Systemic Therapy for Hepatocellular Carcinoma

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KEYWORDS

• Atezolizumab • Bevacizumab • Durvalumab • Tremelimumab • Ipilimumab
• Nivolumab • Cabozantinib • Lenvatinib

KEY POINTS

- First-line systemic therapy for unresectable hepatocellular carcinoma (HCC) generally involves an immune checkpoint blockade antibody combined with an anti–vascular endothelial growth factor antibody or a second immune-oncology agent. For those not candidates for immune therapy or who desire an oral therapy, a multikinase inhibitor may be used.
- The ideal second-line systemic treatment for unresectable HCC remains undefined because all of the pivotal trials were initiated when sorafenib was the standard first-line therapy; however, multikinase inhibitors are typically the standard second-line therapy.
- Adjuvant therapy with immune checkpoint blockade has demonstrated activity after transarterial chemoembolization and is awaiting the Food and Drug Administration approval.

INTRODUCTION

Systemic therapy for hepatocellular carcinoma (HCC) had historically been of limited efficacy because of HCC's chemoresistance. The critical breakthrough was the approval of the multikinase inhibitor (MKI) sorafenib in 2007. Subsequently, the armamentarium expanded with other MKIs, antiangiogenic antibodies, and most recently, immunotherapy (IO) with immune checkpoint inhibitors (ICIs). These agents have lengthened survival of patients with unresectable HCC and have recently demonstrated utility in preventing or delaying relapse or progression following local therapies or surgery and raise the prospect of "downstaging" some cancers to allow resection or transplantation. In this review, we will discuss the mechanism of action, efficacy, and side-effect data for the current systemic therapies, emphasizing those aspects of direct relevance to the multidisciplinary team for these complicated patients.

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MECHANISM OF ACTION OF SYSTEMIC THERAPY FOR HEPATOCELLULAR CARCINOMA

Current systemic strategies for treating HCC fall into 2 broad categories, those that address the vascular supply and those that address the immune response to HCC. Synergy between these strategies has also been demonstrated.

As HCC is a highly vascular tumor, various proangiogenic factors play a role in the development and progression of HCC, including vascular endothelial growth factor (VEGF-A, subsequently shortened to VEGF), among others. VEGF is secreted by hypoxic tumor cells when the growth of primary tumors exceeds the ability of diffusion to supply oxygen from extant blood vessels. Binding of VEGF to its receptors on endothelial cells, VEGF-R1, VEGF-R2, and VEGF-R3, with VEGF-R2—the most relevant in HCC—results in a cascade of events that culminate in neovascularization of the tumor.[1] Preventing engagement of VEGF with its receptor or inhibiting the signaling function of the VEGF-R to reduce tumor vascularity is now a well-established strategy across many malignancies. Because the VEGF receptors signal through their tyrosine kinase function, they can be inhibited by VEGFR MKI. The MKIs currently approved for use in the treatment of HCC include sorafenib, lenvatinib, cabozantinib, and regorafenib (and shortly rivoceranib). In addition to VEGF-R inhibition, these oral MKIs also inhibit a variety of other targets, including FGF receptor, c-KIT, RET, c-MET, AXL, MER, and PDGF receptor, depending on the particular drug.

The engagement of VEGF with its receptor can also be prevented by monoclonal antibodies against VEGF or its receptor. Bevacizumab binds to and inactivates circulating VEGF-A.[2] Ramucirumab binds to the VEGF-R2, blocking its interaction with VEGF. By inhibiting VEGF/VEGFR signaling, these antiangiogenic treatments limit the microvascular blood supply to growing tumors. Bevacizumab leads to vascular normalization as well, which can promote synergy with immunotherapy agents by enhancing delivery of immune cells and other systemic therapeutics.[3] Bevacizumab also has immunomodulatory properties, including the upregulation of T cells, inhibition of immunosuppressive cells, and promotion of an immunoactive tumor microenvironment.[4] Toxicity of these agents is provided in **Tables 1** and **2** but in general are those related to effects on the vascular supply such as hypertension, proteinuria, arterial and venous thromboses, and wound healing complications. Also, the oral MKIs frequently cause diarrhea, palmar-plantar erythrodysesthesia, fatigue, rash, and oral lesions.

The liver balances a unique immune microenvironment with constant exposure to neoantigens from the gut that requires a tolerogenic state. A background of chronic inflammation in cirrhosis exhausts the liver's immune system and causes the liver to be more susceptible to carcinogenesis, often leading to the development of HCC.[5] Immune checkpoints on T cells such as programmed cell death protein 1 (PD1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA4) are natural downregulators of the immune system, and these cell surface receptors inhibit T-cell activation or T-cell cytokine production and cytolytic activity. Tumor cells (or suppressive infiltrating immune cells) can upregulate ligands (PD-L1or PD-1) permitting tumor cell evasion of the immune system's clearance mechanisms. ICIs block the interaction of inhibitory receptors with their ligands, leading to immune activation and immune surveillance and resulting in tumor cell death. Various ICIs are Food and Drug Administration (FDA) approved for use in HCC including PD1 inhibitors (pembrolizumab, nivolumab, and shortly camrelizumab), PD-L1 inhibitors (durvalumab, atezolizumab), and CTLA inhibitors (ipilimumab, tremelimumab). Other immunotherapy agents targeting other immune checkpoints including LAG3 (relatlimab) and TIGIT (tiragolumab) are in clinical trials. These IO agents have revolutionized the first-line treatment for patients with

Table 1
First-line systemic therapy: positive phase 3 trials

Study (n =) Year	Intervention	Eligibility Criteria	Safety and Adverse Events	Time-Dependent Endpoints	ORR and DCR
SHARP (n = 602) 2008	Sorafenib 400 mg PO BID vs placebo	Not eligible for or had disease progression after surgical or locoregional therapies Portal vein invasion allowed ECOG 0–2 Child-Pugh A	All TRAEs 80% vs 52% Serious AEs 52% vs 54% Interruption caused by AEs 38% vs 37% Permanent discontinuation caused by AEs 11% vs 5% TRAE include diarrhea, weight loss, hand-foot skin reaction, and hypophosphatemia.	OS 10.7 vs 7.9 mo (HR 0.69; *P*<.001) 1 y survival 44% vs 33% Time to symptomatic progression 4.1 vs 4.9 mo; *P* = .77 Time to radiologic progression: 5.5 vs 2.8 mo; (HR 0.58, *P*<.001)	ORR: 2% vs 1% DCR 43% vs 32%, *P* = .002
REFLECT (n = 954) 2018	Lenvatinib 12 mg PO QD (if >60 kg) or 8 mg QD (if <60 kg) vs sorafenib 400 mg PO BID	Unresectable Could not have main portal vein invasion, >50% liver involvement, obvious invasion into bile duct ECOG 0–1 Child-Pugh A	Grade 3–4 treatment-related treatment emergent AEs 57% vs 49% Most common TRAE: hypertension, diarrhea, decreased appetite, decreased weight, fatigue	OS 13.6 vs 12.3 mo (HR 0.92; CI 0.79–1.06); noninferior PFS 7.4 vs 3.7 mo (HR 0.66; *P*<.0001) TTP 8.9 vs 3.7 mo (HR 0.63; *P*<.0001)	ORR 24.1% vs 9.2%; OR 3.13, *P*<.0001) DCR: 75.5% vs 60.5% QOL Scores declined faster with sorafenib for pain, diarrhea, nutrition, role functioning and body image

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Table 1
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Study (n =) Year	Intervention	Eligibility Criteria	Safety and Adverse Events	Time-Dependent Endpoints	ORR and DCR
IMbrave 150 (n = 501) 2020	Atezolizumab 1200 mg IV and bevacizumab 15 mg/kg IV every 3 wk vs sorafenib 400 mg PO BID	Unresectable No history of autoimmune disease No varices at high risk of bleeding (required EGD within 6 mo of enrollment) Included patients with main portal vein invasion or > 50% liver involvement Could not have coinfection with HBV and HCV ECOG 0–1 Child-Pugh A	Treatment-related grade 3/4 AEs 43 vs 46%. Treatment-related grade 5 events (death) in 2% vs <1%. Most common AEs were those related to the bevacizumab: hypertension (30%), fatigue/asthenia (26%), and proteinuria (20%).	OS 19.2 vs 13.4 mo (HR 0.58, *P*<.001) 12 mo OS 67.2% vs 54.6% PFS 6.8 vs 4.3 mo HR 0.59 *P*<.001 6 mo PFS 54.5% vs 37.2% Time to deterioration of QOL: 11.2 vs 3.6 mo Time to deterioration of physical functioning: 13.1 vs 4.9 mo Time to deterioration of role functioning: 9.1 vs 3.6 mo	ORR: 27.3% vs 11.9% (RECIST) 33.2% vs 13.3% (mRECIST) DCR: 73.6% vs 55.3% (RECIST 1.1) 72.3% vs 55.1% (mRECIST)
HIMALAYA (n = 1171) 2022	Tremelimumab (300 mg IV once) plus durvalumab (1500 mg IV every 4 wk) (STRIDE regimen) vs durvalumab 1500 mg IV every 4 wk vs sorafenib (400 mg PO BID)	Ineligible for locoregional therapy Could not have main portal vein thrombosis Could not have clinically meaningful ascites Could not have coinfection with HBV and HCV No EGD required ECOG 0–1 Child-Pugh A	Grade 3–4 TRAEs 25.8% vs 12.9%. 35.8% experienced an immune mediated AE of any grade on the STRIDE regimen	OS −16.43 vs 13.77 mo (HR 0.78, *P* = .0035) 18 mo OS: 58.7% and 41.5% 24 mo OS: 40.5% and 32.6% 36 mo OS: 30.7% and 20.2% (update in 2024 showed 19.6 % 60 month OS) Noninferiority of durvalumab vs sorafenib OS: 72.0% vs 75.3%, HR 0.86, CI 0.73–1.03; noninferiority was met	ORR: 20.1%, 17%, 5.1% DCR: 60.1%; 54.8%; 60.7%

CARES-310 (n = 543) 2023	Camrelizumab 200 mg IV q2 weeks plus rivoceranib 250 mg PO QD vs sorafenib 400 mg PO BID	Ineligible for locoregional therapy Excluded patients with metastatic disease involving main airway or blood vessels Partial occlusion of the main trunk of the portal vein was allowed Excluded patients with complete occlusion of the main trunk of the portal vein Excluded patients with recent bleeding within 6 mo Included patients with HBV and HCV with some stipulations ECOG 0–1 Child-Pugh A	Grade 3–4 TRAEs 81% vs 52%	OS 22.1 vs 15.2 mo (HR 0.62, *P*<.0001) 12 mo OS 76.5% vs 60.8% 18 mo OS: 60.9% vs 45.2% PFS 5.6 vs 3.7 mo HR 0.52, *P*<.0001	ORR: 25% vs 6% DCR: 78% vs 54%
RATIONALE 301 (n = 674) 2023	Tislelizumab 200 mg IV every 3 wk vs sorafenib 400 mg PO BID	Ineligible for or had progressed after locoregional therapy Excluded patients with tumor thrombus of main trunk of the portal vein Excluded patients with active immune deficiency or autoimmune disease ECOG 0–1 Child-Pugh A	Grade 3–4 TRAEs 22.2% vs 53.4%	OS 15.9 vs 14.1 mo (HR 0.85; CI 0.71–1.02); non-inferior Duration of Response: 36.1 vs 11 mo	ORR 14.3% vs 5.4% DCR 44.2% vs 50.3%

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Table 1
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Study (n =) Year	Intervention	Eligibility Criteria	Safety and Adverse Events	Time-Dependent Endpoints	ORR and DCR
CHECKMATE 9DW (n = 668) 2024	Nivolumab 1 mg/kg + ipilimumab 3 mg/kg q 3 wk x 4 cycles followed by nivolumab 480 mg q4 weeks up to 2 y vs lenvatinib or sorafenib until disease progression	Untreated HCC not eligible for curative surgical or locoregional therapies ECOG 0–1 CP A	Grade 3–4 TRAEs 41% vs 42% Grade 3–4 TRAEs leading to discontinuation 13% vs 6%	OS 23.7 vs 20.6 mo (HR 0.79, CI 0.65–0.96), $P = .0180$ 24 mo OS rates of 49% vs 39% Duration of Response: 30.4 vs 12.9 mo	ORR 36% vs 13% CR in 7% vs 2%

Note that the COSMIC-312 study of cabozantinib/atezolizumab versus sorafenib met its PFS endpoint but not OS endpoint and is not included.
Abbreviations: AEs, adverse events; DCR, disease control rate; ORR, objective response rate; OS, overall survival; TRAEs, treatment-related adverse events.

Table 2
Subsequent line systemic therapy: positive phase 3 trials

Study (n =) Year	Intervention	Eligibility Criteria	Adverse Events	Key Results	ORR and DCR
CELESTIAL (n = 707; 2:1 randomization) 2018	Cabozantinib 60 mg po QD vs placebo	• Had received previous treatment with sorafenib • Had disease progression after at least one systemic treatment • May have received up to 2 previous systemic regimens for advanced hepatocellular carcinoma Portal vein invasion allowed ECOG 0–1 Child-Pugh A	Grade 3–4 AEs in 68% vs 31%. Most common grade 3–4 AEs in the cabozantinib arm were palmar-plantar erythrodysesthesia (16%), hypertension (16%) and increased aspartate aminotransferase (12%). Duration of prior sorafenib had no impact on AE rates	mOS 10.2 vs 8.0 mo (HR 0.76; *P*=.005) 11.3 vs 7.2 mo for the purely second line patients mPFS 5.2 mo (95% CI, 4.0–5.5) vs 1.9 mo (95% CI, 1.9–1.9) (HR 0.44, 95% CI, 0.36–0.52; *P*<.001.)	ORR: 4% vs <1% DCR 64% vs 33%, *P* = .002
RESORCE (n = 573) 2018	Regorafenib 160 mg PO QD day 1–21 of 28 d cycle vs placebo	Progressed on sorafenib - tolerated sorafenib ECOG 0–1 Child-Pugh A	Grade 3, 4 hypertension (15%), hand-foot skin reaction (13%), fatigue (9%), diarrhea (3%)	OS 10.6 vs 7.8 mo (HR, 0.63; 95% CI, 0.50–0.79; *P*<.001) mPFS (mRECIST) 3.1 vs 1.5 mo; (HR, 0.46; 95% CI, 0.37–0.56; *P*<.001) TTP (mRECIST) 3.2 vs 1.5 mo (HR, 0.44; 95% CI, 0.36–0.55; *P* <.001)	ORR 11% vs 4% (*P*=.005) DCR (65% vs 36%; *P*<.001).

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Table 2
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Study (n =) Year	Intervention	Eligibility Criteria	Adverse Events	Key Results	ORR and DCR
REACH-2 (n = 292) 2019	Ramucirumab 8 mg/kg IV (plus BSC) vs placebo (plus BSC)	Progression on or after sorafenib Baseline AFP level $\geq$400 ng/mL ECOG 0–1 Child-Pugh A	Grade $\geq$ 3 adverse events occurring in $\geq$ 5% patients were hypertension (12.2% vs 5.3%) and hyponatremia (5.6% vs 0%).	mOS, 8.5 vs 7.3 mo; (HR, 0.71; 95% CI, 0.53–0.95; *P*=.0199); mPFS 2.8 vs 1.6 mo; (HR, 0.45; 95% CI, 0.34–0.60; *P*<.0001)	ORR 4.6% vs 1.1% DCR: 59.9% vs 38.9% (*P* = .0006).
CHECKMATE-040 (n = 148, 1:1:1)	Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg IV q3wk (4 doses), followed by nivolumab 240 mg q2wk vs nivolumab 3 mg/kg plus ipilimumab 1 mg/kg IV q3wks (4 doses), followed by nivolumab 240 mg q2 wks vs nivolumab 3 mg/kg q2wks plus ipilimumab 1 mg/kg q6wks.	Previously treated with sorafenib ECOG 0–1 Child-Pugh A	TRAE leading to discontinuation in 18% vs 6% vs 2%	mOS 22.8 mo (95% CI, 9.4 mo–not reached) mDOR: NR vs 15.2 mo vs 21.7 mo	ORR 32% vs 27% vs 29%
KEYNOTE-394 (n = 453, 2:1) (Asian study)	Pembrolizumab 200 mg IV q 3 wk vs placebo	Advanced HCC with progression on or after or intolerance to sorafenib or oxaliplatin-based chemotherapy	Grade 3,4,5 TRAE in 12.0%, 1.3%, and 1.0% vs 5.9%, 0%, and 0%	mOS (14.6 vs 13.0 mo for placebo; HR, 0.79 [95% CI, 0.63–0.99]; *P*=.0180) mPFS 2.6 vs 2.3 mo for placebo; (HR, 0.74 [95% CI, 0.60–0.92]; *P*=.0032).	ORR of 12.7% (95% CI, 9.1%–17.0%) vs 1.3% (95% CI, 0.2%–4.6%) (*P*< .0001)

Abbreviations: AEs, adverse events; DCR, disease control rate; ORR, objective response rate; OS, overall survival; TRAEs, treatment-related adverse events.

advanced HCC. The toxicity of ICI is generally related to immune attack against normal tissues (see **Tables 1** and **2**) with common toxicities including rash, hypothyroidism, colitis, and pneumonitis. Hepatitis can occur but is uncommon.

CHOOSING A PATIENT FOR SYSTEMIC THERAPY

HCC is best managed in a multidisciplinary environment that includes access to hepatology, interventional radiology, medical oncology, radiation oncology, hepatobiliary, and transplant surgeons. Given the multidisciplinary nature of the treatment of HCC, patients should be discussed at a tumor board to determine the best treatment options. Patients are treated at an earlier stage, are more likely to receive treatment, and have improved prognosis when they are managed through a multidisciplinary tumor board.[6,7] A medical oncologist should be in the team to provide input on the timing of systemic therapy. Several patient- and tumor-specific factors are considered when determining if a patient is appropriate for systemic therapy (**Fig. 1**).

Patient-Specific Factors

The Barcelona Clinic Liver Cancer (BCLC) staging system accounts for performance status (PS), liver function, and extent of disease. Declining PS indicates limited life expectancy and minimal benefit from treatment.[8] Given the competing risk of death due to advanced cirrhosis, patients with PS 3 or 4 and/or Child-Pugh (CP) C cirrhosis are rarely candidates for treatment, regardless of the tumor burden.[9] For patients with advanced liver disease who already have a poor prognosis from cirrhosis, treating the HCC imparts risk with little benefit. The clinical trials that led to approval of agents used in HCC only included patients with CP A cirrhosis and PS 0-1. Despite not being represented heavily in the trials, patients with a PS of 2 or early CP B cirrhosis will likely

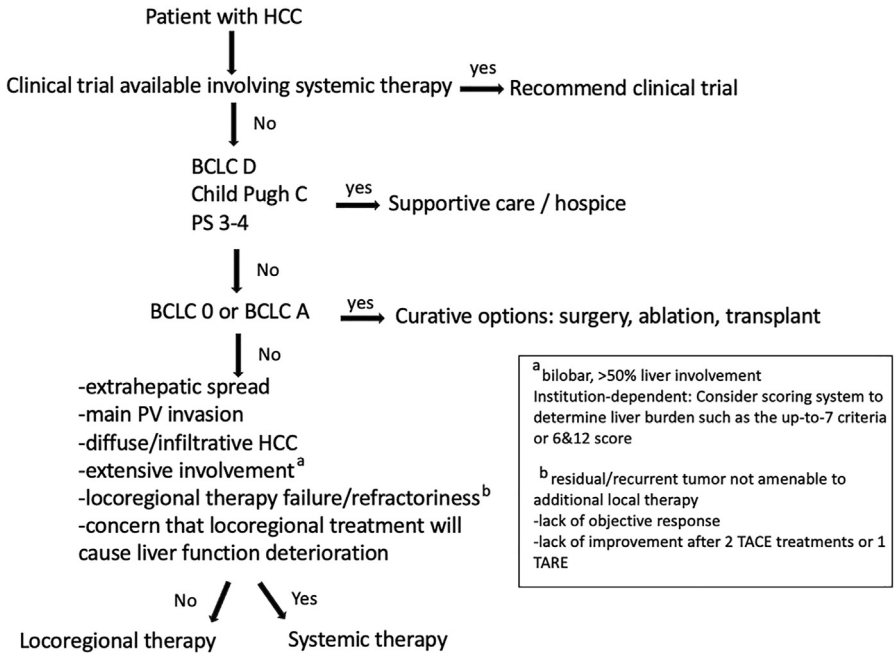

Fig. 1. Choosing a patient for systemic therapy.

still be offered treatment by most oncologists. For these patients, modifications may have to be made to provide a tolerable option, such as single-agent checkpoint inhibitors. Durvalumab monotherapy has been shown to be safe and tolerable for patients with PS 2, and the combination of durvalumab and tremelimumab is being tested in patients with HCC with PS 2.[10,11] The management of patients with CP B cirrhosis will be discussed in more detail in the following sections.

Tumor-Specific Factors

Tumor location, infiltrative growth pattern, vascular invasion, progression after locoregional therapies, and tumor burden are important factors in the decision to start systemic treatment. If extrahepatic disease is present, systemic treatment should be initiated. Extrahepatic spread occurs in approximately 50% of patients, with the most common metastatic site of disease being the lung.[12] These patients have a prognosis of 3 months if left untreated, which is in contrast to the median survival of around 18 months with systemic treatment.[13]

Portal Vein Tumor Thrombosis

The presence and extent of vascular invasion should be considered when choosing whether to recommend locoregional therapy or systemic treatment. Portal vein tumor thrombus (PVTT) is a marker of advanced disease as it often correlates with tumor dissemination and liver function decline. Once the tumor thrombus extends into the main portal vein (VP4), the prognosis is significantly worse than if it was only present more distally.[14] Although Y90 radioembolization (and stereotactic radiotherapy) are locoregional options for patients with portal vein thrombosis (PVT), patients with main PVTT have a much worse survival with locoregional treatment than patients without PVTT (a few months vs over a year).[15,16] Furthermore, the SorAfenib versus Radioembolization in Advanced Hepatocellular carcinoma trial comparing Y90 to sorafenib in patients with HCC (~60% of whom had macrovascular invasion) failed to show superiority of Y90 in the overall population. In the subgroup of patients with PVTT, there was a trend toward benefit with sorafenib over Y90.[17] Although Y90 and immunotherapy combinations have not been compared head-to-head, the current systemic therapies available now are superior to sorafenib and are often a first choice when presented with a patient with main PVTT.

To predict which patients with PVTT (excluding main PVT) might be better candidates for systemic therapy, a prognostic scoring system utilizing bilirubin level, extent of PVTT, and tumor burden was developed.[18] For patients in the dismal prognosis category, the median overall survival (OS) was 7.8 months with a 1-year survival of only 24% and a high risk of liver deterioration within 3 months (21.6%). Y90 was thought to be potentially harmful in this group, so these patients should be offered systemic therapy instead. Others with a better prognostic score would be candidates for Y90 radioembolization.

Extensive Tumor Burden

Deciding when to start systemic therapy in patients with liver-only disease without PVTT is even more nuanced. There are no clear guidelines to advise which patients with liver-only disease would benefit from starting systemic therapy instead of locoregional treatments. Intermediate-stage HCC is a heterogeneous group with respect to liver function and tumor burden. In the BCLC algorithm and in the National Comprehensive Cancer Network guidelines, systemic therapy is recommended for any patient with “extensive” tumor burden. In general, bilobar disease with more than 50% of liver involvement or diffuse, infiltrative HCC warrants systemic therapy. Otherwise, the

criteria to categorize tumor burden as extensive is not well defined, and it can vary dramatically by institution.

When determining who in this group should receive locoregional therapy, the importance of preserving liver function and the continued improvements in systemic therapy need to be considered. A number of different models have been proposed to help define extensive tumor burden to more precisely determine who should receive systemic therapy instead of locoregional therapy including the Hepatoma Arterial Embolization Prognostic score (HAP),[19] Barcelona Clinic Liver Cancer, Child-Pugh and Response score (ABCR),[20] albumin-bilirubin grade (ALBI), tumor size, AFP, first TACE response score (ASAR),[21] assessment for retreatment with TACE (ART) scores, the 6 & 12 score,[22] and Up-to-7 criteria.[23] Although these models have some differences, common features among many of them include tumor size (>5-7 cm), baseline alpha-fetoprotein (AFP) level (>200), and liver function. For example, the Asia-Pacific Primary Liver Cancer Expert (APPLE) Consensus Statement declared that patients were unlikely to respond to transarterial chemoembolization (TACE) if the tumor burden exceeded the Up-to-7 criteria. In a retrospective study, lenvatinib as an initial treatment provided a more favorable outcome to the initial treatment with TACE with respect to survival, response, and progression-free survival (PFS) in patients with tumor burden beyond the Up-to-7 criteria.[24] The REPLACEMENT study also demonstrated the benefit of starting systemic therapy in patients beyond Up-to-7. This study was a nonrandomized phase II study evaluating the efficacy of atezolizumab and bevacizumab in TACE-naïve patients beyond the Up-to-7 criteria. In an exploratory propensity score matching analysis, the authors compared their results with retrospective results from similar patients treated with TACE, and they found a benefit of using atezolizumab and bevacizumab in this population compared with TACE with a hazard ratio of 0.59 ($P = .042$).[25] Ultimately, a multidisciplinary team should evaluate the patient's tumor size, number of lesions, AFP level, and liver function to determine if systemic therapy or locoregional therapy should be recommended.

Refractory to Local Therapy

Systemic therapy is recommended for patients who are refractory to local therapies.[26] The number of times a patient has had locoregional therapy should be taken into consideration when deciding to switch to systemic therapy. Locoregional therapies carry a risk of worsening liver function, with liver decompensation more likely in patients who receive a greater number of treatments.[16] The response rates to locoregional therapy decline after the first attempt, whereas progressive disease rates rise with each subsequent treatment.[27] Patients treated with systemic therapy have a higher survival if patients received lesser than or equal to 2 consecutive TACE procedures than those who receive greater than or equal to 3 procedures.[28] For these reasons, repeated attempts at locoregional therapy after locoregional therapy failure is not recommended. The criteria proposed to define TACE/transarterial radio-embolization (TARE) refractoriness include greater than 50% viable disease, development of new lesions in the treatment area, or lack of improvement in tumor markers after 2 TACE or 1 TARE treatment.[26] Patients who do not respond to TACE have outcomes similar to that of patients who receive supportive care only.[29] In these TACE/TARE refractory patients, systemic therapy is indicated.

SYSTEMIC THERAPY OPTIONS IN THE FIRST-LINE SETTING

For many years, single-agent MKIs were the standard of care for first-line treatment. In recent years, combination therapy with ICIs has supplanted MKIs because of their

superior efficacy and durability. Unless patients are not candidates for immunotherapy, prefer an oral treatment option, or have poor performance status, these combination regimens are the preferred initial treatment strategy (Fig. 2). The 2 currently FDA-approved regimens that are both listed as category one, preferred in the NCCN guidelines and listed as first-line treatment options in the American Association for the Study of Liver Diseases (AASLD) guidelines, are atezolizumab/bevacizumab and durvalumab/tremelimumab. Patients who are eligible for combination immunotherapy should discuss both options, understanding the pros and cons of each regimen (such as bleeding, cardiovascular events, immune-mediated adverse reaction risk, availability of long-term data, preferences on frequency of visits for treatment, need for endoscopy, etc.) to determine the most appropriate option for the individual based on toxicity profile, patient preferences, and goals of care. Other treatment strategies that have demonstrated either superiority or noninferiority over sorafenib but are not yet FDA approved or included in the NCCN guidelines include camrelizumab and rivoceranib, tislelizumab, toripalimab, and ipilumumab with nivolumab. Some patients with HCC are not candidates for immunotherapy, including those who have had a liver transplant, who have life-threatening autoimmune conditions, or who may prefer an oral therapy. For these patients, MKIs are the preferred initial treatment option. See Table 1 for details of the first-line trials which met their primary endpoints.

SYSTEMIC THERAPY OPTIONS IN THE SECOND-LINE SETTING

Because the 2 preferred front-line immunotherapy options only became available recently, no large trials have been completed to guide decision-making in the second-line setting after these regimens. The drugs with randomized data for later

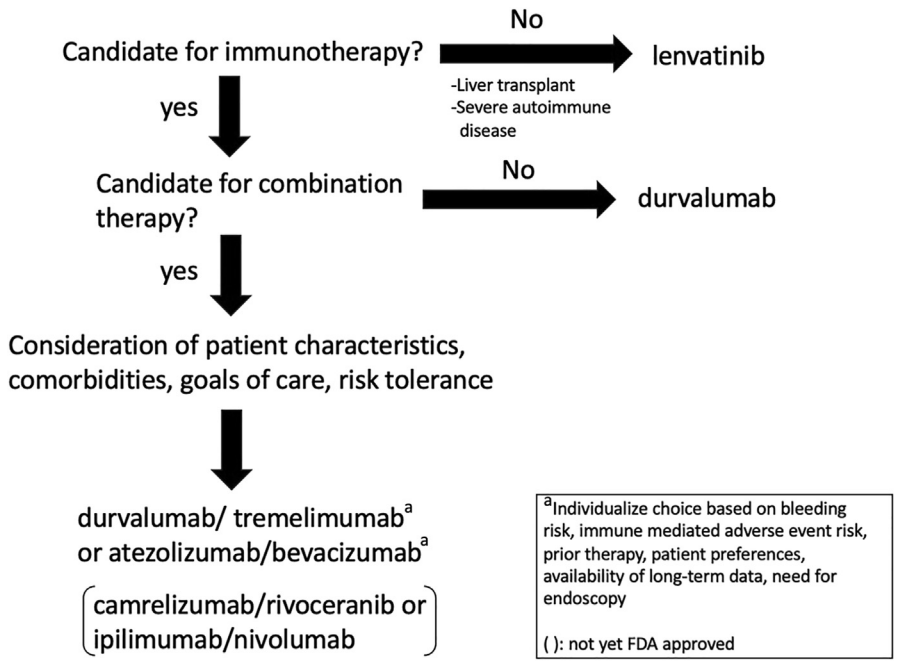

Fig. 2. Choosing first-line systemic therapy.

lines of treatment in HCC were studied after sorafenib, which is a treatment that is rarely used front-line anymore. **Table 2** provides data derived from these older studies of MKIs versus placebo following sorafenib. Choice of second-line options depends on which regimen was used previously and includes switching to a different IO regimen, monotherapy with PD1/PDL1 inhibitors (if MKI used first-line), traditional first-line MKIs (if IO used first line), traditional second-line MKIs, or locoregional therapy with continuation of IO beyond progression. Sequential introduction to multiple active treatments is correlated with better outcomes, so it is reasonable to continue treating patients so long as liver function and performance status will allow.[30–32]

PATIENTS WITH CHILD-PUGH B CIRRHOSIS

The randomized trials that led to drug approvals in HCC only included patients with CP A cirrhosis, excluding CP B because of the competing risk of death. Patients with CP B cirrhosis can still benefit from treatment, albeit with reduced survival compared to patients with CP A cirrhosis.[33,34] The lack of high-quality data in this patient population makes choosing a treatment more challenging. A significant proportion of patients in the clinic with HCC have CP B cirrhosis, and physicians need to determine which regimen is the best based on early-phase trials, retrospective data, and real-world experience. The Checkmate 040 study was the only prospective study to evaluate patients with CP B cirrhosis at baseline undergoing systemic treatment, and it demonstrated the safety of nivolumab in this population. The safety of single-agent IO in CP B cirrhosis seen with nivolumab can likely be extrapolated to other PD1/PDL1 inhibitors as well, such as durvalumab and pembrolizumab. None of the other therapies have studied patients with CP B cirrhosis prospectively. The NCCN guidelines do not restrict durvalumab/tremelimumab to CP class A. Atezolizumab/bevacizumab, on the other hand, is listed as “useful in certain circumstances” for CP B cirrhosis, but there are ongoing prospective clinical trials for atezolizumab/bevacizumab in the CP B patient population. Data are conflicting regarding safety and efficacy of this regimen, and further prospective data will help guide the use of this regimen in the future. For now, given the conflicting data, clinicians can give atezolizumab and bevacizumab in patients with early CP B cirrhosis after a thorough discussion of risks, benefits, and lack of data while taking patient comorbidities and risk tolerance into account.

Multikinase Inhibitors in Child-Pugh B

Because MKIs have been used for many years, there are more data available to demonstrate their safety and efficacy in the CP B patient population. The Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial, the landmark phase III trial that led to the approval of sorafenib, included 5% of patients on the sorafenib arm with CP B cirrhosis.[31] In the NCCN guidelines, sorafenib is listed as an option for patients with CP B cirrhosis but the other MKIs are not. While there are no prospective phase III trials that included a significant number of patients with CP B cirrhosis, retrospective data have demonstrated the safety of lenvatinib in this group.[35] In secondary analyses of the REFLECT and CELESTIAL trials, lenvatinib and cabozantinib were found to be safe in patients who progressed to CP B.[36–38]

CRITERIA TO CHANGE THERAPIES

When determining when to switch therapy, many factors are considered simultaneously. Patient-specific factors include tolerance for the current regimen, clinical status, trajectory of tumor markers, and goals of care. Tumor-specific factors include the degree of radiographic progression, the presence of new or growing lesions,

oligoprogression versus progression at multiple sites, and whether progression is intrahepatic or extrahepatic. Given the limited treatment options, if a patient has intrahepatic progression, liver-directed therapy while continuing current systemic therapy is an option. Similarly, if a site of oligoprogression is found, local therapy to that site with continuation of current treatment is encouraged to gain more time on the current treatment. Retrospective data suggest that liver-directed therapy with TACE is superior to second-line systemic therapy, supporting the practice of treating liver-only progression while maintaining the current treatment. Treatment beyond progression with IO regimens is another potential option for patients, especially given that pseudoprogression can occur. Patients with minimal radiographic progression, who are thriving clinically, and have acceptable treatment tolerance could be considered for treatment beyond progression with close follow-up. In the HIMALAYA trial, rechallenge with a second dose of tremelimumab was allowed at the time of radiographic progression if patients were felt to be benefitting from treatment without clinical progression or evidence of rapid progression.[39] In a retrospective international, second-line study, patients who received IO treatment beyond progressive disease followed by MKI at progression had the longest OS of all the treatment sequences.[30] The decision to switch therapy is sometimes obvious, but it can also be a nuanced decision with multiple different treatment paths.

ADJUVANT AND NEOADJUVANT THERAPY

Clinical trials are currently underway to determine if systemic therapy should be given routinely to patients in the adjuvant or neoadjuvant setting or for intermediate stage HCC after liver-directed therapies. Even in patients who have a successful resection with negative margins, the rate of recurrence is high. Most recurrences occur inside the liver but outside of the resection cavity, indicating that micrometastatic disease at the time of surgery may lead to recurrences. Systemic therapy either pre or post surgery could eradicate the micrometastatic cells and decrease the recurrence rates.

Unfortunately, adjuvant therapy trials have not shown benefit following surgery or ablation. For example, the STORM trial that evaluated sorafenib or placebo in the adjuvant setting after surgical resection or ablation showed no improvement in recurrence-free survival or OS with the addition of sorafenib after curative-intent therapies.[40]

In contrast to the failure of adjuvant sorafenib, early data had suggest that adjuvant immunotherapy may be more successful. The IMBrave 050 trial was a phase III trial comparing adjuvant atezolizumab and bevacizumab to placebo in patients with high-risk resected or ablated HCC.[41] Patients were considered at high risk based on tumor size, tumor number, presence of vascular invasion, segmental portal vein invasion, and grade. At the pre-specified interim analysis , the primary endpoint of recurrence-free survival was met, with a hazard ratio of 0.72 (P = .012). However, in a recent updated analysis, the initial recurrence free survival was not seen (Annals of Oncology (2024) 35 (suppl_2): 1-72. 10.1016/annonc/annonc1623) Therefore, this combination is not recommended for use as an adjuvant therapy after surgery or ablation of HCC. An ongoing three-arm phase III trial (EMERALD-2) is evaluating adjuvant durvalumab monotherapy, durvalumab plus bevacizumab, or placebo. Other adjuvant studies include CheckMate 9DX, evaluating nivolumab, and KEYNOTE 937 evaluating pembrolizumab in the adjuvant setting.

ICIs are often more effective when the tumor is still in vivo due to a more vigorous immune response to the high tumor antigen load. Neoadjuvant therapy can prevent unnecessary surgery in patients who have aggressive tumors that do not respond

to treatment. On the other hand, in patients who respond, neoadjuvant treatment can lead to cytoreduction and facilitate surgery in patients who may not have initially been candidates. Given the impressive survival benefits of immunotherapy combinations in advanced HCC, moving these therapies to the neoadjuvant setting is an area of active clinical investigation.

SYSTEMIC THERAPY AS AN ADJUVANT TO LOCOREGIONAL THERAPY

When comparing TACE alone with TACE plus sorafenib, a meta-analysis concluded that time to progression (TTP) was improved but not OS.[42] For patients who are candidates for locoregional therapy, adding systemic therapy is controversial (discussed in more detail below). On the other hand, if a patient is appropriate for systemic therapy because of extensive tumor burden, then locoregional consolidation therapy can still be performed at a later time to control intrahepatic tumor burden.[43] The LAUNCH trial, conducted in China, showed that there may be a benefit of adding locoregional therapy to systemic therapy in patients with advanced HCC who would otherwise receive systemic treatment. In this trial, patients who received lenvatinib and TACE followed by on-demand TACE had superior PFS and OS compared with those who received lenvatinib alone.[44]

Many trials have been performed to see if the addition of systemic therapy to TACE improves outcomes. In the sorafenib era, multiple phase III trials did not show any improvement in adding sorafenib to TACE.[42,45,46] The TACTICs trial was a phase II trial that showed an improvement in PFS with the addition of sorafenib.[47] The improvement in OS was not statistically significant, however, so it was a negative study. The numerical advantage in survival was impressive in patients with high tumor burden (improvement of 11.3 months outside Up-to-7 criteria).[48] The authors concluded that this advantage in patients with high tumor burden supports the practice of starting systemic therapy in patients with high tumor burden and following with selective local therapy. The LAUNCH trial compared lenvatinib plus on-demand TACE with lenvatinib alone, and the positive results of this trial also support the sequence of systemic therapy followed by liver-directed therapy. This new paradigm of treatment strategy is also discussed in the Japan Society of Hepatology Consensus Statements (2021) and the APPLE Consensus Statements (2020).[43,49]

With modern therapies, the question of systemic therapy after liver-directed therapies is being revisited. Both TACE and Y90 activate the immune system and can theoretically augment the effects of immunotherapy. A phase II trial of nivolumab after TACE had encouraging results, with an overall response rate of 71% with a median time to a subsequent therapy of 24.9 months.[50] The phase III LEAP-012 trial investigating lenvatinib plus pembrolizumab followed by TACE versus placebo plus TACE in patients with intermediate stage disease recently reported a progression free survival for the combination therapy (Annals of Oncology (2024) 35 (suppl_2): 1-72. 10.1016/annonc/annonc1623). EMERALD-1 is a phase III trial that randomized patients who received TACE to placebo, durvalumab monotherapy, or durvalumab and bevacizumab in the post–locoregional therapy setting. The results were recently reported, with a PFS improvement of 6.8 months (15 vs 8.2 months) for patients who received durvalumab and bevacizumab compared with patients who received placebo after TACE.[51(p1)] The OS data are immature, but this was the first positive global phase III trial to show a significant improvement in PFS with systemic therapy and TACE compared with TACE alone. EMERALD-3 is an ongoing multicenter, randomized, phase III trial, which is evaluating TACE alone or TACE in addition to tremelimumab and durvalumab with or without lenvatinib.

At many centers, Y90 is utilized more frequently than TACE because of studies showing improved tolerability and efficacy.[52] Similar to the TACE trials, many trials are ongoing in the intermediate stage setting with patients who plan to undergo Y90 as the locoregional therapy of choice. Emerald Y90 is an ongoing phase II trial evaluating durvalumab and bevacizumab with Y90, and ROWAN is a phase II trial evaluating durvalumab and tremelimumab after Y90. Early-phase, single-arm trials have looked at Y90 for monotherapy with nivolumab, pembrolizumab, or durvalumab, all indicating safety and efficacy of the combination of Y90 and immunotherapy.[53–55] Similarly, ongoing trials are looking at the efficacy of immunotherapy around the time of radiation, but this is not a standard practice at this time.

USE OF SYSTEMIC THERAPY BEFORE LIVER TRANSPLANT

For HCC patients awaiting liver transplantation or who are beyond Milan criteria and for whom locoregional therapies are inadequate, systemic therapy may provide a bridge or "down-stage" the malignancy to meet the criteria. The recent efficacy data for immune checkpoint blockade raise the possibility of incorporating them in the pretransplant setting but also raises concern about graft loss. Currently, most of the data for ICIs given before liver transplant derive from case reports or case series. No large, randomized trials have been published, but studies are ongoing to determine how we can maximize safety and efficacy of this approach.

The appropriate washout period between the last dose of ICI and transplant needs to be determined, and the ideal time is controversial.[56] A recent study to investigate this question further analyzed data from 44 patients who received atezolizumab, nivolumab, or pembrolizumab before transplant and had data on washout time of the drug. They found that the ideal washout period was 1.5 half-lives (or 42 days) to avoid post–liver transplant rejection[57] (Mention AASLD guidelines).

SUMMARY

As systemic therapy options have expanded, so too have the points at which hepatologists will interact with patients who may be candidates for or receiving these therapies. For patients being referred for surgery, ablation, transarterial embolization, and potential liver transplant, there may be periprocedural roles for systemic therapies. For patients with advanced disease or who have progressed after attempts at locoregional therapy, declining liver function raises questions about the appropriate use of systemic therapy. For those receiving systemic therapy, particularly immune checkpoint blockade, adverse events can include, albeit uncommonly, hepatic dysfunction. Finally, as complications of cirrhosis continue to be a major cause of morbidity and mortality in HCC patients, continued input from a hepatologist as part of the multidisciplinary team is critical to achieving the best outcomes.

CLINICS CARE POINTS

- Systemic therapy is demonstrating utility in an expanding range of clinical indications for HCC, thus necessitating referral to medical oncology for many HCC patients as part of their multidisciplinary management.
- The improved efficacy of systemic therapy has also made it posssible to return to locoregional therapies or consider patients for surgical approaches or transplant who had previously been declared ineligible for these approaches.

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