

ASCO® Guidelines

SYSTEMIC THERAPY FOR ADVANCED HEPATOCELLULAR CARCINOMA: ASCO GUIDELINE		
Category	Recommendation	Evidence Rating
First-line therapy	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
	<p><i>Qualifying statements:</i></p> <ul style="list-style-type: none"> • Recommendation 1.1 is based on results from the IMbrave150 phase III RCT¹ 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.² 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. 	
	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

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	<p><i>Qualifying statements:</i></p> <ul style="list-style-type: none"> • 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 <i>Clinical Interpretation</i>. • 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.³⁻⁵ In the REFLECT trial there was a trend towards improvements across endpoints for lenvatinib over sorafenib in the HBV subgroup, though not significant.⁶ • 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.⁷ 	
Second-line therapy	<p>Following first-line treatment with atezo+bev, second-line therapy with a TKI (i.e. sorafenib, lenvatinib, cabozantinib, or regorafenib) may be recommended.</p>	<p>Type: informal consensus; benefits may outweigh harms Evidence quality: low Strength of recommendation: weak</p>
	<p><i>Qualifying statement:</i></p> <ul style="list-style-type: none"> • 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. 	
	<p>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 <i>Clinical Interpretation</i>.</p>	<p>Type: informal consensus; benefits may outweigh harms Evidence quality: low to moderate Strength of recommendation: weak</p>
	<p><i>Qualifying statement:</i></p> <ul style="list-style-type: none"> • 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. 	
	<p>Following first-line therapy with sorafenib or lenvatinib, pembrolizumab or nivolumab are reasonable options that may be considered for appropriate candidates.</p>	<p>Type: informal consensus; benefits may outweigh harms Evidence quality: low Strength of recommendation: weak</p>

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Category	Recommendation	Evidence Rating
	<p><i>Qualifying statement:</i></p> <ul style="list-style-type: none"> • Immune checkpoint inhibitors pembrolizumab or nivolumab may be especially beneficial for patients who have contraindications to or cannot tolerate TKIs. 	

References

1. Finn RS: Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 382:1894-905, 2020
2. El-Khoueiry A: Atezolizumab and Bevacizumab Combination Therapy for Hepatocellular Carcinoma. Gastroenterology and Hepatology 16:145-148, 2020
3. Jackson R, Psarelli EE, Berhane S, et al: Impact of Viral Status on Survival in Patients Receiving Sorafenib for Advanced Hepatocellular Cancer: A Meta-Analysis of Randomized Phase III Trials. J Clin Oncol 35:622-628, 2017
4. Bruix J, Cheng AL, Meinhardt G, et al: Prognostic factors and predictors of sorafenib benefit in patients with hepatocellular carcinoma: Analysis of two phase III studies. J Hepatol 67:999-1008, 2017
5. Park J, Cho J, Lim JH, et al: Relative Efficacy of Systemic Treatments for Patients with Advanced Hepatocellular Carcinoma According to Viral Status: A Systematic Review and Network Meta-Analysis. Target Oncol 14:395-403, 2019
6. Kudo M, Finn RS, Qin S, et al: Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 391:1163-1173, 2018
7. Sangro B: State of the Art Management of Advanced Hepatocellular Carcinoma, Gastrointestinal Cancers Symposium. San Francisco, California, 2020