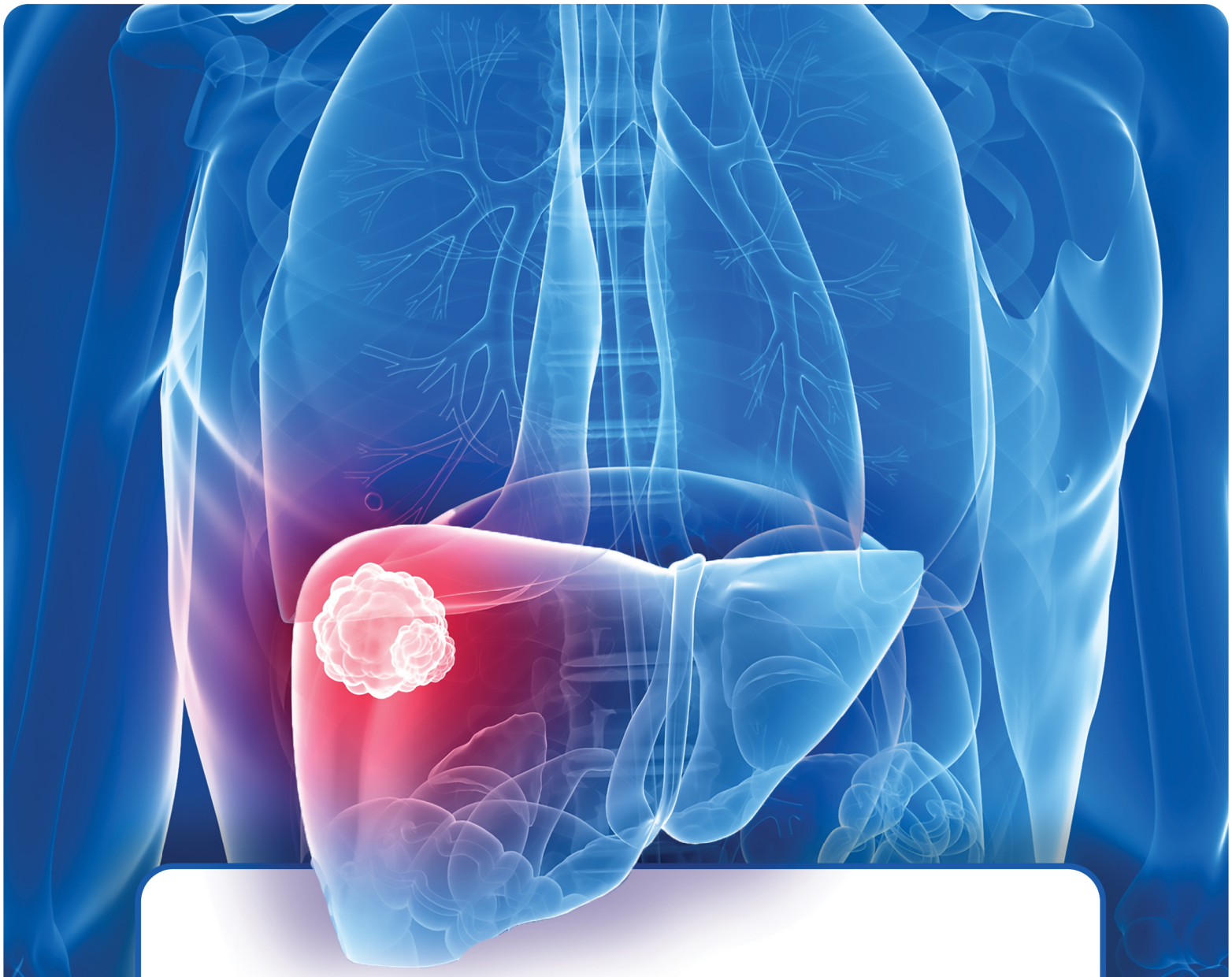

Recent Advances in the Management of Patients with

ADVANCED HEPATOCELLULAR CARCINOMA:

How Does Your Approach Compare with the Experts'?

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Medical Director, Hepatitis B Foundation
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San Diego, California

This activity is provided by Med Learning Group.
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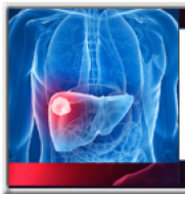

Recent Advances in the Management of Patients with **ADVANCED HEPATOCELLULAR CARCINOMA:**
How Does Your Approach Compare with the Experts'?

AGENDA

I. **A Look at Hepatocellular Cancer**
II. **Targeted Therapies for the Treatment of Patients With Advanced and/or mHCC**
    a. Current treatment landscape of approved systemic therapies (i.e., TKIs/MKIs and immune checkpoint inhibitors)
    b. MOAs and clinical profiles of therapies in development
III. **Management of Therapy-related Side Effects Associated with Immunotherapies**
    a. Pathophysiologic basis for irAEs in patients treated with immune checkpoint inhibitors for HCC
    b. Early diagnosis and intervention of TKI/MKI-associated AEs and immunecheckpoint inhibitor-associated irAEs
IV. **Biomarker-driven Targeted Therapy**
    a. Current state of biomarker-driven clinical trials
V. **Case studies**
VI. **Conclusions**
VII. **Questions and answers**
VIII. **Adjournment**

Recent Advances in the Management of Patients with Advanced Hepatocellular Carcinoma: How Does Your Approach Compare with the Experts'?

FACULTY

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PROGRAM OVERVIEW

These live virtual TeleECHO® sessions will be a faculty-led didactic and case-based lecture focusing on the management of patients with Hepatocellular carcinoma (HCC).

TARGET AUDIENCE

This activity is intended for U.S.-based hematologists/oncologists, hepatologists, gastroenterologists, interventional radiologists, pathologists, and other members of the multidisciplinary oncology team (NPs, PAs, pharmacists) responsible for the care of patients with HCC.

LEARNING OBJECTIVES

Upon completion of the program, attendees should be able to:

- Evaluate evidence from clinical trials assessing emerging therapies for the treatment of patients with advanced HCC
- Devise strategies to manage the therapy-related AEs associated with guideline-recommended systemic therapies for the treatment of advanced HCC
- Interpret data on biomarkers that may help inform treatment decision making for patients with advanced HCC

Accreditation Statement

Med Learning Group is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. This CME activity was planned and produced in accordance with the ACCME Essentials.

Credit Designation Statement

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Nursing Credit Information

Purpose: This program would be beneficial for nurses involved in the management of patients with HCC.

CNE Credits: 1.0 ANCC Contact Hour.

CNE Accreditation Statement

Ultimate Medical Academy/Complete Conference Management (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.

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Current Clinical Trial Alliance	Topography Healthy
Chair Clinical Advisory Board	Prodigy

Relationship	Manufacturer
Advisory Consultants: Diagnostic Companies	Fibronostics, Fujifilm/Wako, Perspectum, Quest, Sonic Incytes
Speakers Bureau	AbbVie, BMS, Eisai, Genentech, Gilead Sciences Inc., Intercept
Data Safety Monitoring Board	Arrowhead, CymaBay Therapeutics, Durect
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Minor stock shareholder (liver space noted only)	RiboSciences, CoCrystal
Stock Options	Eiger, Genlantis, HepQuant, AngioCrine

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.

Douglas Cox, MSN, MHA, RN
Ultimate Medical Academy/CCM – Lead Nurse Planner

The reviewer of this activity has nothing to disclose

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2. Participate in the live virtual activity.
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- If you would like to post a question or answer during the presentation, please submit your question or response in the chat feature.
- Remember to direct all questions to the "co-host." There is a toggle button above the typing space that allows you to specify the location of your message delivery.

Recent Advances in the Management of Patients with Advanced Hepatocellular Carcinoma: How Does Your Approach Compare with the Experts'?

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Learning Objectives

- Evaluate evidence from clinical trials assessing emerging therapies for the treatment of patients with advanced HCC
- Devise strategies to manage the therapy-related AEs associated with guideline-recommended systemic therapies for the treatment of advanced HCC
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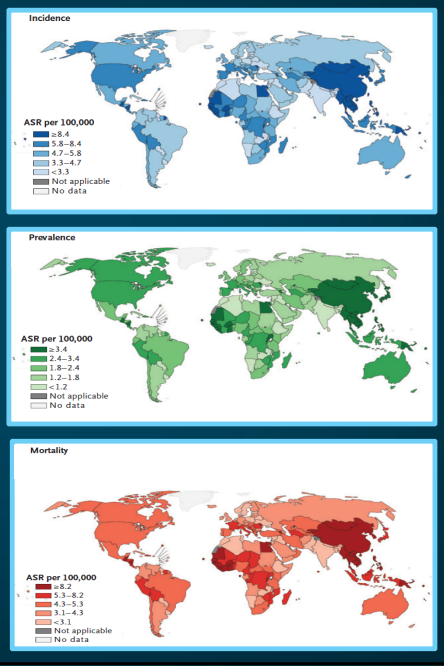
A Look at Hepatocellular Carcinoma

Hepatocellular Carcinoma (HCC)

- HCC accounts for the majority of primary liver cancers
- As of 2018, liver cancers were the 4th most common cause of cancer-related death
  - Prior to 2018, liver cancers were the 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 United States, 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

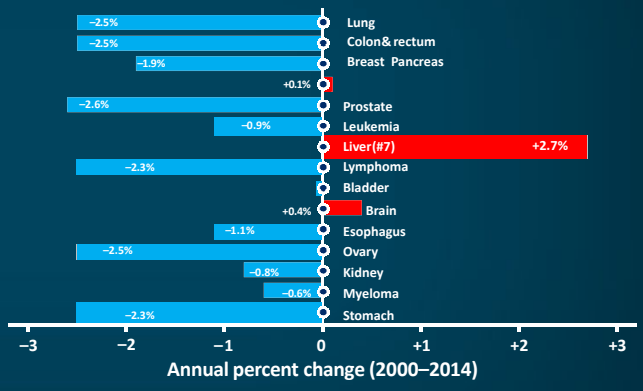


Villanueva A. *N Engl J Med*. 2019;380:1450-1462.

HCC Mortality in United States Is Increasing

- Approximately 42,000 cases of primary liver cancer and intrahepatic bile-duct cancer were diagnosed in the 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

Top 15 causes of cancer death in the US 2000–2014



Siegel RL, et al. *CA Cancer J Clin*. 2019;69:7-34. American Cancer Society (ACS). *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 September 1, 2021.

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 1 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).

Biomarker Panel May Improve Early HCC Detection: GALAD

- **GALAD**: **G**ender, **A**ge, AFP-**L**3, **A**FP, and **D**CP
- Performance evaluated in multinational cohort study of 6834 patients (2430 with HCC, 4404 with 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 <5 cm)	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.

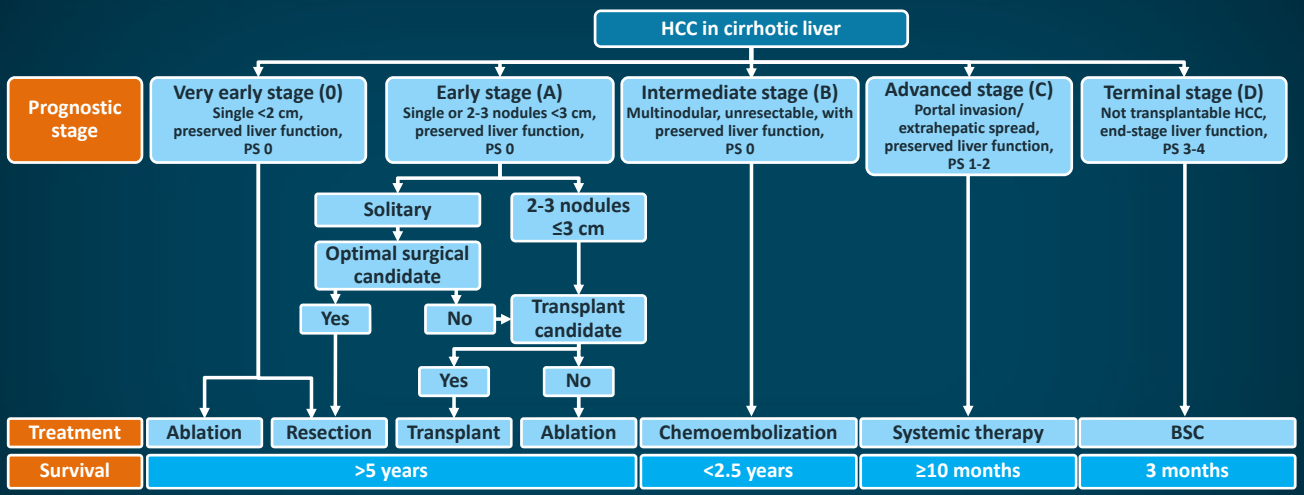
Berhane S, et al. *Clin Gastroenterol Hepatol*. 2016;14:875-886.e6.

Child-Pugh Scoring System

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

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

Modified BCLC Staging and Treatment (EASL)



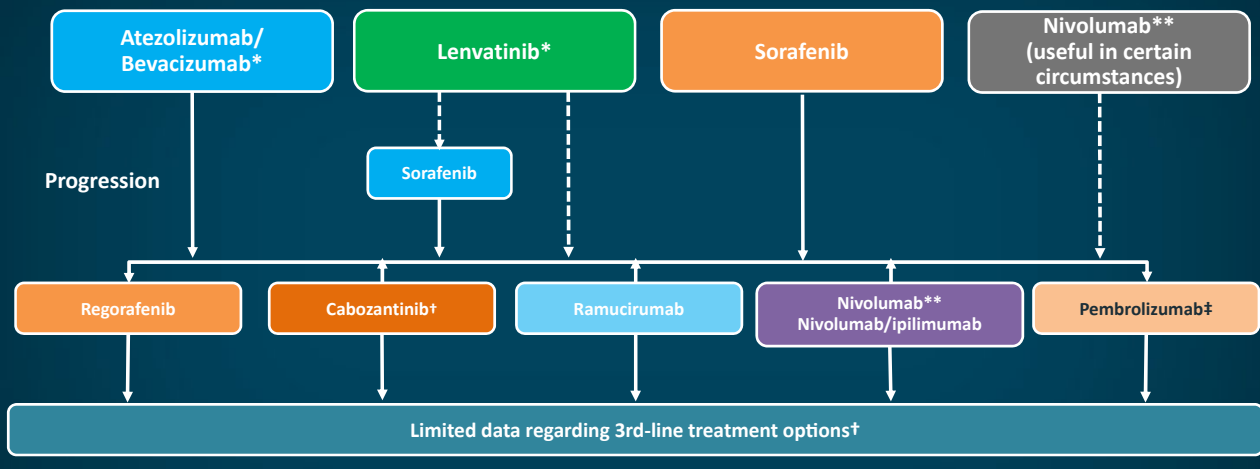
Modified BCLC is used to predict prognosis of patients with HCC based on tumor burden, liver function (Child-Pugh), clinical status, and cancer-related symptoms (ECOG PS)

BCLC = Barcelona Clinic Liver Cancer; ECOG = Eastern Cooperative Oncology Group; PS = performance status; BSC = best supportive care.

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.

Targeted Therapies for the Treatment of Patients With Advanced and/or mHCC

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.
**As of July 2021, the FDA has withdrawn the indication for nivolumab as a single agent for patients with HCC who were previously treated with sorafenib; off-label use.

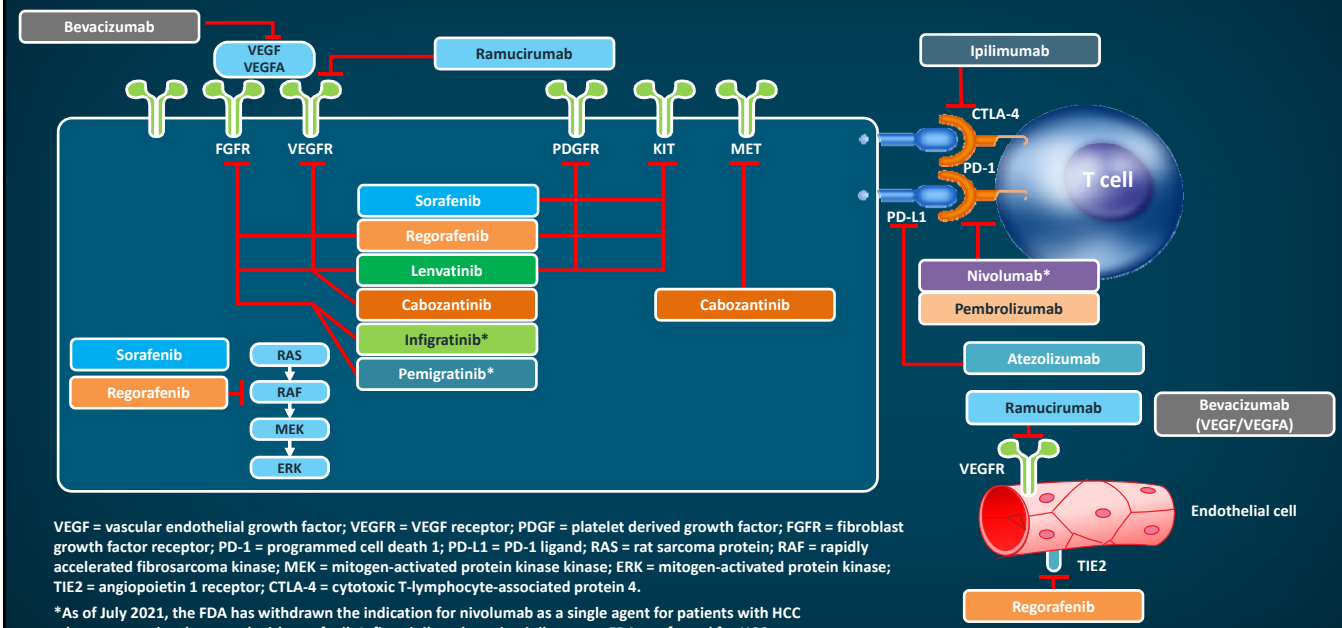
Adapted from Li D, et al. *Cancers (Basel)*. 2019;11:841. National Comprehensive Cancer Network (NCCN). Hepatobiliary cancers. Version 4.2021. 8.26.2021. (www.nccn.org/professionals/physician_gls/PDF/ hepatobiliary.pdf).

Approved First-Line Systemic Therapy Options for HCC

Agent	FDA indication	Key trial	Population
Sorafenib	Unresectable HCC	SHARP	Child-Pugh A or B7
Lenvatinib	Unresectable HCC	REFLECT	Child-Pugh A
Atezolizumab	In combination with bevacizumab for patients with unresectable or metastatic HCC	IMbrave150	Child-Pugh A

Sorafenib (Nexavar®) PI 2018. (http://labeling.bayerhealthcare.com/html/products/pi/Nexavar_PI.pdf). Lenvatinib (Lenvima®) PI 2019. (www.lenvima.com/ pdfs/prescribing-information.pdf). Atezolizumab (Tecentriq®) PI 2020. (https://www.gene.com/download/pdf/tecentriq_prescribing.pdf). All URLs accessed September 1, 2021.

Targeted Therapies for HCC



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.

*As of July 2021, the FDA has withdrawn the indication for nivolumab as a single agent for patients with HCC who were previously treated with sorafenib.Infigratinib and pemigatinib are not FDA-app[roved for HCC.

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

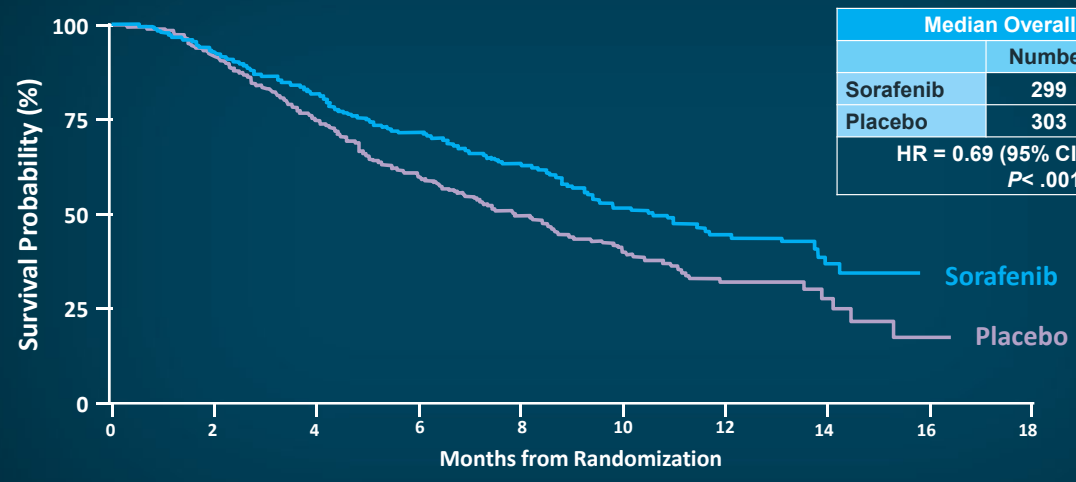
NCCN Recommended Therapies for HCC

Therapies	Disease characteristics
Subsequent-line therapy	
Preferred	
Regorafenib	• Child-Pugh Class A only
Cabozantinib	• Child-Pugh Class A only
Ramucirumab	• AFP ≥400 ng/mL only
Lenvatinib	• Child-Pugh Class A only
Sorafenib	• Child-Pugh Class A or B7 (after first-line lenvatinib)
Other recommended regimens	
Pembrolizumab	• Child-Pugh Class A only
Nivolumab/ipilimumab	• Child-Pugh Class A only
Useful in certain circumstances	
Nivolumab*	• Child-Pugh Class A or B

*As of July 2021, the FDA has withdrawn the indication for nivolumab as a single agent for patients with HCC who were previously treated with sorafenib.

NCCN. Hepatobiliary cancers. Version 4.2021. 8.26.2021. (www.nccn.org/professionals/physician_gls/PDF/ hepatobiliary.pdf).

Sorafenib Improves Survival for Advanced HCC

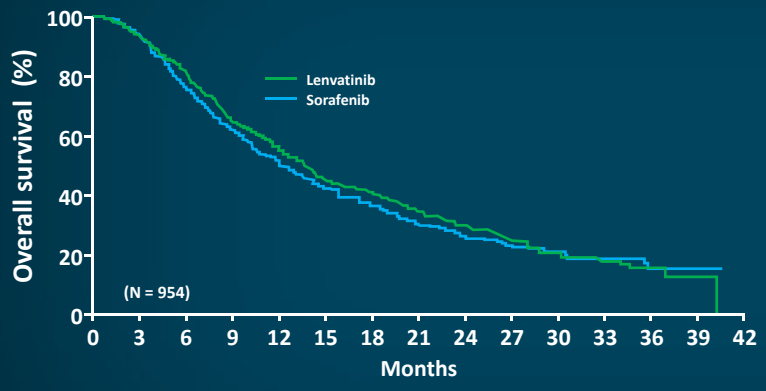


Median Overall Survival		
	Number	Months
Sorafenib	299	10.7
Placebo	303	7.9
HR = 0.69 (95% CI: 0.55–0.87) *P*< .001		

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

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

Lenvatinib Is Noninferior to Sorafenib



Outcomes		
Outcome	Lenvatinib (n = 478)	Sorafenib (n = 476)
mOS, months (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, months	8.9	3.7
HR for TTP = 0.60 (95% CI: 0.51–0.71)		

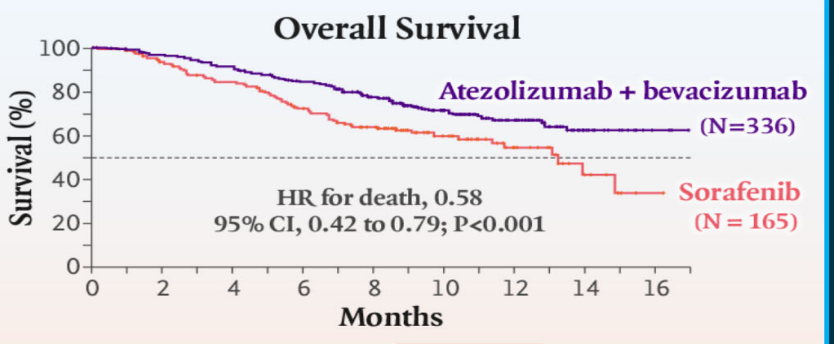
mOS = median overall survival; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; TTP = time to progression.

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

Atezolizumab/Bevacizumab as First-Line Therapy in HCC: IMbrave150

PHASE 3, OPEN-LABEL, MULTICENTER, RANDOMIZED TRIAL

501
Patients with locally advanced hepatocellular carcinoma (metastatic, unresectable, or both)



Median progression-free survival

Atezolizumab + bevacizumab	Sorafenib
6.8 Mo	4.3 Mo

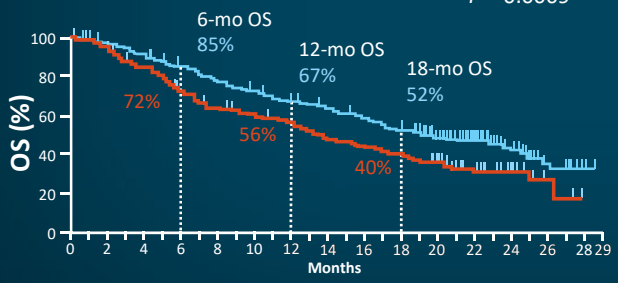
HR for disease progression or death, 0.59; 95% CI, 0.47 to 0.76; P<0.001

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

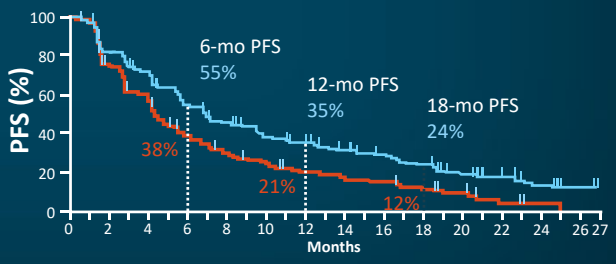
IMbrave150: Updated OS and PFS

Primary analysis OS/PFS HR: 0.58/0.59 (median follow-up 8.6 months)

	Atezo + Bev (n = 336)	Sorafenib (n = 165)
Median OS, months (95% CI)	19.2 (17.0-23.7)	13.4 (11.4-16.9)
Stratified HR (95% CI)	0.66 (0.52-0.85) *P* = 0.0009	



	Atezo + Bev (n = 336)	Sorafenib (n = 165)
Median PFS, months (95% CI)	6.9 (5.7-8.6)	4.3 (4.0-5.6)
Stratified HR (95% CI)	0.65 (0.53-0.81) *P* = 0.0001	



Median follow-up: 15.6 months.

Finn RS, et al. *N Engl J Med*. 2020;382:1894-1905. Finn RS, et al. American Society of Clinical Oncology (ASCO) Gastrointestinal (GI) 2021; Abstract 267.

IMbrave150: Updated Response (cont)

July 2021

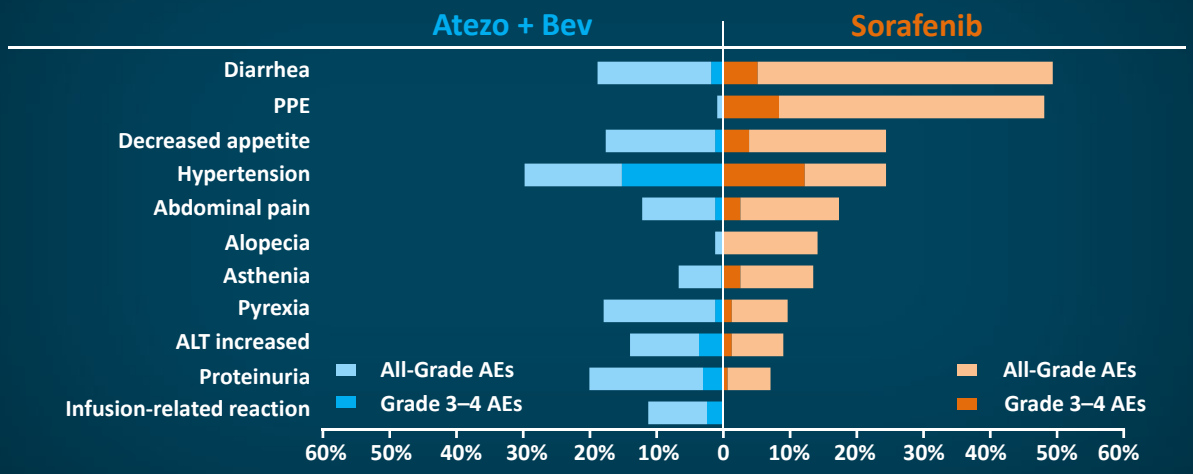
Outcome	Non High Risk		High Risk		ITT	
	Atezo + Bev	Sorafenib	Atezo + Bev	Sorafenib	Atezo + Bev	Sorafenib
Evaluable for OS/PFS, n	272	128	64	37	336	165
Median OS (95% CI), mo	22.8 (19.1, 24.9)	15.7 (13.2, 19.0)	7.6 (6.6, 12.8)	5.5 (4.1, 6.7)	19.2 (17.0, 23.7)	13.4 (11.4, 16.9)
HR (95% CI)	0.68 (0.51, 0.91)		0.62 (0.39, 1.00)		0.66 (0.52, 0.85)	
Median PFS (95% CI), mo	7.2 (6.5, 9.6)	4.4 (4.0, 5.8)	5.4 (4.0, 6.9)	2.8 (2.5, 5.3)	6.9 (5.7, 8.6)	4.3 (4.0, 5.6)
HR (95% CI)	0.61 (0.48, 0.78)		0.74 (0.47, 1.17)		0.65 (0.53, 0.81)	
Evaluable for ORR, n	263	124	63	35	326	159
Confirmed ORR, n (%)	81 (31)	13 (10)	16 (25)	5 (14)	97 (30)	18 (11)
Complete response, n (%)	20 (8)	0	5 (8)	1 (3)	25 (8)	1 (1)
Median DoR (95% CI), mo	19.0 (14.6, NE)	12.6 (4.9, 17.0)	16.3 (13.5, NE)	16.5 (3.9, NE)	18.1 (14.6, NE)	14.9 (4.9, 17.0)

High-risk pts were defined as those who had tumor invasion of the main trunk of the portal vein and/or the portal vein branch contralateral to the primarily involved lobe (Vp4), and/or bile duct invasion and/or tumor occupancy of ≥ 50% of liver

Finn RS, et al. In: Proceedings of the American Association for Cancer Research Annual Meeting 2021; 2021 Apr 10-15 and May 17-21. Philadelphia (PA): AACR; *Cancer Res*. 2021;81(13_Suppl):Abstract nr CT009; https://cancerres.aacrjournals.org/content/81/13_Supplement/CT009.

IMBrave 150: Safety*

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



*Safety-evaluable population

PPE = palmar-plantar erythrodysesthesia.

Finn R, et al. *Liver Cancer Summit.* 2021: abstract O05

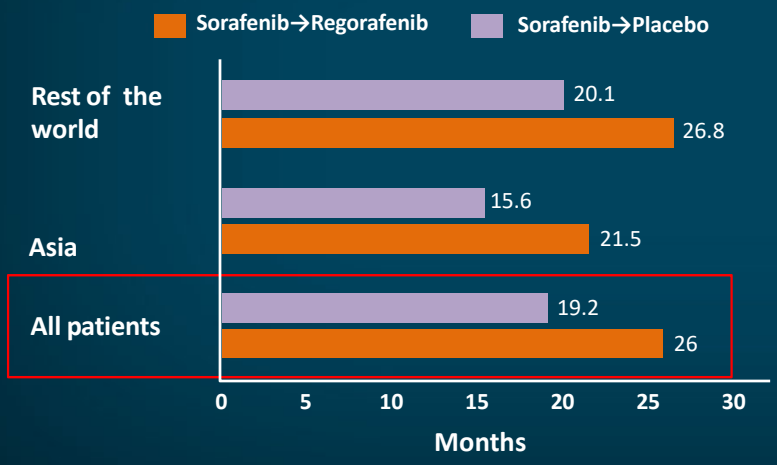
Key Warnings and Precautions for First-Line Atezolizumab/Bevacizumab

- Atezolizumab
  - History of organ transplant
  - History of autoimmune disease
  - Immune-mediated pneumonitis, hepatitis, colitis, endocrinopathies
- Bevacizumab
  - GI perforations
  - Surgery in last 28 days; incompletely healed wound
  - Recent hemoptysis or major bleed (variceal bleeding)
  - Fistula
  - Uncontrolled hypertension
  - >2 g proteinuria
  - Congestive heart failure

Atezolizumab (Tecentriq®) PI 2020. Bevacizumab (Avastin®) PI 2021.

Sequential Therapy Prolongs Survival

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

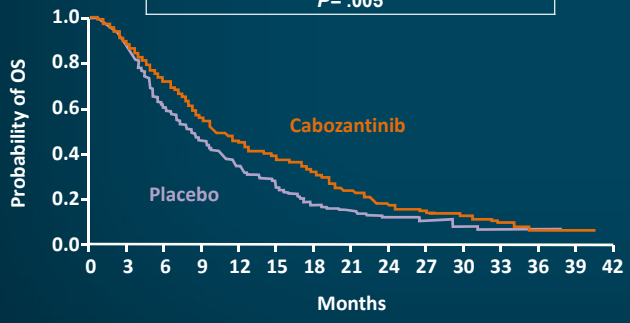


Survival	Sorafenib-regorafenib (n = 379)	Sorafenib-placebo (n = 194)
12 months	82%	76%
24 months	53%	42%
36 months	31%	20%
48 months	19%	12%
60 months	16%	3%
72 months	10%	3%

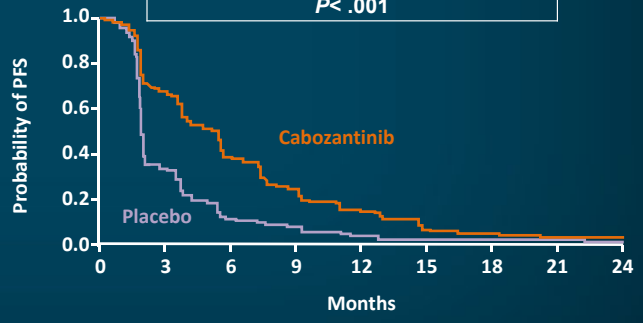
Finn RS, et al. *J Hepatology*. 2018;69(2):353-358.

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.

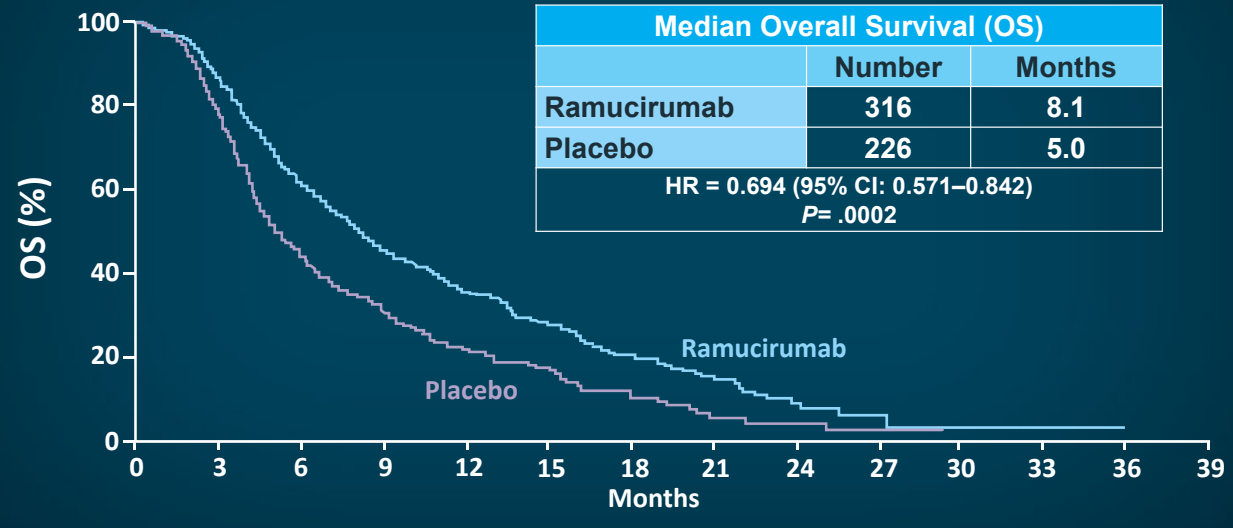
CELESTIAL: Select Treatment-Related AEs

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

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

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

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



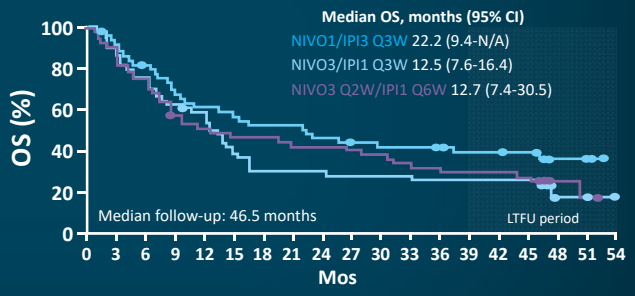
Median Overall Survival (OS)		
	Number	Months
Ramucirumab	316	8.1
Placebo	226	5.0
HR = 0.694 (95% CI: 0.571–0.842) *P*= .0002		

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

CheckMate 040: Nivolumab + Ipilimumab for Advanced HCC

- Open-label phase 1/2 trial of 3 different dosing schemes of **nivolumab + ipilimumab** for patients with advanced HCC and prior sorafenib treatment; Child-Pugh score A5-A6; ECOG PS 0/1
- Dosing
  - **NIVO1/IPI3 Q3W**: nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W (4 doses)
  - **NIVO3/IPI1 Q3W**: nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W (4 doses), each followed by nivolumab 240 mg Q2W
  - **NIVO3 Q2W/IPI1 Q6W**: nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W

	NIVO1/IPI3 Q3W (n = 50)	NIVO3/IPI1 Q3W (n = 49)	NIVO3 Q2W/ IPI1 Q6W (n = 49)
ORR, % (95% CI)	32 (20-47)	31 (18-45)	31 (18-45)



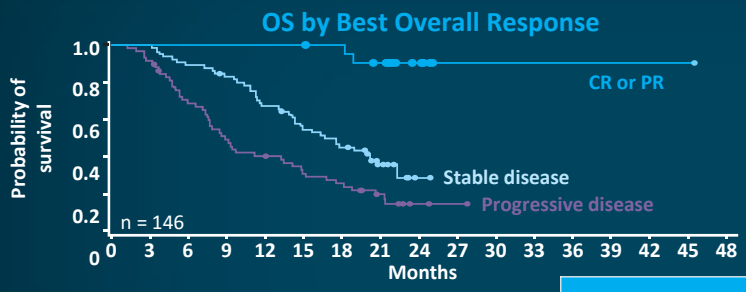
Nivolumab + ipilimumab FDA-approved for patients with HCC who have been previously treated with sorafenib

LTFU = lost to follow-up.

Yau T, et al. *JAMA Oncol*. 2020;6:e204564. El-Khoueiry AB, et al. ASCO GI 2021; Abstract 269.

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

Nivolumab Alone



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)

*As of July 2021, the FDA has withdrawn the indication for nivolumab as a single agent for patients with HCC who were previously treated with sorafenib.

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

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 patients randomized to NIVO + CABO (n = 36) or NIVO + IPI + CABO (n = 35)
- Investigator-assessed ORR was 17% (6 patients with partial response [PR]) in the NIVO + CABO arm; 26% (9 patients with PR) in the NIVO + IPI + CABO arm
- DCR was 81% for the NIVO + CABO arm; 83% for the NIVO + IPI + CABO arm
- Median PFS was 5.5 months for the NIVO + CABO arm and 6.8 months 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

***Investigational combination.**

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

Selected Ongoing Trials* Assessing Combination Therapies for Advanced and/or mHCC

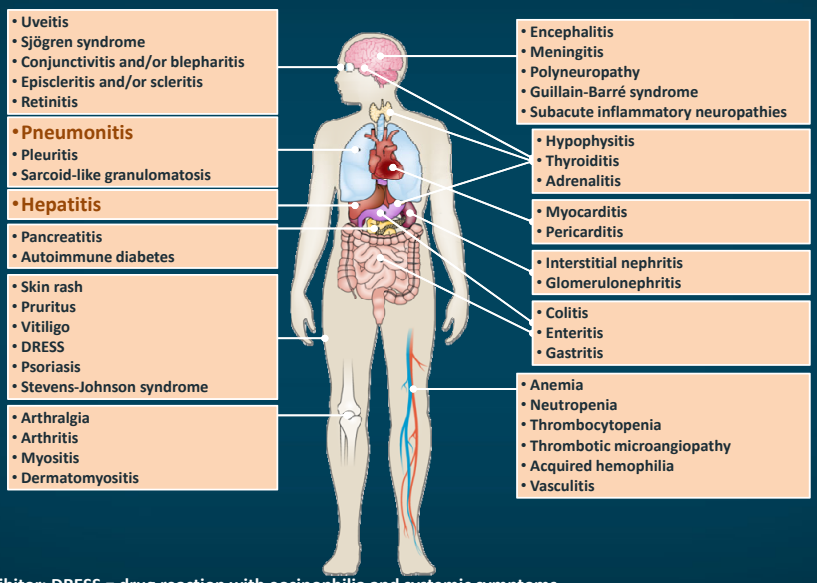
Study	Agent(s)	Phase
LEAP-002[1]	Lenvatinib + pembrolizumab vs lenvatinib	3
HIMALAYA[2]	Durvalumab + tremelimumab vs sorafenib	3
COSMIC-312[3]	Cabozantinib ± atezolizumab vs sorafenib	3
CheckMate 9DW[4]	Nivolumab + ipilimumab vs sorafenib or lenvatinib	3

***Investigational approaches.**

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.

Management of Therapy-related Side Effects Associated with Systemic Therapies for HCC

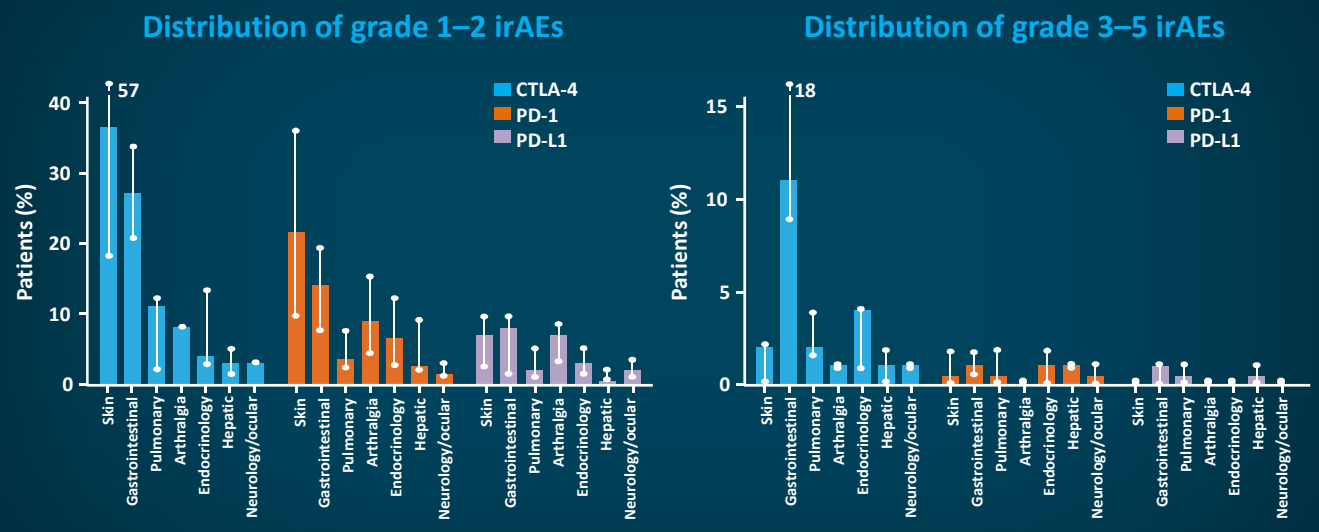
Autoimmune Organ Targets and Disease From ICI Therapy



ICI = immune checkpoint inhibitor; DRESS = drug reaction with eosinophilia and systemic symptoms.

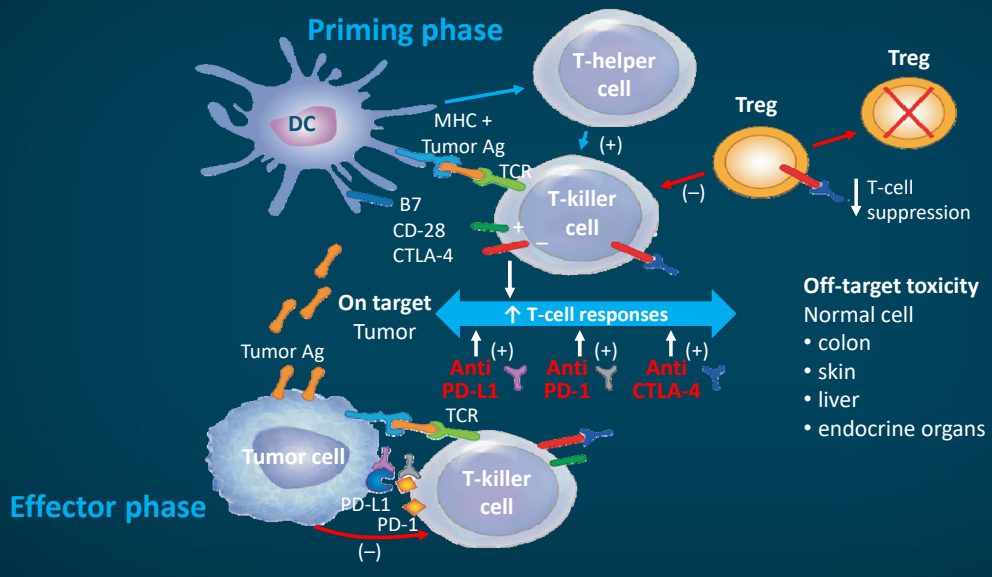
Modified from Michot JM, et al. *Eur J Cancer*. 2016;54:139-148.

Immune-Related Adverse Events (irAEs)



Modified from Michot JM, et al. *Eur J Cancer*. 2016;54:139-148.

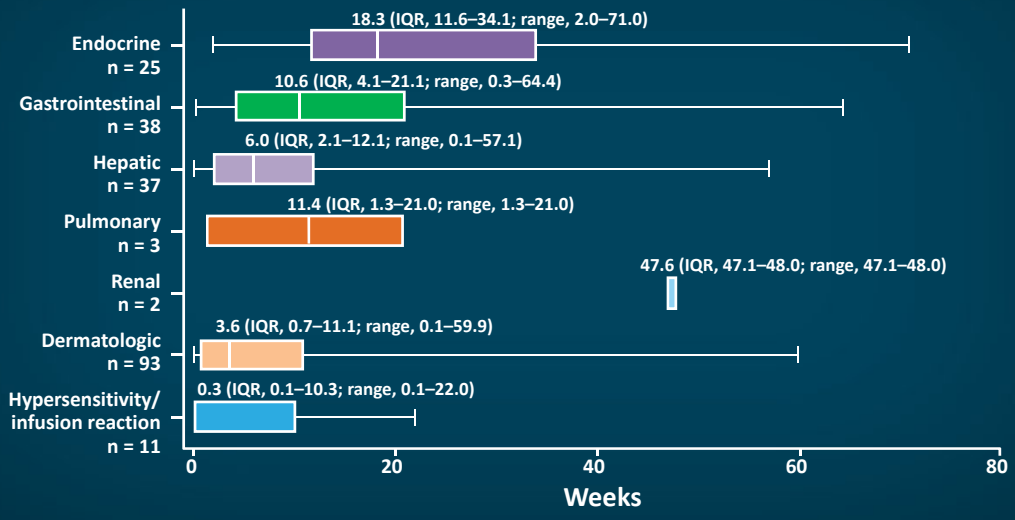
Pathogenesis of Immune-Related AEs



MHC = major histocompatibility complex.

irAEs May Occur Even After Therapy Ends

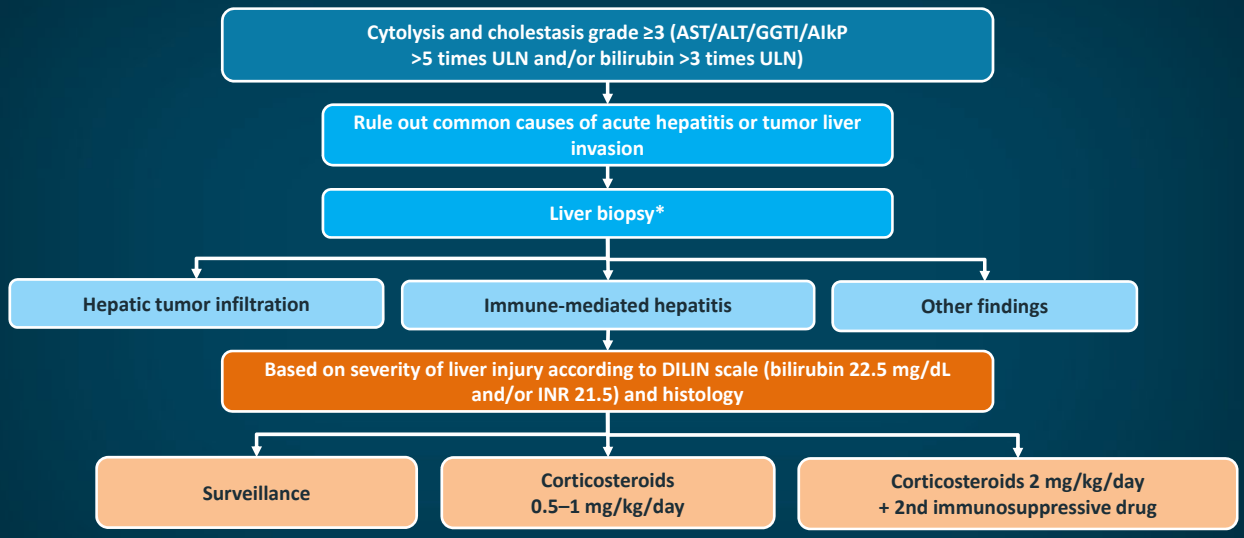
PD-1 inhibition with nivolumab—time to onset of irAEs



IQR = interquartile range.

Sangro B, et al. *Hepatology.* 2017;66(1 suppl):82A (abstract 141).

Immunotherapy-Related Hepatitis



*liver biopsy is not required in case of acute viral hepatitis

GGTI = gamma-glutamyl transpeptidase test; AlkP = alkaline phosphatase; ULN = upper limit of normal; DILIN = Drug-Induced Liver Injury Network; INR = international normalized ratio.

De Martin E et al, *Jhep*. 2018;68(6):1181-1190.

Grading for Hepatotoxicity

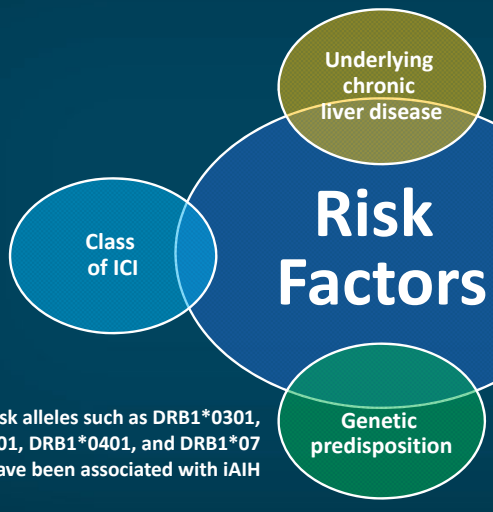
Utilize common terminology criteria of AEs: CTCAE—NCI

- Severity based on peak abnormalities of liver biochemistry AST/ALT/ALP/GGT
- Higher grades of severity—3 and 4
- INR not included
- Always check bilirubin, including direct bilirubin. ALT and AST are not liver-function tests

CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute;

Colevas D, Setser A. *J Clin Oncol*. 2004;22(14 suppl): abstract 6098.

Risk Factors That May Predispose to Checkpoint Inhibitor-Induced Hepatotoxicity



PD-1/PD-L1 pathway is known to be upregulated in chronic viral hepatitis and blocking this pathway may have a clinical benefit in these diseases

CTLA-4 inhibitors have been associated with a higher incidence of irAEs than PD-1 and PD-L1 inhibitors when used as monotherapy

In dose-ranging study of ipilimumab for retreating advanced melanoma, no grade 3–4 hepatic AEs observed at dose of 0.3 mg/kg, but these toxicities increased to 30% with 10 mg/kg dose

HLA risk alleles such as DRB1*0301, DRB3*0101, DRB1*0401, and DRB1*07 have been associated with iAIH

iAIH = idiopathic autoimmune hepatitis.

Jennings JJ, et al. *Expert Opin Drug Metab Toxicol.* 2019;15:231-244.

Clinicopathologic Features and Outcomes of Hepatic Injury

Feature	ICI-IMH	iAIH	DI-AIH
Onset following drug exposure	3–9 weeks	Not applicable	Months to years
Presence of other autoimmune disorders	Data unavailable	25–40%	21%
Mean peak liver enzymes, including jaundice	Usually <5 ULN, Less than 2% >10 ULN	AST: 154–1031 IU; ALT: 185–1141 IU; Bili: 2–4 mg	ALT: 291–956 AST: 255–1141; Bili: 4–13 mg
Clinical presentation	Most commonly asymptomatic on routine monitoring	20% present with acute hepatitis; others are insidious	Insidious
Autoimmune serology	Absent or rare	Type I: ANA (70–80%); SMA (34–45%); Anti-LKM1 (3%)	ANA positivity 83% SMA (16–50%)
Histology	**CTLA-4:** panlobular hepatitis with centrilobular necrosis, granulomatous hepatitis with fibrin ring granulomas, central vein endothelitis **PD-1/L1:** lobular hepatitis with centrilobular necrosis, periportal inflammation; however, no fibrin-ring granulomas. Rare cholestatic injury with ductopenia	Interface hepatitis with lymphocytic/lymphoplasmacytic infiltrate, rosettes, and emperipolesis (presence of intact cell within cytoplasm of another cell)	Indistinguishable from iAIH
Immunohistochemistry	Usually CD3+ and CD8+	Usually CD4+ and CD20+	Indistinguishable from iAIH
Response to steroids	88% for grade 3 or 4 hepatitis	20% achieve complete remission; 80% require ongoing immunosuppression due to relapse on withdrawal	Resolves on withdrawal of agent in 40% patients; 60% required steroids but rarely relapsed after withdrawal

ICI-IMH = immune-mediated hepatitis from ICIs; DI-AIH = drug-induced AIH; ANA = antinuclear antibodies; SMA = smooth-muscle antibodies; LKM1 = liver kidney microsomal-1.

Jennings JJ, et al. *Expert Opin Drug Metab Toxicol.* 2019;15:231-244.

Immunotherapy-Related Hepatitis ASCO Guidelines for Treatment

	Immunotherapy Recommendations and Monitoring	Treatment
AST/ALT <3x ULN **Total bilirubin <1.5x ULN**	• Continue therapy • Monitor labs 1–2x/week	• None
AST/ALT 3–5x ULN **Total bilirubin 1.5–3x ULN**	• Hold therapy until recovered • Monitor labs every 3 days	• Prednisone 0.5–1 mg/kg/d if persists more than 3–5 days • Taper over at least 1 month
AST/ALT 5–20x ULN **Total bilirubin 3–10x ULN**	• Permanently discontinue • Monitor labs every 1–2 days	• Methylprednisolone 1–2 mg/kg • If no improvement after 3 days, consider mycophenolate mofetil or azathioprine (test for TPMT deficiency) • Taper steroids around 4–6 weeks
AST/ALT >20x ULN **Total bilirubin >10x ULN** **Decompensated liver function**	• Permanently discontinue • Inpatient monitoring • Consider transfer to tertiary care facility	• Methylprednisolone 2 mg/kg • If no improvement after 3 days, consider mycophenolate mofetil • Taper steroids around 4–6 weeks

ASCO = American Society of Clinical Oncology; TPMT = thiopurine methyltransferase.

Brahmer JR, et al. *J Clin Oncol.* 2018;36:1714-1768.

Clinically Significant Hepatotoxicity Often Leads to Treatment Discontinuation

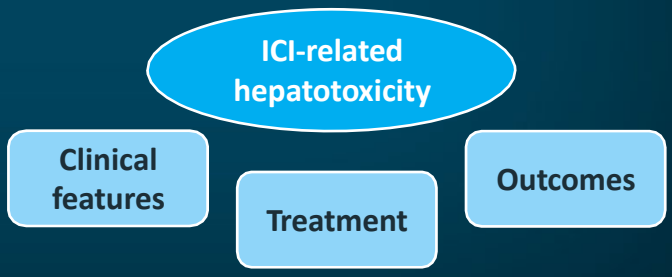
Background

- Immune checkpoint inhibitors are efficacious in advanced cancer
- Hepatotoxicity can impact ICI-based therapy
- Limited information about features of ICI hepatotoxicity (ICI-HT)

Design

- Retrospective
- ICI exposure
- ICI-HT ALT >5x ULN
- January 2010–March 2018

Objectives



Miller ED, et al. *Am J Gastroenterol.* 2020;115:251-261. Abu-Sbeih H, et all. *Hepatology*. 2018;68(suppl 1):25A-26A(abstract 39).

Clinical Profiles of Patients with Immune-Related ICI-Related Hepatic AEs

Characteristics	Steroids n = 67	No steroids n = 33	P-value
ALT, median U/L (IQR)	540 (300–2100)	408 (297–1188)	.075
Underlying liver disease, n (%)	27 (40)	11 (33)	.768
ICI discontinued, n (%)	49 (73)	20 (61)	—
Time from liver injury to ALT improvement, days (IQR)	23 (14–35)	14 (8–27)	.043

Miller ED, et al. *Am J Gastroenterol.* 2020;115:251-261. Abu-Sbeih H, et all. *Hepatology*. 2018;68(suppl 1):25A-26A(abstract 39).

Biomarker-Driven Targeted Therapy

Biomarkers for HCC management

Not ready for prime time (yet)

- Need advances in PD1 and PDL1 detection
- FNA tools need to be refined to supplement or replace liver biopsy
- ctDNA and cfDNA in blood and urine are in development
- Immunotyping the patient, the liver around the tumor, and the cancer itself are in development
- Formalizing liver biopsy and tumor biopsy as a tool to guide therapy is also evolving

HCC Practice Points

- Sorafenib, lenvatinib, and atezolizumab/bevacizumab are FDA-approved as first-line therapies for the management of HCC
- Regorafenib, cabozantinib, ramucirumab, nivolumab*, nivolumab/ ipilimumab, sorafenib, and pembrolizumab are FDA-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 and adverse event profile
  - ECOG status, BCLC, frailty, sarcopenia
- Single-agent immune checkpoint inhibitors have not met end points in phase 3 studies to date; however, combinations are showing promise

*As of July 2021, the FDA has withdrawn the indication for nivolumab as a single agent for patients with HCC who were previously treated with sorafenib.

Case 1

- 61 yo man; smoker; recently stopped drinking 2 large bottles of beer daily
- Dyspepsia and lethargy for 2-3 months

Physical Exam
- Alert, oriented, no flap
- Palmar erythema, 7-8 spider naevi
- 1 FB hepatomegaly, barely palpable spleen
- No ascites

- Alb 35 g/L, 1.2 mg/dL, INR 1.09, ALT 187 U/L
- Creatinine 1.0 mg/dL, platelet 123x10^9/L
- HBsAg (–), Anti-HBc total (+), HBV DNA (-)
- Anti-HCV (+), HCV RNA 6.16 log IU/mL, G3A
- AFP 124 ug/L
- Small esophageal varices on EGD
- CT April: 4 LIRADs 5 HCCs ranging from 1.6 - 4.8cm
- TACEs x 3 performed over next 2 years in referring hospital to control HCC

Disease Course

- Sept – TACE, with complete response
- Oct 15 – May 16: No active disease/stable disease
- Jun-Nov : Recurrence, TACE x 2 segment 5,6
- Peak AFP 134
- Referred to UH in Jan following year
- Child Pugh A6
- MRI Feb – 4 LIRAD 5 T lesions with active AE
  - Focus of arterial enhancement with nodular washout in the post TACE nodule in the caudate lobe is suspicious for residual disease (2.3cm).
  - Seg VII 2.8cm arterial enhancement with washout
  - 2 other nodules (1.8cm, 2cm) in Seg VI with arterial enhancement but no washout
- AFP 123 ug/L

Question

Which of the following treatment options should you consider?

A. TACE+/-RFA
B. Y90 radioembolization
C. Liver transplant
D. Stereotactic body radiation therapy
E. Systemic therapy

Case 1: Results

- FDG-PET: mild FDG-avidity (SUVmax 2.5, TNR 1.2) in caudate lobe lesion
- Acetate-PET: 5 strongly avid lesions (SUVmax >10) in seg VI and VII
- No living donor
- Failed Y90 workup – due to lung shunting

Question

Which of the following treatment options would you consider now?

A. A/B
B. Sorafenib
C. Lenvatinib
D. Stereotactic body radiation therapy
E. Clinical trial
F. Best supportive care

- Patient opted to accept A/B
- Started on trial therapy in July
- Pre-trial bloods:
  - Alb 37, Bil 33, INR 1.11, Creatinine 73, **ALT 147**
  - HCV 6.54 log IU/mL
- August
  - No ascites, no flap, no symptoms
  - Alb 32, Bil 57 (G2 A/E), INR 1.28, **ALT 516** (G3 A/E)

Question

How would you manage this patient's worsening liver enzymes?

A. Treat with steroids
B. Treat the hepatitis C with DAAs
C. Liver biopsy
D. Treat with steroids and DAAs

Case 2: Mr. TSH

- 67 yo retired engineer

Chronic HCV cirrhosis GT1 since 2005

- Treatment failure with PR
- SVR24 with SOF/DAC/RIB 12w in 2015 cure
- Childs A cirrhosis
- Esophageal varices treated with EVL 2008
- Hypertension
- No allergies
- Meds: Propranolol, nifedipine

Family History

- Brother also has HCV

Disease Course

Developed HCC (multifocal)

- After treatment with TACE x5, in April 2 years later liver shunting found on MRI, making further TACE unsuitable
- HCC status: multifocal HCC 1.3 to 1.7cm (4 lesions) LIRADs 5 with washout, portal vein patent, no thrombus, no extrahepatic disease
- AFP 22
- LFT: Alb 42, bil 8, AST 47, ALT 32, ALP 111
- INR 1.09
- FBC: HB 13.7, WCC 4.94, Plts 135,000

Question

What is the best option?

A. Y90 radioembolization
B. Liver transplantation
C. Best supportive care
D. Systemic therapy

Does not meet criteria for liver transplantation

- Offered sorafenib/lenvatinib or AB immunotherapy
- Patient opted for oral therapy due to inability to travel for IV therapy given COVID
- AFP 254
- Patient developed HTN and proteinuria on LEN but tolerable protein was <1 gm per day and HTN well controlled on dual therapy
- After 13 weeks, noted to have new lung lesions and disease progression in the liver
- AFP 3250

Question

What would you recommend next?

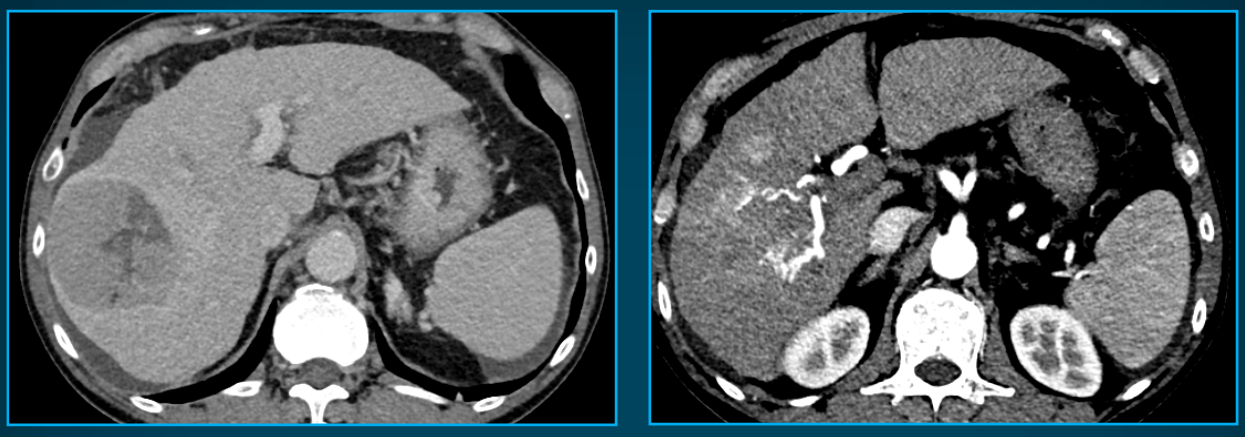
A. Best supportive care
B. Sorafenib
C. AB therapy
D. Clinical trial

Patient agrees to participate in AB as a second-line therapy

- Progresses after 17 weeks of therapy
- MRI shows interval worsening with multiple new lung metastases, subphrenic mass in seg 7 infiltrating IVC, and new enhancing lesions in liver
- AFP 26,572
- Oncologist advises to stop therapy and refer for clinical trials
  - Discussed ramucirumab

Case 3

- 48 yo man, ECOG 0
- HBV cirrhosis (Child Pugh A6) on tenofovir
  - Bili 1.g mg/dL, Alb 3.2 mg/dL, INR 1.19, Cr 1.4mg /dL
  - Platelet 79k
  - Large esophageal varices
  - No ascites
- HCC first diagnosed June
  - Right lobe 4 lesions (size 6.1/2.3/1.9/1cm, AFP 2297, no vascular invasion, no extra-hepatic spread)



HBV cirrhosis (A6), multifocal BCLC B HCC
No vascular invasion, no extra-hepatic spread

Question

Which of the following treatment options would you consider?

A. Living related liver transplant
B. TACE
C. Y90
D. Multikinase inhibitor
E. Immunotherapy/VEGF
F. Clinical trial

First TACE

- Repeat CT 1 month later: Largest lesion showed partial response, other 3 lesions stable in size but still arterially enhanced with washout

Second TACE

- CT 1 month later: Largest lesion increases to 6.9 cm with arterial enhancement; 1 of the smaller lesions is now 2.5cm. The other 2 lesions are stable in size but with no arterial enhancement or washout.
- AFP 2977
- Bilirubin 25, albumin 34, INR 1.12, Cr 55, no HE/ascites

Question

Which of the following treatment options would you consider?

A. Microwave ablation
B. Y90
C. Stereotactic body radiation therapy
D. Kinase inhibitor
E. Immunotherapy

- Underwent Y90 workup
- CT hepatic angiogram:
  - Large tumor blush from right hepatic artery
  - Large arterial to hepatic venous shunt seen on angiogram
  - Calculated lung shunting 21.3%
- TCMAA: some uptake seen in large right lobe tumor; significant uptake seen in surrounding liver parenchyma
- Underwent SBRT (30Gy in 5 fractions) Sep 2016
- CT scan next 1-3 months: largest tumor grew in size to 8.3cm, AFP 2891, Child A6

Thank You!

Project ECHO®

Med Learning Group - Hepatocellular Carcinoma

Recent Advances in the Management of Patients with Advanced Hepatocellular Carcinoma: How Does Your Approach Compare with the Experts'?

TOOLKIT

Resources	Address
Abou-Alfa GK, et al. A randomized, multicenter phase 3 study of durvalumab (D) and tremelimumab (T) as first-line treatment in patients with unresectable hepatocellular carcinoma (HCC): HIMALAYA study. *J Clin Oncol*. 2018;36(suppl; abstr TPS4144).	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01789128/full
Abou-Alfa GK, et al. Cabozantinib in patients with advanced and progressing hepatocellular Carcinoma. *N Engl J Med.* 2018; 379(1):54-63.	https://www.nejm.org/doi/full/10.1056/nejmoa1717002
Abu-Sbeih H, et al. Clinically significant hepatotoxicity due to immune checkpoint inhibitors is rare but leads to treatment discontinuation in a high proportion. *Hepatology*. 2018;68(suppl 1):25A-26A.	https://aasldpubs.onlinelibrary.wiley.com/doi/epdf/10.1002/hep.30256
American Cancer Society (ACS). 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
Atezolizumab (Tecentriq®) PI 2020	https://www.gene.com/download/pdf/tecentriq_prescribing.pdf
Berhane S, et al. Role of the GALAD and BALAD-2 serologic models in diagnosis of hepatocellular carcinoma and prediction of survival in patients. *Clin Gastroenterol Hepatol*. 2016;14(6):875-886.e6.	https://pubmed.ncbi.nlm.nih.gov/26775025/
Bevacizumab (Avastin®) PI 2021.	https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125085s0169lbl.pdf
Brahmer JR, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2018;36(17):1714-1768.	https://pubmed.ncbi.nlm.nih.gov/29442540/
Colevas AD, Setser A. The NCI Common Terminology Criteria for Adverse Events (CTCAE) v 3.0 is the new standard for oncology clinical trials. *J Clin Oncol*. 2004;22(14 suppl):6098.	https://ascopubs.org/doi/abs/10.1200/jco.2004.22.90140.6098
CT/MRI LI-RADS v2018 CORE.	www.acr.org/-/media/ACR/Files/RADS/LI-RADS/LI-RADS-2018-Core.pdf?la=en
De Martin E, et al. Characterization of liver injury induced by cancer immunotherapy using immune checkpoint inhibitors. *J Hepatol*. 2018;68(6):1181-1190.	https://pubmed.ncbi.nlm.nih.gov/29427729/
El-Khoueiry AB, et al. Impact of antitumor activity on survival outcomes, and nonconventi benefit, with nivolumab (NIVO)	https://ascopubs.org/doi/abs/10.1200/JCO.2018.36.4_suppl.475

Resources	Address
in patients with advanced hepatocellular carcinoma (aHCC): Subanalyses of CheckMate-040. *J Clin Oncol.* 2018;36(4_suppl):475-475.	
El-Khoueiry AB, et al. Nivolumab (NIVO) plus ipilimumab (IPI) combination thera patients (Pts) with advanced hepatocellular carcinoma (aH Long-term results from CheckMate 040. *J Clin Oncol.* 2021;39(3_suppl):269-269.	https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.3_suppl.269
European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol.* 2018;69(1):182-236.	https://pubmed.ncbi.nlm.nih.gov/29628281/
Finn R, et al. IMbrave150: updated overall survival (OS) data from a global, randomized, open-label Phase III study of atezolizumab (atezo) + bevacizumab (bev) vs sorafenib (sor) in patients (pts) with unresectable hepatocellular carcinoma (HCC). *Liver Cancer Summit.* 2021. Abstract 005.	https://easl.eu/wp-content/uploads/2021/01/Digital-Liver-Cancer-Summit-2021-Abstract-book.pdf
Finn RS, et al. Mbrave150: Updated efficacy and safety by risk status in patients (pts) receiving atezolizumab (atezo) + bevacizumab (bev) vs sorafenib (sor) as first-line treatment for unresectable hepatocellular carcinoma (HCC) *Cancer Res*. 2021;81(13_Suppl):Abstract nr CT009;	https://cancerres.aacrjournals.org/content/81/13_Supplement/CT009
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(2):353-358. doi:10.1016/j.jhep.2018.04.010	https://pubmed.ncbi.nlm.nih.gov/29704513/
Finn RS, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382(20):1894-1905.	https://www.nejm.org/doi/10.1056/NEJMoa1915745
Finn RS, et al. IMbrave150: Updated overall survival (OS) data from a global, randomized, open-label Phase III study of atezolizumab (atezo) + bevacizumab (bev) vs sorafenib (sor) in patients (pts) with unresectable hepatocellular carcinoma (HCC). *J Clin Oncol.* 2021;39(3 suppl):267.	https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.3_suppl.267
Golfieri R, et al. Patients with Barcelona Clinic liver cancer stages B and C hepatocellular carcinoma: Time for a subclassification. *Liver Cancer*. 2019;8(2):78-91.	https://pubmed.ncbi.nlm.nih.gov/31019899/
Jennings JJ, et al. Hepatotoxicity induced by immune checkpoint inhibitors: A comprehensive review including current and alternative management strategies *Expert Opin Drug Metab Toxicol.* 2019;15(3):231-244.	https://www.tandfonline.com/doi/full/10.1080/17425255.2019.1574744
Kelley RK, et al. Phase 3 (COSMIC-312) study of cabozantinib (C) in combination with atezolizumab (A) versus sorafenib (S) in patients (pts) with advanced hepatocellula carcinoma (aHCC) who have not received previous systemic anticancer therapy. *J Clin Oncol.* 2019;37(15_suppl):TPS4157-TPS4157.	https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.TPS4157

Resources	Address
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(10126):1163-1173.	https://pubmed.ncbi.nlm.nih.gov/29433850/
Lenvatinib (Lenvima®) PI 2019.	www.lenvima.com/pdfs/prescribing-information.pdf
Li D, et al. Current treatment landscape for advanced hepatocellular carcinoma: Patient outcomes and the impact on quality of life. *Cancers (Basel)*. 2019;11(6):841.	https://pubmed.ncbi.nlm.nih.gov/31216701/
Llovet JM, t al. Lenvatinib (len) plus pembrolizumab (pembro) for the first-line treatment of patients (pts) with advanced hepatocellular carcinoma (HCC): Phase 3 LEAP-002 study. *J Clin Oncol.* 2019;37(15_suppl): TPS4152-TPS4152.	https://ascopubs.org/doi/abs/10.1200/jco.2019.37.15_suppl.tps4152
Llovet JM,. Molecular therapies and precision medicine for hepatocellular carcinoma. *Nat Rev Clin Oncol*. 2018;15(10):599-616.	https://www.nature.com/articles/s41571-018-0073-4?WT.feed_name=subjects_cancer-therapy
Llovet JM, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008;359(4):378-390.	https://pubmed.ncbi.nlm.nih.gov/18650514/
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(2):723-750.	https://pubmed.ncbi.nlm.nih.gov/29624699/
Michot JM, et al. Immune-related adverse events with immune checkpoint blockade: A comprehensive review. *Eur J Cancer*. 2016;54:139-148.	https://www.ejcancer.com/article/S0959-8049(15)01112-0/fulltext
Miller ED, et al. Clinical characteristics and adverse impact of hepatotoxicity due to immune checkpoint inhibitors. *Am J Gastroenterol.* 2020;115(2):251-261.	https://pubmed.ncbi.nlm.nih.gov/31789632/
National Comprehensive Cancer Network (NCCN). Hepatobiliary cancers. Version 4.2021. 8.26.2021.	www.nccn.org/professionals/physician_gls/PDF/hepatobiliary.pdf
Pugh RN, et al. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg*. 1973;60(8):646-649.	https://pubmed.ncbi.nlm.nih.gov/4541913/
Sangro B, et al. Nivolumab in sorafenib-naive and -experienced patients with advanced hepatocellular carcinoma (HCC): Survival, hepatic safety, and biomarker assessments in CheckMate 040. Presented at AASLD The Liver Meeting 2017. Abstract 141.	https://www.natap.org/2017/AASLD/AASLD_34.htm
Siegel RL, et al. Cancer statistics, 2019. CA Cancer J Clin. 2019;69(1):7-34.	https://pubmed.ncbi.nlm.nih.gov/30620402/

Resources	Address
Sorafenib (Nexavar®) PI 2018.	http://labeling.bayerhealthcare.com/html/products/pi/Nexavar_PI.pdf
Villanueva A. Hepatocellular carcinoma. *N Engl J Med*. 2019;380(15):1450-1462.	https://pubmed.ncbi.nlm.nih.gov/30970190/
Yau T, et al. Efficacy and safety of nivolumab plus ipilimumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib: The CheckMate 040 randomized clinical trial [published correction appears in JAMA Oncol. 2021 Jan 1;7(1):140]. *JAMA Oncol*. 2020;6(11):e204564. doi:10.1001/jamaoncol.2020.4564	https://pubmed.ncbi.nlm.nih.gov/33001135/
Yau T, et al. Nivolumab (NIVO) + ipilimumab (IPI) + caboza (CABO) combination therapy in patients (pts) with advanced hepatocellular carcinoma (aHCC): Results from CheckMate 040. *J Clin Oncol.* 2020;38(4_suppl):478-478.	https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.4_suppl.478
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(2):282-296.	https://pubmed.ncbi.nlm.nih.gov/30665869/