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CLINICAL PRACTICE GUIDELINES

AGA Clinical Practice Guideline on Systemic Therapy for Hepatocellular Carcinoma

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BACKGROUND & AIMS: Hepatocellular carcinoma (HCC), the most common primary liver cancer, remains a deadly cancer, with an incidence that has tripled in the United States since 1980. In recent years, new systemic therapies for HCC have been approved and a critical assessment of the existing data is necessary to balance benefits and harms and inform the development of evidence-based guidelines. **METHODS:** The American Gastroenterological Association formed a multidisciplinary group consisting of a Technical Review Panel and a Guideline Panel. The Technical Review Panel prioritized clinical questions and outcomes according to their importance for clinicians and patients and conducted an evidence review of systemic therapies in patients with advanced-stage HCC. The Grading of Recommendations Assessment, Development and Evaluation framework was used to assess evidence. The Guideline Panel reviewed the evidence and used the Evidence-to-Decision Framework to develop recommendations. **RESULTS:** The Panel reviewed the evidence, summarized in the Technical Review, for the following medications approved by the US Food and Drug Administration for HCC: first-line therapies: bevacizumab+atezolizumab, sorafenib, and lenvatinib; second-line therapies: cabozantinib, pembrolizumab, ramucirumab, and regorafenib; and other agents: bevacizumab, nivolumab, and nivolumab+ipilimumab. **CONCLUSIONS:** The Panel agreed on 11 recommendations focused on systemic therapy for HCC in patients who are not eligible for locoregional therapy or resection, those with metastatic disease and preserved liver function, those with poor liver function, and those on systemic therapy as adjuvant therapy.

Keywords: Hepatocellular Carcinoma; Systemic Therapy; Liver Cancer.

Hepatocellular carcinoma (HCC), the most common primary liver cancer, remains a deadly cancer, with an incidence that has tripled in the United States since 1980, accompanied by a substantial mortality rate.[1] Typically arising in the context of a diseased liver, HCC is unique because prognosis and treatment are intimately related to both the severity of the underlying chronic liver disease and tumor biology. Individuals with HCC often present at an intermediate or advanced stage, when decisions regarding systemic therapy are critical. Curative options, such as surgery (including resection and liver transplantation), and some locoregional therapies (LRTs), such as ablation, are reserved for early-stage disease, and other LRTs, such as transarterial chemoembolization (TACE), transarterial radioembolization (TARE), and systemic therapy, are needed for advanced and metastatic disease.[2] Traditional cytotoxic chemotherapy and hormonal therapy have not proven to be effective in HCC. Until 2007, when sorafenib, a multi-kinase inhibitor, was approved by the US Food and Drug Administration (FDA) for inoperable HCC, there was no approved systemic therapy.[3] Sorafenib remained the only systemic option for almost a decade, with failures of multiple alternatives in clinical trials. However, in recent years, a multitude of new systemic options have arisen, including molecularly targeted therapies and immunotherapies, which have shown promise in HCC.[4] In this exciting era of newly approved systemic therapies for HCC, a critical assessment of the existing data is necessary to balance benefits and harms.

The focus of this guideline was to provide guidance on the use of systemic therapy in the treatment of HCC. We only addressed treatments that have received FDA approval,

Abbreviations used in this paper: **AFP, α-fetoprotein; AGA, American Gastroenterological Association; BCLC, Barcelona Clinic Liver Cancer staging system; CI, confidence interval; CoE, certainty of evidence; CTP, Child-Turcotte-Pugh score; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for the Research and Treatment of Cancer; FDA, US Food and Drug Administration; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HCC, hepatocellular carcinoma; HR, hazard ratio; IV, intravenously; LRT, locoregional therapy; OS, overall survival; PFS, progression-free survival; PICO, population, intervention, comparator, and outcomes; PS, performance status; QoL, quality of life; RCT, randomized controlled trial; SAE, serious adverse event; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; TR, technical review; TTP, time to progression.**

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and not emerging therapies. This guideline is intended to inform and advise clinicians regarding options for first-line therapy and to define second-line therapy for those who fail first-line systemic treatment, as well as systemic therapy as adjuvant therapy for those individuals who are candidates for LRT or surgery. In addition, we will examine the question of systemic therapy in individuals with poor liver function.

The target audience of this guideline encompasses health care professionals, including gastroenterologists, transplant hepatologists, medical oncologists, and pharmacists, as well as patients and policy makers.

Methods

Overview

This document represents the official recommendations of the American Gastroenterological Association (AGA) and was approved by the AGA Governing Board. The guideline was developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework and adhered to best practices in guideline development. A detailed synthesis of the evidence from which these recommendations were formulated can be found in the accompanying Technical Review (TR).[5]

Guideline Panel Composition and Conflict of Interest

Members of the Guideline Panel and Technical Review Panel were selected by the AGA Governing Board and Clinical Guidelines Committee based on their clinical and methodological expertise with careful consideration of all National Academy of Medicine standards for trustworthy guidelines. The multidisciplinary team included transplant and non–transplant hepatologists, general gastroenterologists, a medical oncologist, a pharmacist, and guideline methodologists with expertise in GRADE. A patient representative was also included in the development of the guideline and review process. Panel members disclosed all potential conflicts of interest. Conflicts were managed according to AGA policies. The guideline methodologists and chairs had no conflicts of interest. No Guideline Panel member was excused from participation in the process owing to disqualifying conflict. A full list of conflicts can be accessed at AGA's National Office in Bethesda, MD.

Formulation of Clinical Questions and Determining Outcomes of Interest

A protocol was developed *a priori* by the TR Panel to guide the systematic review. The PICO format was used to outline the specific patient population (P), intervention (I), comparator (C), and outcomes (O) for each clinical question. The panel selected desirable (benefits) and undesirable (harms) patient-important outcomes and summarized the evidence for the following medications approved by the FDA for HCC: first-line therapies: bevacizumab+atezolizumab, sorafenib, and lenvatinib; second-line therapies: cabozantinib, pembrolizumab, ramucirumab, and regorafenib; and other agents: bevacizumab, nivolumab, and nivolumab+ipilimumab. The following outcomes were considered critical or important: overall mortality, HCC-related mortality, health-related quality of life (QoL), disease progression (or recurrence), progression (or recurrence)-free survival, harms (serious adverse events [SAEs] and/or treatment discontinuation due to adverse events), and cost or resource use.

Evidence Review and Development of Recommendations

For each guideline question, the TR Panel created an evidence profile and Evidence to Decision tables. The certainty in the body of evidence was assessed for each effect estimate of the outcomes of interest following the GRADE approach based on the following domains: risk of bias, imprecision, inconsistency and magnitude of the estimates of effects, indirectness of the evidence, risk of publication bias, presence of large effects, dose–effect relationship, and an assessment of the effect of plausible residual and opposing confounding. The certainty was categorized into 4 levels ranging from very low to high (Table 1).

The Guideline Panel and the authors of the TR met virtually on June 11, 2021. During this virtual meeting, the Guideline Panel developed recommendations based on the evidence summarized in the Evidence to Decision tables. For each recommendation, the Panel took a population perspective and reached consensus on the following: certainty of evidence (CoE); balance of benefits and harms; and assumptions about the values and preferences associated with the decision, health equity, acceptability, and feasibility. The Guideline Panel did not explicitly incorporate cost or cost-effectiveness. The panel agreed on the recommendations (including direction and strength), remarks, and qualifications by consensus.

Interpretation of Strong and Conditional Recommendations

The CoE and the strength of recommendation are provided for each clinical question. The recommendations are labeled as "strong" or "conditional" according to the GRADE approach. The words "the guideline panel recommends" are used for strong recommendations, and "the guideline panel suggests" for conditional recommendations. Table 2 provides GRADE's interpretation of strong and conditional recommendations by patients, clinicians, health care policy makers, and researchers.

Review Process

Draft recommendations were reviewed by all members of the panel and the guideline and accompanying TR were made available online for a 14-day, open, public comment period. All comments were reviewed and carefully considered by the Guideline Panel and TR Panel, respectively. Changes were incorporated in revised documents and when changes were not accepted, an internal response document was created. The document was revised to address pertinent comments and minor changes were made to the recommendations. The TR and Guideline also underwent independent peer review and were approved by the AGA Governing Board.

How to Use This Guideline

This Guideline is not intended to impose a standard of care. Rather, it provides the basis for rational informed decisions for patients and health care professionals. Statements regarding the underlying values and preferences, as well as qualifying remarks accompanying each recommendation, should never be omitted when quoting or translating recommendations from

Table 1. Interpretation of the Certainty in Evidence of Effects Using the Grading of Recommendations, Assessment, Development and Evaluation Framework

Certainty	Description
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

this guideline. Recommendations provide guidance for typical patients; no recommendation can take into account all of the unique individual circumstances that must be considered when making recommendations for individual patients. However, discussions around benefits and harms can be used for shared decision making, especially for conditional recommendations when it is important to consider patients' values.

Recommendations

See Table 3 for a summary of recommendations.

First-Line Treatment for Hepatocellular Carcinoma in Individuals With Preserved Liver Function

Recommendation: In patients with HCC with preserved liver function not eligible for LRT or resection or with metastatic disease, the AGA suggests atezolizumab+bevacizumab over sorafenib. *Conditional recommendation, low certainty evidence.*
Comment: Gastrointestinal bleeding is a known adverse effect of bevacizumab and individuals should undergo endoscopic evaluation and treatment for esophageal varices before treatment.

The AGA suggests atezolizumab+bevacizumab over sorafenib in patients with advanced HCC (who are not eligible for LRT or resection or metastatic disease) and preserved liver function. The TR identified 1 study, the IMBrave150 trial,[6] which showed superiority of the combination of the immune checkpoint inhibitor (anti–programmed death ligand-1 antibody) atezolizumab (1200 mg intravenously [IV] once every 3 weeks) and the anti-angiogenic agent (anti–vascular endothelial growth factor antibody) bevacizumab (15 mg/kg IV every 3 weeks) over sorafenib (400 mg twice daily, orally) in individuals with HCC who had not previously had systemic therapy. The trial excluded individuals with a history of autoimmune diseases, allogeneic stem cell or solid organ transplantation, idiopathic pulmonary fibrosis or pneumonitis, co-infection with hepatitis B or hepatitis C viruses, and untreated or incompletely treated esophageal or gastric varices with bleeding or high risk for bleeding. Trial participants had to undergo endoscopic evaluation and treatment for varices before enrollment. This open-label study was limited to individuals with preserved liver function—99% of participants were Child-Turcotte-Pugh (CTP) A—and to individuals with good functional status, with Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 in 62.5% of participants and ECOG PS 1 in 27.5%. Most participants (81.5%) were at Barcelona Clinic Liver

Table 2. Interpretation of Strong and Conditional Recommendations Using the Grading of Recommendations Assessment, Development and Evaluation Framework

Recommendation	For patients	For clinicians
Strong	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.
Conditional	The majority of individuals in this situation would want the suggested course of action, but many would not.	Different choices will be appropriate for individual patients consistent with their values and preferences. Decision aids may be useful in helping patients make decisions consistent with their individual risks, values, and preferences. Clinicians should expect to spend more time with patients when working toward a decision.

Table 3. Executive Summary of Recommendations[a]

Recommendations	Strength of recommendation	Certainty of evidence
1. First-line treatment for HCC in patients with preserved liver function		
In patients with HCC with preserved liver function not eligible for LRT or resection or with metastatic disease, the AGA suggests atezolizumab+bevacizumab over sorafenib.	Conditional	Low
Comment: Gastrointestinal bleeding is a known adverse effect of bevacizumab and individuals should undergo endoscopic evaluation and treatment for esophageal varices before treatment.		
In patients with HCC with preserved liver function not eligible for LRT or resection or with metastatic disease who are not candidates for treatment with atezolizumab+bevacizumab, the AGA suggests either lenvatinib or sorafenib over no systemic therapy.	Conditional	Low
Comments: Patients who place a higher value on delayed radiologic disease progression and lower value on the increase in adverse events (both serious and leading to discontinuation of the drug) may reasonably choose lenvatinib over sorafenib. Patients who place a higher value on blood pressure control and a lower value on the adverse skin reactions would reasonably select sorafenib over lenvatinib. It should be noted that lenvatinib has not been studied in patients with invasion of the main portal vein and thus may not be appropriate for this population. Patients who place a higher value on the adverse events associated with sorafenib or lenvatinib and lower value on the reduction in mortality (2.8 mo for sorafenib, unknown for lenvatinib) may reasonably select no systemic therapy.		
2. Second-line treatment for individuals with disease progression or intolerance to first-line systemic therapy		
In patients with HCC with preserved liver function not eligible for LRT or resection or with metastatic disease, who had progression of disease on sorafenib, the AGA suggests cabozantinib over no systemic therapy.	Conditional	Very low
Comment: Patients who place a higher value on adverse effects associated with cabozantinib and lower value on the reduction in mortality (2.2 mo) may reasonably decline cabozantinib.		
In patients with HCC with preserved liver function not eligible for LRT or resection or with metastatic disease, and who had progression of disease on sorafenib, the AGA suggests using pembrolizumab over no systemic therapy.	Conditional	Low
Comments: Patients who place a higher value on adverse effects associated with pembrolizumab and lower value on the reduction in mortality (3.3 mo) may reasonably decline pembrolizumab. Patients with main portal vein invasion or inferior vena cava or cardiac involvement of HCC on the basis of imaging were not studied.		
In patients with HCC with preserved liver function and AFP >400 ng/mL not eligible for LRT or resection or with metastatic disease who had progression of disease on sorafenib, the AGA suggests using ramucirumab over no systemic therapy.	Conditional	Low
Comments: Patients who place a higher value on adverse effects associated with ramucirumab and lower value on the reduction in mortality (1.2 mo) may reasonably decline ramucirumab. In patients with AFP < 400 ng/mL, the AGA suggests against the use of ramucirumab.		
In patients with HCC with preserved liver function not eligible for LRT or resection or with metastatic disease, who had progression of disease on sorafenib, the AGA suggests regorafenib over no systemic therapy.	Conditional	Low

Table 3. Continued

Recommendations	Strength of recommendation	Certainty of evidence
Comment: Patients who place a higher value on adverse effects associated with regorafenib and lower value on the reduction in mortality (2.8 mo) may reasonably decline regorafenib. Regorafenib should not be used in patients who did not tolerate sorafenib due to toxicity.		
3. Systemic therapy for HCC in patients with poor liver function		
In patients with HCC with poor liver function not eligible for LRT or resection or with metastatic disease, the AGA suggests against routine use of sorafenib.	Conditional	Very low
Comment: Patients, particularly those who are not CTP C, who place a higher value on the uncertain reduction in mortality and lower value on the harms, may reasonably select to use sorafenib.		
4. Systemic therapy for HCC as adjuvant therapy		
In patients with HCC undergoing curative surgical resection, the AGA suggests against adjuvant sorafenib therapy.	Conditional	Low
In patients with HCC undergoing curative local ablation, the AGA suggests against adjuvant sorafenib therapy.	Conditional	Low
In patients with HCC undergoing TACE LRT, the AGA suggests against adjuvant sorafenib therapy.	Conditional	Very low
In patients with HCC undergoing TACE LRT the AGA suggests against adjuvant bevacizumab therapy.	Conditional	Very low

[a]Please see the accompanying Technical Review[5] for supporting evidence.

Cancer (BCLC) stage C, but earlier-stage diseases were also included, with 15% at BCLC stage B and 3% at BCLC stage A. Median overall survival (OS) was 19.2 months in the atezolizumab+bevacizumab group vs 13.4 months in the sorafenib group, and was consistent with an improvement in progression-free survival (PFS). Although participants were randomized to each treatment arm, neither the participants nor the investigators were blinded, which could have affected the decision to continue treatment and introduced bias. Furthermore, the lack of blinding could also differentially affect the choice of post-protocol therapies in the post-discontinuation period, which could affect survival, as this was not regulated. Deterioration of QoL was reported using the European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life of Cancer Patients questionnaire. Deterioration was slower in the atezolizumab+bevacizumab group compared with the sorafenib group. However, the risk of bias was very serious, as neither participants nor investigators were blinded to the treatment arm and the number of participants who completed the QoL questionnaire was not clear; 93% completed it by week 51, but the 7% of participants with missing values might have changed the direction of effect in the confidence interval (CI). Although more adverse events and discontinuations due to adverse events were reported in the atezolizumab+bevacizumab group, the difference was not considered significant, as there was evidence of serious imprecision. It should be noted that gastrointestinal bleeding is a known adverse effect of bevacizumab and all participants had to have endoscopic evaluation and treatment for esophageal varices before treatment. With this practice, the incidence of gastrointestinal bleeding was 7% in the atezolizumab+bevacizumab group vs 4.5% in the sorafenib group.

Recommendation: In patients with HCC with preserved liver function not eligible for LRT or resection or with metastatic disease who are not candidates for treatment with atezolizumab+bevacizumab, the AGA suggests either lenvatinib or sorafenib over no systemic therapy. *Conditional recommendation, low certainty evidence.*

Comments: Patients who place a higher value on delayed radiologic disease progression and lower value on the increase in adverse events (both serious and leading to discontinuation of the drug) may reasonably choose lenvatinib over sorafenib. Patients who place a higher value on blood pressure control and a lower value on the adverse skin reactions may reasonably select sorafenib over lenvatinib. It should be noted that lenvatinib has not been studied in patients with invasion of the main portal vein and thus may not be appropriate for this population. Patients who place a higher value on the adverse events associated with sorafenib or lenvatinib and lower value on the reduction in mortality (2.8 months for sorafenib, unknown for lenvatinib) may reasonably select no systemic therapy.

The AGA suggests either lenvatinib or sorafenib for patients with advanced HCC and preserved liver function. The TR identified 2 randomized controlled trials (RCTs) of the multi-tyrosine kinase inhibitor sorafenib (400 mg twice daily orally) vs placebo in individuals with advanced HCC who did not receive prior systemic therapy: the Sorafenib Hepatocellular Carcinoma Assessment Randomised Protocol trial[7] and a trial conducted in the Asia-Pacific region.[8] All

participants had preserved liver function; 95%–98% were CTP A and 2%–5% CTP B. No participants in the studies were CTP C. The majority had good functional status, with 25%–54% at ECOG PS 0, 38%–69% at ECOG PS 1, and only 2%–8% at ECOG PS 2. The participants were at BCLC stage B in 17%–18% of cases or at stage C in 82%–96.1%. Median OS was improved in both trials with use of sorafenib compared with placebo (10.7 vs 7.9 months and 6.5 vs 4.2 months in Sorafenib Hepatocellular Carcinoma Assessment Randomised Protocol and Asia-Pacific trials, respectively). The discrepancy in OS durations between the 2 trials was postulated to be due to differences in patient populations (etiology of HCC, worse disease, and PS). Similar improvements were seen in disease progression across the 2 studies, with a median increase of 2.7 and 1.4 months in sorafenib vs placebo for time to progression (TTP). In the Asia-Pacific study,[8] TTP was determined by a composite of radiological or (subjective) symptomatic progression. Lack of reporting or blinding for post-protocol therapies (treatment after discontinuation of the study drug), which can affect OS, was noted as a risk for bias.

Although survival and progression of disease were improved, few data were found regarding the effect on QoL. One study[8] reported that both treatment and placebo groups had similar QoL, but the details and results of the survey were not presented, and numbers were relatively small. There did not appear to be a difference with regard to SAEs, with high adverse event rates in both placebo and sorafenib groups (50.2%–52.5%). The TR identified 1 open-label RCT of the multi-kinase inhibitor lenvatinib (12 mg/d for $\geq$60 kg patient and 8 mg/d $<$60 kg, orally) vs sorafenib (400 mg twice daily, orally) for the treatment of patients with advanced HCC.[9] This study, known as the REFLECT trial, was powered for noninferiority and showed equal efficacy between lenvatinib and sorafenib, with median OS of 13.6 vs 12.3 months, respectively. As in previous studies, nearly all participants had preserved liver function (99% were CTP A) and good functional status (63% were ECOG PS 0 and 37% ECOG PS 1). Risk of bias was serious in the assessment of impact on OS, as the lack of blinding could theoretically lead to differences in treatments during the post-progression survival period. Although OS was not different between lenvatinib and sorafenib, median PFS was longer with lenvatinib at 7.4 vs 3.7 months. Serious risk of bias was noted for the mortality data due to the lack of reporting for post-protocol therapies and blinding after discontinuation of study drug. Progression was measured radiologically using the modified Response Evaluation Criteria in Solid Tumors.[10] In contrast to radiologic progression, there were more SAEs and a higher rate of discontinuation due to adverse events in the lenvatinib arm. However, the risk of bias was serious, as there was no blinding of participants or investigators. Investigators were responsible for determining whether adverse events were related to the treatment or not. Furthermore, there was serious imprecision due to the relatively small number of SAEs requiring discontinuation. Although lenvatinib and sorafenib have very similar adverse effect profiles, there was a tendency for more hypertension with lenvatinib and more skin toxicity with sorafenib; this information may be helpful when determining choice of multi-kinase inhibitor therapy for individual patients. In addition, for this study, patients with $>$50% liver involvement and main portal vein invasion were explicitly excluded. Lenvatinib, therefore, has not been studied in patients with main portal vein invasion.

QoL was examined using the EORTC Quality of Life of Cancer Patients Questionnaire version 3 and Hepatocellular Carcinoma questionnaires. These questionnaires showed similar baseline scores, which declined in both groups. The time to decline was observed earlier in patients in the sorafenib arm, but the summary score for between-group comparisons was not significantly different.[9]

Other Agents

Although the TR did identify an RCT comparing another immune checkpoint inhibitor, nivolumab (anti–programmed death ligand-1 antibody), with sorafenib as primary therapy for HCC, this study, known as CheckMate 459, has only been published in abstract form[11] and insufficient data are available to allow an assessment of the CoE, which would be required for guideline formulation.

Second-Line Treatment for Individuals With Disease Progression or Intolerance to First-Line Systemic Therapy

In individuals who fail first-line systemic therapy but continue to have preserved liver function, several options can be considered. It should be noted that the majority of the trials were conducted in participants who had disease progression or intolerance to sorafenib and not lenvatinib or atezolizumab+bevacizumab. At this time there are no comparative studies among approved second-line therapies to guide decision making on a first option for second-line treatment. Therefore, the different therapies are discussed below in alphabetical order.

Recommendation: In patients with HCC with preserved liver function not eligible for LRT or resection or with metastatic disease who had progression of disease on sorafenib, the AGA suggests cabozantinib over no systemic therapy. *Conditional recommendation, very low certainty evidence.*

Comment: Patients who place a higher value on adverse effects associated with cabozantinib and lower value on the reduction in mortality (2.2 months) may reasonably decline cabozantinib.

The AGA suggests cabozantinib over no systemic therapy for patients with advanced HCC and preserved liver function who received prior treatment that included sorafenib and had disease progression after at least 1 but no more than 2 prior lines of therapy. The TR identified 1 international RCT, the CELESTIAL trial,[12] which examined cabozantinib (60 mg once daily, orally) vs placebo in individuals with preserved liver function who have progressed on sorafenib.

Participants were predominantly CTP A (99%) and ECOG PS 0/1 (53.5%/44.5%). There was significant improvement in OS, with median survival of 10.2 months in the cabozantinib group compared with 8.0 months in the placebo group. Indirect evidence for an effect on mortality was also demonstrated with improvement in PFS. However, the CoE was downgraded because of an imbalance in post-protocol treatments, which can affect overall mortality. QoL data were not reported, but we examined the rate of adverse events leading to treatment discontinuation as an indirect assessment of possible important impact on QoL. We found significantly higher rates of SAEs in the cabozantinib group than in the placebo group (49.7% vs 21%, respectively) as well a higher rate of discontinuation due to adverse events in the cabozantinib group (21% vs 4.6%). These results indirectly suggest high uncertainty about the effect of cabozantinib on QoL, with concern for worsening of quality in patients treated with cabozantinib.

Recommendation: In patients with HCC with preserved liver function not eligible for LRT or resection or with metastatic disease, and who had progression of disease on sorafenib, the AGA suggests using pembrolizumab over no systemic therapy. *Conditional recommendation, low certainty evidence.*
Comments: Patients who place a higher value on adverse effects associated with pembrolizumab and lower value on the reduction in mortality (3.3 months) may reasonably decline pembrolizumab. Patients with main portal vein invasion or inferior vena cava or cardiac involvement of HCC on the basis of imaging were not studied.

The AGA suggests pembrolizumab over no systemic therapy for patients with preserved liver function and advanced HCC who have progressed on sorafenib. The TR identified 1 international RCT, KEYNOTE-240,[13] in which participants were randomized to pembrolizumab (200 mg IV every 3 weeks) or placebo. Participants were predominantly CTP A (99%) and ECOG PS 0 (56%). The remainder were CTP B (1%) and ECOG PS 1 (44%). Individuals who had received prior immunotherapy or previous systemic therapy other than sorafenib and those with main portal vein invasion or inferior vena cava or cardiac involvement were excluded. Median OS was improved in the pembrolizumab group compared with the placebo group (13.9 vs 10.6 months, respectively). Similar improvements were seen in the surrogate markers of mortality, including PFS and TTP. However, the CoE was downgraded due to concerns of serious risk of bias resulting from unclear blinding and selection for post-protocol therapy, as well as imprecision due to the low event rate. QoL was not different between the 2 groups, but there is concern for the quality of data due to a low survey completion rate of 68%. SAEs were reported in 37.3% and 27.6% of participants in the pembrolizumab and placebo groups, respectively (hazard ratio [HR], 1.35). The rate of discontinuation due to adverse events was significantly higher in the pembrolizumab group (17.2%) than in the placebo group (9.0%).

Recommendation: In patients with HCC with preserved liver function and α-fetoprotein (AFP) >400 ng/mL not eligible for LRT or resection or with metastatic disease who had progression of disease on sorafenib, the AGA suggests using ramucirumab over no systemic therapy. *Conditional recommendation, low certainty evidence.*
Comments: Patients who place a higher value on adverse effects associated with ramucirumab and lower value on the reduction in mortality (1.2 months) may reasonably decline ramucirumab. In patients with AFP <400 ng/mL, the AGA suggests against the use of ramucirumab.

The AGA suggests ramucirumab over no systemic therapy for patients with advanced HCC with preserved liver function and AFP >400 ng/mL who have had disease progression on sorafenib. The TR identified 2 international RCTs, REACH[14] and REACH-2,[15] which examined ramucirumab (a vascular endothelial growth factor receptor 2 antagonist; 8 mg/kg IV every 2 weeks) vs placebo. In both trials, all participants were CTP A and ECOG PS 0 or 1. A protocol change in the REACH study excluded CTP B patients after initiation of the trial, possibly contributing to a risk of bias. This study also did not show improvement in mortality with ramucirumab. However, in a post-hoc analysis, significant improvement in OS was noted in the subgroup of individuals with AFP >400 ng/mL. The REACH-2 trial followed up on these findings with recruitment of only CTP A participants with AFP >400 ng/mL. This subgroup of participants with high AFP showed a median OS of 8.5 months when given ramucirumab vs 7.3 months for placebo. Similarly, indirect evidence for improved OS was seen with improved PFS and decreased TTP. The CoE was decreased due to serious risk of bias resulting from unclear continued blinding for post-protocol therapies, high attrition rate, and early stopping of the protocol for benefit. Although stopping for benefit occurred in other studies, there was particular concern for bias in this study due to the relatively small sample size.[16] QoL and time to deterioration were similar in both the ramucirumab and placebo groups. SAEs were reported in both groups. In REACH-2,[15] SAEs were reported at a rate of 34.5% and 29.5% in the ramucirumab and placebo groups, respectively. In the REACH trial,[14] the rate of SAEs was significantly higher in the ramucirumab group than in the placebo group (44.0% vs 32.2%).

Recommendation: In patients with HCC with preserved liver function not eligible for LRT or resection or with metastatic disease, who had progression of disease on sorafenib, the AGA suggests regorafenib over no systemic therapy. *Conditional recommendation, low certainty evidence.*
Comments: Patients who place a higher value on adverse effects associated with regorafenib and lower value on the reduction in mortality (2.8 months) may reasonably decline regorafenib.

The AGA suggests regorafenib over no systemic therapy for patients with advanced HCC and preserved liver function

who had disease progression on sorafenib. The TR identified 1 RCT, the multinational RESORCE study,[17] comparing regorafenib (160 mg/d for 3 weeks in a 4-week cycle, orally) to placebo in individuals with advanced HCC who progressed on sorafenib. Similar to the previous studies, participants had to have preserved liver function at enrollment (98% were CTP A and 2% were CTP B) and good functional status (66% were ECOG PS 0 and 34% were ECOG PS 1). There were no patients with CTP C or ECOG PS >1, and all participants had to have tolerated a total daily sorafenib dose of at least 400 mg. There was significant improvement in mortality in the regorafenib group, with a median OS of 10.6 months vs 7.8 months in the placebo group. High but comparable rates of adverse events were reported in both groups, with SAEs reported in 44.4% of participants in the regorafenib group compared with 46.6% in the placebo group. However, adverse effects requiring dose reductions or interruptions attributed to drug effect were higher in the regorafenib group than in the placebo group (54% vs 10%, respectively), although the ascertainment method was not clear. Most importantly, no clinically important differences in QoL were noted.

Other Systemic Therapies

Additional systemic therapies considered by the TR for second-line therapy in patients who failed first-line systemic therapy included nivolumab in combination with the anti-cytotoxic T lymphocyte antigen 4 antibody, ipilimumab. Although the combination has received FDA approval as a second-line therapy in patients with advanced HCC treated previously with sorafenib,[18] this decision was based on the phase 1/2 open-label CheckMate 040 study,[19] which evaluated multiple different dose combinations of nivolumab and ipilimumab. Because the trial did not compare any of the interventions with placebo, best supportive care, or previously established treatments, it did not inform any of the PICO questions and was insufficient for guideline development.

Most notably, the TR did not identify any trials that evaluated the use of atezolizumab+bevacizumab as second-line therapy in patients who failed prior multi-kinase inhibitors, such as sorafenib or lenvatinib. Furthermore, there were no available trials that evaluated multi-kinase inhibitors or immunotherapy as second-line therapy after failure with the atezolizumab+bevacizumab combination.

Systemic Therapy for Hepatocellular Carcinoma in Patients with Poor Liver Function

Recommendation: In patients with HCC with poor liver function not eligible for LRT or resection or with metastatic disease, the AGA suggests against routine use of sorafenib. *Conditional recommendation, very low certainty evidence.*
Comment: Patients, particularly those who are not CTP C, who place a higher value on the uncertain reduction in mortality and lower value on the harms, may reasonably select to use sorafenib.

The AGA suggests against routine use of sorafenib in patients with advanced HCC and poor liver function. Most systemic therapy studies in advanced HCC explicitly excluded individuals with poor liver function. In most prior RCTs, 99% of participants were CTP A.[9] The highest percentage of non–CTP A patients was found in the initial trials of sorafenib vs placebo.[7,8] Even in these studies, only 2%–5% of patients were CTP B and none were CTP C. The TR group found 1 RCT that examined sorafenib in CTP B/C patients.[20] In this open-label study, 189 patients were randomized to oral sorafenib 400 mg twice daily or to best supportive care. Three-quarters (75%) of the patients were CTP B and 25% were CTP C. Although an improvement in mortality was seen (HR, 0.48), the median OS was very poor: 4 months in the sorafenib group and 3.5 months in the best supportive care group. Risk of bias was high, given the lack of blinding and an unclear allocation concealment. For harms, only discontinuation related to adverse events was reported. The reported discontinuation rate of 2.2% with sorafenib was very low compared with prior studies, which reported rates of approximately 31.8%.[7,8] The TR Panel did not identify any RCT that evaluated the use of agents other than sorafenib in patients with poor liver function.

Systemic Therapy for Hepatocellular Carcinoma as Adjuvant Therapy

In addition to systemic therapy for advanced HCC, we also explored its efficacy for use as concurrent, adjuvant, or neoadjuvant therapy with other modalities including surgery and LRT.

Adjuvant therapy following surgical resection.

Recommendation: In patients with HCC undergoing curative surgical resection, the AGA suggests against adjuvant sorafenib therapy. *Conditional recommendation, low certainty evidence.*

The AGA suggests against adjuvant sorafenib for patients with HCC undergoing curative surgical resection. The authors of the TR could not identify any RCT that addressed the role of systemic therapy as concurrent or neoadjuvant therapy, but did identify 1 international RCT, the STORM trial,[21] that reported data on individuals with HCC who were randomized to sorafenib (400 mg twice per day, orally) vs placebo starting 6–12 weeks after curative treatment, which consisted of either surgical resection (n = 900) or local ablation (n = 214). Inclusion criteria for surgical resection included individuals with a single lesion of any size, CTP score ≤ B7 without ascites, ECOG PS 0, and AFP level <400 ng/mL. Risk of recurrence was assessed based on tumor characteristics on pathology and only participants at intermediate or high risk of recurrence were included. There was no difference in mortality for participants treated with sorafenib vs placebo (HR, 0.995; 95% CI, 0.76–1.30). Similarly, the HRs for recurrence-free survival (0.94; 95% CI, 0.76–1.16) and disease recurrence (0.89; 95% CI, 0.74–1.08) were not affected by treatment with sorafenib. CoE was downgraded due to concerns about the indirectness of

the data, as participants included in the mortality and disease recurrence end points underwent either resection or ablation and imprecision.

The STORM investigators reported no difference in SAEs, which affected 40.7% of participants in the sorafenib group and 41.2% in the placebo group. However, a strong signal for harms was estimated by assessing discontinuation rates due to adverse events, which amounted to 24.1% in the sorafenib group and 7.4% in the placebo group.[21]

Adjuvant therapy before liver transplantation. In addition to surgical resection, the TR sought to evaluate systemic therapy in patients with HCC undergoing liver transplantation; however, the studies identified were not sufficient for making a recommendation. These included 2 RCTs that used sorafenib in patients awaiting transplantation. One RCT[22] compared the combination of sorafenib and TARE with Y-90 vs TARE alone. This study reported 3-year survival data in a population of only 23 individuals with cirrhosis and HCC. Inclusion criteria used the University of California, San Francisco size criteria[23] (solitary tumor $\leq$6.5 cm or $\leq$3 nodules with the largest lesion $\leq$4.5 cm and total tumor diameter $\leq$8 cm) and liver disease up to CTP B 7. Median time to transplantation was similar between the 2 groups. The overall 3-year survival rate was 72% in the combination group vs 70% in the Y-90-alone group. There were no recurrences in either group at 3 years; the risk of harm was likely higher in the sorafenib arm, based on a 50% discontinuation rate due to adverse effects.[22]

A second study[24] examined sorafenib vs no sorafenib as neoadjuvant therapy in patients undergoing TACE treatment while listed for liver transplantation. This study reported data on only 50 participants. Outcomes included PFS, which was associated with HR of 1.26 (95% CI, 0.48–3.27), raising serious and very serious concerns about data indirectness and imprecision, respectively. Seven participants in each group developed tumor progression at a median of 71 days in the sorafenib group vs 85 days in the no sorafenib group, with HR of 1.11 (95% CI, 0.39–3.16). There was no significant difference in the rate of SAEs or in the rate of discontinuation due to adverse events, although there were very serious concerns regarding imprecision.

Adjuvant or concurrent therapy with locoregional therapy. The TR identified 2 studies that evaluated the role of sorafenib as adjuvant therapy after curative local ablation therapy, and 7 studies of either sorafenib or bevacizumab as concurrent therapy for patients undergoing TACE.

Recommendation: In patients with HCC undergoing curative local ablation, the AGA suggests against adjuvant sorafenib therapy. *Conditional recommendation, low certainty evidence.*

The AGA suggests against adjuvant sorafenib in patients undergoing curative ablation therapy. The TR identified only 1 RCT, the STORM trial[21] (discussed previously), that addressed curative ablation therapy. Only a minority of the participants in this study had local ablation as the treatment (n = 214). Within the local ablation group, a participant could have either radiofrequency ablation or percutaneous ethanol injection as the treatment, followed by either sorafenib or placebo given 6–12 weeks after the curative treatment. Maximal tumor burden allowed could not exceed Milan Criteria, defined as 1 lesion $\leq$5 cm or 3 lesions $\leq$3 cm. As noted above there were no significant differences in mortality, recurrence-free survival, or disease recurrence, but the data are shown for the combined group, leading to serious concerns regarding indirect comparisons and imprecision of the data.

Recommendation: In patients with HCC undergoing TACE LRT, the AGA suggests against adjuvant sorafenib therapy. *Conditional recommendation, low certainty evidence.*

The AGA suggests against the use of sorafenib in conjunction with TACE for the treatment of patients with HCC. The TR identified 5 RCTs with a total of 1284 patients.[24–28] The combined HR for mortality was 0.92 (95% CI, 0.76–1.10) in 4 of the trials, which compared 620 patients treated with sorafenib vs 614 not treated after treatment with TACE.[25–28] The fifth RCT, the HeiLivCa trial,[24] examined sorafenib after TACE in patients awaiting liver transplantation, but did not report on OS and thus was not included for this outcome.

Among the 4 trials that reported rates of PFS in 519 patients (with follow-up ranging from 23 to 28 months), 1 study[27] demonstrated improvement in the sorafenib+TACE combination arm, compared with TACE alone (HR, 0.66; 95% CI, 0.47–0.94). The other 2 studies[24,25] showed comparable PFS rates (HR, 0.99 and 1.3, respectively). All 5 RCTs reported on rate of disease progression, with disparate results: 1 study, the TACTICS trial,[27] demonstrated a strong effect of combination sorafenib+TACE therapy vs TACE alone (HR, 0.54), with median TTP of 22.8 vs 13.5 months, respectively. The results of the remaining studies were less optimistic; a study in Japanese and Korean patients[28] reported a median TTP of 5.4 vs 3.7 months; a third study[26] reported a median TTP of 5.6 vs 5.5 months; and the TACE 2 trial[25] reported a median TTP of 10.9 vs 10.7 months. One trial[24] reported a higher rate of progression in the sorafenib+TACE combination arm, with a median TTP of 2.4 vs 2.8 months.

QoL was assessed in the TACE 2 trial[25] with the use of the EORTC Quality of Life of Cancer Patients Questionnaire version 3; EORTC Quality of Life Questionnaire for Hepatocellular Carcinoma; and European Quality of Life 5 Dimensions (EQ–5D) questionnaires. Among the 313 participants who were sent surveys, there were significantly lower social/role functioning scores in the sorafenib group (approximately 6%) compared with the placebo group, as well as up to a 13% higher average diarrhea score, up to a 10% higher mean appetite loss score, and up to a 7% worse mean nutritional problem score. Overall, there was low CoE due to a number of issues in the 5 TACE studies summarized herein, including lack of blinding, questions of allocation concealment, and unmasking at the time of progression based on investigator's assessment rather than central review, as well as indirectness, and imprecision.[24–28]

Rates of SAEs were reported in 4 trials,[24–26,28] with a statistically higher rate in the combination arms compared with placebo (35.2% vs 23.2%, respectively) and HR of 1.48. Estimating harms based on rates of discontinuation due to adverse events was possible in 3 trials,[25,26,28] with a higher discontinuation rate in the combination arms than in the placebo arms (21.3% vs 11.8%, respectively) and HR of 1.81.

Recommendation: In patients with HCC undergoing TACE LRT, the AGA suggests against adjuvant bevacizumab therapy. *Conditional recommendation, very low certainty evidence.*

The AGA suggests against the use of bevacizumab in conjunction with TACE for the treatment of patients with HCC. The TR identified 2 RCTs[29,30] with a total of 62 patients randomized to bevacizumab+TACE vs placebo or observation+TACE. The first study[29] randomized 30 CTP A and B participants with HCC undergoing TACE to placebo or bevacizumab (10 mg/kg IV every 14 days, beginning 1 week before TACE); TACE was repeated at weeks 10 and 14. Participants randomized to TACE alone were allowed to crossover after week 16 if they had developed disease progression. Although the primary end point was not survival, the study found no statistically significant difference in median OS in the TACE+observation group compared with the TACE+bevacizumab group. The crossover design limited the ability to draw conclusions regarding efficacy. There was evidence of improvement in PFS over a median follow-up of 16 weeks in participants who were randomized to the observation TACE+observation arm (19%) compared with the TACE+bevacizumab group (79%), with HR of 4 (95% CI, 1.4–11.3). Median OS was 61 months in the TACE+observation group and 49 months in the TACE+bevacizumab group. There was a very low overall CoE, based on serious risk of bias and indirectness and very serious risk of imprecision. The authors reported rates of discontinuation due to adverse events, but noted only 1 event in the TACE+bevacizumab arm, and none in the TACE+observation group.

The second study[30] randomized 32 CTP A and B participants to either TACE with doxorubicin or TACE+doxorubicin along with bevacizumab (5 mg/kg IV every 14 days); participants had BCLC A and B disease and were either treatment-naïve or had recurrent disease after resection or ablation. The trial was stopped early after finding a worse OS in the combination group compared with the placebo group, with a median survival of 5.3 vs 13.7 months, respectively. There was a substantial increase in harms in the TACE+doxorubicin+bevacizumab group compared with the TACE+doxorubicin group. There were serious concerns regarding the risk of bias, inconsistency, and imprecision, leading to a very low overall CoE.

Health Equity Considerations

The TR Panel conducted a search to identify studies that assessed the potential impact of different treatments on health equity and disparities, but no studies were identified. However, due to the significant cost of the drugs evaluated, the Panel agreed that a negative impact on health equity could not be excluded.

Implementation

Implementation of this guideline may also be facilitated with the use of the accompanying Clinical Decision Support Tool[31] and Spotlight.[32] In addition, a table outlining the mechanism of action, indication, and additional considerations may help improve decision making (Table 4).

Limitations and Evidence Gaps

In the second-line setting, no high-quality direct comparative evidence is available for either atezolizumab+bevacizumab, sorafenib, or lenvatinib. However, patients who place a high value on the uncertain benefit of these agents as second-line therapies, and a low value on their adverse events, may reasonably select to use either atezolizumab+bevacizumab, sorafenib, or lenvatinib in this setting. Thus, ultimate decisions for treatment selection need to weigh patient preferences as well as risks and benefits. At the present time, there is limited information and few biomarkers to guide patient selection for different regimens; this remains an area of great importance for future research.

It should be noted that in all studies summarized herein, the clinical trials were limited to participants with preserved liver function. These were individuals with CTP A cirrhosis with good functional status, as indicated by ECOG PS scores of 1 or less. Patients with CTP C cirrhosis do not have any options for systemic therapy; future research in this area would be of great importance. In addition, the TR examined the question of systemic therapy as an adjuvant treatment and found no evidence to support its use at this time. With more treatments on the horizon, including single-agent and combination regimens, we anticipate the availability of additional options in the near future.

Summary

The advent of multiple new FDA-approved systemic therapies for HCC brings new hope to patients with advanced disease who are not candidates for curative treatments, such as liver resection, transplantation, and locoregional ablation, as well as noncurative LRTs, such as TACE and TARE. For more than a decade, the oral multikinase inhibitor sorafenib was the only approved systemic therapy for this patient population. However, in recent years, the IV combination of an anti-angiogenic agent with a checkpoint inhibitor (bevacizumab+atezolizumab) showed a small to moderate survival benefit over sorafenib in the primary treatment setting, increasing therapeutic options for patients. In addition, lenvatinib, another oral multikinase inhibitor, showed equivalence to sorafenib for primary treatment of advanced HCC. For second-line treatment of patients who failed sorafenib, multiple regimens, including the oral multi-kinase inhibitors cabozantinib and

Table 4. Implementation Table

Drug and indication	Mechanism of action	Dose	Limitations of the evidence	Implementation considerations
First-line treatment for individuals with HCC				
Atezolizumab+bevacizumab First-line agent in individuals with preserved liver function	Atezolizumab: Checkpoint inhibitor, anti-programmed death ligand-1 (anti–PD-L1) antibody Bevacizumab: Anti-angiogenic agent: anti–vascular endothelial growth factor (VEGF) antibody	Atezolizumab: 1200 mg IV every 3 wk Bevacizumab: 15 mg/kg IV every 3 wk	There are no data on efficacy and adverse events in individuals with Child Turcotte Pugh B or C. There are no studies reporting efficacy of atezolizumab+bevacizumab as second-line therapy in individuals with disease progression on sorafenib or lenvatinib.	Gastrointestinal bleeding is a known adverse effect of bevacizumab and individuals should undergo endoscopic evaluation and treatment for esophageal varices before treatment. Atezolizumab may not be appropriate in patients with prior autoimmune diseases, allogeneic stem cell or solid organ transplantation, idiopathic pulmonary fibrosis or pneumonitis, and co-infection with hepatitis B and hepatitis C viruses, as they were excluded from the IMBrave150 trial.[6]
Sorafenib First-line agent in individuals who are precluded from receiving atezolizumab+bevacizumab and have preserved liver function	Multi-tyrosine kinase inhibitor	400 mg oral twice daily	There are limited data on efficacy and adverse events in individuals with CTP B or C. There are no studies reporting efficacy of sorafenib as second-line therapy in individuals with disease progression on lenvatinib or atezolizumab+bevacizumab.	
Lenvatinib First-line agent in individuals who are precluded from receiving atezolizumab+bevacizumab and have preserved liver function	Multi-tyrosine kinase inhibitor	12 mg oral once daily, if weight $\geq$60 kg 8 mg oral once daily, if weight $<$60 kg	There are limited data on efficacy and adverse events in individuals with CTP B or C. There are no studies reporting efficacy of lenvatinib as second-line therapy in individuals with disease progression on sorafenib or atezolizumab+bevacizumab.	Lenvatinib has not been studied in individuals with HCC and invasion of the main portal vein.

Table 4. Continued

Drug and indication	Mechanism of action	Dose	Limitations of the evidence	Implementation considerations
Second-line treatment for individuals with disease progression or intolerance to sorafenib (listed in alphabetical order)				
Cabozantinib	Multi-tyrosine kinase inhibitor	60 mg orally once daily	There are limited data on efficacy and adverse events in individuals with CTP B or C. There are no studies reporting efficacy of cabozantinib as second-line therapy in individuals with disease progression on atezolizumab+bevacizumab or lenvatinib. There are no studies comparing the efficacy of different second-line treatments for HCC.	
Pembrolizumab	Checkpoint inhibitor, anti–PD-1 antibody)	200 mg IV every 3 wk	There are limited data on efficacy and adverse events in individuals with CTP B or C. Individuals who had received prior immunotherapy or systemic therapy other than sorafenib were excluded from the KEYNOTE-240 trial.[13] There are no studies reporting efficacy of pembrolizumab as second-line therapy in individuals with disease progression on atezolizumab+bevacizumab or lenvatinib. There are no studies comparing the efficacy of different second-line treatments for HCC.	Pembrolizumab may not be appropriate for individuals with invasion of the main portal vein or vena cava, as it has not been studied in this patient population. Pembrolizumab may not be appropriate as a second-line treatment in patients who received treatment with a PD-targeted agent (eg, atezolizumab or nivolumab) and had progressive disease or those who were intolerant to immunotherapy due to immune-related adverse events.

Table 4. Continued

Drug and indication	Mechanism of action	Dose	Limitations of the evidence	Implementation considerations
Ramucirumab	Vascular endothelial growth factor receptor 2 (VEGFR 2) antagonist	8 mg/kg IV every 2 wk	There are limited data on efficacy and adverse events in individuals with CTP B or C. There are no studies reporting efficacy of ramucirumab as second-line therapy in individuals with disease progression on atezolizumab+bevacizumab or lenvatinib. There are no studies comparing the efficacy of different second-line treatments for HCC.	Improvement in overall survival was only seen in individuals with AFP >400 ng/mL. Individuals should undergo endoscopic evaluation and treatment for esophageal varices before treatment.
Regorafenib	Multi-tyrosine kinase inhibitor	160 mg orally once daily on days 1–21 of each 28-day cycle	There are no studies reporting efficacy of regorafenib as second-line therapy in individuals with disease progression on atezolizumab+bevacizumab or lenvatinib. There are no studies comparing the efficacy of different second-line treatments for HCC.	Regorafinib may not be appropriate in individuals with if prior intolerance to or toxicity with sorafenib, as these patients were excluded from the RESORCE trial.[17] However, preliminary data from the ongoing REFINE[35] study showed that regorafenib may be tolerated in patients who did not tolerate sorafenib previously.

regorafenib, as well as the IV monoclonal antibody ramucirumab (anti–vascular endothelial growth factor and the checkpoint inhibitor pembrolizumab (anti-PD1), have shown some improvement in OS. In the case of ramucirumab, the effect was limited to individuals with serum AFP >400 ng/mL. Although most RCTs showed benefit in OS, the evidence was downgraded due to serious concern of bias. The majority of the trials continued treatment until disease progression (based on imaging studies) or the development of serious adverse events. In addition, the effects of post-protocol treatments (treatments received after the discontinuation of the trial interventions) were not considered in the design of any of the trials, and only a few trials performed post-hoc adjustments to account for those effects. Post-protocol treatments were administered after the trial treatment allocation was revealed, which may have influenced the decision regarding these treatments and led to differences in OS. Furthermore, differences in median OS were often modest and improvement in QoL was not clearly demonstrated.

The recommendations of this guideline are overall consistent with those from the American Society of Clinical Oncology[33] and the National Comprehensive Cancer Network,[34] with a few differences. The American Society of Clinical Oncology guidelines provide recommendations for second-line therapy in patients who received atezolizumab+bevacizumab as first-line treatment; however, we identified this as a knowledge gap in the absence of RCTs evaluating the role of other treatments as second-line therapies after first-line treatment with atezolizumab+bevacizumab. Similarly, the American Society of Clinical Oncology guidelines suggest using atezolizumab+bevacizumab or nivolumab as second-line treatments in patients who failed first-line sorafenib or lenvatinib treatment, a recommendation that we also identified as a knowledge gap due to lack of RCTs. The National Comprehensive Cancer Network guidelines list nivolumab as a preferred first-line therapy in certain circumstances, which we do not comment on because the CheckMate 459 trial has not been published, thus limiting our ability to assess the CoE. The National Comprehensive Cancer Network guidelines also list nivolumab+ipilimumab as another recommended subsequent-line regimen, which we do not include because the CheckMate 040 trial was a phase 1/2 study that did not compare nivolumab+ipilimumab to a treatment that was shown in RCTs to be superior to standard therapies.

Plans for Updating the Guideline

In accordance with the Clinical Guidelines Committee policies, all clinical guidelines are reviewed annually at the AGA Clinical Guidelines Committee meeting for new information. The next update for this guideline is anticipated in 3 years from publication.

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