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REVIEW

Lenvatinib for the treatment of unresectable hepatocellular carcinoma: evidence to date

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Abstract: During the last 10 years, the multikinase inhibitor sorafenib has emerged as the only systemic treatment for unresectable hepatocellular carcinoma (HCC). More recently, data from the Phase III REFLECT trial showed that another multikinase inhibitor, namely, lenvatinib, was non-inferior to sorafenib in terms of overall survival (OS). In contrast, with respect to OS, previous randomized Phase III trials have been negative, and several agents tested have failed to prove non-inferiority (or superiority) when compared with sorafenib in a first-line setting. Furthermore, the REFLECT trial demonstrated that lenvatinib, in comparison with sorafenib, significantly increased progression-free survival, time to progression, and objective response rate. Overall, the incidence of grade ≥3 treatment-emergent adverse events (TEAEs) was similar in the two treatment arms of the trial, with a higher incidence of serious TEAEs in the lenvatinib arm. Encouraging efficacy signals had already been reported for immune checkpoint inhibitors in HCC, and different synergisms have been postulated in the frame of interplay between vascular endothelial growth factor receptor-2 inhibitors and immunotherapy. Given these premises, future approaches are being developed in Phase I trials testing lenvatinib in combination with pembrolizumab or nivolumab. As the treatment landscape of HCC is expanding with novel agents being approved for patients who are intolerant or are progressing on prior sorafenib, we will discuss current challenges pertaining to the optimal sequencing of active agents in first- and second-line setting.

Keywords: hepatocellular carcinoma, unresectable, first line, lenvatinib, angiogenesis, immunotherapy

Introduction

Hepatocellular carcinoma (HCC) is the most frequent primary liver cancer with a worldwide incidence of 10.1 cases per 100,000 person-years. The incidence is expected to increase as a consequence of chronic liver disease with its multiple risk factors, including chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, excessive alcohol consumption, nonalcoholic fatty liver disease, hemochromatosis, and aflatoxin B1.[1] Systemic treatment is the only therapeutic option in patients with well-preserved liver function (Child–Pugh class A) at an advanced stage and intermediate stage unsuitable for locoregional treatment. Sorafenib has been the standard of care since 2007, when the SHARP trial demonstrated that sorafenib improved median overall survival (OS) compared to placebo in patients who had not received prior systemic therapy (10.7 vs 7.9 months, HR =0.69, $P<0.001$).[2] The subsequent Asia-Pacific trial confirmed these results in Asian patients.[3] In the last 10 years, several

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Phase III trials assessing new targeted agents as monotherapy (brivanib, sunitinib, linifanib)[4–6] or in combination with sorafenib (erlotinib),[7] chemotherapy in combination with sorafenib (doxorubicin),[8] and radioembolization with SIR-Spheres® Y-90 resin microspheres[9,10] failed to demonstrate a survival benefit or showed a worse safety profile compared to sorafenib in the first-line setting. Eventually, the Phase III non-inferiority REFLECT trial showed that lenvatinib was non-inferior compared to sorafenib.[11] Also, several clinical trials assessed new systemic agents in second line in patients who progressed on or were intolerant to sorafenib, but failed to demonstrate any benefit compared to placebo (brivanib, everolimus, ramucirumab, tivantinib, ADI-PEG 20).[12–17] Only in 2017, the Phase III randomized RESORCE trial showed positive results for regorafenib in patients with disease progression on sorafenib, with a median OS of 10.6 vs 7.8 months (HR =0.63, $P<0.0001$).[18] In 2018, the Phase III randomized CELESTIAL trial met its primary endpoint and showed that cabozantinib improved OS vs placebo in patients previously treated with sorafenib. Patients might have received up to two lines of previous treatment and had to have disease progression on at least one of them. Median OS was 10.2 vs 8.0 months (HR =0.76, $P=0.005$). In patients who had received sorafenib as the only prior therapy, median OS was 11.3 vs 7.2 months (HR =0.70).[19] Finally, the randomized Phase III REACH-2 trial evaluated ramucirumab vs placebo as a second-line treatment in patients with baseline elevated AFP levels (≥400 ng/mL).[20] The REACH-2 population was selected based on the results of the previous REACH trial which showed positive results in this subgroup of patients.[14] The REACH-2 trial met its primary endpoint: treatment with ramucirumab significantly improved OS (median 8.5 vs 7.3 months, HR =0.71; $P=0.0199$) compared to placebo with a manageable safety profile.[20] The use of immune checkpoint inhibitors seems to be a promising approach both in first and second line. The Phase I/II CheckMate 040 trial showed durable responses, long-term survival, and a favorable safety profile of nivolumab (anti-programmed death-1 [anti-PD-1]) in first- and second-line patients with well-preserved liver function, with or without chronic viral hepatitis. Overall, there were no treatment-related deaths, and grade 3/4 AST and ALT increase occurred in 4% and 2% of patients, respectively. The most common adverse events (AEs) of any grade were fatigue (23%), pruritus (21%), and rash (15%). Expression of programmed death-ligand 1 (PD-L1) on tumor cells was not found to be predictive of benefit of nivolumab. In 80 first-line patients, an impressive median OS of 28.6 months was reported, the objective response rate (ORR) was 23%, disease control rate (DCR) was 63%, and 40% of patients had stable disease lasting ≥6 months.[21,22] These results compare favorably with all previously reported Phase III data in HCC. Similarly, the KEYNOTE-224 Phase II trial of pembrolizumab as second-line treatment reported an ORR of 16.3%, median progression-free survival (PFS) of 4.9 months, and median OS of 12.9 months, in line with the results of nivolumab.[23] On this basis, the United States Food and Drug Administration (FDA) granted accelerated approval for the use of nivolumab and pembrolizumab in patients previously treated with sorafenib.

Lenvatinib for first-line treatment of HCC

Lenvatinib is an oral multikinase inhibitor that inhibits vascular endothelial growth factor (VEGF) receptors (VEGFR 1–3), fibroblast growth factor (FGF) receptors (FGFR1–4), platelet-derived growth factor (PDGF) receptor α, KIT, and RET. The dual inhibition of VEGF and FGF pathways in endothelial and tumor cells results in the concomitant suppression of the activity of factors involved both in angiogenesis and tumor growth.[24] A Phase I trial of lenvatinib in 20 patients with advanced HCC and Child–Pugh A and B liver cirrhosis defined the maximum tolerable dose of 12 mg for patients with Child–Pugh A score and 8 mg for patients with Child–Pugh B score administered continuously once daily in 28-day cycles, and showed preliminary efficacy with a manageable toxicity profile. The recommended dose for Phase II trials for patients with Child–Pugh A score was established at 12 mg once daily.[25] A multicentre, single-arm, Phase II study enrolled 46 Asian patients with advanced HCC unsuitable for locoregional therapies.[26] Patients received lenvatinib at the dose of 12 mg once daily in 28-day cycles. The primary endpoint was time to progression (TTP) according to modified Response Evaluation Criteria in Solid Tumors (mRECIST);[27] the secondary endpoints were ORR, DCR, and OS. Median TTP was 7.4 months (95% CI =5.5–9.4). ORR was 37% (partial response in 17 patients) and stable disease was 41% (19 patients) with a DCR of 78% and the median OS was 18.7 months (95% CI =12.7–25.1). Median duration of treatment was 7.3 months. All patients reported at least one AE, graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0. Most common AEs included hypertension (76%), palmar-plantar erythrodysesthesia (65%), decreased appetite (61%), and proteinuria (61%). Ten patients (22%) discontinued treatment and 34 patients (74%) required dose reduction due to AEs. The most frequent AE

leading to treatment discontinuation was proteinuria (11%). An exploratory analysis showed that median body weight was lower in patients with early dose interruption or reduction.[26] A population pharmacokinetic (PK) analysis, including patients with HCC and Child–Pugh class A, defined the optimal dose according to body weight as 12 mg once daily for patients ≥60 kg and 8 mg once daily for patients <60 kg for patients with HCC.[28] Based on the Phase II results, lenvatinib has been compared to sorafenib as the first-line treatment for unresectable HCC in the multicenter, randomized (1:1 ratio), open-label, non-inferiority REFLECT Phase III trial.[29] The REFLECT trial enrolled HCC patients untreated with systemic therapy, with Barcelona Clinic Liver Cancer stage B or C, preserved liver function (Child–Pugh class A), and good performance status (PS) (Eastern Cooperative Oncology Group [ECOG] 0 or 1). Patients had to have histologically/cytologically or clinically confirmed diagnosis of HCC and at least one measurable lesion according to mRECIST. Of note, patients with ≥50% liver involvement, clear invasion of the bile duct, or main portal vein invasion were excluded from the trial. Randomization was stratified by region (Asia-Pacific or Western), macroscopic portal vein invasion and/or extrahepatic spread (yes or no), ECOG PS (0 or 1), and body weight (<60 or ≥60 kg). The primary endpoint was OS, and the secondary endpoints were PFS, TTP, ORR, quality of life (QOL) measured according to the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) and the HCC-specific EORTC QLQ-HCC18 questionnaires, and PK lenvatinib exposure parameters. Efficacy was evaluated in the intent-to-treat (ITT) population. Tumor assessment was performed by local investigators using mRECIST. A post hoc exploratory tumor assessment according to mRECIST and RECIST version 1.1[30] was performed by a masked independent review committee. Treatment-emergent AEs (TEAEs) were graded using NCI-CTCAE version 4.0. Patients received lenvatinib orally at the dose of 12 mg (body weight ≥60 kg) or 8 mg (body weight <60 kg) once daily or sorafenib orally at the dose of 400 mg twice daily, continuously in 28-day cycles. Dose interruption/reduction for lenvatinib-related AEs (to 8 and 4 mg daily, or 4 mg every other day) was allowed. Sorafenib dose modifications were applied according to prescribing information in each country. Between March 2013 and July 2015, 954 patients were randomized to receive lenvatinib (n=478) or sorafenib (n=476). Baseline patient characteristics were well balanced between the two treatment groups, except for HCV etiology (higher in the sorafenib group) and AFP baseline levels (lower in the sorafenib group). Median treatment duration was 5.7 months with lenvatinib and 3.7 months with sorafenib. After a median follow-up of 27.7 months in the lenvatinib arm and 27.2 months in the sorafenib arm, median OS was 13.6 months on lenvatinib vs 12.3 months on sorafenib, with an HR of 0.92 (95%CI =0.79–1.06), showing non-inferiority of lenvatinib compared to sorafenib. Also, lenvatinib showed statistically significant superiority compared to sorafenib in terms of PFS, TTP, and ORR, as determined by the local investigator tumor assessments per mRECIST (Table 1). All the efficacy results were consistent across all predefined subgroups. PFS, TTP, and ORR results based on local assessment per mRECIST were confirmed by masked independent imaging review, which also showed similar PFS, TTP, and ORR results according to mRECIST and RECIST 1.1 (Table 1). One hundred and fifty-six patients (33%) in the lenvatinib arm and 184 (39%) in the sorafenib arm received post-study drugs, including sorafenib in 121 patients (25%) in the lenvatinib arm and 56 patients (12%) in the sorafenib arm. In Western countries, 44 patients (28%) in the lenvatinib arm received any post-study treatment compared to 71 patients (45%) in the sorafenib arm, 41 patients (26%) in the lenvatinib arm received post-study drugs compared to 61 patients (39%) in the sorafenib arm, and 11 patients (7%) in the lenvatinib arm had post-study procedures compared to 18 patients (11%) in the sorafenib arm. In the Asia-Pacific region, the percentages of patients who received post-study treatments were well balanced between the two treatment groups.

Of the 954 randomized patients, 951 patients started treatment (476 in the lenvatinib group and 475 in the sorafenib group) and were included in the safety analysis. Most patients in both arms had at least one TEAE, and the incidence of grade ≥3 TEAEs was similar in the two treatment arms (Table 2). Most commonly reported TEAEs were hypertension, diarrhea, decreased appetite, and decreased weight on lenvatinib, and palmar-plantar erythrodysesthesia, diarrhea, hypertension, and decreased appetite on sorafenib (Table 2). Serious TEAE (SAE) rates were higher in the lenvatinib arm (43% vs 30%), death rates were similar in the two study arms (2% vs 1%), and SAEs were deemed treatment related in 18% of patients on lenvatinib and 10% of patients on sorafenib. One hundred and ninety patients (40%) in the lenvatinib arm and 153 (32%) in the sorafenib arm required drug interruption, 176 patients (37%) in the lenvatinib arm and 181 (38%) in the sorafenib arm required dose reduction, and 42 patients (9%) in the lenvatinib arm and 34 (7%) in the sorafenib arm discontinued treatment, due to treatment-related AEs. Baseline QOL scores were similar in the two

Table 1 Efficacy results of the REFLECT Phase III trial

Outcome based on investigator assessment per mRECIST	**Lenvatinib (n=478)**	**Sorafenib (n=476)**	**HR (95% CI)**	***P*-value**
Overall response rate	115 (24%)	44 (9.2%)	OR 3.13 (2.15–4.56)	<0.0001
Response				
Complete	6 (1%)	2 (<1%)	–	–
Partial	109 (23%)	42 (9%)	–	–
Stable disease	246 (51%)	244 (51%)	–	–
Disease control rate	361 (75.5%)	288 (60.5%)	–	–
Overall survival (months)				
Median	13.6	12.3	0.92 (0.79–1.06)	–
95% CI	12.1–14.9	10.4–13.9		
Progression-free survival (months)				
Median	7.4	3.7	0.66 (0.57–0.77)	<0.0001
95% CI	6.9–8.8	3.6–4.6		
Time to progression (months)				
Median	8.9	3.7	0.63 (0.53–0.73)	<0.0001
95% CI	(7.4–9.2)	(3.6–5.4)		
Outcome based on independent imaging review per mRECIST	**Lenvatinib (n=478)**	**Sorafenib (n=476)**	**HR (95% CI)**	***P*-value**
Overall response rate	194 (40.6%)	59 (12.4%)	OR 5.01 (3.59–7.01)	<0.0001
Response				
Complete	10 (2%)	4 (1%)	–	–
Partial	184 (38%)	55 (12%)	–	–
Stable disease	159 (33%)	219 (46%)	–	–
Disease control rate	353 (73.8%)	278 (58.4%)	–	–
Progression-free survival (months)				
Median	7.3	3.6	0.64 (0.55–0.75)	<0.0001
95% CI	5.6–7.5	3.6–3.7		
Time to progression (months)				
Median	7.4	3.7	0.60 (0.51–0.71)	<0.0001
95% CI	(7.2–9.1)	(3.6–3.9)		
Outcome based on independent imaging review per RECIST 1.1	**Lenvatinib (n=478)**	**Sorafenib (n=476)**	**HR (95% CI)**	***P*-value**
Overall response rate	90 (18.8%)	31 (6.5%)	OR 3.34 (2.17–5.14)	<0.0001
Response				
Complete	2 (<1%)	1 (<1%)	–	–
Partial	88 (18%)	30 (6%)	–	–
Stable disease	258 (54%)	250 (53%)	–	–
Disease control rate	348 (72.8%)	281 (59%)	–	–
Progression-free survival (months)				
Median	7.3	3.6	0.65 (0.56–0.77)	<0.0001
95% CI	5.6–7.5	3.6–3.9		
Time to progression (months)				
Median	7.4	3.7	0.61 (0.51–0.72)	<0.0001
95% CI	(7.3–9.1)	(3.6–5.4)		

Abbreviations: mRECIST, modified Response Evaluation Criteria in Solid Tumors; RECIST, Response Evaluation Criteria in Solid Tumors.

treatment groups and declined during treatment in both groups. Patients treated with lenvatinib observed delays in clinically meaningful worsening of role functioning (nominal $P=0.0193$), pain (nominal $P=0.0105$), and diarrhea (nominal $P<0.0001$) from EORTC QLQ-C30, and nutrition (nominal $P=0.0113$) and body image (nominal $P=0.0051$) from EORTC QLQ-HCC18, compared to patients treated with sorafenib. The summary score for between-group comparison was not significantly different between the two treatment arms (HR =0.87; 95%CI =0.754–1.013). PK analysis confirmed the weight-based dosing with no difference according to ethnicity. Preplanned, exploratory, optional biomarker analyses on archival tumor tissues and serum samples collected at baseline and at specified time points were performed to identify potential biomarkers correlating with clinical outcomes.[31,32] Of note, in the biomarker analysis set, more patients were

Table 2 Most frequent (≥15% of patients) TEAEs in the REFLECT Phase III trial – safety population

Adverse event, n (%)	Lenvatinib (n=476)		Sorafenib (n=475)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any TEAE	470 (99)	357 (75)	472 (99)	316 (67)
Any treatment-related TEAE	447 (94)	270 (57)	452 (95)	231 (49)
Hypertension	201 (42)	111 (23)	144 (30)	68 (14)
Diarrhea	184 (39)	20 (4)	220 (46)	20 (4)
Decreased appetite	162 (34)	22 (5)	127 (27)	6 (1)
Decreased weight	147 (31)	36 (8)	106 (22)	14 (3)
Fatigue	141 (30)	18 (4)	119 (25)	17 (4)
PPE	128 (27)	14 (3)	249 (52)	54 (11)
Proteinuria	117 (25)	27 (6)	54 (11)	8 (2)
Dysphonia	113 (24)	1 (<1)	57 (12)	0
Nausea	93 (20)	4 (1)	68 (14)	4 (1)
Decreased platelet	87 (18)	26 (5)	58 (12)	16 (3)
Abdominal pain	81 (17)	8 (2)	87 (18)	13 (3)
Vomiting	77 (16)	6 (1)	36 (8)	5 (1)
Constipation	76 (16)	3 (1)	52 (11)	0
Hypothyroidism	78 (16)	0	8 (2)	0
Increased bilirubin	71 (15)	31 (7)	63 (13)	23 (5)
Increased AST	65 (14)	24 (5)	80 (17)	38 (8)
Rash	46 (10)	0	76 (16)	2 (<1)
Alopecia	14 (3)	0	119 (25)	0

Abbreviations: AST, aspartate aminotransferase; PPE, palmar-plantar erythrodysesthesia; TEAE, treatment-emergent adverse event.

from Western countries, lesser patients had HBV etiology, and more patients had lower baseline AFP levels compared to the ITT population, due to easier availability of tumor tissue and blood samples in Western countries. Serum samples were assessed for 395 patients (267 in the lenvatinib arm and 128 in the sorafenib arm) for VEGF, angiopoietin-2 (ANG-2), FGF19, FGF21, and FGF23.[32] FGF21 was evaluated only at baseline since its levels did not consistently change over time based on preliminary results from a smaller subset of patients.[31] An association between higher VEGF, ANG-2, and FGF21 baseline levels and shorter OS was observed in both arms, suggesting a prognostic role of these biomarkers. Patients with higher baseline FGF21 levels had a longer OS in the lenvatinib arm compared to those in the sorafenib arm (median OS 10.9 vs 6.8 months; $P_{interaction}$ =0.04), suggesting that FGF21 may be predictive of outcome with lenvatinib. Patients with higher baseline ANG-2 levels had a longer OS in the lenvatinib arm compared to patients in the sorafenib arm (median OS 9.4 vs 7.7 months; $P_{interaction}$ =0.075). Increased VEGF levels during treatment were observed with both drugs, with a greater change observed with lenvatinib. Increased FGF19 and FGF23 levels and decreased ANG-2 levels were observed with lenvatinib. Also, in the lenvatinib arm, an association between objective response and greater increases in FGF19 and FGF23 levels from baseline was detected, supporting lenvatinib's inhibition of FGFR4 and FGFR1.[32] Only 58 archival tissue samples (from 34 patients in the lenvatinib arm and 24 patients in the sorafenib arm) passed quality assurance and were tested. Gene expression analysis showed that a small subgroup of patients (n=21) with higher VEGF- and FGF-family gene expression levels had a longer OS in the lenvatinib arm.[31] Of note, due to the small number of patients and the differences in baseline characteristics, these results can be considered only hypothesis generating and warrant further investigation. A cost-effectiveness analysis, conducted in Japan and adjusted for baseline AFP levels, showed an increase of 0.27 life year (LY), an improvement of 0.23 quality-adjusted LY, and a negative incremental cost for lenvatinib compared with sorafenib, therefore suggesting that lenvatinib is a new first-line therapeutic option with potential lower cost compared to sorafenib.[33]

Based on the results of the Phase III REFLECT study, lenvatinib has been approved in Japan, by the FDA, and the European Medicines Agency (EMA) for the treatment of patients with advanced or unresectable HCC who have received no prior systemic therapy.

Ongoing studies with lenvatinib

The hypoxic tumor microenvironment, which results from an abnormal blood supply, helps cancer cells escape the

immune surveillance and impairs the function of resident and transiting immune effector cells. Hypoxia upregulates the expression of the immune checkpoint protein PD-L1, which is downstream the hypoxia inducible factor 1α activation, in cancer cells, myeloid-derived suppressor cells, and dendritic cells.[34] In HCC, hypoxia may also result from antiangiogenic treatments such as sorafenib, which was previously shown to induce an increase of PD-L1 expression in HCA-1 tumors after 28 days of treatment. Similar findings were reported in resected human tumors, where PD-L1 is preferentially expressed in hypoxic areas triggering immune evasion.[35]

In addition, mounting evidences suggest that excessive VEGF production (which is principally driven by hypoxia) can exert immunosuppressive effects in tumors by inhibiting maturation of dendritic cells and priming subsets of immunosuppressive inflammatory cells.[36,37] On the other hand, further investigations on anti-VEGF strategies suggest antitumor responses related to an improvement of tumor-specific T-cell activity. When tested in mice, DC101, which is an antiangiogenic monoclonal antibody specific for VEGFR-2, increased tumor-specific CD8+ T cells, favoring tumor regression.[38] Also, Terme et al demonstrated that targeting the VEGF/VEGFR axis with sunitinib or bevacizumab selectively reduces proliferation of regulatory T cells in mouse models of colorectal cancer and restores their physiologic densities in the face of a tolerogenic tumoral environment.[39]

While novel immune checkpoints inhibitors are making their way in HCC, we may hypothesize that concomitant targeting VEGF and its cognate receptors would synergistically improve the outcome of current immunotherapies by alleviating tumor hypoxia. Several preclinical observations support these hypotheses. Yasuda et al, indeed, tested a combination therapy of DC101 and an anti-PD-1 antibody in a mouse model of colorectal cancer. Although there were no statistically significant differences, when they compared the anti-PD-1 antibody, alone or in combination with DC101, to control, or to DC101 alone, they found that only the anti-PD-1 antibody was able to increase CD4+ and CD8+ T-cell infiltrates in tumors.[40] Consistently, in HCC models treated with sorafenib, blockade of the C–X–C receptor type 4 four pathway (which is induced by hypoxia) may decrease sorafenib-related immunosuppression; however, only the addition of an anti-PD-1 antibody is able to stimulate T lymphocytes' infiltration.[35]

Since the VEGF/VEGFR axis blockade may behave as a double-edged sword that may both reduce and increase immunosuppression, one can envision rational combinations of immune checkpoint inhibitors and antiangiogenics within optimal treatment schedules.

This hypothesis is being tested in the frame of ongoing first-line clinical trials. Pishvaian et al recently updated the results of the GO30140 multiarm Phase Ib study of the anti-PD-L1 antibody atezolizumab combined with bevacizumab (NCT02715531).[41] Responses were assessed per RECIST v1.1 and among 73 evaluable patients, the ORR was 32% by investigator assessment: 18 responses are ongoing for ≥6 months, including 6 that have continued for ≥1 year. Median PFS was 14.9 months, while median duration of response and OS had not been reached by the time of the results presentation. Following earlier data[42] provided as per FDA request, the "breakthrough therapy" designation has been granted.[43] All antiangiogenic agents proven effective in HCC, including lenvatinib, sorafenib, regorafenib, cabozantinib, and ramucirumab, target, to some extent, VEGFR-2 signaling, along with other receptors involved in angiogenesis processes.

Given these premises, lenvatinib (and potentially all other aforementioned VEGFR-2 inhibitors) may synergistically be combined with immune checkpoint inhibitors. Preliminary data of a Phase Ib study testing pembrolizumab plus lenvatinib for first-line treatment of unresectable HCC indicated an acceptable safety profile, with an ORR of 42.3% and a median PFS of 9.69 months (95%CI =5.55–not evaluable). However, there were three deaths on study, including two (acute respiratory distress syndrome and intestinal perforation) that were deemed to be treatment related. An additional five patients had SAEs. Sixty percent of patients had a dose interruption or reduction of lenvatinib and/or pembrolizumab due to TEAEs. Decreased appetite and hypertension (53.3% each) were the most common any-grade TEAEs, followed by diarrhea (43.3%) and fatigue (40%). Consistent with known safety profiles of lenvatinib and pembrolizumab, the most common grade ≥3 AE was hypertension (16.7%), along with AST increase (16.7%), decreased white blood cell count (13.3%), and hyponatremia (10.0%).[44] In January 2018, the same combination of pembrolizumab and lenvatinib was granted by the FDA a "breakthrough therapy" designation for treatment of patients with advanced and/or metastatic renal cell carcinoma.[45] Additionally, a Phase Ib trial of lenvatinib plus nivolumab in subjects with HCC is currently recruiting at Japanese sites (NCT03418922).

Lenvatinib as the first-line treatment: challenges in current clinical practice

Prior to recent marketing authorizations of lenvatinib by the FDA and the EMA, only two tyrosine kinase inhibitors had the approval for treatment of HCC, namely, sorafenib in the first-line setting and regorafenib in the second-line setting.

On top of that, the immune checkpoint inhibitors nivolumab and pembrolizumab were conditionally approved by the FDA for second-line treatment of sorafenib-experienced HCC patients and, more recently, cabozantinib has been approved by the EMA in a similar setting.

To better understand the positive results of the REFLECT study, it would be helpful to briefly clarify the statistical basis of the non-inferiority design. Following recommendations for non-inferiority trial design, the upper boundary of the HR for survival was set at 1.08. Phase III trials comparing new treatments to sorafenib may have three potential results: the new treatment is superior to sorafenib if the HR boundaries do not cross the unity (all the superiority studies have been negative so far); the new treatment is non-inferior compared to sorafenib if the HR boundaries are between 1 and 1.08 (as for lenvatinib); the new treatment is inferior to sorafenib if the HR boundaries cross the 1.08 upper limit for non-inferiority (as for brivanib and linifanib). Importantly, if a trial has been designed for superiority and this has not been demonstrated (as for radioembolization trials), a new trial with non-inferiority design is needed to claim non-inferiority.[46]

Since the publication of the REFLECT trial, it is not yet clear which compound should be selected between sorafenib and lenvatinib in a first-line setting. In the near future, it is expected that real-life data on their true tolerability will partly inform the clinicians' therapeutic decisions. For the time being, further considerations pertain to the lack of data on lenvatinib in patients with ≥50% liver involvement, clear invasion of the bile duct, or main portal vein invasion, and to the optimal sequencing of active agents for advanced HCC in molecularly unselected "all-comer" cohorts of patients who may benefit from second-line regorafenib,[18] cabozantinib,[19]or ramucirumab.[20]

Importantly, these novel treatment options have been proven effective only in sorafenib-experienced patients, and these data cannot be extrapolated to infer the efficacy of a compound when it is given after lenvatinib. As such, post-study survivals observed in the REFLECT trial do not allow to conclude on the efficacy of potential second-line treatments given after lenvatinib. This is not a trivial point. Although the spectrum of kinase inhibition generated by lenvatinib and sorafenib is partially overlapping, substantial differences exist when these two compounds are compared. Indeed, lenvatinib retains a more potent VEGFR-inhibiting activity than sorafenib and it targets other receptors such as FGFR1–4, KIT, and RET, which are not included among sorafenib targets.[47] It is unknown to which extent these differences may affect the clinical efficacy of the two drugs and the molecular make-up of HCC[15] and its microenvironment;[35] nevertheless, they clearly are determinants of specific AEs related to their respective safety profiles.

For such reasons, it cannot be assumed that the benefit observed with second-line therapies in patients who are sorafenib experienced will also apply to lenvatinib-experienced ones. On clinical grounds, additional insights on the optimal drug sequencing after first-line lenvatinib are expected to derive from a pragmatic Phase II study (NCT03433703) currently ongoing in the USA. Patients enrolled receive first-line lenvatinib until disease progression, unacceptable toxicity, withdrawal of consent, or study termination. Available second-line treatments will be delivered in the subsequent post-lenvatinib period. Of note, patients with ≥50% liver involvement, clear invasion of the bile duct, or main portal vein invasion are excluded from this study. Given that OS mirrors the benefit provided by first-line treatment and subsequent lines of treatment, rather than considering one single drug at a time, one could evaluate such benefit in terms of strategies that encompass both first and second lines. An example is provided by the sequence sorafenib–regorafenib,[48] which, nonetheless, is applicable only to sorafenib-tolerant patients who responded to sorafenib, during a certain amount of time.

HCC is a global disease, which more than others mirrors different regional etiologies, ethnicities,[49] and treatment approaches.[50] As a result, on a worldwide scale, a certain treatment may paradoxically yield discrepant outcomes, as previously shown, for instance, by the SHARP[2] and the Asia-Pacific[3] trials of sorafenib. In the REFLECT trial, 33% of patients were from Western countries, while the remaining 67% came from the Asia-Pacific region. Such diverse geographical origins may underlie remarkable differences in terms of access to post-study anticancer therapies, particularly after lenvatinib among Western and Asia-Pacific subgroups. In fact, compared to their Western counterparts, patients belonging to the latter subgroup more frequently received further treatments, clearly reflecting different patterns of care. It is still unclear whether these attitudes affect OS; however, analyses of post-study therapies should provide sound explanations on survival in Western patients receiving sorafenib, which is numerically longer than the survival with lenvatinib in the same geographical area. For both arms of the REFLECT trial, detailed information on subsequent medications or procedures is obviously needed to clarify these issues, which are at present speculative in nature.

Despite substantial improvements in OS due to the availability of more effective second-line treatments, it

has been estimated that only 40%–50% of the patients who receive frontline therapy receive a second line.[29] In other words, for roughly half of Child–Pugh A patients, sorafenib or lenvatinib represents the only foreseeable treatment option in the management of the disease, indicating that efficacy should be maximized since the earliest treatment stages. It will be, therefore, of great interest to learn about the results of three ongoing trials challenging first-line sorafenib. These include: CheckMate-459 – nivolumab vs sorafenib (NCT02576509); HIMALAYA – durvalumab with or without tremelimumab (a CTLA-4 inhibitor) vs sorafenib (NCT03298451); and IMbrave 150 – atezolizumab plus bevacizumab vs sorafenib (NCT03434379). Upcoming results from these trials are expected to re-inform novel treatment strategies, should immunotherapy be confirmed as a mainstay in HCC.

Conclusion

Lenvatinib is a new treatment option for the first-line treatment of HCC; however, an optimal treatment strategy that includes lenvatinib has still to be defined. Major efforts are ongoing in order to provide molecular biomarkers that can assist treating physician's choices, though the present results are far from being conclusive.[31,32] With the eagerly awaited pending results of ongoing first-line Phase III trials comparing sorafenib and checkpoint inhibitors, novel combinations of lenvatinib and immunotherapy may herald a promising step forward in the HCC landscape.

Disclosure

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References

1. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. *Lancet*. 2018;391(10127):1301–1314.
2. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008;359(4):378–390.
3. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a Phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol*. 2009;10(1):25–34.
4. Johnson PJ, Qin S, Park JW, et al. Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized Phase III BRISK-FL study. *J Clin Oncol*. 2013;31(28):3517–3524.
5. Cheng AL, Kang YK, Lin DY, et al. Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized Phase III trial. *J Clin Oncol*. 2013;31(32):4067–4075.
6. Cainap C, Qin S, Huang WT, et al. Linifanib versus sorafenib in patients with advanced hepatocellular carcinoma: results of a randomized Phase III trial. *J Clin Oncol*. 2015;33(2):172–179.
7. Zhu AX, Rosmorduc O, Evans TR, et al. Search: a Phase III, randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with advanced hepatocellular carcinoma. *J Clin Oncol*. 2015;33(6):559–566.
8. Abou-Alfa GK, Niedzwieski D, Knox JJ et al. Phase III randomized study of sorafenib plus doxorubicin versus sorafenib in patients with advanced hepatocellular carcinoma (HCC): CALGB 80802 (Alliance). *J Clin Oncol*. 2016;34(4_Suppl).192–192
9. Vilgrain V, Pereira H, Assenat E, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled Phase 3 trial. *Lancet Oncol*. 2017;18(12):1624–1636.
10. Chow PKH, Gandhi M, Tan SB, et al. SIRveNIB: selective internal radiation therapy versus sorafenib in Asia-Pacific patients with hepatocellular carcinoma. *J Clin Oncol*. 2018;36(19):1913–1921.
11. Kudo M, Finn RS, Qin S, 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(10126):1163–1173.
12. Llovet JM, Decaens T, Raoul JL, et al. Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: results from the randomized Phase III BRISK-PS study. *J Clin Oncol*. 2013;31(28):3509–3516.
13. Zhu AX, Kudo M, Assenat E, et al. Effect of everolimus on survival in advanced hepatocellular carcinoma after failure of sorafenib: the EVOLVE-1 randomized clinical trial. *JAMA*. 2014;312(1):57–67.
14. Zhu AX, Park JO, Ryoo BY, et al. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (reach): a randomised, double-blind, multicentre, Phase 3 trial. *Lancet Oncol*. 2015;16(7):859–870.
15. Rimassa L, Assenat E, Peck-Radosavljevic M, et al. Tivantinib for second-line treatment of MET-high, advanced hepatocellular carcinoma (METIV-HCC): a final analysis of a Phase 3, randomised, placebo-controlled study. *Lancet Oncol*. 2018;19(5):682–693.
16. Kobayashi S, Ueshima K, Moriguchi M, et al. 619OJET-HCC: a Phase 3 randomized, double-blind, placebo-controlled study of tivantinib as a second-line therapy in patients with c-Met high hepatocellular carcinoma. *Ann Oncol*. 2017;28(suppl_5):v209–v268.
17. Abou-Alfa GK, Qin S, Ryoo BY, et al. Phase III randomized study of second line ADI-PEG 20 plus best supportive care versus placebo plus best supportive care in patients with advanced hepatocellular carcinoma. *Ann Oncol*. 2018;29(6):1402–1408.
18. Bruix J, Qin S, Merle P, 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(10064):56–66.
19. Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. *N Engl J Med*. 2018;379(1):54–63.
20. Zhu AX, Kang YK, Yen CJ, 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 Jan 18. [Epub ahead of print].
21. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, Phase 1/2 dose escalation and expansion trial. *Lancet*. 2017;389(10088):2492–2502.

22. Crocenzi TS, El-Khoueiry AB, Yau TC, et al. Nivolumab (nivo) in sorafenib (sor)-naive and -experienced pts with advanced hepatocellular carcinoma (HCC): CheckMate 040 study. *J Clin Oncol*. 2017;35(15_suppl):4013.
23. Zhu AX, Finn RS, Edeline J, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label Phase 2 trial. *Lancet Oncol*. 2018;19(7):940–952.
24. Kudo M. Lenvatinib may drastically change the treatment landscape of hepatocellular carcinoma. *Liver Cancer*. 2018;7(1):1–19.
25. Ikeda M, Okusaka T, Mitsunaga S, et al. Safety and pharmacokinetics of lenvatinib in patients with advanced hepatocellular carcinoma. *Clin Cancer Res*. 2016;22(6):1385–1394.
26. Ikeda K, Kudo M, Kawazoe S, et al. Phase 2 study of lenvatinib in patients with advanced hepatocellular carcinoma. *J Gastroenterol*. 2017;52(4):512–519.
27. Lencioni R, Llovet J. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis*. 2010;30(1):52–60.
28. Tamai T, Hayato S, Hojo S, et al. Dose finding of lenvatinib in subjects with advanced hepatocellular carcinoma based on population pharmacokinetic and exposure–response analyses. *J Clin Pharmacol*. 2017;57(9):1138–1147.
29. Kudo M, Finn RS, Qin S, 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(10126):1163–1173.
30. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228–247.
31. Finn RS, Kudo M, Cheng A-L, et al. LBA30Analysis of serum biomarkers (BM) in patients (PTS) from a Phase 3 study of lenvatinib (LEN) vs sorafenib (SOR) as first-line treatment for unresectable hepatocellular carcinoma (uHCC). *Ann Oncol*. 2017;28(suppl_5).
32. Finn RS, Kudo, M, Cheng A-L, et al. Final analysis of serum biomarkers in patients from the Phase 3 study of lenvatinib in unresectable hepatocellular carcinoma (REFLECT). *Ann Oncol*. 2018;29(Suppl; abstr: 59PD).
33. Kudo M, Izumi N, Kaneko S, et al. A cost-effectiveness analysis of lenvatinib compared with sorafenib in unresectable hepatocellular carcinoma allowing for AFP adjustment in overall survival in Japan from the REFLECT Phase 3 clinical trial. In: 12th ILCA annual conference; London, September 14–16, 2018;abstr: O-021.
34. Noman MZ, Desantis G, Janji B, et al. PD-L1 is a novel direct target of HIF-1α, and its blockade under hypoxia enhanced MDSC-mediated T cell activation. *J Exp Med*. 2014;211(5):781–790.
35. Chen Y, Ramjiawan RR, Reiberger T, et al. CXCR4 inhibition in tumor microenvironment facilitates anti-programmed death receptor-1 immunotherapy in sorafenib-treated hepatocellular carcinoma in mice. *Hepatology*. 2015;61(5):1591–1602.
36. Terme M, Colussi O, Marcheteau E, Tanchot C, Tartour E, Taieb J. Modulation of immunity by antiangiogenic molecules in cancer. *Clin Dev Immunol*. 2012;2012:492920.
37. Rivera LB, Meyronet D, Hervieu V, Frederick MJ, Bergsland E, Bergers G. Intratumoral myeloid cells regulate responsiveness and resistance to antiangiogenic therapy. *Cell Rep*. 2015;11(4):577–591.
38. Manning EA, Ullman JG, Leatherman JM, et al. A vascular endothelial growth factor receptor-2 inhibitor enhances antitumor immunity through an immune-based mechanism. *Clin Cancer Res*. 2007;13(13):3951–3959.
39. Terme M, Pernot S, Marcheteau E, et al. VEGFA–VEGFR pathway blockade inhibits tumor-induced regulatory T-cell proliferation in colorectal cancer. *Cancer Res*. 2013;73(2):539–549.
40. Yasuda S, Sho M, Yamato I, et al. Simultaneous blockade of programmed death 1 and vascular endothelial growth factor receptor 2 (VEGFR2) induces synergistic anti-tumour effect in vivo. *Clin Exp Immunol*. 2013;172(3):500–506.
41. Pishvaian MJ, Lee MS, Ryoo B-Y, et al. LBA26Updated safety and clinical activity results from a Phase Ib study of atezolizumab + bevacizumab in hepatocellular carcinoma (HCC). *Ann Oncol*. 2018;29(suppl_8):ix46–ix66.
42. Stein S, Pishvaian MJ, Lee MS, et al. Safety and clinical activity of 1L atezolizumab + bevacizumab in a Phase Ib study in hepatocellular carcinoma (HCC). *J Clin Oncol*. 2018;36(15_suppl):4074.
43. Roche. FDA grants Breakthrough Therapy Designation for Roche's Tecentriq in combination with Avastin as first-line treatment for advanced or metastatic hepatocellular carcinoma (HCC) [media release]. Roche Group Media Relations, 2018 [July18]. Available from: https://www.roche.com/media/releases/med-cor-2018-07-18.htm.
44. Ikeda M, Sung MW, Kudo M, et al. A Phase 1B trial of lenvatinib (LEN) plus pembrolizumab (PEM) in patients (PTS) with unresectable hepatocellular carcinoma (uHCC). *J Clin Oncol*. 2018;36(15_suppl):4076–4076.
45. Merck. Eisai and Merck Receive Breakthrough Therapy Designation from FDA for LENVIMA® (lenvatinib mesylate) and KEYTRUDA® (pembrolizumab) as Combination Therapy for Advanced and/or Metastatic Renal Cell Carcinoma. Eisai Public Relations Department 2018 [January 09]. Available from: https://investors.merck.com/news/press-release-details/2018/Eisai-and-Merck-Receive-Breakthrough-Therapy-Designation-from-FDA-for-LENVIMA-lenvatinib-mesylate-and-KEYTRUDA-pembrolizumab-as-Combination-Therapy-for-Advanced-and-or-Metastatic-Renal-Cell-Carcinoma-/default.aspx.
46. Galle PR, Forner A, Llovet JM, Mazzaferro V, Piscaglia F, Raoul JL, Schirmacher P, Vilgrain V. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2018;69(1):182–236.
47. Yamamoto Y, Matsui J, Matsushima T, et al. Lenvatinib, an angiogenesis inhibitor targeting VEGFR/FGFR, shows broad antitumor activity in human tumor xenograft models associated with microvessel density and pericyte coverage. *Vasc Cell*. 2014;6(1):18.
48. Finn RS, Merle P, Granito A, et al. Outcomes of sequential treatment with sorafenib followed by regorafenib for HCC: additional analyses from the Phase III RESORCE trial. *J Hepatol*. 2018;69(2):353–358.
49. Lamarca A, Mendiola M, Barriuso J. Hepatocellular carcinoma: exploring the impact of ethnicity on molecular biology. *Crit Rev Oncol Hematol*. 2016;105:65–72.
50. Personeni N, Rimassa L. Hepatocellular carcinoma: a global disease in need of individualized treatment strategies. *J Oncol Pract*. 2017;13(6):368–369.

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