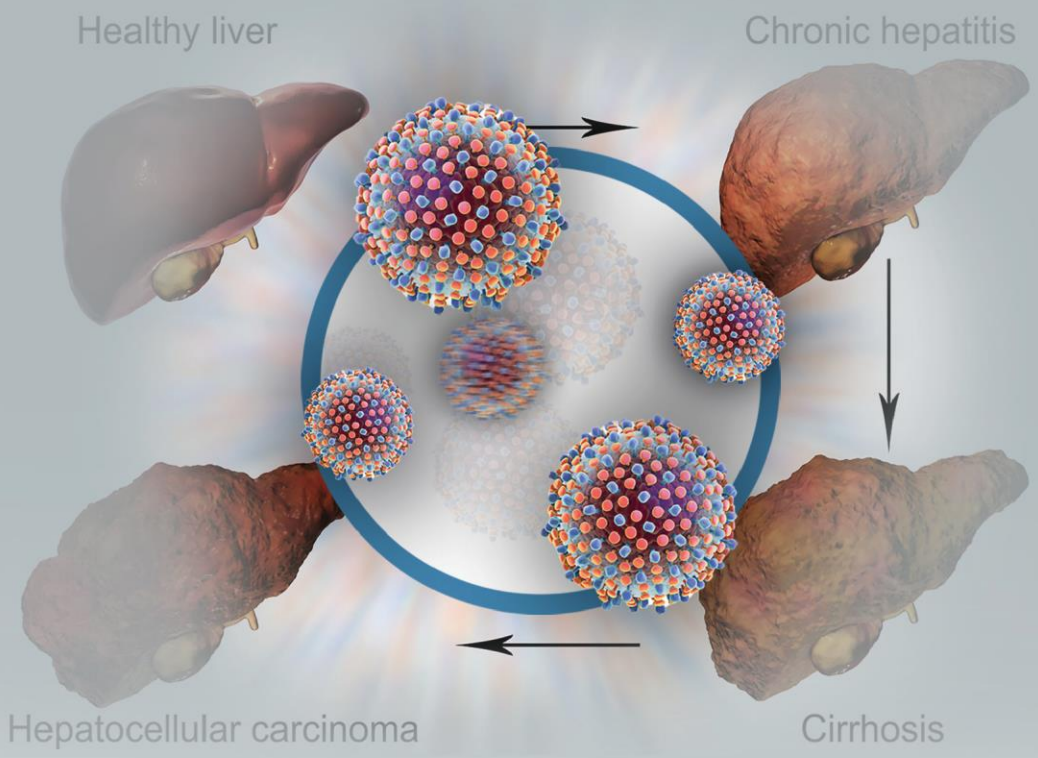
A Specialty Series Review of Targeted Tyrosine Kinase Inhibitors Used for the Management of

Advanced Hepatocellular Carcinoma



This activity is provided by Med Learning Group.
This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM).
Supported by an educational grants from Bayer HealthCare Pharmaceuticals, Inc., Eisai, Exelixis, and Merck & Co., Inc.

A Specialty Series Review of Targeted Tyrosine Kinase Inhibitors Used for the Management of Advanced Hepatocellular Carcinoma

FACULTY

Robert G. Gish, MD (Program Chair)
Principal, Robert G Gish Consultants LLC
La Jolla, California
Adjunct Professor of Medicine, University of Nevada, Reno and University of Nevada, Las Vegas
Medical Director, Hepatitis B Foundation
Adjunct Professor, UC San Diego Skaggs School of Pharmacy and Pharmaceutical Sciences
San Diego, California

Speaking Faculty

Christopher Lieu, MD
Assistant Professor
Director, Colorectal Medical Oncology
Deputy Director, Cancer Clinical Trials Office
University of Colorado Anschutz Medical Campus
Aurora, Colorado

Stanley Cohen, MD
Professor of Medicine
Case Western Reserve University
Cleveland, Ohio

Michael Morse, MD
Professor of Medicine
Professor in the Department of Surgery
Member of the Duke Cancer Institute
Duke Cancer Institute
Durham, North Carolina

Efrat Dotan, MD
Assistant Professor
Program Director Hematology/Oncology Fellowship Program
Department of Medical Oncology
Fox Chase Cancer Center
Philadelphia, Pennsylvania

Thomas Cartwright, MD
Co-chairman, US Oncology GI Research
Associate Professor of Medicine
University of Central Florida College of Medicine
Ocala, Florida

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 education needs of hepatologists, oncologists, interventional radiologists, and other members of the multidisciplinary oncology team (NPs, PAs, pharmacists) responsible for caring for patients with HCC.

LEARNING OBJECTIVES

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

- Explain how recent HCC pathophysiologic findings have informed potential treatment targets
- Review the clinical profiles of established and investigational systemic and targeted therapies, as well as combination therapies, for patients with advanced HCC
- Design individualized management plans for sequencing treatment regimens for those with advanced HCC based on patient-specific characteristics

ACCREDITATION STATEMENT

Med Learning Group is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Med Learning Group designates this live activity for a maximum of 1.0 *AMA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the live activity.

NURSING CREDIT INFORMATION

Purpose: This program would be beneficial for nurses involved in caring for patients with HCC.
Credits: 1.0 ANCC Contact Hour

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 hour of continuing nursing education of RNs and APNs.

DISCLOSURE POLICY STATEMENT

In accordance with the Accreditation Council for Continuing Medical Education (ACCME) Standards for Commercial Support, educational programs sponsored by Med Learning Group must demonstrate balance, independence, objectivity, and scientific rigor. All faculty, authors, editors, staff, and planning committee members participating in a MLG-sponsored activity are required to disclose any relevant financial interest or other relationship with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services that are discussed in an educational activity.

DISCLOSURE OF CONFLICTS OF INTEREST

Faculty	Relationship	Manufacturer
Robert G. Gish, MD	Grants/Research Support	Gilead
	Consultant	Abbott, AbbVie, Access Biologicals, Alexion, Antios, Arena, Arrowhead, Bayer AG, Bristol-Myers Squibb (BMS), Eiger, Eisai, Enyo, eStudySite, Forty-Seven Inc, Genlantis, Gerson Lehrman Group, Gilead Sciences, HepaTX, HepQuant, Intercept, Ionis Pharmaceuticals, Janssen, Laboratory for Advanced Medicine, Lilly, Merck, Salix, Shionogi, Trimaran, Viking Therapeutics, Biocollections, Fujifilm/Wako, and Quest
	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
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	Medimmune, Boston Medical, AstraZeneca, Incyte, GSK, Merck, Bayer
Christopher Lieu, MD	No relationships to report	N/A
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

CME content review

The content of this activity was independently peer reviewed.

The reviewer of this activity has nothing to disclose.

CNE Content Review

The content of this activity was peer reviewed by a nurse reviewer.

The reviewer of this activity has nothing to disclose.

The staff, planners, and managers reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME/CE activity:

Matthew Frese, MBA, General Manager of Med Learning Group, has nothing to disclose.

Christina Gallo, SVP, Educational Development for Med Learning Group, has nothing to disclose.

Sharine Griggs, Program Manager for Med Learning Group, has nothing to disclose.

Chris Drury, MD, MPH, Medical Director for Med Learning Group, has nothing to disclose.

Lauren Welch, MA, VP, Accreditation and Outcomes for Med Learning Group, has nothing to disclose.
Brianna Hanson, Accreditation and Outcomes Coordinator for Med Learning Group, has nothing to disclose.

DISCLOSURE OF UNLABELED USE

Med Learning Group requires that faculty participating in any CME activity disclose to the audience when discussing any unlabeled or investigational use of any commercial product or device not yet approved for use in the United States.

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

METHOD OF PARTICIPATION

There are no fees for participating and receiving CME credit for this live activity. To receive CME/CNE credit participants must:

1. Read the CME/CNE information and faculty disclosures.
2. Participate in the live activity.
3. Submit the pre- and post-test and evaluation form to Med Learning Group.

You will receive your certificate as a downloadable file.

DISCLAIMER

Med Learning Group makes every effort to develop CME activities that are scientifically based. This activity is designed for educational purposes. Participants have a responsibility to utilize this information to enhance their professional development in an effort to improve patient outcomes. Conclusions drawn by the participants should be derived from careful consideration of all available scientific information. The participant should use his/her clinical judgment, knowledge, experience, and diagnostic decision-making before applying any information, whether provided here or by others, for any professional use.

For CME questions, please contact Med Learning Group at info@medlearninggroup.com.

Contact this CME provider at Med Learning Group for privacy and confidentiality policy statement information at http://medlearninggroup.com/privacy-policy/

AMERICANS WITH DISABILITY ACT

Event staff will be glad to assist you with any special needs (eg, physical, dietary, etc.). Please contact Med Learning Group prior to the event at info@medlearninggroup.com.

Copyright © 2020 Med Learning Group. All rights reserved. These materials may be used for personal use only. Any rebroadcast, distribution, or reuse of this presentation or any part of it in any form for other than personal use without the express written permission of Med Learning Group is prohibited.

This activity is provided by Med Learning Group.

This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM).

This activity is supported by an educational grants from Bayer HealthCare Pharmaceuticals, Inc., Eisai, Exelixis, and Merck & Co., Inc.

A Specialty Series Review of Targeted Tyrosine Kinase Inhibitors Used for Managing Advanced Hepatocellular Carcinoma

AGENDA

I. A Brief Look at HCC

- **a.** Prevalence/incidence
- **b.** Death rates/survival
- **c.** Etiology
- **d.** Risk factors
- **e.** Pathogenesis
- **f.** Surveillance and diagnosis
- **g.** Diagnosis: current and evolving strategies

II. Overview of Therapeutic Options in HCC

- **a.** Treatment options and level of evidence
- **b.** Molecular therapies tested
- **c.** NCCN guidelines for first- and second-line therapy
- **d.** Targeted therapies – kinase inhibitors
- **e.** Sequencing therapy
- **f.** Team-based care in HCC
- **g.** Shared decision-making and education
- **h.** Case Study

III. Conclusions and Q/A

WELCOME!

We will start momentarily

Your line will automatically be muted upon entry. Please stay muted.

Things to Know

- ✓ Please type questions in the Q&A section. The speaker will answer questions later in the presentation.
- ✓ At the conclusion of the program to receive credit please visit: **www.medlearninggroup.com/event**

A Specialty Series Review of Targeted Tyrosine Kinase Inhibitors Used for the Management of Advanced Hepatocellular Carcinoma

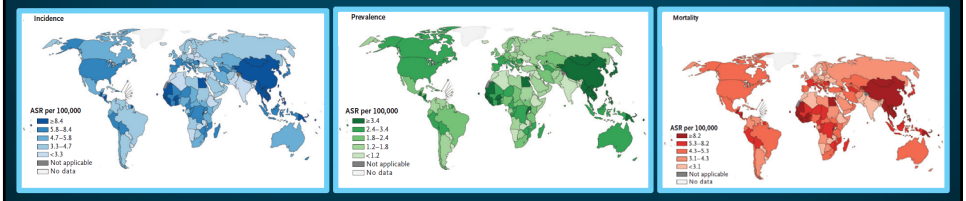
Learning Objectives

- Explain how recent HCC pathophysiologic findings have informed potential treatment targets
- Review the clinical profiles of established and investigational systemic and targeted therapies, with a particular focus on tyrosine kinase inhibitors, for patients with advanced HCC
- Design individualized management plans for sequencing treatment regimens for those with advanced HCC based on patient-specific characteristics

A Brief Look at Hepatocellular Carcinoma

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

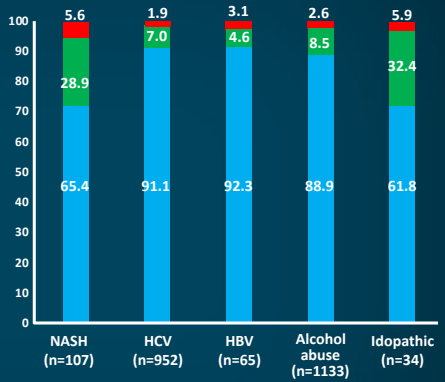


Villanueva A. N Engl J Med. 2019;380:1450-1462.

HCC Incidence 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 result of increasing cirrhosis
  - Half of increase is attributed to aging cohort with chronic HCV
  - Increasing obesity/NAFLD
- **However, incidence has plateaued and declined in the past 5-7 yrs**
  - **Better HBV/HCV cure rates?**

Many NASH pts with HCC do not have cirrhosis



Very high probability noncirrhotic:
Histology and no features on imaging

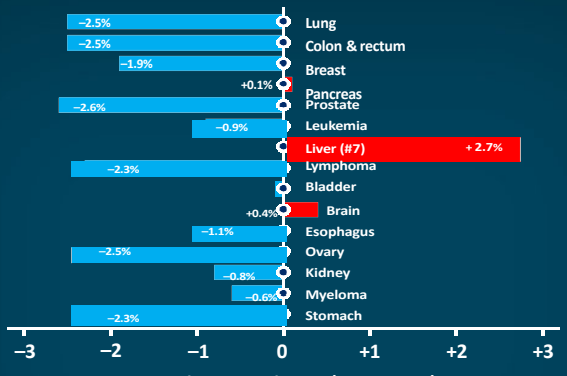
High probability noncirrhotic:
APRI <1; no features on imaging; NL albumin, plt, INR

HCV = hepatitis C virus; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; 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. Mittal S, et al. *Clin Gastroenterol Hepatol*. 2015;13(3):594–601.e1. Shiels M, et al. *Gastroenterology*. 2020;158:1503-5.

HCC Mortality in United States Is Increasing

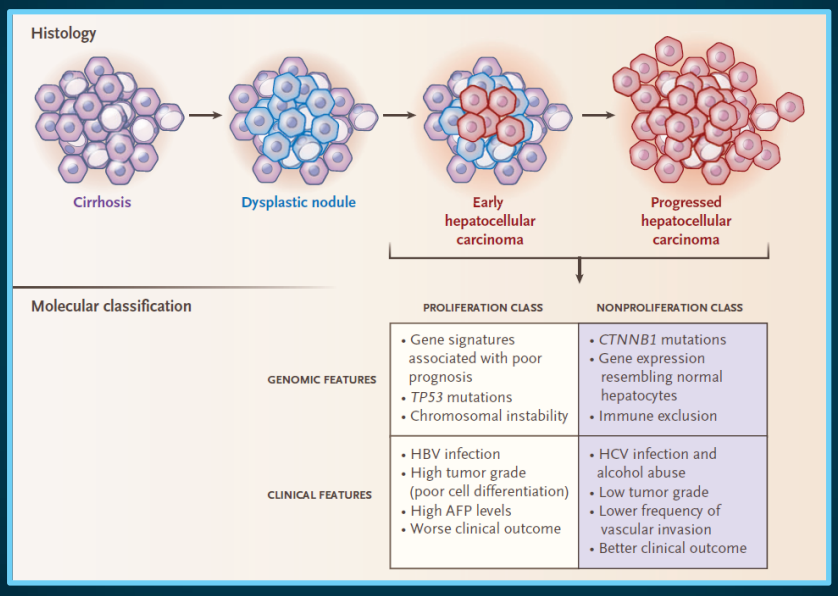
Top 15 causes of cancer death in United States 2000–2014



- 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

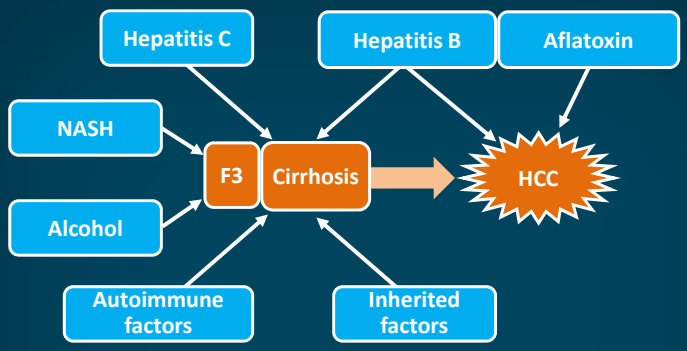
Siegel RL, et al. *CA Cancer J Clin*. 2019;69:7-34. American Cancer Society (ACS). Cancer Facts & Figures 2019 (www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf).

Etiology of Hepatocellular Carcinoma



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

Risk Factors for the Development of HCC



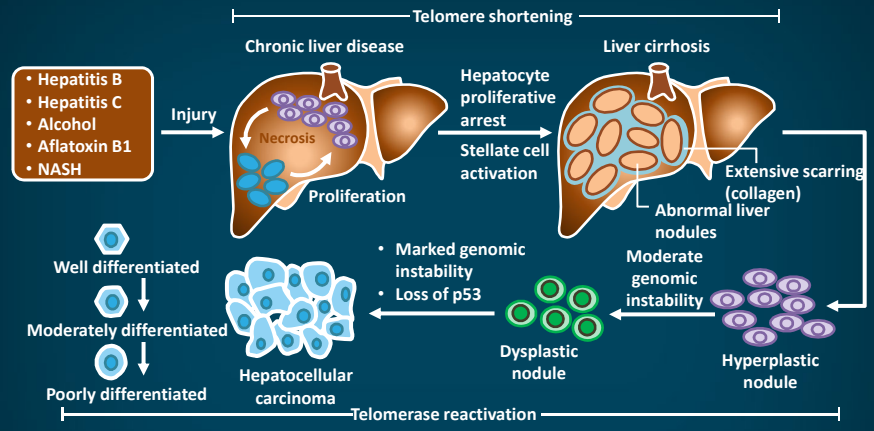
- 2–5% of patients with cirrhosis develop HCC each year
- Most cases of HCC arise in a cirrhotic liver
- Cirrhosis is not always symptomatic, and HCC may be the first indication of underlying cirrhosis

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.

Pathogenesis of HCC

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.

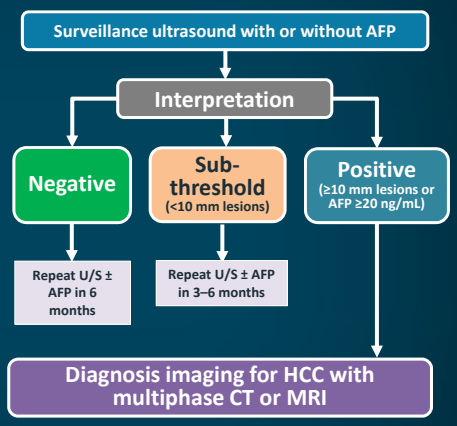
Pathogenesis of HCC

Video 1
Pathogenesis

Surveillance and Diagnosis of HCC

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.

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)

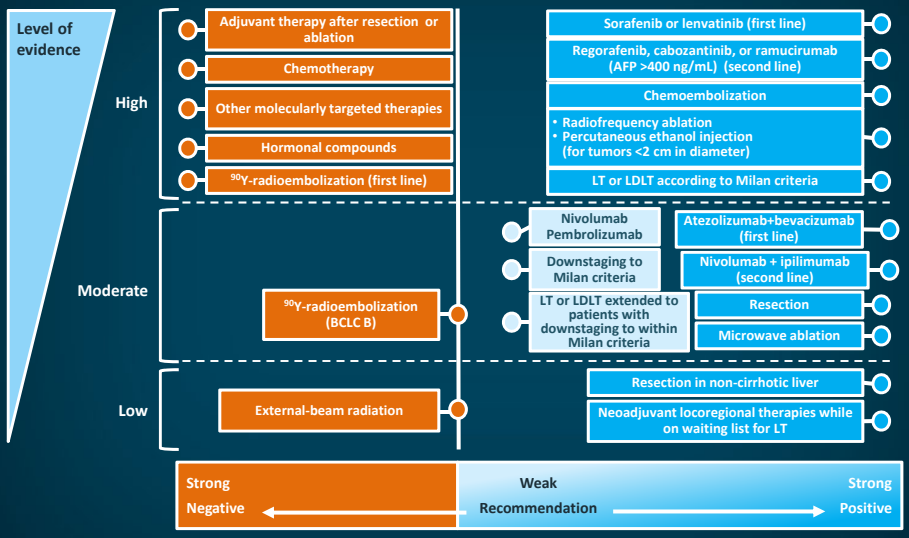
- Advantages
  - Lack of radiation
  - Higher contrast resolution
- Disadvantages
  - Requires at least 30 minutes in the magnet (maybe shorter with updated MRI protocols)
  - Motion artifact (patient participation)
  - Claustrophobia

LiRADS = Liver Reporting and Data System.

An Overview of Therapeutic Options in HCC

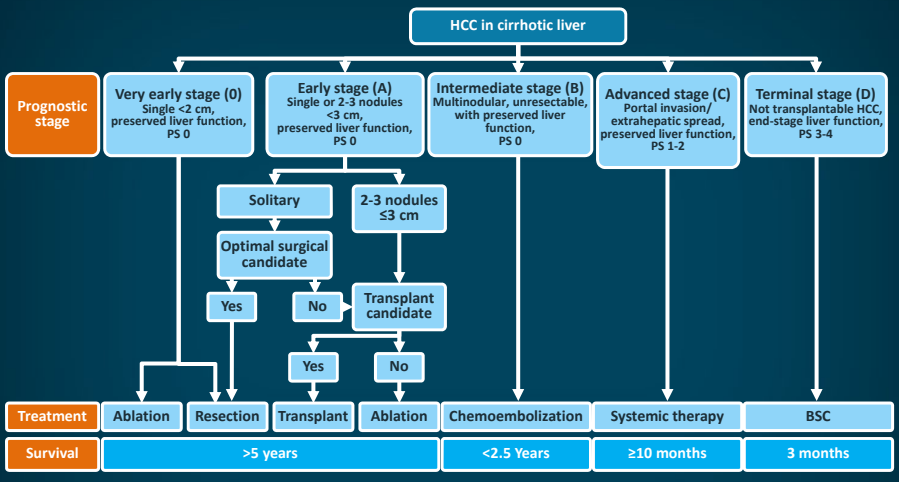
Surgical Resection, Embolization, Thermal Ablation, and External Beam Radiation

HCC Treatment Options and Level of Evidence



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

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.

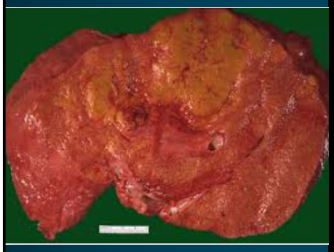
Case

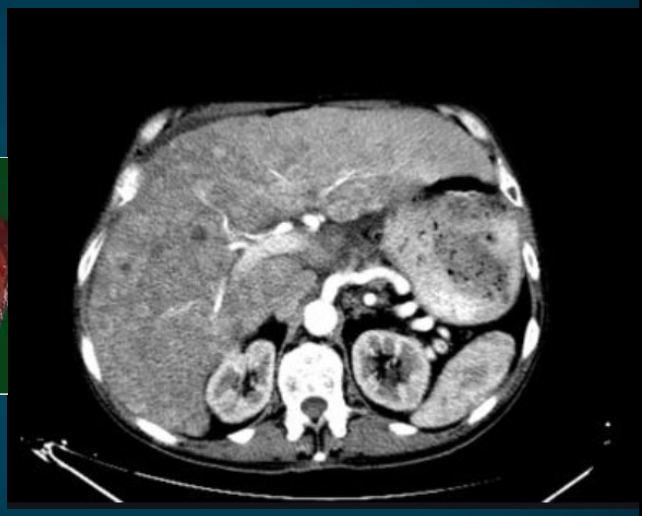
Case: Mr. M

- 70-year-old man with hepatitis B presents with abdominal pain
- CT scan shows a large, infiltrative mass with areas of arterial enhancement and definite washout
- AFP = 1540 ng/ml
- Biopsy showed poorly differentiated HCC, Child-Pugh A
- He was treated with TACE; post TACE CT scan showed increase in size of mass and new pulmonary metastasis
- Patient initiated on sorafenib 400 mg BID
  - 3 weeks later, patient experiences grade 3 hand-foot skin reaction and grade 3 diarrhea
- CT scan at 2 months showed stable disease
- CT scan at 4 months showed new liver masses;
  AFP = 28,000 ng/L

TACE = transarterial chemoembolization.

Mr. M





What would you do for Mr. M?

Therapeutic Options in HCC

Systemic Therapies

Molecular Therapies Tested for HCC in Phase III Trials

Adjuvant: Prevent Recurrences	Intermediate HCC: Improve TACE	Advanced HCC: First Line	Advanced HCC: Second Line
Sorafenib vs placebo	RF vs RF-Dox	Sorafenib vs placebo	Brivanib vs placebo
Retinoids vs placebo	TACE ± sorafenib	Sorafenib ± erlotinib	Everolimus vs placebo
	TACE ± brivanib	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 Y-90	Nivolumab/ipilimumab
		Sorafenib vs nivolumab	
		Atezolizumab + bevacizumab vs sorafenib	

Negative study. Positive study. Study in which noninferiority shown. *AFP > 400 ng/mL.

Retinoids, linifanib, tivantinib, brivanib, erlotinib, sunitinib, everolimus, and doxorubincin are not FDA approved for HCC.

Kudo. *Cancers (Basel)*. 2018;10(11). Press Release: Bristol Myers Squibb. Available at: https://news.bms.com/press-release/corporatefinancial-news/us-food-and-drug-administration-approves-opdivo-nivolumab-ye-0.

HCC Treatment

Video 2
Treatments

Therapeutic Options in HCC

Systemic Therapies: First-Line

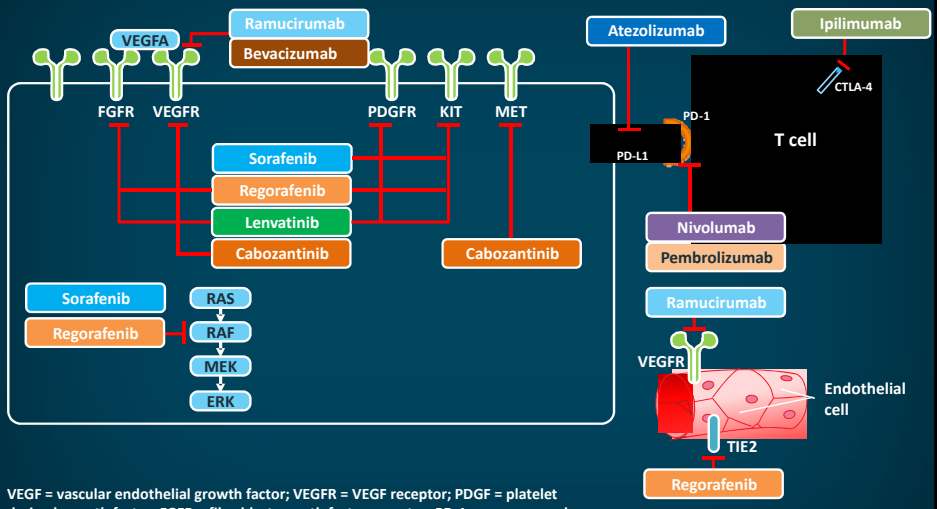
NCCN Recommended Therapies for HCC

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 TKI or other or other antiangiogenic agents (Category 2B)
FOLFOX	• 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)
Lenvatinib	• Child Pugh Class A only
Nivolumab	• Child-Pugh Class A or B7
Nivolumab + Ipilimumab	• Child-Pugh Class A only
Sorafenib	• Child-Pugh Class A or B7
Pembrolizumab	• Child-Pugh Class A only (category 2B)

FOLFOX is not FDA approved for HCC.

National Comprehensive Cancer Network (NCCN). Hepatobiliary cancers. Version 1.2020. March 23, 2020. (https://www.nccn.org/professionals/physician_gls/PDF/hepatobiliary.pdf).

Targeted Therapies for Hepatocellular Carcinoma



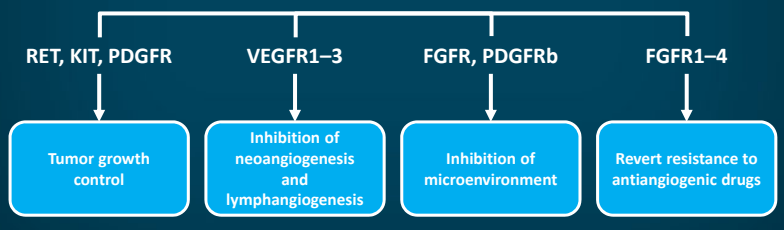
VEGF = vascular endothelial growth factor; VEGFR = VEGF receptor; PDGF = platelet derived growth factor; FGFR = fibroblast growth factor receptor; PD-1 = programmed cell death 1; PD-L1 = PD-1 ligand; RAS = rat sarcoma protein; RAF = rapidly accelerated fibrosarcoma kinase; MEK = mitogen-activated protein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

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.

Sorafenib for First Line Advanced HCC

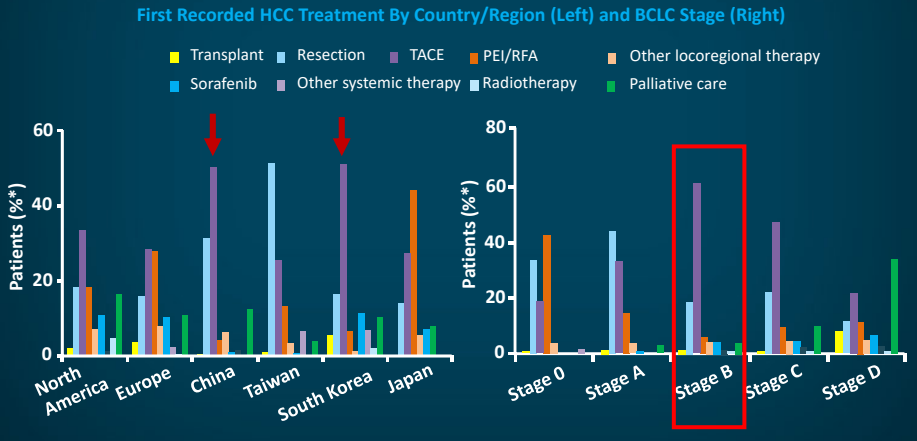
SHARP vs Asia-Pacific Study: Efficacy

Endpoint	SHARP[1] Sorafenib vs Placebo		Asia-Pacific[2] Sorafenib vs Placebo	
	Hazard Ratio (95% CI)	*P* value	Hazard Ratio (95% CI)	*P* value
OS	10.7 vs 7.9 mo 0.69 (0.55-0.87)	<0.001	6.5 vs 4.2 mo 0.68 (0.50-0.93)	0.014
TTSP	1.08 (0.88-1.31)	0.768	0.90 (0.67-1.22)	0.50
TTP	5.5 vs 2.8 mo 0.58 (0.45-0.74)	<0.001	2.8 vs 1.4 mo 0.57 (0.42-0.79)	<0.001
RR	2% vs 1%		3.3% vs 1.3%	

1. Llovet JM, et al. NEJM 2008;359(4):378-390.
2. Cheng AL, et al. Lancet Oncol. 2009;10(1)25-34.

Applicability of Sorafenib in HCC: BRIDGE study

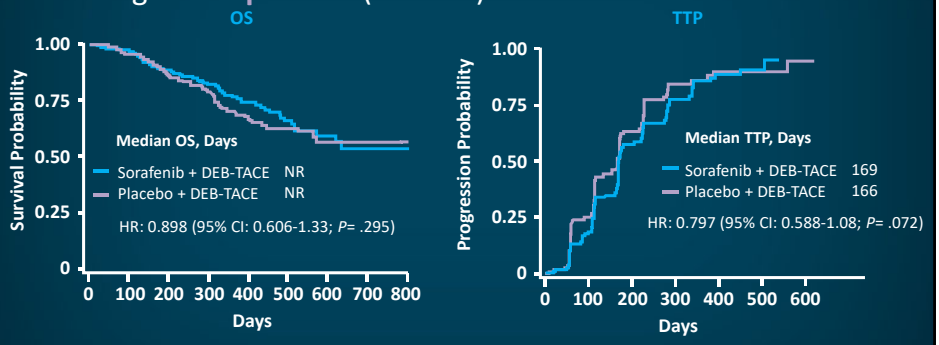
- Retrospective chart review of patients with newly diagnosed HCC (N = 18,031, followed 2005-2012)



Park J-W. *Liver Int*. 2015;35:2155-2166.

Expected Outcome With TACE: SPACE

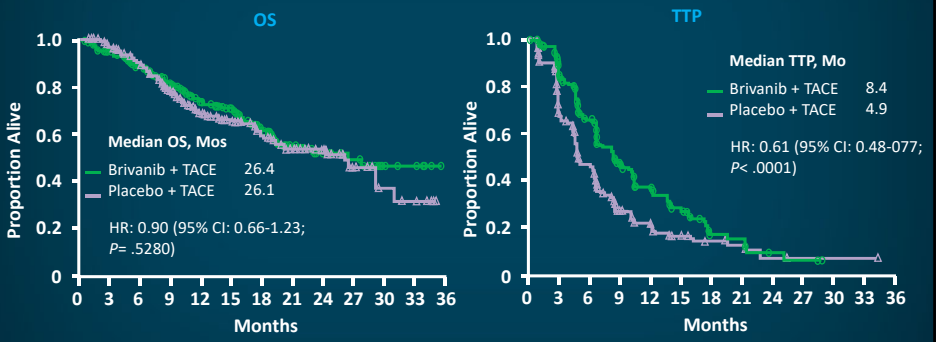
- Randomized phase 2 trial in patients with BCLC stage B HCC treated with **DEB-TACE** (150 mg doxorubicin) plus **sorafenib** 400 mg BID vs **placebo** (N = 307)



Lencioni. *J Hepatol*. 2016;64:1090-1098.

Expected Outcome With TACE: Brivanib

- Randomized, double-blind phase 3 trial in patients with TACE-eligible HCC treated with **TACE** followed by **brivanib** 800 mg QD vs **placebo** (N = 870)



Not FDA approved for HCC.

Kudo M, et al. *Hepatology*. 2014;60:1697-1707.

Recent Studies of Radioembolization vs Sorafenib for Locally Advanced HCC

- 2 randomized, open-label phase 3 studies of **yttrium-90 (^{90}Y) resin microspheres** vs **sorafenib** for pts with PS < 2 and locally advanced, unresectable Child-Pugh A/B7 HCC

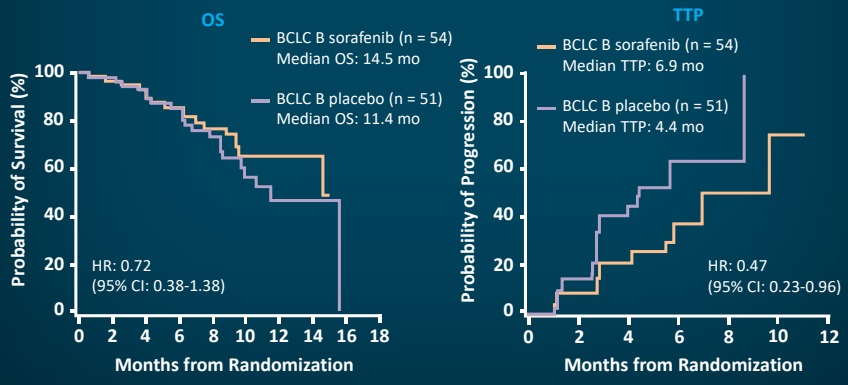
Study	N	Findings
SARAH[1]	459	• Median OS, mo: ^{90}Y RE 8.0 vs sorafenib 9.9 (HR: 1.15; ***P*= .18**) • Improved QoL, lower proportion of pts with grade ≥ 3 AEs in ^{90}Y RE group
SIRveNIB[2]	360	• Median OS, mo: ^{90}Y RE 8.8 vs sorafenib 10.0 (HR: 1.1; ***P*= .36**) • Lower proportion of patients with grade ≥ 3 AEs in ^{90}Y RE group

- SORAMIC (palliative arm): randomized phase 2 study of **^{90}Y microspheres + sorafenib** vs **sorafenib** for patients with locally advanced, unresectable Child-Pugh A/B7 HCC showed similar median OS between treatment groups (12.1 vs 11.5 mo; *P*= .951)[3]
- **Discussion: What are indications for transition to systemic therapy?**

1. Vilgrain V, et al. *Lancet Oncol*. 2017;18:1624-1636. 2. Chow PKH, et al. *J Clin Oncol*. 2018 Jul 1;36(19):1913-1921. 3. Ricke J. World Congress on Gastrointestinal Cancer *2018*. Abstr O-029.

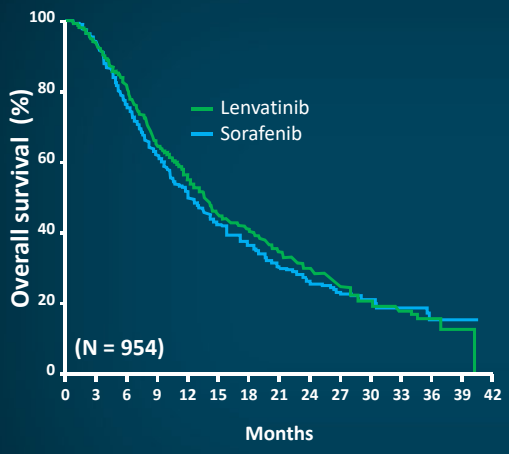
Concept of Treatment Stage Migration: Survival Outcomes with Sorafenib in Pts w/ BCLC Stage B HCC in SHARP Trial

- Randomized phase 3 trial in patients with advanced HCC who were treated with sorafenib vs placebo (n = 105 patients with BCLC stage B disease in subgroup analysis)



Bruix J, et al. *J Hepatol*. 2012;57:821-829.

Lenvatinib is Noninferior to Sorafenib

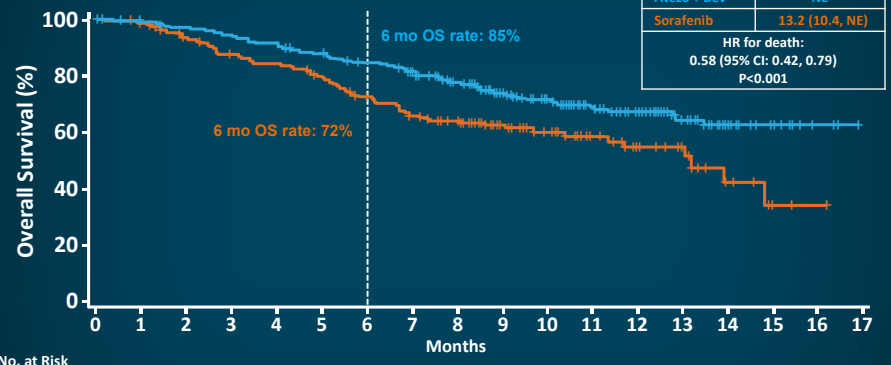


Outcomes		
Outcome	Lenvatinib (n = 478)	Sorafenib (n = 476)
mOS, mo (95% CI)	13.6 (12.1–14.9)	12.3 (10.4–13.9)
HR for mOS = 0.92 (95% CI: 0.79–1.06)		
Response rate	41%	12%
CR	2%	1%
PR	38%	12%
SD	33%	46%
PD	17%	32%
TTP, mo	8.9	3.7
HR for TTP = 0.60 (95% CI: 0.51–0.71)		

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.

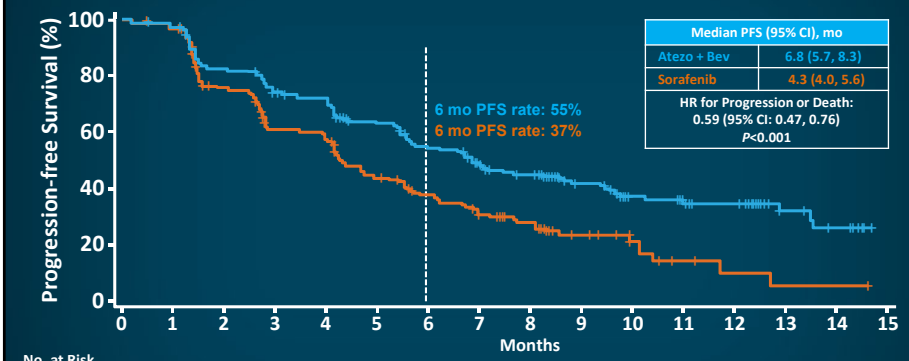
Atezolizumab + Bevacizumab
OS: Coprimary Endpoint



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

Finn R, et al. *NEJM*. 2020;382:1894-1905.

Atezolizumab + Bevacizumab
Confirmed PFS: Coprimary Endpoint

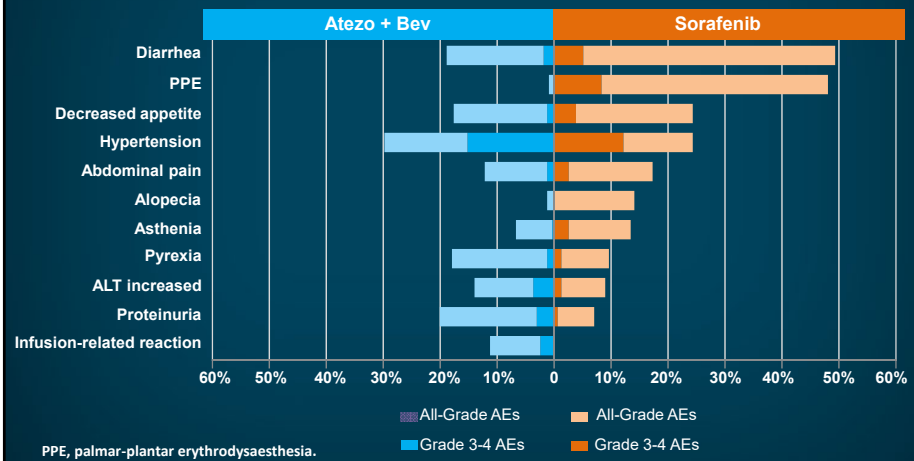


No. at Risk															
Sorafenib	165	148	109	84	80	57	44	34	27	15	9	4	2	1	1	NE
Atezo + Bev	336	322	270	243	232	201	169	137	120	74	50	46	34	11	7	NE

Finn R, et al. *NEJM*. 2020;382:1894-1905.

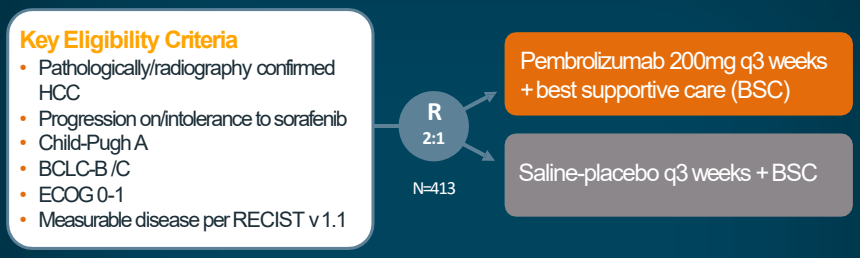
Atezolizumab + Bevacizumab
Safety[a]

≥ 10% frequency of AEs in either arm and > 5% difference between arms



PPE, palmar-plantar erythrodysaesthesia.
a Safety-evaluable population.
Finn R, et al. *NEJM*. 2020;382:1894-1905.

Pembrolizumab in HCC: Phase 3 Keynote-240



Primary Endpoints: OS and PFS

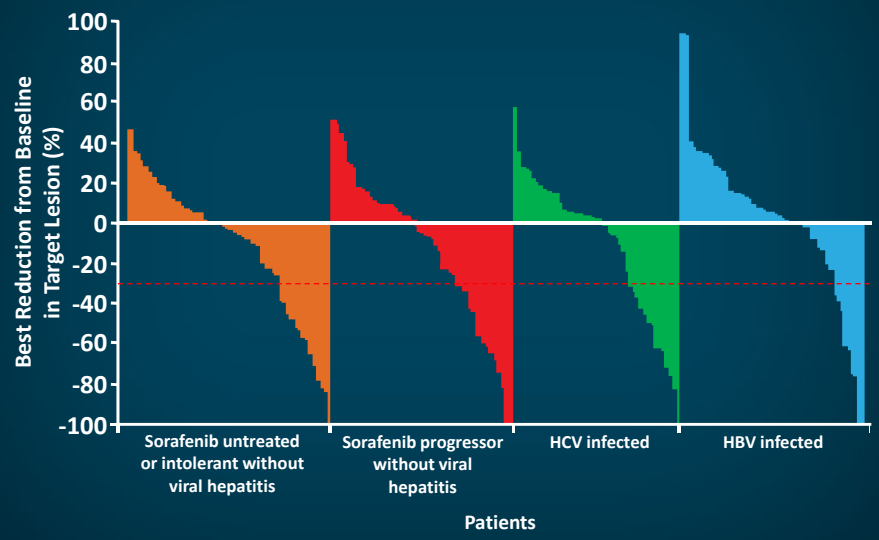
Finn R. Abstract #4004. Presented at ASCO 2019.

Pembrolizumab in HCC: Keynote-240 Results

- OS: Pembro 13.9 months vs. BSC 10.6 months (p=0.0238)
- PFS: Pembro 3.0 months vs. BSC 2.8 months (p=0.186)
- Reasons for failure to reach pre-specified statistical significance:
  - Statistical design
  - Underestimation of OS for BSC group
  - ~50% of the study population going on to a 3rd line treatment that may have confounded the OS endpoint
  - PFS may not be an ideal endpoint for immunotherapy
- Results are consistent with KEYNOTE-224, "further supporting second line therapy with pembro in HCC pts."
- Further data are required on immune checkpoint inhibitors in HCC
  - KEYNOTE-394: pembrolizumab
  - CHECKMATE-459: nivolumab vs sorafenib

Finn R. Abstract #4004. Presented at ASCO 2019.

Nivolumab Single Agent Activity (Checkmate 40)



El-Khoueiry A, *Lancet* 2017; 389: 2492–502

Nivolumab + Ipilimumab (CheckMate 040)

	Arm A NIVO1/IPI3 q3w* (n=50)	Arm B NIVO3/IPI1 q3w† (n=49)	Arm C NIVO3 q2w/IPI1 q6w (n=49)
ORR by BICR using RECIST v1.1,‡ n (%)	16 (32)	15 (31)	15 (31)
BOR, n (%) CR PR SD§ PD Unable to determine	 4 (8) 12 (24) 9 (18) 20 (40) 3 (6)	 3 (6) 12 (24) 5 (10) 24 (49) 4 (8)	 0 15 (31) 9 (18) 21 (43) 4 (8)
DCR,‖ n (%)	27 (54)	21 (43)	24 (49)
Median TTR (range), months	2.0 (1.1-12.8)	2.6 (1.2-5.5)	2.7 (1.2-8.7)
Median DOR (range), months	17.5 (4.6 to 30.5+)	22.2 (4.2 to 29.9+)	16.6 (4.1+ to 32.0+)
ORR by investigator assessment using RECIST v1.1, n (%)	16 (32)	13 (27)	14 (29)

*NIVO1/IPI3 q3w x 4 followed by nivolumab 240 mg IV q2w flat dose. †NIVO3/IPI1 q3w x 4 followed by nivolumab 240 mg IV q2w flat dose. ‡Defined as CR+PR; §SD does note include 2 patients in Arm A and 1 patient in Arm B who were reported as non-CR/non-PD. ‖Defined as CR+PR+SD+non-CR/non-PD.

BICR=blinded independent central review; DCR=disease control rate; IPI=ipilimumab; IV=intravenous; NIVO=nivolumab; q2w=every 2 weeks; q3w=every 3 weeks; q6w=every 6 weeks; RECIST=Response Evaluation Criteria in Solid Tumors.
Data cutoff: January 2019.

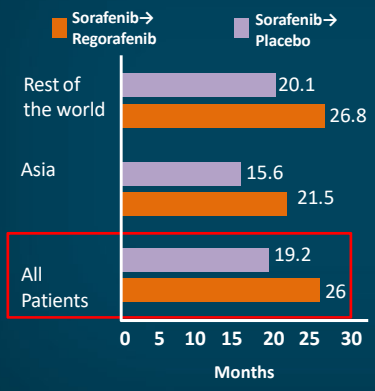
Yau T, et al. Poster. ASCO. 2019 (abstr 4012).

Therapeutic Options in HCC

Systemic Therapies: Second-Line and Subsequent

Sequential Therapy Prolongs Survival

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

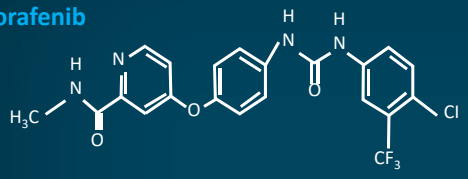


Survival	Sorafenib-regorafenib (n=379)	Sorafenib-placebo (n=194)
12 months	82%	76%
24 months	53%	42%
36 months	31%	20%
48 months	19%	12%
60 months	16%	3%
72 months	10%	3%

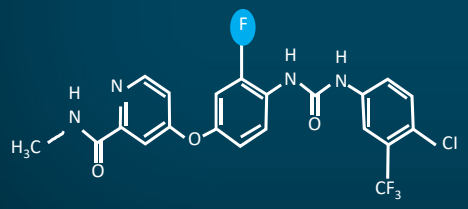
Finn RS, et al. *J Hepatology.* 2018;69(2):353-358.

Sorafenib vs Regorafenib: Key Molecular Difference

Sorafenib



Regorafenib

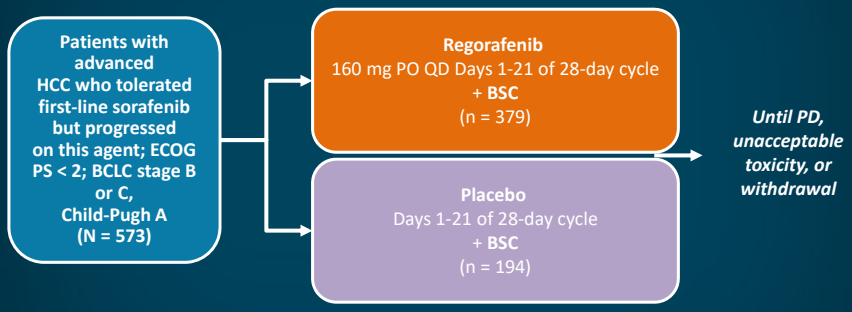


- Broader and more potent target profile than sorafenib: VEGFR1-3, c-KIT, TIE-2, PDGFR-β, FGFR-1, RET, c-RAF, BRAF, and p38 MAP kinase
- Regorafenib metabolites (M-2 and M-5) have continued antineoplastic effect during 1-wk washout period

Trojan J, Waidmann O. *J Hepatocell Carcinoma*. 2016;3:31-36. Kline C, El-Deiry W. *Pharmaceuticals* (Basel). 2013 Aug 21;6(8):988-1038.

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

- Multicenter, randomized, double-blind phase 3 trial

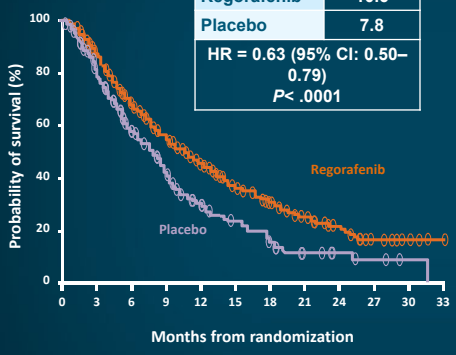


- Primary endpoint: OS
- Secondary endpoints: PFS, TTP, ORR, and disease control rate

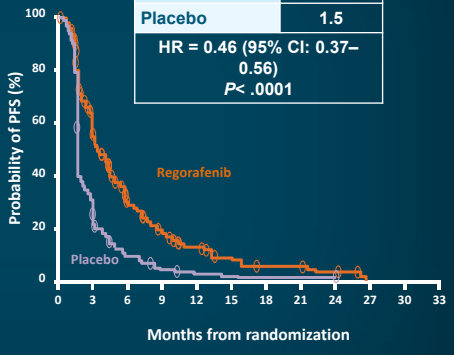
Bruix J, et al. *Lancet*. 2017;389:56-66.

RESORCE: Survival with Regorafenib

Median Overall Survival	
	Months
Regorafenib	10.6
Placebo	7.8
HR = 0.63 (95% CI: 0.50–0.79) *P*< .0001	



Median PFS	
	Months
Regorafenib	3.1
Placebo	1.5
HR = 0.46 (95% CI: 0.37–0.56) *P*< .0001	

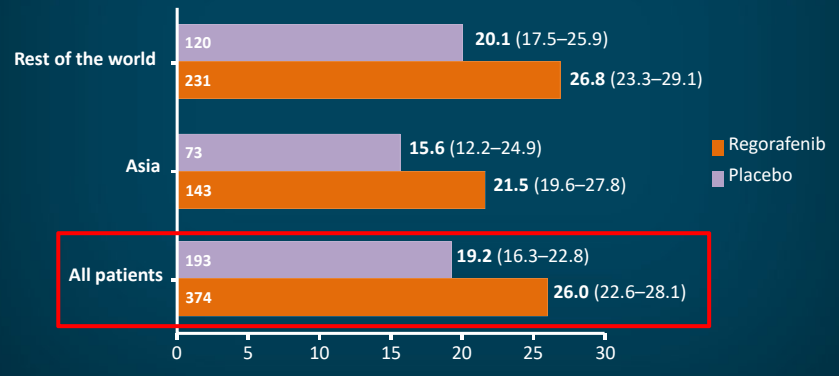


PFS = progression-free survival.

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

RESORCE: Exploratory Analysis of Time from Sorafenib Start to Death

Median survival from first sorafenib dose, months (95% CI)



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

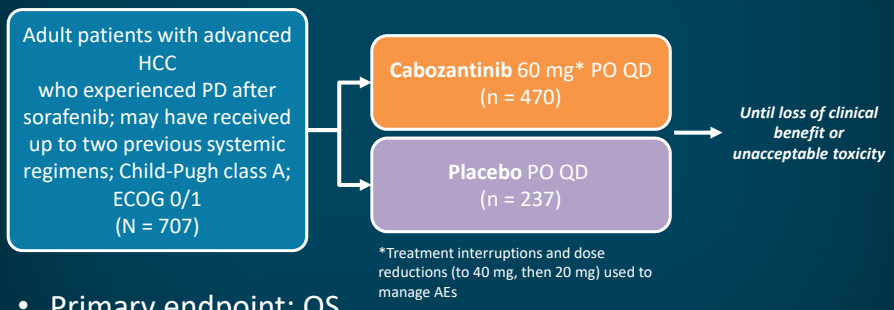
RESORCE: Select Treatment-Emergent AEs

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	0	22	4	0
AST increased	25	10	1	20	10	2
Ascites	16	4	0	16	6	0
Anemia	16	4	1	11	5	1
Hypophos-phatemia	**10**	**8**	**1**	**2**	**2**	**0**

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

CELESTIAL: Cabozantinib for Previously Treated HCC

- Randomized, double-blind phase 3 trial
  - **Cabozantinib**: multitargeted TKI; inhibits MET, VEGFR-1, -2, -3, AXL, RET, ROS1, TYRO3, MER, KIT, TRKB, FLT-3, and TIE-2



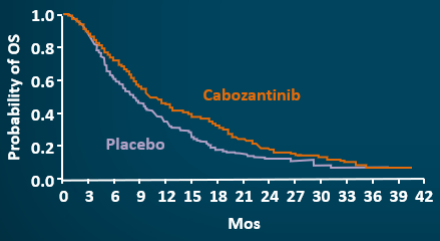
- Primary endpoint: OS
- Secondary endpoints: PFS, ORR

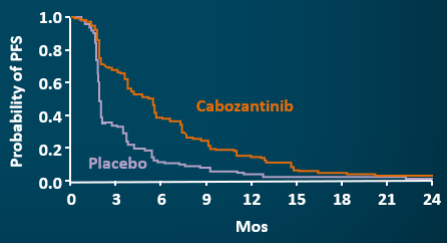
Abou-Alfa GK, et al. *N Engl J Med*. 2018 Jul 5;379(1):54-63. Cabozantinib PI.

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 Jul 5;379(1):54-63.

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)

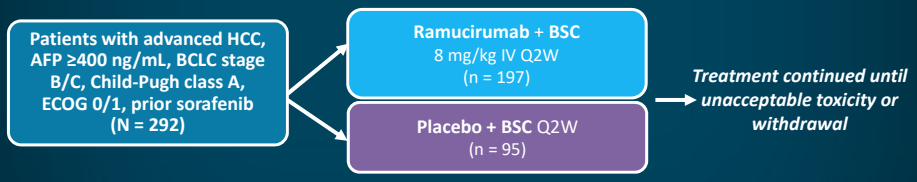
Outcome	Prior Sorafenib Only, Overall		Prior Sorafenib Only, Duration (Mo)					
			<3 mo		3 to <6 mo		≥6 mo	
	CABO n = 331	PBO n = 164	CABO n = 89	PBO n = 47	CABO n = 98	PBO n = 43	CABO n = 143	PBO n = 74
Median OS, mo	11.3	7.2	8.9	6.9	11.5	6.5	12.3	9.2
HR (95% CI)	0.70 (0.55–0.88)		0.72 (0.47–1.10)		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.

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]



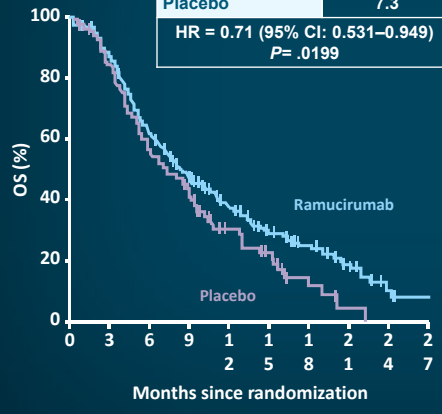
- Primary endpoint: OS; secondary endpoints: PFS, ORR, time to radiographic progression, time to FHSI-8 score decline, time to ECOG PS decline[1]

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

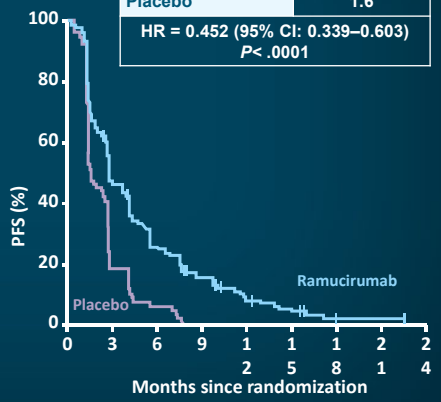
1. Zhu AX, et al. *Lancet Oncol*. 2019;20:282-296. 2. Zhu AX, et al. *Lancet Oncol*. 2015;16:859-870.

REACH-2: Survival

Median Overall Survival	
	Months
Ramucirumab	8.5
Placebo	7.3
HR = 0.71 (95% CI: 0.531–0.949) *P*= .0199	

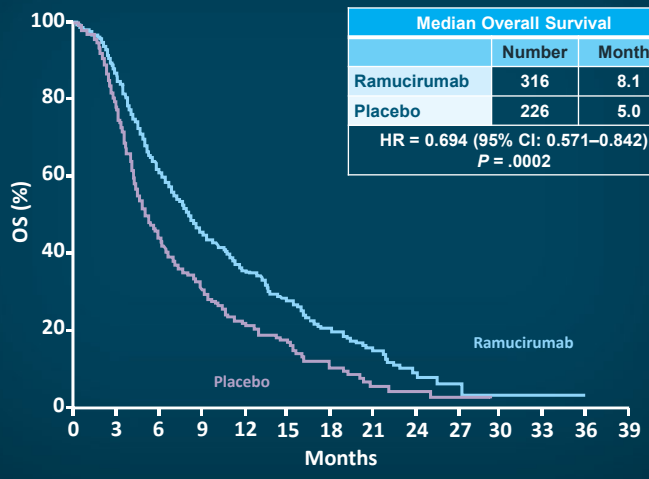


Median PFS	
	Months
Ramucirumab	2.8
Placebo	1.6
HR = 0.452 (95% CI: 0.339–0.603) *P*< .0001	



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

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



Median Overall Survival		
	Number	Months
Ramucirumab	316	8.1
Placebo	226	5.0
HR = 0.694 (95% CI: 0.571–0.842) *P* = .0002		

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

REACH-2: Select Treatment-Related AEs

AE, %*	Ramucirumab (n = 197)		Placebo (n = 95)	
	Grades 1/2	Grades 3-5	Grades 1/2	Grades 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

AE, %*	Ramucirumab (n = 197)		Placebo (n = 95)	
	Grades 1/2	Grades 3-5	Grades 1/2	Grades 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

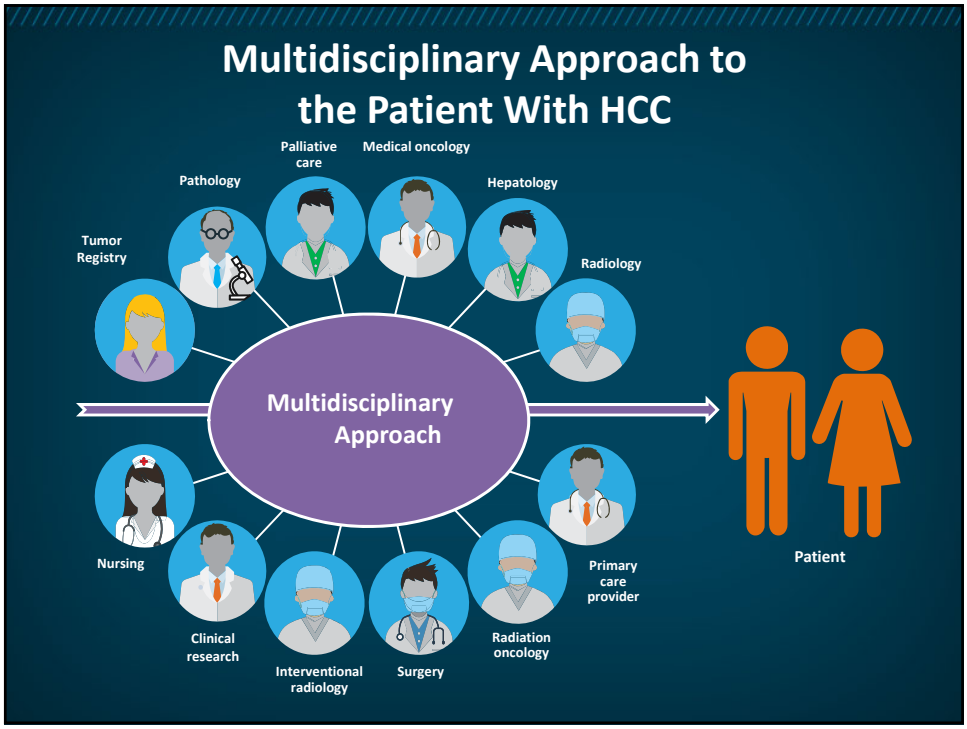
*Occurring in ≥ 10% of patients in one treatment group.

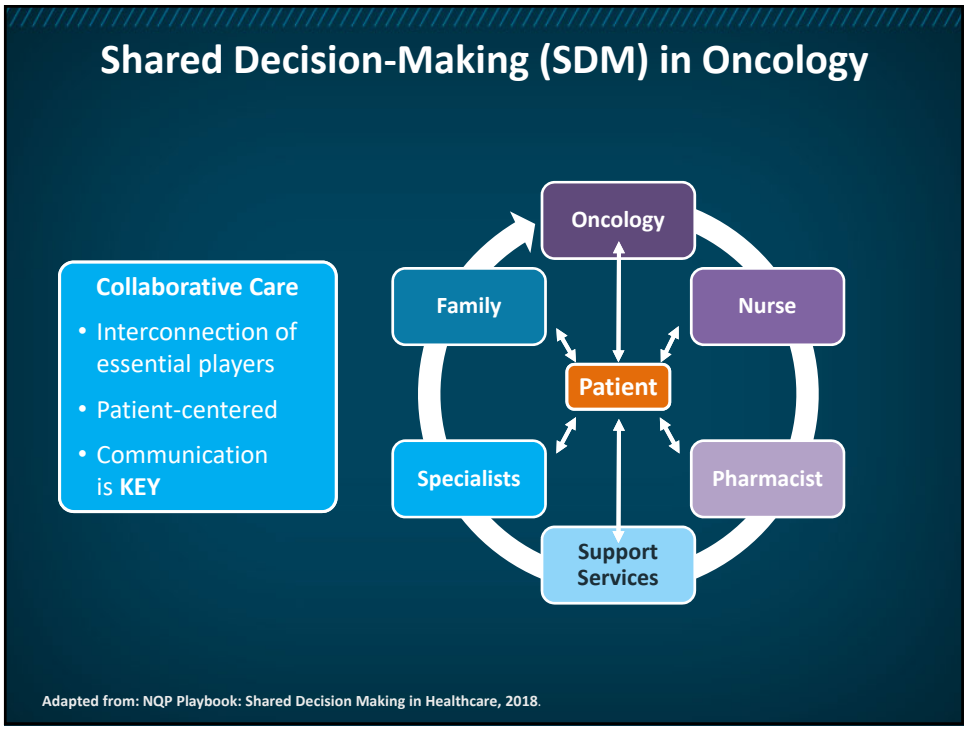
Zhu AX, et al. *Lancet Oncol*. 2019;20:282.

How to Choose and Sequence Different Drugs in HCC

- Regorafenib: prior sorafenib tolerability
- Cabozantinib: up to two prior regimens, sorafenib intolerance
- Ramucirumab: baseline AFP ≥ 400 ng/mL
- Nivolumab and pembrolizumab: durable response

Team-Based Care in HCC


Multidisciplinary Approach to the Patient With HCC
Palliative care
Medical oncology
Pathology
Hepatology
Tumor Registry
Radiology
Multidisciplinary Approach
Nursing
Primary care provider
Clinical research
Radiation oncology
Interventional radiology
Surgery
Patient


Shared Decision-Making (SDM) in Oncology
Collaborative Care
• Interconnection of essential players
• Patient-centered
• Communication is KEY
Oncology
Family
Nurse
Patient
Specialists
Pharmacist
Support Services
Adapted from: NQP Playbook: Shared Decision Making in Healthcare, 2018.

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:

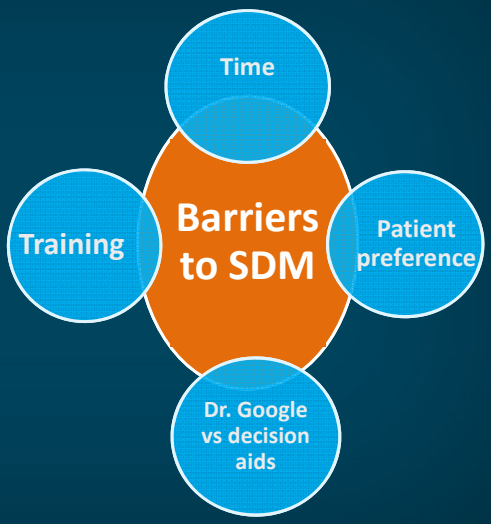
- Ensure each patient understands the risks and benefits of their options
- Incorporate patient preference(s) and goals to reach clinical decisions

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

Barriers to SDM

SDM obstacles include:

- Patients who prefer provider-based decisions
- Lack of encouragement to improve suboptimal 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.

Patient Education

Educational discussion	• Review mechanisms of treatment(s) • Use 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 • Use tools to recall dosing schedules, 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.

Revisiting the Case

Case: Mr. M

- 70-year-old man with hepatitis B presents with abdominal pain
- CT scan large, infiltrative mass with areas of arterial enhancement but no definite washout
- AFP = 1540 ng/ml
- Biopsy showed poorly differentiated HCC, Child-Pugh A
- Patient was treated with TACE; post TACE CT scan showed increase in size of mass and new pulmonary metastasis
- Patient initiated on sorafenib 400 mg BID
  - 3 weeks later, patient experiences grade III hand-foot skin reaction and grade 3 diarrhea
- CT scan at 2 months showed stable disease
- CT scan at 4 months showed new liver masses; AFP = 28,000 ng/L

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

Conclusions

HCC Practice Points

- Sorafenib, lenvatinib and atezolizumab+bevacizumab are recommended as first-line therapies for managing HCC
- Regorafenib, cabozantinib, ramucirumab, lenvatinib, nivolumab, nivolumab+ipilimumab, sorafenib, and pembrolizumab are recommended as second-line therapies for managing HCC
- Factors to take into account when selecting subsequent-line therapy include prior lines of therapy and 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

A Specialty Series Review of Targeted Tyrosine Kinase Inhibitors Used for the Management of
Advanced Hepatocellular Carcinoma

Receive your Certificate of Credit

Let us know how you liked the program

Please follow instructions below to obtain your certificate

Step 1: Go to ***www.medlearninggroup.com/event***

Step 2: Select an event

Step 3: Log in or create your free MLG account

Step 4: Complete your evaluation

Step 5: Print your certificate and download a PDF of the program slides

This activity is provided by Med Learning Group.
This activity is co-provided by Ultimate Medical Academy/CCM.

Supported by an educational grants from Bayer HealthCare Pharmaceuticals, Inc., Eisai, and Merck & Co., Inc.

THANK YOU

PLEASE TYPE QUESTIONS IN THE Q&A SECTION AT THIS TIME

Hepatocellular Carcinoma: Identification, Staging, and Management

Resource	Address
Bishayee A. The role of inflammation and liver cancer. *Adv Exp Med Biol*. 2014;816:401-435.	https://www.ncbi.nlm.nih.gov/pubmed/24818732
Eishaarawy O, et al. Intermediate stage hepatocellular carcinoma: a summary review. *J Hepatocell Carcinoma*. 2019;6;105-117.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6628956/
Finn RS, et al. Outcomes of sequential treatment with sorafenib followed by regorafenib for HCC: Additional analyses from the phase III RESORCE trial. *J Hepatology.* 2018;69(2):353-358.	https://www.ncbi.nlm.nih.gov/pubmed/29704513
Frerichs W, et al. Shared Decision-Making in Oncology – A Qualitative Analysis of Healthcare Providers' Views on Current Practice. *PLoS One*. 2016;11:e0149789.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4788421/
Hawley ST, Jagsi R. Shared Decision Making in Cancer Care: Does One Size Fit All? *JAMA Oncol*. 2015;1:58-59.	https://www.ncbi.nlm.nih.gov/pubmed/26182304
Kato S, et al. *RET* Aberrations in Diverse Cancers: Next-Generation Sequencing of 4,871 Patients. *Clin Cancer Res*. 2017;23:1988-1997.	https://www.ncbi.nlm.nih.gov/pubmed/27683183
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
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
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

Mittal S, et al. Temporal trends of nonalcoholic fatty liver disease-related hepatocellular carcinoma in the veteran affairs population. *Clin Gastro Hep*. 2015;13(3):594–601.e1.	https://www.ncbi.nlm.nih.gov/pubmed/25148760
Schrager SB, et al. A Simple Approach to Shared Decision Making in Cancer Screening. *Fam Pract Manag*. 2017;24:5-10.	https://www.ncbi.nlm.nih.gov/pubmed/28671358
Siegel RL, et al. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;69:7-34.	https://www.ncbi.nlm.nih.gov/pubmed/30620402
Vilgrain V, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. *Lancet Oncol*. 2017;18:1624.	https://www.ncbi.nlm.nih.gov/pubmed/29107679
Villanueva A. Hepatocellular Carcinoma. *N Engl J Med*. 2019;380:1450-1462.	https://www.ncbi.nlm.nih.gov/pubmed/30970190
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

Resources and Societies

Resource	Address
American Association for Cancer Research	https://www.aacr.org/
American Cancer Society	https://www.cancer.org/cancer/liver-cancer.html
American Society of Clinical Oncology	https://www.asco.org/
International Liver Cancer Association	https://ilca-online.org/
National Cancer Institute	https://www.cancer.gov/types/liver
National Comprehensive Care Network Guidelines	https://www.nccn.org/professionals/physician_gls/PDF/hepatobiliary.pdf