Hepatocellular Carcinoma Treatment Regimens

Clinical Trials: The NCCN recommends cancer patient participation in clinical trials as the gold standard for treatment.

Cancer therapy selection, dosing, administration, and the management of related adverse events can be a complex process that should be handled by an experienced health care team. Clinicians must choose and verify treatment options based on the individual patient; drug dose modifications and supportive care interventions should be administered accordingly. The cancer treatment regimens below may include both U.S. Food and Drug Administration-approved and unapproved indications/regimens. These regimens are provided only to supplement the latest treatment strategies.

These Guidelines are a work in progress that may be refined as often as new significant data become available. The NCCN Guidelines® are a consensus statement of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

Note: All recommendations are category 2A unless otherwise indicated.

▶First Line Systemic Therapy[1]

REGIMEN	DOSING
Preferred Regimens	
Atezolizumab + Bevacizumab (Child-Pugh Class A only) (Category 1)[2-5, a-c]	**Day 1:** Atezolizumab 1200mg IV **Day 1:** Bevacizumab 15mg/kg IV. Repeat cycle every 3 weeks.
Other Recommended Regimens	
Lenvatinib (Child-Pugh Class A only) (Category 1)[6,7,d]	**Days 1-28 (patients ≥60kg):** Lenvatinib 12mg orally once daily. Repeat cycle every 4 weeks. **OR** **Days 1-28 (patients <60kg):** Lenvatinib 8mg orally once daily. Repeat cycle every 4 weeks.
Sorafenib (Child-Pugh Class A [Category 1] or B7)[8-10,d,e]	**Days 1-28:** Sorafenib 400mg orally twice daily. Repeat cycle every 4 weeks.
Useful in Certain Circumstances	
FOLFOX (Category 2B)[11-13,f,g]	**Day 1:** Oxaliplatin 85mg/m^2 IV over 2 hours, **with:** **Day 1-2:** Leucovorin 200mg/m^2 IV over 2 hours daily. **followed by:** **Days 1-2:** Fluorouracil 400mg/m^2 IV push over 15 minutes daily, **followed by:** **Days 1-2:** Fluorouracil 600mg/m^2 IV continuous infusion over 22 hours daily. Repeat cycle every 2 weeks. **OR** **Day 1:** Oxaliplatin 85mg/m^2 IV over 2 hours, **with:** **Day 1:** Leucovorin 500mg/m^2 IV over 2 hours, **followed by:** **Days 1-2:** Fluorouracil 1500-2000mg/m^2 IV continuous infusion over 22 hours daily. Repeat cycle every 2 weeks.
Nivolumab (if ineligible for tyrosine kinase inhibitors or other anti-angiogenic agents) (Child-Pugh Class A or B) (Category 2B)[14,15]	**Day 1:** Nivolumab 240mg IV over 30 minutes. Repeat cycle every 2 weeks. **OR** **Day 1:** Nivolumab 480mg IV over 30 minutes. Repeat cycle every 4 weeks.

▶Subsequent-Line Systemic Therapy if Disease Progression[1]

Options	
Cabozantinib (Child-Pugh Class A only) (Category 1)[16,17,d,h]	**Days 1-28:** Cabozantinib 60mg orally once daily. Repeat cycle every 4 weeks.
Entrectinib (for patients with *NTRK* gene fusion-positive disease)[18,19,d]	**Days 1-28:** Entrectinib 600mg orally once daily. Repeat cycle every 4 weeks.
Larotrectinib (for patients with *NTRK* gene fusion-positive disease)[20,21,d]	**Days 1-28:** Larotrectinib 100mg orally twice daily. Repeat cycle every 4 weeks.
Lenvatinib (Child-Pugh Class A only)[6,7,d]	**Days 1-28 (patients ≥60kg):** Lenvatinib 12mg orally once daily. Repeat cycle every 4 weeks. **OR** **Days 1-28 (patients <60kg):** Lenvatinib 8mg orally once daily. Repeat cycle every 4 weeks.

continued

Hepatocellular Carcinoma Treatment Regimens

▶Subsequent-Line Systemic Therapy if Disease Progression[1] (continued)

REGIMEN	DOSING
Options (continued)	
Ramucirumab (AFP ≥ 400 ng/mL only) (Category 1)[22,23,i]	**Day 1:** Ramucirumab 8mg/kg IV over 60 minutes. Repeat cycle every 2 weeks.
Regorafenib (Child-Pugh Class A only) (Category 1)[24,25,d]	**Days 1-21:** Regorafenib 160mg orally once daily. Repeat cycle every 4 weeks.
Sorafenib (Child-Pugh Class A or B7)[8-10,d,e]	**Days 1-28:** Sorafenib 400mg orally twice daily. Repeat cycle every 4 weeks.
Other Recommended Regimens	
Nivolumab (Child-Pugh Class A or B)[14,15]	**Day 1:** Nivolumab 240mg IV over 30 minutes. Repeat cycle every 2 weeks. **OR** **Day 1:** Nivolumab 480mg IV over 30 minutes. Repeat cycle every 4 weeks.
Nivolumab + Ipilimumab (Child-Pugh Class A only)[14,26,27]	**Day 1:** Nivolumab 1mg/kg IV over 30 minutes, **followed by:** **Day1:** Ipilimumab 3mg/kg IV over 90 minutes Repeat cycle every 3 weeks for 4 cycles, **followed by:** **Day 1:** Nivolumab 240mg IV over 30 minutes. Repeat cycle every 2 weeks. **OR** **Day 1:** Nivolumab 1mg/kg IV over 30 minutes, **followed by:** **Day 1:** Ipilimumab 3mg/kg IV over 90 minutes. Repeat cycle every 3 weeks for 4 cycles, **followed by:** **Day 1:** Nivolumab 480mg IV over 30 minutes. Repeat cycle every 4 weeks.
Pembrolizumab (Child-Pugh Class A only) (Category 2B)[28-31,j]	**Day 1:** Pembrolizumab 200mg IV over 30 minutes. Repeat cycle every 3 weeks up to 2 years. **OR** **Day 1:** Pembrolizumab 400mg IV over 30 minutes. Repeat cycle every 6 weeks up to 2 years.

[a] Administer initial infusion of Atezolizumab over 60 minutes. If first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.
[b] The recommended infusion rate of Bevacizumab is 90 minutes for the first infusion, 60 minutes for the second infusion, and 30 minutes for any subsequent infusions.
[c] An FDA-approved biosimilar is an appropriate substitute for Bevacizumab.
[d] This agent has multiple potential drug-drug and/or drug-food interactions.
[e] Caution: There are limited safety data available for Child-Pugh Class B or C patients and dosing is uncertain. Use with extreme caution in patient with elevated bilirubin levels. (Miller, AA, et al. *J Clin Oncol.* 2009;27:1800-1805). The impact of sorafenib on patients potentially eligible for transplant is unknown.
[f] Leucovorin infusion time should match the infusion time of Oxaliplatin when these agents are given concurrently.
[g] For leucovorin: The dose listed above is based on racemic leucovorin product. Levoleucovorin is not interchangeable and the product does are not equivalent.
[h] Cabozantinib tablets and cabozantinib capsules are not interchangeable products. The dosage strengths of each product and dosing recommendations for specific indications differ.
[i] Extreme caution should be used in patients with Child-Pugh B or C hepatic impairment.
[j] Consider if microsatellite instability-high (MSI-H).

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