Systemic Therapy for Advanced Hepatocellular Carcinoma: ASCO Guideline

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Introduction

- In the United States, it is estimated that liver cancer will account for approximately 42,810 new cases and about 30,160 deaths in 2020.[1]
- Risk factors vary by geographic region and include chronic viral hepatitis, alcohol-related liver disease, environmental exposures, and morbid obesity and diabetes.[2]
- Effective treatment options exist for early-stage HCC, and patients with locally advanced disease may be candidates for liver directed therapies, however, historically HCC was diagnosed at an advanced, incurable stage and had a poor prognosis.[3]
- Trials of systemic therapy for advanced HCC failed to show improved outcomes until the advent of the tyrosine kinase inhibitor sorafenib.[4]
- Recently, several newer systemic therapy options have shown efficacy in the first and second-line settings. Evidence of the effectiveness of combination therapy has also been reported.[5-7]
- This guideline incorporates the evidence for systemic therapy options for patients with advanced HCC to provide recommendations to clinicians.

ASCO Guideline Development Methodology

The ASCO Clinical Practice Guidelines Committee guideline process includes:

- a systematic literature review by ASCO guidelines staff
- an expert panel provides critical review and evidence interpretation to inform guideline recommendations
- final guideline approval by ASCO CPGC

The full ASCO Guideline methodology manual can be found at:

www.asco.org/guideline-methodology

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Clinical Question

This clinical practice guideline addresses the following clinical question:

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

Target Population and Audience

Target Population

Patients with advanced hepatocellular carcinoma.

Target Audience

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

Summary of Recommendations

First-Line Therapy

Recommendation 1.1

Atezolizumab-bevacizumab (atezo+bev) may be offered as first-line treatment for most patients with advanced HCC, Child-Pugh class A, ECOG PS 0-1 and following management of esophageal varices, when present, according to institutional guidelines.

(Type: evidence-based; benefits outweigh harms; Evidence quality: moderate to high, Strength of recommendation: strong)

Summary of Recommendations

First-Line Therapy

Qualifying statements for Recommendation 1.1

- Recommendation 1.1 is based on results from the IMbrave150 phase III RCT[6] comparison of atezo+bev to sorafenib (HR for OS: 0.58, 95% CI: 0.42 to 0.79, *P* = .0006) in Child-Pugh class A patients. Caution should be exercised when applying these results to patients with more advanced liver disease who have a greater likelihood of portal hypertension because of the risk of bleeding complications associated with bevacizumab.
- Due to risk of bleeding, patients in this trial were required to have undergone esophagogastroduodenoscopy (EGD) within 6 months of trial initiation and to have received treatment for esophageal varices when necessary.[8] The Expert Panel recognizes that some patients may have been evaluated for varices outside the 6-month window, are receiving treatment (e.g. adequately dosed non-selective beta-blockers), and/or are deemed to be low risk for variceal bleed by a hepatology specialist. In these patients the decision to forgo an EGD prior to initiation of therapy with atezo+bev may be carefully considered.
- Patients who had a myocardial infarction or stroke within the previous 3 months, a history of autoimmune disease, were on therapeutic anticoagulation or had coinfection with HBV and HCV were also excluded from the IMbrave150 RCT.

Summary of Recommendations

First-Line Therapy

Recommendation 1.2

Where there are contraindications to atezolizumab and/or bevacizumab, tyrosine kinase inhibitors sorafenib or lenvatinib may be offered as first-line treatment for patients with advanced HCC, Child-Pugh class A, and ECOG PS 0-1.

(Type: evidence-based; benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong)

Summary of Recommendations

First-Line Therapy

Qualifying statements for Recommendation 1.2

- Treatment with recommended TKIs may be less effective for patients with more advanced liver cirrhosis. Careful patient selection is recommended.
- The choice of treatment with lenvatinib or sorafenib should be made through a discussion involving the physician and patient (and caregiver, where applicable), and should include factors such as medical history, viral etiology of liver disease, toxicities associated with treatment, cost, goals of treatment, patient preference and expected treatment benefit. Factors affecting this choice, including response rates, are discussed further in the Clinical Interpretation.
- Several meta-analyses of randomized controlled trials have shown sorafenib to be more beneficial in patients with HCV, especially as compared to patients with HBV.[9-11] In the REFLECT trial there was a trend towards improvements across endpoints for lenvatinib over sorafenib in the HBV subgroup, though not significant.[12]
- Patients with a high tumor burden, more than 50% liver involvement, or those with main portal vein invasion were excluded from the REFLECT trial of sorafenib vs. lenvatinib.[13]

Summary of Recommendations

Second-Line Therapy

Recommendation 2.1

Following first-line treatment with atezo+bev, second-line therapy with a TKI (i.e. sorafenib, lenvatinib, cabozantinib, or regorafenib) may be recommended.

(Type: informal consensus; benefits may outweigh harms; Evidence quality: low; Strength of recommendation: weak)

Qualifying statement for Recommendation 2.1

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

Summary of Recommendations

Second-Line Therapy

Recommendation 2.2

Following first-line therapy with sorafenib or lenvatinib, second-line therapy with another TKI (cabozantinib, or regorafenib), ramucirumab (AFP ≥400 ng/mL), or atezo+bev, may be recommended for appropriate candidates. Considerations regarding choice of therapy are included in the Clinical Interpretation.

(Type: informal consensus; benefits may outweigh harms; Evidence quality: low to moderate; Strength of Recommendation: weak)

Qualifying statement for Recommendation 2.2

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

Summary of Recommendations

Second-Line Therapy

Recommendation 2.3

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

(Type: informal consensus; benefits may outweigh harms; Evidence quality: low; Strength of Recommendation: weak)

Qualifying statement for Recommendation 2.3

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

Patient and Clinician Communication

- Poor adherence to oral chemotherapy is an ongoing concern with profound clinical implications and reduced therapeutic efficacy,[14-16] which is especially relevant for HCC patients at risk for encephalopathy, esophageal varices, and/or ascites.
- Interventions to optimize patient adherence should be considered, for example, involvement of pharmacists in managing oral chemotherapy, which has been shown to increase knowledge levels in a pilot study,[17] and has resulted in improved adherence and response outcomes.[18]
- For recommendations and strategies to optimize patient-clinician communication, readers are referred to Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline.[19]

Health Disparities

- Studies have shown disparate access to care for patients with HCC, including liver transplantation, by race/ethnicity.[20-23] HCC was detected at a more advanced stage in an African American study population, compared to other racial/ethnic groups.[24] Earlier detection could help reduce disparities in outcomes.[25]
- Differences in outcomes persist even when receipt of treatment is the same and a significant negative impact of low income has been found on overall survival.[22]
- Data from a Medicare population show that only 27% of patients with advanced HCC were initially treated with sorafenib after diagnosis,[26] and in a SEER data analysis, only 29.5% of patients received any treatment for HCC.[27]
- Providers should be aware of these disparities and should strive to deliver the highest level of care to more vulnerable populations.
- HCC disparity research should assess of the impact of socioeconomic factors and social policies to inform strategies to minimize disparities. Social and health policies must emphasize prevention of risk factors for HCC and early detection campaigns should be promoted within racial/ethnic groups.

Cost Implications

- The Expert Panel conducted an informal scan for independently-conducted cost utility or economic analyses that might inform the relative value of available treatment options, identifying 12 studies of cost effectiveness of systematic therapy options for advanced HCC.[28-39]
- These studies found that the cost of these drugs exceeds willingness-to-pay thresholds in most cases, reflecting the balance of utility in terms of survival and other outcomes and disutility resulting from adverse events and relatively high drug costs.
- Generally, for HCC, costs of care are highest in the initial treatment and terminal phases and lower in the continuing care phase.[40] Study authors reported the ICER could be improved by lowering the cost,[33,35] or improving patient selection, ideally with the use of biomarkers.[37]
- Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[41,42]
- Patients should be made aware that different products may be preferred or covered by their insurance plan and that price may vary between pharmacies. Patients should also be aware of any financial counseling services available to address this complex set of issues.[43]

Discussion

- Despite recent advances, there are still significant areas of uncertainty and unmet need, including appropriate sequencing of therapy, subgroups that may benefit more than others from current treatment options, and treatment benefit in Child-Pugh class B patients.
- Due to lack of data, the Expert Panel did not include a recommendation but acknowledges third-line therapy may be considered in Child-Pugh A patients with good performance status, using a shared decision-making, multidisciplinary approach.
- Immune checkpoint inhibitors (ICIs) have a role in the treatment of patients with advanced HCC and benefit patients who have contraindications to or cannot tolerate TKIs. Patients and clinicians should be aware that life-threatening toxicities can occur with ICIs. Future research on these options may provide additional information on patient subpopulations that could potentially benefit.
- Recent studies of systemic therapy in advanced HCC have demonstrated an increased benefit in terms of response rate and survival from combined therapy.[6] Future directions in advanced HCC include emerging data on combinations of TKIs and ICIs.[7,44-46]

Additional Resources

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

Patient information is available at www.cancer.net

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Abbreviations

- AFP, alpha-fetoprotein
- ASCO, American Society of Clinical Oncology
- atezo+bev, atezolizumab + bevacizumab
- CI, confidence interval
- CPGC, Clinical Practice Guidelines Committee
- ECOG, Eastern Cooperative Oncology Group
- EGD, esophagogastroduodenoscopy
- HBV, hepatitis B virus
- HCC, hepatocellular carcinoma
- HCV, hepatitis C virus
- HR, hazard ratio
- ICER, incremental cost effectiveness ratio
- ICI, immune checkpoint inhibitor
- OS, overall survival
- PGIN, Practice Guidelines Implementation Network
- PS, performance status
- RCT, randomized control trial
- SEER, Surveillance, Epidemiology, and End Results Program
- TKI, tyrosine kinase inhibitor

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