Systemic Therapy for Advanced Hepatocellular Carcinoma: ASCO Guideline Update

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ABSTRACT

PURPOSE To update an evidence-based guideline to assist in clinical decision-making for patients with advanced hepatocellular carcinoma (HCC).

METHODS ASCO convened an Expert Panel to update the 2020 guideline on systemic therapy for HCC. The panel updated the systematic review to include randomized controlled trials (RCTs) published through October 2023 and updated recommendations.

RESULTS Ten new RCTs met the inclusion criteria and were added to the evidence base.

RECOMMENDATIONS Atezolizumab + bevacizumab (atezo + bev) or durvalumab + tremelimumab (durva + treme) may be offered first-line for patients with advanced HCC, Child-Pugh class A liver disease, and Eastern Cooperative Oncology Group performance status 0-1. Where there are contraindications to these therapies, sorafenib, lenvatinib, or durvalumab may be offered first-line. Following first-line treatment with atezo + bev, second-line therapy with a tyrosine kinase inhibitor (TKI), ramucirumab (for patients with alpha-fetoprotein [AFP] ≥400 ng/mL), durva + treme, or nivolumab + ipilimumab (nivo + ipi) may be recommended for appropriate candidates. Following first-line therapy with durva + treme, second-line therapy with a TKI is recommended. Following first-line treatment with sorafenib or lenvatinib, second-line therapy options include cabozantinib, regorafenib for patients who previously tolerated sorafenib, ramucirumab (AFP ≥400 ng/mL), nivo + ipi, or durvalumab; atezo + bev or durva + treme may be considered for patients who did not have access to these therapies in the first-line setting, and do not have contraindications. Pembrolizumab or nivolumab are also options for appropriate patients following sorafenib or lenvatinib. Third-line therapy may be considered in Child-Pugh class A patients with good PS, using one of the agents listed previously that has a nonidentical mechanism of action with previously received therapy. A cautious approach to systemic therapy is recommended for patients with Child-Pugh class B advanced HCC. Further guidance on choosing between options is included within the guideline.

Additional information is available at www.asco.org/gastrointestinal-cancer-guidelines.

ACCOMPANYING CONTENT

Listen to the podcast by Dr Gordan at https://ascopubs.org/journal/jco/asco-guidelines-podcast

Appendix

Data Supplement

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View Online Article

INTRODUCTION

There were approximately 725,000 new cases and 664,000 deaths worldwide due to hepatocellular carcinoma (HCC) in 2020. HCC comprises 75%-85% of primary liver cancer cases and is the fourth-leading cause of annual cancer deaths worldwide.[1] In the United States, it is estimated that liver cancer will account for approximately 41,210 new cases and about 29,380 deaths in 2023.[2] Risk factors vary by geographic region and include chronic viral hepatitis (hepatitis B virus [HBV] infection, hepatitis C virus [HCV] infection); alcohol-related liver disease; environmental exposures,

THE BOTTOM LINE

Systemic Therapy for Advanced Hepatocellular Carcinoma: ASCO Guideline

Guideline Question

What are the recommended treatment options for first-line and subsequent systemic therapy for patients with advanced hepatocellular carcinoma (ie, patients who are unresectable and not amenable to local therapies)?

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.

Methods

An Expert Panel was convened to develop clinical practice guideline recommendations based on a systematic review of the medical literature.

Recommendations

First-Line Therapy

Recommendation 1.1. Atezolizumab + bevacizumab (atezo + bev) or durvalumab + tremelimumab (durva + treme) may be offered as first-line treatment for patients with Child-Pugh class A, and Eastern Cooperative Oncology Group performance status (ECOG PS) 0-1 advanced hepatocellular carcinoma (HCC) (Evidence quality: Moderate to High, Strength of recommendation: Strong).

Qualifying statements.

- 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.

Recommendation 1.2. 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 (Evidence quality: Moderate; Strength of recommendation: Strong).

Qualifying statements.

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

Second-Line Therapy.

Recommendation 2.1. Following first-line treatment with atezo + bev, second-line therapy with a tyrosine kinase inhibitor (TKI; ie, sorafenib, lenvatinib, or cabozantinib), or ramucirumab (AFP ≥400 ng/mL) are recommended (Evidence quality: Low; Strength of recommendation: Weak).

Qualifying statements.

- 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.[16-18]
- 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.

Recommendation 2.2. Following first-line treatment with durva + treme, second-line therapy with a TKI is recommended (Evidence quality: Low; Strength of recommendation: Weak).

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THE BOTTOM LINE (CONTINUED)

Qualifying statement.

- 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 versus second-line therapy with a TKI.

Recommendation 2.3. 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* (Evidence quality: Low to Moderate; Strength of recommendation: Weak).

Qualifying statement.

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

Third-Line Therapy

Recommendation 3.1. 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 (Evidence quality: Low; Strength of recommendation: Weak).

Child-Pugh Class B

Recommendation 4.1. 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 (Evidence quality: Very Low; Strength of recommendation: Weak).

Additional Resources

Definitions for the quality of the evidence and strength of recommendation ratings are available in Appendix Table A1 (online only). More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/gastrointestinal-cancer-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

specifically aflatoxin-contaminated foods; and steatotic liver disease.[3] Three-quarters of cases occur in the Asia-Pacific region, where the main risk factor outside of Japan is HBV.[4] HCC is two to three times as common in men as in women.[5] Incidence of HCC is currently on the rise in the United States,[6] related in part to a rise in the incidence of obesity, type II diabetes, and metabolic syndrome over the past several decades.[7] Decreases in incidence rates among Asian-Pacific Islanders and younger cohorts may contribute to an overall reduction in cases of HCC in future years.[8]

Effective treatment options, such as resection, liver transplantation, and ablation, exist for early-stage HCC, and patients with locally advanced disease may be candidates for liver-directed therapies, including transarterial therapies chemoembolization (TACE), bland embolization, and radioembolization, and external-beam radiation therapy. Historically, the majority of HCC cases were diagnosed at an advanced, incurable stage and had a poor prognosis due to the palliative nature of currently available local and systemic therapies.[9] Trials of systemic therapy for advanced HCC failed to show improved outcomes until the advent of the tyrosine kinase inhibitor sorafenib,[10] followed by randomized controlled trials (RCTs) published in 2008 and 2009 demonstrating a survival benefit with sorafenib versus placebo.[9,11] Following the availability of sorafenib, no further effective systemic therapy options were identified for almost a decade. In recent years, however, several newer systemic therapy options have shown efficacy in the first- and second-line settings, including evidence of the effectiveness of combination therapy.[12-14] These studies were included in a 2020 guideline published by ASCO.[15] 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 are outside the scope of this guideline update.

GUIDELINE 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?

METHODS

Guideline Development Process

This systematic review-based guideline was developed by a multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise. The Expert Panel (Appendix Table A2) met via teleconference and/or webinar and corresponded through e-mail. Based upon the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. The guideline recommendations were sent for an open comment period of 2 weeks allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were taken into consideration while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then circulated for external review, and submitted to the *Journal of Clinical Oncology* (*JCO*) for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Evidence Based Medicine Committee prior to publication. All funding for the administration of the project was provided by ASCO.

The systematic search that was conducted for the previous version of this guideline was of PubMed for phase III RCTs published between January 1, 2007, and May 15, 2020. An update to this search was conducted to bring the search strategy current to October 5, 2023. Articles were selected for inclusion in the systematic review of the evidence based on the following criteria:

- Population: Patients with unresectable advanced hepatocellular carcinoma, including patients who are no longer candidates for surgical or liver-directed therapies, that is, patients with characteristics such as multifocal and/or infiltrative disease within the liver, vascular invasion, or extrahepatic spread.
- Intervention: First-line or greater-line (due to progression or toxicity) systemic therapy with tyrosine kinase inhibitors (TKIs), including sorafenib, regorafenib, lenvatinib, and cabozantinib; immune checkpoint inhibitors (ICIs), including atezolizumab, durvalumab, tremelimumab, nivolumab, pembrolizumab, sintilimab, and ipilimumab; and/or antiangiogenic agents including bevacizumab and ramucirumab (in patients with alpha-fetoprotein [AFP] ≥ 400 ng/mL). For this guideline update, any targeted agents or immunotherapy agents alone or in combination with other therapies that were the subject of RCTs in the target population were considered eligible for inclusion. Studies of targeted agents or immunotherapy agents not available in the United States that otherwise met inclusion criteria are discussed in this guideline update but not included in the recommendations.
- Comparison: Interventions listed or placebo control.
- Outcomes: Overall survival (OS), progression-free survival (PFS), time to progression, objective response rate (ORR), adverse events (AEs), and quality of life.

Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals within a 2-year time frame; (2) editorials, commentaries, letters, news articles, case reports, and narrative reviews; and (3) published in a non-English language, given the confined medical language expertise of the panel members. In addition, a guideline implementability review was conducted. Based on the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for the type and strength of recommendation, and evidence quality are provided with each recommendation. Evidence quality for each outcome was assessed using the Cochrane Risk of Bias tool and elements of the GRADE quality assessment and recommendations development process.[19] In order to facilitate the quality assessment ratings, MAGICApp guideline development software program was used; within this framework, outcomes from RCTs are rated high quality and can subsequently be downgraded as factors that affect quality (ie, certainty) are identified.[20] GRADE quality assessment labels (ie, high, moderate, low, very low) were assigned for each outcome by the project methodologist in collaboration with the Expert Panel co-chairs and reviewed by the full Expert Panel. Relative risk values were calculated using Review Manager 5.3.

The ASCO Expert Panel and guidelines staff will work with the co-chairs to monitor emerging literature requiring updates to the guideline. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This is the most recent information as of the publication date.

Guideline Disclaimer

The Clinical Practice Guidelines and other guidance published herein are provided by the 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.

Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at https://www.asco.org/guideline-methodology). All members of the Expert Panel (Appendix Table A2) completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

Eight phase III RCTs from the 2020 version of the guideline were retained for inclusion in the evidence base for the 2023 update.[11,13,21-26] Updates were incorporated for two previously published studies: CheckMate459[27] and IMbrave150.[28] In addition, 10 new RCTs were added to the evidence base,[29-38] including seven RCTs of first-line therapy options,[29-32,34,37,38] two RCTs of second-line interventions,[35,36] and one trial that included patients who had not received treatment or were initially recurrent.[33] Results from each study are included following the relevant recommendations, and detailed patient characteristics are included in Table 1 and the Data Supplement (Tables S1-S4, online only). Results of study quality assessment are included in the table footnotes.

RECOMMENDATIONS

Clinical Question 1

What are the preferred treatment options for first-line systemic therapy for patients with advanced hepatocellular carcinoma?

Recommendation 1.1

Atezolizumab + bevacizumab (atezo + bev) or durvalumab + tremelimumab (durva + treme) may be offered as first-line treatment for patients with Child-Pugh class A, and Eastern Cooperative Oncology Group performance status (ECOG PS) 0-1 advanced HCC (Evidence quality: Moderate to High, Strength of recommendation: Strong).

Qualifying statements.

- 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 vascular endothelial growth factor (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.

Literature review and analysis. Six RCTs of combination therapy options compared to sorafenib alone in the first-line setting met the inclusion criteria for this guideline update.[28-32,38] The IMbrave150 RCT of atezo + bev compared to sorafenib was included in the previous version of this guideline.[39] Newer comparisons added for this guideline include sorafenib as the control arm compared to durva + treme, cabozantinib + atezolizumab, sintilimab + a bevacizumab biosimilar, and camrelizumab + rivoceranib, respectively.[29-32] Results of the LEAP-002 RCT of lenvatinib + pembrolizumab

TABLE 1. Characteristics of Patients in Phase III Randomized Controlled Trials of First-Line Combination Systemic Therapy Options Recommended for Advanced Hepatocellular Carcinoma

	Finn et al[13] (IMbrave150)		Abou-Alfa et al [31] (HIMALAYA)		
Patient Characteristic	Atezolizumab and Bevacizumab (n = 336)	Sorafenib (n = 165)	Tremelimumab and Durvalumab (n = 393)	Durvalumab (n = 389)	Sorafenib (n = 389)
Age, years, median, range	64 (IQR: 56-71)	66 (IQR: 59-71)	65 (22-86)	64 (20-86)	64 (18-88)
Sex, %					
Male	82	83	83	83	87
Female	18	17	17	17	13
Region, %					
Asia (excluding Japan)	40	41	40	43	40
Rest of the world (including Japan)	60[a]	59	60[b]	57	60
Disease etiology, %					
Hepatitis C	21	22	28	28	27
Hepatitis B	49	46	31	31	31
Nonviral	30	32	41	42	43
ECOG PS, %					
0	62	62	62	61	62
1	38	38	38	39	38
2	0	0	0.3	0.5	0.3
BCLC stage, %					
A (early)	2	4			
B (intermediate)	15	16	20	21	17
C (advanced)	82	81	80	79	83
MVI (yes), %	38	43	26 (note: patients with main portal vein invasion (VP4) were excluded from HIMALAYA)	24	26
EH spread (yes), %	63	56	53	55	52
MVI and/or EH spread (yes), %	77	73			
Child-Pugh class, %					
A/5	72	73	75	73	71
A/6	28	27	23	25	26
B/7			1	2	3
Other			0.5	0.3	0
Alpha-fetoprotein, ng/mL					
≥400 ng/mL (%)	38	37	37	35	32
Varices, %					
Present at baseline	26	26			
Treated at baseline	11	14			
Previous therapy, %					
Radiotherapy			12	8	10
Any anticancer therapy	48	52			

Abbreviations: BCLC, Barcelona Clinic Liver Cancer staging; BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; EH, extrahepatic; MVI, macrovascular invasion.
[a]United States, Australia, New Zealand, and Japan.
[b]Brazil, Canada, France, Germany, Italy, Japan, Russia, Spain, Ukraine, and the United States.

versus lenvatinib have been reported in an abstract.[38] Across included fully published studies, most patients were male (>80%), and the median age was 64-66 years across treatment and control groups in three of the trials,[28,31,32] and 53-58 years of age in two of the included trials.[29,30] IMbrave150 and HIMALAYA included similar proportions of patients from Asia versus the rest of the world (approximately 40% *v* 60%). COSMIC-312 recruited more patients from Europe (approximately 40%), with relatively fewer from Asian countries (approximately 26%). The percentage of patients with HBV

etiology was 47% and 31% in the IMbrave150 and HIMALAYA studies, respectively, and more than 60% of patients in these two studies had ECOG PS 0. Approximately 80% of patients in three studies had Barcelona Clinic Liver Cancer (BCLC) stage C, whereas in the COSMIC-312 study, only two-thirds of the patients had BCLC C and the remainder had stage B. Across studies, almost all patients were Child-Pugh A, with a high rate of macrovascular invasion and extrahepatic spread. Patients with main portal vein invasion were excluded from the HIMALAYA trial, but this was not an exclusion criterion in IMbrave150. Results from each study are included subsequently, and detailed patient characteristics are included in Table 1 for IMbrave150 and HIMALAYA. Patient characteristics for COSMIC-312, CARES-310, and ORIENT-32 can be found in the Data Supplement (Table S1).

Durvalumab + tremelimumab versus sorafenib (HIMALAYA). The HIMALAYA trial[31] is a global open-label phase III RCT in which patients were randomly assigned to treatment with the anti-PD-L1 + anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) combination durva + treme or durvalumab alone versus sorafenib. Patients were from Asia, excluding Japan (41%) and the rest of the world (59%). The underlying cause of HCC was HBV (31%), or HCV (28%), with the remainder attributable to nonviral causes. Approximately 80% of patients were BCLC stage C, with the remainder BCLC B, and approximately 25% and 53% had macrovascular invasion and extrahepatic spread, respectively (Table 1). Patients with main portal vein thrombosis were excluded from the HIMALAYA RCT. OS with durva + treme was significantly improved compared to sorafenib alone (hazard ratio [HR], 0.78 [96.02% CI, 0.65 to 0.93]), however, there was no improvement in PFS (HR, 0.90 [95% CI, 0.77 to 1.05]) for durva + treme compared to sorafenib. Grade 3-4 AEs were not significantly different between durva + treme and sorafenib (relative risk, 0.96 [95% CI, 0.84 to 1.11]; Table 2).

Atezolizumab + bevacizumab (atezo + bev) versus sorafenib (IMbrave150).[13] In the IMbrave150 RCT, patients were randomly assigned to treatment with atezo + bev or sorafenib. Patients were from Asia, excluding Japan (40%) or the United States, Australia, New Zealand, and Japan (60%). The underlying cause of HCC was HBV (48%) or HCV (22%), with the remainder attributable to nonviral causes. All patients underwent screening for varices prior to initiating study treatment. Twenty-six percent had varices at baseline, and 11% in the treatment and 14% in the control groups underwent treatment. Approximately half of the patients had received prior local therapy for HCC (Table 1). For this update, data were available from an additional 12 months of follow-up. Results for OS significantly favored atezo + bev compared to sorafenib, with an HR of 0.66 (95% CI, 0.52 to 0.85). Median OS was 13.4 months (95% CI, 11.4 to 16.9) in the sorafenib group and 19.2 months (95% CI, 17.0 to 23.7) in the atezo + bev group. PFS (HR, 0.65 [95% CI, 0.53 to 0.81]) was significantly improved in the atezo + bev group (Table 4). Grade 3-4 AEs for atezo + bev versus sorafenib included hand-foot skin reaction (HFSR; 0% *v* 8%), diarrhea (2% *v* 5%), hypertension (15% *v* 12%), as well as increases in AST (7% *v* 5%) (Table 3).[13] In addition, time to deterioration of quality of life was significantly delayed in the atezo + bev group (median TTD, 11.2 months), compared with sorafenib (median TTD, 3.6 months).[40]

Cabozantinib + atezolizumab versus sorafenib (COSMIC-312). There were 372 participants in the open-label, global, multicenter COSMIC-312 RCT,[32] which included OS and PFS as coprimary endpoints. There was a significant PFS benefit with the combination therapy (HR, 0.63 [95% CI, 0.44 to 0.919]), but no significant difference in OS (HR, 0.90 [95% CI, 0.69 to 1.18]), and the risk of grade 3-4 treatment-related AEs was higher in the combination therapy group (RR, 1.39 [95% CI, 1.18 to 1.6385]; Data Supplement, Table S6).

Lenvatinib + pembrolizumab versus lenvatinib (LEAP-002). LEAP-002[38] is a 794-patient, double-blind, global, phase III RCT that evaluated the efficacy of lenvatinib + pembrolizumab versus lenvatinib, with OS at final analysis and PFS at first interim analysis as the coprimary endpoints. Results were reported in an abstract for this RCT. Using a prespecified *P* value for significance of .002 and .0185 for PFS and OS, respectively, the study found that neither of these endpoints were significantly different for the combination therapy group compared to single-agent lenvatinib. Grade 3-5 treatment-related AEs were 62.5% in the lenvatinib + pembrolizumab group versus 57.5% in the lenvatinib group.

Clinical interpretation. For the previous version of this guideline, the combination of atezo + bev was recommended as first-line therapy based on the results of the Imbrave150 trial (Recommendation 1.1). For this guideline update, the durva + treme regimen has been added as a first-line option, based on the OS benefit with this combination. Choice of treatment may be based on patient preference and toxicity profile; for example, with a higher risk of bleeding and thrombosis associated with bevacizumab. COSMIC-312, which was the first phase III trial to report outcomes from a TKI (cabozantinib) in combination with an ICI (atezolizumab), found no differences in OS with the combination therapy compared to sorafenib, although PFS was significantly improved; the population in this study included patients with relatively less advanced BCLC stage.

Recommendation 1.2

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 (Evidence quality: Moderate; Strength of recommendation: Strong).

Qualifying statement.

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

TABLE 2. Durva + Treme versus Sorafenib in Hepatocellular Carcinoma Patients who are Barcelona Clinic Liver Cancer (BCLC) B (20%) or C (80%) With No Prior Therapy and Ineligible for Local Therapy, and Without Main Portal Vein Invasion (HIMALAYA).[31]

Outcome Time Frame	Study Results	Absolute Effect Estimates Sorafenib	 Durva + Treme	Quality of Evidence	Plain Language Summary
OS 18 months	HR: 0.78 (96.02% CI, 0.65 to 0.93) 782 participants in 1 study	585 per 1,000	496 per 1,000 Difference: 89 fewer per 1,000 (95% CI, 99 fewer to 26 fewer)	High[a]	Durva + treme improves OS, compared to sorafenib
PFS 18 months	HR: 0.90 (95% CI, 0.77 to 1.05) 782 participants in 1 study	820 per 1,000	786 per 1,000 Difference: 34 fewer per 1,000 (95% CI, 67 fewer to 15 more)	Moderate[a,b]	Durva + treme probably has little or no effect on PFS, compared to sorafenib
Grade 3-4 TEAEs 18 months	RR: 0.96 (95% CI, 0.84 to 1.11) 762 participants in 1 study	524 per 1,000	503 per 1,000 Difference: 21 fewer per 1,000 (95% CI, 84 fewer to 58 more)	Moderate[a,b]	Durva + treme probably has little or no effect on grade 3-4 TEAEs, compared to sorafenib (Table 3)

Abbreviations: durva + treme, durvalumab + tremelimumab; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RR, relative risk; TEAEs, treatment-emergent adverse events.
[a]Open-label trial.
[b]Downgrade: imprecision (CI includes 1).

Literature review and analysis. RCTs of single-agent therapies sorafenib and lenvatinib were reviewed for the previous version of this guideline, including two studies of sorafenib versus placebo, and one study of lenvatinib versus sorafenib. Patient characteristics of these studies are included in the Data Supplement (Table S2). Durvalumab was a second treatment arm included in the HIMALAYA trial, which is new for this update; patient characteristics of this study arm are similar to the overall HIMALAYA patient characteristics described previously following Recommendation 1.1, and are summarized in Table 1. Outcomes and quality assessment results are included in the footnotes to Data Supplement tables.

Durvalumab versus sorafenib (HIMALAYA). Durvalumab[31] alone was found to be noninferior to sorafenib for OS (HR, 0.86 [95.67% CI,: 0.73 to 1.03], noninferiority margin: 1.08). HR for PFS was 1.02 (95% CI, 0.88 to 1.19) for durvalumab alone compared to sorafenib. Patients treated with durvalumab alone had a significantly lower rate of grade 3-4 AEs compared to sorafenib (RR, 0.71 [95% CI, 0.60 to 0.83]; Table 5).

Sorafenib versus placebo (SHARP, Asia-Pacific). The study by Llovet et al (SHARP, 2008)[11,24] included 602 advanced HCC patients who were not eligible for or who had disease progression after local therapies. Patients were from centers mostly located in Europe and Australasia (88%). The most common liver disease etiologies across the study population were HCV (28%), HBV (19%), or alcohol (26%). The trial was stopped early after an interim analysis detected a significant OS advantage for sorafenib. The smaller study by Cheng et al (N = 271) was subsequently performed to confirm the former study's results in an Asian population (China, South Korea, and Taiwan); the cause of liver disease in this study was HBV in the majority of patients (71% of sorafenib-treated patients and 78% of placebo-treated patients; Data Supplement, Table S2). These patients were also more likely to have extrahepatic spread and/or macrovascular invasion compared to Llovet et al (79% *v* 70%, respectively), and their median age was 52, compared to the median age of 65 in the SHARP trial.

Both studies reported significantly better OS with sorafenib, compared to placebo, with similar hazard ratios for Llovet et al and Cheng et al: 0.69 (95% CI, 0.55 to 0.87) and 0.68 (95% CI, 0.50 to 0.93), respectively. Both studies also reported a significant benefit for sorafenib over placebo in time to progression measured by RECIST, and stable disease, but no difference in symptomatic time to progression, which was the co-primary endpoint along with OS in the trial by Llovet et al. Median survival time in both experimental and control groups was lower in the Asia-Pacific trial, potentially due to patient characteristics. AEs were similar across the two trials, with patients treated with sorafenib more likely to report HFSR, diarrhea, and hypophosphatemia (Table 6).

TABLE 3. Grade 3 or 4 Adverse Events Associated That Were Experienced by ≥5% of Patients in Either Arm of Phase III Trials of Guideline-Recommended Combination First-Line Therapy for Advanced Hepatocellular Carcinoma

Comparison	HFSR	Diarrhea	Hyperbilirubinemia/Blood Bilirubin Increase	Hypertension	AST Increase	Lipase Increase
Atezo + bev *v* sorafenib[13]	0 *v* 8.3%	1.8% *v* 5.1%	2.4% *v* 6.4%	15.2% *v* 12.2%	7.0% *v* 5.1%	
Durva + treme *v* sorafenib[31]	0% *v* 9.1%			1.8% *v* 6.1%	5.2% *v* 3.2%	6.2% *v* 2.9%

Abbreviations: atezo + bev, atezolizumab + bevacizumab; durva + treme, durvalumab + tremelimumab; HFSR, hand-foot skin reaction.

TABLE 4. Atezolizumab + Bevacizumab Versus Sorafenib in Patients With Early (3% BCLC A) Intermediate (15% BCLC B) or Advanced (82% BCLC C) Unresectable Hepatocellular Carcinoma (IMbrave150, Cheng et al)[28]

Outcome Time Frame	Study Results	Absolute Effect Estimates		Quality of Evidence	Plain Text Summary
		Sorafenib	Atezo + Bev		
OS 12 months	HR: 0.66 (95% CI, 0.52 to 0.85) 501 patients in one study	440 deaths per 1,00	318 deaths per 1,00	High[a]	Atezo + bev improves OS compared to sorafenib
		Difference: 122 fewer per 1,000 (95% CI, 260 fewer to 51 fewer)			
PFS[b] 12 months	HR: 0.65 (95% CI, 0.53 to 0.81) 501 patients in one study	720 progressions or deaths per 1,00	563 progressions or death per 1,000	High[a]	Atezo + bev improves PFS compared to sorafenib
		Difference: 157 fewer per 1,000 (95% CI, 491 fewer to 77 fewer)			
Grade 3-4 TRAEs	RR: 0.94 (95% CI, 0.76 to 1.16) 485 patients in one study	460 events per 1,00	432 events per 1,00	Moderate,[a,c]	Atezo + bev probably has little or no effect on overall rate of grade 3-4 TRAEs compared to sorafenib (Table 3)
		Difference: 28 more per 1,000 (95% CI, 110 fewer to 74 more)			

Abbreviations: Atezo + bev, atezolizumab + bevacizumab; BCLC, Barcelona Clinic Liver Cancer; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RR, relative risk; TRAEs, treatment-related adverse events.
[a]Open-label design.
[b]Independently assessed (mRECIST 1.1).
[c]Downgrade: imprecision (CI includes 1).

Lenvatinib versus sorafenib (REFLECT). In 2018, Kudo et al[23] published the results of a multisite global 954-patient RCT of sorafenib versus lenvatinib. Patients were from the Western region (33%, ie, Europe, North America, Israel, and Russia) or Asia-Pacific region (67%, ie, China, Hong Kong, Japan, South Korea, Malaysia, Philippines, Singapore, Taiwan, and Thailand). The underlying cause of HCC (lenvatinib *v* sorafenib, respectively) was HBV (53% *v* 48%) or HCV (19% *v* 26%), with a minority attributable to alcohol (8% *v* 4%). Greater than 50% liver involvement and main portal vein invasion were exclusion criteria for this trial.

The HR for OS (0.92 [95% CI, 0.79 to 1.06]) indicates that lenvatinib was noninferior to sorafenib. PFS (HR, 0.64 [95% CI, 0.55 to 0.76]) and objective response rates (HR, 5.01 [95% CI, 3.59 to 7.01]) were significantly higher in the lenvatinib group (Data Supplement, Table S9). AEs for lenvatinib versus sorafenib included HFSR (grade ≥3: 3% *v* 11%), diarrhea (any grade: 39% *v* 46%), alopecia (any grade: 3% *v* 25%), hypertension (grade ≥3: 23% *v* 14%), and proteinuria (grade ≥3: 6% *v* 2%). Patients in the lenvatinib group were more likely to discontinue treatment due to AEs (RR, 1.46 [95% CI, 1.01 to 2.1]). Median duration of treatment was 5.7 months versus 3.7 months in the lenvatinib and sorafenib groups.

Nivolumab versus sorafenib (CheckMate 459). This update includes[27] data from the full publication of the randomized phase III multicenter CheckMate 459 trial, which included 743 patients (98% Child-Pugh A) who received first-line therapy with nivolumab or sorafenib. Most patients included in the trial were BCLC B (15%) or C (80%). Results showed no significant difference between treatment and control groups for the primary outcome OS (HR, 0.85 [95% CI, 0.72 to 1.02]), or PFS (HR, 0.98 [95% CI, 0.82 to 1.18]). Grade 3 AEs related to treatment were reported in 18% of nivolumab patients and 47% of sorafenib patients (RR, 0.38 [95% CI, 0.30 to 0.49]). Grade 4 AEs were experienced by 4% of patients in the nivolumab group compared to 2% of patients in the sorafenib group (RR, 1.65 [95% CI, 0.73 to 3.72]; Data Supplement, Table S10).

Studies of first-line therapy primarily or exclusively conducted in China.

Tislelizumab versus sorafenib (RATIONALE-301). This RCT[37] included 674 participants with ECOG PS 0-1, Child-Pugh class A, and BCLC stage B or C HCC who were receiving first-line systemic therapy after disease progression following locoregional therapy (or who were not amenable to local therapy). Most participants were from Asia (63%), with the remainder from Japan (11%) or the rest of the world (25%). This study met its primary endpoint of noninferiority of OS (HR, 0.85 [95.003% CI, 0.71 to 1.02]). HR for PFS was 1.11 (95% CI, 0.92 to 1.33]). Grade 3 or greater treatment-related AEs were experienced by 22.2% of those in the tislelizumab group and 53.4% of those in the sorafenib group (Data Supplement, Table S19).

Camrelizumab + rivoceranib versus sorafenib (CARES-310). This RCT[29] included 542 participants with unresectable Child-Pugh A, ECOG 0-1, and BCLC B or C HCC, and included patients with main portal vein invasion. The majority of patients (83%) were from China, Hong Kong, Taiwan, and South Korea, while the remainder were from Europe or the United States (Data Supplement, Table S1). In this study, OS was significantly improved with the combination of camrelizumab + rivoceranib, compared to sorafenib (HR, 0.62 [95% CI, 0.49 to 0.80]). PFS was also significantly improved in the combination group (HR, 0.52 [95% CI, 0.41 to 0.65]). Grade 3 and grade 4 AEs were significantly more likely in the combination therapy group and are reported at a higher rate than seen in Imbrave150 or HIMALAYA (Data Supplement, Table S5).

TABLE 5. Durvalumab Versus Sorafenib in Hepatocellular Carcinoma Patients BCLC B (20%) or C (80%) With No Prior Therapy and Ineligible for Local Therapy (HIMALAYA)[31]

Outcome Time Frame	Study Results	Absolute Effect Estimates		Quality of Evidence	Plain Language Summary
		Sorafenib	Durvalumab		
OS 18 months	HR: 0.86 (95.67% CI, 0.73 to 1.03) 778 participants in one study	585 per 1,000	531 per 1,000 Difference: 54 fewer per 1,000 (95% CI, 67 fewer to 11 more)	High[a,b]	For OS, durvalumab is noninferior to sorafenib
PFS 18 months	HR: 1.02 (95% CI, 0.88 to 1.19) 778 participants in one study	820 per 1,000	826 per 1,000 Difference: 6 more per 1,000 (95% CI, 40 fewer to 50 more)	High[a]	Durvalumab probably has little or no effect on PFS, compared to sorafenib
Grade 3-4 TEAEs 18 months	RR: 0.71 (95% CI, 0.60 to 0.83) 762 participants in one study	524 per 1,000	372 per 1,000 Difference: 152 fewer per 1,000 (95% CI, 210 fewer to 89 fewer)	High[a]	Durvalumab probably reduces risk of grade 3-4 TEAEs, compared to sorafenib (Table 6)

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RR, relative risk; TEAEs, treatment-emergent adverse events.

[a]Open-label trial.

[b]The noninferiority margin had an upper bound of 1.08, therefore noninferiority was met; a subsequent test showed that durvalumab was not superior to sorafenib ($P = .0674$).

Sintilimab + bevacizumab biosimilar IBI305 versus sorafenib (ORIENT-32). This RCT[30] included 595 participants with unresectable HBV-associated HCC, recruited from 50 centers in China. In this study, OS was significantly improved with the combination of sintilimab + IBI305, compared to sorafenib (HR, 0.57 [95% CI, 0.43 to 0.75]) in a first interim analysis. PFS was also significantly improved in the combination group (HR, 0.56 [95% CI, 0.46 to 0.70]; Data Supplement, Table S20). Grade 3 and grade 4 AEs were significantly more likely in the combination therapy group.

Lenvatinib + TACE versus lenvatinib (LAUNCH). This study included[33] 388 participants with untreated or initially recurrent advanced Child-Pugh A HCC, and was conducted in China. Results from an interim analysis showed that the combination of lenvatinib + TACE was superior to lenvatinib alone in terms of the primary outcome OS (HR, 0.45 [95% CI, 0.33 to 0.61], superiority margin: 0.697). PFS (HR, 0.43 [95% CI, 0.34 to 0.55]) and ORR (54.1% *v* 25.0%, $P < .001$) were also significantly improved in the combination group (Data Supplement, Table S11). Some grade 3-4 AEs were more common with lenvatinib + TACE, including ALT elevation (17.6% *v* 1.2%, $P < .001$), AST elevation (22.9% *v* 1.8%, $P < .001$), hyperbilirubinemia (9.4% *v* 3.0%, $P = .014$), and grade 3-4 hypertension (20.6% *v* 19.6%) (Data Supplement, Table S21).

Donafenib versus sorafenib (Qin et al 2021). In this phase II/III RCT[34] of donafenib versus placebo in the first-line setting, 80% of 665 included patients had received previous locoregional therapy. Patients in this study were from China and had Child-Pugh A5-B7 unresectable or metastatic HCC. Study authors characterize the study population as having more advanced-stage disease than the typical Western patient population. Superiority of donafenib over sorafenib was demonstrated for OS (HR, 0.83 [95% CI, 0.73 to 0.99]), but not PFS (HR, 0.91 [95% CI, 0.76 to 1.08]). The rate of grade ≥3 AEs was significantly lower in the donafenib group (RR, 0.76 [95% CI, 0.63 to 0.90]; Data Supplement, Table S12).

Clinical interpretation. Sorafenib and lenvatinib are recommended where there are contraindications to atezo + bev or durva + treme, and durvalumab alone may be considered, based on its demonstrated noninferiority to sorafenib in the HIMALAYA trial (Recommendation 1.2). When selecting a TKI, clinicians and patients should note that there is a higher rate of hypertension with lenvatinib, and more HFSR with sorafenib.[28]

Emerging data, mostly from China, are included within this guideline for several new therapy options, including the

TABLE 6. Grade 3-4 Adverse Events Experienced by ≥5% of Patients in Either Arm of Phase III Trials of Guideline-Recommended Single-Agent First-Line Therapy for Advanced Hepatocellular Carcinoma

Comparison	HFSR	Diarrhea	Hypertension	AST Increase	Hypophosphatemia	Proteinuria	Hypothyroidism	Lipase Increase
Sorafenib *v* placebo[24]	8% *v* <1%	8% *v* 2%			11% *v* 2%			
Sorafenib *v* placebo[11]	10.7% *v* 0	6.0% *v* 0						
Lenvatinib *v* sorafenib[23]	≥grade 3: 3% *v* 11%		≥grade 3: 23% *v* 14%			≥grade 3: 6% *v* 2%		
Durvalumab *v* sorafenib [31]	0% *v* 9.1%		1.0% *v* 6.1%	6.7% *v* 3.2%				4.1% *v* 2.9%

Abbreviation: HFSR, hand-foot skin reaction.

orally administered antiantiangiogenic TKI apatinib (also called rivoceranib), donafenib, which is a minimally modified form of sorafenib and inhibitor of multiple kinases including vascular endothelial growth factor receptor (VEGFR), and the addition of TACE to lenvatinib as an intervention to potentially improve control of intrahepatic disease. These treatment options are approved by the Chinese Medicines Agency, however, they are not widely available or approved outside of China, and the study patient populations have a specific disease profile, etiology, and patient characteristics. The etiology of HCC differs between Asian countries and Western populations, Japan, and Indonesia; in China, the main risk factor is HBV, while in Western countries the main risk factor is HCV and steatotic liver disease. Other risk factors in China include water pollution, aflatoxins in food, and excessive alcohol consumption. Patients diagnosed in China tend to be younger, and have a heavier tumor burden and more advanced disease than their Western counterparts, which can result in poorer prognosis and a shorter duration of OS following targeted therapy.[33,34] Therefore, recommendations for these agents and procedures are not included within the Bottom Line Box, while recognizing that they may have a valuable treatment effect in patients who share clinical features with the HCC populations enrolled in these studies.

Clinical Question 2

What are the preferred treatment options for second- and later-line systemic therapy for patients with advanced hepatocellular carcinoma?

Recommendation 2.1

Following first-line treatment with atezo + bev, second-line therapy with a tyrosine kinase inhibitor (TKI; ie, sorafenib, lenvatinib, or cabozantinib), or ramucirumab (AFP ≥400 ng/mL) are recommended (Evidence quality: Low; Strength of recommendation: Weak).

Qualifying statements.

- 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.[16-18]
- 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.

Recommendation 2.2

Following first-line treatment with durva + treme, second-line therapy with a TKI is recommended (Evidence quality: Low; Strength of recommendation: Weak).

Qualifying statement.

- 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 versus second-line therapy with a TKI.

Literature review and analysis. Evidence for sorafenib, lenvatinib, and combination therapy with durva + treme has been reviewed in earlier sections of this guideline. The evidence base for regorafenib or cabozantinib was included in the previous version of this guideline and is reproduced in subsequent paragraphs. The rationale for using nivo + ipi is outlined in the *Clinical Interpretation*.

Regorafenib versus placebo (RESORCE). The study by Bruix et al[22] compared regorafenib versus placebo in 573 patients who had previously tolerated treatment and experienced radiologically documented progression with sorafenib. The patient population was from Asia (38%, ie, China, Japan, South Korea, Singapore, and Taiwan) or elsewhere (62%). The cause of liver disease was HBV (38%), HCV (21%), alcohol (25%), or nonalcoholic steatohepatitis (7%). Twenty-eight percent of patients had macrovascular invasion and 72% had extrahepatic spread (70% in the regorafenib group *v* 76% in the placebo group). The pattern of progression after sorafenib for both treatment and control groups was new extrahepatic lesion (41%), new intrahepatic lesion (45%), or both (81%).

OS was significantly better with regorafenib compared to placebo (median survival 10.6 months for regorafenib versus 7.6 months for placebo, HR, 0.63 [95% CI, 0.50 to 0.79]; Data Supplement, Table S13). Long survival time from start of treatment with first-line sorafenib was noted (regorafenib, 26.0 months [22.6 to 28.1] *v* placebo, 19.2 months [16.3 to 22.8]), indicating that this was a population with relatively stable disease and good tolerance to sorafenib.[41] Other outcomes, including PFS, disease control rate, and ORR also significantly favored regorafenib. AEs that were significantly more likely to occur with regorafenib were hypertension (15% *v* 5%), HFSR (13% *v* 1%), and fatigue (9% *v* 5%; Table 7). Seven deaths were considered by investigators to be due to treatment with regorafenib.[42]

Cabozantinib versus placebo (CELESTIAL). The study by Abou-Alfa et al[21] compared cabozantinib to placebo in 707 patients who had previously received treatment with one regimen of sorafenib (71%-73%) or up to two previous systemic treatment regimens (26%-28%) and were not considered amenable to curative treatment. The patient population was from Europe (48%), Asia (25%, ie, Hong Kong, South Korea, Singapore, and Taiwan), Canada and the United States (24%), and Australia and New Zealand (4%). Cases were attributed to HBV (38%), HCV (24%), alcohol (24% in the cabozantinib group, 16% in the placebo group), nonalcoholic steatohepatitis (10%), or unknown or other causes (21%). Eighty-five percent of patients had macrovascular invasion and/or extrahepatic spread.

OS was significantly better with cabozantinib compared to placebo (median survival 10.2 months for cabozantinib *v* 8.0 months for placebo; HR, 0.76 [95% CI, 0.63 to 0.92]). Other outcomes, including PFS, disease control rate, and ORR also significantly favored cabozantinib. There were

18 partial responses out of 471 patients in the treatment group and one partial response among patients in the control group; no complete responses were observed across study groups (Data Supplement, Table S14). Grade 3 or 4 AEs were significantly more common with cabozantinib versus placebo (68% *v* 37%, RR, 1.86 [95% CI, 1.56 to 2.23]), and patients in the former group were more likely to discontinue therapy due to AEs related to the trial regimen (16% *v* 3%). Patients treated with cabozantinib were more likely to experience grade 3 or 4 hypertension (16% *v* 2%), increased AST (12% *v* 7%), HFSR (17.0% *v* 0), fatigue (10% *v* 4%), and diarrhea (10% *v* 2%; Table 7).

Clinical interpretation. The Expert Panel agrees that due to their differing mechanisms of action, second-line treatment with a TKI may offer clinical benefit following treatment with atezo + bev.

In 2020, the combination of nivo + ipi as second-line therapy was given accelerated approval by the US Food and Drug Administration (FDA),[43] based on a 33% response rate in a subgroup of patients who were previously treated with sorafenib in the CheckMate 040 phase I/II study.[44] This approval was conditional on the results of other confirmatory trials.[43,45] Since that time, case series have demonstrated response with nivolumab + ipilimumab following atezo + bev.[16-18] On this basis, nivo + ipi is included in the list of options in the qualifying statements of Recommendation 2.1, although we await the results of CheckMate 9DW, a phase III RCT of the combination therapy compared to sorafenib or lenvatinib in the first-line setting (ClinicalTrials.gov identifier: NCT04039607). The inclusion of ramucirumab as a treatment option is supported by recent real-world data demonstrating that this agent works similarly following atezo + bev as it does in other settings.[46]

Recommendation 2.3

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* (Evidence quality: Low to Moderate; Strength of recommendation: Weak).

Qualifying statement.

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

Literature review and analysis. Evidence for sorafenib, lenvatinib, cabozantinib, regorafenib, and nivo + ipi has been reviewed in earlier sections of this guideline. Patient characteristics and outcomes for included studies of ramucirumab[26] and suggested options pembrolizumab and nivolumab were outlined in the previous version of this guideline and are reproduced in subsequent paragraphs. Patient characteristics for these studies can be found in the Data Supplement.

Ramucirumab versus placebo (REACH 2). The study by Zhu et al[26] of ramucirumab versus placebo included 292 patients from the Americas, Europe, Australia, and Israel (52%); Asia (excluding Japan; 28%); and Japan (20%). Eligibility criteria included an AFP level of ≥400 ng/mL. There were 197 patients assigned to treatment with ramucirumab and 95 patients received a placebo. Approximately 63% of cases were attributed to HBV or HCV and 37% to other causes. Thirty-five percent of patients had macrovascular invasion and 72% had extrahepatic spread. All patients were previously treated with sorafenib only, and a subset of patients had also undergone surgery (41%) or radiotherapy (19%). Sorafenib was discontinued due to progressive disease in 83% of patients and toxicity in 17% of patients (Data Supplement, Table S4).

The REACH study,[47] published in 2015, found no difference in OS between patients with advanced HCC who were randomly assigned to either ramucirumab or placebo (HR, 0.87 [95% CI, 0.72 to 1.05]), but found a significant benefit of ramucirumab for subgroups of patients with extrahepatic metastases (HR, 0.79 [95% CI, 0.63 to 0.98]) and AFP level of ≥400 ng/mL (HR, 0.67 [95% CI, 0.51 to 0.90]). The REACH-2 study was conducted as a follow-up trial to explore the efficacy of ramucirumab in the group of patients with elevated AFP. Within this specific patient population, Zhu et al found a

TABLE 7. Grade 3-4 Adverse Events Experienced by ≥5% of Patients in Either Arm of Phase III Trials of Second- or Greater-Line Therapy for Advanced Hepatocellular Carcinoma (for additional data, see the Data Supplement, Table S22)

Comparison	HFSR	Diarrhea	Hypertension	Increased Blood Bilirubin	AST Increase	Fatigue	Hyponatremia	Ascites	Anemia	Decreased Appetite	Asthenia	Liver Injury or Failure
Regorafenib *v* placebo[22]	13% *v* 1%		15% *v* 5%	10% *v* 11%	11% *v* 11%	9% *v* 5%		4% *v* 6%	5% *v* 6%			
Cabozantinib *v* placebo[21]	17% *v* 0%	10% *v* 2%	16% *v* 2%		12% *v* 7%	10% *v* 4%				6% *v* <1%	7% *v* 2%	
Ramucirumab *v* placebo (AFP ≥400 ng/mL); combined data from REACH and REACH-2 trials[26]			13% *v* 4%		3% *v* 5%		5% *v* 2%					16% *v* 16%

Abbreviations: AFP, alpha-fetoprotein; HFSR, hand-foot skin reaction.

significant improvement in OS (HR, 0.710 [95% CI, 0.531 to 0.949]) and PFS (HR, 0.45 [95% CI, 0.34 to 0.60]; Data Supplement, Table S15). ORR did not differ significantly between groups, with nine responses experienced in the experimental group and one response experienced in the control group. In a pooling of data from REACH and REACH-2, AEs affecting at least 5% of patients in the ramucirumab or placebo groups, respectively, included hypertension (13% *v* 4%) and hyponatremia (5% *v* 2%; Data Supplement, Table S22).

Pembrolizumab versus placebo (KEYNOTE-240). The study by Finn et al[25] of pembrolizumab versus placebo included 413 patients in Japan (14%), elsewhere in East Asia (24%), Europe (34%), and the United States (9%). Patients had experienced progressive disease (87%) or intolerable toxicity (13%) with sorafenib. Sixteen percent of all cases were HCV-positive and 26% and 22% were HBV-positive in the pembrolizumab and placebo groups, respectively. Patients with main portal vein or inferior vena cava or cardiac involvement were excluded from the study. Median duration of follow-up was 13.8 months (range 0.9-30.4 months) for pembrolizumab and 10.6 months (range 0.9-29.5 months) for placebo. Some patients received additional treatment after progression, although the percent who received treatment was not reported.

The HR for OS (0.781 [95% CI, 0.611 to 0.998], $P = .0238$) did not reach statistical significance as per the prespecified statistical plan, which accounted for hypothesis testing at multiple time points as well as coprimary endpoints (OS and PFS). To reach statistical significance, *P* values of .0174 for OS at final analysis and .002 for PFS at primary analyses were required. Likewise, the PFS difference (HR, .72 [95% CI, 0.57 to 0.90]) did not reach statistical significance as per the prespecified plan. ORRs were significantly higher in the pembrolizumab group (RR, 4.13 [95% CI, 1.82 to 9.38]), and in this group, there were six complete (2.2%) and 45 partial (16.2%) responses, while there were no complete and six partial (4.4%) responses in the placebo group. There was no difference in rate of stable disease between groups, but progressive disease was less likely with pembrolizumab (RR, 0.77 [95% CI, 0.59 to 0.99]; Data Supplement, Table S16).

The most common grade 3 or four AEs in the pembrolizumab or placebo groups were AST increase (13.3% *v* 7.5%), serum bilirubin increase (7.5% *v* 5.2%), ALT increase (6.1% *v* 3.0%), and anemia (3.9% *v* 9.0%). Treatment discontinuation due to grade 3 or 4 AEs was significantly more likely in the pembrolizumab group (17.2% *v* 9.0%, RR, 2.74 [95% CI, 1.26 to 5.96]; Data Supplement, Table S22).

Studies of later-line therapy primarily or exclusively conducted in China.

Pembrolizumab versus placebo (KEYNOTE-394). New for this guideline update is KEYNOTE-394,[35] a 453-patient, phase III RCT of pembrolizumab + best supportive care (BSC) versus placebo + BSC. The majority of the patients in this study were treated in China (85%), and had progressed on or discontinued treatment with sorafenib or oxaliplatin-based chemotherapy. The primary outcome OS, and PFS were significantly improved with pembrolizumab compared to placebo, with HRs of 0.79 (95% CI: 0.63 to 0.99) and 0.74 (95% CI, 0.60 to 0.92), respectively (Data Supplement, Table S17). Median PFS at the time of final analysis was 2.7 months in the intervention group and 1.7 months in the control group; however, at 12 months, 15.9% of patients in the intervention group were alive without progression versus 1.4% in the control group, while at 18 months, the rates were 11.8% versus 0%, respectively. Grade 3 treatment-related AEs were more common in the pembrolizumab group (12.1% *v* 5.9%). Qin et al noted that their patient population was younger, had a higher rate of BCLC stage C disease, higher rate of AFP ≥200, more HBV positivity, and administration of PD-1 or PD-L1 inhibitors following study treatment compared to KEYNOTE-240 (Data Supplement, Table S16).

Apatinib versus placebo (AHELP). Another new study[36] for this guideline update is AHELP, a 393-patient, phase III RCT of apatinib versus placebo in patients in China who were intolerant or refractory to systemic chemotherapy or targeted therapy. Of patients in this study, 85% had HBV, 90% BCLC C, and 75% ECOG PS of 1. The primary outcome OS, and PFS were significantly improved with apatinib compared to placebo, with HRs of 0.785 (95% CI, 0.617 to 0.998) and 0.47 (95% CI, 0.37 to 0.60), respectively. Grade 3-4 treatment-related AEs were more common in the apatinib group (RR, 4.03 [95% CI, 2.81 to 5.76]; Data Supplement, Table S18).

Clinical interpretation. To date, second-line therapy options have only been evaluated prospectively following therapy with sorafenib. It is the opinion of the Expert Panel that data for treatment options following sorafenib may be cautiously extrapolated to the population that has received first-line therapy with lenvatinib, as both agents are TKIs. Following toxicity with or progression on sorafenib, OS was improved compared to placebo with ramucirumab in patients with higher AFP levels, regorafenib, and cabozantinib. Some considerations regarding treatment selection are outlined in the following bullets:

- Regorafenib is US FDA-approved as second-line therapy for patients who have progressed on sorafenib, based on data from the phase III placebo-controlled RESORCE trial that excluded patients who were intolerant to sorafenib. Sorafenib and regorafenib have almost identical molecular structures, and regorafenib may have a similar but stronger toxicity profile.[48] Therefore, the appropriate population for regorafenib would be patients with Child-Pugh A liver function who tolerated at least 400 mg of sorafenib for 20 days or longer during the 28-day period prior to disease progression.[48]
- Cabozantinib was evaluated in patients who were not amenable to curative treatment, and would be an option for patients who were intolerant or refractory to sorafenib or other previous lines of systemic therapy.

- A survival benefit was found in the second-line setting with the antiangiogenic agent ramucirumab in patients refractory and/or intolerant to sorafenib with AFP ≥400 ng/mL.[26]

Another newer positive trial conducted in China of apatinib versus placebo was also included in this update. As mentioned previously, while these studies provide data on emerging therapies, their results are not considered widely applicable until further studies in patient populations outside of China have been undertaken.

Extrapolating from the IMbrave150 study in the first-line setting, it is the opinion of the Expert Panel that atezo + bev may be considered as second-line therapy in select patients who have progressed on or are intolerant of first-line sorafenib or lenvatinib and do not have contraindications to this combination.[49]

In addition, a phase III RCT of ICI pembrolizumab as second-line therapy following sorafenib was included in the systematic review. The response rate of 18% in the pembrolizumab group was similar to that observed in previous smaller studies, however, there was no difference in PFS or OS compared to placebo.[25] One newer study of pembrolizumab versus placebo in a Chinese patient population detected a difference in OS and PFS between the treatment and control groups, despite a lower response rate.[35] A recommendation for consideration of nivolumab as a second-line option is the consensus opinion of the Expert Panel, based on a response rate that was similar to pembrolizumab in a single-arm study[50]; however, this should be interpreted with caution as no randomized trial data are available for this agent in the second-line setting. Furthermore, the indication for nivolumab was voluntarily withdrawn following the negative results of the CheckMate-459 trial of sorafenib versus nivolumab in the first-line setting,[51] however, the Expert Panel considered that because nivolumab is still in clinical use, it could remain as a reasonable option within the relevant qualifying statement for later-line treatment. The Expert Panel agrees that anti-PD1 or anti-PD-L1 ICIs in the second-line setting may be especially beneficial for patients who have contraindications to or cannot tolerate TKIs and have not previously received treatment with an ICI. Further discussion of the role of ICIs in the context of second-line therapy is included in the *Discussion*.

The decision to pursue second-line therapy and choice of treatment should be based on patient and clinician preferences and other factors including comorbidities, liver function, performance status, and potential for benefit and risk of harm associated with the treatment options.

Recommendation 3.1

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 (Evidence quality: Low; Strength of recommendation: Weak).

Literature review and clinical interpretation. In the CELESTIAL trial of cabozantinib, 192 patients (27%) were treated with third-line systemic therapy. Within this subgroup of patients, the median survival was 8.6 months for both the placebo and cabozantinib groups (HR, 0.90 [95% CI, 0.63 to 1.29]), although PFS was significantly improved by cabozantinib (HR, 0.58 [95% CI, 0.41 to 0.83]), suggesting cabozantinib is an appropriate option to consider in the third-line setting.[21] Cabozantinib is approved as a second-line and third-line therapy option for patients with advanced HCC.[52] The sequence of therapy used in this trial is unlikely to be offered, given the more recent publication of data that have impacted recommendations for therapy in the first-line setting. No formal recommendation for third-line therapy was made for the previous version of this guideline. Given the expanded range of treatment options since that publication, for this update, the Expert Panel included a recommendation for third-line therapy within the Recommendations section for patients with Child-Pugh A with good performance status, and using a shared decision-making, multidisciplinary approach. At the same time, the Expert Panel recognizes that this recommendation will not be widely applicable because only a small percentage of patients will present with Child-Pugh A with good performance status who have remaining unutilized treatment options with a unique mechanism of action.

Recommendation 4.1

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 (Evidence quality: Very Low; Strength of recommendation: Weak).

Literature review and clinical interpretation. There is little evidence to support recommendations for therapy options in patients with advanced HCC and Child-Pugh B status, as most of the data for the advanced HCC population is from studies conducted in patients with Child-Pugh class A cirrhosis. Limited evidence for immunotherapy with nivolumab in the CheckMate 040 phase I/II trial demonstrated a median OS of 7.6 months for Child-Pugh B patients, and the safety profile was comparable to patients with Child-Pugh A cirrhosis.[53] On this basis, the Expert Panel recommends PD-1 or PD-L1 inhibitors, as well as sorafenib or lenvatinib; however, a cautious approach is recommended, as the potential for benefit should be weighed against the risk of toxicity with these therapy options.

DISCUSSION

Following the FDA approval of sorafenib for advanced liver disease in December 2007, almost a decade passed before additional therapy options became available. Despite recent advances, there are still significant areas of uncertainty and unmet need, including appropriate sequencing of therapy and lack of adequately powered studies to identify subgroups that may benefit more than others from currently available treatment options. There also continues to be a large unmet need for data to support treatment benefit in Child-Pugh class B patients.

The majority of patients included in RCTs of systemic therapy were relatively healthy, with preserved liver function, defined as Child-Pugh class A, and with an ECOG PS of 0-1. A review of observational studies on the effectiveness of sorafenib in Child-Pugh class B reported a range of recommendations across studies, from limiting the indication to Child-Pugh class A, cautiously expanding the indication to a subset of Child-Pugh class B, or avoiding a recommendation in the absence of data.[54] The review authors' analysis of a sorafenib-treated non-SHARP-eligible patient population found OS to be similar to BSC (ie, approximately 5 months[55]), although the safety profile of sorafenib does not differ by Child-Pugh class. A large multicenter prospective registry-based single-arm study found that there was a higher rate of sorafenib treatment discontinuation in the Child-Pugh B and C groups, compared to the Child-Pugh A group.[56]

The use of immunotherapy in Child-Pugh B liver disease is also supported by real-world data and limited prospective data. The CheckMate 040 phase I/II trial prospectively treated 49 patients with Child-Pugh B7-B8 HCC with nivolumab. Objective response was achieved in 12% of patients, and the safety and tolerability were similar to that observed in studies of anti-PD-1 therapy in Child-Pugh A cirrhosis.[44] In a retrospective case series of 18 Child-Pugh class B patients treated with nivolumab, rates of AEs were also similar to those seen in a previous study of Child-Pugh A patients, and two partial responses and one complete response were recorded.[57] The use of bevacizumab and atezolizumab in patients with Child-Pugh B cirrhosis is not currently recommended by some published guidelines due to particular concerns about bleeding with bevacizumab in this population. Recent retrospective analyses of bevacizumab plus atezolizumab in Child-Pugh B cirrhosis have reported similar or higher rates of AEs than the Child-Pugh A population.[58-60] As expected, OS in these retrospective studies has been lower than previously reported in the Child-Pugh A population. In addition, a study of lenvatinib in Child-Pugh A and B patients showed that the frequency of treatment-related AEs was higher in Child-Pugh B patients, OR was better in patients with good liver function, and OS was also associated with liver function. The authors of that study conclude that further research is needed to understand which Child-Pugh B7 patients should be eligible for lenvatinib.[61] A similar conclusion regarding the need for more data was reached in a systematic review of ICIs in Child-Pugh B patients; this study found that although safety and responses were observed, there was a reduced survival benefit compared to patients with less advanced liver disease.[62]

The Expert Panel agrees on a cautious approach to systematic 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. Furthermore, the Expert Panel recommends that wherever possible, treatment decisions for patients with advanced HCC be made by a multidisciplinary team, including hepatologists, surgeons, radiologists (including interventional radiologists), pathologists, and oncologists. Given the modest expectations for clinical benefit from systemic therapy in this population, the Expert Panel emphasizes shared decision-making with patients. The systemic therapy options outlined within this guideline are not recommended for patients with Child-Pugh class C HCC.

Treatment with monoclonal antibodies pembrolizumab and nivolumab has resulted in response rates of 15%-20%.[25,63] As mentioned previously, in a phase III study of pembrolizumab as second-line therapy following sorafenib, the response rate was 18% (16% partial and 2% complete response) in the pembrolizumab group, which is similar to that observed in previous smaller studies. However, there was no difference in PFS or OS compared to placebo, therefore the study did not reach its primary and secondary endpoints.[25] The previous version of this guideline included abstract results from CheckMate 459, a phase III study of nivolumab as first-line therapy, which found a 10% response rate for patients treated with nivolumab and no difference in OS compared to sorafenib. Therefore, the study did not meet its primary endpoint.[64] Nivolumab was FDA-approved in September 2017 as a second-line therapy option, based on a single-arm study that demonstrated an overall response rate of 14.3%, according to blinded independent central review (RECIST 1.1).[50,65] This guideline update includes the full publication from CheckMate 459. It is the Expert Panel's opinion that ICIs have a role in the treatment of patients with advanced hepatocellular carcinoma and may be especially beneficial for patients who have contraindications to or cannot tolerate TKIs. On the other hand, patients and clinicians should be aware that life-threatening toxicities can occur with ICIs. Future research on these options may provide additional information on specific patient subpopulations for which they could potentially be beneficial.

In addition, Expert Panel members highlighted special considerations for patients who develop liver cancer recurrence after liver transplantation. There are limited data to suggest that TKIs (sorafenib, lenvatinib, and regorafenib) have a survival benefit ranging from 7.5 to 20 months when compared to BSC.[66] Several case series have suggested that ICIs may be used successfully in this population, although graft rejection has been reported and

these agents must be used with caution.[67-69] While the post-transplant population clearly requires further study, one very important development is the revision of United Network for Organ Sharing (UNOS) bylaws to allow immunotherapies in the pretransplant setting as a means to downstage HCC or bridge patients to transplantation. Based on several studies that have shown positive outcomes post-transplant after immunotherapy,[70-72] the bylaws have been revised to state the use of these therapies does not preclude consideration for an HCC exception.[73] These changes in organ allocation policy underscore the importance of multidisciplinary care along the continuum of HCC management, as liver transplantation is the best option for durable cure in patients who are transplant-eligible at diagnosis or who become eligible through downstaging.

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 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. A recent systematic review summarizes the current status of biomarkers in advanced HCC; however, none are sufficiently established to warrant incorporation in guideline recommendations at this time.[74] This is an important future direction that we hope to update for the next iteration of this guideline. Another gap is the topic of sequencing of therapy in later lines; we await future studies on this topic, while acknowledging that they are likely to be retrospective.

New for this guideline update is the LAUNCH trial of TACE + lenvatinib versus lenvatinib alone. LAUNCH was conducted in a relatively advanced-disease patient population, and its results were not widely generalizable; however, we do anticipate expanded use of locoregional + systemic therapy in the future. Other studies that have incorporated locoregional therapies include TACTICS (TACE + sorafenib *v* TACE alone)[75] and RTOG 1112 (stereotactic body radiation therapy + sorafenib *v* sorafenib),[76] although the latter of these was closed early due to a change in the HCC standard of care. Finally, in future directions, several trials that met the inclusion criteria for this review were conducted in predominantly Chinese patient populations, and therefore were not considered widely generalizable for incorporation in the Bottom Line recommendations. For the next iteration of this guideline, we look forward to the replication of the efficacy of these agents in a broader patient population.

PATIENT AND CLINICIAN COMMUNICATION

Poor adherence to oral chemotherapy is an ongoing concern with profound clinical implications and reduced therapeutic efficacy,[77-79] which is especially relevant for HCC patients at risk for encephalopathy, esophageal varices, and/or ascites. Interventions to optimize patient adherence should be considered, for example, involvement of pharmacists in managing oral chemotherapy, which has been shown to increase knowledge levels in a pilot study[80] and has resulted in improved adherence and response outcomes.[81]

For recommendations and strategies to optimize patient-clinician communication, readers are referred to Patient-Clinician Communication: ASCO Consensus Guideline.[82]

HEALTH DISPARITIES

Although ASCO clinical practice 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. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial and/or ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, present at a more advanced stage, and are at greater risk of receiving care of poor quality compared to other Americans.[83-86] Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities.

Up to 5.3 million people—two percent of the US 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. In 2013, to address HCV infection, and again in 2015 to address HBV infection, enhanced testing was initiated in the United States.[87] These initiatives were intended to make screening a standard of care for appropriate patient populations, as well as to further other goals, such as earlier detection and reducing stigma that may discourage testing.

In the United States, overall incidence of HCC is 9.4 per 100,000 persons per year, but incidence of HCC varies by race and ethnicity. According to an analysis of the Surveillance, Epidemiology, and End Results (SEER) database, incidence rates for the time period 2003-2011 were Asian: 18.6 per 100,000; Black: 15.7 per 100,000; Hispanic: 11.8 per 100,000; and non-Hispanic Whites: seven per 100,000. The incidence rate in the Asian population fell by 5.5% during this time, while incidence of both localized and advanced HCC increased over this time period for other ethnic groups.[88] The study authors also found a trend toward detection at an earlier stage for Asian populations, possibly due to successful screening and surveillance. Better OS for Asian individuals has also been observed, which is likely related to this group's relatively higher proportion of patients with HCC due to HBV infection, and lower rate of underlying liver cirrhosis.[89] Across all

ethnicities, there is a higher incidence among males than females.

For patients with HCC, studies have shown disparities in access to care, including liver transplantation, by race and/or ethnicity.[88,90-92] HCC was also detected at a more advanced stage in an African American study population, compared to other racial and ethnic groups.[93] Detection at an earlier stage could help to reduce ethnic and racial disparities in outcomes.[94] Differences in outcomes are also evident and persist even when receipt of treatment is the same and a significant negative impact of low income has been found on OS.[91] Furthermore, geographic location in southern US states, which have a higher proportion of Black populations and prevalence of known risk factors, has been associated with higher mortality risk in HCC.[95] At the same time, fewer than 10% of patients who take part in clinical trials are from racial and/or ethnic minority groups.[96] Underuse of curative treatment options can be due to patient factors such as comorbidities, poor liver function, other patient characteristics, and provider-related factors including lack of expertise or knowledge, and technical factors such as tumor location or limited organ availability.

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.

COST IMPLICATIONS

While conducting the systematic review for clinical interventions, an informal scan for recent independently conducted cost utility or economic analyses that might inform the relative value of available treatment options was also conducted. As part of the previous iteration of this guideline, [15] 12 studies of cost-effectiveness of systematic therapy options for advanced HCC were identified (Data Supplement).[97-108] Results of the base-case analyses from these studies generally found that in most scenarios, newer targeted therapy and immunotherapy options have cost estimates that would be above the willingness-to-pay threshold without subsidies.[97-110] The scan for cost utility analyses was not updated for this version of the guideline.

In addition, the discussion of cost has implications for the disparities in care that are discussed in the *Health Disparities* section; higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[111,112] There remains an urgent need for simplified standardized methodologies to assess treatment costs and survival value,[113] and periodic recurrent team-based patient engagement around financial toxicities related to cancer treatment [114,115] and independent impact on quality of life. Across all disease sites, ASCO recommends that patients be made aware that different products may be preferred or covered by their particular insurance plan and that even with the same insurance plan, the price may vary between different pharmacies. Patients should also be made aware of any financial counseling services—including the many Patient Assistance Programs offered by drug manufacturers—available to address this complex set of issues.[116] Studies that examine impact of early involvement of palliative care and hepatology to minimize inpatient hospitalizations that drive 64% of the cost of care are also warranted.[6]

OPEN COMMENT

The draft recommendations were released to the public for open comment from September 1 through September 15, 2023. Response categories of "Agree as written," "Agree with suggested modifications" and "Disagree. See comments" were captured for every proposed recommendation with written comments received. Depending on the recommendation, a range of 86%-100% of the 24 respondents either agreed or agreed with slight modifications to the recommendations. A range of 0%-14% of respondents disagreed with the recommendations. The rationale for these disagreements was reviewed and modifications were made, including the additional qualifying statements to some of the recommendations for which there was lower-quality evidence. All changes were incorporated prior to ASCO Evidence Based Medicine Committee review and approval.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes one or more member from ASCO's Practice Guideline Implementation Network (PGIN) on the panel. The additional role of this PGIN representative on the guideline panel is to assess the suitability of the recommendations to implementation in the community setting, but also to identify other barriers to implementation. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers, and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO PGIN. ASCO guidelines are posted on the ASCO website and most often published in the *JCO*.

This guideline included three panel members who are members of PGIN. Their comments were combined with implementation considerations from the previous guideline iteration. In general, PGIN members indicated that the guideline recommendations will be helpful for community oncologists. Some considerations regarding implementation included the potential difficulty of independent medical oncology practitioners to easily access the expertise of GI or radiation oncology specialists when necessary, as well as the uncertainty of the evidence for certain subgroups of patients, such as Child-Pugh class B or patients with portal hypertension. All PGIN members indicated that the considerations outlined in the *Cost Implications* section are a factor in implementation of the guideline recommendations so that patients can receive appropriate and timely care. One PGIN member reported that the insurance approval for some of the options after first-line therapy is uncertain. Another noted that issues with approval of drugs that could result in delays in treatment, as well as a concern about the inability of some patients to afford copayments. It was noted that it is not uncommon for patients who are unable to pay for medications but who do qualify for financial assistance from a drug company to experience a delay in assistance that results in cancer progression and patient comorbidities worsening to an extent that the cancer treatment becomes intolerable.

ADDITIONAL RESOURCES

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/gastrointestinal-cancer-guidelines. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

RELATED ASCO GUIDELINES

- Integration of Palliative Care into Standard Oncology Care[117] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[82] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)

GENDER-INCLUSIVE LANGUAGE

ASCO is committed to promoting the health and well-being of individuals regardless of sexual orientation or gender identity.[118] Transgender and nonbinary people, in particular, may face multiple barriers to oncology care including stigmatization, invisibility, and exclusiveness. One way exclusiveness or lack of accessibility may be communicated is through gendered language that makes presumptive links between gender and anatomy.[119-122] With the acknowledgment that ASCO guidelines may impact the language used in clinical and research settings, ASCO is committed to creating gender-inclusive guidelines. For this reason, guideline authors use gender-inclusive language whenever possible throughout the guidelines. In instances in which the guideline draws upon data based on gendered research (eg, studies regarding women with ovarian cancer), the guideline authors describe the characteristics and results of the research as reported.

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EDITOR'S NOTE

This ASCO Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/gastrointestinal-cancer-guidelines.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Systemic Therapy for Advanced Hepatocellular Carcinoma: ASCO Guideline Update

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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APPENDIX

TABLE A1. Recommendation Rating Definitions[20]

Term	Definitions[20]
Quality of evidence	
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Strength of recommendation	
Strong	In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects All or almost all informed people would make the recommended choice for or against an intervention
Weak	In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists Most informed people would choose the recommended course of action, but a substantial number would not

TABLE A2. Systemic Therapy for Advanced Hepatocellular Carcinoma Expert Panel Membership

Name	Affiliation	Role or Area of Expertise
John D. Gordan, MD, PhD (co-chair)	University of California, San Francisco, San Francisco, CA	Medical Oncology
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