The emerging therapies are reshaping the first-line treatment for advanced hepatocellular carcinoma: a systematic review and network meta-analysis

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Abstract

Background: Given the superior performance of various therapies over sorafenib in advanced hepatocellular carcinoma (HCC) and the absence of direct comparisons, it is crucial to explore the efficacy of these treatments in phase III randomized clinical trials.

Objectives: The goal is to identify which patients are most likely to benefit significantly from these emerging therapies, contributing to more personalized and informed clinical decision-making.

Design: Systematic review and network meta-analysis

Data sources and methods: PubMed, Embase, ClinicalTrials.gov, and international conference databases have been searched from 1 January 2010 to 1 December 2023.

Results: After screening, 17 phase III trials encompassing 18 treatments were included. In the whole-population network meta-analysis, the newly first-line tremelimumab plus durvalumab (Tre + Du) was found to be comparable with atezolizumab plus bevacizumab (Atezo + Beva) in providing the best overall survival (OS) benefit [hazard ratio (HR) 1.35, 95% confidence interval (CI): 0.93–1.92]. Concerning OS benefits, sintilimab plus bevacizumab biosimilar (Sint + Beva), camrelizumab plus rivoceranib (Camre + Rivo), and lenvatinib plus pembrolizumab (Lenva + Pemb) appear to exhibit similar effects to Tre + Du and Atezo + Beva. In the context of progression-free survival, Atezo + Beva seemed to outperform Tre + Du (HR: 0.66 CI: 0.49–0.87), while the effects are comparable to Sint + Beva, Camre + Rivo, and Lenva + Pemb. Upon comparison between Asia-Pacific and non-Asia-Pacific cohorts, as well as between hepatitis B virus (HBV)-infected and non-HBV-infected populations, immune checkpoint inhibitor (ICI)-based treatments seemed to exhibit heightened efficacy in the Asia-Pacific group and among individuals with HBV infection. However, combined ICI-based therapies did not show more effectiveness than molecular-targeted drugs in patients without macrovascular invasion and/or extrahepatic spread. As for grades 3–5 adverse events, combined therapies showed comparable safety to sorafenib and lenvatinib.

Conclusion: Compared with sorafenib and lenvatinib, combination therapies based on ICIs significantly improved the prognosis of advanced HCC and demonstrated similar safety. At the same time, the optimal treatment approach should be tailored to individual patient characteristics, such as etiology, tumor staging, and serum alpha-fetoprotein levels. With lower incidence rates of treatment-related adverse events and non-inferior efficacy compared to sorafenib, ICI monotherapies should be prioritized as a first-line treatment approach for patients who are not suitable candidates for ICI-combined therapies.

Trial registration: PROSPERO, CRD42022288172.

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Plain language summary

Lay summary/Key points

The efficiency of various systemic therapies in advanced HCC patients with specific characteristics remains to be explored. This study revealed that the efficacy of ICI combined therapies is influenced by factors such as tumor staging, etiology, patient demographics, and more. Additionally, ICI monotherapies should be prioritized as a first-line treatment approach for patients who are not suitable candidates for ICI combined therapies. Complementing to recent guidelines, this study indicated that several critical factors needed to be took into consideration for patients with advanced HCC.

Keywords: first-line, hepatocellular carcinoma, immune checkpoint inhibitors, molecular-targeted therapy, network meta-analysis

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Introduction

Hepatocellular carcinoma (HCC), representing approximately 90% of primary liver cancers, stands as the third leading cause of cancer-related deaths globally.[1] Curative interventions, including resection, transplantation, and ablation, significantly enhance the prognosis for early-stage HCC patients.[2] Unfortunately, 25–70% of those diagnosed at median-to-advanced stages do not have access to curative treatments, rendering their condition regarded as incurable.[3,4]

With the efficacy of reducing the risk of cancer-related death by 31–32%, sorafenib, a tyrosine kinase inhibitor, became the first-line recommended therapy for advanced HCC in 2007.[5,6] Even after lenvatinib, which shows non-inferior efficacy to sorafenib, molecular-targeted therapies (MTDs) remained the first-line therapies for advanced HCC.[7,8] With the advent of immune checkpoint inhibitors (ICIs) and the promising outcomes of the combinations of MTDs and ICIs, this hard nut begins to crack.[9] The IMbrave150 study found that atezolizumab plus bevacizumab (Atezo + Beva), a combination of programmed cell death ligand 1 (PD-L1) inhibitor and vascular endothelial growth factor (VEGF) inhibitor, surpassed sorafenib in achieving prolonged overall survival (OS). Due to the benefits observed in advanced HCC patients, Atezo + Beva was recommended as the preferred first-line option.[9–11] Moreover, combinations such as sintilimab plus bevacizumab biosimilar (Sint + Beva), tremelimumab plus durvalumab (Tre + Du), camrelizumab plus rivoceranib (Camre + Rivo), and donafenib have shown favorable prognostic benefits and low rates of adverse events (AEs) in advanced HCC patients.[12–15]

Nowadays, the majority of guidelines highly recommend combination therapies, including MTDs and ICIs (Atezo + Beva and Sint + Beva) or combinations of ICIs (Tre + Du), as the first-line treatment for advanced HCC patients.[9,11,12,14] There is currently a lack of direct head-to-head studies comparing the merits of these first-line treatment strategies. In addition, in comparison to MTDs, the extent of benefits from combined therapies within various subgroups remains unclear.[16–18] Furthermore, some studies suggested that the etiology of HCC can exert a substantial influence in modulating the response to these therapies.[16,19,20] Some patients with specific characteristics may benefit from MTDs alone rather than the combinations in the view of long-term and economic perspective, and which characteristics should be taken into account to make the optimal decisions is largely unknown.

Currently, most network meta-analyses primarily focus on comparing the advantages of existing therapies with sorafenib or emphasize the comparison of A + T with other regimens.[21–23] However, there is limited coverage of comparative analyses between current first-line therapies and emerging treatments. Therefore, our meta-analysis is specifically dedicated to examining the strengths and weaknesses among first-line therapies and emerging therapies, concurrently exploring potential variations in responsiveness to emerging therapies across different subgroups. This study aims to address existing gaps in the

literature, providing a comprehensive perspective on the performance of various first-line treatment strategies within specific patient subgroups.

Methods

This network meta-analysis was reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Supplemental Table S1) for network meta-analysis.[24] We have applied the frequentist network meta-analysis for the present analysis. The protocol was registered in the Prospective Register of Systematic Reviews (PROSPERO, CRD42022288172).

Data sources and searches

We conducted a comprehensive search among the online databases, including PubMed, Embase, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov. The related studies were identified from 1 January 2010 to 1 December 2023 in English by using combinations of the following terms, 'hepatocellular carcinoma', 'tyrosine kinase inhibitors', 'immunotherapy', 'immune checkpoint inhibitors', 'first-line', within the restrictive limit of 'randomized controlled trials'. We also scanned the abstracts and presentations of ongoing randomized controlled trials on HCC from several international conferences (American Society of Clinical Oncology, European Society of Medical Oncology) from 2014 to 2023. Finally, the candidate studies were perused for details.

Study selection

Phase III randomized controlled trials that met the following criteria were included: (1) Participants: patients with advanced HCC who were diagnosed histopathologically, cytologically, or clinically (adapted from the Guidelines of the European Association for the Study of the Liver[25] or Guidelines for Diagnosis and Treatment of Primary Liver Cancer in China[26]), (2) Intervention: systemic regimens as first-line treatment, (3) Comparison: sorafenib or lenvatinib as the control group, (4) Outcomes: the primary outcomes are OS, progression-free survival (PFS), and the secondary outcomes are overall response rate (ORR) and Grade 3 or higher treatment-related adverse events (TRAEs).

Exclusion criteria included: (1) incomplete reported outcomes, (2) repeated reports, and (3) sample size of fewer than 100 patients.

Data extraction and risk of bias assessment

Two investigators conducted study selection and data extraction independently, with the disagreements adjudicated by a third consultant. To avoid potential assessment bias caused by investigators, clinical outcomes of interests assessed by the independent review facility were primarily extracted. The TRAEs were employed, and if TRAEs were not reported, general grade 3–5 AEs were used for the network meta-analysis instead. ClinicalTrials.gov and other available sources were evaluated based on the up-to-date data. The qualitative assessment of individual studies was performed using the Cochrane Risk of Bias Tool.[27]

Data synthesis and statistical analysis

Frequentist framework network meta-analysis (including subgroup analysis based on several standards and integrated analysis) was performed with the 'netmeta' package (version 2.0-1, R Foundation, https://cran.r-project.org/web/packages/netmeta/netmeta.pdf) of R software (version 4.0.2, R Project for Statistical Computing, https://www.r-project.org/) to compare and rank the treatment effects directly or indirectly across the regimens. A random-effects model was used to explain the substantial heterogeneity across the studies. The global heterogeneity between treatment effects among the included studies was assessed using Chi^2 and I^2 statistics and p values of $Chi^2 > 0.05$ or $I^2 < 50\%$ were considered as low heterogeneity, respectively.

Results

Literature search

The process of study selection has been shown in the flow diagram (Figure 1). Initially, we identified 2748 studies from the online database mentioned above. After screening the title/abstract and full text for eligibility, 17 studies involving 18 regimens for advanced HCC were included for further analysis.[9,13–15,28–37]

Study characteristics and data processing

The characteristics of 17 studies are shown in Supplemental Table S2. To summarize, there were 11,922 patients included in these studies, and the number of participants ranged from 323 to 1155. The age range was between 18 and 88 years. The correlation network figures in terms of OS and PFS are presented in Figure 2.

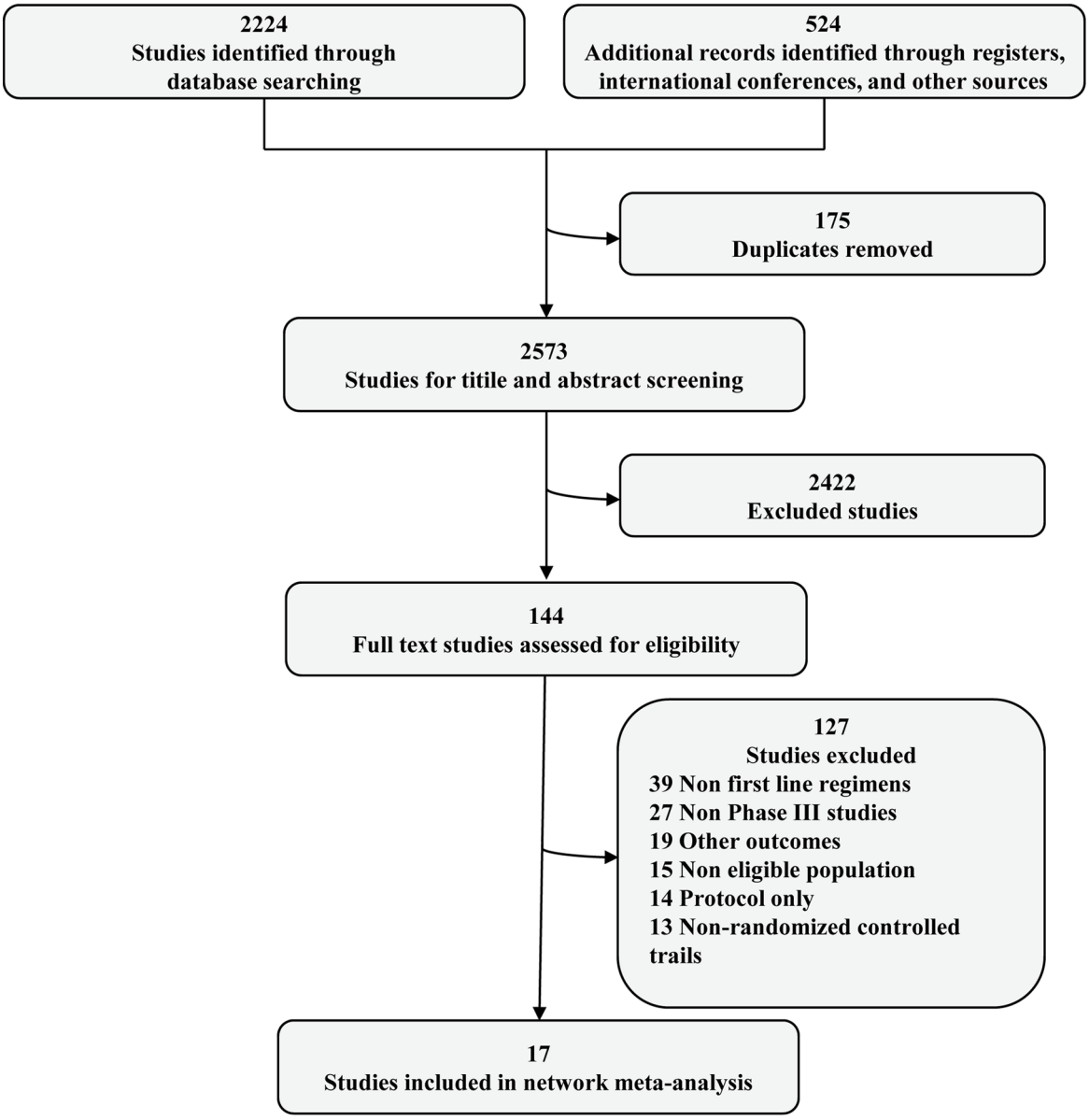

Figure 1. PRISMA flow diagram showing the study selection process.
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

The primary outcomes were OS and PFS, and the secondary outcome was ORR and grade 3 or higher AEs. As a result, both OS and PFS of 17 regimens, ORR of 15 regimens, and AEs of 14 regimens were included in the network meta-analysis. For integrated analysis, Sint + Beva, Atezo + Beva, Camre + Rivo, lenvatinib plus pembrolizumab (Lenva + Pemb), Tre + Du, and cabozantinib plus atezolizumab (Cabo + Atezo) were integrated as the ICI-combined therapies, patients who received lenvatinib or donafenib were pooled as the MTDs group, and patients who received sorafenib were set as placebo. At the same time, nivolumab, durvalumab, and tislelizumab were integrated into the ICI-monotherapies group.

Efficacy and safety among whole-population analysis

As for the overall network analysis [Figure 3(a)], Sint + Beva, Atezo + Beva, Camre + Rivo, Lenva + Pemb, and Tre + Du stand out as the top five

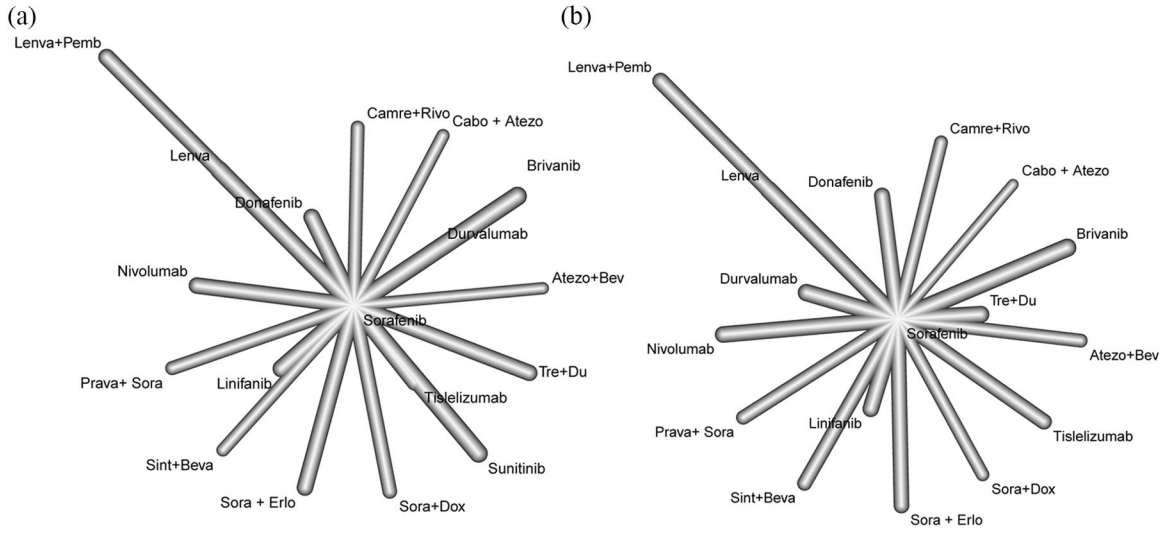

Figure 2. Network diagrams of comparisons on OS and PFS of treatments: (a) overall survival and (b) progression-free survival.

Each line represents a type of head-to-head comparison. The width of the lines is proportional to the standard error of comparing the connected treatments.

Atezo + Beva, atezolizumab plus bevacizumab; Cabo + Atezo, cabozantinib plus atezolizumab; Camre + Rivo, camrelizumab plus rivoceranib; Lenva, lenvatinib; Lenva + Pemb, lenvatinib plus pembrolizumab; OS, overall survival; PFS, progression-free survival; Sint + Beva, sintilimab plus bevacizumab biosimilar; Sora + Erlo, sorafenib plus erlotinib; Sora + Dox, sorafenib plus doxorubicin; Sora + Prava, sorafenib plus pravastatin; Tre + Du, tremelimumab plus durvalumab.

regimens in conferring OS benefits, and all of them exhibited greater OS benefits compared to sorafenib and lenvatinib. Even if no significant difference were observed among these five treatment regimens in terms of providing OS benefits, Sint + Beva, Atezo + Beva, and Camre + Rivo outperformed not only all kinds of MTDs but also ICI monotherapies, while Lenva + Pemb and Tre + Du failed to do so. In the meanwhile, three ICI monotherapies failed to offer marked benefits in comparison with MTDs, which is similar within their corresponding trials. To comprehend the overall effects of ICI-combined therapies, ICI monotherapies, and MTDs, we conducted an integrated analysis. In our integrated analysis, ICI-based combined regimens showed OS benefits compared to various MTD and ICI monotherapies. Interestingly, while ICI monotherapies did not exhibit a significant OS benefit compared to MTDs, this group demonstrated a notable OS advantage over sorafenib [hazard ratio (HR): 0.85; 95% confidence interval (CI): 0.76–0.96] (Supplemental Figure 1A).

With regard to PFS [Figure 3(a)], with comparable efficacy among themselves, Camre + Rivo exhibited the most significant benefit, followed by Sint + Beva, Lenva + Pemb, and Atezo + Beva – all of which outperformed sorafenib and ICI monotherapies. Notably, Tre + Du was inferior to each of the four therapies and lenvatinib. And, in contrast to its performance in OS, Tre + Du failed to show PFS benefits compared to sorafenib and ICI monotherapies. Interestingly, none of the ICI-combined therapies demonstrated their superiority in PFS improvements when compared to lenvatinib. In integrated analysis, ICI-based combined regimens showed PFS benefits *versus* sorafenib and ICI monotherapies; however, such superiority was absent when compared to MTDs (HR: 0.84; 95% CI: 0.67–1.07) (Supplemental Figure 1A). ICI monotherapies did not demonstrate PFS benefit over sorafenib in this analysis.

In terms of ORRs [Figure 3(b)], all the ICI-based combinational therapies, ICI monotherapies, and lenvatinib demonstrated ORR benefits over sorafenib. Notably, in accordance with the outcomes in PFS, our analysis revealed that none of these therapies exhibited ORR superiority over lenvatinib. Nevertheless, when contrasted with donafenib, an alternative first-line therapy in China, Sint + Beva, Camre + Rivo, and Tre + Du exhibited an ORR advantage. The duration of response could not be evaluated due to the lack of data from the included trials.

(a)

Progression free survival

Overall survival																
Camre+Rivo	0.93 (0.68 - 1.28)	0.91 (0.66 - 1.26)	0.88 (0.63 - 1.24)	0.83 (0.53 - 1.27)	0.79 (0.59 - 1.04)	0.69 (0.51 - 0.92)	**0.58 (0.43 - 0.77)**	**0.57 (0.43 - 0.77)**	**0.56 (0.42 - 0.75)**	0.57 (0.40 - 0.80)	0.53 (0.40 - 0.69)	0.52 (0.38 - 0.72)	**0.52 (0.41 - 0.66)**	0.51 (0.38 - 0.68)	0.47 (0.35 - 0.63)	0.46 (0.34 - 0.62)	0.46 (0.35 - 0.61)
Rank 1st	**Sint+Beva**	0.98 (0.72 - 1.33)	0.95 (0.69 - 1.31)	0.89 (0.58 - 1.35)	0.85 (0.66 - 1.10)	0.74 (0.56 - 0.96)	**0.62 (0.48 - 0.81)**	**0.62 (0.47 - 0.81)**	**0.60 (0.46 - 0.79)**	0.61 (0.44 - 0.85)	0.57 (0.44 - 0.73)	0.56 (0.41 - 0.76)	**0.56 (0.45 - 0.69)**	0.55 (0.42 - 0.71)	0.50 (0.38 - 0.67)	0.49 (0.37 - 0.65)	0.50 (0.39 - 0.64)
Sint+Beva	**Rank 2nd**	**Lenva+Pemb**	0.97 (0.70 - 1.35)	0.91 (0.59 - 1.39)	0.87 (0.73 - 1.02)	0.75 (0.57 - 1.00)	**0.64 (0.48 - 0.84)**	**0.63 (0.47 - 0.84)**	**0.62 (0.47 - 0.81)**	0.62 (0.44 - 0.87)	0.58 (0.44 - 0.75)	0.57 (0.42 - 0.79)	**0.57 (0.46 - 0.72)**	0.56 (0.43 - 0.74)	0.52 (0.39 - 0.69)	0.50 (0.38 - 0.67)	0.51 (0.39 - 0.66)
0.98 (0.65 - 1.50)	**Atezo+Bev**	**Rank 3rd**	**Atezo+Bev**	0.94 (0.61 - 1.45)	0.89 (0.67 - 1.19)	0.78 (0.58 - 1.04)	**0.66 (0.49 - 0.87)**	**0.65 (0.48 - 0.87)**	**0.63 (0.47 - 0.85)**	0.64 (0.45 - 0.91)	0.60 (0.45 - 0.79)	0.59 (0.43 - 0.82)	**0.59 (0.46 - 0.75)**	0.58 (0.44 - 0.77)	0.53 (0.39 - 0.72)	0.52 (0.38 - 0.70)	0.52 (0.40 - 0.69)
0.92 (0.63 - 1.33)	0.94 (0.63 - 1.40)	**Camre+Rivo**	**Rank 4th**	**Cabo+Atezo**	0.95 (0.64 - 1.41)	0.83 (0.56 - 1.24)	0.70 (0.47 - 1.04)	0.69 (0.46 - 1.04)	0.68 (0.45 - 1.01)	0.68 (0.44 - 1.07)	0.64 (0.43 - 0.94)	0.63 (0.41 - 0.96)	**0.63 (0.44 - 0.91)**	0.62 (0.42 - 0.92)	0.57 (0.38 - 0.85)	0.56 (0.37 - 0.83)	0.56 (0.38 - 0.82)
0.74 (0.52 - 1.06)	0.75 (0.51 - 1.11)	0.80 (0.57 - 1.12)	**Lenva+Pemb**	**Rank 5th**	**Lenva**	0.87 (0.70 - 1.09)	**0.73 (0.59 - 0.91)**	**0.73 (0.58 - 0.91)**	**0.71 (0.57 - 0.89)**	0.72 (0.53 - 0.96)	0.67 (0.54 - 0.82)	0.66 (0.50 - 0.86)	**0.66 (0.57 - 0.77)**	0.65 (0.52 - 0.80)	0.59 (0.47 - 0.75)	0.58 (0.46 - 0.74)	0.58 (0.48 - 0.72)
0.73 (0.52 - 1.02)	0.74 (0.52 - 1.07)	0.79 (0.59 - 1.08)	0.99 (0.74 - 1.32)	**Tre+Du**	**Rank 6th**	**Linifanib**	0.84 (0.67 - 1.06)	0.83 (0.66 - 1.06)	0.82 (0.65 - 1.03)	0.83 (0.61 - 1.12)	0.77 (0.62 - 0.95)	0.76 (0.57 - 1.00)	**0.76 (0.64 - 0.90)**	0.74 (0.59 - 0.93)	0.68 (0.53 - 0.88)	0.67 (0.52 - 0.86)	0.67 (0.54 - 0.83)
0.68 (0.49 - 0.94)	**0.69 (0.48 - 0.99)**	**0.74 (0.55 - 1.00)**	0.92 (0.69 - 1.22)	0.93 (0.73 - 1.19)	**Donafenib**	**Rank 7th**	**Tre+Du**	0.99 (0.78 - 1.25)	0.97 (0.77 - 1.21)	0.98 (0.73 - 1.32)	0.91 (0.74 - 1.12)	0.90 (0.69 - 1.18)	0.90 (0.77 - 1.05)	0.88 (0.71 - 1.10)	0.81 (0.64 - 1.03)	0.79 (0.62 - 1.01)	0.80 (0.65 - 0.98)
0.67 (0.48 - 0.93)	**0.68 (0.48 - 0.98)**	**0.73 (0.54 - 0.99)**	0.91 (0.68 - 1.21)	0.92 (0.71 - 1.18)	0.99 (0.77 - 1.26)	**Nivolumab**	**Rank 8th**	**Donafenib**	0.98 (0.77 - 1.24)	0.99 (0.73 - 1.34)	0.92 (0.73 - 1.15)	0.91 (0.68 - 1.21)	0.91 (0.76 - 1.08)	0.89 (0.71 - 1.12)	0.82 (0.64 - 1.06)	0.80 (0.62 - 1.03)	0.80 (0.64 - 1.00)
0.67 (0.48 - 0.93)	**0.68 (0.47 - 0.98)**	**0.73 (0.54 - 0.99)**	0.91 (0.68 - 1.21)	0.92 (0.71 - 1.18)	0.99 (0.77 - 1.27)	1.00 (0.78 - 1.29)	**Tislelizumab**	**Rank 9th**	**Nivolumab**	1.01 (0.75 - 1.37)	0.94 (0.76 - 1.17)	0.93 (0.70 - 1.23)	0.93 (0.79 - 1.10)	0.91 (0.73 - 1.14)	0.84 (0.65 - 1.07)	0.82 (0.64 - 1.05)	0.82 (0.66 - 1.02)
0.66 (0.48 - 0.92)	**0.67 (0.47 - 0.97)**	**0.72 (0.53 - 0.97)**	0.90 (0.68 - 1.19)	0.91 (0.71 - 1.16)	0.98 (0.76 - 1.24)	0.99 (0.77 - 1.26)	0.99 (0.77 - 1.27)	**Durvalumab**	**Rank 10th**	**Sora+Dox**	0.93 (0.70 - 1.24)	0.92 (0.66 - 1.29)	0.92 (0.71 - 1.19)	0.90 (0.67 - 1.21)	0.83 (0.61 - 1.13)	0.81 (0.59 - 1.11)	0.81 (0.61 - 1.09)
0.63 (0.43 - 0.93)	**0.64 (0.43 - 0.98)**	**0.69 (0.48 - 0.99)**	0.86 (0.60 - 1.22)	0.87 (0.63 - 1.20)	0.93 (0.68 - 1.28)	0.94 (0.69 - 1.30)	0.94 (0.68 - 1.31)	0.96 (0.69 - 1.31)	**Cabo+Atezo**	**Rank 11th**	**Brivanib**	0.99 (0.76 - 1.29)	0.99 (0.86 - 1.14)	0.97 (0.79 - 1.19)	0.89 (0.71 - 1.12)	0.87 (0.69 - 1.10)	0.88 (0.72 - 1.06)
0.62 (0.45 - 0.85)	**0.63 (0.44 - 0.89)**	**0.67 (0.51 - 0.90)**	**0.84 (0.71 - 1.00)**	0.85 (0.67 - 1.07)	0.91 (0.73 - 1.14)	0.92 (0.74 - 1.16)	0.92 (0.73 - 1.17)	0.93 (0.75 - 1.17)	0.98 (0.72 - 1.33)	**Lenva**	**Rank 12th**	**Prava+ Sora**	1.00 (0.80 - 1.25)	0.98 (0.75 - 1.28)	0.90 (0.67 - 1.20)	0.88 (0.66 - 1.18)	0.88 (0.68 - 1.15)
0.61 (0.43 - 0.87)	0.62 (0.42 - 0.92)	0.67 (0.48 - 0.93)	0.83 (0.61 - 1.14)	0.84 (0.63 - 1.11)	0.90 (0.68 - 1.19)	0.91 (0.69 - 1.21)	0.91 (0.69 - 1.21)	0.92 (0.70 - 1.22)	0.97 (0.68 - 1.37)	0.99 (0.76 - 1.29)	**Sora+Dox**	**Rank 13th**	**Sorafenib**	0.98 (0.84 - 1.14)	0.90 (0.75 - 1.08)	0.88 (0.73 - 1.06)	0.88 (0.77 - 1.01)
0.61 (0.44 - 0.85)	0.62 (0.44 - 0.90)	0.67 (0.49 - 0.90)	0.83 (0.63 - 1.11)	0.84 (0.65 - 1.08)	0.90 (0.71 - 1.15)	0.91 (0.72 - 1.17)	0.91 (0.71 - 1.18)	0.93 (0.72 - 1.18)	0.97 (0.70 - 1.33)	0.99 (0.79 - 1.24)	1.00 (0.76 - 1.32)	**Sora + Erlo**	**Rank 14th**	**Durvalumab**	0.92 (0.72 - 1.17)	0.90 (0.71 - 1.14)	0.90 (0.74 - 1.11)
0.61 (0.45 - 0.83)	0.62 (0.44 - 0.87)	0.66 (0.50 - 0.88)	0.83 (0.64 - 1.08)	0.83 (0.67 - 1.04)	0.90 (0.72 - 1.12)	0.91 (0.73 - 1.13)	0.91 (0.73 - 1.14)	0.92 (0.74 - 1.14)	0.96 (0.71 - 1.30)	0.98 (0.81 - 1.20)	1.00 (0.77 - 1.29)	0.99 (0.80 - 1.24)	**Brivanib**	**Rank 15th**	**Tislelizumab**	0.98 (0.75 - 1.27)	0.98 (0.78 - 1.24)
0.57 (0.39 - 0.82)	0.58 (0.39 - 0.86)	0.62 (0.44 - 0.87)	0.77 (0.56 - 1.08)	0.78 (0.58 - 1.05)	0.84 (0.62 - 1.13)	0.85 (0.63 - 1.14)	0.85 (0.63 - 1.15)	0.86 (0.64 - 1.16)	0.90 (0.63 - 1.29)	0.92 (0.69 - 1.22)	0.93 (0.67 - 1.29)	0.93 (0.69 - 1.25)	0.93 (0.71 - 1.23)	**Prava+ Sora**	**Rank 16th**	**Sora + Erlo**	1.00 (0.80 - 1.26)
0.57 (0.43 - 0.75)	**0.58 (0.42 - 0.80)**	**0.62 (0.49 - 0.79)**	**0.77 (0.62 - 0.97)**	**0.78 (0.65 - 0.93)**	**0.84 (0.71 - 1.00)**	0.85 (0.71 - 1.01)	0.85 (0.71 - 1.02)	0.86 (0.72 - 1.02)	0.90 (0.69 - 1.18)	0.92 (0.79 - 1.07)	0.93 (0.75 - 1.16)	0.93 (0.78 - 1.11)	0.93 (0.82 - 1.07)	1.00 (0.79 - 1.27)	**Sorafenib**	**Rank 17th**	**Sunitinib**
0.54 (0.40 - 0.75)	0.55 (0.39 - 0.79)	0.59 (0.44 - 0.79)	0.74 (0.56 - 0.97)	0.75 (0.59 - 0.94)	0.80 (0.64 - 1.01)	0.81 (0.64 - 1.03)	0.81 (0.64 - 1.03)	0.82 (0.65 - 1.04)	0.86 (0.63 - 1.17)	0.88 (0.71 - 1.09)	0.89 (0.68 - 1.16)	0.89 (0.70 - 1.12)	0.89 (0.73 - 1.10)	0.96 (0.72 - 1.27)	0.96 (0.82 - 1.12)	**Linifanib**	**Rank 18th**
0.44 (0.32 - 0.60)	0.45 (0.32 - 0.63)	0.48 (0.36 - 0.63)	0.59 (0.46 - 0.78)	0.60 (0.48 - 0.75)	0.65 (0.52 - 0.81)	0.65 (0.52 - 0.82)	0.65 (0.52 - 0.82)	0.66 (0.53 - 0.83)	0.69 (0.51 - 0.94)	0.71 (0.58 - 0.87)	0.72 (0.55 - 0.93)	0.71 (0.57 - 0.89)	0.72 (0.59 - 0.87)	0.77 (0.58 - 1.02)	0.77 (0.67 - 0.89)	0.80 (0.65 - 0.99)	**Sunitinib**

(b)

Objective response rate

Rank 1st															
Sint+Beva	**Rank 2nd**														
1.31 (0.51 - 3.39)	**Tre+Du**	**Rank 3rd**													
1.38 (0.52 - 3.65)	1.05 (0.49 - 2.24)	**Camr+Rivo**	**Rank 4th**												
1.62 (0.62 - 4.20)	1.23 (0.59 - 2.56)	1.17 (0.55 - 2.51)	**Durvalumab**	**Rank 5th**											
1.83 (0.74 - 4.53)	1.39 (0.71 - 2.72)	1.33 (0.66 - 2.67)	1.13 (0.58 - 2.23)	**Lenva**	**Rank 6th**										
1.91 (0.63 - 5.79)	1.46 (0.58 - 3.67)	1.38 (0.54 - 3.57)	1.18 (0.47 - 2.99)	1.04 (0.43 - 2.52)	**Cabo+Atez**	**Rank 7th**									
2.09 (0.79 - 5.55)	1.59 (0.74 - 3.41)	1.51 (0.69 - 3.33)	1.29 (0.60 - 2.79)	1.14 (0.56 - 2.32)	1.09 (0.42 - 2.83)	**Tislelizumab**	**Rank 8th**								
2.20 (0.84 - 5.77)	1.68 (0.80 - 3.53)	1.60 (0.74 - 3.45)	1.36 (0.64 - 2.88)	1.20 (0.60 - 2.40)	1.15 (0.45 - 2.94)	1.05 (0.48 - 2.30)	**Atezo+Bev**	**Rank 9th**							
2.52 (0.99 - 6.43)	1.92 (0.95 - 3.90)	1.83 (0.87 - 3.82)	1.56 (0.76 - 3.19)	1.38 (0.72 - 2.64)	1.32 (0.53 - 3.28)	1.21 (0.57 - 2.54)	1.15 (0.55 - 2.37)	**Nivolumab**	**Rank 10th**						
3.02 (1.22 - 7.45)	**2.30 (1.18 - 4.48)**	**2.19 (1.09 - 4.39)**	1.87 (0.95 - 3.66)	1.65 (0.90 - 3.02)	1.58 (0.66 - 3.80)	1.44 (0.71 - 2.93)	1.37 (0.69 - 2.72)	1.20 (0.63 - 2.29)	**Linifanib**	**Rank 11th**					
3.19 (0.97 - 10.51)	2.43 (0.87 - 6.76)	2.31 (0.81 - 6.56)	1.97 (0.71 - 5.52)	1.74 (0.65 - 4.66)	1.67 (0.52 - 5.39)	1.53 (0.54 - 4.36)	1.45 (0.51 - 4.08)	1.27 (0.46 - 3.48)	1.06 (0.40 - 2.82)	**Sora+Dox**	**Rank 12th**				
3.49 (1.23 - 9.94)	**2.66 (1.14 - 6.22)**	**2.53 (1.06 - 6.06)**	2.16 (0.92 - 5.08)	1.91 (0.86 - 4.25)	1.83 (0.66 - 5.09)	1.67 (0.69 - 4.03)	1.59 (0.67 - 3.76)	1.38 (0.60 - 3.19)	1.16 (0.52 - 2.57)	1.09 (0.36 - 3.33)	**Sora + Erlo**	**Rank 13th**			
3.53 (1.20 - 10.43)	**2.69 (1.10 - 6.58)**	**2.56 (1.02 - 6.40)**	2.18 (0.89 - 5.37)	1.93 (0.82 - 4.51)	1.85 (0.64 - 5.34)	1.69 (0.67 - 4.26)	1.60 (0.65 - 3.98)	1.40 (0.58 - 3.38)	1.17 (0.50 - 2.73)	1.11 (0.35 - 3.49)	1.01 (0.37 - 2.74)	**Donafenib**	**Rank 14th**		
5.57 (2.18 - 14.21)	**4.24 (2.08 - 8.63)**	**4.03 (1.92 - 8.45)**	**3.44 (1.68 - 7.05)**	**3.04 (1.58 - 5.84)**	**2.91 (1.17 - 7.25)**	**2.66 (1.26 - 5.63)**	**2.53 (1.22 - 5.24)**	**2.21 (1.10 - 4.41)**	1.84 (0.96 - 3.53)	1.74 (0.63 - 4.80)	1.59 (0.69 - 3.68)	1.58 (0.65 - 3.81)	**Sunitinib**	**Rank 15th**	
6.10 (2.75 - 13.54)	**4.64 (2.78 - 7.75)**	**4.41 (2.54 - 7.68)**	**3.77 (2.24 - 6.35)**	**3.33 (2.17 - 5.12)**	**3.19 (1.48 - 6.88)**	**2.92 (1.66 - 5.12)**	**2.77 (1.62 - 4.74)**	**2.42 (1.48 - 3.94)**	**2.02 (1.32 - 3.09)**	1.91 (0.79 - 4.62)	1.74 (0.89 - 3.43)	1.73 (0.83 - 3.59)	1.09 (0.67 - 1.79)	**Sorafenib**	**Rank 16th**
9.00 (2.80 - 28.91)	**6.85 (2.53 - 18.52)**	**6.51 (2.36 - 17.99)**	**5.56 (2.05 - 15.11)**	**4.91 (1.89 - 12.76)**	**4.71 (1.49 - 14.82)**	**4.31 (1.55 - 11.95)**	**4.08 (1.49 - 11.18)**	**3.56 (1.34 - 9.52)**	**2.98 (1.15 - 7.72)**	2.82 (0.82 - 9.62)	2.57 (0.87 - 7.64)	2.55 (0.83 - 7.84)	1.62 (0.60 - 4.32)	1.48 (0.63 - 3.46)	**Prava+ Sora**

Figure 3. Pooled estimates of the network meta-analysis. (a) Pooled hazard ratios (95% credible intervals) for progression-free survival (upper triangle) and overall survival (lower triangle). Data in each cell are hazard ratios (95% credible intervals) for the comparison of row-defining treatment *versus* column-defining treatment. And hazard ratio of less than 1 favors row-defining treatment. (b) Pooled odds ratios (95% credible intervals) of objective response rate (lower triangle). Data in each cell are odds ratios (95% credible intervals) for the comparison of row-defining treatment *versus* column-defining treatment. An odds ratio of more than one favors row-defining treatment.

Sint + Beva, sintilimab plus bevacizumab biosimilar; Atezo + Beva, atezolizumab plus bevacizumab; Cabo + Atezo, cabozantinib plus atezolizumab; Camre + Rivo, camrelizumab plus rivoceranib; Lenva, lenvatinib; Lenva + Pemb, lenvatinib plus pembrolizumab; Sora + Dox, sorafenib plus doxorubicin; Sora + Erlo, sorafenib plus erlotinib; Sora + Prava, sorafenib plus pravastatin; Tre + Du, tremelimumab plus durvalumab.

As for safety analysis (Supplemental Table S3), the ICI monotherapies, durvalumab (52.1%), nivolumab (73.3%), and tislelizumab (76.6%), demonstrated superiority in safety compared to other regimens with fewer TRAEs of all grades. The addition of anti-CTLA-4 (Cytotoxic

T-lymphocyte-associated protein 4) tremelimumab to Durvalumab significantly increased the incidence of TRAEs of all grades (52.1–75.8%) and grade 3–5 (12.9–25.8%). Despite this, Tre + Du induced TRAEs of all grades and grade 3–5 TRAEs comparable to the other two ICI monotherapies. Despite significantly increasing the incidence of TRAEs compared to ICI monotherapies, the occurrence rate of TRAEs with the addition of MTDs to ICIs is similar to that of sorafenib and lenvatinib, except for Camre + Rivo. Notably, compared to other combinations of MTDs and ICIs, Camre + Rivo led to a significantly higher incidence of grade 3–5 TRAEs and TRAEs that led to discontinuation. For the ICI therapies, the most common grade 3–5 TRAEs were lipase increased and aspartate aminotransferase increased in Tre + Du groups, and aspartate aminotransferase increased in nivolumab or durvalumab groups. The combinations of ICIs and MTDs, including Atezo + Beva, Sint + Beva, Cabo + Atezo, Camre + Rivo, and shared similar types of grades 3–5 AEs, such as hypertension and aspartate aminotransferase increase.

Subgroup analysis

Subgroup analyses were performed to answer the question of whether specific patients would benefit from particular regimens, hoping to provide preliminary evidence for decision-making in future clinical practice.

It is generally believed that the etiology of HCC differs between the Western and Eastern populations and subgroup analyses were performed according to the geographical region [Figure 4(a)]. In subgroup analyses for the Asia-Pacific and non-Asia-Pacific regions, there were no significant differences among the five treatment regimens – Sint + Beva, Atezo + Beva, Camre + Rivo, Lenva + Pemb, and Tre + Du. In the Asia-Pacific region, all five regimens demonstrated superiority over sorafenib. However, in the non-Asia-Pacific region, Atezo + Beva emerged as the exclusive regimen exhibiting superiority over sorafenib and simultaneously demonstrating advantages over lenvatinib. In our subgroup integrated analysis (Supplemental Figure 1C), in both the Asia-Pacific and non-Asia-Pacific populations, ICI-based combined therapies exhibited superior efficacy compared to MTDs, including sorafenib. Notably, in the Asia-Pacific region, the HR values were even smaller, underscoring the heightened effectiveness of these combined therapies in this specific demographic. Interestingly, while ICI monotherapies did not exhibit superiority over the MTDs group, they demonstrated OS benefits compared to sorafenib in both subgroups.

Several studies have observed that hepatitis B virus (HBV)-related HCC tends to exhibit better OS outcomes when treated with immune-based therapies, in contrast to cases without HBV etiologies. In light of these findings, we conducted a subgroup analysis based on the HBV status to further explore the nuanced treatment responses within specific etiological subgroups. We observed significant OS benefits over sorafenib in the HBV-positive group across five ICI-combined therapies, while none of them performed better than sorafenib in the non-HBV group [Figure 4(b)]. At the same time, while no discernible differences in efficacy were observed among these five treatments, it is noteworthy that only Lenva + Pemb and Sint + Beva retained their association with superior OS benefits when compared to lenvatinib in the HBV-positive subgroup. Given the challenging nature of the results presented above, making analysis and summarization difficult, we conducted an integrated subgroup analysis. We found that, in comparison to sorafenib, ICI-combined therapies provide significant survival benefits in both HBV-positive groups and non-HBV groups. Notably, in the HBV-positive group, the HR values were significantly smaller. In addition, these therapies demonstrated OS benefits compared to MTD in the HBV-positive group, while no such benefits were observed in the non-HBV group (Supplemental Figure 1D). Interestingly, similar to the performance in a demographical subgroup, though ICI monotherapies did not exhibit superiority over the MTDs group, they demonstrated OS benefits compared to sorafenib regardless of HBV status.

Given tumor staging may influence the treatment decision, subgroup analysis was performed according to macrovascular invasion (MVI) and/or extrahepatic spread (EHS) status [Figure 4(c)]. Regardless of tumor stage, there were no significant differences among the five treatment regimens – Sint + Beva, Atezo + Beva, Camre + Rivo, Lenva + Pemb, and Tre + Du. In HCC patients diagnosed with MVI/EHS, Sint + Beva, Atezo + Beva, Camre + Rivo, and Lenva + Pemb consistently outperform sorafenib and lenvatinib

(a)

Other regions

Asia-Pacific															
Camr+Rivo	0.85 (0.40 - 1.78)	0.75 (0.37 - 1.55)	0.67 (0.34 - 1.30)	0.65 (0.34 - 1.27)	0.61 (0.31 - 1.19)	0.60 (0.31 - 1.16)	0.59 (0.29 - 1.21)	0.59 (0.30 - 1.15)	0.58 (0.30 - 1.12)	0.55 (0.28 - 1.08)	0.55 (0.29 - 1.03)	0.53 (0.27 - 1.07)	0.51 (0.26 - 1.01)	0.50 (0.25 - 0.99)	0.34 (0.17 - 0.68)
Rank 1st	Atezo+Bev	0.89 (0.52 - 1.52)	0.79 (0.50 - 1.25)	0.77 (0.49 - 1.22)	0.72 (0.45 - 1.15)	0.71 (0.45 - 1.11)	0.70 (0.41 - 1.18)	0.70 (0.44 - 1.10)	0.68 (0.44 - 1.07)	0.65 (0.41 - 1.04)	**0.65 (0.44 - 0.97)**	0.63 (0.38 - 1.04)	**0.60 (0.37 - 0.98)**	0.59 (0.36 - 0.95)	0.40 (0.24 - 0.66)
Atez+Beva	Rank 2nd	Tislelizumab	0.89 (0.59 - 1.35)	0.87 (0.57 - 1.32)	0.81 (0.53 - 1.24)	0.79 (0.52 - 1.20)	0.79 (0.48 - 1.29)	0.78 (0.52 - 1.19)	0.77 (0.51 - 1.16)	0.73 (0.47 - 1.12)	0.73 (0.51 - 1.04)	0.71 (0.45 - 1.12)	0.68 (0.43 - 1.06)	0.45 (0.28 - 0.72)	0.45 (0.28 - 0.72)
0.93 (0.52 - 1.65)	Sint+Beva	Rank 3rd	Tre+Du	0.98 (0.72 - 1.33)	0.91 (0.66 - 1.25)	0.89 (0.66 - 1.21)	0.88 (0.59 - 1.32)	0.88 (0.65 - 1.20)	0.86 (0.64 - 1.16)	0.82 (0.59 - 1.13)	0.82 (0.66 - 1.02)	0.80 (0.55 - 1.15)	0.76 (0.53 - 1.08)	0.74 (0.52 - 1.05)	0.50 (0.34 - 0.73)
0.80 (0.45 - 1.42)	0.86 (0.59 - 1.27)	Camr+Rivo	Rank 4th	Durvalumab	0.93 (0.68 - 1.28)	0.91 (0.67 - 1.24)	0.90 (0.60 - 1.36)	0.90 (0.66 - 1.23)	0.88 (0.65 - 1.19)	0.84 (0.61 - 1.16)	0.84 (0.67 - 1.05)	0.82 (0.57 - 1.18)	0.78 (0.55 - 1.11)	0.76 (0.53 - 1.08)	0.51 (0.35 - 0.75)
0.77 (0.42 - 1.43)	0.83 (0.53 - 1.31)	0.96 (0.61 - 1.51)	Lenv+Pemb	Rank 5th	Brivanib	0.98 (0.71 - 1.34)	0.97 (0.64 - 1.46)	0.97 (0.70 - 1.33)	0.95 (0.70 - 1.29)	0.90 (0.64 - 1.26)	0.90 (0.71 - 1.14)	0.87 (0.60 - 1.27)	0.83 (0.58 - 1.20)	0.81 (0.57 - 1.16)	0.55 (0.37 - 0.81)
0.75 (0.42 - 1.32)	0.80 (0.55 - 1.18)	0.93 (0.64 - 1.36)	0.97 (0.62 - 1.52)	Tre+Du	Rank 6th	Nivolumab	0.99 (0.66 - 1.48)	0.99 (0.73 - 1.34)	0.97 (0.72 - 1.30)	0.92 (0.67 - 1.27)	0.92 (0.74 - 1.14)	0.89 (0.62 - 1.28)	0.85 (0.60 - 1.21)	0.83 (0.59 - 1.18)	0.56 (0.38 - 0.82)
0.76 (0.37 - 1.55)	0.81 (0.45 - 1.46)	0.94 (0.53 - 1.68)	0.98 (0.53 - 1.84)	1.01 (0.57 - 1.81)	Cabo+Atez	Rank 7th	Lenv+Pemb	1.00 (0.67 - 1.50)	0.98 (0.66 - 1.45)	0.93 (0.61 - 1.41)	0.93 (0.66 - 1.30)	0.90 (0.58 - 1.41)	0.86 (0.70 - 1.05)	0.84 (0.54 - 1.30)	0.57 (0.36 - 0.90)
0.72 (0.40 - 1.27)	0.77 (0.52 - 1.14)	0.89 (0.60 - 1.32)	0.93 (0.59 - 1.47)	0.96 (0.65 - 1.41)	0.95 (0.53 - 1.70)	Nivolumab	Rank 8th	Sora+Dox	0.98 (0.73 - 1.32)	0.93 (0.67 - 1.29)	0.93 (0.75 - 1.16)	0.90 (0.63 - 1.30)	0.86 (0.61 - 1.22)	0.84 (0.59 - 1.19)	0.57 (0.39 - 0.83)
0.63 (0.37 - 1.07)	**0.68 (0.49 - 0.94)**	0.79 (0.57 - 1.08)	0.82 (0.55 - 1.22)	0.85 (0.62 - 1.16)	0.83 (0.49 - 1.43)	0.88 (0.64 - 1.22)	Donafenib	Rank 9th	Sora + Erlo	0.95 (0.69 - 1.30)	0.95 (0.77 - 1.17)	0.92 (0.65 - 1.32)	0.88 (0.62 - 1.24)	0.86 (0.61 - 1.21)	0.58 (0.40 - 0.84)
0.62 (0.36 - 1.05)	**0.66 (0.48 - 0.92)**	0.77 (0.56 - 1.06)	0.80 (0.58 - 1.10)	0.83 (0.60 - 1.13)	0.81 (0.47 - 1.40)	0.86 (0.62 - 1.20)	0.98 (0.76 - 1.25)	Lenva	Rank 10th	Prava+Sora	1.00 (0.79 - 1.27)	0.97 (0.66 - 1.42)	0.93 (0.64 - 1.33)	0.90 (0.63 - 1.30)	0.61 (0.41 - 0.91)
0.60 (0.33 - 1.10)	**0.65 (0.42 - 1.00)**	0.75 (0.49 - 1.16)	0.78 (0.48 - 1.28)	0.81 (0.53 - 1.24)	0.80 (0.43 - 1.47)	0.84 (0.55 - 1.30)	0.96 (0.66 - 1.39)	0.98 (0.67 - 1.43)	Sora + Erlo	Rank 11th	Sorafenib	0.97 (0.73 - 1.30)	0.93 (0.70 - 1.22)	0.90 (0.69 - 1.19)	0.61 (0.44 - 0.84)
0.60 (0.35 - 1.03)	**0.65 (0.46 - 0.92)**	0.75 (0.53 - 1.05)	0.78 (0.52 - 1.18)	0.81 (0.58 - 1.13)	0.80 (0.46 - 1.38)	0.84 (0.59 - 1.19)	0.95 (0.73 - 1.25)	0.98 (0.75 - 1.28)	1.00 (0.67 - 1.48)	Tislelizumab	Rank 12th	Cabo+Atez	0.95 (0.64 - 1.42)	0.93 (0.62 - 1.39)	0.63 (0.41 - 0.97)
0.60 (0.34 - 1.04)	**0.64 (0.44 - 0.93)**	0.74 (0.51 - 1.07)	0.77 (0.50 - 1.20)	0.80 (0.55 - 1.15)	0.79 (0.44 - 1.39)	0.83 (0.57 - 1.21)	0.94 (0.70 - 1.28)	0.97 (0.71 - 1.31)	0.99 (0.65 - 1.50)	0.99 (0.72 - 1.37)	Durvalumab	Rank 13th	Lenva	0.97 (0.66 - 1.44)	0.66 (0.43 - 1.00)
0.57 (0.34 - 0.97)	0.62 (0.44 - 0.85)	0.71 (0.52 - 0.98)	0.74 (0.50 - 1.11)	0.77 (0.56 - 1.05)	0.76 (0.44 - 1.30)	0.80 (0.58 - 1.11)	0.91 (0.71 - 1.15)	0.93 (0.73 - 1.19)	0.95 (0.65 - 1.38)	0.95 (0.73 - 1.24)	0.96 (0.71 - 1.30)	Brivanib	Rank 14th	Linifanib	0.68 (0.44 - 1.03)
0.52 (0.31 - 0.89)	0.56 (0.41 - 0.79)	0.65 (0.47 - 0.90)	0.68 (0.46 - 1.02)	0.70 (0.51 - 0.97)	0.69 (0.40 - 1.19)	0.73 (0.53 - 1.02)	0.83 (0.65 - 1.06)	0.85 (0.66 - 1.09)	0.87 (0.60 - 1.27)	0.87 (0.66 - 1.14)	0.88 (0.65 - 1.20)	0.92 (0.72 - 1.17)	Linifanib	Rank 15th	Sunitinib
0.53 (0.32 - 0.87)	**0.57 (0.43 - 0.75)**	**0.66 (0.50 - 0.87)**	**0.69 (0.48 - 0.99)**	**0.71 (0.54 - 0.93)**	**0.70 (0.42 - 1.17)**	**0.74 (0.56 - 0.98)**	**0.84 (0.71 - 1.00)**	0.86 (0.72 - 1.02)	0.88 (0.63 - 1.23)	0.88 (0.72 - 1.08)	0.89 (0.69 - 1.14)	0.93 (0.78 - 1.10)	1.01 (0.85 - 1.21)	Sorafenib	Rank 16th
0.44 (0.26 - 0.74)	0.47 (0.34 - 0.65)	0.55 (0.40 - 0.75)	0.57 (0.38 - 0.84)	0.59 (0.43 - 0.80)	0.58 (0.34 - 0.99)	0.61 (0.44 - 0.84)	0.69 (0.55 - 0.88)	0.71 (0.56 - 0.90)	0.73 (0.50 - 1.05)	0.73 (0.56 - 0.94)	0.74 (0.55 - 0.99)	0.77 (0.61 - 0.97)	0.83 (0.66 - 1.06)	0.83 (0.70 - 0.97)	Sunitinib

(b)

non-HBV

HBV Positive															
Camr+Rivo	0.90 (0.45 - 1.79)	0.82 (0.45 - 1.52)	0.73 (0.41 - 1.29)	0.72 (0.41 - 1.27)	0.71 (0.40 - 1.26)	0.76 (0.19 - 3.07)	0.69 (0.36 - 1.33)	0.76 (0.19 - 3.07)	0.66 (0.37 - 1.17)	0.66 (0.36 - 1.21)	0.54 (0.22 - 1.35)	0.61 (0.36 - 1.04)	0.55 (0.31 - 0.98)	**0.54 (0.29 - 0.99)**	
Rank 1st	Atezo+Bev	0.92 (0.54 - 1.55)	0.81 (0.50 - 1.31)	0.80 (0.50 - 1.29)	0.79 (0.49 - 1.28)	0.85 (0.22 - 3.30)	0.77 (0.43 - 1.37)	0.76 (0.47 - 1.23)	0.73 (0.45 - 1.19)	0.73 (0.43 - 1.24)	0.61 (0.26 - 1.42)	0.68 (0.44 - 1.05)	0.61 (0.38 - 0.99)	0.60 (0.35 - 1.01)	
Atezo+Bev	Rank 2nd	Tislelizumab	0.88 (0.62 - 1.26)	0.87 (0.62 - 1.24)	0.86 (0.60 - 1.23)	0.93 (0.25 - 3.45)	0.84 (0.52 - 1.35)	0.83 (0.58 - 1.19)	0.80 (0.55 - 1.15)	0.80 (0.52 - 1.21)	0.66 (0.30 - 1.46)	**0.74 (0.55 - 0.99)**	0.66 (0.46 - 0.96)	0.65 (0.43 - 0.98)	
0.96 (0.49 - 1.88)	Cabo+Atezo	Rank 3rd	Tre+Du	0.99 (0.75 - 1.30)	0.98 (0.73 - 1.30)	1.05 (0.29 - 3.85)	0.95 (0.62 - 1.46)	0.94 (0.71 - 1.25)	0.90 (0.67 - 1.22)	0.90 (0.63 - 1.29)	0.75 (0.35 - 1.60)	0.84 (0.69 - 1.03)	0.75 (0.56 - 1.01)	0.74 (0.52 - 1.05)	
0.88 (0.51 - 1.52)	0.91 (0.52 - 1.60)	Sint+Beva	Rank 4th	Brivanib	0.99 (0.75 - 1.30)	1.06 (0.29 - 3.88)	0.96 (0.63 - 1.46)	0.95 (0.72 - 1.25)	0.91 (0.68 - 1.22)	0.91 (0.64 - 1.29)	0.76 (0.35 - 1.61)	0.85 (0.70 - 1.02)	0.76 (0.57 - 1.01)	0.74 (0.53 - 1.05)	
0.82 (0.46 - 1.45)	0.85 (0.47 - 1.53)	0.93 (0.60 - 1.44)	Lenva+Pemb	Rank 5th	Nivolumab	1.08 (0.29 - 3.95)	0.97 (0.63 - 1.50)	0.97 (0.72 - 1.29)	0.92 (0.68 - 1.26)	0.92 (0.64 - 1.33)	0.77 (0.36 - 1.65)	0.86 (0.70 - 1.06)	0.77 (0.57 - 1.04)	0.75 (0.53 - 1.08)	
0.80 (0.46 - 1.38)	0.83 (0.47 - 1.46)	0.91 (0.60 - 1.36)	0.97 (0.63 - 1.51)	Tre+Du	Rank 6th	Sint+Beva	0.91 (0.24 - 3.45)	0.90 (0.25 - 3.30)	0.86 (0.23 - 3.17)	0.86 (0.23 - 3.21)	0.71 (0.16 - 3.13)	0.80 (0.22 - 2.89)	0.72 (0.20 - 2.64)	0.70 (0.19 - 2.62)	
0.77 (0.45 - 1.33)	0.80 (0.46 - 1.40)	0.88 (0.59 - 1.31)	0.94 (0.61 - 1.45)	0.97 (0.65 - 1.45)	Camr+Rivo	Rank 7th	Lenva+Pemb	0.99 (0.65 - 1.52)	0.95 (0.61 - 1.47)	0.95 (0.75 - 1.20)	0.79 (0.35 - 1.80)	0.88 (0.61 - 1.29)	0.79 (0.51 - 1.22)	0.78 (0.48 - 1.25)	
0.66 (0.38 - 1.16)	0.69 (0.39 - 1.23)	0.75 (0.49 - 1.15)	0.81 (0.51 - 1.27)	0.83 (0.54 - 1.28)	0.86 (0.56 - 1.30)	Nivolumab	Rank 8th	Durvalumab	0.96 (0.71 - 1.30)	0.96 (0.67 - 1.37)	0.79 (0.37 - 1.70)	0.89 (0.73 - 1.09)	0.80 (0.60 - 1.07)	0.78 (0.55 - 1.11)	
0.65 (0.39 - 1.09)	0.68 (0.40 - 1.15)	0.74 (0.52 - 1.06)	0.80 (0.54 - 1.18)	0.82 (0.57 - 1.18)	0.85 (0.60 - 1.20)	0.99 (0.68 - 1.44)	Durvalumab	Rank 9th	Sora+Erlo	1.00 (0.69 - 1.45)	0.83 (0.38 - 1.79)	0.93 (0.74 - 1.17)	0.84 (0.61 - 1.14)	0.82 (0.56 - 1.18)	
0.61 (0.37 - 1.02)	**0.64 (0.38 - 1.08)**	**0.70 (0.49 - 0.99)**	0.75 (0.58 - 0.97)	0.77 (0.54 - 1.10)	0.80 (0.56 - 1.12)	0.93 (0.64 - 1.35)	0.94 (0.70 - 1.26)	Lenva	Rank 10th	Lenva	0.83 (0.38 - 1.83)	0.93 (0.69 - 1.25)	0.84 (0.58 - 1.21)	0.82 (0.54 - 1.24)	
0.60 (0.36 - 0.99)	**0.62 (0.37 - 1.05)**	**0.68 (0.49 - 0.96)**	0.73 (0.50 - 1.06)	0.75 (0.53 - 1.06)	0.78 (0.56 - 1.08)	0.91 (0.63 - 1.30)	0.92 (0.69 - 1.21)	0.98 (0.74 - 1.28)	Donafenib	Rank 11th	Donafenib	1.12 (0.54 - 2.34)	1.01 (0.47 - 2.17)	0.98 (0.45 - 2.17)	
0.56 (0.33 - 0.94)	**0.58 (0.34 - 0.99)**	**0.64 (0.44 - 0.92)**	0.68 (0.46 - 1.02)	0.70 (0.49 - 1.02)	0.73 (0.51 - 1.03)	0.85 (0.58 - 1.24)	0.86 (0.63 - 1.17)	0.91 (0.67 - 1.23)	0.93 (0.70 - 1.24)	Tislelizumab	Rank 12th	Sorafenib	0.90 (0.72 - 1.11)	0.88 (0.65 - 1.18)	
0.53 (0.32 - 0.88)	**0.55 (0.32 - 0.93)**	**0.60 (0.42 - 0.86)**	**0.65 (0.44 - 0.95)**	**0.66 (0.46 - 0.95)**	**0.68 (0.48 - 0.97)**	0.80 (0.55 - 1.16)	0.81 (0.60 - 1.09)	0.86 (0.64 - 1.15)	0.88 (0.67 - 1.16)	0.94 (0.69 - 1.28)	Linifanib	Rank 13th	Linifanib	0.98 (0.68 - 1.41)	
0.52 (0.30 - 0.90)	**0.54 (0.31 - 0.95)**	**0.60 (0.40 - 0.89)**	**0.64 (0.41 - 0.99)**	**0.66 (0.44 - 0.99)**	0.68 (0.46 - 1.01)	0.79 (0.52 - 1.21)	0.80 (0.56 - 1.14)	0.85 (0.60 - 1.21)	0.87 (0.62 - 1.22)	0.93 (0.65 - 1.34)	0.99 (0.70 - 1.41)	Sora+Erlo	Rank 14th	Cabo+Atezo	
0.51 (0.32 - 0.81)	**0.53 (0.33 - 0.86)**	**0.58 (0.44 - 0.77)**	**0.62 (0.45 - 0.86)**	**0.64 (0.48 - 0.86)**	**0.66 (0.50 - 0.87)**	0.77 (0.56 - 1.05)	**0.78 (0.63 - 0.96)**	0.83 (0.68 - 1.02)	0.85 (0.71 - 1.02)	0.91 (0.73 - 1.14)	0.96 (0.78 - 1.19)	0.97 (0.73 - 1.30)	Sorafenib	Rank 15th	
0.50 (0.30 - 0.83)	**0.52 (0.31 - 0.88)**	**0.57 (0.40 - 0.80)**	**0.61 (0.42 - 0.89)**	**0.63 (0.44 - 0.89)**	**0.65 (0.46 - 0.91)**	0.75 (0.52 - 1.09)	0.76 (0.57 - 1.02)	0.81 (0.61 - 1.08)	0.83 (0.64 - 1.09)	0.89 (0.66 - 1.20)	0.95 (0.71 - 1.26)	0.95 (0.67 - 1.35)	0.98 (0.80 - 1.20)	Brivanib	Rank 16th
0.46 (0.28 - 0.76)	**0.48 (0.29 - 0.81)**	**0.53 (0.38 - 0.74)**	**0.57 (0.39 - 0.82)**	**0.58 (0.41 - 0.82)**	**0.60 (0.43 - 0.84)**	**0.70 (0.49 - 1.01)**	**0.71 (0.53 - 0.94)**	**0.75 (0.57 - 0.99)**	**0.77 (0.60 - 1.00)**	0.83 (0.62 - 1.11)	0.88 (0.66 - 1.16)	0.89 (0.63 - 1.24)	0.91 (0.75 - 1.09)	0.93 (0.71 - 1.22)	Sunitinib

Figure 4. (Continued)

(c)

MVI and/or EHS negative

MVI and/or EHS positive													
Sint+Beva	0.66 (0.27 - 1.59)	0.62 (0.19 - 2.04)	0.55 (0.23 - 1.31)	0.54 (0.23 - 1.29)	0.53 (0.20 - 1.39)	0.51 (0.22 - 1.21)	0.51 (0.22 - 1.17)	0.49 (0.21 - 1.15)	**0.43 (0.19 - 0.96)**	0.41 (0.17 - 1.02)	**0.41 (0.17 - 0.96)**	**0.38 (0.16 - 0.91)**	**0.30 (0.11 - 0.77)**
Rank 1st	Donafenib	0.95 (0.37 - 2.45)	0.84 (0.51 - 1.38)	0.83 (0.51 - 1.34)	0.81 (0.42 - 1.54)	0.78 (0.48 - 1.26)	0.77 (0.50 - 1.20)	0.74 (0.46 - 1.20)	**0.66 (0.45 - 0.95)**	0.62 (0.35 - 1.10)	**0.62 (0.39 - 1.00)**	**0.57 (0.35 - 0.96)**	**0.45 (0.24 - 0.86)**
Atezo+Beva	Rank 2nd	Atezo+Beva	0.88 (0.35 - 2.24)	0.87 (0.35 - 2.19)	0.85 (0.31 - 2.35)	0.82 (0.33 - 2.06)	0.81 (0.33 - 2.00)	0.78 (0.31 - 1.97)	0.69 (0.29 - 1.65)	0.66 (0.25 - 1.73)	0.66 (0.26 - 1.64)	0.61 (0.24 - 1.54)	0.48 (0.17 - 1.31)
0.93 (0.60 - 1.45)	Camr+Rivo	Rank 3rd	Tislelizumab	0.99 (0.63 - 1.54)	0.96 (0.52 - 1.78)	0.93 (0.60 - 1.44)	0.92 (0.62 - 1.37)	0.89 (0.57 - 1.38)	0.78 (0.56 - 1.08)	0.74 (0.44 - 1.27)	0.74 (0.48 - 1.14)	0.68 (0.43 - 1.10)	**0.54 (0.29 - 0.99)**
0.92 (0.59 - 1.43)	0.98 (0.66 - 1.47)	Sint+Beva	Rank 4th	Tre+Du	0.98 (0.53 - 1.79)	0.94 (0.62 - 1.44)	0.93 (0.64 - 1.37)	0.90 (0.59 - 1.37)	0.79 (0.58 - 1.07)	0.75 (0.45 - 1.26)	0.75 (0.50 - 1.14)	0.69 (0.44 - 1.10)	**0.54 (0.30 - 0.99)**
0.81 (0.52 - 1.25)	0.87 (0.59 - 1.28)	0.88 (0.60 - 1.31)	Lenva+Pemb	Rank 5th	Camr+Rivo	0.97 (0.53 - 1.77)	0.96 (0.54 - 1.70)	0.92 (0.50 - 1.68)	0.81 (0.48 - 1.37)	0.77 (0.39 - 1.51)	0.77 (0.42 - 1.40)	0.71 (0.38 - 1.33)	0.56 (0.27 - 1.17)
0.75 (0.51 - 1.12)	0.81 (0.57 - 1.14)	0.82 (0.58 - 1.17)	0.93 (0.66 - 1.31)	Tre+Du	Rank 6th	Linifanib	0.99 (0.68 - 1.45)	0.95 (0.63 - 1.45)	0.84 (0.62 - 1.13)	0.80 (0.48 - 1.34)	0.80 (0.53 - 1.21)	0.74 (0.47 - 1.16)	0.58 (0.32 - 1.05)
0.74 (0.50 - 1.10)	0.80 (0.57 - 1.12)	0.81 (0.57 - 1.15)	0.92 (0.66 - 1.28)	0.99 (0.74 - 1.31)	Nivolumab	Rank 7th	Brivanib	0.96 (0.66 - 1.41)	0.85 (0.67 - 1.07)	0.81 (0.50 - 1.31)	0.81 (0.56 - 1.17)	0.74 (0.49 - 1.13)	0.58 (0.33 - 1.03)
0.71 (0.45 - 1.10)	0.76 (0.50 - 1.13)	0.77 (0.51 - 1.16)	0.87 (0.58 - 1.30)	0.94 (0.65 - 1.34)	0.95 (0.67 - 1.35)	Cabo+Atezo	Rank 8th	Durvalumab	0.88 (0.65 - 1.19)	0.84 (0.50 - 1.41)	0.84 (0.55 - 1.27)	0.77 (0.49 - 1.22)	0.61 (0.33 - 1.10)
0.67 (0.45 - 1.00)	0.72 (0.51 - 1.01)	0.73 (0.52 - 1.04)	0.83 (0.59 - 1.16)	0.89 (0.67 - 1.19)	0.90 (0.68 - 1.19)	0.95 (0.67 - 1.36)	Durvalumab	Rank 9th	Sorafenib	0.95 (0.62 - 1.45)	0.95 (0.72 - 1.27)	0.88 (0.62 - 1.24)	0.69 (0.41 - 1.16)
0.64 (0.43 - 0.95)	**0.69 (0.49 - 0.97)**	**0.70 (0.49 - 0.99)**	0.79 (0.57 - 1.11)	0.85 (0.64 - 1.13)	0.86 (0.65 - 1.14)	0.91 (0.64 - 1.29)	0.96 (0.72 - 1.27)	Donafenib	Rank 10th	Lenva+Pemb	1.00 (0.73 - 1.36)	0.92 (0.53 - 1.59)	0.72 (0.37 - 1.41)
0.64 (0.43 - 0.95)	**0.69 (0.48 - 0.97)**	**0.70 (0.49 - 0.99)**	0.79 (0.56 - 1.11)	0.85 (0.63 - 1.14)	0.86 (0.65 - 1.14)	0.91 (0.63 - 1.30)	0.95 (0.71 - 1.27)	1.00 (0.75 - 1.33)	Tislelizumab	Rank 11th	Lenva	0.92 (0.59 - 1.44)	0.72 (0.40 - 1.31)
0.63 (0.43 - 0.93)	**0.68 (0.49 - 0.94)**	**0.69 (0.49 - 0.97)**	**0.78 (0.64 - 0.96)**	0.84 (0.64 - 1.10)	0.85 (0.65 - 1.11)	0.90 (0.64 - 1.26)	0.94 (0.72 - 1.23)	0.99 (0.76 - 1.28)	0.99 (0.75 - 1.30)	Lenva	Rank 12th	Nivolumab	0.79 (0.42 - 1.47)
0.57 (0.39 - 0.83)	0.61 (0.44 - 0.84)	0.62 (0.44 - 0.86)	0.70 (0.51 - 0.96)	0.75 (0.58 - 0.98)	0.76 (0.59 - 0.99)	0.80 (0.57 - 1.13)	0.84 (0.65 - 1.10)	0.88 (0.68 - 1.14)	0.89 (0.68 - 1.16)	0.90 (0.70 - 1.14)	Brivanib	Rank 13th	Cabo+Atezo
0.55 (0.39 - 0.77)	**0.59 (0.45 - 0.78)**	**0.60 (0.45 - 0.80)**	**0.68 (0.52 - 0.89)**	**0.73 (0.59 - 0.90)**	**0.74 (0.61 - 0.90)**	0.78 (0.58 - 1.04)	**0.82 (0.67 - 1.00)**	0.86 (0.70 - 1.04)	0.86 (0.70 - 1.06)	0.87 (0.73 - 1.04)	0.97 (0.82 - 1.15)	Sorafenib	Rank 14th
0.49 (0.34 - 0.72)	0.53 (0.38 - 0.73)	0.54 (0.38 - 0.75)	0.61 (0.44 - 0.84)	0.65 (0.50 - 0.85)	0.66 (0.51 - 0.86)	0.70 (0.50 - 0.98)	0.73 (0.56 - 0.96)	0.77 (0.59 - 1.00)	0.77 (0.59 - 1.01)	0.78 (0.61 - 1.00)	0.87 (0.68 - 1.11)	0.89 (0.75 - 1.06)	Linifanib	Rank 15th
0.42 (0.28 - 0.64)	0.45 (0.31 - 0.65)	0.46 (0.31 - 0.67)	0.52 (0.36 - 0.74)	0.56 (0.41 - 0.77)	0.56 (0.41 - 0.77)	0.60 (0.41 - 0.87)	0.63 (0.46 - 0.86)	0.65 (0.48 - 0.89)	0.66 (0.48 - 0.90)	0.66 (0.49 - 0.90)	0.74 (0.55 - 1.00)	0.76 (0.60 - 0.97)	0.85 (0.63 - 1.15)	Sunitinib

(d)

AFP Low

AFP High											
Atezo+Bev	0.96 (0.52 - 1.78)	0.81 (0.47 - 1.41)	0.67 (0.40 - 1.12)	0.67 (0.40 - 1.10)	0.64 (0.38 - 1.08)	0.63 (0.39 - 1.03)	0.60 (0.36 - 1.02)	0.60 (0.37 - 0.98)	**0.57 (0.35 - 0.92)**	**0.53 (0.32 - 0.87)**	**0.52 (0.34 - 0.80)**
Rank 1st	Sint+Beva	0.84 (0.49 - 1.46)	0.70 (0.42 - 1.16)	0.69 (0.42 - 1.14)	0.67 (0.40 - 1.12)	0.66 (0.41 - 1.07)	0.62 (0.37 - 1.05)	0.63 (0.39 - 1.01)	**0.59 (0.37 - 0.96)**	**0.55 (0.34 - 0.90)**	**0.54 (0.35 - 0.83)**
Lenva+Pemb	Rank 2nd	Camre+Rivo	0.83 (0.54 - 1.27)	0.82 (0.54 - 1.25)	0.79 (0.51 - 1.23)	0.78 (0.52 - 1.16)	0.74 (0.47 - 1.16)	0.74 (0.50 - 1.10)	0.70 (0.47 - 1.04)	**0.65 (0.43 - 0.98)**	**0.64 (0.46 - 0.90)**
0.89 (0.53 - 1.49)	Sint+Beva	Rank 3rd	Donafenib	0.99 (0.69 - 1.43)	0.96 (0.65 - 1.41)	0.94 (0.67 - 1.33)	0.90 (0.60 - 1.33)	0.90 (0.64 - 1.26)	0.85 (0.61 - 1.19)	0.79 (0.55 - 1.12)	0.77 (0.59 - 1.01)
0.83 (0.50 - 1.39)	0.94 (0.56 - 1.56)	Camre+Rivo	Rank 4th	Durvalumab	0.96 (0.66 - 1.41)	0.95 (0.68 - 1.33)	0.90 (0.61 - 1.33)	0.90 (0.65 - 1.25)	0.86 (0.62 - 1.19)	0.80 (0.57 - 1.12)	**0.78 (0.61 - 1.00)**
0.82 (0.49 - 1.36)	0.92 (0.56 - 1.53)	0.98 (0.60 - 1.63)	Tre+Du	Rank 5th	Tislelizumab	0.99 (0.69 - 1.41)	0.94 (0.62 - 1.41)	0.94 (0.66 - 1.33)	0.89 (0.63 - 1.27)	0.83 (0.57 - 1.19)	0.81 (0.61 - 1.08)
0.78 (0.49 - 1.23)	0.88 (0.56 - 1.39)	0.94 (0.60 - 1.47)	0.96 (0.61 - 1.49)	Nivolumab	Rank 6th	Tre+Du	0.95 (0.66 - 1.37)	0.95 (0.70 - 1.28)	0.90 (0.67 - 1.22)	0.84 (0.61 - 1.15)	0.82 (0.66 - 1.02)
0.77 (0.43 - 1.39)	0.87 (0.48 - 1.56)	0.93 (0.52 - 1.66)	0.94 (0.53 - 1.68)	0.99 (0.58 - 1.68)	Atezo+Beva	Rank 7th	Lenva+Pemb	1.00 (0.70 - 1.44)	0.95 (0.77 - 1.17)	0.88 (0.61 - 1.28)	0.86 (0.64 - 1.16)
0.72 (0.44 - 1.18)	0.81 (0.49 - 1.32)	0.86 (0.53 - 1.41)	0.88 (0.54 - 1.42)	0.92 (0.60 - 1.41)	0.93 (0.53 - 1.64)	Durvalumab	Rank 8th	Brivanib	0.95 (0.71 - 1.27)	0.88 (0.65 - 1.20)	0.86 (0.70 - 1.06)
0.67 (0.50 - 0.90)	0.76 (0.49 - 1.16)	0.81 (0.53 - 1.23)	0.82 (0.54 - 1.24)	0.86 (0.60 - 1.22)	0.87 (0.52 - 1.45)	0.94 (0.63 - 1.39)	Lenva	Rank 9th	Lenva	0.93 (0.68 - 1.27)	0.91 (0.74 - 1.12)
0.61 (0.40 - 0.94)	0.69 (0.45 - 1.06)	0.74 (0.48 - 1.13)	0.75 (0.49 - 1.14)	0.79 (0.55 - 1.12)	0.80 (0.48 - 1.33)	0.86 (0.57 - 1.28)	0.92 (0.67 - 1.26)	Donafenib	Rank 10th	Nivolumab	0.98 (0.78 - 1.24)
0.61 (0.38 - 0.96)	0.69 (0.43 - 1.08)	0.73 (0.47 - 1.15)	0.74 (0.48 - 1.16)	0.78 (0.53 - 1.15)	0.79 (0.46 - 1.35)	0.85 (0.55 - 1.31)	0.91 (0.64 - 1.29)	0.99 (0.69 - 1.42)	Tislelizumab	Rank 11th	Sorafenib
0.54 (0.36 - 0.81)	0.61 (0.40 - 0.91)	0.65 (0.43 - 0.97)	0.66 (0.44 - 0.98)	0.69 (0.50 - 0.96)	0.70 (0.43 - 1.15)	0.75 (0.51 - 1.10)	0.80 (0.60 - 1.07)	0.88 (0.66 - 1.17)	0.89 (0.64 - 1.23)	Brivanib	Rank 12th
0.52 (0.36 - 0.75)	**0.59 (0.41 - 0.85)**	**0.63 (0.44 - 0.90)**	**0.64 (0.45 - 0.91)**	**0.67 (0.51 - 0.88)**	0.68 (0.43 - 1.08)	0.73 (0.52 - 1.02)	**0.78 (0.63 - 0.97)**	0.85 (0.68 - 1.07)	0.86 (0.65 - 1.13)	0.97 (0.81 - 1.17)	Sorafenib

Figure 4. Pooled estimates of the subgroup network meta-analysis in terms of OS. Pooled estimates of subgroup analysis: (a) Pooled hazard ratios of OS for other regions (upper triangle) and Asia-Pacific (lower triangle). (b) Pooled hazard ratios of OS for non-HBV (upper triangle) and HBV positive (lower triangle). (c) Pooled hazard ratios of OS for VI and/or EHS negative (upper triangle) and VI and/or EHS positive (lower triangle). (d) Pooled hazard ratios of OS for AFP low (upper triangle) and AFP high (lower triangle). Data in each cell are hazard ratios for the comparison of row-defining treatment *versus* column-defining treatment. And hazard ratio of less than one favors row-defining treatment.

AFP, serum alpha-fetoprotein; EHS, extrahepatic spread; HBV, hepatitis B virus; OS, overall survival.

in terms of OS. However, Tre + Du exhibited superiority only compared to sorafenib and lacked an advantage over lenvatinib. While in the MVI/EHS negative subgroup, only Sint + Beva and donafenib demonstrated OS benefits over sorafenib. In addition, an integrated subgroup analysis was conducted. We found that in the MVI/EHS-positive group, ICI-combined therapies demonstrated advantages over ICI monotherapies and MTDs, while in the absence of MVI/EHS, no such advantages were observed (Supplemental Figure 1E). Besides, ICI monotherapies also showed a better OS benefit over sorafenib in the MVI/EHS-positive group.

As tumor biomarkers may indicate treatment efficacy according to previous studies,[38,39] serum alpha-fetoprotein (AFP) was used as a useful biomarker for treatment decisions under second-line treatment of HCC.[40] Subgroup analyses were performed based on AFP status. In Figure 4(d), no significant differences were observed among these five regimens, including Sint + Beva, Atezo + Beva, Camre + Rivo, Lenva + Pemb, and Tre + Du, in both the AFP high and low subgroups. However, only Sint + Beva and Camre + Rivo demonstrated OS benefits over sorafenib in patients, irrespective of whether AFP was high or low. Furthermore, Atezo + Beva exhibited OS benefits exclusively in the AFP low subgroup, whereas Tre + Du and Lenva + Pemb demonstrated OS benefits solely in the AFP high subgroup [Figure 4(d)]. Nevertheless, in our integrated subgroup analysis, we observed that ICI-combined therapies consistently outperformed both MTDs and sorafenib, regardless of AFP status, while ICI monotherapies exhibited greater benefit over sorafenib but not over MTDs (Supplemental Figure 1F).

Risk of bias

The Cochrane tool was used to assess the risk bias of included studies. After the assessment, most of the studies we included were considered low risk in terms of most aspects. Nine studies were ranked as high risk with respect to blinding of participants and personnel.[7,32,34,35] Due to the lack of a detailed description of the blinding of outcome assessment of PFS, the interpretation of outcomes regarding PFS should be cautious (Supplemental Figure 2).

Discussion

Recently, emerging drugs and regimens have continuously challenged sorafenib's status as the first-line treatment. As the landscape of advanced HCC treatment evolves, there is an urgent need for a comprehensive review and summarization of the efficiency and safety of both current first-line therapies and emerging schemes. Such an analysis could provide crucial insights for clinical decisions in the ever-changing landscape of HCC treatment. Sonbol *et al.*[41] and Fulgenzi *et al.*[23] conducted separate network meta-analyses on first-line treatments for advanced HCC, but it is worth mentioning that their studies did not include several high-quality studies reporting impressive results in recent years. At the same time, Liu *et al.*[21] and Fulgenzi *et al.*[23] conducted separate meta-analyses, assessing the comparative effectiveness of current therapies against sorafenib. In addition, they explored the efficacy of Atezo + Beva in comparison to other treatments. By contrast, we also analyzed the distinctions between emerging combination therapies and novel treatments in comparison to other MTDs, such as lenvatinib and donafenib. Furthermore, comprehensive subgroup analyses were also valuable to fully understand the optimal combination for advanced HCC patients with specific characteristics, which might help us figure out the population who might benefit from the specific regimens. Our preliminary results indicated that (1) ICI-combined regimens, including Sint + Beva, Atezo + Beva, Tre + Du, Lenva + Pemb, and Camre + Rivo, demonstrated OS benefits compared to both sorafenib and lenvatinib, except for Tre + Du, which exhibited OS benefits only compared to sorafenib. (2) The OS benefits of first-line regimens were affected by patient characteristics, including etiologies, tumor burdens, AFP levels, and so on. (3) ICI not only demonstrated comparable efficacy to sorafenib but sometimes surpassed it, exhibiting a lower incidence of AEs. (4) While the ICI-based combined regimens did not significantly increase grade 3–5 TRAEs compared to sorafenib and lenvatinib, a notable increase was observed when compared to ICI monotherapies.

ICIs targeted the molecular markers on the immune cells or tumor cells and were able to activate or block the immune cell response or tumor cell escapes, respectively. Although ICIs have achieved unprecedented clinical benefits, there is only a subset of patients reaching limited benefits.[42] On the other hand, MTDs targeted intracellular signaling pathways associated with angiogenesis, cancer cell survival, or growth have been proven to be effective in improving disease

control rates, including HCC. Moreover, some studies indicate that MTDs also possess the capability to regulate immune cells and the immune microenvironment,[43,44] which suggests that their combination with ICIs may have a synergistic effect. And mounting evidence has shown that the addition of MTDs to ICIs was able to enhance anti-tumor immunity by blocking the intracellular pathways associated with immune evasion.[45,46] Promising results in other cancers[47,48] encouraged the following clinicians to practice the novel MTD and ICI regimens clinically and basically in HCC. In this network meta-analysis, we observed that most ICI-combined therapy regimens were basically successful. Particularly, Sint + Beva, Atezo + Beva, and Camre + Rivo exhibited superiority not only over current MTDs but also over emerging ICI monotherapies. Though Tre + Du did not show superiority over lenvatinib and donafenib, the recently released exploratory 4-year follow-up data from the HIMALAYA trial show that it exhibits unprecedented 3- and 4-year OS rates (30.7% and 25.2%, respectively).[49] In LEAP002, Lenva + Pemb did not demonstrate an OS benefit over lenvatinib. However, our network meta-analysis revealed an OS advantage when comparing Lenva + Pemb against both lenvatinib and sorafenib. This phenomenon may be explained by the longest-ever observed OS in the lenvatinib arm (19.0 months; 95% CI: 17.2–21.7) in LEAP002. When conducting the network meta-analysis, all studies related to lenvatinib were integrated into a single overall effect for comparison. Besides, the failure of the Cabo + Atezo combination suggests that the role of MTDs independent of their anti-VEGF action in antitumor effects requires further illustration.

Though nivolumab, anti-PD-1 therapy, did not achieve what they expected, patients who received nivolumab had marginally higher objective response rates and more durable disease control (median 7.5 months *versus* 5.7 months) with relatively low rates of grade 3–5 AEs (22% *versus* 49%).[28] And responders had higher PD-L1 expression in tumor tissue, which indicated that nivolumab might function well in a specific group.[28,50] Besides, durvalumab and tislelizumab, the other two ICI monotherapies, demonstrated non-inferiority to sorafenib in extending OS and exhibited comparatively lower rates of TRAEs. Moreover, our integrated analysis indicates that ICI monotherapies exhibit OS benefits over sorafenib. As mentioned earlier, considering the significantly lower incidence of TRAEs in ICI monotherapies, they may emerge as a preferred first-line treatment option over sorafenib for patients who are not suitable for ICI-combined therapies.

As we know, HCC primarily develops in the context of chronic liver inflammation, and the immune dysfunction varies from different hepatitis viruses to non-alcoholic steatohepatitis (NASH).[16,51] Our subgroup and integrated analysis provides further indication that the efficacy of ICIs-based combination therapies shrank among the non-HBV subgroup compared with the HBV-positive subgroup. This might result from that HBV-related HCC increased immunogenicity provided by viral nonpeptides,[52] which facilitated ICI-combined therapies to exert greater efficacy. Besides, Cheng *et al.* found that tumor-resident memory (Trm) $CD8^+$ T cells were associated with a favorable outcome in patients with HBV-related HCC.[20,53] However, Pfister *et al.*[16] reported that a subset of protumorigenic cells in NASH favors the development of HCC and hamper response to ICIs. In the meanwhile, a former study found that hepatitis C virus (HCV)-related HCC tended to induce more exhausted and dysfunctional $CD8^+$ T cells, which might impair the efficacy of ICI-based combination therapies.[19,20] Interestingly, our subgroup analysis based on different regions showed that patients from Asia-Pacific tend to benefit more from regimens containing ICIs than those from the rest of the world [Figure 4(a)]. It is generally believed that the types of viral hepatitis between the Asia-Pacific region and the non-Asia-Pacific region were dramatically different. Patients from Asia-Pacific, especially China, were usually diagnosed with HBV hepatitis. By contrast, in the European and American regions, patients tended to be diagnosed with HCV hepatitis or alcoholic steatohepatitis.[54] This medical phenomenon was consistent with our subgroup analysis associated with HBV status [Figure 4(b) and Supplemental Figure 1D]. Certainly, the discrepancy of efficacy that ICIs exerted on patients from different regions could not be simply accounted for the status of hepatitis infection, as such phenomenon has also been observed in other kinds of cancer, such as lung cancer and renal cell carcinoma.[47,55] Thus, the factors that affected the efficacy of ICI-based therapy in patients from the western world should be identified, which might help us comprehensively understand more mechanisms of ICI therapy and become a target in the future.

A study has suggested that customized dosing strategies can contribute to an extended OS with sorafenib.[56] At the same time, we found that ICI-combined therapies did not always improve OS among patients without MVI and EHS, which indicated relatively low risk [Figure 4(c) and Supplemental Figure 1E]. This suggests that the benefit level for intermediate-stage patients receiving ICI-combined therapies is likely comparable to those receiving MTDs. However, it is crucial to note that clinical trials are typically designed with relatively short follow-up periods and a higher proportion of participants in the advanced stage. This circumstance makes it challenging to demonstrate clear advantages in the intermediate-stage subgroup. Therefore, when formulating recommendations for intermediate-stage HCC, it is essential to consider the broader clinical context. Decisions should not solely rely on subgroup analyses with acknowledged limitations. In renal cell carcinoma, given ICI-based therapies did not significantly improve OS compared with MTDs, MTDs alone are listed as the preferred option in the low-risk group according to International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) by NCCN kidney cancer guidelines.[48,55,57] However, both ICIs combined with targeted therapy and the combinations of ICIs provided significant OS benefits *versus* targeted monotherapies in the high-risk group, according to IMDC, and NCCN kidney cancer guidelines listed combination regimens as the preferred option in first-line therapies.[48,55,57] Thus, patients classified as low risk were advised to use MTD monotherapy first, which might ease the economic burden of patients and be suitable for follow-up treatment decisions after progression. So, there remains uncertainty regarding whether ICI-combined therapies are superior to sorafenib across all subgroups. Inspired by these results mentioned above, there is an urgent need to identify and stratify HCC patients who would receive ICI-based regimens into different risk subgroups according to some characteristics.

Although various treatments may exhibit differences in performance based on AFP levels, our integrated analysis revealed that ICI-based therapies consistently outperformed both MTDs and sorafenib in both AFP high and AFP low subgroups [Figure 4(d) and Supplemental Figure 1F]. However, a study reported that AFP combined with C-reactive protein was able to predict the response to ICI therapy, independent of Child-Pugh class and performance status.[58] In the meantime, our former study indicated that the early reductions in AFP and prothrombin induced by vitamin K deficiency or antagonist-II (PIVKA-II) could be predictors of the efficacy of ICI therapy in HCC patients.[38] The difference between our analysis and former studies may derive from the different standards of high AFP levels and low AFP levels in each study. And some information might be covered up after pooling the data. Therefore, the follow-up studies should aim to explore better-predicting combinations that can provide the immune status of HCC patients for clinical decisions.

In the present study, we first included all the phase III RCTs that were published or up-to-date recently and comprehensively analyzed the major outcomes of efficacy and toxicity. By synthesizing evidence with the most extensive data, our results will assist clinical decisions for evaluating different regimens in treating patients with advanced HCC. For example, though there is no significant difference among the first-line or potential first-line regimens, including Sint + Beva, Atezo + Beva, Camre + Rivo, Lenva + Pemb, and Tre + Du, these three regimens (Sint + Beva, Atezo + Beva, and Camre + Rivo) demonstrate superior efficacy compared to other treatments, such as lenvatinib and ICI monotherapies. We were the first to propose that ICI monotherapies may emerge as a preferred first-line treatment option over sorafenib for patients who are not suitable for ICI-combined therapies. Moreover, this study separately analyzed the efficacy of treatments based on several factors that might play critical roles in affecting antitumor effectiveness, which has never spotted before. For instance, though the efficacy of ICI-combined regimens showed no significant differences in various subgroups, unlike the Asia-Pacific population, Atezo + Beva is the only one demonstrating superiority over sorafenib and lenvatinib in the non-Asia-Pacific population. Just as described earlier, the performance of ICI-combined therapies varies among different groups. These findings could provide valuable insights to assist clinicians in customizing the most suitable treatment plan based on the individual characteristics of the patients.

This network meta-analysis has several limitations. First, the estimations of this study were based on observational data from clinical trials, which contain unavoidable confounding factors.

Second, each comparison between treatments included only one or two studies, which may cause lower statistical power and uncertainty in estimation due to heterogeneity. Third, patients were not stratified according to the volume and number of tumors which might influence the treatment benefits. For example, our analysis involved *post hoc* stratification based on factors such as MVI/EHS, HBV status, AFP levels, and geographical regions. This *post hoc* nature introduces the risk of potential biases, and caution is warranted in interpreting the results. Fourth, this network meta-analysis was conducted with summary aggregated data rather than individual patient data, which would impair the power of this analysis. For example, in the HBV-negative subgroup, we pooled the effect of HCV-infected or non-viral infection patients, which might impair their efficacy.

Conclusion

The ICI-combined therapies significantly improved the prognosis of advanced HCC and demonstrated similar safety compared with sorafenib and lenvatinib. However, the optimum treatment regimens should be shaped by patient characteristics, such as etiologies, tumor stage, and AFP. It is important to note that ICI monotherapies, with lower incidence rates of TRAEs, not only demonstrated comparable efficacy to sorafenib but sometimes surpassed it.

Declarations

Ethics approval and consent to participate

No ethical approval was required as this was a systematic review and meta-analysis and used the published data.

Consent for publication

Not applicable.

Author contributions

Wei Peng: Investigation; Methodology; Writing – original draft; Writing – review & editing.

Yangxun Pan: Conceptualization; Data curation; Methodology; Writing – original draft; Writing – review & editing.

Lan Xie: Supervision; Validation; Visualization; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Only publicly available data were used in this study. And these data are available with a reasonable request.

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Supplemental material

Supplemental material for this article is available online.

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