Evolution of Systemic Therapy in Advanced Hepatocellular Carcinoma

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KEYWORDS

• Hepatocellular carcinoma • HCC • Systemic therapy • Immunotherapy • Treatment

KEY POINTS

- This clinical activity of systemic therapies has significantly improved over time with modern immunotherapy doublets being the standard of care with significant improvements in overall survival and favorable side effect profiles.
- With the large number of approved drugs to treat HCC, the appropriate transition to systemic treatment is critical to maximize the benefit of these drugs and to sequence treatments at progression.
- Moving systemic therapy to earlier stages of HCC is appropriate, recognizing that patients with large, multifocal, and/ or infiltrative HCC are less likely to benefit from loco-regional approaches and are better served with systemic therapy.
- There is now positive phase 3 date for the use of systemic therapy (atezolizumab and bevacizumab) in the adjuvant setting post-curative resection and other studies are ongoing in this setting and in combination with TACE.

INTRODUCTION

The recognition that hepatocellular carcinoma (HCC) is a rising problem globally dates back decades; however, the development of effective medical treatment for the disease has only led to robust improvements in patient outcomes in the recent past. Despite multiple efforts to demonstrate that medical therapy can improve survival in advanced HCC, only in 2008 was the oral multikinase inhibitor sorafenib shown to improve outcomes versus placebo/best supportive care.[1] Key to its success was the definition of appropriate candidates for systemic therapy and clinical trial enrollment. To that end, the development, validation, and deployment of the Barcelona Clinic Liver Cancer (BCLC) staging system for patient stratification was key,[2]

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Surg Oncol Clin N Am 33 (2024) 73–85
https://doi.org/10.1016/j.soc.2023.06.003
surgonc.theclinics.com

recognizing important prognostic factors for outcomes in HCC including performance status, liver function/Child-Pugh, and tumor characteristics including vascular invasion. With the approval of sorafenib, it was recognized that a disease once viewed as impossible for novel drug development became a crowded space for clinical trials that have resulted in several approved agents that are significantly improving survival for patients (Fig. 1). These have been a springboard to development in earlier-stage disease, with studies now showing a role for adjuvant therapy after curative resection. As knowledge evolves and regimens are proven to be more active, the importance of multidisciplinary management in patients with all stages of HCC will become more important to optimize patient outcomes. Key to optimizing patient outcomes is an understanding of the evolution and current role of these therapies in the HCC landscape.

SORAFENIB, MULTITARGETED TYROSINE KINASE INHIBITORS, AND VASCULAR ENDOTHELIAL GROWTH FACTOR TARGETING

Sorafenib, a multikinase inhibitor targeting vascular endothelial growth factor (VEGF) receptors 1-3 (VEGFR1-3), platelet-derived growth factor receptor-β (PDGFR-β), and rapidly accelerated fibrosarcoma (RAF), proceeded through clinical development given its dual targeting of angiogenesis and growth pathways.[1] The overall survival (OS) benefit in the phase III SHARP trial, later complemented by a similarly designed phase III trial in the Asia Pacific region, led to its approval by the US Food and Drug Administration (FDA) in 2007.[1,3] Careful selection of patients in the design of these trials, namely limiting recruitment to patients with well compensated cirrhosis (Child Pugh A), likely contributed to successfully capturing the benefit of sorafenib. Although objective response rates were not high (2%), improvements in OS, progression-free survival (PFS), and time to progression (TTP) all favored sorafenib, suggesting that preservation of liver function by halting progression of HCC may have contributed to the overall survival benefit.[1]

Similar multikinase inhibitors with slightly different kinase profiles though still with antiangiogenesis components were selected for further development, balancing efficacy and safety in a group of patients with cancer and underlying liver disease. Tyrosine kinase inhibitors (TKIs) with more potent inhibition of VEGF, such as sunitnib,[4] brivanib (specific for VEGFR and fibroblast growth factor receptors [FGFR]), and linifanib (specific for all VEGFR and PDGFR isoforms), all failed to show either noninferiority (linifanib) or superiority (sunitinib, linifanib, and brivanib) to sorafenib for overall

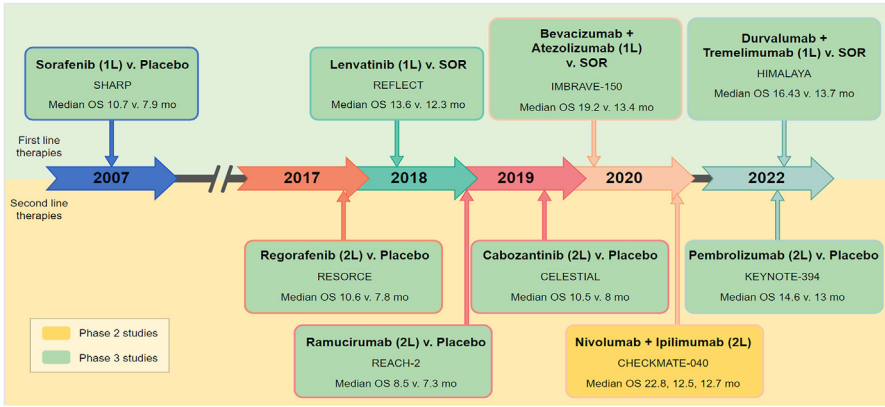

Fig. 1. Evolution of systemic therapy in advanced hepatocellular carcinoma.

survival.[4–6] Brivanib, the first molecule to move into the newly found second-line setting for advanced HCC, also failed to improve overall survival in patients who already progressed on sorafenib (BRISK-PS).[7]

In the front-line setting, lenvatinib, an inhibitor of VEGFR 1-3, FGFR1-4, PDGFRα, RET, and KIT, demonstrated noninferiority to sorafenib for initial treatment of advanced HCC in the REFLECT trial[8] leading to global approval. Although median survival for lenvatinib was longer at 13.6 months vs 12.3 months for sorafenib, the hazard ratio (HR) 0.92 (95% confidence interval [CI] 0.79–1.06) only met the criteria for noninferiority. Key secondary endpoints favored lenvatinib, including an objective response rate (ORR) of 18.8%, and progression-free survival (PFS) of 7.4 months versus 3.7 months. Lenvatinib was associated with more and higher-grade hypertension and proteinuria, whereas the reverse was true for sorafenib in regards to hand-foot skin reaction. Donafenib, a deuterated form of sorafenib, with similar kinase activity, showed improved overall survival (OS) in Chinese patients with advanced HCC over sorafenib.[9]

Alongside TKI development came trials looking at monoclonal antibodies towards VEGF signaling.[10] Bevacizumab, a monoclonal antibody towards a ligand, VEGF-A, was originally evaluated as a single agent[11] and in combination with TACE[12] but did not move into full development in HCC until a decade later. Initial concerns about bleeding risk with bevacizumab were eventually mitigated by refining inclusion criteria and the requirement of a screening endoscopy. Ramucirumab, a monoclonal antibody towards VEGFR-2, had an acceptable safety profile but limited efficacy in all patients with advanced HCC in the initial phase 3 REACH trial looking at its use after sorafenib progression.[13] A preplanned analysis of the AFP high subgroup, however, identified a treatment effect and subsequently led to the phase 3 REACH-2 trial, in which ramucirumab improved overall survival compared with placebo, in patients with AFP of at least 400 ng/mL.[14] This remains the only biomarker approved therapy for HCC.

The second-line setting was a long felt unmet need as there were no drugs shown to improve outcomes for patients intolerant to, or with progression on sorafenib. Approved TKIs in second-line all inhibited VEGF receptor but also targeted other pathways critical for growth and survival such as rearranged during transfection (RET), MET (hepatocyte growth factor receptor), and RAF. Regorafenib, which retains sorafenib's structure with the exception of fluorination in 1 position, has a broader kinase profile including inhibition of VEGFR, PDGFR, RET, KIT, FGFR1, and TIE-2.[15] The phase III RESORCE trial selected patients with advanced HCC and documented progression (versus discontinuing for intolerance) on sorafenib, who had stayed on drug for a minimum period of time, and remained as compensated CP A cirrhosis.[15] The addition of regorafenib led to an improvement in median OS by 2.8 months with a HR of 0.63 compared with placebo.[15] Cabozantinib, an inhibitor of VEGFR1-3, MET, and AXL, improved median OS by 2.2 months compared with placebo after progression on sorafenib in the CELESTIAL trial.[16] Uniquely, this trial also had about 25% of patients who were third-line. Key results from front-line and second-line phase 3 studies are in **Table 1**.

THE CHECKPOINT INHIBITOR REVOLUTION

Monoclonal antibodies targeting 2 immune checkpoints, CTLA-4/B27 and PD-1/PD-L1, have impacted the care of patients with most solid tumors in some way. These agents restore anticancer immunity and by doing so stimulate an immune response to the tumor. This antitumor effect is balanced against the potential for immune-related adverse events that can affect almost any organ. For safety reasons, early

Table 1
Phase III studies

	Trial Name	Active Arm	Control	OS Benefit	ORR
Front-line	SHARP	Sorafenib	Placebo	10.7 vs 7.9 months HR 0.69; 95% CI, 0.55-0.87; *P*<.001	2%
	REFLECT	Lenvatinib	Sorafenib	13.6 vs 12.3 months HR 0.92; 95% CI, 0.79–1.06, noninferior	18.8%
	IMbrave150	Atezolizumab/ bevacizumab	Sorafenib	19.2 vs 13.4 months HR 0.58; 95% CI, 0.42–0.79, *P*<.001	30%
Second-line	HIMALAYA	Durvalumab/ tremlimumab	Sorafenib	16.43 vs 13.77 months HR 0.78; 96.02% CI, 0.65–0.93, *P*=.0035	20%
	RESORCE	Regorafenib	Placebo	10.6 vs 7.8 months HR 0.63; 95% CI 0.50–0.79, *P*<.0001	7%
	CELESTIAL[a]	Cabozantinib	Placebo	10.2 vs 8.0 months HR, 0.76; 95% CI 0.63-0.92; *P*=.005	7%
	REACH-2	Ramucirumab	Placebo	8.5 vs 7.3 months HR 0.71; 95% CI 0.531–0.949; *P*=.0199	5%
	KEYNOTE 240	Pembrolizumab	Placebo	13.8 vs 10.6 months HR 0.781; 95% CI, 0.611–0.998; *P*=.0238	18.3%
	CHECKMATE 040 (Phase 1b/2)	Nivolumab/ ipilimumab	Single-arm	mOS 22.8 months (95% CI 9.4-NE)	32%

Abbreviation: ORR, objective response rate by RECIST 1.1.
[a] Also included third-line.

clinical trials with these agents excluded patients with cirrhosis and/or active viral hepatitis. This led to a paucity of data about the safety of these medications in patients with chronic liver disease, a critical deficiency given that more than 90% of patients with HCC have underlying cirrhosis.[17] Initial landmark studies with single-agent checkpoint inhibitors were the single-arm phase I/II Checkmate 040 trial and single-arm phase II Keynote 224 trial, evaluating nivolumab and pembrolizumab, respectively, in patients previously treated with sorafenib.[18,19] Both agents had objective response rates (ORR) of approximately 15-20% and were well tolerated in mostly Child Pugh A cirrhosis patients, leading to accelerated approval by the FDA.[18,19] Data from case series and another cohort of Checkmate 040 showed that Child Pugh B7/8 patients with HCC had comparable safety profiles to Child Pugh A patients, although with OS only in range of 5.9 to 8.6 months.[20–22] Nivolumab and pembrolizumab were then evaluated in randomized phase III trials – Checkmate 459 for nivolumab and KEYNOTE 240 (worldwide)/KEYNOTE 394 (Asia) for pembrolizumab.[23–25] Nivolumab was evaluated in the front-line setting versus sorafenib with the primary endpoint of improving OS. The phase III study recapitulated the single-agent activity of nivolumab that supported its accelerated approval and the favorable safety profile but failed to meet the primary endpoint of improving OS. Survival was 16.4 months with nivolumab and 14.7 months with sorafenib (HR 0.85 [95% CI 0.72–1.02];

P=.075).[25] Interestingly, the upper limit of the CI here was 1.02, less than the 1.08 used in other trials to declare noninferiority; however, the study was designed as a superiority trial. Two phase III trials evaluated pembrolizumab versus placebo in the second-line setting. Again, the safety and single-agent response rates were confirmed, but in KEYNOTE 240 overall survival narrowly missed this coprimary endpoint, whereas in KEYNOTE 394, it did meet its survival endpoint.[23,24] More recently, the results of the RATIONALE-301 study evaluating the single-agent PD-1 inhibitor tislelizumab versus sorafenib in the front-line setting were presented.[26] This study met its noninferiority endpoint with similar results as CHECKMATE 459 with an HR for OS 0.85 (95% CI 0.712–1.019; P=.0398) and an ORR of 14.3% and a long median duration of response of 36.1 months, no %. Adverse events with single-agent checkpoint inhibitors in HCC patients are similar to other malignancies and most commonly include fatigue, hypothyroidism, and rash.[27] The predominant difference is how to manage immune-related hepatitis, accounting for a difference in baseline liver function.[27]

The results of studies with single-agent checkpoint inhibitors suggested that strategies to improve response rates may yield significant improvements in OS. Despite efforts, no single biomarker has been validated to help select patients who may benefit from these agents. In addition, there are no clinical criteria that identify patients who respond better or worse to these agents. Preclinical studies demonstrated that targeting VEGF induces changes in the tumor microenvironment and provided rationale to evaluate anti-VEGF/checkpoint inhibitor combinations in clinical trials.[28] Atezolizumab, a PD-L1 inhibitor, and bevacizumab, were explored initially in a phase Ib trial that demonstrated a strong signal of antitumor efficacy with an ORR of 36% and really no new safety signals as compared with single-agent PD-1 therapies.[29] This led to IMbrave150, a global Phase III randomized study comparing atezolizumab and bevacizumab to sorafenib as initial treatment for patients with advanced HCC.[30] The study mandated endoscopy within 6 months of trial enrollment to minimize the risk of variceal bleeding seen in the first studies of single-agent bevacizumab HCC studies.[11,30] The study accrued a global population of patients with high-risk characteristics including main portal vein invasion. The study met its coprimary endpoints of improving PFS and OS, with mature results showing median OS of 19.2 months with atezolizumab and bevacizumab compared to 13.4 months with sorafenib (HR, 0.66 [95% CI, 0.52, 0.85]; P=.0009).[31] In addition, ORR was 30% with combination. Again, there were no new safety signals with the combination, which was better tolerated than sorafenib. Notably, the combination had higher grade and frequency of hypertension and proteinuria, but was otherwise better tolerated than sorafenib with improved quality of life. With these data, atezolizumab and bevacizumab defined a new standard for front-line HCC. The anti-VEGF antibody and checkpoint inhibitor approach was further supported by a phase III study in China comparing the combination of sintilimab (anti PD-1 antibody) and IBI305 (bevacizumab biosimilar) to sorafenib with a HR of 0.57 (95% CI, 0.43 to 0.75; P<.0001) for OS favoring the combination in its first interim analysis.[32]

A similar effort was underway to combine anti-VEGF TKIs and checkpoint inhibitors. Pembrolizumab, combined with lenvatinib, demonstrated safety with a response rate of 36% and median OS of 22 months in a single-arm phase Ib study.[33] This led to the global randomized phase III LEAP-002 study comparing pembrolizumab and lenvatinib to lenvatinib alone. Of note, this was the first phase III study in advanced HCC using lenvatinib, instead of sorafenib, as a control arm. It was also one of the few placebo-controlled and double-blind studies, whereas other phase 3 studies were open-label since their designs compared an intravenous to oral regimen. Despite an

ORR of 26.1%, and an OS of 21.2 months, the combination did not statistically improve OS versus 19.0 months with lenvatinib (HR = 0.840; *P*=.0227), missing the statistical threshold of *P*=.0185.[34] The OS of the lenvatinib arm of 19 months was unexpected given the survival time 13.4 months for lenvatinib in the reflect study. These data represent the improvement in survival in HCC that has occurred over time with improved access after progression on first-line therapy to active drugs approved in HCC. Atezolizumab and cabozantinib similarly missed its endpoint of OS in initial treatment of patients with HCC, compared with sorafenib, in the Phase III COSMIC-312 study, with a median OS of 15.4 months in the combination group versus 15.5 months in the sorafenib group (HR 0.90, 96% CI 0.69–1·18; *P*=.44).[35] The objective response rates and PFS were lower than expected for the combination arm.[35] Unlike the 2 trials previously mentioned, a recently presented study using the PD-1 inhibitor camrelizumab and the VEGFR2-TKI rivoceranib did meet both its primary endpoints in a phase III study versus sorafenib.[36] PFS was improved from 3.7 to 5.6 months (HR 0.5, 95% CI 0.41–0.65; *P*<.000) and OS from 15.2 to 22.1 months (HR, 0.62, 95% CI 0.49–0.80; *P*<.0001). The study accrued over 80% of the patients from Asia and as a result over 70% of the patients had hepatitis B virus (HBV)-related liver cancer. The confirmed ORR for the combination was 25.4%. The regimen was associated with a higher than expected side effect profile, with over 80% of patients having grade 3/4 treatment-related adverse events. Although most of the adverse events are similar to other VEGFR targeted TKIs, rivoceranib uniquely is associated with reactive cutaneous capillary endothelial proliferation. Approval of this regimen is pending.

The success of dual checkpoint inhibition (CTLA-4 and PD-(L)-1) in other solid tumors led to exploring their use in patients with HCC. The Checkmate 040 trial included multiple dosing schedules of nivolumab and the CTLA4 antibody ipilimumab in patients after prior sorafenib.[37] The nivolumab/ipilimumab arm with nivolumab dosed at 1 mg/kg and ipilimumab at 3 mg/kg (4 total doses) followed by nivolumab 240 mg every 2 weeks received accelerated approval given ORR 33% and the highest median OS of the combinations (22.8 months [9.4 to NE]).[37] Tremelimumab, a CTLA-4 inhibitor, had shown some clinical activity in patients with HCC coinfected with hepatitis C, but had not yet been approved for any indication in other cancers.[38] A phase I/II study established using a 1-time dose of tremelimumab 300 mg along with durvalumab 1500 mg as what would be recommended to proceed in a phase III study.[39] In the phase III HIMALAYA trial, the combination arm (STRIDE) and durvalumab monotherapy arm were individually compared with sorafenib for superiority in overall survival and noninferiority for overall survival, respectively.[40] The primary endpoint of the study being the combination arm versus sorafenib. The median OS was 16.43 months with STRIDE (HR 0.78, *P*=.0035), 16.56 months with durvalumab (HR 0.86, 95.67% CI 0.73-1.03; noninferiority margin 1.08).[40] Neither regimen improved PFS, but the ORR with the combination was 20.1%. These regimens are generally well-tolerated, but consistent with both of these PD-1/CTLA-4 combinations, there is an increase in immune-mediated adverse events compared with regimens that contain only a PD-(L)-1 antibody.

BRINGING SYSTEMIC THERAPY TO EARLIER-STAGE DISEASE

Before there were effective systemic therapies, the use of local-regional approaches such as TACE expanded to fill a void. Now, with more active regimens that have double-digit response rates and improve survival, there is increased recognition that some patients with intermediate-stage (BCLC B) HCC may be better served with

systemic therapy. The phase III studies discussed previously consistently have 15% to 20% of patients who are BCLC B and felt not to be appropriate for locoregional therapy (LRT) or have progressed after LRT. There is increased recognition that BCLC stage B patients still represent a large unmet need given the heterogeneity of the group, with some patients presenting with multiple large lesions having the same prognosis as those with advanced BCLC C stage.[41] In an updated BCLC strategy, it is recognized that some patients, such as those with diffuse, infiltrating tumors, may be better served with systemic therapy.[42]

In the context of a clinical trial, there is strong rationale to combine systemic treatment with LRT. From a clinical standpoint, LRT is not curative, and although it has been shown to improve survival, patients eventually become refractory or develop contraindications such as migration to an advanced stage. Therefore, a systemic treatment that can improve tumor control and delay progression would be of value. Scientifically, ischemia induced by TACE leads to an increase in angiogenic factors like VEGF, which may potentially be exploited by the various anti-VEGF therapies approved for treatment in HCC. After its approval, sorafenib was evaluated with TACE in numerous trials that were largely negative.[43,44] In a phase III open-label study from China, lenvatinib significantly improved OS (17.8 versus 11.5 months; HR, 0.45; $P<.001$) when added to TACE in a phase III trial compared with lenvatinib monotherapy.[45] This trial accrued patients with mostly HBV-related HCC and included a diverse population of patients including those with macrovascular invasion and extrahepatic spread. The applicability to a Western population is not entirely clear; however, the trial demonstrated that combining newer active agents with TACE may be safe and effective. In addition, tumor necrosis induced by LRT may stimulate antigen release and modify the tumor microenvironment, which in combination with immunotherapy, can augment an antitumor response with checkpoint inhibitors.[46] There are several ongoing studies assessing the efficacy of this approach (**Table 2**), and if positive, it could establish a new standard of care for intermediate HCC.

HCC is a curable disease when found early. Resection and ablation have been shown to curative in select patients, but the recurrence rate is high.[47,48] Recurrence in HCC follows a bimodal pattern, with early recurrences felt to be secondary to the primary tumor, whereas a later recurrence is felt to be a result of de novo HCC occurring in a diseased organ. Some patients with BCLC stage A also may have a high risk of recurrence and prognosis similar to stage B patients based on tumor characteristics.[49] Management strategies may overlap for those with BCLC stage A and B, where resection may be feasible for some staged as B without portal hypertension, and be at high risk for recurrence. Examples may include resection of a primary tumor greater than 5 cm in diameter or resection of multifocal disease with microvascular invasion. Adjuvant studies with sorafenib after curative resection in patients at high risk for recurrence did not show any benefit. There are several ongoing phase III studies using checkpoint inhibitor-based therapies in this setting (**Table 3**). Data from the IMbrave050 phase III trial were recently presented.[50] The study evaluated the ability of atezolizumab and bevacizumab to delay recurrence following curative resection or ablation in patients at high risk of recurrence (**Table 4**). Patients were randomized in an open-label study to receive 1 year of atezolizumab and bevacizumab every 3 weeks or active surveillance. The primary endpoint was recurrence free-survival (RFS). With a median follow-up of 17.4 months, there was a significant decrease in the risk of recurrence with atezolizumab and bevacizumab; HR = 0.72 (95% CI: 0.56, 0.93, $P=.012$). The median RFS was not reached in either arm. The benefit was consistent across subgroups, and the safety profile of the combination was as expected based on prior studies. Given this is an adjuvant study with tissue readily

Table 2
Phase III trials for concurrent/adjuvant treatment after locoregional treatment for hepatocellular carcinoma

Systemic Therapy Used	Locoregional Treatment Used	Comparator Group	Disease Setting	Target Number of Patients	Name of Trial	NCT Identifier
Lenvatinib and camrelizumab	TACE	Lenvatinib	BCLC stage C	168	LEN-TAC	NCT05738616
Lenvatinib and sintilimab	TACE	Lenvatinib	BCLC stage C	427	N/A	NCT05608200
Lenvatinib and pembrolizumab	TACE	TACE + placebo	BCLC stage A or B not amenable to curative ablation or resection	450	LEAP-012	NCT04246177
Lenvatinib with TACE	TACE	Lenvatinib after progression after TACE	BCLC stage C	299	N/A	NCT05220020
Durvalumab/tremelimumab or Durvalumab/tremelimumab/ lenvatinib	TACE	TACE alone	BCLC stage A or B not amenable to curative ablation or resection	525	EMERALD-3	NCT05301842
Durvalumab/bevacizumab or durvalumab	TACE	TACE + placebo	BCLC stage A or B not amenable to curative ablation or resection	724	EMERALD-1	NCT03778957
Nivolumab/ipilimumab or nivolumab	TACE	Active surveillance after TACE	BCLC stage A or B not amenable to curative ablation or resection	N/A	CheckMate 74W	NCT04340193
Nivolumab	TACE	Active surveillance after TACE	BCLC stage A or B not amenable to curative ablation or resection	522	TACE-3	NCT04268888

Table 3
Adjuvant phase III trials in early hepatocellular carcinoma

Checkpoint Regimen	Treatment	Control Arm	N	Title	Trial Number
Pembrolizumab	Resection or ablation	Placebo	950	KEYNOTE-937	NCT03867084
Nivolumab	Resection or ablation	Placebo	545	CheckMate 9DX	NCT03383458
Durvalumab/ bevacizumab or durvalumab	Resection or ablation	Placebo	908	EMERALD-2	NCT03847428
Atezolizumab/ bevacizumab	Resection or ablation	Active surveillance	668	IMbrave050	NCT04102098

available, biomarker studies to help identify patients who may get a greater benefit are awaited. The study data were too immature to assess effects on OS. Taken together, these data hold promise that systemic therapy will be an option for patients after resection or ablation to help reduce the risk of recurrence. Results from single-agent immunotherapy trials and other combinations are awaited.

FUTURE DIRECTIONS

The therapeutic options for patients with HCC is changing rapidly. Survival for patients with advanced disease has markedly improved with the introduction of checkpoint inhibitors in the front-line setting. How to optimally sequence the available drugs is not known, but as in other malignancies, exposing patients to sequential active agents may continue to improve survival. Already, there are numerous early phase studies evaluating novel combination to approach to new clinical scenarios:

What to do for patients who do not benefit from front-line IO (de novo resistance)
How best to treat patients who originally benefit from IO but then progress (acquired resistance)

Molecular studies have identified several potential targets for therapy, and results are awaited.[48] In addition, the safety of newer regimens has been established, and their use in the presurgical/neoadjuvant setting is yielding important biomarker insights and higher response rates than have been seen with their use in the advanced

Table 4
Definition of high-risk of recurrence used in the IMBRAVE 050 study

Curative Treatment	Criteria for High Risk of HCC Recurrence
Resection	• $\leq$3 tumors, with largest tumor >5 cm regardless of vascular invasion[a] or poor tumor differentiation (grade 3 or 4) • $\geq$4 tumors, with largest tumor $\leq$5 cm regardless of vascular invasion[a] or poor tumor differentiation (grade 3 or 4) • $\leq$3 tumors, with largest tumor $\leq$5 cm with vascular invasion[a] and/or poor tumor differentiation (grade 3 or 4)
Ablation	• 1 tumor >2 cm but $\leq$5 cm • Multiple tumors ($\leq$4 tumors), all $\leq$ 5 cm

[a] Microvascular invasion or minor macrovascular portal vein invasion of the portal vein—Vp1/Vp2.

setting.[51–54] The use of this approach to assess novel regimens and incorporating pathologic response rates as an endpoint will soon occur. Taken together, this is an exciting time for clinicians in the HCC space, as research efforts are being translated into better outcomes for patients.

CLINICS CARE POINTS

- Systemic therapy improves survival in patients with advanced HCC and those with intermediate disease that are unsuitable for locoregional therapies.
- Atezolizumab and bevacizumab is the most acitve systmeic therapy available based on its magnitude of benefit in OS and PFS and ORR.
- For patients that cannot receive bevacizumab, durvalumab and tremelimumab is an acceptable option.
- At progression on an IO regimen, sequencing other approved drugs is an appropriate options.
- Systemic therapy is active in early stage disease as seen in the IMBRAVE 050 study in the adjuvant seeting.

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