Original Article

Efficacy and Safety of Second-line Treatments in Patients with Advanced Hepatocellular Carcinoma after Sorafenib Failure: A Meta-analysis

Limin An[1#] , Haotian Liao[1#] and Kefei Yuan[1,2*]

[1]Department of Liver Surgery & Liver Transplantation, State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University and Collaborative Innovation Center of Biotherapy, Chengdu, Sichuan, China; [2]Laboratory of Liver Surgery, West China Hospital, Sichuan University, Chengdu, Sichuan, China

Abstract

Background and Aims: In the last decade, several second-line therapies followed by sorafenib in patients with advanced hepatocellular carcinoma (HCC) have been reported. But the outcomes were different from each other. This meta-analysis aimed to evaluate the efficacy and safety of the second-line therapies followed by sorafenib in patients with advanced HCC. ***Methods:*** Embase (1974 to October 2019) and Ovid MEDLINE (1946 to October 2019) were searched for randomized clinical trials on second-line therapies followed by sorafenib in patients with advanced HCC. The quality of each study was assessed by the modified Jadad scale. Statistical analysis was carried out by RevMan5.3 software. Efficacy and safety were analyzed. Efficacy included overall survival (OS), disease control rate, time to progression, and progression-free survival. ***Results:*** Eight studies involving 3,173 patients were eligible. No difference in OS was found between the second-line treatment group and the control group (HR=0.87, 95% CI: 0.74–1.01, *p*=0.06). Disease control rate (relative risk (RR)=1.36, 95% CI: 1.16–1.60, *p*=0.0002), time to progression (HR=0.64, 95% CI: 0.51–0.81, *p*=0.0002) and progression-free survival (HR=0.60, 95% CI: 0.46–0.77, *p*<0.0001) were significantly improved by the second-line therapies. There was a slight difference in adverse events of any grade (RR=1.07, 95% CI: 1.00–1.14, *p*=0.03) between the two groups. ***Conclusions:*** These second-line therapies followed by sorafenib may potentially improve the prognosis in patients with advanced HCC. Compared with other second-line therapies, regorafenib seemed to be more effective.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and remains a worldwide disease burden.[1,2] The tyrosine kinase inhibitor (TKI) sorafenib has become the standard first-line therapy for patients with advanced HCC who are not candidates for locoregional therapy. Moreover, it has shown survival benefits over placebo.[3,4] However, for most patients, the benefits of sorafenib are not sustainable and the disease eventually progresses.[5] Furthermore, many patients will experience dose reduction and treatment discontinuation due to the high rate of adverse events (AEs).[6–8] It has been reported that 40–56% of patients were potentially amenable to second-line clinical trials due to resistance to sorafenib.[9] In the last decade, several second-line therapies, such as cabozantinib,[10] pembrolizumab[11] and ADI-PEG,[12] have been reported. However, the outcomes were different from each other. Therefore, there is still no standard second-line treatment followed for sorafenib.[13,14]

Therefore, this meta-analysis of randomized controlled trials (RCTs) was conducted to evaluate the efficacy and safety of the second-line therapies followed by sorafenib.

Methods

Search strategy

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (http://www.prisma-statement.org/).[15] A comprehensive

search of studies was performed in Embase (1974 to October 2019) and Ovid MEDLINE (1946 to October 2019). The search terms were: hepatocellular carcinoma, liver cancer, HCC, nexavar, BAY 43-9006, BAY 43 9006, BAY 439006, sorafenib N-oxide, sorafenib N oxide, BAY-673472, BAY 673472, BAY 545-9085, BAY 545 9085, BAY 5459085, BAY-545-9085, BAY5459085, and sorafenib tosylate. We also manually searched the reference lists of the identified studies for related articles. Two authors (LA and HL) independently screened titles and abstracts. We obtained full texts for further assessment if the publications potentially met the inclusion criteria. Any disagreement between the two authors would be solved by consulting the third author (KY).

Inclusion and exclusion criteria

The eligibility criteria for this study were as follows: 1. Only patients (age >18 years) with advanced HCC-confirmed progression during or after sorafenib treatment or sorafenib resistance were included in these trials. 2. RCTs that compared the second-line treatment with placebo or best supportive care were included. 3. Any of the following data was reported in the articles: overall survival (OS) (defined as the time from the date of randomization to that of death of any cause), disease control rate (DCR) (defined as the percentage of patients who achieved complete, partial response or stable disease), time to progression (TTP) (defined as the time from the date of randomization to that of first observation of disease progression), progression-free survival (PFS) (defined as the time from date of randomization to that of first observation of recurrence or death due to any cause) or AEs (such as decreased appetite, edema peripheral and diarrhea).

Animal studies, reviews, letters, editorials, commentaries, abstracts, unpublished studies, case reports, duplicate studies, and studies without full articles were excluded. Also, we excluded studies that involved some patients who received other therapies instead of sorafenib as the first-line treatment.

Data extraction

The extracted data included: general information, such as year of publication, sample size, and geographical region; population characteristics, including Eastern Cooperative Oncology Group (ECOG) performance status, Barcelona Clinic Liver Cancer (BCLC) stage, Child-Pugh score, α-fetoprotein (AFP), characteristics of the previous sorafenib therapy and the reasons for discontinuation of sorafenib; characteristics of the second-line treatment; primary outcome: median OS, hazard ratios (HRs) and their 95% confidence intervals (CIs) and log-rank *p* values; Secondary outcomes: median PFS and median TTP with HRs and their 95% CIs and log-rank *p* values, number of patients who achieved disease control and number and type of adverse events.

Two authors (LA and HL) independently extracted the data using a standardized data collection form. Any disagreement was solved by discussion with the third author (KY) and a consensus was finally achieved.

Quality assessment

The quality of each study was assessed by the modified Jadad scale.[16] Six items were included in the modified Jadad scale, the full score of which was 8 points. A higher score indicates better quality.[16] For each question, we awarded one point for an affirmative response or zero points for a negative response. These six items were: (i) was the study described as randomized? "yes or no"; award a bonus point if the method of randomization is appropriate (score 2) (e.g., computer-generated), deduct one point if the method of randomization is inappropriate (score 1); (ii) was the study described as double-blind? "yes or no"; award a bonus point if the method of double-blinding is appropriate (score 2) (e.g., identical placebo), deduct one point if the method of double-blinding is inappropriate (score 1); (iii) was there a description of withdrawals and dropouts? "yes (score 1) or no (score 0)"; (iv) was there a clear description of the inclusion/exclusion criteria? "yes (score 1) or no (score 0)"; (v) was the method used to assess adverse effects described? "yes (score 1) or no (score 0)"; (vi) were the methods of statistical analysis described? "yes (score 1) or no (score 0)".[16]

Two authors (LA and HL) performed the assessments independently. They resolved disagreements by discussion with the third author (KY).

Statistical analysis

Meta-analysis was performed with Cochrane Collaboration's Review Manager (version 5.3). Continuous variables were assessed by calculating HRs with their 95% CIs. Results were showed by forest plots. Treatment effects were expressed as relative risks (RRs) with 95% CIs for discontinuous outcomes and HRs for continuous outcomes. It was considered statistically significant when *p* was <0.05. Heterogeneity of the studies was measured by the I^2 statistic.[17] If I^2 <50%, it represented homogeneity and we would use the fixed-effects model.[18] Otherwise, we would use the random-effects model.[18] Subgroup analysis and sensitivity analysis would be performed if heterogeneity existed.

Results

Study selection

A total of 906 studies were identified. The results of literary searches are presented in Figure 1. After adjusting for duplicates, 676 remained. By reviewing abstracts, 661 studies were excluded because these studies clearly did not meet the eligibility criteria. Subsequently, the full text of the remaining 15 citations was examined in more detail. Five studies were excluded because sorafenib was not included in the first-line therapy for some patients and two studies were excluded because the data were insufficient. As a result, eight studies were included in the meta-analysis.[19–26]

Study characteristics and quality assessment

Eight studies were included in the meta-analysis, which were all randomized controlled multicenter trials. In total, 3,173 patients were involved. There were 2,018 patients in the second-line treatment group and 1,155 patient in the control group. For the modified Jadad scale (Table 1), two studies[19,21] received 7 points and five studies[20,22–25] received 8 points, indicating that they were of high quality. Only one study[26] received a Jadad score of 5 because it was not double-blinded and the methods of statistical analyses were not described. Most patients (66–100%) discontinued sorafenib because of progression. The majority of patients were of BCLC B or C stage (93–100%) and most of them had Child-Pugh class A or B severity of disease (95–100%). The ECOG performance status for most patients was 0 or 1. The results of the study characteristics are shown in Table 2.[19–26]
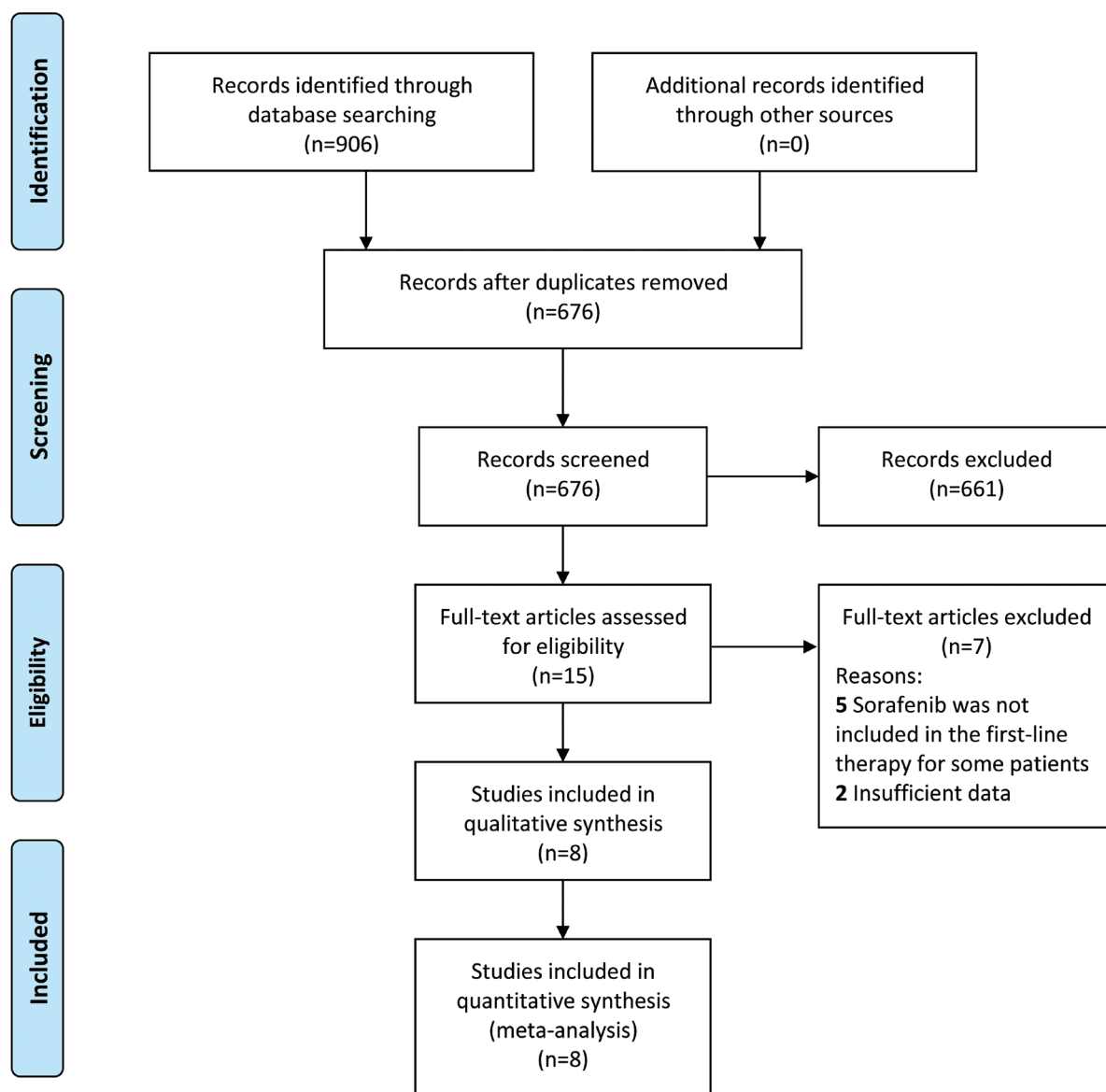
Fig. 1. PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1. Modified Jadad scale for randomized controlled trials included in the meta-analysis

Study (Year)	Randomi-zation	Blind-ing	Description of with-drawals and dropouts	Inclusion/ex-c1usion criteria	AEs	Statistical analysis	Overall
Llovet (2013)[19]	2	1	1	1	1	1	7
Zhu (2014)[20]	2	2	1	1	1	1	8
Zhu (2015)[21]	2	1	1	1	1	1	7
Bruix (2017)[22]	2	2	1	1	1	1	8
Kudo (2017)[23]	2	2	1	1	1	1	8
Rimassa (2018)[24]	2	2	1	1	1	1	8
Zhu (2019)[25]	2	2	1	1	1	1	8
Moehler (2019)[26]	2	0	1	1	1	0	5

AEs, adverse events.

Table 2. Characteristics of studies included in the meta-analysis

Study (Year)	Region	Group	Sample size	Best supportive care	Second-line treatment characteristics	Reason for discontinuation of sorafenib	ECOG score	BCLC performance status	Child-Pugh class	AFP, ng/mL
Llovet (2013)[19]	Europe, Asia, Americas	Brivanib	263	Y	661 mg/day [201–802]	Radiographic or symptomatic progression=86%; Intolerance=13%	0=57%; 1=39%; 2=4%	A=3%; B=9%; C=87%; D=1%	A=92%; B=7%; C=1%	Median (range)=204 [1.2–13.6×10^5]
		Placebo	132	Y	800 mg/day [324–819]	Radiographic or symptomatic progression=88%; Intolerance=12%	0=61%; 1=35%; 2=4%	A=1%; B=14%; C=85%; D=0%	A=91%; B=9%; C=0%	Median (range)=100 [1.0–5.1×10^5]
Zhu (2014)[20]	Europe, Asia, Americas, Oceania	Everolimus	362	Y	7.5 mg/day	Radiographic progression=81.2%; Intolerance=18.5%; Other=0.3%	0=59.1%; 1=35.6%; 2=5.2%	B=13.5%; C=86.5%	A=97.8%; B=2.2%	<200=49.4%; ≥200=47.2%; Missing=3.3%
		Placebo	184	Y		Radiographic progression=79.9%; Intolerance=20.1%; Other=0%	0=56.5%; 1=40.2%; 2=3.3%	B=14.1%; C=85.9%	A=98.9%; B=1.1%	<200=47.8%; ≥200=47.8%; Missing=4.3%
Zhu (2015)[21]	Europe, Asia, Americas, Oceania	Ramucirumab	283	Y	8 mg/kg intravenously over 1 h every 2 weeks	Radiographic progression=87%; Toxicity=13%	0=56%; 1=44%	B=12%; C=88%	A=98%	<400=57%; ≥400=42%; Missing=1%; Median (range)=174 (0–853,200)
		Placebo	282	Y		Radiographic progression=85%; Toxicity=15%	0=54%; 1=46%	B=12%; C=88%	A=98%	<400=53%; ≥400=46%; Missing=1%; Median (range)=330 (0–628,390)
Bruix (2017)[22]	Europe, Asia, Americas, Oceania	Regorafenib	379	Y	160 mg/day for the first three weeks of each 4-week cycle	Radiographic progression	0=65%; 1=35%	A<1%; B=14%; C=86%	A=98%; B=1%; (Missing one person)	≥400=43%
		Placebo	194	Y			0=67%; 1=33%	A=0; B=11%; C=89%	A=97%; B=3%	≥400=45%
Kudo (2017)[23]	57 sites in Japan	S-1	222	NA	Dose: 80 mg/m²; Cycle: twice daily in the first cycle for 28 days. Then, patients underwent a minimum 14-day drug-free period followed by a second cycle.	Disease progression=66%; AE=34%	0=85%; 1=15%	A=3%; B=31%; C=66%	A=81%; B=19%	<400=59%; ≥400=41%

Table 2. - *(continued)*

Study (Year)	Region	Group	Sample size	Best supportive care	Second-line treatment characteristics	Reason for discontinuation of sorafenib	ECOG score	BCLC performance status	Child-Pugh class	AFP, ng/mL
		Placebo	111			Disease progression=69%; AE=31%	0=81%; 1=19%	A<1%; B=32%; C=67%	A=81%; B=19%	<400=56%; ≥400=44%
Rimassa (2018)[24]	Europe, Americas, Oceania	Tivantinib	226	NA	120 mg twice daily	Radiographic progression=82%; Intolerance=17%	0=62%; 1=38%	A=7%; B=12%; C=81%	A=95%	>200=43%; Median (range)=149 (2–347,837)
		Placebo	114			Radiographic progression=78%; Intolerance=21%	0=58%; 1=42%	A=6%; B=15%; C=79%	A=95%	>200=42%; Median (range)=509 (2–440,008)
Zhu (2019)[25]	Europe, Asia, Americas, Oceania	Ramucirumab	197	Y	Intravenous ramucirumab (8 mg/kg) or placebo for 1 h every 14 days	Progressive disease=84%; Intolerance=16%	0=57%; 1=43%;	B=17%; C=83%	A=100%	≥400=100%; Median (range)=3,920 (1,175–20,000)
		Placebo	95	Y		Progressive disease=80%; Intolerance=20%	0=58%; 1=42%;	B=21%; C=79%	A=100%	≥400=100%; Median (range)=2,741 (1,178–11,681)
Moehler (2019)[26]	Europe, Asia, North America	Pexa-Vec	86	Y	Doses of 10^9 plaque forming units intravenously on day 1 followed by up to 5 intratumoral treatments at day 8 and weeks 3, 6, 12 and 18.	Intolerance=13%; Radiographic progression=87%	2=95%; 2=5%	B=13%; C=87%	A=88%; B=12%	200=62%; Median (range)=863 (2–1,802,066);
		Best Supportive Care	43	Y	—	Intolerance=12%; Radiographic progression=88%	2=100%; 2=0%	B=21%; C=79%	A=86%; B=14%	>200=50%; Median (range)=398 (1–516,204)

AE, adverse event; BCLC, The Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; NA, Not described in the study; Pexa-Vec, Pexastimogene devacirepvec.

Efficacy

DCR: Five studies[20,21,23–25] used RECIST (Response Evaluation Criteria in Solid Tumors), two studies[19,26] used modified RECIST (mRECIST) and one study[22] used both RECIST and mRECIST to assess tumor response (Table 3). DCR was reported in all the studies,[19–25] ranging from 13% to 65% in the second-line treatment group and 19% to 50% in the control group (Table 3). The random-effects meta-analysis showed that the RR for DCR was 1.36 (95% CI: 1.16–1.60, p=0.0002) with high heterogeneity (I^2=71%, p=0.001), suggesting that DCR may be significantly improved in the second-line treatment group (Fig. 2A). However, among these therapies, only tivantinib[24] and pexastimogene devacirepvec (Pexa-Vec)[26] might be unable to increase DCR. Sensitivity analysis did not change the heterogeneity significantly.

OS: In the included eight studies,[19–26] median OS in the second-line treatment group ranged from 4.2 to 11.1 months, while in the control group it ranged from 4.4 to 11.2 months (Table 3). Seven studies[20–26] provided HRs and 95% CIs of OS. The random-effects meta-analysis showed no difference in OS between two groups (HR=0.87, 95% CI: 0.74–1.01, p=0.06) with high heterogeneity (I^2=62%, p=0.02) (Fig. 2B). However, ramucirumab in patients with increased AFP concentrations (HR=0.71, 95% CI: 0.53–0.95)[25] and regorafenib (HR=0.63, 95% CI: 0.50–0.79)[22] appeared to significantly prolong OS, indicating that they might be superior to other second-line treatments.

Sensitivity analysis by omitting Bruix 2017[22] reduced the heterogeneity significantly (I^2=28%, p=0.22) with the HR of 0.92 (95% CI: 0.81–1.03, p=0.16), which might be the reason for the high heterogeneity.

TTP: All the studies[19–26] provided available data on TTP. Median TTP ranged from 1.8 to 4.2 months in the second-line treatment group and 1.4 to 3 months in the controlled group (Table 3). We used the random-effects model for when heterogeneity was high (I^2=85%, p<0.00001), and sensitivity analysis made no difference to it. It showed that TTP was significantly improved in the second-line treatment group (HR=0.64, 95% CI: 0.51–0.81, p=0.0002) (Fig. 2C). What's more, regorafenib in Bruix 2017[22] (HR=0.44, 95% CI: 0.36–0.54) and ramucirumab in Zhu 2019[25] (HR=0.43, 95% CI: 0.31–0.58) seemed to have an advantage over the other therapies in TTP.

PFS: Five studies[21–25] presented data of PFS. Median PFS reported in these five studies ranged from 2.1 to 3.1 months in the second-line treatment group and 1.4 to 2.1 months in the placebo group (Table 3). The HR for PFS was 0.60 (95% CI: 0.46–0.77, p<0.0001) by the random-effects model, with a high heterogeneity (I^2=83%, p<0.0001) (Fig. 2D), indicating that the second-line treatment, especially regorafenib (HR=0.46, 95% CI: 0.37–0.57)[22] and ramucirumab (HR=0.45, 95% CI: 0.34–0.60),[25] might improve PFS. Sensitivity analysis did not change the heterogeneity significantly.

Safety

The most frequently reported AEs are shown in Table 4.[19–26] There was a slight difference in AEs of any grade (RR=1.07, 95% CI: 1.00–1.14, p=0.03) between the two groups.[19,20,22–24,26] The rate of decreased appetite (RR=1.58, 95% CI: 1.15–2.16, p=0.005),[19–21,23–26] edema peripheral (RR=1.91, 95% CI: 1.59–2.29, p<0.00001),[20,21,23–26] diarrhea (RR=1.73, 95% CI: 1.33–2.24, p<0.0001),[19–26] pyrexia (RR=2.64, 95% CI: 2.04–3.40, p<0.00001),[20–23,25,26] fatigue (RR=1.43, 95% CI: 1.14–1.80, p=0.002),[19–26] nausea (RR=1.37, 95% CI: 1.15–1.64, p=0.0004),[19–26] and

vomiting (RR=1.61, 95% CI: 1.07–2.42, p=0.02)[20–23,25,26] appeared to be higher in the second-line treatment group. No difference was found in abdominal pain (RR=0.99, 95% CI: 0.85–1.15, p=0.90),[19–26] ascites (RR=1.33, 95% CI: 0.95–1.86, p=0.10),[20–26] or constipation[20–23,25,26] (RR=1.06, 95% CI: 0.75–1.50, p=0.74).

For efficacy and safety, subgroup analysis of sample size failed to reduce the high heterogeneity and it was hard to carry out other subgroup analyses. The results of sensitivity analysis and subgroup analysis are shown in Supplementary Tables 1 and 2, respectively.

Discussion

This meta-analysis comprehensively analyzed the efficacy and safety of the second-line treatment after sorafenib failure in patients with advanced HCC. From the result, we found that DCR, TTP, and PFS were significantly improved by the second-line treatments of patients with advanced HCC after sorafenib failure. However, similar to a relevant meta-analysis,[27] no statistical difference in OS was observed between the two groups. It might indicate that DCR, TTP, and PFS do not accurately correlate with OS in advanced HCC.[13,28,29] Brivanib (BRISK-PS),[19] S-1 (S-CUBE),[23] tivantinib (METIV-HCC),[24] everolimus (EVOLVE-1),[20] ramucirumab (REACH),[21] and Pexa-Vec[26] did not meet the primary endpoint (i.e. OS). The poor outcome of OS improvement may due to the following reasons: high molecular heterogeneity of HCC;[27] patients enrolled with favorable prognosis;[19,23] and, imbalanced stratification. However, compared with REACH, ramucirumab in REACH-2 significantly improved OS,[25] which might have been caused by the poor prognosis and more aggressive tumor features in patients with increased AFP.[30] In our study, we found that regorafenib seemed to be the most effective second-line treatment after sorafenib failure, which not only showed significant improvements in OS but also seemed to have more advantages in DCR, TTP and PFS.[22] Regorafenib has also been recommended by the USA's National Comprehensive Cancer Network (NCCN) for patients with Child-Pugh liver function class A who have disease progression on or after sorafenib.[31] Therefore, it may be possible for regorafenib to be considered as the standard second-line treatment. However, more studies are needed to prove its safety and improvement in efficacy. Compared with the controlled groups, second-line treatments may lead to a higher rate of AEs.

Unlike the previous studies, we analyzed not only OS but also other outcomes, including DCR, TTP, and PFS comprehensively, at the overall level. Another advantage of this meta-analysis was that all the studies included were multicenter RCTs and the quality of them was satisfactory in general. However, there were a few limitations of this meta-analysis. (1) The heterogeneity level was high in this study. Several possible hypotheses may be proposed to explain it; first, the different antitumor mechanisms of each drug may lead to various results of both efficacy and safety. For example, Brivanib works as a TKI of vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) receptor,[32,33] while tivantinib is a TKI targeting the MET receptor.[34,35] Second, the high heterogeneity may be attributed to different baseline characteristics among these studies, such as different AFP levels and ECOG performance status. Third, the usage of different criteria for tumor progression evaluation may also result in high heterogeneity because there are some inconsistencies in defining new lesions between RECIST 1.1 and mRECIST.[28] Subgroup analysis of sample size and Child-Pugh liver function classification failed to reduce the heterogeneity and it was hard to carry out other subgroup analyses. Moreover, sensitivity analysis

Table 3. OS, TTP, PFS, and DCR in the included studies

Study (Year)	Response Criteria	Group	Median OS in months	Median TTP in months	Median PFS in months	DCR
Llovet (2013)[19]	mRECIST	Brivanib	9.4	4.2	NA	61%
		Placebo	8.2	2.7	NA	40%
Zhu (2014)[20]	RECIST version 1.0	Everolimus	7.6 (95% CI: 6.7–8.7)	3.0 (95% CI: 2.8–4.0)	NA	56.1% (95% CI: 50.8–61.3%)
		Placebo	7.3 (95% CI: 6.3–8.7)	2.6 (95% CI: 1.5–2.8)	NA	45.1% (95% CI: 37.8–52.6%)
Zhu (2015)[21]	RECIST version 1.1	Ramucirumab	9.2 (95% CI: 8.1–10.6)	3.5 (95% CI: 2.8–4.5)	2.8 (95% CI: 2.7–3.9)	56% (95% CI: 50.4–61.8%)
		Placebo	7.6 (95% CI: 6.0–9.3)	2.6 (95% CI: 1.6–2.8)	2.1 (95% CI: 1.6–2.7)	46% (95% CI: 40.0–51.6%)
Bruix (2017)[22]	mRECIST and RECIST version 1.1	Regorafenib	10.6 (95% CI: 9.1–12.1)	3.2 (95% CI: 2.9–4.2)	3.1 (95% CI: 2.8–4.2)	65%
		Placebo	7.8 (95% CI: 6.3–8.8)	1.5 (95% CI: 1.4–1.6)	1.5 (95% CI: 1.4–1.6)	36%
Kudo (2017)[23]	RECIST version 1.1	S-1	11.1 (95% CI: 9.7–13.1)	2.6 (95% CI: 2.6–2.8)	2.6 (95% CI: 2.6–2.8)	43% (95% CI: 37–50%)
		Placebo	11.2 (95% CI: 9.2–12.8)	1.4 (95% CI: 1.3–2.3)	1.4 (95% CI: 1.3–2.3)	24% (95% CI: 17–33%)
Rimassa (2018)[24]	RECIST version 1.1	Tivantinib	8.4 (95% CI: 6.8–10.0)	2.4 (95% CI: 1.9–3.6)	2.1 (95% CI: 1.9–3.0)	50%
		Placebo	9.1 (95% CI: 7.3–10.4)	3.0 (95% CI: 1.9–3.7)	2.0 (95% CI: 1.9–3.6)	50%
Zhu (2019)[25]	RECIST version 1.1	Ramucirumab	8.5 (95% CI: 7.0–10.6)	3.0 (95% CI: 2.8–4.2)	2.8 (95% CI: 2.8–4.1)	59.9% (95% CI: 53.1–66.7%)
		Placebo	7.3 (95% CI: 5.4–9.1)	1.6 (95% CI: 1.5–2.7)	1.6 (95% CI: 1.5–2.7)	38.9% (95% CI: 29.1–48.8%)
Moehler (2019)[26]	mRECIST	Pexa-Vec	4.2	1.8 (95% CI: 1.5–2.8)	NA	13% (95% CI: 7–22%)
		Best Supportive Care	4.4	2.8 (95% CI: 1.5 to not unable to evaluate due to censoring)	NA	19% (95% CI: 8–33%)

CI, confidence interval; DCR, disease control rate; mRECIST, modified Response Evaluation Criteria in Solid Tumors; NA, Not described in the study; OS, overall survival; PFS, progression-free survival; Pexa-Vec, pexastimogene devacirepvec; RECIST, Response Evaluation Criteria in Solid Tumors; TTP, time to progression.
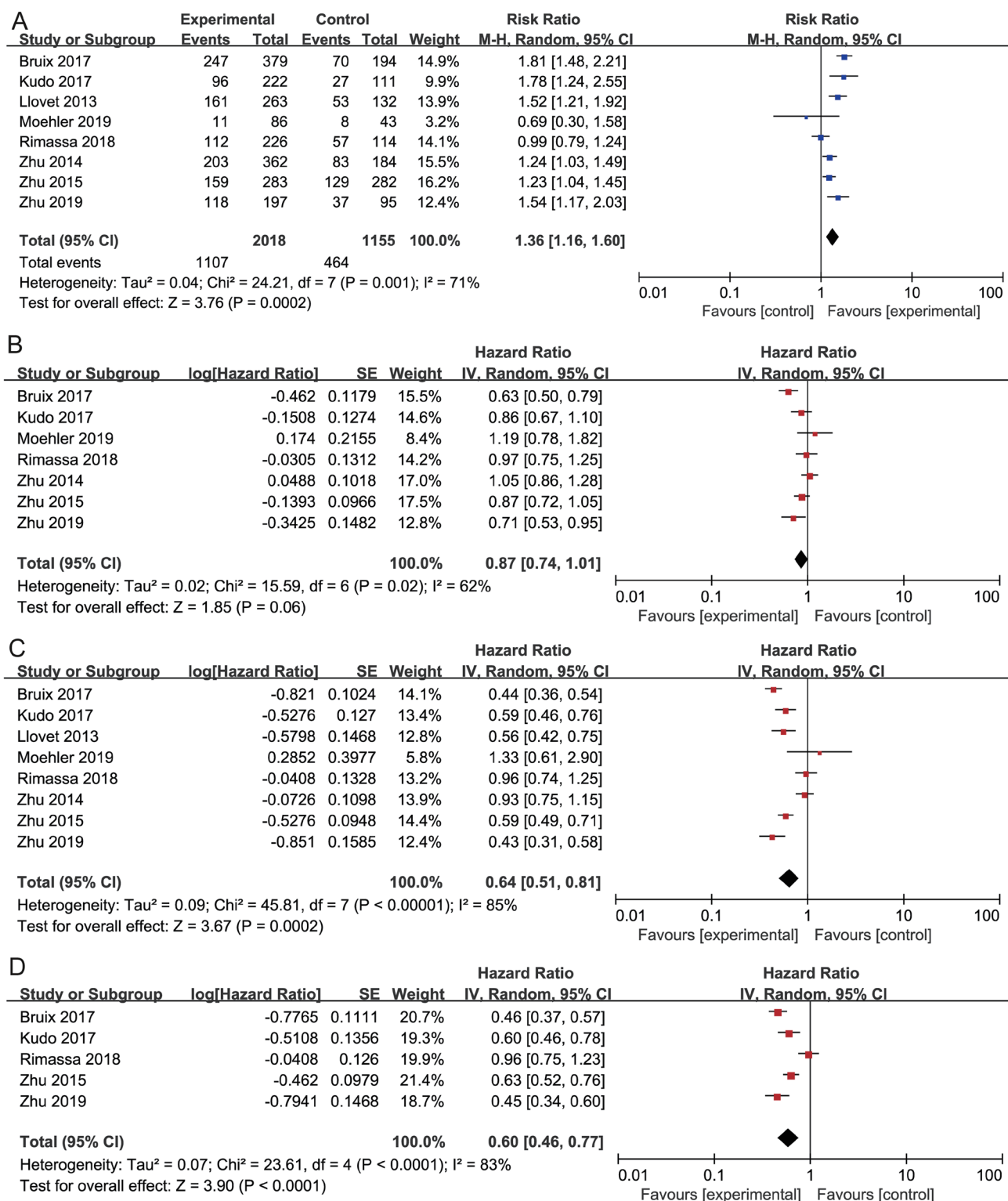
Fig. 2. Efficacy. (A) DCR. (B) OS. (C) TTP. (D) PFS. DCR, disease control rate; OS, overall survival; PFS, progression-free survival; TTP, time to progression; CI, confidence interval.

did not reduce the heterogeneity of many results, such as DCR, TTP and PFS. (2) Only a small number of studies were included, which might affect the reliability of this study. (3)

Some statistical analysis methods were limited, such as assessing heterogeneity by evaluating I^2.

In view of the poor improvement in OS, future explora-

Table 4. Comparison of AEs between the second-line treatment group and control group

AE	Total no. events/ patients (%) in the second-line treatment group	Total no. events/patients (%) in the controlled group	RR (95% CI), *p*	*I²*, *p*
Adverse events of any grade[19,20,22–24,26]	1,345/1,527 (88.1)	631/756 (83.5)	1.07 (1.00–1.14), 0.03	80%, 0.0002
Decreased appetite[19–21,23–26]	445/1,627 (27.4)	156/934 (16.7)	1.58 (1.15–2.16), 0.005	68%, 0.005
Edema peripheral[20,21,23–26]	390/1,366 (28.6)	126/803 (15.7)	1.91 (1.59–2.29), 0.00001	0%, 0.64
Diarrhoea[19–26]	515/2,001 (25.7)	154/1,127 (13.7)	1.73 (1.33–2.24), 0.0001	55%, 0.03
Pyrexia[20–23,25,26]	328/1,515 (21.7)	69/882 (7.8)	2.64 (2.04–3.40), 0.00001	48%, 0.09
Fatigue[19–26]	583/2,001 (29.1)	232/1,127 (20.6)	1.43 (1.14–1.80), 0.002	59%, 0.02
Abdominal pain[19–26]	391/2,001 (19.5)	220/1,127 (19.5)	0.99 (0.85–1.15), 0.90	26%, 0.22
Nausea[19–26]	382/2,001 (19.1)	158/1,127 (14.0)	1.37 (1.15–1.64), 0.0004	39%, 0.12
Ascites[20–26]	335/1,740 (19.3)	151/996 (15.2)	1.33 (0.95–1.86), 0.10	70%, 0.002
Vomiting[20–23,25,26]	237/1,776 (13.3)	93/1,013 (9.2)	1.61 (1.07–2.42), 0.02	59%, 0.02
Constipation[20–23,25,26]	209/1,515 (13.8)	112/882 (12.7)	1.06 (0.75–1.50), 0.74	56%, 0.05

AE, adverse event.

tion of more effective therapies for patients with HCC after sorafenib failure is urgently needed. Also, further studies to prove the good outcomes of regorafenib and to explore its biological mechanisms are necessary. Furthermore, when conducting clinical trials of the second-line treatments, a more detailed patient stratification, such as the stratification of biomarkers, should be considered in the aim of predicting treatment efficacy and helping select additional therapies.[36]

Conclusions

Our findings indicate that the second-line treatments significantly improved DCR, TTP, and PFS for patients with advanced HCC who progressed during or after sorafenib or were intolerant to the drug. However, improvement in OS was not observed and the second-line treatments led to a higher rate of adverse events. Regorafenib may be possibly considered as the standard second-line treatment. However, further studies to prove its good outcomes are necessary. In the future, more effective therapies and more specific patient stratification are needed to improve survival.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Contributed to concept, searched literature, collected the data (LA, HL, KY), analyzed the data, wrote the manuscript (LA, HL), revised the manuscript (KY), all authors read and approved the final manuscript.

Data sharing statement

No additional data are available.

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