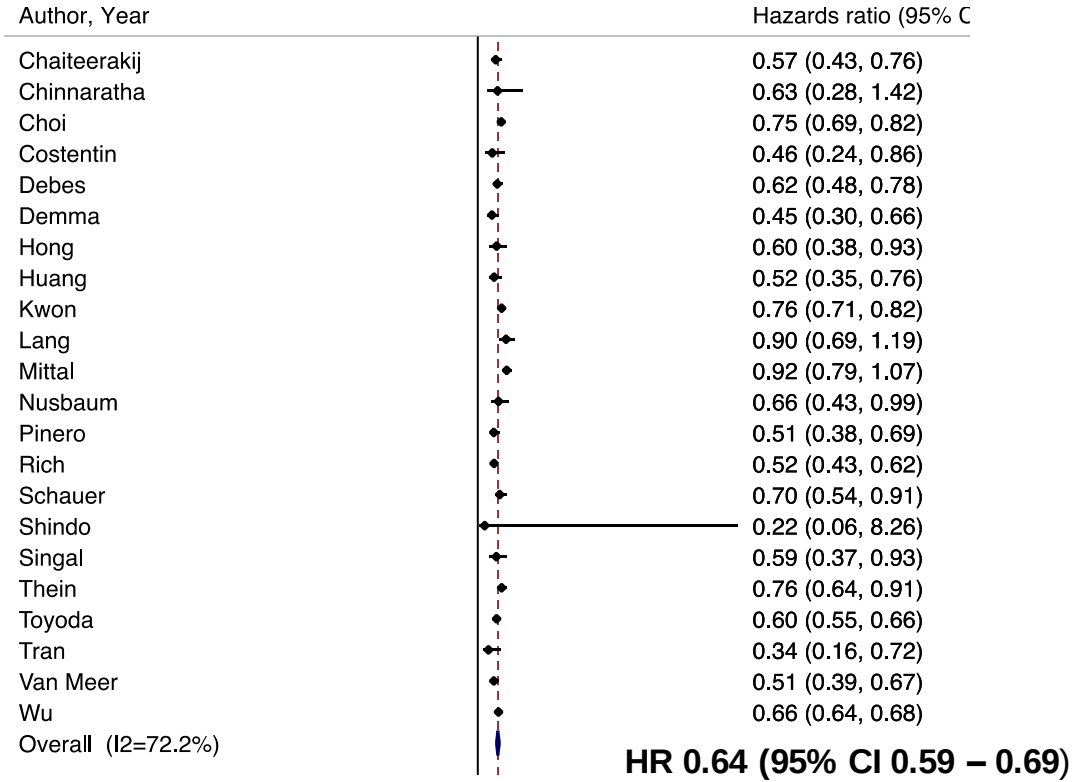
HCC Surveillance associated with:



Early stage detection:
OR 1.86, 95%CI 1.73 – 1.98

Receipt of curative therapy:
OR 1.83, 95%CI 1.69 – 1.97

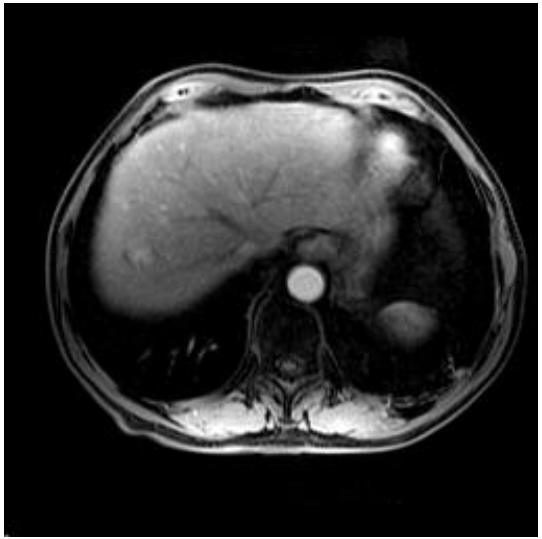
Overall survival:
HR 0.64, 95%CI 0.59 – 0.69



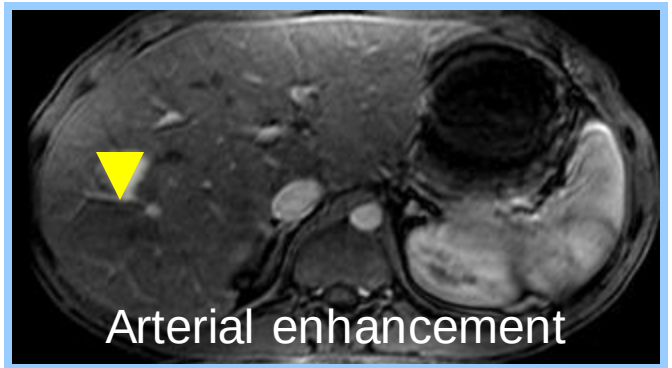
Singal et al. *J Hepatology*. 2022.

Patient Case 1

- Mr. Jones is a 54-year-old male who initially presented for HCV treatment
- During evaluation, diagnosed with early-stage (BCLC A) HCC
  - Unifocal with max diameter 3.4 cm (LR-5 on imaging)
- He has compensated cirrhosis without portal HTN.
  - Child Pugh A: Bilirubin 0.7, Albumin 4.0, INR 1.0
  - Platelet count 172
  - AFP 42
  - Good performance status, ECOG 0
- What is the best treatment option?

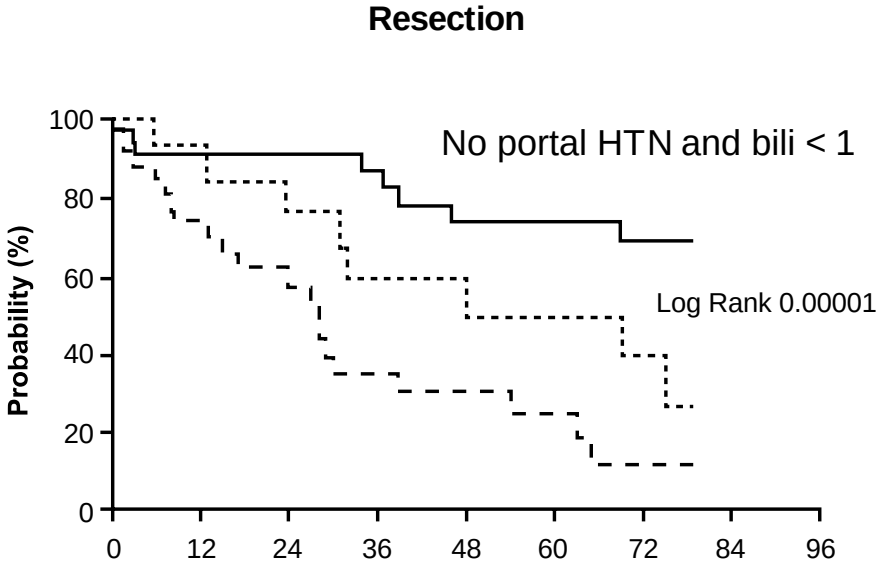


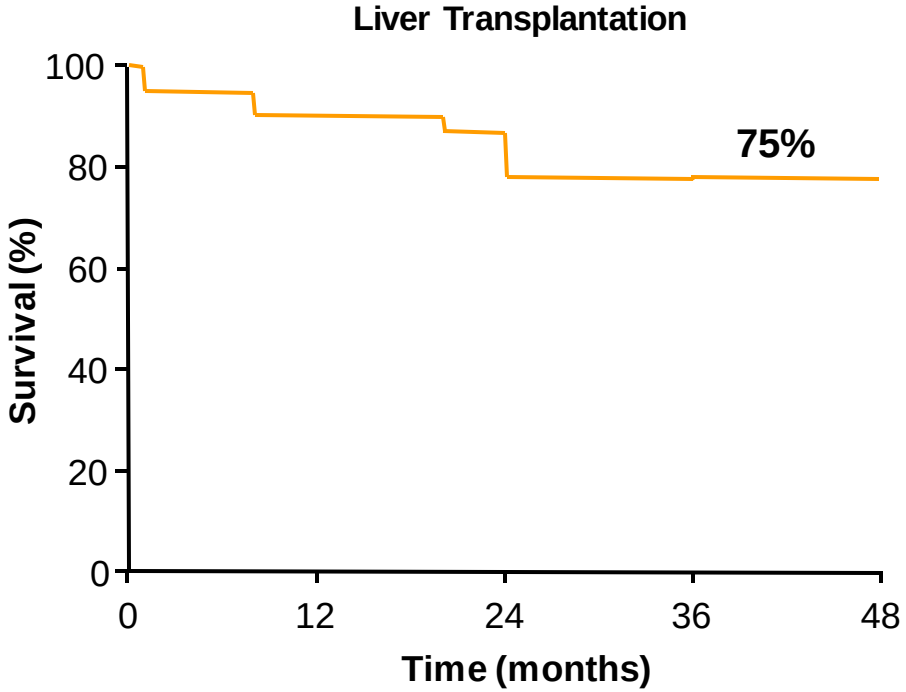
HCC Can Be Diagnosed Radiographically With Need for Biopsy



LI-RADS Category	Concept and Definition
LR-1 Definitely Benign	**Concept:** 100% certainty observation is benign. **Definition:** Observation with imaging features diagnostic of a benign entity, or definite disappearance at follow up in absence of treatment.
LR-2 Probably Benign	**Concept:** High probability observation is benign. **Definition:** Observation with imaging features suggestive but not diagnostic of a benign entity.
LR-3 Intermediate probability for HCC	**Concept:** Both HCC and benign entity have moderate probability. **Definition:** Observation that does not meet criteria for other LI-RADS categories.
LR-4 Probably HCC	**Concept:** High probability observation is HCC but there is not 100% certainty. **Definition:** Observation with imaging features suggestive but not diagnostic of HCC.
LR-5 Definitely HCC	**Concept:** 100% certainty observation is HCC. **Definition:** Observation with imaging features diagnostic of HCC or proven to be HCC at histology.
LR-5V Definitely HCC with Tumor in Vein	**Concept:** 100% certainty that observation is HCC invading vein. **Definition:** Observation with imaging features diagnostic of HCC invading vein.
LR-M Probable malignancy, not specific for HCC	**Concept:** High probability that observation is a malignancy, but imaging features are not specific for HCC. **Definition:** Observation with one or more imaging features that favor non-HCC malignancy.
LR-Treated Treated Observation	**Concept:** Loco-regionally treated observation. **Definition:** Observation that has undergone loco-regional treatment

Surgical Therapy Affords Excellent Long-Term Survival for Early-Stage HCC





Llovet et al. *Hepatology*. 1999; Mazzaferro et al. *N Engl J Med*. 1996.

SBRT Has Increasing Data Supporting Role in HCC Treatment

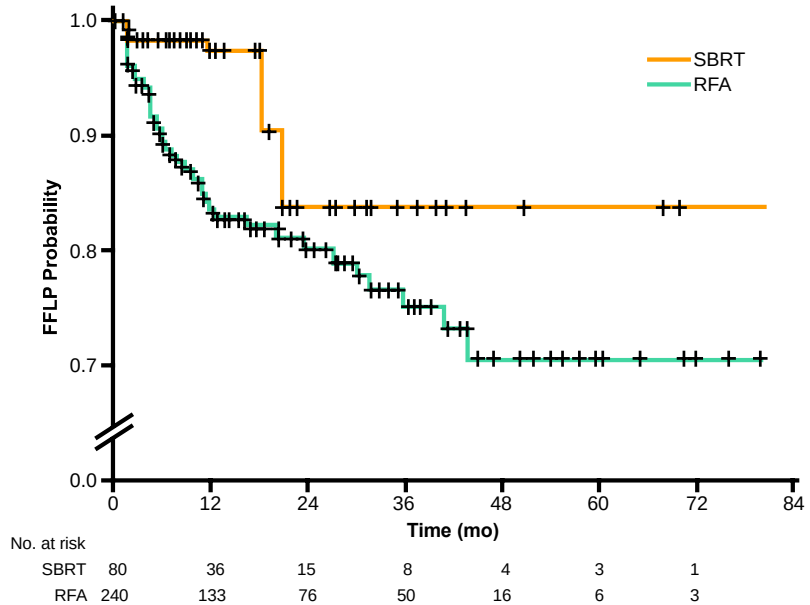


Table 3. Multivariate Cox Proportional Hazards Analysis of Factors Associated With Local Progression

	HR	95% CI	*P*
Treatment RFA v SBRT	3.84	1.62 to 9.09	.002
Age	1.01	0.97 to 1.06	.514
Tumor size	1.35	0.99 to 1.84	0.55
Child-Pugh Score	0.95	0.74 to 1.22	.703
AFP	1.12	0.97 to 1.30	.130
No. prior treatments	1.25	1.00 to 1.56	0.55

SBRT associated with better outcomes than RFA for HCC > 2cm in propensity matched analyses

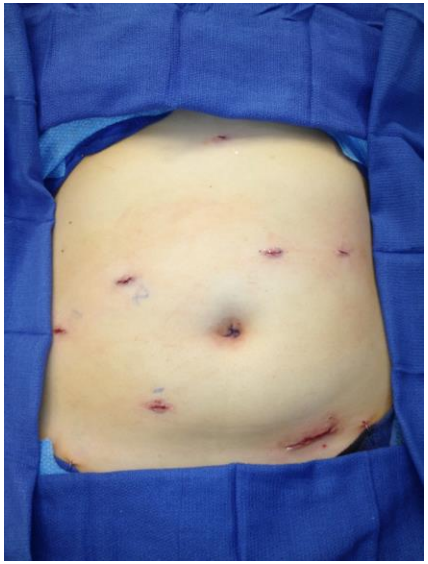
NOTE. Age (per year), tumor size (per cm), Child-Pugh score (per point), AFP (per doubling) and No. prior treatments (per treatment) were treated as continuous variables.

Abbreviations: AFP, alpha-fetoprotein; HR, hazard ration; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy.

Wahl et al. *JCO.* 2016.

Patient Case 1 Follow-Up

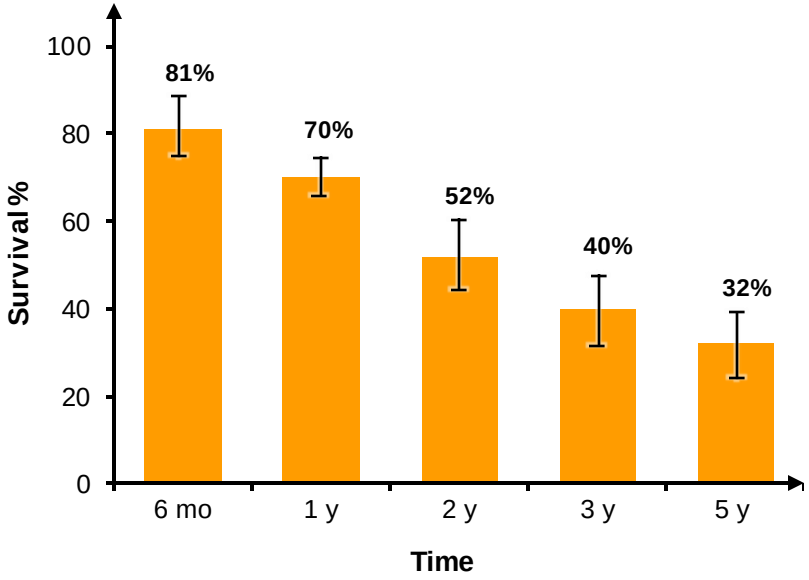
- Mr. Jones is a 54-year-old male with Child A cirrhosis, no significant portal HTN, who was found to have early-stage (BCLC A) HCC, max 3.4 cm
  - Child Pugh A: Bilirubin 0.7, Albumin 4.0, INR 1.0
  - Platelet count 172
  - AFP 42
- Patient underwent robotic resection without complication
  - Discharged 3 days later
  - Doing well with no recurrence on surveillance imaging



Patient Case 2

- Ms. Smith is a 52-year-old female with history of NASH cirrhosis who was incidentally found to have a liver lesion
- MRI shows intermediate stage (BCLC stage B) HCC, 2 lesions (LR-5) – 4.9 cm and 2.0 cm in maximum diameter, both in right lobe
  - Child Pugh B: Bilirubin 1.1, Albumin 3.4, INR 1.1, well controlled ascites
  - Platelet count 59
  - AFP 79
  - Good performance status, ECOG 0
- What is the best treatment option?

TACE Provides High Response Rate and Improves Survival

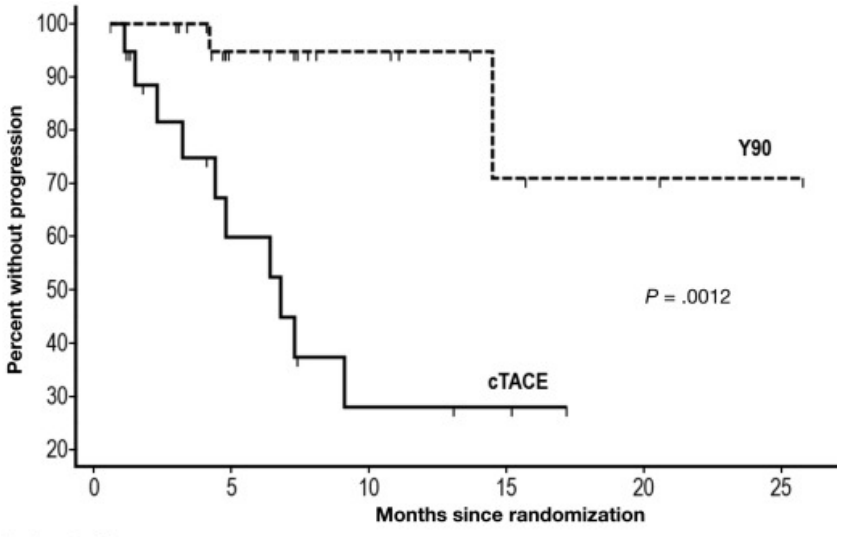


Pooled ORR was 52% and median survival ~19 months

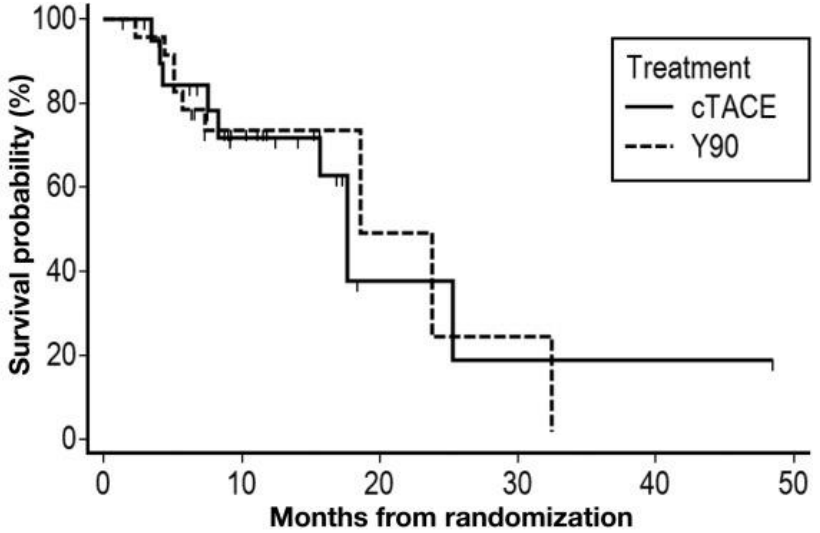
	No. of Studies	Estimate	Lower 95% CI	Upper 95% CI
Median, mo				
≤2002	19	18.5	14.6	22.4
>2002	44	19.8	15.5	24.1
1-year, %				
≤2002	19	70.7	63.2	78.3
>2002	71	70.4	65.2	75.5
2-year, %				
≤2002	21	51.1	37.1	65.1
>2002	50	52.0	43.9	60.2
3-year, %				
≤2002	13	27.8	18.3	37.4
>2002	53	43.4	34.9	51.8

Lencioni et al. *Hepatology.* 2016.

TARE Likely Has Role in Treatment of BCLC Stage B HCC



TTP: >26 vs.6.8 months
(HR 0.12, 95%CI 0.03-0.56)



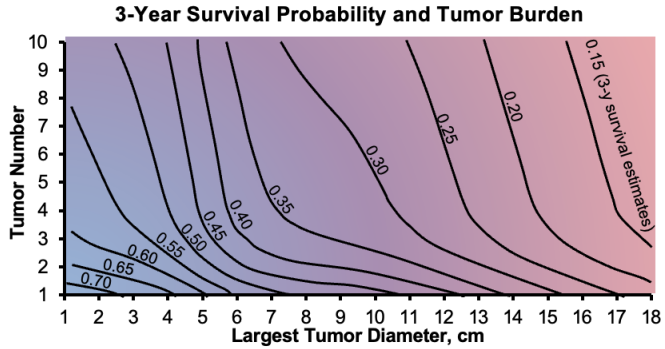
Median survival: 17.7 vs. 18.6 mo
(p=0.99)

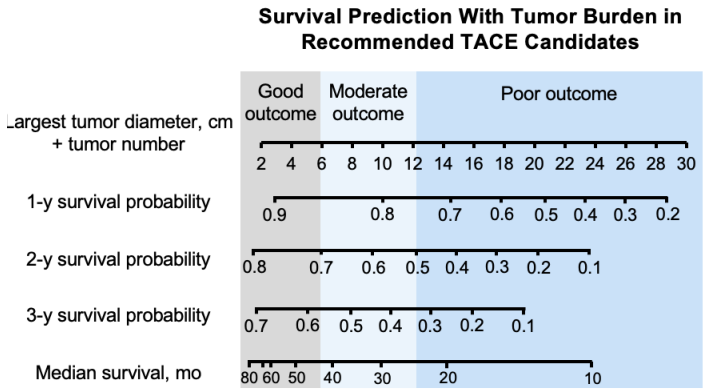
Salem et al. *Gastro.* 2016.

BCLC Stage B Has Heterogeneous Prognosis

- Prognostic model specifically developed for ideal TACE candidates (N = 1,604; treatment naïve)
  - Child-Pugh A-B7
  - PS 0
  - No VI/mets
  - No history of tumor rupture
  - No GIB, ascites, HE, or jaundice
- BCLC B: 74%
- "Linear predictor = largest tumor diameter (cm) + tumor number"

Median OS, mo	32.9 (95% CI, 30.4–35.4)
≤6	49.1 (95% CI, 43.7–59.4)
> but ≥12	32.0 (95% CI, 29.0–37.5)
>12	15.8 (95% CI, 14.1–17.7)



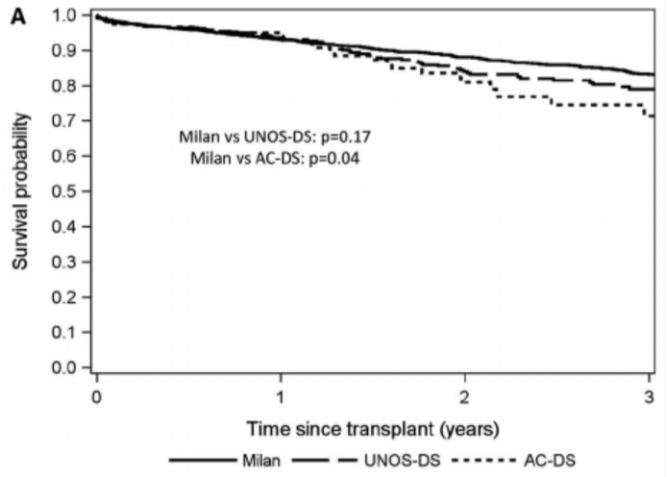


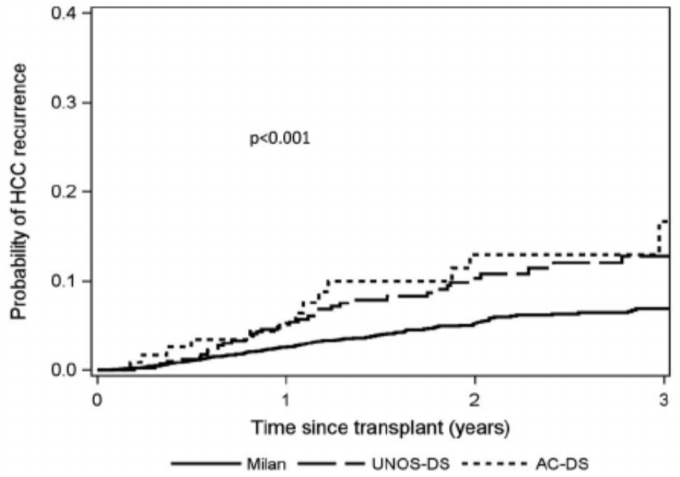
Wang et al. *J Hepatology.* 2019.

Patients Within UNOS-DS Criteria Can Achieve Good Survival

Multicenter study of patients undergoing LT from 2012-2015
comparing downstaged patients (n=422) vs. within Milan (n=3276) vs. beyond Milan (n=121)

UNOS-DS: One HCC >5 and ≤8 cm, two to three HCC >3 cm and ≤5 cm and diameter ≤8 cm,
or four to five lesions each ≤3 cm and diameter ≤8 cm





Mehta et al. *Hepatology*. 2020.

Asia-Pacific Expert Consensus Statement for TACE Unsuitability

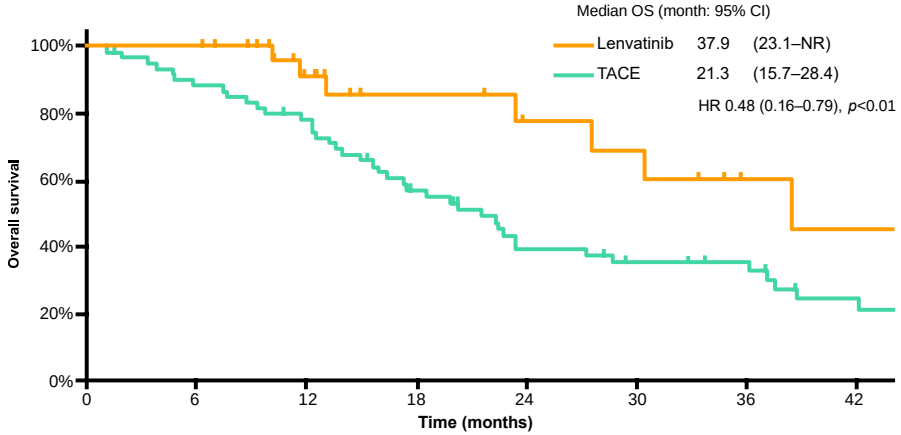
A. Conditions that easily become refractory to TACE:
   - Beyond up-to-seven criteria

B. Conditions in which TACE causes deterioration of liver function to Child-Pugh class B:
   - Beyond up-to-seven criteria
   - ALBI grade 2

C. Conditions that are unlikely to respond to TACE (TACE-resistant tumor):
   - Simple nodular type tumor with extranodular growth
   - Confluent multinodular type tumor
   - Massive type tumor
   - Poorly differentiated HCC
   - Intrahepatic multifocal metastasis
   - Sarcomatous change caused by TACE

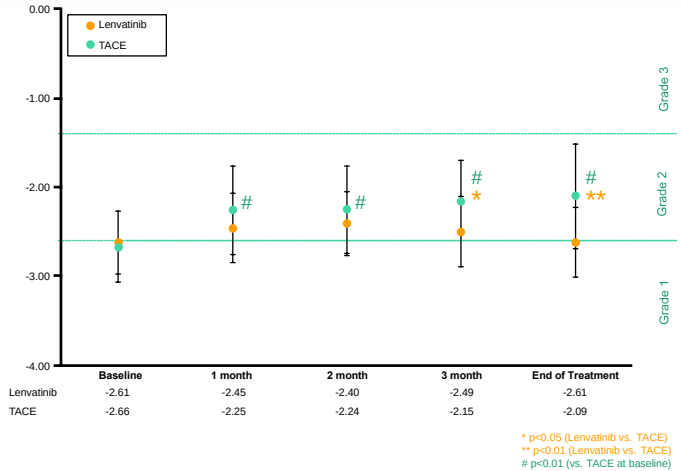
Kudo et al. *Liver Cancer.* 2020.

Systemic Therapy May Be Preferred in Patients With Large or Multinodular BCLC B HCC



Number at risk

Lenvatinib	30	30	19	12	9	8	4	3
TACE	60	52	44	31	20	16	13	7



ABC-HCC Trial: Randomized, multi-center open-label, phase 3 study

- Multifocal HCC beyond Milan
- No massive multinodular pattern precluding TACE (e.g., infiltrative HCC)
- No portal vein thrombosis or metastases
- ≥1 measurable target lesion per mRECIST
- Child-Pugh A
- ECOG PS 0
- EGD within 6 months and varices treated per local standard of care
- Adequate organ function

N = 434

R

Atezolizumab and bevacizumab q3 weeks (n = 217)

cTACE or DEB-TACE (n = 217)

Kudo et al. *Cancers.* 2019.

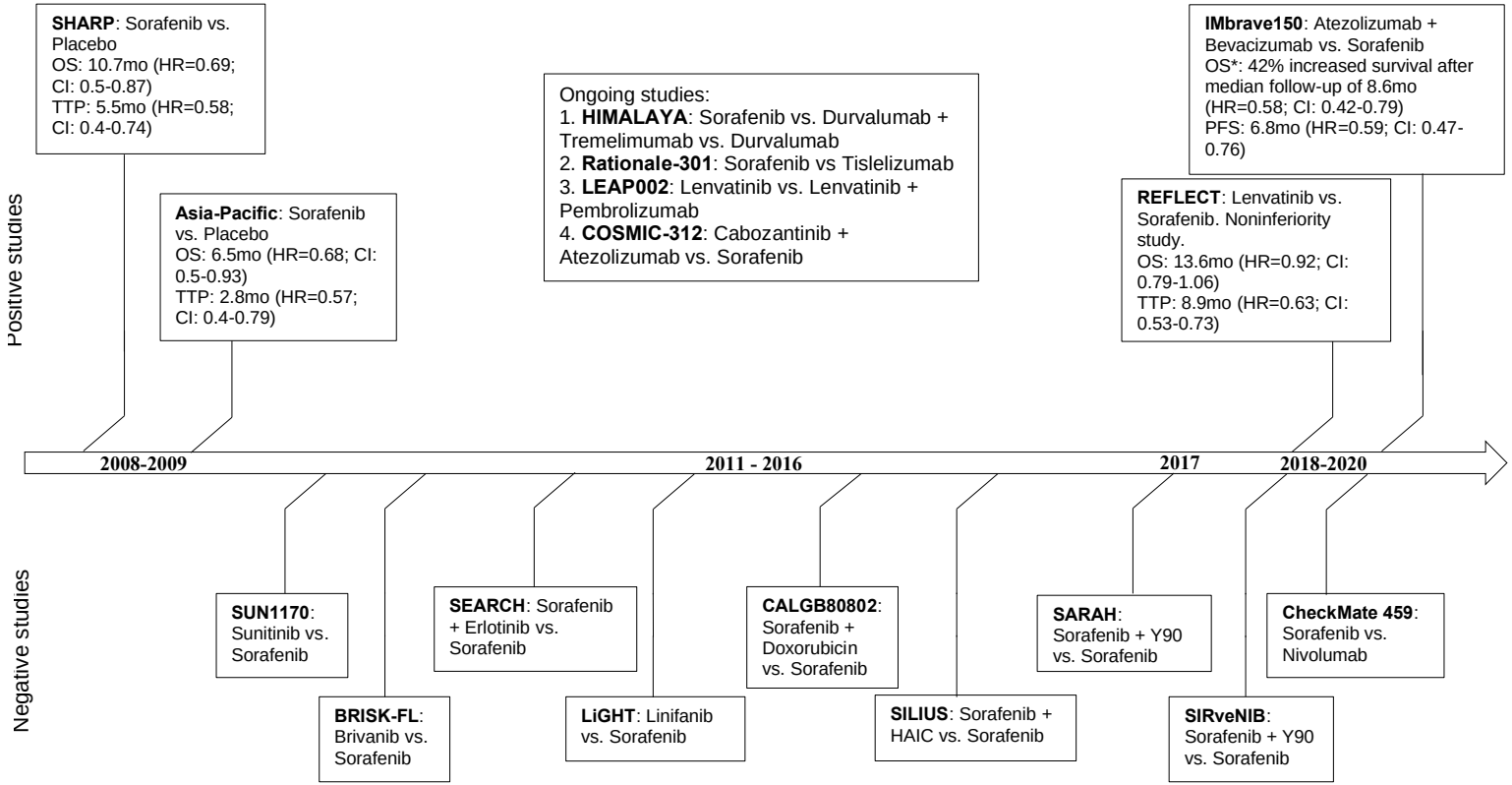
Patient Case 2 Follow-Up

- Ms. Smith is 52-year-old female with Child B NASH cirrhosis who had BCLC stage B HCC – 4.9 cm and 2.0 cm in max diameter
  - Child Pugh B: Bilirubin 1.1, Albumin 3.4, INR 1.1, well controlled ascites
  - Platelet count 59 and AFP 79
- Ms. Smith undergoes radioembolization without complication
- Imaging 3 months after treatment demonstrates partial response with tumor burden now within Milan Criteria
  - 4.9 cm HCC → 2 cm viable disease and 2 cm HCC → complete response
- She is listed for liver transplantation and underwent transplant without complication after stable disease * 6 months

Patient Case 3

- Mr. Brown is a 63-year-old male with compensated EtOH cirrhosis who presented with abdominal pain
- Large liver mass found on CT performed in ED
- MRI shows advanced (BCLC stage C) HCC with main portal vein invasion and adrenal metastasis
- Compensated cirrhosis and good performance status
  - Child Pugh A: Bilirubin 1.2, Albumin 3.2, INR 1.1
  - AFP 1729
- What is the best treatment option?

Notable advances in treatment options for advanced stage HCC

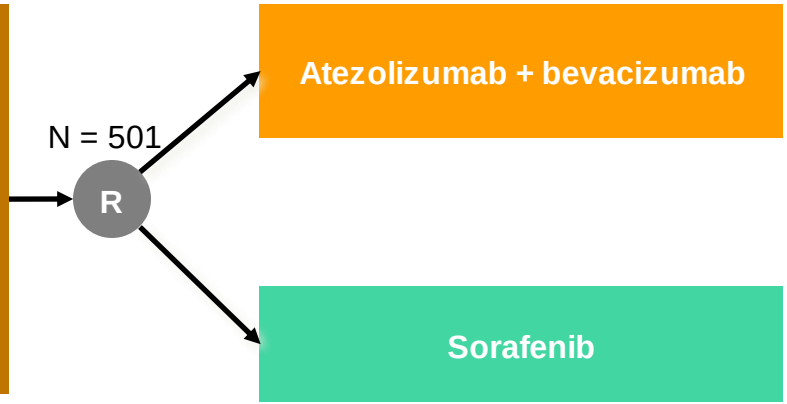


Ferrante et al. *Gastro Hep*. 2020.

IMBrave150: Atezolizumab/ Bevacizumab vs. Sorafenib

Key eligibility criteria

- Locally advanced or metastatic and/or unresectable HCC
- No prior systemic therapy for HCC
- ≥1 measurable untreated lesion
- ECOG PS 0 or 1
- Adequate hematologic and end-organ function
- Child–Pugh class A



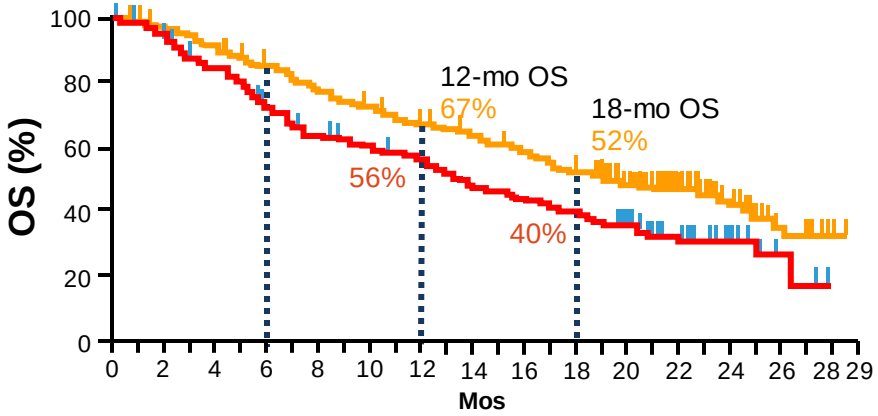
- **Primary endpoints:** PFS and OS

All patients were required to have recent EGD to risk stratify risk of bleeding

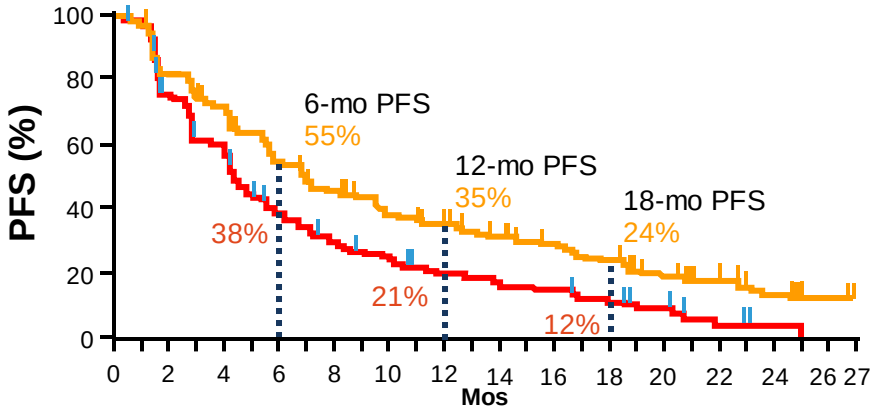
Finn et al. *New Eng J Med*. 2020.

Atezolizumab and Bevacizumab Improves Survival for Patients With Advanced-Stage HCC

	Atezo + Bev (n = 336)	Sorafenib (n = 165)
Median OS, mos	**19.2**	**13.4**
Stratified HR (95% CI)	0.66 (0.52-0.85)	

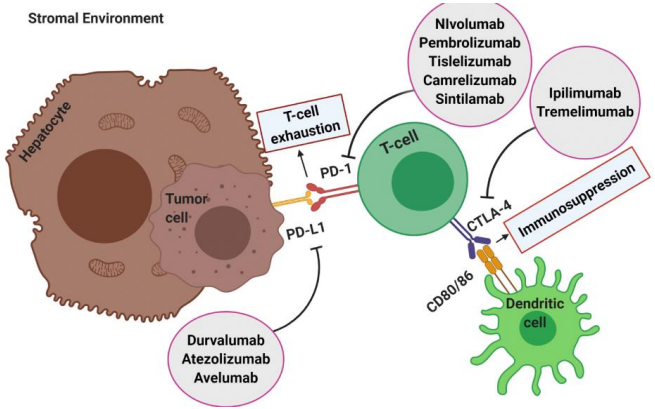


	Atezo + Bev (n = 336)	Sorafenib (n = 165)
Median PFS, mos	**6.9**	**4.3**
Stratified HR (95% CI)	0.65 (0.53-0.81)	

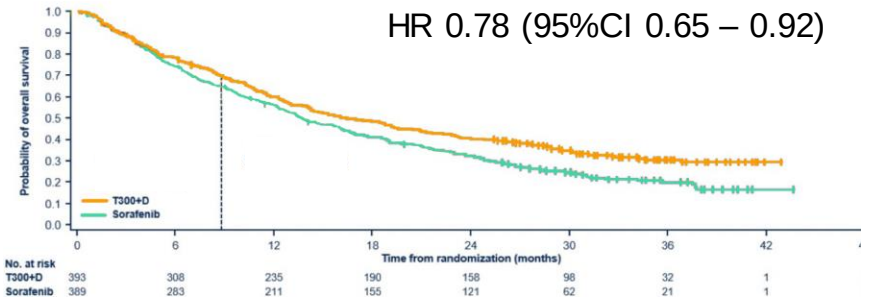


Finn et al. *New Eng J Med*. 2020.

Durvalumab + Tremelimumab Improves Survival in Front-Line Setting for Advanced Stage HCC



Median survival 16.4 vs. 13.8 months
HR 0.78 (95%CI 0.65 – 0.92)

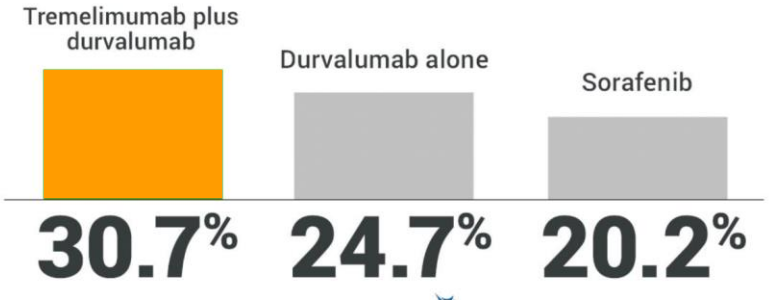


- Unresectable HCC not eligible for LRTs
- BCLC stage B or C
- Child-Pugh A
- No prior systemic therapy

N = ~1,200

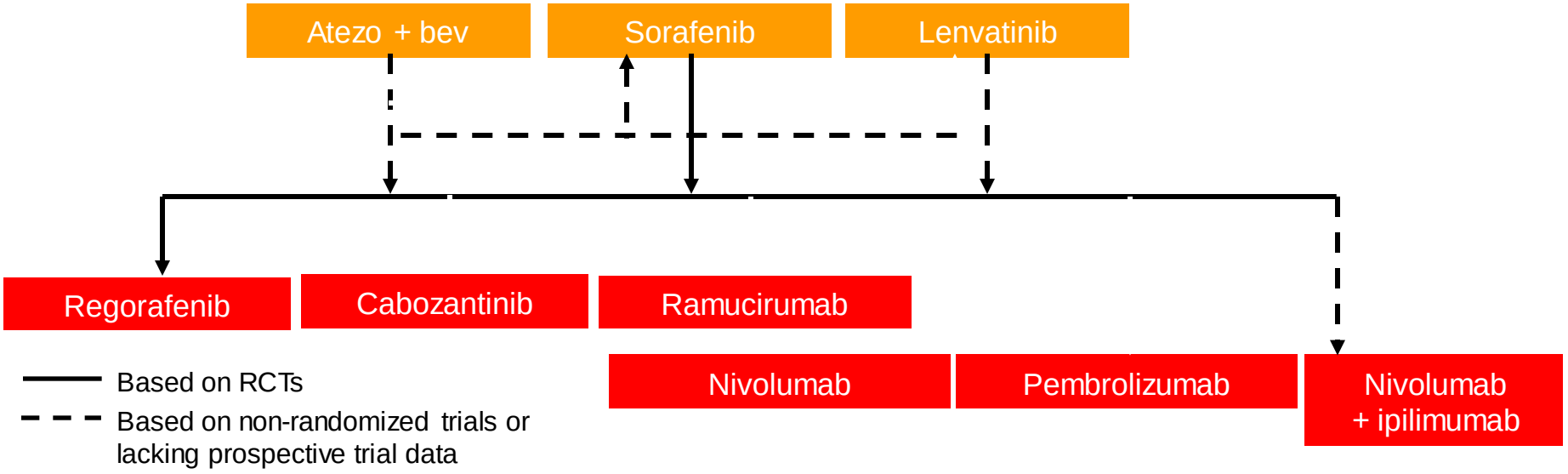
R

- Durvalumab 1,500 mg Q4W
- Durvalumab 1,500 mg Q4W + Tremelimumab 75 mg x 4 dose
- Durvalumab 1,500 mg Q4W + Tremelimumab 300 mg x 4 dose
- Sorafenib



Abou-Alfa et al. *ASCO GI*. 2022.

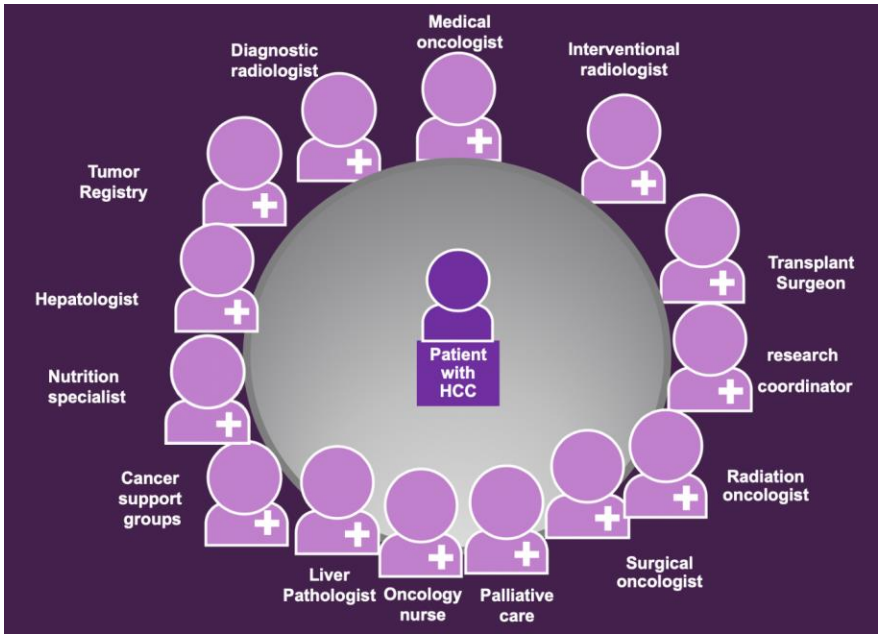
There Are Sequential Systemic Therapy Options Available



Patient Case 3 Follow-Up

- Mr. Brown is a 63-year-old male with compensated EtOH cirrhosis who is found to have advanced stage HCC
  - Child Pugh A: Bilirubin 1.2, Albumin 3.2, INR 1.1
  - AFP 1729
- EGD shows small varices but no other high-risk stigmata
- Started on atezolizumab and bevacizumab, tolerated well with no complication
- Partial response on imaging at 2 months and continues to have stable disease

Multidisciplinary Care Improves HCC Outcomes



Study	Description	Outcomes
Serper 2017 (n=3988)	Multi-specialty evaluation or tumor board	Increase HCC treatment receipt and improve survival
Yopp 2014 (n=355)	Single day MDT clinic and conference	Improve early detection, curative treatment, time to treatment, and survival
Zhang 2013 (n=343)	Single day MDT clinic	Changed imaging/pathology interpretation and therapy plan
Chang 2008 (n=183)	Fluid referrals and joint conference	Improve early detection, curative treatment, and survival

Serper et al. *Gastro.* 2017; Yopp et al. *Ann Surg Onc*. 2014; Chang et al. *HPB.* 2008; Zhang et al. *Curr Oncol.* 2013.

Ongoing Trials of Immunotherapy in Earlier Stages of Disease

Select Phase III Trials of Adjuvant Therapy	
Trial	**Description**
IMbrave050	Adjuvant atezolizumab + bevacizumab
CheckMate 9DX	Adjuvant nivolumab
KEYNOTE-937	Adjuvant pembrolizumab
EMERALD-2	Adjuvant durvalumab ± bevacizumab

Select Phase III Trials with Locoregional Therapy	
Trial	**Description**
EMERALD-1	Durvalumab ± bevacizumab + TACE
CheckMate 74W	Nivolumab ± ipilimumab + TACE
LEAP-012	Lenvatinib + pembrolizumab + TACE
TACE-3	Nivolumab + TACE
EMERALD-1	Durvalumab ± bevacizumab + TACE

Summary

- Best survival observed in patients with early-stage HCC given curative options including surgical resection, liver transplantation, and local ablation
  - Highlights importance of surveillance and early referral
- TACE and TARE are primary therapies for intermediate stage HCC
  - Important to consider downstaging for patients with extended criteria
- There are a growing number of systemic treatment options for advanced HCC
  - 1st line: Atezolizumab/bevacizumab, Durvalumab/tremelimumab, Sorafenib, or Levantinib
  - 2nd line: Regorafenib, Cabozantinib, Ramucirumab, Pembrolizumab, Ipilimumab/Nivolumab
- Multidisciplinary care improves outcomes for patients with HCC, particularly as treatment landscape evolves


UT Southwestern


Liver
Cancer
Awareness
Month
October