

American Gastroenterological Association Clinical Practice Guideline on Systemic Therapy for Hepatocellular Carcinoma

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This document presents the official recommendations of the American Gastroenterological Association (AGA) on systemic therapy for hepatocellular carcinoma. The guideline was developed by the AGA's Clinical Practice Guideline Committee and approved by the AGA Governing Board. Development of this guideline and its accompanying technical review was fully funded by the AGA Institute with no additional outside funding.

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Conflicts of Interest:

Grace L. Su, MD has no relevant conflict to report.

Robert S. O'Shea has no relevant conflicts to report.

Abbreviations and acronyms: AGA: American Gastroenterological Association; GRADE: Grading of Recommendations Assessment, Development and Evaluation; RCT: randomized controlled trial

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Technical Review Panel: XXX

List of Abbreviations and Acronyms

HCC, hepatocellular carcinoma

AFP, alpha-fetoprotein

BCLC, Barcelona Clinic Liver Cancer

CTP score, Child Turcotte Pugh score

TACE, transarterial chemoembolization

TARE, transarterial radioembolization

FDA, Food and Drug Administration

PICO: population, intervention, comparator, and outcomes

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RCT, randomized controlled trial

RFA, radiofrequency ablation

HRQOL, health-related quality of life

SAE, serious adverse event

HR, hazard ratio

CI, confidence interval

CoE, certainty of evidence

ECOG, Eastern Cooperative Oncology Group performance status

RR, relative risk

BSC, best supportive care

MELD, Model for End-Stage Liver Disease

mg/kg, milligram/kilogram

ng/mL, nanogram/milliliter

EORTC QLQ, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire

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Versus, vs.

QLQ-HCC18, EORTC Quality of Life Questionnaire for Hepatocellular Carcinoma

GRADE, Grading of Recommendations Assessment, Development and Evaluation

DRAFT

This document presents the official recommendations of the American Gastroenterological Association (AGA) on systemic therapy for hepatocellular carcinoma (HCC). Developed by the AGA Institute's Clinical Guidelines Committee, this guideline was approved by the AGA Governing Board. A detailed synthesis of the evidence from which these recommendations were formulated can be found in the accompanying technical review [technical review REF and link]. Development of this guideline and the accompanying technical review was fully funded by the AGA Institute without additional outside funding. Members of the guideline panel and technical review panel were selected by the AGA Governing Board in consultation with the Clinical Guidelines Committee with careful consideration of all Institute of Medicine recommendations for clinical guideline development. A patient representative was also included in the development of the guidelines and review process. The guideline panel and the authors of the technical review met virtually on June 11, 2021. The information in the technical review was discussed in a systematic manner, facilitating subsequent creation of the guideline recommendations for or against each intervention. The guideline panel independently formulated the guideline recommendations. The guideline and accompanying technical review underwent independent peer review and a 30-day open public comment period. All comments were reviewed and carefully considered by the guideline panel and technical review teams, respectively. Changes were incorporated in revised documents, and where changes were not accepted, a thoughtful response document was created. In accordance with the Clinical Guidelines Committee policies, all clinical guidelines are reviewed annually at the AGA Clinical Guideline Committee meeting for new information. The next update for these guidelines is anticipated in three years from publication.

INTRODUCTION:

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 rate¹. 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 as well as tumor biology. Patients 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 therapy (LRT) such as ablation are reserved for early stage disease while other LRT such as transarterial chemoembolization (TACE), radioembolization (TARE) and systemic therapy are needed for advanced and metastatic disease². Traditional cytotoxic chemotherapy and hormonal therapy are not 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 therapy³. For almost a decade, sorafenib remained the only systemic option with failure 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 shown promise in HCC⁴. In this exciting era of newly approved systemic therapies for HCC, a critical assessment of the existing data is necessary which balances benefits and harms. The focus of this guideline is to provide guidance on the use of systemic therapy in the treatment of hepatocellular carcinoma. We will only address treatments which have FDA approval and not emerging therapies. These guidelines will inform and advise clinicians regarding options for initial therapy, secondary therapy for those who fail initial systemic treatment as well as systemic therapy as adjuvant therapy for those patients who are candidates for LRT or surgery. In addition, we will examine the question of systemic therapy in patients with poor liver function.

METHODS:

This guideline was developed utilizing a process previously outlined⁵. Briefly, the AGA process for developing clinical practice guidelines follows the GRADE approach⁵ and best practices as outlined by the National Academy of Science (formerly Institute of Medicine)⁶. *A priori*, the guideline development panel and methodologist identified and formulated clinically relevant questions. Each PICO question identified the population, intervention, comparator(s), and patient-important outcomes. The technical review panel reviewed and assessed relevant systematic reviews that addressed the PICO questions [REF-technical review], then updated the systematic reviews or conducted new high-quality systematic reviews through June 9, 2021 to inform the recommendations when possible. The findings from each systematic review were assessed using the GRADE approach and presented in an evidence profile. The guideline panel and the authors of the technical review met face-to-face on June 11, 2021 to discuss the findings from the technical review. Following this meeting, the guideline panel independently formulated guideline recommendations. The technical review panel was not involved in formulating or finalizing recommendations. Although the quality of evidence (Table 1) was a key factor in determining the strength of the recommendations (Table 2), the panel also considered the balance between the benefits and harms of the interventions, as well as patients' values and preferences, resource use (i.e. cost), health equity, acceptability, and feasibility (the Evidence to Decision Framework). The recommendations, certainty of evidence, and strength of recommendations are summarized in Table 4. The guideline and technical review went through a 30-day public comment period between XXX to XXX. AGA staff collated the comments, the guideline panel deliberated in their response and, when appropriate, modified the document text. An update for this guideline will be considered by the AGA within 3 years as new and emerging evidence becomes available. We hope to provide clinicians with clear guidance regarding when and which systemic regimens are appropriate in patients with HCC. In particular, we focused on populations which vary regarding candidacy for local regional therapy (LRT) and degree of liver dysfunction. We provide

recommendations for systemic therapy as first line vs. second line therapy and also in the settings of adjuvant therapy. The target audience for this guideline includes healthcare providers and patients.

RECOMMENDATIONS:

Initial Treatment for HCC in patients with preserved liver function

Recommendation 1A: In patients with HCC with preserved liver function not eligible for LRT/resection or with metastatic disease, the AGA suggests sorafenib over no sorafenib. (conditional recommendation, low certainty evidence).

Comment: Patients who place a higher value on the adverse events associated with sorafenib and lower value on the reduction in mortality (2.8 months) may reasonably select no sorafenib.

The AGA suggests sorafenib over best supportive care in patients with advanced HCC (who are not eligible for LRT/resection or metastatic disease) and preserved liver function. The technical review identified two randomized control trials (RCT) of multi-tyrosine kinase inhibitor sorafenib (400 mg twice daily orally) vs. placebo in patients with advanced HCC who did not receive prior systemic therapy⁷,⁸[technical review with link][REF] (*SHARP*, n= 602 and *Asia-Pacific* trials, n= 271). All had preserved liver function with 95-98% being Child Turcotte Pugh (CTP) A and 2-5% CTP B. No patients in the studies were CTP C. The majority had good functional status with 25-54% at *Eastern Cooperative Oncology Group performance status* (ECOG) 0, 38-69% at ECOG 1 and only 2-8% at ECOG 2. The patients were at Barcelona liver clinic stage (BCLC) B in 17-18% or C 82-96.1%. Median survival was significantly improved in both trials with use of sorafenib compared to placebo (10.7 months vs. 7.9 months and 6.5 vs. 4.2 months, in *SHARP* and *Asia-Pacific trials, respectively*). Similar improvements were seen in disease progression, with a median increase of 2.7 and 1.4 months in sorafenib vs. placebo for time to progression. A risk of indirectness in one⁷ of studies was noted where time to progression was determined by a composite of radiological or symptomatic progression, the latter being subjective.

Another notable risk for bias was the lack of reporting or blinding for post-protocol therapies (treatment after discontinuation of the study drug) which can affect overall survival.

While survival and progression of disease was improved, little data was found regarding the effect on quality of life. One study⁷ reported that both treatment groups had similar quality of life but the details of the survey and survey results were not presented and numbers were relatively small. There did not appear to be a difference with regard to serious adverse events, with high adverse event rates in both placebo and sorafenib groups (50.2-52.5%).

Recommendation 1B: In patients with HCC with preserved liver function not eligible for LRT/resection or with metastatic disease, the AGA suggests either lenvatinib or sorafenib. (*conditional recommendation, low certainty evidence*).

Comments: Comments: 1) 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. 2) 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. 2) 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.

The AGA suggests either lenvatinib or sorafenib for patients with advanced HCC and preserved liver function. The technical review identified one open label RCT of another multikinase inhibitor, lenvatinib (12 mg/day for ≥ 60 kg patient and 8 mg/day < 60 kg, orally) vs. sorafenib (400 mg twice daily, orally) for the treatment of patients with advanced HCC⁹ (*REFLECT trial*). This study was powered for non-inferiority and showed equal efficacy between lenvatinib and sorafenib with median overall survival of 13.6 vs. 12.3 months, respectively. Lenvatinib was dosed based on body weight with those above 60 kg receiving 12 mg per day while those below 60 kg receiving 8 mg per day. Sorafenib was dosed at 400 mg in 2 divided doses similar to prior studies. Similar to previous studies, nearly all patients had preserved

liver function with 99% of patients being CTP and functional status with 63% being ECOG 0 and 37% being ECOG 1. Risk of bias was serious in the assessment of overall survival as the lack of blinding could theoretically lead to differences in treatments during the post progression survival period. While overall mortality was not different between lenvatinib vs. sorafenib, the median progression free survival 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 (mRECIST) criteria. Contrary to radiologic progression, there were more serious adverse events and discontinuation due to adverse events in the lenvatinib arm. However, the risk of bias was serious as there was no blinding of patients or investigators. Investigators were responsible for making the determination of whether adverse events were related to the treatment or not. Furthermore, there was serious imprecision as the number of serious adverse events requiring discontinuation was relatively small. While lenvatinib and sorafenib have very similar side effect profiles, there was a tendency for more hypertension with lenvatinib and more skin toxicity with sorafenib which may be helpful when determining choice of multi-kinase inhibitor 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.

Quality of life examined using the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ)-C30 and EORTC QLQ-HCC18 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.

Recommendation 1C: In patients with HCC with preserved liver function not eligible for LRT/resection or with metastatic disease, the AGA suggests atezolizumab/bevacizumab over sorafenib. (*conditional recommendation, low certainty evidence*).

Comment: Esophageal varices screening and treatment prior to starting atezolizumab/bevacizumab is recommended.

The AGA suggests atezolizumab/bevacizumab over sorafenib in patients with advanced HCC and preserved liver function. The technical review identified one study¹⁰ (IMBrave 150 trial) [technical review REF and link] which showed superiority of the combination of the immune checkpoint inhibitor (anti-PD-L1 antibody), atezolizumab (1,200 mg IV once every 3 weeks) with the anti-angiogenic agent (anti-VEGF antibody) bevacizumab (15 mg/kg IV every 3 weeks) over sorafenib (400 mg twice daily, orally) in a global open label study of patients with HCC who had not previously had systemic therapy. The study was limited to patients with preserved liver function with 99% of patients being CTP A and good functional status with ECOG of 0 in 62.5% and ECOG 1 in 27.5%. Most patients were BCLC C at 81.5% but earlier stage diseases were also included with 15% BCLC B and 3% BCLC A. The median overall survival was 19.2 vs. 13.4 months in the atezolizumab/bevacizumab group vs. sorafenib group and was consistent with an improvement in progression free survival. 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, this 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 quality of life was reported using the EORTC QLQ-C30 questionnaire for cancer and showed slower deterioration in the atezolizumab/bevacizumab group compared to 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 patients who completed the quality of life 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. 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 side effect of bevacizumab and all the participants had to have endoscopic evaluation and treatment for esophageal varices prior to enrollment. With this practice the incidence of gastrointestinal bleeding was 7% vs. 4.5% in the atezolizumab/bevacizumab group vs. sorafenib group, respectively.

Other agents

While the technical review did identify a RCT comparing another immune checkpoint inhibitor, nivolumab (anti-PD-1 antibody) with sorafenib as primary therapy for HCC (CheckMate 459), this study has only been published in abstract form¹¹ and insufficient data is available to assess for the certainty of the evidence which would be required for guideline formulation.

Second line treatment for patients who failed initial systemic therapy

In patients who fail first line systemic therapy but continue to have preserved liver function, several options can be considered.

Recommendation 2A: In patients with HCC with preserved liver function not eligible for LRT or with metastatic disease with progressive disease on sorafenib, the AGA suggests regorafenib over no regorafenib. (conditional recommendation, low certainty evidence)

Comments: 1) 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. 2) Regorafenib should not be used in patients who did not tolerate sorafenib due to toxicity.

The AGA suggests regorafenib over no regorafenib for patients with advanced HCC and preserved liver function who have progressed on sorafenib. The technical review identified one RCT (*RESOURCE trial*)¹², a multi-national study comparing regorafenib (160 mg per day for 3 weeks in a 4-week cycle, orally) (n = 379) to placebo (n= 194) in patients with advanced HCC who progressed on sorafenib. Similar to the previous studies, patients had to have preserved liver function at enrollment with 98% who were CTP A and 2% CTP B and good functional status with 66% who were ECOG 0 and 34% who were ECOG 1. There were no patients with CTP C ECOG greater than 1 and all patients 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 overall survival of 10.6 months vs. 7.8 months for the placebo group. High but comparable rates of adverse events were reported in both groups with serious side effects reported in 44.4% in the regorafenib group compared to 46.6% in the placebo group. However, side effects requiring dose reductions or interruptions attributed to drug effect were higher in the regorafenib group at 54% vs., 10%, respectively, although the ascertainment method was not clear. Most importantly, no clinically important differences in quality of life was noted.

Recommendation 2B: In patients with HCC with preserved liver function not eligible for LRT or with metastatic disease who progressed on sorafenib, the AGA suggests cabozantinib over no cabozantinib. (*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 best supportive care for patients with advanced HCC and preserved liver function who have progressed on sorafenib. The technical review identified one international RCT¹³ (*CELESTIAL trial*) which examined Cabozantinib (60 mg once daily, orally) vs. placebo in patients with

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

Recommendation 2C: In patients with HCC with preserved liver function and AFP > 400 ng/mL not eligible for LRT or with metastatic disease who progressed on sorafenib, the AGA suggests using ramucirumab over no ramucirumab (conditional recommendation, low certainty evidence)

Comments: 1) 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. 2) In patients with AFP < 400 ng/mL, the AGA suggests against the use of ramucirumab over no ramucirumab.

The AGA suggests ramucirumab over no ramucirumab for patients with advanced HCC with preserved liver function and AFP > 400 who have progressed on sorafenib. The technical review identified two international RCT^{14, 15} (REACH and REACH-2) which examined ramucirumab (8 mg/kg IV every 2 weeks) vs. placebo. In both trials, all patients were CTP A and ECOG 0 or 1. For the first study (REACH), there was a protocol change excluding CTP B patients after initiation of the trial which may contribute 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 overall survival was noted in the subgroup of patients with alpha fetoprotein (AFP) > 400 ng/ml. The REACH-2 trial followed up on these findings with recruitment of only CTP A patients with AFP > 400 ng/ml. This subgroup of patients with high AFP showed a median overall survival of 8.5 months vs. 7.3 months when given ramucirumab vs. placebo, respectively. Similarly, indirect evidence for improved overall survival was seen with improved progression free survival and decreased time to progression. The certainty of evidence 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 size¹⁶. Quality of life and time to deterioration were similar in both the ramucirumab and placebo groups. Serious adverse events were reported in both groups. In REACH-2¹⁴ trial, serious adverse events were reported at a rate of 34.5% and 29.5% in the ramucirumab and placebo groups, respectively. In the REACH¹⁵ trial, the rate of serious adverse events was significantly higher with the ramucirumab group versus placebo group (44.0% vs. 32.2%, RR 1.37, 1.10-1.70).

Recommendation 2D: In patients with HCC with preserved liver function not eligible for LRT or with metastatic disease who progressed on sorafenib, the AGA suggests using pembrolizumab over no pembrolizumab. (*conditional recommendation, low certainty evidence*)

Comments: 1) 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. 2) 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 best supportive care for patients with preserved liver function and advanced HCC who have progressed on sorafenib. The technical review identified 1 international RCT (KEYNOTE-240) where patients were randomized to pembrolizumab (200 mg IV every 3 weeks)

or placebo. Patients were predominantly CTP A (99%) and ECOG 0 (56%). The remainder were CTP B (1%) and ECOG 1 (44%). Patients 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 overall survival was improved in the pembrolizumab group compared to the placebo group at 13.9 months vs. 10.6 months, respectively. Similar improvements were seen in the surrogate markers of mortality including progression free survival and time to disease progression. However, the certainty of the evidence was downgraded due to concerns of serious risk of bias due to unclear blinding and selection for post-protocol therapy and imprecision due to the low event rate. Quality of life was not different between the 2 groups but there is concern for the quality of data due to low survey completion rate of 68%. Serious adverse events were reported in both groups with 37.3% and 27.6% (Hazard Ratio-HR 1.35, CI 0.99-1.85) for pembrolizumab and placebo, respectively. The rate of discontinuation due to adverse events was significantly higher in the pembrolizumab group (17.2%) vs. placebo group (9.0%).

Other systemic therapies

Additional systemic therapies considered by the technical review for second line therapy in patients who failed initial systemic therapy included nivolumab with the anti-cytotoxic T lymphocyte antigen 4 (CTLA-4) antibody, ipilimumab. Although the combination of nivolumab and ipilimumab has received approval as a second line therapy of patients with advanced HCC previously treated with sorafenib¹⁷ this decision was based on a phase 1/2 study (*CheckMate 040*). In this open label study¹⁸, multiple different dose combinations of nivolumab and ipilimumab were evaluated. Because the trial did not compare any of the interventions to placebo, best supportive care, or previously established treatments, it did not inform any of the PICO questions and thus was insufficient for guideline development.

Most notably, the technical review did not identify any trials which evaluated the use of atezolizumab/bevacizumab as second line therapy for patients who failed prior multikinase inhibitors such as sorafenib or lenvatinib. Furthermore, there were no available trials which evaluated multikinase inhibitors or immunotherapy as second line therapy after failure with the atezolizumab/bevacizumab combination [REF-technical review]

Systemic therapy for HCC in patients with poor liver function

Recommendation 3: In patients with HCC with poor liver function not eligible for LRT/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 of systemic therapy studies in advanced HCC explicitly excluded patients with poor liver function. In most prior randomized controlled studies, 99% of patients were CTP A^{9,10}. The highest percentage of non-Child A patients was found in the initial trials of sorafenib vs. placebo^{7,8}. Even in this study, only 2-5% of patients were Child B and none were Child C. The technical review group found one RCT which examined sorafenib in Child B/C patients¹⁹. In this open-label randomized controlled study, 189 patients were randomized to sorafenib 400 mg twice a day vs. best supportive care. 75% of the patients were Child B and 25% were Child C. While an improvement in mortality was seen with an HR of 0.48, the overall survival 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 lack of blinding and 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 to prior studies which reported rates of approximately 31.8%^{7,8}.

Systemic therapy as adjuvant therapy

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

Surgical Resection

Recommendation 4A: In patients with HCC undergoing curative surgical resection, the AGA suggests against adjuvant sorafenib. (conditional recommendation, low certainty evidence).

The AGA suggests against adjuvant sorafenib for patients with HCC undergoing curative surgical resection. The authors of the technical review could not identify any RCT which addressed the role of systemic therapy as concurrent or neoadjuvant therapy but did identify only one international RCT (*STORM trial*)²⁰ that reported data on patients with HCC who were randomized to sorafenib (400 mg twice a day, orally) vs. placebo starting 6-12 weeks after curative treatment, either curative surgical resection (n = 900) or curative local ablation (n= 214). Inclusion criteria for surgical resection included patients with single lesion of any size, CTP of less than or equal to 7 without ascites, ECOG 0 and AFP level < 400 ng/ml. Risk of recurrence was assessed based on tumor characteristics on pathology and only patients at intermediate or high risk of recurrence were included. There was no difference in mortality for patients treated with sorafenib vs. placebo, 18.7%, vs. 20.3% (HR 0.995; 95% CI, 0.761 - 1.30). Similarly, the hazard ratios for recurrence free survival (0.937; 95% CI, 0.759 – 1.156) and disease recurrence (0.891; 95% CI, 0.735 – 1.081) were not affected by treatment with sorafenib. The data for mortality and disease recurrence was a composite for patients who underwent either resection or ablation leading to serious

concerns about the indirectness of the data. Given the wide confidence intervals, there was also serious concern for imprecision.

No difference in serious adverse events was reported, with 40.7% in the sorafenib group and 41.2% in the placebo group (RR 0.989; 95% CI, 0.860 – 1.140). However, a strong signal for harms was estimated by assessing discontinuation rates due to adverse events, with 24.1% in the sorafenib arm and 7.4% discontinuation in the placebo vs. (RR 3.25; 95% CI, 2.34 – 4.52). Although there was serious risk of imprecision, the overall certainty of the evidence for harm was moderate.

Liver transplantation

In addition to surgical resection, the technical review sought to evaluate systemic therapy in patients with HCC undergoing liver transplantation but the studies found were not sufficient for making a recommendation. Two studies were found utilizing sorafenib in patients awaiting transplantation. One RCT²¹ examined the role of sorafenib combined transarterial radioembolization (TARE) with Y-90 vs. TARE alone. This study reported data on 3-year survival in a population of only 23 patients with cirrhosis and HCC. Inclusion utilized the University of California in San Francisco (UCSF) size criteria²² (solitary tumor ≤ 6.5 cm, or ≤ 3 nodules with the largest lesion ≤ 4.5 cm and total tumor diameter ≤ 8 cm) and liver disease up to Child Pugh B7. Median time to transplant was similar between the two groups. The overall 3-year survival was 72% in the combination group vs. 70% in the Y-90 group alone. 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 side effects.

A second study²³ examined sorafenib vs. no sorafenib as neoadjuvant therapy in patients undergoing transarterial chemoembolization (TACE) treatment while listed for liver transplant. This study reported data on only 50 patients. Outcomes included progression free survival (a composite of death or progression), which was associated with a HR of 1.26 (95% CI 0.48 – 3.27), with serious and very serious

concerns about data indirectness and imprecision, respectively. Seven patients in each group developed tumor progression at a median of 71 days in the sorafenib vs. 85 days in the no sorafenib group, with a HR of 1.106 (95% CI 0.387 – 3.162). There was no significant difference noted in the rate of serious adverse events (RR 1.08, 95% CI 0.24 – 4.86), nor in the rate of discontinuation due to adverse events (RR 6.50, 95% CI 0.84 – 50.14) although there were very serious concerns raised regarding imprecision due to the small sample size. The overall certainty of the evidence regarding benefits (progression free survival and time to progression) was very low, and the certainty of evidence regarding harms was low.

Locoregional therapy

The technical review identified two studies which evaluated the role of sorafenib as adjuvant therapy after curative local ablation therapy, and seven studies of either sorafenib or bevacizumab as concurrent therapy for patients undergoing transarterial chemoembolization (TACE).

Recommendation 4B: 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 technical review identified only one RCT (*STORM trial*)²⁰ discussed previously that addressed curative ablation therapy. Only a minority of the patients in this study had local ablation as the treatment (n = 214). Within the local ablation group, patient could have either RFA or percutaneous ethanol injection as the treatment and sorafenib vs. placebo and given 6-12 weeks after the curative treatment. Maximal tumor burden allowed could not exceed Milan Criteria, one lesion ≤ 5 cm or $3 \leq 3$ cm. As noted above there was no significant difference in mortality, recurrence free survival or disease recurrence but the data is

shown for the combined group as noted above leading to serious concerns regarding indirect comparisons and imprecision of the data.

Recommendation 4C: In patients with HCC undergoing transarterial chemoembolization, the AGA suggests against adjuvant sorafenib therapy (conditional recommendation, low certainty evidence).

The AGA suggests against the use of sorafenib in conjunction with transarterial chemoembolization (TACE) for the treatment of patients with HCC. The technical review identified 5 RCTs with a total of 1284 patients²³⁻²⁷. The combined hazard ratio for mortality was 0.92 (95% CI 0.76 – 1.1) in 4 of the trials and compared 620 patients treated with sorafenib vs. 614 not treated after treatment with TACE²⁴⁻²⁷. The fifth trial²³ (HeiLivCa trial) examined sorafenib after TACE in patients awaiting liver transplantation but did not report on the outcome of overall survival and thus was not included for this outcome. Among the other studies analyzed, there was serious concern for risk of bias, imprecision, and low certainty of evidence due to a number of issues in different studies including lack of blinding, question of allocation concealment as well as unmasking at the time of progression based on investigator's assessment rather than central review.

Among the 3 trials that reported rates of progression free survival in 519 patients (with follow-up ranging from 23 months to 28 months), one study²⁶ demonstrated improvement in the combined sorafenib with TACE vs. TACE alone (HR 0.66, 95% CI 0.47 – 0.94). The other two studies^{23, 24} showed comparable progression free survival rates (HR 0.99; 95% CI, 0.8 – 1.3, and HR 1.3; 95% CI, 0.5- 3.3, respectively). Concerns were raised regarding serious risk of bias, indirectness of data, and imprecision, leading to a very low certainty of evidence.

All 5 RCTs reported on rate of disease progression, with disparate results: one study (Kudo et al) demonstrated a strong effect of combination sorafenib + TACE therapy vs. TACE alone (HR 0.54, 95%

CI 0.35 – 0.83, with median time to progression of 22.8 months vs. 13.5 months). The results of the remaining studies were less optimistic: Kudo et al²⁷ noted a HR 0.87 (95% CI 0.7 – 1.09), with a median time to progression of 5.4 months vs. 3.7 months; Lencioni et al²⁵ noted a HR 0.8 (95% CI 0.59 – 1.08), with a median time to progression of 5.6 months vs. 5.5 months, and Meyer et al²⁴ reported a HR 0.88 (95% CI 0.67 – 1.17), with a median time to progression of 10.9 vs. 10.7 months. One trial²³ reported a higher rate of progression in the combination sorafenib with TACE therapy arm with HR 1.21 (95% CI 0.39 – 3.16), and a median time to progression of 2.4 vs. 2.8 months. There were serious risk of bias and indirectness, which led to a low overall certainty of evidence.

Quality of life was assessed in one trial²⁴ with the use of several questionnaires, EORTC QLQ-C30, EORTC QLQ-HCC18, and the European Quality of Life 5 Dimensions (EQ-5D) questionnaires. Among the 313 patients who were sent surveys, there was significantly lower social/role functioning scores in the sorafenib group (approximately 6%), as well as 13% higher diarrhea score, 10% higher mean appetite loss score, and 7% worse nutritional problem score. The overall certainty of evidence was considered low, with serious concern for imprecision, and risk of bias.

Rates of serious adverse events were reported in 4 trials^{23-25, 27}, with a statistically higher rate in the combination arm (35.2% vs. 23.2%), with a HR of 1.48 (95% CI 1.24 – 1.77). There was a risk of bias that was serious; the overall certainty of evidence was moderate.

Estimating harms based on rates of discontinuation due to adverse events was possible in 3 trials^{24, 25, 27}, with a higher discontinuation rate in the combination arm (21.3% vs. 11.8%), with an HR of 1.81 (95% CI 1.36- 2.4). The data again were judged to have a serious risk of bias, and moderate overall certainty of the evidence.

Recommendation 4D: In patients with HCC undergoing transarterial chemoembolization, 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 technical review identified 2 RCT^{28, 29} that with a total of 62 patients randomized to bevacizumab plus TACE vs. placebo or observation plus TACE.

Britten et al randomized 30 CTP A and B patients with HCC (mean tumor burden of 7.4 ± 2.9 cm in the TACE + observation group, compared to 6.5 ± 2 cm in the TACE + bevacizumab group). They found no statistically significant difference in median overall survival in the TACE + observation group (61 months) vs. TACE and bevacizumab arm (49 months); the cross over design limited the ability to draw conclusions regarding efficacy. Pinter et al randomized 32 CTP A and B patients with histologically confirmed HCC up to 15 cm in diameter to bevacizumab and TACE vs. bevacizumab and placebo. Patients had BCLC A and B disease, and were both treatment naïve or had recurred after resection or ablation. The study found a worse overall survival in the combination group compared to placebo group with a median survival of 5.3 months vs. 13.7 months (HR 1.7, 95% CI 0.8- 3.6).

There were serious concerns regarding the risk of bias, inconsistency, and imprecision, leading to a very low overall certainty of the evidence.

Progression free survival over a median follow-up of 16 weeks was assessed in the Britten study, with a rate of 19% in the TACE plus observation group, compared to 79% in the TACE + bevacizumab group, with an HR of 4 (95% CI 1.4 – 11.3). Median overall survival was 61 months in the TACE plus observation group, and 49 months in the TACE plus bevacizumab group. There was a very low overall certainty of evidence, based on serious risk of bias and indirectness, and very serious risk of imprecision. Disease progression over a median of 1 year of follow up was reported in one study²⁸, with a HR of 0.9 (95% CI

0.3 – 2.4). Again, a very low overall certainty of evidence, based on serious risk of bias and indirectness, and very serious risk of imprecision was found.

Harms based on rates of discontinuation due to adverse events were reported in the one study²⁹, with only one event in the TACE + bevacizumab group, and none in the TACE + placebo group, yielding a HR of 3.0 (95% CI 0.1 – 68.3); limitations of the data included a serious risk of bias and very serious risk of imprecision, yielding a very low overall certainty of evidence.

Harms related to deaths from the treatment intervention were reported in the one study²⁸, and occurred in 1 patient in the TACE plus observation group, and 8 patients in the TACE plus bevacizumab group – with an HR of 11 (95% CI 1.6 – 75.5). The data were judged to have a serious risk of bias and very serious risk of imprecision, with a very low overall certainty of evidence.

SUMMARY

The advent of multiple new FDA approved systemic therapies in HCC brings new hope for patients with advanced HCC who are not candidates for curative treatments including, liver resection, transplantation and locoregional ablation as well as non-curative locoregional therapies, such as TACE and TARE. For over a decade, the oral multi-kinase inhibitor sorafenib was the only approved systemic therapy for this population of patients. However, in recent years, the intravenous combination of an antiangiogenic agent with checkpoint inhibitor (bevacizumab and atezolizumab) showed small to moderate survival benefit over sorafenib for the primary treatment of patients, increasing therapeutic options for patients. In addition, lenvatinib, another oral multikinase inhibitor, showed equivalence to sorafenib for primary treatment of advanced HCC. For secondary treatment of patients who failed sorafenib, multiple regimens including other oral multikinase inhibitors, regorafenib and cabozantinib as well as intravenous monoclonal antibodies ramucirumab (anti-VEGFR2) and check point inhibitor pembrolizumab (anti-PD1)

have shown some improvement in overall survival. In the case of ramucirumab, the effect was limited to patients with serum AFP greater than 400 ng/ml.

While these RCTs showed survival benefit, the evidence was downgraded due to serious concern of bias as most lacked reporting or blinding for subsequent therapies which can affect overall mortality. Furthermore, differences in median survival were often modest and improvement in quality of life was not clearly demonstrated. No high-quality direct comparative evidence is available for either atezolizumab/bevacizumab, sorafenib, or lenvatinib as second-line therapies. However, patients who put a high value on the uncertain benefit of atezolizumab/bevacizumab, sorafenib, or lenvatinib as second-line therapies and low value on their adverse events could reasonably select to use either atezolizumab/bevacizumab, sorafenib, or lenvatinib as second-line therapies. Thus, ultimate decisions for treatment regimens need to weigh patient preferences as well as risks and benefits. At the present time, there is limited information/biomarkers to guide patient selection for different regimens and remain an area of great importance for future research.

It should be noted that in all these studies, the clinical trials were limited to patients with preserved liver function. These were patients who were Child A cirrhotics with good functional status with ECOG scores of 1 or less. Patients with Child C cirrhosis do not have any options for systemic therapy and future research in this area would be of great importance.

In addition, the technical review examined the question of systemic therapy as an adjuvant treatment and found no evidence to support its use at this time. As more treatments are on the horizon including single agent and combination treatments, we anticipate that there may be more options in the near future.

Comparison to prior guidelines

The recommendations of this guideline are overall consistent with recommendations of guidelines from the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN)^{30, 31} with few differences. The ASCO guidelines gave recommendations for second-line therapies in patients who received atezolizumab + bevacizumab first line treatment, however, we identified this as a knowledge gap in the absence of randomized controlled trials evaluating the role of other treatments as second line treatments after first line treatment with atezolizumab + bevacizumab. Similarly, they suggested using atezolizumab + bevacizumab or nivolumab as second-line treatments in patients who failed sorafenib or lenvatinib first-line treatment, which we also identified as a knowledge gap due to lack of randomized controlled trials. The NCCN guidelines listed nivolumab as a preferred first-line therapy in certain circumstances, which we did not comment on as the CheckMate 459 trial has not been published limiting our ability to assess the certainty in the evidence. They also listed nivolumab + ipilimumab as another recommended subsequent-line therapies which we did not include as the CheckMate 040 trial was a phase 1/2 study that did not compare nivolumab + ipilimumab to a treatment that has shown to be beneficial in randomized controlled trials compared to standard therapies.

Health equity

The technical review 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.

Table 1: Interpretation of the Certainty in Evidence of Effects using the Grading of Recommendations Assessment,

Development and Evaluation Framework

<i>High</i>	We are very confident that the true effect lies close to that of the estimate of the effect.
<i>Moderate</i>	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.
<i>Low</i>	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
<i>Very Low</i>	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

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Table 2: Interpretation of Strong and Conditional Recommendations Using the Grading of Recommendations

Assessment, Development and Evaluation Framework

	<i>For the Patient</i>	<i>For the Clinician</i>
<i>Strong</i>	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.
<i>Conditional</i>	The majority of individuals in this situation would want the suggested course of action, but many would not.	Different choices will be appropriate for different patients. Decision aids may be useful in helping individuals in making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.

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Table 3: Executive Summary of Recommendations*:

Recommendations	Strength of Recommendation	Certainty of Evidence
1. Initial treatment for HCC in patients with preserved liver function		
<p>1A. In patients with HCC with preserved liver function not eligible for LRT/resection or with metastatic disease, the AGA suggests sorafenib over no sorafenib. <i>Comment: Patients who place a higher value on the adverse events associated with sorafenib and lower value on the reduction in mortality (2.8 months) may reasonably select no sorafenib.</i></p>	Conditional	Low
<p>1B. In patients with HCC with preserved liver function not eligible for LRT or with metastatic disease, the AGA suggests either lenvatinib or sorafenib Comments: 1) 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. 2) 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. 2) 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.</p>	Conditional	Low
<p>1C. In patients with HCC with preserved liver function not eligible for LRT or with metastatic disease, the AGA suggests atezolizumab/bevacizumab over sorafenib. <i>Comment: Esophageal varices screening and treatment prior to starting treatment is recommended.</i></p>	Conditional	Low
2. Second line treatment for patients who failed initial systemic therapy		
<p>2A. In patients with HCC with preserved liver function not eligible for LRT or with metastatic disease with progressive disease on sorafenib, the AGA suggests regorafenib over no regorafenib <i>Comment: 1) 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. 2) Regorafenib should not be used in patients who did not tolerate sorafenib due to toxicity.</i></p>	Conditional	Low
<p>2B. In patients with HCC with preserved liver function not eligible for LRT or with metastatic disease who progressed on sorafenib, the AGA suggests cabozantinib over no cabozantinib. <i>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.</i></p>	Conditional	Very low

<p>2C. In patients with HCC with preserved liver function and AFP > 400 ng/mL not eligible for LRT or with metastatic disease who progressed on sorafenib, the AGA suggests using ramucirumab over no ramucirumab.</p> <p><i>Comments: 1) 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. 2) In patients with AFP < 400 ng/mL, the AGA suggests against the use of ramucirumab over no ramucirumab.</i></p>	Conditional	Low
<p>2D. In patients with HCC with preserved liver function not eligible for LRT or with metastatic disease who progressed on sorafenib, the AGA suggests using pembrolizumab over no pembrolizumab.</p> <p><i>Comments: 1) 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. 2) Patients with main portal vein invasion or inferior vena cava or cardiac involvement of HCC on the basis of imaging were not studied.</i></p>	Conditional	Low
<p>3. Systemic therapy for HCC in patients with poor liver function</p>		
<p>In patients with HCC with poor liver function not eligible for LRT/resection or with metastatic disease, the AGA suggests against routine use of sorafenib.</p> <p><i>Comment: Patients, particularly those who are not Child Pugh C, who place a higher value on the uncertain reduction in mortality and lower value on the harms may reasonably select to use sorafenib.</i></p>	Conditional	Very low
<p>4. Systemic therapy for HCC as adjuvant therapy</p>		
<p>4A. In patients with HCC undergoing curative surgical resection, the AGA suggests against adjuvant sorafenib therapy.</p>	Conditional	Low
<p>4B. In patients with HCC undergoing curative local ablation, the AGA suggests against adjuvant sorafenib therapy.</p>	Conditional	Low
<p>4C. In patients with HCC undergoing TACE locoregional therapy, the AGA suggests against adjuvant sorafenib therapy.</p>	Conditional	Very low
<p>4D. In patients with HCC undergoing TACE locoregional therapy, the AGA suggests against adjuvant bevacizumab therapy.</p>	Conditional	Very low

*Please see the accompanying technical review for the supporting evidence [Please place hyperlink and reference]

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