THE IMPORTANCE OF SYSTEMIC TREATMENT SEQUENCING IN IMPROVING SURVIVAL FOR PATIENTS WITH HEPATOCELLULAR CARCINOMA (HCC)

An expert statement by the following contributors:

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FOREWORD

A Foreword by Dr. Catherine Frenette, M.D.

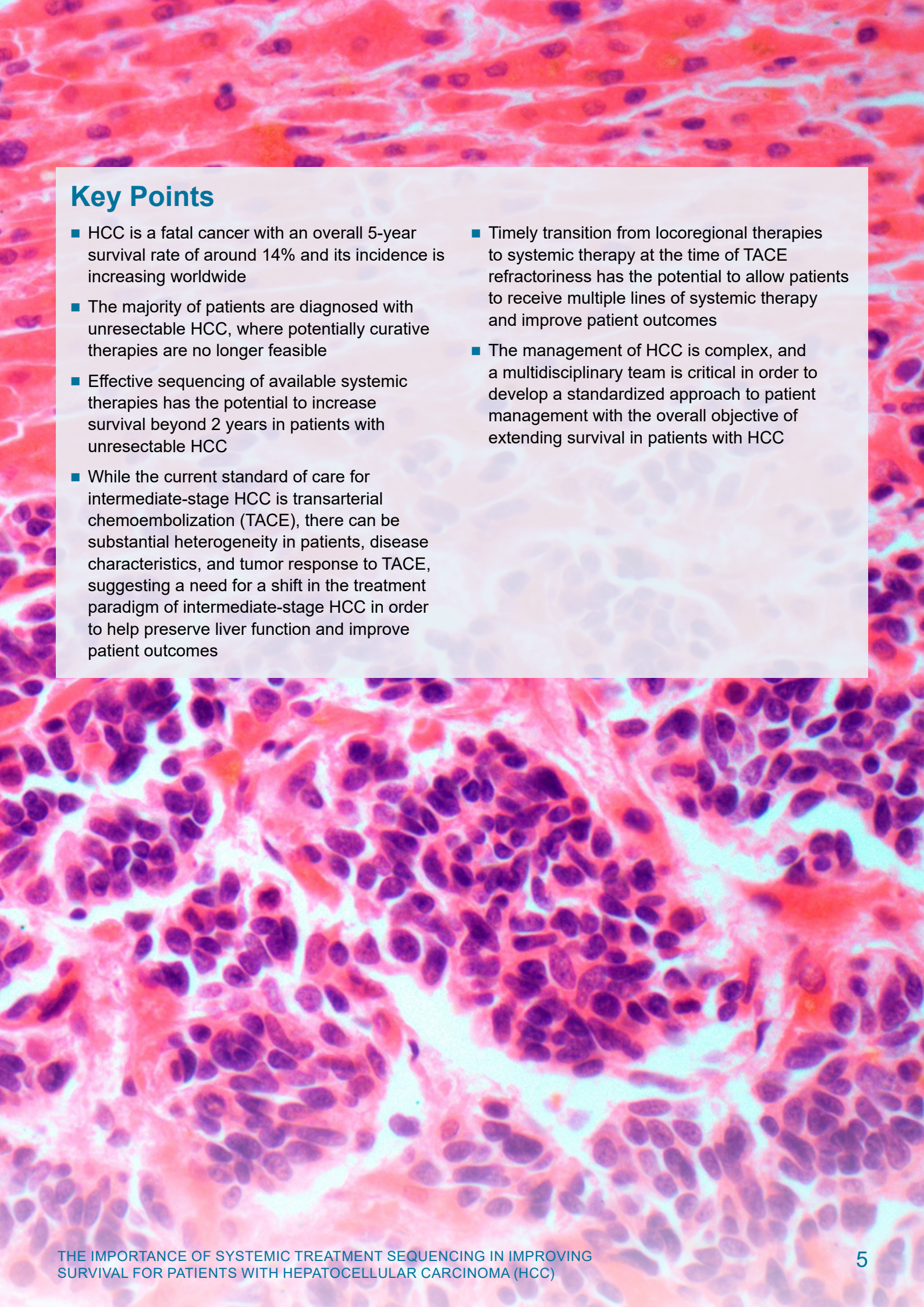
Hepatocellular carcinoma (HCC) is a fatal cancer with a significant global burden, and is one of only a few cancers with a rising incidence worldwide. Despite the significant progress that has been made over the past 10–15 years, there remains an unmet need to improve overall survival and treatment outcomes for our patients.

A lot of progress has been made in systemic treatments for unresectable HCC, with multiple agents now available. Furthermore, there is now published evidence, alongside real-world clinical experience, demonstrating that timely initiation of systemic therapy and optimal sequencing of systemic treatments has the potential to achieve an overall survival of more than two years for patients with unresectable HCC.

Dr. Catherine Frenette, M.D.

In this context, it is our obligation as professionals in the global liver cancer community to re-evaluate and update our treatment practices.

In this Expert Statement, we outline the current challenges of managing patients with HCC and aim to provide clear, straightforward guidance on implementing a robust clinical approach to systemic treatment sequencing, to help drive a universal improvement in overall survival among patients with HCC.



Key Points

- HCC is a fatal cancer with an overall 5-year survival rate of around 14% and its incidence is increasing worldwide
- The majority of patients are diagnosed with unresectable HCC, where potentially curative therapies are no longer feasible
- Effective sequencing of available systemic therapies has the potential to increase survival beyond 2 years in patients with unresectable HCC
- 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
- Timely 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
- The management of HCC is complex, and a multidisciplinary team is critical in order to develop a standardized approach to patient management with the overall objective of extending survival in patients with HCC

INTRODUCTION TO HEPATOCELLULAR CARCINOMA (HCC)

Liver cancer is the sixth most common cancer and the fourth most common cause of cancer death worldwide.[1,2] HCC is the most common primary liver cancer in adults, accounting for 75–85% of all cases.[2] The incidence of liver cancer is increasing globally, with a 38% increase reported between 2006 and 2016 – a trend not seen among other common cancer types.[3]

Chronic liver injury followed by inflammation are crucial steps in the development of HCC, whereby approximately 90% of HCC cases are preceded by chronic liver disease and liver cirrhosis.[4-6] Causes of cirrhosis and risk factors for the development of HCC include hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD), alcohol consumption, obesity, and tobacco smoking.[6,7] In recent years, the incidence of NAFLD-related HCC has increased; in the USA, the incidence is expected to increase by 122% between 2016 and 2030.[8]

HCC has a poor prognosis, with an estimated 5-year survival rate of 14%, which depends on disease stage at diagnosis, treatment availability, and severity of underlying liver disease.[6,9,10] Approximately 30% of patients are eligible for potentially curative therapies, such as resection or transplantation; however, most are diagnosed with unresectable HCC, where such curative therapies are not feasible.[11] Therefore, there is an ongoing need for effective therapies that prolong survival in patients with unresectable HCC.

Current treatment landscape

Several treatment options are currently available for patients with HCC, and treatment decisions are based on numerous factors, including tumor burden, liver function, and performance status.[12,13] The most widely used staging system for HCC, the Barcelona Clinic Liver Cancer (BCLC) system, considers each of these variables to differentiate individual patients with the disease.[1,14,15] Patients with very early-/early-stage disease (BCLC stage 0 or A) are candidates for potentially curative treatment options (resection, transplantation, ablation). For intermediate-stage disease (BCLC stage B), standard of care for most patients is locoregional therapy with TACE, and for advanced-stage disease (BCLC stage C), systemic therapy is the standard treatment. Systemic therapy is also considered appropriate for patients with BCLC stage B if they are not suitable candidates for locoregional therapy. Patients with end-stage disease (BCLC stage D), who are not candidates for liver transplantation, generally receive only best supportive care.[12,13,16,17]

While the current standard of care for intermediate-stage HCC is TACE, it has become apparent that there can be substantial heterogeneity in both the disease state and response to TACE, suggesting the need for a paradigm shift for the treatment of intermediate-stage HCC. Indeed, numerous subclassifications have been proposed for intermediate-stage HCC with the aim of facilitating treatment decisions in this heterogeneous patient population.[18,19] The recently developed Kindai criteria **(Figure 1)** suggests that systemic therapy could be a suitable treatment option for patients who are likely to become TACE-refractory in order to preserve liver function and improve overall survival (OS) in BCLC stage B HCC.[20] Improving patient outcomes in intermediate-stage HCC has the potential to cause a shift in the current treatment paradigm whereby systemic therapy is administered before there is a decline in liver function and/or performance status, thus allowing patients to receive multiple lines of treatment with the potential to extend OS. In this scenario, patients may still be classified as BCLC stage B and be appropriate for systemic therapy.

Figure 1. Heterogeneity of intermediate-stage HCC and potential treatment strategies

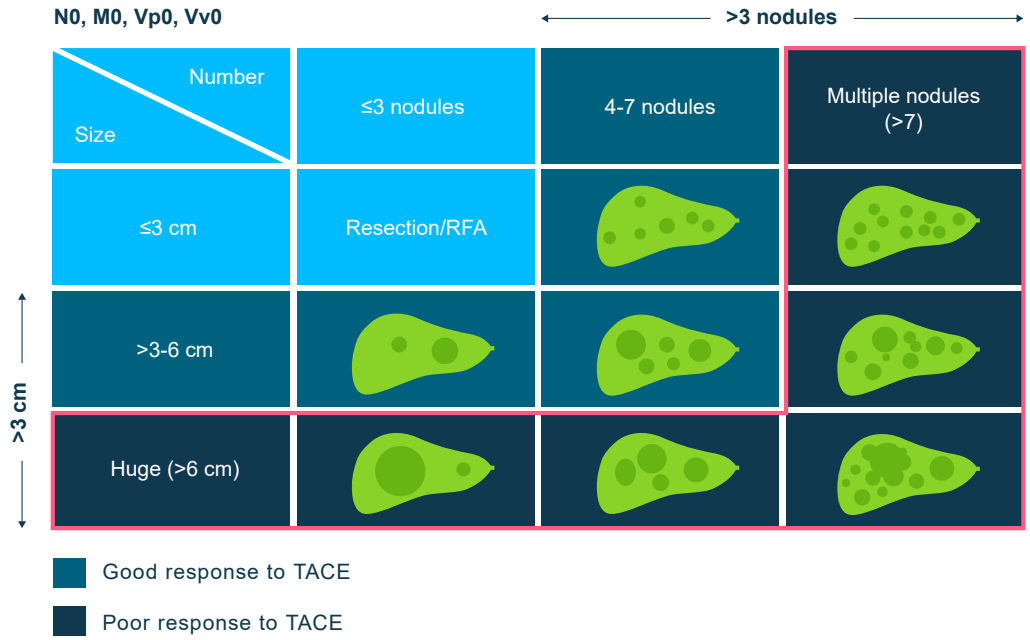


Figure adapted from Kudo M. *Liver Cancer* 2018;7:215–224.[20]

The systemic treatment landscape for unresectable HCC changed over a decade ago, with the results of two phase 3 studies demonstrating a survival benefit in the first-line setting with sorafenib.[21,22] Based on these studies, sorafenib became the first systemic therapy to be approved for unresectable HCC. In 2018, lenvatinib was the second agent that was approved in the first-line setting based on non-inferiority to sorafenib in a phase 3 randomized controlled trial.[23] Atezolizumab in combination with bevacizumab demonstrated improvement in OS versus sorafenib in the first-line setting and is approved for use as a first-line treatment option by the Food and Drug Administration (FDA) and other regulatory authorities.[24–26] The tyrosine kinase inhibitors regorafenib and cabozantinib and the monoclonal antibody ramucirumab (VEGF-2) have been investigated as second-line treatment options; they are all approved for use after sorafenib treatment by both the European Medicines Agency and FDA based on positive data from phase 3 trials.[27–29] Two immuno-oncology agents, nivolumab and pembrolizumab, have also been evaluated; however, they are currently only approved by the FDA (second-line setting), and recent phase 3 data have failed to show improvement versus standard of care **(Table 1)**.[30–32] More recently, the combination of nivolumab plus ipilimumab has received accelerated approval by the FDA for the second-line treatment of HCC, based on overall response data from the phase 1/2 CheckMate 040 trial.[33]

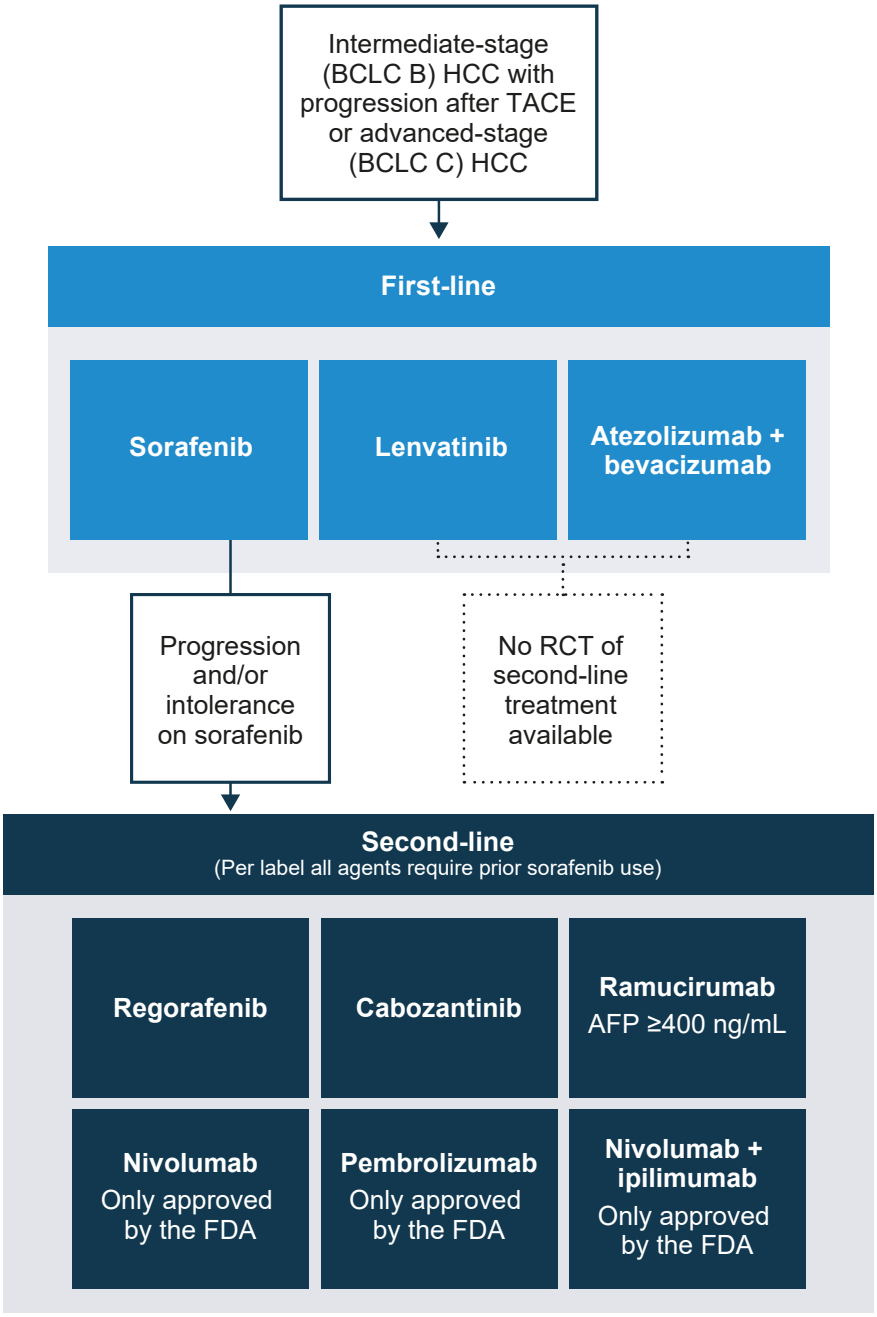
Table 1. Summary of outcomes from pivotal phase 3 HCC trials of systemic therapy

Drug	Trial	Comparator	Median OS, months	HR
First-line HCC				
Sorafenib	SHARP[21]	Placebo	10.7 vs 7.9	0.69 | P<0.001
	Asia-Pacific[22]	Placebo	6.5 vs 4.2	0.68 | P=0.014
Lenvatinib	REFLECT[23]	Sorafenib	13.6 vs 12.3	0.92*
Nivolumab	CheckMate 459[31]	Sorafenib	16.4 vs 14.7	0.85 | P=0.0752
Atezolizumab + bevacizumab	IMbrave150[24]	Sorafenib	NE vs 13.2	0.58 | P<0.001
Second-line HCC				
Regorafenib	RESORCE[27]	Placebo	10.6 vs 7.8	0.63 | P<0.0001
Ramucirumab	REACH-2 (AFP high†)[28]	Placebo	8.5 vs 7.3	0.71 | P=0.0199
Cabozantinib	CELESTIAL[29]	Placebo	10.2 vs 8.0	0.76 | P=0.005
Pembrolizumab	KEYNOTE-240[32]	Placebo	13.9 vs 10.6	0.78 | P=0.0238

Median OS is drug versus comparator, respectively. *Lenvatinib was non-inferior to sorafenib for OS; †AFP ≥400 ng/mL.
AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; HR, hazard ratio; NE, not estimable; OS, overall survival.

With the increasing number of options for the first- and second-line treatment of HCC, understanding and developing optimal systemic treatment strategies is crucial. Future treatment strategies for unresectable HCC include combination treatment approaches with immuno-oncology therapies, including the combination of targeted therapies with checkpoint inhibitors and dual checkpoint inhibition.[34] Recently, the combination of atezolizumab (anti-PD-L1) plus bevacizumab (anti-VEGF) demonstrated improved progression-free survival and OS versus sorafenib in the first-line treatment of HCC,[24] and nivolumab (anti-PD-1) in combination with ipilimumab (anti-CTLA-4) achieved a consistently high objective response rate (>30%) in the second-line setting.[35] A number of additional combination therapies with checkpoint inhibitors are currently being investigated in both early-phase and phase 3 clinical trials. **Figure 2** outlines potential treatment sequences based on current evidence.[12,30] Effective sequencing of systemic therapies has the potential to extend OS; for example, based on the exploratory retrospective analysis of the RESORCE study, the sequence of sorafenib followed by regorafenib has indicated an extended median OS of 26 months.[36] To ensure patients are eligible for multiple treatment lines, which can lead to a prolonged survival, timely initiation of systemic therapy is important.

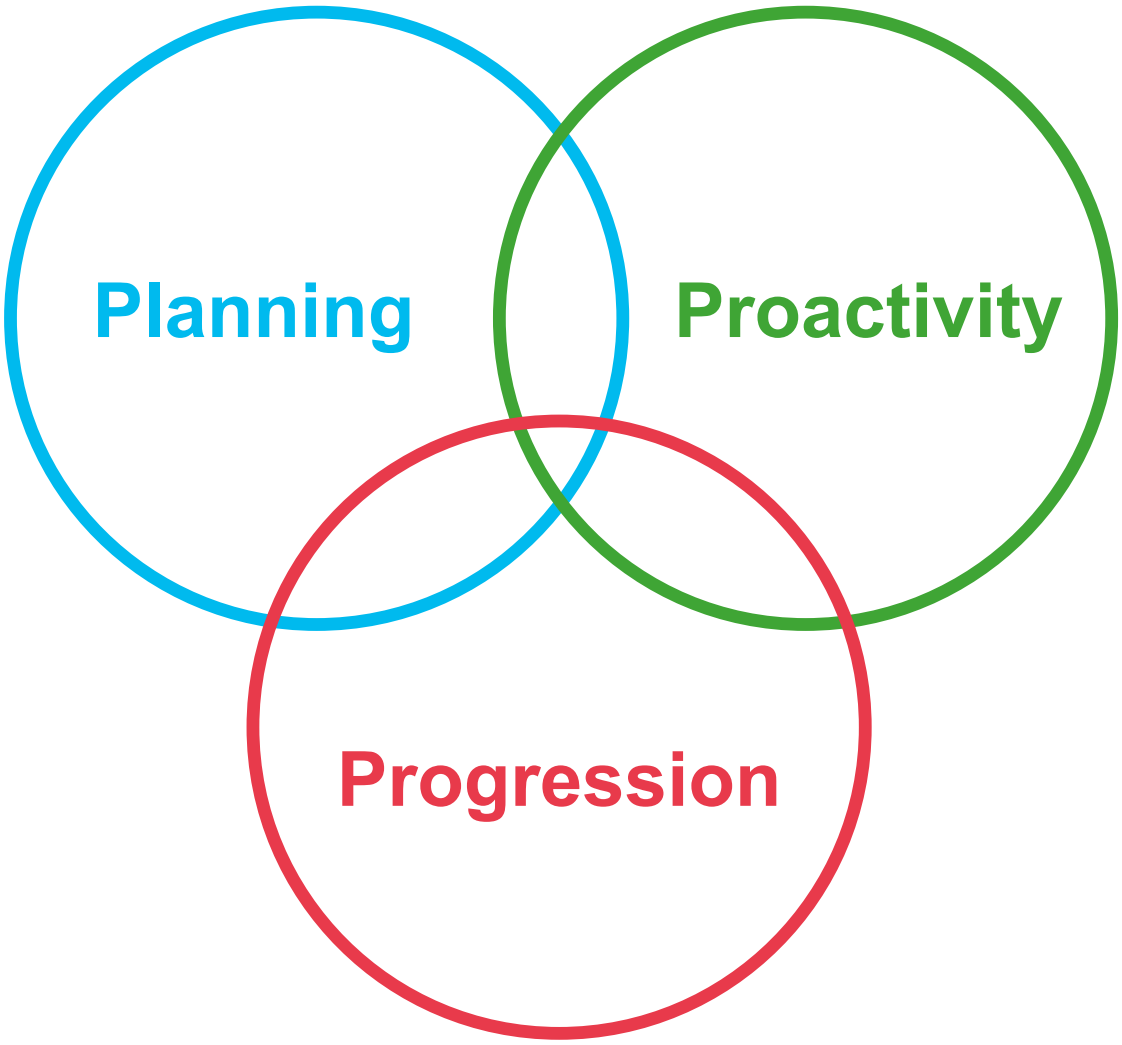
Figure 2. Current systemic treatment options for patients with HCC



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 August 2020.

This Expert Statement highlights three important focus areas for the effective treatment and management of HCC to improve patient survival: Planning, Proactivity, Progression

Figure 3. Planning, Proactivity, Progression



Planning

- Patient selection and eligibility for treatment
- Treatment planning and systemic treatment sequencing
- Importance of MDT involvement

Proactivity

- Proactive management of underlying liver disease
- Proactive assessment of TACE efficiacy
- Proactive monitoring of liver function and toxicity

Progression

- Assessment of disease progression
- Treatment after progression and treatment sequencing

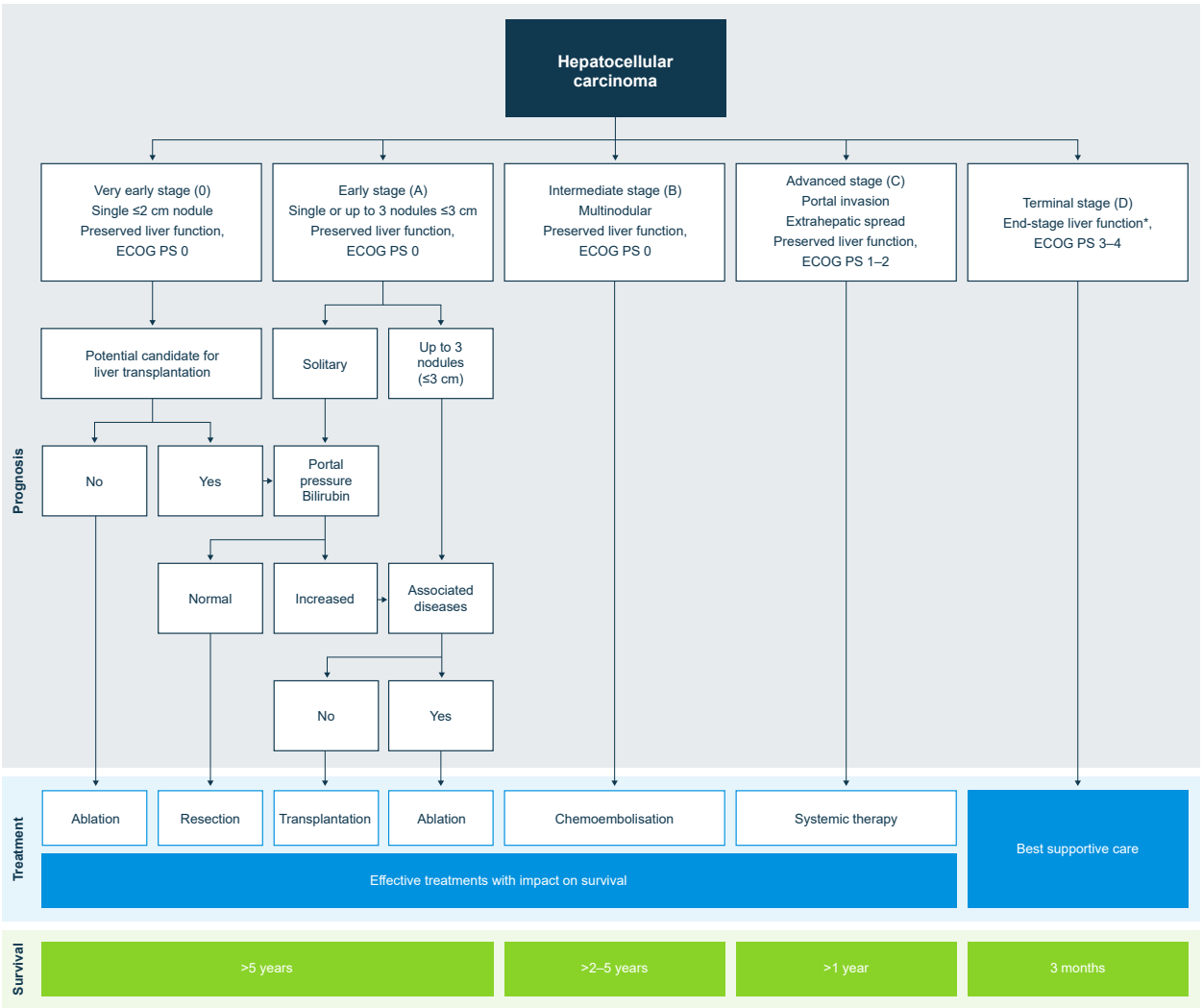
PLANNING: DEVELOPING AND MONITORING TREATMENT PLANS FOR PATIENTS WITH HCC FROM THEIR FIRST VISIT

Key considerations:

Patient selection and eligibility for treatment

- Accurate prognostic assessment and disease staging is a crucial step in the management of HCC. When using a staging system for clinical decision making, one should consider tumor burden and liver function, as well as a patient's performance status[37–41]
  - The BCLC staging system is one of the most commonly used systems that has been externally validated and endorsed by EASL and AASLD; as such, the BCLC staging system is recommended for prognostic prediction and treatment recommendations for patients with HCC[1,12,16]
- Patients with HCC are classified into five stages and therapies are recommended accordingly: Very early stage (BCLC stage 0), early (BCLC stage A), intermediate (BCLC stage B), advanced (BCLC stage C), and terminal-stage HCC (BCLC stage D) **(Figure 4)**[1]

Figure 4. BCLC staging and treatment strategy



*Patients with end-stage cirrhosis due to heavily impaired liver function (Child–Pugh stage C or earlier stages with predictors of poor prognosis or high a MELD score) should be considered for liver transplantation.
BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; MELD, Model of End-Stage Liver Disease.
Figure adapted from Forner A, et al. *Lancet* 2018;391:1301–1314[1]

- Patients with very early- or early-stage disease are eligible for curative therapies, including ablative therapies, surgical resection, and transplantation[1,12]
  - Very early-stage HCC (BCLC stage 0) may be defined as one tumor ≤2 cm, preserved liver function, and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0[1,12]
  - Early-stage HCC (BCLC stage A) includes patients with a single tumor >2 cm or three nodules ≤3 cm, preserved liver function, and an ECOG PS of 0[1,12]
- Intermediate-stage HCC (BCLC stage B) is commonly defined as a multinodular, asymptomatic tumor, without vascular invasion or extrahepatic spread, preserved liver function, and an ECOG PS of 0[1,12]
  - However, there is substantial heterogeneity among patients within this stage and current staging systems may not fully account for tumor burden or liver function, both of which can impact treatment selection[20,42,43] **(Figure 1)**
  - The current standard of care for intermediate-stage HCC is TACE; however, patients should be carefully evaluated for eligibility prior to treatment and monitored closely during treatment to assess refractoriness and liver function deterioration[12,44]
    - Overuse of locoregional therapies, including repeated TACE in TACE-refractory patients, is associated with acute and chronic liver function deterioration, which can impact the use of subsequent, effective, systemic therapies[44,45]
    - Treating patients with TACE who are not appropriate candidates is associated with poorer patient outcomes[46]
    - EASL HCC guidelines do not recommend transarterial radioembolization (TARE), and the subgroup of patients who benefit from TARE needs to be further defined[12]
  - Patients who are ineligible for TACE and those who become TACE refractory may benefit from timely initiation of systemic therapy[45]
- Patients with advanced-stage HCC (BCLC stage C) include those with symptomatic tumors, an ECOG PS of 1–2, and macrovascular invasion or extrahepatic spread[1,12]
  - Systemic therapy is recommended for patients with advanced-stage HCC; current evidence for systemic therapy is outlined in **Table 1**
  - Two randomized controlled trials comparing efficacy and safety in patients treated with selective internal radiation therapy (or TARE) versus sorafenib did not reach statistical significance for superiority in OS[12]
- If a patient does not meet all criteria for a given treatment stage allocation, they should be offered the next most appropriate treatment option, either within the same stage or in the next prognostic stage[12]
  - For example, patients with intermediate-stage HCC (BCLC stage B) who have contraindications or untreatable progression on TACE should be offered first-line systemic therapy[12,20,30]

Treatment planning and systemic treatment sequencing

- Locoregional therapy with TACE is indicated for the treatment of intermediate-stage HCC (BCLC stage B); patient selection for initial TACE treatment, retreatment with TACE, and deciding when to stop TACE, are key considerations for preserving liver function and optimizing survival outcomes[12,47]
  - It is important to understand when to stop TACE and start systemic therapy. It is recommended that TACE should not be repeated if substantial necrosis has not been achieved following two TACE treatments; these patients should be moved to an alternative therapy[12]
    - Unfortunately, none of the available scoring systems (e.g. STATE, HAP, and CHIP) have been widely implemented in clinical practice, and there is insufficient evidence to recommend scoring for the selection of BCLC stage B patients for TACE[48–51]
  - Contraindications to TACE treatment include tumor size ≥10 cm, extensive tumor burden involving massive invasion into both lobes, extrahepatic spread, severely reduced portal vein flow, decompensated cirrhosis (Child–Pugh B ≥8), and renal insufficiency, as well as technical contraindications to hepatic intra-arterial treatment[17,42]
  - Patients should be closely monitored for signs of liver function deterioration before and after TACE treatment; elevated aminotransferases and negative changes in liver function tests are observed in a large proportion of patients with HCC receiving TACE[44,52]
    - Liver function is a key prognostic factor for TACE, with worse liver function leading to poorer survival[53]
    - It is important that TACE is discontinued before liver function deterioration has reached a critical point to ensure patients are still eligible for further alternative treatments – systemic therapies are only indicated in patients with adequate liver function[12,54]
    - The albumin–bilirubin grading system may be more applicable than Child–Pugh in current and future HCC populations, as it has shown to be a prognostic factor for survival[55,56]
- Although TACE is considered the standard of care treatment for patients with intermediate-stage HCC (BCLC stage B), this is a very heterogeneous population and not all patients are suitable for, or will respond to, TACE[47]
  - Patients may vary widely in terms of tumor burden (large/multifocal HCC), liver function (Child–Pugh A or B), and disease etiology[42,43,57]
  - The heterogeneity of these patients has both prognostic and therapeutic implications; in clinical practice, treatment selection for patients with intermediate-stage HCC should always be based on careful evaluation of individual patient's characteristics[19,47]
  - It is also important to note that TACE was developed prior to the availability of effective systemic therapies for the treatment of HCC
- Systemic therapy can be an effective treatment option for patients with intermediate-stage HCC who are unsuitable for, refractory to, or have progressed after TACE, and still have preserved liver function. It is important to note that patients do not require extrahepatic disease to be considered for systemic therapy[12,16,42]
  - First-line systemic therapy has been shown to confer a survival benefit in patients with intermediate-stage HCC (BCLC stage B) and those who have previously been treated with TACE[23,24,58,59]
- With the availability of more systemic therapies that have been proven to extend survival in large randomized studies, it is important that patients are switched from locoregional therapies to systemic therapies when there is radiographic progression, as described above, and before there is decompensation.[12,20,21,23] Stopping locoregional therapy earlier than before (prior to availability of effective systemic therapies), will allow patients to receive multiple lines of systemic therapy[12,20,36]
  - Currently, approved first-line treatment options indicated for patients with unresectable HCC include sorafenib, lenvatinib, and atezolizumab plus bevacizumab[13,60,61]
  - Second-line treatment options approved for patients who have progressed on sorafenib include regorafenib, cabozantinib, ramucirumab (patients with alpha-fetoprotein [AFP] ≥400 ng/mL only), the checkpoint inhibitors nivolumab and pembrolizumab (FDA only), and the combination of nivolumab and ipilimumab (FDA only).[33,62-66] No randomized, controlled, phase 3 studies have evaluated second-line treatment after lenvatinib[30]
  - The established treatment sequencing of sorafenib followed by regorafenib has may extend OS beyond what has previously been reported; based on the exploratory retrospective analysis of the RESORCE trial[36]
  - With increasing clinical experience, OS with systemic therapy continues to improve. In phase 3 trials, OS in patients with HCC treated with sorafenib has increased over time: 10.7 months in 2008 (SHARP trial),[21] 12.3 months in 2018 (REFLECT trial),[23] and 14.7 months and 13.2 months in 2019 (CheckMate 459 trial and IMbrave150 trial, respectively)[24,31]

- Future treatment strategies for unresectable HCC include combination treatment approaches with checkpoint inhibitors[34]
  - The combination of atezolizumab (anti-PD-L1) and bevacizumab (anti-VEGF) resulted in a statistically significant improvement in OS over sorafenib in patients with unresectable HCC[24]
  - In a cohort of patients with HCC from the phase 1/2 CheckMate 040 trial, the combination of nivolumab and ipilimumab resulted in an objective response rate of 33%; verification of its clinical benefit is required from confirmatory clinical trials[33]

Importance of multidisciplinary team (MDT) involvement

- The management of HCC is very complex; therefore, an MDT is critical to ensure that the optimal level of patient care is provided[67,68]
  - For example, understanding individual patient profiles, including tumor characteristics, as well as the presence of comorbidities and underlying liver disease, is important and will require MDT involvement
  - An MDT will support the overall management of patients, including adverse events (AEs), liver function, and quality of life
- An MDT should include liver and transplant surgeons, radiologists, hepatologists, oncologists, pathologists, nurses, caregivers, and patient advocates; discussing treatment options as part of a wider team can optimize treatment planning and outcomes[67,68]
- Disease staging and treatment allocation should be discussed in MDTs to fully capture and tailor individualized treatment options, within the framework of accepted guidelines[12,16,67,68]
- An MDT will enable an effective treatment plan to be developed from the patient's first visit and maintained throughout their entire treatment pathway, allowing for timely management decisions to be made as a patients condition evolves[67]
  - It has been shown that patients who go through an MDT have an earlier, more accurate diagnosis, better treatment options, and better OS[67]

Value of patient education

For optimal care, it is critical that patients are provided with holistic support from an MDT to help with the proactive management of HCC and any underlying disease, and to improve/maintain patients' quality of life.[69,70]

Regarding the management of patients receiving systemic therapy, a key recommendation from this Working Group is to promote close communication between the patient and the physician so that AEs are detected early and managed appropriately, and severe AEs can be prevented. Healthcare professionals have become more efficient in managing AEs, identifying patients who are likely to benefit from treatment, and assessing response to treatment. Additional recommendations include:

- Equipping patients with knowledge on the benefits of systemic therapies in improving OS and how AEs can be effectively managed
  - Proactive management and prevention of AEs can enable patients to stay on therapy longer
- Shared decision making between patients and physicians is key for effective HCC management and patients should be fully informed throughout their entire treatment journey

PROACTIVITY: PROACTIVE MANAGEMENT OF UNDERLYING LIVER DISEASE, MONITORING OF LIVER FUNCTION, AND MANAGEMENT OF ADVERSE EVENTS

Key considerations:

Proactive management of underlying liver disease

- Proactively managing etiological factors can reduce the risk of HCC development[12]
  - Vaccination against HBV reduces the risk of HCC, and in patients with chronic hepatitis, antiviral therapies for HBV and HCV have been shown to prevent progression to cirrhosis and HCC development[12]
  - Lifestyle changes, including healthy diet, stopping tobacco use, and reduced alcohol consumption, should be encouraged; obesity, tobacco use, and alcoholic liver cirrhosis are risk factors for the development of HCC[12,71]
- Nutritional counselling is encouraged for patients with cirrhosis to ensure they achieve adequate caloric and protein intake[71]
  - Malnutrition can be a significant burden in patients with liver cirrhosis and has been reported in more than 50% of patients with decompensated liver disease. Patients who are malnourished have a poorer prognosis; therefore, their dietary intake should be improved[71]
    - It is recommended that patients with liver cirrhosis have a protein intake of 1.2–1.5 g/kg of body weight per day to prevent loss of muscle mass, or reverse muscle loss[71]
  - In NASH/NAFLD-related cirrhosis, obesity is observed in most cases; obese patients with a body mass index >30 kg/m^2 should be provided with a nutrition and lifestyle program to facilitate progressive, but safe, weight loss[71]
    - A reduction in body weight has been shown to improve outcomes in obese patients with compensated cirrhosis[71]
    - There is a strong association between diabetes and NASH/NAFLD, which leads to further complications, including the development of liver cirrhosis and HCC; therefore, proactive management of diabetes is important[72]
- Osteoporosis, characterized by a loss of bone mass and integrity, is commonly observed among patients with chronic liver disease[71]
  - It is important to be able to recognize patients with HCC who are at risk of bone loss. Key risk factors include alcohol abuse, smoking, low body mass index (<19 kg/m^2), male hypogonadism, early menopause, secondary amenorrhea (>6 months), family history, advanced age, and treatment with corticosteroids[71]
  - Patients with chronic liver disease should be advised about a balanced diet, and calcium supplements provided to preserve normal calcium levels[71]
  - Patients should be encouraged to reduce factors that can exacerbate bone loss, including alcohol and tobacco use, and to increase physical activity[71]
- Implementation of screening and surveillance programs can help identify patients at higher risk of developing chronic liver disease and HCC[12]

Proactive assessment of TACE efficacy

- The efficacy of TACE should only be defined by either complete response (CR) or partial response (PR); stable disease (SD) is not sufficient[12,73]
  - The thresholds for defining CR/PR and SD differ between Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and modified RECIST (mRECIST); higher rates of SD and lower rates of CR have been observed after TACE when using RECIST v1.1 compared with mRECIST. As CR and PR are the goal of TACE treatment, careful consideration is needed when choosing which criterion is used to assess response[74-76]
- More than two cycles of TACE should be avoided if substantial tumor necrosis has not been achieved. Additionally, patients should not receive a repeated TACE procedure upon untreatable progression, which includes extensive liver involvement, extrahepatic metastasis or vascular invasion, and minor intrahepatic progression associated with impaired liver function and performance status[12]

Proactive monitoring of liver function

- Patients should be monitored closely for signs of liver function deterioration during locoregional therapy[44]
  - Signs of acute and chronic liver damage are commonly seen following TACE, including elevated aminotransferases, and serum bilirubin, and reduced serum albumin. Such liver damage adversely impacts liver function, can lead to decompensation, and worsens prognosis[44]
  - Patients receiving non-selective TACE procedures may be more likely to suffer liver function deterioration[77]
  - Appropriately timed transition to systemic therapy after TACE has been associated with improved OS compared with patients who receive subsequent TACE and then receive systemic therapy later in their treatment course[78]
- Maintaining adequate liver function will ensure eligibility for subsequent, effective systemic therapy.[44] Systemic therapies have been shown to be most effective and tolerable in patients with preserved liver function (Child–Pugh A) and good performance status[12,16]

Proactive management of AEs

- Each systemic therapy currently available for the treatment of HCC has its own distinct AE profile
  - The most common AEs for tyrosine kinase inhibitors include arterial hypertension, diarrhea, asthenia, hand–foot skin reaction (HFSR), and proteinuria[23,30]
  - Immuno-oncology agents mainly result in rash and other immune-mediated AEs, including immune-mediated hypothyroidism, adrenal insufficiency, colitis, hepatitis, and acute renal injury[30]
- Most AEs associated with tyrosine kinase inhibitors are non-cumulative and tend to occur early in treatment (Cycle 1)[79–82]
  - The occurrence of early skin toxicity with tyrosine kinase inhibitors is associated with a significant OS benefit;[83,84] thus, the development of HFSR may be a pharmacodynamic marker associated with better outcomes and should be managed effectively to keep patients on treatment[85]
- AEs associated with immuno-oncology agents can occur at any time during the course of treatment, and while usually low grade, can be unpredictable and sometimes severe, requiring steroids or other immunosuppressive measures[31,32,86]
- Early monitoring and dose adjustments can improve tolerability and ensure patients stay on treatment for longer, thus maximizing the clinical benefit of systemic therapies without adversely affecting patients' quality of life[87,88]

Adverse event management

Table 2 provides a brief guide on how to effectively manage common AEs associated with systemic therapy.[30] It is important that physicians inform patients on the potential AEs prior to initiating systemic treatment and encourage them to report the signs early in order to effectively treat and manage them.

General management of AEs by grade:

- **Grade 1:** Symptomatic treatment
- **Grade 2:** Symptomatic treatment, dose reduction, and dose interruption
- **Grade 3/4:** Symptomatic treatment and dose interruption

Table 2. Management of AEs associated with systemic therapies for HCC

AE	Management approach
Asthenia	Nutritional support
Arterial hypertension	Antihypertensive treatment
Hand–foot skin reaction	Prophylactic urea cream Therapeutic urea cream Topical corticosteroid
Diarrhea	Loperamide
Rash	Therapeutic urea cream Topical corticosteroid
Immune-mediated AE	Discuss use of corticosteroids

AE, adverse event; HCC, hepatocellular carcinoma.


Profile
tal Cholesterol
Triglyceride
HDL-Chol
LDL-Chol (Dire
Liver function
Total Protein
Albumin
Globulin
Bilirubin

PROGRESSION: ASSESSMENT OF DISEASE PROGRESSION AND TREATMENT AFTER PROGRESSION

Key considerations:

Assessment of disease progression

- In addition to RECIST, HCC tumor response and progression are commonly assessed via imaging using mRECIST, which was developed specifically for the assessment of HCC[76]
  - mRECIST incorporates the concept of viable tumor assessment, defined as the portions of the tumor showing arterial enhancement;[89] unlike RECIST, which relies on the longest tumor diameter, mRECIST measures the longest enhancing component of tumors in the liver[76]
- Four patterns of progression have been identified for HCC: intrahepatic growth, extrahepatic growth, new intrahepatic lesion, and new extrahepatic lesion and/or vascular invasion[90]
  - Progression patterns may be a key prognostic parameter for patients with HCC being treated with a systemic therapy; the development of new extrahepatic lesions is associated with worse survival irrespective of treatment[91,92]
- In HCC, the absence of a tumor response to systemic therapy does not generally correlate with a lack of survival benefit, as confirmed by results from the SHARP, Asia-Pacific, and RESORCE trials[93,94]
  - In recent analyses, objective response was an independent predictor of OS in patients with HCC, regardless of treatment[95]
  - In most patients, systemic therapies in HCC improve OS by delaying progression, and do not just benefit patients who obtain a radiologic response
- For treatment after progression on first-line therapy, it is important to consider the patient's tolerance to prior therapy, general clinical condition, and liver function[96]
- There are currently limited predictive biomarkers in HCC; thus, treatment decisions will be dependent on the patient's clinical profile and physician and/or patient preference
  - Utility of elevated AFP as a predictive marker for antiangiogenic treatment was demonstrated in an enriched population with ramucirumab (AFP ≥400 ng/mL);[97] however, other systemic therapies have also shown benefit in this enriched population[98]

Treatment after progression and treatment sequencing

- Timely transition from first-line to second-line systemic therapy allows patients to benefit from this sequence of treatments. For example, for patients treated in the RESORCE study, an exploratory retrospective analysis indicated an extended survival benefit of 26 months (versus placebo [19.2 months]) with the treatment sequence of sorafenib followed by regorafenib[36]
- Some patients who have received all eligible therapies may benefit from continuing systemic treatment beyond progression, particularly when progression has been deemed 'marginal' and there is no clinical trial available[92,96]

Key points for patient education and shared decision making – Working Group recommendations

- It is important that patients expect and receive robust, holistic clinical support, including guidance on nutrition, physical activity, and bone health from an MDT to ensure both the underlying liver disease and the cancer itself are effectively managed, and consideration is given to how patients' quality of life can be optimized. Caregiver education is also important to ensure optimum care is provided
  - Patients should be informed about the importance of routine monitoring, which will enable proactive management of underlying liver disease, thereby reducing the risk of developing HCC
  - Regular patient visits should be encouraged to assess AEs and treatment compliance
- The goal of treatment for HCC should be made clear, emphasizing the potential for survival beyond 2 years with systemic therapy, while underlining that this is not a curative approach
- Realistic expectations from imaging results following locoregional therapy should be discussed with patients because tumor shrinkage does not necessarily correlate with survival benefit
  - It should be explained that transition from locoregional therapies to systemic treatment, when appropriate, can enable them to receive multiple lines of systemic therapy, providing additional survival benefit
- Information on the multiple systemic therapeutic options that can extend OS should be given to patients with HCC, including those with advanced-stage disease
  - Timely transition from first- to second-line systemic therapy allows patients to benefit from both lines of treatment
- Educating and working with patients to proactively and effectively manage the AEs of systemic treatment is critical to optimize patients' quality of life and maintain treatment benefit

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PRESCRIBING INFORMATION

NEXAVAR®

US: Nexavar (sorafenib) [prescribing Information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals, December 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203085lbl.pdf. Last accessed: July 2020

EU: Nexavar (sorafenib) Summary of Product Characteristics (SmPC), Bayer Pharma AG, 51368 Leverkusen, Germany, 2019. Available at: https://www.ema.europa.eu/en/documents/product-information/stivarga-epar-product-information_en.pdf. Last accessed: July 2020

NEXAVAR® has been approved in other countries beyond the US and EU. Please refer to local labels for further information.

STIVARGA®

US: Stivarga (regorafenib) [prescribing Information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals, June 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021923s008s009lbl.pdf . Last accessed: July 2020

EU: Stivarga (regorafenib) Summary of Product Characteristics (SmPC), Bayer Pharma AG, 51368 Leverkusen, Germany, 2019. Available at: https://www.ema.europa.eu/en/documents/product-information/nexavar-epar-product-information_en.pdf. Last accessed: July 2020

STIVARGA® has been approved in other countries beyond the US and EU. Please refer to local labels for further information.

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