The importance of systemic treatment sequencing in improving survival for patients with hepatocellular carcinoma (HCC)

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Quick reference guide (to be used in conjunction with the full expert statement)

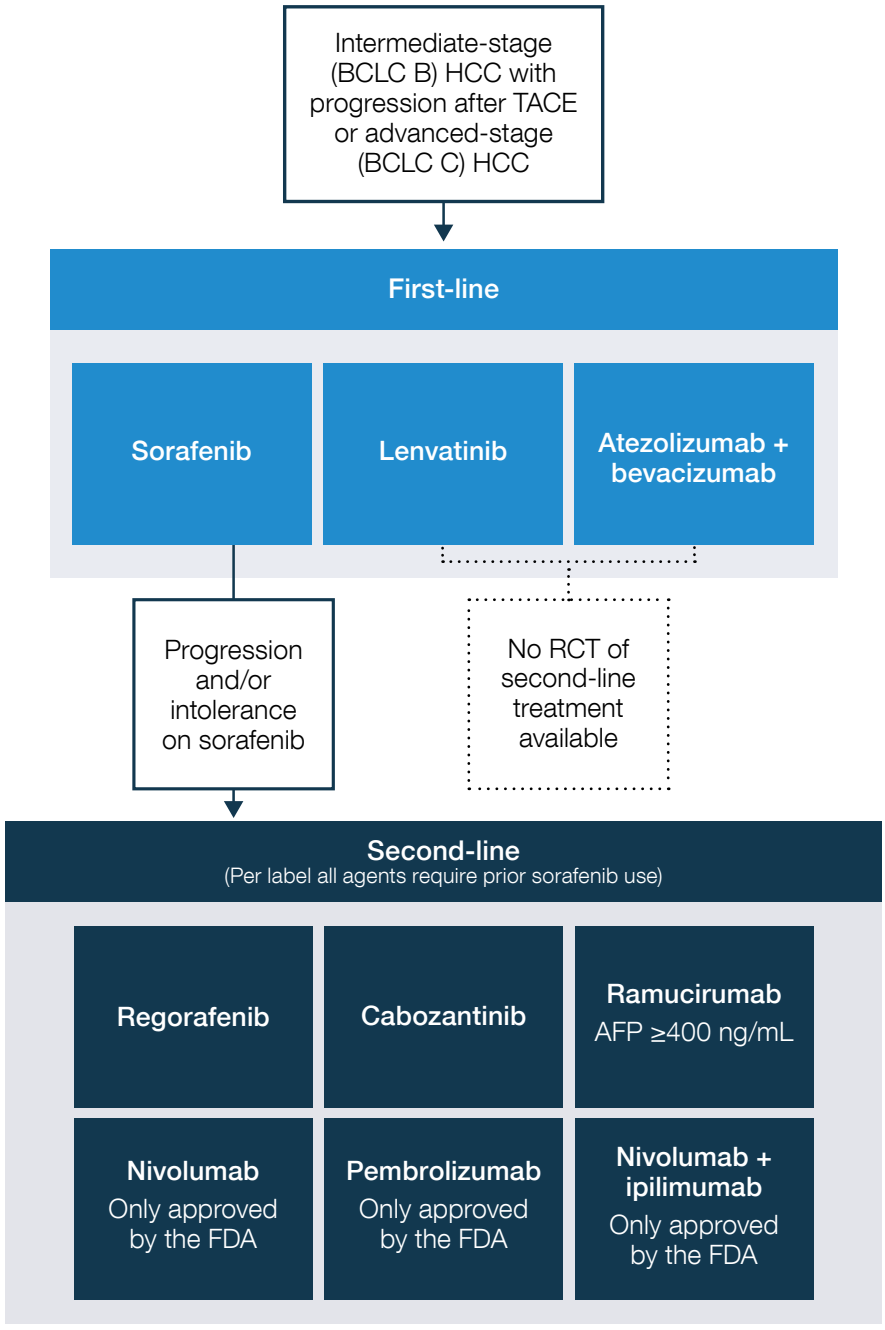
Now that multiple systemic therapies are available for HCC in both the first- and second-line setting, understanding and developing optimal systemic treatment strategies is essential – timely initiation and effective sequencing of systemic therapies has the potential to prolong the survival of patients with unresectable HCC.[1–3]

Key principles

- HCC is a fatal cancer with an overall 5-year survival rate of 14% and its incidence is increasing worldwide[4,5]
- The majority of patients are diagnosed with unresectable HCC, where potentially curative therapies are no longer feasible[6]
- Effective sequencing of available systemic therapies has the potential to increase survival beyond 2 years in patients with unresectable HCC[3]
- While the current standard of care for intermediate-stage HCC is transarterial chemoembolization (TACE), there can be substantial heterogeneity in patients, disease characteristics, and tumor response to TACE, suggesting a need for a shift in the treatment paradigm of intermediate-stage HCC in order to help preserve liver function and improve patient outcomes[7–9]
- Transition from locoregional therapies to systemic therapy at the time of TACE refractoriness has the potential to allow patients to receive multiple lines of systemic therapy and improve patient outcomes[1–3]
- The management of HCC is complex, and a multidisciplinary team (MDT) is critical in order to develop a standardized approach to patient management, with the overall objective of extending survival in patients with HCC[10]

Patient selection and systemic treatment sequencing for patients with HCC

Optimizing survival outcomes for patients with HCC relies on careful patient selection and eligibility for each treatment option; effective sequencing of systemic therapies has been proven to improve patient outcomes and prolong overall survival (OS). Based on the current evidence, the figure below outlines a proposed treatment sequence for systemic therapy.



AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; FDA, Food and Drug Administration; HCC, hepatocellular carcinoma; RCT, randomized controlled trial; TACE, transarterial chemoembolization.
Figure adapted from Bouattour M, et al. *Liver Cancer* 2019;8:341–358 and EASL. *J Hepatol* 2018;69:182–236.
All approvals are current as of July 2020.

Recommended MDT approach for the effective treatment and management of patients with HCC to improve OS: Planning, Proactivity, and Progression

PLANNING

Planning: Developing and monitoring treatment plans from patients' first visit

- An MDT is essential for managing the complexity of HCC[10]
- Accurate prognostic assessment and disease staging is critical. Clinical decision making should consider tumor burden, liver function, and patients' performance status[11–15]
- Current standard of care for intermediate-stage HCC is TACE; however, there is substantial heterogeneity within this stage[1,16]
- Both tumor burden and liver function can impact treatment selection[17–19]
  - Carefully evaluate patients for eligibility pre-treatment; monitor closely during treatment to assess refractoriness and liver function deterioration[16]
  - Offer first-line systemic therapy to patients ineligible for TACE or who progress on TACE - understanding when to stop TACE is important[1]
- Consider a timely switch from TACE to systemic therapies to allow multiple lines of therapy and potentially prolong OS[1,3,20]

PROACTIVITY

Proactivity: Management and monitoring of underlying disease and liver function

- Proactively managing etiologic factors and routine monitoring of patients can reduce the risk of developing HCC[1]
  - Encourage lifestyle changes, including healthy diet and exercise, stopping tobacco, and reducing alcohol consumption[1,21]
- Proactive management during treatment should be encouraged to ensure that optimal outcomes are maintained. Carefully assess patients receiving TACE for both response to TACE and liver function deterioration[1]
  - Efficacy of TACE is defined by complete or partial response; stable disease is not sufficient[1]
  - Timely transition from TACE to systemic therapy before decompensation is associated with improved OS[22]
  - Maintaining adequate liver function will ensure patient eligibility for potential subsequent systemic therapy[1,23,24]

Importance of proactive adverse event (AE) management

- Early monitoring of AEs to systemic therapy, as well as tailored dosing, can improve tolerability and treatment duration to help maximize clinical benefit without impacting quality of life[2,25,26]
- Inform patients on potential AEs prior to initiating systemic treatment and encourage reporting of any early signs to enable effective treatment and management
- Carefully consider the distinct AE profile of each systemic therapy during treatment selection
  - Most AEs associated with tyrosine kinase inhibitors are non-cumulative and tend to occur early[27–30]
  - AEs associated with immuno-oncology agents can occur at any time

PROGRESSION

Progression: Assessment of disease progression and treatment after progression

- Carefully consider the evaluation of tumor response and progression; absence of response to systemic therapy does not always correlate with lack of survival benefit[31,32]
  - Effective systemic therapies for HCC provide both radiological response and delayed progression[31,32]
- For treatment after progression, consider tolerance to prior therapy, patients' general clinical condition and liver function, and radiographic progression[33]
- Timely transition from first- to second-line systemic therapy allows patients to benefit from both treatment lines[3]
  - When progression is marginal, and no clinical trial is available, some patients may benefit from continuing systemic treatment after progression on all eligible therapies[33,34]

Patient education: Key recommendations

Promote close patient–healthcare professional communication by:

- Providing holistic support including routine monitoring from an MDT involving physicians, caregivers, and patient advocacy group to help the proactive management of HCC and any underlying disease as well as patients' quality of life
- Ensuring shared decision making is routine practice
- Providing patients with knowledge on:
  - Benefits of systemic therapies on OS while underlining that this is not a curative treatment approach
  - Proactive management and prevention of AEs to help them stay on therapy longer
- Keeping patients and caregivers fully informed throughout the treatment pathway
- Seeing patients regularly to assess side effects and compliance

References

1. EASL. *J Hepatol* 2018;69:182–236; 2. Bouattour M, et al. *Liver Cancer* 2019;8:341–358; 3. Finn RS, et al. *J Hepatol* 2018;69:353–358; 4. Sachdeva M, et al. *World J Hepatol* 2015;7:2080–2090; 5. Germano D, et al. *World J Gastroenterol* 2014;20:3087–3099; 6. Llovet JM, et al. *Nat Rev Clin Oncol* 2015;12:408–424; 7. Arizumi T, et al. *Dig Dis* 2016;34:671–678; 8. Bolondi L, et al. *Semin Liver Dis* 2012;32:348–359; 9. Kudo M. *Liver Cancer* 2018;7:215–224; 10. Sinn DH, et al. *PLoS One* 2019;14:e0210730; 11. Okuda K, et al. *Cancer* 1985;56:918–928; 12. Cancer of the Liver Italian Program (CLIP) investigators. *Hepatology* 1998;28:751–755; 13. Llovet JM, et al. *Hepatology* 1999;29:62–67; 14. Villa E, et al. *Hepatology* 2000;32:233–238; 15. Cabibbo G, et al. *Hepatology* 2010;51:1274–1283; 16. Sieghart W, et al. *J Hepatol* 2015;62:1187–1195; 17. Raoul JL, et al. *Cancer Treat Rev* 2011;37:212–220; 18. Llovet JM, et al. *J Natl Cancer Inst* 2008;100:698–711; 19. Kudo M. *Liver Cancer* 2019;8:299–311; 20. Labeur TA, et al. *Cardiovasc Intervent Radiol* 2019;42:230–238; 21. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. *J Hepatol* 2019;70:172–193; 22. Cheng AL, et al. *Poster presentation at ILCA* 2019: P-037; 23. Miksad RA, et al. *BMC Cancer* 2019;19:795; 24. Heimbach JK, et al. *Hepatology* 2018;67:358–380; 25. Bekaii-Saab T, et al. Ann Oncol 2018; Oral presentation at WCGIC 2018:O-014; 26. Bekaii-Saab T, et al. J Clin Oncol 2018; Poster presentation at ASCO GI 2018:P 611; 27. Grothey A, et al. J Clin Oncol 2013;31:Abtract 3637. Presented at ASCO 2013; 28. Grothey A, et al. *Lancet* 2013;381:303–312; 29. Grothey A, et al. *The Oncologist* 2014;19:669–680; 30. Blay J, et al. *European Cancer Congress* 2013:Abstract 3827; 31. Huang L, et al. *Ann Oncol* 2017;28(Suppl 5):Poster 702. Presented at ESMO 2017; 32. Bruix J, et al. *Hepatology* 2018;68(Suppl 1):O-0275. Oral presentation at AASLD Liver Meeting 2018; 33. Bruix J, et al. *Nat Rev Gastroenterol Hepatol* 2019;16:617–630; 34. Reig M, et al. *Hepatology* 2013;58:2023–2031.