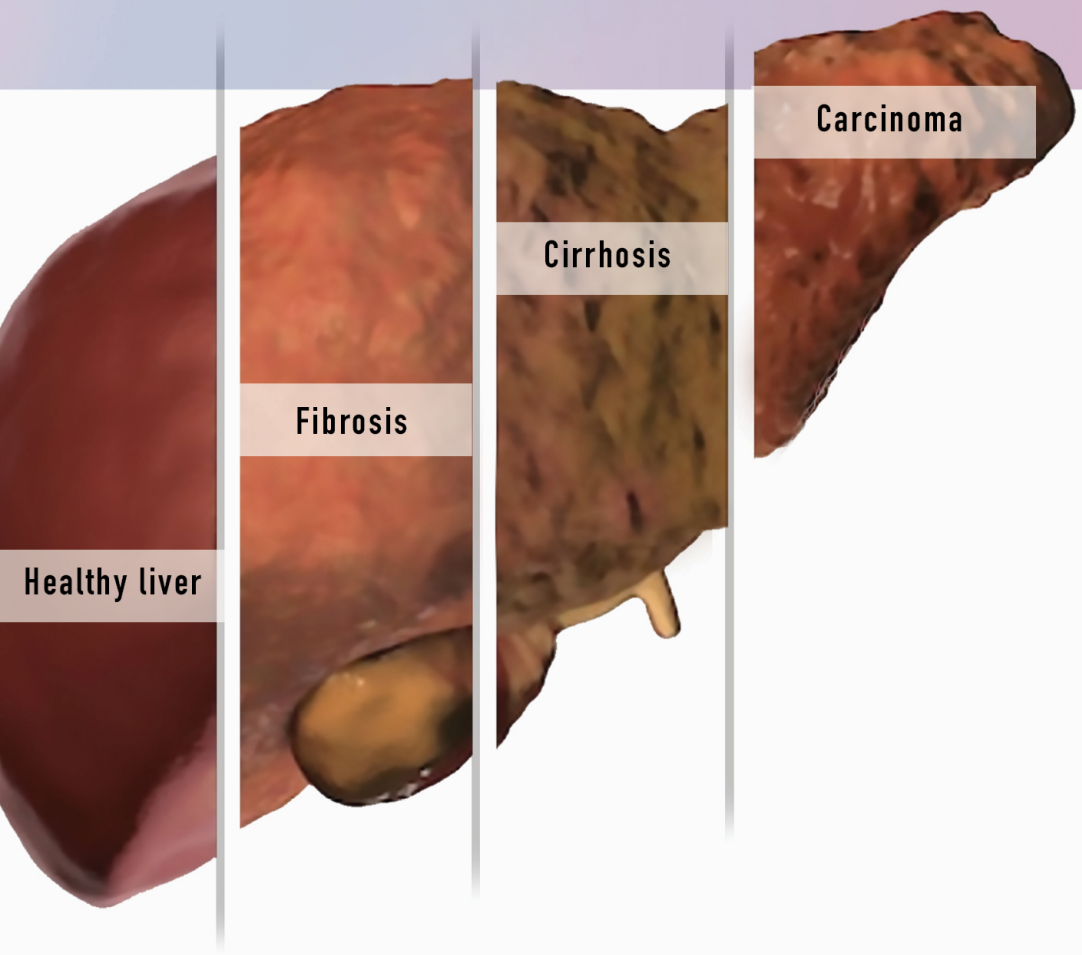
Rethinking the Role of Alpha-fetoprotein as a Prognostic Biomarker in the Management of

ADVANCED HEPATOCELLULAR CARCINOMA



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This activity is supported by an educational grant from Lilly USA, LLC.

Rethinking the Role of Alpha-fetoprotein as a Prognostic Biomarker in the Management of Advanced Hepatocellular Carcinoma

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PROGRAM OVERVIEW

This live activity is focused on treatment strategies for patients with hepatocellular carcinoma (HCC).

TARGET AUDIENCE

This activity is designed to meet the educational needs of US-based medical oncologists, particularly who practice in the community setting, and the multidisciplinary care team responsible for treating patients with gastrointestinal tract cancers that include HCC.

LEARNING OBJECTIVES

After completing the CME activity, learners should be better able to:

- Explain how alpha-fetoprotein contributes to HCC tumor immune escape
- Use AFP as a prognostic biomarker for the management of advanced HCC, based on the evolution of evidence-based clinical practice guidelines and additional data
- Develop individualized plans for the sequencing of treatment regimens for patients with advanced HCC based on patient-specific characteristics including AFP levels

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NURSING CREDIT INFORMATION

Purpose: This program would be beneficial for nurses involved in the care of patients with HCC.
Credits: 1.0 ANCC Contact Hours

CNE Accreditation Statement: Ultimate Medical Academy/CCM is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Awarded 1.0 contact hours of continuing nursing education of RNs and APNs.

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	Medical Lead on Clinical Study FDA 1571 Application	Viking Therapeutics
Tanios S. Bekaii-Saab, MD	**TBD**	**TBD**
Thomas Cartwright, MD	Speakers Bureau	Amgen, Heron, Taiho
Stanley Cohen, MD	No relationships to report	N/A
Efrat Dotan, MD	Consultant	Pfizer, Boston Medical
	Research Support/PI	NCCN/Lilly; Medimmune, Boston Medical, AstraZeneca, Incyte, GSK, Merck
Richard Dunne, MD	Consultant	Exelixis, Inc.
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Michael Morse, MD	Speakers Bureau	Eisai, Exelixis, Genentech, Ipsen, Lexicon, Novartis/AAA, Celgene, Merck, Taiho
	Consultant	Lilly, Bayer
	Research Grant	Bristol-Myers Squibb (BMS), Ipsen, Merck, Eisai, Medimmune/Astrazeneca
Roshan Shrestha, MD, FAASLD, FAST	Speakers Bureau	Boston Scientific, Gilead, Dova, Salix

CME content review

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2. Participate in the online activity.
3. Submit the evaluation form to Med Learning Group.

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This activity is supported by an educational grant from Lilly USA, LLC.

ON-105 HCC Agenda

I. HCC: An Overview

a. Epidemiology
b. Disease course
c. Disease burden/effects on patient quality of life
d. Standard of care treatment options
e. Introduction to the multidisciplinary care team

II. Pathophysiology of HCC

III. Overview of Therapeutic Options in HCC

a. BCLC staging for allocating patients
b. Case Introduction
c. Whiteboard Animation: first- and second-line treatments in HCC

IV. Overview of First-line Treatments in HCC

V. Recently Approved and Emerging Second-line Therapeutic Options for the Treatment of Advanced HCC

a. Multikinase inhibitors
    i. Clinical trial efficacy and safety results
b. AFP as a circulating prognostic biomarker for HCC
    i. Whiteboard animation: role of AFP in HCC immune escape
    ii. Evolution of evidence-based clinical practice guidelines regarding AFP screening
    iii. Data on the utility of AFP as a prognostic biomarker for advanced HCC
c. Novel agents and combinations in development for the treatment of patients with advanced HCC

VI. Individualizing the Sequencing of Care for Patients with HCC

a. Analysis of patient-specific factors that affect outcomes including treatment history, AFP levels, comorbidities, and age
b. Role of newly approved agents in clinical practice
c. Consideration of patient preferences
d. Multidisciplinary care team: members and roles

VII. Conclusions

VIII. Questions and answers

The TAILOR Initiative: Rethinking the Role of Alpha-fetoprotein as a Prognostic Biomarker in the Management of Advanced Hepatocellular Carcinoma

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Learning Objectives

- Explain how alpha-fetoprotein (AFP) contributes to hepatocellular cancer (HCC) tumor immune escape
- Use AFP as a prognostic biomarker for the management of advanced HCC, based on the evolution of evidence-based clinical practice guidelines and additional data
- Develop individualized plans for the sequencing of treatment regimens for patients with advanced HCC based on patient-specific characteristics, including AFP levels

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A Brief Look at Hepatocellular Carcinoma

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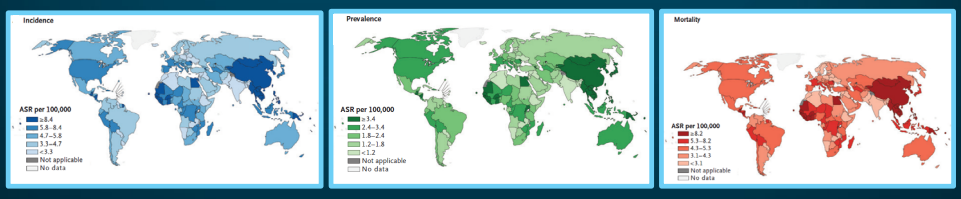
Hepatocellular Carcinoma

- Hepatocellular carcinoma (HCC) accounts for the majority of primary liver cancers
- As of 2018, liver cancers were 4th most common cause of cancer-related death; prior to 2018, liver cancers were 3rd most common cause of cancer-related deaths
- The World Health Organization (WHO) estimates that >1 million patients will die from liver cancer in 2030
- In the US, the rate of death from liver cancer increased by 43% (from 7.2 to 10.3 deaths per 100,000) between 2000 and 2016
- With a 5-year survival of 18%, liver cancer is the second most lethal tumor after pancreatic cancer

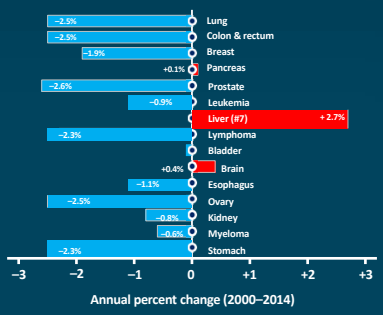


Villanueva A. *N Engl J Med*. 2019;380:1450-1462.

4

HCC Mortality in United States Is Increasing

Top 15 causes of cancer death in United States 2000–2014



- Approximately 42,000 cases of primary liver cancer and intrahepatic bile-duct cancer were diagnosed in US in 2019
- Overall 5-year survival rate of 18% in the US
  - 31% with localized disease and 2% for metastatic disease
  - High mortality rate is largely the result of late-stage diagnosis

Siegel RL, et al. *CA Cancer J Clin*. 2019;69:7-34. American Cancer Society (ACS). *Cancer Facts & Figures 2019* (www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf). Accessed January 20, 2020.

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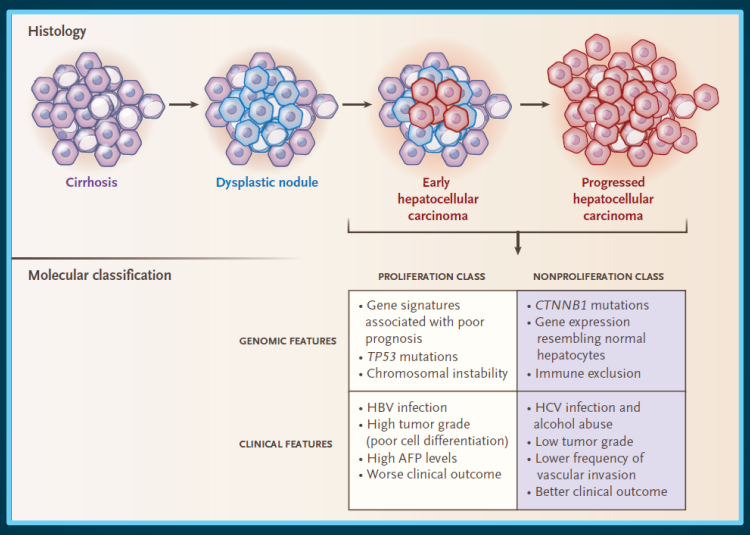
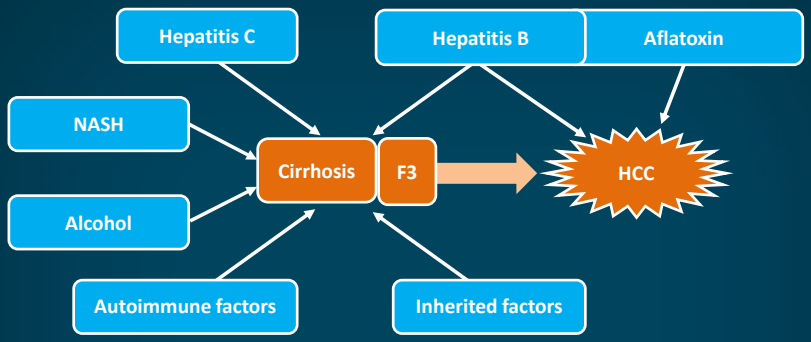
Etiology of Hepatocellular Carcinoma



Modified from Villanueva A. *N Engl J Med*. 2019;380:1450-1462.

6

Risk Factors for the Development of HCC



- 2%–5% of patients with cirrhosis develop HCC each year
- Most cases of HCC arise in a cirrhotic liver
- Cirrhosis is not always symptomatic, and HCC may be the first indication of underlying cirrhosis

NASH = nonalcoholic steatohepatitis.

Shariff MI, et al. *Expert Rev Gastroenterol Hepatol*. 2009;3:353-367. Villanueva A. *N Engl J Med*. 2019;380:1450-1462.

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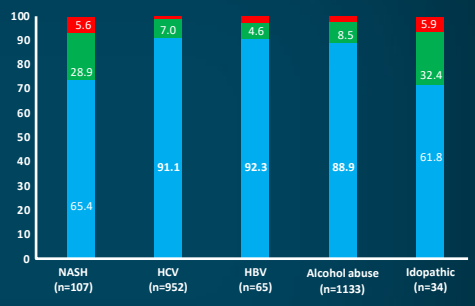
Why is the Incidence of HCC Rising in the US?

- Incidence of HCC has more than tripled in the US since 1980
  - Most rapidly increasing cancer in both men and women
- Increased incidence of HCC is the result of increasing prevalence of cirrhosis
  - Half of increase is attributed to aging cohort with chronic HCV
  - Increasing incidence of obesity and NAFLD in the US

Many NASH patients with HCC do not have cirrhosis



Very high probability non-cirrhotic: Histology and no features on imaging

High probability non-cirrhotic: APRI <1; no features on imaging; NL albumin, plt, INR

HCV = hepatitis C virus; NAFLD = nonalcoholic fatty liver disease; APRI = AST to Platelet Ratio Index; HBV = hepatitis B virus; NL = normal limits; INR = international normalized ratio.

Mittal S, et al. *J Clin Gastroenterol*. 2013;47(0):S2-S6. American Cancer Society. Cancer Facts & Figures 2019. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf. Accessed January 20, 2020. Mittal S, et al. *Clin Gastro Hep*. 2015;13(3):594–601.e1.

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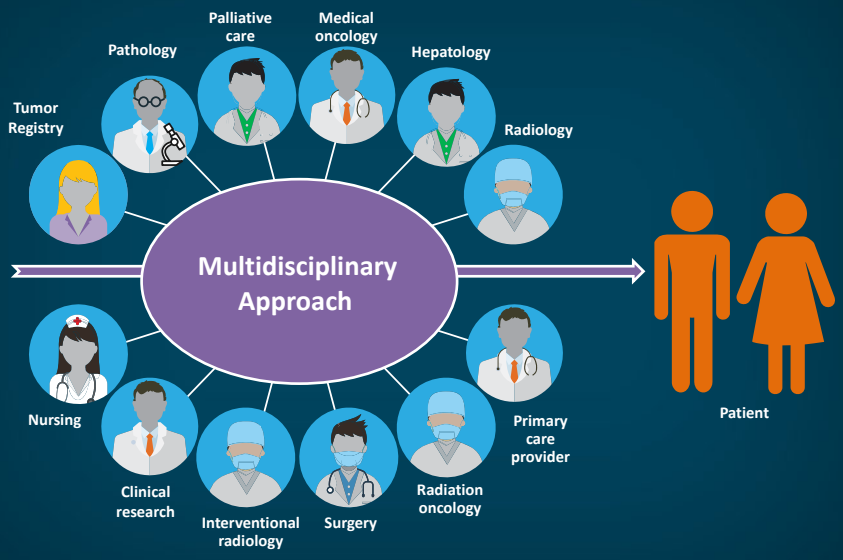
Multidisciplinary Approach to the Patient With HCC



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Pathogenesis of HCC

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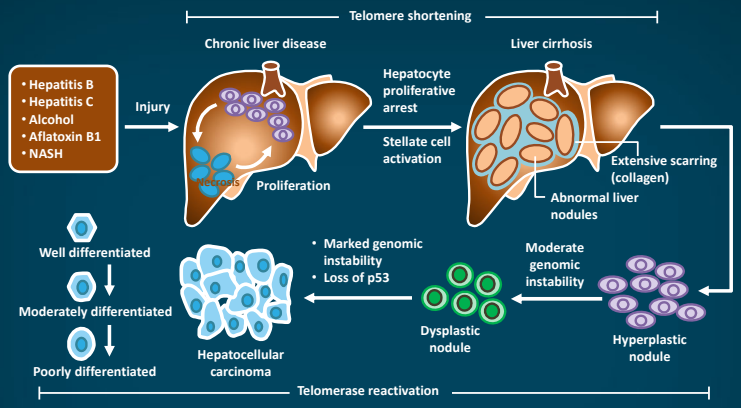
Pathogenesis of HCC



- Persistent inflammation promotes and exacerbates malignancy
- 90% of HCCs arise from chronic unresolved inflammation associated with persistent hepatic injury and concurrent regeneration
- Inflammation leads to the sequential development of fibrosis, cirrhosis, and eventually HCC

Farazi PA, DePinho RA. *Nat Rev Cancer*. 2006;6:674-687. Bishayee A. *Adv Exp Med Biol*. 2014;816:401-435. Villanueva A. *N Engl J Med*. 2019;380:1450-1462.

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Surveillance and Diagnosis of HCC

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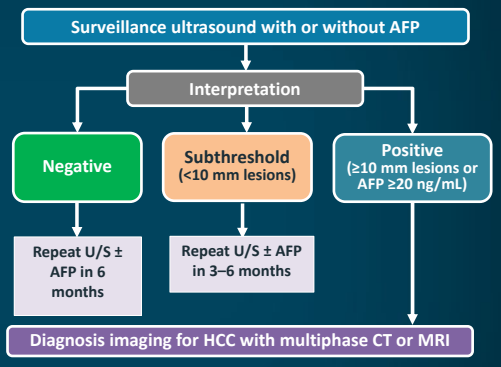
Surveillance of HCC*

- Use of biannual U/S ± AFP is found to be cost effective
- Surveillance should be offered to:
  - Patients with cirrhosis when the risk of HCC is >1.5%/year
  - HBV carriers without cirrhosis
- Surveillance should NOT be offered to patients with cirrhosis with Child's class C unless on the transplant waiting list



*Refer to treatment guidelines.

AFP = alpha-fetoprotein; U/S = ultrasound; CT = computed tomography (scan); MRI = magnetic resonance imaging.

Marrero JA, et al. *Hepatology*. 2018;68:723-750. Lin OS, et al. *Aliment Pharmacol Ther*. 2004;19:1159-1172. Fujiwara N, et al. *J Hepatol*. 2018;68:526-549.

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Diagnosis of HCC Is Dominated by Imaging and Rarely by Pathology

LiRADS

- Arterial hypervascularization and venous washout
- Growth and capsule

Computed tomography (CT)

- Advantages
  - Provides detailed search for primary or secondary lesions outside the abdomen
  - Allows scanning in multiple phases of enhancement
  - Greatly advances the image quality
- Disadvantages
  - Radiation exposure
  - Nephrotoxicity

Magnetic resonance imaging (MRI)

- Advantages
  - Lack of radiation
  - Higher contrast resolution
- Disadvantages
  - Requires at least 30 minutes in the magnet (maybe shorter with updated MRI protocols)
  - Motion artifact (patient participation)
  - Claustrophobia

Li-RADS = Liver Reporting and Data System.

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An Overview of Therapeutic Options in HCC

Surgical Resection, Embolization, Thermal Ablation, and External Beam Radiation

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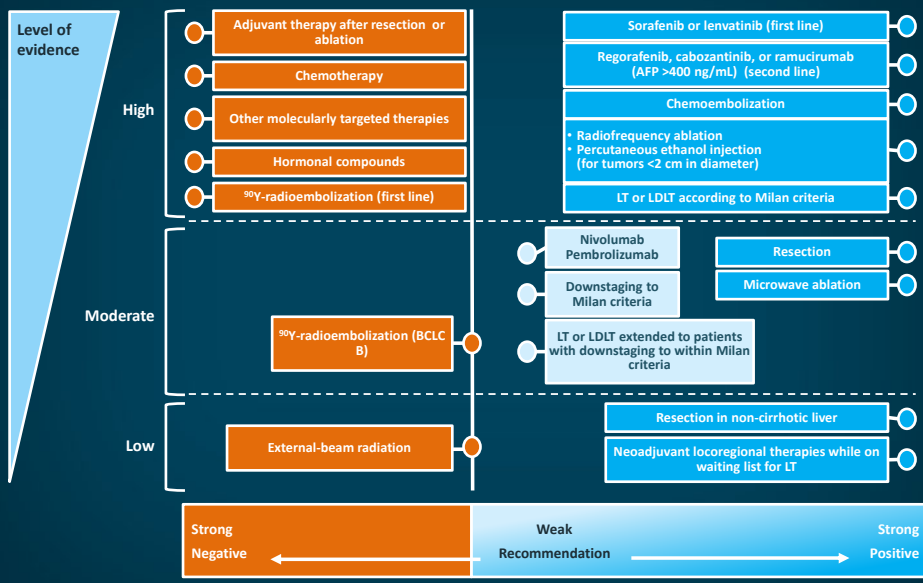
HCC Treatment Options and Level of Evidence

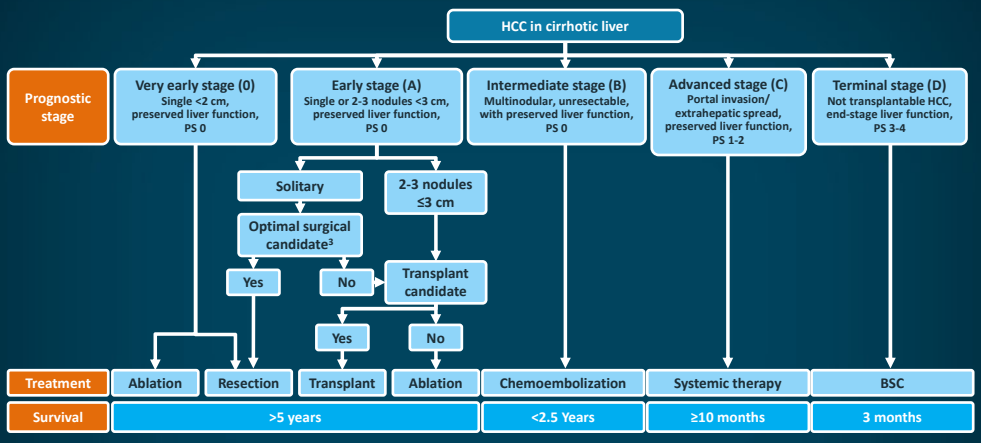


LT = liver transplantation; LDLT = living-donor LT; BCLC B = Barcelona Clinic Liver Cancer (guidelines), stage B.

Llovet JM, et al. *Nat Rev Clin Oncol*. 2018;15:599-616.

16

Modified BCLC Staging and Treatment (EASL)



Modified BCLC is used to predict prognosis of patients with HCC based on tumor burden, liver function (Child-Pugh), clinical status, and cancer-related symptoms (ECOG PS)

ECOG = Eastern Cooperative Oncology Group; PS = performance status; BSC = best supportive care.

European Association for the Study of the Liver (EASL). *J Hepatol*. 2018;69:182-236. Golfieri R, et al. *Liver Cancer*. 2019;8:78-91. Marrero JA, et al. *Hepatology*. 2018;68:723-750.

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Case 1

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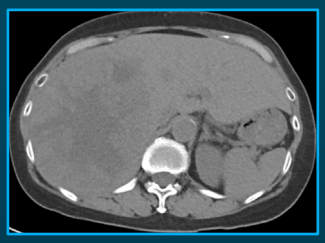
Case 1: Mrs. C

- Mrs. C is a 57-year-old woman with a history of alcohol abuse who presents to the ED with RUQ pain for few weeks
- Dual-phase CT in ED → cirrhosis and liver mass
- MRI with contrast → infiltrative HCC with right PV enhancing thrombus
- ED physician asks if you would like to start anticoagulation



ED = emergency department; RUQ = right upper quadrant; PV = portal vein.

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Case 1: Mrs. C

- Mrs. C is a 57-year-old woman with a history of alcohol abuse who presents to the ED with RUQ pain for few weeks
- CT in ED → cirrhosis and liver mass
- MRI → infiltrative HCC with right PV enhancing thrombus
- ED physician asks if you would like to start anticoagulation
- Child's A—bilirubin = 1.0, albumin = 3.2, INR = 1.0
- What would you recommend for HCC treatment?

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Therapeutic Options in HCC

Systemic Therapies

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Faculty script: The following animation illustrates the mechanisms of action of first- and second-line treatments for hepatocellular carcinoma.

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First- and Second-line Treatments for HCC

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Therapeutic Options in HCC

Systemic Therapies: First-line

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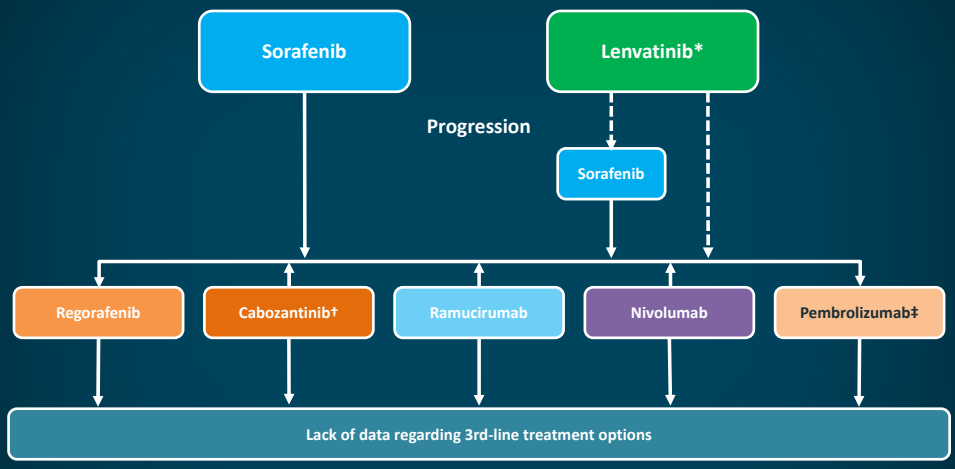
Current Treatment Landscape for Advanced HCC



*There are no data to define optimal treatment for those who progress after lenvatinib; †Possible 3rd-line agent, but there is a lack of data regarding optimal treatment sequence for those who progress after 2nd-line therapy; ‡Although the US Food and Drug Administration (FDA) accelerated approval based on phase 2 trial (KEYNOTE-224), confirmatory phase 2 trial (KEYNOTE-240) did not demonstrate statistically significant improvement in overall survival and progression-free survival.

Li D, et al. *Cancers (Basel)*. 2019;11:E841.

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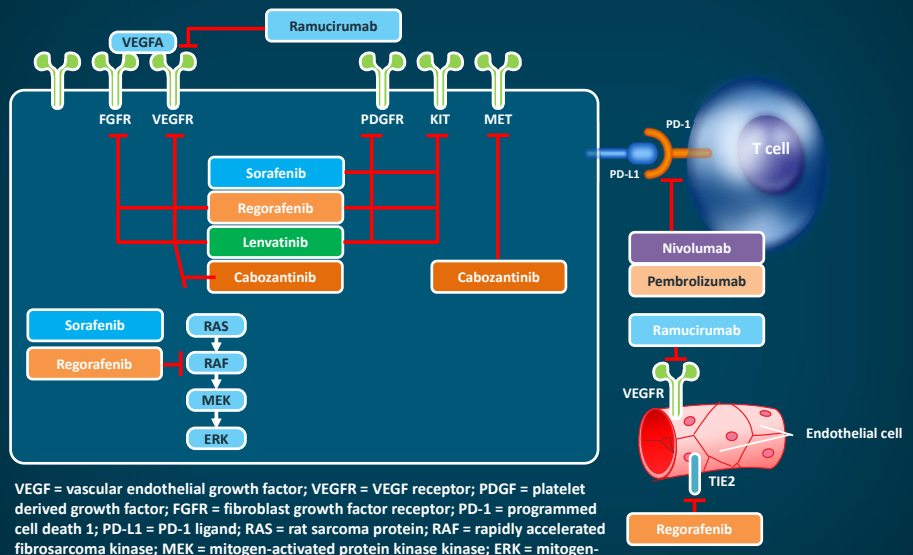
Targeted Therapies for Hepatocellular Carcinoma



VEGF = vascular endothelial growth factor; VEGFR = VEGF receptor; PDGF = platelet derived growth factor; FGFR = fibroblast growth factor receptor; PD-1 = programmed cell death 1; PD-L1 = PD-1 ligand; RAS = rat sarcoma protein; RAF = rapidly accelerated fibrosarcoma kinase; MEK = mitogen-activated protein kinase kinase; ERK = mitogen-activated protein kinase; TIE2 = angiopoietin 1 receptor.

Modified from Llovet JM, et al. *Nat Rev Clin Oncol*. 2018;15:599-616.

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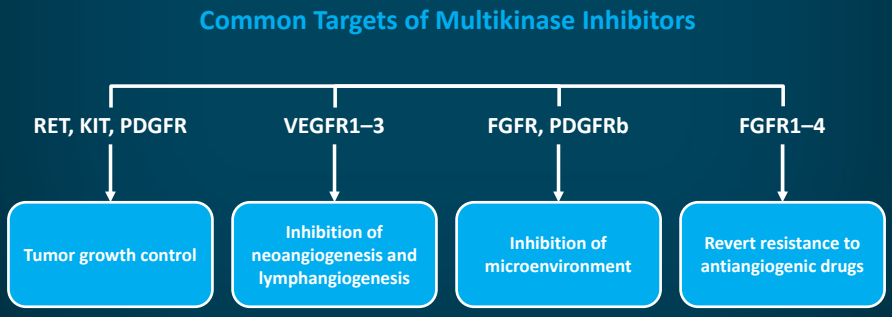
Mechanism of Action of Multikinase Inhibitors (MKIs)

- Tumor progression usually involves the action of multiple kinase pathways
- Targeting several receptors simultaneously with MKIs may provide a synergistic effect and reduce the possibility of drug resistance



RET = rearranged during transfection tyrosine kinase receptor; KIT = a receptor tyrosine kinase; PDGFR = PDGF receptor.

Stjepanovic N, Capdevila J. *Biologics*. 2014;8:129-139. Abbaspour Babaei M, et al. *Drug Des Devel Ther*. 2016;10:2443-2459. Muntané J, et al. *Curr Cancer Drug Targets*. 2013;13:300-312. Kato S, et al. *Clin Cancer Res*. 2017;23:1988-1997. Garuti L, et al. *Curr Med Chem*. 2015;22:695-712.

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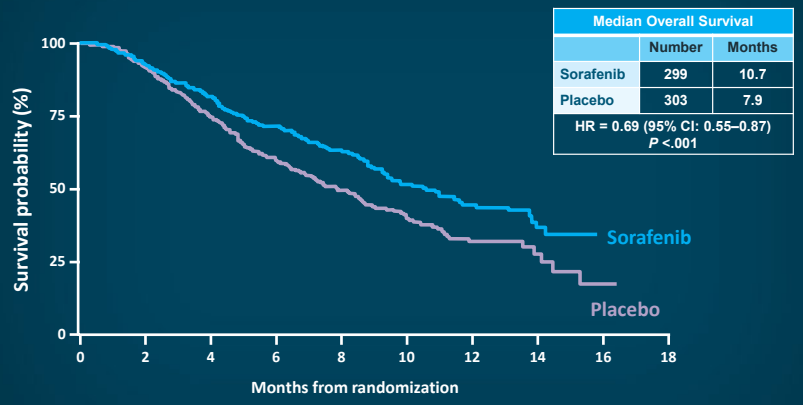
Sorafenib Improves Survival for Advanced HCC



Median Overall Survival		
	Number	Months
Sorafenib	299	10.7
Placebo	303	7.9
HR = 0.69 (95% CI: 0.55–0.87) *P* <.001		

OS = overall survival; HR = hazard ratio; CI = confidence interval.

Llovet JM, et al. *N Engl J Med*. 2008;359:378-390.

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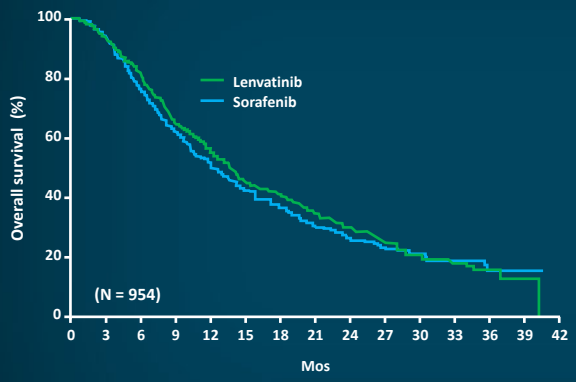
Lenvatinib is Noninferior to Sorafenib



Outcomes		
Outcome	**Lenvatinib (n = 478)**	**Sorafenib (n = 476)**
mOS, mo (95% CI)	13.6 (12.1–14.9)	12.3 (10.4–13.9)
HR for mOS = 0.92 (95% CI: 0.79–1.06)		
Response rate	41%	12%
CR	2%	1%
PR	38%	12%
SD	33%	46%
PD	17%	32%
TTP, mo	8.9	3.7
HR for TTP = 0.60 (95% CI: 0.51–0.71)		

mOS = median overall survival; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; TTP = time to progression.

Kudo M, et al. *Lancet*. 2018;391:1163-1173.

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Therapeutic Options in HCC

Systemic Therapies: Second-Line and Subsequent

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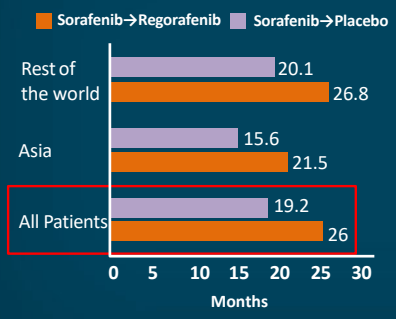
Sequential Therapy Prolongs Survival

Exploratory analysis of time (months) from start of sorafenib to death on RESORCE

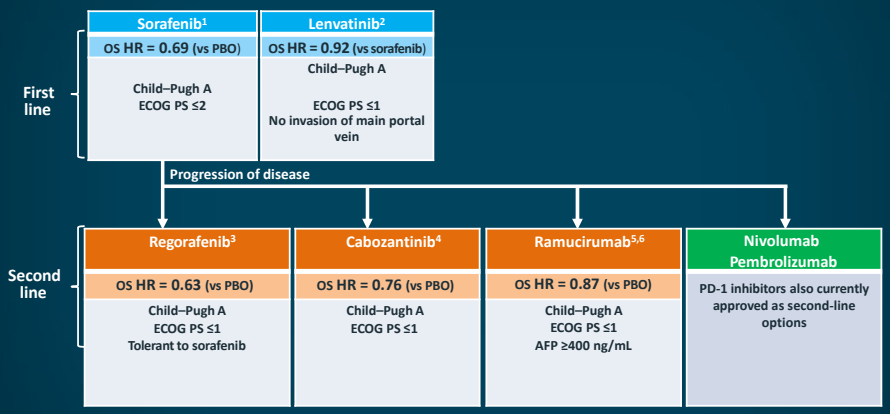


Survival	Sorafenib-regorafenib (n-379)	Sorafenib-placebo (n=194)
12 months	82%	76%
24 months	53%	42%
36 months	31%	20%
48 months	19%	12%
60 months	16%	3%
72 months	10%	3%

Finn RS, et al. *J Hepatology*. 2018;69(2):353-358.

31

Several Options Exist as Second-Line Therapy for Advanced HCC

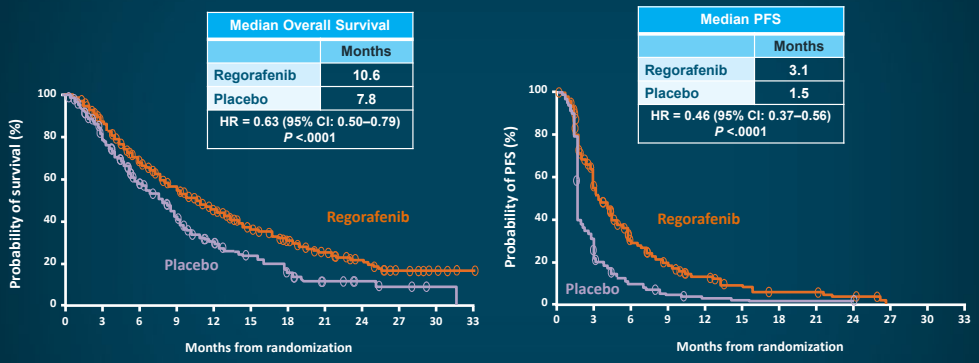


PBO = placebo; EHS = extrahepatic spread.

1. Llovet JM, et al. *N Engl J Med*. 2008;359:378-390. 2. Kudo M, et al. *Lancet*. 2018;391:1163-1173. 3. Bruix J, et at. *Lancet*. 2017;389:56-66. 4. Abou-Alfa GK, et al. *N Engl J Med*. 2018;379:54-63. 5. Zhu AX, et al. *Lancet Oncol*. 2015;16:859-870. 6. Zhu AX, et al. *Lancet Oncol*. 2019;20:282-296.

32

RESORCE: Survival with Regorafenib

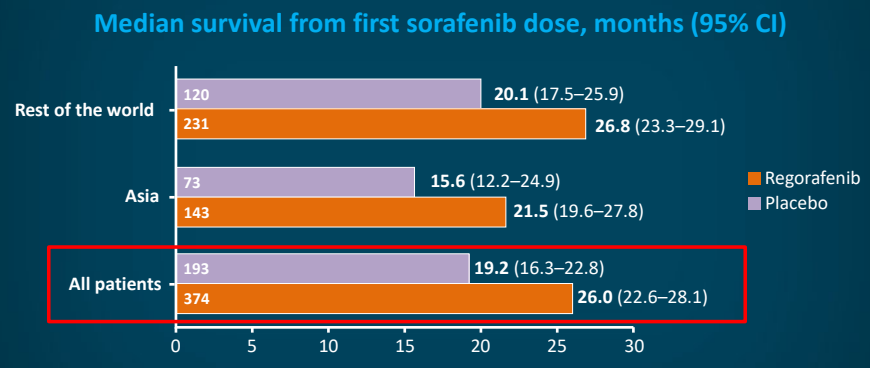


PFS = progression-free survival.

Bruix J, et at. *Lancet*. 2017;389:56-66.

33

RESORCE: Exploratory Analysis of Time from Sorafenib Start to Death

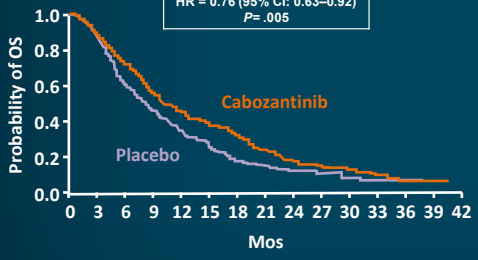


Finn RS, et al. *J Hepatology*. 2018;69:353-358.

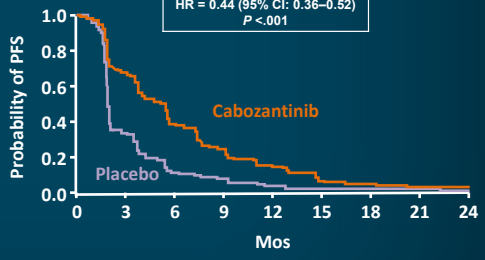
34

CELESTIAL: Survival with Cabozantinib

Median Overall Survival	
	Months
Cabozantinib	10.2
Placebo	8.0
HR = 0.76 (95% CI: 0.63–0.92) *P* = .005	



Median PFS	
	Months
Cabozantinib	5.2
Placebo	1.9
HR = 0.44 (95% CI: 0.36–0.52) *P* <.001	



Abou-Alfa GK, et al. *N Engl J Med*. 2018;379:54-63.

35

CELESTIAL: Analysis of Outcomes in Patients for Whom Sorafenib Was Only Prior Systemic Therapy

70% (495 of 707) randomized patients received sorafenib as the only prior systemic therapy (70% in the cabozantinib arm; 69% in the placebo arm)

Outcome	Prior Sorafenib Only, Overall		Prior Sorafenib Only, Duration (Mos)					
			<3 mo		3 to <6 mo		≥6 mo	
	CABO n = 331	PBO n = 164	CABO n = 89	PBO n = 47	CABO n = 98	PBO n = 43	CABO n = 143	PBO n = 74
Median OS, mo	11.3	7.2	8.9	6.9	11.5	6.5	12.3	9.2
HR (95% CI)	0.70 (0.55–0.88)		0.72 (0.47–1.10)		0.65 (0.43–1.00)		0.82 (0.58–1.16)	
Median PFS, mo	5.5	1.9	3.8	1.8	5.4	1.9	5.7	1.9
HR (95% CI)	0.40 (0.32–0.50)		0.35 (0.23–0.52)		0.37 (0.25–0.56)		0.48 (0.35–0.67)	

CABO = cabozantinib.

Kelley RK, et al. *J Clin Oncol*. 2018;36(15_suppl): Abstract 4088.

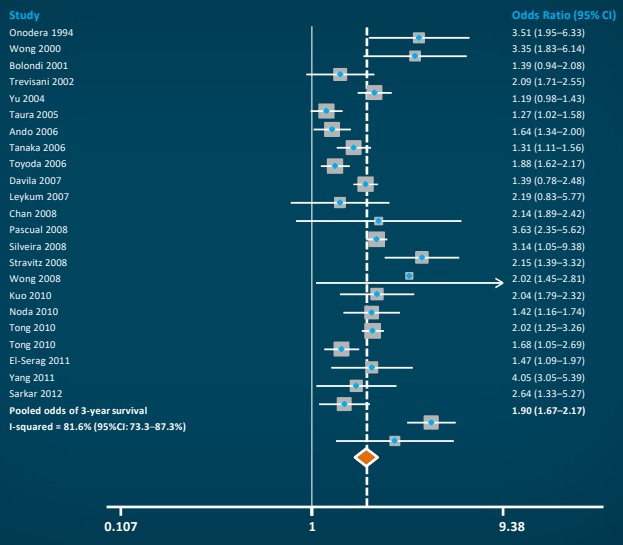
36

Biomarkers and Surveillance in HCC

Use in Guiding Second-line Treatment

37

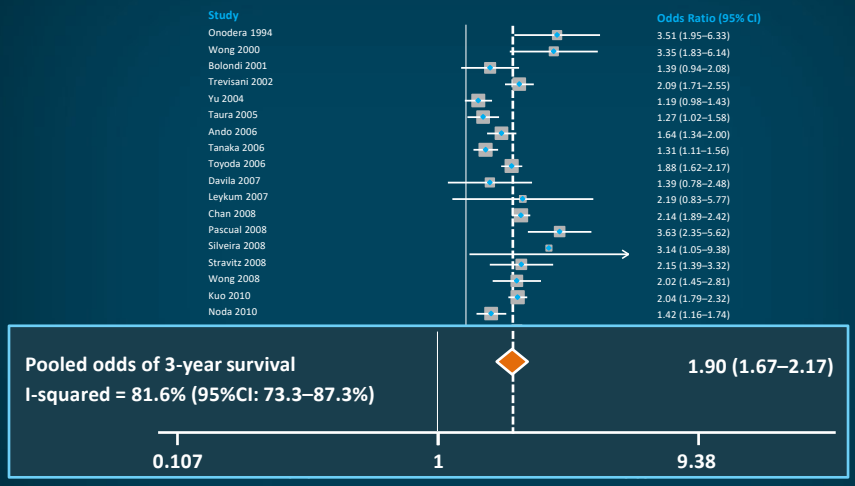
Surveillance Associated With Survival Benefit



Singal AG, et al. *PLoS Med.* 2014;11:e1001624. (Complete references for the studies cited in the table are available in Singal et al.)

38

Surveillance Associated With Survival Benefit



Singal AG, et al. *PLoS Med.* 2014;11:e1001624. (Complete references for the studies cited in the table are available in Singal et al.)

39

Cost-effectiveness of HCC Surveillance in HCV Patients With F3 versus F4 Fibrosis

Fibrosis Status	HCC incidence	ICER Semiannual Surveillance	ICER Annual Surveillance
Cirrhosis	1.39	48,729	37,806
F3 fibrosis*	0.16	Dominated	569,032
FIB-4 >3.25	2.16	40,689	32,701
FIB-41.45–3.25	0.45	124,229	81,346
FIB-4 <1.45	0.34	188,157	111,667

*No cirrhosis.

ICER = incremental cost-effectiveness ratio; F3 = advanced fibrosis; F4 = compensated cirrhosis; FIB-4 = Fibrosis-4 index.

Farhang Zangneh H, et al. *Clin Gastroenterol Hepatol*. 2019;17:1840–1849.e16.

40

Biomarker Panel May Improve Early HCC Detection: GALAD

- **GALAD**: **G**ender, **A**ge, AFP-**L**3, **A**FP, and **D**CP
- Performance evaluated in multi-national cohort study of 6834 patients (2430 HCC, 4404 CLD)

Variable	Sensitivity	Specificity	Correctly classified
UK cohort (all)	91.6%	89.7%	90.6%
UK cohort (Milan)	80.2%	89.7%	87.9%
Japan cohort (all)	70.5%	95.8%	87.2%
Japan cohort (Milan)	60.6%	95.8%	87.7%
Germany cohort (all)	87.6%	88.6%	88.3%
Germany cohort (unifocal <5cm)	67.4%	88.6%	87.5%

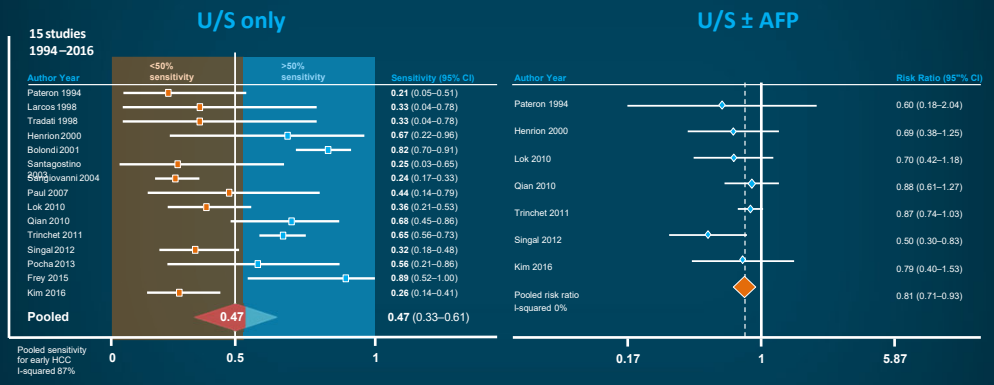
No difference in GALAD performance by cirrhosis etiology, SVR, or HBV treatment

DCP = des-gamma-carboxyprothrombin; CLD = chronic liver disease; SVR = sustained viral response.

Berhane S, et al. *Clin Gastroenterol Hepatol*. 2016;14:875-886.e6.

41

Ultrasound Has Poor Sensitivity for Early HCC Detection if Used in Isolation but Appears to Be of Benefit in Combination with AFP



In early stage HCC, sensitivity is 63% (95% CI: 48%–75%) for ultrasound with AFP and 45% (95% CI: 30%–62%) for ultrasound alone (*P*= .002)

Tzartzeva K, et al. *Gastroenterology*. 2018;154:1706-1718.e1. (Complete references for the studies cited in the table are available in Tzartzeva et al.)

42

Faculty script: The following animation illustrates the role of alpha-fetoprotein—AFP—in immune escape in the development of HCC.

43

INSERT Whiteboard 2: AFP and Immune Escape
(script provided in slide notes)

44

Use of HCC Biomarkers for Prognosis

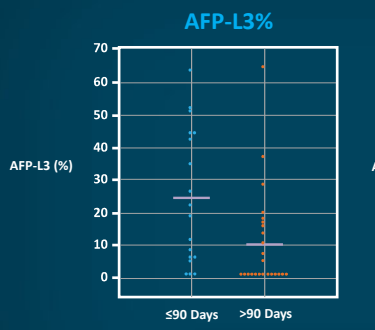
Once HCC is diagnosed, the proposed utility of AFP-L3% (plus AFP) and DCP includes:

- Predicting clinical course
- Presence of vascular invasion
- Risk of developing metastases
- Level of dedifferentiation of HCC tumor
- Mortality risk

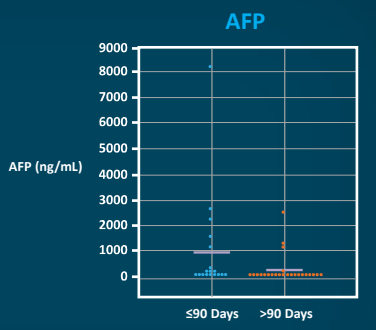
AFP-L3% = lens culinaris agglutinin-reactive fraction of alpha-fetoprotein.

45

Tumor Doubling Time
Higher AFP-L3%, More Rapid Progression in Size



AFP-L3%	Tumor Doubling Time ≤90 Days	>90 Days
Average	24.4	10.1
SD	20.8	15.4
P= .0066* (≤90 days vs >90 days)		



AFP ng/mL	Tumor Doubling Time ≤90 Days	>90 Days
Average	944.3	237.4
SD	1967.0	581.3
P= .0600 (≤90 days vs >90 days)		

**P*-value: Mann-Whitney U Test

Satomura S. *Gastroenterol*. 2005;128(4 Suppl 2):A761. Abstract M1665. https://www.gastrojournal.org/article/S0016-5085(05)00640-2/pdf. Accessed January 26, 2020. Sterling RK, et al. *Am J Gastroenterol*. 2007;102:2196-2205.

46

Current Biomarkers and Risk of Microvascular Invasion

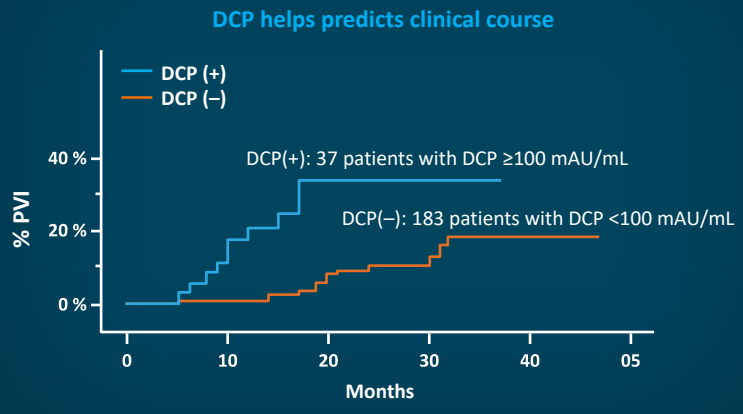
Independent predictors of microvascular invasion include:

- Tumor size (<2, 2–4, >4 cm)
  - Odds ratio: 3.4 (95% CI: 1.5–4.1)
- Preoperative DCP levels (<100, 100–500, >500 mAU/mL)
  - Odds ratio: 2.2 (95% CI: 1.1–2.4)
- Tumor grade (3-grade system)
  - Odds ratio: 2.2 (95% CI: 1.1–3.7)

Shirabe K, et al. *J Surg Oncol*. 2007;95:235-240.

47

Future Development of Portal Venous Invasion (PVI) of HCC in Relation to Serum DCP Level at Diagnosis



Koike Y, et al. *Cancer*. 2001;91:561-569.

48

Current HCC Biomarkers and Risk of Portal Vein Invasion

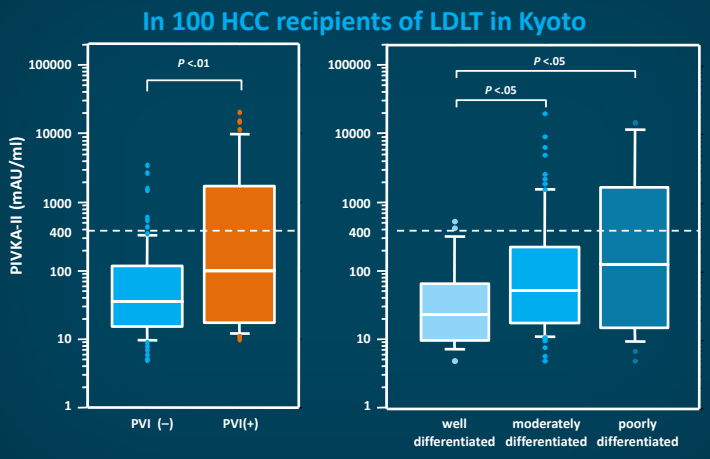
- AFP-L3% ≥15%
  - –RR: 2.459 (95% CI: 1.005–6.017; *P*= .0487)
- DCP ≥100 mAU/mL
  - –RR: 3.019 (95% CI: 1.077–8.464; *P*= .0357)
- Number of HCC tumors ≥2
  - –RR: 4.912 (95% CI: 1.619–14.905; *P*= .0049)

RR = relative risk.

Hagiwara S, et al. *J Gastroenterol*. 2006;41:1214-1219.

49

DCP* and Pathological Variables of HCC



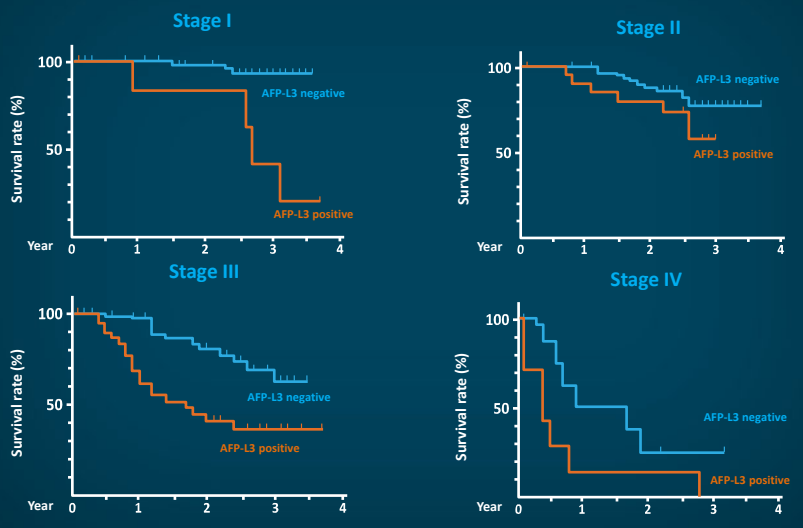
*For DCP, 1 mAU/mL = 0.092ng/mL.

PIVKA-II = Protein Induced by Vitamin K Absence or Antagonist-II.

Courtesy of Hiroto Egawa.

50

Survival Rate with Respect to HCC Stage and AFP-L3% Prior to Therapy



Courtesy of Hiroto Egawa.

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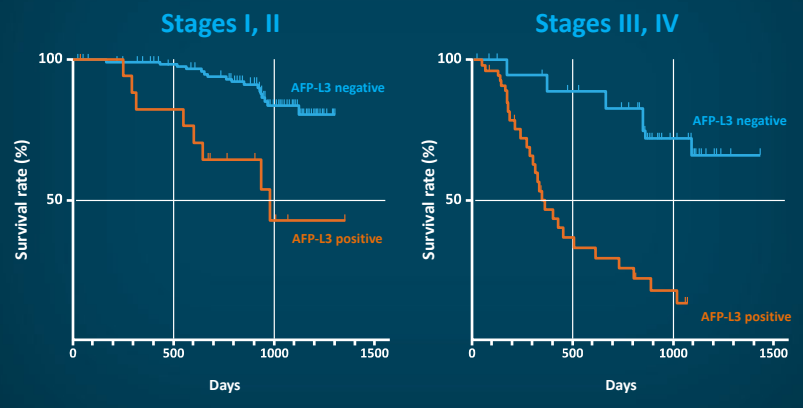
Survival Rate with Respect to HCC Stage and AFP-L3% After Therapies



Courtesy of Hiroto Egawa.

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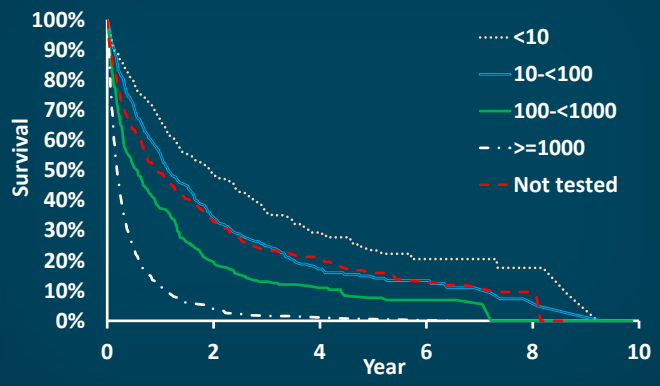
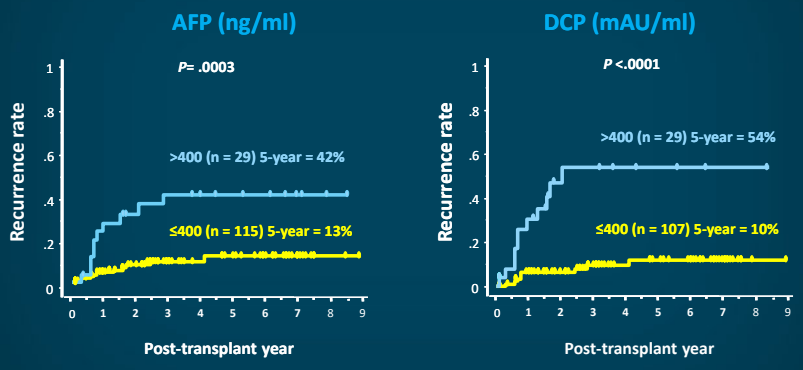
Survival of Patients with HCC Stratified by Serum AFP Levels



Tyson GL, et al. *Clin Gastroenterol Hepatol*. 2011;9(11):989-994.

53

Preoperative Tumor Markers AFP and DCP and Risk of Recurrence After LDLT



Courtesy of Hiroto Egawa.

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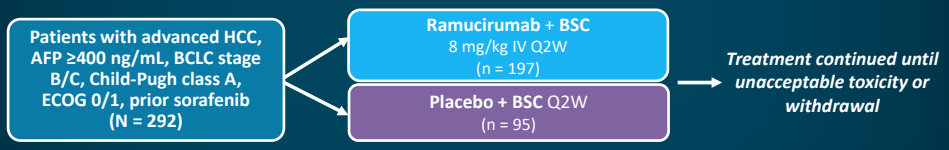
REACH-2: Ramucirumab for Patients With Previously Treated HCC and Higher AFP

- Randomized, double-blind, multicenter phase 3 trial[1]
  - **Ramucirumab: anti-VEGFR2 monoclonal antibody**
  - REACH trial: patients with PD on sorafenib were randomly assigned to ramucirumab vs placebo.
    Although the primary endpoint of OS was not met, a prespecified population of patients with baseline
    AFP ≥400 ng/mL and Child-Pugh class A demonstrated a significant OS advantage[2]



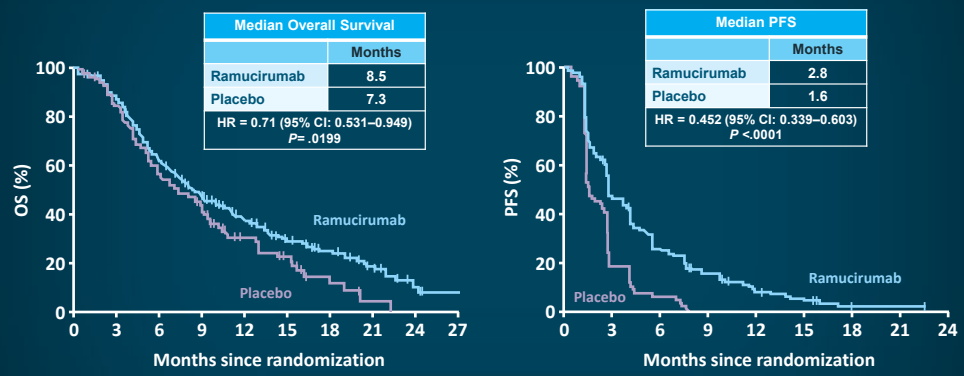
- Primary endpoint: OS; secondary endpoints: PFS, ORR, time to radiographic progression, time to FHSI-8 score decline, time to ECOG PS decline[1]

IV = intravenous; Q2W = every 2 weeks; ORR = Objective/overall response rate; FHSI-8 = Functional Assessment of Cancer Therapy Hepatobiliary Symptom Index 8.

1. Zhu AX, et al. *Lancet Oncol*. 2019;20:282-296. 2. Zhu AX, et al. *Lancet Oncol*. 2015;16:859-870.

55

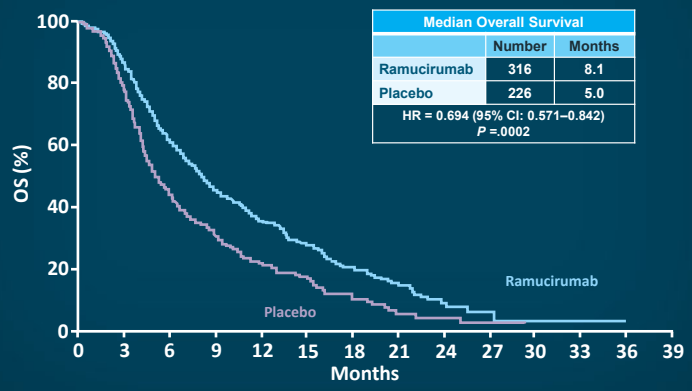
REACH-2: Survival



Zhu AX, et al. *Lancet Oncol*. 2019;20:282-296.

56

Pooled Overall Survival: REACH-2/REACH
(AFP ≥400 ng/mL)



Zhu. AX, et al. *Lancet Oncol*. 2019;20:282-296.

57

Therapeutic Options in HCC

Systemic Therapies: Immune Checkpoint Inhibitors as Second-line Therapy

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Immune Checkpoint Inhibitor Therapy for HCC

- Immune checkpoint inhibitor therapy against PD-1 has shown activity in advanced HCC
  - However, we have 2 phase 3 trials with clinical benefit but not meeting primary endpoints with statistical significance
  - Considerations related to negative phase 3 trials include:
    - Statistics and design
    - Median survival versus "tail of the curve"
    - OS not an ideal endpoint in first line
    - Single-agent activity not sufficient
- Moving forward…
  - Biomarkers needed
  - Expand list of immune targets
  - Smart combinations
  - Leverage biology
  - Cell therapy

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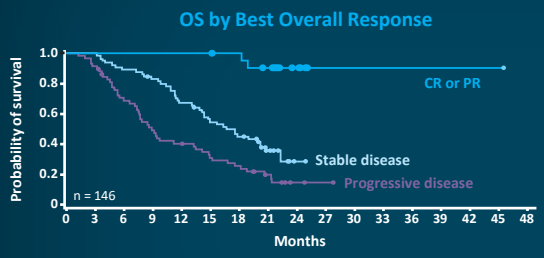
Checkmate 040: OS Analyzed by Best Overall Response or Change in Size of Target Lesion With Nivolumab



Median OS by Best Overall Response		
	Number	Months (95% CI)
CR or PR	22	NR (NE–NE)
SD	65	16.7 (13.8–20.2)
PD	59	8.9 (7.3–13.4)

OS (95% CI), %	CR/PR (n = 22)	SD (n = 65)	PD (n = 59)
12 months	100 (100–100)	67 (55–77)	41 (28–53)
18 months	100 (100–100)	45 (33–57)	26 (15–38)

Median OS = 15.1 months (95% CI: 13.2–18.8) in overall analysis population (N = 154)

El-Khoueiry AB, et al. *J Clin Oncol*. 2018;36(4 suppl): Abstract 475.

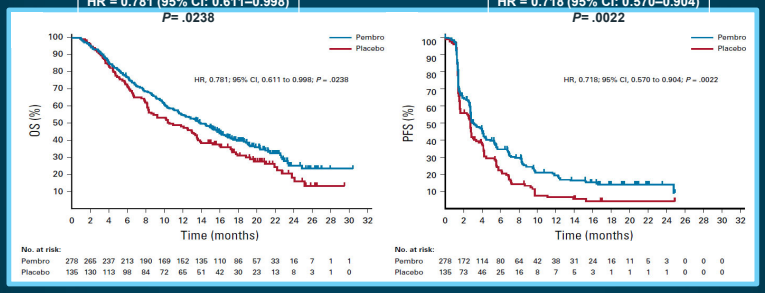
60

KEYNOTE-240: Survival With Pembrolizumab

- Failed to reach prespecified level of statistical significance for OS and PFS

Median Overall Survival	
	Months
Pembrolizumab	13.9
Placebo	10.6
HR = 0.781 (95% CI: 0.611–0.998)	
P= .0238	

Median PFS	
	Months
Pembrolizumab	3.0
Placebo	2.8
HR = 0.718 (95% CI: 0.570–0.904)	
P= .0022	



- ORR was significantly higher with pembrolizumab vs placebo (18.3% vs 4.4%, *P*= 0.00007), median DoR was 13.8 mos with pembrolizumab

Finn RS, et al. *J Clin Oncol*. 2020;38:193-202. Finn RS, et al. *J Clin Oncol*. 2019;37(15 suppl): Abstract 4004.

61

KEYNOTE-240: Influence of Post-Treatment Anticancer Medications on OS (Sensitivity Analyses)

Analysis	Median OS, mos (95% CI)		HR (95% CI)	*P*-value
	Pembrolizumab (n = 278)	Placebo (n = 135)		
ITT	13.9 (11.6–16.0)	10.6 (8.3–13.5)	0.78 (0.61–1.00)	.0238
IPCW	13.9 (11.1–17.2)	9.3 (7.9–13.5)	0.67 (0.48–0.92)	.0066
2-stage model without recensoring	10.6 (9.5–11.6)	7.6 (6.2–9.3)	0.68 (0.53–0.86)	.0011

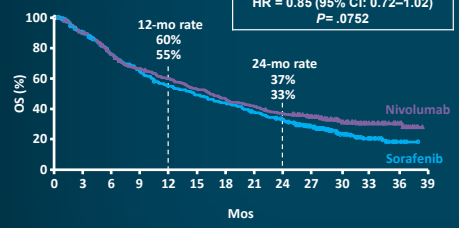
ITT = intention to treat; IPCW = inverse probability of censoring weighting method.

Finn RS, et al. *J Clin Oncol*. 2020;38:193-202. Finn RS, et al. *Ann Oncol*. 2019;30(suppl 4): Abstract O-027.

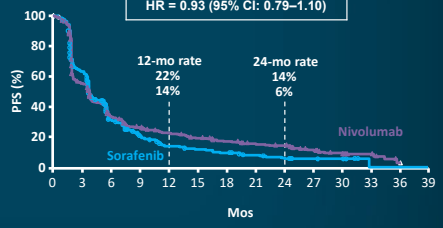
62

CheckMate 459: OS and PFS for Nivolumab vs Sorafenib

Median Overall Survival	
	Months (95% CI)
Nivolumab	16.4 (13.9–18.4)
Sorafenib	14.7 (11.9–17.2)
HR = 0.85 (95% CI: 0.72–1.02) *P*= .0752	



Median OFS	
	Months (95% CI)
Nivolumab	3.7 (3.1–3.9)
Sorafenib	3.8 (3.7–4.5)
HR = 0.93 (95% CI: 0.79–1.10)	



- The predefined threshold of statistical significance for OS with nivolumab was not met, although nivolumab demonstrated clinical benefit
- ORR: nivolumab, 15%; sorafenib, 7%

Yau T, et al. *Ann Oncol.* 2019;30(suppl 5): Abstract LBA38_PR.

63

Investigational Approaches

64

Phase 3 Trials Assessing Immune Checkpoint Inhibitors for First-Line Systemic Therapy

Study	Agent(s)	Findings
Checkmate-459[1]	Nivolumab vs sorafenib	Predefined threshold of statistical significance for OS not met
IMbrave150[2–4]	Atezolizumab + bevacizumab vs sorafenib	Atezolizumab + bevacizumab increased PFS in phase 1b study vs atezolizumab monotherapy and OS and PFS compared with sorafenib in phase 3 study
LEAP-002[5]	Lenvatinib + pembrolizumab vs lenvatinib	Ongoing
HIMALAYA[6]	Durvalumab + tremelimumab vs sorafenib	Ongoing
COSMIC-312[7]	Cabozantinib ± atezolizumab vs sorafenib	Ongoing
CheckMate 9DW[8]	Nivolumab + ipilimumab vs sorafenib or lenvatinib	Ongoing

1. Yau T, et al. *Ann Oncol.* 2019;30(suppl 5): Abstract LBA38_PR. 2. Lee M, et al. *Ann Oncol*. 2019;30(suppl 5): Abstract LBA39. 3. Cheng AL, et al. *Ann Oncol.* 2019;30(suppl 9): Abstract LBA3. 4. IMbrave150 media release (www.roche.com/dam/jcr:9c7034ef-63d6-4529-9be8-afdff2cdb4b0/en/191021_mr_imbrave150_en.pdf). 5. Llovet JM, et al. *J Clin Oncol.* 2019;37 (suppl 15): Abstract TPS4152. 6. Abou-Alfa GK, et al. *J Clin Oncol.* 2019;36(15 suppl): Abstract TPS4144. 7. Kelley RK, et al. *J Clin Oncol.* 2019;37(15 suppl): Abstract TPS4157. 8. NCT04039607.

65

Revisiting the Case

66

Case: Mrs. C Revisited

- Mrs. C is a 57-year-old woman with a history of alcohol abuse who presents to ED with RUQ pain for few weeks
- CT in ED → cirrhosis and liver mass
- MRI → infiltrative HCC with right PV enhancing thrombus
- ED physician asks if you would like to start anticoagulation
- Child's A—bilirubin = 1.0, albumin = 3.2, INR = 1.0

- Patient was initiated on lenvatinib
- CT scan at 4 months showed stable disease
- CT scan at 8 months showed new liver masses

What would you do to determine the next course of treatment?

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Which Treatment Would You Recommend for Mrs. C?

1. Sorafenib
2. Cabozantinib
3. Nivolumab
4. Pembrolizumab
5. Ramucirumab
6. Regorafenib
7. Other

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Team-Based Care in HCC

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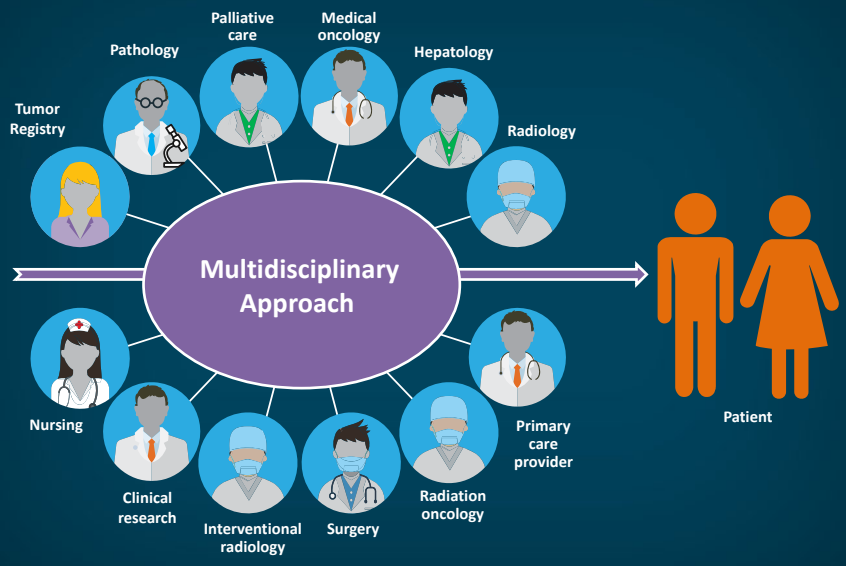
Multidisciplinary Approach to the Patient With HCC



70

Shared Decision-Making (SDM) in Oncology

Collaborative Care

- Interconnection of essential players
- Patient-centered
- Communication is **KEY**

Adapted from: NQP Playbook: Shared Decision Making in Healthcare, 2018.

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Concepts to Consider in SDM

Stage of Cancer
Available treatments
Treatment type (chemo vs immunotherapy)
Sociodemographic characteristics
Preference for involvement (high- vs low-input patients)
Goals of treatment(s)
Complex data delivered in a patient-centered manner
Maintain and update knowledge

SDM Goals:

- Ensure each patient understands the risks and benefits of their options
- Incorporate patient preference(s) and goals to reach clinical decisions

Hawley ST, Jagsi R. *JAMA Oncol*. 2015;1:58-59. Frerichs W, et al. *PLoS One*. 2016;11:e0149789.

72

Barriers to SDM

SDM obstacles include:

- Patients who prefer provider-based decisions
- Lack of encouragement to improve sub-optimal participation in SDM
- Ineffective communication in respect to health literacy/numeracy
- Disregard for the impact SDM has on outcomes

Schrager SB, et al. *Fam Pract Manag.* 2017;24:5-10. AHRQ. Strategy 6I: Shared decision-making (www.ahrq.gov/cahps/quality-improvement/improvement-guide/6-strategies-for-improving/communication/strategy6i-shared-decisionmaking.html). Accessed January 20, 2020. Hawley ST, Jagsi R. *JAMA Oncol.* 2015;1:58-59

73

Patient Education

Educational discussion	• Review mechanisms of treatment(s) • Utilize educational material and decision aids if available
Assess communication	• Assess patient's ability to communicate symptoms • Language barrier • Access to phone/computer
Provide tools	• Provide treatment-plan details • Utilize tools to remember dosing schedules and appointments • Encourage patients to keep treatment diary
Reminders	• Medications for anticipated adverse events • Loperamide, acetaminophen, diphenhydramine

*Wallet card part of Oncology Nursing Society (ONS) publications.

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Conclusions

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NCCN Recommended Therapies for HCC

Therapies	Disease Characteristics
First-Line Systemic Therapy	
Preferred	
Sorafenib	• Child-Pugh Class A (category 1) or B7
Lenvatinib	• Child-Pugh Class A only
Other recommended	
Systemic chemotherapy	• Category 2B
Subsequent-Line Therapy	
Regorafenib	• Child-Pugh Class A only (category 1)
Cabozantinib	• Child-Pugh Class A only (category 1)
Ramucirumab	• AFP ≥400 ng/mL only (category 1)
Nivolumab	• Child-Pugh Class A or B7
Sorafenib	• Child-Pugh Class A or B7 (after first-line lenvatinib)
Pembrolizumab	• Child-Pugh Class A only (category 2B)

National Comprehensive Cancer Network (NCCN). Hepatobiliary cancers. Version 4.2019. December 20, 2019. (www.nccn.org/professionals/physician_gls/PDF/hepatobiliary.pdf).

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HCC Practice Points

- Sorafenib and lenvatinib are approved as first-line therapies for the management of HCC
- Regorafenib, cabozantinib, ramucirumab, nivolumab, sorafenib, and pembrolizumab are approved as second-line therapies for the management of HCC
- Factors to take into account when selecting subsequent-line therapy include:
  - Prior lines of therapy
  - AFP levels
- Single-agent immune checkpoint inhibitors have not met endpoints in phase 3 studies to date; however, combinations are showing promise
- Strategies incorporating team-based care and shared decision-making improve outcomes in patients with HCC

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Q&A

Thank You!

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Additional Backup Slides

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Surveillance for HCC

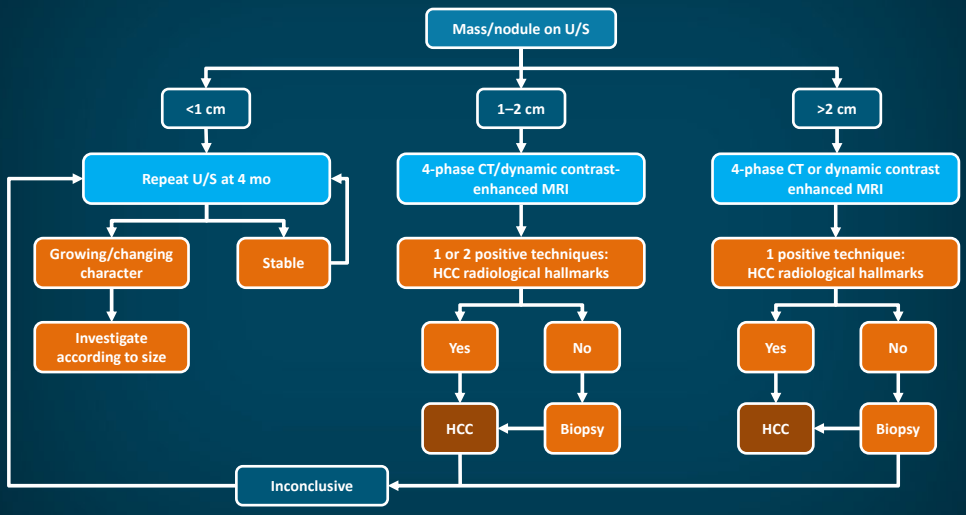
Population Group	Threshold Incidence for Efficacy of Surveillance (>0.25 LYG: % per year)	Incidence of HCC
Surveillance benefit		
Asian male HBV carriers over age 40	0.2	0.4–0.6% per year
Asian female HBV carriers over age 50	0.2	0.3–0.6% per year
HBV carrier with family history of HCC	0.2	Incidence higher than without family history
African and/or North American blacks with HBV	0.2	HCC occurs at a younger age
HBV carriers with cirrhosis	0.2–1.5	3–8% per year
HCV cirrhosis	1.5	3–5% per year
Stage 4 PBC	1.5	3–5% per year
Genetic hemochromatosis and cirrhosis	1.5	Unknown, but probably >1.5% per year
Alpha-1 antitrypsin deficiency and cirrhosis	1.5	Unknown, but probably >1.5% per year
Other cirrhosis		Unknown
Surveillance benefit uncertain		
HBV carriers younger than age 40 (males) or 50 (females)	0.2	<0.2% per year
HCV and stage 3 fibrosis	1.5	<1.5% per year
NAFLD without cirrhosis	1.5	<1.5% per year

LYG = life-years gained; PBC = primary biliary cholangitis.

Marrero JA, et al. *Hepatology*. 2018;68:723-750.

80

Suspicious Liver Nodule on U/S



EASL-EORTC. *J Hepatol*. 2012;56:908-943.

81

Child-Pugh Scoring System

Clinical and Lab Criteria	Points*		
	1	2	3
Encephalopathy	None	Mild-to-moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild-to-moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time Seconds prolonged International normalized ratio	 <4 <1.7	 4–6 1.7–2.3	 >6 >2.3
***Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)**			
Class A = 5 to 6 points (least severe liver disease)			
Class B = 7 to 9 points (moderately severe liver disease)			
Class C = 10 to 15 points (most severe liver disease)			

Modified from Pugh RN, et al. *Br J Surg*. 1973;60:646-649.

82

Surgical Resection vs Transplantation

Surgical Resection

- 5-year survival ~60–70%
- 5-year recurrence ~ 50%
  - Salvage OLT possible
- Requires compensated cirrhosis
- Readily available
- Immediate treatment

Liver Transplantation

- 5-year survival ~65%
- 5-year recurrence ~10%
- Cure for cirrhosis, so best for decompensated cirrhosis
- Shortage of organs
- Drop out on wait list

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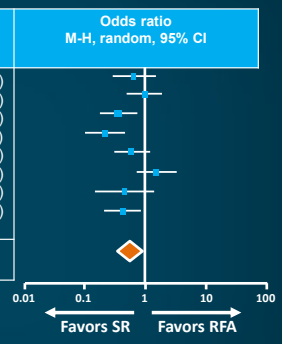
Surgical Resection vs Ablative Therapy

Study or Subgroup	RFA Events	RFA Total	SR Events	SR Total	Weight	Odds ratio M-H, random, 95% CI
Desiderio 2013	16	44	24	52	11.5%	0.67 (0.29–1.52)
Hiraoka 2008	62	105	35	59	13.7%	0.99 (0.52–1.89)
Huang 2010	49	88	55	71	13.0%	0.37 (0.18–0.73)
Imai 2012	49	82	88	101	12.6%	0.22 (0.11–0.46)
Nishikawa 2011	102	162	51	69	14.0%	0.60 (0.32–1.12)
Peng 2012	51	71	46	74	13.0%	1.55 (0.77–3.12)
Wong 2012	26	36	39	46	8.8%	0.47 (0.16–1.38)
Yun 2011	222	255	202	215	13.4%	0.43 (0.22–0.85)
Total (95% CI)		**843**		**687**	**100.0%**	**0.57 (0.37–0.88)**
Total events	**577**		**540**			

Heterogeneity. Tau² = 0.25; Chi² = 19.72, df = 7 (*P*= .006); I²= 64%
Test for overall effect: Z = 2.56 (*P*= 0.01)



Surgical resection and local ablation had similar outcomes for HCC ≤3 cm

RFA = radio-frequency ablation; SR = surgical resection; M-H = Mantel-Haenszel.

Yi HM, et al. *Int J Clin Exp Med.* 2014;7:3150-3163. (Complete references for the studies cited in the table are available in Yi et al.)

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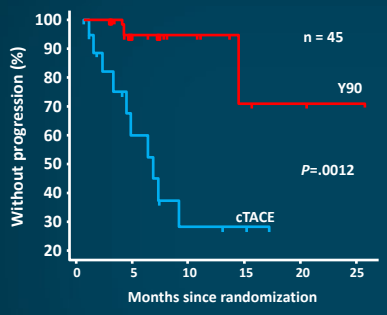
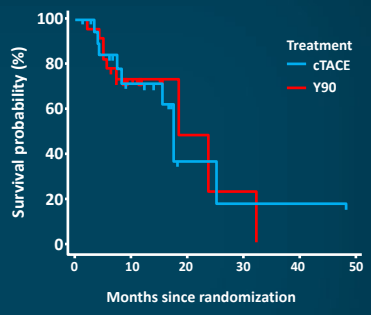
TARE Has Increasing Role in Intermediate HCC



TTP = >26 vs 6.8 months
HR = 0.12 (95%CI: 0.03–0.56)
P= .007



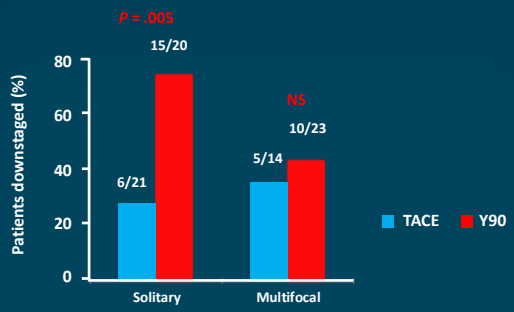
Median survival = 17.7 vs 18.6 months
P= .99

TARE = transarterial radioembolization; cTACE = conventional TACE; Y90 = yttrium-90 radioembolization.

Salem R, et al. *Gastroenterology*. 2016;151:1155-1163.e2.

85

Downstaging with TACE vs TARE

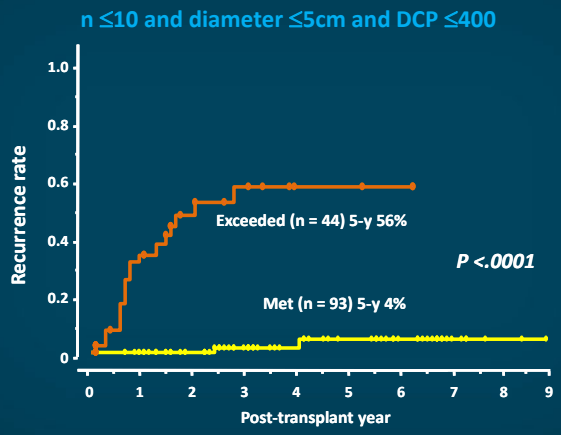


	TACE	TARE	*P*-value
Median pre- and post-tx index tumor size, cm	5.7→4.3	5.6→3.4	<.001
Downstaged T3→T2, N (%)	11 (31)	25 (58)	.023
Progression rate at 1 y	32%	15%	<.005

Lewandowski RJ, et al. *Am J Transplant*. 2009;9:1920-1928.

86

Kyoto Criteria and Recurrence Rate



Courtesy of Hiroto Egawa.

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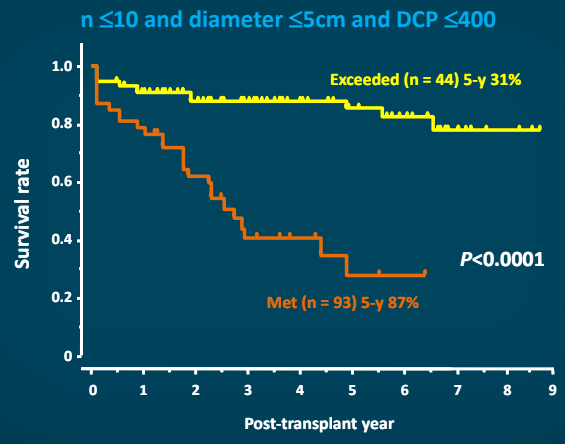
Kyoto Criteria and Patient Survival Rate



Courtesy of Hiroto Egawa.

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KEYNOTE-240: Most Common TRAEs

TRAEs in ≥ 5% of Patients, n (%)	Pembrolizumab (n = 278)		Placebo (n = 135)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Pruritus	37 (13.3)	1 (0.4)	6 (4.5)	0
Fatigue	28 (10.0)	3 (1.1)	19 (14.2)	1 (0.7)
AST increased	25 (9.0)	15 (5.4)	5 (3.7)	2 (1.5)
Diarrhea	23 (8.2)	2 (0.7)	8 (6.0)	1 (0.7)
Rash	23 (8.2)	1 (0.4)	3 (2.2)	0
ALT increased	22 (7.9)	10 (3.6)	4 (3.0)	2 (1.5)
Decreased appetite	16 (5.7)	3 (1.1)	9 (6.7)	0
Nausea	15 (5.4)	0	8 (6.0)	0
Asthenia	9 (3.2)	0	9 (6.7)	0
Arthralgia	7 (2.5)	0	8 (6.0)	0

TRAE = treatment-related adverse event; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

Finn RS, et al. *J Clin Oncol.* 2020;38:193-202 (supplement).

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CheckMate 459: Subsequent Therapy

Treatment, n (%)	Nivolumab (n = 371)	Sorafenib (n = 372)
Any subsequent therapy	181 (49)	195 (53)
Systemic therapy	140 (38)	170 (46)
Tyrosine kinase inhibitor	132 (36)	86 (23)
Chemotherapy	15 (4)	25 (7)
Investigational agent	10 (3)	40 (11)
Immuno-oncology agent	7 (2)	76 (20)
Other	2 (1)	4 ()
Local therapy	63 (17)	61(16)
Radiotherapy	52 (14)	38 (10)
Surgery	10 (3)	14 (4)

Yau T, et al. *Ann Oncol.* 2019;30(suppl 5): Abstract LBA38_PR.

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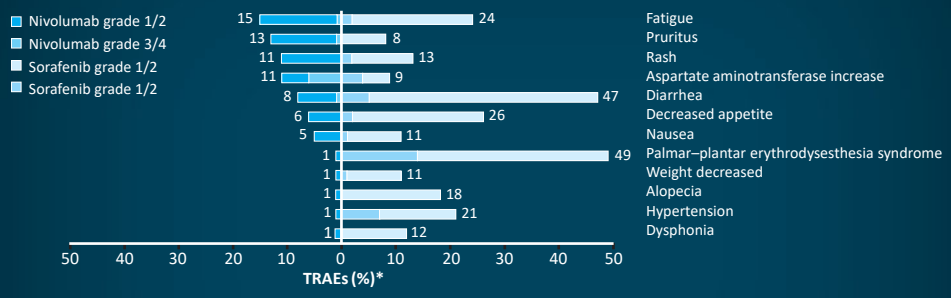
CheckMate 459: Summary of Treatment-Related Adverse Events*



Nivolumab demonstrated an improved safety profile compared with sorafenib, with fewer grade 3/4 TRAEs and TRAEs leading to discontinuation vs sorafenib.

- Grade 3/4 TRAEs: nivolumab = 22%; sorafenib = 49%

***Occurring in >10% of patients in either treatment arm.**

Yau T, et al. *Ann Oncol.* 2019;30(suppl 5): Abstract LBA38_PR.

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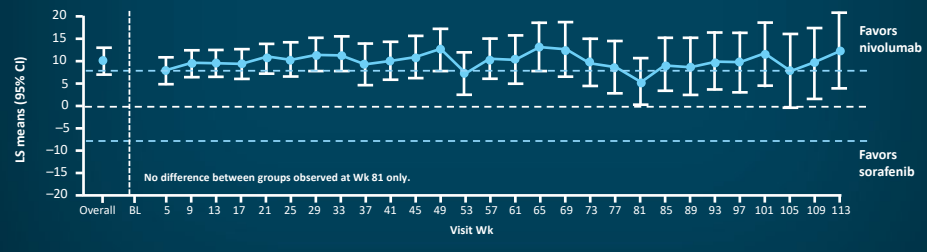
Effect of Nivolumab vs Sorafenib on HRQoL

- FACT-Hep is a disease-specific questionnaire that measures the effects of HCC and its treatment on HRQoL
- Completion rates were ≥70% at all time points through week 113
- Clinically meaningful differences between treatment arms were observed for FACT-Hep total in favor of nivolumab through week 113



FACT-Hep = Functional Assessment in Cancer Therapy, hepatobiliary subscale; LS = least squares.

Yau T, et al. *Ann Oncol.* 2019;30(suppl 5): Abstract LBA38_PR.

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Approved First-line Systemic Therapy Options for HCC

Agent	FDA Indication	Key Trial	Population
Sorafenib	Unresectable HCC	SHARP	Child-Pugh A or B7
Lenvatinib	First-line treatment of patients with unresectable HCC	REFLECT	Child-Pugh A

Sorafenib (Nexavar®) prescribing information, 2018 (http://labeling.bayerhealthcare.com/html/products/pi/Nexavar_PI.pdf). Lenvatinib (Lenvima®) prescribing information, 2019 (www.lenvima.com/pdfs/prescribing-information.pdf). Both accessed January 21, 2020.

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HCC Treatment Landscape: Second-line Options

FDA Approved for Patients Previously Treated With Sorafenib		
Agent	**Key Trials**	**Population**
Cabozantinib[1]	CELESTIAL	Child-Pugh A
Nivolumab[2]	CheckMate-40	Child-Pugh A/B7
Pembrolizumab[3,4]	KEYNOTE-224, -240	Child-Pugh A
Ramucirumab[5]	REACH-2	Child-Pugh A, AFP ≥400 ng/mL
Regorafenib[6]	RESORCE	Child-Pugh A, tolerated first-line sorafenib

1. Abou-Alfa GK, et al. *N Engl J Med*. 2018;379:54-63. 2. El-Khoueiry AB, et al. *Lancet*. 2017;389:2492-2502. 3. Zhu AX, et al. *Lancet Oncol*. 2018;19:940-952. 4. Finn RS, et al. *J Clin Oncol*. 2019;37(suppl): Abstract 4004. 5. Zhu AX, et al. *Lancet Oncol*. 2019;20:282-296. 6. Bruix J, et al. *Lancet*. 2017;389:56-66.

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Molecular Therapies Tested for HCC in Phase 3 Trials

Adjuvant: Prevent Recurrences	Early HCC: Improve RFA	Intermediate HCC: Improve TACE	Advanced HCC: First Line	Advanced HCC: Second Line
Sorafenib vs placebo	RFA vs RFA-LTLD	TACE ± sorafenib	Sorafenib vs placebo	Brivanib vs placebo
Retinoids vs placebo		TACE ± brivanib	Sorafenib ± erlotinib	Everolimus vs placebo
			Sorafenib vs brivanib	Ramucirumab vs placebo*
			Sorafenib vs sunitinib	Regorafenib vs placebo
			Sorafenib vs linifanib	Tivantinib vs placebo
			Sorafenib ± doxorubicin	Cabozantinib vs placebo
			Lenvatinib vs sorafenib	Pembrolizumab vs placebo
			Sorafenib vs Y90	
			Sorafenib vs nivolumab	

Negative study. Positive study. Study in which noninferiority shown.

*Positive in patients with HCC and AFP ≥400 ng/mL.

RFA = radiofrequency ablation; LTLD = lyso-thermosensitive liposomal doxorubicin.

Modified from Kudo M. *Cancers (Basel)*. 2018;10:E412. Zhu AX, et al. *Lancet Oncol*. 2019;20:282-296.

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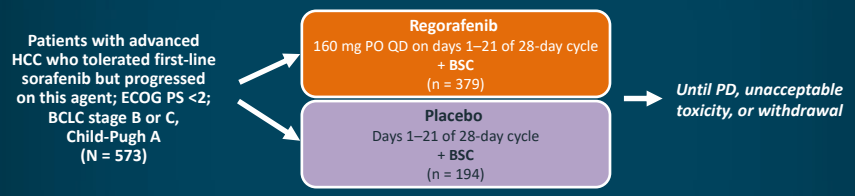
RESORCE: Second-line Regorafenib vs Placebo in HCC With Progression

- Multicenter, randomized, double-blind phase 3 trial



- Primary endpoint: OS
- Secondary endpoints: PFS, TTP, ORR, and disease control rate

PO = orally; QD = daily.

Bruix J, et al. *Lancet*. 2017;389:56-66.

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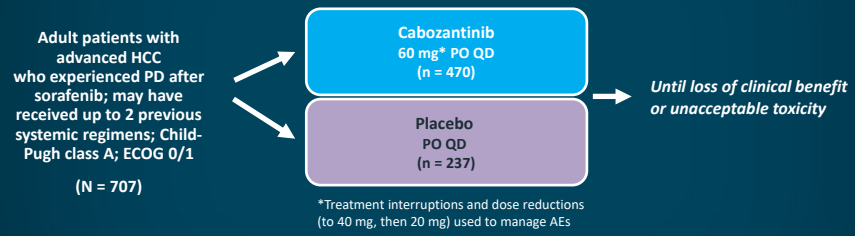
CELESTIAL: Cabozantinib for Previously Treated HCC

- Randomized, double-blind phase 3 trial
  - **Cabozantinib**: multitargeted TKI; inhibits MET, VEGFR1-3, AXL, RET, ROS1, TYRO3, MER, KIT, TRKB, FLT-3, and TIE-2



- Primary endpoint: OS
- Secondary endpoints: PFS, ORR

TKI = tyrosine kinase inhibitor.

Abou-Alfa GK, et al. *N Engl J Med*. 2018;379:54-63. Cabozantinib (Cabometyx®) prescribing information 2019 (https://cabometyx.com/downloads/CABOMETYXUSPI.pdf). Accessed January 21, 2020.

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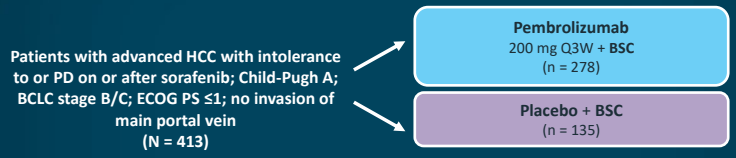
KEYNOTE-240: Pembrolizumab for Patients With Previously Treated HCC

- Randomized, double-blind phase 3 trial



- Coprimary endpoints: PFS* and OS
  - Efficacy boundaries: PFS at first interim cutoff, *P*= .002 (primary analysis for PFS); OS at final analysis cutoff, *P*= .0174
- Secondary endpoints: ORR,* DoR, DCR, TTP, safety

***Secondary response outcomes centrally reviewed.**

Finn RS, et al. *J Clin Oncol*. 2020;38:193-202. NCT02702401 (www.clinicaltrials.gov/ct2/show/NCT02702401?term=NCT02702401&draw=2&rank=1). Accessed January 21, 2020.

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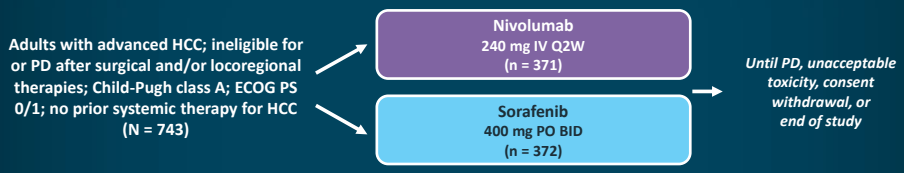
CheckMate 459: Nivolumab vs Sorafenib as First-Line Therapy for Advanced HCC

International, open-label, randomized phase 3 trial (minimum follow-up: 22.8 mos)



- Primary endpoint: OS
  - Predefined threshold for statistical significance: HR of 0.84 (*P*= .0419)
- Secondary endpoints: PFS, ORR, association between PD-L1 expression, and safety

Yau T, et al. Ann Oncol. 2019;30(suppl 5): Abstract LBA38_PR. NCT02576509 (https://clinicaltrials.gov/ct2/show/NCT02576509?term=NCT02576509&rank=1). Accessed January 21, 2020.

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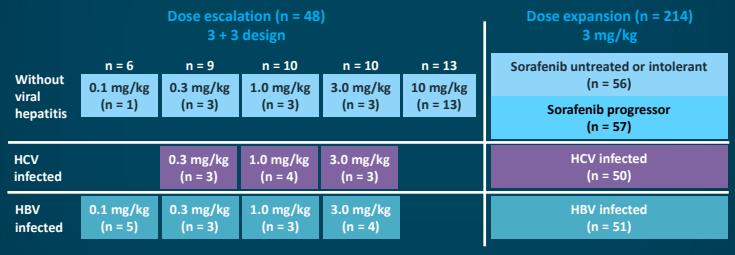
CheckMate 040: Nivolumab for Advanced HCC

- Open-label phase 1/2 trial in adults with advanced HCC with Child-Pugh class A/B7 (escalation phase) and class A (expansion phase) and ECOG PS <1; previous sorafenib treatment allowed



- Primary endpoints: safety and tolerability (escalation) and ORR (expansion)

El-Khoueiry AB, et al. *Lancet*. 2017;389:2492-2502.

100

KEYNOTE-224: Pembrolizumab for Patients With Previously Treated HCC

Nonrandomized, open-label, multicenter phase 2 trial of pembrolizumab 200 mg Q3W for patients with advanced HCC who had PD with or intolerance to sorafenib, Child-Pugh A, BCLC stage B or C, ECOG PS 0/1, life expectancy >3 months, N = 104

Response	n (%)
ORR (CR + PR)*	18 (17) [95% CI: 11–26]
Disease control (CR + PR + SD)	64 (62) [95% CI: 52–71]
Best overall response	
• CR	1 (1)
• PR	17 (16)
• SD	46 (44)
• PD	34 (33)
No assessment	6 (6)

*Primary endpoint.

Zhu AX, et al. *Lancet Oncol*. 2018;19:940-952.

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RESORCE: Select Treatment-Emergent AEs

AEs, %	Regorafenib (n = 379)			Placebo (n = 194)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
HFSR	**53**	**13**	**N/A**	**8**	**1**	**N/A**
Diarrhea	41	3	0	15	0	0
Fatigue	40	9	N/A	32	5	N/A
Hypertension	**31**	**15**	**<1**	**6**	**5**	**0**
Anorexia	31	3	0	15	2	0
Bilirubin increased	29	10	1	18	8	3
Abdominal pain	28	3	N/A	22	4	N/A
AST increased	25	10	1	20	10	2
Ascites	16	4	0	16	6	0
Anemia	16	4	1	11	5	1
Hypophosphatemia	**10**	**8**	**1**	**2**	**2**	**0**

AE = adverse event; HFSR = hand-foot skin reaction; N/A = not applicable.

Bruix J, et al. *Lancet*. 2017;389:56-66.

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CELESTIAL: Select Treatment-Related AEs

AEs, %*	Cabozantinib (n = 467)			Placebo (n = 237)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Diarrhea	54	10	<1	19	2	0
Decreased appetite	48	6	0	18	<1	0
Palmar–plantar erythrodysesthesia	46	17	0	5	0	0
Fatigue	45	10	0	30	4	0
Nausea	31	2	0	18	2	0
Hypertension	29	16	<1	6	2	0
Vomiting	26	<1	0	12	3	0
Increase in AST	22	11	1	11	6	<1
Asthenia	22	7	<1	8	2	0

*Occurring in ≥20% of patients in either treatment group.

Abou-Alfa GK, et al. *N Engl J Med*. 2018;379:54-63.

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REACH-2: Treatment-Related AEs

Treatment-Emergent AEs (≥10% of either group)				
AE, %	Ramucirumab (n = 197)		Placebo (n = 95)	
	Gr 1/2	Gr 3–5	Gr 1/2	Gr 3–5
Fatigue	24	4	14	3
Peripheral edema	24	2	14	0
Decreased appetite	22	2	19	1
Abdominal pain	18	2	11	2
Nausea	19	0	12	0
Diarrhea	16	0	14	1
Headache	14	0	4	1
Constipation	13	1	19	1
Insomnia	11	0	5	1
Pyrexia	10	0	3	0
Vomiting	10	0	7	0

Treatment-Emergent AEs of Special Interest				
AE, %	Ramucirumab (n = 197)		Placebo (n = 95)	
	Gr 1/2	Gr 3–5	Gr 1/2	Gr 3–5
Bleeding/ hemorrhage	19	6	9	3
Epistaxis	13	1	3	0
Hypertension	12	13	7	5
Proteinuria	18	2	4	0
Liver injury/ failure	21	18	14	16
Ascites	14	5	5	2

Zhu AX, et al. *Lancet Oncol*. 2019;20:282-296

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AFP Levels and Mortality in Patients With HCV-related HCC: Results

The 1-, 3-, and 5-year survival rates after HCC diagnosis progressively decreased with increasing serum AFP levels, *P*-value <.0001

AFP Level, ng/mL	Patients (%)	1-Year survival rate	3-Year survival rate	5-Year survival rate
<10	196(13)	67%	37%	24%
10 to <100	322(22)	56%	25%	15%
100 to <1000	238(16)	37%	13%	8%
≥1000	308(21)	12%	2%	1%
Not tested	416(28)	49%	24%	16%

Tyson GL, et al. *Clin Gastroenterol Hepatol*. 2011;9:989-994.

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AFP Levels and Mortality Risk in 1480 HCC Patients
Multivariate Cox Proportional Hazard Model

AFP at HCC diagnosis, ng/mL	Adjusted HR* (95% CI)	*P*-value
<10	Reference	
10 to <100	1.50 (1.22–1.83)	<0.0001
100 to <1000	2.23 (1.80–2.76)	<0.0001
≥1000	4.35 (3.54–5.36)	<0.0001
Not tested	1.53 (1.26–1.86)	<0.0001

Adjusted for age, sex, race/ethnicity, ascites, encephalopathy, MELD, HCC treatment.

MELD = model for end-stage liver disease.

Tyson GL, et al. *Clin Gastroenterol Hepatol*. 2011;9:989-994.

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The TAILOR Initiative: Rethinking the Role of Alpha-fetoprotein as a Prognostic Biomarker in the Management of Advanced Hepatocellular Carcinoma

TOOLKIT

Guidelines, Recommendations, and Articles

Resource	Web Address
American Cancer Society: Cancer Facts and Figures 2019.	https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf
Marrero JA, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American association for the study of liver diseases. *Hepatology*. 2018;68:723-750.	https://www.ncbi.nlm.nih.gov/pubmed/29624699
Fujiwara N, et al. Risk factors and prevention of hepatocellular carcinoma in the era of precision medicine. *J Hepatol*. 2018;68:526-549.	https://www.ncbi.nlm.nih.gov/pubmed/28989095
Llovet JM, et al. Molecular therapies and precision medicine for hepatocellular carcinoma. *Nat Rev Clin Oncol*. 2018;15:599-616.	https://www.ncbi.nlm.nih.gov/pubmed/30061739
Kudo M, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet*. 2018;391:1163-1173.	https://www.ncbi.nlm.nih.gov/pubmed/29433850
Finn RS, et al. Outcomes of sequential treatment with sorafenib followed by regorafenib for HCC: Additional analyses from the phase III RESORCE trial. *J Hepatol*. 2018;69:353-358.	https://www.ncbi.nlm.nih.gov/pubmed/29704513
Zhu AX, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2019;20:282-296.	https://www.ncbi.nlm.nih.gov/pubmed/30665869
Bouattour M, et al. Systemic Treatment for Advanced Hepatocellular Carcinoma. *Liver Cancer*. 2019;8:341-358.	https://www.karger.com/Article/FullText/496439

Resource	Web Address
Rai V, et al. Cellular and molecular targets for the immunotherapy of hepatocellular carcinoma. *Mol Cell Biochem*. 2018;437:13-36.	https://www.ncbi.nlm.nih.gov/pubmed/28593566
Desai J, et al. Systemic therapy for advanced hepatocellular carcinoma: an update. *J Gastrointest Oncol*. 2017;8:243–255.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5401854
El-Khoueiry A. The promise of immunotherapy in the treatment of hepatocellular carcinoma. *Am Soc Clin Oncol Educ Book*. 2017;37:311-317.	https://www.ncbi.nlm.nih.gov/pubmed/28561676

Selected Ongoing Clinical Trials

Resource	Web Address
A Global Study to Evaluate Transarterial Chemoembolization (TACE) in Combination With Durvalumab and Bevacizumab Therapy in Patients With Locoregional Hepatocellular Carcinoma (EMERALD-1) **NCT03778957**	https://clinicaltrials.gov/ct2/show/NCT03778957
Combination Chemoembolization and Stereotactic Body Radiation Therapy in Unresectable Hepatocellular Carcinoma **NCT02513199**	https://clinicaltrials.gov/ct2/show/NCT02513199
Abemaciclib and Nivolumab for Subjects With Hepatocellular Carcinoma **NCT03781960**	https://clinicaltrials.gov/ct2/show/NCT03781960
A Study of Tivozanib in Combination With Durvalumab in Subjects With Untreated Advanced Hepatocellular Carcinoma **NCT03970616**	https://clinicaltrials.gov/ct2/show/NCT03970616
A Study of Pembrolizumab and Bavituximab in Patients With Advanced Hepatocellular Carcinoma **NCT03519997**	https://clinicaltrials.gov/ct2/show/NCT03519997
A Study of Nivolumab in Combination With Ipilimumab in Participants With Advanced Hepatocellular Carcinoma (CheckMate 9DW) **NCT04039607**	https://clinicaltrials.gov/ct2/show/NCT04039607
A Study of Ramucirumab (LY3009806) Versus Placebo in Participants With Hepatocellular Carcinoma and Elevated Baseline Alpha-Fetoprotein (REACH-2) **NCT02435433**	https://clinicaltrials.gov/ct2/show/NCT02435433

Resources: Associations and Foundations

Resource	Address
American Association for Cancer Research (AACR)	http://www.aacr.org/Pages/Home.aspx
American Cancer Society (ACS)	https://www.cancer.org/
American Liver Foundation	https://liverfoundation.org/
American Society of Clinical Oncology (ASCO)	https://www.asco.org/
Hepatocellular Carcinoma Fact Sheet (Cancer.net; ASCO)	http://www.cancer.net/sites/cancer.net/files/asco_answers_liver.pdf
National Cancer Institute	https://www.cancer.gov/types/liver
National Organization for Rare Disorders (NORD)	https://rarediseases.org/rare-diseases/hepatocellular-carcinoma/