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

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INTRODUCTION

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. (2023 August 17 [online ahead of print])

Keywords: Lenvatinib; Immune checkpoint inhibitors; Carcinoma, hepatocellular
based on the non-inferiority REFLECT trial. In the REFLECT 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). 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.

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. 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. 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-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. 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).

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

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

*Non-inferiority criteria met.
ficiency 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.8,9 In particular, patients in IMBrave-150 were required to have pretreatment oesophagogastroduodenoscopy (OGD) to screen for any untreated or incompletely treated oesophageal or gastric varices 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.8 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>
<thead>
<tr>
<th>Trial</th>
<th>Most common treatment-related adverse event</th>
<th>Most common grade 3 or 4 treatment related adverse event</th>
</tr>
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<tbody>
<tr>
<td>REFLECT1</td>
<td>Hypertension (42%), diarrhea (39%), decreased appetite (34%)</td>
<td>Hypertension (23%), decreased weight (8%), increased blood bilirubin (7%)</td>
</tr>
<tr>
<td>IMBrave-150</td>
<td>Hypertension (29.8%), fatigue (20.4%), proteinuria (20.1%)</td>
<td>Hypertension (15.2%), aspartate aminotransferase increase (7.0%), alanine aminotransferase increase (3.6%)</td>
</tr>
<tr>
<td>HIMALAYA3</td>
<td>Diarrhea/colitis (26.5%), pruritus (22.9%), rash (22.4%)</td>
<td>Lipase increase (6.2%), aspartate aminotransferase increase (5.2%), diarrhea/colitis (4.4%)</td>
</tr>
</tbody>
</table>
rejection rate.

On the contrary, both sorafenib and lenvatinib have been shown to be safe for liver transplant 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). On the other hand, both sorafenib and lenvatinib have been shown to be safe for liver transplant 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>
<thead>
<tr>
<th>Study</th>
<th>Objective response rate</th>
<th>Disease control rate</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gile et al. 31</td>
<td>Not provided</td>
<td>Not provided</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>Yoo et al. 30</td>
<td>3 (15.8)</td>
<td>12 (63.2)</td>
<td>6.1</td>
<td>11.2</td>
</tr>
</tbody>
</table>

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.32 In a retrospective controlled study conducted in China, TACE plus lenvatinib was compared with TACE alone in unresectable 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-

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

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Position of lenvatinib</th>
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</table>
| NCCN11 (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 |
| ASCO12 (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 |
| ESMO13 (2021) | First-line systemic option in advanced HCC (while Atezo-Bev regarded as standard)  
Second-line systemic option with progression after Atezo-Bev |
| EASL14 (2021) | First-line systemic treatment for advanced HCC with contraindication to Atezo-Bev  
Second-line systemic therapy after progression of Atezo-Bev |
| KLCA-NCC15 (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 multicenter 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

SCL has served on advisory boards for Astra-Zeneca, MSD, Eisai, BMS, and Roche, and has received research funds from MSD, Bayer, Eisai, Ipsen, SIRTEX. MPL and LLC have no conflicts of interest to disclose.
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Data Availability
Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

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References


