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Systemic Therapies for HCC

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Disclosures

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Disclosures

Patrick M. Horne, MSN, APRN, FNP, AF-AASLD

Consultant: AbbVie, Clinical Area – Hepatitis C

Consultant: Fuji-Film Wako, Clinical Area – HCC

Consultant: Gilead, Clinical Area – Hepatitis B, Hepatitis C, NASH

Consultant: Intercept, Clinical Area – PBC, NASH

Consultant: Salix, Clinical Area – Hepatic Encephalopathy

Hepatocellular Carcinoma (HCC)

- Common malignancy worldwide
  - 5th most common cancer worldwide
  - 2nd leading cause of cancer death ~600,000 deaths annually
- US incidence has more than tripled over the last three decades
  - Estimated new cases: ~40,000 new cases annually
  - Fastest rising cause of cancer related death in US, Dismal 5-year survival <15%
- 85%-95% of HCC cases occur in cirrhotic livers
  - Leading cause of death in cirrhosis
- Complex malignancy
  - Heterogeneous etiologies - HCV, HBV, NAFLD, Alcohol
  - Complex molecular carcinogenesis

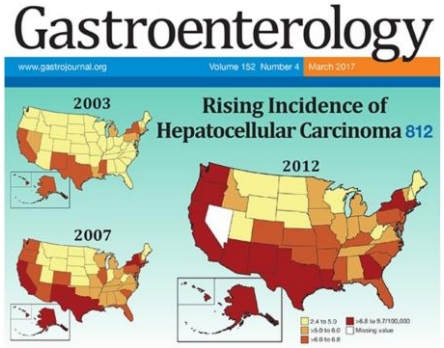
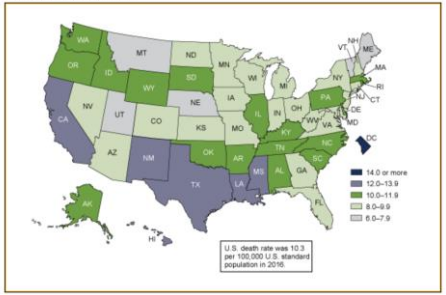
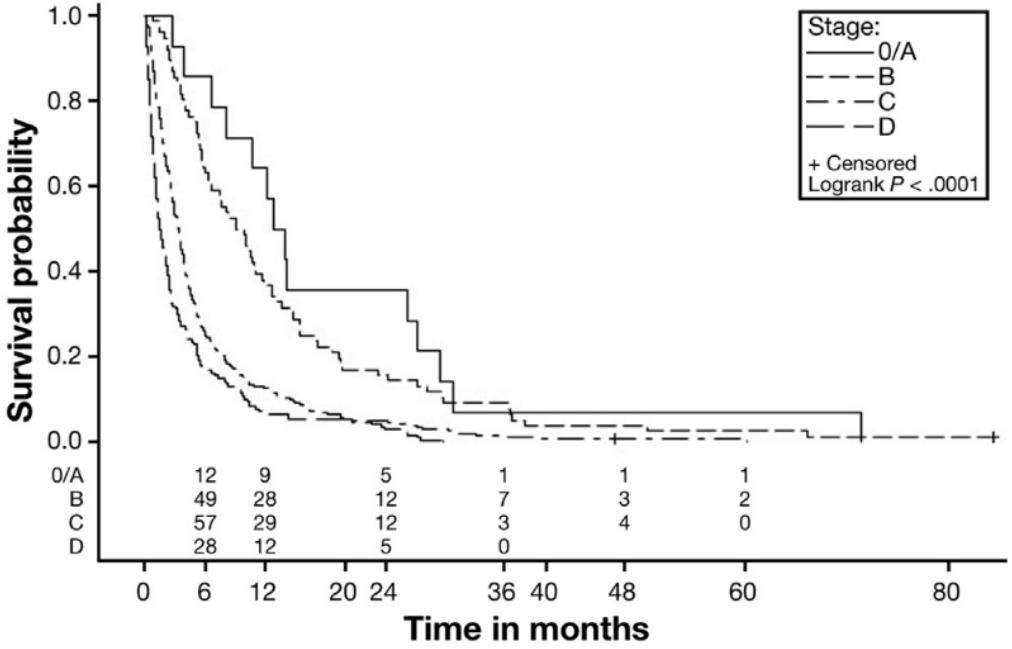


Figure 4. Age-adjusted death rates for liver cancer among adults aged 25 and over, by state: United States, 2016



Mittal S et al. *J Clin Gastroenterol*. 2013;47:S2-S6. Weledji EP et al. Ann Med Surg (Lond). 2014;3:71-76; Ferlay J et al. *Int J Cancer*. 2010;127:2893-2917. Siegel R et al. *CA Cancer J Clin*. 2014;64:9-29; https://www.cdc.gov/nchs/products/databriefs/db314.htm.

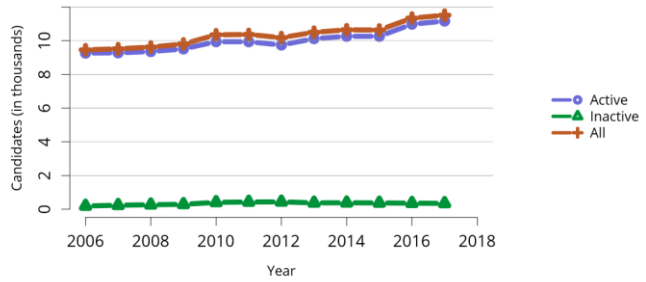
Natural History of Untreated HCC in a US VA Cohort With HCV as the Predominant Etiology – Mortality by BCLC Stage (n=518)



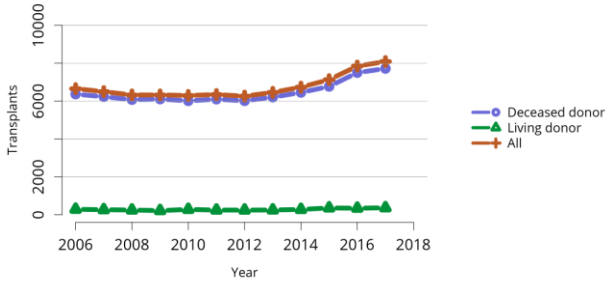
Khalaf N et al. *Clin Gastroenterol Hepatol.* 2016.

UNOS/SRTR 2019 Report – Liver Transplants

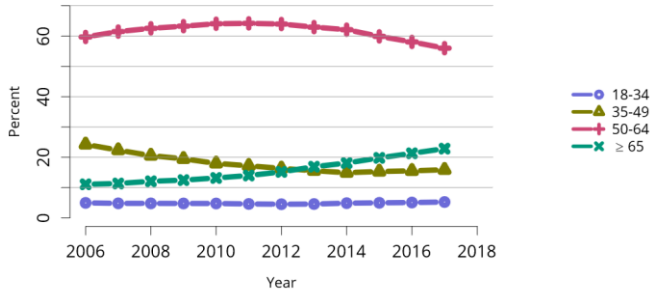
More Candidates



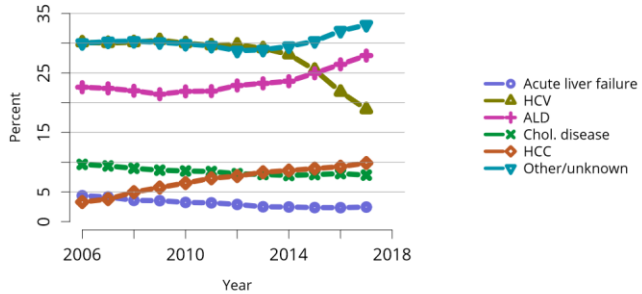
More Liver Transplants



More ≥ 65



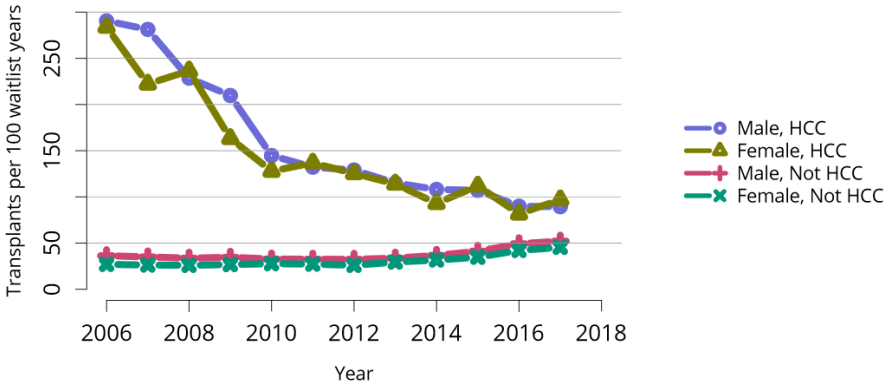
Less HCV



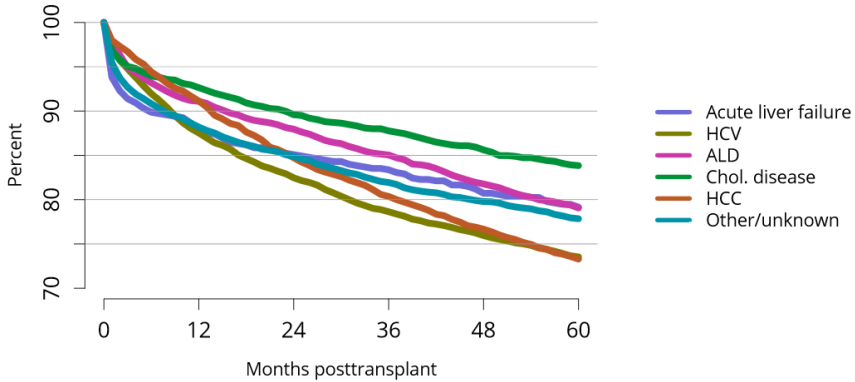
Kim WR et al. *OPTN/SRTR Annual Data Report: Liver*. *Am J Transplantation*. Feb 2019.

UNOS/SRTR 2019 Report – Liver Transplants

Transplant rates among waitlist candidates by sex and HCC status



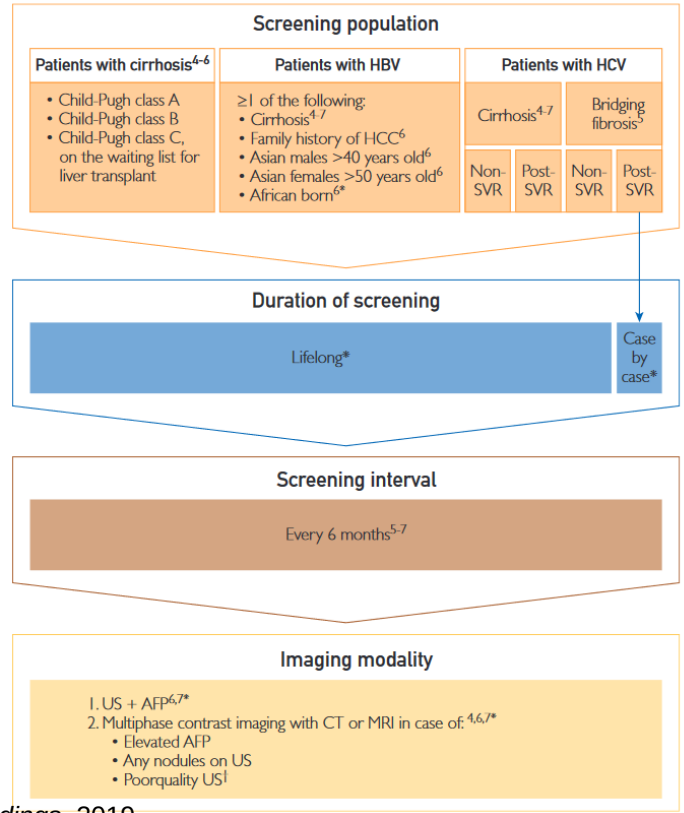
Patient Survival by Diagnosis



Kim WR et al. *OPTN/SRTR Annual Data Report: Liver*. *Am J Transplantation.* Feb 2019.

HCC Screening

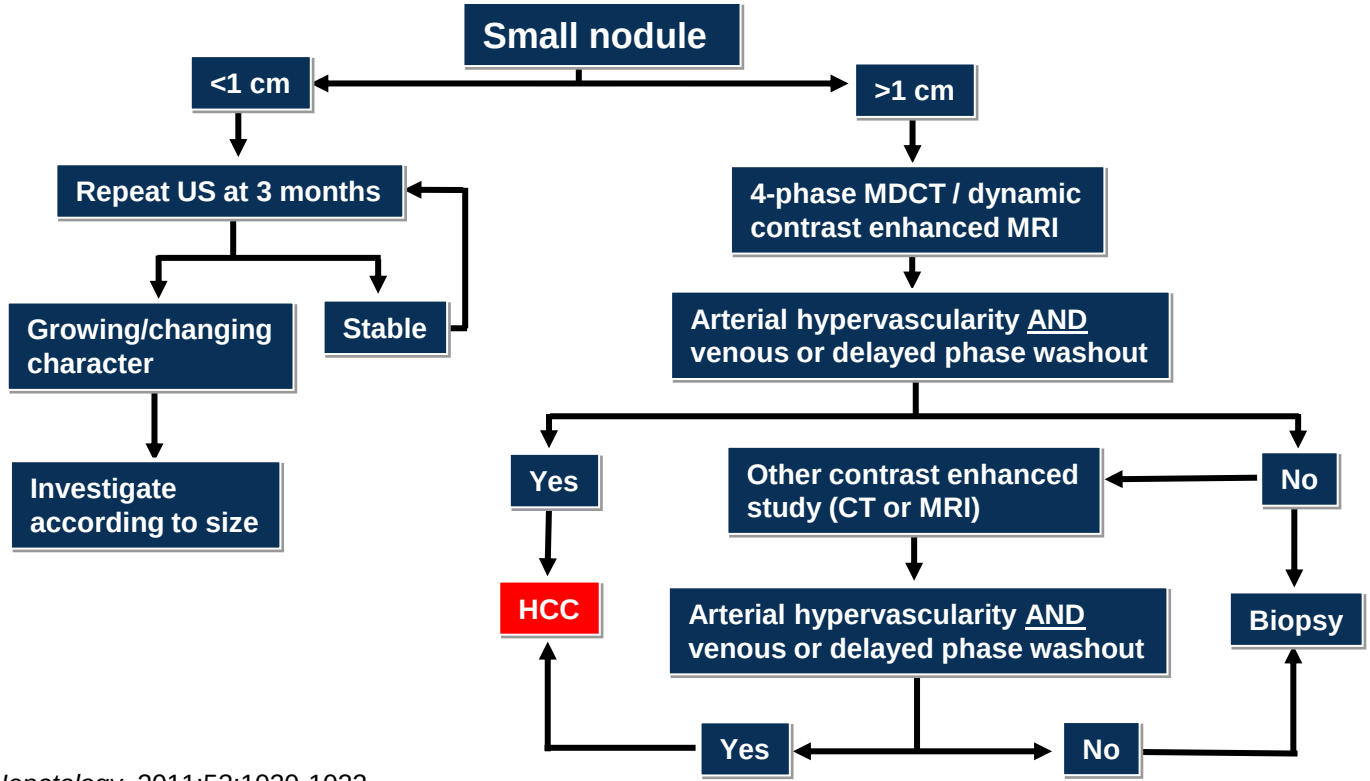
- Early diagnosis of HCC improves survival
- Screen patients with cirrhosis
  - HCV cirrhosis post-SVR
- Selected patients without cirrhosis
  - HBV
- **<u>Ultrasound +/- AFP every 6 months recommended in patients with cirrhosis</u>**
- Consensus lacking (benefit uncertain)
  - Hepatitis C and stage 3 fibrosis
  - NAFLD without cirrhosis
- Do not perform in Child's class C cirrhosis unless on waiting list
- **<u>Majority of patients (~80%) with cirrhosis are not receiving HCC surveillance as recommended by guidelines.</u>**



4-AASLD, 5-EASL, 6-Asia-Pacific, 7-Japanese and *Expert opinion.

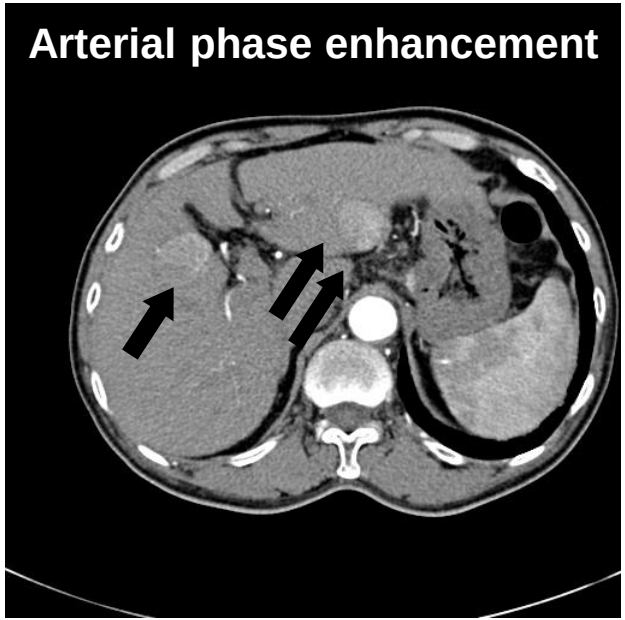
Marrero JA et al. *AASLD Practice Guideline HCC.* 2018; Frenette C et al. *Mayo Clinic Proceedings.* 2019.

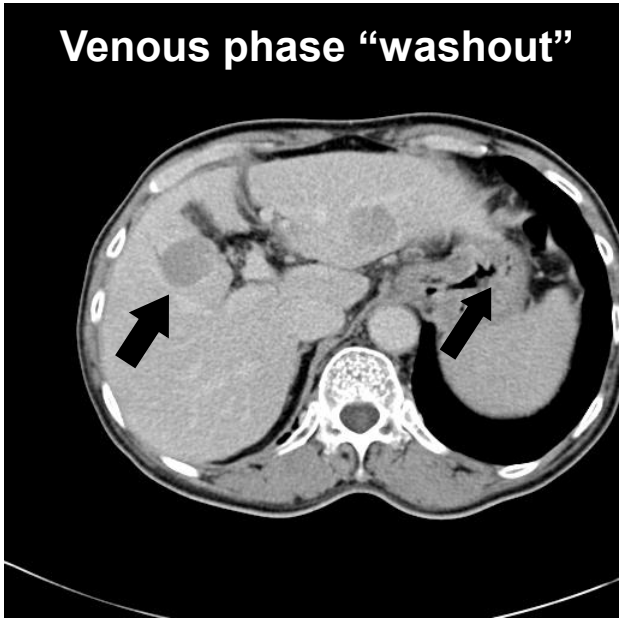
AASLD Diagnostic Criteria for HCC: Liver Nodule on Surveillance Ultrasound or High AFP in a Cirrhotic Liver



Bruix J et al. *Hepatology*. 2011;53:1020-1022.
Available at http://www.aasld.org/practiceguidelines/Pages/NewUpdatedGuidelines.aspx.

Radiologic Diagnosis of HCC in Cirrhosis





Cabrera R, Nelson DR. *Aliment Pharmacol Ther*. 2010 15;31(4):461-76.

Liver Imaging Reporting and Data System (LI-RADS) Standardize Classification of Liver Nodules on Contrast Enhanced Cross-Sectional Imaging

		Arterial phase hypo- or iso-enhancement		Arterial phase hyper-enhancement		
Diameter(mm):		< 20	≥ 20	< 10	10-19	≥ 20
•"Washout" •"Capsule" •Threshold growth	None:	LR-3	LR-3	LR-3	LR-3	LR-4
	One:	LR-3	LR-4	LR-4	LR-4 / LR-5	LR-5
	≥ Two:	LR-4	LR-4	LR-4	LR-5	LR-5

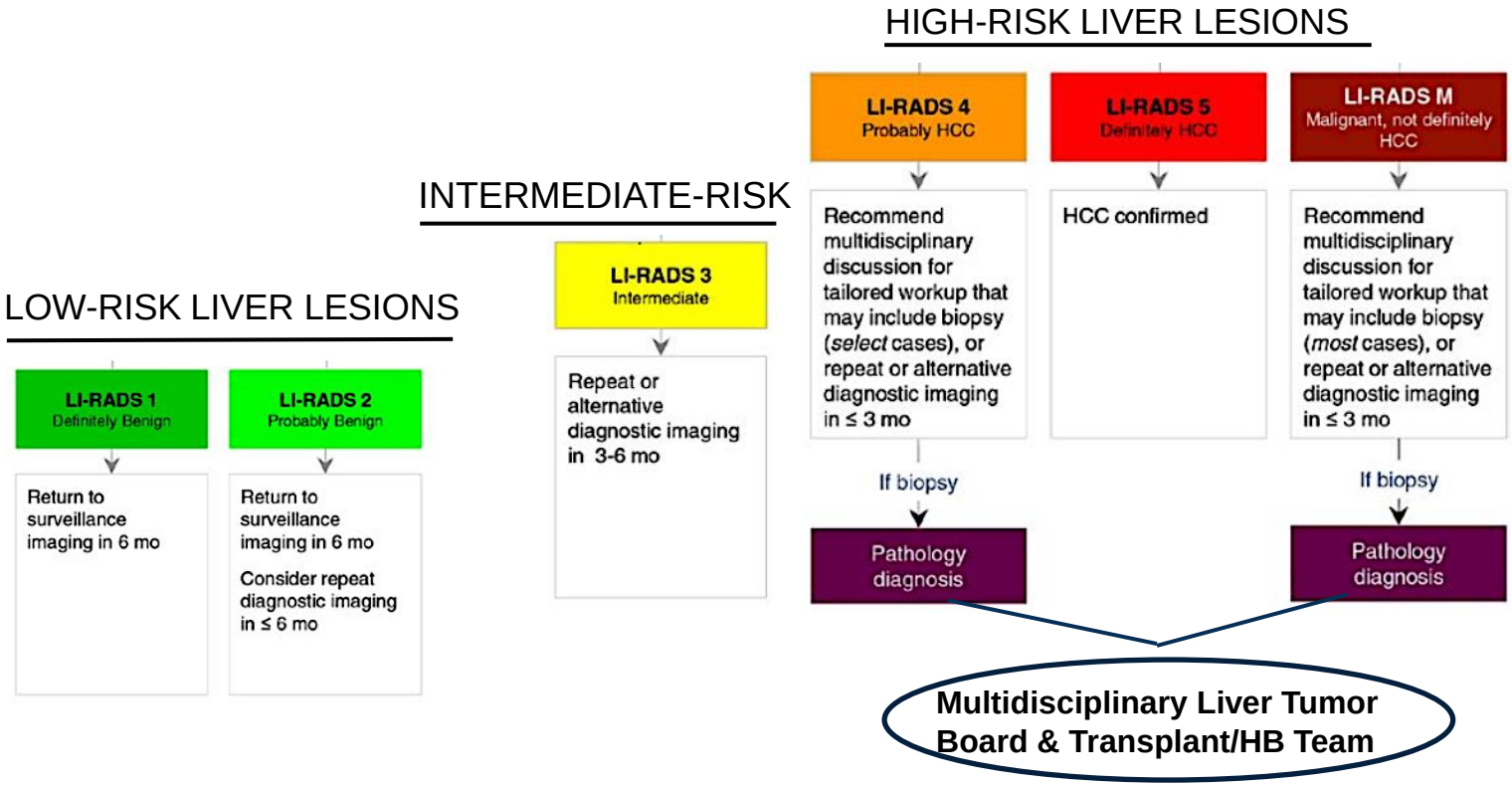
LR-4 / LR-5

Observations in this cell are categorized based on one additional major feature:

- LR-4 – if enhancing "capsule"
- LR-5 – if nonperipheral "washout" **OR** threshold growth

www.acr.org/Quality-Safety/Resources/LIRADS/LIRADS-v2014.

AASLD Guidelines: LI-RADS Diagnostic Algorithm for HCC



Marrero JA et al. *AASLD Practice Guideline HCC.* 2018.

Diagnosis of HCC: To Biopsy or Not?

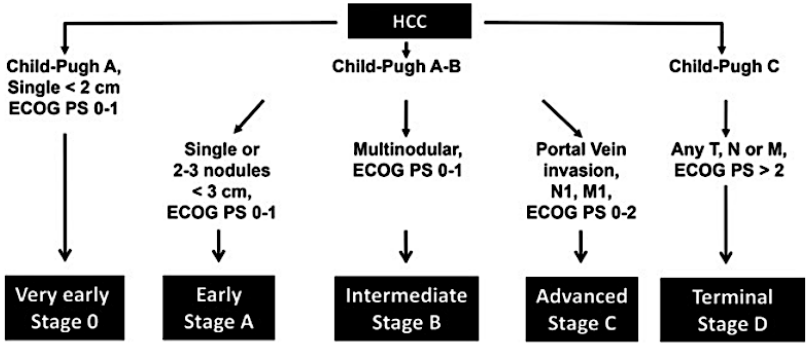
- Yes
  - Imaging is inconsistent with HCC
  - Distinguish HCC from Intrahepatic Cholangiocarcinoma (CCA)
    - Poor prognosis
    - 5-year overall survival 8-50%
    - High recurrence rates 30-40%
  - Avoids inappropriate treatment and misleading “cure”
  - May be required for experimental treatments
  - May permit personalized therapy
- No
  - Not always feasible
  - Not needed if high diagnostic certainty based on imaging
  - Risk
    - Hemorrhage
    - Tumor seeding (2.7% overall incidence)
  - Risk of false negatives
    - Up to 1/3 of biopsies
    - May delay treatment
    - Continue to monitor lesion with imaging

Biopsy is based on clinical picture
No high-risk factors, normal AFP, non-classic radiographic features

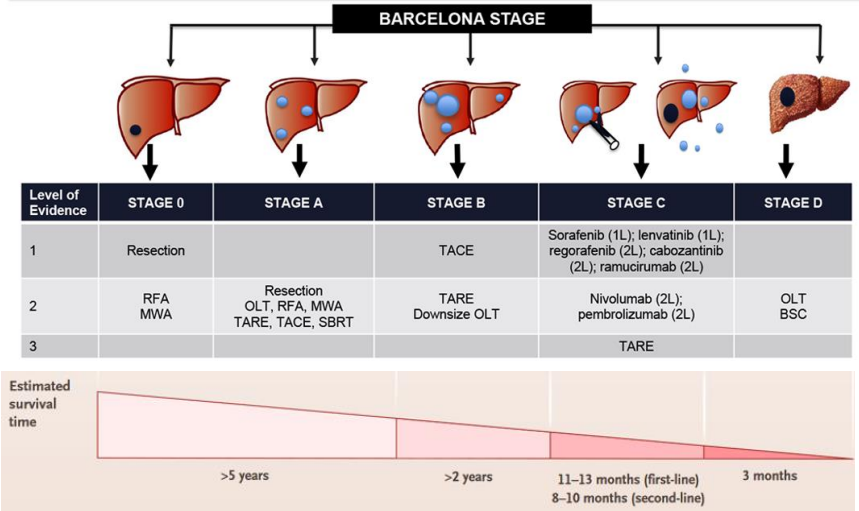
Heuman DM et al. *Eur J Intern Med*. 2012;23:37-39; Rana A et al. *Curr Opin Gastroenterol*. 2012;28(3):258-65; Lee et al. Liver *Transpl* 2018.

HCC Staging and Treatments

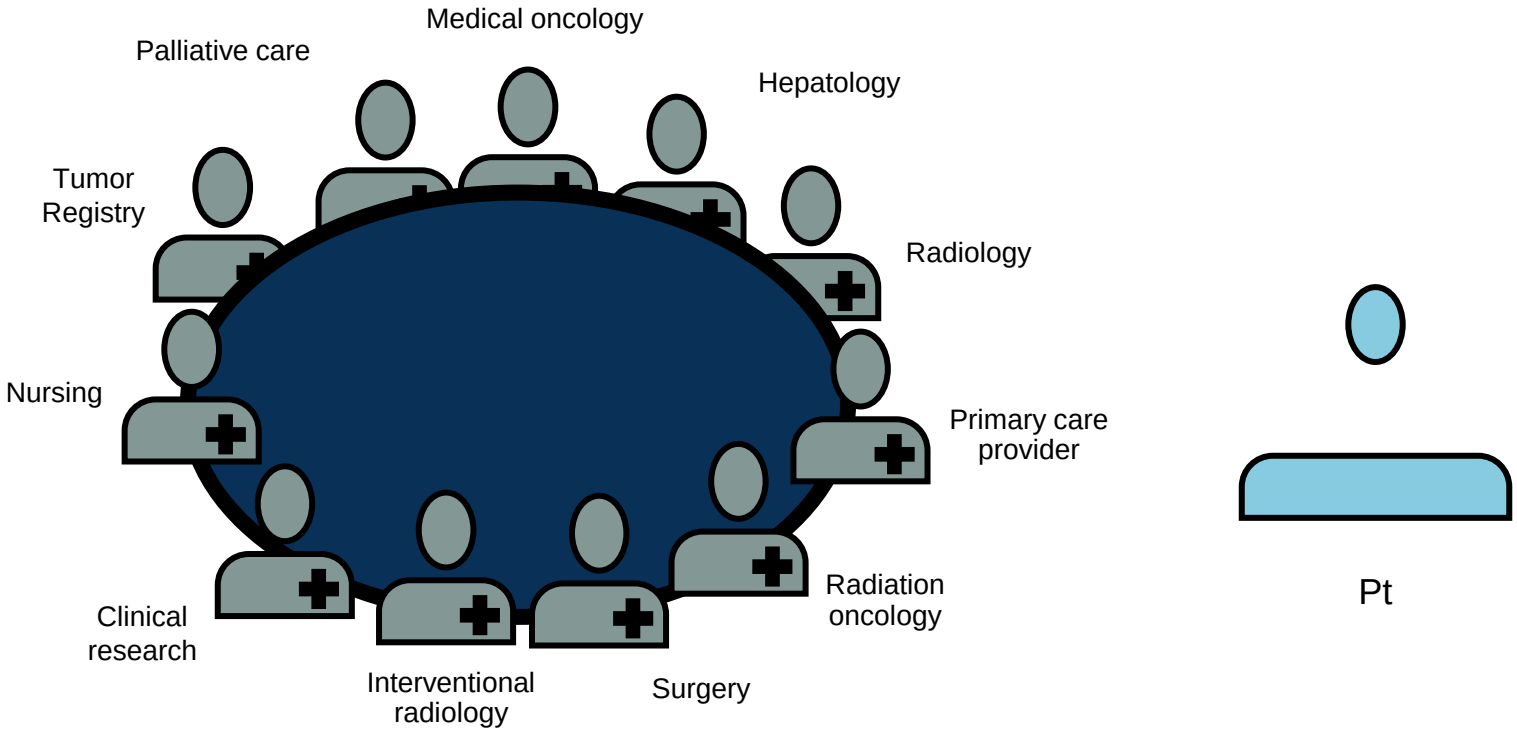
Staging



Treatments



Multidisciplinary Care of Patients With HCC



What Is the Best Treatment Option ?

CURATIVE

Surgery:

- Liver Transplantation
- Resection

Thermal Ablation:

- Microwave (MWA)
- Radiofrequency (RFA)

PALLIATIVE

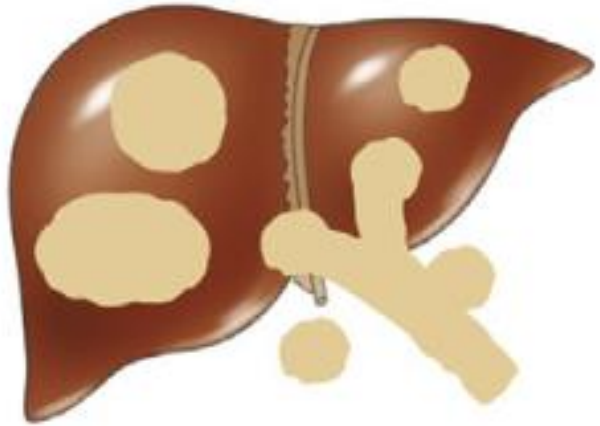
Transarterial:

- Chemoembolization
- Y-90 microspheres

Systemic Therapies:

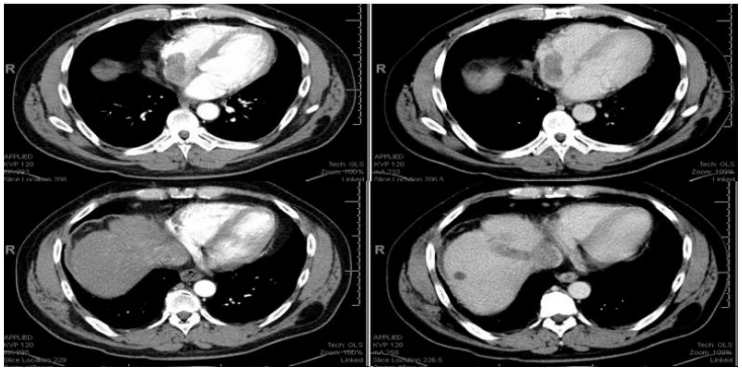
- Sorafenib
- Lenvatinib
- Regorafenib
- Nivolumab
- Cabozantinib
- Pembrolizumab
- Ramucirumab
- Clinical Trials

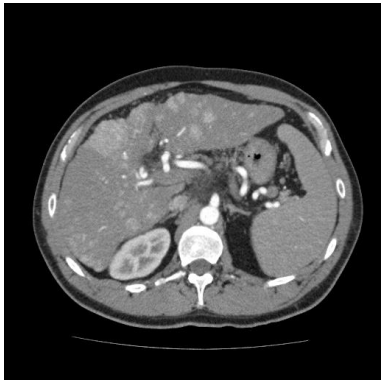
Management of Advanced HCC

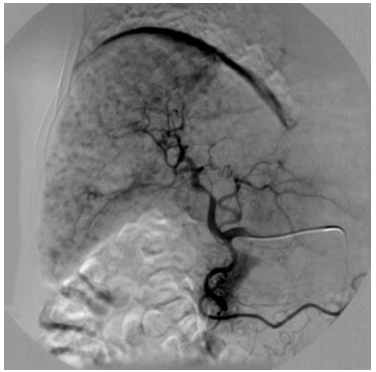


BCLC C

Initial Systemic Therapy Options for Advanced HCC





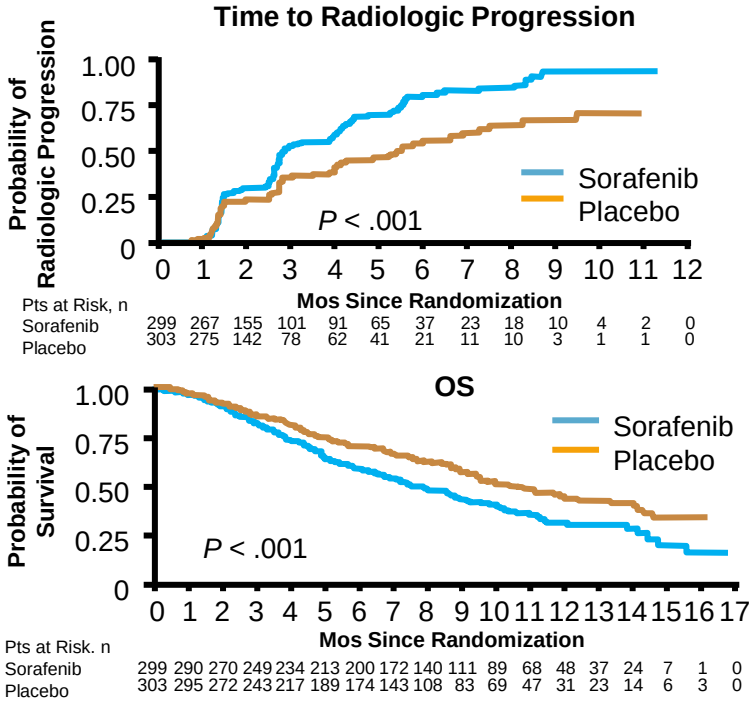


Current Treatment Landscape - 1L Systemic Therapies with TKIs

Agent	FDA Indication	Key Trial
Sorafenib	Unresectable HCC	SHARP
Lenvatinib	First-line treatment of patients with unresectable HCC	REFLECT

Palliation of Advanced HCC: Sorafenib

- Prior to 2007, no therapy was of benefit in advanced HCC
- SHARP trial: CTP A pts with advanced HCC randomized to sorafenib 400 BID vs placebo
- Sorafenib delayed progression and prolonged survival from 7.9 to 10.7 mos
- Led to approval by the FDA in 2007 for palliation of advanced-stage HCC
- First-line systemic therapy for unresectable/advanced HCC

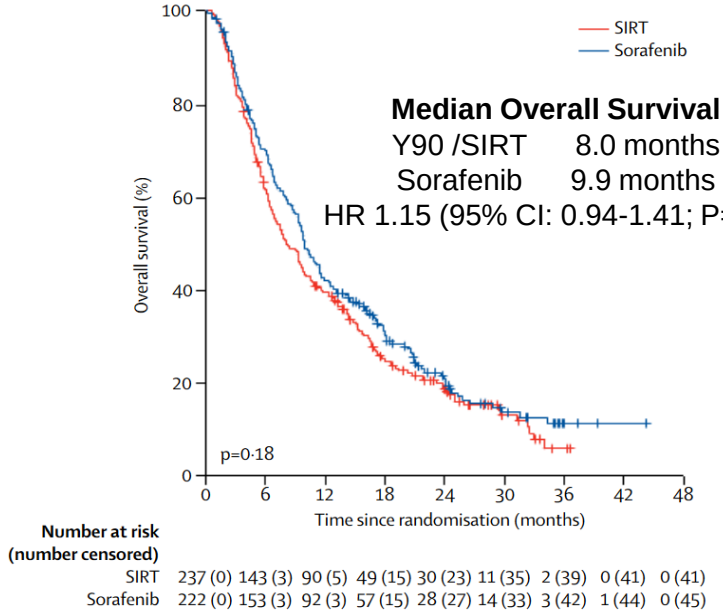


Llovet JM et al. *N Engl J Med*. 2008;359:378-390; Desai JR et al. *J Gastrointest Oncol*. 2017;8:243-255.

Y90 vs Sorafenib in Locally Advanced HCC ± PVT (Stage B and C)

Phase 3 SARAH, Europe/France

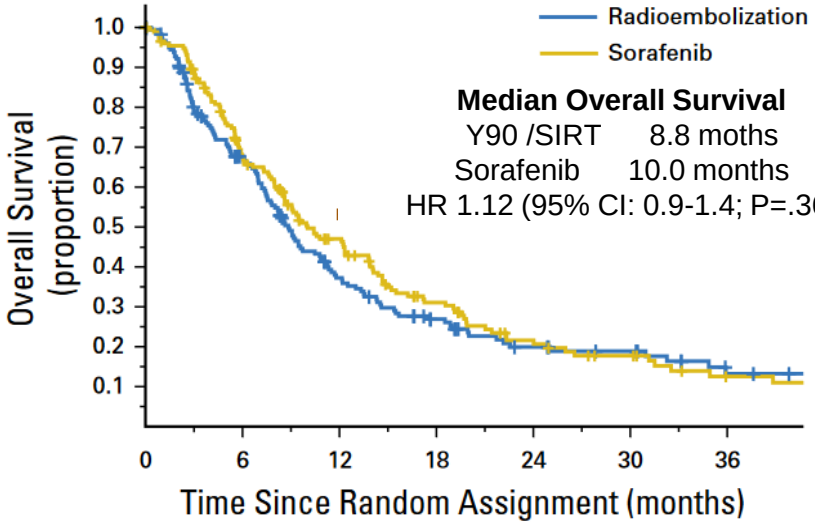
Vilgrain V et al. *Lancet Oncology*. Dec 2018.



Median Overall Survival
Y90 /SIRT 8.0 months
Sorafenib 9.9 months
HR 1.15 (95% CI: 0.94-1.41; P=.18)

Phase 3 SIRveNIB, Asia-Pacific

Chow et al. *Journal Clinical Onc.* July 2018.



Median Overall Survival
Y90 /SIRT 8.8 moths
Sorafenib 10.0 months
HR 1.12 (95% CI: 0.9-1.4; P=.36)

*Y90 versus Sor: Radioembolization has no clinical benefit versus sorafenib in advanced HCC.
*SORAMIC Trial: Y90 plus Sorafenib (n=216) versus Sorafenib (n=208) alone did not improve OS.
-SIRT + Sor, 12.1 months versus Sor alone 11.5 months (Presented EASL 2018, SORAMIC Trial).

Lenvatinib vs Sorafenib in 1L Treatment in Advanced HCC

- Lenvatinib targets VEGFR axis as well as FGFR 1-3
- Compared lenvatinib to sorafenib in the front line setting with a non-inferiority design (Phase 3 REFLECT)
- Patients with unresectable HCC randomized 1:1
  - Len (n=478: <60kg 8mg, >60kg 12 mg)
  - Sor (n=476)
- Excluded patients with Main PV
- BCLC Stage B/C
  - Len 22% / 78%
  - Sor 19% / 81%
- Lenvatinib is noninferior to sorafenib in OS
  - Statistically significant improvements in PFS, TTP, and ORR for lenvatinib vs sorafenib
- First phase 3 trial in HCC to be positive since sorafenib 2007 (SHARP trial)

Outcome	Lenvatinib (n = 478)	Sorafenib (n = 476)	HR
mOS, mos (95% CI)	13.6 (12.1-14.9)	12.3 (10.4-13.9)	0.92 (0.79-1.06)
mPFS, mos (95% CI)	7.4 (6.9-8.8)	3.7 (3.6-4.6)	0.66 (0.57-0.77)
mTTP, mos (95% CI)	8.9 (7.4-9.2)	3.7 (3.6-5.4)	0.63 (0.53-0.73)
ORR, n (%)	115 (24.1)	44 (9.2)	

1L= 1st Line.

Kudo M et al. *Lancet.* Mar 2018.

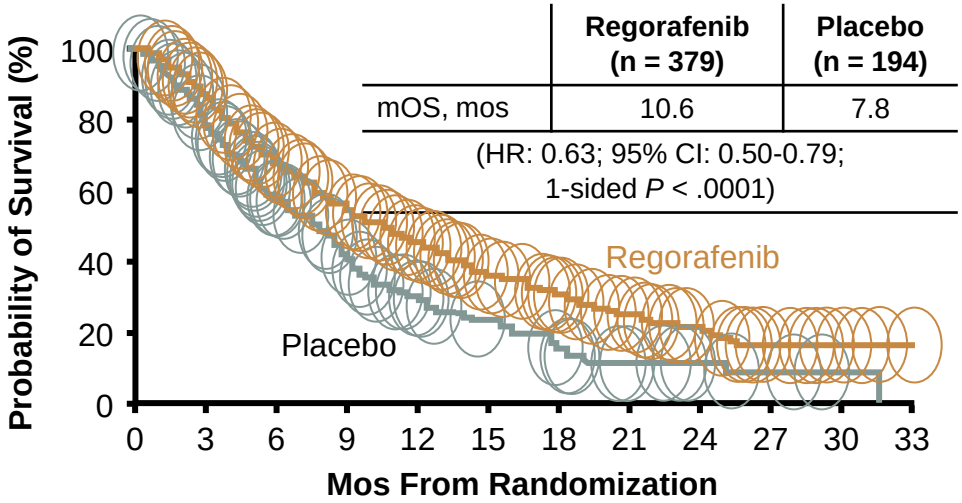
Select Treatment-Emergent AEs (Lenvatinib vs Sorafenib)

AE, %	Lenvatinib (n = 476)		Sorafenib (n = 475)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Total	99	75	99	67
HFSR	27	3	52	11
Hypertension	42	23	30	14
Diarrhea	39	4	46	4
Decreased appetite	34	5	27	1
Decreased weight	31	8	22	3
Fatigue	30	4	25	4
Alopecia	3	0	25	0
Proteinuria	25	6	11	2
Dysphonia	24	< 1	12	2
Nausea	20	1	14	1

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

RESORCE Phase 3: Regorafenib vs Placebo in 2L Advanced HCC

- Pts with HCC with documented radiologic progression on sorafenib (N= 573)
- Randomized 2:1 to Rego (n=379) vs Placebo (n=194)
- Tolerated sorafenib > 400 mg/day for at least 20 of the last 28 days of treatment
- Rego 160 mg PO QD, Days 1-21 of 28-day cycle
- Approved by FDA on April 2017 for HCC previously treated with sorafenib (2L)



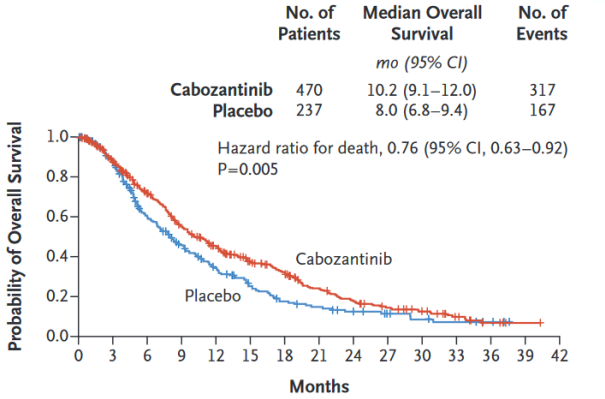
Outcomes of the Sequence of Sorafenib Followed by Regorafenib or Placebo

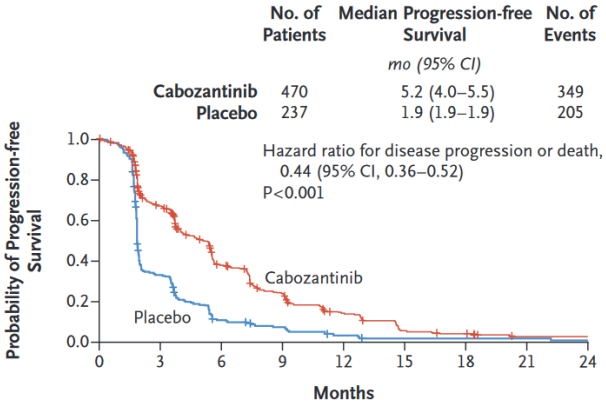
Outcomes From start of sorafenib	Regorafenib (n=374)	Placebo (n=193)
Median survival, months	26.0	19.2
Estimated survival, at 3 yrs	31%	20%
Estimated survival, at 5 yrs	16%	3%

2L=2nd line. Bruix J et al. *Lancet*. 2017;389:56-66. Finn RS et al. *J Hepatol*. 2018.

CELESTIAL Phase 3: Cabozantinib vs Placebo in 2L Advanced HCC

- Cabozantinib targets VEGFR axis and MET.
- Pts with advanced HCC radiologic progression on sorafenib
- No more than 2 prior systemic therapies
- Randomized 2:1 to cabozantinib 60 mg QD (n=470) vs placebo (n=237)
- BCLC Stage C: 85% and 84%
- Cabozantinib significantly prolonged OS in patients with previously treated advanced HCC.
- Corresponding to this survival benefit, a longer duration of PFS was also observed
- Positive Phase 3 in 2L setting for advanced HCC with OS and PFS benefit



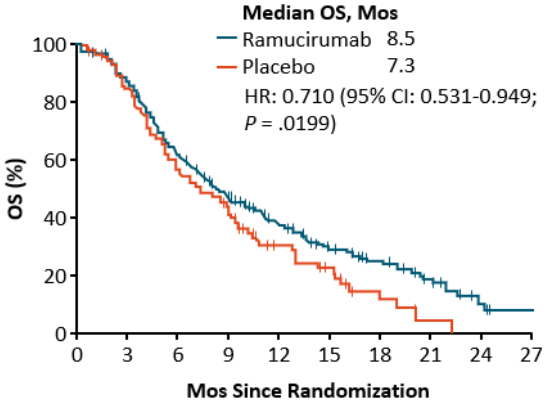


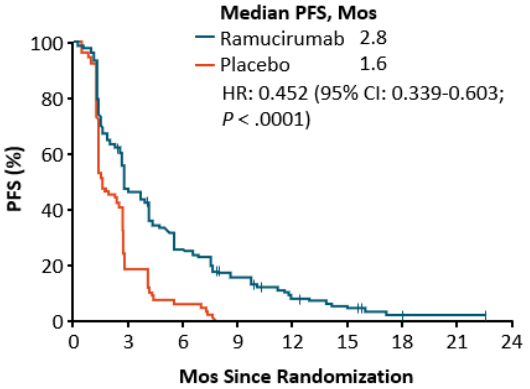
2L = second line.

Abou-Alfa GK et al. *NEJM* July 2018.

REACH-2 Phase 3: Ramucirumab for Patients With Previously Treated HCC and Higher AFP (≥400ng/ml) Advanced HCC

- Ramucirumab anti-VEGR2 monoclonal antibody
- Pts with advanced HCC, AFP > 400 ng/mL, BCLC stage B/C, Child-Pugh A, PS 0/1, prior sorafenib
- Randomized 2:1 to ramucirumab 8 mg/kg IV Q2W (n=197) vs placebo (n=95)
- Ramucirumab prolonged OS in patients with previously treated advanced HCC.
- Positive Phase 3 in 2L setting for advanced HCC with OS and PFS benefit
- FDA approved 2L setting





2L = second line.

Zhu A et al. *Lancet Oncol*. 2019; 20:282.

Immunotherapy as Second Line for Advanced HCC

Both received conditional FDA approval based on Phase 2 non-controlled studies.

	Nivolumab	Pembrolizumab
Sample size	154 sorafenib-treated patients	104 sorafenib-treated patients
Patient features	2L or 3L Sorafenib-intolerants allowed Effective therapy for HBV+ve patients	2L Sorafenib-intolerants allowed Effective therapy for HBV+ve patients No involvement of portal vein trunk
Response rate	14% regardless of etiology or AFP levels	17% regardless of etiology or AFP levels
Duration of response	16.6 months in HCV patients, not reached in other etiologies	≥ 6 months in 77%
mOS	15.1 months (95% CI 13.2–18.8)	12.9 months (95% CI 9.7–15.5)

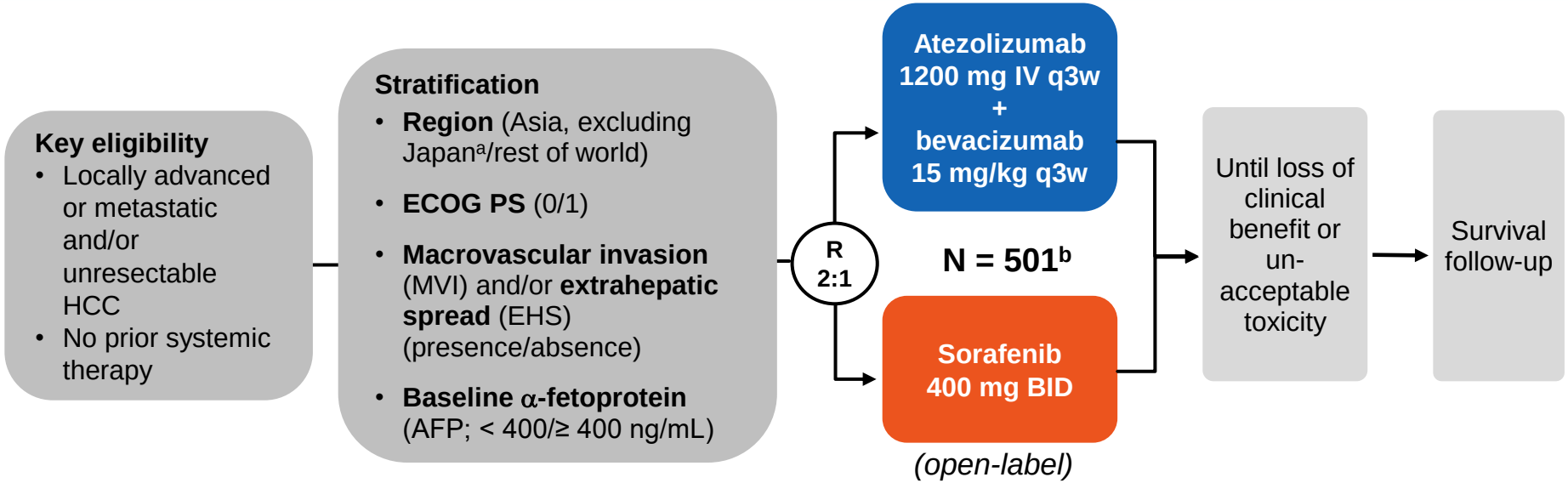
- Lack of predictive biomarker for response: No difference in response by tumor PDL1 expression. MSI high rare (<2%) in HCC.

El-Khoueiry et al. *Lancet.* 2017. Zhu A et al. *Lancet Oncol.* 2018.

HCC Treatment Landscape: Second-Line Options

FDA Approved for Patients Previously Treated With Sorafenib		
Agent	**Key Trial**	**Population**
Cabozantinib	CELESTIAL	Child-Pugh A
Nivolumab	CheckMate-40	Child-Pugh A/B7
Pembrolizumab	KEYNOTE-224	Child-Pugh A
Ramucirumab	REACH-2	Child-Pugh A, AFP ≥ 400 ng/mL
Regorafenib	RESORCE	Child-Pugh A, tolerated first-line sorafenib

Ph3 Atezo+Beva vs Sor Advanced HCC IMbrave150 study design

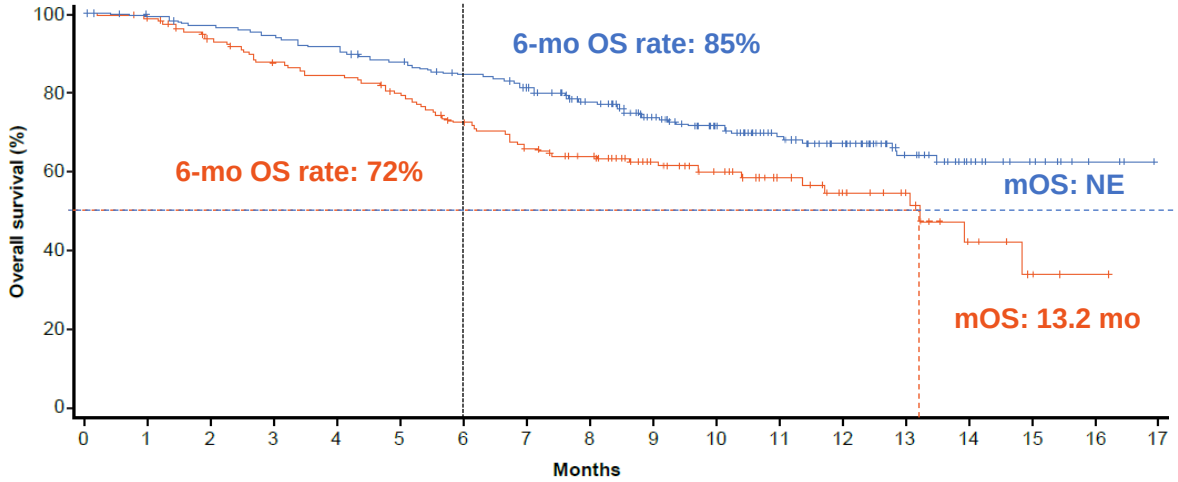


Co-primary endpoints
- OS
- IRF-assessed PFS per RECIST 1.1

Key secondary endpoints (in testing strategy)
- IRF-assessed ORR per RECIST 1.1
- IRF-assessed ORR per HCC mRECIST

[a] Japan is included in rest of world.
[b] An additional 57 Chinese patients in the China extension cohort were not included in the global population/analysis.

OS: Co-Primary Endpoint

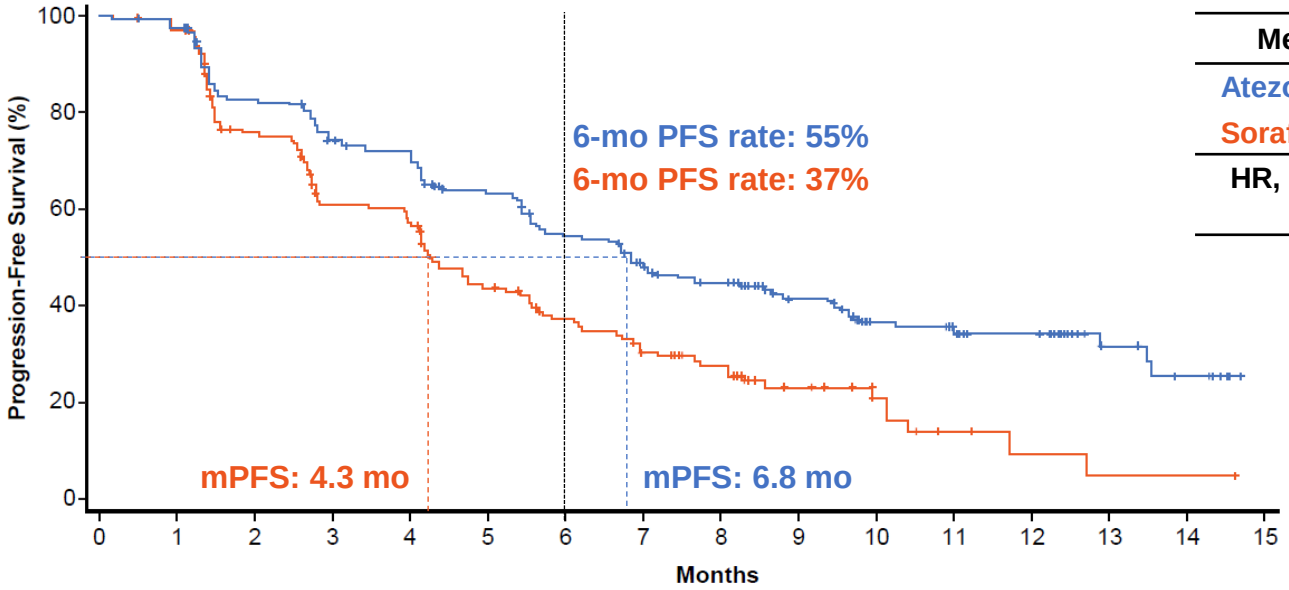


No. at risk																	
Sorafenib	165	157	143	132	127	118	105	94	86	60	45	33	24	16	7	3	1	NE
Atezo + Bev	336	329	320	312	302	288	275	255	222	165	118	87	64	40	20	11	3	NE

Median OS (95% CI), mo[a]	
Atezo + Bev	NE
Sorafenib	13.2 (10.4, NE)
HR, 0.58 (95% CI: 0.42, 0.79)[b]	
***P* = 0.0006[b,c]**	

NE, not estimable. [a] 96 patients (29%) in the Atezo + Bev arm vs 65 (39%) in the sorafenib arm had an event. [b] HR and P value were from Cox model and log-rank test and were stratified by geographic region (Asia vs rest of world, including Japan), AFP level (< 400 vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS. [c] The 2-sided P value boundary based on 161 events is 0.0033. Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

Confirmed PFS[a]: Co-Primary Endpoint



No. at risk

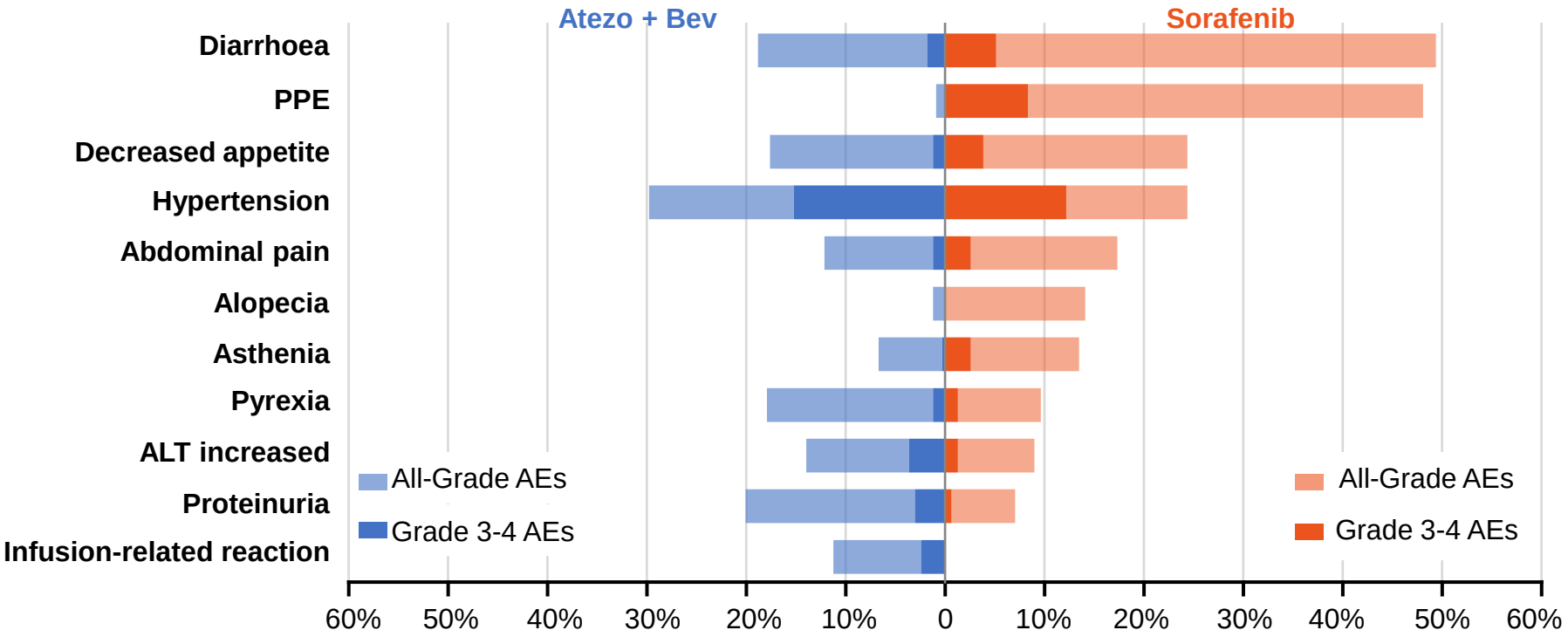
Sorafenib	165	148	109	84	80	57	44	34	27	15	9	4	2	1	1	NE
Atezo + Bev	336	322	270	243	232	201	169	137	120	74	50	46	34	11	7	NE

Median PFS (95% CI), mo[b]	
Atezo + Bev	6.8 (5.7, 8.3)
Sorafenib	4.3 (4.0, 5.6)
HR, 0.59 (95% CI: 0.47, 0.76)[c,d]	
P < 0.0001[d]	

[a] Assessed by IRF per RECIST 1.1. [b] 197 patients (59%) in the Atezo + Bev arm vs 109 (66%) in the sorafenib arm had an event. [c] HR and P value were from Cox model and log-rank test and were stratified by geographic region (Asia vs rest of world, including Japan), AFP level (< 400 vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS. [d] The 2-sided P value boundary is 0.002. Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

Safety[a]

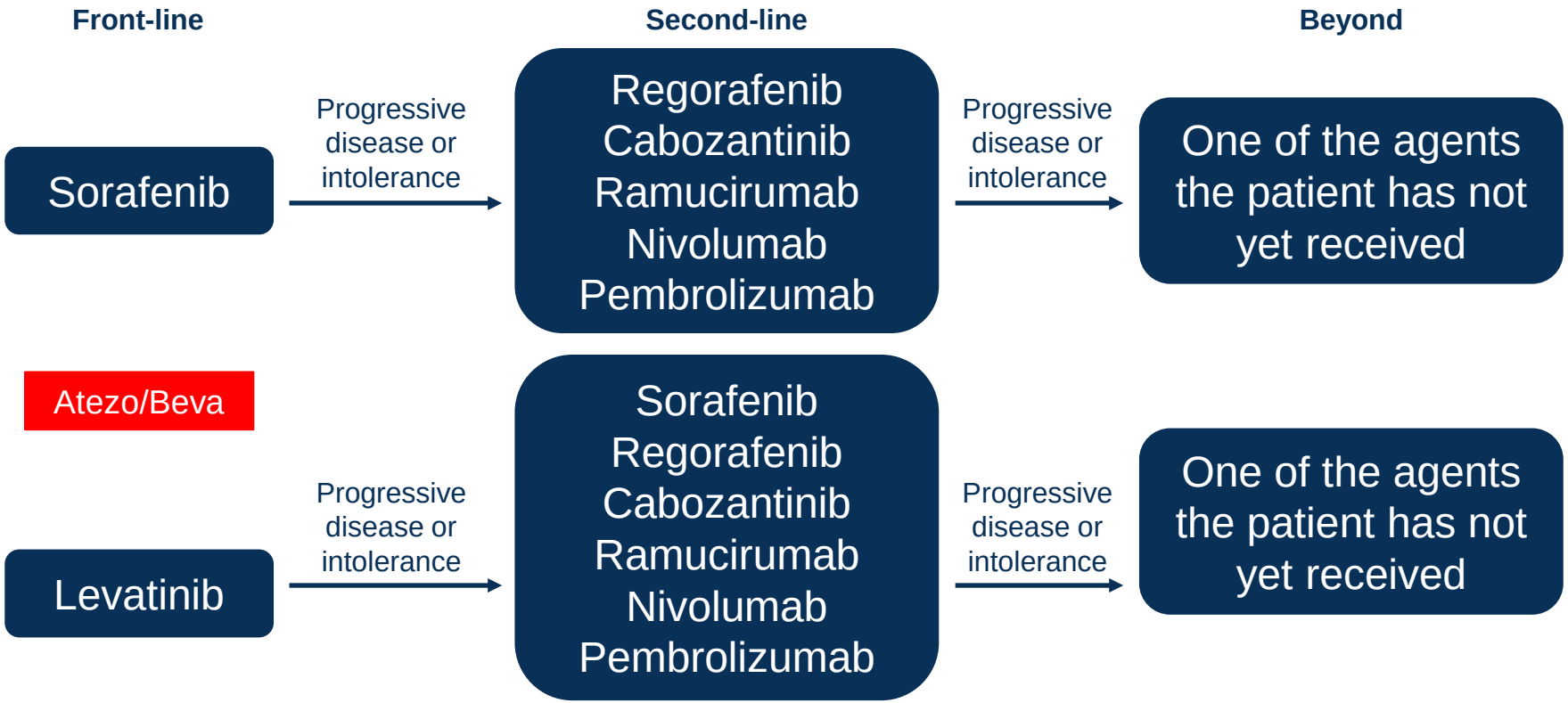
≥ 10% Frequency of AEs in Either Arm and > 5% Difference Between Arms



PPE, palmar-plantar erythrodysaesthesia.

[a] Safety-evaluable population.

Algorithm of Treatment for Advanced HCC



Conclusions

- Burden of HCC is increasing
- Screen your at-risk patients with cirrhosis for HCC with ultrasound and AFP every 6 months for early detection
- Early-stage HCC (BCLC A) may be cured with thermal ablation, resection and/or liver transplantation
- Intermediate-stage HCC (BCLC B) palliated with TACE and Y90
- Local measures often fail in tumors with aggressive biology
- Advanced-stage HCC (BCLC C) palliated with sorafenib
  - Newer 1L (lenvatinib) and 2L therapies (regorafenib, cabozantinib, ramucirumab, nivolumab, pembrolizumab)
- Application of therapies may be limited by severity of cirrhosis
- Multidisciplinary collaboration is paramount for optimal outcome