AGA Clinical Practice Guideline on Systemic Therapy for Hepatocellular Carcinoma

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The Emoroid Digest
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First Line Treatment for HCC with Preserved Liver Function

- If not eligible for locoregional therapy (LRT) or resection or with metastatic disease, **atezolizumab + bevacizumab > sorafenib**
- GI bleeding is a known adverse effect (AEs) of bevacizumab, therefore need endoscopic evaluation and treatment of esophageal varices before starting

- If not a candidate for atezolizumab + bevacizumab, **lenvatinib or sorafenib > no systemic therapy**
- If patients place a higher value on delayed radiologic disease progression and lower value on increase in adverse events, choose **lenvatinib > sorafenib**
- If patients place a higher value on BP control and lower value on adverse skin reactions, choose **sorafenib > lenvatinib**
- Lenvatinib has not been studied in patients with invasion of the main portal vein.
- If patients place a higher value on the AEs associated with sorafenib or lenvatinib and lower value on the reduction in mortality (2.8 months for sorafenib, unknown for lenvatinib), reasonable to choose **no systemic therapy**

HCC + Not eligible for resection, LRT, or transplant

Child-Pugh A

No prior systemic therapy → Atezolizumab + bevacizumab > sorafenib
If ineligible for atezolizumab/bevacizumab, use lenvatinib or sorafenib

Prior systemic therapy →
AFP > 400 ng/mL → regorafenib, cabozantinib, pembrolizumab, or ramucirumab

AFP < 400 ng/mL → regorafenib, cabozantinib, or pembrolizumab

Second Line Treatment for Disease Progression or Intolerance to First Line for Preserved Liver Function

- If preserved liver function and not eligible for LRT or resection or with metastatic disease, and who had progression of disease on sorafenib, **cabozantinib or pembrolizumab > no systemic therapy.** Patients with main portal vein invasion or IVC or cardiac involvement of HCC by imaging were not studied for pembrolizumab

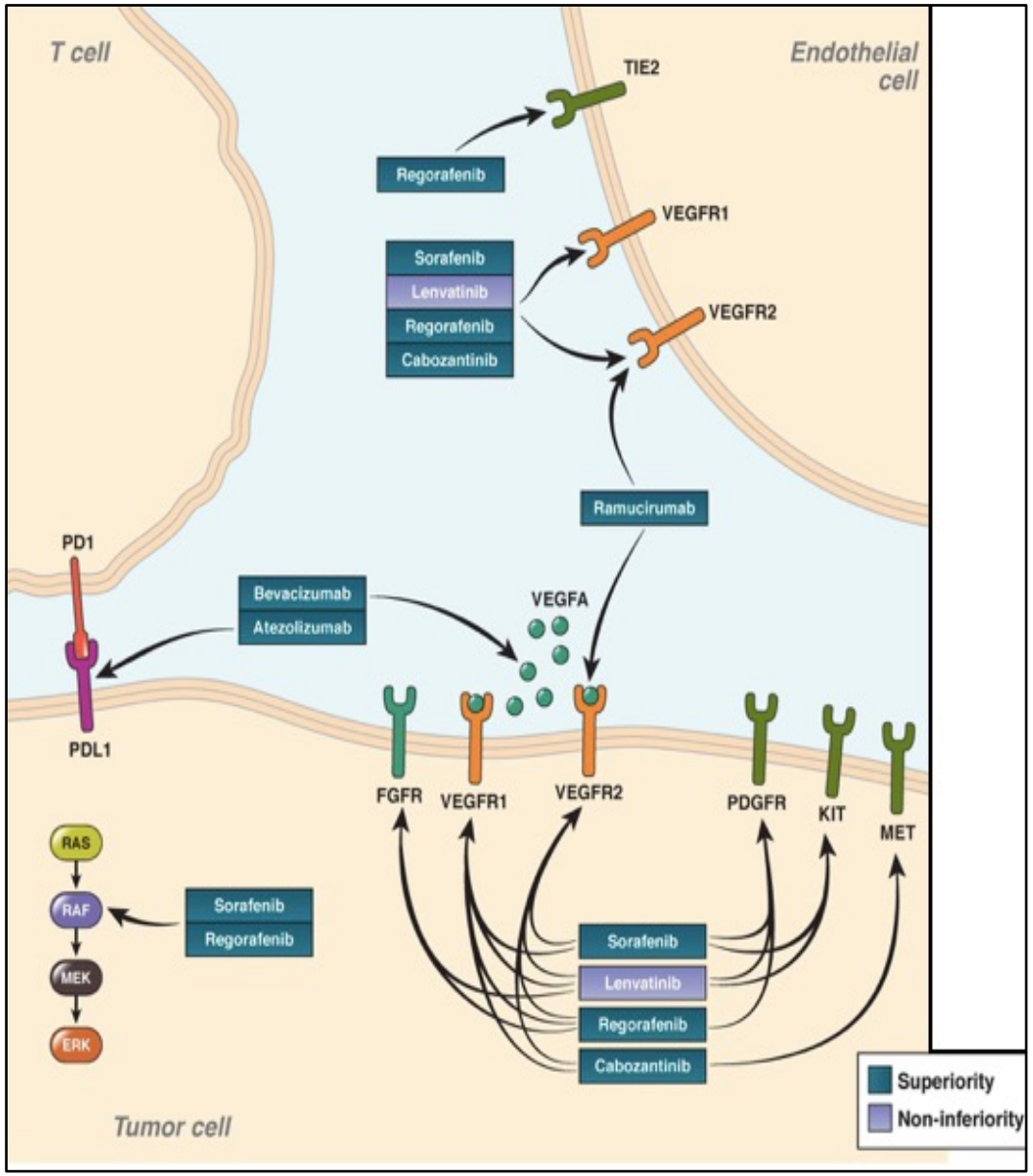
- In patients with HCC with preserved liver function and AFP >400 ng/mL not eligible for LRT or resection or with metastatic disease and who had progression of disease on sorafenib, **ramucirumab > no systemic therapy**
- Do not use ramucirumab if AFP < 400 ng/mL
- In patients with HCC with preserved liver function not eligible for LRT or resection or with metastatic disease, and who had progression of disease on sorafenib, **regorafenib > no systemic therapy.**
- Do not use regorafenib if sorafenib was not tolerated due to toxicity

- If patients place a higher value on AEs associated with these therapies and lower value on reducing mortality (2.2 mos for cabozantinib, 1.2 mos for ramucirumab, 2.8 mos for regorafenib, and 3.3 mos for pembrolizumab), reasonable to decline these therapies

Child-Pugh B/C → Recommendation is for no systemic therapies however if not Child-Pugh C and place higher value on uncertain reduction in mortality and lower value on harms, can choose **sorafenib**

Su GL, Altayar O, O'Shea R, Shah R, Eftan B, Wenzell, C, Sultan S, Falck-Ytter Y. AGA Clinical Practice Guideline on Systemic Therapy for Hepatocellular Carcinoma. Gastroenterology. 2022; 162:920-934.

Mechanism of Action



	Drug	MOA	Dose
First Line Treatment	Atezolizumab + bevacizumab	Atezolizumab: Checkpoint inhibitor: antiprogrammed death ligand-1 (anti–PD-L1) antibody Bevacizumab: Antiangiogenic agent: anti– vascular endothelial growth factor (VEGF) antibody	Atezolizumab: 1200 mg IV every 3 wk Bevacizumab: 15 mg/ kg IV every 3 wk
	Sorafenib	Multi-tyrosine kinase inhibitor	400 mg oral twice daily
	Lenvatinib	Multi-tyrosine kinase inhibitor	12 mg oral once daily, if weight 60 kg 8 mg oral once daily, if weight
Second Line Treatment	Cabozantinib	Multi-tyrosine kinase inhibitor	60 mg orally once daily
	Pembrolizumab	Checkpoint inhibitor, anti– PD-1 antibody)	200 mg IV every 3 wk
	Ramucirumab	Vascular endothelial growth factor receptor 2 (VEGFR 2) antagonist	8 mg/kg IV every 2 wk
	Regorafenib	Multi-tyrosine kinase inhibitor	160 mg orally once daily on days 1–21 of each 28-day cycle

Figure: Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayale S, Lencioni R, Kolke K, Zucman-Rossi J, Finn RS. Hepatocellular carcinoma: Nat Rev Dis Primers. 2021 Jan 21; 7(1):6.
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