Systemic Therapy for Advanced Hepatocellular Carcinoma

ASCO Guideline Update

Gordan JD, et al.

Overview

1. Background & Methodology
   - Introduction
   - ASCO Guideline Development Methodology
   - Clinical Questions
   - Target Population and Audience
2. Summary of Recommendations
3. Discussion
   - Patient and Clinician Communication
   - Cost Implications
   - Additional Resources
   - Expert Panel Members

ASCO®
AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

1 Background & Methodology

Introduction

- There were approximately 725,000 new cases and 664,000 deaths worldwide due to hepatocellular carcinoma (HCC) in 2020.
- In recent years, several newer systemic therapy options have shown efficacy in the first and second-line settings for advanced HCC, including evidence of the effectiveness of combination therapy.[1-3]
- This guideline provides an update to the 2020 recommendations, including updated evidence profiles for treatments included in the previous version of the guideline, and newer data from randomized trials of other agents alone or in combination.
- Data on combination therapy in the adjuvant setting is outside the scope of this guideline update.

ASCO Guideline Development Methodology

- The ASCO Evidence Based Medicine Committee (EBMC) guideline process includes:
  - a systematic literature review by ASCO guidelines staff
  - an expert panel provides critical review and evidence interpretation to inform guideline recommendations
  - final guideline approval by ASCO EBMC

- The full ASCO Guideline methodology manual can be found at: www.asco.org/guideline-methodology

Clinical Questions

This clinical practice guideline addresses the following clinical questions:

1. What are the preferred treatment options for first-line systemic therapy for patients with advanced hepatocellular carcinoma?
2. What are the preferred treatment options for second- or later-line therapy for patients with advanced hepatocellular carcinoma?

Target Population and Audience

Target Population

- Patients with advanced hepatocellular carcinoma.

Target Audience

- Clinicians who are involved in the care and treatment of patients with advanced hepatocellular carcinoma, including medical oncologists, hepatologists, gastroenterologists, surgeons, interventional radiologists, radiation oncologists, radiologists, pathologists, and palliative care specialists.

ASCO®
AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

2 Summary of Recommendations

Summary of Recommendations

First-Line Therapy

Recommendation 1.1

Evidence Quality	Strength of Recommendation
Moderate to High	Strong

- Atezolizumab + bevacizumab (atezo+bev) or durvalumab + tremelimumab (durva+treme) may be offered as first-line treatment for patients with Child-Pugh class A, and ECOG PS 0-1 advanced HCC.

Summary of Recommendations

Qualifying statements for Recommendation 1.1:

- For patients receiving atezo+bev, screening for and management of esophageal varices when present are recommended prior to initiation of therapy and according to institutional guidelines.
- The choice between treatment options in Recommendation 1.1 should be made through a discussion involving the physician and patient (and caregiver, where applicable), and should include factors such as medical history, toxicities associated with treatment, cost, goals of treatment, patient preference, and expected treatment benefit.
- When choosing between the two combination therapy options, consider risk of bleeding and thrombosis with the VEGF inhibitor bevacizumab.
- Patients with active or previously documented autoimmune disease should consider the risk of immune-related adverse effects associated with atezo and durva+treme.

Summary of Recommendations

Recommendation 1.2

Evidence Quality	Strength of Recommendation
Moderate	Strong

- Where there are contraindications to atezo+bev or durva+treme, sorafenib, lenvatinib, or durvalumab may be offered as first-line treatment for patients with Child-Pugh class A, and ECOG PS 0-1 advanced HCC.

Qualifying statements for Recommendation 1.2:

- The choice between treatment options should take into account the factors listed in the second qualifying statement to Recommendation 1.1.

Summary of Recommendations

Second-Line Therapy

Recommendation 2.1

Evidence Quality	Strength of Recommendation
Low	Weak

- Following first-line treatment with atezo+bev, second-line therapy with a tyrosine kinase inhibitor (TKI) (i.e., sorafenib, lenvatinib, or cabozantinib), or ramucirumab (AFP ≥400 ng/mL) are recommended.

Summary of Recommendations

Qualifying statements for Recommendation 2.1:

- The Expert Panel also agreed that nivolumab + ipilimumab (nivo+ipi) is an option that may be considered following first-line treatment with atezo+bev, although the evidence for nivo+ipi is limited to data from case series.[4-6]
- While there is currently no published evidence to support a recommendation for durva+treme, the Expert Panel agreed that this option may be considered following first-line treatment with atezo+bev.

Summary of Recommendations

Recommendation 2.2

Evidence Quality	Strength of Recommendation
Low	Weak

- Following first-line treatment with durva+treme, second-line therapy with a TKI is recommended.

Qualifying statement for Recommendation 2.2:

- The Expert Panel also agreed that atezo+bev may be considered following durva+treme for patients who do not have contraindications to the former combination, although there is no data available to select patients for this combination therapy vs. second-line therapy with a TKI.

Summary of Recommendations

Recommendation 2.3

Evidence Quality	Strength of Recommendation
Low to Moderate	Weak

- Following first-line treatment with sorafenib or lenvatinib, second-line therapy with another TKI (cabozantinib or regorafenib), ramucirumab (AFP ≥400 ng/mL), nivo+ipi, or durvalumab may be recommended for appropriate candidates. Atezo+bev or durva+treme may be considered for patients who may not have had access to these therapies in the first-line setting, and do not have contraindications to these combinations. Considerations regarding choice of therapy are included in the Clinical Interpretation in the full guideline.

Summary of Recommendations

Qualifying statement for Recommendation 2.3:

- In addition, pembrolizumab or nivolumab are reasonable options that may be considered for appropriate candidates following first-line therapy with sorafenib or lenvatinib.

Summary of Recommendations

Third-Line Therapy

Recommendation 3.1

Evidence Quality	Strength of Recommendation
Low	Weak

- Third-line therapy may be considered in Child-Pugh A patients with good performance status, using one of the agents listed previously that has a non-identical mechanism of action with previously received therapy.

Summary of Recommendations

Child-Pugh Class B

Recommendation 4.1

Evidence Quality	Strength of Recommendation
Very Low	Weak

- The Expert Panel agrees on a cautious approach to systemic therapy in advanced HCC patients who are Child-Pugh class B with good PS, considering underlying liver function, bleeding risk, presence of portal hypertension, extent of extrahepatic spread, tumor burden, and major vascular invasion. Limited data suggest that regimens typically used for Child-Pugh A can be beneficial in untreated patients with Child-Pugh B cirrhosis. Given the modest expectations for clinical benefit from systemic therapy in this population, the Expert Panel emphasizes shared decision-making with patients.

ASCO®
AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

3 Discussion

Future Directions

- There is currently no head-to-head data to assist with discrimination between some of the recommended treatment options
  - For example, in Recommendation 1.1 two first-line options combination therapy options are recommended because of their respective demonstrated benefit compared to sorafenib alone.
- Biomarkers that could assist with treatment decision-making would be helpful in this context, and real-world and post-hoc analyses have provided some information on genetic subtyping and biomarkers to guide the selection of patients for treatment.
- Another gap is the topic of sequencing of therapy in later lines; the Expert Panel awaits future studies on this topic, while acknowledging that they are likely to be retrospective.

Health Disparities

- Although ASCO guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care.
- Up to 5.3 million people—two percent of the U.S. population—are living with chronic HBV or HCV. Half of those with chronic HBV infection are Asian and Pacific Islander Americans.
- HBV is the most common serious infection of the liver and can lead to premature death from liver cancer or liver failure.
- For patients with HCC, studies have shown disparities in access to care, including liver transplantation, by race and/or ethnicity.[7-10]
- HCC was also detected at a more advanced stage in an African American study population, compared to other racial and ethnic groups.[11]

Health Disparities

- Detection at an earlier stage could help to reduce ethnic and racial disparities in outcomes.[12]
- Awareness of low rates of treatment with systematic therapy and/or disparities in access to care and clinical trials, and outcomes should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to more vulnerable populations.
- It is equally important to redefine the context of HCC disparity research to include the assessment of the impact of socioeconomic factors, and social policies on outcomes, in order to inform strategies to minimize cancer treatment and outcome disparities.
- Finally, social and health policies must emphasize prevention of known risk factors for HCC and a campaign for early detection methods should be promoted within racial and ethnic groups.

Additional Resources

- More information, including a supplement and clinical tools and resources, is available at www.asco.org/gastrointestinal-cancer-guidelines

- Patient information is available at www.cancer.net

Guideline Panel Members

Name	Affiliation/Institution	Role/Area of Expertise
John D. Gordan, MD, PhD (co-chair)	University of California, San Francisco, San Francisco, CA	Medical Oncology
Michal G. Rose, MD (co-chair)	Yale Cancer Center and VA Connecticut Healthcare System, West Haven, CT	Medical Oncology
Ghassan K. Abou-Alfa, MD, MBA	Memorial Sloan Kettering Cancer Center and Weill Medical College at Cornell University, New York, NY	Medical Oncology
Eliza Beal, MD	Karmanos Cancer Center, Detroit, MI	Medical Oncology
Richard S. Finn, MD	Geffen School of Medicine, UCLA, Los Angeles, CA	Medical Oncology
Terence P. Gade, MD, PhD	Penn Medicine, Philadelphia, PA	Interventional Radiology
Laura Goff, MD	Vanderbilt Ingram Cancer Center, Nashville, TN	Medical Oncology
Shilpi Gupta, MD	Atlantic Medical Group, Morristown, NJ	PGIN Representative
Jennifer Guy, MD	Sutter Health, San Francisco, CA	Medical Oncology
Hang T. Hoang, MD	National Cancer Hospital, Hanoi, Vietnam	Medical Oncology
Renuka Iyer, MD	Roswell Park Comprehensive Cancer Center, Buffalo, NY	Medical Oncology
Ishmael Jaiyesimi, DO, MS	Beaumont Hospital, Royal Oak, MI	PGIN Representative

Guideline Panel Members (cont.)

Name	Affiliation/Institution	Role/Area of Expertise
Minaxi Jhawer, MD	Englewood Hospital, Englewood, NJ	Medical Oncology
Asha Karippot, MD	Texas Oncology, Plano, TX	PGIN Representative
Ahmed O. Kaseb, MD	MD Anderson Cancer Center, Houston, TX	Medical Oncology
R. Kate Kelley, MD	University of California, San Francisco, San Francisco, CA	Medical Oncology
Jeremy Kortmansky, MD	Yale Cancer Center, New Haven, CT	Medical Oncology
Andrea Leaf, MD	VA New York Harbor Healthcare System, Brooklyn, NY	Medical Oncology
William M. Remak, MT	California Hepatitis C Task Force, California Chronic Care Coalition member, FAIR Foundation, San Francisco, CA	Patient Representative
Davendra P. S. Sohal, MD, MPH	University of Cincinnati, Cincinnati, OH	Medical Oncology
Tamar H. Taddei, MD	Yale University School of Medicine and VA Connecticut Health Care System, West Haven, CT	Gastroenterology/Hepatology
Andrea Wilson Woods, MFA	Blue Faery: The Adrienne Wilson Liver Cancer Association, Birmingham, AL	Patient Representative
Mark Yarchoan, MD	Johns Hopkins Medicine, Baltimore, MD	Medical Oncology
Erin B. Kennedy, MHSc	American Society of Clinical Oncology (ASCO), Alexandria, VA	ASCO Practice Guideline Staff (Health Research Methods)

Abbreviations

- AFP, alpha-fetoprotein
- ASCO, American Society of Clinical Oncology
- atezo+bev, atezolizumab + bevacizumab
- durva+treme, durvalumab + tremelimumab
- EBMC, Evidence Based Medicine Committee
- ECOG, Eastern Cooperative Oncology Group
- HBV, Hepatitis B virus
- HCC, hepatocellular carcinoma
- HCV, Hepatitis C virus
- nivo+ipi, nivolumab + ipilimumab
- PGIN, Practice Guidelines Implementation Network
- PS, performance status
- TKI, tyrosine kinase inhibitor
- VEGF, vascular endothelial growth factor

References

1. Llovet J, Finn RS, Ikeda M, et al: A phase 1b trial of lenvatinib (LEN) plus pembrolizumab (PEMBRO) in unresectable hepatocellular carcinoma (UHCC): updated results, European Society for Medical Oncology (ESMO). Barcelona, Spain, 2019
2. Finn RS: Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 382:1894-905, 2020
3. Kelley RK, Sangro B, Harris WP, et al: Efficacy, tolerability, and biologic activity of a novel regimen of tremelimumab (T) in combination with durvalumab (D) for patients (pts) with advanced hepatocellular carcinoma (aHCC), ASCO Annual Meeting. ASCO Virtual Scientific Program, 2020
4. Kim HJ, Hwang SY, Im JW, et al: A case of nearly complete response in hepatocellular carcinoma with disseminated lung metastasis by combination therapy of nivolumab and ipilimumab after treatment failure of atezolizumab plus bevacizumab. J Liver Cancer 23:213-218, 2023
5. Roessler D, Öcal O, Philipp AB, et al: Ipilimumab and nivolumab in advanced hepatocellular carcinoma after failure of prior immune checkpoint inhibitor-based combination therapies: a multicenter retrospective study. Journal of Cancer Research and Clinical Oncology 149:3065-3073, 2023
6. Alden SL, Lim M, Kao C, et al: Salvage Ipilimumab plus Nivolumab after Anti-PD-1/PD-L1 Therapy in Advanced Hepatocellular Carcinoma. Cancer Res Commun 3:1312-1317, 2023
7. Ha J, Yan M, Aguilar M, et al: Race/ethnicity-specific disparities in cancer incidence, burden of disease, and overall survival among patients with hepatocellular carcinoma in the United States. Cancer 122:2512-23, 2016
8. Mathur AK, Osborne NH, Lynch RJ, et al: Racial/ethnic disparities in access to care and survival for patients with early-stage hepatocellular carcinoma. Arch Surg 145:1158-63, 2010
9. Artinyan A, Mailey B, Sanchez-Luege N, et al: Race, ethnicity, and socioeconomic status influence the survival of patients with hepatocellular carcinoma in the United States. Cancer 116:1367-77, 2010
10. Frenette CT: Increasing Awareness on Racial Disparities in Liver Transplantation for Hepatocellular Carcinoma in the United States. Hepatol Commun 3:5-7, 2019
11. Estevez J, Yang JD, Leong J, et al: Clinical Features Associated with Survival Outcome in African-American Patients with Hepatocellular Carcinoma. Am J Gastroenterol 114:80-88, 2019
12. Rich NE, Hester C, Odewole M, et al: Racial and Ethnic Differences in Presentation and Outcomes of Hepatocellular Carcinoma. Clin Gastroenterol Hepatol 17:551-559 e1, 2019

Disclaimer

The Clinical Practice Guidelines and other guidance published herein are provided by the American Society of Clinical Oncology, Inc. (ASCO) to assist providers in clinical decision making. The information herein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. Recommendations specify the level of confidence that the recommendation reflects the net effect of a given course of action. The use of words like “must,” “must not,” “should,” and “should not” indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO does not endorse third party drugs, devices, services, or therapies used to diagnose, treat, monitor, manage, or alleviate health conditions. Any use of a brand or trade name is for identification purposes only. ASCO provides this information on an “as is” basis and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions.