JOURNAL OF
LIVER CANCER

The role of lenvatinib in the era of immunotherapy of hepatocellular carcinoma

Matthew Man Pok Lee[1], Landon Long Chan[1], Stephen Lam Chan[1,2]

[1]Department of Clinical Oncology, Prince of Wales Hospital, The Chinese University of Hong Kong Faculty of Medicine, Shatin, Hong Kong; [2]State Key Laboratory of Translational Oncology, State Key Lab & Research Institutes, Hong Kong Cancer Institute, The Chinese University of Hong Kong Faculty of Medicine, Shatin, Hong Kong, China

Hepatocellular carcinoma (HCC) frequently presents as advanced stage with poor prognosis and high mortality. Systemic treatment is the treatment of choice for advanced disease. In 2007, the first multi-kinase inhibitor (MKI) sorafenib was approved and shown to modestly prolong overall survival (OS). The progress of systemic therapy has been slow afterwards until 2018 when lenvatinib, another MKI, was shown to be non-inferior to sorafenib on median OS as the first-line therapy for HCC. Since then, remarkable progress has been achieved on the treatment of advanced HCC, including the development of second-line targeted treatment, including regorafenib, cabozantinib and ramucirumab from 2017 to 2019. A growing focus has been placed on immune checkpoint inhibitors (ICIs) targeting programmed cell death-1 (PD-1), its ligand PD-L1, and cytotoxic T-lymphocyte-associated protein 4. These ICIs have proven their potency in treating HCC as both initial and subsequent line of therapy. At present, both regimens of atezolizumab combined with bevacizumab, as well as the combination of tremelimumab and durvalumab, are recommended as the first-line treatments based on positive phase III clinical trials. With the advancement of ICIs, it is anticipated that the role of MKIs in the treatment of HCC will evolve. In this article, lenvatinib, one of the most commonly used MKIs in HCC, is chosen to be reviewed. **(J Liver Cancer 2023;23:262-271)**

Keywords: Lenvatinib; Immune checkpoint inhibitors; Carcinoma, hepatocellular

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer and fourth most common cause of cancer related death worldwide.[1] Considerable number of patients with HCC present with advanced disease at the time of diagnosis and are not eligible for treatments with curative intent including resection, transplantation, and ablation. Systemic therapy is the treatment of choice for patients with advanced unresectable HCC who are not amenable to curative or locoregional therapy. Sorafenib was the first multi-kinase inhibitor (MKI) approved in advanced HCC in 2007 based on the SHARP trial.[2] It demonstrated an improvement in progression-free survival (PFS) from 2.8 to 5.5 months, and overall survival (OS) from 7.9 to 10.7 months. Since then, development of systemic treatment for advanced HCC was stalled and it took another 10 years for the second MKI lenvatinib to be developed and approved in the upfront setting in 2018,

Corresponding author: Stephen Lam Chan

Department of Clinical Oncology, Prince of Wales Hospital, The Chinese University of Hong Kong Faculty of Medicine, 30-32 Ngan Shing Street, Shatin, Hong Kong, China
Tel. +852-3505-2166, Fax. +852-2648-7097
E-mail: chanlam_stephen@cuhk.edu.hk

based on the non-inferiority REFLECT trial.[3] In the RE-FLECT trial, lenvatinib demonstrated non-inferior OS compared to sorafenib (13.6 vs. 12.3 months; hazard ratio [HR], 0.92; 95% confidence interval [CI], 0.79-1.06).

In the recent 5 years, the development of systemic therapy of HCC has been rapidly expanding with multiple new regimens improving survival, particularly due to the introduction of immune checkpoint inhibitor (ICI).[4-8] In particular, the IMBrave-150 trial was the first trial to show that treatment of advanced HCC using combination of ICI and anti-vascular endothelial growth factor (VEGF) monoclonal antibodies (atezolizumab plus bevacizumab [Atezo-Bev]) resulted in an unprecedented high objective response rate (29.8% vs. 11.3%) and OS (19.2 vs. 13.4 months) compared to sorafenib. Subsequently, different combinations of ICIs in randomized controlled trials demonstrated their efficacy for advanced HCC.[8-10]

Clearly, the establishment of ICIs in the first-line setting has revolutionized the treatment landscape of advanced HCC, supported by multiple international guidelines such as the National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), European Society for Medical Society (ESMO), European Association for the Study of the Liver (EASL), Korean Liver Cancer Association and National Cancer Center (KLCA-NCC) Korea guidelines.[11-15] This has led to questioning of the role of MKIs including sorafenib and lenvatinib in the management of advanced HCC. This review article aims to discuss the role of

lenvatinib in this expanding era of immunotherapy.

OLD ROLE: FIRST-LINE TREATMENT IN ADVANCED HCC

Lenvatinib is an oral MKI of vascular endothelial growth factor receptor 1-3, fibroblast growth factor receptors 1-4, platelet-derived growth factor receptor alpha, RET, and KIT protooncogenes. In the landmark phase III non-inferiority REFLECT trial comparing lenvatinib vs. sorafenib, lenvatinib showed non-inferiority in OS with duration of 13.6 vs. 12.3 months (HR, 0.92; 95% CI, 0.79-1.06). The survival benefit was seen consistently across multiple subgroups regardless of aetiology, Barcelona Clinic Liver Cancer (BCLC) stage, and baseline alpha-fetoprotein (AFP), and so on.[3] Lenvatinib showed statistically significant improvement over median PFS (7.4 vs. 3.7 months), median time-to-progression (8.9 vs. 3.7 months) and overall response rate (ORR) (18.8% vs. 6.5%). Based on this trial, Food and Drug Administration (FDA) approved lenvatinib as first-line treatment of patients with unresectable HCC in 2018.

Although head-to-head comparison is lacking, in cross-trial comparison, the ORR and OS of lenvatinib are numerically less favourable than immunotherapy combination (Table 1), such as with Atezo-Bev.[6] Similarly, clinical outcomes including ORR and OS were worse with lenvatinib compared to the ICI combination durvalumab plus tremelimumab as in the HIMALAYA trial (Table 1).[8] However, the superior ef-

Table 1. Summary of outcomes of key phase 3 first-line trials in advanced HCC

Trial	Comparator	Median OS (months)	PFS (months)	ORR (%)
REFLECT[3]	Lenvatinib vs. sorafenib (control)	13.6 vs. 12.3; HR, 0.92; 95% CI, 0.79-1.06*	7.4 vs. 3.7; HR, 0.66; 95% CI, 0.57-0.77	18.8 vs. 6.5
SHARP[2]	Sorafenib vs. placebo (control)	10.7 vs. 7.9; HR, 0.69; 95% CI, 0.55-0.87	5.5 vs. 2.8; HR, 0.58; 95% CI, 0.45-0.74	18.8 vs. 6.5
IMBrave-150[6,16]	Atezolizumab plus Bevacizumab vs. sorafenib (control)	19.2 vs. 13.4; HR, 0.66; 95% CI, 0.52-0.85	6.8 vs. 4.3; HR, 0.59; 95% CI, 0.47-0.76	30 vs. 11
HIMALAYA[8]	Durvalumab plus tremelimumab vs. sorafenib (control)	16.4 vs. 13.8; HR, 0.78; 95% CI, 0.65-0.92	3.8 vs. 4.1; HR, 0.90; 95% CI, 0.77-1.05	20.1 vs. 5.1

HCC, hepatocellular carcinoma; OS, overall survival; PFS, progression-free survival; ORR, overall response rate; HR, hazard ratio; CI, confidence interval.
*Non-inferiority criteria met.

ficacy of ICI combination treatments may not be suitable for all patients. For example, patients who had prior gastrointestinal bleeding due to varices within 6 months of treatment initiation were excluded from both the IMBrave-150 and HIMALAYA trial.[6,8] In particular, patients in IMBrave-150 were required to have pretreatment oesophagogastroduodenoscopy (OGD) to screen for any untreated or incompletely treated oesophageal or gastric varcies due to the high risk of bleeding with the use of high dose bevacizumab.

In terms of toxicities, patients treated with ICIs and MKIs experienced similar percentage of adverse events (AEs) but the spectrum of toxicities were different. For instance, serious treatment-related AEs were seen in 23% of patients in the Atezo-Bev group, compared to 16% in the sorafenib group. 22% of patients had withdrawal from any component of treatment due to AEs in the combination group compared to 12% of patients in the sorafenib group.[16] In the HIMALAYA trial, 17.5% of patients developed serious treatment-related AEs with combination of durvalumab and tremelimumab compared to 9.4% of patients in the sorafenib group.[17] But treatment-related AEs leading to discontinuation was higher with sorafenib compared to durvalumab plus tremelimumab (11.0% vs. 8.2%). In the REFLECT trial, serious treatment-related AEs affected 18% of patients. Notably, patients treated with Atezo-Bev and lenvatinib had more AEs related to properties of anti-VEGF agents such as hypertension and proteinuria, whereas patients treated with durvalumab plus tremelimumab developed more immune-mediated AEs such as colitis/diarrhea, dermatitis/skin rash, or hepatitis (Table 2). The patterns and proportions of patients experiencing AEs are also consistent in the real-world setting.[18,19] Therefore, it is important to discuss with patients on the spectrum of

treatment-related toxicities when selecting choice of treatment. Immune-related toxicities are generally managed with steroids, and patients will be suspended from treatment for at least 4 weeks, which may not be ideal as disease may progress without treatment.[20] Currently there is also a lack of predictors of immune-related toxicities. For AEs due to anti-VEGF agents, they can usually be managed by shorter duration of drug suspension, additional medications (e.g., anti-hypertensives) or dose reduction. Furthermore, some patients may have borderline fitness at presentation, and clinicians may want to start a treatment at a lower dose to see if patients can tolerate. Therefore, in these scenarios, lenvatinib may be considered a more appropriate first-line treatment. In particular, previous studies have shown that starting at a lower dose with dose escalation with MKIs were not associated with poorer survival.[21-23]

In addition of toxicity concern, a minority of patients may not be suitable for immunotherapy due to underlying medical conditions, such as the presence of autoimmune disease or underlying organ transplants due to immune flare or graft rejection.[24,25] For instance, post liver transplant HCC recurrence was reported up to 10-18% of patients and median interval from liver transplant to HCC recurrence is 12-13 months.[26] Based on recurrence pattern, loco-regional therapy can be considered while systemic therapy is usually reserved for patients with extra-hepatic metastasis and those who are refractory to local therapy. A systemic review evaluating usage of ICIs in transplant patients with cancer showed rate of allograft rejection up to 39.8% and eventually leading to end stage organ failure in 71% of patients.[27] Hence, immunotherapy approaches should be avoided in HCC patients who recur following liver transplantation because of the high allograft

Table 2. Common toxicities seen in REFLECT, IMBrave-150, and HIMALAYA trial

Trial	Most common treatment-related adverse event	Most common grade 3 or 4 treatment related adverse event
REFLECT[3]	Hypertension (42%), diarrhea (39%), decreased appetite (34%)	Hypertension (23%), decreased weight (8%), increased blood bilirubin (7%)
IMBrave-150[6]	Hypertension (29.8%), fatigue (20.4%), proteinuria (20.1%)	Hypertension (15.2%), aspartate aminotransferase increase (7.0%), alanine aminotransferase increase (3.6%)
HIMALAYA[8]	Diarrhea/colitis (26.5%), pruritus (22.9%), rash (22.4%)	Lipase increase (6.2%), aspartate aminotransferase increase (5.2%), diarrhea/colitis (4.4%)

rejection rate.

On the contrary, both sorafenib and lenvatinib have been shown to be safe for liver transplants patients in retrospective studies. In a meta-analysis evaluating 411 post liver transplant patients receiving sorafenib among 19 studies, median OS of 12.8 months (95% CI, 10.6-15.1) and 1-year survival rate was 56.8% (95% CI, 42.8-70.9).[28] 47.8% and 43.3% of patients required dose reduction and temporary discontinuation due to AEs during sorafenib treatment respectively while majority of patients could tolerate the treatment after adjustment. The most reported grade 3 or 4 AEs were hand-foot skin reaction, diarrhea and fatigue with incidence rate of 11.3%, 23.9%, and 24.7%, respectively. Similarly, in a retrospective cohort of 45 post liver transplant patients with HCC recurrence who received lenvatinib, median OS of 14.5 months (95% CI, 0.8-28.2) and median PFS of 7.6 months (95% CI, 5.3-9.8) with ORR of 20% were reported.[29] The study demonstrated a comparable safety profile as in the REFLECT trial with hypertension (n=25, 55.6%) being most frequent AEs and 22 patients (48.9%) requiring dose reduction to manage AEs.

In summary, despite superior OS and ORR with immunotherapy combination treatment in cross trial comparison, lenvatinib still maintains its old role to demonstrate its importance as first-line treatment option in advanced HCC, such as in situations when there are concerns of patients' tolerance, or when timely OGD could not be scheduled, or when immunotherapy is contraindicated.

NEW OR EMERGING ROLE

Development of various new treatment options provides opportunity for lenvatinib to be used as subsequent line of treatment and part of combination therapy to improve survival. This part of the review article discusses the potential emerging role of lenvatinib.

1. Second line therapy after Atezo−Bev

With Atezo-Bev approved as first-line treatment in advanced HCC, there is a knowledge gap in choosing second-line treatment after progression due to a lack of high-level evidence to guide the optimal management choice and sequence. Most of the positive second-line trials were conducted in the post-sorafenib setting. Yet, there are still a few small-scale retrospective cohorts evaluating treatment after Atezo-Bev failure.

Yoo et al.[30] conducted a multi-national multi-centre retrospective cohort to evaluate the clinical outcomes with MKIs after progression on Atezo-Bev. In this cohort, a total of 49 patients received subsequent therapy with 29 patients (59.2%) using sorafenib, 19 patients (38.8%) using lenvatinib and one patient (1%) using cabozantinib. All candidates were Child Pugh A and BCLC. The ORR of lenvatinib (15.8%) was higher than that of sorafenib (0%). Disease control rate was similar in both groups (62% vs. 63%). In the overall population, median PFS and OS were 3.4 (95% CI, 1.8-4.9) and 14.7 months (95% CI, 8.1-21.2) respectively. The group that received lenvatinib treatment exhibited a longer median PFS compared to those treated with sorafenib (median PFS, 6.1 [95% CI, 1.6-10.5] vs. 2.5 [95% CI, 1.3-3.8] months; P=0.004). Nevertheless, no marked difference was observed in the median OS between two groups (median OS, 16.6 [95% CI, 3.6-29.6] vs. 11.2 [95% CI, 2.7-19.6] months; P=0.347). In this study, both sorafenib and levantinib showed comparable safety profile compared to their pivotal phase III trial with sorafenib group having more hand-foot syndrome (69% vs. 26.3%) and levantinib group having more hypertension (42.1% vs. 17.2%). Nevertheless, grade 3 treatment-related AEs happened in only eight patients (16.3%) and there were no grade 4 events. In

Table 3. Summary of efficacy of lenvatinib post immunotherapy in retrospective cohorts

Study	Objective response rate	Disease control rate	Median PFS (months)	Median OS (months)
Gile et al.[31]	Not provided	Not provided	4	13
Yoo et al.[30]	3 (15.8)	12 (63.2)	6.1	11.2

Values are presented as number or number (%).
PFS, progression-free survival; OS, overall survival.

another multicentric, retrospective analysis of 53 patients with HCC treated with first-line Atezo-Bev followed by lenvatinib in subsequent lines of treatment, median PFS and OS were 4 and 13 months respectively (Table 3). Safety profile was largely consistent with previously studies with the most common grade 3 or higher AEs being hypertension.[31] Hence, lenvatinib showed promising efficacy and tolerable safety as second line therapy after Atezo-Bev. In fact, the latest NCCN, ASCO, ESMO, EASL and KLCA-NCC Korea guidelines also recommend to consider lenvatinib as second-line therapy after Atezo-Bev (Table 4).[11-15]

2. Sequential or combination therapy with trans−arterial chemo−embolisation (TACE)

TACE is the standard treatment in intermediate-stage (BCLC stage B) HCC. BCLC stage B disease is defined as multifocal HCC (exceeding BCLC-A criteria) with preserved liver function, no cancer-related symptoms (performance status=0) and no vascular invasion or extra-hepatic spread.[32] The magnitude of tumor burden is heterogeneous in this stage in terms of hepatic functional reserve, tumor size, and tumor number. Conventionally, TACE would be performed repeatedly until the failure of the treatment. However, not all patients responded well to TACE and repeated use of TACE may not be beneficial since it may potentially cause deterioration of liver function making patients ineligible for further systemic therapy.[33] The OPTIMIS study has shown that patients who switched to systemic therapy early after TACE refractoriness (defined as failure to control target lesions or the appearance of new lesions even after two or more consecutive TACE sessions) had better prognosis than those who did not.[34] Nevertheless, some patients' liver function already deteriorated to Child-Pugh class B or C at the time of TACE refractoriness and hence not eligible for further systemic therapy. Hence, prompt identification for patent who will not benefit from TACE is required and earlier usage of systemic therapy instead of TACE would be beneficial.

The concept of TACE unsuitability was comprised of three situations including 1) conditions that easily refractory to TACE (i.e., tumor beyond up-to-seven-criteria), 2) conditions in which TACE is associated with deterioration of liver reserve to Child-Pugh B (i.e., tumor beyond up-to-seven-criteria and

albumin-bilirubin grade 2), 3) conditions that unlikely to respond to TACE (i.e., simple nodular type tumor with extra-nodular growth, confluent multi-nodular type tumor, massive type tumor, poorly differentiated HCC, intra-hepatic multifocal metastasis, sarcomatous change caused by TACE).[35] Concept of sequential usage of lenvatinib followed by TACE is proposed in these group of patients with an aim to reduce tumor load while maintaining liver function.

A proof-of-concept study was carried out to evaluate the efficacy of lenvatinib as 'induction' treatment followed by subsequent selective TACE (n=30) vs. upfront TACE (n=60) in patients with HCC beyond up-to-seven criteria.[36] The 'up-to-seven' criteria refers to the sum of the number of lesions and the diameters of these lesions being seven or smaller. This criteria was first developed as an extension to Milan's criteria to predict outcomes after liver transplantation.[37] The outcome favoured the lenvatinib group in terms of PFS (16 vs. 3 months), OS (37.9 vs. 21.3 months), and ORR (73.3% vs. 33.3%) while preserving patient liver function. In the lenvatinib group, 14 out of 30 patients were still receiving lenvatinib due to ongoing response and two patients achieved down-staging and had curative ablation or resection subsequently. Ten out of remaining 16 patients (62.5%) received TACE subsequently with three patients achieving complete response and seven patients achieving partial response. Lenvatinib pre-treatment provided the benefit of inducing tumor shrinkage (de-bulking tumor burden) and preserving liver function first before definitive TACE. Besides, upfront incomplete TACE to high tumor burden HCC would increase tumor hypoxia causing up-regulation of hypoxia-inducible factor including VEGF and hence increase tumor angiogenesis. Through blockade of this receptor, lenvatinib prevent the effect of surge of these pro-angiogenic factors and hence progression after TACE.[38,39] Lenvatinib provides a synergistic effect to TACE by normalizing vasculature to enhance distribution of lipiodol-containing anticancer drugs within the tumor.[40] Therefore, lenvatinib followed by TACE is a promising strategy for intermediate-stage HCC with high tumor burden. In the latest 2022 BCLC guideline, the heterogeneity of intermediate stage (BCLC-B) HCC was addressed and it was further subdivided into three groups with systemic therapy recommended as initial treatment

in high tumor-burden subgroups of diffuse, infiltrative, extensive liver involvement.[32]

Given the biological basis of synergistic effect and preclinical models showing benefit of combining anti-angiogenic agents and TACE in prolonging survival,[41] the efficacy of combining TACE and MKIs (sorafenib and lenvatinib) was further evaluated in un-resectable and advanced HCC. The TACTICS trial showed that combination of sorafenib and TACE improved median PFS (25.2 vs. 13.5 months; HR, 0.59; 95% CI, 0.41-0.87; P=0.006) and survival rate (1-year survival rate, 96.2% vs. 82.7%; 2-year survival rate, 77.2% vs. 64.6%) compared with TACE alone in unresectable HCC.[42] In a retrospective controlled study conducted in China, TACE plus lenvatinib was compared with TACE alone in un-resectable HCC and the former group showed superior OS rate (1-year OS rate, 88.4% vs. 79.8%; 2-year OS rate, 79.2% vs. 49.2%; P=0.047), PFS rate (1-year PFS rate, 78.4% vs. 64.7%; 2-year PFS rate, 45.5% vs. 38.0%; P<0.001), and ORR (68.3% vs. 31.7%; P<0.001).[43] Liver function was preserved and there were no new safety signals in TACE plus lenvatinib group. Subgroup analysis also showed that the benefit was seen in both BCLC stage B and C patients. The TACTICS-L trial is a phase II prospective multicenter single-arm study conducted in Japan which evaluates the safety and efficacy of lenvatinib plus TACE in unresectable HCC. Sixty-two patients with BCLC-A (40.3%) or B (59.7%) unresectable HCC was enrolled between 2019 and 2020. ORR was 88.7% with complete response seen in 66.1% of patients. The estimated median PFS and OS were longer than 2 years. The most common AEs were similar to those previously reported, including hypothyroidism (58.1%), hypertension (53.2%), and decreased appetite (50.0%).[44]

TACE plus lenvatinib has also been explored in more advanced stage HCC. In the multi-centre randomised phase III LAUNCH trial in China, lenvatinib with on demand TACE was compared with lenvatinib in patients with advanced HCC (which included patients with large intra-hepatic tumor burden, portal vein thrombosis and extra-hepatic spread).[45] The median OS and PFS was longer in combination treatment arm (OS, 17.8 vs. 11.5 months; HR, 0.45; P<0.001; PFS, 10.6 vs. 6.4 months; HR, 0.43; P<0.001). Patients in the combination group had a higher ORR according to the modified RECIST (54.1% vs. 25.0%; P<0.001). The survival benefit was consistent through subgroups especially in patients with significant tumor burden including those who had portal vein thrombosis (HR for OS, 0.35; 95% CI, 0.25-0.51), AFP level of ≥400 ng/mL (HR for OS, 0.39; 95% CI, 0.26-0.61), three or more intra-hepatic tumors (HR for OS, 0.43; 95% CI, 0.31-0.60), main tumor size of ≥5 cm (HR for OS, 0.47; 95% CI, 0.33-0.66) and extra-hepatic metastasis (HR for OS, 0.56; 95% CI, 0.38-

Table 4. Summary of position of lenvatinib in current international guidelines

Guideline	Position of lenvatinib
NCCN[11] (2023)	Recommended regimen as first-line systemic therapy in Child-Pugh Class A advanced HCC patients (with Atezo-Bev and durvalumab plus tremelimumab as preferred regimen) Subsequent line systemic therapy if disease progression
ASCO[12] (2020)	First-line treatment for Child-Pugh class A and ECOG PS 0-1 patients with advanced HCC where there are contraindication to Atezo-Bev Second line therapy following first-line treatment with Atezo-Bev
ESMO[13] (2021)	First-line systemic option in advanced HCC (while Atezo-Bev regarded as standard) Second-line systemic option with progression after Atezo-Bev
EASL[14] (2021)	First-line systemic treatment for advanced HCC with contraindication to Atezo-Bev Second-line systemic therapy after progression of Atezo-Bev
KLCA-NCC[15] (2022)	Recommended as first-line systemic therapy for Child-Pugh Class A ECOG PS 0-1 patients with advanced HCC who are unsuitable for Atezo-Bev and durvalumab plus tremelimumab Considered as second-line systemic therapy after failure with Atezo-Bev or durvalumab plus tremelimumab

NCCN, National Comprehensive Cancer Network; ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology; EASL, European Association for the Study of the Liver; KLCA-NCC, Korean Liver Cancer Association-National Cancer Center; HCC, hepatocellular carcinoma; Atezo-Bev, atezolizumab and bevacizumab; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

0.82). With high ORR, the combination therapy may potentially become an effective down-staging treatment. In fact, 26 patients (15.3%) in the lenvatinib-TACE group received curative surgical resection because of down-staging, and two patients (1.2%) achieved pathologic complete responses eventually in the trial. Based on the presented data, combination of TACE with lenvatinib would be another attractive option to patients with intermediate-stage HCC with high tumor burden (i.e., up-to-seven criteria) and advanced stage disease, though more prospective trials (including more diverse geographical background especially Western population) are needed to validate the benefit.

3. Combination of lenvatinib with immunotherapy

Combination therapy of lenvatinib with ICIs has been studied in various tumors and FDA has granted approval for this combination in advanced renal cell carcinoma and advanced endometrial carcinoma that is not micro-satellite instability high or mismatch repair deficient, who have disease progression after systemic therapy.[46,47] Lenvatinib provides synergistic effect to pembrolizumab by inhibiting angiogenesis and immuno-suppressive nature of tumor micro-environment and hence improves pembrolizumab effect of boosting anti-tumor immune response.[48,49] KEYNOTE 524 was a phase Ib multi-center open label study of lenvatinib plus pembrolizumab in patients with unresectable HCC (which consist of BCLC stage B not suitable for TACE [29%] and BCLC stage C patients [71%]). The combination therapy showed promising anti-cancer activity with ORR of 46% by mRECIST, median PFS of 9.3 months and median OS of 22 months with no new or unexpected safety signals.[50] Thereafter, a phase III LEAP-002 trial was conducted to evaluate efficacy of lenvatinib plus pembrolizumab versus lenvatinib alone in advanced HCC.[51] Median OS and PFS for lenvatinib plus pembrolizumab was 21.2 months (95% CI, 19.0-23.6) and 8.2 months (95% CI, 6.3-8.3) compared with 19.0 months (95% CI, 17.2-21.7) and 8.1 months (95% CI, 6.3-8.3) with lenvatinib monotherapy respectively. The combination regimen induced an ORR of 26.1%, compared with 17.5% with lenvatinib alone. Sub-group analyses favored the combination regimen particularly in patients with high-risk features including macro-vascular invasion/extra-hepatic spread (HR, 0.78; 95% CI, 0.63-0.95) and elevated AFP status (HR, 0.67; 95% CI, 0.50-0.90). However, despite the numerical improvement of PFS and OS, the statistical threshold of these co-primary endpoints was not met. One proposed reason for the exceptional performance of lenvatinib monotherapy was the use of second-line treatment. Indeed, around half of the patients in the lenvatinib arm received additional therapy, with around a quarter of them received immunotherapy which is thought to be very effective in HCC. These figures were much higher than that in the REFLECT trial (33% received second-line treatment) when there was only a paucity of effective second-line treatments. Although lenvatinib plus pembrolizumab failed to demonstrate its superiority over lenvatinib monotherapy, this trial represented another key trial showing lenvatinib plus immunotherapy could be an effective strategy in advanced HCC, and lenvatinib monotherapy followed by subsequent immunotherapy might also produce similar survival benefit to ICI combination. Looking forward, LEAP-012 trial (NCT04246177) is actively recruiting to evaluate the efficacy of lenvatinib plus pembrolizumab plus TACE and the result is expected to be released in the coming few years.

CONCLUSION

In conclusion, lenvatinib still plays a significant role in advanced HCC as first-line or subsequent line of treatment in the era of immunotherapy. Combining lenvatinib with local therapy like TACE would potentially be a viable option for selected patients while more studies are needed to evaluate the combination of lenvatinib with other systemic therapies. With the expansion of treatment options in advanced HCC, more research would be required to delineate the best sequence of treatment landscape and hence the optimal role of lenvatinib.

Conflicts of Interest

Data Availability

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

ORCID

Matthew Man Pok Lee https://orcid.org/0009-0004-3155-2454
Landon Long Chan   https://orcid.org/0000-0002-1306-5896
Stephen Lam Chan   https://orcid.org/0000-0001-8998-5480

Author Contribution

Conceptualization: MPL, LLC, SLC
Writing - original draft: MPL
Writing - review & editing: MPL, LLC, SLC

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.

2. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-390.

3. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018;391:1163-1173.

4. Abou-Alfa GK, Meyer T, Cheng AL, El-Khoueiry AB, Rimassa L, Ryoo BY, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. N Engl J Med 2018;379:54-63.

5. Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017;389:56-66.

6. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 2020;382:1894-1905.

7. Zhu AX, Kang YK, Yen CJ, Finn RS, Galle PR, Llovet JM, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019;20:282-296.

8. Abou-Alfa GK, Chan SL, Kudo M, Lau G, Kelley RK, Furuse J, et al. Phase 3 randomized, open-label, multicenter study of tremelimumab (T) and durvalumab (D) as first-line therapy in patients (pts) with unresectable hepatocellular carcinoma (uHCC): HIMALAYA. J Clin Oncol 2022;40 Suppl 4:379.

9. Yau T, Kang YK, Kim TY, El-Khoueiry AB, Santoro A, Sangro B, et al. Efficacy and safety of nivolumab plus ipilimumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib: the CheckMate 040 randomized clinical trial. JAMA Oncol 2020;6:e204564.

10. Qin S, Chan LS, Gu S, Bai Y, Ren Z, Lin X, et al. LBA35 camrelizumab (C) plus rivoceranib (R) vs. sorafenib (S) as first-line therapy for unresectable hepatocellular carcinoma (uHCC): a randomized, phase III trial. Ann Oncol 2022;33 Suppl 7:S1401-S1402.

11. National Comprehensive Cancer Network (NCCN). NCCN guidelines: hepatocellular carcinoma [Internet]. Plymouth Meeting (US): NCCN; [cited 2023 May 1]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/hcc.pdf.

12. Gordan JD, Kennedy EB, Abou-Alfa GK, Beg MS, Brower ST, Gade TP, et al. Systemic therapy for advanced hepatocellular carcinoma: ASCO guideline. J Clin Oncol 2020;38:4317-4345.

13. Vogel A, Martinelli E; ESMO Guidelines Committee. Updated treatment recommendations for hepatocellular carcinoma (HCC) from the ESMO clinical practice guidelines. Ann Oncol 2021;32:801-805.

14. Bruix J, Chan SL, Galle PR, Rimassa L, Sangro B. Systemic treatment of hepatocellular carcinoma: an EASL position paper. J Hepatol 2021;75:960-974.

15. Korean Liver Cancer Association (KLCA); National Cancer Center (NCC) Korea. 2022 KLCA-NCC Korea practice guidelines for the management of hepatocellular carcinoma. Clin Mol Hepatol 2022;28:583-705.

16. Cheng AL, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Updated efficacy and safety data from IMbrave150: atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. J Hepatol 2022;76:862-873.

17. Abou-Alfa GK, Lau G, Kudo M, Chan SL, Kelley RK, Furuse J, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. NEJM Evid 2022;1:1-12.

18. Casadei-Gardini A, Rimini M, Tada T, Suda G, Shimose S, Kudo

M, et al. Atezolizumab plus bevacizumab versus lenvatinib for unresectable hepatocellular carcinoma: a large real-life worldwide population. Eur J Cancer 2023;180:9-20.

19. Fulgenzi CAM, Cheon J, D'Alessio A, Nishida N, Ang C, Marron TU, et al. Reproducible safety and efficacy of atezolizumab plus bevacizumab for HCC in clinical practice: results of the AB-real study. Eur J Cancer 2022;175:204-213.

20. Haanen J, Obeid M, Spain L, Carbonnel F, Wang Y, Robert C, et al. Management of toxicities from immunotherapy: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol 2022;33:1217-1238.

21. Reiss KA, Yu S, Mamtani R, Mehta R, D'Addeo K, Wileyto EP, et al. Starting dose of sorafenib for the treatment of hepatocellular carcinoma: a retrospective, multi-institutional study. J Clin Oncol 2017;35:3575-3581.

22. Alghamdi MA, Amaro CP, Lee-Ying R, Sim HW, Samwi H, Chan KK, et al. Effect of sorafenib starting dose and dose intensity on survival in patients with hepatocellular carcinoma: results from a Canadian Multicenter Database. Cancer Med 2020;9:4918-4928.

23. Chan LL, Mo FKF, Law ALY, Shum TCY, Tai AYP, Lee AS, et al. Impact of dose adjustment on clinical outcome of lenvatinib-treated patients with advanced hepatocellular carcinoma (HCC) [Internet]. Shatin (CN): The Chinese University of Hong Kong Faculty of Medicine; [cited 2023 May 1]. Available from: https://www.postersessiononline.eu/173580348_eu/congresos/ILCA2022/aula/-P_108_ILCA2022.pdf.

24. Tison A, Garaud S, Chiche L, Cornec D, Kostine M. Immune-checkpoint inhibitor use in patients with cancer and pre-existing autoimmune diseases. Nat Rev Rheumatol 2022;18:641-656.

25. Kawashima S, Joachim K, Abdelrahim M, Abudayyeh A, Jhaveri KD, Murakami N. Immune checkpoint inhibitors for solid organ transplant recipients: clinical updates. Korean J Transplant 2022;36:82-98.

26. Roayaie S, Schwartz JD, Sung MW, Emre SH, Miller CM, Gondolesi GE, et al. Recurrence of hepatocellular carcinoma after liver transplant: patterns and prognosis. Liver Transpl 2004;10:534-540.

27. d'Izarny-Gargas T, Durrbach A, Zaidan M. Efficacy and tolerance of immune checkpoint inhibitors in transplant patients with cancer: a systematic review. Am J Transplant 2020;20:2457-2465.

28. Li Z, Gao J, Zheng S, Wang Y, Xiang X, Cheng Q, et al. Therapeutic efficacy of sorafenib in patients with hepatocellular carcinoma recurrence after liver transplantation: a systematic review and meta-analysis. Turk J Gastroenterol 2021;32:30-41.

29. Bang K, Casadei-Gardini A, Yoo C, Iavarone M, Ryu MH, Park SR, et al. Efficacy and safety of lenvatinib in patients with recurrent hepatocellular carcinoma after liver transplantation. Cancer Med 2023;12:2572-2579.

30. Yoo C, Kim JH, Ryu MH, Park SR, Lee D, Kim KM, et al. Clinical outcomes with multikinase inhibitors after progression on first-line atezolizumab plus bevacizumab in patients with advanced hepatocellular carcinoma: a multinational multicenter retrospective study. Liver Cancer 2021;10:107-114.

31. Gile J, Palmer ME, Storandt MH, Bekaii-Saab TS, Tran NH, Mahipal A. Outcome of receiving lenvatinib following immunotherapy in patients with advanced hepatocellular carcinoma. J Clin Oncol 2023;41 Suppl 4:507.

32. Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. J Hepatol 2022;76:681-693.

33. Arizumi T, Minami T, Chishina H, Kono M, Takita M, Yada N, et al. Time to transcatheter arterial chemoembolization refractoriness in patients with hepatocellular carcinoma in Kinki criteria stages B1 and B2. Dig Dis 2017;35:589-597.

34. Peck-Radosavljevic M, Kudo M, Raoul JL, Lee HC, Decaens T, Heo J, et al. Outcomes of patients (pts) with hepatocellular carcinoma (HCC) treated with transarterial chemoembolization (TACE): global OPTIMIS final analysis. J Clin Oncol 2018;36 Suppl 15:4018.

35. Kudo M. A new treatment option for intermediate-stage hepatocellular carcinoma with high tumor burden: initial lenvatinib therapy with subsequent selective TACE. Liver Cancer 2019;8:299-311.

36. Kudo M, Ueshima K, Chan S, Minami T, Chishina H, Aoki T, et al. Lenvatinib as an initial treatment in patients with intermediate-stage hepatocellular carcinoma beyond up-to-seven criteria and Child-Pugh A liver function: a proof-of-concept study. Cancers (Basel) 2019;11:1084.

37. Mazzaferro V, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol 2009;10:35-43.

38. Li X, Feng GS, Zheng CS, Zhuo CK, Liu X. Expression of plasma vascular endothelial growth factor in patients with hepatocellular carcinoma and effect of transcatheter arterial chemoembolization therapy on plasma vascular endothelial growth factor level. World J Gastroenterol 2004;10:2878-2882.

39. Sergio A, Cristofori C, Cardin R, Pivetta G, Ragazzi R, Baldan A, et al. Transcatheter arterial chemoembolization (TACE) in hepatocellular carcinoma (HCC): the role of angiogenesis and invasiveness. Am J Gastroenterol 2008;103:914-921.

40. Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. Science 2005;307:58-62.

41. Jiang H, Meng Q, Tan H, Pan S, Sun B, Xu R, et al. Antiangiogenic therapy enhances the efficacy of transcatheter arterial embolization for hepatocellular carcinomas. Int J Cancer 2007;121:416-424.

42. Kudo M, Ueshima K, Ikeda M, Torimura T, Tanabe N, Aikata H, et al. Randomised, multicentre prospective trial of transarterial chemoembolisation (TACE) plus sorafenib as compared with TACE alone in patients with hepatocellular carcinoma: TACTICS trial. Gut 2020;69:1492-1501.

43. Fu Z, Li X, Zhong J, Chen X, Cao K, Ding N, et al. Lenvatinib in combination with transarterial chemoembolization for treatment of unresectable hepatocellular carcinoma (uHCC): a retrospective controlled study. Hepatol Int 2021;15:663-675.

44. Ueshima K, Ishikawa T, Saeki I, Morimoto N, Aikata H, Tanabe N, et al. Transcatheter arterial chemoembolization therapy in combination strategy with lenvatinib in patients with unresectable hepatocellular carcinoma (TACTICS-L) in Japan: final analysis. J Clin Oncol 2022;40 Suppl 4:417.

45. Peng Z, Fan W, Zhu B, Wang G, Sun J, Xiao C, et al. Lenvatinib combined with transarterial chemoembolization as first-line treatment for advanced hepatocellular carcinoma: a phase III, randomized clinical trial (LAUNCH). J Clin Oncol 2023;41:117-127.

46. Motzer R, Alekseev B, Rha SY, Porta C, Eto M, Powles T, et al. Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. N Engl J Med 2021;384:1289-1300.

47. Makker V, Colombo N, Herráez AC, Santin AD, Colomba E, Miller DS, et al. Lenvatinib plus pembrolizumab for advanced endometrial cancer. N Engl J Med 2022;386:437-448.

48. Kato Y, Tabata K, Kimura T, Yachie-Kinoshita A, Ozawa Y, Yamada K, et al. Lenvatinib plus anti-PD-1 antibody combination treatment activates CD8+ T cells through reduction of tumor-associated macrophage and activation of the interferon pathway. PLoS One 2019;14:e0212513.

49. Kimura T, Kato Y, Ozawa Y, Kodama K, Ito J, Ichikawa K, et al. Immunomodulatory activity of lenvatinib contributes to antitumor activity in the Hepa1-6 hepatocellular carcinoma model. Cancer Sci 2018;109:3993-4002.

50. Finn RS, Ikeda M, Zhu AX, Sung MW, Baron AD, Kudo M, et al. Phase Ib study of lenvatinib plus pembrolizumab in patients with unresectable hepatocellular carcinoma. J Clin Oncol 2020;38:2960-2970.

51. Finn RS, Kudo M, Merle P, Meyer T, Qin S, Ikeda M, et al. LBA34 primary results from the phase III LEAP-002 study: lenvatinib plus pembrolizumab versus lenvatinib as first-line (1L) therapy for advanced hepatocellular carcinoma (aHCC). Ann Oncol 2022;33 Suppl 7:S1401.