

Hepatocellular Carcinoma™

U P D A T E

Conversations with Oncology Investigators
Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS

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Hepatocellular Carcinoma™

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Hepatocellular Carcinoma Update

A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

Hepatocellular carcinoma (HCC), the most common form of liver cancer, is the third leading cause of cancer-related deaths worldwide. The rising incidence, multiple etiologies, genetic heterogeneity and concurrent chronic liver disease make the selection of treatment for this cancer challenging. In addition, HCC is often diagnosed in the advanced stage and is associated with a poor prognosis. However, recent breakthroughs in understanding the etiology and pathogenesis have led to the advent of new treatment modalities and investigational therapies. In order to offer optimal patient care, the practicing oncologist must be well informed of these advances. To bridge the gap between research and patient care, this issue of *Hepatocellular Carcinoma Update* uses one-on-one discussions with leading oncology investigators. By providing access to the latest research developments and expert perspectives on the disease, this CME program will assist medical oncologists and select gastroenterology specialists in the formulation of up-to-date clinical management strategies for patients with HCC.

LEARNING OBJECTIVES

- Consider patient age, performance status, liver function and other clinical and logistical factors in the up-front management of newly diagnosed unresectable or metastatic HCC.
- Appreciate the FDA approval of regorafenib for patients who have experienced treatment failure with sorafenib, and discern how regorafenib can be optimally integrated into clinical management.
- Appraise recent Phase III data with lenvatinib, and consider the clinical role of this agent in the management of previously untreated unresectable HCC.
- Recall available efficacy and safety data with cabozantinib, and consider the potential clinical role of this agent for patients who experience disease progression on sorafenib.
- Understand the scientific rationale for and recall available clinical trial data with approved and investigational checkpoint inhibitors in the treatment of HCC.
- Evaluate emerging Phase III data with ramucirumab in patients with advanced HCC and elevated alpha-fetoprotein who have experienced disease progression after treatment with sorafenib.

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Please note, this program has been specifically designed for the following ABIM specialty: **medical oncology**.

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Interview with Richard S Finn, MD

Tracks 1-24

Track 1	Effects of locoregional therapy on underlying liver function in patients with hepatocellular carcinoma (HCC)	Track 13	Activity of nivolumab as second-line therapy for patients with HCC
Track 2	Barcelona Clinic Liver Cancer staging system and treatment strategy	Track 14	Selection of regorafenib versus nivolumab as treatment in the second-line setting
Track 3	Case: A 68-year-old man with chronic hepatitis C and thrombocytopenia undergoes a liver transplant for multifocal HCC	Track 15	Predictors of benefit with checkpoint inhibitors in HCC
Track 4	Risk of recurrence in patients undergoing liver transplantation for HCC	Track 16	Emerging data on the efficacy of anti-PD-1/PD-L1 and anti-CTLA-4 combinations
Track 5	Use of sorafenib in patients who develop disease recurrence after a liver transplant	Track 17	Management of hepatic toxicities in patients receiving checkpoint inhibitors
Track 6	Risks associated with administering immune checkpoint inhibitors to patients who have undergone a liver transplant	Track 18	Biologic rationale for and ongoing investigation of the combination of checkpoint inhibitors and anti-angiogenic agents
Track 7	REFLECT (Study 304): A Phase III trial of lenvatinib versus sorafenib as first-line treatment for unresectable HCC	Track 19	Results of the Phase III CELESTIAL trial of cabozantinib versus placebo for patients with advanced HCC who have previously received sorafenib
Track 8	Design and eligibility criteria for the REFLECT study	Track 20	Improvement in overall survival with ramucirumab versus placebo as second-line treatment for patients with advanced HCC and elevated baseline alpha-fetoprotein (AFP)
Track 9	Activity and side-effect profile of lenvatinib versus sorafenib	Track 21	Selection and sequencing of therapy for patients with HCC
Track 10	Clinical implications of the REFLECT trial results	Track 22	Role of checkpoint inhibitors in the treatment algorithm for HCC
Track 11	Comparison of selective internal radiation therapy (SIRT) to sorafenib for locally advanced HCC	Track 23	Case: A 70-year-old man with metastatic HCC to the lung and a history of hepatitis B achieves a dramatic response to nivolumab
Track 12	Results of the Phase III RESORCE trial evaluating regorafenib for patients with HCC and disease progression after sorafenib	Track 24	Ongoing Phase III evaluation of checkpoint inhibitors for HCC

Interview with Andrew X Zhu, MD, PhD

Tracks 1-19

Track 1	Epidemiology and etiology of HCC	Track 5	Tumor microenvironment in HCC and potential therapeutic role of anti-angiogenic agents and immunotherapies
Track 2	Selection of patients for locoregional treatment	Track 6	Perspective on the results of the RESORCE study evaluating regorafenib after disease progression on sorafenib
Track 3	Available locoregional therapies for HCC		
Track 4	Side effects associated with locoregional therapies		

Interview with Dr Zhu (continued)

Track 7	Dose modifications and side effects associated with regorafenib	Track 14	Combination immunotherapy approaches under investigation for HCC
Track 8	Critical evaluation of the CELESTIAL trial efficacy and tolerability results	Track 15	Case: A 62-year-old man with metastatic HCC achieves a partial response to nivolumab/ipilimumab on the CheckMate 040 study
Track 9	Potential role of cabozantinib in the management of HCC	Track 16	Case: A 72-year-old woman receives nivolumab as second-line therapy for NASH-related HCC
Track 10	Results of the REACH-2 study of ramucirumab as second-line treatment for patients with advanced HCC and elevated AFP after first-line sorafenib	Track 17	Case: A 49-year-old man with a history of hepatitis B receives lenvatinib in combination with nivolumab for multifocal HCC
Track 11	Emerging data on a correlation between high AFP and response to ramucirumab	Track 18	Case: A 64-year-old woman with NASH-related HCC receives regorafenib after disease progression on sorafenib
Track 12	Efficacy and tolerability of lenvatinib versus sorafenib as first-line therapy in the Phase III REFLECT trial (Study 304)	Track 19	Perspective on the use of checkpoint inhibitors for liver transplant recipients
Track 13	Activity of checkpoint inhibitors in patients with HCC		

Related Video Program

View the corresponding video interviews with (from left) Drs Finn and Zhu by Dr Love at www.ResearchToPractice.com/HCCU118/Video



SELECT PUBLICATIONS

Abou-Alfa GK et al. **Cabozantinib (C) versus placebo (P) in patients (pts) with advanced hepatocellular carcinoma (HCC) who have received prior sorafenib: Results from the randomized phase III CELESTIAL trial.** Gastrointestinal Cancers Symposium 2018;**Abstract 207.**

Abou-Alfa GK et al. **Cabozantinib in patients with advanced and progressing hepatocellular carcinoma.** *N Engl J Med* 2018;379(1):54-63.

A randomized, multi-center phase III study of nivolumab versus sorafenib as first-line treatment in patients with advanced hepatocellular carcinoma (CheckMate 459): Checkpoint pathway and nivolumab clinical trial evaluation 459. **NCT02576509**

A randomized, open-label, multi-center phase III study of durvalumab and tremelimumab as first-line treatment in patients with unresectable hepatocellular carcinoma. **NCT03298451**

Bruix J et al. **Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): A randomised, double-blind, placebo-controlled, phase 3 trial.** *Lancet* 2017;389(10064):56-66.

Bruix J et al. **Updated overall survival (OS) analysis from the international, phase 3, randomized, placebo-controlled RESORCE trial of regorafenib for patients with hepatocellular carcinoma (HCC) who progressed on sorafenib treatment.** *Proc ESMO World Congress on Gastrointestinal Cancer* 2017;**Abstract O-009.**

Cheng AL et al. **Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: A phase III randomised, double-blind, placebo-controlled trial.** *Lancet Oncol* 2009;10(1):25-34.

Chow PKH et al. **SIRveNIB: Selective internal radiation therapy versus sorafenib in Asia-Pacific patients with hepatocellular carcinoma.** *J Clin Oncol* 2018;36(19):1913-21.

El-Khoueiry AB et al. **Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): An open-label, non-comparative, phase 1/2 dose escalation and expansion trial.** *Lancet* 2017;389(10088):2492-502.

Frenette CT. **The role of regorafenib in hepatocellular carcinoma.** *Clin Adv Hematol Oncol* 2017;15(2):121-3.

Ikeda M et al. **A phase 1b trial of lenvatinib (LEN) plus pembrolizumab (PEM) in patients (pts) with unresectable hepatocellular carcinoma (uHCC).** *Proc ASCO* 2018;**Abstract 4076.**

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):1163-73.

Lemery S et al. **First FDA approval agnostic of cancer site — When a biomarker defines the indication.** *N Engl J Med* 2017;377(15):1409-12.

Lencioni R et al. **Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: The SPACE trial.** *J Hepatol* 2016;64(5):1090-8.

Llovet JM et al; SHARP Investigators Study Group. **Sorafenib in advanced hepatocellular carcinoma.** *N Engl J Med* 2008;359(4):378-90.

Sangro B et al. **A randomized, multicenter, phase 3 study of nivolumab vs sorafenib as first-line treatment in patients (pts) with advanced hepatocellular carcinoma (HCC): CheckMate-459.** *Proc ASCO* 2016;**Abstract TPS4147.**

Vilgrain V et al; SARAH Trial Group. **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(12):1624-36.

Zhu AX et al. **Pembrolizumab (pembro) in patients with advanced hepatocellular carcinoma (HCC): KEYNOTE-224 update.** *Proc ASCO* 2018;**Abstract 4020.**

Zhu AX et al. **REACH-2: A randomized, double-blind, placebo-controlled phase 3 study of ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma (HCC) and elevated baseline alpha-fetoprotein (AFP) following first-line sorafenib.** *Proc ASCO* 2018;**Abstract 4003.**

Zhu AX et al; REACH Trial Investigators. **Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): A randomised, double-blind, multicentre, phase 3 trial.** *Lancet Oncol* 2015;16(7):859-70.

QUESTIONS (PLEASE CIRCLE ANSWER):

- Results from the REFLECT trial (Study 304) for patients with unresectable HCC in the first-line setting reported _____ with lenvatinib versus sorafenib.
 - Superiority in overall survival (OS)
 - Significant improvement in progression-free survival (PFS)
 - Significant benefit in response rate
 - All of the above
 - Both b and c
- Results of studies evaluating the antitumor activity of checkpoint inhibitors in patients with HCC have demonstrated _____.
 - An overall response rate (ORR) of 15% to 20% as first-line therapy
 - Responses in only those patients with high tumor mutational burdens
 - Both a and b
 - Neither a nor b
- Which of the following is true regarding the Phase III CELESTIAL trial evaluating cabozantinib versus placebo for patients with advanced HCC previously treated with sorafenib?
 - A significant improvement in OS was reported in the cabozantinib arm
 - No dose reductions were required in the cabozantinib arm
 - Both a and b
 - Neither a nor b
- The ongoing CheckMate 459 trial is evaluating sorafenib versus nivolumab for patients with advanced HCC in which setting?
 - First line
 - Second line
 - Late line
- What did the SIRveNIB study comparing SIRT to sorafenib for locally advanced HCC demonstrate in terms of OS?
 - Significant improvement with sorafenib
 - Significant improvement with SIRT
 - No significant difference between the 2 arms
- Preliminary results from a Phase I study presented by Finn and colleagues at ASCO 2018 demonstrated an ORR of approximately 40% with lenvatinib/pembrolizumab for patients with unresectable HCC.
 - True
 - False
- The Phase III REACH-2 trial presented at ASCO 2018 by Zhu and colleagues demonstrated a significant improvement in OS with ramucirumab versus placebo as second-line therapy for patients with advanced HCC and high _____.
 - AFP
 - VEGFR expression
 - Tumor burden
- Which of the following is true regarding the Phase III RESORCE trial evaluating regorafenib versus placebo for patients with HCC with disease progression on sorafenib?
 - A significant improvement in OS was observed with regorafenib
 - A significant improvement in PFS was observed with regorafenib
 - Both a and b
 - Neither a nor b
- The ongoing Phase III HIMALAYA study is investigating _____ in combination with tremelimumab as first-line treatment for unresectable HCC.
 - Pembrolizumab
 - Durvalumab
 - Nivolumab
- Which of the following is true regarding the safety profile of lenvatinib in HCC?
 - Lenvatinib is associated with a higher incidence of hypertension than is sorafenib
 - Lenvatinib is associated with a higher incidence of hand-foot skin reaction than is sorafenib
 - Hepatic function should be monitored
 - All of the above
 - Both a and c

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PART 1 — Please tell us about your experience with this educational activity

How would you characterize your level of knowledge on the following topics?

	4 = Excellent	3 = Good	2 = Adequate	1 = Suboptimal
	BEFORE		AFTER	
Major efficacy and safety findings from the REFLECT study of lenvatinib versus sorafenib for unresectable HCC	4	3	2	1
REACH-2 trial: Efficacy of ramucirumab for patients with advanced HCC and elevated AFP	4	3	2	1
Emerging data with combination immunotherapy approaches under investigation for the treatment of HCC	4	3	2	1
Results of the Phase III CELESTIAL trial evaluating cabozantinib for patients with previously treated, advanced HCC	4	3	2	1
Role of checkpoint inhibitors in the treatment algorithm for HCC	4	3	2	1

Practice Setting:

- Academic center/medical school
 Community cancer center/hospital
 Group practice
 Solo practice
 Government (eg, VA)
 Other (please specify).....

How many new patients with HCC do you see per year? patients

Was the activity evidence based, fair, balanced and free from commercial bias?

- Yes No
 If no, please explain:

Please identify how you will change your practice as a result of completing this activity (select all that apply).

- This activity validated my current practice
 Create/revise protocols, policies and/or procedures
 Change the management and/or treatment of my patients
 Other (please explain):

If you intend to implement any changes in your practice, please provide 1 or more examples:

.....

.....

The content of this activity matched my current (or potential) scope of practice.

- Yes No
 If no, please explain:

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

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As a result of this activity, I will be able to:

- Consider patient age, performance status, liver function and other clinical and logistical factors in the up-front management of newly diagnosed unresectable or metastatic HCC. 4 3 2 1 N/M N/A
- Appreciate the FDA approval of regorafenib for patients who have experienced treatment failure with sorafenib, and discern how regorafenib can be optimally integrated into clinical management. 4 3 2 1 N/M N/A
- Appraise recent Phase III data with lenvatinib, and consider the clinical role of this agent in the management of previously untreated unresectable HCC. 4 3 2 1 N/M N/A
- Recall available efficacy and safety data with cabozantinib, and consider the potential clinical role of this agent for patients who experience disease progression on sorafenib. 4 3 2 1 N/M N/A

EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)

As a result of this activity, I will be able to:

- Understand the scientific rationale for and recall available clinical trial data with approved and investigational checkpoint inhibitors in the treatment of HCC..... 4 3 2 1 N/M N/A
- Evaluate emerging Phase III data with ramucirumab in patients with advanced HCC and elevated alpha-fetoprotein who have experienced disease progression after treatment with sorafenib. 4 3 2 1 N/M N/A

Please describe any clinical situations that you find difficult to manage or resolve that you would like to see addressed in future educational activities:

.....

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Yes No

If no, please explain:

PART 2 — Please tell us about the faculty and editor for this educational activity

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Faculty	Knowledge of subject matter			Effectiveness as an educator	
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Andrew X Zhu, MD, PhD	4	3	2	1	4 3 2 1
Editor	Knowledge of subject matter			Effectiveness as an educator	
Neil Love, MD	4	3	2	1	4 3 2 1

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Hepatocellular Carcinoma™

U P D A T E

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