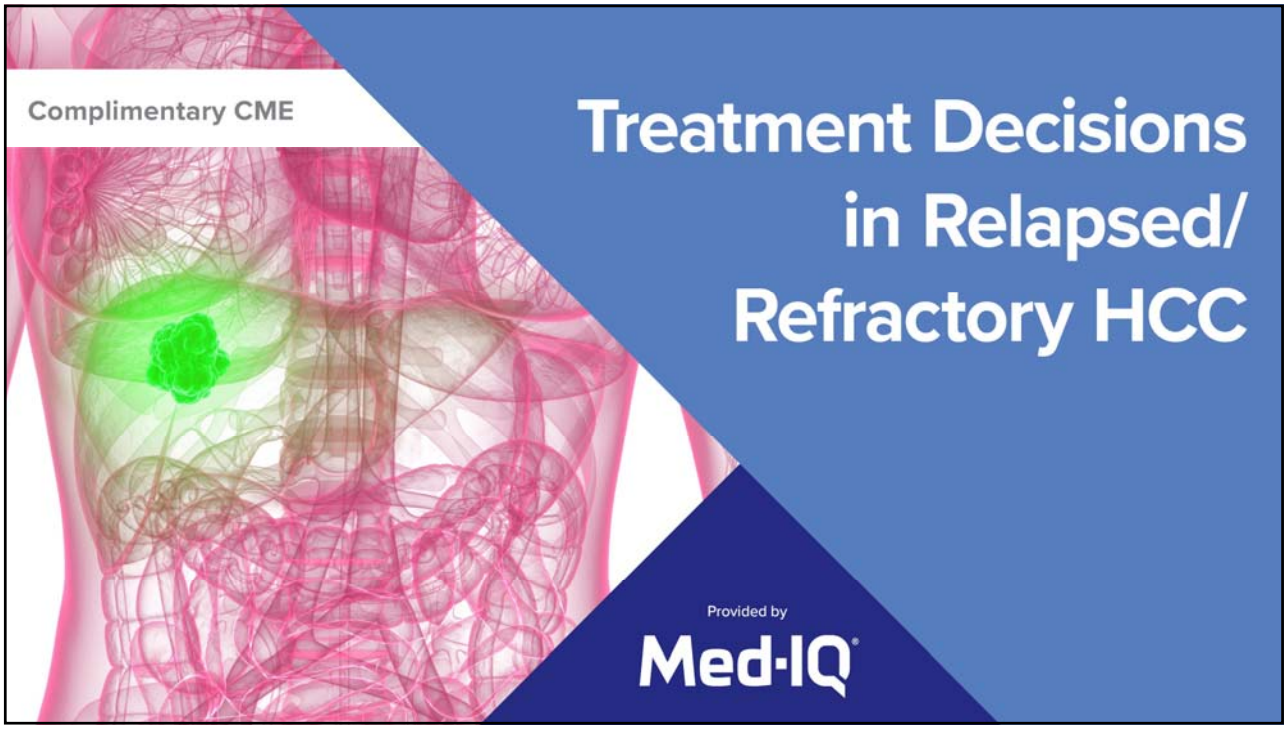

Activity Overview

In this case-based audiocast, expert faculty explore the translation of emerging research to clinical practice for a patient with relapsed/refractory hepatocellular carcinoma.

Target Audience

This activity is intended for community oncologists.

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Faculty Disclosure Statements

Tanios S. Bekaii-Saab, MD

Consulting fees/advisory boards: AbbVie Inc., Imugene, Immuneering Corporation

Other: ARMO Biosciences, Exelixis, Inc., SillaJen Inc.

The peer reviewers and activity planners have no financial relationships to disclose.

Learning Objectives

Upon completion, participants should be able to:

- Select appropriate therapy for patients with relapsed/refractory HCC while taking into consideration multiple factors including AFP levels

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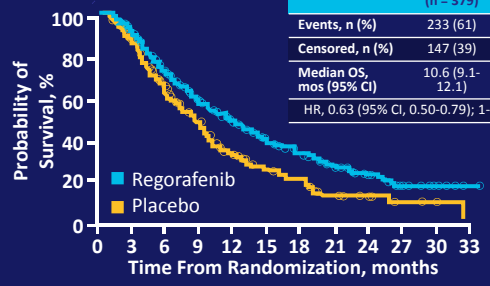
Treatment Decisions in Relapsed/Refractory HCC

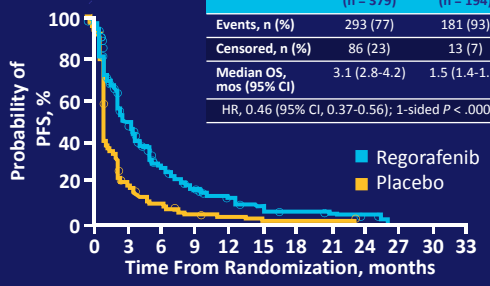
Case Presentation

- A 73-year-old woman with BCLC stage B HCC based on compensated cirrhosis (Child-Pugh A) thought to be secondary to NASH
- CT scans suggest diffuse liver and bony disease; biopsy confirms the diagnosis of HCC
- At the time of presentation, her ECOG PS is 1 and her AFP is 250 ng/mL; she is started on sorafenib 400 mg PO BID
  - After 32 days of sorafenib, she develops HFSR, starting with mild pain in her feet that progresses to moderate pain with no blistering; the sorafenib dose is reduced by 25% with good tolerance
  - After 10 months of treatment and SD, a CT scan shows evidence of PD with extrahepatic dissemination to the lymph nodes in addition to PD in her known areas of disease; her PS remains at 1 and Child-Pugh score at 6, but her AFP is now 505 ng/mL

Phase 3 RESORCE: Second-Line Regorafenib vs Placebo in Patients With HCC and PD on Sorafenib



	Regorafenib (n = 379)	Placebo (n = 194)
Events, n (%)	233 (61)	140 (72)
Censored, n (%)	147 (39)	54 (28)
Median OS, mos (95% CI)	10.6 (9.1-12.1)	7.8 (6.3-8.8)
HR, 0.63 (95% CI, 0.50-0.79); 1-sided *P* < .0001		



	Regorafenib (n = 379)	Placebo (n = 194)
Events, n (%)	293 (77)	181 (93)
Censored, n (%)	86 (23)	13 (7)
Median OS, mos (95% CI)	3.1 (2.8-4.2)	1.5 (1.4-1.6)
HR, 0.46 (95% CI, 0.37-0.56); 1-sided *P* < .0001		

	mRECIST		RECIST 1.1	
Response, %	Regorafenib (n = 379)	Placebo (n = 194)	Regorafenib (n = 379)	Placebo (n = 194)
ORR	10.6	4.1	6.6	2.6
	2-sided *P* = .047		1-sided *P* = .02	
DCR	65.2	36.1	65.7	34.5
	2-sided *P* < .0001		1-sided *P* < .0001	

Not FDA approved.

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

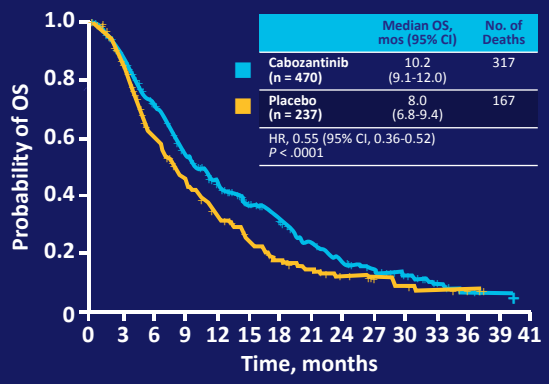
RESORCE: Sorafenib-Regorafenib Sequence

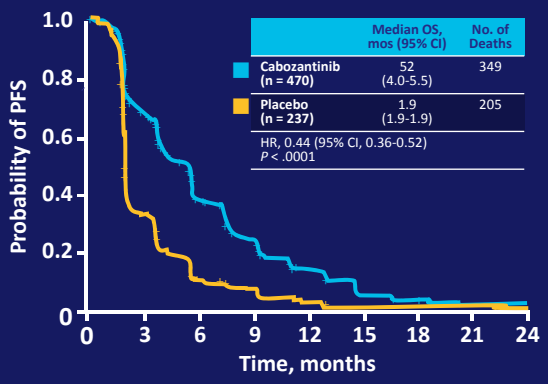
	Regorafenib	Placebo
Time from start of prior sorafenib treatment to death on RESORCE study drug		
All patients		
N	374	193
Median, months (95% CI)	26.0 (22.6-28.1)	19.2 (16.3-22.8)
Asia		
n	143	73
Median, months (95% CI)	21.5 (19.6-27.8)	15.6 (12.2-24.9)
Rest of the world		
n	231	120
Median, months (95% CI)	26.8 (23.3-28.9)	19.9 (17.5-25.9)
Time from start of prior sorafenib treatment to progression on RESORCE study drug		
All patients		
N	374	193
Median, months (95% CI), by mRECIST	14.9 (13.8-16.6)	11.7 (10.4-13.0)
Median, months (95% CI), by mRECIST1.1	15.2 (14.0-17.2)	11.4 (10.3-12.7)
Asia		
n	143	73
Median, months (95% CI), by mRESIST	13.6 (12.0-16.2)	9.4 (8.0-12.1)
Median, months (95% CI), by mRECIST1.1	13.6 (12.0-16.2)	9.4 (8.0-12.1)
Rest of the world		
n	231	120
Median, months (95% CI), by mRESIST	15.9 (14.0-18.2)	12.6 (10.8-14.2)
Medan, months (95% CI), by mRESIST1.1	16.3 (14.5-18.2)	11.9 (10.8-13.7)

Not FDA approved.

Finn RS, et al. *J Clin Oncol*. 2017;35:Abstract 344.

Phase 3 CELESTIAL Trial: Cabozantinib vs Placebo in Patients With HCC and PD on Sorafenib (100%) and Other (28%)

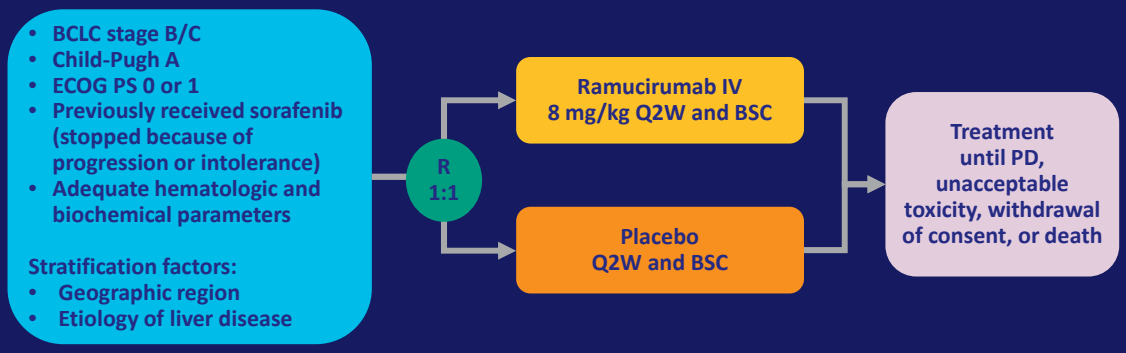




- Treatment-related grade 5 AEs—Cabozantinib (6 pts): hepatic failure, esophagobronchial fistula, portal vein thrombosis, upper GI hemorrhage, pulmonary embolism, hepatorenal syndrome; Placebo (1 pt): hepatic failure
  - Grade 3 AE reported in at least 5% of patients in either treatment group

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

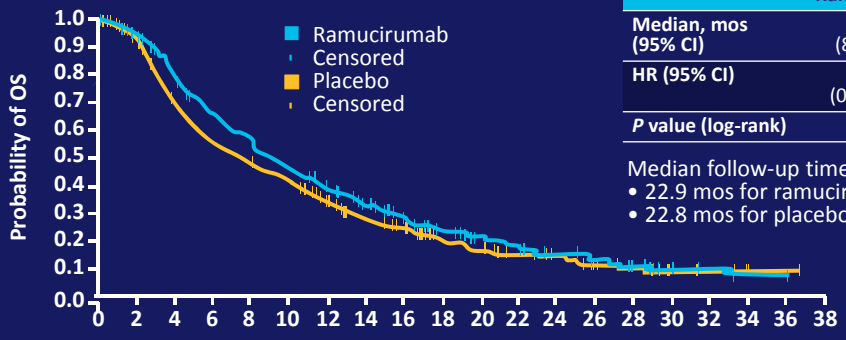
REACH: Study Design



- Primary endpoint: OS
- Secondary endpoints: PFS, TTP, ORR, DCR, safety

Zhu AX, et al. *Lancet Oncol*. 2015;16:859-70.

REACH: OS of ITT Population



	Ramucirumab	Placebo
Median, mos (95% CI)	9.2 (8.1-10.6)	7.6 (6.0-9.3)
HR (95% CI)	0.87 (0.72-1.05)	
***P* value (log-rank)**	.14	

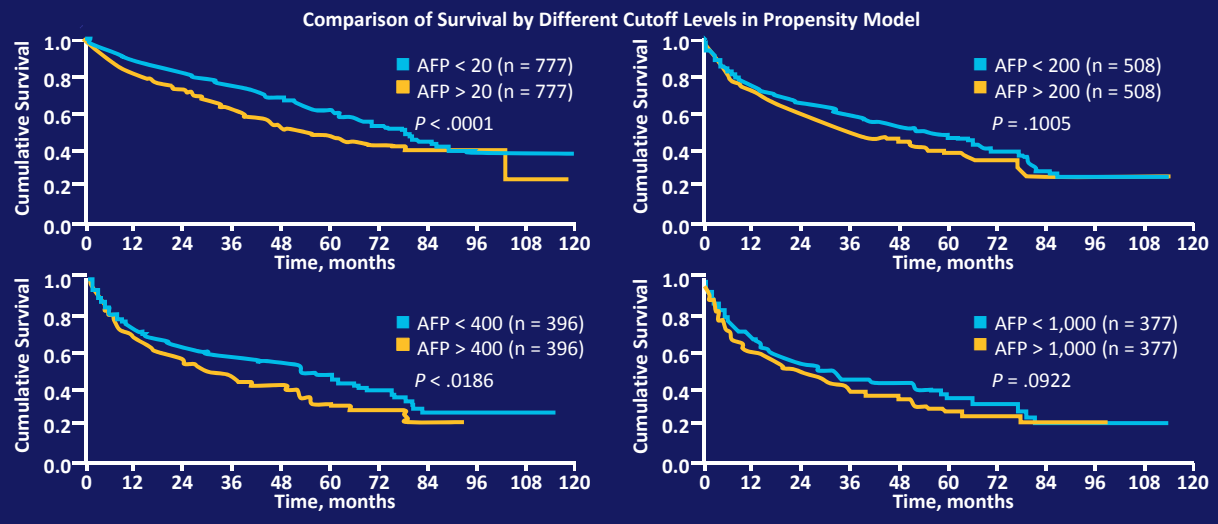
Median follow-up time:
- 22.9 mos for ramucirumab
- 22.8 mos for placebo

Number at risk:

Ramucirumab	283	261	214	175	149	122	101	78	61	43	32	27	20	15	11	5	4	2	1
Placebo	282	255	189	151	129	110	83	63	54	35	30	23	18	12	9	4	3	1	1

Zhu AX, et al. *Lancet Oncol*. 2015;16:859-70.

AFP Cutoff Levels and Long-Term Survival of HCC Patients



Hsu CY, et *al. PLoS One*. 2015;10:e0118825.

REACH-2: Ramucirumab vs Placebo in Patients With HCC and Elevated Baseline AFP

- Adults with advanced HCC
- Child-Pugh A
- BCLC stage B/C
- ECOG PS 0 or 1
- Progression on or intolerance to sorafenib
- No other systemic therapy
- Baseline AFP ≥ 400 ng/mL
- Planned N = 399

R 2:1

- Ramucirumab IV 8 mg/kg Q2W and BSC
- Placebo Q2W and BSC

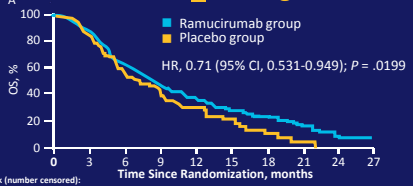
Treatment until PD, unacceptable toxicity, or withdrawal of consent

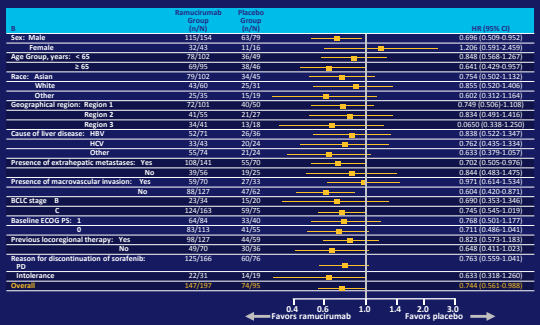
- Primary endpoint: OS

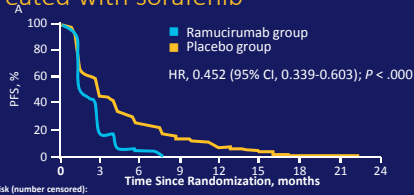
Zhu AX, et al. *Lancet*. 2019;20:282-96.

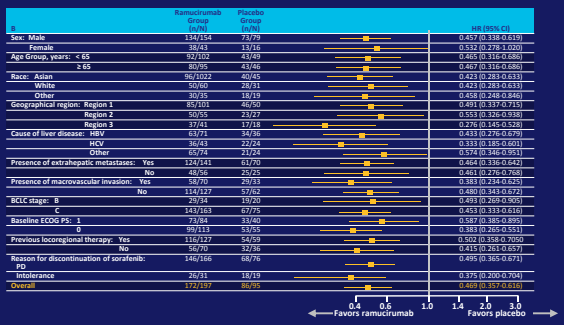
REACH-2: Results

Based in part on these results, the FDA recently approved ramucirumab for the treatment of HCC in patients with AFP levels ≥ 400 ng/mL who were previously treated with sorafenib





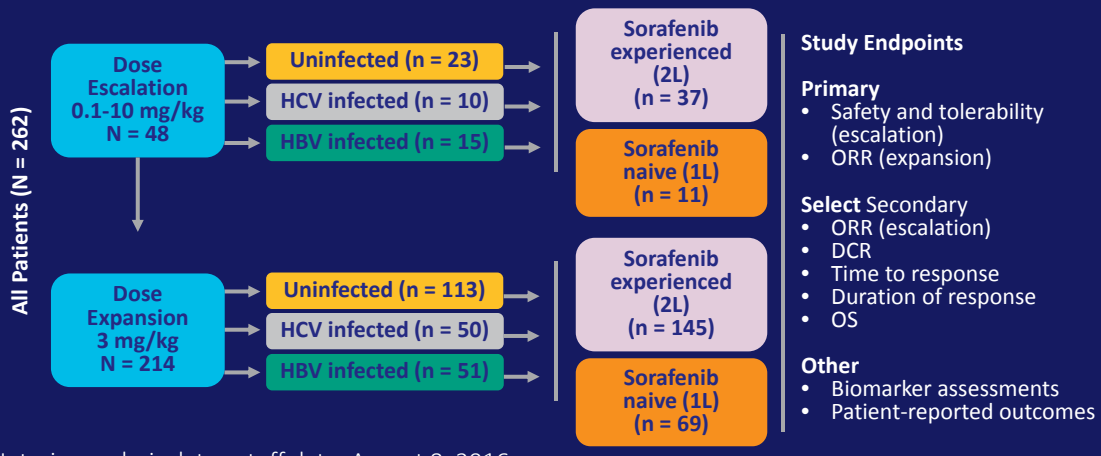




Grade ≥ 3 AEs (≥ 5% patients in the ramucirumab arm): HTN (12.6% RAM, 3.6% PBO) and hyponatremia (5.1% RAM, 2.2% PBO).

Zhu AX, et al. *Lancet*. 2019;20:282-96.

Nivolumab in HCC CheckMate 040: Study Design



- Interim analysis data cutoff date: August 8, 2016
- Median follow-up was 13.3 months in the dose-escalation phase and 10.5 months in the dose-expansion phase

Not FDA approved.

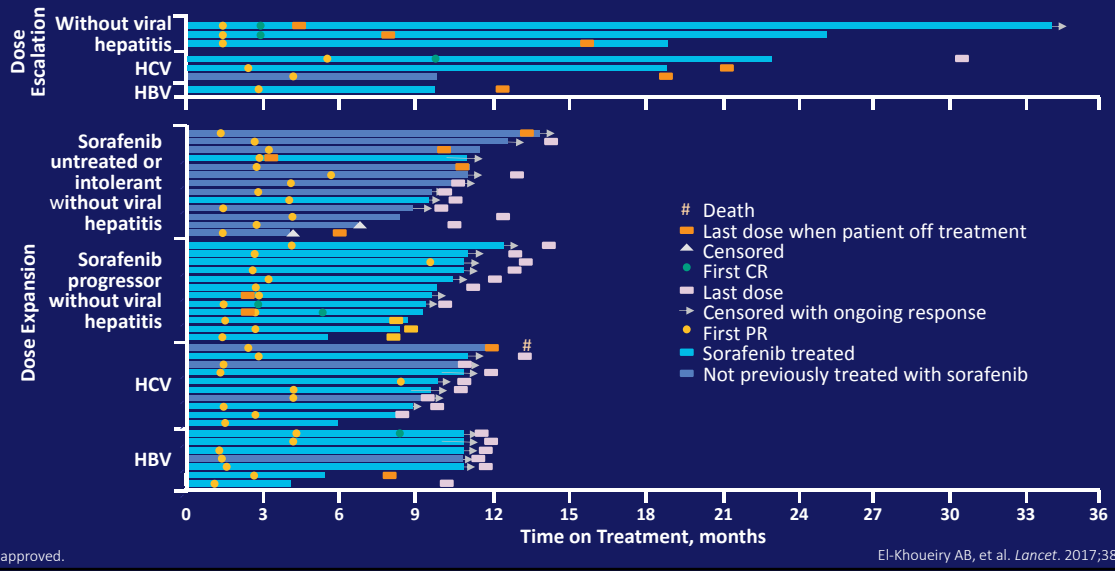
El-Khoueiry AB, et al. *Lancet*. 2017;389:2492-502.

Nivolumab in Advanced HCC (CheckMate 040): Efficacy in Dose-Expansion Phase

Outcome	Uninfected Untreated/ Intolerant (n = 56)	Uninfected Progressor (n = 57)	HCV Infected (n = 50)	HBV Infected (n = 51)	All Pts (N = 214)
ORR, %	23	21	20	14	20
• **CR**	0	4	0	2	1
• **PR**	23	18	20	12	18
• **SD**	52	40	46	41	45
• **PD**	23	32	28	45	32
Median OS, mos	NR	13.2	NR	NR	NR
OS at 6/9 mos, %	89/82	75/63	85/81	84/70	83/74
Median PFS, mos	5.4	4.0	4.0	4.0	4.0

El-Khoueiry AB, et al. *Lancet*. 2017;389:2492-502.

Nivolumab Maintains Benefit Post-Sorafenib



Not FDA approved.

El-Khoueiry AB, et al. *Lancet*. 2017;389:2492-502.

Summary of Agents Beyond the First Line

	Reg[a] vs PBO	Cabo[a] vs PBO	RAM[a] vs PBO (AFP ≥ 400)	Nivo[a,b]	Pembro[a]
mOS (all)	10.6 vs 7.8 mos	10.2 vs 8.0 mos	9.2 vs 7.6[a]	NR	12.9 mos
mOS AFP ≥ 400	HR, 0.68	8.5 vs 5.2 mos	7.8 vs 4.2 mos	/////////	//////////
mPFS	3.1 vs 1.5 mos	5.2 vs 1.9 mos	2.8 vs 2.1 mos	4.0 mos	4.9 mos
ORR	10.6 vs 4.1%	4 vs 0.4%	7% vs < 1%	20%	17%
Grade 3/4 AEs	HFSR, HTN	HFSR, HTN	HTN	IRE	IRE

[a]Not FDA approved.
[b]All AFP.

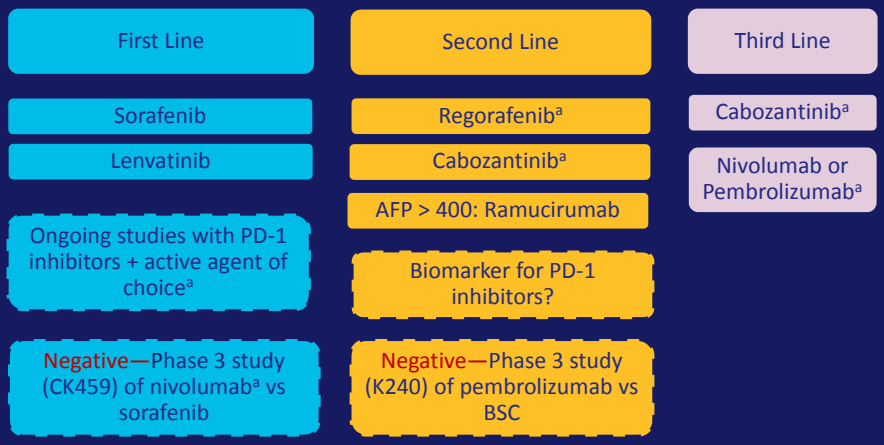
Bruix J, et al. *Lancet*. 2017;389:56-66; Abou-Alfa GK, et al. *N Engl J Med*. 2018;379:54-63; Zhu AX, et al. *Lancet Oncol*. 2015;16:859-70; El-Khoueiry AB, et al. *Lancet*. 2017;389:2492-502; Zhu AX, et al. *Lancet Oncol*. 2018;19:940-52.

Treatment Decisions in the Recurrent Setting

- All studies leading to agents approved beyond the second line were in the setting of PD on sorafenib, not lenvatinib
- No level 1 evidence for immunotherapy options
- Level 1 evidence with survival benefits with regorafenib, cabozantinib, and ramucirumab (if AFP $\geq$ 400 ng/mL)
- Safety profiles of each agent
- Tumor burden and aggressiveness of the tumor
- Predictive biomarkers?

NCCN. Hepatobiliary Cancers V2.2019.

Conclusion: How to Best Sequence Patients With Advanced Disease



[a]Not FDA approved.

EASL. *J Hepatology*. 2018;69:182-236; https://clinicaltrials.gov/ct2/show/NCT02576509; NCCN. Hepatobiliary Cancers V2.2019; Bristol-Myers Squibb press release. June 24, 2019.

Conclusions

- How would you treat this patient?
- What if this patient:
  - Initially received treatment with lenvatinib?
  - Had an AFP of 250 mg/mL?
  - Had a PS of 2?
  - Had a Child-Pugh score of 7? Or 8?
  - Were older, with no social support, and you were concerned about oral medication adherence?

Instructions to Receive Credit

To receive credit, read the introductory CME material, listen to the audiocast, and complete the evaluation, attestation, and post-test, answering at least 70% of the post-test questions correctly.

Contact Information

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Acknowledgment of Commercial Support

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Abbreviations and Acronyms

5-FU = fluorouracil
AE = adverse event
AFP = alpha-fetoprotein
ASC = active symptom control
BCLC = Barcelona Clinic Liver Cancer
BID = twice a day
BSC = best supportive care
CIV = continuous intravenous infusion
COPD = chronic obstructive pulmonary disease
CPS = combined positive score
CR = complete response
CRC = colorectal cancer
CT = computed tomography
DCF = docetaxel, cisplatin, and fluorouracil
DCR = disease control rate
EASL = European Association for the Study of the Liver
ECF = epirubicin, cisplatin, and fluorouracil
ECOG = Eastern Cooperative Oncology Group
EGD = esophagogastroduodenoscopy
ESMO = European Society for Medical Oncology
FDA = Food and Drug Administration
FGFR = fibroblast growth factor receptor
FISH = fluorescence in situ hybridization
FOLFIRI = folinic acid (leucovorin), fluorouracil, and irinotecan
FOLFOX = folinic acid (leucovorin), fluorouracil, and oxaliplatin
GE = gastroesophageal
GEJ = gastroesophageal junction
HBV = hepatitis B virus
HCC = hepatocellular carcinoma
HCV = hepatitis C virus
HFSR = hand-foot skin reaction
HTN = hypertension
IC = irinotecan and cisplatin
IHC = immunohistochemistry
IRE = immune-related event
ITT = intent to treat
MMR = mismatch repair
MMR-D = mismatch repair deficiency
MMR-P = mismatch repair proficiency
MSI = microsatellite instability
MSI-H = microsatellite instability high
MSI-L = microsatellite instability low
MSS = microsatellite stability
NASH = nonalcoholic steatohepatitis
NCCN = National Comprehensive Cancer Network
NE = not estimable
NGS = next generation sequencing
NR = not reached
ORR = overall response rate
OS = overall survival
PBO = placebo
PCP = primary care physician
PCR = polymerase chain reaction
PD = progressive disease
PD-L1 = programmed death ligand-1
PFS = progression-free survival
PPE = palmar-plantar erythrodysesthesia
PS = performance status
Q2W = once every 2 weeks
Q3W = once every 3 weeks
RECIST = Response Evaluation Criteria in Solid Tumors
SCC = squamous cell carcinoma
SD = stable disease
T2DM = type 2 diabetes mellitus
TMB = tumor mutation burden
TML = tumor mutation load
TTP = time to progression
WT = wild type