Beyond the Guidelines

Investigator Perspectives on Current Clinical Issues and Ongoing Research in the Systemic Treatment of Hepatocellular Carcinoma

CME Information

TARGET AUDIENCE

This activity is intended for medical oncologists, hematology-oncology fellows, surgeons and other healthcare providers involved in the treatment of hepatocellular carcinoma (HCC).

OVERVIEW OF ACTIVITY

HCC, the most common form of liver cancer, is a major cause of mortality globally, resulting in an estimated 600,000 deaths per year. The incidence rate of liver cancer in the United States has increased sharply, and it is estimated that approximately 42,220 new cases will be diagnosed in 2018 in this country and 30,200 individuals will die of the disease. Initial management is generally multidisciplinary in nature, and several potentially curative treatment modalities are available for patients with early-stage HCC. Unfortunately, for a number of reasons (eg, tumor extent, underlying liver dysfunction) many patients may not be amenable to potentially curative efforts, and median survival from time of diagnosis remains less than 1 year. This dismal prognosis has created the dramatic need for other therapeutic interventions and has spurred a rigorous research platform spanning several decades and most recently resulting in a number of new FDA approvals and various Phase III clinical trials.

Several consensus- and evidence-based treatment guidelines are available and aim to assist clinicians with making HCC management decisions in this dynamic clinical and research environment. However, in situations where multiple acceptable therapeutic options exist, such guidelines may not be particularly helpful at the time of decision-making. By exploring the perspectives of leading investigators regarding a number of clinical scenarios and reviewing key data sets, this activity will assist medical oncologists and other healthcare professionals in the development of evidence-based strategies for the treatment of HCC.

LEARNING OBJECTIVES

- Develop evidence-based strategies to properly diagnose and stage HCC, and use this information to counsel patients regarding their long-term prognosis.
- Consider age, performance status, liver function and other clinical and logistical factors in the selection and sequencing of available systemic agents for patients with unresectable or metastatic HCC.
- Develop an understanding of the biologic rationale for and available clinical data with anti-PD-1 and/or anti-PD-L1 antibodies in the treatment of HCC.
- Appraise available Phase III data with and consider the potential clinical role of cabozantinib for patients with disease progression on sorafenib.
- Counsel patients regarding the incidence and manifestation of side effects and toxicities associated with existing and emerging targeted agents and immunotherapeutic approaches used in the management of advanced HCC.
- Recall available and emerging data with other investigational agents currently in clinical testing for HCC, and, where applicable, refer eligible patients for trial participation or other expanded access programs.

ACCREDITATION STATEMENT

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AMERICAN BOARD OF INTERNAL MEDICINE (ABIM) — MAINTENANCE OF CERTIFICATION (MOC)

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 2 Medical Knowledge MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

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

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FACULTY — The following faculty (and their spouses/partners) reported relevant conflicts of interest, which have been resolved through a conflict of interest resolution process:

Ghassan Abou-Alfa, MD
Medical Oncologist
Memorial Sloan Kettering Cancer Center
New York, New York

Consulting Agreements: Agios Pharmaceuticals Inc, Amgen Inc, Aptus Clinical, ASLAN Pharmaceuticals, Astellas Pharma Global Development Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Boston Scientific Corporation, Bristol-Myers Squibb Company, CARsgen Therapeutics, CASI Pharmaceuticals, Celgene Corporation, CytomX Therapeutics, Daiichi Sankyo Inc, Debiopharm Group, Delcath Systems Inc, Eisai Inc, Gilead Sciences Inc, Halozyme Inc, Inovio Pharmaceuticals Inc, Ipsen Biopharmaceuticals Inc, Lilly, MedImmune Inc, Merck, Onxeo, PCI Biotech, Roche Laboratories Inc, Sanofi Genzyme, Servier, Silenseed Ltd, SillaJen, Sirtex Medical Ltd, Yakult Pharmaceutical Industry CO LTD; **Contracted Research:** Agios Pharmaceuticals Inc, Array BioPharma Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, CASI Pharmaceuticals, Celgene Corporation, Exelixis Inc, Genentech BioOncology, Incyte Corporation, Lilly, MabVax Therapeutics Holdings Inc, MedImmune Inc, Momenta Pharmaceuticals Inc, Novartis, OncoMed Pharmaceuticals Inc, Roche Laboratories Inc.

Josep M Llovet, MD, PhD
Professor of Medicine
Director, Mount Sinai Liver Cancer Program
Division of Liver Diseases, Tisch Cancer Institute
Icahn School of Medicine at Mount Sinai
New York, New York
Professor of Research — ICREA
Director, Master in Translational Medicine
BCLC Group, Liver Unit, CIBERehd, IDIBAPS
Hospital Clínic de Barcelona
University of Barcelona
Barcelona, Spain

Advisory Committee: Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Lilly; **Consulting Agreements:** Bayer HealthCare Pharmaceuticals, Blueprint Medicines, Bristol-Myers Squibb Company, Celsion Corporation, Eisai Inc, Incyte Corporation, Lilly; **Contracted Research:** Bayer HealthCare Pharmaceuticals, Blueprint Medicines, Bristol-Myers Squibb Company, Eisai Inc, Incyte Corporation.

Bert H O'Neil, MD
Professor of Medicine
Director, Phase I and GI Malignancies Programs
Indiana University Simon Cancer Center
Indianapolis, Indiana

Advisory Committee: Amgen Inc, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Celgene Corporation; **Speakers Bureau:** Bayer HealthCare Pharmaceuticals, Halozyme Inc.

Andrew X Zhu, MD, PhD
Director, Liver Cancer Research
Massachusetts General Hospital Cancer Center
Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Advisory Committee: AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Eisai Inc, Lilly, Merck, Novartis, Sanofi Genzyme; **Contracted Research:** Bayer HealthCare Pharmaceuticals, Lilly, Merck, Novartis.

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Hardware/Software Requirements:
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 11 or later, Firefox 56 or later, Chrome 61 or later, Safari 11 or later, Opera 48 or later
Adobe Flash Player 27 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

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Select Publications

Bert H O'Neil, MD

Cheng AL et al. **Phase III trial of lenvatinib (LEN) vs sorafenib (SOR) in first-line treatment of patients (pts) with unresectable hepatocellular carcinoma (uHCC).** *Proc ASCO* 2017;**Abstract 4001**.

Chow PHW et al. **Phase III multi-centre open-label randomized controlled trial of selective internal radiation therapy (SIRT) versus sorafenib in locally advanced hepatocellular carcinoma: The SIRveNIB study.** *Proc ASCO* 2017;**Abstract 4002**.

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

Marrero J et al. **Observational registry of sorafenib use in clinical practice across Child-Pugh subgroups: The GIDEON study.** *J Hepatol* 2016;65(6):1140-7.

Stjepanovic N, Capdevila J. **Multikinase inhibitors in the treatment of thyroid cancer: Specific role of lenvatinib.** *Biologics* 2014;8:129-39.

Wilhelm SM et al. **BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis.** *Cancer Res* 2004;64(19):7099-109.

Andrew X Zhu, MD, PhD

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.

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.

Ikeda K et al. **Phase 2 study of lenvatinib in patients with advanced hepatocellular carcinoma.** *J Gastroenterol* 2017;52(4):512-9.

Kelley RK et al. **Cabozantinib in hepatocellular carcinoma: Results of a phase 2 placebo-controlled randomized discontinuation study.** *Ann Oncol* 2017;28(3):528-34.

Llovet JM et al; Panel of Experts in HCC-Design Clinical Trials. **Design and endpoints of clinical trials in hepatocellular carcinoma.** *J Natl Cancer Inst* 2008;100(10):698-711.

Melero I et al. **Nivolumab dose escalation and expansion in patients with advanced hepatocellular carcinoma (HCC): The CheckMate 040 study.** Gastrointestinal Cancers Symposium 2017;**Abstract 226**.

Subramanian S et al. **A review of hepatocellular carcinoma (HCC) staging systems.** *Chin Clin Oncol* 2013;2(4):33-46.

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.

Ghassan Abou-Alfa, MD

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 2017;**Abstract 207**.

Abou-Alfa GK et al. **Phase 1/2 study of durvalumab and tremelimumab as monotherapy and in combination in patients with unresectable hepatocellular carcinoma (HCC).** *Proc ASCO* 2017;**Abstract TPS3103**.

Kelley RK et al. **Phase I/II study of durvalumab and tremelimumab in patients with unresectable hepatocellular carcinoma (HCC): Phase I safety and efficacy analyses.** *Proc ASCO* 2017;**Abstract 4073**.

Rimassa L et al. **Second-line tivantinib (ARQ 197) vs placebo in patients (Pts) with MET-high hepatocellular carcinoma (HCC): Results of the METIV-HCC phase III trial.** *Proc ASCO* 2017;**Abstract 4000**.

Rimassa L et al. **Tivantinib (ARQ 197) versus placebo in patients (Pts) with hepatocellular carcinoma (HCC) who failed one systemic therapy: Results of a randomized controlled phase II trial (RCT).** *Proc ASCO* 2012;**Abstract 4006**.

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* 2017;**Abstract TPS4147**.

Select Publications

Josep M Llovet, MD, PhD

Chiang D et al. **Focal gains of VEGFA and molecular classification of hepatocellular carcinoma.** *Cancer Res* 2008;68(16):6779-88.

Coulouarn C et al. **Transforming growth factor-beta gene expression signature in mouse hepatocytes predicts clinical outcome in human cancer.** *Hepatology* 2008;47(6):2059-67.

de Gramont A et al. **Pragmatic issues in biomarker evaluation for targeted therapies in cancer.** *Nat Rev Clin Oncol* 2015;12(4):197-212.

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(0088):2492-502.

Hagel M et al. **First selective small molecule inhibitor of FGFR4 for the treatment of hepatocellular carcinomas with an activated FGFR4 signaling pathway.** *Cancer Discov* 2015;5(4):424-37.

Sawey ET et al. **Identification of a therapeutic strategy targeting amplified FGF19 in liver cancer by oncogenomic screening.** *Cancer Cell* 2011;19(3):347-58.

Schulze K et al. **Exome sequencing of hepatocellular carcinomas identifies new mutational signatures and potential therapeutic targets.** *Nat Genet* 2015;47(5):505-11.

Sia D et al. **Identification of an immune-specific class of hepatocellular carcinoma, based on molecular features.** *Gastroenterology* 2017;153(3):812-26.

Villanueva A et al. **Notch signaling is activated in human hepatocellular carcinoma and induces tumor formation in mice.** *Gastroenterology* 2012;143(6):1660-9.

Vogelstein B et al. **Cancer genome landscapes.** *Science* 2013;39(6127):1546-58.

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.

Zucman-Rossi J et al. **Genetic landscape and biomarkers of hepatocellular carcinoma.** *Gastroenterology* 2015;149(5):1226-39.