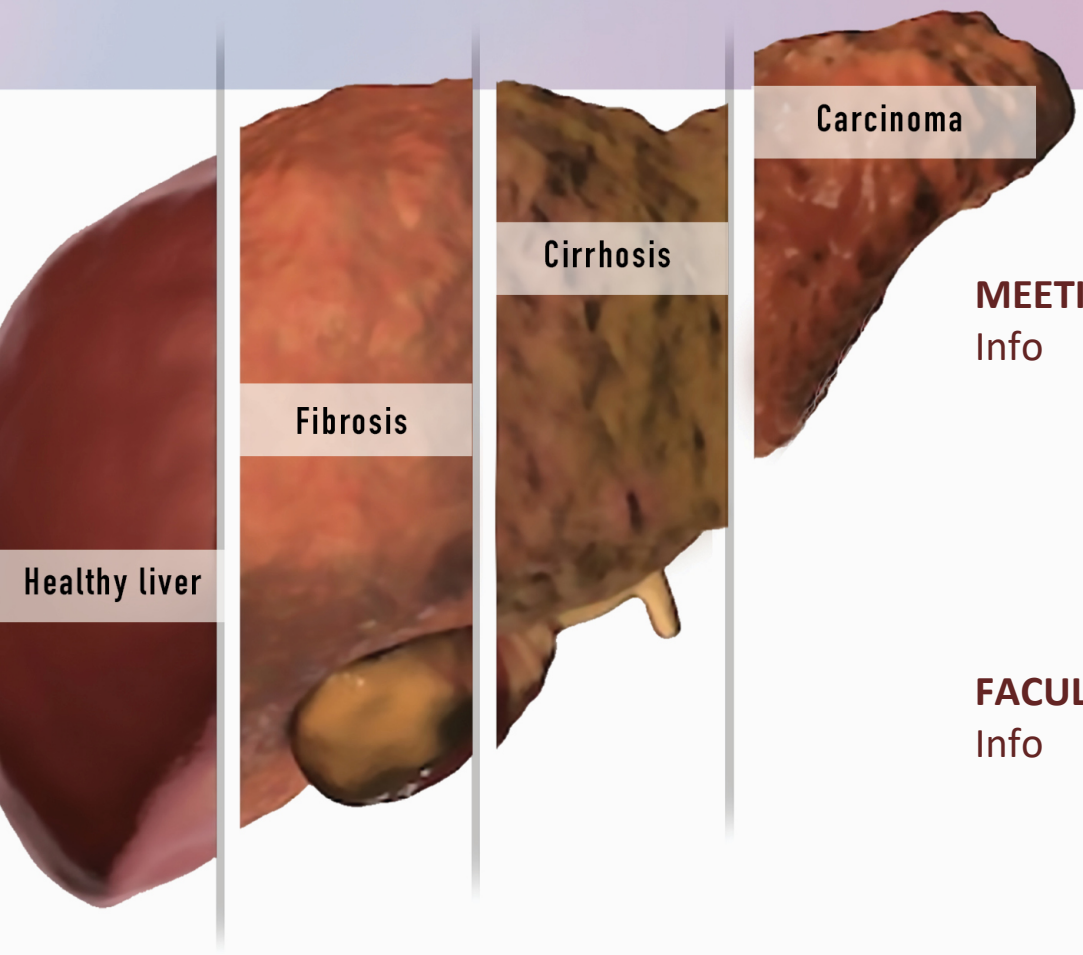
Rethinking the Role of Alpha-fetoprotein as a Prognostic Biomarker in the Management of ADVANCED HEPATOCELLULAR CARCINOMA



MEETING INFO
Info

FACULTY
Info

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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

FACULTY

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Michael Morse, MD Professor of Medicine Professor in the Department of Surgery Member of the Duke Cancer Institute Duke Cancer Institute Durham, NC	**Thomas Cartwright, MD** Co-Chairman, US Oncology GI Research Associate Professor of Medicine University of Central Florida College of Medicine Ocala, FL	**Stephen Leong, MD** Associate Professor University of Colorado Denver School of Medicine Division of Medical Oncology Aurora, CO
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TANIOS S. BEKAII-SAAB, MD Professor, Mayo Clinic College of Medicine and Science Program Co-Leader, Gastrointestinal Cancer, Mayo Clinic Cancer Center Consultant, Mayo Clinic Phoenix, AZ		

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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	Clinical Advisory Boards	Abbott, AbbVie, Merck, Arrowhead, Bayer, Dova Pharmaceuticals, Eiger, Enyo, Hatch BioFund, HepQuant, Intercept, Janssen, Medimmune
	Clinical Trials	eStudySite Advisor
	Data Safety Monitoring Board	Ionis and Eiger
	Medical Lead on Clinical Study FDA 1571 Application	Viking Therapeutics
Tanios S. Bekaii-Saab, MD	Research Funding	Boston Biomedical, Bayer, Amgen, Merck, Celgene, Lilly, Ipsen, Clovis, Seattle Genetics, Array Biopharma, Genentech, Abgenomics, Incyte, BMS
	Consulting (to institution)	Ipsen, Array Biopharma, Seattle Genetics, Bayer, Genentech, Incyte and Merck
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	Inventions/Patents	WO/2018/183488 and WO/2019/055687
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.
Paul Kunk, MD	No relationships to report	N/A
Stephen Leong, MD	Research Support	Bristol-Myers Squibb (BMS), Deciphera, Karyopharm
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	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

The content of this activity was independently peer reviewed.

The reviewer of this activity has nothing to disclose.

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2. Participate in the online activity.
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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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Medical Director, Hepatitis B Foundation

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San Diego, CA

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Disclosures

- Dr. Robert Gish reports the following disclosures:

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Clinical Trials	eStudySite Advisor
Data Safety Monitoring Board	Ionis and Eiger
Medical Lead on Clinical Study FDA 1571 Application	Viking Therapeutics

- During the course of this lecture, the faculty may mention the use of medications for both FDA-approved and non-approved indications.

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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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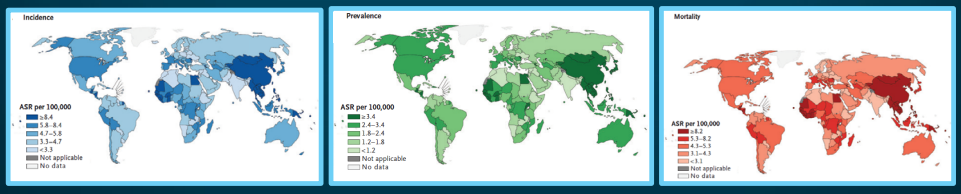
Hepatocellular Carcinoma

- 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.

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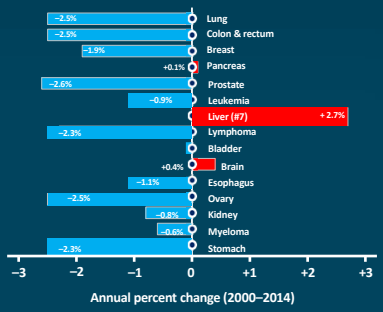
HCC Mortality in United States Is Increasing

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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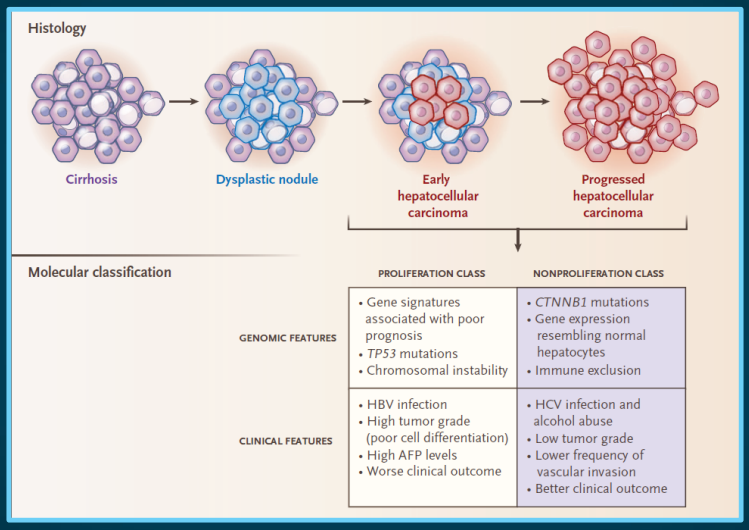
Evolution of Hepatocellular Carcinoma



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

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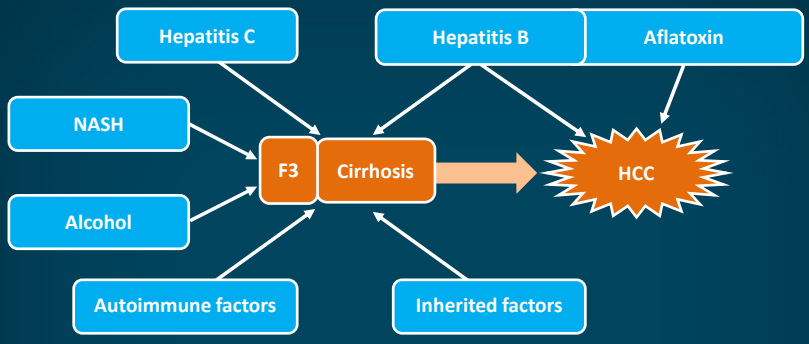
Risk Factors for the Development of HCC



- 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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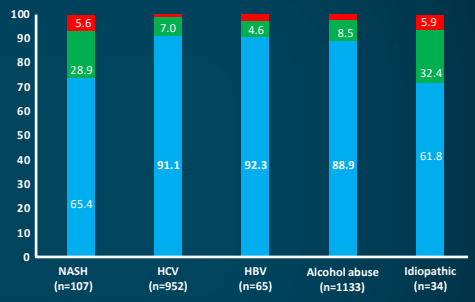
Why is the Incidence of HCC Rising in the US?

- 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

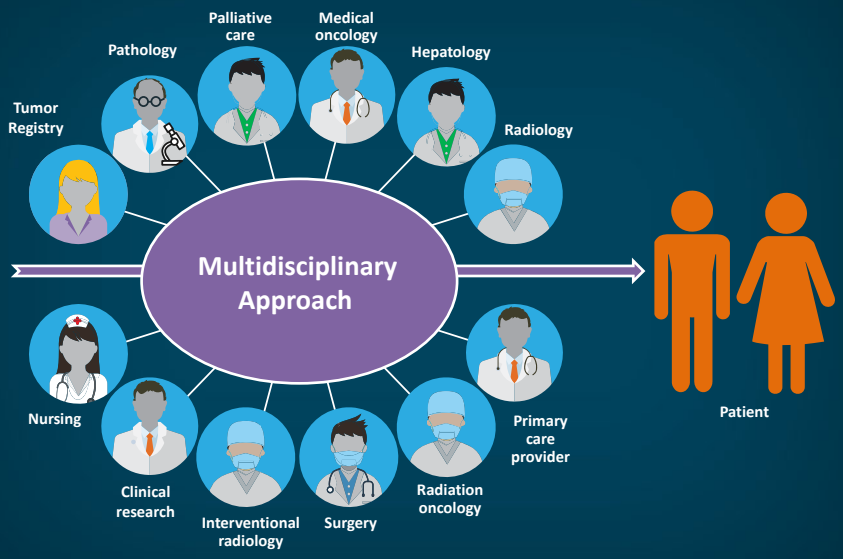
High probability non-cirrhotic: APRI <1; no features on imaging; NL albumin, plt, INR

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.

9

Multidisciplinary Approach to the Patient With HCC



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Pathogenesis of HCC

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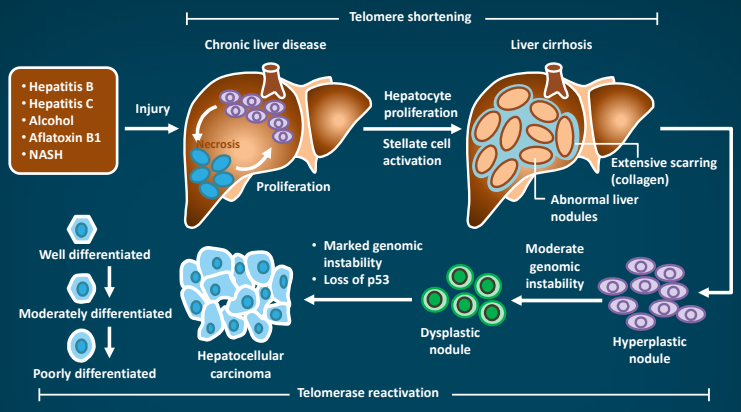
Pathogenesis of HCC



- 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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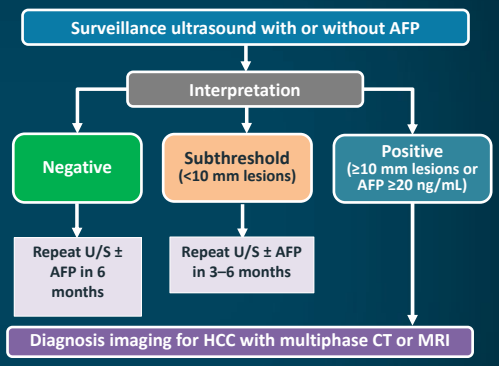
Surveillance of HCC*

- 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
- Consider use of AFP-L3% and DCP to calculate GALAD score



*Refer to treatment guidelines.

AFP = alpha-fetoprotein; U/S = ultrasound; CT = computed tomography (scan); MRI = magnetic resonance imaging, DCP = Des-gamma-carboxy prothrombin.

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

Li-RADS

- Arterial hypervascularization and venous washout
- Growth and capsule

Contrast 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
  - More sensitive and specific than contrast CT in head-to-head studies
- Disadvantages
  - Requires at least 30 minutes in the magnet (maybe shorter with updated MRI protocols)
  - Motion artifact (patient participation)
  - Claustrophobia
  - Cost

Li-RADS = Liver Reporting and Data System.

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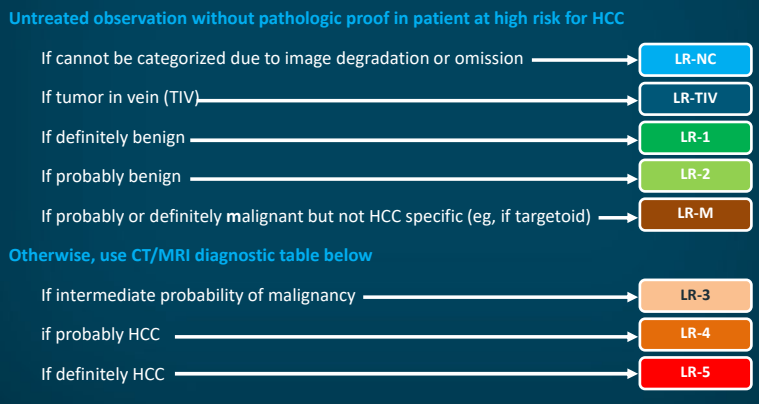
Contrast CT/MRI Li-RADS

- Li-RADS: *Liver Imaging Reporting and Data System*
- Designed to standardize contrast CT and MRI reporting/data in HCC
- Data validation of Li-RADS performed in patients with cirrhosis



American College of Radiology. LI-RADS (www.acr.org/Quality-Safety/Resources/LIRADS). LI-RADS 2018 Core (www.acr.org/-/media/ACR/Files/RADS/LI-RADS/LI-RADS-2018-Core.pdf?la=en). Accessed December 30, 2019.

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LI-RADS: CT/MRI Diagnostic Table

CT/MRI Diagnostic Table						
Arterial phase hyperenhancement (APHE)		**No APHE**		**APHE (not rim)**		
Observation size (mm)		**<20**	**≥20**	**<10**	**10–19**	**≥20**
Count major features: • "Washout" (not peripheral) • Enhancing "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**

Observations in the "diagonal" LR-4/LR-5 cell under APHE 10–19 are categorized based on one additional major feature:

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

If unsure about the presence of any major feature, characterize that feature as absent

LI-RADS 2018 Core (www.acr.org/-/media/ACR/Files/RADS/LI-RADS/LI-RADS-2018-Core.pdf?la=en).

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An Overview of Therapeutic Options in HCC

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

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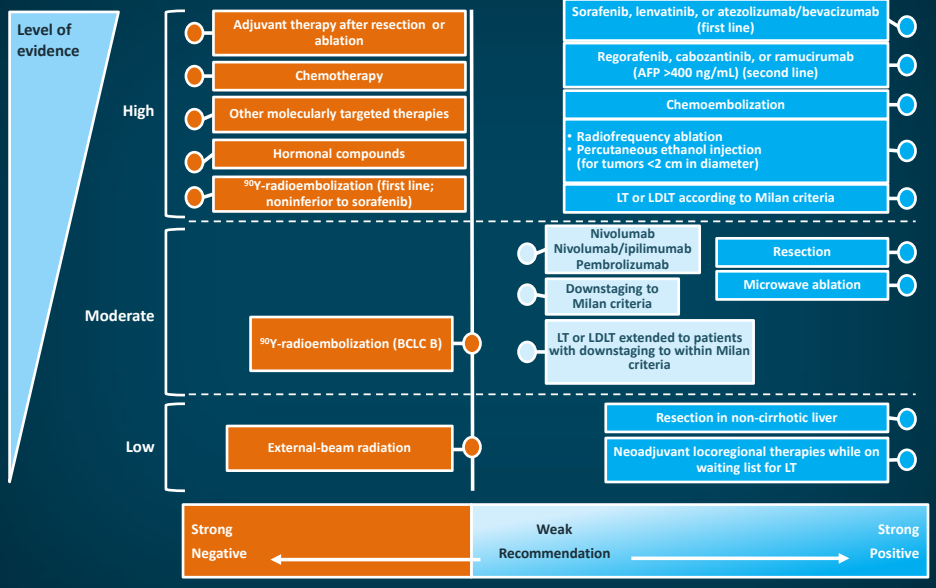
HCC Treatment Options and Level of Evidence



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

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

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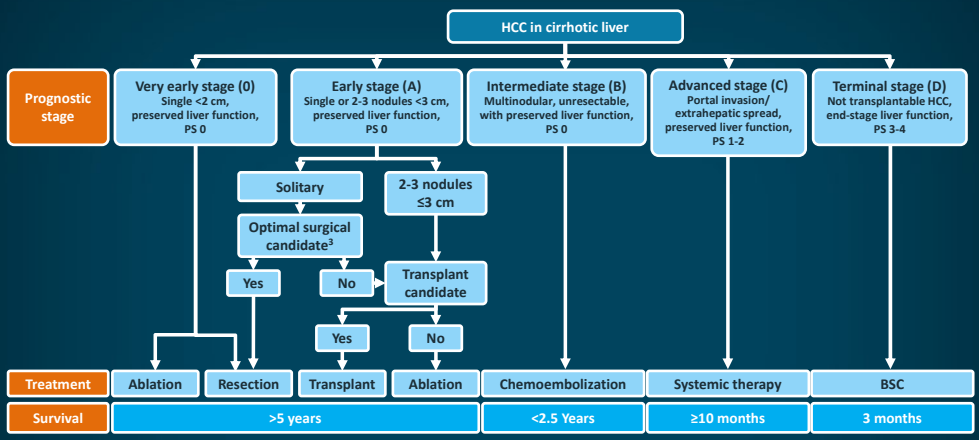
Modified BCLC Staging and Treatment (EASL)



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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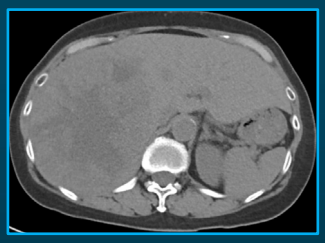
Case 1: Mrs. C

- 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
- AFP = 350 ng/mL

- 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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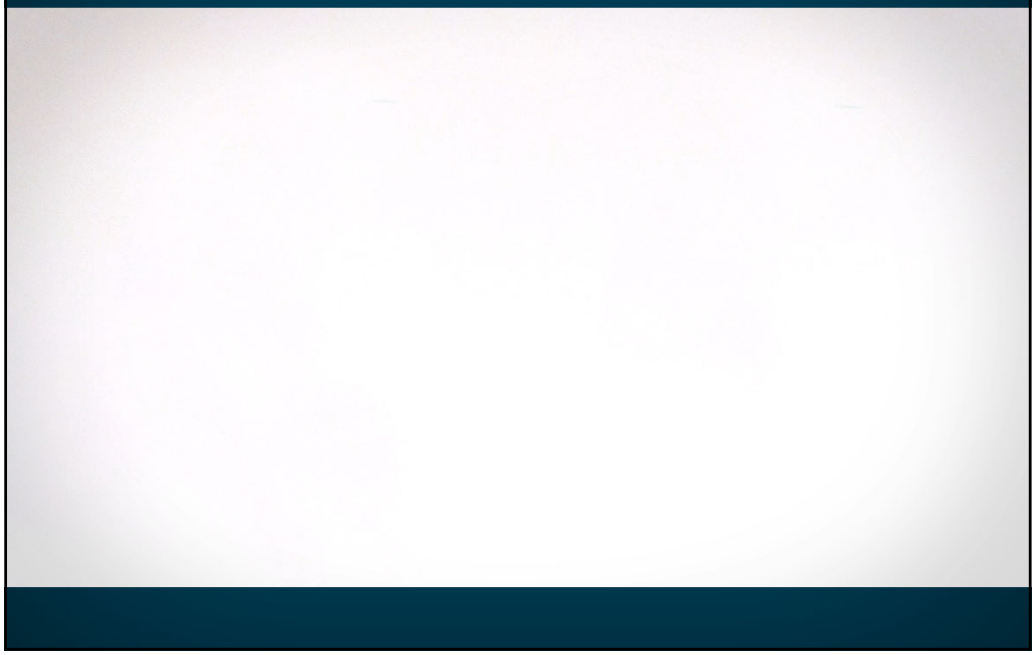
First- and Second-line Treatments for HCC
https://youtu.be/Sr0UdSBD3v0



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Therapeutic Options in HCC

Systemic Therapies: First-line

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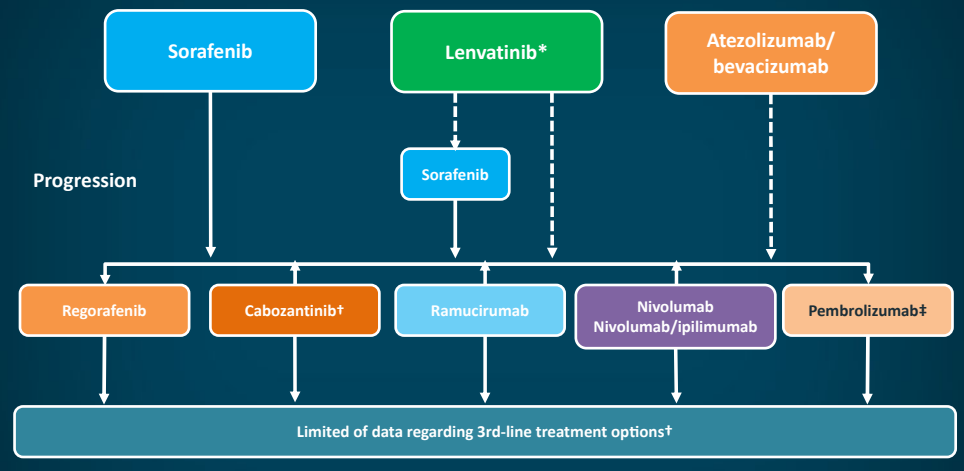
Current Treatment Landscape for Advanced HCC



*There are limited data to define optimal treatment for those who progress after lenvatinib or atezolizumab/bevacizumab; †Possible 3rd-line agent (cabozantinib), but there is limited 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 3 trial (KEYNOTE-240) did not demonstrate statistically significant improvement in overall survival and progression-free survival.

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

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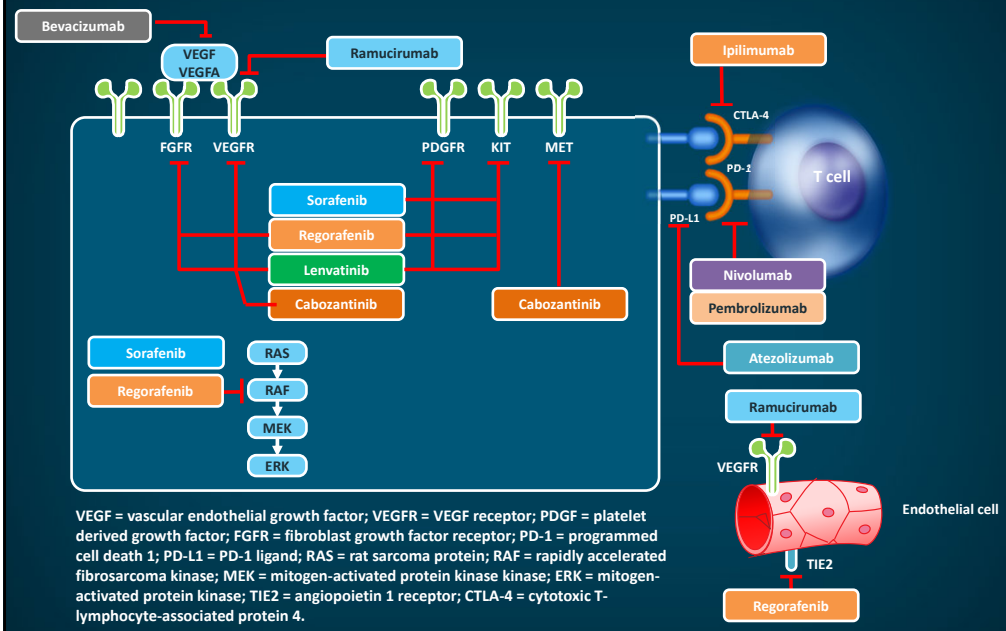
Targeted Therapies for Hepatocellular Carcinoma



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; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4.

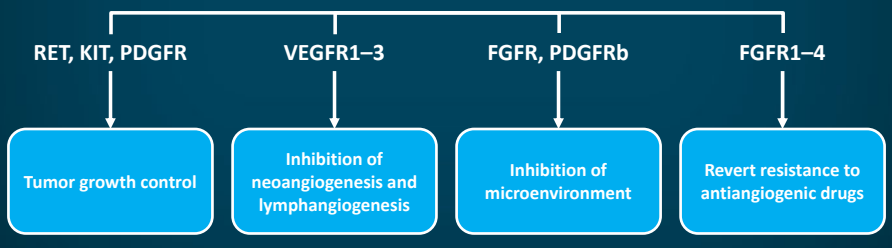
Modified from Llovet JM, et al. *Nat Rev Clin Oncol*. 2018;15:599-616.

29

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

Common Targets of Multikinase Inhibitors

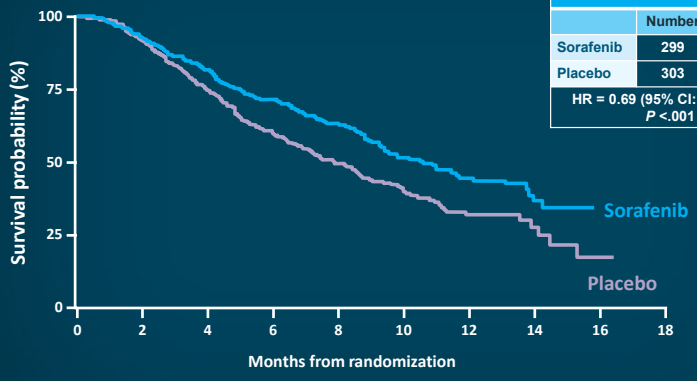


RET = rearranged during transfection tyrosine kinase receptor; KIT = a receptor tyrosine kinase; PDGFR = PDGF receptor.

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.

30

Sorafenib Improves Survival for Advanced HCC



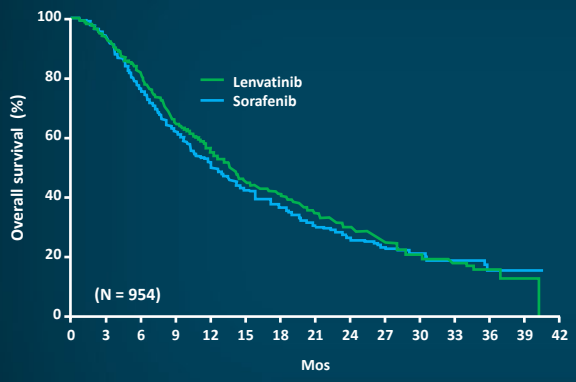
Median Overall Survival		
	Number	Months
Sorafenib	299	10.7
Placebo	303	7.9
HR = 0.69 (95% CI: 0.55–0.87) *P* <.001		

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

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

31

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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Atezolizumab/Bevacizumab as First-Line Therapy in HCC

PHASE 3, OPEN-LABEL, MULTICENTER, RANDOMIZED TRIAL

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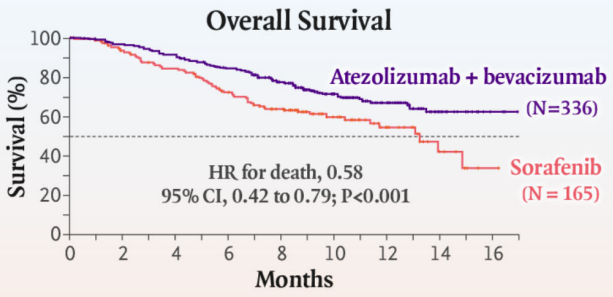
Patients with locally advanced hepatocellular carcinoma (metastatic, unresectable, or both)



Median progression-free survival	Atezolizumab + bevacizumab	Sorafenib
	6.8 Mo	4.3 Mo

HR for disease progression or death, 0.59; 95% CI, 0.47 to 0.76; P<0.001

Finn RS, et al. *N Engl J Med*. 2020;382(20):1894-1905.

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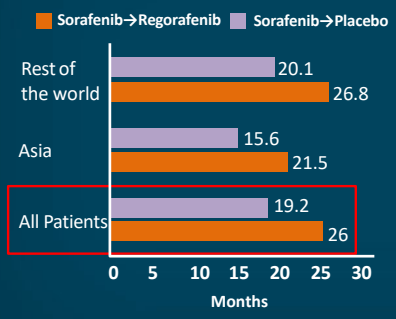
Therapeutic Options in HCC

Systemic Therapies: Second-Line and Subsequent

34

Sequential Therapy Prolongs Survival

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

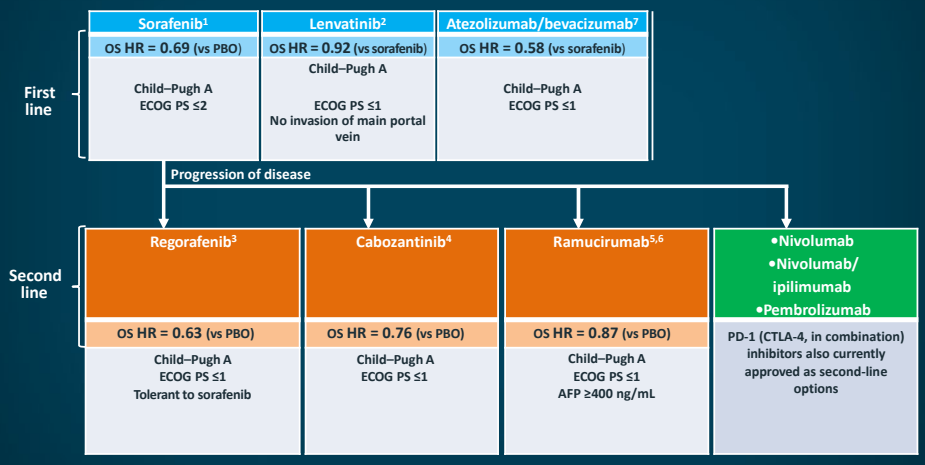


Survival	Sorafenib-regorafenib (n=379)	Sorafenib-placebo (n=194)
12 months	82%	76%
24 months	53%	42%
36 months	31%	20%
48 months	19%	12%
60 months	16%	3%
72 months	10%	3%

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

35

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. 7. Finn RS, et al. *N Engl J Med*. 2020;382(20):1894-1905.

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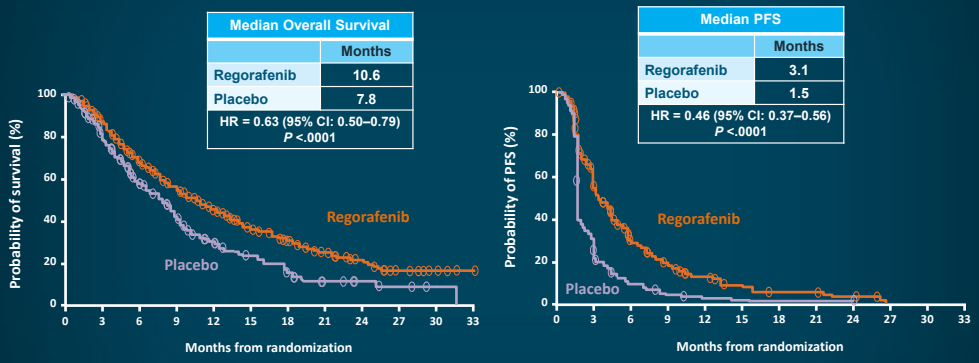
RESORCE: Survival with Regorafenib

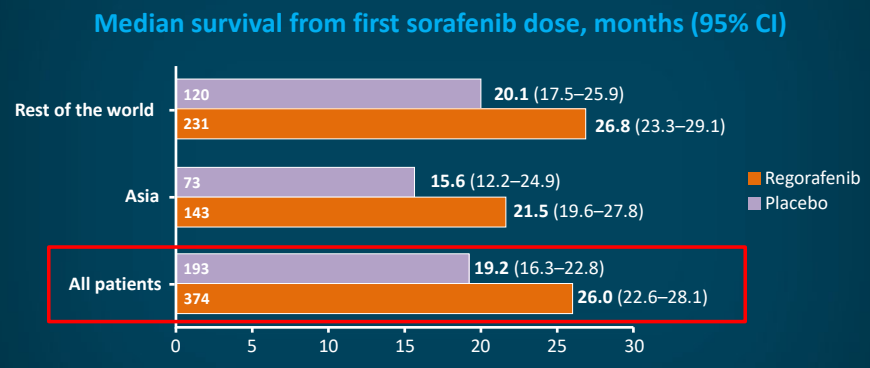


PFS = progression-free survival.

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

37

RESORCE: Exploratory Analysis of Time from Sorafenib Start to Death



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

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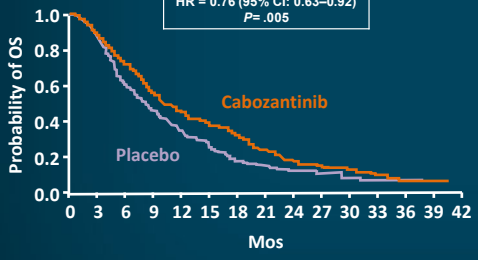
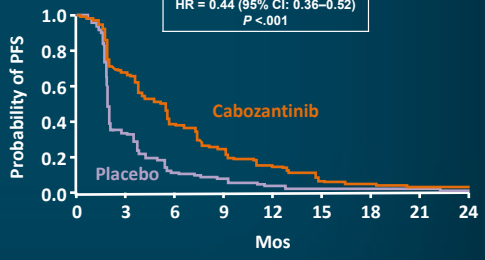
CELESTIAL: Survival with Cabozantinib

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.

39

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.

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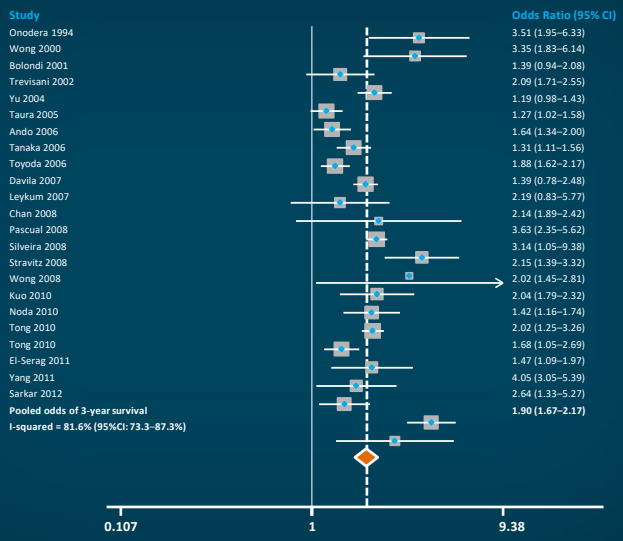
Biomarkers and Surveillance in HCC

Use in Guiding Second-line Treatment

41

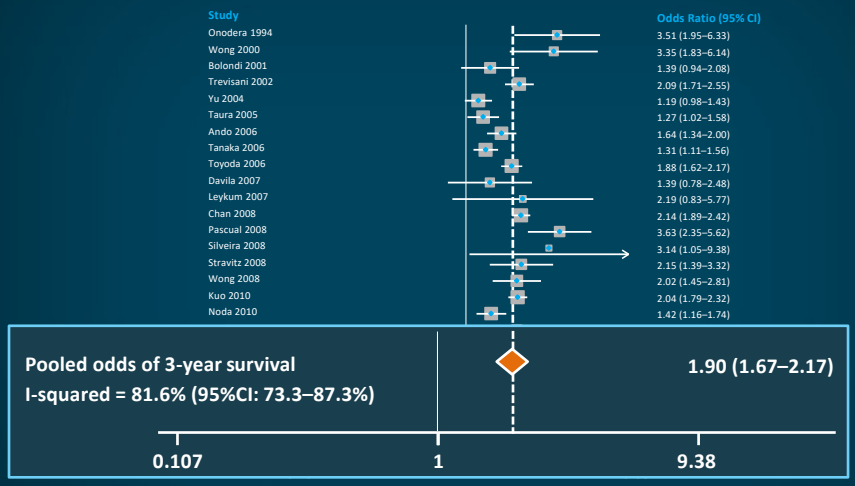
U/S Surveillance Associated With Survival Benefit



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

42

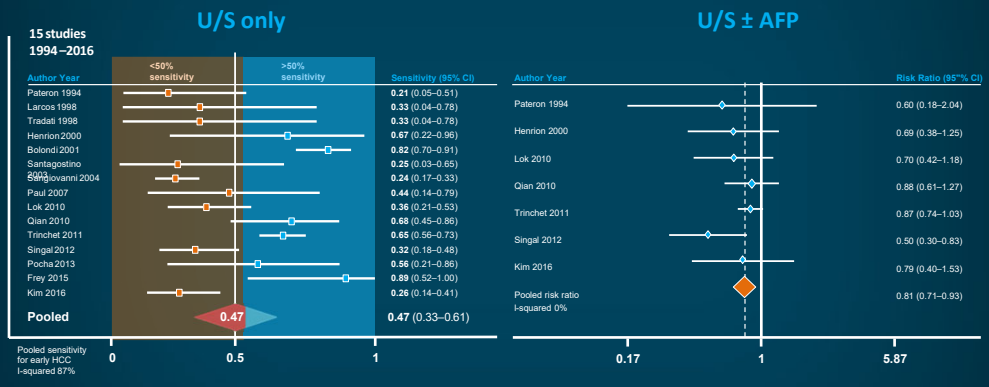
U/S Surveillance Associated With Survival Benefit



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

43

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.)

44

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-4 1.45–3.25	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.

45

Biomarker Panel May Improve Early HCC Detection: GALAD

- GALAD: Gender, Age, AFP-L3, AFP, and DCP
- 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.

46

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

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The Role of AFP in Immune Escape in the Development of HCC

https://youtu.be/K6lJISR-Nv4

48

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.

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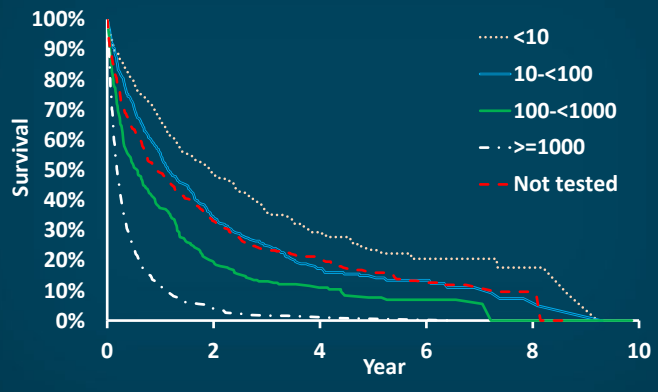
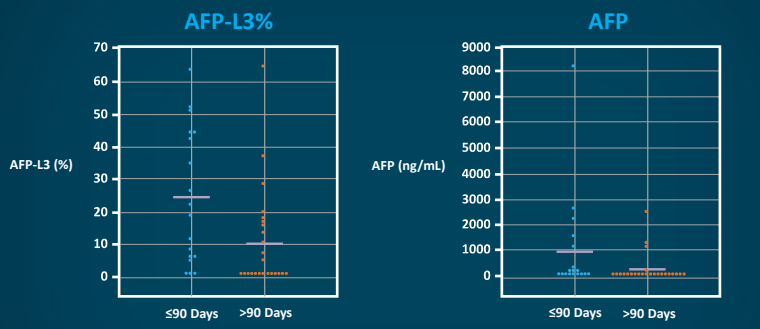
Survival of Patients with HCC Stratified by Serum AFP Levels



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

50

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.

51

Current Biomarkers and Risk of Microvascular Invasion

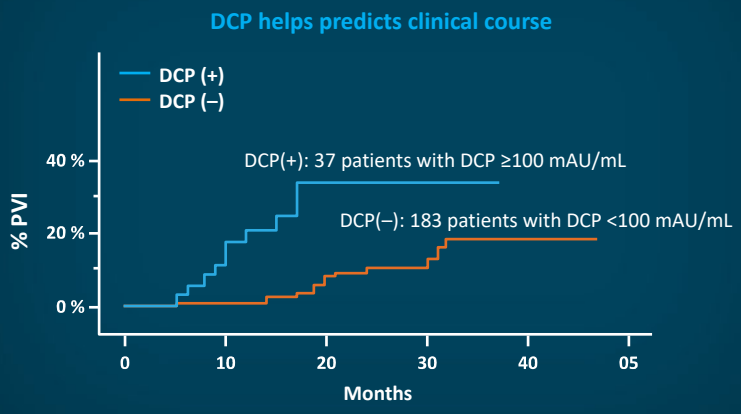
Independent predictors of microvascular invasion include:

- 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.

52

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.

53

Current HCC Biomarkers and Risk of Portal Vein Invasion

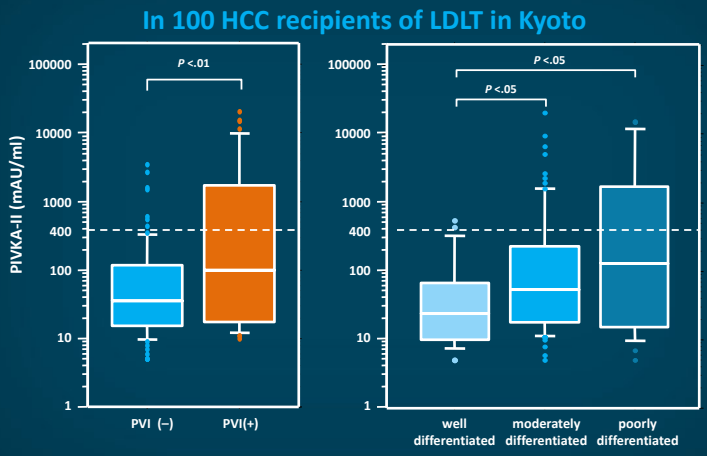
- AFP-L3% ≥15%
  - –RR: 2.459 (95% CI: 1.005–6.017; *P*= .0487)
- DCP ≥100 mAU/mL
  - –RR: 3.019 (95% CI: 1.077–8.464; *P*= .0357)
- Number of HCC tumors ≥2
  - –RR: 4.912 (95% CI: 1.619–14.905; *P*= .0049)

RR = relative risk.

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

54

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.

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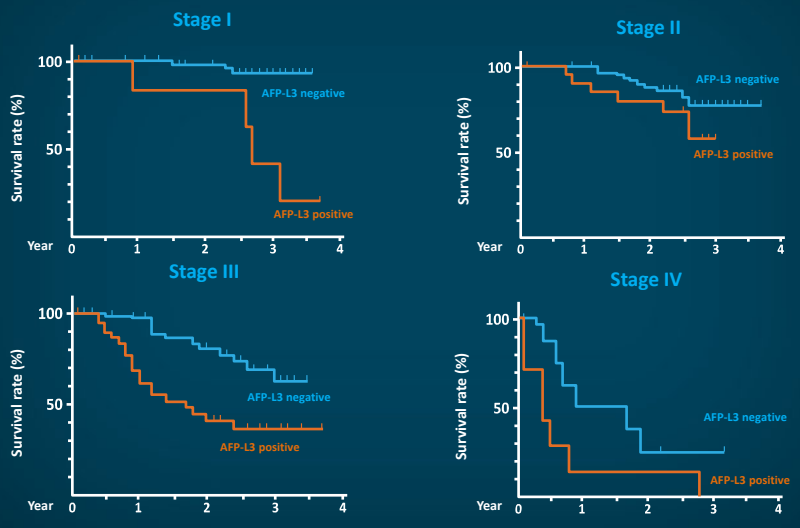
Survival Rate with Respect to HCC Stage and AFP-L3% Prior to Therapy



Courtesy of Hiroto Egawa.

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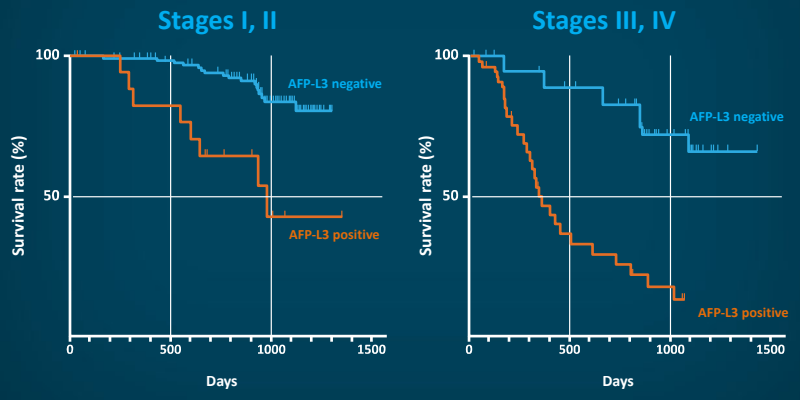
Survival Rate with Respect to HCC Stage and AFP-L3% After Therapies



Courtesy of Hiroto Egawa.

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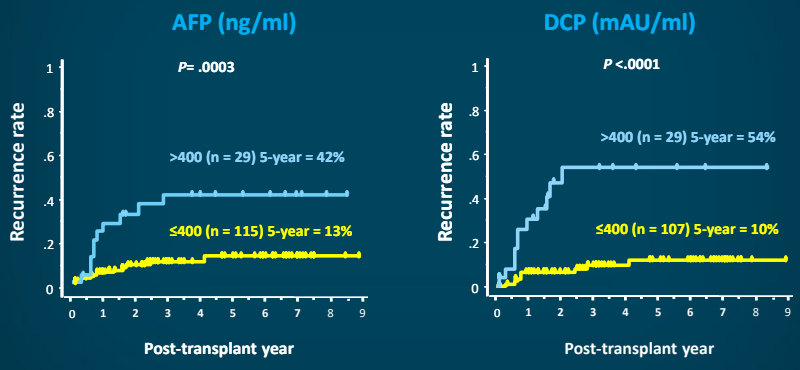
Preoperative Tumor Markers AFP and DCP and Risk of Recurrence After LDLT



Courtesy of Hiroto Egawa.

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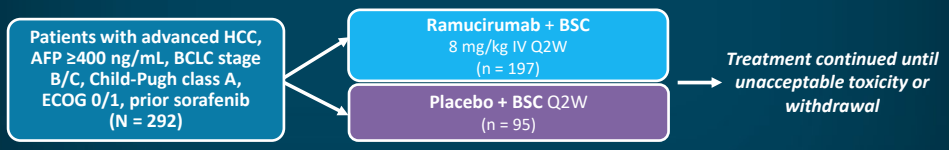
REACH-2: Ramucirumab for Patients With Previously Treated HCC and Higher AFP

- 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.

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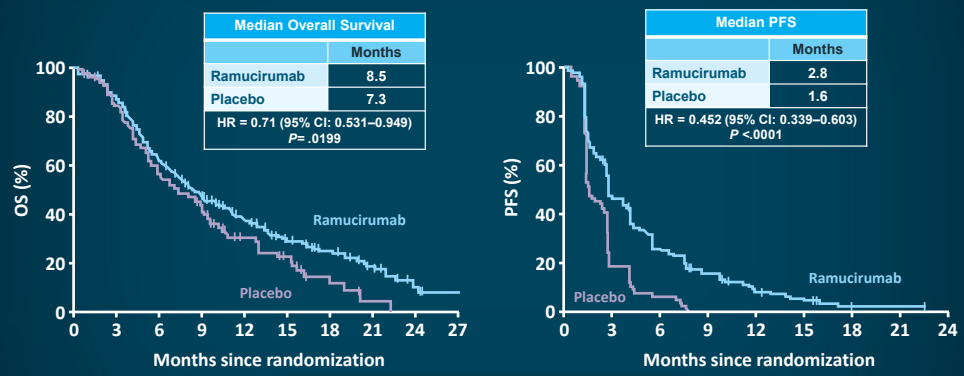
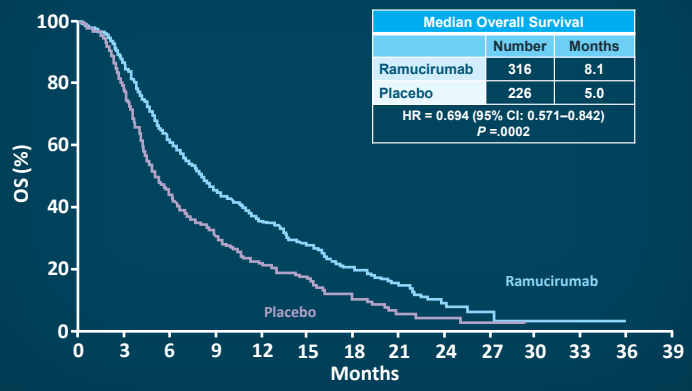
REACH-2: Survival



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

60

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



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

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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, PD-L1, and CTLA-4 has shown activity in advanced HCC
  - However, we have 2 phase 3 trials with clinical benefit but not meeting primary end point with statistical significance (Checkmate 459, KEYNOTE-240)
  - 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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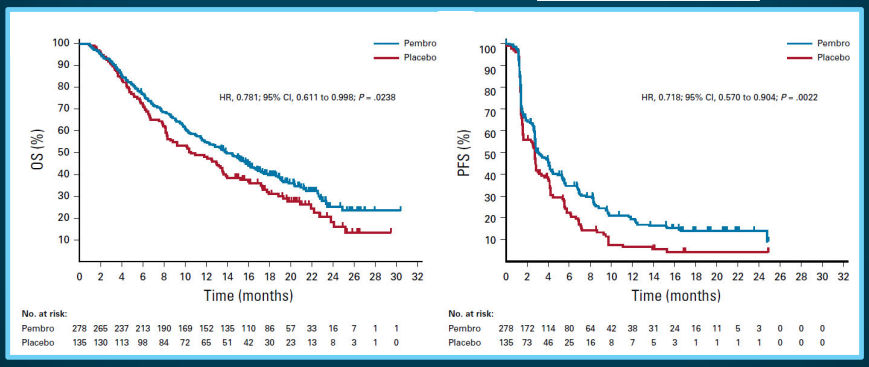
KEYNOTE-240: Survival With Pembrolizumab

- 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.

64

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

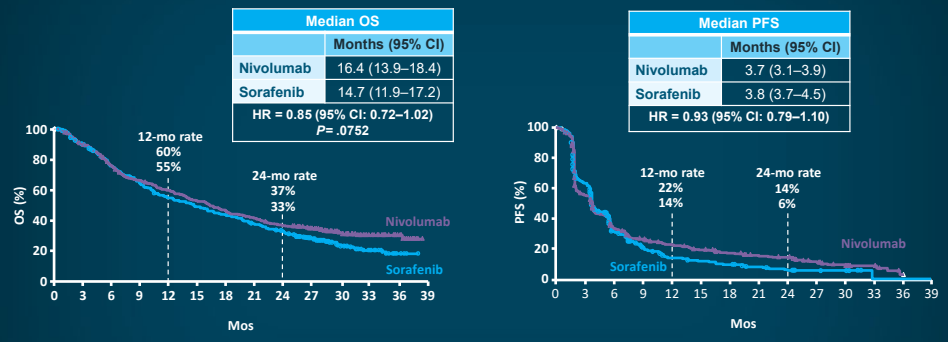
Analysis	Median OS, mos (95% CI)		HR (95% CI)	*P*-value
	Pembrolizumab (n = 278)	Placebo (n = 135)		
ITT	13.9 (11.6–16.0)	10.6 (8.3–13.5)	0.78 (0.61–1.00)	.0238
IPCW	13.9 (11.1–17.2)	9.3 (7.9–13.5)	0.67 (0.48–0.92)	.0066
2-stage model without recensoring	10.6 (9.5–11.6)	7.6 (6.2–9.3)	0.68 (0.53–0.86)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

65

CheckMate 459: OS and PFS for Nivolumab vs Sorafenib



- 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.

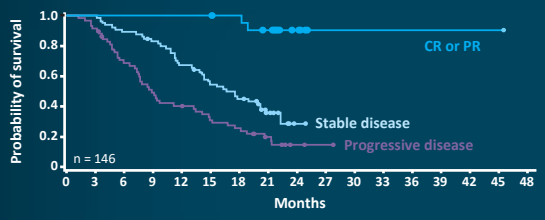
66

MAM90

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

Nivolumab Alone

OS by Best Overall Response



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.

67

Checkmate 040

Nivolumab/Ipilimumab Subgroup Analysis

- Pts were randomized to 3 arms:
  - NIVO 1 mg/kg + IPI 3 mg/kg Q3W (4 doses)
  - NIVO 3 mg/kg + IPI 1 mg/kg Q3W (4 doses), each followed by NIVO 240 mg Q2W
  - NIVO 3 mg/kg Q2W + IPI 1 mg/kg Q6W
- 148 patients were randomized; minimum OS follow-up from last patient randomization date to data cutoff was 28 months
- For all treated pts, ORR was 31% (7 had complete response), with median DOR of 17 months; DCR was 49%; the 30-month OS rate was 37%
- NIVO + IPI was well tolerated
  - 38% of pts had grade 3–4 treatment-related adverse events (TRAEs)
    - Most common TRAEs (any grade): pruritus and rash;
    - Most common grade 3–4 TRAEs: aspartate aminotransferase increase and lipase increase
  - 5% had grade 3–4 TRAEs leading to discontinuation

NOTE: In March 2020, the US FDA granted accelerated approval to the combination of nivolumab and ipilimumab for patients with HCC who have been previously treated with sorafenib. Efficacy of the combination was investigated in Cohort 4 of CHECKMATE-040 (NCT01658878) a multicenter, multiple cohort, open-label trial conducted in patients with HCC who progressed on or were intolerant to sorafenib.[1]

He AR, et al. *J Clin Oncol*. 2020;38(4_suppl: Abstract 512. 1. US FDA. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-nivolumab-and-ipilimumab-combination-hepatocellular-carcinoma. Accessed March 13, 2020.

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Slide 67

MAM89 This is the latest version for this data; nivolumab alone
Marcello Morgan, 7/15/2020

MAM90 Marcello Morgan, 7/15/2020

Checkmate 040

Nivolumab/Ipilimumab/Cabozantinib Subgroup Analysis

- Sorafenib-naive or -experienced patients were randomized to 2 arms:
  - NIVO 240 mg Q2W + CABO 40 mg daily
  - NIVO 3 mg/kg Q2W + IPI 1 mg/kg Q6W + CABO 40 mg daily
- 71 pts were randomized to NIVO + CABO (n = 36) or NIVO + IPI + CABO (n = 35)
- Investigator-assessed ORR was 17% (6 pts with partial response [PR]) in the NIVO + CABO arm and 26% (9 pts with PR) in the NIVO + IPI + CABO arm
- DCR was 81% for the NIVO + CABO arm and 83% for the NIVO + IPI + CABO arm
- Median PFS was 5.5 mo for the NIVO + CABO arm and 6.8 mo for the NIVO + IPI + CABO arm
- Median OS was not reached in either arm
- Grade 3-4 TRAEs were reported in 15 patients (42%) in the NIVO + CABO arm and 25 patients (71%) in the NIVO + IPI + CABO arm
  - Discontinuation in 1 (3%) and 7 (20%) patients, respectively
  - No new safety signals were observed in either arm

Yau T, et al. *J Clin Oncol*. 2020;38(4_suppl): Abstract 478.

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Investigational Approaches

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Selected Ongoing Trials Assessing Immune Checkpoint Inhibitors for First-Line Systemic Therapy

Study	Agent(s)	Phase
LEAP-002[1]	Lenvatinib + pembrolizumab vs lenvatinib	3
HIMALAYA[2]	Durvalumab + tremelimumab vs sorafenib	3
COSMIC-312[3]	Cabozantinib ± atezolizumab vs sorafenib	3
CheckMate 9DW[4]	Nivolumab + ipilimumab vs sorafenib or lenvatinib	3

1. Llovet JM, et al. *J Clin Oncol.* 2019;37 (suppl 15): Abstract TPS4152. 2. Abou-Alfa GK, et al. *J Clin Oncol.* 2019;36(15 suppl): Abstract TPS4144. 3. Kelley RK, et al. *J Clin Oncol.* 2019;37(15 suppl): Abstract TPS4157. 4. NCT04039607.

71

Revisiting the Case

72

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
- AFP = 350 ng/mL

- Patient was initiated on lenvatinib
- CT scan at 4 months showed stable disease
- CT scan at 8 months showed new liver masses
- AFP = 2500 ng/mL

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

73

Which Treatment Would You Recommend for Mrs. C?

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

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Team-Based Care in HCC

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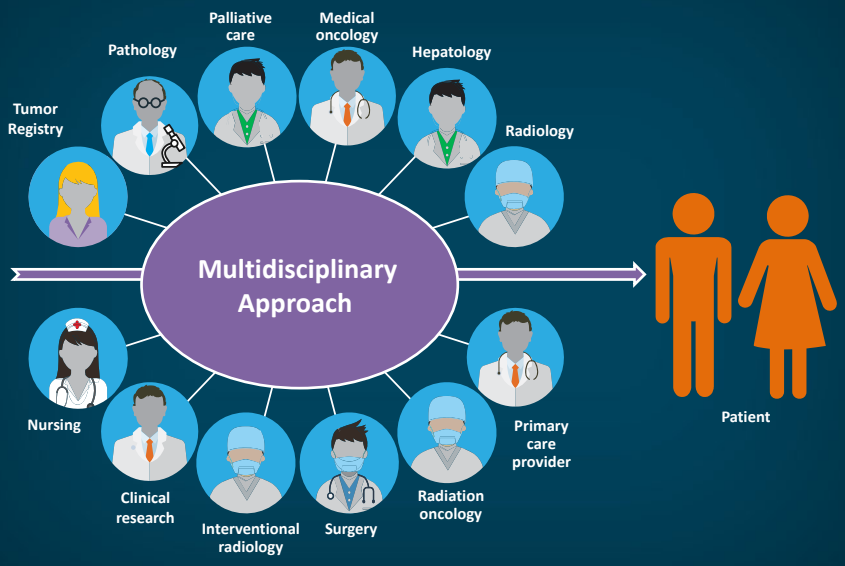
Multidisciplinary Approach to the Patient With HCC



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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.

78

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

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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
Atezolizumab/bevacizumab	• Child-Pugh Class A only
Useful in certain circumstances	
Nivolumab	• If ineligible for TKIs or other antiangiogenic options
FOLFOX	
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)
Lenvatinib	• Child-Pugh Class A only
Nivolumab	• Child-Pugh Class A or B
Nivolumab/ipilimumab	• Child-Pugh Class A only
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 4.2020. June 19, 2020. (www.nccn.org/professionals/physician_gls/PDF/hepatobiliary.pdf).

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HCC Practice Points

- Sorafenib, lenvatinib, and atezolizumab/bevacizumab are approved as first-line therapies for the management of HCC
- Regorafenib, cabozantinib, ramucirumab, nivolumab, nivolumab/ipilimumab, 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/AFP-L3%/DCP levels
- Single-agent immune checkpoint inhibitors have not met end points 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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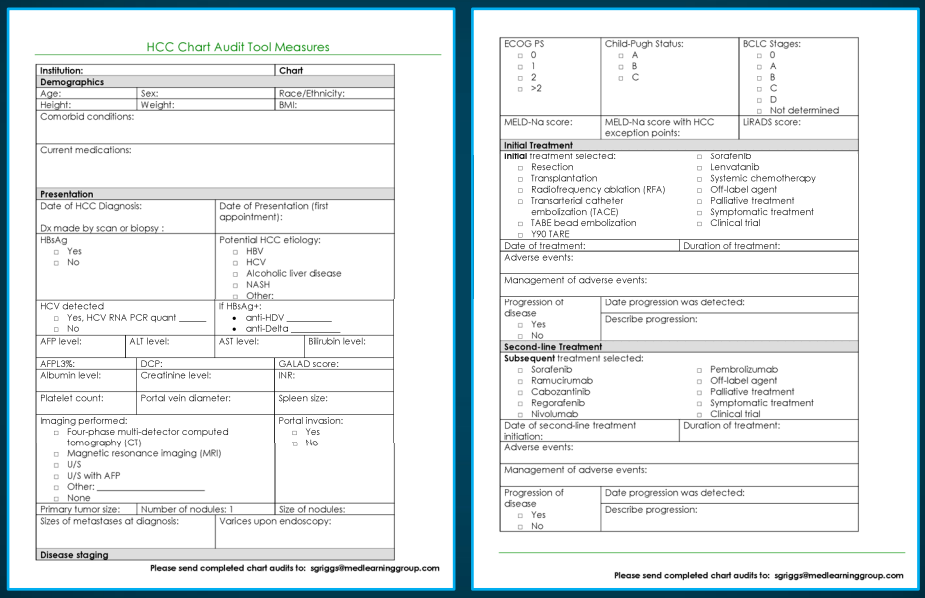
MLG Chart Audit Tool



HCC Chart Audit Tool Measures

Institution:			**Chart**
Demographics			
Age:	Sex:		Race/Ethnicity:
Height:	Weight:		BMI:
Comorbid conditions:			
Current medications:			
Presentation			
Date of HCC Diagnosis: Dx made by scan or biopsy :		Date of Presentation (first appointment):	
HBsAg □ Yes □ No		Potential HCC etiology: □ HBV □ HCV □ Alcoholic liver disease □ NASH □ Other:	
HCV detected □ Yes, HCV RNA PCR quant _____ □ No		If HBsAg+: • anti-HDV _____ • anti-Delta _____	
AFP level:	ALT level:	AST level:	Bilirubin level:
AFPL3%:	DCP:		GALAD score:
Albumin level:	Creatinine level:		INR:
Platelet count:	Portal vein diameter:		Spleen size:
Imaging performed: □ Four-phase multi-detector computed tomography (CT) □ Magnetic resonance imaging (MRI) □ U/S □ U/S with AFP □ Other: _____ □ None			Portal invasion: □ Yes □ No
Primary tumor size:	Number of nodules: 1		Size of nodules:
Sizes of metastases at diagnosis:		Varices upon endoscopy:	
Disease staging			

Please send completed chart audits to: sgriggs@medlearninggroup.com

ECOG PS □ 0 □ 1 □ 2 □ >2	Child-Pugh Status: □ A □ B □ C	BCLC Stages: □ 0 □ A □ B □ C □ D □ Not determined
MELD-Na score:	MELD-Na score with HCC exception points:	LIRADS score:
Initial Treatment		
Initial treatment selected: □ Resection □ Transplantation □ Radiofrequency ablation (RFA) □ Transarterial catheter embolization (TACE) □ TABE bead embolization □ Y90 TARE		□ Sorafenib □ Lenvatanib □ Systemic chemotherapy □ Off-label agent □ Palliative treatment □ Symptomatic treatment □ Clinical trial
Date of treatment:	Duration of treatment:	
Adverse events:		
Management of adverse events:		
Progression of disease □ Yes □ No	Date progression was detected: Describe progression:	
Second-line Treatment		
Subsequent treatment selected: □ Sorafenib □ Ramucirumab □ Cabozantinib □ Regorafenib □ Nivolumab		□ Pembrolizumab □ Off-label agent □ Palliative treatment □ Symptomatic treatment □ Clinical trial
Date of second-line treatment initiation:	Duration of treatment:	
Adverse events:		
Management of adverse events:		
Progression of disease □ Yes □ No	Date progression was detected: Describe progression:	

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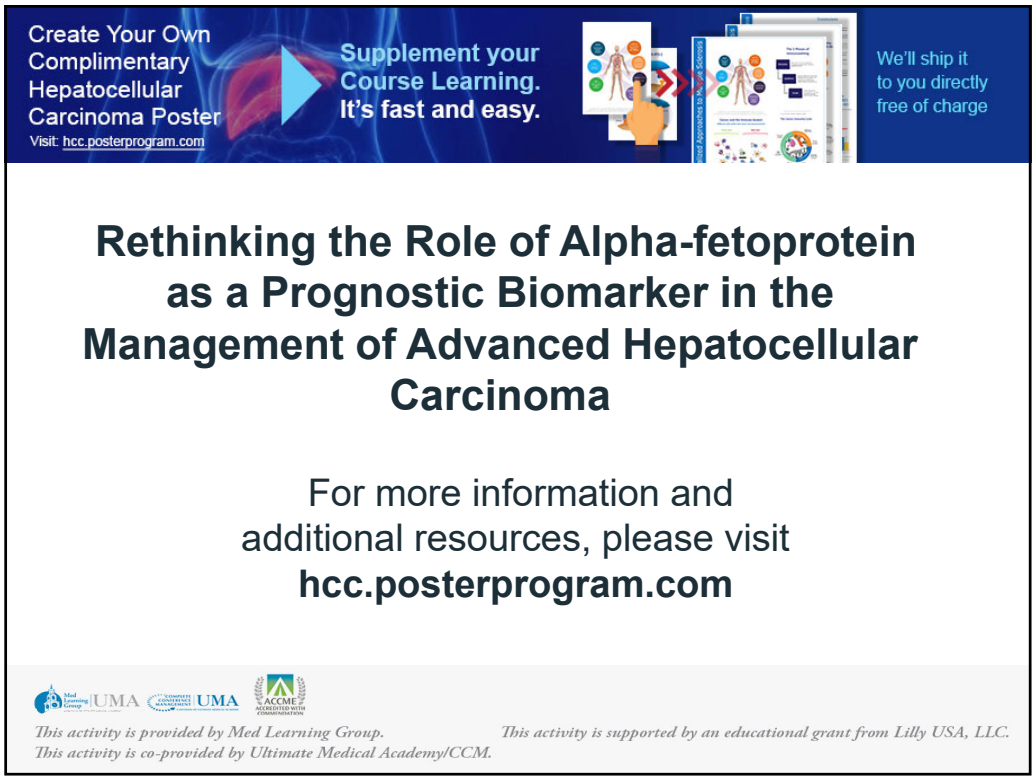
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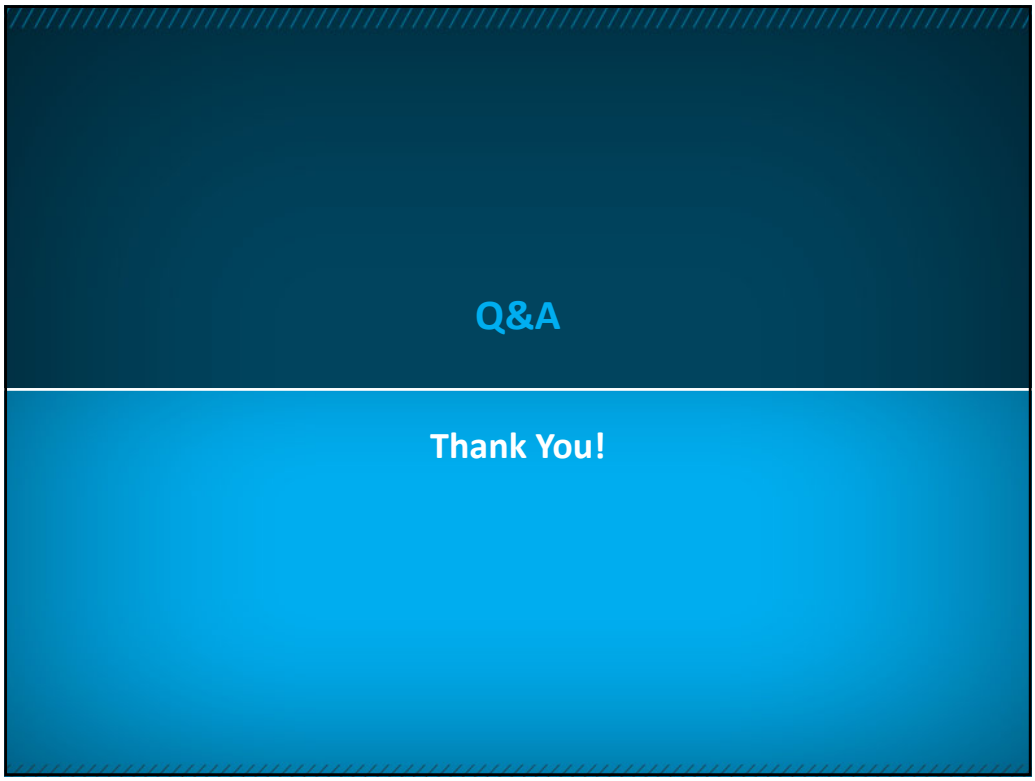

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The TAILOR Initiative: Rethinking the Role of Alpha-fetoprotein as a Prognostic Biomarker in the Management of Advanced Hepatocellular Carcinoma

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/