

Systemic Therapy for Advanced Hepatocellular Carcinoma: ASCO Guideline Update			
Category	Recommendation	Evidence Quality	Strength
First-line therapy	<b>1.1.</b> Atezolizumab + bevacizumab (atezo+bev) or durvalumab + tremelimumab (durva+treme) may be offered as first-line treatment for patients with Child-Pugh class A, and ECOG PS 0-1 advanced HCC.	M-H	S
	<i>Qualifying statements:</i> <ul style="list-style-type: none"> <li>For patients receiving atezo+bev, screening for and management of esophageal varices when present are recommended prior to initiation of therapy and according to institutional guidelines.</li> <li>The choice between treatment options in Recommendation 1.1 should be made through a discussion involving the physician and patient (and caregiver, where applicable), and should include factors such as medical history, toxicities associated with treatment, cost, goals of treatment, patient preference, and expected treatment benefit.</li> <li>When choosing between the two combination therapy options, consider risk of bleeding and thrombosis with the VEGF inhibitor bevacizumab.</li> <li>Patients with active or previously documented autoimmune disease should consider the risk of immune-related adverse effects associated with atezo and durva+treme.</li> </ul>		
	<b>1.2.</b> Where there are contraindications to atezo+bev or durva+treme, sorafenib, lenvatinib, or durvalumab may be offered as first-line treatment for patients with Child-Pugh class A, and ECOG PS 0-1 advanced HCC.	M	S
Second-line therapy	<i>Qualifying statements:</i> <ul style="list-style-type: none"> <li>The choice between treatment options should take into account the factors listed in the second qualifying statement to Recommendation 1.1.</li> </ul>		
	<b>2.1.</b> Following first-line treatment with atezo+bev, second-line therapy with a tyrosine kinase inhibitor (TKI) (i.e., sorafenib, lenvatinib, or cabozantinib), or ramucirumab (AFP $\geq$ 400 ng/mL) are recommended.	L	W
	<i>Qualifying statements:</i> <ul style="list-style-type: none"> <li>The Expert Panel also agreed that nivolumab + ipilimumab (nivo+ipi) is an option that may be considered following first-line treatment with atezo+bev, although the evidence for nivo+ipi is limited to data from case series.<sup>1-3</sup></li> <li>While there is currently no published evidence to support a recommendation for durva+treme, the Expert Panel agreed that this option may be considered following first-line treatment with atezo+bev.</li> </ul>		
	<b>2.2.</b> Following first-line treatment with durva+treme, second-line therapy with a TKI is recommended.	L	W

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	<p><i>Qualifying statement:</i></p> <ul style="list-style-type: none"> <li>The Expert Panel also agreed that atezo+bev may be considered following durva+treme for patients who do not have contraindications to the former combination, although there is no data available to select patients for this combination therapy vs. second-line therapy with a TKI.</li> </ul>		
	<p><b>2.3.</b> Following first-line treatment with sorafenib or lenvatinib, second-line therapy with another TKI (cabozantinib or regorafenib), ramucirumab (AFP <math>\geq</math>400 ng/mL), nivo+ipi, or durvalumab may be recommended for appropriate candidates. Atezo+bev or durva+treme may be considered for patients who may not have had access to these therapies in the first-line setting, and do not have contraindications to these combinations. Considerations regarding choice of therapy are included in the <i>Clinical Interpretation</i> in the full guideline.</p>	L-M	W
	<p><i>Qualifying statement:</i></p> <ul style="list-style-type: none"> <li>In addition, pembrolizumab or nivolumab are reasonable options that may be considered for appropriate candidates following first-line therapy with sorafenib or lenvatinib.</li> </ul>		
Third-line therapy	<p><b>3.1.</b> Third-line therapy may be considered in Child-Pugh A patients with good performance status, using one of the agents listed previously that has a non-identical mechanism of action with previously received therapy.</p>	L	W
Child-Pugh class B	<p><b>4.1.</b> The Expert Panel agrees on a cautious approach to systemic therapy in advanced HCC patients who are Child-Pugh class B with good PS, considering underlying liver function, bleeding risk, presence of portal hypertension, extent of extrahepatic spread, tumor burden, and major vascular invasion. Limited data suggest that regimens typically used for Child-Pugh A can be beneficial in untreated patients with Child-Pugh B cirrhosis. Given the modest expectations for clinical benefit from systemic therapy in this population, the Expert Panel emphasizes shared decision-making with patients.</p>	VL	W

**Abbreviations.** AFP, alpha-fetoprotein; atezo+bev, atezolizumab + bevacizumab; durva+treme, durvalumab + tremelimumab; ECOG, Eastern Cooperative Oncology Group; H, high; HCC, hepatocellular carcinoma; L, low; L-M, low to moderate; M, moderate; M-H, moderate to high; nivo+ipi, nivolumab + ipilimumab; PS, performance status; S, strong; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VL, very low; W, weak

### References.

- Kim HJ, Hwang SY, Im JW, et al: A case of nearly complete response in hepatocellular carcinoma with disseminated lung metastasis by combination therapy of nivolumab and ipilimumab after treatment failure of atezolizumab plus bevacizumab. *J Liver Cancer* 23:213-218, 2023
- Roessler D, Öcal O, Philipp AB, et al: Ipilimumab and nivolumab in advanced hepatocellular carcinoma after failure of prior immune checkpoint inhibitor-based combination therapies: a multicenter retrospective study. *Journal of Cancer Research and Clinical Oncology* 149:3065-3073, 2023
- Alden SL, Lim M, Kao C, et al: Salvage Ipilimumab plus Nivolumab after Anti-PD-1/PD-L1 Therapy in Advanced Hepatocellular Carcinoma. *Cancer Res Commun* 3:1312-1317, 2023