ASCO special articles

Systemic Therapy for Advanced Hepatocellular Carcinoma: ASCO Guideline

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abstract

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

METHODS ASCO convened an Expert Panel to conduct a systematic review of published phase III randomized controlled trials (2007-2020) on systemic therapy for advanced HCC and provide recommended care options for this patient population.

RESULTS Nine phase III randomized controlled trials met the inclusion criteria.

RECOMMENDATIONS Atezolizumab + bevacizumab (atezo + bev) may be offered as first-line treatment of most patients with advanced HCC, Child-Pugh class A liver disease, Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0-1, and following management of esophageal varices, when present, according to institutional guidelines. Where there are contraindications to atezolizumab and/or bevacizumab, tyrosine kinase inhibitors sorafenib or lenvatinib may be offered as first-line treatment of patients with advanced HCC, Child-Pugh class A liver disease, and ECOG PS 0-1. Following first-line treatment with atezo + bev, and until better data are available, second-line therapy with a tyrosine kinase inhibitor may be recommended for appropriate candidates. Following first-line therapy with sorafenib or lenvatinib, second-line therapy options for appropriate candidates include cabozantinib, regorafenib for patients who previously tolerated sorafenib, or ramucirumab (for patients with α-fetoprotein $\geq$ 400 ng/mL), or atezo + bev where patients did not have access to this option as first-line therapy. Pembrolizumab or nivolumab are also reasonable options for appropriate patients following sorafenib or lenvatinib. Consideration of nivolumab + ipilimumab as an option for second-line therapy and third-line therapy is discussed. Further guidance on choosing between therapy options is included within the guideline. Additional information is available at www.asco.org/gastrointestinal-cancer-guidelines.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

There were approximately 670,000 new cases and 625,000 deaths worldwide due to hepatocellular carcinoma (HCC) in 2018. 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 42,810 new cases and approximately 30,160 deaths in 2020.[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, specifically aflatoxin-contaminated foods; and morbid obesity and diabetes.[3] Three-quarters of cases occur in the Asia-Pacific region, where the main risk factor outside of Japan is HBV.[1] HCC is two to three times as common in men as in women.[4] Incidence of HCC is currently on the rise in the United States,[5] related in part to a rise in the incidence of obesity and type II diabetes over the past several decades.[6] Decreases in incidence rates among Asian and Pacific Islanders and younger cohorts may contribute to an overall reduction in cases of HCC in future years.[7]

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 chemoembolization (TACE), bland embolization, and radioembolization. Historically,

THE BOTTOM LINE

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Guideline Question

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

Target Population

Patients with advanced HCC.

Target Audience

Clinicians who are involved in the care and treatment of patients with advanced HCC, 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) may be offered as first-line treatment for most patients with advanced HCC, Child-Pugh class A, ECOG PS 0-1, and following management of esophageal varices, when present, according to institutional guidelines (Type: evidence based, benefits outweigh harms; Evidence quality: moderate to high; Strength of recommendation: strong).

Qualifying statements:

- Recommendation 1.1 is based on results from the IMbrave150 phase III RCT[12] comparison of atezo + bev to sorafenib (HR for OS, 0.58; 95% CI, 0.42 to 0.79; $P = .0006$) in Child-Pugh class A patients. Caution should be exercised when applying these results to patients with more advanced liver disease who have a greater likelihood of portal hypertension because of the risk of bleeding complications associated with bevacizumab.
- Due to risk of bleeding, patients in this trial were required to have undergone esophagogastroduodenoscopy (EGD) within 6 months of trial initiation and to have received treatment of esophageal varices when necessary.[14] The Expert Panel recognizes that some patients may have been evaluated for varices outside the 6-month window, are receiving treatment (eg, adequately dosed nonselective β-blockers), and/or are deemed to be low risk for variceal bleed by a hepatology specialist. In these patients, the decision to forgo an EGD prior to initiation of therapy with atezo + bev may be carefully considered.
- Patients who had a myocardial infarction or stroke within the previous 3 months, had a history of autoimmune disease, were on therapeutic anticoagulation, or had coinfection with HBV and HCV were also excluded from the IMbrave150 RCT.

Recommendation 1.2. Where there are contraindications to atezolizumab and/or bevacizumab, tyrosine kinase inhibitors (TKIs) sorafenib or lenvatinib may be offered as first-line treatment of patients with advanced HCC, Child-Pugh class A, and ECOG PS 0-1 (Type of recommendation: evidence based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

Qualifying statements:

- Treatment with recommended TKIs may be less effective for patients with more advanced liver cirrhosis. Careful patient selection is recommended.
- The choice of treatment with lenvatinib or sorafenib should be made through a discussion involving the physician and patient (and caregiver, where applicable) and should include factors such as medical history, viral etiology of liver disease, toxicities associated with treatment, cost, goals of treatment, patient preference, and expected treatment benefit. Factors affecting this choice, including response rates, are discussed further in the Clinical Interpretation.
- Several meta-analyses of RCTs have shown sorafenib to be more beneficial in patients with HCV, especially as compared with patients with HBV.[15-17] In the REFLECT trial, there was a trend toward improvements across endpoints for lenvatinib over sorafenib in the HBV subgroup, though it was not significant.[18]
- Patients with a high tumor burden, > 50% liver involvement, or those with main portal vein invasion were excluded from the REFLECT trial of sorafenib versus lenvatinib.[19]

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THE BOTTOM LINE (CONTINUED)

Second-Line Therapy

Recommendation 2.1. Following first-line treatment with atezo + bev, second-line therapy with a TKI (ie, sorafenib, lenvatinib, cabozantinib, or regorafenib) may be recommended (Type: informal consensus, benefits may outweigh harms; Evidence quality: low; Strength of recommendation: weak).
Qualifying statement:

- No data have been published on therapy options after first-line treatment with atezo + bev. It is the opinion of the Expert Panel that a TKI, preferably sorafenib or lenvatinib, may be offered. Cabozantinib or regorafenib are also reasonable options for second-line therapy following atezo + bev.

Recommendation 2.2. Following first-line therapy with sorafenib or lenvatinib, second-line therapy with another TKI (cabozantinib or regorafenib), ramucirumab (AFP ≥ 400 ng/mL), or atezo + bev may be recommended for appropriate candidates. Considerations regarding choice of therapy are included in the Clinical Interpretation (Type: informal consensus, benefits may outweigh harms; Evidence quality: low to moderate; Strength of recommendation: weak).
Qualifying statement:

- It is likely that most patients being considered for atezo + bev in the second-line setting did not have access to this combination when they started first-line treatment.

Recommendation 2.3. Following first-line therapy with sorafenib or lenvatinib, pembrolizumab or nivolumab are reasonable options that may be considered for appropriate candidates (Type: informal consensus, benefits may outweigh harms; Evidence quality: low; Strength of recommendation: weak).
Qualifying statement:

- Immune checkpoint inhibitors pembrolizumab or nivolumab may be especially beneficial for patients who have contraindications to or cannot tolerate TKIs.

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. 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.

HCC was diagnosed at an advanced, incurable stage and had a poor prognosis due to the palliative nature of available systemic and local therapies.[8] Trials of systemic therapy for advanced HCC failed to show improved outcomes until the advent of the tyrosine kinase inhibitor (TKI) sorafenib,[9] followed by randomized controlled trials (RCTs) published in 2008 and 2009 demonstrating a survival benefit with sorafenib versus placebo.[9,10] 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. Most recently, evidence of the effectiveness of combination therapy has also been reported.[11-13] This guideline incorporates the evidence for systemic therapy options for patients with advanced HCC to provide recommendations to clinicians who are treating patients within the target population.

GUIDELINE QUESTIONS

This clinical practice guideline addresses the following clinical question: What are the preferred systemic treatment options for first-line and subsequent systemic 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 met via teleconference and/or webinar and corresponded through e-mail (Appendix Table A1, online only). 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 *Journal of Clinical Oncology* for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guidelines Committee prior to publication. All funding for the administration of the project was provided by ASCO.

A systematic search was conducted of PubMed for phase III RCTs published between January 1, 2007 and May 15, 2020. 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 (ie, 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 TKIs, including sorafenib, regorafenib, lenvatinib, and cabozantinib; immune checkpoint inhibitors (ICIs), including atezolizumab, nivolumab, pembrolizumab, and ipilimumab; and/or antiangiogenic agents, including bevacizumab and ramucirumab (in patients with α-fetoprotein [AFP] $\geq$ 400 ng/mL), including combinations of selected agents.
- Comparison: Interventions listed or placebo control.
- Outcomes: Overall survival (OS), progression-free survival (PFS), time to progression, objective response rate (ORR), rate of drug discontinuation, adverse events, 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, narrative reviews; or (3) published in a non-English language, given the confined medical language expertise of the panel members. The guideline recommendation language is crafted, in part, using the Guidelines Into Decision Support (GLIDES) methodology and accompanying BRIDGE-Wiz software.[20] 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. Certainty of the evidence (ie, evidence quality) for each outcome was assessed using the Cochrane Risk of Bias tool and elements of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) quality assessment and recommendations development process.[21] To facilitate the quality assessment ratings, MAGICApp guideline development software 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.[22] 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 guidelines. 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 American Society of Clinical Oncology, Inc. (ASCO) to assist providers in clinical decision making. The information herein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. Recommendations reflect high, moderate, or low 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 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 http://

www.asco.org/rwc). All members of the Expert Panel 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

Nine phase III RCTs met the inclusion criteria, of which eight were fully published[10,12,18,23-27] and one was presented as an abstract.[28]

First-Line Therapy, Full Text Articles

Four of the identified trials assessed systemic therapy options in the first-line setting, including two trials of sorafenib compared with placebo, one trial of lenvatinib compared with sorafenib, and one trial of atezolizumab-bevacizumab (atezo + bev) compared with sorafenib. Across these four studies, patients were predominantly male (≥ 84%). Underlying causes of liver disease included HBV, HCV, alcohol, and other or unknown. Most patients had advanced (Barcelona Clinic Liver Cancer [BCLC] stage C; range, 78%-96% across experimental and control groups) or intermediate stage HCC (BCLC stage B; range, 15%-22%). Macrovascular invasion and/or extrahepatic spread was present in 69%-79% across study groups. Virtually all patients had Child-Pugh class A liver disease (≥ 95% of patients), indicating better prognosis, and Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0-1 (good functional status). Additional descriptions for each study are included below, and additional patient characteristics, including reported AFP levels, involved disease sites, and previous treatment are included in Table 1.

Sorafenib Versus Placebo

The study by Llovet et al (SHARP)[25] included 602 patients with advanced HCC 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 (Asia-Pacific)[10] (N = 271) was subsequently performed to confirm the former study's results in an Asian population (China, South Korea, 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; Tables 2 and 3). These patients were also more likely to have extrahepatic spread and/or macrovascular invasion compared with Llovet et al[25] (79% *v* 70%, respectively), and their median age was 52 years, compared with median age of 65 years in the SHARP trial.

Both studies reported significantly better OS with sorafenib, compared with placebo, with similar hazard ratios for Llovet et al[25] and Cheng et al[10]: 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 coprimary endpoint along with OS in the trial by Llovet et al.[25] Median survival time in both experimental and control groups was lower in the Asia-Pacific trial, potentially due to patient characteristics (Table 1). Adverse events were similar across trials, with patients treated with sorafenib more likely to report hand-foot skin reaction (HFSR), diarrhea, alopecia, fatigue, rash or desquamation, hypertension, and anorexia (Table 4).

Lenvatinib Versus Sorafenib

In 2018, Kudo et al (REFLECT)[18] 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. Additional patient characteristics are included in Table 1.

There was no significant difference in OS between groups (hazard ratio [HR], 0.92; 95% CI, 0.79 to 1.06), indicating the noninferiority of lenvatinib compared with sorafenib. PFS (HR, 0.64; 95% CI, 0.55 to 0.76) and ORRs (HR, 5.01; 95% CI, 3.59 to 7.01) were significantly higher in the lenvatinib group (Table 5). Adverse events 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%), proteinuria (grade ≥ 3: 6% *v* 2%), dysphonia (any grade: 24% *v* 12%), and hypothyroidism (any grade: 16% *v* 2%). Patients in the lenvatinib group were more likely to discontinue treatment due to adverse events (relative risk [RR], 1.46; 95% CI, 1.01 to 2.1; Table 4). Median duration of treatment was 5.7 months versus 3.7 months in the lenvatinib and sorafenib groups.

Atezo + Bev Versus Sorafenib

The IMbrave150 trial randomly assigned 336 patients to treatment with atezo + bev and 165 patients to sorafenib.[12] Patients were from Asia, excluding Japan (40%), and the

TABLE 1. Phase III RCTs of First-Line Systemic Therapy for Advanced HCC

	Llovet et al (2008)[25]		Cheng et al (2009)[10]		Kudo et al (2018)[18]		Finn et al (2020)[12]	
Variable	**Sorafenib (400 mg twice daily) + BSC (n = 299)**	**Matching Placebo + BSC (n = 303)**	**Sorafenib (400 mg twice daily; n = 150)**	**Matching Placebo (n = 76)**	**Lenvatinib (12 mg/d for ≥ 60 kg patients, 8 mg/d for < 60 kg patients, orally, 28-day cycles; n = 478)**	**Sorafenib (400 mg twice daily, 28-day cycles; n = 476)**	**Atezolizumab (1,200 mg IV once every 3 weeks) + Bevacizumab (15 mg/kg IV once every 3 weeks; n = 336)**	**Sorafenib (400 mg twice daily; n = 165)**
Median age, years, ± SD, (range) or (IQR)	64.9 ± 11.2	66.3 ± 10.2	51 (23-86)	52 (25-79)	63 (20-88)	62 (22-88)	64 (IQR, 56-71)	66 (IQR, 59-71)
Sex								
Male	87	87	85	87	85	84	82	83
Female	13	13	15	13	15	16	18	17
Region								
Europe and Australasia	88	87					US, Australia, NZ, Japan: 60	59
North America	9	10						
Western					33	33		
Asia-Pacific			100% China, South Korea, Taiwan		67	67	Asia (excluding Japan): 40	41
Central and South America	3	4						
Disease etiology								
Hepatitis C	29	27	11	4	19	26	21	22
Hepatitis B	19	18	71	78	53	48	49	46
Alcohol only	26	26			8	4	30	32
Unknown	16	19			13	14		
Other	9	10			8	7		
ECOG PS								
0	54	54	25	28	64	63	62	62
1	38	39	69	67	36	37	38	38
2	8	7	5	5	0	0	0	0
BCLC stage								
A (early)							2	4
B (intermediate)	18	17			22	19	15	16
C (advanced)	82	83	95	96	78	81	82	81

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TABLE 1. Phase III RCTs of First-Line Systemic Therapy for Advanced HCC (continued)

	Llovet et al (2008)[25]		Cheng et al (2009)[10]		Kudo et al (2018)[18]		Finn et al (2020)[12]	
Variable	**Sorafenib (400 mg twice daily) + BSC (n = 299)**	**Matching Placebo + BSC (n = 303)**	**Sorafenib (400 mg twice daily; n = 150)**	**Matching Placebo (n = 76)**	**Lenvatinib (12 mg/d for ≥ 60 kg patients, 8 mg/d for < 60 kg patients, orally, 28-day cycles; n = 478)**	**Sorafenib (400 mg twice daily, 28-day cycles; n = 476)**	**Atezolizumab (1,200 mg IV once every 3 weeks) + Bevacizumab (15 mg/kg IV once every 3 weeks; n = 336)**	**Sorafenib (400 mg twice daily; n = 165)**
MVI hepatic and/or portal vein (yes)	36	41	36	34	23 (portal vein)	19 (portal vein)	38	43
EH spread (yes)	53	50	69	68	61	62	63	56
Lymph nodes	30	21	31	34				
Lungs	22	19	52	45				
MVI or EH spread or both (yes)	70	70	79		69	71	77	73
Child-Pugh class								
A	95	98	97	97	99	99	A5: 72	A5: 73
							A6: 28	A6: 27
B	5	2	3	3	1	1		
AFP, ng/mL								
Median	44.3	99.0			133.1	71.2		
Range	0-208 × 10^4	0-5 × 10^5			IQR, 8.0-3,730.6	5.2-1,081.8		
AFP > ULN (laboratory)			77	78				
≥ 400 ng/mL							38	37
Involved disease sites								
Liver					92	90		
Lung					34	30		
No. of tumor sites								
1			13	7	43	43		
2			35	36	35	38		
3			20	18	22 (≥ 3 sites)	18 (≥ 3 sites)		
≥ 4			32	40				
Concomitant hepatitis B or C antiviral therapy	2	1			34	31		
Varices								
Present at baseline							26	26
Treated at baseline							11	14

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TABLE 1. Phase III RCTs of First-Line Systemic Therapy for Advanced HCC (continued)

	Llovet et al (2008)[25]		Cheng et al (2009)[10]		Kudo et al (2018)[18]		Finn et al (2020)[12]	
Variable	**Sorafenib (400 mg twice daily) + BSC (n = 299)**	**Matching Placebo + BSC (n = 303)**	**Sorafenib (400 mg twice daily; n = 150)**	**Matching Placebo (n = 76)**	**Lenvatinib (12 mg/d for ≥ 60 kg patients, 8 mg/d for < 60 kg patients, orally, 28-day cycles; n = 478)**	**Sorafenib (400 mg twice daily, 28-day cycles; n = 476)**	**Atezolizumab (1,200 mg IV once every 3 weeks) + Bevacizumab (15 mg/kg IV once every 3 weeks; n = 336)**	**Sorafenib (400 mg twice daily; n = 165)**
Previous therapy								
Anticancer procedures					68	72	48	52
Radiotherapy	4	5			10	13		
Surgical resection	19	20						
Other locoregional therapy (TACE, PEI, radiofrequency ablation)	44	40						
Systemic anticancer therapy	3	3	0	0				

NOTE. Data are presented as % unless otherwise noted.

Abbreviations: AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer staging; BSC, best supportive care; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EH, extrahepatic; IQR, interquartile range; IV, intravenous; MVI, macrovascular invasion; NZ, New Zealand; PEI, percutaneous ethanol injection; SD, standard deviation; TACE, transarterial chemoembolization; ULN, upper limit of normal.

TABLE 2. Patients With Intermediate (17% BCLC B) or Advanced (83% BCLC C) HCC (Lovet et al)[25]

Outcome	Study Results and Measurements	Absolute Effect Estimates		Certainty of the Evidence (quality of evidence)	Plain Text Summary
		Placebo (comparator)	Sorafenib (intervention)		
Overall survival (primary outcome)	HR, 0.69 (95% CI, 0.55 to 0.87)	330 deaths per 1,000	241 deaths per 1,000	Moderate (1)	Median overall survival 10.7 *v* 7.9 months, $P < .001$
	Based on data from 602 patients in one study; follow-up, 1 year	Difference: 89 fewer per 1,000 (95% CI, 132 fewer to 36 fewer)			Sorafenib probably improves overall survival (primary outcome) compared with placebo
Time to radiologic progression (RECIST)	HR, 0.58 (95% CI, 0.46 to 0.74)	795 progressions per 1,000	601 progressions per 1,000	Low (1, 2)	Sorafenib probably improves time to radiologic progression compared with placebo
	Based on data from 602 patients in one study; follow-up, 4 months	Difference: 194 fewer per 1,000 (95% CI, 277 fewer to 105 fewer)			
Time to symptomatic progression (coprimary outcome)	HR, 1.08 (95% CI, 0.89 to 1.31)	518 progressions per 1,000	545 progressions per 1,000	Low (1, 2)	Sorafenib may have little or no effect on symptomatic time to progression compared with placebo
	Based on data from 602 patients in one study; follow-up, 4 months	Difference: 27 more per 1,000 (95% CI, 44 fewer to 98 more)			
Disease control rate	RR, 1.35 (95% CI, 1.09 to 1.66)	320 per 1,000	432 per 1,000	Moderate (1)	Sorafenib probably improves disease control rate compared with placebo
	Based on data from 602 patients in one study	Difference: 112 more per 1,000 (95% CI, 29 more to 211 more)			
Treatment-related adverse events	RR, 1.54 (95% CI, 1.36 to 1.74)	520 per 1,000	801 per 1,000	Moderate (1)	Sorafenib probably worsens treatment-related adverse events compared with placebo (Table 4)
	Based on data from 599 patients in one study	Difference: 281 more per 1,000 (95% CI, 187 more to 385 more)			

NOTE. Downgrade: (1) commercially funded (risk of publication bias); (2) inconsistent findings for symptomatic and radiologic time to progression.
Abbreviations: BCLC, Barcelona Clinic Liver Cancer staging; HR, hazard ratio; RR, relative risk.

United States, Australia, New Zealand, or 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 patients had received prior local therapy for HCC. Additional patient characteristics are included in Table 1.

Results for OS significantly favored atezo + bev compared with sorafenib, with an HR of 0.58 (95% CI, 0.42 to 0.79). Median OS was 13.2 months (95% CI, 10.4 to not evaluated) in the sorafenib group and could not be evaluated in the atezo + bev group. PFS (HR, 0.59; 95% CI, 0.47 to 0.76) and ORR (RECIST 1.1; odds ratio, 5.01; 95% CI, 3.59 to 7.01) were significantly improved in the atezo + bev group. Grade 3-4 adverse events for atezo + bev versus sorafenib included HFSR (0% *v* 8%), diarrhea (2% *v* 5%), and hypertension (15% *v* 12%), as well as increases in AST (7% *v* 5%) and serum bilirubin (2% *v* 6%). Patients in the atezo + bev group were more likely than patients in the sorafenib group to discontinue treatment due to adverse events (15.5% *v* 10.3%; Table 6). The HR for OS comparing the treatment-emergent antidrug antibody (ADA)-positive subgroup of the atezo + bev arm to sorafenib was 0.93 (95% CI, 0.57 to 1.53). The OS HR comparing the ADA-negative subgroup to sorafenib was 0.39 (95% CI, 0.26 to 0.60).[29] In addition, time to deterioration (TTD) 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).[30]

First-Line Therapy, Abstracts

Nivolumab Versus Sorafenib. The randomized phase III multicenter Checkmate 459 study included 743 patients who received first-line therapy with nivolumab (240 mg intravenously every 2 weeks) or sorafenib (400 mg orally twice per day).[28] Results reported in an abstract showed that a predefined threshold for significance of OS (HR, 0.84; $P = .0419$) was not met; with a minimum follow-up of 22.8 months, HR for OS was 0.85 (95% CI, 0.72 to 1.02; $P = .0752$). Four percent experienced a complete and 12% experienced a partial response in the nivolumab group, while in the sorafenib group, 6% experienced a partial response and 1% experienced a complete response. Grade 3 or 4 adverse events related to treatment were reported in 22% of patients receiving nivolumab and 49% of patients receiving sorafenib.

TABLE 3. Patients With Advanced (95% BCLC C) HCC (Cheng et al)[10]

Outcome	Study Results and Measurements	Absolute Effect Estimates		Certainty of the Evidence (quality of evidence)	Plain Text Summary
		Placebo (comparator)	Sorafenib (intervention)		
Overall survival	HR, 0.68 (95% CI, 0.5 to 0.93)	633 deaths per 1,000	494 deaths per 1,000	Moderate (1)	Sorafenib probably improves overall survival compared with placebo
	Based on data from 226 patients in one study; follow-up, 6 months	Difference: 139 fewer per 1,000 (95% CI, 239 fewer to 27 fewer)			
Time to radiologic progression (RECIST)	HR, 0.57 (95% CI, 0.42 to 0.79)	895 progressions per 1,000	723 progressions per 1,000	Low (1, 2)	Sorafenib probably improves time to radiologic progression compared with placebo
	Based on data from 226 patients in one study; follow-up, 6 months	Difference: 172 fewer per 1,000 (95% CI, 283 fewer to 64 fewer)			
Time to symptomatic progression	HR, 0.9 (95% CI, 0.67 to 1.22)	789 progressions per 1,000	753 progressions per 1,000	Low (1, 2)	Sorafenib may have little or no effect on symptomatic time to progression compared with placebo
	Based on data from 226 patients in one study; follow-up, 6 months	Difference: 36 fewer per 1,000 (95% CI, 142 fewer to 61 more)			
Adverse events	RR, 2.11 (95% CI, 1.58 to 2.84)	387 events per 1,000	817 events per 1,000	Moderate (1)	Sorafenib probably worsens adverse events compared with placebo (Table 4)
	Based on data from 224 patients in one study	Difference: 430 more per 1,000 (95% CI, 224 fewer to 712 more)			

NOTE. Downgrade: (1) commercially funded (risk of publication bias); (2) inconsistent findings for time to radiologic and symptomatic progression.
Abbreviations: BCLC, Barcelona Clinic Liver Cancer staging; HR, hazard ratio; RR, relative risk.

Second-Line Therapy, Full Text Articles

Four placebo-controlled multicenter randomized trials addressed systemic therapy options in the second-line setting following progression or intolerable toxicity with sorafenib, including trials of ramucirumab, regorafenib, cabozantinib, and pembrolizumab.[23,24,26,27] No studies addressing systemic therapy options after lenvatinib or atezolizumab-bevacizumab met the inclusion criteria for these guidelines. Across these four studies, the populations were predominantly male (≥ 81%). The underlying cause of liver disease was most commonly HBV across studies (range, 35%-38%); other causes included HCV, alcohol, nonalcoholic steatohepatitis, or other or unknown etiology. ECOG PS scores were 0-1. Two studies reported BCLC stage, which was predominantly stage C (advanced; range, 86%-88% across groups) or stage B (intermediate; range, 11%-14%). Macrovascular invasion or extrahepatic spread was present in 27%-34% and 70%-79% of experimental and control groups, respectively. Virtually all included patients had Child-Pugh class A liver disease. Additional patient characteristics, including dosing information and reported AFP levels, are included in Table 7.

Regorafenib Versus Placebo

The study by Bruix et al (RESORCE)[24] compared regorafenib versus placebo in 573 patients who had previously

TABLE 4. Grade 3/4 Adverse Events Experienced by ≥ 5% of Patients in Either Arm of Phase III Trials of First-Line Therapy for Advanced HCC

Comparison	HFSR	Diarrhea	Hyperbilirubinemia	Hypertension	AST Increase	Hypophosphatemia	Alopecia	Proteinuria	Dysphonia	Hypothyroidism
Sorafenib *v* placebo [25]	8 *v* < 1	8 *v* 2				11 *v* 2				
Sorafenib *v* placebo[10]	11 *v* 0	6 *v* 0								
Lenvatinib *v* sorafenib[18]	Grade 3 or 4: 3 *v* 11	Any grade: 39 *v* 46		Grade 3 or 4: 23 *v* 14			Any grade: 3 *v* 25	Grade 3 or 4: 6 *v* 2	Any grade: 24 *v* 12	Any grade: 16 *v* 2
Atezo + bev *v* sorafenib[12]	0 *v* 8	2 *v* 5	2 *v* 6	15 *v* 12	7 *v* 5					

NOTE. Data presented as %.
Abbreviations: atezo + bev, atezolizumab + bevacizumab; HFSR: hand-foot skin reaction.

TABLE 5. Patients With Intermediate (21% BCLC B) or Advanced (79% BCLC C) Unresectable HCC (Kudo et al)[18]

Outcome	Study Results and Measurements	Absolute Effect Estimates		Certainty of the Evidence (quality of evidence)	Plain Text Summary
		Sorafenib (comparator)	Lenvatinib (intervention)		
Overall survival (noninferiority primary endpoint)	HR, 0.92 (95% CI, 0.79 to 1.06)	731 deaths per 1,000	701 deaths per 1,000	Moderate (1)	Lenvatinib probably has little or no effect on overall survival compared with sorafenib
	Based on data from 954 patients in one study; follow-up, 6 months	Difference: 30 fewer per 1,000 (95% CI, 85 fewer to 20 more)			
Progression-free survival	HR, 0.64 (95% CI, 0.55 to 0.76)	197 progressions/ deaths per 1,000	131 progressions/ deaths per 1,000	High (1, 2, 3)	Lenvatinib improves progression-free survival compared with sorafenib
	Based on data from 954 patients in one study; follow-up 6 months	Difference: 66 fewer per 1,000 (95% CI, 83 fewer to 43 fewer)			
Objective response rate (mRECIST, independent review)	OR, 5.01 (95% CI, 3.59 to 7.01)	124 responses per 1,000	415 responses per 1,000	High (1, 2, 3)	Of 194 responses in the lenvatinib group, 10 were complete, 184 partial; of 59 responses in the sorafenib group, 4 were complete and 55 partial
	Based on data from 954 patients in one study; follow-up, duration of study	Difference: 291 more per 1,000 (95% CI, 213 more to 374 more)			Lenvatinib improves objective response rate compared with sorafenib
Treatment discontinuation due to adverse events	RR, 1.46 (95% CI, 1.01 to 2.1)	73 discontinuation per 1,000	107 discontinuation per 1,000	Moderate (1, 2)	Lenvatinib has more treatment discontinuations due to adverse events compared with sorafenib[a]
	Based on data from 951 patients in one study; follow-up, duration of study (median follow-up 27.7 in lenvatinib group and 27.2 in sorafenib group)	Difference: 34 more per 1,000 (95% CI, 1 more to 80 more)			
Grade ≥ 3 treatment-related adverse events	OR, 1.38 (95% CI, 1.07 to 1.79)	486 per 1,000	671 per 1,000	Moderate (1, 2)	Lenvatinib may worsen grade ≥ 3 treatment-related adverse events compared with sorafenib[a] (Table 4)
	Based on data from 951 patients in one study	Difference: 185 more per 1,000 (95% CI, 34 more to 384 more)			

NOTE. Downgrade: (1) commercially funded (risk of publication bias); (2) study participants and personnel not blinded to study allocation. (3) Upgrade: large magnitude of effect.

Abbreviations: BCLC, Barcelona Clinic Liver Cancer staging; HR, hazard ratio; mRECIST, modified RECIST; OR, odds ratio; RR, relative risk.

[a]The median duration of lenvatinib treatment was 1.5 times longer than that of sorafenib treatment, which may have contributed to the higher rate of adverse events in the former group.

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 with placebo (median survival, 10.6 months for regorafenib *v* 7.6 months for placebo; HR, 0.63; 95% CI, 0.5 to 0.79; Table 8). Long survival time from start of treatment with first-line sorafenib was noted (regorafenib: 26.0 months; 95% CI, 22.6 to 28.1 months; *v* placebo: 19.2 months; 95% CI, 16.3 to 22.8 months), indicating that this was a population with relatively stable disease and good tolerance to sorafenib.[31] Other outcomes, including PFS, disease control rate, and ORR, also significantly favored regorafenib. Adverse events that were significantly more likely to occur with regorafenib were hypertension (15% *v* 5%), HFSR (13% *v* 1%), fatigue (9% *v* 5%), and diarrhea (3% *v* 0%). Seven deaths were considered by investigators to be due to treatment with regorafenib.[32]

TABLE 6. Patients With Early (3% BCLC A), Intermediate (15% BCLC B) or Advanced (82% BCLC C) Unresectable HCC (Finn et al, 2020)[12]

Outcome	Study Results and Measurements	Absolute Effect Estimates		Certainty of the Evidence (quality of evidence)	Plain Text Summary
		Sorafenib (comparator)	Atezo + Bev (intervention)		
Overall survival	HR, 0.58 (95% CI, 0.42 to 0.79)	278 deaths per 1,000	172 deaths per 1,000	High (1, 2, 3)	Atezo + bev improves overall survival compared with sorafenib
	Based on data from 501 patients in one study; follow-up, 6 months	Difference: 106 fewer per 1,000 (95% CI, 150 fewer to 51 fewer)			
Progression-free survival	HR, 0.59 (95% CI, 0.47 to 0.76)	628 progressions/ deaths per 1,000	442 progressions/ deaths per 1,000	High (1, 2, 3)	Atezo + bev improves progression-free survival compared with sorafenib
	Based on data from 501 patients in one study; median follow-up, 8.6 months	Difference: 186 fewer per 1,000 (95% CI, 256 fewer to 100 fewer)			
Objective response rate (independently assessed RECIST 1.1)	RR, 2.28 (95% CI, 1.45 to 3.61)	119 responses per 1,000	251 responses per 1,000	Moderate (1, 2)	Atezo + bev probably improves objective response rate compared with sorafenib
	Based on data from 485 patients in one study; median follow-up, 8.6 months	Difference: 132 more per 1,000 (95% CI, 49 more to 248 more)			
Objective response rate (independently assessed HCC mRECIST 1.1)	HR, 2.5 (95% CI, 1.63 to 3.83)	133 responses per 1,000	300 responses per 1,000	Moderate (1, 2)	Complete response: atezo + bev: 18 (5.5%) *v* sorafenib: 0; partial response: atezo + bev: 71 (22%) *v* sorafenib: 19 (12%)
	Based on data from 483 patients in one study; median follow-up, 8.6 months	Difference: 167 more per 1,000 (95% CI, 75 more to 288 more)			Atezo + bev probably improves objective response rate compared with sorafenib
Disease control rate (complete response, partial response and stable disease)	RR, 1.33 (95% CI, 1.14 to 1.55)	553 disease controlled per 1,000	657 disease controlled per 1,000	Moderate (1, 2)	Atezo + bev probably improves disease control rate compared with sorafenib
	Based on data from 485 patients in one study; median follow-up, 8.6 months	Difference: 104 more per 1,000 (95% CI, 48 more to 160 more)			
Grade 3-4 adverse events	RR, 1.03 (95% CI, 0.86 to 1.22)	551 events per 1,000	568 events per 1,000	Moderate (1, 2)	Atezo + bev probably has little or no effect on rate of grade 3-4 adverse events compared with sorafenib (Table 4)
	Based on data from 485 patients in one study; median follow-up, 8.6 months	Difference: 17 more per 1,000 (95% CI, 77 fewer to 121 more)			
Grade 5 adverse events	RR, 0.79 (95% CI, 0.35 to 1.77)	58 events per 1,000	46 events per 1,000	Moderate (1, 2)	Atezo + bev probably has little or no effect on rate of grade 5 adverse events compared with sorafenib
	Based on data from 485 patients in one study; median follow-up, 8.6 months	Difference: 12 fewer per 1,000 (95% CI, 38 fewer to 45 more)			

NOTE. Downgrade: (1) commercially funded (risk of publication bias); (2) study participants and personnel not blinded to study allocation (open-label design). Upgrade: (3) large magnitude of effect.

Abbreviations: atezo + bev, atezolizumab + bevacizumab; BCLC, Barcelona Clinic Liver Cancer staging; HCC, hepatocellular carcinoma; HR, hazard ratio; mRECIST, modified RECIST; RR, relative risk.

TABLE 7. Phase III Randomized Controlled Trials of Second-Line or Third-Line Systemic Therapy for Advanced Hepatocellular Carcinoma

	Bruix et al (2017)[24]		Abou-Alfa et al (2018)[23]		Zhu et al (2019)[27]		Finn et al (2020)[26]	
Variable	**Regorafenib (160 mg daily for first 3 weeks of 4-week cycle; n = 379)**	**Matching Placebo (n = 194)**	**Cabozantinib (60 mg daily; n = 470)**	**Matching Placebo (n = 237)**	**Ramucirumab (8 mg/kg IV every 2 weeks; n = 97)**	**Matching Placebo (n = 95)**	**Pembrolizumab (200 mg IV every 3 weeks for at least 35 cycles [approx. 2 years]) plus BSC (n = 278)**	**Placebo (saline) + BSC (n = 135)**
Age, median (range) or (IQR)	64 (54-71)	62 (55-68)	64 (22-86)	64 (24-86)	64 (58-73)	64 (56-71)	67 (18-91)	68 (23-89)
Sex								
Male	88	88	81	85	78	83	81	83
Female	12	12	19	15	22	17	19	17
Region								
Europe and Australasia	Rest of world: 62	62						
Europe			49	46			35	32
Americas, Europe, Australia, Israel					51	53		
Asia	38 (China, Japan, South Korea, Singapore, Taiwan)	38	25 (Hong Kong, South Korea, Singapore, Taiwan)	25	W/out Japan: 28; Japan: 21	W/out Japan: 24; Japan: 19	W/out Japan: 28; Japan: 14	W/out Japan: 23 Japan: 14
Canada/US			23	25			8 (US)	12 (US)
Australia/New Zealand			3	5				
Other							19	19
Disease etiology								
Hepatitis C	21	21	24	23	24	29	16 (HCV+)	16 (HCV+)
Alcohol only	24	28	24	16				
Hepatitis B	38	38	38	38	36	38	26 (HBV+)	22 (HCV+)
Hepatitis B and hepatitis C			2	2				
Nonalcoholic steatohepatitis	7	7	9	10	10	4		
Unknown	17	16	16	20				
Other	7	5	5	7	15	12		
Alcohol					24	22		
Uninfected with HBV or HCV							59	63

(continued on following page)

TABLE 7. Phase III Randomized Controlled Trials of Second-Line or Third-Line Systemic Therapy for Advanced Hepatocellular Carcinoma (continued)

	Bruix et al (2017)[24]		Abou-Alfa et al (2018)[23]		Zhu et al (2019)[27]		Finn et al (2020)[26]	
Variable	Regorafenib (160 mg daily for first 3 weeks of 4-week cycle; n = 379)	Matching Placebo (n = 194)	Cabozantinib (60 mg daily; n = 470)	Matching Placebo (n = 237)	Ramucirumab (8 mg/kg IV every 2 weeks; n = 97)	Matching Placebo (n = 95)	Pembrolizumab (200 mg IV every 3 weeks for at least 35 cycles [approx. 2 years]) plus BSC (n = 278)	Placebo (saline) + BSC (n = 135)
ECOG PS								
0	65	67	52	55	57	58	58	53
1	35	33	48	45	43	42	42	47
2	0	0	< 1	0	0	0	0	0
BCLC stage								
A (early)	< 1	0			0	0	0	0
B (intermediate)	14	11			17	21	20	22
C (advanced)	86	89			83	79	80	79
MVI, hepatic and/or portal vein (yes)	29	28	27	34	36	35		
EH spread (yes)	70	76	79	77	72	74		
MVI or EH spread or both (present)	80	84	85	84				
Child-Pugh class								
A	98	97	100	100	5 points: 62	5 points: 57	A5: 63	A5: 64
					6 points: 38	6 points: 43	A6: 36	A6: 35
B	1	3	0	0			B7: 0.4	B7: 1.5
AFP ≥ 400 ng/mL	43	45	41	43	100	100		
Median AFP (IQR), ng/mL					3,920 (1,175-20,000)	2,741 (1,178-11,681)		
Previous therapy	Sorafenib	Sorafenib	Sorafenib (< 1% ≥ 3 previous, 28% 2 previous, 71% 1 previous regimen)	Sorafenib (< 1% ≥ 3 previous, 26% 2 previous, 73% 1 previous regimen)	In addition to sorafenib:	In addition to sorafenib:	Sorafenib	Sorafenib
					Surgery: 44	Surgery: 41		
					RT: 18	RT: 20		

NOTE. Data are presented as % unless otherwise noted.

Abbreviations: AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer staging; BSC, best supportive care; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EH, extrahepatic; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IQR, interquartile range; MVI, macrovascular invasion.

Cabozantinib Versus Placebo

The study by Abou-Alfa et al (CELESTIAL)[23] 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/United States (24%), and Australia/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

TABLE 8. Patients With Intermediate (13% BCLC B) or Advanced (83% BCLC C) HCC Experiencing Disease Progression While Receiving Sorafenib (Bruix et al, 2017)[24]

Outcome	Study Results and Measurements	Absolute Effect Estimates		Certainty of the Evidence (quality of evidence)	Plain Text Summary
		Placebo (comparator)	Regorafenib (intervention)		
Overall survival (primary outcome)	HR, 0.63 (95% CI, 0.5 to 0.79)	720 deaths per 1,000	552 deaths per 1,000	High (1, 2, 3)	Median overall survival: 10.6 for regorafenib *v* 7.6 for placebo
	Based on data from 573 patients in one study; follow-up, median 7 months	Difference: 168 fewer per 1,000 (95% CI, 249 fewer to 86 fewer)			Regorafenib improves overall survival (primary outcome) compared with placebo
Progression-free survival	HR, 0.43 (95% CI, 0.35 to 0.52)	918 progressions/ deaths per 1,000	641 progressions/ deaths per 1,000	High (1, 2, 3)	Regorafenib improves progression-free survival compared with placebo
	Based on data from 573 patients in one study; follow-up, 6 months	Difference: 277 fewer per 1,000 (95% CI, 345 fewer to 197 fewer)			
Disease control rate (response or stable disease maintained for at least 6 weeks)	RR, 1.81 (95% CI, 1.48 to 2.21)	360 per 1,000	652 per 1,000	Moderate (1, 2)	Regorafenib probably improves disease control rate compared with placebo
	Based on data from 573 patients in one study	Difference: 292 more per 1,000 (95% CI, 173 more to 436 more)			
Objective response rate (investigator-assessed HCC mRECIST)	RR, 2.56 (95% CI, 1.22 to 5.36)	40 per 1,000	102 per 1,000	Moderate (1, 2)	Regorafenib probably improves objective response rate compared with placebo
	Based on data from 573 patients in one study; follow-up, until discontinuation	Difference: 62 more per 1,000 (95% CI, 9 more to 174 more)			
Serious adverse events attributed to study drug	RR, 4.03 (95% CI, 1.61 to 10.05)	30 per 1,000	121 per 1,000	Moderate (1, 2)	Regorafenib probably worsens serious adverse events attributed to study drug compared with placebo
	Based on data from 567 patients in one study; follow-up, continuous monitoring	Difference: 91 more per 1,000 (95% CI, 18 more to 272 more)			
Drug-related adverse events leading to interruptions or dose reductions	RR, 5.21 (95% CI, 3.41 to 7.98)	100 per 1,000	521 per 1,000	High (1, 2, 3)	Regorafenib worsens drug-related adverse events leading to interruptions or dose reductions compared with placebo
	Based on data from 567 patients in one study; follow-up, continuous monitoring	Difference: 421 more per 1,000 (95% CI, 241 more to 697 more)			
Drug-related adverse events leading to discontinuation	RR, 2.88 (95% CI, 1.31 to 6.31)	40 per 1,000	115 per 1,000	Moderate (1, 2)	Regorafenib probably worsens drug-related adverse events leading to discontinuation compared with placebo
	Based on data from 567 patients in one study; follow-up, continuous monitoring	Difference: 75 more per 1,000 (95% CI, 12 more to 212 more)			

NOTE. Downgrade: (1) indirectness: patient population tolerant of first-line sorafenib; (2) commercially funded (risk of publication bias). Upgrade: (3) large magnitude of effect.

Abbreviations: BCLC, Barcelona Clinic Liver Cancer staging; HCC, hepatocellular carcinoma; HR, hazard ratio; mRECIST, modified RECIST; RR, relative risk.

unknown or other causes (21%). Eighty-five percent of patients had macrovascular invasion and/or extrahepatic spread (Table 7).

OS was significantly better with cabozantinib compared with 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 (Table 9). Grade 3 or 4 adverse events 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 adverse events 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 10).

Ramucirumab Versus Placebo

The study by Zhu et al (REACH-2)[27] 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 ≥ 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.

TABLE 9. Patients With Noncurative HCC Previously Treated With Sorafenib and Experiencing Disease Progression After At Least One Systemic HCC Treatment (or up to two; Abou-Alfa et al, 2018)[23]

Outcome	Study Results and Measurements	Absolute Effect Estimates		Certainty of the Evidence (quality of evidence)	Plain Text Summary
		Placebo (comparator)	Cabozantinib (intervention)		
Overall survival (primary outcome)	HR, 0.76 (95% CI, 0.63 to 0.92)	390 deaths per 1,000	313 deaths per 1,000	Moderate (1)	Cabozantinib probably improves overall survival compared with placebo
	Based on data from 707 patients in one1 study; follow-up, 6 months	Difference: 77 fewer per 1,000 (95% CI, 122 fewer to 25 fewer)			
Progression-free survival	HR, 0.44 (95% CI, 0.36 to 0.52)	89 progressions/ deaths per 1,000	40 progressions/ deaths per 1,000	High (1, 2)	Cabozantinib improves progression-free survival compared with placebo
	Based on data from 707 patients in one study; follow-up, 6 months	Difference: 49 fewer per 1,000 (95% CI, 56 fewer to 42 fewer)			
Objective response rate (investigator assessed, RECIST v1.1)	RR, 9.08 (95% CI, 1.22 to 67.58)	4 responses per 1,000	36 responses per 1,000	Low (1, 3)	Cabozantinib: 18 partial responses; placebo: 1 partial response
	Based on data from 707 patients in one study	Difference: 32 more per 1,000 (95% CI, 1 more to 266 more)			Cabozantinib may improve objective response rate compared with placebo
Disease control (partial response or stable disease)	RR, 1.91 (95% CI, 1.58 to 2.32)	330 disease controlled per 1,000	630 disease controlled per 1,000	High (1, 2)	Cabozantinib improves disease control compared with placebo
	Based on data from 707 patients in one study	Difference: 300 more per 1,000 (95% CI, 191 more to 436 more)			
Grade 3 or 4 adverse events	RR, 1.86 (95% CI, 1.56 to 2.23)	360 per 1,000	670 per 1,000	High (1, 2)	Cabozantinib worsens grade 3 or 4 adverse events compared with placebo
	Based on data from 704 patients in one study	Difference: 310 more per 1,000 (95% CI, 202 more to 443 more)			
Discontinuation due to adverse events associated with the trial regimen	RR, 5.51 (95% CI, 2.58 to 11.76)	30 per 1,000	165 per 1,000	High (1, 2)	Cabozantinib worsens discontinuation due to adverse events associated with the trial regimen compared with placebo
	Based on data from 704 patients in one study	Difference: 135 more per 1,000 (95% CI, 47 more to 323 more)			

NOTE. Downgrade: (1) commercially funded (risk of publication bias); (3) imprecision (wide confidence interval). Upgrade: (2) large magnitude of effect.
Abbreviations: HCC, hepatocellular carcinoma; HR, hazard ratio; RR, relative risk.

TABLE 10. 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 HCC

Comparison	HFSR	Diarrhea	Hyperbilirubinemia	Hypertension	AST Increase	ALT Increase	Fatigue	Bleeding or Hemorrhage	Anemia	Hyponatremia	Liver Failure or Injury	Ascites
Regorafenib *v* placebo[24]	13 *v* 1			15 *v* 5			9 *v* 5					
Cabozantinib *v* placebo[23]	17 *v* 0	10 *v* 2		16 *v* 2	12 *v* 7		10 *v* 4					
Ramucirumab *v* placebo (AFP ≥ 400 ng/mL)[27]				13 *v* 5				6 *v* 3			18 *v* 16	5 *v* 2
Ramucirumab *v* placebo (AFP ≥ 400 ng/mL); combined data from REACH and REACH-2 trials[27]				13 *v* 4	3 *v* 5					5 *v* 2		
Pembrolizumab *v* placebo[26]			7.5 *v* 5.2		13.3 *v* 7.5	6.1 *v* 3.0			3.9 *v* 9.0			

NOTE. Data presented as %.

Abbreviations: AFP, α-fetoprotein; ALT: alanine transaminase, HFSR: hand–foot skin reaction.

The REACH study,[33] 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[27] found a 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; Table 11). ORR did not differ significantly between groups, with nine responses experienced in the experimental and one response experienced in the control group. In a pooling of data from REACH and REACH-2, adverse events affecting at least 5% of patients in the ramucirumab or placebo groups, respectively, included hypertension (13% *v* 4%) and hyponatremia (5% *v* 2%; Table 10).

Pembrolizumab Versus Placebo

The study by Finn et al (Keynote 240)[26] 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, 0.72; 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; Table 12).

The most common grade 3 or 4 adverse events in the pembrolizumab or placebo groups were AST increase (13.3% *v* 7.5%), serum bilirubin increase (7.5% *v* 5.2%), alanine transaminase increase (6.1% *v* 3.0%), and anemia (3.9% *v* 9.0%). Treatment discontinuation due to grade 3 or 4 adverse events was significantly more likely in the pembrolizumab group (17.2% *v* 9.0%; RR, 2.74; 95% CI, 1.26 to 5.96; Table 10).

RECOMMENDATIONS

Clinical Question

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

First-Line Therapy

Recommendation 1.1. Atezolizumab-bevacizumab (atezo + bev) may be offered as first-line treatment for most patients with advanced HCC, Child-Pugh class A, ECOG PS 0-1, and following management of esophageal varices, when present, according to institutional guidelines (Type: evidence-based, benefits outweigh harms; Evidence quality: moderate to high; Strength of recommendation: strong).

Qualifying statements:

- Recommendation 1.1 is based on results from the IMbrave150 phase III RCT, which compared atezo + bev to sorafenib (HR for OS, 0.58; 95% CI, 0.42 to 0.79; $P = .0006$) in Child-Pugh class A patients. Caution should be exercised when applying these results to patients with more advanced liver disease who have a greater likelihood of portal hypertension because of the risk of bleeding complications associated with bevacizumab.
- Due to risk of bleeding, patients in this trial were required to have undergone esophagogastroduodenoscopy (EGD) within 6 months of trial initiation and to have received treatment of esophageal varices when necessary.[14] The Expert Panel recognizes that some patients may have been evaluated for varices outside the 6-month window, are receiving treatment (eg, adequately dosed nonselective β-blockers), and/or are deemed to be low risk for variceal bleed by a hepatology specialist. In these patients, the decision to forgo an EGD prior to initiation of therapy with atezo + bev may be carefully considered.
- In an exploratory subgroup analysis, IMBrave150 study authors found that overall survival was not significantly different between treatment and control groups in the subgroup of patients who tested positive for treatment-emergent ADAs at 6 months (HR, 0.93; 95% CI, 0.57 to 1.53). The HR in the ADA-negative subgroup to sorafenib was 0.39 (95% CI, 0.26 to 0.60).[29]
- Patients who had a myocardial infarction or stroke within the previous 3 months, a history of autoimmune disease, were on therapeutic anticoagulation, or had

TABLE 11. Patients With Intermediate (18% BCLC B) or Advanced (82% BCLC C) HCC Previously Treated With Sorafenib, Baseline AFP ≥ 400 ng/mL (Zhu et al, 2019)[27]

Outcome	Study Results and Measurements	Absolute Effect Estimates		Certainty of the Evidence (quality of evidence)	Plain Text Summary
		Placebo (comparator)	Ramucirumab (intervention)		
Overall survival	HR, 0.71 (95% CI, 0.53 to 0.95)	800 deaths per 1,000	681 deaths per 1,000	High (1, 3)	Ramucirumab improves overall survival compared with placebo
	Based on data from 292 patients in one study; follow-up, 12 months	Difference: 119 fewer per 1,000 (95% CI, 226 fewer to 17 fewer)			
Progression-free survival	HR, 0.45 (95% CI, 0.34 to 0.60)	947 progressions/ deaths per 1,000	733 progressions/ deaths per 1,000	High (1, 3)	Ramucirumab improves progression-free survival compared with placebo
	Based on data from 292 patients in one study; follow-up, 6 months	Difference: 214 fewer per 1,000 (95% CI, 315 fewer to 119 fewer)			
Objective response rate (investigator assessed, RECIST 1.1)	RR, 4.34 (95% CI, 0.56 to 33.76)	10 responses per 1,000	43 responses per 1,000	Low (1, 2)	Ramucirumab may improve objective response rate compared with placebo
	Based on data from 292 patients in one study; median follow-up, 7.6 months	Difference: 33 more per 1,000 (95% CI, 4 more to 328 more)			
Serious adverse events (any grade and cause)	RR, 1.21 (95% CI, 0.84 to 1.75)	290 events per 1,000	351 events per 1,000	Low (1)	Ramucirumab may not worsen serious adverse events (any grade or cause) compared with placebo (Table 10)
	Based on data from 292 patients in one study; follow-up, 6 months	Difference: 61 more per 1,000 (95% CI, 46 fewer to 218 more)			

NOTE. Downgrade: (1) commercially funded (risk of publication bias); (2) imprecise estimate (wide confidence interval). Upgrade: (3) large magnitude of effect.

Abbreviations: AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer staging; HCC, hepatocellular carcinoma; HR, hazard ratio; RR, relative risk.

coinfection with HBV and HCV were also excluded from the IMbrave150 RCT.

Recommendation 1.2. Where there are contraindications to atezolizumab and/or bevacizumab, tyrosine kinase inhibitors sorafenib or lenvatinib may be offered as first-line treatment of patients with advanced HCC, Child-Pugh class A, and ECOG PS 0-1 (Type: evidence-based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

Qualifying statements:

- RCTs with the suggested options have been conducted in Child-Pugh A patient populations. Real-world studies and observational studies conducted in patients with Child-Pugh B have shown a similar rate of adverse events to the Child-Pugh A population but relatively shorter overall survival. Treatment with recommended TKIs may be less effective for patients with more advanced liver cirrhosis. Careful patient selection is recommended.
- The choice of treatment with lenvatinib or sorafenib should be made through a discussion involving the physician and patient (and caregiver, where applicable) and should include factors such as medical history, viral etiology of liver disease, toxicities associated with treatment, cost (see Cost Implications), goals of treatment, patient preference, and expected treatment benefit. Factors affecting this choice, including response rates, are discussed further in the Clinical Interpretation.
- Several meta-analyses of RCTs have shown sorafenib to be more beneficial in patients with HCV, especially as compared with patients with HBV.[15-17] In the REFLECT trial there was a trend toward improvements across endpoints for lenvatinib over sorafenib in the HBV subgroup, though it was not significant.[18]
- Patients with a high tumor burden, > 50% liver involvement, or those with main portal vein invasion were excluded from the REFLECT trial of sorafenib versus lenvatinib.[19]

Clinical interpretation. The combination of atezo + bev is recommended as first-line therapy based on the results of the IMbrave150 trial (Recommendation 1.1). Sorafenib and lenvatinib are recommended where there are contraindications to atezo + bev (Recommendation 1.2). The following points may be considered when selecting from the options presented in Recommendation 1.2:

- In an RCT, overall survival was found to be noninferior with lenvatinib compared with sorafenib; however, overall response and PFS were significantly improved with lenvatinib (Table 5).
- The adverse events profiles are similar, and there is a relatively high risk of specific adverse events with these two TKI treatment options (Table 4). There is a higher rate of hypertension with lenvatinib and more HFSR with sorafenib.[18]
- Overall, sorafenib has a low response rate but improves time to radiographic progression and lengthens disease stability.[14]
- Patients treated with lenvatinib reported quality-of-life scores that indicated a delay in deterioration compared with sorafenib.

Second-Line Therapy

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. Options for second-line therapy are included in Recommendations 2.1 to 2.3 and are described in greater detail in the Clinical Interpretation.

Recommendation 2.1. Following first-line treatment with atezo + bev, second-line therapy with a TKI (ie, sorafenib, lenvatinib, cabozantinib, or regorafenib) may be recommended (Type: informal consensus, benefits may outweigh harms; Evidence quality: low; Strength of recommendation: weak).

Qualifying statement:

- No data have been published on therapy options after first-line treatment with atezo + bev. It is the opinion of the Expert Panel that a TKI, preferably sorafenib or lenvatinib, may be offered. Cabozantinib or regorafenib are also reasonable options for second-line therapy following atezo + bev.

Recommendation 2.2. Following first-line therapy with sorafenib or lenvatinib, second-line therapy with another TKI (cabozantinib or regorafenib), ramucirumab (AFP ≥ 400 ng/mL), or atezo + bev may be recommended for appropriate candidates. Considerations regarding choice of therapy are included in the Clinical Interpretation (Type: informal consensus, benefits may outweigh harms; Evidence quality: low to moderate; Strength of recommendation: weak).

Qualifying statement:

- It is likely that most patients being considered for atezo + bev in the second-line setting did not have access to this combination when they started first-line treatment.

Recommendation 2.3. Following first-line therapy with sorafenib or lenvatinib, pembrolizumab or nivolumab are reasonable options that may be considered for appropriate candidates (Type: informal consensus, benefits may outweigh harms; Evidence quality: low; Strength of recommendation: weak).

Qualifying statement:

- Immune checkpoint inhibitors pembrolizumab or nivolumab may be especially beneficial for patients who have contraindications to or cannot tolerate TKIs.

Clinical interpretation. To date, second-line therapy options have only been evaluated following therapy with sorafenib; no second-line therapy options have been evaluated following treatment with first-line therapy options lenvatinib or atezo + bev. 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. The Expert Panel also agrees that due to their differing mechanisms of action, second-line treatment with a TKI may offer clinical benefit following treatment with atezo + bev. Several second-line or greater therapies have been evaluated following toxicity with or progression on sorafenib. In these settings, overall survival was improved compared with placebo with regorafenib, cabozantinib, and ramucirumab in patients with higher AFP levels. In addition to sorafenib and lenvatinib, options for second-line therapy include regorafenib, cabozantinib, and ramucirumab:

- Regorafenib is US Food and Drug Administration (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.[34] 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.[34]
- 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/intolerant to sorafenib with AFP ≥ 400 ng/mL.[27]

In addition, a phase III RCT of immune checkpoint inhibitor 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 with placebo.[26] No other fully published studies of ICIs met the inclusion criteria for this review. 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[35]; however, this should be interpreted with caution, as no randomized trial data are available for this agent in the second-line setting. The Expert Panel agrees that ICIs in the second-line setting may be especially beneficial for patients who have contraindications to or cannot tolerate TKIs due to worsening performance status. Further discussion of the role of ICIs in the context of second-line therapy is included in the Discussion.

Finally, 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. It is likely that most patients receiving atezo + bev in the second-line setting did not have access to this combination when they started first-line treatment.

Third-line therapy. 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.[23] As this subgroup was underpowered for the primary endpoint, however, this result indicates that placebo rather than cabozantinib should remain the comparator in any new clinical trials of third-line systemic therapy options.[36] Cabozantinib is approved as a second-line and third-line therapy option for patients with advanced HCC.[37]

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.

Child-Pugh Class B

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.[38] The review authors' analysis of a sorafenib-treated "non-SHARP-eligible" patient population found OS to be similar to best supportive care (BSC; ie, approximately 5 months[39]), 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 with the Child-Pugh A group.[40]

In a retrospective case series of 18 Child-Pugh class B patients treated with nivolumab, rates of adverse events were high, although similar to those seen in a previous study of Child-Pugh A patients, and two partial and one complete response were recorded.[41]

Some published guidelines specify that certain systemic therapy options are limited to the Child-Pugh class A population.[42,43] On the other hand, allocation systems, such as BCLC, do not exclude Child-Pugh B patients from treatment with sorafenib but recommend careful evaluation of liver function and advise that optimal outcomes of systemic therapy can only be expected with compensated liver disease where the liver is still able to perform most of its basic functions (ie, Child-Pugh stage A without ascites), as well as emphasizing careful patient selection.[8] The tolerable dose of sorafenib in cohorts of patients with hepatic and renal dysfunction has been explored.[44]

Despite the cautions and lack of randomized trials of patients with Child-Pugh class B, data suggest that sorafenib is often prescribed regardless of liver function,[40] with the rate of prescription being approximately 12%-44% in patients with Child-Pugh class B HCC across various studies.[45] In addition, Child-Pugh class is often not assessed among patients in the United States, according to observational study data.[40]

Due to lack of inclusion of Child-Pugh class B patients in randomized trials included in this review, systemic therapy in this population was not included in the Recommendations section of this guideline. The Expert Panel agrees on a cautious approach to systematic therapy in patients with advanced HCC who are Child-Pugh class B with good performance status, 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.

Third-Line Therapy

Patients who received cabozantinib following treatment with one or two other systemic therapy regimens were included in the CELESTIAL phase III RCT. Within this subgroup, the median survival did not differ significantly between treatment and control groups.[23] The sequence of

TABLE 12. Patients With Intermediate (21% BCLC B) or Advanced (79% BCLC C) Hepatocellular Carcinoma Experiencing Disease Progression or Intolerance to First-line Sorafenib (Finn et al, 2020)[26]

Outcome	Study Results and Measurements	Absolute Effect Estimates		Certainty of the Evidence (quality of evidence)	Plain Text Summary
		Placebo (comparator)	Pembrolizumab (intervention)		
Overall survival (coprimary outcome)	HR, 0.78 (95% CI, 0.61 to 1.0)	274 deaths per 1,000	221 deaths per 1,000	Low (1, 2)	Trend toward better survival with pembrolizumab compared with placebo did not reach statistical significance as per the prespecified statistical plan
	Based on data from 413 patients in one study; follow-up, 6 months	Difference: 53 fewer per 1,000 (95% CI, 97 fewer to 0 fewer)			
Progression-free survival (coprimary outcome)	HR, 0.72 (95% CI, 0.57 to 0.9)	815 progressions/ deaths per 1,000	703 progressions/ deaths per 1,000	Low (1, 2)	Trend toward better progression-free survival with pembrolizumab compared with placebo did not reach statistical significance as per the prespecified statistical plan
	Based on data from 413 patients in one study; follow-up, 6 months	Difference: 112 fewer per 1,000 (95% CI, 197 fewer to 34 fewer)			
Objective response rate (central radiology review, RECIST v1.1)	RR, 4.13 (95% CI, 1.82 to 9.38)	44 responses per 1,000	182 responses per 1,000	Moderate (1, 2, 3)	Pembrolizumab group: 6 complete and 45 partial responses; placebo group: 0 complete and 6 partial responses
	Based on data from 413 patients in one study; follow-up, 6 months	Difference: 138 more per 1,000 (95% CI, 36 more to 369 more)			Pembrolizumab may improve objective response rate compared with placebo
Stable disease	RR, 0.9 (95% CI, 0.72 to 1.12)	489 stable disease per 1,000	440 stable disease per 1,000	Low (1, 2)	Pembrolizumab may have little or no effect on stable disease compared with placebo
	Based on data from 413 patients in one study; follow-up, 6 months	Difference: 49 fewer per 1,000 (95% CI, 137 fewer to 59 more)			
Progressive disease	RR, 0.77 (95% CI, 0.59 to 0.99)	422 progressions per 1,000	325 progressions per 1,000	Low (1, 2)	Pembrolizumab may improve progressive disease compared with placebo
	Based on data from 413 patients in one study; follow-up, 6 months	Difference: 97 fewer per 1,000 (95% CI, 173 fewer to 4 fewer)			
Adverse events (grade 3 or 4 due to any cause)	RR, 1.12 (95% CI, 0.91 to 1.39)	463 events per 1,000	519 events per 1,000	Low (1, 2)	Pembrolizumab may not worsen adverse events (grade 3 or 4 due to any cause) compared with placebo
	Based on data from 413 patients in one study; follow-up, 6 months	Difference: 56 more per 1,000 (95% CI, 42 fewer to 181 more)			
Grade 3 or 4 adverse events leading to treatment discontinuation	RR, 1.92 (95% CI, 1.06 to 3.49)	52 events per 1,000	142 events per 1,000	Low (1, 2)	Pembrolizumab may worsen adverse events leading to treatment discontinuation compared with placebo
	Based on data from 413 patients in one study; follow-up, 6 months	Difference: 90 more per 1,000 (95% CI, 14 more to 258 more)			

NOTE. Downgrade: (1) commercially funded (risk of publication bias); (2) indirectness: results potentially affected by patients using other drugs upon progression, patients with main portal vein invasion excluded. Upgrade: (3) large magnitude of effect.

Abbreviations: BCLC, Barcelona Clinic Liver Cancer staging; HR, hazard ratio; RR, relative risk.

therapy used in this trial is unlikely to be offered at the present time, given the more recent publication of data that have impacted recommendations for therapy in the first-line setting. Due to the lack of relevant data, the Expert Panel did not include a formal recommendation for third-line therapy within the Recommendations section but acknowledges that third-line therapy may be considered in Child-Pugh A patients with good performance status, using a shared decision-making, multidisciplinary approach.

ICIs

Treatment with monoclonal antibodies pembrolizumab and nivolumab has previously resulted in response rates of 14%-20%.[46,47] 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 with placebo; therefore, the study did not reach its primary and secondary endpoints.[26] Nivolumab was FDA approved in September 2017 as a second-line therapy option, based on a single-arm study that demonstrated an ORR of 14.3%, according to blinded independent central review (RECIST 1.1).[35,47] More recently, reported in an abstract, a phase III study of nivolumab as first-line therapy found a 10% response rate for patients treated with nivolumab and no difference in OS compared with sorafenib, and, therefore, the study did not meet its primary endpoint.[28] In addition, most recently, the combination of nivolumab and ipilimumab as second-line therapy has been given accelerated approval by the FDA, based on results reported in an abstract from a subgroup analysis of the CheckMate 040 phase I/II study that showed a 33% response rate with treatment.[48] This approval may be conditional on the results of other confirmatory trials.[49,50] 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.

Future Directions

Recent studies of systemic therapy in advanced HCC have demonstrated an increased benefit in terms of response rate and survival from combined therapy.[12] Future directions in advanced HCC include emerging data on combinations of TKIs and immune checkpoint inhibitors, including atezolizumab/cabozantinib,[51] lenvatinib/pembrolizumab,[52] nivolumab/ipilimumab,[53] and other dual checkpoint inhibitors.[13] There is growing interest in combining locoregional with systemic therapies; in a recent study, Kudo et al[54] demonstrated improved PFS in patients with intermediate-stage HCC receiving combined endovascular locoregional and systemic therapy, including sorafenib in combination with on-demand TACE, as compared with patients undergoing TACE alone. Results from currently enrolling clinical trials combining locoregional therapy with systemic therapies including TKIs, checkpoint inhibitors, as well as antivascular agents for the treatment of advanced-stage HCC will inform the role and judicious application of these strategies in this patient population. The linearity of treatments from curative to locoregional to systemic along the continuum of early to advanced HCC may change in response to findings from these trials. Most patients see a number of different stakeholders long before they see an oncologist along the course of care. As more effective therapies emerge, early oncologic referral while hepatic function is still preserved will be imperative. Changing treatment paradigms require a thorough understanding of hepatic reserve and available and emerging treatment options. Multidisciplinary management of the patient with HCC in an environment that fosters dialogue, continuing education, and guideline-driven consensus among stakeholders is key to optimizing patient outcomes.

Limited biomarker data have been published to guide treatment selection for TKIs or ICIs, including the meta-analyses cited previously that showed better efficacy for sorafenib in patients with HCV infection compared with patients with HBV infection. However, there is still a need for genetic and/or IHC biomarkers to guide treatment decision making. The Expert Panel notes the emergence of a subset of patients with HCC with a targetable driver (FGF19) and some early data on the development of FGFR4 inhibitors in this population; however, the efficacy of these agents or the appropriate context for their use (if any) remains to be determined.[55] The emergence of targeted therapies in HCC and other solid tumors, including biomarker-specific/tumor-agnostic FDA-approved treatments, emphasizes the need to obtain histologic diagnosis of HCC.

PATIENT AND CLINICIAN COMMUNICATION

Poor adherence to oral chemotherapy is an ongoing concern with profound clinical implications and reduced therapeutic efficacy,[56-58] which is especially relevant for patients with HCC at risk for encephalopathy, esophageal varices, and/or ascites. Interventions to optimize patient adherence should be considered, such as involvement of pharmacists in managing oral chemotherapy, which has been shown to increase knowledge levels in a pilot study[59] and has resulted in improved adherence and response outcomes.[60]

For recommendations and strategies to optimize patient-clinician communication, readers are referred to Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline.[61]

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/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 with other Americans.[62-65] Many

other patients lack access to care because of their geographic location and distance from appropriate treatment facilities.

Up to 5.3 million people—2% 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.[66] 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/ethnicity. According to an analysis of the 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; non-Hispanic Whites: 7 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.[67] 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.[68] 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/ethnicity.[67,69-71] HCC was also detected at a more advanced stage in an African American study population compared with other racial/ethnic groups.[72] Detection at an earlier stage could help to reduce ethnic and racial disparities in outcomes.[73] 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.[70] 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.[74] At the same time, $<$ 10% of patients who take part in clinical trials are from racial/ethnic minority groups.[75]

Data from a Medicare population show that only 27% of patients with advanced HCC meeting study eligibility criteria were initially treated with sorafenib after diagnosis,[76] and in an analysis of SEER data, authors found that only 29.5% of patients received any treatment of HCC.[68] While there were no articles located as part of this review that specifically addressed socioeconomic or racial and ethnic disparities in the context of the target population of patients receiving systemic therapy for advanced HCC, it seems likely, given the treatment costs outlined in the Cost Implications section, that such disparities exist and may intensify as newer costly options become approved. Underuse of curative treatment options can be due to patient factors such as comorbidities, poor liver function, and other patient characteristics; 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, 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/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 a result, 12 studies of cost-effectiveness of systematic therapy options for advanced HCC were identified (Data Supplement, online only).[77-88] These studies most commonly stated a willingness to pay (WTP) threshold for a quality-adjusted life-year (QALY; ie, 1 year in perfect health) of $100,000 US dollars (USD), while some studies used a WTP threshold of $50,000 USD. In addition to the costs of the drugs, other costs included in the model varied across studies but commonly included management of adverse events, supportive care, follow-up and surveillance, and end-of-life care. Results of the base-case analyses from these studies are briefly described subsequently.

Four studies of first-line sorafenib compared with BSC were identified. Three of these studies, conducted in India,[78] a military hospital in Egypt,[79] and a hypothetical cohort in Italy,[77] respectively, found that sorafenib was not cost-effective at defined WTP thresholds. However, one study found that dose-adjusted sorafenib was more cost-effective than full-dose sorafenib and that the former option was cost-effective at the defined WTP threshold.[77] A study that did not incorporate QALYs found that sorafenib was cost-effective at their WTP threshold for 1 life-year for patients with compensated cirrhosis.[83]

Analyses conducted in Japan and Canada, respectively, compared lenvatinib to sorafenib, applying the characteristics of the patient population from the REFLECT trial.[80,81] In both countries, the incremental cost-effectiveness ratios (ICERs) were found to exceed the respective WTP thresholds for 1 QALY for both drugs. Lenvatinib was found to have higher cost-effectiveness in both countries, but the higher cost of sorafenib was somewhat offset by costs associated with a longer treatment duration with lenvatinib.

Six cost-effectiveness analyses assessed second-line therapy options following treatment with sorafenib. Three of these were studies of cabozantinib compared with BSC or placebo, conducted for populations in the United States, using assumptions based on the CELESTIAL RCT.[82,86,87] One of these studies also provided estimates for the United Kingdom and China. Across all three studies, the ICER for cabozantinib exceeded the WTP threshold for 1 QALY. Studies of the cost-effectiveness of regorafenib + BSC compared with placebo + BSC or BSC alone, conducted in the United States and with assumptions based on the RESORCE RCT, found that the ICERs with regorafenib exceeded the WTP threshold for 1 QALY.[84,85] Likewise, the cost of 1 QALY was found to exceed the ICER for ramucirumab in patients with AFP levels of at least 400 ng/mL.[88]

The finding that the cost of these drugs exceeds WTP thresholds in most cases reflects the balance of utility in terms of survival and other outcomes and disutility resulting from adverse events and relatively high drug costs. In general, for HCC, costs of care are highest in the initial treatment and terminal phases and lower in the continuing care phase.[89] Study authors suggest that the ICER could be improved by lowering the cost[82,84] or improving patient selection, ideally with the use of biomarkers.[86]

Many study assumptions regarding patient characteristics, utility, and disutility estimates are based on randomized trial populations, which may not reflect the characteristics of real-world populations.[90] These analyses are based on available cost information, but it is challenging to determine actual drug costs because information on discounts and rebates that could bring the ICER into the cost-effective range are often not publicly available. On the whole, it is expected that increased use of expensive medications will be the cause of rising costs of HCC treatment; however, incidence of HCC may be reduced by programs that screen for and provide treatment of viral hepatitis and screening among high-risk patients to detect HCC at a stage at which treatment is less costly.[89] Generic sorafenib, expected after patent expiration in 2020,[90] will perhaps make it cost-effective in more scenarios. Going forward, we anticipate that cost-utility analyses will eventually be published for the combination atezo + bev, for which the full trial results have recently been published.[12] It would be helpful to see a comparison of this newer combination with other first-line therapy options, to better inform treatment decision making.

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.[91,92] There remains an urgent need for simplified standardized methodologies to assess treatment costs and survival value[93] and periodic recurrent team-based patient engagement around financial toxicities related to cancer treatment[94,95] 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.[96] 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.[5]

OPEN COMMENT

The draft recommendations were released to the public for open comment from June 8 through June 22, 2020. Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree. See comments" were captured for every proposed recommendation, with written comments received. A total of 100% of the 10 respondents either agreed or agreed with slight modifications to the recommendations, and none of the respondents disagreed. Expert Panel members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions. As a result of feedback from two reviewers, level of AFP was specified in the recommendations for ramucirumab. A reviewer suggested including a recommendation for the FDA-approved combination ipilimumab/nivolumab following sorafenib. The Expert Panel agreed to include this option in the Discussion section, rather than make a recommendation, as the only data available were published as a phase I/II abstract and have yet to be confirmed in a full publication. All changes were incorporated prior to Clinical Practice Guidelines 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 and 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 *Journal of Clinical Oncology*.

This guideline included three panel members who are members of the PGIN. In general, they 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 a concern about the inability of some patients to afford copayments. A third member reported 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: American Society of Clinical Oncology Clinical Practice Guideline Update[97] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline[61] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)

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EDITOR'S NOTE

This American Society of Clinical Oncology 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.

EQUAL CONTRIBUTION

J.D.G. and M.G.R. were Expert Panel co-chairs

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Systemic Therapy for Advanced Hepatocellular Carcinoma: ASCO Guideline

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APPENDIX

TABLE A1. Systemic Therapy for Advanced Hepatocellular Carcinoma Expert Panel Membership

Name	Affiliation/Institution	Role/Area of Expertise
John D. Gordan, MD, PhD, co-chair	University of California, San Francisco, San Francisco, CA	Medical Oncology
Michal G. Rose, MD, co-chair	Yale Cancer Center and VA Connecticut Healthcare System, West Haven, CT	Medical Oncology
Ghassan K. Abou-Alfa, MD, MBA	Memorial Sloan Kettering Cancer Center and Weill Medical College at Cornell University, New York, NY	Medical Oncology
Steven T. Brower, MD	Lefcourt Family Cancer Treatment and Wellness Center, Englewood, NJ	Surgical Oncology (Community Oncology)
Muhammad Shaalan Beg, MD, MS	UT Southwestern, Dallas, TX	Medical Oncology
Terence P. Gade, MD, PhD	Penn Medicine, Philadelphia, PA	Interventional Radiology
Laura Goff, MD	Vanderbilt Ingram Cancer Center, Nashville, TN	Medical Oncology
Shilpi Gupta, MD	Weill Cornell Medicine, New York, NY	PGIN Representative
Jennifer Guy, MD	Sutter Health, San Francisco, CA	Gastroenterology/Hepatology
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R. Kate Kelley, MD	University of California, San Francisco, San Francisco, CA	Medical Oncology
Jennifer J. Knox, MD, MS	Princess Margaret Cancer Centre, Toronto, ON	Medical Oncology
Jeremy Kortmansky, MD	Yale Cancer Center, New Haven, CT	Medical Oncology
Andrea Leaf, MD	VA New York Harbor Healthcare System, Brooklyn, NY	Medical Oncology
William M. Remak, MT	California Hepatitis C Task Force, California Chronic Care Coalition member, FAIR Foundation, San Francisco, CA	Patient Representative
Rachna T. Shroff, MD, MS	University of Arizona Cancer Center, Tucson, AZ	Medical Oncology
Davendra P.S. Sohal, MD, MPH	University of Cincinnati, Cincinnati, OH	Medical Oncology
Tamar H. Taddei, MD	Yale University School of Medicine and VA Connecticut Health Care System, West Haven, CT	Gastroenterology/Hepatology
Neeta K. Venepalli, MD, MBA	University of Illinois Hospital, Chicago, IL	Medical Oncology
Andrea Wilson, MFA	Blue Faery: The Adrienne Wilson Liver Cancer Association, Birmingham, AL	Patient Representative
Andrew X. Zhu, MD, PhD	Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA	Medical Oncology
Erin B. Kennedy, MHSc	American Society of Clinical Oncology, Alexandria, VA	ASCO Practice Guideline Staff (Health Research Methods)

Abbreviation: PGIN, Practice Guidelines Implementation Network.