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Original Article

Lenvatinib versus sorafenib as first-line therapy of advanced hepatocellular carcinoma: a systematic review and meta-analysis

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Abstract: There is limited evidence on the efficacy of lenvatinib in advanced hepatocellular carcinoma (HCC) patients. Aim of this meta-analysis was to compare lenvatinib and sorafenib as first-line treatment. Computerized bibliographic search was performed on main databases through November 2020. The primary outcome was overall survival, whereas survival rate (at 1-, and 2-year), progression-free survival (PFS), tumor response, and severe adverse event rate were the secondary outcomes. Results were expressed in terms of odds ratio (OR) or hazard ratio (HR) and 95% confidence interval (CI). Five studies enrolling 1481 patients were included. No difference in terms of overall survival was detected (HR 0.81, 0.58-1.11) and median survival was 13.4 months (9.38-17.48) in lenvatinib and 11.4 months (8.46-14.47) in sorafenib patients. Lenvatinib led to a significant improvement of PFS (HR 0.67, 0.48-0.94) and median PFS was 5.88 months (3.68-8) in lenvatinib and 4.17 months (3.08-5.25) in sorafenib patients. Lenvatinib determined a considerably higher rate of objective response (33.3%, 23.6%-43% versus 6.5%, 3.5%-9.5%; OR 7.70, 2.99-19.82), and of disease control rate (76.9%, 70.4%-83.5% versus 52.7%, 40.7%-64.6%; OR 2.41, 1.55-3.77). No difference between lenvatinib and sorafenib in terms of severe adverse event rate was observed (OR 1.31, 0.82-2.09). Lenvatinib prolongs progression-free survival as compared to sorafenib in HCC patients, although this result does not translate to a significant survival benefit.

Keywords: HCC, survival, recurrence, liver cancer, systemic therapy

Introduction

Hepatocellular carcinoma (HCC) is the fifth most commonly occurring type of cancer and the leading cause of mortality in cirrhotic patients [1].

Although an increasing number of HCC patients in the developed countries are currently amenable of curative therapies at the time of diagnosis, tumor progression and development of portal vein thrombosis or extrahepatic spread are still detected in a considerable proportion of patients [2].

For these subjects with unresectable advanced HCC who cannot benefit from surgical and loco-regional treatments, the oral multikinase inhibitor sorafenib (Nexavar®, Bayer, Leverkusen, Germany) represents the first-line systemic treatment [3, 4]. However, the narrow therapeutic window, the high rate of progression and the lack of effective second-line treatments represent major pitfalls of sorafenib

therapy. The oral multikinase inhibitor regorafenib (Stivarga®, Bayer, Leverkusen, Germany) was shown to provide favorable outcomes in the second-line setting after sorafenib progression [5] but valuable alternative options in the first line therapy are still lacking.

Lenvatinib (Lenvima®, Eisai Inc., Woodcliff Lake, NJ, USA) is an oral tyrosine kinase inhibitor (TKI) inhibiting vascular endothelial growth factor receptor (VEGFR) 1-2 and 3, fibroblast growth factor receptor (FGFR) 1-2-3 and 4, platelet-derived growth factor receptors (PDGFRs), c-KIT and rearranged during transfection (RET) [6]. Therefore, lenvatinib exerts a dual inhibition both on vascular endotelial growth factor (VEGF) and fibroblast growth factor (FGF) pathways; the potent activity of lenvatinib against FGFRs is a distinctive feature of lenvatinib compared to sorafenib [6].

A recent phase III multicenter randomized-controlled trial (RCT) showed evidence of non-inferiority of lenvatinib as compared to sorafenib in overall survival and safety profile in untreated advanced HCC patients [6]. Since then, several real-life series were published with promising results on the comparison between the two therapeutic agents [7-10]; hence, the pressing need to systematically assess the comparative efficacy of lenvatinib in the first-line setting, based on the current evidence.

In an attempt to address this important point, we performed the current meta-analysis of all available head-to-head studies directly comparing lenvatinib and sorafenib in advanced HCC patients not previously treated with systemic therapy. Primary endpoint was overall survival (OS). Additional endpoints were progression-free survival (PFS), tumor response, and adverse events rate.

Methods

Search strategy and selection criteria

Studies included in this meta-analysis were prospective or case-control studies that met the following inclusion criteria: (a) Patients: adults HCC patients not previously treated with systemic therapies (first-line setting); (b) Interventions: lenvatinib; (c) Comparator: sorafenib; (d) Outcome: overall survival, progression-free survival, tumor response, severe adverse event rate.

We excluded (a) single cohort non-comparative studies, (b) *post-hoc* or sub-analyses of trials already included, (c) studies conducted in a second-line setting (i.e. after sorafenib progression).

We searched MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Scopus, and Web of Science through November 2020; the search strategy used in Medline was based on the following search string: (((sorafenib [MeSH Terms]) OR (lenvatinib [MeSH Terms])) AND (hepatocellular carcinoma [MeSH Terms])) OR (hcc [MeSH Terms]).

An updated literature search of conference proceedings of main international liver meetings was performed on November 20, 2020 to identify additional studies.

Data abstraction and quality assessment

Data on study-, patient- and treatment-related characteristics were abstracted onto a standardized form, by two authors independently (AF, RV).

The risk of bias of individual studies was assessed independently by two authors (AF, CC) in the context of the primary outcome, based on the Cochrane Collaboration's tool for assessing the risk of bias [11] for RCTs and the Newcastle Ottawa scale [12] for non-randomized studies. Eventual disagreements were solved following a third opinion (AA).

Outcomes assessed

The primary outcome was overall survival, computed from the start of the treatment and death or censoring. Secondary outcomes were survival rate at 1 and 2 years, progression-free survival (defined as time elapsed from treatment to radiological evidence of progression), PFS rate at 1 year, tumor response, both in terms of objective response (OR, defined as complete response + partial response) and disease control rate (DCR, defined as complete response + partial response + stable disease), and severe adverse event (SAE) rate.

In the case of propensity score matched studies, only data after matching were considered.

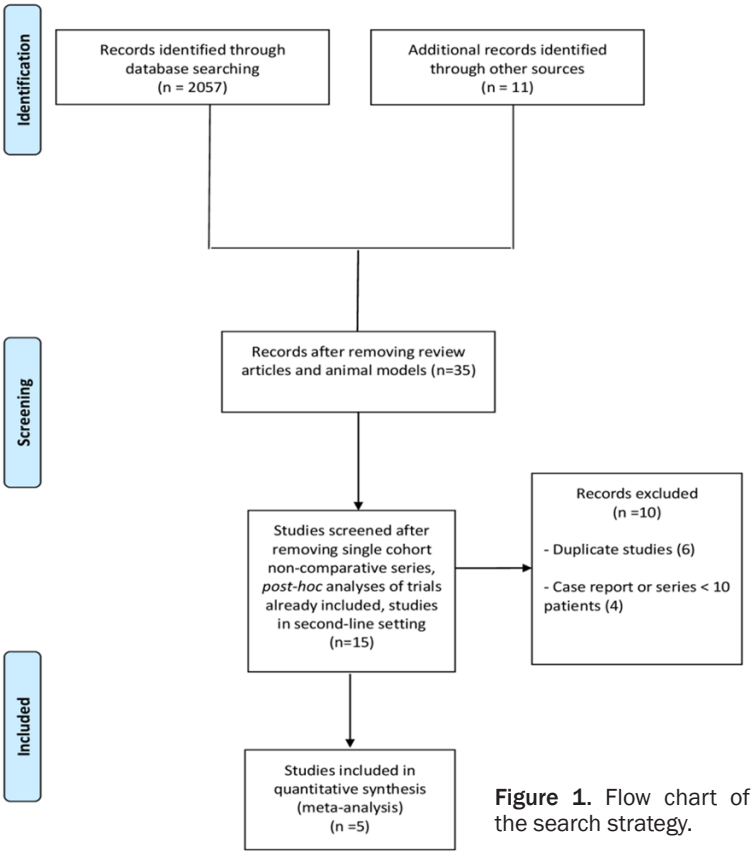

Figure 1. Flow chart of the search strategy.

Statistical analysis

The two treatment groups were compared through a random-effects model based on DerSimonian and Laird test [13], and results were expressed in terms of hazard ratio (HR) in the case of time-to-event outcomes or odds ratio (OR) in the case of dichotomous outcomes, along with the relevant 95% confidence intervals (CIs).

Presence of heterogeneity was measured in terms of I^2 tests with I^2<20% interpreted as low-level heterogeneity and I^2 between 20% and 50% as moderate heterogeneity. Any potential publication bias was verified through visual assessment of funnel plots.

All statistical analyses were conducted using RevMan version 5 from the Cochrane collaboration and R 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

For all calculations a two-tailed *p* value of less than 0.05 was considered statistically significant.

Results

Literature search and characteristics of included studies

Figure 1 shows the flow chart of the search strategy conducted in this meta-analysis.

Out of 2068 studies initially identified, after exclusion of review, case reports, single cohort studies, and animal models, 10 potentially relevant studies were extracted. After exclusion of overlap studies and of small series enrolling less than 10 patients, 5 studies [6-10] were finally included in the meta-analysis.

Table 1 reports the main characteristics of the included studies.

The recruitment period ranged from 2013 to 2020. Four studies [7-10] were retrospective series conducted in Asia, whereas the multicenter RCT included either Asian and Western centers [6]. Globally, 733 patients were treated with lenvatinib and 748 with sorafenib.

Overall, the two arms were well-balanced in terms of clinical and tumoral parameters in the included studies. The vast majority of patients were in Child Pugh stage A and viral etiology was the predominant cause of the underlying liver disease. Barcelona Clinic Liver Cancer (BCLC) stage was mainly classified as advanced (BCLC C) and most patients had been previously treated with loco-regional therapies. The majority of treated patients were male and with performance status 0.

Quality assessment of the included studies is reported in the Supplementary Table 1. Three studies were deemed as high quality [6, 9, 10], whereas the other two retrospective reports [7, 8] were considered at higher risk of bias due to selection and outcome reporting bias.

Overall survival

Comparison of overall survival, based on 4 studies [6, 8-10], was depicted in **Figure 2**.

Table 1. Baseline characteristics of patients recruited in the included studie

Study ID/ Country/Design/ Recruitment period	sample size	Median Duration of follow up, months, Median (IQR)	age	sex (male)	ECOG PS: 0/1	Child-Pugh class: A/B	Maximum tumor size (cm)/ multiple tumor/Macroscopic portal vein invasion/Extra hepatic spread/	BCLC stage: B/C	Etiology of liver disease: HBV/HCV	Baseline AFP; ng/mL, median (range)	Previous therapy
Kudo 2018/ Multinational/RCT/ March 1, 2013, and July 30, 2015	Lenvatinib: 478	27.7 (23.3-32.8)	Median (range) years 63.0 (20-88)	405 (85%)	304 (64%)/ 174 (36%)	475 (99%)/3 (1%)	NR/NR/109 (23%)/291 (61%)	104 (22%)/ 374 (78%)	251 (53%)/91 (19%)	Number of patients: Lenvatinib: 471 (99%) Sorafenib: 463 (97%) Median (IQR): 133.1 (8.0-3730.6) ≥200 ng/mL: 222 (46%)	Previous anticancer procedures: 327 (68%) previous Radiotherapy: 49 (10%) concomitant antiviral therapy for HBV or HCV: 163 (34%)
	Sorafenib: 476	27.2 (22.6-31.3)	62.0 (22-88)	401 (84%)	301 (63%)/ 175 (37%)	471 (99%)/5 (1%)	NR/NR/90 (19%)/295 (62%)	92 (19%)/ 384 (81%)	228 (48%)/126 (26%)	Median (IQR): 71.2 (5.2-1081.8) ≥200 ng/mL: 187 (39%)	Previous anticancer procedures: 344 (72%) previous Radiotherapy: 60 (13%) concomitant antiviral therapy for HBV or HCV: 149 (31%)
Kim 2020, Single center, Korea Retrospective cohort October 2018 to October 2019	Lenvatinib: 44	NR	median (IQR): 56.0 (51.0-66.3)	39 (88.6%)	41 (93.2%)/3 (6.8%)	36 (81.8%)/8 (18.2%)	Median (IQR): 7.0 (2.5-11.4)/34 (77.3%)/26 (59.1%)/25 (56.8%)	NR	27 (61.4)/ NR	Median (IQR): 628.4 (20.8-6,175.5)	Previous anti HCC treatment: 21 (47.7%)
	Sorafenib: 61	NR	64.0 (58.0-70.5)	51 (83.6%)	59 (96.7%)/2 (3.3%)	56 (91.8%)/5 (8.2%)	4.6 (1.8-7.9)/47 (77.0%)/23 (37.7%)/32 (52.5%)	NR	45 (73.8)/ NR	Median (IQR): 116.5 (9.1-1,791.0)	Previous anti HCC treatment: 48 (78.7%)
KUZUYA, 2020, I only report the results after matching. Japan PS matching retrospective cohort June 2011 to September 2019	Lenvatinib: 13	NR	70 (53-92)	11 (84.6%)	12 (92.3%)/1 (7.7%)	5/6: 8 (61.5%)/5 (38.5%)	Tumor burden <50%/≥50%: 8 (61.5%)/5 (38.5%)/NR/portal vein tumor thrombosis: Vp3: PVTT of the first branches/ Vp4: PVTT of the main trunk: 9 (69.2%)/4 (30.8%)/3 (23.1%)	NR	2 (15.4%)/2 (15.4%)	<400/≥400 ng/mL: 3 (23.1%)	History of trans arterial chemoembolization: 5 (38.5%)
	Sorafenib: 13	NR	69 (60-78)	11 (84.6%)	8 (61.5%)/5 (38.5%)	5/6: 7 (53.8%)/6 (46.2%)	Tumor burden <50%/≥50%: 9 (69.2%)/4 (30.8%)/NR/8 (61.5%)/5 (38.5%)/7 (53.8%)	NR	2 (15.4%)/5 (38.5%)	7 (53.8%)	5 (38.5%)
Nakano, 2020 Japan PS matching retrospective cohort May 2009 and October 2019	Lenvatinib: 146	Median duration of treatment: 6.1 months	median (range): 73.9 (44.7-89.8)	125 (86%)	NR	134 (92%)/12 (8%)	Intrahepatic tumor size (mm): 35.9 ± 29.0, median (range): 30.0 (0.0-201.0)/Intrahepatic tumor number (0/1/2 or more): 15 (10%)/8 (6%)/123 (84%)/ macrovascular invasion: 21 (14%)/56 (38%)	B/C: 79 (54%)/67 (46%)	HBV/HCV/ Both: 25 (17%)/77 (53%)/2 (1%)	79 (2-146,260)	NR
	Sorafenib: 146	4.2 months	73.1 (48.3-94.3)	121 (83%)	NR	137 (94%)/9 (6%)	37.9 ± 32.0, median (range): 27.5 (0.0-190.0)/15 (10%)/14 (10%)/117 (80%)/21 (14%)/55 (38%)	81 (55%)/65 (45%)	24 (16%)/81 (56%)/2 (1%)	46 (1-186,300)	NR

Tomonari, 2020 Japan PS matching retrospective cohort June 2009 to June 2020	Lenvatinib: 52	median follow-up period was 288 (range 148 to 1127) days	Median (range) years: 70 [53-88]	36 pts	0/1, n: 38/14	5/6, n Lenvatinib: 27/25 Sorafenib: 27/25	Maximum size of intrahepatic lesion (None/≤50/>50) (mm): 0/37/15 Number of intrahepatic lesions (None/1/2-7/>7): 2/9/25/16 Portal vein invasion (absent/present), n: 41/11 Extra hepatic spread (absent/present), n: 42/10	(B/C), n: 27/25	(HBV/HCV), n: 15/18	41 [1-568,100]	NR
	Sorafenib: 52		71 [43-85]	35 pts	37/15		0/38/14 0/9/21/22 43/9 43/9	29/23	10/19	40 [1-21,314]	NR

Abbreviations: AFP, Alfa-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group.

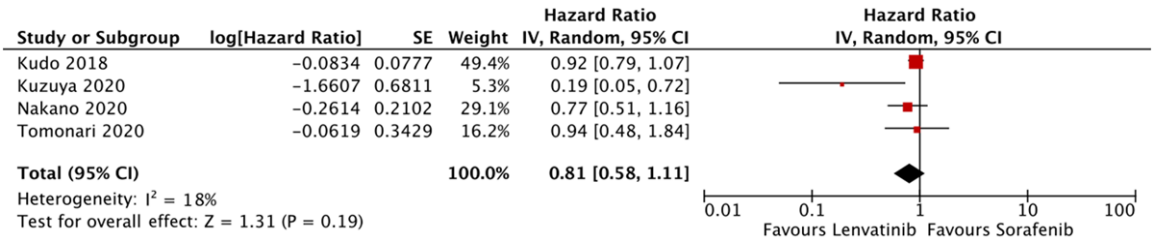

Figure 2. No difference was detected between the two treatments (hazard ratio 0.81, 0.58-1.11) with low evidence of heterogeneity (I^2=18%) and median survival was 13.4 months (9.38-17.48) in lenvatinib and 11.4 months (8.46-14.47) in sorafenib patients.

Table 2. Other outcomes analyzed in the meta-analysis

Outcome	Subgroup	No. of Studies	No. of patients	Odds ratio (95% CI)	Within-group heterogeneity (I^2)
Survival rate	1-year survival rate	4	1391	1.48 (0.84-2.6)	28.8%
	2-year survival rate	2	1058	0.99 (0.66-1.48)	27%
Progression-free survival	Overall[a]	4	1391	0.67 (0.48-0.94)	17%
	1-year PFS rate	3	1350	0.70 (0.68-0.95)	36%
Tumor response	Objective response	4	1391	7.70 (2.99-19.82)	34%
	Disease control	4	1391	2.41 (1.55-3.77)	21%
Severe adverse events	Overall	4	1204	1.31 (0.82-2.09)	29%

[a]Results expressed in terms of hazard ratio. Abbreviation: CI, Confidence Interval; PFS, Progression-Free Survival.

No difference was detected (HR 0.81, 0.58-1.11) with low evidence of heterogeneity (I^2= 18%) and median survival was 13.4 months (9.38-17.48) in lenvatinib and 11.4 months (8.46-14.47) in sorafenib patients, thus supporting the non-superiority of one treatment over the other in terms of overall survival. This finding was confirmed in the comparative analysis of 1- and 2-year survival rate, with ORs 1.48 (0.84-2.6) and 0.99 (0.66-1.48), respectively (**Table 2**). In particular, pooled survival rates at 1- and 2-year were 65.5% (53.8%-77.2%) and 31.1% (27.2%-35.1%) with lenvatinib and 50.8% (34.3%-67.2%) and 34% (21.4%-46.7%) with sorafenib, respectively.

No significant publication bias was found by means of visual examination of funnel plot (Supplementary Figure 1).

Progression-free survival

As reported in **Figure 3** and **Table 2**, lenvatinib led to a significant improvement of PFS (HR 0.67, 0.48-0.94), with low evidence of heterogeneity (I^2=17%).

Median PFS was 5.88 months (3.68-8) in lenvatinib and 4.17 months (3.08-5.25) in sorafenib patients, hence with evidence of more favorable PFS outcomes in patients treated with lenvatinib.

Likewise, PFS rate at 1 year was significantly in favor of lenvatinib as compared to sorafenib (35.7%, 16.5%-54.8% versus 22.7%, 15.8%-29.5%; OR 0.70, 0.68-0.95), with moderate evidence of heterogeneity (I^2=36%).

Again, no evidence of publication bias was found (Supplementary Figure 2).

Other secondary outcomes

The other secondary outcomes were reported in **Table 2**.

As reported in **Figure 4**, based on 4 studies [6, 8-10] lenvatinib determined a considerably higher rate of objective response (33.3%, 23.6%-43% versus 6.5%, 3.5%-9.5%; OR 7.70, 2.99-19.82), with moderate evidence of heterogeneity (I^2=34%). Disease control rate was also significantly higher in patients treated with lenvatinib in comparison to sorafenib (76.9%, 70.4%-83.5% versus 52.7%, 40.7%-64.6%; OR 2.41, 1.55-3.77; I^2=21%).

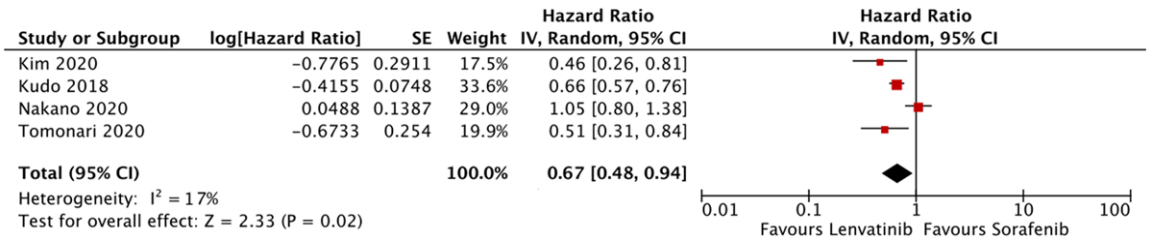

Figure 3. Lenvatinib led to a significant improvement of progression-free survival (hazard ratio 0.67, 0.48-0.94), with low evidence of heterogeneity (I^2=17%). Median progression-free survival was 5.88 months (3.68-8) in lenvatinib and 4.17 months (3.08-5.25) in sorafenib patients.

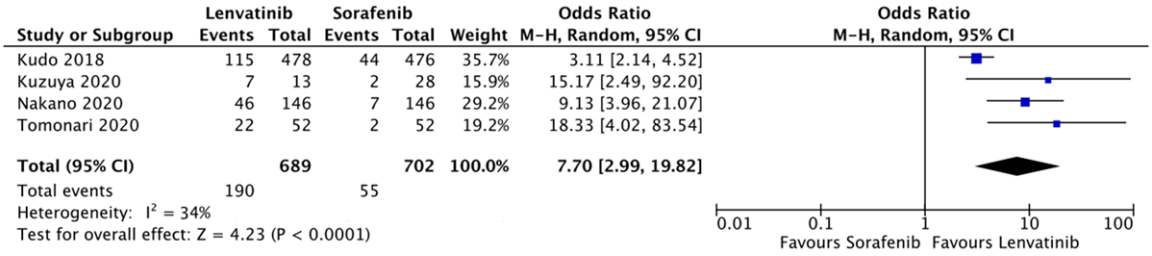

Figure 4. Lenvatinib determined a considerably higher rate of objective response (33.3%, 23.6%-43% versus 6.5%, 3.5%-9.5%; odds ratio 7.70, 2.99-19.82), with moderate evidence of heterogeneity (I^2=34%).

Supplementary Figure 3 reports the forest plot of comparison between the two treatments in terms of severe adverse event rate. Based on 4 studies [6-8, 10], no difference between lenvatinib and sorafenib was observed (OR 1.31, 0.82-2.09; I^2=29%).

Pooled rates of severe complications were 38.2% (95% CI 1.5%-74.9%) and 36.1% (2%-74.3%) with lenvatinib and sorafenib, respectively and hand-foot syndrome, diarrhea and hypertension were the most frequently registered events.

The detailed list of adverse events was reported in the Supplementary Table 2.

Discussion

HCC represents the most frequent type of cancer and the leading cause of tumor-related mortality in cirrhotic patients [1].

Sorafenib, a multikinase inhibitor, has been used since 2008 as a first-line systemic agent in patients with advanced HCC [14, 15]; however, finding a more effective and better tolerated alternative therapeutic regimen in these patients represents still an unmet need in hepato-oncology.

Other agents, such as regorafenib, showed interesting results after sorafenib progression [16] but their use in first-line setting was not adequately explored.

On the other hand, lenvatinib showed interesting and promising results in the pivotal multicenter RCT [6], but there is still limited evidence on its real efficacy and safety in real-world practice; to the best of our knowledge, our manuscript constitutes the first meta-analysis comparing lenvatinib and sorafenib in HCC patients.

Through a pairwise meta-analysis of five studies, of which an RCT and four non-randomized series, we made several key observations. First, the two treatments determined comparable overall survival outcomes (HR 0.81, 0.58-1.11) with only a slight increase in median survival observed with lenvatinib as compared to sorafenib (13.4 versus 11.4 months). Second, lenvatinib led to a significant improvement of PFS (HR 0.67, 0.48-0.94) and median PFS was 5.88 months in lenvatinib and 4.17 months in sorafenib patients. This finding, supported also by the considerably higher rates of either objective response (33.3% versus 6.5%; OR 7.70, 2.99-19.82) and disease control rate (76.9% versus 52.7%; OR 2.41, 1.55-3.77), suggests a stronger antitumoral effect of lenvanitib.

This apparent discrepancy between the similar OS and the more favorable PFS observed with lenvatinib is in keeping with the results of single studies [6, 10] and can be explained with the incidence on post-progression survival of several confounding factors, such as use of locoregional therapies or systemic second-line sequential treatments administered after disease progression [17-19]. Moreover, several studies have shown that the hepatic functional reserve often worsens during systemic treatments and this could represent a further aspect able to prevent the use of second-line therapies. For example, both in the REFLECT trial [6] and in the retrospective cohort by Tomonari *et al* [10] there was a higher decrease in the Child-Pugh scores after lenvatinib as compared to sorafenib. In our analysis we found a slighter increase in the severe adverse event rate, which can explain the eventual lower use of second-line therapies after lenvatinib although this did not reach the significance threshold (OR 1.31, 0.82-2.09). In particular, pooled rates of severe complications were 38.2% and 36.1% with lenvatinib and sorafenib, respectively and hand-foot syndrome, diarrhea and hypertension were the most frequently registered events.

Of note, the vast majority of recruited patients were in Child-Pugh stage A or B, which represent the limit within a curative therapy can be offered to HCC patients.

There are some limitations to our study. First, the limited number of randomized-controlled trials and of recruited patients did not allow to conduct specific subgroup and sensitivity analyses. Second, the impact of several variables on final outcomes could not be investigated due to lack of data, for example tumoral stage and baseline alpha-fetoprotein. However, as clearly reported in **Table 1**, distribution of these variables across the included studies and, within each study, between the two treatment arms was homogeneous, hence this aspect would unlikely represent an issue in our analysis. Third, the insufficient and uneven follow-up time may have overestimated the clinical outcomes and should be expanded. However, we performed a meta-analysis of pooled HRs with the aim to overcome any potential bias related to different follow-up length in the included studies. Fourth, moderate heterogeneity was found in some comparisons, although analysis of the primary outcome was supported by more robust evidence and low heterogeneity. Finally, the analysis of the costs was beyond the scope of the manuscript, therefore we cannot make definitive assumptions in this regard.

Conclusions

The current meta-analysis shows that lenvatinib determined longer PFS and higher response rates as compared to sorafenib, although a clear survival benefit was not observed. Further trials reporting long-term outcomes are needed to confirm these findings.

Disclosure of conflict of interest

None.

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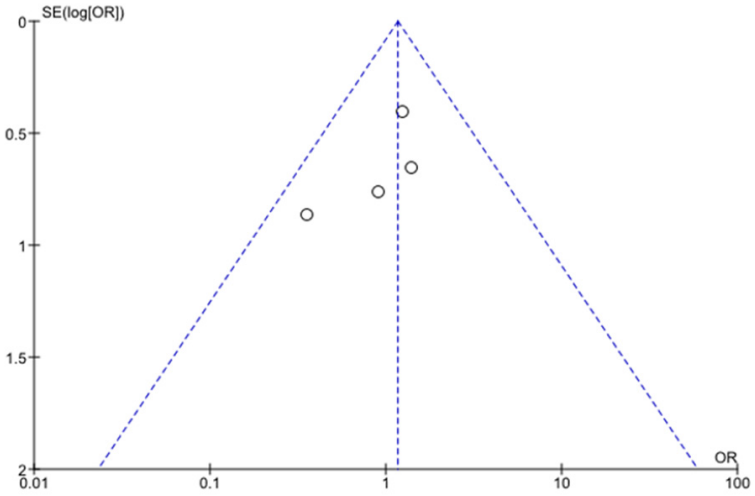
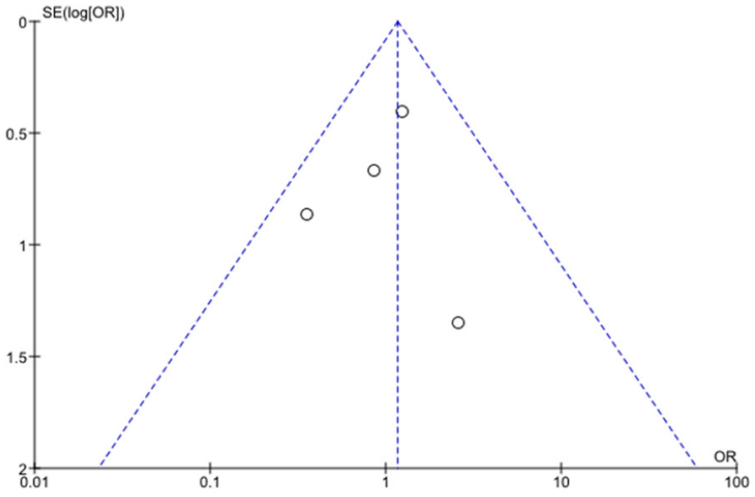
Supplementary Table 1. Risk of bias assessment and quality of included studies

Observational studies[a]								
	Selection		Comparability		Outcome		Overall quality	
Kim 2020	*		**		*		L	
Kuzuya 2020	**		***		**		M	
Nakano 2020	***		***		**		H	
Tomonari 2020	***		***		**		H	
Randomized controlled trials[b]								
	1	2	3	4	5	6	7	
Kudo 2018	L	L	L	L	L	L	L	H

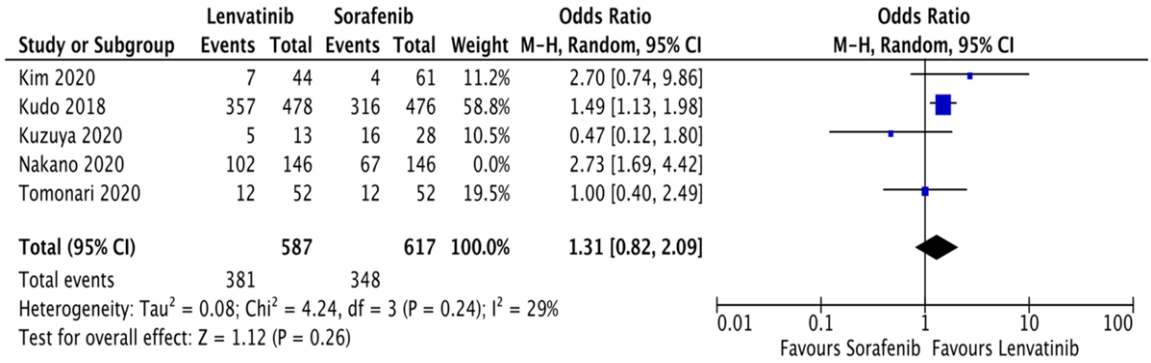
L, low; H, high; U, unclear; M, moderate. [a]Study quality assessment performed by means of Newcastle/Ottawa scale (each asterisk represents if the respective criterion within the subsection was satisfied). [b]Cochrane Collaboration's tool for assessing the risk of bias across 7 domains: 1 (Random sequence generation), 2 (Allocation concealment), 3 (Blinding of participants and personnel), 4 (Blinding of outcome assessment), 5 (Incomplete outcome data), 6 (Selective reporting) and 7 (Other bias).



Supplementary Figure 1. Funnel plot concerning overall survival analysis.



Supplementary Figure 2. Funnel plot concerning overall progression-free survival analysis.



Supplementary Figure 3. Forest plot of severe adverse event rate.

Supplementary Table 2. Grade ≥3 side effects (Lenvatinib/sorafenib)

Study ID	PPE	Diarrhea	HTN	Decreased appetite	Decreased weight	Proteinuria	Elevated AST	Hypothyroidism	Rash	Increased blood bilirubin
Kudo 2018	14 (3%)/54 (11%)	20 (4%)/20 (4%)	111 (23%)/68 (14%)	22 (5%)/6 (1%)	36 (8%)/14 (3%)	27 (6%)/8 (2%)	24 (5%)/38 (8%)	0/0	0/2 (<1%)	31 (7%)/23 (5%)
Kim 2020	0/2 (3.3)	1 (2.3%)/0	0/0	1 (2.3%)/0	1 (2.3%)/0	0/0	1 (2.3%)/2 (3.3%)	0/0	0/0	0/0
KUZUYA, 2020	1 (7.7)/5 (17.9)	1 (7.7)/2 (7.1)	2 (15.4)/0	1 (7.7)/1 (3.6)	NR	0	NR	0	0/4 (14.3%)	NR
Nakano, 2020[a]	43 (29%)/64 (44%)	35 (24%)/23 (16%)	44 (30%)/10 (7%)	54 (37%)/3 (2%)	NR	13 (9%)/5 (3%)	Liver dysfunction: 20 (14%)/22 (15%)	14 (10%)/0	NR	NR
Tomonari, 2020	0/2 (3.8%)	2 (3.8%)/2 (3.8%)	2 (3.8%)/0	2 (3.8%)/1 (1.9%)	NR	4 (7.7%)/0	0/3 (5.8%)	0/0	NR	NR

[a]All adverse events (not only severe adverse events) were reported. PPE: Palmar-plantar erythrodysesthesia, HTN: hypertension, NR: not reported, AST: Aspartate aminotransferase.