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REVIEW

Systemic Treatment for Unresectable Hepatocellular Carcinoma: A Surgeon's Perspective

Xiao-Dong Zhu[1], Lei Zhao[2], Binkui Li[3], Yuan Cheng[4], Hui-Chuan Sun[1]

[1]Department of Liver Surgery and Transplantation, Liver Cancer Institute and Zhongshan Hospital, Fudan University, Shanghai, People's Republic of China; [2]Department of Hepatobiliary Surgery, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, People's Republic of China; [3]Department of Liver Surgery, Sun Yat-Sen University Cancer Center, Guangzhou, People's Republic of China; [4]Department of Medical Oncology, Jinling Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, People's Republic of China

Correspondence: Hui-Chuan Sun, Email sun.huichuan@zs-hospital.sh.cn

Abstract: In recent years, the standard treatment for hepatocellular carcinoma (HCC) has changed dramatically due to the emergence of potent systemic treatment options. These advanced therapies have led to increased survival benefits for patients with advanced or intermediate-stage HCC. Advancements in HCC treatments also offer the possibility of conversion therapy for initially unresectable HCC. However, the treatment of HCC is becoming increasingly complex, due to the expanding availability of systemic therapies, their use in combination with locoregional therapies, and their perioperative applications. Patient characteristics such as liver function, esophageal and gastric variceal status, and treatment goal (downstaging resection or long-term maintenance treatment), are the most critical factors when selecting a systemic treatment strategy. Consequently, the necessity to tailor a personalized and comprehensive treatment strategy for individual patients is growing. This review briefly summarizes the current systemic treatment regimens for HCC from a surgeon's perspective. It is based on results from clinical studies as well as personal experience and introduces the concept of a patient-centered, treatment goals-driven, individualized systemic treatment strategy for managing HCC.

Keywords: hepatocellular carcinoma, systemic therapy, targeted therapy, immune-checkpoint inhibitor, conversion therapy, patient-centered

Introduction

According to the World Health Organization (WHO), there were approximately 905,677 new cases of liver cancer worldwide in 2020, approximately half of which were in China.[1] Liver cancer is the fourth most common cancer and the second leading cause of cancer-related death in China, with a 5-year survival rate of less than 20%.[2–4] Consequently, liver cancer continues to pose a considerable threat to the Chinese population.[2,3] Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, accounting for 75–85% of all cases.[2] For patients with intermediate or advanced-stage HCC who cannot receive radical or locoregional treatment, international guidelines generally recommend systemic treatment.[2,5–10]

Before 2017, sorafenib was the only FDA-approved systemic therapy for HCC.[11,12] However, treatment with sorafenib provides limited survival benefits.[11,12] In recent years, HCC therapy has changed substantially due to remarkable advances in systemic treatment options. Novel regimens with improved efficacy and survival benefits have led to an increased median survival time of about 20 months for patients with unresectable or advanced-stage HCC.[5–10] These systemic treatment regimens have also facilitated substantial progress in making treatment decisions for patients with early- or intermediate-stage HCC.[2,5–10] The heterogeneities among patients with Barcelona Clinic Liver Cancer (BCLC) stage B (intermediate-stage) HCC have also been identified. Major guidelines further stratify patients with stage B BCLC into stages B1, B2, and B3, according to their liver function and tumor burden.[10,13] These guidelines

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recommend systemic treatment as a first-line treatment for patients with BCLC stage B HCC who are unsuitable for or are resistant to transcatheter arterial chemoembolization (TACE).[9,10,13]

Advancements in systemic treatments also offer the possibility of conversion therapy for patients with initially unresectable HCC. In the past, the treatment goal for patients with unresectable HCC was to pursue long-term survival, while downstaging after systemic therapy was rare. For some of these patients, downstaging resections with potent systemic therapies can now be carried out. The conversion therapy strategy offers some initially unresectable patients access to curative resection, leading to long-term disease-free survival.[14] However, questions regarding the identification of patients with "potentially" resectable HCC, the choice of a systemic treatment regimen, and when to perform surgical resection have led to greater complexity in patient management.[14] In China, more treatment regimens were approved as first-line therapy for unresectable or advanced HCC and making the treatment choice more difficult. It is vital that clinicians fully understand the benefits and risks associated with the different systemic treatment strategies, thereby helping patients to make decisions. Various guidelines typically rely on evidence from large-scale, Phase III trials to make therapy recommendations, limiting access to personalized treatment regimen advice.[2,5,10,14] These trials only recruited fit patients with compensated liver function and sometimes excluded those with high risk of upper gastrointestinal bleeding, and the long-term maintenance therapy were the main goal. In clinical practice, patient characteristics including liver function, esophageal and gastric variceal status, and treatment goal (downstaging resection or long-term maintenance treatment), present a greater challenge in choosing a treatment. Furthermore, in the absence of head-to-head studies, guidelines generally recommend multiple treatment regimens without giving any one therapy priority. As such, it is difficult for clinicians to detect any nuances among the different regimens. This review briefly comments on the current systemic treatment regimens for HCC based on results from clinical trials. Furthermore, it introduces the concept of a patient-centered, treatment goals-driven, individualized systemic treatment strategy for treating patients with unresectable HCC.

First-Line Systemic Treatment Strategies

Factors to Consider When Choosing a Systemic Treatment Strategy

When selecting an appropriate systemic therapy approach for a patient, clinicians should consider the following elements (Tables 1 and 2):

1) *Overall survival (OS)* is the most critical outcome that can be used to evaluate the efficacy of any anti-cancer treatment strategy[6] and should be given top priority during evaluation.

2) *Safety of a treatment strategy*, mainly grade ≥3 treatment-related adverse events (TRAEs), especially the exposure-adjusted incidence of TRAEs (average incidence of TRAEs per month of treatment exposure). Although exposure-adjusted TRAEs are not routinely reported in studies, a crude estimation can be made by dividing the total TRAE incidence by the drug exposure time.

3) *Health-related quality of life (HRQoL)* should be considered alongside OS improvement. Individuals without the option of downstaging resection may have to receive systemic therapies for the rest of their lives. For these patients, HRQoL may help to determine the choice of systemic regimen. In phase III clinical trials, the expected survival time is about 20 months using various combination therapies with anti-PD-L1/PD-1 antibodies and molecular targeted agents. Treatment-related quality of life is thus a key consideration when choosing systemic therapy.

4) *Treatment goal(s)* may involve aggressive interventions with systemic therapies for patients with potentially resectable HCC. When evaluating a systemic treatment regimen for conversion therapy, objective response rate (ORR) should be the key factor.[14] A systemic treatment strategy with a high ORR means that a high percentage of patients may achieve post-treatment tumor shrinkage or even downstaging and thus be eligible for subsequent radical resection.[14] Equally important is the progressive disease (PD) rate.[14] A patient with potentially resectable HCC whose tumor progresses after conversion or neoadjuvant therapy may become ineligible for radical resection. Hence, when considering neoadjuvant therapy or conversion therapy, it is advisable to choose a systemic treatment with a low PD rate, if possible. Additionally, incorporating locoregional therapy into the treatment may enhance the ORR and reduce the PD rate but lead

Table 1 Summary of Efficacy and Safety Data From Recent Phase III RCTs on First-Line Systemic Combination Treatments for HCC

Study name	Regimen category	Treatment regimen	mOS, mo	OS, HR (95% CI)	mPFS, mo	PFS, HR (95% CI)	ORR*, %	DCR, %	PD rate, %	≥ Grade 3 TRAEs, %
LEAP-002[24]	ICI+TKI	lenvatinib + pembrolizumab	21.2	0.84	8.2	0.867	26.1	81.3	12.2	62.5
		lenvatinib + placebo	19.0	(0.708–0.997)	8.0	(0.734–1.024)	17.5	78.4	15	57.5
CARES-310[16,17]	ICI+TKI	apatinib + camrelizumab	23.8	0.64	5.6	0.54	26.8	78.3	16.2	80.9
		sorafenib	15.2	(0.52–0.79)	3.7	(0.44–0.67)	5.9	53.9	36.5	52.4
COSMIC-312[35]	ICI+TKI	cabozantinib + atezolizumab	15.4	0.90	6.8	0.63	11	78	14	76
		sorafenib	15.5	(99% CI 0.69–1.18)	4.2	(96% CI 0.44–0.91)	4	65	20	57
IMbrave150[19–21]	ICI+anti-VEGF	atezolizumab + bevacizumab	19.2	0.66	6.9	0.65	30	74	19	43
		sorafenib	13.4	(0.52–0.85)	4.3	(0.53–0.81)	11	55	25	46
ORIENT-32[15]	ICI+anti-VEGF	sintilimab + bevacizumab biosimilar (IBI305)	NR	0.57	4.6	0.56	21	72	27	34
		sorafenib	10.4	(0.43–0.75)	2.8	(0.46–0.70)	4	64	33	36
CheckMate 9DW[23]	ICI+ICI	nivolumab + ipilimumab	23.7	0.79	9.1	0.87	36	68	20	41
		lenvatinib or sorafenib	20.6	(0.65–0.96)	9.2	(0.72–1.06)	13	75	14	42
HIMALAYA[34]	ICI+ICI	tremelimumab + durvalumab	16.4	0.78	3.8	0.90	20.1	60.1	39.9	25.8
		sorafenib	13.8	(96.02% CI 0.65–0.92)	4.1	(0.77–1.05)	5.1	60.7	39.3	36.9
APOLLO[25]	ICI+TKI	anlotinib + penpulimab	16.5	0.69	6.9	0.53	NA	NA	NA	48.2
		sorafenib	13.2	(98.8% CI 0.52–0.92)	2.8	(96% CI 0.41–0.68)	NA	NA	NA	47.4
HEPATORCH[26]	ICI+anti-VEGF	toripalimab+ bevacizumab	20.0	0.76	5.8	0.69	25.3	71.0	25.3	45.7
		sorafenib	14.5	(0.579–0.987)	4.0	(0.525–0.913)	6.1	65.2	25	52.4
NCT04560894[18]	ICI+anti-VEGF	SCT-110A+SCT510	22.1	0.60	7.1	0.50	32.8	78.6	17.9	84.8**
		sorafenib	14.2	(0.44–0.81)	2.9	(0.38–0.65)	4.3	60.3	23.3	87.1**

Notes: *according to blinded independent central review-assessed RECIST v1.1;**TEAEs.

Abbreviations: RCT, randomized controlled trial; HCC, hepatocellular carcinoma; mOS, median overall survival; HR, hazard ratio. mPFS, median progression-free survival; ORR, objective response rate; DCR, disease control rate; PD, progressive disease; TRAEs, treatment-related adverse events; NR, not reported; TEAEs, treatment-emergent adverse events; ICI, immune checkpoint inhibitors; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

Table 2 Pros and Cons of Different Combination Regimens

Treatment regimen	Pros	Cons
Atezolizumab + bevacizumab[19–21]	• Balance of efficacy and side effects • Higher quality of life	• Inconvenient for conversion surgery: requires bevacizumab discontinuation • Slightly higher PD rate
Lenvatinib + pembrolizumab[24]	• Reliable efficacy • Lowest PD rate: Suitable for conversion/neoadjuvant therapy	• Higher side effects • Lack of positive Phase III studies
Sintilimab + bevacizumab biosimilar (IBI305)[15]	• Fewer side effects • Higher quality of life	• mOS was not reported • High PD rate
Apatinib + camrelizumab[16,17]	• Reliable efficacy • Conversion and neoadjuvant applications	• Highest side effects • HRQoL not superior to sorafenib
Tremelimumab + Durvalumab[34]	• Relative lower toxicity profile	• Relatively high PD rate (39.9%) • May not be suitable for patients with borderline resectable patient or patients with a large tumor burden
Nivolumab + Ipilimumab[23]	• Best OS and highest ORR among all the phase III RCTs	• High rates of treatment-related death (4%) • High rates of immune-related adverse effects

to more adverse events. Besides, the patterns of response (tumor necrosis or shrinkage), depth of response, time to response (TTR), and duration of response (DoR) should also be considered.[14]

5) Other factors include the accessibility of treatment regimens, patient willingness, and comorbidities.

First-Line Combination Treatment Strategies

Atezolizumab Plus Bevacizumab

The IMbrave150 study was a global phase III randomized controlled trial (RCT) conducted at 111 sites in 17 countries. It investigated 501 patients with unresectable HCC who had not received systemic treatment. The patients were randomly assigned to receive either atezolizumab plus bevacizumab (atezo/bev; n = 336) or sorafenib (n = 165). The results of the study indicated that atezo/bev led to significantly longer OS (19.2 months vs 13.4 months) and progression-free survival (PFS; 6.8 months vs 4.3 months) than sorafenib.[19,20] The findings also revealed that compared to sorafenib, atezo/bev offered a considerably better HRQoL.[21] Additionally, an extension phase of the IMbrave150 study that enrolled patients from China also showed clinically meaningful improvements in both OS and PFS with atezo/bev.[27] The effectiveness of the atezo/bev combination was further validated by retrospective studies.[28–30] Atezo/bev is currently viewed as the preferred first-line systemic treatment option in most guidelines.[2,9,10,14] However, bevacizumab may induce an elevated risk of bleeding in patients with severe esophageal and gastric varices. Thus, it is necessary for patients seeking atezo/bev treatment to undergo an esophagogastroduodenoscopy to exclude those with untreated or severe esophageal or gastric varices.[5,6,10,19] The PD rate associated with atezo/bev is 19%, which is higher than that of anti-PD-1 antibody plus tyrosine kinase inhibitor (TKI) combinations (Table 1).[19] In patients planning to undergo downstaging resection, bevacizumab treatment must be suspended 4–6 weeks before liver resection.[14,31] After bevacizumab treatment is discontinued, atezolizumab monotherapy is used for one treatment cycle. This treatment schedule will not compromise the safety of the surgery but may lead to tumor rebound.

Sintilimab Plus a Bevacizumab Biosimilar

This combination exhibits almost the same anti-cancer mechanism of action as atezo/bev.[14,15] The ORIENT-32 study was a multicenter, phase III RCT conducted in China. In this study, 571 systemic treatment-naïve patients with unresectable or metastatic HCC were randomized to receive either sintilimab plus a bevacizumab biosimilar (n = 380) or sorafenib (n

= 191).[15] The study confirmed that the anti-cancer efficacy of sintilimab plus a bevacizumab biosimilar was superior to sorafenib, as demonstrated by better OS and PFS benefits.[15] The combination of sintilimab plus a bevacizumab biosimilar is recommended as the first-line systemic treatment option in Chinese guidelines.[2,15] However, the PFS, ORR, and PD rate data associated with sintilimab plus a bevacizumab biosimilar were slightly inferior to other first-line combination treatment options such as atezo/bev and len/pembro. This may be due to delays in the administration of intravenous medication caused by lockdowns during the COVID-19 pandemic (Table 1).[15,19,24] Furthermore, since there are no available data regarding median survival time, the efficacy of sintilimab plus a bevacizumab biosimilar should be validated using real-world data. The concerns about this combination are the same as for atezo/bev, such as a mandatory esophagogastroduodenoscopy examination before therapy and bevacizumab discontinuation for one cycle before planned surgery.

Recently, two RCTs conducted in China utilized two anti-PD-1 antibodies, including SCT-I10A and toripalimab (both are anti-PD-1 antibodies), in combination with a bevacizumab biosimilar.[18,32] Compared to sorafenib, they met their primary endpoints more quickly when used as first-line therapies for advanced-stage HCC. While these combination therapies possess the same action mechanisms, they cannot further prolong patient survival time, but they can improve the drug availability in China.

Rivoceranib (Apatinib) Plus Camrelizumab, and Anlotinib Plus Penpulimab

Apatinib is a multi-target TKI with potent anti-tumor angiogenic effects. The CARES-310 study was an international phase III RCT conducted at 95 sites in 13 countries and regions. Here, 543 systemic treatment-naïve-patients with unresectable or metastatic HCC were randomized to receive apatinib plus camrelizumab (n = 272) or sorafenib (n = 271).[16] Most of the patients recruited in this study were from Asia, and more than 70% of them were HBV-related HCC.[16] The findings of the study revealed that apatinib plus camrelizumab was associated with a 36% lower risk of death and a 48% reduced risk of tumor progression or death compared to sorafenib.[16,17] Although apatinib plus camrelizumab demonstrated superior efficacy, the number of grade ≥ 3 TRAEs associated with this combination was high (80.9%), leading to relatively low patient tolerance.[16] Hence, the patient-reported outcome was not better than sorafenib in most functioning domains.[16] Apatinib plus camrelizumab had a relatively high ORR and low PD rate compared with some other bevacizumab-based combinations (Table 1).[15,18–20] Therefore, this combination may be the ideal option for short-term peri-operative treatments in patients with resectable or borderline resectable HCC.

Most recently, anlotinib, another multi-target TKI, in combination with penpulimab (anti-PD-1 antibody) shower superior OS (median OS, 16.5 vs 13.2 months, HR=0.69, 95% CI, 0.52–0.92) and PFS (median PFS, 6.9 vs 2.8 months, HR=0.53, 95% CI, 0.41–0.68) benefit compared with sorafenib in the phase III APOLLO study.[25] The grade ≥3 TRAE of this combination is relatively lower (48.2%) as compared with other TKI and anti-PD-1 combinations (Table 1).

Lenvatinib Plus Pembrolizumab or Other Immune Checkpoint Inhibitors (ICIs)

In the LEAP-002 study, a global phase III RCT, 794 patients with advanced HCC were randomly assigned to receive either lenvatinib plus pembrolizumab (len/pembro; n = 395) or lenvatinib plus a placebo (n = 399).[24] The coprimary endpoint for OS and PFS did not satisfy pre-specified statistical significance and hazard ratio (HR) targets, with len/pembro vs lenvatinib plus placebo values of 0.84 (95% CI: 0.71–1.00; P = 0.023) and 0.83 (95% CI: 0·71-0·98), respectively.[24] The mOS and mPFS values of the len/pembro combination were comparable to previous systemic combination treatment regimens (Table 1).[19,24,34,35] Additionally, the OS associated with lenvatinib first-line treatment was superior to previous findings regarding lenvatinib monotherapy.[22] This is probably because lenvatinib has been more widely used and there are more post-progression options available. A subgroup analysis of the LEAP-002 study for Asian patients was conducted, and nearly 80% have hepatitis B virus (HBV)-associated HCC. In this subgroup, there were more pronounced survival benefits associated with len/pembro (the HR for OS and PFS were 0.73 and 0.71, respectively).[36] Data also demonstrated the efficacy and safety of lenvatinib and anti-PD-1 antibodies.[37] Several phase Ib/II studies using various anti-PD-1 antibodies or anti-PD-1/CTLA-4 bispecific antibodies, including nivolumab, sintilimab, tislelizumab, cadonilimab, and KN046, in combination with lenvatinib revealed a similar antitumor efficacy and safety profile to the len/pembro combination.[38–43] However, grade ≥3 TRAE associated with len/pembro (62.5%) is

higher than that of atezo/bev (45%) (Table 1). However, given the longer exposure time for len/pembro (8.6 months)[44] than atezo/bev (7.4 and 6.9 months with atezolizumab and bevacizumab, respectively),[19] The difference in exposure-adjusted TRAE rates between the combinations would be much smaller.

Lenvatinib monotherapy and lenvatinib-based combination treatments have relatively high ORRs and disease control rates (DCRs), and comparatively low PD rates (Table 1).[15,19,24,33–35] As a result, a combination of lenvatinib and anti-PD-1 antibody is the preferred first-line systemic treatment option for patients hoping to undergo downstaging resection. The combination is not approved as a first-line systemic treatment for hepatocellular carcinoma in China. Real-world studies from different centers also reported on the efficacy and safety of conversion therapy with lenvatinib-based treatments for patients with unresectable HCC, providing further clinical experience using lenvatinib-based treatments in conversion surgery for patients with unresectable HCC.[45–51]

Most recently, the LEAP-012 study, with compare TACE in combination with len/pembro and TACE in combination with placebos as first-line therapy for intermediate-stage HCC patients published the primary study results.[52] In this study, the adding len/pembro to TACE significantly prolonged PFS (median PFS, 14.6 vs 10.0 months; HR=0.66; 95% CI, 0.51–0.84). In the interim analysis, OS, a co-primary end point of this study, showed a trend toward improvement (HR=0.80, 95% CI, 0.57–1.11). Based on this study, TACE in combination with len/pembro may become the new standard-of-care for patients with intermediate-stage HCC.

Tremelimumab Plus Durvalumab

In the global phase III HIMALAYA study, 1171 systemic treatment-naïve patients with unresectable HCC were randomized to receive single tremelimumab (anti-CTLA-4 antibody) regular interval durvalumab (anti-PD-L1 antibody) (STRIDE; n = 393), durvalumab (n = 389), or sorafenib (n = 389) treatments.[34] The results indicated that compared to sorafenib, the STRIDE regimen presented a significant reduction in risk of death (28%).[34] The tremelimumab plus durvalumab combination has been approved for the treatment of patients with unresectable HCC by the US Food and Drug Administration (FDA) and the European Medicine Agency (EMA) and is considered one of the preferred first-line treatment options by guidelines.[8,10] An issue with this combination is that it has a relatively high PD rate (39.9%),[34] indicating that nearly half of the patients may exhibit primary resistance to anti-PD-L1/anti-CTLA-4 immunotherapy. Besides, because of the high PD rate, this combination may be not suitable for patients with borderline resectable HCC, whose treatment goal is downstaging resection. It also may not be appropriate for patients with a large tumor burden since if PD occurs, they may lose the opportunity to receive second-line therapy. However, due to its relatively low toxicity profile, the STRIDE regimen was considered in patients with Eastern Cooperative Oncology Group Performance Status (ECOG PS) 2 or Child-Pugh B liver cirrhosis in a phase IIIb study in China (CTR20222433).

Nivolumab Plus Ipilimumab

In the CheckMate 9DW study, the combination of nivolumab and ipilimumab (anti-CTLA-4 antibody) demonstrated improved OS in patients with unresectable HCC over sorafenib or lenvatinib when used as a first-line treatment.[23] The efficacy results for the nivolumab-ipilimumab combination were the best among all phase III clinical trials for advanced HCC. OS in the nivolumab-ipilimumab arm was 23.7 months, compared to 20.6 months in the control group. Moreover, the ORR assessed by response evaluation criteria in solid tumors v1.1 (RECIST v1.1) criteria was 36%, which is the highest ORR among all phase III RCTs (Table 1). However, patients exhibited poorer overall survival in the first year, high PD rates (20%, with 12% unevaluatable), and high rates of treatment-related death (4%) and immune-related adverse effects. Consequently, they had to receive high-dose steroid treatment (29%). These issues may limit the clinical use of nivolumab-ipilimumab.

First-Line Monotherapy Options

Tyrosine kinase inhibitor monotherapies include lenvatinib, sorafenib, and donafenib (only in China). Monotherapies are ideal first-line treatment options for patients who cannot tolerate immune-based therapies because of active auto-immune diseases or previous organ transplantation.[2,10]

Lenvatinib

In a multicenter phase III randomized non-inferiority study conducted at 154 sites in 20 countries, 954 treatment-naïve patients with unresectable HCC were randomized to receive either lenvatinib (n = 478) or sorafenib (n = 476).[22] The findings revealed that lenvatinib-associated OS was similar to sorafenib (mOS: 13.6 months vs 12.3 months; HR = 0.92; 95% CI: 0.79–1.06; non-inferiority margin: 1.08).[22] A subgroup analysis of Chinese patients found that lenvatinib provided numerically superior survival benefits than sorafenib (OS: 15.0 months vs 10.2 months).[53] This is probably because patients with Hepatitis B Virus (HBV) related HCC benefit less from sorafenib therapy than those with Hepatitis C Virus (HCV) related HCC.[54] In two RCTs, when lenvatinib monotherapy was used in the control arm, the median OS associated with first-line lenvatinib therapy was significantly longer. The LEAP-002 study disclosed that patients with lenvatinib plus placebo treatment had a median OS of 19.0 months,[24] while a subgroup analysis of Asian patients with mainly HBV-related HCC had a median OS of 22.4 months.[36] In the CheckMate 9DW study, 85% of patients in the control arm received lenvatinib, while 15% received sorafenib as the first-line therapy, and the median OS reached 20.6 months.[23] Possible reasons for the prolonged median survival time in the lenvatinib group are the accumulated experience in lenvatinib treatment and the availability of subsequent treatments.

The control arms of the pivotal phase III studies of other combination therapies, including atezo/bev,[19,20] apatinib plus camrelizumab,[16] sintilimab plus a bevacizumab biosimilar,[15] and STRIDE,[34] all use sorafenib. Thus, these combination therapies cannot be directly compared with lenvatinib. In a multicenter real-world study of patients with HCC from 46 centers in Italy, Germany, Japan, and the Republic of Korea, 1312 and 823 patients were treated with lenvatinib or atezo/bev, respectively.[55] The ORRs (by modified RECIST criteria) for patients with lenvatinib and atezo/bev were 38.6% and 27.3%, respectively ($P < 0.01$).[55] After inverse probability of treatment weighting (IPTW) adjustments, atezo/bev had similar survival benefits to lenvatinib (HR = 0.97, P = 0.739). Another retrospective analysis which was conducted across 18 university hospitals in Europe also showed that survival rates were similar between patients treated with lenvatinib and those treated with atezo/bev.[56] Thus, despite the emergence of immune-based therapies, lenvatinib-based systemic treatments are still essential first-line treatment options.

Sorafenib and Donafenib

In two multicenter phase III RCTs (the SHARP and ORIENTAL studies), the mOS for systemic treatment-naïve patients with advanced HCC receiving sorafenib were 6.5 months and 10.7 months, respectively, compared with 4.2 and 7.9 months in the placebo groups. Furthermore, the ORRs in the sorafenib group were 2% and 3.3%, respectively.[11,12] Subsequent phase III RCTs using sorafenib as a control reported increased median OS of more than 15 months.[16,35] However, multiple studies have demonstrated that sorafenib is inferior to various systemic treatment regimens, putting its suitability as a first-line treatment option for HCC in doubt.

Since donafenib is a modified form of sorafenib, it has a similar mechanism of action.[57] In an open-label parallel-controlled multicenter Phase II–III RCT conducted at 37 sites across China, systemic treatment-naïve patients with unresectable or metastatic HCC were randomized to receive donafenib (n = 328) or sorafenib (n = 331).[57] Donafenib exhibited significantly longer mOS than sorafenib (12.1 months vs 10.3 months; HR = 0.831; $P = 0.0245$).[57] Besides, donafenib and sorafenib had comparable anti-cancer activity (ORR: 4.6% vs 2.7%; $P = 0.2448$).[57] However, donafenib was associated with fewer incidence grade ≥ 3 TRAEs than sorafenib (57% vs 67%). This difference may be attributable to the lower daily dosage of donafenib (0.2 g twice daily) than sorafenib (0.4 g twice daily), indicating that donafenib has a superior safety profile.[57]

First-Line Immune-Checkpoint Inhibitor (ICI) Monotherapies

The phase III HIMALAYA study also met its secondary endpoint, revealing that durvalumab monotherapy was not inferior to sorafenib regarding OS (HR = 0.86; 95.67% CI: 0.73–1.03; noninferiority margin: 1.08).[34] In the phase III RATIONALE-301 study, a total of 674 patients with unresectable HCC who had not undergone any prior systemic treatment were randomly assigned to receive either tislelizumab (n = 342) or sorafenib (n = 332).[58] Patients treated with tislelizumab had a 15% lower risk of death than those treated with sorafenib, thereby meeting the primary OS endpoint of non-inferiority for tislelizumab (HR = 0.85; 95% CI: 0.71–1.02; noninferiority margin: 1.08).[58] Some reports have

indicated that nivolumab exhibits anti-cancer effects and has a tolerable safety profile in HCC patients with impaired liver function (Child-Pugh B cirrhosis).[59,60] Thus, it is possible that tislelizumab monotherapy could also be used to treat such patients. Because the adverse effects of ICI are different from those of TKIs, durvalumab or tislelizumab monotherapy may be suitable for patients with contraindications for targeted therapy or those who cannot tolerate targeted therapy, such as patients with low platelet count or refractory hypertension.

Second-Line Treatment Strategies And Beyond

Second-Line Systemic Treatment Strategies

To improve the clinical outcomes for patients with advanced HCC, it is essential to optimize the timing and order of treatment switching during sequential systemic treatment.[61] There are several approved treatment options available for the second-line treatment of HCC. However, they are only used after the failure of first-line sorafenib treatment or chemotherapy.[5–10] Currently, there is no standard second-line treatment regimen after treatment failure from an ICI-based combination therapies, eg, atezo/bev and STRIDE regimen, which are the preferred first-line therapies for advanced-stage HCCs.[5–10]

When selecting a second-line systemic treatment, we should consider the following scenarios: mechanism of action of the first-line treatment regimen;[62] pattern of progression (enlargement of target lesions, new lesions, or progression with vascular invasion or extrahepatic metastasis); patient's general condition and liver function; adverse events that occur during first-line treatment. The safety profiles of potential second-line treatments and their impact on the patient's quality of life should also be assessed, along with the administration method, schedule, and duration of these treatments.[6]

Systemic Therapies

Various guidelines/consensuses recommend different types of second-line treatment regimens.[2,5,6,8,10] Nevertheless, most guidelines concur that lenvatinib or sorafenib should be used as a second-line therapy following tumor progression on non-lenvatinib first-line treatments such as atezo/bev and STRIDE regimen.[2,5,6,8,10] The European Society for Medical Oncology (ESMO) guidelines further recommend lenvatinib as the preferred second-line treatment option in such settings due to its superior ORR and PFS compared to sorafenib.[8] Based on the currently limited evidence and the mechanism of action of the drugs, we suggest the following recommendations for the second-line treatment for HCC (Figure 1).

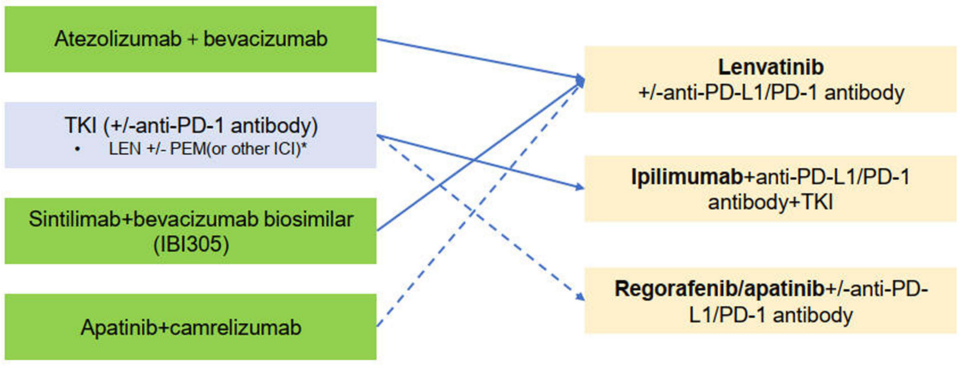

Figure 1 Algorithm for patient-centered, individualized systemic treatment strategy for patients with potentially resectable HCC in China.
Notes: The flow chart diagram is for discussion only and is not for a medication recommendation. *The combination is not approved as a first-line systemic treatment for hepatocellular carcinoma in China. Lenvatinib monotherapy and lenvatinib-based combination treatments have relatively high ORRs and DCRs, and comparatively low PD rates. As a result, lenvatinib monotherapy or used in combination with other drugs is a widely used treatment option for patients in clinical practice in China. Solid lines represent second-line treatment recommendations with greater certainty; dotted lines represent those with less certainty.
Abbreviations: ICI, immune checkpoint inhibitors; TKI, tyrosine kinase inhibitor; PD-1, programmed death-1; PD-L1, Programmed cell death ligand 1; LEN, lenvatinib; PEM, pembrolizumab. ORR, objective response rate; DCR, disease control rate; PD, progressive disease.

Overcoming Treatment Resistance to the Anti-PD-L1/PD-1 Antibody

Immune-checkpoint inhibitors, more specifically the PD-L1 or PD-1 antibody, are already the de facto backbone of first-line systemic therapy for HCC. However, should ICI be continuously used when an ICI-based therapy (atezo/bev or treme/durva) fails remains unknown. A retrospective study from the Asia-Pacific region revealed that in patients whose atezo/bev treatment failed, those receiving ICI in combination with TKI therapy had the longest median OS and PFS, suggesting that continuing ICI in second-line therapy is beneficial.[63] The emergence of anti-drug antibodies (ADAs) after treatment may be another reason for employing ICI rechallenge in second-line treatment. In the IMbrave150 study, 29.6% of patients receiving the atezo/bev treatment produced ADAs,[64] which are associated with reduced survival benefits. In ADA-positive patients, the OS HR was 0.96 (95% CI: 0.62–1.48) with atezo/bev vs sorafenib, while in ADA-negative patients, the OS HR was 0.55 (95% CI: 0.41–0.74).[64] Another cohort study revealed that high ADA levels were associated with the inferior anticancer efficacy of atezo/bev.[65] Using the anti-PD-1 antibody or another anti-PD-L1 antibody may overcome the reduced efficacy caused by ADAs.

Second-Line Therapy After Atezo/Bev

Existing recommendations are consistent with real-world data.[66,67] A multinational multicenter retrospective study investigated the clinical outcomes in 49 patients with advanced HCC who were administered TKI following tumor progression on first-line atezo/bev therapy.[66] Of the 49 patients, 29 (59.2%), 19 (38.8%), and one (2.0%) subsequently received sorafenib, lenvatinib, or cabozantinib treatments, respectively. Compared with the patients who received sorafenib, patients who were given lenvatinib had significantly longer mPFS (6.1 vs 2.5 months; $P = 0.004$), and a trend toward of higher ORR (15.8% vs 0; $P = 0.062$) and longer mOS (16.6 vs 11.2 months; $P = 0.347$). Another multinational multicenter retrospective proof-of-concept study assessed the clinical outcomes of various second-line treatments.[67] In patients whose tumors progressed after atezo/bev (n = 464), subsequent lenvatinib treatment led to significantly longer OS than those who received other treatments. Specifically, the HRs for sorafenib, lenvatinib, cabozantinib, and other therapies were 1, 0.50, 1.29, and 0.54; $P < 0.01$.[67] Another retrospective study from the Asia-Pacific region demonstrated that in patients whose atezo/bev treatment failed, lenvatinib was associated with longer PFS and OS than sorafenib. A multicenter Phase II trial evaluated lenvatinib in patients with uHCC after progression on first-line atezo/bev lenvatinib demonstrated clinically meaningful efficacy outcomes without a new safety signal.[68] Therefore, in the absence of a standard second-line treatment regimen for patients whose condition progresses after first-line atezo/bev, lenvatinib-based treatments are generally the preferred options. However, it remains unknown whether the anti-PD-L1/anti-PD-1 antibody should be continued beyond atezo/bev treatment failure. Further clinical trials, including the IMbrave251 study (NCT04770896), are required to answer this question. The IMbrave251 study is a multicenter phase III RCT that compares the efficacy and safety of atezolizumab plus either lenvatinib or sorafenib with lenvatinib or sorafenib alone in patients with locally advanced or metastatic HCC whose tumor progressed after systemic treatment with atezo+bev.[69] The data obtained from this study will provide insights into whether adding an anti-PD-1/PD-L1 antibody to a second-line TKI treatment is beneficial for HCC patients whose combined targeted therapy-immunotherapy fails. Most recently, renal cell carcinoma data indicated that ICI rechallenge did not lead to additional effects in late-line therapy. The CONTACT-03 study showed that adding atezolizumab to cabozantinib did not improve PFS or OS, compared with cabozantinib alone.[70] Moreover, the TiNivo-2 study (NCT04987203) indicated that the addition of nivolumab to low-dose tivozanib was not more effective than the standard dose of tivozanib alone in terms of PFS.[71]

Second-Line Therapy After Lenvatinib or Lenvatinib Plus an Anti-PD-1 Antibody

For patients whose tumors progress after first-line lenvatinib monotherapy, various guidelines recommend sorafenib, cabozantinib, regorafenib, or immune-based therapies such as pembrolizumab or ipilimumab plus nivolumab.[5,6,10] A retrospective cohort study established that patients with unresectable HCC whose diseases progressed after first-line lenvatinib exhibited improvements when the anti-PD-1 antibody was added to lenvatinib as a second-line therapy.[72] In another multinational retrospective study, the clinical outcomes of various second-line treatments were assessed in HCC patients with tumor progression after first-line lenvatinib treatment (n = 917).[67] For patients whose tumors progressed after lenvatinib, the OS associated with various second-line treatment regimens presented no statistically significant

Table 3 The IC_{50} on Specific Signaling Pathways of Targeted Agents for HCC (Approved and Investigating Agents)

	sorafenib	lenvatinib	regorafenib	cabozantinib	apatinib	anlotinib	bevacizumab	ramucirumab
VEGFR-1	21	4.7	13	5294	-	26.9	0.15	-
VEGFR-2	21	3	4.2	0.035	1	0.2		1–2
VEGFR-3	16	2.3	46	-	-	0.7		-
FGFR-1	340	61	202	-	>10,000	-	-	-
FGFR-2	150	27	~200	-	-	-	-	-
FGFR-3	340	52	-	-	-	-	-	-
FGFR-4	3400	43	-	-	-	-	-	-
PDGFRα	1.6	29	136	-	>1000	-	-	-
PDGFRβ	27	160	22	234	-	115	-	-
c-KIT	140	85	7	4.6	429	14.8	-	-
RET	15	6.4	1.5	4	13	-	-	-
AXL	-	-	-	7	-	-	-	-

Abbreviations: VEGFR, vascular endothelial growth factor receptor; FGFR, fibroblast growth factor receptor; PDGFR, platelet-derived growth factor receptor; c-KIT, c-kit proto-oncogene protein; RET, rearranged during transfection; AXL, Anexelekto.

differences (HRs for sorafenib, immunotherapy, and other therapies were 1, 0.69, and 0.85, respectively; $P = 0.27$). Ultimately, immunotherapy was associated with better survival.

Lenvatinib targets a more broad-spectrum signaling pathway than other agents (Table 3),[73–77] so switching to another TKI, bevacizumab, or ramucirumab after lenvatinib treatment failure may not be a good choice. However, regorafenib and apatinib exhibit more robust inhibitory impacts on vascular endothelial growth factor receptor 2 (VEGFR2). Consequently, they may have stronger anti-angiogenic activity than lenvatinib (Table 3) and may be considered for individuals experiencing tumor progression on lenvatinib.[2,8,78,79] Another multicenter retrospective study conducted in Japan reported on patients with unresectable HCC whose disease progressed after first-line lenvatinib. Provided that the patients' performance status and hepatic reserve function allowed, continuing lenvatinib treatment in the second-line setting after tumor progression led to improved survival benefits over patients who switched to other TKIs.[80] Such observations could probably be explained by the phenomenon of "mixed tumor response".[81] For patients with mixed tumor response, continuing the original treatment or adding additional therapies after tumor progression may still provide survival benefits.[81]

Anti-PD-1/PD-L1 antibody combined with an anti-CTLA-4 antibody may be considered for patients whose disease progresses after lenvatinib or lenvatinib plus an anti-PD-1/PD-L1 antibody.[82–84] Some retrospective reports have indicated that certain patients who experience tumor progression on anti-PD-1/PD-L1 antibody treatment may benefit from the addition of ipilimumab (anti-CTLA-4 antibody) to the anti-PD-1/PD-L1 regimen, with an ORR of 16% to 30%.[82–84] Because the STRIDE combination was only recently approved, there are no reports regarding second-line therapy using this treatment.

Locoregional Therapies

It remains unknown whether locoregional control of intrahepatic lesions prolongs the survival of patients with advanced-stage HCC. However, it has been reported that in patients with BCLC stage C HCC, the addition of lenvatinib therapy with TACE prolongs survival, compared with lenvatinib as a first-line treatment.[85] Most patients with advanced HCC die from intrahepatic tumor progression, so local control of intrahepatic lesions may delay liver function deterioration. Therefore, patients may benefit from TACE or other locoregional therapies. In a retrospective study, TACE was

associated with significantly longer OS than sorafenib in patients whose lenvatinib treatment failed (24.7 vs 15.8 months; HR = 0.64; P < 0.01).[67] Nevertheless, locoregional therapy may be not suitable for patients heavily pretreated with TACE, including those whose condition progressed after TACE combined with systemic therapy or those who received systemic therapy after progression from TACE. In such patients, hepatic arterial infusion chemotherapy (HAIC) or stereotactic body radiation therapy (SBRT) may be used as alternative locoregional therapies to TACE. The indications for HAIC and TACE have significant overlap, each with its own advantages and disadvantages, but they can complement each other. For example, in patients with higher tumor burden, such as those exceeding the up-to-7 criteria, or those with a main portal vein tumor thrombus, HAIC should be prioritized. For patients with a low tumor burden or multiple tumors located in different lobes of the liver, TACE should be prioritized.[86]

Treatment Strategies For Patients With Borderline/Potentially Resectable HCC

Conversion therapy-driven HCC management strategies are not fully compatible with current HCC systemic treatment strategies because the treatment goals are different. Conversion therapy is only the initial stage of anti-cancer treatment, and patients have the opportunity to receive curative resection after successful downstaging or downsizing, thereby gaining improved survival benefits.[14,87] Patients with potentially resectable HCC include those who have surgically unresectable early-stage HCC and surgically resectable intermediate-to-advanced stage HCC. Provided these patients have good hepatic reserve function, more aggressive conversion therapy strategies involving multi-modal and high-intensity treatments to facilitate subsequent curative resection could be considered.[2,14] In a recent retrospective study, we proposed and validated criteria that could be used to identify potentially resectable patients with initially unresectable HCC before they received combination therapy with lenvatinib plus an anti-PD-1 antibody.[88] The criteria were as follows: (1) ECOG PS 0–1; (2) Child-Pugh class A; (3) Intrahepatic tumors confined to one liver lobe or present in one lobe alongside either a single tumor with ≤ 5 cm diameter or 2–3 tumors each with ≤ 3 cm diameter in the contralateral lobe; (4) Portal vein tumor thrombus does not involve the contralateral liver lobe or does not reach the superior mesenteric vein; hepatic vein tumor thrombus does not involve more than two major hepatic vein branches on the tumor side, or tumor thrombus of the inferior vena cava does not reach the atrium; (5) No extrahepatic metastasis.[88] In our study, patients who met these criteria had a much higher rate of successful downstaging than those who did not meet the criteria (46.4% vs 2.3%; $P < 0.001$). These criteria may allow selected patients to receive aggressive anti-cancer therapy.[88] Wang et al also reported in a prospective study that in patients with vascular invasion, those met these criteria: (1) portal vein invasion (Vp) 1–2 portal vein tumor thrombosis (in contrast to Vp3-4); (2) serum AFP < 400 ng/mL; (3) neutrophil-lymphocyte ratio (NLR) < 2.63; (4) tumor diameter < 10 cm, had a high chance of surgical resection after three cycles of atezo/bev and one cycle of atezolizumab therapy.[89] Most recently, oncological resectability criteria were also proposed in a Japanese expert consensus.[90] Patients were divided into resectable, borderline resectable 1, and borderline resectable 2 (initially unsuitable for resection) based on tumor number, tumor size, and vascular invasion status. Patients meeting borderline resectable 1 or 2 criteria may benefit from more aggressive treatment, increasing their chances of curative surgery following treatment.

Discussion And Conclusions

In this perspective, we propose the incorporation of a novel concept into HCC treatment, that is, the theory of a patient-centered, treatment goals-driven, individualized systemic treatment strategy, illustrated by the treatment algorithms in Figure 1. The selection of an appropriate second-line treatment regimen following the failure of targeted therapy in combination with immunotherapy is a subject that requires further investigation. Unfortunately, the wide range of first-line treatment options complicates the exploration and decision-making process for subsequent second-line treatments. Furthermore, it remains unclear whether persisting with immunotherapy following the failure of combined treatment involving targeted therapy and immunotherapy is advantageous.

Finally, sub-classifying HCC according to its molecular and histological subtype may also facilitate the individualized management of patients with advanced HCC.[6,10] Additionally, research on emerging treatment targets such as T cell

immunoreceptors with immunoglobulin and ITIM domains (TIGIT) is currently being carried out. TIGIT is an emerging immune checkpoint that serves as a target for immunotherapy, alongside PD-1/PD-L1 and CTLA-4.[91] It has been reported that tiragolumab, an anti-TIGIT antibody, has therapeutic anti-cancer potential.[91] Taking molecular subtypes and HCC biomarkers into consideration when making individualized treatment decisions may improve survival in patients and eventually lead to some patients being cured.

Disclosure

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