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SYSTEMATIC REVIEW

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Efficacy and safety of second-line therapies for advanced hepatocellular carcinoma: a network meta-analysis of randomized controlled trials

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Abstract

Background The selection of appropriate second-line therapy for liver cancer after first-line treatment failure poses a significant clinical challenge due to the lack of direct comparative studies and standard treatment protocols. A network meta-analysis (NMA) provides a robust method to systematically evaluate the clinical outcomes and adverse effects of various second-line treatments for hepatocellular carcinoma (HCC).

Methods We systematically searched PubMed, Embase, Web of Science and the Cochrane Library to identify phase III/IV randomized controlled trials (RCTs) published up to March 11, 2024. The outcomes extracted were median overall survival (OS), median progression-free survival (PFS), time to disease progression (TTP), disease control rate (DCR), objective response rate (ORR), and adverse reactions. This study was registered in the Prospective Register of Systematic Reviews (CRD42023427843) to ensure transparency, novelty, and reliability.

Results We included 16 RCTs involving 7,005 patients and 10 second-line treatments. For advanced HCC patients, regorafenib (HR = 0.62, 95%CI: 0.53–0.73) and cabozantinib (HR = 0.74, 95%CI: 0.63–0.85) provided the best OS benefits compared to placebo. Cabozantinib (HR = 0.42, 95%CI: 0.32–0.55) and regorafenib (HR = 0.46, 95% CI: 0.31–0.68) also offered the most significant PFS benefits. For TTP, apatinib (HR = 0.43, 95% CI: 0.33–0.57), ramucirumab (HR = 0.44, 95% CI: 0.34–0.57), and regorafenib (HR = 0.44, 95% CI: 0.38–0.51) showed significant benefits over placebo. Regarding ORR, ramucirumab (OR = 9.90, 95% CI: 3.40–42.98) and S-1 (OR = 8.68, 95% CI: 1.4–154.68) showed the most significant increases over placebo. Apatinib (OR = 3.88, 95% CI: 2.48–6.10) and cabozantinib (OR = 3.53, 95% CI: 2.54–4.90) provided the best DCR benefits compared to placebo. Tivantinib showed the most significant advantages in terms of three different safety outcome measures.

Conclusions Our findings suggest that, in terms of overall efficacy and safety, regorafenib and cabozantinib are the optimal second-line treatment options for patients with advanced HCC.

Keywords Hepatocellular carcinoma, Second-line, Network meta-analysis, Efficacy, Safety

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most prevalent cancer globally and the third leading cause of cancer-related mortality. World Health Organization (WHO) projections indicate that liver cancer incidence will increase by 55.0% between 2020 and 2040, leading to an estimated 1.3 million deaths. This represents a significant 56.4% rise from 2020 statistics [1].

HCC is the predominant subtype of liver cancer, accounting for approximately 90% of cases [2]. Primary treatments for early-stage HCC include liver resection, transplantation, and radiofrequency ablation [3]. However, due to the lack of early clinical symptoms, over 50% of cases are diagnosed at an advanced stage, making surgical interventions unsuitable [4]. Immune checkpoint inhibitors (ICIs), tyrosine kinase inhibitors (TKIs), and monoclonal antibodies are now the primary treatments for advanced liver cancer, enhancing patient survival and quality of life [5].

In first-line treatment, immunotherapy and immune-based combinations (paired with TKIs or anti-angiogenic drugs, among others) have emerged as one of the most promising therapeutic strategies evaluated in recent years [6, 7]. However, due to the significant heterogeneity of liver cancer, the susceptibility to resistance of multi-kinase target drugs, and the adverse reactions of ICIs (such as elevated transaminase levels) [8, 9], disease progression and recurrence can occur post-initial treatment, leading to multiple second-line treatment recommendations in guidelines [10]. Second-line treatments include targeted therapies (e.g., sorafenib, lenvatinib), immunotherapies (e.g., nivolumab, pembrolizumab), radioembolization with Yttrium-90, chemotherapeutic agents (e.g., cabozantinib, regorafenib), or participation in clinical trials for novel therapies [11, 12]. These treatments aim to target various aspects of cancer cells or the tumor microenvironment to manage the disease and improve patient outcomes. However, clinical guidelines lack consensus on second-line treatments for liver cancer due to limited evidence post-sorafenib failure and insufficient high-level evidence for new first-line regimens [13, 14].

With the increasing number of randomized controlled trials (RCTs), most compare second-line treatments against placebo. Therefore, establishing optimal second-line treatment strategies is crucial for designing future head-to-head clinical studies. To address this, we have integrated data from several large phase III clinical trials to perform indirect comparisons of key outcomes, including overall survival (OS), progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), time to progression (TTP), adverse events (AEs), incidence of grade 3-4AEs, and treatment discontinuations. This network meta-analysis (NMA) of second-line treatments aims to provide valuable insights into their effectiveness, thereby aiding in clinical decision-making for liver cancer treatment.

Methods

This NMA adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement [15]. The study protocol has been registered in the Prospective Register of Systematic Reviews (CRD42023427843) to ensure transparency, reliability, and novelty.

Literature search

The search was conducted across databases, including PubMed, Embase, Web of Science, and the Cochrane Library. Additional manual searches of references were performed to prevent any oversights. The search terms utilized were "hepatocarcinoma," "hepatocellular carcinoma," "second-line," "immunotherapy," and "targeted therapy." The search period spans from the inception of each database to March 10, 2024. The details of all search strategies employed for the four targeted databases are presented in Table S1, following the completion of the electronic search.

Inclusion and exclusion criteria

Inclusion criteria

All clinical studies included in the analysis adhered to the PICOS criteria [16]:

1) Patients aged 18 years or older with advanced HCC who have received first-line treatments.
2) Patients who received a second-line treatment in phase III/IV prospective RCTs.
3) Comparator options included systemic therapy, placebo, or best supportive care.
4) Prognoses included at least one of the following components: OS, PFS, TTP, ORR, DCR, the rate of all grade and grade 3-4AEs, and the rate of treatment discontinuation due to AEs.
5) Publications were restricted to those in English.

Exclusion criteria

1) Duplicated publications.
2) Inability to fully obtain outcome measures (e.g., some outcome measures not reported using mean and variance or data errors).

Literature selection

Two researchers independently screened literature titles and abstracts based on inclusion and exclusion criteria, excluding studies that did not meet the criteria. Full-text screening was then conducted to select studies for inclusion. EndNote software was used for literature management, and an Excel spreadsheet was created to extract data. In cases of disagreement during screening, a third researcher assessed the studies, and consensus was reached through discussion.

Data extraction

Extracted data included:

1) Basic information of the clinical trial, including authorship, publication date, and clinical trial registration number.
2) Study design of the clinical trial, including sample size, allocation, intervention model, masking, and primary purpose.
3) Basic characteristics of included patients, including gender ratio, median age, and baseline liver condition.
4) Treatments of the experimental and control groups.
5) Outcomes of the study, including PFS, OS, ORR, DCR, the rate of all grade and grade 3-4AEs, and the rate of treatment discontinuation due to AEs.

Quality assessment

According to the Cochrane Handbook version 5.1.0, the quality of included studies was assessed using recommended tools for evaluating bias risk. This assessment covered random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of data, selective outcome reporting, and other biases. The risk levels for the included RCT studies were categorized as low risk, high risk, and unclear.

Statistical analysis

The primary endpoints were OS, PFS, TTP, ORR, and DCR. The secondary endpoints included all-grade and grade 3–4 AEs and the rate of treatment discontinuation due to AEs. Hazard ratios (HRs) with 95% confidence intervals (CIs) were used as effect measures for OS, PFS, and TTP, while odds ratios (ORs) with 95% CIs were used for ORR, DCR, all-grade and grade 3–4 AEs, and the rate of treatment discontinuation due to AEs.

NMA was conducted within a Bayesian framework using the "rjags" and "gemtc" packages in R software to evaluate the efficacy and safety of second-line therapies for advanced HCC. A fixed-effects model was employed to establish three independent Markov chains, each running 20,000 burn-in iterations followed by 50,000 sampling iterations. The iteration results of the Markov chains, represented as HRs and ORs, were used to rank the efficacy and safety of the different treatment regimens, with the findings visualized through graphical representations. Publication bias was assessed using funnel plots.

Results

Study selection

Preliminary retrieval yielded 597 relevant articles, of which 263 remained after deduplication. Following screening of titles and abstracts to exclude review articles, experimental studies, and conference papers, 160 articles were retained. After full-text review and adherence to inclusion and exclusion criteria, a total of 16 articles were included [17–32]. Finally, the study involved a total of 7,005 participants, with 4,573 in the experimental group and 2,432 in the control group. The literature screening process is depicted in Fig. 1.

Study and characteristics

All included studies were prospective, phase III clinical RCTs. A total of 11 studies were multi-center, 2 were conducted in mainland China, and of the remaining trials, 2 were in USA and 1 in Japan. The drugs tested in the active treatments were pembrolizumab (2), ramucirumab (3), apatinib (1), cabozantinib (2), tivantinib (2), regorafenib (2), ADI-PEG20 (1), S-1 (1), everolimus (1), brivanib (1). The included populations were not discernibly different. The results of the risk of bias are provided in Fig. 2. No trials directly compared different active treatments, and detailed characteristics of the included studies are presented in Table 1.

Network *meta*-analyses

Comparisons of OS, PFS

The primary outcomes of this study were OS and PFS. The NMA included 10 second-line treatment regimens reporting OS (Fig. 3A) and 8 regimens reporting PFS (Fig. 3B) for patients with HCC.

Regarding OS, 16 studies were included, encompassing a total of 10 different treatment regimens: pembrolizumab (2), everolimus (1), brivanib (1), apatinib (1), cabozantinib (2), ADI-PEG20 (1), tivantinib (2), S-1 (1), regorafenib (2),and ramucirumab (3). Due to the lack of a closed-loop structure, a consistency model was used.

Compared to the placebo group, regorafenib (HR = 0.62, 95% CI: 0.53–0.73) provided the best OS benefit, followed by cabozantinib (HR = 0.74, 95% CI: 0.63–0.85), apatinib (HR = 0.78, 95% CI: 0.62–1.00), and

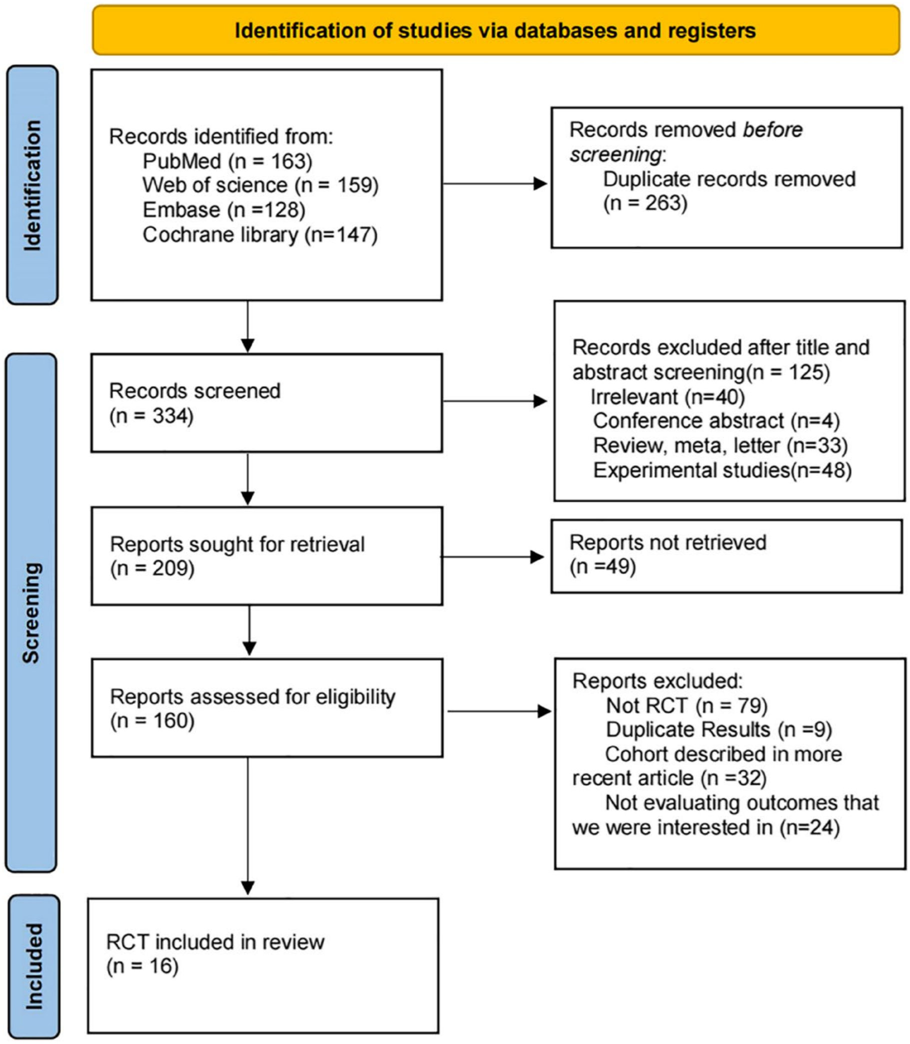

Fig. 1 Flowchart of study identification and selection process

pembrolizumab (HR = 0.79, 95% CI: 0.67–0.93). Everolimus (HR = 1.05, 95% CI: 0.86–1.27) was the only second-line treatment that did not show an OS benefit compared to placebo (Fig. 4A).

Regarding PFS, 13 studies were included, encompassing a total of 8 different treatment regimens: pembrolizumab (2), apatinib (1), cabozantinib (2), ADI-PEG20 (1), tivantinib (2), S-1 (1), regorafenib (2), and ramucirumab (3). Due to the lack of a closed-loop structure, a consistency model was used.

Almost all second-line treatments provided better PFS compared to the placebo group, with the sole exception being ADI-PEG20 (HR = 1.17, 95% CI: 0.80–1.72), which showed the least PFS benefit among all treatments. Among second-line treatments, cabozantinib (HR = 0.42, 95% CI: 0.32–0.55) and regorafenib (HR = 0.46, 95% CI: 0.31–0.68) offered the greatest PFS benefits compared to placebo, followed by apatinib (HR = 0.47, 95% CI: 0.32–0.70), ramucirumab (HR = 0.55, 95% CI: 0.42–0.69), and S-1 (HR = 0.60, 95% CI: 0.40–0.90). Additionally, pembrolizumab (HR = 0.73, 95% CI: 0.55–0.69) also provided significant PFS benefits compared to placebo (Fig. 4B).

Comparisons of TTP, ORR and DCR

The secondary outcomes of this study were TTP, ORR, and DCR. The NMA included 7 second-line treatment regimens for TTP (Fig. 3C), 8 for ORR (Fig. 3D), and 9 for DCR (Fig. 5A) in patients with HCC.

Regarding TTP, 10 studies were included, encompassing a total of 7 different treatment regimens: everolimus (1), brivanib (1), apatinib (1), tivantinib (1), S-1 (1), regorafenib (2), and ramucirumab (3). Due to the lack of a closed-loop structure, a consistency model was used.

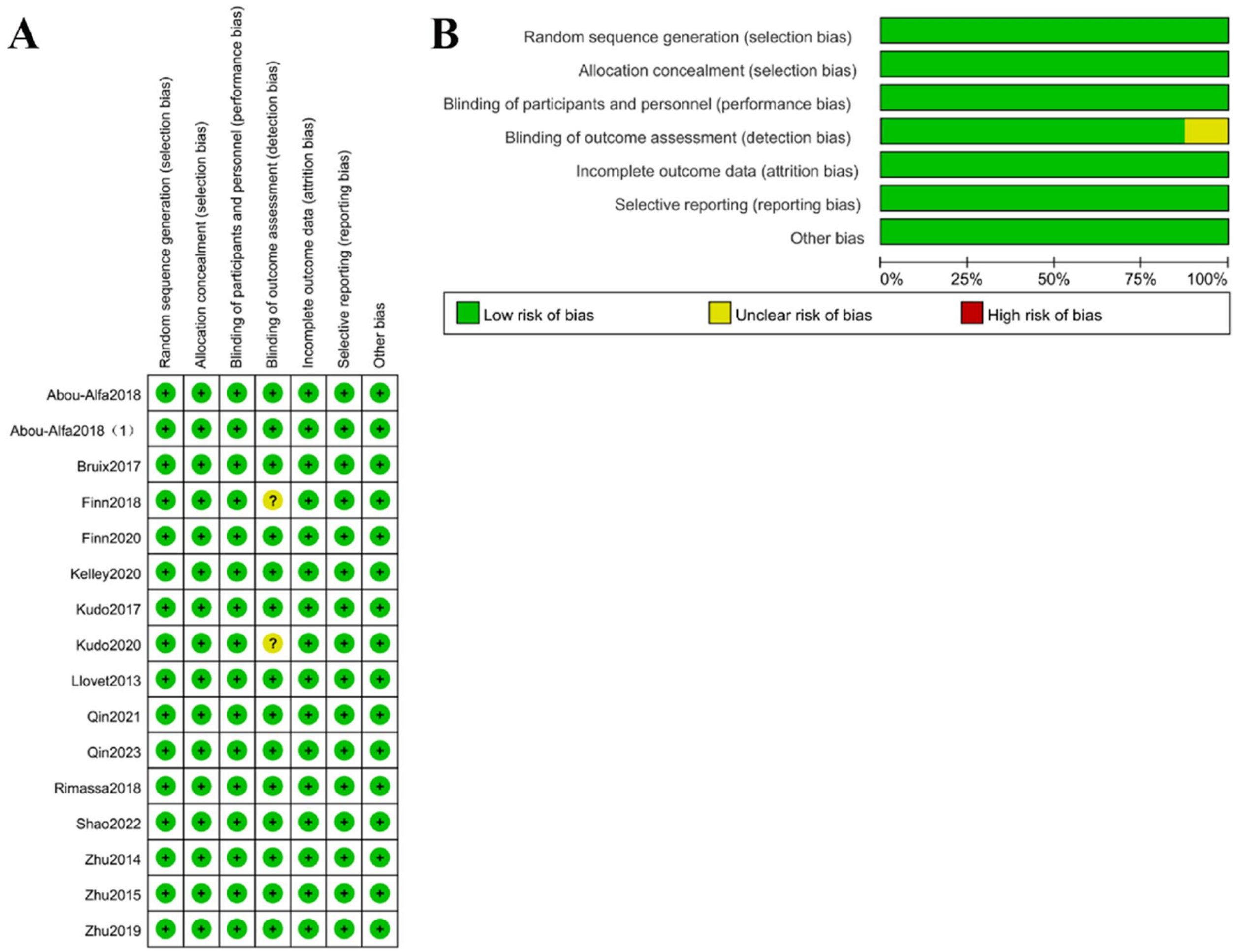

Fig. 2 The risk of bias of included studies. **A** Methodological quality summary: authors' judgment about each methodological quality item for each included study. Performance bias and detection bias presented were for risk of bias; (**B**) Methodological quality graph: authors' judgment about each methodological quality item presented as percentages across all included studies

All second-line treatments showed benefits compared to the placebo group. Apatinib (HR = 0.43, 95% CI: 0.33–0.57), ramucirumab (HR = 0.44, 95% CI: 0.34–0.57), regorafenib (HR = 0.44, 95% CI: 0.38–0.51), brivanib (HR = 0.56, 95% CI: 0.42–0.75), and S-1 (HR = 0.59, 95% CI: 0.46–0.76) provided significant benefits compared to the placebo group. Further comparisons of the active interventions suggest that apatinib (HR = 0.47, 95% CI: 0.33–0.65) and brivanib (HR = 0.60, 95% CI: 0.42–0.87) are superior to everolimus and tivantinib. Ramucirumab (HR = 0.46, 95% CI: 0.32–0.67), regorafenib (HR = 0.46, 95% CI: 0.34–0.62), and S-1 (HR = 0.61, 95% CI: 0.43–0.88) are also superior to tivantinib (Fig. 6C).

Regarding ORR, 12 studies were included, encompassing a total of 8 different treatment regimens: cabozantinib (2), apatinib (1), tivantinib (1), brivanib (1), S-1 (1), regorafenib (1), ramucirumab (3), and pembrolizumab (2). Due to the lack of a closed-loop structure, a consistency model was used.

Except for tivantinib (OR = 0.46, 95% CI: 0.01–17.43), all second-line treatments significantly improved ORR compared to the placebo group. Ramucirumab (OR = 9.90, 95% CI: 3.4–42.98), S-1 (OR = 8.68, 95% CI: 1.40–154.68), and cabozantinib (OR = 6.95, 95% CI: 2.40–31.31) showed the most significant improvements compared to placebo. Pembrolizumab (OR = 6.92, 95% CI: 3.47–15.86), apatinib (OR = 5.92, 95% CI: 2.00–27.35), and brivanib (OR = 5.23, 95% CI: 1.71–24.27) also showed considerable improvements compared to placebo (Fig. 6D).

Regarding DCR, 12 studies were included, covering 9 different treatment regimens: pembrolizumab (2), everolimus (1), cabozantinib (1), brivanib (1), apatinib (1), tivantinib (1), S-1 (1), regorafenib (1), and ramucirumab

Table 1 Baseline characteristics of studies included in the network meta-analysis

Study name	Trial registration number	Sex- Male no. (%) (experimental/control)	Age-(Median age (range)) (experimental/ control)	Macrovascular invasion-no. (%) (experimental/ control)	Extrahepatic spread-no. (%) (experimental/ control)	Child–Pugh liver -no. (%) classification A (experimental/ control)	BCLC stage C-no. (%) (experimental/ control)	ECOG0(%) (experimental/ control)	arm(n) (experimental/ control)
Qin 2023 [26]	NCT03062358	257 (85.7%)/ 126 (82.4%)	54 (22 – 82)/ 54 (22 – 78)	33 (11.0%)/ 17 (11.1%)	232 (77.3%)/ 120 (78.4%)	300(100%)/ 153(100%)	277 (92.3%)/ 146 (95.4%)	124 (41.3%) / 60 (39.2%)	pembrolizumab (300)/Placebo(153)
Shao 2022 [29]	NCT02435433	55 (78.6%)/ 31 (91.2%)	57 (24 – 80)/ 55 (31 – 76)	24 (34.3%)/ 13 (38.2%)	50 (71.4%)/ 27 (79.4%)	70(100%)/ 34(100%)	60 (85.7%)/ 32 (94.1%)	35 (50.0%)/ 17 (50.0%)	Ramucirumab(70)/ Placebo(34)
Qin 2021 [27]	NCT02329860	223 (85.0%)/ 116 (88.0%)	51 (27–78)/ 50 (25–77)	68 (26.0%)/ 29 (22.0%)	205 (79.0%)/ 106 (80.0%)	249 (95.0%)/ 123 (93.0%)	233 (89.0%)/ 122 (92.0%)	65 (25.0%)/ 33 (25.0%)	Apatinib(261)/pla-cebo(132)
Kelley 2020 [22]	NCT01908426	264 (80.0%)/ 144 (88.0%)	63.0 (22–86)/ 63.5 (34–86)	84 (25.0%)/ 61 (37.0%)	255 (77.0%)/ 122 (74.0%)	/	/	186 (56.0%)/ 96 (59.0%)	Cabozantinib(331)/ Placebo(164)
Kudo 2020 [24]	NCT02029157	110 (82.1%)/ 52 (85.2%)	70 (36 – 86)/ 72 (47 – 83)	34 (25.4%)/ 17 (27.9%)	/	130 (97.0%)/ 59 (96.7%)	89 (66.4%)/ 35 (57.4%)	111 (82.8%) / 51 (83.6%)	Tivantinib (134)/ Placebo(61)
Zhu 2019 [30]	NCT02435433	154 (78.0%)/ 79 (83.0%)	64 (58–73)/ 64 (56–71)	70 (36.0%)/ 33 (35.0%)	141 (72.0%)/ 70 (74.0%)	197 (100%)/ 95 (100%)	163 (83.0%)/ 75 (79.0%)	113 (57.0%)/ 55 (58.0%)	Ramucirumab(197)/ Placebo(95)
Finn 2020 [21]	NCT02702401	226 (81.3%)/ 112 (83.0%)	67(18 – 91)/ 65(23 – 89)	36 (12.9%)/ 16 (11.9%)	195 (70.1%)/ 93 (68.9%)	277(99.6%)/ 133(98.5%)	222 (79.9%)/ 106 (78.5%)	162 (58.3%) / 71 (52.6%)	Pembrolizumab(278)/ placebo(135)
Abou-Alfa 2018 [17, 18]	NCT01908426	379 (81.0%)/ 202 (85.0%)	64 (22–86) / 64 (24–86)	129 (27.0%) / 81 (34.0%)	369 (79.0%) / 182 (77.0%)	/	/	245 (52.0%) / 131 (55.0%)	Cabozantinib(470)/ placebo(237)
Finn 2018 [21]	NCT01774344	/	64 (54–71)/ 62 (55–68)	/	/	373 (98.0%) / 188 (97.0%)	325 (86.0%)/ 172 (89.0%)	247 (65.0%)/ 130 (67.0%)	Regorafenib(379)/ placebo(194)
Abou-Alfa 2018(1) [17]	NCT 01287585	352(83.0%)/ 168(80.0%)	61/ 62	/	/	387(91.0%)/ 188(89.0%)	347(82.0%)/ 170 (81.0%)	/	ADI-PEG(424)/pla-cebo(211)
Rimassa 2018 [28]	NCT01755767	199 (88.0%)/ 107 (94.0%)	66 (19–87)/ 65 (26–84)	79 (35.0%)/ 38 (33.0%)	160 (71.0%)/ 81 (71.0%)	215 (95.0%)/ 108 (95.0%)	184 (81.0%)/ 90 (79.0%)	141 (62.0%)/ 66 (58.0%)	Tivantinib(226)/pla-cebo(114)
Kudo2017 [23]	JapicCTI-090920	183 (82.0%)/ 85 (77.0%)	70 (64–75)/ 70 (64–75)	36 (16.0%)/ 23 (21.0%)	121 (55.0%)/ 58 (52.0%)	104 (47.0%)/ 45 (41.0%)	/	188 (85.0%)/ 90 (81.0%)	S1(222)/placebo(111)
Bruix 2017 [19]	NCT01774344	333 (88.0%)/ 171 (88.0%)	64 (54–71)/ 62 (55–68)	110 (29.0%)/ 54 (28.0%)	265 (70.0%)/ 147 (76.0%)	373 (98.0%)/ 188 (97.0%)	325 (86.0%)/ 172 (89.0%)	247 (65.0%)/ 130 (67.0%)	Regorafenib(373)/ placebo(193)
Zhu 2015 [30]	NCT01140347	236 (83.0%)/ 242 (86.0%)	64 (28–87)/ 62 (25–85)	82 (29.0%)/ 79 (28.0%)	207 (73.0%)/ 200 (71.0%)	82 (29%)/ 79 (28%)	250 (88.0%)/ 248 (88.0%)	159 (56.0%)/ 153 (54.0%)	Ramucirumab (283)/placebo(282)
Zhu 2014 [31]	NCT01035229	303 (83.7%)/ 160 (87.0%)	67.0 (21 – 86)/ 67.0 (21 – 86)	119 (32.9%)/ 60 (32.6%)	269 (74.3%)/ 135 (73.4%)	354 (97.8%)/ 182 (98.9%)	313 (86.5%)/ 158 (85.9%)	214 (59.1%)/ 104 (56.5%)	Everolimus (362)/placebo(184)
Llovet 2013 [25]	NCT00825955	216(82.0%)/113(86.0%)	64(19 – 89)/62(19 – 87)	81(31.0%)/ 24 (18.0%)	171(65.0%)/ 84 (64.0%)	229 (87.0%)/ 112 (85.0%)	242 (92.0%)/ 120(91.0%)	151 (57.0%)/ 81(61.0%)	Brivanib(263)/pla-cebo(132)

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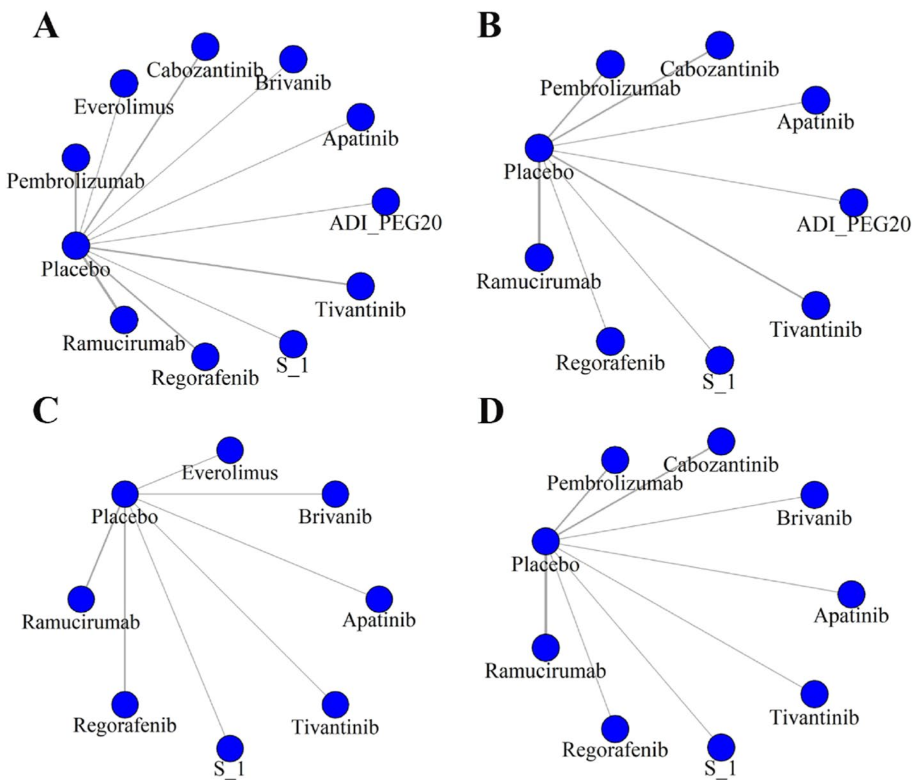

Fig. 3 Network diagram comparing the efficacy of various second-line treatments in patients with advanced HCC. Comparisons were generated using the Bayesian framework on (**A**) OS (**B**) PFS (**C**) TTP (**D**) ORR

A

ADI_PEG	0.77 (0.57, 1.04)	0.87 (0.63, 1.2)	0.72 (0.57, 0.92)	1.03 (0.78, 1.35)	0.77 (0.6, 0.99)	0.98 (0.81, 1.18)	0.8 (0.63, 1.02)	0.61 (0.48, 0.78)	0.84 (0.62, 1.15)	0.89 (0.68, 1.18)
1.3 (0.96, 1.76)	Apatinib	1.13 (0.8, 1.61)	0.94 (0.71, 1.24)	1.34 (0.98, 1.82)	1 (0.75, 1.33)	1.27 (1, 1.62)	1.05 (0.79, 1.39)	0.8 (0.6, 1.06)	1.09 (0.77, 1.55)	1.16 (0.85, 1.59)
1.15 (0.84, 1.58)	0.88 (0.62, 1.25)	Brivanib	0.83 (0.62, 1.11)	1.18 (0.86, 1.62)	0.88 (0.65, 1.19)	1.12 (0.87, 1.45)	0.92 (0.69, 1.24)	0.7 (0.52, 0.95)	0.97 (0.68, 1.37)	1.03 (0.74, 1.42)
1.39 (1.09, 1.76)	1.07 (0.81, 1.42)	1.21 (0.9, 1.62)	Cabozantinib	1.43 (1.12, 1.82)	1.07 (0.86, 1.33)	1.36 (1.17, 1.58)	1.12 (0.91, 1.38)	0.85 (0.68, 1.06)	1.17 (0.88, 1.56)	1.24 (0.97, 1.6)
0.97 (0.74, 1.27)	0.75 (0.55, 1.02)	0.85 (0.62, 1.17)	0.7 (0.55, 0.89)	Everolimus	0.75 (0.58, 0.97)	0.95 (0.78, 1.16)	0.78 (0.61, 1)	0.59 (0.46, 0.77)	0.82 (0.6, 1.12)	0.87 (0.66, 1.16)
1.3 (1.01, 1.67)	1 (0.75, 1.34)	1.13 (0.84, 1.53)	0.94 (0.75, 1.17)	1.34 (1.03, 1.72)	Pembrolizumab	1.27 (1.08, 1.5)	1.05 (0.84, 1.31)	0.8 (0.63, 1)	1.09 (0.81, 1.48)	1.16 (0.89, 1.51)
1.02 (0.85, 1.23)	0.78 (0.62, 1)	0.89 (0.69, 1.15)	0.74 (0.63, 0.85)	1.05 (0.86, 1.27)	0.79 (0.67, 0.93)	Placebo	0.82 (0.71, 0.96)	0.62 (0.53, 0.73)	0.86 (0.67, 1.1)	0.91 (0.74, 1.12)
1.24 (0.98, 1.58)	0.96 (0.72, 1.27)	1.08 (0.8, 1.46)	0.89 (0.72, 1.1)	1.28 (1, 1.64)	0.96 (0.76, 1.19)	1.22 (1.05, 1.42)	Ramucirumab	0.76 (0.61, 0.95)	1.04 (0.78, 1.4)	1.11 (0.86, 1.43)
1.64 (1.28, 2.09)	1.26 (0.94, 1.68)	1.42 (1.05, 1.92)	1.18 (0.95, 1.47)	1.68 (1.3, 2.17)	1.26 (1, 1.58)	1.6 (1.36, 1.88)	1.32 (1.05, 1.64)	Regorafenib	1.38 (1.03, 1.85)	1.46 (1.13, 1.89)
1.19 (0.87, 1.62)	0.91 (0.65, 1.29)	1.04 (0.73, 1.48)	0.86 (0.64, 1.14)	1.22 (0.89, 1.67)	0.91 (0.68, 1.23)	1.16 (0.91, 1.49)	0.96 (0.71, 1.28)	0.73 (0.54, 0.97)	S_1	1.06 (0.77, 1.47)
1.12 (0.85, 1.47)	0.86 (0.63, 1.18)	0.97 (0.7, 1.35)	0.81 (0.63, 1.04)	1.15 (0.87, 1.52)	0.86 (0.66, 1.12)	1.09 (0.89, 1.34)	0.9 (0.7, 1.16)	0.68 (0.53, 0.89)	0.94 (0.68, 1.3)	Tivantinib

B

ADI_PEG	0.4 (0.23, 0.7)	0.36 (0.22, 0.57)	0.62 (0.39, 0.99)	0.86 (0.58, 1.24)	0.47 (0.29, 0.71)	0.39 (0.23, 0.68)	0.51 (0.29, 0.9)	0.74 (0.45, 1.18)
2.48 (1.43, 4.32)	Apatinib	0.89 (0.55, 1.45)	1.55 (0.96, 2.52)	2.12 (1.43, 3.17)	1.16 (0.71, 1.82)	0.97 (0.57, 1.71)	1.27 (0.72, 2.27)	1.84 (1.09, 3.02)
2.78 (1.75, 4.46)	1.12 (0.69, 1.82)	Cabozantinib	1.73 (1.18, 2.56)	2.37 (1.81, 3.11)	1.3 (0.87, 1.82)	1.09 (0.68, 1.77)	1.43 (0.87, 2.33)	2.06 (1.36, 3.04)
1.61 (1.01, 2.58)	0.65 (0.4, 1.05)	0.58 (0.39, 0.85)	Pembrolizumab	1.37 (1.04, 1.81)	0.75 (0.5, 1.06)	0.63 (0.4, 1.01)	0.82 (0.5, 1.35)	1.19 (0.78, 1.78)
1.17 (0.8, 1.72)	0.47 (0.32, 0.7)	0.42 (0.32, 0.55)	0.73 (0.55, 0.96)	Placebo	0.55 (0.42, 0.69)	0.46 (0.31, 0.68)	0.6 (0.4, 0.9)	0.87 (0.63, 1.16)
2.13 (1.41, 3.47)	0.86 (0.55, 1.41)	0.77 (0.55, 1.15)	1.33 (0.94, 1.98)	1.83 (1.46, 2.4)	Ramucirumab	0.84 (0.55, 1.38)	1.1 (0.7, 1.81)	1.59 (1.08, 2.39)
2.55 (1.47, 4.36)	1.03 (0.59, 1.76)	0.92 (0.57, 1.46)	1.59 (0.99, 2.52)	2.19 (1.47, 3.18)	1.2 (0.73, 1.83)	Regorafenib	1.31 (0.74, 2.25)	1.9 (1.13, 3)
1.95 (1.12, 3.42)	0.79 (0.44, 1.39)	0.7 (0.43, 1.15)	1.22 (0.74, 1.99)	1.67 (1.11, 2.52)	0.91 (0.55, 1.44)	0.76 (0.44, 1.35)	S_1	1.45 (0.86, 2.38)
1.35 (0.85, 2.24)	0.54 (0.33, 0.91)	0.49 (0.33, 0.74)	0.84 (0.56, 1.29)	1.15 (0.86, 1.58)	0.63 (0.42, 0.92)	0.53 (0.33, 0.88)	0.69 (0.42, 1.17)	Tivantinib

Fig. 4 League table of the efficacy of various second-line treatments for advanced HCC based on Bayesian network meta-analysis. (**A**)OS (**B**)PFS. An HR < 1.00 indicates better survival benefits

(3). Due to the lack of a closed-loop structure, a consistency model was used.

For DCR, all second-line treatments showed significant improvements compared to the placebo group, except for tivantinib (OR = 0.98, 95% CI: 0.62–1.54). Apatinib (OR = 3.88, 95% CI: 2.48–6.10), cabozantinib (OR = 3.53, 95% CI: 2.54–4.90), and regorafenib (OR = 3.31, 95% CI: 2.32–4.79) provided the best DCR benefits compared to the placebo group. S-1 (OR = 2.39, 95% CI: 1.46–4.05) and brivanib (OR = 2.32, 95% CI: 1.50–3.58) also showed significant DCR advantages compared to placebo (Fig. 6E).

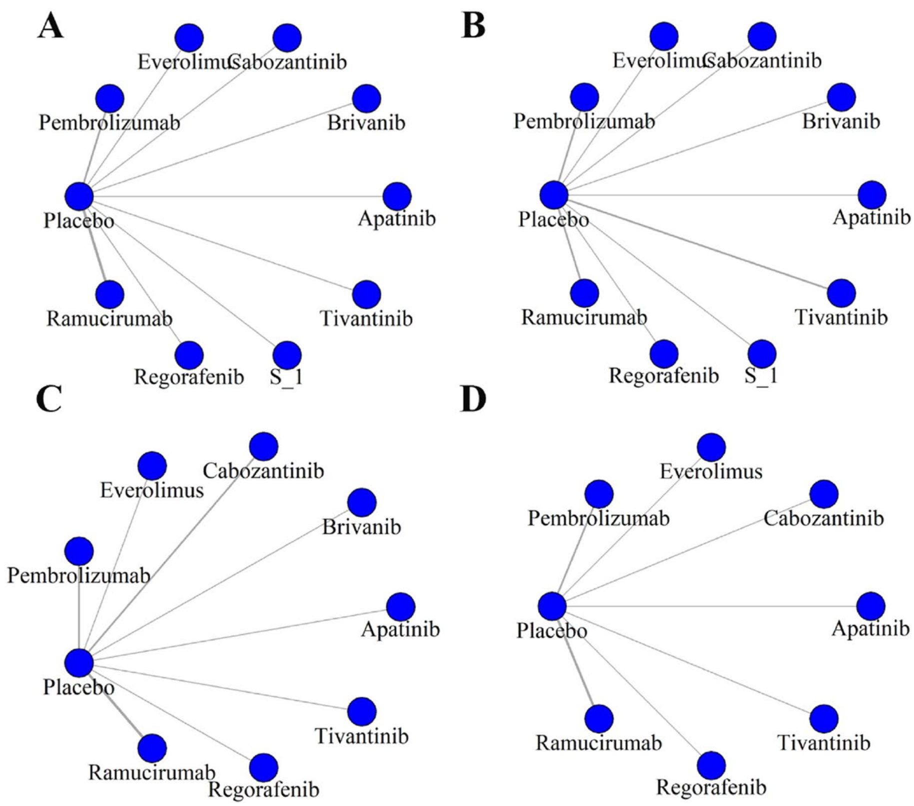

Fig. 5 Network diagram comparing the efficacy of various second-line treatments in patients with advanced HCC. Comparisons were generated using the Bayesian framework on (**A**) DCR (**B**) Any grade AEs (**C**) Grade3-4 AEs (**D**) AEs requiring treatment discontinuation

C

Apatinib	1.3 (0.87, 1.93)	2.15 (1.53, 3.02)	2.31 (1.76, 3.02)	1.02 (0.7, 1.48)	1.02 (0.75, 1.38)	1.36 (0.94, 1.97)	2.22 (1.53, 3.21)
0.77 (0.52, 1.15)	Brivanib	1.66 (1.15, 2.39)	1.79 (1.33, 2.4)	0.79 (0.53, 1.17)	0.79 (0.56, 1.09)	1.05 (0.72, 1.55)	1.72 (1.15, 2.55)
0.47 (0.33, 0.65)	0.6 (0.42, 0.87)	Everolimus	1.08 (0.87, 1.33)	0.48 (0.34, 0.67)	0.47 (0.37, 0.61)	0.63 (0.46, 0.88)	1.03 (0.73, 1.45)
0.43 (0.33, 0.57)	0.56 (0.42, 0.75)	0.93 (0.75, 1.15)	Placebo	0.44 (0.34, 0.57)	0.44 (0.38, 0.51)	0.59 (0.46, 0.76)	0.96 (0.74, 1.25)
0.98 (0.67, 1.42)	1.27 (0.85, 1.88)	2.1 (1.5, 2.94)	2.26 (1.74, 2.94)	Ramucirumab	0.99 (0.74, 1.35)	1.33 (0.93, 1.91)	2.17 (1.49, 3.15)
0.98 (0.73, 1.34)	1.27 (0.92, 1.78)	2.11 (1.64, 2.73)	2.27 (1.97, 2.63)	1.01 (0.74, 1.36)	Regorafenib	1.34 (1, 1.8)	2.18 (1.61, 2.95)
0.73 (0.51, 1.06)	0.95 (0.64, 1.4)	1.58 (1.14, 2.19)	1.7 (1.32, 2.18)	0.75 (0.52, 1.08)	0.75 (0.56, 1)	S_1	1.63 (1.13, 2.34)
0.45 (0.31, 0.65)	0.58 (0.39, 0.87)	0.97 (0.69, 1.36)	1.04 (0.8, 1.36)	0.46 (0.32, 0.67)	0.46 (0.34, 0.62)	0.61 (0.43, 0.88)	Tivantinib

D

Apatinib	0.87 (0.13, 5.69)	1.17 (0.18, 7.54)	1.16 (0.22, 4.6)	0.17 (0.04, 0.5)	1.67 (0.26, 10.16)	0.47 (0.09, 1.93)	1.44 (0.14, 31.17)	0.07 (0, 3.59)
1.14 (0.18, 7.46)	Brivanib	1.34 (0.21, 8.69)	1.33 (0.25, 5.39)	0.19 (0.04, 0.58)	1.9 (0.29, 12.16)	0.54 (0.1, 2.21)	1.67 (0.15, 35.24)	0.08 (0, 3.92)
0.86 (0.13, 5.46)	0.74 (0.12, 4.8)	Cabozantinib	0.99 (0.19, 3.92)	0.14 (0.03, 0.42)	1.42 (0.23, 8.52)	0.41 (0.08, 1.61)	1.24 (0.12, 26.8)	0.06 (0, 2.81)
0.86 (0.22, 4.48)	0.75 (0.19, 4.04)	1.01 (0.26, 5.25)	Pembrolizumab	0.14 (0.06, 0.29)	1.44 (0.37, 7.14)	0.41 (0.13, 1.21)	1.26 (0.17, 23.68)	0.07 (0, 2.79)
5.92 (2, 27.35)	5.23 (1.71, 24.27)	6.95 (2.4, 31.31)	6.92 (3.47, 15.86)	Placebo	9.9 (3.4, 42.98)	2.82 (1.35, 6.66)	8.68 (1.4, 154.68)	0.46 (0.01, 17.43)
0.6 (0.1, 3.82)	0.53 (0.08, 3.43)	0.71 (0.12, 4.35)	0.69 (0.14, 2.73)	0.1 (0.02, 0.29)	Ramucirumab	0.28 (0.06, 1.13)	0.87 (0.09, 18.5)	0.04 (0, 1.95)
2.12 (0.52, 11.41)	1.85 (0.45, 10.04)	2.46 (0.62, 13.06)	2.46 (0.83, 7.43)	0.36 (0.15, 0.74)	3.54 (0.88, 17.14)	Regorafenib	3.07 (0.41, 61.15)	0.16 (0, 6.65)
0.69 (0.03, 7.32)	0.6 (0.03, 6.62)	0.81 (0.04, 8.41)	0.8 (0.04, 6.04)	0.12 (0.01, 0.72)	1.15 (0.05, 11.6)	0.33 (0.02, 2.46)	S_1	0.05 (0, 2.84)
13.48 (0.28, 626.38)	11.79 (0.26, 559.14)	15.77 (0.36, 736.29)	15.28 (0.36, 597.6)	2.16 (0.06, 79.99)	22.3 (0.51, 1054.1)	6.24 (0.15, 252.67)	20.94 (0.35, 1794.66)	Tivantinib

E

Apatinib	0.6 (0.32, 1.11)	0.91 (0.52, 1.6)	0.4 (0.22, 0.71)	0.34 (0.2, 0.58)	0.26 (0.16, 0.4)	0.46 (0.27, 0.77)	0.86 (0.48, 1.52)	0.62 (0.31, 1.24)	0.25 (0.13, 0.48)
1.67 (0.9, 3.11)	Brivanib	1.52 (0.88, 2.61)	0.67 (0.38, 1.17)	0.57 (0.34, 0.95)	0.43 (0.28, 0.66)	0.76 (0.46, 1.26)	1.43 (0.81, 2.52)	1.03 (0.53, 2.03)	0.42 (0.23, 0.79)
1.1 (0.63, 1.92)	0.66 (0.38, 1.13)	Cabozantinib	0.44 (0.27, 0.72)	0.37 (0.24, 0.58)	0.28 (0.2, 0.39)	0.5 (0.33, 0.77)	0.94 (0.58, 1.54)	0.68 (0.37, 1.26)	0.28 (0.16, 0.49)
2.5 (1.4, 4.46)	1.49 (0.85, 2.62)	2.27 (1.39, 3.7)	Everolimus	0.85 (0.54, 1.35)	0.64 (0.45, 0.92)	1.14 (0.73, 1.78)	2.14 (1.27, 3.57)	1.54 (0.84, 2.93)	0.63 (0.35, 1.12)
2.93 (1.73, 5.01)	1.75 (1.06, 2.96)	2.67 (1.73, 4.13)	1.18 (0.74, 1.86)	Pembrolizumab	0.76 (0.57, 1.01)	1.34 (0.91, 1.97)	2.51 (1.59, 3.99)	1.81 (1.02, 3.29)	0.74 (0.43, 1.27)
3.88 (2.48, 6.1)	2.32 (1.5, 3.58)	3.53 (2.54, 4.9)	1.55 (1.08, 2.23)	1.32 (0.99, 1.76)	Placebo	1.77 (1.37, 2.31)	3.31 (2.32, 4.79)	2.39 (1.46, 4.05)	0.98 (0.62, 1.54)
2.19 (1.3, 3.69)	1.31 (0.79, 2.17)	2 (1.31, 3.04)	0.88 (0.56, 1.38)	0.75 (0.51, 1.1)	0.57 (0.43, 0.73)	Ramucirumab	1.87 (1.2, 2.94)	1.35 (0.77, 2.42)	0.56 (0.33, 0.93)
1.17 (0.66, 2.08)	0.7 (0.4, 1.23)	1.07 (0.65, 1.73)	0.47 (0.28, 0.79)	0.4 (0.25, 0.63)	0.3 (0.21, 0.43)	0.53 (0.34, 0.84)	Regorafenib	0.72 (0.39, 1.36)	0.3 (0.16, 0.53)
1.62 (0.81, 3.18)	0.97 (0.49, 1.88)	1.48 (0.79, 2.67)	0.65 (0.34, 1.2)	0.55 (0.3, 0.98)	0.42 (0.25, 0.68)	0.74 (0.41, 1.29)	1.39 (0.74, 2.58)	S_1	0.41 (0.2, 0.8)
3.94 (2.1, 7.53)	2.36 (1.26, 4.4)	3.6 (2.06, 6.29)	1.58 (0.89, 2.82)	1.34 (0.79, 2.31)	1.02 (0.65, 1.61)	1.8 (1.07, 3.07)	3.37 (1.88, 6.07)	2.43 (1.24, 4.9)	Tivantinib

Fig. 6 League table of the efficacy of various second-line treatments for advanced HCC based on BayesianNMA. (C)TTP (D)ORR (E)DCR. An HR < 1.00 indicates better survival benefits. An OR > 1.00 indicates better efficacy

Safety and toxicity

To evaluate the safety and toxicity across studies, we assessed the rate of all-grade and grade 3–4 AEs and the rate of treatment discontinuation due to AEs. The NMA included 10 second-line treatment regimens reporting AEs (Fig. 5B), 9 regimens reporting grade 3–4 AEs (Fig. 5C), and 8 regimens reporting the rate of treatment discontinuation due to AEs (Fig. 5D) in patients with HCC.

Regarding any grade AEs, 12 studies were included, covering 9 different treatment regimens: pembrolizumab (2), everolimus (1), cabozantinib (1), brivanib (1), apatinib (1), tivantinib (2), S-1 (1), regorafenib (1), and ramucirumab (2). All second-line treatments had higher AE incidence rates compared to the placebo group. Among these treatments, tivantinib (OR = 1.23, 95% CI: 0.19–7.41), pembrolizumab (OR = 2.41, 95% CI: 0.44–15.73), and cabozantinib (OR = 3.83, 95% CI: 0.31–48.53) had relatively lower AE incidence rates, which were not statistically significant compared to placebo (Fig. 7F).

Regarding grade 3–4 AEs, 12 studies were included, covering 8 different treatment regimens: pembrolizumab (2), everolimus (1), cabozantinib (1), brivanib (1), apatinib (1), tivantinib (1), regorafenib (2), and ramucirumab (3). All second-line treatments had higher grade 3–4 AE incidence rates compared to the placebo group. Among these treatments, tivantinib (OR = 1.00, 95% CI: 0.18–5.34) and ramucirumab (OR = 1.95, 95% CI: 0.96–10.82) had relatively lower incidence rates of grade 3–4 AEs, which were not statistically significant compared to placebo (Fig. 7G).

Regarding AEs requiring treatment discontinuation, 10 studies were included, covering 7 different treatment regimens: pembrolizumab (2), everolimus (1), cabozantinib (1), apatinib (1), tivantinib (1), regorafenib (1), and ramucirumab (3). All second-line treatments had higher incidence rates of AEs requiring treatment discontinuation compared to the placebo group. Among these treatments, tivantinib (OR = 1.33, 95% CI: 0.65–2.89) and regorafenib (OR = 1.41, 95% CI: 0.92–2.18) had relatively lower incidence rates of AEs requiring treatment discontinuation, which were not statistically significant compared to placebo (Fig. 7H).

Rank

Ranking analysis was conducted based on Bayesian ranking profiles. For all efficacy assessment indicators in advanced HCC patients, regorafenib is most likely to rank first in OS with a cumulative probability of 98.06%, followed by cabozantinib (80.19%) and pembrolizumab (68.06%). Cabozantinib has the highest probability of ranking first in PFS (90.52%), followed by regorafenib (81.38%) and apatinib (78.54%). In ORR, ramucirumab has the highest probability of ranking first (77.67%), followed by S-1 (70.95%), pembrolizumab (66.59%), and cabozantinib (66.46%). In DCR, apatinib is most likely to rank first (91.04%), followed by cabozantinib (86.76%) and regorafenib (82.67%). In TTP, apatinib is most likely to rank first (84.93%), followed by regorafenib (83.90%) and ramucirumab (82.08%).

F

Apatinib	0.83 (0.02, 28.06)	0.38 (0.01, 13.21)	0.62 (0.02, 22.54)	0.24 (0.01, 5.75)	0.1 (0.01, 1.2)	0.39 (0.02, 12.97)	6.15e+13 (13.07, 1.28e+84)	1.21 (0.04, 41.41)	0.12 (0.01, 2.74)
1.2 (0.04, 41.58)	Brivanib	0.46 (0.01, 15.41)	0.71 (0.02, 29.42)	0.28 (0.02, 6.42)	0.12 (0.01, 1.38)	0.47 (0.03, 15.31)	7.68e+13 (16.16, 1.26e+84)	1.45 (0.04, 45.31)	0.14 (0.01, 3.02)
2.63 (0.08, 92.8)	2.18 (0.06, 73.79)	Cabozantinib	1.61 (0.04, 64.03)	0.62 (0.03, 14.93)	0.26 (0.02, 3.25)	1.03 (0.06, 33.22)	1.54e+14 (40.97, 3.14e+84)	3.19 (0.09, 106.94)	0.33 (0.01, 6.76)
1.62 (0.04, 53.49)	1.4 (0.03, 47.77)	0.62 (0.02, 23.36)	Everolimus	0.39 (0.02, 9.45)	0.16 (0.01, 2.2)	0.65 (0.03, 21.9)	1.59e+14 (20.93, 2.00e+84)	1.98 (0.05, 66.64)	0.2 (0.01, 4.57)
4.24 (0.17, 76.9)	3.56 (0.16, 63.42)	1.61 (0.07, 31.99)	2.53 (0.11, 58.66)	Pembrolizumab	0.42 (0.06, 2.26)	1.68 (0.14, 28.96)	2.78e+14 (62.71, 4.87e+84)	5.08 (0.22, 96.75)	0.51 (0.04, 5.87)
10.21 (0.83, 125.81)	8.51 (0.73, 95.02)	3.83 (0.31, 48.53)	6.17 (0.46, 91.41)	2.41 (0.44, 15.73)	Placebo	4.06 (0.75, 38.44)	6.09e+14 (166.54, 1.14e+85)	12.29 (1.08, 140.89)	1.23 (0.19, 7.41)
2.55 (0.08, 43.84)	2.12 (0.07, 34.78)	0.97 (0.03, 17.81)	1.54 (0.05, 33.25)	0.6 (0.03, 6.98)	0.25 (0.03, 1.33)	Ramucirumab	1.52e+14 (38.39, 2.95e+84)	3.05 (0.1, 51.86)	0.3 (0.01, 3.27)
0 (0, 0.08)	0 (0, 0.06)	0 (0, 0.02)	0 (0, 0.05)	0 (0, 0.02)	0 (0, 0.01)	0 (0, 0.03)	Regorafenib	0 (0, 0.09)	0 (0, 0.01)
0.83 (0.02, 26.92)	0.69 (0.02, 22.38)	0.31 (0.01, 10.64)	0.51 (0.02, 18.77)	0.2 (0.01, 4.52)	0.08 (0.01, 0.93)	0.33 (0.02, 9.58)	4.98e+13 (11.36, 1.00e+84)	S_1	0.1 (0, 2.2)
8.18 (0.37, 192.81)	6.92 (0.33, 155.45)	3.07 (0.15, 70.32)	5.02 (0.22, 142.16)	1.96 (0.17, 28.36)	0.81 (0.14, 5.15)	3.31 (0.31, 67.91)	4.96e+14 (112.87, 1.09e+85)	10.07 (0.45, 226.37)	Tivantinib

G

Apatinib	0.48 (0.04, 5.78)	0.29 (0.04, 2.4)	0.16 (0.01, 1.76)	0.12 (0.01, 0.96)	0.07 (0.01, 0.4)	0.14 (0.03, 1.89)	0.23 (0.02, 2.53)	0.07 (0.01, 0.82)
2.08 (0.17, 23.81)	Brivanib	0.6 (0.08, 4.85)	0.33 (0.03, 3.73)	0.25 (0.03, 2)	0.15 (0.03, 0.81)	0.28 (0.06, 4.05)	0.47 (0.05, 5.13)	0.15 (0.01, 1.66)
3.45 (0.42, 26.99)	1.67 (0.21, 13.14)	Cabozantinib	0.55 (0.07, 4.36)	0.4 (0.08, 2.2)	0.25 (0.07, 0.8)	0.48 (0.15, 4.48)	0.78 (0.1, 6.03)	0.24 (0.03, 1.87)
6.34 (0.57, 68.87)	3.03 (0.27, 32.77)	1.83 (0.23, 14.12)	Everolimus	0.74 (0.1, 5.67)	0.45 (0.08, 2.36)	0.86 (0.19, 11.63)	1.42 (0.14, 15.44)	0.45 (0.04, 4.66)
8.61 (1.04, 67.77)	4.07 (0.5, 32.94)	2.47 (0.45, 12.81)	1.35 (0.18, 10.45)	Pembrolizumab	0.61 (0.18, 1.99)	1.18 (0.37, 11.16)	1.92 (0.25, 15.01)	0.6 (0.07, 4.73)
14.06 (2.48, 77.4)	6.75 (1.23, 36.72)	4.07 (1.26, 13.35)	2.22 (0.42, 12.29)	1.64 (0.5, 5.58)	Placebo	1.95 (0.96, 10.82)	3.17 (0.61, 16.89)	1 (0.18, 5.34)
7.32 (0.53, 32.93)	3.52 (0.25, 16.11)	2.1 (0.22, 6.47)	1.16 (0.09, 5.27)	0.85 (0.09, 2.73)	0.51 (0.09, 1.04)	Ramucirumab	1.66 (0.13, 7.36)	0.52 (0.04, 2.35)
4.43 (0.39, 47.93)	2.12 (0.2, 22.1)	1.27 (0.17, 10.01)	0.7 (0.06, 7.28)	0.52 (0.07, 4.05)	0.32 (0.06, 1.64)	0.6 (0.14, 7.94)	Regorafenib	0.31 (0.03, 3.39)
14.24 (1.21, 152.13)	6.77 (0.6, 73.85)	4.11 (0.54, 30.58)	2.23 (0.21, 24.5)	1.66 (0.21, 13.55)	1 (0.19, 5.49)	1.94 (0.43, 27.02)	3.19 (0.29, 35.44)	Tivantinib

F

H

Apatinib	0 (0, 0.09)	0 (0, 0.02)	0 (0, 0.01)	0 (0, 0.01)	0 (0, 0.03)	0 (0, 0.01)	0 (0, 0.01)
6.05e+15 (11.62, 1.22e+52)	Cabozantinib	0.2 (0.04, 0.7)	0.16 (0.03, 0.52)	0.08 (0.02, 0.23)	0.35 (0.07, 1.26)	0.11 (0.02, 0.36)	0.11 (0.02, 0.4)
3.21e+16 (62.39, 5.79e+52)	5.06 (1.43, 24.86)	Everolimus	0.8 (0.36, 1.72)	0.41 (0.22, 0.74)	1.78 (0.73, 4.4)	0.58 (0.27, 1.2)	0.54 (0.21, 1.45)
3.93e+16 (79.57, 6.60e+52)	6.34 (1.94, 29.87)	1.26 (0.58, 2.8)	Pembrolizumab	0.52 (0.31, 0.82)	2.24 (1.03, 5.04)	0.72 (0.38, 1.38)	0.69 (0.29, 1.68)
7.83e+16 (154.95, 1.43e+53)	12.26 (4.26, 54.64)	2.44 (1.36, 4.64)	1.94 (1.22, 3.2)	Placebo	4.35 (2.38, 8.61)	1.41 (0.92, 2.18)	1.33 (0.65, 2.89)
1.70e+16 (35.07, 2.88e+52)	2.84 (0.79, 14.12)	0.56 (0.23, 1.37)	0.45 (0.2, 0.97)	0.23 (0.12, 0.42)	Ramucirumab	0.32 (0.14, 0.68)	0.31 (0.12, 0.81)
5.51e+16 (109.27, 1.04e+53)	8.78 (2.74, 40.41)	1.74 (0.83, 3.72)	1.38 (0.73, 2.65)	0.71 (0.46, 1.09)	3.09 (1.47, 6.9)	Regorafenib	0.95 (0.41, 2.29)
580.e+16 (114.74, 9.49e+52)	9.33 (2.47, 47.26)	1.84 (0.69, 4.78)	1.45 (0.6, 3.46)	0.75 (0.35, 1.53)	3.27 (1.24, 8.67)	1.06 (0.44, 2.43)	Tivantinib

Fig. 7 League table of the safety of various second-line treatments for advanced HCC based on Bayesian NMA. **F** Any grade AEs (**G**) grade3-4 adverse events (**H**) AEs requiring treatment discontinuation. An OR < 1.00 indicates better safety

For all safety and toxicity assessment indicators, regarding any grade AEs, excluding the placebo group, tivantinib is most likely to rank first (85.35%), followed by pembrolizumab (69.14%) and cabozantinib (56.81%). For grade 3-4AEs, excluding the placebo group, tivantinib is most likely to rank first (85.77%), followed by pembrolizumab (67.15%) and ramucirumab (57.25%). For AEs requiring treatment discontinuation, excluding the placebo group, tivantinib ranks first (77.81%), regorafenib ranks second (75.24%), and pembrolizumab ranks third (58.00%) (Fig. S1–7).

Heterogeneity and inconsistency

Publication bias analysis was conducted using funnel plots for six different outcome indicators. The results indicated that the scatter plot distribution of the studies was symmetrical, with no scattered distribution of study points, suggesting a low likelihood of publication bias in this study (Fig. S9, S10). The pairwise meta-analysis results based on frequentist methods were consistent with the corresponding pooled results from the Bayesian framework (Fig. S11). Heterogeneity was assessed using the Q-test and I^2 statistic. Results showed that if $I^2 = 0\%$ or $I^2 \leq 50\%$, indicating low heterogeneity, a fixed-effects model was used. If $I^2 > 50\%$, indicating heterogeneity, a random-effects model was used.

Discussion

Our study provides evidence-based support for clinical practice, including the following findings:

1) Almost all second-line treatments provided survival advantages over the placebo group in terms of OS, PFS, ORR, TTP, and DCR.
2) None of the second-line treatments showed safety or toxicity advantages over the placebo group.
3) For advanced HCC patients, regorafenib has the highest probability of providing the best OS among second-line treatments, cabozantinib has the highest probability of providing the best PFS, ramucirumab ranks highest in ORR, and apatinib ranks highest in both DCR and TTP.
4) For advanced HCC patients, tivantinib has the highest probability of ranking first in any grade AEs, grade 3–4 AEs, and AEs requiring treatment discontinuation among second-line treatments.
5) Regorafenib shows a good balance of efficacy and safety, ranking first in OS, second in PFS, third in DCR, second in TTP, and second in AEs requiring treatment discontinuation. Cabozantinib also shows excellent efficacy and safety, ranking second in OS, first in PFS, second in DCR, fourth in ORR, and third in any grade AEs. Regorafenib, cabozantinib, and ramucirumab have very similar HRs for OS. Upon further analysis, it was found that a higher proportion of patients in the ramucirumab trial had alpha-fetoprotein (AFP) levels above 400 ng/mL, indicating more aggressive and rapidly progressing disease. This may explain why the HR for OS in the ramucirumab trial is not as favorable as those for regorafenib and cabozantinib. In the regorafenib trial, patients had to tolerate 400 mg of sorafenib for at least 72% of the time during first-line treatment before progressing to second-line treatment with regorafenib. This restriction was not present in the cabozantinib trial. Based on our study results, cabozantinib should be prioritized for advanced HCC patients who do not meet this criterion, while regorafenib should be chosen for those who do.

In addition to targeted therapies, our study also included the PD-1 inhibitor pembrolizumab as a second-line treatment. Pembrolizumab demonstrated significant OS benefits compared to placebo (HR = 0.79, 95% CI: 0.67–0.93) and ranked second in safety, just behind tivantinib. PD-1 inhibitors block the interaction between PD-1 and its ligands PD-L1 and PD-L2, thereby inhibiting immune escape. Unlike traditional chemotherapy, these inhibitors have a selective immune function, which explains why pembrolizumab shows substantial OS benefits while maintaining relatively good safety. A NMA by Lei et al. evaluated the effectiveness and safety of ICIs as a primary treatment for unresectable liver cancer. Their findings support the higher survival rates of patients receiving ICI-based treatments when treatment-related AEs are tolerable. This further corroborates the excellent performance of pembrolizumab in our study [33].

Previous NMAs focused on the efficacy and safety of second-line treatments for advanced HCC, limited to patients resistant to or progressing after sorafenib [34, 35]. In 2020, Wang et al. compared only four second-line treatment drugs (pembrolizumab, ramucirumab, cabozantinib, and regorafenib), indicating that regorafenib and cabozantinib improved OS in patients with HCC [34]. In 2022, Solimando AG et al. demonstrated through their NMA that regorafenib, cabozantinib, and ramucirumab significantly extended OS in patients. Additionally, cabozantinib, regorafenib, ramucirumab, brivanib, S-1, axitinib, and pembrolizumab significantly improved PFS. They recommended regorafenib and cabozantinib as the best second-line treatment options [35]. Differing from our study, that research did not evaluate the endpoints of TTP, ORR, and DCR, which introduces certain limitations to its results.

In our study, regorafenib and cabozantinib are identified as the optimal second-line treatments, not only significantly improving OS and PFS but also showing advantages in DCR, TTP, and ORR, which is consistent with previous study results. The detailed comparison information between the different studies can be found in Table S2.

Strengths and limitations

Compared to previous studies, our research offers several significant advantages: First, the first-line treatment regimens are not limited to patients with sorafenib resistance or post-treatment progression, but also include other treatment options such as ICIs, other targeted therapies like lenvatinib, systemic chemotherapy or combinations of targeted and immune therapies. Second, all the studies we included are phase III RCTs, ensuring high-quality evidence. Third, the range of second-line treatment regimens considered is broad, not restricted to single-agent targeted therapies or immunotherapies. Fourth, we conducted a comprehensive evaluation of multiple outcome indicators, including OS, PFS, TTP, ORR, DCR, all-grade and grade 3–4 AEs, and the rate of treatment discontinuation due to AEs. Additionally, we updated the included literature to ensure the recency and comprehensiveness of our data. This demonstrates the thoroughness of our analysis. To the best of our knowledge, this is the most comprehensive systematic review and NMA comparing the efficacy and safety of all second-line treatments for HCC. This study includes the most extensive range of drugs and evaluates the broadest set of outcome indicators.

Despite the many important conclusions drawn from this study, several limitations should be noted. First, there are baseline differences among patients in the different studies, such as varying AFP levels and ECOG performance statuses, which may limit the generalizability of our conclusions. Second, although this study evaluated the efficacy and safety of second-line treatments using seven outcome indicators, not all indicators included all second-line treatments. For instance, studies on ADI-PEG20 only reported OS and PFS, without other efficacy-related outcome indicators. Third, we used the rate of treatment discontinuation due to AEs as one of the safety evaluation indicators. However, considering that the study population may have underlying cirrhosis, the degree of treatment discontinuation could be confounded by the severity of underlying liver disease, potentially introducing bias. Lastly, the quality of life for advanced HCC patients is also an important measure of drug efficacy, but due to a lack of relevant data, we did not evaluate the impact of second-line treatments on quality of life.

In summary, while current limitations present challenges, the future of liver disease management is promising. To address the baseline differences among patients, future research must prioritize the standardization of patient selection criteria and stratification methods. This will improve the generalizability of conclusions. Moreover, as whole-genome sequencing technology becomes more widespread and sophisticated, the assessment of treatment outcomes and prognosis for liver cancer patients is progressively shifting towards a more personalized and precise approach. We anticipate the integration of precision medicine approaches, leveraging genomic, proteomic, and metabolomic data to tailor treatments to individual patients. This advancement is expected to lead to substantial improvements in treatment efficacy, safety, and patient quality of life.

Conclusions

Despite these limitations, our study provides a comprehensive summary of RCTs for second-line treatments in advanced HCC. It demonstrates that different second-line treatments have their own advantages and disadvantages in terms of efficacy and safety. Considering both safety and efficacy, regorafenib and cabozantinib emerge as the optimal second-line treatment options for advanced HCC patients.

Abbreviations

HCC	Hepatocellular carcinoma
NMA	Network Meta-analysis
RCT	Randomized Controlled Trials
OS	Overall Survival
PFS	Progression-free Survival
TTP	Time to Disease Progression
DCR	Disease Control Rate
ORR	Objective Response Rate
AEs	Adverse events
BCLC	Barcelona Clinic Liver Cancer,
ECOG	Eastern Cooperative Oncology Group

Supplementary Information

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Supplementary Material 1

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Authors' contributions

Fenping Lu,Kai Zhao (Co-frst author): Conducted literature searches and screened articles for inclusion. Performed data extraction and quality assessment of studies. Analyzed and interpreted the data. Drafted and revised the manuscript. Miaoqing Ye, Guangyan Xing: Conducted literature searches and screened articles for inclusion. Performed data extraction and quality assessment of studies. Analyzed and interpreted the data. Drafted and revised the manuscript. Bowen Liu, Xiaobin Li: Advised on study design and data analysis. Reviewed and provided feedback on manuscript drafts. Yun Ran, Fenfang Wu, Wei Chen: Contributed to the interpretation of the data. Reviewed and provided feedback on manuscript drafts. Shiping Hu(Corresponding author):Conceptualized the study and secured funding. Provided guidance on study design and data analysis. Facilitated communication among the authors. Ensured adherence to ethical standards and manuscript guidelines. Reviewed and provided feedback on manuscript drafts. Submitted the manuscript for publication. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Availability of data and materials
All data generated or analysed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

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